Studies on the 4-Dimethylallyltryptophan Synthase Mechanism - Development of a Divinylcyclopropane Rearrangement based Strategy for the Formation of Cyclohepta[*cd*]oxindoles and its Application on the Synthesis of 5-(10⟶9)*Abeo*-Ergot Alkaloids

Dissertation submitted for the degree of Doctor of Natural Sciences
(Dr. rer. nat.)

Presented by
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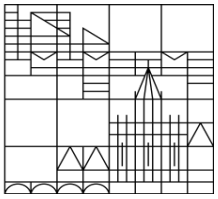
At the

Universität Konstanz



Faculty of Sciences
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Konstanz, 2017

To my parents

"Vanity of vanities, says the Preacher, vanity of vanities! All is vanity. What does man gain by all the toil at which he toils under the sun? All things are full of weariness; a man cannot utter it; the eye is not satisfied with seeing, nor the ear filled with hearing. What has been is what will be, and what has been done is what will be done, and there is nothing new under the sun. There is no remembrance of former things, nor will there be any remembrance of later things yet to be among those who come after."

-Ecclesiastes 1

Scientific Contributions from 2011 to 2016

Publications

Schwarzer D. D.; Gritsch P. J.; Gaich, T. “How to "COPE" with the prenylation of the indole C-4-position“, *Synlett.* **2013**, *24*, 1025.

Schwarzer, D. D.; Gritsch, P. J.; Gaich, T. “Mimicking the Dimethylallyltryptophan Synthase - Experimental Evidence for a Biosynthetic Cope Rearrangement Process“, *Angew. Chem. Int. Ed.* **2012**, *51*, 11514.

El-Seply, O.; **Schwarzer, D**.; Oswarek, P.; Mlynarski, J. “Direct Aldol Reaction of Pyruvic Derivatives; Catalytic Attempt to Synthesise Ulosonic Acids“, *Eur. J. Org. Chem.* **2012**, *14*, 2724.

Poster & Talks

The Münster Symposium on Cooperative Effects in Chemistry, 2014 Münster, Germany,
Poster: “*How to “Cope” with prenylation of the indole C4-position*”

14th Tetrahedron-Symposium, 2013 Vienna, Austria
Poster: “*Mimicking the DMAT-Synthase - Evidence for a Biosynthetic Cope Rearrangement*”

8th Status Seminar Biological Chemistry, 2013, Frankfurt am Main, Germany
Poster: “*Mimicking the DMAT-Synthase - Evidence for a Biosynthetic Cope Rearrangement*”

2nd Winterfeld Symposium, 2012, Leibniz University of Hannover, Germany
Talk: “Anwendung der Divinylcyclopropanumlagerung in der Synthese von Indolalkaloiden”

Abstract

1. Experimental evidence was found to support the enzymatic [3,3]-sigmatropic rearrangement catalysed by dimethylallyltryptophan (DMAT) synthase. A bio-inspired system showed the feasibility of Cope rearrangement to the C-4 position of the indole nucleus. This experiment supports the theory which says that 4-DMATS reverse prenylates C-3 and catalyses the Cope rearrangement into C-4.
2. A new methodology for the construction of cyclohepta[*cd*]oxindoles has been established. The presented methodology is intended to serve as a general approach to the functionalization of the 4-position of indole. It serves as an alternative to reactions where the toxic elements thallium and mercury are used, and offers broader scope compared to the Witkop cyclisation. The reaction is generally not affected by substituents on the aromatic core and tolerates many functional groups at the cyclopropane and the olefinic parts.
3. This work features the synthetic approach towards 5(10⟶9)*abeo*-ergoline derivatives, unnatural products derived from methyl lysergate. The key features of our synthesis is the divinylcyclopropane rearrangement to establish the tricyclic cyclohepta[*cd*]indole core. Gold (I) catalysis and Jeffrey cross coupling conditions furnished the pyrrolidine moiety and completed the carbon skeleton. Nevertheless, the adverse alignment of the orbitals on C-9 and C-10, that could be proven by force field calculations, prevented the completion of our common intermediate.
4. The mechanism of the divinylcyclopropane rearrangement for the formation of cyclohepta-[*cd*]oxindoles has been investigated with respect to the dependence of the rate constants k and the *cis-trans* isomerization on the Thorpe-Ingold effect. The presence of a substituent on C-9 revealed a great increase of the rate constant compared to the unsubstituted compound. Furthermore, the *cis-trans* isomerization could be detected by NMR by using the C-9 nor-alkyl compound. Moreover, X-ray single crystal structure of the two corresponding *trans*-aldehydes showed the influence of the Thorpe-Ingold effect on the molecules.

Keywords: *4-DMAT, biomimicking, divinylcyclopropane rearrangement, cyclohepta[cd]-indoles, total synthesis, Thorpe-Ingold effect, kinetic.*

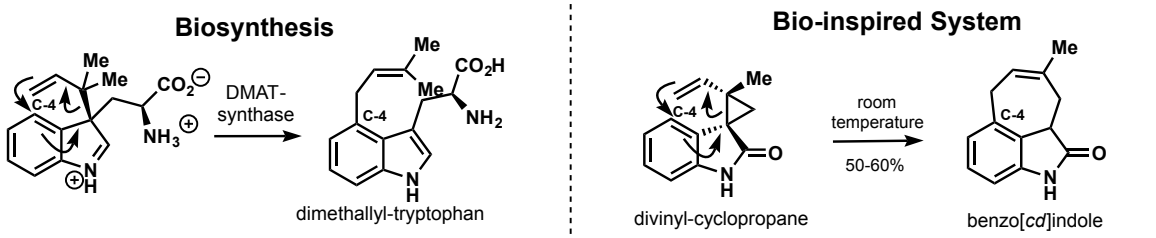
Zusammenfassung

1. Der Experimentelle Beweis für eine enzymkatalysierte [3,3]-sigmatrope Umlagerung durch die 4-Dimethylallyltryptophan Synthase wurde erbracht. Das von der Natur abgeleitete System zeigt die Realisierbarkeit einer Cope-Umlagerung in die C-4 Position des Indols. Dieses Experiment unterstützt die Theorie, dass 4-DMATS zunächst C-3 revers prenyliert und anschließend mittels der Cope Umlagerung C-4 alkyliert.
2. Eine neue Methode zur Synthese von Zyklohepta[*cd*]oxindolen wurde bearbeitet. Die vorgestellte Methode soll dazu dienen einen allgemeinen Zugang zur Funktionalisierung der Indol-4 Position zu etablieren. Dabei erlaubt sie das Umgehen von giftigen Reagenzien wie Thallium und Quecksilber und zeigt einen breiteren Anwendungsbereich auf als die Witkop-Zyklisierung auf. Die Reaktion wird dabei nur wenig von verschiedensten Substituenten am aromatischen Kern beeinflusst und es können viele verschiedene Substituenten sowohl am Cyclopropan als auch am Vinylrest verwendet werden.
3. Diese Arbeit befasst sich mit dem synthetischen Ansatz zur Darstellung 5(10⟶9)*abeo*-Ergolin Derivaten, welche nicht natürlich vorkommende Derivate von Lysergsäuremethylester sind. Ein Schlüsselmerkmal dieser Synthese ist die Divinylzykopropanumlagerung, welche dazu verwendet wird, um den trizyklischen Zyklohepta[*cd*]indol Kern aufzubauen. Die Pyrrolidinstruktur, welche das Kohlenstoff Skelett komplettiert, wird durch Gold(I) Katalyse oder unter Jeffrey Kreuzkupplungsbedinungen erhalten. Nichtsdestotrotz hat die Ungünstige Anordnung der Orbitale an C-9 und C-10, welche über Kraftfeld Berechnungen nachgewiesen werden konnte, die Fertigstellung des privilegierten Intermediates verhindert.
4. Der Mechanismus der Divinylcyclopropanumlagerung zur Darstellung von Zyklohepta-[*cd*]oxindolen wurde im Hinblick auf den Einfluss des Thorpe-Ingold Effekts auf die Geschwindigkeitskonstanten k, sowie die *cis-trans* Isomerisierung untersucht. Die Anwesenheit eines weiteren Substituenten an C-9 offenbarte eine starke Erhöhung der Geschwindigkeitskonstante. In Abwesenheit eben jenen Substituenten konnte die *cis-trans* Isomerisierung über NMR-beobachtet werden. Zudem konnte mittels Röntgenkristallographie der Einfluss Thorpe Ingold Effekt auf die entsprechenden *trans*-Aldehyde nachgewiesen werden.

Schlagworte: *4-DMAT, biomimicking, Divinylcyclopropanumlagerung, Cyclohepta[cd]indole, Totalsynthese, Thorpe-Ingold Effekt, Kinetik.*

Graphical Abstract

1.



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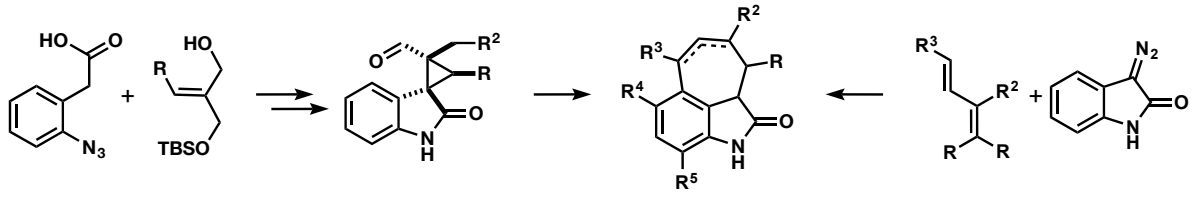
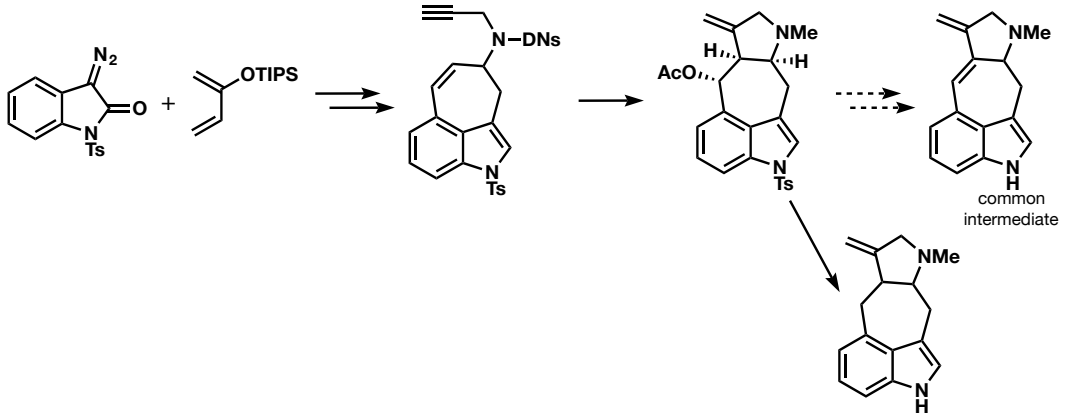


R = Me or H
R^2= H, Me, CH_2Br, $C(SC_3H_6S)$
R^3= H, CO_2Me, CO_2Et
R^4= F, Cl, Br, Me, OMe, NO_2
R^5= F, Cl, Br, Me, OMe

3.



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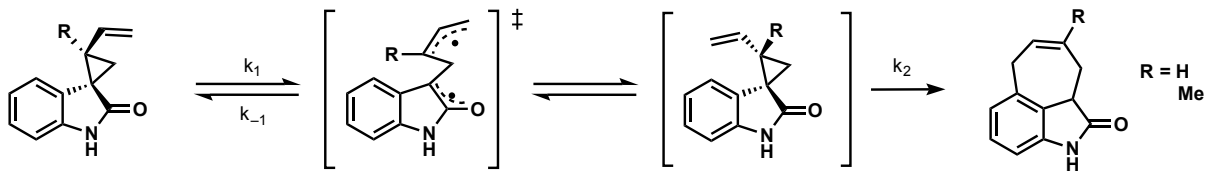

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General Introduction

This PhD thesis was performed from April 2012 till August 2016 in the group of Prof. Dr. Tanja Gaich. The main topic of this thesis is the divinylcyclopropane rearrangement and its application in the synthesis of indole alkaloids. The dissertation is split into four parts describing (chapter 1) the investigation of the [3,3]-sigmatropic rearrangement catalysed by dimethylallyltryptophan (DMAT) synthase by *in vitro* experiments, (chapter 2) the development of a divinylcyclopropane rearrangement based methodology for the preparation of cyclohepta[*cd*]oxindoles, (chapter 3) the application of the above-mentioned methodology on the total synthesis of 5(10 – 9)*abeo* ergoline alkaloids and (chapter 4) the investigation of the Thorpe-Ingold effect on the kinetics of the divinylcyclopropane rearrangement.

An important reaction in the biosynthesis of ergot alkaloids is the C-4 prenylation of the indole core. Since the mechanism is not fully understood, an academic discussion has been held for decades whether the prenylation takes place directly Fridel-Crafts like into the indole C-4 or *via* a [3,3]-sigmatropic rearrangement. The first part of this thesis (chapter 1) is the development of a molecule mimicking 3-dimethylallyltryptophan. This should undergo the Cope rearrangement providing the first *in vitro* experiment for a naturally occurring [3,3]-sigmatropic rearrangement.

Additionally, the influence of the two *germinal*-methyl groups on the rate constant of the rearrangement and the *cis-trans* isomerisation of the vinyl-cyclopropane will be investigated (chapter 4). The result obtained should provide further support for an *in vivo* occurring [3,3]-sigmatropic rearrangement.

As there are just three methods known for a direct activation of the indole C-4 position, the [3,3]-sigmatropic rearrangement mentioned in Chapter 1 should provide a general approach for the functionalisation of the above-mentioned C-4 position (chapter 2). This methodology holds the advantage as no poisonous heavy metals are necessary. Furthermore, it should offer a broader scope compared to the Witkop cyclisation. Thus, the optimised methodology should be applied on the total synthesis of the nor naturally occurring 5(10 – 9)*abeo* ergoline alkaloids which hold the cyclohepta[*cd*]oxindole scaffold. Products containing the above-mentioned scaffold are of general interest as they are known for their biological properties. These propertiescomprise antifungal and larvicidal activities, the depolymerisation of microtubule

and the ability to reverse P-glycoprotein-mediated multiple drug resistance (MRD) in human cancer cells.

For the reason of clarity, the combined experimental procedures as well as the NMR spectra are located in the rear part of the thesis, in particular in Chapter 5, 6, 7, and 8.

1 Cope Mechanism of the DMAT-Synthase

“Du bist aber auch ein ganz gescheites Kindi. Warum machst du das denn auch?“

Dr. Philipp J. Gritsch

1.1 Introduction

1.1.1 *Indole alkaloids*

Alkaloids based on tryptophan can be found in higher plants and microorganisms. They represent the majority of the known alkaloids. Due to their resemblance to the amino acid tryptophan itself and for example serotonin, this class of alkaloids possessed a salient position. Since most of the indole alkaloids possess biological activity they are valuable therapeutics.[1] Their biosynthesis is based on tryptophan and mostly terpenoids, but also other substrates.[2] The monoterpene secologanine (Scheme 1) is responsible for the isoprenoide moiety of most of the indole alkaloids. Based on that, eight biogenetical structural groups can be derived in which the majority of these indole alkaloids can be classed into (Figure 1): Corynanthean (C) (**1**), Vincosan (D) (**2**), Vallesitacotaman (V)-(**3**), Strychnan (S)-(**4**), Aspidospermatan (A)-(**5**), Eburnan (I)-(**6**), Plumeran (P)-(**7**), and Ibogan (I)-type (**8**).[3]

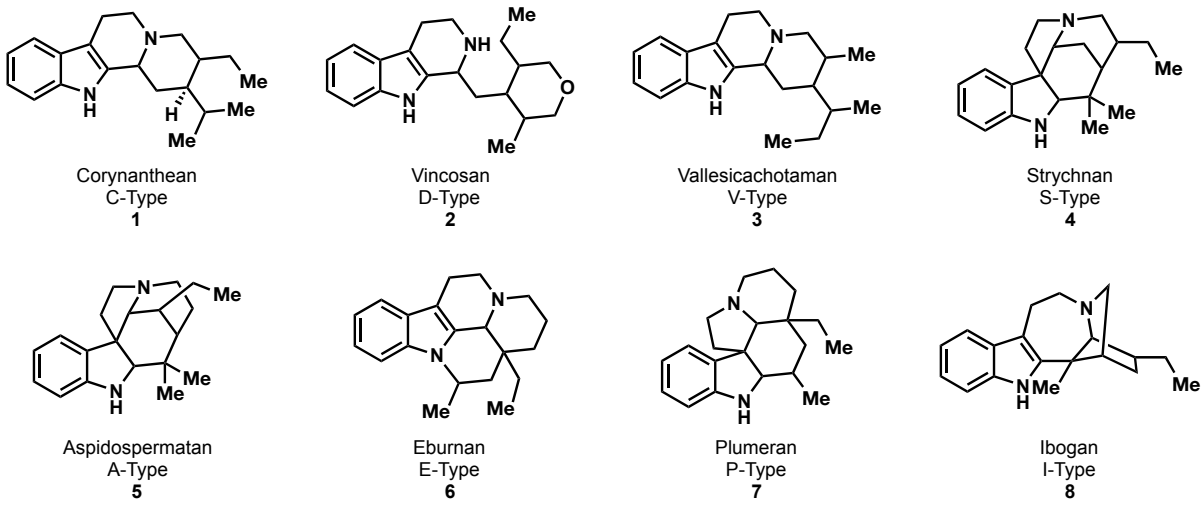
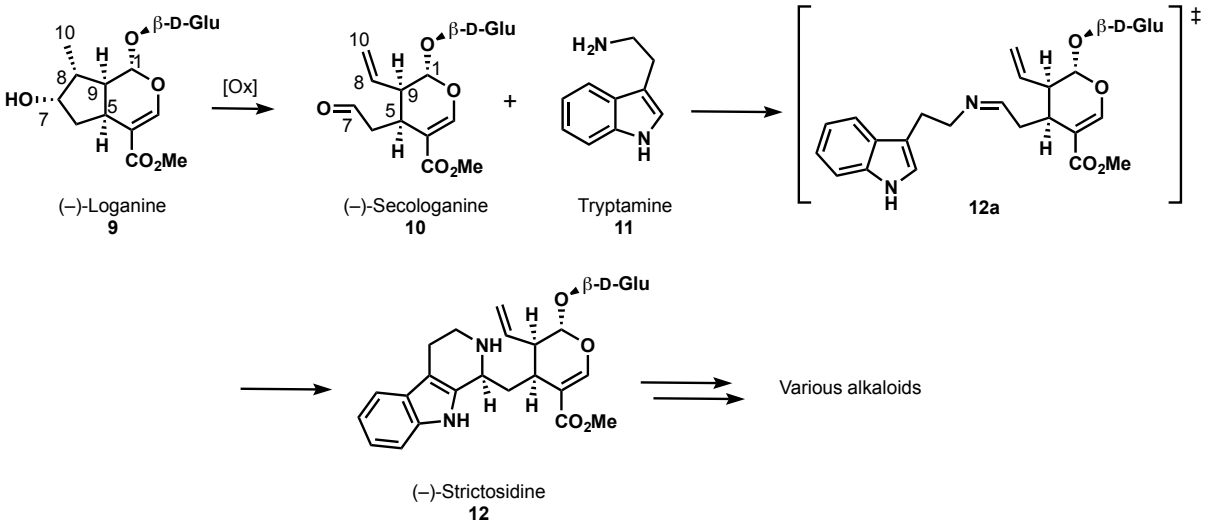


Figure 1. Skeletal types of monoterpenoid indole alkaloids.

To elucidate the biosynthesis, *in vivo* feeding experiments were performed which were replaced by cell-free preparations utilising enzymes and the extraction of the produced intermediates.[4] The five reactive sites which are present in Secologanine (**10**; Scheme 1, ester, vinyl-group, and three carbonyl moieties), are responsible for the diversity of the structures in these indole alkaloids.

Rotation about the C-5, C-9 bond of secologanine (**10**; Scheme 1) is suitable to apply the characteristic quinolizidine partial structure **12** of the majority of these indole alkaloids. The aldehyde functionality is used to establish the tryptoline unit, which is a common structure motif.



Scheme 1. Indole alkaloid biosynthesis starting from (–)-secologanine (**10**).

1.1.2 *Ergot alkaloids*

The class of ergot alkaloids belongs to the prenylated indole alkaloids, which are secondary metabolites containing an isoprenoid moiety or a structure deduced from, as well as an indole related core. Often these alkaloids have a diketopiperazine (**13**, Figure 2) or a bicycle[2.2.2]-diazaoctane (**14**) in common.[5]

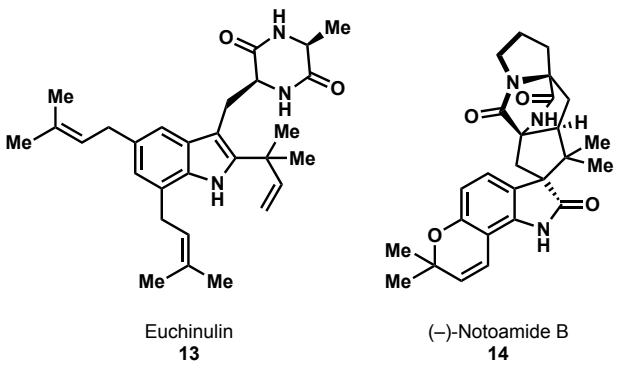


Figure 2. Structure of Euchinulin (**13**) and (–)-Notoamide B (**14**).

Ergot alkaloids possess structural motifs that are similar to neurotransmitters such as noradrenaline (**17**; Figure 3), dopamine (**16**) and serotonin (**18**). Therefore, they have an impact on the human nervous system, as they usually act as non-selective agonists and antagonists.[6]

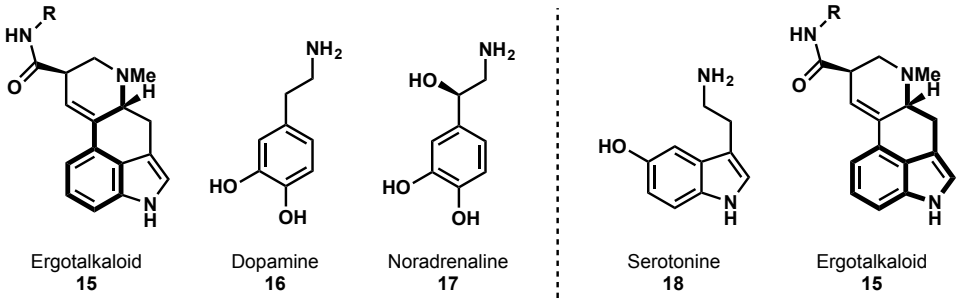


Figure 3. Structure motifs of neurotransmitters mimicked by ergot alkaloids.

Naturally occurring ergot alkaloids and semi synthetic derivatives are used for many medicinal applications (Figure 4). The area of application includes also cytotoxicity and anthelmintic qualities.

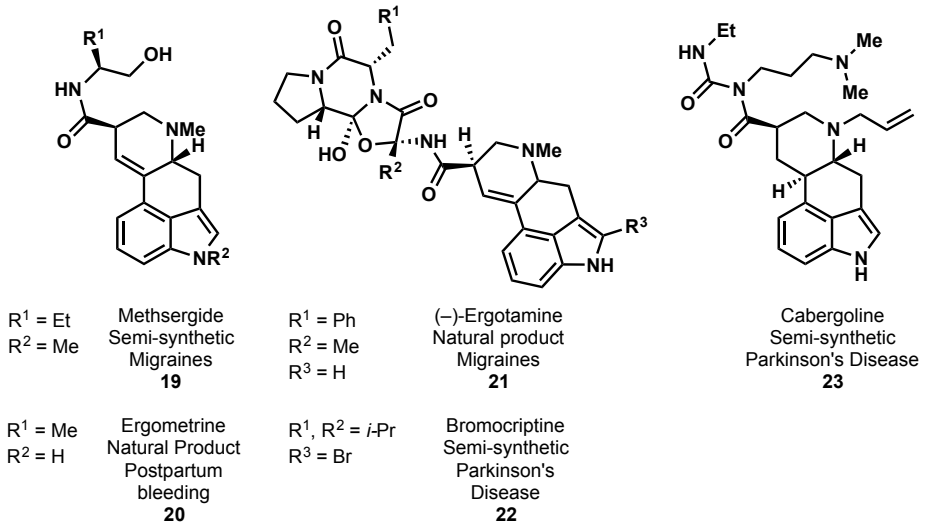


Figure 4. Examples for ergot alkaloids with medicinal application.

As the serotonin receptor in the central and peripheral nervous systems is closely linked to a many processes in the human body, for instance the blood coagulation, mood, sleep, aggression and anxiety, a selective control holds great potential. Especially malfunctions or perturbations in the activation of this 5-HT receptor (serotonin = 5-hydroxytryptamine) can lead to a lot of diseases, including migraines or depression. Similar to tryptanes, ergotamines act as agonist at the 5-HT1B/1D receptors and can be applied in the treatment of migraine. Additionally, dihydroergotamines find its application in the treatment of cluster-headaches.[7],[8],[9] A well-known ergot alkaloid with an impact on the 5-HT-receptor is LSD - the abbreviation indicating the linkage already, as LSD stands for Lysergic acid diethylamide. It is known as a psychedelic drug and can have a psychiatric use.

Ergometrine (**20**; Figure 4) is often used on women in labour, as an oxytoxic in the prevention of uterine bleeding after Caesarian operations. It stimulates α-adrenergic receptors and leads to a faster stimulation of the uterine muscle.[9] [10]

Ergot alkaloids also support the treatment of Parkinson's disease. For example, bromocriptine (**22**; Figure 4), lisuride and pergolide are known to relieve the symptoms. These ergot alkaloids function as dopamine agonists, but lisuride also has an impact on serotonine-receptors and therefore strong psychiatric adverse side effects.[11]

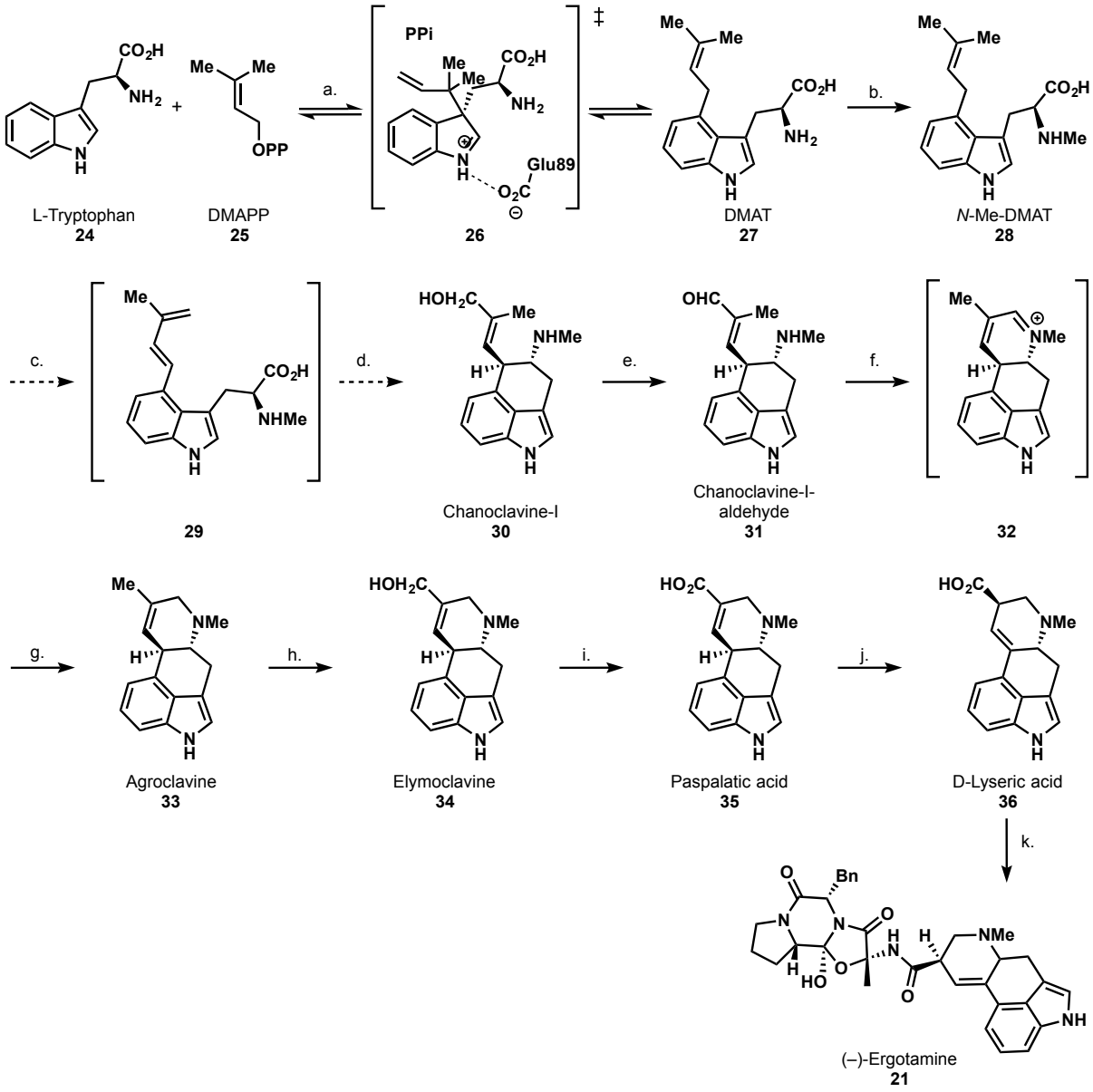
1.1.3 *Mechanistic studies*

An important reaction in the biosynthesis of indole alkaloids is the prenylation of the indole core. This step is catalysed by a variety of enzymes.[12] These prenyltransferases catalyse a normal prenylation, where C-1 adds to the indole or a reverse prenylation where C-3, the tertiary carbon, forms a C-C bond with the indole.[13] Plenty prenyltransferases have been discovered since 2005. With the exception of the indole C-3a and C-7a, these enzymes address every other position of the indole core.

The prenyltransferase which was identified first is the 4-dimethylallyltryptophan synthase (4-DMATS/FgaPT2).[14] This synthase catalyses the normal prenylation at C-4 of tryptophan which is also the first step in the biosynthesis of the ergot alkaloids.

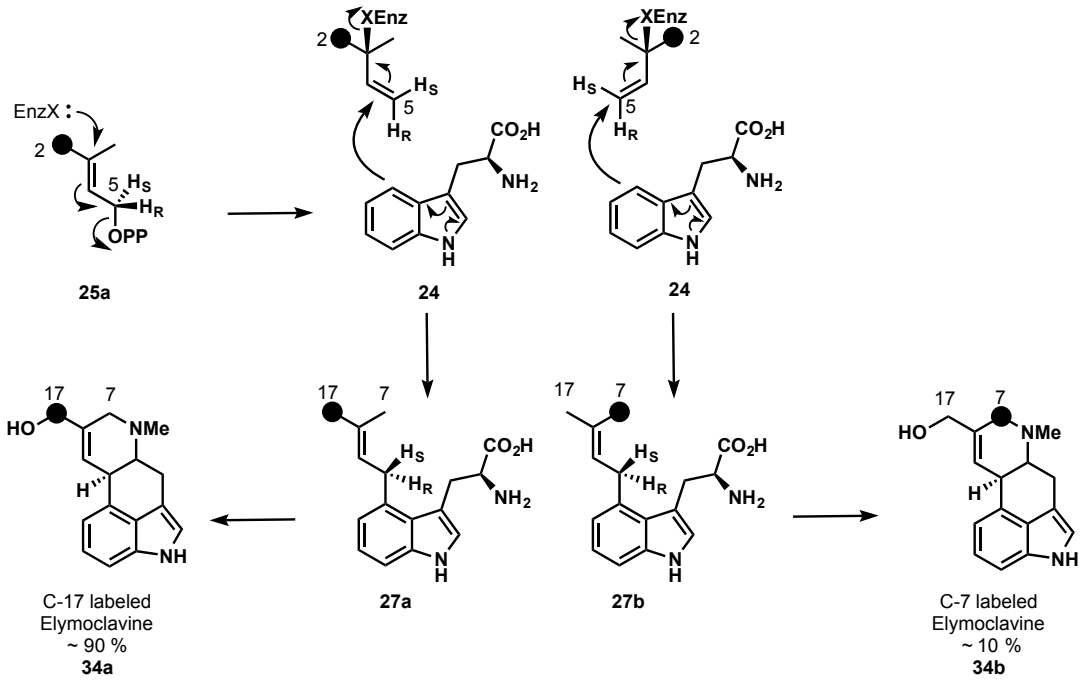
Based on the research of Floss *et al*. [14a, 15] on ergot alkaloids, a generally accepted biosynthetic pathway could be established (Scheme 2).

The first committed step in the biosynthesis is the prenylation at C-4 of L-tryptophan (**24**; Scheme 2). This mechanism is still a subject of controversial scientific discussion. It may either proceed *via* a Cope rearrangement as displayed in Scheme 2 or *via* a direct Friedel-Crafts alkylation into C-4.[15b, 16] Subsequent *N*-methylation with *S*-adenosylmethionine (SAM) and two not fully elucidated oxidation-reduction steps provide Chanoclavine-I (**30**) which is also the first regularly isolable product of this pathway.[17],[18],[19],[20] Compound **30** is then oxidised to the corresponding aldehyde **31** which can undergo an imine condensation. The obtained iminium ion **32** is then reduced by agroclavine dehydrogenase. Further oxidations lead to paspalatic acid (**35**), which spontaneously isomerises to lysergic acid (**36**). Enzymes LPS1 and LPS2 finally complete the biosynthesis of ergotamine (**21**).



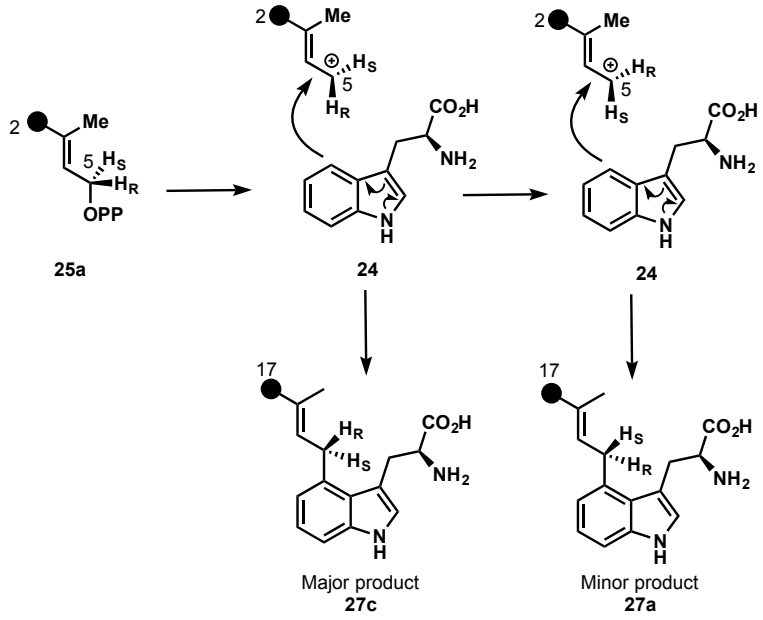
Scheme 2. Biosynthesis of Ergotamine. Dashed arrows display not confirmed steps. a. DmaW (prenyltransferase), b. EasF (*N*-methyltransferase), c. EasE/EasC (oxidoreductase/catalase), d. EasE/EasC (oxidoreductase/catalase), $-CO_2$ e. EasD (oxidase), f. imin condensation, spontaneous, g. EasG (reductase), h. p450 (monooxigenase), i. 2x CloA (monooxigenase), j. spontaneous/isomerase, k. LPS1 (D-lysergyl-peptide synthase 1), LPS2 (D-lysergyl-peptide synthase 2).[21]

As it was mentioned before, the mechanism of the prenylation catalysed by 4-DMATS is a contentious scientific point. Floss *et al*. examined the prenylation mechanism into the notably unreactive C-4 position by labelling experiments (Scheme 3).[15] In the beginning, they used mevalonate which was labelled with ^{14}C at C-2. For two further feeding experiments the *pro-R* and *pro-S* hydrogen atoms at C-5 were replaced by ^{3}H. The isolated Elymoclavine (**34a, b**) displayed a 90% labelling of C-17 and 10% of C-7. This indicates a double S_N2 attack at DMAPP.



Scheme 3. ^{14}C labelling experiment by Floss *et al*.

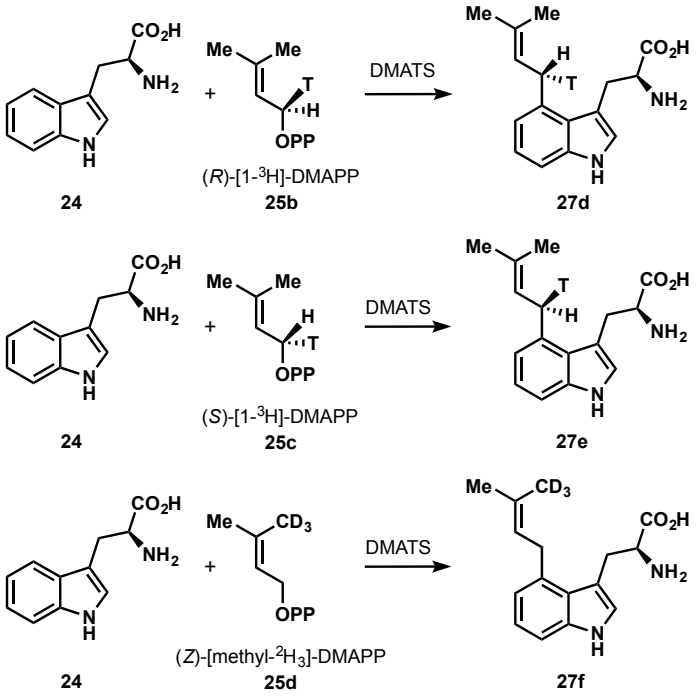
To undergird their results Floss *et al*. performed further feeding experiments applying cultures of *Caviceps sp*. strain SD58 (Scheme 4). In this case they used mevalonate with (5*S*)- and (5*R*)-[2-^{13}C, 5-$^{2}H1$]. They were able to ascertain that the scrambling of the protons and the carbon atoms are independent processes.



Scheme 4. Further feeding experiment using mevalonate with (5*S*)- and (5*R*)-[2-^{13}C, 5-$^{2}H1$].

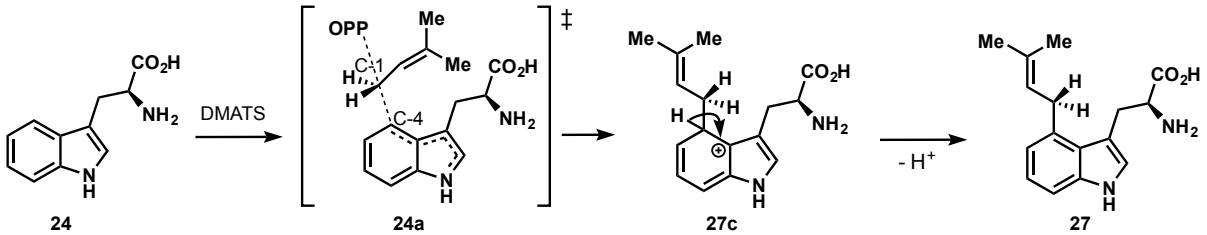
The loss of stereochemical information during or before the biosynthesis of dimethylallyl diphosphate (DMAPP, **25**; Scheme 4) has been proposed earlier by Arigoni *et al*.[22] This proposal was confirmed by an experiment where (*Z*)-[*methyl*-$^{2}H_3$] DMAPP (**25b, c**) was used

with DMATS, yielding the corresponding (*Z*)-[*methyl*-$^{2}H_3$] DMAT (**27d–f**, Scheme 5). Subsequent conversion yielded the analogue Chanoclavine (**30**) and Elymoclavine (**34**). Throughout the examination, the stereochemical information was preserved in *Caviceps sp.* SD58.



Scheme 5. Feeding experiments to show the preservation of the stereochemical information.

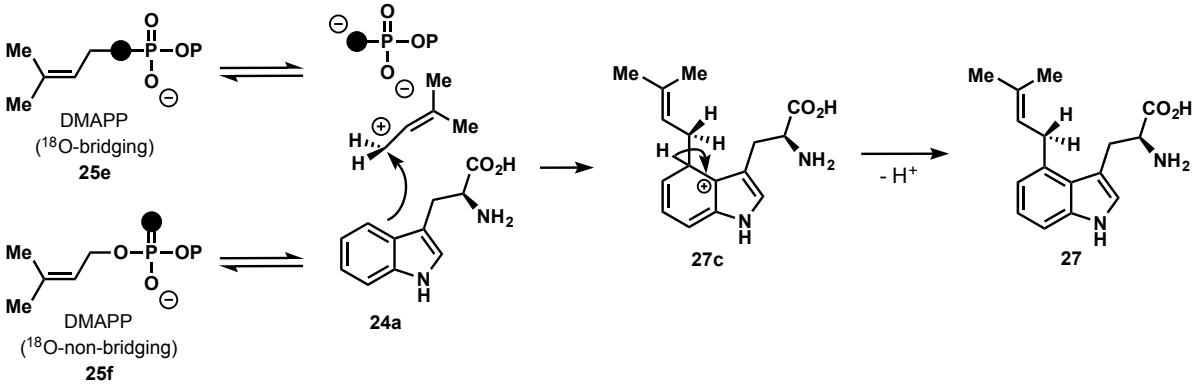
These results led to the assumption that DMAPP which is bound to the enzyme dissociates into a dimethylallyl cation/pyrophosphate ion pair (Scheme 6). During the reaction progress the indole C-4 performs a nucleophilic attack on the C-1 of the prenyl cation. Subsequent deprotonation of the indole C-4 should lead to the rearomatisation of the tryptophan (Scheme 6). Mechanistic studies performed by Poulter *et al*.[16a] confirmed Floss' results.



Scheme 6. Direct S_N2 prenylation of tryptophan.

Tanner *et al*. were able to undergird the suggestion of a dimethylallyl cation/ pyrophosphate ion pair by performing a positional isotopic exchange experiment (PIX; Scheme 7) in 2009.[16b] They applied an ^{18}O-isotopic label in the bridging position of [1-^{18}O]-DMAP (**25e**) for the

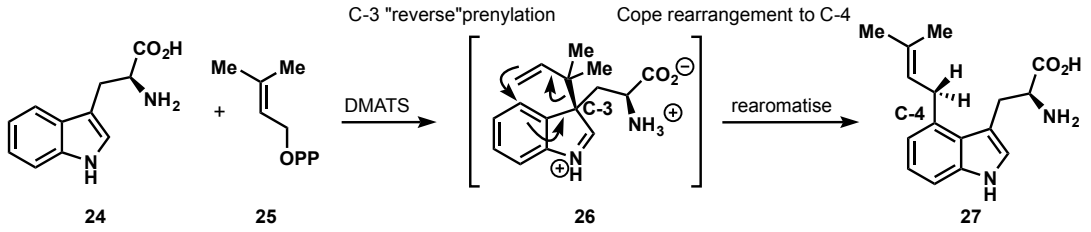
enzymatic reaction. Analysis of the remaining DMAPP after the reaction displayed that the ^{18}O-isotope was scrambled from the bridged position into a non-bridged position (**25f**).



Scheme 7. Tanner's PIX experiment in order to show the existence of an allyl cation.

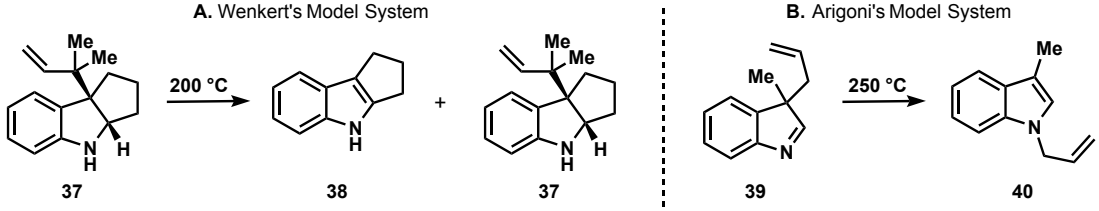
Nevertheless, these results were not able to explain why the reactive positions of the indole core (C-3 and C-2) should be passed over in order to alkylate the least reactive C-4 position.[23] Therefore, another mechanism has to be considered.

In the 1970's Arigoni[22] and Wenkert[24] proposed a mechanism (Scheme 8) which took the low nucleophilicity of the indole C-4 into account. In their hypothesis, the indole C-3 position is reverse prenylated by DMAPP (**25**). Intermediate **26** undergoes a Cope rearrangement into the indole C-4 and the rearomatisation should yield DMAT (**27**).



Scheme 8. Proposed mechanism of prenylation of indole C-4 *via* a [3,3]-sigmatropic rearrangement.

Since they were not able to prove their hypothesis by *in vitro* experiments (Scheme 9) and enzymes which catalyse sigmatropic rearrangements are uncommon, this idea was dismissed. Instead of the desired rearrangement into the indole C-4 position, they obtained decomposition (**38**) and rearrangement into *N*-1 (**40**).



Scheme 9. Biosynthetic hypothesis of Arigoni & Wenkert. A. **38**, 45%, **37**, 37% yield.

Li *et al*. were able to overproduce the 4-DMAT synthase in *Aspergillus fumigatus*.[25] This facilitated the research in this field. The first structure of 4-DMATS was reported in 2009 and the corresponding Michaelis complex was identified subsequently (Figure 5).[26] Instead of the reactive DMAPP, dimethylallyl *S*-thiolodiphosphate (DMSPP) has been utilised which is the unreactive analog. The complex displays a distance of 3.5 Å between DMSPP C-3 and tryptophan C-3 as well as 3.8 Å between tryptophan C-4 and DMSPP C-1. Furthermore, the indole core and the dimethylallylpart of DMSPP are coplanar. In combination with the nucleophilicity of indole C-3 a [3,3]-sigmatropic rearrangement is most likely.

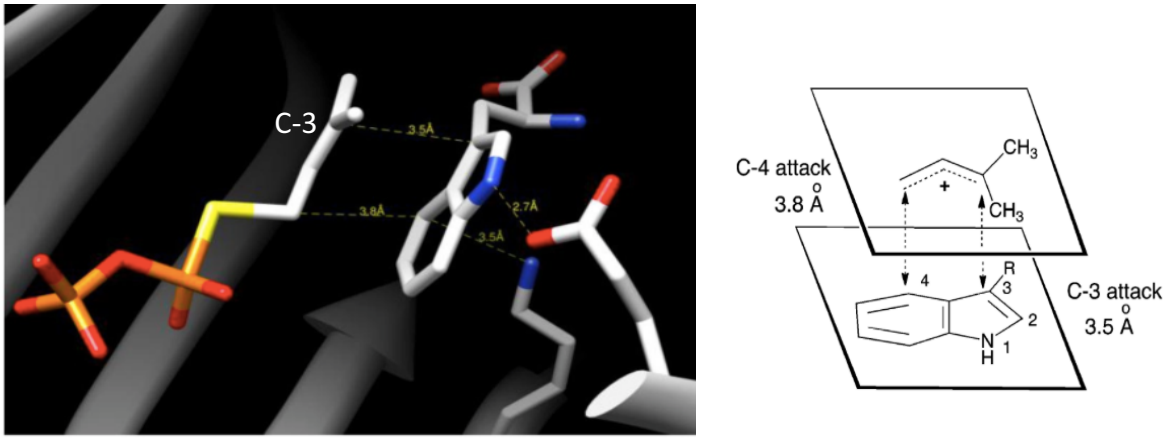
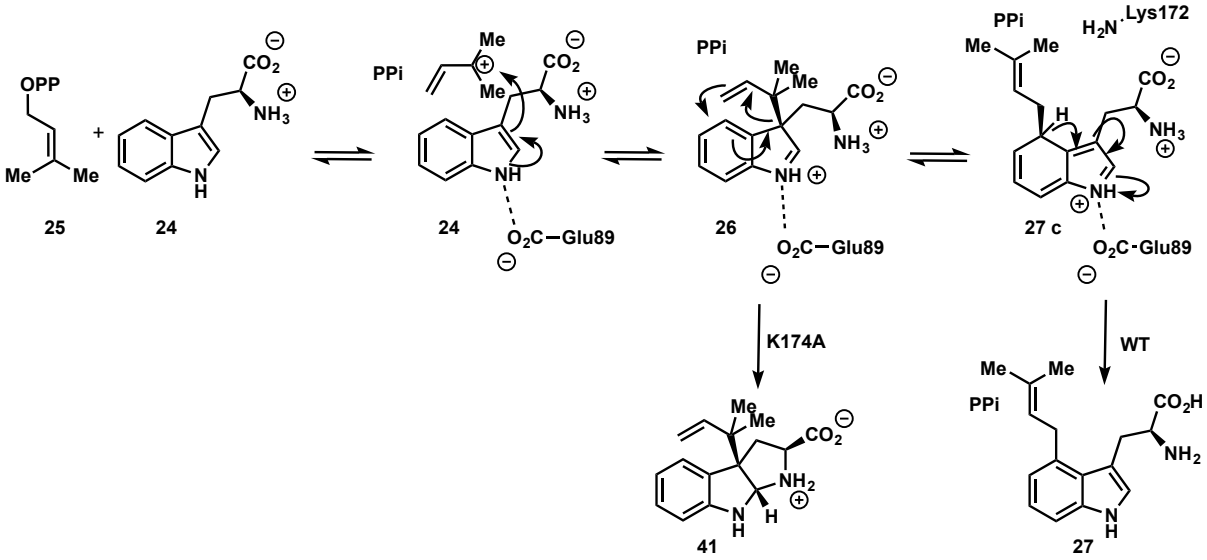


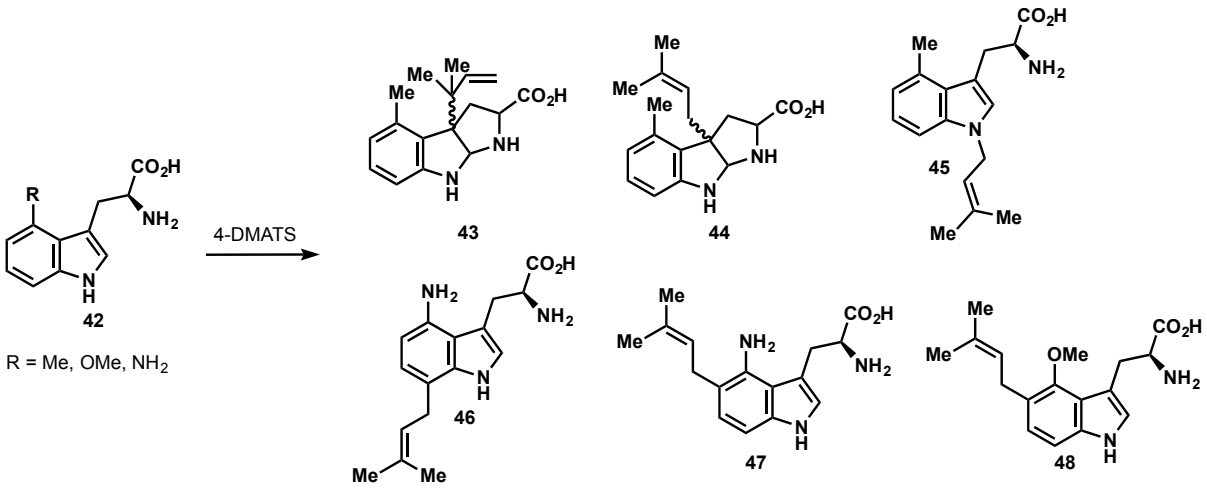
Figure 5. Michaelis complex of DMSPP (an unreactive DMAPP analogon, left side, white orange) and L-tryptophan in the active site of the 4-DMATS. The L-tryptophan is stabilised by two residues seen on the right side, Glu and Lys. Schematic dimensional sketch of the Michaelis complex. The distances between the two reaction partners are given. The orientation of the components already indicates a favoured reverse prenylation of the C-3.

The Cope mechanism got further support by Tanner *et al*. utilising a catalytically active mutant of the DMATS (K174A) by a site-directed mutagenesis in the active site of the enzyme (Scheme 10).[27] Only 10% DMAT (**27**) were isolated. 90% of the isolated product was the reverse prenylated tricycle **41**. This was highly surprising, as pericyclic rearrangements do not occur often in enzymes since it is very difficult to stabilise the transition state within the enzyme. The structure could be affirmed by comparing **41** to the saponificated ester, Danishefsky *et al*.[28] prepared during their synthesis of amauromine. Even though the results were promising, Tanner mentioned that it cannot be excluded that the observed reaction is caused by the mutation itself.



Scheme 10. Proposed mechanism with a sigmatropic rearrangement. In the K174A mutant a lysine was mutated to alanine and gave only a reverse-prenylated pre-Cope product and not 4-DMAT.

Very recently, 4-substituted tryptophans **42** were exposed to 4-DMATS (Scheme 11).[29] As the C-4 position was blocked, the substrates reacted very slow and delivered product mixtures. Depending on the substituents which blocked C-4, different positions of the tryptophan derivative were addressed by the enzyme. In case of a methyl substituent the two major products were C-3 revers prenylated tryptophan **43** (44%) and normal *N*-prenylation **45** (44%). Also small amounts of C-3 normal prenylation **44** (7%) and C-5 normal prenylation products (5%) were detected.

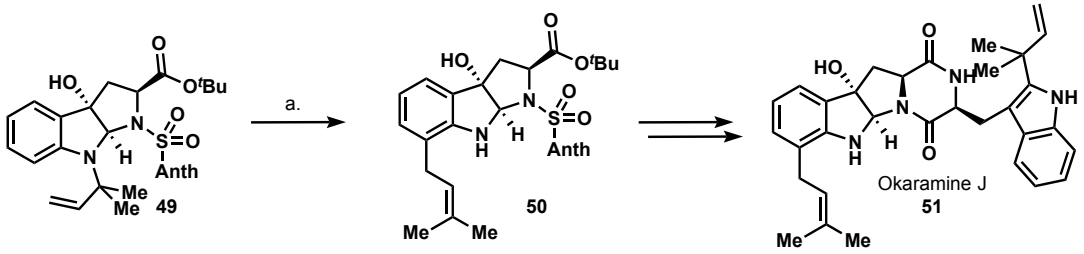


Scheme 11. Poulter's experiment with 4 substituted tryptophan.

When C-4 was blocked by substituents revealing a +M-effect, a different distribution of the prenyl-chain was observed (Scheme 11). In case of 4-methoxy-L-tryptophan the prenylation took only place at C-5 (**48**) while 4-amino- L-tryptophan delivered normal prenylation at indole C-5 (**47**) and C-7 (**46**). Since no prenylation at C-3 has been observed, Poulter *et al*. suggested

that this experiment proved the simple direct electrophilic addition for that class of enzymes. Even for the less nucleophilic C-4 positions the Cope mechanism does not have to be taken into consideration. Others emphasise that the methoxy and amine substituents at C-4 increased the reactivity of C-5 and C-7 for electrophilic aromatic substitutions.[30] The substitution of the C-4 also hamper the enzyme which could lead to a loss of control of the reactants and the emerge of different products.

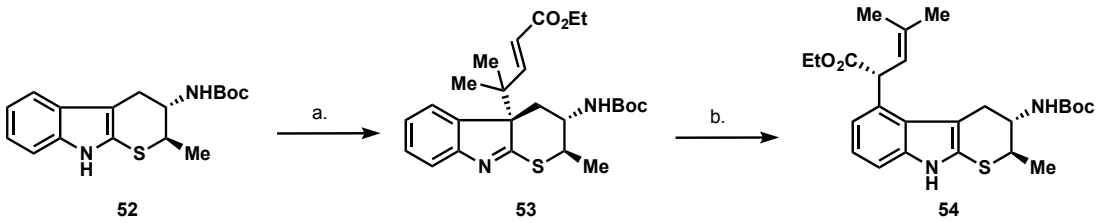
Turning the attention from the biochemical toward the chemical line of argumentation, it becomes apparent that not much effort has been put in this field since Arigoni and Wenkert. Ganesan *et al*. (Scheme 12)[31] performed an aza-Claisen rearrangement in their total synthesis of Okaramine J (**51**) in 2003. After *N*-alkylation using 3-bromo-3-methylbut-1-yne, the triple bond was reduced with Lindlar catalyst. Treating **49** with TFA in CH_2Cl_2 initiated a charge accelerated *N*-1 to C-7 aza-Claisen rearrangement with regioinversion of the *tert*-prenyl group.



Scheme 12. Charge accelerated aza-Claisen rearrangement. a. TFA (5 equiv.), CH_2Cl_2, rt., 16 h, 84%.

Even though charge accelerated aza-Claisen[32] reactions have been reported before by Hurd, Jenkins and Carnahan[33], Ganesan *et al*. were the first ones performing this reaction using an indole. Furthermore, the rearrangement did not need to be heated such as the aza-Claisen reactions reported previously. They explained the rection by the *gem*-dialkyl which places the vinyl group into the necessary conformation. Moreover, the sulphonamide directed the vinyl group towards the aromatic ring so the reaction could be performed under these mild conditions.

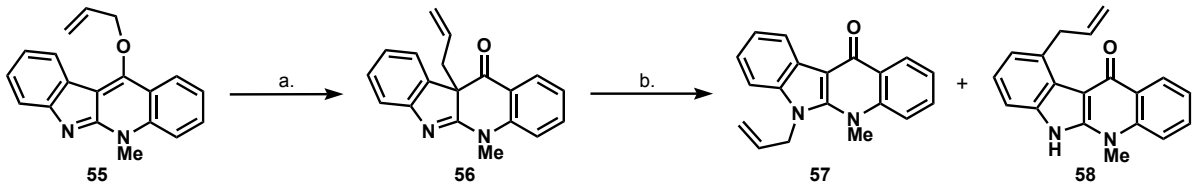
Rainier *et al*.[34] induced a stereoselective Cope rearrangement of thioamide **52** (Scheme 13) into C-4 in 2005. They exposed **53**, which contains an electron poor prenyl derivative, to an aqueous solution of $HgCl_2$ at ambient temperature.



Scheme 13. Prenylation of C-4 by Rainier *et al*. using $HgCl_2$. a. dimethylvinyl diazoacetate (2 equiv.), $Rh_2(OAc)_4$ (5 mol%), CH_2Cl_2, 88%, b. $HgCl_2$ (4 equiv.), H_2O:MeCN, 85%.

Their report also mentioned that they were able to observe the reaction under thermal conditions. The result was a 1.6:1 mixture of diastereomers obtained in 80% yield. Nevertheless, they remained short on experimental details for the thermal rearrangement. This system looks similar to the test system of Wenkert *et al*. (Scheme 9) which failed to undergo the rearrangement. The fundamental difference between the two systems is that Rainier's substrate contains an imine functionality which is missing in Wenkert's.

Five years later the Cope rearrangement into C-4 was reported by Westwood *et al*. (Scheme 14).[35] They observed the rearrangement as a side reaction during their studies on the Claisen rearrangements with the indolo[2,3-*b*]quinolone system.

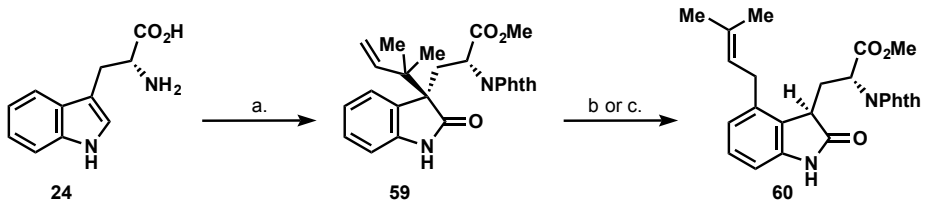


Scheme 14. Thermal Cope rearrangement of vinyl group from C-3 to C-4. a. PhMe, reflux, 5 h, 89%, b. PhMe, reflux, 5 d, **57** 12% and **58** 72% yield.

Altering from the previous two examples, they utilised a simple vinyl group, as Arigoni did (Scheme 9). Heating **55** (Scheme 14) for five hours led to the desired Claisen rearrangement product **56**. When **56** was refluxed in toluene for a further five days, they were able to isolate either, the *N*-1-allylated Cope rearrangement product **57** and **58**, the C-4 allylated as minor product.

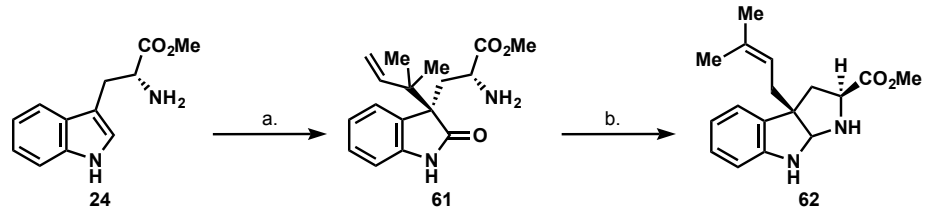
Even though these systems were able to generate C-4 substituted products, they are far away from being similar to simple tryptophan.

Viswanathan *et al*.[36] reported a regioselective Cope rearrangement of prenyl on indoles in 2015 (Scheme 15). Their methodology utilises L-tryptophan (**24**) which is first protected and then reverse prenylated and oxidised. The resulting product **59** is then heated in DMAc to 150 °C or exposed to microwave in a phosphate buffer.



Scheme 15. Viswanathan's biomimetic 4-DMAT synthesis. a. 1,3 dimethylpiperazine (0.6 equiv.), NCS (1.1 equiv.), CH_2Cl_2, 0 °C, 2 h, then Cl_3CCO_2H (24 mol%), prenyl alcohol (2 equiv.), 12 h, b. DMAc, 155 °C, 55 h, c. phosphate buffer (pH 8.8), 150 W, 150 °C, 40 min.

Even though they applied an oxindole in the rearrangement instead of an indole (Scheme 16), these experiments revealed that the mechanism proposed by Arigoni and Wenkert is plausible. Without the protecting groups the prenyl moiety stays at C-3 when heated and a [1,3]-shift is observed (**62**).

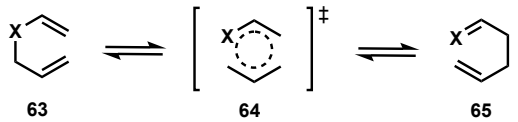


Scheme 16. [1,3]-shift when nitrogen is not protected. a. 1,3 dimethylpiperazine (0.6 equiv.), NCS (1.1 equiv.), CH_2Cl_2, 0 °C, 2 h, then Cl_3CCO_2H (24 mol%), prenyl alcohol (2 equiv.), 12 h, b. DMAc, 155 °C, 55 h, c. phosphate buffer (pH 8.8), 150 W, 150 °C, 40 min.

Additionally, lactam **62** (Scheme 16) is obtained as shown by Tanner's mutant 4-DMATS (Scheme 10). As Ganesan implied for their system, the bulky phthalimide here might be necessary for the Cope rearrangement as it directs the prenyl moiety towards the benzene core.

1.1.4 *Cope Rearrangement*

Since the discovery by A. C. Cope and E. M. Hardy in 1940 (Scheme 17)[37] the Cope-rearrangement became a very important method in organic chemistry. In addition to the Claisen rearrangement, this is the most considerable [3,3]-sigmatropic shift.



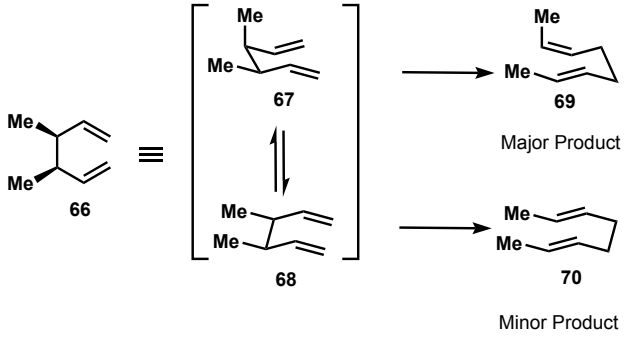
Claisen rearrangement if X = O

Cope rearrangement if X = CH_2

Scheme 17. Mechanism of Cope and Claisen rearrangement.

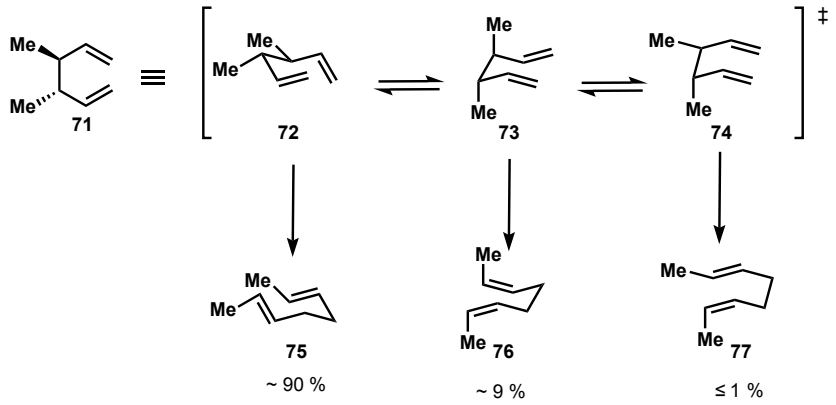
In these thermal isomerisation reactions (Scheme 17), a σ-bond is shifted along the π-system. Most of the known Cope-rearrangements are proceeding through a concerted mechanism

passing through a six-membered, cyclic, conjugated transition state.[38] Abandoning of the original and the formation of the new sigma bond is not necessarily a concerted process. In particular cases, where the 2- and 5-position are substituted with radical stabilising groups (R = vinyl, phenyl, CN or COOMe), a two-step diradical mechanism can be observed.[39] A Cope rearrangement with a zwitterionic intermediate is also possible with the appropriate substitution pattern.[40] The regio- and stereochemistry of pericyclic reactions can be explained by the principle of orbital symmetry conservation, which is expressed by the Woodward Hoffmann rules. Thus, the transition state of the Cope-rearrangement can be described as a set of two allylic fragments (Scheme 18). As a consequence, two geometric arrangements are possible: The transition state can take the chair like or the boat like conformation. E. Doering and W. R. Roth were able to prove that the chair like transition state in the Cope rearrangement is favoured over the boat transition state.[41] After thermal conversion of *meso*-3,4-dimethylhexa-1,5-dien (**66**; Scheme 18) 99.7% of the *cis*-, *trans*- (**69**) and only 0.3% of the *trans*-, *trans*-isomer (**70**) were obtained, the latter of them formed by a boat like transition state.



Scheme 18. Thermal conversion of *meso*-3, 4-dimethylhexa-1,5-dien (**66**).

During the thermal rearrangement of racemic 3,4-dimethylhexa-1,5-dien (**71**;
Scheme 19) the major products were the *trans*-, *trans*- **75** (~90%) and the *cis*-, *cis*-isomer **76** (~9%), which are delineated through the chair-like transition state. The *cis*-, *trans*-product **77** can be traced back to a boat-like transition state and was obtained in less than 1% yield.



Scheme 19. Thermal conversion of racemic 3,4-dimethylhexa-1,5-dien (**71**).

R. K. Hill and N. W. Gilman revealed, that transition states in which the sterically demanding groups are in equatorial position are more favoured than those where the substituents are in axial position, which explains the results of Doering and Roth.[42] If the geometry of the transition state is known, the stereochemistry of the resulting product can be predicted. Thus, the Cope rearrangement proves to be a valuable method for the transmission of stereo-information.

1.1.5 *Cyclopropane*

The smallest existing carbocycle is the cyclopropane. It was first isolated by A. Freund[43] who prepared it *via* an intramolecular Wurtz reaction utillising 1,3-dibromopropane and sodium. Gustavson published a more feasible synthesis in 1887, applying zinc instead of sodium.[44] It did not take long until it was realised that the reactivity of trimethylene is different to that of other carbocycles. Even though the C-C cleavage energy and the strain energies of cyclobutanes and cyclopropanes are similar, the reactivity is not. While cyclobutanes react similar to other cycloalkanes, the reactivity of cyclopropanes closely resembles the reactivity of olefins.[45]

Förster revealed in 1939 that the valence direction and the direction of bonding may deviate. This model was further developed by Coulson and Moffitt in 1949 and 1951. They described a cyclopropane as a ring which is formed by three sp^3 hybridised CH_2 groups. In this case, the orbital overlap is weak and in line with the carbon atoms. By decreasing the s-character to 17% for the C-C bond, the orbital overlap is increased (Figure 6). These sp^5-Orbitals are the reason for the stability of cyclopropanes. As they are bent, they are also called “banana bonds” with an inner orbital angle of 104°. The bending can also be an explanation for the shorter C-C bonds in the cyclopropane.

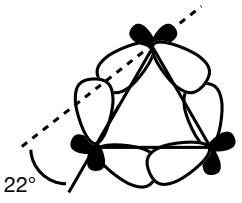


Figure 6. Bend bonds with an increased angle.

Walsh proposed that cyclopropanes have a significant sp^2 character and therefore should react similar to olefins. He considered a cyclopropane as a combination of three methylene groups (Figure 7). The combination of the σ and π orbitals is unable to combine as it has different symmetries. Walsh separated the two sets of orbitals giving rise to the D_3h symmetric group. In this model the three σ-type orbitals are symmetrically combined with the orbitals overlapping in the centre of the cyclopropane. Ψ_2 displays a distorted π-bond which might give an explanation regarding the reactivity of cyclopropanes toward electrophilic reagents.[45]

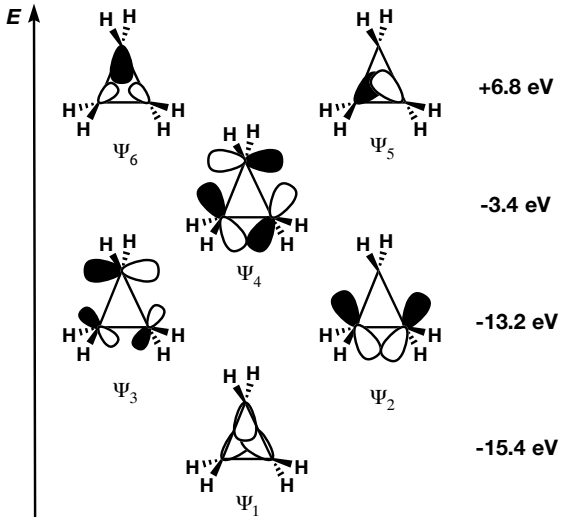


Figure 7. Walsh orbitals.

Even though cyclopropanes represent a special case of cycloalkanes, the range of possible reactions for ther preparation is quite broad. The three major reaction types used for cyclopropane synthesis are the Michael induced ring closing type reaction (Figure 8),[46] the synthesis *via* cationic cyclisation[47] and the metal catalysed cyclopropanation of olefins *via* metal-carbenoids derived from diazo-carbonyl compounds.[48]

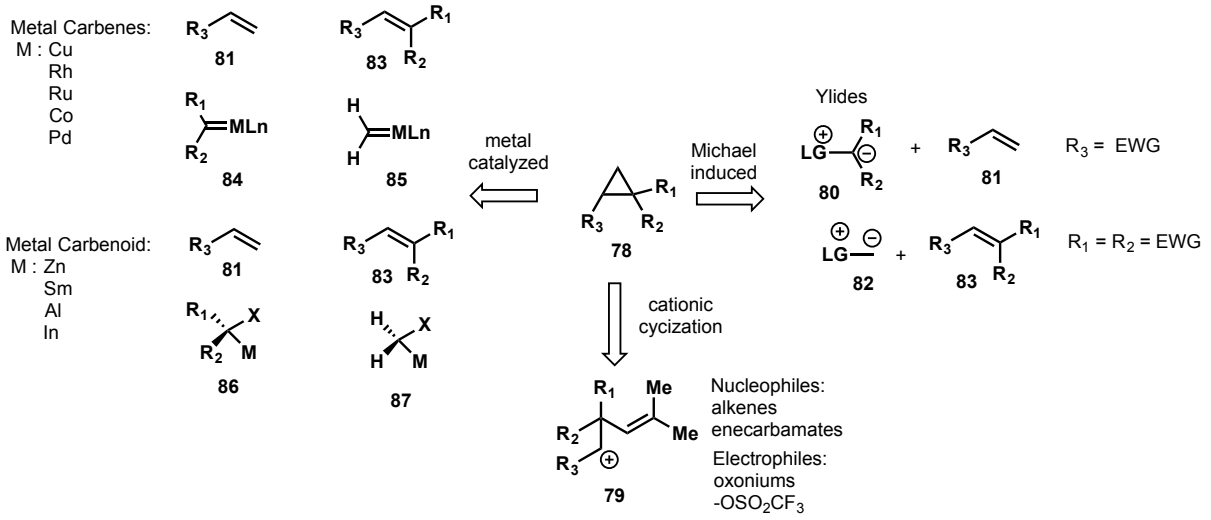


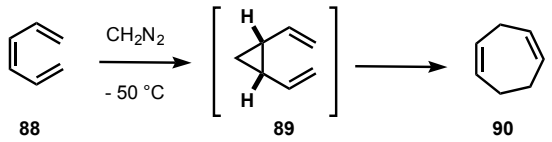
Figure 8. Preparation of 1,1-disubstituted cyclopropanes. [49]

Yates proposed a mechanism for the decomposition of diazo-compounds by transition metals in 1952.[50] The first and reversible step is a nucleophilic attack of the diazo-compound on the metal. The second and irreversible step is the liberation of nitrogen, which is also the rate-determining step. This step depends on the steric hindrance and the electronic character of

the carbenoid. The last step is the concerted, asynchronous [2+1]-cycloaddition of the carbenoid and the olefin. Due to the high reactivity, no rhodium carbenoids have been isolated yet.[51] However, copper (I)[52] and ruthenium (II) [53] complexes could be isolated which are active in cyclopropanation reactions too.

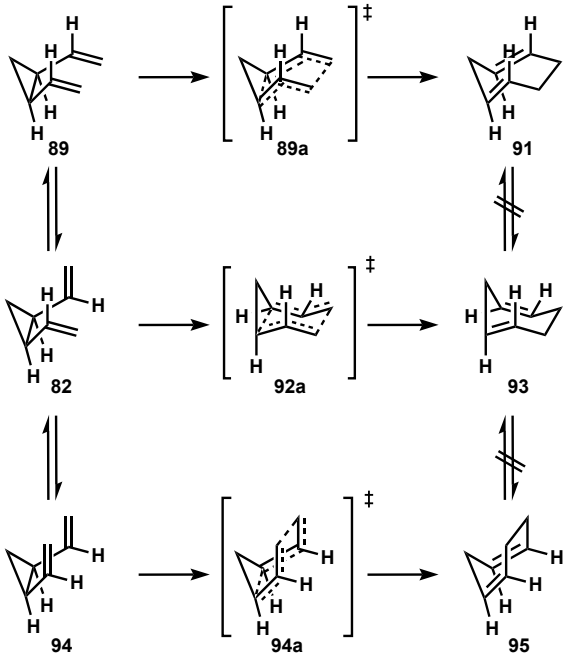
1.1.6 *Divinylcyclopropane rearrangement*

A special case of the Cope rearrangement is the divinylcyclopropane-cycloheptadiene rearrangement yielding 1,4-cycloheptadienes (**90**; Scheme 20). The driving force of this Cope rearrangement related reaction is the ring strain release. The ring strain of the cyclopropane unit lowers the activation energy of this particular reaction. Vogel *et al*.[53] first observed the reaction while exposing a mixture of benzene and diazo methane to sunlight or ultra violett light. The *in situ* formed divinylcyclopropane underwent the rearrangement directly. Also the cyclopropanation performed by Doeringer *et al*. using triene **88** at –50 °C with diazomethane and copper chloride, provided only the divinylcyclopropane rearrangement product **90**.[53-54] Brown *et al*. were the first to isolate **89** at –20 °C and determine the half-life time (11 min. at 288 K) by NMR experiments.[54c, d]



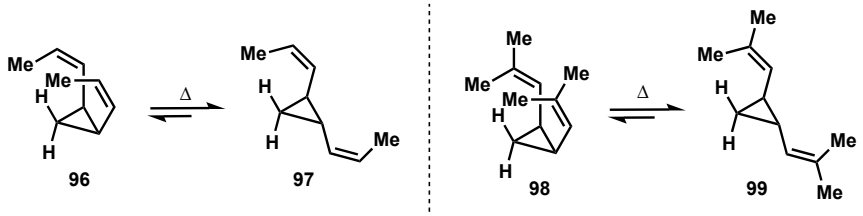
Scheme 20. Formation of 1,4-cycloheptadiene (**90**) at –50 °C.

The conformation of the substrate is important for this reaction. Due to the restrictions of the configuration of the olefins in a cycloheptene system, the only possible transition state is **94a** (Scheme 21). The boat like transition state **94a** leads to **95** containing two *cis*-double bonds. Transition states such as **84a** and **92a** would lead to a cycloheptadiene containing a *trans*-double bond which cannot be obtained, since (*E*)-cyclooctene is the smallest sized ring containing a stable (*E*)-double bond in the ring.



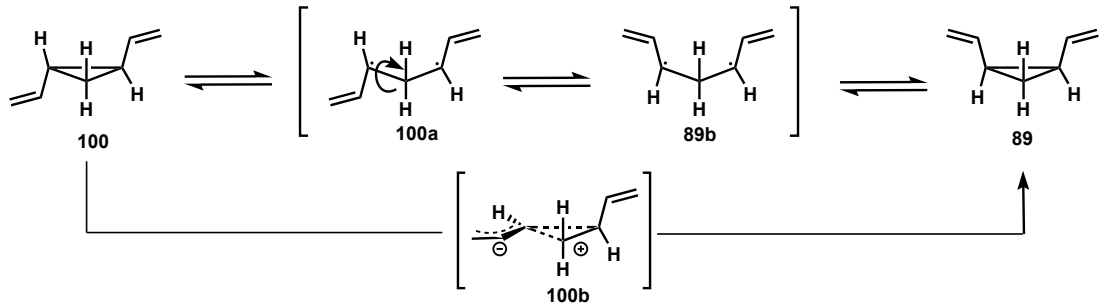
Scheme 21. Transition state of the divinylcyclopropane cyclisation. [55]

Substituents on the olefins destabilise the boat like transition state (Scheme 22) by interacting sterically with the cyclopropane.[56] Substrates with a pronounced steric hindrance do not undergo the Cope rearrangement, instead a *cis*-*trans*-isomerisation takes place.[56-57]



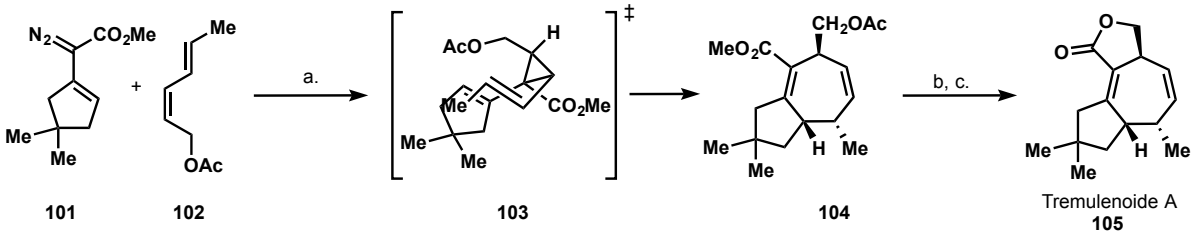
Scheme 22. *cis*-*trans* isomerisation of hindered divinylcyclopropanes.

Trans-1,2-divinylcyclopropane (**100**; Scheme 23) is thermally more stable than the corresponding *cis*-compound **89**.[53] While **89** rearranges to **90** at room temperature, **100** needs to be heated up to 190 °C for a couple of hours, finally yielding the same rearrangement product as **89**. The product can be explained by homolytic dissociation of the central linkage providing *trans*-allyl biradical **100a**.[58] Isomerisation of the allyl-groups to *cis*-compound **89** enables the Cope rearrangement. It is not proven whether only the isomerisation occurs *via* a biradical mechanism or also the cyclisation itself. Another possible pathway proceeds *via* the zwitterionic species **100b**.



Scheme 23. Biradical mechanism of the *cis-trans*-isomerisation of **100** and **89**.

Nevertheless the divinylcyclopropane rearrangement has become an important methodology for the total synthesis of natural products containing a seven membered ring, such as Davies' Tremulenoide A (**105** ;Scheme 24).[59]



Scheme 24. Total synthesis of Tremulenoide A (**105**). a. $Rh_2(OC_8H_{17})_4$, hexane, reflux. b. Pd/C, H_2, c. K_2CO_3, MeOH.

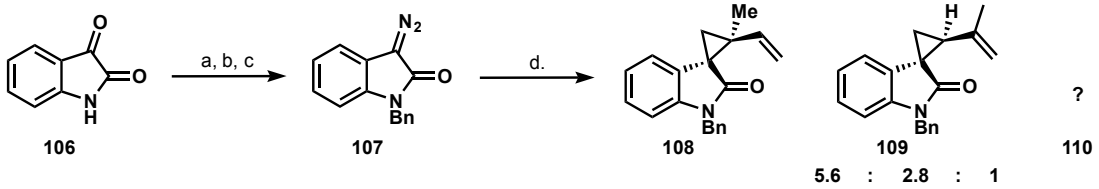
1.2 Aim of this Project

The aim of this project is the preparation of a system mimicking intermediate **26** (Scheme 8) during the prenylation of tryptophan by 4-DMAT-synthase. This should provide the first *in vitro* experiment supporting the hypothesis made by Arigoni and Wenkert. This should help to resolve an academic discussion held for decades whether the prenylation takes place directly Friedel-Crafts like into indole C-4 or *via* a [3,3]-sigmatropic rearrangement. Furthermore, the system should also reveal, that the indole reactivity is not skipped by nature. To do so, the system needs to fulfill four requirements.

1. The rearrangement needs to proceed at room temperature.
2. The reaction should not need any manipulations at the benzene core.
3. Any sort of conventional catalysts has to be avoided for the reaction.
4. The system should contain all important functionalities and features the natural intermediate possess.

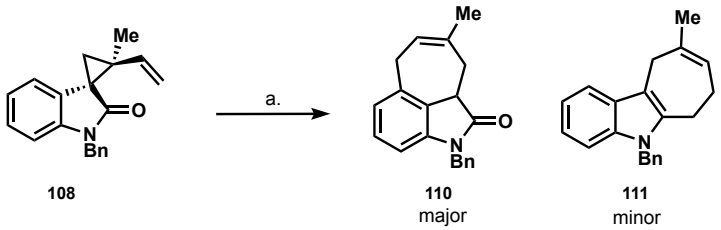
1.3 Own Contributions

During preliminary studies towards the total synthesis of Actinophylic acid, P. J. Gritsch[60] was seeking for a test-system to obtain a convenient access to cyclohepta[*b*]indoles *via* a divinylcyclopropane rearrangement. Cyclopropanation of **107** (Scheme 25) and isoprene,[61] led to the desired *spiro*-vinylcyclopropane **108** and two other products.



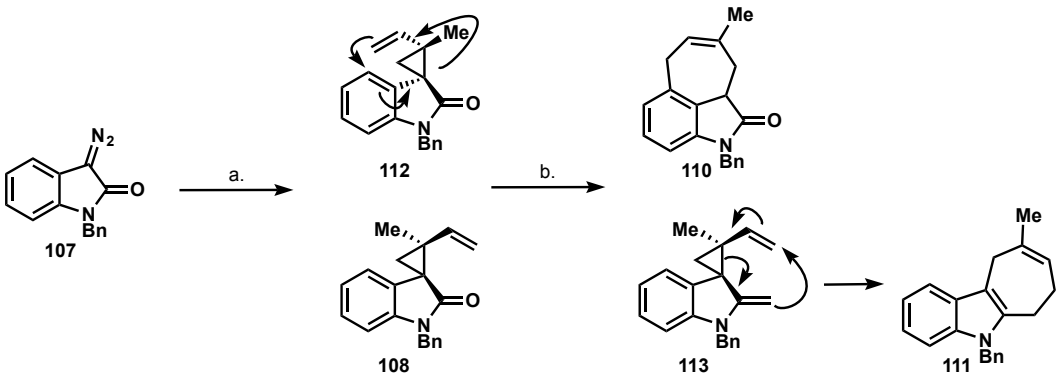
Scheme 25. Gritsch DVCPR precursor synthesis. a. NaH, BnBr, DMF, 0 °C, 90%, b. $TsNHNH_2$, MeOH, 60 °C, 80%, c. NaOH, H_2O, THF, 73%, c. $Rh_2(OAc)_4$, isoprene, reflux, 69%.

During the interconversion of oxindole **108** (Scheme 26) into the cyclohepta[*b*]indole **111**, methyllithium was used as nucleophile. Afterwards, the crude reaction mixture was heated to reflux in benzene in order to eliminate water. Instead of the desired cyclohepta[*b*]indole **111**, the corresponding cyclohepta[*cd*]oxindole **110** was obtained as major product.



Scheme 26. Divinylcyclopropane rearrangement on the test system. a. MeLi, THF, –78 °C, then PhH reflux.

Since compound **108** (Scheme 26) cannot undergo the rearrangement into indole C-4, it was assumed that the stereochemistry of the *spiro*-cyclopropane **108** was not determined correctly (Scheme 27). Comparing the NMR spectra of **110** and the former by-product (Scheme 25) revealed, that cyclohepta[*cd*]oxindole **110** has also been achieved during the first cyclopropanation reaction (Scheme 25).



Scheme 27. Formation of the two DVCPR products. a. $Rh_2(OAc)_4$ isoprene, CH_2Cl_2, b. MeLi, THF, then reflux.

The formation of **110** (Scheme 26) is surprising in two ways. First of all, it is remarkable that the rearrangement takes place at one of the least reactive positions of the indole nucleus. Furthermore, this reaction allows the substitution of indole C-4 without a pre-functionalisation at that position, which will be the topic of chapter two.

A closer look on the assumed reactive substrate **114** (Figure 9) and taking the biological point of view into account, this molecule would support perfectly the hypothesis of Arigoni and Wenkert (Scheme 8).

The system itself mimics the conformational restrictions the substrate is subjected to by the enzyme in the active site (Figure 9). The rigidity of the system is ensured by the *spiro*-fused cyclopropane. As the orbital overlap is mandatory for the reaction, the stereochemistry with the vinyl group pointing towards the benzene core of the indole is critical. The two *geminal* methyl groups of **26** facilitating the Cope-rearrangement in the enzyme are represented here by the methyl group of **114**. In both cases the Thorpe-Ingold effect forces the vinyl substituents toward the benzene core and enables the Cope rearrangement.

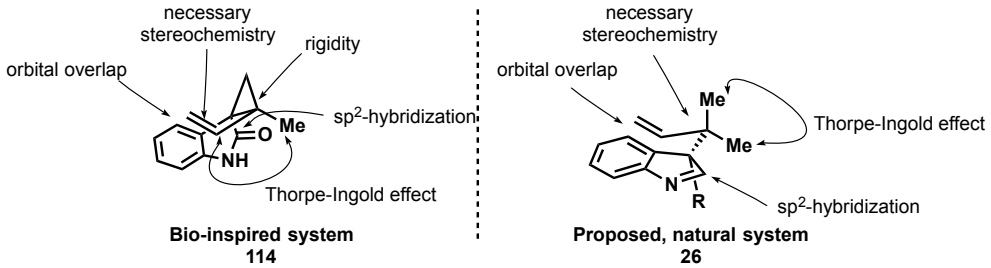
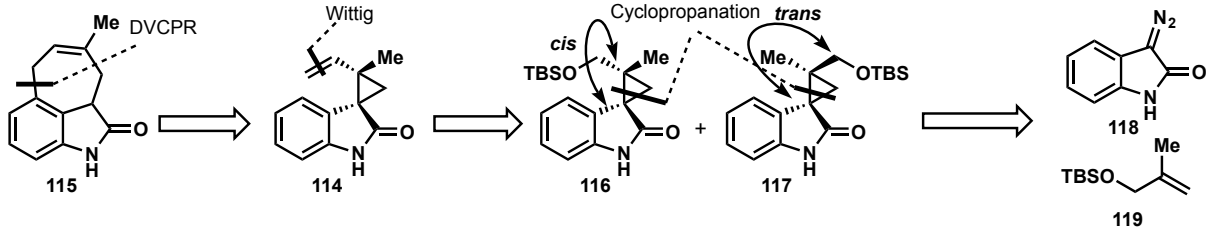


Figure 9. Comparison between our bio-inspired system and the proposed natural intermediate.

In regard to the oxidation state of the indole, compound **114** (Figure 9) differs. However, indole C-2 displays the same hybridisation (sp^2) as it was predicted for the reverse prenylated intermediate by Arigoni and Wenkert (Scheme 8). A comparison of the first two test systems **37**/**39** (Scheme 9) and the bio-mimicking system **114** reveals differences. While **114** is rigid, **37**

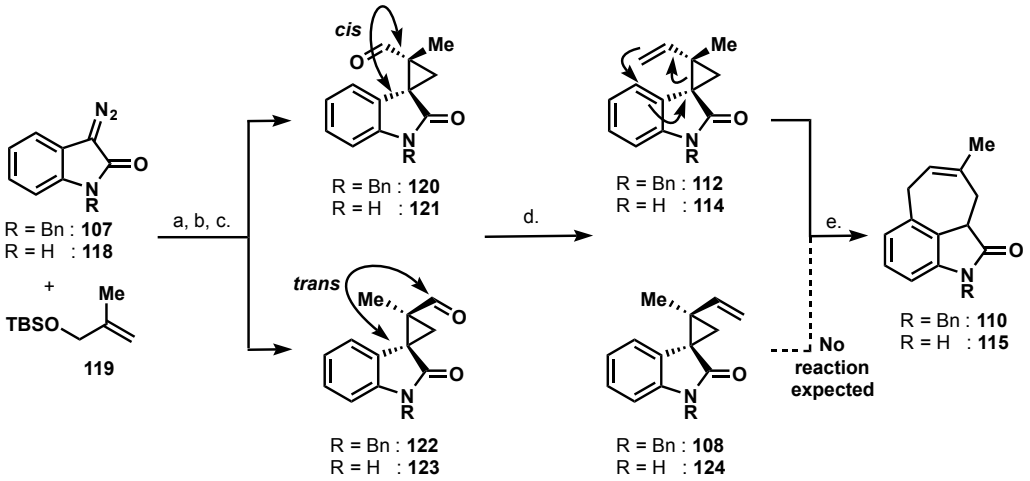
and **39** are flexible, thus an orbital overlap of the vinyl moiety with the benzene core cannot be ensured.

In order to get access to the bio-mimicking *cis*-vinylcyclopropane **114** (Scheme 28) we could not proceed *via* a selective route, since this would extend the synthesis tremendously. The short retrosynthetic analysis starts with the divinylcyclpropane rearrangement of **114**. Olefin **114** should be obtained from *spiro*-cyclopropane **116** by deprotection, oxidation and olefination. A cyclopropanation of diazo isatin **118** with TBS protected β-methallyl-alcohol (**119**) should deliver a diastereomeric mixture of **116** and **117**.



Scheme 28. Retrosynthesis for the bioinspired system.

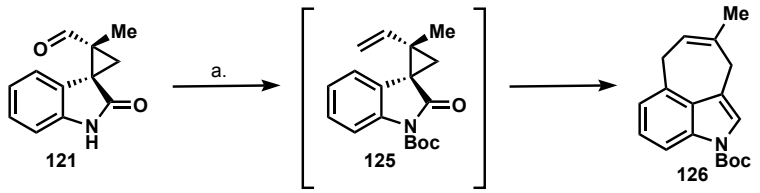
The route was based on an intermolecular cyclopropanation utilising a slightly modified procedure of Carreira *et al*.[61-62] In a first reaction benzyl protected oxindole was transferred into the corresponding diazo compound **107** (Scheme 29). β-Methallyl-alcohol was protected with TBSCl. Furthermore, diazo **107** and TBS-β-methallyl-alcohol (**119**) were stirred in presence of rhodium(II) acetate dimer at room temperature providing a 1:1 mixture of the two diastereomeres **116** and **117.** The obtained diastereomers were separated by flash column chromatography. Deprotection of the TBS-group, oxidation of the alcohol and subsequent olefination of the aldehyde (**120**/**122**) *via* Wittig olefination led to the corresponding vinylcyclopropanes **108** and **112**.



Scheme 29. Selective synthesis of *cis* and *trans* diastereomer. a. $Rh_2(OAc)_4$ (3 mol%), CH_2Cl_2, 60%, 1:1 **116** and **117** (33% if R=H), b. TBAF (2 equiv.), THF, 87%, c. IBX (1.05 equiv.), DMSO, 95% (91% if R=H), d. Ph_3PCH_3Br (3 equiv.), NaHMDS (3 equiv.), THF, –78 °C to 0 °C, 84% (85% if R=H). E. PhH, 60 °C, 55% (58% if R=H).

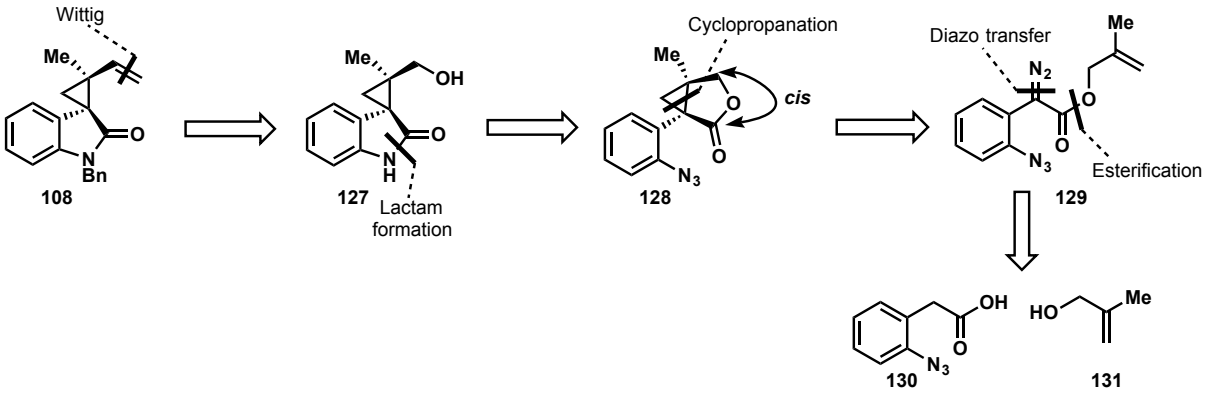
As expected, **112** (Scheme 29) rearranged slowly at room temperature, while **108** was stable even at 40 °C.

The corresponding indole **126** (Scheme 30) was prepared by Boc protection and subsequent olefination of **121.** The obtained olefin **125** rearrangeged immediately. The remaining oxindole was reduced by $NaBH_4$ and the obtained hemi aminal subsequently underwent the elimination to yield **126**.



Scheme 30. Formation of indole **126**. a. Boc_2O (1.2 equiv.), THF, then Ph_3PCH_3Br (2 equiv.), NaHMDS (2 equiv.), THF, –78 °C to 0 °C, then $NaBH_4$ (1 equiv.), MeOH, 0 °C, 42%.

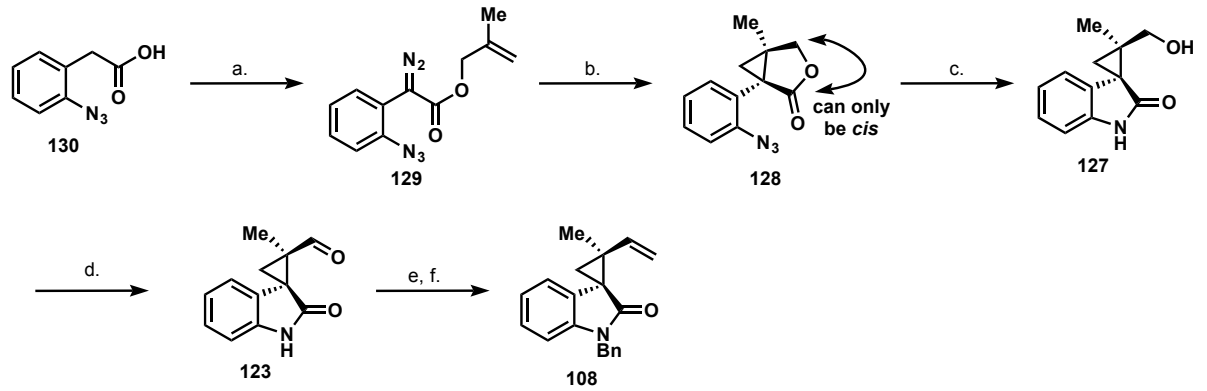
To confirm the relative stereochemistry of the two diastereomers (Scheme 29), selective preparation of the *cis*- or the *trans*-diastereomer was necessary. We developed a *trans*-selective route (Scheme 31) based on the intramolecular cyclopropanation reaction introduced by Qin *et al*.[63] in their biomimetic approach to Perophoramidine and Communesin. Olefin **108** should be achieved by oxidation, benzyl protection and olefination. Reduction of the azide functionality should provide alcohol **127**. Intramolecular cyclopropanation of α-diazo ester **129** should establish the *cis*-fashioned lactone **128**. An esterification of acid **130** and alcohol **131** and subsequent diazo transfer into the α-position should provide diazo compound **129**.



Scheme 31. Retrosynthesis of *cis*-selective route.

In the first step, acid **130** (Scheme 32) was esterified utilising β-methallyl-alcohol (**131**), DIC and 4-DMAP. Using ABSA and DBU the diazo functionality could be introduced into the α-position delivering **129**. The subsequent intramolecular cyclopropanation yielded **128**. As the cyclopropanation proceeds *via* an intramolecular mechanism, the *cis*-fashion of lactone **128** is assured.

The azide functionality was suspected to interfere somehow with the functionalities (Scheme 32) under the given conditions, but luckily it remained passive. In order to obtain oxindole **127**, azide **128** was reduced utilising Pd/C under hydrogen atmosphere. Since the corresponding aniline did not open the lactone, acetic acid was added and the reaction mixture was heated yielding oxindole **127**. As alcohol **127** caused solubility problems, IBX was utilised for oxidation as the reaction is performed in DMSO. The oxidation proceeded slowly but aldehyde **123** was obtained in a very good yield. Aldehyde **123** was further benzyl protected and subsequent Wittig reaction provided **108**.



Scheme 32. Selective synthesis of *trans*-olefin **108**. a. β-methallyl-alcohol (1.05 equiv.), DMAP (20 mol%), CH_2Cl_2, then ABSA (1.05 equiv.), DBU (2 equiv.), THF, 92% over two steps, b. $[(CuOTf)_2 \bullet Tol]$ (1.5 mol%), CH_2Cl_2 84%, c. Pd/C (10 mol%), H_2 (5 bar), EtOH then HOAc, reflux. 89%, d. IBX (1.1 equiv.), DMSO, 94%, e. NaH (1.05 equiv.), BnBr (5 equiv.), DMF, 80%, f. Ph_3PCH_3Br (5 equiv.), NaHMDS (5 equiv.), THF, –78 °C to 0 °C, 80%.

Since **123** (Figure 10) crystallised readily, the relative stereochemistry of this compound could be confirmed by single-crystal X-ray analysis easily.[64]

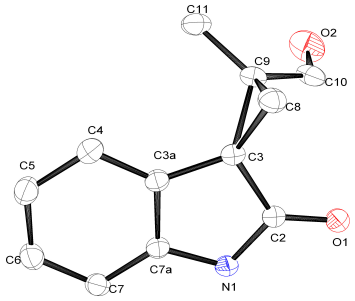


Figure 10. Single crystal X-ray structure of **123**.

With both diastereomers in hands the investigation of the different reactivities of the two vinylcyclopropanes **108** (Figure 11) and **112** was of particular interest. Therefore, the two diastereomers were subjected to a NMR experiment. To indicate the reaction progress during the experiment we chose to observe the CH_2 group of the cyclopropane, since the signals of that group do not overlap in NMR. Furthermore, the chemical shift of the protons changes during the reaction so the reaction progress is easily comprehensible. Benzene-d_6 was used as solvent and the reaction temperature was set to 60 °C.

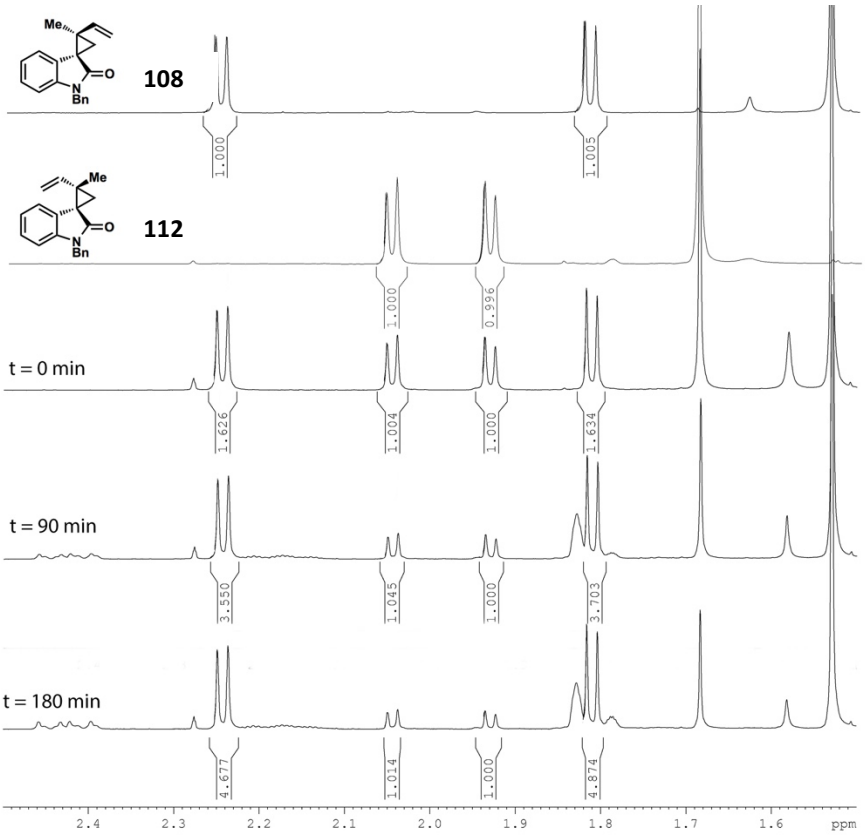


Figure 11. Reactivity of **108** in contrast to **112** at 60 °C.

In the first two rows of Figure 11, the pure diastereomers (**108**/**112**) are depicted. The third row shows a mixture the two diastereomers (**108**/**112**). In the rows below the reaction progress of the diastereomeric mixture is logged. The NMR revealed that diastereomer **112** reacts under the given conditions while the CH_2 group of **108** remains essentially untouched.
To exclude the influence of the protecting group on the rearrangement, the unprotected *cis*-vinylcyclopropane **114** had to be prepared (Scheme 29). The preparation proved to be challenging. Since the protecting group free diazo **118** is poorly soluble in most solvents, the reaction temperature had to be elevated to 65 °C. This provided an acceptable combined yield of 33% in a 1.6:1 diastereomeric ratio in favour for *cis*-diastereomer **116**. The solubility problems continued during the synthesis making the purification a tough task. Nevertheless, the desired vinylcyclopropanes were obtained and exhibited a higher reactivity than its protected pedant as it rearranged faster at room temperature than **112**. The spontaneous rearrangement is also a strong support for the Cope-rearrangement hypothesis of Arigoni and Wenkert since elevated temperatures rarely appear in living organisms.

1.4 Summary and Outlook

By retro analysis of DVCPR product **110** (Scheme 29) it was possible to prepare a system mimicking the reverse prenylated intermediate **26** (Scheme 8) during the C-4 prenylation, as proposed by Arigoni and Wenkert. It was possible to point out the basic demants necessary for an *in vitro* experiment in order to support the [3,3]-sigmatropic rearrangement hypothesis. The designed system involved the conformational restrictions which the substrate is subjected to in the enzyme. Also, the stereochemistry and the *gem*-dialkyl group could be installed in the mimicking system **110**. Compounds **112** and **114** (Scheme 29) were able to undergo the DVCPR even at room temperature which is a great indication that this reaction may occur in nature as well. Generally speaking the prepared system provided the first experimental evidence for a possible enzyme-catalysed sigmatropic process in the C-4 prenylation of indole alkaloids. The system also allows a direct C-C bond formation with a synthetic access to cyclohepta[*cd*]indoles.

As this system needs no pre-functionalisation or heavy metals to form a C-C bond into the relatively unreactive indole C-4, further research is necessary in order to investigate the scope for the reaction. This will be part chapter two and three. Furthermore the influence of the Thorpe-Ingold effect needs to be investigated (chapter four)

2 DVPR Methodology

“Herr Schwarzer, machen Sie sich einen Plan und seien Sie anderen ein Licht. Machen Sie sich einen zweiten, denn funktionieren, werden sie alle nicht.“

Prof. Dr. Johann Mulzer

2.1 Introduction

2.1.1 *Cyclohepta[cd]indole*

Cyclohepta[*cd*]indoles are molecules comprising an indole core fused to a seven-membered ring at indole C-3 and C-4 (see **131**; Figure 12). The tricyclic scaffold can be found in nature but it is limited to a small group of natural products such as the Welwitindolinones or Dragmacidin E (**133**). The family of Welwitindolinones is known for their biological properties such as antifungal and larvicidal activities, the depolimerisation of microtubili and the ability reverse multi drug resistance (MDR) in human cancer cells.[65] Dragmacidin E (**133**) acts as an inhibitor of serine-threonine protein phosphatase[66].

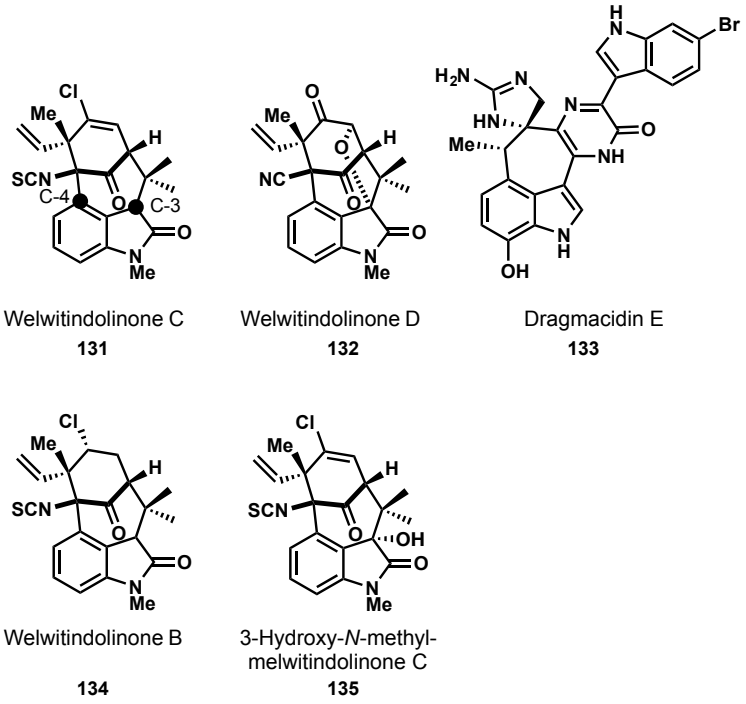


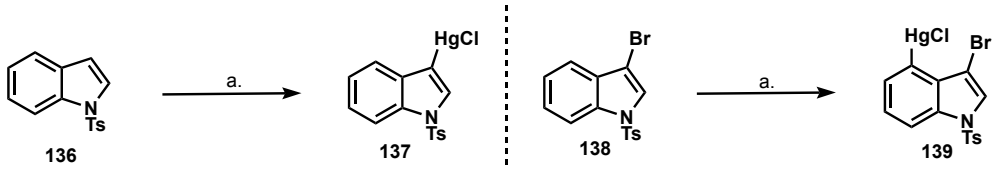
Figure 12. Known cyclohepta[*cd*]indoles.

As these cyclohepta[*cd*]indoles (Figure 12) display an array of biological activities, new substrates containing this motif are of interest. A good source which was found providing a great variety of cyclohepta[*cd*]indoles are the ergot alkaloids[67] which have to be synthetically transformed.

2.1.2 *Direct C-4 activation*

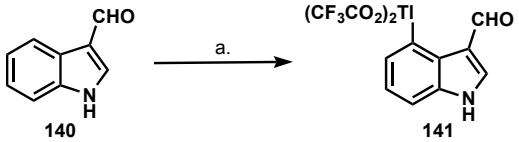
As the reactivity of the indole nucleus at the C-4-position is low, direct functionalisation remains somewhat difficult for a synthetic chemist. In fact, up to date there are only a few reagents known providing functionalisation at this position.

One reagent is mercuric acetate reacting already at room temperature with the indole, providing 3-mercurated product **137** (Scheme 33).[68] If C-3 is already substituted, the mercuration takes place at C-4 yielding **139**. Mercurated indoles can be applied for the preparation of boronic acids and 4-iodo-indoles. Furthermore, they can be applied directly in palladium catalysed cross-coupling reactions.[69]



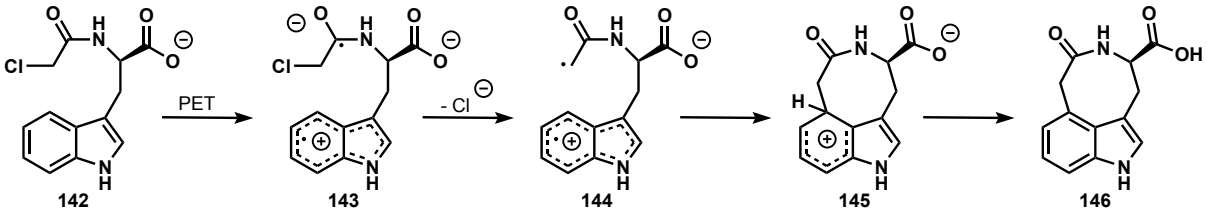
Scheme 33. Mercuration of indoles. a. $Hg(OAc)_2$, AcOH, rt, then NaCl.

Another method to activate indole C-4 is to treat the indoles with thallium trifluoroacetate (Scheme 34). Utilising simple indoles, this reaction provides no defined products. Having an electron-withdrawing substituent at C-3 which is able to chelate thallium yields the 4-thallated product **141**. This product can be used to prepare different 4-substituted indoles *via* palladium catalysed cross-couplings.[70]



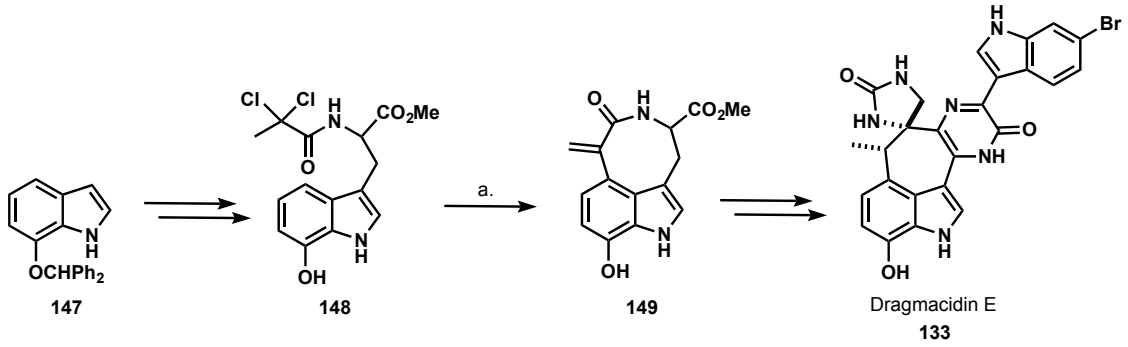
Scheme 34. Thalliation of 3-substituted indole **140**. a. $Tl(O_2CCF_3)_3$, TFA, rt.

Although these reagents allow a direct activation of C-4 they are avoided in synthesis as they proved to be highly toxic. A method which allows the alkylation at C-4 without using highly toxic reagents is the Witkop cyclisation (Scheme 35).[71] It is the result of an attempted photo-reduction of chloroacetyltryptophan **142** providing the C-4 substituted tricyclic product **146**. Mechanistically, the reaction proceeds *via* an intramolecuar photon-induced electron transfer generating a diradical. The generation of a radical anion and a radical cation in close proximity allows the C-C bond formation at C-4. The intermediate rearomatise or it can be captured by a nucleophile to obtain a non-aromatic product.



Scheme 35. Mechanism of the Witkop cyclisation.

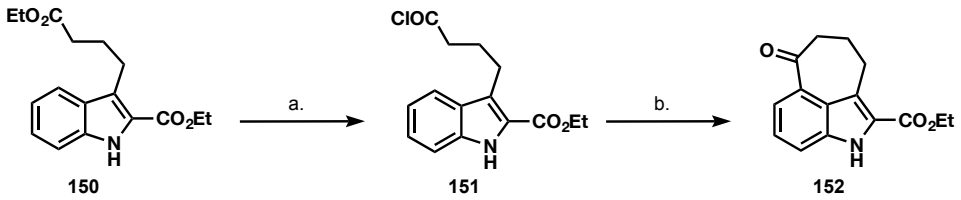
Although this reaction is limited to α-chloroacetyl derivatives of aromatic amino-acids and amines it is nevertheless a useful tool in chemical synthesis. For instance, the methodology was applied in the total synthesis of Dragmacidin E (**133**, Scheme 36).[72]



Scheme 36. Total synthesis of Dramacidin E (**133**). a. hv, 254 nm, MeCN.

2.1.3 *Formation of cyclohepta[cd]indoles*

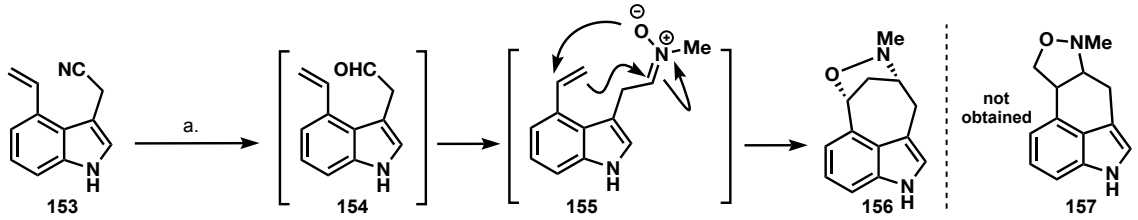
The scaffold of cyclohepta[*cd*]indoles is an interesting target for drug discovery. Even though they do not appear frequently in nature, the natural products containing this scaffold address a variety of biological targets. In order to build up this scaffold directly some few methods have been developed. The very first method providing cyclohept[*cd*]indoles was developed by Nagasaka *et al*. (Scheme 37).[73] In a first step **150** was transferred into the corresponding acid chloride **151**. The subsequent Friedel-Crafts acylation provided the derived Uhle ketone **152** in 24% yield over two steps.[74]



Scheme 37. Friedel-Crafts reaction providing cyclohepta[*cd*]indole. a. $SOCl_2$, $CHCl_3$, steambath, b. $AlCl_3$, DCE, rt, 24% over two steps.

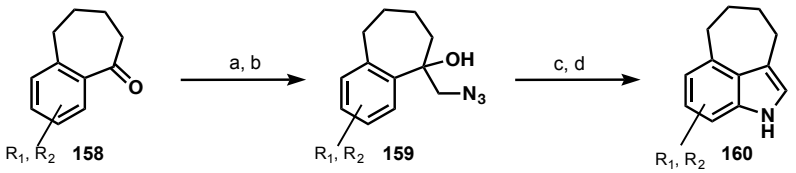
Oppolzer *et al.* stumbled over **156** (Scheme 38) in their total syntheses of Clavine alkaloids in 1983.[75] Reduction of **153** led to aldehyde **154** which was treated with methylhydroxylamine to obtain the transient nitrone **155**. Refluxing the reaction mixture in benzene provided the

[3 + 2] cycloaddition reaction to form the bridged cycloadduct **156** instead of the desired isoxazolidine **157**. By introducing substituents to the vinyl moiety, the formation of then non-bridged isoxazolidine is favoured limiting the scope of the reaction dramatically.



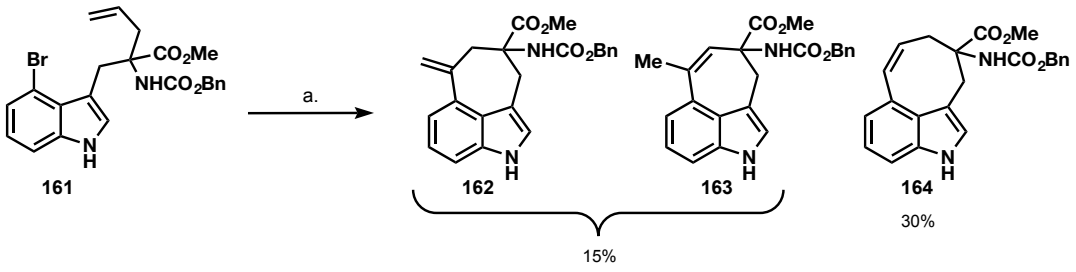
Scheme 38. [3 + 2] aproach to cyclus **157**. a. DiBAl-H, PhMe, then, MeNHOH, NaOMe, PhH, reflux, 56%.

Moody *et al*.[76] were following a different approach in 1989. Instead of starting from an indole or its derivatives they applied different cyclic ketones (Scheme 39). In a first step ketone **158** was transferred into an epoxide which was selectively opened by NaN_3. The tertiary alcohol was eliminated and the vinyl azide was refluxed in mesitylene undergoing a thermolysis which provided indole **160**. Despite the new approach, a significant drawback of this method is that no further functionality is provided. Every functionality needed on the seven-membered ring has to be toilsome introduced.



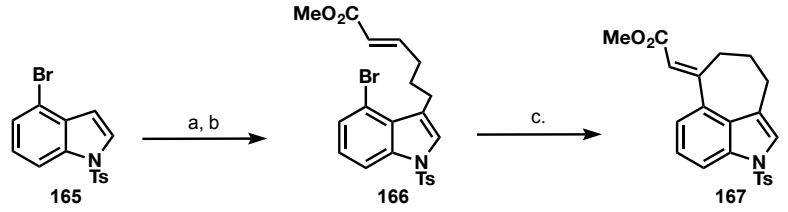
Scheme 39. Cyclohepta[*cd*]indole synthesis by Moody's thermolysis route. a. $Me_2S^+OCH_2^-$, DMSO, 55 °C, b. NaN_3, LiCl, DMF, 65 °C, c. $SOCl_2$, pyridine, rt., d. mesitylene, reflux.

Even though palladium catalysed reactions were used in the synthesis of ergotalkaloids earlier[69a, 77] the first palladium catalysed synthesis of cyclohepta[*cd*]indoles has been reported by Roberts *et al*. (Scheme 40) in 1994.[78] Using **161** under standard Heck conditions they obtained a mixture of three different products **162**, **163** and **164** in poor yields.



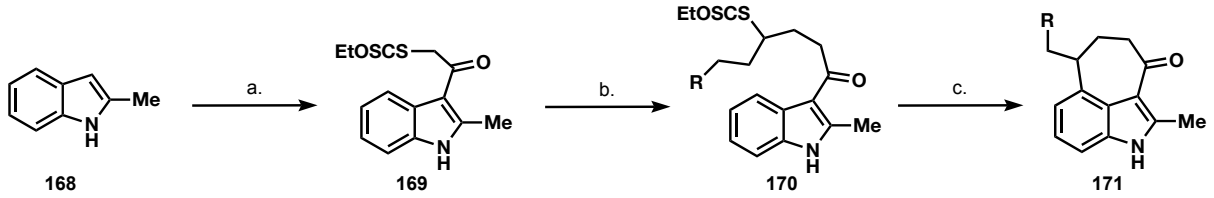
Scheme 40. First reported palladium catalysed synthesis of cychlohepta[*cd*]indoles. a. 1. Et_3N (2 equiv.), $(PhO)_3P$ (12 mol%), $Pd(OAc)_2$ (5 mol%), MeCN, 85 °C.

Murakami *et al*. (Scheme 41)[79] were able optimise the reaction and made it suitable for organic synthesis. In their synthesis, indole C-3 is acylated by Friedel-Crafts reaction followed by the de-functionalisation of the benzylic ketone using triethylsilane in TFA to obtain **166**. Heck reaction provided bridged indole **167**.

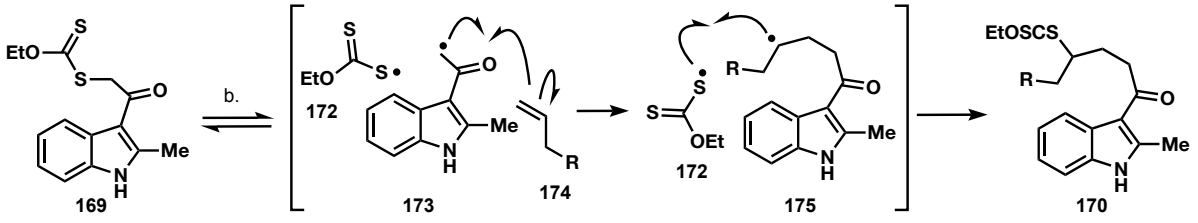


Scheme 41. Heck reaction in the synthesis of cyclohepta[*cd*]indoles. a. $ClOCC_2H_4C_2H_2CO_2Me$, $AlCl_3$, 54%, b. Et_3SiH, TFA, 54%, c. $PdCl_2(PPh_3)_2$, DMF:Et_3N, 100 °C, 7 h, 67%.

The synthesis of Zard *et al*. (Scheme 42)[80] avoids expensive and pre-functionalised starting materials. In their three-step synthesis, the key-feature is a radical cyclisation.The first step is a Friedel-Crafts reaction to acylate indole C-3. The product was further transferred into xanthate **170**. Catalytic amounts of lauroyl peroxide and an excess of allyl compound reacted in a dithiocarbonate group transfer reaction yielding xanthate **170** (Scheme 43). The annelation to indole C-4 took place when **170** was exposed to an excess of lauroyl peroxide in refluxing chlorobenzene.



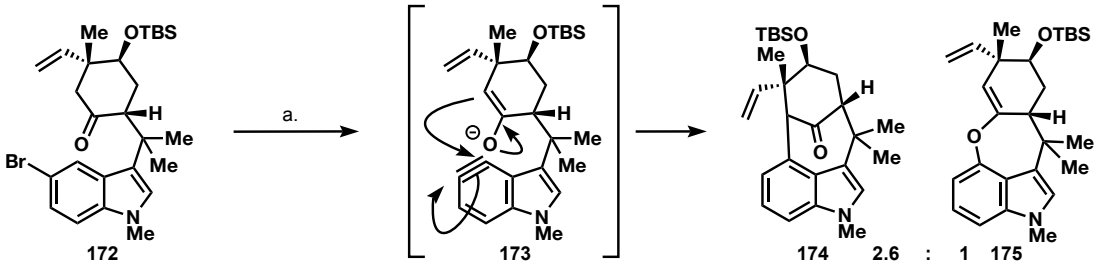
Scheme 42. Annelation of **170** *via* radical reaction. a. $ClCH_2COCl$, $AlCl_3$, CH_2Cl_2, then $EtOCS_2K$, acetone, b. allyl-compound, lauroyl peroxide (10 mol%), DCE:PhCl, reflux, 77%, c. lauroyl peroxide (1.25 equiv.), PhCl, reflux, 54%.



Scheme 43. Dithiocarbonate group transfer. b. see Scheme 42.

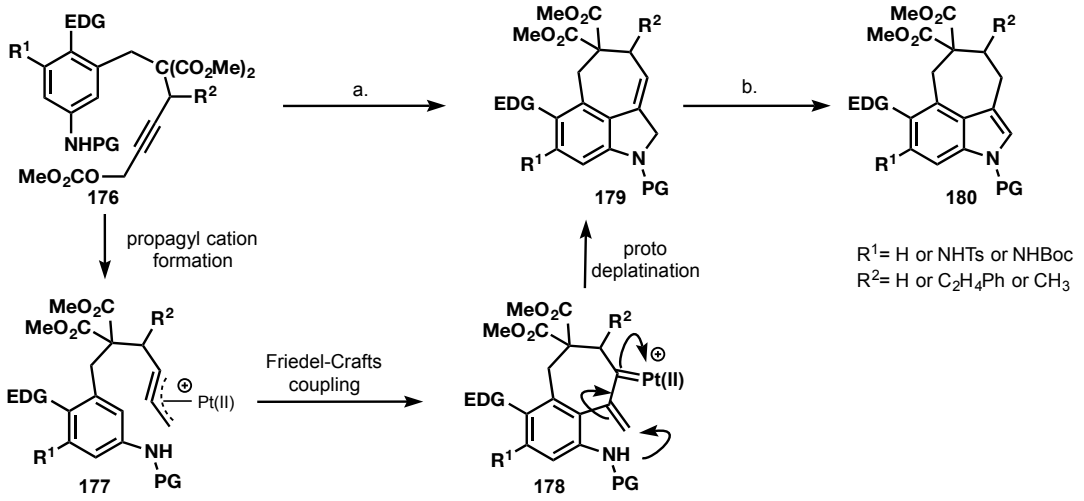
In the total synthesis of *N*-methylwelwitindolinone-C (**131**; Scheme 44) Garg *et al*. applied an indolyne cyclisation to afford the cyclohepta[*cd*]indole **174**.[81] Their synthesis starts with easy accessible 5-substituted indole **172** and sodium amide providing aryne **173**. Sodium amide causes also the enolisation of the ketone. The enolate reacts subsequent with aryne **173**

providing 3,4-fused indole **174**. The second seven membered heterocycle **175** is obtained when the oxygen of the enolate undergoes a reaction with the aryne.



Scheme 44. Garg's indolyne cyclisation. a. $NaNH_2$ (10.5 equiv.), *t*-BuOH, (3.5 equiv.), THF, rt., 46%.

Most recently Nemoto *et al*. (Scheme 45)[82] reported the application of platinum in the synthesis of 3,4-fused tricyclic indoles (**180**). As control experiments excluded an *in situ* formation of allenyl intermediates, the first step is a propagyl cation formation. Cation **177** is able to react in a Friedel-Crafts type C-H coupling, providing **178**. The remaining cation **178** is then trapped by the nitrogen of the aniline. Treating **179** with TFA provides indole **180**. This method is useful if substituents in C-5 are desired and the product contains either a nitrogen or a *geminal* ester in homo-benzylic position.



Scheme 45. Nemoto`s platinum catalysed synthesis of cyclohepta[*cd*]indoles. a. $[Pt(dba)_3]$ (5 mol%), DPEphos (6 mol%), DMSO, 100 °C, 16 h, 42 – 91%, b. TFA, CH_2Cl_2, rt, 12 h, 61 – 99%.

Of all these methods, only the cross-coupling variant (Scheme 41) and the indolyne cyclisation (Scheme 44) were applied in total synthesis. These two methods have the advantage that they tolerate a good many of functionalities and enable the installation of complex substituents to C-4.

2.2 Aim of this Project

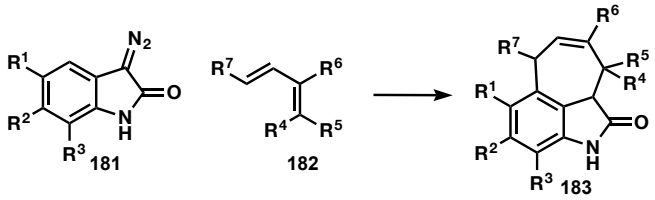
Even though methodologies for C-C bond formation into indole C-4 have been investigated, most of them are limited to a few substrates or special substitution patterns. The most feasible methodology is the cross-coupling which has already been applied to total synthesis. A drawback here is the necessity of C-4 pre-functionalised indoles. They are generally expensive, since their synthesis takes either heavy metals or several tedious reaction- and purification-steps.

This project should lead to a generalised and practical access of cyclohepta[*cd*]oxindoles. The substrates applied for the synthesis have to be easily accessible and the conditions used should be in no need of inert gas.

The diversification of substrates prepared by a multistep synthesis should be performed late stage in order to make use of a privileged intermediate. This should ensure a broad application. Furthermore, the reaction has to tolerate a variety of functional groups on the oxindole core as well as on the bridging chain.

2.3 Own Contributions

Most of the methods for the preparation of cyclohepta[*cd*]indoles are restricted to specific structural motifs (see Scheme 38, 39, 40, 42) in one or the other way, as well as pre-functionalisations (see Scheme 40, 41, 42, 45). We desired to introduce a methodology which is more versatile (Scheme 46). The methodology should allow the application of substituted as well as plain indoles. Furthermore, it should provide the possibility to install functionalities in every position of the seven-membered ring.



Scheme 46. Positions to be substituted for the DVCPR.

We decided to evaluate mainly the effects of the isatine core on the reaction outcome and keep the isoprene moiety, functioning as the diene reaction partner, constant. In case of the substituents at the benzene core of the isatine (Figure 13), we decided to introduce halogens which may be applied in subsequent reactions. Nitro- and methoxy groups should expose the influence of mesomeric effects and a methyl substituent should serve as an example for alkyl substituents.

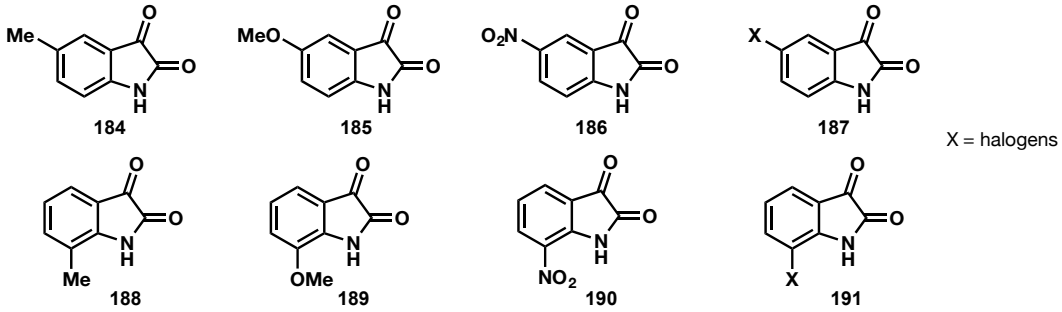
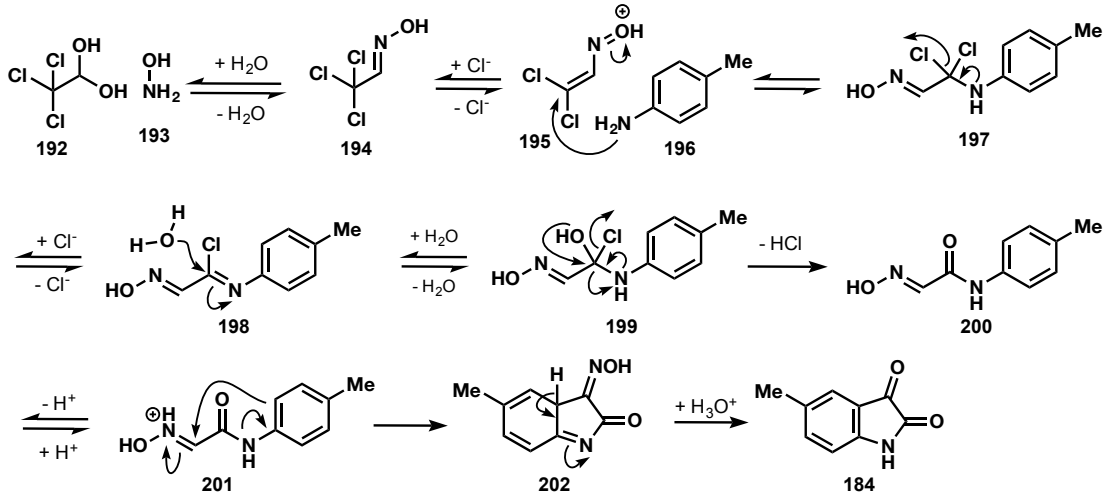


Figure 13. Isatines that should be used in the synthesis of cyclohepta[*cd*]indoles.

Even though cyclohepta[*cd*]oxindoles (chapter one, Scheme 29) have been prepared *via* an established route, a shorter, more efficient route to generate the "simple" products was required. Considering the preliminary studies of P. J. Gritsch (chapter one, Scheme 27), the desired cyclohepta[*cd*]oxindoles should be obtained in a one pot reaction, even though the yield of 7.3% was not encouraging.

The required isatines were prepared by Sandmeyer's isatine synthesis (Scheme 47).[83] The corresponding aniline was dissolved in aqueous hydrochloric acid with hydroxylamine

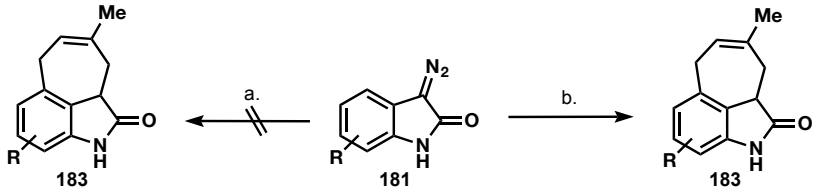
hydrochloride, Na_2SO_4 and chloralhydrate. Afterwards the reaction mixture was heated and the obtained solid has been treated with sulfuric acid. This step appeared to be sensitive to temperature. When the reaction temperature of 85 °C has been exceeded, in case of the OMe and NO_2 substituents the product decomposed in the sulfuric acid. Once the reaction temperature dropped below the lower limit of 80 °C the reaction did not take place.



Scheme 47. Sandmeyer isatine synthesis.

In case of the diazotation only the substrates featuring mesomeric effects were fraught with problems, since they decomposed easily. 7-NO_2 diazoisatine proved to be fairly instable, decomposing immediately during workup. Consequently, this compound was excluded from the table.

The first tandem cyclopropanation DVCPR tandem reactions failed (Scheme 48), as the diazo compounds were little soluble in isoprene. The problem was simply solved by performing the reaction in CH_2Cl_2, isoprene and $Rh_2(OAc)_4$ at 40 °C in a sealed tube. By lowering the temperature, the amount of side products could be decreased.



Scheme 48. First attempts on short route toward cyclohepta[*cd*]oxindoles. a. Isoprene (10 equiv.), $Rh_2(OAc)_4$ (2 mol%), sealed tube, reflux. b. Isoprene (10 equiv.), CH_2Cl_2, $Rh_2(OAc)_4$ (2 mol%), reflux.

Another problem appeared when a new batch of the catalyst was used (Table 1). It became apparent that we were not able to reproduce the results applying the new batch. Even changing to another supplier (from Alfa Aesar® to Sigma Aldrich®) could not solve this issue.

The problem has been addressed by preparing the catalyst from $RhCl_3 \bullet X(H_2O)$. Applying the abovementioned catalyst, we were able to deliver reproducible results with a slight increase of the yield compared to the first catalyst batch of Alfa Aesar®.

Table 1. Yields achieved with $Rh_2(OAc)_4$ (2 mol%) from different sources using different diazo isatines with isoprene (10 equiv.) at 40 °C in CH_2Cl_2 in a sealed tube.

Entry	Product	Yield: Alfa 1 $Rh_2(OAc)_4$	Yield: Alfa 2 $Rh_2(OAc)_4$	Yield: Sigma $Rh_2(OAc)_4$	Yield: self prep. $Rh_2(OAc)_4$
1	5-F (**203**)	50	35	40	55
2	5-Br (**204**)	47	32	36	47
3	5-Cl (**205**)	40	30	35	44
4	5-Me (**206**)	45	33	37	49
5	5-OMe (**207**)	55	35	42	56
6	5-NO_2 (**208**)	35	24	30	37
7	7-F (**209**)	40	27	34	41
8	7-Br (**210**)	50	36	41	52
9	7-Cl (**211**)	49	34	40	52
10	7-Me (**212**)	51	34	42	53
11	7-OMe (**213**)	42	32	35	44

A look at Table 1 reveals that the nitro group and fluoride substituent affect the reaction negatively. The yields of both differ significantly from the other substrates.

As the substituents on the benzene core proved to be suitable for the reaction, the attention was directed to the use of different dienes (Figure 14).

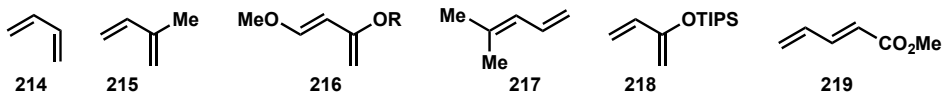
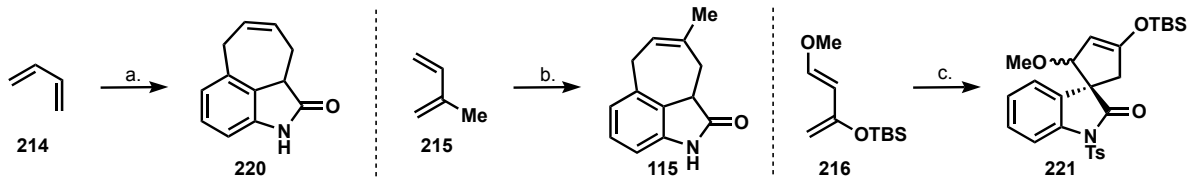


Figure 14. Dienes used in the Cyclopropanation-DVCP tandem reaction.

Utilising butadiene (**214**; Scheme 49) and isoprene (**215**) generated the desired product **220** in 40% and **115** in 56% yield. In case of butadiene (**214**) we had to change the solvent after cyclopropanation, since no rearrangement could be observed at 40 °C.



Scheme 49. a. butadiene (10 equiv.), $Rh_2(OAc)_4$ (2 mol%), CH_2Cl_2, then DMSO reflux., 54%, b. isoprene (10 equiv.), CH_2Cl_2, $Rh_2(OAc)_4$ (2 mol%), reflux, 53%, c. Denishefsky diene (1.2 equiv.), $Rh_2(OAc)_4$ (2 mol%), neat, 70 °C, 50%.

The classic Danishefsky diene did not react under standard conditions. This was surprising as this is a very electron rich diene and therefore it should be very suitable for a rhodium catalysed cyclopropanation. In order to investigate the reason, a few experiments were executed (Table 2).

Table 2. Approaches toward the cyclopropanation of Danishefsky diene.

Entry	Diene Eq.	Solvent	Catalyst	Conditions	Outcome
1	2.5	PhH	-	rt, 48 h	SM
2	2.5	PhH	-	40 °C, 24 h	SM
3	2.5	PhH	-	100 °C, 12 h, sealed tube	Diene recovered decomp. diazo.
4	2.5	PhH	$Rh_2(OAc)_4$, (1 mol%)	40 °C, 24 h	SM
5	2.5	PhH	$Rh_2(OAc)_4$, (5 mol%)	40 °C, 24 h	Diene recovered decomp. diazo.
6	2.5	PhH	$[Cu(OTf)]_2PhMe$ (1 mol%)	40 °C, 24 h	SM
7	2.5	PhH	$[Cu(OTf)]_2PhMe$ (5 mol%)	40 °C, 24 h	Diene recovered decomp. diazo.
8	2.5	-	$Rh_2(OAc)_4$, (2 mol%)	rt to 40 °C, 40 min	Decomp. Diene

It became apparent that TMS Danishafsky diene did not react in solution. Utilising neat starting materials with $Rh_2(OAc)_4$ led to decomposition of the enolether. Therefore, TBS protected Danishefsky diene **216** (Scheme 49) was prepared and applied in the reaction. Obviously the desired rearrangement did not take place as all four aromatic NMR signals remained in the spectrum (Figure 15). After NMR analysis, the structure could be elucidated. Instead of the divinylcyclopropane rearrangement, the vinyl cyclopropane rearrangement occurred and the corresponding *spiro* compound **221** (Scheme 49) was obtained.

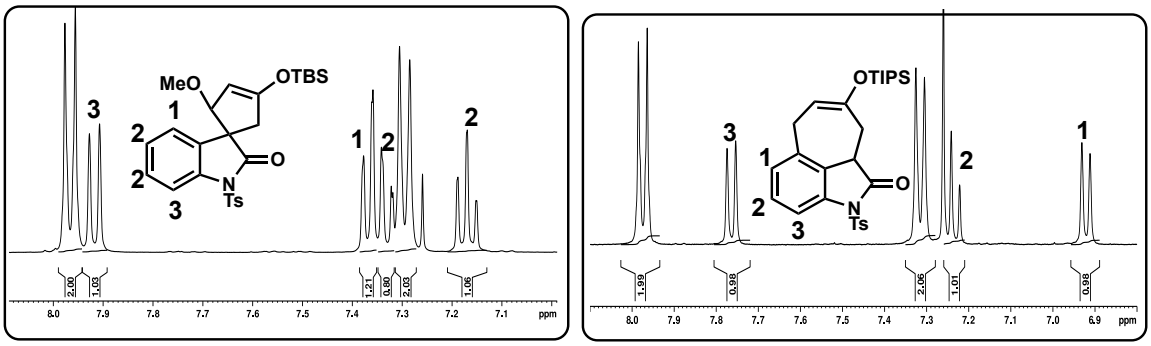
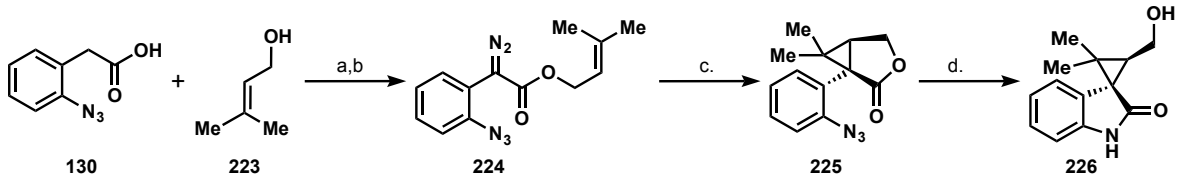


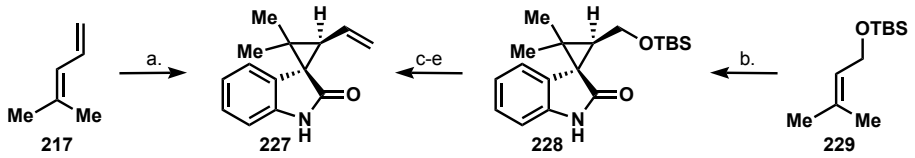
Figure 15. Four aromatic integrals of *spiro-oxindole* ***221*** and characteristic signal pattern for DVCPR-products.

Applying prenylene **217** (Scheme 51) as diene provided only the *trans*-vinyl-cyclopropane **227** which could be proven by its *trans* selective preparation (Scheme 50).



Scheme 50. Selective preparation of **226**. prenyl -alcohol (1 equiv.), DMAP (20 mol%), DIC (1.05 equiv.), CH_2Cl_2, 92%, b. ABSA (1.05 equiv.), DBU (2 equiv.), THF, 96%, c. $[(CuOTf)_2 \bullet PhMe]$ (1.5 mol%), CH_2Cl_2 80%, d. PBu_3 (1.05 equiv.), THF then PhMe, reflux. 80%.

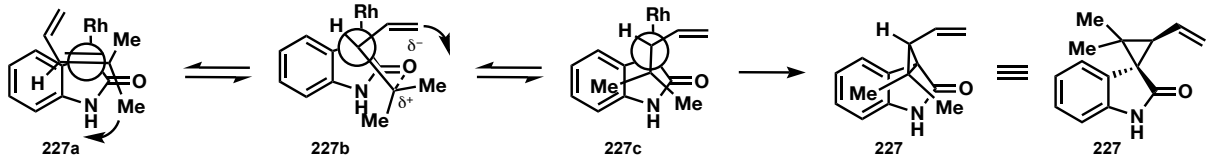
Even heating **227** (Scheme 51) to 120 °C in DMSO resulted in decomposition only. In order to examine whether we were able to obtain the corresponding *cis*-compound, TBS-protected prenyl alcohol **229** (Scheme 51) was applied in a cyclopropanantion reaction. This experiment led to the same result. The only product obtained was *trans*-cyclopropane **228**. The alcohol was deprotected, oxidized and olefinated to obtain **227**.



Scheme 51. a. prenylene (10 equiv.), $Rh_2(OAc)_4$ (2 mol%), CH_2Cl_2, then DMSO reflux., 45%, b. TBS-prenyl alcohol (10 equiv.), CH_2Cl_2, $Rh_2(OAc)_4$ (2 mol%), reflux, 53%, c. TBAF (4 equiv.), THF, 0 °C, 71%, d. IBX (1.1 equiv.), DMSO, 44%, e. Ph_3PCH_3Br (5 equiv.), NaHMDS (5 equiv.), THF, – 78 °C to rt., 83%.

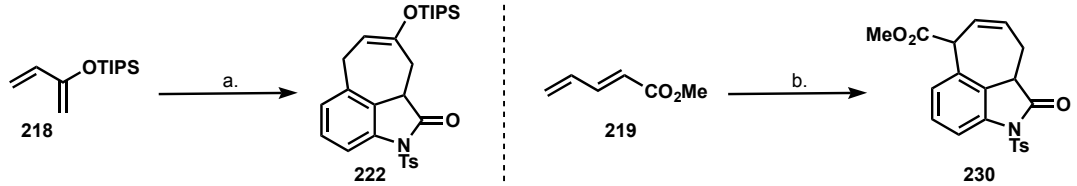
The formation of **227** (Scheme 51) can be explained by the mechanistic model of Doyle (Scheme 52),[84] even though it was once developed for more simple systems. The two methyl groups of **227a** avoid the benzene core as well as the catalyst complex. The developing electrophilic character on the tertiary carbon is stabilised by the nucleophilic carbonyl oxygen. The nitrogen of the oxindole enhances the nucleophilicity resulting in a more stable transition

state. The vinyl-group on the other hand is able to turn out of plane to minimise the interactions with the catalyst complex and the benzene core.



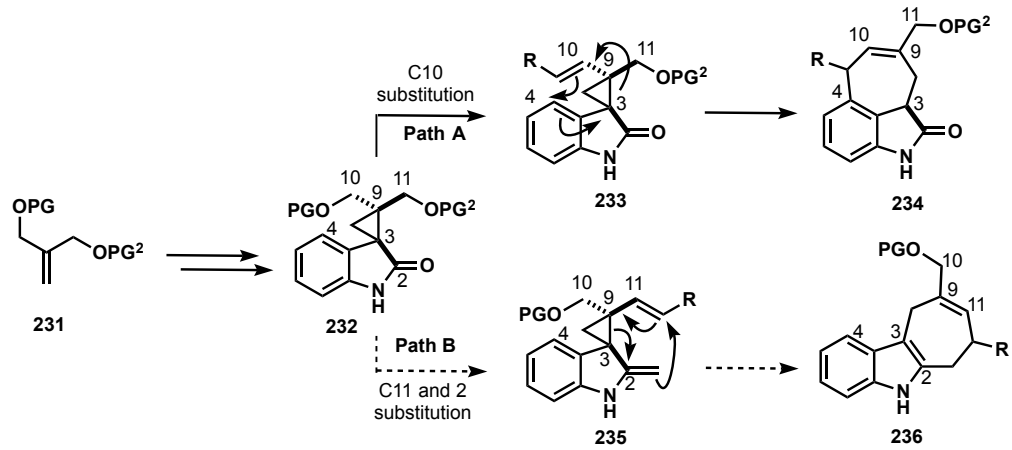
Scheme 52. Possible transition states for cyclopropanation.

Compounds **222** (Scheme 53) and **230** are part of chapter three. Nevertheless, both substrates were prepared successfully in a tandem cyclopropanation-DVCPR-reaction.



Scheme 53. NTs diazoisatine (1 equiv.), $Rh_2(OAc)_4$ (1 mol%), diene **218** (1.5 equiv.), PhH, 65 °C, 39%, b. NTs diazoisatine (1 equiv.), **219** (4.5 equiv.), $Rh_2(OAc)_4$ (1 mol%), PhH, 80 °C, then DMSO, 100 °C, 33% over two steps.

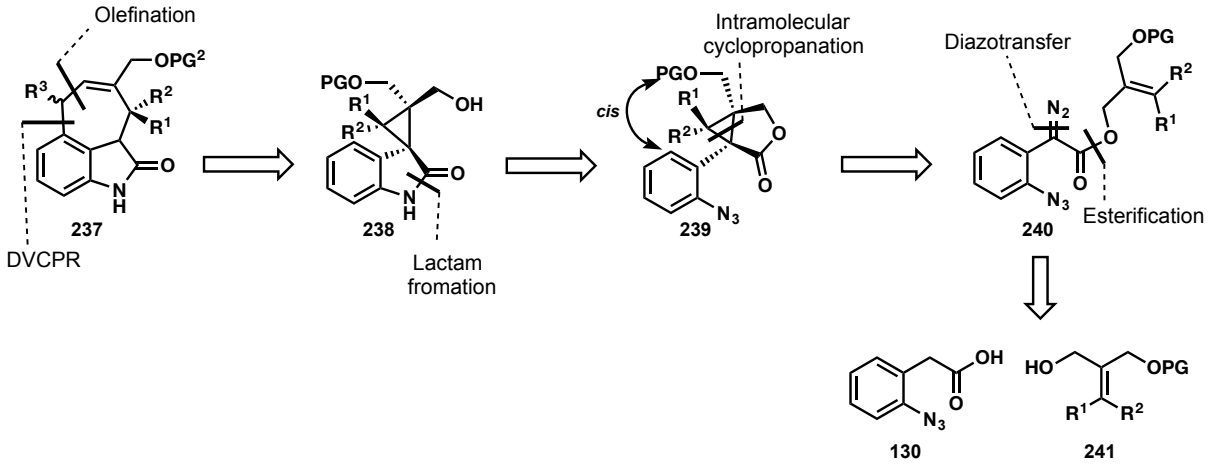
The next step in this methodology was to introduce highly versatile substrates. Cyclopropanes deriving from bis-allylic alcohols (Scheme 54) hold the advantage as they allow to target both, cyclohepta[*cd*]indoles (**234**) and cyclohepta[*b*]indoles (**236**) respectively. This may lead to a unified route in order prepare one substrate addressing two different positions selectively.



Scheme 54. Use of bis-allylic diols for the synthesis of cyclohepta[*cd*]oxindole and cyclohepta[*b*]indoles.

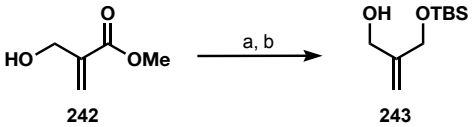
With respect to selectivity problems which appeared while using **231 (**Scheme 54**)** in an intermolecular reaction, the strategy for more complex substrates had to be reconsidered. Also the use of an excess of the diol would be a disadvantage in a synthesis. Therefore, a new route has been developed (Scheme 55) which allows to perform an intramolecular

cyclopropanation reaction, delivering the desired *cis*-olefin **233 (**Scheme 54**)** necessary for the rearrangement.



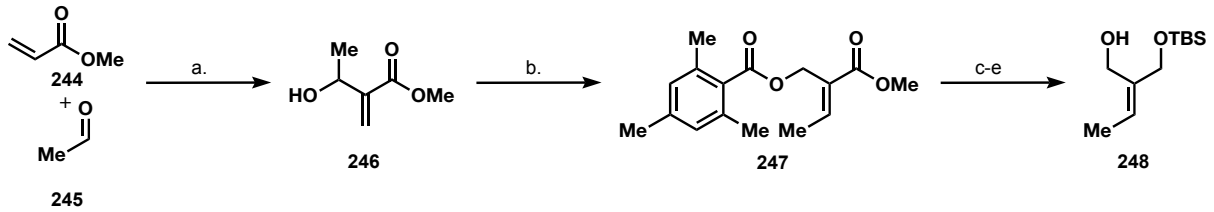
Scheme 55. Retrosyntheic analysis for the use of diols in a selective synthesis.

We decided to prepare two allylic alcohols. Diol **243** (Scheme 56), containing an *exo*-methylene group and **248** (Scheme 57), comprising an alkyl substituent in order to show the selective introduction of substituents into the cyclohepta[*cd*]oxindole **237** (Scheme 53). Following Crimmins' protocol, diol **243** (Scheme 56) could be obtained.[85] TBS-protection of hydroxyacrylate (**242**) and subsequent reduction of the ester provided the diol **243**.



Scheme 56. Synthesis of diol **243**. a. Imidazole (2.5 equiv.), TBSCl (2.5 equiv.) CH_2Cl_2, b. DiBAl-H (3 equiv.), Et_2O, –78 °C, 90% over two steps.

The second diol should have an increased substitution pattern on the cyclopropane. Following the procedure of Gilbert *et. al.* (Scheme 57)[86], the first step was a Baylis-Hillman reaction of **244** and **245**.[86b] Subsequent Mitsunobu reaction[87] using **246** and mesitoic acid yielded *trans* ester **247**. After chemoselective reduction[88] of ester **247** and silylation of the resulting alcohol, the mesitoic acid was cleaved[89] and alcohol **248** has been obtained in good yields.

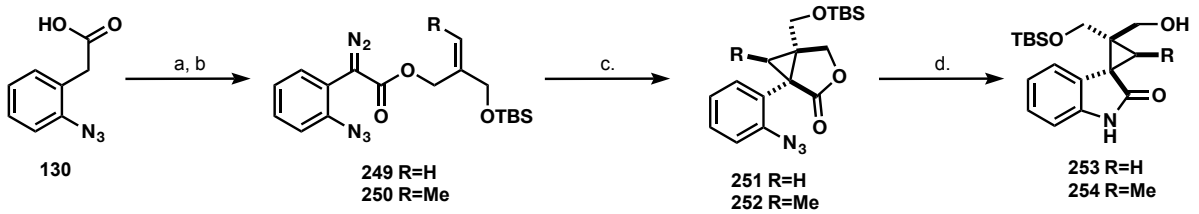


Scheme 57. Synthesis of diol **248**. a. DABCO (5 mol%), 7d, rt., 92%, b. PPh_3 (1.2 equiv.), mesitoic acid (1.2 equiv.), DEAD (1.2 equiv.), THF, –42 °C, 75%, c. DiBAl-H (2.2 equiv.) CH_2Cl_2, –78 °C, d. Imidazole (2.4 equiv.) TBSCl (1.2 equiv.), DMF, 0 °C, 85% over two steps, e. MeLi (3 equiv.), Et_2O, 0 °C, 93%.

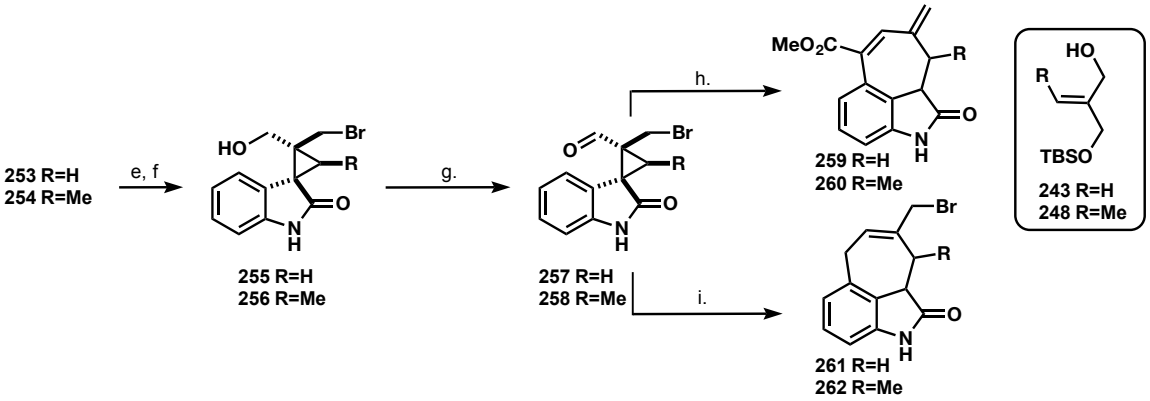
Both substrates could be successfully esterificated and transferred to the α-diazo compound **249**/**250** (Scheme 58). The cyclopropanation delivered solid yields of 74% and 84%. To obtain the *spiro* oxindole we could not carry out the standard procedure. The application of hot acetic acid to a TBS protected primary alcohol to obtain oxindole **238** did not seem practicable. The discriminability of the two alcohols would get lost when the protecting group got cleaved. After screening different reaction conditions (Table 3), entry 8 proved to be the most practible conditions.

Table 3. Conditions used in order to form the oxindole under non-acidic conditions.

Entry	Solvent	Conditions	Temperature	Yield.
1	3:1 THF:H_2O	PBu_3 (1.1 equiv.)	0 °C to rflx	-
2	THF	PBu_3 (1.1 equiv.)	0 °C to rflx	-
3[90]	MeCN	PBu_3 (1.1 equiv.), then Et_3N; DBU	0 °C to rflx	-
4	MeOH	Pd/C, H_2 (25 bar)	rt.	-
5[91]	MeOH, then THF	Pd/C, H_2 (25 bar), then NaH (3 equiv.)	rt. 0 °C to rflx.	20%
6[92]	3:1 THF:H_2O, then THF	PBu_3 (1.1 equiv.) then EtMgBr (4 equiv.)	0 °C	65%
7[93]	9:1 THF:H_2O, then THF	PBu_3 (1.1 equiv.) then *i*-PrMgCl (2.1 equiv.)	0 °C	94%
8[93]	MeOH, then THF	Pd/C, H_2 (25 bar), then *i*-PrMgCl (2.1 equiv.)	rt. then 0 °C	93%



Scheme 58. Selective synthesis of **259**, **260**, **261** and **262**. a. **130** (1 equiv.), 4-DMAP (20 mol%), CH_2Cl_2, b. ABSA (2 equiv.), DBU (3.5 equiv.), MeCN, 86% **250** over two steps, 81% **249** over two steps, c [$(CuOTf)_2PhMe$] (3 mol%), CH_2Cl_2, 74% **252**, 84% **251**, d. Pd/C (10 mol%), H_2 (25 bar), EtOH, then *i*-PrMgCl (2.1 equiv.), THF, 0 °C, 87% **254** over two steps, 93% **253** over two steps.



Scheme 59. CBr_4 (1.1 - 2 equiv.), PPh_3 (1.1 - 2 equiv.), CH_2Cl_2, 0 °C, f. R=Me, TBAF (1.2 equiv.), THF, 0 °C, 72% **256** over two steps; f. R = H HF*pyridine (120 equiv.), pyridine, THF, 0 °C, 77% **255** over two steps, g. IBX (1.2 equiv.), DMSO, h. Ph_3PCHCO_2Me (1.1 - 1.2 equiv.), 45 - 60 °C, 84% **259**/**260** over two steps, i. Ph_3PCH_3Br (2.5 - 4 equiv.), NaHMDS (2.5 – 4 equiv.), –78 °C to 40 °C, 69% **262,** 68% **261** over two steps.

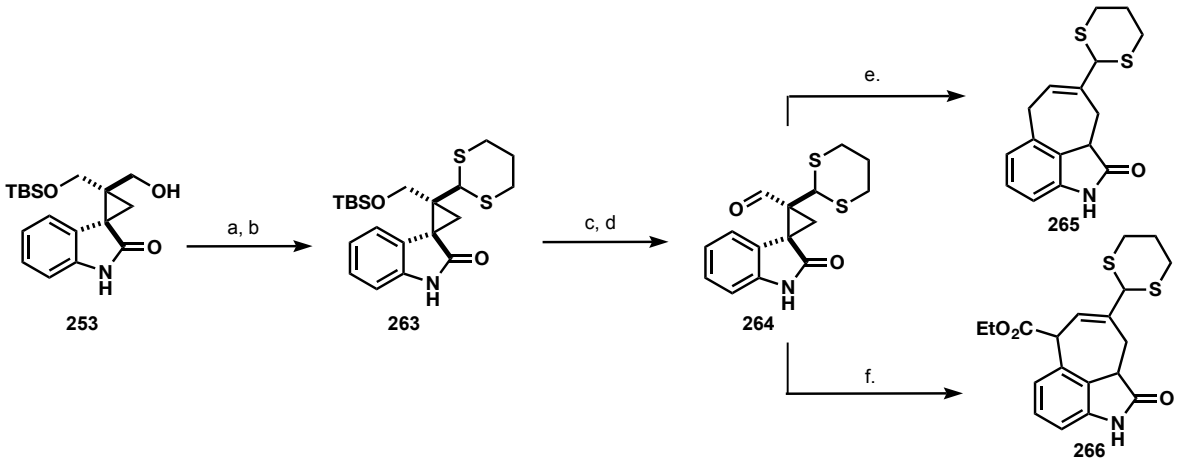
To maintain the discriminability of the two diol positions, the free alcohol (**253**/**254**; Scheme 59) was transferred into the corresponding bromide. Subsequent deprotection of the alcohol and oxidation delivered aldehyde **257**/**258**. After performing the Wittig olefination, the resulting cyclohepta[*cd*]oxindoles (**259**/**260**/**261**/**262**) were obtained in good yields. In case of **259**/**260**, the bromide was eliminated, yielding a 1,6 system.

Since the elimination to the 1,6 system was not intended, we decided to convert the alcohol into a carbonyl group, which would not undergo an elimination reaction (Scheme 60). Starting the synthesis from **253** we had to realise that the oxidation protocol needed to be reconsidered as the formation of many side products was observed applying IBX (Table 4).

Table 4. Oxidation of **253**.

Entry	Solvent	Conditions	Yield	remark
1	DMSO	IBX (1.2 equiv.) 24 h	80%	many side products
2	CH_2Cl_2	DMP (1.25 equiv.), $NaHCO_3$ (10 equiv.)	82%	Purification problems
3	CH_2Cl_2	DMSO, SO_3•pyr., Et_3N	75%	Purification problems
4	CH_2Cl_2	PDC (2 equiv.), 3 Å MS 100 mg/mmol$_{(PDC)}$, 2 h	82%	-

Masking the carbonyl as dithiane (**263**; Scheme 60) revealed a sensitivity of the TBS-alcohol towards Lewis acids. Following the very mild conditions of James' protocol[94] using iodine as Lewis acid led to a mixture of deprotected and decomposed products. Praseodymium triflate proved to be more suitable Lewis acid as it provided **263** in 62% yield.[95]



Scheme 60. a. PDC (2 equiv.), CH_2Cl_2, MS 3 Å, b. HSC_3H_6SH (1.2 equiv.), $Pr(OTf)_3$ (5 mol%), MeCN, 62% over two steps, c. HF•pyridine (120 equiv.), pyridine, THF, 0 °C, d. SO_3•pyr. (4 equiv.), Et_3N (5 equiv.) CH_2Cl_2:DMSO (1:1), 0 °C, 86% over two steps, e. Ph_3PCH_3Br (2.5 equiv.), NaHMDS (2.5 equiv.), THF, –78 to 0 °C, then PhH 50 °C, 71% over two steps, f. α-TMS-ethylacetate (2.6 equiv.), LiHMDS (2.5 equiv.), THF, –78 °C, then C_6D_6 40 °C, 75% over two steps.

The TBS group of **263** (Scheme 60) was cleaved by HF•pyridine and the resulting alcohol was oxidised using Parikh-Doering protocol which provided aldehyde **264**. Tandem Wittig-DVCPR reaction yielded **265** in 71% over two steps. Unexpectedly the Wittig reaction to **266** did not proceed. Applying ethyl-diethylphosphonoacetate under HWE conditions allowed the isolation of **266** in poor yields of 23%. The best result has been achieved under Peterson olefination conditions (see entry 5, Table 5) using α-TMS-ethylacetate and LiHMDS.[96]

Table 5. Olefination of **264**.

Entry	Conditions	Yield	remark
1	Methyl(triphenylphosphoranylidene)acetate (1.1 equiv.), benzene (0.1 M), 60 °C then rflx	-	SM could be re-isolated
2	Methyl(triphenylphosphoranylidene)acetate (1.1 equiv.), DMSO d_6 (0.1 M), 60 °C	-	progress observed by NMR
3	Ethyl diethylphosphonoacetate 2.5 equiv., NaHMDS (2 M in THF, 2.5 equiv.), –78 °C to 50 °C, THF (0.2 M)	23%	-
4	Ethyl diethylphosphonoacetate (4 equiv.), BuLi (2.5 M in hexane, 4 equiv.), –78 °C to 50 °C, 2d, THF (0.2 M)	-	marginal progress
5[96]	TMS-Ethylacetate (2.6 equiv.), LiHMDS (1 M in THF, 2.5 equiv.), THF (0.15 M), –78 °C, then benzene 40 °C, 20h	75%	increased formation of side products above 40 °C

2.4 Summary and Outlook.

Summarising the project, two procedures have been developed providing general access to cyclohepta[*cd*]oxindoles. Most starting materials utilised, are readily accessible using short synthetic procedures. It was possible to introduce different substituents on the oxindole core. Furthermore, by using different dienes and allylic alcohols, the bridging seven-membered ring could be substituted in various positions. C-9 provided the opportunity to introduce different functionalities such as olefins, halogenides and carbonyls into the cyclohepta[*cd*]oxindoles.

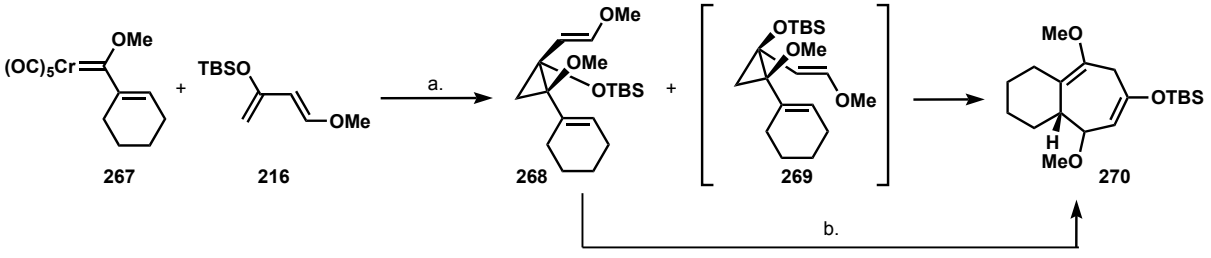
The yields achieved in the one-pot syntheses are acceptable as the substrates are cheap and can be prepared in bulk respectively. The multistep syntheses starting from different allylic diols provided always good yields. With exception of the Peterson olefination all reactions could be carried out on a bench-top without the need of inert gas.

By now the scope is only limited by the accessibility of *cis*-vinylcyclopropanes and the corresponding *E*-olefins. Within this methodological studies, the boundaries of the reaction regarding substitution pattern and functional groups have yet to be discovered.

Both substrates, Danishefsky diene (**216**; Scheme 61) and **217** failed to form the *cis*-diastereomer under the given conditions. In case of **216** the chosen conditions led to vinylcyclopropane rearrangement to yielding *spiro*-compound **221** instead of the bridged system.

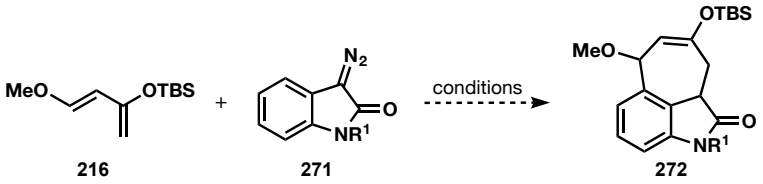
With respect to the prenyl moiety neither **217** nor **229** (Scheme 51) led to the desired *cis*-diastereomer under the chosen conditions, even though one might expect that π-stacking could support the formation of the *cis*-diastereomer during the reaction. Instead both the vinyl group and CH_2OTBS most likely turn out of plane to minimise interactions with the aromatic ring and the catalyst, resulting in the *trans*-diastereomer.

Future endeavours should have a focus on *cis*-selective cyclopropanation of electron rich dienes such as the Danishefsky diene. **216** (Scheme 61) is known to be suitable for cyclopropanation and even DVCPR.[97]



Scheme 61. Cyclopropanation of Danishefsky diene using Fisher carbenes. Following DVCPR works for both diastereomers. a. 25 °C, benzene, 2d, **268** 40%, **270** 23%, b. 90 °C, 3 h, quant.

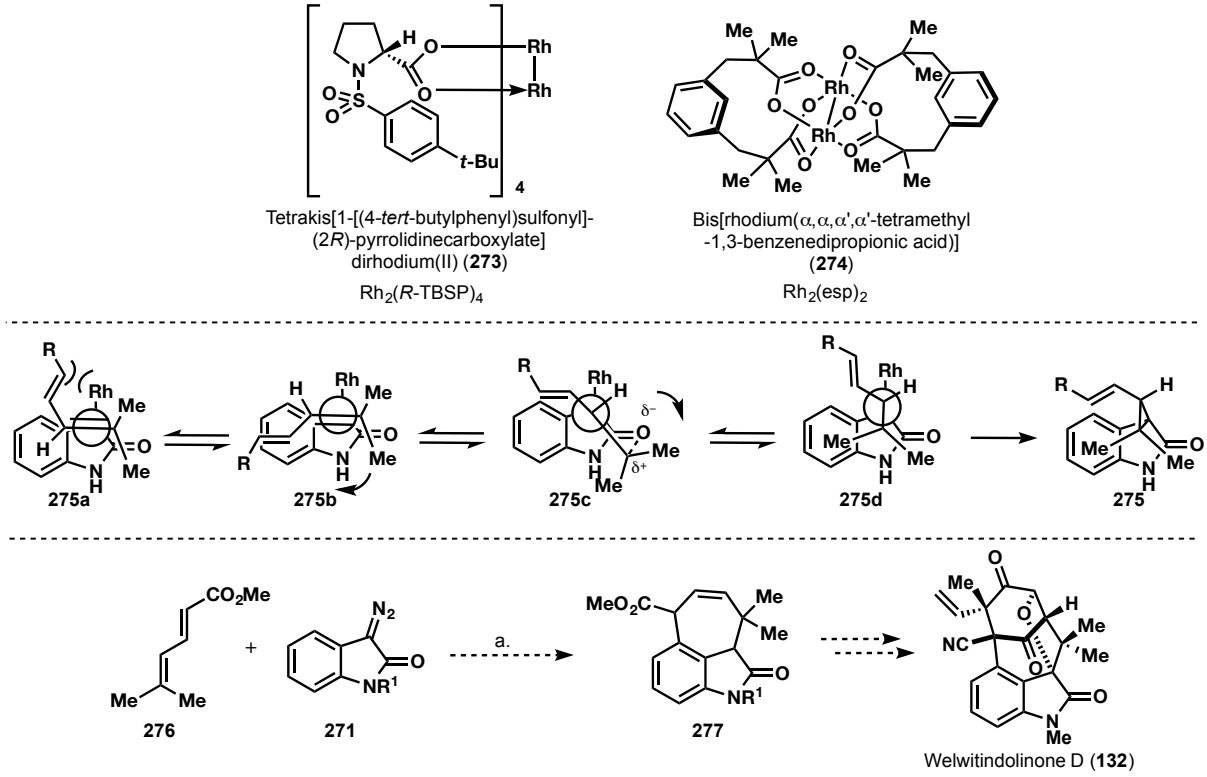
System **272** (Scheme 62) would allow the introduction of functionalities directly at the core utilising an easily accessible substrate. Moreover, the orthogonal protecting groups would also allow to address both functionalities independently.



Scheme 62. Cyclopropanation/divinylcyclopropane rearrangement using Danishefsky diene.

A decrease in reaction temperature and the formation of a stable carbene might lead to the goal of *cis*-Danishefsky cyclopropane. The example of **268** (Scheme 61) shows also that in this case even the *trans*-diastereomer may react to **270**.

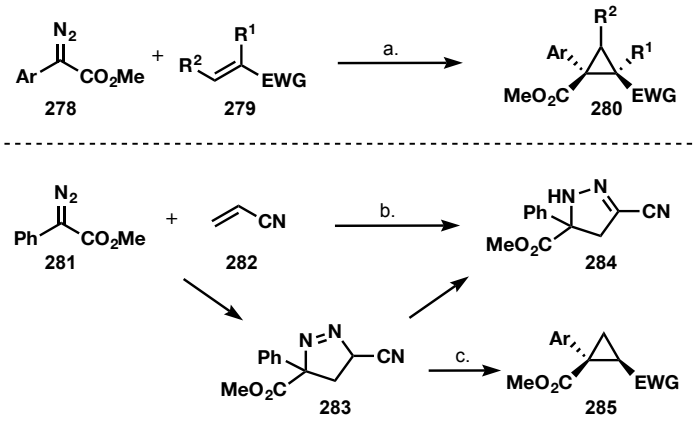
In case of prenyl type olefins, the *cis*-diastereomer might be obtained an increase of the steric demand of the ligands in order to force the vinyl group toward the benzene core (Scheme 63). The prenyl moiety is interesting regarding the total synthesis of Welwitindolinones. Utilising an α,β,γ,δ unsaturated system would provide an easy access to the core structure.



Scheme 63. Theoretical inversion of diastereoselectivity by increasing steric demand of the catalyst. a. Rh_2L (1 mol%), neat or benzene, heat.

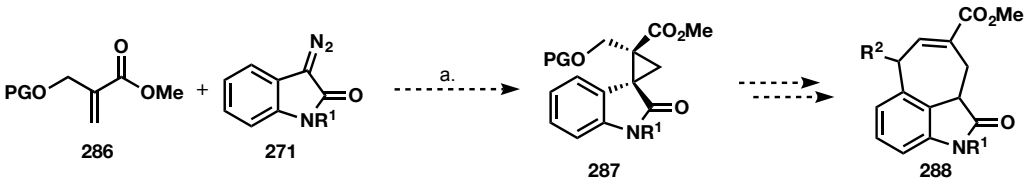
A very interesting field is the selective intermolecular cyclopropanation of allylic diols. This would make the methodology more feasible, since the amount of reaction steps would be minimised.

Two promising methods were published by Wang[98] and Davies.[99] Wang utilised $Pd(OAc)_2$ as catalytical Lewis acid for the cycloproapanation of electron deficient olefins. The cyclopropanation proved to be highly stereoselective (*cis*:*trans* 95:5, Scheme 64).



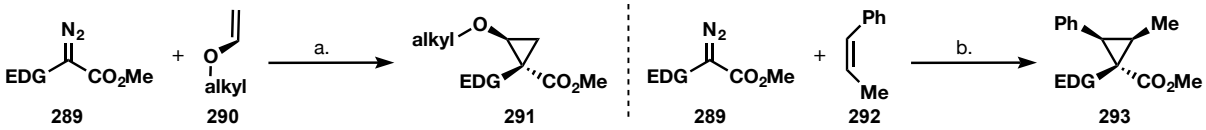
Scheme 64. Wang's Lewis acid catalysed cyclopropanation. a. $Pd(OAc)_2$ (5 mol%), PhMe, 80 °C, b. $Pd(OAc)_2$ (5 mol%), Ligand (6 mol%), DCE, rt., 10d, c. 80 °C.

Diol **286** (Scheme 65) could lead to **287**, where the alcohol is pointing towards the benzene core and the two carbonyls are *cis*-fashioned. The subsequent procedure would be similar to Scheme 58. Deprotection, oxidation and olefination would provide the necessary *cis*-vinyl-cyclopropane which should then undergo the rearrangement providing **288**.



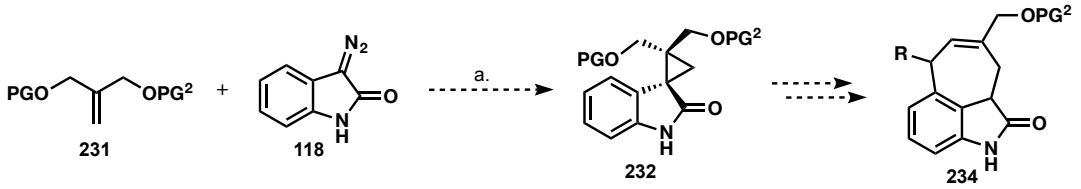
Scheme 65. Wang's route used on oxindole **271**. a. $Pd(OAc)_2$ (5 mol%), PhMe, 80 °C.

The second method to introduce the diols is a thermally induced cycloaddition (Scheme 66). Reacting electron rich olefins under thermal conditions with diazo compounds provides *trans*-cyclopropanes (**291**/**293**) in good yields and diastereomeric ratios up to 19:1.



Scheme 66. Davies thermal cyclopropanation. a. $PhCF_3$, 102 °C, 86:14 dr, 85%, b. $PhCF_3$, 102 °C, 92:8 dr, 72%.

In this case diols such as **231** (Scheme 67) would need orthogonal protecting groups to maintain the discriminability of the two alcohols. This route would also lead to a much shorter synthesis of **232**. Utilising Davies' methodology (Scheme 66) necessitates the investigation of protecting group systems and their influence on the selectivity. In Davies' publication the size of the functional groups does not seem to hamper the selectivity of the reaction. It is very likely that the use of electron rich protecting groups might be the decisive factor with respect to the selectivity.[44]



Scheme 67. Cyclopropanation using Davies conditions. a. $PhCF_3$, 102 °C.

3 5(10⟶9)*Abeo*-Ergoline Project

“What’s wrong with gold?”

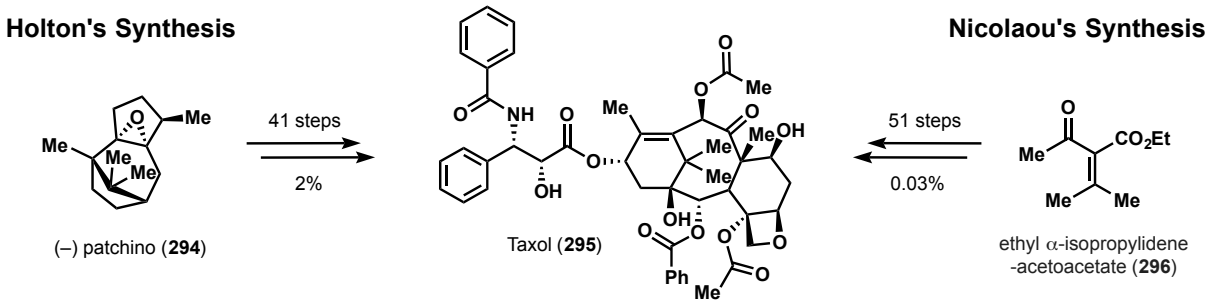
Haihua Liu

3.1 Introduction

3.1.1 *Total synthesis*

Natural product synthesis is a part of organic chemistry dealing with the development of efficient syntheses of naturally occurring compounds. Although these compounds are often pharmacologically active, it is not only their activity that attracts the scientists' interest, but also interesting and challenging structures or structure motifs and the structure elucidation.

The major problem of natural products is their low availability from natural sources. A famous example is Taxol® (**295**, Scheme 68), an anti-cancer drug.[100] In order to obtain one gram of that compound, the bark of twelve Pacific yew trees (*Taxus brevifolia*) is necessary.[101] During the second clinical trial, it became apparent that the amount of bark needed would be a minimum of 30,000 kilogram. Furthermore, it was calculated that annually 360,000 trees would be necessary in order to obtain enough Taxol® (**295**) to treat all malenoma and ovarian cancer cases in the USA. Holton[102] and Nicolaou[103] published their total syntheses of Taxol® (**295**) independently in 1994. Based on Holton's approach, a demand-satisfying industrial semisynthesis of Taxol® (**295**) could be established (Scheme 68).



Scheme 68. The first two total syntheses of Taxol® (**295**) by Holton and Nicolaou.

In general, a total synthesis has to be efficient and the requirements are:

1. keeping the number of steps low
2. avoiding the formation of side-products or the use of highly toxic reagents
3. using catalytic processes
4. using cheap and commercially available starting materials

The definitions were refined and concepts of an ideal synthesis introduced by Hendrickson and Baran.[104] There is even an equation to calculate the "ideality" of a synthesis.

$$\%ideality = \frac{[(no.of\ construction\ rxns) + (no.\ of\ strategic\ redox\ rxns)]}{(total\ no.of\ steps)} \times 100$$

Along with these theoretical reflections, there are two general concepts (Figure 16). The first one is the classic approach in which a great amount of starting material is used in order to get to one target *via* a linear reaction sequence. Most total syntheses are based on this approach. The second approach, the so called divergent approach, is based on a common intermediate that may be used to prepare different natural products, which do not necessarily belong to the same family of natural products. The advantage is evident, as diversification to the different natural products occurs in a late stage of the synthesis and the route to the common intermediate needs be optimised just once for all the natural products derived from.

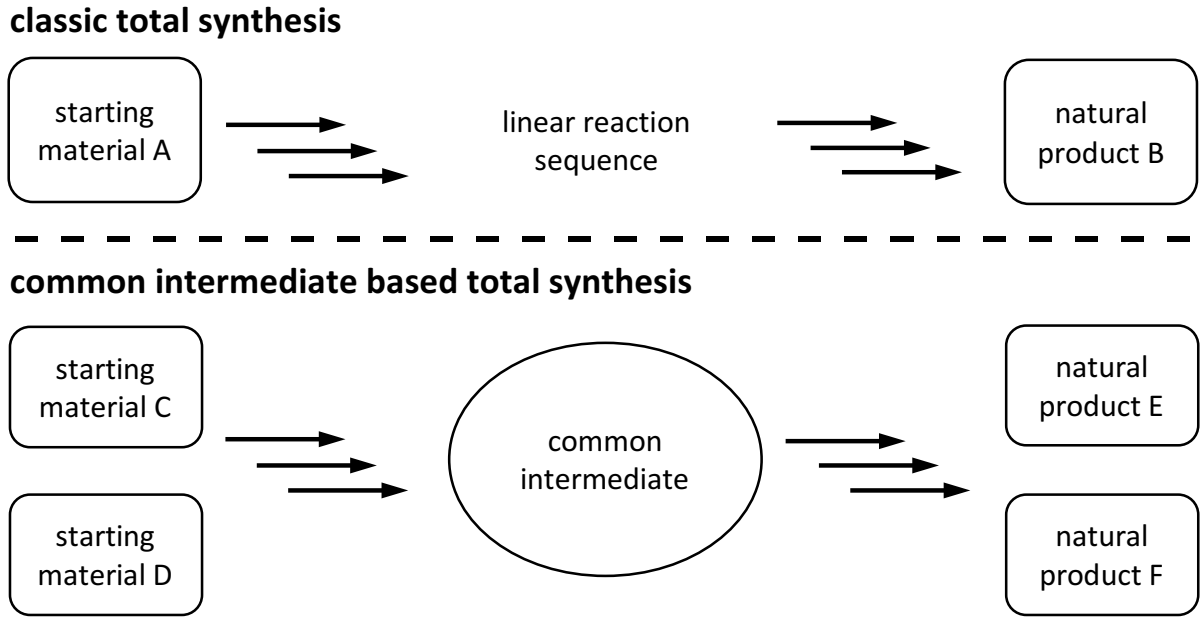
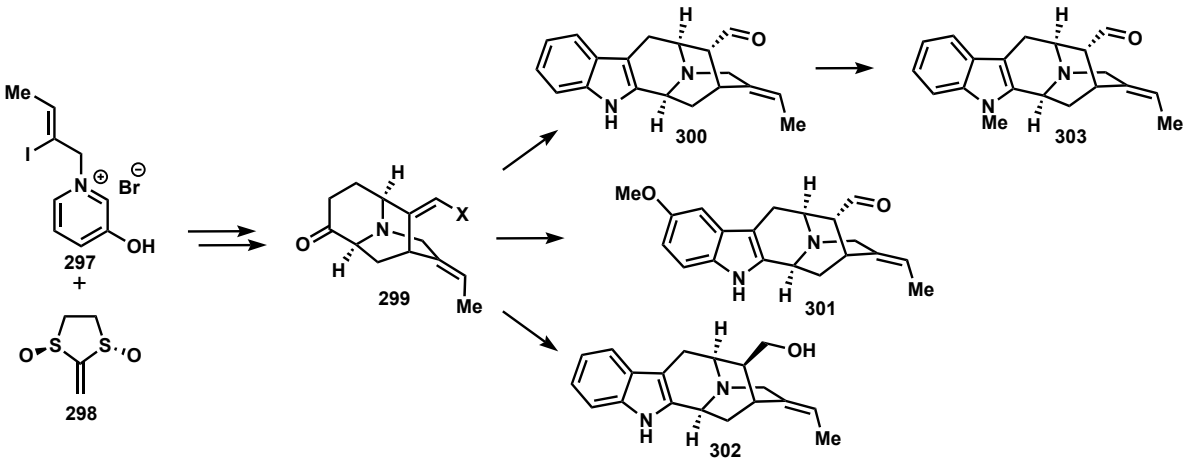


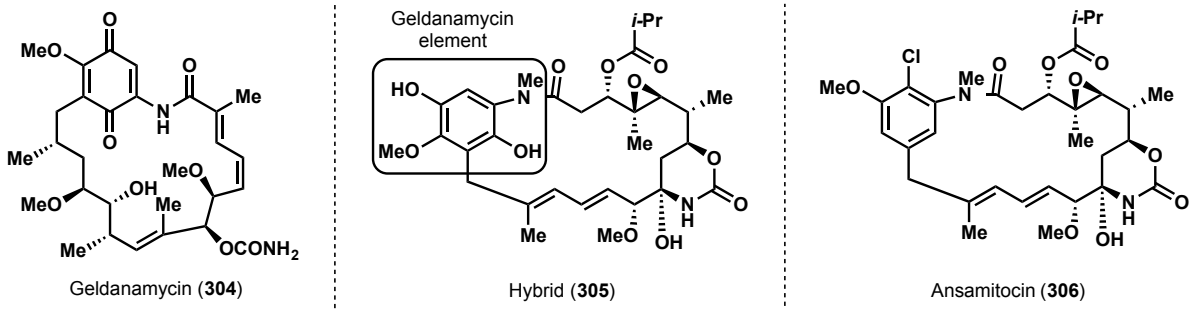
Figure 16. The two general concepts in total synthesis.[105]

A good example for the common intermediate based total synthesis has been published by Krüger.[106] In order to prepare various sarpagine alkaloids, **299** (Scheme 69) was synthesised by a [5+2] cycloaddition and a late stage fisher indole synthesis. Utilising this common intermediate, Krüger was able to complete four different sarpagine alkaloids.



Scheme 69. Krüger's synthesis of sarpagine alkaloids *via* common intermediate.

Another reason for total synthesis is the availability of natural product derivatives, as natural products are often unselective regarding their pharmaceutical profile. Therefore, the variation of functional groups or changes in the molecular structure may increase the selectivity or alter the potency of the derivatives. Furthermore, it is possible to get access to hybrids containing structural features of two or more different natural products. An example for a hybrid product is the ansamitocin hybrid **305** (Scheme 70), containing the aromatic structure of geldanamycin (**304**).[107] It is very unlikely that this product occurs in nature, as the two natural products are produced by different organisms.



Scheme 70. Jürjens' hybrid **305** from ansamitocin (**306**) with the aromatic element of geladanamycin (**304**).

3.1.2 *5(10⟶9)Abeo-Ergoline derivatives.*

As mentioned in chapter one, ergot alkaloids and their derivatives are used to treat pathophysiological disturbances. They all share the tetracyclic core structure that is a common feature of ergot alkaloids. This tetracyclic core contains parts which are related to catecholamines as well as indolethylamines and they react with the monoaminergic recognition sites. Therefore, it is important to prepare derivatives that do not react unselectively with the serotonergic system. The group of Vasari[67] dealt with this topic and focused their research on the development of 5-HT_{1A} ligands. They were able to prepare 21

compounds (Figure 17) derived from methyl-lysergate (**328**) with moderate to high affinity and selectivity for the 5-HT_{1A} receptor.

This receptor is of interest, as it is widely spread in vertebrates and can be found in the cerebral cortex and the hippocampus, such as the raphe nucleus. This serotonin receptor is therefore a good target for drugs to treat anxiety disorders and depression.

Vasari *et al*. prepared all their compounds (Figure 17) by a semi synthetic approach utilising, methyl-lysergate (**328**) as starting material, which can be obtained by fermentation. This allowed them to reduce the total amount of reaction steps. Furthermore, they were able to get their complex and highly functionalised substrates in multi gram scale at relatively low cost.

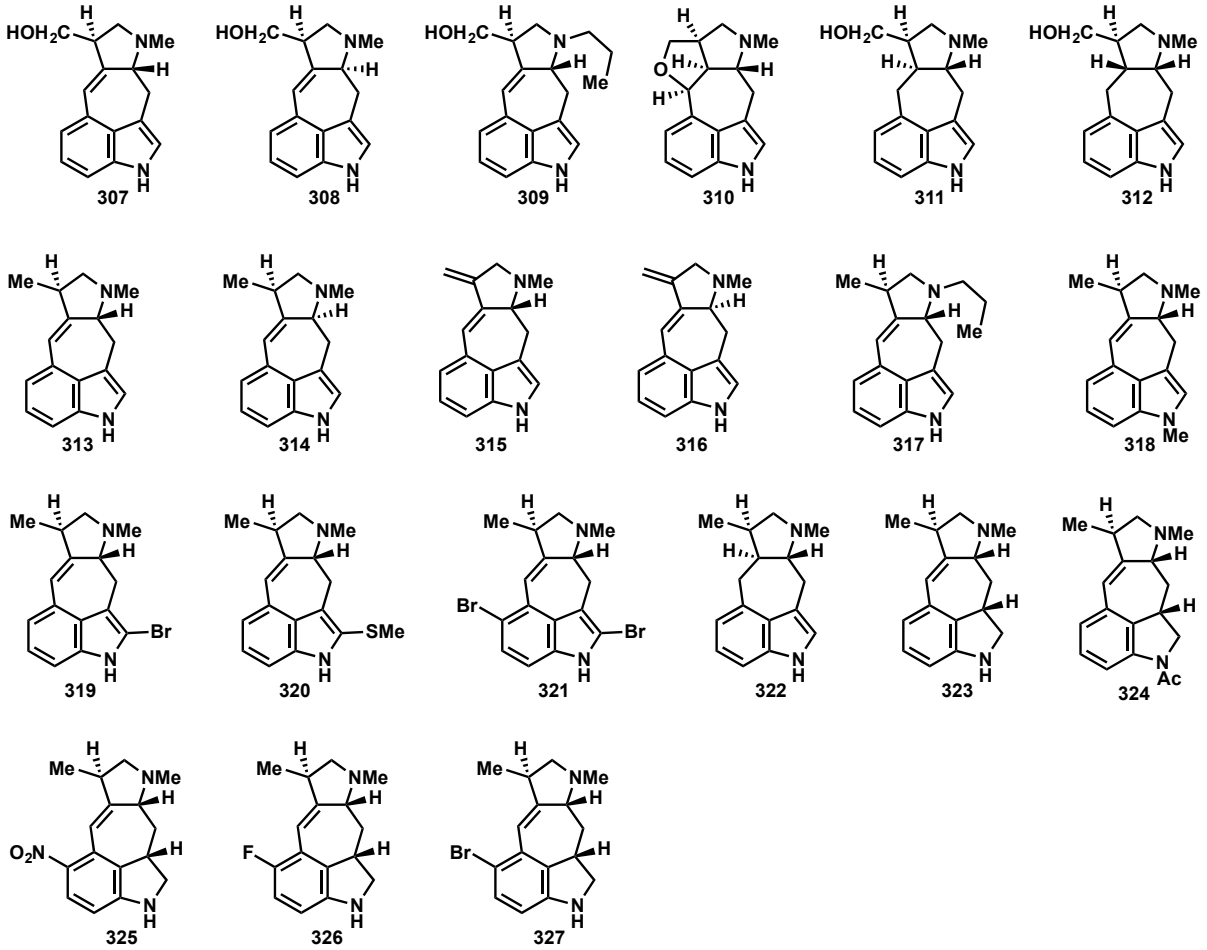
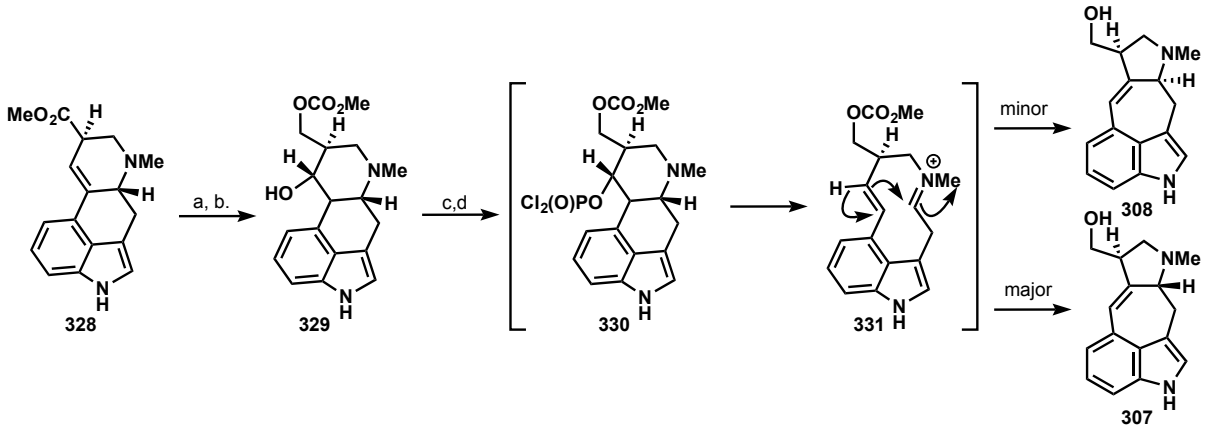


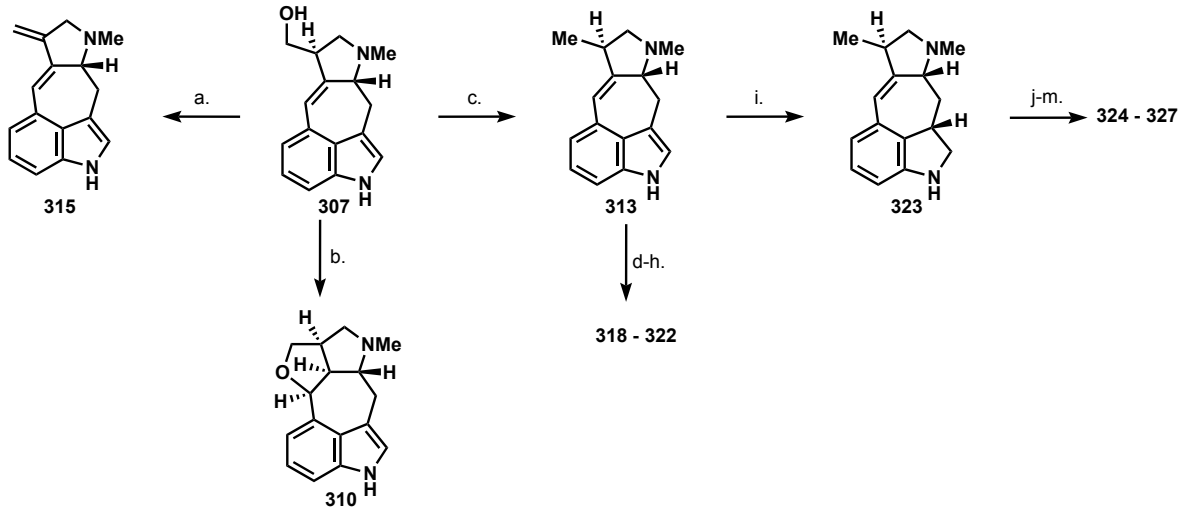
Figure 17. 5(10⟶9)*abeo*-ergoline derivatives.

Starting with **328** (Scheme 71), hydroboration, protection of the primary alcohol and Grob fragmentation led to **331**. When the carbonate was saponificated, **307** and **308** were obtained.



Scheme 71. a. $NaBH_4$, BF_3•OEt_2, THF, –30 °C, then H_2O_2, KOH, THF, 40 – 50 °C, then MeOH, reflux, b. CH_3COCl, pyridine, rt., c. $POCl_3$, pyridine:HCl, pyridine, 40 – 50 °C, d. NaOH, MeOH, rt.

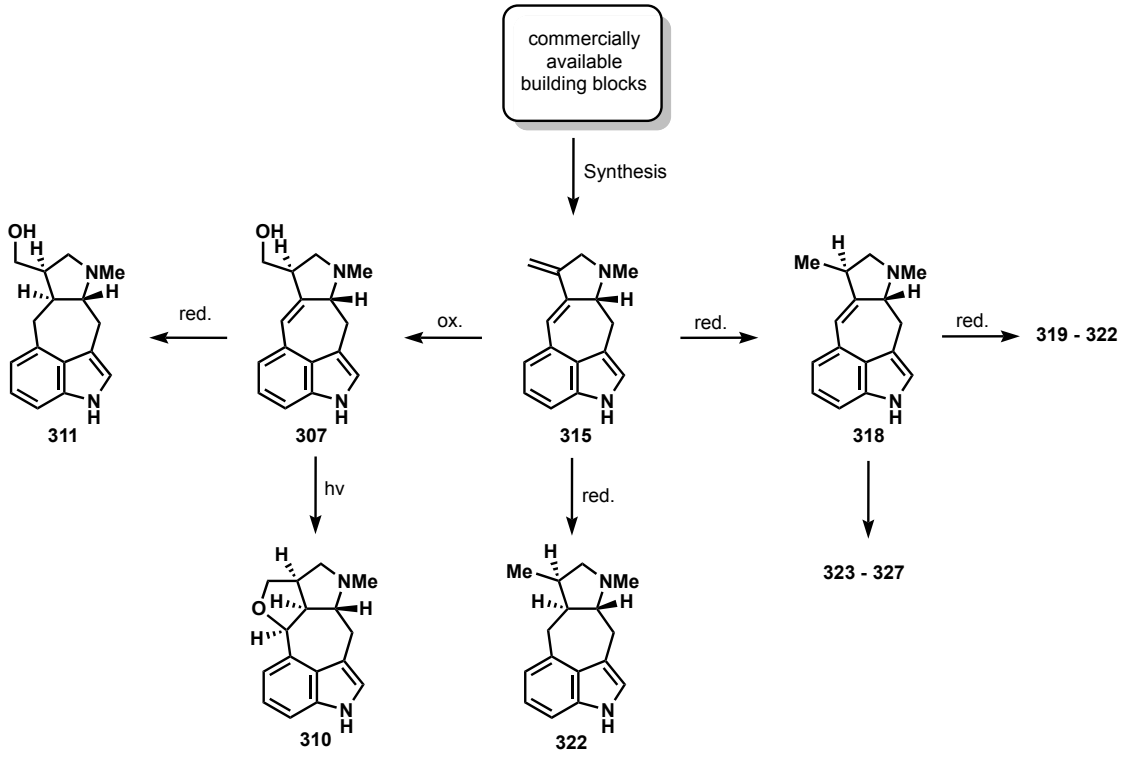
With alcohol **307** (Scheme 72) in hands, they were able to prepare **310**, **313** or **315** in only one reaction step. From **313** four different compounds could be derived. Reduced indole **323** has been the source for further various derivatives.



Scheme 72. a. DBU, DMF, 10 °C, b. MsOH, *i*-PrOH, hv, c. $POCl_3$, pyridine, then $NaBH_4$, DMSO, d. KOH, MeI, DMSO, e.NBS, dioxane, 40 °C, f. MeSSMe, SO_2Cl_2, CH_2Cl_2, –20 °C, then –35 °C, g. Br_2, HOAc, rt. h. Pd/C, H_2; EtOH, i.$NaBH_4$, TFA, 10 °C, j. Ac_2O, pyridine, 50 °C, k. fuming HNO_3, HOAc, rt., then dil. H_2SO_4, reflux,l. $SnCl_2$, EtOH, 70 °C, then $NOBF_4$, CH_2Cl_2, 0 °C, then 120 °C, *o*-dichlorobenzene, then dil. KOH, EtOH, reflux. m. Br_2, HOAc, rt., then dil. KOH, EtOH, reflux.

3.2 Aim of this Project

The aim of this project is a generalised total synthetic approach to the 5(10⟶9)*abeo*-ergoline alkaloids based on the divinylcyclopropane rearrangement. The synthesis should allow the preparation of an advanced intermediate from which a variety of 5(10⟶9)*abeo*-ergoline derivatives can be obtained. In Varasi's semi synthesis alcohol **307** (Scheme 72) is the common intermediate. In this project, compound **315** should be the privileged intermediate. The reason for this intermediate can be seen in Scheme 73. By hydroboration of **315**, compound **310** and **311** can be addressed. Selective reduction of the *exo*-methylene group of **315** will lead to **318** and therefore to nine more products. Reduction of both doublebonds will provide **322**.



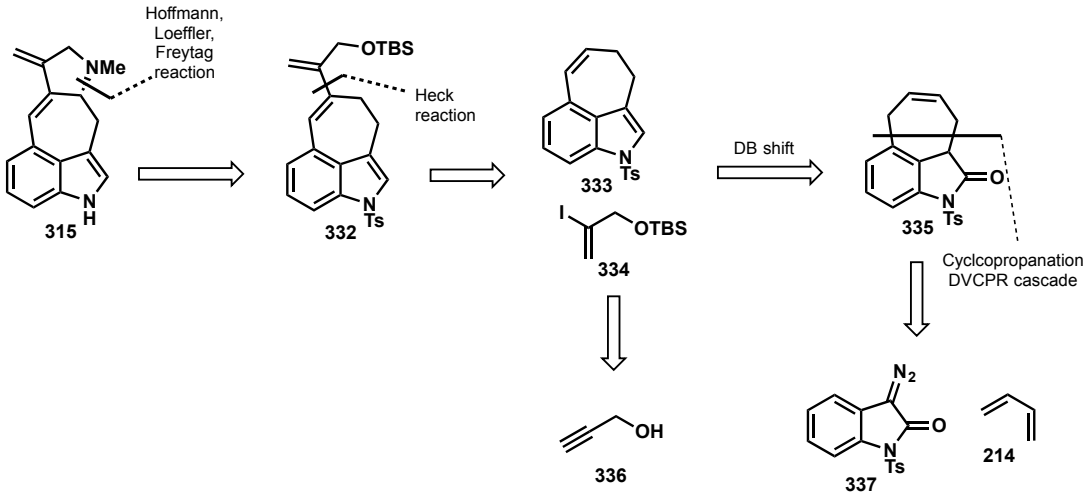
Scheme 73. Advantage of advanced intermediate **315**.

The divinylcyclopropane rearrangement is the preferred method to build up the cyclohepta-[*cd*]indole structure. It allows the introduction of different functional groups which are suitable for further functionalisation, here in particular for the introduction of the pyrrolidine moiety.

3.3 Own Contriutions

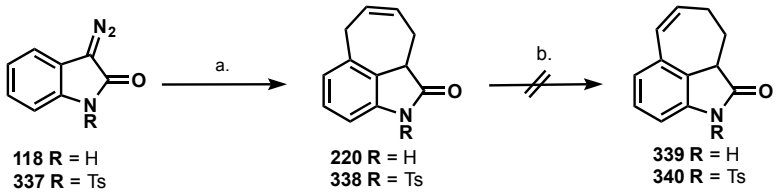
3.3.1 *1st Approach*

The first approach to **315** (Scheme 74) starts with a Hoffmann-Löffler-Freytag reaction[108] of the corresponding amine of **332**. Alcohol **334** should be introduced *via* a Heck coupling to obtain **333**. A decisive step in this retrosynthesis is the shift of the doublebond (DB shift) which is formed in the divinylcyclopropane rearrangement. Cyclohepta[*cd*]oxindole **335** should be obtained *via* cyclopropananation of butadiene (**214**) and diazoisatin **337**, followed by a DVCPR.



Scheme 74. First retrosyntheic approach towards **315**.

The synthesis was started with the cyclopropanation of diazoistaine **337** (Scheme 75) and butadiene (**214**), catalysed by bis-rhodiumtetraacetate. The yields varied between 40% for the unprotected diazo **118** and up to 80% for the tosyl protected derivative **337** (Scheme 75).



Scheme 75. Formation of **220**/**338** and isomerisation of the olefin to **339**/**340**. a. butadiene (10 equiv.), CH_2Cl_2, then DMSO reflux., b. see Table 6.

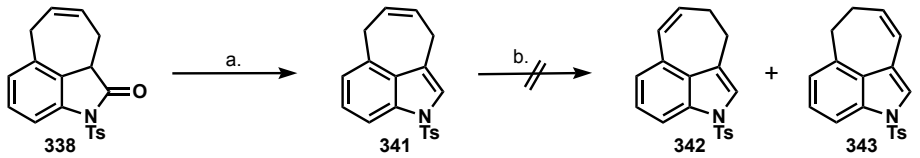
The obtained substrates **220** (Scheme 75) and **338** were exposed to different conditions in oder to obtain the desired products **339** and **340** (Table 6).

Table 6. Conditions and catalysts used for the isomerisation of the olefin.

Entry	Catalyst	Solvent	Conditions	Outcome
1[109]	$RhCl_3$	H_2O/EtOH	room temperature	no reaction
2[109]	$RhCl_3$	EtOH	refluxing	decomposition
3[110]	Howeyda Grubbs II	MeOH	room temperature refluxing	no reaction no reaction
4[111]	$(PPh_3)_3RhCl$	PhH	refluxing	no reaction
5[112]	Rh/Al_2O_3	EtOH	refluxing	no reaction
6[112]	Rh/C	EtOH	refluxing	no reaction
7	Pd/C	EtOH	refluxing	decomposition
8	Pd/C	EtOH	room temperature	no reaction
9[113]	Grubbs II	MeOH	refluxing	no reaction
10[114]	$PdCl_2(MeCN)_2$	CH_2Cl_2	refluxing	no reaction
11[115]	$RuCl_2PPh_3$	PhMe	room temperature	no reaction
12[115]	$RuCl_2PPh_3$	PhMe	refluxing	decomposition
13[116]	$RuCl_2PPh_3$, DIPEA	PhMe	refluxing	decomposition
14	AcOH	THF	refluxing	no reaction
15	DiPEA	MeCN	room temperature	slow decomposition
16	TEA	MeCN	refluxing	decomposition
17	DBU	MeCN	refluxing	decomposition
18[117]	$PdCl_2(PhCN)_2$	PhH	refluxing	no reaction
19[118]	$RhCl(PPh_3)_3$, DABCO	EtOH 10%	refluxing	no reaction
20[119]	$Ni(P(OEt)_3)_4$	MeOH, H_2SO_4	room temperature	decomposition
21[120]	Crabtree	THF	room temperature	no reaction

However, after extensive experimentation, we were not able to shift the double bond into conjugation. It did not matter if the oxindol was protected or not. To exclude the reactivity of the oxindole C-3, we decided to repeat the experiments using the corresponding indole **341**

(Scheme 76). It was expected that this conversion would deliver product mixtures (**342, 343**) depending on whether the doublebond shifts in conjugation with the benzene core or the pyrrole of the indole.



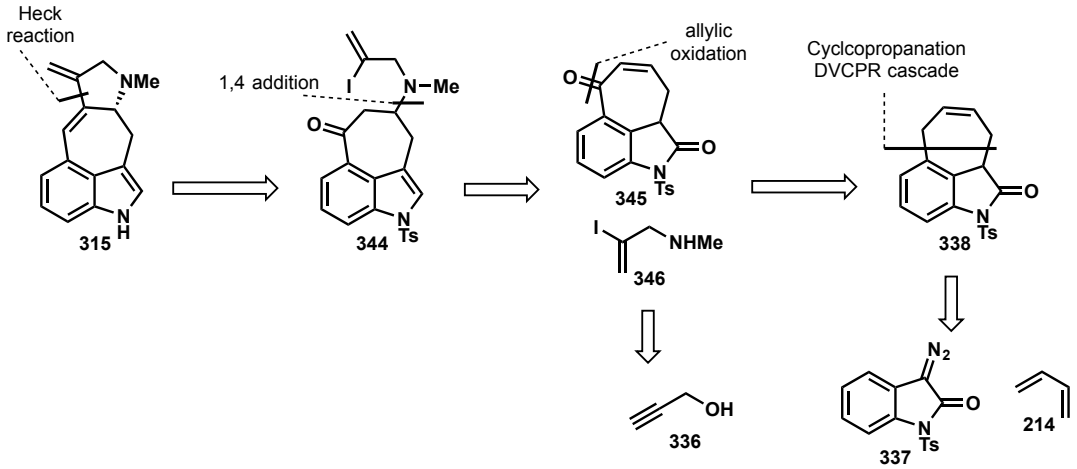
Scheme 76. Expected isomerisation of the alkene using indole **341**. a. $NaBH_4$ (2 equiv.), MeOH:THF 0 °C, then TFA in CH_2Cl_2, 0 °C, 84%, b. see Table 6.

Disappointingly, the examination delivered the same result as the screening using oxindole **338** (Table 6) neither did it shift into the one nor into the other position.

Since we were not able to shift the double bond into conjugation, a different approach needed to be found.

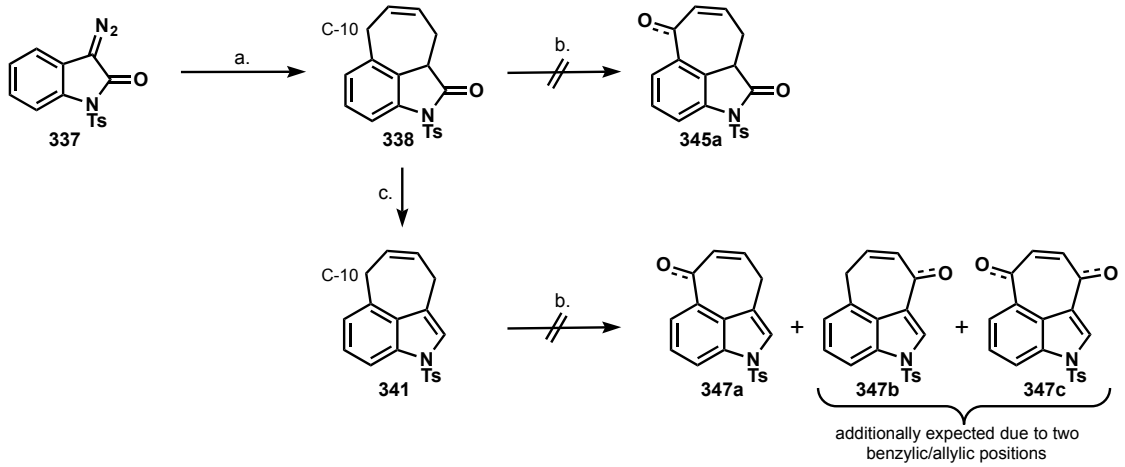
3.3.2 *2nd approach*

Based on the easily accessible starting material **338** (Scheme 77), the retrosynthesis was redesigned. The first step of this retrosynthesis is the Heck reaction which is supposed to close the pyrrolidine ring. The β-hydride elimination should recreate the double bond on the seven-membered ring (**315**). A 1,4 addition of **345** and **346** should introduce the tertiary amine to obtain **344**. The ketone has to be eliminated afterwards by reduction and treatment with trifluoroacetic acid to obtain the system necessary for the Heck reaction. Amine **346** will be obtained from propargylic alcohol (**336**) *via* a literature known procedure. Allylic oxidation of the DVCPR product **338** is supposed to deliver the α,β-unsaturated ketone **345**. Cyclohepta-[*cd*]oxindole **338** should be obtained *via* a cyclopropanation and subsequent divinyl-cyclopropane rearrangement using **337** and **214**.



Scheme 77. 2nd retrosynthetic approach towards **315**.

Since the reagents for the allylic oxidation could also attack the unprotected nitrogen of the oxindole, tosyl protected substrate **337** (Scheme 78) should be used exclusively. As in the first approach, we started with the cyclopropanation of **337** with butadiene (**214**) followed by DVCPR to receive **338**. With **338** in hands, the product was exposed to different reagents and catalysts (Table 7) in order to perform an allylic oxidation. We expected the allylic/benzylic C-10 position of the cyclohepta[*cd*]oxindole **338** to undergo the oxidation.



Scheme 78. Preparation of DVCPR product **338**, formation of indole **341** and subsequent allylic oxidation. a. butadiene (10 equiv.), CH_2Cl_2, $Rh_2(OAc)_4$ (1 mol%), then DMSO 110 °C, 54%. b. see Table 7, c. $NaBH_4$ (2 equiv.), THF:MeOH 0 °C, then TFAA CH_2Cl_2, 84%.

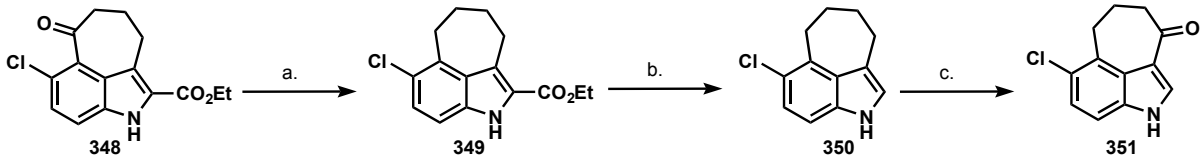
Table 7. Conditions used for allylic oxidation of **338** and **341**.

Entry	Conditions	Outcome
1[121]	SeO_2 (6.3 equiv.), TBHP, CH_2Cl_2. rt.	n.r.
2[122]	SeO_2 (2.2 equiv.), KH_2PO_4 (3.2 equiv.), PhMe, rflx.	decomp.
3[123]	SeO_2 (3 equiv.), dioxane, rflx.	decomp.
4[124]	SeO_2, (1.2 equiv.) PNO (4 equiv.), dioxane, 90 °C	decomp.
5[125]	CrO_3 (20 equiv.) 3,5-DMP (20 equiv.), –25 °C, CH_2Cl_2	decomp.
6[126]	Ph_2Se_2 (10 mol%), $PhIO_2$ (3 equiv.), Pyridine (10 equiv.), PhCl, 100 °C	decomp.
7[127]	CrO_3 (10 equiv.), AcOH	decomp.
8[128]	CrO_3 (18 equiv.), pyridine (38 equiv.),4 Å MS, CH_2Cl_2, 0 °C to rt.	decomp
9[129]	PIFA (3 equiv.), TBHP (2 equiv.), Cs_2CO_3 (4 equiv.), 4 Å MS, EtOH, –78 °C to 0 °C	n.r.

10[130]	$RuCl_3$ xH_2O (1 mol%), TBHP, cychohexane, water, rt.	n.r.
11[131]	$Mn(OAc)_3$ (35 mol%), TBHP (5 equiv.), 4 Å MS, O_2, EtOAc, rt.	n.r.
12[132]	Pd/C (2.5 mol%), TBHP (2.5 equiv.), K_2CO_3 (25 mol%), CH_2Cl_2, 0 °C	n.r.
13[133]	$Pd(OH)_2$ (5 mol%), TBHP (5 equiv.) K_2CO_3 (0.5 equiv.), CH_2Cl_2, rt.	n.r.
14	$Pd(OH)_2$ (2 equiv.), K_2CO_3 (0.5 equiv.), CH_2Cl_2, rt	n.r.
15[134]	PDC (4 equiv.), TBHP (4 equiv.), PhH, rt.	decomp.
16[135]	IBX (3 equiv.), DMSO, flourobenzene, 85 °C	decomp.
17[136]	DDQ (1.3 equiv.), acetone, water, 0 °C	n.r.

Contrary to the expectations, mostly decomposition products were obtained. In one case a mixture of three different products could be isolated, but only one of them contained a ketone which could not be separated. To exclude the oxidation of oxindole C-3, the series was repeated utilising corresponding indole **341** (Scheme 78).

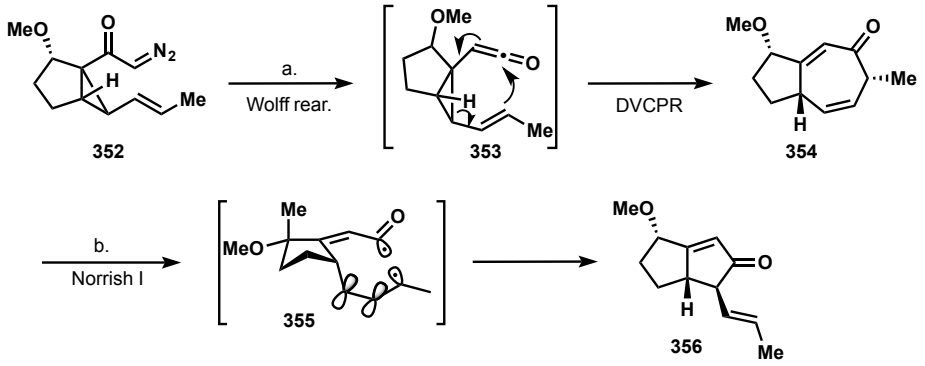
Similar to the first approach, indole **341** was expected to deliver more than one oxidation product due to the two allylic/benzylic positions. It emerged that also indole **341** was not suitable for the allylic oxidation, as only decomposition could be observed. We were surprised by these results, as Li *et al*. (Scheme 79) reported the benzylic oxidation of cyclohepta-[*cd*]indole **350** employing DDQ.[137]



Scheme 79. Li's allylic oxidation with DDQ. a. Et_3SiH, TFA, rt, 95%, b. LiOH, H_2O, MeOH, reflux, then $Cr_2Cu_2O_5$, quinolone, 200 °C, 85% c. DDQ, THF, H_2O, 0 °C, 91%.

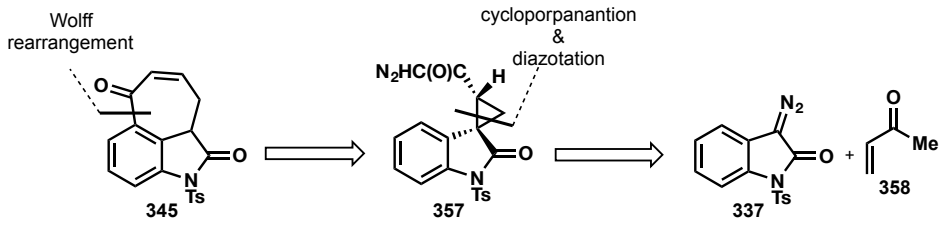
As the oxidation did not deliver the desired Michael system we had to reconsider the retrosynthetic analysis and try a different approach in order to obtain the unsaturated ketone **345** (Scheme 77).

In this case we wanted to prepare an α-diazoketone which should undergo a Wolff-rearrangement similar to the reaction cascade shown by Stoltz *et al.* (Scheme 80).[138] In absence of a nucleophile, the ketene undergoes the DVCP-rearrangement to deliver 1,4 system **354**.



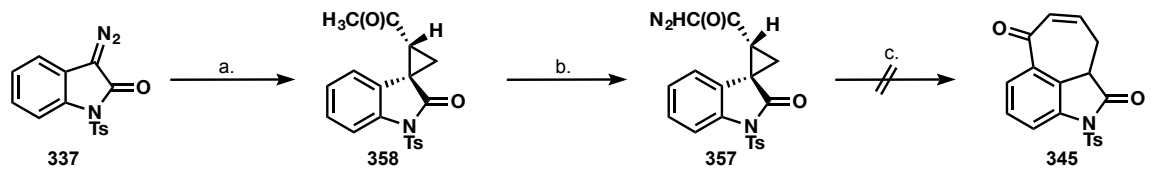
Scheme 80. Tandem Wolff-Cope rearrangement with an option for a Norrish type I reaction. a. AgOBz (10 mol%), Et_3N (1 equiv.), THF, 45 °C, ultrasonic sound; alternative hv, 254 nm, THF, rt., b. hv 310 nm, PhH, rt, 72%.

The revised retrosynthesis needed just a few alternations. Ketone **345** (Scheme 81) should be obtained by the Wolff-DVCPR tandem reaction of **357**. The cyclopropanation of MVK **358** and **337** followed by a diazo transfer reaction α-diazoketone **357** should be received.



Scheme 81. Variations of the retrosynthesis for the Wolff-Cope tandem reaction.

The first reaction in this sequence was the literature known, thermally initiated cyclopropanation of MVK (**358**; Scheme 82) and diazo compound **337**.[139] The desired *cis*-ketone **358** could be separated and obtained in 60% yield. Preparation of diazo compound **357** proved to be difficult, since only freshly distilled THF and freshly prepared LiHMDS led to satisfying results.[140] In a first reaction the LiHMDS forms the enol which is acylated by trifluoroethyl trifluoroacetate (TFETFA). Addition of MsN_3 and TEA delivered α-diazo ketone **357** in 70% yield.



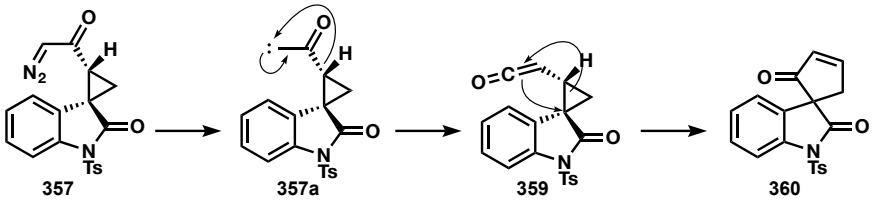
Scheme 82. a. MVK **358** (3 equiv.), 95 °C, 10 min. 95% total yield, b. HMDS (1.3 equiv.), THF, –78 °C, *n*BuLi (1.3 equiv.), then THF $CF_3CO_2CH_2CF_3$ (1.4 equiv.), then Et_3N (10 equiv.), MsN_3 (3 equiv.), THF 16 h, 70% at 2 mmol scale, c. see Table 8.

With the desired product **357** in hands, different Wolff rearrangement conditions were examined (Table 8).

Table 8. Reaction conditions used on **357** in order to undergo a Wolff, DVCP rearrangement cascade.

Entry	Conditions	Product	Outcome
1[141]	PhMe, 70 °C, 24 h	-	no reaction
2	PhMe, 140 °C, sealed tube, 24 h	-	no reaction
3[142]	$Rh_2(OAc)_4$ (2.5 mol%), CH_2Cl_2, rt.	-	decomposition
4[138]	AgOBz (10 mol%), Et_3N (3 equiv.), THF, U/S, 45 °C	**360**	75%
5[138]	AgOBz (20 mol%), THF, U/S, 45 °C	-	no reaction
6	Ag_2O (20 mol%), THF, 20 to 50 °C	-	no reaction
7	Ag_2O (10 mol%), Et_3N (3 equiv.), THF, U/S, 45 °C	**360**	53%
8[143]	$Cu(OTf)_2$ (5 mol%), cyclohexane, rt	-	no reaction
9[143]	$Cu(OTf)_2$ (5 mol%), cyclohexane, rflx.	-	decomposition
10[144]	$AgNO_3$ (1.05 equiv.), THF, rt.	-	decomposition
11[145]	$[(CuOTf)_2PhMe]$, CH_2Cl_2, rt.	-	no reaction
12[145]	$[(CuOTf)_2PhMe]$, CH_2Cl_2, 40 °C	-	decomposition
13[138]	h*v*, 254 nm, PhH	-	decomposition

Only the conditions of entry 4 and 7 (Table 8) delivered an isolable product. After extensive NMR analysis, we were able to elucidate the structure of the Wolff product (Scheme 83). It appeared that the Wolff rearrangement took place without subsequent Cope rearrangement. Instead a vinyl cyclopropane rearrangement provided **360**.

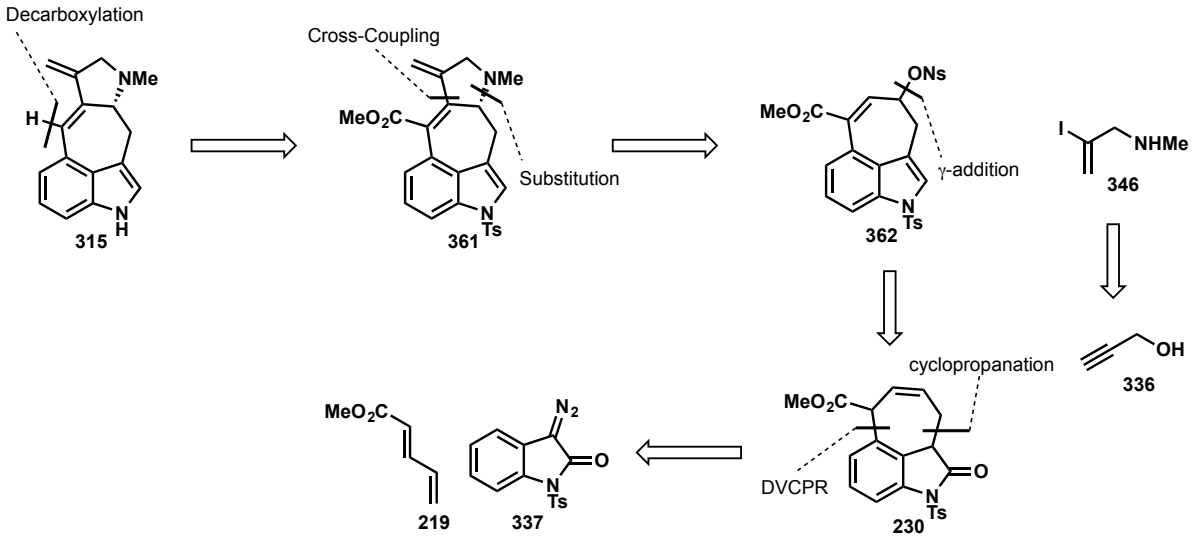


Scheme 83. Vinyl cyclopropane rearrangement to *spiro*-oxindole **360**.

We suggested that the *spiro*-oxindole **360** might be an intermediate of the alkylation into C-4, wherefore **360** has been exposed to elevated temperatures of 200 °C. Unfortunately, compound **360** proved to be very stable and we had to establish another approach.

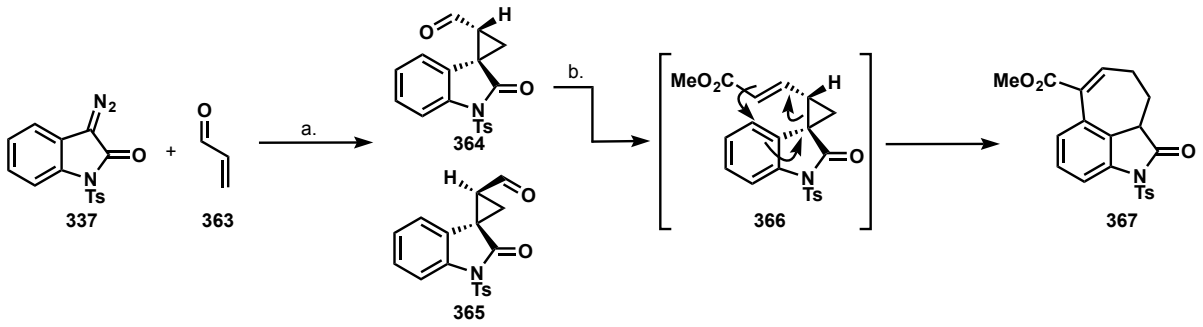
3.3.3 *3rd approach*

During the first two synthetic approaches, we had to learn, that the basic functionalisation of the core system is not as straightforward as expected. We decided to switch to a system containing an ester functionality, even though it meant an increase of synthetic steps. The key feature of this synthesis is a γ-functionalisation (**362**, Scheme 84),[146] successive substitution and a cross coupling reaction to obtain pyrrolidine **361**. Subsequent decarboxylation should provide the desired product **315**. Cyclopropanation of **337** and **219** and successive DVCPR should yield **230**. Reduction and elimination should provide the precursor of the γ-functionalisation.



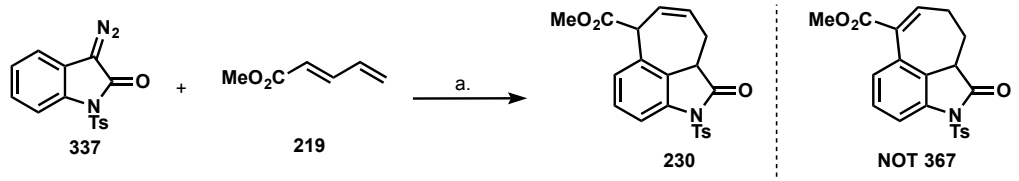
Scheme 84. 3rd retrosynthetic analysis.

The synthesis started with the preparation of aldehyde **364** (Scheme 85) as the distinguishability of the two aldehydes is less difficult compared to the corresponding ester. To avoid the longer route *via* the allylic alcohol, a thermally induced cyclopropanation based on Subba Reddy's protocol was applied.[139] Instead of MVK **358**, acrolein (**363**) was heated to 95 °C. Cyclopropylaldehydes **364** and **365** were obtained in 83% in a 3:2 ratio in favour of the desired *cis*-cyclopropylaldehyde **364**. The following Wittig reaction was performed in DMSO since this solvent allowes a subsequent DVCPR at elevated temperatures. Contrary to the expectations, the olefin in the resulting product **367** has shifted into conjugation. Nevertheless, the conjugated system should not hamper the following γ-functionalisation, as LDA should be able to deprotonate an allylic position.



Scheme 85. First synthesis of **367** with unexpected doublebond shift. a. acroleine (**363**; 3 equiv.), 95 °C, 83%, 3:2 ration **364:365**, b, Ph_3PCCO_2Me (1.2 equiv.), PhH, rflx .70%.

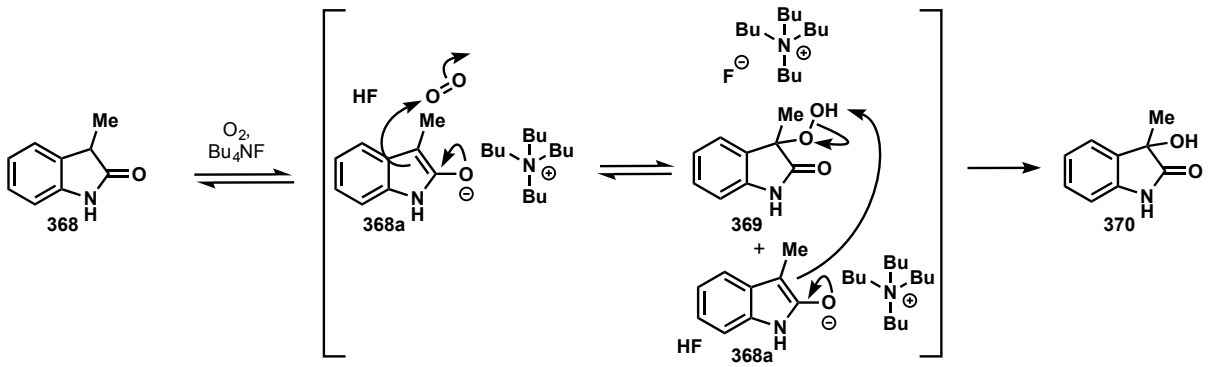
Knowing that the ester **366** (Scheme 85) rearranges to the desired product, diene **219**[147] was prepared and the cyclopropanation reaction has been performed in benzene (Scheme 86). The resulting product **366** was obtained in 79% yield in a 7:1 ration in favour of the *cis*-diastereomer. Subsequent DVCPR in DMSO yielded in 58% cyclohepta[*cd*]oxindole **230**. Surprisingly, the olefin in the resulting product did not shift into conjugation.



Scheme 86. Preparation of **230** *via* tandem cyclopropanation/DVCPR.

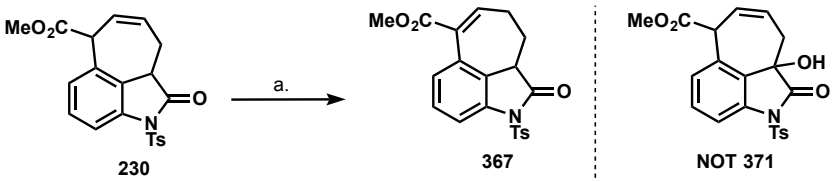
Nevertheless, we wanted to know what caused the olefin shift at this point. The only difference between the two DVCPR was that the Wittig route contained Ph_3PO and Ph_3PCHCO_2Me. To examine whether the olefin could be shifted into conjugation with these reagents or not, **230** (Scheme 86) was exposed to the reagents in three experiments. The first contained Ph_3PO (1 equiv.), the second Ph_3PCHCO_2Me (1 equiv.) and the third a mixture of both reagents in a 1:1 mixture in DMSO. In all three cases, we were not able to observe a shift of the doublebond. In addition, the variation of equivalents and increased temperature had no influence.

To avoid the reactivity of C-3 of the oxindole, we decided to block that position by oxidation. A very easy and selective method to oxidise oxindoles at C-3 is the use of catalytic amounts of TBAF and air (Scheme 87).[148] The resulting hydroxyl functionality should then be protected.



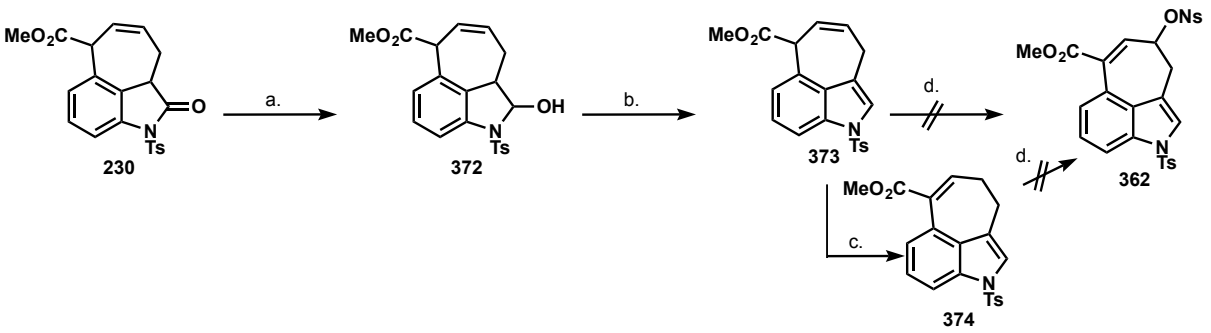
Scheme 87. TBAF catalysed C-3 oxidation.

When the oxidation reaction was performed, a slight decrease of polarity and the complete conversion of the substrate could be observed in about two minutes. After workup, product **367** was obtained in 74% yield (Scheme 88). Contratry to the expectations, the proton at C-3 remained. Comparing the NMR results with those of the tandem Wittig-DVCP-reaction (Scheme 85) displayed the shift of the olefin into conjugation. The nonappearance of the oxidation seems reasonable in this case, as freshly distilled THF has been used which contained no oxygen and the isomerisation proceeded much faster than oxygen could dissolve in THF.



Scheme 88. TBAF initiated doublebond shift.

Since we wanted to keep the doublebond in that position, an oxidation was no option anymore. In order to discard the oxindol C-3 position indole **373** (Scheme 89) was prepared. In this case, only $NaBH_4$ was suitable for the reduction of oxindole **230**, while most of the other reagents would unselectively react with both, the ester and oxindole. The resulting hemi aminal **372** was then treated with $BF_3 \bullet OEt_2$[149] in THF at room temperature. The resulting indole **373** was then exposed to the nosylation conditions (Table 9).



Scheme 89. Formation of indole **373** and its exposition to nosylation conditions. a. $NaBH_4$ (2.2 equiv.), –30 °C, THF:MeOH (6:1), b. BF_3*OEt_2 (2 equiv.), MeCN, 94% over two steps, c. TBAF, THF, 65%, , d. see Table 9.

Since **362** (Scheme 89) could not be obtained, we decided to use different conditions for the enolisation (Table 9). Ester **373** was also treated with TBAF to obtain 1,4 system **374** which was also subsequently exposed to the γ-functionalisation conditions (Table 9).

Table 9. Attempts to obtain a silylenolether using **373** and **374**.

Entry	Conditions	Outcome
1[146b, 150]	HMPA, LDA (1.1 equiv.), THF, –78 °C, TMSCl (2 equiv.), then EtOAc, *p*NBSP (1 equiv.), $ZnCl_2$ (1.2 equiv.)	no reaction
2[151]	HMPA, LDA (1.1 equiv.), THF, –78 °C, TMSCl (2 equiv.)	no reaction
3[152]	KHMDS (1 equiv.), THF, –78 °C, TMSCl or TBSCl (1 equiv.)	no reaction
4[153]	LDA (1.1 equiv.), THF, 0 °C to –78 °C, TBSCl (1.1 equiv.), HMPA (2.2 equiv.)	no reaction
5[154]	TMSOTf or TBSOTf (1.3 equiv.), CH_2Cl_2, 0 °C to rt.	no reaction
6[155]	NaHMDS (1.5 equiv.), TBSCl or TBSOTf (2 equiv.), THF, –78 °C	no reaction

Unfortunately, nosylation product **362** (Scheme 89) was not obtained and we had to examine whether this is an enolisation or a reagent problem. Therefore, ethyl crotonoate was transferred into the corresponding silylenol ether and then exposed to the nosylation conditions. The results were the same as R. V. Hoffman[146b] published for the test system. It appeared that we had a general problem regarding the silyl enolether which proved to be very instable. The substrate decomposed before the reaction could be performed.

To determine the general feasibility to functionalise **373** and **374**, they were exposed to different conditions (Table 10).

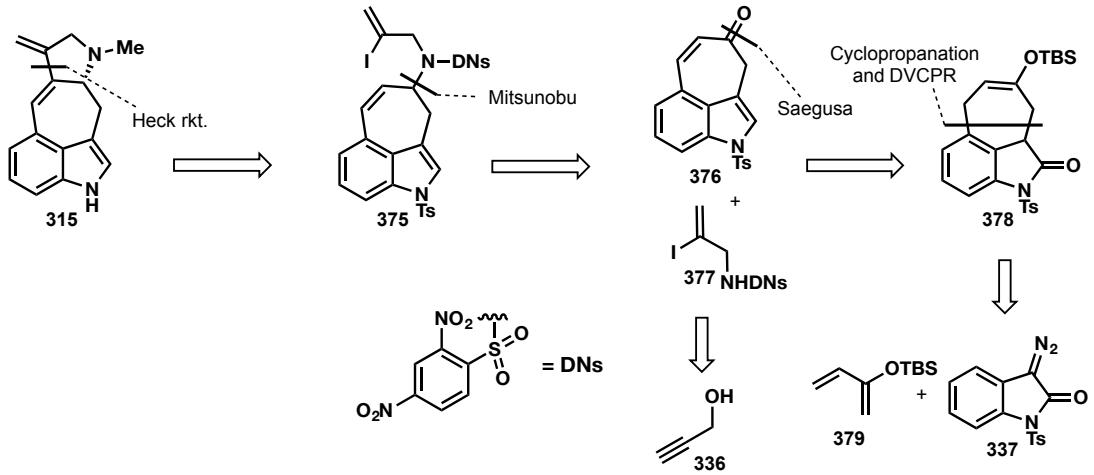
Table 10. Conditions, in order to functionalise **373** and **374**.

Entry	Substrate	Conditions	Outcome
1[156]	**374**	AIBN, NBS (1.1 equiv.), CCl_4, reflux	decomposition
2[157]	**374**	SeO_2 (1.4 equiv.), dioxane, reflux	decomposition
3[157]	**374**	SeO_2 (1.4 equiv.), H_2O, dioxane, reflux	decomposition
4[158]	**374**	LiHMDS (1 equiv.) THF, 0 °C, O_2	no reaction
5[159]	**374**	KOH, MeOH, rt.	no reaction
6[160]	**374**	Br_2 (1 equiv.), Na_2CO_3 (2 equiv.), CH_2Cl_2, -70 °C	decomposition
7[161]	**373**	*m*CPBA (2.1 equiv.), CH_2Cl_2, then TBAF (2 equiv.)	decomposition
8[162]	**373**	PDC (2 equiv.), DMF	no reaction

Unfortunately, these attempts failed, making a new retrosynthetic analysis necessary.

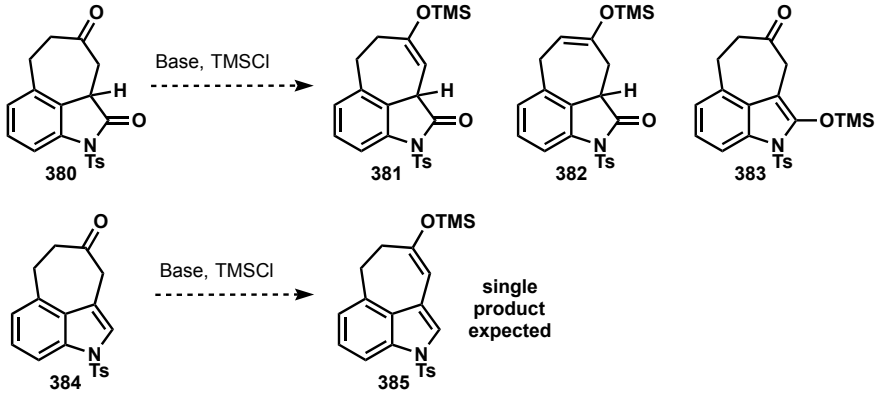
3.3.4 *4th approach*

The key feature of the 4th retrosynthesis to **315** (Scheme 90) is a Saegusa reaction which should generate the α,β-unsaturated ketone **376**. Ketone **376** ought to be reduced to an allylic alcohol which should further be transformed into the sulphonamide **375** *via* a Mitsunobu reaction. A Heck reaction is supposed to provide the five membered ring and finish the carbon skeleton of 5(10⟶9)*abeo*-ergoline alkaloids. Cyclopropanation and DVCPR cascade of diazoisatine **337** and enolether **379** should generate **378**.



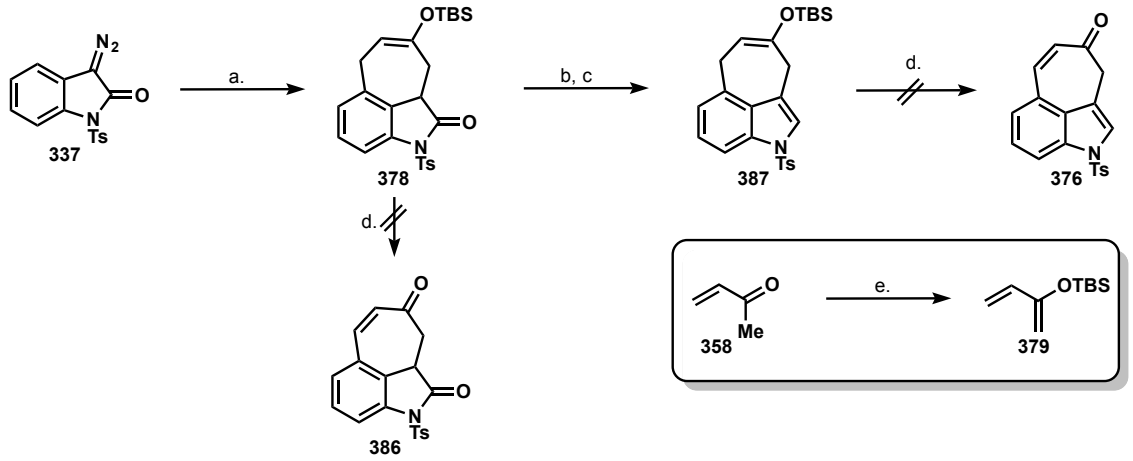
Scheme 90. 4th retrosyntheic approach towards **315**.

As it is known from literature, Saegusa type reactions work best using TMS-enolethers which are often instable. To avoid the decomposition, they are often prepared *in situ.* In this case, a TMS-enolether would not work, as it would decompose under these cyclopropanation conditions. Even if the cyclopropanation and DVCPR would succeed, the resulting product would most propably decompose to the corresponding ketone **380** (Scheme 91). Application of ketone **380** would not be easy as we were not able to predict which enol would be obtained. In case of the oxindol **380** the proton on C-3 would be problematic. However, using the corresponding indole **384** most propably enol **385** would be obtained which is not suitable for the Saegusa Ito reaction. Therefore, it was of particular interest to prepare a silylenolether that would not decompose under the cyclopropanation and DVCPR conditions.



Scheme 91. Possible enolisation products of cyclohepta[cd]ox/indole **380** and **384**.

Reisig *et al*.[163] showed in their studies that TBS-enolether were stable in presence of $Rh_2(OAc)_4$. They are also known to be applied in Saegusa reactions. We started the synthesis by preparing TBS-enolether **379** (Scheme 92) utilising freshly distilled MVK **358** (81.5°C only), LDA, HMPA and TBSCl (Scheme 92).[164]. The cyclopropanation of **337** and **379,** following Reisig's protocol, led predominantly to dimerisation. Utilising neat **337** at 65 °C with $Rh_2(OAc)_4$, provided directly cyclohepta[*cd*]oxindole **378** in 32% yield. This compound was instable to air and decomposed easily. In order to avoid the oxidation of oxindole C-3, we decided to use the crude reaction mixture to prepare the indole **387**. The crude product was dissolved in CH_2Cl_2, reduced with DiBAl-H which provided the hemiaminal. The obtained product was then subsequently treated with TFAA to form the desired indole **387**. To suppress the hydrolysis of the TBS-enolether by the *in situ* formed TFA, the reaction was buffered by an excess of triethylamine. Indole **387** was obtained in an overall yield of 42%.



Scheme 92. Preparation of Saegusa susbtrate **378** and **387**. a. $Rh_2(OAc)_4$ (1 mol%), enolether **379** (10 equiv.), 65 °C, 32%, b. DiBAl-H (1.5 equiv.), CH_2Cl_2, –78 °C to rt., c. TFAA (5 eauiv.), Et_3N (15 equiv.), CH_2Cl_2, 0 °C, 42% over two steps, d. see Table 11, e. LDA, HMPA, TBSCl, THF, – 78°C to 0 °C.

To perform the Saegusa oxidation **378** and **387** (Scheme 92) were subjected to different conditions (Table 11).

Table 11. Conditions used for Saegusa oxidation of **378** and **387**.

Entry	Conditions	Outcome
1[165]	$Pd(OAc)_2$ (1.1 equiv.), MeCN, O_2, rt.	decomposition
2[166]	DDQ (5 equiv.), collidine (6 equiv.), PhH, rt.	decomposition
3[167]	NBS (1.01 equiv), THF, 0 °C	SM
4[168]	Ph_3CBF_4 (1.1 equiv.) CH_2Cl_2, rt.	decomposition
5[169]	IBX (2 equiv.), NMR (2 equiv.), DMSO, 45 °C	decomposition
6[170]	$Pd(OAc)_2$ (5 mol%), O_2, DMSO	decomposition
7[171]	$Pd(OAc)_2$ (1.2 equiv.), CH_2Cl_2, MeCN, rt.	traces **376**
8[172]	CsF (5 equiv.), PhSeBr (1.3 equiv.), $NaHCO_3$, DMF, –25 °C	no product
9	$Pd(OAc)_2$ (1.5 equiv), CD_3CN	traces **376** & decomposition
10	$Pd(OAc)_2$ (2 equiv.), C_6D_6, rt.	< 5% **376**

Only entry 10 (Table 11) provided the product in less than 5% yield. Many conditions resulted in the decomposition of the enolether without undergoing the envisaged Saegusa oxidation. Performing the reaction in deuterated solvents allowed the visualisation of the reaction progress by NMR. It became obvious that TBS enolether **387** (Scheme 92) was instable towards

$Pd(OAc)_2$ and decomposed much faster than the reaction proceeded (Table 11, Entry 9, 10; Figure 18).

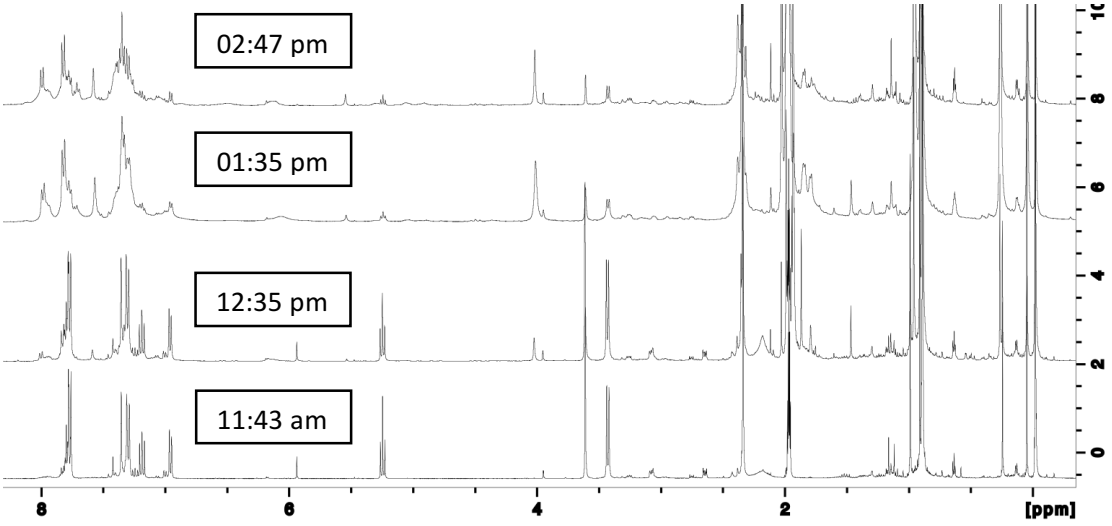
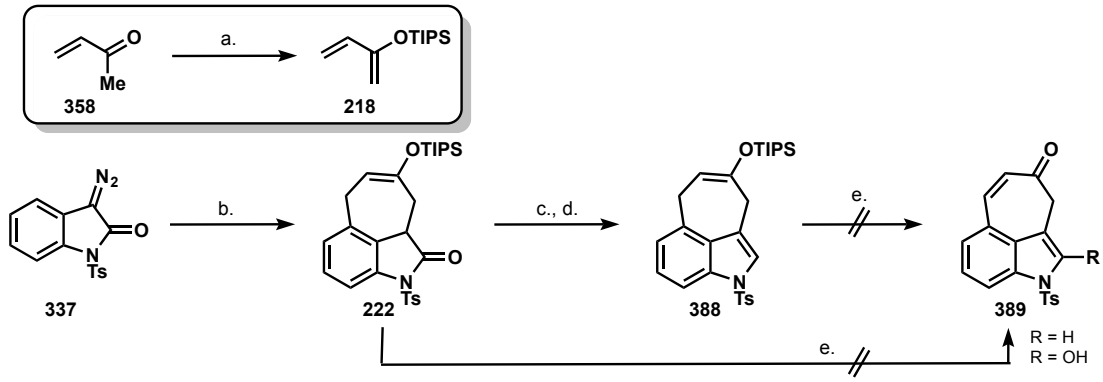


Figure 18. Reaction progress of Saegusa reaction over time in CD_3CN.

The screening of the reaction indicated that a more stable enolether is necessary. A disadvantage of an increased stability is a decrease in reactivity which narrows down possible reagents for the reaction. We decided to prepare the TIPS enolether since it should be stable towards the cyclopropanation and DVCPR.

TIPS-enolether **218** (Scheme 93) was obtained following the same procedure as employed for the preparation of **379** (Scheme 92). Instead of the silylchloride, the corresponding triflate was utilised. The cyclopropanation gave the desired oxindole **222** in 35% yield. Oxindole **222** was reduced by $NaBH_4$ and subsequently treated with TFAA and Et_3N to obtain indole **388** in 44% over all yield.



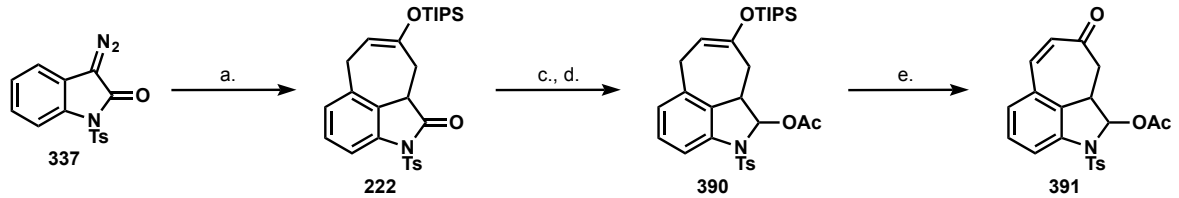
Scheme 93. Synthesis of TIPS-enolether **218** and synthesis of TIPS Saegusa substrates **222** and **388**. a. LDA, HMPA, TIPSOTf, THF, –78 °C to 0 °C, 54%, b. $Rh_2(OAc)_4$ (1 mol%), enolether **218** (1.5 equiv.), 70 °C, 35%. c. $NaBH_4$ (2 equiv.), MeOH:THF, –78 °C to rt., d. TFAA (5 equiv.), Et_3N (15 equiv.), CH_2Cl_2, 0 °C, 44% over three steps, e. see Table 12.

Both substrates, oxindole **222** (Scheme 93) and indole **388** were subjected to the Saegusa conditions (Table 12).

Table 12. Saegusa conditions using **222** and **388**.

Entry	Catalyst	Reagent	Base	Solvent	Temp.	Outcome
1[173]	$Pd(OH)_2$/C (5 mol%)	*t*-BuO_2H (5 equiv.)	Cs_2CO_3	CH_2Cl_2	4 °C	decomp.
2[173]	$Pd(OH)_2$/C (5 mol%)	*t*-BuO_2H (5 equiv.)	Na_2HPO_4	CH_2Cl_2	rt.	decomp.
3[174]	$TMSN_3$ (2.4 equiv.), PhIO (1.2 equiv.), TBAF (4 equiv.)			CH_2Cl_2	–5 °C to rt.	decomp.
4[175]	-	CAN (4 equiv.)	-	DMF	0 °C	decomp
5[172]	CsF (5 equiv.), PhSeBr (1.3 equiv.)		$NaHCO_3$	DMF	–25 °C	SM

Again, the substrates were either re-isolated or decomposed completely. We assumed the reactivity of both, indole **388** (Scheme 93) and oxindole **222** might cause the problems. As R.B. Woodward in his total synthesis of lysergic acid,[176] we needed to circumvent the reactivity. We decided to generate the less reactive aminal **390** (Scheme 94). Therefore, oxindole **222** has been reduced and the crude reaction mixture was exposed to Ac_2O buffered by Et_3N.



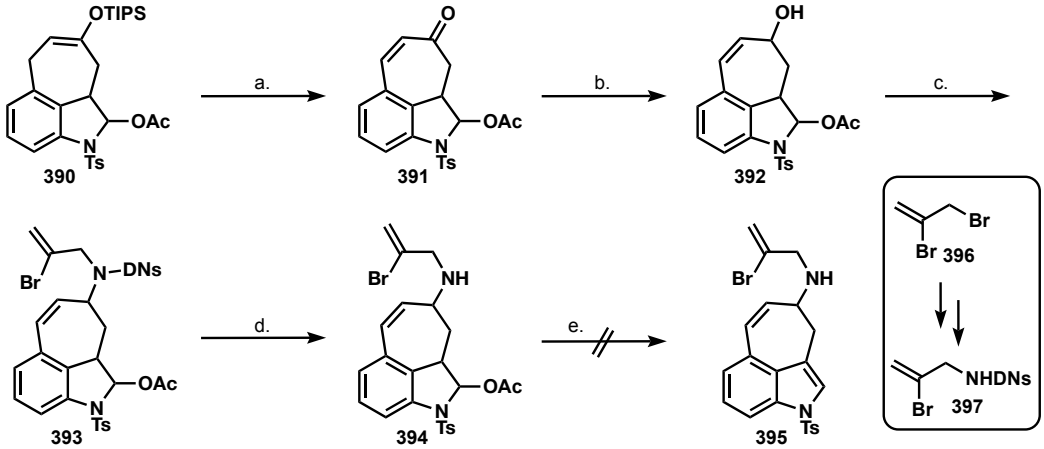
Scheme 94. Formation of aminal **390** and Saegusa oxidation to **391**. a. $Rh_2(OAc)_4$ (1 mol%), diene **218** (1.5 equiv.), benzene, 65 °C, 39%, b. $NaBH_4$ (2 equiv.), MeOH:THF 0 °C, c. Ac_2O (2 equiv.), Et_3N (5 equiv.), CH_2Cl_2, 0 °C, 80% over two steps, d. see entry 4 Table 13.

Aminal **390** in hands, several attempts were executed to perform the Saegusa type reaction (Table 13).

Table 13. Conditions for Saegusa type reaction.

Entry	Catalyst	Reagent	Base	Solvent	Temp.	Outcome
1[173]	$Pd(OH)_2$/C 5 mol%	*t*-BuOOH 5 equiv.	Cs_2CO_3	CH_2Cl_2	4 °C	SM
2[173]	$Pd(OH)_2$/C 5 mol%	*t*-BuOOH, 5 equiv.	Na_2HPO_4	CH_2Cl_2	rt.	SM
3[174]	$TMSN_3$ 2.4 equiv., PhIO 1.2 equiv., TBAF 4 equiv.			CH_2Cl_2	–5 °C to rt.	SM
4[175]	-	CAN 4 equiv.	-	DMF	0 °C	75% **391**
5[177]	$Pd(OAc)_2$ 1.1 equiv.	-	-	MeCN	rt.	SM

To our delight, we were able to isolate the desired α,β-unsaturated ketone **391** (Scheme 94) in a good yield. Furthermore, subsequent Luche reduction gave the allylic alcohol **392** in 91% yield (Scheme 95). Sulphonamide **397** needed to be prepared for the Mitsunobu reaction. We used dibromide **396** in a Gabriel synthesis to obtain the allylamine which was further protected with 2,4-dinitrotoluenesulfonic acidchloride (DNsCl). Since the proton of the nitrogen was acidic enough, Mitsunobu reaction could be performed using amide **397** to obtain **393** in 95% yield.



Scheme 95. Synthesis of Heck precursor **395**. a. CAN (4 equiv.), DMF, 0 °C, 75%, b. $CeCl_3$*7 H_2O (2 equiv.), $NaBH_4$ (1.5 equiv.), MeOH:THF, 91%, c. amide **397** (1.05 equiv.), PPh_3 (1.1 equiv.), DEAD (1.1 equiv.), PhMe, 0 °C, 95%, d. HOC_2H_4SH (1.2 equiv.), Et_3N (7 equiv.), 0 °C, CH_2Cl_2, 95%, e. TFA (5 equiv.), CH_2Cl_2, 0 °C to rt.

To examine in how far the DNs deprotection could be troublesome, **393** (Scheme 95) was exposed to mercapto ethanol and triethylamine. In order to prepare indole **395**, acetic acid had to be eliminated from **394**. Even though the formation of the corresponding ammonium salt was expected, **394** was exposed to TFA in CH_2Cl_2. Even under refluxing conditions no

progress could be observed. By increasing the pH to nine with $NaHCO_3$, amine **394** could be re-isolated.

We changed the sequence in reverse order and obtained indole **395** in a one pot reaction in 95% yield. In order to screen more than one substrate for the cyclisation, secondary amine **395** (Figure 19), tertiary amine **398** and carbamate **399** should be employed to the Heck reaction.

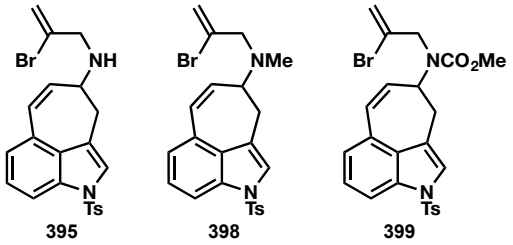
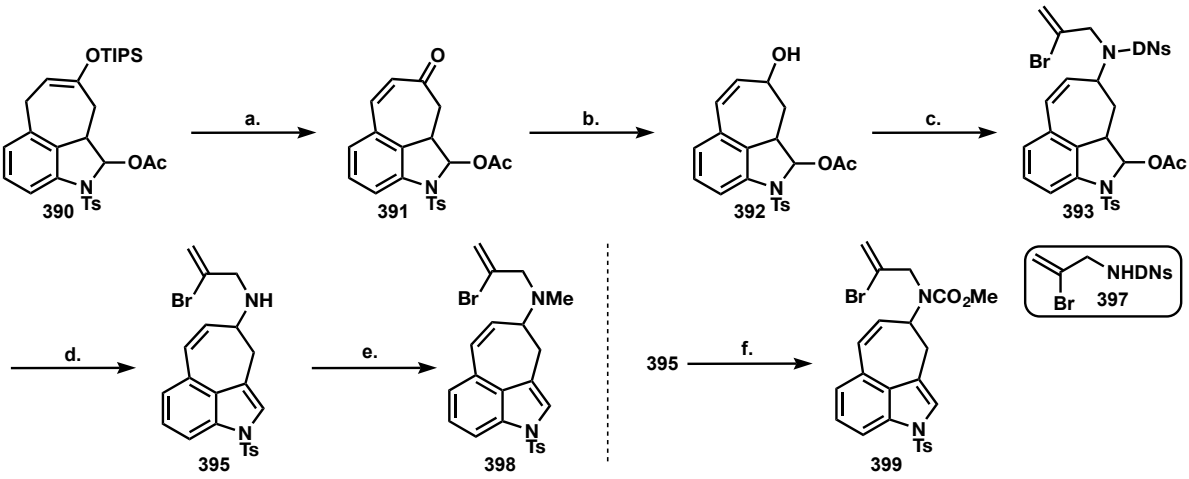


Figure 19. Compounds used in Heck screening.

Extending the one pot indole formation-sequence by a reductive amination, **398** (Scheme 96) could be isolated in 82% yield. Therefore, the reaction mixture was diluted with methanol and formalin solution, acidified with acetic acid and finally $NaBH_3CN$ was added. Carbamate **399** was obtained in 80% yield by dissolving amine **395** in pyridine and exposing the reaction mixture to methyl chlorocarbonate.



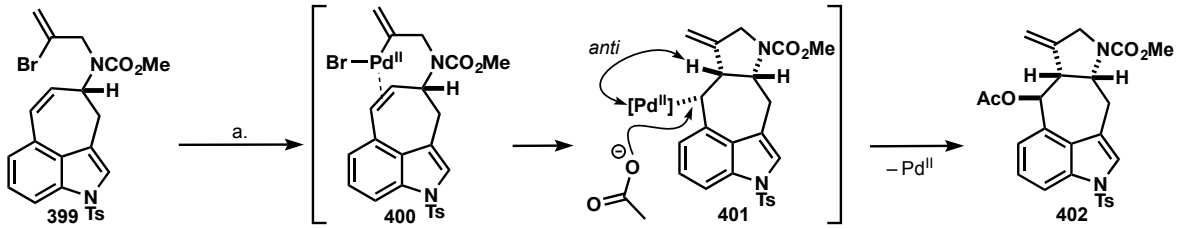
Scheme 96. Sequence to Heck-substrates **395**, **398** and **399**. a. CAN (4 equiv.), DMF, 0 °C, 75%, b. $CeCl_3*7H_2O$ (2 equiv.), $NaBH_4$ (1.5 equiv.), MeOH:THF, 0°C, 91%, c. amide **397** (1.05 equiv.), PPh_3 (1.1 equiv.), DEAD (1.1 equiv.), PhMe, 0 °C, 95%, d. TFA (4 equiv.), CH_2Cl_2, then HOC_2H_4SH (1.2 equiv.), Et_3N (7 equiv.) 95%, e. CH_2O, MeOH:H_2O, $NaBH_3CN$ (3 equiv.), HOAc (5 equiv.), 0 °C, 82% over three steps from **393**, f. $ClCO_2Me$ (1.1 equiv.), pyridine, 0 °C. 80%.

The three substrates **395** (Scheme 96), **398** and **399** were exposed to different Heck reaction-conditions (Table 14) to examine the envisaged ring-closure.

Table 14. Conditions used for Heck reaction.

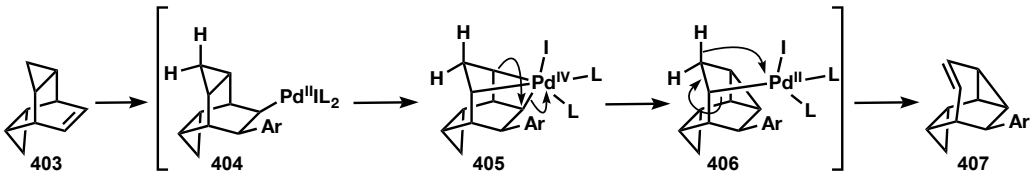
Entry	Catalyst	Conditions	Outcome
1[178]	$Pd(PPh_3)_4$ (5 mol%)	K_2CO_3 (3 equiv.), DMF, 120 °C	SM
2[179]	$Pd(OAc)_2$ (3 mol%)	Et_3N (3 equiv.), $AgNO_3$ (1 equiv.), DMSO, 50 °C	SM
3[180]	$Pd(OAc)_2$ (3 mol%), PPh_3 (6 mol%)	Ag_2CO_3 (2 equiv.), MeCN, rflx.	decomp.
4[181]	$Pd(OAc)_2$ (3 mol%), PPh_3 (6 mol%)	Ag_2CO_3 (3 equiv.), DMF, rt.	SM
5[182]	$PdCl_2(MeCN)_2$ (10 mol%), *S*-*t*BuPHOX (20 Mol%)	TMG (5 equiv.), MeCN, 80 °C	decomp.
6[183]	$Pd(OAc)_2$ (10 mol%)	TBAC (2 equiv.), KOAc (5.5 equiv.), DMF, 100 °C	20%
7[184]	$Pd(OAc)_2$ (0.5 mol%), PPh_3 (2 mol%)	CsOAc (2 equiv.), DMA, 40 °C	SM
7[184]	$Pd(OAc)_2$ (0.5 mol%), PPh_3 (2 mol%)	CsOAc (2 equiv.), DMA, 120 °C	decomp.
8[185]	$[PdCl_2(cod)]$ (5 mol%), $HBF_4P(tBu)_3$ (10 mol%)	Cy_2NMe (2 equiv.), LiCl (1 equiv.), DMF, 100 °C	decomp.
9[186]	$Pd(OAc)_2$ (10 mol%), PPh_3 (20 mol%)	Et_3N (2.5 equiv.), Bu_4NHSO_4 (1 equiv.), MeCN, H_2O, 80 °C	decomp.
10[187]	$Pd(OAc)_2$ (10 mol%), PPh_3 (20 mol%)	Et_3N (2.5 equiv.), TBAB (1 equiv.), MeCN, H_2O, 80 °C	traces

Classical Jeffrey conditions for the Heck crosscoupling were the only ones which delivered a product (**402**, Scheme 97) in 20% yield. Extensive NMR analysis was necessary to elucidate the structure. Since the structure did not allow the β-hydride elimination of palladium, we expected the aromatic core to push the catalyst out of the system (Scheme 97). Whereas the aromatic system did not affect the palladium complex, it was removed *via* a S_N2 replacent by acetate.



Scheme 97. Heck reaction under Jeffrey conditions. Palladium is not able to undergo the β-hydride elimination. a. TBAC (2.1 equiv.), CsOAc (5.8 equiv.), $Pd(OAc)_2$ (10 mol%), DMF, 65 °C, 25%.

Kaufmann *et al.*[188] described a similar case, when they treated *endo*, *exo*-bis-homo-barrelene (**403**; Scheme 98) with iodobenzene under hydroarylation conditions. Lacking a β-hydride, the palladium interacts with the Walsh orbitals of the cyclopropane which leads to the highly strained octahedral complex **405** that further undergoes a reductive elimination to form **406**. Only this complex compiles the requirements for a β-hydride elimination to form **407**.



Scheme 98. Hydroarylation of *endo*,*exo* bishomobarrelene (**403**). a. $Pd(OAc)_2$ (2.5 mol%), $AsPh_3$ (11 mol%), ArI (1.5 equiv.), Et_3N (3.5 equiv.), HCO_2H (3 equiv.), DMF (0.3M), 65 °C, 15 h, 81%.

In order to optimise the Heck reaction, different parameters were varied such as the amount of catalyst, base and additives (Table 15).

Table 15. Parameters changed in order to optimise the yield.

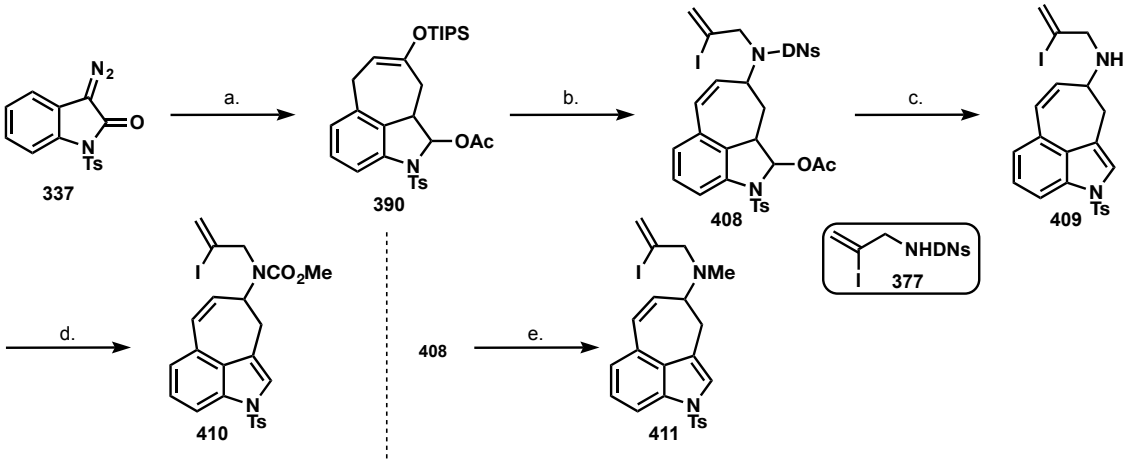
Entry	Catalyst	Base	Additive	Outcome
1	$Pd(OAc)_2$ (10 mol%)	KOAc (5.8 equiv.)	TBAC (2.1 equiv.)	20%
2	$Pd(OAc)_2$ (10 mol%)	CsOAc (5.8 equiv.)	TBAC (2.1 equiv.)	25%
3	$Pd(OAc)_2$ (10 mol%)	AgOAc (5.8 equiv.)	TBAC (2.1 equiv.)	15%
4	$Pd(OAc)_2$ (10 mol%)	CsOAc (5.8 equiv.)	TBAC (5.8 equiv.)	decomp.
5	$Pd(OAc)_2$ (10 mol%)	CsOAc (5.8 equiv.)	TBAC (1 equiv.)	10%
6	$Pd(OAc)_2$ (10 mol%)	TBAOAc (5.8 equiv.)	TBAC (2.1 equiv.)	decomp.
7	$Pd(OAc)_2$ (10 mol%)	TBAOAc (2.1 equiv.)	TBAC (2.1 equiv.)	decomp.
8	$Pd(OAc)_2$ (10 mol%)	CsOAc (2.1 equiv.)	TBAC (2.1 equiv.)	8%

A slight increase of the yield has been achieved when KOAc was displaced by CsOAc (Table 15, Entry 2). The change of every other parameter caused a decrease in yield.

To enhance the yield of the reaction, the reactivity of the substrate had to be increased. The bromide had to be replaced by an iodide since vinyl iodides are much more reactive. Starting from propargylic alcohol, iodine **377** (Scheme 99) was easily obtained. After mesylation and the Gabriel synthesis, we were not able to isolate a proper amount of the amine which in

addition was sensitive to air and light. We were able to solve the isolation problem by preparing the corresponding hydrochloride. Protecting the amine with DNsCl was not possible under the conditions utilised for the corresponding bromide **397** (Scheme 96). Therefore, the substrate has been dissolved in CH_2Cl_2 and pyridine at –78°C before DNsCl in CH_2Cl_2 was added. After workup, the sulphonamide **377** was obtained which was also much more stable to air and light.

In order to save time and purification steps, we pooled the reaction sequences which also caused a slight increase in the overall yield of this sequences (Scheme 99). Tandem cyclopropanation, DVCP-reaction, subsequent reduction and protection delivered **390** in 34% yield over three steps. Further Saegusa oxidation followed by Luche reduction and Mitsunobu reaction gave **408** in 70% yield over three steps.

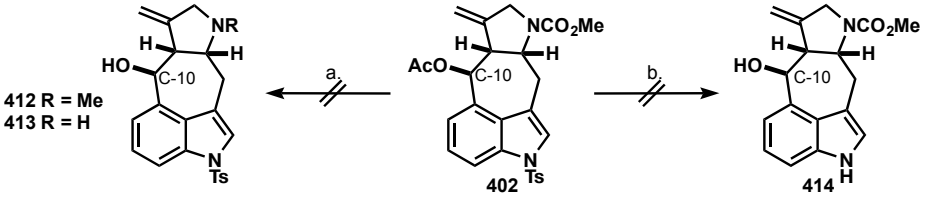


Scheme 99. Pooled synthesis of vinyl iodides **409**, **410** and **411**. a. $Rh_2(OAc)_4$ (1 mol%), diene **218** (1.5 equiv.), benzene, 70 °C, then $NaBH_4$ (2 equiv.), MeOH:THF 0 °C, then Ac_2O (2 equiv.), Et_3N (5 equiv.), CH_2Cl_2, 0 °C, 34% over three steps, b. CAN (4 equiv.), DMF, 0 °C, then $CeCl_3*7H_2O$ (2 equiv.), $NaBH_4$ (1.5 equiv.), MeOH:THF, 0°C, then amide **377** (1.05 equiv.), PPh_3 (1.1 equiv.), DEAD (1.1 equiv.), PhMe, 0 °C, 70% over three steps, c. TFA (4 equiv.), CH_2Cl_2, then HOC_2H_4SH (1.2 equiv.), Et_3N (7 equiv.) 75%, d. $ClCO_2Me$ (1.1 equiv.), pyridine, 0 °C. 82%, e. TFA (4 equiv.), CH_2Cl_2, then HOC_2H_4SH (1.2 equiv.), Et_3N (7 equiv.), then CH_2O, MeOH:H_2O, $NaBH_3CN$ (3 equiv.), HOAc (5 equiv.), 0 °C, 78% over two steps.

After Mitsunobu reaction with the allylic alcohol, the resulting product was converted into the indole and the DNs group was cleaved (Scheme 99) in one pot. Again, the methylamine **411** was prepared using the extended one pot reaction (Scheme 99). Furthermore, **409** was also used to provide carbamate **410**. The three compounds were exposed to the same conditions as the corresponding bromide (Table 14). Again, only the carbamate underwent the coupling in 50% yield along with CsOAc as the base (Table 15, entry 2).

The next steps to prepare **315** were the reduction of the carbamate to the methylamine,[189] elimination of the acetate group and deprotection of the indole (Scheme 100). LAH reduction

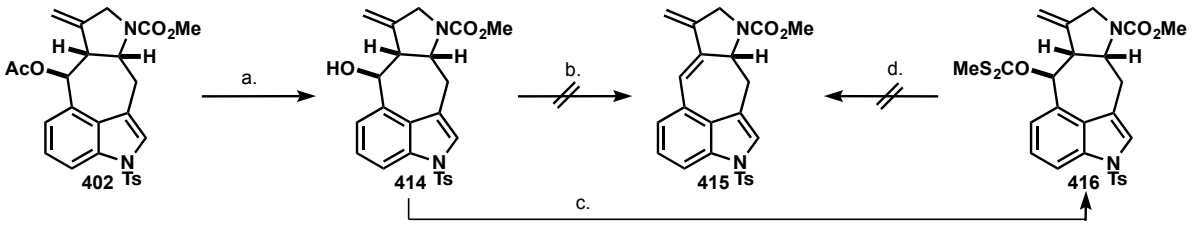
of carbamate **402** which would also liberate the alcohol at C-10 (utilising ergoline nomenclature[190]) led exclusively to a brown slurry where no product could be isolated from. Using DiBAl-H led to the same result. Performing the synthesis sequence in reverse order, **402** was exposed to magnesium in methanol which was treated by ultrasonic sound. Again, only decomposition of the starting material could be observed by TLC and NMR spectroscopy.



Scheme 100. If R = Me a. LAH (10 equiv.), THF, rt. to reflux. If R = H a. DiBAl-H (3 equiv.) CH_2Cl_2, –78 °C to rt. b. Mg (10 equiv.), MeOH, ultrasonic sound.

As it was not possible to combine two transformations in one reaction, we decided to proceed stepwise. In the first step, the acetate should be saponificated and the resulting alcohol should be eliminated to provide the necessary olefin. In order to decide which elimination conditions we needed, it was decisive to know the relative stereochemistry of the alcohol and the allyl substituent. Therefore, we had to take a closer look at the mechanism of this Heck reaction (Scheme 97). As the allyl palladium species adds in a *syn* fashion to the double bond, the S_N2 reaction of the acetate has to deliver a *trans* relation between the acetate and the allyl substituent. This means that a *syn*-elimination should provide **415**.

In a first step, the acetate was cleaved under basic conditions using K_2CO_3 in methanol treated with ultrasonic sound (Scheme 101). The desired alcohol **414** could be obtained in 75% yield. Subsequently, alcohol **414** was converted into the xanthogenate **416** to perform the Chugaev reaction.[191]



Scheme 101. a. K_2CO_3 (2 equiv.), MeOH, ultrasonic sound, 75%, b. see Table 16, c. CS_2 (10 equiv.), NaH (5 equiv.), MeI (20 equiv.), THF 70%, d. xylene, 180 °C, no conversion.

In order to perform a *syn* elimination, **414** was exposed to different reagents and conditions, summarised in Table 16.

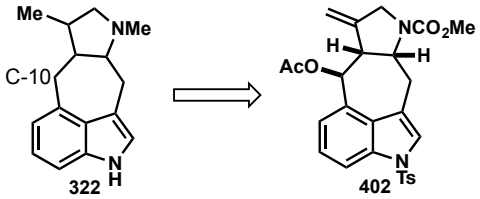
Table 16. Elimination conditions used for **414**.

Entry	Conditions	Outcome
1[192]	2-nitrophenyl selenocyanate (1.2 equiv.), pyridine (1 equiv.), PBu_3 (1.2 equiv.), THF, rt. then reflux	SM
2[193]	$MeO_2CNSO_2NEt_3$ (Burgess Reagent, 1.5 equiv.), PhH, reflux	SM
3	DEAD (1.2 equiv.), PPh_3 (1.2 equiv), PhH, reflux	SM
4	DCC (2 equiv.), 4-DMAP (10 mol%) DMF, 80 °C	SM
5	TFA (50 equiv.), CH_2Cl_2:MeOH, reflux	decomp.
6[194]	$[Ph_3POPPh_3](OTf)_2$ (1.5 equiv.), CH_2Cl_2, 0 °C to rt	SM

To exclude a wrong determination of the relative stereochemistry, **414** (Scheme 101) was also exposed to mesylation and triflation conditions.

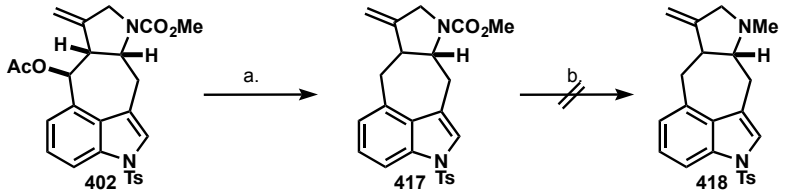
Also, these attempts did not deliver elimination product **415**. At this point, the plan to prepare common intermediate **315** *via* this method had to be abandoned, as it was not possible to establish the diene system we had focused on.

In order to prepare at least one *abeo*-ergot alkaloid, we focused on **322** (Scheme 102). This member from the *abeo*-ergot alkaloid family does not contain the two double bonds. To achieve the goal, the acetate and the carbamate had to be removed and the olefin needed to be reduced.



Scheme 102. **322** from **402**.

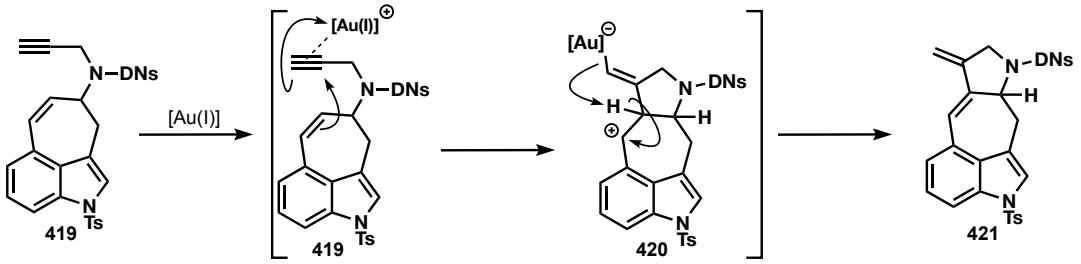
Fortunately, the first attempt to de-functionalise C-10 at **402** (Scheme 103) has been successful, giving a moderate yield of 50% utilising $InBr_3$, Et_3SiH in freshly distilled trichoromethane as described in Sakai's protocol.[195] Attempts to de-functionalise the acetate using Bu_3SnH and AIBN failed. Compound **417** was further exposed to LAH which led to decomposition of the starting material.



Scheme 103. Defunktionalisation of **402**. a. $InBr_3$ (5 mol%), Et_3SiH (4 equiv.), $CHCl_3$, 55 °C, 50%, b. LAH (10 equiv.), THF, rt. to reflux, decomposition.

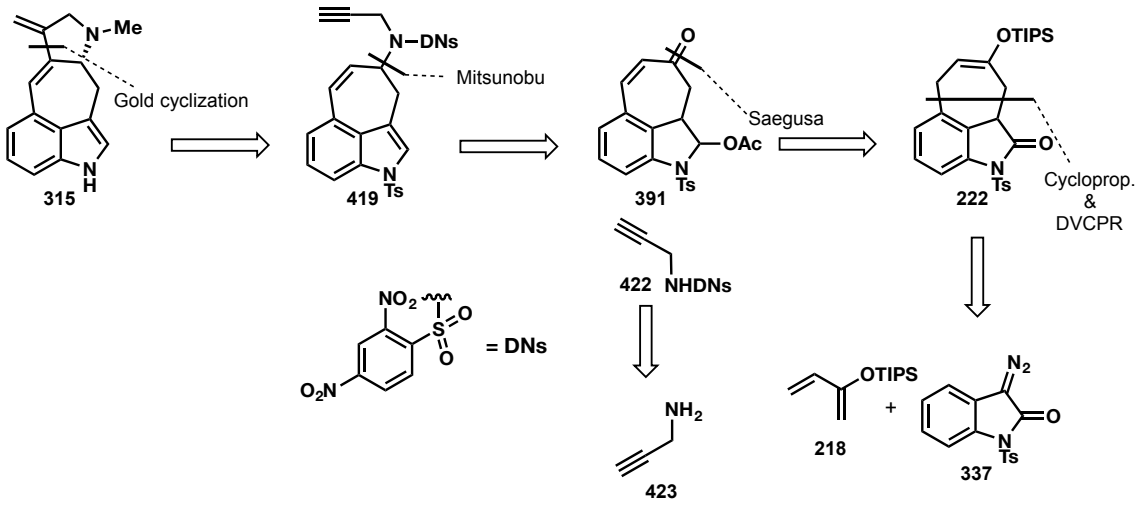
As the 4th approach also seemed to be a dead end, an extensive revision of our strategy was necessary. In this revision, a few important aspects had to be considered. The first point was to avoid the carbamate since we were not able to convert it into the methyl group. Second, a method was needed for the formation of the five-membered ring which avoided nucleophilic bases.

Having another look at the structure, we considered the synthesis of the pyrrolidine moiety a perfect target for gold catalysis. Gold tolerates many functional groups and a cation is formed as an intermediate (**420**). This cation should promote the deprotonation to form the desired olefin between C-9 and C-10 (Scheme 104). Therefore, the retrosynthesis was revised (Scheme 105).



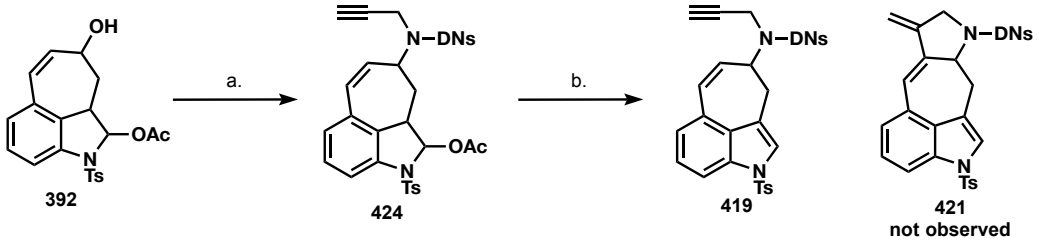
Scheme 104. Proposed formation of **421** *via* gold catalysis.

The key step of this revised retrosynthesis (Scheme 105) is the gold catalysed 5-*exo*-*dig* cyclisation to form **315**. The precursor can be obtained by a Mitsunobu reaction of **422** and **391**. Alkyne **422** is easily accessed by protecting propagylamine (**423**) with DNsCl. Saegusa type reaction of **390** provides **391** which is further reduced under Luche conditions. Cyclo-propanation and DVCPR of **337** and **218** yield **222**.



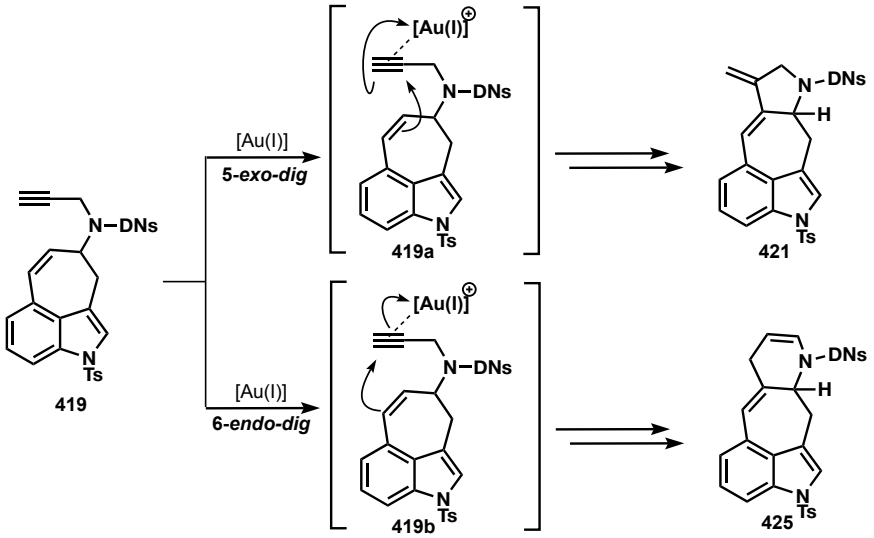
Scheme 105. Revised retrosynthesis towards **315**.

The revised synthesis started with a Mitsunobu reaction of Luche product **392** (Scheme 106) using DNs protected propagylamine **422** which was obtained following Chakrapani's protocol in a very good yield of 98%.[196] Amide **424** was exposed to $AuPPh_3^+SbF_6^-$ in dry and degassed CH_2Cl_2. When the reaction was complete, the reaction mixture was immediately cooled to 0 °C and the solvent has been removed *in vacuo* at that temperature. Contrary to the expectations the alkyne remained untouched. Instead, corresponding indole **419** was obtained in 95% yield.



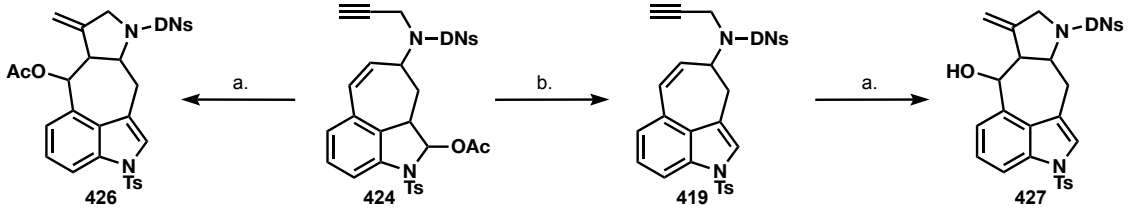
Scheme 106. a. DNsNHpropagyl **422** (1.1 equiv.), PPh_3 (1.2 equiv.), DEAD (1.2 equiv.), PhMe, 0 °C, 95%, b. $AuClPPh_3$ (2 mol%), $AgSbF_6$ (2 mol%), CH_2Cl_2, 5 min, rt. 95%. **421** was not observed.

It was surmised that the reaction time has been too short, so the reaction was repeated and the reaction mixture was stirred until either **424** and **419** were consumed. The isolated product was indeed the desired 5-*exo*-*dig* **426** (Scheme 108) and not the also possible 6-*endo*-*dig* product **425** (Scheme 107).



Scheme 107. Formation of 5-*exo-dig* (**421**) and 6-*endo-dig* (**425**) product *via* gold catalysis.

Instead of the elimination product **421** (Scheme 107), acetate has been introduced at C-10 (**426**; Scheme 108). This is reasonable, since the reaction conditions involve acetate as an *in situ* nucleophile. To prove this hypothesis, **424** was treated with TFA in CH_2Cl_2 to form indole **419**. When the gold cyclisation was repeated, only a slight conversion could be observed after three hours. The reaction mixture was purified and 91% of substrate **419** was recovered, while the new product **427** was obtained in 4% yield. Extensive NMR analysis led to the conclusion that the residual water in the dry solvents from Acros Organics® reacted as nucleophile in this case. Repeating the reaction in freshly distilled solvent led to no conversion.



Scheme 108. Formation of **426** and **427** *via* gold catalysis. a. $AuClPPh_3$ (2 mol%), $AgSbF_6$ (2 mol%), CH_2Cl_2, >15 min, rt., b. TFA (4 equiv.), CH_2Cl_2, 0 °C, 92%.

In order to increase the yield of **427** (Scheme 108), compound **419** and the gold catalyst were exposed to an excess of water. The best results were achieved when treating the reaction mixture with ultrasonic sound and water in dioxane. Under these conditions alcohol **427** was obtained in 52% yield (89% brsm.). It is noticeable that the reaction stops at one point at which the addition of catalyst or/and water does not cause further progress. To see if the alcohol can be eliminated or de-functionalised, **427** was exposed to different conditions (Table 16,

entry 2-6). Utilising Burgess reagent delivered traces of a product. But neither *syn* nor *anti* elimination conditions delivered the desired diene **421** (Scheme 106).

As these results were dissatisfying, we needed to investigate whether the used physical model deviated from the real structure or if the chosen methods to achieve the elimination were insufficient. Using Avogadro®, we were able to calculate the energy minima of tetracycle **427** by the force field method (Figure 20). The result revealed that the system obtained by gold-cyclisation is not suitable for any kind of *syn*-elimination, as the hydroxyl group **III** and the *syn*-proton **I** cannot take the *eclipsed* conformation. Furthermore, it is clearly evident from the model that any kind of S_N2 reaction with the alcohol and its derivatives is prohibited by the sevenmembered ring.

A non-representative energy minimisation of cation **420** (Scheme 104) using Chem3D® also revealed that the empty orbital and the corresponding proton always adopt a *gauche* configuration so the elimination of the proton cannot take place.

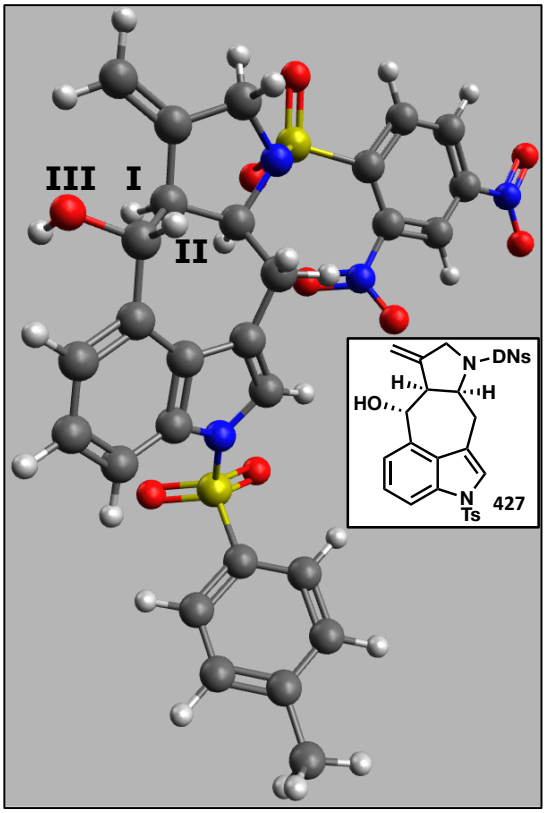


Figure 20. Avogadro energy minimisation *via* forcefield calculation.

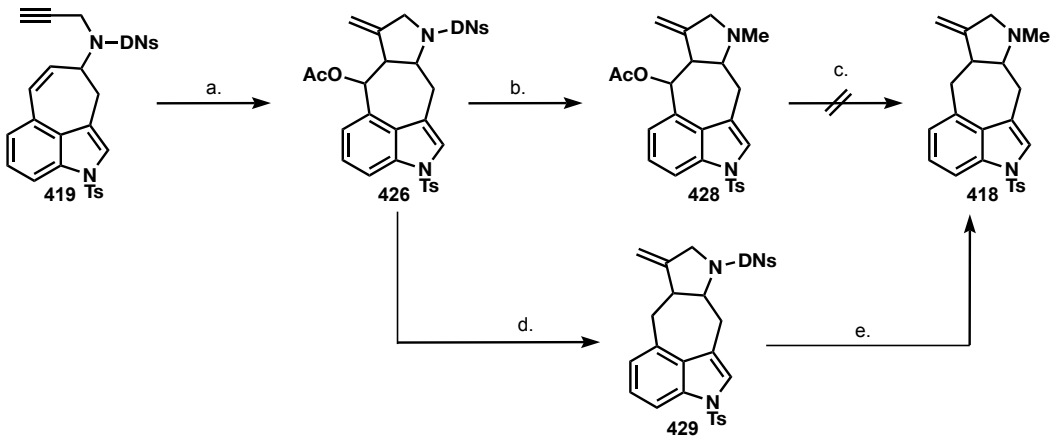
Therefore, once again the synthesis was focused on the preparation of **322** as it lacks the two olefins. Since the de-functionalisation of the acetate provided acceptable yields, it was decided to proceed the synthesis *via* **426** (Scheme 109). To improve the yield of acetate **426**, it needed to be prepared under controlled conditions (Table 17).

Table 17. Conditions for the synthesis of acetate **426**.

Entry	Conditions	Outcome
1	$AuPPh_3SbF_6$ (4 mol%), CsOAc (20 equiv.) CH_2Cl_2, U/S, 55°C	SM
2	$AuPPh_3SbF_6$ (4 mol%), CsOAc (10 equiv.), AcOH (5 equiv.) CH_2Cl_2, U/S, 55°C	SM
3	$AuPPh_3SbF_6$ (4 mol%), AcOH (10 equiv.) CH_2Cl_2, U/S, 55°C	40% **426**, 6% **427**
4	$AuPPh_3SbF_6$ (4 mol%), AcOH (26 equiv.), Ac_2O (16 equiv.) CH_2Cl_2, U/S, 55°C	90 – 97% **426**

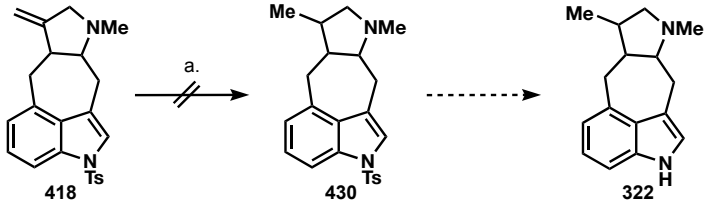
The highest yield could be obtained by the addition of acetic acid and acetic anhydride (Table 17, Entry 4). These conditions led to the lowest formation of side products. Unfortunately, the results were not reproducible while using a new batch of alkyne **419** (Scheme 109), even though there was no difference in analytical data. Since we knew that the substrate decomposed after five to ten minutes, we started the reaction and an aliquot was taken every 30 seconds from the reaction mixture and cooled it to –78 °C. TLC control as well as crude NMR spectra revealed that the new batch was much more reactive than the first one. The reaction was complete after 60 to 120 seconds. After this timespan the degradation of the product started and proceeded quickly. Neither the substrate nor the product could be isolated after 300 seconds had passed.

Having acetate **426** (Scheme 109) in hands, we cleaved the DNs-group with thiophenole. When the reaction was complete, acetic acid was added until Cs_2CO_3 was neutralised followed by the addition of formalin solution, $NaBH_3CN$ and more acetic acid. Amine **428** was obtained in 63% yield. Under the known de-functionalisation conditions no conversion could be achieved. The reason might be the formation of a Lewis acid base pair, as the amine is a perfect electron donor while the sulphonamide or the carbamate were poor Lewis bases.



Scheme 109. Synthesis of **418**. a. $AuPPh_3SbF_6$ (4 mol%), AcOH (26 equiv.), Ac_2O (16 equiv.) CH_2Cl_2, ultrasonic sound, 55°C, 90-97%, b. thiophenol (1.15 equiv.), Cs_2CO_3 (1.15 equiv.), MeCN, 0 °C, then HOAc (0.6 equiv.), CH_2O (2.5 equiv.), $NaBH_3CN$ (1.1 equiv.), HOAc (3 equiv.), H_2O, 63%, c. $InBr_3$ (5 mol%), Et_3SiH (4 equiv.), $CHCl_3$, 55 °C, SM only, d. $InBr_3$ (5 mol%), Et_3SiH (4 equiv.), $CHCl_3$, 55 °C, 49%, e. thiophenol (1.15 equiv.), Cs_2CO_3 (1.15 equiv.), MeCN, 0 °C, then HOAc (0.6 equiv.), CH_2O (2.5 equiv.), $NaBH_3CN$ (1.1 equiv.), HOAc (3 equiv.), H_2O, not optimised.

Using acetate **426** under the given de-functionalisation conditions, sulphonamide **429** could be obtained in 49% yield. Cleavage of the protecting group utilising thiophenole and Cs_2CO_3 and subsequent reductive amination delivered amine **418**. To reduce the remained olefin, amine **418** was exposed to the conditions listed in Table 18 (Scheme 110).

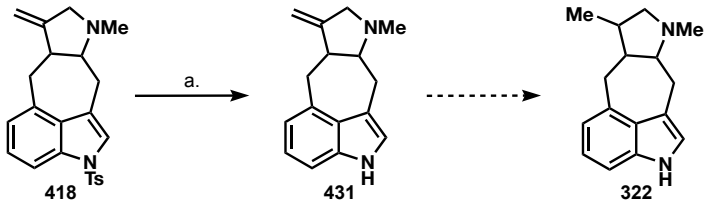


Scheme 110. Preparation of **430**. a. See Table 18.

Table 18. Hydrogenation conditions used on **418**.

Entry	Catalyst	Solvent	H_2	Outcome
1[197]	10% Pd/C (10mol%)	EtOH/EtOAc	1 atm.	SM
2	10% Pd/C (10mol%)	MeOH	10-80 atm.	SM
3[198]	20% $Pd(OH)_2$/C (10mol%)	MeOH/EtOAc	1 atm.	SM
4[199]	5% Pt/C (5mol%)	MeOH	1 atm.	SM
5	5% Pt/C (5mol%)	MeOH	10-80 atm.	SM
6[200]	PtO_2 (5mol%)	EtOAc	1 atm.	decomp.

As the given conditions did not result in the desired amine **430**, we decided to de-protect the indole (Scheme 111, Table 19) before reducing of the *exo*-methylene group of amine **431**.



Scheme 111. De-tosylation and reduction to **322**. a. SeeTable 19.

Table 19. De-tosylation conditions for indole.

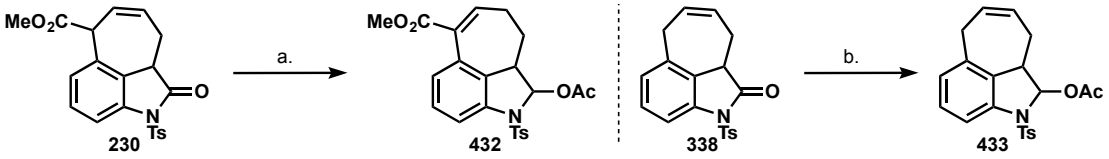
Entry	reagent	additive	conditions	solvent	temp.	outcome
1[201]	Mg (10 equiv.)	-	U/S	MeOH	rt.	SM
2[201]	Mg (10 equiv.)	NH_4Cl (1 equiv.)	U/S	MeOH	rt.	SM
3[202]	Cs_2CO_3 (3 equiv.)	-	-	THF:MeOH	rt.	SM
4[203]	SmI_2 (6 equiv.)	Pyrrolidine (12 equiv.): H_2O (24 equiv.)	-	THF	rt.	50% **431**
5[204]	KOH (5 equiv.)	N_2H_4 (3 equiv.)	-	THF:MeOH	rflx.	SM

Finally, the tosyl group was cleaved utilising SmI_2 and pyrrolidine (Entry 4; Table 19). Samarium diiodide was prepared under less conventional conditions by treating Samarium and diiodoethane in THF with ultrasonic sound at 60 °C. This foreshortened the preparation time to 20 minutes instead of 18 h.

At this point neither material nor time has been left to complete this synthesis which resulted in the halt of the project.

3.4 Additional Material

During the 4th synthetic approach, we figured out how to circumvent the reactivity of indole and oxindol. To leave the door open for future approaches, it was decided to prepare aminal **432** and **433** (Scheme 112).



Scheme 112. Preparation of aminals **432** and **433**. a. $NaBH_4$ (2.2 equiv.), MeOH:THF –30 °C °C, then Ac_2O (2 equiv.), Et_3N (4 equiv.), CH_2Cl_2, 0 °C 70% b. $NaBH_4$ (2.2 equiv.), MeOH:THF –30 °C °C, then Ac_2O (2 equiv.), Et_3N (5 equiv.), CH_2Cl_2, 0 °C 30%.

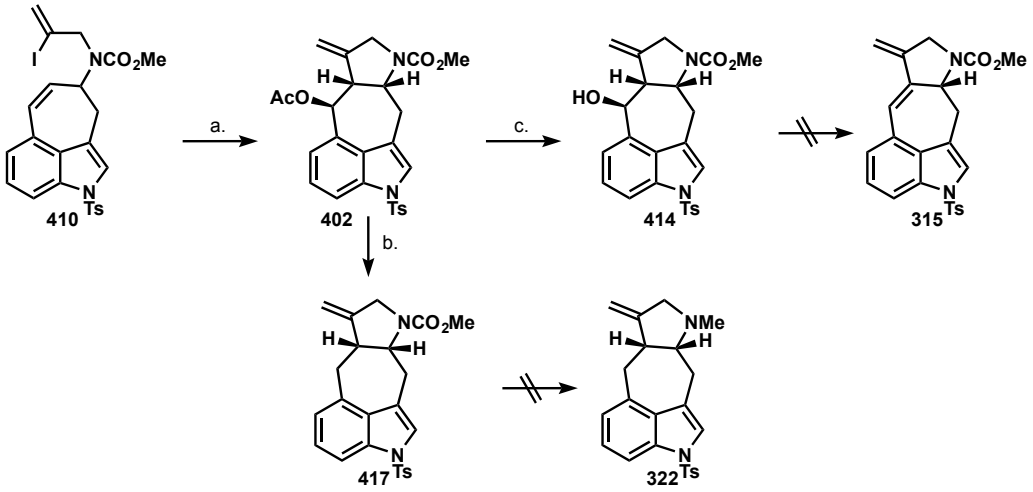
Testing the conditions shown in Table 6, 7, 9 and 10 may establish new routes toward the synthesis of 5(10⟶9)*abeo*-ergolines based on the 1st and 3rd approach.

3.5 Summary and Outlook

This work examined the synthesis of 5(10⟶9)*abeo*-ergoline derivatives **315** and **322** which are originally derived from methyl lysergate (**328**) in order to apply the divinylcyclopropane rearrangement to a total synthesis. The general synthetic access should lead to the privileged intermediate **315** from which the other substrates (Figure 17) would be derived from.

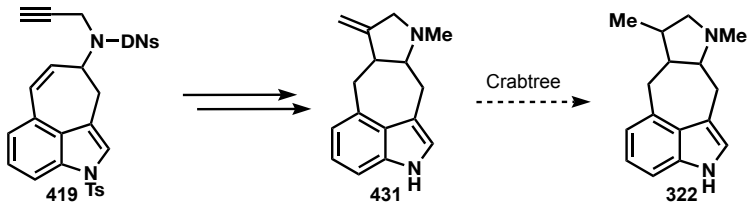
The synthesis of **315** starting from commercially available substrates was based on four different retrosynthetic approaches. The first was based on a Heck reaction to the core structure followed by a Hoffmann-Löffler-Freytag reaction which should close the five-membered ring. Since it was impossible to shift the doublebond into conjugation, the route was discarded. In the second approach a selective allylic/benzylic oxidation should deliver an unsaturated ketone. Then a 1,4 addition and Heck reaction should lead to the pyrrolidine moiety. The unefficient selectivity of the reagents led to a quick dismiss of that route. The Wolff approach also failed by forming a spiro oxindole **360**. The key features of the third approach were the cyclopropanation/DVCPR to **230** and a γ-functionalisation with dinosylperoxide. In this case, the formation of the necessary enolate failed so no further functionalisation could be performed.

The fourth approach was based on a cyclopropanation/DVCPR of **222** followed by a Saegusa type reaction in order to functionalise the seven-membered ring (Scheme 113). Furthermore, an amide based Mitsunobu and Heck reaction should complete the system. We were able to obtain the Heck product in a low yield in eight steps from **337**. Since no β-hydride elimination was possible, palladium intermediate was substituted by acetate. Neither the elimination of the acetate nor the reduction of the carbamate to the corresponding methyl amine worked.



Scheme 113. Failed approach towards the synthesis of **315** and **322**. a. TBAC (2.1 equiv.), CsOAc (5.8 equiv.), $Pd(OAc)_2$ (10 mol%), DMF, 65 °C, b. $InBr_3$ (5 mol%), Et_3SiH (4 equiv.), $CHCl_3$, 55 °C, c. K_2CO_3 (2 equiv.), MeOH, ultrasonic.

Replacement of the vinyl halogenides by a propagylic amide and use of gold-(I) catalyst lead to the same result since the orbitals neither allow a *syn*, nor an *anti*-elimination (Scheme 114). Furthermore, an inversion of the stereogenic centre would not work as the seven membered ring blocks the backside of the corresponding alcohol. Considering that we would not be able to prepare common intermediate **315** *via* this route, this project should be finished by the synthesis of **322**. Due to the lack of time and material, the synthesis of **322** remains unfinished with the last step missing.



Scheme 114. Missing transformation for the completed total synthesis of **322**.

Future investigations should focus on the optimisation of the defunctionalisation, as it is presumed that the radical conditions lead to a ring opening and rearrangement of the bonds. Additionally, the reduction of the remaining doublebond using Crabtree's catalyst should be performed to finish the synthesis.

In order to get to **322** (Scheme 114), other gold catalysts should be tested as well as the corresponding reaction conditions.

Regarding the first three approaches, two substrates were prepared baring the reactivity of indole and oxindole (Scheme 112). Exposing them to the given conditions may answer the question whether the system is not suitable at all for these reactions or if? the typical reactivity of indole and oxindole caused the failing.

4 Thorpe-Ingold Effect on the DVCPR

“Kinetik ist wohl nicht Ihr Gebiet. Sie sind in jede meiner Fallen getappt.“

Prof. Dr. Ronald Imbihl

4.1 Introduction

4.1.1 *Thorpe Ingold effect*

Thorpe, Ingold and Beesely reported a correlation between the change of bond angles of acyclic carbon centres and the rate constant for the formation of cyclisation products in 1915. They observed that an increase of alkyl substituents at the carbon centre causes a decrease of the internal bond angle (Figure 21).[205] They postulated that this decreased angle moves the reactive groups closer together, facilitating the cyclisation event and stabilising the newly formed small ring.

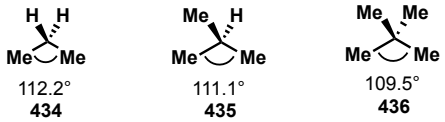


Figure 21. Thorpe-Ingold effect.

The decrease of the inner bond angle has been proven by X-ray measurements of malonic acid derivatives. While the angle for malonic acid is 110° (Figure 22),[206] the angle of dimethyl malonic acid is decreased to 106.2°. Subsequently, the formation of the dimethyl malonic anhydride should be favoured. On the other hand, a cyclopropyl substituent, which resembles a *gem*-dimethyl group, increases the angle to 118.4°.

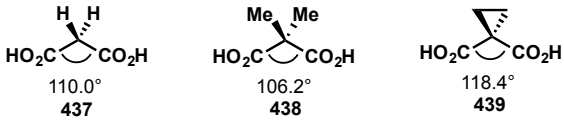
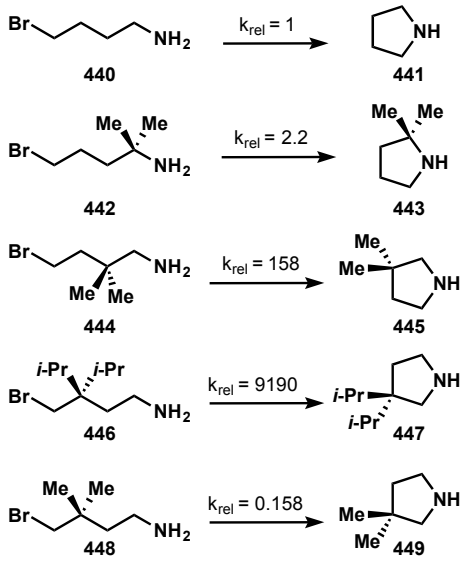


Figure 22. *gem*-dialkylsubstituent effect on bond angle.

Von Schleyer was the first to question this explanation in 1961.[207] According to him, the change in bond angle of 2-3° cannot explain the large increase of rate during the cyclisation. The results of Brown *et al*. reveal that the size of the *gem*-dialkyl substituents may be the reason for rate enhancement (Scheme 115).[208] They executed experiments with differently substituted bromobutylamines in order to prepare pyrrolidines. While **442** caused a two folded and **444** a 158 folded increase of the rate constant, **448** led even to a decrease to 0.158 which is reasonable for a substrate with a leaving group in neopentylic position. On the other hand, **446**, entry 4 and 6 in Table 20 exhibited a tremendous increase of the rate constant. The authors explained the result with the distribution of rotational conformations. The *gem*-dialkyl effect favours the folded configuration instead of the "zig zag" form of the non-substituted chains.

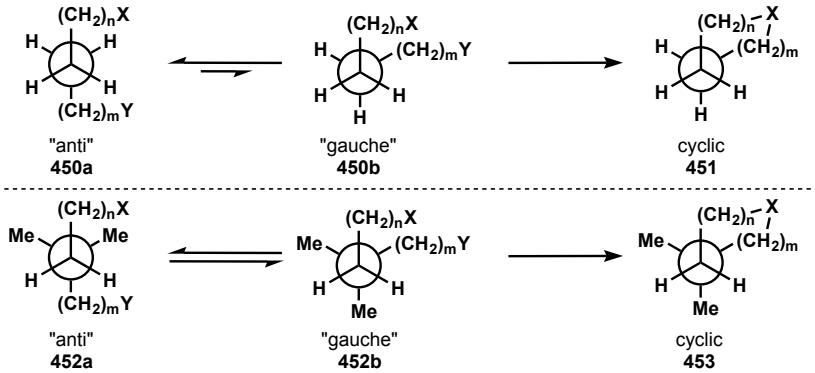


Scheme 115. Relative rate of cyclisation to pyrrolidines.

Table 20. Substituents and the relative rate constant.

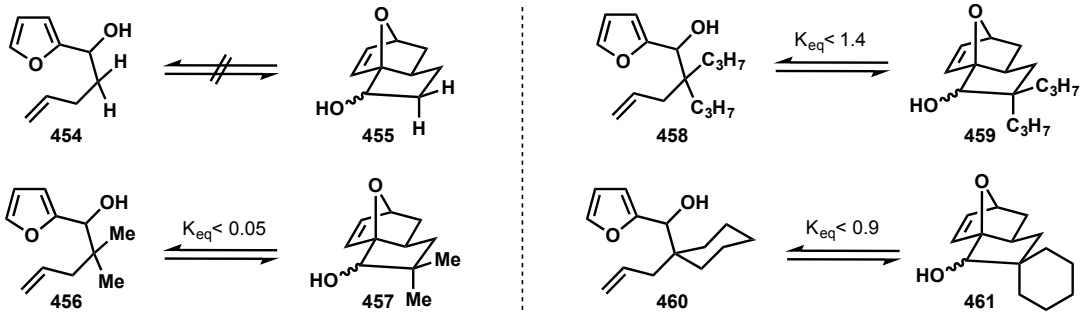
Entry	Substituents	k_{rel}
1	-	1
2	1,1-dimethyl	2.2
3	2,2-dimethyl	158
4	2,2-diethyl	594
5	2,2-diisopropyl	9190
6	2,2-diphenyl	5250
7	3,3-dimethyl	0.158

Bruice *et al*. took another approach.[209] They surmised the reason for the increased reactivity in reactive rotameres (Scheme 116). In their hydrolysis studies of monophenyl succinate, glutarate and their disubstituted derivatives, they concluded that substituents in β-position increase the rate for the ring closure and cause a decrease for the following ring opening. It was deduced that the β-substituents decrease the distribution of unfavourable ground state rotamers by increasing the energy of the whole system. While the unsubstituted substrates (**450a**; Scheme 116) favour the *anti*-rotamer, in case of β-*gem*-dialkyl substituted substrates (**452a**) the energy of *anti* and *gauche* rotamers is equal. Thus, the energy necessary to switch between the rotamers is decreased while the population of the reactive rotameres is increased. Therefore, the activation energy for the ring closure will also be decreased.



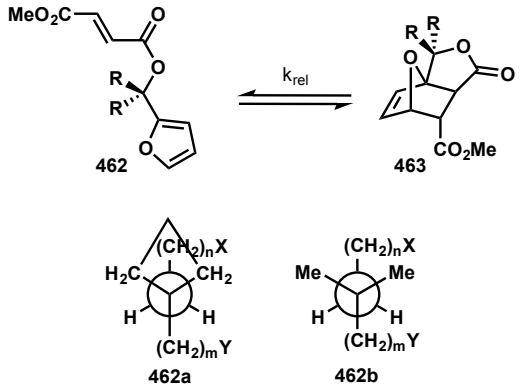
Scheme 116. Effect of reactive rotamers on cyclisation.

The theory of the reactive rotameres has been supported by the results of intramolecular Diels-Alder reaction experiments (Scheme 117). In the first example, the core system **454** did not react at all while 5% of the *gem*-dimethyl substrate **456** could undergo the reaction.[210] Replacement of the two methyl groups by a cyclohexane (**460**) or two propyl groups (**458**) increased both yield and rate.



Scheme 117. Substituent-effect on intramolecular Diels-Alder.

Based on the hypothesis of Thorpe and Ingold, the cyclic substituent should slower the reaction compared to the corresponding dimethyl substrate as the inner bond angle is increased. Jung *et al*. have described similar results (Scheme 118).[211] They developed a system allowing the obversation of the two effects and comparing them. They assumed the cyclobutyl and cyclopropyl substituents to slow the reaction if the *gem*-dialkyl effect is only based on angle compression. On the other Hand, the relative rates of **462a** and **462b** should be similar if the effect is based only on the reactive rotamere effect. The rates obtained for cyclobutyl and cyclopropyl were neither the same as **462b** nor lower than entry 1, Table 21. The aforementioned results contradict the theory of Thorpe and Ingold who proposed that the rate enhancement is exclusively based on the compression of the angle as the cyclic substituents cause an angle enlargement. Furthermore, these results support those who claim that the *gem*-dialkyl effect is based on multiple factors.



Scheme 118. IMDA with different substituents.

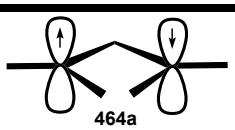
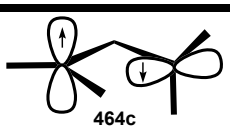
Table 21. Substituents and the relative rate constant.

Entry	Compound	k_{rel}
1	R = H	1
2	R = Me	2123
3	R = $(CH_2)_2$	10.5
4	R = $(CH_2)_3$	208

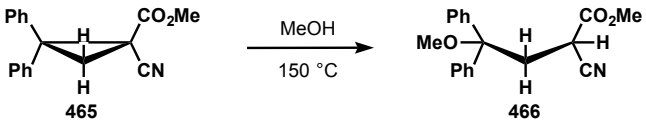
4.1.2 *Divinylcyclopropane rearrangement*

The racemisation of cyclopropanes is a generally known reaction. Rabinovitch and Schlag were able to proof the reversible *cis*-*trans*-isomerisation by heating *trans*-1,2-dideuteriocyclopropane to 450 °C and quenching the reaction after passing 50% of the reaction time.[212] They were able to isolate 25% *cis*-, 65% *trans*-1,2-dideuteriocyclopropane and 8% propene. The common intermediate leading to all three products is proposed to be trimethylene (Table 22), a diradical species. Hoffmann and Hammond described the trimethylene in more detail,[213] as they calculated three conformations for it. The three-possible species 0.0 (**464a**), 90.90 (**464b**) and 0.90 (**464c**) can be transferred into one another. Nevertheless, they have to overcome a rotation barrier of 8 kcal/mol, indicating the π-character of 90.90 trimethylene (**464b**). Furthermore, Hoffmann interprets his results as a proof for the isomerisation to be a Woodward-Hoffmann controlled reaction. However, the orbital-symmetry control of this reaction could not be proven in various experiments.

Table 22. Conformations and energies of trimethylene.

	 464a	 464b	 464c
Label	0.0	90.90	0.90
Energy	$44\frac{kcal}{mol}$	$> 52\frac{kcal}{mol}$	$52\frac{kcal}{mol}$

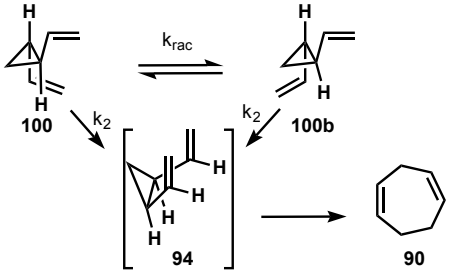
Cram on the other side was able to proof a zwitterionic intermediate (Scheme 119), depending on the substituents on the cyclopropane.[214] Applying cyclopropanes with electron withdrawing groups to methanol at 150 °C, both the racemisation and the solvolysis product **466** were isolated.



Scheme 119. Cram's zwitterionic thermoylsis.

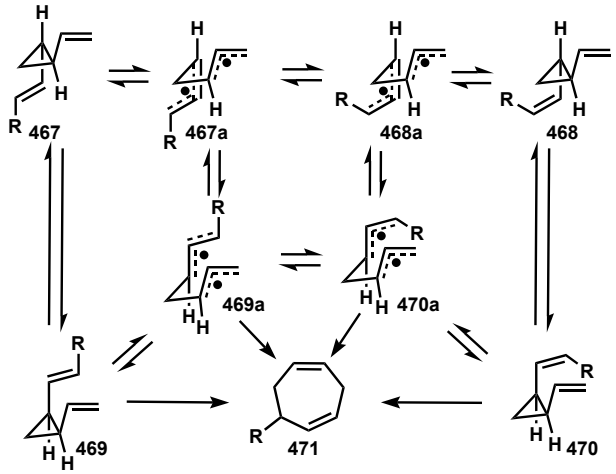
Divinylcyclopropanes are more feasible for the investigation of the racemisation of cyclopropanes. They offer the advantage of confined reactivity of these compounds to the bond between the two vinyl groups. Crawford *et al*. used (*1S:2S*)-*trans*-1,2-divinylcyclopropane (**100**; Scheme 120) in order to investigate whether 0.0-trimethylene (**464a**) is

formed by orbital control or not.[215] They proposed that the rate of racemisation should exceed the rate of the formation of **94** ($k_{rac} > k_2$) if the ring-opening and closing proceeds *via* a preferred mode. In all their experiments, they obtained $k_2 > k_{rac}$ which led them and many others to the conclusion that the isomerisation is a diradical and not an orbital controlled process.



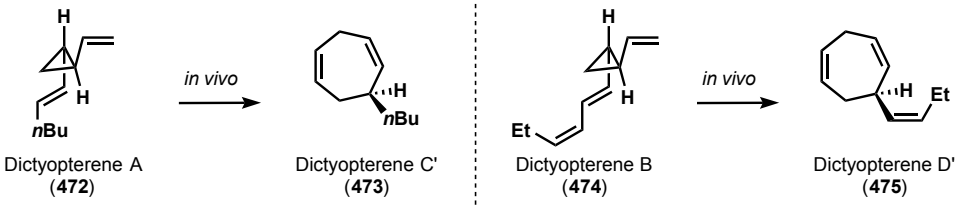
Scheme 120. Crawford's racemisation experiments.

In opposite to Crawford, Perlberger *et al*. proposed not only the racemisation to occur most probably *via* a di-radical, but also the thermally induced Cope rearrangement itself may proceed *via* a radical mechanism (Scheme 121).[216]



Scheme 121. Perlberger's proposed mechanism for the formation of **471** from *cis*- and *trans*-divinylcyclopropane.

During their investigations to elucidate the mechanism of the *in vivo* formation of **473** and **475** (Scheme 122), **472** and **474** have been irradiated by a mercury lamp in benzene at 40 °C.



Scheme 122. *In vivo* synthesis of **473** and **475** by Dictyopteris.

Upon irradiation, a mixture of **471**, **470** and the starting materials **467** and **468** were obtained in different ratios. The presence of **470** led them to the conclusion that the cyclisation has to proceed *via* a radical mechanism. It has been not concidered that the rearrangement may be caused by the isomerisation of **467** to **469** and subsequent DVCPR induced by the elevated temperature of 40 °C. Although ongoing investigations were mentioned, they remained short on experimental evidence.

4.1.3 *Chemical kinetics*

A general chemical reaction can be written as the following reaction equation (a):

$$|\upsilon_A|A + |\upsilon_B|B + \cdots \rightarrow |\upsilon_C|C + |\upsilon_D|D + \cdots \quad \text{(a)}$$

The progress of the reaction can be observed by the alteration of the concentration depending on the time from which a rate law (b) is deduced.

$$r = -\frac{d[A]}{dt} = -\frac{d[B]}{dt} = k[A]^{\upsilon_A}[B]^{\upsilon_B} \quad \text{(b)}$$

$[A]$ and $[B]$ express the concentration of the substances A and B, k the rate constant and ν_A and ν_B the stoichiometric coefficients. The sum of the stoichiometric coefficients implies the order of the reaction. E.g. a first order reaction, like an intramolecular divinlcyclopropane reaction, depends on the concentration of only one reactant. The reaction law simplifies to equation (c):

$$r = -\frac{d[A]}{dt} = k[A] \quad \text{(c)}$$

Recognising that the reaction law is a differential equation (c), it can be transformed to an integrated reaction law (d) after separation variables.

$$[A] = [A]_0 \cdot e^{-kt} \quad \text{(d-1)}$$

$$\ln[A] = \ln[A]_0 - kt \quad \text{(d-2)}$$

4.1.4 *Arrhenius equation and Arrhenius plot*

The temperature dependence of the rate constant k is given by the Arrhenius equation (e)

$$k = k_o e^{-\frac{E_A}{RT}} \quad \text{(e)}$$

This shows the dependence of the rate constant on the pre-exponential factor k_0, the activation energy E_A, the universal gas constant R and the temperature T.

To determine the activation energy E_A equation (e) can be transferred to a logarithmic function (f):

$$\ln k = \ln k_0 - \frac{E_A}{RT} \quad \text{(f)}$$

Equation (f) illustrates a linear equation so if $ln\ k$ is plotted again $1/T$ a straight line will follow (Figure 3). From the slope of the curve the activation energy can be determined by using the following relation:

$$E_A = -mR \quad \text{(g)}$$

The y-intercept represents the pre-exponential factor k_0.[217]

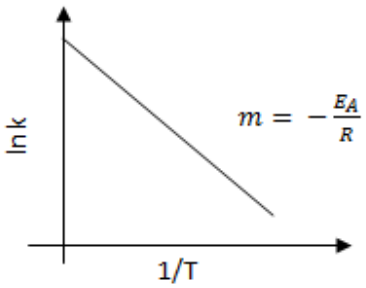


Figure 23. Arrhenius plot.

4.2 Aim of this Project

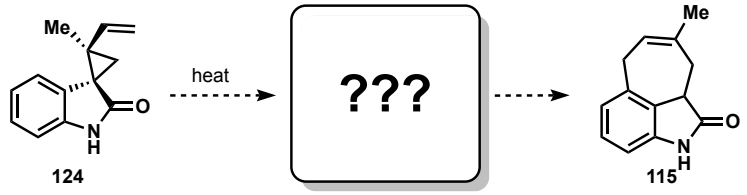
The *trans*-divinylcyclopropane has long been known to be transferrable into its *cis*-isomer by irradiation or the increase of temperature. Based on that, the first aim of this project is to reveal that **124** (Scheme 123) is able to undergo isomerisation and subsequent Cope rearrangement employing various temperature experiments.

The second aim is the investigation of the solvent dependence of both the isomerisation and the Cope rearrangement. The results thus gained should facilitate the calculation of the rate constants and the activation energy for both partial reactions. Furthermore, we should be enabled to draw conclusions on the reaction mechanism from these results.

The third part of this project focuses on the influence of the Thorpe-Ingold effect on both partial reactions. Therefore, the two diastereomers of a nor-methyl-divinylcyclopropane have to be prepared and their reaction progress monitored utilising high temperature NMR techniques. The comparison of the rate constants of the methyl and the nor-methyl series at the same temperature should make the influence of the Thorpe-Ingold effect apparent.

4.3 Own Contribution

As the racemisation and geometrical isomerisation for all 1,2-divinylcyclopropanes is known, the examination of the isomerisation of **124** (Scheme 123) was of particular interest. This isomerisation would be advantageous as the yield of the non-selective cyclopropanation could be increased by using both diastereomers.



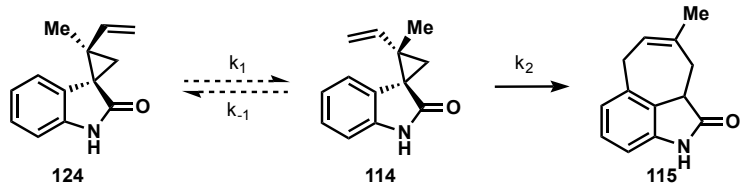
Scheme 123. Divinylcyclopropane rearrangement using **124**.

In order to investigate the *trans*-rearrangement (Scheme 123), a series of experiments has been planed. Utilising benzene-d_6 as reaction solvent allows higher reaction temperatures than chloroform-d_1. Furthermore, the lowest temperature was set at room temperature since the *cis*-diastereomer already rearranges at room temperature and the highest was set to 80 °C oil-bath temperature (Table 23). Every reaction was stirred at the corresponding temperature for 90 minutes, then cooled to room temperature and submitted to NMR.

Table 23. Temperature series to achieve the conversion of **124**.

Temperature	20 °C	30 °C	40 °C	50 °C	60 °C	70 °C	80 °C
Conversion	✗	✗	✗	✗	✓	✓	✓

Fortunately, **124** (Scheme 123) underwent the desired rearrangement at low rate at 60 °C oil-bath temperature. This is around 40 °C higher than **114** (Scheme 124) but still much lower than a regular *trans*-divinylcyclopropane isomerisation and rearrangement takes place.[56-57] Knowing both diastereomers were suitable for the rearrangement, the detection of **114** has been of particular interest, since **124** cannot react to the cyclohepta[*cd*]oxindole directly. Furthermore, the two diasteremoers had to be investigated regarding the isomerisation mechanism and the solvent dependence of the rate constant. Therefore, a test series was designed within which all three questions should be answered. We decided to use benzene-d_6, DMSO-d_6 for the series of **114** and toluene-d_8, $CDBr_3$ and DMSO-d_6 for **124**. As the two diastereomers did not react in the same temperature range, the reaction temperatures were set to 310 K, 320 K and 330 K using **114** and for **124** to 360 K, 370 K and 380 K.



Scheme 124. Divinylcyclopropanrearrangement in different solvents using both diastereomers.

It was known from preliminary studies performed by Silke Kayser during her bachelor thesis, that $CDCl_3$ does not accelerate the divinylcyclopropane rearrangement. We decided to repeat the measurement series of $CDCl_3$ if the curve characteristics would deviate significantly from the results of the other solvents.

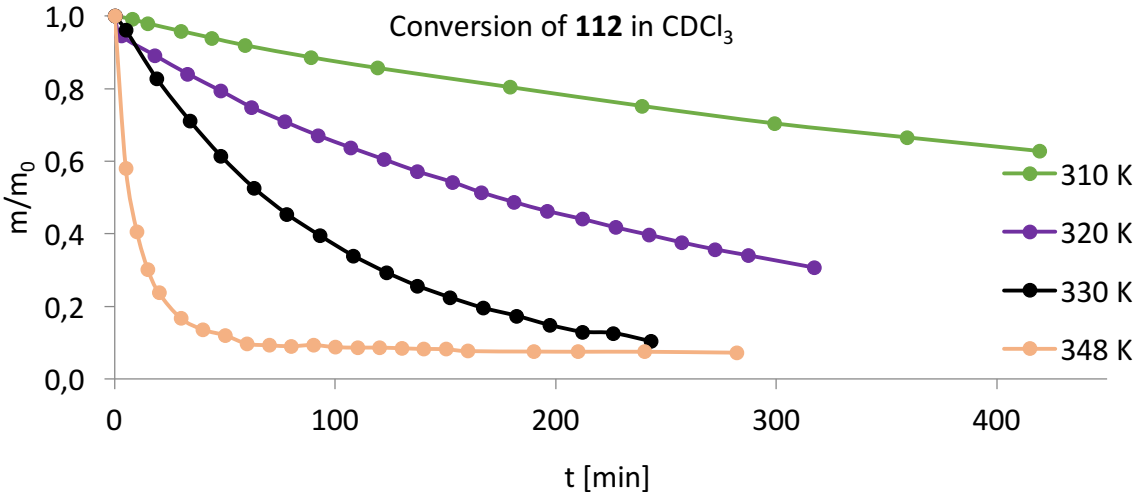


Figure 24. Excerpt from the bachelor thesis of Silke Kayser. Reaction progress of **112** to **110** in $CDCl_3$ at different temperatures. Reaction for 310 K and 320 K has been aborted when the curve progression became obvious.

For the experiment 15 mg **114** (Scheme 124) were dissolved in the corresponding solvent and the solution was submitted to NMR. The reaction mixture was heated in the NMR-device and the spectra were acquired at the corresponding temperature in defined time intervals (Figure 25, 26, 27).

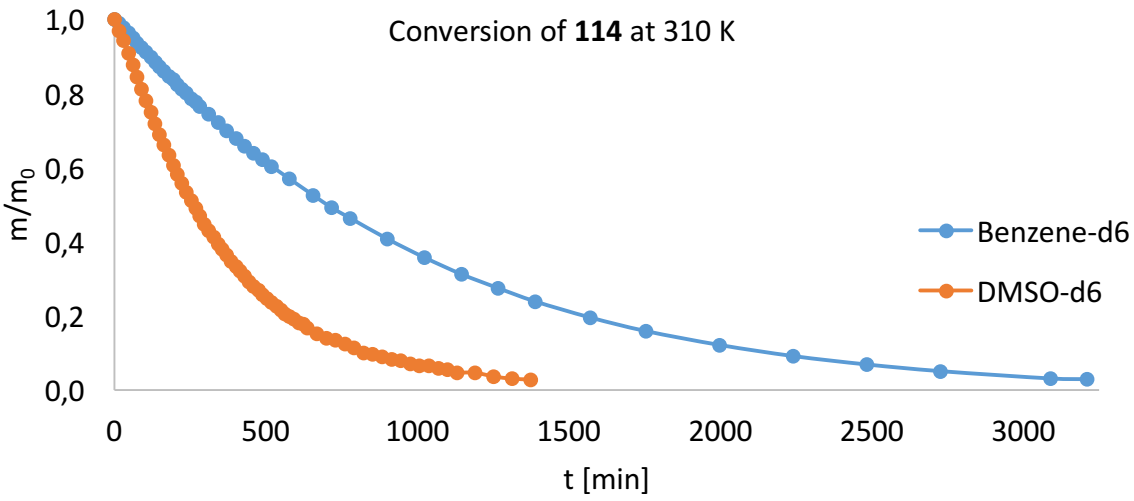


Figure 25. Conversion of **114** at 310 K in benzene-d_6 and DMSO-d_6.

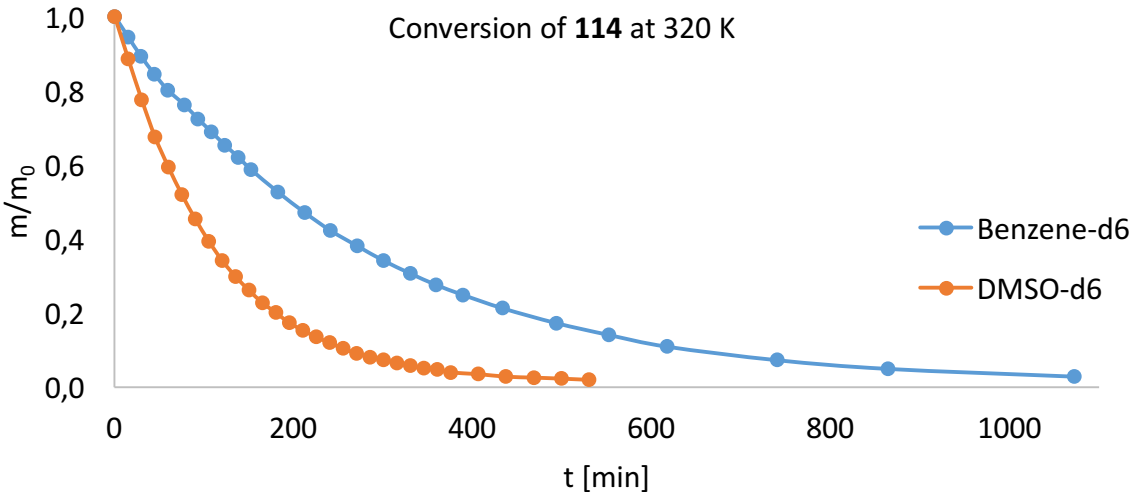


Figure 26. Conversion of **114** at 320 K in benzene-d_6 and DMSO-d_6.

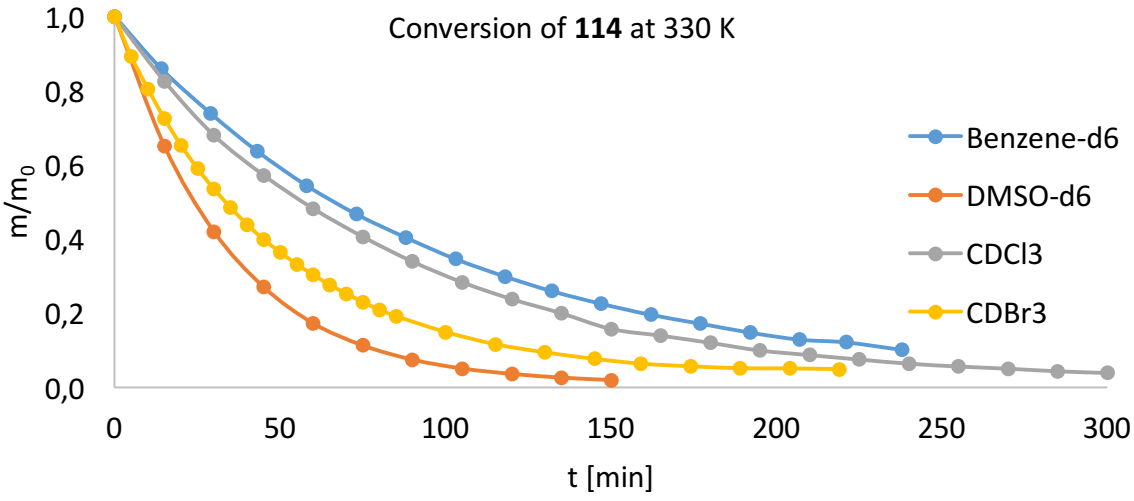


Figure 27. Conversion of **114** at 330 K in benzene-d_6, DMSO-d_6, $CDCl_3$ and $CDBr_3$.

With these results in hands, the rate constants k and the activation energy E_A were calculated. Assuming that the divinylcyclopropane rearrangement is a first order reaction, $\ln[A]$ was plotted against the time to calculate the rate constant k at different temperatures (Figure 28). Therefore, a linear regression was carried out. Rate constant k was calculated from the slope of the curve (Table 24).

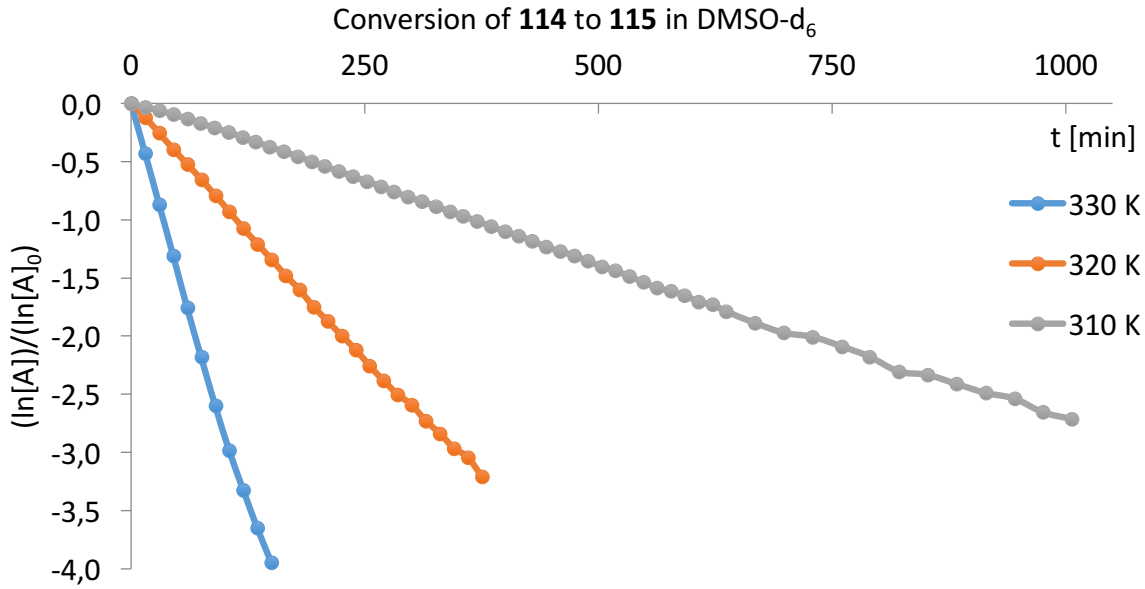


Figure 28. Calculation of the rate constants at different temperatures.

In order to display an Arrhenius plot (Figure 29), the logarithmic rate constants were plotted against $1/T$. The activation energy (Table 25) was obtained from the slope of the curve (equation (g)).

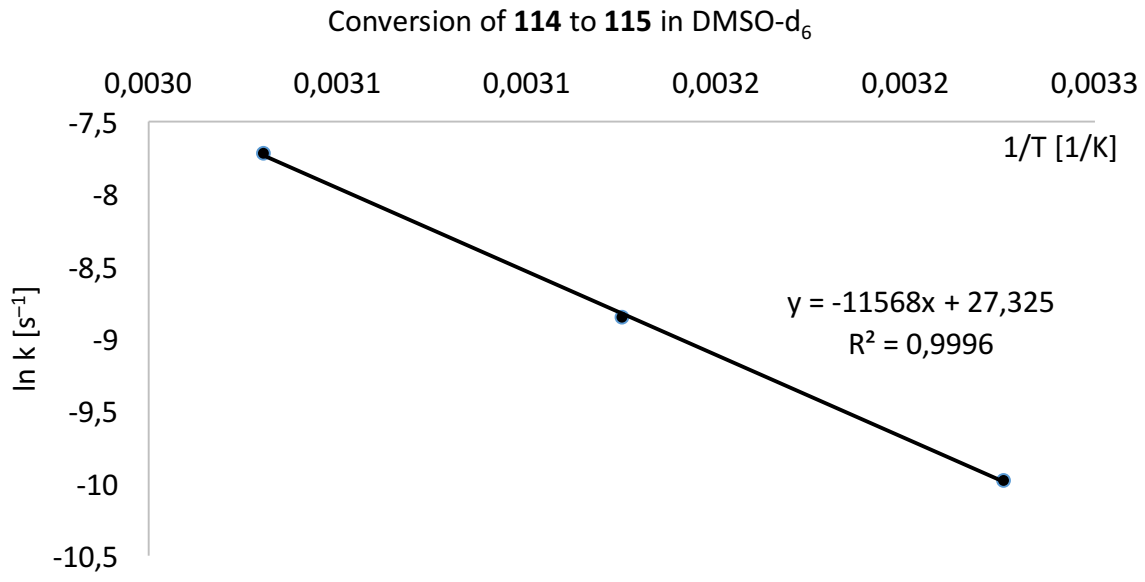


Figure 29. Arrhenius plot with the corresponding parameters.

Table 24. Solvent and temperature dependent change of the rate constant. [a] the values of the benzene-d_6 series at 330 K became inconsistent after 200 minutes, therefore they were excluded, [b] relative rate is based on the aborted series of benzene-d_6.

Entry	Solvent	Temperature	rate constant $k[s^{-1}]$	relative rate
1	benzene-d_6	310 K	$1.8\times10^{-5} \pm 8.4\times10^{-8}$	1
2	DMSO-d_6	310 K	$4.6\times10^{-5} \pm 2.0\times10^{-7}$	2.6
3	benzene-d_6	320 K	$5.7\times10^{-5} \pm 2.3\times10^{-7}$	1
4	DMSO-d_6	320 K	$1.4\times10^{-4} \pm 9.5\times10^{-7}$	2.5
5[a]	benzene-d_6	330 K	$1.6\times10^{-4} \pm 1.1\times10^{-6}$	1
6[b]	$CDCl_3$	330 K	$2.0\times10^{-4} \pm 2.5\times10^{-6}$	1.3
7[b]	$CDBr_3$	330 K	$3.0\times10^{-4} \pm 4.2\times10^{-6}$	1.9
8[b]	DMSO-d_6	330 K	$4.5\times10^{-4} \pm 6.9\times10^{-6}$	2.8

Table 25. Activation energy in different solvents.

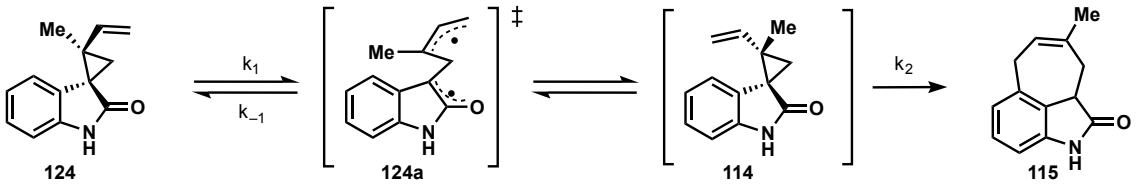
Entry	Solvent	Activation energy E_A $\left[\frac{kJ}{mol}\right]$
1	DMSO-d_6	96.2 ± 1.9
2	benzene-d_6	93.5 ± 0.2

Following the Hughes-Ingold rules,[218] the only slight increased rate by using DMSO has been expected for a pericyclic reaction. Known from experiments with barbaralane, dipolar polarisable solvents such as DMSO, HMTP and DMPU stabilise polarisable delocalised activated complexes. Compared to benzene-d_6 the rate of rearrangement is increased by the factor of 2.2 to 2.7 (Table 24). If the reaction would proceed *via* a zwitterionic intermediate, the rate constant in DMSO-d_6 would deviate from the other solvents significantly.

A noticeable result of the benzene-d_6 series is that the activation energy for the divinylcyclopropane rearrangement is 2.7 $\left[\frac{kJ}{mol}\right]$ lower than for DMSO-d_6. In combination with the lower rates, it can be implied that benzene stabilises the transition state which lowers the energy but it is less suitable for the whole reaction.

Interestingly, we were not able to detect **124** (Scheme 125) during the reaction of **114** to **115** which we expect to be in equilibrium with **114**.

The series of experiments was repeated with **124** under the previously defined conditions (Scheme 125).



Scheme 125. Proposed mechanism for the reaction of **124** to **115** with the radical intermediate **124a**.

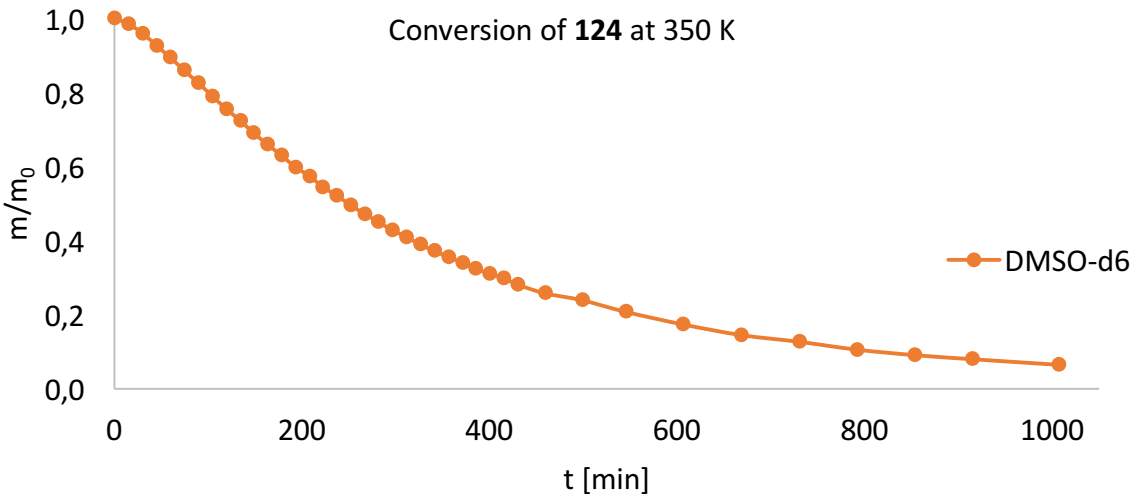


Figure 30. Conversion of **124** at 350 K in DMSO-d_6.

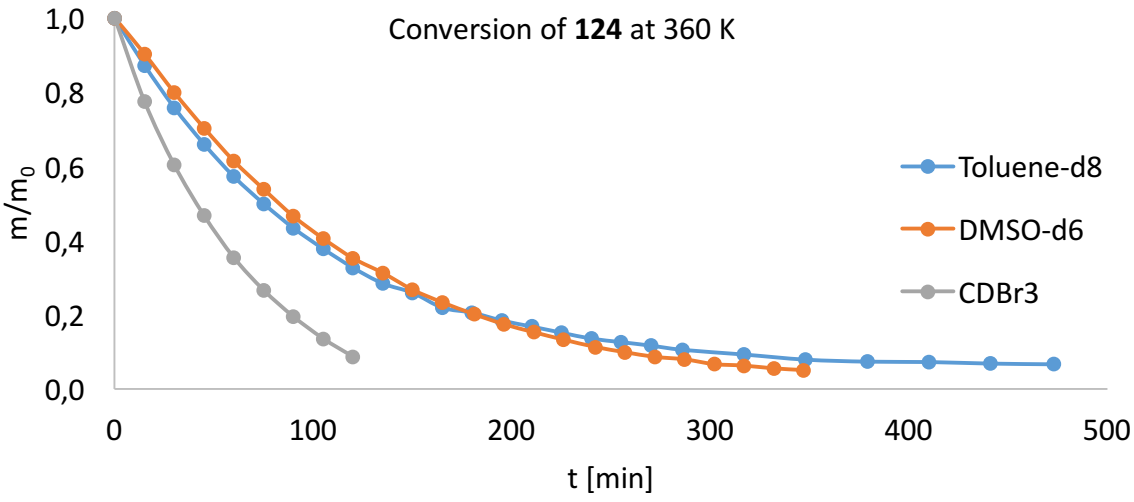


Figure 31.Conversion of **124** at 360 K in toluene-d_8, DMSO-d_6, and $CDBr_3$.

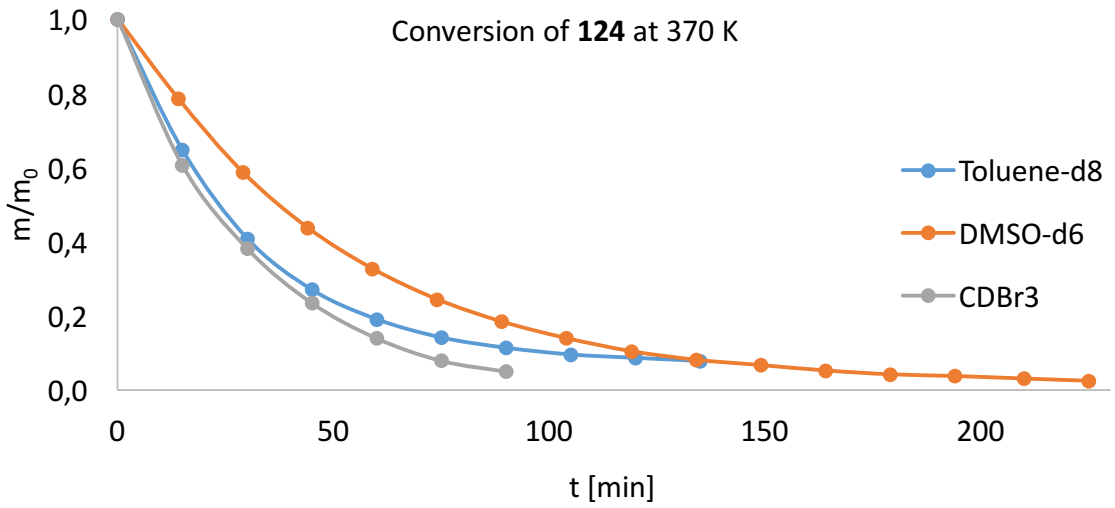


Figure 32. Conversion of **124** at 370 K in toluene-d_8, DMSO-d_6, and $CDBr_3$.

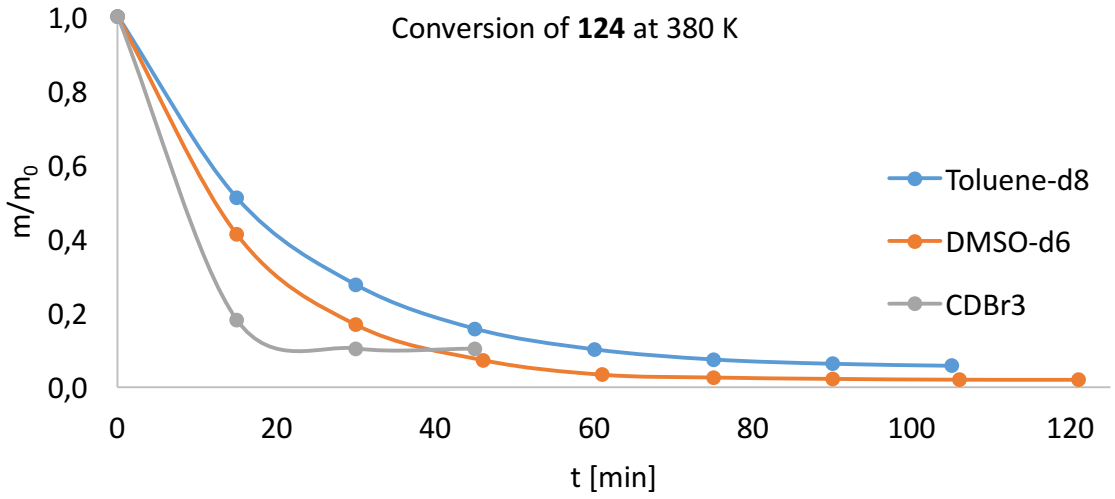


Figure 33. Conversion of **124** at 375 K in toluene-d_8 and 380 K in DMSO-d_6, and $CDBr_3$.

Assuming the divinylcyclopropane rearrangement to be a first order reaction, $\ln[A]$ was plotted against the time to calculate the rate constant k at different temperatures (Figure 34). A linear regression was carried out and from the slope of the curve the rate constant k was calculated (Table 26).

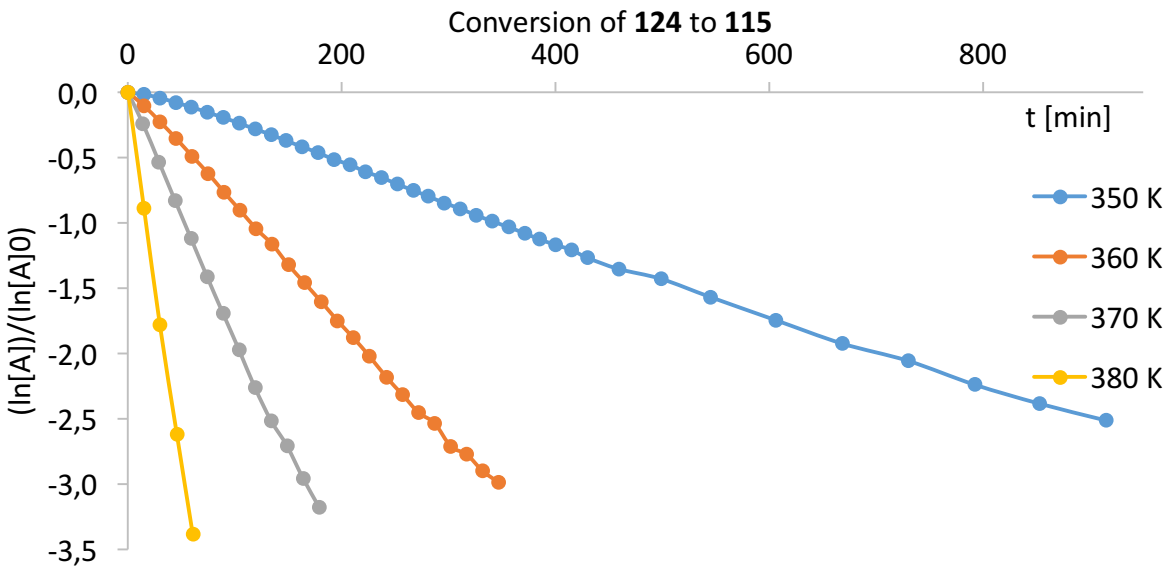


Figure 34. Calculation of the rate constants at different temperatures

To calculate the activation energy the results were displayed in an Arrhenius plot (Figure 35). Therefore, the logarithmic rate constants k were plotted against $\frac{1}{T}$. The activation energy (Table 27) was also calculated by the slope of the curve by using equation (g).

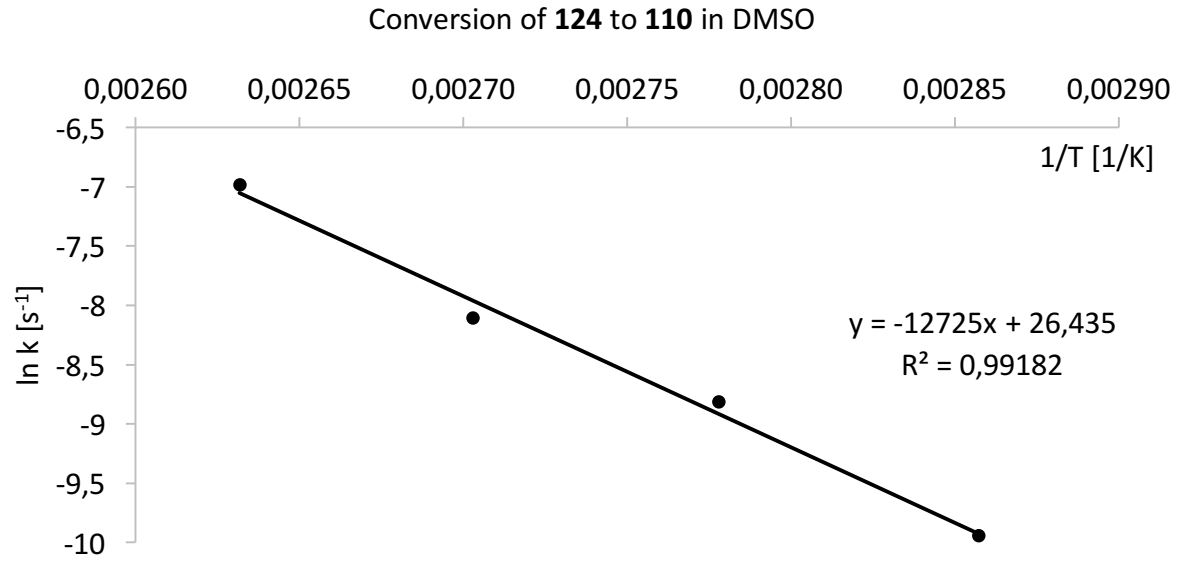


Figure 35. Arrhenius Parameter for **124**.

Table 26. Rate constants at different temperatures in different solvents. [a.] relative rate has not been determined as the reaction temperature was 5 K below the other two used solvents, [b.] this measurement series consists of three values.

Entry	Solvent	Temperature	rate constant $k[s^{-1}]$	relative rate
1	DMSO-d_6	350 K	$4.8\times10^{-5} \pm 3.9\times10^{-7}$	-
2	DMSO-d_6	360 K	$1.5\times10^{-4} \pm 1.1\times10^{-6}$	1
3	toluene-d_8	360 K	$1.4\times10^{-4} \pm 2.9\times10^{-6}$	0.9
4[a]	$CDBr_3$	360 K	$3.3\times10^{-4} \pm 1.2\times10^{-5}$	2.4
5	DMSO-d_6	370 K	$3.0\times10^{-4} \pm 4.4\times10^{-6}$	1
6	toluene-d_8	370 K	$4.1\times10^{-4} \pm 2.1\times10^{-5}$	1.4
7[a]	$CDBr_3$	370 K	$5.6\times10^{-4} \pm 6.7\times10^{-6}$	1.9
8	DMSO-d_6	380 K	$9.3\times10^{-4} \pm 2.0\times10^{-5}$	1
9[a]	toluene-d_8	375 K	$6.4\times10^{-4} \pm 2.9\times10^{-5}$	-
10[b]	$CDBr_3$	380 K	$1.3\times10^{-3} \pm 3.7\times10^{-4}$	1.4

Table 27. Activation energy in different solvents. [a.] The low activation energy might be caused by the presence of oxygen in the solution.

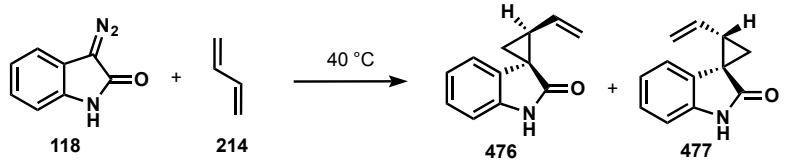
Entry	Solvent	Activation energy E_A $\left[\frac{kJ}{mol}\right]$
1	DMSO-d_6	105.8 ± 6.8
2	toluene-d_8	117.2 ± 5.1
3[a]	$CDBr_3$	75.7 ± 10.6

Interestingly, in case of *trans*-compound **124** (Scheme 125) the reaction proceeds the fastest in $CDBr_3$. Under these conditions the activation energy is significantly lowered. This indicates a change in the mechanism. Again, a zwitterionic intermediate or transition state can be excluded as DMSO would stabilise it much better compared to the other two solvents. This would result in a significant increased rate constant. Hence, the isomerisation has to take place *via* the diradical intermediate.

The solvents, especially $CDBr_3$, have not been degassed so that radical formation has likely been induced by oxygen causing a faster reaction at relatively low temperature. This effect seems to become less important when the reaction temperature is raised.

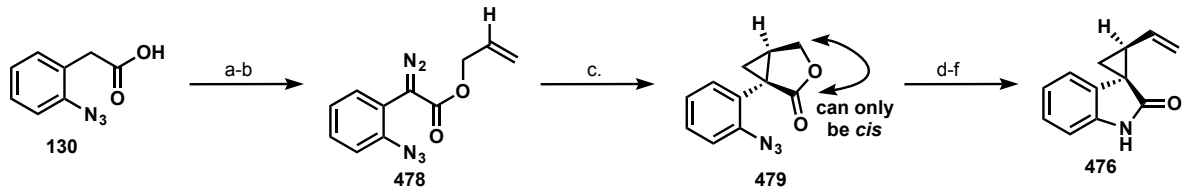
Furthermore, it has to be mentioned that the rate constants calculated from the measurements of $CDBr_3$ are inconclusive. At some point during the measurements a new signal appeared too close to the reference signal making it impossible to obtain reliable data henceforth.

Having the most suitable solvent in hands, we focused on relevance of the quaternary substitution on the cyclopropane for the divinylcyclopropane rearrangement. As we already had the data for **114** and **124** (Table 24 – 27), *cis*-nor-methyl **476** and the *trans*-nor-methyl compound **477** (Scheme 126) needed to be prepared. We knew from earlier studies that both diastereomers can be obtained by simply heating butadiene (**214**) and diazoisatine **118** to 40 °C in a sealed tube. However, the diastereomers could not be separated. Therefore, we chose two different routes to prepare *cis*-nor-methyl compound **477** and *trans*-nor-methyl compound **476**.



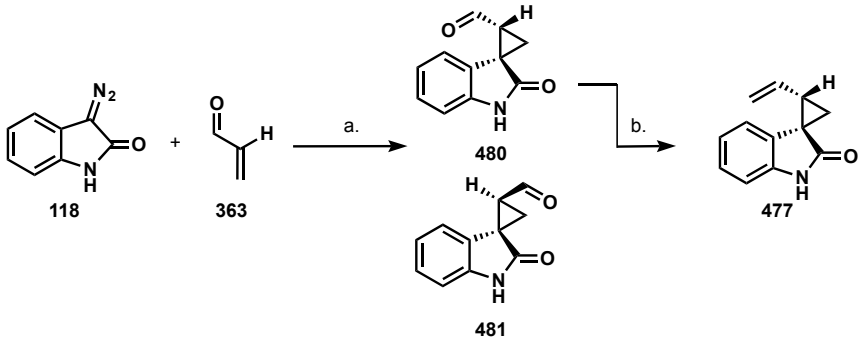
Scheme 126. Synthesis of an inseparable mixture of **476** and **477**.

In order to prepare **476** (Scheme 127), we started from acid **130** and allylic alcohol. After esterification and diazo transfer, **478** was converted to cyclopropane **479**. Azide **479** was reduced under Staudinger conditions and the lactone was opened using *i*-PrMgCl as base. The resulting alcohol was oxidised to aldehyde **481** using IBX, which was further converted into olefin **476** under Wittig conditions. All the reactions in this sequence delivered satisfying to very good yields and **476** could be obtained with an overall yield of 39% in a six-step linear sequence.



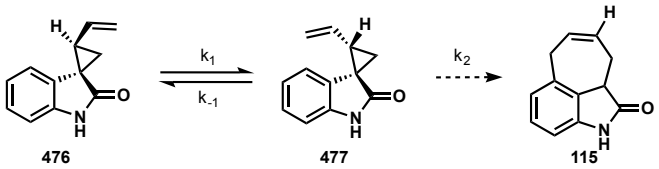
Scheme 127. Preparation of **476**, a. DIC (1.05 equiv.), allylic alcohol (1 equiv.), 4-DMAP (10 mol%), CH_2Cl_2, 92% b. ABSA (1.5 equiv.), DBU (3 equiv.), MeCN, 88%, c. $[(CuOTf)_2PhMe]$ (2 mol%), CH_2Cl_2, 75%, d. PBu_3 (1.1 equiv.), THF:H_2O, then THF, *i*PrMgCl (2.05 equiv.), 77%, e. IBX (1.2 equiv.), DMSO, 94%, f. Ph_3PMeBr (4 equiv.), NaHMDS (4 equiv.), –78 °C to rt, THF, 95%,

A slightly modified protocol of Subba Reddy furnished *cis*-compound **477** (Scheme 128).[139] In this case acrolein (**363**) was used instead of methylvinylketone to deliver a mixture of the two diastereomers (**480**/**481**). The excess of **480** was chromatographically separated in a yield of 53%, while a mixture of **481** containing 1-2% of **480** remained. Even after three column chromatographic purifications **481** could not be obtained in pure form. Finally, **477** was obtained by performing Wittig olefination on **480**.



Scheme 128. Preparation of **477**, a. acrolein (**363**; 5 equiv.), 95 °C, 53%, b. Ph_3PMeBr (4 equiv.), NaHMDS (4 equiv.), –78 °C to rt, THF, 89%.

With the two diastereomers in hands, the measurements could be executed. Therefore, a sample of **477** (Scheme 129) in DMSO-d_6 was heated in intervals of 10 °C to detect the reaction temperature. At 90 °C a second spot on TLC has been detected and therefore the crude was submitted to NMR. Instead of **115,** *trans*-nor-methyl compound **476** has been identified as the new formed product (Scheme 129). We assumed that the E_a for the cyclisation might be higher than for the isomerisation. A similar observation has been described by Cargle *et al*. during their investigations on vinylcyclopropane rearrangements in which the isomerisation was favoured over the rearrangement itself.[219]



Scheme 129. Isomerisation of **476** and **477** without divinylcyclopropane Rearrangement at 90 °C.

In order to overcome the isomerisation, the reaction temperature was set 20 °C higher for the NMR experiments. At 110 °C both the isomerisation and the product formation could be observed in an acceptable timeframe.

For the experiments a solution of 15 mg of the corresponding diastereomer (**476**/**477**) in DMSO-d_6 (700 µL) was submitted to NMR. The measurement started, when the reaction

temperature had been reached, which is also the reason for presence of all three compounds at the beginning of each measurement.

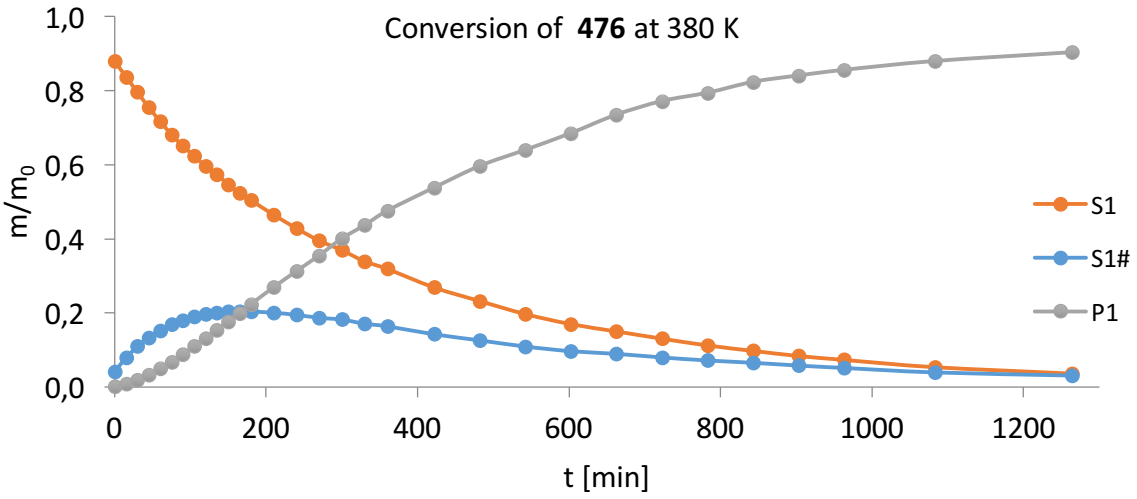


Figure 36. Reaction progress of the divinylcyclopropane rearrangement using **476** as starting material.

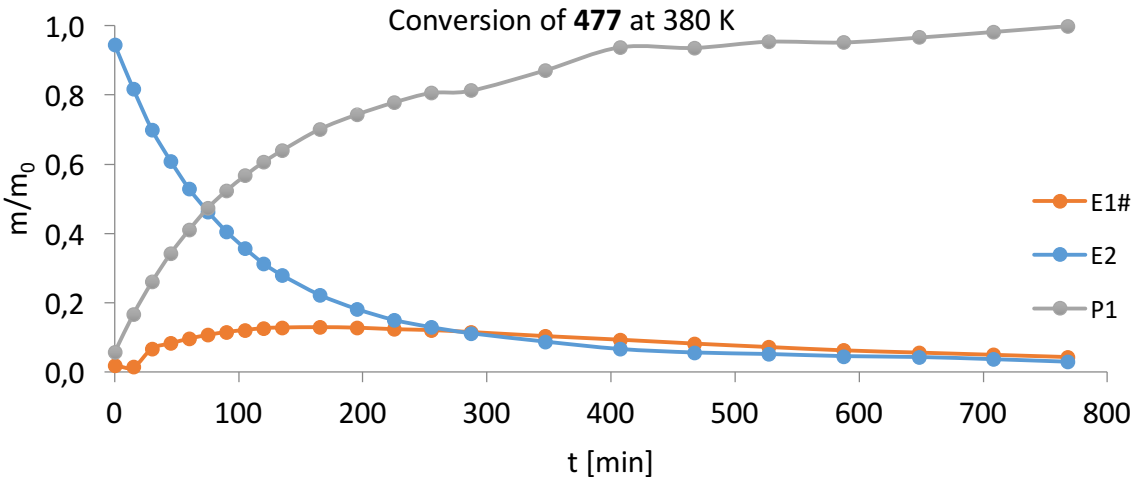


Figure 37. Reaction progress of the divinylcyclopropane rearrangement using cis as starting material.

Without calculations, it becomes obvious from the curve progressions of **477** (Figure 37) that k_2 has to be greater than k_1 and k_{-1}, as the concentration of **477** decreases quite fast. In the same time the concentration of **476** increases just to a maximum of 13% at minute 255. k_{-1} also has to be smaller than k_1, as otherwise **476** would accumulate more significantly.

Even though the kinetic scheme remains, calculation of the k values here becomes a tough task as the reaction of **476** and **477** (Scheme 129) does not proceed *via* a first order rate law. Here we have a reaction following the quasi stationary principle which makes the equation more difficult to solve by hand.

$$(1)\ \frac{d[cis]}{dt} = \frac{k_1[trans]}{(k_{-1} + k_2)[cis]} \quad \text{(h)}$$

$$(2)\ \frac{d[trans]}{dt} = k_{-1}[cis] - k_1[trans] \quad \text{(i)}$$

$$(3)\ \frac{d[prod]}{dt} = k_2[cis] \quad \text{(j)}$$

Rate constants k_1 and k_{-1} were calculated from the time-concentration relation of **477** at 380 K by Professor Herzig using a self-designed Fortran-program to give $k_1 = 5.8^{-5}s^{-1}$ and $k_{-1} = 2.8^{-5}s^{-1}$. Furthermore Professor Zifferer could validate the rate constants utilising the program Mathematika. To confirm these results, the following consideration was made.

In Figure 37 $\frac{d[trans]}{dt} = 0$ denotes the maximum concentration $[trans]_{M1}$of **476** ($[\mathbf{476}]_{M1} = 0.122, t_{M1} = 8100\ s$). Because the concentration of **477** at the same time is $[cis]_{M1} = 0.260$, insertion into eq. (i) furnishes a ratio of $R_1 = \frac{[\mathbf{476}]_{M1}}{[\mathbf{477}]_{M1}} = \frac{k_{-1}}{k_1} = 0.47$. With the above values of k_{-1} and k_1 we obtain R_1 = 0.47.

In Figure 36 $\frac{d[\mathbf{477}]}{dt} = 0$ denotes the maximum concentration $[cis]_{M2} = 0.22$ of **477** ($t_{M2} = 10{,}000\ s$), and $[trans]_{M2} = 0.566$ of **476** at the same time. These values introduced in equation (h) leads to

$$R_2 = \frac{[cis]_{M2}}{[trans]_{M2}} = \frac{k_1}{k_{-1} + k_2} = 0.39 \quad \text{(k)}$$

$$\text{with } R_3 = \frac{k_2}{k_1} \quad \text{(l)}$$

$$R_2 = \frac{1}{R_1 + R_3} \quad \text{(k)}$$

it follows that

$$R_3 = \frac{1 - R_1R_2}{R_2} = \frac{k_2}{k_1} = 2.09 \quad \text{(l)}$$

With $k_1 = 5.8{\times}10^{-5}s^{-1}$ we get for $k_2 = 1.2{\times}10^{-4}s^{-1}$

As measuring k_2 value for **114** (Scheme 125) at 380 K was not possible, it needed to be extrapolated from the obtained Arrhenius parameters.

$$k_2 = e^{27.32 - \frac{96177.95\frac{J}{mol}}{8.3144\frac{J}{K\times mol}\times 380K}} = 4.4{\times}10^{-2}s^{-1} \quad \text{(g)}$$

Table 28. relative rate constants at 380 K in DMSO.

Compound	$k_1\ [s^{-1}]$	$k_{-1}\ [s^{-1}]$	$k_2\ [s^{-1}]$
Methyl	9.2×10^{-4}	not detectable	4.4×10^{-2}
nor	5.8×10^{-5}	2.8×10^{-5}	1.2×10^{-4}

It is remarkable that the substitution of a hydrogen by a methyl group causes an overall reactivity span of a factor of 1570 (Table 28). Comparing the rate constants for the Cope rearrangement, *cis*-compound **114** (Scheme 125) still reacts 367 times faster than nor-methyl compounds **476** and **477** revealing the significant influence of the methyl substituent. In theory we know that the decreased angle cannot influence the reaction to that extent. It is more likely that the effect of the reactive rotamere is decisive in this case as the acceleration is within the range.

Not less important is the comparison of the relative rates of the ring opening (k_1 and k_{-1}; Table 28) and the Cope rearrangement (k_2). In case of the nor-methyl series, the rates of *cis* and *trans* configured cyclopropane do not differ greatly. Here the divinylcyclopropane rearrangement (k_2) is 4.3 times faster than the isomerisation from *cis* to *trans* (k_{-1}) and 2.1 times faster than the isomerisation from *trans* to *cis* (k_1). In addition, the formal equilibrium constant can be obtained which means that **114** is thermodynamically more stable than **124**.

$$K_{eq} = \frac{cis}{trans} = \frac{1.2\times10^{-4}s^{-1}}{5.8\times10^{-5}s^{-1}} = 2.1 \qquad \text{(m)}$$

In case of **124** and **114** (Scheme 125), the Cope rearrangement is 476 times faster than the isomerisation and for that reason the ring opening cannot be observed. Generally speaking, the methyl group stabilises the ring opening of the cyclopropane (rate factor 16) which is in line with enhanced radical stabilisation in **124a**. On the other hand, the rate constant of the Cope rearrangement is increased overproportional making the reaction the greatest beneficiary of the methyl group.

Since aldehyde **123** (Figure 38) and **418** (Figure 39) crystallised readily, we were able to measure the change of the angles in the X-ray structure.

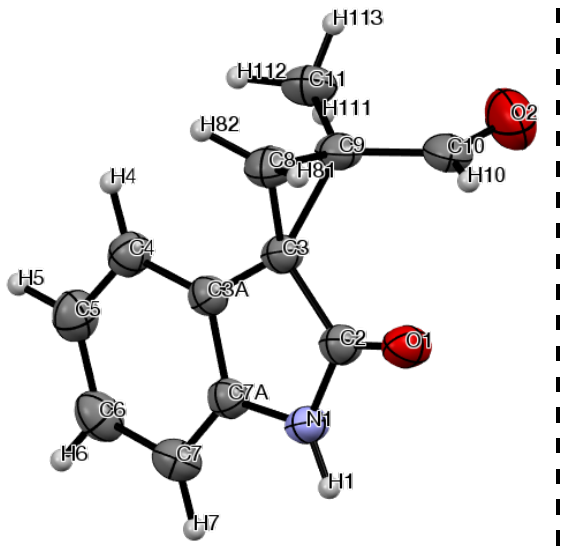


Figure 38. X-ray structure of **123**

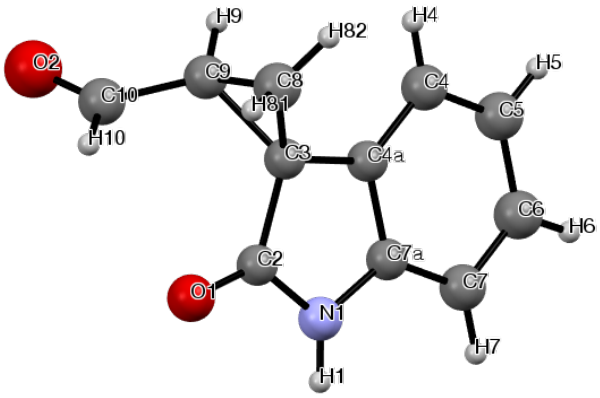


Figure 39. X-ray structure of **418**

Table 29. Table of angles of **123** and **418**.

Entry	Label	Methyl	Nor	Difference
1	α	115.3°	116.2°	+0.9°
2	β	115.0°	119.9°	+4.9°
3	γ	116.1°	117.0°	+0.9°
4	δ	58.37°	58.6°	+0.23°
5	ε	58.16°	59.1°	+0.94°
6	η	63.5°	62.3°	–1.2°

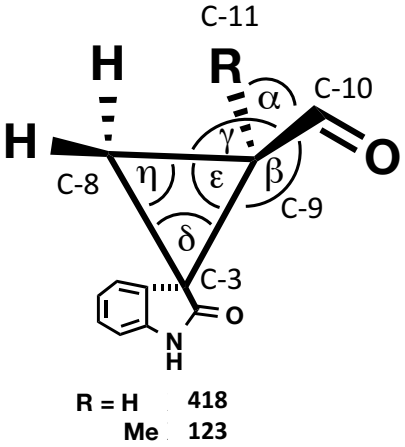


Figure 40. Angles of **481** and **123**.

The classic Thorpe-Ingold theory is primarily concerned with the change of the angles α and ε (Entry 1 and 4, Table 29). In this case the angle decreases in presence of the methyl-group by 0.9° for α and ε. This is only 30% of the maximum effect of 3° which cannot have such an influence on the rate constant.

Considering the change of angle β (Entry 2, Table 29) may give an explanation for the dramatic increase of the rate constant, if the effect is similar for **114**. Here, the presence of the methyl group causes an anglecompression by 4.9°, suggesting a closer positioning of the vinyl substituent to the benzene core. This proximity guarantees a good orbital overlap causing the rearrangement to occur at room temperature.

Another aspect might be the change in the inner bond angles of the cyclopropane. In case of **123** (Table 29), ε is decreased by 0.94° to 58.16° and on the other side η widened by 1.2° to 63.5°. This imbalance of the inner bond angles of the cyclopropane may cause an increase of the ring strain, which facilitates the ring opening and therefore the isomerisation and the Cope rearrangement.

The hypothesis is supported by the deviations of the bond length (Table 30). While the bond length of an unsubstituted cyclopropane is 1.510 Å,[220] the two systems prepared reveal deviations for all three bonds. Furthermore, the differences among the two diastereomers are apparent.

Table 30. Length of the cyclopropane bonds of **123** and **418**.

Entry	Label	Methyl	Nor-methyl	Difference
1	C-9;C-3	1.577 Å	1.544 Å	0.033 Å
2	C-9;C-8	1.501 Å	1.489 Å	0.012 Å
3	C-8;C-3	1.497 Å	1.497 Å	±0.000 Å

With the introduction of the methyl group, the bond length between C-9;C-3 and C-9;C-8 is extended compared to **418** (Table 30). In this case the lengthening of the C-9;C-3 bond by 0.033Å causes a weakening of this bond which is also beneficial for both, the isomerisation and the Cope rearrangement.

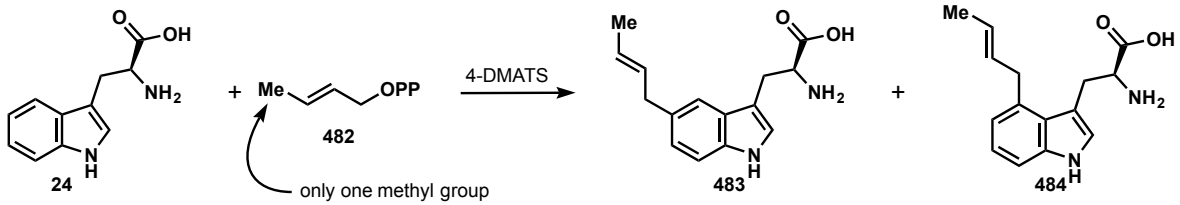
4.4 Summary and Outlook

This project examined the influence of the *gem*-dialkyl effect on the divinylcyclopropane rearrangement. Introducing a methyl-group on the cyclopropane caused a tremendous increase of the reaction rate presumably attributable to two factors:

1. Thorpe-Ingold effect, more precise, the effect of the reactive rotamere. Here, the steric demand of the methyl group constrains the flexibility of the vinyl group. This increases the energy of the overall system meaning in effect that the activation energy is decreased.
2. A hyperconjugative stabilisation of the incipient endocyclic double bond in **124** by the methyl substituent.

Moreover, we were able to proof the influence of the Thorpe-Ingold effect by X-ray single crystal structure of **123** and **418.** The methyl group of **123** caused an angle decrease of β by 4.9° generating proximity between the benzene core and the vinyl group and therefore it promotes the Cope rearrangement. Furthermore, a significant change of the inner bond angles of the cyclopropane was detected, leading to an increased ring strain which should promote both the isomerisation and the Cope rearrangement.

As implied in Chapter 1 the effects exerted by **114** (Figure 9) may be essential in the DMAT-synthase. In the reverse prenylated tryptophan, the *gem*-dimethyl group may also induce a Thorpe-Ingold effect which accelerates the Cope rearrangement. The two alkyl groups also ensure that the reaction does only proceed into indole C-4. The necessity of the *gem*-dimethyl group in the biological system is revealed by experiments performed by Liebhold *et al*. Utilising **482** (Scheme 130) which cannot exert the Thorpe-Ingold effect caused the formation of a mixture of C-4 (**484**) and C-5 (**483**) prenylated products.

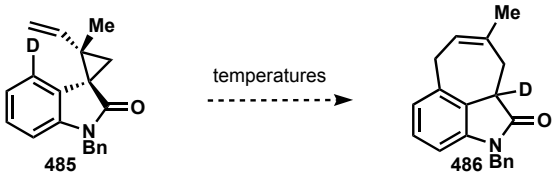


Scheme 130. Liebhold's experiments with 4-DMATS and different substrates.

In order to continue this project, the experiments should be repeated in degassed solvents, to exclude the influence of oxygen on this reaction. Furthermore, benzene should be replaced by toluene to obtain more consistent results in the unipolar series as the methyl group may interfere with the reaction.

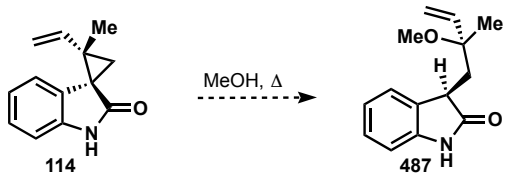
Another interesting aspect of this divinylcyclopropane rearrangement is to clarify the whereabouts of the proton on C-4. On the one hand, it can be cleaved and dissolved in the surrounding solution, not impairing the reaction. On the other hand, the C-4 proton can be delivered internally into C-3. In a first experiment the reaction should be performed under absolutely dry and aprotic conditions. If the proton is delivered internally, it should not hamper the reaction rate. If the proton is cleaved and dissolved in the solution before it re-protonates C-3, the rate should drop or the reaction should stop at some point delivering no or decomposition products.

An additional experiment would be to perform the reaction with the deuterated derivative **485** (Scheme 131). Internal delivery would cause a significant amount of C-3 deuterated product. A drawback of this experiment is that deuterium has a different acidity and creactivity compared to protons This experiment should be only performed with protected oxindoles as the proton of the nitrogen may affect the results.



Scheme 131. Labeling experiment.

The mechanism of the isomerisation may simply be elucidated by performing the reaction in a protic and nucleophile solvent as performed by Cram (Scheme 119, Scheme 132).



Scheme 132. Solvatisation experiment.

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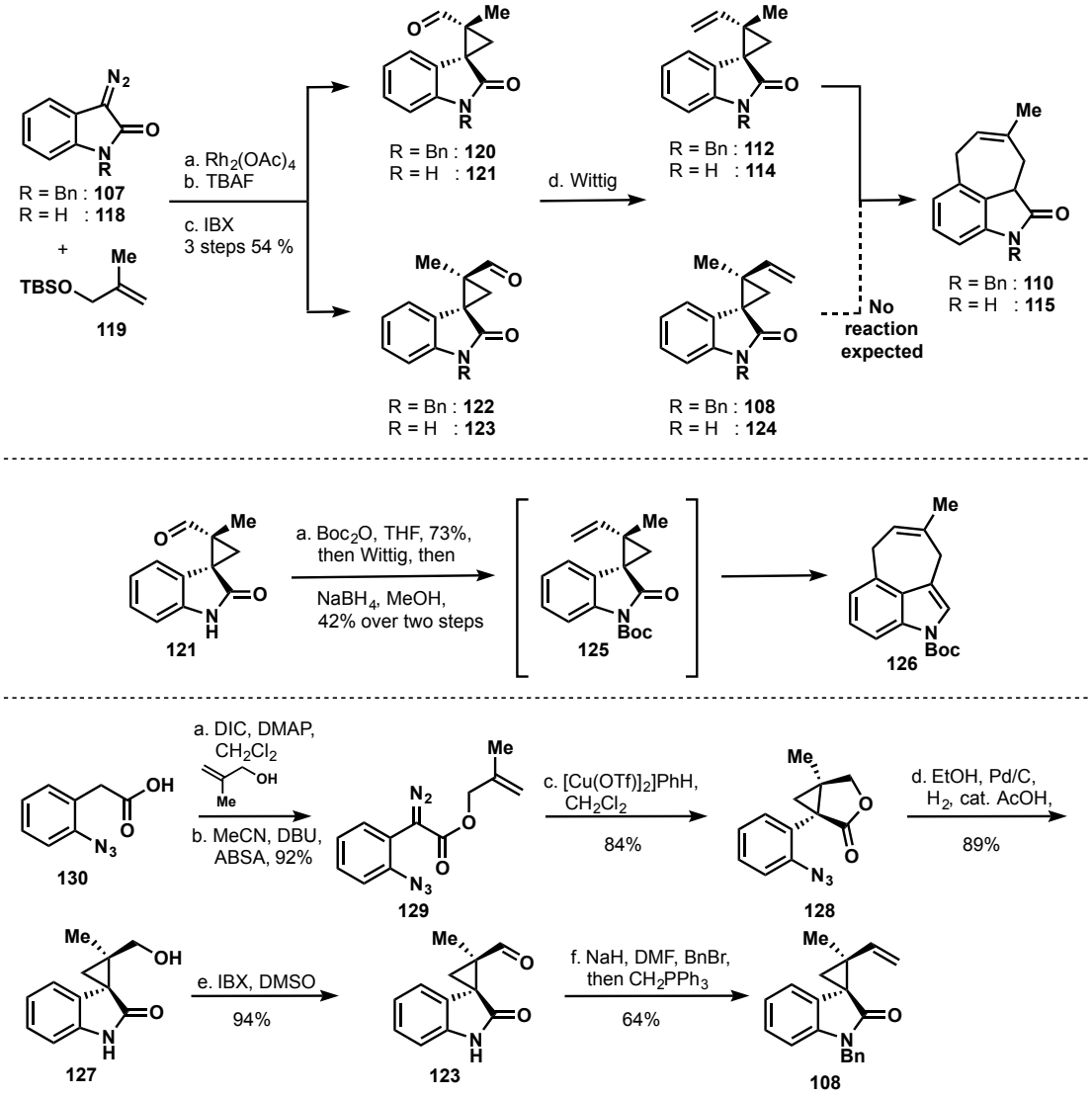


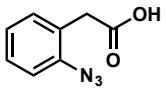
5.2 General

All reactions were carried out in oven-dried glassware under an argon atmosphere, unless otherwise stated. Anhydrous CH_2Cl_2 (DCM) was distilled from CaH_2 under argon and anhydrous THF was distilled from Na and benzophenone under argon atmosphere. Other anhydrous solvents were obtained by filtration through drying columns (Et_2O, DMF, CH_3CN, toluene, benzene, hexane, methanol) on a GlassContour system. Reactions were magnetically and mechanically stirred and monitored by thin layer chromatography (TLC) with silica gel 60-F254 plates. Flash column chromatography was performed with silica gel 60 Å of Acros under pressure. Yields refer to chromatographically and spectroscopically pure compounds, unless otherwise stated. NMR spectra were recorded on a 400 MHz spectrometer of Bruker. Unless otherwise stated, all NMR spectra were measured in $CDCl_3$ solution and referenced to the residual $CHCl_3$ signal (^1H, δ = 7.26 ppm, ^{13}C, δ = 77.16 ppm). All ^1H and ^{13}C shifts are given in

ppm (*s* = singlet, *d* = doublet, *t* = triplet, *q* = quadruplet, *m* = multiplet, *b* = broad signal). Assignments of proton resonance were confirmed, when possible, by correlated spectroscopy.

5.3 Procedures

5.3.1 *2-azidophenylacetic acid (130)*

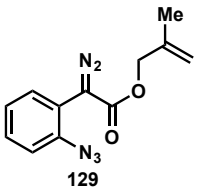


130

2-Nitrophenylacetic acid (10.0 g, 55.0 mmol, 1 equiv.) was reduced with Pd/C (10%, 650 mg, 5.50 mmol, 0.1 equiv.) in EtOH (60 mL) and K_2CO_3 (7.70 g, 55.0 mmol, 1 equiv.) under H_2-pressure (30 bar) for 18 h. After complete consumption of the starting material (TLC-control hexane:EtOAc 1:1) the crude material was dissolved in a solution of NaOH (2.20 g, 55.0 mmol, 1 equiv.) in H_2O (36 mL), cooled to 0 °C and added to a precooled solution of $NaNO_2$ (3.80 g, 55.0 mmol, 1 equiv.) in H_2O (14 mL). The combined solutions were added dropwise over 2 h to a –5 °C precooled solution of H_2SO_4 (8.80 mL, 165 mmol, 3 equiv.) in H_2O (172 mL) whereas the reaction temperature should never get over 0 °C. Then a solution of NaN_3 (3.60 g, 55.0 mmol, 1 equiv.) in H_2O (20 mL) was added slowly and after complete addition the reaction mixture was stirred for 30 min, quenched by the addition of H_2O (250 mL) and EtOAc (250 mL). The phases were separated and the aqueous layer was saturated with NaCl and extracted with EtOAc (3 x 200 mL), the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford the desired product **130** in 74% (7.20 g, 40.1 mmol) yield as an orange/yellow solid.

^{1}H-NMR (400 MHz, CD_3OD, δ): 3.59 (*s*, 2H), 7.12 (ddd, *J* = 1.0, 7.5, 7.5 Hz, 1H), 7.21 (dd, *J* = 0.8, 8.0 Hz, 1H), 7.25 (dd, *J* = 1.3, 7.5 Hz, 1H), 7.35 (ddd, *J* = 1.5, 7.7, 7.7 Hz, 1H) ppm. **^{13}C-NMR** (100 MHz, CD_3OD, δ): 37.2, 119.1, 125.9, 127.8, 129.8, 132.7, 140.1, 174.9 ppm.**IR (neat sample)**: 2923, 2131, 1688, 1285, 1237, 952, 754 cm^{-1}.

5.3.2 *2-methylallyl 2-(2-azidophenyl)-2-diazoacetate (129)*



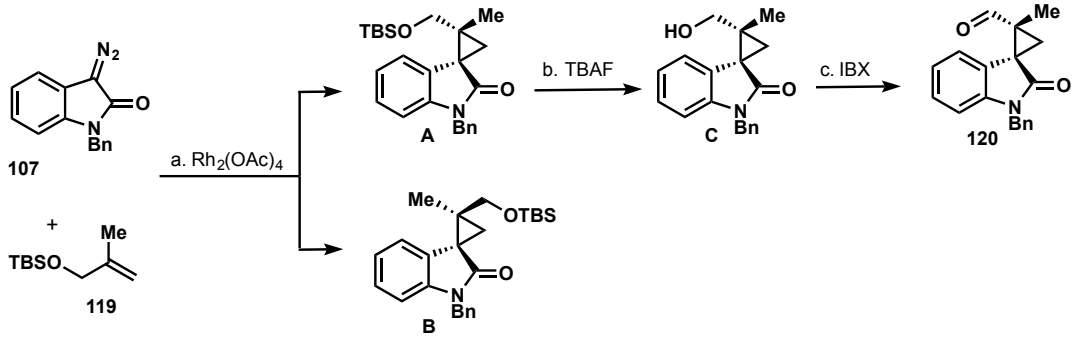
129

Azide **130** (2.00 g, 11.3 mmol, 1 equiv.), β-methallylalcohol (1.00 mL, 11.9 mmol, 1.05 equiv.) and DMAP (300 mg, 2.30 mmol, 0.2 equiv.) were dissolved in CH_2Cl_2 (38 mL). Then DIC (800 µL,

11.9 mmol, 1.05 equiv.) was slowly added to the solution. After complete consumption of the starting material the reaction was quenched with water and extracted with EtOAc (3 x 100 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was then purified by flash chromatography (hexane:EtOAc 20:1). The obtained 2-methallyl-2-(2-azidophenyl)-acetate was used directly for the diazotation reaction. The β-methallylester (2.40 g, 10.4 mmol, 1 equiv.) and ABSA (4.40 g, 10.9 mmol, 1.05 equiv.) were dissolved in THF (64 mL). DBU (3.10 mL, 20.7 mmol, 2 equiv.) was added and the solution was stirred for 18 h. After complete consumption of the substrate, the reaction was hydrolysed by addition of NH_4Cl solution. The aqueous layer was extracted with EtOAc (3 x 250 mL), the combined organic layers were washed with brine solution, dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was then purified by flash chromatography (hexane:EtOAc 40:1) to afford the desired product **129** in 92% (2.50 g, 9.60 mmol) yield as a bright orange oil.

^{1}H-NMR (400 MHz, $CDCl_3$, δ): 1.78 (s, 3H), 4.66 (s, 2H), 4.94 – 4.97 (m, 1H), 4.98 - 5.00 (m, 1H), 7.17 – 7.21 (m, 2H), 7.33 – 7.37 (m, 1H), 7.55 (dd, *J* = 1.5, 8.0 Hz, 1H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$, δ): 19.6, 68.3, 113.1, 116.6, 118.7, 125.3, 129.1, 129.4, 131.5, 137.4, 140.0, 165.5 ppm. **IR (neat sample)**: 3019, 2127, 2096, 1699, 1282, 1153, 1017, 749 cm^{-1}. **HRMS** (ESI) (*m*/*z*): $[M]^+$ calcd for $C_{12}H_5N_5O_2$ 257.0913; not found, decomposition.

5.3.3 *1'-benzyl-2-(((tert-butyldimethyl-silyl)-oxy)methyl)-2-methylspiro[cyclo-propane-1,3'-indolin]-2'-one (A and B)*



$Rh_2(OAc)_4$ (5.00 mg, 12.0 µmol, 3 mol%) was added to a solution of diazooxindole (200 mg, 800 µmol, 1 equiv.) in *tert*-butyldimethyl((2-methylallyl)oxy)silane (3 mL) and CH_2Cl_2 (500 µL). The addition was accompanied by a slow color change from orange to dark red brown and the evolution of nitrogen gas. After complete consumption of the starting material, the crude product was concentrated *in vacuo* and purified by flash chromatography (hexane:EtOAc 30:1) to give diastereomers **A** and **B** in a combined yield of 60% in a 1:1 ratio (100 mg, 240 µmol of **A** and 100 mg, 240 µmol of **B**).

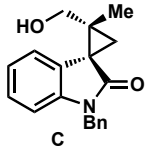
Diastereomer A

^{1}H-NMR (400 MHz, $CDCl_3$, δ): –0.11 (s, 3H), 0.01 (s, 3H), 0.75 (s, 9H), 1.60 (s, 3H), 1.75 (d, *J* = 4.8 Hz, 1H), 1.86 (d, *J* = 4.9 Hz, 1H), 3.76 (d, *J* = 10.8 Hz, 1H), 3.90 (d, *J* = 10.8 Hz, 1H), 4.81 (d, *J* = 15.9 Hz, 1H), 5.17 (d, *J* = 15.8 Hz, 1H), 6.73 (d, *J* = 7.7 Hz, 1H), 6.94 (ddd, *J* = 1.0, 7.6, 7.6 Hz, 1H), 7.05 (dd, *J* = 0.8, 7.5 Hz, 1H), 7.10 (ddd, *J* = 1.3, 7.7, 7.7 Hz, 1H), 7.21 – 7.31 (m, 5H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$, δ): –5.4, –5.3, 15.5, 18.2, 25.8, 28.0, 36.0, 38.4, 43.9, 65.9, 108.8, 121.4, 126.4, 127.2, 127.5, 128.9, 129.0, 136.6, 143.1, 175.8 ppm. **IR (neat sample)**: 2928, 2854, 1706, 1464, 1360, 1094, 834, 729 cm^{-1}. **HRMS** (ESI) (*m*/*z*): $[M]^+$ calcd for $C_{25}H_{33}NO_2Si$ 407.2281; found $C_{25}H_{33}NO_2SiLi^+$ 413.2667.

Diastereomer B

^{1}H-NMR (400 MHz, $CDCl_3$, δ): 0.06 (s, 3H), 0.09, (s, 3H), 0.90 (s, 9H), 1.50 (s, 3H), 1.57 (d, *J* = 4.6 Hz, 1H), 1.96 (d, *J* = 4.8 Hz, 1H), 4.04 (d, *J* = 10.4 Hz, 1H), 4.29 (d, *J* = 10.3 Hz, 1H), 4.84 (d, *J* = 15.8 Hz, 1H), 5.15 (d, *J* = 15.7 Hz, 1H), 6.76 (d, *J* = 7.6 Hz, 1H), 6.99 (ddd, *J* = 0.9, 7.3, 7.3 Hz, 1H), 7.00 – 7.02 (m, 1H), 7.03 (dd, *J* = 1.4, 7.4 Hz, 1H), 7.14 (ddd, *J* = 1.4, 7.5, 7.5 Hz, 1H), 7.16 – 7.32 (m, 5H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$, δ): –5.2, 17.6, 18.5, 26.1, 29.1, 35.5, 38.2, 44.0, 64.1, 108.8, 121.2, 121.7, 126.5, 127.3, 127.4, 128.8, 128.9, 136.6, 143.5, 175.9 ppm. **IR (neat sample)**: 2928, 2854, 1706, 1464, 1360, 1094, 834, 729 cm^{-1}. **HRMS** (ESI) (*m*/*z*): $[M]^+$ calcd for $C_{25}H_{33}NO_2Si$ 407.2281; found $C_{25}H_{33}NO_2SiLi^+$ 413.2667.

5.3.4 *1'-benzyl-2-(hydroxymethyl)-2-methylspiro[cyclopropane-1,3'-indolin]-2'-one (C)*

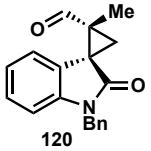


C

TBAF (1 M in THF, 100 µL, 100 µmol, 1 equiv.) was added to a solution of diastereomer **A** (40.0 mg, 100 µmol, 1 equiv.) in THF (1 mL). The addition was accompanied by a colour change from red to yellow. After 10 min. another equivalent of TBAF (1 M in THF, 100 µL, 100 µmol, 1 equiv.) was added to the solution, which was stirred for further 10 min, then quenched with NH_4Cl-solution and extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash chromatography (hexane:EtOAc 1:1) to afford the free alcohol **C** in 87% (25.0 mg, 84.0 µmol) yield.

^{1}H-NMR (400 MHz, $CDCl_3$, δ): 1.68 (s, 3H), 1.76 (d, *J* = 4.8 Hz, 1H) 1.92 (d, *J* = 4.9 Hz, 1H), 3.89 (d, *J* = 12.2 Hz, 1H), 3.96 (d, *J* = 12.3 Hz, 1H), 4.93 (d, *J* = 15.8 Hz, 1H), 5.04 (d, *J* = 15.8 Hz, 1H), 6.80 (d, *J* = 7.8 Hz, 1H), 6.98 (ddd, *J* = 1.0, 7.6, 7.6 Hz,1H), 7.10 (d, *J* = 7.5 Hz, 1H), 7.15 (ddd, *J* = 1.2, 7.7, 7.7 Hz, 1H), 7.24 – 7.34 (m, 5H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$, δ): 14.5, 29.2, 35.7, 39.0, 44.2, 66.9, 109.2, 120.7, 122.0, 127.1, 127.4, 127.6, 128.2, 128.9, 136.3, 143.3, 175.3 ppm. **IR (neat sample)**: 3436, 2927, 1686, 1438, 1186, 907, 726, 696 cm^{-1}. **HRMS** (ESI) (*m*/*z*): $[M]^+$ calcd for $C_{19}H_{19}NO_2$ 293.1416; found $C_{19}H_{20}NO_2$ 294.1491.

5.3.5 *(1S,2R)-1'-benzyl-2-methyl-2'-oxospiro[cyclopropane-1,3'-indoline]-2-carbaldehyde (120)*

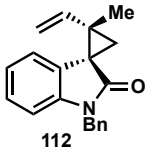


120

IBX (110 mg, 360 µmol, 1.05 equiv.) was added to a solution of alcohol **C** (100 mg, 340 µmol, 1 equiv.) in DMSO (1 mL). After 1.5 h the reaction was quenched with water, extracted with EtOAc (3 x 50 mL), the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash chromatography (hexane:EtOAc 3:1) to afford aldehyde **120** in 95% (94.0 mg, 320 µmol) yield.

^{1}H-NMR (400 MHz, $CDCl_3$, δ): 1.75 (s, 3H), 2.16 (d, *J* = 5.3 Hz, 1H) 2.51 (d, *J* = 5.3 Hz, 1H), 4.88 (d, *J* = 15.7 Hz, 1H), 5.08 (d, *J* = 15.7 Hz, 1H), 6.79 (d, *J* = 7.8 Hz, 1H), 6.93 – 6.97 (m, 1H), 7.04 (d, *J* = 7.2 Hz, 1H), 7.15 (ddd, *J* = 0.9, 7.8, 7.8 Hz, 1H), 7.24 – 7.34 (m, 5H), 9.57 (*s*, 1H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$, δ): 11.0, 25.9, 38.1, 43.1, 44.3, 109.2, 122.1, 122.8, 126.0, 127.4, 127.7, 127.8, 128.9, 135.9, 143.1, 173.2, 198.5 ppm. **IR (neat sample)**: 3077, 1685, 1611, 1346, 1184, 752, 700 cm^{-1}. **HRMS** (ESI) (*m*/*z*): calcd for $C_{19}H_{17}NO_2$ $[M + H]^+$ 292.1338; found 292.1339.

5.3.6 *1'-benzyl-2-methyl-2-vinylspiro[cyclopropane-1,3'-indolin]-2'-one (112)*



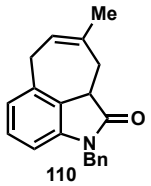
112

A suspension of methyl triphenylphosphonium bromide (170 mg, 460 µmol, 3 equiv.) in THF (0.8 mL) was cooled to –78 °C. To this solution was added NaHMDS (2M in THF, 230 µL, 460 µmol, 3 equiv.) which was accompanied by a color change to bright orange. The solution was stirred at –78 °C for 10 min, then warmed up to 0 °C, stirred for further 20 min and cooled

to –78 °C again. Then a solution of aldehyde **120** (45.0 mg, 150 µmol, 1 equiv.) in THF (0.2 mL) was added slowly. The solution was stirred for 10 min and warmed up to 0 °C. It was quenched with saturated NH_4Cl solution, then diluted with water, extracted with EtOAc (3 × 60 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash chromatography (hexane:EtOAc 3:1) to afford olefin **112** in 84% (45.0 mg, 130 µmol) yield as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$, δ): 1.69 (s, 3H), 1.94 (d, *J* = 4.8 Hz, 1H) 2.05 (d, *J* = 4.8 Hz, 1H), 4.93 (d, *J* = 15.7 Hz, 1H), 5.05 (d, *J* = 15.7 Hz, 1H), 5.31 (dd, *J* = 1.2, 10.4 Hz, 1H), 5.35 (dd, *J* = 1.2, 17.2 Hz, 1H), 5.96 (dd, *J* = 10.2, 17.1 Hz, 1H), 6.78 (d, *J* = 7.5 Hz, 1H), 6.94 (ddd, *J* = 0.7, 7.2, 7.5 Hz, 1H), 6.98 (dd, *J* = 1.7, 7.5 Hz, 1H), 7.12 (ddd, *J* = 1.7, 7.5, 7.5 Hz, 1H), 7.24 – 7.36 (m, 5 H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$, δ): 16.5, 29.7, 36.7, 38.9, 44.2, 108.8, 117.0, 121.3, 122.1, 126.5, 127.5, 127.6, 128.3, 128.8, 136.5, 139.5, 143.0, 175.4 ppm. **IR (neat sample)**: 2922, 1699, 1487, 1342, 906, 725 cm^{-1}. **HRMS** (ESI) (*m*/*z*): calcd for $C_{20}H_{19}NO$ $[M + Na]^+$ 312.1364; found 312.1361.

5.3.7 *1-benzyl-4-methyl-2a,3-dihydro-1H-cyclohepta[cd]indol-2(6H)-one (110)*

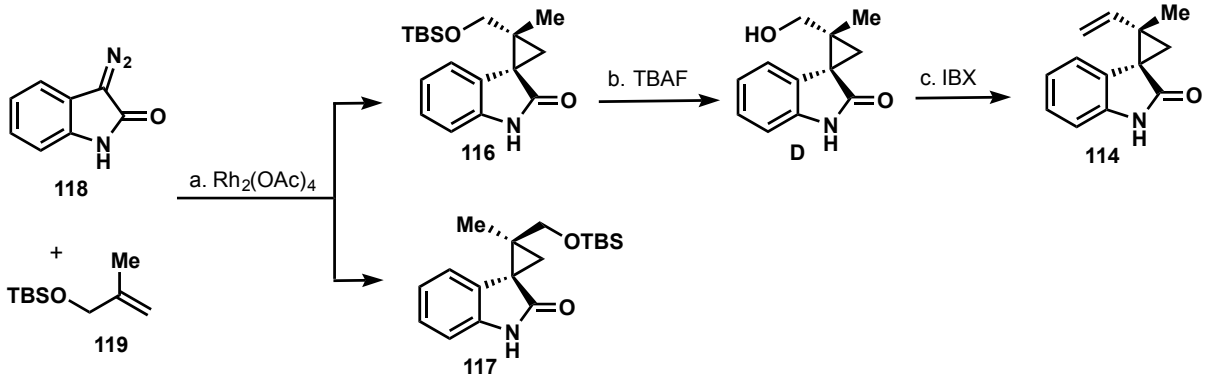


110

Rearrangement of olefin **112** (100 mg, 350 µmol) took already place at room temperature but to speed up the reaction was dissolved in benzene (1.8 mL) and was heated at 60 °C in a sealed tube. After complete consumption the product was concentrated *in vacuo* and purified by flash chromatography (hexane:EtOAc 3:1) to afford the cyclisation product **110** in 55% (55.0 mg, 190 µmol) yield.

^{1}H-NMR (400 MHz, $CDCl_3$, δ): 1.79 (s, 3H), 2.16 (dd, *J* = 15.4, 15.4 Hz, 1H), 2.78 (ddd, *J* = 2.9, 4.6, 16.9 Hz, 1H), 3.19 (dd, *J* = 7.2, 19.1 Hz, 1H), 3.74 – 3.78 (m, 1H), 3.82 (dd, *J* = 4.8, 13.0 Hz, 1H), 4.91 (d, *J* = 2.7 Hz, 1H), 5.53 (d, *J* = 6.1 Hz, 1H), 6.59 (d, *J* = 7.5 Hz, 1H), 6.76 (d, *J* = 7.9 Hz, 1H), 7.06 (dd, *J* = 7.9, 7.9 Hz, 1H), 7.22 – 7.33 (m, 5H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$, δ): 27.8, 33.0, 33.7, 43.6, 43.9, 106.9, 120.1, 122.2, 127.4, 127.7, 127.8, 128.7, 128.9, 134.1, 136.1, 137.3, 142.3, 177.8 ppm. **IR (neat sample)**: 2904, 1700, 1608, 1494, 1341, 982, 775, 726 cm^{-1}. **HRMS** (ESI) (*m*/*z*): $[M]^+$ calcd for $C_{20}H_{19}NO$ 289.1467; found $C_{20}H_{20}NO$ 290.1479.

5.3.8 *2-(((tert-butyldimethylsilyl)oxy)methyl)-2-methylspiro[cyclopropane-1,3'-indolin]-2'-one (116 and 117).*



$Rh_2(OAc)_4$ (21.0 mg, 50.3 µmol, 0.02 equiv.) in dioxane (1 mL) was heated to 65 °C for ten minutes. To the warm solution was added TBS-alcohol **119** (6 mL) and then diazoisatine (**118**, 400 mg, 2.51 mmol, 1 equiv.) in dioxane (8 mL). After full consumption of diazoistaine, the solvent was removed *in vacuo* and the crude product was purified by flash chromatography (hexane:EtOAc 4:1) to give diastereomers **116** and **117** in a combined yield of 33% in a 1.6:1 ratio (160 mg, 504 µmol of **116** and 100 mg, 315 µmol of **117**).

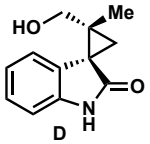
Diastereomer 116

^{1}H-NMR (400 MHz, $CDCl_3$, δ): 0.03 (s, 3H), 0.05 (s, 3H), 0.85 (s, 9H), 1.46 (s, 3H), 1.52 (d, *J* = 4.8 Hz, 1H), 1.91 (d, *J* = 4.8 Hz, 1H), 4.01 (d, *J* = 10.2 Hz, 1H), 4.17 (d, *J* = 10.2 Hz, 1H), 6.96 (d, *J* = 7.6 Hz, 1H), 6.98 (d, *J* = 4.1 Hz, 2H), 7.17 – 7.21 (m, 1H), 9.31 (b, 1H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$, δ): –5.2, –5.2, 17.6, 18.5, 26.0, 29.2, 36.0, 38.3, 64.0, 109.7, 121.1, 122.0, 126.5, 129.4, 141.8, 178.6 ppm. **IR (neat sample)**: 3228, 2926, 2855, 1711, 1471, 1345, 1227, 1106, 977 cm^{-1}. **HRMS** (ESI) (*m*/*z*): calcd for $C_{18}H_{27}NO_2Si$ $[M + Na]^+$ 340.1709; found 340.1693.

Diastereomer 117

^{1}H-NMR (400 MHz, $CDCl_3$, δ): –0.07 (s, 3H), 0.01, (s, 3H), 0.79 (s, 9H), 1.56 (s, 3H), 1.72 (d, *J* = 4.8 Hz, 1H), 1.80 (d, *J* = 4.8 Hz, 1H), 3.74 (d, *J* = 10.9 Hz, 1H), 3.88 (d, *J* = 10.6 Hz, 1H), 6.92 (d, *J* = 7.8 Hz, 1H), 6.96 (ddd, *J* = 1.0, 7.5, 7.5 Hz, 1H), 7.03 (d, *J* = 7.5 Hz, 1H), 7.16 (ddd, *J* = 1.2, 7.7, 7.7 Hz, 1H), 8.51 (b, 1H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$, δ): –5.3, –5.3, 15.2, 18.3, 25.8, 28.1, 36.3, 38.5, 66.0, 109.5, 121.3, 121.8, 126.5, 129.5, 141.2, 178.0 ppm. **IR (neat sample)**: 3228, 2926, 2855, 1711, 1471, 1345, 1227, 1106, 977 cm^{-1}. **HRMS** (ESI) (*m*/*z*): $[M]^+$ calcd for $C_{18}H_{27}NO_2Si$ 317.1811; found $C_{18}H_{28}NO_2Si$ 318.1865.

5.3.9 *(1S,2R)-2-(hydroxymethyl)-2-methylspiro[cyclopropane-1,3'-indolin]-2'-one (D)*

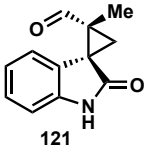


D

TBAF (1 M in THF, 84.4 µL, 84.4 µmol, 4 equiv.) was added to a solution of diastereomer **116** (67.0 mg, 21.1 µmol, 1 equiv.) in THF (0.7 mL). After complete consumption of the startingmaterial the reaction mixture quenched with NH_4Cl-solution and extracted with EtOAc (3 x 40 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash chromatography (hexane:EtOAc 1:1) to afford the free alcohol **D** in 86% (41.2 mg, 20.3 µmol) yield.

^{1}H-NMR (400 MHz, $(CD_3)_2SO$, δ): 1.43 (s, 3H), 1.48 (d, *J* = 4.4 Hz, 1H) 1.68 (d, *J* = 4.4 Hz, 1H), 3.56 (d, *J* = 11.6 Hz, 1H), 3.68 (d, *J* = 11.6 Hz, 1H), 4.66 (b, 1H), 6.82 – 6.90 (m, 2H), 7.10 – 7.14 (m, 2H), 10.42 (b, 1H) ppm. **^{13}C-NMR** (100 MHz, $(CD_3)_2SO$, δ): 14.7, 27.4, 35.5, 37.1, 63.7, 108.9, 120.5, 121.9, 126.1, 129.2, 142.0, 176.5 ppm. **IR (neat sample)**: 3209, 2927, 1687, 1464, 1210, 1022, 964 cm^{-1}. **HRMS** (ESI) (*m/z*): calcd for $C_{12}H_{14}NO_2$ $[M + H]^+$ 204.1025; found $C_{12}H_{14}NO_2$ 204.1019.

5.3.10 *2-methyl-2'-oxospiro[cyclopropane-1,3'-indoline]-2-carbaldehyde (121)*

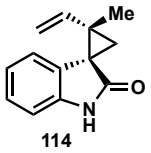


121

To a solution of alcohol **D** (30.0 mg, 147 µmol, 1 equiv.) in DMSO (0.5 mL) was added IBX (45.4 mg, 162 µmol, 1.1 equiv.). The suspension was stirred for 24 h until complete consumption of the starting material. The reaction was quenched with water and extracted with EtOAc (4 × 25 mL), the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash chromatography (hexane:EtOAc 3:1) to afford aldehyde **121** in 91% (27.0 mg, 134 µmol) yield as a white solid.

^{1}H-NMR (400 MHz, $CDCl_3$, δ): 1.71 (s, 3H), 2.09 (d, *J* = 5.1 Hz, 1H) 2.48 (d, *J* = 5.1 Hz, 1H), 6.94 (d, *J* = 7.9 Hz, 1H), 6.98 (ddd, *J* = 1.0, 7.5, 7.5 Hz, 1H), 7.03 (d, *J* = 6.1 Hz, 1H), 7.21 (ddd, *J* = 1.4, 7.5, 7.5 Hz, 1H), 8.45 (b, 1H) 9.56 (s, 1H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$, δ): 11.0, 25.8, 38.4, 43.2, 110.1, 122.2, 123.1, 126.5, 127.9, 141.0, 175.3, 198.4 ppm. **IR (neat sample)**: 3206, 1694,1620, 1470, 1221, 958 cm^{-1}. **HRMS** (ESI) (*m/z*): calcd for $C_{12}H_{12}NO_2$ $[M + H]^+$ 202.0868; found 202.0867.

5.3.11 *2-methyl-2-vinylspiro[cyclopropane-1,3'-indolin]-2'-one (114)*

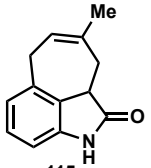


114

A suspension of methyl triphenylphosphonium bromide (118 mg, 328 µmol, 3 equiv.) in THF (300 µL) was cooled to –78 °C. To this solution was added NaHMDS (2M in THF, 164 µL, 328 µmol, 3 equiv.) which was accompanied by a color change to bright orange. The solution was stirred at –78 °C for 10 min, then warmed to 0 °C, stirred for further 20 min and cooled to –78 °C again. Then a solution of aldehyde **121** (22.0 mg, 109 µmol, 1 equiv.) in THF (0.1 mL) was added slowly. The solution was stirred for 10 minutes and warmed up to 0 °C. It was quenched with saturated NH_4Cl solution, then diluted with water, extracted with EtOAc (3 × 30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash chromatography (hexane:EtOAc 1:1) to afford olefin **114** in 85% (18.7 mg, 92.9 µmol) yield as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$, δ): 1.63 (s, 3H), 1.88 (d, *J* = 4.8 Hz, 1H) 1.97 (d, *J* = 4.8 Hz, 1H), 5.29 (dd, *J* = 1.0, 10.6 Hz, 1H), 5.32 (dd, *J* = 1.2, 16.2 Hz, 1H), 5.92 (dd, *J* = 10.4, 17.2 Hz, 1H), 6.88 (d, *J* = 7.9 Hz, 1H), 6.94 – 6.98 (m, 2H), 7.16 (ddd, *J* = 2.5, 6.4, 7.8 Hz, 1H), 7.52 (b, 1H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$, δ): 16.4, 29.6, 37.0, 39.0, 109.3, 117.2, 121.3, 122.5, 126.6, 138.2, 139.3, 170.9 ppm. **IR (neat sample)**: 3167, 2908, 1698, 1619, 1463, 1041 cm^{-1}. **HRMS** (ESI) (*m/z*): $[M]^+$ calcd for $C_{13}H_{13}NO$ 199.0997; found $C_{13}H_{14}NO$ 200.1075.

5.3.12 *4-methyl-2a,3-dihydro-1H-cyclohepta[cd]indol-2(6H)-one (115)*



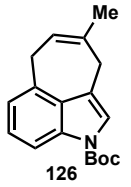
115

Rearrangement of olefin **114** (18.7 mg, 92.9 µmol) took already place at room temperature but to speed up the reaction was dissolved in benzene (800 µL) and was heated at 60 °C in a sealed tube. After complete consumption the product was concentrated *in vacuo* and purified by flash chromatography (hexane:EtOAc 3:1) to afford the cyclisation product **115** in 58% (11.0 mg, 54.0 µmol) yield.

^{1}H-NMR (400 MHz, $CDCl_3$, δ): 1.77 (s, 3H), 2.18 (dd, *J* = 14.8, 14.8 Hz, 1H), 2.69 (ddd, *J* = 2.8, 4.7, 16.8 Hz, 1H), 3.19 (dd, *J* = 7.6, 19.2 Hz, 1H), 3.74 (dd, *J* = 4.7, 12.9 Hz, 2H), 5.52 (dd, *J* = 1.1,

7.1 Hz, 1H), 6.74 (d, *J* = 7.6 Hz, 1H), 6.78 (d, *J* = 7.8 Hz, 1H), 7.11 (dd, *J* = 7.8, 8.0 Hz, 1H) 7.93 (s, 1H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$, δ):27.9, 33.0, 33.4, 43.9, 107.3, 120.2, 122.2, 127.9, 129.5, 134.1, 137.7, 140.0, 179.7 ppm. **IR (neat sample)**: 3167, 2908, 1698, 1619, 1463, 1041 cm^{-1}. **HRMS** (ESI) (*m*/*z*): calcd for $C_{13}H_{13}NO$ $[M + Na]^+$ 222.0895; found 222.0885.

5.3.13 *tert-butyl 4-methyl-3,6-dihydro-1H-cyclohepta[cd]indole-1-carboxylate (126)*



126

Aldehyde **121** (58.0 mg, 288 µmol, 1 equiv.) was dissolved in THF (1.44 mL) and Boc-anhydride (75.0 mg, 346 µmol, 1.2 equiv.) was added at room temperature in one portion. The reaction mixture was stirred for 2.5 hours. After complete consumption of the starting material (TLC-control hexane:EtOAc 20:1) the solution was diluted with water and ethyl acetate. The layers were separated and the water phase was extracted two times with 50 mL ethyl acetate. The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo.* The crude material was then purified by flash chromatography (hexane:EtOAc 20:1) to deliver 73% (63.0 mg, 210 µmol) of the desired product (yellow foam).

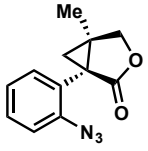
A suspension of methyl triphenylphosphonium bromide (149 mg, 418 µmol, 2 equiv.) in THF (4.2 mL) was cooled to –78 °C. To this solution was added NaHMDS (2M in THF, 210 µL, 418 µmol, 2 equiv.), which was accompanied by a color change to bright orange. The solution was stirred at –78 °C for 10 min, then warmed up to 0 °C, stirred for further 20 min and cooled to –78 °C again. Then a solution of the aldehyde (63.0 mg, 210 µmol, 1 equiv.) in THF (1.2mL) was added slowly. The solution was stirred for 10 min and warmed up to 0 °C. It was quenched with saturated NH_4Cl solution, then diluted with water, extracted with EtOAc (3 × 60 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was passed through a short path silica gel column and was directly subjected to the next reaction.

Crude olefin from the previous reaction was dissolved in methanol (2 mL) and cooled to 0 °C. Afterwards, sodium borohydride (8.0 mg, 210 µmol, 1 equiv.) was added in one portion. The reaction mixture was stirred for 1 h. After complete consumption of the starting material the reaction was quenched with water, diluted with ethyl acetate, extracted with ethyl acetate (2 × 30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by

flash chromatography (hexane:EtOAc 20:1) to deliver indole **126** in 42% (25.0 mg, 88.0 µmol) yield over two steps (yellow oil).

^{1}H-NMR (400 MHz, $CDCl_3$, δ): 1.65 (s, 9H), 1.85 (s, 3H), 3.46 (s, 2H), 3.54 (d, *J* = 6.8 Hz, 2H), 6.85 (ddd, *J* = 1.6, 6.9, 6.9 Hz, 1H), 6.89 (dd, *J* = 0.9, 7.1 Hz, 1H), 7.13 (dd, *J* = 7.2, 8.2 Hz, 1H), 7.28 (s, 1H), 7.87 (d, *J* = 8.2 Hz, 1H), ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$, δ): 24.8, 27.4, 28.4, 30.5, 32.1, 113.5, 115.4, 117.5, 120.2, 120.9, 122.5, 124.3, 124.4, 133.4, 138.1, 152.9 ppm. **IR (neat sample)**: 2976, 1726, 1434, 1383, 1156, 1106, 940 cm^{-1}. **HRMS** (ESI) (*m/z*): calcd for $C_{18}H_{21}NO_2$ $[M + H]^+$ 284.1651; found 284.1646.

5.3.14 *1-(2-azidophenyl)-5-methyl-3-oxabicyclo[3.1.0]hexan-2-one (128)*

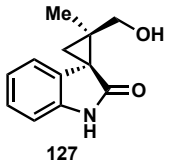


128

Diazo compound **129** (250 mg, 1.00 mmol, 1 equiv.) was dissolved in anhydrous CH_2Cl_2 (10 mL). The solution was added *via* syringe into a solution of $(CuOTf)_{2*}Tol$ (15.0 mg, 39.0 µmol, 0.015 equiv.) in anhydrous CH_2Cl_2 (10 mL) at rt over ten min. The solution was stirred for 30 min until complete consumption of the starting material. The reaction mixture was then concentrated *in vacuo* and purified by flash chromatography (hexane:EtOAc 20:1 to 3:1) to afford **128** in 84% (190 mg, 840 µmol) yield.

^{1}H-NMR (400 MHz, $CDCl_3$, δ): 1.10 (s, 3H), 1.37 (d, *J* = 5.1 Hz, 1H), 1.47 (d, *J* = 5.1 Hz, 1H), 4.32 (d, *J* = 8.9 Hz, 1H), 4.37 (d, *J* = 8.9 Hz, 1H), 7.16 (ddd, *J* = 1.0, 7.4, 7.4 Hz 1H), 7.20 (dd, *J* = 0.7, 7.9 Hz, 1H), 7.24 (dd, *J* = 1.4, 7.5 Hz, 1H), 7.40 (ddd, *J* = 1.7, 7.5, 8.2 Hz, 1H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$, δ): 15.1, 21.5, 30.6, 34.7, 73.3, 118.2, 124.2, 125.2, 130.0, 132.3, 140.9, 176.8 ppm. **IR (neat sample)**: 2963, 2121, 1761, 1279, 1075, 1004, 751 cm^{-1}. **HRMS** (ESI) (*m/z*): calcd for $C_{12}H_{11}N_3O_2$ $[M + Na]^+$ 252.0749; found 252.0741.

5.3.15 *2-(hydroxymethyl)-2-methylspiro[cyclopropane-1,3'-indolin]-2'-one (127)*



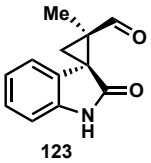
127

Azide **128** (25.0 mg, 110 µmol, 1 equiv.) in EtOH (2.2 mL) was reduced with Pd/C 10% (12.0 mg, 10.0 µmol, 10 mol%) at 5 bar hydrogen gas pressure. After complete consumption of the

starting material, concentrated acetic acid (300 µL) was added to the reaction mixture and it was stirred for 18 h at 70 °C. The crude product was concentrated *in vacuo* and purified by flash chromatography (hexane:EtOAc 1:1 to 1:5) to afford alcohol **127** in 89% (20.0 mg, 100 µmol) yield as a white solid.

^{1}H-NMR (400 MHz, $CDCl_3$, δ): 1.45 (s, 3H), 1.59 (d, *J* = 4.6 Hz, 1H), 2.32 (d, *J* = 5.1 Hz, 1H), 4.03 – 4.10 (m, 2H), 6.92 (d, *J* = 7.5 Hz, 1H), 6.97 (d, *J* = 6.8 Hz, 1H), 7.01 (ddd, *J* = 1.0, 7.2, 7.5 Hz, 1H), 7.17 (ddd, *J* = 1.5, 7.4, 7.4 Hz, 1H), 9.24 (b, 1H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$, δ): 17.9, 28.7, 36.8, 40.5, 64.7, 110.0, 121.9, 126.9, 129.3, 140.7, 180.0 ppm. **IR (neat sample)**: 3172, 1690, 1465, 1223, 960, 914, 750 cm^{-1}. **HRMS** (ESI) (*m/z*): $[M]^+$ calcd for $C_{12}H_{13}NO_2$ 203.0946; found $C_{12}H_{14}NO_2$ 204.1025.

5.3.16 *2-methyl-2'-oxospiro[cyclopropane-1,3'-indoline]-2-carbaldehyde (123)*

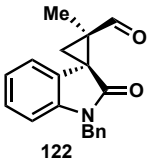


123

To a solution of alcohol **127** (150 mg, 740 µmol, 1 equiv.) in DMSO (1.5 mL) was added IBX (230 mg, 810 µmol, 1.1 equiv.). The suspension was stirred for 24 h until complete consumption of the starting material. The reaction was quenched with water and extracted with EtOAc (4 × 30 mL), the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash chromatography (hexane:EtOAc 3:1) to afford aldehyde **123** in 94% (140 mg, 700 µmol) yield as a white solid.

^{1}H-NMR (400 MHz, $CDCl_3$, δ): 1.47 (s, 3H), 1.95 (d, *J* = 5.4 Hz, 1H), 2.76 (d, *J* = 5.4 Hz, 1H), 6.95 (dd, *J* = 7.5, 10.6 Hz, 2H), 7.04 (ddd, *J* = 1.0, 7.7, 7.7 Hz, 1H), 7.25 (ddd, *J* = 1.4, 7.7, 7.7 Hz, 1H) 8.50 (b, 1H), 9.91 (s, 1H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$, δ): 12.5, 28.4, 40.5, 41.9, 110.3, 122.1, 122.7, 126.0, 128.2, 141.9, 176.6, 201.4 ppm. **IR (neat sample):** 3172, 1690, 1465, 1223, 960, 914, 750 cm^{-1}. **HRMS** (ESI) (*m/z*): calcd for $C_{12}H_{11}NO_2$ $[M + H]^+$ 201.0790; found $C_{12}H_{12}NO_2$ 202.0868.

5.3.17 *1'-benzyl-2-methyl-2'-oxospiro[cyclopropane-1,3'-indoline]-2-carbaldehyde (122)*



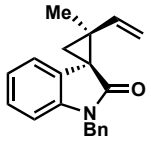
122

123 (10.0 mg, 54.0 µmol, 1 equiv.) was dissolved in DMF (0.1 mL) and treated with NaH (80% in oil, 1.70 mg, 60.0 µmol, 1.05 equiv.) and stirred for 1 h. Benzylbromide (30.0 µL, 270 µmol,

5 equiv.) was added and stirred until the consumption of the substrate was complete. The reaction was quenched by addition of NH_4Cl solution, extraceted with EtOAc (3 x 10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash chromatography (hexane:EtOAc 5:1) to give **122** in 80% (13.0 mg, 40.0 µmol) yield.

^{1}H-NMR (400 MHz, $CDCl_3$, δ): 1.49 (s, 3H), 1.98 (d, *J* = 5.4 Hz, 1H), 2.83 (d, *J* = 5.5 Hz, 1H), 4.94 (d, *J* = 1.7 Hz, 2H), 6.80 (d, *J* = 7.8 Hz, 1H) 6.98 (dd, *J* = 0.8, 7.3 Hz ,1H), 7.02 (ddd, *J* = 1.0, 7.4, 7.4 Hz, 1H), 7.20 (ddd, *J* = 1.5, 7.4, 7.6 Hz, 1H), 7.22 – 7.38 (m, 5 H), 9.98 (s, 1H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$, δ): 12.6, 28.6, 40.2, 41.8, 44.4, 109.6, 122.1, 122.4, 125.4, 127.5, 127.9, 128.1, 129.0, 135.8, 144.0, 174.6, 201.6 ppm. **IR (neat sample)** : 3077, 1685, 1611, 1346, 1184, 752, 700 cm^{-1}. **HRMS** (ESI) (*m*/*z*): $[M]^+$ calcd for $C_{19}H_{17}NO_2$ 291.1259; found $C_{19}H_{18}NO_2$ 292.1338.

5.3.18 *1'-benzyl-2-methyl-2-vinylspiro[cyclopropane-1,3'-indolin]-2'-one (108)*

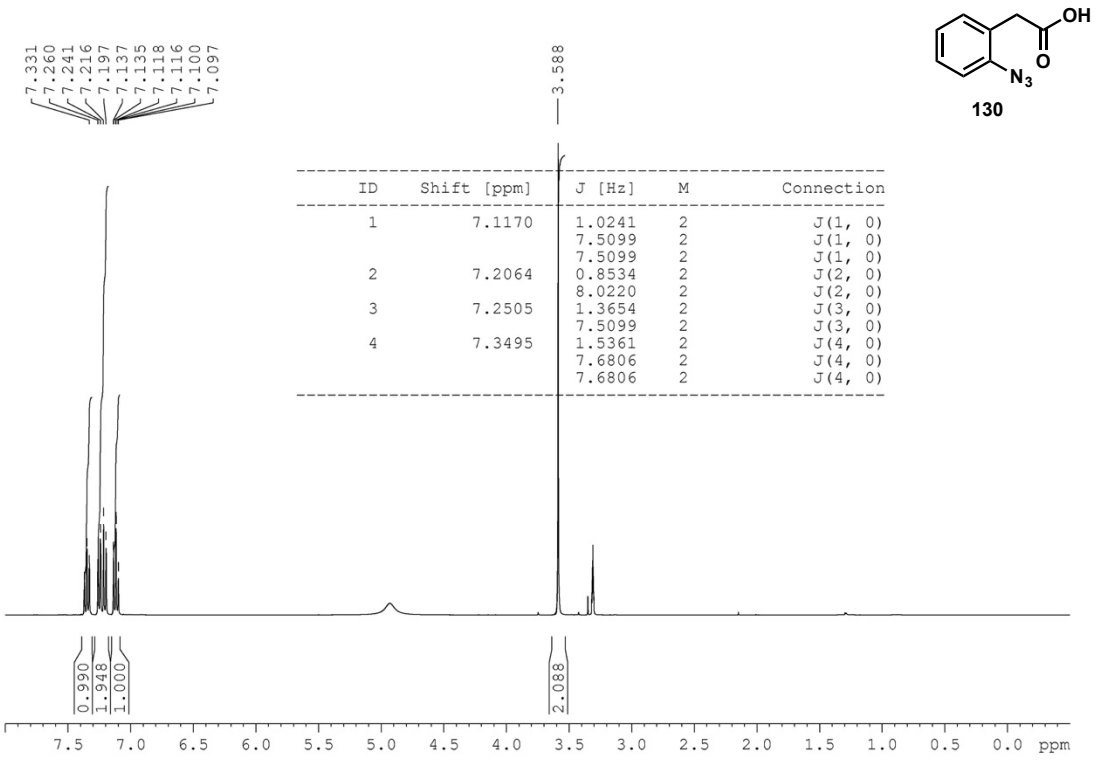


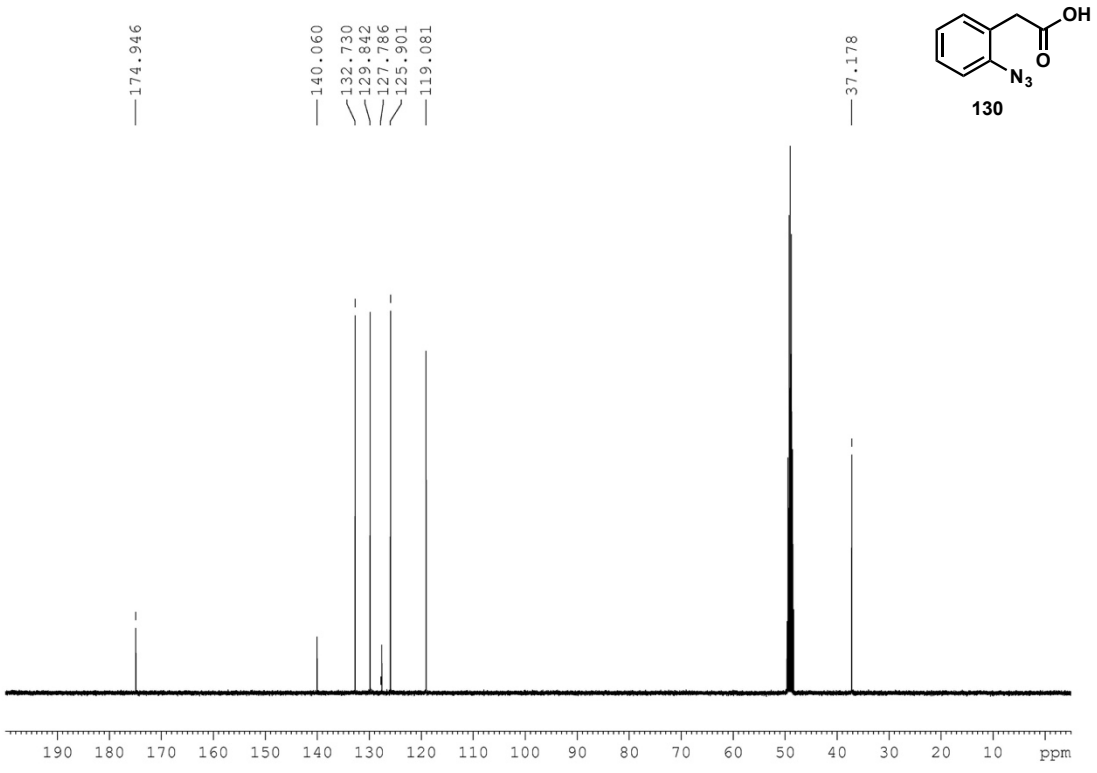
108

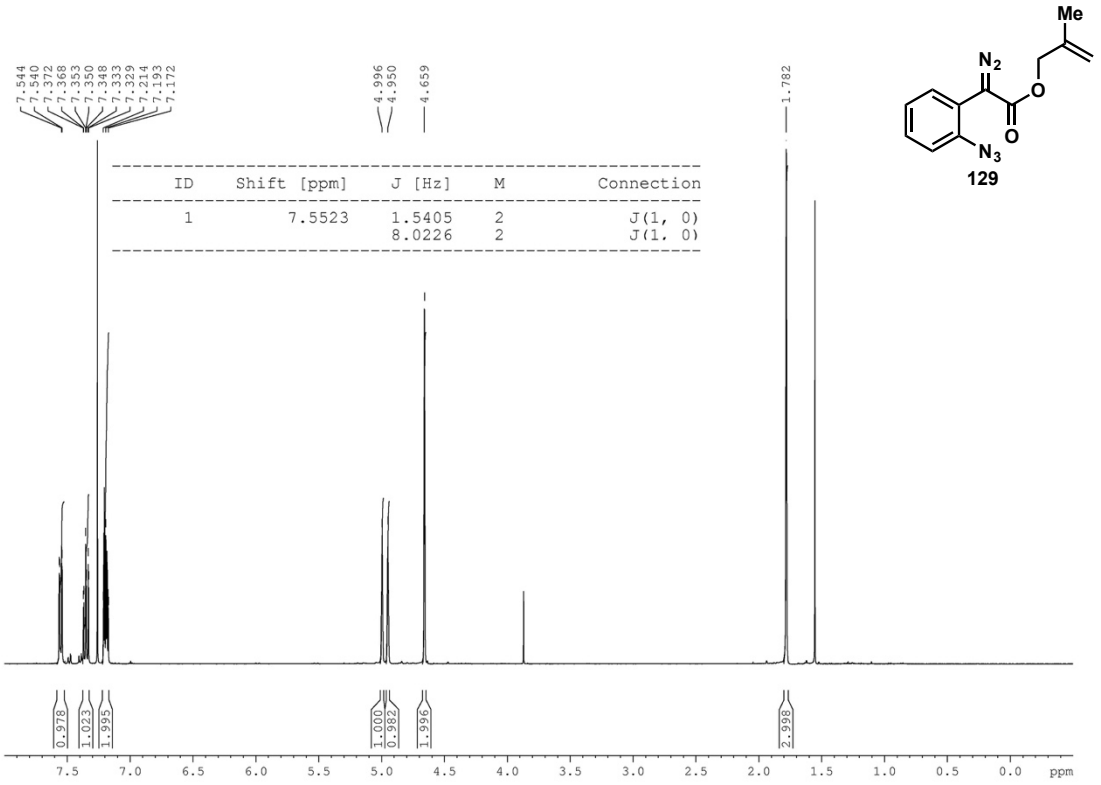
A suspension of methyl triphenylphosphonium bromide (310 mg, 860 µmol, 5 equiv.) in THF (0.9 mL) was cooled to –78 °C. To this solution was added NaHMDS (2M in THF, 430 µL, 860 µmol, 5 equiv.), which was accompanied by a color change to bright orange. The solution was stirred for 45 min. Then a solution of aldehyde **122** (50.0 mg, 170 µmol, 1 equiv.) in THF (0.4 mL) was added slowly. The solution was stirred for 18 h and warmed up to -15 °C. It was quenched with saturated NH_4Cl solution, then diluted with water, extracted with EtOAc (3 × 60 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash chromatography (hexane:EtOAc 3:1) to afford olefin **108** in 80% (40.0 mg, 140 µmol) yield as a yellow oil.

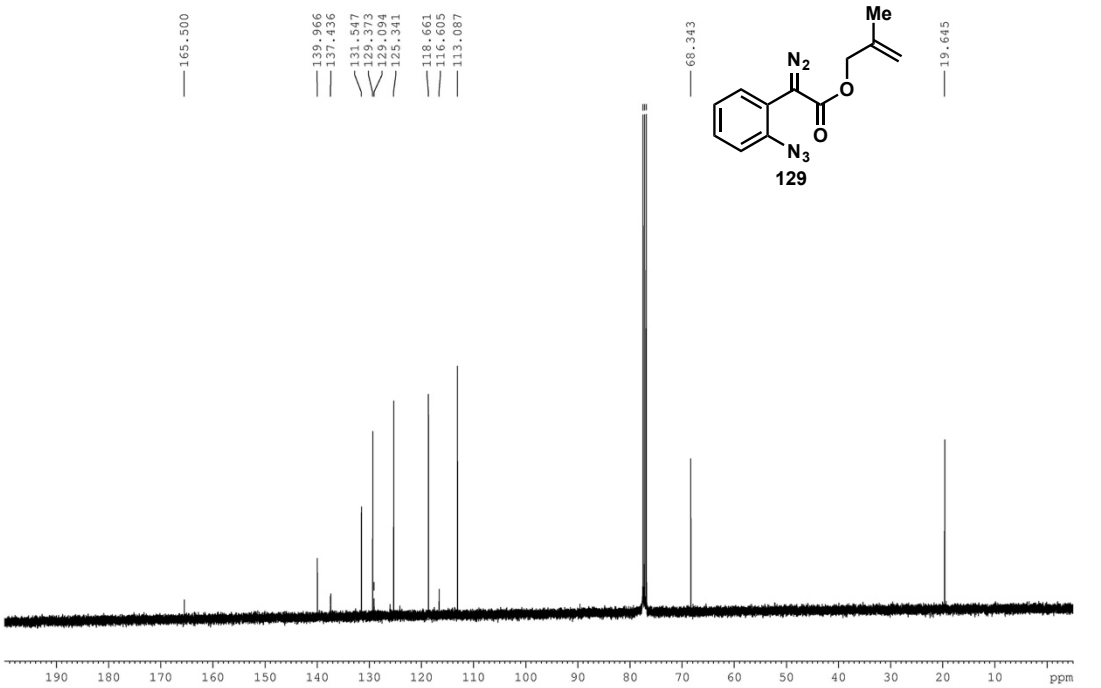
^{1}H-NMR (400 MHz, $CDCl_3$, δ): 1.54 (s, 3 H), 1.82 (d, *J* = 4.8 Hz, 1H), 2.25 (d, *J* = 4.8 Hz, 1H), 4.91 (d, *J* = 15.7 Hz, 1H), 5.02 (d, *J* = 15.6 Hz, 1H), 5.19 (dd, *J* = 1.0, 9.9 Hz, 1H), 5.23 (dd, *J* = 1.4, 3.8 Hz, 1H), 6.61 (dd, *J* = 10.9, 17.0 Hz, 1H), 6.78 (d, *J* = 7.8 Hz, 1H) 6.99 (ddd, *J* = 1.0, 7.5, 7.5 Hz, 1H), 7.05 (dd, *J* = 1.0, 7.5 Hz, 1H), 7.14 (ddd, *J* = 1.4, 7.5, 7.5 Hz, 1H), 7.22 – 7.33 (m, 5 H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$, δ): 17.4, 31.3, 37.1, 39.2, 44.1, 109.0, 114.8, 121.4, 122.0, 126.7, 127.5, 127.6, 127.9, 128.8, 136.5, 139.3, 143.6, 175.2 ppm. **IR (neat sample)**: 3369, 2922, 1697, 1611, 1351, 1187, 748 cm^{-1}. **HRMS** (ESI) (*m*/*z*): $[M]^+$ calcd for $C_{20}H_{19}NO$ 289.1467; found $C_{20}H_{19}NONa^+$ 312.1364.

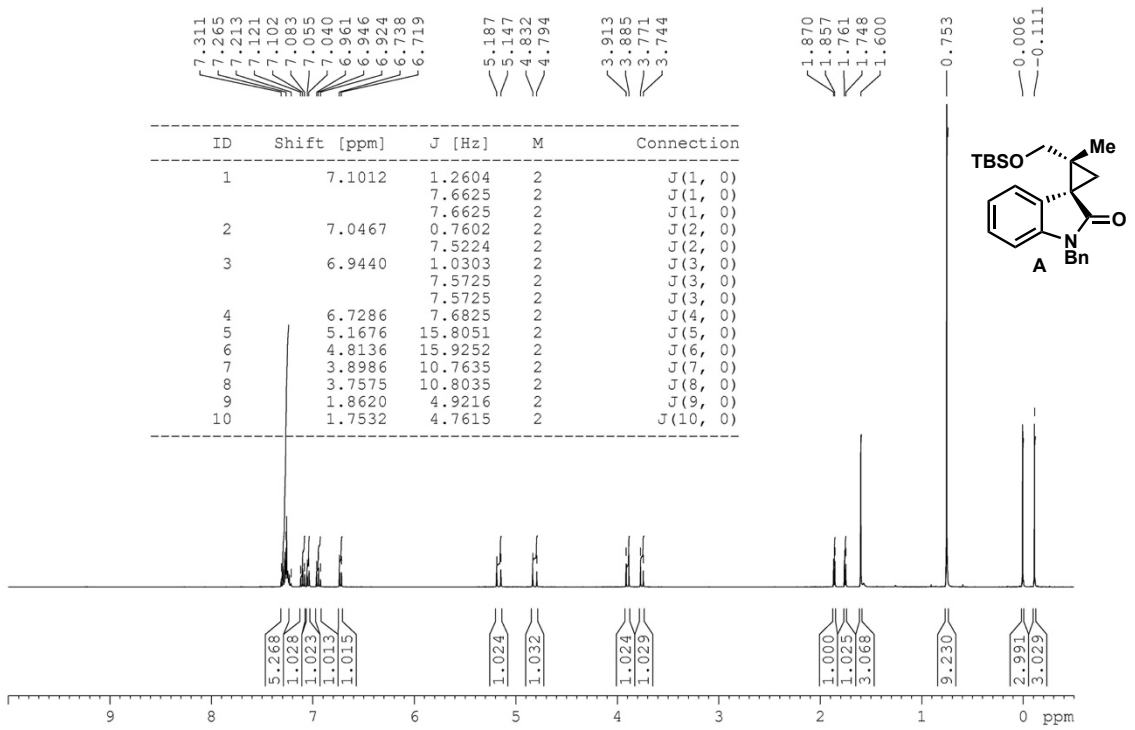
5.4 Spectra

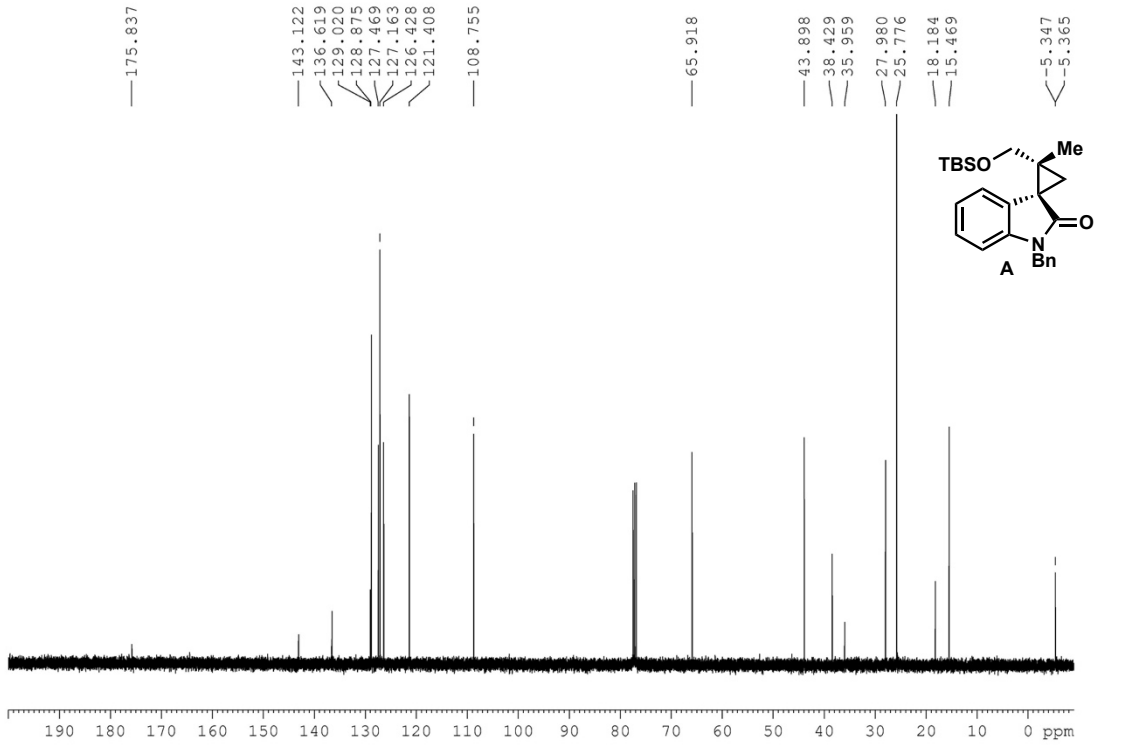

7.331
7.260
7.241
7.216
7.197
7.137
7.135
7.118
7.116
7.100
7.097
3.588
OH
O
N3
130
ID Shift [ppm] J [Hz] M Connection
1 7.1170 1.0241 2 J(1, 0)
7.5099 2 J(1, 0)
7.5099 2 J(1, 0)
2 7.2064 0.8534 2 J(2, 0)
8.0220 2 J(2, 0)
3 7.2505 1.3654 2 J(3, 0)
7.5099 2 J(3, 0)
4 7.3495 1.5361 2 J(4, 0)
7.6806 2 J(4, 0)
7.6806 2 J(4, 0)
0.990
1.948
1.000
2.088
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm

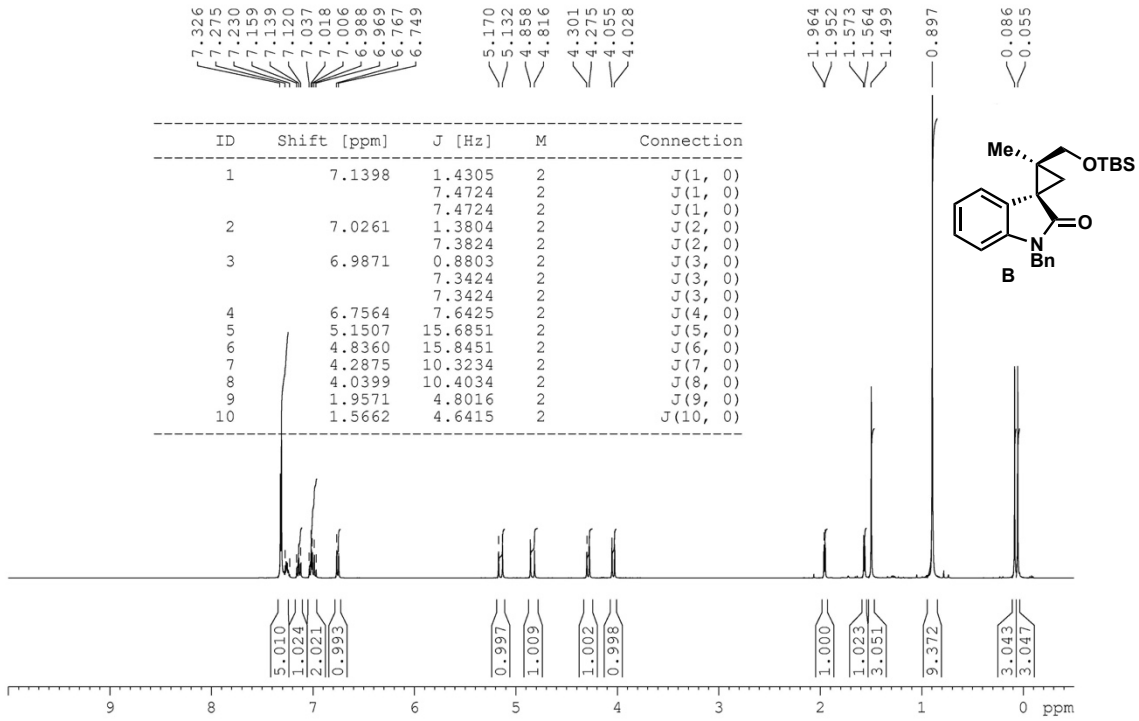

174.946
140.060
132.730
129.842
127.786
125.901
119.081
37.178
OH
O
N3
130
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

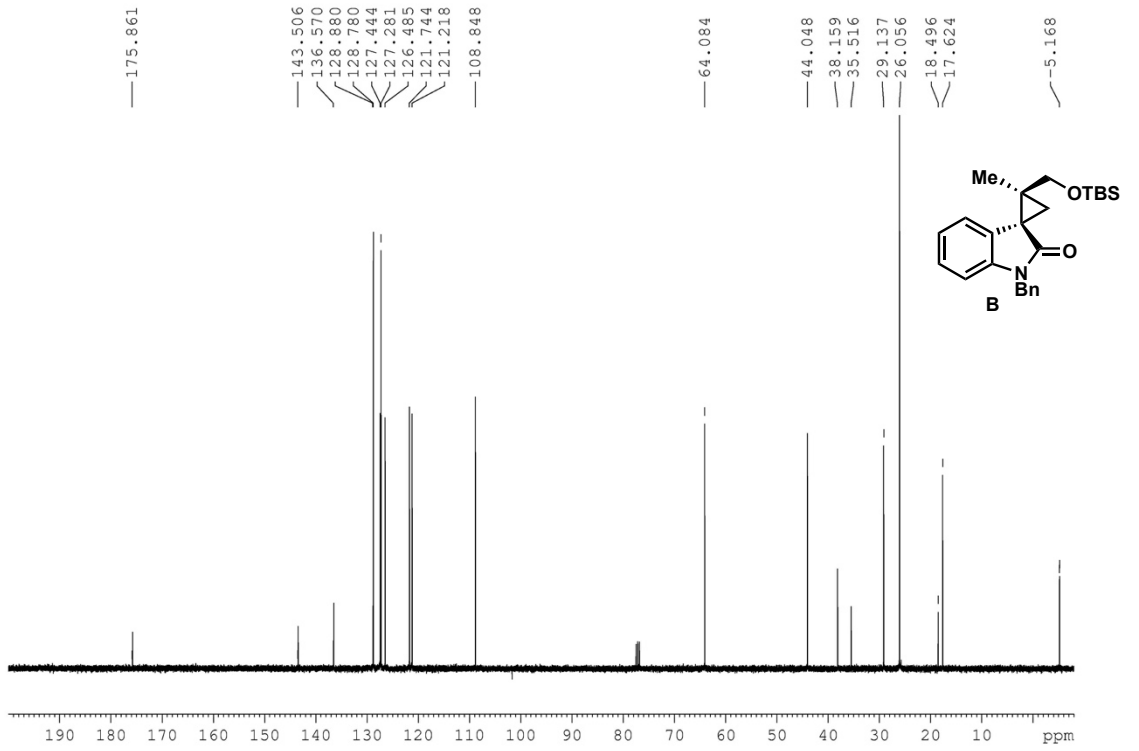

7.544
7.540
7.372
7.368
7.353
7.350
7.348
7.333
7.329
7.214
7.193
7.172
4.996
4.950
4.659
1.782
ID Shift [ppm] J [Hz] M Connection
1 7.5523 1.5405 2 J(1, 0)
8.0226 2 J(1, 0)
0.978
1.023
1.995
1.000
0.982
1.996
2.998
ppm
Me
N2
O
O
N3
129

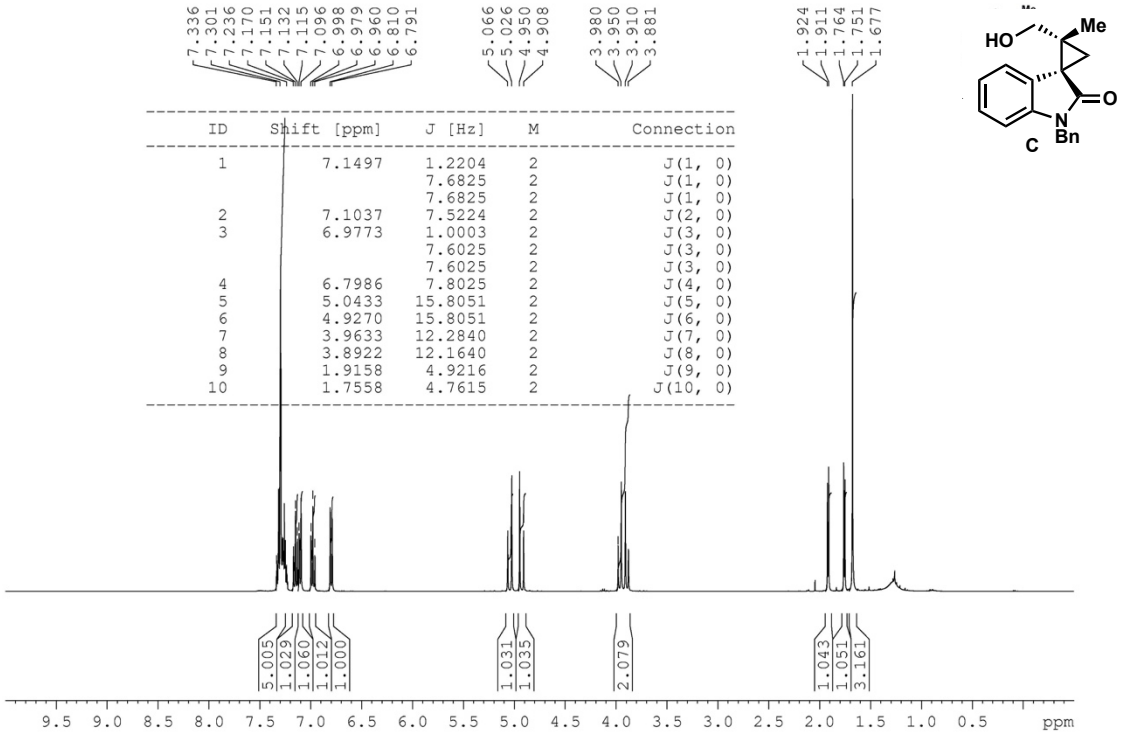

165.500
139.966
137.436
131.547
129.373
129.094
125.341
118.661
116.605
113.087
68.343
19.645
ppm
Me
N2
O
O
N3
129

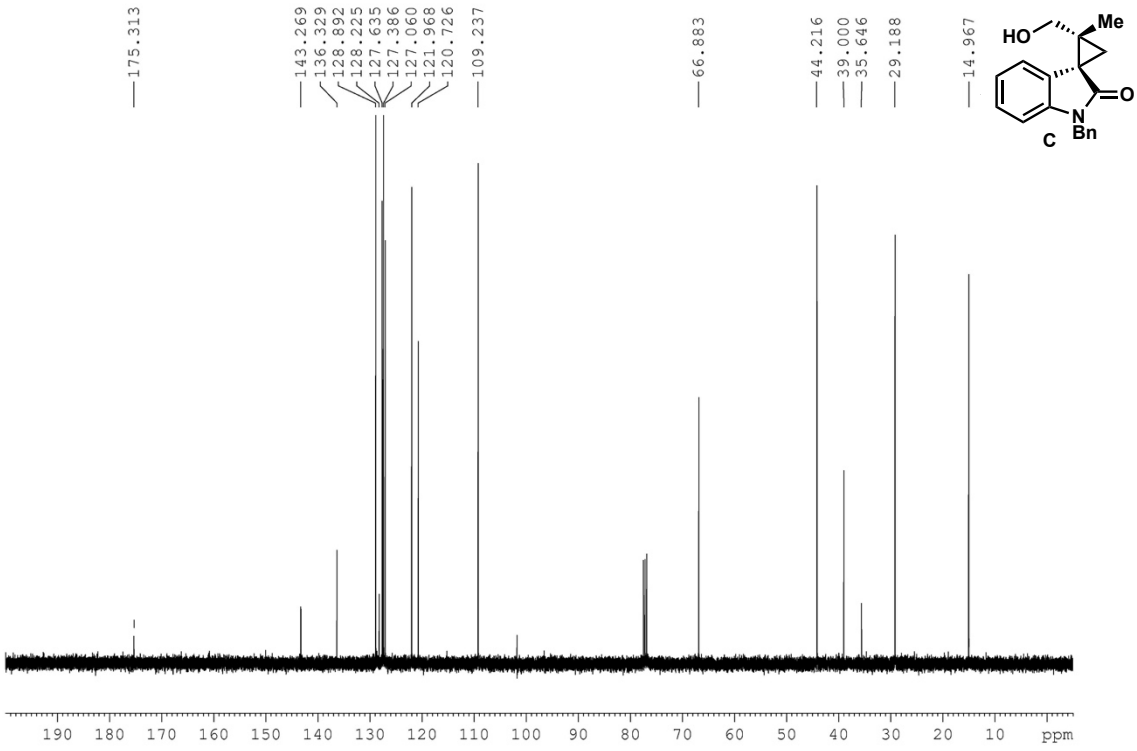

7.311
7.265
7.213
7.121
7.102
7.083
7.055
7.040
6.961
6.946
6.924
6.738
6.719
5.187
5.147
4.832
4.794
3.913
3.885
3.771
3.744
1.870
1.857
1.761
1.748
1.600
0.753
0.006
-0.111
ID Shift [ppm] J [Hz] M Connection
1 7.1012 1.2604 2 J(1, 0)
7.6625 2 J(1, 0)
7.6625 2 J(1, 0)
2 7.0467 0.7602 2 J(2, 0)
7.5224 2 J(2, 0)
3 6.9440 1.0303 2 J(3, 0)
7.5725 2 J(3, 0)
7.5725 2 J(3, 0)
4 6.7286 7.6825 2 J(4, 0)
5 5.1676 15.8051 2 J(5, 0)
6 4.8136 15.9252 2 J(6, 0)
7 3.8986 10.7635 2 J(7, 0)
8 3.7575 10.8035 2 J(8, 0)
9 1.8620 4.9216 2 J(9, 0)
10 1.7532 4.7615 2 J(10, 0)
TBSO
Me
O
N
Bn
A
5.268
1.028
1.023
1.013
1.015
1.024
1.032
1.024
1.029
1.000
1.025
3.068
9.230
2.991
3.029
9 8 7 6 5 4 3 2 1 0 ppm

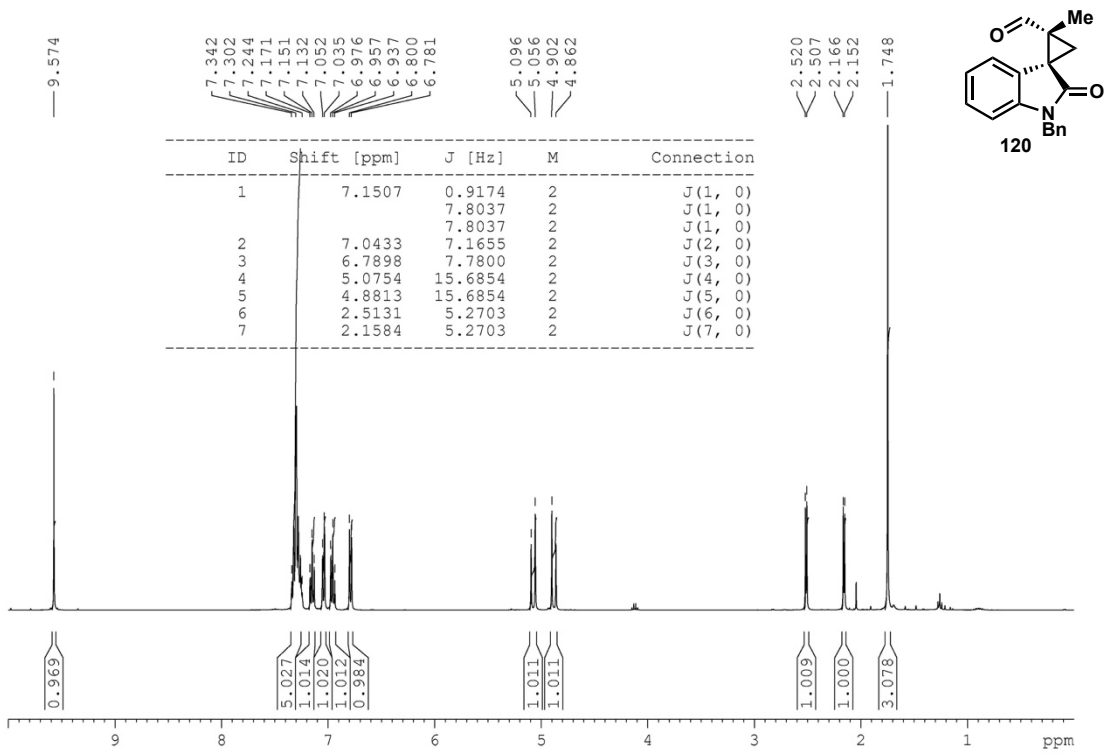

175.837
143.122
136.619
129.020
128.875
127.469
127.163
126.428
121.408
108.755
65.918
43.898
38.429
35.959
27.980
25.776
18.184
15.469
-5.347
-5.365
TBSO
Me
O
N
Bn
A
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

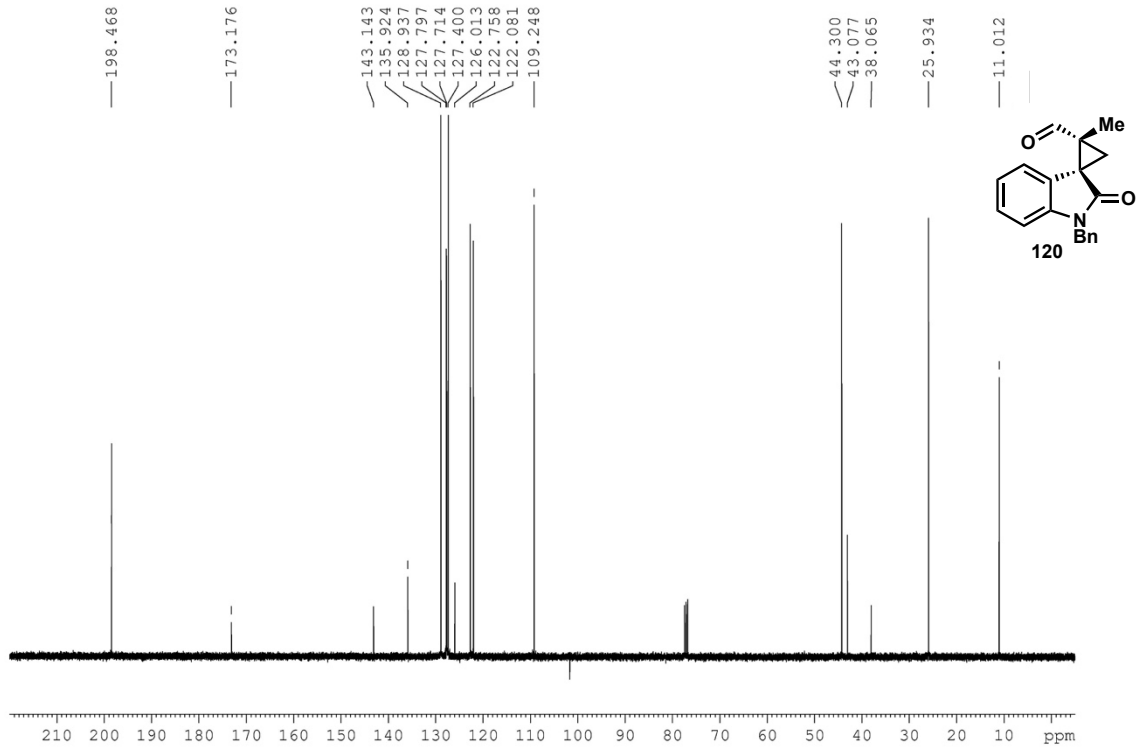

7.326
7.275
7.230
7.159
7.139
7.120
7.037
7.018
7.006
6.988
6.969
6.767
6.749
5.170
5.132
4.858
4.816
4.301
4.275
4.055
4.028
1.964
1.952
1.573
1.564
1.499
0.897
0.086
0.055
ID Shift [ppm] J [Hz] M Connection
1 7.1398 1.4305 2 J(1, 0)
7.4724 2 J(1, 0)
7.4724 2 J(1, 0)
2 7.0261 1.3804 2 J(2, 0)
7.3824 2 J(2, 0)
3 6.9871 0.8803 2 J(3, 0)
7.3424 2 J(3, 0)
7.3424 2 J(3, 0)
4 6.7564 7.6425 2 J(4, 0)
5 5.1507 15.6851 2 J(5, 0)
6 4.8360 15.8451 2 J(6, 0)
7 4.2875 10.3234 2 J(7, 0)
8 4.0399 10.4034 2 J(8, 0)
9 1.9571 4.8016 2 J(9, 0)
10 1.5662 4.6415 2 J(10, 0)
Me
OTBS
O
N
Bn
B
5.010
1.024
2.021
0.993
0.997
1.009
1.002
0.998
1.000
1.023
3.051
9.372
3.043
3.047
9 8 7 6 5 4 3 2 1 0 ppm

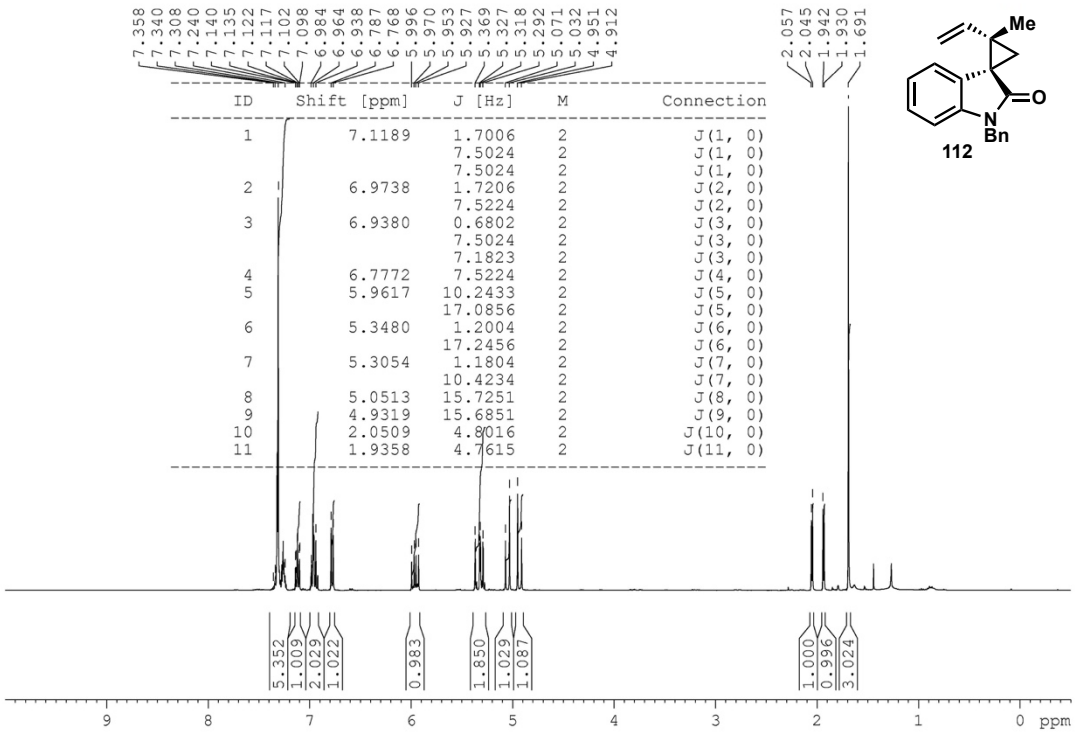

175.861
143.506
136.570
128.880
128.780
127.444
127.281
126.485
121.744
121.218
108.848
64.084
44.048
38.159
35.516
29.137
26.056
18.496
17.624
5.168
Me
OTBS
O
N
Bn
B
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

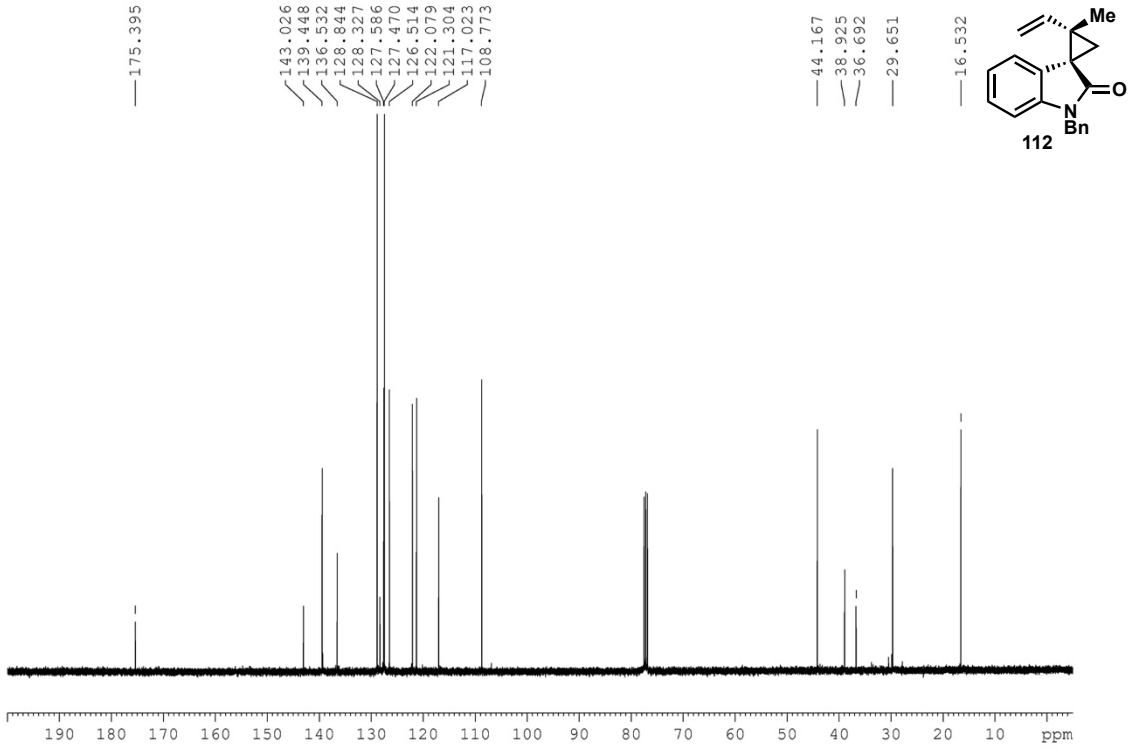

7.336
7.301
7.236
7.170
7.151
7.132
7.115
7.096
6.998
6.979
6.960
6.810
6.791
5.066
5.026
4.950
4.908
3.980
3.950
3.910
3.881
1.924
1.911
1.764
1.751
1.677
HO
Me
O
N
Bn
C
ID Shift [ppm] J [Hz] M Connection
1 7.1497 1.2204 2 J(1, 0)
7.6825 2 J(1, 0)
7.6825 2 J(1, 0)
2 7.1037 7.5224 2 J(2, 0)
3 6.9773 1.0003 2 J(3, 0)
7.6025 2 J(3, 0)
7.6025 2 J(3, 0)
4 6.7986 7.8025 2 J(4, 0)
5 5.0433 15.8051 2 J(5, 0)
6 4.9270 15.8051 2 J(6, 0)
7 3.9633 12.2840 2 J(7, 0)
8 3.8922 12.1640 2 J(8, 0)
9 1.9158 4.9216 2 J(9, 0)
10 1.7558 4.7615 2 J(10, 0)
5.005
1.029
1.060
1.012
1.000
1.031
1.035
2.079
1.043
1.051
3.161
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
ppm

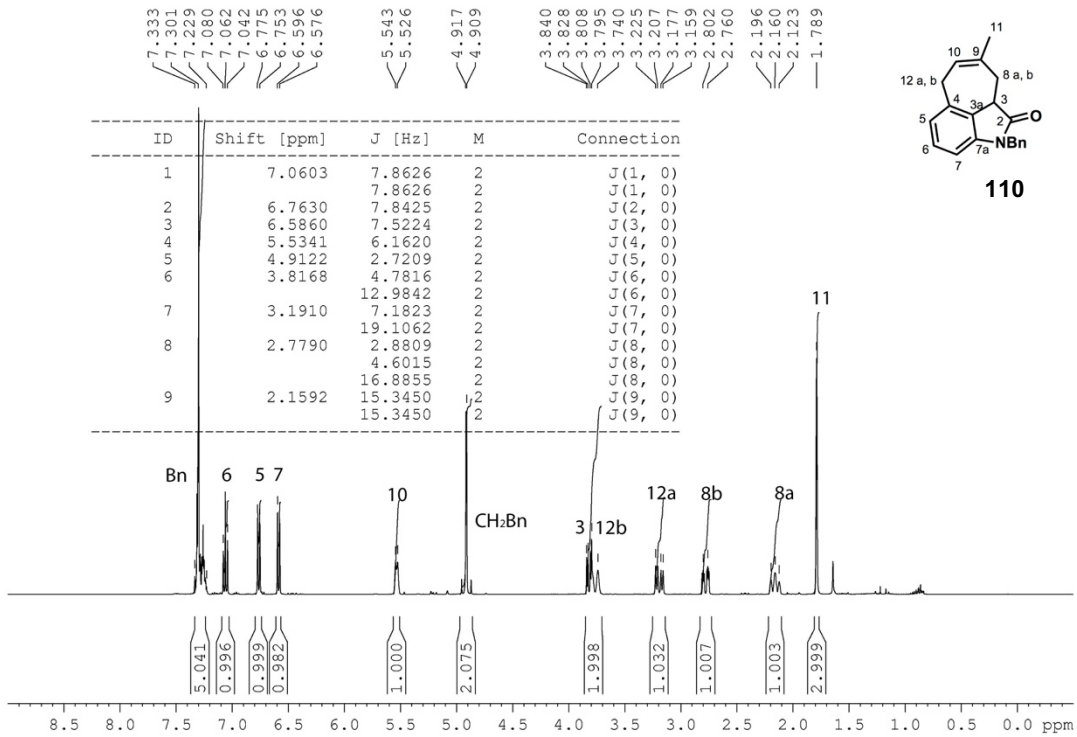

175.313
143.269
136.329
128.892
128.225
127.635
127.386
127.060
121.968
120.726
109.237
66.883
44.216
39.000
35.646
29.188
14.967
HO
Me
O
N
Bn
C
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
ppm

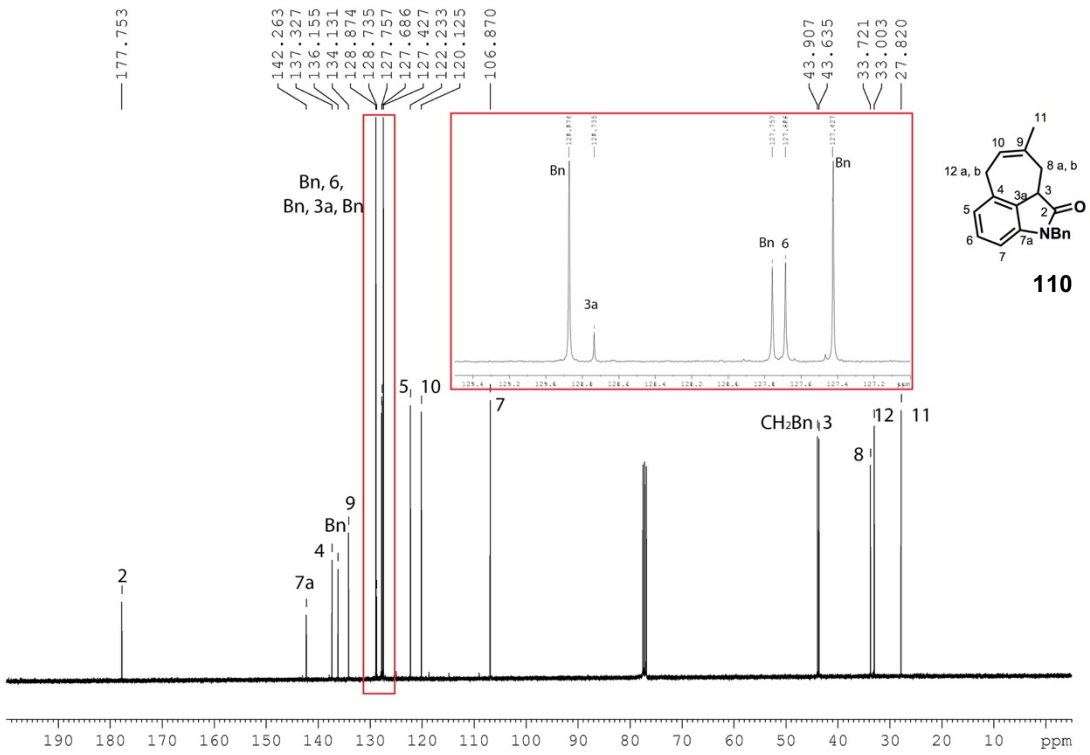

9.574
7.342
7.302
7.244
7.171
7.151
7.132
7.052
7.035
6.976
6.957
6.937
6.800
6.781
5.096
5.056
4.902
4.862
2.520
2.507
2.166
2.152
1.748
Me
O
O
N
Bn
120
ID Shift [ppm] J [Hz] M Connection
1 7.1507 0.9174 2 J(1, 0)
7.8037 2 J(1, 0)
7.8037 2 J(1, 0)
2 7.0433 7.1655 2 J(2, 0)
3 6.7898 7.7800 2 J(3, 0)
4 5.0754 15.6854 2 J(4, 0)
5 4.8813 15.6854 2 J(5, 0)
6 2.5131 5.2703 2 J(6, 0)
7 2.1584 5.2703 2 J(7, 0)
0.969
5.027
1.014
1.020
1.012
0.984
1.011
1.011
1.009
1.000
3.078
9
8
7
6
5
4
3
2
1
ppm

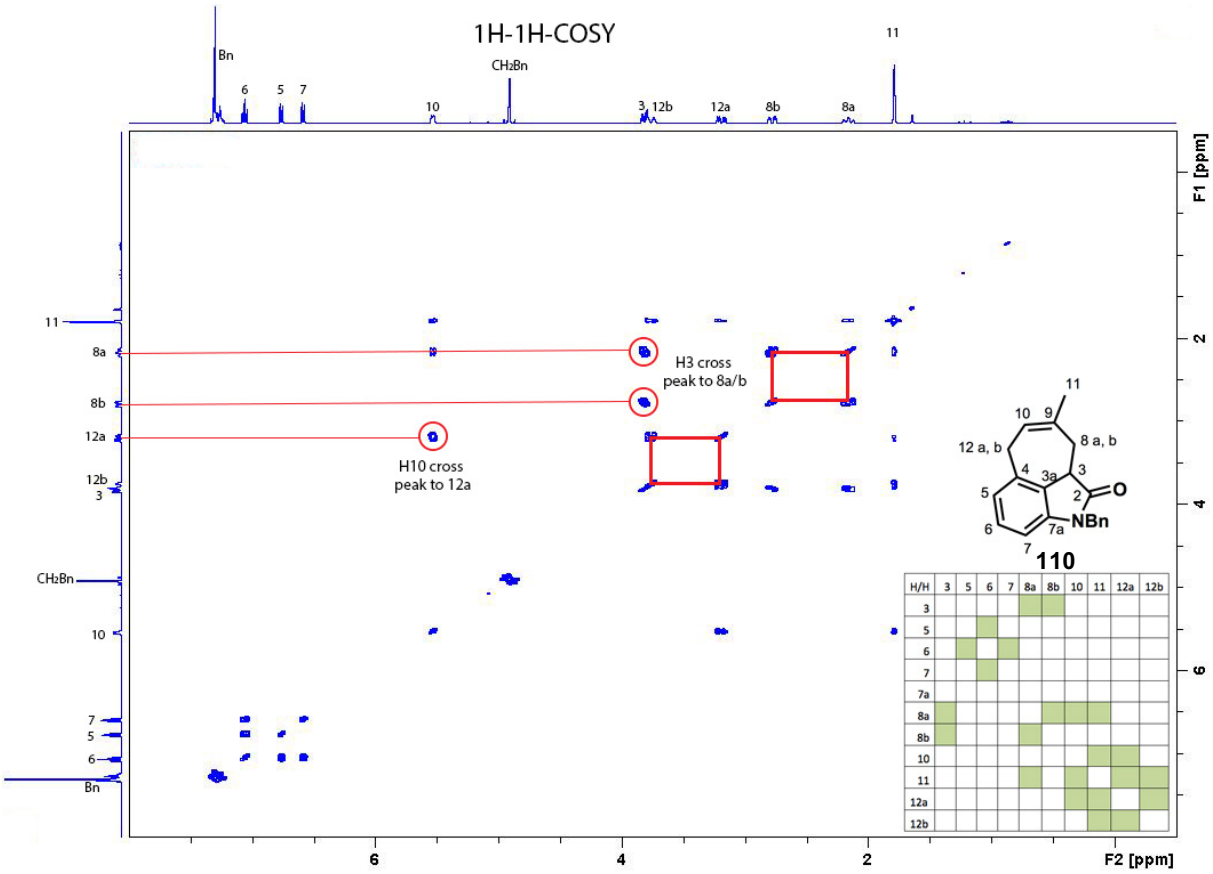

198.468
173.176
143.143
135.924
128.937
127.797
127.714
127.400
126.013
122.758
122.081
109.248
44.300
43.077
38.065
25.934
11.012
Me
O
O
N
Bn
120
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

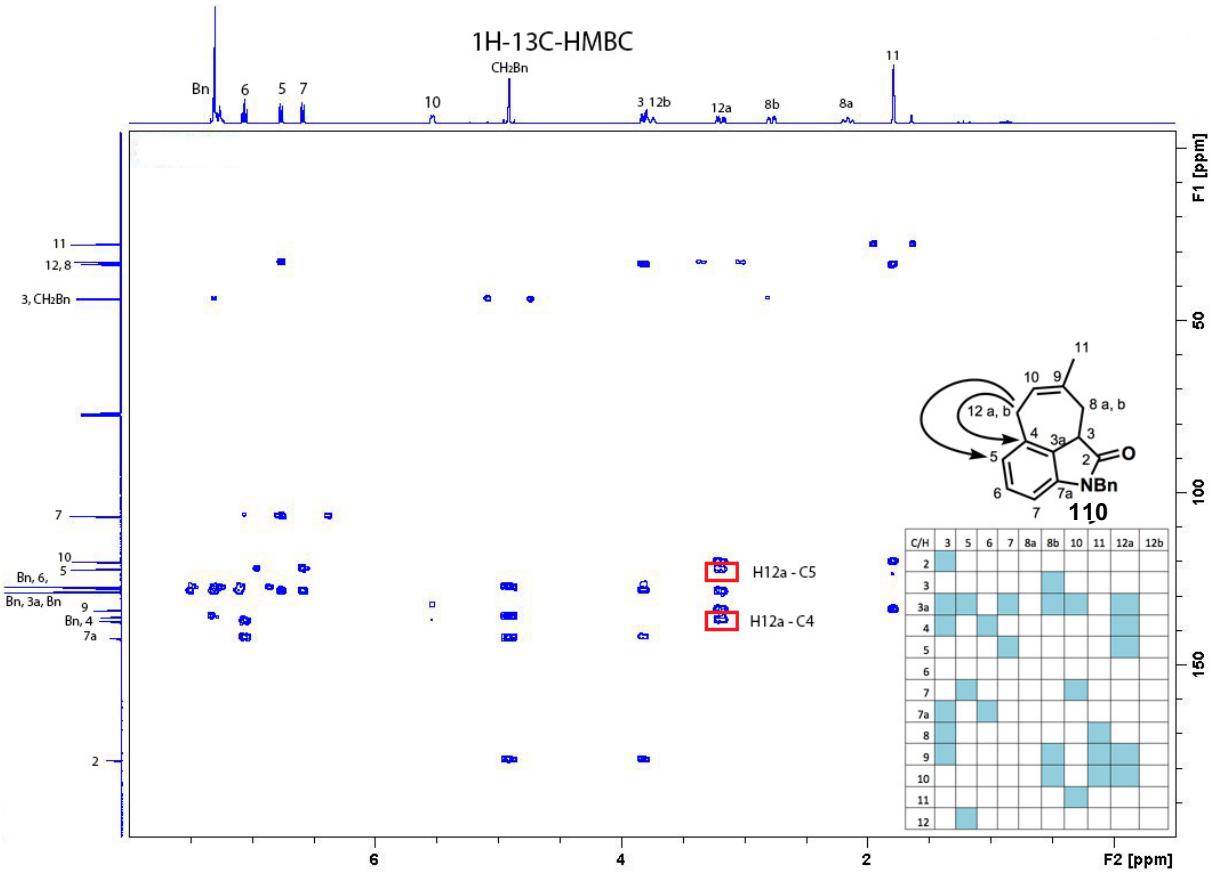

7.358
7.340
7.308
7.240
7.140
7.135
7.122
7.117
7.102
7.098
6.984
6.964
6.938
6.787
6.768
5.996
5.970
5.953
5.927
5.369
5.327
5.318
5.292
5.071
5.032
4.951
4.912
2.057
2.045
1.942
1.930
1.691
ID Shift [ppm] J [Hz] M Connection
1 7.1189 1.7006 2 J(1, 0)
7.5024 2 J(1, 0)
7.5024 2 J(1, 0)
2 6.9738 1.7206 2 J(2, 0)
7.5224 2 J(2, 0)
3 6.9380 0.6802 2 J(3, 0)
7.5024 2 J(3, 0)
7.1823 2 J(3, 0)
4 6.7772 7.5224 2 J(4, 0)
5 5.9617 10.2433 2 J(5, 0)
17.0856 2 J(5, 0)
6 5.3480 1.2004 2 J(6, 0)
17.2456 2 J(6, 0)
7 5.3054 1.1804 2 J(7, 0)
10.4234 2 J(7, 0)
8 5.0513 15.7251 2 J(8, 0)
9 4.9319 15.6851 2 J(9, 0)
10 2.0509 4.8016 2 J(10, 0)
11 1.9358 4.7615 2 J(11, 0)
5.352
1.009
2.029
1.022
0.983
1.850
1.029
1.087
1.000
0.996
3.024
9 8 7 6 5 4 3 2 1 0 ppm
Me
O
N
Bn
112

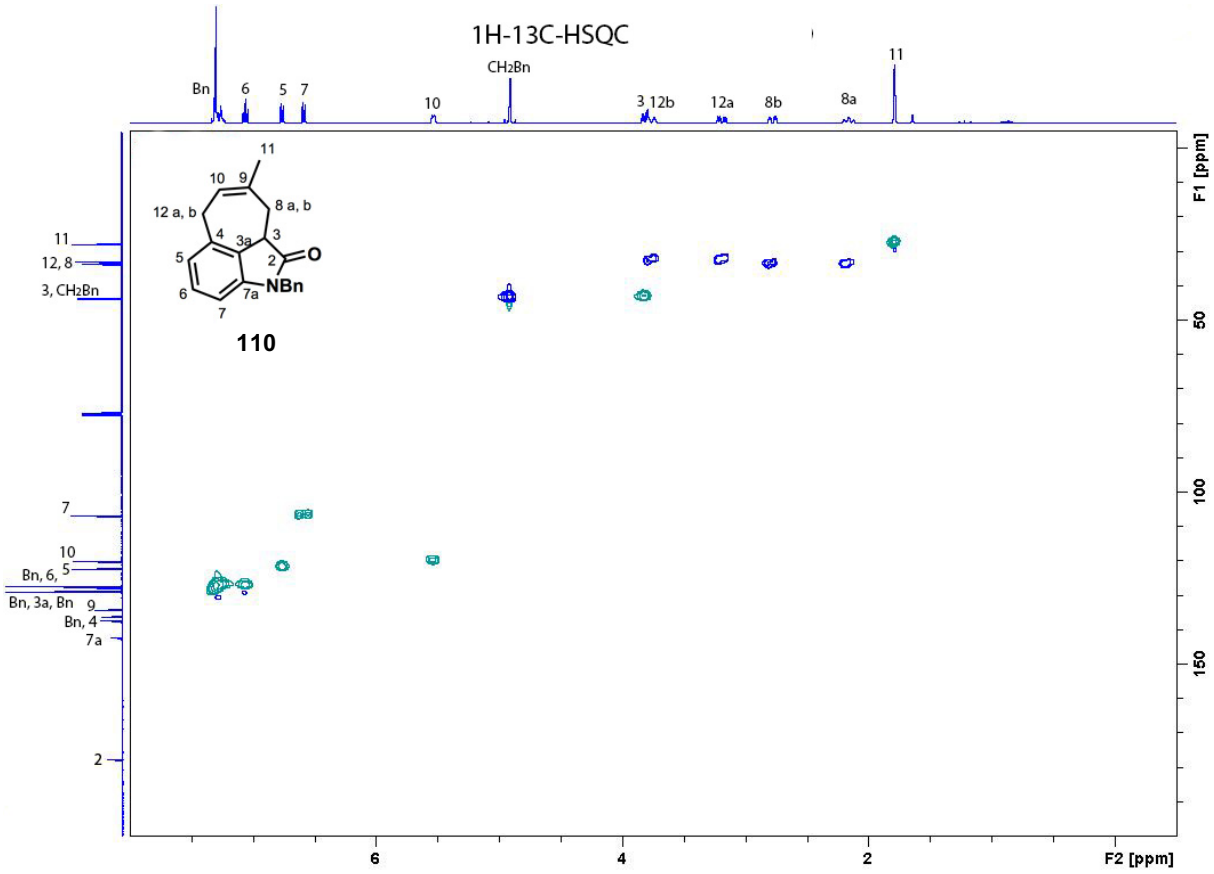

175.395
143.026
139.448
136.532
128.844
128.327
127.586
127.470
126.514
122.079
121.304
117.023
108.773
44.167
38.925
36.692
29.651
16.532
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm
Me
O
N
Bn
112

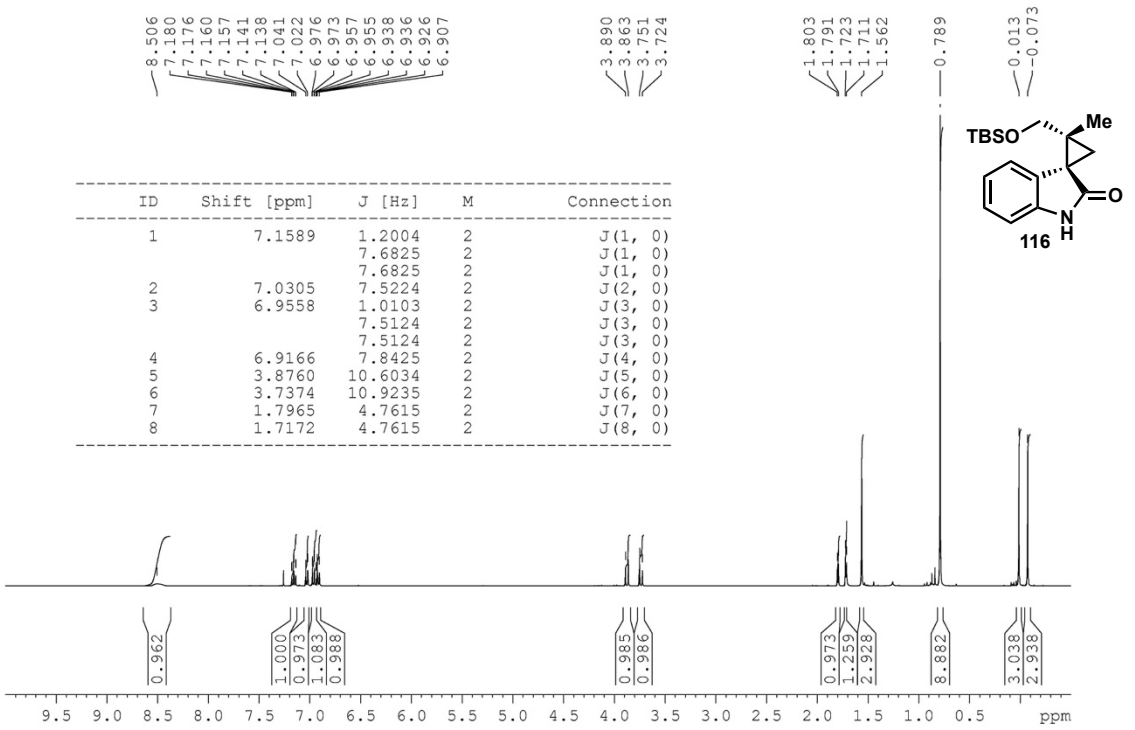

7.333
7.301
7.229
7.080
7.062
7.042
6.775
6.753
6.596
6.576
5.543
5.526
4.917
4.909
3.840
3.828
3.808
3.795
3.740
3.225
3.207
3.177
3.159
2.802
2.760
2.196
2.160
2.123
1.789
ID | Shift [ppm] | J [Hz] | M | Connection
1 | 7.0603 | 7.8626 | 2 | J(1, 0)
7.8626 | 2 | J(1, 0)
2 | 6.7630 | 7.8425 | 2 | J(2, 0)
3 | 6.5860 | 7.5224 | 2 | J(3, 0)
4 | 5.5341 | 6.1620 | 2 | J(4, 0)
5 | 4.9122 | 2.7209 | 2 | J(5, 0)
6 | 3.8168 | 4.7816 | 2 | J(6, 0)
12.9842 | 2 | J(6, 0)
7 | 3.1910 | 7.1823 | 2 | J(7, 0)
19.1062 | 2 | J(7, 0)
8 | 2.7790 | 2.8809 | 2 | J(8, 0)
4.6015 | 2 | J(8, 0)
16.8855 | 2 | J(8, 0)
9 | 2.1592 | 15.3450 | 2 | J(9, 0)
15.3450 | 2 | J(9, 0)
Bn
6
5 7
10
CH2Bn
3
12b
12a
8b
8a
11
5.041
0.996
0.999
0.982
1.000
2.075
1.998
1.032
1.007
1.003
2.999
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
11
10
9
8 a, b
12 a, b
4
3a
3
5
2
O
6
7a
NBn
7
110


177.753
142.263
137.327
136.155
134.131
128.874
128.735
127.757
127.686
127.427
122.233
120.125
106.870
43.907
43.635
33.721
33.003
27.820
Bn, 6,
Bn, 3a, Bn
Bn
3a
Bn 6
Bn
5 10
7
CH2Bn 3
12
11
8
9
Bn
4
7a
2
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm
11
10
9
8 a, b
12 a, b
4
3a
3
5
2
O
6
7a
NBn
7
110

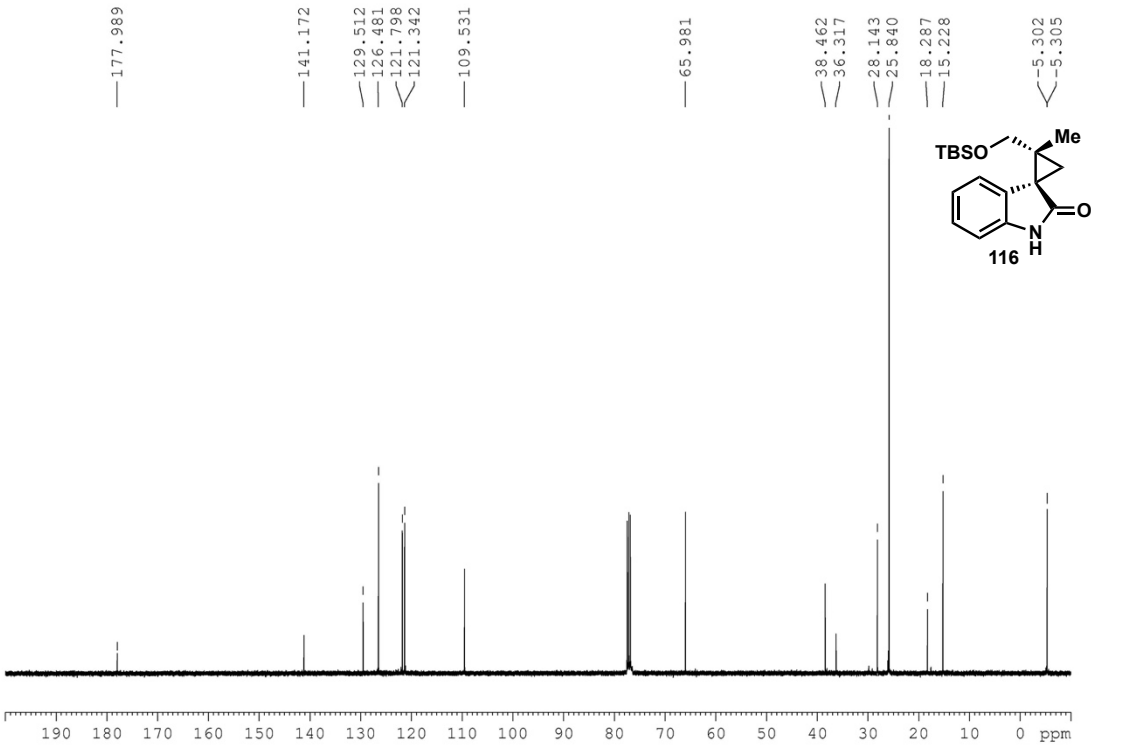

1H-1H-COSY
Bn
CH2Bn
11
6
5
7
10
3, 12b
12a
8b
8a
F1 [ppm]
F2 [ppm]
H3 cross peak to 8a/b
H10 cross peak to 12a
12 a, b
8 a, b
110
H/H
C/H

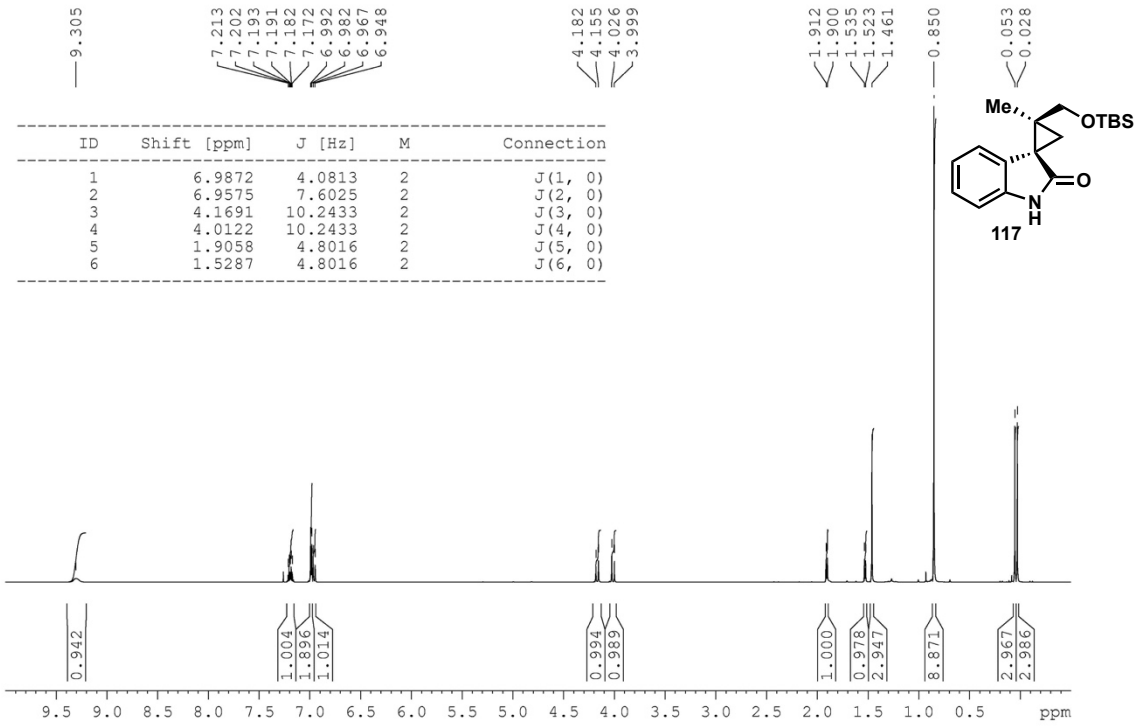

1H-13C-HMBC
Bn
CH2Bn
11
6
5
7
10
3, 12b
12a
8b
8a
F1 [ppm]
F2 [ppm]
12, 8
3, CH2Bn
Bn, 6,
Bn, 3a, Bn
Bn, 4
7a
H12a - C5
H12a - C4
12 a, b
8 a, b
110
C/H


1H-13C-HSQC
Bn
6
5
7
10
CH2Bn
3, 12b
12a
8b
8a
11
F1 [ppm]
50
100
150
F2 [ppm]
6
4
2
11
12, 8
3, CH2Bn
7
10
Bn, 6, 5
Bn, 3a, Bn
9
Bn, 4
7a
2
12 a, b
8 a, b
NBn
O
110

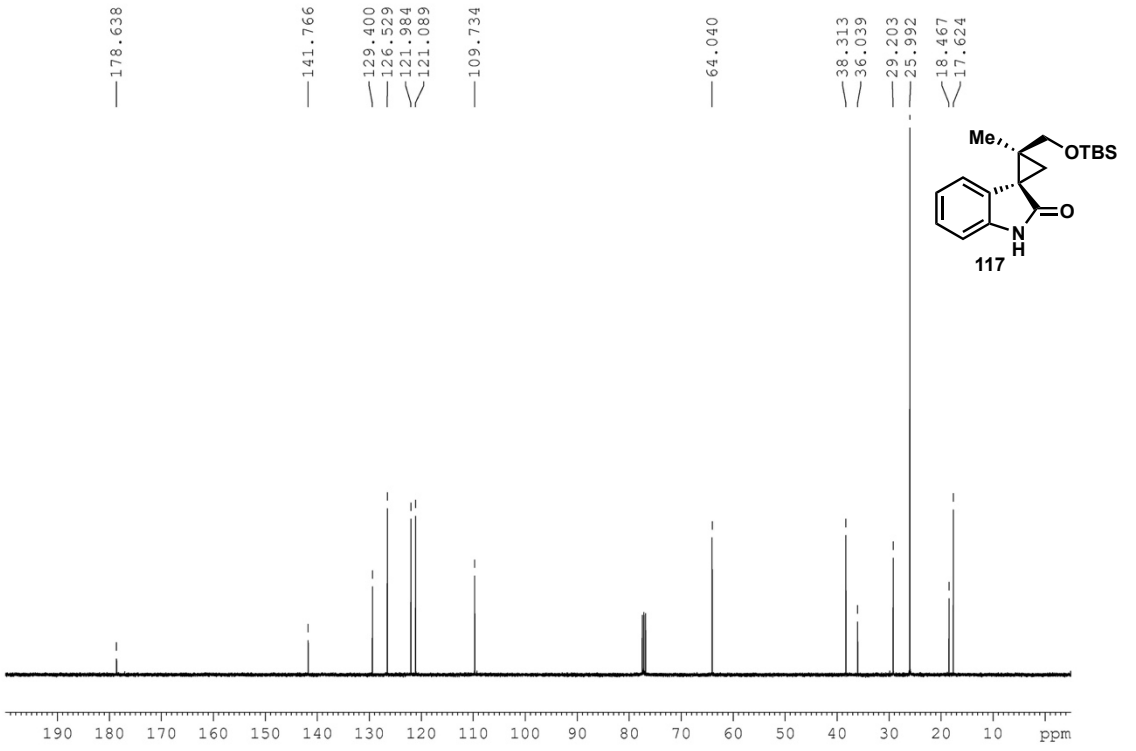


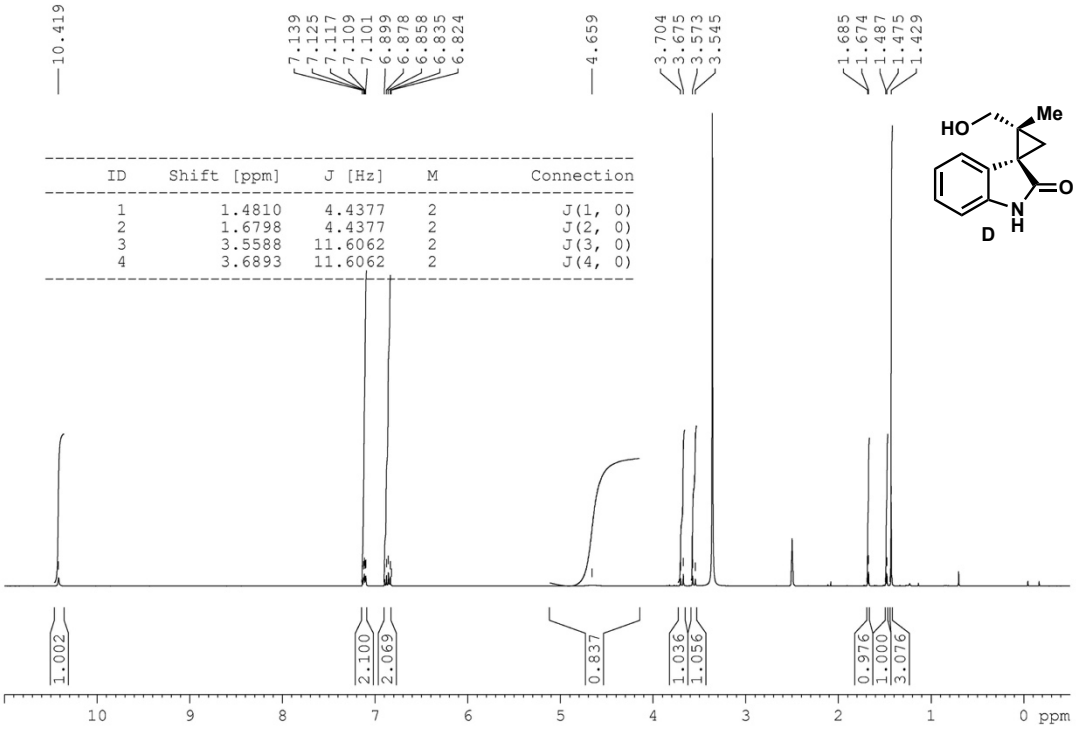
ID	Shift [ppm]	J [Hz]	M	Connection
1	7.1589	1.2004	2	J(1, 0)
		7.6825	2	J(1, 0)
		7.6825	2	J(1, 0)
2	7.0305	7.5224	2	J(2, 0)
3	6.9558	1.0103	2	J(3, 0)
		7.5124	2	J(3, 0)
		7.5124	2	J(3, 0)
4	6.9166	7.8425	2	J(4, 0)
5	3.8760	10.6034	2	J(5, 0)
6	3.7374	10.9235	2	J(6, 0)
7	1.7965	4.7615	2	J(7, 0)
8	1.7172	4.7615	2	J(8, 0)

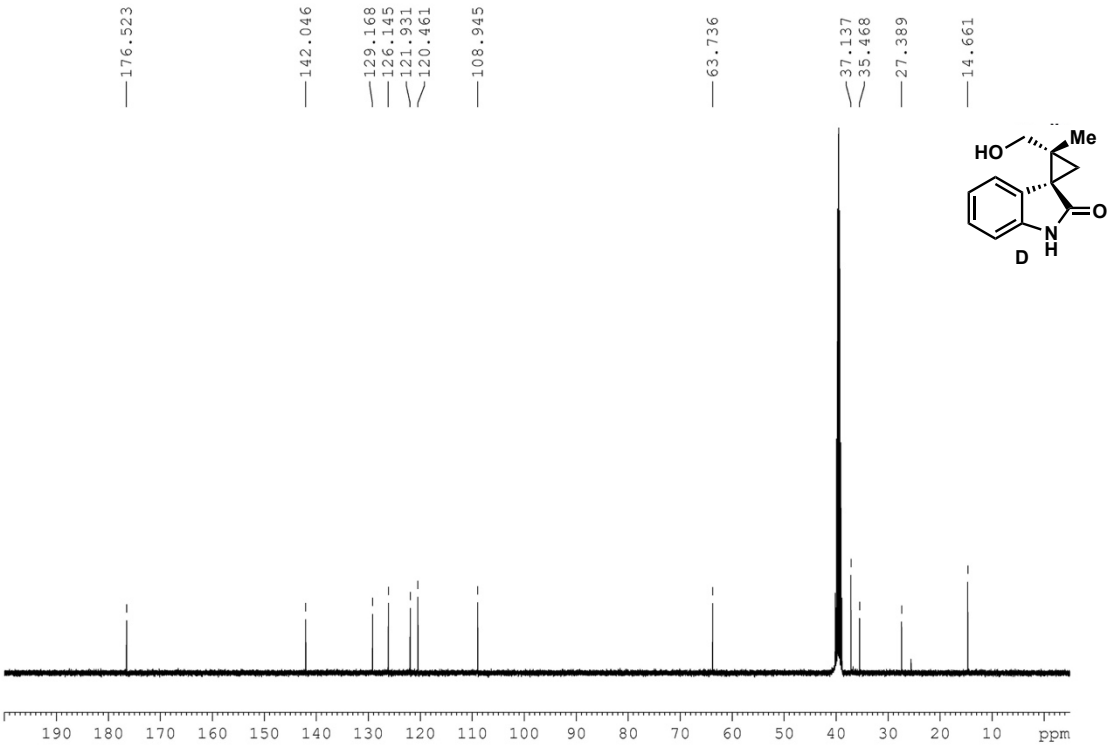


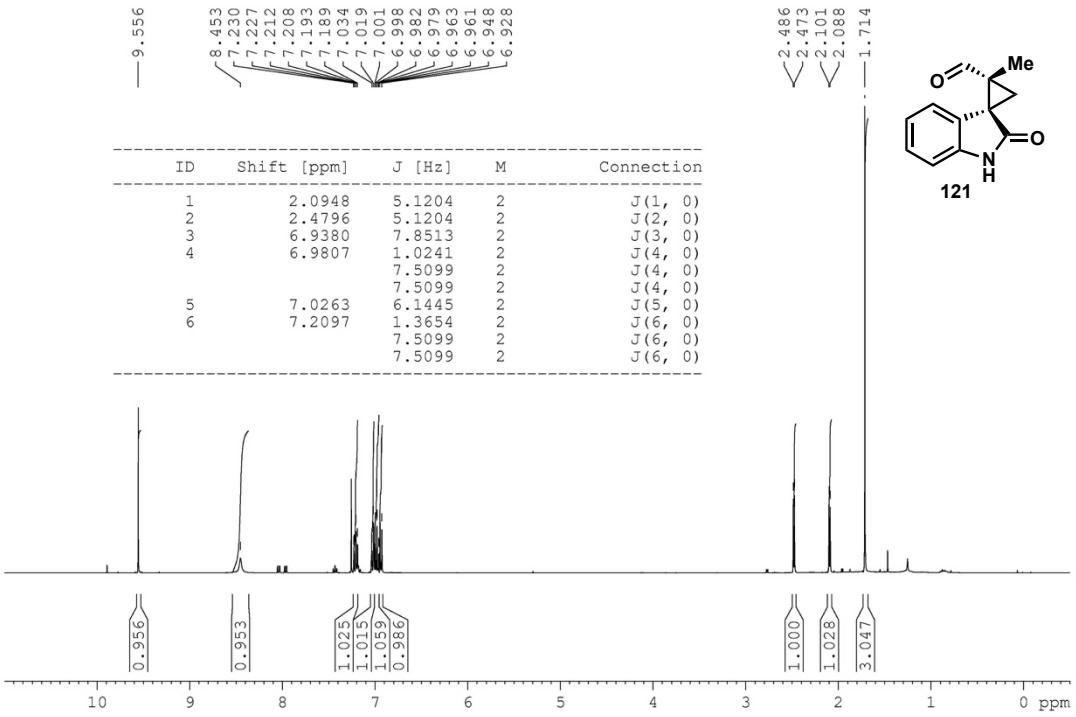


ID	Shift [ppm]	J [Hz]	M	Connection
1	6.9872	4.0813	2	J(1, 0)
2	6.9575	7.6025	2	J(2, 0)
3	4.1691	10.2433	2	J(3, 0)
4	4.0122	10.2433	2	J(4, 0)
5	1.9058	4.8016	2	J(5, 0)
6	1.5287	4.8016	2	J(6, 0)

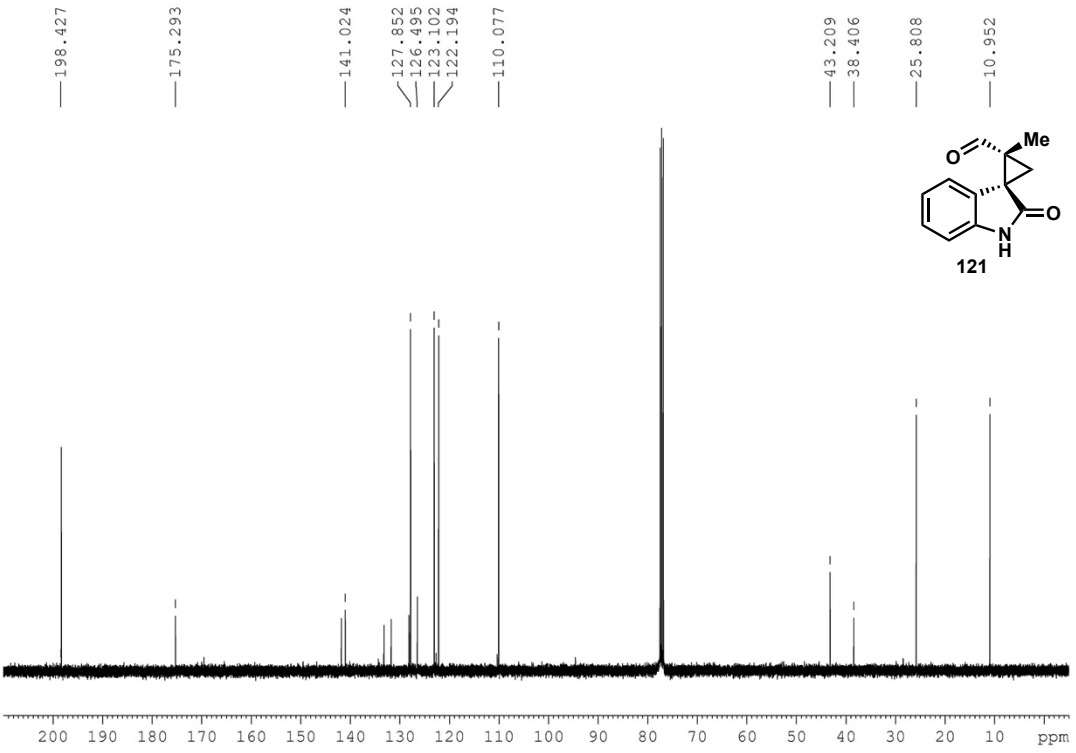


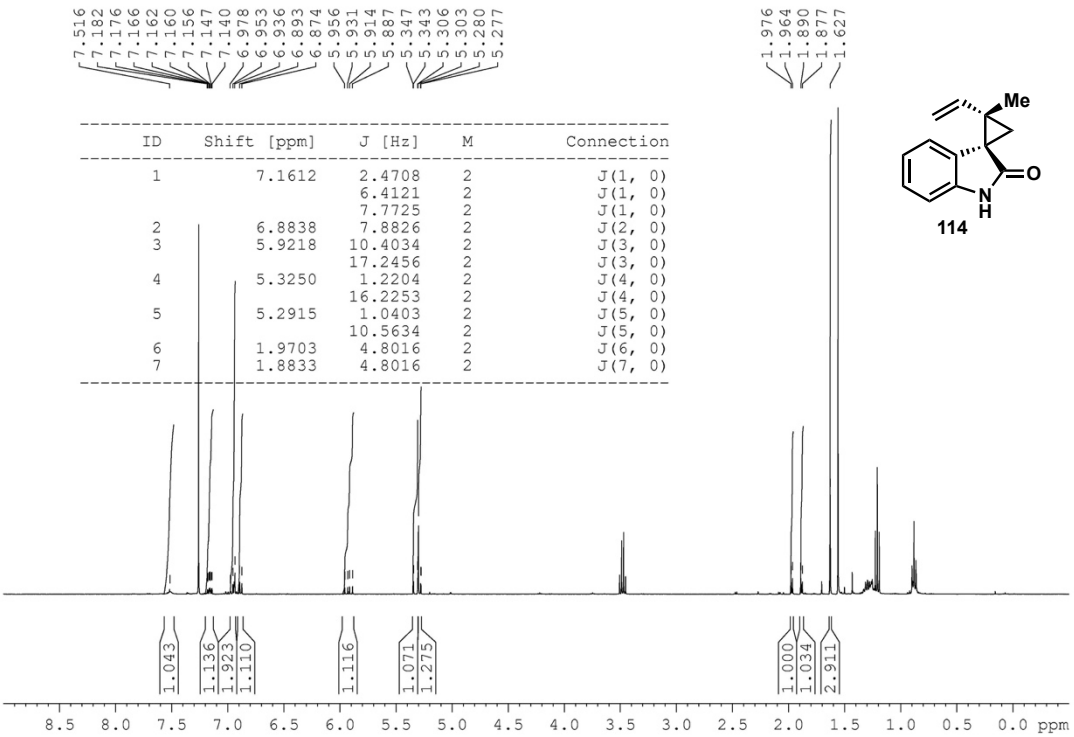

10.419
7.139
7.125
7.117
7.109
7.101
6.899
6.878
6.858
6.835
6.824
4.659
3.704
3.675
3.573
3.545
1.685
1.674
1.487
1.475
1.429
HO
Me
O
N
H
D
ID Shift [ppm] J [Hz] M Connection
1 1.4810 4.4377 2 J(1, 0)
2 1.6798 4.4377 2 J(2, 0)
3 3.5588 11.6062 2 J(3, 0)
4 3.6893 11.6062 2 J(4, 0)
1.002
2.100
2.069
0.837
1.036
1.056
0.976
1.000
3.076
10 9 8 7 6 5 4 3 2 1 0 ppm

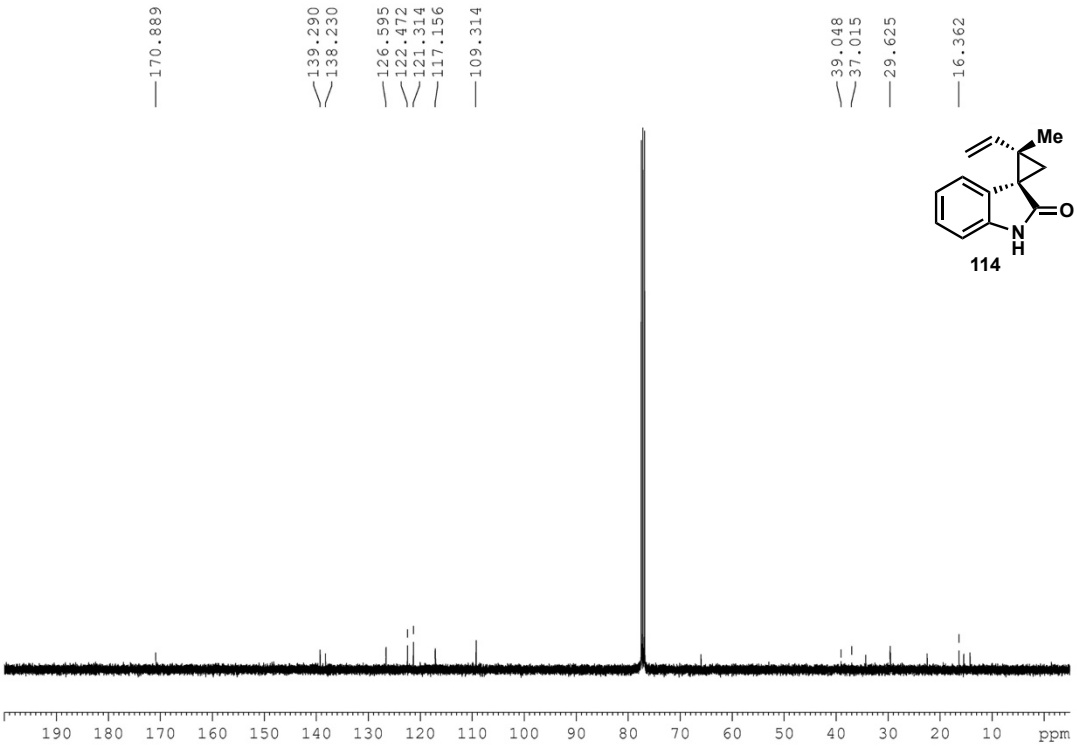

176.523
142.046
129.168
126.145
121.931
120.461
108.945
63.736
37.137
35.468
27.389
14.661
HO
Me
O
N
H
D
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

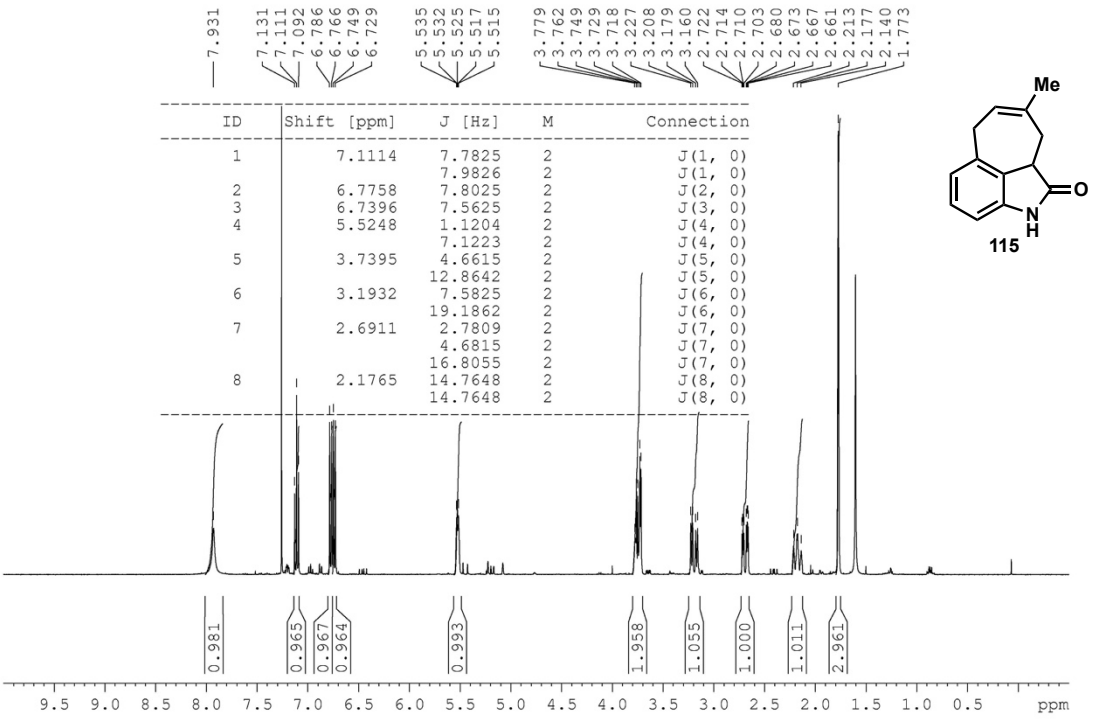


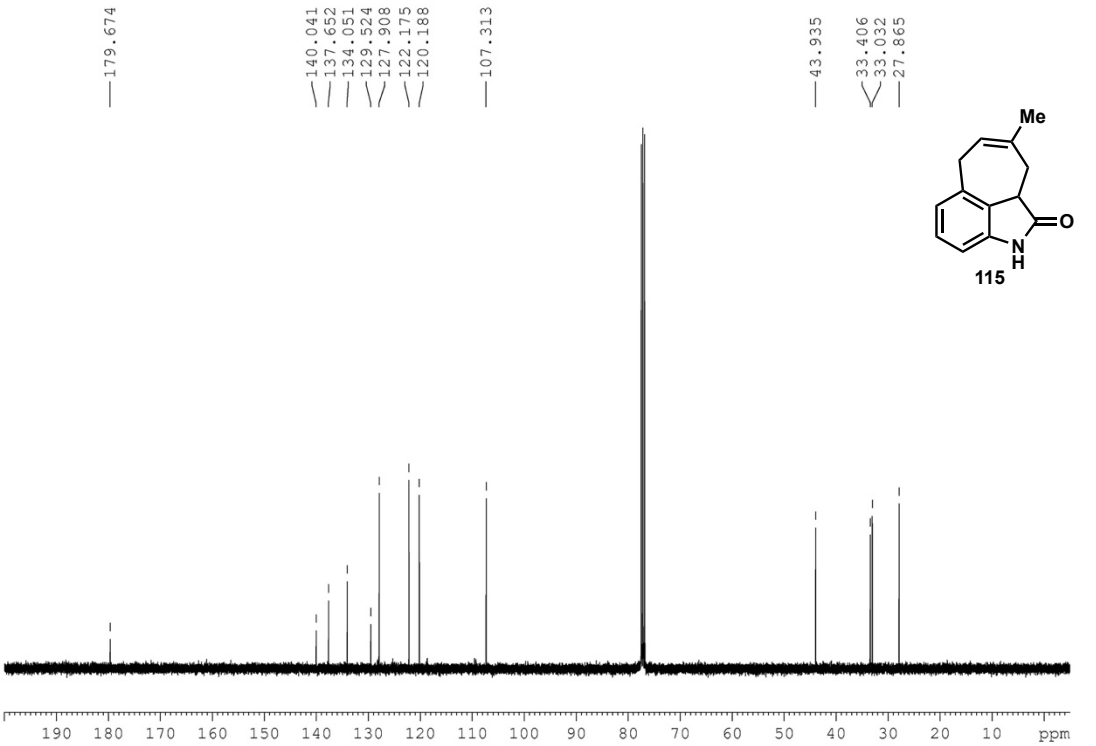
ID	Shift [ppm]	J [Hz]	M	Connection
1	2.0948	5.1204	2	J(1, 0)
2	2.4796	5.1204	2	J(2, 0)
3	6.9380	7.8513	2	J(3, 0)
4	6.9807	1.0241	2	J(4, 0)
		7.5099	2	J(4, 0)
		7.5099	2	J(4, 0)
5	7.0263	6.1445	2	J(5, 0)
6	7.2097	1.3654	2	J(6, 0)
		7.5099	2	J(6, 0)
		7.5099	2	J(6, 0)

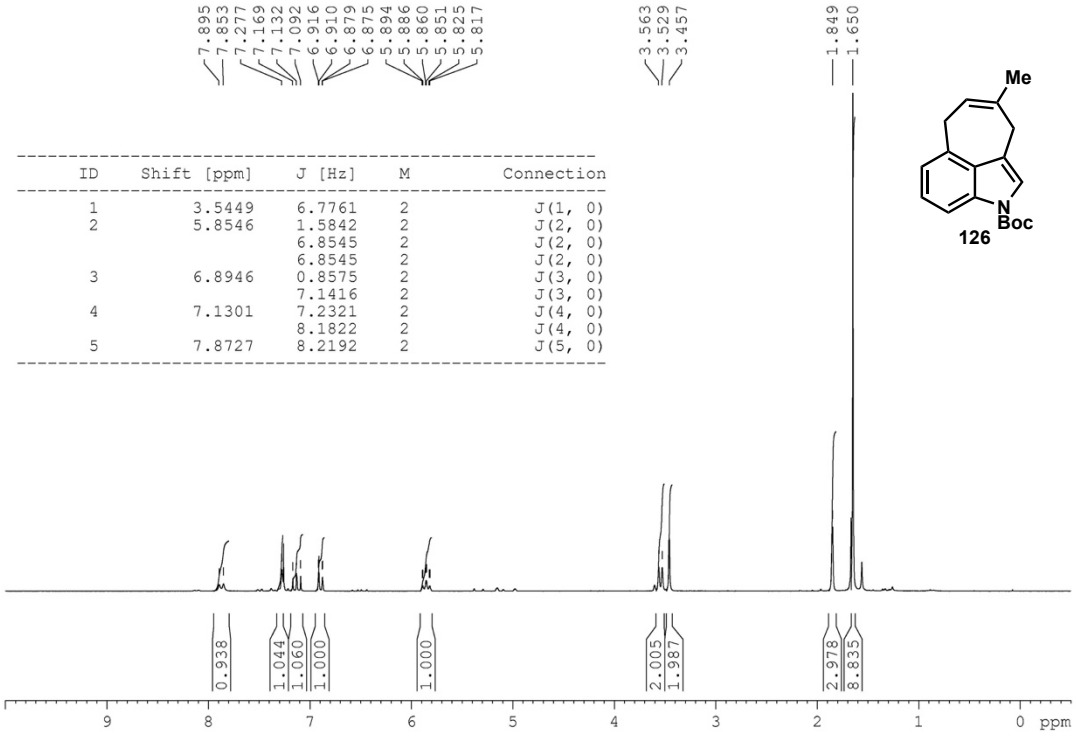



7.516
7.182
7.176
7.166
7.162
7.160
7.156
7.147
7.140
6.978
6.953
6.936
6.893
6.874
5.956
5.931
5.914
5.887
5.347
5.343
5.306
5.303
5.280
5.277
1.976
1.964
1.890
1.877
1.627
ID Shift [ppm] J [Hz] M Connection
1 7.1612 2.4708 2 J(1, 0)
6.4121 2 J(1, 0)
7.7725 2 J(1, 0)
2 6.8838 7.8826 2 J(2, 0)
3 5.9218 10.4034 2 J(3, 0)
17.2456 2 J(3, 0)
4 5.3250 1.2204 2 J(4, 0)
16.2253 2 J(4, 0)
5 5.2915 1.0403 2 J(5, 0)
10.5634 2 J(5, 0)
6 1.9703 4.8016 2 J(6, 0)
7 1.8833 4.8016 2 J(7, 0)
Me
O
N
H
114
1.043
1.136
1.923
1.110
1.116
1.071
1.275
1.000
1.034
2.911
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm

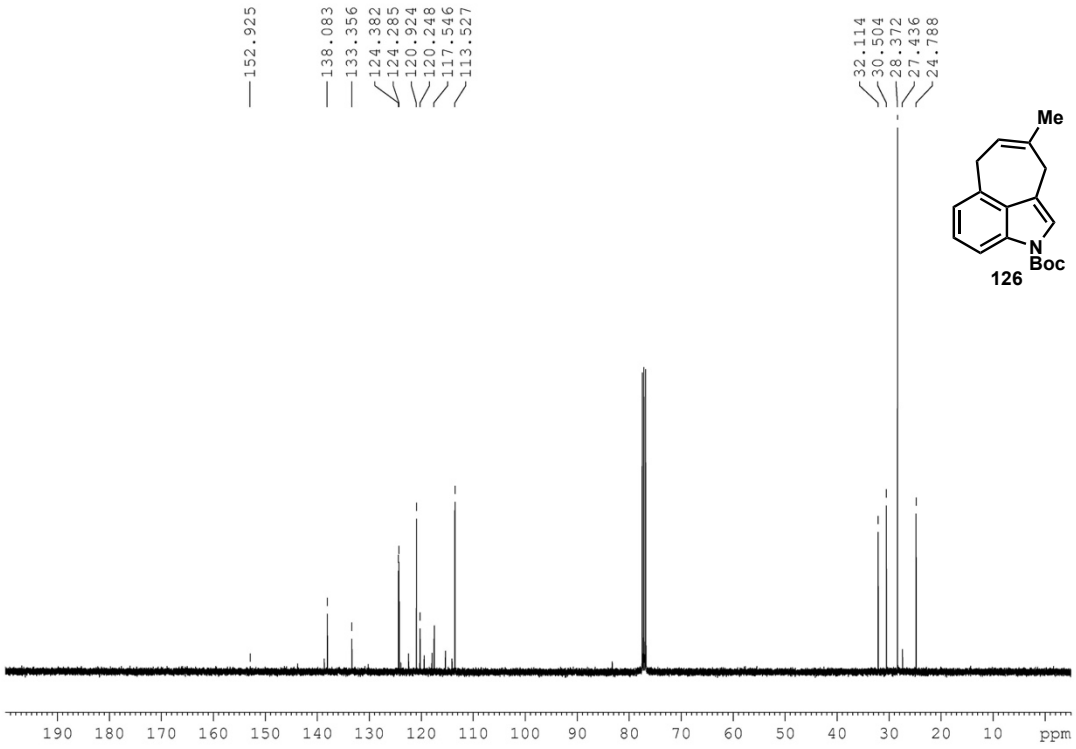

170.889
139.290
138.230
126.595
122.472
121.314
117.156
109.314
39.048
37.015
29.625
16.362
Me
O
N
H
114
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

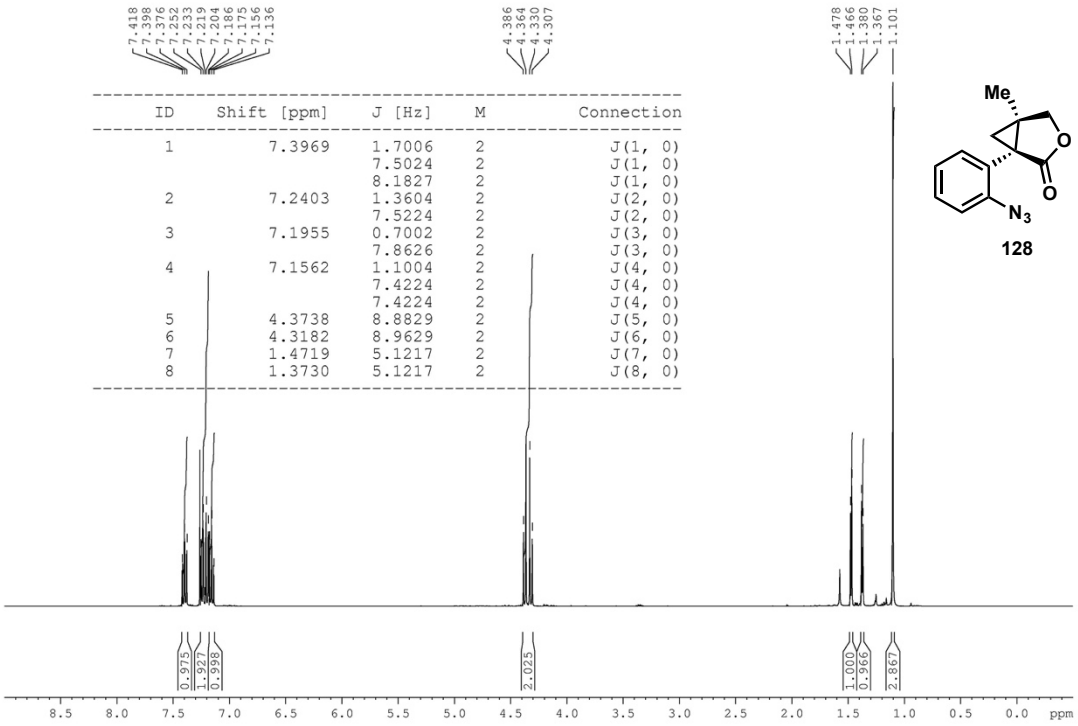

7.931
7.131
7.111
7.092
6.786
6.766
6.749
6.729
5.535
5.532
5.525
5.517
5.515
3.779
3.762
3.749
3.729
3.718
3.227
3.208
3.179
3.160
2.722
2.714
2.710
2.703
2.680
2.673
2.667
2.661
2.213
2.177
2.140
1.773
ID | Shift [ppm] | J [Hz] | M | Connection
1 | 7.1114 | 7.7825 | 2 | J(1, 0)
7.9826 | 2 | J(1, 0)
2 | 6.7758 | 7.8025 | 2 | J(2, 0)
3 | 6.7396 | 7.5625 | 2 | J(3, 0)
4 | 5.5248 | 1.1204 | 2 | J(4, 0)
7.1223 | 2 | J(4, 0)
5 | 3.7395 | 4.6615 | 2 | J(5, 0)
12.8642 | 2 | J(5, 0)
6 | 3.1932 | 7.5825 | 2 | J(6, 0)
19.1862 | 2 | J(6, 0)
7 | 2.6911 | 2.7809 | 2 | J(7, 0)
4.6815 | 2 | J(7, 0)
16.8055 | 2 | J(7, 0)
8 | 2.1765 | 14.7648 | 2 | J(8, 0)
14.7648 | 2 | J(8, 0)
Me
O
N
H
115
0.981
0.965
0.967
0.964
0.993
1.958
1.055
1.000
1.011
2.961
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
ppm


179.674
140.041
137.652
134.051
129.524
127.908
122.175
120.188
107.313
43.935
33.406
33.032
27.865
Me
O
N
H
115
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
ppm

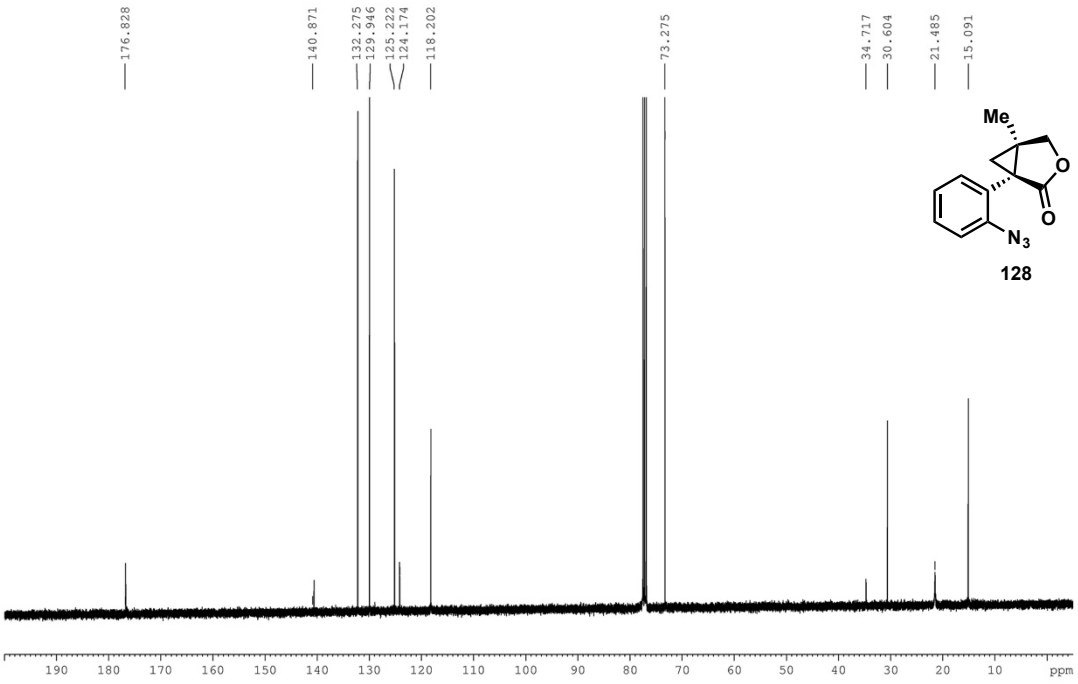


ID	Shift [ppm]	J [Hz]	M	Connection
1	3.5449	6.7761	2	J(1, 0)
2	5.8546	1.5842	2	J(2, 0)
		6.8545	2	J(2, 0)
		6.8545	2	J(2, 0)
3	6.8946	0.8575	2	J(3, 0)
		7.1416	2	J(3, 0)
4	7.1301	7.2321	2	J(4, 0)
		8.1822	2	J(4, 0)
5	7.8727	8.2192	2	J(5, 0)

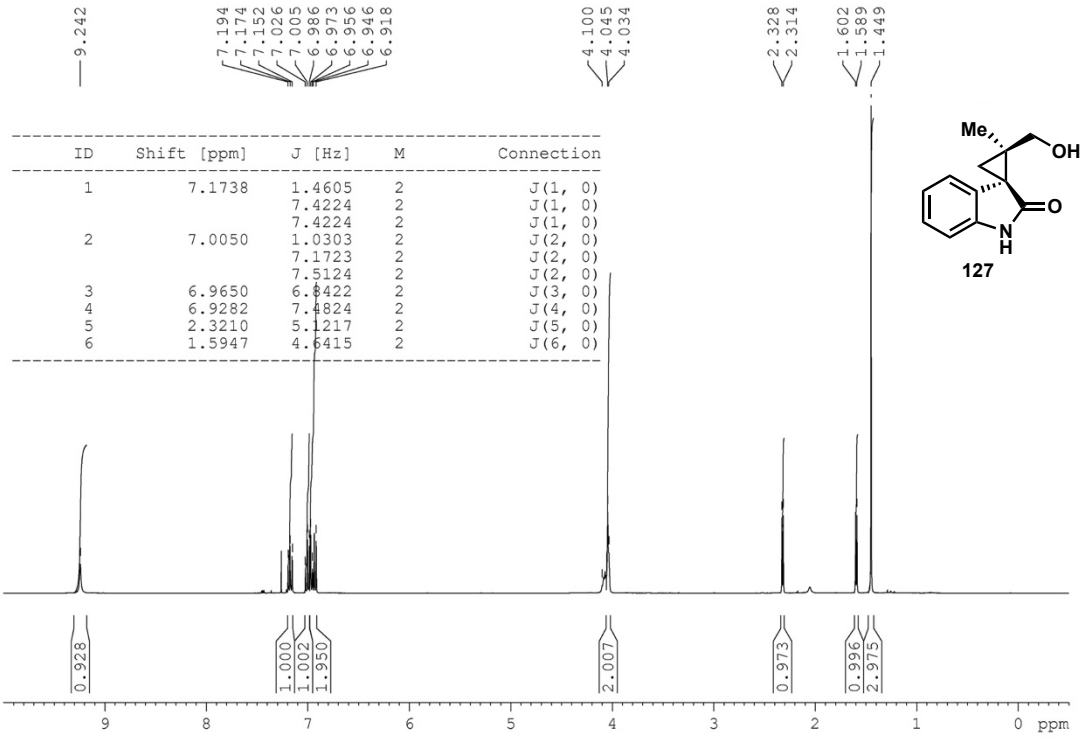


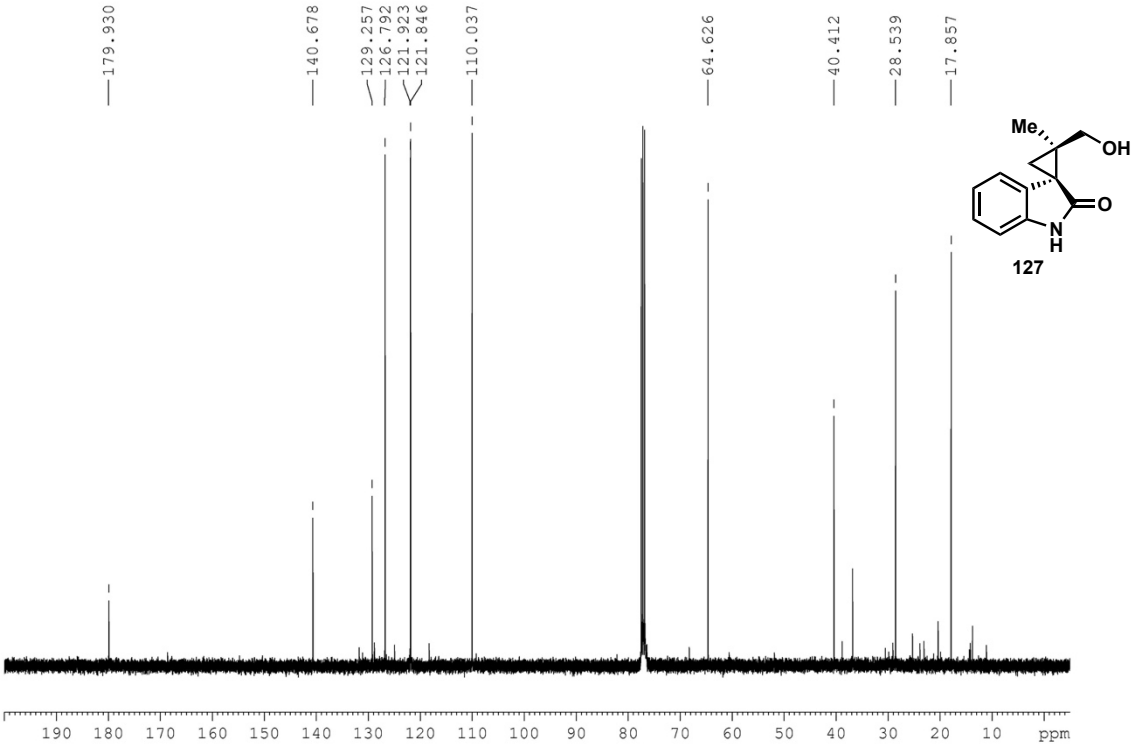

7.418
7.398
7.376
7.252
7.233
7.219
7.204
7.186
7.175
7.156
7.136
4.386
4.364
4.330
4.307
1.478
1.466
1.380
1.367
1.101
ID Shift [ppm] J [Hz] M Connection
1 7.3969 1.7006 2 J(1, 0)
7.5024 2 J(1, 0)
8.1827 2 J(1, 0)
2 7.2403 1.3604 2 J(2, 0)
7.5224 2 J(2, 0)
3 7.1955 0.7002 2 J(3, 0)
7.8626 2 J(3, 0)
4 7.1562 1.1004 2 J(4, 0)
7.4224 2 J(4, 0)
7.4224 2 J(4, 0)
5 4.3738 8.8829 2 J(5, 0)
6 4.3182 8.9629 2 J(6, 0)
7 1.4719 5.1217 2 J(7, 0)
8 1.3730 5.1217 2 J(8, 0)
Me
O
O
N3
0.975
1.927
0.998
2.025
1.000
0.966
2.867
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm

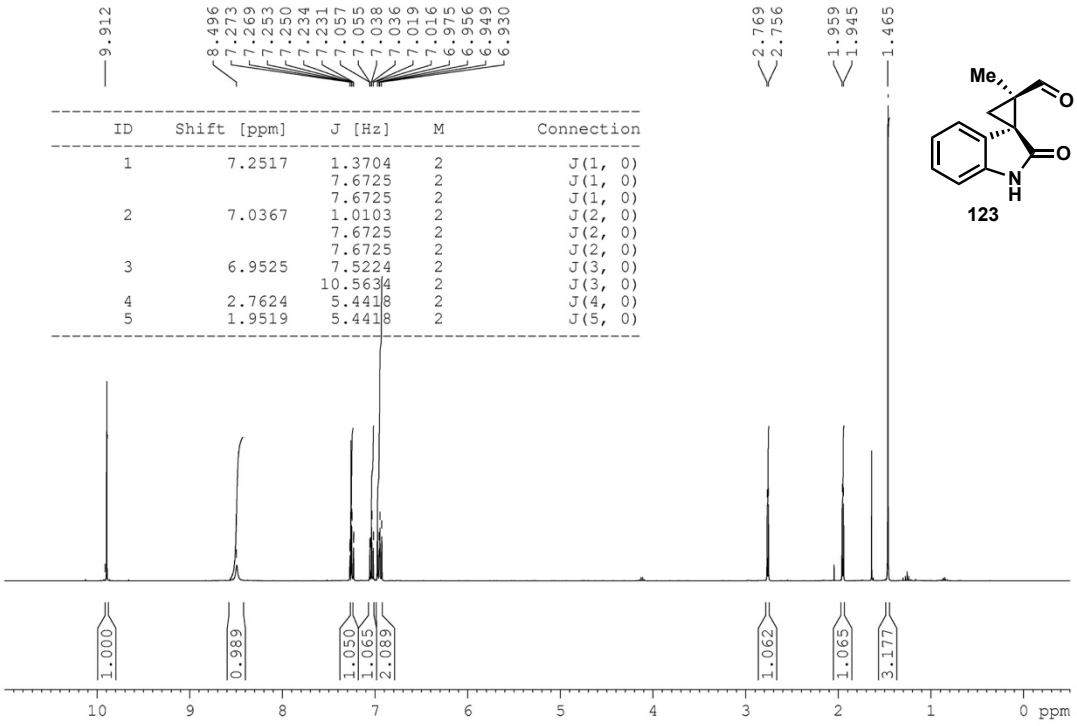
128

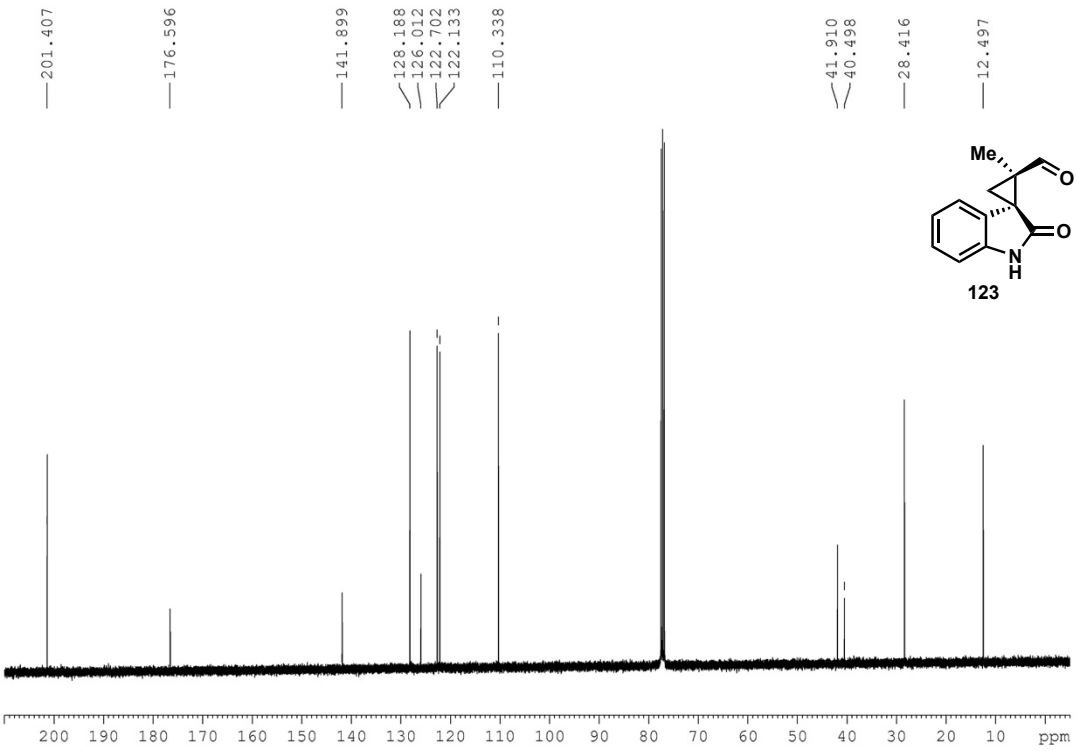

176.828
140.871
132.275
129.946
125.222
124.174
118.202
73.275
34.717
30.604
21.485
15.091
Me
O
O
N3
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

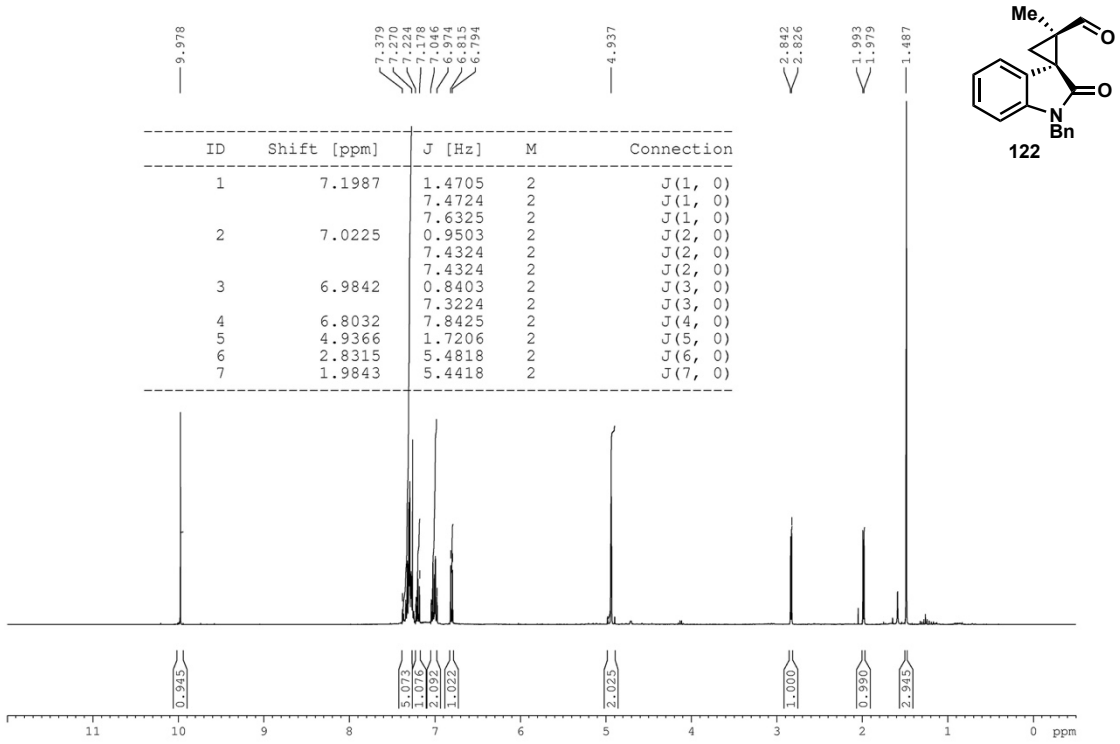
128


9.242
7.194
7.174
7.152
7.026
7.005
6.986
6.973
6.956
6.946
6.918
4.100
4.045
4.034
2.328
2.314
1.602
1.589
1.449
ID Shift [ppm] J [Hz] M Connection
1 7.1738 1.4605 2 J(1, 0)
7.4224 2 J(1, 0)
7.4224 2 J(1, 0)
2 7.0050 1.0303 2 J(2, 0)
7.1723 2 J(2, 0)
7.5124 2 J(2, 0)
3 6.9650 6.8422 2 J(3, 0)
4 6.9282 7.4824 2 J(4, 0)
5 2.3210 5.1217 2 J(5, 0)
6 1.5947 4.6415 2 J(6, 0)
Me
OH
O
N
H
127
0.928
1.000
1.002
1.950
2.007
0.973
0.996
2.975
9
8
7
6
5
4
3
2
1
0 ppm


179.930
140.678
129.257
126.792
121.923
121.846
110.037
64.626
40.412
28.539
17.857
Me
OH
O
N
H
127
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


9.912
8.496
7.273
7.269
7.253
7.250
7.234
7.231
7.057
7.055
7.038
7.036
7.019
7.016
6.975
6.956
6.949
6.930
2.769
2.756
1.959
1.945
1.465
Me
O
O
N
H
123
ID Shift [ppm] J [Hz] M Connection
1 7.2517 1.3704 2 J(1, 0)
7.6725 2 J(1, 0)
7.6725 2 J(1, 0)
2 7.0367 1.0103 2 J(2, 0)
7.6725 2 J(2, 0)
7.6725 2 J(2, 0)
3 6.9525 7.5224 2 J(3, 0)
10.5634 2 J(3, 0)
4 2.7624 5.4418 2 J(4, 0)
5 1.9519 5.4418 2 J(5, 0)
1.000
0.989
1.050
1.065
2.089
1.062
1.065
3.177
10 9 8 7 6 5 4 3 2 1 0 ppm


201.407
176.596
141.899
128.188
126.012
122.702
122.133
110.338
41.910
40.498
28.416
12.497
Me
O
O
N
H
123
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm



ID	Shift [ppm]	J [Hz]	M	Connection
1	7.1987	1.4705	2	J(1, 0)
		7.4724	2	J(1, 0)
		7.6325	2	J(1, 0)
2	7.0225	0.9503	2	J(2, 0)
		7.4324	2	J(2, 0)
		7.4324	2	J(2, 0)
3	6.9842	0.8403	2	J(3, 0)
		7.3224	2	J(3, 0)
4	6.8032	7.8425	2	J(4, 0)
5	4.9366	1.7206	2	J(5, 0)
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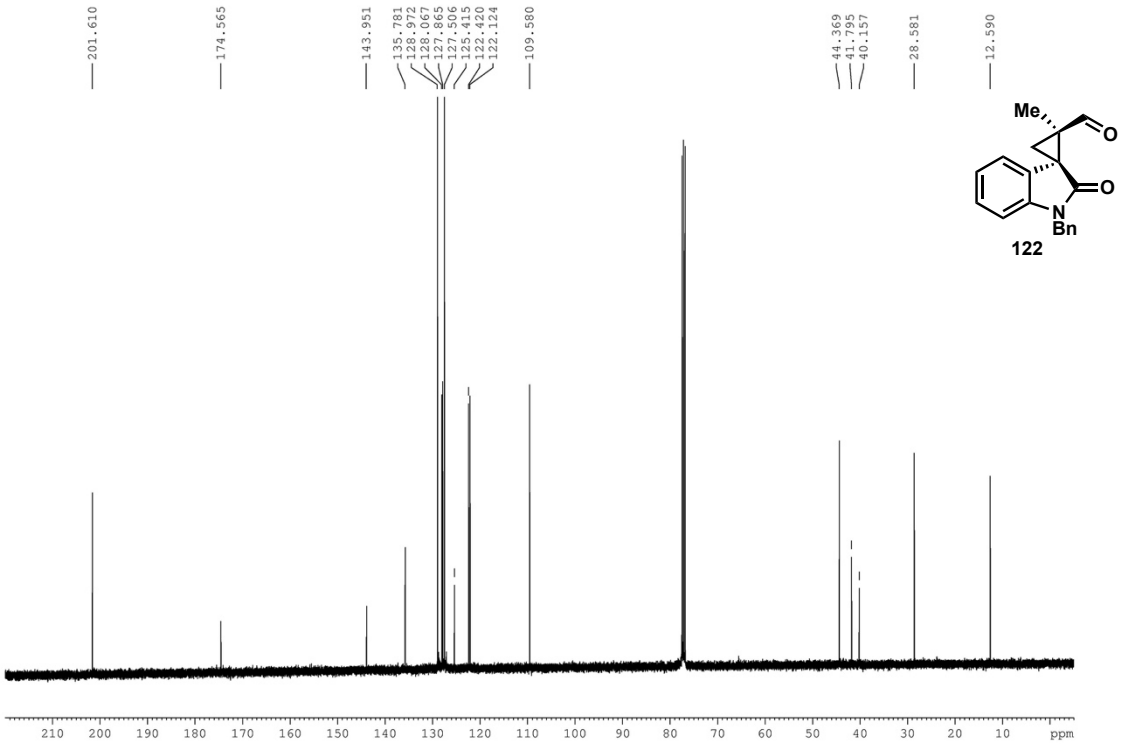

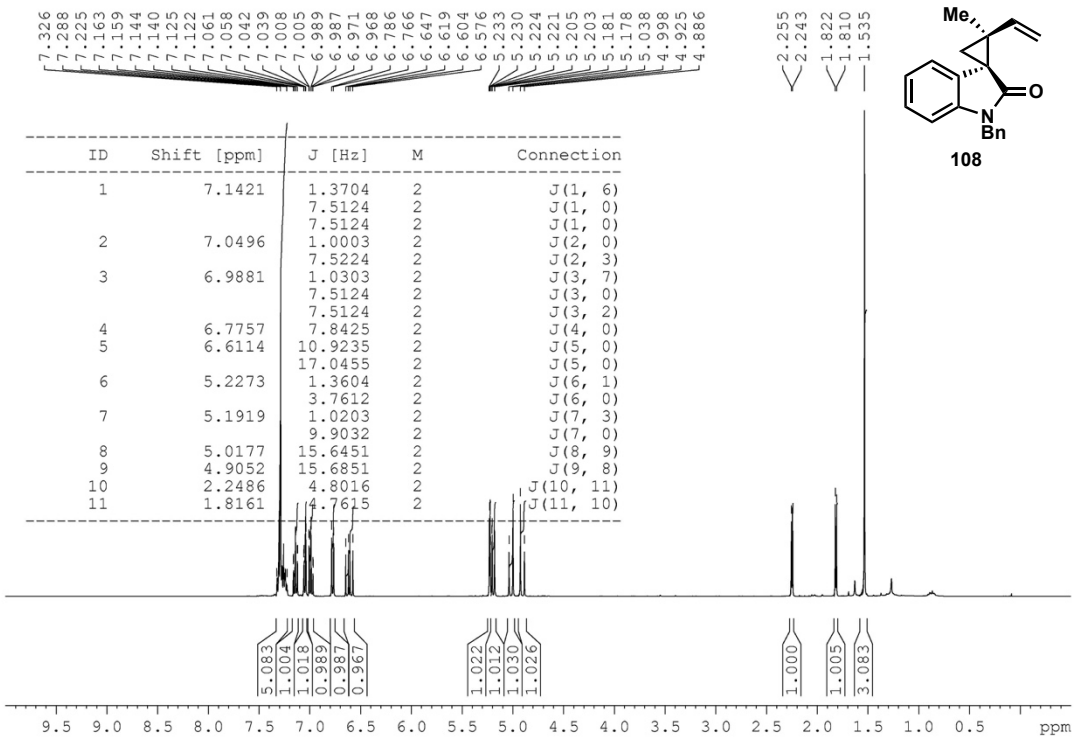
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O
N
Bn
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5 6.6114 10.9235 2 J(5, 0)
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1.022 1.012 1.030 1.026
1.000 1.005 3.083
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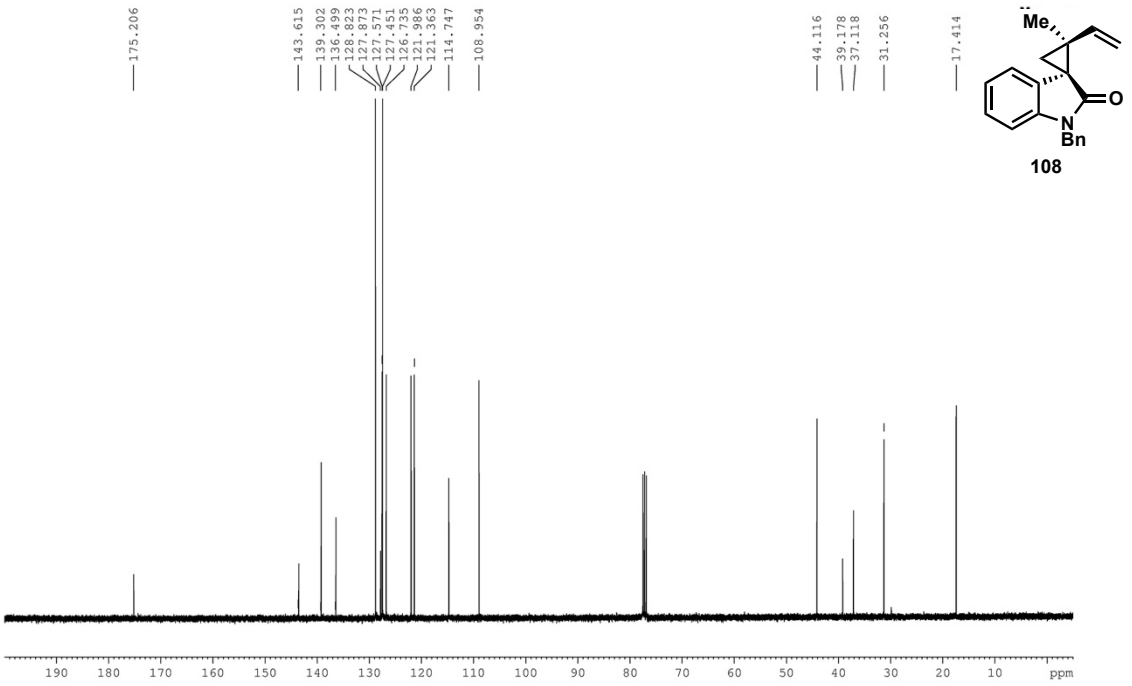
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Me
O
N
Bn
108
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

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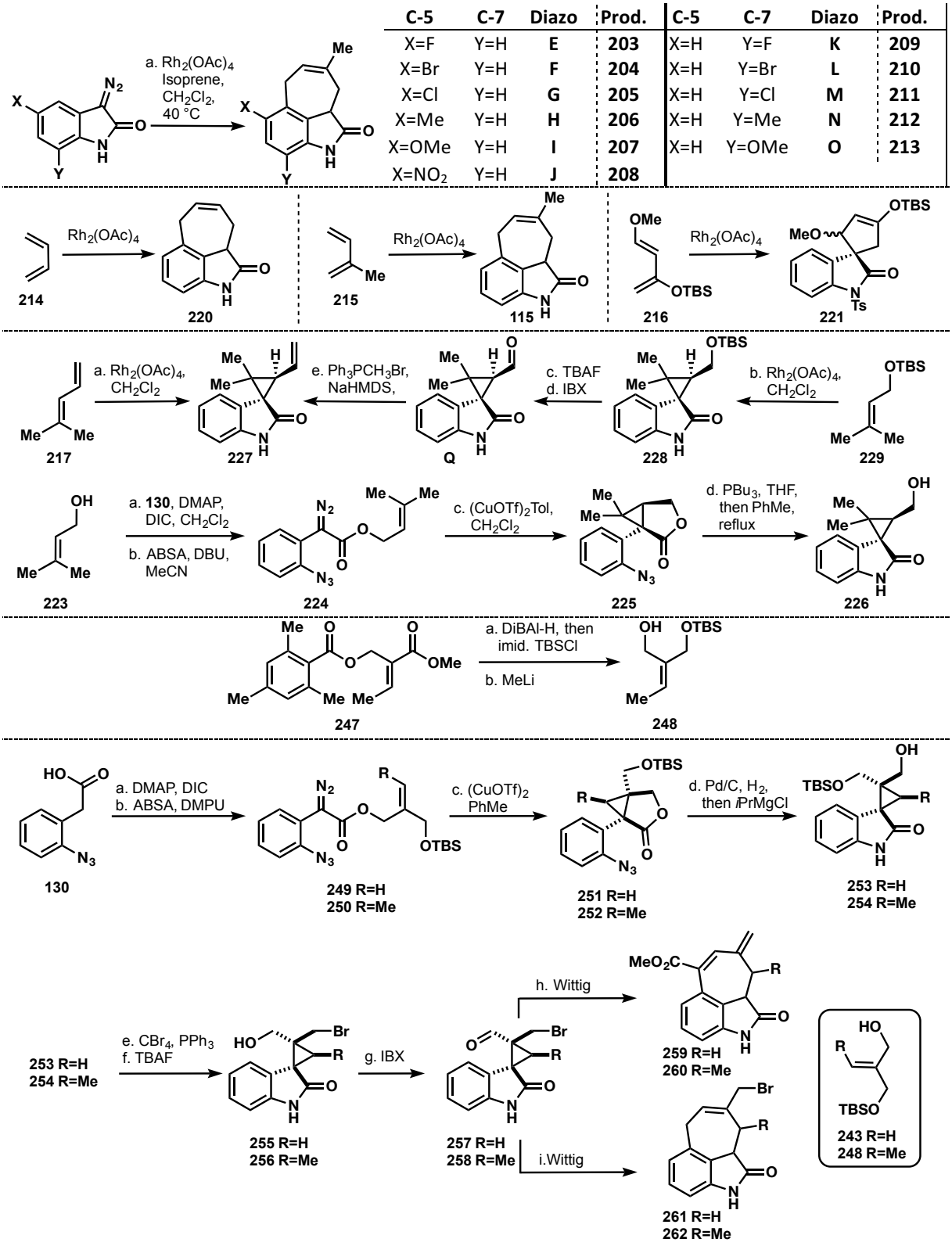
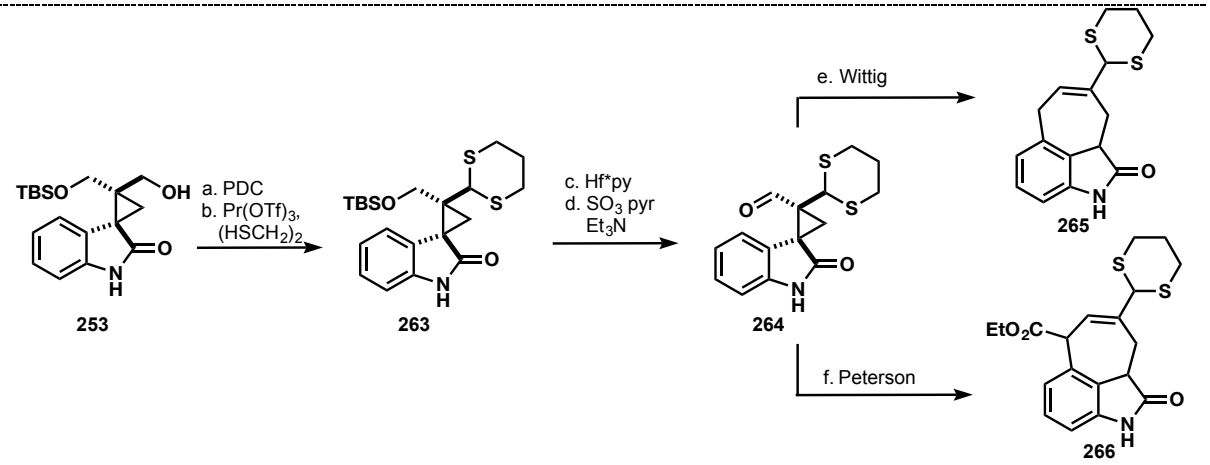




6.2 General

All reactions were carried out in oven-dried glassware under an argon atmosphere, unless otherwise stated. Commercially available anhydrous DMF, DMSO, MeCN, PhH, Pyridine THF (Acros Organics, Alfa Aesar) were used without further manipulation. Other anhydrous solvents were obtained by filtration through drying columns (Et_2O, CH_2Cl_2) on a Glass Contour system. Rhodium (II)-acetate dimer powder was obtained from Sigma-Aldrich. Reactions were magnetically and mechanically stirred and monitored by thin layer chromatography (TLC) with silica gel 60-F254 plates. Flash column chromatography was performed with silica gel 60 Å of Macherey-Nagel under pressure. Preparative TLC was performed with pre-coated TLC-plates Adamant UV_{254} of Mancherey-Nagel. Yields refer to chromatographically and spectroscopically pure compounds, unless otherwise stated. NMR spectra were recorded on a 400 MHz spectrometer of Bruker. Unless otherwise stated, all NMR spectra were measured in $CDCl_3$ solution and referenced to the residual $CHCl_3$ signal (^1H, δ = 7.26 ppm, ^{13}C, δ = 77.16 ppm). All ^1H and ^{13}C shifts are given in ppm (*s* = singlet, *d* = doublet, *t* = triplet, *q* = quadruplet, *m* = multiplet, *b* = broad signal). Assignments of proton resonance were confirmed, when possible, by correlated spectroscopy

6.3 Procedures

6.3.1 *General procedure for cyclopropanation and rearrangement with Isoprene*

$Rh_2(OAc)_4$ (2 mol%) are heated to 40 °C in CH_2Cl_2 (0.2 M) in a sealed tube for five minutes. Isoprene (10 equiv.) is added followed by the corresponding diazoisatine (1 equiv.). The mixture is stirred at 40 °C until the complete consumption of the corresponding diazooxindole and the second cyclopropane diastereomere. The solvent is subsequently removed *in vacuo* and the crude is purified by chromatographically.

6.3.2 *5-fluoro-8-methyl-2,6,9,9a-tetrahydro-1H-cyclohepta[cd]indol-1-one (203)*

203 was prepared by general procedure, starting from **E**, and purified chromatographically (hexane:EtOAc 3:1). 55% (12.0 mg, 55.2 µmol) yield.

^{1}H-NMR (400 MHz, $CDCl_3$, δ): 1.80 (s, 3H), 2.21 (dd, *J* = 16.0, 16.0 Hz, 1H), 2.67 (ddd, *J* = 2.5, 4.5 Hz, 16.8 Hz, 1H), 3.43 (d, *J* = 20.2 Hz, 1H), 3.59 (dd, *J* = 6.8, 20.1 Hz, 1H), 3.74 (dd, *J* = 4.4, 12.6 Hz, 1H), 5.49 – 5.53 (m, 1H), 6.65 (dd, *J* = 3.8, 8.5 Hz, 1H), 6.87 (dd, *J* = 8.5, 10.2 Hz, 1H), 7.96 (s, 1H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$, δ): 25.0 (d, *J* = 3.3 Hz), 27.9, 33.2, 44.9 (d, *J* = 2.1 Hz), 107.5 (d, *J* = 8.1 Hz), 113.9 (d, *J* = 24.9 Hz), 125.1 (d, *J* = 18.8 Hz), 131.4 (d, *J* = 4.8 Hz), 135.7 (d, *J* = 2.4 Hz), 156.1 (d, *J* = 239.8 Hz), 179.4 ppm. **IR (neat sample)**: 3177, 2920, 2852, 1700, 1664, 1629, 1320, 1301, 1240, 903, 810, 789, 619 cm^{-1}. **HRMS** (ESI) (*m/z*): calcd for $C_{13}H_{12}FNO$ $[M + H]^+$, 218.0981; found, 218.0985.

6.3.3 *5-bromo-8-methyl-2,6,9,9a-tetrahydro-1H-cyclohepta[cd]indol-1-one (204)*

204 was prepared by general procedure, starting from **F**, and purified chromatographically (hexane:EtOAc 4:1). 47% (13.0 mg, 47.0 µmol) yield.

^{1}H-NMR (400 MHz, $CDCl_3$, δ): 1.79 (s, 3H), 2.19 (dd, *J* = 14.7, 14.7 Hz, 1H), 2.69 (ddd, *J* = 2.7, 4.5, 17.0 Hz, 1H), 3.54 (d, *J* = 19.4 Hz, 1H), 3.67 – 3.77 (m, 2H), 5.50 – 5.54 (m, 1H), 6.63 (d, *J* = 8.2 Hz, 1H), 7.39 (d, *J* = 8.2 Hz, 1H), 7.29 (s, 1H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$, δ): 27.6, 32.5, 33.4, 44.5, 108.9, 116.5, 119.6, 131.1, 131.9, 134.3, 136.9, 139.3, 179.0 ppm. **IR (neat sample)**: 3261, 3174, 2966, 2920, 2855, 1713, 1613, 1558, 1451, 1285, 1255, 1173, 1039, 805, 651 cm^{-1}. **HRMS** (ESI) (*m/z*): calcd for $C_{13}H_{12}BrNO$ $[M + H]^+$, 278.0181; found, 278.0182.

6.3.4 *5-chloro-8-methyl-2,6,9,9a-tetrahydro-1H-cyclohepta[cd]indol-1-one (205)*

205 was prepared by general procedure, starting from **G**, and purified chromatographically (hexane:EtOAc 3:1). 44% (10.3 mg, 44.0 µmol) yield.

^{1}H-NMR (400 MHz, $CDCl_3$, δ): 1.79 (s, 3 H), 2.20 (dd, *J* = 14.8, 14.8 Hz, 1H), 2.69 (ddd, *J* = 2.6, 4.5, 17.0 Hz, 1H), 3.50 (d, *J* = 19.8 Hz, 1H), 3.69 – 3.79 (m, 2H), 5.50 – 5.55 (m, 1H), 6.68 (d, *J* = 8.2 Hz, 1H), 7.20 (d, *J* = 8.2 Hz, 1H), 8.01 (s, 1H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$, δ): 27.7, 29.6, 33.4, 44.6, 108.3, 119.6, 126.6, 128.6, 131.2, 134.3, 135.2, 138.6, 179.2 ppm. **IR (neat sample)**: 3146, 3075, 2974, 2912, 1703, 1619, 1486, 1443, 1377, 1311, 1280, 1233, 1074, 916, 792, 704 cm^{-1}. **HRMS** (ESI) (*m/z*): calcd for $C_{13}H_{12}ClNO$ $[M + H]^+$, 234.0686; found, 234.0681.

6.3.5 *5,8-dimethyl-2,6,9,9a-tetrahydro-1H-cyclohepta[cd]indol-1-one (206)*

206 was prepared by general procedure, starting from **H**, and purified chromatographically (hexane:EtOAc 4:1). 49% (11.0 mg, 49.3 µmol) yield.

^{1}H-NMR (400 MHz, $CDCl_3$, δ): 1.78 (s, 3H), 2.18 (dd, *J* = 16.2, 16.2 Hz, 1H), 2.25 (s, 3H), 2.69 (ddd, *J* = 2.5, 4.5, 17.0 Hz, 1H), 3.39 (dd, *J* = 7.2, 19.4 Hz, 1H), 3.49 (d, *J* = 19.4 Hz, 1H), 3.72 (dd, *J* = 4.6, 12.8 Hz, 1H), 5.50 – 5.56 (m, 1H), 6.66 (d, *J* = 7.9 Hz, 1H), 6.98 (d, *J* = 7.8 Hz, 1H), 8.24 (s, 1H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$, δ): 19.2, 27.6, 29.2, 33.6, 44.5, 107.1, 129.1, 129.2, 129.9, 134.4, 136.1, 138.2, 180.0 ppm. **IR (neat sample)**: 3208, 2964, 1704, 1620, 1471, 1321, 1295, 1253, 1203, 1154, 799, 630 cm^{-1}. **HRMS** (ESI) (*m/z*): calcd for $C_{14}H_{15}NO$ $[M + Na]^+$, 236.1051; found, 236.1051.

6.3.6 *5-methoxy-8-methyl-2,6,9,9a-tetrahydro-1H-cyclohepta[cd]indol-1-one (207)*

207 was prepared by general procedure, starting from **I**, and purified chromatographically (hexane:EtOAc 2:1). 56% (13.0 mg, 56.0 µmol) yield.

^{1}H-NMR (400 MHz, $CDCl_3$, δ): 1.79 (s, 3H), 2.21 (dd, *J* = 14.2, 14.2 Hz, 1H), 2.67 (ddd, *J* = 2.4, 4.4, 16.7 Hz, 1H), 3.32 (d, *J* = 20.1Hz, 1H), 3.66 – 3.75 (m, 2H), 3.78 (s, 3H), 5.49 – 5.55 (m, 1H), 6.67 (s, 2H), 7.89 (s, 1H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$, δ): 25.5, 27.9, 33.4, 44.8, 56.3, 106.9, 109.4, 120.4, 126.8, 131.4, 133.3, 134.0, 152.6, 179.5 ppm. **IR (neat sample)**: 3171, 2963, 1692, 1619, 1470, 1298, 1246, 1221, 1205, 1090, 1063, 784, 631 cm^{-1}. **HRMS** (ESI) (*m/z*): calcd for $C_{14}H_{15}NO_2$ $[M + H]^+$, 230.1181; found, 230.1180.

6.3.7 *8-methyl-5-nitro-2,6,9,9a-tetrahydro-1H-cyclohepta[cd]indol-1-one (208)*

208 was prepared by general procedure, starting from **J**, and purified chromatographically (hexane:EtOAc 1:1). 37% (45.0 mg, 184 µmol) yield.

^{1}H-NMR (400 MHz, $CDCl_3$, δ): 1.77 (s, 3H), 2.16 (dd, *J* = 15.2, 15.2 Hz, 1H), 2.75 (ddd, *J* = 3.0, 5.0, 17.2 Hz, 1H), 3.66 (d, *J* = 18.8 Hz, 1H), 3.87 (dd, *J* = 5.1, 13.0 Hz, 1H), 3.97 (dd, *J* = 7.6, 18.8 Hz, 1H), 5.52 – 5.59 (m, 1H), 6.83 (d, *J* = 8.5 Hz, 1H), 7.90 (d, *J* = 8.5 Hz, 1H), 8.16 (s, 1H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$, δ): 25.5, 27.9, 33.4, 44.8, 56.3, 106.9, 109.4, 120.4, 126.8, 131.4, 133.3, 134.0, 152.6, 179.5 ppm. **IR (neat sample)**: 3145, 2906, 1713, 1679, 1604, 1512, 1458, 1342, 1252, 1195, 1039, 827, 734, 674 cm^{-1}. **HRMS** (ESI) (*m/z*): calcd for $C_{13}H_{12}N_2O_3$ $[M + H]^+$, 245.0926; found, 245.0917.

6.3.8 *3-fluoro-8-methyl-2,6,9,9a-tetrahydro-1H-cyclohepta[cd]indol-1-one (209)*

209 was prepared by general procedure, starting from **K**, and purified chromatographically (hexane:EtOAc 5:1). 41% (9.00 mg, 41.0 µmol) yield.

^{1}H-NMR (400 MHz, $CDCl_3$, δ): 1.77 (s, 3H), 2.19 (dd, *J* = 14.9, 14.9 Hz, 1H), 2.69 (ddd, *J* = 3.0, 4.7, 17.0 Hz, 1H), 3.17 (dd, *J* = 7.3, 19.3 Hz, 1H), 3.69 (d, *J* = 19.3 Hz, 1H), 3.77 (dd, *J* = 4.5, 12.8 Hz, 1H), 5.49 – 5.54 (m, 1H), 6.70 (dd, *J* = 4.6, 9.0 Hz, 1H), 6.87 (dd, *J* = 9.0, 9.0 Hz, 1H), 7.79 (s, 1H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$, δ): 27.9, 23.4, 33.3, 44.2 (d, *J* = 2.3 Hz), 114.8 (d, *J* = 17.4 Hz), 120.2, 122.5 (d, *J* = 5.6 Hz), 126.8 (d, *J* = 12.5 Hz), 131.6 (d, *J* = 3.3 Hz), 133.1 (d, *J* = 3.5 Hz), 133.4, 145.6 (d, *J* = 241.5 Hz), 178.4 ppm. **IR (neat sample)**: 3187, 2920, 2852, 1696, 1629, 1469, 1288, 1240, 1204, 783, 630, cm^{-1}. **HRMS** (ESI) (*m*/*z*): calcd for $C_{13}H_{13}FNO$ $[M + H]^+$, 218.0981; found 218.0978.

6.3.9 *3-bromo-8-methyl-2,6,9,9a-tetrahydro-1H-cyclohepta[cd]indol-1-one (210)*

210 was prepared by general procedure, starting from **L**, and purified chromatographically (hexane:EtOAc 6:1). 52% (14.4 mg, 52.0 µmol) yield.

^{1}H-NMR (400 MHz, $CDCl_3$, δ): 1.77 (*s*, 3 H), 2.15 – 2.25 (*m*, 1H), 2.68 (*ddd*, *J* = 2.8, 4.5, 17.0 Hz, 1H), 3.16 (*dd*, *J* = 7.5, 19.5 Hz, 1H), 3.68 (*d*, *J* = 19.1 Hz, 1H), 3.83 (*dd*, *J* = 4.8, 12.6 Hz, 1H), 5.48 – 5.52 (*m*, 1H), 6.67 (*d*, *J* = 8.2 Hz, 1H), 7.21 (*d*, *J* = 8.2 Hz, 1H), 7.51 (*s*, 1H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$, δ): 27.8, 32.6, 33.3, 45.2, 99.8, 119.8, 123.7, 130.4, 130.4, 134.0, 136.6, 139.3, 177.8 ppm. **IR (neat sample)**: 3146, 3075, 2974, 2912, 1703, 1619, 1486, 1443, 1377, 1311, 1280, 1233, 1074, 916, 792, 704 cm^{-1}. **HRMS** (ESI) (*m*/*z*): calcd for $C_{13}H_{12}ClNO$ $[M + H]^+$, 234.0686; found, 234.0683.

6.3.10 *3-chloro-8-methyl-2,6,9,9a-tetrahydro-1H-cyclohepta[cd]indol-1-one (211)*

211 was prepared by general procedure, starting from **M**, and purified chromatographically (hexane:EtOAc 8:1 to 4:1). 52% (12.0 mg, 52.0 µmol) yield.

^{1}H-NMR (400 MHz, $CDCl_3$, δ): 1.77 (s, 3H), 2.20 (dd, *J* = 14.9, 14.9 Hz, 1H), 2.69 (ddd, *J* = 2.8, 4.7, 16.8 Hz, 1H), 3.17 (dd, *J* = 7.2, 19.5 Hz, 1H), 3.70 (d, *J* = 19.5 Hz, 1H), 3.80 (dd, *J* = 4.7, 13.0 Hz, 1H) 5.48 – 5.52 (m, 1H), 6.72 (d, *J* = 8.2 Hz, 1H), 7.09 (d, *J* = 8.2 Hz, 1H), 7.67 (s, 1H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$, δ): 27.9, 32.6, 33.2, 44.9, 112.3, 119.9, 123.2, 127.7, 130.5, 134.0, 136.0, 137.6, 178.1 ppm. **IR (neat sample)**: 3146, 3075, 2974, 2912, 1703, 1619, 1486, 1443, 1377, 1311, 1280, 1233, 1074, 916, 792, 704 cm^{-1}. **HRMS** (ESI) (*m*/*z*): calcd for $C_{13}H_{12}ClNO$ $[M + H]^+$, 234.0686; found, 234.0683.

6.3.11 *3,8-dimethyl-2,6,9,9a-tetrahydro-1H-cyclohepta[cd]indol-1-one (212)*

212 was prepared by general procedure, starting from **N**, and purified chromatographically (hexane:EtOAc 5:1). 53% (11.3 mg, 53.0 µmol) yield.

^{1}H-NMR (400 MHz, $CDCl_3$, δ): 1.77 (s, 3H), 2.17 (dd, *J* = 14.2, 14.2 Hz, 1H), 2.26 (s, 3H), 2.69 (ddd, *J* = 2.9, 4.6, 17.1 Hz, 1H), 3.16 (dd, *J* = 7.5, 19.1 Hz, 1H), 3.66 – 3.79 (m, 2H), 5.50 – 5.54 (m, 1H), 6.69 (d, *J* = 7.8 Hz, 1H), 6.93 (d, *J* = 7.8 Hz, 1H), 8.46 (s, 1H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$, δ): 16.3, 27.9, 32.8, 33.5, 44.5, 116.6, 120.4, 122.0, 129.1, 133.9, 134.8, 138.9, 180.2 ppm. **IR (neat sample)**: 3163, 3041, 2908, 2852, 1700, 1617, 1436, 1234, 1185, 799, 726 cm^{-1}. **HRMS** (ESI) (*m*/*z*): calcd for $C_{14}H_{15}NO$ $[M + Na]^+$, 236.1051; found, 236.1061.

6.3.12 *3-methoxy-8-methyl-2,6,9,9a-tetrahydro-1H-cyclohepta[cd]indol-1-one (213)*

213 was prepared by general procedure, starting from **O**, and purified chromatographically (hexane:EtOAc 3:1). 44% (10.0 mg, 44.0 µmol) yield.

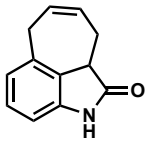
^{1}H-NMR (400 MHz, $CDCl_3$, δ): 1.76 (s, 3H), 2.18 (dd, *J* = 14.8, 14.8 Hz, 1H), 2.68 (ddd, *J* = 2.7, 4.8, 17.1 Hz, 1H), 3.14 (dd, *J* = 7.5, 19.1 Hz, 1H), 3.65 – 3.77 (m, 2H), 3.85 (s, 3H), 5.50 – 5.54 (m, 1H), 6.71 (s, 2H), 7.45 (s, 1H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$, δ): 25.5, 27.9, 33.4, 44.8, 56.3, 106.9, 109.4, 120.4, 126.8, 131.4, 133.3, 134.0, 152.6, 179.5 ppm. **IR (neat sample)**: 3171, 2963, 1692, 1619, 1470, 1298, 1246, 1221, 1205, 1090, 1063, 784, 631 cm^{-1}. **HRMS** (ESI) (*m*/*z*): calcd for $C_{14}H_{15}NO_2$ $[M + H]^+$, 230.1181; found, 230.1180.

6.3.13 *4-methyl-2a,3-dihydro-1H-cyclohepta[cd]indol-2(6H)-one (115)*

115 was prepared by general procedure, starting from **118**, and purified chromatographically (hexane:EtOAc 1:1). 53% (10.0 mg, 50.0 µmol) yield.

Analytical data see **5.3.12**

6.3.14 *2,6,9,9a-tetrahydro-1H-cyclohepta[cd]indol-1-one (220)*



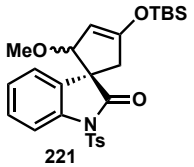
220

220 was prepared by general procedure, starting from **118** using butadiene instead of isoprene. After cyclopropanation, the solvent was replaced by DMSO and the mixture was

heated to 110 °C until complete by TLC (hexane:EtOAc 1:1). The crude was purified chromatographically (hexane:EtOAc 3:2). 53% (11.7 mg, 63.0 µmol) yield.

Analytical data see **8.3.8**

6.3.15 *(1S)-4-((tert-butyldimethylsilyl)oxy)-2-methoxy-1'-tosylspiro[cyclopentane-1,3'-indolin]-3-en-2'-one (221)*

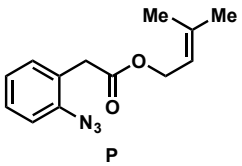


221

Diazo **337** (103 mg, 330 µmol, 1 equiv) was dissolved in benzene (300 µL) and mixed with Danishefsky diene **216** (130 mg, 600 µmol, 1.8 equiv). Then $Rh_2(OAc)_4$ (1.30 mg, 3.20 µmol, 1 mol%) was added and the mixture was stirred at 40 °C for 3 h. The reaction progress was monitored by thin layer chromatography. (hexane:EtOAc 6:1) The crude product was purified by flash chromatography on silica gel with hexane:EtOAc (6:1), what yielded to approximately 50% of compound **221** (79.0 mg, 160 µmol).

^{1}H-NMR (400 MHz, $CDCl_3$, δ): 0.19 (s, 3H), 0.20 (s, 3H), 0.91 (s, 9H), 2.40 (s. 3H), 2.47 (s, 3H), 2.47 (ddd, *J* = 1.9, 2.1, 16.0 Hz, 1H), 2.75 (d, *J* = 16.3 Hz, 1H), 4.37 (d, *J* = 0.5 Hz, 1H), 4.74 (d, *J* = 1.8 Hz, 1H), 7.17 (dd, *J* = 7.1, 7.5 Hz, 1H), 7.30 (d, *J* = 8.3 Hz, 2H), 7.32 – 7.38 (m, 2H), 7.92 (d, *J* = 8.2 Hz, 1H), 7.97 (d, *J* = 8.3 Hz, 2H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$, δ): –4.6, –4.5, 18.2, 21.8, 25.7, 45.1, 55.9, 57.2, 89.7, 102.5, 113.4, 125.0, 125.5, 128.0, 128.8, 129.4, 129.8, 135.2, 138.6, 145.7, 155.9, 178.7 ppm. **IR (neat sample)**: 1756, 1716, 1595, 1461, 1376, 1228, 1175, 1140, 1080, 957, 818, 762, 656 cm^{-1}. **HRMS** (ESI) (*m/z*): calcd for $C_{26}H_{33}NO_5SSi$ $[M + Na]^+$, 522.1746; found, 522.1746.

6.3.16 *3-methylbut-2-en-1-yl 2-(2-azidophenyl)acetate (P)*

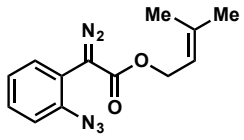


P

Azide **130** (1.0 equiv.), prenyl alcohol (1.0 equiv.) and DMAP (0.2 equiv.) were dissolved in CH_2Cl_2 (0.5 mol/L). Then DIC (1.05 equiv.) was slowly added to the solution. After complete consumption of the starting material, the reaction was quenched with water and extracted with EtOAc, dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was then purified by flash chromatography (hexane:EtOAc 40:1). **P** was obtained in 92% (2.55 g) yield.

^{1}H-NMR (400 MHz, $CDCl_3$ δ): 1.71 (s, 3H), 1.77 (s, 3H), 3.61 (s, 2H), 4.62 (d, J = 7.5 Hz, 2H), 5.35 (dd, *J* = 7.0, 7.5 Hz, 1H), 7.10 – 7.30 (m, 3H), 7.34 (m, 1H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$ δ): – 5.3, 18.5, 26.0, 36.8, 63.8, 65.3, 113.0, 118.3, 125.0, 125.7, 128.9, 131.7, 138.8, 143.2, 170.8 ppm. **IR (neat sample)**: 2916, 2121, 1733, 1491, 1286, 1155, 965, 750 cm^{-1}. **HRMS** (ESI) (*m*/*z*): calcd for $C_{13}H_{15}N_3O_2$ $[M + Na]^+$, 268.1062; found 268.1049 .

6.3.17 *3-methylbut-2-en-1-yl 2-(2-azidophenyl)-2-diazoacetate (224)*

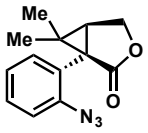


224

To a solution of the ester **P** (1.0 equiv.) and ABSA (1.0 equiv.) in THF (0.2 mol/L) DBU (2.0 equiv) was added. The solution was stirred for 18 h, then quenched with NH_4Cl solution, the aqueous layer was extracted with EtOAc, the combined organic layers were washed with brine solution, dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was then purified by flash chromatography (hexane:EtOAc). **224** was obtained in yield 96% (2.70 g) yield.

^{1}H-NMR (400 MHz, $CDCl_3$, δ): 1.74 (s, 3H), 1.77 (s, 3 H), 4.74 (d, *J* = 7.2 Hz, 2H), 5.38 (dd, *J* = 7.2, 7.2 Hz, 1H), 7.17 – 7.21 (m, 2H), 7.31 – 7.37 (m, 1H), 7.54 (d, *J* = 1.5, 8.0 Hz, 1H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$, δ): 18.2, 25.9, 62.2, 116.8, 118.6, 118.8, 125.2, 129.1, 131.5, 137.3, 139.4, 166.0 ppm. **IR (neat sample)**: 2917, 2126, 2091, 1698, 1280, 1242, 1151, 1008, 751 cm^{-1}.

6.3.18 *1-(2-azidophenyl)-6,6-dimethyl-3-oxabicyclo[3.1.0]hexan-2-one (225)*



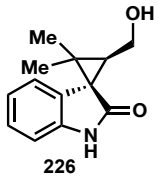
225

Under argon, a solution of diazo **224** (1.0 equiv.) in anhydrous CH_2Cl_2 (0.1 mol/L) was added *via* syringe onto a solution of $[(CuOTf)_2PhMe]$ (1.5 mol%) in anhydrous CH_2Cl_2 (0.1 mol/L) at rt. over ten minutes. The solution was stirred for 30 minutes until complete consumption of the starting material. The reaction mixture was then concentrated *in vacuo* and purified by flash chromatography. (hexane:EtOAc 20:1 to 3:1). **225** was obtained in 80% (2.13 g) yield.

^{1}H-NMR (400 MHz, $CDCl_3$ δ): 1.05 (s, 3H), 1.32 (s, 3H), 2.29 (d, *J* = 5.1 Hz, 1H), 4.27 (d, *J* = 10.0 Hz, 1H), 4.27 (dd, *J* = 10.0, 5.1 Hz, 1H), 7.15 (m, 2H), 7.23 (d, *J* = 7.8 Hz, 1H), 7.36 (dd, *J* = 7.00, 7.00 Hz, 1H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$ δ): 16.0, 24.1, 28.1, 36.6, 40.6, 65.9,

118.5, 124.9, 129.6, 131.2, 133.5, 141.4, 175.6 ppm. **IR (neat sample)**: 2962, 2906, 2122, 2088, 1758, 1287, 1173, 754 cm^{-1}. **HRMS** (ESI) (*m/z*): calcd for $C_{13}H_{13}N_3O_2$ $[M + Na]^+$, 266.0905; found 266.0914.

6.3.19 *3-(hydroxymethyl)-2,2-dimethylspiro[cyclopropane-1,3'-indolin]-2'-one (226)*

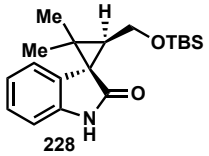


226

Under argon azid **225** (660 mg, 2.73 mmol, 1.0 equiv.) was dissolved in anhydrous THF (5 mL), tributylphosphine (750 µL, 3.00 mmol, 1.05 equiv.) was added and the solution was stirred for 10 minutes. The crude substrate was concentrated *in vacuo*, dissolved in toluene (5 mL) and refluxed in a sealed tube for 10 further minutes. The crude product was concentrated *in vacuo* and purified by flash chromatography (hexane:EtOAc 3:1) to afford the oxindol in 80% (470 mg, 2.20 mmol) yield.

^{1}H-NMR (400 MHz, $CDCl_3$ δ): 1.33 (s, 3H), 1.48 (s, 1H), 2.66 (dd, *J* = 0.9, 4.9 Hz, 1H), 4.79 (dd, *J* = 0.9, 9.9 Hz, 1H), 4.92 (dd, *J* = 4.9, 9.9 Hz, 1H), 7.02 (ddd, *J* = 1.0, 7.6, 7.6 Hz, 1H), 7.16 (dd, *J* = 0.7, 7.6 Hz, 1H) 7.28 (m, 1H), 7.41 (d, *J* = 7.6 Hz, 1H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$ δ): 15.7, 23.1, 30.2, 37.4, 50.1, 77.6, 119.9, 121.2, 122.2, 127.7, 132.3, 133.1, 159.3, 186.8 ppm. **IR (neat sample)**: 2954, 1623, 1589, 1384, 956, 770 cm^{-1}. **HRMS** (ESI) (*m/z*): calcd for $C_{13}H_{15}N_1O_2$ $[M + H]^+$, 218.1181; found 218.1176.

6.3.20 *(1*R*,3*R*)-3-(((*tert*-butyldimethylsilyl)oxy)methyl)-2,2-dimethylspiro[cyclopropane-1,3'-indolin]-2'-one (228)*



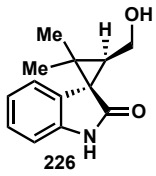
228

Before the reaction could be started, compound **229** had to be filtrated through silica gel. Compound **118** (265 mg, 1.02 mmol, 1 equiv.) and compound **229** (2.04 g, 10.2 mmol, 10 equiv.) were heated to 65 °C and rhodium(II) acetate (5.00 mg, 10.0 µmol, 1 mol%) was added. The reaction progress was monitored by TLC (hexane:EtOAc 5:1). Gas evolution could be observed. A small amount of toluene for a better miscibility of polar and nonpolar reactants was added. Afterwards the temperature was increased to 80 °C and another 1.5 eq of compound **118** were dissolved in toluene and added dropwise to the red reaction mixture to

prevent dimer formation. The solvent was evaporated and the red liquid was cooled to –5 °C with an Ice/NaCl-mixture for 10 minutes and dissolved in CH_2Cl_2 (6 mL). Subsequently trifluoroacetic acid (1 mL) was added dropwise to remove the *tert*-butyloxycarbonyl protecting group. The reaction mixture was neutralised with saturated aqueous bicarb solution (50 mL) and gas evolution could be observed. The aqueous phase was extracted three times with ethyl acetate. The combined organic phases were washed with brine and dried over magnesium sulfate. The solvent was evapotared *in vacuo*. The crude was dissolved in dichloromethane and silica gel was added. The solvent was evaporated *in vaco* and the product **228** was purified by flash chromatography with hexane:ethyl acetate 5:1 to receive as colorless to reddish oil in 76% (244 mg, 770 µmol) yield.

^{1}H-NMR (400 MHz, $CDCl_3$, δ): 0.00 – 0.02 (m, 6H), 0.84 (s, 9H), 1.40 (s, 3H), 1.56 (s, 3H), 2.25 (dd, *J* = 6.5, 8.0 Hz, 1H), 3.90 (dd, *J* = 8.3, 11.5 Hz, 1H), 4.03 (dd, *J* = 8.3, 11.5 Hz, 1H), 6.92, (d, *J* = 7.7 Hz, 1H), 6.96 (dd, *J* = 7.7, 7.7 Hz, 1H), 7.05 (d, *J* = 7.4 Hz, 1H), 7.18 (ddd, *J* = 0.7, 7.6, 7.5 Hz, 1H) 8.16 (s, 1H) ppm.**^{13}C-NMR** (100 MHz, $CDCl_3$, δ): –5.1, –5.0, 17.3, 18.3, 21.1, 25.9, 35.7, 39.9, 43.4, 58.2, 109.7, 121.2, 123.7, 126.3, 127.6, 141.5, 177.4 ppm. **IR (neat sample)**: 1700, 1621, 1469, 1237, 1105, 1025, 744, 697 cm^{-1}. **HRMS** (ESI) (*m/z*): calcd for $C_{20}H_{29}NO_2Si$ $[M + Na]^+$, 354.1865; found, 354.1866.

6.3.21 *(1*R*,3*R*)-3-(hydroxymethyl)-2,2-dimethylspiro[cyclopropane-1,3'-indolin]-2'-one (226)*



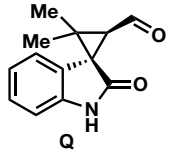
226

Compound **228** (224 mg, 773 µmol, 1 equiv.) was dissolved in THF (2.5 mL) and cooled to 0 °C with an ice:water-bath. After 10 minutes TBAF (3.10 mL, 3.09 mmol, 4 equiv.) was added drop by drop. The red solution was stirred for 3.5 h and the reaction progress was monitored by TLC (hexane:EtOAc 1:1). The reaction mixture was quenched with a saturated NH_4Cl solution (25 mL) and extracted with ethyl acetate. Subsequently the combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The red oil was purified by flash column chromatography (hexane:EtOAc 1:1). The yellowish white solid was washed with chloroform and methanol to receive the product **226** as a white solid with 90% (150 mg, 690 µmol) yield.

^{1}H-NMR (400 MHz, DMSO-d_6, δ): 1.29 (s, 3H), 1.43 (s, 3H), 1.94 (t, *J* = 7.2 Hz, 1H), 3.62 – 3.68 (m, 1H), 3.81 – 3.87 (m, 1H), 4.60 (dd, *J* = 5.4, 5.4 Hz, 1H), 6.85 – 6.91 (m, 2H), 7.12 – 7.15 (m,

2H), 10.41 (s, 1H) ppm.**^{13}C-NMR** (100 MHz, DMSO-d_6, δ): 16.7, 20.4, 33.7, 42.6, 55.6, 109.1, 120.3, 123.3, 125.9, 127.0, 142.5, 176.2 ppm. **IR (neat sample)**: 1700, 1621, 1469, 1237, 1105, 1025, 744, 697 cm^{-1}. **HRMS** (ESI) (*m/z*): calcd for $C_{13}H_{15}NO_2$ $[M + Na]^+$, 240.1000; found, 240.1000.

6.3.22 *(1*R*,3*R*)-2,2-dimethyl-2'-oxospiro[cyclopropane-1,3'-indoline]-3-carbaldehyde (Q)*

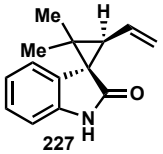


Q

IBX (56.6 mg, 202 µmol, 1.1 equiv.) was added to a solution of compound **226** (40.0 mg, 184 µmol, 1 equiv.) in DMSO (1.5 mL). The reaction mixture was stirred for 16h and the progress was monitored by TLC (hexane:EtOAc 1:1). After reaction was complete, it was quenched with water and extracted with EtOAc (4x 25 mL), the combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure at 40 °C bath temperature. Crude compound **G** was purified by flash column chromatography (hexane:EtOAc 3:1) yielding 17.3 mg (80.0 µmol, 43.5%) of compound **Q** as a yellow oil.

^{1}H-NMR (400 MHz, C_6D_6, δ): 1.21 (s, 3H), 1.42 (s, 3H), 2.73 (d, *J* = 4.0 Hz, 1H), 3.62 – 3.68 (m, 1H), 3.81 – 3.87 (m, 1H), 6.57 (d, *J* = 7.7 Hz, 1H), 6.80 (dd, *J* = 7.6, 7.6 Hz, 1H), 6.95 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.31 (d, *J* = 7.5 Hz, 1H), 8.93 (s, 1H), 9.43 (d, *J* = 4.0 Hz, 1H) ppm. **^{13}C-NMR** (100 MHz, C_6D_6, δ): 16.9, 20.5, 37.2, 45.1, 48.1, 110.2, 121.8, 125.7, 125.9, 127.5, 142.2, 175.8, 196.4 ppm. **IR (neat sample)**: 3265, 2926, 1696, 1619, 1468, 1342, 1222, 1106, 1008, 752, 737 cm^{-1}. **HRMS** (ESI) (*m/z*): calcd for $C_{13}H_{13}NO_2$ $[M + H]^+$, 216.1025; not found.

6.3.23 *(1*R*,3*R*)-2,2-dimethyl-3-vinylspiro[cyclopropane-1,3'-indolin]-2'-one (227)*



227

A suspension of Ph_3PMeBr (70.5 mg, 200 µmol, 5 equiv.) in THF (200 µL) was cooled to –78°C and NaHMDS (2M in THF, 280 µL, 200 µmol, 5 equiv.) was added slowly under inert gas conditions. The reaction mixture was stirred for 10 min at –78°C and for 45 min at 0 °C. The suspension was cooled to –78 °C again and a solution of compound **Q** (8.50 mg, 40.0 µmol, 1 equiv.) of in THF (200 µL) was added carefully and the reaction mixture was stirred for 10 min. After warming up to 0°C the reaction mixture is quenched with sat. aqueous NH_4Cl solution and diluted with water. The aqueous layer is extracted with EtOAc (3x 30 ml). The

combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure at 40 °C bath temperature. Crude compound **227** was purified by flash column chromatography (hexane:EtOAc 1:1) yielding 7 mg (32.0 µmol, 83%) of compound **227** as a light yellowish solid.

^{1}H-NMR (400 MHz, $CDCl_3$ δ): 1.47 (s, 3H), 1.57 (s, 3H), 2.46 (d, *J* = 9.6 Hz, 1H), 5.15 (dd, *J* = 1.7, 10.2 Hz, 1H), 5.22 (dd, *J* = 1.5, 17.2 Hz, 1H), 6.44 (dd, *J* = 9.6, 10.6 Hz, 1H), 6.48 (dd, *J* = 9.9, 9.9 Hz, 1H), 6.99 (ddd, *J* =1.0, 7.3, 7.3 Hz, 1H), 7.03 (dd, *J* = 1.7, 7.5 Hz, 1H), 7.17 (ddd, *J*=1.7, 7.3, 7.3 Hz, 1H), 7.74 (s, 1H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$, δ): 15.6, 23.4, 37.2, 47.9, 109.2, 117.4, 121.3, 121.9, 126.4, 129.6, 131.7, 141.0, 175.7 ppm. **IR (neat sample)**: 2923, 1695, 1620, 1469, 1375, 1339, 1224, 1105, 985, 813, 752, 740, 687 cm^{-1}. **HRMS** (ESI) (*m/z*): calcd for $C_{14}H_{15}NO$ $[M + H]^+$, 214.1232; found, 214.1228.

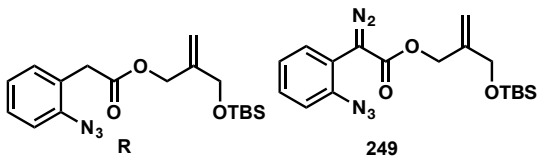
6.3.24 *(1*R*,3*R*)-2,2-dimethyl-3-vinylspiro[cyclopropane-1,3'-indolin]-2'-one (227)*

227 was prepared by general procedure, starting from **118** and using prenylene instead of isoprene. After cyclopropanation, the solvent was replaced by DMSO and the mixture was heated to 110 °C. The crude was purified chromatographically (hexane:EtOAc 1:1). 45% (45.1 mg, 220 µmol) yield.

Advice: The heating in DMSO should have induced the rearrangement, what did not appear. It is not necessary to perform.

Analytical data see: **6.3.23**

6.3.25 *2-(((tert-butyldimethylsilyl)oxy)methyl)allyl 2-(2-azidophenyl)acetate (R)*
2-(((tert-butyldimethylsilyl)oxy)methyl)allyl 2-(2-azidophenyl)-2-diazoacetate (249)



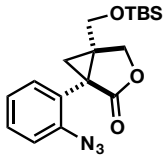
Azide **130** (3.50 g, 19.8 mmol, 1 equiv.), diol **243** (4.20 g, 20.7 mmol, 1.05 equiv.) and DMAP (506 mg, 4.15 mmol, 20 mol%) were dissolved in CH_2Cl_2 (30 mL). Then DIC (3.90 mL, 21.8 mmol, 1.1 equiv.) was slowly added to the solution. After complete consumption of the alcohol (TLC, hexane:EtOAc 4:1) the reactionmixture was filtered over Celite® and concentrated *in vacuo*. The crude material was then purified by flash column chromatography (hexane:EtOAc 25:1) to give the desired ester in 85% (5.44 g, 14.5 mmol) yield as yellow oil.

^{1}H-NMR (200 MHz, $CDCl_3$, δ): 0.06 (s, 6H), 0.90 (s, 9H), 3.64 (s, 2H), 4.12 (s, 2H), 4.63 (s, 2H), 5.09 (q, *J* = 1.3 Hz, 1H), 5.22 (q, *J* = 1.4 Hz, 1H), 7.06 – 7.38 (m, 4H) ppm. **HRMS** (ESI) (*m*/*z*): calcd for $C_{18}H_{27}N_3O_3Si$ $[M + H]^+$, 362.1900; found, 362.1898.

DBU (8.77 mL, 58.8 mmol, 3.5 equiv.) was added slowly to a solution of ester **R** (6.07 g, 16.8 mmol, 1 equiv.) and ABSA (68.1 g, 33.6 mmol, 2 equiv.) in acetonitrile (56 mL). The reaction mixture was stirred for 8 h. After complete consumption of the substrate (TLC, hexane:EtOAc 20:1; very low difference in r_f), the reaction was hydrolysed by addition of NH_4Cl solution. The aqueous layer was extracted with hexane (3x 100 mL), the combined organic layers were washed with brine solution, dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was then purified by flash chromatography (hexane:EtOAc 25:1) to afford the desired product **249** in 95% (6.12 g, 15.8 mmol) yield as bright orange oil.

^{1}H-NMR (400 MHz, $CDCl_3$, δ): 0.07 (s, 6H), 0.91 (s, 9H), 4.74 (s, 2H), 5.16 (m, 1H), 5.26 (m, 1H), 7.16 – 7.22 (m, 2H), 7.33 – 7.37 (m, 1H), 7.54 (dd, *J* = 1.5, 8.0 Hz, 1H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$, δ): 18.2, 25.9, 62.2, 116.8, 118.6, 118.8, 125.2, 129.1, 131.5, 137.3, 139.4, 166.0 ppm. **IR (neat sample)**: 2929, 2856, 2128, 2095, 1704, 1250, 1101, 836, 751 cm^{-1}. **HRMS** (ESI) (*m*/*z*): calcd for $C_{18}H_{25}N_5O_3Si$ $[M + Na]^+$, 410.1624; found, 410.1618.

6.3.26 *(1R,5S)-1-(2-azidophenyl)-5-(((tert-butyldimethylsilyl)oxy)methyl)-3-oxabicyclo [3.1.0] hexan 2-one (251)*



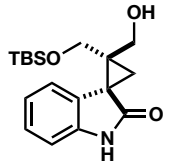
251

Diazoester **249** (6.16 g, 15.9 mmol, 1 equiv.) in degased CH_2Cl_2 (160 mL) was added to a suspension of $[(CuOTf)_2PhMe]$ (165 mg, 320 µmol, 3 mol%) in degased CH_2Cl_2 (160 mL) *via* a dropping funnel over 30 minutes. The reactionmixture was heated smoothly until a gas evolution could be observed. After the complete consumption of diazoester **249** (TLC, hexane:EtOAc 20:1) the crude was concentrated *in vacuo* and was purified by flash column chromatography (hexane:EtOAc 10:1 to 3:1) to give the desired product as white crystals in 84% (4.80 g, 13.4 mmol) yield.

^{1}H-NMR (400 MHz, $CDCl_3$, δ): –0.13 (s, 3H), -0.10 (s, 3H), 0.80 (s, 9H), 1.39 (d, *J* = 5.1 Hz, 1H), 1.72 (d, *J* = 5.1 Hz, 1H), 3.48 (d, *J* = 5.1 Hz, 1H), 3.64 (d, *J* = 5.1 Hz, 1H), 4.37 (d, *J* = 9.2 Hz, 1H),

4.54 (d, *J* = 9.2 Hz, 1H), 7.10 – 7.18 (m, 2H), 7.25 (d, *J* = 7.4 Hz, 1H), 7.25 (dd, *J* = 7.4, 7.4 Hz, 1H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$, δ): –5.7, –5.6, 18.2, 23.5, 25.8, 34.0, 36.3, 61.8, 70.5, 118.2, 123.9, 125.1, 130.0, 131.8, 141.4, 176.2 ppm. **IR (neat sample)**: 2928, 2855, 2125, 1766, 1289, 1054, 835, 767 cm^{-1}. **HRMS** (ESI) (*m/z*): calcd for $C_{18}H_{25}N_3O_3Si$ [M + Na]$^+$, 382.1563; found, 382.1566.

6.3.27 *2-(((tert-butyldimethylsilyl)oxy)methyl)-2-(hydroxymethyl)spiro[cyclopropane-1,3'-indolin]-2'-one (253)*

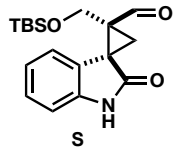


253

Azide **251** (4.80 g, 12.0 mmol, 1 equiv.) was dissolved in MeOH (40 mL) and Pd/C (10%, 1.23 g, 1.20 mmol, 10 mol%) was added to that solution. It was stirred under H_2 atmosphere (25 bar) for 20 minutes (TLC, hexane:EtOAc 3:1), then filtered over Celite® and concentrated *in vacuo*. The crude was dissolved in THF (120 mL), cooled to 0 °C and *i*PrMgCl (2M in THF, 12.6 mL, 25.2 mmol, 2.1 equiv.) was added slowly. After the complete consumption of the aniline derivative (TLC, hexane:EtOAc 3:1) the mixture was hydrolysed by addition of NH_4Cl solution. The aqueous layer was extracted with EtOAc (3x 100 mL), the combined organic layers were washed with brine solution, dried over $MgSO_4$ and concentrated *in vacuo*. The crude was purified by flash column chromatography (CH_2Cl_2:MeOH 40:1) to obtain the desired product in 93% (3.73 g, 11.2 mmol) yield as a white solid.

^{1}H-NMR (400 MHz, $CDCl_3$, δ): –0.09 (s, 3H), 0.02 (s, 3H), 0.77 (s, 9H), 1.70 (d, *J* = 5.1 Hz, 1H), 2.20 (d, *J* = 5.1 Hz, 1H), 3.49 (s, 1H), 3.92 (d, *J* = 10.9 Hz, 1H), 4.06 (d, *J* = 10.9 Hz, 1H), 4.08 – 4.25 (m, 2H), 6.92 (d, *J* = 7.9 Hz, 1H), 6.98 – 7.03 (m, 2H), 7.20 (ddd, *J* = 2.4, 6.5, 7.9 Hz, 1H), 7.73 (s, 1H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$, δ): –5.5, –5.4, 18.2, 24.7, 25.8, 35.7, 44.5, 62.5, 64.2, 109.7, 121.7, 121.9, 127.0, 128.8, 140.6, 178.1 ppm. **IR (neat sample)**: 3498, 3169, 3066, 2956, 2886, 1678, 1619, 1470, 1442, 1347, 1252, 1215, 1175, 1076, 1053, 1028, 1010, 962, 866, 747, 664, 629 cm^{-1}. **HRMS** (ESI) (*m/z*): calcd for $C_{18}H_{27}NO_3Si$ [M + Na]$^+$, 356.1658; found, 356.1659.

6.3.28 *2-(((tert-butyldimethylsilyl)oxy)methyl)-2'-oxospiro[cyclopropane-1,3'-indoline]-2-carbaldehyde (J)*

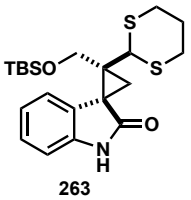


S

PDC (1.35 g, 3.60 mmol, 2 equiv.) was added to a suspension of alcohol **253** (600 mg, 1.80 mmol, 1 equiv.) and activated molecular sieves (3 Å, 100 mg/mmol$_{(PDC)}$) in CH_2Cl_2 (9 mL). The colour changed from reddish to black brown. After the complete consumption of the starting material (TLC, hexane:EtOAc 1:1) the mixture was concentrated *in vacuo* and purified by flash column chromatography (hexane:EtOAc 3:1 to 1:1) to give the aldehyde as a colourless solid in 82% (490 mg, 1.48 mmol) yield.

^{1}H-NMR (400 MHz, $CDCl_3$, δ): 0.06, (s, 3H), 0.09 (s, 3H), 0.88 (s, 9H), 2.33 (d, *J* = 5.5 Hz, 1H), 2.63 (d, *J* = 5.5 Hz, 1H), 3.79 (d, *J* = 11.9 Hz, 1H), 4.51 (d, *J* = 11.9 Hz, 1H), 6.91 (d, *J* = 7.5 Hz, 1H), 7.03 (ddd, *J* = 1.1, 7.5, 7.5 Hz, 1H), 7.17 (d, *J* = 7.5 Hz, 1H), 7.22 – 7.26 (m, 1H), 7.90 (s, 1H), 9.85 (s, 1H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$, δ): -5.3, -5.3, 18.8, 24.1, 26.0, 40.5, 48.3, 56.3, 110.0, 122.4, 122.9, 126.2, 128.8, 141.4, 175.7, 199.9 ppm. **IR (neat sample)**: 3217, 2954, 2929, 2886, 2856, 1703, 1621, 1471, 1347, 1254, 1219, 1108, 1007, 838, 778, 751, 644 cm^{-1}. **HRMS** (ESI) (*m*/*z*): calcd for $C_{18}H_{25}NO_3Si$ $[M + Na]^+$, 354.1501; found, 354.1500.

6.3.29 *2-(((tert-butyldimethylsilyl)oxy)methyl)-2-(1,3-dithian-2-yl)spiro[cyclopropane-1,3'-indolin]-2'-one (263)*



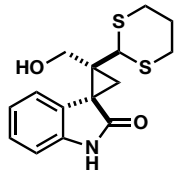
263

To a stirred mixture of aldehyde **S** (190 mg, 573 µmol, 1 equiv.) and 1,3-propanedithiol (69.0 µL, 688 µmol, 1.2 equiv.) in MeCN (2.9 mL) was added $Pr(OTf)_3$ (16.9 mg, 29.0 µmol, 0.05 equiv.). After stirring for 24 h (TLC, hexane:EtOAc 2:1) the mixture was diluted with EtOAc (30 mL) and washed with water (20 mL). The aqueous layer was washed with EtOAc (5 mL) and the combined organic layers were dried over $MgSO_4$. The crude was concentrated *in vacuo* and purified by flash column chromatography (hexane:EtOAc 5:1 to 3:1) to give the dithiane **263** in 75% (182 mg, 432 µmol) yield as pale yellow crystals.

^{1}H-NMR (400 MHz, $CDCl_3$, δ): 0.17 (s, 3H), 0.17 (s, 3H), 0.94 (s, 9H), 1.72 – 1.83 (m, 1H), 1.93 (d, *J* = 5.1 Hz, 1H), 2.04 – 2.09 (m, 1H), 2.17 (d, *J* = 5.1 Hz, 1H), 2.67 – 2.70 (m, 1H), 2.81 – 2.88

(m, 2H), 3.00 – 3.07 (m, 1H), 3.83 (d, *J* = 12.3 Hz, 1H), 4.35 (d, *J* = 12.3 Hz, 1H), 5.16 (s, 1H), 6.90 (d, *J* = 7.7 Hz, 1H), 6.98 (ddd, *J* = 1.0, 7.7, 7.7 Hz, 1H), 7.19 (ddd, *J* = 1.0, 7.7, 7.7 Hz, 1H), 7.30 (d, *J* = 7.7 Hz, 1H), 7.48 (s, 1H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$, δ): –5.1, –4.9, 18.4, 26.0, 26.1, 26.5, 31.2, 31.6, 37.9, 45.1, 50.3, 59.4, 109.5, 121.8, 123.0, 127.0, 128.3, 140.6, 176.5 ppm. **IR (neat sample)**: 3186, 2928, 2898, 2854, 1691, 1622, 1470, 1422, 1252, 1230, 1100, 835, 777, 747, 647 cm^{-1}. **HRMS** (ESI) (*m/z*): calcd for $C_{21}H_{31}NO_3S_2Si$ $[M + Na]^+$, 444.1463; found, 444.1464.

6.3.30 *2-(1,3-dithian-2-yl)-2-(hydroxymethyl)spiro[cyclopropane-1,3'-indolin]-2'-one (T)*

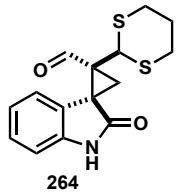


T

To a 0 °C cold solution of HF (70% in pyridine, 2.57 mL, 102 mmol, 120 equiv.) in pyridine (2.57 mL) and THF (2.5 mL) was added a solution of TBS-Ether **263** (360 mg, 855 µmol, 1 equiv.) in THF (3 mL). The mixture was stirred at 0 °C for 15 minutes before the ice bath was removed. After the complete consumption of the starting material (TLC, hexane:EtOAc 3:1) the mixture was pured onto saturated $NaHCO_3$ solution, the aqueous layer was extracted with EtOAc (3x 25 mL), the combined organic layers were successifely washed with saturated $CaCl_2$ solution, HCl solution (1 M, 2x 50 mL) and water before they were dried over $MgSO_4$ and concentrated *in vacuo.* The crude was used without further purification. The NMR sample was purified by flash column chromatography (CH_2Cl_2:MeOH 30:1).

^{1}H-NMR (400 MHz, CD_3OD, δ): 1.67 − 1.77 (m, 1H), 1.82 (d, *J* = 5.1 Hz, 1H), 2.05 – 2.12 (m, 1H), 2.09 (d, *J* = 5.0 Hz, 1H), 2.66 – 2.70 (m, 1H), 2.79 – 2.89 (m, 2H), 3.00 (ddd, J = 2.4, 12.6, 14.0 Hz, 1H), 3.74 (d, *J* = 12.6 Hz, 1H), 4.28 (d, *J* = 12.7 Hz, 1H), 5.16 (s, 1H), 6.95 (d, *J* = 7.9 Hz, 1H), 6.98 (ddd, *J* = 1.0, 7.4, 7.4 Hz, 1H), 7.19 (ddd, *J* = 1.3, 7.8, 7.8 Hz, 1H), 7.24 (d, *J* = 7.5 Hz, 1H) ppm. **^{13}C-NMR** (100 MHz, CD_3OD, δ): 26.7, 27.2, 32.0, 32.2, 39.1, 45.5, 51.1, 59.5, 110.8, 112.6, 123.6, 128.1, 129.2, 143.0, 178.9 ppm. **IR (neat sample)**: 3235, 2934, 2898, 1695, 1621, 1470, 1343, 1275, 1207, 1029, 1207, 909, 753, 733, 649 cm^{-1}. **HRMS** (ESI) (*m/z*): calcd for $C_{15}H_{17}NO_2S_2$, $[M]^+$, 330.0598; found, 330.0597.

6.3.31 *2-(1,3-dithian-2-yl)-2'-oxospiro[cyclopropane-1,3'-indoline]-2-carbaldehyde (264)*

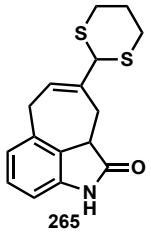


264

SO_3•Py (32.0 mg, 200 µmol, 4 equiv.) was dissolved in a 0 °C cold solution of CH_2Cl_2:DMSO (500 µL, 1:1). Alcohol **T** (15.4 mg, 50.0 µmol, 1 equiv.) was added in one portion to the cold solution followed by NEt_3 (32.0 µL, 250 µmol, 5 equiv.). The mixture was stirred for 1.5 h at 0 °C before it was quenched by addition of water, diluted with EtOAc and poured onto HCl solution (0.2 M, 10 mL). The phases were separated and the aqueous layer was extracted with EtOAc (2x 15 mL). The combined organic layers were dried over $MgSO_4$, concentrated *in vacuo* and the crude was purified by flash column chromatography (hexane:EtOAc 1:1) to give aldehyde **264** as a white solid in 86% (13.2 mg, 43.3 µmol) yield.

^{1}H-NMR (400 MHz, $CDCl_3$, δ): 1.75 – 1.85 (m, 1H), 2.09 – 2.14 (m, 1H), 2.14 (d, *J* = 5.1 Hz, 1H), 2.58 (d, *J* = 5.1 Hz, 1H), 2.80 (d, *J* = 14.0 Hz, 1H), 2.85 – 2.94 (m, 2H), 3.02 − 3.06 (m, 1H), 5.24 (s, 1H), 6.89 (d, *J* = 7.7 Hz, 1H), 6.96 (ddd, *J* = 1.0, 7.7, 7.7 Hz, 1H), 7.05 (d, *J* = 7.5 Hz, 1H), 7.21 (ddd, *J* = 1.0, 7.7, 7.7 Hz, 1H), 7.72 (s, 1H), 9.83 (s, 1H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$, δ): 24.3, 25.2, 32.3, 31.3, 39.7, 44.7, 49.5, 109.7, 122.4, 124.0, 125.1, 128.2, 140.8, 174.4, 195.1 ppm. **IR (neat sample)**: 3274, 2902, 1698, 1616, 1469, 1336, 1274, 1109, 1028, 1015, 752 cm^{-1}. **HRMS** premier (ESI) (*m*/*z*): calcd for $C_{15}H_{15}NO_2S_2$, $[M + Na]^+$, 328.0442; found, 328.0450.

6.3.32 *8-(1,3-dithian-2-yl)-2,6,9,9a-tetrahydro-1H-cyclohepta[cd]indol-1-one (265)*



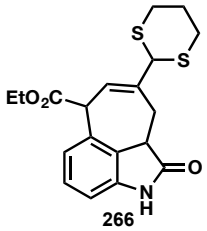
265

NaHMDS (2 M in THF, 43.4 µL, 86.8 µmol, 2.5 equiv.) was added to a –78 °C cold suspension of Methyltriphenylphosphonium bromide (29.4 mg, 86.8 µmol, 2.5 equiv.) in THF (100 µL). The mixture was allowed to stir at –78 °C for 10 minutes before the temperature was raised to 0 °C and the mixture was stirred for further 60 minutes (colour change from pale yellow to bright yellow). The ylide was cooled to –78 °C and aldehyde **264** (10 mg, 32.7 µmol, 1 equiv.) in THF (200 µL) was added. The reaction was stirred at –78 °C for 5 minutes before the temperature was again raised to 0 °C. After the complete consumption of the aldehyde (TLC, hexane:EtOAc

1:1) the reaction was quenched by the addition of NH_4Cl solution, the aqueous layer was extracted with Et_2O (3x 10 mL) and the combined organic layers were dried over $MgSO_4$. The crude was concentrated *in vacuo*, dissolved in $CDCl_3$ (700 µL) and heated to 50 °C (reaction progress by NMR). After the reaction was complete the crude was concentrated *in vacuo* and purified by preparative TLC (hexane:EtOAc 2:1) to obtain the rearranged product in 71% (7.00 mg, 23.1 µmol) yield.

^{1}H-NMR (400 MHz, $CDCl_3$, δ): 1.77 – 1.89 (m, 1H), 2.07 − 2.15 (m, 1H), 2.35 – 2.45 (m 1H), 2.82 − 3.09 (m, 5H), 3.38 (ddd, *J* = 1.6, 7.0, 20.3 Hz, 1H), 3.72 (dd, *J* = 4.2, 12.5 Hz, 1H), 3.84 (dd, *J* = 2.1, 20.3 Hz, 1H), 4.49 (s, 1H), 6.00 − 6.05 (m, 1H), 6.72 (d, *J* = 7.7 Hz, 1H), 6.77 (d, *J* = 7.7 Hz, 1H), 7.12 (dd, *J* = 7.7, 7.7 Hz, 1H), 7.43 (s, 1H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$, δ): 25.5, 31.9, 32.0, 33.5, 44.2, 56.4, 107.3, 122.5, 126.0, 128.1, 129.2, 136.3, 136.4, 140.0, 178.5 ppm. **IR (neat sample)**: 3210, 2922, 2852, 1704, 1619, 1462, 1421, 1316, 1277, 1249, 1083, 1015, 909, 774, 735, 628 cm^{-1}. **HRMS** (ESI) (*m*/*z*): calcd for $C_{16}H_{17}NOS_2$ $[M + Na]^+$, 326.0649; found, 326.0652.

6.3.33 *Ethyl 8-(1,3-dithian-2-yl)-1-oxo-2,6,9,9a-tetrahydro-1H-cyclohepta[cd]indole-6-carboxylate (266)*

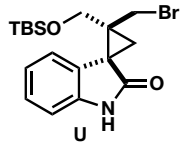


266

TMS-Ethylacetate (20.3 µL, 111 µmol, 2.6 equiv.) was added to a solution of LiHMDS (1 M in THF, 106 µL, 106 µmol, 2.5 equiv.) in THF (200 µL) at –78 °C. After stirring for 30 minutes at –78 °C a solution of aldehyde **264** (13.0 mg, 42.6 µL, 1 equiv.) in THF (400 µL) was added. After complete consumption of the starting material (2 h) (TLC, hexane:EtOAc 2:1) the reaction was quenched by addition of NH_4Cl solution. The aqueous layer was extracted with EtOAc (3x 20 mL), the combined organic layers were dried over $MgSO_4$ and the solvent was removed *in vacuo*. The crude was dissolved in benzene-d_6 (600 µL) and heated to 40 °C for 20 h. The reaction progress was observed by NMR and TLC (hexane:EtOAc 1:1). After the complete consumption of the olefin the crude was purified by preparative TLC (hexane:EtOAc 2:1) to obtain the rearrangement product **266** in 75% (12.0 mg, 32.0 µmol) yield in an inseparable diasteromeric mixture of 10:1.

^{1}H-NMR (400 MHz, $CDCl_3$, δ): 1.23 (t, *J* = 7.2 Hz, 3H), 1.83 – 1.90 (m, 1H), 2.07 – 2.15 (m, 1H), 2.34 – 2.42 (m, 1H), 2.83 – 2.98 (m, 4H), 3.07 (dd, *J* = 4.6, 17.2 Hz, 1H), 4.05 (dd, *J* = 4.6, 12.7 Hz, 1H), 4.12 (q, *J* = 7.2 Hz, 2H), 4.39 (dd, *J* = 1.3, 7.3 Hz, 1H), 4.48 (s, 1H), 6.12 (dd, *J* = 2.8, 7.2 Hz, 1H), 6.79 (d, *J* = 7.7 Hz, 1H), 6.83 (d, *J* = 7.7 Hz, 1H), 7.15 (dd, *J* = 7.7, 7.7 Hz, 1H), 7.60 (s, 1H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$, δ): 1.2, 14.3, 25.5, 31.6, 32.0, 43.5, 51.4, 56.3, 61.8, 108.8, 123.2, 124.0, 128.3, 129.9, 133.9, 139.3, 140.5, 170.9, 178.5 ppm. **IR (neat sample)**: 2929, 2856, 2122, 1736, 1585, 1491, 1454, 1288, 1252, 1154, 1104, 1063, 1006, 834, 775, 749, 667 cm^{-1}. **HRMS** (ESI) (*m/z*): calcd for $C_{19}H_{21}NO_3S_2$ $[M + H]^+$, 376.1041; found, 376.1031.

6.3.34 *2-(bromomethyl)-2-(((tert-butyldimethylsilyl)oxy)methyl)spiro[cyclopropane-1,3'-indolin]-2'-one (U)*

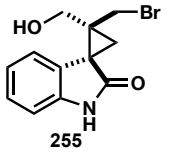


U

A solution of alcohol **253** (590 mg, 1.77 mmol, 1 equiv.) and carbon tetrabromide (645 mg, 1.95 mmol, 1.1 equiv.) in CH_2Cl_2 (9 mL) was cooled to 0 °C. Powdered triphenyl phosphine (510 mg, 1.95 mmol, 1.1 equiv.) was added in portions over 5 minutes with vigorous stirring. The mixture was stirred at 0 °C until the complete consumption of the alcohol (TLC, hexane:EtOAc 1:1, 20 minutes). The crude was concentrated *in vacuo* and purified by flash column chromatography (hexane:EtOAc 7:1) to give bromide **U** in 79% (552 mg, 1.39 mmol) yield as a white solid.

^{1}H-NMR (400 MHz, $CDCl_3$, δ): 0.01 (s, 3H), 0.08 (s, 3H), 0.83 (s, 9H), 1.91 (d, *J* = 5.4 Hz, 1H), 2.01 (d, *J* = 5.5 Hz, 1H), 3.93 (d, *J* = 11.0 Hz, 1H), 4.05 (d, *J* = 11.0 Hz, 1H), 4.07 (d, *J* = 10.2 Hz, 1H), 4.30 (d, *J* = 10.2 Hz, 1H), 6.93 (d, *J* = 7.8 Hz, 1H), 6.99 (ddd, *J* = 1.0, 7.5, 7.9 Hz, 1H), 7.05 (d, *J* = 7.5 Hz, 1H), 7.21 (ddd, *J* = 1.4, 7.5, 7.5 Hz, 1H), 8.02 (s, 1H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$, δ): –5.3, 18.3, 25.9, 28.4, 33.8, 38.2, 42.3, 61.8, 109.9, 121.8, 122.2, 127.4, 127.8, 141.1, 176.5 ppm. **IR (neat sample)**: 3218, 2951, 2927, 2882, 2855, 1702, 1667, 1625, 1469, 1345, 1252, 1229, 1095, 896, 834, 773, 731, 653 cm^{-1}. **HRMS** (ESI) (*m/z*): calcd for $C_{18}H_{26}NO_2SiBr$ $[M + Na]^+$, 418.0814; found, 418.0796.

6.3.35 *2-(bromomethyl)-2-(hydroxymethyl)spiro[cyclopropane-1,3'-indolin]-2'-one (255)*



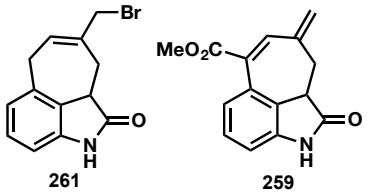
255

A solution of TBS-ether **L** (498 mg, 1.26 mmol, 1 equiv.) in THF (8 mL) was added to a 0 °C cold solution of hydrogenfluoride (70% in pyridine, 3.80 mL, 151 mmol, 120 equiv.) in pyridine (5 mL) and THF (4 mL). The mixture was stirred at 0 °C for 1 h before the ice bath was removed. The mixture was stirred at room temperature until the complete consumption of the starting material (TLC, hexane/EtOAc 3:1). The crude was poured onto saturated $NaHCO_3$ solution, the aqueous layer was extracted with EtOAc (3x 75 mL), the combined organic layers were successively washed with saturated $CaCl_2$ solution, HCl (1 M, 2x 100 mL) and water before they were dried over $MgSO_4$ and concentrated *in vacuo* to give the free alcohol as white crystals in 98% (346 mg, 1.23 mmol) yield. The substrate was used without further purification.

^{1}H-NMR (400 MHz, CD_3OD, δ): 1.89 (d, *J* = 5.1 Hz, 1H), 1.99 (d, *J* = 5.2 Hz, 1H), 3.92 (3.92, *J* = 12.1 Hz, 1H), 4.01 (d, *J* = 12.1 Hz, 1H), 4.13 (d, *J* = 10.1 Hz, 1H), 4.33 (d, *J* = 10.3 Hz, 1H), 6.95 (d, *J* = 7.7 Hz, 1H), 6.99 (ddd, *J* = 1.0, 7.6, 7.6 Hz, 1H), 7.16 (d, *J* = 7.7 Hz, 1H), 7.21 (ddd, *J* = 1.3, 7.7, 7.7 Hz, 1H) ppm. **^{13}C-NMR** (100 MHz, CD_3OD, δ): 28.9, 34.0, 39.3, 42.6, 61.5, 111.0, 122.6, 123.3, 128.4, 143.4, 144.9, 178.5 ppm. **IR (neat sample)**: 3499, 3169, 3066, 2962, 2886, 1679, 1619, 1470, 1443, 1348, 1303, 1275, 1214, 1175, 1053, 1012, 963, 748, 664, 629 cm^{-1}. **HRMS** (ESI) (*m/z*): calcd for $C_{12}H_{12}NO_2Br$ $[M + Na]^+$, 303.9949; found, 303.9935.

6.3.36 *8-(bromomethyl)-2,6,9,9a-tetrahydro-1H-cyclohepta[cd]indol-1-one (261)*

6.3.37 *methyl 8-methylene-1-oxo-2,8,9,9a-tetrahydro-1H-cyclohepta[cd]indole-6-carboxylate (259)*



261 259

IBX (84.6 mg, 302 µmol, 1.2 equiv.) was added to a solution of alcohol **255** (71.0 mg, 252 µmol, 1 equiv.) in DMSO (840 µL). After the complete consumption of the starting material (TLC, hexane:EtOAc 1:1) water was added to the reaction. The aqueous layer was extracted with Et_2O (3x 10 mL) and the combined organic layers were dried over $MgSO_4$. The solvent was removed *in vacuo* and the product was used without further purification

Methyltriphenylphosphonium bromide (102 mg, 286 µmol, 4 equiv.) in THF (250 µL) was cooled to –78 °C before NaHMDS (2 M in THF, 143 µL, 286 µmol, 4 equiv.) was added. The suspension was stirred for 10 minutes at –78 °C before the temperature was raised to 0 °C. During this time the colour of the suspension changed from pale yellow to bright yellow and the majority of the Wittig reagent dissolved. After stirring for 30 minutes at 0 °C the temperature was lowered to –78 °C and aldehyde **V** (20.0 mg, 71.4 µmol, 1 equiv.) in THF (500 µL) was added. The mixture was stirred for 10 minutes before the temperature was raised again to 0 °C. After the complete consumption of aldehyde **V** (TLC, hexane:EtOAc 3:1) the reaction was hydrolysed by addition of NH_4Cl solution, the aqueous layer was extracted with Et_2O (3x 10 mL), the combined organic layers were dried over $MgSO_4$ and the crude was concentrated *in vacuo* (T≤ 20 °C). The crude was filtered over a short column (pentane:Et_2O 1:1), concentrated *in vacuo*, dissolved in benzene-d_6 (700 µL) and heated to 40 °C for 8 h. The reaction progress was observed by NMR. After the rearrangement was complete, the crude was purified by flash column chromatography (hexane:EtOAc 1:1) to give the desired product in 76% (15.0 mg, 54.0 µmol) yield.

Compound 261

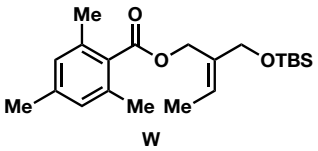
^{1}H-NMR (400 MHz, $CDCl_3$, δ): 2.33 – 2.41 (m, 1H), 2.98 (ddd, *J* = 2.5, 4.3, 16.7 Hz, 1H), 3.35 (dd, *J* = 6.9, 20.3 Hz, 1H), 3.73 (dd, *J* = 4.5, 12.7 Hz, 1H), 3.81 (d, *J* = 20.1 Hz, 1H), 3.95 (d, *J* = 9.6 Hz, 1H), 4.05 (d, *J* = 9.5 Hz, 1H), 5.98 – 6.01 (m, 1H), 6.77 (d, *J* = 7.5 Hz, 1H), 7.78 (d, *J* = 7.5 Hz, 1H), 7.13 (dd, *J* = 7.5, 7.5 Hz, 1H), 8.00 (s, 1H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$, δ): 30.9, 33.6, 42.6, 43.8, 107.7, 122.4, 127.1, 128.2, 129.2, 134.7, 135.9, 140.3, 179.0 ppm. **IR (neat sample)**: 3160, 2964, 1695, 1615, 1461, 1289, 1260, 1207, 780, 632 cm^{-1}. **HRMS** (ESI) (*m*/*z*): calcd for $C_{13}H_{12}ClNO$ $[M + H]^+$, 234.0686; found, 234.0681.

Compound 259

A suspension of aldehyde **V** (4.60 mg, 16.4 µmol, 1 equiv.) and Methyl (triphenyl-phosphoranylidene)acetate (6.60 mg, 19.7 µmol, 1.2 equiv.) in benzene (160 µL) was warmed to 50 °C. After the complete consumption of the starting material (TLC, hexane:EtOAc 1:1) the temperature was raised to 60 °C. The mixture was stirred at that temperature until the rearrangement was complete (TLC, hexane:EtOAc 1:1). The crude was purified by preparative TLC (hexane:EtOAc, 1:1) to give the desired rearrangement product in 93% (3.90 mg, 15.3 µmol) yield.

^{1}H-NMR (400 MHz, $CDCl_3$, δ): 2.46 (dd, *J* = 13.0, 14.7 Hz, 1H), 3.21 (d, *J* = 14.7 Hz, 1H), 3.44 (dd, *J* = 2.4, 12.6 Hz, 1H), 3.88 (s, 3H), 5.52 (d, *J* = 14.4 Hz, 1H), 6.85 (d, *J* = 7.4 Hz, 1H), 7.18 (dd, *J* = 1.1, 8.2 Hz, 1H), 7.23 (d, *J* = 8.2 Hz, 1H), 7.24 − 7.26 (m, 1H) 7.96 (s, 1H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$, δ): 44.8, 52.6, 10.4, 123.6, 127.6, 128.0, 128.9, 129.5, 130.3, 139.9, 140.0, 142.8, 169.3, 178.3 ppm. **IR (neat sample)**: 3185, 1711, 1615, 1437, 1330, 1245, 1217, 1084, 984, 923, 793, 747, 628 cm^{-1}. **HRMS** (ESI) (*m/z*): calcd for $C_{15}H_{13}NO_3$ $[M + H]^+$, 256.0974; found, 256.0975.

6.3.38 *(E)-2-(((tert-butyldimethylsilyl)oxy)methyl)but-2-en-1-yl 2,4,6-trimethylbenzoate (W)*



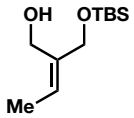
W

Ester **247** (12.8 g, 46.1 mmol, 1 equiv.) was dissolved in CH_2Cl_2 (230 mL) and cooled to −78 °C. DiBAl-H (1 M in hexane, 102 mL, 102 mmol, 2.2 equiv.) was added *via* dropping funnel. After complete addition, the mixture was allowed to stir for 3 h at –78 °C before it was quenched by saturated Rochelle-salt solution. The mixture was stirred over night; the phases were separated and the aqueous phase was extracted with EtOAc (3x 100 mL). The combined organic phases were washed with brine solution, dried over $MgSO_4$ before they were concentrated *in vacuo*.

The crude was dissolved with imidazole (7.11 g, 105 mmol, 2.4 equiv.) in DMF (35 mL) and cooled to 0 °C. TBSCl (7.87 g, 52.2 mmol, 1.2 equiv.) in DMF (9 mL) was added slowly. After complete consumption of the starting material (TLC, hexane:EtOAc 4:1) the mixture was quenched by addition of NH_4Cl solution. The product was extracted with hexane:Et_2O (10:1, 3x 100 mL), the combined organic phases were washed with water, then brine solution, before they were dried over $MgSO_4$, filtered off and concentrated *in vacuo*. The crude was purified by flash column chromatography (hexane:EtOAc 15:1 to 10:1) to obtain the TBS-ether **W** in 85% (14.2 g, 39.2 mmol) yield as colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$, δ): 0.05 (s, 6H), 0.90 (s, 9H), 1.78 (ddd, *J* = 1.4, 1.4, 7.0 Hz, 3H), 2.28 (s, 9H), 4.17 (dd, *J* = 1.4, 1.4 Hz, 2H), 4.87 (s, 2H), 5.82 (q, *J* = 7.1 Hz, 1H), 6.84 (s, 2H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$, δ): -5.2, 13.4, 18.5, 19.9, 21.3, 26.1, 59.9, 65.7, 126.6, 128.5, 131.2, 134.1, 135.2, 139.3, 170.4 ppm. **IR (neat sample)**: 2954, 2929, 2856, 1726, 1463, 1382, 1253, 1167, 834, 773, 667 cm^{-1}. **HRMS** (ESI) (*m/z*): calcd for $C_{21}H_{34}O_3Si$ $[M + Na]^+$, 385.2975; found, 385.2172.

6.3.39 *(E)-2-(((tert-butyldimethylsilyl)oxy)methyl)but-2-en-1-ol (248)*

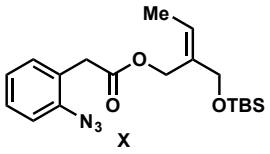


248

To a 0 °C cold solution of ester **W** (6.00 g, 16.5 mmol, 1 equiv.) in Et_2O (83 mL) was slowly added Methyllithium (1.6 M in Et_2O, 82.7 mL, 49.6 mmol, 3 equiv.). The reaction was stirred at 0 °C for 2 h until complete consumption of the starting material (TLC, hexane:EtOAc 5:1). The crude was quenched by carefully addition of NH_4Cl solution (200 mL) before it was diluted with water (300 mL). The aqueous layer was extracted with Et_2O (3x 100 mL), the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude was purified by flash column chromatography (hexane:EtOAc 15:1 to 5:1) to get the monoprotected diol **248** in 93% (3.32 g, 15.3 mmol) yield as colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$, δ): 0.08 (s, 6H), 0.90 (s, 9H), 1.69 (d, *J* = 7.0 Hz, 3H), 2.43 (br, 1H), 4.21 (s, 2H), 4.24 (s, 2H), 5.57 (q, *J* = 6.9 Hz, 1H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$, δ): -5.3, 13.1, 18.4, 26.0, 59.8, 68.4, 124.1, 137.7 ppm. **IR (neat sample)**: 3338, 2929, 2857, 1486, 1253, 1101, 1059, 1004, 834, 775, 669 cm^{-1}. **HRMS** (ESI) (*m/z*): calcd for $C_{11}H_{24}O_2Si$ $[M + Na]^+$, 239.1443; found, 239.1438.

6.3.40 *(E)-2-(((tert-butyldimethylsilyl)oxy)methyl)but-2-en-1-yl 2-(2-azidophenyl)-acetate (X)*



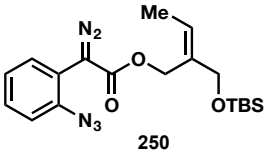
X

Azide **130** (2.85 g, 16.1 mmol, 1.05 equiv.), diol **248** (3.32 g, 15.3 mmol, 1 equiv.) and DMAP (370 mg, 3.07 mmol, 0.2 equiv.) were dissolved in CH_2Cl_2 (31 mL). Then DIC (2.99 mL, 16.9 mmol, 1.1 equiv.) was slowly added to the solution. After complete consumption of the alcohol (TLC, hexane:EtOAc 4:1) the reactionmixture was filtered over Celite® and concentrated *in vacuo*. The crude material was then purified by flash column chromatography (hexane:EtOAc 25:1) to give the desired ester in 94% (5.44 g, 14.5 mmol) yield as pale yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$, δ): 0.05 (s, 6H), 0.90 (s, 9H), 1.71 (d, *J* = 6.9 Hz, 3H), 3.6 (s, 2H), 4.08 (s, 2H), 4.69 (s, 2H), 5.76 (q, *J* = 6.9 Hz, 1H), 7.10 (ddd, *J* = 1.2, 7.5, 7.5 Hz, 1H), 7.16 (d, *J* = 7.5 Hz, 1H), 7.22 (dd, *J* = 1.2, 7.7 Hz, 1H), 7.32 (ddd, *J* = 1.2, 7.7, 7.7 Hz, 1H) ppm. **^{13}C-NMR** (100 MHz,

$CDCl_3$, δ): –5.3, 13.2, 18.5, 26.1, 36.7, 60.2, 65.3, 118.3, 124.9, 125.9, 126.1, 128.9, 131.6, 134.0, 138.8, 171.1 ppm. **IR (neat sample)**: 2953, 2929, 2856, 2121, 1736, 1491, 1453, 1288, 1453, 1288, 1251, 1153, 1104, 1064, 834, 775, 749, 667 cm^{-1}. **HRMS** (ESI) (*m*/*z*): calcd for $C_{19}H_{29}N_3O_3Si$ $[M + Na]^+$, 398.1876 ; found, 398.1880.

6.3.41 *(E)-2-(((tert-butyldimethylsilyl)oxy)methyl)but-2-en-1-yl 2-(2-azidophenyl)-2-diazo-acetate (250)*

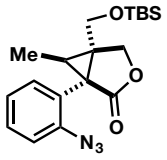


250

DBU (7.23 mL, 48.4 mmol, 3.5 equiv.) was added slowly to a solution of ester **X** (5.00 g, 13.8 mmol, 1 equiv.) and ABSA (6.65 g, 27.7 mmol, 2 equiv.) in acetonitrile (46 mL). The reaction mixture was stirred for 8 h. After complete consumption of the substrate (TLC, hexane:EtOAc 20:1; very low difference in r_f), the reaction was hydrolysed by addition of NH_4Cl solution. The aqueous layer was extracted with hexane (3 x 100 mL), the combined organic layers were washed with brine solution, dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was then purified by flash chromatography (hexane:EtOAc 25:1) to afford the desired product **250** in 91% (5.05 g, 12.6 mmol) yield as bright orange oil.

^{1}H-NMR (400 MHz, $CDCl_3$, δ): 0.07 (s, 6H), 0.91 (s, 9H), 1.76 (d, *J* = 6.9 Hz, 3H), 4.14 (s, 2H), 4.83 (s, 2H), 5.79 (q, *J* = 6.9 Hz, 1H), 7.16 − 7.21 (m, 2H), 7.34 (ddd, *J* = 1.4, 7.3, 8.2 Hz, 1H), 7.54 (dd, *J* = 1.4, 8.2 Hz, 1H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$, δ): –5.3, 13.3, 18.5, 26.1, 60.3, 65.4, 116.7, 118.6, 125.3, 126.3, 129.1, 129.2, 131.5, 134.0, 137.3, 165.7 ppm. **IR (neat sample)**: 2953, 2929, 2856, 2126, 2092, 1739, 1702, 1493, 1369, 1349, 1281, 1240, 1151, 1101, 1009, 835, 776, 751, 684 cm^{-1}. **HRMS** (ESI) (*m*/*z*): calcd for $C_{19}H_{27}N_5O_3Si$ $[M + Na]^+$, 424.1781; found, 424.1774.

6.3.42 *(1R,5S,6S)-1-(2-azidophenyl)-5-(((tert-butyldimethylsilyl)oxy)methyl)-6-methyl-3-oxabicyclo[3.1.0]hexan-2-one (252)*



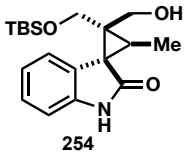
252

A solution of diazoester **250** (4.00 g, 9.96 mmol, 1 equiv.) in degased CH_2Cl_2 (100 mL) was added to a suspension of the $[(CuOTf)_2PhMe]$ (155 mg, 300 µmol, 3 mol%) in degased CH_2Cl_2

(100 mL) *via* a dropping funnel. After the complete consumption of the starting material (TLC, hexane:EtOAc 20:1) the crude was concentrated under reduced pressure and was purified by flash column chromatography (hexane:EtOAc 10:1 to 3:1) to give the desired product as white crystals in 74% (2.74 g, 7.34 mmol) yield.

^{1}H-NMR (400 MHz, $CDCl_3$, δ): -0.12 (s, 3H), -0.09 (s, 3H), 0.80 (s, 9H), 1.31 (d, *J* = 6.5 Hz, 3H), 1.92 (br, 1H), 3.42 (br, 1H), 3.61 (br, 1H), 4.29 (d, *J* = 9.6 Hz, 1H), 4.60 (d, *J* = 9.6 Hz, 1H), 7.12 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.16 (d, *J* = 7.8 Hz), 7.28 (d, *J* = 7.5 Hz, 1H), 7.37 (ddd, *J* = 1.6, 7.8, 7.8 Hz, 1H) ppm. **^{13}C-NMR** (100 MHz, C_6D_6, δ): −5.7, 8.0,18.2, 23.6, 25.8, 39.2, 40.2, 62.8, 66.6, 118.3, 124.8, 126.0, 129.7, 132.0, 141.1, 173.4 ppm. **IR (neat sample)**: 2954, 2931, 2897, 2857, 2124, 2093, 1494, 1453, 1290, 1256, 1290, 1256, 1081, 1026, 838, 778, 754 cm^{-1}. **HRMS** (ESI) (*m*/*z*): calcd for $C_{19}H_{27}N_3O_3Si$ $[M + Na]^+$, 396.1719; found, 396.1721.

6.3.43 *(1S,2R,3R)-2-(((tert-butyldimethylsilyl)oxy)methyl)-2-(hydroxymethyl)-3-methylspiro [cyclopropane-1,3'-indolin]-2'-one (254)*



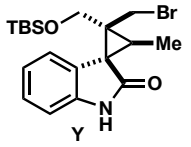
254

Azide **250** (2.74 g, 7.34 mmol, 1 equiv.) was dissolved in MeOH (37 mL) and Pd/C (10%, 0.1 equiv.) was added to that solution. It was stirred under H_2 atmosphere (25 bar) for 20 minutes (TLC, hexane:EtOAc 3:1), then filtered over Celite® and concentrated *in vacuo*. The crude was dissolved in THF (73 mL), cooled to 0 °C and *i*PrMgCl (7.70 mL, 15.4 mmol, 2.1 equiv.) was added slowly. After the complete consumption of the aniline derivative (TLC, hexane:EtOAc 3:1) the mixture was hydrolysed by addition of NH_4Cl solution. The aqueous layer was extracted with EtOAc (3x100 mL), the combined organic layers were washed with brine solution, dried over $MgSO_4$ and concentrated *in vacuo*. The crude was purified by flash column chromatography (CH_2Cl_2:MeOH 40:1) to obtain the desired product in 87% (2.22 g, 6.40 mmol) yield as a white solid.

^{1}H-NMR (400 MHz, $CDCl_3$, δ): –0.06 (s, 3H), 0.05 (s, 3H), 0.80 (s, 9H), 1.50 (d, *J* = 6.4 Hz, 3H), 2.10 (q, *J* = 6.5 Hz, 1H), 2.75 (s, 1H), 3.99 (d, *J* = 10.8 Hz, 1H), 4.10 (d, *J* = 10.8 Hz, 1H), 4.34 (d, *J* = 11.8 Hz, 1H), 4.46 (d, *J* = 11.7 Hz, 1H) 6.90 (d, *J* = 7.2 Hz, 1H), 6.95 − 6.99 (m, 2H), 7.16 (ddd, *J* = 3.0, 5.7, 7.8 Hz, 1H), 8.52 (s, 1H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$, δ): -5.4, -5.4, 7.3, 18.1, 25.8, 34.8, 37.2,46.2,59.0, 65.5, 109.6, 121.4, 121.4, 126.6, 141.1, 176.6 ppm. **IR (neat**

sample): 3207, 2953, 2929, 2885, 2856, 1739, 1693, 1470, 1365, 1346, 1228, 1086, 1086, 837, 777, 739 cm^{-1}. **HRMS** (ESI) (*m/z*): calcd for $C_{19}H_{29}NO_3Si$ $[M + Na]^+$, 370.1807; found, 370.1818.

6.3.44 *(1S,2S,3S)-2-(bromomethyl)-2-(((tert-butyldimethylsilyl)oxy)methyl)-3-methylspiro [cyclopropane-1,3'-indolin]-2'-one (Y)*

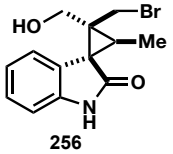


Y

To a 0 °C solution of alcohol **254** (562 mg, 1.62 mmol, 1 equiv.) and CBr_4 (1.07 g, 3.23 mmol, 2 equiv.) in CH_2Cl_2 (6.5 mL) was added PPh_3 (848 mg, 3.23 mmol, 2 equiv.) in one portion. After complete consumption of the starting material (45 min, TLC hexane:EtOAc 1:1) the reaction mixture was poured onto water (100 mL) and extracted with Et_2O (3x 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude was purified by flash column chromatography (hexane:EtOAc 7:1 to 4:1) to give the desired product as white solid in 85% (685 mg, 1.97 mmol) yield.

^{1}H-NMR (400 MHz, $CDCl_3$, δ): –0.07 (s, 3H), 0.04 (s, 3H), 0.77 (s, 9H), 1.53 (d, *J* = 6.6 Hz, 3H), 2.22 (q, *J* = 6.5 Hz, 1H), 3.88 (d, *J* = 11.0 Hz, 1H), 4.07 (d, *J* = 10.2 Hz, 1H), 4.20 (d, *J* = 11.0 Hz, 1H), 4.52 (d, *J* = 10.2 Hz, 1H) 6.90 (d, *J* = 7.5 Hz, 1H), 6.98 (ddd, *J* = 1.0, 7.5, 7.5 Hz, 1H), 7.03 (d, *J* = 7.5 Hz, 1H), 7.19 (ddd, *J* = 1.3, 7.5, 7.5 Hz, 1H), 8.19 (s, 1H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$, δ): -5.3, -5.3, 6.8, 18.2, 25.8, 31.2, 35.8, 39.4, 45.8, 62.3, 109.6, 121.6, 121.7, 126.9, 128.9, 140.7, 175.6 ppm. **IR (neat sample)**: 3203, 2953, 2929, 2884, 2856, 1739, 1692, 1620, 1470, 1365, 1253, 1218, 1104, 1087, 836, 776, 740, 666 cm^{-1}. **HRMS** (ESI) (*m/z*): calcd for $C_{19}H_{28}NO_2SiBr$ $[M + Na]^+$, 432.0970; found 432.0966.

6.3.45 *(1S,2S,3S)-2-(bromomethyl)-2-(hydroxymethyl)-3-methylspiro[cyclopropane-1,3'-indolin]-2'-one (256)*



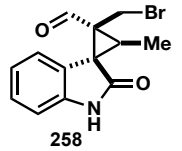
256

TBAF (1 M in THF, 1.52 mL, 1.52 mmol, 1.2 equiv.) was added to a 0 °C cold solution of TBS-ether **Y** (520 mg, 1.27 mmol, 1 equiv.) in THF (6.5 mL). After 10 minutes the cooling bath was removed and the mixture was allowed to stir for 12 h. After the complete consumption of the starting material (TLC, hexane:EtOAc 3:1) the reaction was quenched by addition of NH_4Cl solution. The aqueous layer was extracted with EtOAc (3x 50 mL), the combined organic layers

were dried over $MgSO_4$ and the crude was concentrated *in vacuo.* After purification by flash column chromatography (hexane:EtOAc 1:1) the alcohol was obtained as white solid in 84% (315 mg, 1.38 mmol) yield.

^{1}H-NMR (400 MHz, CD_3OD, δ): 1.48 (d, *J* = 6.5 Hz, 3H), 2.29 (q, *J* = 6.5 Hz, 1H), 3.92 (d, *J* = 11.8 Hz, 1H), 4.14 (d, *J* = 11.9 Hz, 1H), 4.17 (d, *J* = 10.1 Hz, 1H), 4.51 (d, *J* = 10.0 Hz, 1H), 6.91 (d, *J* = 7.7 Hz, 1H), 6.97 (ddd, *J* = 1.1, 7.6, 7.6 Hz, 1H), 7.14 (d, *J* = 7.7 Hz, 1H), 7.18 (ddd, *J* = 1.1, 7.7, 7.7 Hz, 1H) ppm. **^{13}C-NMR** (100 MHz, CD_3OD, δ): 7.0, 31.3, 36.9, 40.6, 46.3, 62.1, 110.6, 122.5, 122.8, 127.9, 129.8, 142.9, 177.3 ppm. **IR (neat sample)**: 3295, 2969, 1739, 1683, 1613, 1486, 1338, 1261, 1229, 1085, 1021, 700, 665 cm^{-1}. **HRMS** (ESI) (*m/z*): calcd for $C_{13}H_{14}BrNO_2$ $[M + H]^+$, 296.0286; found, 296.0283.

6.3.46 *(1S,2S,3S)-2-(bromomethyl)-3-methyl-2'-oxospiro[cyclopropane-1,3'-indoline]-2-carbaldehyde (258)*

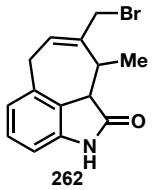


258

IBX (113 mg, 405 µmol, 1.2 equiv.) was added to a solution of alcohol **256** (100 mg, 338 µmol, 1 equiv.) in DMSO (560 µL). After the complete consumption of the starting material (TLC, hexane:EtOAc 1:1) water was added to the reaction. The aqueous layer was extracted with EtOAc (3x 10 mL) and the combined organic layers were dried over $MgSO_4$. The solvent was removed *in vacuo* and the crude was purified by flash column chromatography (hexane:EtOAc 2:1) to give the aldehyde in 90% (89 mg, 303 µmol) yield.

^{1}H-NMR (400 MHz, $CDCl_3$, δ): 1.62 (d, *J* = 6.5 Hz, 3H), 2.99 (q, *J* = 6.5 Hz, 1H), 4.20 (d, *J* = 10.9 Hz, 1H), 4.61 (d, *J* = 10.9 Hz, 1H), 6.92 (d, *J* = 7.5 Hz, 1H), 6.99 (ddd, *J* = 1.4, 7.6, 7.6 Hz, 1H), 7.04 (d, *J* = 7.5 Hz, 1H), 7.22 (ddd, *J* = 1.4, 7.5, 7.5 Hz, 1H), 8.49 (s, 1H), 9.63 (s, 1H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$, δ): 6.1, 25.7, 33.4, 42.8, 50.6, 109.9, 122.4, 123.2, 126.0, 128.1, 140.6, 173.5, 196.1 ppm. **IR (neat sample)**: 3200, 3057, 2929, 1691, 1618, 1469, 1423, 1260, 1232, 1190, 1153, 1098, 1036, 1012, 860, 750, 736, 661 cm^{-1}. **HRMS** (ESI) (*m/z*): calcd for $C_{13}H_{12}NO_2Br$ $[M + H]^+$, 294.0130; found, 294.0133.

6.3.47 *8-(bromomethyl)-9-methyl-2,6,9,9a-tetrahydro-1H-cyclohepta[cd]indol-1-one (262)*

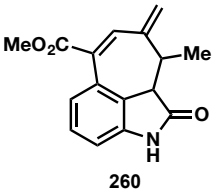


262

Methyltriphenylphosphonium bromide (48.0 mg, 133 µmol, 2.5 equiv.) in THF (200 µL) was cooled to –78 °C before NaHMDS (2 M in THF, 67.0 µL, 133 µmol, 2.5 equiv.) was added. The suspension was stirred for 10 minutes at –78 °C before the temperature was raised to 0 °C. During this time the colour of the suspension changed from pale yellow to bright yellow and the majority of the Wittig reagent dissolved. After stirring for 30 minutes at 0 °C the temperature was lowered to –78 °C and aldehyde **258** (15.7 mg, 53.4 µmol, 1 equiv.) in THF (300 µL) was added. The mixture was stirred for 10 minutes before the temperature was raised again to 0 °C. After the complete consumption of aldehyde **258** (TLC, hexane:EtOAc 3:1) the reaction was hydrolysed by addition of NH_4Cl solution, the aqueous layer was extracted with Et_2O (3x 10 mL), the combined organic layers were dried over $MgSO_4$ and the crude was concentrated *in vacuo* (T≤ 20 °C). The crude was filtered over a short column (pentane:Et_2O 1:1), concentrated *in vacuo*, dissolved in $CDCl_3$ (700 µL) and heated to 40 °C for 8 h. The reaction progress was observed by NMR. After the complete olefin has rearranged, the crude was purified by flash column chromatography (hexane:EtOAc 1:1) to give the desired product in 77% (12.0 mg, 41.1 µmol) yield.

^{1}H-NMR (400 MHz, $CDCl_3$, δ): 0.81 (d, *J* = 6.8 Hz, 3H), 3.26 − 3.33 (m, 1H), 3.48 (dd, *J* = 5.6, 21.2 Hz, 1H), 3.81 (d, *J* = 3.4 Hz, 1H), 3.82 (d, *J* = 21.2 Hz, 1Hz), 4.03 (d, *J* = 9.9 Hz, 1H), 4.10 (d, *J* = 9.9 Hz, 1H), 5.89 (dd, *J* = 3.9, 5.6 Hz, 1H), 6.74 (d, *J* = 7.8 Hz, 1H), 6.78 (d, *J* = 7.8 Hz, 1H), 7.15 (dd, *J* = 7.8, 7.8 Hz, 1H), 7.72 (s, 1H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$, δ): 15.8, 34.6, 35.1,41.3, 49.7, 107.2, 122.5, 126.3, 127.2, 128.1, 135.2, 140.4, 178.2 ppm. **IR (neat sample)**: 3157, 2965, 1702, 1618, 1456, 1294, 1255, 1206, 781, 630 cm^{-1}. **HRMS** (ESI) (*m*/*z*): calcd for $C_{14}H_{14}NOBr$ $[M + Na]^+$, 314.0156; found, 314.0157.

6.3.48 *methyl 9-methyl-8-methylene-1-oxo-2,8,9,9a-tetrahydro-1H-cyclohepta[cd]indole-6-carboxylate (260)*

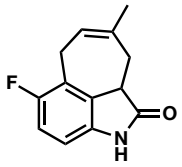


260

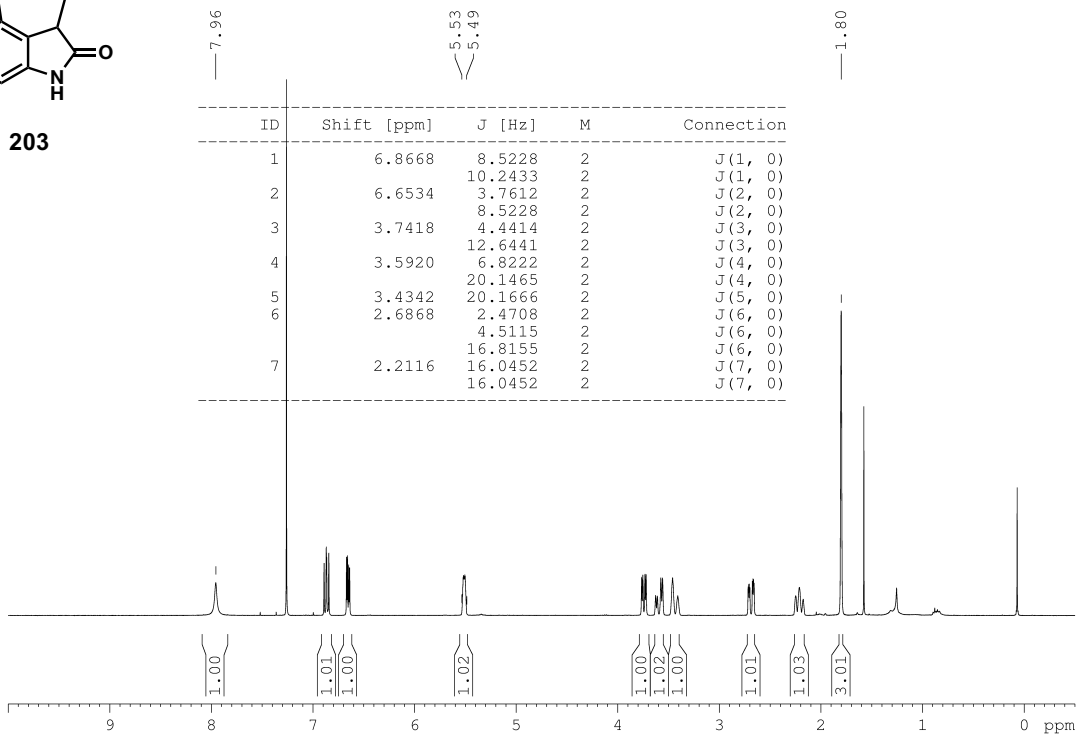
A suspension of aldehyde **258** (14.1 mg, 48.0 µmol, 1 equiv.) and methyl(triphenyl-phosphoranylidene)acetate (17.6 mg, 52.7 µmol, 1.1 equiv.) in benzene (480 µL) was warmed to 45 °C. After the complete consumption of the starting material (TLC, hexane:EtOAc 3:1) the temperature was raised to 60 °C. The mixture was stirred at that temperature until the rearrangement was complete (TLC, hexane:EtOAc 1:1). The crude was purified by preparative TLC (hexane:EtOAc, 1:1) to give the desired rearrangement product in 93% (12.0 mg, 44.6 µmol) yield.

^{1}H-NMR (400 MHz, $CDCl_3$, δ): 0.67 (d, *J* = 7.2 Hz, 3H), 3.40 − 3.47 (m, 1H), 3.59 (d, *J* = 2.8 Hz, 1H), 3.89 (s, 3H), 6.87 (d, *J* = 7.2 Hz, 1H), 5.48 (s, 1H), 5.50 (s, 1H) 7.18 − 7.22 (m, 2H), 7.25 (dd, *J* = 7.8, 7.8 Hz, 1H), 8.44 (s, 1H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$, δ): 16.3, 40.1, 49.2, 42.6, 109.4, 123.2, 126.1, 126.8, 128.0, 128.6, 130.6, 139.0, 140.9, 148.5, 169.5, 178.5 ppm. **IR (neat sample)**: 3260, 2963, 1707, 1615, 1448, 1321, 1234, 1087, 1003, 910, 798, 733, 635 cm^{-1}. **HRMS** (ESI) (*m*/*z*): calcd for $C_{16}H_{15}NO_3$ $[M + Na]^+$, 292.0950; found, 292.0947.

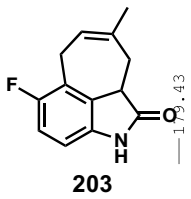
6.4 Spectra



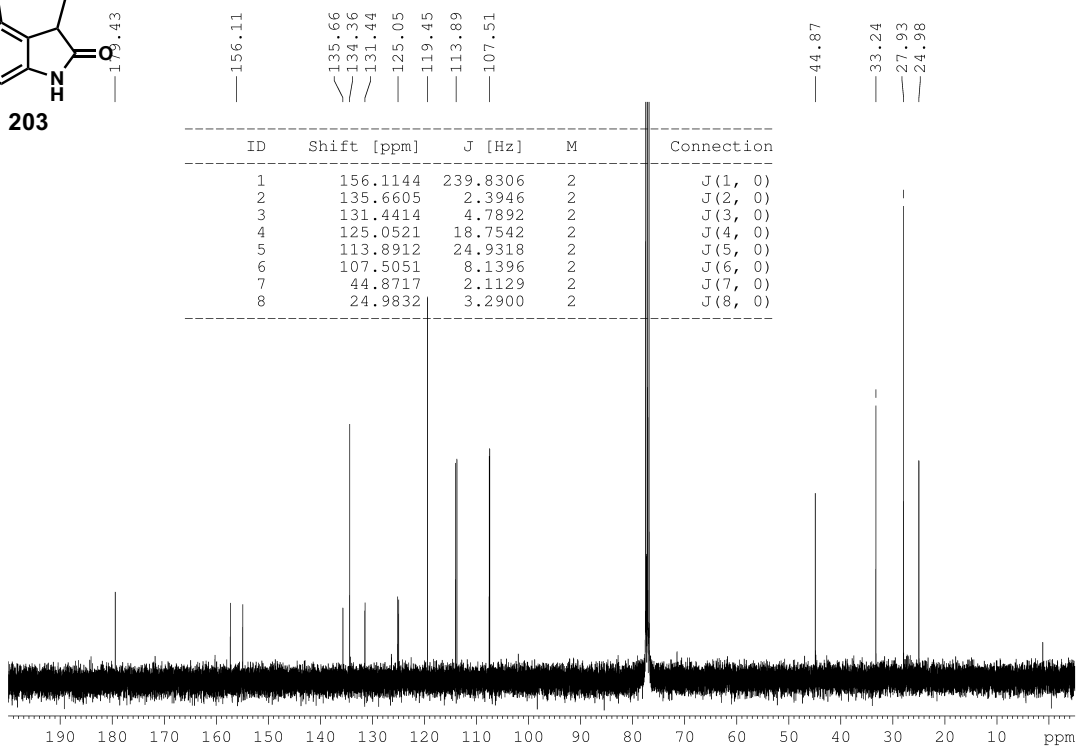
203



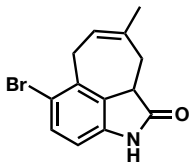
ID	Shift [ppm]	J [Hz]	M	Connection
1	6.8668	8.5228	2	J(1, 0)
		10.2433	2	J(1, 0)
2	6.6534	3.7612	2	J(2, 0)
		8.5228	2	J(2, 0)
3	3.7418	4.4414	2	J(3, 0)
		12.6441	2	J(3, 0)
4	3.5920	6.8222	2	J(4, 0)
		20.1465	2	J(4, 0)
5	3.4342	20.1666	2	J(5, 0)
6	2.6868	2.4708	2	J(6, 0)
		4.5115	2	J(6, 0)
		16.8155	2	J(6, 0)
7	2.2116	16.0452	2	J(7, 0)
		16.0452	2	J(7, 0)



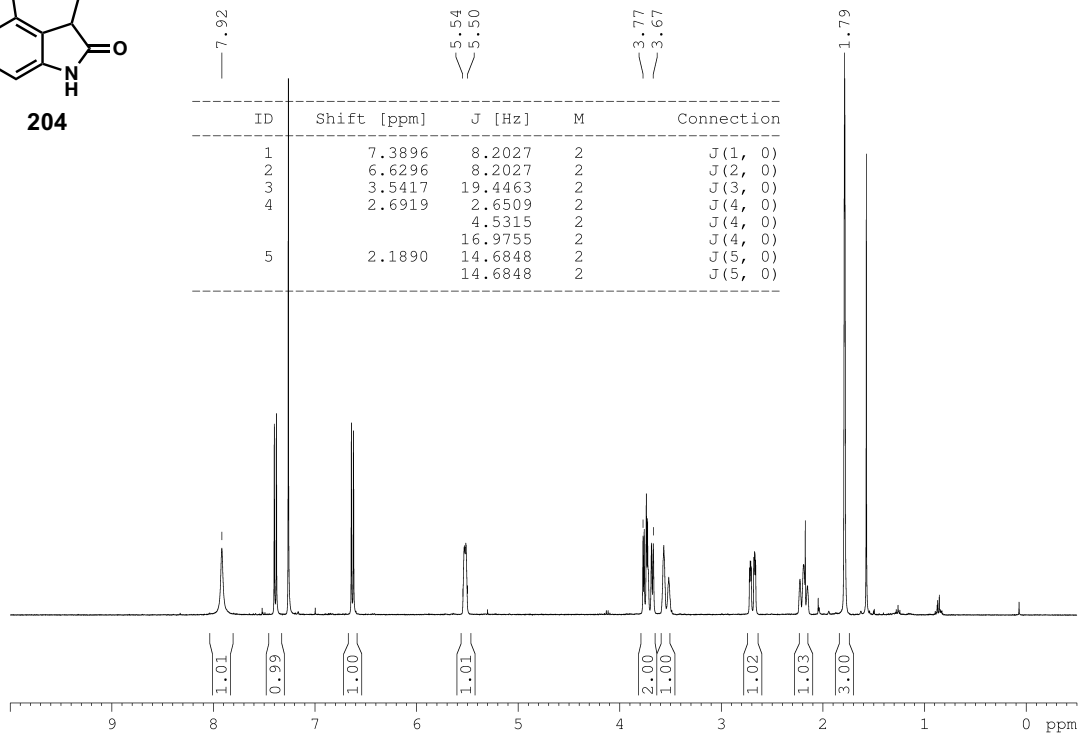
203



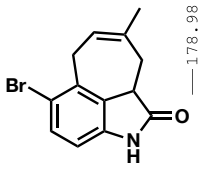
ID	Shift [ppm]	J [Hz]	M	Connection
1	156.1144	239.8306	2	J(1, 0)
2	135.6605	2.3946	2	J(2, 0)
3	131.4414	4.7892	2	J(3, 0)
4	125.0521	18.7542	2	J(4, 0)
5	113.8912	24.9318	2	J(5, 0)
6	107.5051	8.1396	2	J(6, 0)
7	44.8717	2.1129	2	J(7, 0)
8	24.9832	3.2900	2	J(8, 0)



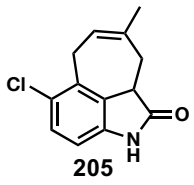
204



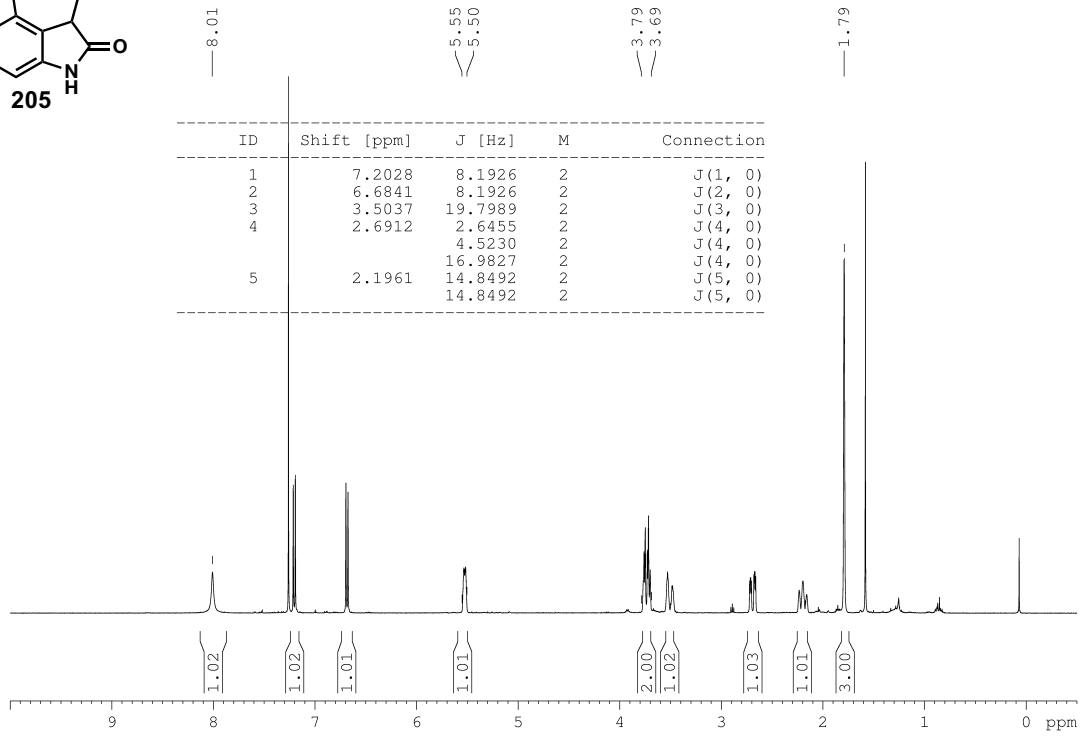
ID	Shift [ppm]	J [Hz]	M	Connection
1	7.3896	8.2027	2	J(1, 0)
2	6.6296	8.2027	2	J(2, 0)
3	3.5417	19.4463	2	J(3, 0)
4	2.6919	2.6509	2	J(4, 0)
		4.5315	2	J(4, 0)
		16.9755	2	J(4, 0)
5	2.1890	14.6848	2	J(5, 0)
		14.6848	2	J(5, 0)



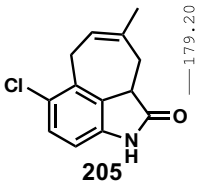
204



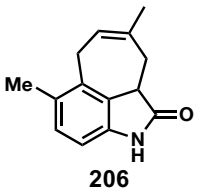
205



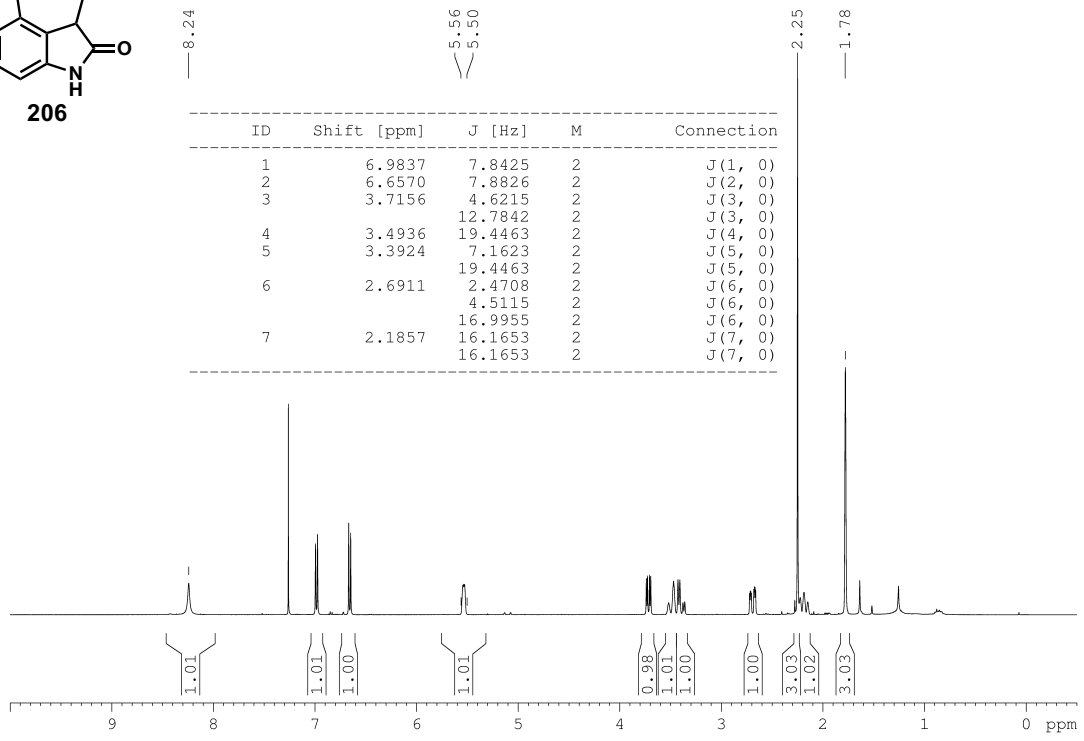
ID	Shift [ppm]	J [Hz]	M	Connection
1	7.2028	8.1926	2	J(1, 0)
2	6.6841	8.1926	2	J(2, 0)
3	3.5037	19.7989	2	J(3, 0)
4	2.6912	2.6455	2	J(4, 0)
		4.5230	2	J(4, 0)
		16.9827	2	J(4, 0)
5	2.1961	14.8492	2	J(5, 0)
		14.8492	2	J(5, 0)



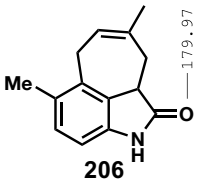
205



206



ID	Shift [ppm]	J [Hz]	M	Connection
1	6.9837	7.8425	2	J(1, 0)
2	6.6570	7.8826	2	J(2, 0)
3	3.7156	4.6215	2	J(3, 0)
		12.7842	2	J(3, 0)
4	3.4936	19.4463	2	J(4, 0)
5	3.3924	7.1623	2	J(5, 0)
		19.4463	2	J(5, 0)
6	2.6911	2.4708	2	J(6, 0)
		4.5115	2	J(6, 0)
		16.9955	2	J(6, 0)
7	2.1857	16.1653	2	J(7, 0)
		16.1653	2	J(7, 0)



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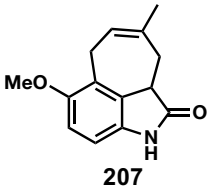
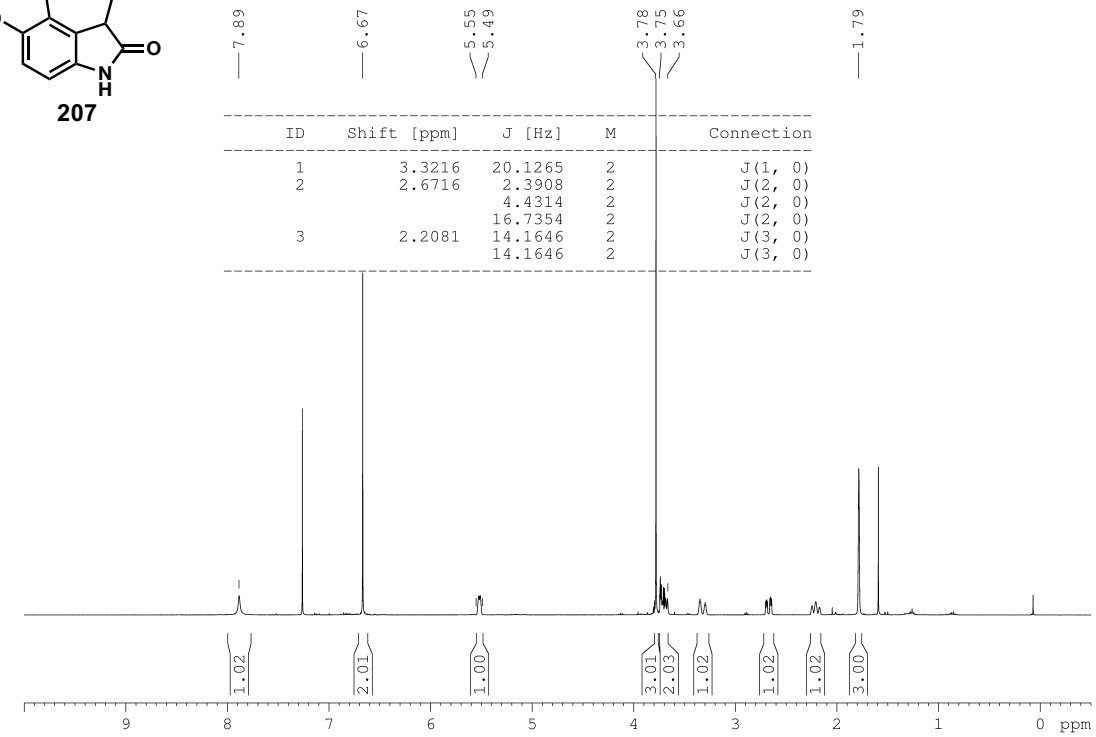
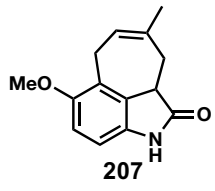


207



ID	Shift [ppm]	J [Hz]	M	Connection
1	3.3216	20.1265	2	J(1, 0)
2	2.6716	2.3908	2	J(2, 0)
		4.4314	2	J(2, 0)
		16.7354	2	J(2, 0)
3	2.2081	14.1646	2	J(3, 0)
		14.1646	2	J(3, 0)



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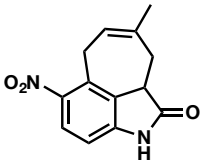
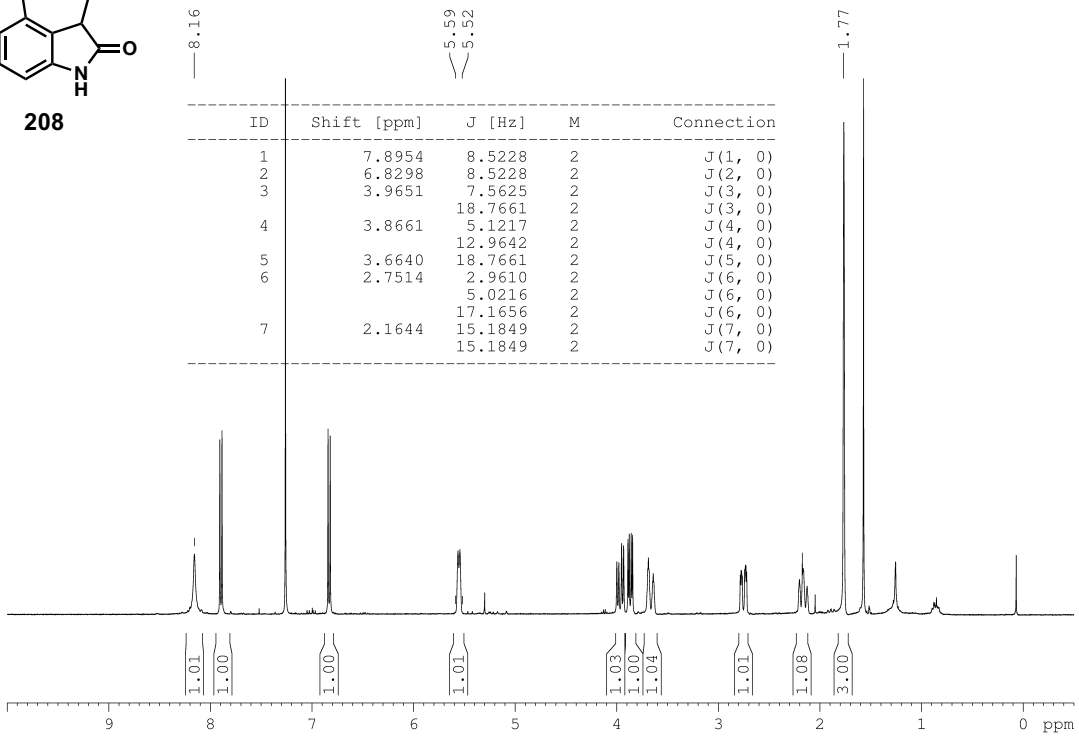
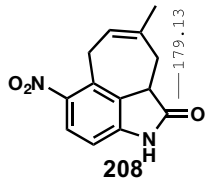


208



ID	Shift [ppm]	J [Hz]	M	Connection
1	7.8954	8.5228	2	J(1, 0)
2	6.8298	8.5228	2	J(2, 0)
3	3.9651	7.5625	2	J(3, 0)
		18.7661	2	J(3, 0)
4	3.8661	5.1217	2	J(4, 0)
		12.9642	2	J(4, 0)
5	3.6640	18.7661	2	J(5, 0)
6	2.7514	2.9610	2	J(6, 0)
		5.0216	2	J(6, 0)
		17.1656	2	J(6, 0)
7	2.1644	15.1849	2	J(7, 0)
		15.1849	2	J(7, 0)



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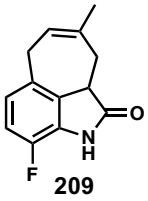

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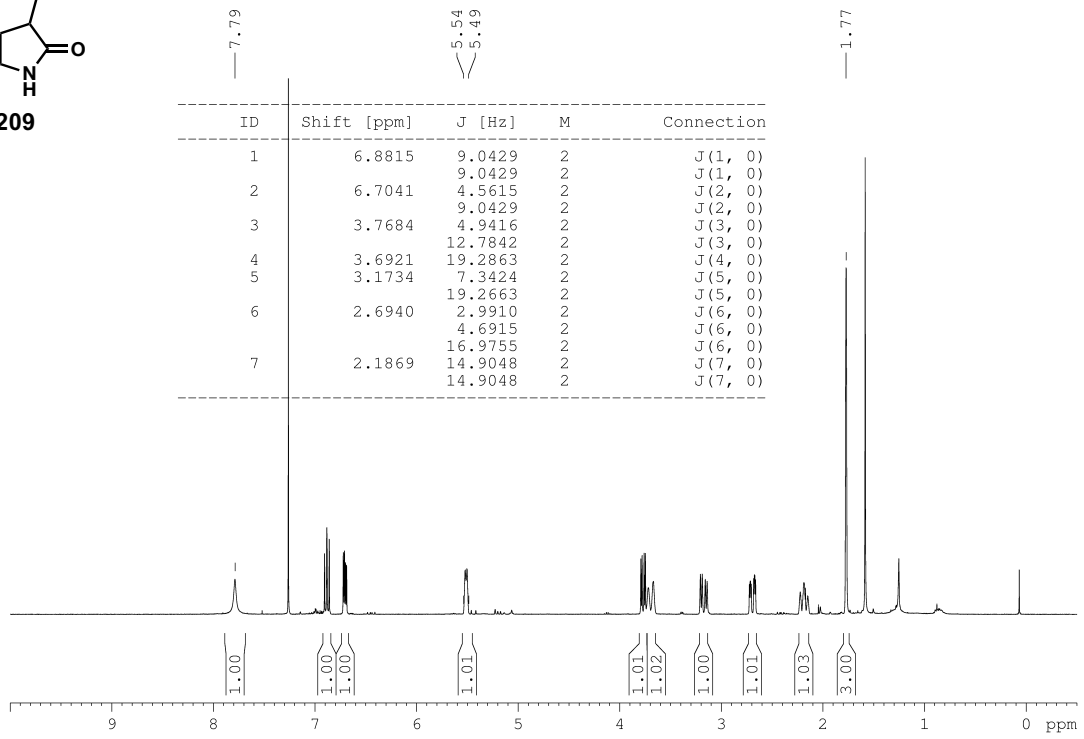
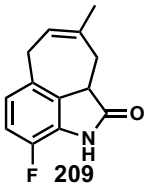


ID	Shift [ppm]	J [Hz]	M	Connection
1	6.8815	9.0429	2	J(1, 0)
		9.0429	2	J(1, 0)
2	6.7041	4.5615	2	J(2, 0)
		9.0429	2	J(2, 0)
3	3.7684	4.9416	2	J(3, 0)
		12.7842	2	J(3, 0)
4	3.6921	19.2863	2	J(4, 0)
5	3.1734	7.3424	2	J(5, 0)
		19.2663	2	J(5, 0)
6	2.6940	2.9910	2	J(6, 0)
		4.6915	2	J(6, 0)
		16.9755	2	J(6, 0)
7	2.1869	14.9048	2	J(7, 0)
		14.9048	2	J(7, 0)



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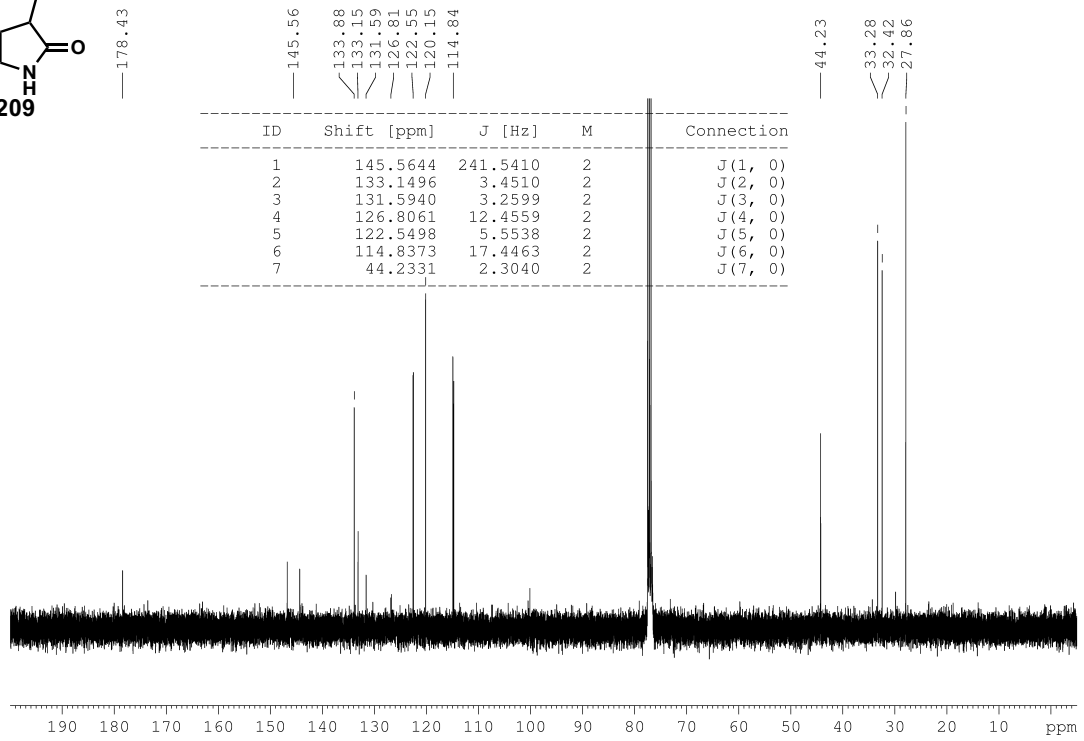
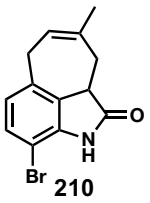


ID	Shift [ppm]	J [Hz]	M	Connection
1	145.5644	241.5410	2	J(1, 0)
2	133.1496	3.4510	2	J(2, 0)
3	131.5940	3.2599	2	J(3, 0)
4	126.8061	12.4559	2	J(4, 0)
5	122.5498	5.5538	2	J(5, 0)
6	114.8373	17.4463	2	J(6, 0)
7	44.2331	2.3040	2	J(7, 0)



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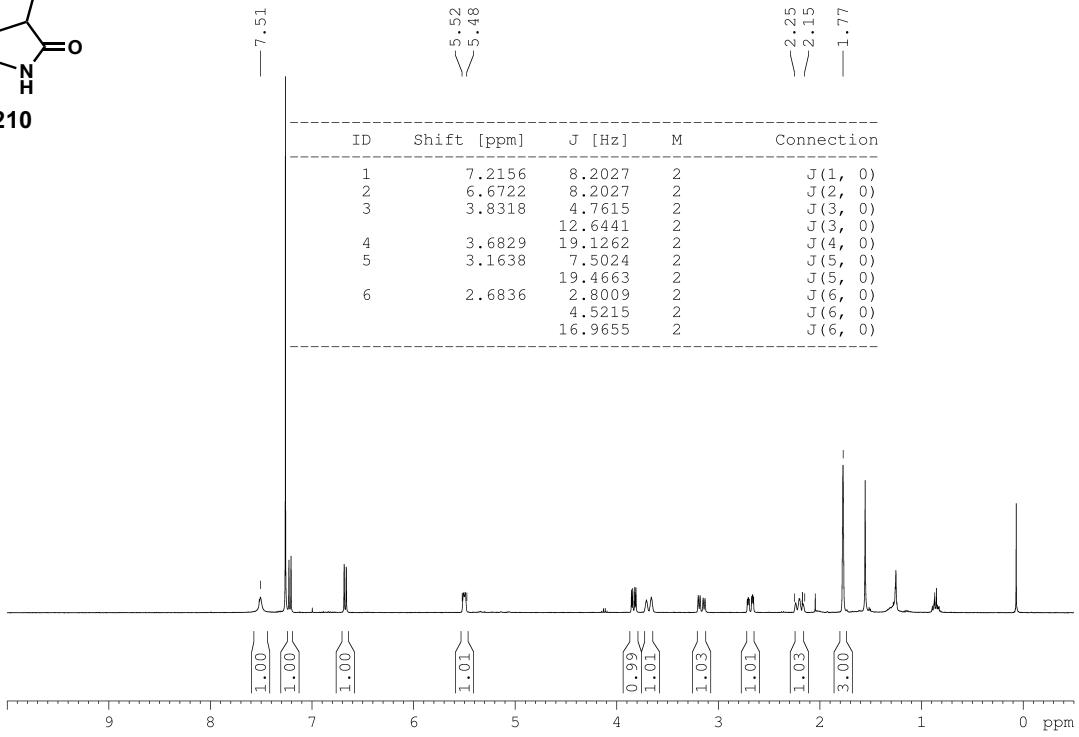
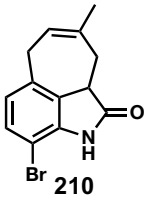
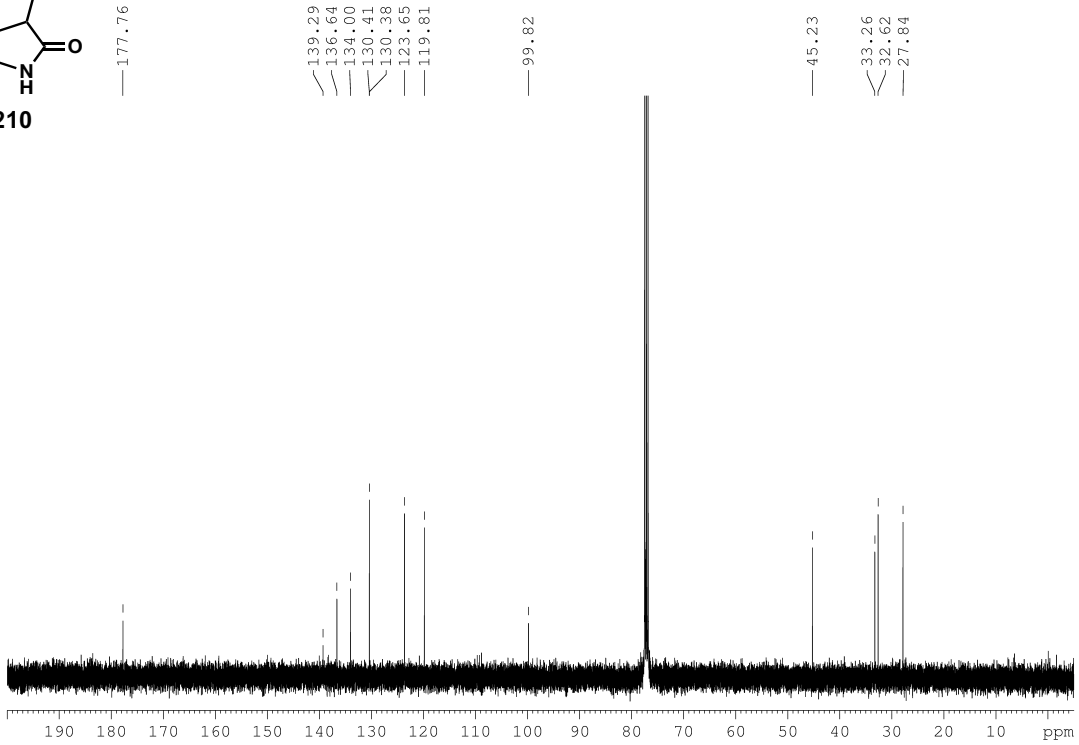
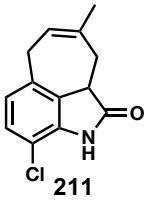


ID	Shift [ppm]	J [Hz]	M	Connection
1	7.2156	8.2027	2	J(1, 0)
2	6.6722	8.2027	2	J(2, 0)
3	3.8318	4.7615	2	J(3, 0)
		12.6441	2	J(3, 0)
4	3.6829	19.1262	2	J(4, 0)
5	3.1638	7.5024	2	J(5, 0)
		19.4663	2	J(5, 0)
6	2.6836	2.8009	2	J(6, 0)
		4.5215	2	J(6, 0)
		16.9655	2	J(6, 0)

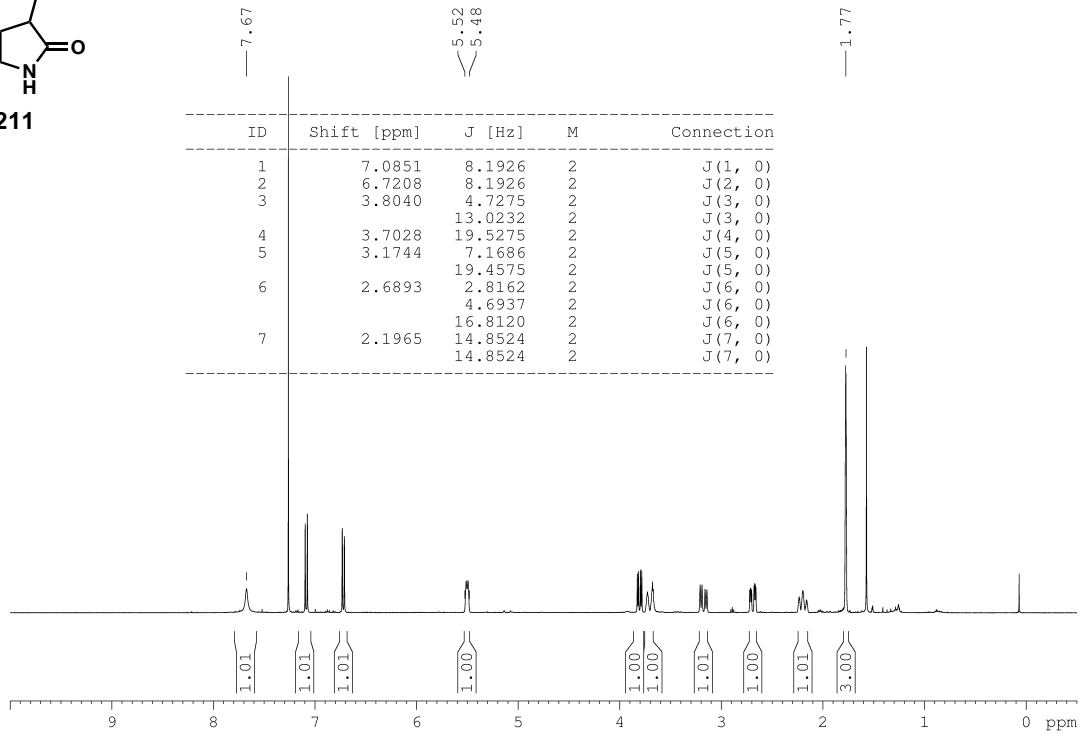


210

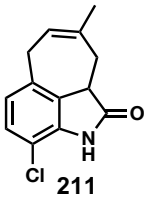




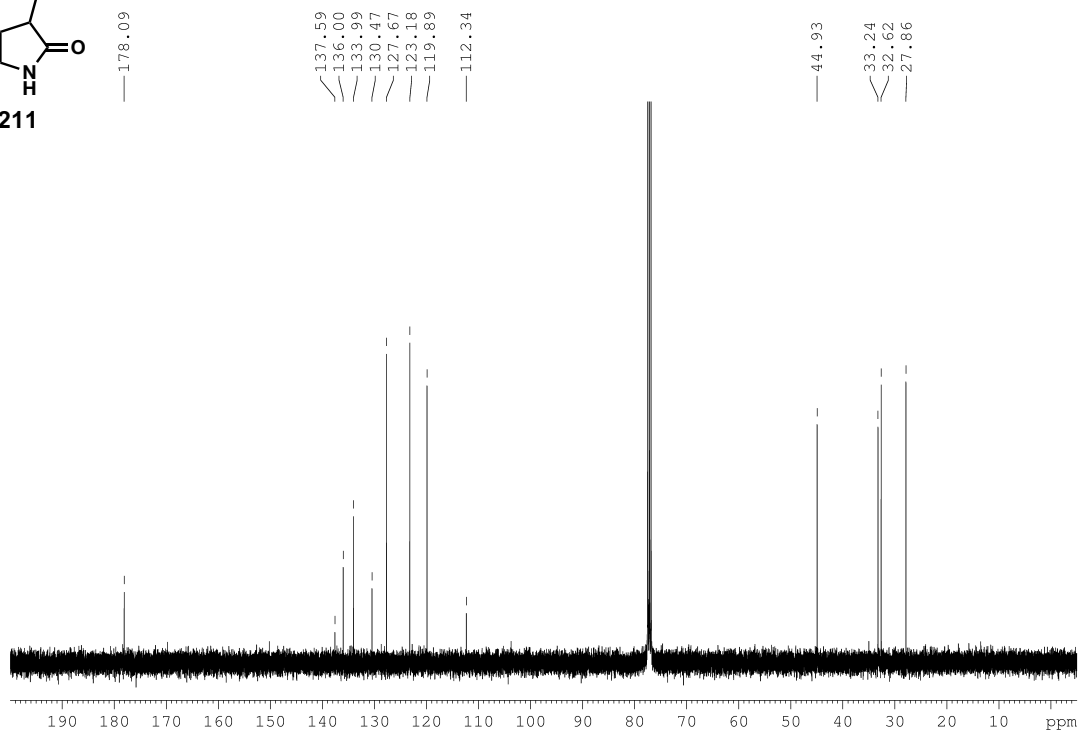
211

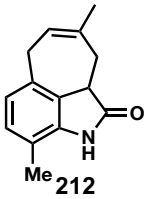


ID	Shift [ppm]	J [Hz]	M	Connection
1	7.0851	8.1926	2	J(1, 0)
2	6.7208	8.1926	2	J(2, 0)
3	3.8040	4.7275	2	J(3, 0)
		13.0232	2	J(3, 0)
4	3.7028	19.5275	2	J(4, 0)
5	3.1744	7.1686	2	J(5, 0)
		19.4575	2	J(5, 0)
6	2.6893	2.8162	2	J(6, 0)
		4.6937	2	J(6, 0)
		16.8120	2	J(6, 0)
7	2.1965	14.8524	2	J(7, 0)
		14.8524	2	J(7, 0)



211

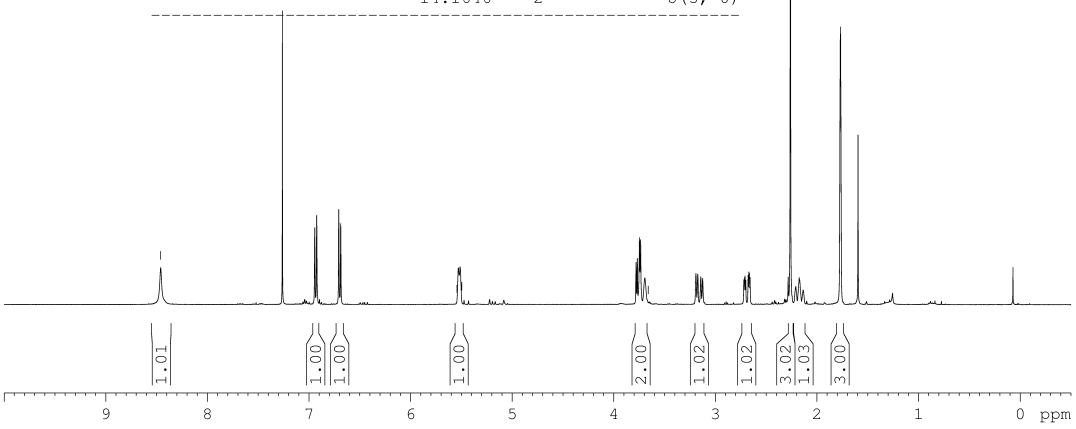


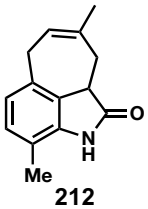


212

8.46 5.54 5.50 3.79 3.66 2.26 1.77

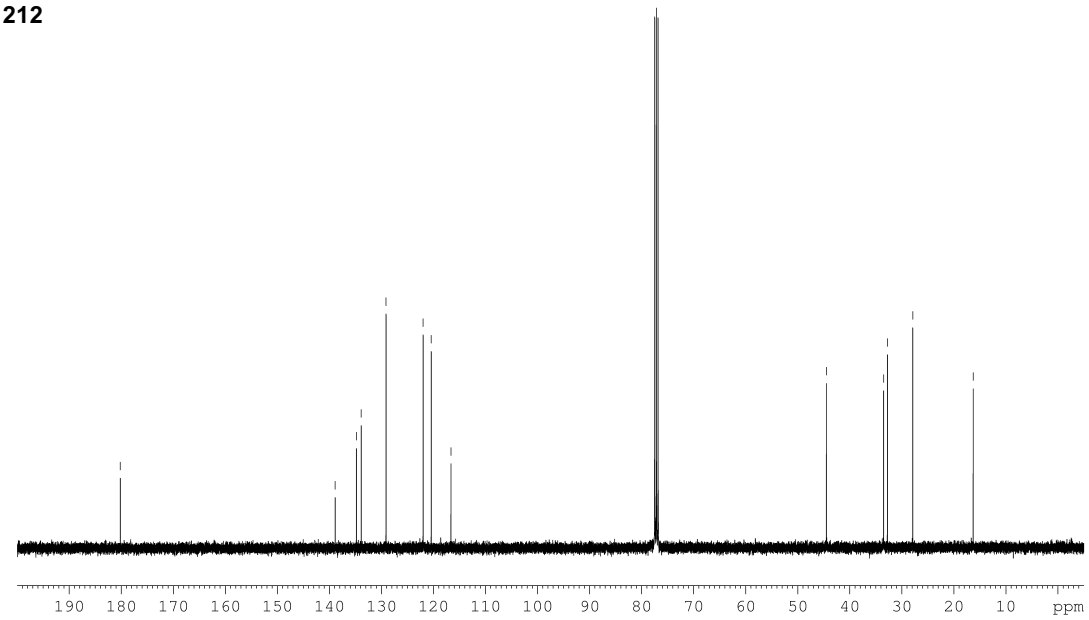
ID	Shift [ppm]	J [Hz]	M	Connection
1	6.9319	7.8425	2	J(1, 0)
2	6.6965	7.8425	2	J(2, 0)
3	3.1573	7.5224	2	J(3, 0)
		19.1262	2	J(3, 0)
4	2.6883	2.8909	2	J(4, 0)
		4.6115	2	J(4, 0)
		17.0755	2	J(4, 0)
5	2.1712	14.1646	2	J(5, 0)
		14.1646	2	J(5, 0)

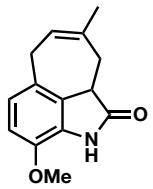




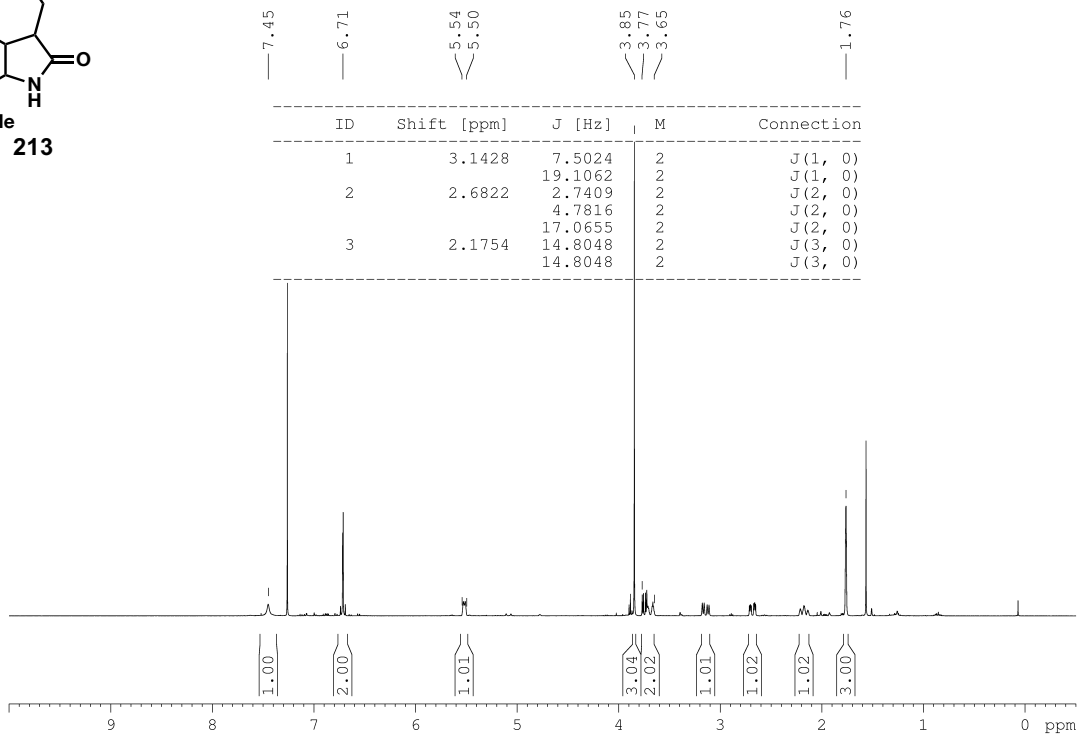
212

180.20 138.89 134.81 133.89 129.12 121.99 120.43 116.63 44.48 33.48 32.76 27.88 16.27

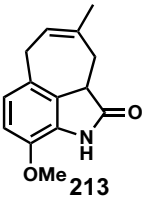




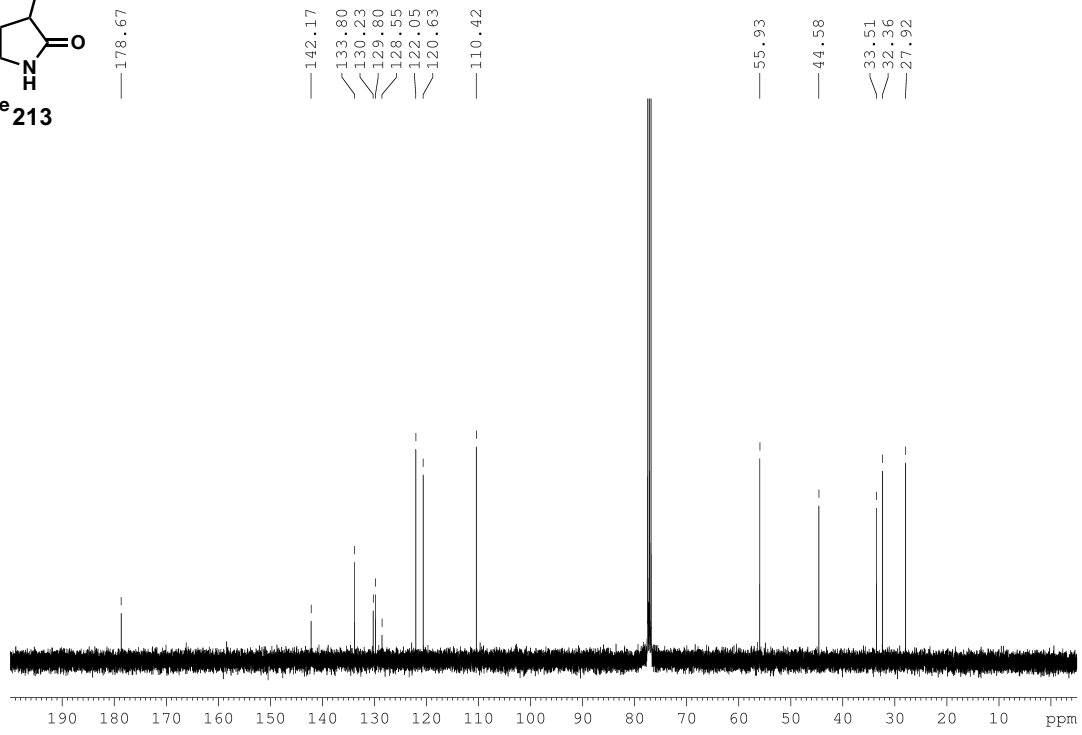
213

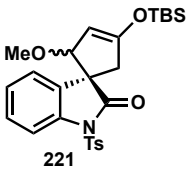


ID	Shift [ppm]	J [Hz]	M	Connection
1	3.1428	7.5024	2	J(1, 0)
		19.1062	2	J(1, 0)
2	2.6822	2.7409	2	J(2, 0)
		4.7816	2	J(2, 0)
		17.0655	2	J(2, 0)
3	2.1754	14.8048	2	J(3, 0)
		14.8048	2	J(3, 0)



213





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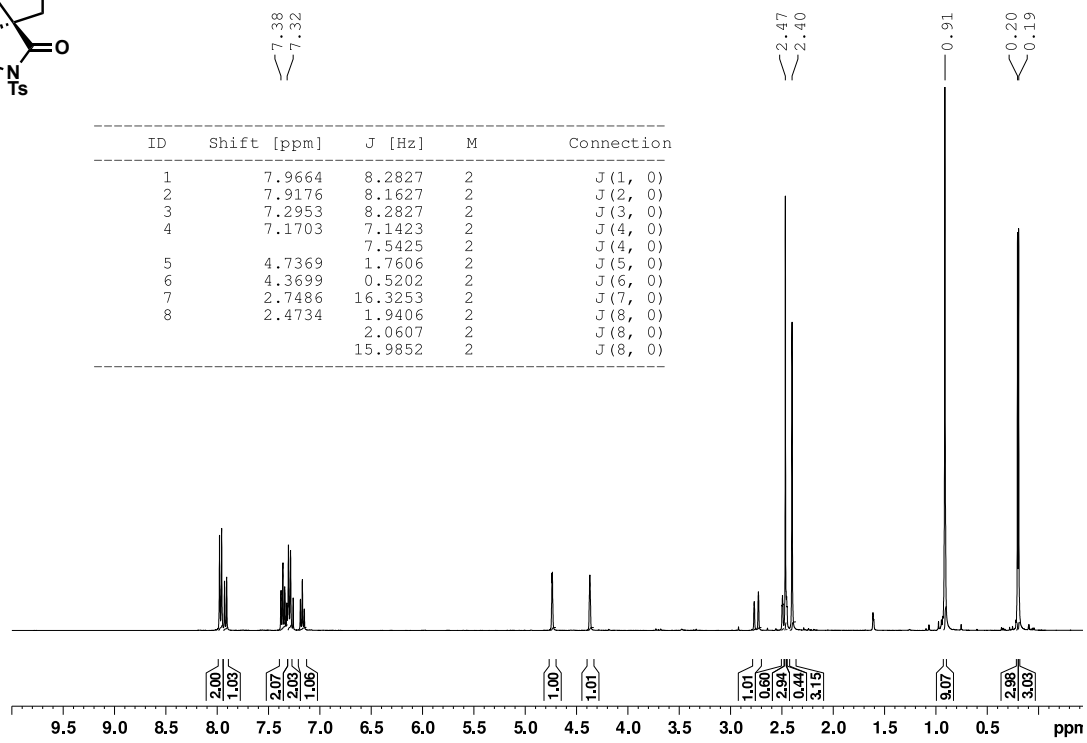
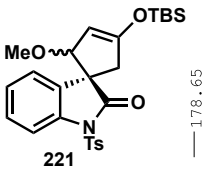


ID	Shift [ppm]	J [Hz]	M	Connection
1	7.9664	8.2827	2	J(1, 0)
2	7.9176	8.1627	2	J(2, 0)
3	7.2953	8.2827	2	J(3, 0)
4	7.1703	7.1423	2	J(4, 0)
		7.5425	2	J(4, 0)
5	4.7369	1.7606	2	J(5, 0)
6	4.3699	0.5202	2	J(6, 0)
7	2.7486	16.3253	2	J(7, 0)
8	2.4734	1.9406	2	J(8, 0)
		2.0607	2	J(8, 0)
		15.9852	2	J(8, 0)



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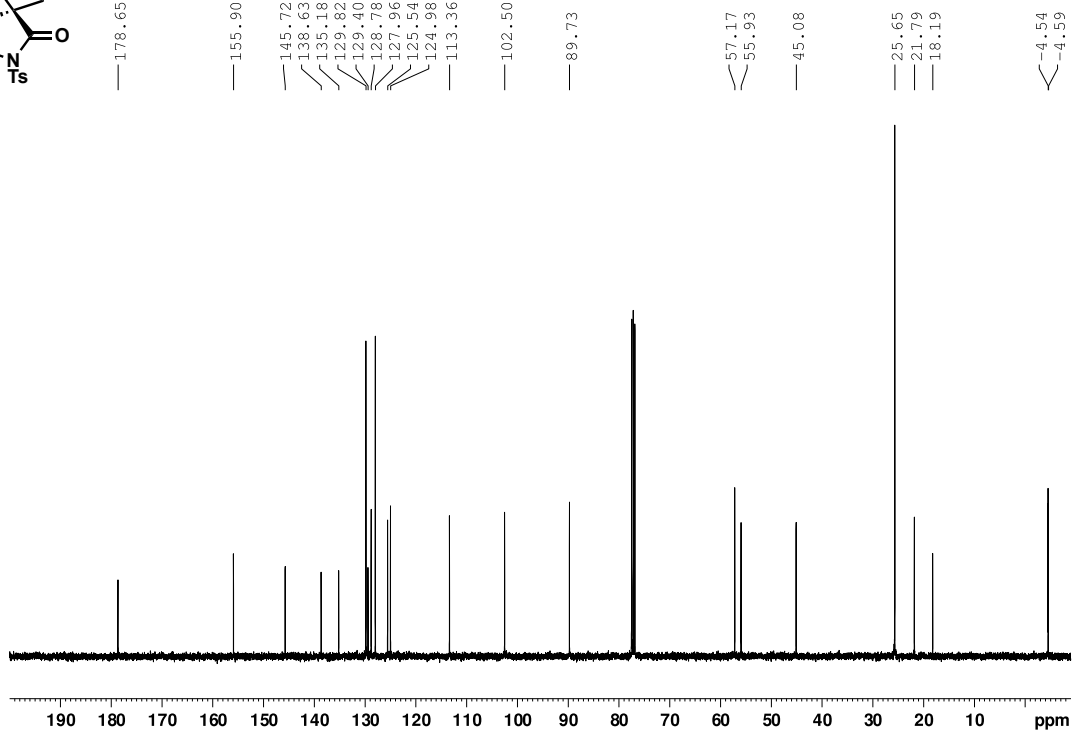
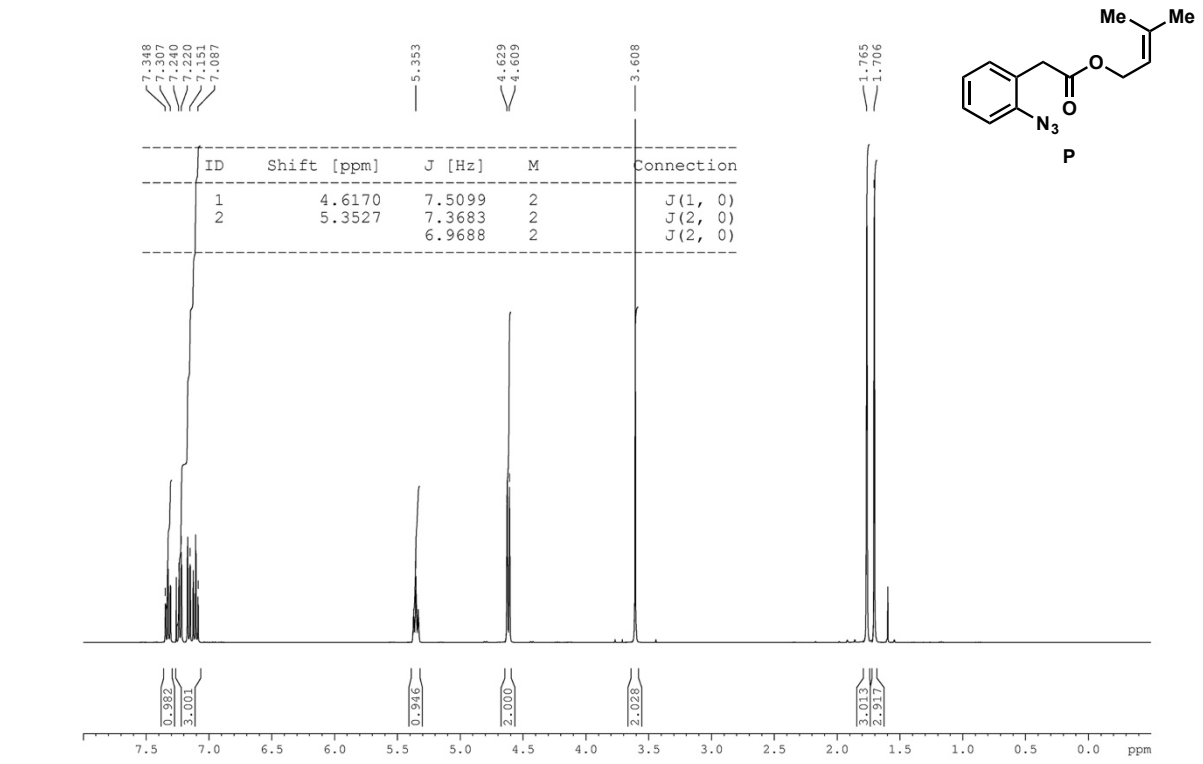
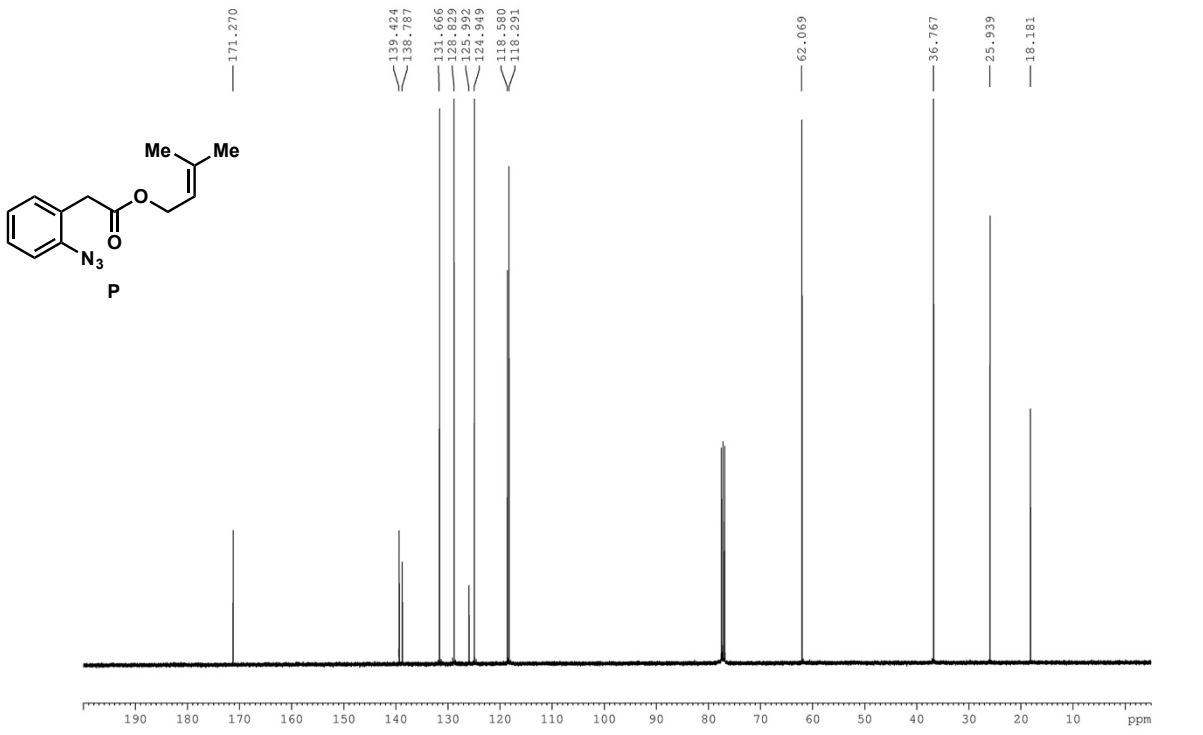
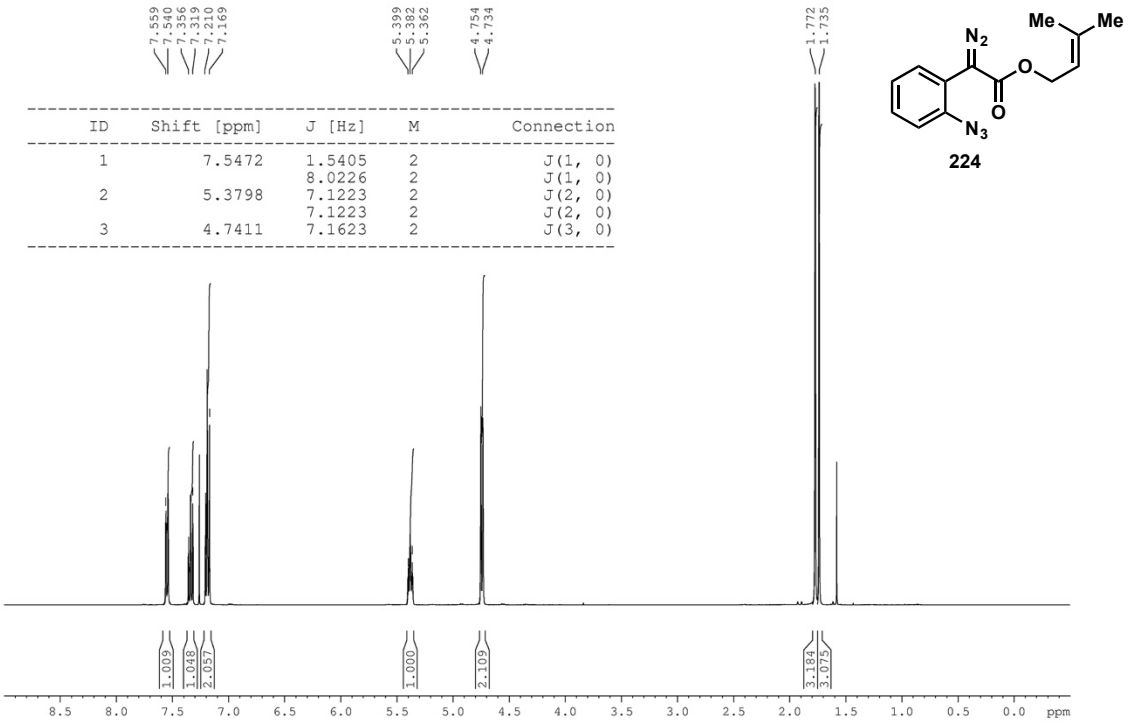
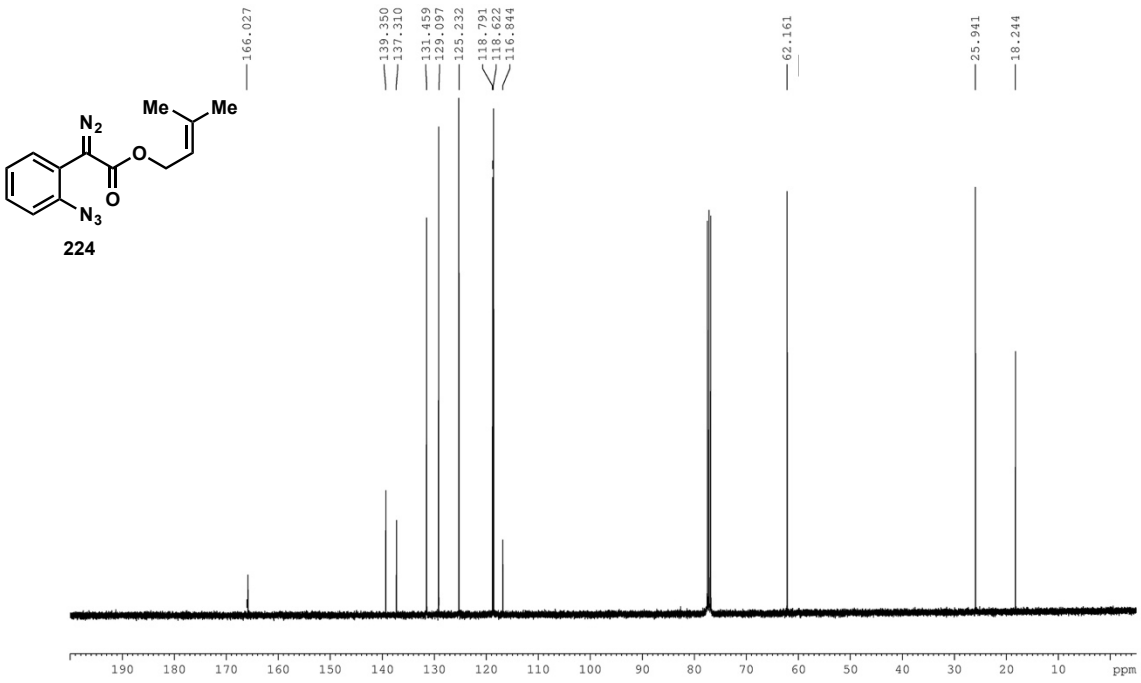


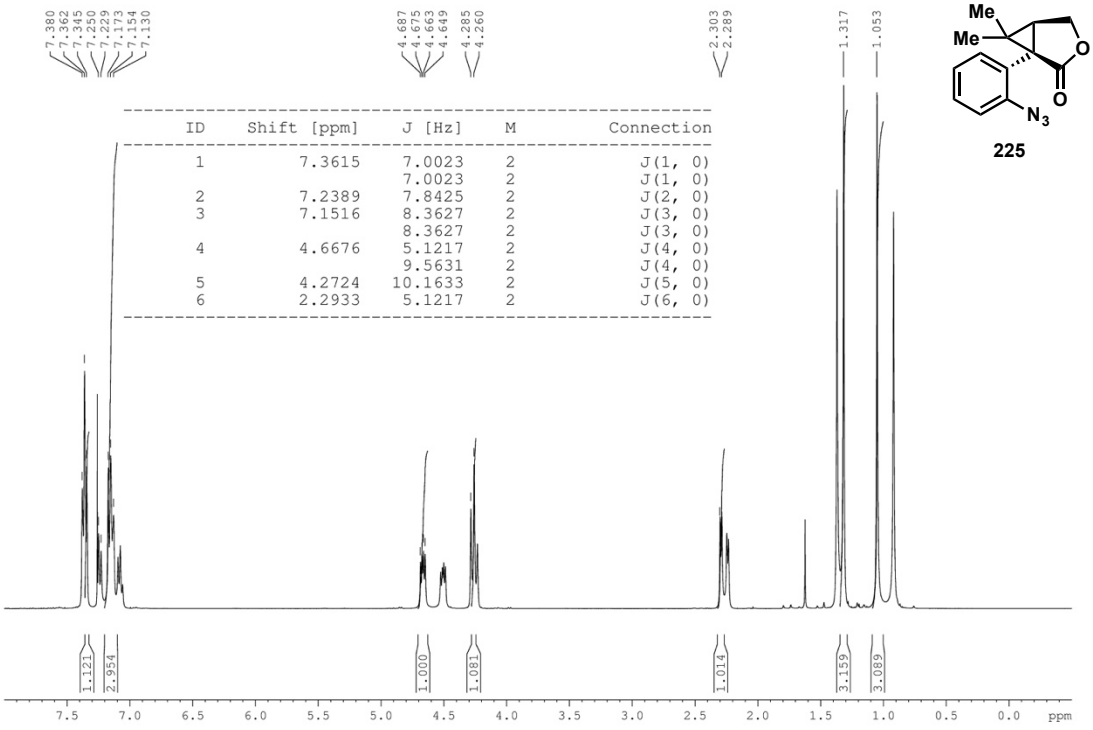

7.348
7.307
7.240
7.220
7.151
7.087
5.353
4.629
4.609
3.608
1.765
1.706
ID Shift [ppm] J [Hz] M Connection
1 4.6170 7.5099 2 J(1, 0)
2 5.3527 7.3683 2 J(2, 0)
6.9688 2 J(2, 0)
0.982
3.001
0.946
2.000
2.028
3.013
2.917
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
Me
Me
O
O
N3
P


171.270
139.424
138.787
131.666
128.829
125.992
124.949
118.580
118.291
62.069
36.767
25.939
18.181
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm
Me
Me
O
O
N3
P

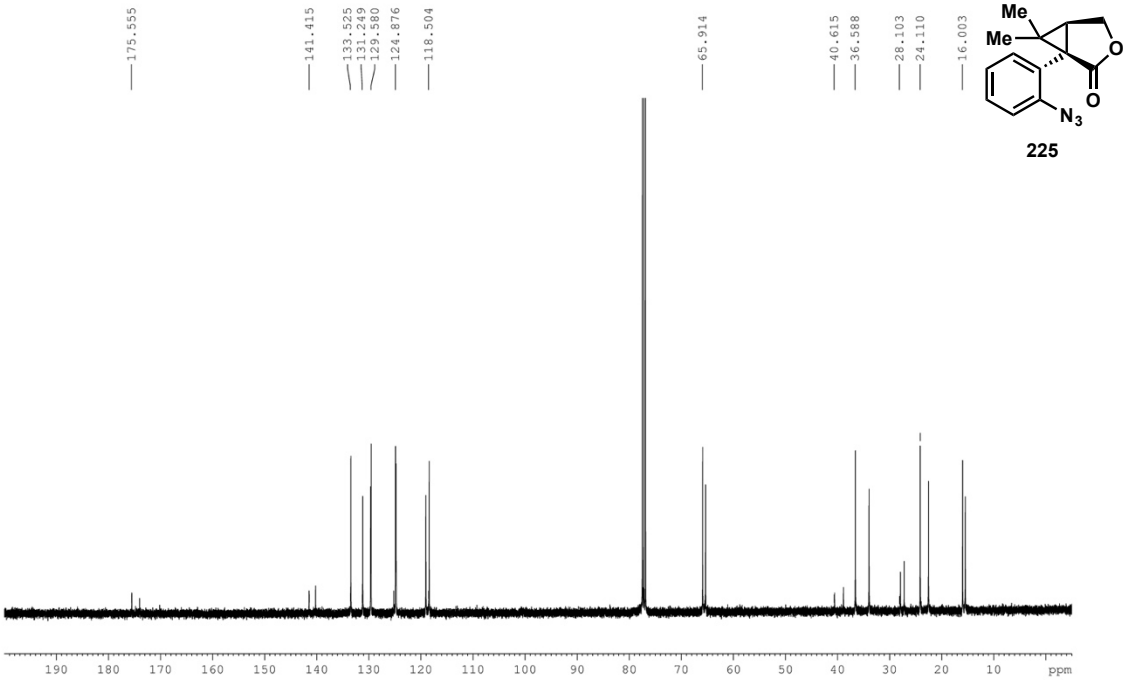


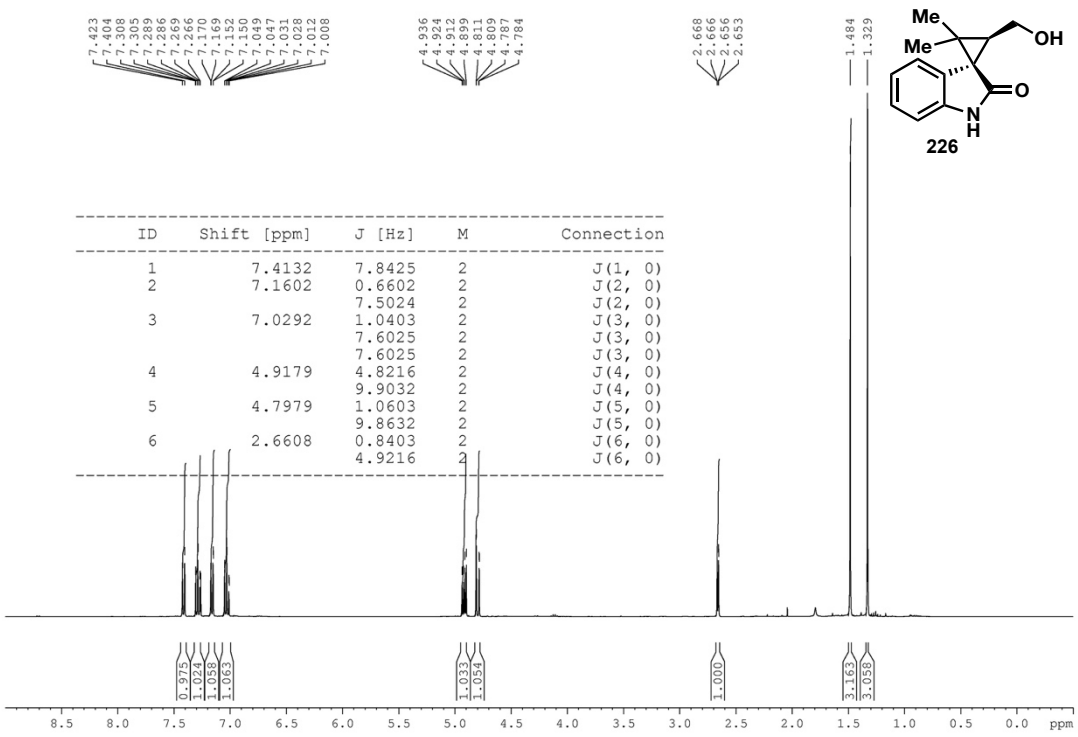
ID	Shift [ppm]	J [Hz]	M	Connection
1	7.5472	1.5405	2	J(1, 0)
		8.0226	2	J(1, 0)
2	5.3798	7.1223	2	J(2, 0)
		7.1223	2	J(2, 0)
3	4.7411	7.1623	2	J(3, 0)

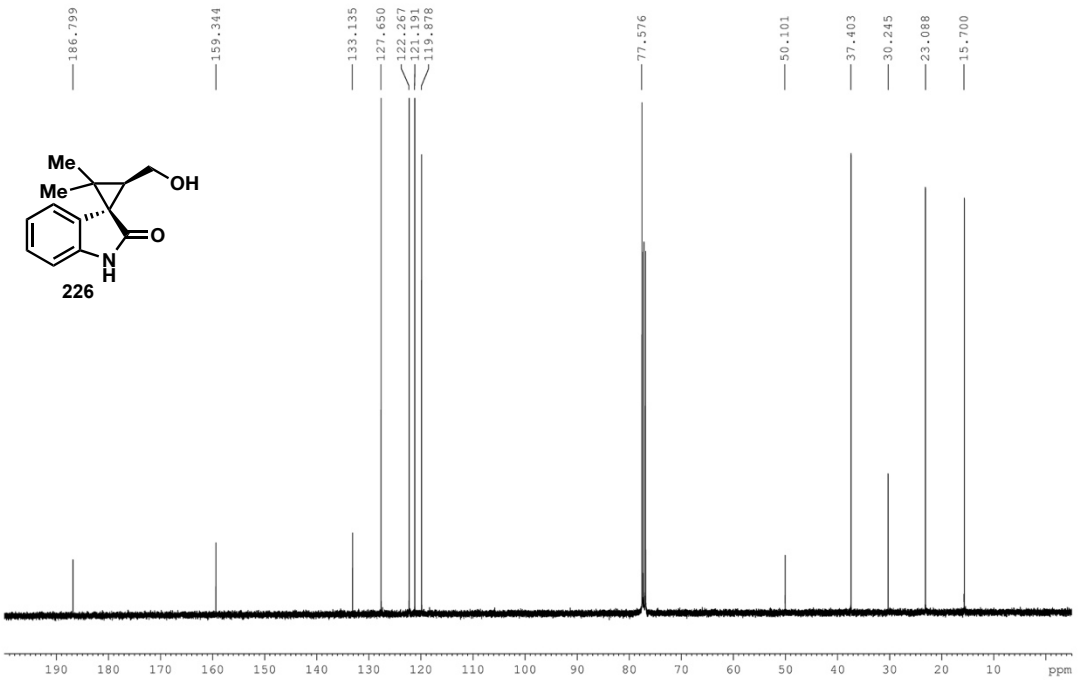


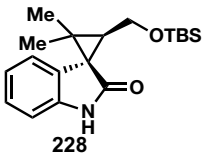


ID	Shift [ppm]	J [Hz]	M	Connection
1	7.3615	7.0023	2	J(1, 0)
		7.0023	2	J(1, 0)
2	7.2389	7.8425	2	J(2, 0)
3	7.1516	8.3627	2	J(3, 0)
		8.3627	2	J(3, 0)
4	4.6676	5.1217	2	J(4, 0)
		9.5631	2	J(4, 0)
5	4.2724	10.1633	2	J(5, 0)
6	2.2933	5.1217	2	J(6, 0)



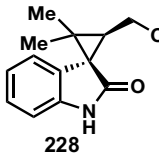

7.423
7.404
7.308
7.305
7.289
7.286
7.269
7.266
7.170
7.169
7.152
7.150
7.049
7.047
7.031
7.028
7.012
7.008
4.936
4.924
4.912
4.899
4.811
4.809
4.787
4.784
2.668
2.666
2.656
2.653
1.484
1.329
Me
Me
OH
O
N
H
226
ID Shift [ppm] J [Hz] M Connection
1 7.4132 7.8425 2 J(1, 0)
2 7.1602 0.6602 2 J(2, 0)
7.5024 2 J(2, 0)
3 7.0292 1.0403 2 J(3, 0)
7.6025 2 J(3, 0)
7.6025 2 J(3, 0)
4 4.9179 4.8216 2 J(4, 0)
9.9032 2 J(4, 0)
5 4.7979 1.0603 2 J(5, 0)
9.8632 2 J(5, 0)
6 2.6608 0.8403 2 J(6, 0)
4.9216 2 J(6, 0)
0.975
1.024
1.058
1.063
1.033
1.054
1.000
3.163
3.058
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm


186.799
159.344
133.135
127.650
122.267
121.191
119.878
77.576
50.101
37.403
30.245
23.088
15.700
Me
Me
OH
O
N
H
226
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

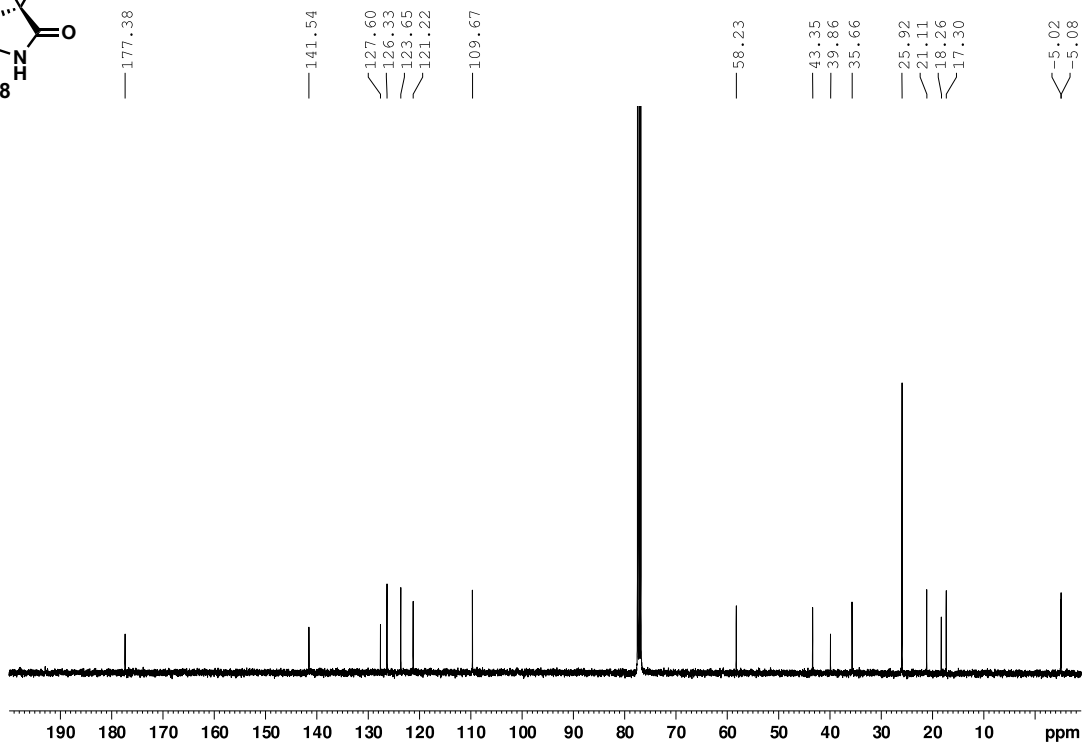


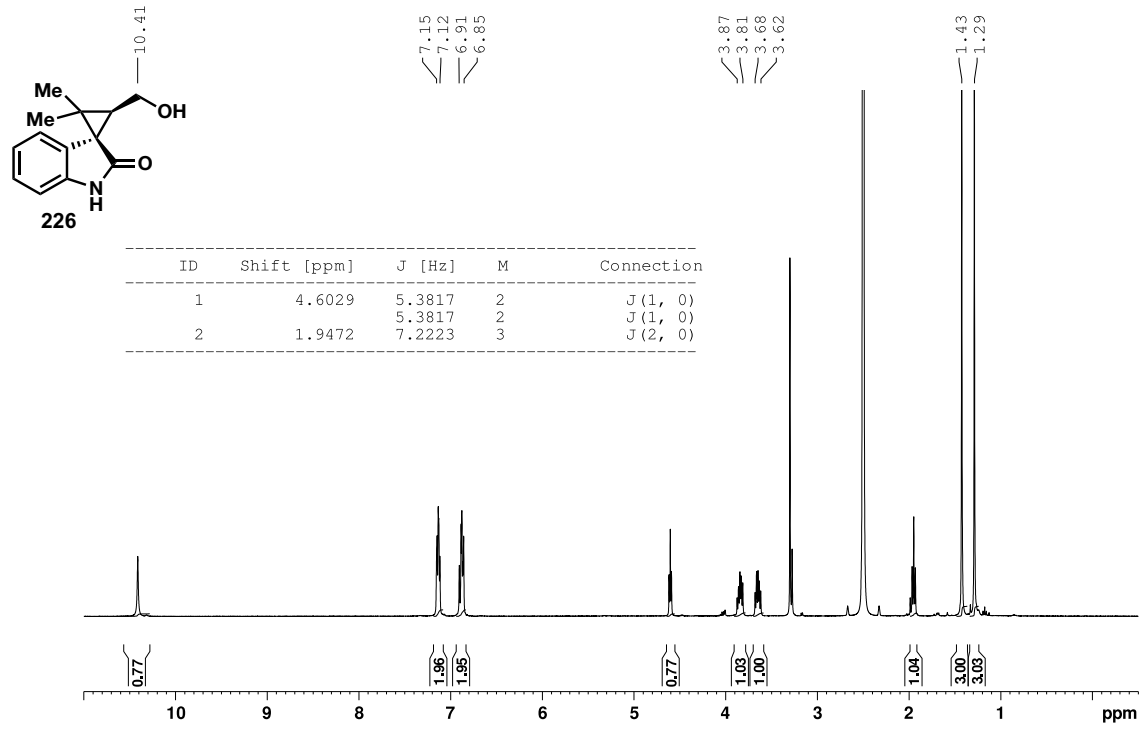
228

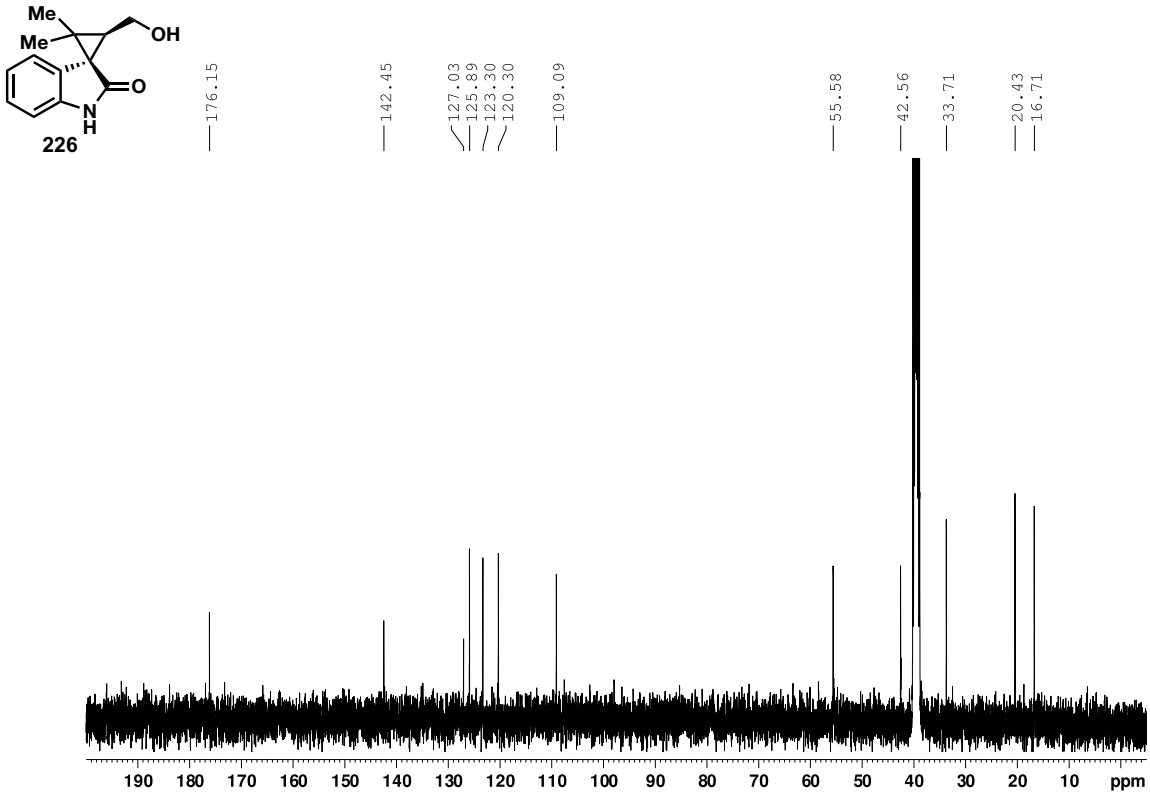
ID	Shift [ppm]	J [Hz]	M	Connection
1	7.1769	0.7202	2	J(1, 0)
		7.6425	2	J(1, 0)
		7.5024	2	J(1, 0)
2	7.0451	7.4024	2	J(2, 0)
3	6.9637	7.6625	2	J(3, 0)
		7.6625	2	J(3, 0)
4	6.9247	7.6825	2	J(4, 0)
5	4.0308	8.3427	2	J(5, 0)
		11.5037	2	J(5, 0)
6	3.9021	6.3421	2	J(6, 0)
		11.5037	2	J(6, 0)
7	2.2528	8.0026	2	J(7, 0)
		6.5221	2	J(7, 0)

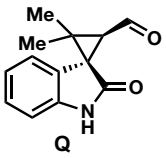


228




10.41
7.15
7.12
6.91
6.85
3.87
3.81
3.68
3.62
1.43
1.29
Me
Me
OH
O
N
H
226
ID Shift [ppm] J [Hz] M Connection
1 4.6029 5.3817 2 J(1, 0)
5.3817 2 J(1, 0)
2 1.9472 7.2223 3 J(2, 0)
0.77
1.96
1.95
0.77
1.03
1.00
1.04
3.00
3.03
10 9 8 7 6 5 4 3 2 1 ppm

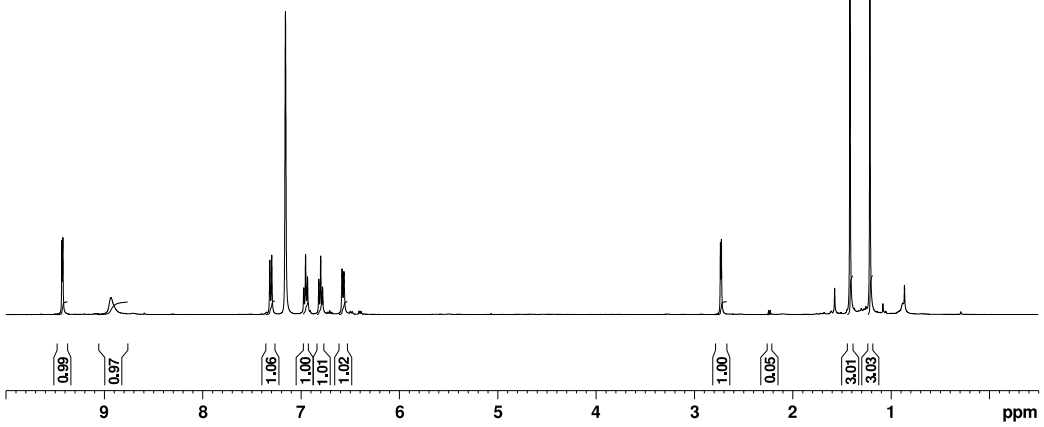

Me
Me
OH
O
N
H
226
176.15
142.45
127.03
125.89
123.30
120.30
109.09
55.58
42.56
33.71
20.43
16.71
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

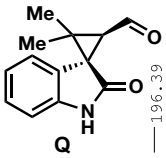


8.93

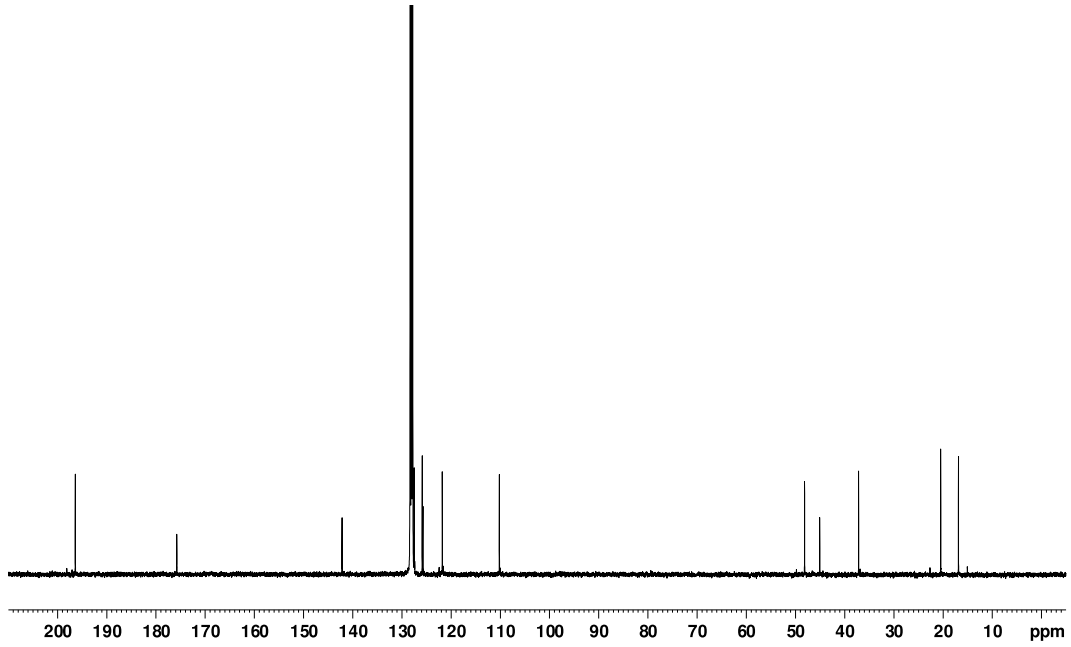
1.42
1.21

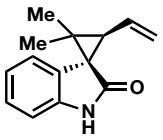
ID	Shift [ppm]	J [Hz]	M	Connection
1	9.4262	4.0155	2	J(1, 0)
2	7.3069	7.5290	2	J(2, 0)
3	6.9527	7.5917	2	J(3, 0)
		7.5917	2	J(3, 0)
4	6.7991	7.5917	2	J(4, 0)
		7.5917	2	J(4, 0)
5	6.5723	7.6545	2	J(5, 0)
6	2.7295	4.0155	2	J(6, 0)





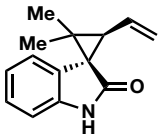
196.39
175.77
142.17
127.48
125.86
125.72
121.78
110.18
48.13
45.06
37.16
20.47
16.86



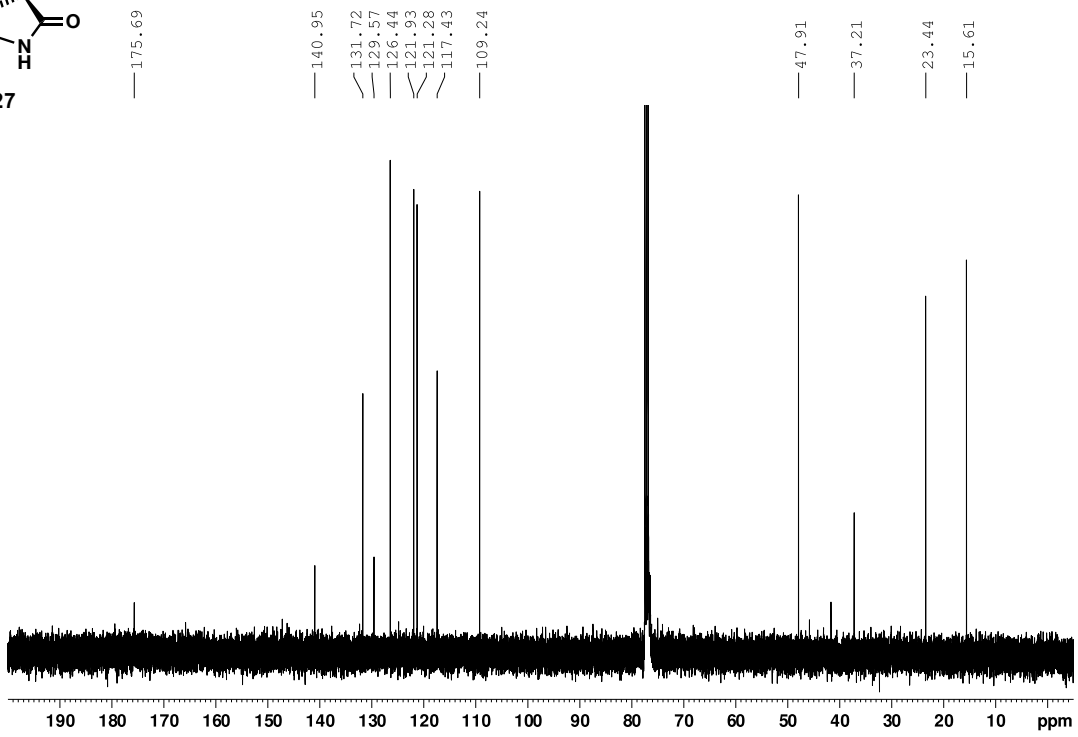


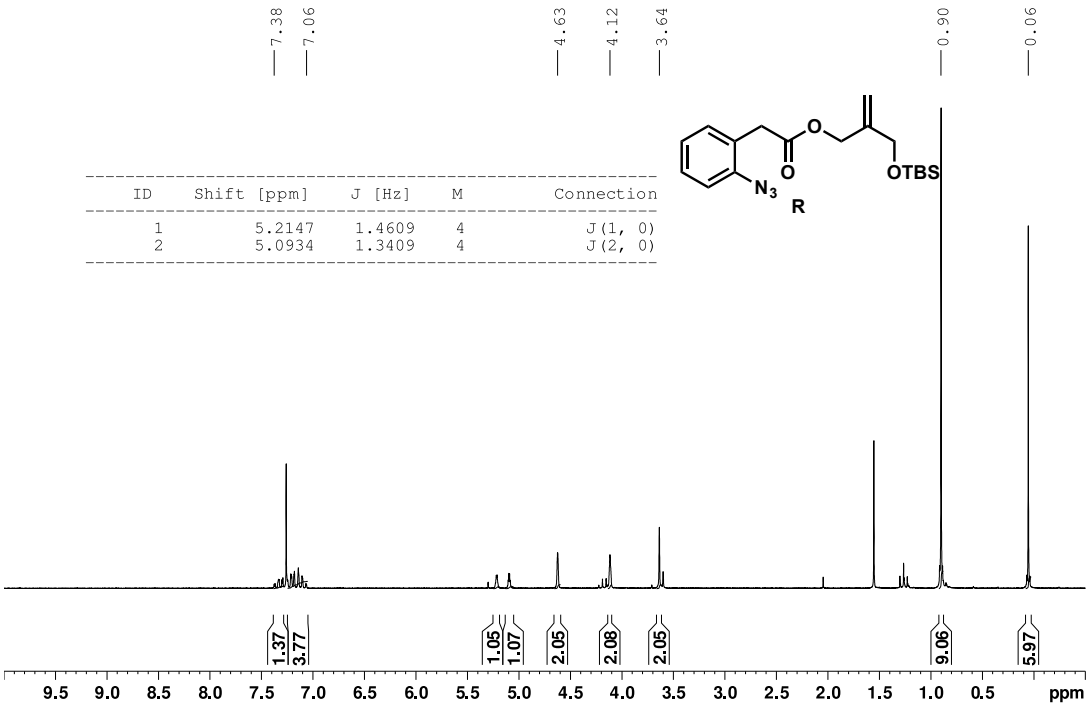
227

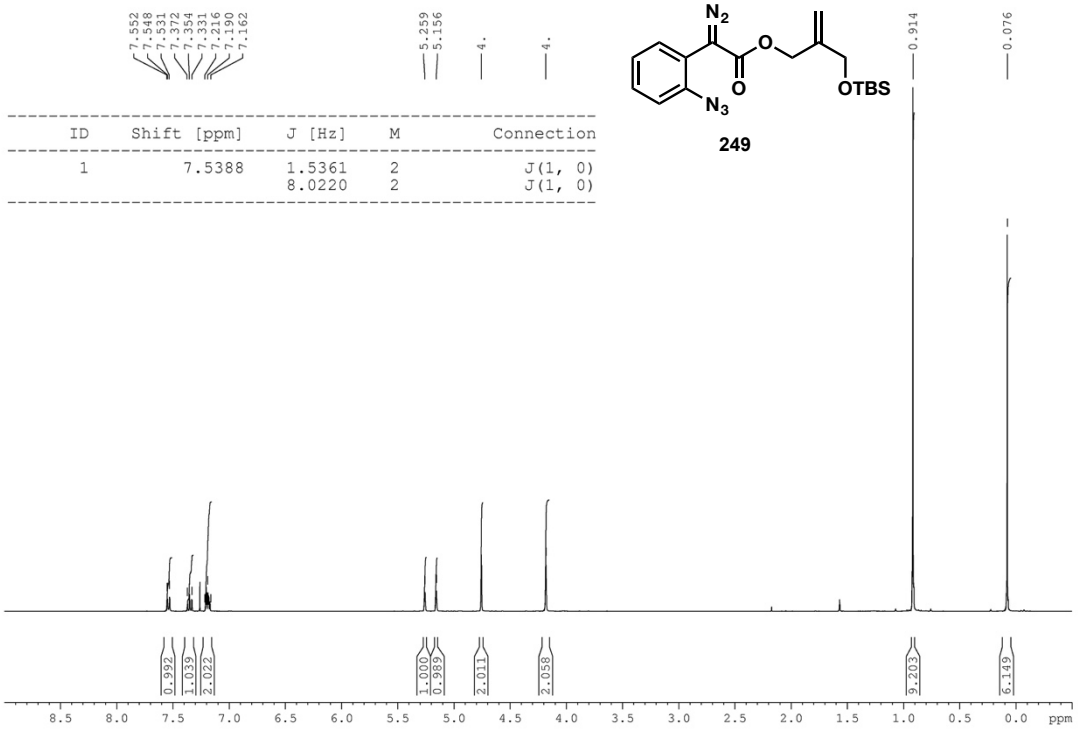
ID	Shift [ppm]	J [Hz]	M	Connection
1	7.1758	1.7206	2	J(1, 0)
		7.3424	2	J(1, 0)
		7.3424	2	J(1, 0)
2	7.0297	1.7006	2	J(2, 0)
		7.5024	2	J(2, 0)
3	6.9928	1.0303	2	J(3, 0)
		7.3324	2	J(3, 0)
		7.3324	2	J(3, 0)
4	6.8885	7.5224	2	J(4, 0)
5	6.4880	9.9032	2	J(5, 0)
		9.9032	2	J(5, 0)
6	6.4444	9.5631	2	J(6, 0)
		10.5634	2	J(6, 0)
7	5.2238	1.5205	2	J(7, 0)
		17.2456	2	J(7, 0)
8	5.1502	1.7206	2	J(8, 0)
		10.2433	2	J(8, 0)
9	2.4616	9.5631	2	J(9, 0)

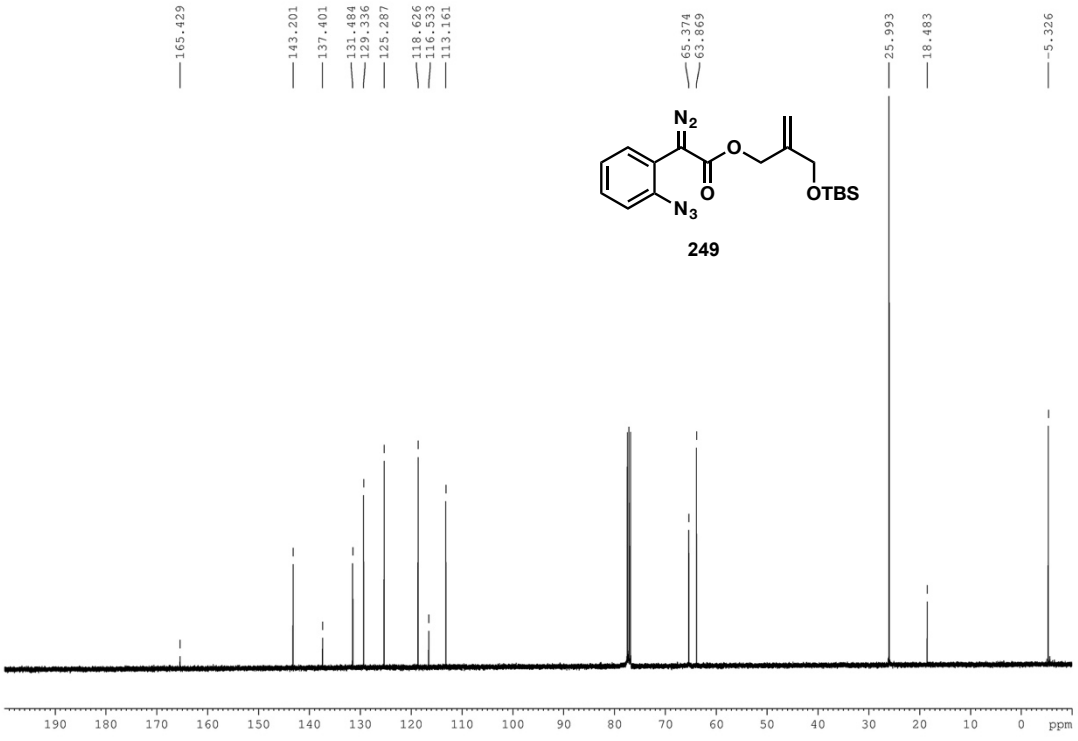


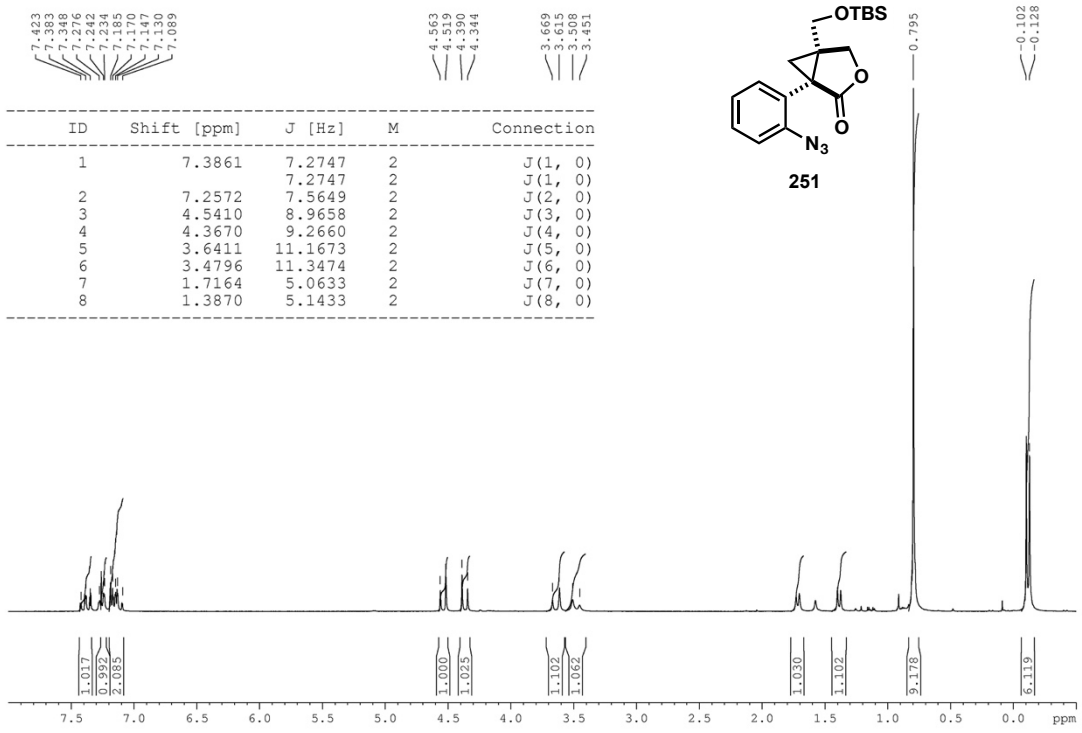
227



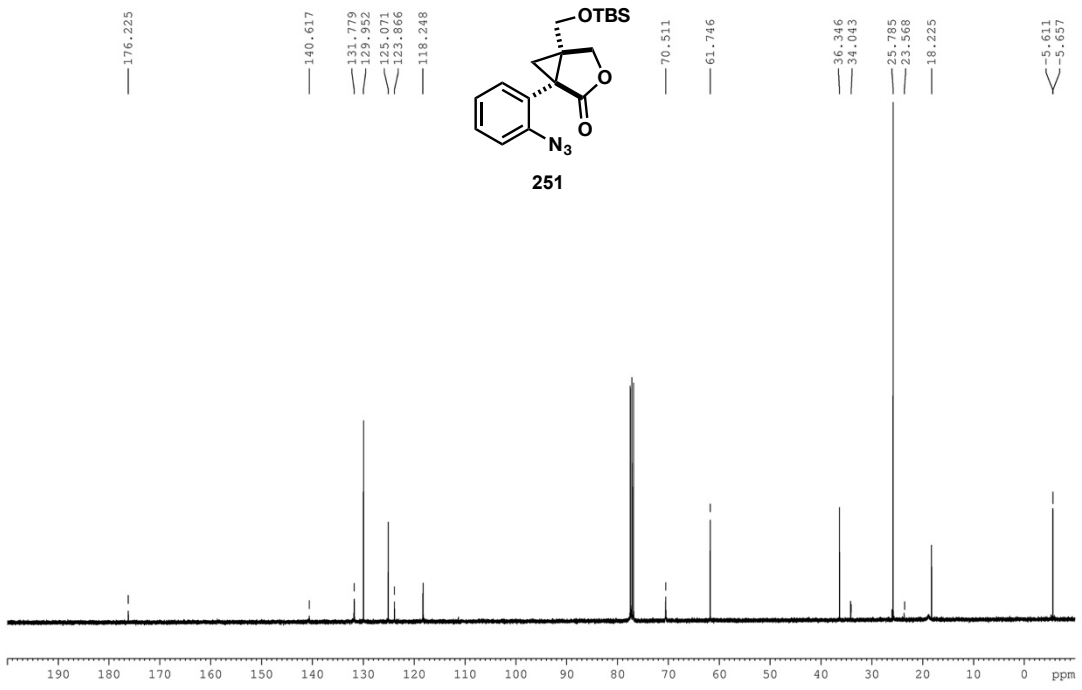

7.38
7.06
4.63
4.12
3.64
0.90
0.06
O
O
OTBS
N3
R
ID Shift [ppm] J [Hz] M Connection
1 5.2147 1.4609 4 J(1, 0)
2 5.0934 1.3409 4 J(2, 0)
1.37
3.77
1.05
1.07
2.05
2.08
2.05
9.06
5.97
ppm

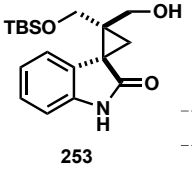

7.552
7.548
7.531
7.372
7.354
7.331
7.216
7.190
7.162
5.259
5.156
4.
4.
N2
O
O
OTBS
N3
249
0.914
0.076
ID Shift [ppm] J [Hz] M Connection
1 7.5388 1.5361 2 J(1, 0)
8.0220 2 J(1, 0)
0.992
1.039
2.022
1.000
0.989
2.011
2.058
9.203
6.149
ppm


165.429
143.201
137.401
131.484
129.336
125.287
118.626
116.533
113.161
65.374
63.869
25.993
18.483
-5.326
N2
O
O
N3
OTBS
249
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm



ID	Shift [ppm]	J [Hz]	M	Connection
1	7.3861	7.2747	2	J(1, 0)
		7.2747	2	J(1, 0)
2	7.2572	7.5649	2	J(2, 0)
3	4.5410	8.9658	2	J(3, 0)
4	4.3670	9.2660	2	J(4, 0)
5	3.6411	11.1673	2	J(5, 0)
6	3.4796	11.3474	2	J(6, 0)
7	1.7164	5.0633	2	J(7, 0)
8	1.3870	5.1433	2	J(8, 0)





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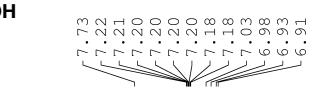
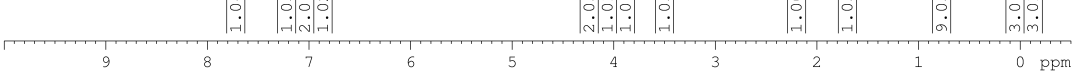
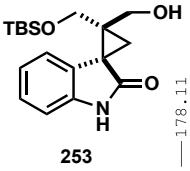
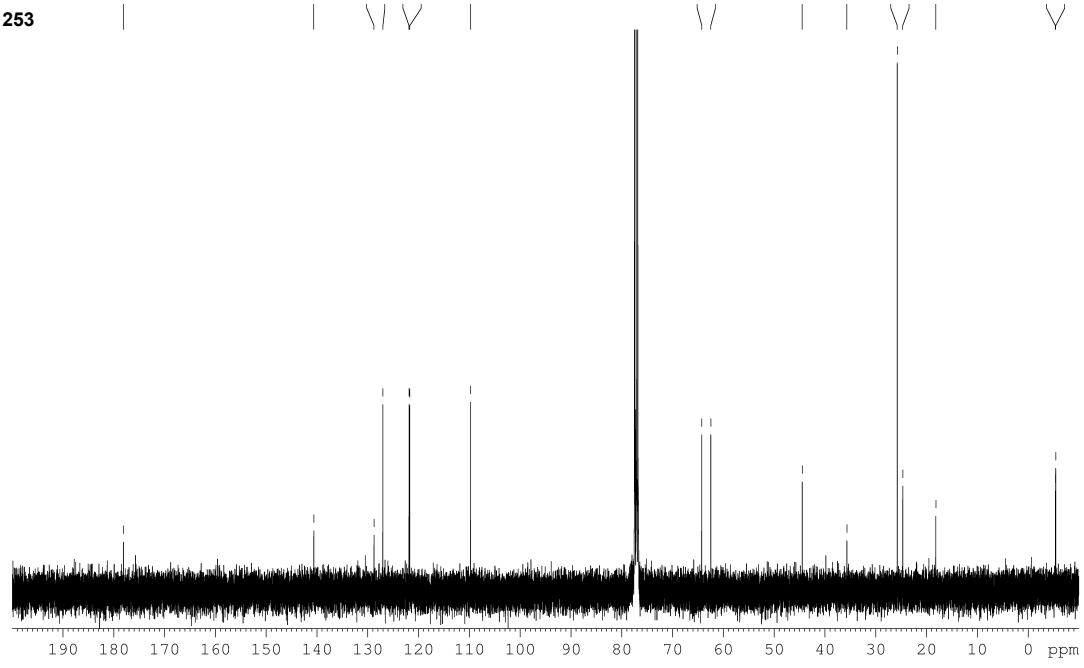


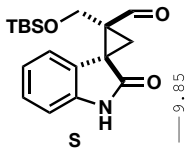
ID	Shift [ppm]	J [Hz]	M	Connection
1	7.1998	2.3908	2	J(1, 0)
		6.4521	2	J(1, 0)
		7.8526	2	J(1, 0)
2	6.9174	7.8425	2	J(2, 0)
3	4.0642	10.9235	2	J(3, 0)
4	3.9208	10.9235	2	J(4, 0)
5	2.1971	5.1217	2	J(5, 0)
6	1.6989	5.1217	2	J(6, 0)





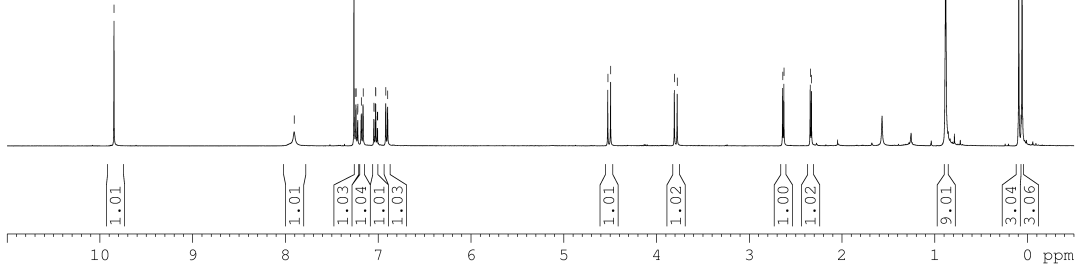
253

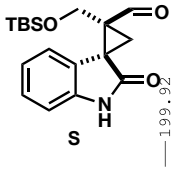




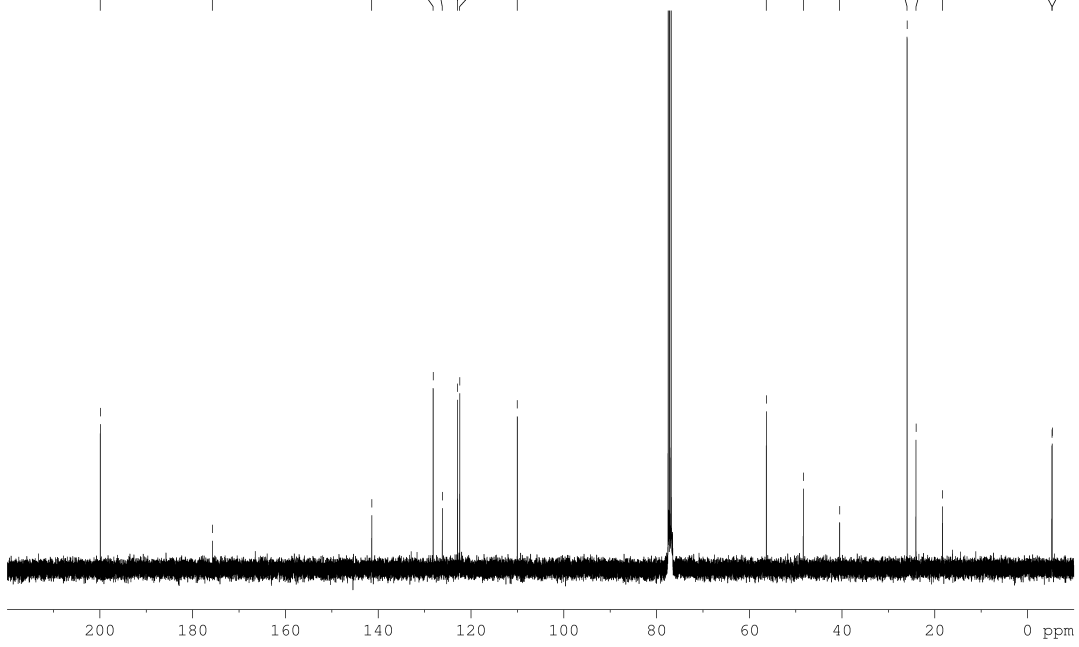
9.85 | 7.90 7.26 7.24 7.24 7.22 7.22 7.18 7.16 7.05 7.04 7.03 7.03 7.01 7.01 6.92 6.90 | 4.52 4.49 | 3.81 3.78 | 2.64 2.63 2.34 2.33 | 0.88 | 0.09 0.06

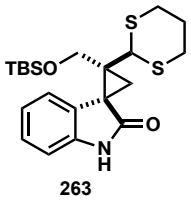
ID	Shift [ppm]	J [Hz]	M	Connection
1	7.1722	7.5224	2	J(1, 0)
2	7.0266	1.0603	2	J(2, 0)
		7.5024	2	J(2, 0)
		7.5024	2	J(2, 0)
3	6.9076	7.5224	2	J(3, 0)
4	4.5091	11.9153	2	J(4, 0)
5	3.7916	11.9239	2	J(5, 0)
6	2.6326	5.4618	2	J(6, 0)
7	2.3349	5.4618	2	J(7, 0)





199.92 | 175.74 | 141.38 | 128.16 126.17 122.89 122.41 | 110.02 | 56.30 | 48.33 | 40.51 | 25.97 24.05 | 18.33 | -5.26 -5.33





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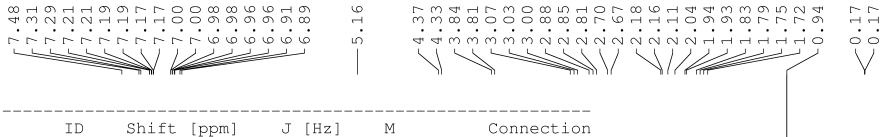
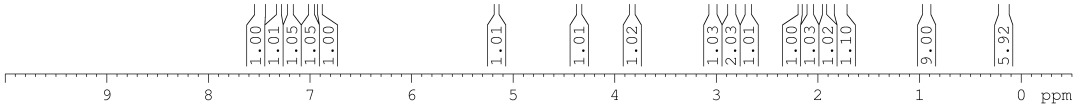
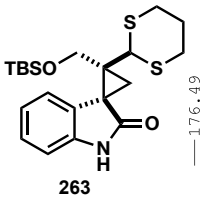


ID	Shift [ppm]	J [Hz]	M	Connection
1	7.3045	7.6825	2	J(1, 0)
2	7.1908	1.0403	2	J(2, 0)
		7.6825	2	J(2, 0)
		7.6825	2	J(2, 0)
3	6.9820	1.0203	2	J(3, 0)
		7.6825	2	J(3, 0)
		7.6825	2	J(3, 0)
4	6.9008	7.6825	2	J(4, 0)
5	4.3500	12.2840	2	J(5, 0)
6	3.8270	12.2840	2	J(6, 0)
7	2.1715	5.1217	2	J(7, 0)
8	1.9335	5.1217	2	J(8, 0)





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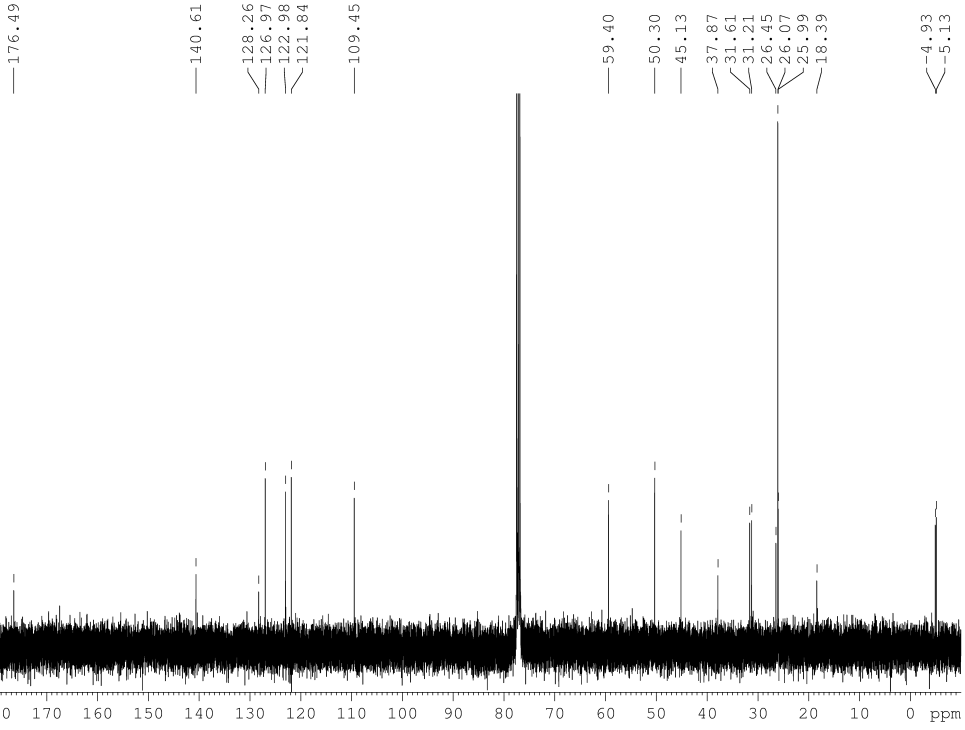
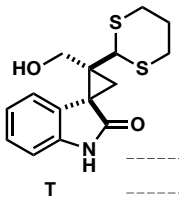


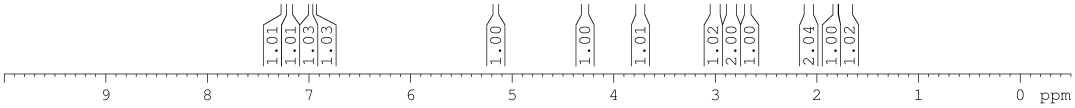


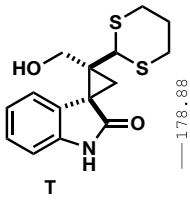
T

7.25 7.23 7.21 7.21 7.19 7.19 7.17 7.17 7.00 6.99 6.98 6.98 6.96 6.94

5.16 4.30 4.26 3.75 3.72 3.04 3.03 3.01 3.00 3.00 2.97 2.97 2.89 2.83 2.79 2.70 2.66 2.12 2.10 2.09 2.05 1.82 1.81 1.77 1.74 1.70 1.67

ID	Shift [ppm]	J [Hz]	M	Connection
1	7.2438	7.4824	2	J(1, 0)
2	7.1927	1.2604	2	J(2, 0)
		7.7625	2	J(2, 0)
		7.7625	2	J(2, 0)
3	6.9772	0.9603	2	J(3, 0)
		7.4424	2	J(3, 0)
		7.4424	2	J(3, 0)
4	6.9516	7.8826	2	J(4, 0)
5	4.2796	12.6841	2	J(5, 0)
6	3.7361	12.6441	2	J(6, 0)
7	3.0025	2.3678	2	J(7, 0)
		12.5971	2	J(7, 0)
		14.0376	2	J(7, 0)
8	2.0947	5.0416	2	J(8, 0)
9	1.8166	5.1204	2	J(9, 0)





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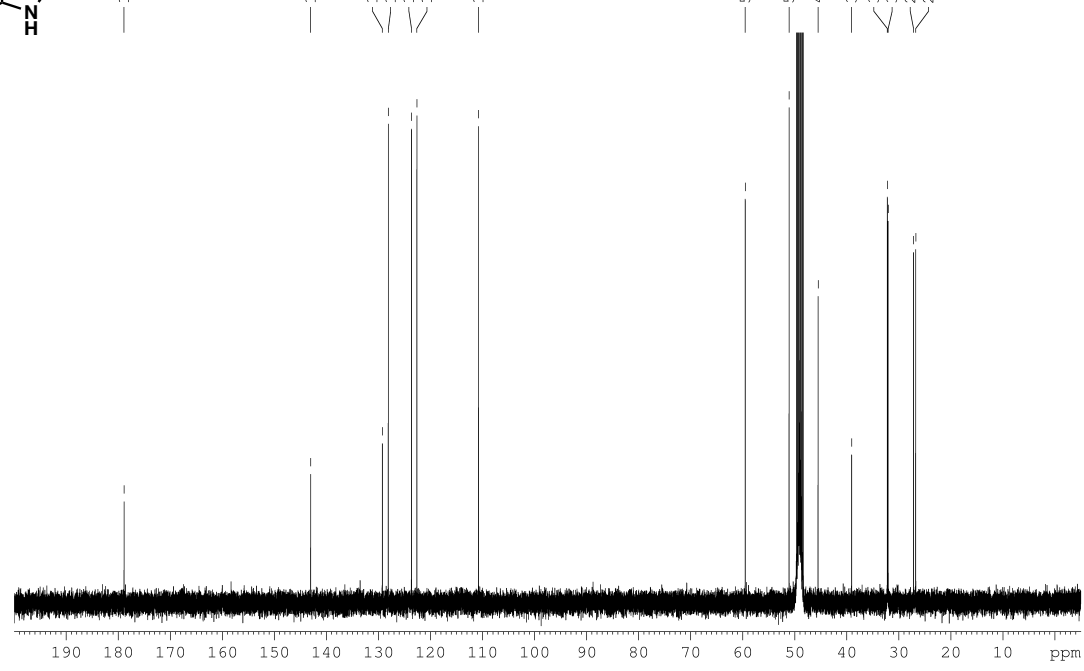
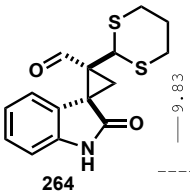
178.88 143.01 129.24 128.09 123.64 122.61 110.76 59.51 51.07 45.50 39.05 32.20 32.04 27.15 26.74





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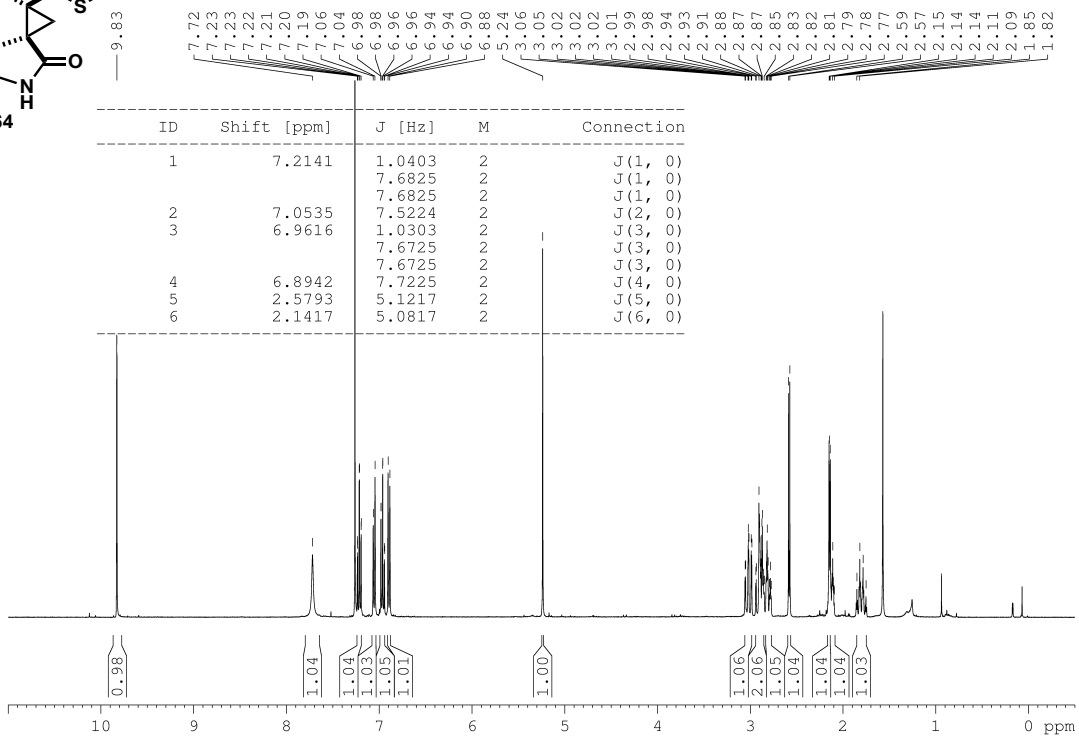
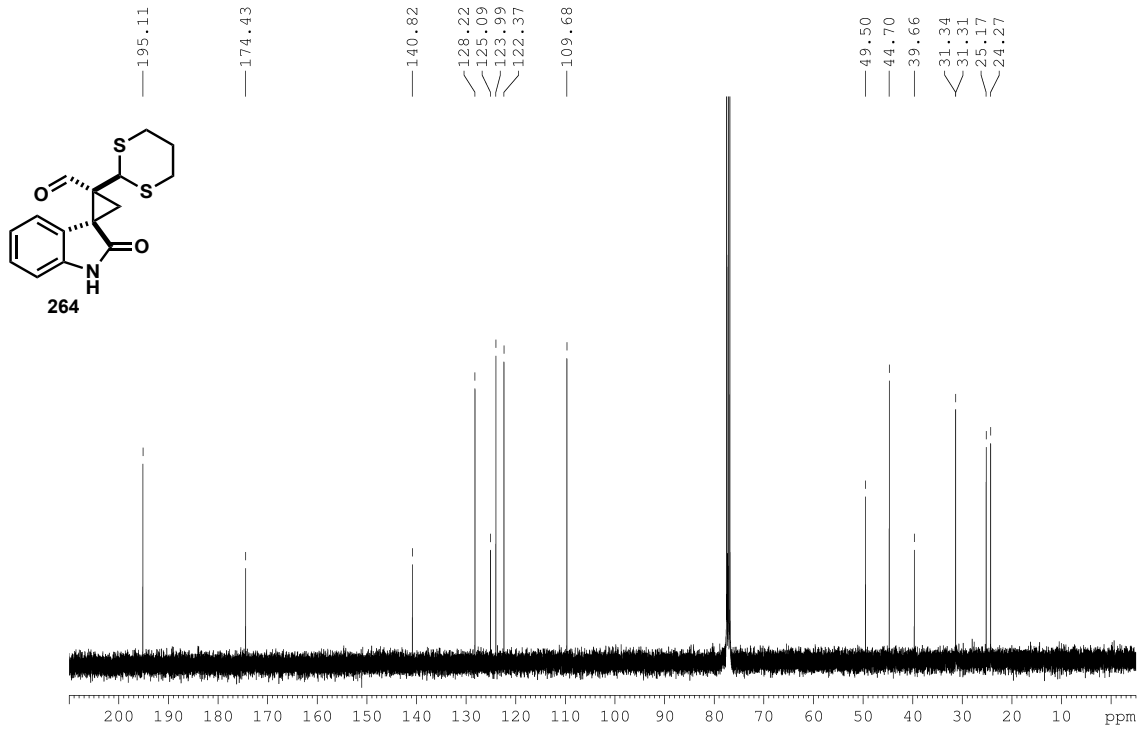


ID	Shift [ppm]	J [Hz]	M	Connection
1	7.2141	1.0403	2	J(1, 0)
		7.6825	2	J(1, 0)
		7.6825	2	J(1, 0)
2	7.0535	7.5224	2	J(2, 0)
3	6.9616	1.0303	2	J(3, 0)
		7.6725	2	J(3, 0)
		7.6725	2	J(3, 0)
4	6.8942	7.7225	2	J(4, 0)
5	2.5793	5.1217	2	J(5, 0)
6	2.1417	5.0817	2	J(6, 0)



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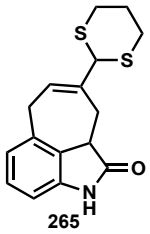

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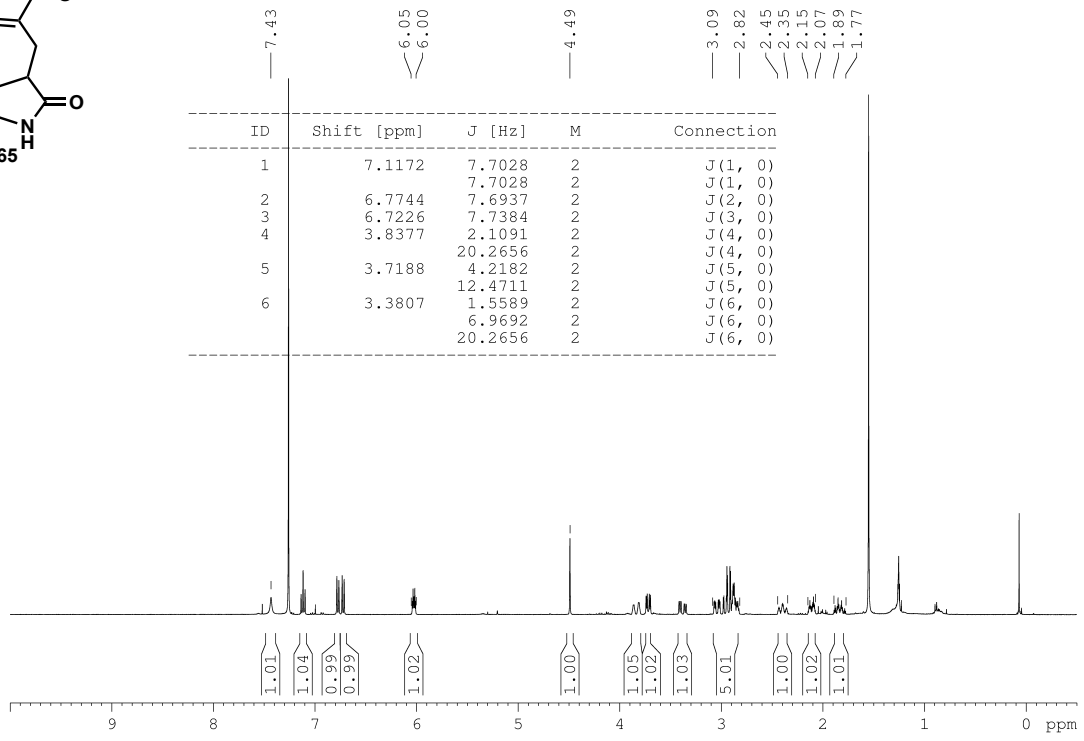
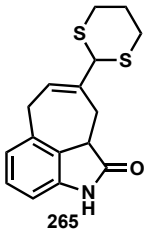
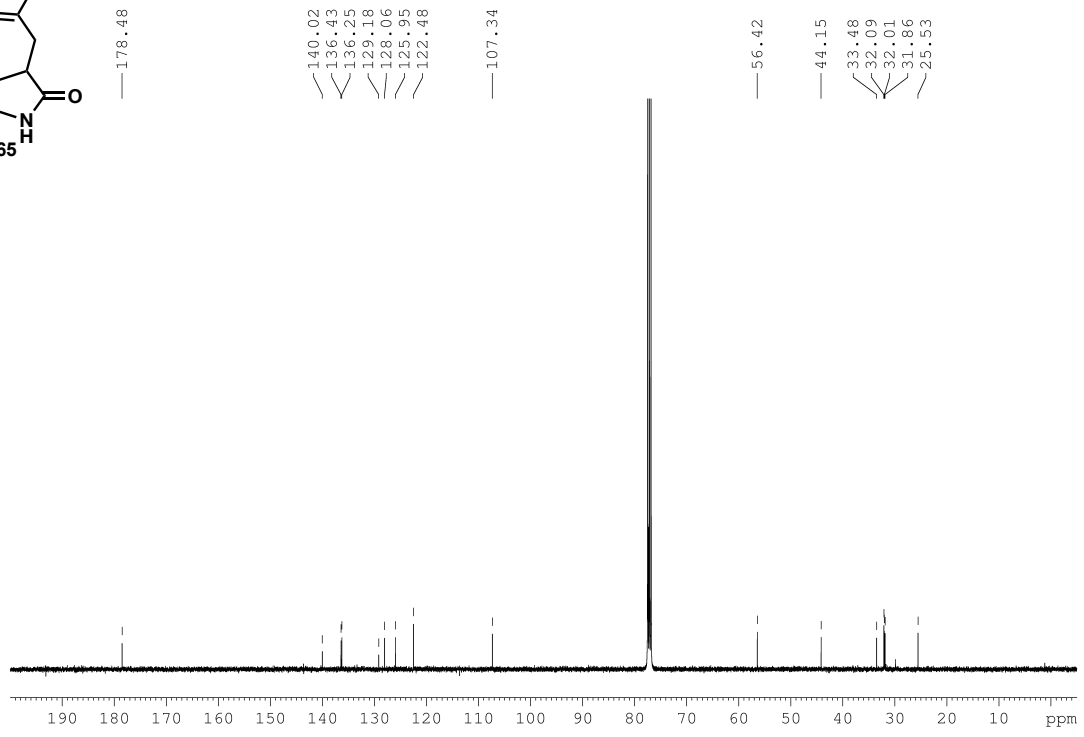
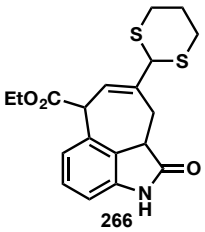


ID	Shift [ppm]	J [Hz]	M	Connection
1	7.1172	7.7028	2	J(1, 0)
		7.7028	2	J(1, 0)
2	6.7744	7.6937	2	J(2, 0)
3	6.7226	7.7384	2	J(3, 0)
4	3.8377	2.1091	2	J(4, 0)
		20.2656	2	J(4, 0)
5	3.7188	4.2182	2	J(5, 0)
		12.4711	2	J(5, 0)
6	3.3807	1.5589	2	J(6, 0)
		6.9692	2	J(6, 0)
		20.2656	2	J(6, 0)



265




S
S
EtO2C
O
N
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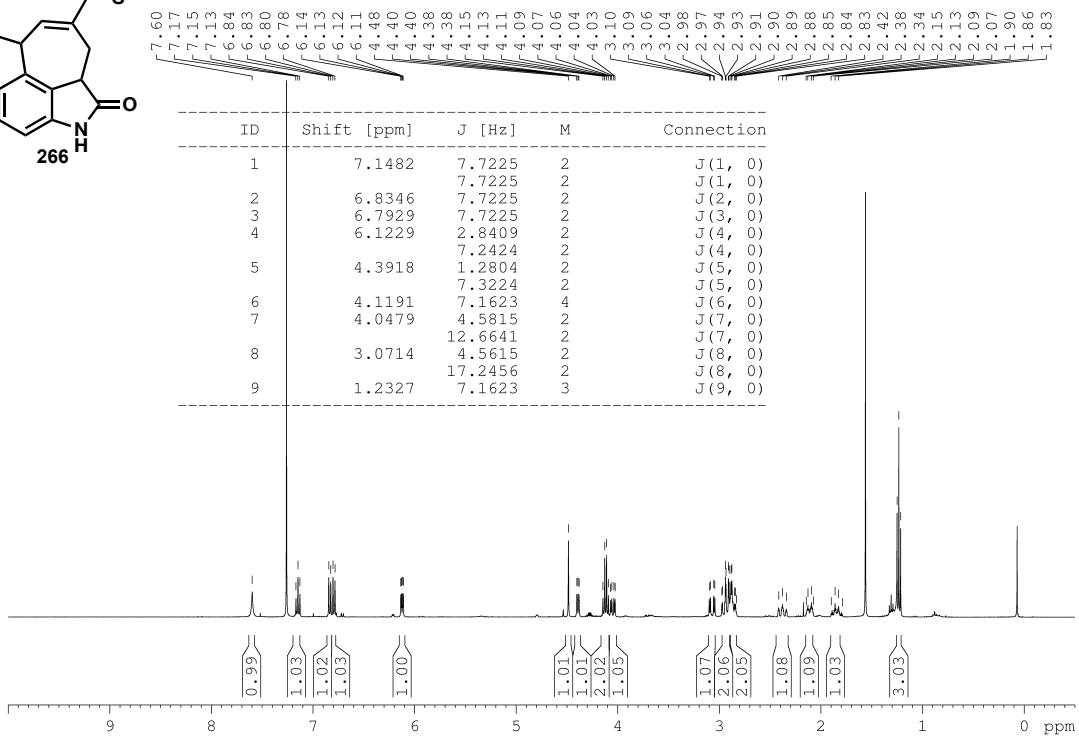
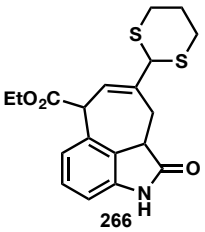
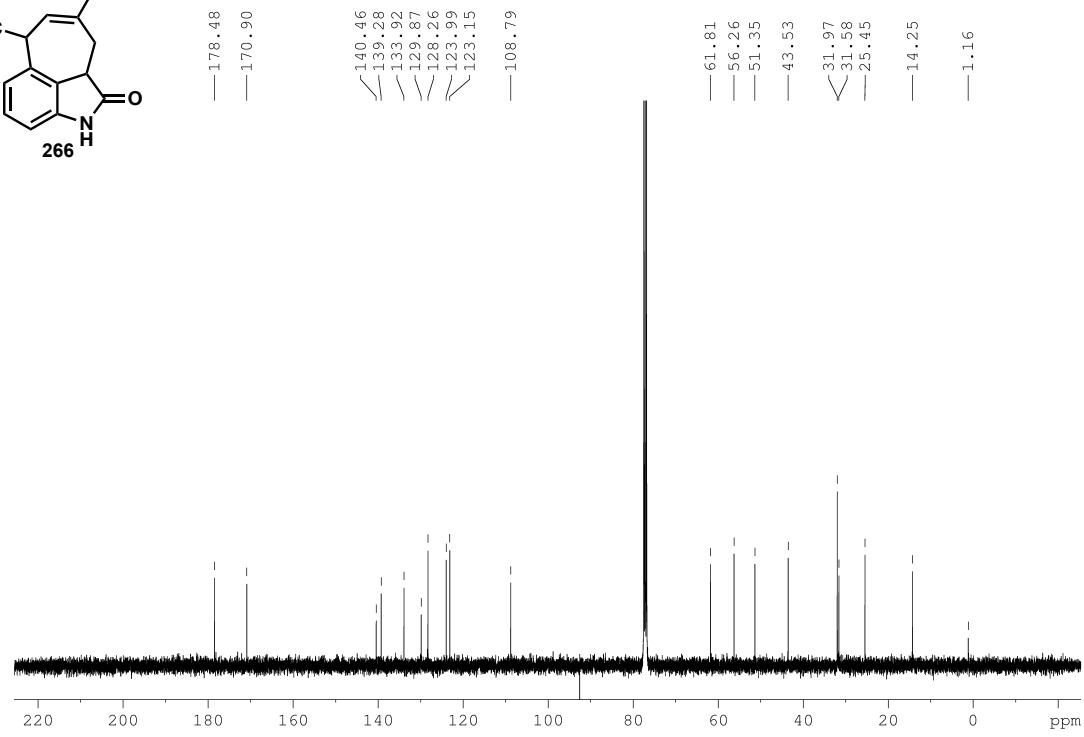
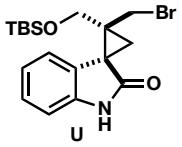
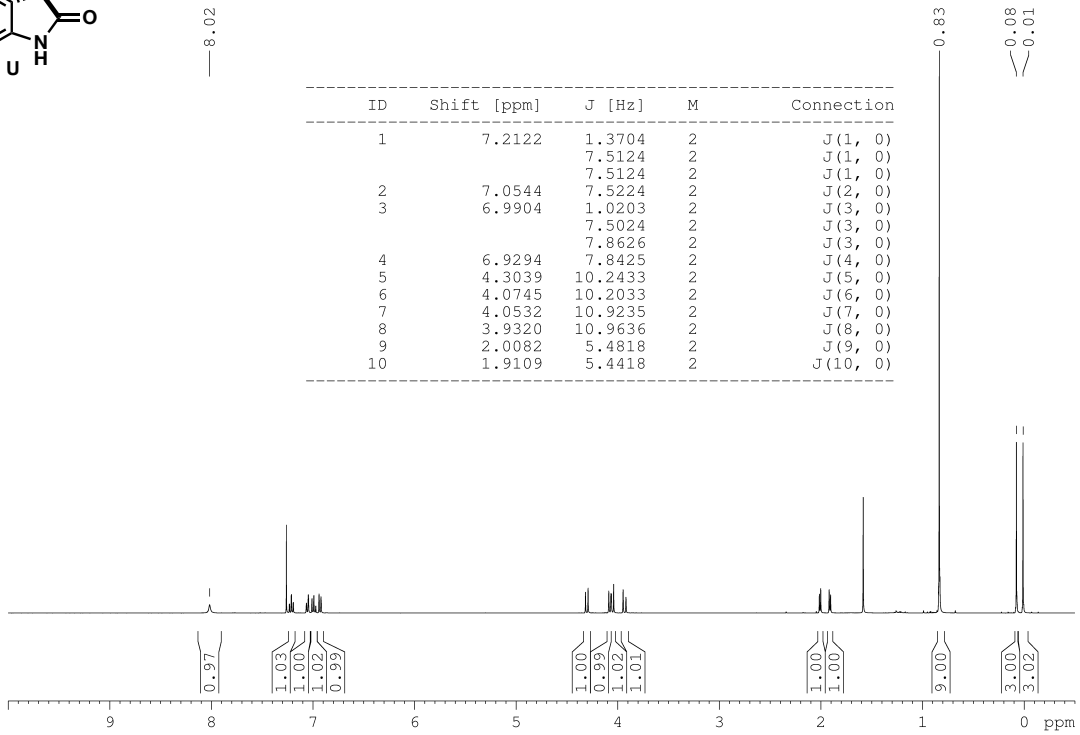
266


7.60 7.17 7.15 7.13 6.84 6.83 6.80 6.78 6.14 6.13 6.12 6.11 4.48 4.40 4.40 4.38 4.38 4.15 4.13 4.11 4.09 4.07 4.06 4.04 4.03 3.10 3.09 3.06 3.04 2.98 2.97 2.94 2.93 2.91 2.90 2.89 2.88 2.85 2.84 2.83 2.42 2.38 2.34 2.15 2.13 2.09 2.07 1.90 1.86 1.83
ID | Shift [ppm] | J [Hz] | M | Connection
1 | 7.1482 | 7.7225 | 2 | J(1, 0)
7.7225 | 2 | J(1, 0)
2 | 6.8346 | 7.7225 | 2 | J(2, 0)
3 | 6.7929 | 7.7225 | 2 | J(3, 0)
4 | 6.1229 | 2.8409 | 2 | J(4, 0)
7.2424 | 2 | J(4, 0)
5 | 4.3918 | 1.2804 | 2 | J(5, 0)
7.3224 | 2 | J(5, 0)
6 | 4.1191 | 7.1623 | 4 | J(6, 0)
7 | 4.0479 | 4.5815 | 2 | J(7, 0)
12.6641 | 2 | J(7, 0)
8 | 3.0714 | 4.5615 | 2 | J(8, 0)
17.2456 | 2 | J(8, 0)
9 | 1.2327 | 7.1623 | 3 | J(9, 0)
0.99 1.03 1.02 1.03 1.00 1.01 1.01 2.02 1.05 1.07 2.06 2.05 1.08 1.09 1.03 3.03
9 8 7 6 5 4 3 2 1 0 ppm

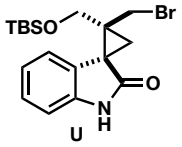

S
S
EtO2C
O
N
H
266

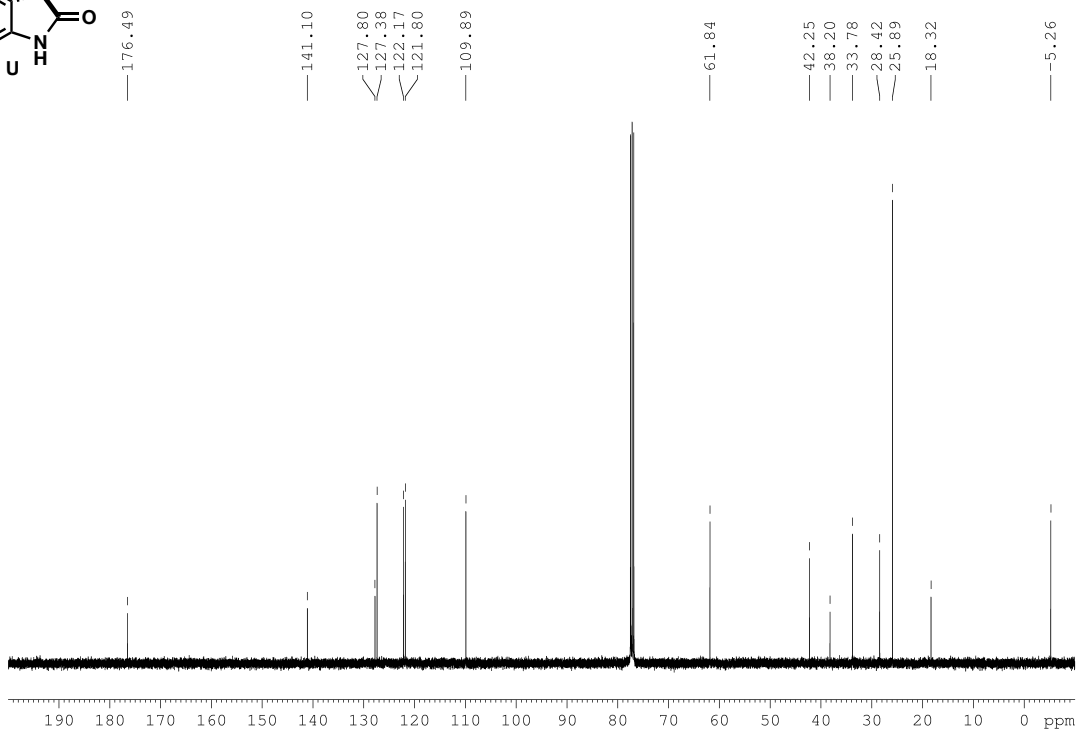

178.48 170.90 140.46 139.28 133.92 129.87 128.26 123.99 123.15 108.79 61.81 56.26 51.35 43.53 31.97 31.58 25.45 14.25 1.16
220 200 180 160 140 120 100 80 60 40 20 0 ppm

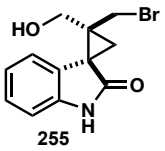




ID	Shift [ppm]	J [Hz]	M	Connection
1	7.2122	1.3704	2	J(1, 0)
		7.5124	2	J(1, 0)
		7.5124	2	J(1, 0)
2	7.0544	7.5224	2	J(2, 0)
3	6.9904	1.0203	2	J(3, 0)
		7.5024	2	J(3, 0)
		7.8626	2	J(3, 0)
4	6.9294	7.8425	2	J(4, 0)
5	4.3039	10.2433	2	J(5, 0)
6	4.0745	10.2033	2	J(6, 0)
7	4.0532	10.9235	2	J(7, 0)
8	3.9320	10.9636	2	J(8, 0)
9	2.0082	5.4818	2	J(9, 0)
10	1.9109	5.4418	2	J(10, 0)

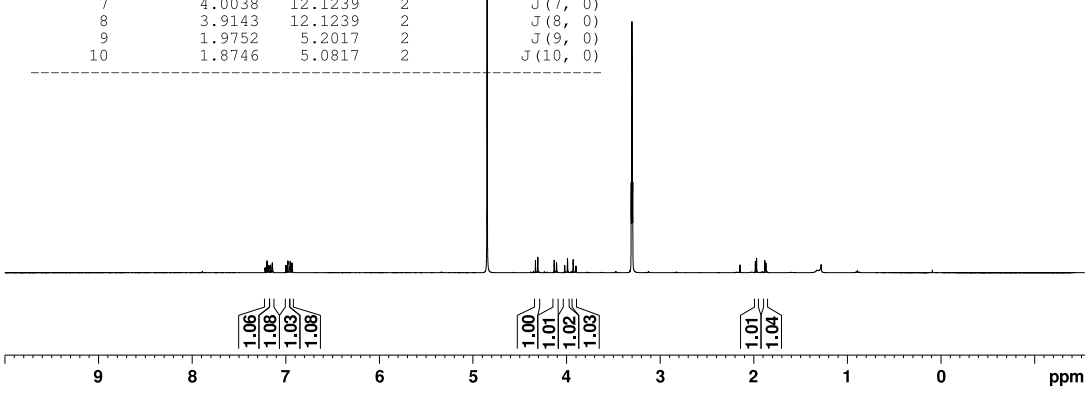


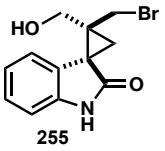




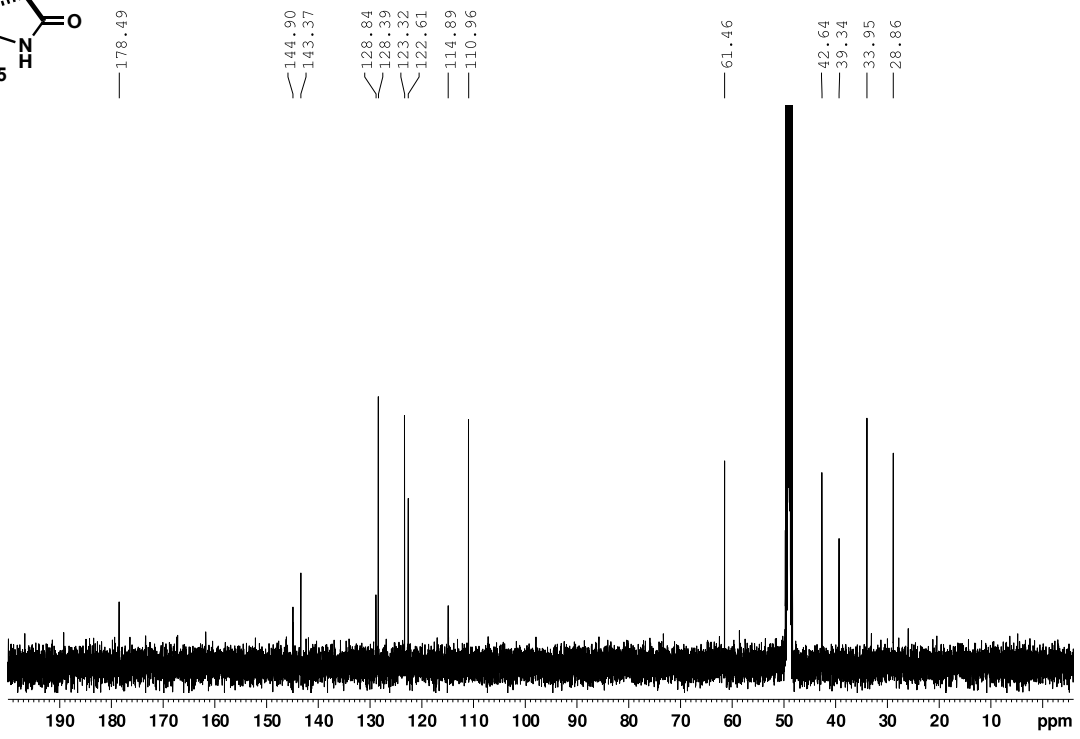
255

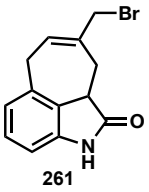
ID	Shift [ppm]	J [Hz]	M	Connection
1	7.2004	1.3304	2	J(1, 0)
		7.6925	2	J(1, 0)
		7.6925	2	J(1, 0)
2	7.1526	7.7625	2	J(2, 0)
3	6.9777	0.9703	2	J(3, 0)
		7.5725	2	J(3, 0)
		7.5725	2	J(3, 0)
4	6.9428	7.6825	2	J(4, 0)
5	4.3186	10.2833	2	J(5, 0)
6	4.1185	10.0833	2	J(6, 0)
7	4.0038	12.1239	2	J(7, 0)
8	3.9143	12.1239	2	J(8, 0)
9	1.9752	5.2017	2	J(9, 0)
10	1.8746	5.0817	2	J(10, 0)





255





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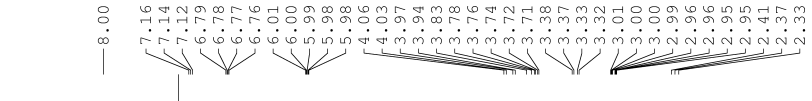
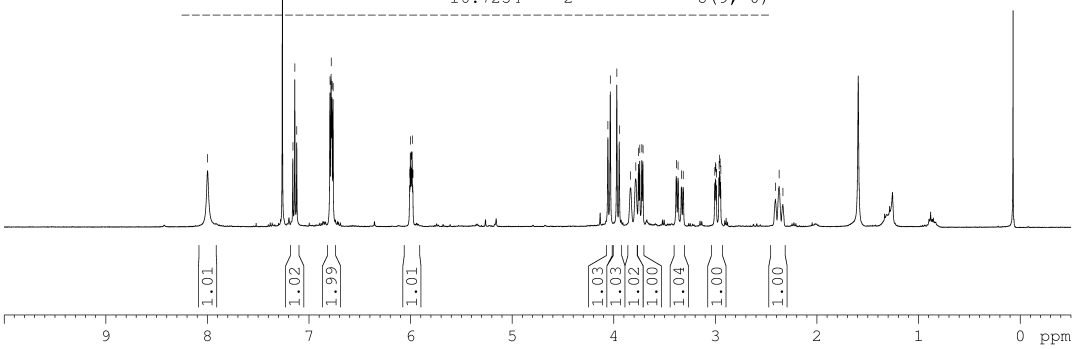
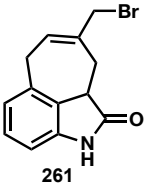


ID	Shift [ppm]	J [Hz]	M	Connection
1	7.1389	7.4824	2	J(1, 0)
		7.5224	2	J(1, 0)
2	6.7832	7.4824	2	J(2, 0)
3	6.7720	7.4824	2	J(3, 0)
4	4.0455	9.5231	2	J(4, 0)
5	3.9576	9.5631	2	J(5, 0)
6	3.8084	20.1265	2	J(6, 0)
7	3.7340	4.4614	2	J(7, 0)
		12.6641	2	J(7, 0)
8	3.3505	6.8622	2	J(8, 0)
		20.2666	2	J(8, 0)
9	2.9763	2.5608	2	J(9, 0)
		4.3614	2	J(9, 0)
		16.7254	2	J(9, 0)





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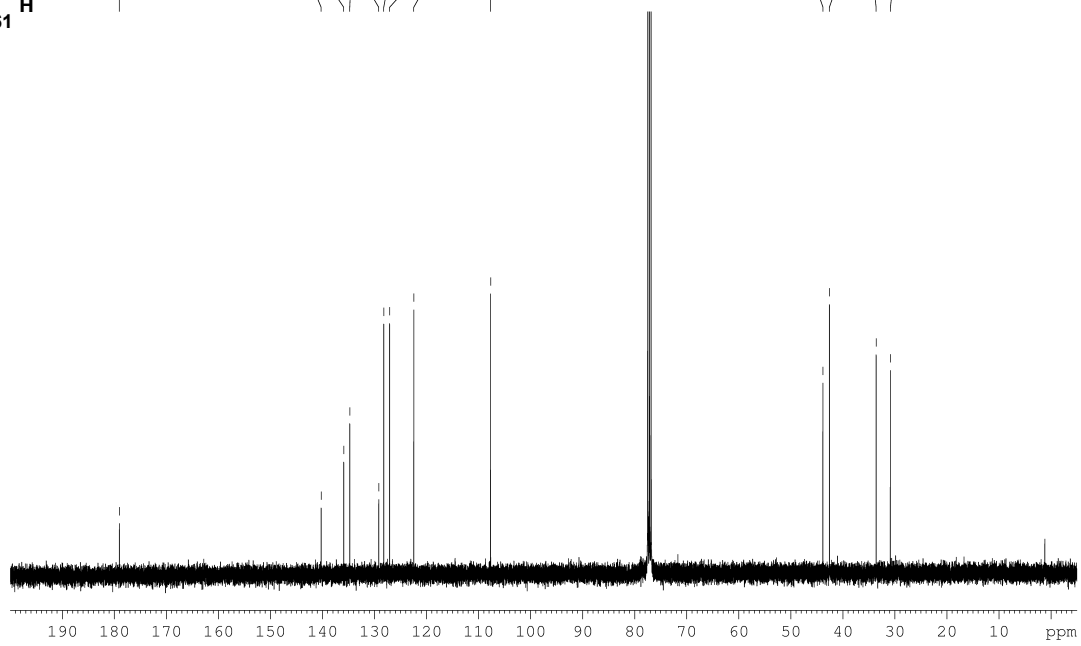

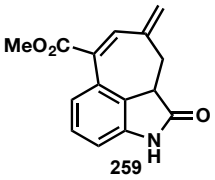

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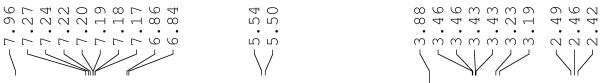
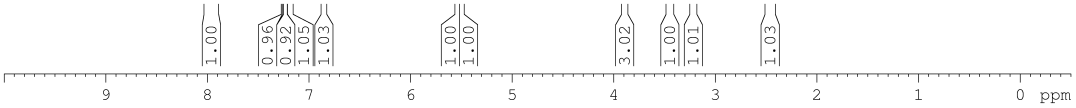
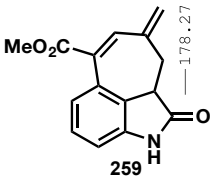


ID	Shift [ppm]	J [Hz]	M	Connection
1	7.2310	8.2027	2	J(1, 0)
2	7.1844	1.0603	2	J(2, 0)
		8.2227	2	J(2, 0)
3	6.8521	7.4424	2	J(3, 0)
4	5.5170	14.3647	2	J(4, 0)
5	3.4448	2.4008	2	J(5, 0)
		12.6441	2	J(5, 0)
6	3.2114	14.6848	2	J(6, 0)
7	2.4574	12.9642	2	J(7, 0)
		14.6848	2	J(7, 0)





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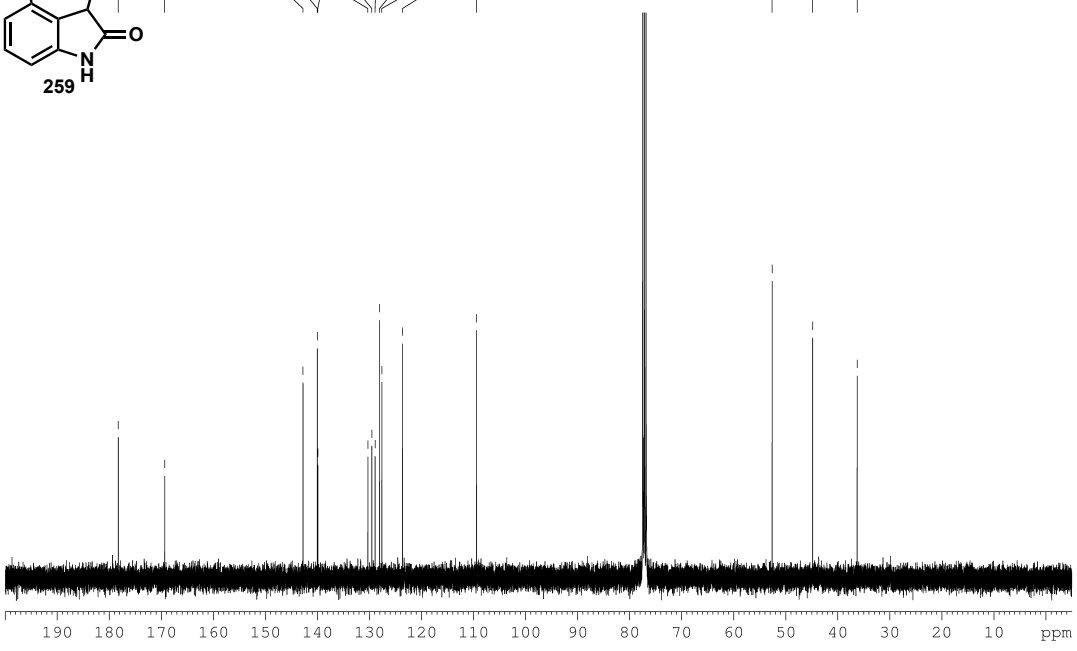
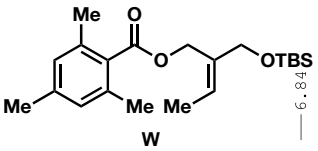
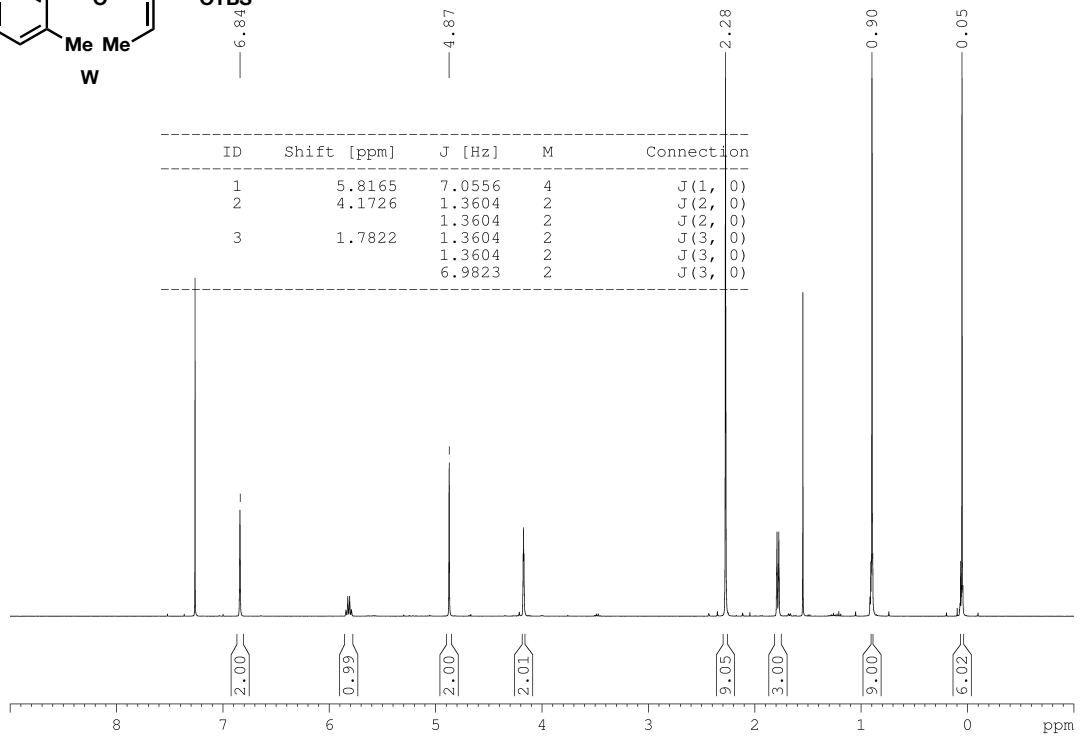
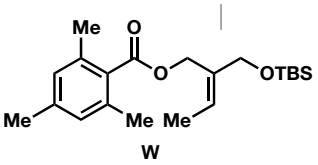
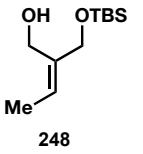






ID	Shift [ppm]	J [Hz]	M	Connection
1	5.8165	7.0556	4	J(1, 0)
2	4.1726	1.3604	2	J(2, 0)
		1.3604	2	J(2, 0)
3	1.7822	1.3604	2	J(3, 0)
		1.3604	2	J(3, 0)
		6.9823	2	J(3, 0)





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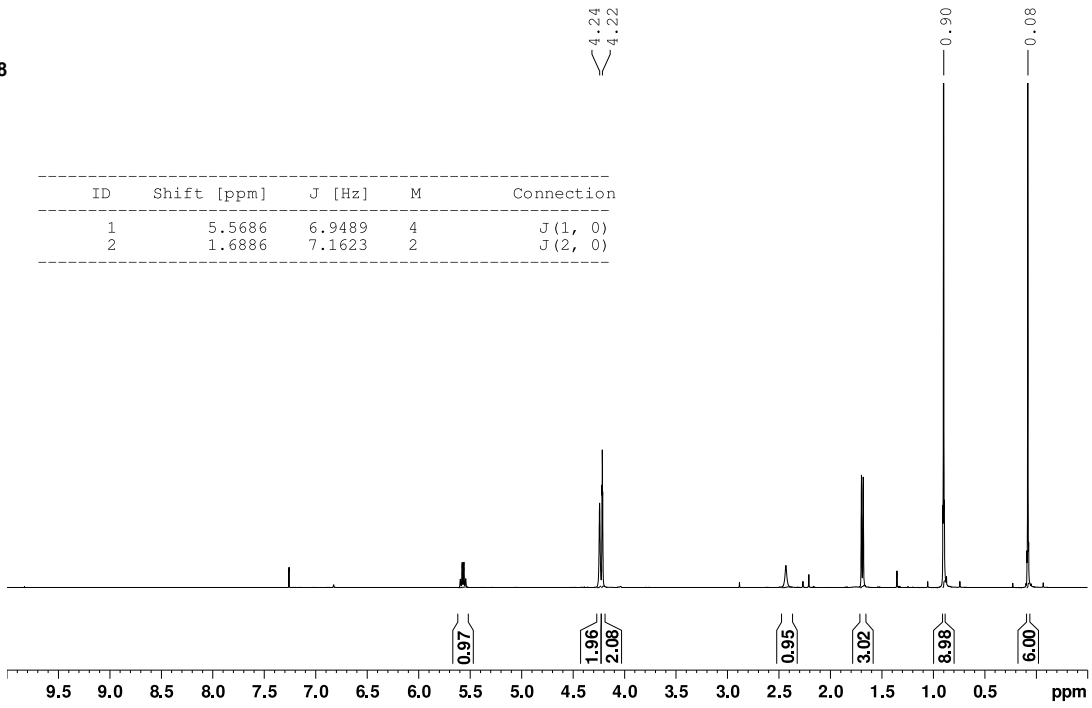
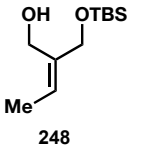


ID	Shift [ppm]	J [Hz]	M	Connection
1	5.5686	6.9489	4	J(1, 0)
2	1.6886	7.1623	2	J(2, 0)



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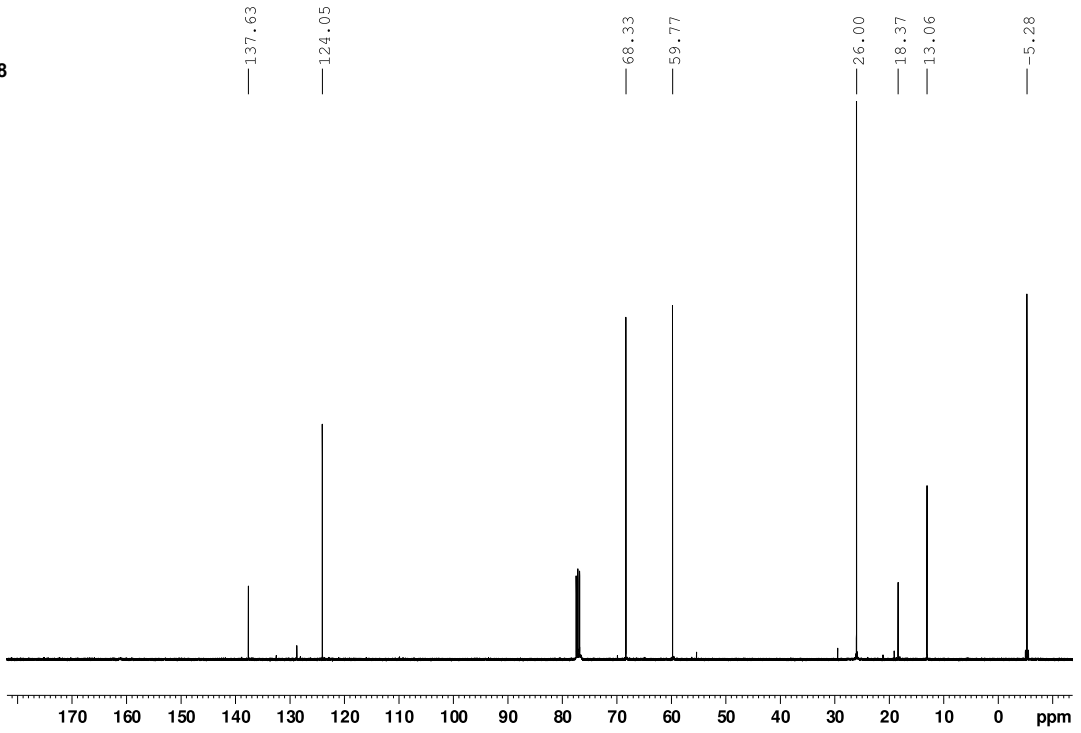
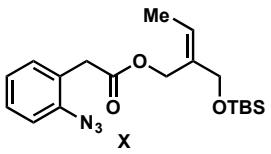
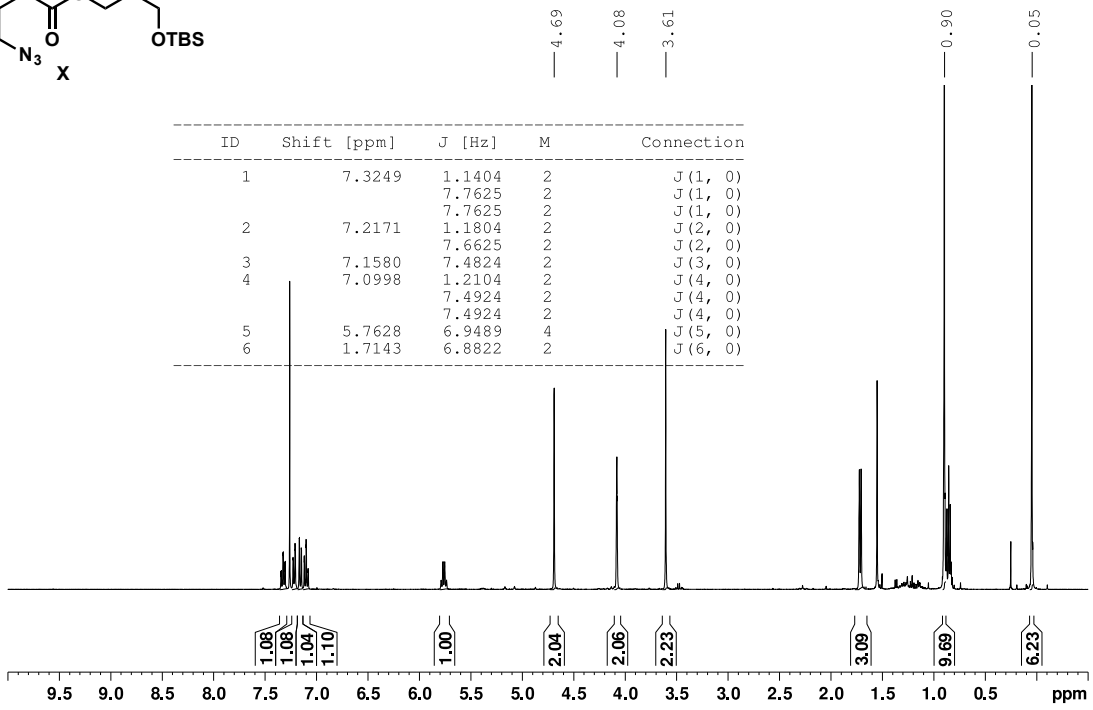
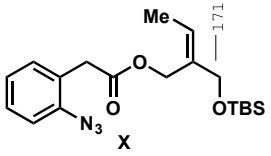
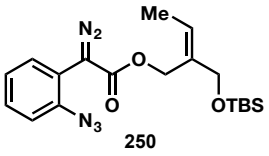






ID	Shift [ppm]	J [Hz]	M	Connection
1	7.3249	1.1404	2	J(1, 0)
		7.7625	2	J(1, 0)
		7.7625	2	J(1, 0)
2	7.2171	1.1804	2	J(2, 0)
		7.6625	2	J(2, 0)
3	7.1580	7.4824	2	J(3, 0)
4	7.0998	1.2104	2	J(4, 0)
		7.4924	2	J(4, 0)
		7.4924	2	J(4, 0)
5	5.7628	6.9489	4	J(5, 0)
6	1.7143	6.8822	2	J(6, 0)





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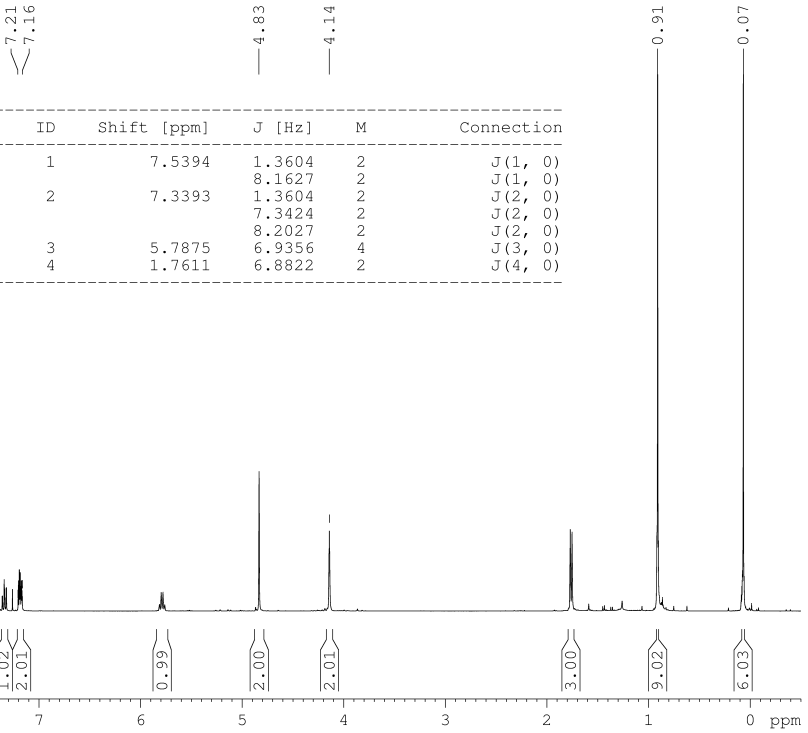
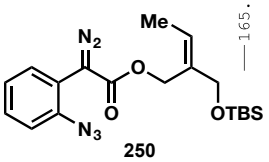


ID	Shift [ppm]	J [Hz]	M	Connection
1	7.5394	1.3604	2	J(1, 0)
		8.1627	2	J(1, 0)
2	7.3393	1.3604	2	J(2, 0)
		7.3424	2	J(2, 0)
		8.2027	2	J(2, 0)
3	5.7875	6.9356	4	J(3, 0)
4	1.7611	6.8822	2	J(4, 0)



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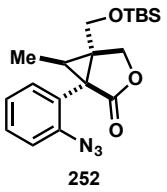

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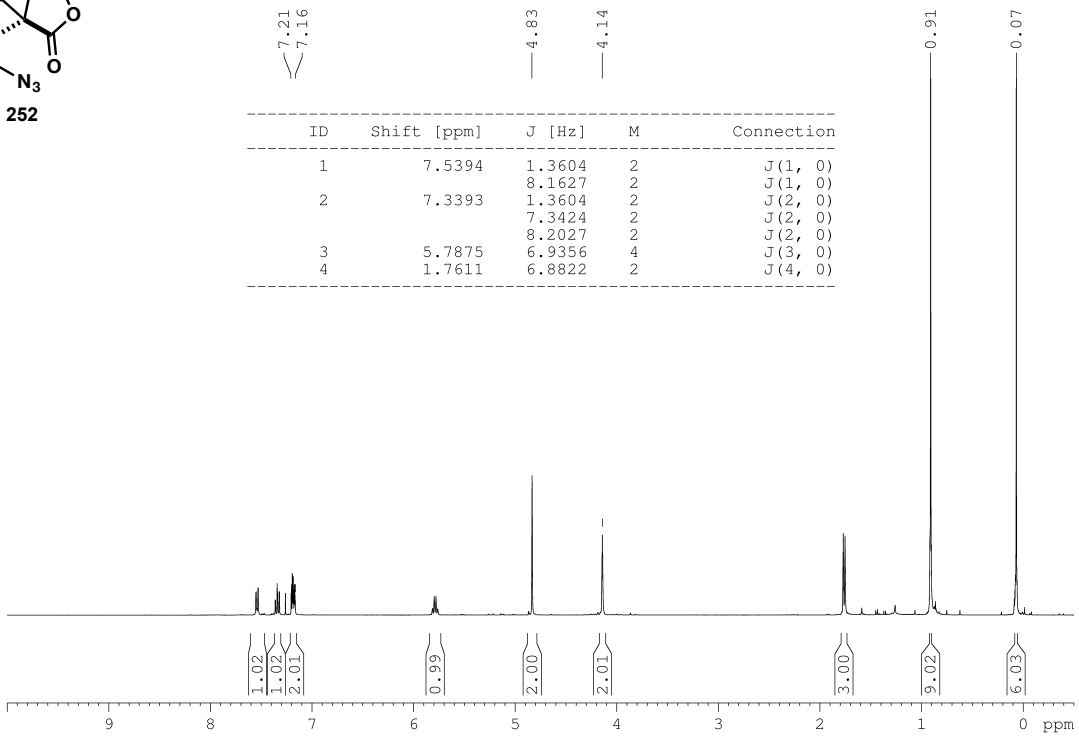
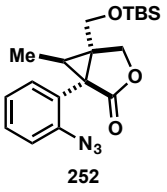


ID	Shift [ppm]	J [Hz]	M	Connection
1	7.5394	1.3604	2	J(1, 0)
		8.1627	2	J(1, 0)
2	7.3393	1.3604	2	J(2, 0)
		7.3424	2	J(2, 0)
		8.2027	2	J(2, 0)
3	5.7875	6.9356	4	J(3, 0)
4	1.7611	6.8822	2	J(4, 0)



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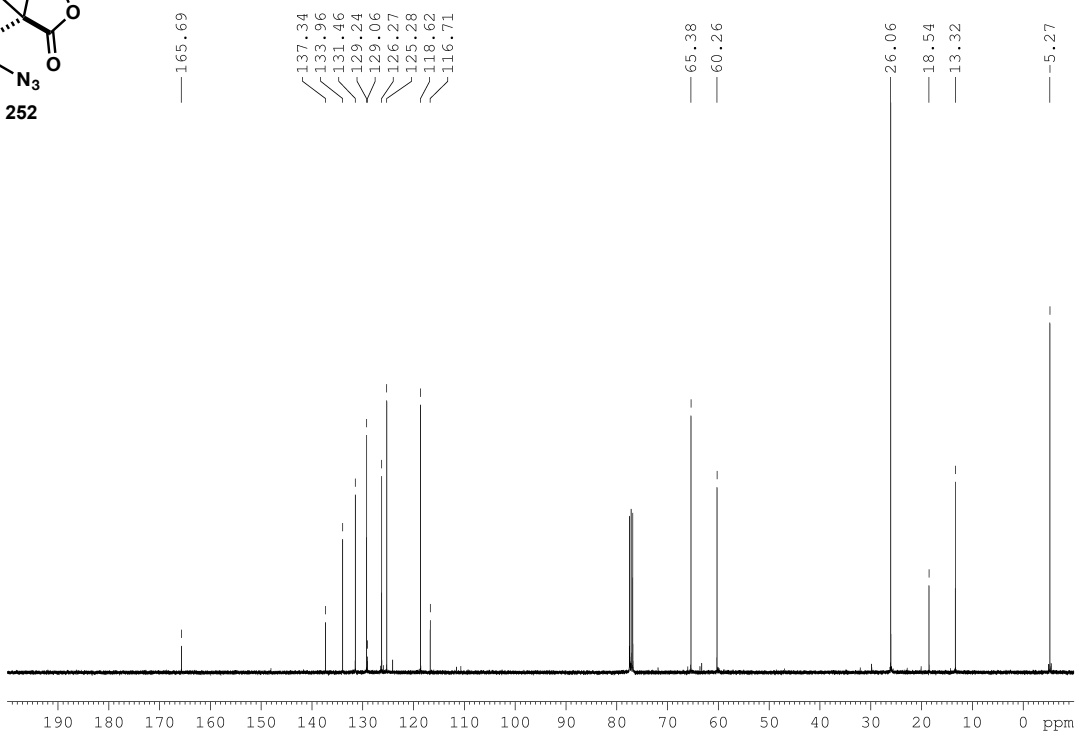

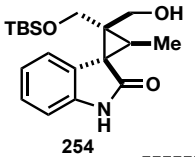

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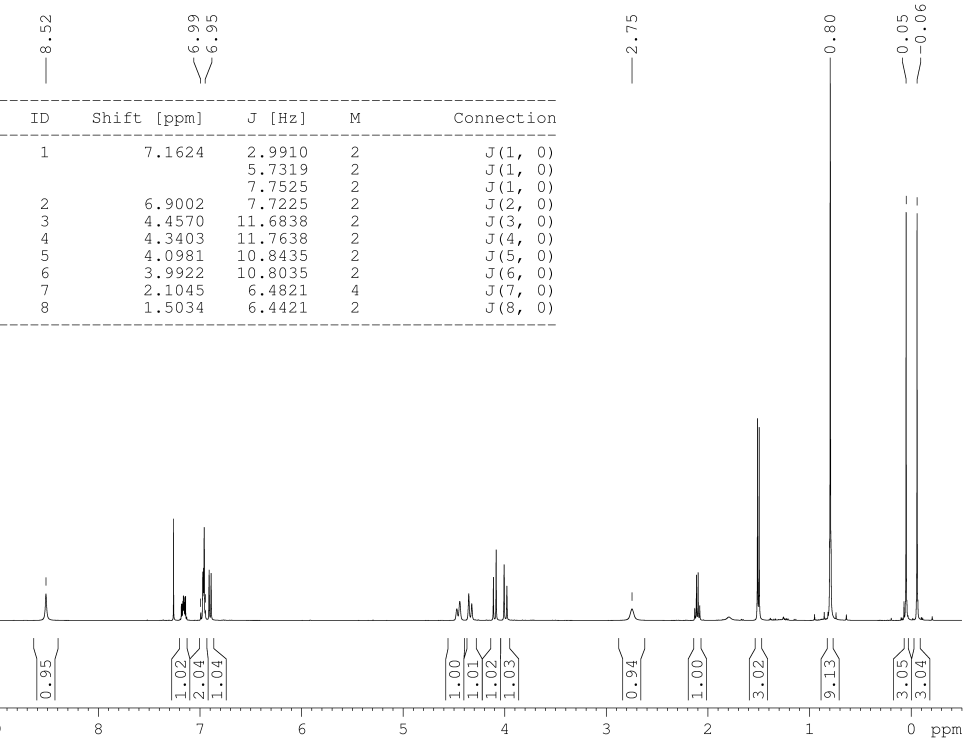
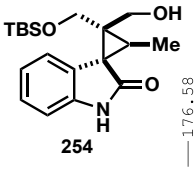


ID	Shift [ppm]	J [Hz]	M	Connection
1	7.1624	2.9910	2	J(1, 0)
		5.7319	2	J(1, 0)
		7.7525	2	J(1, 0)
2	6.9002	7.7225	2	J(2, 0)
3	4.4570	11.6838	2	J(3, 0)
4	4.3403	11.7638	2	J(4, 0)
5	4.0981	10.8435	2	J(5, 0)
6	3.9922	10.8035	2	J(6, 0)
7	2.1045	6.4821	4	J(7, 0)
8	1.5034	6.4421	2	J(8, 0)



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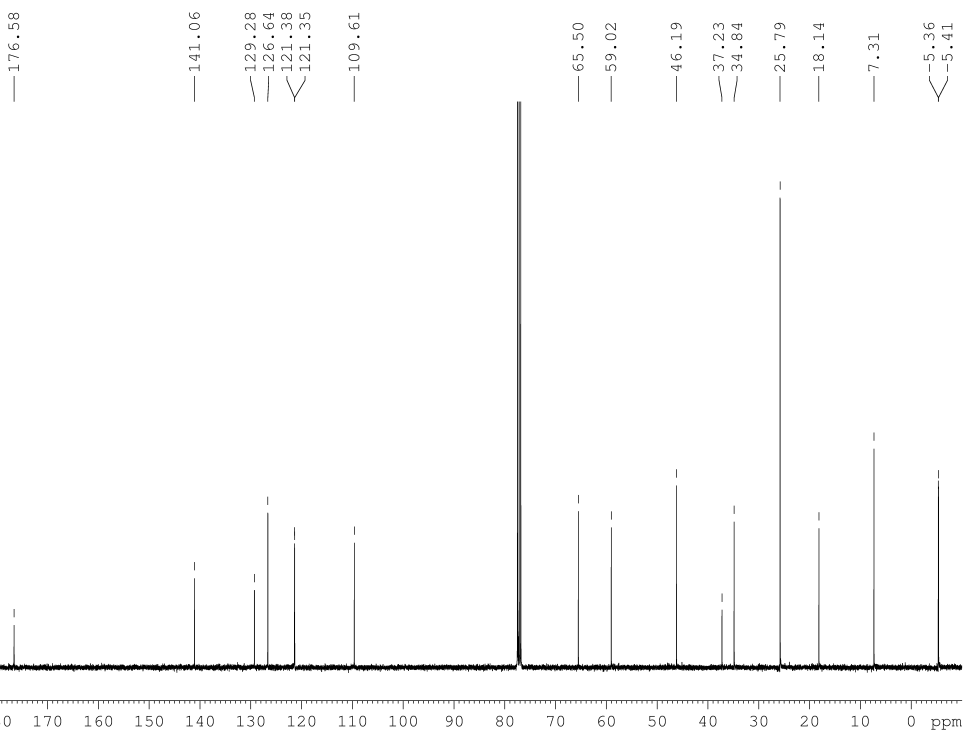
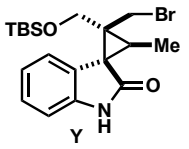
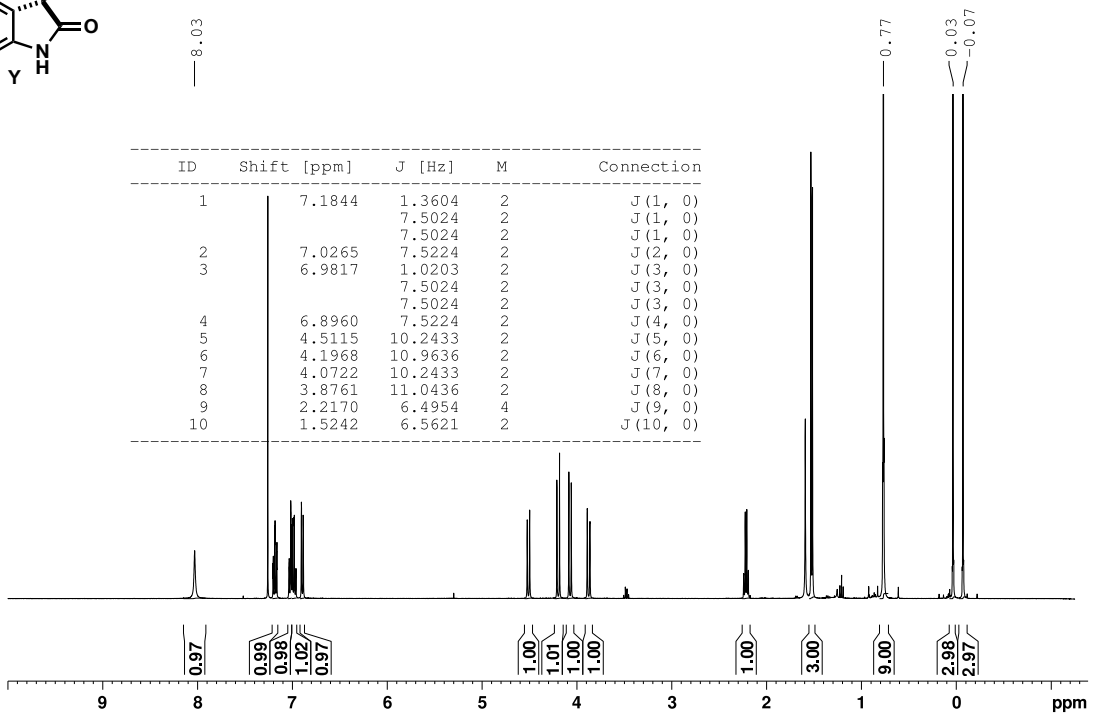
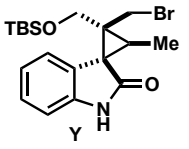
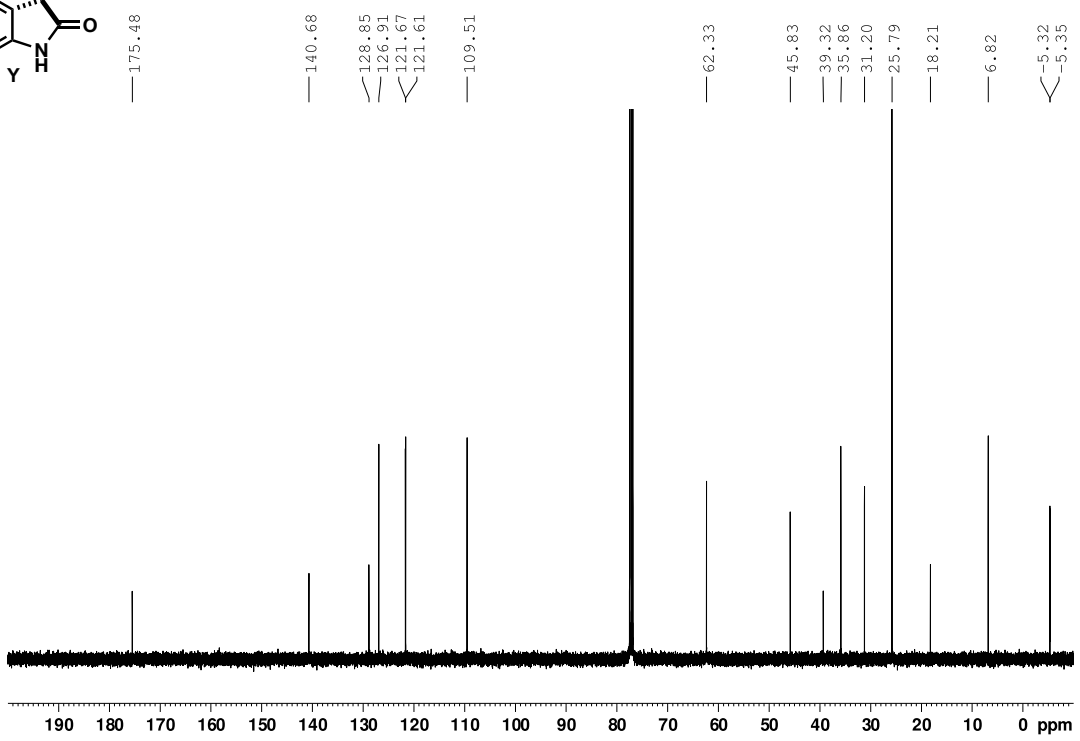


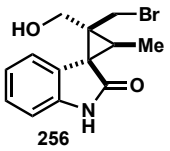




ID	Shift [ppm]	J [Hz]	M	Connection
1	7.1844	1.3604	2	J(1, 0)
		7.5024	2	J(1, 0)
		7.5024	2	J(1, 0)
2	7.0265	7.5224	2	J(2, 0)
3	6.9817	1.0203	2	J(3, 0)
		7.5024	2	J(3, 0)
		7.5024	2	J(3, 0)
4	6.8960	7.5224	2	J(4, 0)
5	4.5115	10.2433	2	J(5, 0)
6	4.1968	10.9636	2	J(6, 0)
7	4.0722	10.2433	2	J(7, 0)
8	3.8761	11.0436	2	J(8, 0)
9	2.2170	6.4954	4	J(9, 0)
10	1.5242	6.5621	2	J(10, 0)







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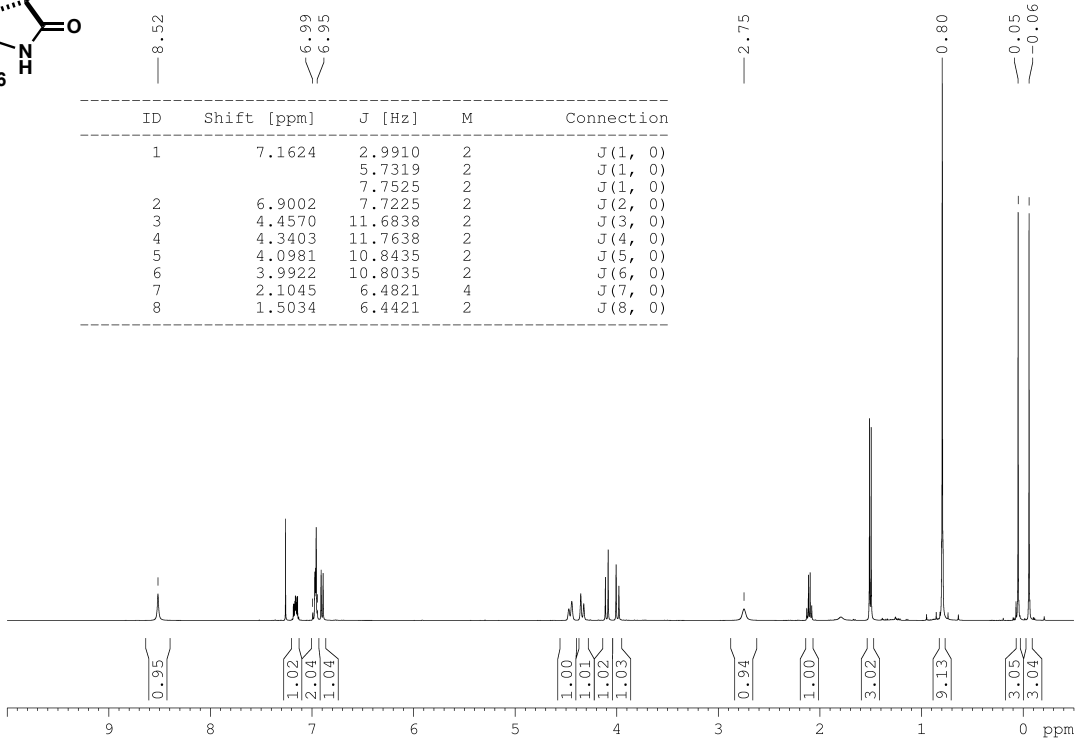
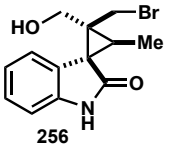


ID	Shift [ppm]	J [Hz]	M	Connection
1	7.1624	2.9910	2	J(1, 0)
		5.7319	2	J(1, 0)
		7.7525	2	J(1, 0)
2	6.9002	7.7225	2	J(2, 0)
3	4.4570	11.6838	2	J(3, 0)
4	4.3403	11.7638	2	J(4, 0)
5	4.0981	10.8435	2	J(5, 0)
6	3.9922	10.8035	2	J(6, 0)
7	2.1045	6.4821	4	J(7, 0)
8	1.5034	6.4421	2	J(8, 0)



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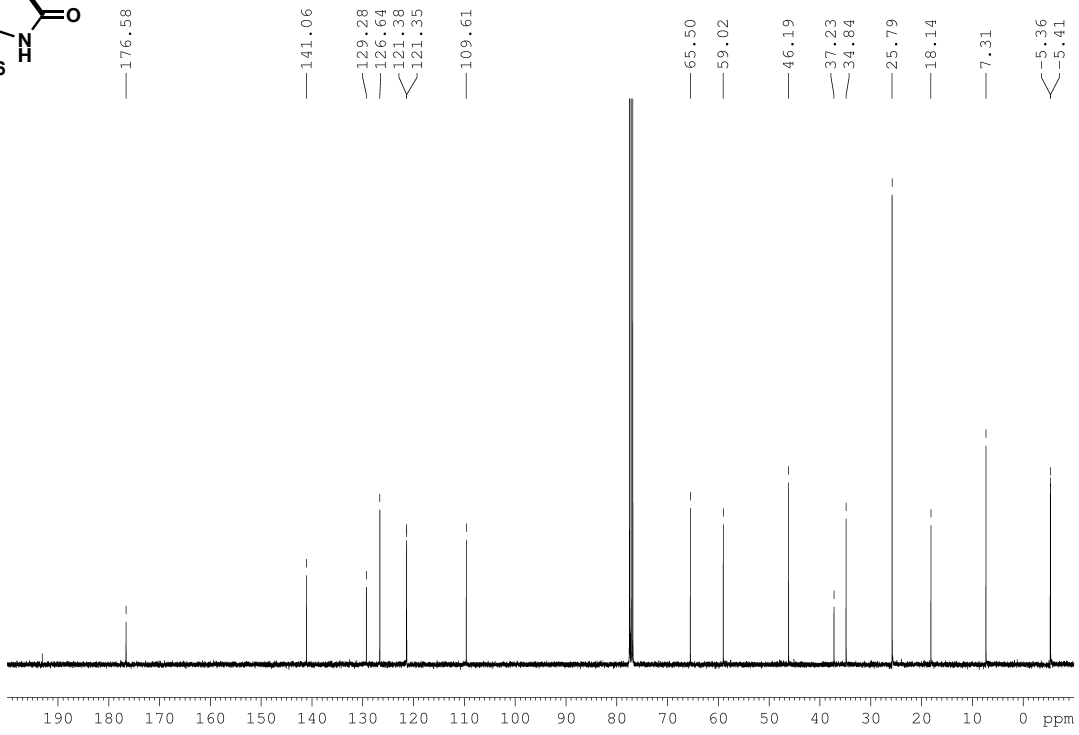

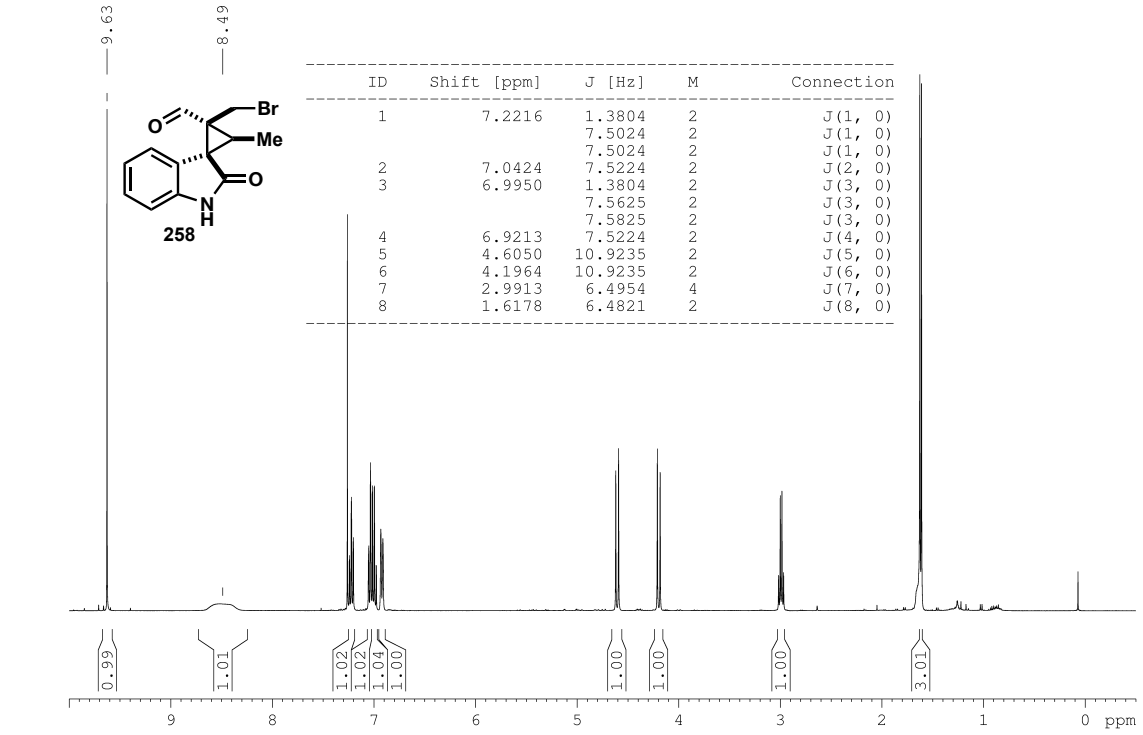
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Me
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O
N
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3 6.9950 1.3804 2 J(3, 0)
7.5625 2 J(3, 0)
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4 6.9213 7.5224 2 J(4, 0)
5 4.6050 10.9235 2 J(5, 0)
6 4.1964 10.9235 2 J(6, 0)
7 2.9913 6.4954 4 J(7, 0)
8 1.6178 6.4821 2 J(8, 0)
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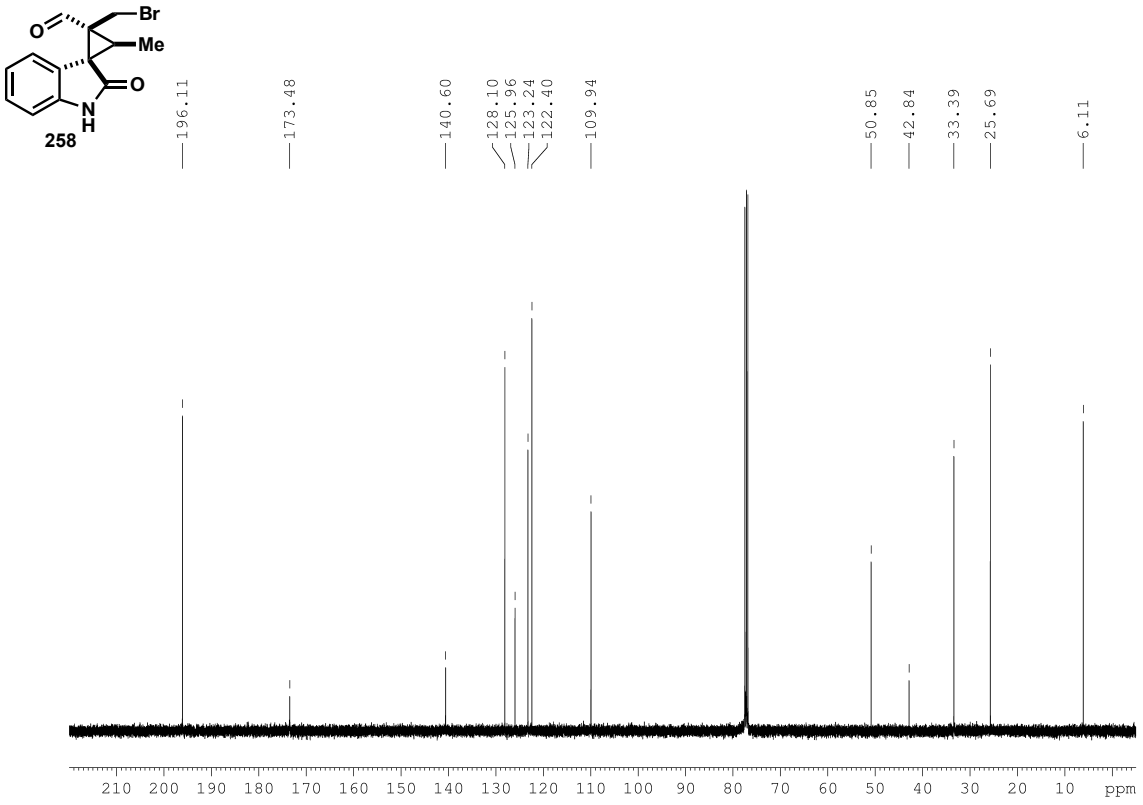
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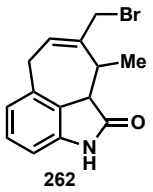

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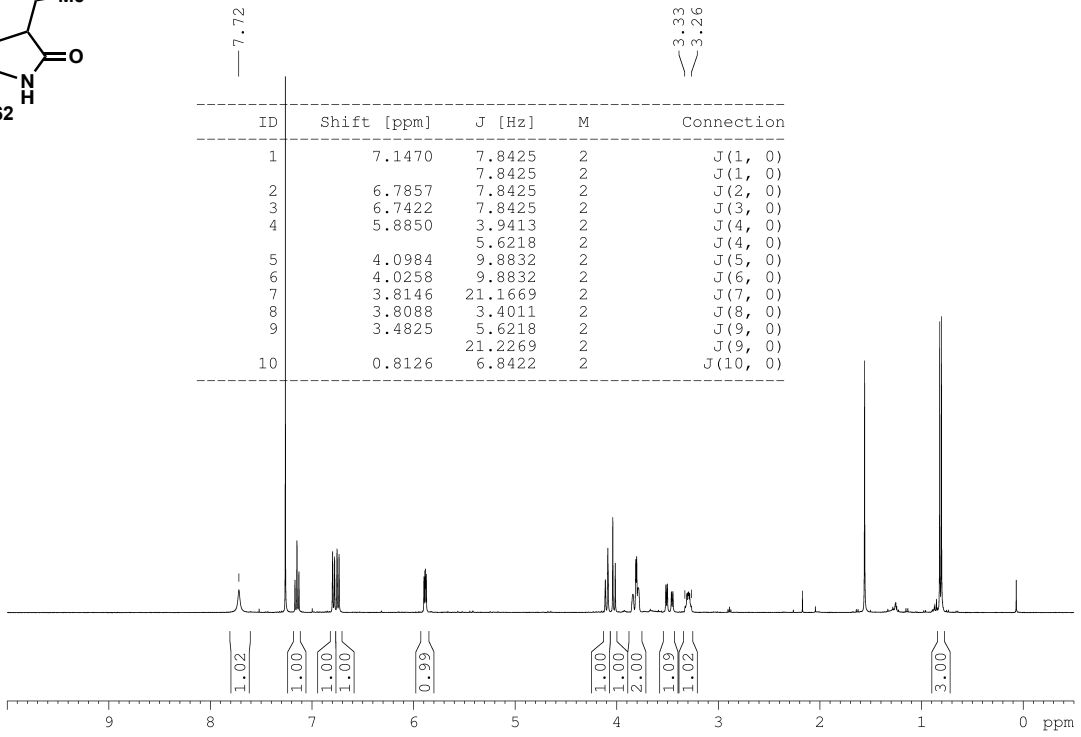

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		5.6218	2	J(4, 0)
5	4.0984	9.8832	2	J(5, 0)
6	4.0258	9.8832	2	J(6, 0)
7	3.8146	21.1669	2	J(7, 0)
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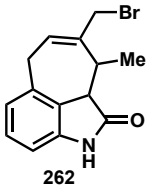

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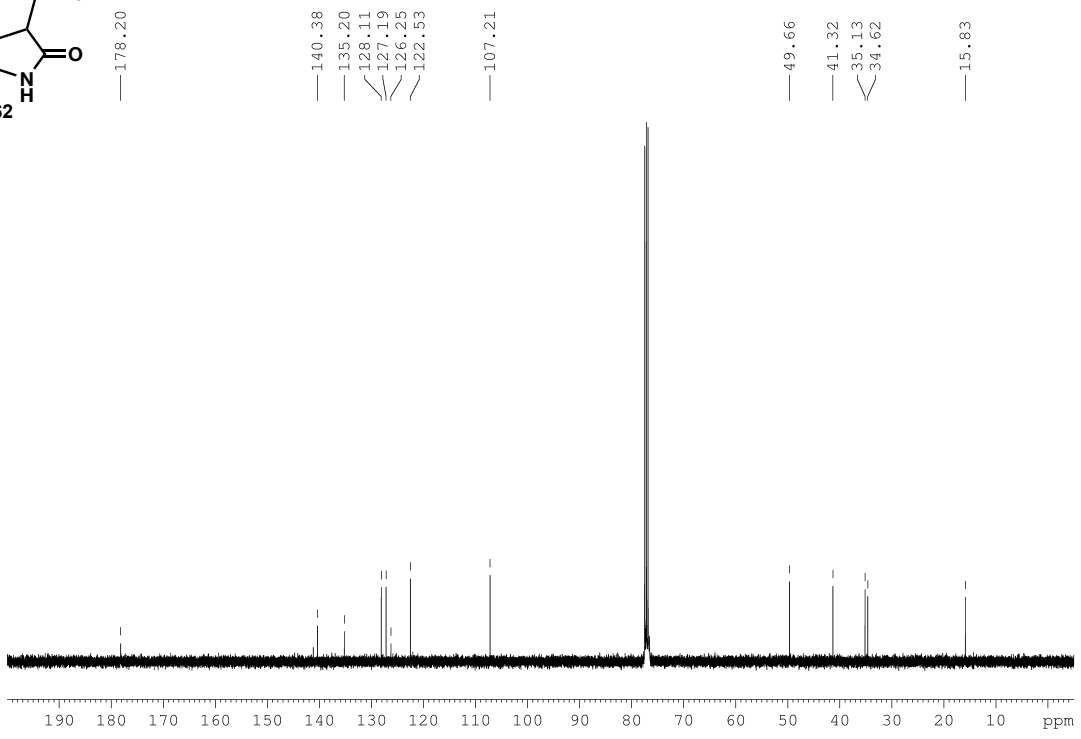

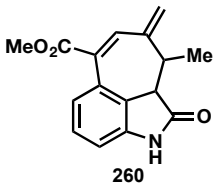

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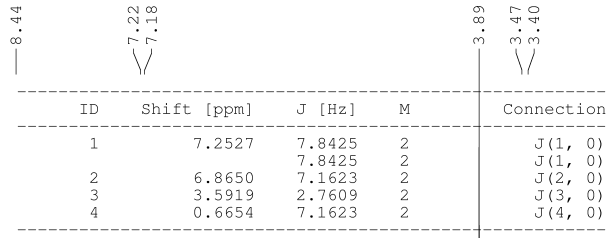

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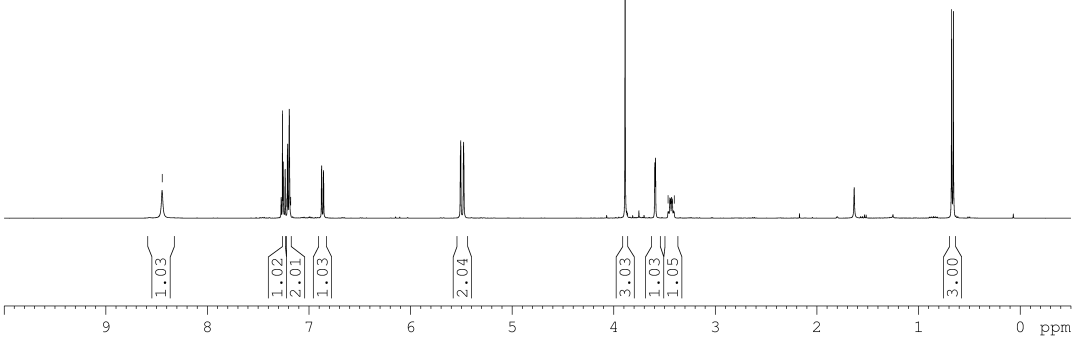

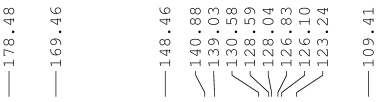

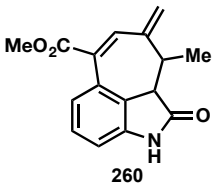

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7 Experimental
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7.3.31 *methyl (6*R*,6a*S*,9a*S*)-7-methylene-6-(((methylthio)carbonothioyl)oxy)-2-tosyl-6,6a,7,8,9a,10-hexahydropyrrolo[3',2':5,6]cyclohepta[1,2,3-*cd*]indole-9(2*H*)-carboxylate (416)* ..*280*
7.3.32 *8-((2,4-dinitro*-N-*(prop-2-yn-1-yl)phenyl)sulfonamido)-2-tosyl-2,8,9,9a-tetrahydro-1*H-*cyclohepta[*cd*]indol-1-yl acetate (424)* *281*
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7.3.34 *2,4-dinitro*-N-*(prop-2-yn-1-yl)*-N-*(2-tosyl-8,9-dihydro-2*H-*cyclohepta[*cd*]indol-8-yl)benzenesulfonamide (419)* *282*
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7.3.36 *(6*R*,6a*S*,9a*S*)-9-((2,4-dinitrophenyl)sulfonyl)-7-methylene-2-tosyl-2,6,6a,7,8,9,9a,10-octahydropyrrolo[3',2':5,6]cyclohepta[1,2,3-*cd*]indol-6-yl acetate (426)* *284*
7.3.37 *(6*R*,6a*S*,9a*S*)-9-methyl-7-methylene-2-tosyl-2,6,6a,7,8,9,9a,10-octahydropyrrolo[3',2':5,6]cyclohepta[1,2,3-*cd*]indol-6-yl acetate (428)* *285*
7.3.38 *(6a*S*,9a*S*)-9-((2,4-dinitrophenyl)sulfonyl)-7-methylene-2-tosyl-2,6,6a,7,8,9,9a,10-octahydropyrrolo[3',2':5,6]cyclohepta[1,2,3-*cd*]indole (429)* *286*
7.3.39 *(6a*S*,9a*S*)-9-methyl-7-methylene-2-tosyl-2,6,6a,7,8,9,9a,10-octahydropyrrolo[3',2':5,6]cyclohepta[1,2,3-*cd*]indole (418)* *287*
7.3.40 *(6a*S*,9a*S*)-9-methyl-7-methylene-2,6,6a,7,8,9,9a,10-octahydropyrrolo[3',2':5,6]cyclohepta[1,2,3-*cd*]indole (431)* *288*
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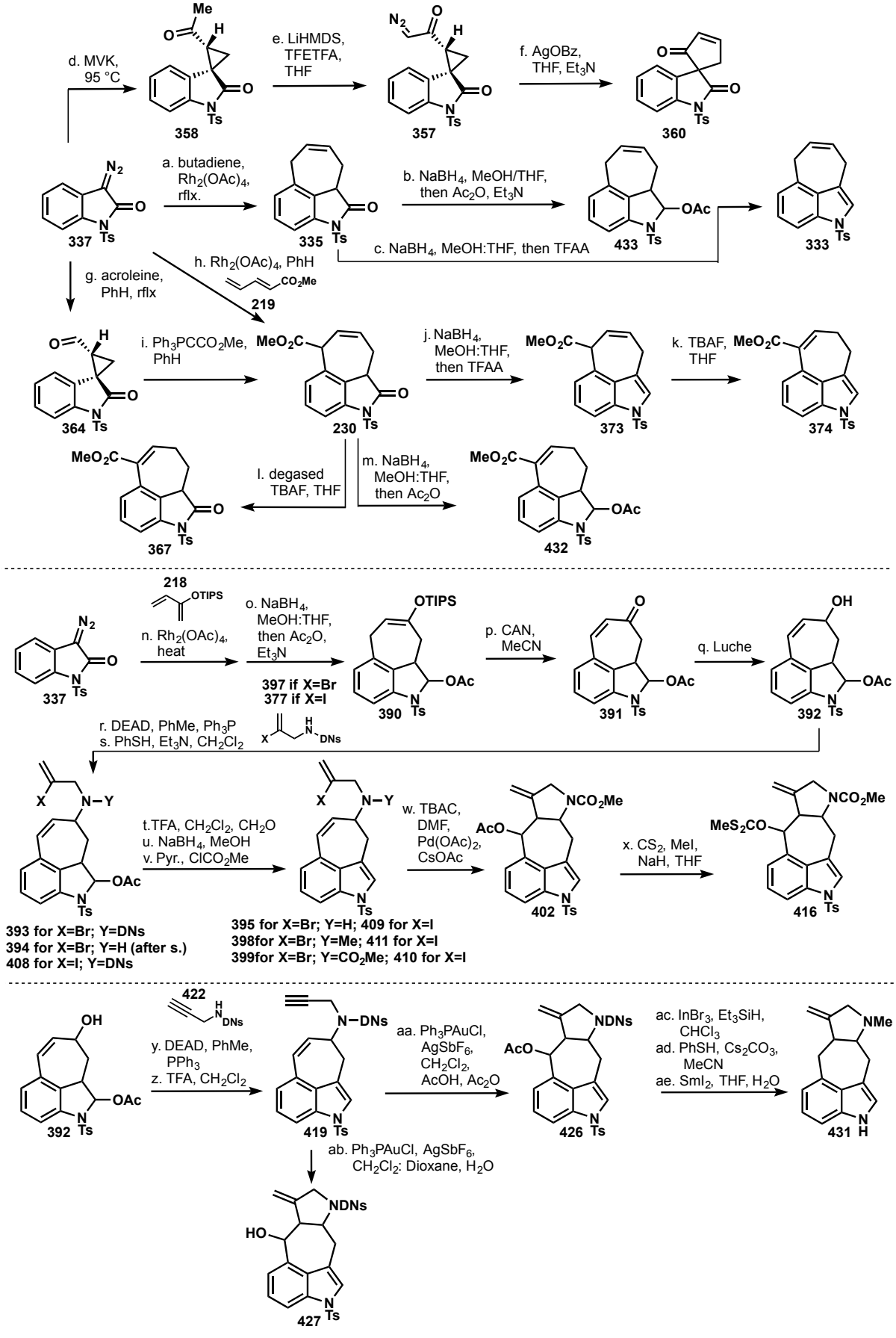
7.1 Graphical Overview

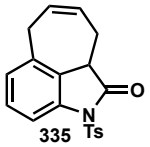


7.2 General

All reactions were carried out in oven-dried glassware under an argon atmosphere, unless otherwise stated. Commercially available anhydrous DMF, DMSO, MeCN, PhH, Pyridine THF (Acros Organics, Alfa Aesar) were used without further manipulation. Other anhydrous solvents were obtained by filtration through drying columns (Et_2O, CH_2Cl_2) on a Glass Contour system. Rhodium (II)-acetate dimer powder was obtained from Sigma-Aldrich. Reactions were magnetically and mechanically stirred and monitored by thin layer chromatography (TLC) with silica gel 60-F254 plates. Flash column chromatography was performed with silica gel 60 Å of Macherey-Nagel under pressure. Preparative TLC was performed with pre-coated TLC-plates Adamant UV_{254} of Mancherey-Nagel. Yields refer to chromatographically and spectroscopically pure compounds, unless otherwise stated. NMR spectra were recorded on a 400 MHz spectrometer of Bruker. Unless otherwise stated, all NMR spectra were measured in $CDCl_3$ solution and referenced to the residual $CHCl_3$ signal (^1H, δ = 7.26 ppm, ^{13}C, δ = 77.16 ppm). All ^1H and ^{13}C shifts are given in ppm (*s* = singlet, *d* = doublet, *t* = triplet, *q* = quadruplet, *m* = multiplet, *b* = broad signal). Assignments of proton resonance were confirmed, when possible, by correlated spectroscopy.

7.3 Procedures

7.3.1 *6.2.4 2-tosyl-2,6,9,9a-tetrahydro-1H-cyclohepta[cd]indol-1-one (335)*



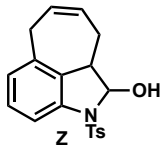
335

Diazo **337** (2.00 g, 6.40 mmol, 1 equiv.) was dissolved in the butadiene in toluene (3.60 g, 63.9 mmol, 10 equiv.) and the $Rh_2(OAc)_4$ (13.9 mg, 3.20 µmol, 0.5 mol%) was added to the sealed tube. The solution was heated to 80°C for two days. The solid turned to light pink. The solvent was removed in vacuo and the solid dissolved in DMSO (10 mL) and stirred for 36 h at 90 °C. The solution was poured on water and extracted with EtOAc (3x 50 mL). The combined organic phases were washed with water, dried over $MgSO_4$ and the solvent was removed *in vacuo*. The crude was purified by flash column chromatography (hexane:EtOAc 5:1) and gave the Oxindole **335** (500 mg, 1.60 mmol) with a yield of 25%.

^{1}H-NMR (400 MHz, $CDCl_3$, δ): 2.06 (m, 1H), 2.42 (s, 3H), 2.71 (m, 4H), 3.22 (m, 1H), 3.75 (d, *J* = 4.3, 1H), 3.81 (m, 2H), 5.66 (t, *J* = 3.1 Hz, 2H), 6.91 (d, *J* = 7.7 Hz, 1H), 7.23 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.31 (d, *J* = 8.1 Hz, 2H), 7.77 (d, *J* = 8.2 Hz, 1H), 7.97 (d, *J* = 8.4 Hz, 2H) ppm **^{13}C-NMR** (100

MHz, $CDCl_3$, δ): 21.8, 29.6, 33.7, 44.7, 111.7, 124.7, 125.9, 126.5, 127.7, 128.0, 128.4, 129.9, 135.4, 137.8, 138.6, 145.7, 175.3 ppm. **IR (neat sample)**: 1756, 1597, 1452, 1371, 1188, 1177, 1126, 1090, 960, 879, 813, 799, 779, 738, 703, 663 cm^{-1}. **HRMS** (ESI) (m/z): calc for $C_{19}H_{17}NO_3S$ $[M + Na]^+$, 326.0827; found 326.0826.

7.3.2 *6.2.5 2-tosyl-2,6,9,9a-tetrahydro-1H-cyclohepta[cd]indol-1-ol (Z)*

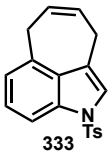


Z

Oxindole **335** (300 mg, 885 µmol, 1 equiv.) was dissolved in MeOH:THF (5:1, 2.3 mL), cooled to –30 °C and stirred for 4 h until TLC (hexane:EtOAc 1:1) showed complete reaction and no side product. NH_4Cl-solution was added and extracted with Et_2O (3x 20 mL), the combined organic layers were washed with water and dried over $MgSO_4$. The solvent was removed *in vacuo* and the crude was purified by flash column chromatography (hexane:EtOAc 1:1) to give the tricyclic hemi-aminal **Z** as a white solid (139 g, 406 µmol) with a yield of 69%.

^{1}H-NMR (400 MHz, C_6D_6, δ): 1.82 (s, 1H) 1.85 (s, 3H), 2.43 (m, 1H), 2.78 (dd, *J* = 19.1, 7.1 Hz, 1H), 3.12 (dd, *J* = 12.6, 4.6 Hz, 1H), 3.32 (d, *J* = 19.3 Hz, 2H), 5.29 (m, 2H), 6.63 (d, *J* = 7.7 Hz, 1H), 6.76 (d, *J* = 8.0 Hz, 2H), 7.10 (dd, *J* = 8.0, 8.0 Hz, 1H), 8.18 (d, *J* = 9.1 Hz, 3H) ppm. **^{13}C-NMR** (100 MHz, C_6D_6, δ): 21.1, 29.4, 33.4, 44.1, 111.9, 124.3, 125.5, 126.7, 128.6, 129.7, 136.48, 137.8, 139.3, 145.1 ppm. **IR (neat sample)**: 1756. 1597, 1453, 1371, 1189, 1177, 1126, 1090, 961, 813, 799, 778, 739, 703, 663 cm^{-1}. **HRMS** (ESI) (m/z): calc for $C_{19}H_{19}NO_3S$ $[M + H]^+$, 342.4250; not found.

7.3.3 *6.2.6 2-tosyl-6,9-dihydro-2H-cyclohepta[cd]indole (333)*



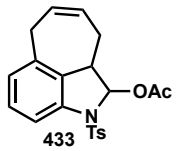
333

To a –20 °C cold solution of hemiaminal **Z** (1.37 g, 4.00 mmol, 1 equiv.) in CH2Cl2 (40 mL) was successively added Et_3N (2.80 mL, 20.0 mmol, 5 equiv.) and TFAA (1.20 mL, 8.80 mmol, 2.2 equiv.). When the reaction was complete by TLC (hexane:EtOAc 3:1) it was quenched by addition of bicarb solution, the phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3x 20 mL). The combined organic layers were dried over $MgSO_4$, concentrated *in*

vacuo and the crude was purified by flash column chromatography (hexane:EtOAc 15:1 to 5:1) to give the desired product in 90% (1.16 g, 3.60 mmol) as white crystals.

^{1}H-NMR (400 MHz, $CDCl_3$, δ): 2.34 (s, 3H), 3.47 (d, *J* = 6.2 Hz, 1H), 3.60 (d, *J* = 6.6 Hz, 2H), 6.05 (m, 2H), 6.91 (d, *J* = 7.5 Hz, 1H), 7.15 (dd, *J* = 7.9, 7.6 Hz, 1H), 7.20 (s, 1H), 7.23 (d, *J* = 4.8 Hz, 2H), 7.76 (m, 2H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$, δ): 21.7, 24.8, 32.2, 112.0, 119.7, 120.6, 121.8, 124.8, 126.9, 129.1, 129.9, 130.7, 131.0, 132.8, 135.8, 144.8 ppm. **IR (neat sample)**: 2927, 1724, 1597, 1428, 1369, 1260, 1176, 1131, 1107, 1090, 1018, 905, 811, 753, 713, 666 cm^{-1}. **HRMS** (ESI) (m/z): calc for $C_{19}H_{17}NO_2S$ [M + Na]$^+$, 346.0878; found 346.0880.

7.3.4 *6.2.7 2-tosyl-2,6,9,9a-tetrahydro-1H-cyclohepta[cd]indol-1-yl acetate (433)*

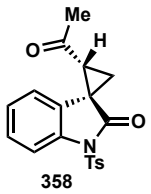


433

The crude hemi aminal **Z** (250 mg, 732 µmol, 1 equiv.) was dissolved in CH_2Cl_2 at –20 °C, then Et_3N (370 mg, 3.70 mmol, 5 equiv.) was added and the mixture was stirred for 5 min. Then Ac_2O (307 mg, 1.50 mmol, 2 equiv.) was added and the stirring continued for 4 h until the reaction was completed by TLC (hexane:EtOAc 5:1). The mixture was poured on water, extracted with CH_2Cl_2 (3x 20 mL) and washed with 50% bicarbonate-solution. The solvent was removed *in vacuo*. The crude was purified by flash column chromatography (hexane:EtOAc 5:1), giving compound **433** (198 mg, 600 µmol) as a yellow-white solid with a yield of 56%.

^{1}H-NMR (400 MHz, C_6D_6, δ): 1.64 (s, 3H), 1.71 (s, 3H), 2.41 (m, 1H), 2.60 (dd, *J* = 18.4, 7.10.1, 4.3 Hz, 1H), 5.29 (m, 1H), 6.50 (d, *J* = 7.7 Hz, 1H), 6.53 (d, *J* = 7.8 Hz, 2H) 6.67 (d, *J* = 1.1 Hz, 1H), 6.96 (dd, *J* = 7.9, 7.9 Hz, 1H), 7.72 (d, *J* = 8.4 Hz, 2H), 7.79 (d, *J* = 8.1 Hz, 1H) ppm. **^{13}C-NMR** (100 MHz, C_6D_6, δ): 20.6, 21.0, 31.0, 33.0, 48.3, 91.3, 113.2, 123.9, 125.7, 127.0, 127.4, 128.7, 129.8, 132.8, 136.5, 138.8, 140.4, 144.0, 169.8 ppm. **IR (neat sample)**: 2920, 1732, 1598, 1457, 1373, 1357, 1238, 1220, 1168, 1157, 1091, 1014, 957, 808, 773, 744, 702, 675, 656 cm^{-1}. **HRMS** (ESI) (m/z): calc for $C_{21}H_{21}NO_4S$ [M + Na]$^+$, 406.1089; found 406.1086.

6.2.8 2-acetyl-1'-tosylspiro[cyclopropane-1,3'-indolin]-2'-one (358)

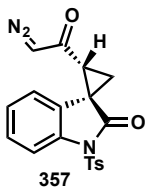


358

Diazo **337** (400 mg, 1.30 mmol, 1 equiv.) was dissolved in the methylvinylketone (358 mg, 5.10 mmol, 4 equiv.) and the solution was heated with an oil bath to 95 °C for 20 hours until complete by TLC (hexane:EtOAc 3:1). The solvent was removed *in vacuo* and the crude was purified via flash column chromatography (hexane:EtOAc 4:1), giving a total yield of 95% of ketone compound 39 (441 mg, 1.24 mmol). The *cis*-Isomer **358** could be gained with a yield of 42% (277 mg, 780 µmol).

^{1}H-NMR 358 (400 MHz, $CDCl_3$, δ): 1.96 (dd, *J* = 8.4, 4.5 Hz, 1H), 2.15 (s, 3H), 2.17 (dd, *J* = 7.8, 4.5 Hz, 1H), 2.43 (s, 3H), 2.96 (dd, *J* = 8.1, 8.1 Hz, 1H), 7.13 (m, 2H), 7.33 (d, *J* = 8.2 Hz, 3H), 7.99 (dd, *J* = 8.3, 3.6 Hz, 3H) ppm. **^{13}C-NMR 358** (100 MHz, $CDCl_3$, δ): 21.8, 21.9, 32.0, 35.5, 41.6, 113.6, 122.9, 124.5, 124.8, 128.1, 128.6, 130.0, 135.3, 139.5, 146.0, 173.5, 200.8 ppm. **IR (neat sample)**: 1748, 1713, 1596, 1464, 1374, 1339, 1307, 1247, 1189, 1175, 1131, 1089, 1057, 960, 907, 813, 726, 689, 661 cm^{-1}. **HRMS** (ESI) (m/z): calc for $C_{19}H_{17}NO_4S$ $[M + Na]^+$, 378.0776; found 378.0776.

6.2.9 2-(2-diazoacetyl)-1'-tosylspiro[cyclopropane-1,3'-indolin]-2'-one (357)



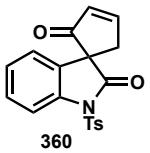
357

The 98% HMDS (171 mg, 1.10 mmol, 1.3 equiv.) was dissolved in dry THF (2.1 mL) and cooled to –78 °C. The *n*-BuLi (2.5 M in hexane, 70.3 mg, 1.10 mmol, 1.3 equiv.) was added and the solution was stirred for 10 min at 0°C. Then, it was cooled to –78 °C again. The ketone **358** (300 mg, 800 µmol, 1 equiv.) was dissolved in dry THF (1.7 mL) and added drop wise to the solution. The colour changed from yellow to brown and the stirring was continued for 40 min at –78 °C. The 2,2,2-TFETFA (235 mg, 1.20 mmol, 1.4 equiv.) was added. After the reaction was complete by TLC (hexane:EtOAc 5:1), it was warmed to 0 °C, H_2O (46.2 mg, 2.5 mmol, 3 equiv.) was added and the mixture stirred for 1 hour. Et_3N (878 mg, 8.40 mmol, 10 equiv.) and NsN_3

(583 mg, 2.50 mmol, 3 equiv.) were added and the mixture stirred for 2 hours at 40 °C. When the reaction was complete by TLC (hexane:EtOAc 3:1), Et_2O (40 mL) was added and the organic phase was washed with 10% NaOH, dried over Na_2SO_4 and the solvent was removed *in vacuo*. The crude was purified by flash colum chromatography (hexane:EtOAc 5:1) and gave the diazoketone **357** (214 mg, 560 µmol) with a yield of 70%.

^{1}H-NMR (400 MHz, $CDCl_3$, δ): 1.64 (dd, *J* = 8.6, 4.5 Hz, 1H), 1.85 (s, 3H), 2.07 (dd, *J* = 7.6 4.5, Hz, 1H), 2.39 (t, *J* = 8.1 Hz, 1H), 3.84 (s, 1H) 6.77 (d, *J* = 8.1 Hz, 2H), 6.93 (m, 1H), 7.13 (dd, *J* = 8.1, 8.0, 1H), 7.55 (d, *J* = 7.8 Hz, 1H), 8.21 (d, *J* = 8.0 Hz, 2H), 8.38 (d, *J* = 8.2 Hz, 1H) ppm. **^{13}C-NMR** (100 MHz, C_6D_6, δ): 21.2, 40.1, 55.8, 113.6, 123.8, 124.7, 128.5, 128.5, 129.8, 136.3, 140.2, 145.3 ppm. **IR (neat sample)**: 3094, 2100, 1750, 1625, 1598, 1462, 1399, 1379, 1336, 1299, 1242, 1189, 1175, 1140, 1088, 1064, 961, 906, 809, 775, 747, 702, 690, 665 cm^{-1}. **HRMS** (ESI) (m/z): calc for $C_{19}H_{15}N_3O_4S$ [M + Na]$^+$, 404.0681; found 404.0680.

6.2.10 1'-tosylspiro[cyclopentane-1,3'-indolin]-3-ene-2,2'-dione (360)

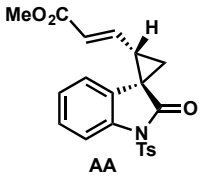


360

The DiazoKetone **357** (20.0 mg, 52.4 µmol, 1 equiv.) was dissolved in dry THF (500 µL) and the AgOBz (1.20 mg, 5.20 µmol, 10 mol%) was dissolved in the Et_3N (21.8 mL, 157 µmol, 3 equiv.). The Ag_2OBz in $Et_3N$was added dropwise to the solution. The colour changed from yellow to blackish brown. When the reaction was complete by TLC (hexane:EtOAc 2:1) the mixture was filtered through a plug of celite, the solvent was removed *in vacuo* and the crude was purified by flash column chromatography (hexane:EtOAc 2:1) to give spirooxindole **360** (13.9 mg, 39.3 µmol) in 75% yield.

^{1}H-NMR (400 MHz, $CDCl_3$, δ): 2.32 (s, 3H), 2.85 (m, 1H), 3.22 (m, 1H), 6.10 (m, 1H), 6.85 (d, *J* = 7.0 Hz, 1H), 7.05 (dd, *J* = 9.2, 8.0 Hz, 1H), 7.22 (d, *J* = 8.5 Hz, 2H), 7.27 (dd, *J* = 8.5, 7.1 Hz, 1H), 7.87 (m, 4H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$, δ): 21.9, 40.8, 60.2, 114.4, 122.2, 125.4, 128.2, 129.6, 129.9, 131.8, 135.1, 140.5, 145.9, 165.3, 172.6, 200.6 ppm. **IR (neat sample)**: 1755, 1709, 1595, 1462, 1376, 1233, 1189, 1176, 1141, 1083, 960, 824, 787, 753, 733, 689, 659 cm^{-1}. **HRMS** (ESI) (m/z): calc for $C_{19}H_{15}NO_4S$ [M + H]$^+$, 354.0722; not found.

7.3.5 *Methyl (E)-3-((1R,2S)-2'-oxo-1'-tosylspiro[cyclopropane-1,3'-indolin]-2-yl)acrylate (AA)*

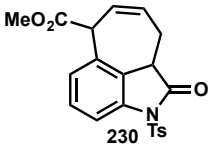


AA

Diazo **337** (1.00 g, 3.20 mmol, 1 equiv.) and the Diene **219** (1.60 g, 14.4 mmol, 4.5 equiv.) were stirred in benzene (4.8 mL) in a tube and rhodium(II)acetate (14 mg, 30 µmol, 1 mol%) was added. The tube was sealed and the mixture was heated up to 80 °C. After 20 min the colour changed to dark-red and strong gas development occurred. After 1 h TLC showed full consumption of the starting material and the solvent was removed *in vacuo*. The crude product was purified by column chromatography on silica gel (hexane:EtOAc 3:1) to give a mixture of two diastereomers in a ratio of 7:1 in favour of compound **AA** (1.00 g, 2.50 mmol, 79%) as a pale brownish solid.

^{1}H-NMR (400 MHz, C_6D_6, δ): 8.26 (d, *J* = 8.0 Hz, 1H), 8.06 (d, *J* = 8.3 Hz, 2H), 6.99 (td, *J* = 8.3, 1.3 Hz, 1H), 6.70 (td, *J* = 7.6, 1.0 Hz, 1H), 6.62 (d, *J* = 8.0 Hz, 2H), 6.56 (d, *J* = 15.4 Hz, 1H), 6.38 – 6.33 (m, 1H), 5.51 (dd, *J* = 15.4, 0.6 Hz, 1H), 3.30 (s, 3H), 2.30 – 2.21 (m, 1H), 1.71 (s, 3H), 1.57 (dd, *J* = 9.0, 5.0 Hz, 1H), 0.86 (dd, *J* = 7.6, 5.0 Hz, 1H) ppm. **^{13}C-NMR** (101 MHz, C_6D_6, δ): 173.4, 165.6, 145.2, 142.3, 140.3, 136.4, 129.8, 128.4, 128.2, 125.9, 124.8, 124.5, 121.5, 114.2, 51.1, 35.7, 34.8, 24.5, 21.1 ppm. **IR (neat sample)**: 1742, 1715, 1652, 1595, 1462, 1433, 1371, 1307, 1262, 1237, 1214, 1188, 1172, 1138, 1090, 1073, 1061, 1017, 978, 963, 924, 907, 865, 809, 769, 756, 744, 733, 702, 688, 666 cm^{-1}. **HRMS** (ESI) (m/z): calc. for $C_{21}H_{19}NO_5S$ $[M + Na]^+$, 420.0882; found 420.0887.

7.3.6 *Methyl 1-oxo-2-tosyl-2,6,9,9a-tetrahydro-1H-cyclohepta[cd]indole-6-carboxylate (230)*



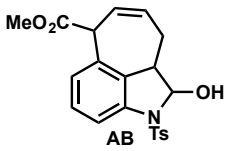
230

Cyclopropane **AA** (1.40 g, 3.5 mmol, 1 equiv.) was dissolved in DMSO (20 mL) and the mixture was stirred at 100 °C until complete consumption of the starting material (ca. 2 h). Water was added and the mixture was extracted with ethyl acetate (3x 50 mL). The combined organic phases were washed with sodium bicarbonate solution and brine. After the solvent was

removed *in vacuo*, the crude product was purified by column chromatography on silica gel (hexane:EtOAc 3:1) yielding **230** as colourless solid (810 mg, 2.10 mmol, 58%).

^{1}H NMR (400 MHz, $CDCl_3$, δ): 2.08 (qdd, *J* = 2.3, 12.9, 17.7 Hz, 1H), 2.43 (s, 3H), 2.77 (td, *J* = 5.5, 17.8 Hz, 1H), 3.65 (s, 3H), 4.17 (dd, *J* = 4.8, 13.0 Hz, 1H), 4.32 (d, *J* = 6.8 Hz, 1H), 5.76 (ddd, *J* = 2.2, 7.0, 12.3 Hz, 1H), 5.84 (ddd, *J* = 1.7, 6.1, 12.5 Hz, 1H), 6.96 (d, *J* = 8.1 Hz, 1H), 7.26 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.33 (d, *J* = 8.8 Hz, 2H), 7.85 (d, *J* = 8.2 Hz, 1H), 7.98 (d, *J* = 8.5 Hz, 2H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$, δ): 21.9, 29.1, 44.0, 51.4, 52.9, 113.1, 123.8, 125.6, 128.1, 128.3, 128.6, 129.8, 129.9, 134.8, 135.3, 139.2, 145.8, 171.8, 175.0 ppm. **IR (neat sample)**: 2955, 1753, 1725, 1600,1452, 1379, 1311, 1272, 1250, 1231, 1211, 1190, 1177, 1141, 1086, 1008, 995, 960, 908, 876, 810, 782, 746, 703, 664 cm^{-1}. **HRMS** (ESI) (m/z): calc. for $C_{21}H_{19}NO_5S$ $[M + Na]^+$, 420.0882; found 420.0880.

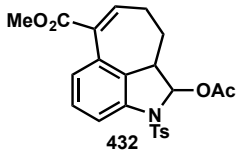
7.3.7 *Methyl 1-hydroxy-2-tosyl-2,6,9,9a-tetrahydro-1H-cyclohepta[cd]indole-6-carboxylate (AB)*



Oxindole **230** (400 mg, 1.0 mmol, 1 equiv.) was dissolved in THF (1.7 mL) and methanol (8.3 mL) and the solution was cooled to –30 °C. Sodium boron hydride (84 mg, 2.2 mmol, 2.2 equiv.) was added and the mixture was stirred until TLC showed complete consumption of the starting material. The reaction was quenched with saturated ammonium chloride solution and extracted with EtOAc (3 x 50 mL). The combined organic phases were dried over sodium sulfate and the solvent was removed *in vacuo*. After purification with column chromatography on silica gel (hexane: ethyl acetate 3:1) **AB** was received as a white solid (348 mg, 0.87 mmol, 87%).

HRMS (ESI) (m/z): calc. for $C_{21}H_{21}NO_5S$ $[M + Na]^+$, 422.1038; found 420.1039. **IR (neat sample)**: 3443, 2953, 1724, 1599, 1456, 1433, 1350, 1251, 1216, 1158, 1088, 991, 924, 874, 812, 771, 746, 705, 661 cm^{-1}.

7.3.8 *Methyl 1-acetoxy-2-tosyl-2,8,9,9a-tetrahydro-1H-cyclohepta[cd]indole-6-carboxylate (432)*



432

Hemi-aminal **AB** (250 mg, 630 µmol, 1 equiv.) was dissolved in dichloromethane (630 µL) and the mixture was cooled to –25 °C. Et_3N (350 µL) was added and the mixture was stirred for 5 min. Acetic anhydride (120 µL, 1.3 mmol, 2.1 equiv.) was added dropwise and the reaction was stirred until TLC showed complete consumption. The reaction was quenched with sodium bicarbonate solution and was extracted with ethyl acetate (3 x 50 mL). The combined organic phases were washed with brine and dried over sodium sulfate. Purification by column chromatography on silica gel (hexane:EtOAc 5:1, 1% Et_3N) afforded **432** as a colourless solid (220 mg, 0.50 mmol, 80%).

Due to the acidity of the silica gel, a part of **432** decomposed to indole **374** during purification, although triethyl amine was added to decrease the acidity.

^{1}H NMR (400 MHz, C_6D_6, δ): 7.79 (d, *J* = 8.0 Hz, 1H), 7.71 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 7.5 Hz, 1H), 7.14 – 7.08 (m, 2H), 6.68 – 6.66 (m, 1H), 6.57 (d, *J* = 8.1 Hz, 2H), 3.40 (s, 3H), 2.78 (dd, *J* = 11.2, 8.5 Hz, 1H), 2.20 (dddd, *J* = 13.0, 11.4, 8.3, 6.6 Hz, 1H), 1.76 (s, 3H), 1.49 (s, 3H), 1.47 – 1.41 (m, 1H), 1.33 – 1.19 (m, 1H), 1.15 – 1.03 (m, 1H) ppm. **^{13}C NMR** (101 MHz, C_6D_6, δ): 169.3, 165.5, 143.6, 143.5, 139.9, 136.4, 133.1, 132.1, 129.3, 128.4, 128.2, 127.1, 125.1, 114.0, 91.4, 51.1, 47.3, 36.3, 24.9, 20.7, 20.1 ppm. **IR (neat sample)**: 2951, 1714, 1597, 1447, 1361, 1275, 1256, 1211, 1186, 1166, 1087, 1063, 1009, 924, 881, 815, 798, 747, 706, 666 cm^{-1}. HRMS (ESI) (m/z): calc. for $C_{23}H_{23}NO_6S$ $[M + Na]^+$, 464.1144; found 464.1144.

7.3.9 *Alternative route to Cyclopropane AA*

Starting from the diazo-isatin **337**, the carben-insertion was performed under thermic conditions with acroleine (**363**), which lead to a mixture of **364** and its diastereomer. Wittig-reaction of **364** with the Ph_3PCCO_2Me (1.05 equiv.) worked quantitatively and lead to the cyclopropane **AA**.

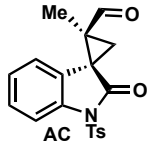
7.3.10 *(1R,2R)-2'-oxo-1'-tosylspiro[cyclopropane-1,3'-indoline]-2-carbaldehyde (364)*

364

Diazo **337** (2.00 g, 6.40 mmol, 1 equiv.) and acroleine (2.20 mL, 31.9 mmol, 5 equiv.) were stirred in a sealed tube and the mixture was heated to 95 °C. After 3 h the reaction was complete and remaining acroleine was removed *in vacuo*. The crude product was purified by column chromatography on silica gel (hexane:EtOAc 3:1) yielding two diastereomers in a 1.1:1 mixture in favour of **364** as a beige solid (1.55 g, 4.60 mmol, 72%).

^{1}H NMR (400 MHz, C_6D_6, δ): 9.48 (d, *J* = 6.2 Hz, 1H), 8.14 (d, *J* = 8.2 Hz, 1H), 7.97 (d, *J* = 8.4 Hz, 2H), 6.99 (td, *J* = 8.3, 1.3 Hz, 1H), 6.67 (td, *J* = 7.6, 0.9 Hz, 1H), 6.59 (d, *J* = 8.1 Hz, 2H), 5.83 – 5.76 (m, 1H), 1.84 (ddd, *J* = 8.6, 7.8, 6.2 Hz, 1H), 1.70 (s, 3H), 1.65 (dd, *J* = 7.8, 5.4 Hz, 1H), 0.85 (dd, *J* = 8.7, 5.4 Hz, 1H) ppm. **^{13}C-NMR** (101 MHz, C_6D_6, δ): 195.3, 172.3, 145.5, 140.0, 136.0, 129.8, 128.6, 128.5, 127.9, 124.7, 118.8, 114.2, 41.2, 34.8, 23.0, 21.1 ppm. **IR (neat sample)**: 2951, 1746, 1706, 1595, 1436, 1414, 1371, 1243, 1213, 1187, 1172, 1135, 1088, 1031, 1001, 962, 924, 903, 856, 814, 799, 755, 703, 689, 665 cm^{-1}**. HRMS** (ESI) (m/z): calc. for $C_{18}H_{15}NO_4S$ $[M + Na]^+$, 364.0619; found 364.0622.

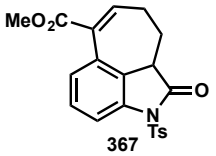
(1R,2S)-2'oxo-1'tosylspiro[cyclopropane-1,3'-indoline]-2-carbaldehyde (AC)



AC

^{1}H NMR (400 MHz, C_6D_6, δ): 8.61 (d, *J* = 1.8 Hz, 1H, H-p), 8.25 (d, *J* = 8.2 Hz, 1H), 8.07 (d, *J* = 8.4 Hz, 2H), 7.03 (td, *J* = 8.3, 1.3 Hz, 1H), 6.96 – 6.92 (m, 1H), 6.77 (td, *J* = 7.7, 0.9 Hz, 1H), 6.64 (d, *J* = 8.1 Hz, 2H), 2.25 (td, *J* = 7.9, 1.9 Hz, 1H), 1.72 (s, 3H), 1.54 (dd, *J* = 7.8, 4.7 Hz, 1H), 1.38 (dd, *J* = 8.6, 4.7 Hz, 1H) ppm. **^{13}C-NMR** (101 MHz, C_6D_6, δ). 194.0, 172.6, 145.4, 140.3, 136.2, 129.8, 128.6, 128.6, 128.4, 124.5, 123.1, 113.9, 40.6, 36.0, 21.2, 20.6 ppm. **IR (neat sample)**: 2950, 1740, 1716, 1597, 1494, 1463, 1414, 1373, 1297, 1244, 1213, 1189, 1174, 1140, 1090, 1077, 1024, 1003, 960, 924, 905, 861, 816, 799, 756, 704, 681, 662 cm^{-1}. **HRMS** (ESI) (m/z): calc. for $C_{18}H_{15}NO_4S$ $[M + Na]^+$, 364.0619; found 364.0619.

7.3.11 *Methyl 1-oxo-2-tosyl-2,8,9,9a-tetrahydro-1H-cyclohepta[cd]indole-6-carboxylate (367)*

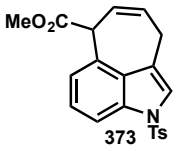


367

A solution of TBAF in THF (1 M, 0.5 mL) was degassed by freeze-pump-thaw and Oxindole **230** (200 mg, 500 µmol, 1 equiv.) was added. The solution turned red and was stirred for 30 min under nitrogen. After TLC showed completion the reaction was quenched with saturated ammonium chloride solution and was extracted with ethyl acetate (3 x 50 mL). The combined organic phases were dried over sodium sulfate and the solvent was removed *in vacuo*. Purification by column chromatography on silica gel (hexane:EtOAc 4:1) gave **367** as colourless solid (150 mg, 370 µmol, 75%).

^{1}H NMR (400 MHz, C_6D_6, δ): 8.14 (d, *J* = 8.2 Hz, 1H), 8.11 (d, *J* = 8.4 Hz, 2H), 7.39 – 7.33 (m, 1H), 7.13 – 7.09 (m, 1H), 6.96 – 6.90 (m, 1H), 6.68 (d, *J* = 8.1 Hz, 2H), 3.43 (s, 3H), 2.36 (t, *J* = 9.2 Hz, 1H), 2.04 – 1.90 (m, 1H), 1.76 (s, 3H), 1.42 (ddtd, *J* = 12.4, 9.8, 5.8, 5.1, 2.6 Hz, 2H), 1.36 – 1.28 (m, 1H) ppm. **^{13}C NMR** (101 MHz, C_6D_6, δ): 175.4, 166.3, 145.2, 143.5, 139.4, 136.5, 132.7, 132.0, 129.8, 128.6, 128.5, 127.5, 126.0, 113.2, 51.5, 43.2, 34.3, 26.5, 21.2 ppm. **IR (neat sample)**: 2951, 1756, 1717, 1597, 1583, 1443, 1433, 1374, 1433, 1374, 1271, 1247, 1223, 1186, 1176, 1132, 1076, 1018, 973, 934, 805, 791, 737, 700, 662 cm^{-1}. **HRMS** (ESI) (m/z): calc. for $C_{21}H_{19}NO_5S$ $[M + Na]^+$, 420.0882; found 420.0878.

7.3.12 *Methyl 2-tosyl-6,9-dihydro-2H-cyclohepta[cd]indole-6-carboxylate (373)*



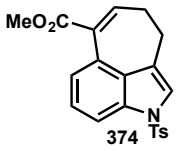
373

Ester **230** (150 mg, 376 µmol 1 equiv.) was dissolved completely in THF (750 µL) at room temperature. MeOH (3 mL) was added, what caused the precipitation of a fluffy white solid. The suspension was cooled to 0 °C and $NaBH_4$ was added in one portion. After 10 minutes at 0 °C the mixture became a clear solution. TLC (hexane:EtOAc 1:1) showed the complete consumption of the starting material. The reaction was quenched by addition of water. The aqueous layer was extracted with EtOAc (3x 20 mL), the combined organic layers were washed with brine solution, dried over $MgSO_4$ and the solvent was removed *in vacuo.* The crude was

dissolved in MeCN (2 mL) and the solution was cooled to –30 °C. BF_3*OEt_2 (95.0 µL, 751 µmol, 2 equiv.) was added in one portion, the cooling bath was removed and the solution was stirred until complete by TLC (hexane:EtOAc 1:1, 5 min) the reaction was quenched by addition of water, the aqueous layer was extracted with EtOAc (3x 20 mL), the combined organic layers were washed with brine solution, dried over $MgSO_4$ and concentrated *in vacuo*. The crude was purified by flash column chromatography (hexane:EtOAc 2:1) to give the desired product as yellowish oil in in 94% (129 mg, 338 µmol) yield over two steps.

^{1}H NMR (400 MHz, $CDCl_3$, δ): 2.36 (s, 3H), 3.43 (ddd, *J* = 0.8, 6.9, 16.3 Hz, 1H), 3.61 (tdd, *J* = 1.3, 5.3, 16.2 Hz, 1H), 3.76 (s, 3H), 4.73 (d, *J* = 7.5 Hz, 1H), 6.08 – 6.21 (m, 2H), 6.91 (d, *J* = 7.5 Hz, 1H), 7.19 – 7.25 (m, 3H), 7.30 (s, 1H), 7.76 (d, *J* = 8.2 Hz, 2H), 7.87 (d, *J* = 8.2 Hz, 1H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$, δ): 21.7, 25.7, 49.2, 52.5, 113.1, 118.6, 121.5, 122.0, 124.7, 127.0, 129.0, 129.9, 130.0, 130.2, 135.5, 135.9, 145.0, 172.4 ppm. **IR (neat sample)**: 2950, 1713, 1597, 1493, 1435, 1414, 1357, 1245, 1210, 1167, 1137, 1087, 1050, 1002, 924, 812, 795, 742, 703, 666 cm^{-1}. **HRMS** (ESI) (m/z): calc. for $C_{21}H_{19}NO_4S$ $[M + Na]^+$, 404.0932; found 404.0931.

7.3.13 *Methyl 2-tosyl-8,9-dihydro-2H-cyclohepta[cd]indole-6-carboxylate (374)*



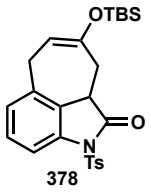
374

A solution of TBAF in THF (1 M, 1 mL) was degassed by freeze-pump-thaw and indole 13 (110 mg, 290 µmol, 1 equiv.) was added as solution in THF (1 mL). The reaction was stirred until TLC showed completion and was then quenched with saturated ammonium chloride solution. The mixture was extracted with ethyl acetate (3 x 50 mL), the combined organic phases were dried over sodium sulfate and the solvent was removed in vacuo. Purification by column chromatography on silica gel (hexane:EtOAc 4:1 with 1% Et_3N) gave indole **374** as a colourless solid (70 mg, 180 µmol, 65%).

^{1}H NMR (400 MHz, C_6D_6, δ): 8.31 – 8.10 (m, 1H), 7.66 (d, *J* = 8.3 Hz, 2H), 7.61 – 7.50 (m, 1H), 7.21 (s, 1H, H-k), 7.17 (m, 1H), 6.92 (t, *J* = 7.4 Hz, 1H), 6.50 (d, *J* = 8.0 Hz, 2H), 3.45 (s, 3H), 2.39 – 2.23 (m, 2H), 2.07 – 1.87 (m, 2H), 1.66 (s, 3H) ppm. **^{13}C NMR** (101 MHz, C_6D_6, δ): 168.8, 144.5, 141.1, 136.4, 136.3, 134.2, 129.8, 128.8, 128.6, 126.9, 125.5, 124.8, 124.2, 122.3, 113.7, 51.6, 27.7, 25.9, 21.0 ppm. **IR (neat sample)**: 2950, 1713, 1597, 1493, 1435, 1414, 1357, 1245, 1210,

1167, 1137, 1087, 1050, 1002, 924, 812, 795, 742, 703, 666 cm^{-1}. **HRMS** (ESI) (m/z): calc. for $C_{21}H_{19}NO_4S$ $[M + Na]^+$, 404.0932; found 404.0931.

7.3.14 *8-((*tert-*butyldimethylsilyl)oxy)-2-tosyl-2,6,9,9a-tetrahydro-1*H-*cyclohepta[*cd*]indol-1-one (378)*

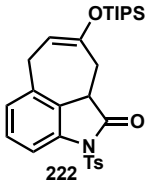


378

Diazo **337** (200 mg, 638 µmol, 1 equiv.) and dien **379** (118 mg, 638 µmol, 1 equiv.) were dissolved in benzene (50 µL). Rhodium (II) acetate (2.82 mg, 6.00 µmol, 1 mol%) was added and the mixture was heated to 50 °C. The reaction was stirred for 2.5 hours until no gas development could be observed. The product was purified by flash column chromatography (hexane:EtOAc 100:1) to give the product as a yellow oil. (191 mg, 382 µmol, 60%).

^{1}H-NMR (400 MHz, $CDCl_3$, δ): 0.05 (s, 3H), 0.11 (s, 3H), 0.88 (s, 9H), 2.10 (dd, 1 H, *J* = 14.7, 15.3 Hz, 1H), 2.42 (s, 3H), 2,68 (ddd, *J* = 4.9, 2.8, 17.0 Hz, 1H), 3.09 (dd, *J* = 8.1, 18.5 Hz, 1H), 3.59 (dd, *J* = 2.6, 18.6 Hz, 1H), 3.69 (dd, *J* = 5.0, 12.7 Hz, 1H), 5.03 (dd, *J* = 2.4, 8.2 Hz, 1H), 6.92 (d, *J* = 7.8 Hz, 1H), 7.24 (dd, *J* = 7.8, 7.8 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 2H) 7.76 (d, *J* = 8.2 Hz, 1H) 7.97 (d, *J* = 8.3 Hz, 2H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$, δ): –4.5, –4.3, 18.0, 21.8, 25.7, 29.7, 34.37, 42.47, 104.6, 111.6, 124.36, 126.9, 128.1, 128.7, 129.9, 135.4, 138.0, 138.5, 145.8, 148.9, 175.0 ppm.

7.3.15 *2-tosyl-8-((triisopropylsilyl)oxy)-2,6,9,9a-tetrahydro-1*H-*cyclohepta[*cd*]indol-1-one (222)*



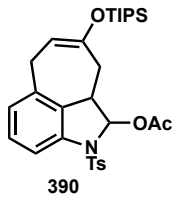
222

Enol **218** (8.46 g, 37.4 mmol, 2.25 equiv.) and diazo **337** (5.20 g, 16.6 mmol, 1 equiv.) were stirred at 70 °C and $Rh_2(OAc)_4$ (73.0 mg, 166 µmol, 1 mol%) was added. The mixture was stirred until complete by TLC (hexane:EtOAc 5:1). The crude was purified by flash column chromatography (hexane:EtOAc 25:1) to give the desired [*cd*]oxindole **222** in 39% (3.26 g, 6.37 mmol) yield as yellow solid. 38% (3.24 g, 14.3 mmol) of the TIPSEnol **218** could be recovered. The author wants to mention that the crude does not need to be purified for

further reaction.

^{1}H-NMR (400 MHz, $CDCl_3$, δ): 1.01 – 1.14 (m, 21H). 2.15 (dd, *J* = 14.9, 14.9 Hz, 2H), 2.42 (s, 3H), 2.75 (ddd, *J* = 2.7, 5.0, 16.9 Hz, 1H), 3.07 (dd, *J* = 8.2, 8.6 Hz, 1H), 3.58 (dd, *J* = 4.9, 18.5 Hz, 1H), 3.68 (dd, *J* = 4.9, 12.8 Hz, 1H), 5.05, (ddd, *J* = 2.4, 2.4, 8.2 Hz, 1H), 6.92 (d, *J* = 7.9 Hz, 1H), 7.24 (dd, *J* = 7.6, 7.8 Hz, 1H), 7.32 (d, *J* = 7.8 Hz, 2H), 7.76 (d, *J* = 8.2 Hz, 1H) 7.97 (d, *J* = 8.4 Hz, 2H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$, δ): 17.7, 18.2, 21.9, 29.6, 34.3, 42.4, 103.5, 111.6, 124.3, 126.9, 128.1, 128.7, 129.9, 135.5, 138.0, 138.5, 145.8, 149.2, 175.1 ppm. **IR (neat sample)**: 2944, 2866, 1751, 1660, 1606, 1455, 1367, 1306, 1243, 113, 1143, 1090, 883, 868, 815, 776, 727, 660 cm^{-1}. **HRMS** (ESI) (*m*/*z*): calcd for $C_{28}H_{37}NO_4SSi$ $[M + Na]^+$,534.2110; found 534.2110.

7.3.16 *2-tosyl-8-((triisopropylsilyl)oxy)-2,6,9,9a-tetrahydro-1*H-*cyclohepta[*cd*]indol-1-yl acetate (390)*



390

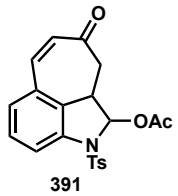
Oxindole **222** (9.61 g, 17.3 mmol, 1 equiv.) was dissolved in THF before MeOH was added. The solution was cooled to –20 °C and a white solid started to precipitate. $NaBH_4$ (1.30 g, 34.6 mmol, 2.2 equiv.) was added in one portion. The mixture was stirred until complete by TLC (hexane:EtOAc 5:1) [the author wants to mention to use vanillin stain. A side product is formed with nearly the same Rf as the starting material. It colors yellow while the substrate is blue.] The mixture was quenched by addition of NH_4Cl solution. The aqueous layer was extracted with Et_2O (3x 100 mL), the combined organic layers were washed with water, brine and dried over Na_2SO_4. The solvent was removed *in vacuo* and the crude was used without further purification.

The crude was dissolved in CH_2Cl_2 (90 mL), cooled to –20 °C and Et_3N (12.0 mL, 86.7 mmol, 5 equiv.) was added. After stirring for 5 minutes Ac_2O (4.90 mL, 34.7 mmol, 2 equiv.) was added and the reaction mixture was allowed to stir over night while warming to rt. When the reaction was complete by TLC (hexane:EtOAc 5:1) the crude was poured into water, the phases were separated and the aqueous layer was extracted with CH_2Cl_2 (1x 100 mL). The combined organic layers were a successively washed with 50% bicarb solution, NH_4Cl solution and brine before they were dried over Na_2SO_4. The solvent was removed *in vacuo* and the crude was purified by flash column chromatography to give **390** as off-white solid in 80%

(7.67 g, 13.8 mmol) yield. Advice: If the product stays oil, dissolve in Et_2O and concentrate slowly. The solid should appear immediately.

^{1}H-NMR (400 MHz, $CDCl_3$, δ): 0.93 – 1.06 (m, 21H), 1.32 (dd, *J* = 15.2 Hz, 15.4 Hz, 1H), 2.09 (s, 3H), 2.35 (s, 3H), 2.55 (ddd, *J* = 3.8, 3.8, 16.5 Hz, 1H), 2.88 (dd, *J* = 8.9, 17.6 Hz, 1H), 3.30 (dd, *J* = 4.4, 13.3 Hz, 1H), 3.54 (dd, *J* = 2.3, 17.5 Hz, 1H), 4.98 (d, *J* = 8.9 Hz, 1H), 6.29 (s, 1H), 6.80 (d, *J* = 7.6 Hz, 1H), 7.17 (dd, *J* = 7.8, 7.8 Hz, 1H), 7.22 (d, *J* = 8.0 Hz, 2H), 7.49 (d, *J* = 3.8 Hz, 1H), 7.72 (d, *J* = 8.1 Hz, 2H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$, δ): 21.6, 18.1, 21.3, 21.7, 29.1, 35.8, 45.6, 91.1, 103.7, 112.8, 123.3, 127.2, 128.8, 129.9, 131.7, 135.6, 138.9, 139.3, 144.6, 149.3, 170.1 ppm. **HRMS** (ESI) (*m*/*z*): calcd for $C_{30}H_{41}NO_5SSi$ $[M+ Na]^+$, 578.2372; found 578.2372.

7.3.17 *8-oxo-2-tosyl-2,8,9,9a-tetrahydro-1*H*-cyclohepta[*cd*]indol-1-yl acetate (391)*

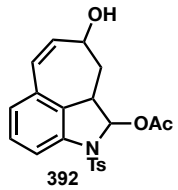


391

In two batches of same size! The triisopropylsilyl enol ether **390** (3.78 g, 7.40 mmol, 1 equiv.) was dissolved in anhydrous dimethylformamide (75 mL, 0.1 M) and cooled with stirring to 0 °C under a nitrogen atmosphere. Ceric ammonium nitrate (16.1 g, 39.4 mmol, 4 equiv.) was then added in five portions over ca.20 min. The resulting bright orange solution was then stirred for an additional 3 h (TLC, hexane:EtOAc 5:1). The reaction mixture was then poured into water and extracted with diethyl ether (5x 100 mL). The combined organic phases were washed with saturated $NaHCO_3$ solution, brine solution, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to afford a pale yellow oil. Purification by flash chromatography on silica gel (hexane:EtOAc 3:1 to 1:1) gave the desired ketone **391** in 80% (2.17 g, 5.50 mmol) yield as yellowish solid.

^{1}H-NMR (400 MHz, $CDCl_3$, δ): 2.05 – 2.12 (m, 1H), 2.13 (s, 3H), 2.38 (s, 3H), 3.00 (d, *J* = 16.2 Hz, 1H), 3.40 (d, *J* = 15.2 Hz, 1H), 6.11 (dd, *J* = 0.9, 12.3 Hz, 1H), 6.45 (d, *J* = 2.8 Hz, 1H), 7.00 (d, *J* = 12.4 Hz, 1H), 7.04 (d, *J* = 7.7 Hz, 1H), 7.26 (d, *J* = 8.0 Hz, 2H), 7.35 (dd, *J* = 7.9, 7.9 Hz, 1H), 7.68 (d, *J* = 8.3 Hz, 1H), 7.70 (d, *J* = 8.3 Hz, 2H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$, δ): 21.2, 21.7, 44.3, 45.6, 90.3, 116.6, 126.2, 127.4, 129.8, 130.1, 131.1, 131.4, 131.6, 134.6, 139.6, 140.2, 145.2, 169.9, 197.1 ppm. **HRMS** (ESI) (*m*/*z*): calcd for $C_{21}H_{19}NO_5S$ $[M + Na]^+$, 420.0882; found 420.0882.

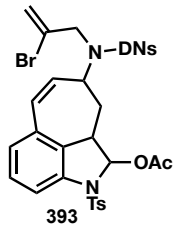
7.3.18 *8-hydroxy-2-tosyl-2,8,9,9a-tetrahydro-1*H-*cyclohepta[*cd*]indol-1-yl acetate (392)*



392

To a solution of ketone **391** (1.58 g, 3.98 mmol, 1 equiv.) in CH_2Cl_2 (35 mL) was added MeOH (70 mL) and $CeCl_3$*$7H_2O$ (2.96 g, 7.95 mmol, 2 equiv.). After stirring for 10 minutes the solution was cooled to 0 °C and $NaBH_4$ (221 mg, 5.96 mmol, 1.5 equiv.) was added slowly. When the reaction was complete by TLC (hexane:EtOAc 2:1) the reaction was quenched by addition of NH_4Cl solution. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3x 75 mL). The combined organic layers were washed with water and brine solution before they were dried over $MgSO_4$ and concentrated *in vacuo*. The crude was purified by flash column chromatography (hexane:EtOAc 1:1) to give the desired allylic alcohol **391** in 91% (1.44 g, 3.60 mmol) yield as white solid. (The crude can be used without further purification.) **^{1}H-NMR** (400 MHz, $CDCl_3$, δ): 1.48 (q, *J* = 11.9 Hz, 1H), 1.76 – 1.97 (m, 1H), 2.16 (s, 3H), 2.37 (s, 3H), 2.40 – 2.45 (m, 1H), 3.24 (dd, *J* = 3.3, 12.1 Hz, 1H), 4.58 – 4.71 (m, 1H), 5.72 (d, *J* = 12.4 Hz, 1H), 6.21 (d, *J* = 12.4 Hz, 1H), 6.44 (d, *J* = 3.9 Hz, 1H), 6.80 (d, *J* = 7.8 Hz, 1H), 7.18 (dd, *J* = 7.9, 7.9 Hz, 1H), 7.23 (d, *J* = 8.3 Hz, 2H), 7.46 (d, *J* = 8.0 Hz, 1H), 7.69 (d, *J* = 8.3 Hz, 2H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$, δ): 21.3, 21.7, 35.8, 45.4, 70.7, 91.3, 114.0, 125.6, 126.6, 127.5, 129.0, 129.7, 130.0, 132.0, 134.3, 134.7, 139.5, 144.9, 170.3 ppm. **IR (neat sample)**: 1710, 1597, 1424, 1359, 1291, 1237, 1174, 1137, 1088, 1035, 907, 810, 794, 727, 675, 657 cm^{-1}.

7.3.19 *8-((*N*-(2-bromoallyl)-2,4-dinitrophenyl)sulfonamido)-2-tosyl-2,8,9,9a-tetrahydro-1*H-*cyclohepta[*cd*]indol-1-yl acetate (393)*



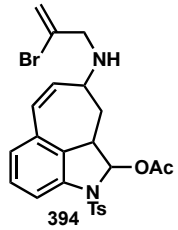
393

DEAD (135 µL, 854 µmol, 1.1 equiv.) in toluene (400 µL) was added dropwise to a 0 °C cold suspension of allylic alcohol **392** (310 mg, 776 µmol, 1 equiv.), sulphonamide **397** (300 mg, 815 µmol, 1.1 equiv.) and PPh_3 (262 mg, 854 µmol, 1.1 equiv.) in benzene (8 mL). Since the substrates hardly dissolved in benzene the reaction took six hours. Solvent was removed *in*

vacuo when the reaction was complete by TLC (hexane:EtOAc 1:1). The crude was purified by flash column chromatography (hexane:EtOAc 6:1 to 3:1) to give the desired product **393** in 87% (505 mg, 677 µmol) yield.

^{1}H-NMR (400 MHz, $CDCl_3$, δ): 1.64 (qd, *J* = 6.6, 13.7 Hz, 1H). 2.11 (s, 3H), 2.40 (s, 3H), 2.66 (td, *J* = 5.4, 13.9 Hz, 1H), 2.97 (d, *J* = 10.0 Hz, 1H), 4.19 (d, *J* = 17.6 Hz, 1H), 4.35 (d, *J* = 17.4 Hz, 1H), 4.51 (d, *J* = 5.9 Hz, 1H), 5.59 (s, 1H), 5.72 (dd, *J* = 4.8, 11.6 Hz, 1H), 5.92 (s, 1H), 6.36 (d, *J* = 2.4 Hz, 1H), 6.53 (dd, *J* = 2.2, 11.7 Hz, 1H), 6.88 (d, *J* = 7.6 Hz, 1H), 7.27 — 7.33 (m, 3H), 7.56 (d, *J* = 8.1 Hz, 1H), 7.70 (d, *J* = 8.3 Hz, 2H), 8.16 (d, *J* = 8.6 Hz, 1H), 8.44 (dd, *J* = 2.2, 8.6 Hz, 1H), 8.49 (d, *J* = 2.2 Hz, 1H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$, δ): 21.2, 21.8, 29.8, 41.8, 45.8, 54.0, 57.0, 90.8, 114.7, 120.1, 120.4, 124.6, 126.2, 127.2, 128.2, 129.4, 130.0, 130.2, 130.4, 132.0, 132.5, 133.7, 134.5, 138.8, 140.0, 145.3, 148.1, 150.0, 170.1 ppm. **IR (neat sample)**: 3363, 3114, 1630, 1597, 1538, 1430, 1411, 1347, 1246, 1167, 1153, 1093, 905, 894, 830, 749, 735, 707, 659 cm^{-1}. **HRMS** (ESI) (*m/z*): calcd for $C_{30}H_{27}N_4O_{10}S_2Br$ $[M + Na]^+$, 769.0250; found 769.0230.

7.3.20 *8-((2-bromoallyl)amino)-2-tosyl-2,8,9,9a-tetrahydro-1*H*-cyclohepta[*cd*]indol-1-yl acetate (394)*

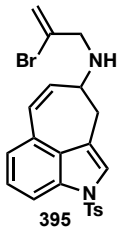


394

Thiophenol (59.0 µL, 835 µmol, 1.2 equiv.), followed by Et_3N (289 mg, 2.09 mmol, 3 equiv.) were added to a 0 °C cold solution of sulphonamide **393** (520 mg, 696 µmol, 1 equiv.) in CH_2Cl_2 (7 mL). The reaction mixture was stirred until complete by TLC (hexane:EtOAc 1:1) and the solvent was removed *in vacuo*. The crude was purified by flash column chromatography (hexane:EtOAc: Et_3N 100:100:1) to obtain the desired product **394** in 71% (256 mg, 495 µmol). **^{1}H-NMR** (400 MHz, $CDCl_3$, δ) 1.14 (qd, *J* = 3.3, 12.7 Hz, 1H), 2.14 (s, 3H), 2.30 – 2.35 (m, 1H), 2.37 (s, 3H), 3.29 – 3.33 (m, 2H), 3.52 (d, *J* = 2.6 Hz, 2H), 5.57 (s, 1H), 5.79 – 5.84 (m, 2H), 6.40 (d, *J* = 12.2 Hz, 1H), 6.48 (d, *J* = 3.0 Hz, 1H), 6.89 (d, *J* = 7.6 Hz, 1H), 7.18 – 7.25 (m, 3H), 7.47 (d, *J* = 8.0 Hz, 1H), 7.71 (d, *J* = 8.1 Hz, 2H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$, δ): 21.3, 21.7, 34.4, 45.0, 53.2, 54.4, 92.4, 113.4, 118.4, 118.5, 125.3, 127.5, 128.3, 128.5, 129.9, 131.6, 132.7, 132.9, 135.0, 139.5, 144.7, 170.3 ppm. **IR (neat sample)**: 1749, 1628, 1586, 1451, 1358, 1212, 1168, 1095, 1017, 907, 806, 733, 658 cm^{-1}. **HRMS** (ESI) (*m*/*z*): calcd for $C_{24}H_{25}N_2O_4SBr$ [M + Na]$^+$, 539.0616; found, 539.0618.

7.3.21 N-*(2-bromoallyl)-2-tosyl-8,9-dihydro-2*H-*cyclohepta[*cd*]indol-8-amine (395)*

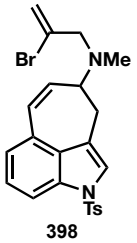


395

TFA (205 µL, 2.70 mmol, 4 equiv.) was added to a –78 °C cold solution of acetate **393** (505 mg, 676 µmol, 1 equiv.) in CH_2Cl_2 (7 mL) and the reaction mixture was allowed to warm to 0 °C. When the reaction was complete by TLC (hexane:EtOAc 2:1) it was cooled to –10 °C, Et_3N (656 µL, 4.73 mmol, 7 equiv.) was added, followed by mercaptoethanol (65.0 µL, 810 µmol, 1.2 equiv.). The temperature was raised to 0 °C. After the complete consumption of the starting material (TLC, hexane:EtOAc 2:1) the reaction mixture was concentrated *in vacuo* and the crude was purified by flash column chromatography (hexane:EtOAc 2:1) to give the amine **395** in 95% yield (292 mg, 639 µmol) as yellowish oil.

H-NMR (400 MHz, C_6D_6, δ): 1.64 (s, 3H), 2.57 – 2.65 (m, 2H), 3.16 (s, 2H), 3.24 – 3.29 (m, 1H), 5.29 (s, 1H), 5.49 (d, *J* = 1.4 Hz, 1H), 5.70 (dd, *J* = 4.4, 11.9 Hz, 1H), 6.28 (dd, *J* = 1.5, 11.9 Hz, 1H), 6.48 (d, *J* = 8.0 Hz, 2H), 6.83 (d, *J* = 8.0 Hz, 1H), 7.08 (dd, *J* = 7.9, 7.9 Hz, 1H), 7.28 (s, 1H), 7.66 (d, *J* = 8.6 Hz, 1H), 8.13 (d, *J* = 8.3 Hz, 1H) ppm. **^{13}C-NMR** (100 MHz, C_6D_6, δ): 21.0, 33.0, 55.2, 55.4, 113.2, 116.9, 121.0, 123.4, 124.8, 125.1, 126.9, 128.6, 128.7, 129.3, 129.9, 131.5, 133.8, 136.1, 136.2, 136.8, 144.5 ppm. **IR (neat sample)**: 2919, 2850, 1705, 1463, 1364, 1259, 1176, 1089, 798 ,664 cm^{-1}. **HRMS** (ESI) (*m*/*z*): calcd for $C_{22}H_{21}N_2O_2SBr$ [M + H]$^+$, 457.0585; not found.

7.3.22 N-*(2-bromoallyl)*-N-*methyl-2-tosyl-8,9-dihydro-2*H-*cyclohepta[*cd*]indol-8-amine (398)*



398

TFA (256 µL, 3.37 mmol, 4 equiv.) was added to a –78 °C cold solution of acetate **393** (630 mg, 842 µmol, 1 equiv.) in CH_2Cl_2 (8.5 mL) and the reaction mixture was allowed to warm to 0 °C. When the reaction was complete by TLC (hexane:EtOAc 2:1) it was cooled to –10 °C, Et_3N (820 µL, 5.90 mmol, 7 equiv.) was added, followed by mercaptoethanol (72.0 µL, 1.01 mmol, 1.2 equiv.). The temperature was raised to 0 °C. After the complete consumption of the starting material (TLC, hexane:EtOAc 2:1), the reaction mixture was diluted with MeOH (8.5 mL), the reaction mixture was cooled to 0 °C, AcOH (240 µL, 4.21 mmol, 5 equiv.), formalin solution (37% in water, 3.3 mL) and $NaBH_3CN$ (159 mg, 4.21 mmol,) were added successively. During the reaction, a precipitate could be observed that disappeared when the reaction proceeded. When the reaction was complete by TLC (hexane:EtOAc 2:1) the reaction mixture was poured into HCl solution (1 M) and the aqueous layer was extracted with CH_2Cl_2 (3x 20 mL), the combined organic layers were washed successively with bicarb solution, water and brine solution before they were dried over $MgSO_4$ and concentrated *in vacuo*.The crude was purified by flash column chromatography (hexane:EtOAc 4:1 to 2:1) to give the desired methylamine **398** in 82% (324 mg, 687 µmol) yield.

^{1}H-NMR (400 MHz, C_6D_6, δ): 1.64 (s, 3H), 2.03 (s, 3H), 2.42, (ddd, *J* = 1.8, 10.8, 14.1 Hz, 1H), 2.76 (d, *J* = 13.7 Hz, 1H), 3.02 (q, *J* = 16.9 Hz, 2H), 3.26 (ddd, *J* = 2.3, 5.7, 10.8 Hz, 1H),5.39 (d, *J* = 1.0 Hz, 1H), 5.64 (d, *J* = 1.2 Hz, 1H), 5.86 (ddd, *J* = 1.3, 3.5, 12.1 Hz, 1H), 6.33 (dd, *J* = 2.4, 12.2 Hz, 1H), 6.50 (d, *J* = 8.0 Hz, 1H), 6.85 (d, *J* = 7.6 Hz, 1H), 7.10 (dd, *J* = 7.9, 7.9 Hz, 1H), 7.25 (d, *J* = 1.9 Hz, 1H), 7.68 (d, *J* = 8.5 Hz, 2H), 8.15 (d, *J* = 8.3 Hz, 1H) ppm. **^{13}C-NMR** (100 MHz, C_6D_6, δ): 21.0, 28.8, 37.6, 61.9, 65.6, 113.1, 117.3, 121.4, 122.7, 124.7, 125.1, 127.0, 129.1, 129.3, 129.8, 131.7, 133.0, 135.5, 136.3, 136.3, 144.5 ppm. **IR (neat sample)**: 2924, 1749, 1629, 1595, 1423, 1359, 1213, 1163, 1110, 1088, 1016, 906, 818, 800, 752, 734, 704, 659 cm^{-1}

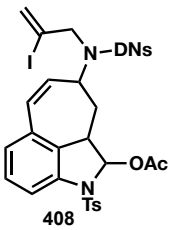
7.3.23 *methyl (2-bromoallyl)(2-tosyl-8,9-dihydro-2*H*-cyclohepta[*cd*]indol-8-yl)carbamate (399)*

399

Methyl chloroformate (55.0 µL, 703 µmol, 1.1 equiv.) was added dropwise to a –10 °C cold solution of amine **395** (292 mg, 639 µmol, 1 equiv.) in pyridine (640 µL). Since the acid chloride became solid at that temperature it was allowed to warm up slowly. (The author wants to mention, that warming to room temperature causes a heavy exothermic reaction) When the reaction was complete by TLC (hexane:EtOAc 2:1) the crude was cooled to room temperature or below. It was diluted with Et_2O (50 mL) and successively washed with HCl (1 M, 2x 25 mL), bicarb solution and brine. The organic phase was dried over $MgSO_4$, concentrated *in vacuo* and the crude was purified by flash column chromatography (hexane:EtOAc 4:1 to 3:1) to give the carbamate **399** in 80% (265 mg, 514 µmol) yield as brownish foam.

^{1}H-NMR (400 MHz, $CDCl_3$, δ): 2.35 (s, 3H), 3.09 – 3.14 (m, 1H), 3.22 – 3.40 (m, 1H), 3.75 (s, 3H), 3.98 – 4.27 (m, 2H), 4.46 – 4.76 (m, 1H) 5.58 (s, 1H), 5.77(s, 1H), 5.96 (ddd, *J* = 1.2, 3.5, 12.1 Hz, 1H), 6.5 (d, *J* = 11.7 Hz, 1H), 7.05 (d, *J* = 7.3 Hz, 1H), 7.22 (d, *J* = 8.0 Hz, 2H), 7.27 (dd, *J* = 7.8, 7.8 Hz, 1H), 7.33 (s, 1H), 7.76 (d, *J* = 8.3 Hz, 2H), 7.87 (d, *J* = 8.3 Hz, 1H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$, δ): 21.7, 33.2$^{(HSQC)}$, 53.1, 53.8$^{(HSQC)}$, 57.4, 113.0, 120.0, 122.7, 124.8, 125.0, 127.0, 128.6, 130.0, 130.6, 135.5, 135.6, 145.1, 156.6$^{(HMBC)}$ppm. **IR (neat sample)**: 2953, 1699, 1596, 1453, 1360, 1255, 1173, 1138, 1111, 1088, 1046, 914, 797, 771, 752, 662 cm^{-1}. **HRMS** (ESI) (*m*/*z*): calcd for $C_{24}H_{23}N_2O_4SBr$ $[M + Na]^+$, 537.0460; found, 537.0459.

7.3.24 *8-((*N*-(2-iodoallyl)-2,4-dinitrophenyl)sulfonamido)-2-tosyl-2,8,9,9a-tetrahydro-1*H*-cyclohepta[*cd*]indol-1-yl acetate (408)*



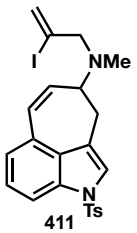
408

DEAD (190 µL, 1.20 mmol, 1.2 equiv.) in toluene (800 µL) was added dropwise to a 0 °C cold suspension of allylic alcohol **392** (400 mg, 1.00 mmol, 1 equiv.), sulphonamide **377** (455 mg,

1.10 mmol, 1.1 equiv.) and PPh_3 (315 mg, 1.20 mmol, 1.2 equiv.) in toluene (10.0 mL). Solvent was removed *in vacuo* when the reaction was complete by TLC (hexane:EtOAc 1:1). The crude was purified by flash column chromatography (hexane:EtOAc 6:1 to 3:1) to give the desired product **408** in 88% (662 mg, 886 µmol) yield. The excess of the sulphonamide **377** could also be re-isolated 9% (40.0 mg, 96.8 µmol).

^{1}H-NMR (400 MHz, $CDCl_3$, δ): 1.59 – 1.67 (m, 1H), 2.11 (s, 3H), 2.40 (s, 3H), 2.64 (ddd, *J* = 5.5, 5.5, 14.1 Hz, 1H), 2.95 (d, *J* = 10.3 Hz, 1H), 4.17 (d, *J* = 17.6 Hz, 1H), 4.35 (d, *J* = 17.8 Hz, 1H), 4.48 (d, *J* = 5.6 Hz, 1H), 5.69 (dd, *J* = 4.6, 11.7 Hz,, 1H), 5.88 (s, 1H), 6.36 (d, *J* = 2.4 Hz, 1H), 6.38 (d, *J* = 1.7 Hz, 1H), 6.52 (dd, *J* = 2.0, 11.7 Hz, 1H), 6.87 (d, *J* = 7.8 Hz, 1H), 7.24 – 7.32 (m, 3H), 7.55 (d, *J* = 8.1 Hz, 1H), 7.69 (d, *J* = 8.3 Hz, 2H), 8.14 (d, *J* = 8.8 Hz, 1H),8.44 (dd, *J* = 2.2, 8.6 Hz, 1H), 8.49(d, *J* = 2.0 Hz, 1H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$, δ): 21.3, 21.8, 41.8, 45.7, 57.0, 57.9, 90.8, 105.1, 114.7, 120.1, 124.6, 126.2, 127.3, 128.5, 129.4, 130.0, 130.2, 130.4, 132.0, 132.6, 133.8, 134.7, 138.8, 140.1, 145.3, 170.0 ppm. **IR (neat sample)**: 3102, 1734, 1596, 1538, 1453, 1351, 1216, 1164, 1093, 1012, 906, 851, 813, 733, 659 cm^{-1}. **HRMS** (ESI) (*m*/*z*): calcd for $C_{30}H_{27}N_4O_{10}S_2I$ $[M + Na]^+$, 817.0111; found 817.0107.

7.3.25 N-*(2-iodoallyl)*-N-*methyl-2-tosyl-8,9-dihydro-2*H-*cyclohepta[*cd*]indol-8-amine (411)*



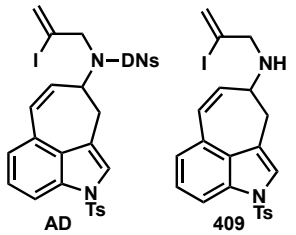
411

TFA (250 µL, 3.33 mmol, 4 equiv.) was added to a –25 °C cold solution of acetate **408** (662 mg, 833 µmol, 1 equiv.) in CH_2Cl_2 (9 mL) and the reaction mixture was allowed to warm to 0 °C. When the reaction was complete by TLC (hexane:EtOAc 2:1) it was cooled to –10 °C, Et_3N (810 µL, 5.83 mmol, 7 equiv.) was added, followed by mercaptoethanol (78.0 µL, 1.00 mmol, 1.2 equiv.). The temperature was raised to 0 °C. After the complete consumption of the starting material (TLC, hexane:EtOAc 2:1) the reaction mixture was diluted with MeOH (9 mL) and formaldehyde solution (37% in H_2O, 3.2 mL) before it was acidified with acetic acid (240 µL, 4.17 mmol, 5 equiv.) and treated with $NaBH_3CN$ (157 mg, 2.50 mmol, 3 equiv.) which was added in one portion. When the reaction was complete by TLC (hexane:EtOAc 2:1) the reaction mixture was concentrated *in vacuo* and purified by flash column chromatography

(hexane:EtOAc 6:1) to give the desired product **411** in 75% (324 mg, 625 µmol) yield as a dark yellow foam.

^{1}H-NMR (400 MHz, $CDCl_3$, δ): 2.35 (s, 6H), 2.82 (dd, *J* = 12.5, 12.5 Hz, 1H), 3.14 – 3.29 (m, 3H), 3.57 (d, *J* = 9.3 Hz, 1H), 5.85 (s, 1H), 6.08 (dd, *J* = 2.2, 11.9 Hz, 1H), 6.35 (s, 1H), 6.53 (d, *J* = 11.9 Hz, 1H), 7.03 (d, *J* = 7.3 Hz, 1H), 7.21 – 7.27 (m, 3H), 7.33 (s, 1H), 7.76 (d, *J* = 8.3 Hz, 2H), 7.84 (d, *J* = 8.3 Hz, 1H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$, δ): 21.7, 29.0, 37.9, 62.1, 65.0, 112.1, 112.7, 121.2, 122.3, 124.5, 124.9, 126.6, 127.0, 128.9, 129.0, 130.0, 135.4, 135.4, 135.5, 135.6, 145.0 ppm. **IR (neat sample)**: 2793, 1597, 1424, 1361, 1298, 1187, 1175, 1137, 1111, 1089, 1034, 911, 810, 753, 733, 670 cm^{-1}. **HRMS** (ESI) (*m*/*z*): calcd for $C_{23}H_{23}N_2O_2SI$ $[M + H]^+$, 519.0603; found 519.0606.

7.3.26 N-*(2-iodoallyl)-2,4-dinitro*-N-*(2-tosyl-8,9-dihydro-2*H-*cyclohepta[*cd*]indol-8-yl)benzenesulfonamide (AD) and* N-*(2-iodoallyl)-2-tosyl-8,9-dihydro-2*H-*cyclohepta[*cd*]indol-8-amine (409)*



TFA (510 µL, 6.70 mmol, 4 equiv.) was added to a –78 °C cold solution of acetate **408** (1.33 g, 1.68 mmol, 1 equiv.) in CH_2Cl_2 (17 mL) and the reaction mixture was allowed to warm to 0 °C. When the reaction was complete by TLC (hexane:EtOAc 2:1) it was cooled to –10 °C, Et_3N (1.63 mL, 11.8 mmol, 7 equiv.) was added, followed by mercaptoethanol (140 µL, 2.01 mmol, 1.2 equiv.). The temperature was raised to 0 °C. After the complete consumption of the starting material (TLC, hexane:EtOAc 2:1) the reaction mixture was concentrated *in vacuo* and the crude was purified by flash column chromatography (hexane:EtOAc 2:1) to give amine **409** in 70% yield (590 mg, 1.17 mmol) as yellowish brown oil. (The author wants to mention that the free amine decomposes quickly so the conversion to the carbamate should be performed quickly.)

Indole AD

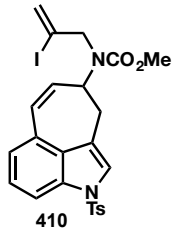
^{1}H-NMR (400 MHz, $CDCl_3$, δ): 2.36 (s, 3 H), 3.14 (dd, *J* = 10.7, 13.1 Hz, 1H), 3.38 (d, *J* = 14.1 Hz, 1H), 4.15 (d, *J* = 16.9 Hz, 1H), 4.36 (d, *J* = 16.9 Hz, 1H), 4.86 (d, *J* = 9.8 Hz, 1H), 5.81 (dd, *J* = 3.1, 12.2 Hz,, 1H), 5.92 (s, 1H), 6.48 – 6.53 (m, 2H), 7.01 (d, *J* = 7.4 Hz, 1H), 7.23 – 7.29 (m, 3H), 7.38

(s, 1H), 7.78 (d, *J* = 8.3 Hz, 2H), 7.89 (d, *J* = 8.3 Hz, 1H), 8.23 (d, *J* = 8.7 Hz, 1H), 8.40 (dd, *J* = 2.0, 8.7 Hz, 1H), 8.50 (d, *J* = 1.8 Hz, 1H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$, δ): 21.7, 33.7, 57.5, 58.6, 105.9, 113.5, 118.3, 120.1, 123.5, 125.2, 125.2, 126.3, 127.0128.4, 129.2, 129.7, 130.2, 130.7, 131.4, 134.0, 135.3, 135.4, 139.1, 145.3, 148.1, 150.0 ppm. **IR (neat sample)**: 2926, 1598, 1552, 1539, 1426, 1363, 1302, 1165, 1141, 1089, 917, 812, 745, 664 cm^{-1}. **HRMS** (ESI) (*m*/*z*): calcd for $C_{28}H_{23}N_4O_8S_2I$ $[M + Na]^+$, 756.9900; found 756.9903.

7.3.27 N-*(2-iodoallyl)-2-tosyl-8,9-dihydro-2*H-*cyclohepta[*cd*]indol-8-amine (409)*

^{1}H-NMR (400 MHz, $CDCl_3$, δ): 1.65 (s, 3H), 2.58 – 2.67 (m, 2H), 3.09 (s, 2H), 3.24 – 3.29 (m, 1H), 5.56 (s, 1H), 5.71 (dd, *J* = 4.4, 11.9 Hz, 1H), 5.93 (s, 1H), 6.28 (dd, *J* = 1.3, 11.8 Hz, 1H), 6.49 (d, *J* = 8.0, Hz, 2H), 6.83 (d, *J* = 7.5 Hz, 1H), 7.08 (dd, *J* = 7.9, 7.9 Hz, 1H), 7.29 (s, 1H), 7.66 (d, *J* = 8.3 Hz, 2H), 8.13 (d, *J* = 8.5 Hz, 1H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$, δ): 21.0, 33.0, 55.1, 58.9, 113.0, 113.2, 121.0, 123,4, 124.7, 125.1, 128.6, 128.8, 129.3, 131.5, 136.2, 136.2, 136.8, 144.4 ppm. **IR (neat sample)**: 1597, 1424, 1360, 1295, 1264, 1175, 1137, 1088, 913, 810, 795, 733, 702, 661 cm^{-1}. **HRMS** (ESI) (*m*/*z*): calcd for $C_{22}H_{21}N_2O_2SI$ $[M + H]^+$, 505.0447; found 505.0447.

7.3.28 Methyl (2-iodoallyl)(2-tosyl-8,9-dihydro-2H-cyclohepta[cd]indol-8-yl)carbamate (410)



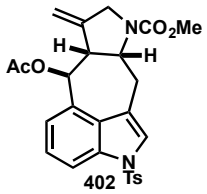
410

To a solution of amine **409** (215 mg, 426 µmol, 1 equiv.) in pyridine (450 µL) at 0 °C was added Chlorameisensäuremethylester (43.0 µL, 554 µmol, 1.3 equiv.). The acidchlorid became instantly solid. The reaction mixture was allowed to warm to 5 °C. When the reaction was complete by TLC (hexane:EtOAc 1:1) the reaction was diluted with Et_2O (20 mL) and quenched by pouring into HCl (1 M). The phases were separated and the aqueous layer was extracted with Et_2O (2x 30 mL), the combined organic layers were washed with bicarb solution, water and brine solution, before they were dried over $MgSO_4$. The crude was concentrated *in vacuo* and purified by flash column chromatography (hexane:EtOAc 3:2 to 2:1) to give the desired carbamate **410** as off white foam in 82% (197 mg, 350 µmol) yield. .

^{1}H-NMR (400 MHz, DMSO-d_6 340 K, δ): 2.33 (s, 3H), 3.19 (d, *J* = 14.3 Hz, 1H), 3.26 (dd, *J* = 11.4, 14.0 Hz, 1H), 3.66 (s, 3H), 4.06 (d, *J* = 17.0 Hz, 1H), 4.13 (d, *J* = 16.3 Hz, 1H), 4.40 (d, *J* = 8.5 Hz,

1H), 5.85 (d, *J* = 1.4 Hz, 1H), 6.04 (dd, *J* = 3.4, 12.0 Hz, 1H), 6.32 (d, *J* = 1.6 Hz, 1H), 6.52 (dd, *J* = 2.7, 12.2 Hz, 1H), 7.13 (d, *J* = 7.5 Hz, 1H), 7.31 (dd, *J* = 7.9, 7.9 Hz, 1H), 7.37 (d, *J* = 8.2 Hz, 2H), 7.58 (s, 1H), 7.79 (d, *J* = 7.9 Hz, 1H), 7.82 (d, *J* = 8.6 Hz, 1H) ppm. **^{13}C-NMR** (100 MHz, DMSO-d_6, 340 K, δ): 21.4, 53.0, 57.4, 108.5, 112.8, 120.5, 123.5, 125.0, 125.5, 125.9, 127.1, 127.9, 128.5, 130.7, 130.8, 135.0, 135.3, 135.8, 145.8 ppm. **IR (neat sample)**: 2952, 1697, 1538, 1454, 1361, 1235, 1165, 1089, 1046, 1012, 944, 914, 798, 751, 662 cm^{-1}. **HRMS** (ESI) (*m*/*z*): calcd for $C_{24}H_{23}N_2O_4SI$ [M + Na]$^+$, 585.0321; found 585.0323.

7.3.29 *methyl (6*R*,6a*S*,9a*S*)-6-acetoxy-7-methylene-2-tosyl-6,6a,7,8,9a,10-hexahydropyrrolo-[3',2':5,6]cyclohepta[1,2,3-*cd*]indole-9(2*H*)-carboxylate (402)*

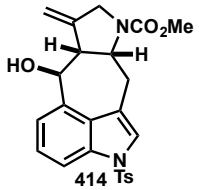


402

Iodide **402** (20.0 mg, 35.6 µmol, 1 equiv.) TBAC (21.0 mg, 74.7 µmol, 2.1 equiv.), CsOAc (40.0 mg, 206 µmol, 5.8 equiv.) were stirred in degased 1,4-Dioxane (100 µL) for 10 minutes. $Pd(OAc)_2$ (800 µg, 3.60 µmol, 10 mol%) was added and the reaction mixture was stirred at 55 to 60 °C for 2 hours. When the reaction was complete by TLC (hexane:EtOAc 1:1) it was quenched by addition of water. The aqueous layer was extracted with EtOAc (3x 10 mL). The combined organic layers were dried over $MgSO_4$ concentrated *in vacuo* and purified by flash column chromatography (hexane:EtOAc 3:2 to 1:1) to give the desired product **402** in 52% yield (8.70 mg, 17.6 mmol) as orange brown oil.

^{1}H-NMR (400 MHz, DMSO-d_6, 380 K, δ): 2.06, (s, 3H), 2.34 (s, 3H), 3.33 – 3.40 (m, 2H), 3.64 (s, 3H), 3.78 (dd, *J* = 7.0, 7.0 Hz, 1H), 3.83 (d, *J* = 14.9 Hz, 1H), 4.85 (dd, *J* = 2.2, 8.3 Hz, 2H), 6.14 (d, *J* = 6.2 Hz, 1H), 7.13 (d, *J* = 7.1 Hz, 1H), 7.26 (dd, *J* = 7.8, 7.8 Hz, 1H), 7.34 (d, *J* = 8.1 Hz, 2H), 7.45 (s, 1H), 7.70 (d, *J* = 85 Hz, 2H), 7.81 (d, *J* = 8.4 Hz, 1H) ppm. **^{13}C-NMR** (100 MHz, DMSO-d_6, 380 K, δ): 20.2, 20.3, 49.0, 50.5, 51.3, 59.2, 74.8, 108.2, 113.1, 116.3, 119.7, 123.5, 124.0, 125.7, 129.2, 129.5, 130.2, 134.3, 134.6, 144.2, 144.6, 153.4, 168.5 ppm. **IR (neat sample)**: 1737, 1697, 1597, 1448, 1358, 1223, 1176, 1105, 1090, 1017, 959, 907, 812, 758, 702, 665 cm^{-1}. **HRMS** (ESI) (*m*/*z*): calcd for $C_{26}H_{26}N_2O_6S$ [M + Na]$^+$, 517.1409; found 517.1407.

7.3.30 *methyl (6*R*,6a*S*,9a*S*)-6-hydroxy-7-methylene-2-tosyl-6,6a,7,8,9a,10-hexahydropyrrolo[3',2':5,6]cyclohepta[1,2,3-*cd*]indole-9(2*H*)-carboxylate (414)*

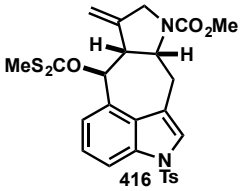


414

Acetate **402** (100 mg, 202 µmol, 1 equiv.) and Mg (24.3 mg, 1.01 mmol, 5 equiv.) were suspended in MeOH (2 mL) and the reaction mixture was treated with ultrasonic. When the reaction was complete by TLC (hexanes:EtOAc 1:1) the solid was filtered off, the curde was concentrated *in vacuo* and purified by preparative TLC (hexane:EtOAc 1:2) to give the desired product **414** in 55% (50.0 mg, 111 µmol) yield.

^{1}H-NMR (400 MHz, $CDCl_3$, δ): 2.33 (s, 3H), 2.95 – 4.05 (m, 9H), 4.44 (s, 1H), 4.94 (s, 1H), 5.07 (s, 1H), 5.11 (d, *J* = 6.9 Hz, 1H), 7.30 (s, 1H), 7.12 – 7.24 (m, 4H), 7.68 (d, *J* = 7.9 Hz, 2H), 7.85 (d, *J* = 8.04 Hz, 1H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$, δ): 27.0, 29.8, 50.9, 52.3, 52.6, 60.1, 74.5, 109.2, 113.7, 120.5, 122.1, 123.5, 124.7, 126.8, 129.9, 135.6, 144.9 ppm.

7.3.31 *methyl (6*R*,6a*S*,9a*S*)-7-methylene-6-(((methylthio)carbonothioyl)oxy)-2-tosyl-6,6a,7,8,9a,10-hexahydropyrrolo[3',2':5,6]cyclohepta[1,2,3-*cd*]indole-9(2*H*)-carboxylate (416)*



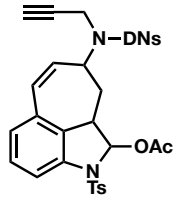
416

To a 0 °C cold suspension of NaH (60%, 13.3 mg, 332 µmol, 5 equiv.), in THF (1.5 mL), was added CS_2 (40.0 µL, 663 µmol, 10 equiv.) and alcohol **414** (30 mg, 66.3 µmol, 1 equiv.) in THF (1.7 mL). After stirring for 90 minutes, MeI (83.0 µL, 1.33 mmol, 20 equiv.) was added and the reaction mixture was stirred for further 60 minutes. The reaction was quenched by the addition of water, the aqueous layer was extracted with EtOAc (3x 20 mL), the combined organic layers were washed with brine solution and dried over $MgSO_4$. The solvent was removed *in vacuo* and the crude was purified by flash column chromatography (hexane:EtOAc 1:1) to give the desired product **416** as colourless oil in 69% (25.0 mg, 46.1 µmol) yield.

^{1}H-NMR (400 MHz, DMSO-d_6, 380 K, δ): 2.34 (s, 3H), 2.48 (s, 3H), 2.93 (qd, *J* = 2.0, 15.8 Hz, 1H), 3.25 (qd, *J* = 1.7, 15.8 Hz, 1H), 3.42 (dd, *J* = 3.4, 16.1 Hz, 1H), 3.65 (s, 3H), 3.82 – 3.87 (m, 2H), 4.58 (td, *J* = 3.5,9.3 Hz, 1H), 4.76 (qd, *J* = 2.2, 16.7 Hz, 1H), 5.40 (d, *J* = 5.2 Hz, 1H), 7.15 (d,

J = 7.3 Hz, 1H), 7.22 (dd, *J* = 7.9, 7.9 Hz, 1H), 7.34 (d, *J* = 7.9 Hz, 2H), 7.43 (d, *J* = 1.7 Hz, 1H), 7.67 (d, *J* = 8.2 Hz, 2H), 7.75 (d, *J* = 8.2 Hz, 1H) ppm. **^{1}H-NMR** (400 MHz, $CDCl_3$, δ): 2.07 (s, 3H), 2.35 (s, 3H), 3.01 (d, *J* = 15.1 Hz, 1H), 3.44 (s, 2H), 3.65 – 3.92 (m, 6H), 5.57 (s, 1H), 4.81 (s, 1H), 4.87 (s, 1H), 5.35 (s, 1H), 6.19 (d, *J* = 7.0 Hz, 1H), 7.11 (d, *J* = 7.1 Hz, 1H), 7.19 – 7.22 (s, 3H), 7.33 (s, 1H), 7.67 (d, *J* = 8.0 Hz, 2H), 7.88 (d, *J* = 8.0 Hz, 1H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$, δ): 1.2, 19.4, 21.7, 27.1, 29.8, 49.4, 51.3, 52.5, 60.4, 85.0, 109.7, 114.8, 120.0, 124.5, 125.7, 126.8, 128.9, 130.0, 135.7, 145.0, 154.8, 215.0 ppm. **IR (neat sample)**: 2366, 1699, 1449, 1361, 1175, 1138, 1090, 869, 812, 757, 671, 663 cm^{-1}. **HRMS** (ESI) (*m*/*z*): calcd for $C_{26}H_{26}N_2O_5S_3$ $[M + Na]^+$, 565.0902; found 565.0904.

7.3.32 *8-((2,4-dinitro*-N-*(prop-2-yn-1-yl)phenyl)sulfonamido)-2-tosyl-2,8,9,9a-tetrahydro-1*H-*cyclohepta[*cd*]indol-1-yl acetate (424)*

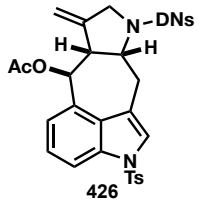


424

DEAD (60.0 µL, 376 µmol, 1.2 equiv.) in toluene (100 µL) was added dropwise to a suspension of alcohol **392** (125 mg, 313 µmol, 1 equiv.), sulphonamide **422** (100 mg, 344 µmol, 1.1 equiv.) and PPh_3 (100 mg, 376 µmol, 1.2 equiv.) at 0 °C. The reaction mixture was stirred for 1 h until complete by TLC (hexane:EtOAc 1:1). The solvent was removed *in vacuo* and the crude was purified by flash column chromatography (hexane:EtOAc 3:1) to give the desired product **424** as a pale yellow foam in 98% (205 mg, 308 µmol) yield.

^{1}H-NMR (400 MHz, $CDCl_3$, δ):1.62 (ddd, *J* = 6.3, 13.4, 13.4 Hz, 1H), 2.09 (s, 3H), 2.20 (t, *J* = 2.4 Hz, 1H), 2.39 (s, 3H), 2.67 (td, *J* = 4.9, 14.1 Hz, 1H), 3.14 (dd, *J* = 2.3, 12.8 Hz, 1H), 4,28 (d, *J* = 2.4 Hz, 2H), 4.59 – 4.65 (m, 1H), 5.86 (dd, *J* = 4.7, 11.9 Hz, 1H), 6.35 (d, *J* = 2.5 Hz, 1H), 6.59 (dd, *J* = 2.2, 11.9 Hz, 1H), 6.92 (d, *J* = 7.7 Hz, 1H), 7.26 – 7.28 (m, 2H), 7.30 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.55 (d, *J* = 7.9 Hz, 1H), 7.68 (d, *J* = 8.5 Hz, 2H), 8.33 (d, *J* = 8.6 Hz, 1H), 8.46 – 8.53 ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$, δ): 20.4, 21.8, 29.8, 33.5, 34.6, 58.4, 74.3, 78.7, 91.3, 113.5, 118.4, 120.0, 123.5, 125.1, 126.2, 127.0, 128.5, 129.8, 130.2, 131.1, 131.2, 133.8, 135.2, 135.4, 139.5, 145.3, 148.3, 150.0 ppm.

7.3.33 *(6*R*,6a*S*,9a*S*)-9-((2,4-dinitrophenyl)sulfonyl)-7-methylene-2-tosyl-2,6,6a,7,8,9,9a,10-octahydropyrrolo[3',2':5,6]cyclohepta[1,2,3-*cd*]indol-6-yl acetate (426)*



426

$Au(PPh_3)Cl$ (300 µg, 600 nmol, 2 mol%) and $AgSbF_6$ (210 µg, 600 nmol, 2 mol%) were stirred in degased and dry CH_2Cl_2 (100 µL). To the blue/purple solution was added enyne **424** (20.0 mg, 30.0 µmol, 1 equiv.).

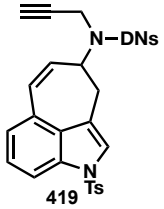
1. if reaction is concentrated after 5 minutes only elimination of acetic acid takes place quantitatively to give **419**.

2. reaction time up to 15 minutes gives the ring closure product containing the acetate in benzylic position.

The crude was concentrated *in vacuo* and purified by flash column chromatography (hexane:EtOAc 2:1) to give product **426** in 25% (5.00 mg, 7.50 µmol) yield.

^{1}H-NMR (400 MHz, $CDCl_3$, δ): 2.04 (s, 3H), 2.36 (s, 3H), 3.09 (dd, *J* = 1.7, 13.4 Hz, 1H), 3.28 (dd, *J* = 5.4, 15.3 Hz, 1H), 3.58 (d, *J* = 15.4 Hz, 1H), 3.76 (ddd, *J* = 1.5, 6.1, 8.6 Hz, 1H), (d, *J* = 15.4 Hz, 1H), 3.88 (dd, *J* = 14.4 Hz, 1H), 4.75 (dd, *J* = 2.7, 8.8 Hz, 1H), 4.88 (d, *J* = 1.4 Hz, 1H), 4.96 (d, *J* = 1.2 Hz, 1H), 6.09 (d, *J* = 5.8 Hz, 1H), 7.05 (s, 1H), 7.11 (d, *J* = 7.3 Hz, 1H), 7.20 – 7.25 (m, 3H), 7.70 (d, *J* = 8.3 Hz, 2H), 8.07 (d, *J* = 8.6 Hz, 1H), 8.46 – 8.50 (m, 2H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$, δ): 21.5, 21.7, 29.6, 51.4, 53.5, 63.6, 76.4, 110.9, 114.6, 118.7, 120.1, 124.3, 124.9, 125.3, 126.2, 126.9, 129.6, 129.8, 130.1, 132.0, 135.2, 135.5, 138.3, 142.9, 145.3, 148.4, 150.0, 169.8 ppm. **IR (neat sample)**: 2924, 2854, 1730, 1661, 1598, 1537, 1461, 1351, 1260, 1167, 1088, 1017, 797, 736, 702, 665 cm^{-1}. **HRMS** (ESI) (*m/z*): calcd for $C_{30}H_{26}N_4O_{10}S_2$ $[M + Na]^+$, 689.0988; found 689.0991.

7.3.34 *2,4-dinitro-*N*-(prop-2-yn-1-yl)-*N*-(2-tosyl-8,9-dihydro-2*H*-cyclohepta[*cd*]indol-8-yl)benzenesulfonamide (419)*



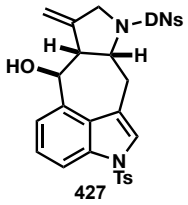
419

TFA (23.0 µL, 300 µmol, 4 equiv.) was added to a –78 °C cold solution of acetate **424** (50.0 mg, 75.0 mmol, 1 equiv.) in CH_2Cl_2 (750 µL). After stirring for 10 minutes the reaction mixture was

allowed to warm to 0 °C. When the reaction was complete by TLC (hexane:EtOAc 2:1) the reaction mixture was poured into bicarb solution, the aqueous layer was extracted with CH_2Cl_2 (3x 10 mL), the combined organic layers were dried over $MgSO_4$ and the solvent was removed *in vacuo*. The crude was purified by flash column chromatography (hexane:EtOAc 3:1) to give the desired product **419** as pale yellow semi solid 92%.

^{1}H-NMR (400 MHz, $CDCl_3$, δ): 2.23 (t, *J* = 2.3 Hz, 1H), 2.36 (s, 3H), 3.26 – 3.39 (m, 2H), 4.19 (dd, *J* = 2.4, 18.8 Hz, 1H), 4.35 (dd, *J* = 2.4, 18.8 Hz, 1H), 4.87 (ddd, *J* = 3.2, 3.2, 6.8 Hz, 1H), 5.86 (dd, *J* = 2.8, 12.0 Hz, 1H), 6.54 (dd, *J* = 2.4, 12.2 Hz, 1H), 7.04 (d, *J* = 7.3 Hz, 1H), 7.24 – 7.26 (m, 2H), 7.26 - 7.29(m, 1H), 7.39 (s, 1H), 7.77 (d, *J* = 8.6 Hz, 2H), 7.88 (d, *J* = 8.5 Hz, 1H), 8.36 (d, *J* = 8.8 Hz, 1H), 8.45 (dd, *J* = 2.2, 8.5 Hz, 1H), 8.49 (d, *J* = 2.2 Hz, 1H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$, δ): 21.8, 33.5, 34.7, 58.5, 74.3, 78.7, 113.5, 118, 4, 120.0, 123.5, 125.1, 126.2, 127.0, 128.5, 129.8, 130.2, 131.1, 131.2, 133.8, 135.3, 135.5, 139.2, 145.3, 148.2, 150.0 ppm. **IR (neat sample)**: 1597, 1551, 1537, 1349, 1165, 1140, 1087, 1041, 902, 812, 734, 702, 671, 662 cm^{-1}. **HRMS** (ESI) (*m*/*z*): calcd for $C_{28}H_{22}N_4O_8S_2$ $[M + Na]^+$, 629.0777; found 629.0775.

7.3.35 *(6*R*,6a*S*,9a*S*)-9-((2,4-dinitrophenyl)sulfonyl)-7-methylene-2-tosyl-2,6,6a,7,8,9,9a,10-octahydropyrrolo[3',2':5,6]cyclohepta[1,2,3-*cd*]indol-6-ol (427)*



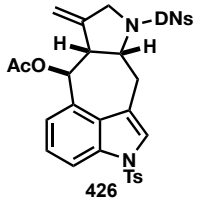
427

For preparation of the catalyst Au(I)(PPh_3)Cl (6.50 mg, 13.2 µmol) and $AgSbF_6$ (4.53 mg, 13.2 µmol) were added in a glovebox to a flame dried Schlenk flask which was sealed with a rubber septum. After unloading from the glovebox dry and degased CH_2Cl_2 (2 mL) was added and the reaction mixture was stirred under exclusion of light until a purple suspension has been formed.

The catalyst solution (350 µL, 2 mol%) was added to a solution of alkyne **419** (78.0 mg, 129 µmol, 1 equiv.) in degased and dry CH_2Cl_2 (2.2 mL) followed by dioxane:water (5:1, 200 µL). The reaction mixture treated with ultrasonic until no further conversion could be observed. The solvent was removed *in vacuo* and the crude was purified by flash column chromatography (hexane:EtOAc 3:1 to 3:2) to give the desired product **427** in 52% (41.5 mg, 66.4 µmol) as yellow oil and the substrate **419** in 37% (29.0 mg, 47.8 µmol) yield.

^{1}H-NMR (400 MHz, $CDCl_3$, δ): 2.35 (s, 3H), 3.18 – 3.22 (m, 2H), 3.63 – 3.67 (m, 2H), 3.97 (d, *J* = 14.3 Hz, 1H), 4.68 (ddd, *J* = 2.3, 6.4, 8.8 Hz, 1H), 4.96 (d, *J* = 1.8 Hz, 1H), 5.02 (d, *J* = 6.1 Hz, 1H), 5.06 (d, *J* = 1.7 Hz, 1H), 6.96 (s, 1H) 7.08 (d, *J* = 7.3 Hz, 1H), 7.22 (dd, *J* = 7.9, 7.9 Hz, 2H), 7.69 (d, *J* = 8.4 Hz, 2H), 7.88 (d, *J* = 8.4 Hz, 1H), 8.07 (d, *J* = 8.6 Hz, 1H), 8.46 (d, *J* = 2.0 Hz, 1H), 8.48 (dd, *J* = 2.3, 8.5 Hz, 1H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$, δ): 21.7, 29.2, 53.5, 53.5, 63.7, 110.4, 114.3, 119.1, 120.1, 122.9, 123.9, 125.0, 126.1, 126.9, 129.1, 130.1, 131.9, 134.0, 135.2, 135.6, 138.5, 143.8, 145.2, 148.2, 150.0 ppm. **IR (neat sample)**: 2355, 1730, 1597, 1553, 1539, 1434, 1359, 1249, 1167, 1137, 1090, 907, 745, 671, 663 cm^{-1}. **HRMS** (ESI) (*m*/*z*): calcd for $C_{28}H_{24}N_4O_9S_2$ $[M + Na]^+$, 647.0882; found 647.0883.

7.3.36 *(6*R*,6a*S*,9a*S*)-9-((2,4-dinitrophenyl)sulfonyl)-7-methylene-2-tosyl-2,6,6a,7,8,9,9a,10-octahydropyrrolo[3',2':5,6]cyclohepta[1,2,3-*cd*]indol-6-yl acetate (426)*



426

For preparation of the catalyst Au(I)(PPh_3)Cl (18.0 mg, 36.4 µmol) and $AgSbF_6$ (18.0 mg, 52.4 µmol) were added in a glovebox to a flame dried Schlenk flask which was sealed with a rubber septum. After unloading from the glovebox dry and degased CH_2Cl_2 (3 mL) was added and the reaction mixture was stirred for 10 minutes under exclusion of light.

The reaction has been performed in 33 µmol batches.

Procedure A: To a suspension of alkyn **419** (20.0 mg, 33.0 µmol, 1 equiv.) in CH_2Cl_2 (500 µL) was added a solution of acetic acid (50.0 µL, 857 µmol, 26 equiv.) and acetic anhydride (50.0 µL, 528 µmol, 16 equiv.) followed by the gold catalyst solution (200 µL, 2.40 µmol, 7 mol%). The vessel was sealed and treated with ultrasonic at 55 °C. The suspension became a yellow solution, then orange finally black brown suspension. When the reaction was complete by TLC (hexane:EtOAc 3:1) the solvent was removed *in vacuo* and the crude was purified by flash column chromatography (toluene:EtOAc 10:1) to give the desired product **426** in 90 to 97% yield (20 mg, 32.0 µmol).

Advice:

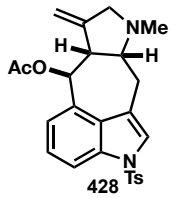
Product crystalizes on column if hexane is used.

repeat the column if necessary otherwise defunctionalization will not work.

Procedure B: If A gives just baseline spot and a red solution.

To a suspension of alkyn **419** (20.0 mg, 33.0 µmol, 1 equiv.) in CH_2Cl_2 (500 µL) was added acetic acid (50.0 µL, 857 µmol, 26 equiv.) and acetic anhydride (50.0 µL, 528 µmol, 16 equiv.). The reaction mixture was treated with ultrasonic at 40 °C for 3 minutes. Gold catalyst solution (200 µL, 2.40 µmol, 7 mol%) was added, the vessel was sealed and treated with ultrasonic at 40 °C. The reaction mixture became light red after 60 to 120 seconds. TLC control (hexane:EtOAc 2:1) of the reaction showed complete consumption of the starting material. The reaction mixture was cooled to 0 °C. And the solvent was removed *in vacuo* at room temperature (no water bath). Purification was performed by flash column chromatography (hexane:toluene:EtOAc 3:1:1 - 1:1:1) to give **426** in 90 to 97% yield. An increased temperature during workup causes further reaction which leads to decomposition.

7.3.37 *(6*R*,6a*S*,9a*S*)-9-methyl-7-methylene-2-tosyl-2,6,6a,7,8,9,9a,10-octahydropyrrolo-[3',2':5,6]cyclohepta[1,2,3-*cd*]indol-6-yl acetate (428)*



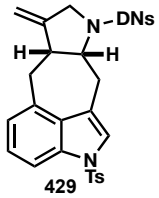
428

Thiophenol (7.00 µL, 69.0 µmol, 1.15 equiv.), followed by Cs_2CO_3 (23.0 mg, 69.0 µmol, 1.15 equiv.) were added to a 0 °C cold solution of sulphonamide **426** (40.0 mg, 60.0 µmol, 1 equiv.) in MeCN (1.2 mL). The reaction mixture was stirred until complete by TLC (hexane:EtOAc 1:1). Acetic acid (2.0 µL, 36.0 µmol, 0.6 equiv.) was added. When no further gas evolution could be observed formaldehyde solution (37% in water:MeOH, 13.0 µL, 150 µmol, 2.5 equiv.) was added. The reaction mixture was stirred at the same temperature for 10 minutes before $NaBH_3CN$ (4.00 mg, 66.0 µmol, 1.1 equiv.) and acetic acid (10.0 µL, 180 µmol, 3 equiv.) were added. When the reaction was complete by TLC (EtOAc:Hexane: 7N NH_3 in MeOH 200:100:3) the reaction mixture was neutralised with bicarb (solid), solvent was removed *in vacuo* and the crude was purified by flash column chromatography (hexane:EtOAc: 7N NH_3 in MeOH 100:100:1) to give the desired product **428** in 63% (17.0 mg, 37.7 µmol) yield.

^{1}H-NMR (400 MHz, $CDCl_3$, δ): 2.02 (s, 3H), 2.19 (s, 3H), 2.35 (s, 3H), 2.79 – 3.06 (m, 3H), 3.29 – 3.48 (m, 3H), 5.00 (d, *J* = 14.1 Hz, 2H), 6.16 (d, *J* = 6.2 Hz, 1H), 7.11 (d, *J* = 7.2 Hz, 1H), 7.16 – 7.22 (m, 3H)2, 7.33 (s, 1H), 7.73 (d, *J* = 8.3 Hz, 2H), 7.85 (d, *J* = 8.3 Hz, 1H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$, δ): 21.6, 21.7, 25.6, 39.7, 51.1, 61.6, 67.6, 107.5, 114.0, 120.9, 122.8, 124.1, 124.3, 126.9, 129.9, 130.4, 135.7, 135.8, 144.8, 146.2, 169.9 ppm.

7.3.38 *(6a*S*,9a*S*)-9-((2,4-dinitrophenyl)sulfonyl)-7-methylene-2-tosyl-2,6,6a,7,8,9,9a,10-octahydropyrrolo[3',2':5,6]cyclohepta[1,2,3-*cd*]indole (429)*



429

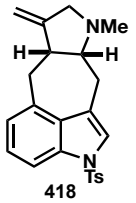
Acetate **426** (10.0 mg, 15.0 µmol, 1 equiv.) was dissolved in freshly distilled $CHCl_3$ (150 µL). $InBr_3$ (300 µg, 700 nm, 5 mol%) and Et_3SiH (10.0 µL, 60.0 µmol, 4 equiv.) was added and the reaction mixture was treated with ultrasonic at 55 °C. First the suspension became a clear solution, then yellow suspension and the reaction is complete when the suspension becomes orange (TLC, hexane:EtOAc 3:2). The crude was purified by flash column chromatography (toluene:EtOAc 30:1) to give the desired product **429** in 49% (4.50 mg, 7.40 µmol) yield.

Advidce:

1) The substrate has to be absolutely pure
2) The solvent has to be freshly distilled
3) Aqueous workup caused drop of yield.
4) Hexane for column chromatography cause crystallization on column.

^{1}H-NMR (600 MHz, CD_3CN, δ): 2.34 (s, 3H), 3.13 – 3.18 (m, 2H), 3.18 (dd, *J* = 1.2, 8.9 Hz, 1H), 3.25 (dd, *J* = 4.3, 15.2 Hz, 1H), 3.37 – 3.41 (m, 1H), 3.75 (d, *J* = 14.1 Hz, 1H), 4.08 (d, *J* = 14.3 Hz, 1H), 4.33 (dd, *J* = 2.8, 9.1 Hz, 1H), 5.01 (q, *J* = 2.3 Hz, 1H), 5.05 (q, *J* = 2.2 Hz, 1H), 6.95 (d, *J* = 7.4 Hz, 1H), 7.18 (dd, *J* = 7.8, 7.8 Hz, 1H), 7.30 – 7.32 (m, 3H), 7.73 (d, *J* = 8.5 Hz, 1H), 7.75 (d, *J* = 8.4 Hz, 2H), 8.10 (d, *J* = 8.8 Hz, 1H), 8.43 (dd, *J* = 2.2, 8.2 Hz, 1H), 8.55 (d, *J* = 8.5 Hz, 1H) ppm. **^{13}C-NMR** (150 MHz, CD_3CN, δ): 21.6, 30.0, 33.8, 47.7, 53.7, 64.7, 108.9, 113.0, 120.8, 121.5, 123.9, 124.4, 124.5, 126.3, 127.7, 127.7, 127.8, 131.0, 131.4, 133.0, 134.5, 135.7, 135.9, 137.2, 146.8, 147.8 ppm. **IR (neat sample)**: 2956, 2924, 2854, 1697, 1597, 1450, 1374, 1360, 1264, 1175, 1131, 1088, 894, 812, 733, 702, 670 cm^{-1}. **HRMS** (ESI) (*m*/*z*): calcd for $C_{28}H_{24}N_4O_8S_2$ $[M + Na]^+$, 631.0933; found, 631.0934.

7.3.39 *(6a*S*,9a*S*)-9-methyl-7-methylene-2-tosyl-2,6,6a,7,8,9,9a,10-octahydropyrrolo-[3',2':5,6]cyclohepta[1,2,3-*cd*]indole (418)*

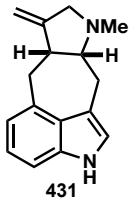


418

Thiophenol (8.00 µL, 75.6 µmol, 1.15 equiv.), followed by Cs_2CO_3 (25.0 mg, 75.6 µmol, 1.15 equiv.) were added to a 0 °C cold solution of sulphonamide **429** (40.0 mg, 65.7 µmol, 1 equiv.) in MeCN (1.3 mL). The reaction mixture was stirred until complete by TLC (hexane:EtOAc 1:1). Acetic acid (2.30 µL, 39.4 µmol, 0.6 equiv.) was added. When no further gas evolution could be observed formaldehyde solution (37% in water/MeOH, 15.0 µL, 164 µmol, 2.5 equiv.) was added. The reaction mixture was stirred at the same temperature for 10 minutes before $NaBH_3CN$ (4.50 mg, 72.3 µmol, 1.1 equiv.) and acetic acid (11.3 µL, 197 µmol, 3 equiv.) were added. When the reaction was complete by TLC (EtOAc:Hexane: 7N NH_3 in MeOH 200:100:3) the reaction mixture was neutralised with bicarb (solid), solvent was removed *in vacuo* and the crude was purified by flash column chromatography (hexane:EtOAc: 7N NH_3 in MeOH 100:100:1) to give the desired product **418**. Yield is not optimised.

^{1}H-NMR (600 MHz, CD_3CN, δ): 2.26 (s, 3H), 2.33 (s, 3H), 2.74 (s, 1H), 2.81 (d, *J* = 12.5 Hz, 1H), 2.92 (dd, *J* = 9.1, 14.8 Hz, 1H), 3.02 – 3.04 (m, 2H), 3.11 (dd, *J* = 3.5, 14.8 Hz, 1H), 3.22 (dd, *J* = 9.3, 15.4 Hz, 1H), 3.34 (d, *J* = 12.2 Hz, 1H), 4.96 (d, *J* = 20.3 Hz, 2H), 6.95 (d, *J* = 7.1 Hz, 1H), 7.15 (dd, *J* = 7.8, 7.8 Hz, 1H), 7.30 (d, *J* = 7.9 Hz, 2H), 7.34 (s, 1H), 7.69 (d, *J* = 8.4 Hz, 1H), 7.76 (d, *J* = 8.5 Hz, 1H) ppm. **^{13}C-NMR** (150 MHz, CD_3CN, δ): 21.6, 27.2, 35.2, 40.3, 48.1, 62.5, 69.6, 105.4, 112.5, 123.0, 124.1, 125.9, 127.7, 131.0, 132.0, 135.9, 135.9, 136.6, 146.6 ppm. **IR (neat sample)**: 2929, 1734, 1596, 1454, 1433, 1361, 1211, 1176, 1133, 1090, 1044, 883, 813, 765, 671 cm^{-1}. **HRMS** (ESI) (*m*/*z*): calcd for $C_{23}H_{25}N_2O_2S$ $[M + H]^+$, 393.1637; found, 393.1638.

7.3.40 *(6a*S*,9a*S*)-9-methyl-7-methylene-2,6,6a,7,8,9,9a,10-octahydropyrrolo[3',2':5,6]-cyclohepta[1,2,3-*cd*]indole (431)*



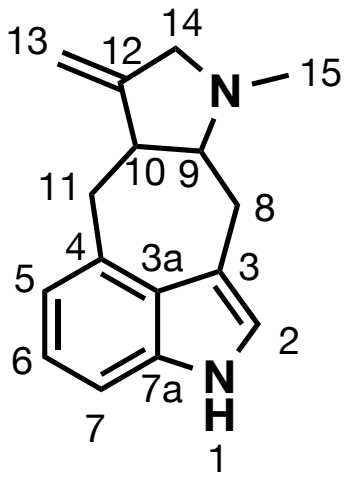
431

Preparation of SmI_2:

1) Diiodomethane was dissolved in Et_2O. The organic phase was successively washed with $Na_2S_2O_3$ solution (3x), water and brine soltuion. The organic layer was dried over $MgSO_4$ and the solvent was removed *in vacuo* at room temperature to give a white solid.
2) Sm (76.7 mg, 510 µmol, 1 equiv.) and diiodoethane (129 mg, 459 µmol, 0.9 equiv.) were suspended in dry THF (4.6 mL). The Schlenktube was sealed with a rubber septum and the reaction mixture treated with ultrasonic at 50 °C until it became a deep blue solution (15 min.).

Indole **418** (1.00 mg, 2.60 µmol, 1 equiv.) was dissolved in a solution of SmI_2 (153 µL, 15.3 µmol, 6 equiv.). After stirring the reaction mixture for 20 seconds, water (830 nL, 46.0 µmol, 18 equiv.) was added followed by pyrrolidine (2.50 µL, 30.6 µmol, 12 equiv.). Stirring the solution for some minutes caused the formation of a white precipitate. TLC (EtOAc:Hexane: 7N NH_3 in MeOH 100:100:1) control showed the complete consumption of the starting material. The crude was concentrated *in vacuo* at room temperature and purified by TLC (EtOAc:Hexane: 7N NH_3 in MeOH 100:100:1) to give the desired product **431** in 50% yield.

^{1}H-NMR (600 MHz, CD_3CN, δ): 2.72 (s, 3H), 3.25 (dd, *J* = 7.7, 16.3 Hz, 1H), 3.35 (dd, *J* = 7.4, 15.9 Hz, 1H), 3.48 (d, *J* = 14.6 Hz, 1H), 3.54 – 3.64 (m, 3H), 3.78 (d, *J* = 14.1 Hz, 1H), 3.96 (s, 1H), 5.23 (s, 1H), 5.27 (s, 1H), 6.77 (d, *J* = 7.0 Hz, 1H), 7.01 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.13 (s, 1H), 7.22 (d, *J* = 8.2 Hz, 1H), 9.20 (s, 1H) ppm. **^{13}C-NMR** (150 MHz, CD_3CN, δ): 24.1, 33.1, 38.3, 45.5, 59.7, 71.6, 108.3, 109.8, 110.8, 119.5, 122.6, 123.1, 126.4, 131.5, 136.7 ppm.



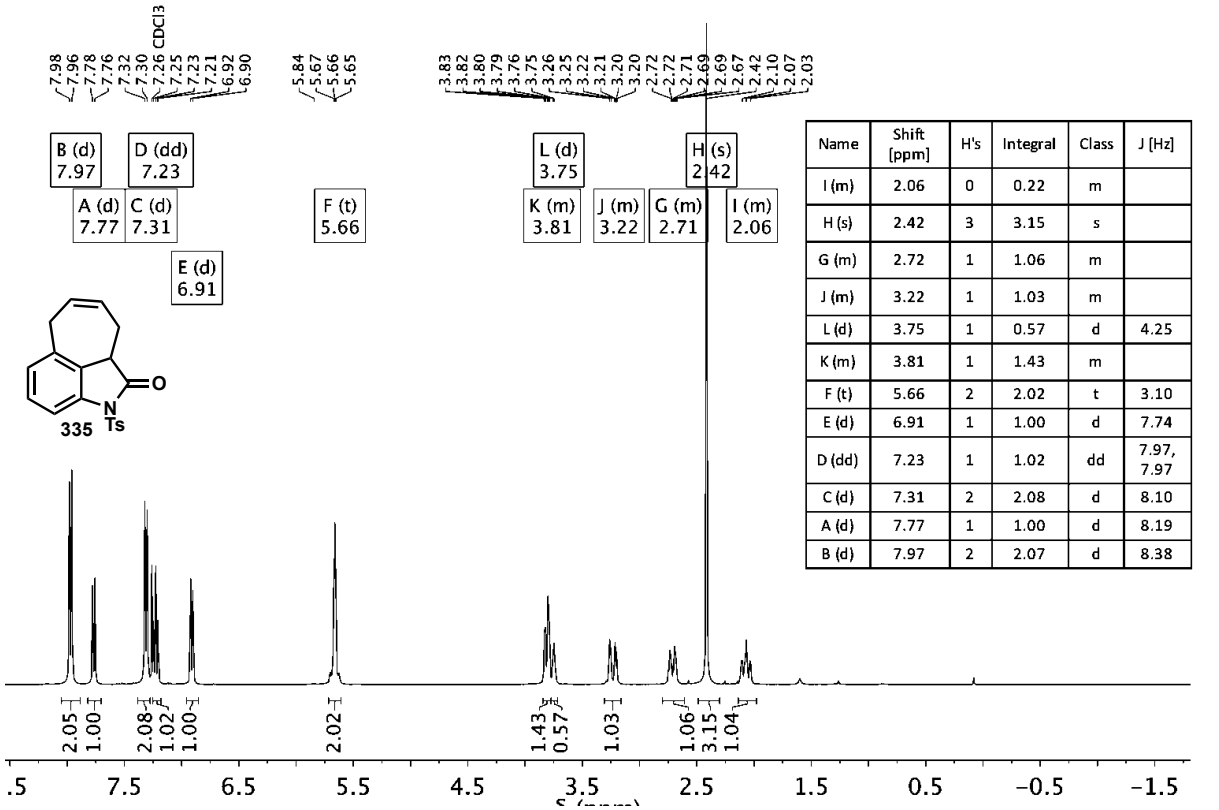
HSQC

^{1}**H** [ppm]	^{13}**C** [ppm]
2.71 (**15**)	38.3
3.35 & 3.57 (**8**)	24.1
3.25 & 3.50 (**11**)	33.1
3.60 (**10**)	45.5
3.63 & 3.79 (**14**)	59.7
3.96 (**9**)	71.6
5.25 (**13**)	110.8
6.77 (**5**)	119.5
7.01 (**6**)	122.6
7.12 (**2**)	123.1
7.22 (**7**)	109.8

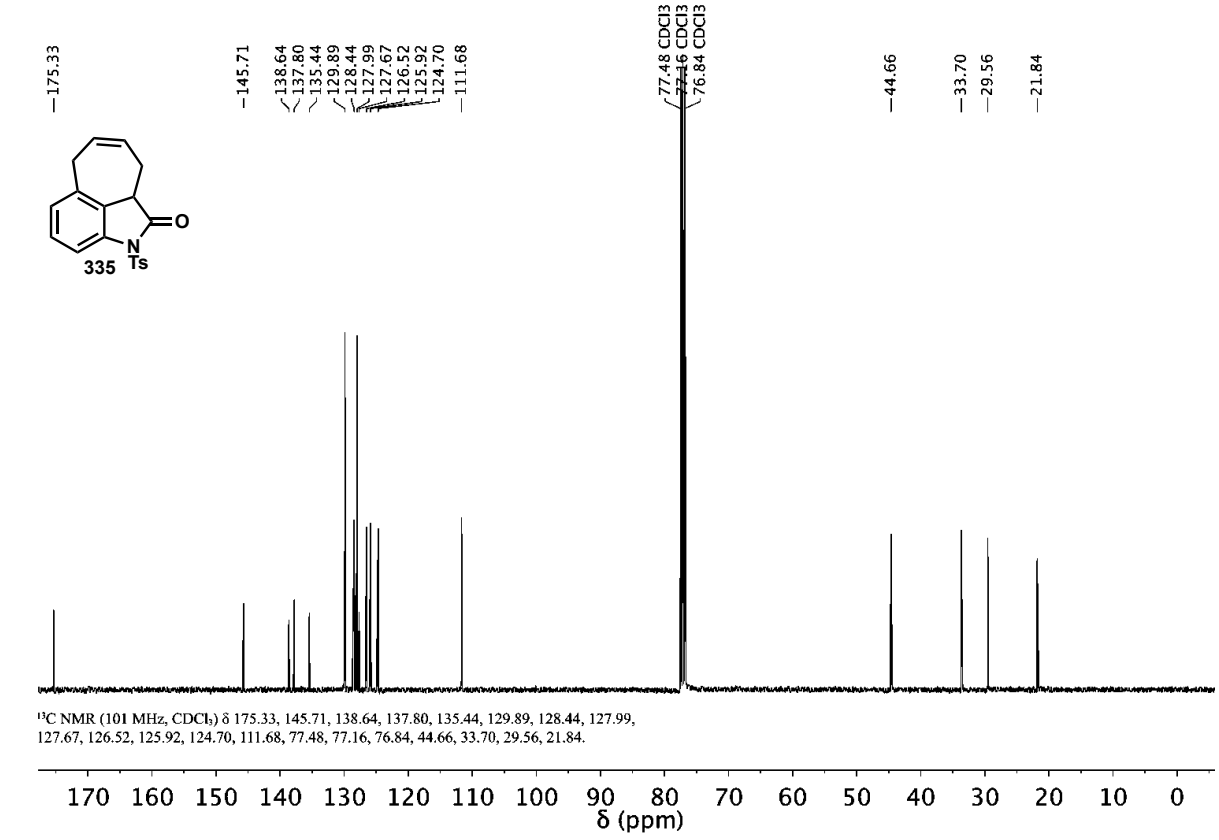
HMBC

^{1}**H** [ppm]	^{13}**C** [ppm]	^{1}**H** [ppm]	^{13}**C** [ppm]
2.71 (**15**)	59.7 (**14**), 71.6 (**9**)	6.77 (**5**)	33.2 (**11**), 109.8 (**7**), 122.6 (**6**), 126.4 (**4**)
3.25 (**11**)	45.5 (**10**), 71.6 (**9**), 119.5 (**5**), 126.4 (**4**), 131.5 (**3a**)	7.01 (**6**)	109.8 (**7**), 119.5 (**5**), 131.5 (**3a**), 136.7 (**7a**)
3.35 (**8**)	45.5 (**10**), 71.6 (**9**), 108.3, (**3**) 123.1 (**2**), 126.4 (**4**)	7.12 (**2**)	108.3 (**3**), 126.4 (**4**), 136.7 (**7a**)
3.79 (**14**)	45.5 (**10**), 71.6 (**9**)	7.22 (**7**)	119.5 (**5**), 126.4 (**4**)
5.25 (**13**)	45.5 (**10**), 59.7 (**14**)		

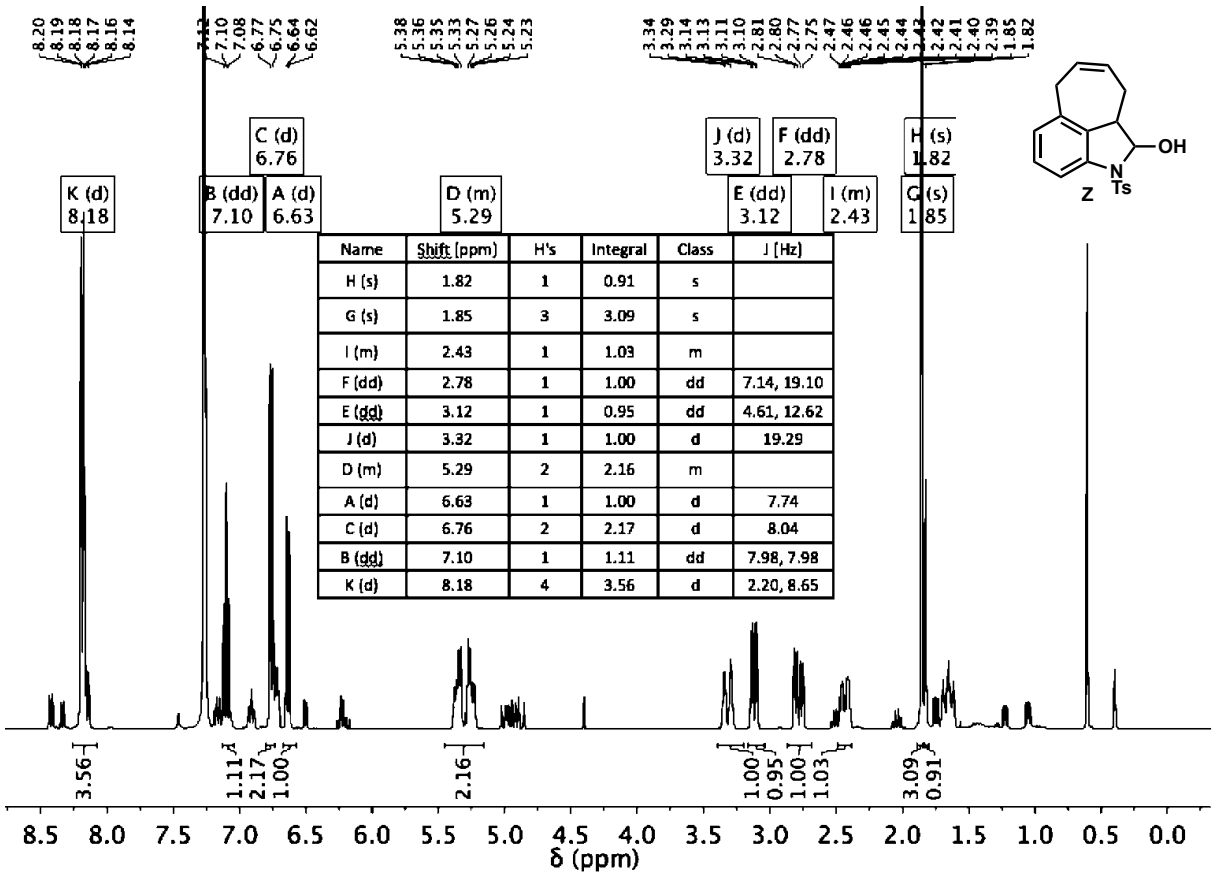
7.4 Spectra



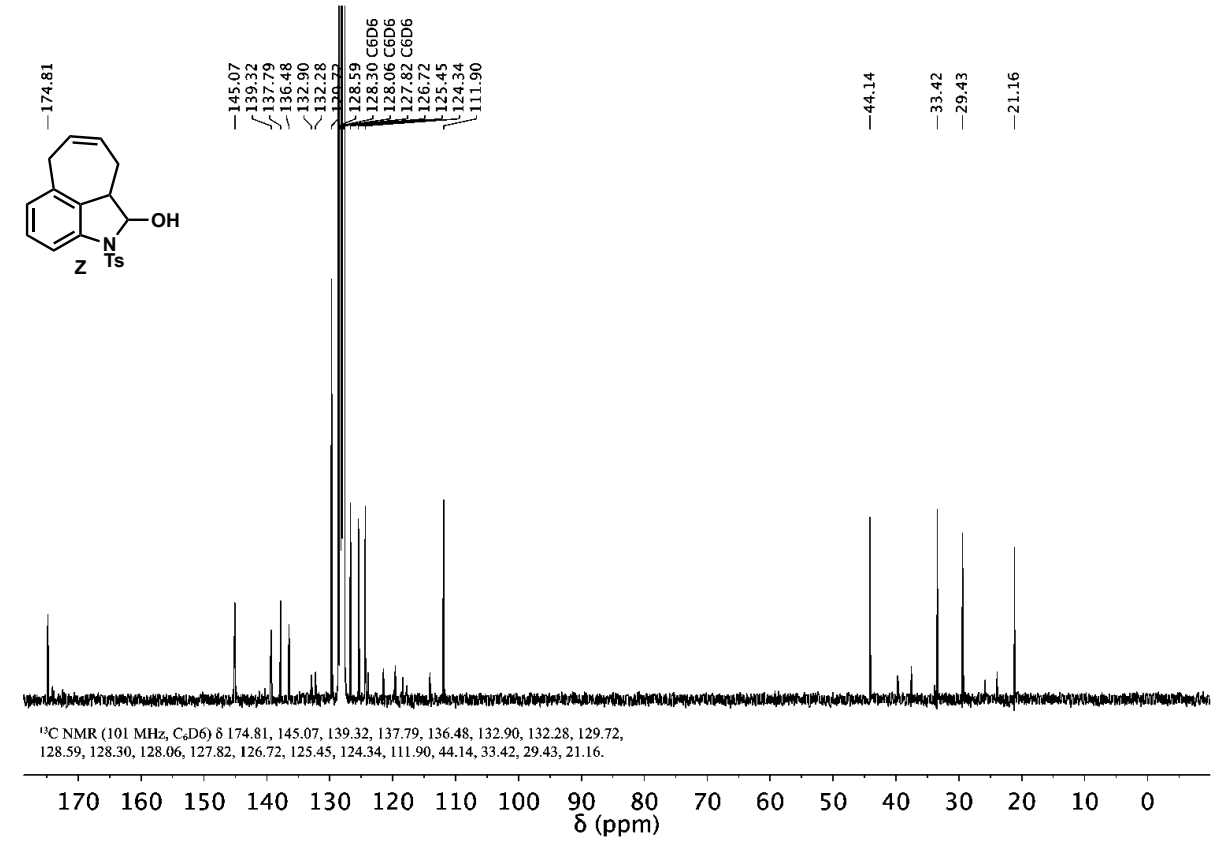
Name	Shift [ppm]	H's	Integral	Class	J [Hz]
I (m)	2.06	0	0.22	m	
H (s)	2.42	3	3.15	s	
G (m)	2.72	1	1.06	m	
J (m)	3.22	1	1.03	m	
L (d)	3.75	1	0.57	d	4.25
K (m)	3.81	1	1.43	m	
F (t)	5.66	2	2.02	t	3.10
E (d)	6.91	1	1.00	d	7.74
D (dd)	7.23	1	1.02	dd	7.97, 7.97
C (d)	7.31	2	2.08	d	8.10
A (d)	7.77	1	1.00	d	8.19
B (d)	7.97	2	2.07	d	8.38



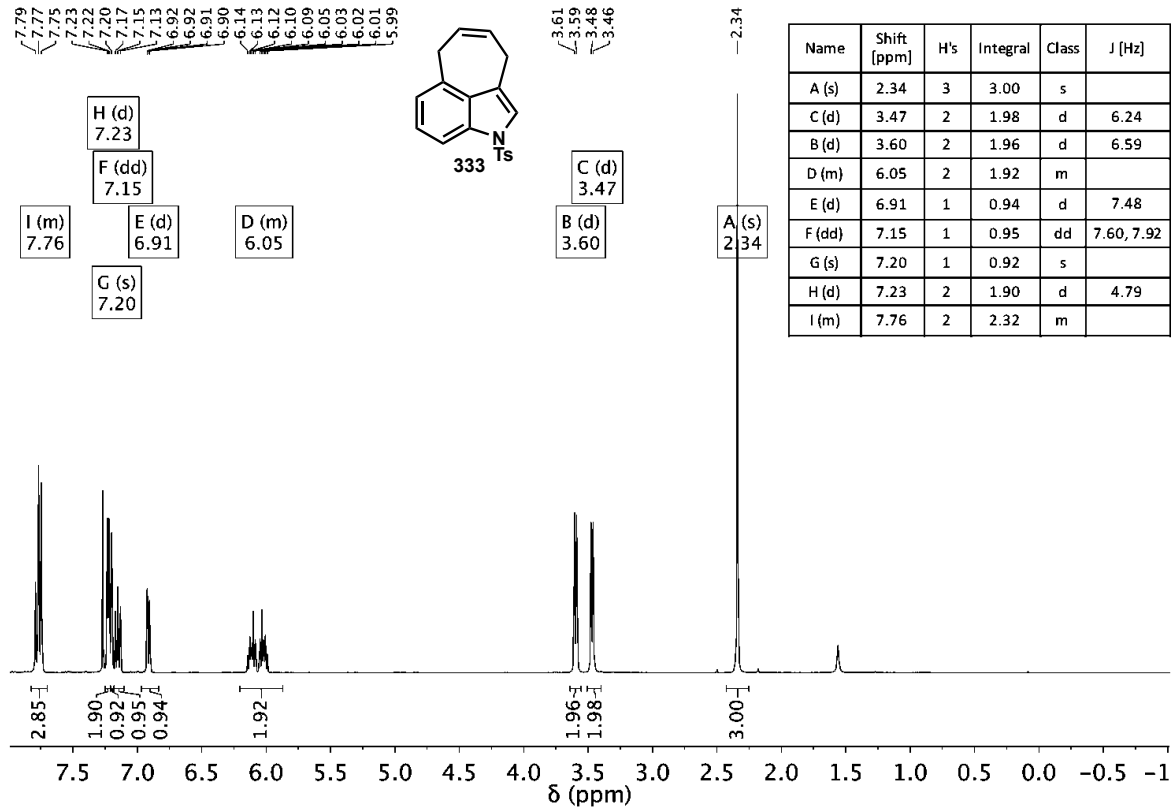
^{13}C NMR (101 MHz, $CDCl_3$) δ 175.33, 145.71, 138.64, 137.80, 135.44, 129.89, 128.44, 127.99, 127.67, 126.52, 125.92, 124.70, 111.68, 77.48, 77.16, 76.84, 44.66, 33.70, 29.56, 21.84.



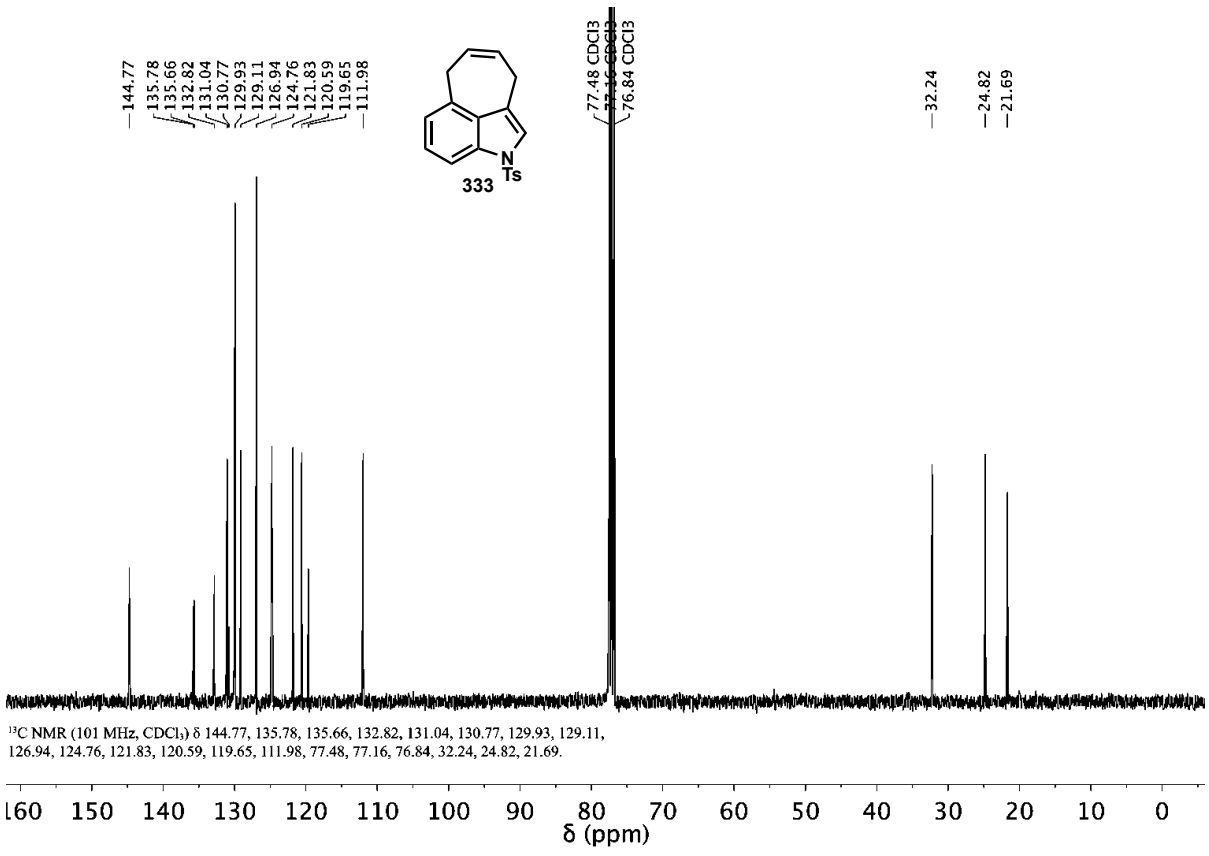
Name	Shift [ppm]	H's	Integral	Class	J [Hz]
H (s)	1.82	1	0.91	s	
G (s)	1.85	3	3.09	s	
I (m)	2.43	1	1.03	m	
F (dd)	2.78	1	1.00	dd	7.14, 19.10
E (dd)	3.12	1	0.95	dd	4.61, 12.62
J (d)	3.32	1	1.00	d	19.29
D (m)	5.29	2	2.16	m	
A (d)	6.63	1	1.00	d	7.74
C (d)	6.76	2	2.17	d	8.04
B (dd)	7.10	1	1.11	dd	7.98, 7.98
K (d)	8.18	4	3.56	d	2.20, 8.65



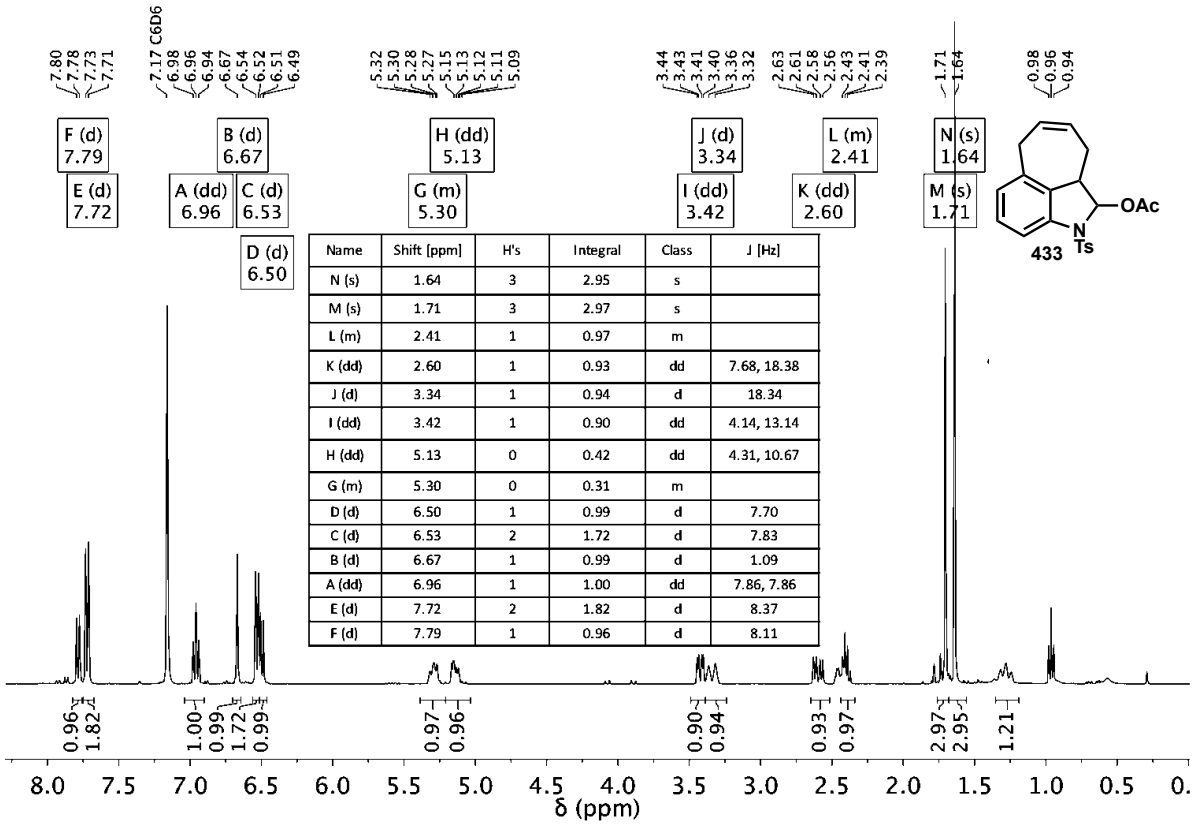
^{13}C NMR (101 MHz, C_6D6) δ 174.81, 145.07, 139.32, 137.79, 136.48, 132.90, 132.28, 129.72, 128.59, 128.30, 128.06, 127.82, 126.72, 125.45, 124.34, 111.90, 44.14, 33.42, 29.43, 21.16.



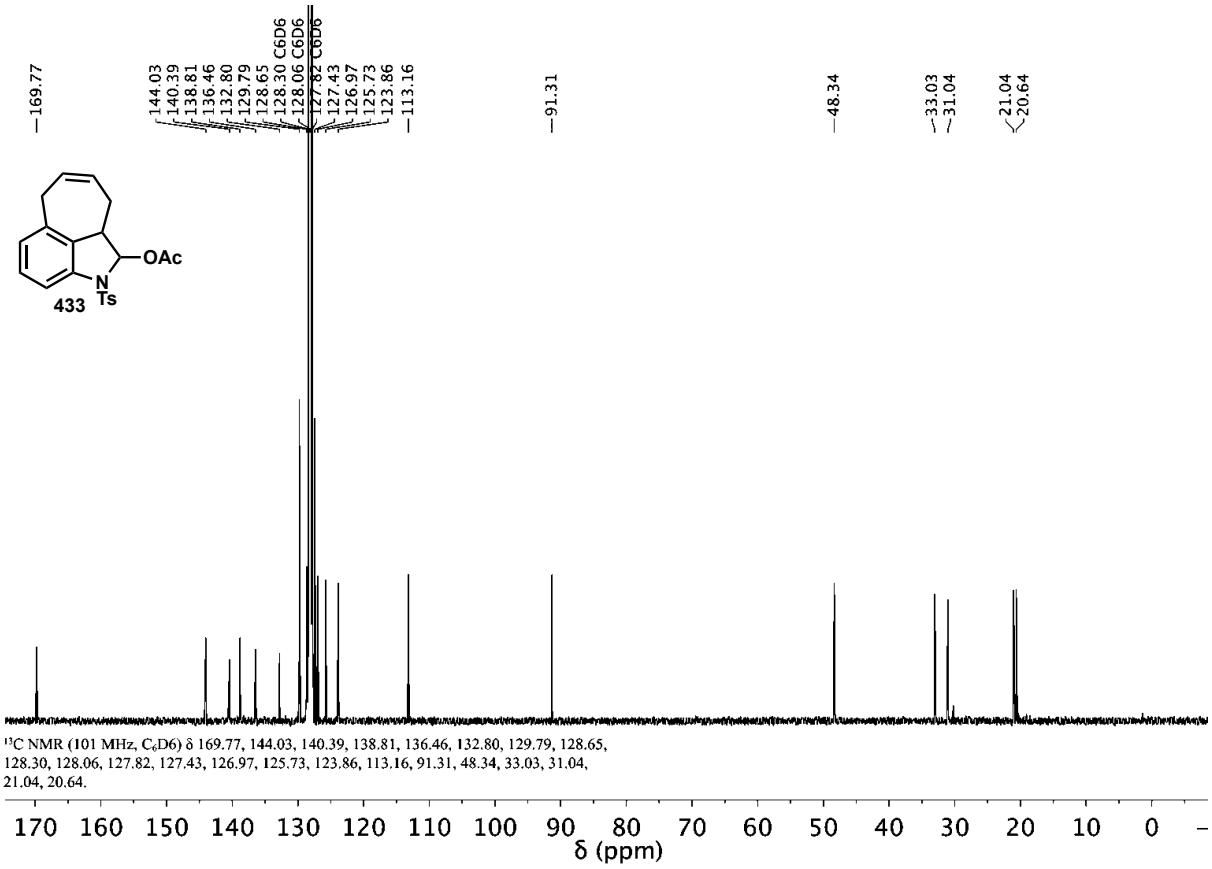
Name	Shift [ppm]	H's	Integral	Class	J [Hz]
A (s)	2.34	3	3.00	s	
C (d)	3.47	2	1.98	d	6.24
B (d)	3.60	2	1.96	d	6.59
D (m)	6.05	2	1.92	m	
E (d)	6.91	1	0.94	d	7.48
F (dd)	7.15	1	0.95	dd	7.60, 7.92
G (s)	7.20	1	0.92	s	
H (d)	7.23	2	1.90	d	4.79
I (m)	7.76	2	2.32	m	



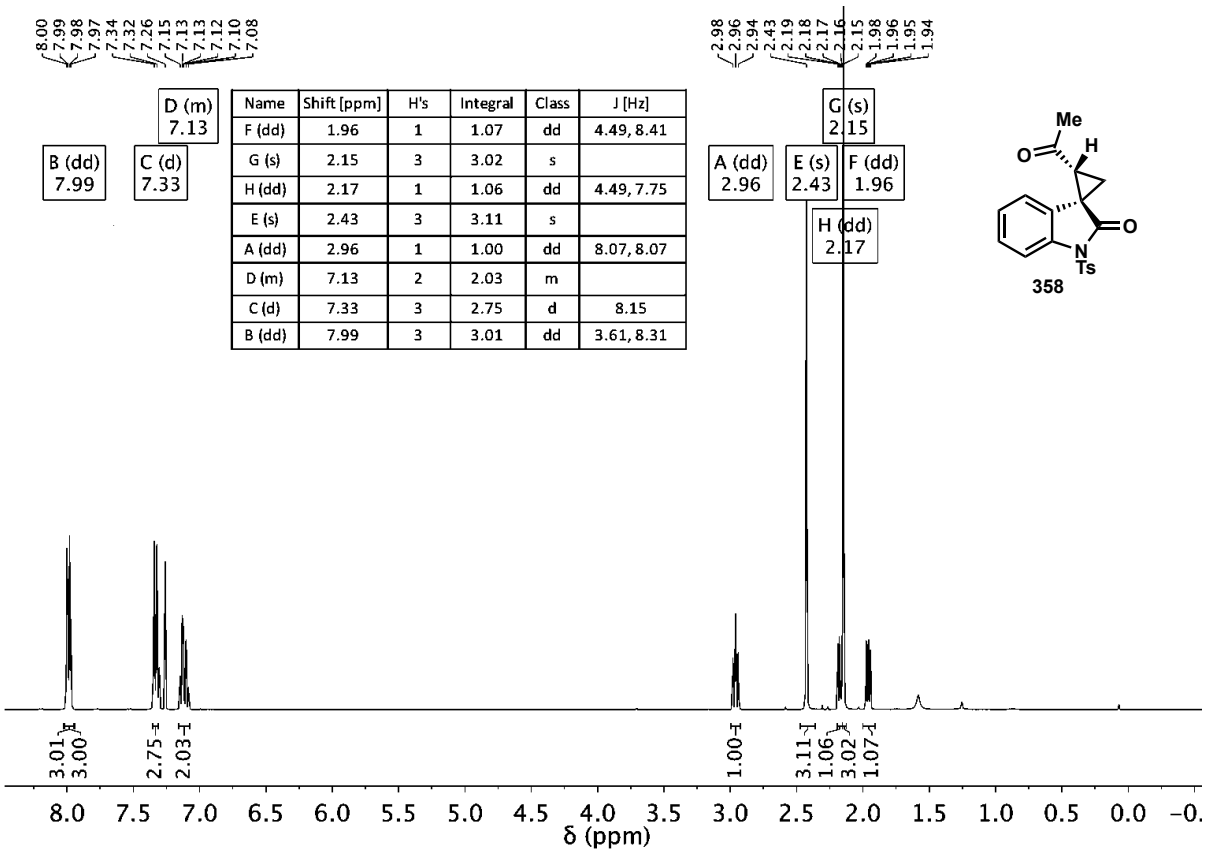
^{13}C NMR (101 MHz, $CDCl_3$) δ 144.77, 135.78, 135.66, 132.82, 131.04, 130.77, 129.93, 129.11, 126.94, 124.76, 121.83, 120.59, 119.65, 111.98, 77.48, 77.16, 76.84, 32.24, 24.82, 21.69.



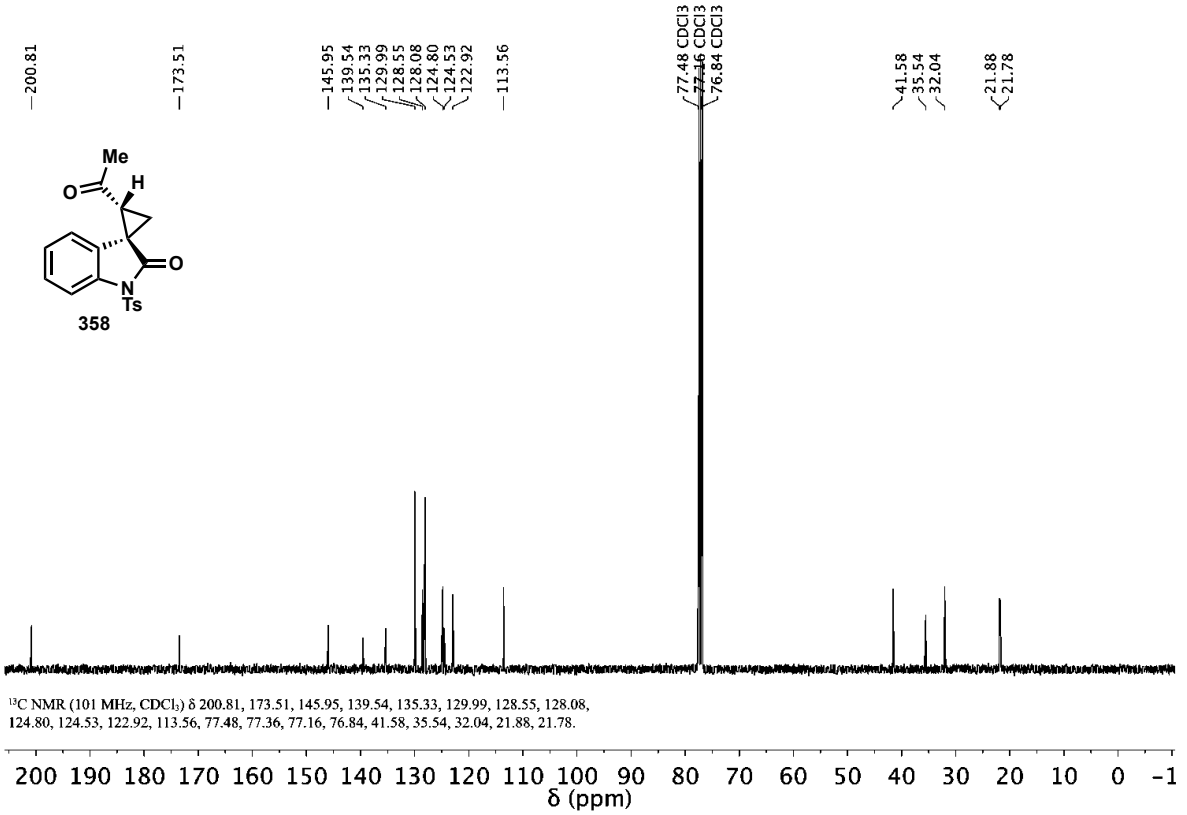
Name	Shift [ppm]	H's	Integral	Class	J [Hz]
N (s)	1.64	3	2.95	s	
M (s)	1.71	3	2.97	s	
L (m)	2.41	1	0.97	m	
K (dd)	2.60	1	0.93	dd	7.68, 18.38
J (d)	3.34	1	0.94	d	18.34
I (dd)	3.42	1	0.90	dd	4.14, 13.14
H (dd)	5.13	0	0.42	dd	4.31, 10.67
G (m)	5.30	0	0.31	m	
D (d)	6.50	1	0.99	d	7.70
C (d)	6.53	2	1.72	d	7.83
B (d)	6.67	1	0.99	d	1.09
A (dd)	6.96	1	1.00	dd	7.86, 7.86
E (d)	7.72	2	1.82	d	8.37
F (d)	7.79	1	0.96	d	8.11



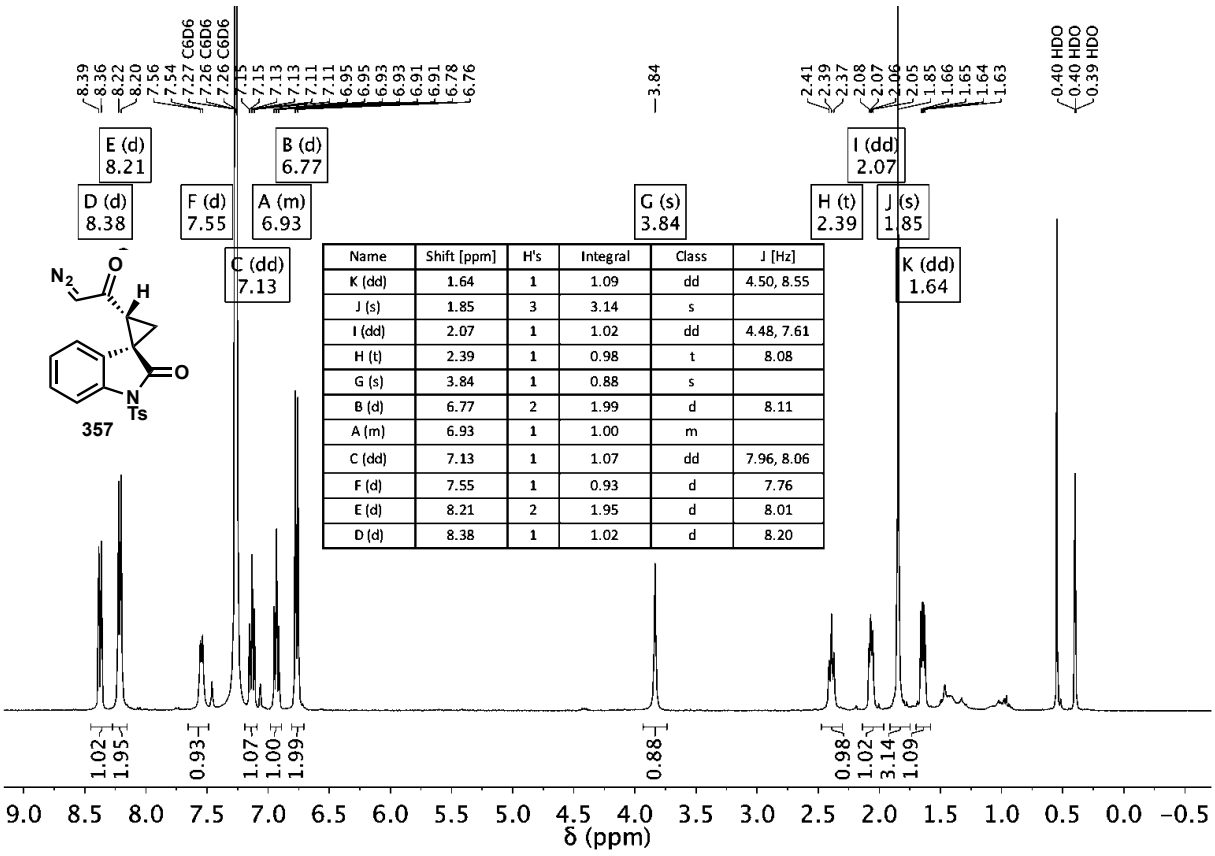
^{13}C NMR (101 MHz, C_6D6) δ 169.77, 144.03, 140.39, 138.81, 136.46, 132.80, 129.79, 128.65, 128.30, 128.06, 127.82, 127.43, 126.97, 125.73, 123.86, 113.16, 91.31, 48.34, 33.03, 31.04, 21.04, 20.64.



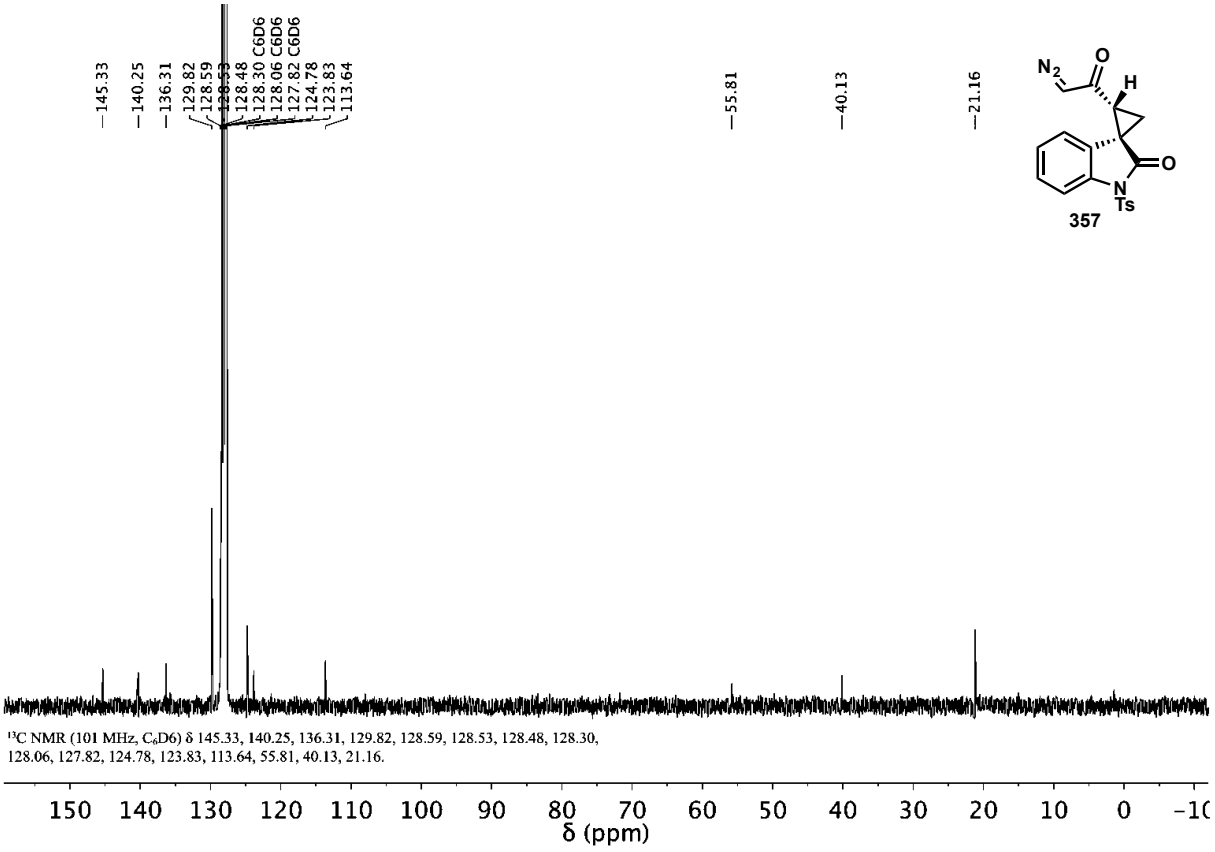
Name	Shift [ppm]	H's	Integral	Class	J [Hz]
F (dd)	1.96	1	1.07	dd	4.49, 8.41
G (s)	2.15	3	3.02	s	
H (dd)	2.17	1	1.06	dd	4.49, 7.75
E (s)	2.43	3	3.11	s	
A (dd)	2.96	1	1.00	dd	8.07, 8.07
D (m)	7.13	2	2.03	m	
C (d)	7.33	3	2.75	d	8.15
B (dd)	7.99	3	3.01	dd	3.61, 8.31



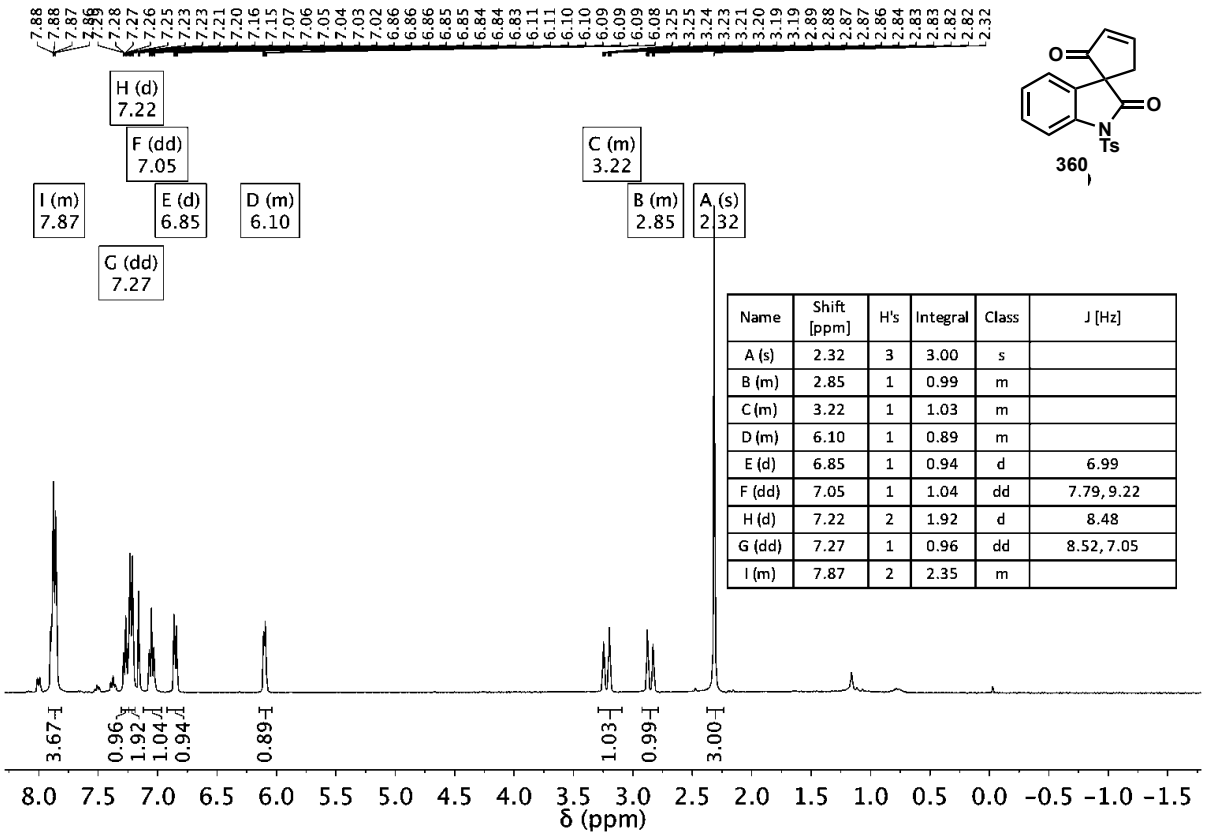
^{13}C NMR (101 MHz, $CDCl_3$) δ 200.81, 173.51, 145.95, 139.54, 135.33, 129.99, 128.55, 128.08, 124.80, 124.53, 122.92, 113.56, 77.48, 77.36, 77.16, 76.84, 41.58, 35.54, 32.04, 21.88, 21.78.



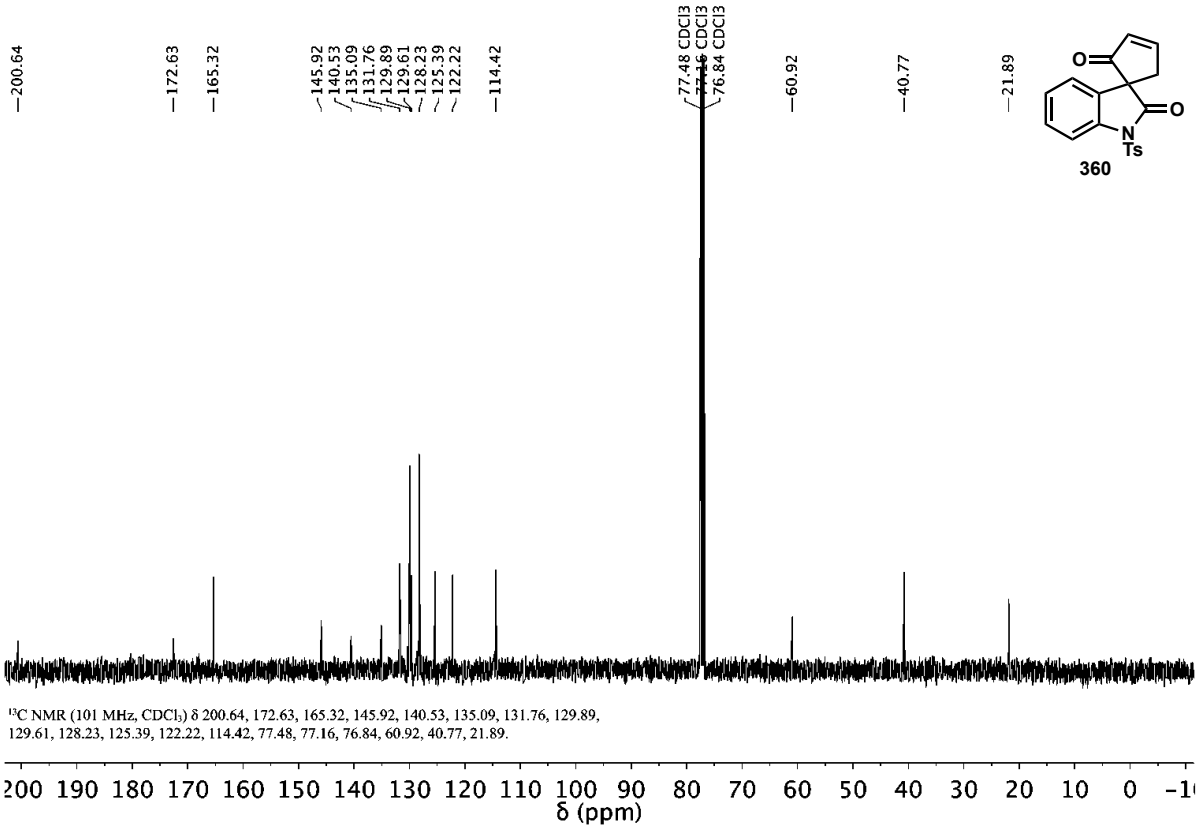
Name	Shift [ppm]	H's	Integral	Class	J [Hz]
K (dd)	1.64	1	1.09	dd	4.50, 8.55
J (s)	1.85	3	3.14	s	
I (dd)	2.07	1	1.02	dd	4.48, 7.61
H (t)	2.39	1	0.98	t	8.08
G (s)	3.84	1	0.88	s	
B (d)	6.77	2	1.99	d	8.11
A (m)	6.93	1	1.00	m	
C (dd)	7.13	1	1.07	dd	7.96, 8.06
F (d)	7.55	1	0.93	d	7.76
E (d)	8.21	2	1.95	d	8.01
D (d)	8.38	1	1.02	d	8.20



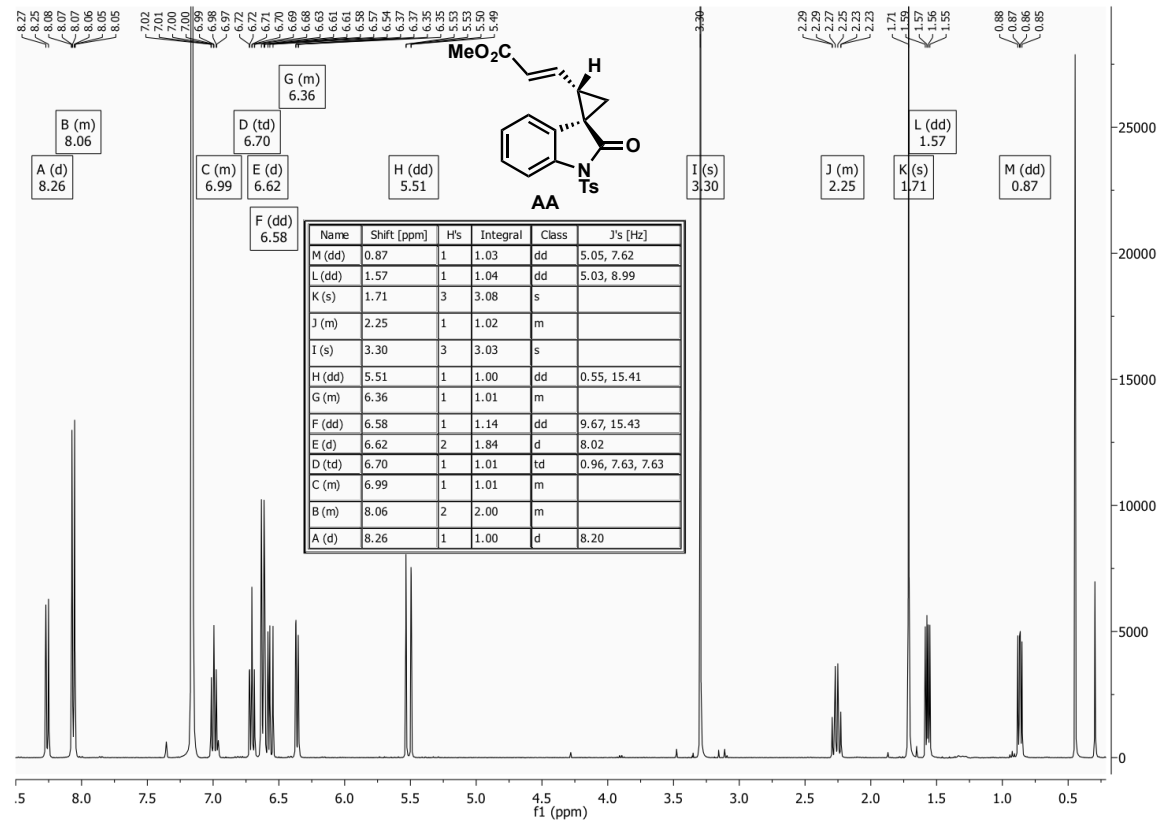
^{13}C NMR (101 MHz, C_6D6) δ 145.33, 140.25, 136.31, 129.82, 128.59, 128.53, 128.48, 128.30, 128.06, 127.82, 124.78, 123.83, 113.64, 55.81, 40.13, 21.16.



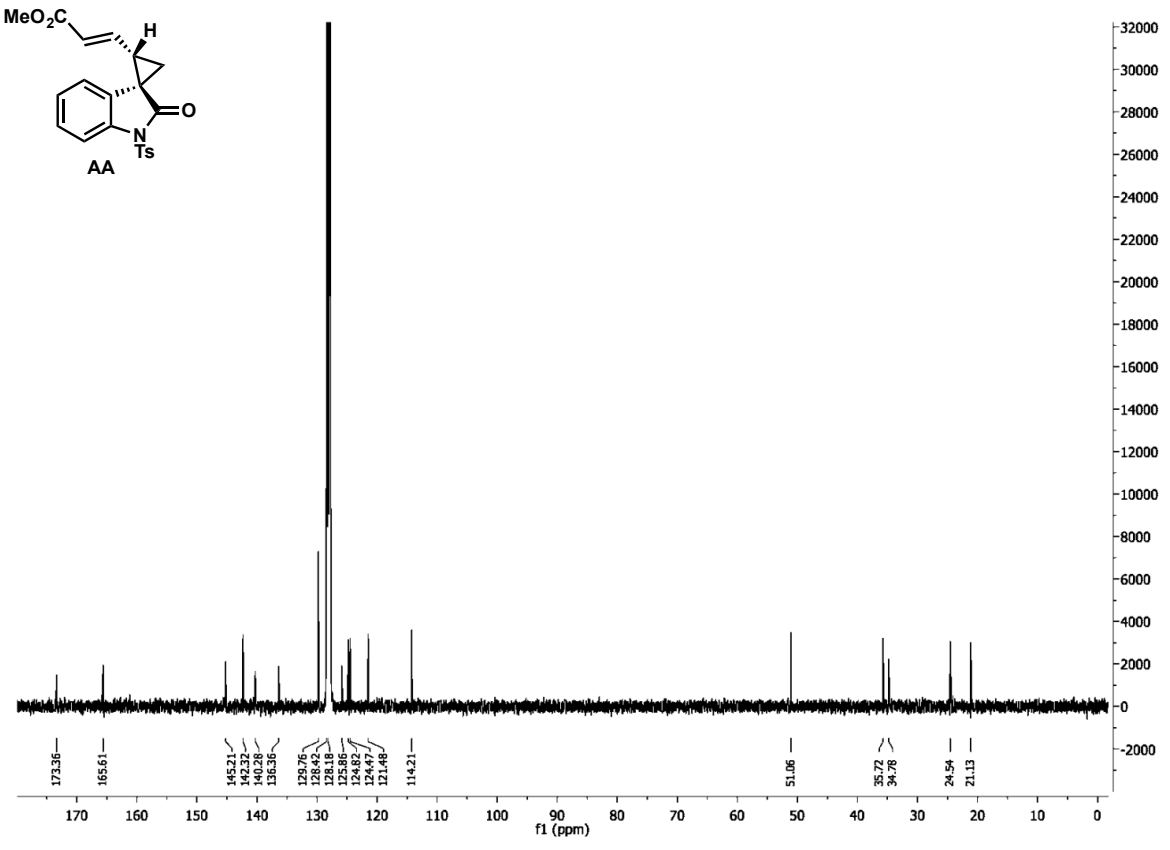
Name	Shift [ppm]	H's	Integral	Class	J [Hz]
A (s)	2.32	3	3.00	s	
B (m)	2.85	1	0.99	m	
C (m)	3.22	1	1.03	m	
D (m)	6.10	1	0.89	m	
E (d)	6.85	1	0.94	d	6.99
F (dd)	7.05	1	1.04	dd	7.79, 9.22
H (d)	7.22	2	1.92	d	8.48
G (dd)	7.27	1	0.96	dd	8.52, 7.05
I (m)	7.87	2	2.35	m	

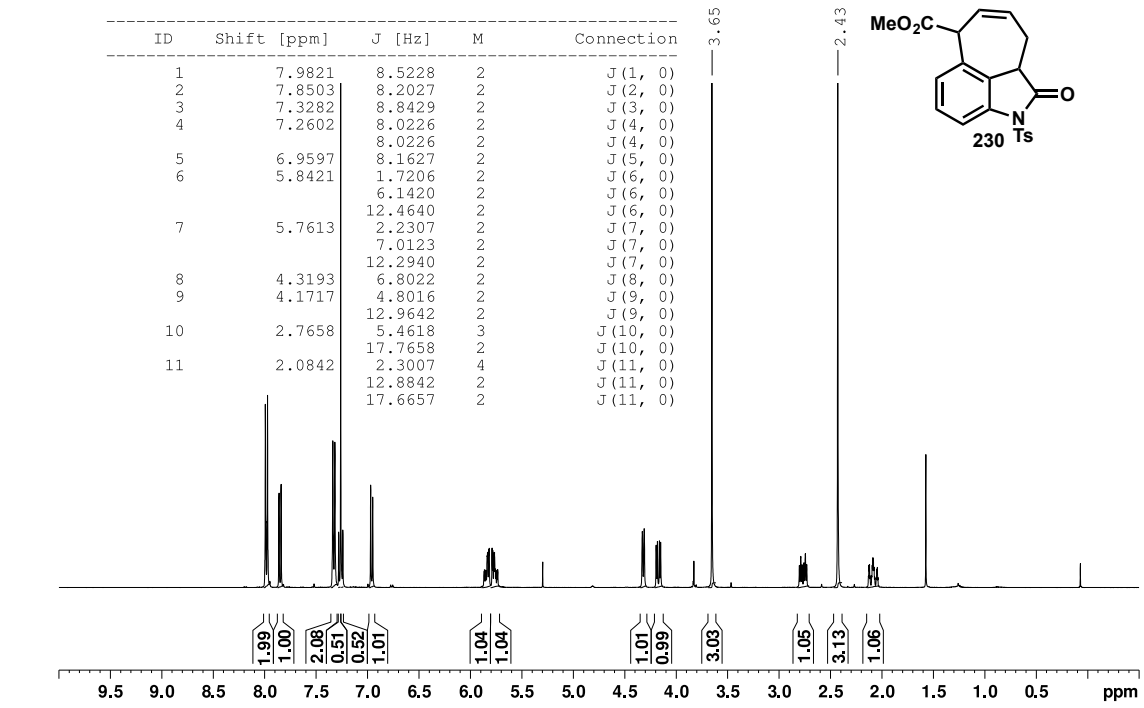


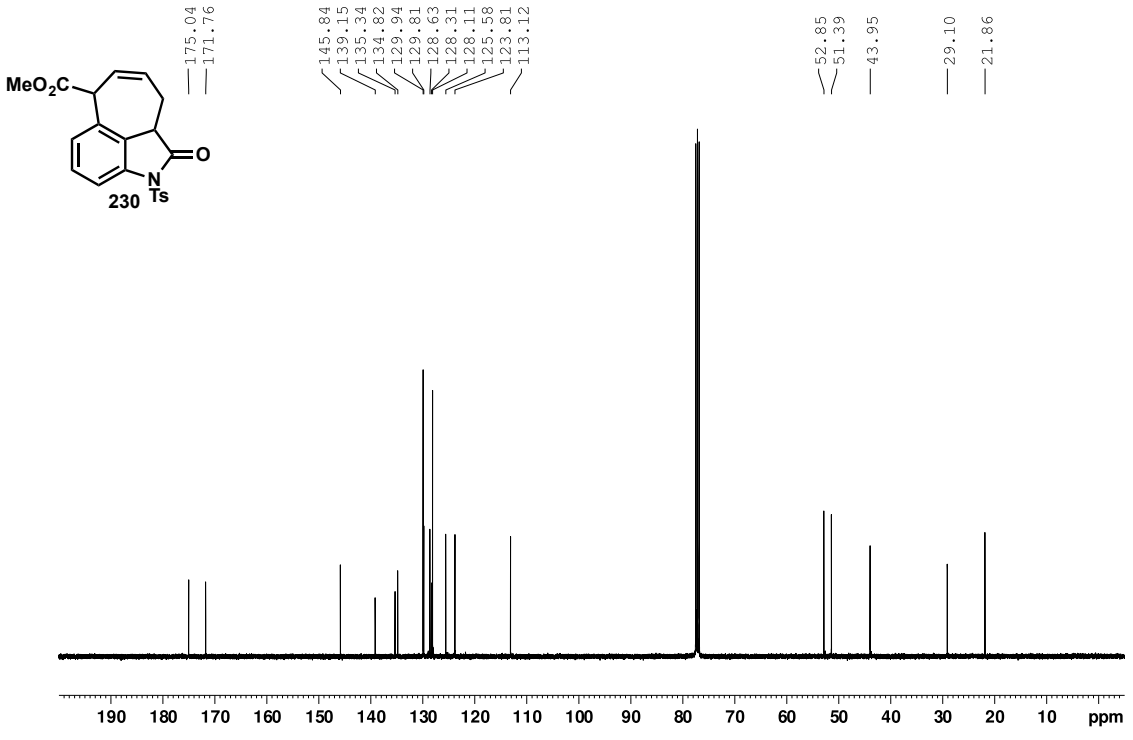
^{13}C NMR (101 MHz, $CDCl_3$) δ 200.64, 172.63, 165.32, 145.92, 140.53, 135.09, 131.76, 129.89, 129.61, 128.23, 125.39, 122.22, 114.42, 77.48, 77.16, 76.84, 60.92, 40.77, 21.89.

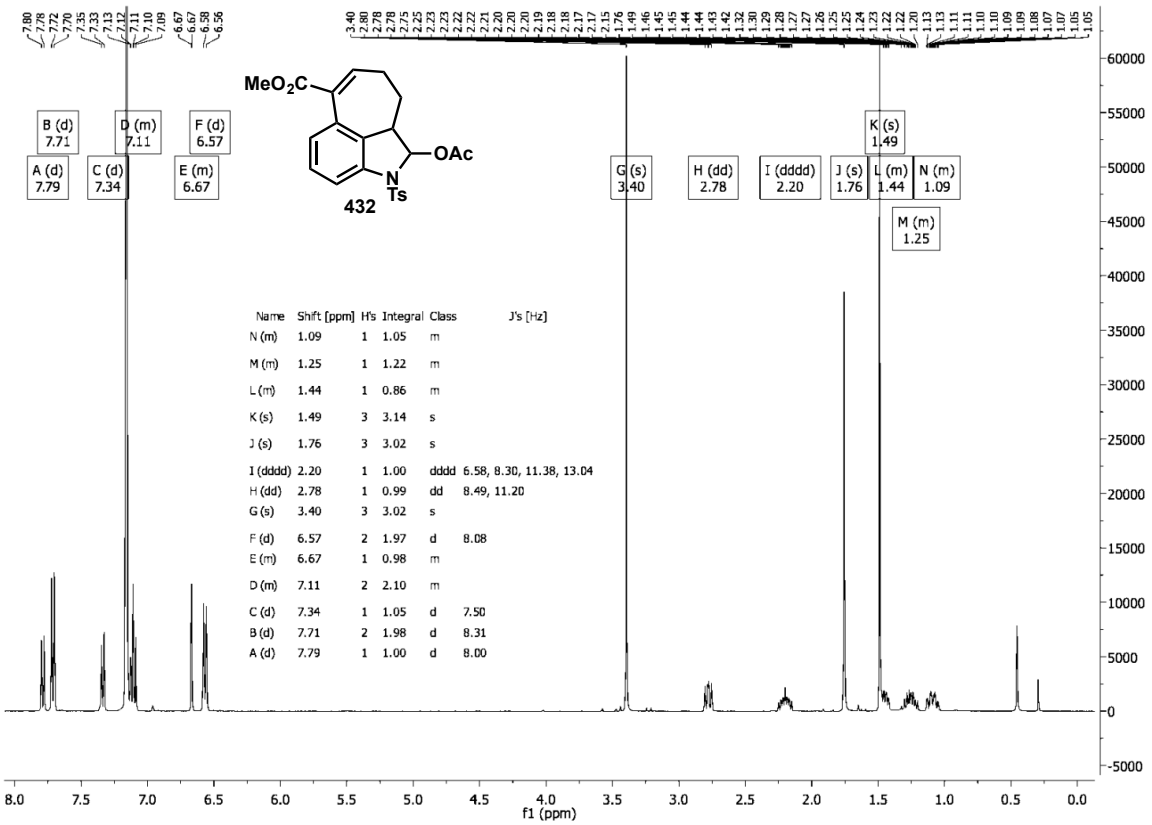


Name	Shift [ppm]	H's	Integral	Class	J's [Hz]
M (dd)	0.87	1	1.03	dd	5.05, 7.62
L (dd)	1.57	1	1.04	dd	5.03, 8.99
K (s)	1.71	3	3.08	s	
J (m)	2.25	1	1.02	m	
I (s)	3.30	3	3.03	s	
H (dd)	5.51	1	1.00	dd	0.55, 15.41
G (m)	6.36	1	1.01	m	
F (dd)	6.58	1	1.14	dd	9.67, 15.43
E (d)	6.62	2	1.84	d	8.02
D (td)	6.70	1	1.01	td	0.96, 7.63, 7.63
C (m)	6.99	1	1.01	m	
B (m)	8.06	2	2.00	m	
A (d)	8.26	1	1.00	d	8.20

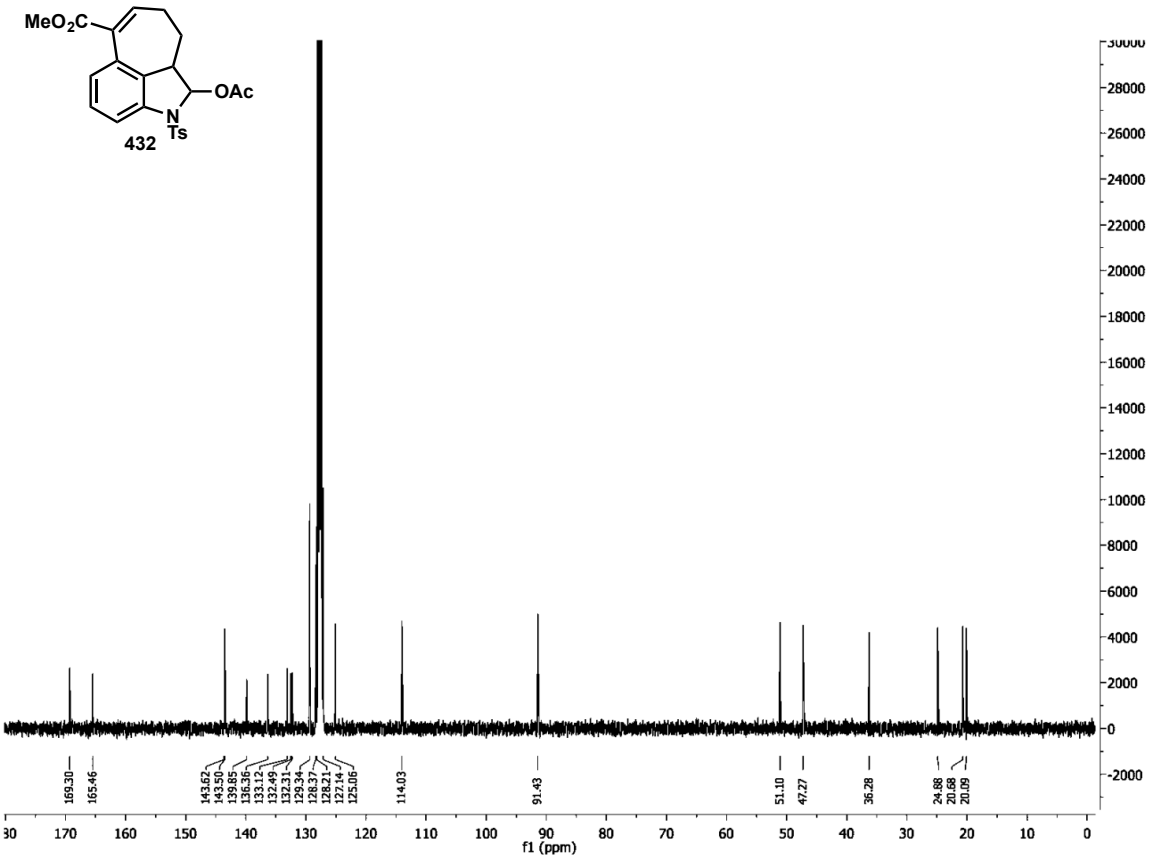


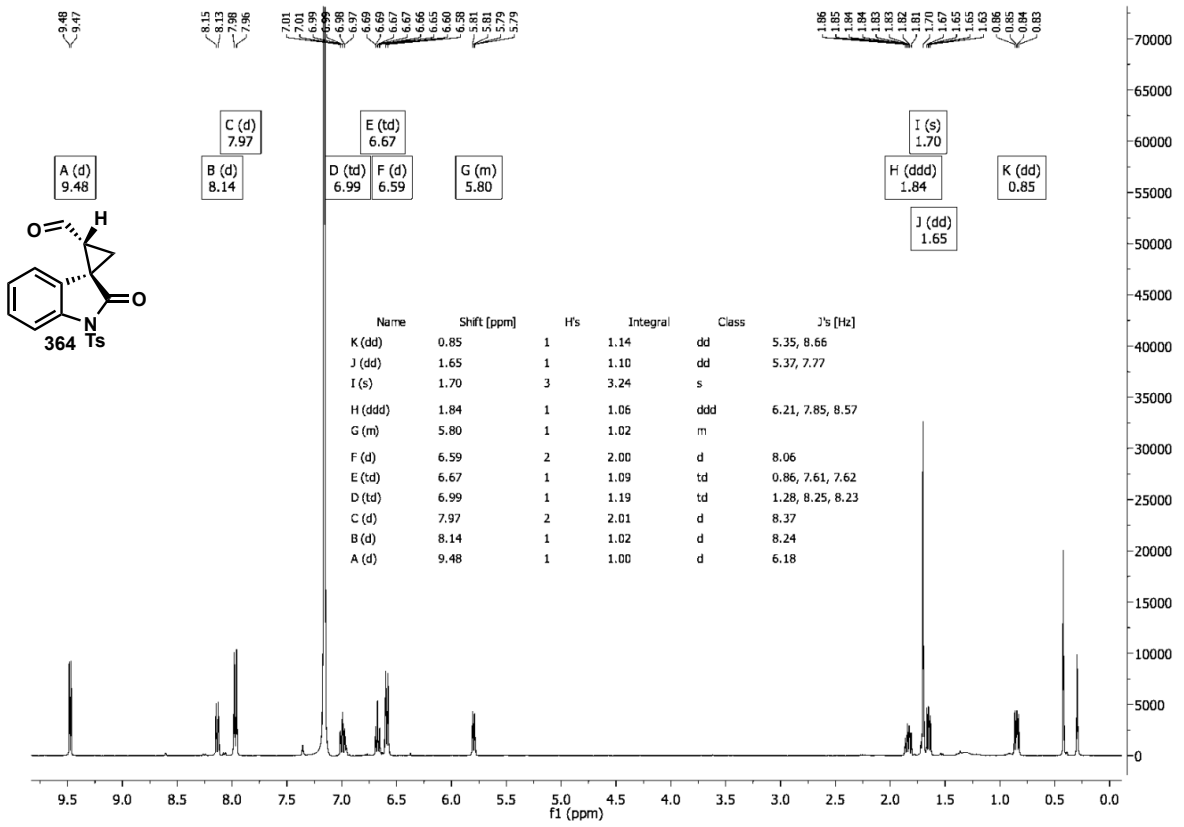

ID Shift [ppm] J [Hz] M Connection
1 7.9821 8.5228 2 J(1, 0)
2 7.8503 8.2027 2 J(2, 0)
3 7.3282 8.8429 2 J(3, 0)
4 7.2602 8.0226 2 J(4, 0)
8.0226 2 J(4, 0)
5 6.9597 8.1627 2 J(5, 0)
6 5.8421 1.7206 2 J(6, 0)
6.1420 2 J(6, 0)
12.4640 2 J(6, 0)
7 5.7613 2.2307 2 J(7, 0)
7.0123 2 J(7, 0)
12.2940 2 J(7, 0)
8 4.3193 6.8022 2 J(8, 0)
9 4.1717 4.8016 2 J(9, 0)
12.9642 2 J(9, 0)
10 2.7658 5.4618 3 J(10, 0)
17.7658 2 J(10, 0)
11 2.0842 2.3007 4 J(11, 0)
12.8842 2 J(11, 0)
17.6657 2 J(11, 0)
3.65
2.43
MeO2C
O
N
Ts
230
1.99
1.00
2.08
0.51
0.52
1.01
1.04
1.04
1.01
0.99
3.03
1.05
3.13
1.06
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
ppm


175.04
171.76
145.84
139.15
135.34
134.82
129.94
129.81
128.63
128.31
128.11
125.58
123.81
113.12
52.85
51.39
43.95
29.10
21.86
MeO2C
O
N
Ts
230
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
ppm

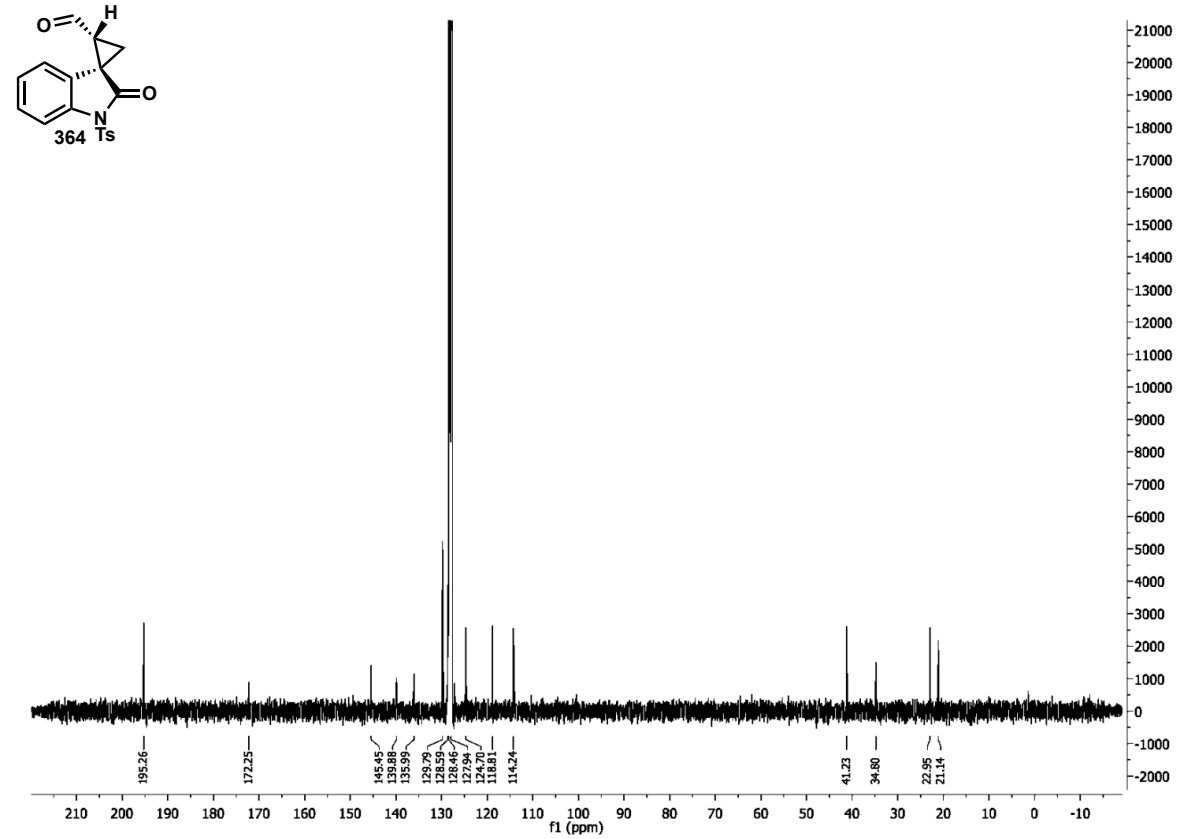


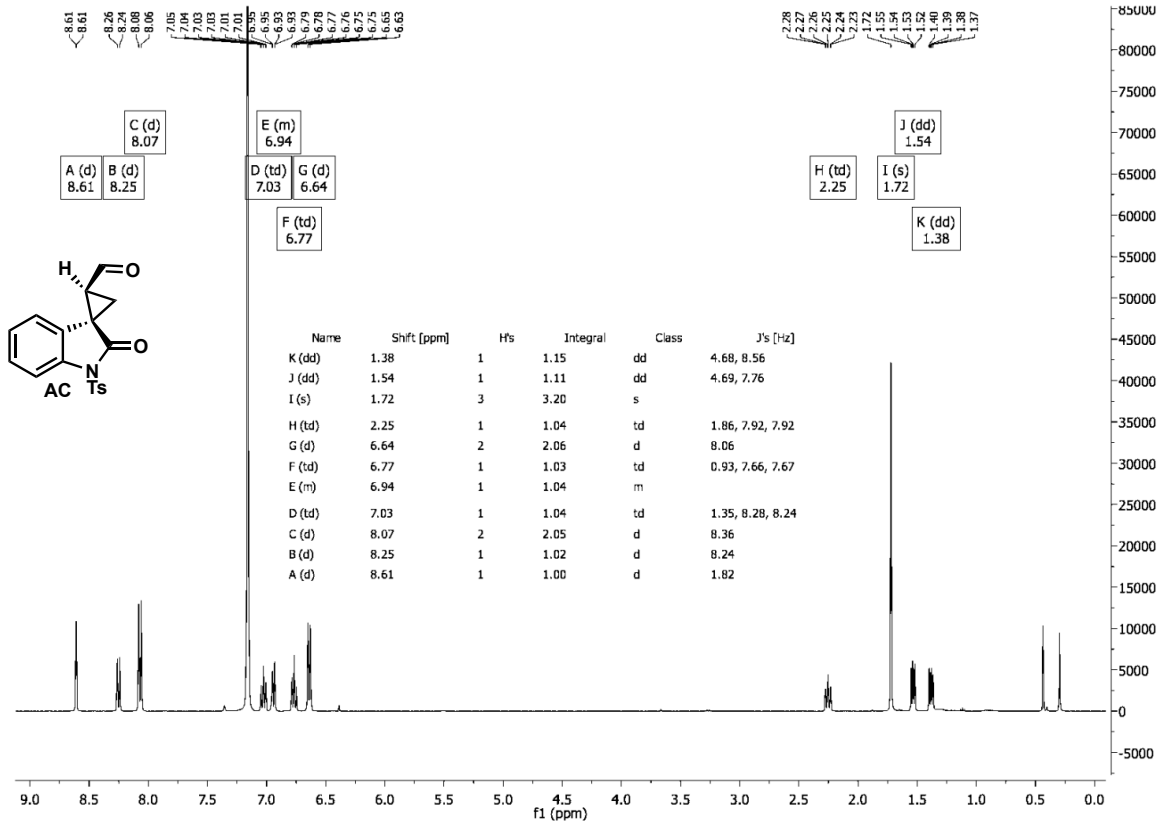
Name	Shift [ppm]	H's	Integral	Class	J's [Hz]
N (m)	1.09	1	1.05	m	
M (m)	1.25	1	1.22	m	
L (m)	1.44	1	0.86	m	
K (s)	1.49	3	3.14	s	
J (s)	1.76	3	3.02	s	
I (dddd)	2.20	1	1.00	dddd	6.58, 8.30, 11.38, 13.04
H (dd)	2.78	1	0.99	dd	8.49, 11.20
G (s)	3.40	3	3.02	s	
F (d)	6.57	2	1.97	d	8.08
E (m)	6.67	1	0.98	m	
D (m)	7.11	2	2.10	m	
C (d)	7.34	1	1.05	d	7.50
B (d)	7.71	2	1.98	d	8.31
A (d)	7.79	1	1.00	d	8.00



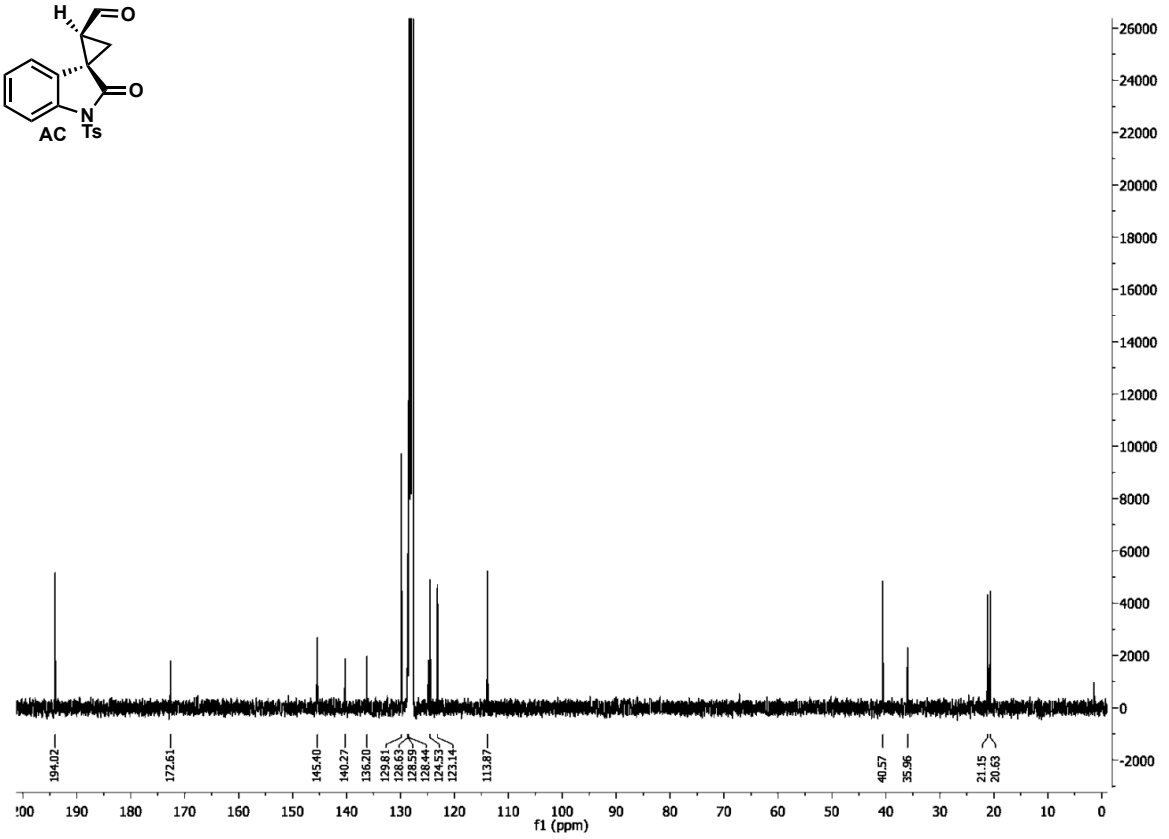


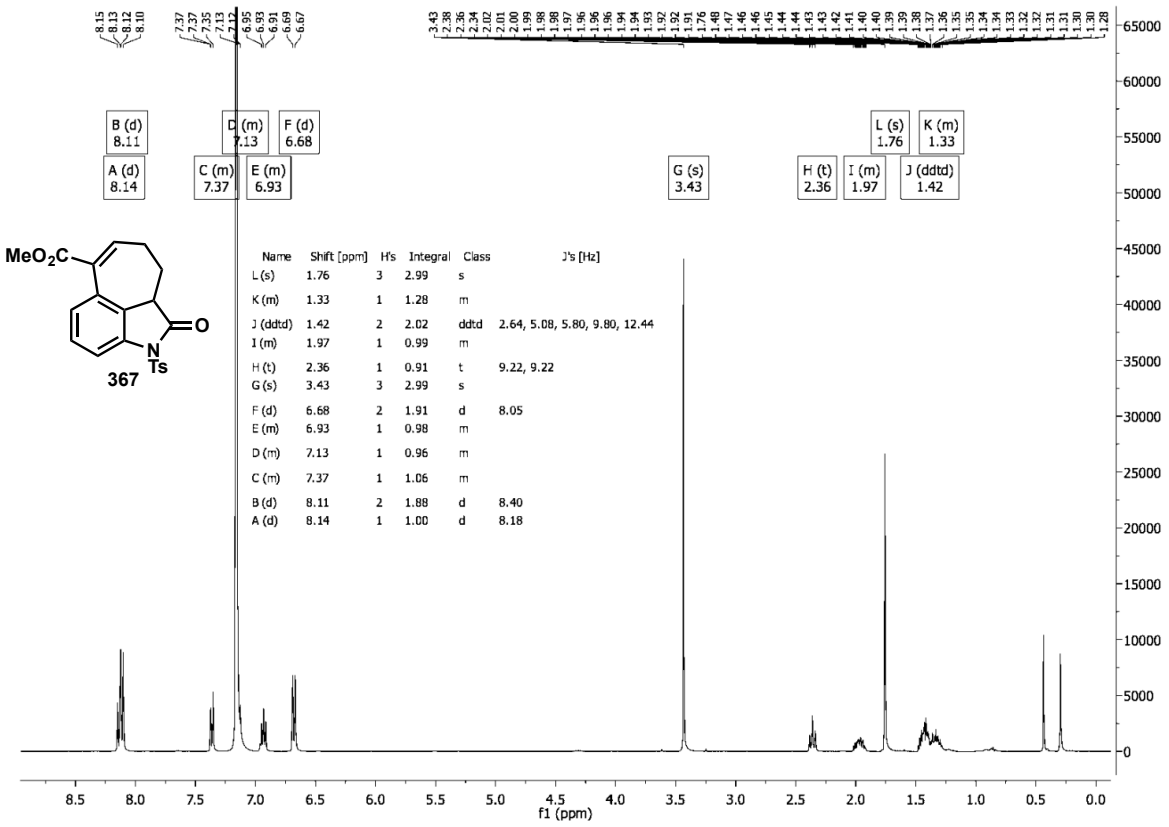
Name	Shift [ppm]	H's	Integral	Class	J's [Hz]
K (dd)	0.85	1	1.14	dd	5.35, 8.66
J (dd)	1.65	1	1.10	dd	5.37, 7.77
I (s)	1.70	3	3.24	s	
H (ddd)	1.84	1	1.06	ddd	6.21, 7.85, 8.57
G (m)	5.80	1	1.02	m	
F (d)	6.59	2	2.00	d	8.06
E (td)	6.67	1	1.09	td	0.86, 7.61, 7.62
D (td)	6.99	1	1.19	td	1.28, 8.25, 8.23
C (d)	7.97	2	2.01	d	8.37
B (d)	8.14	1	1.02	d	8.24
A (d)	9.48	1	1.00	d	6.18

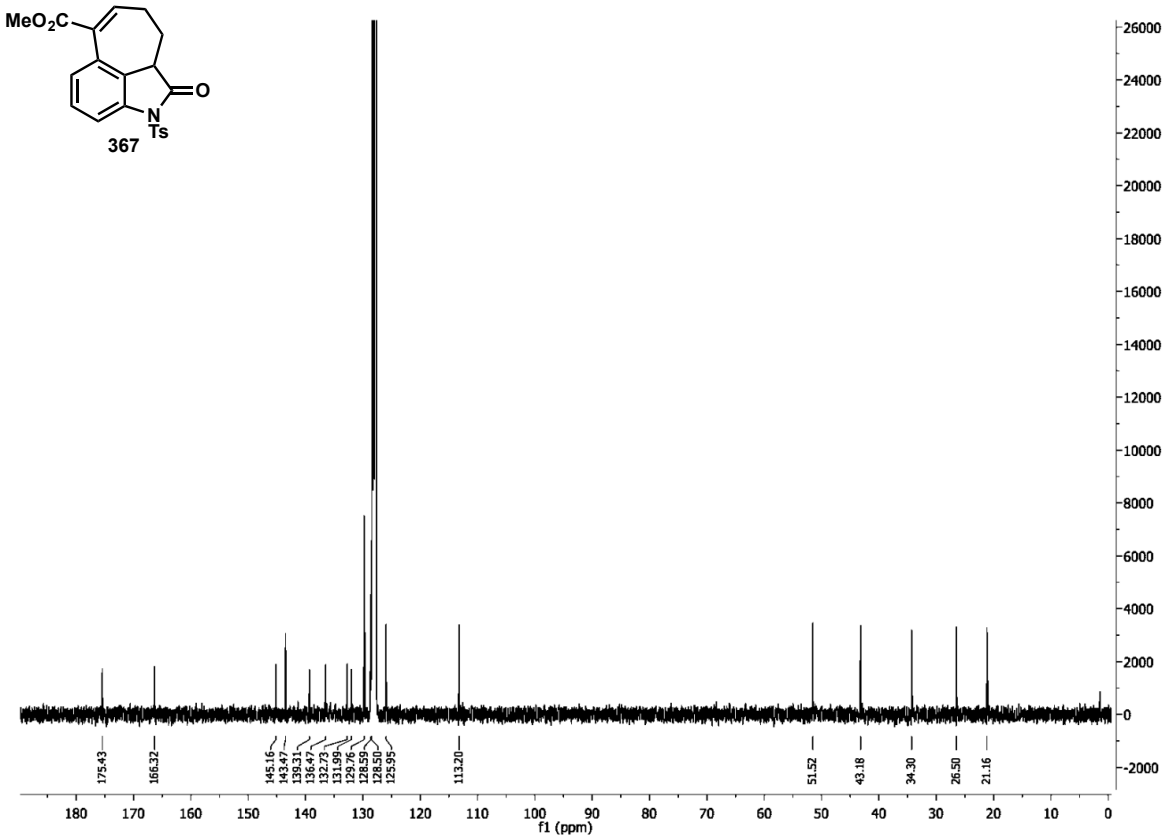


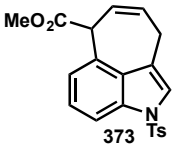


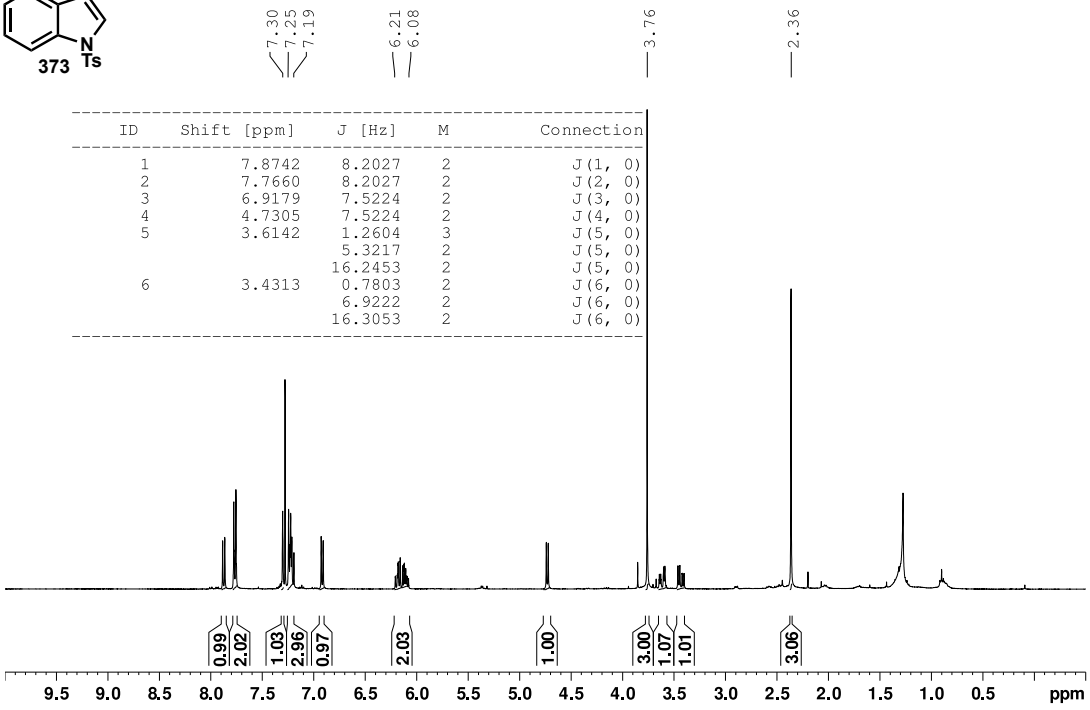
Name	Shift [ppm]	H's	Integral	Class	J's [Hz]
K (dd)	1.38	1	1.15	dd	4.68, 8.56
J (dd)	1.54	1	1.11	dd	4.69, 7.76
I (s)	1.72	3	3.20	s	
H (td)	2.25	1	1.04	td	1.86, 7.92, 7.92
G (d)	6.64	2	2.06	d	8.06
F (td)	6.77	1	1.03	td	0.93, 7.66, 7.67
E (m)	6.94	1	1.04	m	
D (td)	7.03	1	1.04	td	1.35, 8.28, 8.24
C (d)	8.07	2	2.05	d	8.36
B (d)	8.25	1	1.02	d	8.24
A (d)	8.61	1	1.00	d	1.82



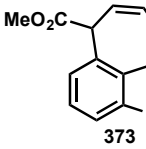

B (d) 8.11
A (d) 8.14
D (m) 7.13
C (m) 7.37
F (d) 6.68
E (m) 6.93
G (s) 3.43
L (s) 1.76
K (m) 1.33
H (t) 2.36
I (m) 1.97
J (ddtd) 1.42
MeO2C
O
N
Ts
367
Name Shift [ppm] H's Integral Class J's [Hz]
L (s) 1.76 3 2.99 s
K (m) 1.33 1 1.28 m
J (ddtd) 1.42 2 2.02 ddtd 2.64, 5.08, 5.80, 9.80, 12.44
I (m) 1.97 1 0.99 m
H (t) 2.36 1 0.91 t 9.22, 9.22
G (s) 3.43 3 2.99 s
F (d) 6.68 2 1.91 d 8.05
E (m) 6.93 1 0.98 m
D (m) 7.13 1 0.96 m
C (m) 7.37 1 1.06 m
B (d) 8.11 2 1.88 d 8.40
A (d) 8.14 1 1.00 d 8.18
f1 (ppm)

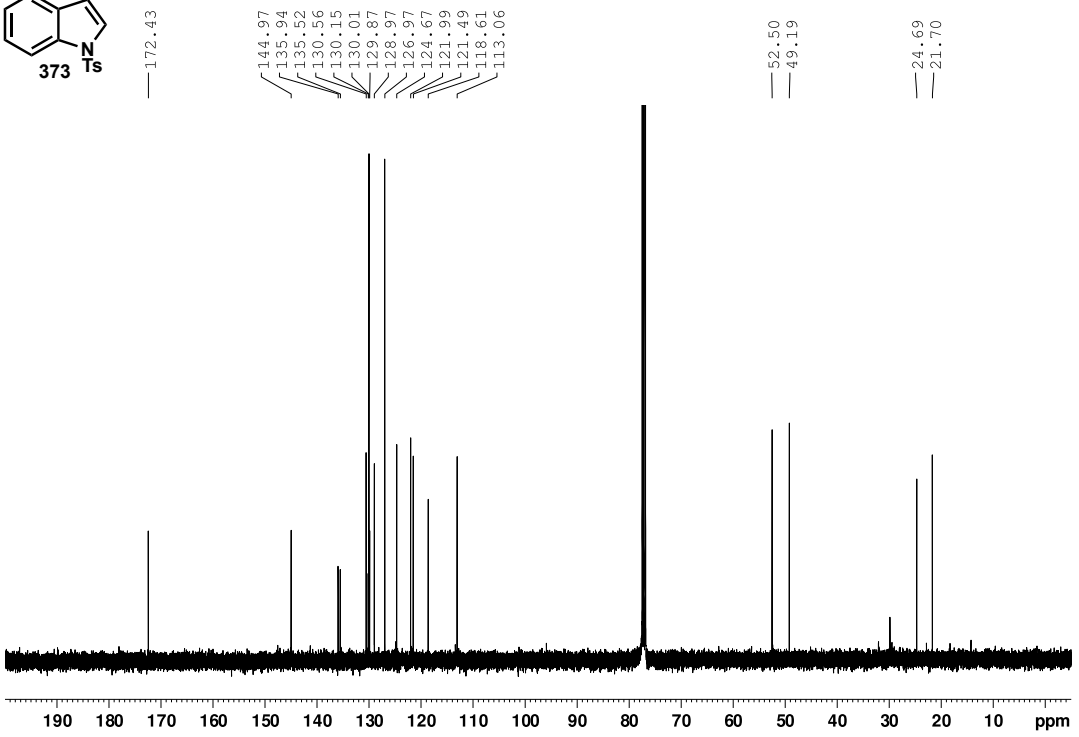

MeO2C
O
N
Ts
367
175.43
166.32
145.16
143.47
139.31
136.47
132.73
131.99
129.76
128.59
128.50
125.95
113.20
51.52
43.18
34.30
26.50
21.16
f1 (ppm)

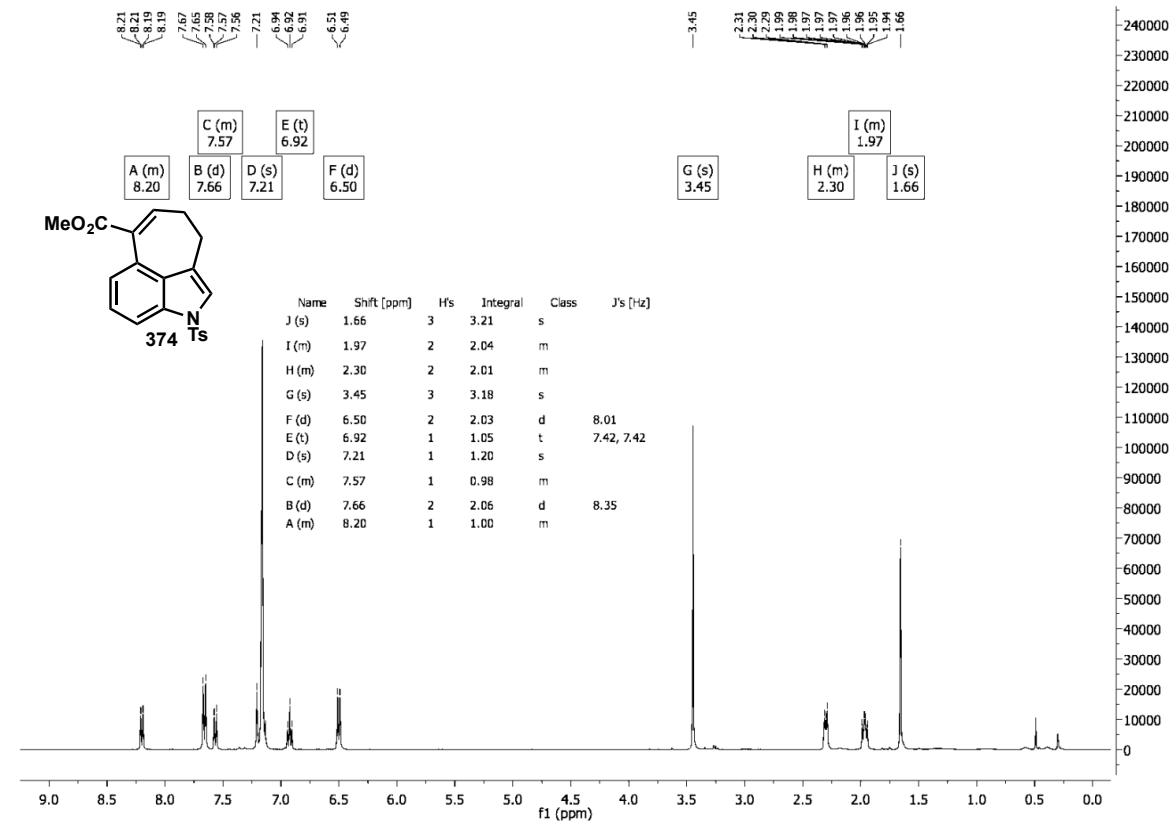


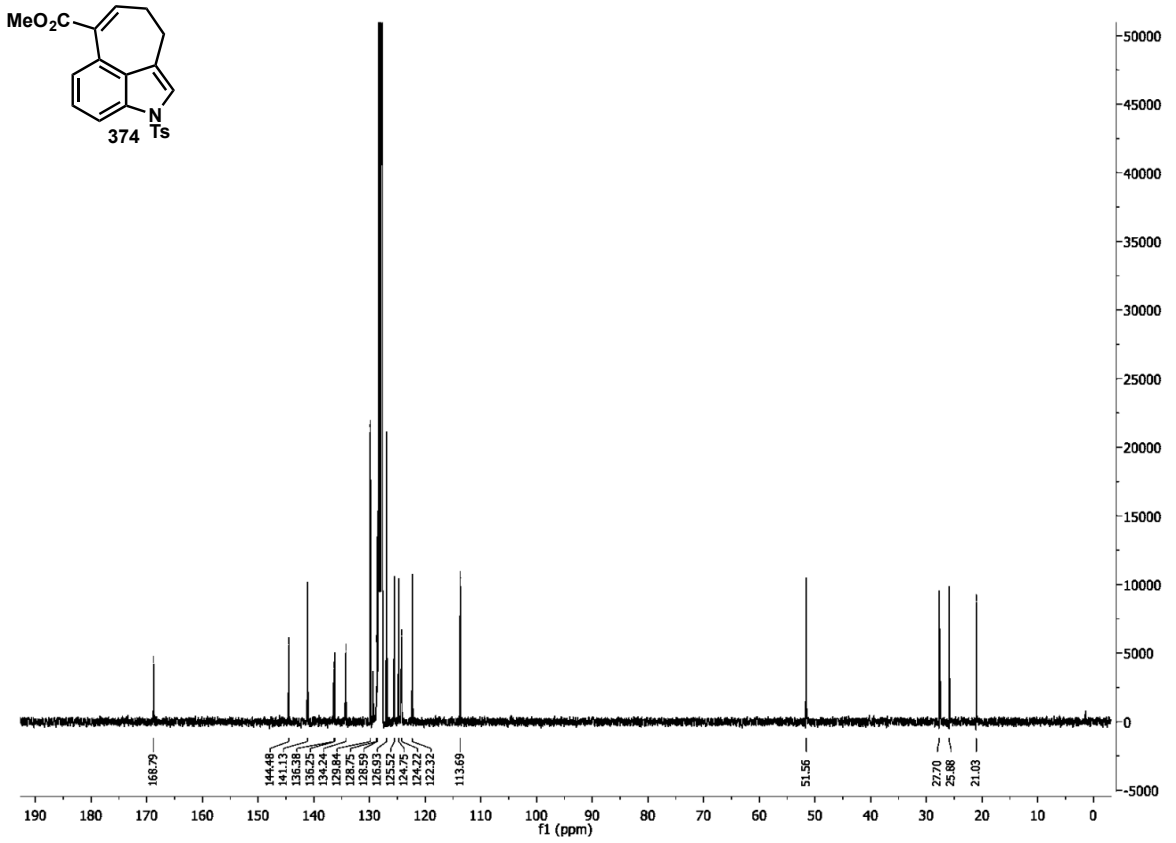


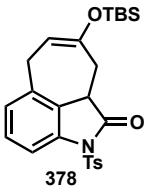
ID	Shift [ppm]	J [Hz]	M	Connection
1	7.8742	8.2027	2	J(1, 0)
2	7.7660	8.2027	2	J(2, 0)
3	6.9179	7.5224	2	J(3, 0)
4	4.7305	7.5224	2	J(4, 0)
5	3.6142	1.2604	3	J(5, 0)
		5.3217	2	J(5, 0)
		16.2453	2	J(5, 0)
6	3.4313	0.7803	2	J(6, 0)
		6.9222	2	J(6, 0)
		16.3053	2	J(6, 0)






8.21
8.21
8.19
8.19
7.67
7.65
7.58
7.57
7.56
7.21
6.94
6.92
6.91
6.51
6.49
3.45
2.31
2.30
2.29
1.99
1.98
1.97
1.97
1.97
1.96
1.96
1.95
1.94
1.66
A (m) 8.20
B (d) 7.66
C (m) 7.57
D (s) 7.21
E (t) 6.92
F (d) 6.50
G (s) 3.45
H (m) 2.30
I (m) 1.97
J (s) 1.66
MeO2C
N
Ts
374
Name Shift [ppm] H's Integral Class J's [Hz]
J (s) 1.66 3 3.21 s
I (m) 1.97 2 2.04 m
H (m) 2.30 2 2.01 m
G (s) 3.45 3 3.18 s
F (d) 6.50 2 2.03 d 8.01
E (t) 6.92 1 1.05 t 7.42, 7.42
D (s) 7.21 1 1.20 s
C (m) 7.57 1 0.98 m
B (d) 7.66 2 2.06 d 8.35
A (m) 8.20 1 1.00 m
f1 (ppm)


MeO2C
N
Ts
374
168.79
144.48
141.13
136.38
136.25
134.24
129.84
128.75
128.59
126.93
125.52
124.75
124.22
122.32
113.69
51.56
27.70
25.88
21.03
f1 (ppm)



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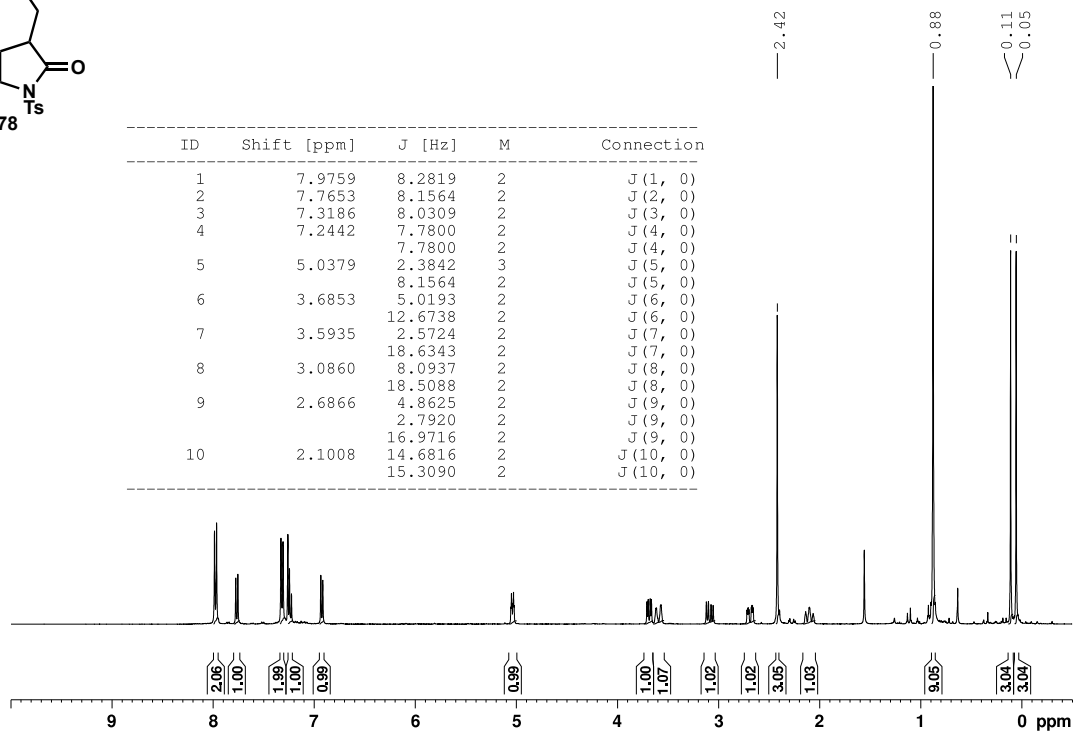
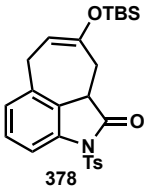
ID	Shift [ppm]	J [Hz]	M	Connection
1	7.9759	8.2819	2	J(1, 0)
2	7.7653	8.1564	2	J(2, 0)
3	7.3186	8.0309	2	J(3, 0)
4	7.2442	7.7800	2	J(4, 0)
		7.7800	2	J(4, 0)
5	5.0379	2.3842	3	J(5, 0)
		8.1564	2	J(5, 0)
6	3.6853	5.0193	2	J(6, 0)
		12.6738	2	J(6, 0)
7	3.5935	2.5724	2	J(7, 0)
		18.6343	2	J(7, 0)
8	3.0860	8.0937	2	J(8, 0)
		18.5088	2	J(8, 0)
9	2.6866	4.8625	2	J(9, 0)
		2.7920	2	J(9, 0)
		16.9716	2	J(9, 0)
10	2.1008	14.6816	2	J(10, 0)
		15.3090	2	J(10, 0)





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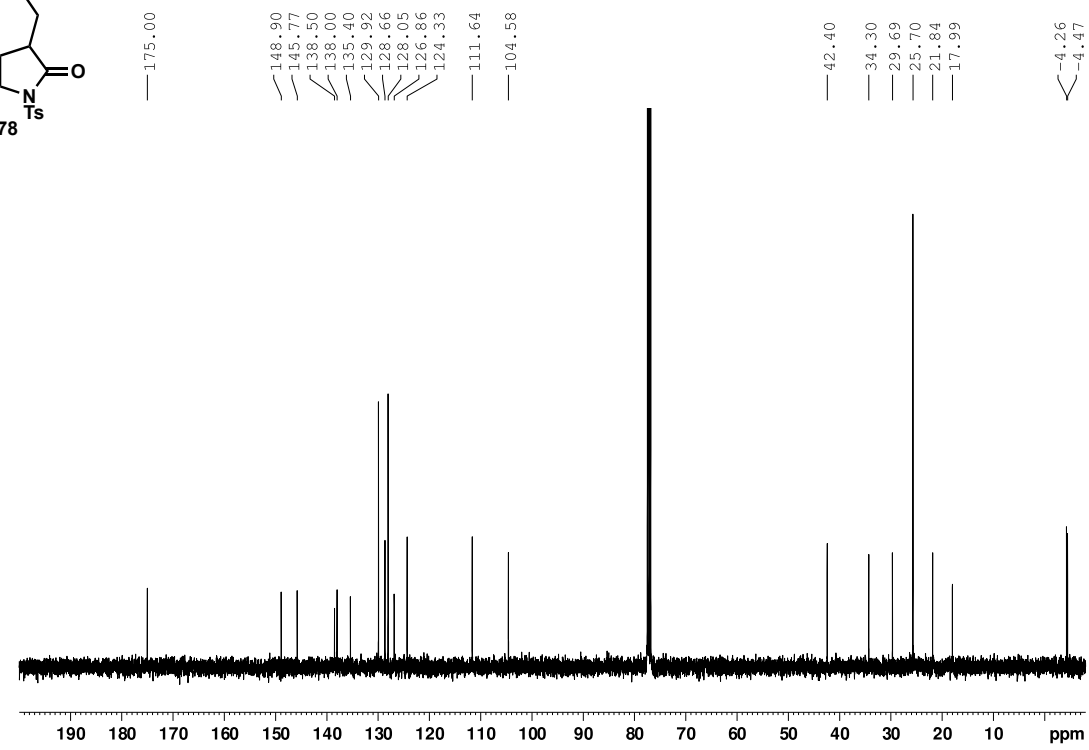
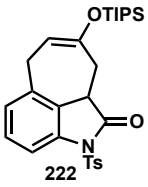
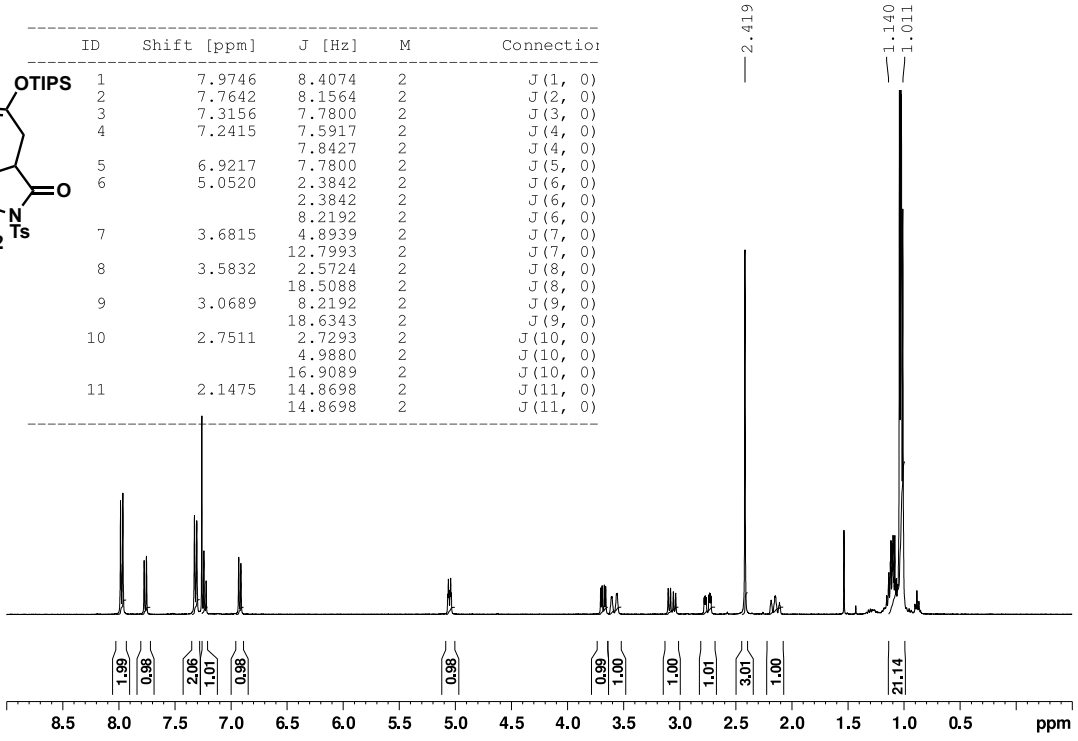
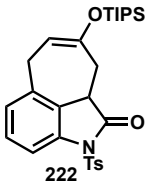
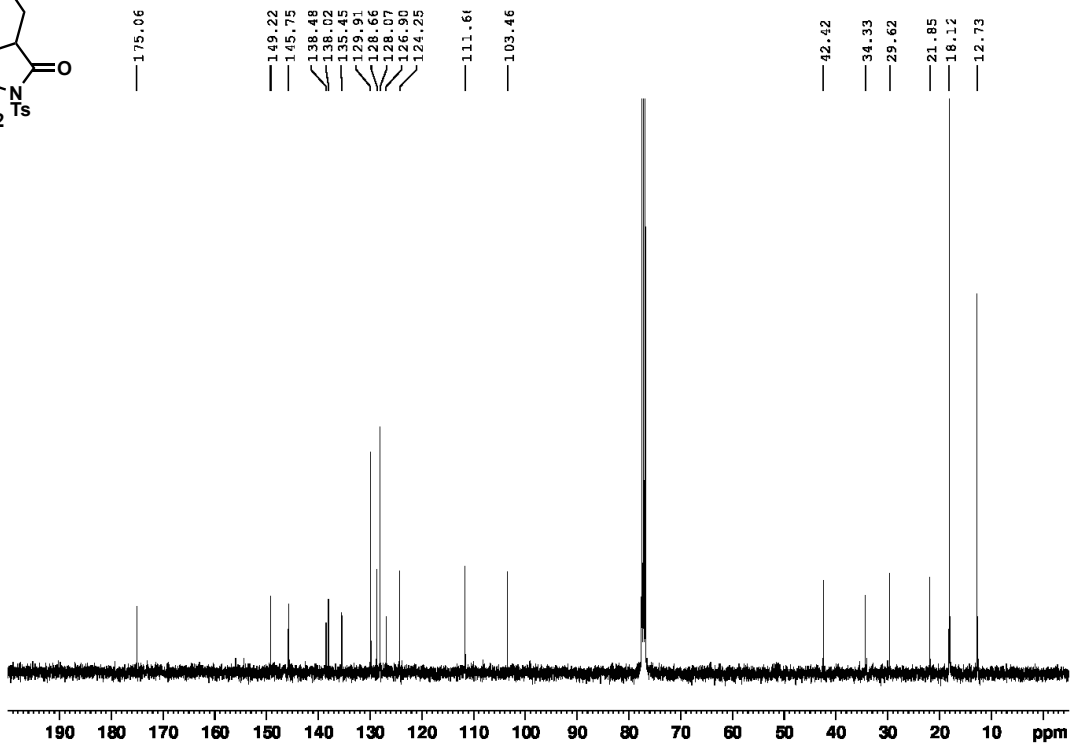


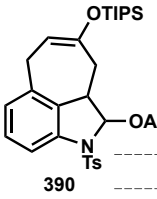


ID	Shift [ppm]	J [Hz]	M	Connectio
1	7.9746	8.4074	2	J(1, 0)
2	7.7642	8.1564	2	J(2, 0)
3	7.3156	7.7800	2	J(3, 0)
4	7.2415	7.5917	2	J(4, 0)
		7.8427	2	J(4, 0)
5	6.9217	7.7800	2	J(5, 0)
6	5.0520	2.3842	2	J(6, 0)
		2.3842	2	J(6, 0)
		8.2192	2	J(6, 0)
7	3.6815	4.8939	2	J(7, 0)
		12.7993	2	J(7, 0)
8	3.5832	2.5724	2	J(8, 0)
		18.5088	2	J(8, 0)
9	3.0689	8.2192	2	J(9, 0)
		18.6343	2	J(9, 0)
10	2.7511	2.7293	2	J(10, 0)
		4.9880	2	J(10, 0)
		16.9089	2	J(10, 0)
11	2.1475	14.8698	2	J(11, 0)
		14.8698	2	J(11, 0)









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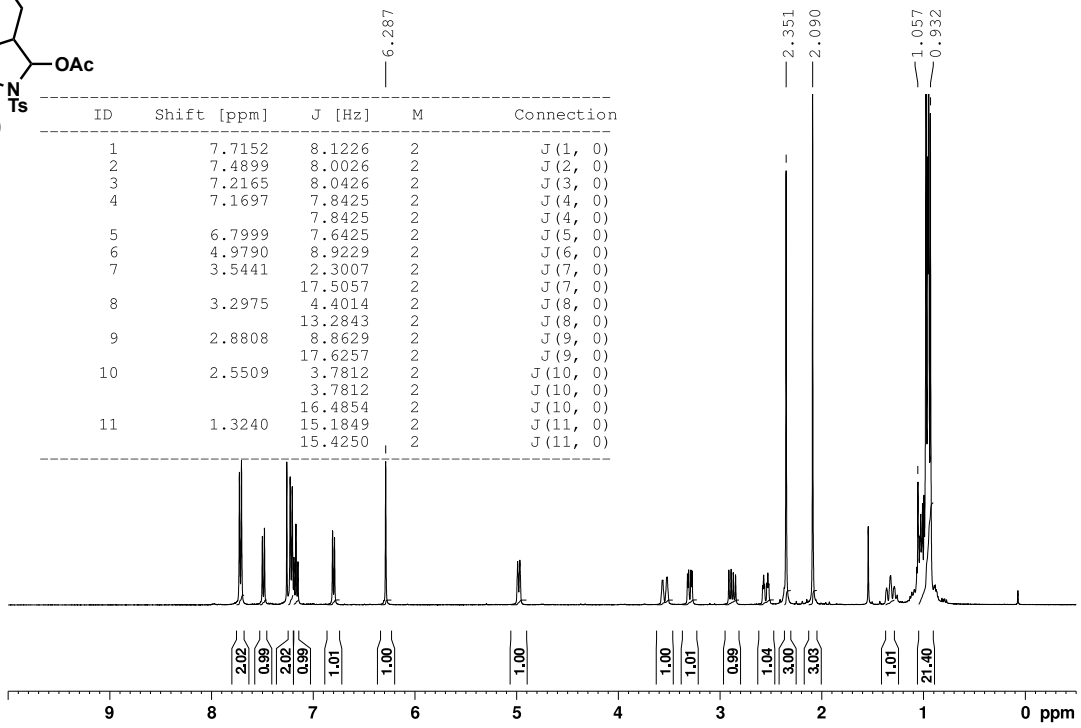
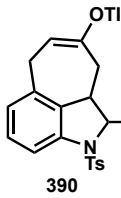
ID	Shift [ppm]	J [Hz]	M	Connection
1	7.7152	8.1226	2	J(1, 0)
2	7.4899	8.0026	2	J(2, 0)
3	7.2165	8.0426	2	J(3, 0)
4	7.1697	7.8425	2	J(4, 0)
		7.8425	2	J(4, 0)
5	6.7999	7.6425	2	J(5, 0)
6	4.9790	8.9229	2	J(6, 0)
7	3.5441	2.3007	2	J(7, 0)
		17.5057	2	J(7, 0)
8	3.2975	4.4014	2	J(8, 0)
		13.2843	2	J(8, 0)
9	2.8808	8.8629	2	J(9, 0)
		17.6257	2	J(9, 0)
10	2.5509	3.7812	2	J(10, 0)
		3.7812	2	J(10, 0)
		16.4854	2	J(10, 0)
11	1.3240	15.1849	2	J(11, 0)
		15.4250	2	J(11, 0)





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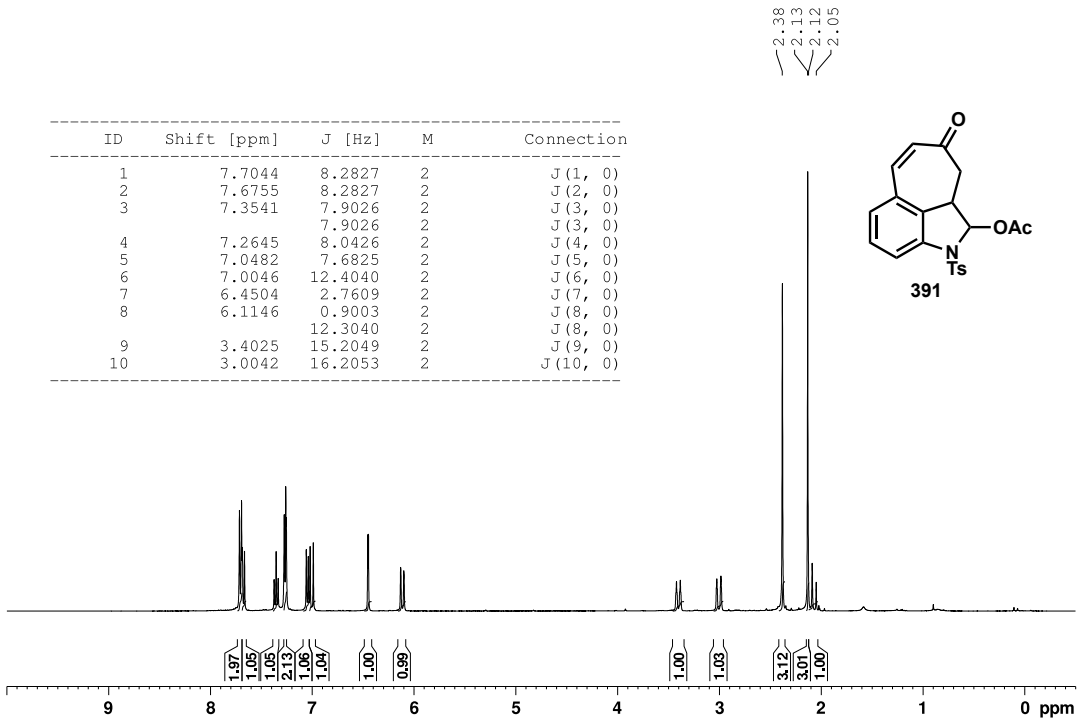
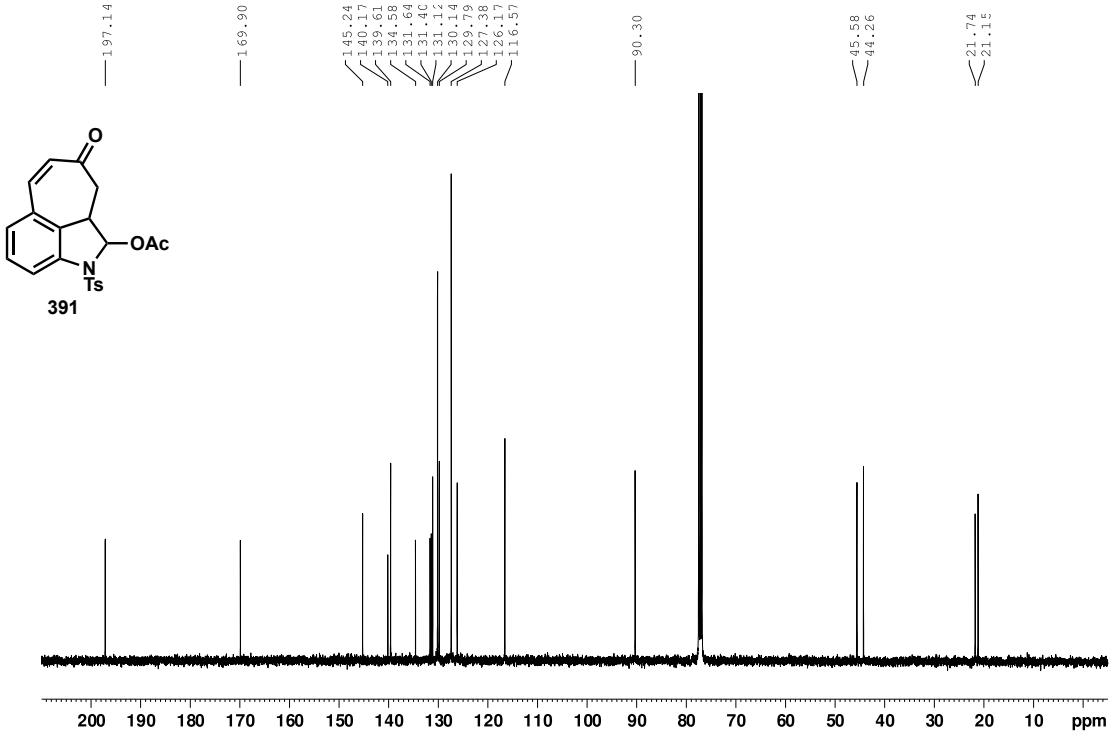
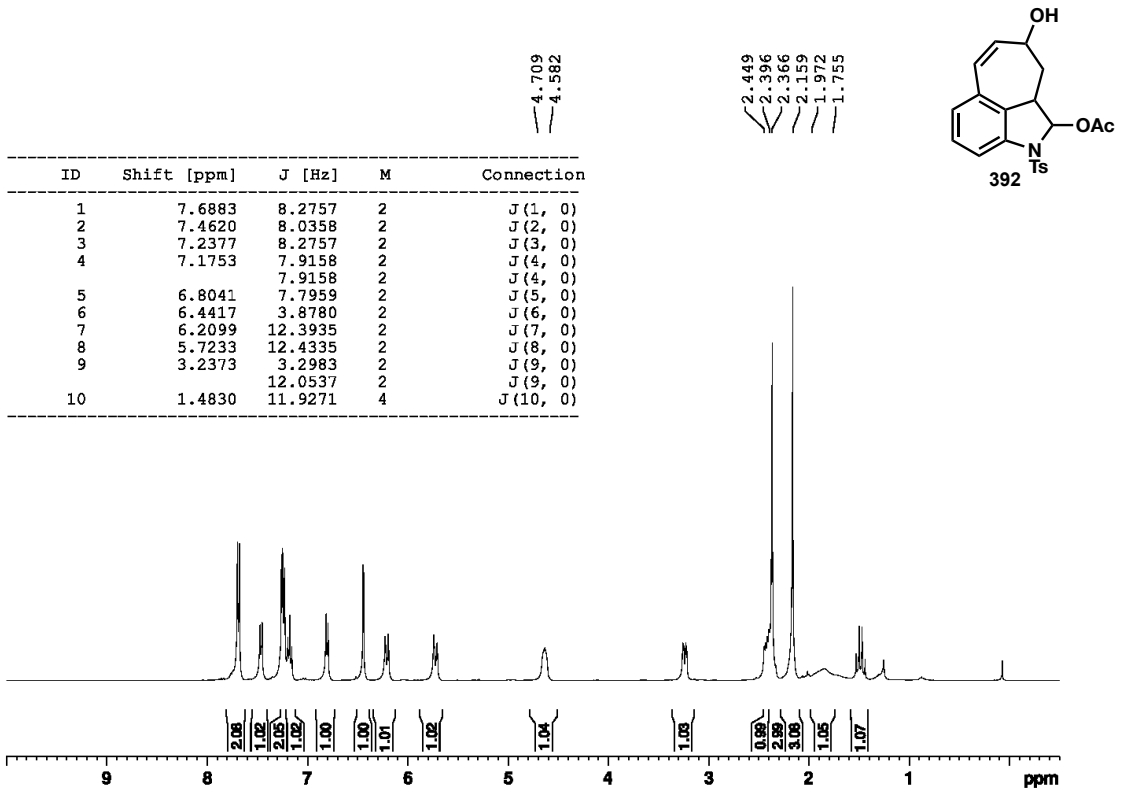


ID	Shift [ppm]	J [Hz]	M	Connection
1	7.7044	8.2827	2	J(1, 0)
2	7.6755	8.2827	2	J(2, 0)
3	7.3541	7.9026	2	J(3, 0)
		7.9026	2	J(3, 0)
4	7.2645	8.0426	2	J(4, 0)
5	7.0482	7.6825	2	J(5, 0)
6	7.0046	12.4040	2	J(6, 0)
7	6.4504	2.7609	2	J(7, 0)
8	6.1146	0.9003	2	J(8, 0)
		12.3040	2	J(8, 0)
9	3.4025	15.2049	2	J(9, 0)
10	3.0042	16.2053	2	J(10, 0)




4.709
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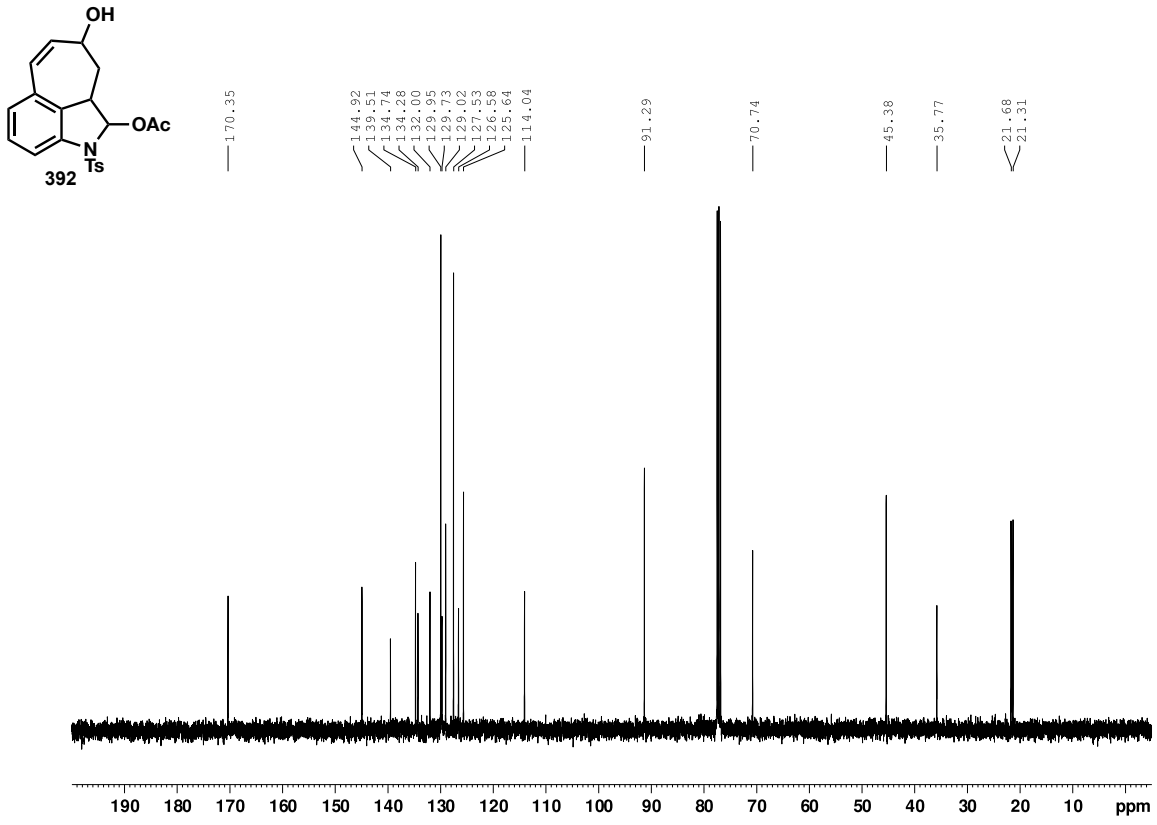
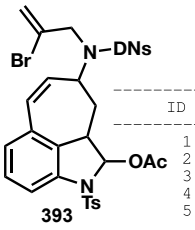
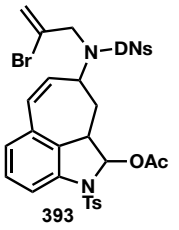
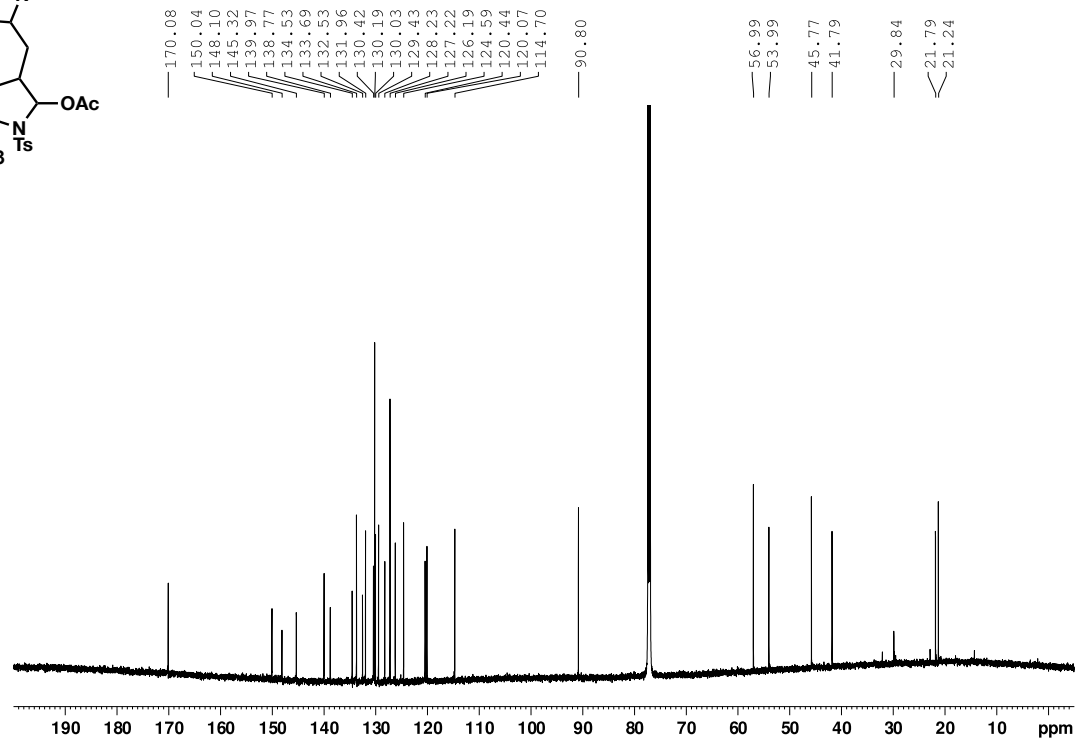
2.396
2.366
2.159
1.972
1.755
OH
OAc
N
Ts
392
ID Shift [ppm] J [Hz] M Connection
1 7.6883 8.2757 2 J(1, 0)
2 7.4620 8.0358 2 J(2, 0)
3 7.2377 8.2757 2 J(3, 0)
4 7.1753 7.9158 2 J(4, 0)
7.9158 2 J(4, 0)
5 6.8041 7.7959 2 J(5, 0)
6 6.4417 3.8780 2 J(6, 0)
7 6.2099 12.3935 2 J(7, 0)
8 5.7233 12.4335 2 J(8, 0)
9 3.2373 3.2983 2 J(9, 0)
12.0537 2 J(9, 0)
10 1.4830 11.9271 4 J(10, 0)
2.08
1.02
2.05
1.02
1.00
1.00
1.01
1.02
1.04
1.03
0.99
2.89
3.08
1.05
1.07
9
8
7
6
5
4
3
2
1
ppm

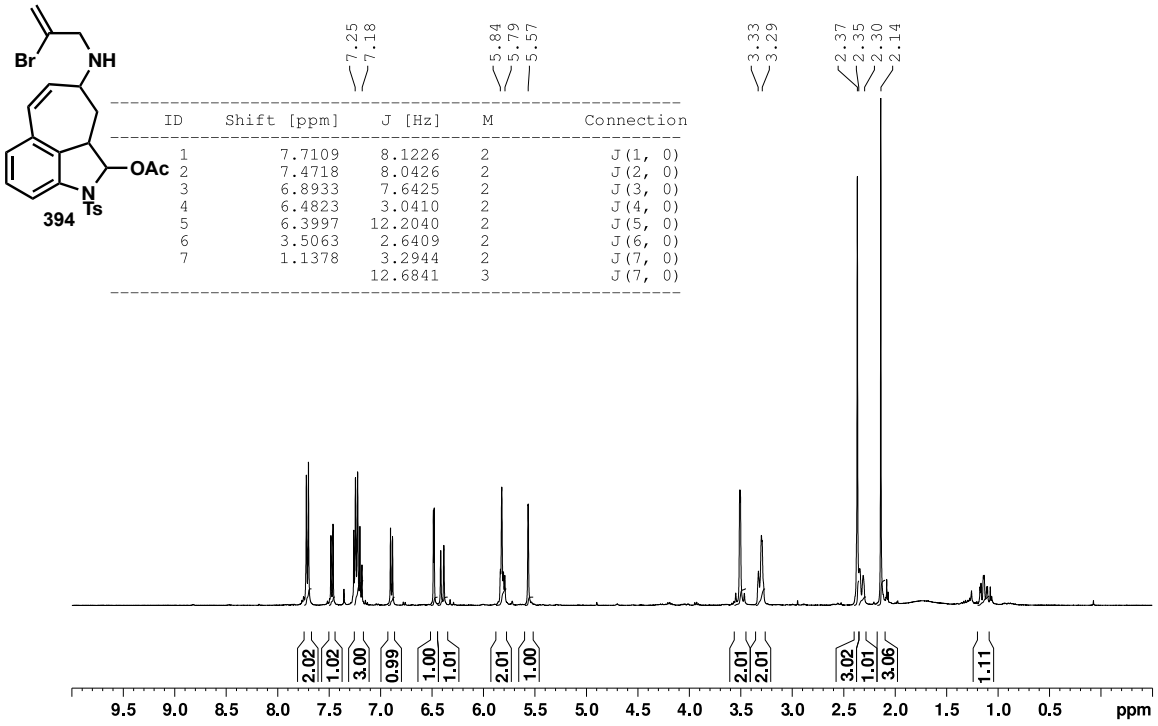

OH
OAc
N
Ts
392
170.35
144.92
139.51
134.74
134.28
132.00
129.95
129.73
129.02
127.53
126.58
125.64
114.04
91.29
70.74
45.38
35.77
21.68
21.31
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm



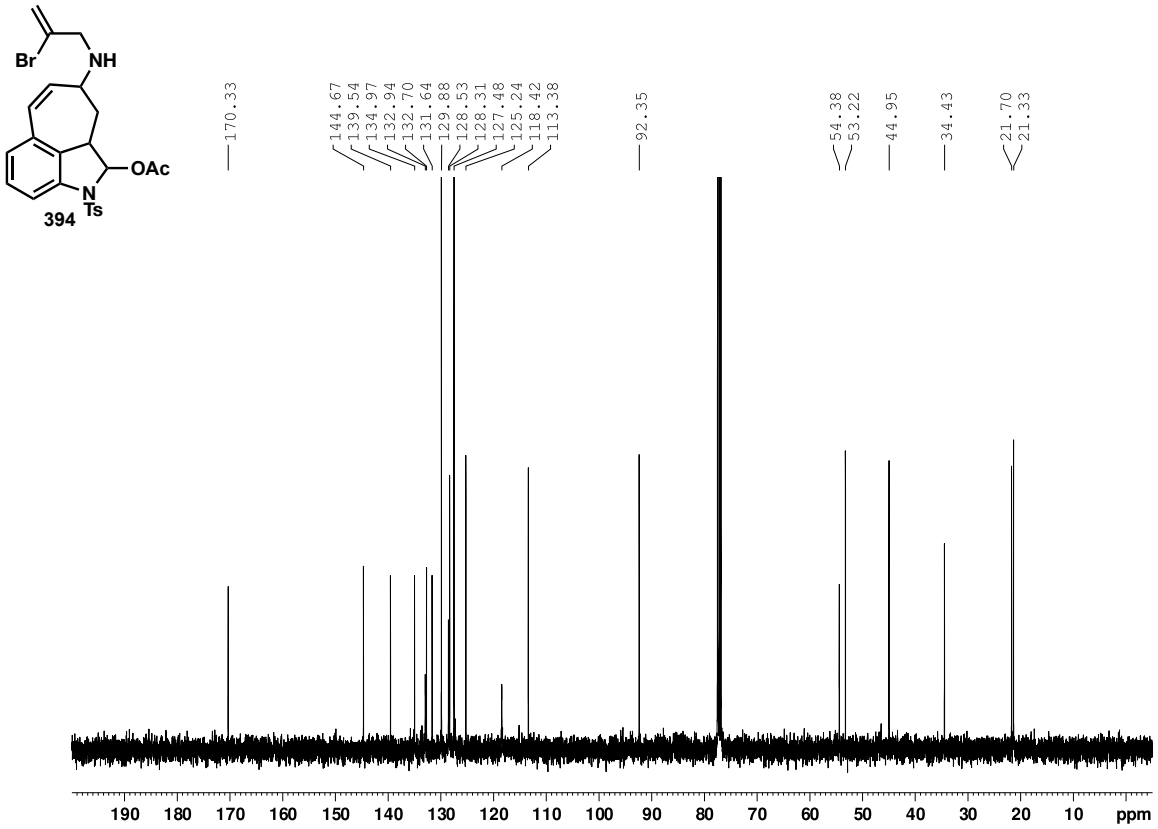
ID	Shift [ppm]	J [Hz]	M	Connection
1	7.7989	7.7959	2	J(1, 0)
2	7.7156	8.2757	2	J(2, 0)
3	7.5731	1.9590	2	J(3, 0)
4	7.3608	8.5155	2	J(4, 0)
5	7.3152	2.0789	2	J(5, 0)
		8.6355	2	J(5, 0)
6	6.9946	7.9158	2	J(6, 0)
		7.9158	2	J(6, 0)
7	6.6993	2.6786	2	J(7, 0)
8	6.6725	8.0358	2	J(8, 0)
9	6.5202	7.5560	2	J(9, 0)
10	6.1034	2.1789	2	J(10, 0)
		11.9337	2	J(10, 0)
11	5.6880	2.4387	2	J(11, 0)
12	5.4922	4.3977	2	J(12, 0)
		11.9137	2	J(12, 0)
13	5.2863	0.9795	2	J(13, 0)
		1.2194	2	J(13, 0)
14	4.1736	17.2709	2	J(14, 0)
15	4.0338	17.5508	2	J(15, 0)
16	2.9607	3.4182	3	J(16, 0)
		12.6733	2	J(16, 0)
17	2.6412	4.2578	3	J(17, 0)
		14.1526	2	J(17, 0)

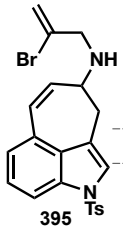


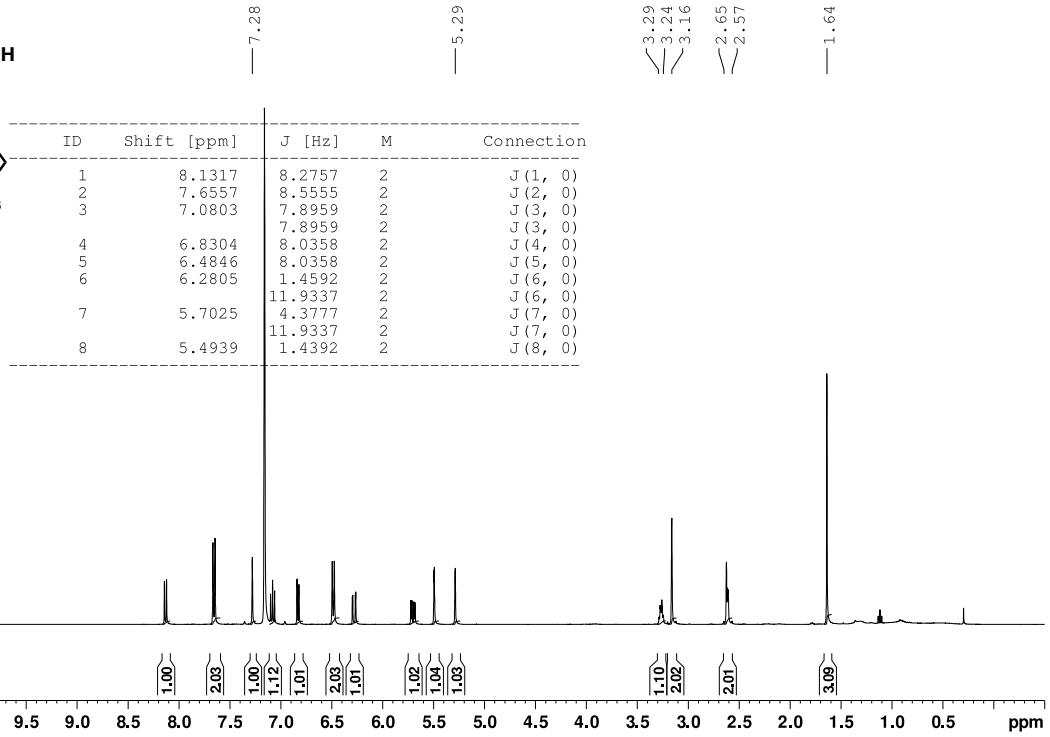




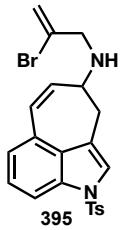
ID	Shift [ppm]	J [Hz]	M	Connection
1	7.7109	8.1226	2	J(1, 0)
2	7.4718	8.0426	2	J(2, 0)
3	6.8933	7.6425	2	J(3, 0)
4	6.4823	3.0410	2	J(4, 0)
5	6.3997	12.2040	2	J(5, 0)
6	3.5063	2.6409	2	J(6, 0)
7	1.1378	3.2944	2	J(7, 0)
		12.6841	3	J(7, 0)

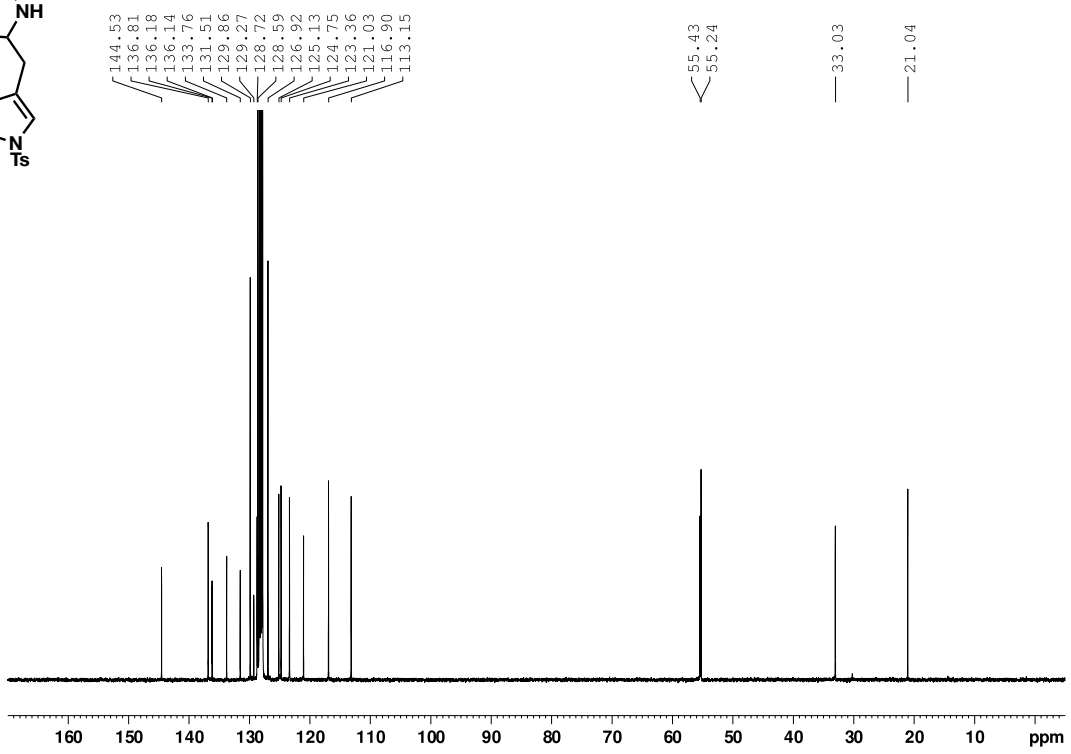


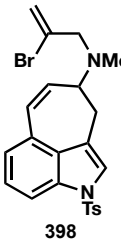




ID	Shift [ppm]	J [Hz]	M	Connection
1	8.1317	8.2757	2	J(1, 0)
2	7.6557	8.5555	2	J(2, 0)
3	7.0803	7.8959	2	J(3, 0)
		7.8959	2	J(3, 0)
4	6.8304	8.0358	2	J(4, 0)
5	6.4846	8.0358	2	J(5, 0)
6	6.2805	1.4592	2	J(6, 0)
		11.9337	2	J(6, 0)
7	5.7025	4.3777	2	J(7, 0)
		11.9337	2	J(7, 0)
8	5.4939	1.4392	2	J(8, 0)







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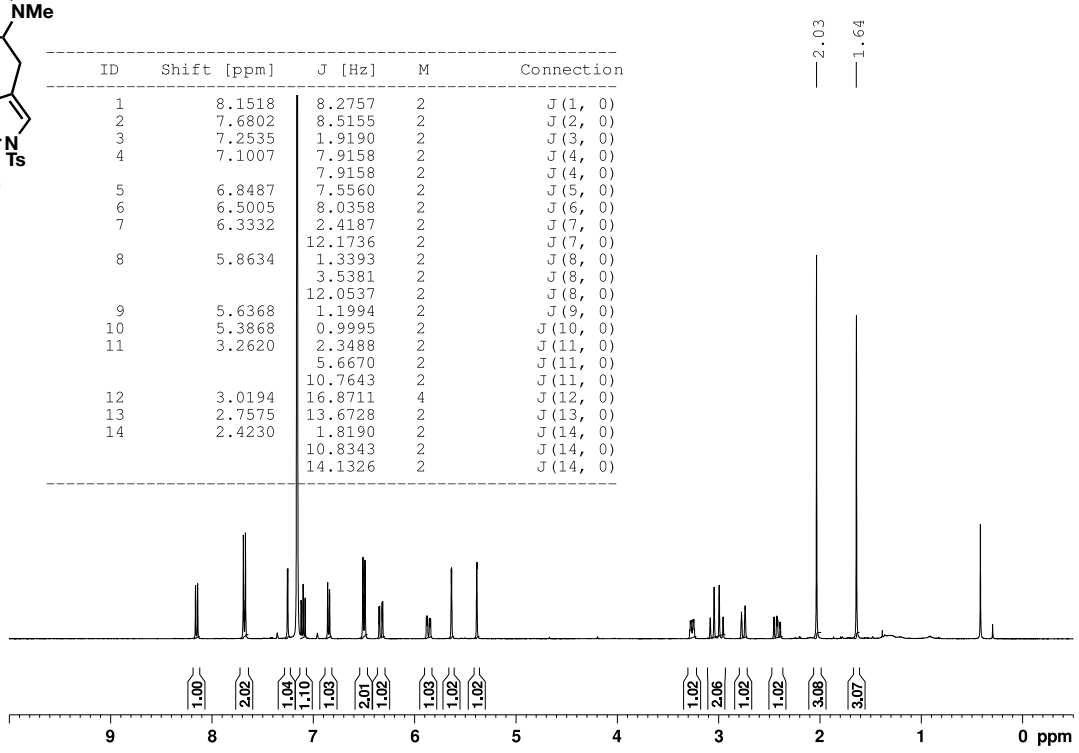
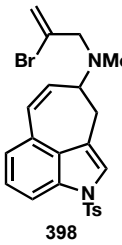
ID	Shift [ppm]	J [Hz]	M	Connection
1	8.1518	8.2757	2	J(1, 0)
2	7.6802	8.5155	2	J(2, 0)
3	7.2535	1.9190	2	J(3, 0)
4	7.1007	7.9158	2	J(4, 0)
		7.9158	2	J(4, 0)
5	6.8487	7.5560	2	J(5, 0)
6	6.5005	8.0358	2	J(6, 0)
7	6.3332	2.4187	2	J(7, 0)
		12.1736	2	J(7, 0)
8	5.8634	1.3393	2	J(8, 0)
		3.5381	2	J(8, 0)
		12.0537	2	J(8, 0)
9	5.6368	1.1994	2	J(9, 0)
10	5.3868	0.9995	2	J(10, 0)
11	3.2620	2.3488	2	J(11, 0)
		5.6670	2	J(11, 0)
		10.7643	2	J(11, 0)
12	3.0194	16.8711	4	J(12, 0)
13	2.7575	13.6728	2	J(13, 0)
14	2.4230	1.8190	2	J(14, 0)
		10.8343	2	J(14, 0)
		14.1326	2	J(14, 0)





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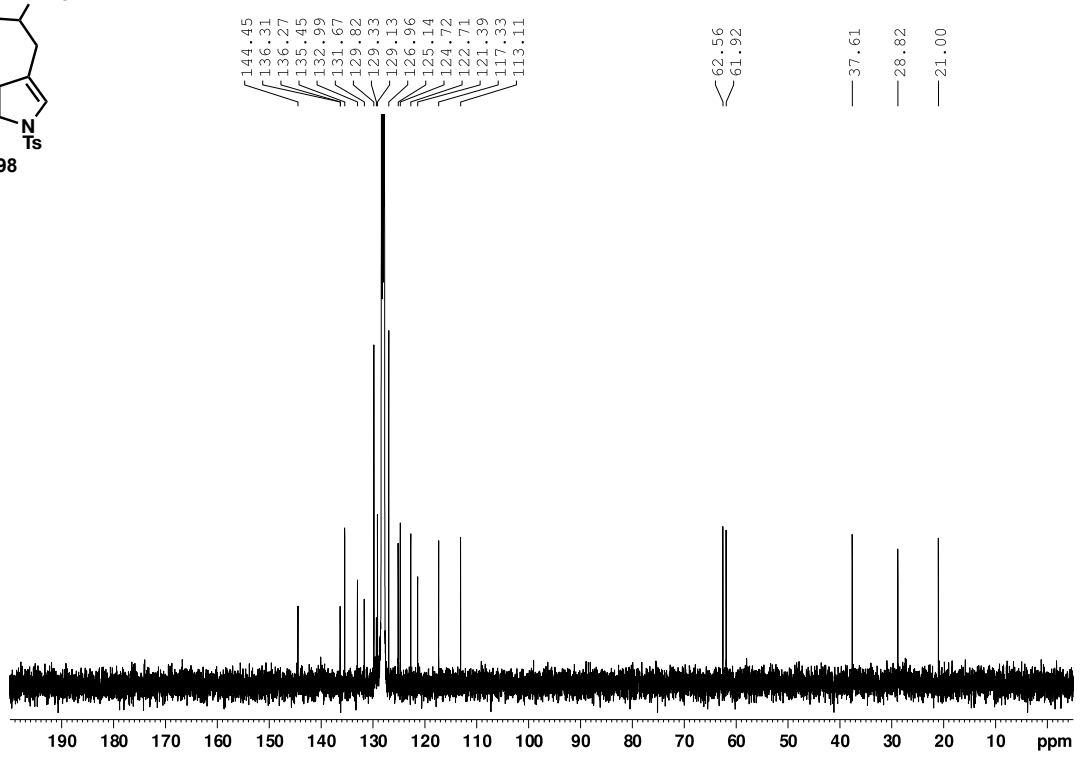

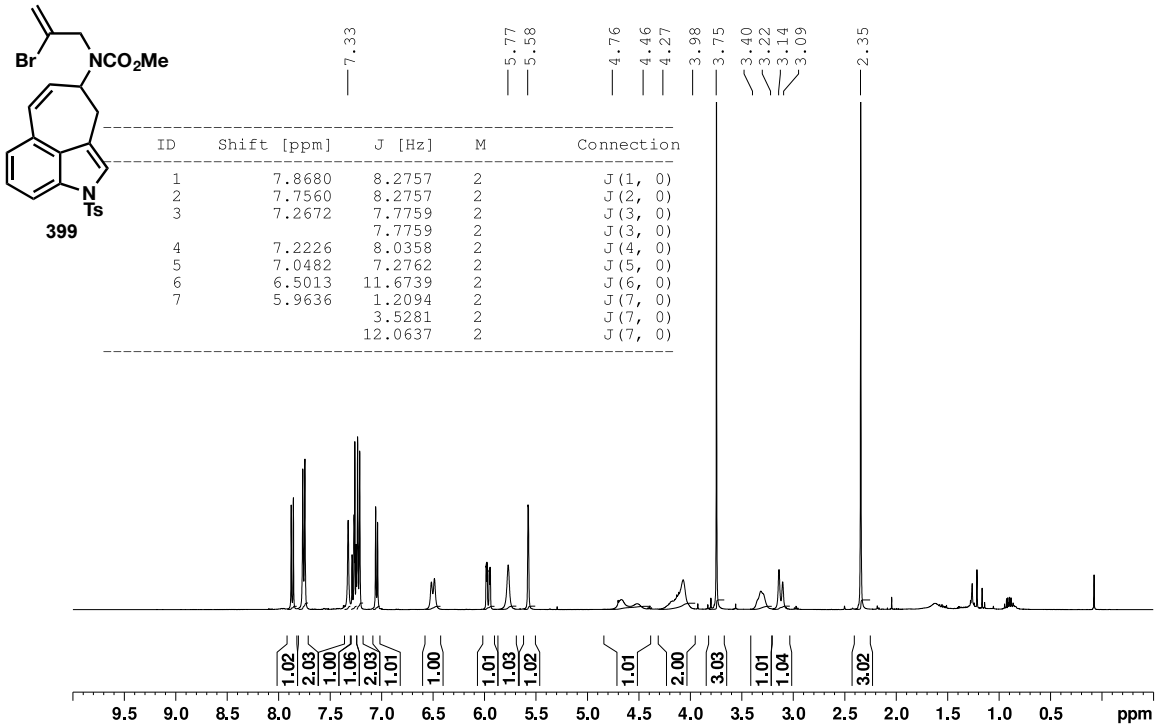
Br
NCO2Me
N
Ts
399
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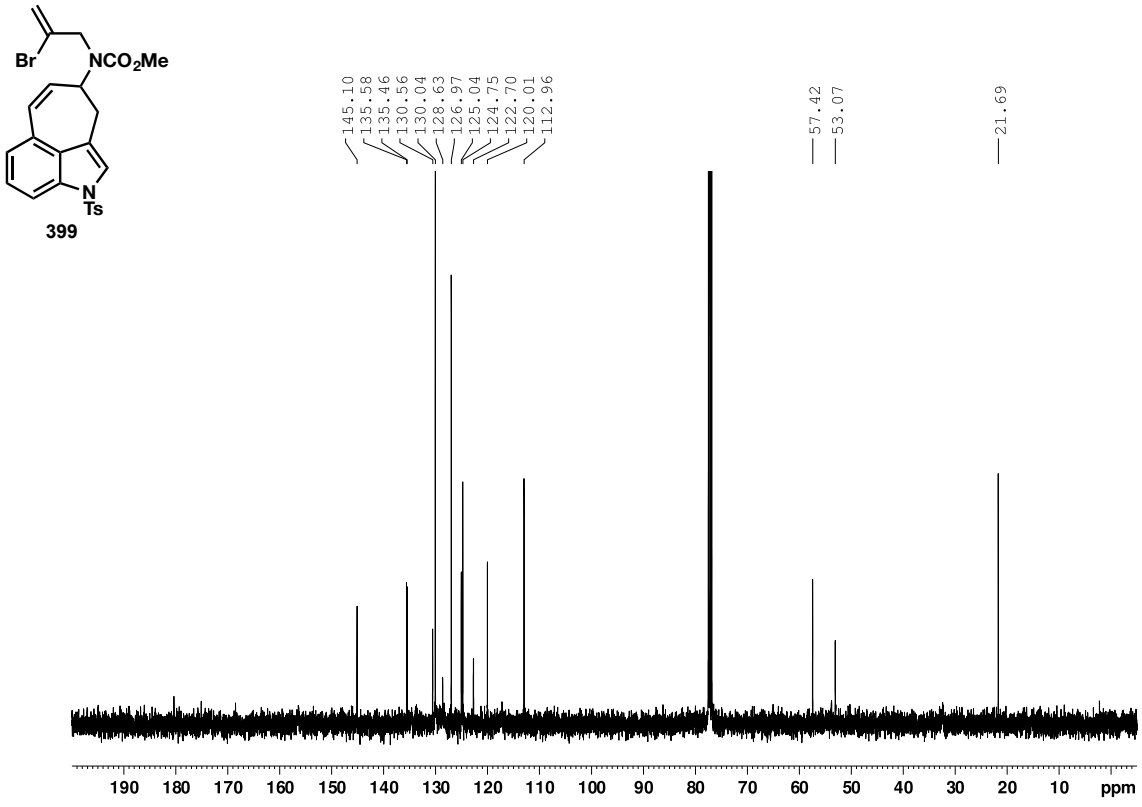
5.77
5.58
4.76
4.46
4.27
3.98
3.75
3.40
3.22
3.14
3.09
2.35
ID Shift [ppm] J [Hz] M Connection
1 7.8680 8.2757 2 J(1, 0)
2 7.7560 8.2757 2 J(2, 0)
3 7.2672 7.7759 2 J(3, 0)
7.7759 2 J(3, 0)
4 7.2226 8.0358 2 J(4, 0)
5 7.0482 7.2762 2 J(5, 0)
6 6.5013 11.6739 2 J(6, 0)
7 5.9636 1.2094 2 J(7, 0)
3.5281 2 J(7, 0)
12.0637 2 J(7, 0)
1.02
2.03
1.00
1.06
2.03
1.01
1.00
1.01
1.03
1.02
1.01
2.00
3.03
1.01
1.04
3.02
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm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N
Ts
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122.70
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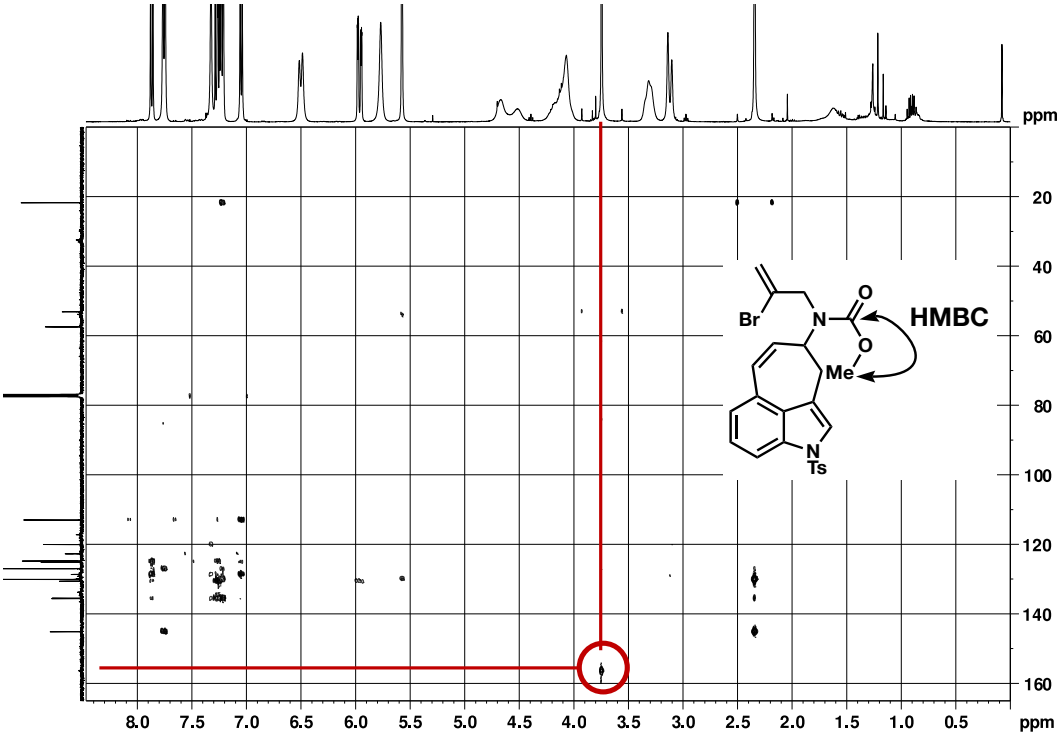
112.96
57.42
53.07
21.69
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


ppm
20
40
60
80
100
120
140
160
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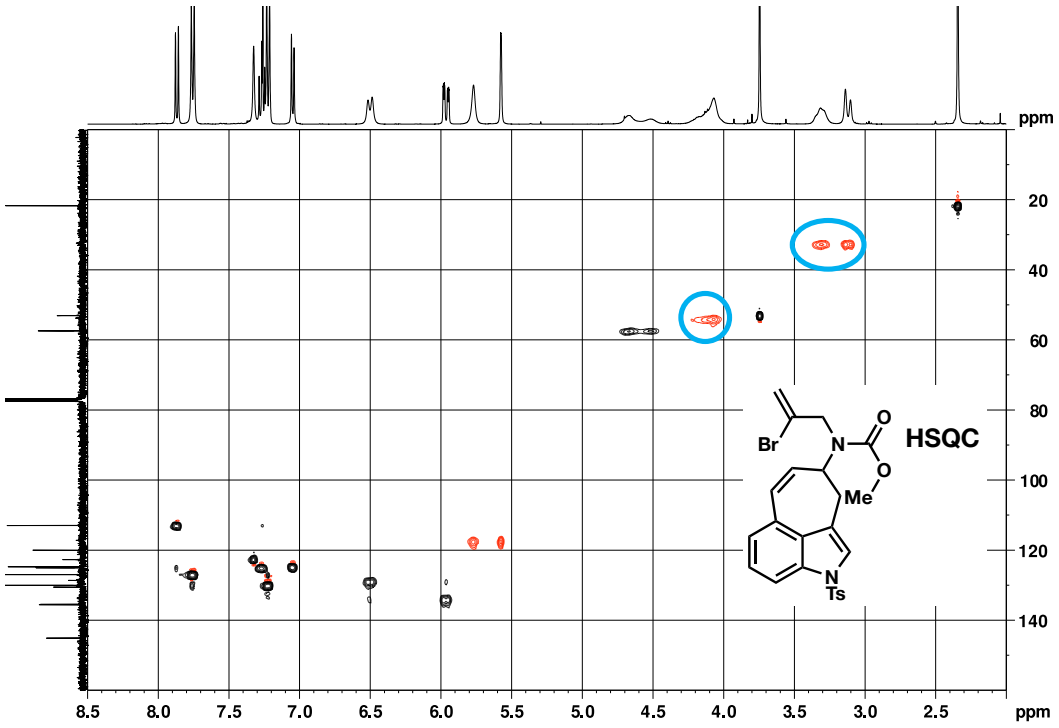
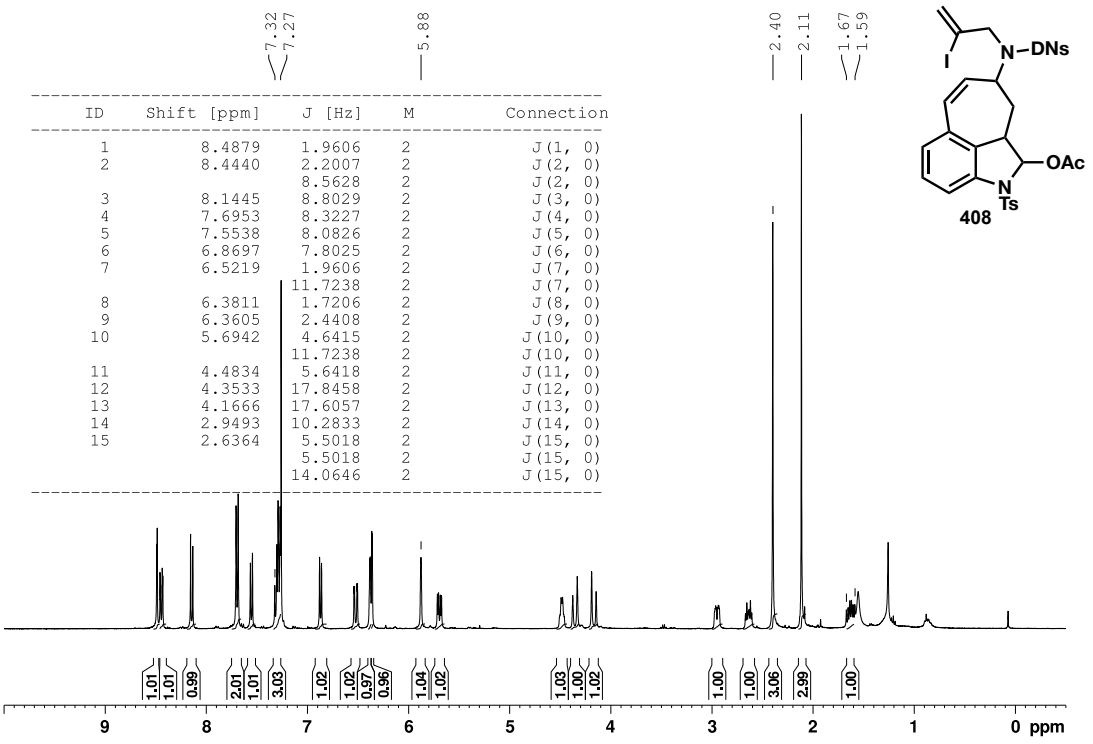
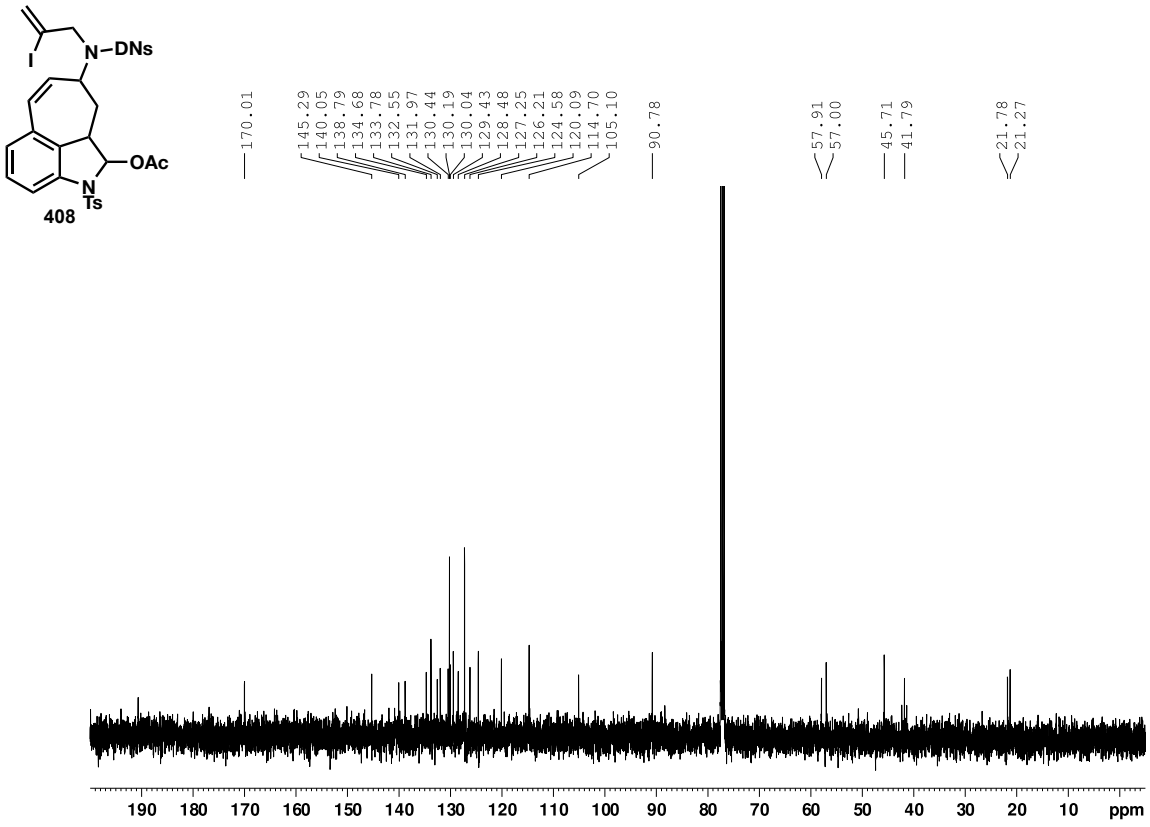
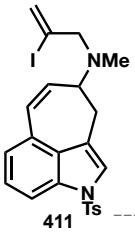
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
Br
N
O
O
Me
N
Ts
HMBC


ppm
20
40
60
80
100
120
140
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
ppm
Br
N
O
O
Me
N
Ts
HSQC


7.32
7.27
5.88
2.40
2.11
1.67
1.59
ID Shift [ppm] J [Hz] M Connection
1 8.4879 1.9606 2 J(1, 0)
2 8.4440 2.2007 2 J(2, 0)
8.5628 2 J(2, 0)
3 8.1445 8.8029 2 J(3, 0)
4 7.6953 8.3227 2 J(4, 0)
5 7.5538 8.0826 2 J(5, 0)
6 6.8697 7.8025 2 J(6, 0)
7 6.5219 1.9606 2 J(7, 0)
11.7238 2 J(7, 0)
8 6.3811 1.7206 2 J(8, 0)
9 6.3605 2.4408 2 J(9, 0)
10 5.6942 4.6415 2 J(10, 0)
11.7238 2 J(10, 0)
11 4.4834 5.6418 2 J(11, 0)
12 4.3533 17.8458 2 J(12, 0)
13 4.1666 17.6057 2 J(13, 0)
14 2.9493 10.2833 2 J(14, 0)
15 2.6364 5.5018 2 J(15, 0)
5.5018 2 J(15, 0)
14.0646 2 J(15, 0)
N–DNs
I
OAc
N
Ts
408
1.01 1.01 0.99 2.01 1.01 3.03 1.02 1.02 0.97 0.96 1.04 1.02 1.03 1.00 1.02 1.00 1.00 3.06 2.99 1.00
9 8 7 6 5 4 3 2 1 0 ppm


N–DNs
I
OAc
N
Ts
408
170.01
145.29
140.05
138.79
134.68
133.78
132.55
131.97
130.44
130.19
130.04
129.43
128.48
127.25
126.21
124.58
120.09
114.70
105.10
90.78
57.91
57.00
45.71
41.79
21.78
21.27
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm



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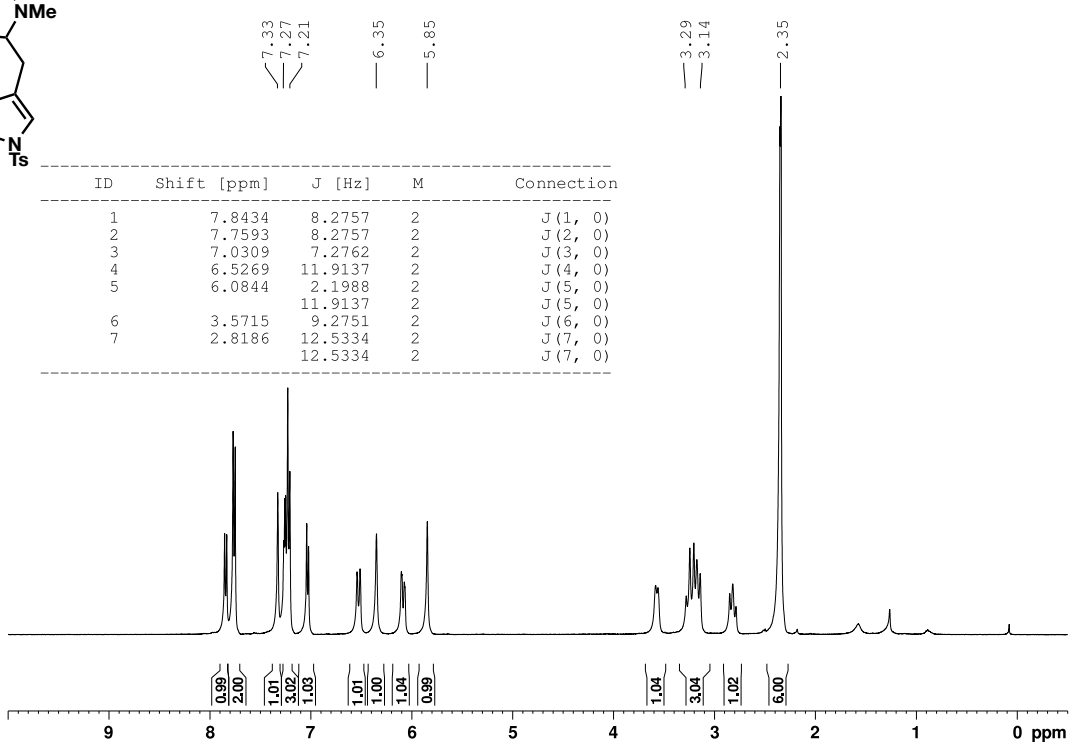
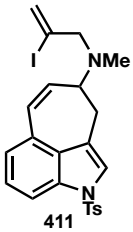
ID	Shift [ppm]	J [Hz]	M	Connection
1	7.8434	8.2757	2	J(1, 0)
2	7.7593	8.2757	2	J(2, 0)
3	7.0309	7.2762	2	J(3, 0)
4	6.5269	11.9137	2	J(4, 0)
5	6.0844	2.1988	2	J(5, 0)
		11.9137	2	J(5, 0)
6	3.5715	9.2751	2	J(6, 0)
7	2.8186	12.5334	2	J(7, 0)
		12.5334	2	J(7, 0)





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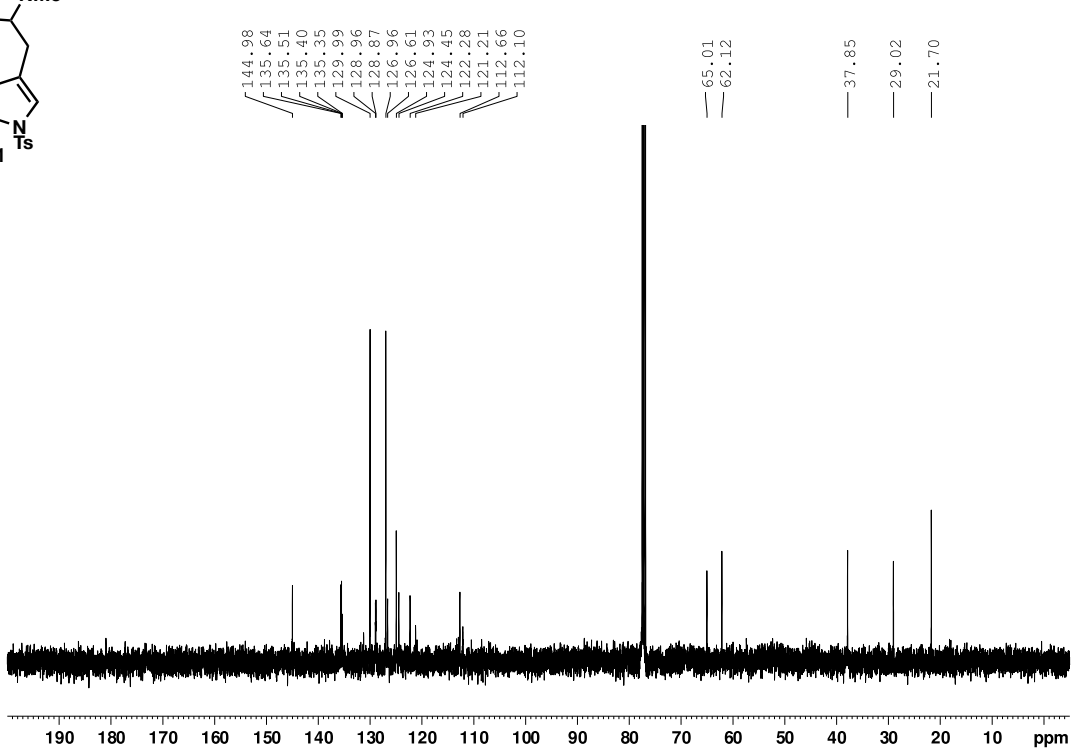
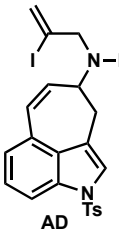
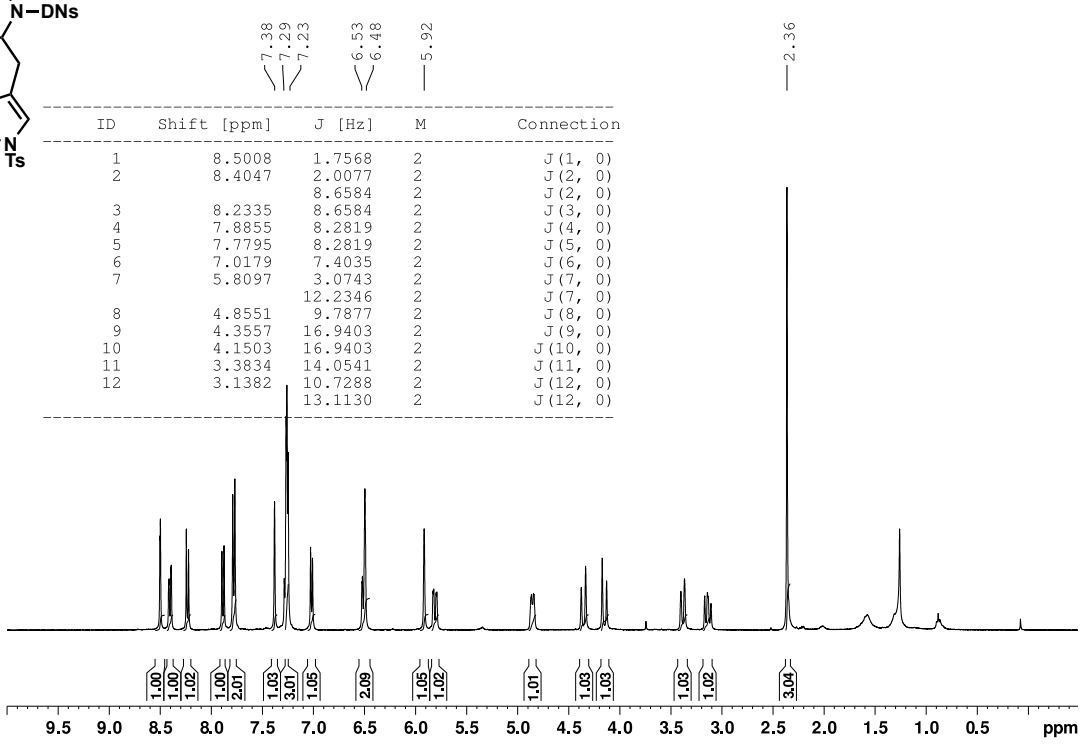
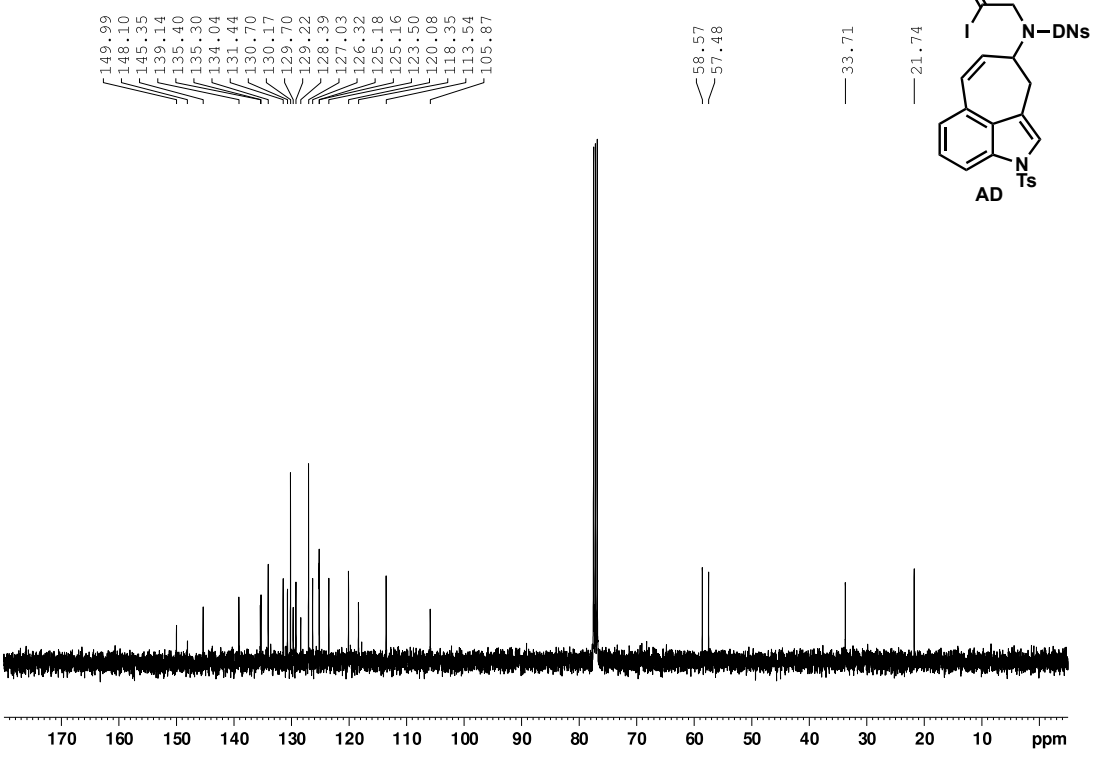
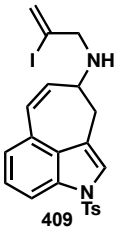






ID	Shift [ppm]	J [Hz]	M	Connection
1	8.5008	1.7568	2	J(1, 0)
2	8.4047	2.0077	2	J(2, 0)
		8.6584	2	J(2, 0)
3	8.2335	8.6584	2	J(3, 0)
4	7.8855	8.2819	2	J(4, 0)
5	7.7795	8.2819	2	J(5, 0)
6	7.0179	7.4035	2	J(6, 0)
7	5.8097	3.0743	2	J(7, 0)
		12.2346	2	J(7, 0)
8	4.8551	9.7877	2	J(8, 0)
9	4.3557	16.9403	2	J(9, 0)
10	4.1503	16.9403	2	J(10, 0)
11	3.3834	14.0541	2	J(11, 0)
12	3.1382	10.7288	2	J(12, 0)
		13.1130	2	J(12, 0)





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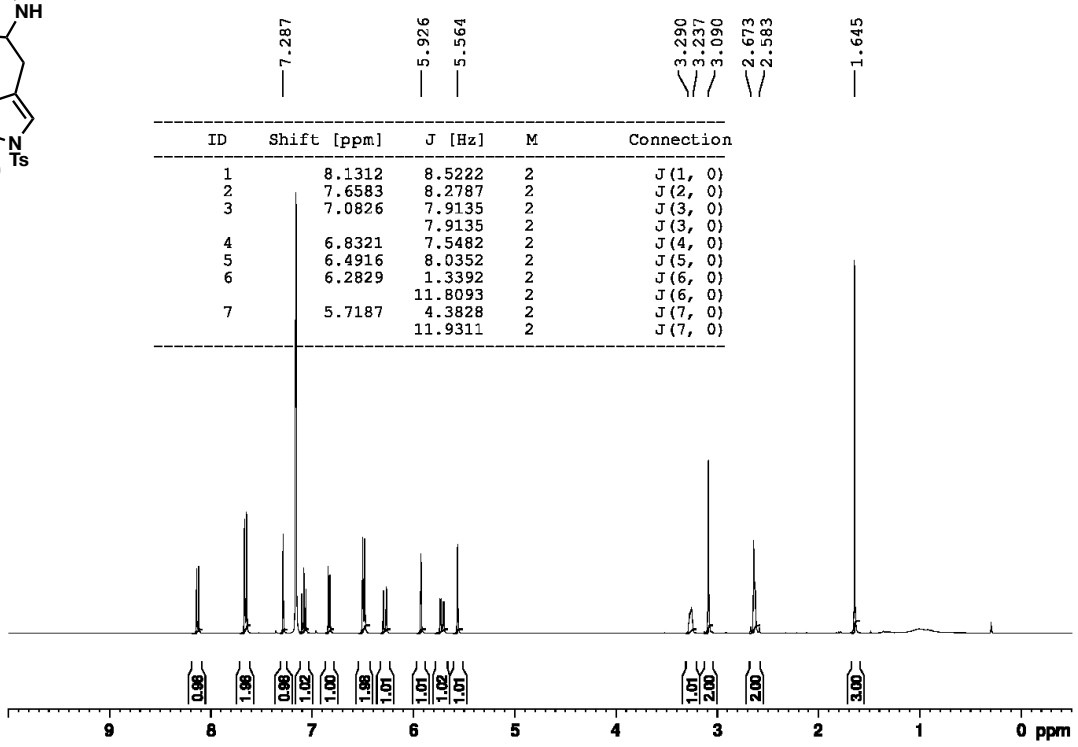
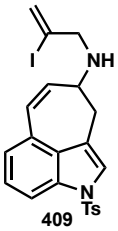


ID	Shift [ppm]	J [Hz]	M	Connection
1	8.1312	8.5222	2	J(1, 0)
2	7.6583	8.2787	2	J(2, 0)
3	7.0826	7.9135	2	J(3, 0)
		7.9135	2	J(3, 0)
4	6.8321	7.5482	2	J(4, 0)
5	6.4916	8.0352	2	J(5, 0)
6	6.2829	1.3392	2	J(6, 0)
		11.8093	2	J(6, 0)
7	5.7187	4.3828	2	J(7, 0)
		11.9311	2	J(7, 0)



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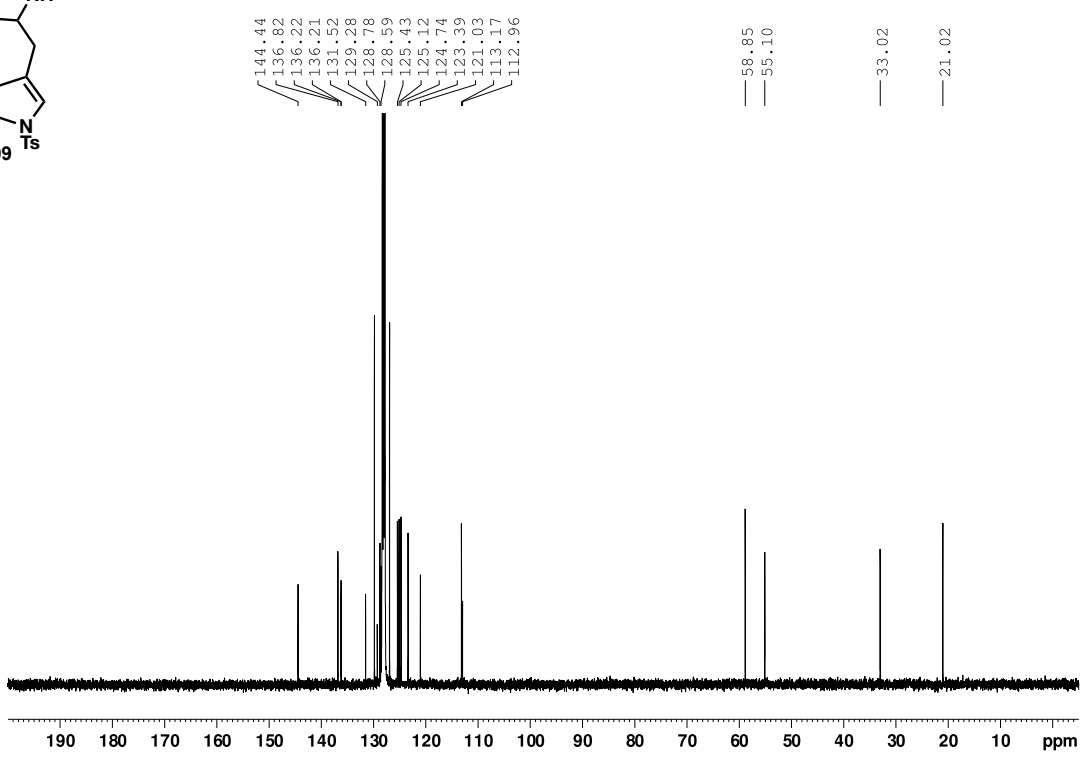
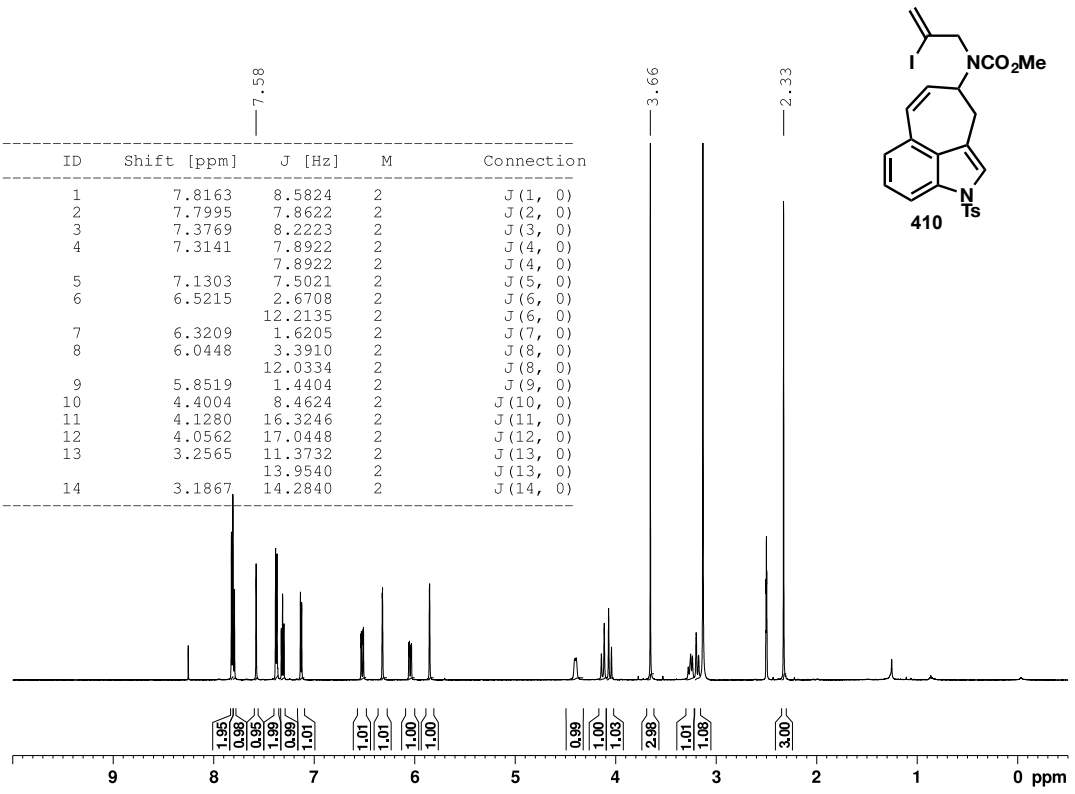
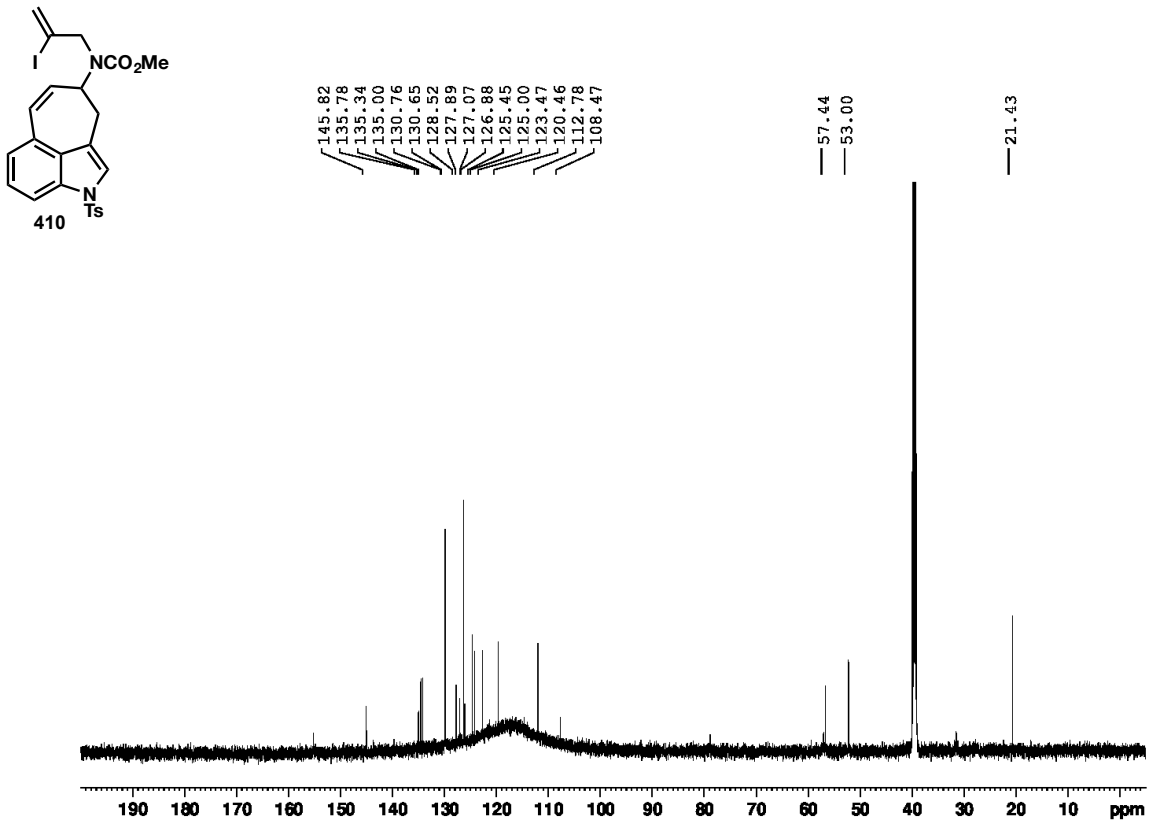
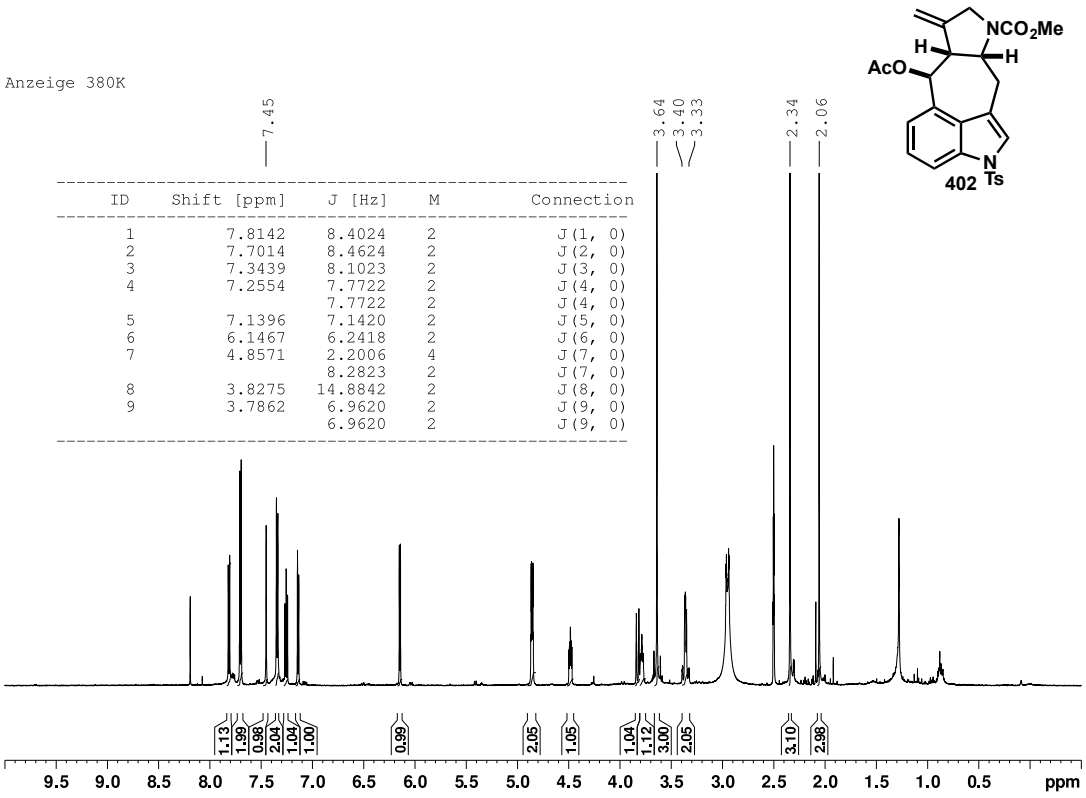
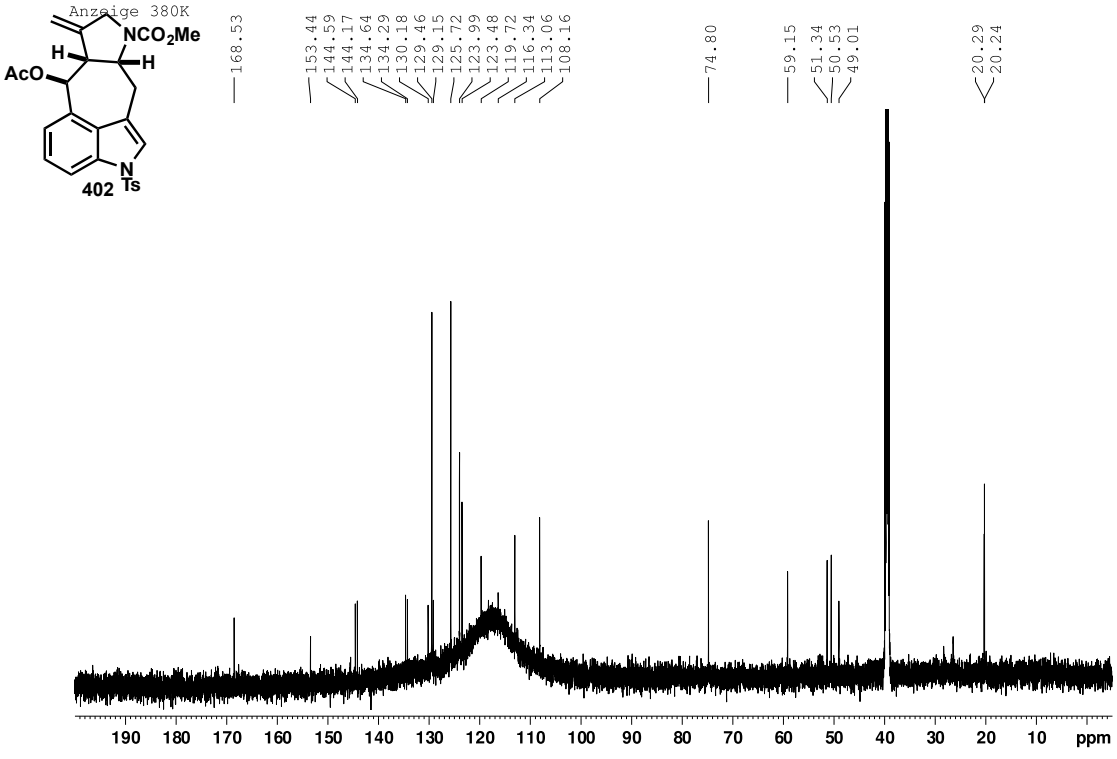


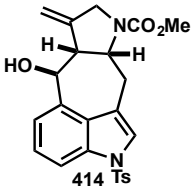


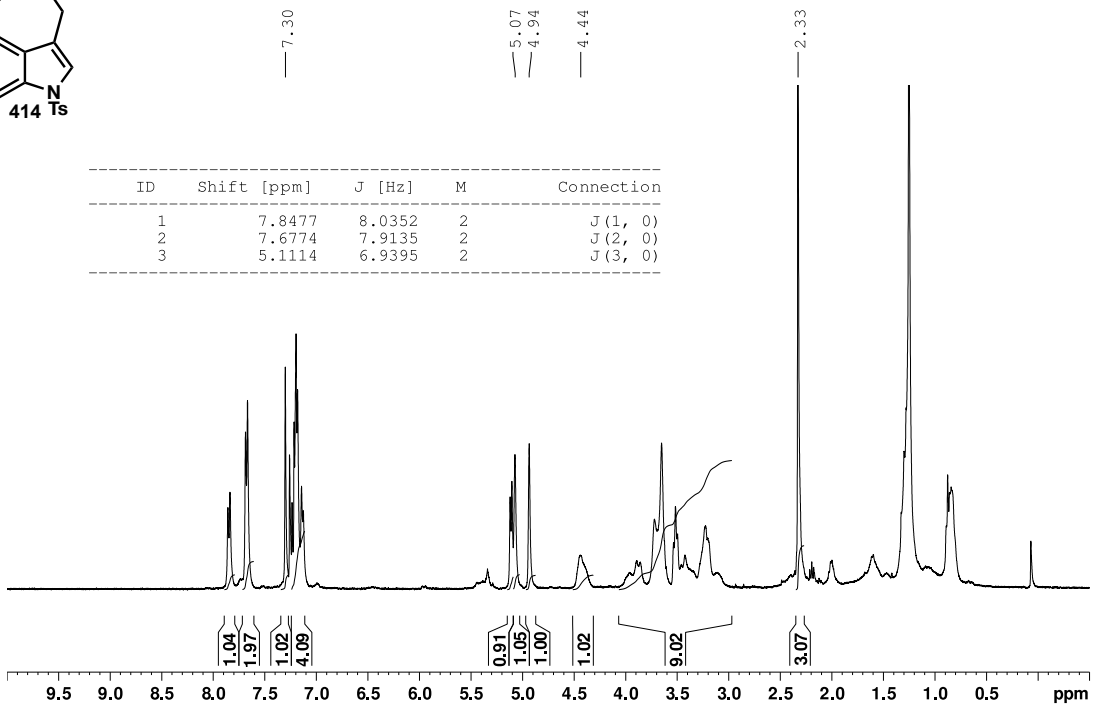
ID	Shift [ppm]	J [Hz]	M	Connection
1	7.8163	8.5824	2	J(1, 0)
2	7.7995	7.8622	2	J(2, 0)
3	7.3769	8.2223	2	J(3, 0)
4	7.3141	7.8922	2	J(4, 0)
		7.8922	2	J(4, 0)
5	7.1303	7.5021	2	J(5, 0)
6	6.5215	2.6708	2	J(6, 0)
		12.2135	2	J(6, 0)
7	6.3209	1.6205	2	J(7, 0)
8	6.0448	3.3910	2	J(8, 0)
		12.0334	2	J(8, 0)
9	5.8519	1.4404	2	J(9, 0)
10	4.4004	8.4624	2	J(10, 0)
11	4.1280	16.3246	2	J(11, 0)
12	4.0562	17.0448	2	J(12, 0)
13	3.2565	11.3732	2	J(13, 0)
		13.9540	2	J(13, 0)
14	3.1867	14.2840	2	J(14, 0)



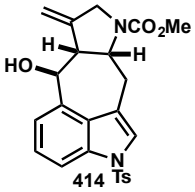

Anzeige 380K
7.45
3.64
3.40
3.33
2.34
2.06
NCO2Me
H
AcO
H
N
Ts
402
ID Shift [ppm] J [Hz] M Connection
1 7.8142 8.4024 2 J(1, 0)
2 7.7014 8.4624 2 J(2, 0)
3 7.3439 8.1023 2 J(3, 0)
4 7.2554 7.7722 2 J(4, 0)
7.7722 2 J(4, 0)
5 7.1396 7.1420 2 J(5, 0)
6 6.1467 6.2418 2 J(6, 0)
7 4.8571 2.2006 4 J(7, 0)
8.2823 2 J(7, 0)
8 3.8275 14.8842 2 J(8, 0)
9 3.7862 6.9620 2 J(9, 0)
6.9620 2 J(9, 0)
1.13
1.99
0.98
2.04
1.04
1.00
0.99
2.05
1.05
1.04
1.12
3.00
2.05
3.10
2.98
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

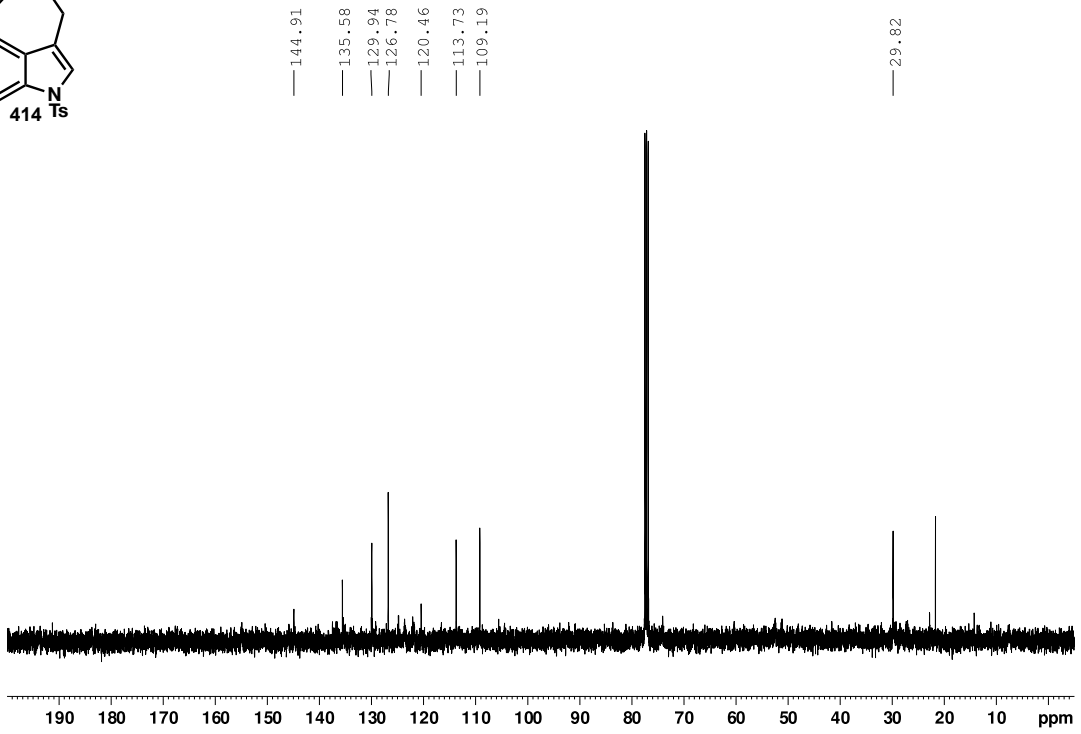

Anzeige 380K
NCO2Me
H
AcO
H
N
Ts
402
168.53
153.44
144.59
144.17
134.64
134.29
130.18
129.46
129.15
125.72
123.99
123.48
119.72
116.34
113.06
108.16
74.80
59.15
51.34
50.53
49.01
20.29
20.24
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

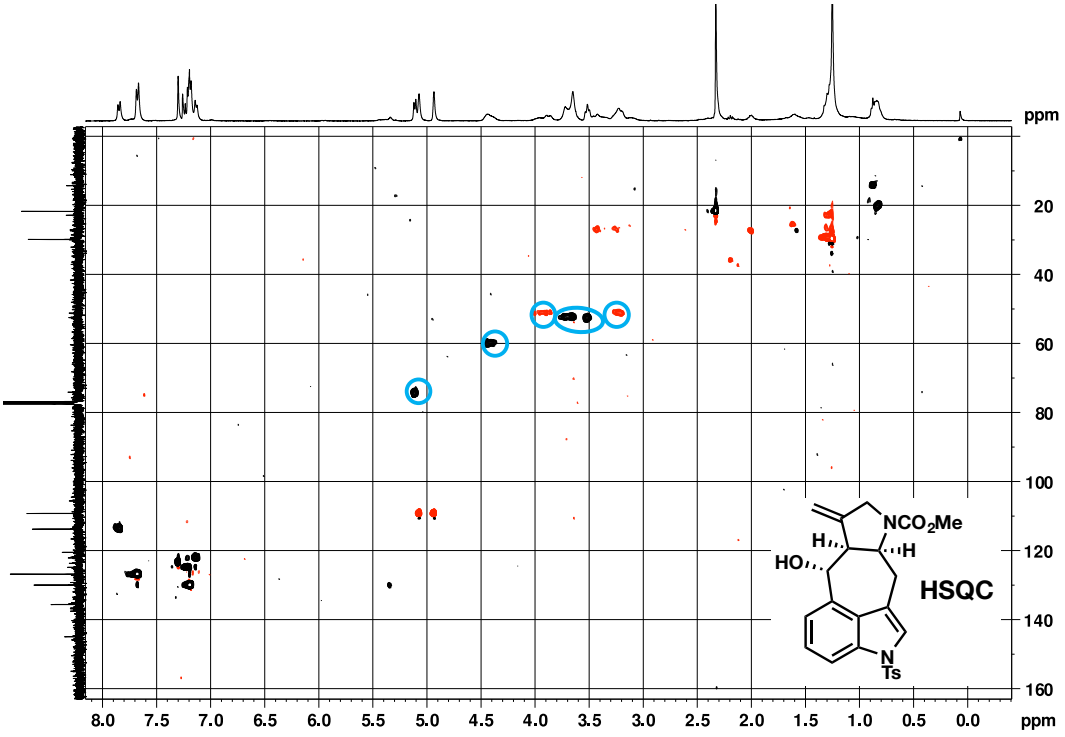


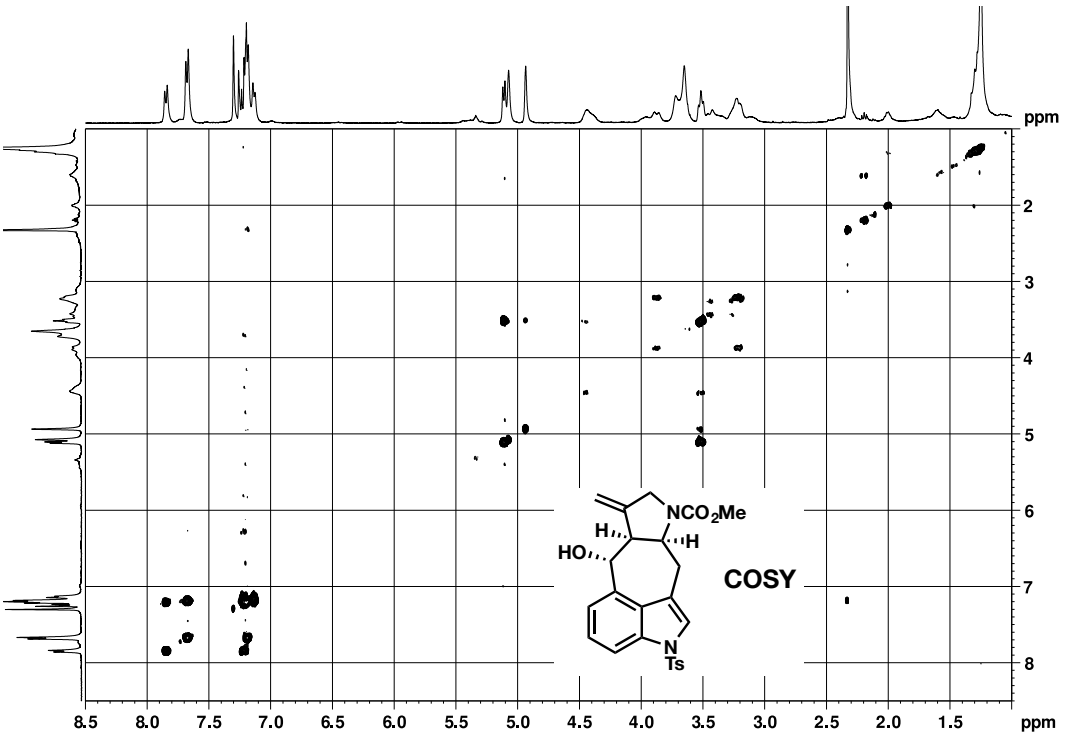


ID	Shift [ppm]	J [Hz]	M	Connection
1	7.8477	8.0352	2	J(1, 0)
2	7.6774	7.9135	2	J(2, 0)
3	5.1114	6.9395	2	J(3, 0)

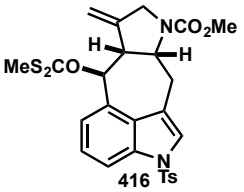




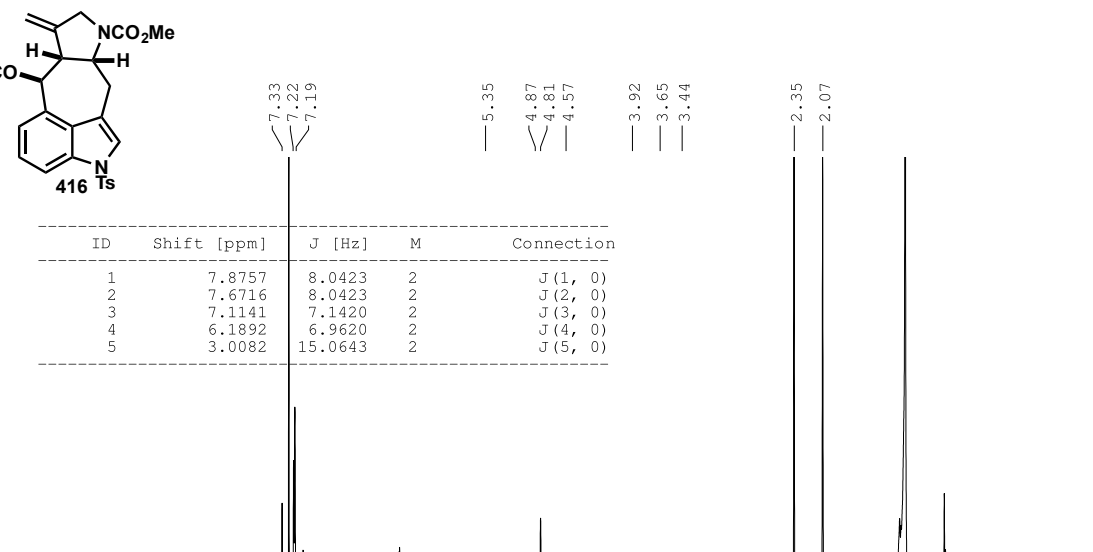

ppm
20
40
60
80
100
120
140
160
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
NCO2Me
H
H
HO
N
Ts
HSQC


ppm
2
3
4
5
6
7
8
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm
NCO2Me
H
H
HO
N
Ts
COSY

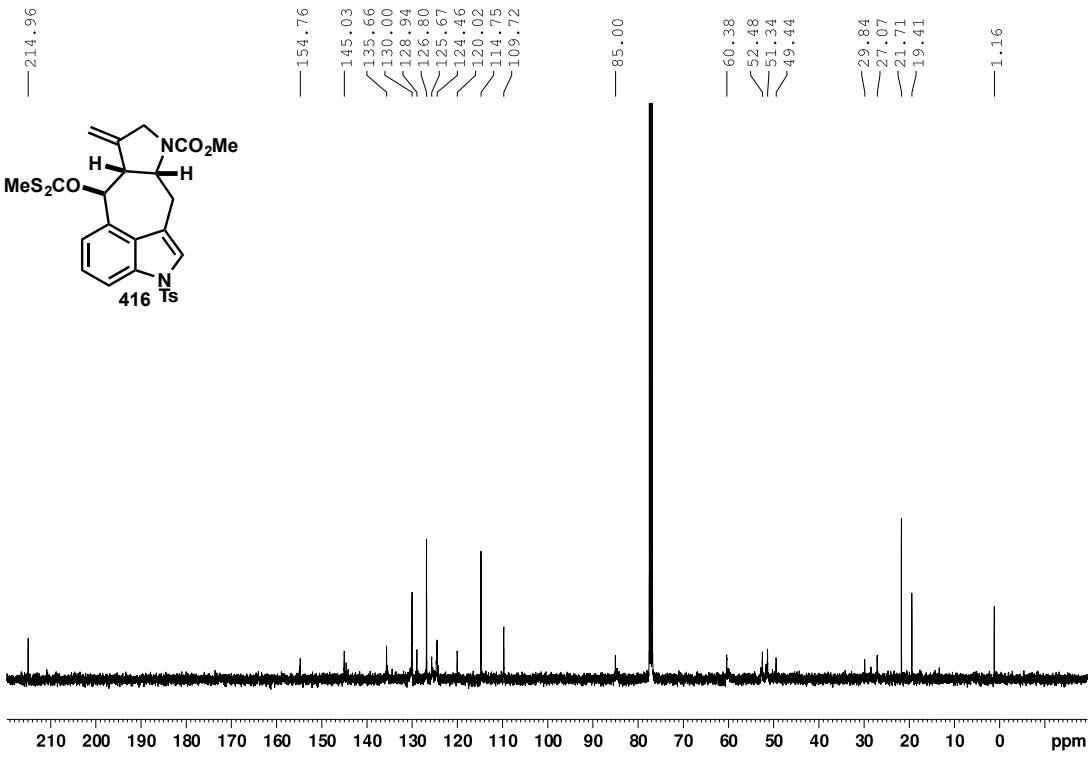
DMSO-d_6, 380K

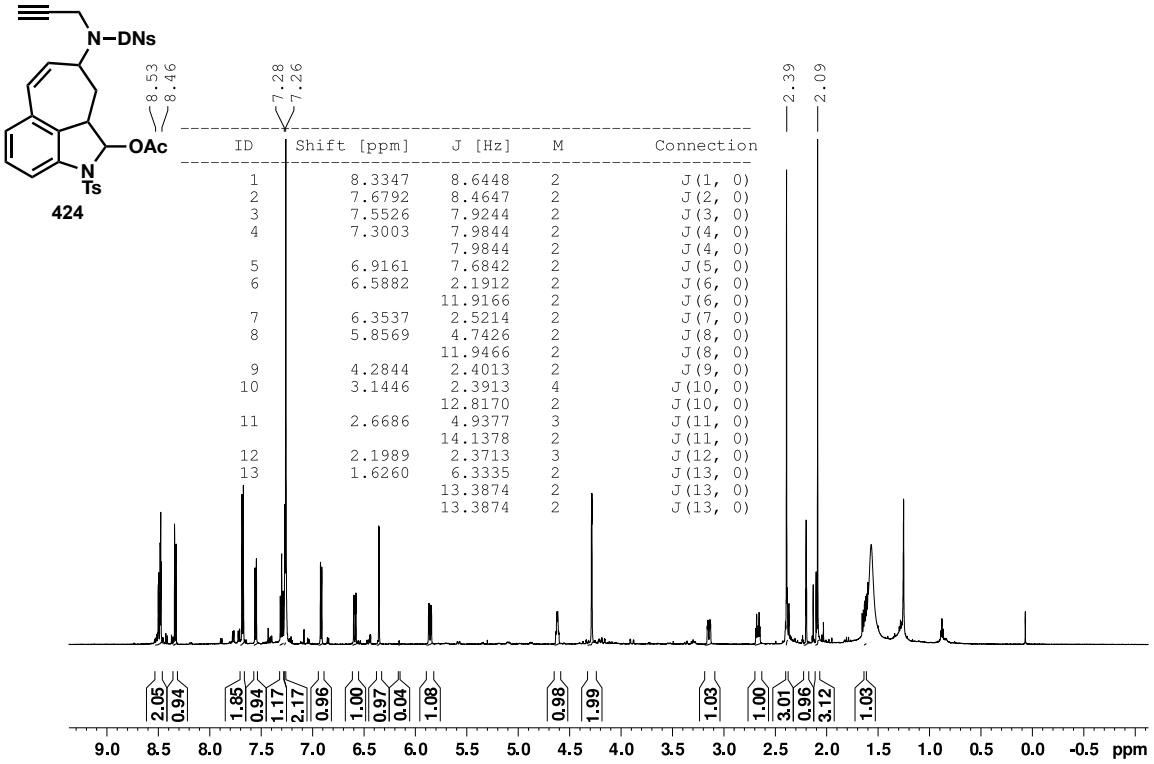


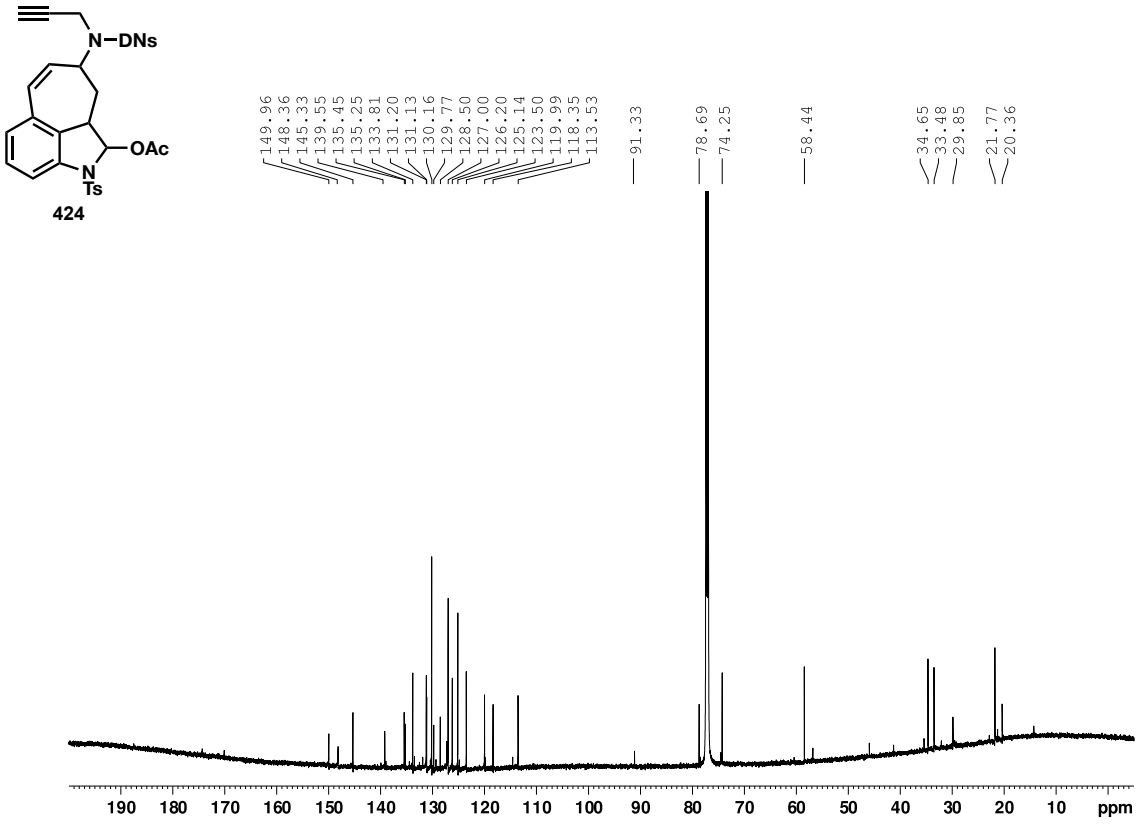
ID	Shift [ppm]	J [Hz]	M	Connection
1	7.7486	8.2223	2	J(1, 0)
2	7.6670	8.2223	2	J(2, 0)
3	7.4284	1.6805	2	J(3, 0)
4	7.3352	7.9222	2	J(4, 0)
5	7.2278	7.8922	2	J(5, 0)
		7.8922	2	J(5, 0)
6	7.1560	7.3221	2	J(6, 0)
7	5.3989	5.1615	2	J(7, 0)
8	4.7610	2.2006	4	J(8, 0)
		16.6847	2	J(8, 0)
9	4.5767	3.5260	3	J(9, 0)
		9.2726	2	J(9, 0)
10	3.4234	3.3910	2	J(10, 0)
		16.0545	2	J(10, 0)
11	3.2452	1.6805	4	J(11, 0)
		15.8445	2	J(11, 0)
12	2.9291	2.0406	4	J(12, 0)
		15.8445	2	J(12, 0)

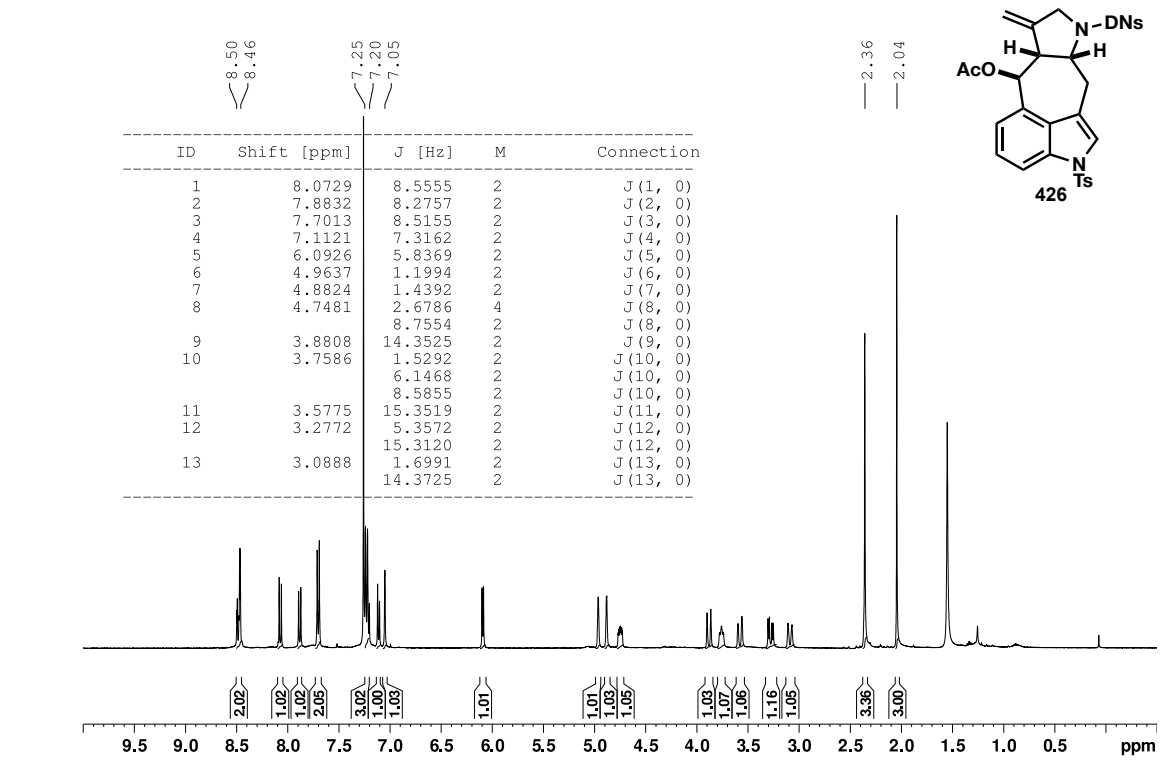


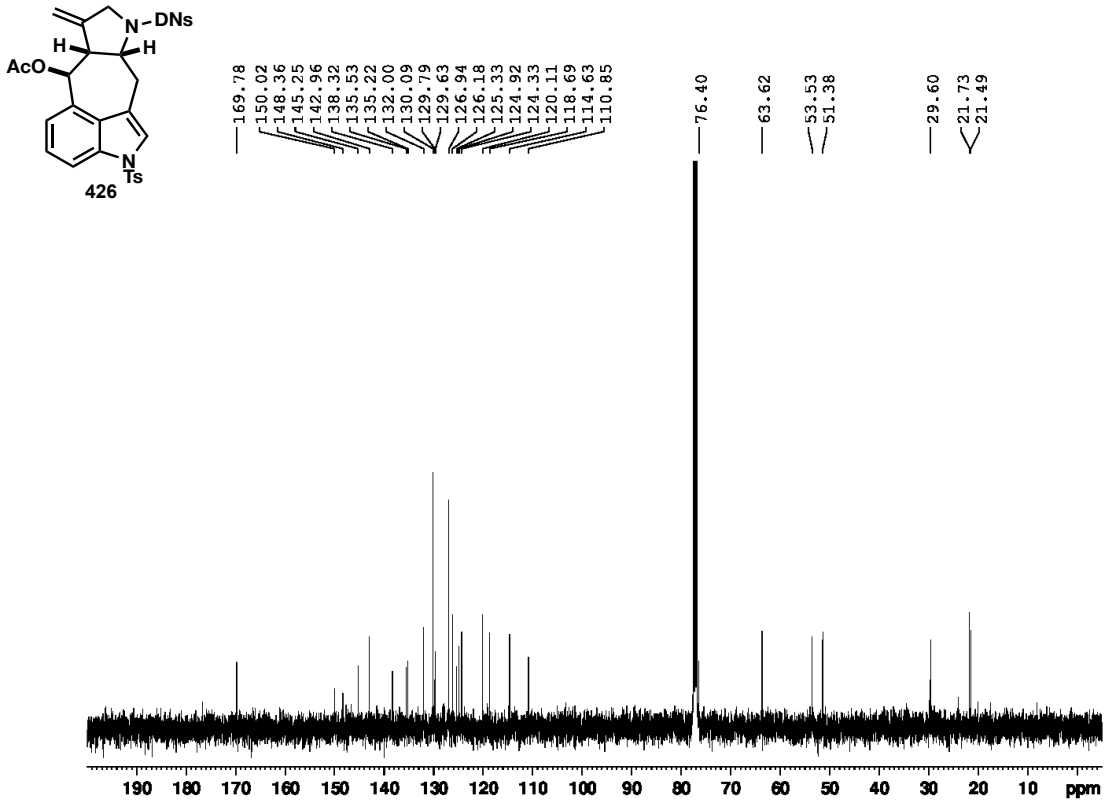
ID	Shift [ppm]	J [Hz]	M	Connection
1	7.8757	8.0423	2	J(1, 0)
2	7.6716	8.0423	2	J(2, 0)
3	7.1141	7.1420	2	J(3, 0)
4	6.1892	6.9620	2	J(4, 0)
5	3.0082	15.0643	2	J(5, 0)

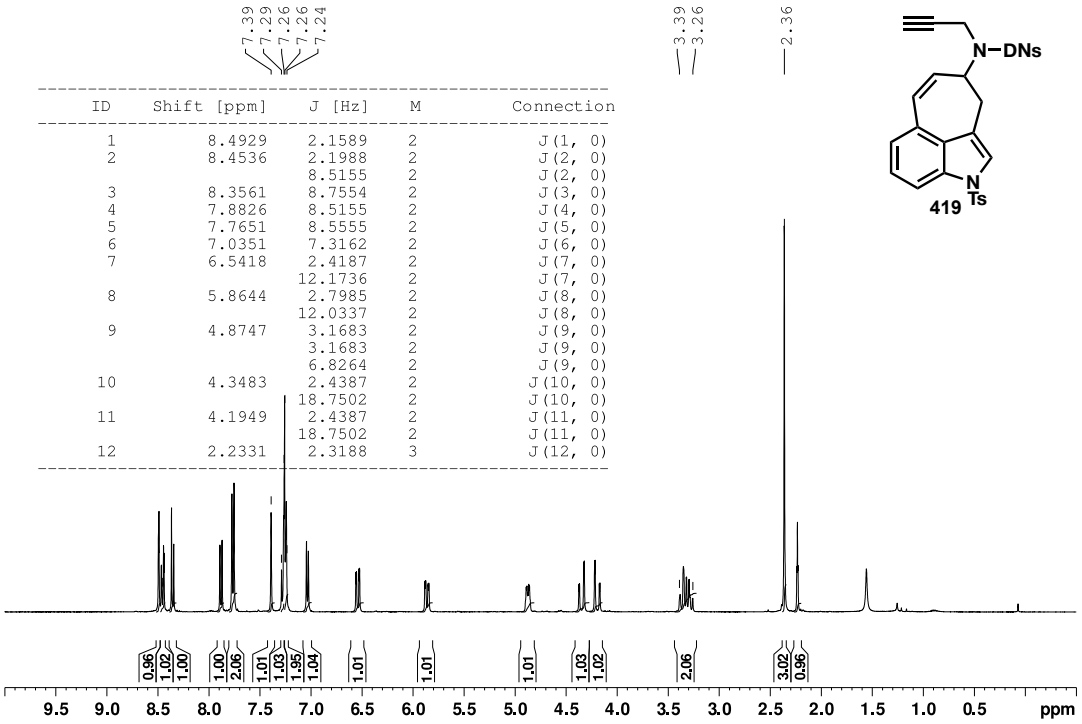

214.96
154.76
145.03
135.66
130.00
128.94
126.80
125.67
124.46
120.02
114.75
109.72
85.00
60.38
52.48
51.34
49.44
29.84
27.07
21.71
19.41
1.16
NCO2Me
H
H
MeS2CO
N
Ts
416
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

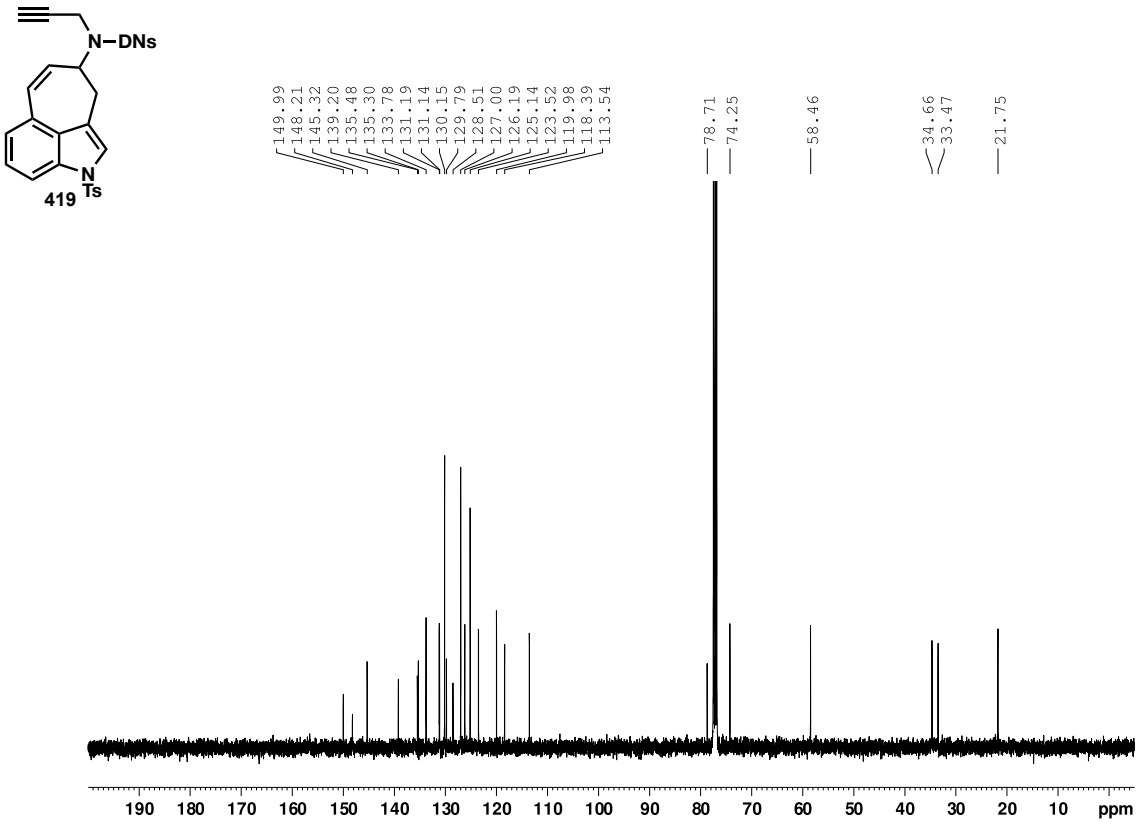

N–DNs
OAc
N
Ts
424
8.53
8.46
7.28
7.26
2.39
2.09
ID | Shift [ppm] | J [Hz] | M | Connection
1 | 8.3347 | 8.6448 | 2 | J(1, 0)
2 | 7.6792 | 8.4647 | 2 | J(2, 0)
3 | 7.5526 | 7.9244 | 2 | J(3, 0)
4 | 7.3003 | 7.9844 | 2 | J(4, 0)
7.9844 | 2 | J(4, 0)
5 | 6.9161 | 7.6842 | 2 | J(5, 0)
6 | 6.5882 | 2.1912 | 2 | J(6, 0)
11.9166 | 2 | J(6, 0)
7 | 6.3537 | 2.5214 | 2 | J(7, 0)
8 | 5.8569 | 4.7426 | 2 | J(8, 0)
11.9466 | 2 | J(8, 0)
9 | 4.2844 | 2.4013 | 2 | J(9, 0)
10 | 3.1446 | 2.3913 | 4 | J(10, 0)
12.8170 | 2 | J(10, 0)
11 | 2.6686 | 4.9377 | 3 | J(11, 0)
14.1378 | 2 | J(11, 0)
12 | 2.1989 | 2.3713 | 3 | J(12, 0)
13 | 1.6260 | 6.3335 | 2 | J(13, 0)
13.3874 | 2 | J(13, 0)
13.3874 | 2 | J(13, 0)
2.05
0.94
1.85
0.94
1.17
2.17
0.96
1.00
0.97
0.04
1.08
0.98
1.99
1.03
1.00
3.01
0.96
3.12
1.03
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 ppm

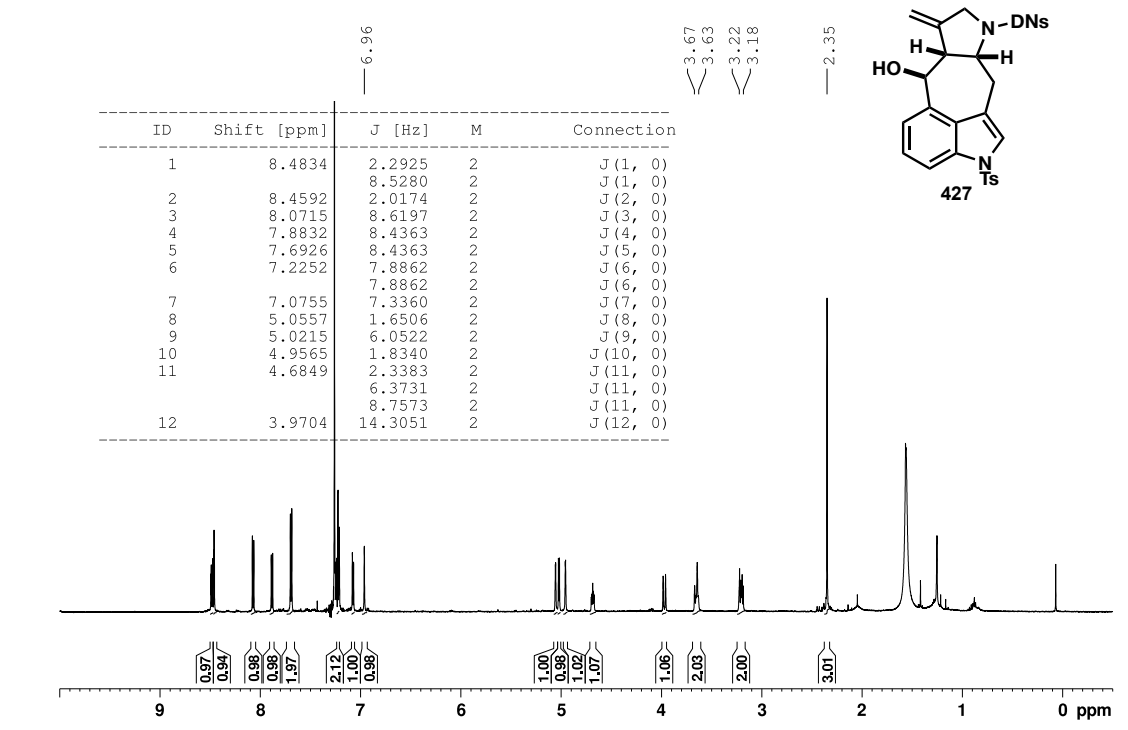

N–DNs
OAc
N
Ts
424
149.96
148.36
145.33
139.55
135.45
135.25
133.81
131.20
131.13
130.16
129.77
128.50
127.00
126.20
125.14
123.50
119.99
118.35
113.53
91.33
78.69
74.25
58.44
34.65
33.48
29.85
21.77
20.36
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

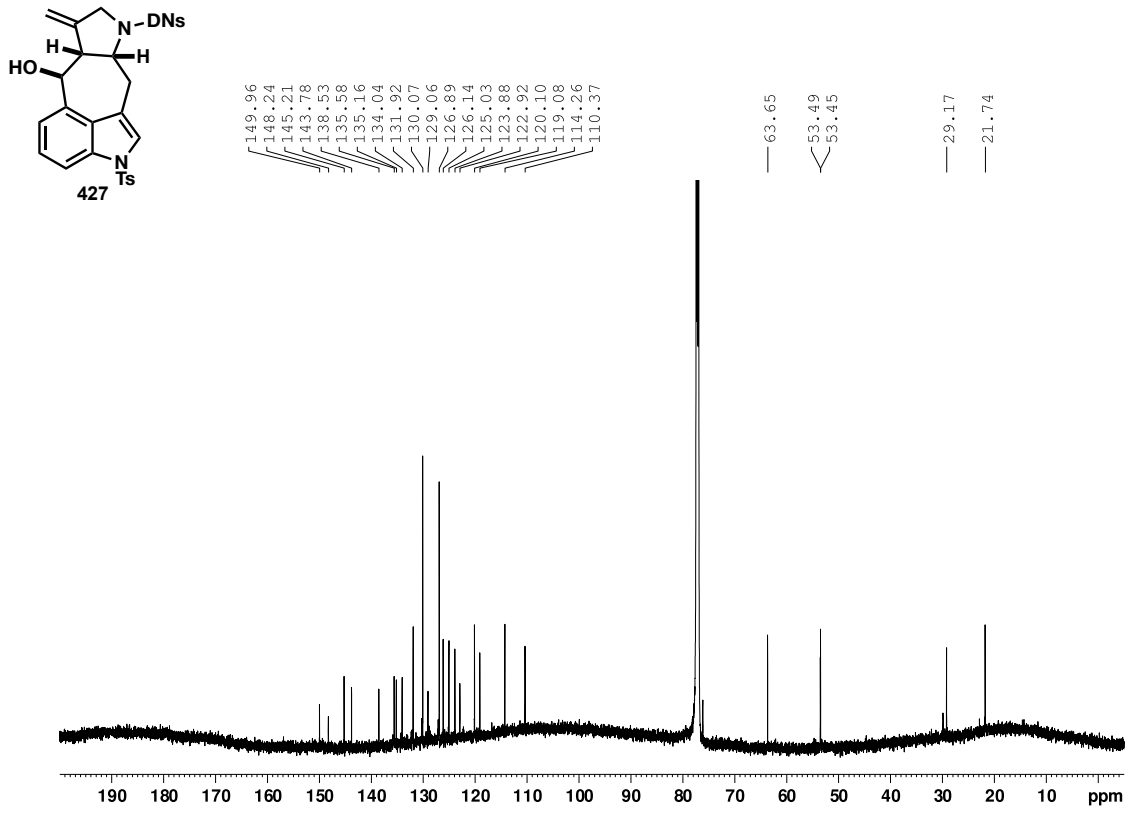

8.50
8.46
7.25
7.20
7.05
2.36
2.04
N-DNs
H
H
AcO
N
Ts
426
ID Shift [ppm] J [Hz] M Connection
1 8.0729 8.5555 2 J(1, 0)
2 7.8832 8.2757 2 J(2, 0)
3 7.7013 8.5155 2 J(3, 0)
4 7.1121 7.3162 2 J(4, 0)
5 6.0926 5.8369 2 J(5, 0)
6 4.9637 1.1994 2 J(6, 0)
7 4.8824 1.4392 2 J(7, 0)
8 4.7481 2.6786 4 J(8, 0)
8.7554 2 J(8, 0)
9 3.8808 14.3525 2 J(9, 0)
10 3.7586 1.5292 2 J(10, 0)
6.1468 2 J(10, 0)
8.5855 2 J(10, 0)
11 3.5775 15.3519 2 J(11, 0)
12 3.2772 5.3572 2 J(12, 0)
15.3120 2 J(12, 0)
13 3.0888 1.6991 2 J(13, 0)
14.3725 2 J(13, 0)
2.02
1.02
1.02
2.05
3.02
1.00
1.03
1.01
1.01
1.03
1.05
1.03
1.07
1.06
1.16
1.05
3.36
3.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

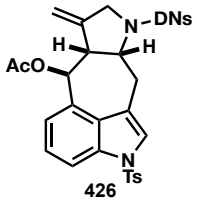

N-DNs
H
H
AcO
N
Ts
426
169.78
150.02
148.36
145.25
142.96
138.32
135.53
135.22
132.00
130.09
129.79
129.63
126.94
126.18
125.33
124.92
124.33
120.11
118.69
114.63
110.85
76.40
63.62
53.53
51.38
29.60
21.73
21.49
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


7.39
7.29
7.26
7.26
7.24
3.39
3.26
2.36
N–DNs
N
Ts
419
ID Shift [ppm] J [Hz] M Connection
1 8.4929 2.1589 2 J(1, 0)
2 8.4536 2.1988 2 J(2, 0)
8.5155 2 J(2, 0)
3 8.3561 8.7554 2 J(3, 0)
4 7.8826 8.5155 2 J(4, 0)
5 7.7651 8.5555 2 J(5, 0)
6 7.0351 7.3162 2 J(6, 0)
7 6.5418 2.4187 2 J(7, 0)
12.1736 2 J(7, 0)
8 5.8644 2.7985 2 J(8, 0)
12.0337 2 J(8, 0)
9 4.8747 3.1683 2 J(9, 0)
3.1683 2 J(9, 0)
6.8264 2 J(9, 0)
10 4.3483 2.4387 2 J(10, 0)
18.7502 2 J(10, 0)
11 4.1949 2.4387 2 J(11, 0)
18.7502 2 J(11, 0)
12 2.2331 2.3188 3 J(12, 0)
0.96 1.02 1.00 1.00 2.06 1.01 1.03 1.95 1.04 1.01 1.01 1.01 1.03 1.02 2.06 3.02 0.96
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm


N–DNs
N
Ts
419
149.99
148.21
145.32
139.20
135.48
135.30
133.78
131.19
131.14
130.15
129.79
128.51
127.00
126.19
125.14
123.52
119.98
118.39
113.54
78.71
74.25
58.46
34.66
33.47
21.75
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


6.96
3.67
3.63
3.22
3.18
2.35
N-DNs
H
HO
H
N
Ts
427
ID Shift [ppm] J [Hz] M Connection
1 8.4834 2.2925 2 J(1, 0)
8.5280 2 J(1, 0)
2 8.4592 2.0174 2 J(2, 0)
3 8.0715 8.6197 2 J(3, 0)
4 7.8832 8.4363 2 J(4, 0)
5 7.6926 8.4363 2 J(5, 0)
6 7.2252 7.8862 2 J(6, 0)
7.8862 2 J(6, 0)
7 7.0755 7.3360 2 J(7, 0)
8 5.0557 1.6506 2 J(8, 0)
9 5.0215 6.0522 2 J(9, 0)
10 4.9565 1.8340 2 J(10, 0)
11 4.6849 2.3383 2 J(11, 0)
6.3731 2 J(11, 0)
8.7573 2 J(11, 0)
12 3.9704 14.3051 2 J(12, 0)
0.97
0.94
0.98
0.98
1.97
2.12
1.00
0.98
1.00
0.98
1.02
1.07
1.06
2.03
2.00
3.01
9
8
7
6
5
4
3
2
1
0 ppm


N-DNs
H
HO
H
N
Ts
427
149.96
148.24
145.21
143.78
138.53
135.58
135.16
134.04
131.92
130.07
129.06
126.89
126.14
125.03
123.88
122.92
120.10
119.08
114.26
110.37
63.65
53.49
53.45
29.17
21.74
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm



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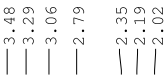
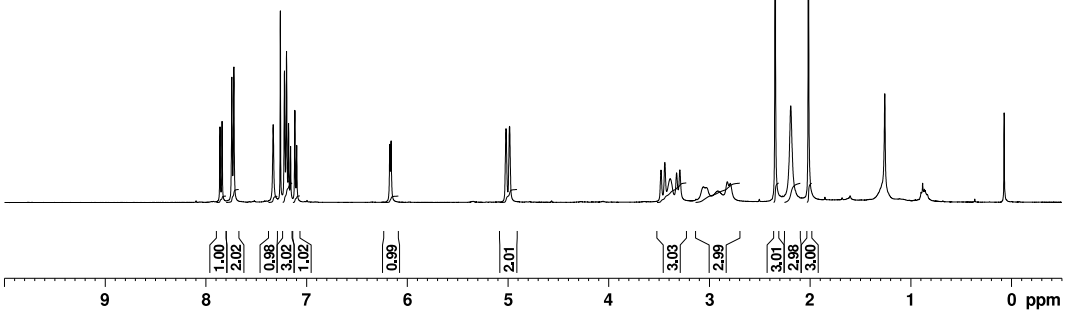
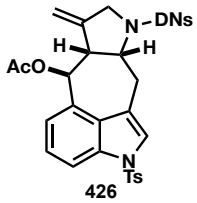


ID	Shift [ppm]	J [Hz]	M	Connection
1	7.8491	8.2757	2	J(1, 0)
2	7.7316	8.2757	2	J(2, 0)
3	7.1067	7.2762	2	J(3, 0)
4	6.1663	5.3572	2	J(4, 0)
5	5.0013	14.1126	2	J(5, 0)





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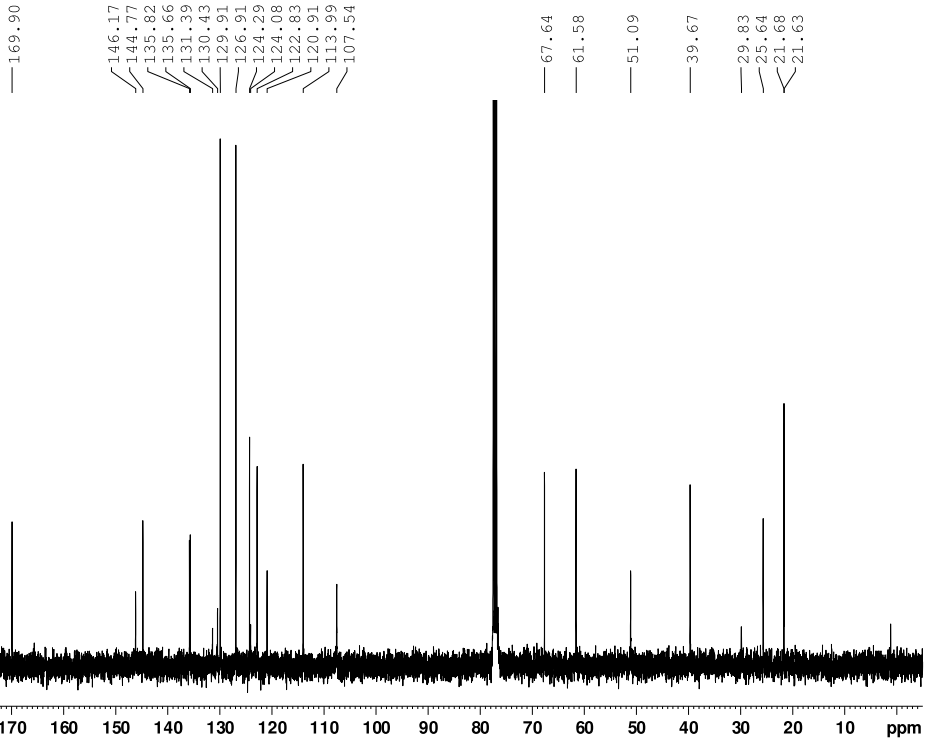

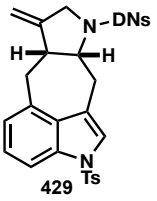

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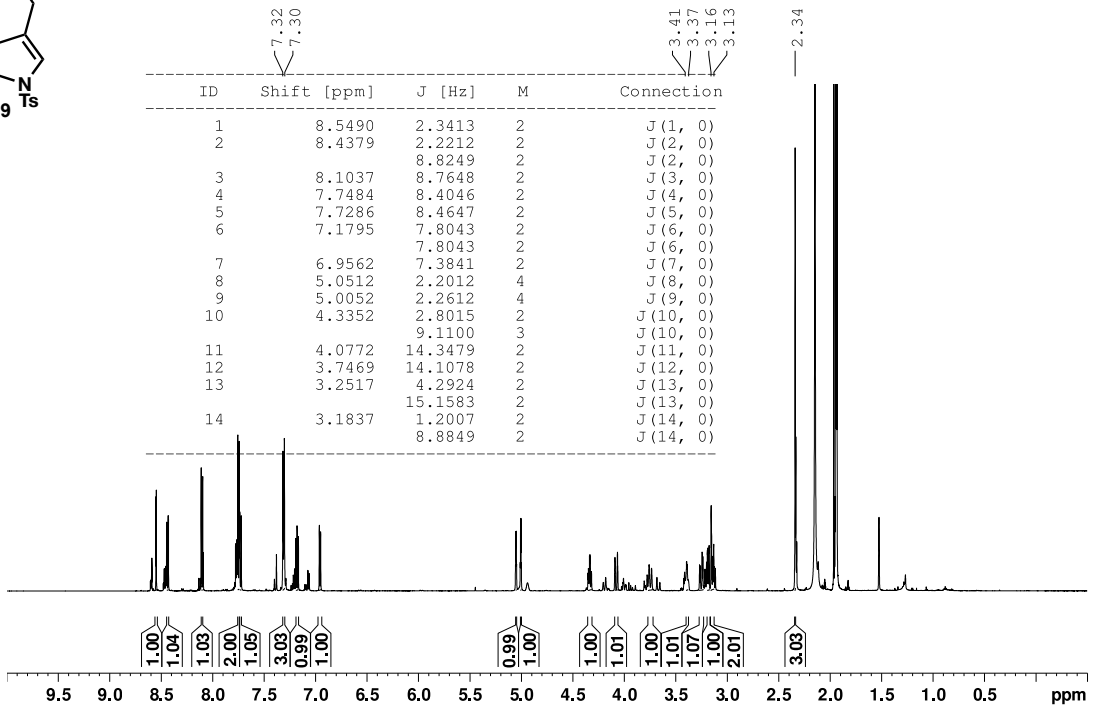
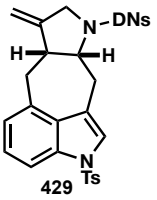


ID	Shift [ppm]	J [Hz]	M	Connection
1	8.5490	2.3413	2	J(1, 0)
2	8.4379	2.2212	2	J(2, 0)
		8.8249	2	J(2, 0)
3	8.1037	8.7648	2	J(3, 0)
4	7.7484	8.4046	2	J(4, 0)
5	7.7286	8.4647	2	J(5, 0)
6	7.1795	7.8043	2	J(6, 0)
		7.8043	2	J(6, 0)
7	6.9562	7.3841	2	J(7, 0)
8	5.0512	2.2012	4	J(8, 0)
9	5.0052	2.2612	4	J(9, 0)
10	4.3352	2.8015	2	J(10, 0)
		9.1100	3	J(10, 0)
11	4.0772	14.3479	2	J(11, 0)
12	3.7469	14.1078	2	J(12, 0)
13	3.2517	4.2924	2	J(13, 0)
		15.1583	2	J(13, 0)
14	3.1837	1.2007	2	J(14, 0)
		8.8849	2	J(14, 0)



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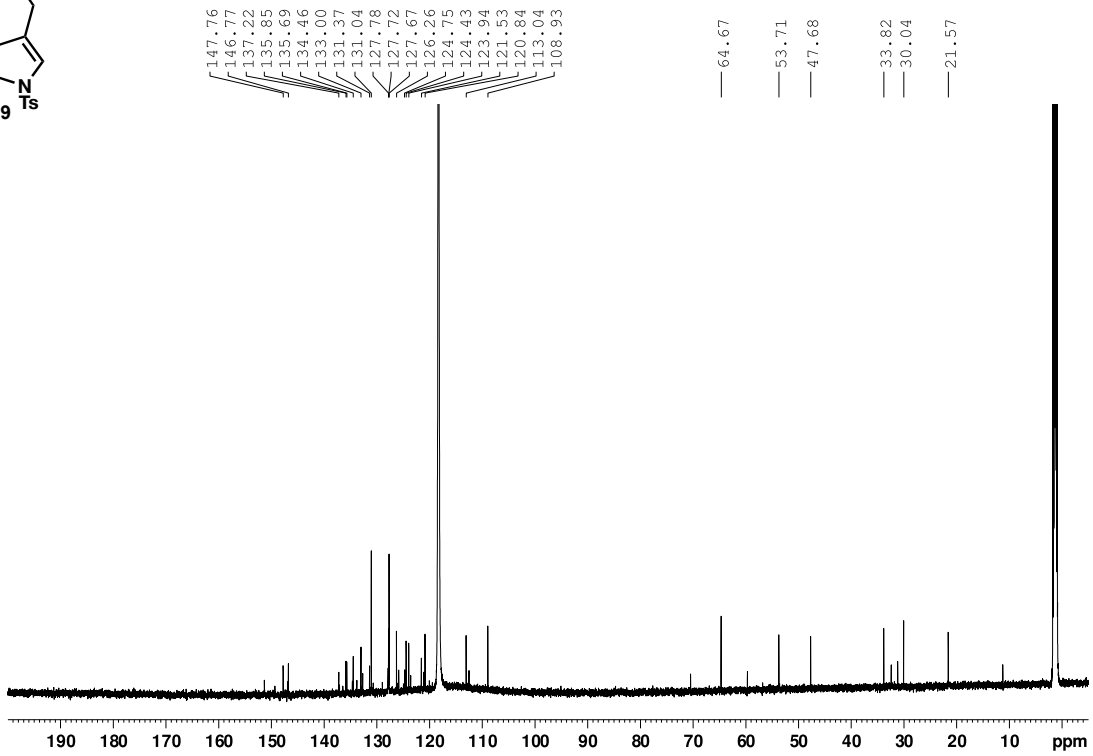

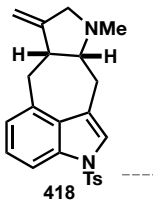

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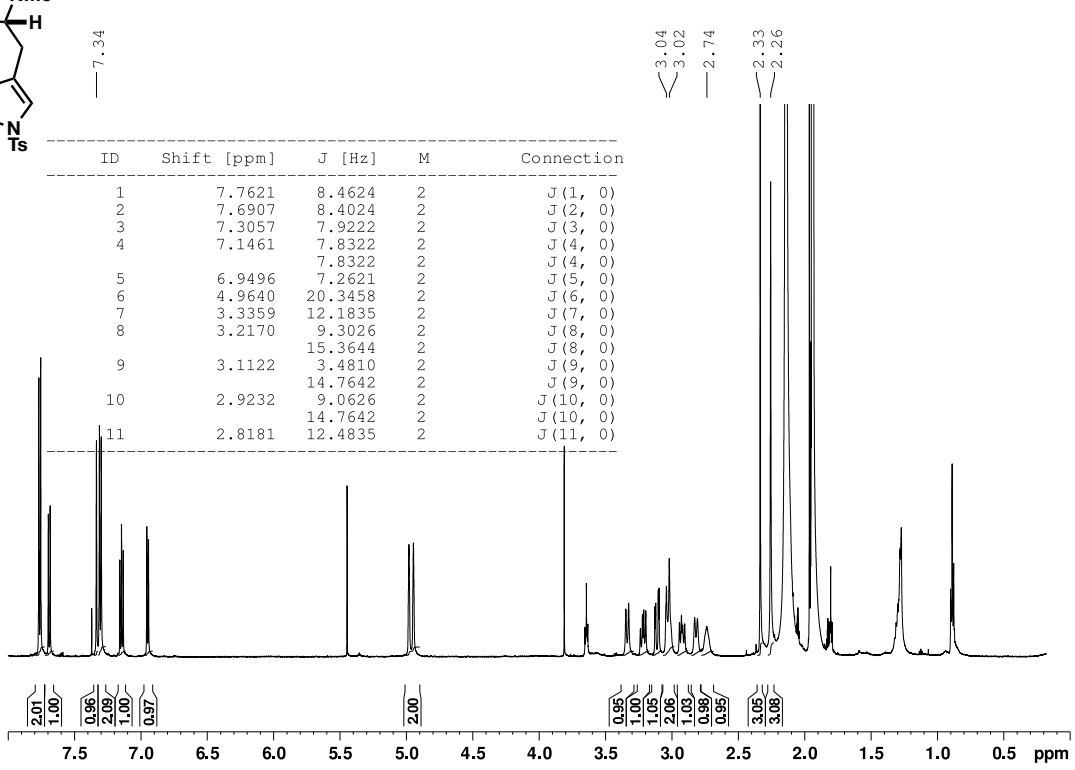
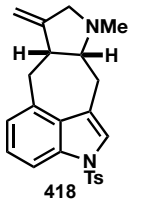


ID	Shift [ppm]	J [Hz]	M	Connection
1	7.7621	8.4624	2	J(1, 0)
2	7.6907	8.4024	2	J(2, 0)
3	7.3057	7.9222	2	J(3, 0)
4	7.1461	7.8322	2	J(4, 0)
		7.8322	2	J(4, 0)
5	6.9496	7.2621	2	J(5, 0)
6	4.9640	20.3458	2	J(6, 0)
7	3.3359	12.1835	2	J(7, 0)
8	3.2170	9.3026	2	J(8, 0)
		15.3644	2	J(8, 0)
9	3.1122	3.4810	2	J(9, 0)
		14.7642	2	J(9, 0)
10	2.9232	9.0626	2	J(10, 0)
		14.7642	2	J(10, 0)
11	2.8181	12.4835	2	J(11, 0)



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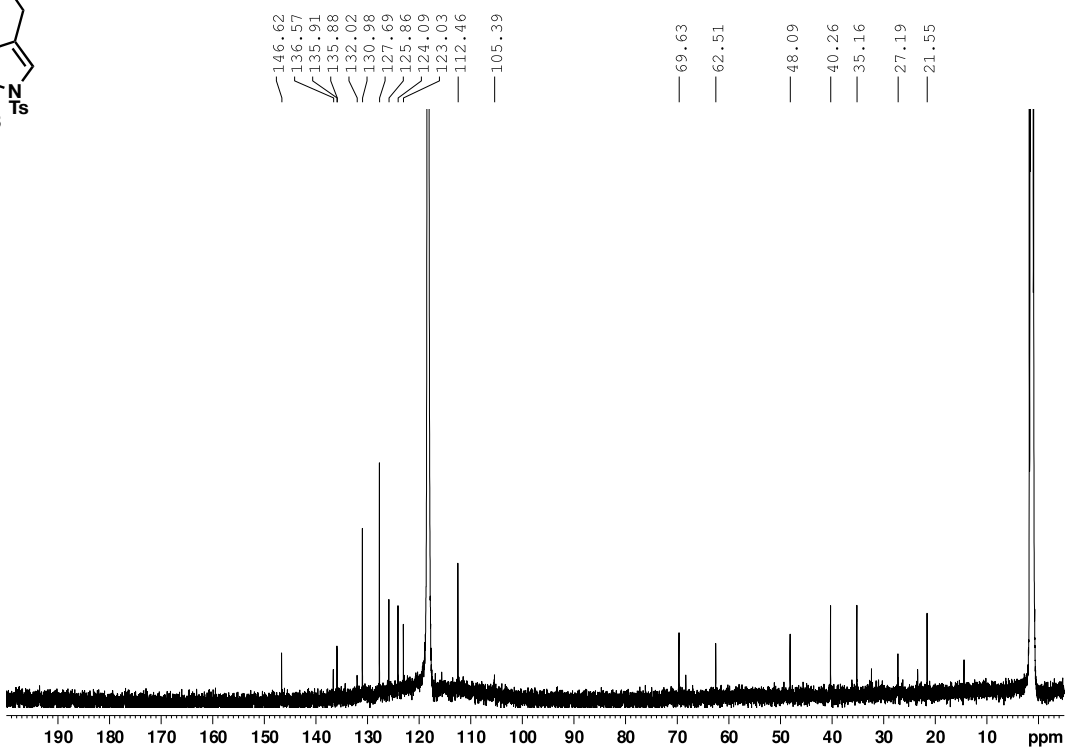

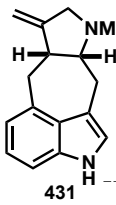

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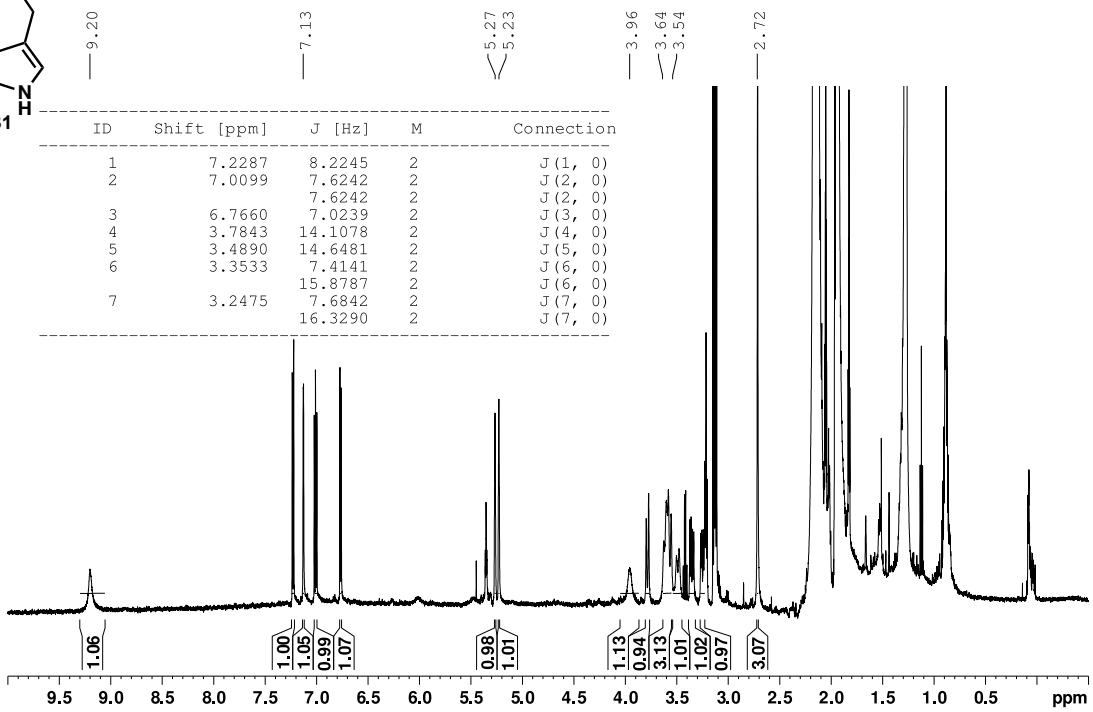
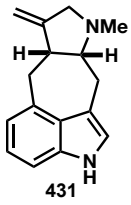
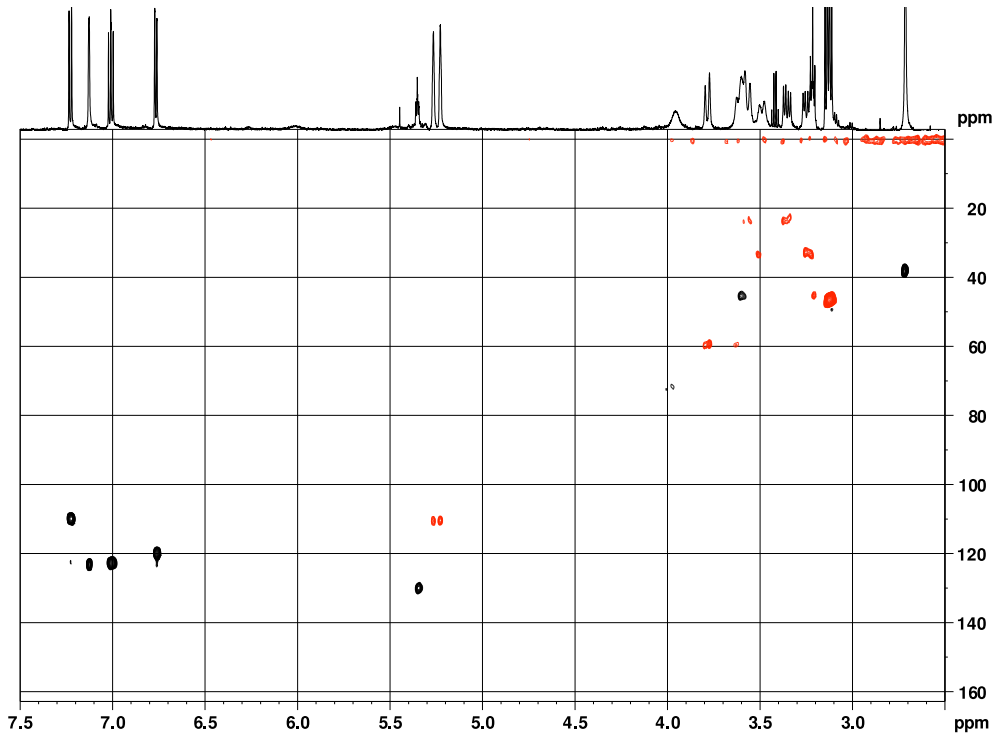
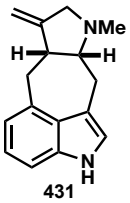


ID	Shift [ppm]	J [Hz]	M	Connection
1	7.2287	8.2245	2	J(1, 0)
2	7.0099	7.6242	2	J(2, 0)
		7.6242	2	J(2, 0)
3	6.7660	7.0239	2	J(3, 0)
4	3.7843	14.1078	2	J(4, 0)
5	3.4890	14.6481	2	J(5, 0)
6	3.3533	7.4141	2	J(6, 0)
		15.8787	2	J(6, 0)
7	3.2475	7.6842	2	J(7, 0)
		16.3290	2	J(7, 0)

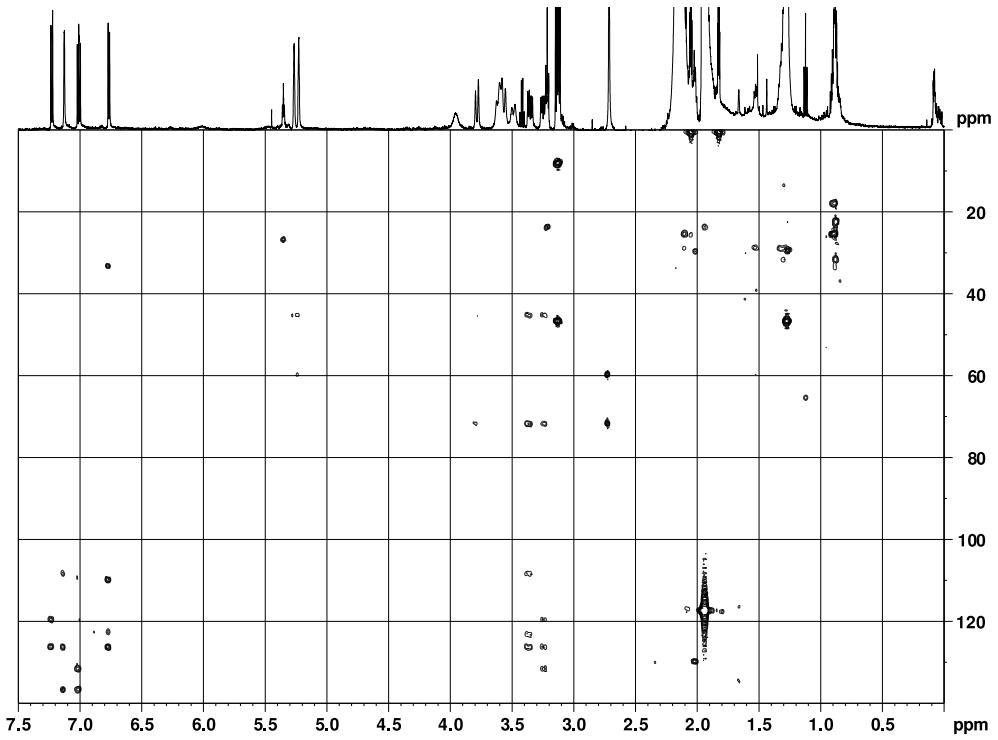


431




NMe
H
H
N
H

431


ppm
20
40
60
80
100
120
7.5
7.0
6.5
6.0
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4.5
4.0
3.5
3.0
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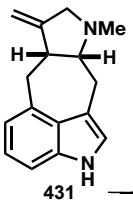
2.0
1.5
1.0
0.5
ppm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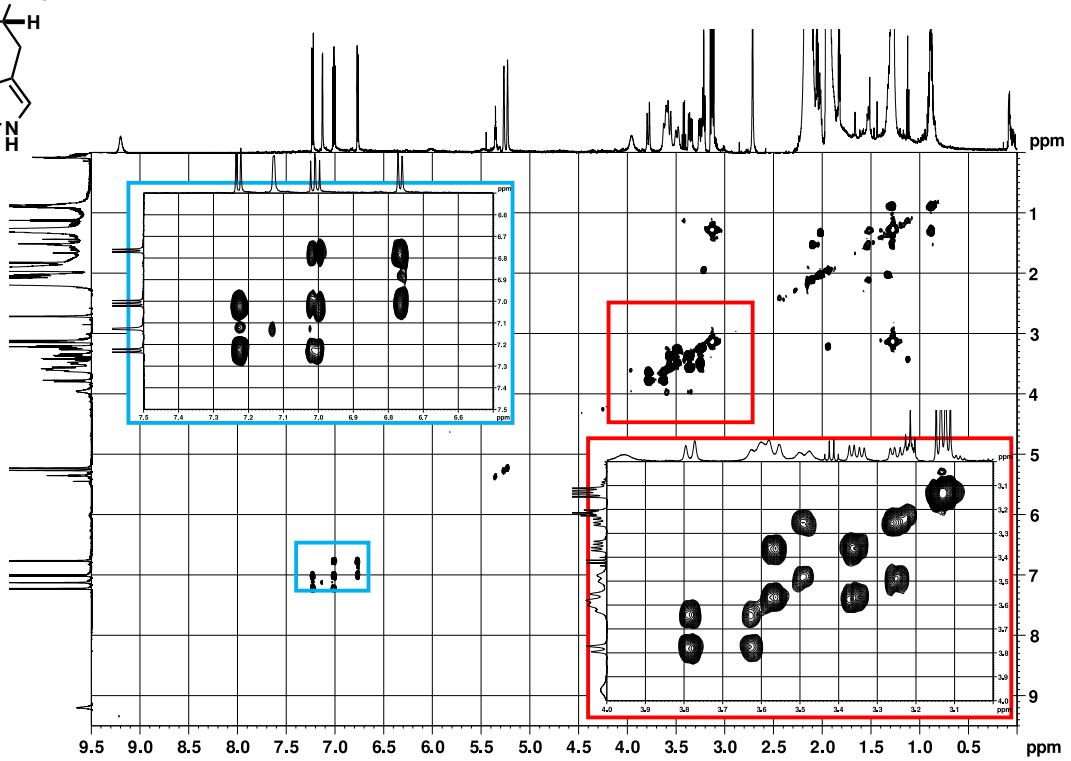
H
H
N
H

431


ppm
1
2
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4
5
6
7
8
9
9.5
9.0
8.5
8.0
7.5
7.0
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6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

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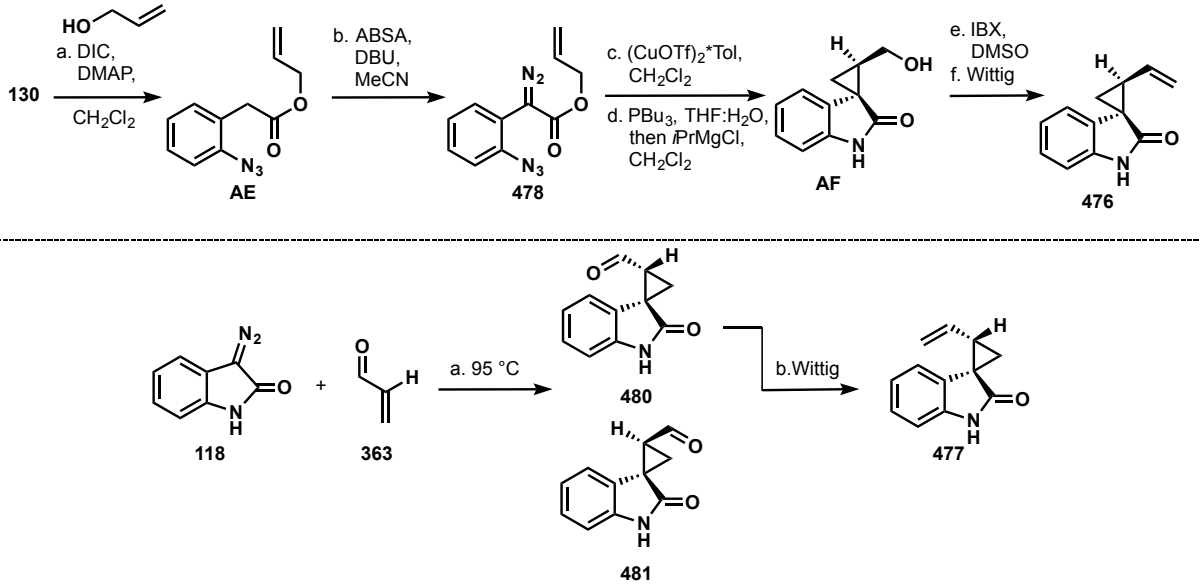
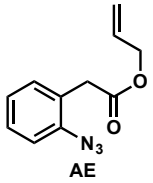


8.2 General

All reactions were carried out in oven-dried glassware under an argon atmosphere, unless otherwise stated. Commercially available anhydrous DMF, DMSO, MeCN, PhH, Pyridine THF (Acros Organics, Alfa Aesar) were used without further manipulation. Other anhydrous solvents were obtained by filtration through drying columns (Et_2O, CH_2Cl_2) on a Glass Contour system. Rhodium (II)-acetate dimer powder was obtained from Sigma-Aldrich. Reactions were magnetically and mechanically stirred and monitored by thin layer chromatography (TLC) with silica gel 60-F254 plates. Flash column chromatography was performed with silica gel 60 Å of Macherey-Nagel under pressure. Preparative TLC was performed with pre-coated TLC-plates Adamant UV_{254} of Mancherey-Nagel. Yields refer to chromatographically and spectroscopically pure compounds, unless otherwise stated. NMR spectra were recorded on a 400 MHz spectrometer of Bruker. Unless otherwise stated, all NMR spectra were measured in $CDCl_3$ solution and referenced to the residual $CHCl_3$ signal (^1H, δ = 7.26 ppm, ^{13}C, δ = 77.16 ppm). All ^1H and ^{13}C shifts are given in ppm (*s* = singlet, *d* = doublet, *t* = triplet, *q* = quadruplet, *m* = multiplet, *b* = broad signal). Assignments of proton resonance were confirmed, when possible, by correlated spectroscopy.

8.3 Procedures

8.3.1 *allyl 2-(2-azidophenyl)acetate (AE)*

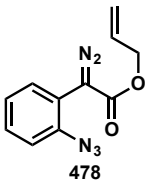


AE

DIC (99.0 µL, 630 µmol, 1.05 equiv.) was added to a stirred suspension of acid **130** (106 mg, 600 µmol, 1 equiv.), allylalcohol (41.0 µL, 600 µmol, 1 equiv.) and 4–DMAP (7.30 mg, 60.0 µmol, 10 mol%) in CH_2Cl_2 (1.20 mL). The solvent was removed *in vacuo* when the reaction was complete by TLC (hexane:EtOAc 10:1). The crude was purified by flash column chromatography (hexane:EtOAc 15:1) to give the desired ester **AE** in 92% (120 mg, 553 µmol) yield as colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$, δ): 3.64 (*s*, 2 H), 4.62 (*ddd*, *J* = 1.4, 1.4, 5.5 Hz, 2 H), 5.23 (*ddd*, *J* = 1.2, 2.6, 10.4 Hz, 1 H), 5.29 (*ddd*, *J* = 1.5, 3.1, 17.2 Hz, 1 H), 5.92 (*dddd, J* = 5.7, 5.7, 10.5, 17.2 Hz, 1 H), 7.11 (*ddd, J* = 1.4, 7.5, 7.5 Hz, 1 H), 7.17, (*dd, J* = 1.0, 8.2 Hz, 1 H), 7.24 (*dd, J* = 1.4, 7.5 Hz, 1 H), 7.34 (*ddd*, *J* = 1.4, 7.5, 7.8 Hz, 1 H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$, δ) 36.7, 65.7, 118.3, 118.4, 125.0, 125.8, 128.9, 131.6, 132.2, 138.8, 170.9 ppm.

8.3.2 *allyl 2-(2-azidophenyl)-2-diazoacetate (478)*



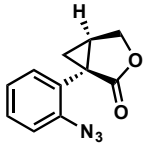
478

Allylester **AE** (1.14 g, 5.26 mmol, 1 equiv.) and ABSA (1.90 g, 7.89 mmol, 1.5 equiv.) were dissolved in MeCN (18 mL). DBU (2.36 mL, 15.8 mmol, 3 equiv.) was added and the solution was stirred until complete by TLC (hexane:EtOAc 15:1). The reaction was hydrolysed by addition of NH_4Cl solution. The aqueous layer was extracted with EtOAc (3 x 70 mL), the combined organic layers were washed with brine solution, dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was then purified by flash chromatography (hexane:EtOAc 20:1) to afford the desired product **478** in 88% (1.12 g, 4.16 mmol) yield as bright orange oil.

^{1}H-NMR (400 MHz, $CDCl_3$, δ) 4.74 (*d*, *J* = 5.4 Hz, 2 H), 5.26 (*qd*, *J* = 1.3, 10.4 Hz, 1 H), 5.34 (*qd*, *J* = 1.5, 17.4 Hz, 1 H), 5.97 (*dddd*, *J* = 5.5, 5.5, 10.7, 17.1 Hz, 1 H), 7.17 – 7.21 (*m*, 2 H), 7.35

(*ddd*, *J* = 1.2, 7.2, 8.2 Hz, 1 H), 7.55 (*dd*, *J* = 1.5, 8.0 Hz, 1 H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$, δ) 65.8, 116.6, 118.4, 118.6, 125.3, 129.3, 131.5, 132.3, 137.4, 165.5 ppm. **IR (neat sample)**: 2128, 2095, 1700, 1493, 1367, 1282, 1244, 1154, 1104, 1021, 936, 753 cm^{-1}

8.3.3 *(1*R*,5*S*)-1-(2-azidophenyl)-3-oxabicyclo[3.1.0]hexan-2-one (479)*

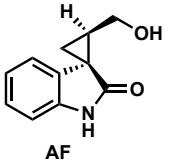


479

Diazo compound **478** (1.24 g, 5.10 mmol, 1 equiv.) was dissolved in anhydrous CH_2Cl_2 (145 mL). The solution was added *via* dropping funnel into a solution of $(CuOTf)_2$*Tol (53.0 mg, 102 µmol, 2 mol%.) in anhydrous CH_2Cl_2 (145 mL) at rt over 30 minutes. The solution was stirred until complete by TLC (hexane:EtOAc 3:1). The reaction mixture was then concentrated *in vacuo* and purified by flash chromatography (hexane:EtOAc 5:1 → 3:1) to afford **479** in 75% (938 mg, 3.82 mmol) yield.

^{1}H-NMR (400 MHz, $CDCl_3$, δ) 1.31 (*dd*, *J* = 4.8, 4.8 Hz, 1 H), 1.70 (*dd*, *J* = 5.1, 7.8 Hz, 1 H), 2.26 (*ddd*, *J* = 4.6, 4.6, 8.0 Hz, 1 H), 4.32 (*d*, *J* = 9.2 Hz, 1 H), 4.62 (*dd*, *J* = 4.8, 9.2 Hz, 1 H), 7.14 (*ddd, J* = 1.0, 7.5, 7.5 Hz, 1 H), 7.18 (*dd, J* = 0.9, 8.0 Hz, 1 H), 7.30 (*dd*, *J* = 1.5, 7.7 Hz, 1 H), 7.39 (*ddd*, *J* = 1.9, 7.7, 7.7 Hz, 1 H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$, δ) 16.7, 25.2, 30.0, 68.5, 118.1, 124.9, 125.6, 129.8, 131.5, 140.5, 176.0 ppm. **IR (neat sample)**: 2127, 1749, 1492, 1451, 1371, 1283, 1263, 1142, 1111, 1058, 1041989, 921, 743, 703, 626 cm^{-1}. **HRMS** (ESI) (*m*/*z*): calcd for $C_{11}H_9N_3O_2$ $[M + Na]^+$, 238.0592; found, 238.0598.

8.3.4 *(1*R*,2*S*)-2-(hydroxymethyl)spiro[cyclopropane-1,3'-indolin]-2'-one (AF)*



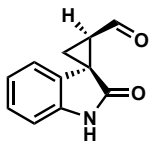
AF

PBu_3 (900 µL, 3.60 mmol, 1.1 equiv.) was added to a stirred solution of azide **479** (705 mg, 3.28 mmol, 1 equiv.) in THF:H_2O (11 mL; 10:1). The reaction mixture was stirred for 15 minutes, before it was diluted with CH_2Cl_2, dried over $MgSO_4$ and concentrated *in vacuo*. The crude was dissolved in anhydrous THF (30 mL) and cooled to 0 °C. *i*PrMgCl (2 M in THF, 3.60 mL, 6.20 mmol, 2.05 equiv.) was added slowly to the solution. The reaction was allowed to stir for 10 minutes, before it was quenched by addition of water. The aqueous layer was

extracted with EtOAc (3x 50 mL), the combined organic layers were dried over $MgSO_4$, concentrated *in vacuo* and the crude was purified by flash column chromatography (CH_2Cl_2:MeOH 30:1 to 15:1) to give the spirooxindol **AF** 77% (483 mg, 2.56 mmol) yield as white solid.

^{1}H-NMR (400 MHz, DMSO-d_6, δ) 1.49 (dd, *J* = 4.1, 7.8 Hz, 1H), 1.73 (dd, *J* = 4.1, 8.9 Hz, 1H), 2.03 – 2.11 (*m*, 1 H), 3.73 – 3.84 (*m*, 2 H), 4.60 (t, *J* = 5.5 Hz, 1H), 6.85 (d, *J* = 7.8 Hz, 1H), 6.88 – 6.93 (m, 2H), 7.12 (ddd, *J* = 2.6, 6.1, 7.7 Hz, 1H), 10.46 (s, 1H) ppm. **^{13}C-NMR** (100 MHz, DMSO-d_6, δ) 22.3, 30.0, 35.2, 57.0, 108.9, 118.6, 120.9, 126.3, 131.5, 141.2, 176.5 ppm. **IR (neat sample)**: 2459, 2349, 1680, 1614, 1467, 1347, 1199, 1126, 1019, 977, 909, 750, 637 cm^{-1}. **HRMS** (ESI) (*m*/*z*): calcd for $C_{11}H_{11}NO_2$ $[M + Na]^+$, 212.0687; found, 212.0688.

8.3.5 *(1R,2S)-2'-oxospiro[cyclopropane-1,3'-indoline]-2-carbaldehyde (481)*

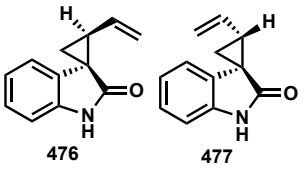


481

To a solution of alcohol **AF** (400 mg, 2.11 µmol, 1 equiv.) in DMSO (4 mL) was added IBX (710 mg, 2.54 µmol, 1.2 equiv.). The suspension was stirred for 18 h until complete consumption of the starting material. The reaction was quenched with water and extracted with EtOAc (4 × 25 mL), the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash chromatography (CH_2Cl_2:MeOH 30:1) to afford aldehyde **481** in 94% (373 mg, 199 µmol) yield as a white solid.

^{1}H-NMR (400 MHz, DMSO-d_6, δ) 2.24 (*dd*, *J* = 4.8, 8.5 Hz, 1 H), 2.45 (*dd*, *J* = 4.8, 7.5 Hz, 1 H), 2.62 (*ddd*, *J* = 6.9, 6.9, 8.2 Hz, 1 H), 6.89 (*d*, *J* = 7.8 Hz, 1 H), 6.96 (*ddd*, 1.4, 7.5, 7.5 Hz, 1 H), 7.03 (*d*, *J* = 8.2 Hz, 1 H), 7.20 (*ddd, J* = 1.4, 7.6, 7.6 Hz, 1 H), 9.52 (*d*, *J* = 6.5 Hz, 1 H), 10.77 (*s*, 1 H) ppm. **^{13}C-NMR** (100 MHz, DMSO-d_6, δ) 21.6, 35.8, 109.6, 119.8, 121.6, 127.7, 128.3, 141.8, 175.1, 199.5 ppm. **IR (neat sample)**: 3231, 1696, 1621, 1486, 1344, 1194, 1159, 998, 749, 694, 643 cm^{-1}. **HRMS** (ESI) (*m*/*z*): calcd for $C_{11}H_9NO_2$ $[M + H]^+$, 188.0712; found, 188.0714.

8.3.6 *(1*R*,2*R*)-2-vinylspiro[cyclopropane-1,3'-indolin]-2'-one (476) and (1*R*,2*S*)-2-vinylspiro-[cyclopropane -1,3'-indolin] -2'-one (477)*



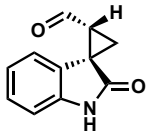
General procedure for Olefination.

A suspension of methyl triphenylphosphonium bromide (4 equiv.) in THF (0.4 M) was cooled to –78 °C. To this solution was added NaHMDS (2 M in THF, 4 equiv.), which was accompanied by a colour change to bright orange. The solution was stirred for 45 minutes at room temperature before it was cooled to –78 °C again. Then a solution of aldehyde **481**/**480** (1 equiv.) in THF (0.4 M) was added slowly. The solution was stirred for 15 minutes at –78 °C, then the cooling bath was removed and the reaction was allowed to stir for another 60 minutes. The reaction was quenched with saturated NH_4Cl solution, then diluted with water, extracted with EtOAc (3×), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash chromatography (hexane:EtOAc 3:1) to afford olefin **476** in 9% yield as white solid. Olefin **477** in was obtained in 89% yield as white solid.

Trans ^{1}H-NMR (400 MHz, $CDCl_3$, δ) 1.94 (*dd*, *J* = 4.8, 8.9 Hz, 1 H), 1.98 (*dd*, *J* = 4.9, 7.7 Hz, 1 H), 2.50 (*q*, *J* = 8.7 Hz, 1 H), 5.13 (*dd*, *J* = 1.2, 10.4 Hz, 1 H), 5.25 (*dd*, 1.2, 17.2 Hz, 1 H), 6.22 (*ddd*, 9.9, 9.9, 17.3 Hz, 1 H), 6.83 (*d, J* = 7.5 Hz, 1 H), 6.92 (*d*, *J* = 7.5 Hz, 1 H), 7.02 (*ddd*, 1.1, 7.6, 7.6 Hz, 1 H), 7.19 (*ddd*, *J* = 1.2, 7.8, 7.8 Hz, 1 H), 7.89 (*s*, 1H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$, δ) 24.9, 33.9, 37.6, 109.4, 116.9, 118.3, 122.0, 126.8, 130.9, 133.9, 140.3, 176.5 ppm. **IR (neat sample)**: 3078, 3030, 2855, 1689, 1622, 1492, 1436, 1358, 1267, 1229, 1172, 1113, 1060, 1017, 982, 906, 786, 747, 677, 641 cm^{-1}. **HRMS** (ESI) (*m*/*z*): calcd for $C_{12}H_{11}NO$ $[M + H]^+$, 186.0919; found, 186.0919.

CIS ^{1}H-NMR (400 MHz, $CDCl_3$, δ) 1.69 (*dd*, *J* = 4.6, 7.7 Hz, 1 H), 2.08 (*dd*, *J* = 4.6, 9.0 Hz, 1 H), 2.64 (*q*, *J* = 8.1 Hz, 1 H), 5.25 (*ddd*, *J* = 0.7, 1.4, 10.2 Hz, 1 H), 5.36 (*ddd*, *J* = 1.0, 1.5, 16.9 Hz, 1 H), 5.83 (*ddd*, *J* = 7.9, 10.2, 17.1 Hz, 1 H), 6.92 (*d*, *J* = 7.5 Hz, 1 H), 6.97 – 7.02 (*m*, 2 H), 7.20 (*ddd*, *J* = 1.4, 7.7, 7.7 Hz, 1 H), 8.86 (*s*, 1 H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$, δ) 23.3, 33.9, 35.8, 110.1, 119.1, 121.4, 121.7, 127.0, 128.1, 133.4, 141.4, 178.7 ppm.

8.3.7 *(1*R*,2*R*)-2'-oxospiro[cyclopropane-1,3'-indoline]-2-carbaldehyde (480)*

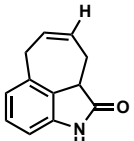


480

A suspension of diazo **118** (1.00 g, 6.00 mmol, 1 equiv.) in freshyls distilled acrolein (2.10 mL, 31.0 mmol, 5 equiv.) was heated in a sealed tube to 95 °C. After 60 minutes the reaction mixture was cooled to room temperature. Excess of acroleine was removed *in vacuo.* The crude was purified by flash column chromatography (hexane:EtOAc 3:2) to give the desired aldehyde **480** in 53% (620 mg, 3.30 mmol) yield as white solid.

^{1}H-NMR (400 MHz, $CDCl_3$, δ) 2.15 (*dd, J* = 4.8, 8.5 Hz, 1 H), 2.32 (*dd*, *J* = 4.6, 7.3 Hz, 1 H), 2.94 (*ddd*, *J* = 3.2, 7.6, 8.4 Hz, 1 H), 6.96 (*d*, *J* = 7.5 Hz, 1 H), 7.01 (*dd, J* = 7.6, 7.8 Hz, 1 H), 7.14 (*d*, 7.5 Hz, 1 H, 7.22 – 7.26 (*m*, 1 H), 8.35 (*s*, 1 H), 9.71 (*d, J* = 3.1 Hz, 1 H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$, δ) 210.3, 36.3, 39.5, 110.1, 122.4, 122.8, 125.6, 128.1, 141.1, 175.9, 195.9 ppm. **IR (neat sample)**: 3257, 1705, 1620, 1469, 1362, 1220, 1168, 752 cm^{-1}. **HRMS** (ESI) (*m*/*z*): calcd for $C_{11}H_9NO_2$ $[M + Na]^+$, 210.0531; found, 210.0532.

8.3.8 *2,6,9,9a-tetrahydro-1*H*-cyclohepta[*cd*]indol-1-one (115)*



115

General procedure for the rearrangement

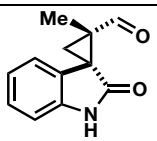
A solution of the corresponding olefin **476** or **477** (10.0 mg, 54.0 µmol, 1 equiv.) in DMSO-d_6 (700 µL) was heated to 383.15 K in the NMR. The measurement started when the probe reached the desired temperature. After complete consumption of the starting material, the crude was added to water, the aqueous layer was extracted with EtOAc (3x 10 mL), the combined organic layers were dried over MgSO4, concentrated *in vacuo* and the crude was purified by flash column chromatography (hexane:EtOAc 3:2) to obtain the desired product **115** in 93% (9.3 mg, 50.2 µmol) yield as yellow foam.

^{1}H-NMR (400 MHz, $CDCl_3$, δ) 2.19 – 2.27 (*m*, 1 H), 2.83 (*d*, *J* = 16.8 Hz, 1 H), 3.28 (*dd, J* = 6.5, 19.4 Hz, 1 H), 3.78 – 3.87 (*m*, 2 H), 5.67 – 5.73 (*m*, 1 H), 5.75 – 5.82 (*m*, 1 H), 6.75 – 6.80 (*m*, 2 H), 7.11 (*dd, J* = 7.7, 7.7 Hz, 1 H), 8.74 (*s*, 1 H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$, δ) 29.1, 34.0, 45.0, 107.6, 122.5, 126.2, 127.1, 127.9, 129.6, 137.5, 140.5, 180.1 ppm. **IR (neat sample)**:

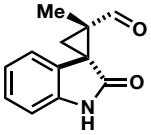
3018, 2914, 1699, 1615, 1459, 1318, 1288, 1248, 1166, 939, 757, 730, 632 cm^{-1}. **HRMS** (ESI) (*m*/*z*): calcd for $C_{12}H_{12}NO$ $[M + H]^+$, 186.0919; found, 186.0917.

8.4 Crystalographic Data

Bondlength of (1*S*,2*S*)-2-methyl-2'-oxospiro[cyclopropane-1,3'-indoline]-2-carbaldehyde

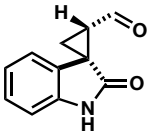


Number	Atom1	Atom2	Type	Polymeric	Cyclicity	Length	SybylType
1	N1	H1	Unknown	no	acyclic	0.90(2)	1
2	N1	C2	Unknown	no	cyclic	1.352(2)	un
3	N1	C7A	Unknown	no	cyclic	1.402(2)	un
4	O1	C2	Unknown	no	acyclic	1.230(2)	2
5	O2	C10	Unknown	no	acyclic	1.206(2)	2
6	C2	C3	Unknown	no	cyclic	1.510(2)	1
7	C3	C3A	Unknown	no	cyclic	1.482(2)	1
8	C3	C8	Unknown	no	cyclic	1.497(2)	1
9	C3	C9	Unknown	no	cyclic	1.577(2)	1
10	C3A	C4	Unknown	no	cyclic	1.383(2)	un
11	C3A	C7A	Unknown	no	cyclic	1.397(2)	un
12	C4	H4	Unknown	no	acyclic	0.99(2)	1
13	C4	C5	Unknown	no	cyclic	1.392(2)	un
14	C5	H5	Unknown	no	acyclic	1.00(2)	1
15	C5	C6	Unknown	no	cyclic	1.384(2)	un
16	C6	H6	Unknown	no	acyclic	1.00(2)	1
17	C6	C7	Unknown	no	cyclic	1.393(2)	un
18	C7	H7	Unknown	no	acyclic	0.95(2)	1
19	C7	C7A	Unknown	no	cyclic	1.380(2)	un
20	C8	H81	Unknown	no	acyclic	1.00(2)	1
21	C8	H82	Unknown	no	acyclic	1.02(2)	1
22	C8	C9	Unknown	no	cyclic	1.501(2)	1
23	C9	C10	Unknown	no	acyclic	1.485(2)	1
24	C9	C11	Unknown	no	acyclic	1.503(2)	1
25	C10	H10	Unknown	no	acyclic	1.01(2)	1
26	C11	H111	Unknown	no	acyclic	0.92(3)	1
27	C11	H112	Unknown	no	acyclic	0.97(3)	1
28	C11	H113	Unknown	no	acyclic	0.89(4)	1

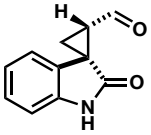
Bondangles of (1*S*,2*S*)-2-methyl-2'-oxospiro[cyclopropane-1,3'-indoline]-2-carbaldehyde				
				
Number	Atom1	Atom2	Atom3	Angle
1	H1	N1	C2	122(1)
2	H1	N1	C7A	126(1)
3	C2	N1	C7A	111.7(1)
4	N1	C2	O1	125.8(1)
5	N1	C2	C3	107.0(1)
6	O1	C2	C3	127.2(1)
7	C2	C3	C3A	104.6(1)
8	C2	C3	C8	119.0(1)
9	C2	C3	C9	119.4(1)
10	C3A	C3	C8	127.6(1)
11	C3A	C3	C9	122.9(1)
12	C8	C3	C9	58.37(9)
13	C3	C3A	C4	133.8(1)
14	C3	C3A	C7A	107.1(1)
15	C4	C3A	C7A	119.1(1)
16	C3A	C4	H4	122(1)
17	C3A	C4	C5	118.9(1)
18	H4	C4	C5	119(1)
19	C4	C5	H5	118(1)
20	C4	C5	C6	121.0(2)
21	H5	C5	C6	121(1)
22	C5	C6	H6	121(1)
23	C5	C6	C7	121.0(1)
24	H6	C6	C7	118(1)
25	C6	C7	H7	123(1)
26	C6	C7	C7A	117.1(1)
27	H7	C7	C7A	120(1)
28	N1	C7A	C3A	109.5(1)
29	N1	C7A	C7	127.7(1)
30	C3A	C7A	C7	122.8(1)
31	C3	C8	H81	115(1)
32	C3	C8	H82	117(1)
33	C3	C8	C9	63.5(1)
34	H81	C8	H82	115(1)
35	H81	C8	C9	119(1)
36	H82	C8	C9	118(1)
37	C3	C9	C8	58.16(9)
38	C3	C9	C10	115.0(1)
39	C3	C9	C11	119.5(1)
40	C8	C9	C10	116.1(1)
41	C8	C9	C11	120.8(1)
42	C10	C9	C11	115.3(1)
43	O2	C10	C9	123.1(2)
44	O2	C10	H10	119(1)

45	C9	C10	H10	118(1)
46	C9	C11	H111	113(2)
47	C9	C11	H112	112(2)
48	C9	C11	H113	111(2)
49	H111	C11	H112	101(2)
50	H111	C11	H113	113(3)
51	H112	C11	H113	105(3)

Bondlength of (1*R*,2*S*)-2'-oxospiro[cyclopropane-1,3'-indoline]-2-carbaldehyde

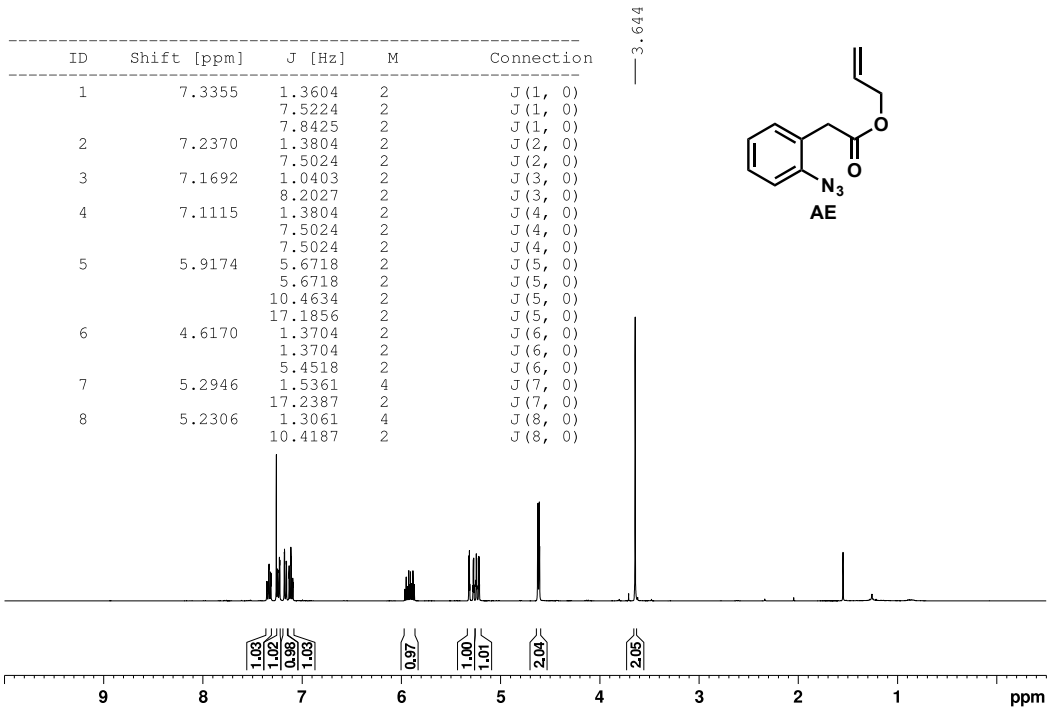


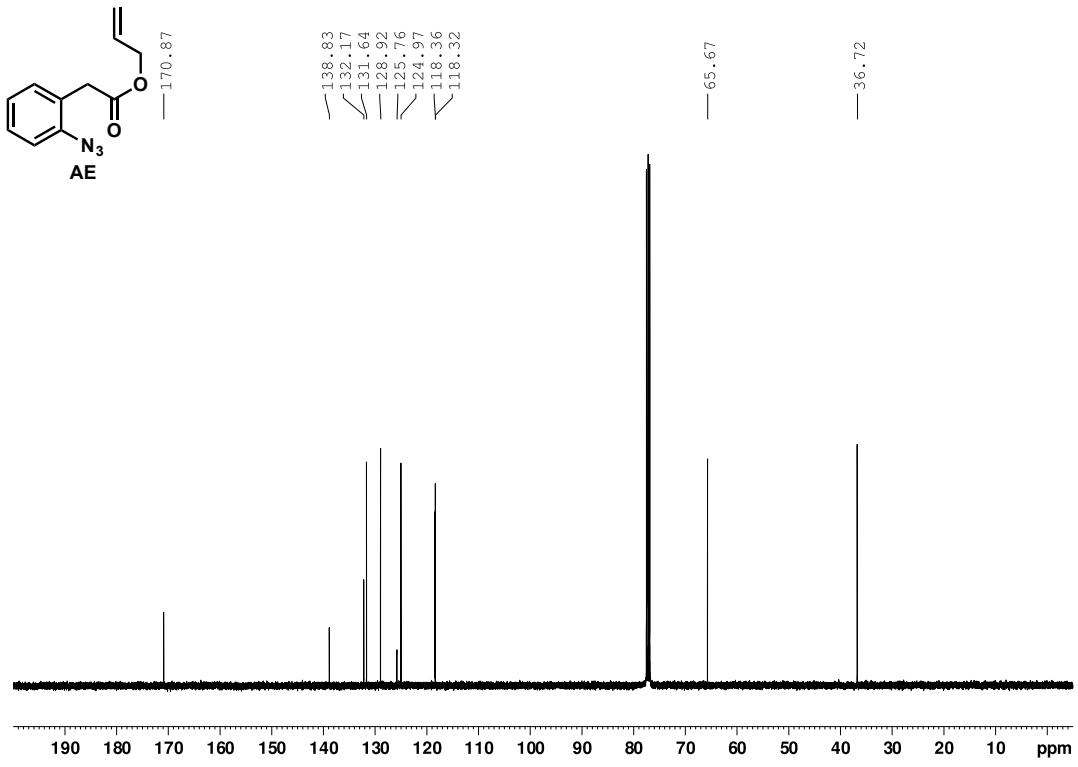
Number	Atom1	Atom2	Type	Polymeric	Cyclicity	Length	SybylType
1	O1	C2	Unknown	no	acyclic	1.228(5)	2
2	N1	H1	Unknown	no	acyclic	0.860	1
3	N1	C2	Unknown	no	cyclic	1.350(5)	un
4	N1	C7a	Unknown	no	cyclic	1.403(5)	un
5	O2	C10	Unknown	no	acyclic	1.204(6)	2
6	C4a	C3	Unknown	no	cyclic	1.481(5)	1
7	C4a	C7a	Unknown	no	cyclic	1.392(5)	un
8	C4a	C4	Unknown	no	cyclic	1.395(5)	un
9	C2	C3	Unknown	no	cyclic	1.507(5)	1
10	C3	C9	Unknown	no	cyclic	1.544(5)	1
11	C3	C8	Unknown	no	cyclic	1.497(6)	1
12	C7a	C7	Unknown	no	cyclic	1.376(6)	un
13	C9	H9	Unknown	no	acyclic	0.980	1
14	C9	C10	Unknown	no	acyclic	1.475(6)	1
15	C9	C8	Unknown	no	cyclic	1.489(6)	1
16	C7	H7	Unknown	no	acyclic	0.930	1
17	C7	C6	Unknown	no	cyclic	1.376(6)	un
18	C4	H4	Unknown	no	acyclic	0.930	1
19	C4	C5	Unknown	no	cyclic	1.397(6)	un
20	C5	H5	Unknown	no	acyclic	0.930	1
21	C5	C6	Unknown	no	cyclic	1.389(6)	un
22	C10	H10	Unknown	no	acyclic	0.930	1
23	C8	H81	Unknown	no	acyclic	0.969	1
24	C8	H82	Unknown	no	acyclic	0.971	1
25	C6	H6	Unknown	no	acyclic	0.930	1

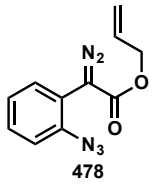
Bondangles of (1*R*,2*S*)-2'-oxospiro[cyclopropane-1,3'-indoline]-2-carbaldehyde				
				
Number	Atom1	Atom2	Atom3	Angle
1	H1	N1	C2	123.9
2	H1	N1	C7a	123.9
3	C2	N1	C7a	112.2(3)
4	C3	C4a	C7a	107.5(3)
5	C3	C4a	C4	132.6(3)
6	C7a	C4a	C4	119.9(3)
7	O1	C2	N1	125.9(3)
8	O1	C2	C3	127.4(3)
9	N1	C2	C3	106.7(3)
10	C4a	C3	C2	104.7(3)
11	C4a	C3	C9	122.7(3)
12	C4a	C3	C8	123.9(3)
13	C2	C3	C9	121.4(3)
14	C2	C3	C8	120.8(3)
15	C9	C3	C8	58.6(3)
16	N1	C7a	C4a	108.9(3)
17	N1	C7a	C7	128.8(4)
18	C4a	C7a	C7	122.3(4)
19	C3	C9	H9	116.2
20	C3	C9	C10	119.9(3)
21	C3	C9	C8	59.1(3)
22	H9	C9	C10	116.2
23	H9	C9	C8	116.2
24	C10	C9	C8	117.0(4)
25	C7a	C7	H7	121.0
26	C7a	C7	C6	118.0(4)
27	H7	C7	C6	121.1
28	C4a	C4	H4	121.2
29	C4a	C4	C5	117.6(4)
30	H4	C4	C5	121.2
31	C4	C5	H5	119.4
32	C4	C5	C6	121.3(4)
33	H5	C5	C6	119.4
34	O2	C10	C9	123.6(4)
35	O2	C10	H10	118.2
36	C9	C10	H10	118.2
37	C3	C8	C9	62.3(3)
38	C3	C8	H81	117.6
39	C3	C8	H82	117.5
40	C9	C8	H81	117.5
41	C9	C8	H82	117.5
42	H81	C8	H82	114.7
43	C7	C6	C5	121.0(4)
44	C7	C6	H6	119.5

8.5 Spectra

ID	Shift [ppm]	J [Hz]	M	Connection
1	7.3355	1.3604	2	J(1, 0)
		7.5224	2	J(1, 0)
		7.8425	2	J(1, 0)
2	7.2370	1.3804	2	J(2, 0)
		7.5024	2	J(2, 0)
3	7.1692	1.0403	2	J(3, 0)
		8.2027	2	J(3, 0)
4	7.1115	1.3804	2	J(4, 0)
		7.5024	2	J(4, 0)
		7.5024	2	J(4, 0)
5	5.9174	5.6718	2	J(5, 0)
		5.6718	2	J(5, 0)
		10.4634	2	J(5, 0)
		17.1856	2	J(5, 0)
6	4.6170	1.3704	2	J(6, 0)
		1.3704	2	J(6, 0)
		5.4518	2	J(6, 0)
7	5.2946	1.5361	4	J(7, 0)
		17.2387	2	J(7, 0)
8	5.2306	1.3061	4	J(8, 0)
		10.4187	2	J(8, 0)



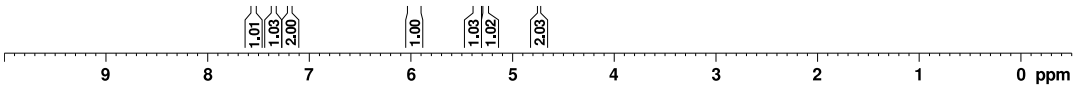


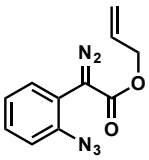


478

7.21
7.17

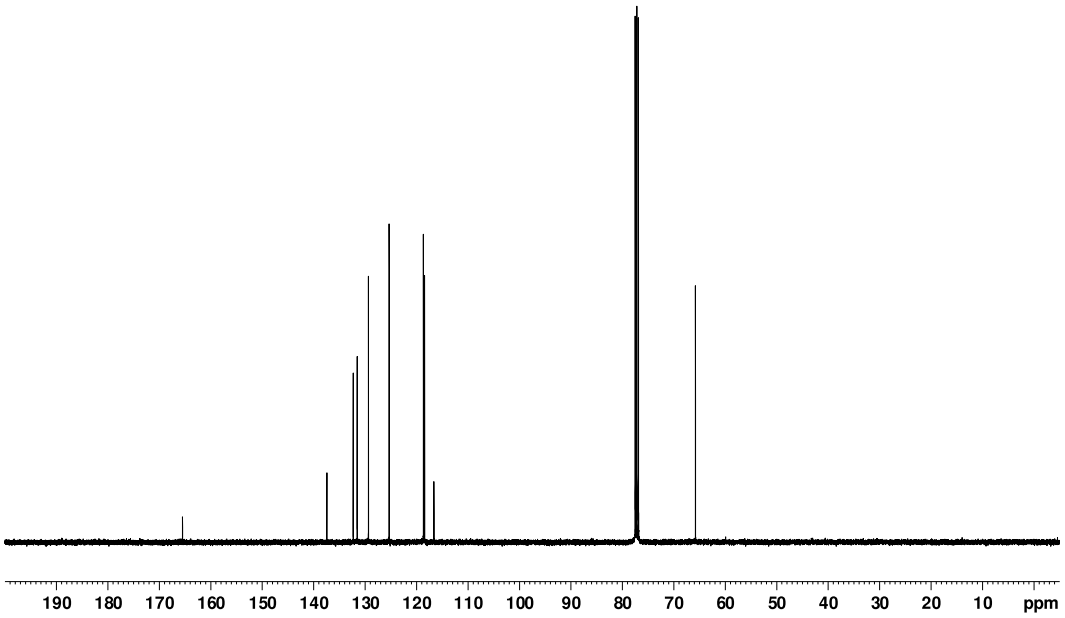
ID	Shift [ppm]	J [Hz]	M	Connection
1	7.5480	1.5405	2	J(1, 0)
		8.0226	2	J(1, 0)
2	7.3496	1.2004	2	J(2, 0)
		7.1623	2	J(2, 0)
		8.1827	2	J(2, 0)
3	5.9666	5.4718	2	J(3, 0)
		5.4718	2	J(3, 0)
		10.6935	2	J(3, 0)
		17.1356	2	J(3, 0)
4	5.3446	1.4805	4	J(4, 0)
		17.4057	2	J(4, 0)
5	5.2624	1.3138	4	J(5, 0)
		10.3834	2	J(5, 0)
6	4.7414	5.4418	2	J(6, 0)

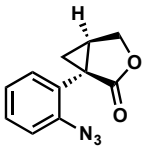




478

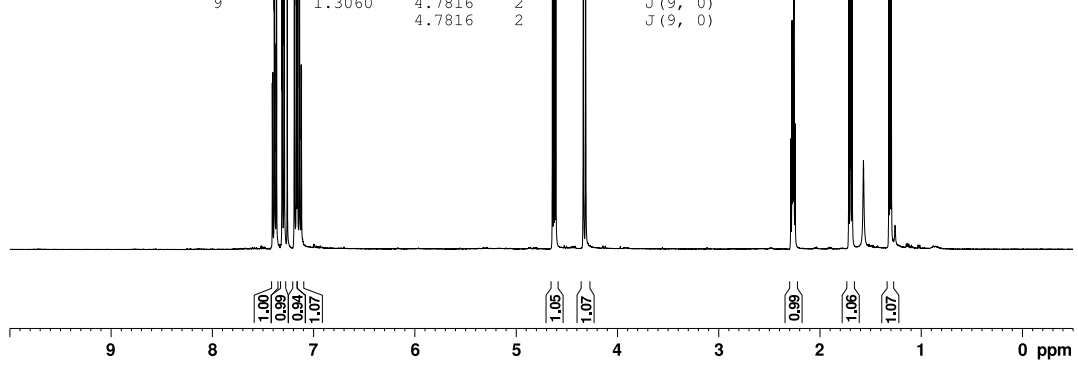
165.47
137.40
132.28
131.51
129.32
125.30
118.64
118.41
116.60
65.76

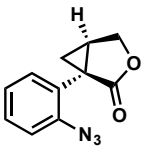




479

ID	Shift [ppm]	J [Hz]	M	Connection
1	7.3862	1.8806	2	J(1, 0)
		7.6825	2	J(1, 0)
		7.6825	2	J(1, 0)
2	7.3007	1.5405	2	J(2, 0)
		7.6625	2	J(2, 0)
3	7.1796	0.8603	2	J(3, 0)
		8.0226	2	J(3, 0)
4	7.1393	1.0303	2	J(4, 0)
		7.5124	2	J(4, 0)
		7.5124	2	J(4, 0)
5	4.6243	4.7816	2	J(5, 0)
		9.2230	2	J(5, 0)
6	4.3240	9.2030	2	J(6, 0)
7	2.2647	4.6115	2	J(7, 0)
		4.6115	2	J(7, 0)
		8.0126	2	J(7, 0)
8	1.6968	5.1217	2	J(8, 0)
		7.8425	2	J(8, 0)
9	1.3060	4.7816	2	J(9, 0)
		4.7816	2	J(9, 0)





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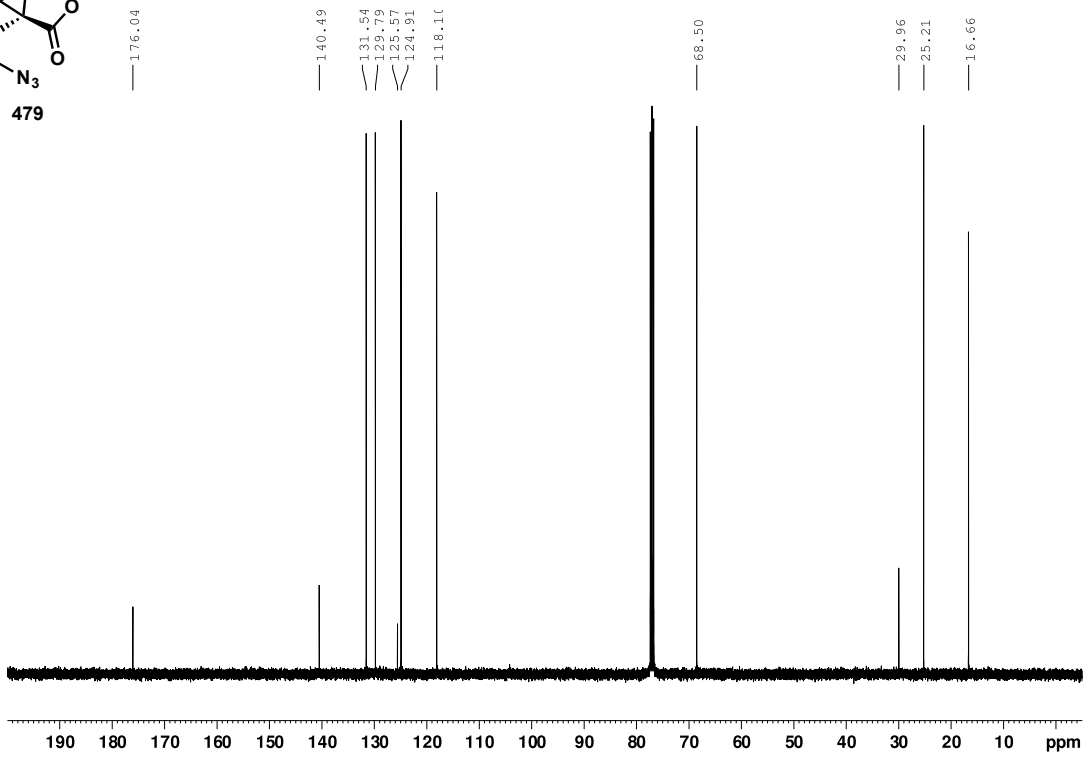
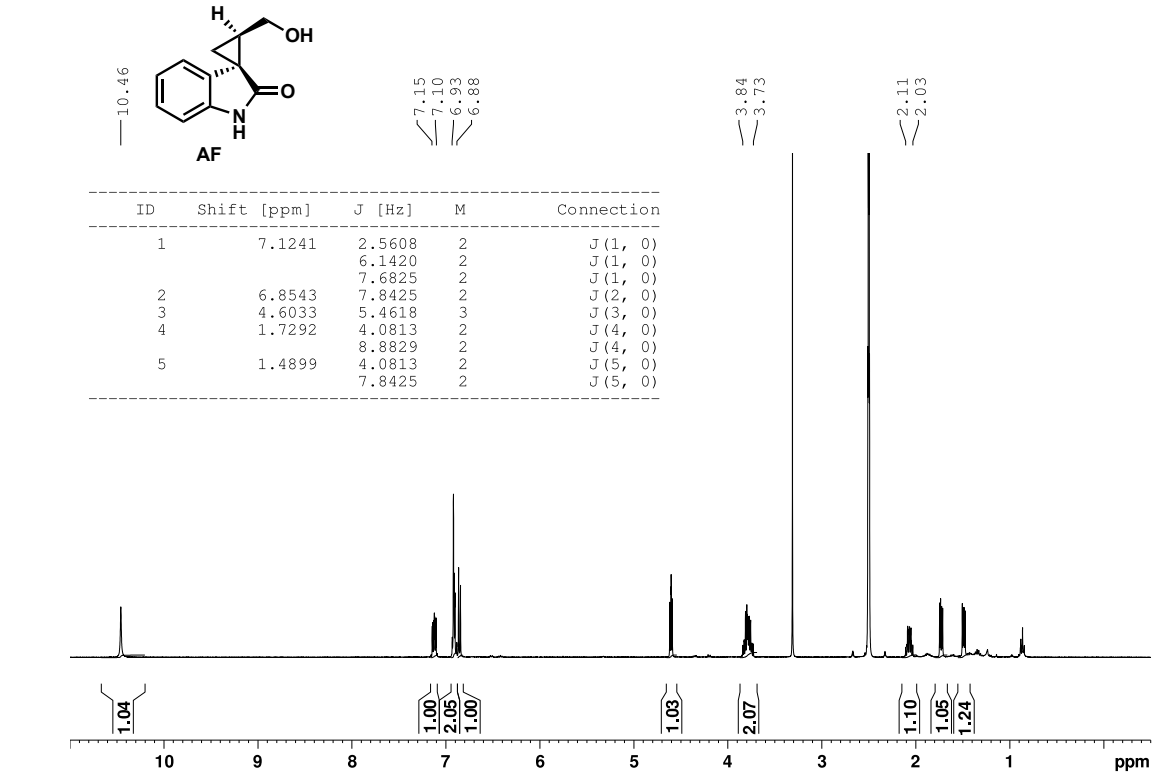
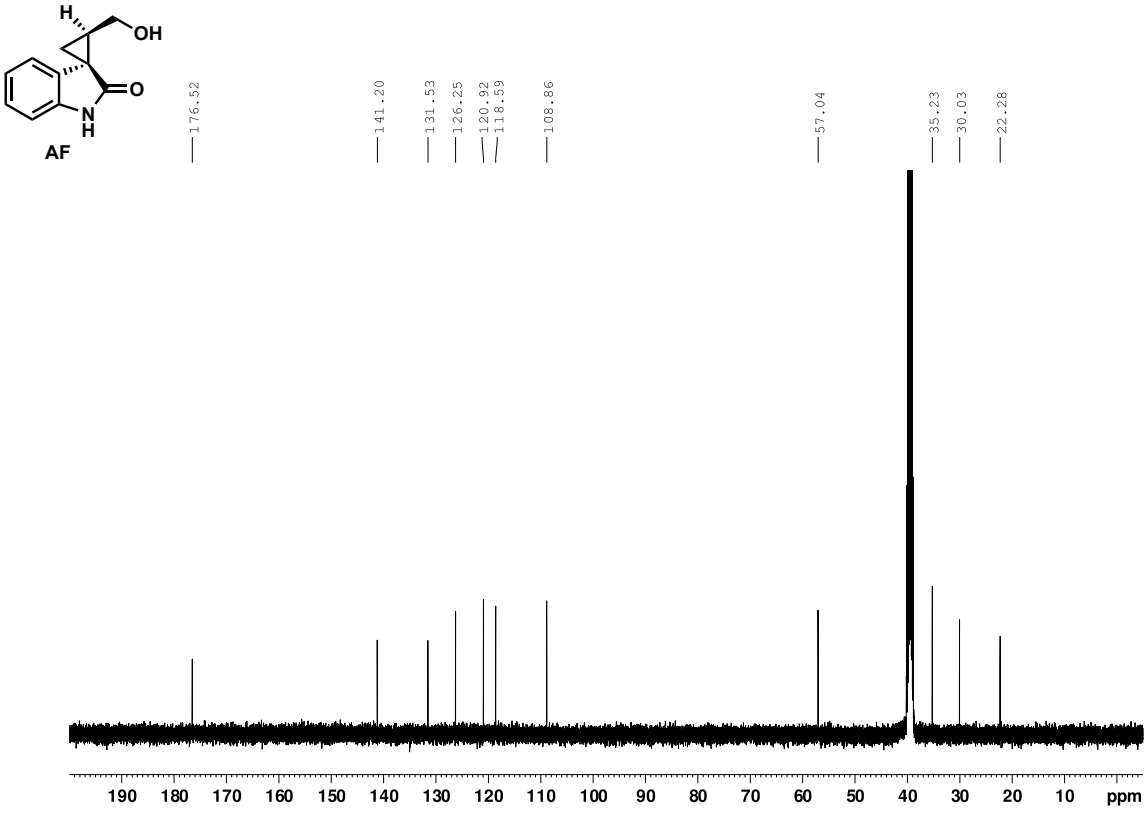
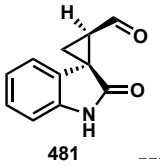




ID	Shift [ppm]	J [Hz]	M	Connection
1	7.1241	2.5608	2	J(1, 0)
		6.1420	2	J(1, 0)
		7.6825	2	J(1, 0)
2	6.8543	7.8425	2	J(2, 0)
3	4.6033	5.4618	3	J(3, 0)
4	1.7292	4.0813	2	J(4, 0)
		8.8829	2	J(4, 0)
5	1.4899	4.0813	2	J(5, 0)
		7.8425	2	J(5, 0)

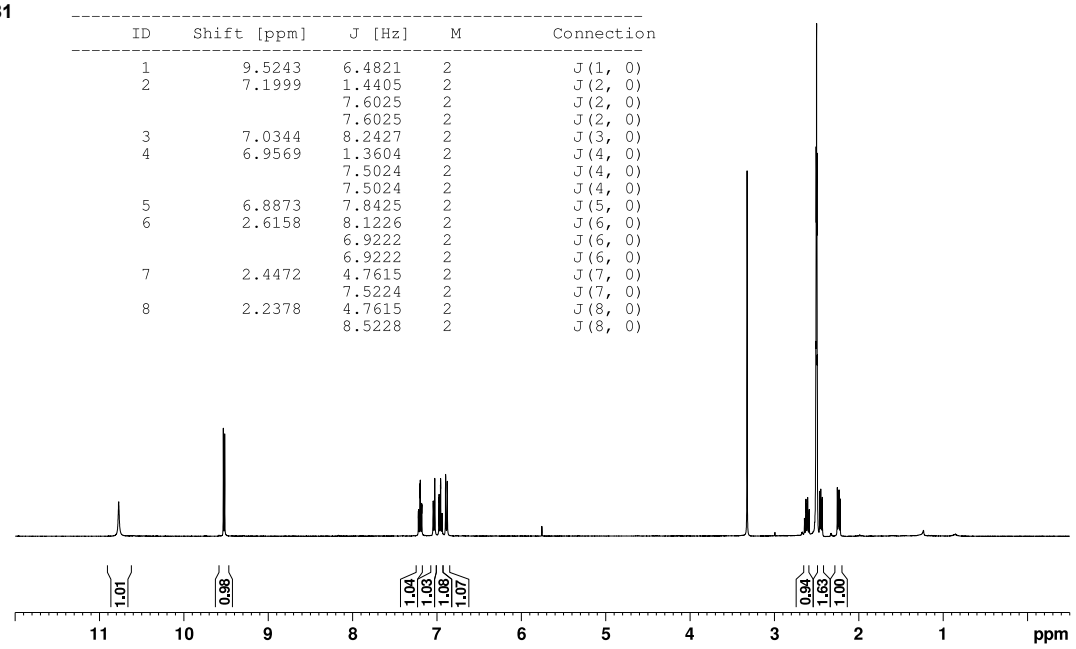


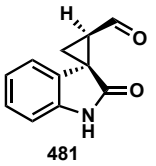


481

10.77

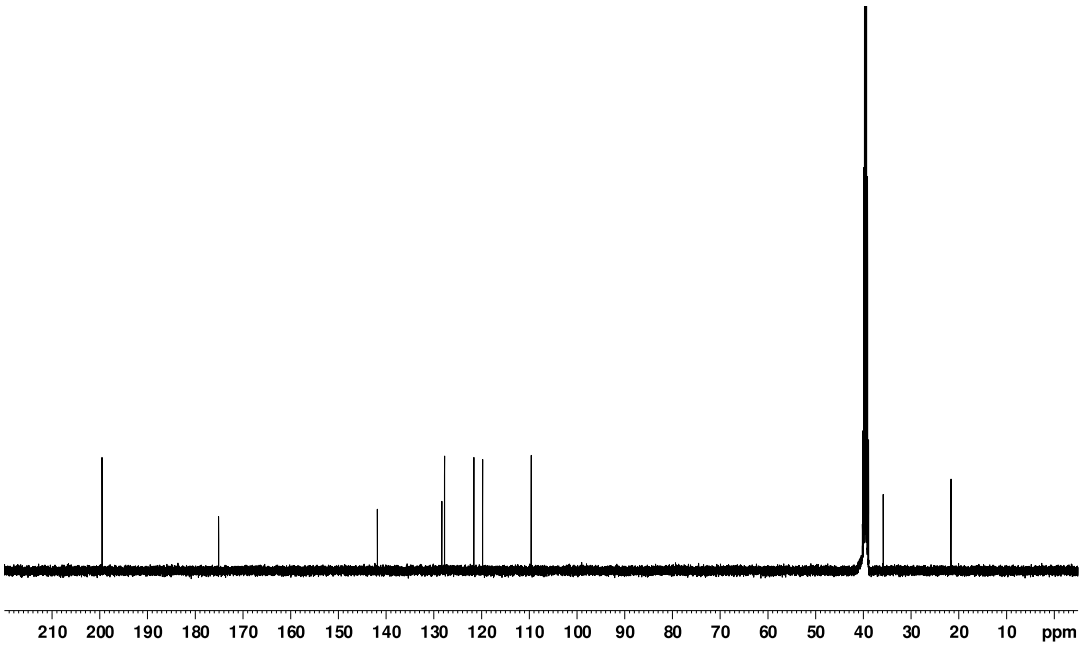
ID	Shift [ppm]	J [Hz]	M	Connection
1	9.5243	6.4821	2	J(1, 0)
2	7.1999	1.4405	2	J(2, 0)
		7.6025	2	J(2, 0)
		7.6025	2	J(2, 0)
3	7.0344	8.2427	2	J(3, 0)
4	6.9569	1.3604	2	J(4, 0)
		7.5024	2	J(4, 0)
		7.5024	2	J(4, 0)
5	6.8873	7.8425	2	J(5, 0)
6	2.6158	8.1226	2	J(6, 0)
		6.9222	2	J(6, 0)
		6.9222	2	J(6, 0)
7	2.4472	4.7615	2	J(7, 0)
		7.5224	2	J(7, 0)
8	2.2378	4.7615	2	J(8, 0)
		8.5228	2	J(8, 0)

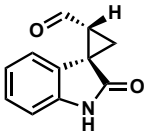




481

199.51
175.08
141.82
128.31
127.74
121.60
119.76
109.58
35.82
21.61

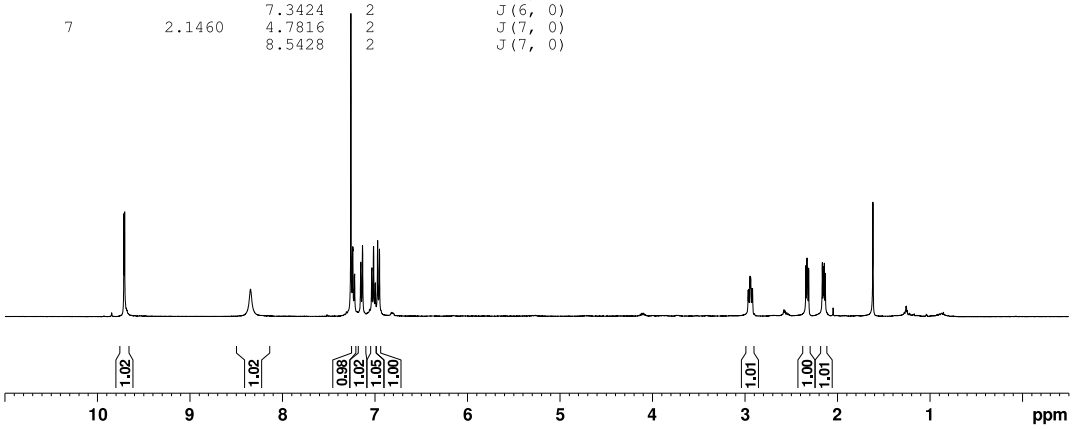


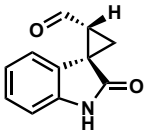


480

8.35
7.26
7.22

ID	Shift [ppm]	J [Hz]	M	Connection
1	9.7098	3.0810	2	J(1, 0)
2	7.1432	7.4824	2	J(2, 0)
3	7.0138	7.5625	2	J(3, 0)
		7.8025	2	J(3, 0)
4	6.9606	7.5224	2	J(4, 0)
5	2.9408	3.1610	2	J(5, 0)
		7.5825	2	J(5, 0)
		8.4427	2	J(5, 0)
6	2.3249	4.6215	2	J(6, 0)
		7.3424	2	J(6, 0)
7	2.1460	4.7816	2	J(7, 0)
		8.5428	2	J(7, 0)





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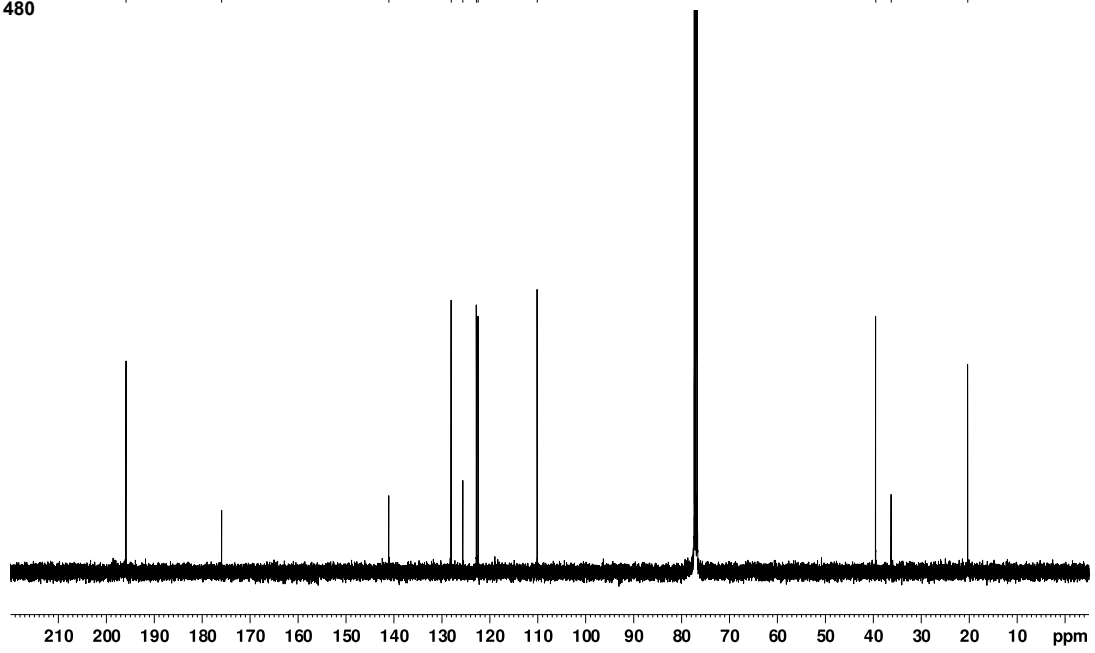

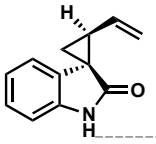

476

7.98

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		7.7525	2	J(1, 0)
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		7.6025	2	J(2, 0)
		7.6025	2	J(2, 0)
3	6.9167	7.4824	2	J(3, 0)
4	6.8330	7.4824	2	J(4, 0)
5	6.2158	9.9232	2	J(5, 0)
		9.8632	2	J(5, 0)
		17.2656	2	J(5, 0)
6	5.2507	1.1804	2	J(6, 0)
		17.2256	2	J(6, 0)
7	5.1304	1.2004	2	J(7, 0)
		10.4034	2	J(7, 0)
8	2.4974	8.6561	4	J(8, 0)
9	1.9768	7.7025	2	J(9, 0)
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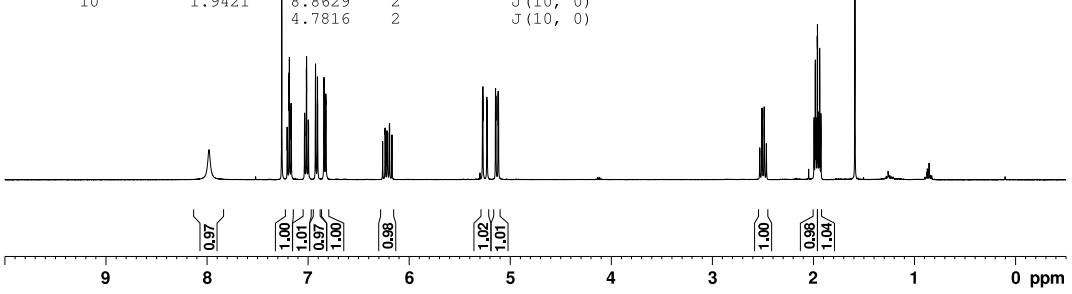

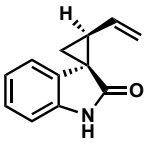

476

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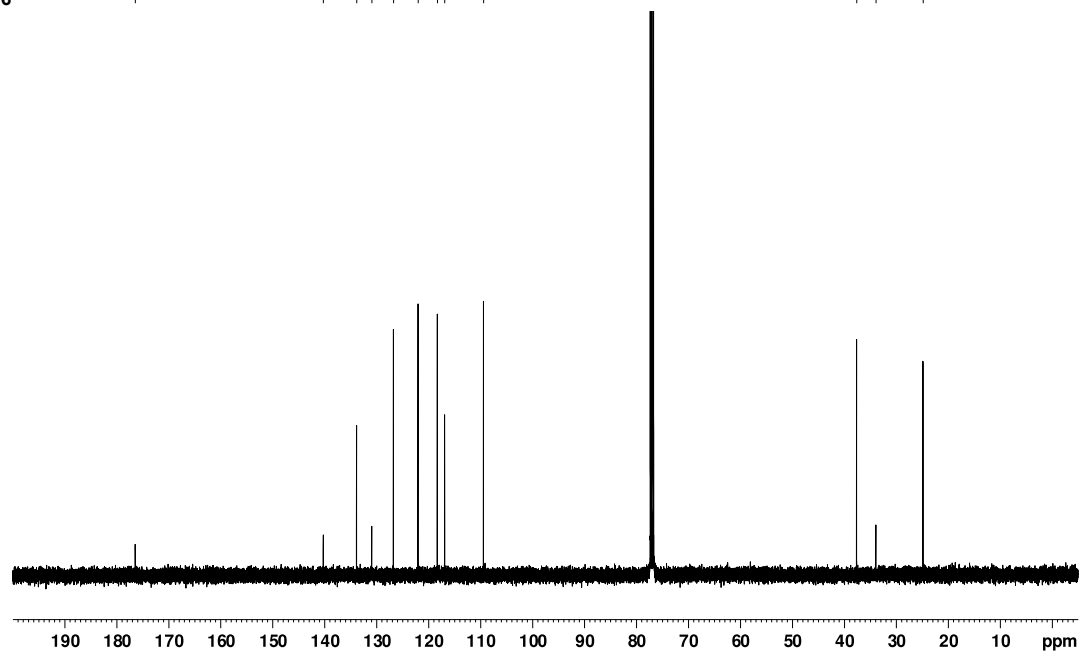

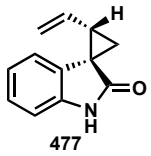

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4	5.3569	1.0303	2	J(4, 0)
		1.5305	2	J(4, 0)
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5	5.2487	0.6802	2	J(5, 0)
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		10.2433	2	J(5, 0)
6	2.6429	8.0826	4	J(6, 0)
7	2.0834	4.6015	2	J(7, 0)
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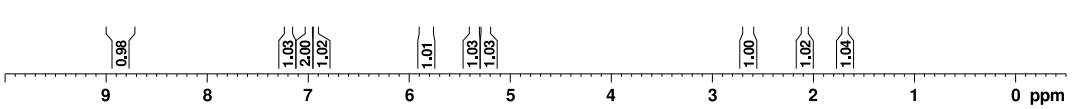

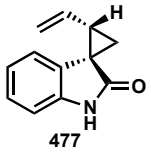

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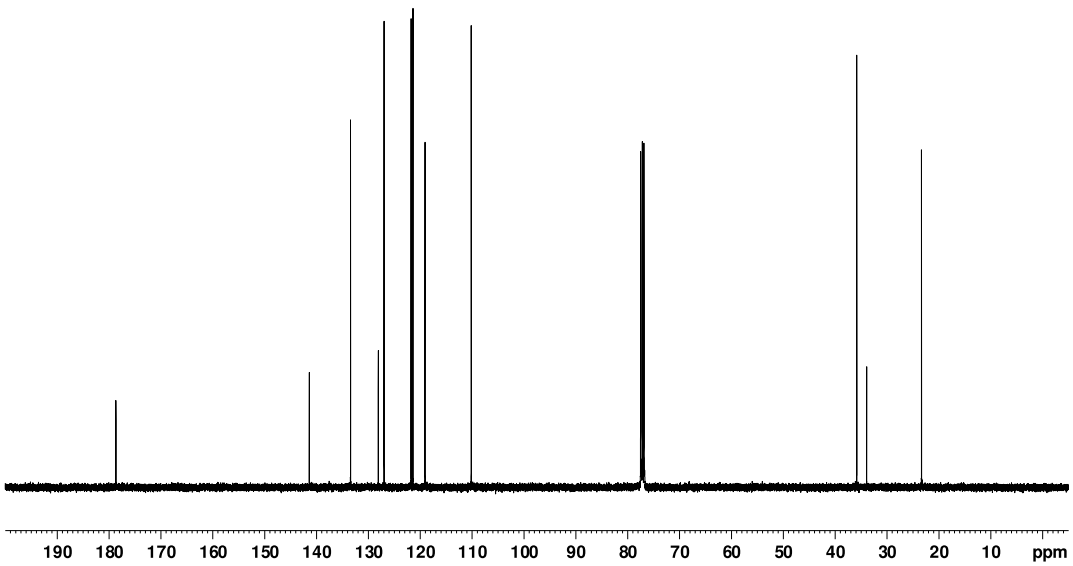

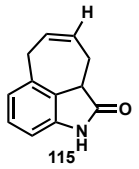
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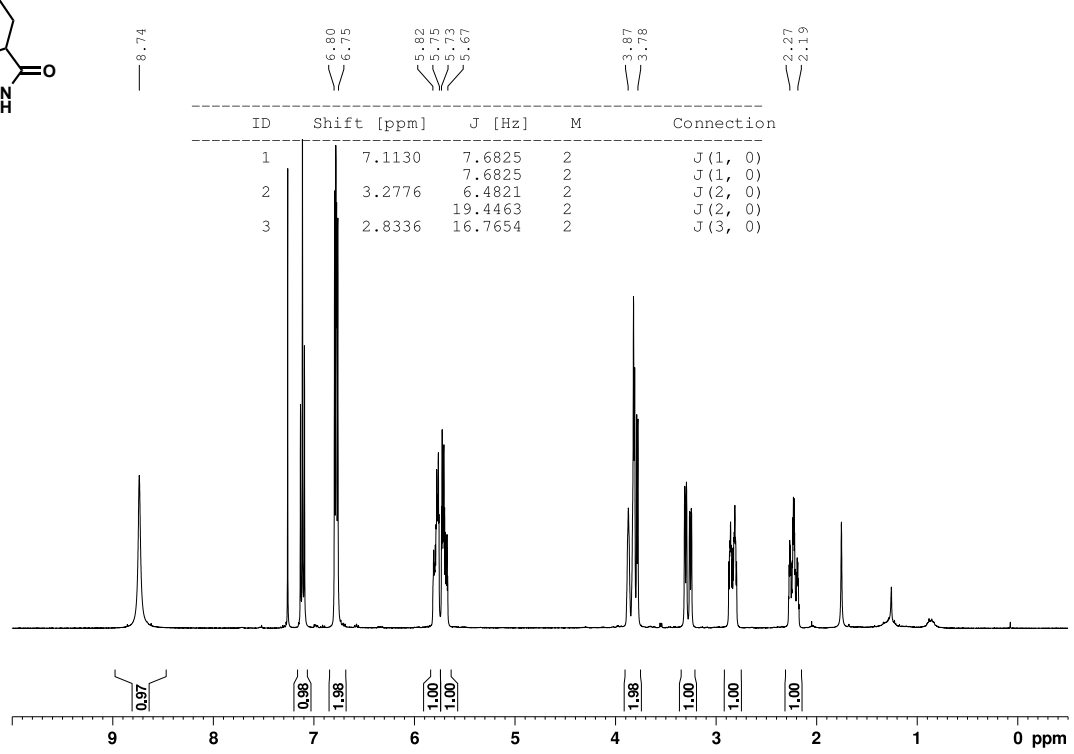
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2 3.2776 6.4821 2 J(2, 0)
19.4463 2 J(2, 0)
3 2.8336 16.7654 2 J(3, 0)
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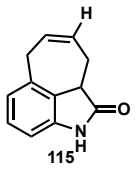
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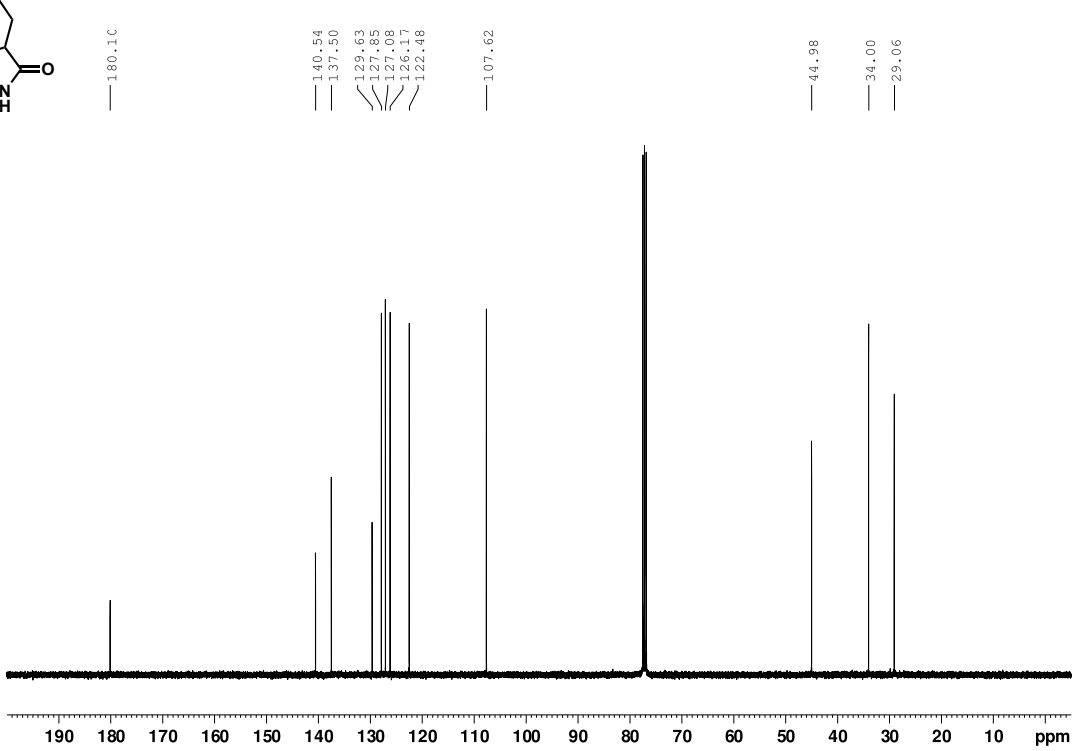
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170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

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Scheme 50. Selective preparation of **226**. prenyl -alcohol (1 equiv.), DMAP (20 mol%), DIC (1.05 equiv.), CH_2Cl_2, 92%, b. ABSA (1.05 equiv.), DBU (2 equiv.), THF, 96%, c. $(CuOTf)_2$•Tol (1.5 mol%), CH_2Cl_2 80%, d. PBu_3 (1.05 equiv.), THF then PhMe, reflux. 80%..... 51

Scheme 51. a. prenylene (10 equiv.), $Rh_2(OAc)_4$ (2 mol%), CH_2Cl_2, then DMSO reflux., 45%, b. TBS-prenyl alcohol (10 equiv.), CH_2Cl_2, $Rh_2(OAc)_4$ (2 mol%), reflux, 53%, c. TBAF (4 equiv.), THF, 0 °C, 71%, d. IBX (1.1 equiv.), DMSO, 44%, e. Ph_3PCH_3Br (5 equiv.), NaHMDS (5 equiv.), THF, – 78 °C to rt., 83%..... 51

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Scheme 58. Selective synthesis of **259**, **260**, **261** and **262**. a. **130** (1 equiv.), 4-DMAP (20 mol%), CH_2Cl_2, b. ABSA (2 equiv.), DBU (3.5 equiv.), MeCN, 86% **250** over two steps, 81% **249** over two steps, c $(CuOTf)_2$PhMe (3 mol%), CH_2Cl_2, 74% **252**, 84% **251**, d. Pd/C (10 mol%), H_2 (25 bar), EtOH, then *i*-PrMgCl (2.1 equiv.), THF, 0 °C, 87% **254** over two steps, 93% **253** over two steps. 54

Scheme 59. CBr_4 (1.1 - 2 equiv.), PPh_3 (1.1 - 2 equiv.), CH_2Cl_2, 0 °C, f. R=Me, TBAF (1.2 equiv.), THF, 0 °C, 72% **256** over two steps; f. R = H HF*pyridine (120 equiv.), pyridine, THF, 0 °C, 77% **255** over two steps, g. IBX (1.2 equiv.), DMSO, h. Ph_3PCHCO_2Me (1.1 - 1.2 equiv.), 45 - 60 °C, 84% **259**/**260** over two steps, i. Ph_3PCH_3Br (2.5 - 4 equiv.), NaHMDS (2.5 - 4 equiv.), –78 °C to 40 °C, 69% **262,** 68% **261** over two steps..... 55

Scheme 60. a. PDC (2 equiv.), CH_2Cl_2, MS 3 Å, b. HSC_3H_6SH (1.2 equiv.), $Pr(OTf)_3$ (5 mol%), MeCN, 62% over two steps, c. HF•pyridine (120 equiv.), pyridine, THF, 0 °C, d. SO_3•pyr.

(4 equiv.), Et_3N (5 equiv.) CH_2Cl_2:DMSO (1:1), 0 °C, 86% over two steps, e. Ph_3PCH_3Br (2.5 equiv.), NaHMDS (2.5 equiv.), THF, –78 to 0 °C, then PhH 50 °C, 71% over two steps, f. α-TMS-ethylacetate (2.6 equiv.), LiHMDS (2.5 equiv.), THF, –78 °C, then C_6D_6 40 °C, 75% over two steps. 56

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12 List of Abbreviations

Å	Angstrom
ð	*NMR*: chemical shift
Δ	heating to reflux
5-HT	5-hydroxytryptamine
4-DMATS	4-dimethylallyltryptophan synthase
ABSA	4-acetamidobenzenesulfonyl azide
Ac	acetyl
AIBN	azobisisobutyronitrile
Anth	anthracene
Ar	aryl
Bn	benzyl
Boc	*tret*-butoxycarbonyl
Bu	butyl
CAN	Ceric ammonium nitrate
cod	1,5-cyclooctadiene
d	day; *NMR*: dublett
DABCO	1,4-diazabicyclo[2.2.2]octane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexycarbodiimide
DCE	dichloroethane
DEAD	diethyl azodicarboxylate
decomp.	decomposition
DIC	diisopropoxycarbodiimide
DiBAl-H	diisobutylaluminiumhydride
DIPA	diisoproylamine
DIPEA	diisopropylethylamine
DMAc	dimethylacetylamide
DMAP	4-dimethylaminopyridine
DMAPP	Dimethylallyl pyrophosphate
DMAT	dimethylallyltryptophan
DMF	dimethylformamide
DMP	Dess-Martin periodinane; 3,5-dimethylpyrazole
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DMSO	dimethylsulfoxide
DMSPP	dimethylallyl-*S-thiolodophosphate*
DPEphos	bis[(2-diphenylphosphino)phenyl]ether
DVCP	divinylcyclopropane
DVCPR	divinylcyclopropane rearrangement
EDG	electron donating group
ESI	*MS*: electron spray ionization
Et	ethyl
equiv.	equivalent
EWG	electron withdrawing group
g	gram
HMTP; HMPA	hexamethylphosporamide
Hz	Hertz
hv	irradiation with light
IBX	2-iodoxybenzoic acid
IMDA	intramolecular Diels-Alder
i-Pr	*iso*-propyl
IR	infrared spectroscopy
J	coupling constant
K	Kelvin; equilibrium konstant
k	rate constant
LAH	lithium aluminium hydride
LDA	lithium diisopropylamide

LiHMDS	lithium hexamethydisilazane
LSD	lyseric acid diethylamide
M	any metal
*m*CPBA	*metha*-chloroperbenzoic acid
Me	methyl
MeCN	acetonitrile
MeOH	methanol
MHz	mega Hertz
min	minute
Ms	methane sulfonic acid
NaHMDS	sodium hexamethyldisilazane
NBS	*N*-bromosuccinimide
nm	nano meter
NMR	nuclear magnetic resonance spectroscopy
Pd/C	palladium on charcoal
PDC	pyridinium dichromate
PG	protecting group
Ph	phenyl
PhCl	chlorobenzene
PhH	benzene
PhMe; Tol	toluene
PIFA	[bis(trifluoroacetoxy)iodo]benzene
PIX	positional isotopic exchange experiment
PNO	pyridine-N-oxide
ppm	parts per million
rflx.	heating to relfux
rt.	room temperature
s	second; *NMR*: singulett
SAM	(*S*)-adenosylmethionine
SM	starting material
T	temperature
t	time; *NMR*: triplett
TBABr	tetra-*n*-butylammonium bromide
TBAF	tetra-*n*-butylammonium fluoride
TBAI	tetra-*n*-butylammonium iodide
^{t}Bu	*tert*-butyl
TBS	*tert*-butyldimethylsilyl
TBHP	tetrabutyl hydroperoxide
TEA	triethylamine
Tf	triflate
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
TFETFA	trifluoroethyl trifluoroacetate
THF	tetrahydrofurane
TIPS	triisopropylsilyl
TMS	trimethylsilyl
Ts	toluenesulfonic acid
U/S	sltrasonic sound
X	any halogen

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