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Natural Products from Corals and Bacteria:

Photochemical Formation of Intricarene

and

Total Synthesis of Crocagin

von

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aus Göttingen

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Julia Desiree Stichnoth

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Abstract

This dissertation describes the synthetic progress towards different classes of natural products, diterpenoids and peptides, which were isolated from corals and a bacterium, respectively.

The first part deals with the furanocembranoids, a family of diterpenoids, which have all been isolated from marine sources. One of these furanocembranoids is bielschowskysin, which exhibits a highly oxygenated hexacyclic structure. For this natural product the planed total synthesis is presented as well as the synthesis of the building blocks necessary in the synthesis. Combination attempts of these building blocks are presented and the synthetic challenge caused by the instability of several building blocks is explained.

The second covered furanocembranoid is intricarene, which shows a pentacyclic carbon skeleton with three spiro centers. A photochemical transformation of the furanocembranoid bipinnatin J into intricarene was elaborated, which may be the biosynthetic pathway. Detailed description of the synthesis of bipinnatin J is presented, as well as the modifications of bipinnatin J, which lead to an intermediate, whose irradiation yielded intricarene. Theoretical calculation on the photochemical transformation clarified the mechanism.

The second part focuses on the total synthesis of crocagin, a peptidic natural product isolated from a myxobacterium. It consists of three modified aminoacids, cyclized to a peptide. Its total synthesis should prove the identity of the isolated molecule and deliver material for further biological testing. A first-generation strategy of the total synthesis is presented. It includes the synthesis of three different building blocks, which are all modified amino acids, the combination of them and the studies towards a biomimetic synthesis. The elaboration of a second-generation strategy is presented as well as the synthesis of the intermediates that lead to the natural product using a linear strategy with various synthetic transformations.

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Ich möchte allen Personen danken, die zum Gelingen dieser Arbeit beigetragen haben. Allen voran Herrn Prof. Dirk Trauner, speziell für das hervorragende Arbeitsumfeld, das er mir ermöglicht hat, für die Themenstellung und die Möglichkeit mich in verschiedene Felder der Totalsynthese einzuarbeiten, sowie die Betreuung während der letzten vier Jahre.

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Vielen Dank an alle die direkt oder indirekt einen Beitrag zum Gelingen dieser Arbeit geleistet haben.

List of Abbreviations

Å	Ångström, 1 Å = 10^{-10} m
Ac	acetyl
AD	asymmetric dihydroxylation
aq	aqueous
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
BOP	benzotriazolyloxytris(dimethylamino)phosphonium hexafluorophosphate
br	broad
Bu	butyl
c	concentration
calc.	calculated
Cbz	carboxybenzyl
Cod	1,5-cyclooctadien
Cp	cyclopentadienyl
m-CPBA	*meta*-chlorperbenzoic acid
DCE	1,2-dichloroethane
DCM	dichloromethane
DBU	1,8-diazabicyclo[5.4.0]undec-7-en
DIPEA	*N*,*N*-diisopropylamin
DMAP	*N*,*N*-dimethylaminopyridine
DME	dimethoxyethane

DMF	dimethlyformamide
DMP	Dess-Martin-Periodinane
DMSO	dimethylsulfoxide
dppf	bis(diphenylphosphino)ferrocene
EDCI	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimid
ee	enantiomeric excess
EI	electron ionisation
Et	ethyl
ESI	electron spray ionisation
Fmoc	fluorenylmethyloxycarbonyl
g	gram(s)
GGPP	geranyl-geranyl-diphosphate
h	hour(s)
HMDS	hexamethylendisilazan
HOBt	1-hydroxybenzotriazol
HRMS	high resolution mass spectrometry
Hz	Hertz
IC	inhibitory concentration
im	imidazol
IR	infra red
LDA	lithiumdiisopropylamid
Me	methyl
min	minutes

MMPP	magnesium monoperoxophtalat
m.p.	melting point
Ms	methanesulfonyl
NBS, NCS, NIS	*N*-bromo/cloro/iodosuccinimid
NBSH	2-nitrobenzenesulfonylhydrazide
NMM	*N*-methylmorpholin
NMO	*N*-methylmorpholin *N*-oxid
NMP	*N*-methyl-2-pyrrolodinon
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
Ns	4-nitrobenzenesulfonyl
Ph	phenyl
Pin	pinacolato
ppm	parts per million
PPTS	pyridinium *para*-toluenesulfonic acid
PSP	phenylselenophtalat
quant.	quantitative
R_f	retardation factor
r.t.	room temperature
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TES	triethlysilyl
Tf	triflate, trifluoromethanesulfonate

TFA	trifluoroacetic acid
TMP	2,2,6,6-tetramethylpiperidin
TMS	trimethylsilyl
THF	tetrahydrofuran
Ts	tosyl, 4-toluenesulfonyl
TMP	2,2,6,6-tetramethylpiperidine
UV	ultra violett
W	Watt
X-ray	X-radiation

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1 Studies on Furanocembranoids

1.1 Background on the Furanocembranoids

The furanocembranoids, a large family of diterpenoids, have been isolated from marine sources, most from gorgonian corals, which have proven to be a rich source of terpenoid secondary metabolites.[1] They gained the interest of many chemists not only by their considerable bioactivity, but also by their challenging molecular architecture.[2]

The basic skeleton of these marine natural products is displayed in Figure 1.1 and shows the characteristic 14-membered carbocyclic system with a furan ring.

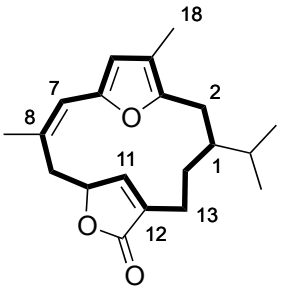
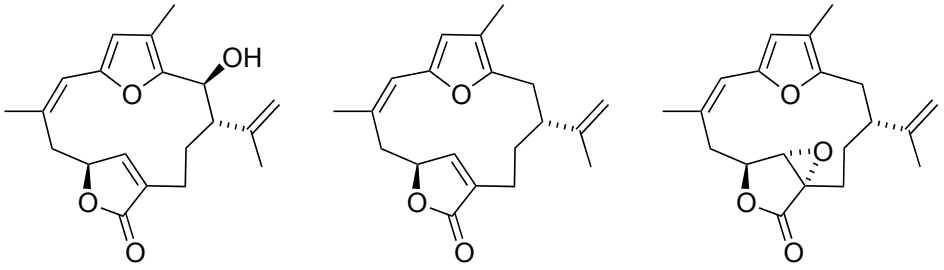


Figure 1.1 Basic skeleton of members of the furanocembranoid family.

Modifications, leading to a wide structural diversity are found in position C-2, which is often hydroxylated, as well as in position C-13 that can be oxidized and in position C-18 that can occur in all possible oxidations states. The double bonds between C-7 and C-8 as well as between C-11 and C-12 are often oxidized, especially in the form of an epoxide.[2]

In Figure 1.2, selected members of regular furanocembranoids are depicted. Bipinnatin J (**I-1**) was first isolated, together with several other bipinnatins (bipinnatin A-G), from *Pseudopterogorgia bipinnata*.[3] Some of the bipinnatins show strong cytotoxicity against tumor and cancer cell lines.[4] Rubifolide (**I-2**) is the C-2 deoxygenated version of bipinnatin J (**I-1**) and was first isolated from the coral *Gersemia rubiformis*.[5] Coralloidolide A (**I-3**), which was found in *Alcyonium coralloides*, is the C-11/C-12 epoxidized version of rubifolide (**I-2**).[6]

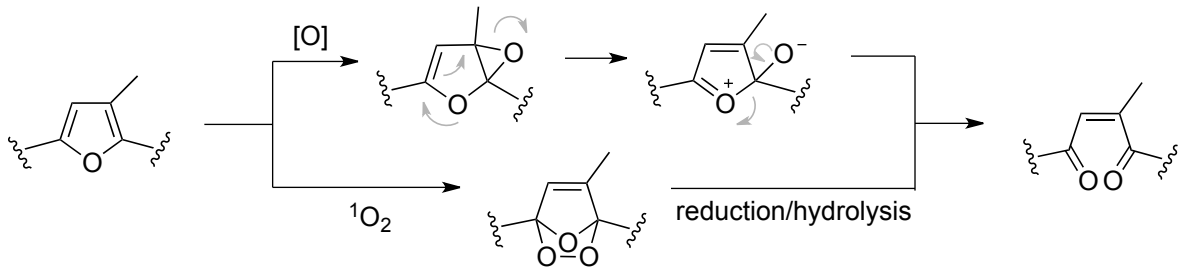


bipinnatin J (**I-1**) rubifolide (**I-2**) coralloidolide A (**I-3**)

Figure 1.2 Selected regular furanocembranoids.

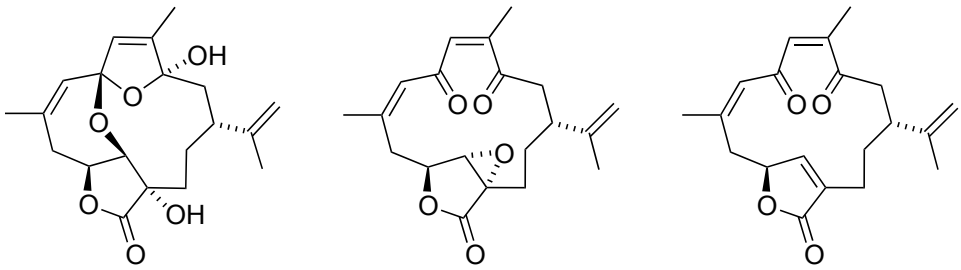
Synthetic chemists were attracted by the furanocembranoids, either by their bioactivity or their complex architecture. Two racemic total syntheses of bipinnatin J (**I-1**) were published in 2006, one by our group[7] and one by the group of V. H. Rawal.[8] Later that year, an enantioselective total synthesis for (−)-bipinnatin J followed, also published by our group.[9] Within the same publication the synthesis of (+)-rubifolide (**I-2**) was disclosed. A total synthesis of coralloidolide A (**I-3**) was completed by our group in 2010.[10]

More structural diversity within the furanocembranoids is observed upon oxidation and ring opening of the furan ring. Two mechanisms are proposed for this oxidation. Either an epoxidized furan ring rearranges to the enedione or a Diels-Alder reaction with singlet oxygen results in a peroxide whose reduction yields the enedione (Scheme 1.1).[2]



Scheme 1.1 Possible mechanisms for oxidative ring opening of the furan ring in furanocembranoids.

Selected furanocembranoids resulting from the oxidative opening of the furan ring are shown in Figure 1.3. Coralloidolides B (**I-4**) and E (**I-5**) were isolated together with the other coralloidolides from *Alcyonium coralloides*,[6,11] while isoepilophodione B (**I-6**) was isolated together with its putative biosynthetic precursor rubifolide (**I-2**) from *Gersemia rubiformis*.[5,12] Isoepilophodione B is the oxidized version of rubifolide, while coralloidolide E is the epoxidized version of isoepilophodione B. In coralloidolide B an additional oxygen bridge is observed.



coralloidolide B (**I-4**) coralloidolide E (**I-5**) isoepilophodione B (**I-6**)

Figure 1.3 Selected furanocembranoids resulting from the oxidative cleavage of the furanring.

The total syntheses of coralloidolides B (**I-4**) and E (**I-5**) were achieved in 2010 by our group,[10] whereas the total synthesis of isoepilophodione B (**I-6**) has already been achieved in 2006 by our group.[9]

An even higher degree of structural diversity within the furanocembranoids can be observed not only by oxidative cleavage of the furan ring, but also by additional C – C bond formations. For example transannular ring closure alters the macrocyclic skeleton, creating highly fused and bridged ring systems.[2] Five prominent members of this class are presented in Figure 1.4. Coralloidolides C (**I-7**) and F (**I-8**) were isolated together with the already mentioned Coralloidolides from *Alcyonium coralloides*.[11,13] In these molecules a cyclopentenone moiety is formed *via* ring contraction. Verrillin (**I-9**) was found in *Pseudopterogorgia bipinnata*,[14] wherein several new C – C bonds form a complex polycyclic ring system. The pentacyclic natural product intricarene (**I-10**) and the hexacyclic natural product bielschowskysin (**I-11**) were isolated from *Pseudopterogorgia kallos*.[15,16]

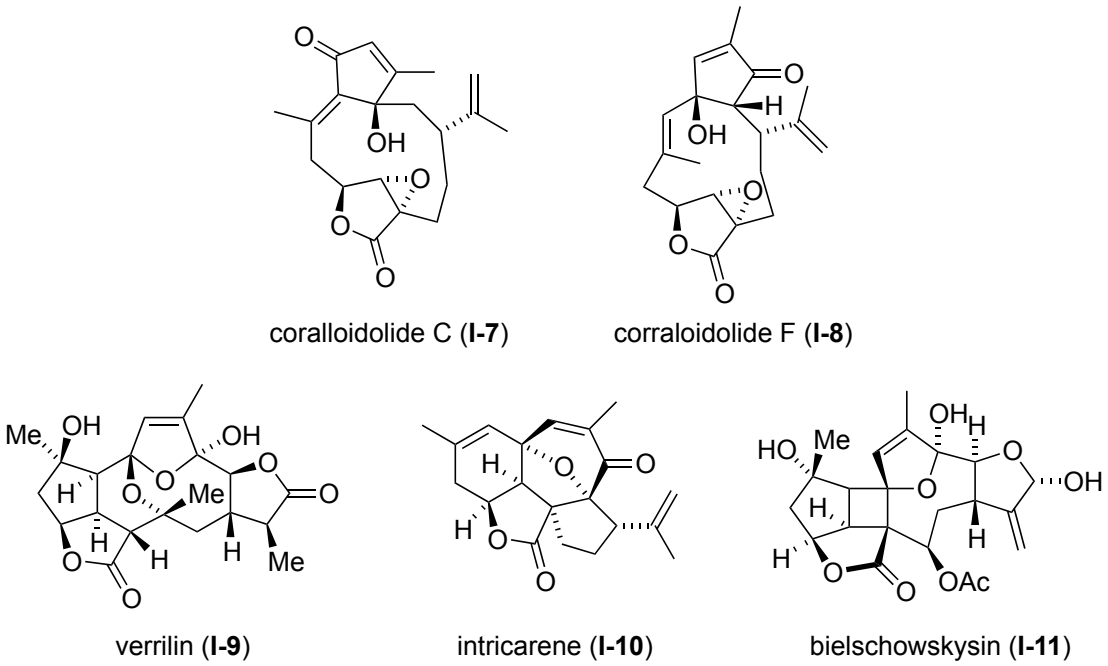


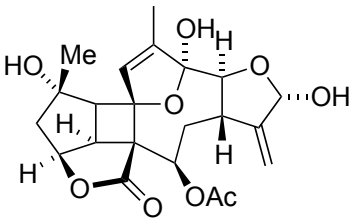
Figure 1.4 Selected members of the furanocembranoids with complex polycyclic carbon skeleton.

For coralloidolide C (**I-7**), our group published a total synthesis in 2010.[10] Bielschowskysin (**I-11**) and intricarene (**I-10**) will be discussed in more detail in the following chapters.

1.2 Studies Towards the Total Synthesis of Bielschowskysin

1.2.1 The Furanocembranoid Bielschowskysin - Background

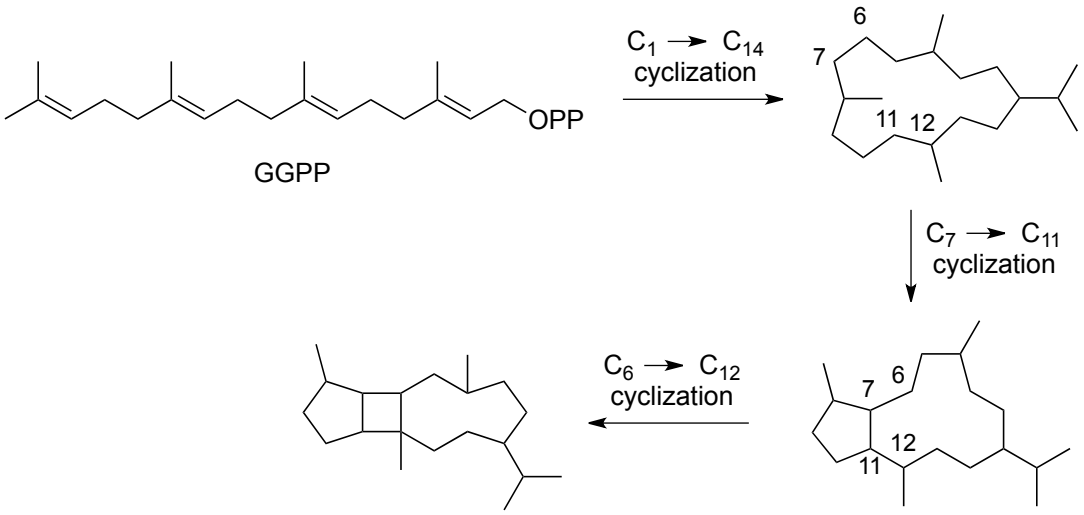
The furanocembranoid bielschowskysin (**I-11**) (Figure 1.5) was first isolated in 2004 from the gorgonian octocoral *Pseudopterogorgia kallos* by Rodríguez and coworkers. This coral was discovered in 1918 by Bielschowsky, giving the molecule its name. This diterpene exhibits a highly oxygenated hexacyclic structure with eleven stereogenic centers. A previously undescribed tricyclo[9.3.0.$0^{2,10}$]tetradecane ring system forms the carbon skeleton. The [5-4-9] ring architecture discloses a new class of regular diterpenes. Spectroscopic analysis as well as X-ray diffraction proved the identity of this molecule.[16]



bielschowskysin (**I-11**)

Figure 1.5 Structure of the hexacyclic furanocembranoid bielschowskysin (**I-11**).

Together with bielschowskysin (**I-11**) a wide range of other furanocembranoids was isolated from the same coral, which leads to the assumption that bielschowskysin (**I-11**) is a modification of an existing metabolite. Therefore the biosynthesis of bielschowskysin (**I-11**), comparable to all other furanocembranoids, starts most likely from geranyl-geranyl-diphosphate (GGPP), which is cyclized to the 14-membered cembrane macrocycle. Formation of a C – C bond between C-7 and C-11 results in the verrilane skeleton and finally in the bielschowskyane skeleton by C-C bond formation between C-6 and C-12. Further oxidation yield bielschowskysin (**I-11**) (Scheme 1.2).[16]

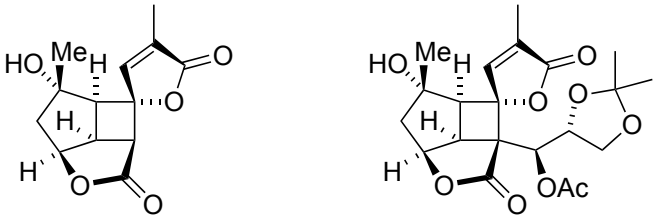


Scheme 1.2 Proposed biosynthesis for the skeleton of bielschowskysin (**I-11**) starting from GGPP.[16]

Beside its unique and complex structure, also the biological activity of this molecule attracted attention. Bielschowskysin (**I-11**) shows antiplasmodial activity (IC_{50} = 10 µg/mL) against *Plasmodium falciparum*, which causes malaria in humans. Furthermore it shows strong and specific *in vitro* cytotoxicity against two cancer cell lines (lung and renal cancer).[16]

A total synthesis of bielschowskysin (**I-11**) would provide material for further biological tests and the yet unknown absolute configuration could be revealed while developing new synthetic strategies.

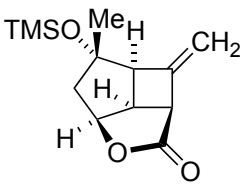
Motivated by these facts several groups embarked on a total synthesis of this molecule. The first to mention were Sulikowski and coworkers who published the synthesis of the tetracyclic core **I-12** *via* a stereoselective intramolecular [2+2] cycloaddition in 2006,[17] displayed in Figure 1.6 left. In 2013 the group was able to introduce the quartenary center C-12 and the neighboring stereocenter C-13 leading to **I-13**,[18] displayed in Figure 1.6 right.



I-12 **I-13**

Figure 1.6 Advanced intermediates *en* route to bielschowskysin (**I-11**), published by Sulikowski and coworkers.[17,18]

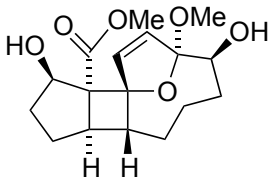
In 2009 Lear and coworkers achieved the formation of the cyclobutane ring, embedded in the tricyclic core **I-14**, by a [2+2] photocycloaddition.[19] The same group published studies towards the macrocyclization of the bielschowskysin core in 2013.[20]



I-14

Figure 1.7 Tricyclic system *en* route to bielschowskysin (**I-11**), synthesized by Lear and coworkers.[19]

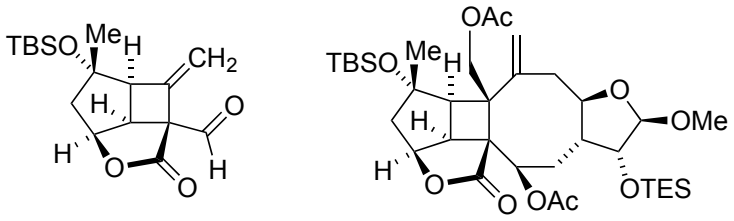
In 2011 Nicolaou and coworkers were able to make large progress with the synthesis of the 14-membered carbocyclic system of bielschowskysin cyclizing the precursor *via* a [2+2] photocycloaddition to the displayed molecule **I-15**.[21]



I-15

Figure 1.8 Functionalized 14-membered carbocyclic system *en* route to bielschowskysin (**I-11**), synthesized by Nicolaou and coworkers.[21]

Mulzer and coworkers were able to synthesize the tricyclic core **I-16** including the cyclobutane ring and the quartenary center C-12 in a non-photochemical way in 2012 (Figure 1.9 left).[22] Furthermore, they synthesized an advanced tetracyclic intermediate (**I-17**) of bielschowskysin using a palladium catalyzed carbo oxygenation for the macrocyclization. This intermediate also features the cyclobutane ring fused to the five membered ring, the quarternary C-12 center, the stereocenter at C-13 and the functionalized γ-lactol (Figure 1.9 right).[23,24]



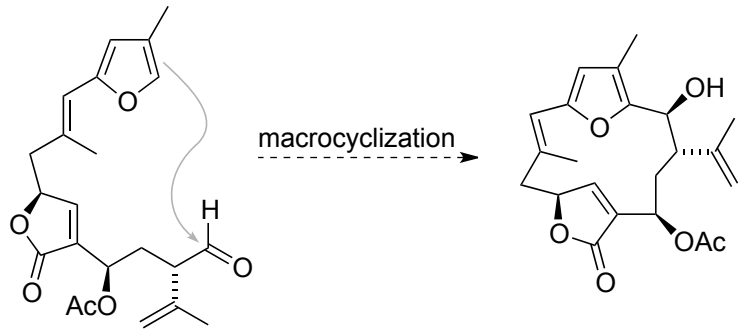
I-16 **I-17**

Figure 1.9: Synthesized intermediates *en* route to bielschowskysin (**I-11**) by Mulzer and coworkers.[22-24]

Several other groups made progress towards the total synthesis of bielschowskysin, for example Stoltz[25] and Ghosh.[26]

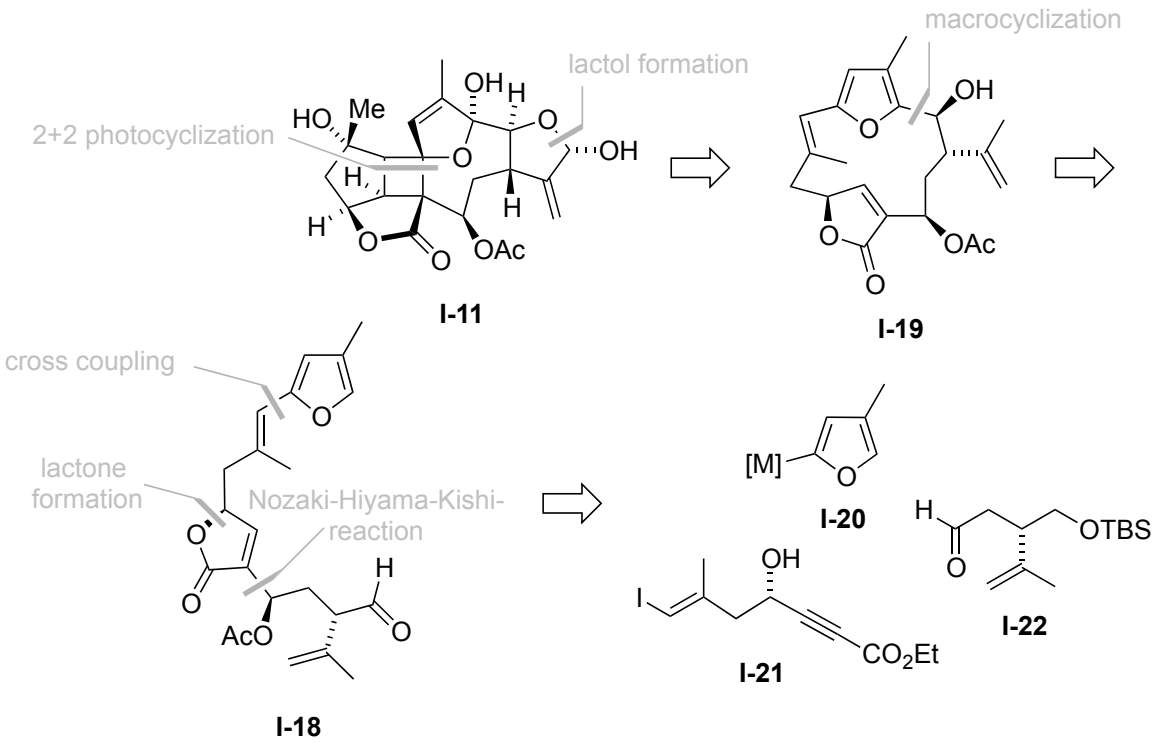
1.2.2 Goal, Retrosynthetic Analysis and Strategy

In our planned synthesis of bielschowskysin (**I-11**) the high nucleophilicity of 3-methyl furans was envisaged to play a key role.[27] The 14-membered cycle, which is the basic skeleton of all furanocembranoids, should be formed in a Friedel-Crafts macrocyclization taking advantage of this reactivity. Scheme 1.3 shows the planned macrocyclization step from **I-18** to the 14-membered carbocycle **I-19**.



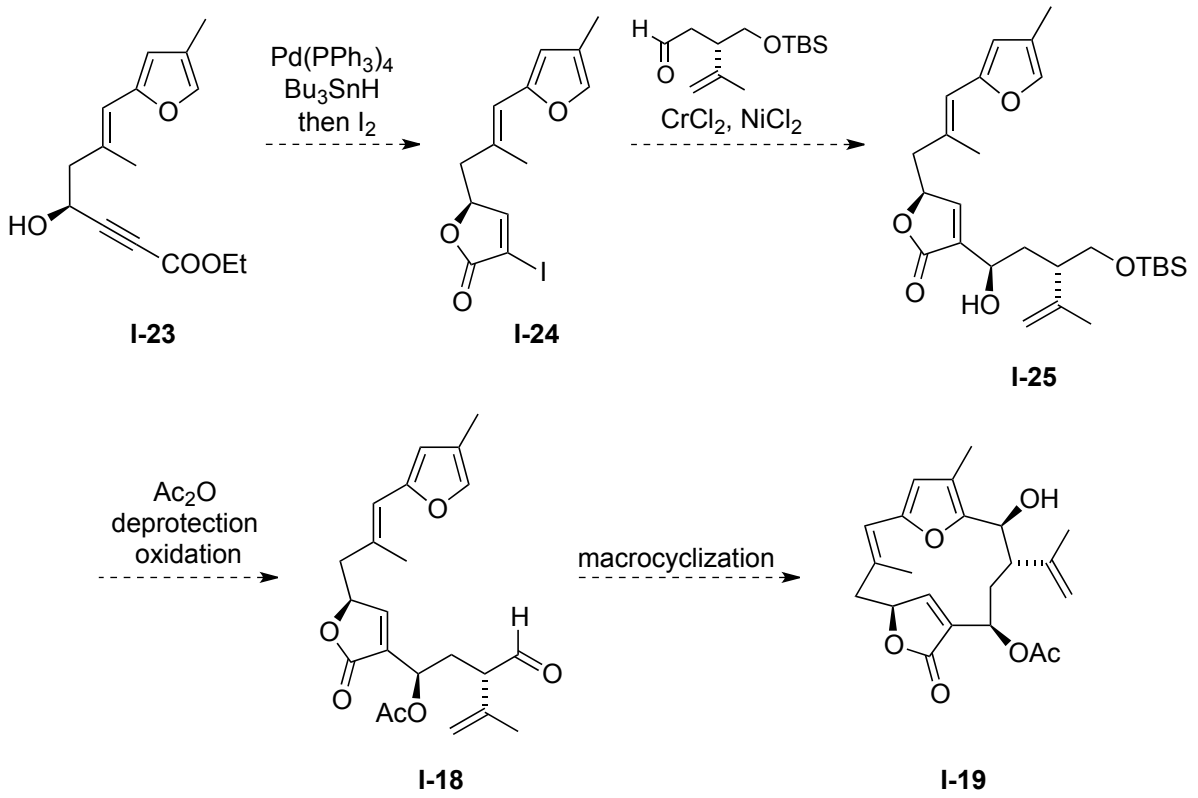
Scheme 1.3 Envisaged macrocyclization step in the planned total synthesis of bielschowskysin.

This leads to the retrosynthesis presented in Scheme 1.4. The natural product should be completed with the photochemical [2+2] cycloaddition to form the cyclobutane ring. The lactol of the eastern part should be formed by allylic oxidation. This dissection leads to the 14-membered macrocycle **I-19**, which is formed by the mentioned nucleophilic attack of a furan on an aldehyde. Precursor **I-18** should be accessible from three building blocks: a furan with an unsubstituted C-2 position (**I-20**), a vinyl iodide with an alkyne appropriate for a lactonisation (**I-21**) and aldehyde **I-22**. The furan **I-20** and the vinyl iodide **I-21** should be coupled in a cross coupling reaction, while the aldehyde chain is meant to be attached in a Nozaki-Hiyama-Kishi reaction.



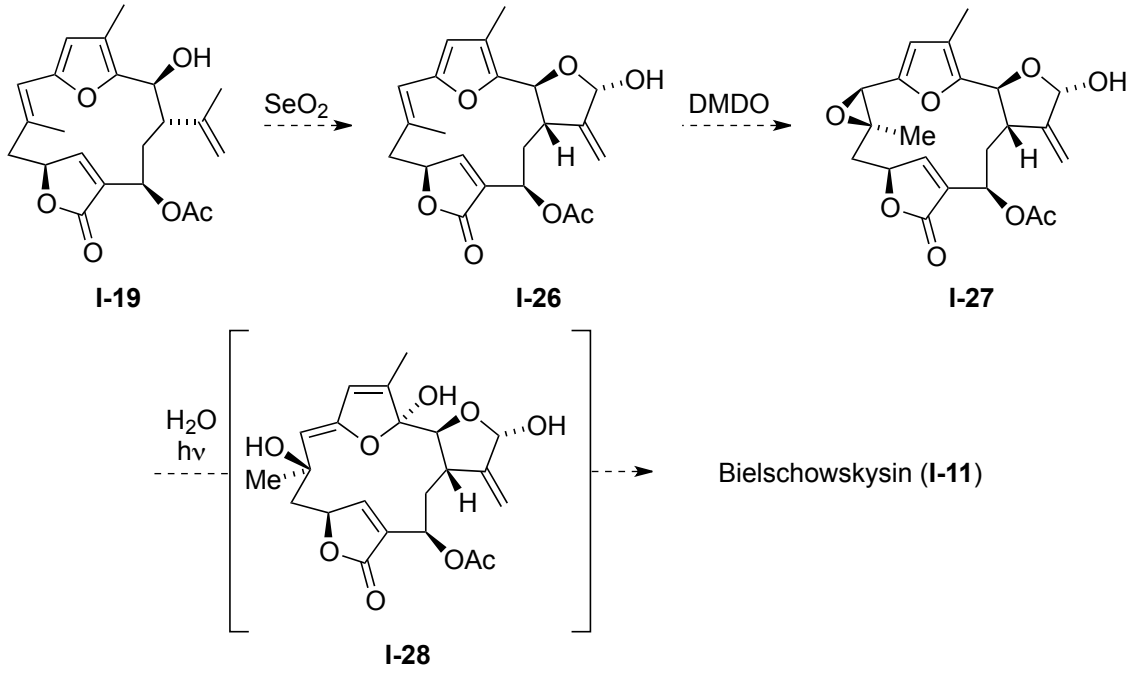
Scheme 1.4 Retrosynthetic overview of the planned total synthesis of bielschowskyin (**I-11**).

A detailed synthesis starting in the forward sense from the coupling product of the furan **I-20** and the vinyl iodide **I-21** is presented in Scheme 1.5. Formation of lactone **I-24** should be achieved by a Pd-catalyzed hydrostannylation,[28] with the remaining stannyl moiety being replaced by iodine.[29] In a stereoselective Nozaki-Hiyama-Kishi reaction the side chain **I-22** should be attached to the lactone **I-24** to result insecondary alcohol **I-25**.[30] An undesired stereochemical outcome of this alcohol could be corrected by an oxidation/reduction sequence. Acetylation and a deprotection/oxidation sequence should result in macrocyclization precursor **I-18**.



Scheme 1.5 Planned forward synthesis towards the 14-membered carbocycle **I-19**.

The envisaged synthetic end game is shown in Scheme 1.6: Functionalized lactole **I-26** should be formed in an allylic oxidation using SeO_2.[31] Epoxidation should install the missing tertiary alcohol. Irradiation and simultaneous attack of water should result in the natural product **I-11** *via* **I-28** in a biomimetic fashion.



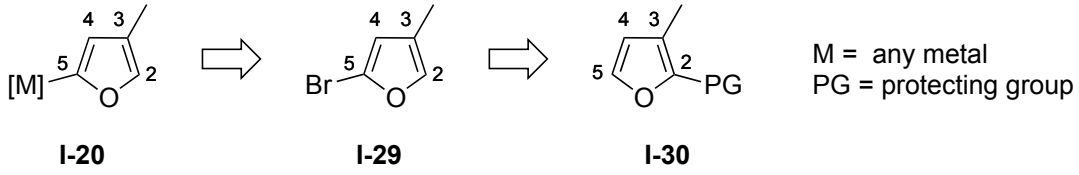
Scheme 1.6 Planned endgame for the synthesis of bielschowskysin (**I-11**).

1.2.3 Results and Discussion

In this chapter the syntheses of the desired building blocks are presented, as well as attempts towards their combination.

a) Furan building block[1]

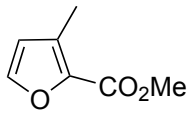
The goal was to synthesize a furan building block **I-20** bearing a methyl group at C-3, further C-2 should be unsubstituted and C-5 bearing a metal, like tin, which could be made from the corresponding bromide **I-29**. Since bromination of 3-methylfuran favors C-2 and not C-5,[32] C-2 has to be substituted by a removable protecting group like in structure **I-30** (Scheme 1.7).



Scheme 1.7 Retrosynthetic overview for the synthesis of furan building block (**I-20**).

[1] Parts of this chapter are also found in the bachelor thesis of Michael Stadlmeier.

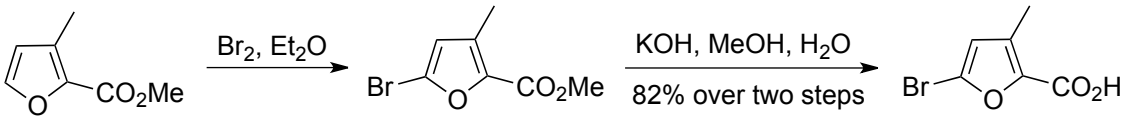
Methyl-3-methyl-2-furoate (**I-31**) (Figure 1.10) was chosen as the appropiate starting material for this reaction sequence, as ester hydrolysis and decarboxylation of this compound are known in literature.[33-35]



I-31

Figure 1.10 Methyl-3-methyl-2-furoate (**I-31**).

The synthesis started with bromination of compound **I-31**.[34] This resulted in the volatile bromofuran **I-32**, which had to be directly hydrolyzed in the next step to yield **I-33** (Scheme 1.8).[33-35]

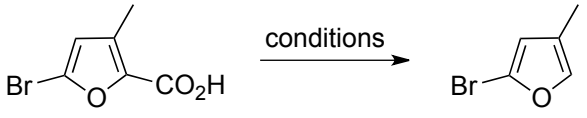


I-31 **I-32** **I-33**

Scheme 1.8 Bromination and ester hydrolysis of **I-31** to yield the decarboxylation precursor **I-33**.

For the decarboxylation step, several conditions were tested (Table 1.1). In a reaction using quinoline and copper at 260 °C [33-35] (bulb to bulb distillation apparatus) full conversion to the desired product was observed, but separation from the solvent proved to be problematic (Entry 1). Neither extraction nor distillation gave clean product. Column chromatography with pentane gave the product in poor yield (15%). A solvent-free reaction with copper lead to decomposition at 160 °C (Entry 2). The product was obtained neither with Ag_2CO_3 in DMSO and acetic acid (Entry 3) nor with Cu_2O in NMP and 1,10-phenanthroline (Entry 4).

Table 1.1 Tested decarboxylation conditions in order to synthesize **I-29**.

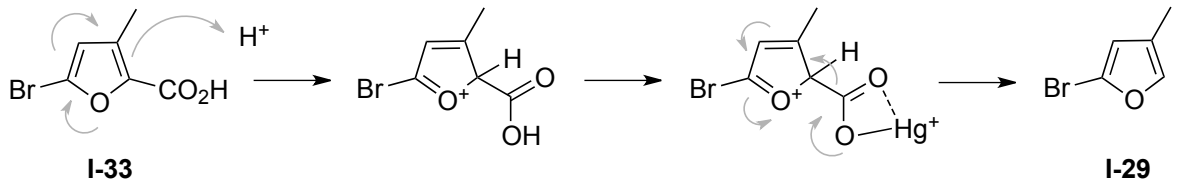


I-33 **I-29**

Entry	conditions	observation
1	Cu, quinoline, 260 °C (bulb to bulb distillation)	separation from quinolin complicated, full conversion, 15% product isolated
2	Cu, 160 °C	dec.
3	Ag_2CO_3, DMSO, AcOH	s.m.
4	Cu_2O with NMP and 1,10-phenanthroline	s.m.
5	$HgCl_2$, H_2O, 100 °C	27% product
6	$HgCl_2$, H_2O, MeOH, 100 °C	40% product
7	$HgCl_2$, H_2O, HCl, 100 °C	44% product

dec. = decomposition, s.m. = starting material

The yield could be improved by heating **I-33** with $HgCl_2$ in H_2O at 100 °C and careful distillation of the product from the aqueous phase.[36,37] Without any further additives the maximum yield of isolated product was 27% yield (Entry 5). Adding 25 vol% of methanol to the reaction the yield could be improved to 40% (Entry 6). The addition of 7 vol% conc. HCl improved the yield to 44% (Entry 7). The reason therefor might be that HCl assists protonation of the furan during the decarboxylation, as can be seen from the mechanism (Scheme 1.9).

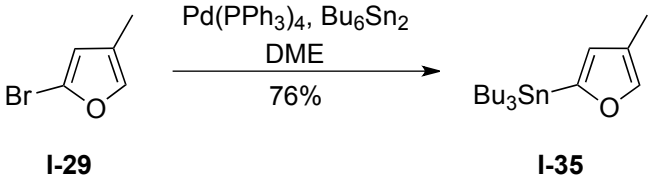


I-33 **I-29**

Scheme 1.9 Mechanism for the Hg(II) assisted decarboxylation of bromofuran **I-33**.

The highly volatile product **I-34** decomposed easily and had to be stored in diethylether at −20 °C. As an potentially appropriate metal for the following cross coupling tin was chosen. Therefore the brominated compound **I-29** had to be converted into its stannylated version. Reaction using *n*-BuLi

and $SnBu_3Cl$ failed, while Stille-Kelly-reaction using Bu_6Sn_2 and $Pd(PPh_3)_4$ yielded the product **I-35** (Scheme 1.10). Purification was possible using basic Al_2O_3, whereas the use of silica lead to proto-de-stannylation. The product decomposed after several days at low temperature and therefore was stored in diethylether at −20 °C.

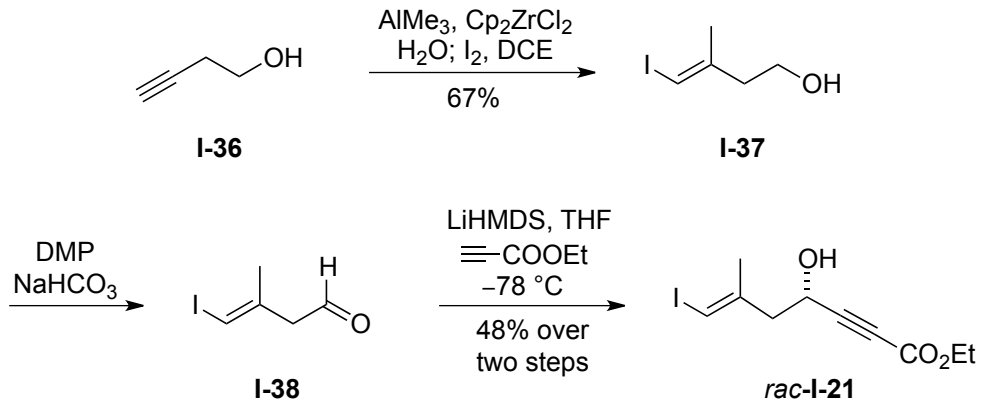


I-29 **I-35**

Scheme 1.10 Stille-Kelly reaction affording stannylated furane **I-35**.

b) Vinyl iodide building block

Vinyl iodide **I-21** as the coupling partner for the furan building block was synthesized starting from 3-butynol (**I-36**) (Scheme 1.11). The vinyl iodide **I-37** was formed in a carboalumination reaction.[38-40] Oxidation with DMP to **I-38** and subsequent attack of deprotonated ethyl propiolate resulted in the desired building block **I-21**.[7,41] For preliminary reactivity screening, the synthesis was first conducted in a racemic way. Later on the reaction is meant to be conducted in an enantioselective way using (*S*)-alpine borane in a stereoselective reduction (known for the *Z*-isomer).[9]

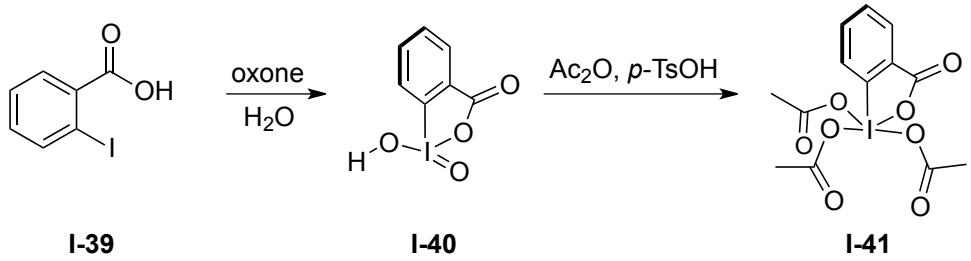


I-36 **I-37** **I-38** ***rac*-I-21**

Scheme 1.11 Racemic synthesis of vinyl iodide bulding block **I-21**.

c) The crystal structure of Dess-Martin-Periodinane (**I-41**)[2]

In the course of preparation of the oxidant DMP (**I-41**) (necessary for the above mentioned reaction) starting from 3-iodobenzoic acid (**I-39**) *via* IBX (**I-40**) (Scheme 1.12)[42,43] a crystal structure of Dess-Martin-periodinane (**I-41**) was obtained (Figure 1.11).[44]



Scheme 1.12 Preparation of DMP (**I-41**) starting from 3-iodobenzoic acid (**I-39**) *via* IBX (**I-40**).

Crystals suitable for X-ray crystallography were obtained by slow evaporation of the filtrate under a constant stream of nitrogen at ambient temperature over the course of four days.

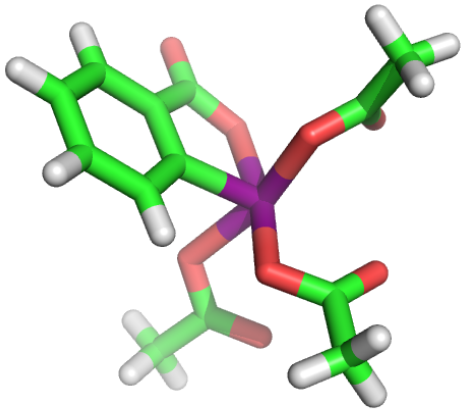


Figure 1.11 Obtained crystal structure of DMP (**I-41**).

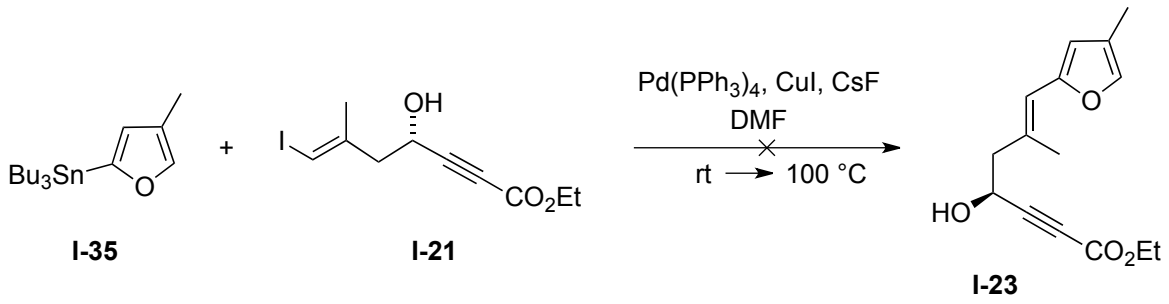
A crystal structure of DMP was not known before. A reason for this can be that the reagent precipitates as a microcrystalline powder, which complicates the growth of crystals suitable for X-ray crystallography. In this obtained crystal structure (Figure 1.11) it can be clearly seen that all acetoxy groups are bound in a covalent η-1 fashion to the iodine, showing typical O-I bond lengths: 2.0656(13) Å, 2.0670(13) Å and 2.1141(13) Å).[45] The central iodine atom resides in a distorted octahedral environment. Oxygen atoms occupy the equatorial positions, whereas the phenyl ring and

[2] This chapter can also be found in the thesis of Albert Schröckeneder, LMU München.

the lone pair occupy the apical positions. Steric demand of the electron pair pushes the acetoxy substituents toward the phenyl ring so that the iodine atom lies 0.315(1) Å below a plane formed by the oxygens. In the supramolecular structure it is observable that one unit cell consists of a centrosymmetric dimer, which is held together by intermolecular halogen bonds between the iodine and a carbonyl group of the second molecule. The intermolecular iodine-oxygen distance of 3.3 Å is below the sum of the van der Waals radii (3.46 Å)[46] and also the angles are consistent with typical halogen bonds.[47] Hydrogen bonds stabilize the dimeric structure. All together these intermolecular interactions explain the high crystallinity of DMP (**I-41**). This crystal structure could serve as a starting point for detailed quantum chemical calculations comprising the mechanism of the DMP oxidation.[44]

d) Coupling of the building blocks

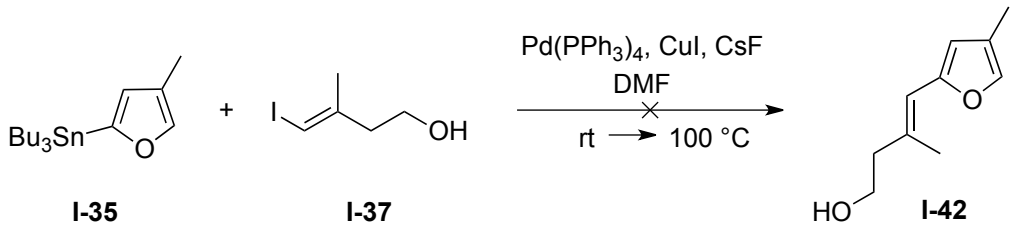
The stannylated furan building block **I-35** was envisaged to be coupled to the vinyl iodide building block **I-21** employing transition metal catalyzed coupling conditions. A Stille coupling using $Pd(PPh_3)_4$, CuI and CsF in DMF at temperatures up to 100 °C did not give any of the desired product (Scheme 1.13).



I-35 **I-21** **I-23**

Scheme 1.13 Unsuccessful Stille coupling between furan building block **I-35** and vinyl iodide **I-21**.

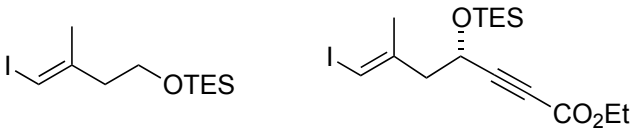
Using vinyl iodide precursor **I-37** as a coupling partner did not result in a coupling product either (Scheme 1.14).



I-35 **I-37** **I-42**

Scheme 1.14 Failed Stille coupling between furan building block **I-35** and alcohol **I-37**.

In addition, Stille reaction of *O*-TES protected vinyl iodides **I-43** and **I-44** (Figure 1.12) with **I-35** did not result in coupling products, either.



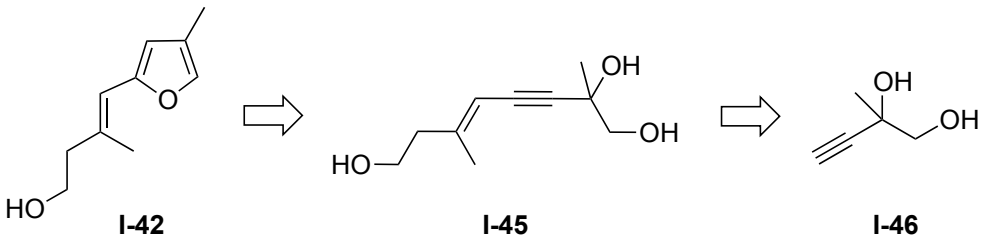
I-43 **I-44**

Figure 1.12 *O*-TES protected building blocks **I-43** and **I-44**.

As an alternative cross coupling reaction, Negishi conditions were considered. To this end, there were attempts to convert 2-bromo-3-methlyfuran (**I-29**) into its zincated congener by direct insertion of Zn into the C-Br bond in presence of LiCl in THF. Further, TMSCl and 1,2-dibromoethane were used as additives to increase the reactivity of zink. Direct cross coupling of the *in situ* formed zink species to the *O*-TES vinyl iodide **I-43** however did not result in the desired coupling product (not depicted). For a potential Suzuki coupling, the corresponding boron furan was synthesized from 2-bromo-3-methylfuran (**I-29**) using bis(pinacolato)diboran, KOAc and Pd(dppf)Cl_2. This boron species was presumably formed according to TLC analysis but it was not stable upon purification (not depicted).

d) Alternative route

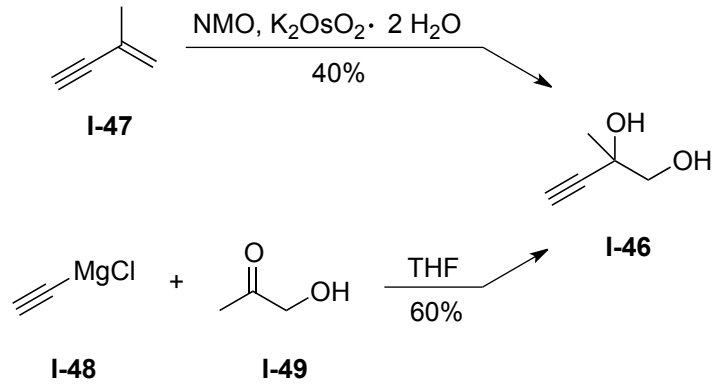
In order to avoid cross coupling between synthesized vinyl iodides (**I-21**, **I-37**, **I-43**, **I-44**) and furan **I-35**, another strategy was envisaged wherein the critical bond is already constructed before the furan is formed. This leads to the following retrosynthesis (Scheme 1.15). The desired furan is formed in a silver mediated furan cyclization reaction from alkyne **I-45**, which in turn can be made from 2-methylbut-3-yne-1,2-diol (**I-46**).



I-42 **I-45** **I-46**

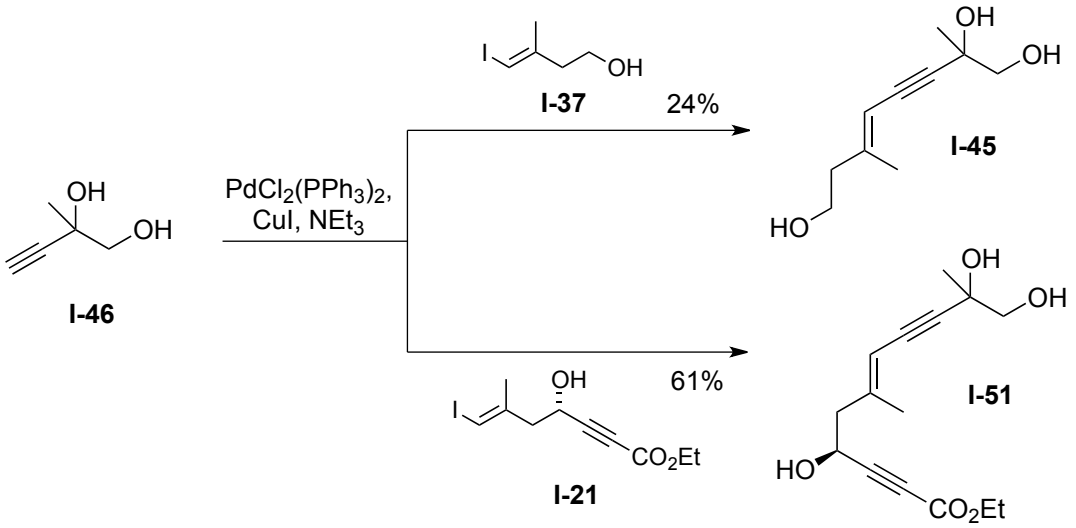
Scheme 1.15 Alternative retrosynthesis for the formation of the functionalized furan (**I-42**).

2-Methylbut-3-yne-1,2-diol (**I-46**) was synthesized using two different protocols, either dihydroxylation conditions [48] or a Grignard reaction (Scheme 1.16).



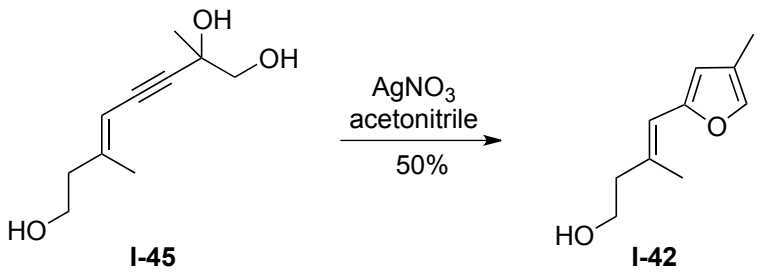
Scheme 1.16 Two possible ways for the synthesis of 2-methylbut-3-yne-1,2-diol (**I-46**).

Synthesized 2-Methylbut-3-yne-1,2-diol (**I-46**) was coupled to both vinyl iodides **I-21** and **I-37** using Sonogashira conditions,[49] displayed in Scheme 1.17.



Scheme 1.17 Sonogashira reactions to afford cyclization precursors **I-45** and **I-51**.

The coupling product **I-45** was cyclized with $AgNO_3$ in acetonitrile[50] to the desired furan **I-42**, while coupling product **I-51** did not yield the desired furan even using different silver salts in various solvents.



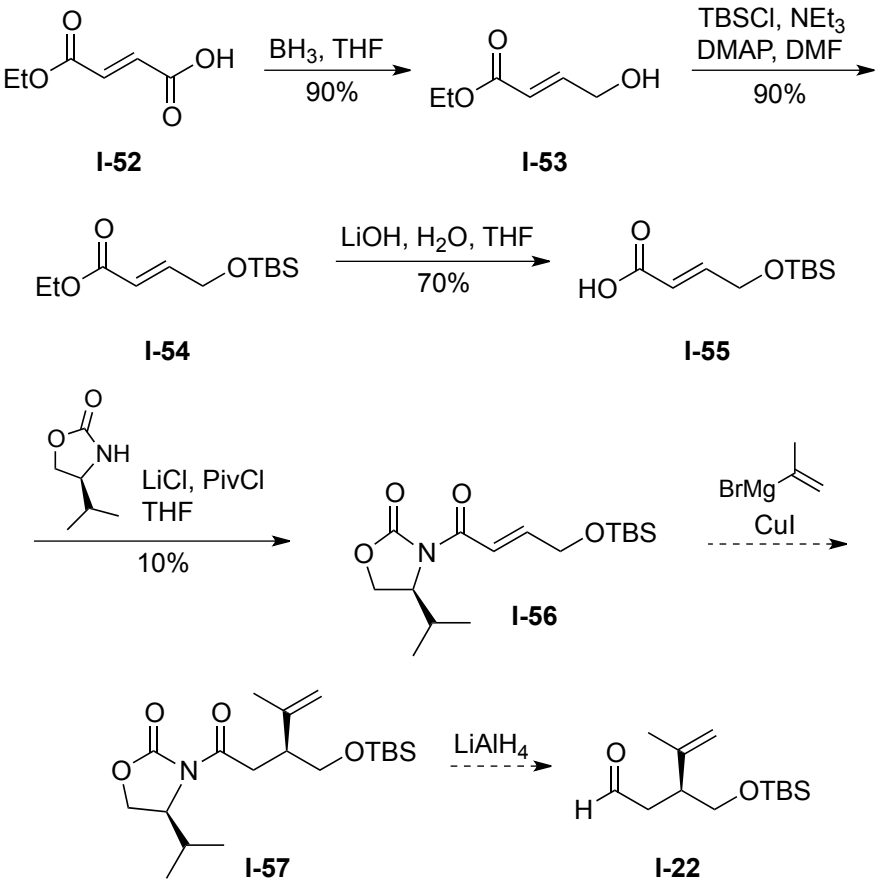
I-45 **I-42**

Figure 1.13 Ag(I) mediated cyclization to furan **I-42**.

Oxidation and subsequent attack of deprotonated alkyne did not result in product formation. During conducted synthetic steps all C-5-unsubtituted furans behaved very unstable and lead to decomposition under all applied reaction conditions. Therefore, it was decided to stop the strategy at this point and consider another synthetic route to the natural product bielschowskysin.

e) Aldehyde chain

For the sake of integrity, undertaken synthetic efforts towards the aldehyde chain will be presented shortly (Scheme 1.18). Starting from mono ethyl fumarate (**I-52**), which was reduced to the corresponding allylic alcohol **I-53** with borane in THF and then protected using TBSCl, **I-54** was afforded.[51] The hydrolyzed ester **I-55** allows the installation of the Evans auxiliary to yield **I-56**. The product was then envisaged to react in a 1,4-cuprate addition with isopropenyl cuprate to **I-57**. Reductive cleavage of the auxiliary should finalize the synthesis of building block **I-22**.[52] Intermediates **I-55** and **I-56** were only identified by mass spectrometry.



Scheme 1.18 Synthesis and planned synthesis of side chain **I-22**.

1.2.4 Conclusion and Outlook

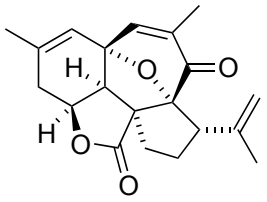
In this chapter the natural product bielschowskysin (**I-11**) is introduced. Strategies from other groups towards the synthesis of this furanocembranoid are explained as well as our synthetic plan, which implies a nucleophilic attack from a furan as a keystep, is presented. The synthetic studies towards bielschowskysin (**I-11**) start from three different building blocks: a furan building block **I-20**, a vinyl iodide **I-21** and an aldehyde chain **I-22**. The furan building block **I-20** and the vinyl iodide building block **I-21** were successfully synthesized. However, they could not be coupled so far. Another approach at which the critical bond between the furan and vinyl residue is installed before the furan is formed, did not yield the desired final building block. Due to the instability of the C-5 unsubstituted furan, which was inevitable for the key step, this strategy was abandoned and alternative synthetic strategies will be explored, where the macrocycle is not formed *via* a nucleophilic attack of the unsubstituted furan. Thinkable are strategies similar to the bipinnatin J (**I-1**) synthesis (cf. chapter 1.3.2), where the macrocycle is formed in a Nozaki-Hiyama-Kishi reaction or non-biomimetic ways,

where the cyclobutane ring is formed in an earlier step and the missing parts are constructed around the core (cf. methods published by other groups in chapter 1.2.1).

1.3 Photochemical Formation of Intricarene

1.3.1 The Furanocembranoid Intricarene – Background

The furanocembranoid intricarene (**I-10**) (Figure 1.14) was first isolated in 2005 form the gorgonian octocoral *Pseudoperogorgia kallos* by Rodríguez and coworkers.[15]

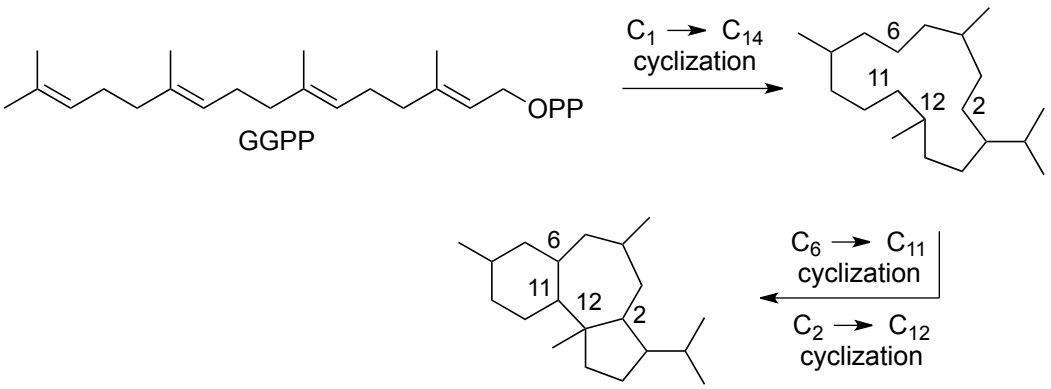


intricarene (**I-10**)

Figure 1.14 Structure of the pentacyclic furanocembranoid intricarene (**I-10**).

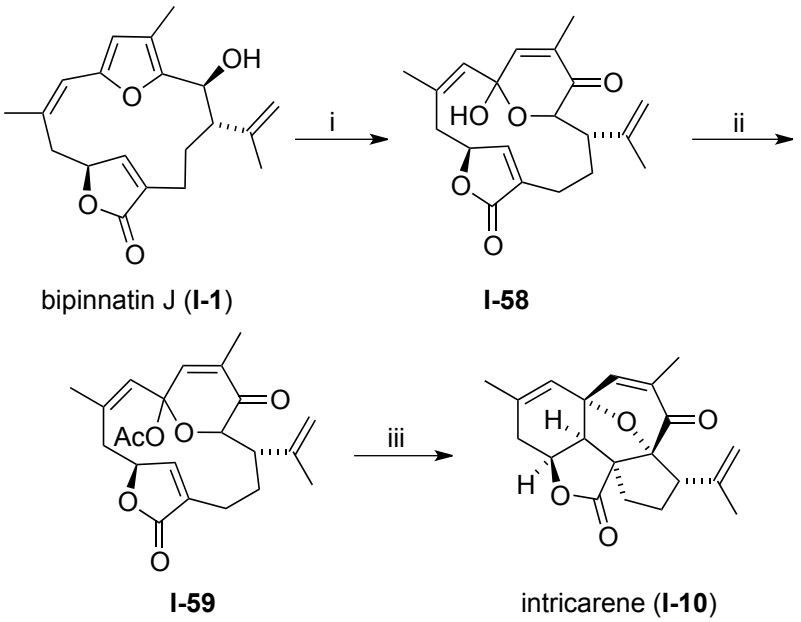
The diterpene shows a pentacyclic carbon skeleton with three spiro centers, which is unprecedented so far in natural products. An oxygen atom bridging the seven membered ring leads to an oxapolycyclic system. Methylation and isopropylation pattern complete the uniqueness of the intricarene skeleton. Spectroscopic analysis as well as X-ray diffraction proved the identity of this molecule. Paucity of the natural product prevented intense biological testing up to date.[15]

Comparable to bielschowskysin (**I-11**) and all other furanocembranoids the biosynthesis of intricarene (**I-10**) commences from geranyl-geranyl-diphosphate (GGPP). C-1 to C-14 cyclization results in the cembrane skeleton where upon sequential bond formations between C-6 and C-11 as well as between C-2 and C-12 yield the intricarane skeleton.[15] Oxidation steps finalize intricarene (Scheme 1.19).



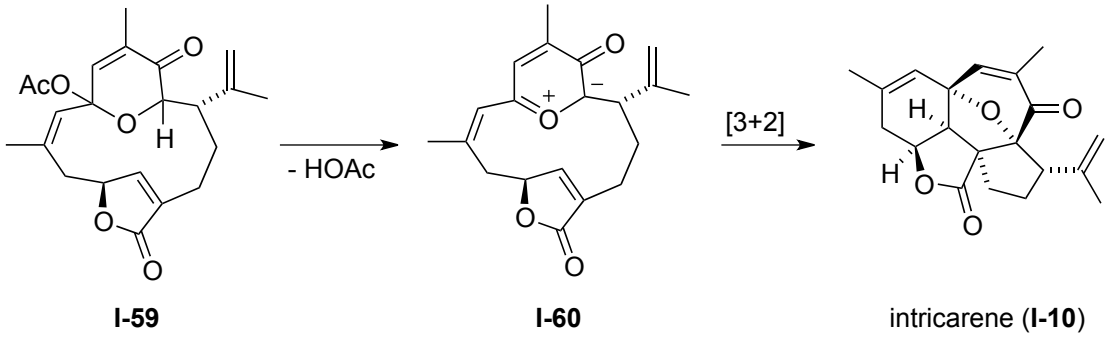
Scheme 1.19 Proposed biosynthesis for the skeleton of intricarene (**I-10**) starting from GGPP.[15]

So far two groups accomplished a total synthesis of intricarene (**I-10**). In 2006 our group as well as the group of Pattenden synthesized intricarene in three steps from its putative biosynthetic precursor bipinnatin J (**I-1**) using harsh conditions (Scheme 1.20).[9,53]



Scheme 1.20 Published total syntheses of intricarene (**I-10**): i = $VO(acac)_2$, *t*-BuOOH (Pattenden), *m*-CPBA (Trauner), ii = Ac_2O, iii = DBU, MeCN, 90 °C (Pattenden), TMP, DMSO, 150 °C (Trauner).

Both syntheses assume that the reaction proceeds *via* a 1,3-dipolar cycloaddition between an oxidopyrilium ion and the unsaturated lactone moiety (Scheme 1.21).



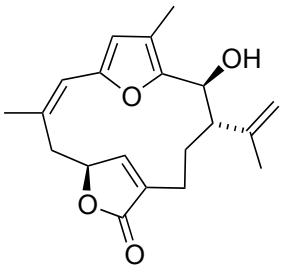
Scheme 1.21 Proposed mechanism for the formation of intricarene *via* an oxidopyrilium ion **I-60**.

Cycloaddition *via* the oxidopyrilium ion (**I-60**) is also the proposed biosynthetic origin for the formation of intricarene (**I-10**).[2,9,53] In 2008 Tantillo and Wang examined this transformation in detail using quantum chemical calculations to predict whether this cycloaddition can occur during the biosynthesis of intricarene. Calculations based on energy differences, suggest that an enzyme is

needed to generate the oxidopyrilium species, whereas subsequent cycloaddition itself can occur without an enzyme.[54] Instead of an enzyme, light could also be a possibility to overcome the high barrier of energy.

1.3.2 The Furanocembranoid Bipinnatin J

As mentioned before, bipinnatin J (**I-1**) (Figure 1.15) is supposedly the biosynthetic precursor of intricarene (**I-10**). It is also assumed to be the precursor for a wide range of other furanocembranoids. [2]

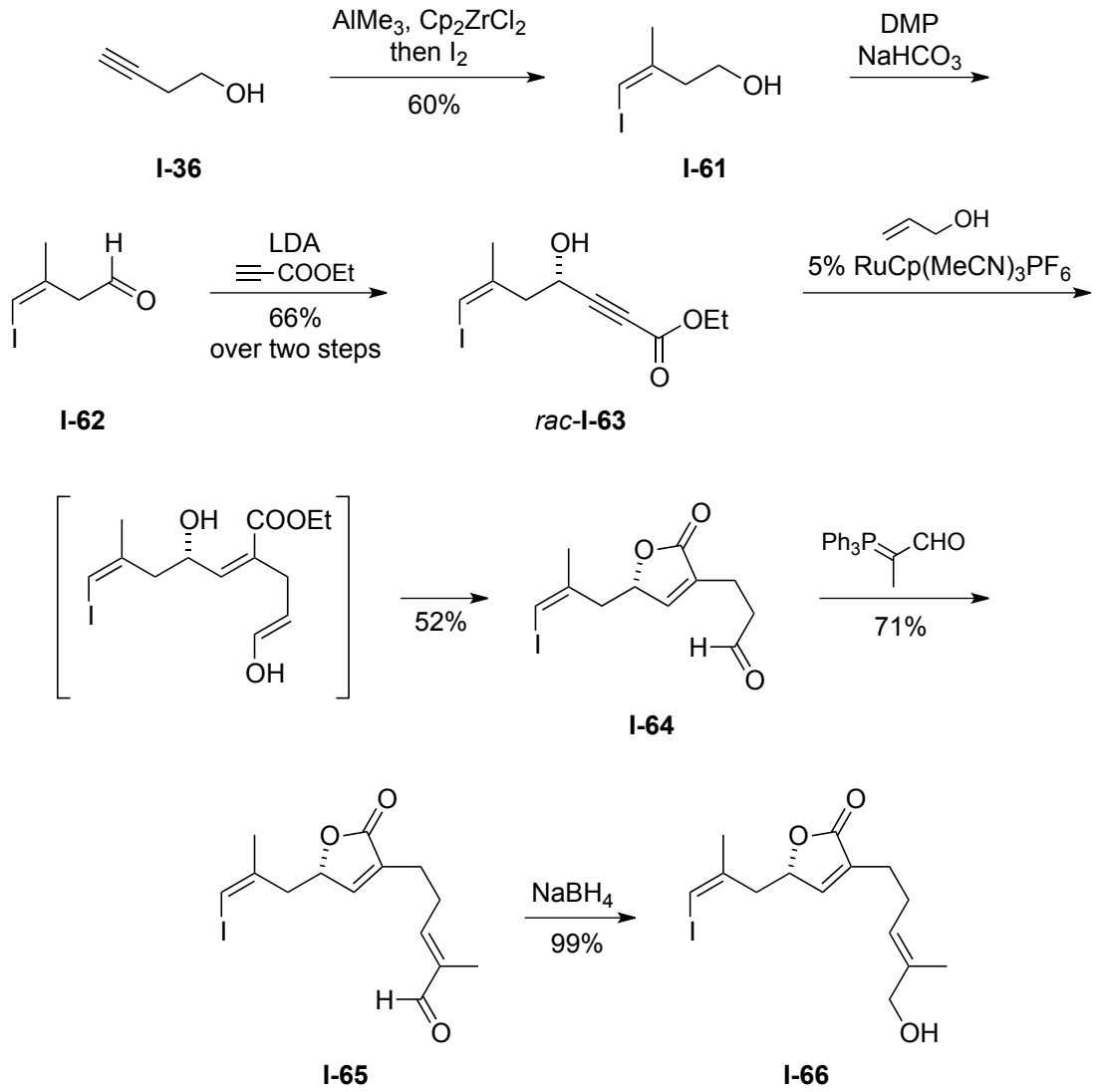


bipinnatin J (**I-1**)

Figure 1.15 Structure of bipinnatin J (**I-10**) – the biosynthetic precursor for a wide range of other furanocembranoids.

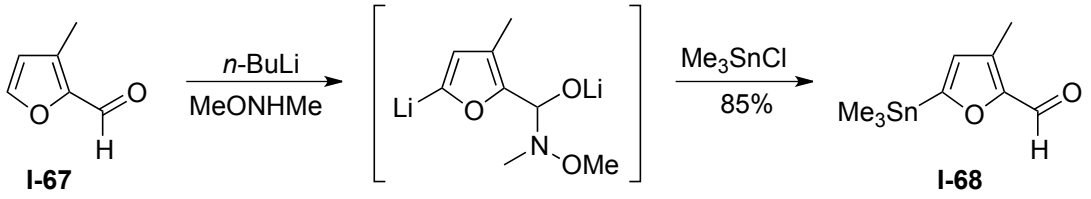
Bipinnatin J (**I-1**) was first isolated in 1998 from *Pseudopterogorgia bipinnata*.[3] Since then, a few total syntheses of this biosynthetic key compound were published. In 2006 our group and the group of Rawal simultaneously reported the first racemic syntheses.[7,8] Later that year our group and the group of Pattenden followed with a stereoselective synthesis of (−)-bipinnatin J.[9,53] In the synthesis of intricarene, which is presented later, bipinnatin J (**I-10**) plays an important role and was synthesized following the route of Roethle and Trauner,[7] which is illustrated in the following paragraph.

As shown in Scheme 1.22, the synthesis commences with commercially available 3-butynol (**I-36**), which reacts in a zirconium-mediated carboalumination with subsequent thermal isomerization and iodination to the (*Z)*-vinyliodide (**I-61**). Oxidation with DMP results in the corresponding aldehyde **I-62**. Addition of lithiated ethyl propiolate, affords propargylic alcohol **I-63**. Next ruthenium(II)-catalyzed Trost enyne reaction with allyl alcohol provides aldehyde **I-64**, which then is submitted to Wittig conditions to yield elongated aldehyde **I-65**. Reduction with $NaBH_4$ gives building block **I-66** being ready for Stille coupling.



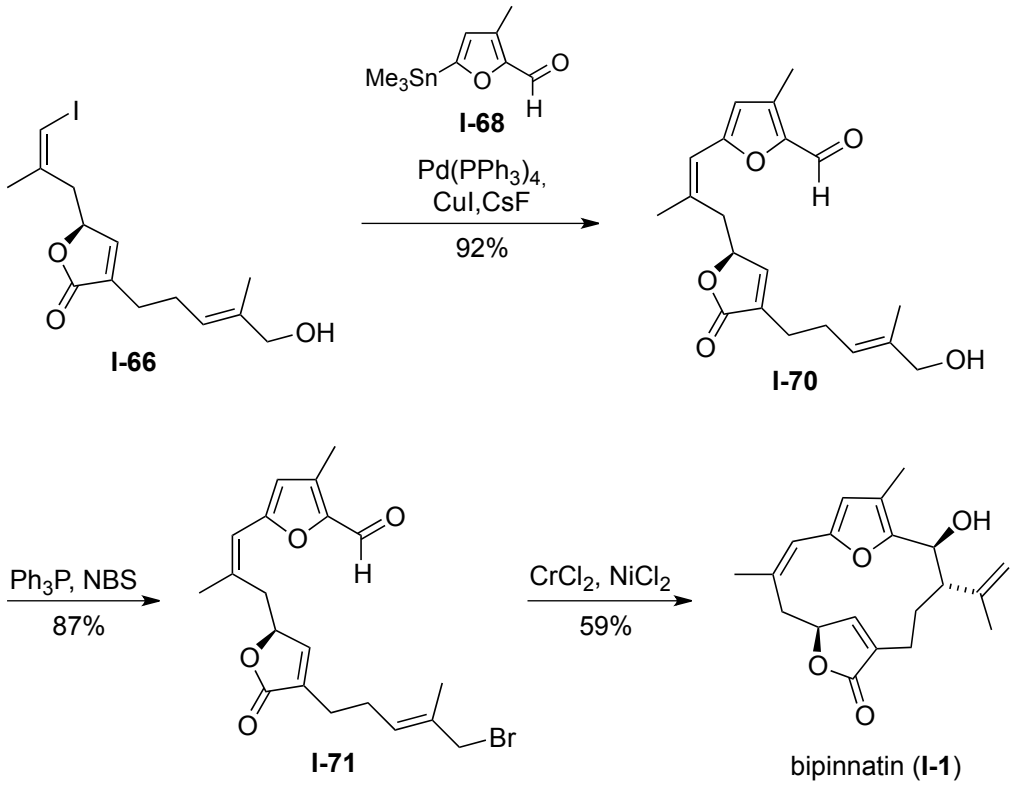
Scheme 1.22 Trauner's synthesis of bipinnatin J (**I-1**) – Part I.

The synthesis of the required furan building block starts from known 3-methylfurfural (**I-67**). *In situ* protection of the aldehyde in form of a lithio-hemiaminal, subsequent deprotonation of the furan and a lithium-tin exchange furnishes the desired stannyl furfural **I-68**, presented in Scheme 1.23.



Scheme 1.23 Trauner's synthesis of bipinnatin J (**I-1**) – Part II.

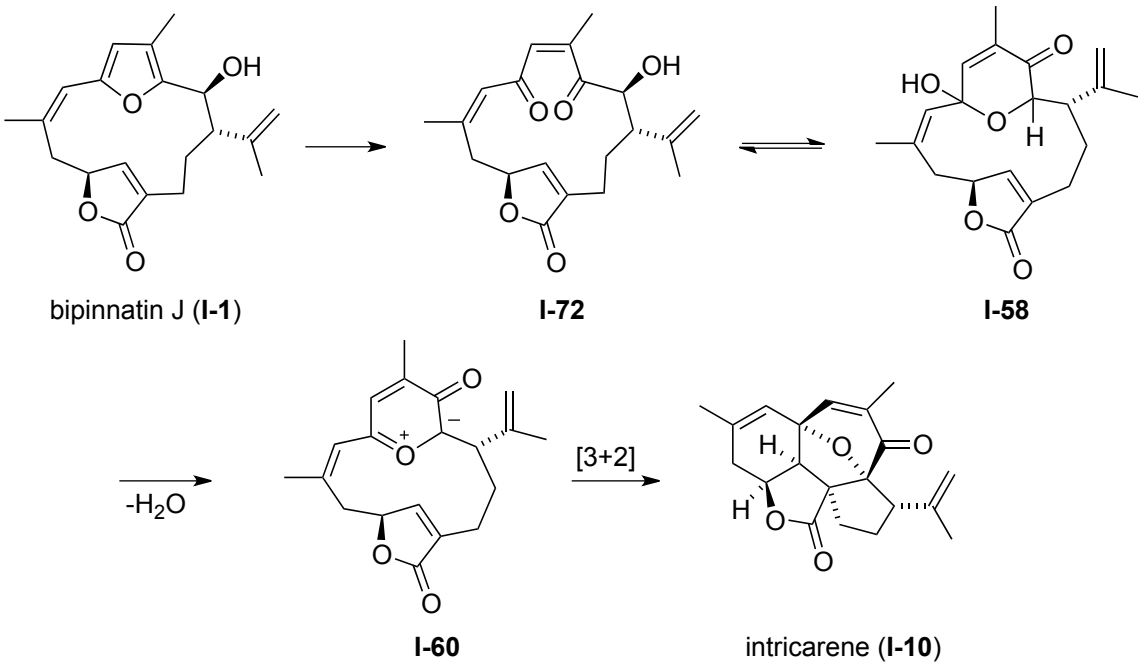
As depicted in Scheme 1.24, the two building blocks **I-66** and **I-68** were coupled using Stille coupling conditions. Allylic alcohol **I-70** was converted into the corresponding bromide **I-71** necessary for the Nozaki-Hiyama-Kishi-reaction. This macrocyclization step finishes the synthesis of the natural product bipinnatin J (**I-1**).



Scheme 1.24 Trauner's synthesis of bipinnatin J (**I-1**) – Part III.

1.3.3 Goal and Strategy

The aim of this project was to convert bipinnatin J (**I-1**) into intricarene (**I-10**) in a biomimetic way using photochemical conditions. This reaction would prove the proposed biosynthetic pathway. It has already been mentioned that the formation of an oxidopyrilium ion is the crucial step. The high barrier of energy of its formation, which was calculated by Tantillo and Wang,[54] is supposed to be overcome by light. This is reasonable for the biosynthetic pathway, since the corals live in shallow water in the Caribbean Sea and are exposed to sunlight.[15]



Scheme 1.25 Biosynthetic proposal for the formation of intricarene.

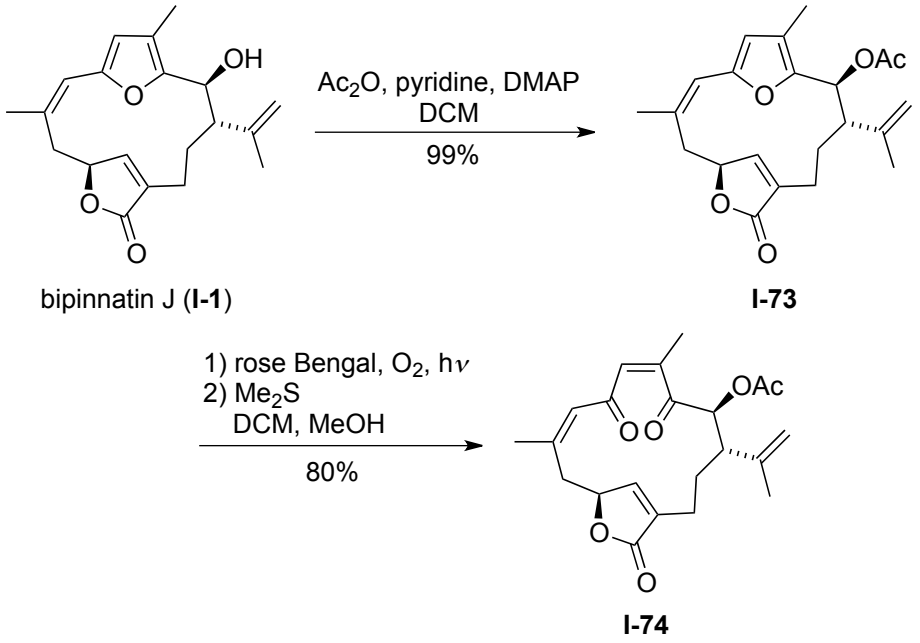
According to the biosynthetic proposal (Scheme 1.25)[9] and as in the already published syntheses of intricarene, bipinnatin J (**I-1**) has to be oxidized before, under loss of water, the formation of the oxidopyrilium ion **I-60** takes place.

1.3.4 Results and Discussion[3]

Bipinnatin J (**I-1**), which was the starting point for this transformation, was prepared using the literature known procedure of Roethle and Trauner (Chapter 1.3.2).[7]

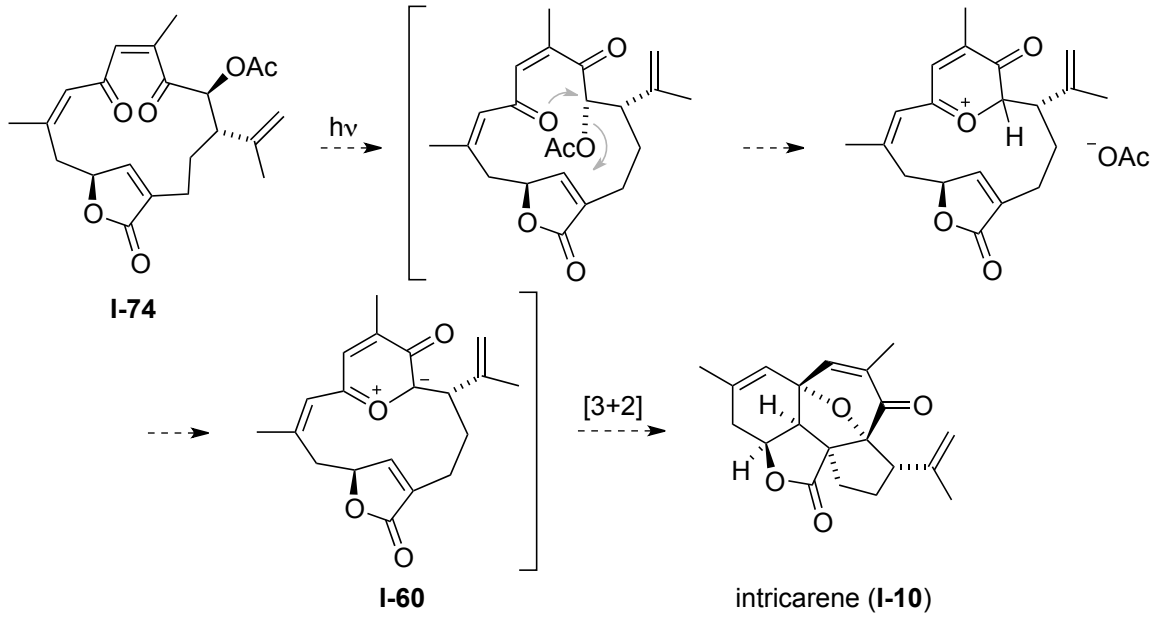
To activate the C-2-hydroxy group, the latter was converted into the acetate **I-73** using acetic anhydride in pyridine (Scheme 1.26). Acetyl-Co enzyme A could be responsible for this acetylation in nature. The oxidation of the furan ring was achieved with singlet oxygen. Singlet oxygen, which was prepared *in situ* from oxygen and light using rose Bengal as a sensitizer, reacted with the furan in a Diels-Alder reaction. Reductive workup with dimethyl sulfide resulted in the desired *O*-acetate-enedione **I-74** (Scheme 1.26).

[3] Parts of this chapter are also found in the thesis of Thomas J. Kimbrough, University of California, Berkely and in the thesis of Patrick Kölle, LMU München.



Scheme 1.26 Acetylation and oxidation of bipinnatin J (**I-1**) resulting in *O*-acetate enedione **I-74**.

In the following step *O*-acetate enedione **I-74** should be irradiated with light forming intricarene *via* an oxidopyrilium ion, illustrated in Scheme 1.27.

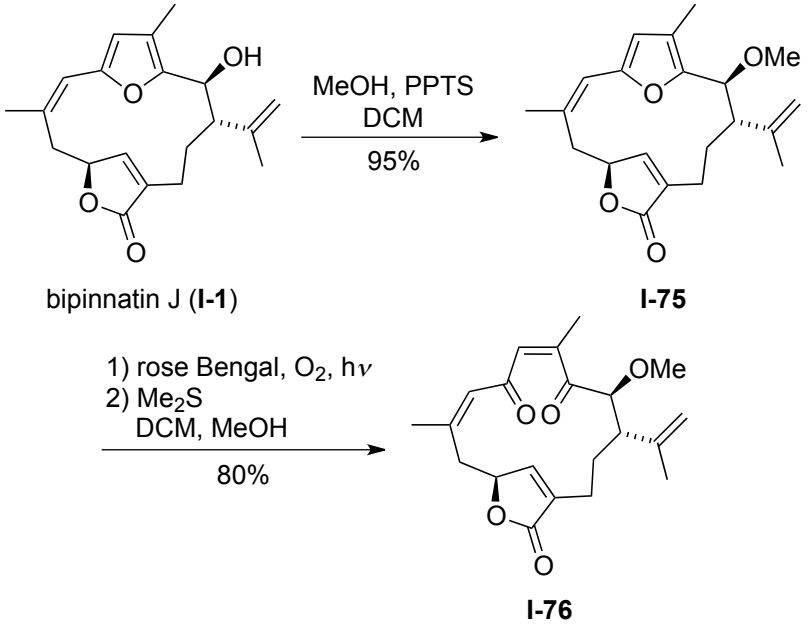


Scheme 1.27 Planned conversion of *O*-acetate enedione **I-74** into intricarene (**I-10**) using photochemical conditions.

O-Acetate-enedione **I-74** was dissolved in deuterated acetone and D_2O in a NMR tube, which was then irradiated for 10 h with a commercially available reptile lamp (T-Rex, nominal power 275 W). No

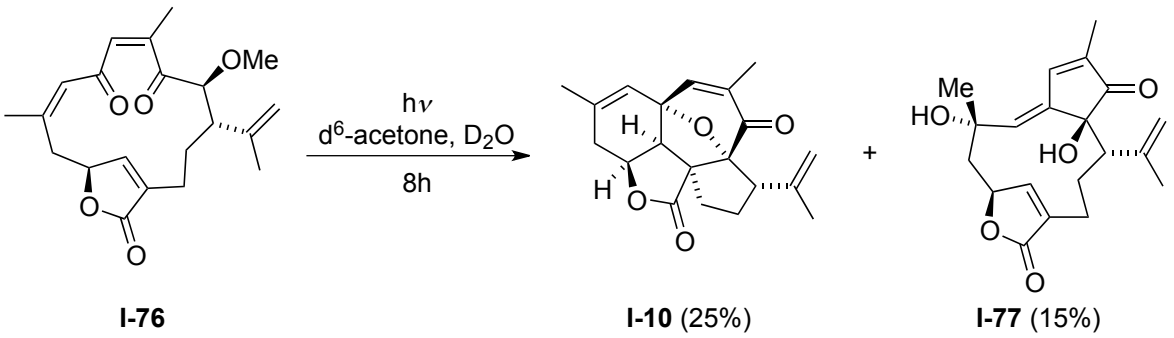
desired product was obtained although different light sources, different reaction vessels and different solvents were tried. Irradiation at the absorption maximum (268 nm) did not give any product, either.[55]

As an alternative starting point bipinnatin J (**I-1**) was treated with methanol under slightly acidic conditions to give *O*-methyl-bipinnatin J **I-75** (Scheme 1.28), a known natural product.[56] We suppose that in nature *S*-adenosylmethionine as an *O*-methyl transferase could be responsible for this methylation. Oxidative ring opening was again achieved using singlet oxygen to result in **I-76** (Scheme 1.28).



Scheme 1.28 Methylation and oxidation of bipinnatin J (**I-1**) resulting in *O*-methyl enedione **I-76**.

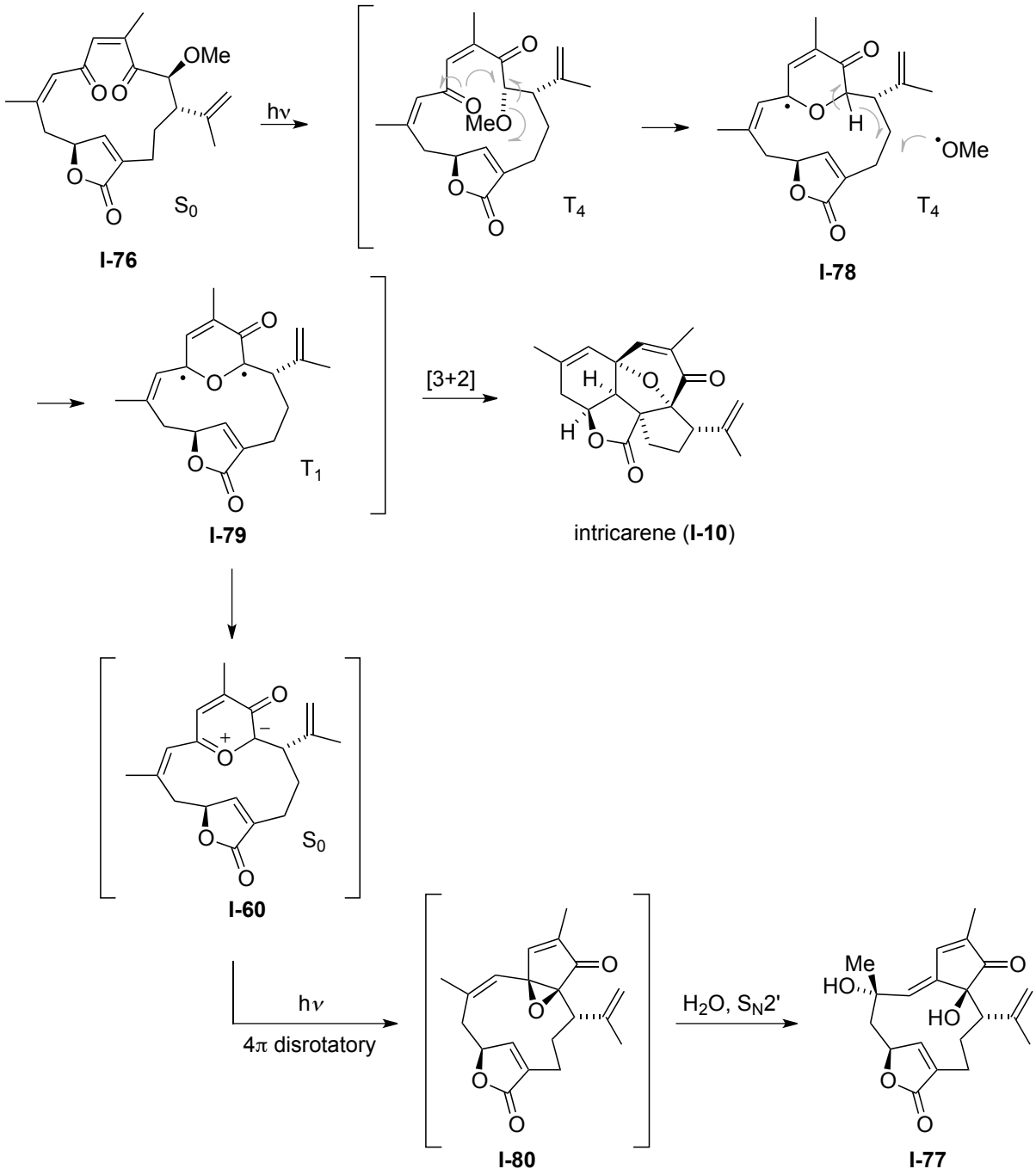
O-Methyl-enedione **I-76** was dissolved in deuterated acetone and D_2O in a NMR tube, which was then irradiated for 8 h with a commercially available reptile lamp (T-Rex, nominal power 275 W). Intricarene (**I-10**) was obtained from this reaction. In addition, another product **I-77** was isolated from the reaction, which is not yet known as a natural product (Scheme 1.29).



I-76 **I-10** (25%) **I-77** (15%)

Scheme 1.29 Photochemical formation of intricarene (**I-10**) and furanocembranoid **I-77**, not yet known as a natural product.

The mechanism for this transformation is shown in Scheme 1.30. Irradiation of *O*-methyl enedione **I-76** with light leads to loss of methanol *via* a radical pathway. The formed oxidopyrilium diradical **I-79** (*via* **I-78**) can then react in a cycloaddition to intricarene (**I-10**). Alternatively, a 4 π disrotatory ring closure in the oxidopyrilium ion can take place, forming an epoxide **I-80**, which then in turn can be opened by an S_N2' attack of water directly leading to the isolated product **I-77**.



Scheme 1.30 Mechanism for the formation of intricarene (**I-10**) and rearranged furanocembranoid **I-77**, supported by theoretical studies.

Crystal structures of compounds **I-10** and **I-77**, which are depicted in Figure 1.16, proved their identity.

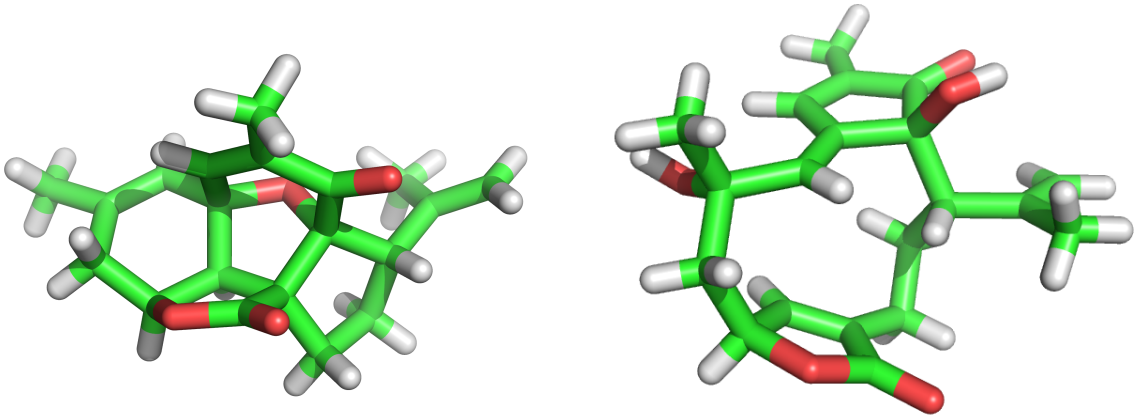


Figure 1.16 Crystal structure of intricarene (**I-10**) (left) and furanocembranoid **I-77** (right).[4]

No other light source, even irradiation at the absorption maximum of 265 nm, lead to any formation of intricarene (**I-10**). Apparently, this particular reptile lamp was the only light source triggering this transformation.

1.3.5 Theoretical Consideration and Calculations

To understand this transformation in more detail the absorption spectrum of *O*-methyl-enedione **I-76** was compared with the emission spectrum of the reptile lamp. The absorption spectrum of *O*-methyl-enedione **I-76** is shown in Figure 1.17 (in $CHCl_3$). The absorption maximum is at 265 nm. The emission spectrum of the lamp is shown in Figure 1.18. It has sharp lines in the visible and UV-A region of the electromagnetic spectrum and only negligible contributions below 360 or above 700 nm. The peak emissions at λ_{max} = 366, 405, 436, 492, 546, 578 and 679 nm can all be assigned to Hg emissions. This means that UV-B light is apparently absent in this type of lamp.

[4] Parameters for the crystals structures can be found in the thesis of Thomas J. Kimbrough, University of California, Berkely.

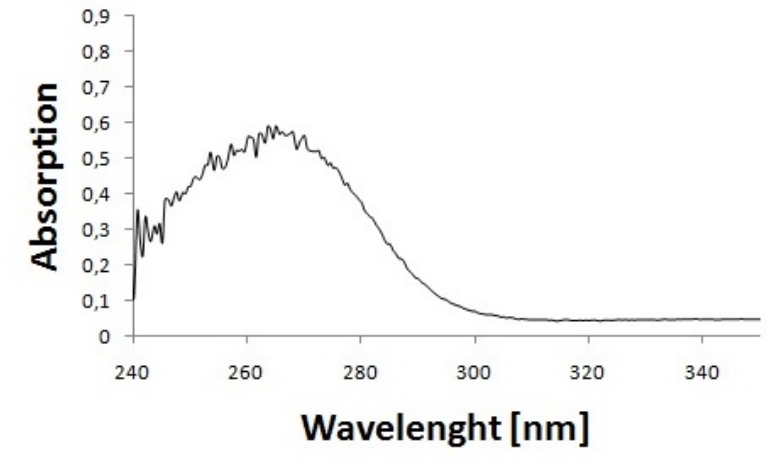


Figure 1.17 Absorption spectrum of *O*-methyl-enedione **I-76** (in $CHCl_3$).

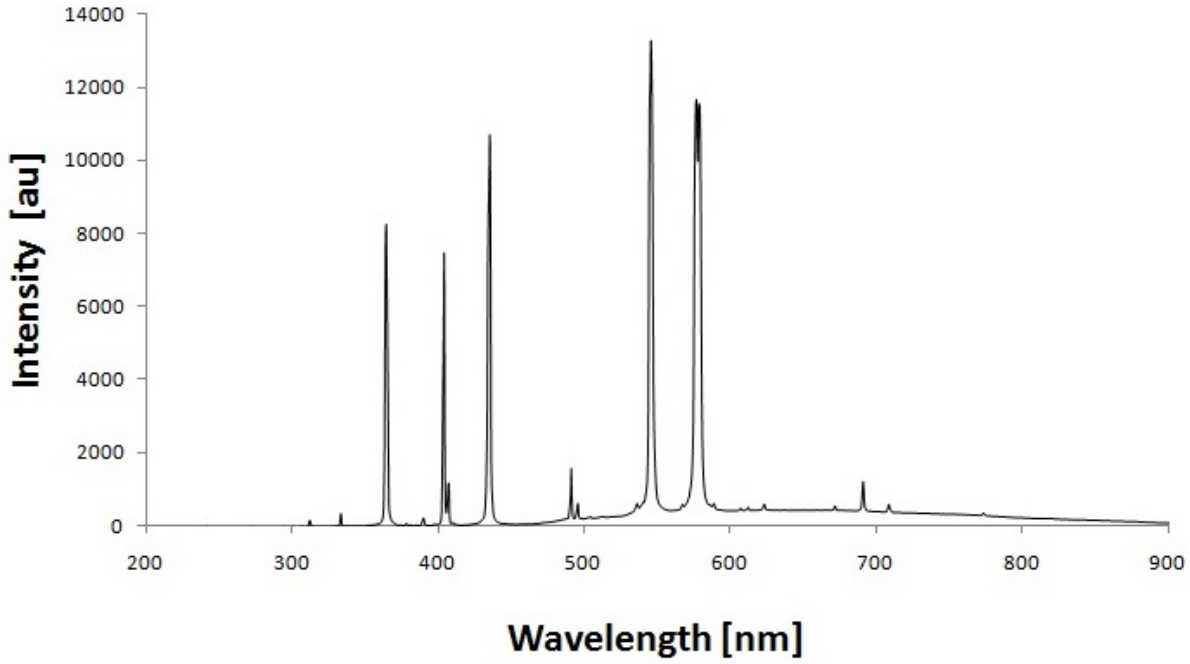


Figure 1.18 Emission spectrum of the used reptile lamp (T-Rex, nominal power 275 W).

To our surprise no emission from the reptile lamp is at the absorption maximum of *O*-methyl enedione **I-76**.

A closer look at the absorption spectrum showed that there is another local maximum around 360 nm (Figure 1.19). Enhancement by ten times shows this clear. This weak absorption band matches with the emission of the lamp. Obviously the photo-initiation proceeds through the 360 nm transition.

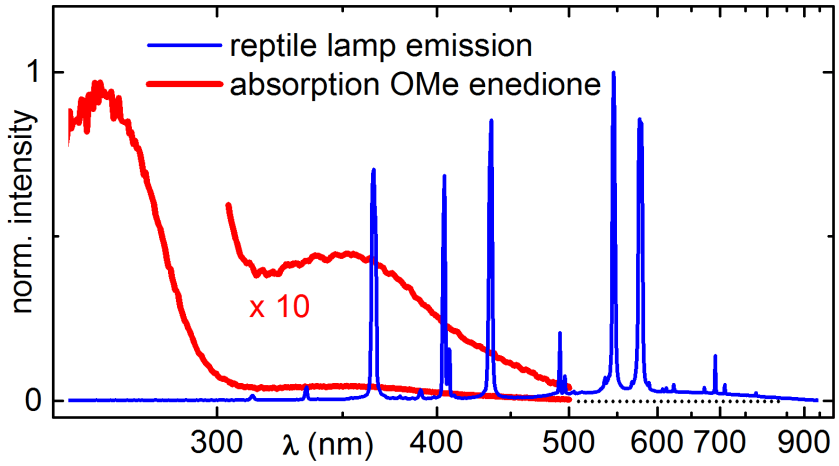
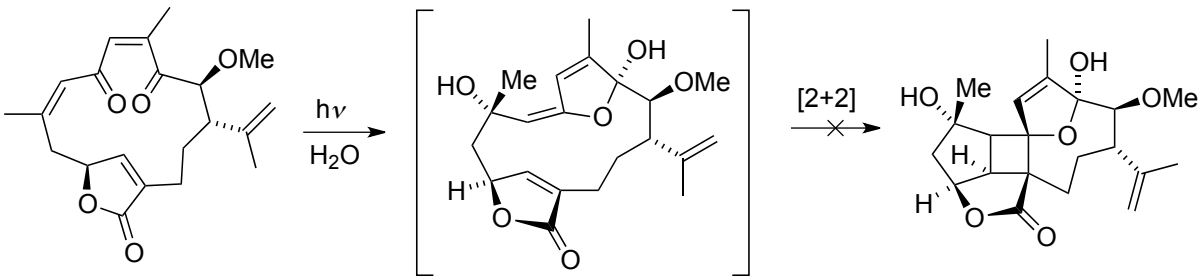


Figure 1.19 Combined spectrum of emission spectrum of the reptile lamp (blue), absorption spectrum of OMe enedione (**I-76**) (red) and ten times enhanced absorption spectrum of *O*-methyl enedione.

In collaboration with a theoretical chemistry group (P. Kölle, R. de Vivie-Riedle; LMU München), this transformation was investigated further. Results of the theoretical calculations are presented in Scheme 1.30. Irradiation excites **I-76** from groundstate S_0 to excited state S_4. Intersystem crossing (ISC) results in triplett state T_4, which reacts stepwise *via* homolytic bond cleavage and the loss of methanol to **I-78** in T_1 first, then to diradical **I-79** in T_1. In a formal [3+2] reaction two new bonds are stepwise formed to result in intricarene (**I-10**). **I-79** (in T_1) can also relax back to the groundstate S_0 (**I-60**). Reirradiation excites to S_2 (**I-60**) and from there a 4 π disrotatory ring closure can happen, forming epoxide **I-80**, which then in turn can be opened by an S_N2' attack of water, directly leading to the isolated product **I-77**. Main result is that the formation of the oxidopyrilium ion goes *via* homolytic bond cleavage of the methoxy group. That means a radical pathway is responsible for the formation of the oxidopyrilium ion *via* radical **I-78** and diradical **I-79**. This mechanism explains why the reaction can take place in the presence of water and why *O*-acetate enedione **I-74** failed to yield intricarene. On the one hand the bond dissociation energy (BDE) of methanol (DH_{298} = 104.6 ± 0.7 kcal mol^{-1}) is lower than that of water (DH_{298} = 118.82 ± 0.07 kcal mol^{-1}). On the other hand, homolytic bond cleavage of the acetate in **I-74** would yield an unstable acetoxy radical (the BDE of acetic acid is DH_{298} = 112 ± 3 kcal mol^{-1}) and is therefor less favorable than the homolytic cleavage of methylether in **I-76**.[57]

An alternative outcome of this reaction, which we thought might be possible, is shown in Scheme 1.31.



I-76 **I-81**

Scheme 1.31 Thinkable alternative outcome of the reaction that was not observed.

Instead of forming an oxidoypyrilium ion, light could trigger water attack and a subsequent [2+2] cycloaddition would form the core of bielschowskysin. This reaction however was not observed.

1.3.6 Conclusion

A photochemical formation of intricarene (**I-10**) has been demonstrated. Chemical modifications of bipinnatin J (**I-1**), namely methylation of the C-2-hydroxy group and oxidation of the furan moiety, gave a precursor suitable for the photochemical reaction. Using a commercially available reptile lamp with emission in the visible and UV-A region, *O*-methyl enedione **I-76** was converted into intricarene (**I-10**). Besides intricarene (**I-10**) another product was obtained, which is not yet known as a natural product. To gain a deeper understanding of this transformation, theoretical calculations were performed, showing that an oxidopyrilium ion **I-60** formed by homolytic bond dissociation, is the key compound. Since intricarene (**I-10**) producing corals live in shallow water, exposed to sunlight, this is a possible pathway for the biosynthesis of intricarene (**I-10**).

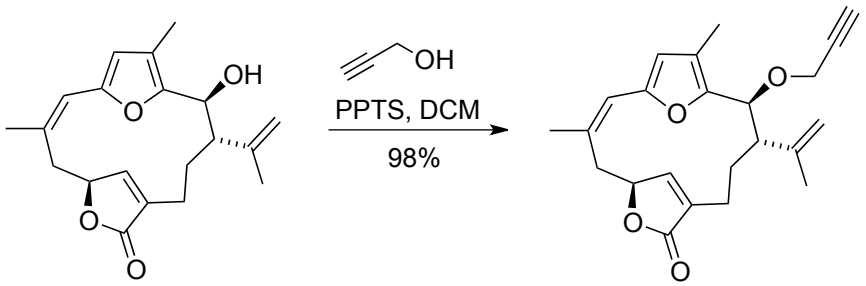
1.4 Synthesis of a Bipinnatin J Derivative for Proteom Labelling

In addition to being a precursor for a wide range of furanocembranoids, bipinnatin J (**I-1**) was chosen as a potential target molecule for proteom labeling. These kinds of targets are natural products with a position that potentially reacts with proteins, for example an electrophilic moiety, which can be attacked by the nucleophilic aminoacids. In bipinnatin J (**I-1**) the unsaturated lactone was identified as an appropriate position. These targets need a second characteristic: an alkyne or a position that can be attached to an alkyne.

Proteins are treated with the appropriately labeled natural products in order to react with each other. Probe-labeled proteins are modified with a reporter tag *via* click-chemistry allowing the flexible attachment of rhodamine for target detection and identification. Enzyme activities can be

compared and visualized by fluorescent in-gel analysis and subsequently identified by mass-spectrometry methods.[58]

In bipinnatin J (**I-1**) the C-2-hydroxy group was seen as a possible position for attaching the alkyne linker. Therefore bipinnatin J (**I-1**) was modified using propargylic alcohol under acidic conditions.



bipinnatin J (**I-1**) **I-82**

Scheme 1.32 Synthesis of alkyne labelled bipinnatin J **I-82**.

The modified bipinnatin J **I-82** was tested in several cell lines (J. Eirich, S. Sieber). Reaction with several proteins was observed, but during purification the rhodamin part, which is attached *via* click chemistry to the bipinnatin J-protein-part, was cleaved from the latter. This leads to the assumption that the C-2-hydroxy is not the appropriate position for the attachment of the alkyne. As seen in the methylation and propargylation of bipinnatin J this position is very reactive, especially under acidic conditions.

2 The Total Synthesis of Crocagin

2.1 Introduction

2.1.1 Hydropyrroloindole Natural Products

Natural products containing a hydropyrroloindole subunit (Figure 2.1) have been isolated from a wide range of different organisms, like plants, marine organisms, frogs, fungi or bacteria. They can show different types of bioactivity, like antifungal, antiviral, antitumor or antimicrobial activitiy. Several are known to be cholinesterase inhibitors, inhibitors of acyl-CoA and there exist hydropyrroloindoles that are in use to treat alzheimer's disease and orthostatic hypotension. In addition vasodilating activity is known for several of these natural products.[59]

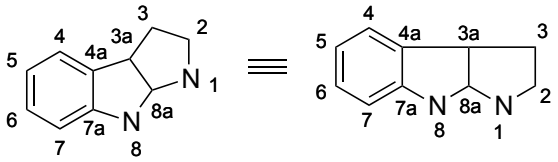
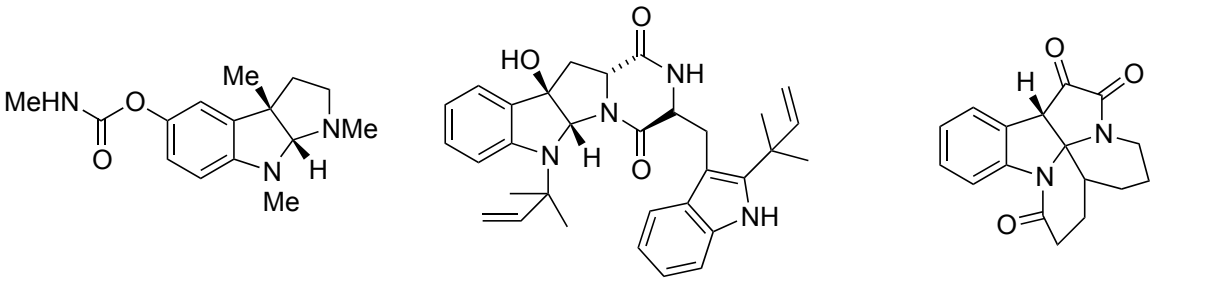


Figure 2.1 Hydropyrroloindole subunit with IUPAC numbering in two different drawings.

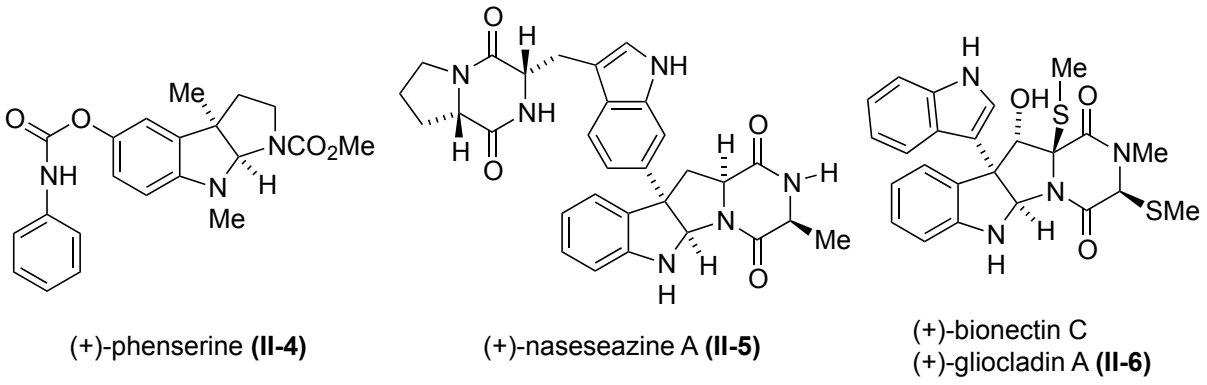
A few selected hydropyrroloindole natural products are presented in Figure 2.2. Physostigmine (**II-1**) was isolated from the seeds of the Calabar bean plant and is a cholinesterase inhibitor. It exhibits a methylgroup in C-3a position, while C-2 and C-3 are unsubtituted.[60] Okaramine C (**II-2**) was isolated from the fungus *Penicillium simplicissum*. Structurally, in okaramine C a diketopiperazine is present, which is condensed to the hydropyrroloindole subunit. C-3a position is substituted with a hydroxy group and C-3 is unsubstiututed.[59] 6-oxoleuconoxine was isolated from the leaf extract of *Kopsia griffithii*. It exhibits a hydrogen in position C-3a, which is very rare observed in hydropyrrolindole natural products. Furthermore a polycyclic motiv completes the structure.[61]



(–)-physostigmine (**II-1**) (+)-okaramine C (**II-2**) (+)-6-oxoleuconoxine (**II-3**)

Figure 2.2 Structures of selected hydropyrroloindole natural products.

Recently, several total syntheses of hydropyrroloindole natural products were published, a selection is presented in Figure 2.3. Garg and coworkers synthesized phenserine **(II-4)** in 2011 using an interrupted Fischer Indolization reaction.[62] (+)-Naseseazine A (**II-5**) (and B) were synthesized in 2011 by Movassaghi and coworker and in 2013 by Reisman and coworkers. Movassaghi achieved the cyclization to the hydropyrroloindole using $PyHBr_3$,[63] Reisman and coworkers used their methodology of the copper-catalyzed diastereoselective C-3 alkylation-cyclisation for the formation of the hydropyrrolindole.[64] Bionectin C and gliocladin A (**II-6**) describe the same molecule. Overman and coworkers[65] as well as Movassaghi and coworkers[66] synthesized this natural product separately in 2013. Overman used a strategy, which has already been established in 2011 for gliocladine C[67] wherein the piperazine moiety is condensed to the indole core whereas Movassaghi used bromine and anisole for the hydropyrroloindole cyclization.[66]



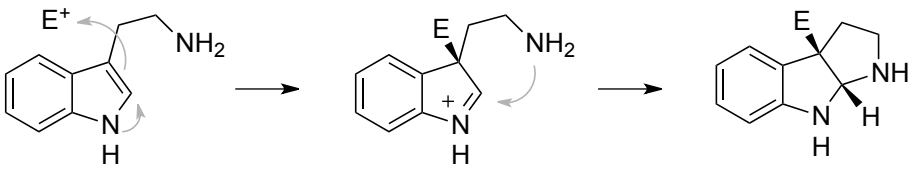
(+)-phenserine **(II-4)** (+)-naseseazine A **(II-5)** (+)-bionectin C
(+)-gliocladin A **(II-6)**

Figure 2.3 Selected hydropyrroloindole natural products that were synthesized recently.

2.1.2 Cyclisation Methods for Hydropyrroloindoles

As displayed in these total syntheses, there are several methods to build hydropyrroloindoles, depending on the substitution pattern and stereochemistry around the core.

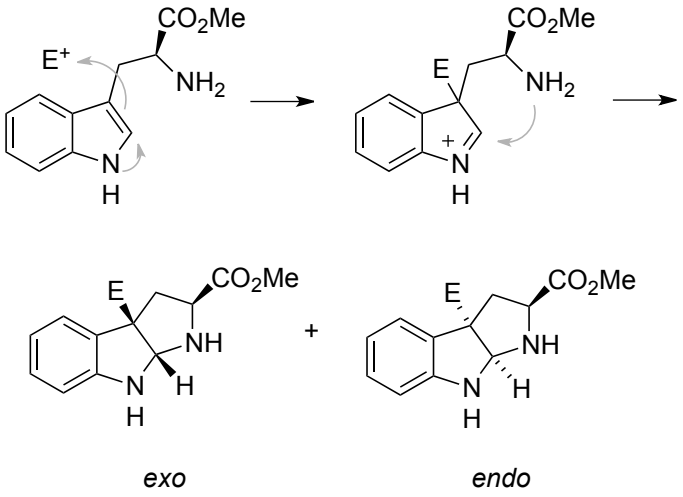
The basic hydropyrroloindole framework can be traced back to tryptamine. An electrophilic attack at the C-3 position followed by a nucleophilic attack of the nitrogen results in the hydropyrroloindole core (Scheme 2.1).



Scheme 2.1 Formation of the hydropyrroloindole skeleton, starting from tryptamine.

The electrophile can either be a proton (cyclization with Brønsted acids like TFA, H_3PO_4) or a halogen (cyclization with NBS, NIS, NCS). Selenium (with PhSeCl, *N*-Phenylselenophtalimid) or metal-based cyclization are known as well.[59]

As soon as the precursor has a substituent in C-2 position, like in tryptophan, two diastereomers have to be distinguished. The *exo* product, when the substituent points into the convex site and the *endo* product where the substituent points into the concave site, depicted in Scheme 2.2



Scheme 2.2 Formation of *exo* and *endo* hydropyrroloindol starting from tryptophan.

The *endo* product is the thermodynamic product while *exo* is the kinetic. Cyclization under acidic conditions favors the *endo* product, while cyclization with all other electrophiles favors the *exo* product.[68]

2.1.3 The Target Molecule Crocagin

Crocagin (**II-7**), shown in Figure 2.4, was isolated from the myxobacterium *Chandromyces crocatus* as a colorless amorphous powder by the group of R. Müller (Saarbrücken) in 2012. The structure was elucidated by ^{1}H, ^{13}C and 2D-NMR spectroscopy. The absolute stereochemistry was elucidated using the phenylglycine methyl ester (PGME) method.[69]

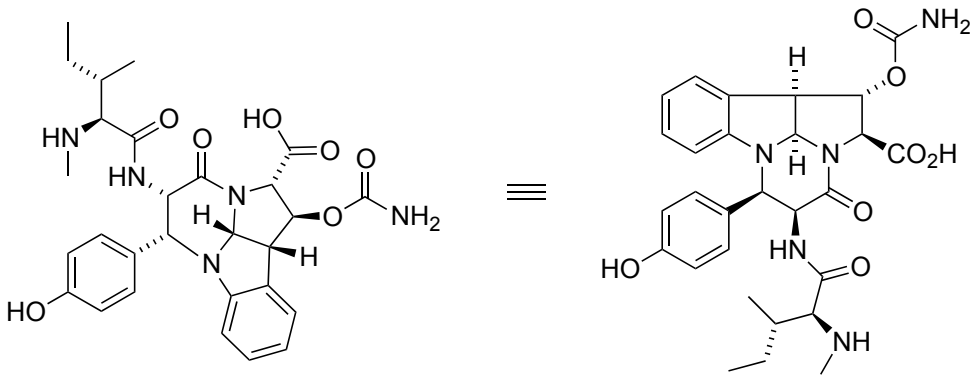


Figure 2.4 Structure of crocagin (**II-7**) in two different drawings.

Structurally crocagin (**II-7**) is a tripeptide, consisting of the aminoacids tryptophan, tyrosine and isoleucine. The amino acids are connected *via* peptide bonds. Furthermore tryptophan is cyclized to an *endo* hydropyrroloindole unit, which has a carbamoylated oxygen in position C-3 that points into the convex site of the molecule. Tyrosine is connected to tryptophan *via* an amide bond N (Trp) – C (Tyr) and *via* an additional bond between the indole nitrogen and the benzylic position of the tyrosine, forming the six-membered D-ring. Finally isoleucine is *N*-methylated. All amino acids are (*S*)-configured. A detailed description of these properties is depicted in Figure 2.5.

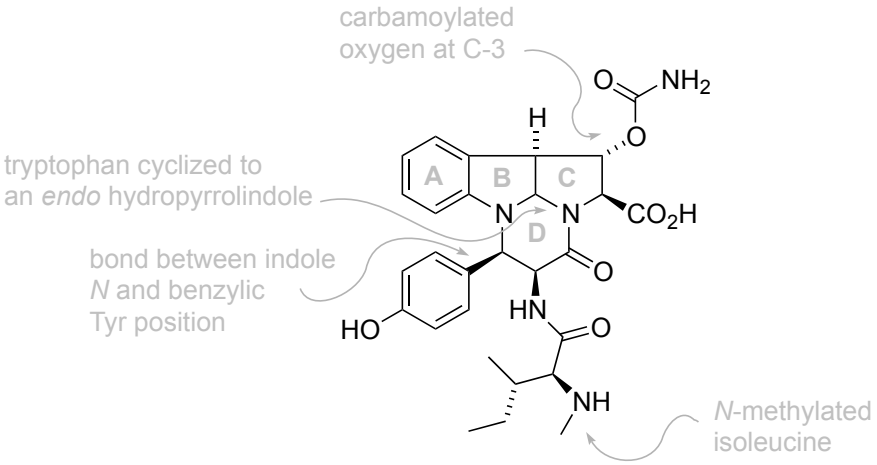


Figure 2.5 Structure of crocagin (**II-7**) – special structural features highlighted.

Biosynthetically, crocagin (**II-7**) is a ribosomal peptide, which is translationally modified. Most likely the tripeptide Trp-Tyr-Ile is formed and then oxidized, methylated and cyclized.[69]

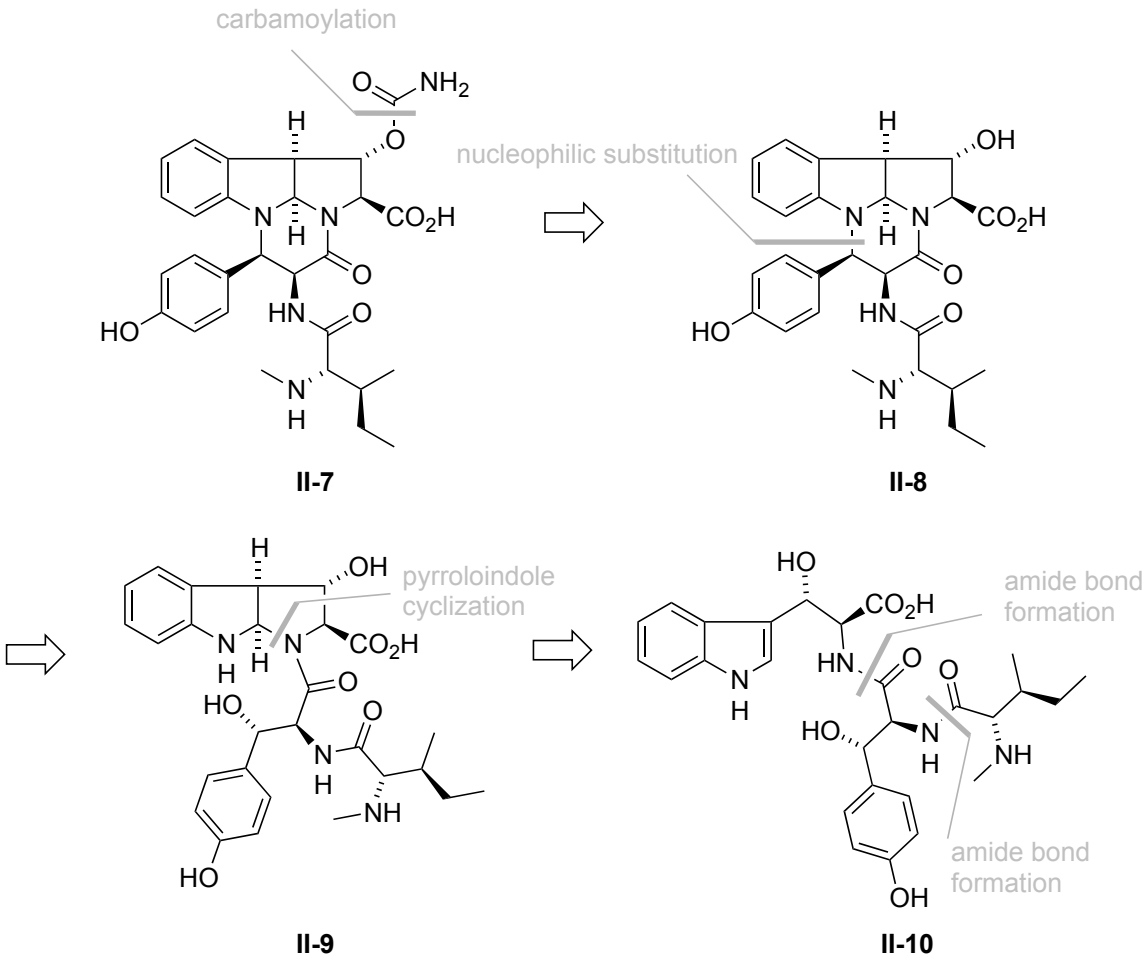
2.2 Goal

The goal of this project was to develop a total synthesis of the natural product crocagin (**II-7**). Since there is no crystal structure of the isolated compound a total synthesis would have to prove the proposed structure of the molecule. As no bioactivity is known of crocagin (**II-7**), a scalable total synthesis would provide more material for biological testing. Within this total synthesis different possibilities for cyclization methods to hydropyrroloindoles will be explored and would enrich this field and assist future total syntheses of hydropyrroloindole natural products.

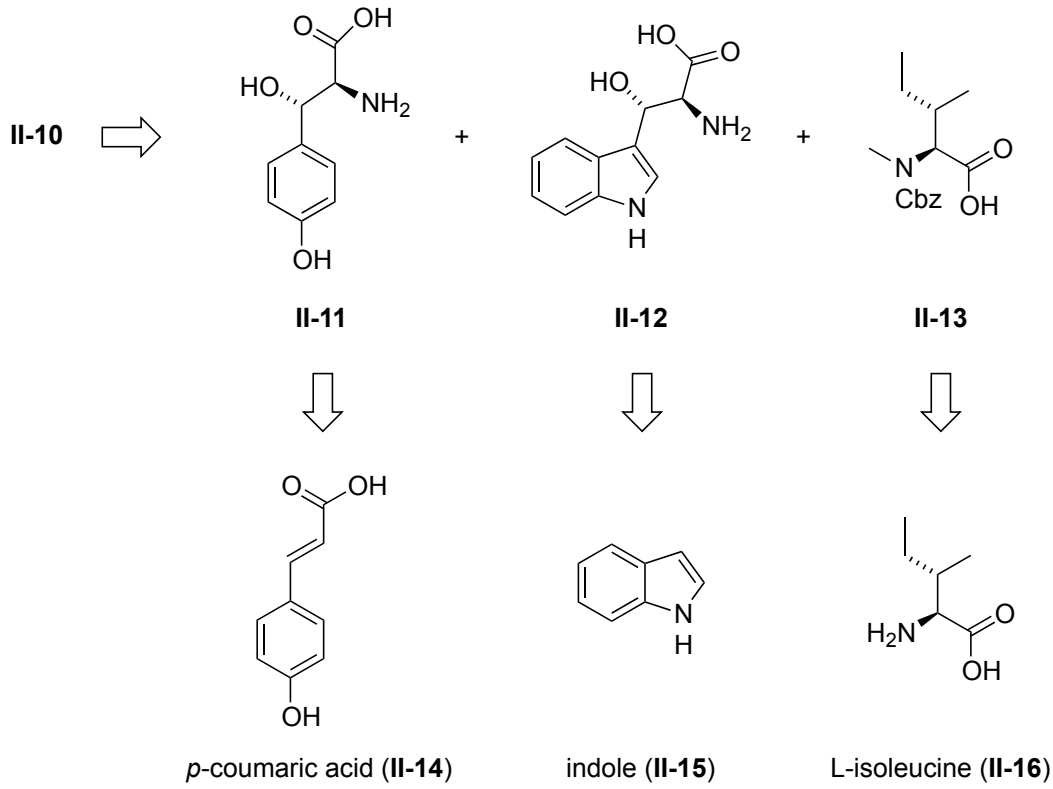
2.3 Results and Discussions

2.3.1 First Generation Strategy and Retrosynthetic Analysis

The first retrosynthetic analysis (Scheme 2.3) follows the proposed biosynthetic hypothesis and completes the total synthesis with the final carbamoylation of the oxygen in position C-3. The bond between the indole nitrogen and the benzylic position of tyrosine should form the D-ring *via* a nucleophilic substitution leading to tetracyclic compound **II-8**. This requires a leaving group at the benzylic position in **II-9**. The hydropyrroloindole **II-9** is supposed to be formed from a tryptophan building block in a hydropyrroloindole cyclization. This leads back to the tripepdide **II-10**, which in turn is traced back to the three modified amino acids hydroxy-tryptophan (**II-11**), hydroxy-tyrosine (**II-12**) and methyl-isoleucine (**II-13**) (Scheme 2.4).



Scheme 2.3 First generation retrosynthetic analysis for crocagin (**II-7**).



Scheme 2.4 First retrosynthetic analysis for crocagin (**II-7**), tracing back to *p*-coumaric acid (**II-14**), indole (**II-15**) and L-isoleucine (**II-16**).

2.3.2 The Realization of the First Generation Strategy

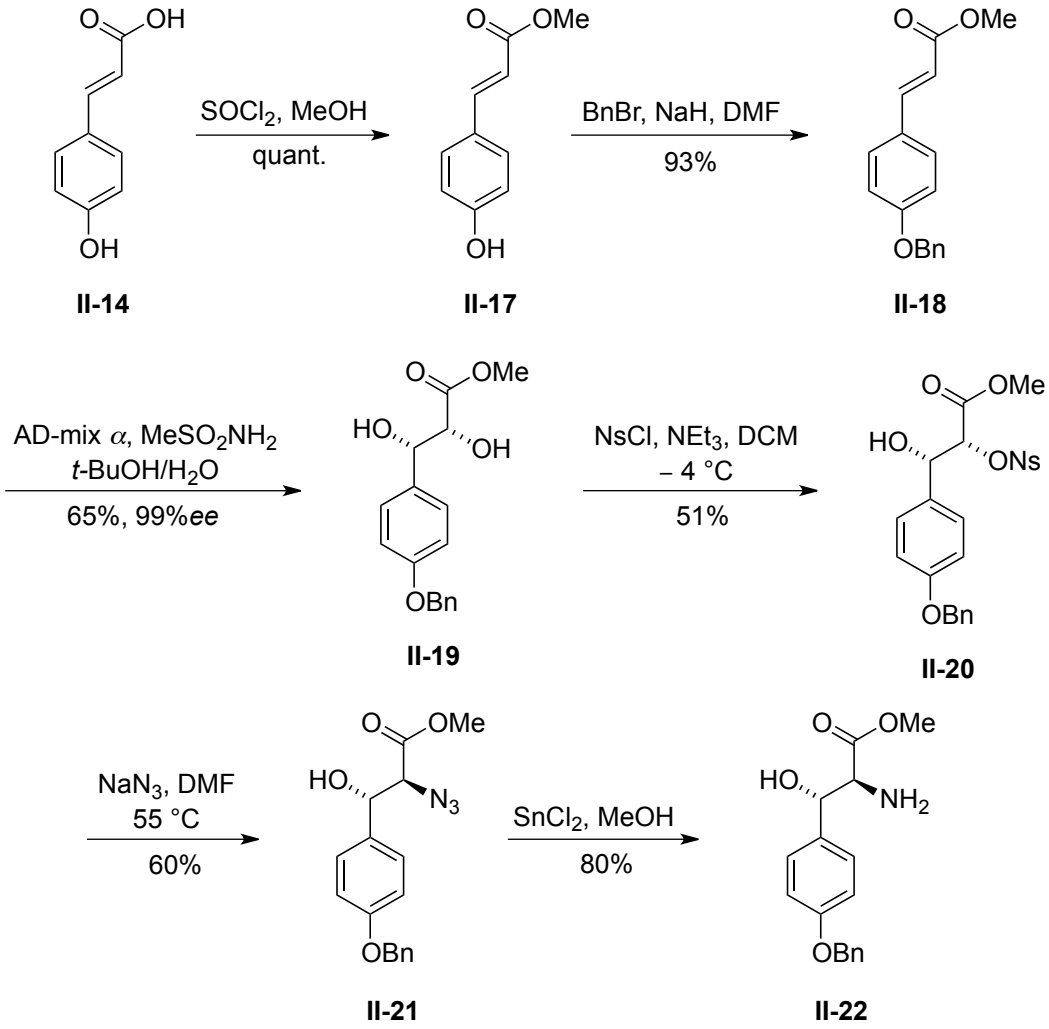
In the following the syntheses of the desired building blocks hydroxy-tyrosine (**II-11**), hydroxy-tryptophan (**II-12**) and methyl-isoleucine (**II-13**) are presented. The installation of different protecting groups, which are necessary for later reactions, is also illustrated.

a) Synthesis of the hydroxy-tyrosine and methyl-iosleucine building blocks[5]

The synthesis of the hydroxy-tyrosine building block **II-22**, which is shown in Scheme 2.5, starts from *para*-coumaric acid (**II-14**), which is protected in the first two steps: the carboxylic acid in form of a methylester in **II-17** and the phenolic OH as a benzyl ether in **II-18**. The stereochemical information is introduced using Sharpless dihydroxylation conditions. AD-mix *α* in combination with methanesulfonamide in *t*-BuOH and water yields the diol **II-19** with the desired stereochemistry in 99%*ee*. A crystal structure proves the syn relationship of the diol in this molecule (Figure 2.6 left).

[5] Parts of this chapter are also found in the bachelor thesis of Janina Ehses.

Transformation of the α-hydroxy group into the nosylate **II-20** and subsequent nucleophilic substitution with azide results in tyrosine azide **II-21**. This molecule in turn is reduced to hydroxy-tyrosine **II-22**, whose crystal structure is shown in Figure 2.6 right, wherein it is illustrated that the two aromatic rings are not any more in the same plane. The synthesis was adapted from Nicolaou and coworkers. [70]



Scheme 2.5 Synthesis of the hydroxy-tyrosine building block **II-22**.

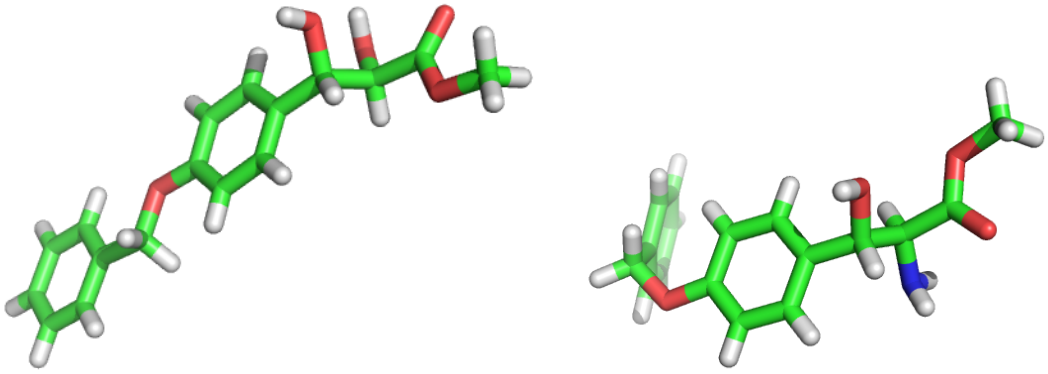
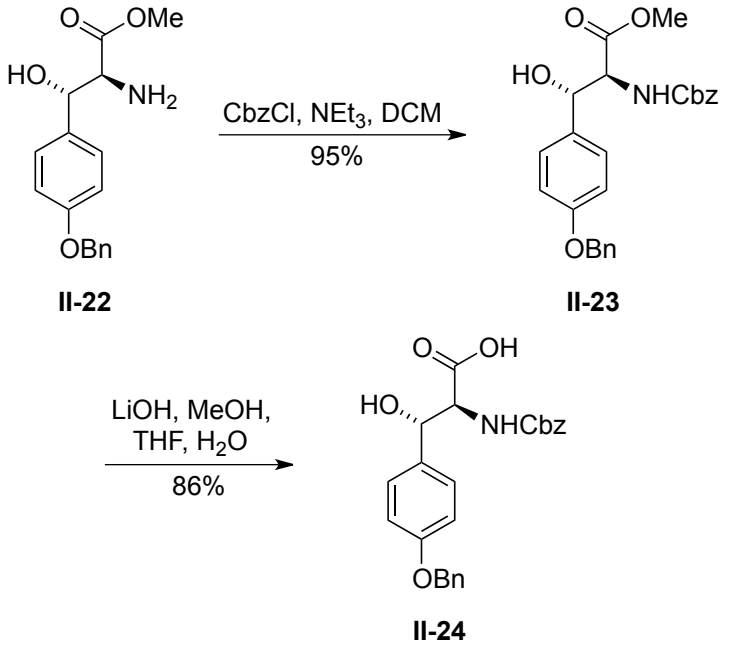


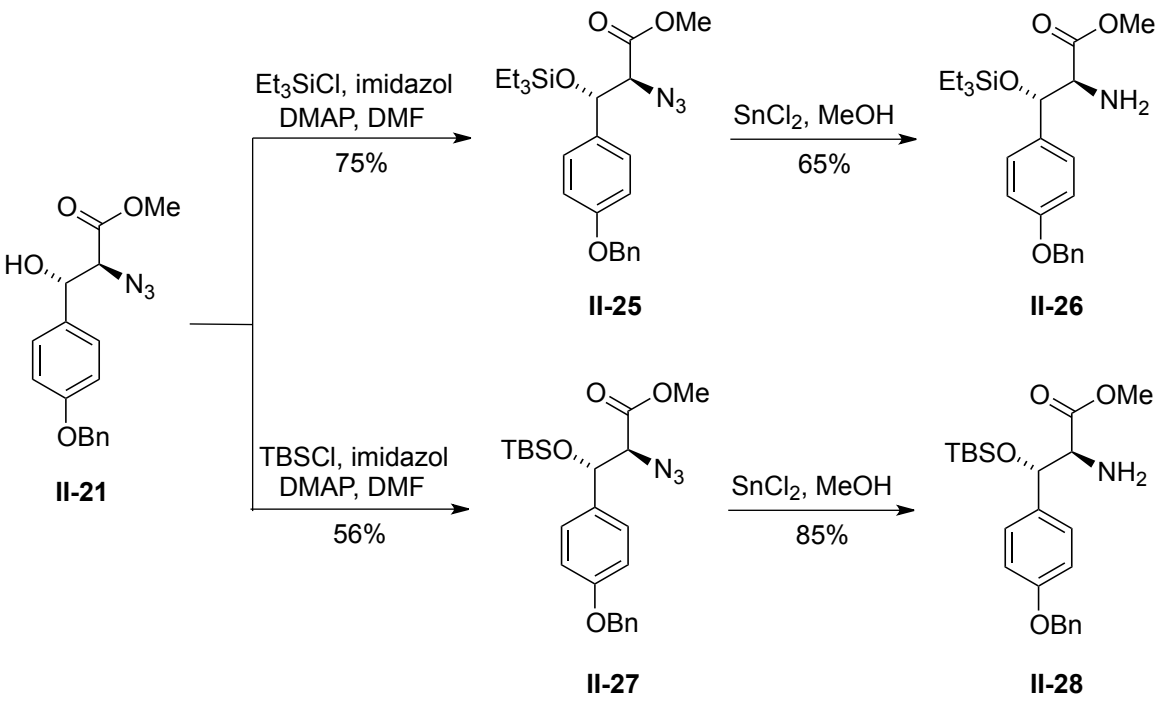
Figure 2.6 Crystal structure of diol **II-19** (left) and amine **II-22** (right).

These building blocks proved to be versatile. Aiming for the use of this building block in test reactions the amine in **II-22** was protected with a carboxybenzylgroup to yield **II-23**. Hydrolysis of the ester was then achieved with LiOH in water/methanol to result in **II-24**, shown in Scheme 2.6.



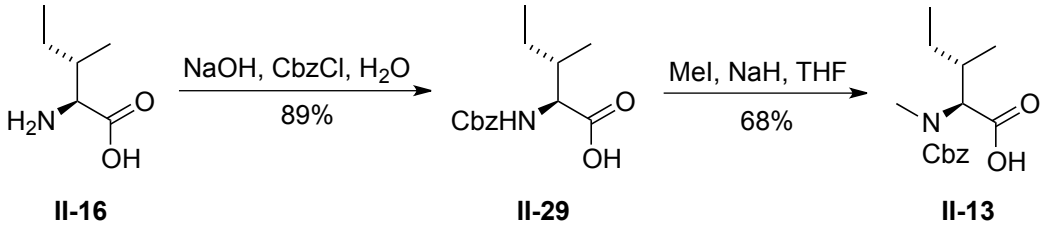
Scheme 2.6 Cbz-protection and hydrolysis of hydroxy-tyrosine building block **II-22**.

For later coupling attempts the hydroxy group was protected with a TES (Et_3Si) group and a TBS group respectively to give **II-26** and **II-28** (Scheme 2.7).



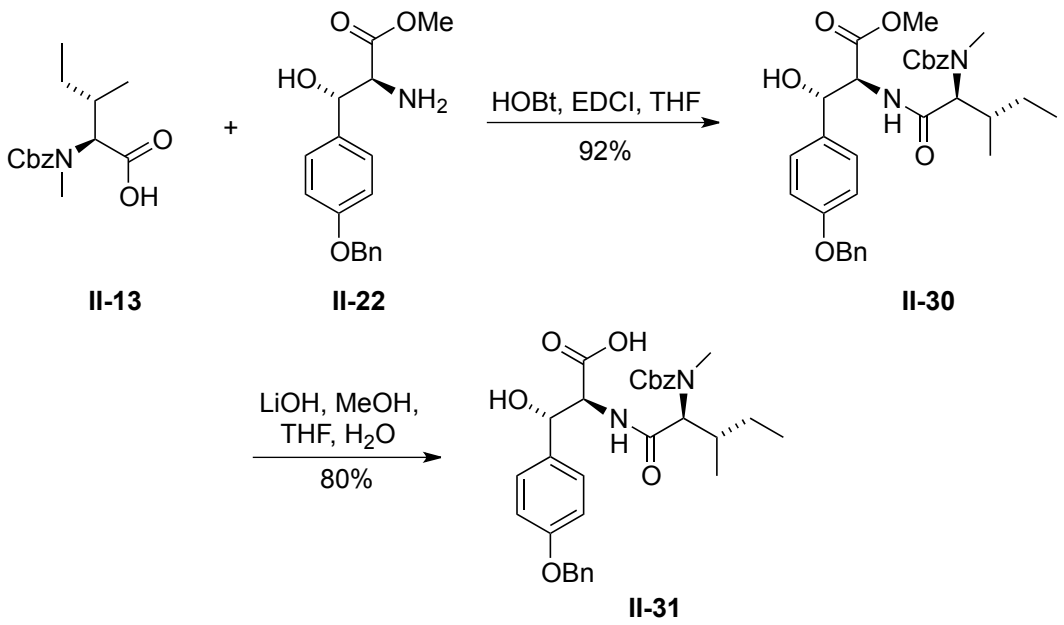
Scheme 2.7 TES and TBS protection of the hydroxy-tyrosin building block **II-21**.

Modified isoleucine **II-13** was synthesized in two steps, shown in Scheme 2.8. Protection of the amine in **II-16** was achieved using benzylchloroformate to yield **II-29**.[71] Methylation of the aminofunction of Cbz-isoleucine **II-29** was conducted with MeI in THF.[72]



Scheme 2.8 Synthesis of protected methyl-isoleucine **II-13**.

Isoleucine building block **II-13** was successfully coupled to the tyrosine building block **II-22** resulting in dipeptide **II-30**, followed by hydrolysis of its ester moiety to acid **II-31** (Scheme 2.9), which allows a later peptide coupling to the tryptophan building block.



II-13 **II-22** **II-30** **II-31**

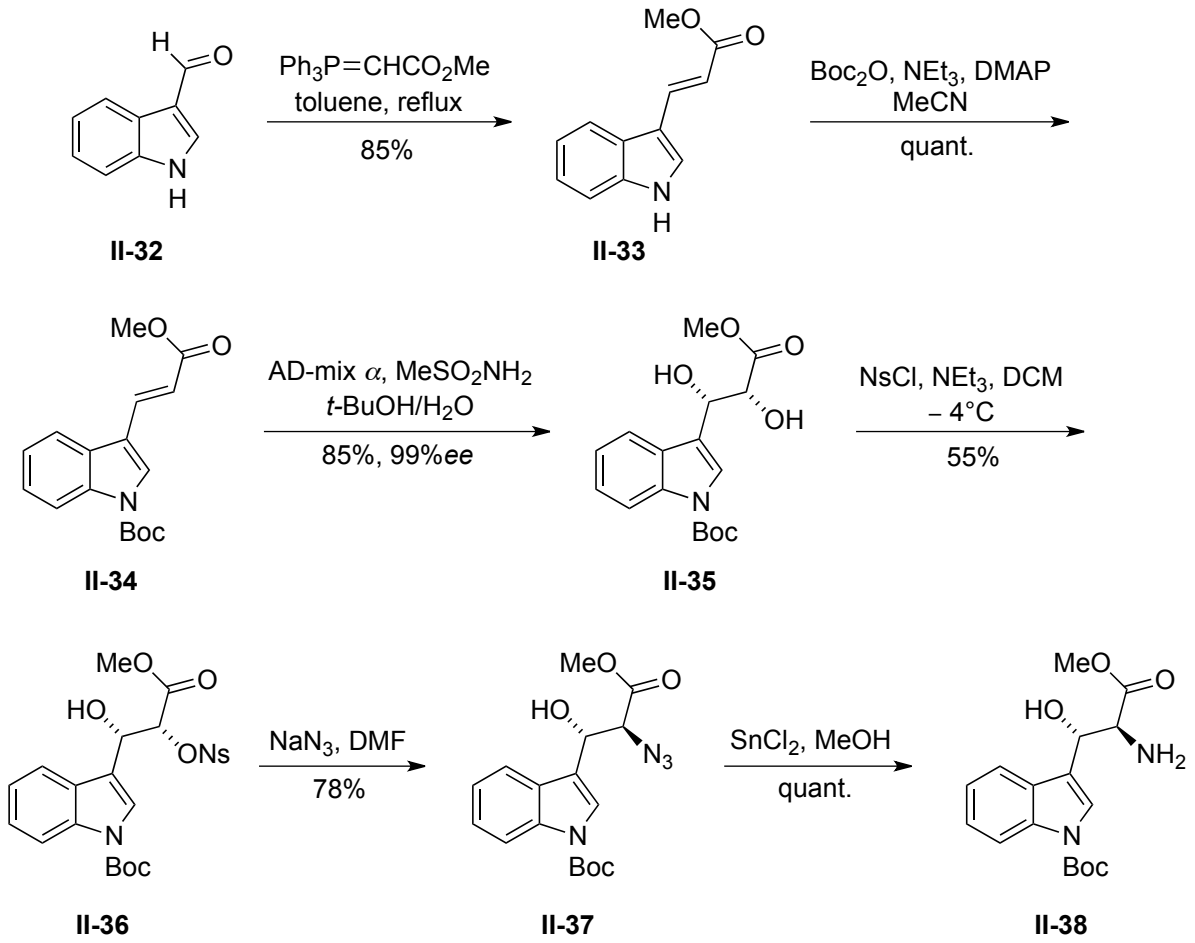
Scheme 2.9 Coupling of isoleucine **II-13** and tyrosine building block **II-22** with subsequent ester hydrolysis.

With the tyrosine-isoleucine building block in hand the focus was set on the synthesis of the tryptophan building block.

b) Tryptophan building block[6]

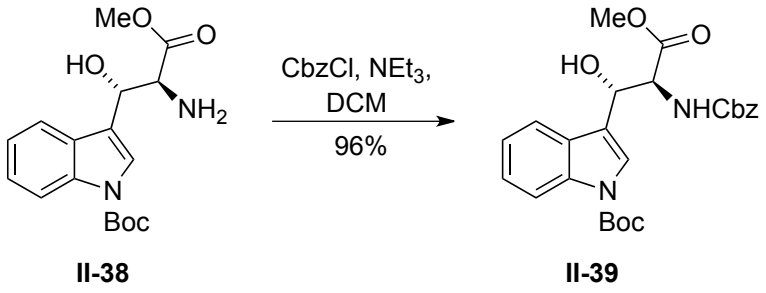
For the synthesis of the hydroxy-tryptophan building block a strategy analogous to the hydroxy-tyrosine strategy was applied. The synthesis started with 3-indole-aldehyde (**II-32**) (Scheme 2.10), which was elongated in a Wittig reaction to the unsaturated ester **II-33**, whereupon the indole nitrogen was Boc-protected to give **II-34**. The stereocenters were set using Sharpless dihydroxylation conditions, resulting in the desired diol **II-35** in 99%*ee*. Analogous, nosylation to **II-36**, azide substitution to **II-37** and reduction yielded the double protected hydroxy-tryptophan **II-38**. The strategy was adapted from Koketsu and coworkers.[73]

[6] Parts of this chapter are also found in the bachelor thesis of Susanne Gerndt.



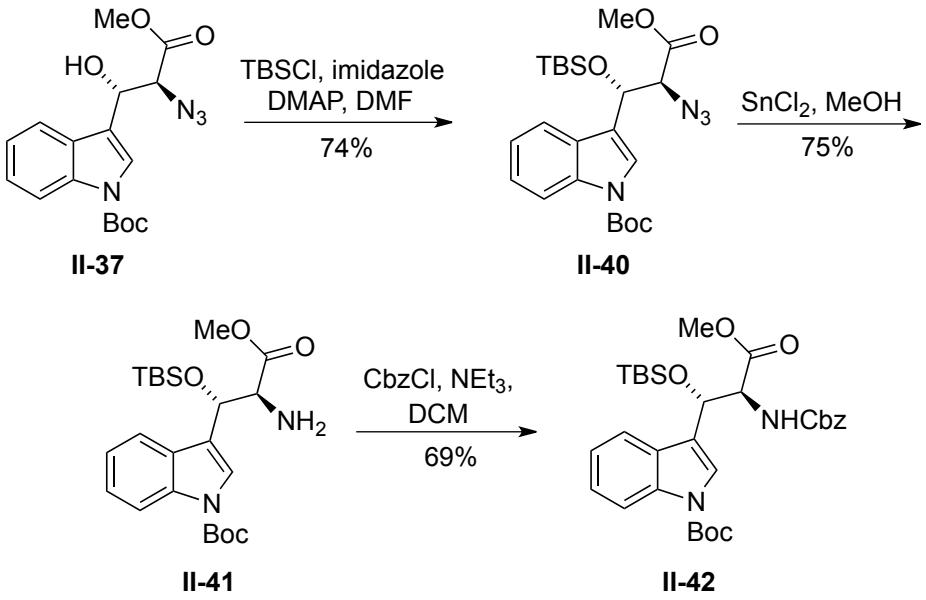
Scheme 2.10 Synthesis of hydroxy tryptophan building block **II-38**.

In order to explore cyclization reactions with this tryptophan building block, the amino group was protected with a carboxybenzoyl group to yield **II-39** (shown in Scheme 2.11).



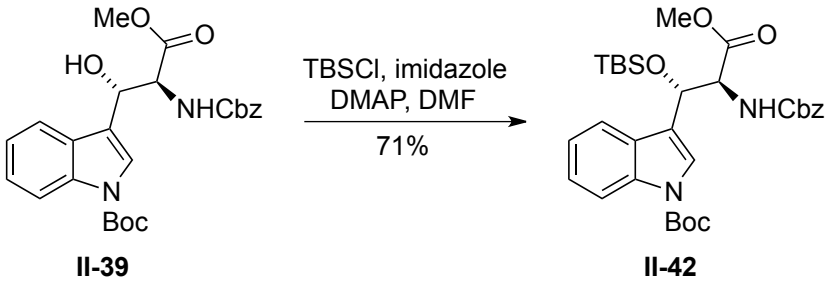
Scheme 2.11 Cbz-protection of hydroxy tryptophan **II-38**.

It was also possible to protect the hydroxy group as a silyl ether. For this step the building block was reacted with TBSCl at the stage of the azide **II-37** to result in **II-42** (Scheme 2.12).



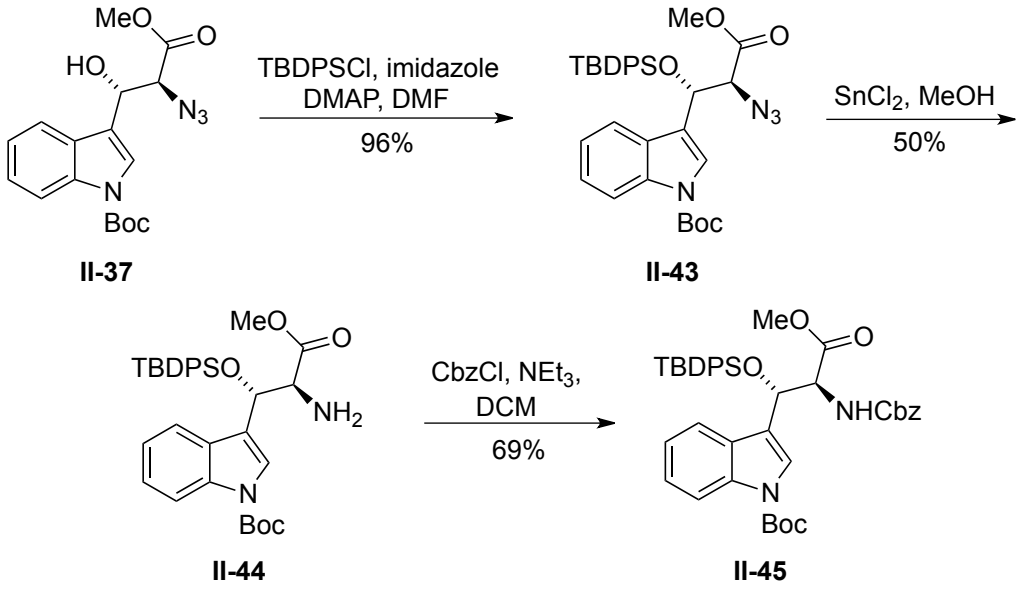
Scheme 2.12 TBS protection of hydroxy tryptophan at the stage of the azide **II-37**.

Direct protection of the amine **II-39** lead to the desired compound **II-42** as well, presented in Scheme 2.13.



Scheme 2.13 TBS protection at the stage of protected amine **II-39**.

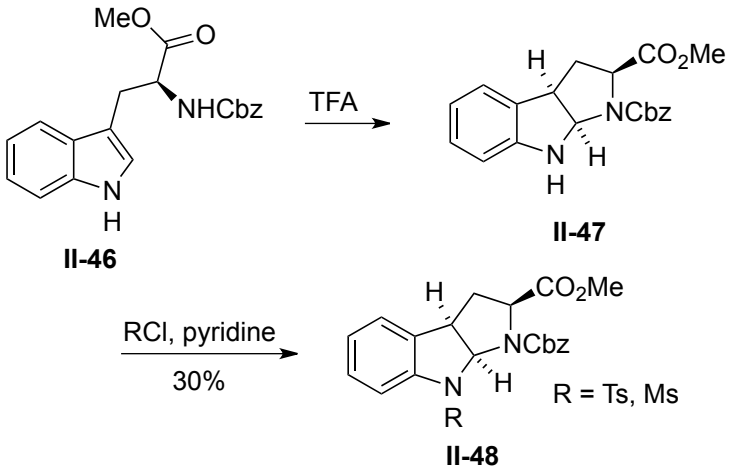
Protection with TBDPS group was also possible, as depicted in Scheme 2.14. In this case azide **II-37** was reacted with TBDPSCl, followed by reduction and protection.



Scheme 2.14 TBDPS protection at the stage of the azide.

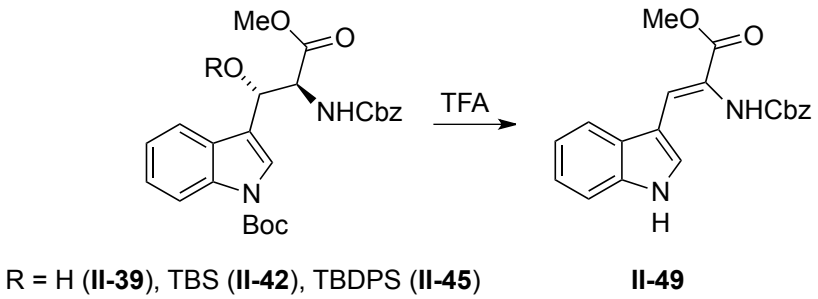
c) Cyclization attempts towards hydropyrroloindoles

With the synthesized building blocks in hand, cyclization towards hydropyrroloindoles was investigated. As mentioned before (Scheme 2.15) tryptophan can be cyclized to *endo* hydropyrroloindoles using acidic conditions.[68] *N*-Cbz protected tryptophan methylester **II-46** is known to cyclize to the corresponding hydropyrroloindole in TFA. Since hydropyrroloindoles with free N-8 are unstable with respect to uncyclized tryptophan, they have to be trapped with an electrophile, for example with TsCl or MsCl (a deprotection of Cbz is presented in the Experimental Part).



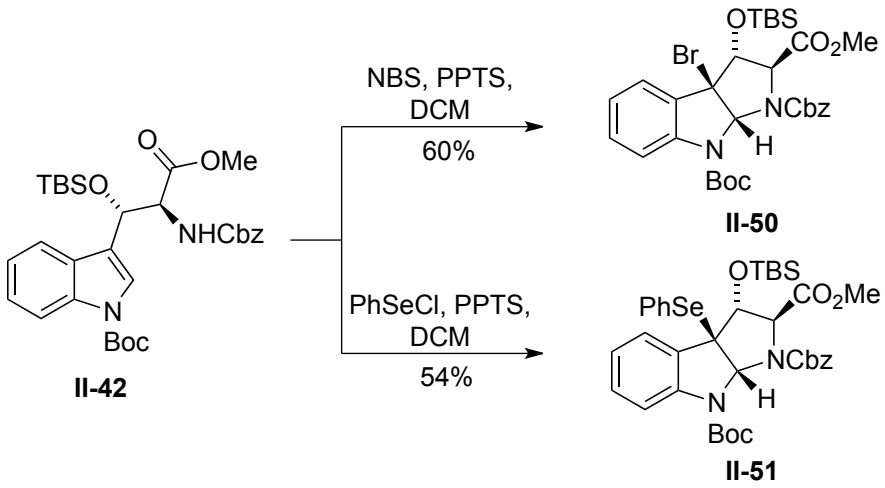
Scheme 2.15 Cyclization of tryptophan methylester **II-46** to the corresponding hydropyrroloindoles **II-47** and **II-48** (yields not optimized).

This reaction was taken as a starting point for the cyclization of hydroxy-tryptophan. Therefore double-protected hydroxy tryptophan methylester **II-39** was dissolved in TFA. Under these conditions no cyclization to the hydropyrroloindole was observed, but elimination of the benzylic hydroxy group took place. Protection of the hydroxy group with TBS (**II-42**) and TBDPS (**II-45**) and subsequent exposure to TFA lead to the elimination product **II-49** as well (Scheme 2.16).



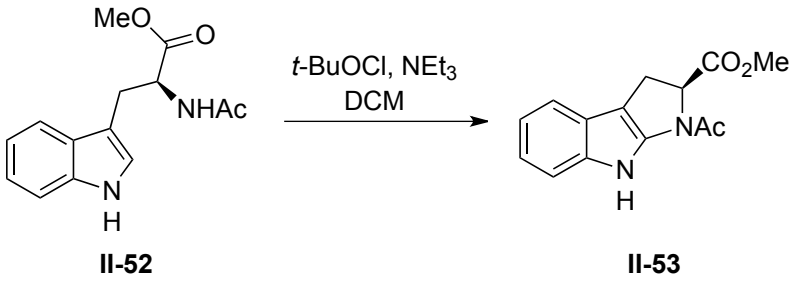
Scheme 2.16 Unsuccessful cyclization attempt of hydroxy-tryptophan.

With this knowledge protic cyclization was abonded and other methods were explored. Cyclizations with NBS or PhSeCl are usually known to give the undesired *exo* hydropyrroloindole.[68] Assuming that a bulky OTBS group in the benzylic position could change the selectivity towards the desired *endo* product, both conditions were tried, but the *exo* product was observed, indicated by the shift of the methyl ester at 3.8 ppm in ^{1}H-NMR spectra of the crude products (Scheme 2.17)[68] (plus minor amounts of *endo* diastereomer in the case of **II-50**, only one diastereomer in the case of **II-51**).



Scheme 2.17 Cyclization of protected hydroxy tryptophan **II-42** with PhSeCl and NBS.

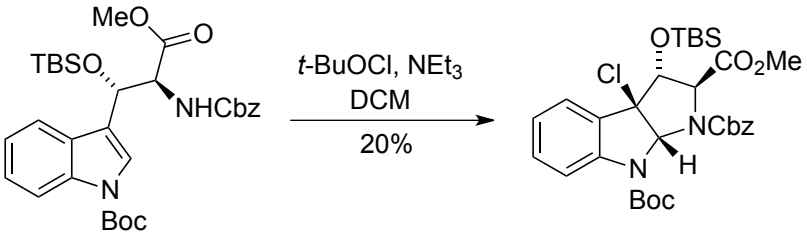
Witkop and coworkers described a method using *t*-BuOCl resulting in an unsaturated pyrroloindole **II-53** (Scheme 2.18), which can be reduced stereoselectively afterwards to the *endo* or *exo* product.[74]



II-52 **II-53**

Scheme 2.18 Witkop's formation of an unsaturated hydropyrroloindole **II-53**.

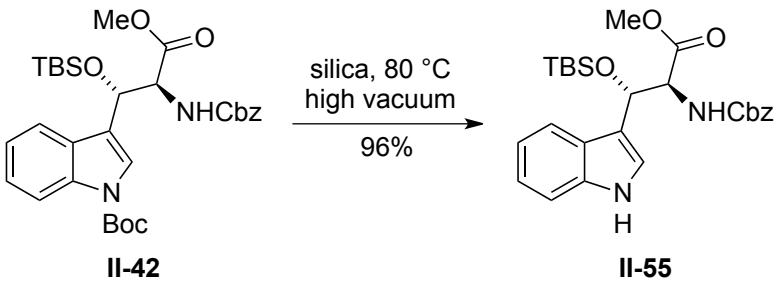
These conditions were applied to the protected hydroxy tryptophan building block **II-42**, which unexpectedly resulted in a hydropyrroloindole **II-54**, and not in an unsaturated version, as shown in Scheme 2.19. Elimination seems hindered either by the Boc protecting group or the TBS protecting group.



II-42 **II-54**

Scheme 2.19 Witkop's procedure applied to hydroxy tryptophan **II-42** (yields not optimized).

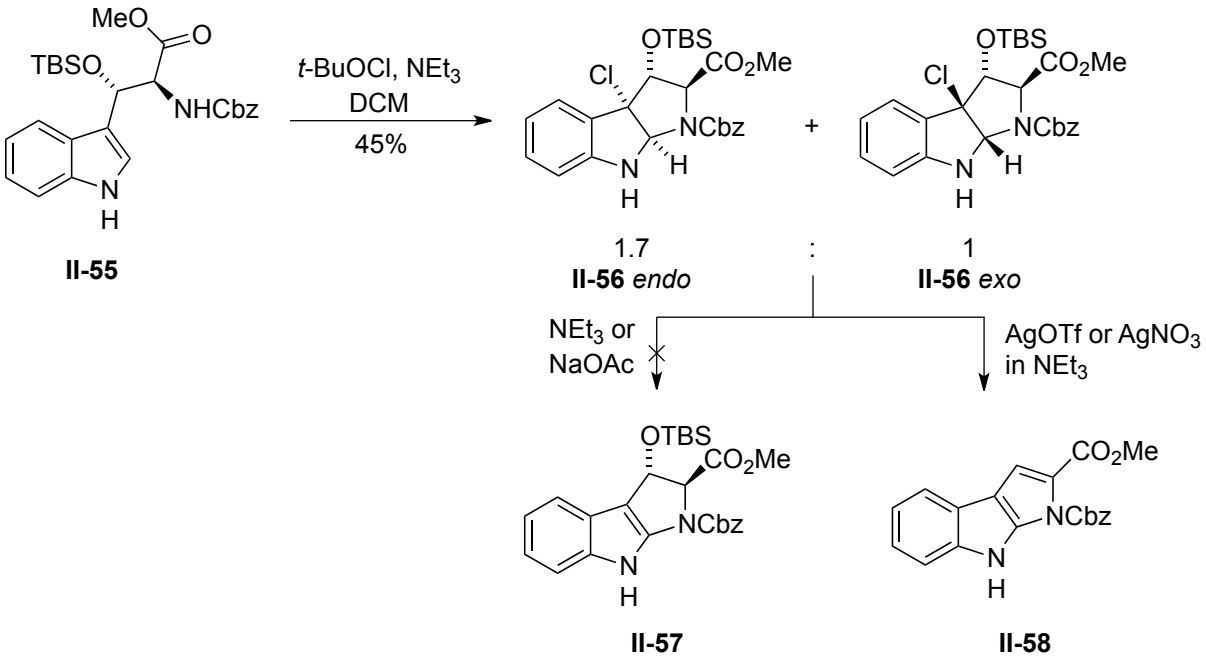
As a consequence, the Boc protecting group was removed from the indole. This was not possible using standard deprotection conditions like treatment with TFA, TMSOTf or high temperature and high vacuum. All these conditions lead to the elimination product. Finally silica at 80 °C under high vacuum was the condition of choice (Scheme 2.20).



II-42 **II-55**

Scheme 2.20 Boc deprotection of **II-42** using silica and high vacuum at 80 °C.

With this deprotected building block **II-55** in hand, Witkop's conditions were tried again. Surprisingly this attempt did not result in the desired unsaturated product, but in a mixture of inseparable *endo* and *exo* diastereromers **II-56** (Scheme 2.21).



II-55

II-56 *endo* : **II-56** *exo*

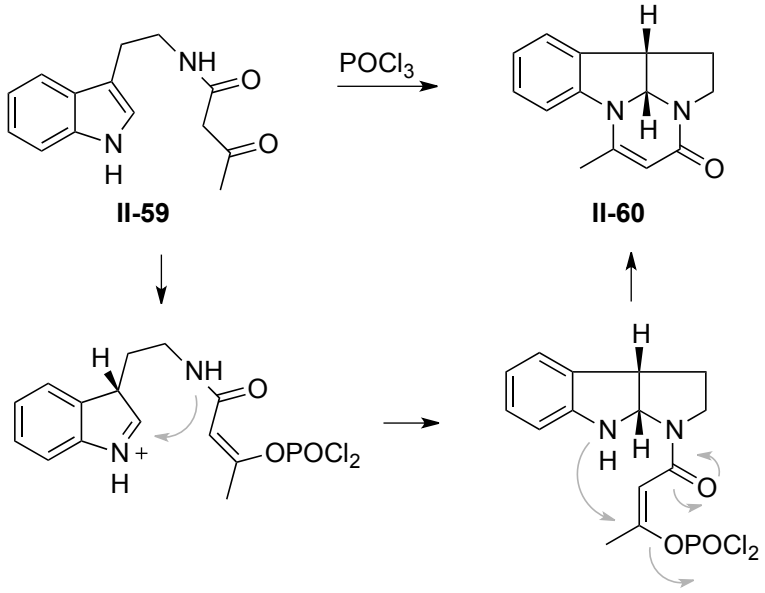
II-57 **II-58**

Scheme 2.21 Witkop's procedure applied to deprotected indole **II-55** with subsequent elimination attempts.

To facilitate the elimination, more equivalents of NEt_3 (up to 20 eq) were added. The reaction time was prolonged to five days and by substituting dichloromethane for dichloroethane, the reaction temperature was raised up to 60 °C, however not resulting in the desired elimination product **II-57**. Finally a method also described in the literature was tried: NaOAc in EtOH was added to the reaction two hours after adding *t*-BuOCl and NEt_3.[74] None of these conditions however lead to the desired elimination product. Use of AgOTf and $AgNO_3$ in NEt_3 lead to elimination, but also to elimination of the OTBS group to result in pyrroloindole **II-58** (Scheme 2.21).

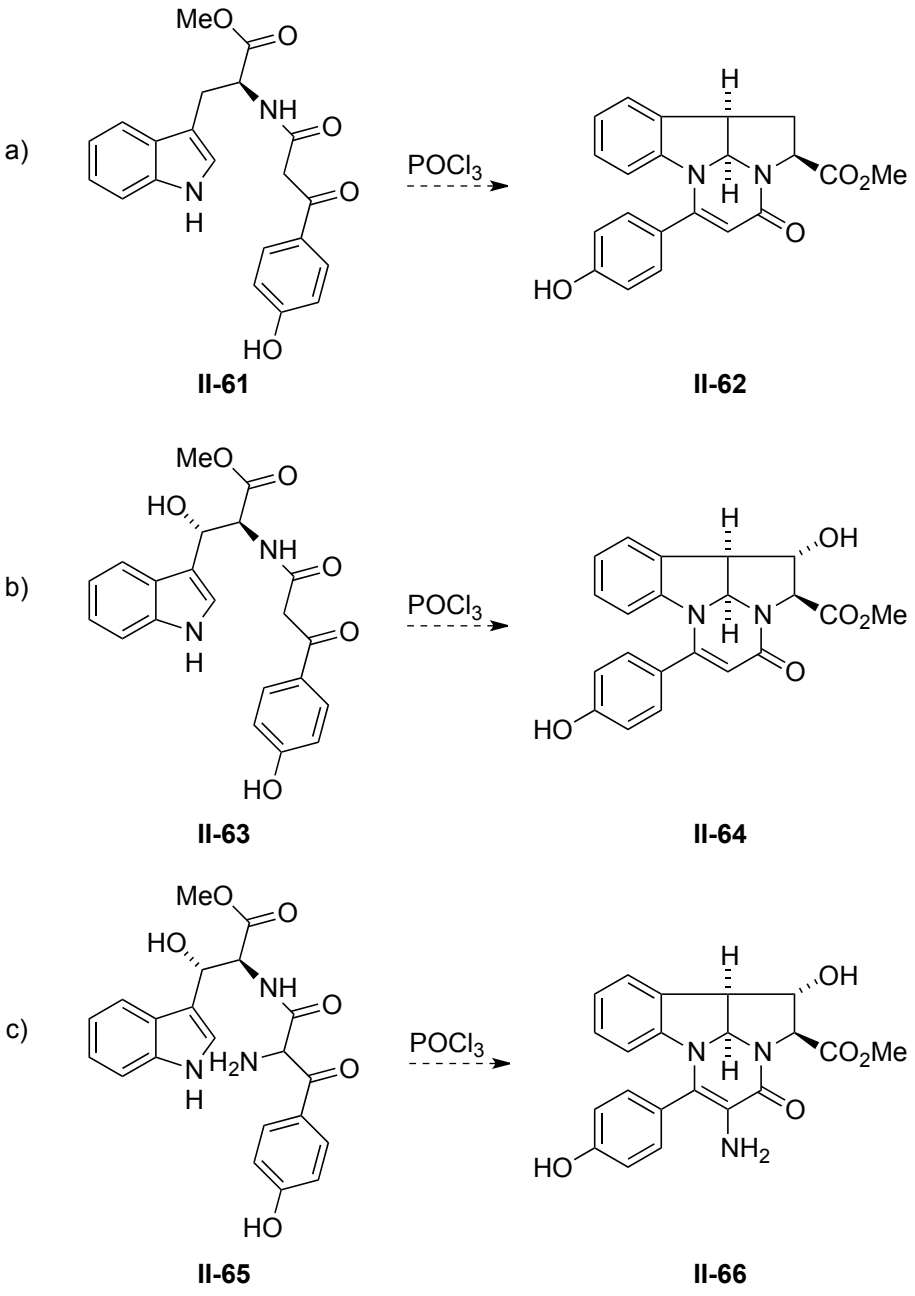
2.3.3 New Strategy Towards the Tetracyclic Core

A method by Jackson *et al*. describes envisaged cyclization of a modified tryptamine **II-59** to the tetracyclic ring system, corresponding to the crocagin core, using $POCl_3$.[75] As shown in Scheme 2.22 $POCl_3$ reacts with the enol, forming HCl and converting oxygen into the leaving group $OPOCl_2$. HCl protonates the nitrogen of the indole. Attack of amide forms the hydropyrroloindole. Subsequently the indole nitrogen attacks the carbon bearing the leaving group, forming the six-membered D-ring in **II-60** by a conjugate addition-elimination mechanism.



Scheme 2.22 Formation of the tetracyclic core present in **II-60** using $POCl_3$.

Substitution of tryptamine by tryptophan and substitution of the methyl group in the β-keto part by hydroxy phenyl would yield the desired precursor **II-61** for the cyclization to the crocagin tetracycle **II-62** (Scheme 2.23 a). Further modification of tryptophan to hydroxy tryptophan **II-63** would install the hydroxy group at an earlier step resulting in **II-64** (Scheme 2.23 b). Installation of a nitrogen at the β-keto part as depicted in **II-65** would put all desired atoms of the crocagin core in **II-66** in place (Scheme 2.23 c).

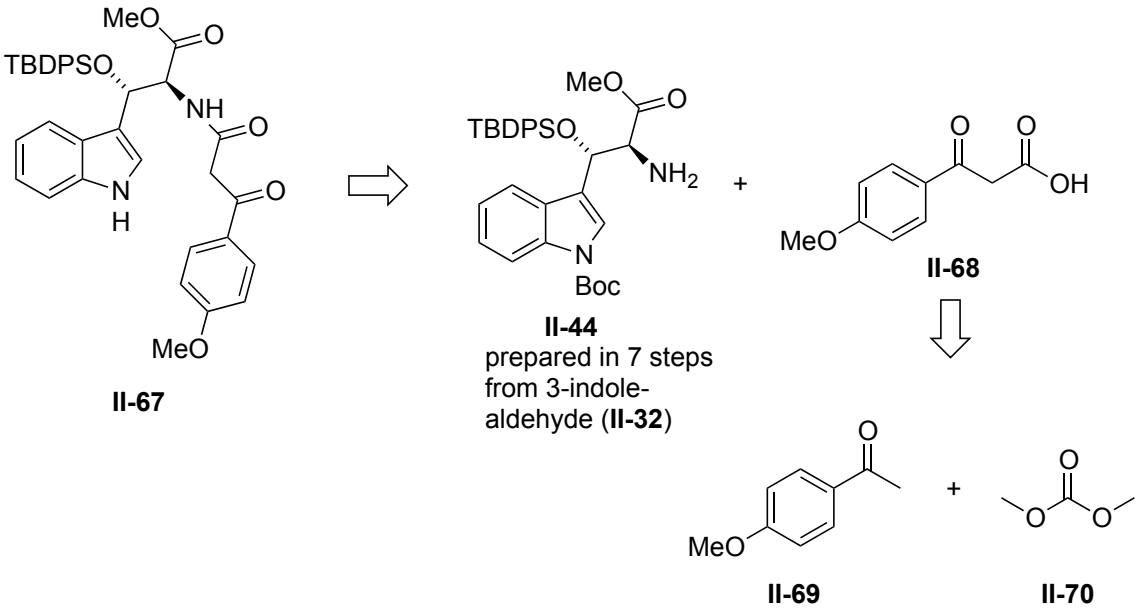


Scheme 2.23 Possible cyclization precursors to obtain the tetracyclic core of crocagin (**II-7**).

2.3.4 Second Generation Strategy – The Retrosynthesis

Cyclization precursor **II-67** featuring a hydroxy group in the benzylic position (Scheme 2.23 b) was chosen to be the first target. From a retrosynthetic point of view (Scheme 2.24), the cyclization precursor can be made from protected hydroxy tryptophan **II-44**, which had already been prepared in seven steps from 3-indole-aldehyde **II-32**, and 3-(4-methoxyphenyl)-3-oxopropanoic acid **II-68**,

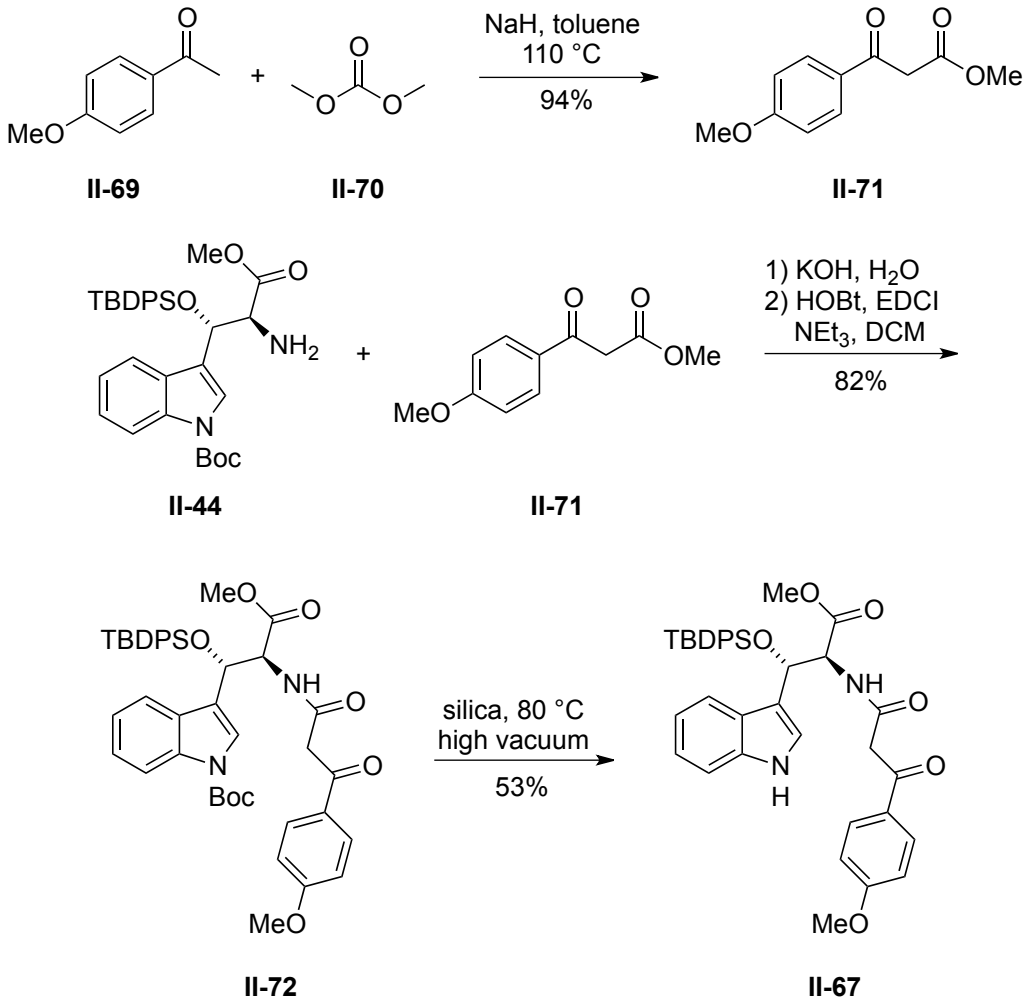
which is obtained from the corresponding ester, made from 1-(4-methoxyphenyl)ethanone **II-69** and dimethyl carbonate **II-70**.



Scheme 2.24 Retrosynthesis for cyclization precursor **II-67**.

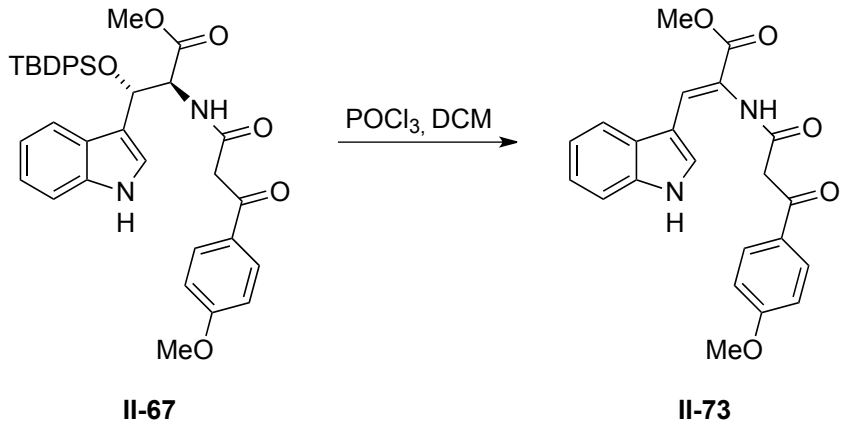
2.3.5 Realization of the Second Generation Strategy

Synthesis of the β-keto ester **II-71** was achieved from protected acetophenon **II-69** and dimethylcarbonat **II-70** using NaH in toluene at 110 °C.[76] Hydrolysis under basic conditions resulted in the corresponding β-keto acid **II-68**, which had to be used directly in the coupling reaction with tryptophan building block **II-44** due to fast decarboxylation. The coupling product **II-67** was obtained in good yield using standard coupling conditions. The Boc group at the indole moiety could be deprotected yielding **II-72** using the previously established deprotection condition (silica, 80 °C, high vacuum) that prevents elimination of the secondary alcohol. The sequence is shown in Scheme 2.25.



Scheme 2.25 Synthesis of cyclization precursor **II-67**.

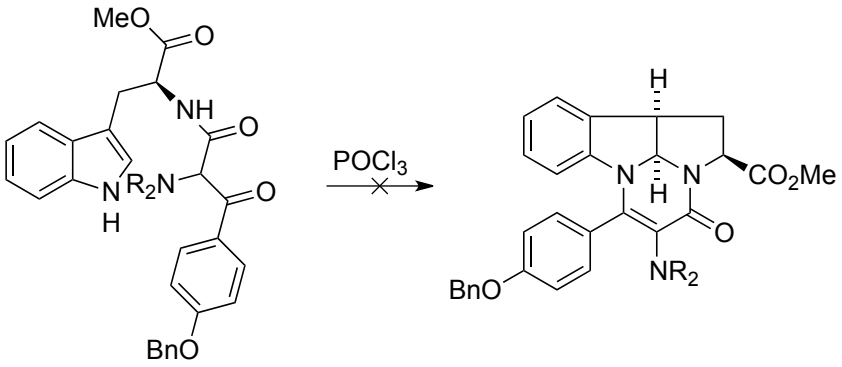
Exposure of **II-67** to cyclization conditions ($POCl_3$ in CH_2Cl_2) resulted in the elimination product **II-73** only.



Scheme 2.26 Unsuccessful cyclization attempt of **II-67** in $POCl_3$.

Since elimination of the secondary alcohol seemed to be an inevitable problem in the hydropyrroloindole cyclization, it was decided to explore a late stage oxidation, wherein the hydroxy group is introduced after the cyclization.

Cyclization attempts bearing a nitrogen in the β-keto part as in **II-74** were conducted by Filip Bihelovic and can be found in the Postdoctoral report. None of the tested cyclization however afforded the desired product **II-75** (Scheme 2.27).

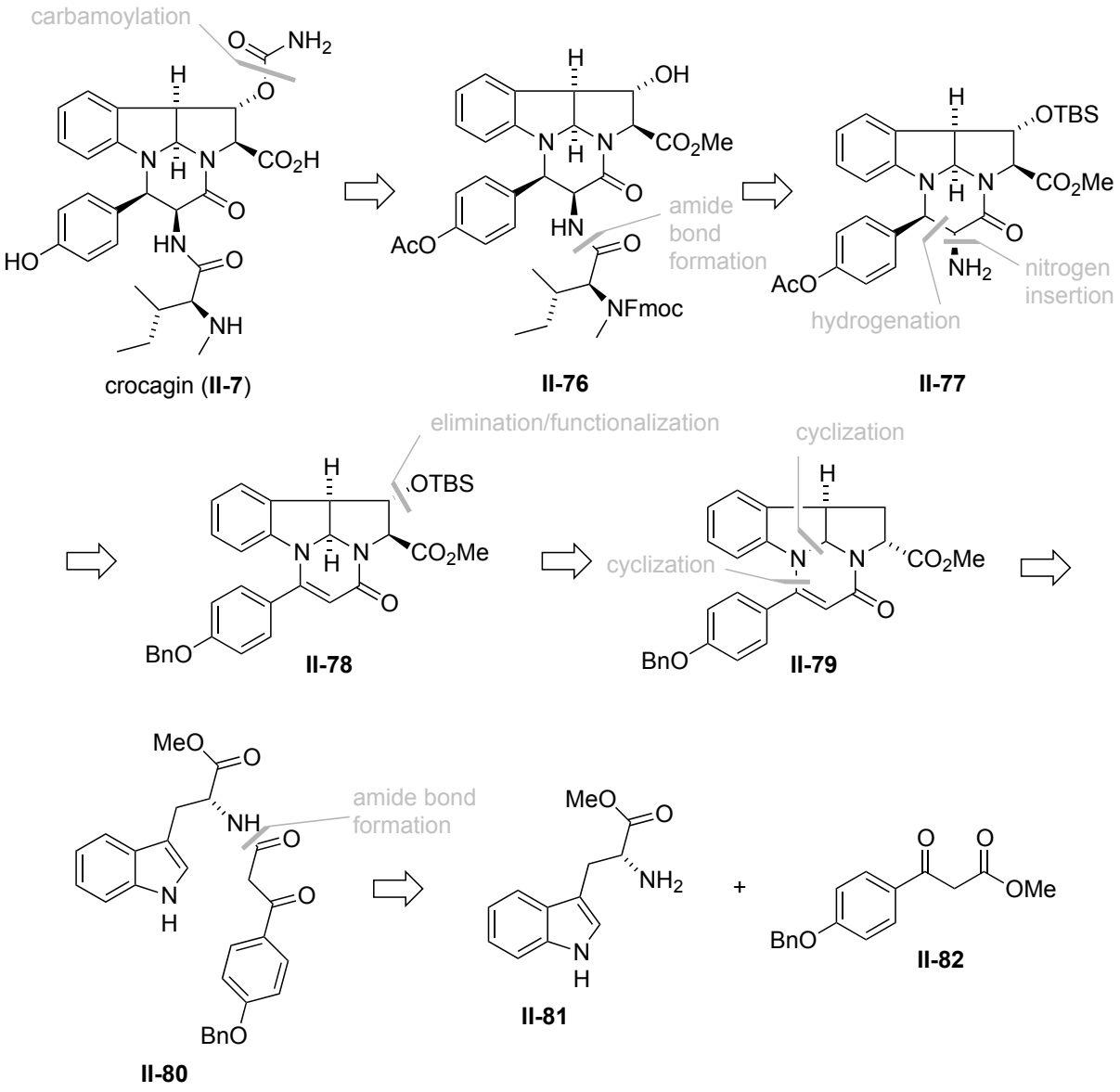


II-74 **II-75**

Scheme 2.27 Tested conditions towards an enamine containing D-ring failed.

2.3.6 Modification of the Second Generation Strategy – The Retrosynthesis

With these results in mind, a protected version of building block **II-61** (Scheme 2.23a) was envisaged as the cyclization precursor. Oxygen in position C-3 and nitrogen at the D-ring should be inserted at a later stage. The new retrosynthesis is shown in Scheme 2.28. The synthesis should be completed by carbamoylation of the oxygen in **II-76**. The isoleucine part should be coupled to the amino group in **II-77** *via* a peptide coupling. This amine **II-77** is formed by reduction of the double bond and nitrogen insertion. The C-3 oxygen should be inserted by hydroboration of the unsaturated system. This leads back to the tetracyclic core **II-79**, which results from cyclization of **II-80** (protected version of **II-61**) that in turn can be accessed through coupling of tryptophan methylester **II-81** and β-keto ester **II-82**.

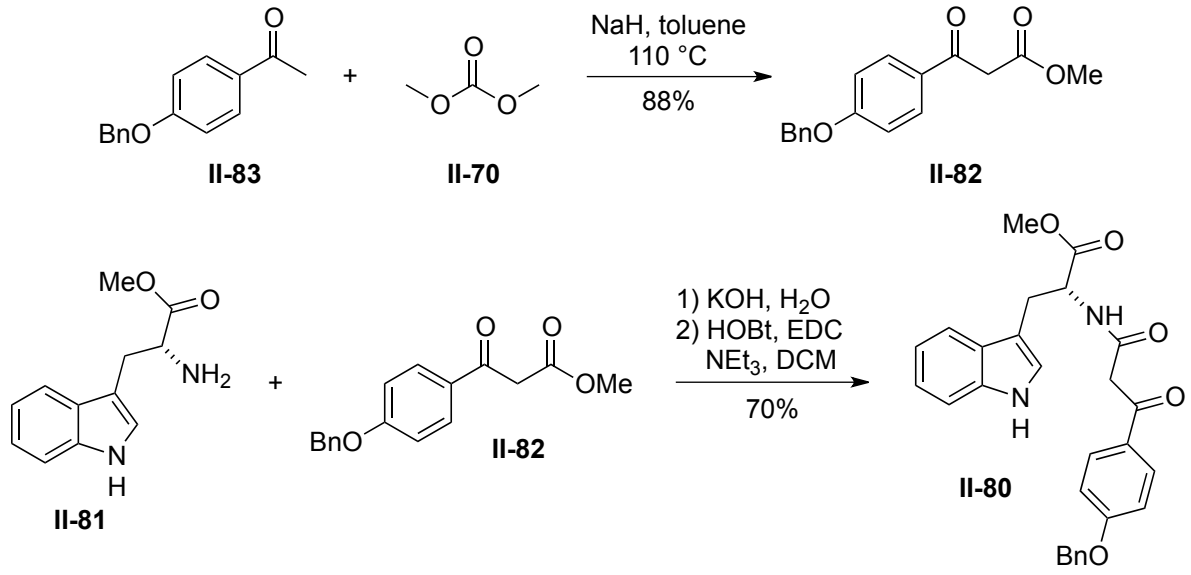


Scheme 2.28 Retrosynthetic overview for the synthesis of crocagin (**II-7**), using a late stage oxidation to install C-3 oxygen at the C-ring and late stage amination to insert amine at the D-ring.

2.3.7 Realization of the Modified Second Generation Strategy

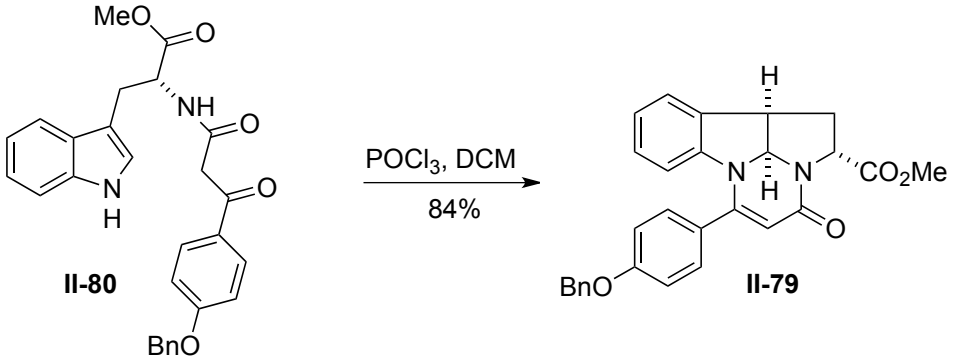
a) Cyclization precursor and cyclization

The synthesis starts with the preparation of the cyclization precursor **II-80**. The β-keto ester **II-82** was synthesized from protected acetophenon **II-83** and dimethylcarbonat **II-70**. Hydrolysis under basic conditions resulted in the corresponding β-keto acid, which was, again due to fast decarboxylation, used directly in the coupling reaction with D-tryptophan methylester (**II-81**). The substance **II-80** was obtained in good yield using standard coupling conditions (Scheme 2.29).

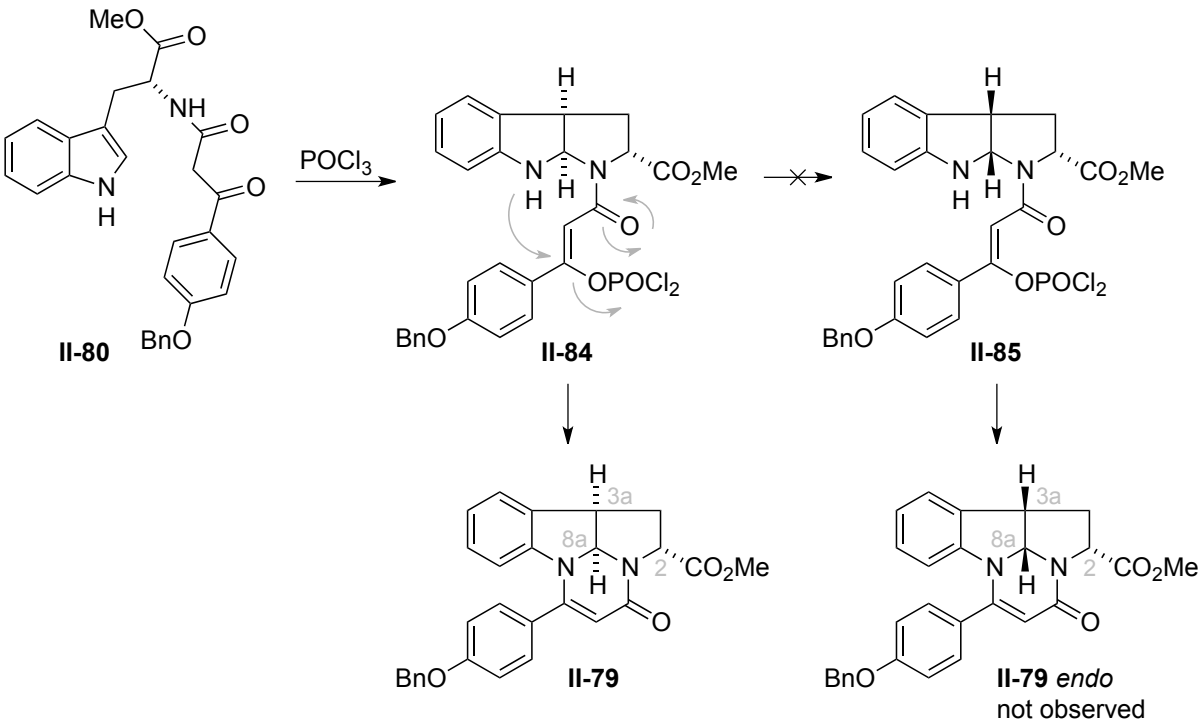


Scheme 2.29 Synthesis of cyclization precursor **II-80**.

Exposure of **II-80** to cyclization conditions ($POCl_3$ in CH_2Cl_2) resulted in the tetracyclic compound **II-79** (Scheme 2.30), exclusively in the form of the *exo* isomer, indicated by the chemical shift of the methylester at 3.8 ppm.[68] The acid catalyzed mechanism should allow formation of the thermodynamically more stable *endo* compound (**II-79** *endo*). Apparently cyclization to the six-membered D-ring happens fast from the kinetic *exo* product **II-84**. As a consequence only this isomer is observed (Scheme 2.31).



Scheme 2.30 Cyclization to tetracyclic compound **II-79**.



Scheme 2.31 Mechanism for the formation of the tetracyclic compound **II-79**.

The unnatural D-tryptophan is necessary to adapt the stereochemistry of the C-3a and C-8a protons. In this cyclization product the ester in C-2 shows the undesired stereochemistry. It was envisaged to correct this in a epimerization sequence later.

A crystal structure of the *p*-NO_2-benzoyl compound **II-86** proved the identity as well as the relative stereochemistry of the tetracyclic structure (Figure 2.7).

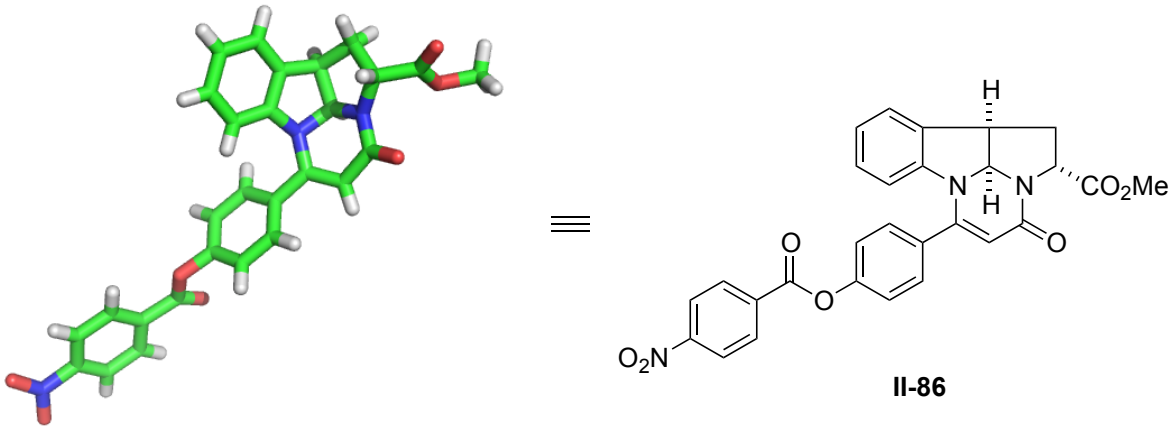
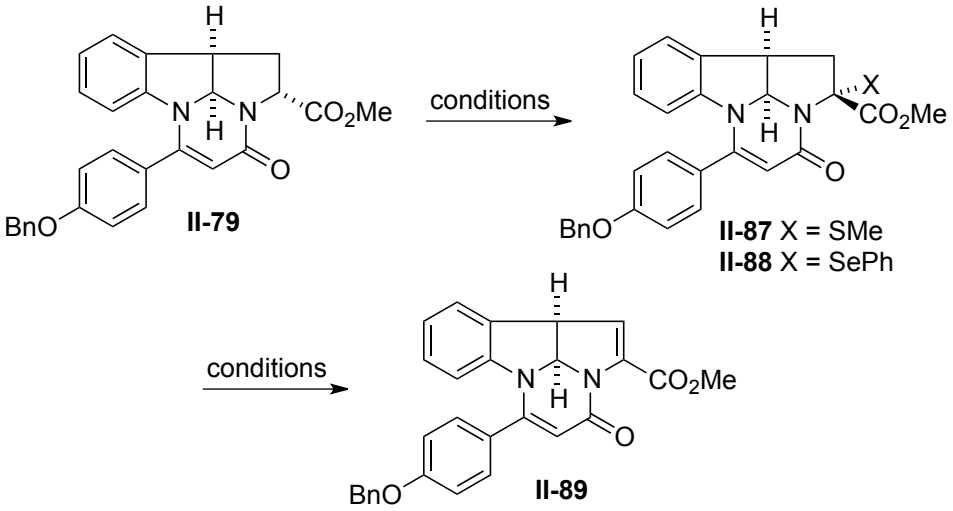


Figure 2.7 Crystal structure of tetracyclic compound **II-86**.

b) Elimination and Oxidation

The next synthetic step comprised the elimination and subsequent oxidation of building block **II-79** at the C-ring. Elimination should be effected *via* a base-mediated introduction of a sulfur or selenium electrophile, followed by an oxidation.[77] Table 2.1 summarizes attempts for the formation of **II-89**.

Table 2.1 Elimination attempts in order to obtain elimination product **II-89**.

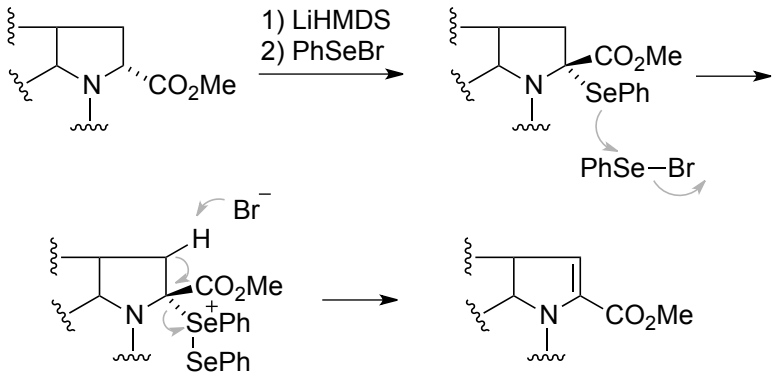


Entry	Base (1 eq)	Electrophile	Temperature	Observation
1	LDA	PhSeCl (1 eq)	−78 °C	s.m.
2	LDA	PhSeBr (1 eq)	−78 °C	s.m.
3	LDA	Me_2S_2 (1 eq)	−78 °C	s.m.
4	LDA	*N*-PSP (1 eq)	−40 °C	c.m.
5	LiHMDS	PhSeBr (1 eq)	−78 °C	**II-88** and **II-89** (ratio 3:1, yield 40%)
6	LiHMDS	PhSeBr (2 eq)	−40 °C	**II-88** and **II-89** (ratio 1:2, yield 68%)

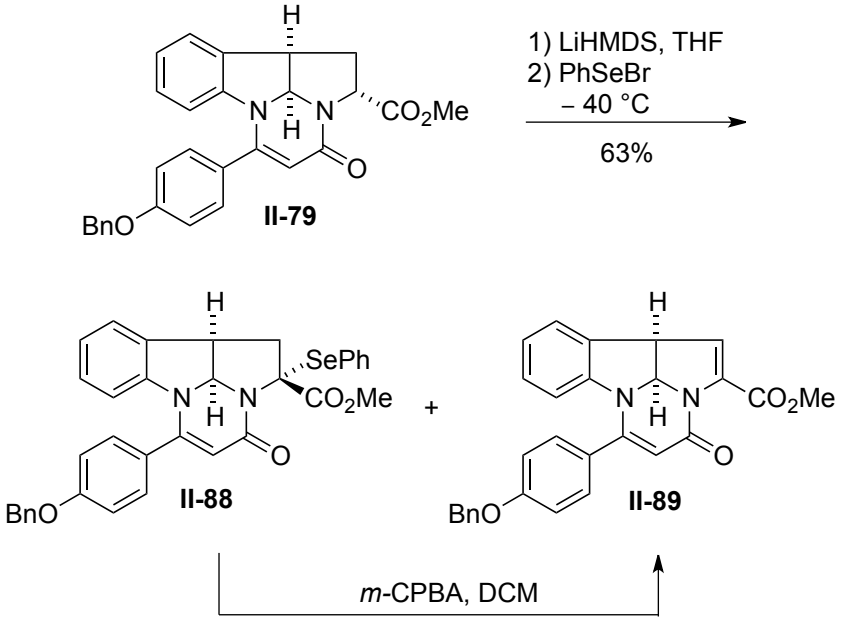
s.m. = starting material, c.m. = crude mixture

LDA as base in combination with PhSeCl, PhSeBr, Me_2S_2 and *N*-Phenylselenophtalimid (*N*-PSP) did not result in the desired product (Entries 1-4). LiHMDS as base and PhSeBr as electrophile resulted in a

mixture of selenium-containing product **II-88** and elimination product **II-89** (Entries 5-6). The direct elimination can be explained either by air, present during the workup or by the mechanism shown in Scheme 2.32: a second molecule PhSeBr is attacked by the organoselen species and deprotonation of the β-proton triggers the elimination. This is reasonable because a second equivalent raises the yield and the ratio in favor of elimination product **II-89**. The mixture of selenium containing product **II-88** and elimination product **II-89** was then subjected to oxidative conditions. *m*-CPBA proved to be the best reagent for this oxidation and elimination sequence to obtain unsaturated ester **II-89** (Scheme 2.33).



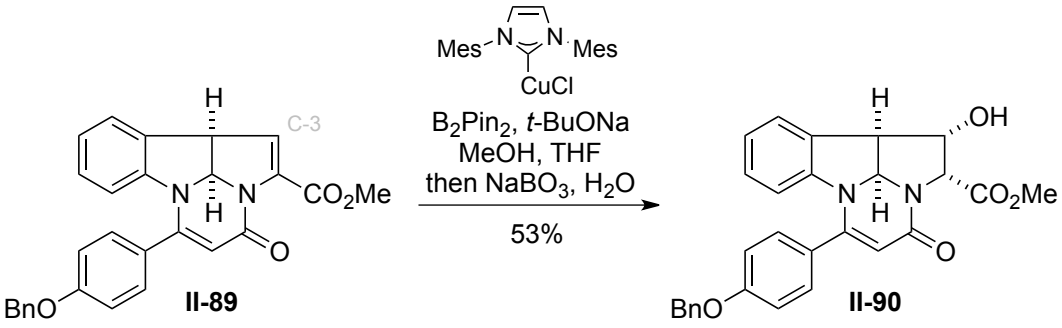
Scheme 2.32 Mechanism for the direct formation of the elimination product.



Scheme 2.33 Optimized conditions to yield the elimination product **II-89**.

To introduce oxygen in position C-3 of unsaturated ester **II-89** modified hydroboration conditions for double bonds bearing an electron withdrawing group were found in the literature.[78,79]

Application of the described conditions to the unsaturated tetracyclic core **II-89** with subsequent oxidative work up resulted in the desired alcohol **II-90**.



Scheme 2.34 Hydroboration conditions yielding desired hydroxy compound **II-90**.

A possible catalytic cycle is displayed in Figure 2.8.[78] The copper-boryl complex, formed from the copper species and bispinakolatoborane (**A**) as the key-intermediate undergoes a conjugate addition at the α,β-unsaturated system (**B**). The organocopper species is then protodemetallated by MeOH (**C**). The resulting copper alkoxide is regenerated to the active catalyst with bispinakolatoborane (**D**). The boryl compound is oxidized and rearranges to the desired alcohol **II-90** (**E**).

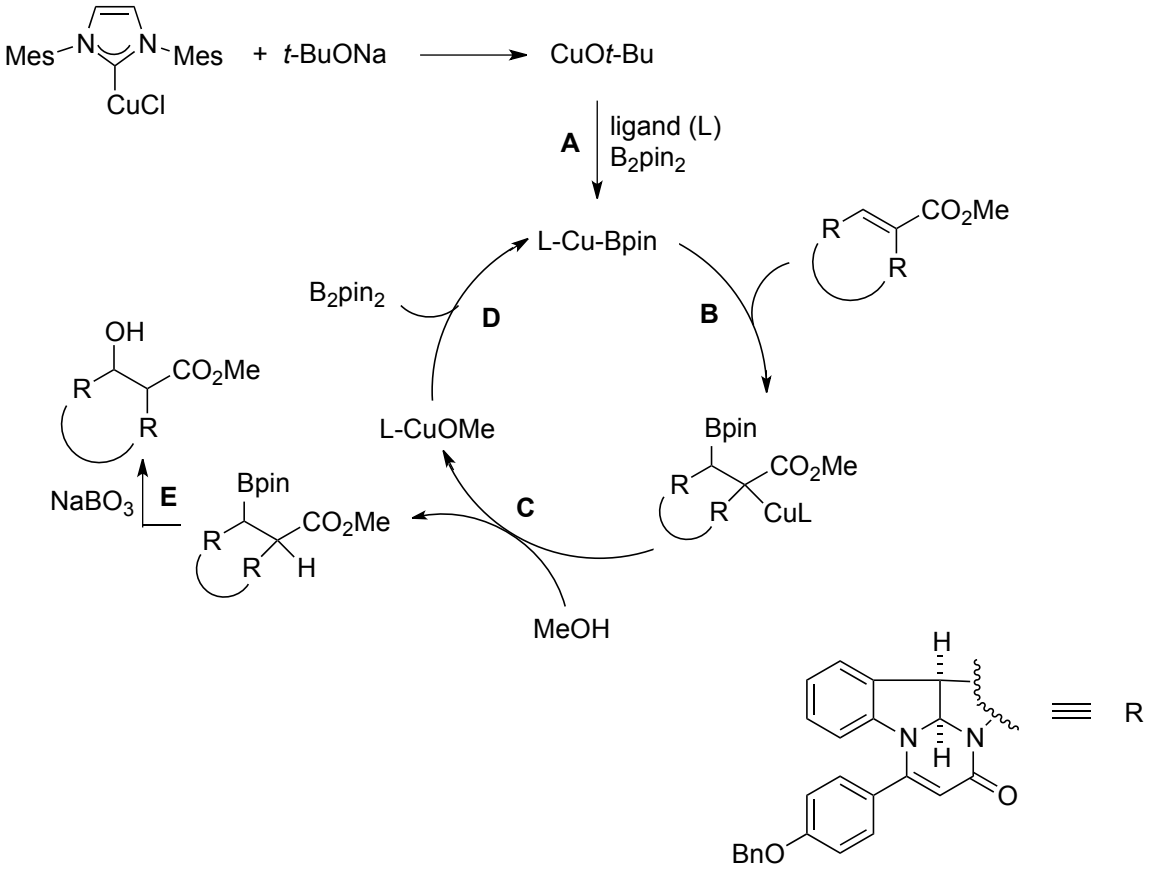
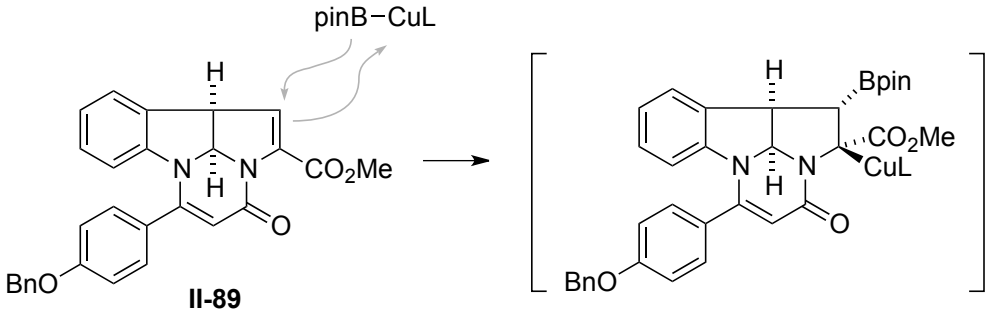


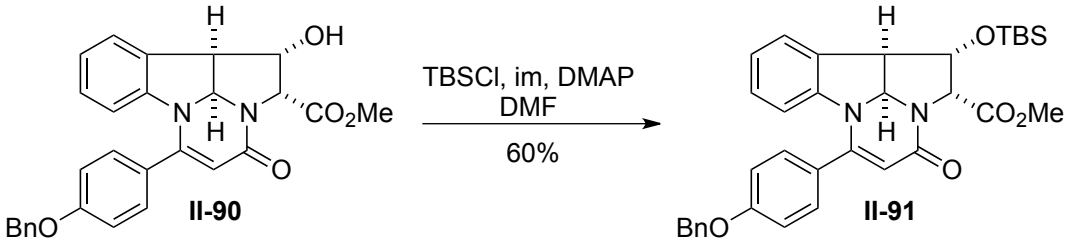
Figure 2.8 Catalytic cycle explaining hydroboration of **II-89**.

In contrast to normal hydroborations, the conjugate addition at the α,β-unsaturated system proceeds *via* an *anti* attack, which results in the *exo* isomer. The attack of the boron species happens from the less hindered convex face (Scheme 2.35).



Scheme 2.35 Stereoselective anti attack at **II-89** explains formation of the *syn*-product.

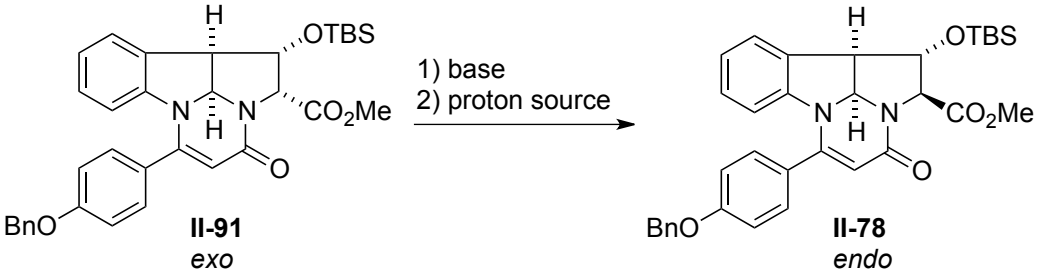
Since the *exo* isomer is not the desired one, the ester had to be epimerized to result in the *endo* isomer. First the hydroxy group was protected with a TBS group (Scheme 2.36) and different epimerization conditions were tested with compound **II-90**.



Scheme 2.36 TBS protection of hydroxy tetracycle **II-90**.

NaOMe in MeOH did not lead to conversion to **II-78** and even at higher temperature only starting material **II-91** was recovered (Table 2.2, Entry 1). Deprotonation with LiHMDS and subsequent reprotonation with water, *i*-PrOH or EtOH yielded mixtures of both isomers (Entries 2-6), which could not be separated by column chromatography. Tested conditions are summarized in Table 2.2.

Table 2.2 Evaluated epimerization conditions for TBS protected tetracycle **II-91**.

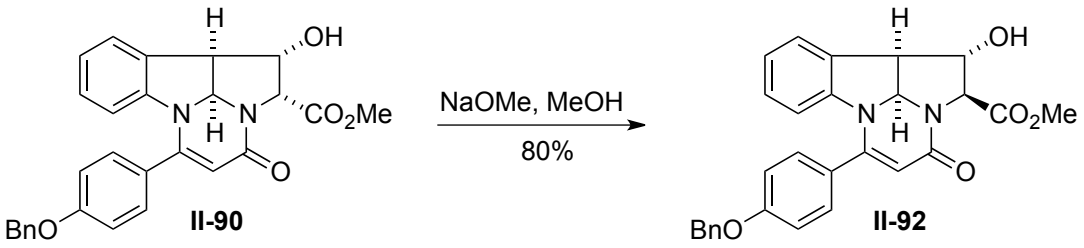


Entry	Base (2 eq)	Proton source	Temperature Substrate	Temperature Proton source	Ratio *exo*/*endo*
1	NaOMe	MeOH	60 °C		only *exo*
2	LiHMDS	*i*-PrOH	−78 °C	r.t.	2:1
3	LiHMDS	H_2O in THF	−78 °C	r.t.	only *exo*
4	LiHMDS	EtOH	−78 °C	−78 °C	3:2
5	LiHMDS	EtOH*	−78 °C	−78 °C	5:2
6	LiHMDS	*i*-PrOH	−40 °C	−40 °C	3:2

* deprotonated substrate was cannulated to the proton source.

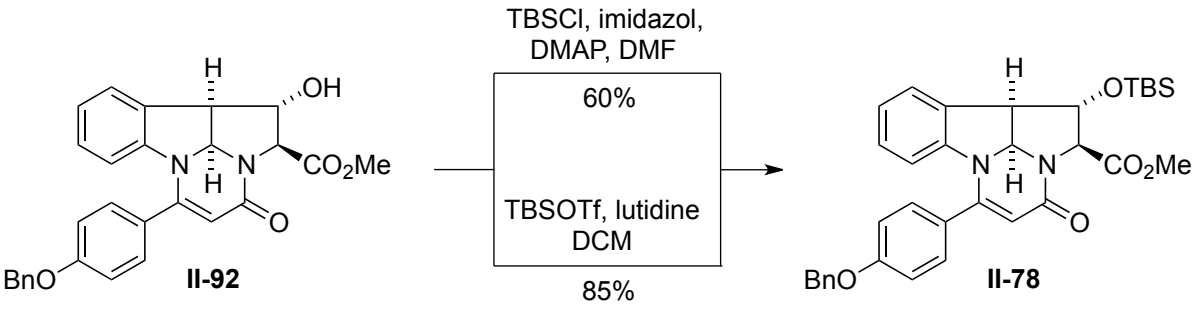
According to the literature the desired *endo* isomer is the thermodynamic more stable product.[68] That means conditions like NaOMe should yield this product at elevated temperature. In the TBS protected version **II-91** the bulky TBS group apparently hinders the reprotonation from the convex

site. As a consequence these conditions were tried also on the unprotected system (Scheme 2.37), which resulted in the desired *endo* isomer (which could be separated by column chromatography from the *exo* isomer).



Scheme 2.37 Epimerization of methyl ester in **II-90** using NaOMe.

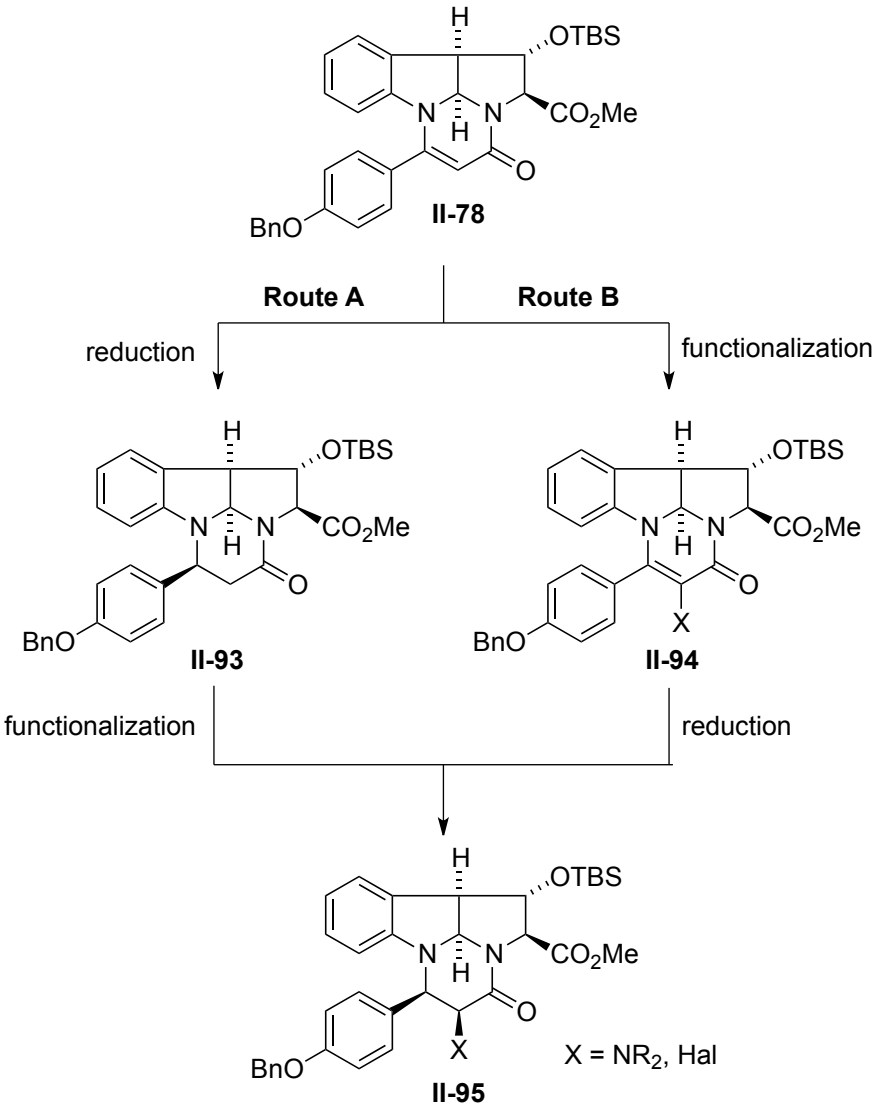
Subsequent TBS protection of secondary alcohol present on compound **II-92**, which was necessary for later steps, was also possible on the *endo* isomer. Substitution of TBSCl by TBSOTf increased the yield (Scheme 2.38).



Scheme 2.38 TBS protection of the *endo* isomer **II-92**.

c) Functionalization of the D-ring

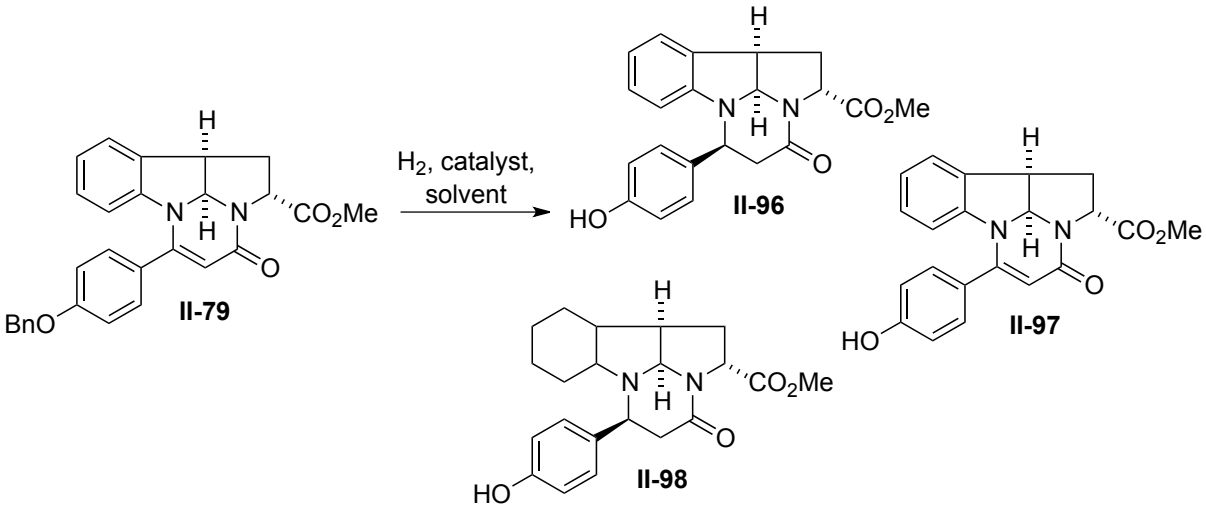
In order to complete the synthesis, the double bond of the Michael system in the D-ring of compound **II-78** has to be hydrogenated and the α-position of the Michael system has to be functionalized. To achieve this functionalization, there are two possible pathways (Scheme 2.39), either reduction of the trisubstituted double bond first and then functionalization (Route A) or functionalization first and then reduction of the tetrasubstituted double bond (Route B).



Scheme 2.39 Two possible ways for the reduction/functionalization sequence of the D-ring.

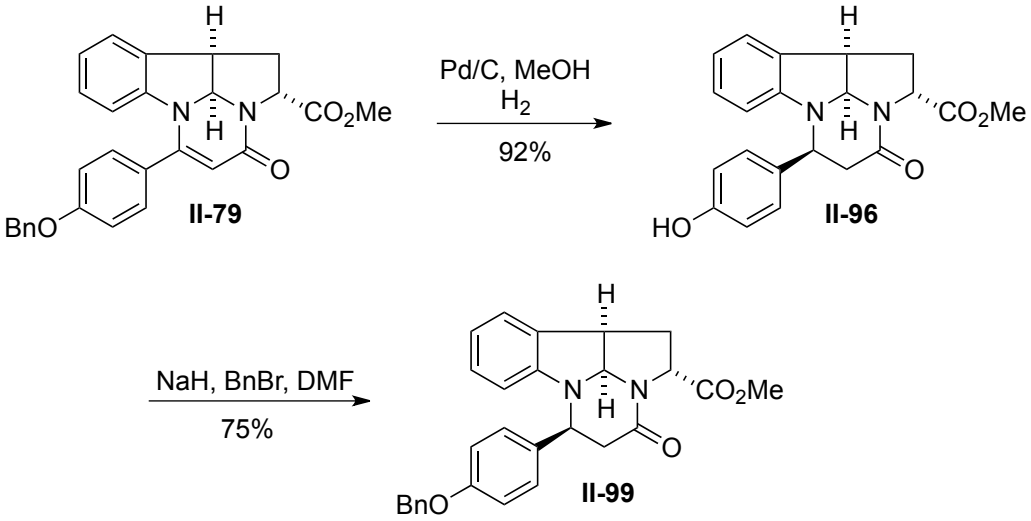
Using route A, several conditions were tried for reduction of the trisubstituted double bond on **II-79**, a model system lacking the C-3-oxygen and showing the opposite stereochemistry at C-2 (Table 2.3). With PtO_2 either starting material (Entries 1 and 3) or complete reduction of the aromatic ring of the indole was observed (Entries 2 and 4), which is in agreement with the literature for similar systems.[75] Using Pd/C short reaction time lead to a mixture of debenzylated starting material and product (Entry 5), which were not separable by column chromatography. Pd/C in MeOH lead to the desired product in very good yield after 18 h (Entry 6). Since Pd/C also deprotects benzyl groups, the benzylgroup had to be reinstalled afterwards (Scheme 2.40).

Table 2.3 Tested conditions for reduction of the trisubstituted double bond.



Entry	Catalyst (1 atm H_2)	Solvent	Time	Observation
1	PtO_2	MeOH	1 h	s.m.
2	PtO_2	MeOH	18 h	**II-98***
3	PtO_2	EtOAc	1 h	s.m.
4	PtO_2	EtOH	2 h	**II-98***
5	Pd/C	MeOH	3 h	**II-97**
6	Pd/C	MeOH	18 h	**II-96** (92% yield)

s.m. = starting material *Formation of **II-98** was assumed according to ^{1}H NMR of the crude product. **II-98** was not fully characterized.



Scheme 2.40 Reduction and reprotection sequence to yield **II-99**.

During hydrogenation, surface bound hydrogen atoms should attack the double bond from the less hindered convex face of the molecule, yielding the desired stereochemistry. This assumption was enforced by a 1D NOESY experiment, shown in Figure 2.9: hydrogen c shows NOE coupling to hydrogen b (and a and d), which strongly suggests that these hydrogens point in the same direction.

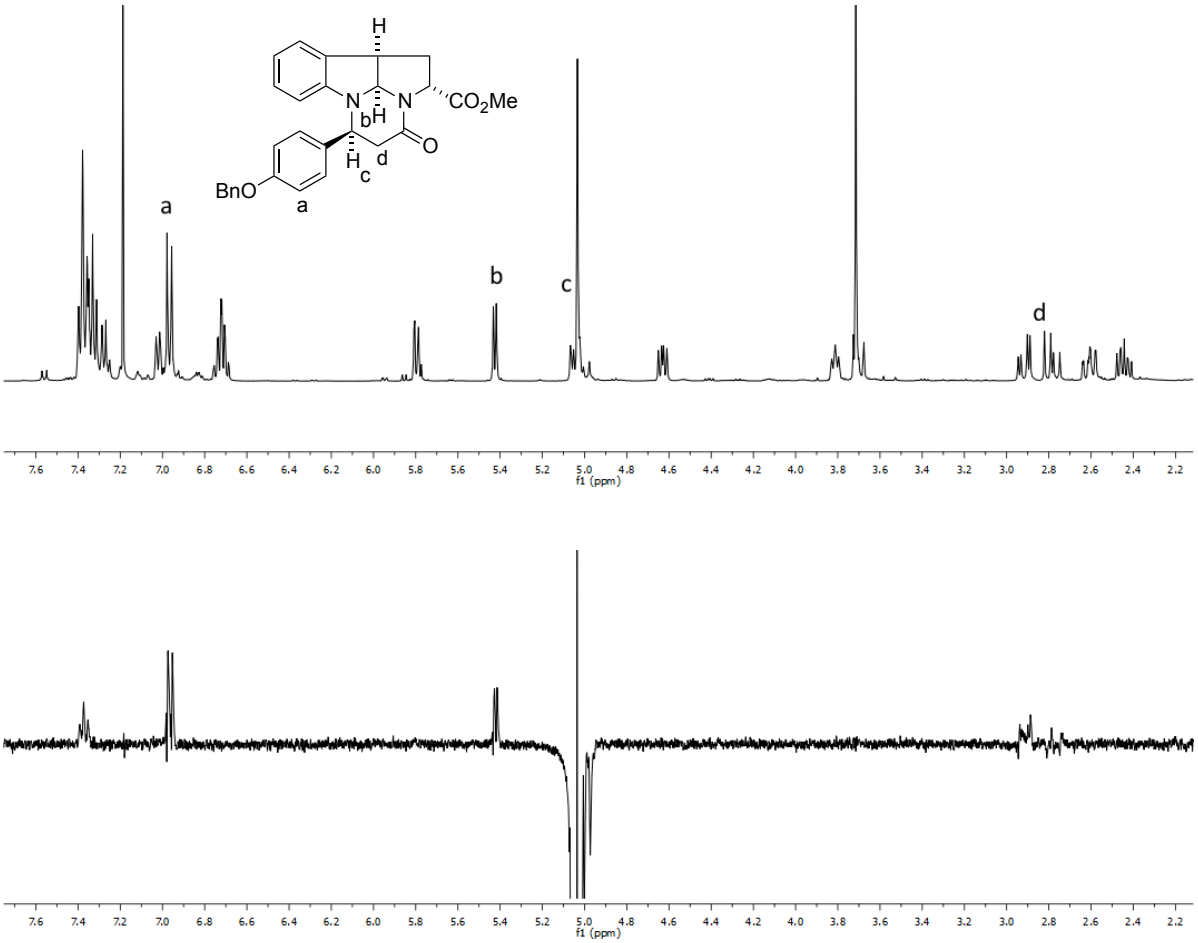
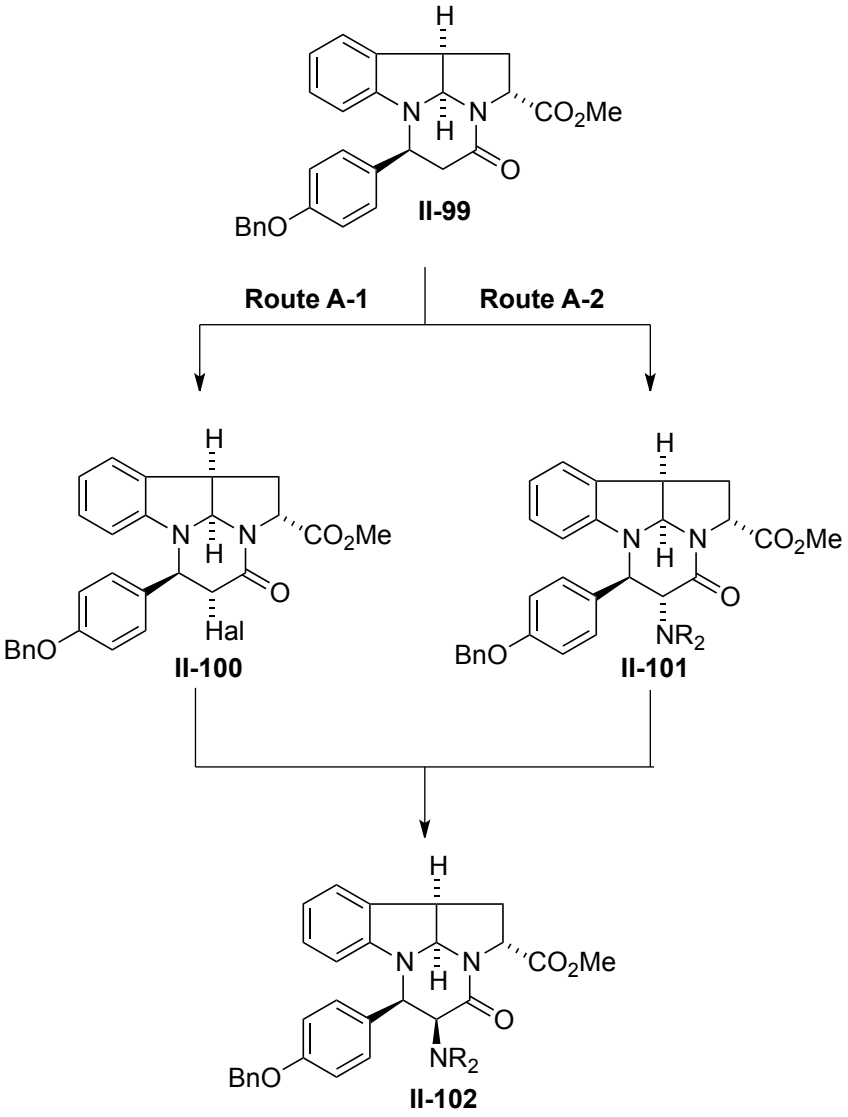


Figure 2.9 ^{1}H-NMR (top) and 1D-NOESY NMR (bottom) for compound **II-99**. Irradiation on H-b reveals NOE correlation to H-a, H-c, H-d.

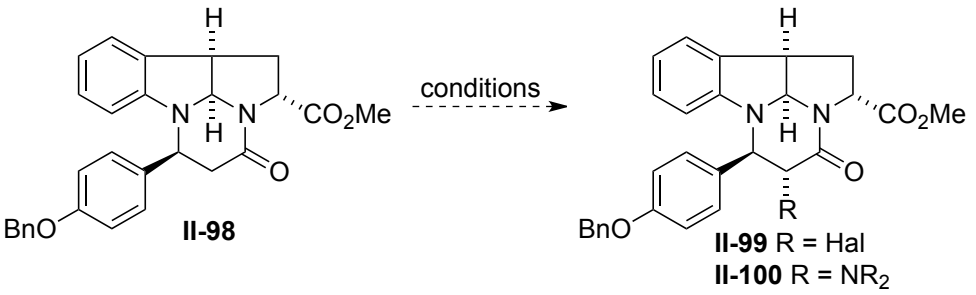
With the hydrogenated compound **II-99** in hand, the next step was an α-functionalization next to the amide function *via* two different routes (Scheme 2.41). For the functionalization with a halogen atom (Cl, Br, I) the caved structure of the molecule would allow attack only with the convex site. Nucleophilic substitution, for example with an azide, would give the functionalized compound then with the desired stereochemistry (Route A-1). As an alternative way, functionalization with nitrogen and then adjustment of the stereochemistry by epimerization was considered (Route A-2).



Scheme 2.41 Two different routes for the functionalization of the hydrogenated D-ring.

Deprotonation with lithium bases (LiHMDS, LDA, LiTMP) and subsequent treatment with NBS did not give any of the desired product (Table 2.4, Entries 1-3). With KHMDS and 2,4,6-triisopropylbenzenesulfonyl azide the product could not be isolated either (Entry 4). The same negative outcome was observed with $CuBr_2$ (Entry 5) and $PyHBr_3$ (Entry 6) as summarized in Table 2.4.

Table 2.4 Functionalization attempts for the hydrogenated D-ring in **II-98**.

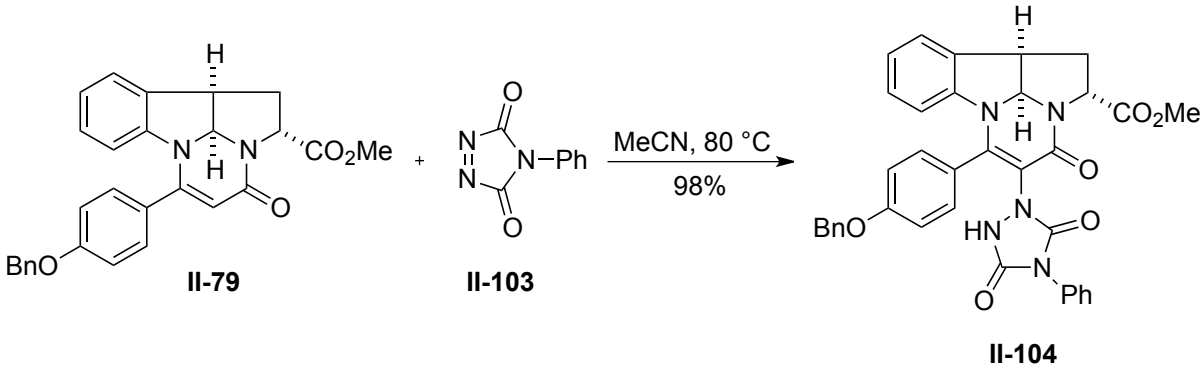


Entry	Conditions	Observation
1	LiHMDS, NBS, −40 °C	s.m.
2	LDA, NBS, −78 °C	s.m. + methyl ester cleavage
3	LiTMP, NBS, −78 °C	s.m. + methyl ester cleavage
4	KHMDS, −78 °C, 2,4,6-triisopropylbenzenesulfonyl azide	c.m., correct mass in HRMS
5	$CuBr_2$, 60 °C, pressure tube	s.m.
6	$PyHBr_3$	c.m., HRMS indicated bromine containing product

s.m. = starting material, c.m. = complex mixture

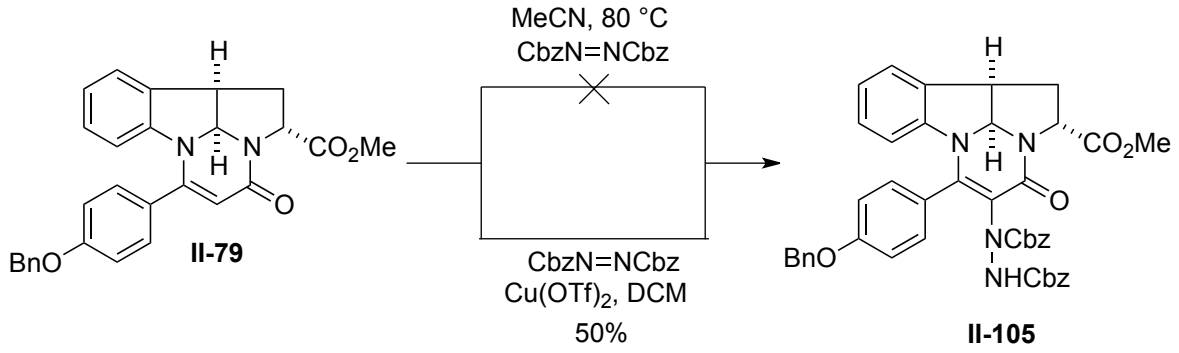
All functionalization conditions α to the amide were probably disturbed by the presence of the ester, since ester and amide have similar pk_a-values. To circumvent this, reduction of the ester to the alcohol and reoxidation after the functionalization could be considered.

Since this is not a step economic solution, the focus was set on the functionalization of the double bond with subsequent hydrogenation (Route B, Scheme 2.39). Experiments were first tried on the models system **II-79**, lacking C-3 oxygen and showing the wrong stereochemistry at C-2 and later on compound **II-78**. The double bond is not only an unsaturated amide, but also an enamine, which is nucleophilic. 4-Phenyl-3*H*-1,2,4-triazole-3,5(4*H*)-dione (**II-103**) is known to react with nucleophilic double bonds.[80] The tetracyclic compound **II-79** indeed reacted with the triazole **II-103** in acetonitrile at 80 °C to yield **II-104** (Scheme 2.42).



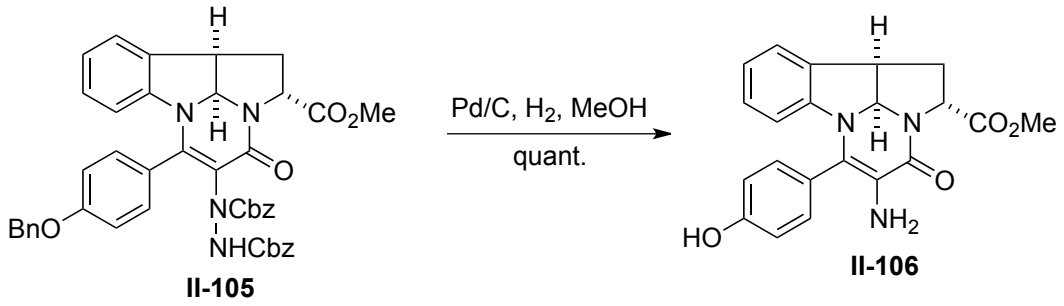
Scheme 2.42 Reaction of 4-Phenyl-3*H*-1,2,4-triazole-3,5(4*H*)-dione (**II-103**) with the tetracyclic compound **II-79**.

In literature, no conditions are known to cleave this triazole in order to convert it to an amine. Therefor other nitrogen electrophiles were explored. Dibenzyl azodicarboxylate itself did not react, but upon addition of $Cu(OTf)_2$ the desired product **II-105** was obtained (Scheme 2.43).[81] $Cu(OTf)_2$ presumably coordinates to the nitrogen of dibenzyl azodicarboxylate, activates it and allows a nucleophilic attack of the enamine.



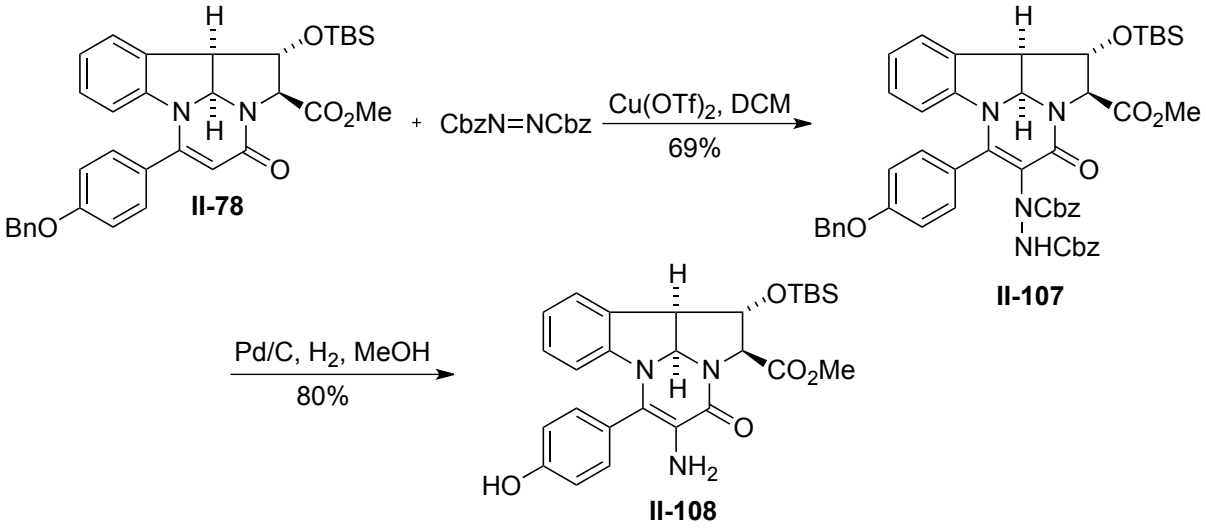
Scheme 2.43 Functionalization of the D-ring in **II-79** using dibenzyl azodicarboxylate to yield **II-105**.

The free enamine **II-106** could then be obtained by hydrogenation, shown in Scheme 2.44.



Scheme 2.44 Treatment with Pd/C and H_2 gas afforded the free enamine **II-106** with simultaneous deprotection of the benzyl group.

This reaction sequence could be transferred to the advanced system **II-78**, featuring C-3-oxygen and the desired stereochemistry at C-2. Reaction with dibenzyldicarboxylate yielded **II-107** and subsequent hydrogenation lead to **II-108**.



Scheme 2.45 Funtionalization of the D-ring in the advanced system **II-78** yielding **II-108**.

The identity of enamine **II-108** was proven by a crystal structure of the corresponding *p*-nitro benzoyl species **II-109**. The crystal structure is shown in Figure 2.10.

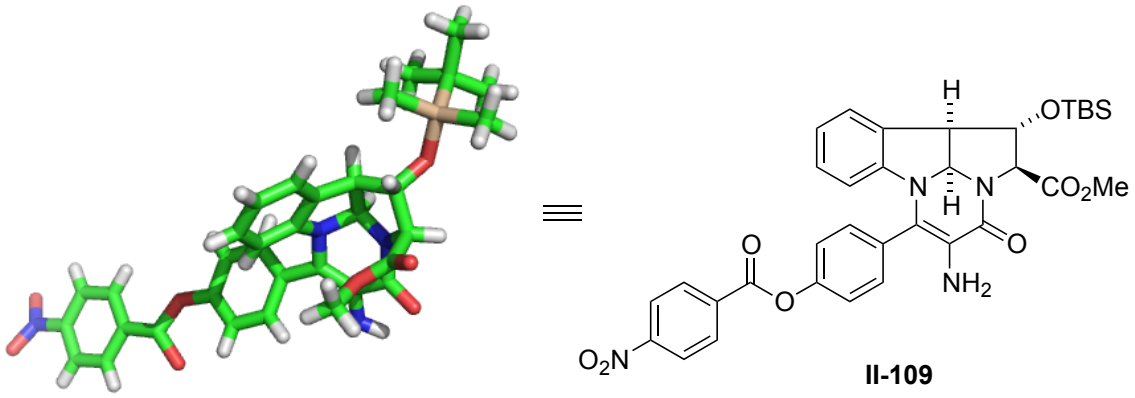
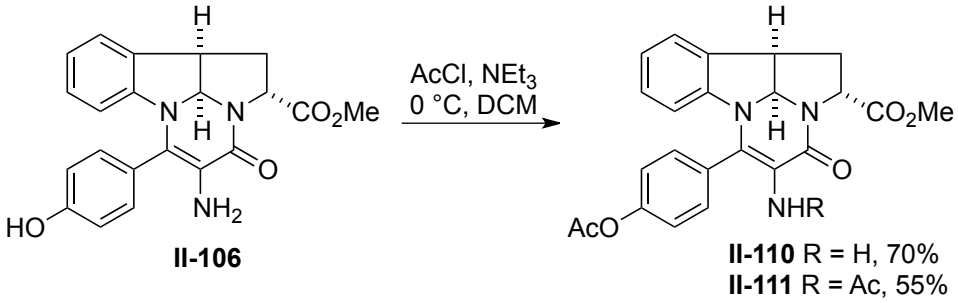


Figure 2.10 *p*-Nitro benzoyl species **II-109**, proving the identitiy of synthesized enamine **II-108**.

Reduction of the tetrasubstituted double bond was first tested on a model system **II-106** lacking C-3 oxygen and showing the wrong stereochemistry at C-2.

It was found out that acetylation of the phenolic moiety and enamine is possible. Using one equivalent of AcCl and NEt_3 afforded *O*-acetylated product, using two equivalents afforded *O*- and *N*-acetylated product (Scheme 2.46).



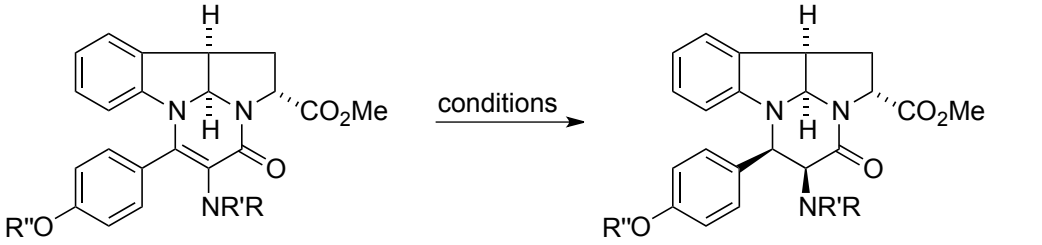
Scheme 2.46 Acetylation of **II-106** yielding mono (**II-110**) or bis (**II-111**) acetylated product.

With compounds **II-106**, **II-110**, **II-111** and compound **II-105** several hydrogenation conditions were tested, summarized in Table 2.5.

Compound **II-105** was reacted with [Rh]- and [Ir]-catalysts under an athmosphere of hydrogen, but only starting material was observed (Entries 2, 3, 4). Reaction with imin (formed *in situ* from NBSH) gave only starting material (Entry 7) as well as reaction with trifluoroacetic acid as proton source and triethlysilane as hydride source (Entry 8). Hydrogenation with Pd/C as catalyst (Entries 1, 5, 6) lead to deprotection of all benzyl and carboxybenzyl groups as well as to N – N bond cleavage, which gave compound **II-106**. Under a pressure of 8 bar hydrogen gas in acetic acid as solvent, acetylation of amino- and hydroxy group was observed (Entry 6). Hydrogenation of **II-106** was tried with imin (Entry

10), trifluoroacetic acid and triethlysilane (Entry 11) and [Ir]-catalyst (Entry 12), which all resulted in starting material only. Hydrogenation with Pd/C as catalyst (Entries 9 and 13) lead to formation of traces of product, in case of acetic acid as the solvent. The product could not be isolated, but HRMS indicated product formation (Entry 13). Hydrogenation attempts of **II-111** lead to starting material, respectively deactylated starting material in all cases (Entries 14-17). Product formation was finally observed in the case of Entry 18. Compound **II-110** was hydrogenated using EtDuPhosRh as catalyst at 80 bar of hydrogen gas and 90 °C.

Table 2.5 Tested conditions for the reduction of the tetra substituted double bond.



II-105 R = NHCbz, R' = Cbz, R" = Bn
II-106 R = H, R' = H, R" = H
II-111 R = Ac, R' = H, R" = Ac
II-110 R = H, R' = H, R" = Ac

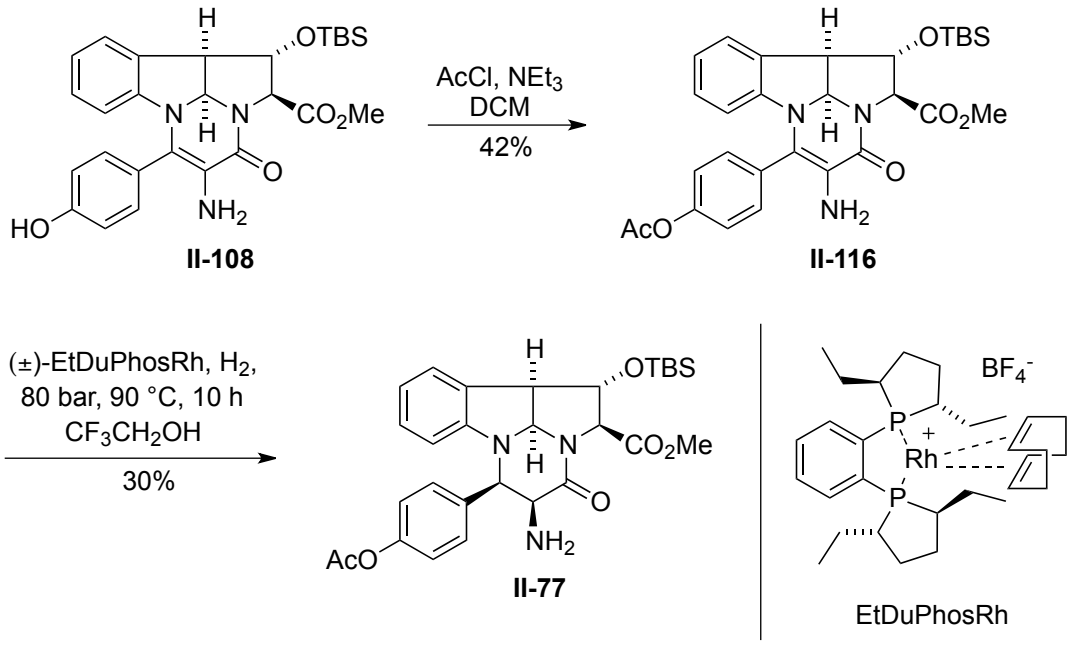
II-112 R = NHCbz, R' = Cbz, R" = Bn
II-113 R = H, R' = H, R" = H
II-114 R = Ac, R' = H, R" = Ac
II-115 R = H, R' = H, R" = Ac

Entry	substrate	conditions	observation
1	**II-105**	Pd/C, H_2, 8 bar, CH_3OH	**II-106**, quant.
2	**II-105**	$[RhCODCl]_2$, dppf, H_2, toluene, 50 bar, 70 °C	s.m.
3	**II-105**	Crabtree's, CH_2Cl_2, H_2, 6 bar	s.m.
4	**II-105**	Crabtree's, 1,2-DCE, H_2, 50 bar, 50 °C	s.m.
5	**II-105**	Pd/C, HOAc, H_2, 1 atm	**II-106** + c.m.
6	**II-105**	Pd/C, HOAc, H_2, 8 bar	**II-106** + **II-111**
7	**II-105**	NBSH, NEt_3, 1,2-DCE	s.m.
8	**II-105**	CF_3SO_3H, Et_3SiH, CH_2Cl_2	s.m.
9	**II-106**	Pd/C, 8 bar, CH_3OH	s.m.
10	**II-106**	NBSH, NEt_3, 1,2-DCE	s.m.
11	**II-106**	CF_3SO_3H, Et_3SiH, CH_2Cl_2	s.m.

12	**II-106**	Crabtree's, CH_2Cl_2, H_2, 6 bar	s.m.
13	**II-106**	Pd/C, HOAc, H_2, 8 bar	**II-113** traces[1]
14	**II-111**	Pd/C, HOAc, H_2, 25 bar	s.m.
15	**II-111**	$[RhCODCl]_2$, dppf, H_2, CH_3OH, 18 bar	deacetylated s.m.
16	**II-111**	$Pd(OH)_2$, CH_3OH, 1 atm	s.m.
17	**II-111**	Crabtree's, 1,2-DCE, H_2, 50 bar, 50 °C	s.m.
18	**II-110**	EtDuPhosRh, H_2, CF_3CH_2OH, 80 bar, 90 °C, 4 h	**II-115**, 30%

1: not isolated, HRMS indicated product formation, s.m. = starting material

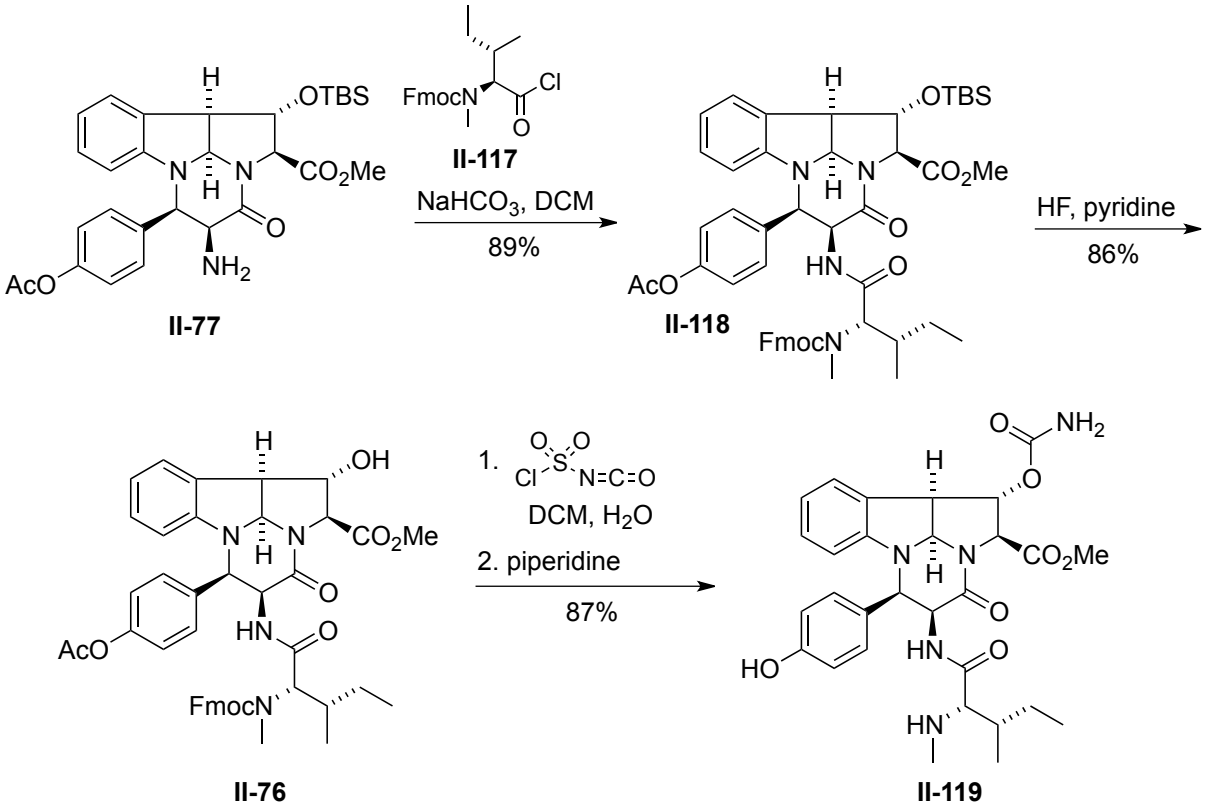
Entry 18 (the method was adapted from Hsiao)[82] was most promising and therefore tried on the advanced system. Enamine **II-108** was monoacetylated to yield **II-116** and subsequent hydrogenation yielded amine **II-77**.



Scheme 2.47 Monoacetylation and reduction of enamin **II-116** to yield reduced compound **II-77**.

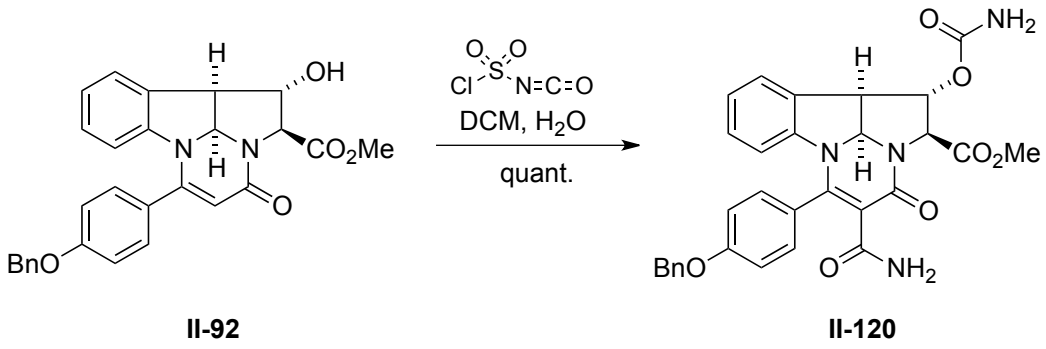
With the reduced compound in hand, protected isoleucine **II-117** could be coupled in form of the acyl chloride to yield **II-118**, followed by deprotection of the TBS group using HF in pyridine resulting in alcohol **II-76**. Carbamoylation was possible using chlorosulfonylisocyanate.[83] Deprotection of acetate and Fmoc groups was achieved using piperidine yielding crocagin methylester **II-119**. The

sequence is displayed in Scheme 2.48. Filip Bihelovic conducted this sequence, therefore Experimental Details for this sequence are not found in this thesis.



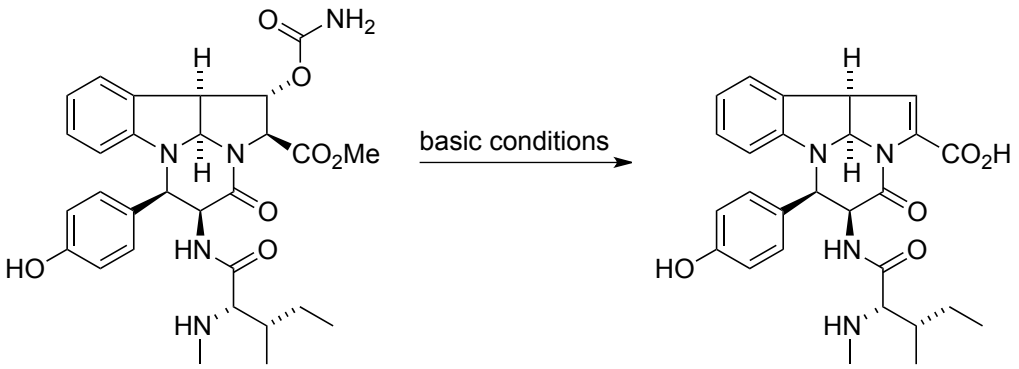
Scheme 2.48: Final steps *en* route to crocagin methyl ester **II-119**, including coupling to the isoleucine building block, TBS deprotection, carbamoylation, acetate and Fmoc deprotection (conducted by Filip Bihelovic).

The carbamoylation was tested on the earlier intermediate **II-92** first. Using an excess of chlorosulfonylisocyanate showed a single interesting product. Not only the hydroxy group was carbamoylated, but also the nucleophilic enamine attacks isocyanate, which results in **II-120** (shown in Scheme 2.49).



Scheme 2.49: Outcome of the carbamoylation step on intermediate **II-92**.

To finish the total synthesis of crocagin (**II-7**), the methyl ester in **II-119** had to be hydrolyzed to the corresponding acid, which proved surprisingly challenging. Basis conditions (LiOH, NaOH) lead to the hydrolyzed elimination product **II-121** exclusively (Scheme 2.50). Me_3SnOH, Me_3SiOK and Krapcho conditions (LiCl, DMF, 120 °C) lead to decomposition or complex mixture of products. Enzymatic hydrolysis did not react at all.



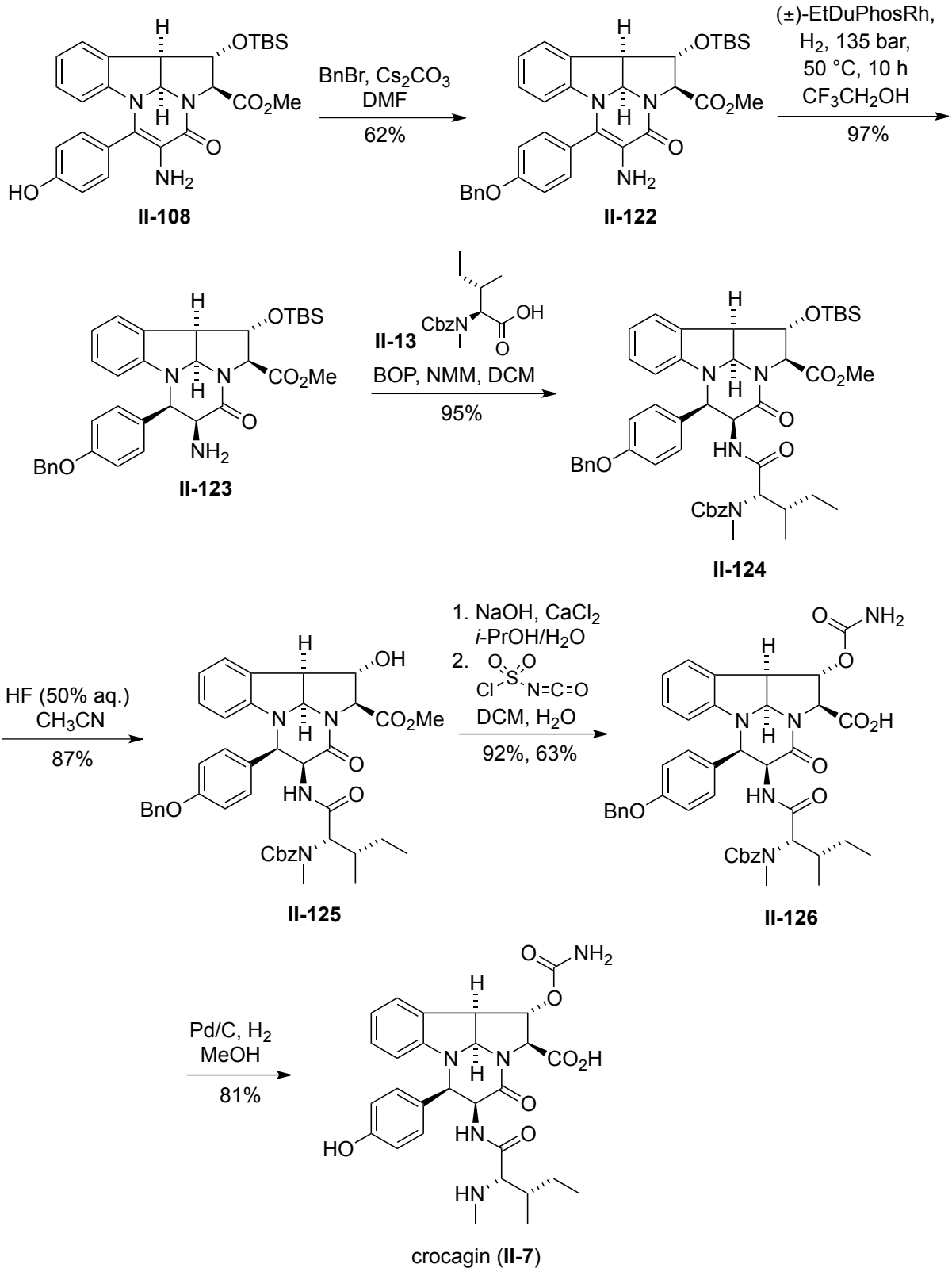
II-119 **II-121**

Scheme 2.50: Applied basic conditions in order to hydrolyze the methyl ester in **II-119** lead to the elimination product **II-121**.

2.3.8 Modified Second Generation Strategy – Protecting Group Swap

In order to overcome this challenge it was decided to change the order of deprotection whereupon the protecting groups had to be changed: a benzyl group replaces phenolic acetate and a carboxybenzyl group is used instead of Fmoc at the isoleucine group.

Phenolic hydroxy group in **II-108** was protected using benzyl bromide (Scheme 2.51). The resulting free enamine **II-122** was reduced to the amine **II-123** using again EtDuPhosRh under high pressure of hydrogen gas and high temperature. Isoleucine part **II-13** was attached using standard coupling conditions to yield **II-124**. For the deprotection sequence, it was started to deprotect TBS group carefully using HF in water resulting in **II-125**. At this step, ester hydrolysis worked successfully using NaOH and $CaCl_2$. Addition of $CaCl_2$ reduced the amount of epimerized product at C-2. Reaction using chlorosulfonylisocyanate resulted in the desired carbamoylated compound **II-126**. Final reductive deprotection removed benzyl and carboxybenzyl groups and yields the natural product crocagin (**II-7**).



Scheme 2.51 Endgame for the total synthesis of crocagin (**II-7**).

Spectra of synthetic crocagin (**II-7**) were compared with the spectra of isolated crocagin. While carbon spectrum matches well (max difference 1.7 ppm) (Table 2.6), the proton spectrum shows certain deviations (Table 2.7). Signals of amino acids are strongly dependent on the concentration in the sample and the level of protonation. Since every signal is shifted, different concentration of the compound, different content of water and different pH-value could be an explanation for the deviations. COSY, HSQC, HMBC and ROESY strengthen this assumption, because all couplings and correlations confirm the structure of the proposed structure of crocagin. To prove the identity of isolated and synthesized crocagin, these two compounds were mixed together in a NMR tube. The spectrum of this sample (Figure 2.11) showed only one set of signals, which is a strong hint for identity of the two compounds.

Table 2.6 Comparison of ^{13}C shifts of isolated and synthesized crocagin (**II-7**) with numbering of the molecule.

# carbon	isolated	synthesized
1	169.3	170.6 (from HMBC)
2	64.6	66.3
3	82.0	82.9
4	51.9	52.3
5	75.9	75.9
6	126.3	127.1
7	124.7	124.8
8	117.5	117.3
9	127.4	126.6
10	110.8	110.7
11	148.1	148.4
12	155.6	155.9
13	165.6	165.2
14	53.2	53.2
15	60.0	60.2
16	124.6	124.7
17/21	114.5	not detected
18/20	135.8	136.2
19	157.0	156.9
22	172.2	172.5
23	69.0	69.5
24	37.3	37.5
25	24.4	24.4
26	11.6	11.8
27	15.3	15.6
28	35.1	35.4

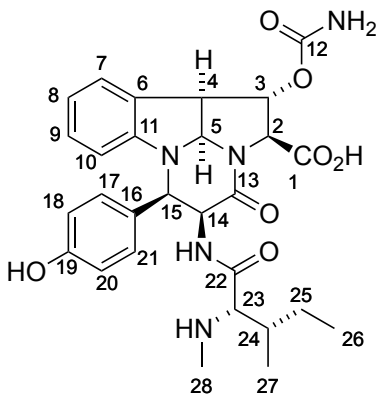


Table 2.7 Comparison of ^{1}H shifts of isolated and synthesized crocagin (**II-7**) including HMBC, ROESY and COSY correlations. Numbering see Table 2.6.

# proton	isolated with multiplicity and coupling constant (Hz)	synthesized with multiplicity and coupling constant (Hz)	HMBC	COSY	ROESY
2	4.20 d (3.7)	4.10 d (2.9)	C-3	H-3	
3	5.33 dd (3.7, 2.2)	5.29 ?		H-2	H-4
4	3.91 brd (8.1)	3.80 d (8.4)	C-3, C-6	H-5	H-3, H-5
5	5.96 d (8.1)	5.89 d (8.4)	C-6, C-11	H-4	H-4, H-14, H-15
7	7.22 d (7.7)	7.21 d (7.3)	C-9, C-11	H-8, H-9	H-8, H-10
8	6.51 dd (7.7, 7.7)	6.48 t (7.3)	C-6, C-9, C-10	H-7, H-10	H-7
9	6.66 dd (7.7, 7.7)	6.61 t (7.6)	C-7, C-11	H-7, H-10	H-10
10	5.35 d (7.7)	5.28 ?	C-6, C-8	H-8, H-9	H-7, H-9
14	5.22 dd (7.3, 7.3)	5.13 ?	C-15, C-16		H-5, NH
15	5.14 d (7.3)	5.13 ?	C-14		H-5, NH
17/21	6.55 m	6.75 m			
18/20	7.13 m	6.96 m			
23	2.72 m	2.64 d (4.8)	C-22, C-24, C-25, C-27, C-28	H-24	NH
24	1.48 m	1.45 m		H-23, H-25, H-27	H-27
25	1.26 m 0.97 m	1.22 m 0.94 m	C-24	H-24, H-26	H-26
26	0.78 t (7.3)	0.77 t (7.3)	C-24, C-25	H-25	H-25
27	0.75 d (6.6)	0.72 d (6.9)	C-23, C-24, C-25	H-24	H-24, NH
28	2.15 s	2.13 s	C-23		NH
NH	7.35 d (7.3)	7.31 d (6.6)		H-14/15	H-14, H-15, H-23, H-27, H-28
OH	9.33 brs	9.34 brs			

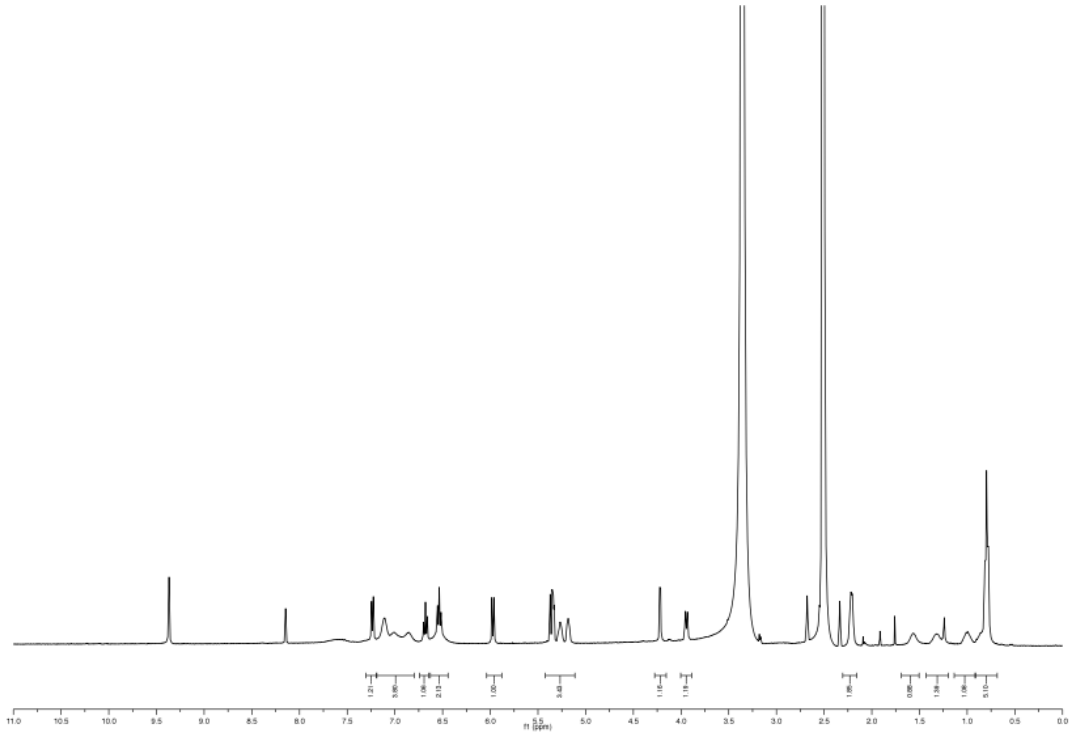


Figure 2.11 NMR-Spectrum (400 MHz, DMSO, 25 °C) of isolated and synthesized crocagin (ratio = 1:2).

2.4 Conclusion and Outlook

In chapter 2 the elaboration of the total synthesis of crocagin (**II-7**) is presented. A first generation strategy demonstrated the limitation of biomimetic total syntheses for peptidic natural products. In a second generation strategy the core of the natural product was synthesized and all missing substituents were built around the core to finally yield the target molecule crocagin (**II-7**). In order to prove identity of isolated and synthesized compound, a sample of both was mixed together and a NMR spectrum was recorded. The spectrum showed one set of signals, which is a strong hint for identity of the two compounds. With this scalable total synthesis further biological testings will be possible.

3 Summary

Chapter 1 describes syntheses towards furanocembranoids, a large family of diterpenoic natural products, which were all isolated from marine sources. The furanocembranoids gained the interest of many chemists not only by their considerable bioactivity, but also by their attractive molecular architecture. Structurally they all stem from a 14-membered carbocyclic skeleton, in which a furan ring is embedded (Figure 3.1).[2]

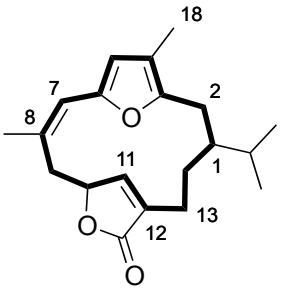


Figure 3.1 Basic skeleton of members of the furanocembranoid family.

Oxidation and subsequent new bond formations of this skeleton lead to a wide structural diversity within the furanocembranoids. One of these natural products is bielschowskysin (**I-11**) (Figure 3.2), which shows a highly oxygenated hexacyclic structure.[16] Many chemists endeavored synthetic progress towards a total synthesis of this natural product,[17-26] in order to provide material for further biological tests and to reveal the yet unknown absolute configuration while developing new synthetic strategies.

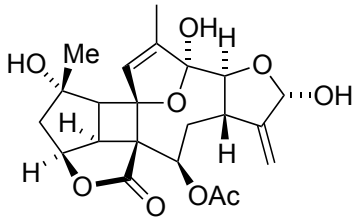
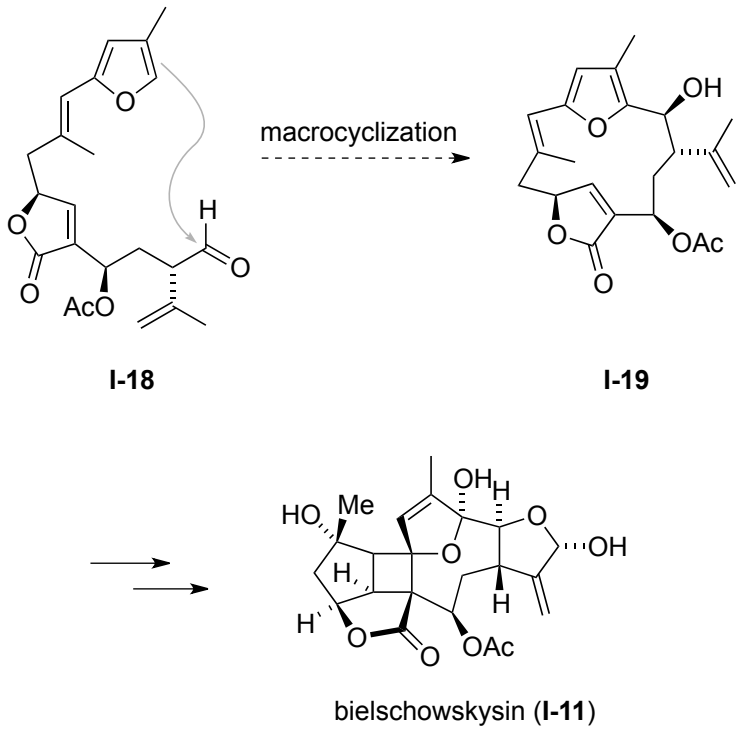


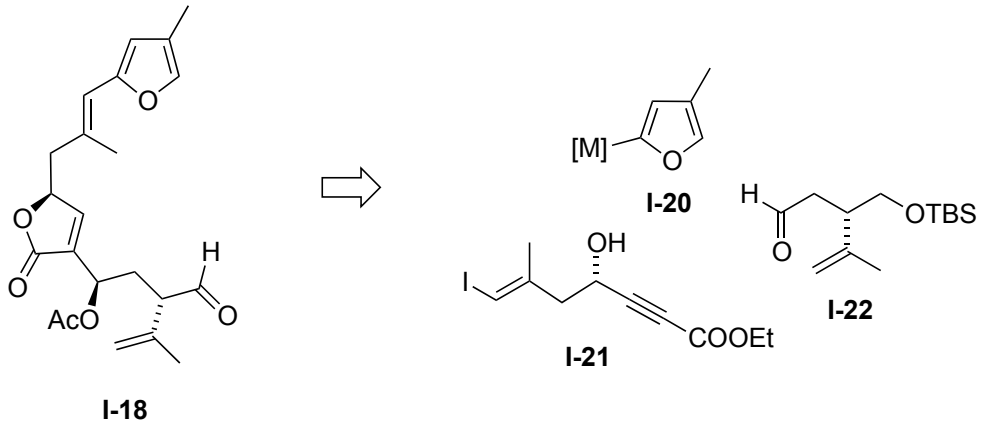
Figure 3.2 Structure of the hexacyclic furanocembranoid bielschowskysin (**I-11**).

In this work a retrosynthesis for bielschowskysin (**I-11**) is presented, which uses the high nucleophilicity of furans[27] to close the 14-membered macrocycle (Scheme 3.1). It is envisaged that this macrocycle will be an intermediate in the synthesis of bielschowskysin (**I-11**).



Scheme 3.1 Planned key step *en* route to bielschowskysin (**I-11**).

The macrocyclization precursor **I-18** can be traced back to three building blocks: a furan **I-20**, a vinyl iodide **I-21** and an aldehyde **I-22** (Scheme 3.2).



Scheme 3.2 Retrosynthetic overview for the synthesis of the macrocyclization precursor **I-18**.

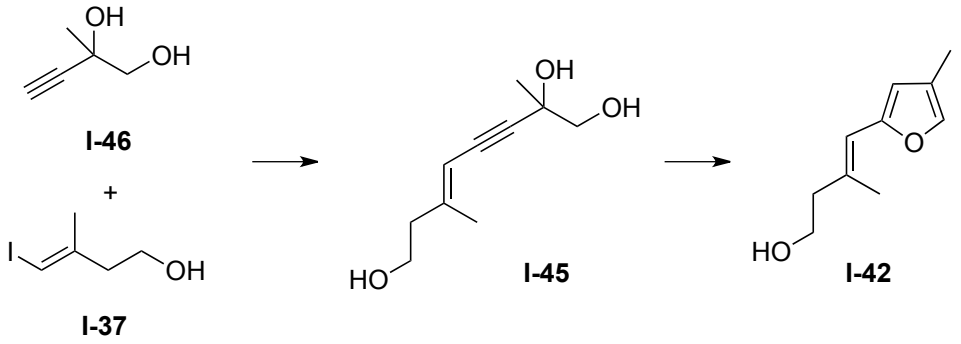
The stannylated furan building block (stannylated version of **I-20**) was prepared in four steps from commercially available methyl-3-methyl-2-furoate in 27% overall yield.

The vinyl iodide **I-21** was prepared in three steps from commercially available 3-butynol in 32% yield. Amongst others, carboalumination conditions and the Dess-Martin-Periodinane reagent were used.

During these studies a crystal structure of the Dess-Martin-Periodinane reagent was obtained, which was not previously known.[44]

The envisaged coupling of the vinyl iodide building block **I-21** and the furan building block **I-20** using cross coupling conditions (Stille, Negishi and Suzuki conditions) was not possible. Changing from vinyl iodide **I-21** to a protected vinyl iodide did not result in the desired product.

Another strategy was envisaged where the critical bond is already constructed before the furan is formed. Applying a silver mediated furan cyclization yielded vinyl furan **I-42** (Scheme 3.3).



Scheme 3.3 Silver mediated cyclization to vinyl furan **I-42**.

Further reaction with vinyl furan **I-42** did not result in product formation. Vinyl furan **I-42**, as well as all other C-5 unsubstituted furans, which have been synthesized within this work, were very unstable with respect to decomposition. Since the unsubstituted C-5 position was the key characteristic for the envisaged total synthesis, it was decided to stop the strategy at this point and consider other synthetic pathways for the total synthesis of bielschowskysin (**I-11**) without an unsubstituted C-5 position in the furan moiety. Possible strategies were similar to the bipinnatin J (**I-1**) synthesis (cf. chapter 1.3.2),[7] where the macrocycle is formed in a Nozaki-Hiyama-Kishi reaction or by implementing non-biomimetic methods, where the cyclobutane ring is formed in an earlier step and the missing parts are constructed around the core (cf. methods published by other groups in chapter 1.2.1).[17-26]

The second part of chapter 1 describes the furanocembranoid intricarene (**I-10**) (Figure 3.3), which exhibits a pentacyclic carbon skeleton with three spiro centers that is unprecedented so far in natural products.[15] An oxygen atom bridging the seven membered ring leads to an oxapolycyclic system.

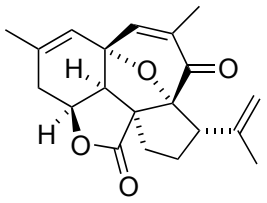
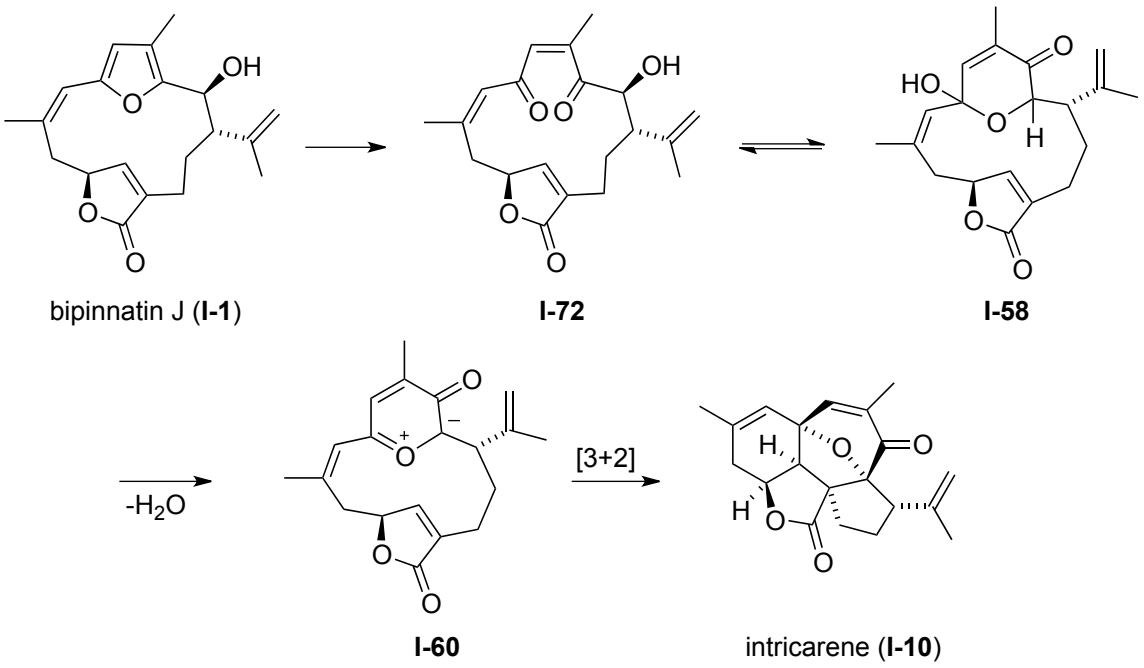


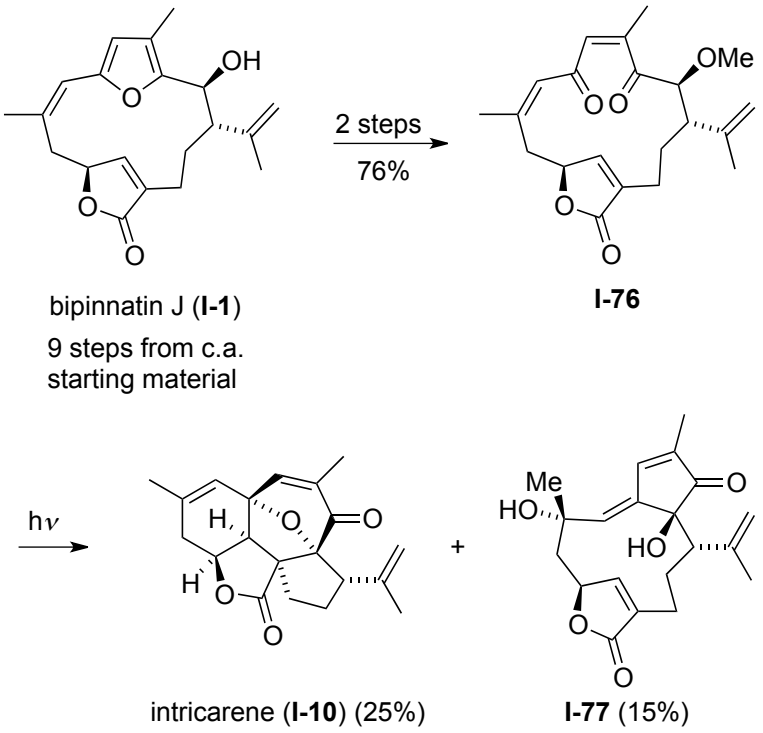
Figure 3.3 Structure of the pentacyclic furanocembranoid intricarene (**I-10**).

For this natural product two total syntheses have already been published.[9,53] Both syntheses follow the biosynthetic proposal (Scheme 3.4), in which intricarene is made from the furanocembranoid bipinnatin J (**I-1**), but they use very harsh conditions for the final formation of intricarene.



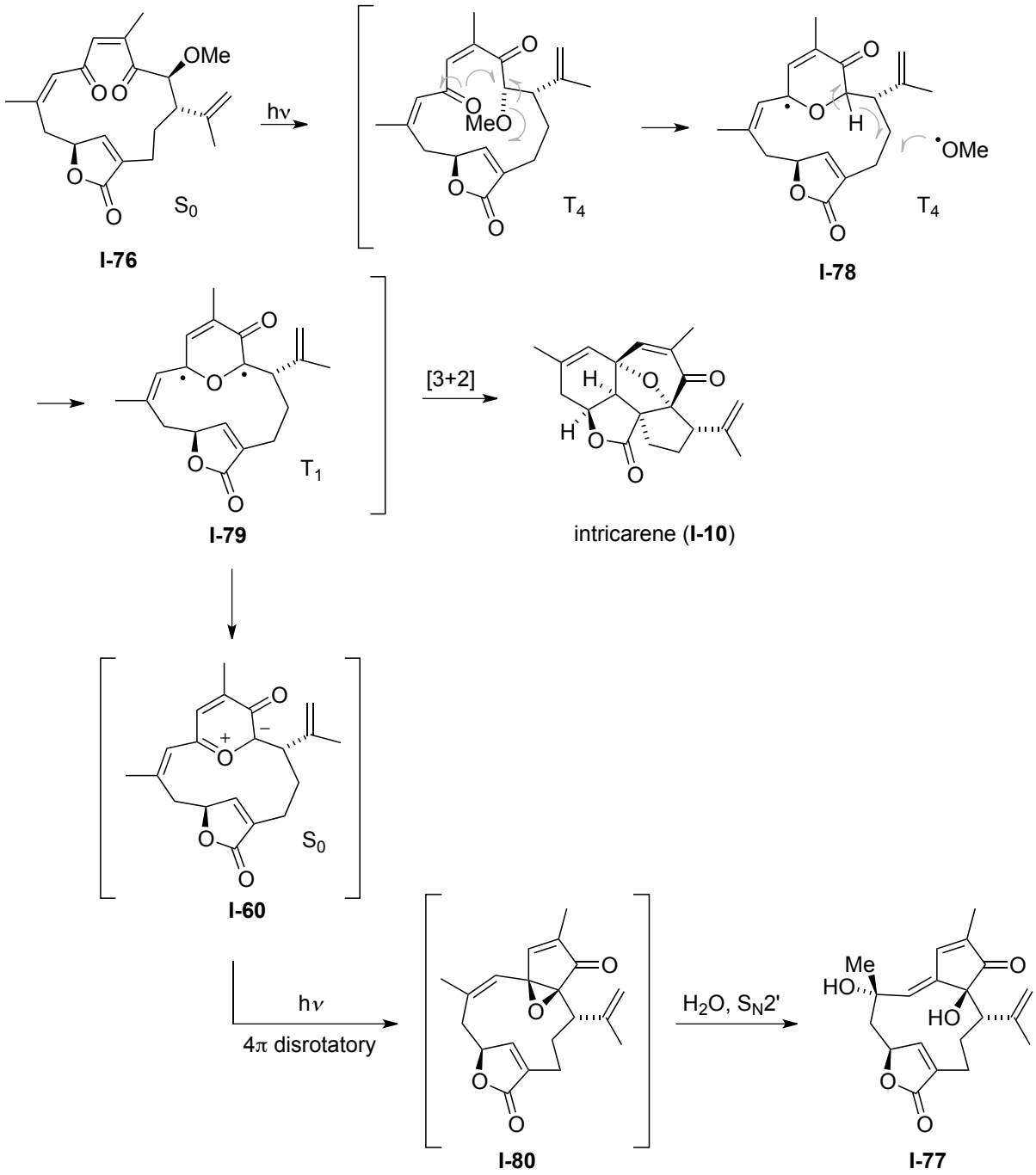
Scheme 3.4 Biosynthetic proposal for the formation of intricarene (**I-10**) starting from bipinnatin J (**I-1**).

In this work a biomimetic transformation of bipinnatin J (**I-1**) into intricarene (**I-10**) is presented. Bipinnatin J (**I-1**) was synthesized using a nine step synthesis published by our group.[7] Modification of bipinnatin J, namely methylation and oxidation, lead to a precursor **I-76** whose irradiation resulted in the formation of intricarene (**I-10**) and another furanocembranoid **I-77**, not yet known as a natural product (Scheme 3.5).



Scheme 3.5 Photochemical formation of intricarene (**I-10**) and furanocembranoid **I-77**.

In collaboration with a theoretical chemistry group (P.Kölle, R. de Vivie-Riedle, LMU München, Theoretical Chemistry), the mechanism for this transformation was clarified. Irradiation leads to an attack of the carbonyl group. Subsequent homolytic bond cleavage results in an oxidopyrilium diradical **I-79**, which undergoes an intramolecular [3+2] ring closure to form intricarene (**I-10**). Reaction to the oxidopyrilium ion **I-60** and 4π disrotatory ring closure to **I-80** with subsequent S_N2' water attack yields the second isolated product **I-77**.



Scheme 3.6 Mechanism for the formation of **I-10** and **I-77**, supported by theoretical calculations.

Chapter 2 focuses on the total synthesis of crocagin (**II-7**), a hydropyrroloindole, isolated from the myxobacterium *Chandromyces crocatus*.[69] Hydropyrrolindoles have been isolated from a wide range of different organisms and can show many different substitution patterns around the

hydropyrroloindole core.[59] Crocagin (**II-7**) is a tripeptide, consisting of the aminoacids tryptophan, tyrosine and isoleucine. They are connected *via* peptide bonds (Figure 3.4).

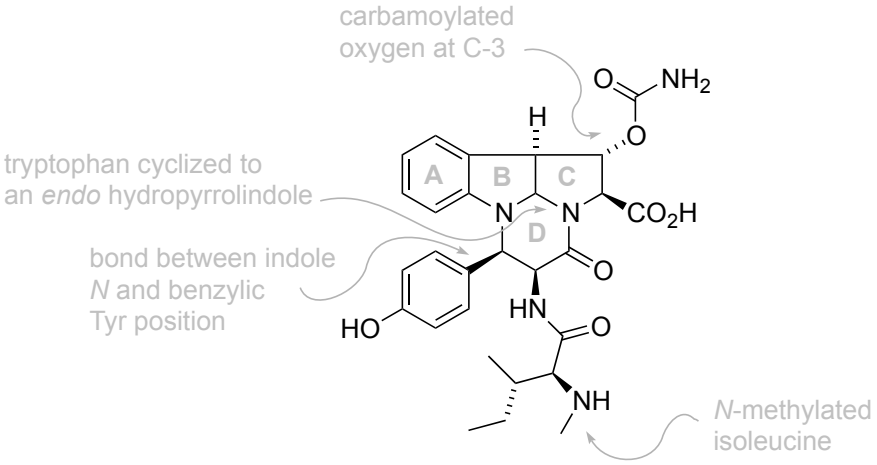
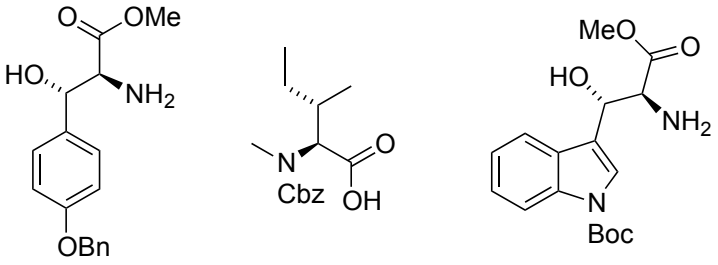


Figure 3.4 Structure of crocagin (**II-7**) – special structural features highlighted.

In a first generation strategy it was envisaged to synthesize the natural product in a biomimetic fashion. Therefore three building blocks **II-22**, **II-13** and **II-38**, all modified amino acids, were synthesized (Figure 3.5). The developed syntheses started from *para*-coumaric acid, 3-indole aldehyde and isoleucine, respectively. For **II-22** and **II-38** they include an asymmetric dihydroxylation reaction to introduce the desired stereochemistry.

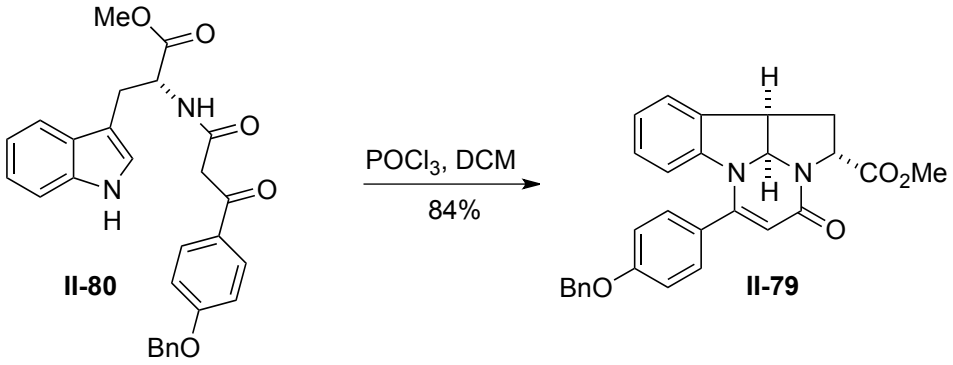


II-22 **II-13** **II-38**

Figure 3.5 Synthesized building blocks *en* route towards a total synthesis of crocagin (**II-7**).

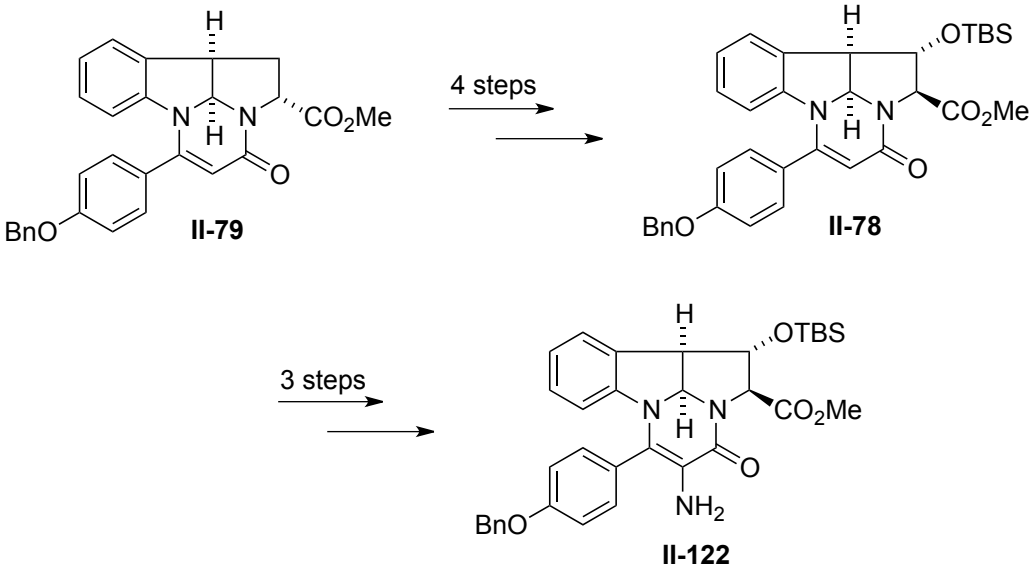
Different protecting groups on oxygen and amino groups were installed and the building blocks were connected in peptide couplings. Attempts to cyclize the precursors to the hydropyrroloindole core demonstrated the limit of biomimetic total syntheses, especially in the case of peptidic natural products. Either elimination of heteroatoms occurred or the undesired diastereomer was obtained. Hydropyrroloindoles were obtained from protected versions of **II-38** using *N*-bromosuccinimide, PhSeCl and *t*-BuOCl.

As a result, a second generation strategy was envisaged, where the hydropyrroloindole core, fused to the 6-membered D-ring, is formed in an early step and all missing heteroatoms are introduced at a later stage. A dipeptide synthesized in three steps from tryptophan and a β-keto acid, was cyclized to the tetracyclic core using $POCl_3$ (Scheme 3.7).



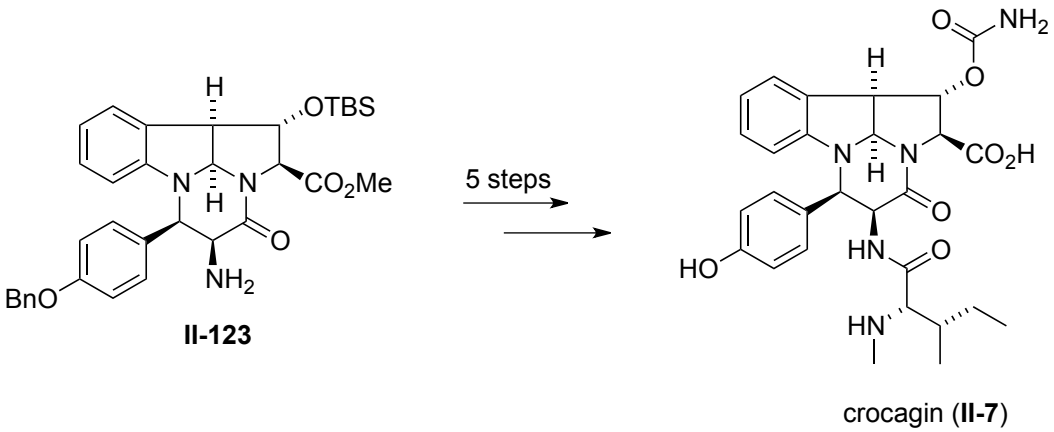
Scheme 3.7 Formation of the tetracyclic core of crocagin (**II-7**).

This tetracyclic core already shows the basic skeleton of the target molecule crocagin (**II-7**). The oxygen in C-3 position was introduced using modified hydroboration conditions, subsequent to an elimination step. Correction of the stereochemistry at the ester moiety was possible using Na in MeOH. The amino group, attached to the D-ring, was introduced using dibenzyl azodicarboxylate, followed by reduction and reprotection (Scheme 3.8).



Scheme 3.8 Introduction of the oxygen in the C-3 position and the amino group attached to the D-ring.

In a high pressure reduction (135 bar, 50 °C) the tetrasubstituted enamine was hydrogenated. Finally a peptide coupling to isoleucine, carbamoylation with chlorosulfonylisocyanate and deprotection yielded the natural product crocagin (**II-7**) (Scheme 3.9).



Scheme 3.9 Final steps to finish the total synthesis of crocagin (**II-7**).

In order to prove that the isolated compound is the same as the synthesized, a sample of both was mixed together and a NMR spectrum was recorded. The spectrum showed one set of signals, which gives strong assumption that isolated and synthesized compound are identical. With this efficient and scalable total synthesis further biological evaluation of crocagin (**II-7**) will be possible.

4 Experimental Part

4.1 General Procedure

Unless otherwise specified, all reactions were carried out under Ar atmosphere in oven-dried glassware.

Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled over sodium and benzophenone, Triethylamin (NEt_3) and *N*,*N*-Diisopropylamin (DIPA) over calcium hydride. *N*-Butyllithium (*n*-BuLi) was titrated using diphenylaceticacid prior to use. All other solvents as well as starting materials and reagents were obtained from commercial sources and used without further purification.

Flash column chromatography was performed using the analytical grade solvents indicated and Merck silica gel (40–63 μm, 60 Å) as the stationary phase. Reactions and chromatography fractions were monitored with Merck silica gel 60 F_{254} glass plates and visualized using a 254 nm UV lamp and/or by treatment with a suitable dip (potassium permanganate, ceric ammonium molybdate or anisaldehyde) followed by heating.

Proton (^1H) and carbon (^{13}C) NMR spectra were recorded, unless otherwise stated, at 23 °C on Varian 300 , Varian 400, Inova 400, Bruker 400 or Varian 600 spectrometers (300, 400, 600 MHz for proton; 75, 100, 150 MHz for carbon). Chemical shifts (δ) are expressed in parts per million (ppm) and are calibrated using residual protic solvent as an internal reference for proton ($CHCl_3$: δ = 7.26 ppm, CH_3OH: δ = 3.31 ppm, DMSO: δ = 2.50 ppm), and for carbon the central carbon resonance of the solvent ($CDCl_3$: δ = 77.16 ppm, CD_3OD: δ = 49.00 ppm, DMSO: δ = 39.52 ppm).[84] Multiplicity is defined as: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet, br = broad or combinations of the above. To assign proton and carbon spectra, a range of 2D-NMR experiments (COSY, HSQC, HMBC, NOESY) were used. The numbering of atoms in the molecules does not correspond to the IUPAC nomenclature.

Infrared spectra were recorded on a Perkin-Elmer BXII-FTIR spectrometer. Samples were analyzed as neat materials.

Mass spectrometry experiments were performed on a Thermo Finnigan MAT 95 (Electron Ionisation, EI) and on a Thermo Finnigan LTQ FT (Electrospray Ionisation, ESI) instrument.

UV/Vis spectra were recorded on a Varian Cary 50 Bio UV-Vis Spectrophotometer using STARNA 29/B/12 quartz cuvettes with 10 mm section thickness.

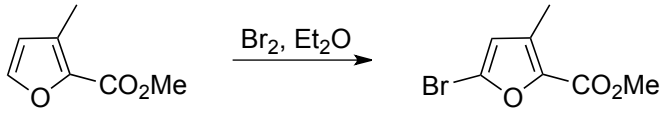
Melting points were measured on a Büchi melting point B-540 system and are uncorrected.

Optical rotations were measured at the given temperature (T in [°C]) on a Perkin-Elmer 241 or Krüss P8000-T polarimeter using a sodium lamp (Na D-line, 589 nm). Measurements were carried out in a cell with path length (l) of 0.5 dm. Concentrations are given in g/100 mL.

Enantiomeric excess (*ee*) was determined using a High Performance Liquid Chromatography (HPLC) system from Varian (Galaxie Chromatography Software, two PrepStar pumps Model SD-1, manual injection, ProStar 335 Photo Diode Array Detector, 380-LC Evaporative Light Scattering Detector) with chiral column Cellulose Delta S.

4.2 Experimental Procedures for Chapter 1

Methyl 5-bromo-3-methylfuran-2-carboxylate[34]

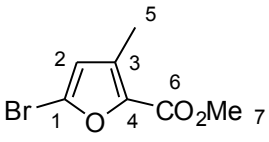


I-31 **I-32**

Methyl 3-methyl-2-furoate (**I-31**) (5.00 g, 35.7 mmol) was dissolved in Et_2O (40 mL) and cooled to 0 °C. Bromine (5.48 mL, 107 mmol) was added slowly to the solution, which was stirred for 3 h at r.t. before the reaction was quenched with ½ sat. aq. $Na_2S_2O_3$ solution. (35 mL). The layers were separated and the aqueous was extracted with Et_2O (150 mL). The combined organic layers were dried over $MgSO_4$ and carefully concentrated to give the volatile product **I-32** as a yellow oil, which was used without further purification in the next step.

R_f: 0.20, hexanes.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm = 6.31 (s, 1H, H-2), 3.88 (s, 3H, 3xH-7), 2.34 (s, 3H, 3xH-5).

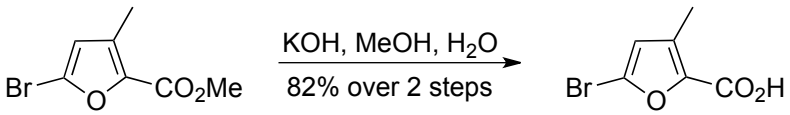


^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 159.03 (C-6), 142.26 (C-4), 133.76 (C-3), 126.62 (C-1), 117.03 (C-2), 51.84 (C-7), 11.63 (C-5).

IR ($\tilde{\nu}$ /cm^{-1}): 3109, 3003, 2952, 1746, 1706, 1475, 1437, 1395, 1381, 1240, 1191, 1153, 1191, 1153, 1069.

HRMS (EI): calculated for $C_7H_7O_3{}^{79}Br$ $[M]^+$ 217.9579; found 217.9581.

5-Bromo-3-methylfuran-2-carboxylic acid[34]



I-32 **I-33**

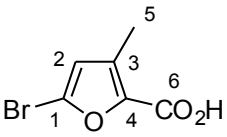
Crude methylester **I-32** (estimated: 7.82 g, 35.7 mmol) was added to a solution of KOH (4.00 g, 71.3 mmol) in MeOH (76 mL) and water (4 mL) at 0 °C. After 10 minutes the reaction mixture was allowed

to warm to r.t. and stirred for 20 h before the reaction was quenched with water (70 mL), acidified to pH = 3 with 10% aq. HCl solution and extracted with Et_2O (3 x 200 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. Column chromatography (20% EtOAc, 1% TFA in hexanes) gave the product **I-33** as a colorless solid (6.00 g, 82% over two steps).

R_f: 0.30, 10% EtOAc, 1% TFA in hexanes.

m.p.: 160.4 – 162.6 °C.

^{1}H NMR (400 MHz, CD_3OD) δ/ppm = 6.36 (s, 1H, H-2), 2.28 (s, 3H, 3xH-5).

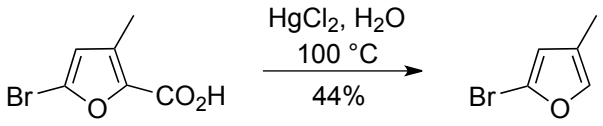


^{13}C NMR (101 MHz, CD_3OD) δ/ppm = 164.58 (C-6), 146.62 (C-4), 132.14 (C-3), 125.58 (C-1), 117.62 (C-2), 11.66 (C-5).

IR ($\tilde{\nu}$ /cm^{-1}): 3130, 2855, 2633, 2535,1751, 1669, 1596, 1472, 1428, 1379, 1272, 1170, 1158, 1111, 1087.

HRMS (EI): calculated for $C_6H_5O_3{}^{79}Br$ $[M]^+$ 203.9417; found 203.9412.

2-Bromo-4-methylfuran[36]



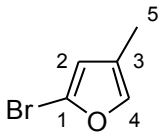
I-33 **I-29**

Carboxylic acid **I-33** (1.00 g, 4.88 mmol) and $HgCl_2$ (1.32 g, 4.88 mmol) were added to a solution of degassed water (10 mL) and concentrated HCl (1 mL). The stirred solution was heated to reflux under argon atmosphere, while the steam distillate was collected in a solid CO_2/acetone cooled flask (−78 °C) for 5 h. The distillate was extracted with Et_2O (2 x 45 mL) and the combined organic layers were dried over $MgSO_4$. Et_2O was partially removed in a distillation using a vigreux column (35 °C, 1 bar). Caused by the volatileness of the product **I-29** not all Et_2O was removed. The yield of 44% (344 mg) was determined by integration of NMR spectrum (product in Et_2O). To avoid decomposition of the unstable product **I-29**, it was stored in ether at −20 °C.

R_f: 0.80, 10% EtOAc in hexanes.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm = 7.18 (s, 1H, H-4), 6.16 (s, 1H, H-2), 2.00 (s, 3H, 3xH-5). In ether.

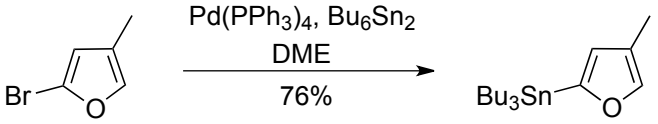
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 141.07 (C-4), 123.08 (C-3), 121.98 (C-1), 113.76 (C-2), 9.98 (C-5). In ether.



IR was not recorded as the compound was stored in ether.

HRMS (EI): calculated for $C_5H_5O^{79}Br$ $[M]^+$ 159.9518; found 159.9517.

Tributyl(4-methylfuran-2-yl)stannane

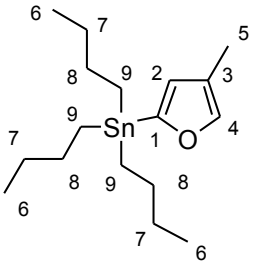


I-29 **I-35**

An aliquot of 2-bromo-4-methylfuran (**I-29**) (135 mg, 0.839 mmol) in Et_2O (2 mL) was added to degassed dimethoxyethane (11 mL). Bu_6Sn_2 (405 mg, 0.699 mmol) and Pd $(PPh_3)_4$ (20.2 mg, 0.0175 mmol) were added. The yellow solution was stirred at r.t. for 2 h and then under reflux for 20 h. The black solution was allowed to cool to r.t. and diluted with Et_2O (13 mL). Filtration over a plug of basic aluminium oxide afforded the product **I-35** as a yellow oil (238 mg, 76%). To avoid decomposition the product **I-35** was stored in Et_2O at −20 °C.

R_f: 0.90, 20% EtOAc in hexanes.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 7.15 (s, 1H, H-4), 6.37 (s, 1H, H-2), 2.05 – 2.04 (m, 3H, 3xH-5), 1.70 – 1.58 (m, 6H, 6xH-7), 1.45 – 1.23 (m, 12H, 6xH-8, 6xH-9), 0.92 (t, *J* = 7.3 Hz, 9H, 9xH-6). With Bu_3Sn-residues.

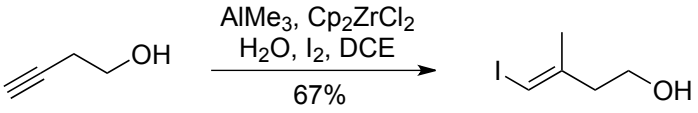


^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm = 146.77 (C-1), 138.49 (C-4), 121.78 (C-3), 107.64 (C-2), 28.42 (C-7), 26.93 (C-8), 17.45 (C-9), 13.75 (C-6), 9.89 (C-5).

IR ($\tilde{\nu}$ /cm^{-1}): 2955, 2918, 2871, 2854, 2360, 2338, 1462, 1417, 1376, 1340, 1290, 1247, 1188, 1146, 1071. With Bu_3Sn-residues.

HRMS (EI): Sn containing fragmentation products.

(*E*)-4-Iodo-3-methylbut-3-en-1-ol[39,40]

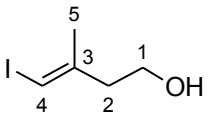


I-36 **I-37**

Cp_2ZrCl_2 (3.79 g, 13.0 mmol) was dissolved in dichloroethane (250 mL) and cooled to –20 °C before $AlMe_3$ (2 M in toluene, 90.9 mL, 182 mmol) was added slowly over 25 minutes. After stirring for 20 minutes, water (1.64 mL, 91.1 mmol) was added very slowly over 10 minutes and the yellow mixture was stirred for further 20 minutes. Meanwhile, 3-butyn-1-ol (**I-36**) (4.40 mL, 58.8 mmol) was dissolved in 1,2-dichloroethane (50 mL) and cooled to 0 °C, then treated with $AlMe_3$ (2 M in toluene, 9.10 mL, 18.2 mmol). The alkyne-solution was cannulated to Cp_2ZrCl_2-solution over 15 minutes at –20 °C. After 35 minutes, the slurry yellow reaction mixture was allowed to warm to room temperature and stirred for 22 h. After cooling the reaction mixture to –20 °C, a solution of iodine (24.5 g, 96.3 mmol) in Et_2O (95 mL) was added *via* cannula over 10 min. The resulting brown reaction mixture was stirred at room temperature for 2 h, then cooled to 0 °C before a ½ sat. aq. Na-K-tartrate solution (90 mL) was added slowly. The suspension was allowed to warm to r.t. before water (150 mL) was added. The layers were separated and the aqueous layer was extracted with Et_2O (450 mL). The organic layers were washed with sat. aq. $Na_2S_2O_3$ solution, brine, dried over $MgSO_4$ and concentrated in *vacuo*. Column chromatography (15% EtOAc in hexanes) gave the product **I-37** as a brown oil (8.30 g, 67%).

R_f: 0.30, 20% EtOAc in hexanes.

^{1}H NMR (599 MHz, $CDCl_3$) δ/ppm = 6.02 (dd, *J* = 1.1, 2.2 Hz, 1H, H-4), 3.72 (t, *J* = 6.0 Hz, 2H, 2xH-1), 2.48 (td, *J* = 1.1, 6.0 Hz, 2H, 2xH-2), 1.87 (d, *J* = 1.1 Hz, 3H, 3xH-5).

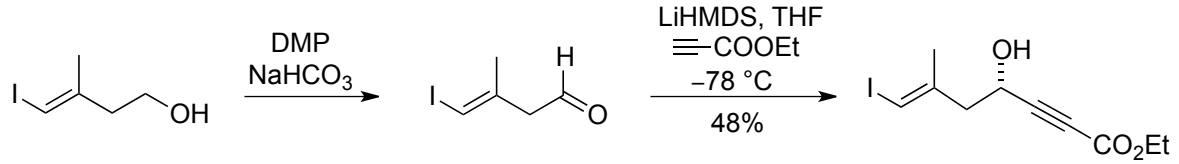


^{13}C NMR (151 MHz, $CDCl_3$) δ/ppm = 144.70 (C-3), 77.00 (C-4), 60.28 (C-1), 42.58 (C-2), 23.96 (C-5).

IR ($\tilde{\nu}$ /cm^{-1}): 3318, 2881, 2340, 2360, 1616, 1429, 1375, 1271, 1177, 1141, 1037, 999.

HRMS (EI): calculated for C_5H_9OI $[M]^+$ 211.9693; found 211.9697.

(*E*)-Ethyl 4-hydroxy-7-iodo-6-methylhept-6-en-2-ynoate

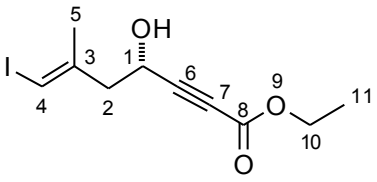


I-37 **I-38** **I-21**

Alcohol **I-37** (3.00 g, 14.2 mmol) was dissolved in CH_2Cl_2 (210 mL). $NaHCO_3$ (5.97 g, 71.0 mmol) and DMP[42, 43] (12.0 g, 28.4 mmol) were added and the mixture was stirred for 1 h at r.t. before a 1:1:1 solution (90 mL) of sat. aq. $NaHCO_3$ solution, sat. aq. $Na_2S_2O_3$ solution and water was added. The biphasic mixture was stirred for 30 min before the aqueous layer was extracted with CH_2Cl_2 (100 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude aldehyde **I-38** was dissolved in THF (28 mL) and cooled to −78 °C. *n*-BuLi (2.5 M in hexanes, 16.5 mL, 41.2 mmol) was added dropwise to a stirred solution of HMDS (8.88 mL, 42.6 mmol) in THF (42 mL) at −78 °C. The resulting solution was warmed to 0 °C and stirred at this temperature for 30 min and then cooled to −78 °C. Ethyl propiolate (4.32 mL, 42.6 mmol) was dissolved in THF (28 mL), cooled to −78 °C and cannulated to the LiHMDS solution, which was stirred for 1 h at −78 °C before the aldehyde solution was cannulated to the deprotonated alkyne. The mixture was stirred for 30 min before sat. aq. NH_4Cl solution was added (100 mL). It was extracted with Et_2O (300 mL), washed with brine, dried over $MgSO_4$ and concentrated in *vacuo*. Column chromatography (5% EtOAc in hexanes) gave the racemic product **I-21** as a brown oil (2.10 g, 48%).

R_f: 0.50, 20% EtOAc in hexanes.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 6.16 (dd, *J* = 1.1, 2.2 Hz, 1H, H-4), 4.61 (dd, *J* = 5.8, 12.8 Hz, 1H, H-1), 4.24 (q, *J* = 7.1 Hz, 2H, 2xH-10), 2.69 – 2.66 (m, 2H, 2xH-2), 2.06 (d, *J* = 5.8 Hz, 1H, OH), 1.92 (d, *J* = 1.1 Hz, 3H, 3xH-5), 1.32 (t, *J* = 7.1 Hz, 3H, 3xH-11).

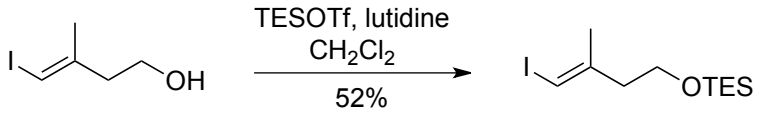


^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm = 153.27 (C-8), 142.33 (C-3), 86.37 (C-6), 79.77 (C-4), 77.36 (C-7), 62.45 (C-10), 60.25 (C-1), 46.34 (C-2), 24.38 (C-5), 14.14 (C-11).

IR ($\tilde{\nu}$ /cm^{-1}): 3421, 2979, 2237, 1706, 1366, 1237, 1143, 1079, 1048, 1010, 858.

HRMS (EI): calculated for $C_{10}H_{13}O_3I$ $[M]^+$ 307.9904; found 307.9892.

(*E*)-Triethyl((4-iodo-3-methylbut-3-en-1-yl)oxy)silane

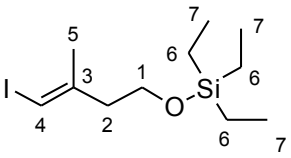


I-37 **I-43**

Alcohol **I-37** (50.0 mg, 0.236 mmol) was dissolved in CH_2Cl_2 (1 mL) and cooled to −40 °C. TESOTf (56.6 µL, 0.250 mmol) was added and the reaction was stirred for 10 min before 2,6-lutidine (33.6 µL, 0.290 mmol) was slowly added. The reaction mixture was stirred for 20 h at r.t. before it was quenched with water (2 mL) followed by extraction with Et_2O (10 mL). The organic layers were washed with brine, dried over $MgSO_4$ and concentrated in *vacuo*. Column chromatography (3% EtOAc in hexanes) gave the product **I-43** as a yellow oil (40.0 mg, 52%).

R_f: 0.30, 3% EtOAc in hexanes.

^{1}H NMR (599 MHz, $CDCl_3$) δ/ppm = 5.94 (dd, *J* = 1.1, 2.2 Hz, 1H, H-4), 3.69 (t, *J* = 6.8, 2H, 2xH-1), 2.43 (t, *J* = 7.3 Hz, 2H, 2xH-2), 1.86 (d, *J* = 1.1 Hz, 3H, 3xH-5), 0.95 (t, *J* = 8.0 Hz, 9H, 9xH-7), 0.59 (t, *J* = 8.0 Hz, 6H, 6xH-6).

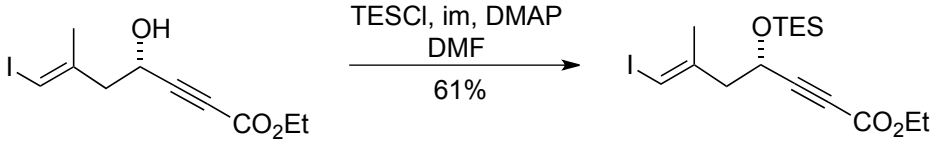


^{13}C NMR (151 MHz, $CDCl_3$) δ/ppm = 145.29 (C-3), 76.51 (C-4), 61.26 (C-1), 42.78 (C-2), 24.45 (C-5), 6.90 (C-7), 4.55 (C-6).

IR ($\tilde{\nu}$ /cm^{-1}): 2952, 2909, 2875, 1617, 1457, 1413, 1378, 1272, 1237, 1142, 1095, 1004, 973.

HRMS (EI): calculated for $C_9H_{18}OISi$ $[M-Et]^+$ 297.0166; found 297.0162.

(*E*)-Ethyl 7-iodo-6-methyl-4-((triethylsilyl)oxy)hept-6-en-2-ynoate

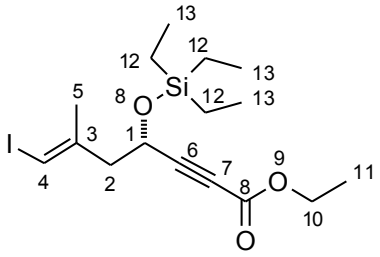


I-21 **I-44**

Alkyne alcohol **I-21** (50.0 mg, 0.162 mmol) was dissolved in DMF (2 mL). Et_3SiCl (30.0 µL, 0.179 mmol), imidazol (24.3 mg, 0.357 mmol) and DMAP (1.95 mg, 0.0162 mmol) were added and the mixture was stirred for 1 h before it was quenched with water (4 mL), extracted with Et_2O (10 mL),

washed with brine, dried over $MgSO_4$ and concentrated in *vacuo*. Column chromatography (5% EtOAc in hexanes) gave the product **I-44** as a yellow oil (42.0 mg, 61%).

R_f: 0.30, 5% EtOAc in hexanes.



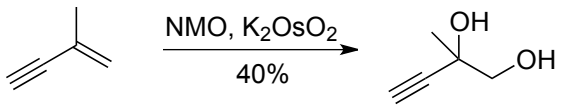
^{1}H NMR (599 MHz, $CDCl_3$) δ/ppm = 6.08 (d, *J* = 1.9 Hz, 1H, H-4), 4.54 (dd, *J* = 5.3, 7.7 Hz, 1H, H-1), 4.23 (q, *J* = 7.1 Hz, 2H, 2xH-10), 2.61 (ddd, *J* = 6.9, 14.1, 19.8 Hz, 2H, 2xH-2), 1.88 (d, *J* = 1.1 Hz, 3H, 3xH-5), 1.31 (t, *J* = 7.1 Hz, 3H, 3xH-11), 0.96 (t, *J* = 7.9 Hz, 9H, 9xH-13), 0.70 – 0.58 (m, 6H, 6xH-12).

^{13}C NMR (151 MHz, $CDCl_3$) δ/ppm = 153.44 (C-8), 142.71 (C-3), 87.43 (C-6), 79.46 (C-4), 76.73 (C-7), 62.20 (C-10), 61.00 (C-1), 47.31 (C-2), 24.55 (C-5), 14.15 (C-11), 6.81 (C-13), 4.78 (C-12).

IR ($\tilde{\nu}$ /cm^{-1}): 2955, 2911, 2876, 2238, 1712, 1458, 1365, 1230, 1143, 1092, 1074.

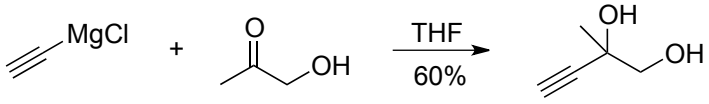
HRMS (EI): fragmentation

2-Methylbut-3-yne-1,2-diol[48]



I-47 **I-46**

THF (10 mL), *t*-BuOH (3 mL) and H_2O (1 mL) were degassed. *N*-Methylmorpholin-*N*-oxid · H_2O (2.05 g, 15.1 mmol), $K_2OsO_2 \cdot 2\,H_2O$ (27.9 mg, 0.0756 mmol) and 2-methylbut-1-en-3-yne (**I-47**) (500 mg, 7.56 mmol) were added to the solvents in a pressure tube. The reaction was stirred in a sealed pressure tube for 24 h before it was quenched with $Na_2S_2O_3$ (10 mL), extracted with EtOAc (30 mL), washed with brine, dried over $MgSO_4$ and concentrated in *vacuo*. Column chromatography (90% Et_2O in hexanes) gave the product **I-46** as a colorless oil (300 mg, 40 %).

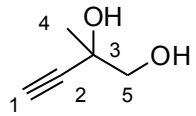


I-48 **I-49** **I-46**

Hydroxyaceton (**I-49**) (231 µL, 3.37 mmol) was dissolved in THF (2 mL) and cooled to −78 °C. Ethynylmagnesium chloride (**I-48**) (0.5 M in THF, 13.5 mL, 6.75 mmol) was dissolved in THF (2 mL), cooled to −78 °C and cannulated to the hydroxyaceton solution. The mixture was warmed to r.t. and stirred for 3 h at r.t. before it was quenched with NH_4Cl (2 mL), extracted with EtOAc (10 mL), washed with brine, dried over $MgSO_4$ and concentrated in *vacuo*. Column chromatography (90% Et_2O in hexanes) gave the product **I-46** as a colorless oil (200 mg, 60%).

R_f: 0.30, 90% ether in hexanes.

^{1}H NMR (599 MHz, $CDCl_3$) δ/ppm = 3.68 (d, *J* = 11.1 Hz, 1H, H-5α), 3.50 (d, *J* = 11.1 Hz, 1H, H-5β), 3.20 (br s, 2H, OH), 2.48 (s, 1H, H-1), 1.47 (s, 3H, 3xH-4).

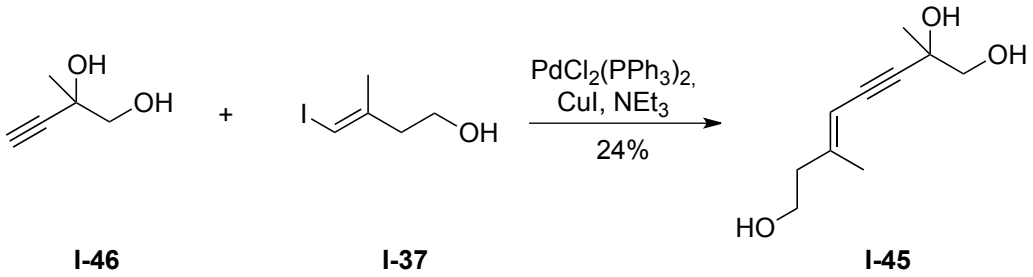


^{13}C NMR (151 MHz, $CDCl_3$) δ = 85.46 (C-2), 72.47 (C-1), 70.58 (C-3), 68.40 (C-5), 25.04 (C-4).

IR ($\tilde{\nu}$ /cm^{-1}): 3366, 3287, 2984, 2113, 1456, 1377, 1253, 1116, 1045, 951, 920.

HRMS (EI): calculated for $C_5H_9O_2$ $[M+H]^+$ 101.0597; found 101.0597.

(*E*)-2,6-Dimethyloct-5-en-3-yne-1,2,8-triol



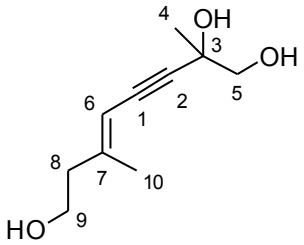
I-46 **I-37** **I-45**

NEt_3 (16 mL) was degassed before iodo alcohol **I-37** (424 mg, 2.00 mmol), 2-methylbut-3-yne-1,2-diol (**I-46**) (400 mg, 4.00 mmol)), CuI (38.1 mg, 0.200 mmol) and $PdCl_2(PPh_3)_2$ (140 mg, 0.200 mmol) were added. The mixture was stirred for 16 h before it was concentrated in *vacuo*. Column chromatography (80% EtOAc in hexanes) gave the product **I-45** as a colorless solid (400 mg, 24%), inseparable from PPh_3O.

R_f: 0.30, 90% EtOAc in hexanes.

m.p.: n.d., product inseparable from $OPPh_3$

^{1}H NMR (599 MHz, $CDCl_3$) δ/ppm = 5.38 (s, 1H, H-6), 3.74 (t, *J* = 6.3 Hz, 2H, 2xH-9), 3.67 (d, *J* = 11.0 Hz, 1H, H-5α), 3.52 (d, *J* = 11.0 Hz, 1H, H-5β), 2.57 (s, 1H, OH), 2.36 (t, *J* = 6.3 Hz, 2H, 2xH-8), 1.92 (s, 3H, 3xH-10), 1.50 (s, 3H, 3xH-4).

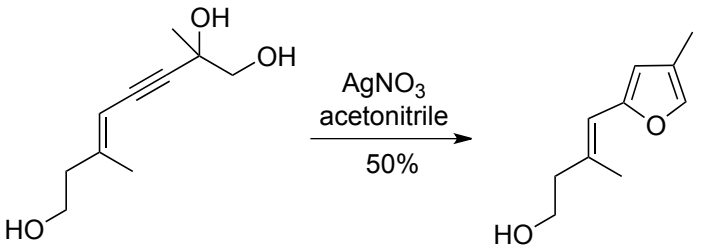


^{13}C NMR (151 MHz, $CDCl_3$) δ/ppm = 149.48 (C-7), 106.53 (C-6), 93.61 (C-2), 82.17 (C-1), 71.03 (C-5), 69.29 (C-3), 60.46 (C-9), 41.75 (C-8), 25.61 (C-4), 19.47 (C-10).

IR ($\tilde{\nu}$ /cm^{-1}): 3266, 2938, 2871, 1627, 1472, 1438, 1368, 1261, 1211, 1164, 1124, 1037, 999, 953.

HRMS (EI): calculated for $C_{10}H_{16}O_3$ $[M]^+$ 184.1099; found 184.1100.

(*E*)-3-Methyl-4-(4-methylfuran-2-yl)but-3-en-1-ol

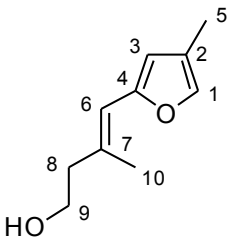


I-45 **I-42**

Triole **I-45** (20.0 mg, 0.109 mmol) was dissolved in MeCN (2 mL). $AgNO_3$ (18.5 mg, 0.109 mmol) was added and the mixture was stirred for 48 h before it was concentrated in *vacuo*. $CHCl_3$ (2 mL) was added and the precipitate was filtered off, the filtrate was concentrated. Column chromatography (50% EtOAc in hexanes) gave the sensitive product **I-42** as a colorless oil (9.00 mg, 50%).

R_f: 0.80, 80% EtOAc in hexanes.

^{1}H NMR (599 MHz, $CDCl_3$) δ/ppm = 7.12 (s, 1H, H-1), 6.10 (s, 2H, H-3, H-6), 3.77 (t, *J* = 6.3 Hz, 2H, 2xH-9), 2.41 (t, *J* = 6.3 Hz, 2H, 2xH-8), 2.02 (s, 3H, 3xH-5), 2.00 (s, 3H, 3xH-10).

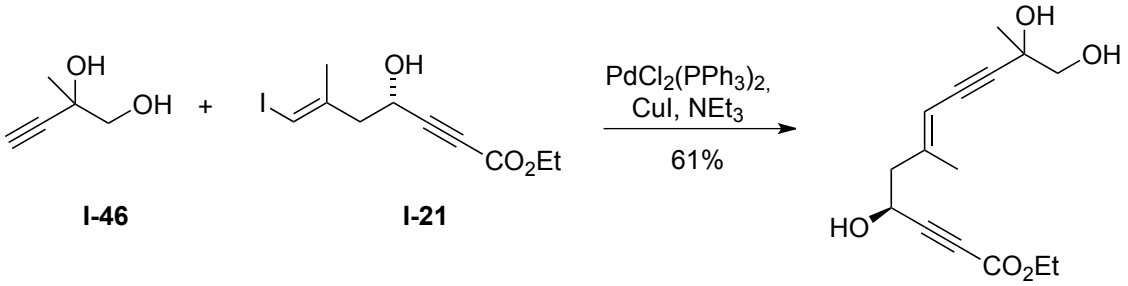


^{13}C NMR (151 MHz, $CDCl_3$) δ/ppm = 153.15 (C-4), 137.81 (C-1), 133.85 (C-7), 121.49 (C-2), 116.93 (C-6), 111.12 (C-3), 60.67 (C-9), 43.98 (C-8), 18.47 (C-10), 9.91 (C-5).

IR ($\tilde{\nu}$ /cm^{-1}): 3365, 2927, 2885, 1758, 1677, 1677, 1443, 1378, 1263, 1233, 1040, 975, 891.

HRMS (EI): calculated for $C_{10}H_{14}O_2$ $[M]^+$ 166.0988; found 166.0980.

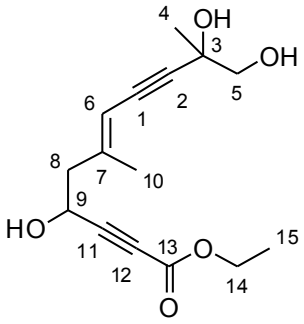
(*E*)-Ethyl 4,10,11-trihydroxy-6,10-dimethylundeca-6-en-2,8-diynoate



I-46 **I-21** **I-51**

NEt_3 (8 mL) was degassed before iodo alkyne **I-21** (307 mg, 1.00 mmol), 2-methylbut-3-yne-1,2-diol (**I-46**) (200 mg, 2.00 mmol)), CuI (18.9 mg, 0.100 mmol) and $PdCl_2(PPh_3)_2$ (69.5 mg, 0.100 mmol) were added. The mixture was stirred for 16 h before it was concentrated in *vacuo*. Column chromatography (70% EtOAc in hexanes) gave the product **I-51** as a yellow oil (171 mg, 61%), inseparable from PPh_3O.

R_f: 0.25, 70% EtOAc in hexanes.



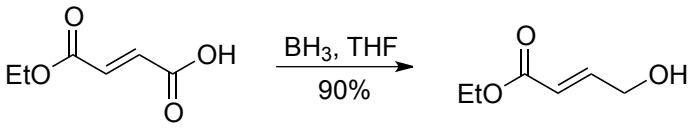
^{1}H NMR (599 MHz, $CDCl_3$) δ/ppm = 5.44 (s, 1H, H-6), 4.61 (t, *J* = 6.6 Hz, 1H, H-9), 4.24 (q, *J* = 7.1 Hz, 2H, 2xH-14), 3.67 (d, *J* = 11.0 Hz, 1H, H-5α), 3.52 (d, *J* = 11.0 Hz, 1H, H-5β), 2.73 (s, 1H, OH), 2.55 (d, *J* = 6.7 Hz, 2H, 2xH-8), 2.38 (s, 1H, OH), 1.95 (s, 3H, 3xH-10), 1.49 (s, 3H, 3xH-4), 1.31 (t, *J* = 7.1 Hz, 3H, 3xH-15).

^{13}C NMR (151 MHz, $CDCl_3$) δ/ppm = 153.36 (C-13), 146.65 (C-7), 108.63 (C-6), 94.58 (C-2), 86.83 (C-12), 81.77 (C-1), 77.16 (C-11), 70.94 (C-5), 69.26 (C-3), 62.43 (C-14), 60.40 (C-9), 45.69 (C-8), 25.57 (C-4), 19.88 (C-10), 14.13 (C-15).

IR ($\tilde{\nu}$ /cm^{-1}): 3367, 2982, 2936, 2237, 1707, 1443, 1367, 1244, 1044, 948, 747.

HRMS (ESI): calculated for $C_{15}H_{19}O_4$ $[M\text{-}OH]^+$ 263.1278; found 263.1277.

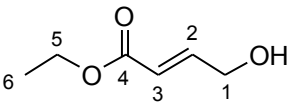
(*E*)-Ethyl 4-hydroxybut-2-enoate[51]



I-52 **I-53**

(*E*)-4-Ethoxy-4-oxobut-2-enoic acid (**I-52**) (5.00 g, 34.7 mmol) was dissolved in THF (15 mL) and cooled to −10 °C before $BH_3 \cdot THF$ (1.0 M in THF, 34.7 mL, 34.7 mmol) was added. The mixture was stirred at r.t. for 12 h before 50% AcOH in water (10 mL) was added. It was extracted with Et_2O (200 mL), washed with brine, dried over $MgSO_4$ and concentrated to give the product **I-53** as a yellow oil (4.10 g, 90%).

R_f: 0.70, 60% EtOAc in hexanes.



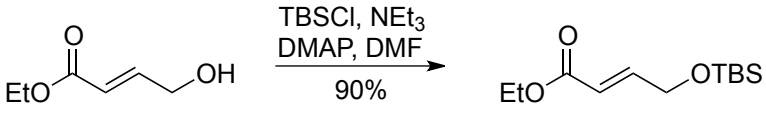
^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm = 7.02 (dt, *J* = 4.0, 15.7 Hz, 1H, H-2), 6.08 (dt, *J* = 2.1, 15.7 Hz, 1H, H-3), 4.33 (dd, *J* = 2.1, 4.0 Hz, 2H, 2xH-1), 4.19 (q, *J* = 7.1 Hz, 2H, 2xH-5), 2.09 (s, 1H, OH), 1.28 (t, *J*=7.1 Hz, 3H, 3xH-6).

^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 166.62 (C-4), 146.99 (C-2), 120.33 (C-3), 61.96 (C-1), 60.59 (C-5), 14.35 (C-6).

IR ($\tilde{\nu}$ /cm^{-1}): 3431, 2982, 1715, 1660, 1593, 1368, 1300, 1273, 1169, 1095, 1031, 958, 913.

HRMS (EI): calculated for $C_6H_{10}O_3$ $[M]^+$ 130.0630; found 130.0635.

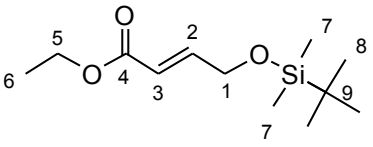
(*E*)-Ethyl 4-((*tert*-butyldimethylsilyl)oxy)but-2-enoate[51]



I-53 **I-54**

Alcohol **I-53** (800 mg, 6.15 mmol) was dissolved in DMF (7 mL). TBSCl (1.02 g, 6.77 mmol), imidazol (921 mg, 13.5 mmol) and DMAP (75.1 mg, 0.615 mmol) were added and the mixture was stirred for 1 h before water (10 mL) was added. The mixture was extracted with EtOAc (50 mL), washed with brine, dried over $MgSO_4$ and concentrated to give the product **I-54** as a yellow oil (1.35 g, 90%).

R_f: 0.70, 60% EtOAc in hexanes.



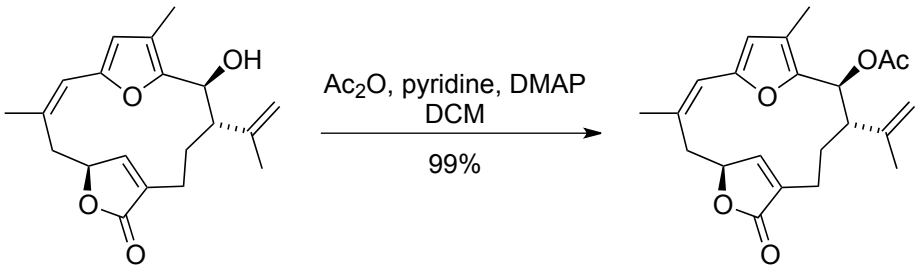
^{1}H NMR (599 MHz, $CDCl_3$) δ/ppm = 6.99 (dt, *J* = 3.5, 15.5 Hz, 1H, H-2), 6.09 (dt, *J* = 2.3, 15.5 Hz, 1H, H-3), 4.33 (dd, *J* = 2.3, 3.5 Hz, 2H, 2xH-1), 4.20 (q, *J* = 7.1 Hz, 2H, 2xH-5), 1.29 (t, *J* = 7.1 Hz, 3H, 3xH-6), 0.92 (s, 9H, 9xH-8), 0.08 (s, 6H, 6xH-7).

^{13}C NMR (151 MHz, $CDCl_3$) δ/ppm = 166.82 (C-4), 147.48 (C-2), 119.79 (C-3), 62.32 (C-1), 60.43 (C-5), 26.01 (C-8), 18.51 (C-9), 14.43 (C-6), -5.28 (C-7).

IR ($\widetilde{\nu}$ /cm^{-1}): 2955, 2930, 1720, 1472, 1295, 1253, 1161, 1134, 1037, 959, 831, 775.

HRMS (EI): calculated for $C_{12}H_{24}O_3Si$ $[M]^+$ 244.1495; found 244.1504.

(*Z*)-3,14-Dimethyl-7-oxo-11-(prop-1-en-2-yl)-6,16-dioxatricyclo[11.2.1.15,8] heptadeca-1(15),2,8(17),13-tetraen-12-ylacetate

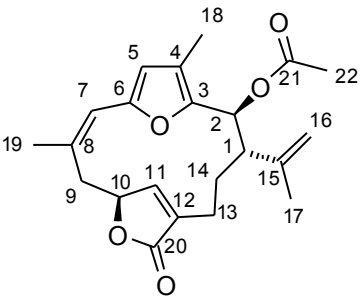


I-1 **I-73**

Bipinnatin J (**I-1**) (45.0 mg, 0.137 mmol) was dissolved in CH_2Cl_2 (2 mL). Pyridine (55.0 µL, 0.685 mmol), acetic anhydride (0.323 mL, 3.43 mmol) and DMAP (1.71 mg, 14.0 µmol) were added. After stirring for 4 h, the clear solution was washed with water, dried over Na_2SO_4, filtered and concentrated *in vacuo* to give of 2-*O*-acetatebipinnatin J (**I-73**) as a colorless powder (50.0 mg, 99%).

R_f: 0.50, 30% EtOAc/Hexanes.

m.p.: 133–135 °C (CH_2Cl_2).



^{1}H NMR (600 MHz, $CDCl_3$) *δ*/ppm = 6.83 (t, *J* = 1.6 Hz, 1H, H-11), 6.09 (s, 1H, H-7), 6.00 (s, 1H, H-5), 5.77 (d, *J* = 11.4 Hz, 1H, H-2), 4.99–4.96 (m, 2H, H-16α, H10), 4.93 (s, 1H, H-16β), 3.20 (t, *J* = 11.8 Hz, 1H, H-9α), 2.73 (dd, *J* = 11.8, 4.5 Hz, 1H, H-9β), 2.48 (t, *J* = 11.4 Hz, 1H, H-

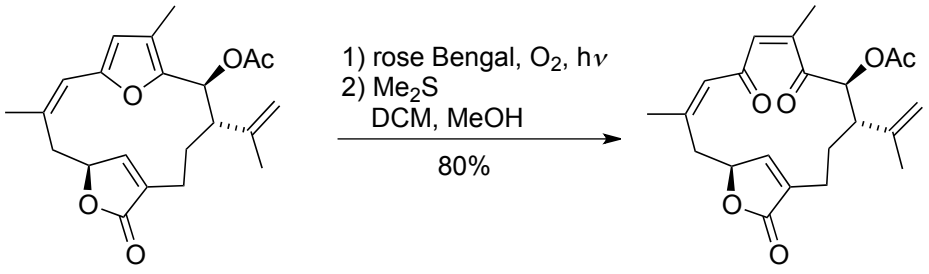
1), 2.41 (td, *J* = 14.4, 2.9 Hz, 1H, H-13α), 2.10–2.06 (m, 1H, 13β), 2.06 (s, 3H, 3xH-18), 1.99 (d, *J* = 1.2 Hz, 3H, 3xH-19), 1.91 (s, 3H, 3xH-22), 1.70–1.68 (m, 3H, 3xH-17), 1.66–1.60 (m, 1H, H-14α), 0.87 (td, *J* = 13.8, 3.6 Hz, 1H, H-14β).

^{13}C NMR (150 MHz, $CDCl_3$) δ/ppm = 174.49 (C-20), 170.29 (C-21), 152.49 (C-11), 151.63 (C-6), 147.19 (C-3), 142.08 (C-15), 133.00 (C-12), 129.79 (C-8), 122.64 (C-4), 117.48 (C-7), 116.73 (C-16), 114.20 (C-5), 78.82 (C-10), 67.21 (C-2), 48.14 (C-1), 40.00 (C-9), 30.50 (C-14), 26.12 (C-19), 21.07 (C-22), 19.84 (C-13), 18.82 (C-17), 9.79 (C-18).

IR ($\tilde{\nu}$ /cm^{-1}): 3461, 2927, 2226, 2161, 2043, 1993, 1784, 1732, 1647, 1440, 1372, 1329, 1291, 1253, 1239, 1195, 1091, 1067, 1020, 971, 950, 893, 867, 799, 754.

HRMS (EI): calculated for $C_{22}H_{26}O_5$ $[M]^+$ 370.1775; found 370. 1767.

(7*Z*,10*Z*)-7,11-Dimethyl-6,9,15-trioxo-4-(prop-1-en-2-yl)-14-oxabicyclo[11.2.1] hexadeca-1(16),7,10-trien-5-ylacetate



I-73 **I-74**

2-*O*-acetatebipinnatin J (**I-73**) (18.0 mg, 49.0 µmol) was dissolved in CH_2Cl_2 (2 mL) and MeOH (1 mL) and rose Bengal (<1 mg) was added. The solution was cooled to –78 °C and O_2 was bubbled through the solution. After 10 min the solution was irradiated with light (160 W) for 15 min. Dimethylsulfide (500 µL, 26.3 mmol) was added and the mixture was stirred for 2 h at 0 °C. The mixture was concentrated *in vacuo*. Filtration through silica (40% EtOAc/hexanes) removed rose Bengal and gave the crude *O*-acetateendione **I-74** as a colorless oil (15 mg, 80%). The product was used without further purification.

R$_f$: 0.20, 40 % EtOAc/hexanes.

^{1}H NMR (400 MHz, $CDCl_3$, −45 °C) δ/ppm = 7.40 (s, 1H), 6.41 (d, *J* = 1.4 Hz, 1H), 6.26 (s, 1H), 5.98 (d, *J* = 4.7 Hz, 1H), 5.37 (d, *J* = 8.3 Hz, 1H), 4.79 (d, *J* = 5.7 Hz, 2H), 3.97 (d, *J* = 12.0 Hz, 1H), 2.74 (dd, *J* =

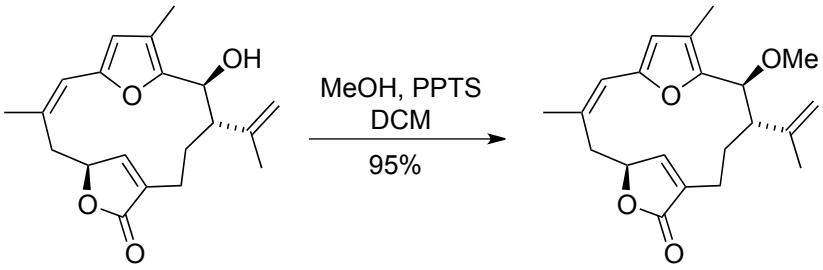
12.0, 8.3 Hz, 1H), 2.56 (dd, *J* = 10.2, 4.7 Hz, 1H), 2.37–2.28 (m, 2H), 2.26 (s, 3H), 2.07 (s, 3H), 1.87 (s, 3H), 1.72 (s, 1H), 1.64 (s, 3H), 1.57 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$, −45 °C) δ/ppm = 201.4, 189.1, 174.0, 171.2, 158.3, 152.4, 146.9, 133.2, 129.3, 124.6, 115.6, 80.5, 77.44, 76.2, 43.1, 35.1, 26.8, 23.4, 22.8, 21.8, 21.3, 21.0.

IR ($\tilde{\nu}$ /cm^{-1}): 3075, 2934, 2254, 1744, 1693, 1668, 1619, 1606, 1439, 1372, 1336, 1226, 1167, 1110, 1074, 1064, 1025, 968, 946, 909, 881, 862, 826, 752, 730.

HRMS (ESI): calculated for $C_{22}H_{27}O_6$ $[M+H]^+$ 387.1802; found 387.1801.

(*Z*)-12-Methoxy-3,14-dimethyl-11-(prop-1-en-2-yl)-6,16-dioxatricyclo[11.2.1.15,8]heptadeca-1(15),2,8(17),13-tetraen-7-one

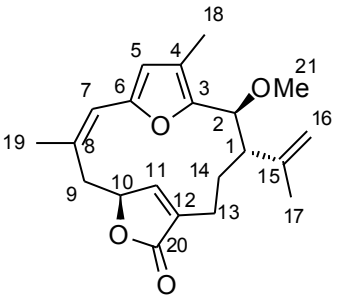


I-1 **I-75**

Bipinnatin J (**I-1**) (45.0 mg, 0.137 mmol) was dissolved in CH_2Cl_2 (5 mL) and MeOH (5 mL). Pyridinium *para*-toluenesulfonate (75.8 mg, 0.302 mmol) was added. The solution was stirred for 2 h at r.t. Et_2O (20 mL) and ½ sat. aq. $NaHCO_3$ solution (5 mL) were added. The layers were separated. The organic layer was washed with brine, dried and concentrated *in vacuo* to give of 2-*O*-methylbipinnatin J (**I-75**) as a colorless solid (44.5 mg, 95%).

R$_f$: 0.70, 40% EtOAC/hexanes.

m.p.: 156–158 °C (Et_2O).



^{1}H NMR (599 MHz, $CDCl_3$) δ/ppm = 6.76 (t, *J* = 1.7 Hz, 1H, H-11), 6.09 (s, 1H, H-7), 6.02 (s, 1H, H-5), 4.99 (t, *J* = 1.4 Hz, 1H, H-16α), 4.94 – 4.90 (m, 2H, H-10, H-10, H-16β), 4.08 (d, *J* = 11.0 Hz, 1H, H-2), 3.20 (t, *J* = 11.8 Hz, 1H, H-9α), 3.11 (s, 3H, 3xH-21), 2.68 (dd, *J* = 11.8, 4.3 Hz, 1H, H-9β), 2.45 (td, *J* = 14.4, 3.0 Hz, 1H, H-13α), 2.39 (t, *J* = 11.0 Hz, 1H,

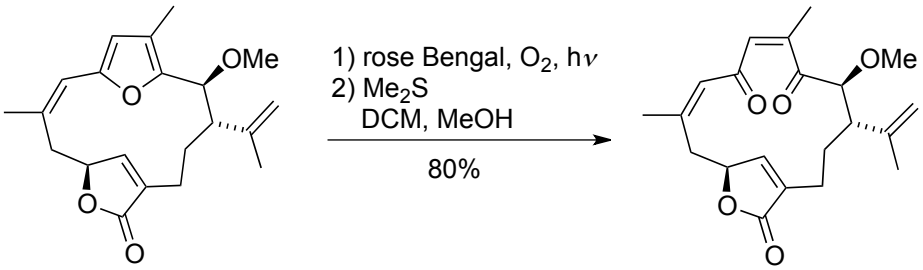
H-1), 2.05 (s, 3H, 3xH-18), 2.04 – 1.99 (m, 1H, H-13β), 1.97 (d, *J* = 1.3 Hz, 3H, 3xH-19), 1.74 (d, *J* = 0.6 Hz, 3H, 3xH-17), 1.55 – 1.47 (m, 1H, H-14α), 0.84 (td, *J* = 13.5, 3.9 Hz, 1H, H-14β).

^{13}C NMR (151 MHz, $CDCl_3$) δ/ppm = 174.48 (C-20), 152.28 (C-11), 151.56 (C-6), 147.41 (C-4), 143.16 (C-15), 132.95 (C-12), 129.57 (C-8), 122.69 (C-3), 117.45 (C-7), 115.70 (C-16), 113.73 (C-5), 78.83 (C-10), 74.64 (C-2), 56.04 (C-21), 48.70 (C-1), 39.84 (C-9), 30.42 (C-14), 26.16 (C-19), 19.72 (C-13), 18.22 (C-7), 10.03 (C-18).

IR ($\tilde{\nu}$ /cm^{-1}): 3071, 2967, 2923, 2815, 1744, 1644, 1520, 1440, 1399, 1373, 1330, 1289, 1199, 1092, 1066, 1034, 1018, 973, 955, 885, 864, 810, 667.

HRMS (ESI): calculated for $C_{21}H_{30}O_4N$ [M+NH_4] 360.2169; found 360.2170.

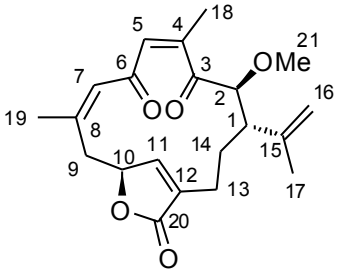
(7*Z*,10*Z*)-5-Methoxy-7,11-dimethyl-4-(prop-1-en-2-yl)-14-oxabicyclo[11.2.1]hexadeca-1(16),7,10-triene-6,9,15-trione



I-75 **I-76**

2-*O*-Methylbipinnatin J (**I-75**) (35.0 mg, 0.102 mmol) was dissolved in CH_2Cl_2 (3 mL) and MeOH (1.5 mL) before rose Bengal (<1 mg) was added. The solution was cooled to –78 °C and O_2 was bubbled through the solution. After 10 min the solution was irradiated with light (light bulb, 160 W) for 20 min. Dimethylsulfide (1.00 mL, 52.6 mmol) was added and the mixture was stirred for 2 h at 0 °C. The mixture was concentrated *in vacuo*. Filtration over silica (40% EtOAc/hexanes) removed rose Bengal and gave the crude *O*-methylenedione **I-76** as a colorless oil (29.0 mg, 80%). The crude product was used without further purification due to rapid decomposition.

R_f: 0.20, 50% EtOAC/hexanes.



^{1}H NMR (599 MHz, $CDCl_3$) δ/ppm = 7.08 (br s, 1H, H-11), 6.31 (s, 1H, H-7), 6.10 (br s, 1H, H-5), 5.08 (s, 1H, H-16α), 4.91 (s, 1H, H-10), 4.78 (s, 1H, H-16β), 4.03 (br s, 1H, H-2), 3.61 (s, 3H, 3xH-21), 2.83 (s, 1H, H-

9α), 2.50 (s, 1H, H-9β), 2.36 – 2.24 (m, 3H, H-1, 2xH-13), 2.06 (s, 3H, 3xH-19), 1.96 (s, 3H, 3xH-17), 1.81 (s, 1H, H-14α), 1.63 (s, 4H, H-14β, 3xH-18).

Broad signals and double methyl groups caused by rotamers.

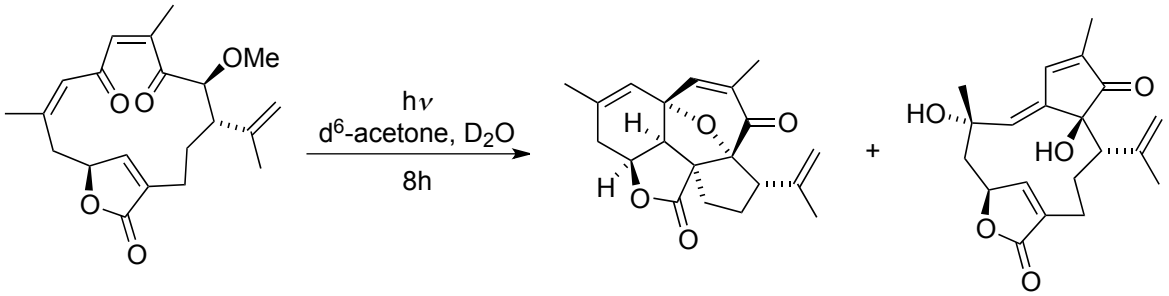
^{13}C NMR (151 MHz, $CDCl_3$) δ/ppm = 205.97 (C-3/6), 202.84 (C-3/6), 193.33 (C-3/6), 173.76 (C-20), 169.73 (C-20), 150.33 (C-11), 147.29, 144.46, 143.04, 137.52, 134.85, 127.62, 117.17, 116.00, 115.04 (for all: C-4/5/7/8/12/15/16), 89.60 (C-2), 78.19 (C-10), 59.36 (C-21), 58.85 (C-21), 46.89, 46.14, 42.28, 33.36, 23.17, 21.67, 20.94, 19.67, 17.97 (for all: C1/9/13/14/17/18/19).

Double signal caused by rotamers.

IR ($\tilde{\nu}$ /cm^{-1}): 2926, 2359, 1749, 1705, 1637, 1597, 1442, 1379, 1236, 1198, 1167, 1124, 1052, 1020, 880, 776, 729, 667.

HRMS (EI): calculated for $C_{21}H_{26}O_5$ $[M]^+$ 358.1775; found 358.1765.

Intricarene and (*E*)-2,10a-Dihydroxy-2,12-dimethyl-10-(prop-1-en-2-yl)-3,4,8,9,10,10a -hexahydro-2*H*-4,7-(metheno)cyclopenta[f][1]oxacyclododecine-6,11-dione

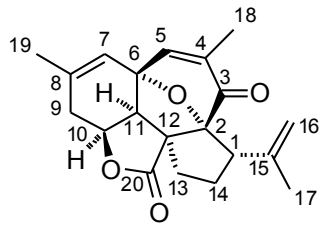


I-76 **I-10** (25%) **I-77** (15%)

O-Methylenedione **I-76** (10.0 mg, 0.0280 mmol) was dissolved in degassed d^6-acetone (0.5 mL) and degassed D_2O (0.5 mL). The solution was irradiated (275 W) for 5 h (NMR tube in a Quartz cooling vessel). Column chromatography (20% → 35% EtOAc/hexanes) afforded intricarene (**I-10**) (2.50 mg, 25%) and **I-77** (1.50 mg, 15%).

Intricarene (I-10):

R_f: 0.50, 40% EtOAC/hexanes.



^{1}H NMR (600 MHz, $CDCl_3$) δ/ppm = 6.41 (dd, *J* = 3.2, 1.5 Hz, 1H, H-7), 6.27 (q, *J* = 1.5 Hz, 1H, H-5), 4.92 (dd, *J* = 2.7, 1.5 Hz, 1H, H-16α), 4.87 (s, 1H, H-16β), 4.77 (ddd, *J* = 8.1, 5.3, 2.7 Hz, 1H, H-10), 3.39 – 3.35 (m, 1H, H-1), 2.82 (dd, *J* = 18.6, 8.6 Hz, 1H, H-9α), 2.54 (d, *J* = 5.3 Hz, 1H, H-11), 2.41 (d, *J* = 18.6 Hz, 1H, H-9β), 2.13 – 2.08 (m, 1H, H-14α), 2.00 (dd, *J* = 11.2, 4.6 Hz, 1H, H-13α), 1.95 – 1.89 (m, 2H, H-13β, H-14β), 1.84 (t, *J* = 1.5 Hz, 3H, 3xH-19), 1.77 – 1.74 (m, 6H, 3xH-17, 3xH-18).

^{13}C NMR (150 MHz, $CDCl_3$) δ/ppm = 193.16 (C-3), 178.10 (C-20), 147.45 (C-5), 141.89 (C-15), 137.34 (C-4), 135.36 (C-8), 128.17 (C-7), 113.42 (C-16), 102.94 (C-2), 84.73 (C-6), 70.86 (C-10), 64.30 (C-12), 58.14 (C-11), 46.48 (C-1), 35.77 (C-9), 29.45 (C-13), 28.67 (C-14), 23.30 (C-17), 23.23 (C-19), 14.52 (C-18).

IR ($\tilde{\nu}$ /cm^{-1}): 2944, 1765, 1691, 1652, 1441, 1340, 1281, 1179, 1164, 1115, 1077, 975, 785, 706.

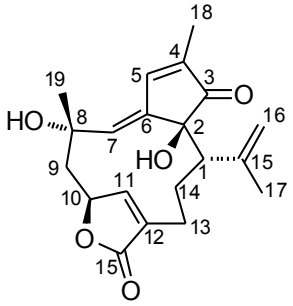
HRMS (EI): calculated for $C_{20}H_{22}O_4$ $[M]^+$ 326.1518; found 326.1514.

^{1}H NMR isolation	**^{1}H NMR synthetic**		**^{13}C NMR isolation**	**^{13}C NMR synthetic**
6.41 (q, *J* = 1.6 Hz, 1H)	6.41 (dd, *J* = 3.2, 1.5 Hz, 1H)		193.0	193.16
6.27 (q, J = 1.6 Hz, 1H)	6.27 (q, *J* = 1.5 Hz, 1H)		177.9	178.10
4.92 (q, J = 1.3 Hz, 1H)	4.92 (dd, *J* = 2.7, 1.5 Hz, 1H)		147.3	147.45
4.86 (br s, 1H)	4.87 (s, 1H)		141.8	141.89
4.77 (ddd, J = 8.6, 5.3, 2.6 Hz, 1H)	4.77 (ddd, *J* = 8.1, 5.3, 2.7 Hz, 1H)		137.2	137.34
3.38 (dd, J = 11.9, 5.7 Hz, 1H)	3.39 – 3.35 (m, 1H)		135.2	135.36
2.82 (dd, J = 18.6, 8.6 Hz, 1H)	2.82 (dd, *J* = 18.6, 8.6 Hz, 1H)		128.1	128.17

2.54 (d, J = 5.3 Hz, 1H)	2.54 (d, *J* = 5.3 Hz, 1H)		113.3	113.42
2.41 (br d, J = 18.6 Hz, 1H)	2.41 (d, *J* = 18.6 Hz, 1H)		102.8	102.94
2.11 (m, 1H)	2.13 – 2.08 (m, 1H)		84.6	84.73
2.01 (m, 1H)	2.00 (dd, *J* = 11.2, 4.6 Hz, 1H)		70.7	70.86
1.92 (m, 1H) 1.91 (m, 1H)	1.95 – 1.89 (m, 2H)		64.2	64.30
1.84 (t, J = 1.2 Hz, 3H)	1.84 (t, *J* = 1.5 Hz, 3H)		58.0	58.14
1.76 (d, J = 1.6 Hz, 3H)	1.77 – 1.74 (m, 6H)		46.4	46.48
1.75 (br s, 3H)			35.7	35.77
			29.3	29.45
			28.5	28.67
			23.13	23.30
			23.06	23.23
			14.4	14.52

Hydroxy cyclopentenone I-77:

R*f*: 0.30, 40% EtOAC/hexanes.



^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 8.39 (s, 1H, H-5), 7.42 (s, 1H, H-11), 5.40 (s, 1H, H-7), 5.25 (s, 1H, H-16α), 5.22 – 5.21 (m, 1H, H-10), 5.08 (s, 1H, H-16β), 3.02 (s, 1H, OH), 2.56 (dd, *J* = 3.1, 15.7 Hz, 1H, H-9α), 2.46 (dd, *J* = 7.6, 15.7 Hz, 1H, H-9β), 2.26 (t, *J* = 13.0 Hz, 1H, H-13α), 2.20 – 2.19 (m, 1H, H-13β), 2.07 (d, *J* = 8.5 Hz, 1H, H-1), 1.90 (s, 3H, H-18), 1.85 (s, 3H, H-17), 1.77 (t, *J* = 6.8, 1H, H-14α), 1.50 (s, 3H, H-19), 1.08 (td, *J* = 3.6, 13.0 Hz, 1H, H-14β).

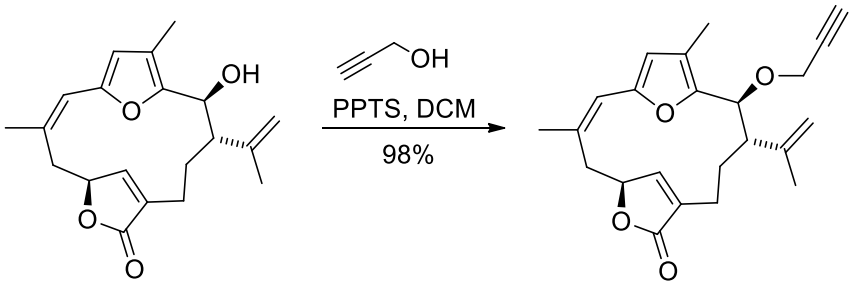
^{13}C NMR (126 MHz, $CDCl_3$) δ/ppm = 206.22 (C-3), 174.86 (C-15), 152.84 (C-11), 152.38 (C-5), 142.13 (C-2), 142.10 (C-15), 139.72 (C-6), 132.51 (C-12), 129.79 (C-7), 120.84 (C-16), 78.71 (C-10), 76.55 (C-

4), 75.90 (C-7), 53.83 (C-1), 48.99 (C-9), 32.36 (C-19), 26.89 (C-14), 21.68 (C-13), 21.28 (C-17), 11.07 (C-18).

IR ($\tilde{\nu}$ /cm^{-1}): 3448, 2923, 2852, 1740, 1704, 1644, 1444, 1373, 1331, 1192, 1136, 1055, 1018, 905.

HRMS (EI): calculated for $C_{20}H_{24}O_5$ $[M]^+$ 344.1624, found 344.1628.

(5*S*,11*S*,12*S*,*Z*)-3,14-dimethyl-11-(prop-1-en-2-yl)-12-(prop-2-yn-1-yloxy)-6,16-dioxatricyclo[11.2.1.15,8]heptadeca-1(15),2,8(17),13-tetraen-7-one

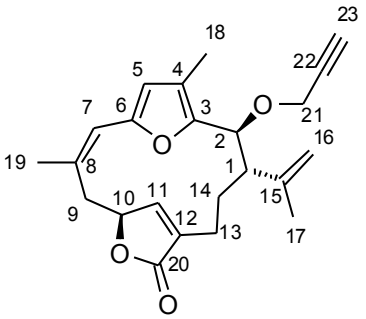


I-1 **I-79**

Bipinnatin J **(I-1)** (5.00 mg, 0.0152 mmol) was dissolved in CH_2Cl_2 (1 mL) and propargylalcohol (1 mL). PPTS (7.65 mg, 0.0305 mmol) was added and the solution was stirred for 2 h before it was washed with sat. aq. $NaHCO_3$ solution and brine. It was dried over $MgSO_4$ and concentrated to give the product **I-79** as a colorless solid (5.50 mg, 98%).

R_f: 0.50, 30% EtOAc in hexanes.

m.p.: 87.0 – 88.1°C (CH_2Cl_2).



^{1}H NMR (599 MHz, $CDCl_3$) δ/ppm = 6.77 (t, *J* = 1.6 Hz, 1H, H-11), 6.12 (s, 1H, H-7), 6.04 (s, 1H, H-5), 5.03 – 4.99 (m, 1H, H-16α), 4.97 – 4.91 (m, 2H, H-16β, H-10), 4.58 (d, *J* = 11.0 Hz, 1H, H-2), 4.09 (dd, *J* = 2.4, 16.3 Hz, 1H, H-21α), 3.82 (dd, *J* = 2.4, 16.3 Hz, 1H, H-21β), 3.22 (t, *J* = 11.8 Hz, 1H, H-9α), 2.70 (dd, *J* = 4.3, 11.8 Hz, 1H, H-9β), 2.49 (td, *J* = 3.5, 14.0 Hz, 1H, H-13α), 2.42 (t, *J* = 11.0 Hz, 1H, H-1), 2.39 (t, *J* = 2.4 Hz, 1H, H-23), 2.12 (s, 3H, 3xH-17), 2.05 (dd, *J* = 6.8, 14.0 Hz, 1H, H-13β), 2.00 (s, 3H, 3xH-19), 1.81 (s, 3H, 3x18), 1.61 – 1.52 (m, 1H, H-14α), 0.86 (td, *J* = 3.5, 13.7 Hz, 1H, H-14β).

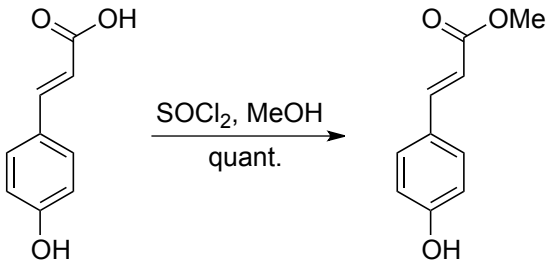
^{13}C NMR (151 MHz, $CDCl_3$) δ/ppm = 174.37 (C-20), 152.11 (C-11), 151.91 (C-6), 146.24 (C-3), 142.74 (C-15), 132.95 (C-12), 129.95 (C-8), 123.98 (C-4), 117.33 (C-7), 115.94 (C-16), 113.63 (C-5), 80.15 (C-22), 78.75 (C-10), 74.50 (C-23), 70.67 (C-2), 54.56 (C-21), 48.89 (C-1), 39.74 (C-9), 30.22 (C-14), 26.16 (C-19), 19.64 (C-13), 17.80 (C-17), 9.87 (C-18).

IR ($\tilde{\nu}$ /cm^{-1}): 3291, 3227, 2926, 1748, 1646, 1440, 1331, 1291, 1062.

HRMS (EI): calculated for $C_{23}H_{26}O_4$ $[M]^+$ 366.1831; found 366.1836.

4.3 Experimental Procedures for Chapter 2

(*E*)-Methyl 3-(4-hydroxyphenyl)acrylate



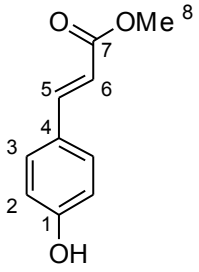
II-14 **II-17**

p-Coumaric acid (**II-14**) (5.00 g, 30.4 mmol) was dissolved in MeOH (40 mL). $SOCl_2$ (5.50 mL, 76.1 mmol) was added at 0 °C and the solution was stirred at r.t. for 6 h, before it was concentrated in *vacuo*. The product **II-17** was obtained as a yellow solid (5.43 g, quant.).

R_f: 0.70, CH_2Cl_2/MeOH/H_2O/AcOH 9:1:0.6:0.6.

m.p.: 86.0 – 88.0°C (MeOH).

^{1}H NMR (300 MHz, CD_3OD) δ/ppm = 7.59 (d, *J* = 15.9 Hz, 1H, H-5), 7.43 (d, *J* = 8.3 Hz, 2H, 2xH-3), 6.78 (d, *J* = 8.3 Hz, 2H, 2xH-2), 6.30 (d, *J* = 15.9 Hz, 1H, H-6), 3.74 (s, 3H, 3xH-8).

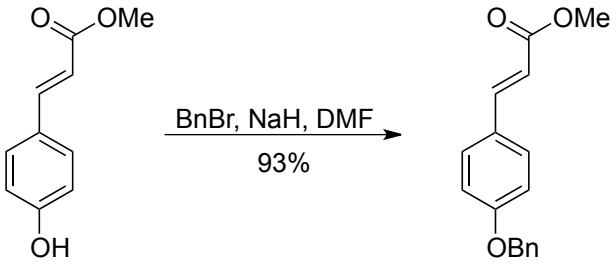


^{13}C NMR (75 MHz, CD_3OD) δ/ppm = 169.82 (C-7), 161.18 (C-1), 146.49 (C-5), 131.09 (C-3), 127.08 (C-4), 116.77 (C-2), 114.88 (C-6), 52.00 (C-8).

IR ($\tilde{\nu}$ /cm^{-1}): 3368, 1682, 1632, 1598, 1582, 1514, 1445, 1432, 1349, 1328, 1281, 1193, 1167, 1103, 984, 827.

HRMS (EI): calculated for $C_{10}H_{10}O_3$ $[M]^+$ 178.0630; found 178.0635.

(*E*)-Methyl 3-(4-(benzyloxy)phenyl)acrylate



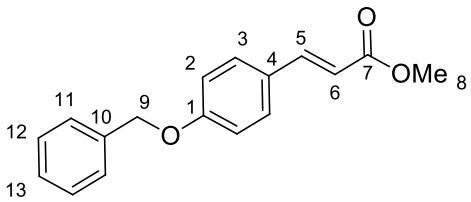
II-17 **II-18**

Ester **II-17** (5.00 g, 28.1 mmol) was dissolved in DMF (80 mL). NaH (60% on mineral oil, 1.35 g, 33.7 mmol) was slowly added at 0 °C. The mixture was stirred at r.t. for 3 h, before water (80 mL) was added. The slurry mixture was extracted with Et_2O (400 mL). The organic layers were washed with brine, dried over Na_2SO_4 and concentrated in *vacuo* to give the product **II-18** as a colorless solid (7.00 g, 93%).

R_f: 0.80, 40% EtOAc in hexanes.

m.p.: 133 – 135 °C (Et_2O).

^{1}H NMR (400 MHz, CD_3OD) δ/ppm = 7.64 (d, *J* = 16.1 Hz, 1H, H-5), 7.55 (d, *J* = 9.1 Hz, 2H, 2xH-3), 7.45 – 7.31 (m, 5H, 2xH-11, 2xH-12, H-13), 7.03 (d, *J* = 9.1 Hz, 2H, 2xH-2), 6.38 (d, *J* = 16.1 Hz, 1H, H-6), 5.13 (s, 2H, 2xH-9), 3.77 (s, 3H, 3xH-8).

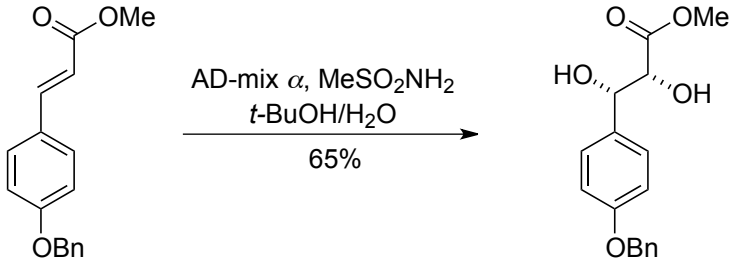


^{13}C NMR (101 MHz, CD_3OD) δ/ppm = 169.51 (C-7), 162.23 (C-1), 146.08 (C-5), 138.31 (C-10), 130.95 (C-3), 129.55 (C-12), 129.00 (C-4), 128.58 (C-13), 128.58 (C-11), 116.39 (C-6), 116.04 (C-2), 71.06 (C-9), 52.01 (C-8).

IR ($\tilde{\nu}$ /cm^{-1}): 2922, 1850, 1714, 1634, 1602, 1571, 1510, 1443, 1380, 1330, 1301, 1286, 1249, 1203, 1162, 1012, 985, 836, 817, 745.

HRMS (EI): calculated for $C_{17}H_{16}O_3$ $[M]^+$ 168.1099; found 168.1092.

(2*R*,3*S*)-Methyl 3-(4-(benzyloxy)phenyl)-2,3-dihydroxypropanoate



II-18 **II-19**

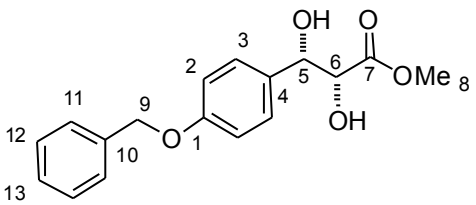
Alkene **II-18** (2.67 g, 9.95 mmol) was suspended in *t*-BuOH/water (1:1, 90 mL). AD-mix *α* (13.9 g, 1.40 g/mmol) and methansulfonamide (2.84 g, 29.9 mmol) were added and the reaction mixture was stirred for 12 h at r.t. Sat. aq. Na_2SO_3 solution (40 mL) was added and the mixture was stirred for 1 h, then extracted with EtOAc (30 mL). The organic layer was washed with brine, dried over Na_2SO_4 and concentrated in *vacuo*. Column chromatography (60% EtOAc in hexanes) gave the product **II-19** as a colorless solid (1.97 g, 65%).

R_f: 0.30, 60% EtOAc in hexanes.

$[a]_D^{22}$ = 3.6 ° (*c* = 1.00, $CHCl_3$).

m.p.: 110.1 – 114.9 (EtOAc).

^{1}H NMR (599 MHz, $CDCl_3$) δ/ppm = 7.43 (d, *J* = 7.0 Hz, 2H, 2xH-2), 7.38 (t, *J* = 7.6 Hz, 2H, 2xH-11), 7.35 – 7.31 (m, 3H, 2xH-12, H-13), 6.98 (d, *J* = 8.7 Hz, 2H, 2xH-3), 5.07 (s, 2H, 2xH-9), 4.97 (d, *J* = 2.9 Hz, 1H, H-5), 4.34 (d, *J* = 2.2 Hz, 1H, H-6), 3.81 (s, 3H, 3xH-8), 3.06 (s, 1H, OH), 2.61 (s, 1H, OH).

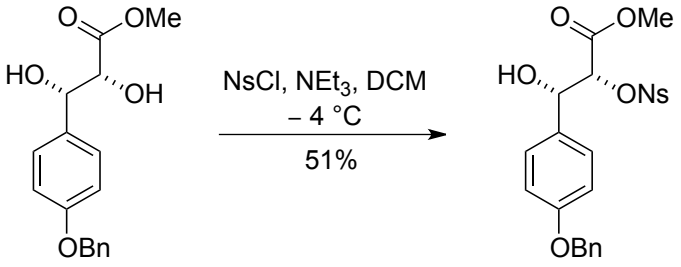


^{13}C NMR (151 MHz, $CDCl_3$) δ/ppm = 173.31 (C-7), 158.81 (C-1), 137.03 (C-10), 132.44 (C-4), 128.74 (C-12), 128.13 (C-13), 127.71 (C-11), 127.59 (C-2), 114.99 (C-3), 74.83 (C-6), 74.25 (C-5), 70.18 (C-9), 53.01 (C-8).

IR ($\tilde{\nu}$ /cm^{-1}): 3483, 2292, 2955, 2349, 1712, 1609, 1583, 1511, 1453, 1511, 1453, 1385, 1314, 1299, 1276, 1220, 1173, 1109, 1043, 1027, 988, 941, 886, 728.

HRMS (ESI): calculated for $C_{17}H_{17}O_5$ $[M-H]^-$ 301.1081; found 301.1083.

(2*R*,3*S*)-Methyl 3-(4-(benzyloxy)phenyl)-3-hydroxy-2-(((4-nitrophenyl)sulfonyl)oxy)propanoate



II-19 **II-20**

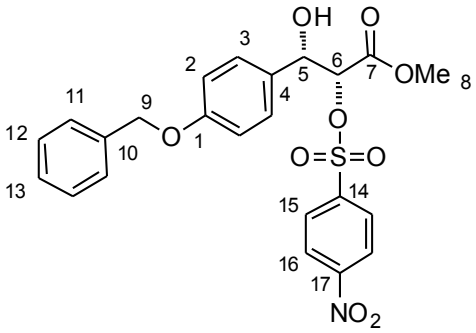
Diol **II-19** (1.50 g, 4.96 mmol) was dissolved in CH_2Cl_2 (25 mL) and cooled to 0 °C. *para*-Nitrobenzene sulfonyl chloride (1.10 g, 4.96 mmol) and NEt_3 (1.37 mL, 9.91 mmol) were added slowly at −4 °C. The solution was stirred at this temperature for 2 h before sat. aq. NH_4Cl solution (10 mL) was added. The organic layer was washed with 10% aq. HCl solution and brine, dried over Na_2SO_4 and concentrated in *vacuo*. Column chromatography (20% EtOAc in hexanes) gave the product **II-20** as a yellow solid (1.23 g, 51%).

R_f: 0.30, 30% EtOAc in hexanes.

$[a]_D^{24}$ = 40.8 ° (*c* = 1.07, $CHCl_3$).

m.p.: 112.3 °C – 113.0 °C (EtOAc).

^{1}H NMR (599 MHz, $CDCl_3$) δ/ppm = 8.22 (d, *J* = 8.8 Hz, 2H, 2xH-15/16), 7.84 (d, *J* = 8.8 Hz, 2H, 2xH-15/16), 7.45 – 7.39 (m, 4H, 2xH-11, 2xH-12), 7.36 – 7.32 (m, 1H, H-13), 7.14 (d, *J* = 8.8 Hz, 2H, 2xH-3), 6.82 (d, *J* = 8.8 Hz, 2H, 2xH-2), 5.17 (d, *J* = 4.0 Hz, 1H, H-5), 5.02 – 4.97 (m, 3H, H-6, 2xH-9), 3.72 (s, 3H, 3xH-8), 2.24 (s, 1H, OH).

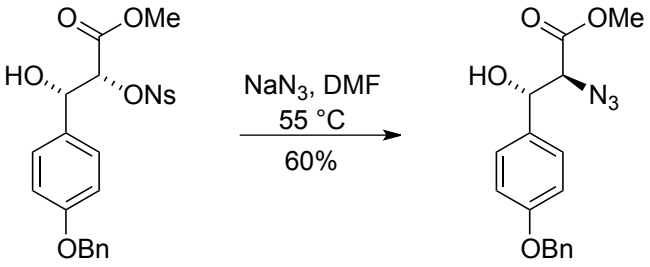


^{13}C NMR (151 MHz, $CDCl_3$) δ/ppm = 167.05 (C-7), 159.20 (C-1), 150.70 (C-14/17), 141.59 (C-14/17), 136.58 (C-10), 129.63 (C-4), 129.29 (C-15/16), 128.79 (C-11/12), 128.31 (C-13), 127.73 (C-11/12), 127.51 (C-3), 124.23 (C-15/16), 114.99 (C-2), 82.42 (C-9), 73.30 (C-5), 70.18 (C-6), 53.25 (C-8).

IR ($\tilde{\nu}$ /cm^{-1}): 3526, 3494, 1766, 1608, 1527, 1349, 1209, 1169, 1083, 1024, 1007, 1939.

HRMS (ESI): calculated for $C_{23}H_{25}N_2O_9S$ $[M+NH_4]^+$ 505.1275; found: 505.1270.

(2*S*,3*S*)-Methyl 2-azido-3-(4-(benzyloxy)phenyl)-3-hydroxypropanoate

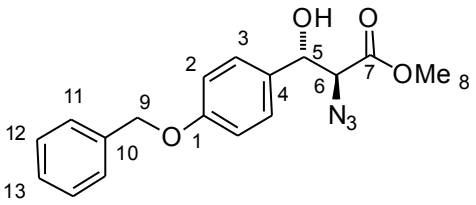


II-20 **II-21**

Nosylate **II-20** (100 mg, 0.205 mmol) was dissolved in DMF (1 mL), NaN_3 (20.0 mg, 0.308 mmol) was added and the mixture was heated to 55 °C for 24 h before water (1 mL) was added. The mixture was extracted with EtOAc (10 mL), the organic layers were washed with brine, dried over Na_2SO_4 and concentrated in *vacuo*. Column chromatography (20% EtOAc in hexanes) gave the product **II-21** as a yellow oil (40.0 mg, 60%).

R_f: 0.80, 50% EtOAc in hexanes.

$[a]_D^{22}$ = 0 ° (*c* = 1.05, $CHCl_3$).



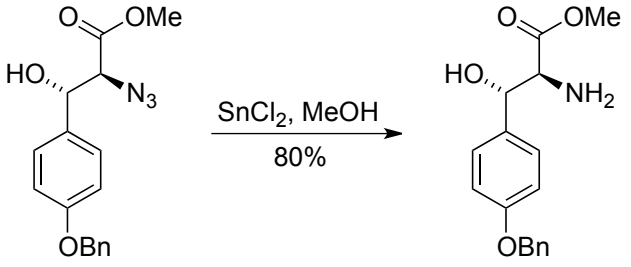
^{1}H NMR (599 MHz, $CDCl_3$) δ/ppm = 7.45 – 7.41 (m, 2H, 2xH-11), 7.41 – 7.37 (m, 2H, 2xH-12), 7.34 (d, *J* = 7.3 Hz, 1H, H-13), 7.31 (d, *J* = 8.6 Hz, 2H, 2xH-3), 6.99 (d, *J* = 8.6 Hz, 2H, 2xH-2), 5.07 (s, 2H, 2xH-9), 4.97 (d, *J* = 7.2 Hz, 1H, H-5), 4.10 (d, *J* = 7.2 Hz, 1H, H-6), 3.80 (s, 3H, 3xH-8), 2.78 (s, 1H, OH).

^{13}C NMR (151 MHz, $CDCl_3$) δ = 169.57 (C-7), 159.27 (C-1), 136.88 (C-10), 131.40 (C-4), 128.73 (C-12), 128.16 (C-13), 128.06 (C-3), 127.60 (C-11), 115.13 (C-2), 73.87 (C-5), 70.17 (C-9), 67.01 (C-6), 52.92 (C-8).

IR ($\tilde{\nu}$ /cm^{-1}): 3427, 2956, 2114, 1731, 1611, 1583, 1512, 1453, 1436, 1381, 1311, 1243, 1169, 1041, 993, 789.

HRMS (ESI): calculated for $C_{17}H_{17}N_3O_4Na$ $[M+Na]^+$ 350.1111; found: 350.1111.

(2*S*,3*S*)-Methyl 2-amino-3-(4-(benzyloxy)phenyl)-3-hydroxypropanoate



II-21 **II-22**

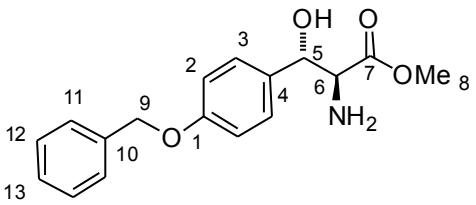
Azide **II-21** (1.70 g, 5.19 mmol) was dissolved in MeOH (15 mL). $SnCl_2 \cdot 2\ H_2O$ (2.34 g, 10.4 mmol) was added and the mixture was stirred for 4 h before it was concentrated in *vacuo*. The crude residue was redissolved in EtOAc (20 mL), washed with 10% NaOH (5 mL), water and brine, dried over Na_2SO_4 and concentrated in *vacuo*. Column chromatography (4% MeOH in CH_2Cl_2) gave the product **II-22** as a colorless solid (1.25 g, 80%).

R_f: 0.30, 5% MeOH in CH_2Cl_2.

$[a]_D^{22}$ = 41.3 ° (*c* = 1.08, MeOH).

m.p.: 103.2 – 104.0°C (CH_2Cl_2).

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm = 7.49 – 7.27 (m, 5H, 2xH-11, 2xH-12, H-13), 7.21 (d, *J* = 8.6 Hz, 2H, 2xH-3), 6.95 (d, *J* = 8.6 Hz, 2H, 2xH-2), 5.05 (s, 2H, 2xH-9), 4.90 (d, *J* = 6.0 Hz, 1H, H-5), 3.79 (d, *J* = 6.0 Hz, 1H, H-6), 3.70 (s, 3H, 3xH-8).

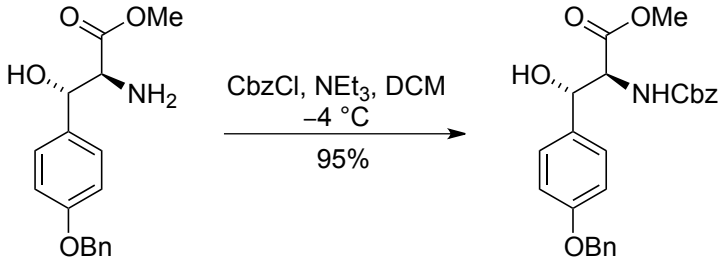


^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 173.87 (C-7), 158.86 (C-1), 137.04 (C-10), 132.26 (C-4), 128.74 (C-12), 128.14 (C-13), 127.73 (C-3), 127.62 (C-11), 114.92 (C-2), 74.16 (C-5), 70.18 (C-9), 60.06 (C-6), 52.22 (C-8).

IR ($\tilde{\nu}$ /cm^{-1}): 3460, 2990, 1699, 1610, 1510, 1431, 1368, 1314, 1283, 1254, 1218, 1202, 1174, 1107, 1045, 1000, 952, 917, 837, 824, 788.

HRMS (ESI): calculated for $C_{17}H_{20}NO_4$ $[M+H]^+$ 302.1387; found: 302.1386.

(2*S*,3*S*)-Methyl 2-(((benzyloxy)carbonyl)amino)-3-(4-(benzyloxy)phenyl)-3-hydroxypropanoate



II-22 **II-23**

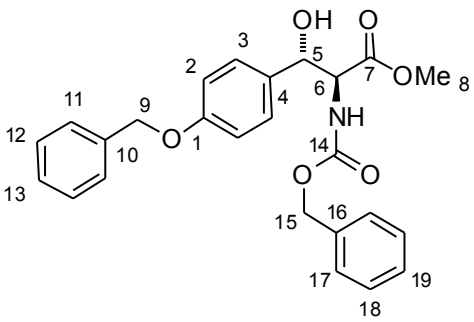
Amine **II-22** (300 mg, 0.996 mmol) was dissolved in CH_2Cl_2 (3 mL) and cooled to −4 °C. Benzyloxycarbonylchlorid (156 µL, 1.09 mmol) and NEt_3 (304 µL, 2.19 mmol) were added slowly. The mixture was stirred at −4 °C for 1.5 h before sat. aq. NH_4Cl solution (2 mL) was added. The layers were separated and the organic layer was washed with brine, dried over Na_2SO_4 and concentrated in *vacuo* to give the product **II-23** as a colorless solid (410 mg, 95%).

R_f: 0.50, 50% EtOAc in hexanes.

$[a]_D^{24}$ = 65.0 ° (*c* = 0.92, $CHCl_3$).

m.p.: 126.8 – 127.0°C (EtOAc).

^{1}H NMR (599 MHz, $CDCl_3$) δ/ppm = 7.43 – 7.31 (m, 10H, 2xH-11, 2xH-12, H-13, 2xH-17, 2xH-18, H-19), 7.18 (d, *J* = 8.6 Hz, 2H, 2xH-3), 6.92 (d, *J* = 8.6 Hz, 2H, 2xH-2), 5.46 (d, *J* = 7.7 Hz, 1H, NH), 5.14 – 5.11 (m, 3H, H-5, 2xH-15), 5.05 (s, 2H, 2xH-9), 4.75 (dd, *J* = 4.2, 7.7 Hz, 1H, H-6), 3.69 (s, 3H, 3xH-8), 3.36 (s, 1H, OH).

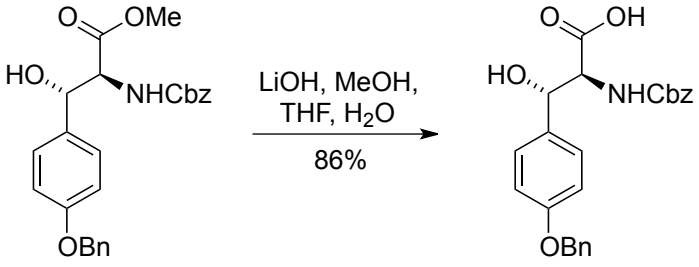


^{13}C NMR (151 MHz, $CDCl_3$) δ/ppm = 170.31 (C-7), 158.83 (C-1), 156.70 (C-14), 136.91 (C-10), 135.80 (C-16), 131.30 (C-4), 128.74 (C-12/18), 128.71 (C-12/18), 128.45 (C-17/19), 128.29 (C-17/19), 128.16 (C-13), 127.63 (C-11), 127.42 (C-3), 114.92 (C-2), 74.64 (C-5), 70.17 (C-9), 67.54 (C-15), 60.04 (C-6), 52.66 (C-8).

IR ($\tilde{\nu}$ /cm^{-1}): 3460, 3382, 2946, 1810, 1726, 1708, 1611, 1586, 1525, 1513, 1497, 1455, 1439, 1375, 1313, 1249, 1200, 1174, 1115, 1063, 1025, 1003.

HRMS (ESI): calculated for $C_{25}H_{25}NO_6Na$ $[M+Na]^+$ 458.1574; found: 458.1571.

(2*S*,3*S*)-2-(((Benzyloxy)carbonyl)amino)-3-(4-(benzyloxy)phenyl)-3-hydroxypropanoic acid



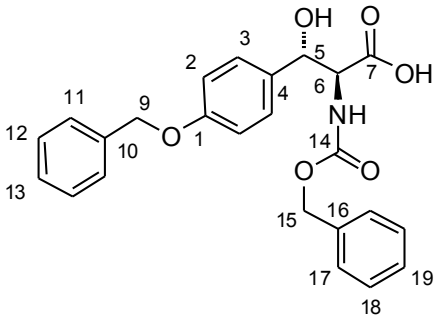
II-23 **II-24**

Ester **II-23** (100 mg, 0.230 mmol) was dissolved in THF (6 mL) and MeOH (2 mL). LiOH (22.5 mg, 0.918 mmol) was dissolved in H_2O (2 mL) and added to the solution. The solution was stirred for 2 h before it was concentrated in vacuo. The aqueous residue was acidified with 10% aq. HCl to pH = 3 and extracted with EtOAc (10 mL). The organic layer was washed with brine, dried over Na_2SO_4 and concentrated in *vacuo* to give the product **II-24** (83.0 mg, 86%) as a colorless solid.

R_f: 0.50, 5% MeOH in CH_2Cl_2.

[a]$_D$ n. d. because of unsatisfactory solubility in common solvents (MeOH, CH_2Cl_2, chloroform, water, DMSO)

m.p.: 170.8 °C (dec.) (EtOAc)



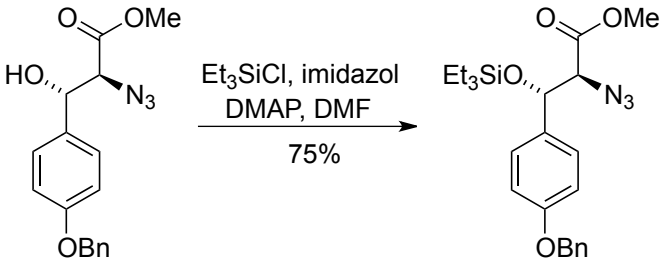
^{1}H NMR (400 MHz, CD_3OD) δ/ppm = 7.47 – 7.23 (m, 12H, 2xH-3, 2xH-11, 2xH-12, H-13, 2xH-17, 2xH-18, H-19), 6.99 (d, *J* = 8.8 Hz, 2H, 2xH-2), 5.86 (d, *J* = 8.8 Hz, 1H, H-6), 5.08 (s, 2H, 2xH-15), 4.65 (d, *J* = 8.8 Hz, 1H, H-5), 4.59 (s, 2H, 2xH-9).

^{13}C NMR (101 MHz, CD_3OD) δ/ppm = 172.21 (C-7), 160.86 (C-1), 142.71 (C-14), 138.75 (C-16), 138.53 (C-10), 129.51 (C-3/13/18/19), 129.33 (C-3/13/18/19), 129.12 (C-4), 128.92 (C-11), 128.55 (C-12), 128.38 (C-3/13/18/19), 128.25 (C-3/13/18/19), 127.98 (C-17), 115.68 (C-2), 80.72 (C-6), 71.03 (C-9), 65.23 (C-15), 61.43 (C-5).

IR ($\tilde{\nu}$ /cm^{-1}): 3369, 3029, 2992, 1732, 1688, 1612, 1586, 1544, 1514, 1497, 1453, 1440, 1408, 1380, 1294, 1233, 1175, 1113, 1080, 1034, 1023.

HRMS (ESI): calculated for $C_{24}H_{23}NO_6Na$ $[M+Na]^+$ 444.1418; found: 444.1417.

(2*S*,3*S*)-Methyl 2-azido-3-(4-(benzyloxy)phenyl)-3-((triethylsilyl)oxy)propanoate

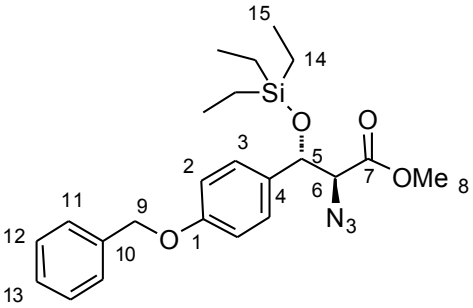


II-21 **II-25**

Azide **II-21** (685 mg, 2.09 mmol) was dissolved in DMF (16 mL) and Et_3SiCl (614 µL, 3.67 mmol), imidazol (366 mg, 5.38 mmol) and DMAP (29.9 mg, 0.244 mmol) were added. The reaction mixture was stirred for 18 h at r.t., before water (20 mL) was added. It was extracted with EtOAc (125 mL), washed with brine, dried over Na_2SO_4 and concentrated. Column chromatography (2%EtOAc in hexanes) gave the product **II-25** as a colorless oil (694 mg, 75%).

R_f: 0.20, 2% EtOAc in hexanes.

$[\alpha]_D^{24}$ = 69.5 ° (*c* = 0.91, MeOH).



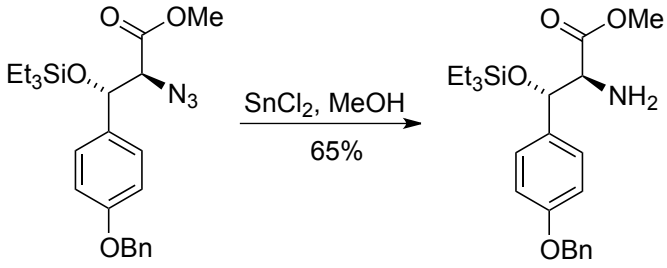
^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 7.46 – 7.32 (m, 5H, 2xH-11, 2xH-12, H-13), 7.29 (d, *J* = 8.4 Hz, 2H, 2xH-3), 6.96 (d, *J* = 8.7 Hz, 2H, 2xH-2), 5.06 (s, 2H, 2xH-9), 4.96 (d, *J* = 7.4 Hz, 1H, H-5), 3.99 (d, *J* = 7.4, 1H, H-6), 3.76 (s, 3H, 3xH-8), 0.84 (t, *J* = 8.1 Hz, 9H, 9xH-15), 0.48 (q, *J* = 8.1 Hz, 6H, 6xH-14).

^{13}C NMR (101 MHz, $CDCl_3$) *δ*/ppm = 169.25 (C-7), 159.14 (C-1), 136.97 (C-10), 132.42 (C-4), 128.72 (C-12), 128.23 (C-3), 128.15 (C-13), 127.71 (C-11), 114.83 (C-2), 75.11 (C-5), 70.17 (C-9), 68.54 (C-6), 52.54 (C-8), 6.72 (C-15), 4.78 (C- 14).

IR ($\tilde{\nu}$ /cm^{-1}): 3035, 2954, 2912, 2877, 2109, 1747, 1610, 1586, 1511, 1455, 1436, 1414, 1381, 1353, 1302, 1241, 1204, 1170, 1115, 1087, 1004.

HRMS (ESI): calculated for $C_{23}H_{31}O_4N_3SiNa$ $[M+Na]^+$ 464.1976; found: 464.1986.

(2*S*,3*S*)-methyl 2-amino-3-(4-(benzyloxy)phenyl)-3-((triethylsilyl)oxy)propanoate

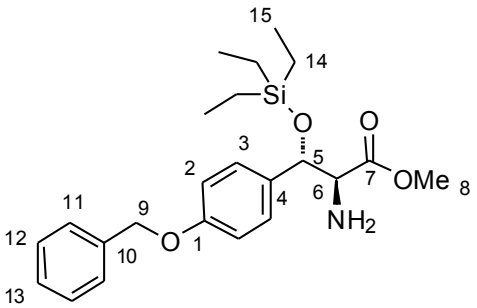


II-25 **II-26**

Azide **II-25** (1.37 g, 3.10 mmol) was dissolved in MeOH (14 mL). $SnCl_2 \cdot 2\ H_2O$ (1.40 g, 6.19 mmol) was added and the reaction mixture was stirred for 1.5 h at r.t. before it was concentrated under reduced pressure. The residue was redissolved in EtOAc (150 mL) and washed with 10% aq. NaOH (100 mL), brine, dried over Na_2SO_4 and concentrated under reduced pressure. Column chromatography (2% MeOH in CH_2Cl_2) gave the product **II-26** as a yellow oil (831 mg, 65%).

R_f: 0.30, 2% MeOH in CH_2Cl_2.

$[\alpha]_D^{24}$ = 49.2 ° (*c* = 0.98, MeOH).



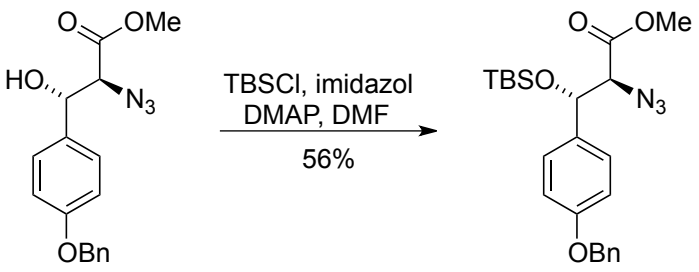
^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 7.45 – 7.30 (m, 5H, 2xH-11, 2xH-12, H-13), 7.21 (d, *J* = 8.4 Hz, 2H, 2xH-3), 6.93 (d, *J* = 8.8 Hz, 2H, 2xH-2), 5.05 (s, 2H, 2xH-9), 4.82 (d, *J* = 6.3 Hz,1H, H-5), 3.70 (s, 3H, 3xH-8), 3.69 (d, *J* = 6.3 Hz, 1H, H-6), 1.71 (s, 2H, NH_2), 0.85 (t, *J* = 7.9 Hz, 9H, 9xH-15), 0.50 (q, *J* = 7.7 Hz, 6H, 6xH-14).

^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm = 173.48 (C-8), 158.78 (C-1), 137.04 (C-10), 132.85 (C-4), 128.71 (C-12), 128.15 (C-3), 128.13 (C-13), 127.70 (C-11), 114.63 (C-2), 76.53 (C-5), 70.16 (C-9), 62.26 (C-6), 51.96 (C-8), 6.81 (C-15), 4.84 (C-14).

IR ($\tilde{\nu}$ /cm^{-1}): 3387, 3326, 3065, 3034, 2952, 2912, 2876, 1738, 1663, 1609, 1585, 1510, 1455, 1436, 1414, 1380, 1302, 1268, 1238, 1197, 1169, 1112, 1079, 1005.

HRMS (ESI): calculated for $C_{23}H_{34}O_4NSi$ $[M+H]^+$ 416.2252; found: 416.2262.

(2*S*,3*S*)-Methyl 2-azido-3-(4-(benzyloxy)phenyl)-3-((*tert*-butyldimethylsilyl)oxy)propanoate

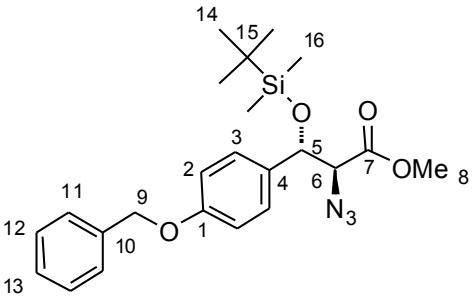


II-21 **II-27**

Azide **II-21** (677 mg, 2.07 mmol) was dissolved in DMF (14 mL) and TBSCl (868 mg, 5.76 mmol), imidazol (310 mg, 4.55 mmol) and DMAP (25.3 mg, 0.210 mmol) were added. The reaction mixture was stirred for 18 h at r.t., before water (20 mL) was added. It was extracted with EtOAc (125 mL), washed with brine, dried over Na_2SO_4 and concentrated. Column chromatography (5%EtOAc in hexanes) gave the product **II-27** as a colorless oil (504 mg, 56%).

R_f: 0.29, 5% EtOAc in hexanes.

$[\alpha]_D^{24}$ = 62.0 ° (*c* = 0.87, MeOH).



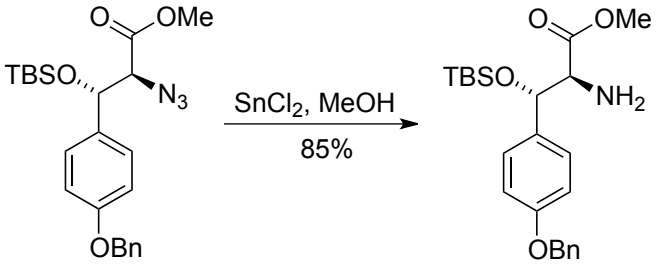
^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 7.4 – 7.25 (m, 5H, 2xH-11, 2xH-12, H-13), 7.28 (d, *J* = 8.6 Hz, 2H, 2xH-3), 6.97 (d, *J* = 8.7 Hz, 2H, 2xH-2), 5.06 (s, 2H, 2xH-9), 4.92 (d, *J* = 7.6 Hz, 1H, H-5), 3.96 (d, *J* = 7.6 Hz, 1H, H-6), 3.77 (s, 3H, 3xH-8), 0.84 (s, 9H, 9xH-14), 0.03 (s, 3H, 3xH-16), −0.20 (s, 3H, 3xH-16).

^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm = 169.29 (C-7), 159.16 (C-1), 136.97 (C-10), 132.38 (C-4), 128.73 (C-12), 128.28 (C-3), 128.16 (C-13), 127.72 (C-11), 114.87 (C-2), 75.28 (C-5), 70.19 (C-9), 68.59 (C-6), 52.56 (C-8),25.69 (C-14), 18.11 (C-15), −4.48 (C-16), −5.27 (C-16).

IR ($\tilde{\nu}$/cm^{-1}): 3033, 2952, 2929, 2886, 2856, 2107, 1744, 1610, 1585, 1511, 1471, 1462, 1454, 1435, 1382, 1361, 1302, 1247, 1203, 1169, 1114, 1085, 1023, 1005.

HRMS (ESI): calculated for $C_{23}H_{31}O_4N_3SiNa$ $[M+Na]^+$ 464.1976; found: 464.1978.

(2*S*,3*S*)-Methyl 2-amino-3-(4-(benzyloxy)phenyl)-3-((*tert*-butyldimethylsilyl)oxy)propanoate

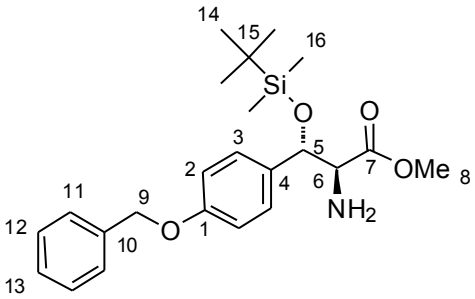


II-27 **II-28**

Azide **II-27** (446 mg, 1.01 mmol) was dissolved in MeOH (5.00 mL). $SnCl_2 \cdot 2\ H_2O$ (456 mg, 2.02 mmol) was added and the reaction mixture was stirred for 15 h at r.t. before it was concentrated under reduced pressure. It was redissolved in EtOAc (150 mL) and washed with 10% aq NaOH (100 mL), brine, dried over Na_2SO_4 and concentrated under reduced pressure. Column chromatography (2% MeOH in CH_2Cl_2) gave the product **II-28** as a colorless oil (356 mg, 85%).

R_f: 0.31, 2% MeOH in CH_2Cl_2.

$[\alpha]_D^{24}$ = 65.8 ° (*c* = 0.76, MeOH).



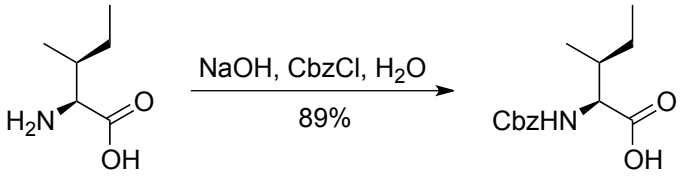
^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 7.47 – 7.30 (m, 5H, 2xH-11, 2xH-12, H-13), 7.21 (d, *J* = 8.6 Hz, 2H, 2xH-3), 6.94 (d, *J* = 8.7 Hz, 2H, 2xH-2), 5.05 (s, 2H, 2xH-9), 4.75 (d, *J* = 6.7 Hz, 1H, H-5), 3.70 (s, 3H, 3xH-8), 3.63 (d, *J* = 6.7 Hz, 1H, H-6), 1.30 (s, 2H, NH_2), 0.85 (s, 9H, 9xH-14), 0.02 (s, 3H, 3xH-16), −0.18 (s, 3H, 3xH-16).

^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm = 173.84 (C-7), 158.78 (C-1), 137.06 (C-10), 133,04 (C-4), 128.73 (C-12), 128.25 (C-3), 128.15 (C-13), 127.71 (C-11), 114.64 (C-2), 77.36 (C-5), 70.18 (C-9), 62.41 (C-6), 51.93 (C-8), 25.81 (C-14), 18.20 (C-15), −4.51 (C-16), −5.15 (C-16).

IR ($\tilde{\nu}$/cm^{-1}): 3385, 3033, 2950, 2927, 2887, 2855, 1737, 1609, 1584, 1510, 1471, 1462, 1454, 1436, 1387, 1360, 1302, 1247, 1196, 1168, 1078, 1025, 1005.

HRMS (ESI): calculated for $C_{23}H_{34}O_4NSi$ $[M+H]^+$ 416.2252; found: 416.2255.

(2*S*,3*R*)-2-(((Benzyloxy)carbonyl)amino)-3-methylpentanoic acid[71]



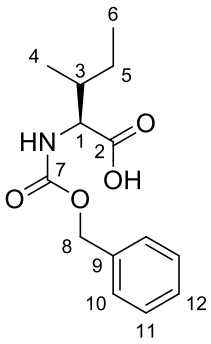
II-16 **II-29**

L-Isoleucine (**II-16**) (1.00 g, 7.62 mmol) and benzyloxycarbonylchlorid (1.20 mL, 8.39 mmol) were added to a solution of NaOH (610 mg, 15.3 mmol) in water (305 mL). The reaction mixture was stirred for 3 h before it was acidified with sat. aq. $NaHCO_3$ solution to pH = 10 and extracted with Et_2O (500 mL). The aqueous layer was acidified to pH = 3 with 10% aq. HCl solution and extracted with Et_2O (300 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to give the desired product **II-29** as a colorless oil (1.83 g, 89%).

R_f: 0.60, DCM/MeOH/AcOH/H_2O 90:10:0.6:0.6.

$[a]_D^{24}$ = 10.2° (c = 0.63, $CHCl_3$).

^{1}H NMR (599 MHz, $CDCl_3$): δ/ppm = 7.37 – 7.21 (m, 5H, 2xH-10, 2xH-11, H-12), 5.25 (d, *J* = 8.8 Hz, 1H, NH), 5.15 (s, 2H, 2×H-8), 4.39 (dd, *J* = 8.8, 4.6 Hz, 1H, H-1), 1.96 (m, 1H, H-3), 1.47 (dqd, *J* = 14.8, 7.5, 4.7 Hz, 1H, H-5α), 1.24 – 1.17 (m, 1H, H-5β), 0.98 (d, *J* = 6.9 Hz, 3H, 3×H-4), 0.94 (t, *J* = 7.5 Hz, 3H, 3×H-6).

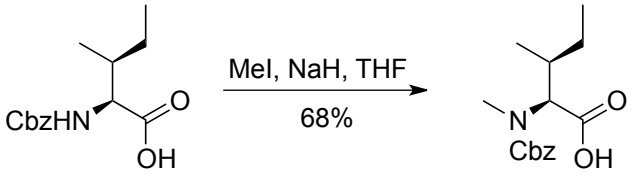


^{13}C NMR (151 MHz, $CDCl_3$): δ/ppm = 176.64 (C-2), 156.31 (C-7), 136.24 (C-9), 128.68 (C-10/11), 128.38 (C-10/11), 128.29 (C-12), 67.31 (C-8), 58.32 (C-1), 37.89 (C-3), 24.99 (C-5), 15.63 (C-4), 11.73 (C-6).

IR ($\tilde{\nu}$ /cm^{-1}): 3316, 2965, 2608, 1699, 1517, 1455, 1414, 1333, 1213, 1040, 775, 735.

HRMS (EI): calculated for $C_{14}H_{19}NO_4$ $[M]^+$ 265.1314; found 265.1307.

(2*S*,3*R*)-2-(((Benzyloxy)carbonyl)(methyl)amino)-3-methylpentanoic acid (*N*-Me-*N*-Cbz-L-Isoleucine)[72]



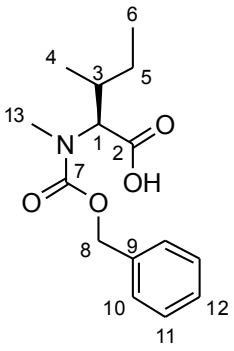
II-29 **II-13**

N-Cbz-L-Isoleucine (**II-29**) (1.74 g, 6.56 mmol) was dissolved in THF (25 mL) before MeI (3.28 mL, 52.4 mmol) was added. The solution was cooled to 0 °C, NaH (60% on mineral oil, 917 mg, 22.9 mmol) was added and the mixture was stirred for 15 min at 0 °C. After further stirring for 52 h at r.t., Et_2O (50 mL) was added, followed by the addition of water (100 mL). The aqueous layer was acidified to pH = 10 with sat. aq. $NaHCO_3$ solution and extracted with Et_2O (200 mL), followed by acidification to pH = 3 with 10% aq. HCl solution and extraction with Et_2O (200 mL). The combined organic layers were washed with water, dried over Na_2SO_4 and concentrated in vacuo. Column chromatography (10% EtOAc in hexanes) gave *N*-methyl-*N*-Cbz-isoleucine (**II-13**) as a colorless oil (1.24 g, 68%).

R_f: 0.20, 50% EtOAc in hexanes.

$[a]_D^{24}$ = 42.9 ° (c = 0.98, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 7.36 – 7.32 (m, 5H, 2xH-10, 2xH-11, H-12), 5.17 (s, 2H, 2xH-8), 4.48 (d, *J* = 10.4 Hz, 1H, H-1), 2.94 (s, 3 H, 3xH-13), 2.09 – 1.96 (m, 1H, H-3), 1.50 – 1.41 (m, 1H, H-5α), 1.17 – 1.06 (m, 1H, H-5β), 1.01 (d, *J* = 6.6 Hz, 3H, 3xH-4), 0.97 (t, *J* = 6.5 Hz, 3H, 3xH-6).

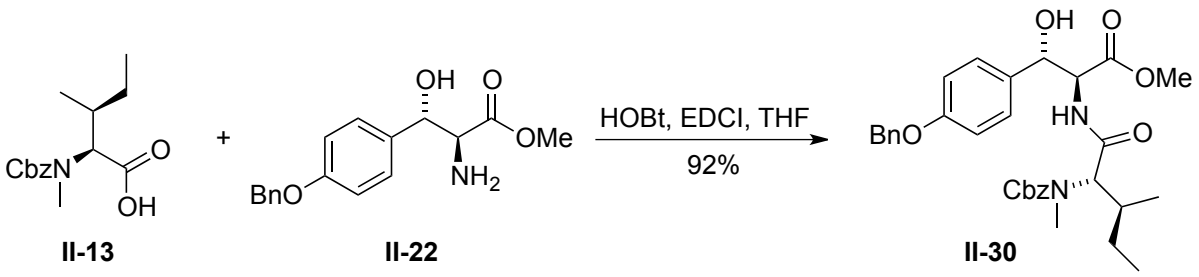


^{13}C NMR (101 MHz, $CDCl_3$): δ/ppm = 175.54 (C-2), 157.46 (C-7), 136.44 (C-9), 128.62 (C-10/11), 128.22 (C-10/11), 127.93 (C-12), 67.93 (C-8), 64.09 (C-1), 33.52 (C-3), 31.61 (C-13), 25.30 (C-5), 15.85 (C-4), 10.78 (C-6).

IR ($\tilde{\nu}$ /cm^{-1}): 2966, 1738, 1701, 1669, 1455, 1400, 1341, 1306, 1252, 1148, 1119, 963, 750.

HRMS (EI): calculated for $C_{15}H_{21}NO_4$ $[M]^+$ 279.1471; found 279.1467.

(2*S*,3*S*)-Methyl 2-((2*S*,3*R*)-2-(((benzyloxy)carbonyl)(methyl)amino)-3-methylpentanamido)-3-(4-(benzyloxy)phenyl)-3-hydroxypropanoate



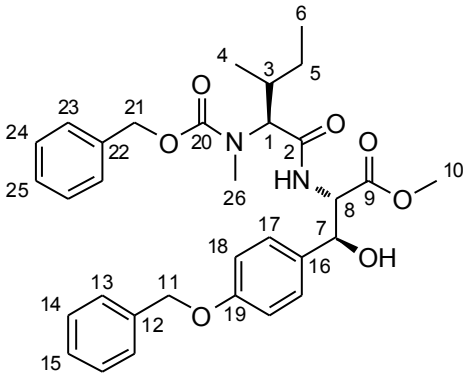
II-13 **II-22** **II-30**

N-Methyl-*N*-Cbz-isoleucine (**II-13**) (100 mg, 0.358 mmol) and tyrosine building block **II-22** (108 mg, 0.358 mmol) were dissolved in THF, followed by the addition of HOBt (169 mg, 1.25 mmol) and EDCI (167 mg, 1.07 mmol) at 0 °C. The reaction mixture was stirred at 0 °C (cryostat) for 16 h before adding EtOAc (100 mL). The organic phase was washed with 5% aq. HCl solution, 5% aq. $NaHCO_3$ solution., water and brine, dried over Na_2SO_4 and concentrated. Column chromatography (20% → 40% EtOAc in hexanes) gave the dipeptide **II-30** as a colorless oil (185 mg, 92%).

R_f: 0.40, 50% EtOAc in hexanes.

$[a]_D^{24}$ = –6.0 ° (c = 1.10, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 7.39 – 7.30 (m, 10H, 2xH-13, 2xH-14, H-15, 2xH-23, 2xH-24, H-25), 7.14 (d, *J* = 8.3 Hz, 2H, 2xH-17), 6.85 (d, *J* = 8.3 Hz, 2H, 2xH-18), 5.17 – 4.99 (m, 5H, H-7, 2xH-11, 2xH-21), 4.91 (dd, *J* = 7.9, 5.1 Hz, 1H, H-8), 4.19 (d, *J* = 11.2 Hz, 1H, H-1), 3.90 (s, 1H, OH), 3.73 (s, 3H, 3xH-10), 2.81 (s, 3H, 3xH-26), 2.09 – 1.98 (m, 1H, H-3), 1.37 (m, 1H, H-5α), 1.00 (m, 1H, H-5β), 0.86 (m, 6H, 3xH-4, 3xH-6).

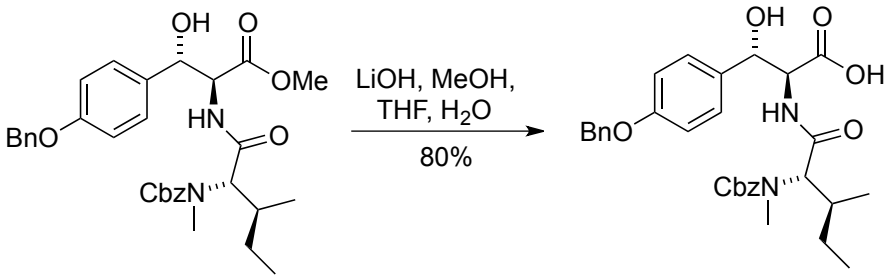


^{13}C NMR (101 MHz, $CDCl_3$): δ/ppm = 170.82 (C-2), 170.38 (C-9), 158.80 (C-19), 157.43 (C-20), 136.99 (C-12), 136.55 (C-22), 131.51 (C-16), 128.70 (C-13/14/15/23/24/25), 128.67 (C-13/14/15/23/24/25), 128.24 (C-13/14/15/23/24/25), 128.07 (C-13/14/15/23/24/25), 127.81 (C-13/14/15/23/24/25), 127.59 (C-13/14/15/23/24/25), 127.55 (C-17), 114.77 (C-18), 74.58 (C-7), 70.05 (C-11), 67.75 (C-21), 63.37 (C-1), 58.27 (C-8), 52.70 (C-10), 31.79 (C-3), 29.80 (C-26), 24.62 (C-5), 15.66 (C-4), 10.50 (C-6).

IR ($\tilde{\nu}$ /cm^{-1}): 3340, 2963, 1742, 1666, 1511, 1454, 1309, 1240, 1171, 1025, 830, 734.

HRMS (ESI): calculated for $C_{32}H_{38}N_2O_7Na$ $[M+Na]^+$ 585.2571; found 585.2561.

(2*S*,3*S*)-2-((2*S*,3*S*)-2-(((benzyloxy)carbonyl)(methyl)amino)-3-methylpentanamido)-3-(4-(benzyloxy)phenyl)-3-hydroxypropanoic acid

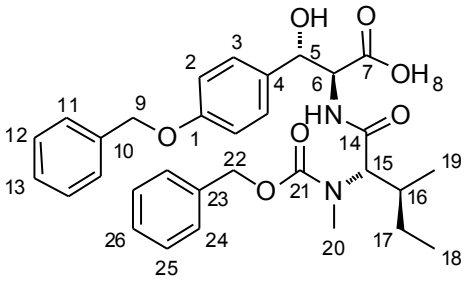


II-30 **II-31**

Dipeptide **II-30** (280 mg, 0.498 mmol) was dissolved in THF (18 mL) and MeOH (6 mL). LiOH (47.7 mg, 2.00 mmol) was dissolved in H_2O (6 mL) and added to the solution. The solution was stirred for 1 h before it was concentrated in *vacuo*. The aqueous residue was acidified with 10% aq. HCl solution to pH = 3 and extracted with EtOAc (15 mL). The organic layer was washed with brine, dried over Na_2SO_4 and concentrated to give the product **II-31** as a colorless solid (215 mg, 80%).

R_f: 0.10, 10% MeOH in CH_2Cl_2.

$[a]_D^{24}$ = –36.8 ° (c = 0.69, MeOH).



^{1}H NMR (400 MHz, CD_3OD) δ/ppm = 7.46 – 7.23 (m, 10H, 2xH-11, 2xH-12, H-13, 2xH-24, 2xH-25, H-26), 7.20 – 7.13 (m, 2H, 2xH-3), 6.92 – 6.73 (m, 2H, 2xH-2), 5.24 – 4.88 (m, 4H, 2xH-9, 2xH-22), 4.80 (d, *J* = 8.0 Hz, 1H, H-5), 4.58 (d, *J* = 8.0 Hz, 1H, H-6), 4.18 (d, *J* = 11.2 Hz, 1H, H-15), 2.45 (s, 3H, H-20), 2.00 – 1.82 (m, 1H, H-16), 1.35 – 1.23 (m, 1H, H-17α), 1.05 – 0.89 (m, 1H, H-17β), 0.91 – 0.69 (m, 6H, 3xH-18, 3xH-19).

H-20: 3 signals caused by rotamers (4:2:1) 2.45, 2.60, 2.83 ppm

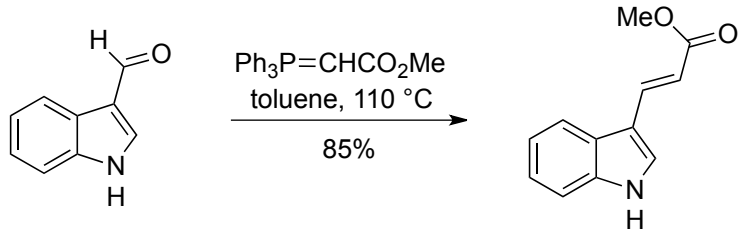
^{13}C NMR (101 MHz, CD_3OD) δ/ppm = 178.18 (C-7), 171.02 (C-14), 159.76 (C-1), 158.46 (C-21), 138.65 (C-10), 137.93 (C-23), 134.44 (C-4), 129.65 (C-3/11/12/13/24/25/26), 129.54 (C-3/11/12/13/24/25/26), 129.47 (C-3/11/12/13/24/25/26), 129.25 (C-3/11/12/13/24/25/26), 129.03(C-3/11/12/13/24/25/26), 128.80(C-3/11/12/13/24/25/26), 128.49(C-3/11/12/13/24/25/26), 115.35 (C-2), 76.26 (C-

5), 70.84 (C-9), 68.73 (C-22), 64.11 (C-15), 60.01 (C-6), 33.03 (C-16), 29.77 (C-20), 25.44 (C-17), 15.83 (C-19), 10.64 (18).

IR ($\tilde{\nu}$ /cm^{-1}): 3317, 2963, 2485, 1655, 1584, 1511, 1453, 1396, 1306, 1239, 1222, 1174, 1117.

HRMS (ESI): calculated for $C_{31}H_{36}N_2O_7Na$ $[M+Na]^+$ 571.2409; found 571.2413.

(*E*)-Methyl 3-(1*H*-indol-3-yl)acrylate



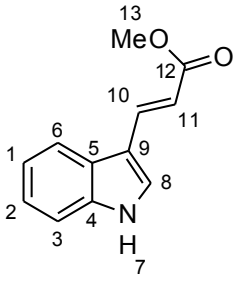
II-32 **II-33**

Indole-3-carboxaldehyde **II-32** (3.00 g, 20.7 mmol) and methyl (triphenylphosphoranylidene) acetate (13.8 g, 41.2 mmol) were dissolved in toluene (60 mL) and heated to 110 °C for 10 h and then directly concentrated under reduced pressure. Column chromatography (30% EtOAc in hexanes) gave the product **II-33** as a colorless solid (3.51 g, 85%).

R$_f$: 0.30, 30% EtOAc in hexanes.

m.p.: 149.8 – 150.5 °C (toluene).

^{1}H NMR (400 MHz, CDCl$_3$) δ/ppm = 8.45 (s, 1H, NH-7), 7.97 – 7.90 (m, 2H, H-10, H-6), 7.50 (d, *J* = 2.8 Hz, 1H, H-8), 7.42 – 7.44 (m, 1H, H-3), 7.30 – 7.24 (m, 2H, H-1, H-2), 6.47 (d, *J* = 16.0 Hz, 1H, H-11), 3.82 (s, 3H, 3xH-13).

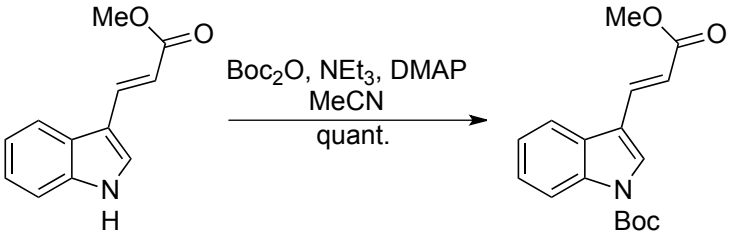


^{13}C NMR (101 MHz, CDCl$_3$) δ/ppm = 168.77 (C-12), 138.48 (C-10), 137.16 (C-5), 128.80 (C-8), 125.45 (C-4), 123.55 (C-1), 121.72 (C-2), 120.64 (C-6), 113.85 (C-9), 113.34 (C-11), 111.87 (C-3), 51.59 (C-13).

IR ($\tilde{\nu}$ /cm^{-1}): 3369, 3099, 1704, 1623, 1569, 1524, 1459, 1424, 1342, 1332, 1302, 1269, 1252, 1210, 1187, 1173, 1147, 1105, 1084, 980, 835, 781.

HRMS (EI): calculated for $C_{12}H_{11}NO_2$ $[M]^+$ 201.0790; found: 201.0790.

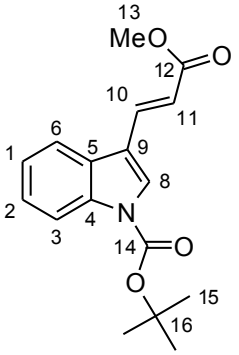
(*E*)-*tert*-Butyl 3-(3-methoxy-3-oxoprop-1-en-1-yl)-1*H*-indole-1-carboxylate



II-33 **II-34**

(*E*)-Methyl 3-(1*H*-indol-3-yl)acrylate (**II-33**) (3.83 g, 19.0 mmol) was dissolved in MeCN (60 mL). Di-*tert*-butyldicarbonat (6.28 g, 28.8 mmol), NEt_3 (7.96 mL, 57.1 mmol) and DMAP (232 mg, 1.90 mmol) were added. The mixture was stirred for 2 h before it was concentrated under reduced pressure. The residue was redissolved in ether (50 mL), washed with sat. aq. $NaHCO_3$ solution, 5% aq. citric acid and brine, dried over Na_2SO_4 and concentrated to give the product **II-34** as an orange oil (5.70 g, quant.).

R_f: 0.20, 5% EtOAc in hexanes.



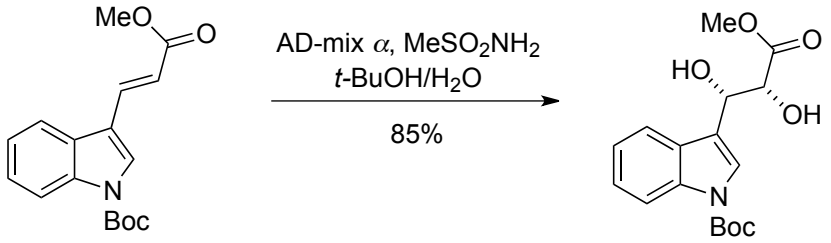
^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm = 8.19 (d, *J* = 7.6 Hz, 1H, H-3), 7.91 – 7.76 (m, 3H, H-8, H-10, H-2), 7.42 – 7.30 (m, 2H, H-6, H-1), 6.54 (d, *J* = 16.4 Hz, 1H, H-11), 3.82 (s, 3H, 3xH-13), 1.69 (s, 9H, 9xH-15).

^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 167.96 (C-12), 149.25 (C-14), 136.78 (C-10), 136.37 (C-4), 128.82 (C-8), 128.03 (C-5), 125.40 (C-6), 123.74 (C-1), 120.35 (C-2), 117.13 (C-11), 116.85 (C-9), 115.72 (C-3), 84.83 (C-16), 51.76 (C-13), 28.29 (C-15).

IR ($\tilde{\nu}$ /cm^{-1}): 2980, 1809, 1739, 1712, 1633, 1545, 1478, 1456, 1433, 1396, 1365, 1282, 1251, 1228, 1125, 1095, 1024, 966, 929, 841.

HRMS (EI): calculated for $C_{17}H_{19}NO_4$ $[M]^+$ 301.1309; found: 301.1307.

***tert*-Butyl 3-((1*S*,2*R*)-1,2-dihydroxy-3-methoxy-3-oxopropyl)-1*H*-indole-1-carboxylate**

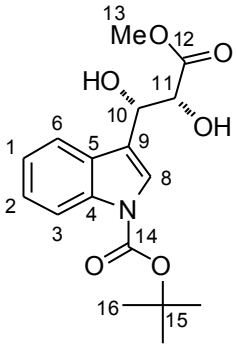


II-34 **II-35**

Alkene **II-34** (6.00 g, 19.9 mmol) was dissolved in *t*-BuOH/water (1:1, 120 mL). AD-mix α (27.9 mmol, 1.40 g/mmol) and methanesulfonamide (5.68 g, 59.7 mmol) were added and the biphasic system was vigorously stirred for 12 h at r. t. before sat. aq. Na_2SO_3 solution (70 mL) was added. This mixture was stirred for 1 h and then extracted with EtOAc (300 mL), washed with brine, dried over Na_2SO_4 and concentrated. Column chromatography (40% EtOAc in hexanes) gave the product **II-35** as a yellow oil (5.70 g, 85%).

R_f: 0.20, 50% EtOAc in hexanes.

$[a]_D^{25}$ = 8.2 ° (*c* = 1.14, $CHCl_3$).



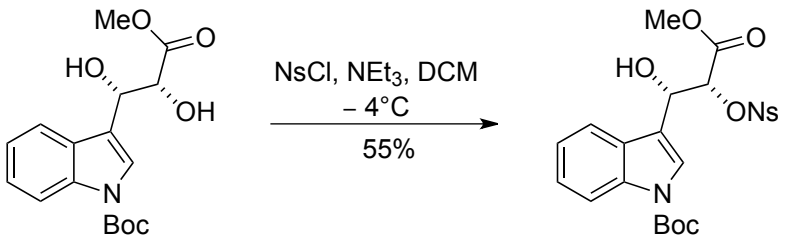
^{1}H NMR (599 MHz, $CDCl_3$) δ/ppm = 8.16 (d, *J* = 7.1 Hz, 1H, H-3), 7.71 (s, 1H, H-8), 7.64 (d, *J* = 7.8 Hz, 1H, H-6), 7.36 – 7.30 (m, 1H, H-2), 7.29 – 7.22 (m, 1H, H-1), 5.32 (s, 1H, H-10), 4.59 – 4.52 (m, 1H, H-11), 3.86 (s, 3H, 3xH-13), 3.25 (s, 1H, OH), 2.60 (s, 1H, OH), 1.67 (s, 9H, 9xH-16).

^{13}C NMR (151 MHz, $CDCl_3$) *δ*/ppm = 173.34 (C-12), 149.72 (C-14), 135.71 (C-5), 128.72 (C-4), 124.86 (C-2), 123.94 (C-8), 122.88 (C-1), 119.89 (C-9), 119.89 (C-6), 115.59 (C-3), 84.07 (C-15), 73.46 (C-11), 68.61 (C-10), 53.24 (C-13), 28.34 (C-16).

IR ($\tilde{\nu}$ /cm^{-1}): 3454, 2979, 1729, 1451, 1369, 1308, 1268, 1254, 1152, 1116, 1086, 1051, 1017, 840.

HRMS (ESI): calculated for $C_{17}H_{25}NO_6$ $[M+NH_4]^+$ 353.1707; found: 353.1706.

***tert*-Butyl 3-((1*S*,2*R*)-1-hydroxy-3-methoxy-2-(((4-nitrophenyl)sulfonyl)oxy)-3-oxopropyl)-1*H*-indole-1-carboxylate**



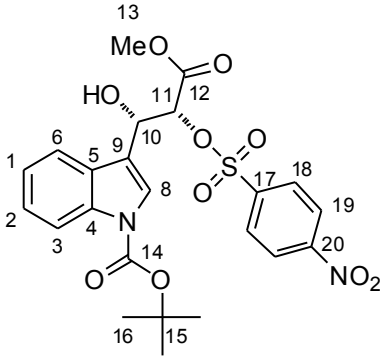
II-35 **II-36**

Diol **II-35** (300 mg, 0.895 mmol) was dissolved in CH_2Cl_2 (5 mL) and cooled to −4 °C. *para*-Nitrobenzene sulfonyl chloride (198 mg, 0.895 mmol) was added and NEt_3 (248 µL, 1.79 mmol) was added dropwise at −4 °C. The solution was stirred at this temperature for 2 h before sat. aq. NH_4Cl solution (3 mL) was added. The organic layer was washed with 10% aq. HCl solution and brine, dried over Na_2SO_4 and concentrated. Column chromatography (20% EtOAc in hexanes) gave the product **II-36** as a yellow solid (255 mg, 55%).

R_f: 0.70, 50% EtOAc in hexanes.

$[a]_D^{24}$ = 41.1 ° (c = 1.06).

m.p.: 105.0 – 112.3 °C (EtOAc).



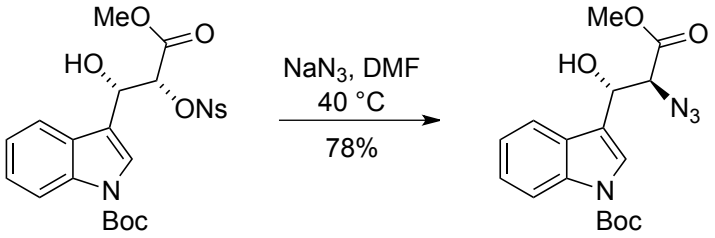
^{1}H NMR (599 MHz, $CDCl_3$) δ/ppm = 7.81 (d, *J* = 8.7 Hz, 3H, H-3, 2xH-19), 7.58 – 7.51 (m, 3H, H-8, 2xH-18), 7.32 (d, *J* = 7.8 Hz, 1H, H-6), 7.24 (t, *J* = 7.8 Hz, 1H, H-2), 7.15 (t, *J* = 7.8 Hz, 1H, H-1), 5.51 (d, *J* = 2.6 Hz, 1H, H-10), 5.10 (d, *J* = 2.6 Hz, 1H, H-11), 3.90 (s, 3H, 3xH-13), 2.65 (s, OH, 1H), 1.70 (s, 9H, 9xH-16).

^{13}C NMR (151 MHz, $CDCl_3$) δ/ppm = 167.20 (C-12), 150.12 (C-20), 149.27 (C-14), 140.59 (C-17), 135.16 (C-4), 128.30 (C-18), 126.97 (C-5), 125.13 (C-2), 124.05 (C-8), 123.29 (C-19), 123.02 (C-1), 118.73 (C-6), 117.76 (C-9), 115.55 (C-3), 85.02 (C-15), 80.44 (C-10), 68.40 (C-11), 53.61 (C-13), 28.23 (C-16).

IR ($\tilde{\nu}$ /cm^{-1}): 3526, 1767, 1731, 1606, 1535, 1477, 1452, 1383, 1354, 1321, 1301, 1280, 1258, 1232, 1206, 1181, 1157, 1026, 977, 947, 881, 853, 821, 852.

HRMS (ESI): calculated for $C_{23}H_{28}N_2O_{10}S$ $[M+NH_4]^+$ 538.1490; found: 538.1483.

***tert*-Butyl 3-((1*S*,2*S*)-2-azido-1-hydroxy-3-methoxy-3-oxopropyl)-1*H*-indole-1-carboxylate**

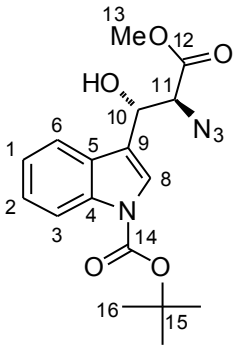


II-36 **II-37**

Nosylate **II-36** (2.00 g, 3.84 mmol) was dissolved in DMF (20 mL) and NaN_3 (374 mg, 5.77 mmol) was added. The mixture was heated to 40 °C for 20 h before water (20 mL) was added. The mixture was extracted with EtOAc (100 mL), washed with brine, dried over Na_2SO_4 and concentrated in *vacuo*. Column chromatography (20% EtOAc in hexanes) gave the product **II-37** as a yellow oil (1.08 g, 78%).

R_f: 0.80, 50% EtOAc in hexanes

$[a]_D^{22}$ = 0 ° (*c* = 0.94, $CHCl_3$).



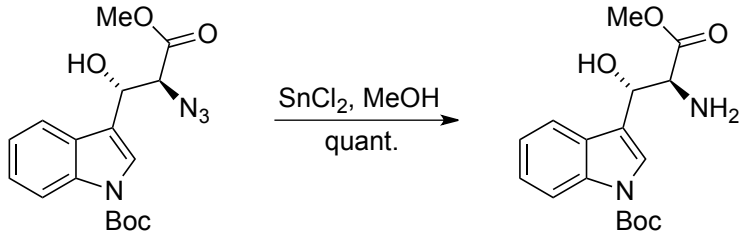
^{1}H NMR (599 MHz, $CDCl_3$) δ/ppm = 8.16 (d, *J* = 7.5 Hz, 1H, H-3), 7.71 – 7.65 (m, 2H, H-6, H-8), 7.34 (t, *J* = 7.5 Hz, 1H, H-2), 7.29 – 7.24 (m, 1H, H-1), 5.32 (d, *J* = 6.7 Hz, 1H, H-10), 4.41 (d, *J* = 6.7 Hz, 1H, H-11), 3.79 (s, 3H, 3xH-13), 2.75 (s, OH, 1H), 1.68 (s, 9H, 9xH-15).

^{13}C NMR (151 MHz, $CDCl_3$) δ/ppm = 169.37 (C-12), 149.60 (C-14), 135.71 (C-4), 128.44 (C-5), 125.01 (C-2), 124.42 (C-6), 123.02 (C-1), 119.66 (C-8), 118.66 (C-9), 115.64 (C-3), 84.33 (C-16), 68.36 (C-10), 65.97 (C-11), 53.04 (C-13), 28.33 (C-15).

IR ($\tilde{\nu}$ /cm^{-1}): 3464, 2980, 2110, 1732, 1451, 1369, 1308, 1254, 1223, 1151, 1090, 1047, 1017, 854, 838.

HRMS (ESI): calculated for $C_{17}H_{20}N_4O_5Na$ $[M+Na]^+$ 383.1326; found: 383.1325.

***tert*-Butyl 3-((1*S*,2*S*)-2-amino-1-hydroxy-3-methoxy-3-oxopropyl)-1*H*-indole-1-carboxylate**

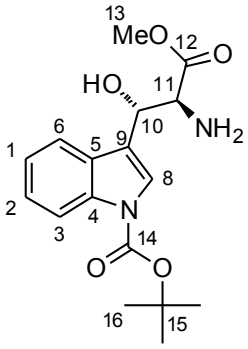


II-37 **II-38**

Azide **II-37** (400 mg, 1.11 mmol) was dissolved in MeOH (6 mL). $SnCl_2 \cdot 2\ H_2O$ (501 mg, 2.20 mmol) was added and the solution was stirred for 1 h at r.t. before it was concentrated in *vacuo*. The residue was redissolved in EtOAc (10 mL), washed with 10% NaOH (aq.), water and brine, dried over Na_2SO_4 and concentrated. Column chromatography (6% MeOH in CH_2Cl_2) gave the product **II-38** as a yellow oil yield (370 mg, quant.).

R_f: 0.30, 6% MeOH in CH_2Cl_2.

$[a]_D^{24}$ = 22.7 ° (c = 1.06, $CHCl_3$).



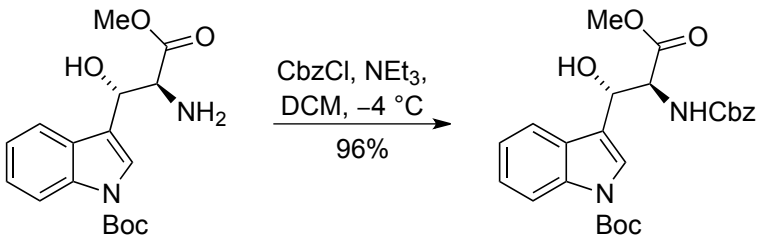
^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm = 8.13 (d, *J* = 8.4 Hz, 1H, H-3), 7.67 – 7.56 (m, 2H, H-6, H-8), 7.34 – 7.27 (m, 1H, H-2), 7.27 – 7.19 (m, 1H, H-1), 5.24 (d, *J* = 5.9 Hz, 1H, H-10), 4.01 (d, *J* = 5.9 Hz, 1H, H-11), 3.65 (s, 3H, H-13), 1.66 (s, 9H, H-16).

^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 173.55 (C-12), 149.64 (C-14), 135.76 (C-4), 128.72 (C-5), 124.82 (C-2), 123.91 (C-8), 122.80 (C-1), 119.80 (C-6), 119.66 (C-9), 115.55 (C-3), 84.10 (C-15), 69.04 (C-10), 58.98 (C-11), 52.36 (C-13), 28.35 (C-16).

IR ($\tilde{\nu}$ /cm^{-1}): 3369, 1980, 1728, 1451, 1368, 1308, 1253, 1223, 1152, 1084, 1049, 1017.

HRMS (ESI): calculated for $C_{17}H_{23}N_2O_5$ $[M+H]^+$ 335.1601; found: 335.1604.

***tert*-Butyl 3-((1*S*,2*S*)-2-(((benzyloxy)carbonyl)amino)-1-hydroxy-3-methoxy-3-oxopropyl)-1*H*-indole-1-carboxylate**

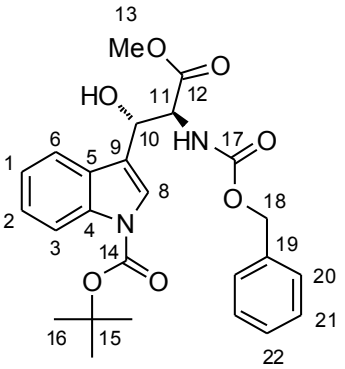


II-38 **II-39**

Amine **II-38** (266 mg, 0.796 mmol) was dissolved in CH_2Cl_2 (3 mL) and cooled to −4 °C. Benzyloxycarbonylchlorid (125 µL, 0.875 mmol) and NEt_3 (224 µL, 1.75 mmol) were slowly added. The mixture was stirred at −4 °C for 2 h before sat. aq. NH_4Cl solution (2 mL) was added. The mixture was extracted with CH_2Cl_2, washed with brine, dried over Na_2SO_4 and concentrated. Column chromatography (30% EtOAc in hexanes) gave the product **II-39** as a yellow oil (358 mg, 96%).

R_f: 0.20, 30% EtOAc in hexanes.

$[a]_D^{21}$ = 44.0 ° (c = 1.05, $CHCl_3$).



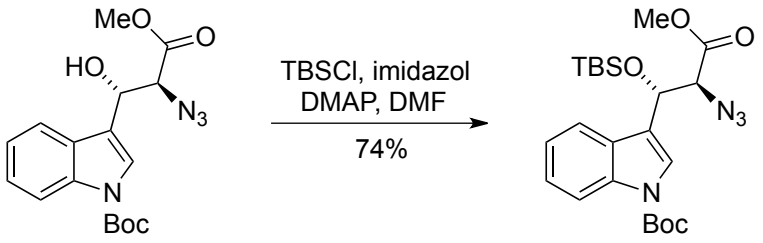
^{1}H NMR (599 MHz, $CDCl_3$) δ/ppm = 8.13 (d, *J* = 7.3 Hz, 1H, H-3), 7.63 (d, *J* = 7.3 Hz, 1H, H-6), 7.58 (s, 1H, H-8), 7.36 – 7.30 (m, 6H, H-1, 2xH-20, 2x-H-21, H-20), 7.23 – 7.19 (m, 1H, H-2), 5.68 (d, *J* = 7.5 Hz, NH, 1H), 5.46 (s, 1H, H-10), 5.15 (s, 2H, 2xH-18), 4.89 (dd, *J* = 4.1, 7.5 Hz, 1H, H-11), 3.65 (s, 3H, 3xH-13), 3.19 (s, O*H*, 1H), 1.66 (s, 9H, 9xH-16).

^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm = 170.16 (C-12), 156.69 (C-17), 149.63 (C-14), 136.05 (C-5), 135.70 (C-19), 128.73 (C-20/21/22), 128.46 (C-4), 128.29 (C-20/21/22), 128.29 (C-20/21/22), 124.87 (C-1), 123.63 (C-8), 122.95 (C-2), 119.75 (C-6), 119.14 (C-9), 115.50 (C-3), 84.13 (C-15), 69.68 (C-10), 67.57 (C-18), 59.10 (C-11), 52.67 (C-13), 28.34 (C-16).

IR ($\tilde{\nu}$ /cm^{-1}): 3416, 2977, 1726, 1608, 1513, 1451, 1368, 1307, 1253, 1222, 1151, 1089, 1055, 1018.

HRMS (ESI): calculated for $C_{25}H_{28}N_2O_7Na$ $[M+Na]^+$ 491.1789; found: 491.1784.

***tert*-Butyl 3-((1*S*,2*S*)-2-azido-1-((tert-butyldimethylsilyl)oxy)-3-methoxy-3-oxopropyl)-1*H*-indole-1-carboxylate**

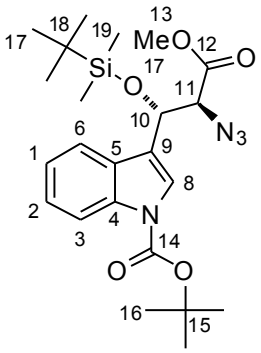


II-37 **II-40**

Azide **II-37** (610 mg, 1.69 mmol) was dissolved in DMF (12 mL). TBSCl (843 mg, 5.59 mmol), imidazol (253 mg, 3.72 mmol) and DMAP (20.6 mg, 0.169 mmol) were added and the mixture was stirred for 3 d before water (10 mL) was added. The mixture was extracted with EtOAc (100 mL) , washed with brine, dried over Na_2SO_4 and concentrated. Column chromatography (5% EtOAc in hexanes) gave the product **II-40** as a yellow oil (594 mg, 74%).

R_f: 0.90, 20% EtOAc in hexanes.

$[a]_D^{23}$ = 46.0 ° (c = 0.83, $CHCl_3$).



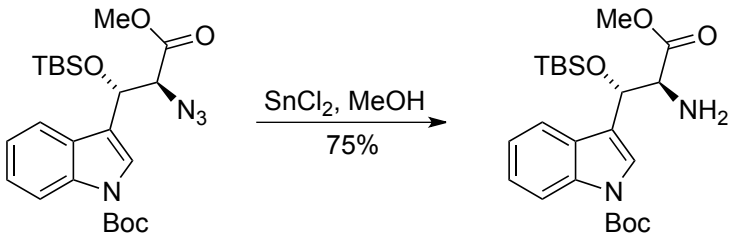
^{1}H NMR (599 MHz, $CDCl_3$) δ/ppm = 8.13 (s, 1H, H-3), 7.71 (d, *J* = 7.9 Hz, 1H, H-6), 7.61 (br s, 1H, H-8), 7.32 (t, *J* = 8.4 Hz, 1H, H-2), 7.24 (t, *J* = 7.1 Hz, 1H, H-1), 5.22 (d, *J* = 7.7 Hz, 1H, H-10), 4.26 (d, *J* = 7.7 Hz, 1H, H-11), 3.76 (s, 3H, 3xH-13), 1.68 (s, 9H, 9xH-15), 0.85 (s, 9H, 9xH-17), 0.07 (s, 3H, 3xH-19), −0.20 (s, 3H, 3xH-19).

^{13}C NMR (151 MHz, $CDCl_3$) δ/ppm = 169.17 (C-12), 149.65 (C-14), 135.86 (C-4), 128.28 (C-5), 124.80 (C-2), 124.50 (C-8), 122.82 (C-1), 120.41 (C-6), 119.56 (C-9), 115.52 (C-3), 84.21 (C-16), 70.20 (C-10), 67.09 (C-11), 52.63 (C-13), 28.36 (C-15), 25.69 (C-17), 18.17 (C-18), −4.60 (C-19), −5.40 (C-19).

IR ($\tilde{\nu}$ /cm^{-1}): 2953, 2929, 2108, 1735, 1450, 1369, 1346, 1251, 1155, 1089, 1017, 835.

HRMS (ESI): calculated for $C_{23}H_{34}N_4O_5SiNa$ $[M+Na]^+$ 497.2191; found: 497.2189.

***tert*-Butyl 3-((1*S*,2*S*)-2-amino-1-((*tert*-butyldimethylsilyl)oxy)-3-methoxy-3-oxopropyl)-1*H*-indole-1-carboxylate**

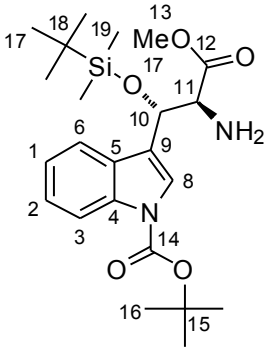


II-40 **II-41**

Azide **II-40** (550 mg, 1.15 mmol) was dissolved in MeOH (8 mL). $SnCl_2 \cdot 2\ H_2O$ (523 mg, 2.32 mmol) was added and the solution was stirred for 2 h at r. t. before it was concentrated. It was redissolved in EtOAc (10 mL), washed with 10% NaOH (4 mL), water and brine and dried over Na_2SO_4. Column chromatography (2% MeOH in CH_2Cl_2) gave the product **II-41** as a yellow oil (394 mg, 75%).

R_f: 0.30, 2% MeOH in DCM.

$[a]_D^{23}$ = 56.6 ° (c = 1.08, $CHCl_3$).



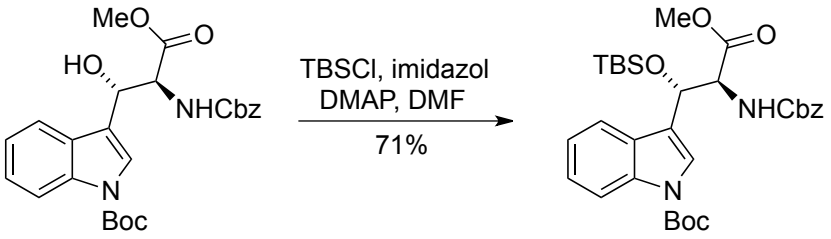
^{1}H NMR (599 MHz, $CDCl_3$) δ/ppm = 8.11 (s, 1H, H-3), 7.70 (d, *J* = 7.9 Hz, 1H, H-6), 7.53 (s, 1H, H-8), 7.31 (t, *J* = 7.9 Hz, 1H, H-2), 7.22 – 7.20 (m, 1H, H-1), 5.02 (d, *J* = 7.0 Hz, 1H, H-10), 3.87 (d, *J* = 7.0 Hz, 1H, H-11), 3.68 (s, 3H, 3xH-13), 1.68 (s, 9H, 9xH-16), 0.85 (s, 9H, 9xH-17), 0.05 (s, 3H, 3xH-19), −0.20 (s, 3H, 3xH-19).

^{13}C NMR (151 MHz, $CDCl_3$) δ = 173.78 (C-12), 149.64 (C-14), 135.66 (C-4), 128.60 (C-5), 124.74 (C-2), 124.21 (C-8), 122.69 (C-1), 120.72 (C-6), 120.27 (C-9), 115.46 (C-3), 84.06 (C-15), 72.45 (C-10), 60.98 (C-11), 52.03 (C-13), 28.37 (C-16), 25.78 (C-17), 18.20 (C-18), −4.62 (C-19), −5.28 (C-19).

IR ($\tilde{\nu}$ /cm^{-1}): 2951, 2928, 2856, 1731, 1607, 1450, 1368, 1249, 1155, 1087, 1017, 855, 834.

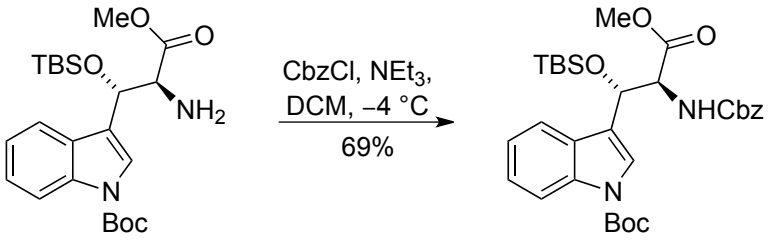
HRMS (ESI): calculated for $C_{23}H_{37}N_2O_5Si$ $[M+H]^+$ 449.2466; found: 449.2464.

***tert*-Butyl 3-((5*S*,6*S*)-5-(methoxycarbonyl)-8,8,9,9-tetramethyl-3-oxo-1-phenyl-2,7-dioxa-4-aza-8-siladecan-6-yl)-1*H*-indole-1-carboxylate**



II-39 **II-42**

Alcohol **II-39** (150 mg, 0.320 mmol) was dissolved in DMF (3 mL). TBSCl (96.5 mg, 0.640 mmol), imidazol (65.3 mg, 0.960 mmol) and DMAP (7.81 mg, 0.0640 mg) were added and the mixture was stirred for 2 d, before water (3 mL) was added. The mixture was extracted with EtOAc (10 mL), washed with brine, dried over Na_2SO_4 and concentrated. Column chromatography (10% EtOAc in hexanes) gave the product **II-42** as a yellow oil (132 mg, 71%).



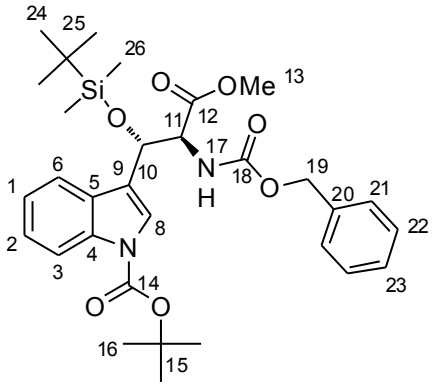
II-41 **II-42**

Amine **II-41** (50.0 mg, 0.111 mmol) was dissolved in CH_2Cl_2 (2 mL) and cooled to −4 °C. Benzyloxycarbonylchlorid (17.5 µL, 0.123 mmol) and NEt_3 (31.3 µL, 0.244 mmol) were added slowly and the solution was stirred at −4 °C for 3 h before it was quenched with sat. NH_4Cl sln. (2 mL). The mixture was washed with $NaHCO_3$ sln., 5% citric acid, brine, dried over Na_2SO_4 and concentrated. Column chromatography (10% EtOAc in hexanes) gave the product **II-42** as a yellow oil (40.0 mg, 63%).

R_f: 0.30, 10% EtOAc in hexanes.

$[a]_D^{23}$ = 51.0 ° (c = 0.37, $CHCl_3$).

^{1}H NMR (599 MHz, $CDCl_3$) δ/ppm = 8.11 (d, *J* = 7.5 Hz, 1H, H-3), 7.81 (d, *J* = 7.5 Hz, 1H, H-6), 7.48 (s, 1H, H-8), 7.41 – 7.27 (m, 6H, H-2, 2xH-21, 2xH-22, H-23), 7.24 (t, *J* = 7.5 Hz, 1H, H-1), 5.60 (d, *J* = 8.0 Hz, 1H, NH-17), 5.32 (d, *J* = 3.7 Hz, 1H, H-10), 5.16 – 5.10 (m, 2H, 2xH-19), 4.77 (dd, *J* = 3.7, 8.0 Hz, 1H, H-11), 3.59 (s, 3H, 3xH13), 1.67 (s, 9H, 9xH-16), 0.89 (s, 9H, 9xH-24), 0.06 (s, 3H, 3xH-26), −0.11 (s, 3H, 3xH-26).

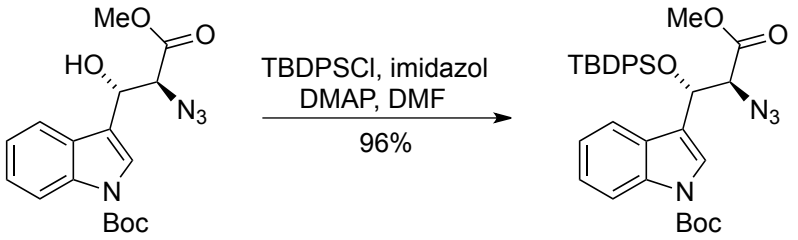


^{13}C NMR (151 MHz, $CDCl_3$) δ/ppm = 169.87 (C-12), 155.75 (C-18), 149.56 (C-14), 136.18 (C-20), 135.66 (C-4), 128.67 (C-21), 128.46 (C-22), 128.32 (C-5), 128.20 (C-23), 124.68 (C-2), 123.67 (C-8), 122.89 (C-1), 120.61 (C-9), 120.40 (C-6), 115.36 (C-3), 83.06 (C-15), 70.69 (C-10), 67.13 (C-19), 60.25 (C-11), 52.19 (C-13), 28.36 (C-16), 25.91 (C-24), 18.25 (C-25), −4.73 (C-26), −5.20 (C-26).

IR ($\tilde{\nu}$ /cm^{-1}): 3436, 3354, 2953, 2929, 2856, 1730, 1499, 1451, 1368, 1250, 1154, 1087.

HRMS (ESI): calculated for $C_{31}H_{42}N_2O_7SiNa$ $[M+Na]^+$ 605.2653; found: 605.2646.

***tert*-Butyl 3-((1*S*,2*S*)-2-azido-1-((*tert*-butyldiphenylsilyl)oxy)-3-methoxy-3-oxopropyl)-1*H*-indole-1-carboxylate**

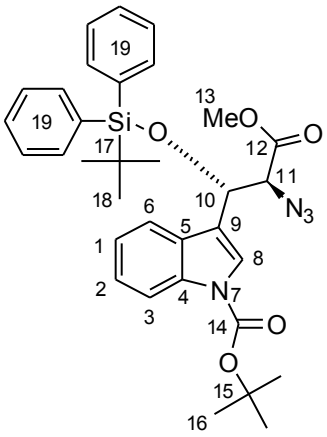


II-37 **II-43**

Azide **II-37** (380 mg, 1.05 mmol) was dissolved in DMF (8 mL). TBDPSCl (318 mg, 1.16 mmol), imidazole (158 mg, 2.32 mmol) and DMAP (12.9 mg, 0.106 mmol) were added and the mixture was stirred for 15 h at r.t. before water was added. It was extracted with EtOAc, washed with brine, dried over Na_2SO_4 and concentrated. Column chromatography (5 → 10% EtOAc in hexanes) gave the product **II-43** as a yellow oil (604 mg, 96%).

R_f: 0.20, 5% EtOAc in hexanes.

$[a]_D^{25}$ = 21.6 ° (c = 1.15, MeOH).



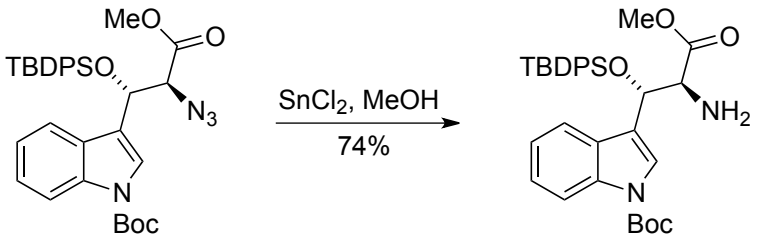
^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 8.02 (d, *J* = 9.4 Hz, 1H, H-3), 7.72 (dd, *J* = 2.3, 5.7 Hz, 7H, H-8, H-19/TBDPSOH), 7.62 (dd, *J* = 2.3, 6.9 Hz, 2H, H-19/TBDPSOH), 7.52 (d, *J* = 7.8 Hz, 1H, H-6), 7.47 – 7.32 (m, 15H, H-19/TBDPSOH), 7.25 (t, *J* = 7.7 Hz, 1H, H-2), 7.13 (dt, *J* = 6.6, 14.5 Hz, 3H, H-1, H-19/TBDPSOH), 5.35 (dd, *J* = 3.1, 7.3 Hz, 1H, H-10), 4.43 (dd, *J* = 3.2, 7.4 Hz, 1H, H-11), 3.65 (s, 3H, H-13), 1.65 (s, 9H, H-16), 1.08 (s, 9H, H-18). Contaminated with TBDPSOH, too high integrals in the aromatic region.

^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm = 168.77 (C-12), 149.43 (C-14), 135.95 (C-19/TBDPSOH), 135.88 (C-19/TBDPSOH), 135.34 (C-4), 134.94 (C-19), 132.91 (C-19/TBDPSOH), 132.48 (C-19/TBDPSOH), 130.03 (C-19/TBDPSOH), 129.80 (C-19), 129.69 (C-19/TBDPSOH), 128.32 (C-19), 127.87 (C8/C-19/TBDPSOH), 127.79 (C8/C-19/TBDPSOH), 127.52 (C8/C-19/TBDPSOH), 127.25 (C8/C-19/TBDPSOH), 125.45 (C-5), 124.54 (C-2), 122.59 (C-1), 120.22 (C-6), 118.38 (C-9), 115.33 (C-3), 83.86 (C-15), 70.53 (C-10), 67.09 (C-11), 52.66 (C-13), 28.34 (C-16), 27.00 (C-18), 19.17 (C-17). Contaminated with TBDPSOH, therefore the missing C-19 and C-8 could not be assigned.

IR ($\tilde{\nu}$ /cm^{-1}): 3520, 2931, 2112, 1737, 1737, 1451, 1427, 1370, 1256, 1154, 1111, 1090, 820.

HRMS (ESI): calculated for $C_{33}H_{42}N_5O_5Si$ $[M+NH_4]^+$ 616.2950; found: 616.2946.

***tert*-Butyl 3-((1*S*,2*S*)-2-amino-1-((*tert*-butyldiphenylsilyl)oxy)-3-methoxy-3-oxopropyl)-1*H*-indole-1-carboxylate**



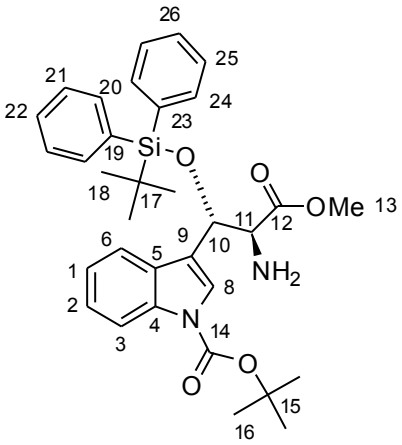
II-43 **II-44**

Azide **II-43** (630 mg, 1.05 mmol) was dissolved in MeOH (20 mL). $SnCl_2 \cdot 2\ H_2O$ (693 mg, 3.07 mmol) was added and the mixture was stirred for 2 h at r.t. before it was concentrated in *vacuo*. The crude product was redissolved in EtOAc (2 mL), washed with 10% NaOH (1 mL), water and brine, dried over

Na_2SO_4 and concentrated. Column chromatography (2% MeOH in CH_2Cl_2) gave the product **II-44** as a yellow oil (444 mg, 74%).

R_f: 0.30, 2% MeOH in CH_2Cl_2.

$[a]_D^{25}$ = 43.3 ° (c = 1.03, MeOH).



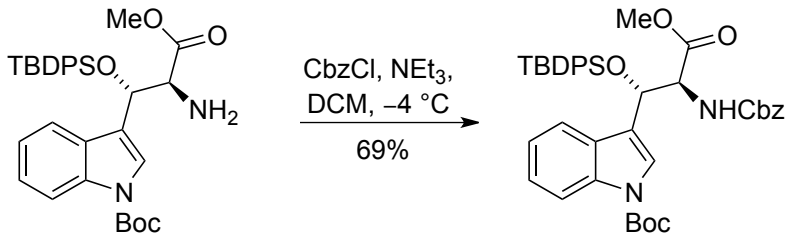
^{1}H NMR (599 MHz, $CDCl_3$) δ/ppm = 8.01 (s, 1H, H-3), 7.61 (dd, *J* = 1.4, 8.0 Hz, 2H, 2xH-24), 7.51 (d, *J* = 8.0 Hz, 1H, H-6), 7.44 – 7.32 (m, 5H, H-26, 2xH-20, 2xH-25), 7.26 – 7.19 (m, 3H, H-2, H-22, H-8), 7.13 (ddd, *J* = 1.0, 7.2, 8.0 Hz, 1H, H-1), 7.09 (t, *J* = 7.7 Hz, 2H, 2xH-21), 5.17 (d, *J* = 6.5 Hz, 1H, H-10), 3.99 (d, *J* = 6.5 Hz, 1H, H-11), 3.59 (s, 3H, 3xH-13), 1.65 (s, 9H, 9xH-16), 1.03 (s, 9H, 9xH-18).

^{13}C NMR (151 MHz, $CDCl_3$) δ/ppm = 173.12 (C-12), 149.47 (C-14), 135.93 (C-24), 135.85 (C-20), 135.61 (C-4), 133.26 (C-23), 132.90 (C-19), 129.90 (C-26), 129.56 (C-22), 128.47 (C-5), 127.73 (C-25), 127.22 (C-21), 125.04 (C-8), 124.53 (C-2), 122.51 (C-1), 120.38 (C-6), 119.02 (C-9), 115.29 (C-3), 83.82 (C-15), 72.52 (C-10), 60.44 (C-11), 52.07 (C-13) , 28.35 (C-16), 27.08 (C-18), 19.46 (C-17).

IR ($\tilde{\nu}$ /cm^{-1}): 3069, 2954, 2929, 2855, 1734, 1588, 1588, 1567, 1471, 1450, 1426, 1368, 1254, 1154, 1110, 1087, 1067, 819.

HRMS (ESI): calculated for $C_{33}H_{41}N_2O_5Si^+$ $[M+H]^+$ 573.2779; found: 573.2776.

***tert*-Butyl 3-((5*S*,6*S*)-5-(methoxycarbonyl)-9,9-dimethyl-3-oxo-1,8,8-triphenyl-2,7-dioxa-4-aza-8-siladecan-6-yl)-1*H*-indole-1-carboxylate**

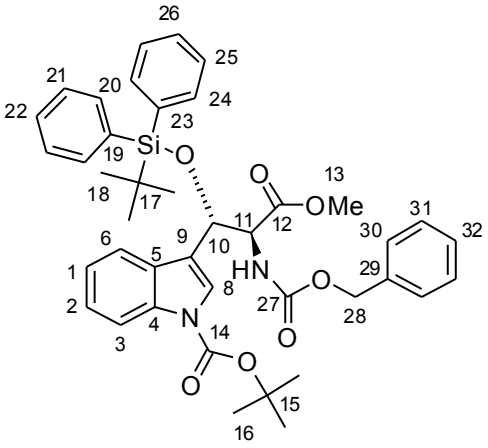


II-44 **II-45**

Amine **II-44** (444 mg, 0.775 mmol) was dissolved in CH_2Cl_2 (4 mL) and cooled to −4 °C. Benzyloxycarbonylchlorid (167 µL, 0.853 mmol) and NEt_3 (236 µL, 1.71 mmol) were added. The solution was stirred at −4 °C for 3.5 h before it was quenched with sat. aq. NH_4Cl solution (4 mL). It was extracted with CH_2Cl_2 (5 mL), washed with brine, dried over $MgSO_4$ and concentrated. Column chromatography (30% EtOAc/hexanes) gave the product **II-45** as a yellow oil (376 mg, 69%).

R_f: 0.80, 50% EtOAc in hexanes.

$[a]_D^{25}$ = 25.8 ° (c = 1.17, MeOH).



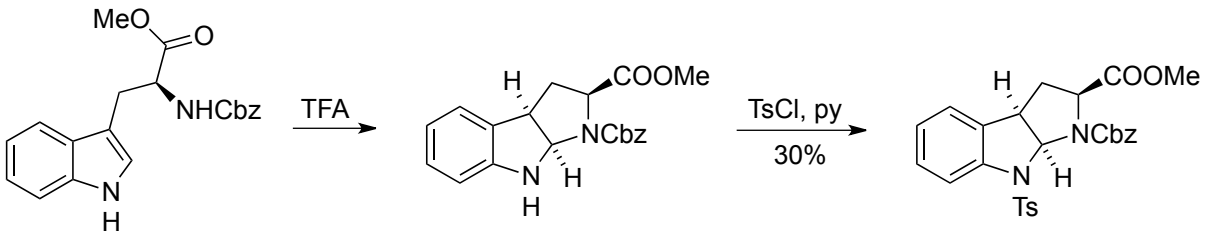
^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 8.04 (d, *J* = 7.7 Hz, 1H, H-3), 7.68 (d, *J* = 7.8 Hz, 2H, 2xH-30), 7.62 (d, *J* = 7.7 Hz, 1H, H-6), 7.42 – 7.23 (m, 13H, 2xH-H-20, 2xH-21, H-22, 2xH-24, 2xH-25,H-26, 2xH-31, H-32), 7.16 (t, *J* = 7.7 Hz, 1H, H-1), 7.11 (t, *J* = 7.5 Hz, 2H, H-2, H-80), 5.38 (d, *J* = 4.1 Hz, 1H, H-10), 5.30 (d, *J* = 8.7 Hz, 1H, NH), 5.06 (s, 2H, H-28), 4.81 (dd, *J* = 4.1, 8.7 Hz, 1H, H-11), 3.58 (s, 3H, 3xH-13), 1.65 (s, 9H, 9xH16), 1.05 (s, 9H, 9xH-18).

^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm = 170.13 (C-12), 155.78 (C-27), 149.54 (C-14), 136.06 (C-20), 135.85 (C-24), 135.59 (C-4), 133.03 (C-23), 132.79 (C-19), 130.04 (C-26), 129.68 (C-22), 128.88 (C-5/25/30/31/32), 128.72 (C-5/25/30/31/32), 128.62 (C-5/25/30/31/32), 128.22 (C-5/25/30/31/32), 128.06 (C-5/25/30/31/32), 127.81 (C-29), 127.40 (C-21), 124.59 (C-8), 124.38 (C-2), 122.75 (C-1), 120.42 (C-6), 119.40 (C-9), 115.21 (C-3), 83.80 (C-15), 71.18 (C-10), 66.97 (C-28), 60.08 (C-11), 52.25 (C-13), 28.34 (C-16), 27.07 (C-18), 19.47 (C-17).

IR ($\tilde{\nu}$ /cm^{-1}): 3435, 2956, 2857, 1733, 1510, 1472, 1452, 1427, 1369, 1255, 1154, 1110, 1018.

HRMS (ESI): calculated for $C_{41}H_{50}N_3O_7Si$ $[M+NH_4]^+$ 724.3413; found: 724.3414.

(2*S*,3a*R*,8a*S*)-1-Benzyl 2-methyl 8-tosyl-3,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indole-1,2(2*H*)-dicarboxylate



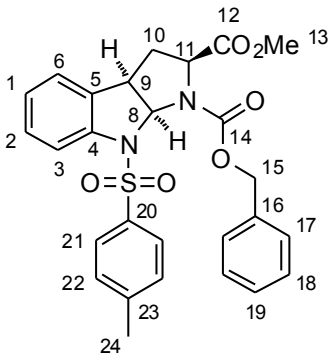
II-46 **II-47** **II-48**

O-Me-*N*-Cbz-Tryptophan (**II-46**) (500 mg, 1.42 mmol) was dissolved in TFA (2 mL) and stirred for 2 h at r.t. $NaHCO_3 \cdot 10\ H_2O$ (37 g) was dissolved in H_2O (100 mL) and CH_2Cl_2 (40 mL). Under vigorous stirring the TFA reaction mixture was dropped slowly into the $NaHCO_3/H_2O$/DCM mixture (20 mL, pH > 8). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The crude product **II-47** was dissolved in pyridine (5 mL) and cooled to 0 °C. TsCl (2.98 g, 15.6 mmol) was added and the mixture was stirred for 20 h before it was concentrated in *vacuo*. Column chromatography (20% EtOAc in hexanes) gave the product **II-48** as a yellow oil (210 mg, 30% over two steps).

R_f: 0.30, 40% EtOAc in hexanes.

$[a]_D^{23}$ = 57.0 ° (c = 0.92, $CHCl_3$).

^{1}H NMR (599 MHz, $CDCl_3$) δ/ppm = 7.53 – 7.47 (m, 4H, 2xH-21, H-3, H-19), 7.35 – 7.32 (m, 4H, 2xH-17, 2xH-18), 7.23 (t, *J* = 8.8 Hz, 1H, H-2), 7.13 (d, *J* = 8.5 Hz, 2H, 2xH-22), 7.08 – 7.00 (m, 2H, H-1, H-6), 6.26 (s, 1H, H-8), 5.30 – 5.15 (m, 2H, 2xH-15), 4.60 (d, *J* = 5.6 Hz, 1H, H-11), 3.57 (s, 1H, H-9), 3.11 (s, 3H, 3xH-13), 2.55 (d, *J* = 13.1 Hz, 1H, H-10α), 2.42 (s, 1H, H-10β), 2.34 (s, 3H, 3xH-24).

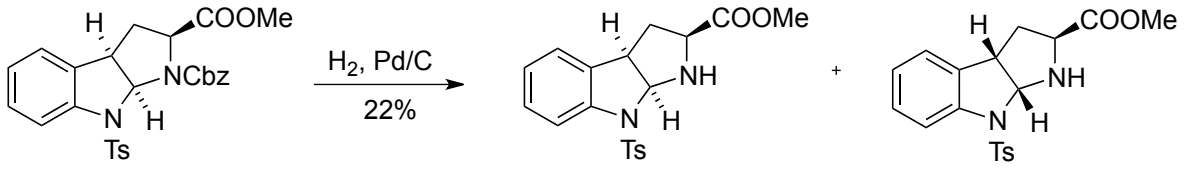


^{13}C NMR (151 MHz, $CDCl_3$) δ/ppm = 171.55 (C-12), 154.34 (C-14), 143.77 (C-23), 142.71 (C-4), 136.41 (C-20), 133.23 (C-5), 129.56 (C-22), 128.99 (C-2), 128.77 (C-16), 128.52 (C-17/18), 128.22 (C-17/18), 126.90 (C-19), 126.90 (C-21), 125.41 (C-1) , 124.47 (C-6), 118.73 (C-3), 80.13 (C-8), 67.57 (C-15), 59.07 (C-11), 52.15 (C-13), 45.92 (C-9), 33.43 (C-10), 21.65 (C-24).

IR ($\tilde{\nu}$ /cm^{-1}): 3393, 3028, 2951, 1707, 1596, 1496, 1476, 1460, 1405, 1355, 1326, 1292, 1268, 1213, 1163, 1114, 1090, 1020.

HRMS (ESI): calculated for $C_{27}H_{26}N_2O_6SK$ $(M+K)^+$ 545.1143; found: 545.1135.

(2*S*,3a*S*,8a*R*)-Methyl 8-tosyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2-carboxylate and (2*R*,3a*S*,8a*R*)-Methyl 8-tosyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2-carboxylate



II-48 2 : 1

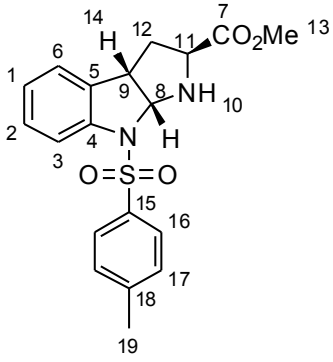
II-127 *endo* **II-127** *exo*

Pyrroloindole **II-48** (2.00 g, 3.95 mmol) was dissolved in MeOH (10 mL) before Pd/C (10% Pd, 420 mg, 3.95 mmol) was added. The mixture was stirred for 48 h under H_2 atmosphere (1 atm) before it was filtered and concentrated. Column chromatography gave the products **II-127** in 22% yield (2:1) as yellow oils (220 mg, 110 mg).

Exo:

R_f: 0.30, 40% EtOAc in hexanes.

$[a]_D^{21}$ = −90.3 ° (c = 0.58, MeOH).



^{1}H NMR (599 MHz, $CDCl_3$) δ/ppm = 7.73 (d, *J* = 8.4 Hz, 2H, 2xH-17), 7.51 (d, *J* = 8.1 Hz, 1H, H-3), 7.23 (d, *J* = 8.4 Hz, 2H, 2xH-16), 7.19 (t, *J* = 7.5 Hz, 1H, H-1), 7.08 (d, *J* = 7.8 Hz, 1H, H-6), 6.99 (td, *J* = 0.9, 7.5 Hz, 1H, H-2), 5.67 (d, *J* = 7.5 Hz, 1H, H-8), 3.88 (dd, *J* = 6.2, 9.6 Hz, 1H, H-11), 3.80 (t, *J* = 7.4 Hz, 1H, H-9), 3.73 (s, 3H, 3xH-13), 2.36 (s, 3H, 3xH-19), 2.31 (dt, *J* = 9.6, 12.4 Hz, 1H, H-12α), 2.15 (ddd, *J* = 2.3, 6.2, 12.4 Hz, 1H, H-12β).

^{13}C NMR (151 MHz, $CDCl_3$) δ/ppm = 173.45 (C-14), 144.32 (C-15), 141.56 (C-5), 135.20 (C-18), 132.38 (C-4), 129.91 (C-16), 128.62 (C-1), 127.35 (C-17), 125.07 (C-6), 124.10 (C-2), 113.82 (C-3), 82.10 (C-8), 57.41 (C-11), 52.36 (C-13), 44.32 (C-9), 37.51 (C-12), 21.68 (C-19).

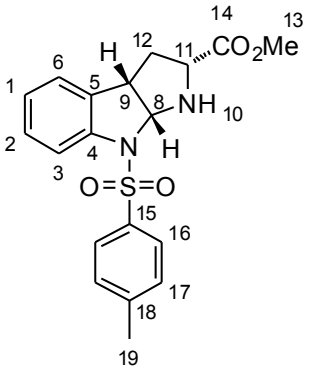
IR ($\tilde{\nu}$ /cm^{-1}): 3369, 2952, 1736, 1598, 1493, 1478, 1459, 1436, 1402, 1346, 1214, 1182, 1163, 1107, 1089, 1026, 993, 978.

HRMS (ESI): calculated for $C_{19}H_{21}N_2O_4S$ $[M+H]^+$ 373.1217; found: 373.1214.

Endo:

R_f: 0.20, 40% EtOAc in hexanes.

$[a]_D^{21}$ = 106.4 ° (c = 0.46, MeOH).



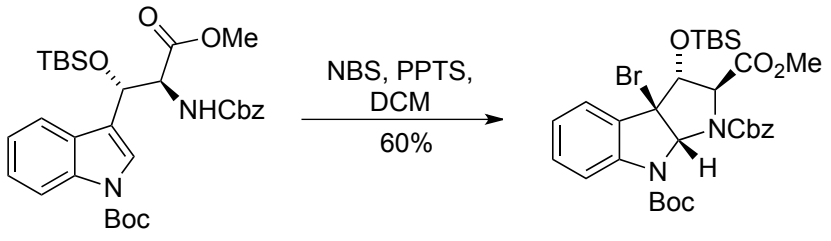
^{1}H NMR (599 MHz, $CDCl_3$) δ/ppm = 7.74 (d, *J* = 8.1 Hz, 2H, 2xH-17), 7.41 (d, *J* = 8.1 Hz, 1H, H-3), 7.22 (d, *J* = 8.1 Hz, 2H, 2xH-16), 7.14 (t, *J* = 7.5 Hz, 1H, H-1), 7.07 (d, *J* = 7.5 Hz, 1H, H-6), 6.96 (t, *J* = 7.5 Hz, 1H, H-2), 5.61 (d, *J* = 7.5 Hz, 1H, H-8), 3.95 (dd, *J* = 2.1, 7.9 Hz, 1H, H-11), 3.75 – 3.72 (m, 1H, H-9), 3.43 (s, 3H, 3xH-13), 2.49 (ddd, *J* = 7.9, 9.3, 12.9 Hz, 1H, H-12α), 2.40 – 2.33 (m, 4H, H-12β, 3xH-19).

^{13}C NMR (151 MHz, $CDCl_3$) δ/ppm = 173.81 (C-14), 144.14 (C-15), 141.03 (C-5), 135.61 (C-18), 132.79 (C-4), 129.84 (C-16), 128.53 (C-1), 127.26 (C-17), 124.98 (C-6), 123.94 (C-2), 113.75 (C-3), 82.19 (C-8), 58.92 (C-11), 52.17 (C-13), 44.28 (C-9), 35.31 (C-12), 21.65 (C-19).

IR ($\tilde{\nu}$ /cm^{-1}): 3400, 2956, 1736, 1595, 1477, 1461, 1437, 1416, 1340, 1305, 1244, 1222, 1107, 1087, 970.

HRMS (ESI): calculated for $C_{19}H_{21}N_2O_4S$ $[M+H]^+$ 373.1217; found: 373.1214.

(2*S*,3*R*,3a*R*,8a*R*)-1-Benzyl 8-*tert*-butyl 2-methyl 3a-bromo-3-((*tert*-butyldimethylsilyl)oxy)-3,3a-dihydropyrrolo[2,3-*b*]indole-1,2,8(2*H*,8a*H*)-tricarboxylate



II-42 **II-50**

Pyridinium *p*-toluenesulfonate (30.2 mg, 0.120 mmol) and *N*-bromosuccinimide (21.4 mg, 0.120 mmol) were dissolved in CH_2Cl_2 (5 mL). Indole **II-42** (70.0 mg, 0.120 mmol) was added and the

reaction was stirred for 20 h before it was washed with sat. aq. $NaHCO_3$ solution, with sat. aq. $Na_2S_2O_3$ solution and brine, dried over Na_2SO_4 and concentrated. Column chromatography (5% EtOAc in hexanes) gave the product as colorless oil (47.5 mg, 60%), which was very sensitive and decomposed quickly.

R_f: 0.2, 5% EtOAc in hexanes.

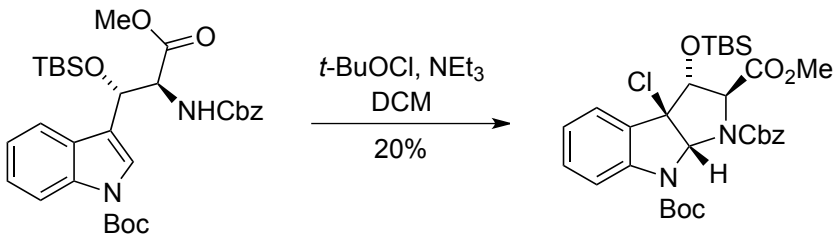
^{1}H-NMR: Broad signal of Boc group caused by rotamers. Double set of signals for TBS and methylester (3.67 and 3.20 ppm). Presumable mixture of unseparable diastereomers

^{13}C-NMR: Double set of signals. Presumable mixture of unseparable diastereomers.

IR ($\tilde{\nu}$ /cm^{-1}): 2953, 1715, 1469, 1405, 1367, 1325, 1281, 1252, 1208, 1130, 1015.

HRMS (ESI): calculated for $C_{31}H_{41}BrN_2O_7SiNa$ $[M+Na]^+$ 683.1759 and 685.1744; found: 683.1750 and 685.1727.

(2*S*,3*R*,3a*R*,8a*R*)-1-Benzyl 8-*tert*-butyl 2-methyl 3-((*tert*-butyldimethylsilyl)oxy)-3a-chloro-3,3a-dihydropyrrolo[2,3-*b*]indole-1,2,8(2*H*,8a*H*)-tricarboxylate



II-42 **II-54**

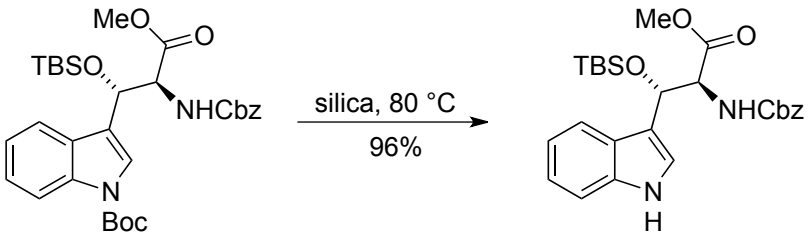
Indole **II-42** (100 mg, 0.172 mmol) was dissolved in CH_2Cl_2 (2 mL) and NEt_3 (95.4 µL, 0.688 mmol) was added. The solution was cooled to 0 °C and *t*-BuOCl (21.4 µL, 0.189 mmol) was carefully added. The reaction mixture was stirred for 1 h at 0 °C and then for 20 h at r.t. before it was diluted with EtOAc, washed with water and brine, dried over Na_2SO_4 and concentrated. Column chromatography (10% EtOAc in hexanes) gave the product **II-54** as colorless oil (21.0 mg, 20%).

R_f: 0.2, 5% EtOAc in hexanes.

^{1}H NMR shows methylester signal at 3.71 ppm, which indicates formation of the *exo*-product. Only one diastereomer. Broad signal of Boc group caused by rotamers.

HRMS (ESI): calculated for $C_{31}H_{41}N_2O_7SiClNa$ $[M+Na]^+$ 639.2264; found: 639.2270.

(2*S*,3*S*)-Methyl 2-(((benzyloxy)carbonyl)amino)-3-((*tert*-butyldimethylsilyl)oxy)-3-(1*H*-indol-3-yl)propanoate

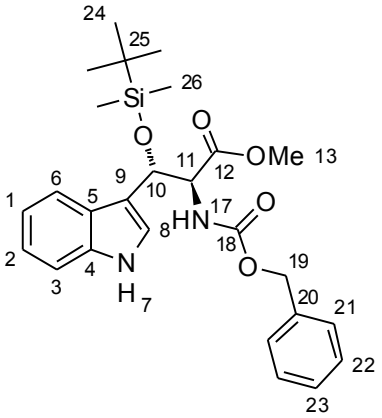


II-42 **II-55**

Boc protected indole **II-42** (100 mg, 0.172 mmol) was dissolved in EtOAc (5 mL). Silica gel (2.20 g) was added and the mixture was concentrated to dryness under reduced pressure. The dry mixture was heated under high vacuum (0.1 mbar) to 80 °C for 1.5 h. The mixture was suspended in EtOAc (20 mL) and filtered through a cotton plug washing with EtOAc. Concentration gave the product **II-55** as a yellow oil (80.1 mg, 96 %), which decomposed under elimination upon storage.

R_f: 0.4, 30% EtOAc in hexanes.

$[a]_D^{21}$ = 46.1 ° (c = 0.66, $CHCl_3$).



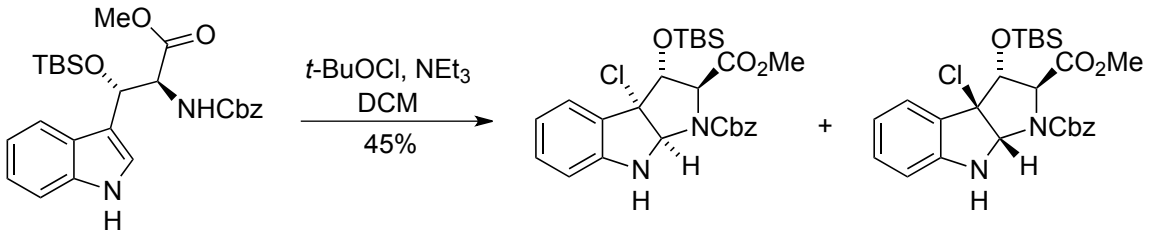
^{1}H NMR (599 MHz, $CDCl_3$) δ/ppm = 8.06 (s, 1H, NH-7), 7.78 (d, *J* = 7.6 Hz, 1H, H-6), 7.34 (dd, *J* = 7.4 Hz, 15.3, 6H, 2xH-21, 2xH-22, H-23, H-3), 7.20 (t, *J* = 7.6 Hz, 1H, H-2), 7.14 – 7.11 (m, 2H, H-1, H-8), 5.41 (d, J = 4.6 Hz, 1H, H-10), 5.09 (s, 2H, 2xH-19), 4.78 (dd, *J* = 4.6, 8.1 Hz, 1H, H-11), 3.61 (s, 3H, 3xH-13), 0.87 (s, 9H, 9xH-24), 0.05 (s, 3H, 3xH-26), −0.16 (s, 3H, 3xH-26).

^{13}C NMR (151 MHz, $CDCl_3$) δ/ppm = 170.64 (C-12), 155.86 (C-18), 136.54 (C-20), 136.46 (C-4), 128.62 (C-21/22), 128.22 (C-21/22), 128.18 (C-23), 125.73 (C-5), 122.48 (C-2), 122.34 (C-8), 120.09 (C-6), 120.04 (C-1), 115.94 (C-9), 111.29 (C-3), 70.71 (C-10), 66.99 (C-19), 60.72 (C-11), 52.16 (C-13), 25.82 (C-24), 18.31 (C-25), −4.75 (C-26), −5.23 (C-26).

IR ($\tilde{\nu}$ /cm^{-1}): 3343, 2951, 2927, 2855, 1707, 1506, 1455, 1435, 1359, 1340, 1249, 1214, 1174, 1083, 1064.

HRMS (ESI): calculated for $C_{26}H_{34}N_2O_5SiNa$ $[M+Na]^+$ 505.2129; found: 505.2134.

(2*S*,3*R*,3a*S*,8a*R*)-1-Benzyl 2-methyl 3-((*tert*-butyldimethylsilyl)oxy)-3a-chloro-3,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indole-1,2(2*H*)-dicarboxylate and (2*S*,3*R*,3a*R*,8a*S*)-1-benzyl 2-methyl 3-((*tert*-butyldimethylsilyl)oxy)-3a-chloro-3,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indole-1,2(2*H*)-dicarboxylate

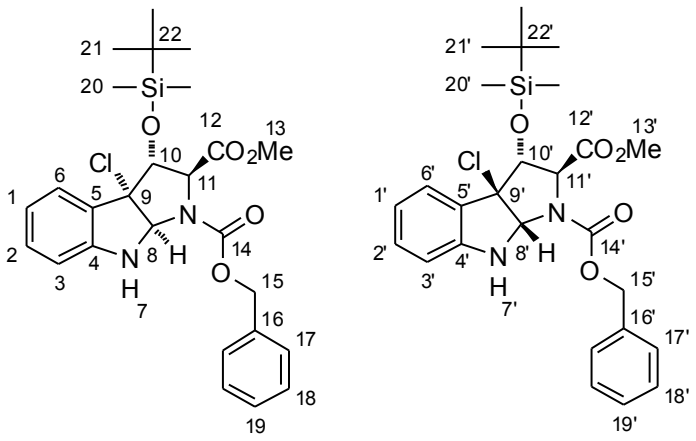


II-55 **II-56** *endo* **II-56** *exo*

Indol **II-55** (14.0 mg, 0.0290 mmol) was dissolved in CH_2Cl_2 (0.5 mL) and NEt_3 (16.1 µL, 0.116 mmol) was added. The solution was cooled to 0 °C and *t*-BuOCl (3.59 µL, 0.0318 mmol) was carefully added. The reaction mixture was stirred for 1 h at 0 °C and then for 20 h at r.t. before it was diluted with EtOAc (1 mL), washed with water and brine, dried over Na_2SO_4 and concentrated. Column chromatography (20% EtOAc in hexanes) gave the product in an inseparable mixture of endo/exo product **II-56** in a ratio of 1:0.7 as colorless oil (7.00 mg, 45%).

R_f: 0.5, 30% EtOAc in hexanes.

$[a]_D$ n. d. (mixture of diast.)



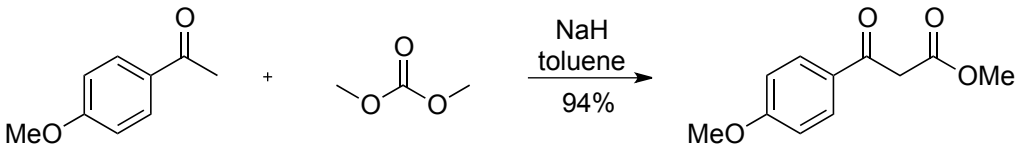
^{1}H NMR (599 MHz, $CDCl_3$) δ/ppm = 7.44 – 7.36 (m, 4H, NH-7, NH-7', H-19, H-19'), 7.31 – 7.28 (m, 4H, 2xH-18, 2xH-18'), 7.26 – 7.23 (m, 4H, 2xH-17, 2xH-17'), 7.17 – 7.14 (m, 2H, H-6, H-6'), 7.11 (t, *J* = 7.5 Hz, 2H, H-2, H-2'), 6.78 – 6.72 (m, 2H, H-1, H-1'), 6.69 (d, *J* = 8.0, 1H, H-3'), 6.65 (d, *J* = 7.2, 1H, H-3), 5.58 (s, 1H, H-8), 5.55 (s, 1H, H-8'), 5.27 (s, 2H, 2xH-15'), 5.15 (s, 2H, H-15), 4.84 (s, 1H, H-10'), 4.81 (s, 1H, H-10), 4.61 (s, 1H, H-11'), 4.49 (s, 1H, H-11), 3.19 (s, 3H, H-13'), 3.11 (s, 3H, H-13), 0.96 (d, *J* = 8.1 Hz, 18H, 9xH-21, 9xH-21'), 0.25 (dd, *J* = 10.1, 11.6 Hz, 12H, 6xH-20, 6xH-20').

^{13}C NMR (151 MHz, $CDCl_3$) δ/ppm = 168.68 (C-12), 168.42 (C-12'), 154.82 (C-14), 154.23 (C-14'), 150.05 (C-4), 149.71 (C-4'), 136.25 (C-16), 136.11 (C-16'), 131.69 (C-6'), 131.62 (C-6), 128.91 (C-19), 128.62 (C-18), 128.56 (C-19'), 128.25 (C-18'), 128.06 (C-17'), 127.75 (C-17), 126.05 (C-5), 125.99 (C-5'), 124.77 (C-2'), 124.67 (C-2), 119.96 (C-1'), 119.70 (C-1), 110.95 (C-3), 110.90 (C-3'), 82.94 (C-8), 82.48 (C-8'), 78.94 (C-10), 78.28 (C-10'), 77.98 (C-9), 77.98 (C-9'), 69.50 (C-11'), 69.36 (C-11), 67.96 (C-15'), 67.45 (C-15), 52.37 (C-13'), 52.27 (C-13), 25.90 (C-21'), 25.86 (C-21), 18.46 (C-22'), 18.42 (C-22), −4.57 (C-20), −4.63 (C-20'), −4.79 (C-20'), −4.88 (C-20).

IR ($\tilde{\nu}$ /cm^{-1}): 3379, 2951, 2856, 1758, 1703, 1610, 1470, 1410, 1352, 1313, 1291, 1249, 1216, 1136, 1103, 1051, 1004, 937.

HRMS (ESI): calculated for $C_{26}H_{34}ClN_2O_5Si$ $[M+H]^+$ 517.1920; found: 517.1926.

Methyl 3-(4-methoxyphenyl)-3-oxopropanoate[76]

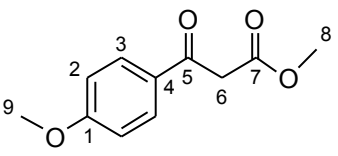


II-69 **II-70** **II-71**

NaH (60% on mineral oil, 2.00 g, 50.0 mmol) was placed in a schlenk flask and washed with hexanes (3x10 mL). Toluene (12 mL) and dimethyl carbonate (**II-70**) (4.50 g, 50.0 mmol) were added and the mixture was heated to 110 °C before *para*-methoxyacetophenone (**II-69**) (3.00 g, 20.0 mmol), dissolved in toluene (18 mL) was slowly added over 10 min. The resulting mixture was stirred for 45 min at 110 °C before cooling to r.t. followed by quenching with H_2O/AcOH (4:1, 20 mL). The mixture was extracted with Et_2O (60 mL), washed with sat. aq. $NaHCO_3$ solution, brine, dried over $MgSO_4$ and concentrated. Column chromatography (15% EtOAC in hexanes) gave the product **II-71** as a yellow oil (3.90 g, 94%).

R_f: 0.30, 20% EtOAc in hexanes.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm = 7.91 (d, *J* = 9.0 Hz, 2H, 2xH-3), 6.93 (d, *J* = 9.0 Hz, 2H, 2xH-2), 3.94 (s, 2H, 2xH-6), 3.86 (s, 3H, 3xH-9), 3.73 (s, 3H, 3xH-8).

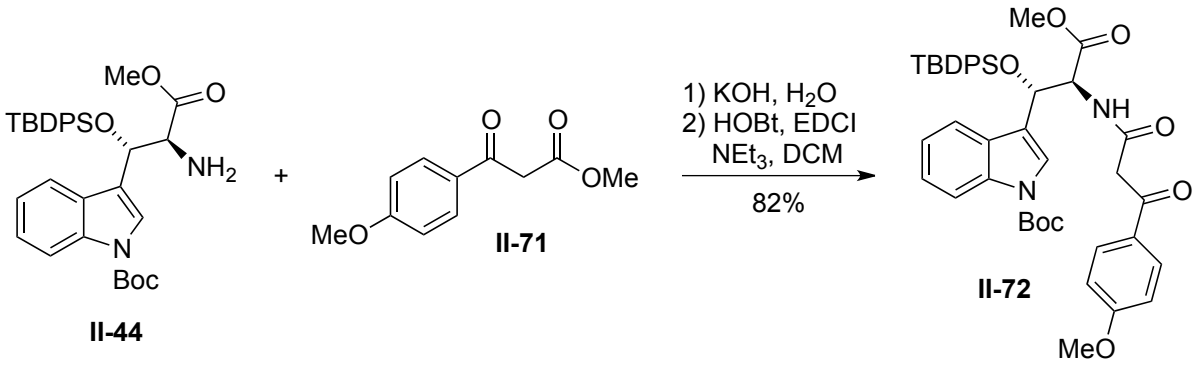


^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 190.98 (C-5), 168.38 (C-7), 164.22 (C-1), 131.09 (C-2), 129.27 (C-4), 114.14 (C-3), 55.69 (C-9), 52.60 (C-8), 45.70 (C-6).

IR ($\tilde{\nu}$ /cm^{-1}): 2958, 1737, 1665, 1599, 1571, 1508, 1438, 1418, 1407, 1320, 1287, 1170, 1170, 1144, 1109, 1023, 1016, 980.

HRMS (EI): calculated for $C_{11}H_{12}O_4$ $[M]^+$ 208.0736; found 208.0734.

***tert*-Butyl 3-((1*S*,2*S*)-1-((*tert*-butyldiphenylsilyl)oxy)-3-methoxy-2-(3-(4-methoxyphenyl)-3-oxo-propanamido)-3-oxopropyl)-1*H*-indole-1-carboxylate**

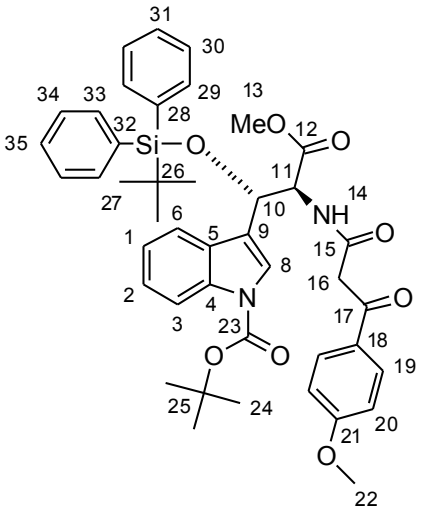


KOH (529 mg, 9.60 mmol) was dissolved in H_2O (20 mL) and added to methyl 3-(4-methoxyphenyl)-3-oxopropanoate (**II-71**) (500 mg, 2.40 mmol). The light yellow solution was stirred for 20 h before it was acidified with 10% aq. HCl solution to pH = 1. The white precipitate was filtered off and dried. The corresponding acid **II-68**, obtained as white crystals was directly used in the next step.

Amine **II-44** (200 mg, 0.349 mmol) and acid **II-68** (135 mg, 0.698 mmol) were dissolved in CH_2Cl_2 (2 mL). HOBt (75.5 mg, 0.558 mmol), EDC (92.7 µL, 0.524 mmol), NEt_3 (53.2 µL, 0.384 mmol) and 4 Å molecular sieves (powdered, 500 mg) were added. The mixture was stirred for 48 h before it was quenched with sat. aq. NH_4Cl solution (2 mL), extracted with CH_2Cl_2 (5 mL), washed with brine, dried over Na_2SO_4 and concentrated. Column chromatography gave the product **II-72** as a yellow oil (215 mg, 82%).

R_f: 0.2, 30% EtOAc in hexanes.

[a]$_D^{23}$ = 28.1 ° (c = 1.03, $CHCl_3$).



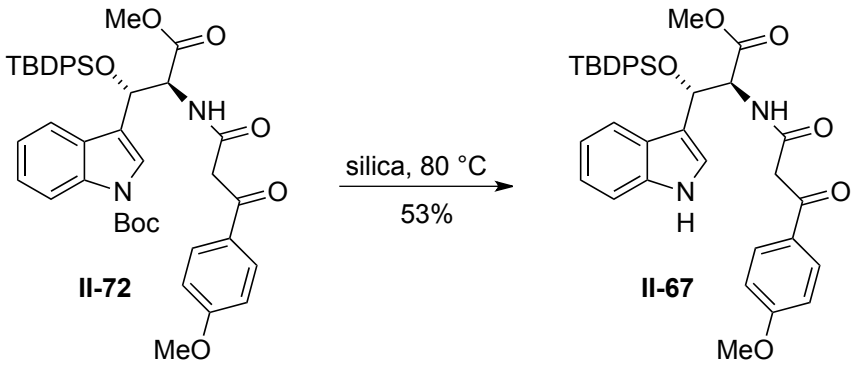
^{1}H NMR (599 MHz, $CDCl_3$) δ/ppm = 8.04 (s, 1H, H-3), 7.90 (d, *J* = 9.0 Hz, 2H, 2xH-19), 7.66 (d, *J* = 6.6 Hz, 2H, 2xH-29), 7.59 – 7.55 (m, 1H, H-2/6), 7.45 (s, 1H, H-8), 7.41 (d, *J* = 6.7 Hz, 2H, 2xH-33), 7.37 (d, *J* = 7.5 Hz, 1H, H-31), 7.33 (t, *J* = 6.5 Hz, 2H, 2xH-30), 7.23 (d, *J* = 5.1 Hz, 2H, H-2/6, H-35), 7.14 – 7.10 (m, 3H, 2xH-34, H-1), 6.92 (d, *J* = 9.0 Hz, 2H, 2xH-20), 5.44 (d, *J* = 4.7 Hz, 1H, H-10), 5.06 (dd, *J* = 4.7, 8.0 Hz, 1H, H-11), 3.88 (s, 3H, 3xH-22), 3.70 (d, *J* = 16.3 Hz, 1H, H-16α), 3.62 (d, *J* = 16.3 Hz, 1H, H-16β), 3.57 (s, 3H, 3xH-13), 1.67 (s, 9H, 9xH-24), 1.01 (s, 9H, 9xH-27).

^{13}C NMR (151 MHz, $CDCl_3$) δ/ppm = 193.28 (C-17), 169.82 (C-12), 166.01 (C-15), 164.24 (C-21), 149.71 (C-23), 136.13 (C-29), 135.86 (C-33), 135.86 (C-4), 133.25 (C-28), 132.90 (C-32), 131.10 (C-19), 129.96 (C-31), 129.64 (C-35), 129.40 (C-5), 129.12 (C-18), 127.80 (C-30), 127.41 (C-34), 124.74 (C-8), 124.49 (C-2/6), 122.66 (C-1), 120.22 (C-2/6), 119.64 (C-9), 115.14 (C-3), 114.08 (C-20), 83.24 (C-25), 70.63 (C-10), 58.45 (C-11), 55.65 (C-22), 52.26 (C-13), 45.13 (C-16), 28.37 (C-24), 27.03 (C-27), 19.45 (C-26).

IR ($\tilde{\nu}$ /cm^{-1}): 2932, 2250, 1734, 1666, 1599, 1573, 1511, 1451, 1368, 1308, 1255, 1170, 1155, 1088, 1070, 907, 833, 822.

HRMS (ESI): calculated for $C_{43}H_{48}N_2O_8SiNa$ $[M+Na]^+$ 771.3072; found: 771.3073.

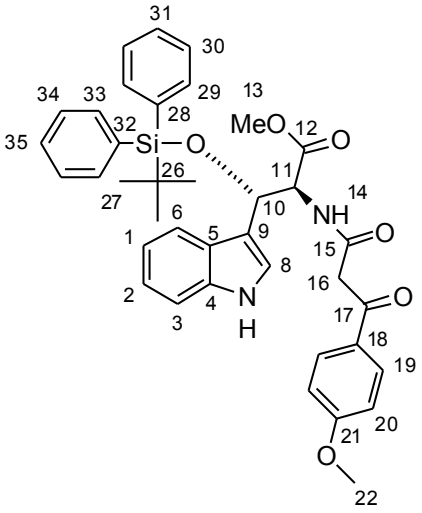
(2*S*,3*S*)-Methyl 3-((*tert*-butyldiphenylsilyl)oxy)-3-(1*H*-indol-3-yl)-2-(3-(4-methoxyphenyl)-3-oxo-propanamido)propanoate



β-Ketoamide **II-72** (65.0 mg, 0.0868 mmol) was dissolved in EtOAc (5 mL). Silica gel (2.10 g) was added and the mixture was concentrated to dryness under reduced pressure. The dry mixture was heated under high vacuum (0.1 mbar) to 80 °C for 4 h. The mixture was suspended in EtOAc (20 mL), filtered through a cotton plug and washed with EtOAc. Column chromatography (40% EtOAC in hexanes) gave the product **II-67** as a yellow oil (30.0 mg, 53 %).

R_f: 0.40, 50% EtOAc in hexanes.

$[a]_D^{23}$ = 30.0 ° (c = 0.40, $CHCl_3$).



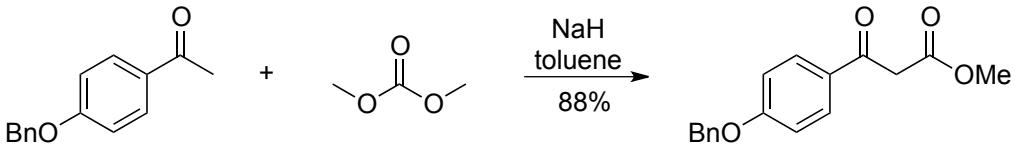
^{1}H NMR (599 MHz, $CDCl_3$) δ/ppm = 8.09 (d, *J* = 9.2 Hz, 1H, H-3), 7.92 (d, *J* = 9.0 Hz, 2H, 2xH-19), 7.67 (d, *J* = 6.6 Hz, 2H, 2xH-30), 7.49 (d, *J* = 8.2 Hz, 1H, H-6), 7.39 (dd, *J* = 7.7, 16.8 Hz, 4H, H-31, 2xH-34, H-35), 7.32 (t, *J* = 6.6 Hz, 2H, 2xH-29), 7.15 (d, *J* = 2.5 Hz, 1H, H-8), 7.11 (t, *J* = 7.7 Hz, 3H, H-2, 2xH-33), 7.01 (t, *J* = 7.5 Hz, 1H, H-1), 6.92 (d, *J* = 8.9 Hz, 2H, 2xH-20), 5.54 (d, *J* = 4.6 Hz, 1H, H-10), 5.06 (dd, *J* = 4.6, 8.1 Hz, 1H, H-11), 3.87 (s, 3H, 3xH-22), 3.74 (d, *J* = 15.9 Hz, 1H, H-16α), 3.69 (d, *J* = 15.9 Hz, 1H, H-16β), 3.50 (s, 3H, 3xH-13), 0.96 (s, 9H, 9xH-27).

^{13}C NMR (151 MHz, $CDCl_3$) δ/ppm = 193.65 (C-17), 170.09 (C-12), 165.88 (C-15), 164.25 (C-21), 136.17 (C-4), 136.12 (C-30), 135.89 (C-34), 133.48 (C-28), 133.19 (C-32), 131.22 (C-19), 129.87 (C-31), 129.52 (C-35), 129.45 (C-18), 127.74 (C-29), 127.32 (C-33), 125.61 (C-5), 123.23 (C-8), 122.26 (C-2), 120.49 (C-3), 119.85 (C-6), 119.83 (C-1), 115.03 (C-9), 114.08 (C-20), 70.45 (C-10), 58.79 (C-11), 55.70 (C-22), 52.22 (C-13), 45.56 (C-16), 26.97 (C-27), 19.54 (C-26)

IR ($\tilde{\nu}$ /cm^{-1}): 3321, 2952, 1737, 1661, 1597, 1573, 1511, 1456, 1426, 1359, 1309, 1259, 1215, 1170, 1103, 1085, 998.

HRMS (ESI): calculated for $C_{38}H_{40}N_2O_6SiNa$ $[M+Na]^+$ 671.2548; found: 671.2551.

Methyl 3-(4-(benzyloxy)phenyl)-3-oxopropanoate

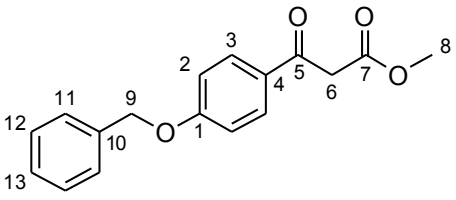


II-83 **II-70** **II-82**

NaH (60% on mineral oil, 1.33 g, 33.2 mmol) was placed in a schlenk flask and washed with hexanes (3x10 mL). Toluene (12 mL) and dimethyl carbonate (**II-70**) (2.99 g, 33.2 mmol) were added and the mixture was heated to 110 °C before 1-(4-(benzyloxy)phenyl)ethanone (**II-83**) (3.00 g, 13.3 mmol), dissolved in toluene (18 mL) was slowly added over 10 min. The resulting mixture was stirred for 4 h at 110 °C before cooling to r.t. followed by quenching with H_2O/AcOH (4:1, 20 mL). The mixture was extracted with ether (60 mL), washed with sat. aq. $NaHCO_3$ solution, brine, dried over $MgSO_4$ and concentrated. Column chromatography (10% EtOAC in hexanes) gave the product **II-82** as a yellow solid (3.33 g, 88%).

R_f: 0.70, 20% EtOAc in hexanes.

m.p.: 63.0 – 64.0 °C (EtOAc).



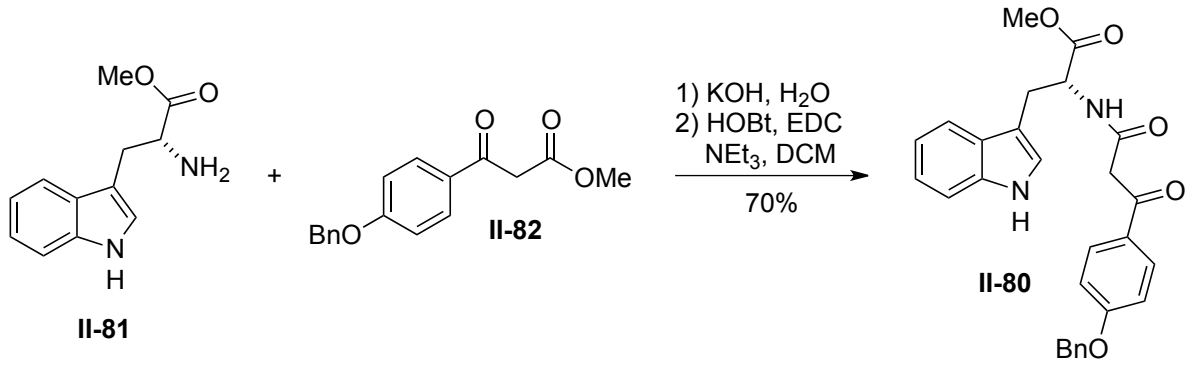
^{1}H NMR (599 MHz, $CDCl_3$) δ/ppm = 7.92 (d, *J* = 9.0 Hz, 2H, 2xH-3), 7.43 – 7.34 (m, 5H, 2xH-11, 2xH-12, H-13), 7.02 (d, *J* = 9.0, 2H, 2xH-2), 5.14 (s, 2H, 2xH-9), 3.96 (s, 2H, 2xH-6), 3.75 (s, 3H, 3xH-8).

^{13}C NMR (151 MHz, $CDCl_3$) δ/ppm = 190.92 (C-5), 168.29 (C-7), 163.32 (C-1), 136.13 (C-10), 131.08 (C-3), 129.38 (C-4), 128.87 (C-12), 128.46 (C-13), 127.62 (C-11), 114.97 (C-2), 70.37 (C-9), 52.61 (C-8), 45.68 (C-6).

IR ($\tilde{\nu}$ /cm^{-1}): 2955, 2874, 1747, 1662, 1599, 1571, 1508, 1455, 1438, 1422, 1402, 1381, 1330, 1251, 1221, 1183, 1157, 1116, 1012, 999, 982.

HRMS (EI): calculated for $C_{17}H_{16}O_4$ $[M]^+$ 284.1049; found 284.1046.

(*R*)-Methyl 2-(3-(4-(benzyloxy)phenyl)-3-oxopropanamido)-3-(1*H*-indol-3-yl)propanoate

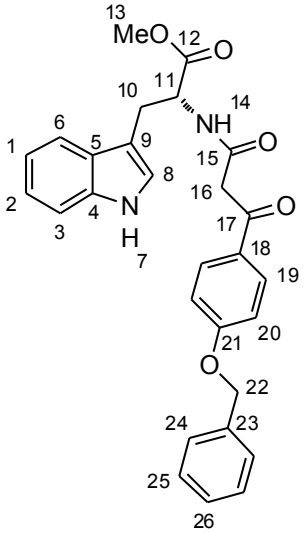


KOH (2.22 g, 40.3 mmol) was dissolved in H_2O (120 mL) and added to methyl 3-(4-(benzyloxy)phenyl)-3-oxopropanoate (**II-82**) (3.00 g, 10.6 mmol). The light yellow solution was stirred for 20 h before it was acidified with 10% aq. HCl solution to pH = 1. The white precipitate was filtered off and dried. The corresponding acid, obtained as white crystals was directly used in the next step.

Amine **II-81** (1.70 g, 7.79 mmol) and acid (2.10 g, 7.79 mmol) were dissolved in CH_2Cl_2 (17 mL). HOBt (1.44 g, 10.7 mmol), EDC (1.77 mL, 9.99 mmol) and NEt_3 (1.19 mL, 8.57 mmol) were added. The mixture was stirred for 48 h before it was quenched with sat. aq. NH_4Cl solution (10 mL). It was extracted with CH_2Cl_2 (20 mL), washed with brine, dried over Na_2SO_4 and concentrated in *vacuo*. Column chromatography gave the product **II-80** as a colorless foam (2.20 g, 70%).

R_f: 0.20, 40% EtOAc in hexanes.

$[a]_D^{26}$ = −49.3° (c = 0.75, $CHCl_3$).



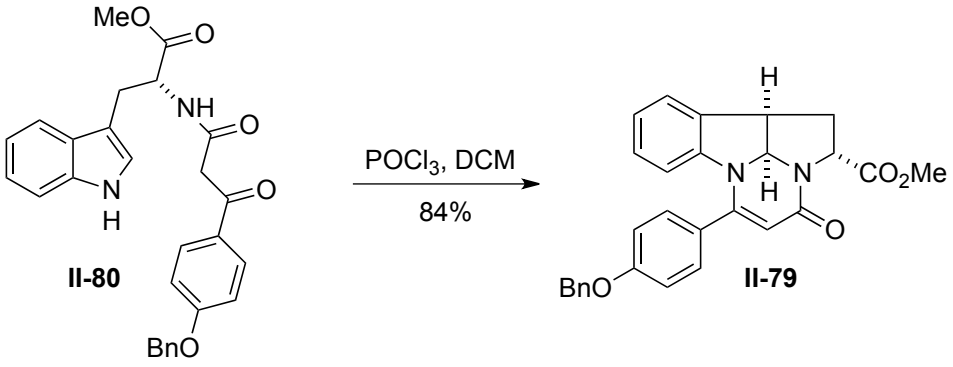
^{1}H NMR (599 MHz, $CDCl_3$) δ/ppm = 8.08 (s, 1H, NH-7), 7.92 (d, *J* = 9.0 Hz, 2H, 2xH-19), 7.53 (d, *J* = 8.0 Hz, 1H, H-6), 7.50 (d, *J* = 7.6 Hz, 1H, NH-14), 7.42 – 7.31 (m, 5H, 2xH-H-24, 2xH-25. H-26), 7.32 (d, *J* = 8.9 Hz, 1H, H-3), 7.18 – 7.13 (m, 1H, H-2), 7.10 – 7.05 (m, 1H, H-1), 7.03 (d, *J* = 2.4 Hz, 1H, H-8), 7.00 (d, *J* = 9.0, 2H, 2xH-20), 5.14 (s, 2H, 2x-22), 4.94 (dt, *J* = 5.7, 7.7 Hz, 1H, H-11), 3.84 (dd, *J* = 16.3, 34.8 Hz, 2H, 2xH-16), 3.65 (s, 3H, 3xH-13), 3.33 (d, *J* = 5.7, 2H, 2xH-10).

^{13}C NMR (151 MHz, $CDCl_3$) δ/ppm = 193.73 (C-17), 172.20 (C-12), 165.93 (C-15), 163.45 (C-21), 136.21 (C-4), 136.11 (C-23), 131.18 (C-19), 129.54 (C-18), 128.88 (C-25), 128.48 (C-26), 127.61 (C-24), 127.61 (C-5), 123.12 (C-8), 122.29 (C-2), 119.72 (C-1), 118.72 (C-6), 114.97 (C-20), 111.32 (C-3), 110.09 (C-9), 70.37 (C-22), 53.15 (C-11), 52.51 (C-13), 45.36 (C-16), 27.79 (C-10).

IR ($\tilde{\nu}$ /cm^{-1}): 3318, 2950, 1737, 1646, 1597, 1573, 1509, 1455, 1421, 1321, 1254, 1211, 1167, 1115, 999, 910, 829.

HRMS (ESI): calculated for $C_{28}H_{27}N_2O_5$ $(M+H)^+$ 471.1914; found: 471.1917.

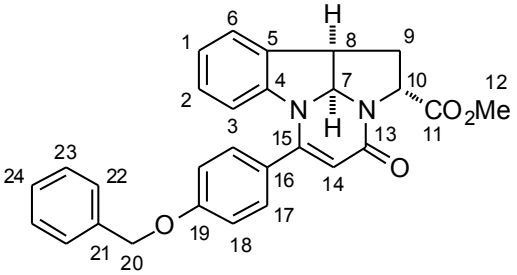
(2*R*,2a1*R*,9b*R*)-Methyl 5-(4-(benzyloxy)phenyl)-3-oxo-2,2a1,3,9b-tetrahydro-1*H*-2a,5a-diazacyclopenta[*jk*]fluorene-2-carboxylate



β-Ketoamide **II-80** (1.00 g, 2.13 mmol) was dissolved in CH_2Cl_2 (25 mL). $POCl_3$ (2.91 mL, 31.9 mmol) was slowly added to the solution, which was stirred for 18 h at r.t. before it was carefully quenched with 5% aq. NH_3 solution (15 mL). It was extracted with CH_2Cl_2, washed with water and brine, dried over Na_2SO_4 and concentrated. Column chromatography (60% EtOAc in hexanes) gave the product **II-79** as a yellow foam (810 mg, 84%).

R$_f$: 0.70, 80% EtOAc in hexanes.

[a]$_D^{26}$ = −248.7° (c = 0.79, $CHCl_3$).



^{1}H NMR (599 MHz, $CDCl_3$) δ/ppm = 7.63 (d, *J* = 8.8 Hz, 2H, 2xH-17), 7.46 (d, *J* = 7.3 Hz, 2H, 2xH-22), 7.42 (t, *J* = 7.5 Hz, 2H, 2xH-23), 7.36 (t, *J* = 7.3 Hz, 1H, H-24), 7.19 (d, *J* = 6.3 Hz, 1H, H-6), 7.06 (d, *J* = 8.8 Hz, 2H, 2xH-18), 6.92 – 6.87 (m, 2H, H-1, H-2), 6.02 (d, *J* = 7.4 Hz, 1H, H-3), 5.93 (d, *J* = 7.2 Hz, 1H, H-7), 5.84 (s, 1H, H-14), 5.14 (s, 2H, 2xH-20), 4.48 (dd, *J* = 5.8, 8.7 Hz, 1H, H-10), 4.20 (td, *J* = 3.6, 8.1 Hz, 1H, H-8), 3.80 (s, 3H, 3xH-12), 2.64 (ddd, *J* = 5.7, 8.7, 14.3 Hz, 1H, H-9α), 2.58 – 2.52 (m, 1H, H-9β).

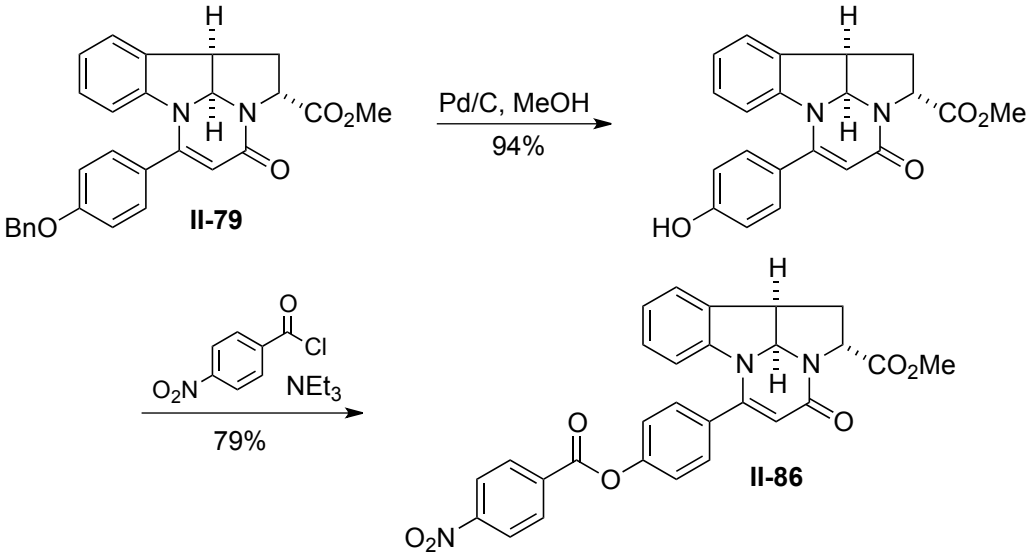
^{13}C NMR (151 MHz, $CDCl_3$) δ/ppm = 172.54(C-11), 162.63 (C-13), 161.38 (C-19), 152.09 (C-15), 145.91 (C-4), 136.48 (C-21), 133.30 (C-5), 130.12 (C-17), 128.83 (C-23), 128.53 (C-2), 128.37 (C-24), 127.69

(C-22), 126.75 (C-16), 124.95 (C-6), 122.21 (C-1), 115.44 (C-18), 112.83 (C-3), 105.85 (C-14), 80.20 (C-7), 70.35 (C-20), 56.81 (C-10), 52.71 (C-12), 44.76 (C-8), 35.52 (C-9).

IR ($\tilde{\nu}$ /cm^{-1}): 3008, 2952, 1738, 1642,1506, 1477, 1427, 1369, 1296, 1240, 1218, 1202, 1171, 1113, 1023, 1007, 826.

HRMS (ESI): calculated for $C_{28}H_{25}N_2O_4$ $[M+H]^+$ 453.1809; found: 453.1814.

(2*R*,2a^1*R*,9b*R*)-methyl 5-(4-((4-nitrobenzoyl)oxy)phenyl)-3-oxo-2,2a^1,3,9b-tetrahydro-1*H*-2a,5a-diazacyclopenta[*jk*]fluorene-2-carboxylate

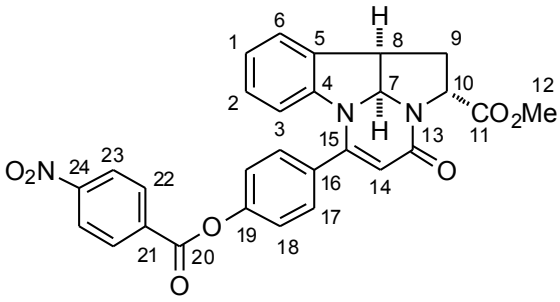


Tetracyclic compound **II-79** (100 mg, 0.221 mmol) was dissolved in MeOH (3 mL). Pd/C (10% Pd, 23.5 mg, 0.221 mmol) was added. The mixture was stirred for 15 min under H_2 atmosphere (1 atm) before it was diluted with EtOAc (10 mL), filtered over celite and concentrated to give the debenzylated product as colorless oil (78.0 mg, 94%). The product was redissolved in CH_2Cl_2 (1.5 mL), NEt_3 (37.5 µL, 0.269 mmol) was added and *para*-nitrobenzoyl chloride, dissolved in CH_2Cl_2 (1.5 mL). The solution was stirred at room temperature for 5 min, before it was diluted with CH_2Cl_2 (5 mL), washed with 10% aq. HCl and brine, dried over Na_2SO_4 and concentrated, to give the product **II-86** as a yellow solid (59.2 mg, 79%). Crystals suitable for X-ray crystallography were obtained from slow evaporation of MeOH.

R_f: 0.20, 60% EtOAc in hexanes.

$[a]_D^{22}$ = −320.9 ° (*c* = 0.24, $CHCl_3$).

m.p.: 192.3 – 194.2 (MeOH).



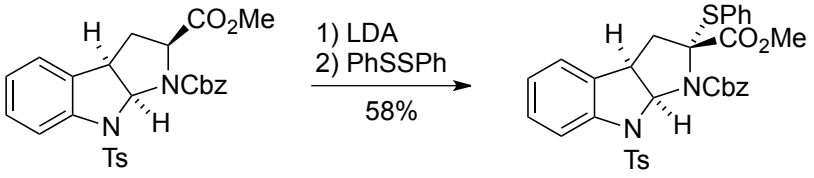
^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 8.40 (d, *J* = 1.9 Hz, 4H, 2xH-22, 2xH-23), 7.80 (d, *J* = 8.7 Hz, 2H, 2xH-17), 7.38 (d, *J* = 8.7 Hz, 2H, 2xH-18), 7.22 (d, *J* = 6.6 Hz, 1H, H-6), 7.00 – 6.88 (m, 2H, H-1, H-2), 6.07 – 6.01 (m, 1H, H-3), 6.00 – 5.94 (m, 2H, H-7, H-14), 4.51 (dd, *J* = 8.7, 5.8 Hz, 1H, H-10), 4.23 (t, *J* = 5.9 Hz, 1H, H-8), 3.81 (s, 3H, 3xH-12), 2.73 – 2.51 (m, 2H, 2xH-9).

^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm = 172.37 (C-11), 163.11 (C-20), 162.16 (C-13), 152.74 (C-19), 151.17 (C-21), 151.15 (C-15), 145.59 (C-4), 134.64 (C-24), 133.31 (C-5), 132.33 (C-16), 131.52 (C-22/23), 129.90 (C-17), 128.66 (C-2), 125.13 (C-6), 123.98 (C-22/23), 122.51 (C-1), 122.38 (C-18), 112.67 (C-3), 107.85 (C-14), 80.34 (C-7), 56.83 (C-10), 52.80 (C-12), 44.79 (C-8), 35.47 (C-9).

IR ($\tilde{\nu}$ /cm^{-1}): 2948, 2357, 1736, 1723, 1652, 1600, 1524, 1504, 1477, 1460, 1423, 1406, 1345, 1321, 1292, 1266, 1209, 1166, 1108, 1083, 1027.

HRMS (ESI): calculated for $C_{28}H_{21}O_7N_3Na$ $[M+Na]^+$ 534.1272; found 534.1272.

(2*R*,3a*R*,8a*S*)-1-Benzyl 2-methyl 2-(phenylthio)-8-tosyl-3,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indole-1,2(2*H*)-dicarboxylate



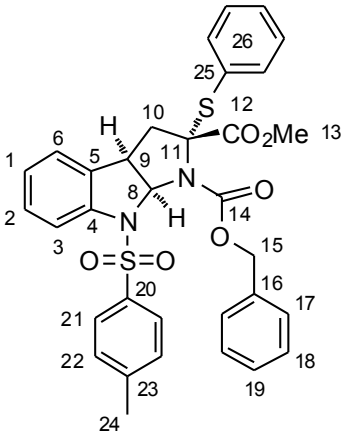
II-48 **II-128**

DIPA (77.9 µL, 0.458 mmol) was dissolved in THF (458 µL) and cooled to −78 °C. *n*-BuLi (2.5 M, 183 µL, 0.458 mmol) was slowly added and the solution was stirred for 5 min at −78 °C, then for 5 min warmed to r. t., then again cooled to −78 °C. Protected hydropyrroloindole **II-48** (200 mg, 0.395 mmol) was dissolved in THF (7 mL), cooled to −78 °C before the prepared LDA solution was slowly cannulated to the reaction, which was then stirred for 30 min at −78 °C. Diphenyldisulfide (94.8 mg, 0.434 mmol) was dissolved in THF (2 mL) and cooled to −78 °C before it was slowly cannulated to the reaction and then stirred for 1 h at −78 °C. The reaction was warmed to r. t. and poured into a

mixture of water (50 mL) and Et_2O (40 mL). It was extracted with Et_2O (15 mL), washed with brine, dried over $MgSO_4$ and concentrated. Column chromatography (30%EtOAc in hexanes) gave the product **II-128** as a yellow oil (140 mg, 58%, BRSM 80%).

R_f: 0.30, 40% EtOAc in hexanes.

$[a]_D^{23}$ = 59.6 ° (c = 0.50, $CHCl_3$).



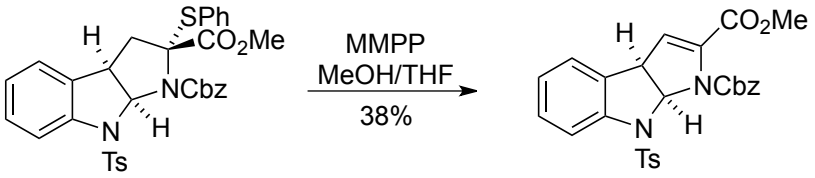
^{1}H NMR (599 MHz, $CDCl_3$) δ/ppm = 7.58 (d, *J* = 7.4 Hz, 2H, 2xH-21), 7.50 (d, *J* = 8.4 Hz, 4H, H-3, 3xH_{Ar}), 7.46 (d, *J* = 7.1 Hz, 2H, 2xH_{Ar}), 7.40 (t, *J* = 7.4 Hz, 4H, 4xH_{Ar}), 7.34 (t, *J* = 7.4 Hz, 2H, 2xH_{Ar}), 7.32 – 7.27 (m, 5H, 2xH-17, 2xH-18, H-19), 7.23 (dt, *J* = 1.5, 3.6 Hz, 2H, 2xH_{Ar}), 7.21 – 7.18 (m, 1H, H-2), 7.06 (d, *J* = 8.0 Hz, 2H, 2xH-22), 7.00 (td, *J* = 0.9, 7.5 Hz, 1H, H-1), 6.84 (d, *J* = 7.5 Hz, 1H, H-6), 5.85 (d, *J* = 6.2 Hz, 1H, H-8), 5.51 (d, *J* = 12.0 Hz, 1H, H-15α), 5.13 (d, *J* = 12.0 Hz, 1H, H-15β), 3.18 (s, 3H, 3xH-13), 2.93 (t, *J* = 5.7 Hz, 1H, H-9), , 2.61 – 2.53 (m, *J* = 5.2, 14.1, 16.8 Hz, 2H, 2xH-10), 2.30 (s, 3H, 3xH-24). H_{Ar} = H-26 and additional protons from RSPh and HOSPh.

^{13}C NMR (151 MHz, $CDCl_3$) δ/ppm = 170.74 (C-12), 153.12 (C-14), 143.96 (C-23), 141.79 (C-4), 137.88, 137.17 (C-25), 136.37 (C-16), 135.45 (C-20), 133.91, 130.82, 129.92, 129.49, 129.27, 129.20, 129.13, 128.73, 128.49 (C-2), 128.27, 127.66, 127.30, 127.27, 125.60 (C-1), 124.09 (C-6), 119.12 (C-3), 81.97 (C-8), 75.97 (C-11), 67.78 (C-15), 53.02 (C-13), 43.44 (C-9), 42.41 (C-10), 21.63 (C-24). Not all carbons could be assigned, additional carbons stem from RSPh and HOSPh.

IR ($\tilde{\nu}$ /cm^{-1}): 3385, 3058, 2949, 2254, 1714, 1596, 1577, 1475, 1438, 1395, 1328, 1268, 1213, 1167, 1089, 1067, 1022, 978.

HRMS (ESI): calculated for $C_{33}H_{30}N_2O_6S_2Na$ $[M+Na]^+$ 637.1437; found: 637.1441.

(3a*R*,8a*S*)-1-benzyl 2-methyl 8-tosyl-8,8a-dihydropyrrolo[2,3-*b*]indole-1,2(3a*H*)-dicarboxylate

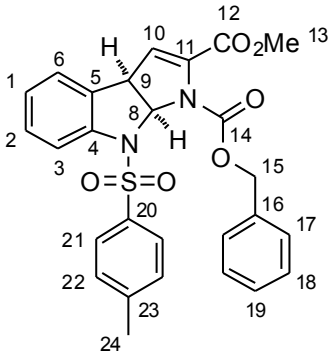


II-128 **II-129**

Hydropyrroloindole **II-128** (240 mg, 0.390 mmol) was dissolved in MeOH (16 mL) and THF (2 mL). It was cooled to 0 °C and magnesiummonoperoxyphtalat (80%, 241 mg, 0.390 mmol) was added. It was stirred for 1 h at 0 °C and for 24 h at r.t. before it was poured into CH_2Cl_2 (100 mL). It was washed with aq. sat. $NaHCO_3$ solution, brine, dried over $MgSO_4$ and concentrated. Column chromatography (20% → 30% EtOAc in hexanes) gave the product **II-129** as a colorless oil (76.0 mg, 38 %).

R_f: 0.30, 40% EtOAc in hexanes

$[a]_D^{23}$ = 234.7 ° (c = 0.15, $CHCl_3$).



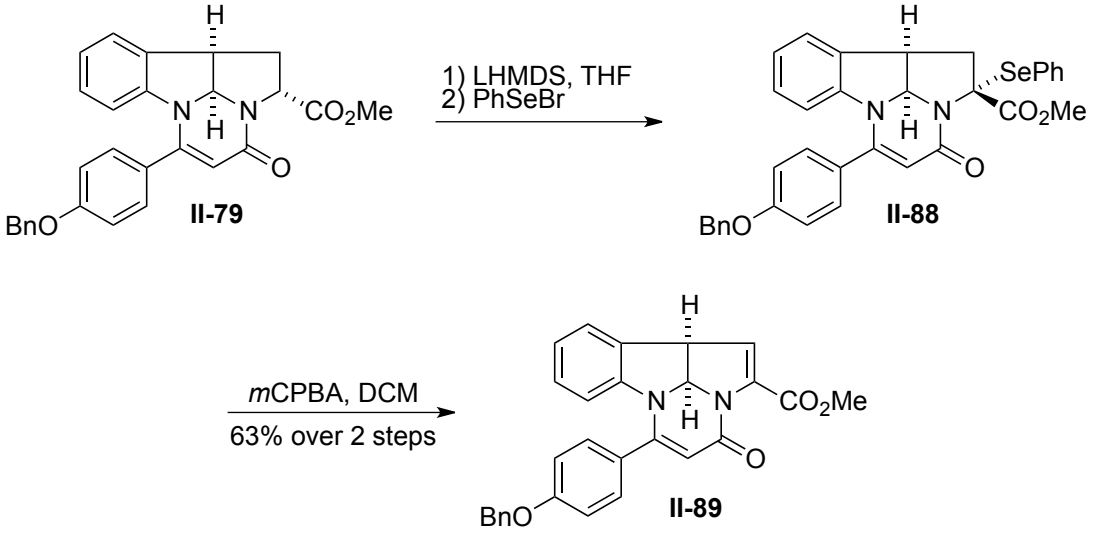
^{1}H NMR (599 MHz, $CDCl_3$) δ/ppm = 7.81 (d, *J* = 8.4 Hz, 2H, 2xH-21), 7.67 (d, *J* = 8.2 Hz, 1H, H-3), 7.42 – 7.36 (m, 5H, 2xH-17, 2xH-18, H-19), 7.22 (d, *J* = 7.5 Hz, 1H, H-2), 7.18 (d, *J* = 8.5 Hz, 2H, 2xH-22), 7.12 (d, *J* = 7.4 Hz, 1H, H-6), 6.99 (t, *J* = 7.9 Hz, 1H, H-1), 6.50 (d, *J* = 7.5 Hz, 1H, H-10), 5.92 (d, *J* = 2.1 Hz, 1H, H-8), 5.33 (d, *J* = 11.9 Hz, 1H, H-15α), 5.15 (d, *J* = 11.9 Hz, 1H, H-15β), 4.54 (dd, *J* = 1.9, 7.5 Hz, 1H, H-9), 3.56 (s, 3H, 3xH-13), 2.36 (s, 3H, 3xH-24).

^{13}C NMR (151 MHz, $CDCl_3$) δ/ppm = 162.18 (C-12), 154.20 (C-14), 144.37 (C-23), 141.39 (C-4), 136.64 (C-11), 135.30 (C-16), 134.84 (C-20), 129.83 (C-22), 129.04 (C-2), 128.84 (C-17/18/19), 128.74 (C-17/18/19), 128.67 (C-17/18/19), 127.87 (C-21), 127.73 (C-5), 124.82 (C-6), 124.13 (C-8), 123.92 (C-1), 115.09 (C-3), 82.30 (C-10), 68.93 (C-15), 52.26 (C-13), 49.70 (C-9), 21.73 (C-24).

IR ($\tilde{\nu}$ /cm^{-1}): 3450, 3027, 1719, 1597, 1477, 1390, 1371, 1312, 1285, 1237, 1237, 1170, 1090, 1040, 994.

HRMS (ESI): calculated for $C_{27}H_{24}N_2O_6SNa$ $[M+Na]^+$ 527.1247; found: 527.1248.

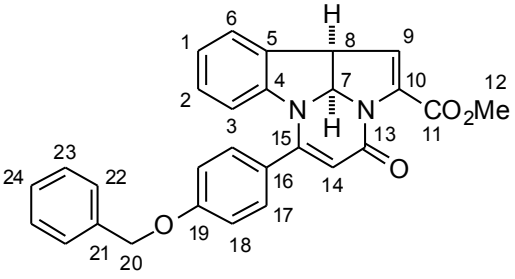
(2a^1*R*,9b*R*)-Methyl 5-(4-(benzyloxy)phenyl)-3-oxo-3,9b-dihydro-2a^{1}H-2a,5a-diazacyclopenta[*jk*] fluorene-2-carboxylate



Tetracyclic compound **II-79** (80.0 mg, 0.177 mmol) was dissolved in THF (3 mL) and cooled to −40 °C. LHMDS (1.0 M in THF, 354 µL, 0.345 mmol) was added and after 2 min PhSeBr (98.9 mg, 0.390 mmol) dissolved in THF (2 mL) was cannulated to the deprotonated species at −40 °C and stirred for 15 min. The reaction mixture was warmed to r.t. and poured into a mixture of water/EtOAC (1:1, 20 mL). It was extracted with EtOAc (20 mL), washed with brine and dried over Na_2SO_4. Column chromatography (10% Et_2O in CH_2Cl_2) gave a mixture of the selenation **II-88** and the elimination product **II-89**, which was directly dissolved in CH_2Cl_2 (3 mL). *m*CPBA (30.5 mg, 0.177 mmol) was added and it was stirred at 0 °C for 15 min before it was quenched with sat. aq. Na_2SO_3 solution (3 mL). It was extracted with CH_2Cl_2 (10 mL), washed with brine and dried over Na_2SO_4. Column chromatography (20% Et_2O in CH_2Cl_2) gave the elimination product **II-89** as a yellow oil (50.2 mg, 63%).

R_f: 0.30, 20% Et_2O in DCM.

$[a]_D^{24}$ = −397.8 ° (c = 0.45, $CHCl_3$).



^{1}H NMR (599 MHz, $CDCl_3$) δ/ppm = 7.64 (d, *J* = 8.9 Hz, 2H, 2xH-17), 7.47 – 7.46 (m, 2H, 2xH-22), 7.43 – 7.41 (m, 2H, 2xH-23), 7.37 – 7.36 (m, 1H, H-24), 7.25 – 7.20 (m, 1H, H-2), 7.07 (d, *J* = 8.9 Hz, 2H, 2xH-18), 6.94 – 6.89 (m, 2H, H-1, H-6), 6.15 – 6.10 (m, 1H, H-3), 6.00 (d, *J* =

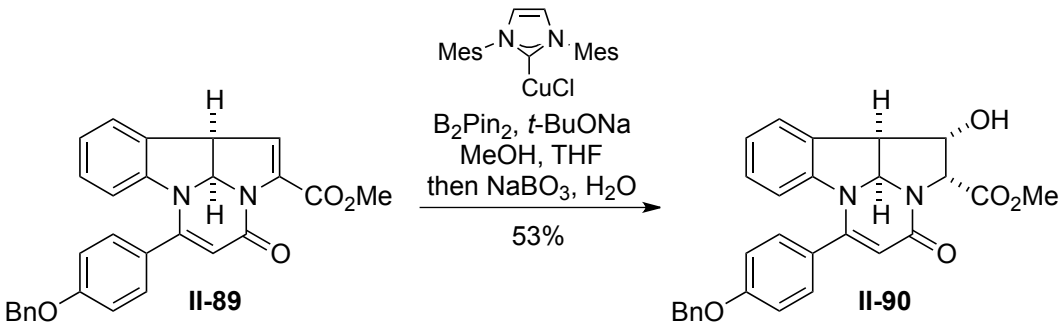
3.6, 1H, H-9), 5.94 (d, *J* = 9.8 Hz, 1H, H-7), 5.91 (s, 1H, H-14), 5.15 (s, 2H, 2xH-20), 4.61 (dd, *J* = 9.8, 3.6 Hz, 1H, H-8), 3.88 (s, 3H, 3xH-12).

^{13}C NMR (151 MHz, $CDCl_3$) δ/ppm = 162.34 (C-11), 161.55 (C-19), 160.11 (C-13), 151.76 (C-15), 145.25 (C-4), 137.09 (C-10), 136.42 (C-21), 130.27 (C-17), 128.85 (C-23), 128.49 (C-6), 128.41 (C-24), 127.70 (C-22), 127.17 (C-5), 126.39 (C-16), 125.21 (C-2), 122.62 (C-1), 116.10 (C-9), 115.55 (C-18), 112.54 (C-3), 105.84 (C-14), 80.20 (C-7), 70.39 (C-20), 52.86 (C-12), 48.40 (C-8).

IR ($\tilde{\nu}$ /cm^{-1}): 2922, 1736, 1649, 1600, 1505, 1476, 1459, 1423, 1409, 1360, 1287, 1244, 1227, 1171, 1120, 1020, 1000, 907, 819.

HRMS (ESI): calculated for $C_{28}H_{23}N_2O_4$ $[M+H]^+$ 451.1652; found: 451.1661.

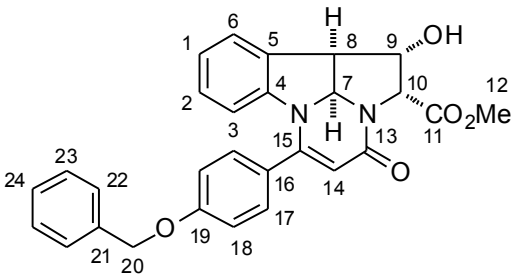
(1*S*,2*R*,2a^{1}R,9b*R*)-Methyl 5-(4-(benzyloxy)phenyl)-1-hydroxy-3-oxo-2,2a^1,3,9b-tetrahydro-1*H*-2a,5a-diazacyclopenta[*jk*]fluorene-2-carboxylate



B_2Pin_2 (561 mg, 2.21 mmol) was added to a solution of chloro[1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene]copper(I) (89.2 mg, 0.221 mmol), and *t*-BuONa (31.9 mg, 0.332 mmol) in THF (5.5 mL). It was stirred for 5 min before alkene **II-89** (830 mg, 1.84 mmol) dissolved in THF (11.5 mL) and MeOH (97.0 µL, 2.39 mmol) was added. The reaction mixture was stirred for 40 min before $NaBO_3$ (1.42 g, 9.21 mmol) and H_2O (14 mL) were added. After 20 min sat. aq. NH_4Cl solution (20 mL) was added and it was extracted with EtOAc (100 mL), washed with brine and dried over Na_2SO_4. Column chromatography (80% EtOAc in hexanes) gave the product **II-90** as a yellow oil (458 mg, 53%).

R_f: 0.30, 80% EtOAc in hexanes.

$[a]_D^{24}$ = −209.7 ° (c = 0.33, $CHCl_3$).



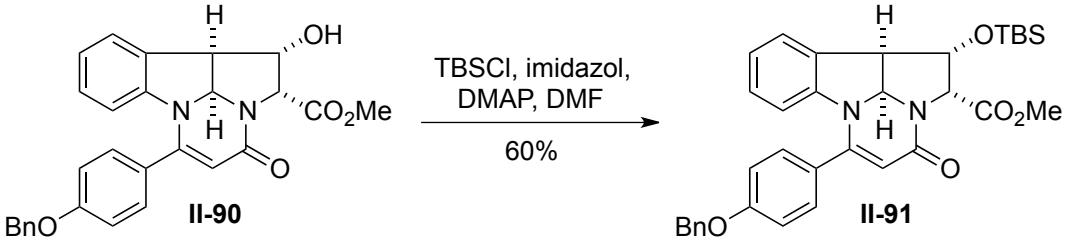
^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 7.61 (d, *J* = 8.8 Hz, 2H, 2xH-17), 7.51 – 7.29 (m, 6H, H-6, 2xH-22, 2xH-23, H-24), 7.05 (d, *J* = 8.8 Hz, 2H, 2xH-18), 6.98 – 6.83 (m, 2H, H-1, H-2), 6.11 (d, *J* = 7.2 Hz, 1H, H-7), 6.02 (d, *J* = 8.5 Hz, 1H, H-3), 5.84 (s, 1H, H-14), 5.13 (s, 2H, 2xH-20), 4.74 (dd, *J* = 6.8, 2.7 Hz, 1H, H-9), 4.61 (d, *J* = 6.8 Hz, 1H, H-10), 4.12 (d, *J* = 7.2 Hz, 1H, H-8), 3.79 (s, 3H, 3xH-12).

^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm = 169.71 (C-11), 163.16 (C-13), 161.43 (C-19), 152.48 (C-15), 145.91 (C-4), 136.39 (C-21), 130.74 (C-5), 130.09 (C-17), 128.85 (C-2), 128.80 (C-22/23), 128.35 (C-24), 127.67 (C-22/23), 126.44 (C-16), 125.23 (C-6), 122.25 (C-1), 115.42 (C-18), 112.90 (C-3), 105.35 (C-14), 79.24 (C-7), 77.51 (C-9), 70.31 (C-20), 62.83 (C-10), 54.46 (C-8), 52.63 (C-12).

IR ($\tilde{\nu}$ /cm^{-1}): 3339, 2975, 1741, 1626, 1601, 1506, 1477, 1433, 1368, 1299, 1248, 1170, 1114, 1076, 1005.

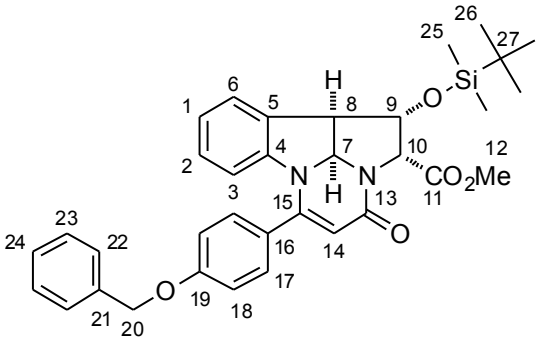
HRMS (ESI): calculated for $C_{28}H_{25}N_2O_5$ $[M+H]^+$ 469.1758; found: 469.1758.

(1*S*,2*R*,2a^1*R*,9b*R*)-Methyl 5-(4-(benzyloxy)phenyl)-1-((*tert*-butyldimethylsilyl)oxy)-3-oxo-2,2a^1,3,9b-tetrahydro-1*H*-2a,5a-diazacyclopenta[*jk*]fluorene-2-carboxylate



Alcohol **II-90** (380 mg, 0.811 mmol) was dissolved in DMF (10 mL). TBSCl (135 mg, 0.893 mmol), imidazol (122 mg, 1.79 mmol) and DMAP (9.92 mg, 0.0812 mmol) were added and the mixture was stirred for 18 h before it was quenched with water (10 mL). It was extracted with EtOAc (50 mL), washed with brine, dried over Na_2SO_4, concentrated. Column chromatography (50%EtOAc in hexanes) gave the product **II-91** as colorless oil (282 mg, 60%).

R_f: 0.30, 50% EtOAc in hexanes.



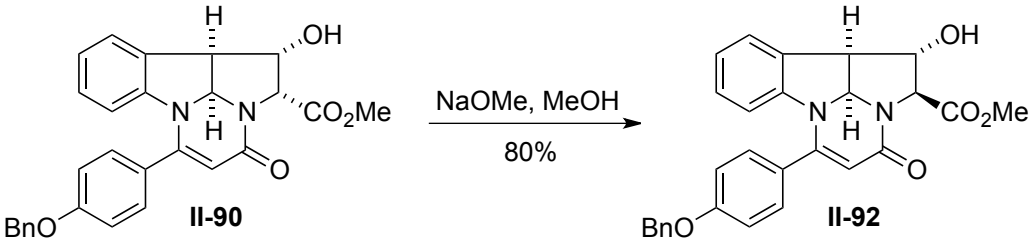
^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 7.60 (d, *J* = 8.8 Hz, 2H, 2xH-17), 7.45 – 7.36 (m, 5H, 2xH-22, 2xH-23, H-24), 7.26 (d, *J* = 7.2 Hz, 1H, H-6), 7.05 (d, *J* = 8.8 Hz, 2H, 2xH-18), 6.98 – 6.84 (m, 2H. H-1, H-2), 6.13 (d, *J* = 7.3 Hz, 1H, H-7), 6.03 (d, *J* = 7.6 Hz, 1H, H-3), 5.80 (s, 1H, H-14), 5.14 (s, 2H, 2xH-20), 4.70 – 4.57 (m, 2H, H-9, H-10), 4.03 (dd, *J* = 7.3, 2.9 Hz, 1H, H-8), 3.78 (s, 3H, 3xH-12), 0.95 (s, 9H, 9xH-26), 0.20 (s, 3H, 3xH-25), 0.15 (s, 3H. 3xH-25).

^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm = 169.03 (C-11), 162.65 (C-13), 161.33 (C-19), 151.85 (C-15), 145.96 (C-4), 136.45 (C-21), 130.79 (C-5), 130.05 (C-17), 128.94 (C-2), 128.82 (C-22/23), 128.36 (C-24), 127.67 (C-22/23), 126.61 (C-16), 124.91 (C-6), 121.93 (C-1), 115.41 (C-18), 113.02 (C-3), 105.54 (C-14), 79.06 (C-7), 78.53 (C-9), 70.33 (C-20), 62.58 (C-10), 54.92 (C-8), 52.25 (C-12), 25.75 (C-26), 17.99 (C-27), -4.68 (C-25).

IR ($\tilde{\nu}$ /cm^{-1}): 2950, 2928, 2245, 1743, 1644, 1602, 1506, 1477, 1460, 1428, 1378, 1336, 1296, 1250, 1201, 1170, 1093, 1005, 906.

HRMS (ESI): calculated for $C_{34}H_{39}N_2O_5Si$ $[M+H]^+$ 583.2623; found: 583.2621.

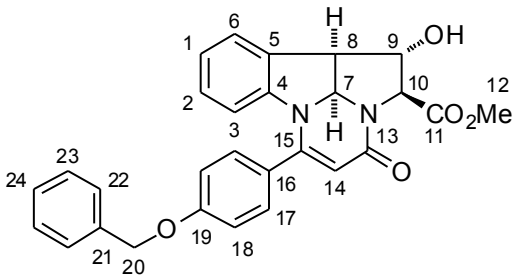
(1*S*,2*S*,2a^1*R*,9b*R*)-Methyl 5-(4-(benzyloxy)phenyl)-1-hydroxy-3-oxo-2,2a^1,3,9b-tetrahydro-1*H*-2a,5a-diazacyclopenta[*jk*]fluorene-2-carboxylate



Sodium (13.9 mg, 0.608 mmol) was dissolved in MeOH (5 mL). Ester **II-90** (95.0 mg, 0.203 mmol) was dissolved in MeOH (2 mL) and cannulated to the NaOMe solution. The reaction mixture was stirred for 2 h at 60 °C. After cooling to room temperature 10% aq. HCl solution was added to pH < 7. It was extracted with EtOAc (100 mL), washed with water, brine, dried over Na_2SO_4 and concentrated. Column chromatography (80% EtOAc in hexanes) gave the product **II-92** as a colorless oil (76.1 mg, 80%).

R_f: 0.30, 100% EtOAc.

$[a]_D^{24}$ = −86.7 ° (c = 0.24, MeOH).



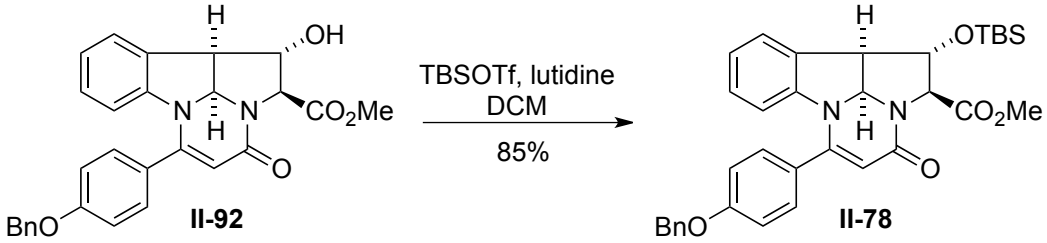
^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 7.70 (d, *J* = 8.8 Hz, 2H, 2xH-17), 7.47 – 7.36 (m, 5H, 2xH-22, 2xH-23, H-24), 7.17 (d, *J* = 7.4, 1H, H-6), 7.07 (d, *J* = 8.8 Hz, 2H, 2xH-18), 6.91 (t, *J* = 7.7 Hz, 1H, H-2), 6.82 (t, *J* = 7.4 Hz, 1H, H-1), 6.08 (d, *J* = 8.0 Hz, 1H, H-3), 5.96 (s, 1H, H-14), 5.91 (d, *J* = 6.7 Hz, 1H, H-7), 5.15 (s, 2H, 2xH-20), 4.86 (d, *J* = 4.3 Hz, 1H, H-9), 4.71 (s, 1H, H-10), 4.15 (d, *J* = 6.7 Hz, 1H, H-8), 3.15 (s, 3H, 3xH-12), 3.07 (d, *J* = 4.6 Hz, 1H, OH).

^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm = 168.73 (C-11), 164.87 (C-13), 161.59 (C-19), 153.55 (C-15), 147.36 (C-4), 136.46 (C-21), 130.40 (C-17), 129.45 (C-5), 129.11 (C-2), 128.85 (C-22/23), 128.40 (C-24), 127.71 (C-22/23), 126.60 (C-16), 125.07 (C-6), 121.90 (C-1), 115.48 (C-18), 112.83 (C-3), 106.35 (C-14), 80.46 (C-7), 80.11 (C-9), 70.37 (C-20), 68.63 (C-10), 53.57 (C-8), 52.42 (C-12).

IR ($\tilde{\nu}$ /cm^{-1}): 3262, 2933, 1733, 1625, 1600, 1504, 1475, 1428, 1333, 1300, 1247, 1171, 1009, 821.

HRMS (ESI): calculated for $C_{28}H_{25}N_2O_5$ $[M+H]^+$ 469.1758; found: 469.1758.

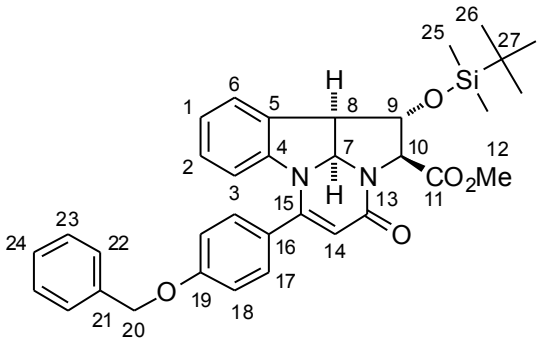
(1*S*,2*S*,2a^1*R*,9b*R*)-Methyl 5-(4-(benzyloxy)phenyl)-1-((*tert*-butyldimethylsilyl)oxy)-3-oxo-2,2a^1,3,9b-tetrahydro-1*H*-2a,5a-diazacyclopenta[*jk*]fluorene-2-carboxylate



Alcohol **II-92** (240 mg, 0.512 mmol) was dissolved in CH_2Cl_2 (3 mL). TBSOTf (130 µL, 0.564 mmol) and 2,6-lutidine (130 µL, 1.13 mmol) were added. The mixture was stirred for 18 h at r.t. before it was quenched with sat. aq. NH_4Cl solution (3 mL), extracted with EtOAc (15 mL), washed with brine, dried over Na_2SO_4 and concentrated. Column chromatography (60% EtOAc in hexanes) gave the product **II-78** as a colorless oil (254 mg, 85%).

R_f: 0.30, 50% EtOAc in hexanes.

$[a]_D^{24}$ = −185.8 ° (c = 0.30, $CHCl_3$).



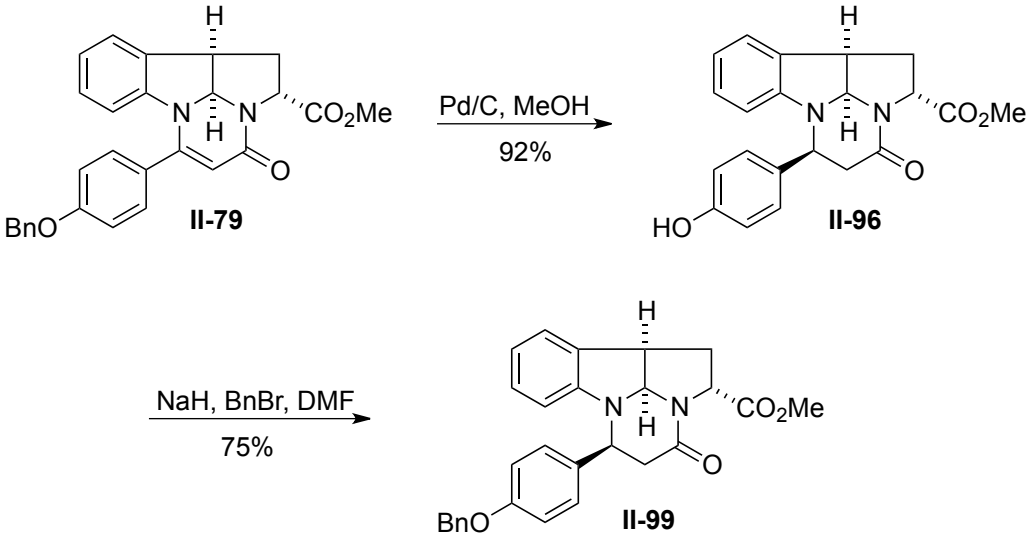
^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 7.69 (d, *J* = 8.9 Hz, 2H, 2xH-17), 7.48 – 7.34 (m, 5H, 2xH-22, 2xH-23, H-24), 7.11 (d, *J* = 7.4 Hz, 1H, H-6), 7.07 (d, *J* = 8.9 Hz, 2H, 2xH-18), 6.91 (t, *J* = 7.7 Hz, 1H, H-2), 6.81 (t, *J* = 7.4 Hz, 1H, H-1), 6.08 (d, *J* = 8.0 Hz, 1H, H-3), 5.96 (s, 1H, H-14), 5.91 (d, *J* = 6.7 Hz, 1H, H-7), 5.15 (s, 2H, 2xH-20), 4.77 (s, 1H, H-9), 4.59 (s, 1H, H-10), 4.01 (d, *J* = 6.7 Hz, 1H, H-8), 3.18 (s, 3H, 3xH-12), 0.98 (s, 9H, 9xH-26), 0.26 (s, 3H, 3xH-25), 0.24 (s, 3H, 3xH-25).

^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm = 168.91 (C-11), 164.39 (C-13), 161.46 (C-19), 153.06 (C-15), 147.45 (C-4), 136.49 (C-21), 130.26 (C-17), 129.59 (C-5), 129.03 (C-2), 128.84 (C-22/23), 128.37 (C-24), 127.69 (C-22/23), 126.77 (C-16), 124.76 (C-6), 121.72 (C-1), 115.45 (C-18), 112.84 (C-3), 106.68 (C-14), 81.01 (C-7), 80.61 (C-9), 70.35 (C-20), 68.74 (C-10), 54.82 (C-8), 52.25 (C-12), 25.91 (C-26), 18.30 (C-27), -4.55 (C-25), -4.82 (C-25).

IR ($\tilde{\nu}$ /cm^{-1}): 2951, 2927, 2360, 1757, 1736, 1644, 1602, 1505, 1476, 1460, 1423, 1409, 1300, 1250, 1171, 1081.

HRMS (ESI): calculated for $C_{34}H_{39}N_2O_5Si$ $[M+H]^+$ 583.2623; found: 583.2620.

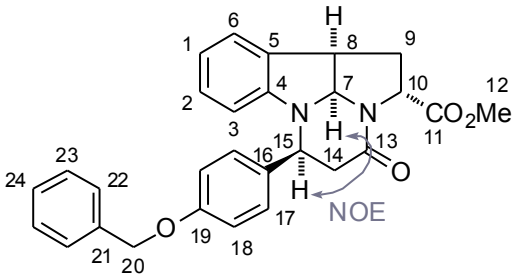
(2*R*,2a^1*R*,5*S*,9b*R*)-Methyl 5-(4-(benzyloxy)phenyl)-3-oxo-2,2a^1,3,4,5,9b-hexahydro-1*H*-2a,5a-diazacyclopenta[*jk*]fluorene-2-carboxylate



Tetracyclic compound **II-79** (250 mg, 0.552 mmol) was dissolved in MeOH (12 mL) before Pd/C (10% Pd, 129 mg, 1.22 mmol) was added. The mixture was stirred for 18 h under H_2 atmosphere (1 atm) before it was diluted with EtOAc (50 mL), filtered over celite and concentrated. Column chromatography (20% Et_2O in CH_2Cl_2) gave the product **II-96** as a colorless oil (186 mg, 92%). The product **II-96** (160 mg, 0.439 mmol) was directly dissolved in DMF (8 mL). NaH (60% on mineral oil, 21.1 mg, 0.527 mmol) and BnBr (57.4 µL, 0.483 mmol) were added and the mixture was stirred for 2 h at room temperature before it was quenched with water (8 mL) and extracted with EtOAc (30 mL). It was washed with ½ sat. aq. NaCl solution, with brine, dried over Na_2SO_4 and concentrated. Column chromatography (5% Et_2O in DCM) gave the product **II-99** as a yellow oil (150 mg, 75%).

R_f: 0.30, 10% Et_2O in CH_2Cl_2.

$[a]_D^{24}$ = 61.1 ° (c = 0.93, $CHCl_3$).



^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 7.47 – 7.34 (m, 7H, 2xH-17, 2xH-22, 2xH-23, H-24), 7.09 (d, *J* = 6.7 Hz, 1H, H-6), 7.04 (d, *J* = 8.8 Hz, 2H, 2xH-18), 6.86 – 6.74 (m, 2H, H-1, H-2), 5.87 (d, *J* = 8.7 Hz, 1H, H-3), 5.50 (d, *J* = 5.6 Hz, 1H, H-7), 5.14 – 5.10 (m, 3H, 2xH-20, H-15), 4.70 (dd, *J* = 9.8, 6.3 Hz, 1H, H-10), 3.89 (t, *J* = 6.5 Hz, 1H, H-8), 3.79 (s, 3H, 3xH-12), 2.99 (dd, *J* = 17.2, 5.0 Hz, 1H, H-14α), 2.86 (dd, *J* = 17.2, 11.9 Hz, 1H, H-14β), 2.71 – 2.65 (m, 1H, H-9α), 2.55 – 2.48 (m, 1H, H-9β).

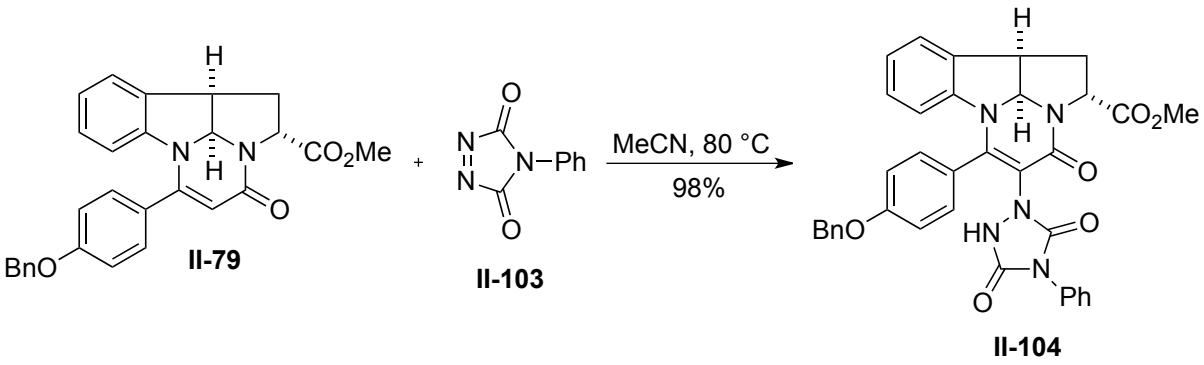
NOESY NOE between H-15 and H-7.

^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm = 172.86 (C-11), 167.45 (C-13), 158.54 (C-19), 147.03 (C-4), 136.94 (C-21), 133.02 (C-5), 131.03 (C-16), 128.77 (C-17/22/23/24), 128.20 (C-1), 128.14 (C-17/22/23/24), 127.91 (C-17/22/23/24), 127.68 (C-17/22/23/24), 125.17 (C-6), 121.10 (C-2), 115.36 (C-18), 112.78 (C-3), 82.82 (C-7), 70.26 (C-20), 56.83 (C-10), 55.60 (C-15), 52.70 (C-12), 44.92 (C-8), 32.33 (C-9), 32.11 (C-14).

IR ($\tilde{\nu}$ /cm^{-1}): 3009, 2949, 1743, 1648, 1606, 1584, 1510, 1474, 1454, 1435, 1408, 1382, 1288, 1213, 1174, 1100, 1022, 975, 909.

HRMS (ESI): calculated for $C_{28}H_{27}N_2O_4$ $[M+H]^+$ 455.1965; found: 455.1967.

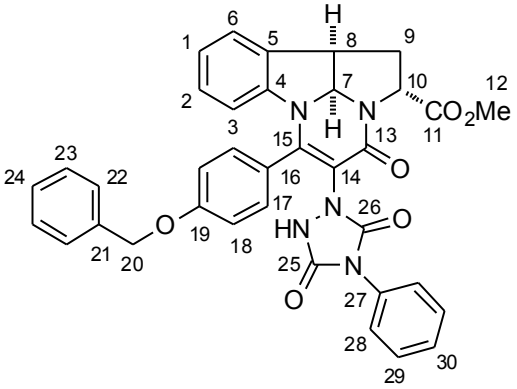
(2*R*,2a^1*R*,9b*R*)-Methyl 5-(4-(benzyloxy)phenyl)-4-(3,5-dioxo-4-phenyl-1,2,4-triazolidin-1-yl)-3-oxo-2,2a^1,3,9b-tetrahydro-1*H*-2a,5a-diazacyclopenta[*jk*]fluorene-2-carboxylate



Tetracyclic compound **II-79** (150 mg, 0.331 mmol) and 4-phenyl-1,2,4-triazoline-3,5-dione (**II-103**) (93.0 mg, 0.531 mmol) were dissolved in MeCN (5 mL) and heated to 80 °C for 1.5 h before it was concentrated. Column chromatography (2% MeOH in CH_2Cl_2) gave the product **II-104** as a yellow foam (204 mg, 98%).

R$_f$: 0.20, 80% EtOAc in hexane.

[a]$_D^{24}$ = −451.3 ° (c = 0.39, MeOH).



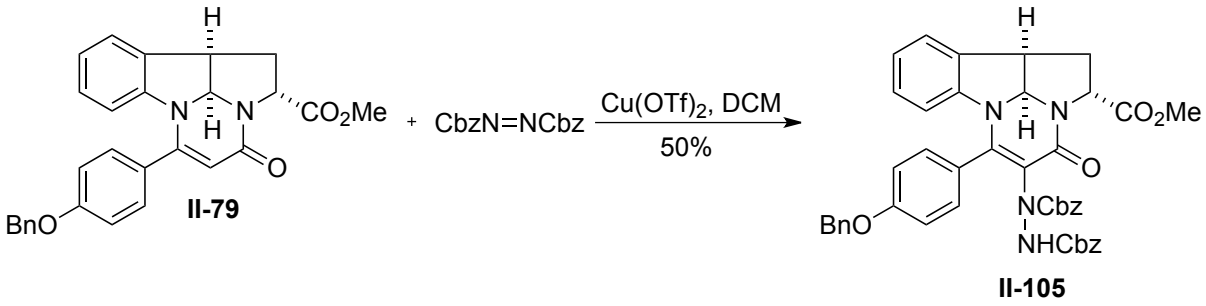
^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 7.63 (s, 1H, NH), 7.49 – 7.28 (m, 11H, 2xH-17, 2xH-22, 2xH-23, H-24, 2xH-28, 2xH-29), 7.20 (d, *J* = 7.2 Hz, 2H, H-6, H-30), 7.09 (d, *J* = 9.0 Hz, 2H, 2xH-18), 6.92 (dt, *J* = 18.7, 7.2 Hz, 2H, H-1, H-2), 6.13 (d, *J* = 7.8 Hz, 1H, H-7), 5.78 (d, *J* = 6.3 Hz, 1H, H-3), 5.12 (s, 2H, 2xH-20), 4.65 (d, *J* = 6.6 Hz, 1H, H-10), 4.29 (q, *J*= 8.4 Hz, 1H, H-8), 3.82 (s, 3H, 3xH-12), 2.74 (t, *J* = 9.6 Hz, 1H, H-9α), 2.39 (s, 1H, H-9β).

^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm = 171.76 (C-11), 161.83 (C-19), 153.59 (C-13), 143.56 (C-4), 136.22 (C-21), 134.26 (C-5), 131.79 (C_{quart}), 131.46 (C_{quart}), 129.19 (CH), 128.87 (CH), 128.84 (CH), 128.48 (C-2), 128.34 (C-17), 127.76 (C-22), 126.03 (C_{quart}), 125.34 (C-6), 123.56 (C-1), 123.25 (C_{quart}), 115.80 (C-18), 113.39 (C-3), 78.97 (C-7), 70.44 (C-20), 56.99 (C-10), 52.99 (C-12), 44.39 (C-8), 36.05 (C-9). Carbon 23, 24, 28, 29, 30 (CH) as well as 14, 15, 25, 26 and 27 (C_{quart}) could not be assigned. Some carbons might not be detected in the NMR measurements.

IR ($\tilde{\nu}$ /cm^{-1}): 3006, 2950, 1771, 1708, 1651, 1601, 1579, 1502, 1479, 1502, 1479, 1423, 1352, 1293, 1249, 1218, 1171, 1117, 1080, 1006.

HRMS (ESI): calculated for $C_{36}H_{30}N_5O_6$ $[M+H]^+$ 628.2191; found: 628.2192.

Dibenzyl 1-((2*R*,2a^1*R*,9b*R*)-5-(4-(benzyloxy)phenyl)-2-(methoxycarbonyl)-3-oxo-2,2a^1,3,9b-tetrahydro-1*H*-2a,5a-diazacyclopenta[*jk*]fluoren-4-yl)hydrazine-1,2-dicarboxylate



Tetracyclic compound **II-79** (500 mg, 1.11 mmol) was dissolved in CH_2Cl_2 (30 mL). Dibenzyl azodicarboxylate (495 mg, 1.66 mmol), $Cu(OTf)_2$ (200 mg, 0.553 mmol) and trifluoroethanol (126 µL, 1.66 mmol) were added. The reaction mixture was stirred for 20 h before it was quenched with 10% aq. NH_3 solution (10 mL). The layers were separated and the organic layer was washed with brine, dried over Na_2SO_4 and concentrated in *vacuo*. Column chromatography (50 % EtOAc in hexanes) gave the product **II-105** as a yellow foam (415 mg, 50 %).

R_f: 0.40, 80% EtOAc in hexane (on TLC only visible at 366 nm).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 7.69 – 7.64 (m, 2H, CH_{Ar}), 7.54 – 7.28 (m, 11H, CH_{Ar}), 7.25 – 6.72 (m, 9H, CH_{Ar}), 5.99 (dd, *J* = 18.0 Hz, 7.7, 1H, H-7), 5.69 – 5.52 (m, 1H, H-3), 5.36 – 4.87 (m, 6H, 2xH-20, 2xH-26, 2xH-30), 4.65 – 4.52 (m, 1H, H-10), 4.26 – 4.22 (m, 1H, H-8), 3.79 (s, 3H, 3xH-12), 2.75 – 2.57 (m, 1H, H-9α), 2.47 – 2.28 (m, 1H, H-9β). Broad signals caused by rotamers of the amides.

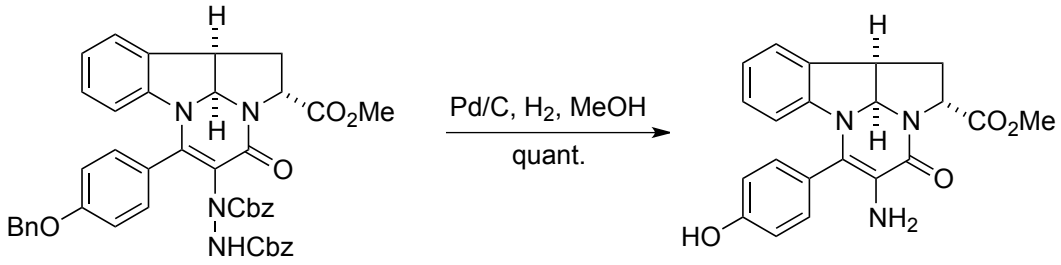
^{13}C NMR impossible to interpret because of numerous signals caused by rotamers of the amides.

Not depicted.

IR ($\tilde{\nu}$ /cm^{-1}): 3297, 2953, 1726, 1648, 1601, 1507, 1478, 1453, 1433, 1381, 1296, 1246, 1208, 1170, 1097, 1063, 1024, 839, 785, 763.

HRMS (ESI): calculated for $C_{44}H_{39}N_4O_8$ $[M+H]^+$ 751.2762; found: 751.2764.

(2*R*,2a^1*R*,9b*R*)-Methyl 4-amino-5-(4-hydroxyphenyl)-3-oxo-2,2a^1,3,9b-tetrahydro-1*H*-2a,5a-diazacyclopenta[*jk*]fluorene-2-carboxylate

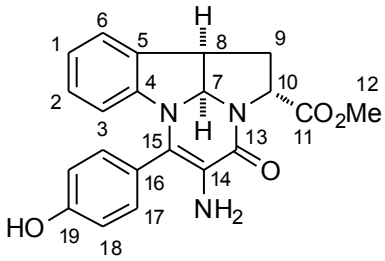


II-105 **II-106**

Dicarboxylate **II-105** (100 mg, 0.133 mmol) was dissolved in MeOH (5 mL). Pd/C (10% Pd, 28.3 mg, 0.266 mmol) was added. The mixture was stirred for 2 h under H_2 atmosphere (1 atm) before it was diluted with EtOAc (10 mL), filtered over celite and concentrated to give the product **II-106** as brown foam (50.1 mg, quant.).

R$_f$: 0.30, 80% EtOAc in hexanes.

[a]$_D^{24}$ = −205.2 ° (c = 0.23, MeOH).



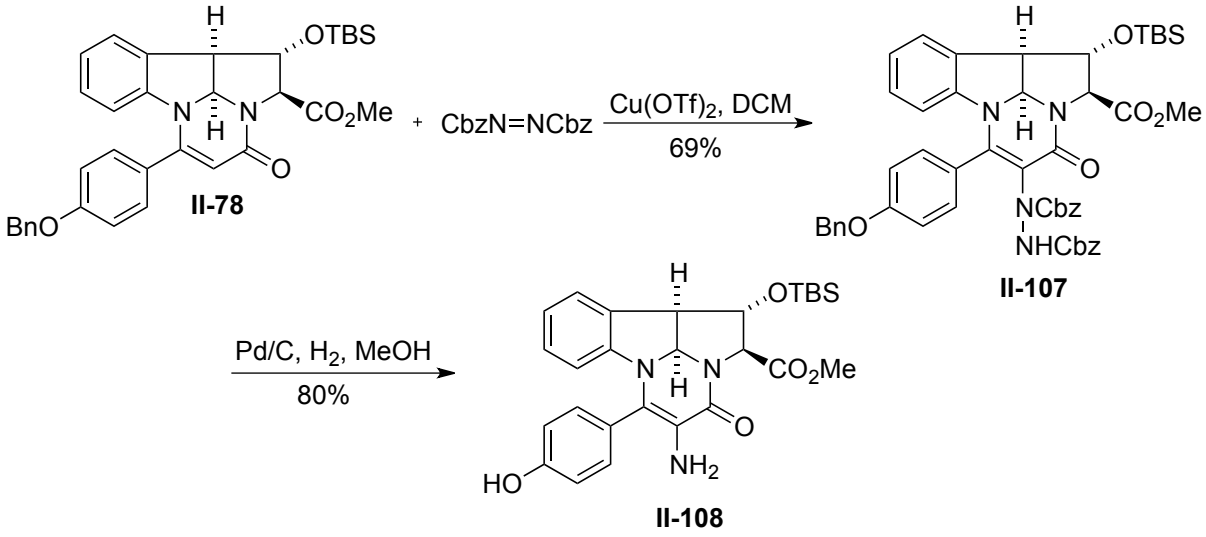
^{1}H NMR (400 MHz, CD$_3$OD) δ/ppm = 7.63 (d, *J* = 8.8 Hz, 2H, 2xH-17), 7.23 (d, *J* = 7.3 Hz, 1H, H-6), 6.92 – 6.81 (m, 4H, 2xH-18, H-1, H-2), 5.93 (d, *J* = 8.2 Hz, 1H, H-3), 5.76 (d, *J* = 6.3 Hz, 1H, H-7), 4.23 (t, *J* = 8.2 Hz, 1H, H-10), 4.15 (t, *J* = 6.9 Hz, 1H, H-8), 3.78 (s, 3H, 3xH-12), 2.83 – 2.76 (m, 1H, H-9α), 2.62 – 2.57 (m, 1H, H-9β).

^{13}C NMR (101 MHz, CD$_3$OD) δ/ppm = 172.38 (C-11), 161.34 (C-13), 157.90 (C-19), 148.29 (C-4), 131.64 (C-5), 129.88 (C-17), 127.88 (C-2), 125.64 (C-16), 125.14 (C-15), 124.17 (C-14), 124.08 (C-6), 120.97 (C-1), 115.61 (C-18), 111.59 (C-3), 79.62 (C-7), 57.18 (C-10), 51.62 (C-12), 44.65 (C-8), 34.12 (C-9).

IR ($\tilde{\nu}$ /cm^{-1}): 3340, 1742, 1637, 1600, 1510, 1476, 1435, 1364, 1269, 1216, 1166, 1020, 841.

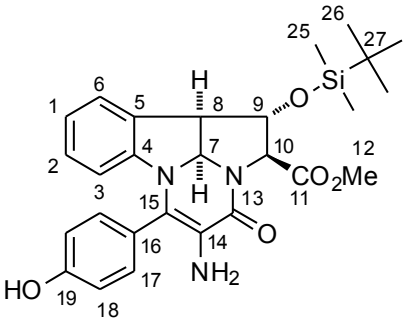
HRMS (ESI): calculated for $C_{21}H_{20}N_3O_4$ $[M+H]^+$ 378.1448; found: 378.1446.

(1*S*,2*S*,2a^1*R*,9b*R*)-Methyl 4-amino-1-((*tert*-butyldimethylsilyl)oxy)-5-(4-hydroxyphenyl)-3-oxo-2,2a^1,3,9b-tetrahydro-1*H*-2a,5a-diazacyclopenta[*jk*]fluorene-2-carboxylate



Protected tetracyclic compound **II-78** (30.0 mg, 0.0515 mmol) was dissolved in CH_2Cl_2 (3 mL). Dibenzyl azodicarboxylate (23.0 mg, 0.0772 mmol), $Cu(OTf)_2$ (9.31 mg, 0.0258 mmol) and trifluoroethanol (5.07 µL, 0.0669 mmol) were added. It was stirred for 5 h before quenching with 10% aq. NH_3 solution (2 mL). The mixture was extracted with EtOAc (30 mL) and the organic layer was washed with brine, dried over Na_2SO_4 and concentrated. Column chromatography (30 % EtOAc in hexanes) gave the product **II-107** (31.0 mg, 69 %) as colorless oil (on TLC only visible at 366 nm). Dicarboxylate **II-107** (31.0 mg, 0.0352 mmol) was redissolved in MeOH (3 mL). Pd/C (10% Pd, 7.49 mg, 0.0704 mmol) was added and the mixture was stirred for 1.5 h under H_2 atmosphere (1 atm) before it was diluted with EtOAc (15 mL), filtered over celite and concentrated to give the product **II-108** as yellow oil (14.0 mg, 80%).

R_f: 0.50, 80% EtOAc in hexane.



[a]$_D^{24}$ = −246.7° (c = 0.33, MeOH).

^{1}H NMR (400 MHz, CD_3OD) δ/ppm = 7.65 (d, *J* = 8.8 Hz, 2H, 2xH-17), 7.10 (d, *J* = 7.4 Hz, 1H, H-6), 6.91 (d, *J* = 8.8 Hz, 2H, 2xH-18), 6.86 (t, *J* = 7.7 Hz, 1H, H-2), 6.74 (t, *J* = 7.9 Hz, 1H, H-1), 5.90 (d, *J* = 8.0 Hz, 1H, H-3), 5.80 (d, *J* = 6.2 Hz, 1H, H-7), 4.88 (s, 1H, H-9), 4.51 (s, 1H, H-10), 3.99 (d, *J* = 6.2 Hz, 1H, H-8), 3.70 (s, 2H, NH_2), 3.17 (s, 3H, 3xH-12), 1.01 (s, 9H, 9xH-26), 0.30 (s, 3H, 3xH-25), 0.28 (s, 3H, 3xH-25).

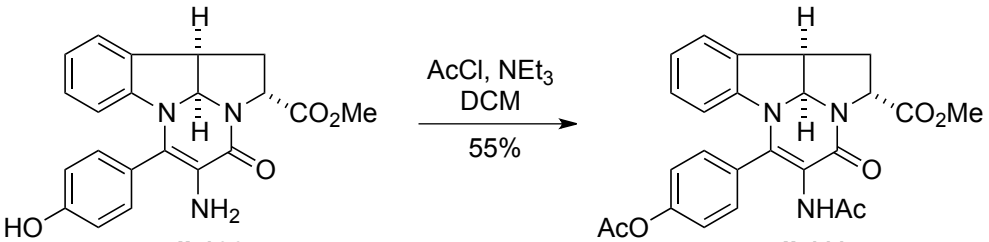
^{13}C NMR (101 MHz, CD_3OD) δ/ppm = 169.46 (C-11), 164.11 (C-13), 159.52 (C-19), 150.31 (C-4), 131.65 (C-17), 129.83 (C-2), 129.76 (C-5), 128.25 (C-15), 126.65 (C-16), 125.46 (C-6), 125.34 (C-14), 121.90 (C-1), 117.05 (C-18), 113.34 (C-3), 81.91 (C-9), 80.86 (C-7), 70.04 (C-10), 55.70 (C-8), 52.69 (C-12), 26.24 (C-26), 18.98 (C-27), -4.71 (C-25), -4.80 (C-25).

IR ($\tilde{\nu}$ /cm^{-1}): 3301, 2949, 2855, 1736, 1639, 1602, 1511, 1476, 1459, 1434, 1360, 1300, 1260, 1168, 1088.

HRMS (ESI): calculated for $C_{27}H_{34}N_3O_5Si$ $[M+H]^+$ 508.2262; found: 508.2260.

Corresponding *para*-nitro benzoyl compound **II-109** was synthesized according to the procedure of **II-86**. Crystals suitable for X-ray crystallography were obtained after slow evaporation of MeOH.

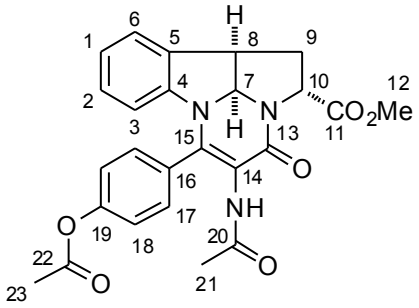
(2*R*,2a^1*R*,9b*R*)-Methyl 4-acetamido-5-(4-acetoxyphenyl)-3-oxo-2,2a^1,3,9b-tetrahydro-1*H*-2a,5a-diazacyclopenta[*jk*]fluorene-2-carboxylate



II-106 **II-111**

Enamine **II-106** (120 mg, 0.318 mmol) was dissolved in CH_2Cl_2 (4 mL). NEt_3 (148 µL, 1.07 mmol) was added and the solution was cooled to 0 °C before AcCl (76.2 µL, 1.07 mmol) was added. The solution was stirred for 2 h at 0 °C before quenching with sat. aq. NH_4Cl solution (4 mL). The mixture was extracted with EtOAc (20 mL), washed with brine, dried over Na_2SO_4 and concentrated in vacuo. Column chromatography (2% MeOH in CH_2Cl_2) gave the diacetylated product **II-111** as a yellow oil (80.0 mg, 55%).

R_f: 0.30, 2% MeOH in DCM.



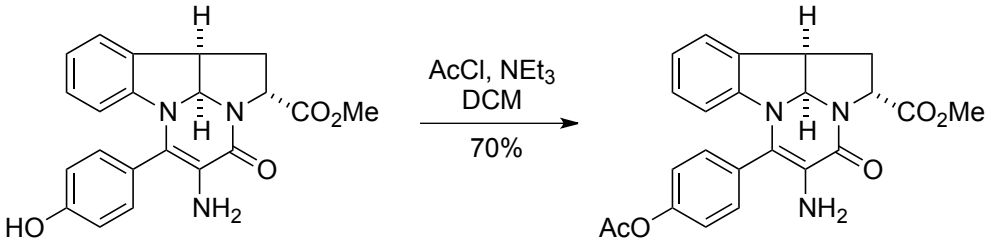
^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 7.64 (d, *J* = 8.7 Hz, 2H, 2xH-17), 7.40 (s, 1H, NH), 7.24 – 7.12 (m, 3H, 2xH-18, H-6), 6.93 – 6.81 (m, 2H, H-1, H-2), 6.02 (d, *J* = 7.2 Hz, 1H, H-7), 5.69 (d, *J* = 9.1 Hz, 1H, H-3), 4.43 (dd, *J* = 8.6, 6.1 Hz, 1H, H-10), 4.27 – 4.13 (m, 1H, H-8), 3.80 (s, 3H, 3xH-12), 2.73 – 2.62 (m, 1H, H-9α), 2.61 – 2.51 (m, 1H, H-9β), 2.32 (s, 3H, 3xH-23), 1.93 (s, 3H, 3xH-21).

^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm = 171.87 (C-11), 168.96 (C-22), 167.58 (C-20), 160.76 (C-13), 152.12 (C-19), 145.35 (C-4), 142.71 (C-15), 133.08 (C-5), 131.15 (C-16), 130.36 (C-17), 128.81 (C-2), 124.94 (C-6), 122.50 (C-1), 122.15 (C-18), 113.28 (C-14), 112.98 (C-3), 79.32 (C-7), 57.05 (C-10), 52.83 (C-12), 44.45 (C-8), 35.62 (C-9), 23.66 (C-21), 21.41 (C-23).

IR ($\tilde{\nu}$ /cm^{-1}): 3256, 2954, 2245, 1745, 1630, 1601, 1504, 1477, 1460, 1432, 1367, 1270, 1164, 1016, 909.

HRMS (ESI): calculated for $C_{25}H_{23}N_3O_6Na$ $[M+Na]^+$ 484.1479; found: 484.1481.

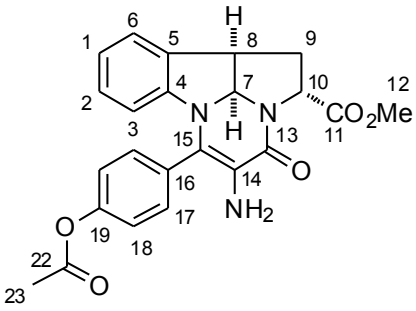
(2*R*,2a^1*R*,9b*R*)-Methyl 5-(4-acetoxyphenyl)-4-amino-3-oxo-2,2a^1,3,9b-tetrahydro-1*H*-2a,5a-diazacyclopenta[*jk*]fluorene-2-carboxylate



II-106 **II-110**

Enamine **II-106** (36.0 mg, 0.0954 mmol) was dissolved in CH_2Cl_2 (1 mL). NEt_3 (13.2 µL, 0.0954 mmol) was added and the solution was cooled to 0 °C before AcCl (6.76 µL, 0.0954 mmol) was added. The solution was stirred at 0 °C for 2 h before it was quenched with sat. aq. NH_4Cl solution (2 mL). It was extracted with EtOAc (15 mL), washed with brine, dried over Na_2SO_4 and concentrated. Column chromatography (60% EtOAc in hexanes) gave the monoacetylated product **II-110** as a yellow oil (28.0 mg, 70%).

R_f: 0.30, 60%EtOAc in hexanes.



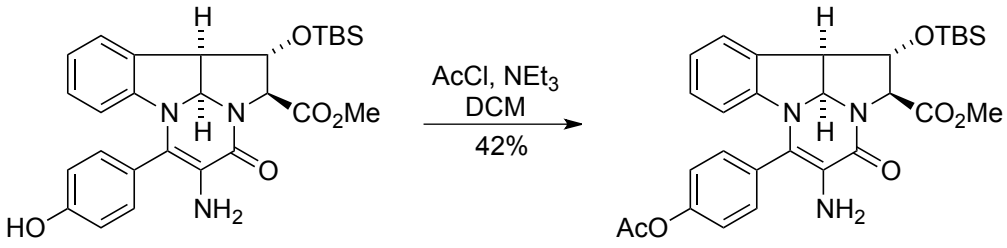
^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm = 7.79 (d, *J* = 8.7 Hz, 2H, 2xH-17), 7.19 (d, *J* = 8.7 Hz, 2H, 2xH-18), 7.14 (d, *J* = 7.3 Hz, 1H, H-6), 6.91 (t, *J* = 7.6 Hz, 1H, H-2), 6.83 (t, *J* = 7.1 Hz, 1H, H-1), 5.97 (d, *J* = 7.9 Hz, 1H, H-3), 5.81 (d, *J* = 6.4 Hz, 1H, H-7), 4.36 (t, *J* = 8.2 Hz, 1H, H-10), 4.09 (t, *J* = 7.0 Hz, 1H, H-8), 3.95 (s, 2H, NH_2), 3.79 (s, 3H, 3xH-12), 2.74 (ddd, *J* = 13.5, 8.9, 1.8 Hz, 1H, H-9α), 2.57 (dt, *J* = 13.5, 7.9 Hz, 1H, H-9β), 2.33 (s, 3H, 3xH-23).

^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm = 172.34 (C-11), 169.41 (C-22), 160.57 (C-13), 150.35 (C-19), 148.56 (C-4), 132.96 (C-16), 131.46 (C-5), 129.62 (C-17), 128.68 (C-2), 126.77 (C-14), 124.41 (C-6), 122.57 (C-18), 121.57 (C-15), 121.39 (C-1), 112.23 (C-3), 79.85 (C-7), 57.22 (C-10), 52.74 (C-12), 44.97 (C-8), 34.82 (C-9), 21.33 (C-23).

IR ($\tilde{\nu}$ /cm^{-1}): 3357, 2952, 2252, 1744, 1655, 1600, 1579, 1502, 1475, 1440, 1366, 1284, 1191, 1014, 907.

HRMS (ESI): calculated for $C_{23}H_{22}N_3O_5$ $[M+H]^+$ 420.1554; found: 420.1552.

(1*S*,2*S*,2a^1*R*,9b*R*)-Methyl 5-(4-acetoxyphenyl)-4-amino-1-((*tert*-butyldimethylsilyl)oxy)-3-oxo-2,2a^1,3,9b-tetrahydro-1*H*-2a,5a-diazacyclopenta[*jk*]fluorene-2-carboxylate

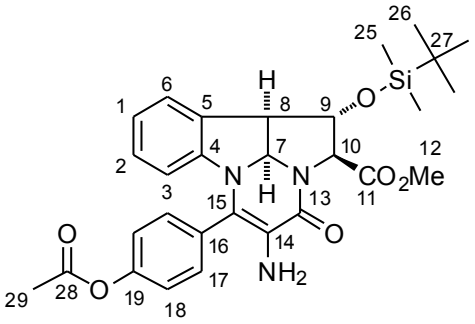


II-108 **II-116**

Enamine **II-108** (199 mg, 0.392 mmol) was dissolved in CH_2Cl_2 (5 mL) and cooled to 0 °C. NEt_3 (54.3 µL, 0.392 mmol) and AcCl (28.0 µL, 0.392 mmol) were added and it was stirred for 30 min before it was quenched with sat. aq. NH_4Cl solution (4 mL). It was extracted with EtOAc (50 mL), washed with brine, dried over Na_2SO_4 and concentrated. Column chromatography (40% EtOAc in hexanes) gave the product **II-116** as a yellow solid (90.0 mg, 42%).

R_f: 0.30, 40% EtOAc in hexanes.

$[a]_D^{22}$ = −208.9 ° (c = 0.14, MeOH).



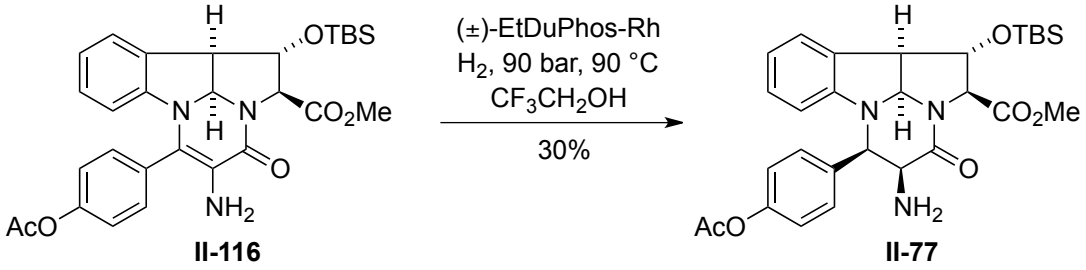
^{1}H NMR (400 MHz, CD_3OD) δ/ppm = 7.86 (d, *J* = 8.8 Hz, 2H, 2xH-17), 7.23 (d, *J* = 8.8 Hz, 2H, 2xH-18), 7.12 (d, *J* = 7.4 Hz, 1H, H-6), 6.87 (t, *J* = 7.7 Hz, 1H, H-2), 6.80 – 6.72 (m, 1H, H-1), 5.93 (d, *J* = 8.0 Hz, 1H, H-3), 5.84 (d, *J* = 6.1 Hz, 1H, H-7), 4.90 (s, 1H, H-9), 4.51 (s, 1H, H-10), 4.00 (d, *J* = 6.1 Hz, 1H, H-8), 3.19 (s, 3H, 3xH-12), 2.31 (s, 3H, 3xH-29), 1.01 (s, 9H, 9xH-26), 0.30 (s, 3H, 3xH-25) 0.28 (s, 3H, 3xH-25).

^{13}C NMR (101 MHz, CD_3OD) δ/ppm = 171.03 (C-28), 169.30 (C-11), 163.80 (C-13), 152.10 (C-19), 150.35 (C-4), 133.81 (C-16), 131.08 (C-17), 129.88 (C-5), 129.65 (C-2), 127.76 (C-14), 125.53 (C-6), 125.01 (C-15), 123.58 (C-18), 122.00 (C-1), 113.16 (C-3), 81.81 (C-9), 81.08 (C-7), 70.03 (C-10), 55.72 (C-8), 52.74 (C-12), 26.24 (C-26), 20.95 (C-29), 18.98 (C-27), -4.71 (C-25), -4.79 (C-25).

IR ($\tilde{\nu}$ /cm^{-1}): 2951, 2927, 2583, 2447, 1768, 1741, 1643, 1603, 1575, 1502, 1475, 1502, 1475, 1459, 1425, 1405, 1364, 1335, 1364, 1335.

HRMS (ESI): calculated for $C_{29}H_{36}N_3O_6Si$ $[M+H]^+$ 550.2368; found: 550.2364.

(1*S*,2*S*,2a^1*R*,4*S*,5*R*,9b*R*)-Methyl 5-(4-acetoxyphenyl)-4-amino-1-((*tert*-butyldimethylsilyl)oxy)-3-oxo-2,2a^1,3,4,5,9b-hexahydro-1*H*-2a,5a-diazacyclopenta[*jk*]fluorene-2-carboxylate

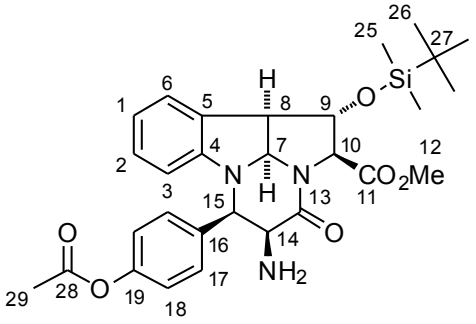


II-116 **II-77**

Enamine **II-116** (40.0 mg, 72.7 µmol) and (±)-1,2-bis(2,5-diethylphospholano)benzene)1,5-cyclooctadiene)rhodium(I) tetrafluoroborate (4.80 mg, 7.27 µmol) were placed in a high pressure reactor. Trifluoroethanol (9 mL) was added and it was stirred under H_2-pressure (90 bar) at 90 °C for 8 h before it was concentrated. Column chromatography (100% EtOAc) gave the product **II-77** as a colorless oil (12.0 mg, 30%).

R_f: 0.30, 2% MeOH in EtOAc.

[a]$_D^{22}$ = 64.4 ° (c = 0.45, CH_3OH).



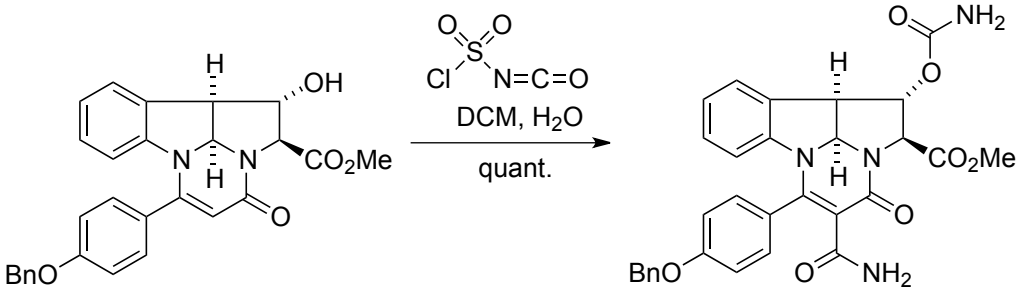
^{1}H NMR (400 MHz, CD_3OD) δ/ppm = 7.41 (d, *J* = 8.6 Hz, 2H, 2xH-17), 7.12 (d, *J* = 7.4 Hz, 1H, H-6), 7.03 (d, *J* = 8.2 Hz, 2H, 2xH-18), 6.73 (t, *J* = 7.5 Hz, 1H, H-2), 6.58 (t, *J* = 7.8 Hz, 1H, H-1), 5.93 (d, *J* = 8.4 Hz, 1H, H-7), 5.48 (d, *J* = 8.0 Hz, 1H, H-3), 5.17 (d, *J* = 7.3 Hz, 1H, H-15), 4.76 – 4.73 (m, 1H, H-9), 4.31 – 4.24 (m, 2H, H-10, H-14), 3.84 (dd, *J* = 8.3, 3.5 Hz, 1H, H-8), 3.68 (s, 3H, 3xH-12), 2.26 (s, 3H, 3xH-29), 0.99 (s, 9H, 9xH-26), 0.22 (s, 3H, 3xH-25), 0.15 (s, 3H, 3xH-25).

^{13}C NMR (101 MHz, CD_3OD) δ/ppm = 169.86 (C-13), 169.68 (C-28), 169.21 (C-11), 150.96 (C-19), 147.36 (C-4), 131.86 (C-16), 131.01 (C-17), 127.64 (C-2), 126.71 (C-5), 123.84 (C-6), 121.21 (C-18), 117.65 (C-1), 110.58 (C-3), 83.20 (C-9), 76.73 (C-7), 66.94 (C-10), 61.84 (C-15), 55.13 (C-14), 54.51 (C-8), 51.61 (C-12), 24.74 (C-26), 19.49 (C-29), 17.40 (C-27), -5.94 (C-25), -6.01 (C-25).

IR ($\tilde{\nu}$ /cm^{-1}): 2952, 2928, 2856, 1746, 1687, 1604, 1482, 1462, 1434, 1367, 1271, 1259, 1166, 1112, 1092, 1016.

HRMS (ESI): calculated for $C_{29}H_{38}N_3O_6Si$ $(M+H)^+$ 552.2524; found: 552.2521.

(1*S*,2*S*,2a^1*R*,9b*R*)-methyl 5-(4-(benzyloxy)phenyl)-4-carbamoyl-1-(carbamoyloxy)-3-oxo-2,2a^1,3,9b-tetrahydro-1*H*-2a,5a-diazacyclopenta[*jk*]fluorene-2-carboxylate

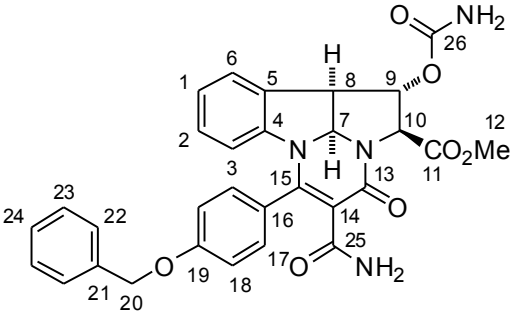


II-92 **II-120**

Tetracyclic compound **II-92** (5.00 mg, 10.7 µmol) was dissolved in CH_2Cl_2 (1 mL) and cooled to 0 °C. Chlorosulfonylisocyanat (2.04 µL, 23.4 µmol) was added and the mixture was stirred for 30 min at room temperature before water (50.0 µL) was added. The mixture was heated to 60 °C and CH_2Cl_2 was distilled from the reaction. Remaining aqueous phase was extracted with EtOAc (3 mL). The

organic layer was washed with sat. aq. $NaHCO_3$ solution, brine, dried over $NaSO_4$ and concentrated to give **II-120** as a colorless oil (6.03 mg, quant.)

R_f: 0.30, 5% MeOH in CH_2Cl_2.



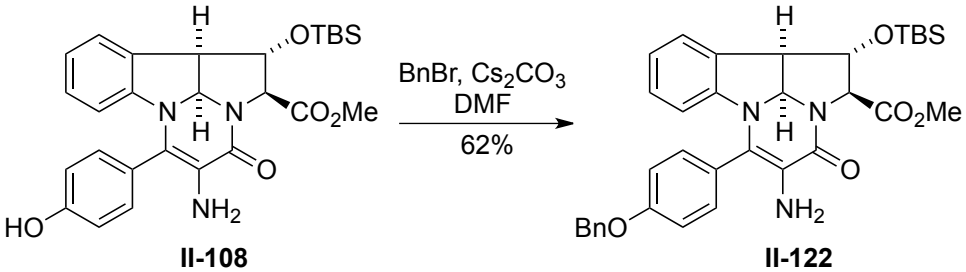
^{1}H NMR (400 MHz, CD_3OD) δ/ppm = 7.58 (d, *J* = 8.8 Hz, 2H, 2xH-17), 7.48 (d, *J* = 8.4 Hz, 2H, 2xH-22), 7.41 (d, *J* = 8.1 Hz, 3H, 2xH-23, H-24), 7.34 (d, *J* = 7.3 Hz, 1H, H-6), 7.15 (d, *J* = 9.0 Hz, 2H, 2xH-18), 6.99 – 6.92 (m, 1H, H-1), 6.87 (t, *J* = 7.7 Hz, 1H, H-2), 5.94 (d, *J* = 7.3 Hz, 1H, H-7), 5.65 (d, *J* = 8.1 Hz, 1H, H-3), 5.47 (s, 1H, H-9), 5.21 (s, 2H, 2xH-20), 4.74 (s, 1H, H-10), 4.37 (d, *J* = 7.3 Hz, 1H, H-8), 3.28 (s, 3H, 3xH-12).

^{13}C NMR (101 MHz, CD_3OD) δ/ppm = 170.16 (C-26), 169.35 (C-11), 165.74 (C-13), 163.55 (C-19), 160.44 (C-15), 158.05 (C-25), 145.97 (C-4), 138.13 (C-21), 133.27 (C-2), 132.06 (C-17), 130.17 (C-5), 129.60 (C-23), 129.11 (C-24), 128.76 (C-22), 127.01 (C-6), 126.88 (C-16), 125.04 (C-1), 116.48 (C-18), 114.72 (C-3), 109.43 (C-14), 82.18 (C-9), 80.20 (C-7), 71.27 (C-20), 67.31 (C-10), 53.10 (C-12), 52.64 (C-8).

IR ($\tilde{\nu}$ /cm^{-1}): 3332, 2924, 2555, 1731, 1641, 1601, 1523, 1478, 1461, 1425, 1391, 1328, 1298.

HRMS (ESI): calculated for $C_{30}H_{27}O_7N_4$ $[M+H]^+$ 555.1874; found 555.1877.

(1*S*,2*S*,2a^1*R*,9b*R*)-methyl 4-amino-5-(4-(benzyloxy)phenyl)-1-((*tert*-butyldimethylsilyl)oxy)-3-oxo-2,2a^1,3,9b-tetrahydro-1*H*-2a,5a-diazacyclopenta[*jk*]fluorene-2-carboxylate



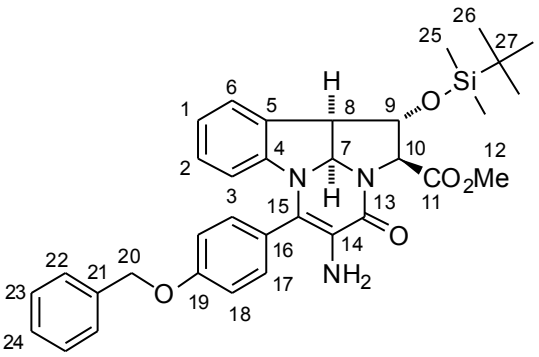
II-108 **II-122**

Enamine **II-108** (50.0 mg, 98.5 µmol) was dissolved in DMF (1 mL). Cs_2CO_3 (48.1 mg, 0.148 mmol) and BnBr (11.7 µL, 98.5 µmol) were added and the mixture was stirred at room temperature for 30 min. It was quenched with water (2 mL) and extracted with EtOAc (20 mL). The organic layers were washed with water and brine, dried over Na_2SO_4 and concentrated. Two column chromatographies

(1.: 30% EtOAc in hexanes, 2.: 2% MeOH in CH_2Cl_2) gave the product **II-122** as a yellow foam (36.5 mg, 62%).

R_f: 0.30, 30% EtOAc in hexanes.

$[a]_D^{23}$ = −166.9° (c = 0.35, MeOH).



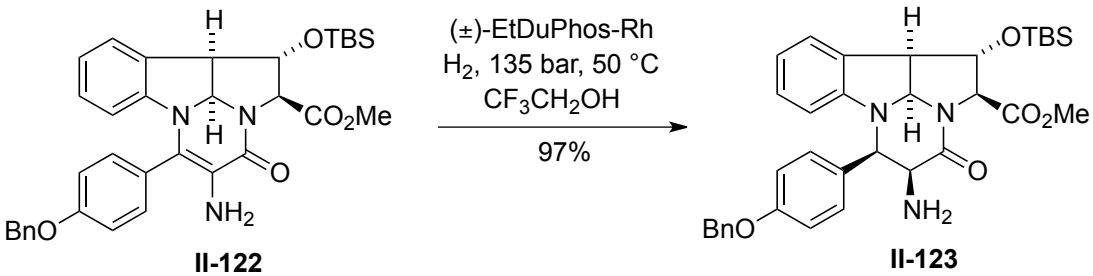
^{1}H NMR (400 MHz, CD_3OD) δ/ppm = 7.75 (d, *J* = 8.9 Hz, 2H, 2xH-17), 7.47 (d, *J* = 8.5 Hz, 2H, 2xH-22), 7.39 (t, *J* = 7.9 Hz, 2H, 2xH-23), 7.35 – 7.30 (m, 1H, H-24), 7.14 – 7.10 (m, 3H, H-6, 2xH-18), 6.85 (t, *J* = 7.7 Hz, 1H, H-2), 6.75 (t, *J* = 7.8 Hz, 1H, H-1), 5.88 (d, *J* = 7.9 Hz, 1H, H-3), 5.81 (d, *J* = 6.2 Hz, 1H, H-7), 5.16 (s, 2H, 2xH-20), 4.89 (s, 1H, H-9), 4.51 (s, 1H, H-10), 3.99 (d, *J* = 6.2 Hz, 1H, H-8), 3.66 (s, 1H, NH_2) 3.17 (s, 3H, 3xH-12), 1.01 (s, 9H, 9xH-26), 0.30 (s, 3H, 3xH-25), 0.28 (s, 3H, 3xH-25).

^{13}C NMR (101 MHz, CD_3OD) δ/ppm = 169.40 (C-11), 164.03 (C-13), 160.59 (C-19), 150.33 (C-4), 138.43 (C-21), 131.52 (C-17), 129.83 (C-2), 129.73 (C-5), 129.56 (C-23), 129.00 (C-24), 128.68 (C-22), 128.32 (C-16), 127.18 (C-15), 126.06 (C-14), 125.49 (C-6), 121.93 (C-1), 116.61 (C-18), 113.26 (C-3), 81.86 (C-9), 80.92 (C-7), 71.09 (C-20), 70.04 (C-10), 55.70 (C-8), 52.72 (C-12), 26.24 (C-26), 18.99 (C-27), -4.71 (C-25), -4.80 (C-25).

IR ($\tilde{\nu}$ /cm^{-1}): 3357, 2950, 2925, 2853, 1758, 1731, 1656, 1601, 1573, 1507, 1475, 1459, 1432, 1361, 1299, 1245, 1222, 1169, 1086, 1005.

HRMS (ESI): calculated for $C_{34}H_{40}N_3O_5Si$ $[M+H]^+$ 598.2732; found 598.2726.

(1*S*,2*S*,2a^1*R*,4*S*,5*R*,9b*R*)-methyl 4-amino-5-(4-(benzyloxy)phenyl)-1-((*tert*-butyldimethylsilyl)oxy)-3-oxo-2,2a^1,3,4,5,9b-hexahydro-1*H*-2a,5a-diazacyclopenta[*jk*]fluorene-2-carboxylate

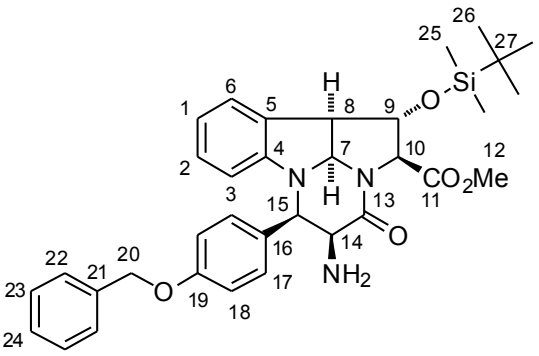


II-122 **II-123**

In a high pressure apparatus enamine **II-122** (100 mg, 0.168 mmol) was dissolved in trifluoroethanol (5 mL). (±)-1,2-Bis(2,5-diethylphospholano)benzene)1,5-cyclooctadiene)rhodium(I) tetrafluoroborate (11.1 mg, 0.0168 mmol) was added and argon was bubbled through the solution for 5 min, which then was stirred under H_2 atmosphere (135 bar) for 10 h at 50 °C. The reaction mixture was concentrated *in vacuo* and column chromatography (5% MeOH in EtOAc) gave the product **II-123** as a colorless oil (98.0 mg, 97%).

R_f: 0.10, EtOAc.

$[a]_D^{23}$ = 79.0° (c = 0.20, MeOH).



^{1}H NMR (500 MHz, CD_3OD) δ/ppm = 7.42 (d, *J* = 8.8 Hz, 2H, 2xH-22), 7.36 (t, *J* = 7.8 Hz, 2H, 2xH-23), 7.32 – 7.26 (m, 3H, 2xH-17, H-24), 7.10 (d, *J* = 7.4 Hz, 1H, H-6), 6.92 (d, *J* = 7.8 Hz, 2H, 2xH-18), 6.71 (t, *J* = 7.5 Hz, 1H, H-2), 6.57 (t, *J* = 7.8 Hz, 1H, H-1), 5.90 (d, *J* = 8.3 Hz, 1H, H-7), 5.47 (d, *J* = 8.0 Hz, 1H, H-3), 5.11 (d, *J* = 7.4 Hz, 1H, H-15), 5.06 (s, 2H, 2xH-20), 4.76 – 4.73 (m, 1H, H-9), 4.28 (d, *J* = 4.3 Hz, 1H, H-10), 4.23 (d, *J* = 7.4 Hz, 1H, H-14), 3.82 (dd, *J* = 8.2, 3.3 Hz, 1H, H-8), 3.66 (s, 3H, 3xH-12), 0.99 (s, 9H, 9xH-26), 0.22 (s, 3H, 3xH-25), 0.15 (s, 3H, 3xH-25).

^{13}C NMR (126 MHz, CD_3OD) δ/ppm = 171.50 (C-13), 170.53 (C-11), 160.45 (C-19), 149.06 (C-4), 138.60 (C-21), 129.57 (C-22/23/24), 129.48 (C-17), 128.97 (C-22/23/24), 128.88 (C-2), 128.63 (C-18), 128.02 (C-5), 127.59 (C-16), 125.12 (C-6), 118.92 (C-1), 115.77 (C-22/23/24), 112.15 (3), 84.52 (C-9), 78.14 (C-7), 71.00 (C-20), 68.38 (C-10), 63.28 (C-15), 56.47 (C-14), 55.94 (C-8), 52.98 (C-12), 26.21 (C-26), 18.82 (C-27), -4.53 (C-25), -4.59 (C-25).

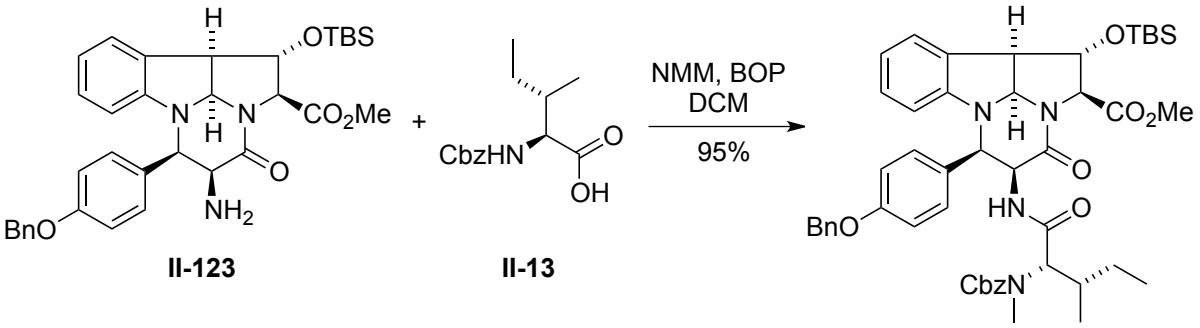
NOESY NOE between H-14 and H-7 and between H-14 and H-8

IR ($\tilde{\nu}$ /cm^{-1}): 3360, 3033, 2953, 2930, 2857, 1746, 1687, 1606, 1510, 1481, 1463, 1431, 1363, 1251, 1174, 1090, 1022.

HRMS (ESI): calculated for $C_{34}H_{42}N_3O_5Si$ $[M+H]^+$ 600.2888; found 600.2889.

Spectra were recorded in collaboration with Filip Bihelovic.

(1*S*,2*S*,2a^1*R*,4*S*,5*R*,9b*R*)-methyl 4-((2*S*,3*S*)-2-(((benzyloxy)carbonyl)(methyl)amino)-3-methylpentan amido)-5-(4-(benzyloxy)phenyl)-1-((*tert*-butyldimethylsilyl)oxy)-3-oxo-2,2a^1,3,4,5,9b-hexahydro-1*H*-2a,5a-diazacyclopenta[*jk*]fluorene-2-carboxylate

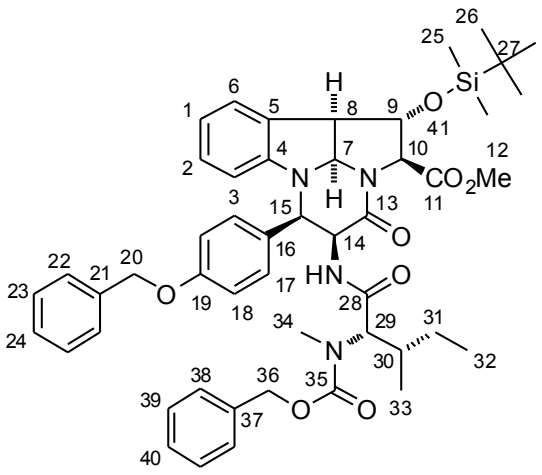


II-123 **II-13** **II-124**

Amine **II-123** (50.0 mg, 83.4 µmol), carboxylic acid **II-13** (46.6 mg, 0.167 mmol) and BOP (74.5 mg, 0.167 mmol) were dissolved in CH_2Cl_2 (1 mL). *N*-Methylmorpholine (36.7 µL, 0.334 mmol) was added and the mixture was stirred for 3 h at r.t.. The mixture was quenched with sat. aq. NH_4Cl solution (1 mL), extracted with EtOAc (10 mL), washed with 10% aq. HCl solution, sat. aq. $NaHCO_3$ solution and brine, dried over Na_2SO_4 and concentrated. Column chromatography (20% EtOAc in hexanes) gave the product as a colorless oil (68.0 mg, 95%).

R_f: 0.30, 40% EtOAc in hexanes.

$[a]_D^{23}$ = 113.3° (c = 0.10, MeOH).



^{1}H NMR (500 MHz, DMSO, 60 °C) δ/ppm = 7.44 – 7.18 (m, 10H, 2xH-22, 2xH-23, H-24, 2xH-38, 2xH-39, H-40), 7.11 (d, *J* = 7.4 Hz, 1H, H-6), 7.04 (d, *J* = 8.8 Hz, 2H, 2xH-17), 6.81 (d, *J* = 8.7 Hz, 2H, 2xH-18), 6.73 (t, *J* = 7.6 Hz, 1H, H-2), 6.61 – 6.49 (m, 2H, H-1, NH), 6.01 (d, *J* = 8.6 Hz, 1H, H-7), 5.47 (d, *J* = 7.9 Hz, 1H, H-3), 5.31 (d, *J* = 7.5 Hz, 1H, H-15), 5.23 (t, *J* = 7.0 Hz, 1H, H-14), 5.10 – 4.89 (m, 4H, 2xH-20, 2xH-36), 4.68 – 4.62 (m, 1H, H-9), 4.19 (d, *J* = 5.0 Hz, 1H, H-10), 4.16 (d, *J* = 10.9 Hz, 1H, H-29), 3.83 (dd, *J* = 8.5, 3.8 Hz, 1H, H-8), 3.64 (s, 3H, 3xH-12), 2.82 (s, 3H, 3xH-34), 2.04 – 1.90 (m, 1H, H-30), 1.38 – 1.14 (m, 2H, 2xH-31), 0.96 (s, 9H, 9xH-26), 0.84 – 0.73 (m, 6H, 3xH-32, 3xH-33), 0.18 (s, 3H, 3xH-25), 0.11 (s, 3H, 3xH-25).

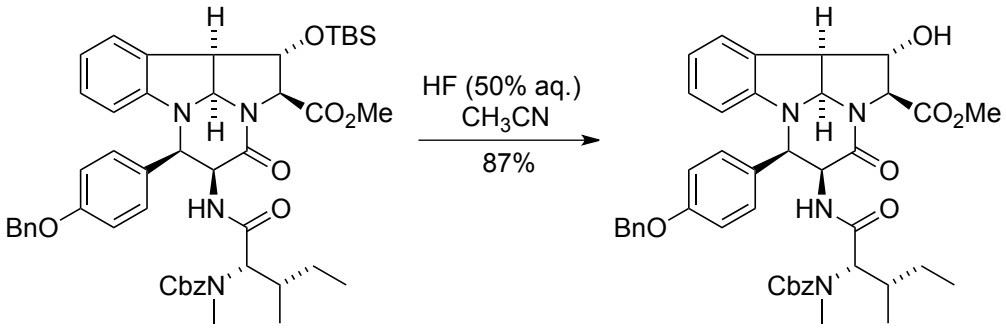
^{13}C NMR (126 MHz, DMSO, 60 °C) δ/ppm = 168.84 (C-28), 168.38 (C-11), 164.63 (C-13), 157.96 (C-19), 155.62 (C-35), 147.17 (C-4), 136.77 (C-21/37), 136.50 (C-21/37), 130.07 (C-17), 128.01 (C-22/23/24/38/39/40), 127.52 (C-2), 127.42 (C-22/23/24/38/39/40), 127.34 (C-22/23/24/38/39/40), 127.20 (C-22/23/24/38/39/40), 126.80(C-22/23/24/38/39/40), 126.80 (C-5), 126.39 (C-22/23/24/38/39/40), 123.69 (C-6), 117.19 (C-1), 114.07 (C-18), 109.86 (C-3), 82.96 (C-9), 75.79 (C-7), 69.12 (C-20/36), 66.18 (C-20/36), 66.18 (C-10), 61.75 (C-29), 58.03 (C-15), 53.63 (C-8), 53.01 (C-14), 51.89 (C-12), 31.40 (C-30), 29.39 (C-34), 25.27 (C-26), 23.87 (C-31), 17.31 (C-27), 14.88 (C-33), 9.71 (C-32), -5.03 (C-25), -5.19 (C-25).

IR ($\tilde{\nu}$ /cm^{-1}): 3398, 3060, 3033, 2956, 2931, 2892, 2858, 1748, 1698, 1607, 1511, 1481, 1435, 1366, 1306, 1250.

HRMS (ESI): calculated for $C_{49}H_{61}N_4O_8Si$ $[M+H]^+$ 861.4253; found 861.4261.

Spectra were recorded in collaboration with Filip Bihelovic.

(1*S*,2*S*,2a^1*R*,4*S*,5*R*,9b*R*)-methyl 4-((2*S*,3*S*)-2-(((benzyloxy)carbonyl)(methyl)amino)-3-methylpentanamido)-5-(4-(benzyloxy)phenyl)-1-hydroxy-3-oxo-2,2a^1,3,4,5,9b-hexahydro-1*H*-2a,5a-diazacyclopenta[*jk*]fluorene-2-carboxylate

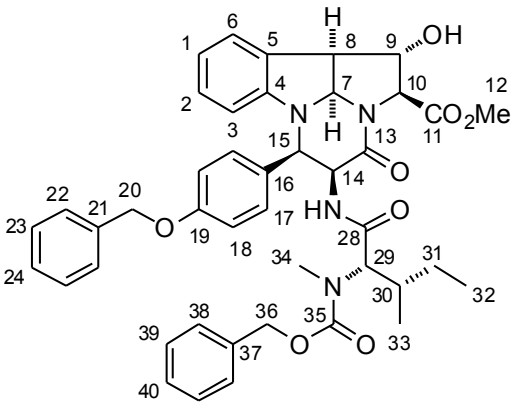


II-124 **II-125**

Protected compound **II-124** (380 mg, 0.441 mmol) was dissolved in CH_3CN (4 mL). HF (50% aq., 1.5 mL) was added and the mixture was stirred for 1 h at 45 °C. It was diluted with EtOAc (10 mL), washed with sat. aq. $NaHCO_3$ solution and brine, dried over Na_2SO_4 and concentrated. Column chromatography (50% EtOAc in hexanes) gave the product **II-125** as a colorless oil (292 mg, 87%).

R_f: 0.30, 50% EtOAc in hexanes.

$[a]_D^{23}$ = 149.2° (c = 0.50, MeOH).



^{1}H NMR (500 MHz, DMSO, 60 °C) δ/ppm = 7.44 – 7.23 (m, 10H, 2xH-22, 2xH-23, H-24, 2xH-38, 2xH-39, H-40), 7.17 (d, *J* = 7.2 Hz, 1H, H-6), 7.05 (d, *J* = 8.6 Hz, 2H, 2xH-17), 6.80 (d, *J* = 8.5 Hz, 2H, 2xH-18), 6.71 (t, *J* = 7.6 Hz, 1H; H-2), 6.54 (t, *J* = 7.3 Hz, 2H, H-1, NH), 6.20 (d, *J* = 5.3 Hz, 1H, OH), 5.97 (d, *J* = 8.6 Hz, 1H, H-7), 5.47 (d, *J* = 7.5 Hz, 1H, H-3), 5.32 (d, *J* = 7.3 Hz, 1H, H-15), 5.21 (t, *J* = 6.8 Hz, 1H, H-14), 4.99 (s, 3H, 2xH-20, 2xH-36), 4.50 (d, *J* = 4.7 Hz, 1H, H-9), 4.16 (d, *J* = 5.5 Hz, 2H, H-10, H-29), 3.78 (dd, *J* = 8.4, 4.3 Hz, 1H, H-8), 3.63 (s, 3H, 3xH-12), 2.83 (s, 3H,3xH-34), 1.98 (br s, 1H, H-30), 1.35 – 1.27 (m, 1H, H-31α), 1.00 – 0.91 (m, 1H, H-31β), 0.86 – 0.75 (m, 6H, 3xH-32, 3xH-33).

^{13}C NMR (126 MHz, DMSO, 60 °C) δ/ppm = 168.87 (C-28), 168.63 (C-11), 164.46 (C-13), 157.92 (C-19), 155.40 (C-35, detected by HMBC), 146.95 (C-4), 136.77 (C-21/37), 136.49 (C-21/37), 130.07 (C-17), 128.01 (C-22/23/38/39, 2 signals), 127.81 (C-5), 127.42 (C-24/40), 127.34 (C-24/40), 127.21 (C-2), 126.83 (C-22/23/38/39, 2 signals), 126.50 (C-16), 123.75 (C-6), 117.13 (C-1), 114.01 (C-18), 109.55 (C-3), 81.99 (C-9), 75.74 (C-7), 69.11 (C-20/36), 66.20 (C-20/36), 65.48 (C-10), 61.78 (C-29), 57.96 (C-15), 53.04 (C-14), 52.94 (C-8), 51.79 (C-12), 31.48 (C-30), 29.41 (C-34), 23.88 (C-31), 14.88 (C-33), 9.71 (C-32).

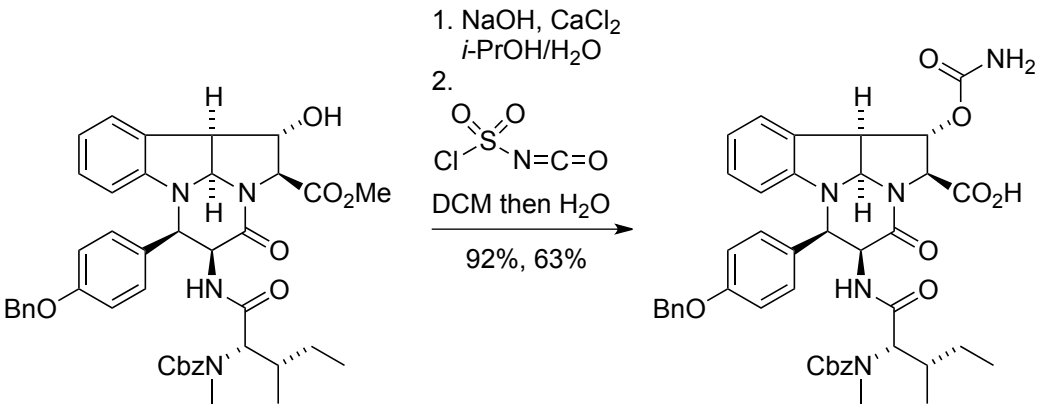
Inseparable from EtOAc, even after 2 days under vacuum of 10^{-3} mbar and coevaporation with toluene.

IR ($\tilde{\nu}$ /cm^{-1}): 3395, 2962, 1748, 1692, 1671, 1607, 1512, 1480, 1439, 1401, 1370, 1308, 1242, 1175, 1114.

HRMS (ESI): calculated for $C_{43}H_{46}N_4O_8Si$ $[M+Na]^+$ 769.3208; found 769.3189.

Spectra were recorded in collaboration with Filip Bihelovic.

(1*S*,2*S*,2a^1*R*,4*S*,5*R*,9b*R*)-4-((2*S*,3*S*)-2-(((benzyloxy)carbonyl)(methyl)amino)-3-methylpentanamido)-5-(4-(benzyloxy)phenyl)-1-(carbamoyloxy)-3-oxo-2,2a^1,3,4,5,9b-hexahydro-1*H*-2a,5a-diazacyclopenta[*jk*]fluorene-2-carboxylic acid

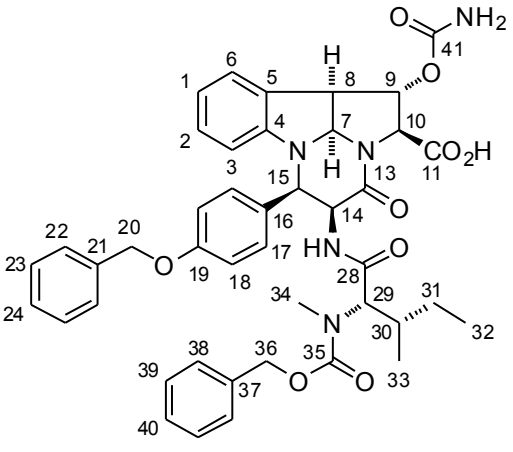


II-125 **II-126**

Methylester **II-125** (100 mg, 0.134 mmol) was dissolved in $CaCl_2$ solution (10 mL, 0.8 M $CaCl_2$ in *i*-PrOH/H_2O 7:3). NaOH (13.4 mg, 0.335 mmol) was dissolved in H_2O (1 mL) and added. The mixture was stirred for 4 h, before it was acidified with 10% aq. HCl solution and extracted with EtOAc (50 mL). The organic layer was washed with brine, dried over Na_2SO_4 and concentrated to give free acid as a colorless solid (90.5 mg, 92%) that (90.5 mg, 0.124 mmol) was directly dissolved in CH_2Cl_2 (6 mL) and THF (1 mL). Chlorosulfonylisocyanate (21.5 µL, 0.250 mmol) was added and the mixture was stirred for 15 min at room temperature. THF (10 mL) and H_2O (10 mL) were added and the mixture was stirred for 10 min at 40 °C. It was extracted with EtOAc (10 mL), washed with brine, dried over Na_2SO_4 and concentrated. Column chromatography (1. Column: 0.4% formic acid in EtOAc, 2. Column: 100% EtOAc → 0.4% formic acid in EtOAc, 3. Column 50% EtOAc in hexanes → 0.4% formic acid in EtOAc) gave the product **II-126** as a colorless solid (60.5 mg, 63%).

R_f: broad spot on TLC.

$[a]_D^{23}$ = 95.6° (c = 0.52, MeOH).



^{1}H NMR (500 MHz, DMSO, 60 °C) δ/ppm = 7.41 – 7.22 (m, 10H, 2xH-22, 2xH-23, H-24, 2xH-38, 2xH-39, H-40), 7.24 (d, *J* = 7.2 Hz, 1H, H-6), 7.17 (d, *J* = 8.5 Hz, 2H, 2xH-17), 6.75 (d, *J* = 7.4 Hz, 2H, 2xH-18), 6.68 (t, *J* = 7.7 Hz, 1H, H-2), 6.55 (t, *J* = 7.2 Hz, 1H, H-1), 6.48 (d, *J* = 5.8 Hz, 1H, NH), 5.99 (d, *J* = 8.5 Hz, 1H, H-7), 5.46 – 5.32 (m, 3H,

H-3, H-9, H-15), 5.27 (t, *J* = 6.9 Hz, 1H, H-14), 5.01 – 4.96 (m, 4H, 2xH-20, 2xH-36), 4.28 (d, *J* = 3.9 Hz, 1H, H-10), 4.14 (d, *J* = 10.3 Hz, 1H, H-29), 3.98 (d, *J* = 8.3 Hz, 1H, H-8), 2.80 (s, 3H, 3xH-34), 1.98 – 1.94 (m, 1H, H-30), 1.33 – 1.26 (m, 1H, H-31α), 0.96 – 0.92 (m, 1H, H-31β), 0.82 – 0.76 (m, 6H, 3xH-32, 3xH-33).

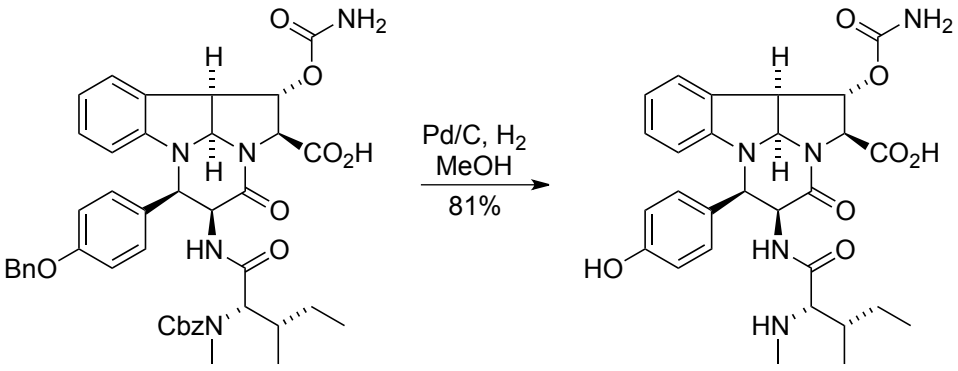
^{13}C NMR (126 MHz, DMSO, 60 °C) δ/ppm = 168.88 (C-11), 168.75 (C-28), 164.77 (C-13), 157.90 (C-19), 156.80 (C-35), 155.23 (C-41), 147.56 (C-4), 136.78 (C-21/37), 136.49 (C-21/37), 130.60 (C-17), 128.05 (C-22/23/38/39), 128.03 (C-22/23/38/39), 127.44 (C-24/40), 127.38 (C-24/40), 127.24 (C-22/23/38/39), 127.21 (C-2), 126.85 (C-22/23/38/39), 126.20 (C-16), 125.98 (C-5), 124.49 (C-6), 117.46 (C-1), 113.90 (C-18), 110.46 (C-3), 81.80 (C-9), 75.80 (C-7), 69.10 (C-20/36), 66.20 (C-20/36), 64.12 (C-10), 61.86 (C-29), 58.61 (C-15), 53.22 (C-14), 51.71 (C-8), 31.39 (C-30), 29.41 (C-34), 23.89 (C-31), 14.95 (C-33), 9.74 (C-32).

IR ($\tilde{\nu}$ /cm^{-1}): 3394, 3193, 3063, 3034, 2964, 2931, 2878, 2502, 2257, 2127, 1736, 1693, 1607, 1512, 1480, 1441, 1390, 1311, 1244, 1180, 1154.

HRMS (ESI): calculated for $C_{43}H_{45}N_5O_9Na$ $[M+Na]^+$ 798.3109; found 798.3093.

Spectra were recorded in collaboration with Filip Bihelovic.

(1*S*,2*S*,2a^1*R*,4*S*,5*R*,9b*R*)-1-(carbamoyloxy)-5-(4-hydroxyphenyl)-4-((2*S*,3*S*)-3-methyl-2-(methylamino)pentanamido)-3-oxo-2,2a^1,3,4,5,9b-hexahydro-1*H*-2a,5a-diazacyclopenta[*jk*]fluorene-2-carboxylic acid (Crocagin)



II-126 **II-7**

Protected crocagin (**II-26**) (30.0 mg, 0.0387 mmol) was dissolved in MeOH (3 mL). Pd/C (10% Pd, 16.5 mg, 0.155 mmol) was added and the mixture was stirred for 1.5 h under H_2 atmosphere (1 atm)

before it was diluted with EtOAc (15 mL), filtered over celite and concentrated to give the product as a colorless solid (17.0 mg, 81%).

R_f: broad spot on TLC.

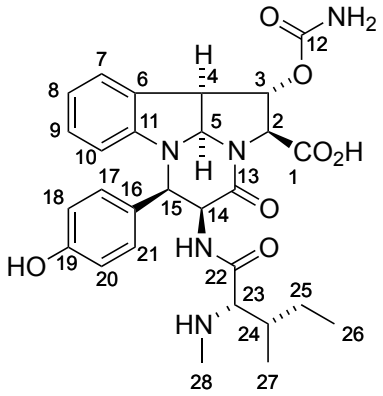
$[a]_D^{24}$ = 129.5° (c = 0.11, MeOH).

^{1}H NMR (400 MHz, DMSO) δ/ppm

# proton	isolated with multiplicity and coupling constant (Hz)	synthesized with multiplicity and coupling constant (Hz)	HMBC	COSY	ROESY
2	4.20 d (3.7)	4.10 d (2.9)	C-3	H-3	
3	5.33 dd (3.7, 2.2)	5.29 ?		H-2	H-4
4	3.91 br d (8.1)	3.80 d (8.4)	C-3, C-6	H-5	H-3, H-5
5	5.96 d (8.1)	5.89 d (8.4)	C-6, C-11	H-4	H-4, H-14, H-15
7	7.22 d (7.7)	7.21 d (7.3)	C-9, C-11	H-8, H-9	H-8, H-10
8	6.51 dd (7.7, 7.7)	6.48 t (7.3)	C-6, C-9, C-10	H-7, H-10	H-7
9	6.66 dd (7.7, 7.7)	6.61 t (7.6)	C-7, C-11	H-7, H-10	H-10
10	5.35 d (7.7)	5.28 ?	C-6, C-8	H-8, H-9	H-7, H-9
14	5.22 dd (7.3, 7.3)	5.13 ?	C-15, C-16		H-5, NH
15	5.14 d (7.3)	5.13 ?	C-14		H-5, NH
17/21	6.55 m	6.75 m			
18/20	7.13 m	6.96 m			
23	2.72 m	2.64 d (4.8)	C-22, C-24, C-25, C-27, C-28	H-24	NH
24	1.48 m	1.45 m		H-23, H-25, H-27	H-27
25	1.26 m 0.97 m	1.22 m 0.94 m	C-24	H-24, H-26	H-26
26	0.78 t (7.3)	0.77 t (7.3)	C-24, C-25	H-25	H-25
27	0.75 d (6.6)	0.72 d (6.9)	C-23, C-24, C-25	H-24	H-24, NH
28	2.15 s	2.13 s	C-23		NH
NH	7.35 d (7.3)	7.31 d (6.6)		H-14/15	H-14, H-15, H-23, H-27, H-28
OH	9.33 brs	9.34 brs			

^{13}C NMR (126 MHz, DMSO) δ/ppm

# carbon	isolated	synthesized
1	169.3	170.6 (from HMBC)
2	64.6	66.3
3	82.0	82.9
4	51.9	52.3
5	75.9	75.9
6	126.3	127.1
7	124.7	124.8
8	117.5	117.3
9	127.4	126.6
10	110.8	110.7
11	148.1	148.4
12	155.6	155.9
13	165.6	165.2
14	53.2	53.2
15	60.0	60.2
16	124.6	124.7
17/21	114.5	not detected
18/20	135.8	136.2
19	157.0	156.9
22	172.2	172.5
23	69.0	69.5
24	37.3	37.5
25	24.4	24.4
26	11.6	11.8
27	15.3	15.6
28	35.1	35.4



Spectrum of isolated compound was recorded at 60 °C. Isolated compound refers to crocagin-acetate.

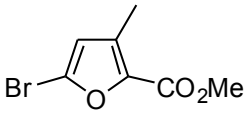
^{13}C shifts of isolated compound were extracted from HMBC/HSQC.

IR ($\tilde{\nu}$ /cm^{-1}): 3276, 3179, 2962, 2361, 1717, 1664, 1597, 1516, 1477, 1461, 1386, 1366, 1331, 1270, 1242, 1180, 1050.

HRMS (ESI): calculated for $C_{28}H_{34}N_5O_7$ $[M+H]^+$ 552.2453; found 552.2441.

5 Appendices

5.1 NMR Spectra

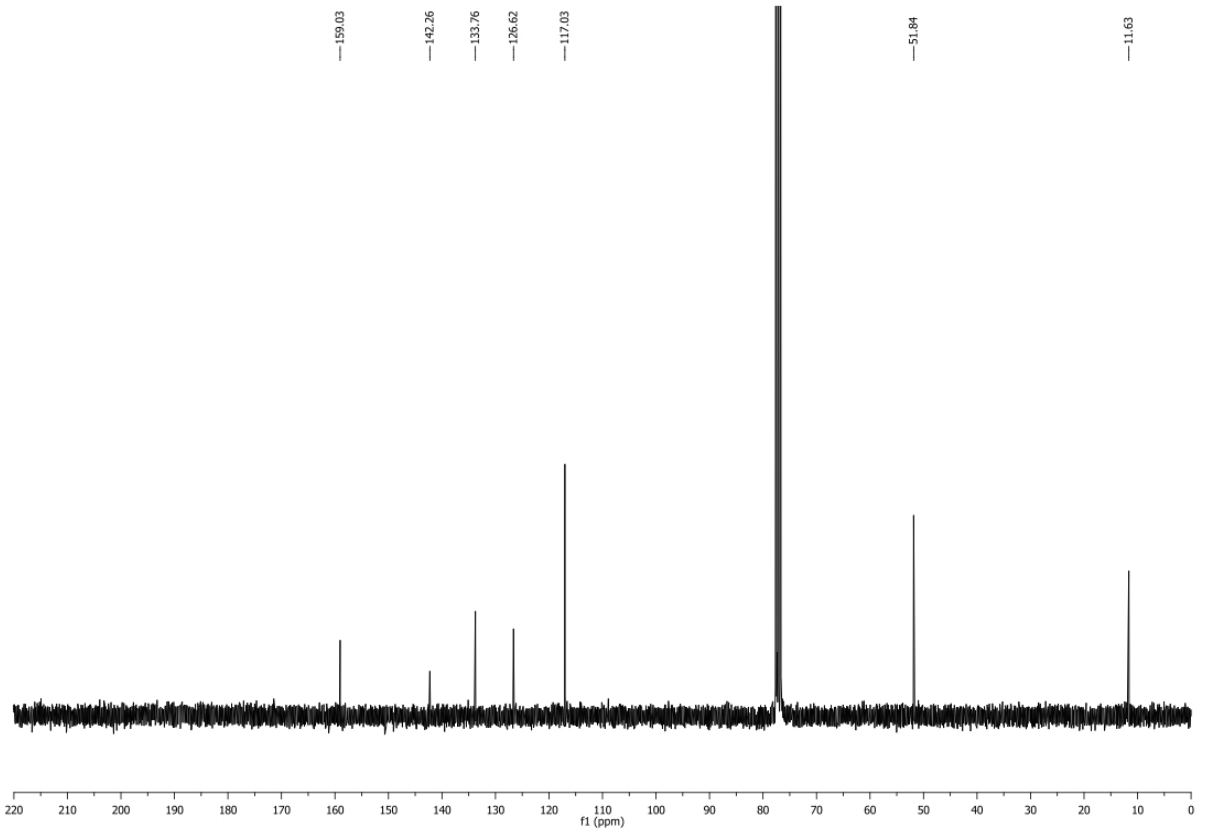


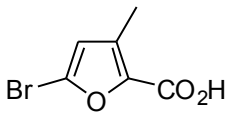
I-32

$CDCl_3$

^{1}H 300 MHz

^{13}C 75 MHz



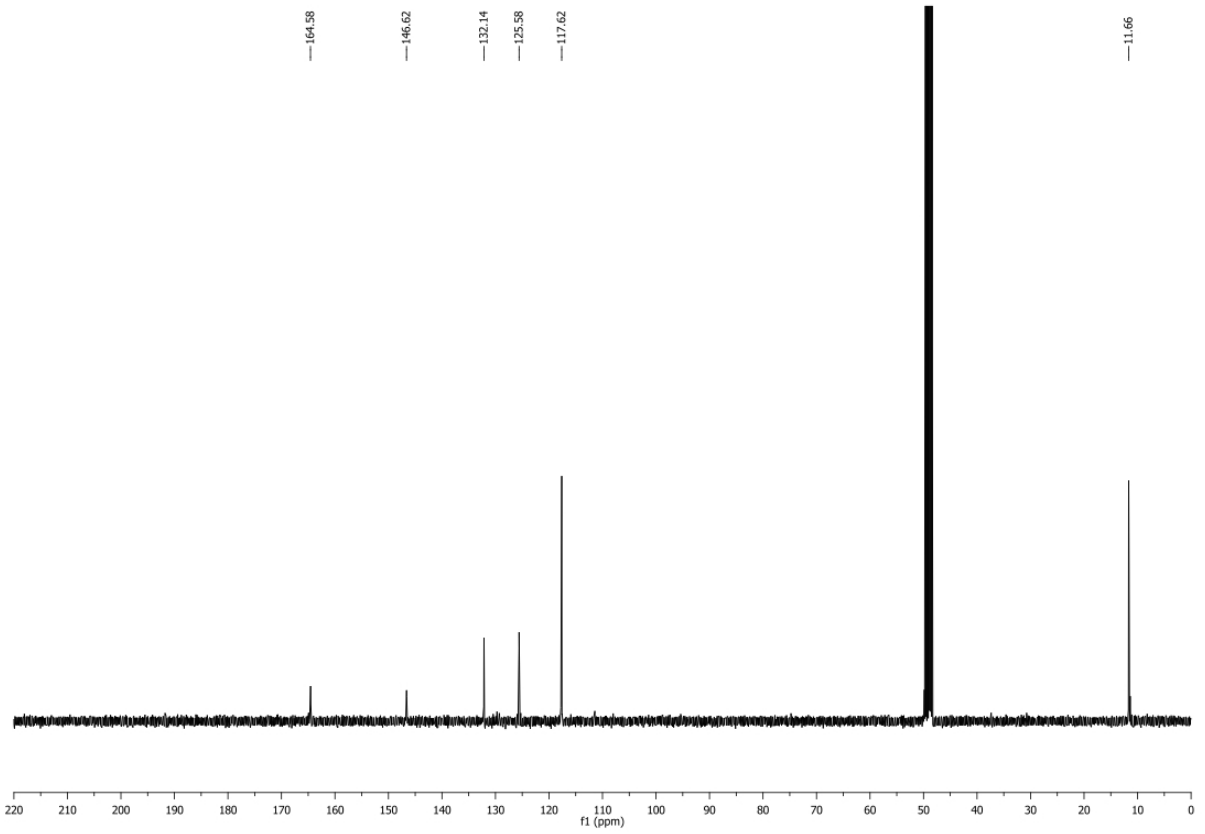


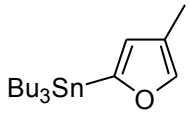
I-33

CD_3OD

^{1}H 400 MHz

^{13}C 100 MHz



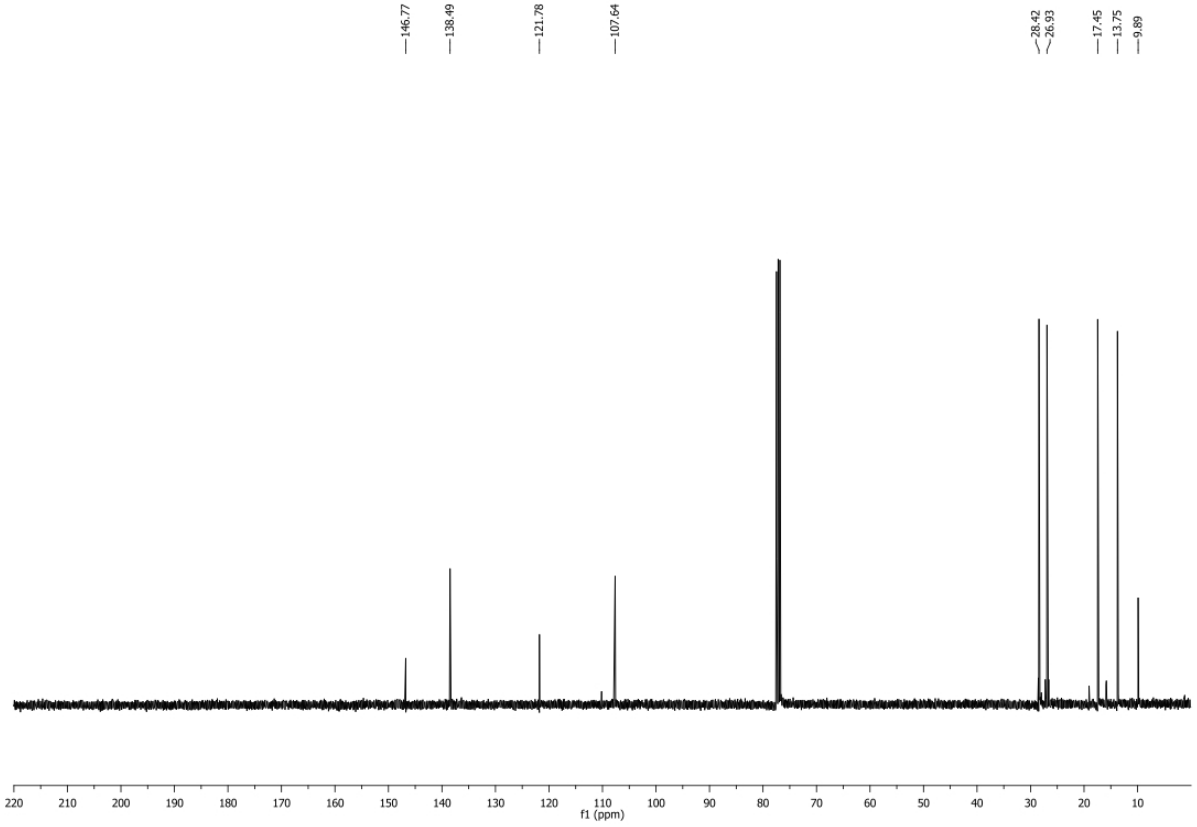


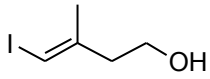
I-35

$CDCl_3$

^{1}H 400 MHz

^{13}C 100 MHz



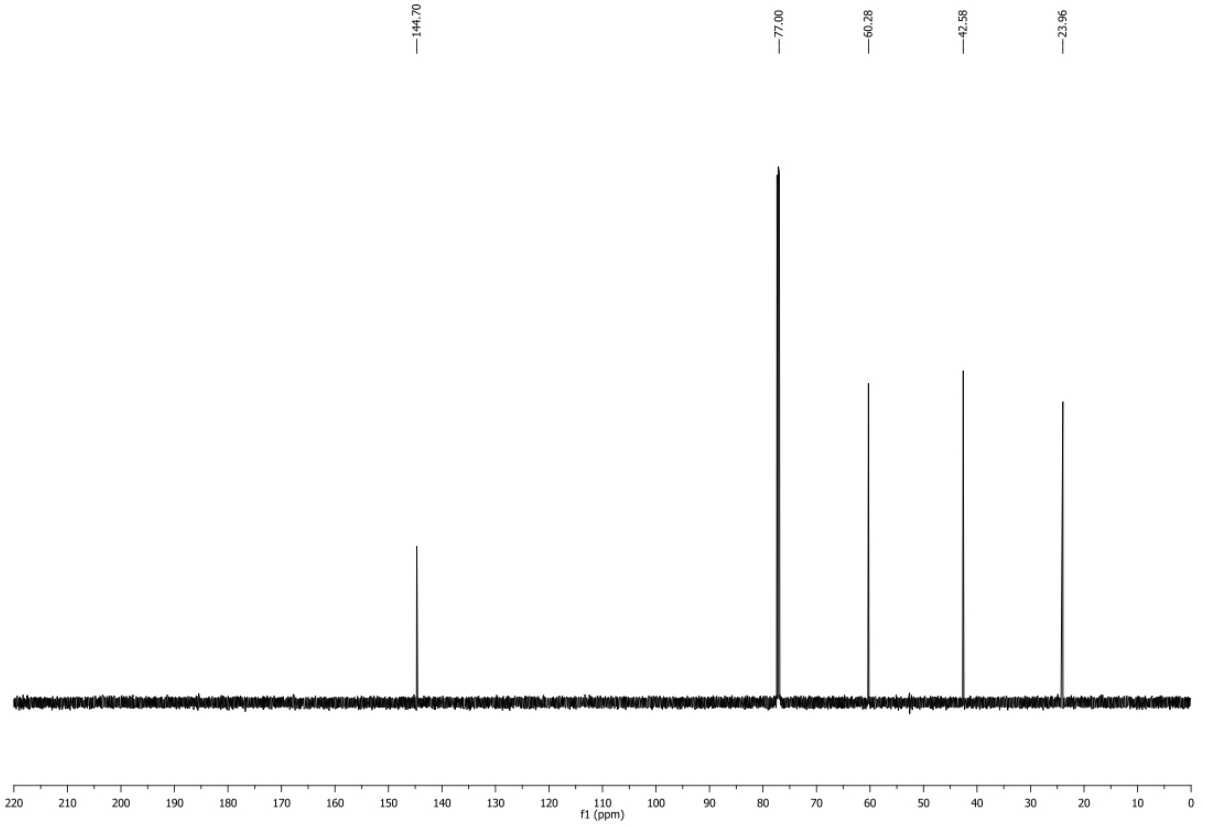


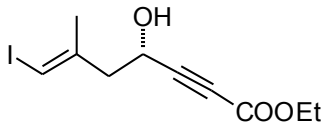
I-37

$CDCl_3$

^{1}H 600 MHz

^{13}C 150 MHz



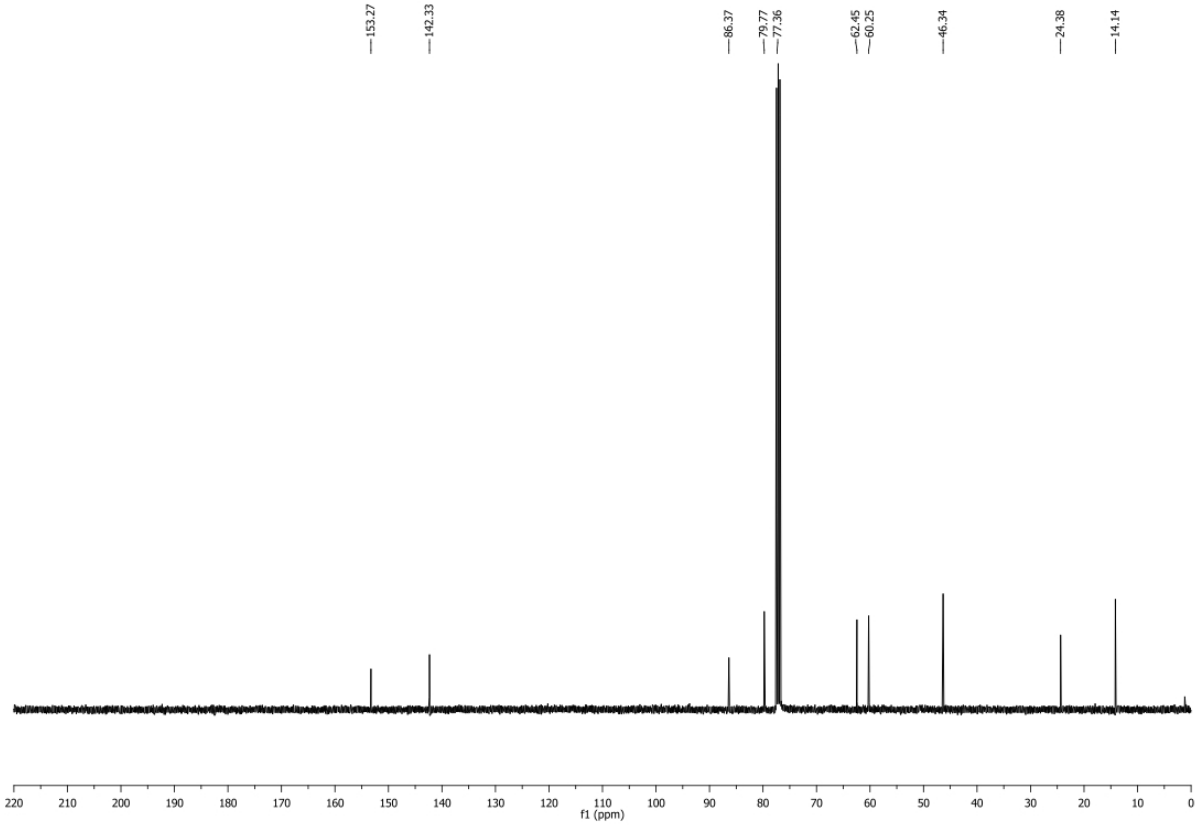


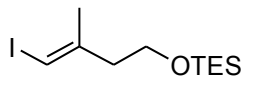
I-21

$CDCl_3$

^{1}H 400 MHz

^{13}C 100 MHz



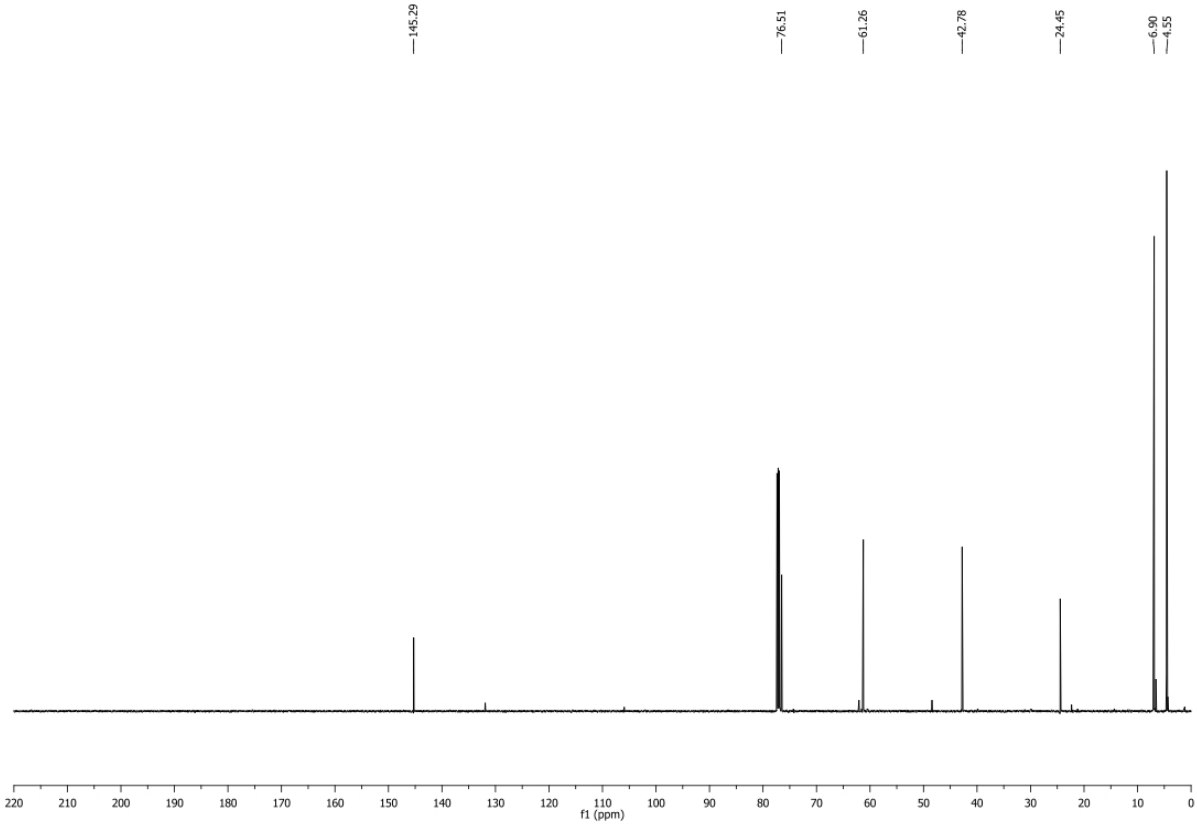


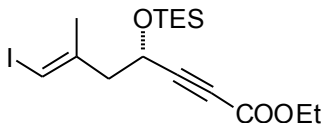
I-43

$CDCl_3$

^{1}H 600 MHz

^{13}C 150 MHz



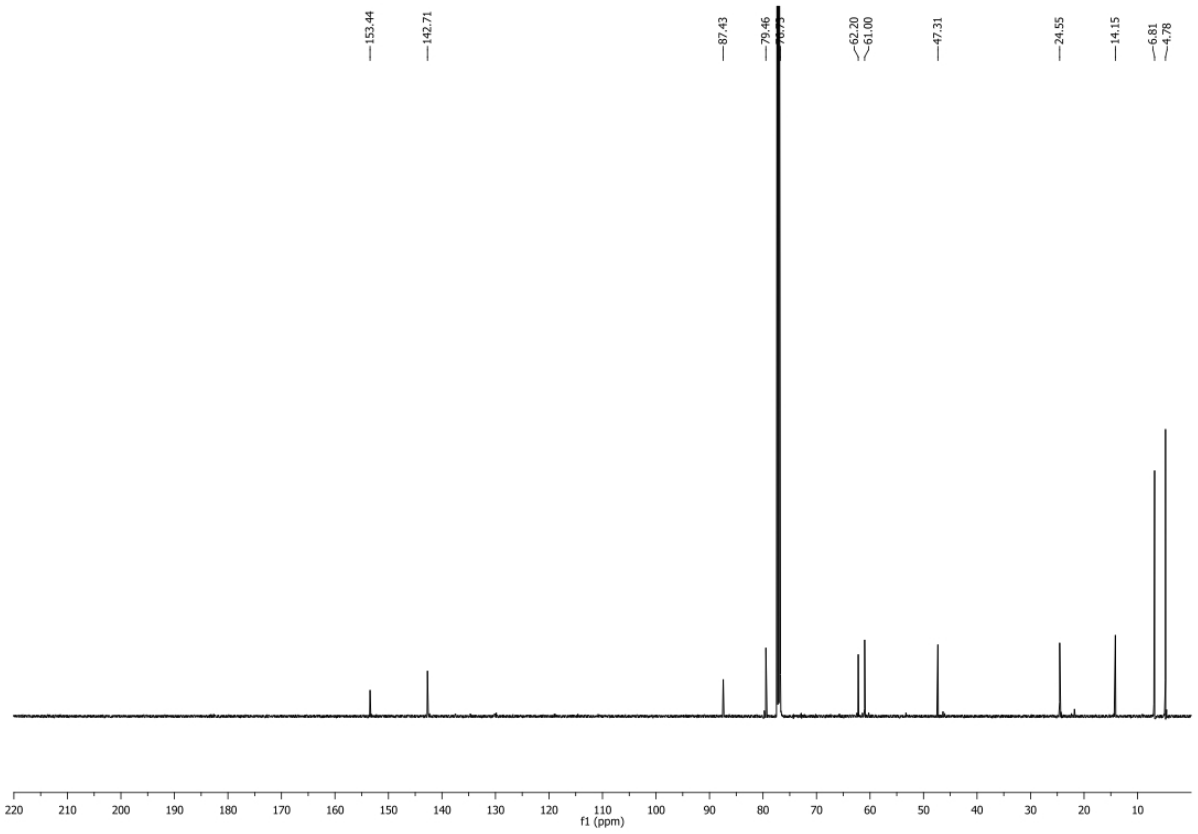


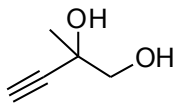
I-44

$CDCl_3$

^{1}H 600 MHz

^{13}C 150 MHz



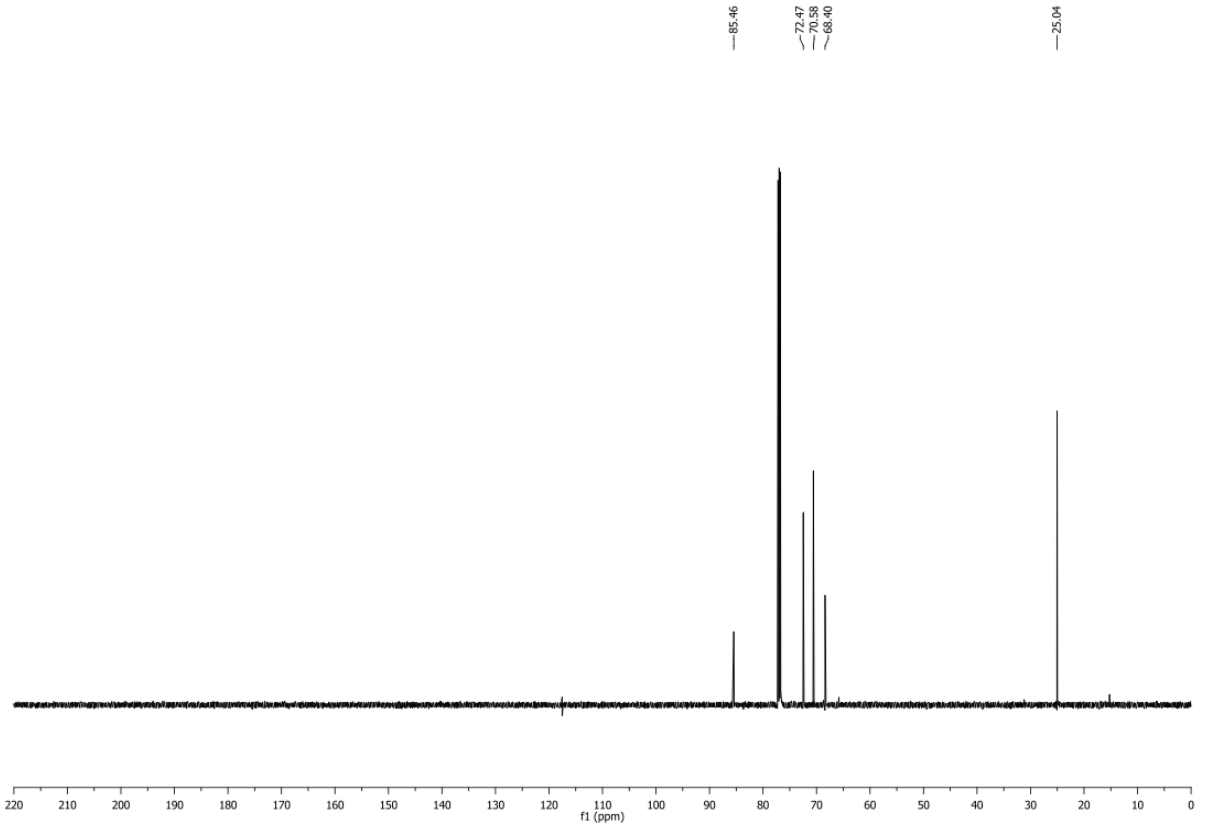


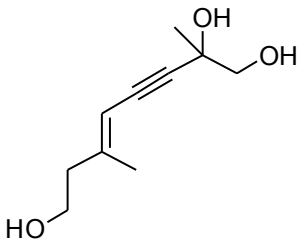
I-46

$CDCl_3$

^{1}H 600 MHz

^{13}C 150 MHz



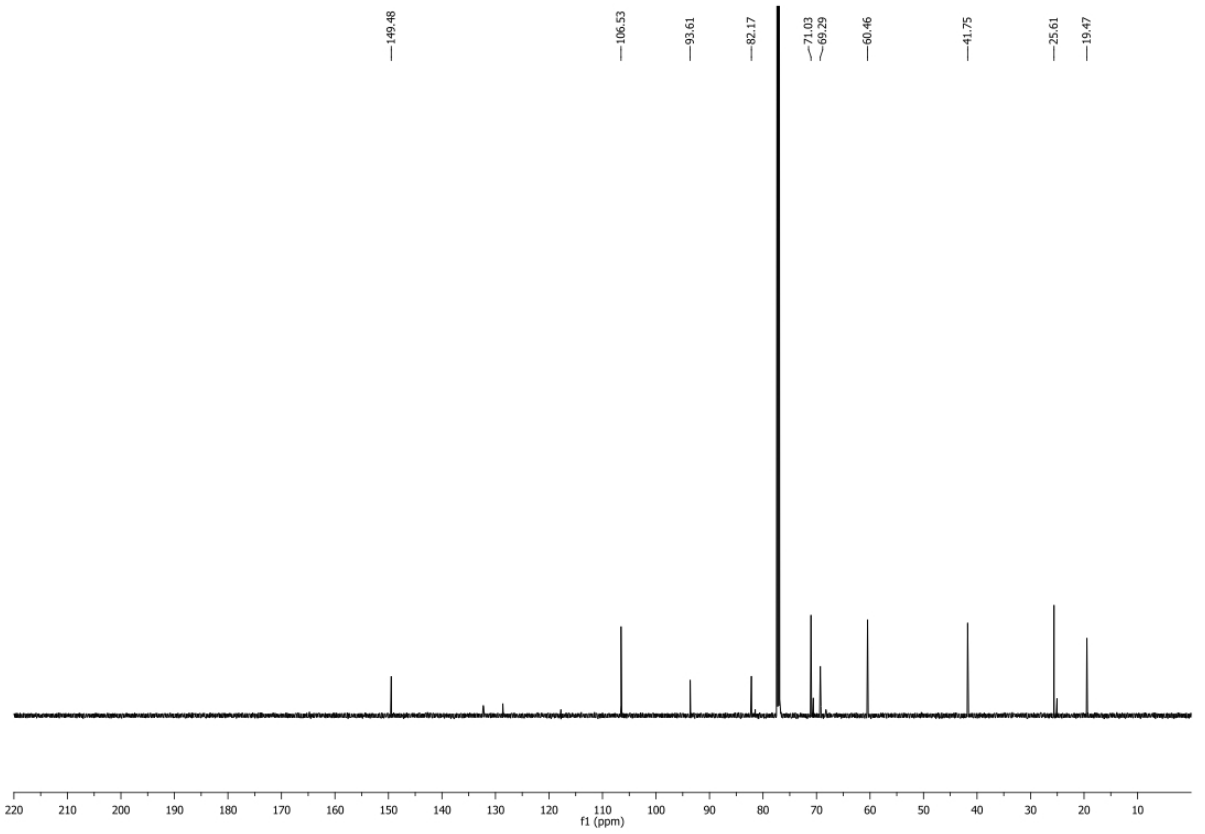


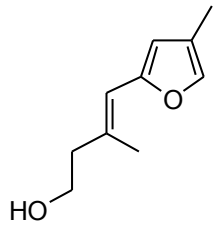
I-45

$CDCl_3$

^{1}H 600 MHz

^{13}C 150 MHz



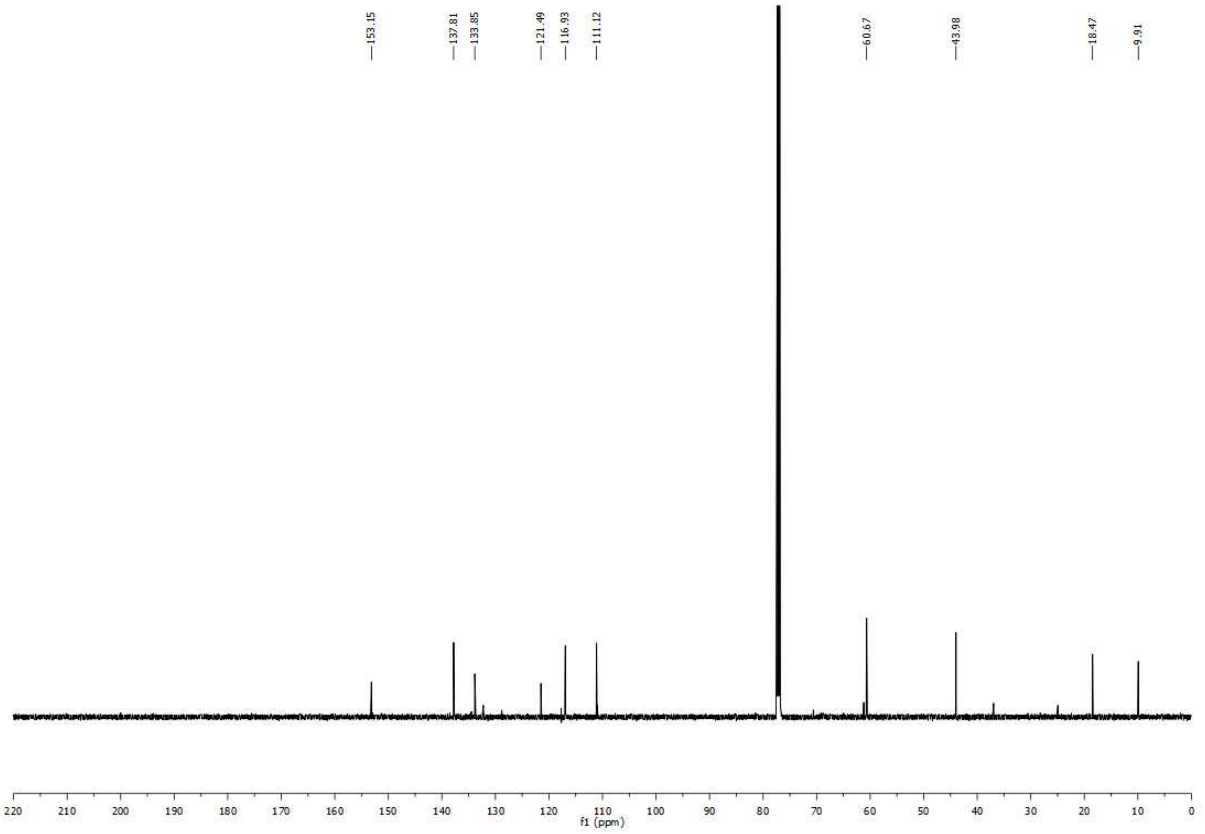


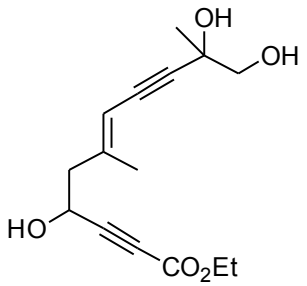
I-42

$CDCl_3$

^{1}H 600 MHz

^{13}C 150 MHz



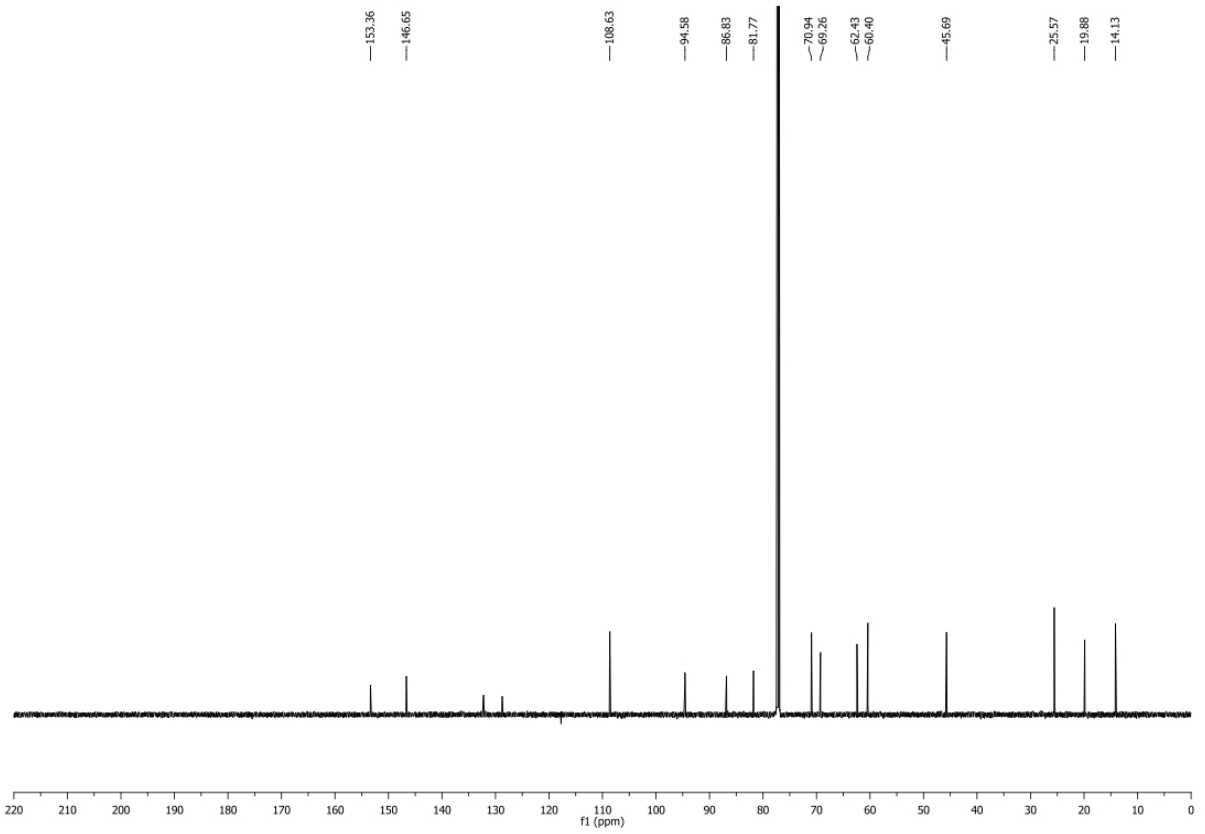


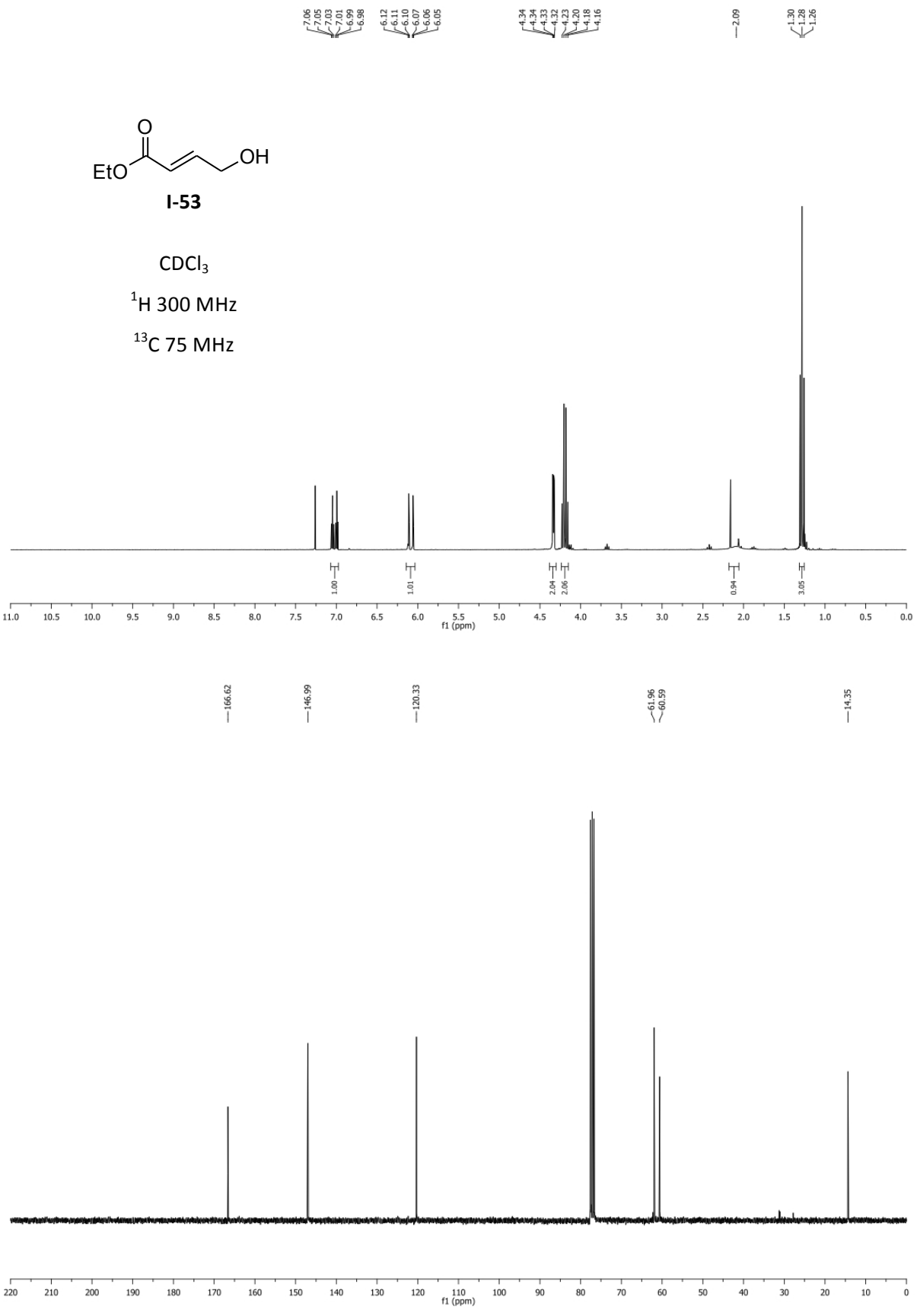
I-51

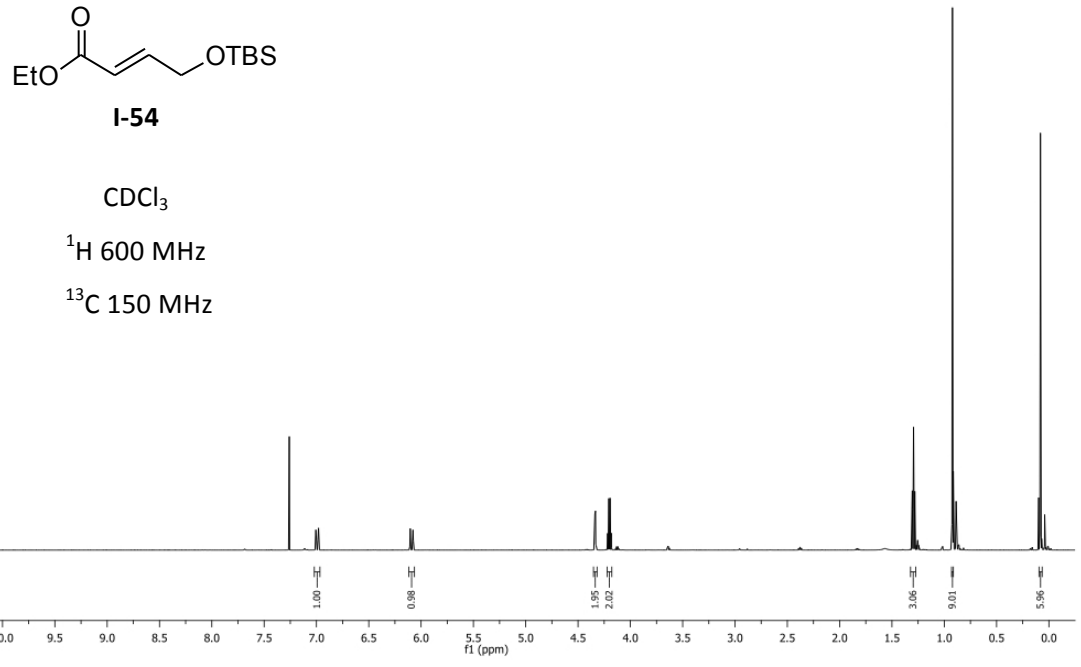
$CDCl_3$

^{1}H 600 MHz

^{13}C 150 MHz




7.06
7.05
7.03
7.01
6.99
6.98
6.12
6.11
6.10
6.07
6.06
6.05
4.34
4.34
4.33
4.32
4.23
4.20
4.18
4.16
2.09
1.30
1.28
1.26
O
EtO
OH
I-53
CDCl3
1H 300 MHz
13C 75 MHz
1.00
1.01
2.04
2.06
0.94
3.05
f1 (ppm)
166.62
146.99
120.33
61.96
60.59
14.35
f1 (ppm)

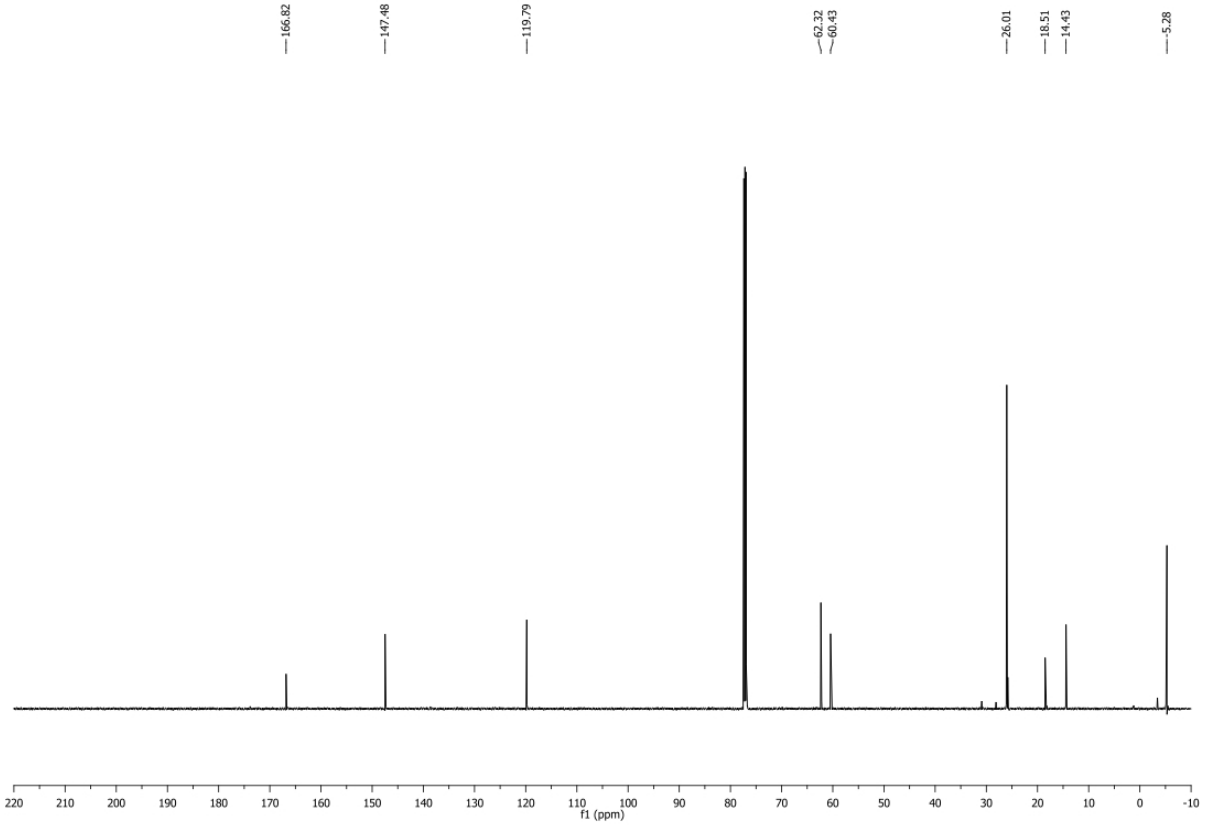


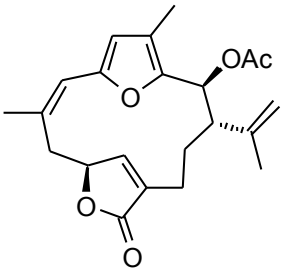
I-54

$CDCl_3$

^{1}H 600 MHz

^{13}C 150 MHz



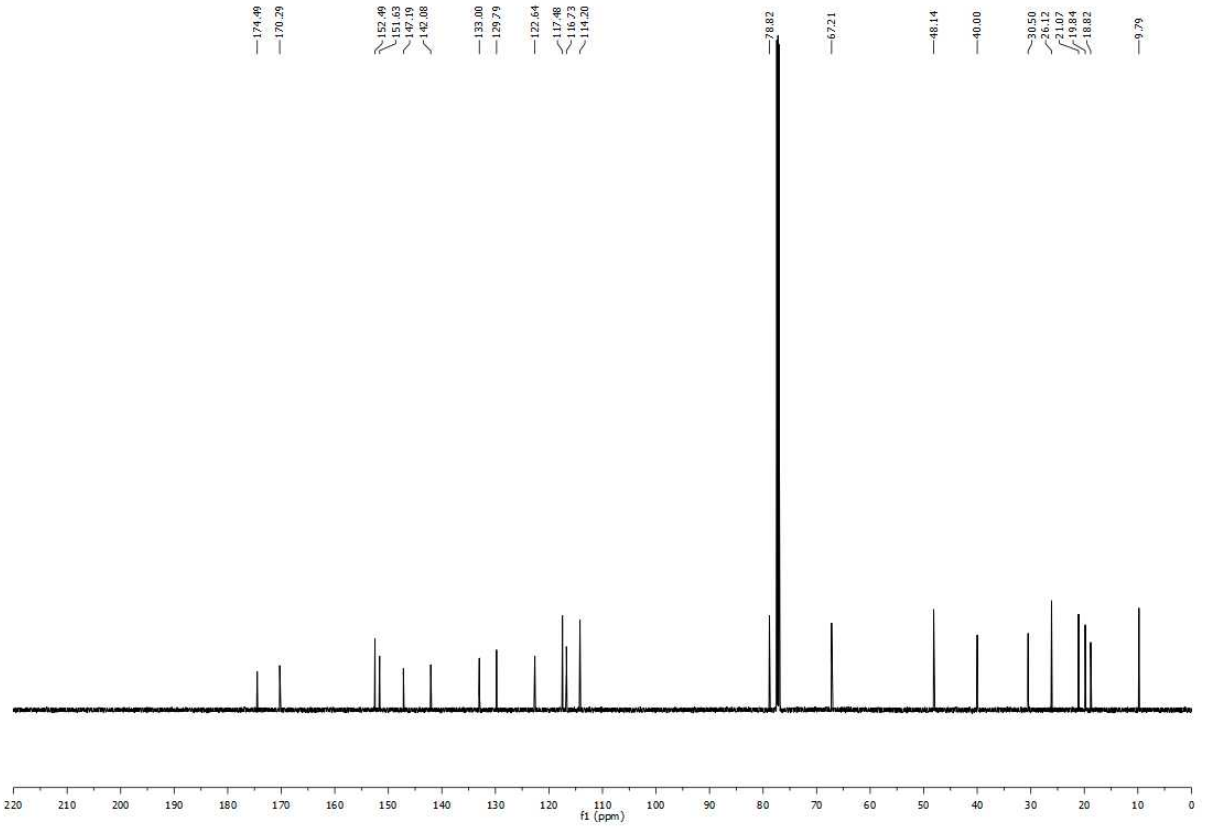


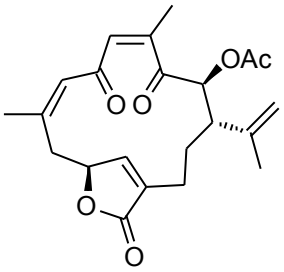
I-73

$CDCl_3$

^{1}H 600 MHz

^{13}C 150 MHz





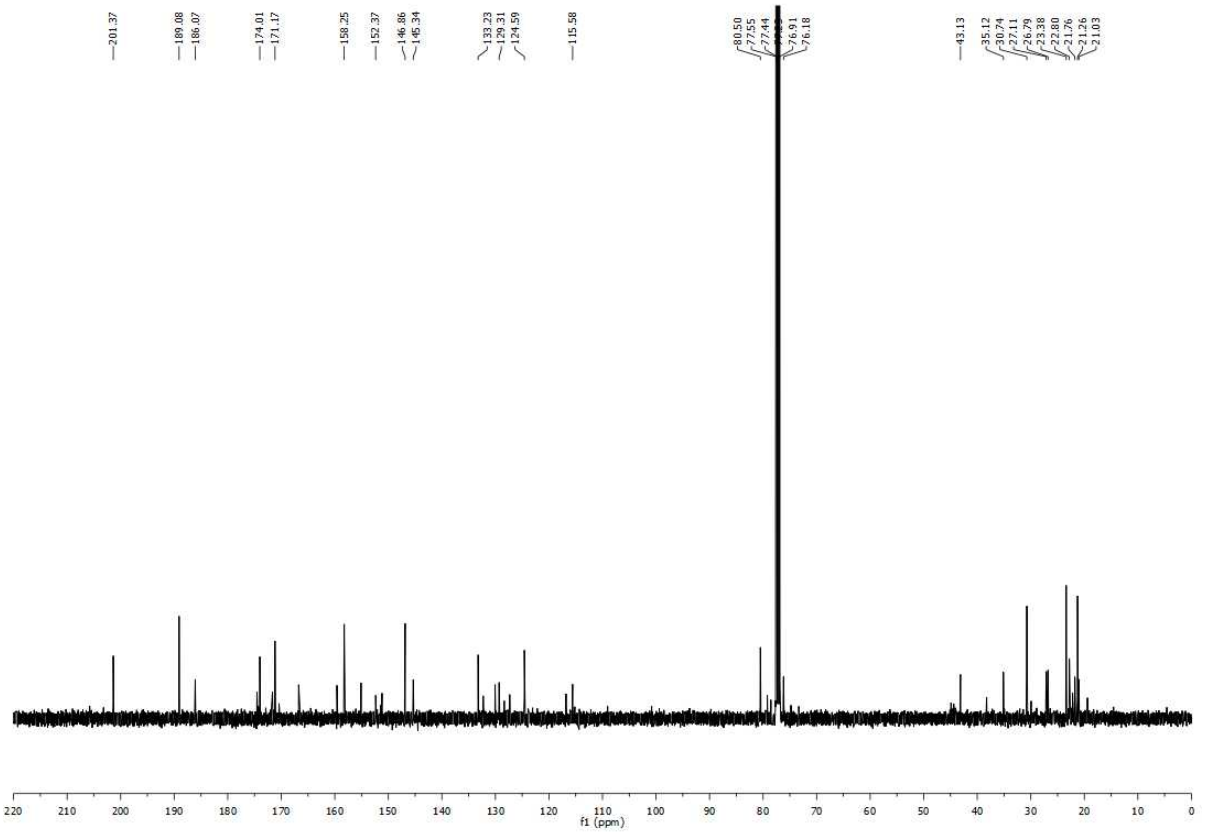
I-74

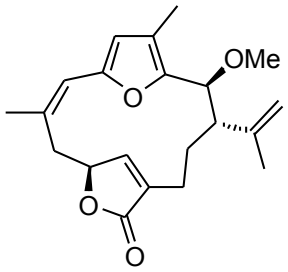
$CDCl_3$

^{1}H 400 MHz

^{13}C 100 MHz

− 45 °C



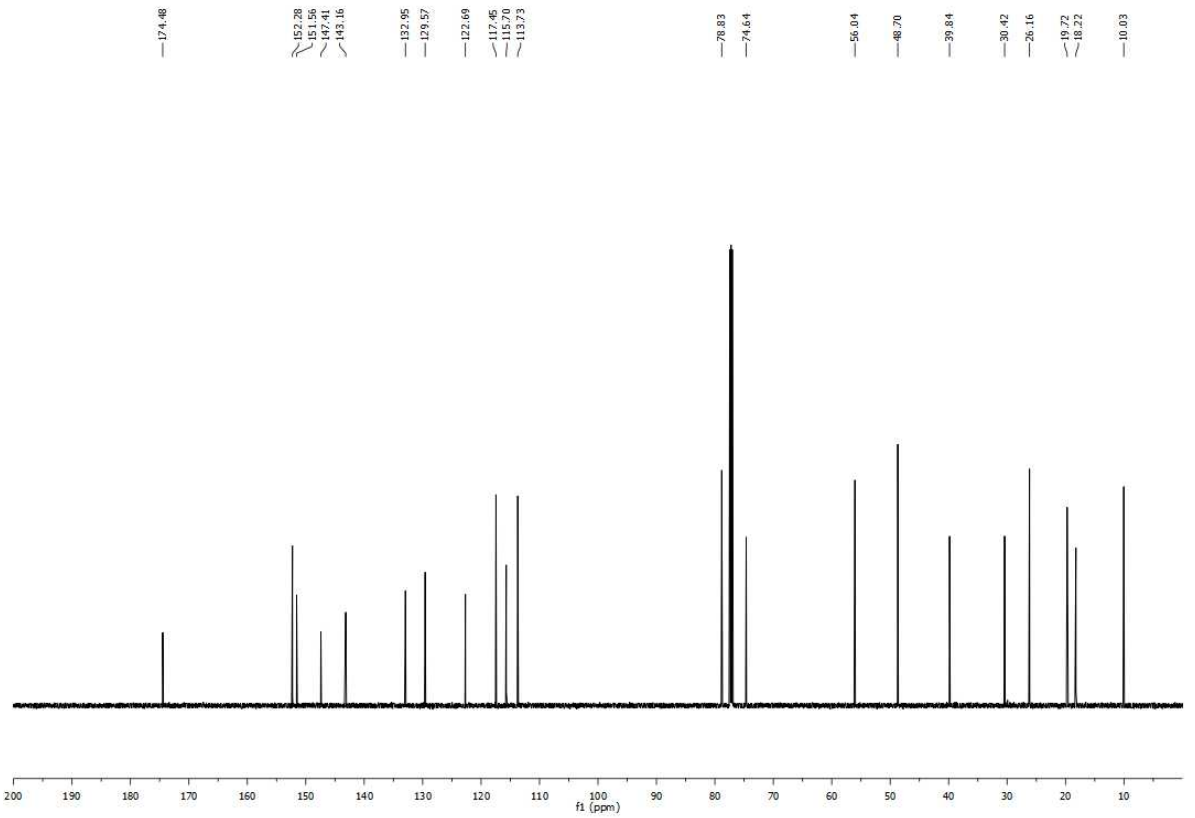


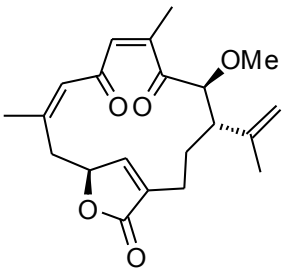
I-75

$CDCl_3$

^{1}H 600 MHz

^{13}C 150 MHz



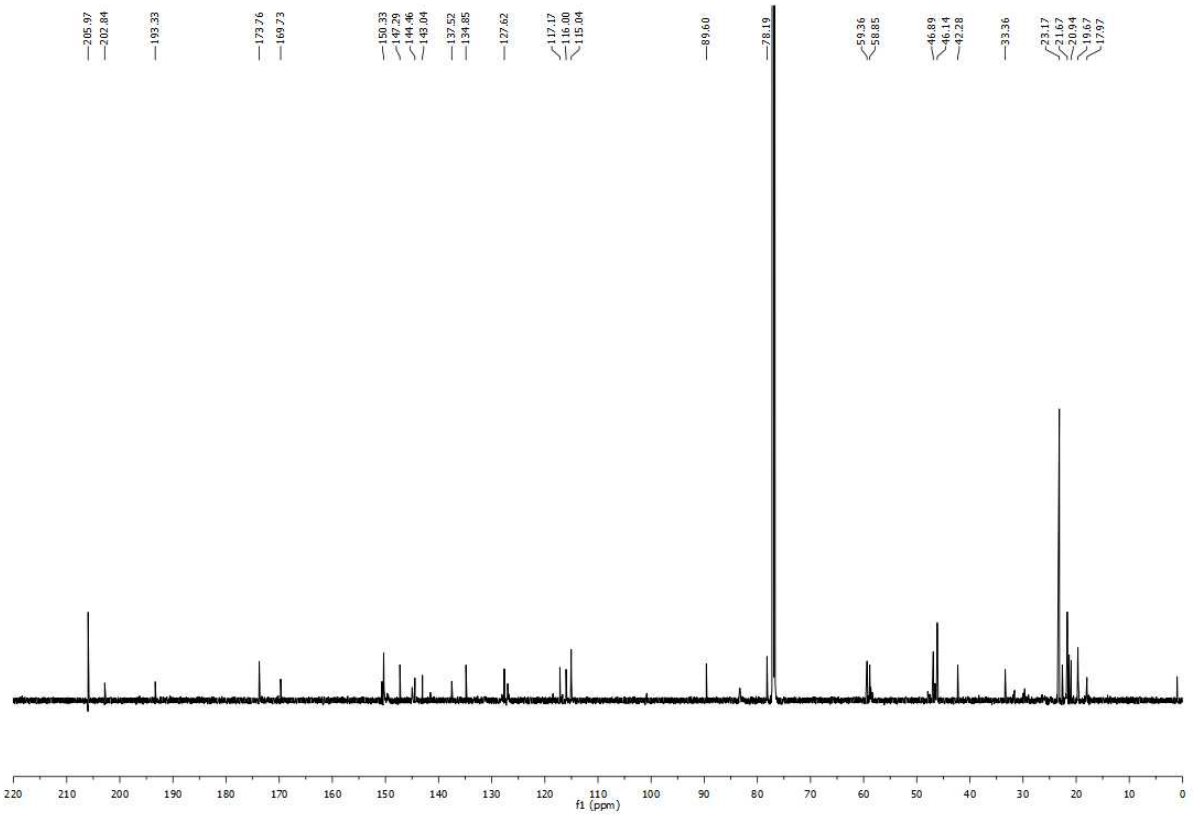


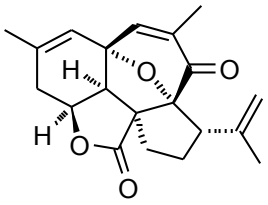
I-76

$CDCl_3$

^{1}H 600 MHz

^{13}C 150 MHz



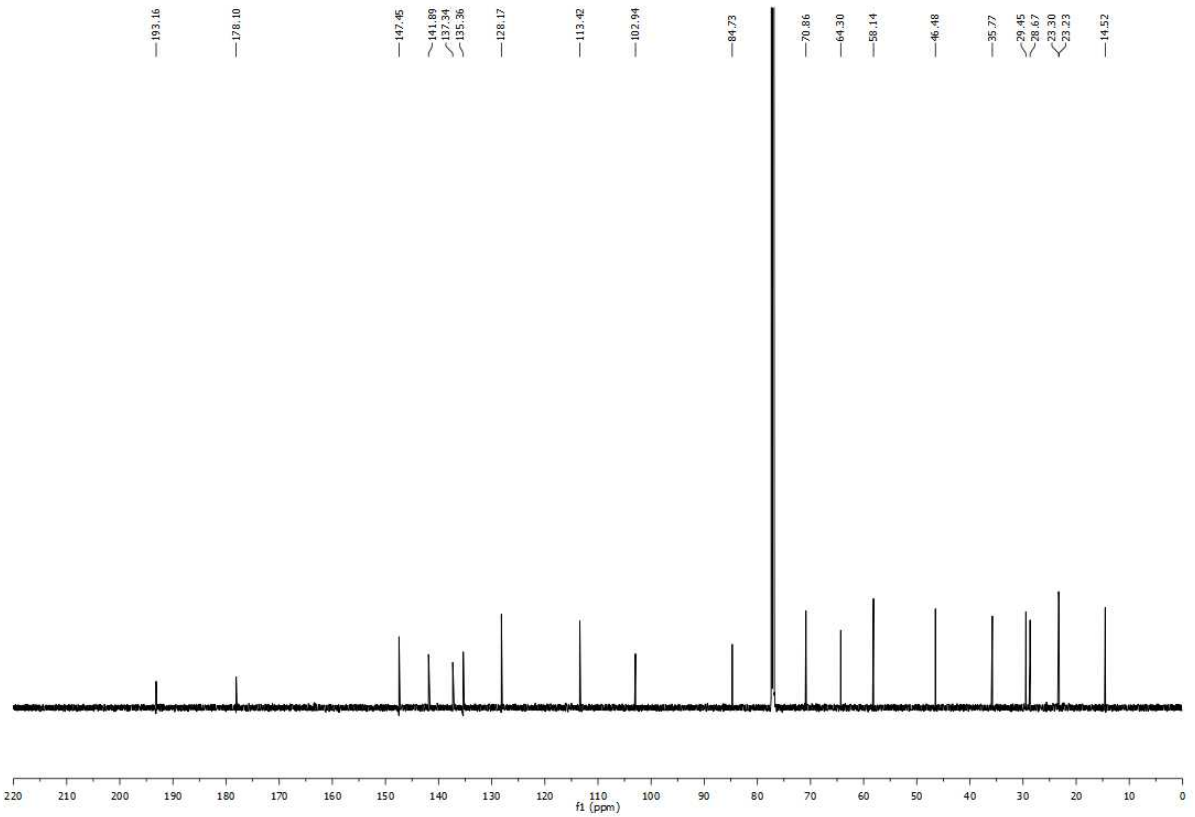


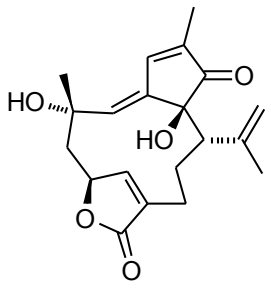
I-10

$CDCl_3$

^{1}H 600 MHz

^{13}C 150 MHz



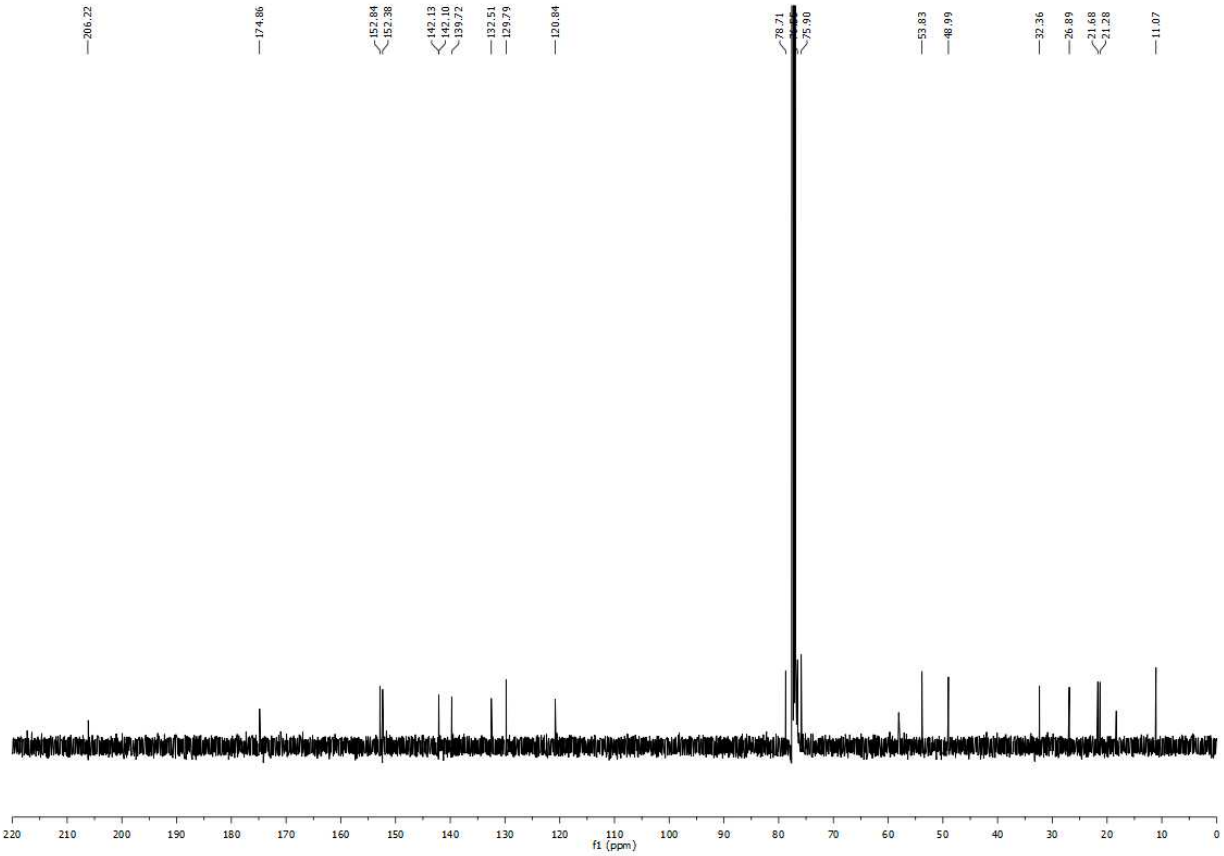


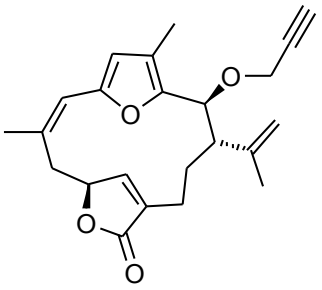
I-77

$CDCl_3$

^{1}H 600 MHz

^{13}C 150 MHz



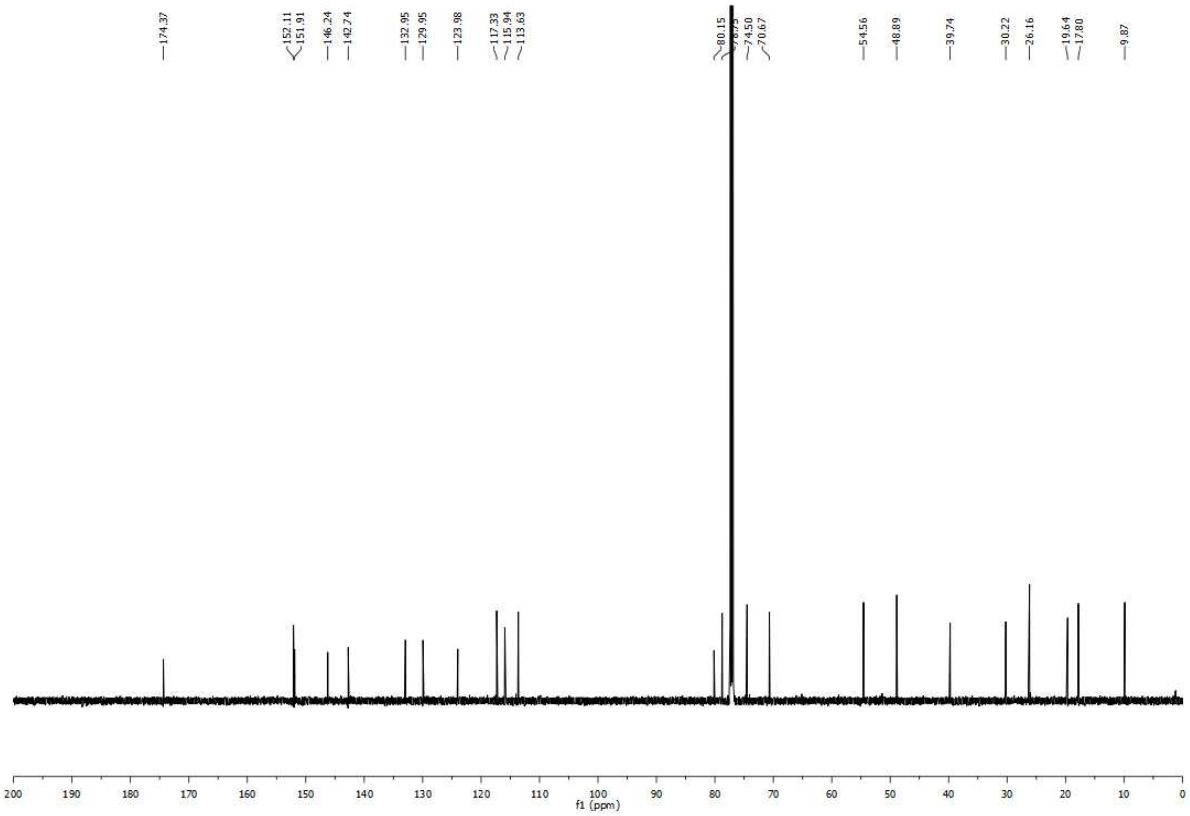


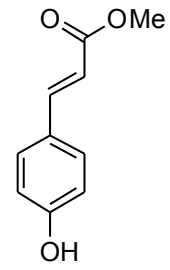
I-82

$CDCl_3$

^{1}H 600 MHz

^{13}C 150 MHz



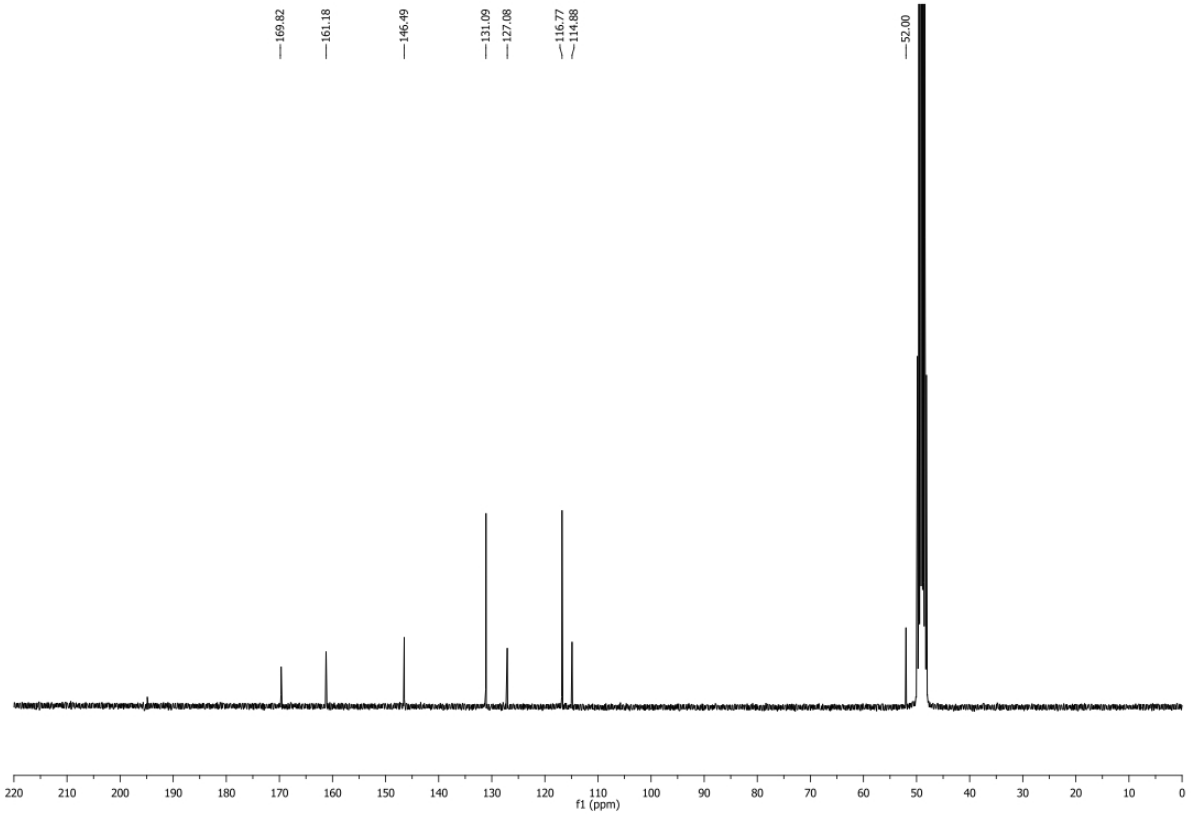


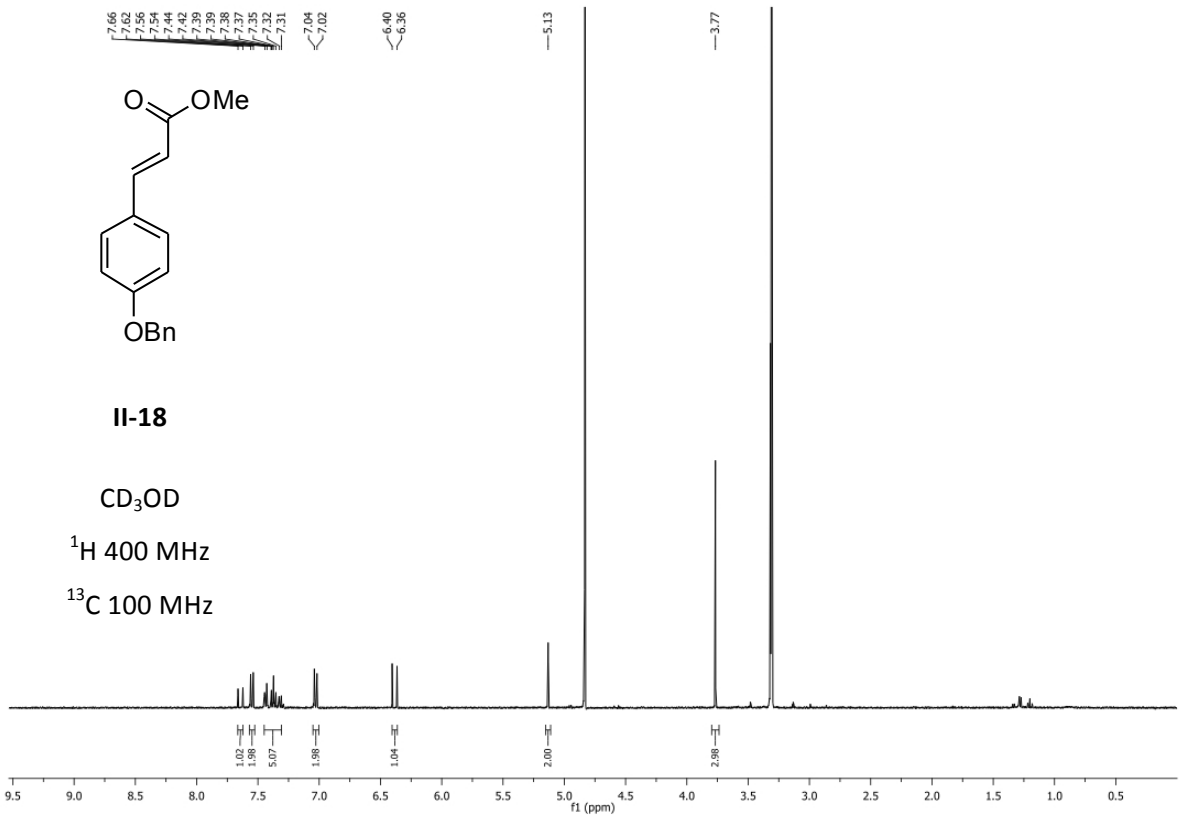
II-17

CD_3OD

^{1}H 300 MHz

^{13}C 75 MHz



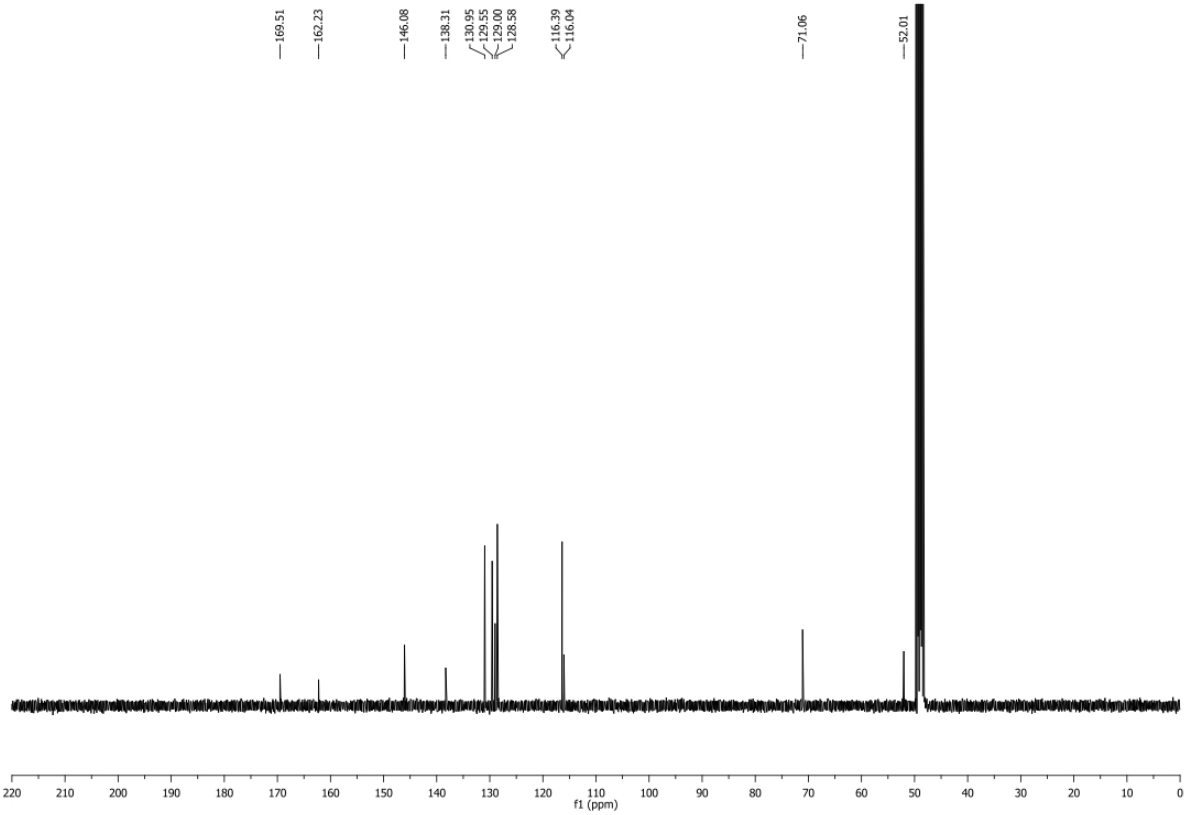


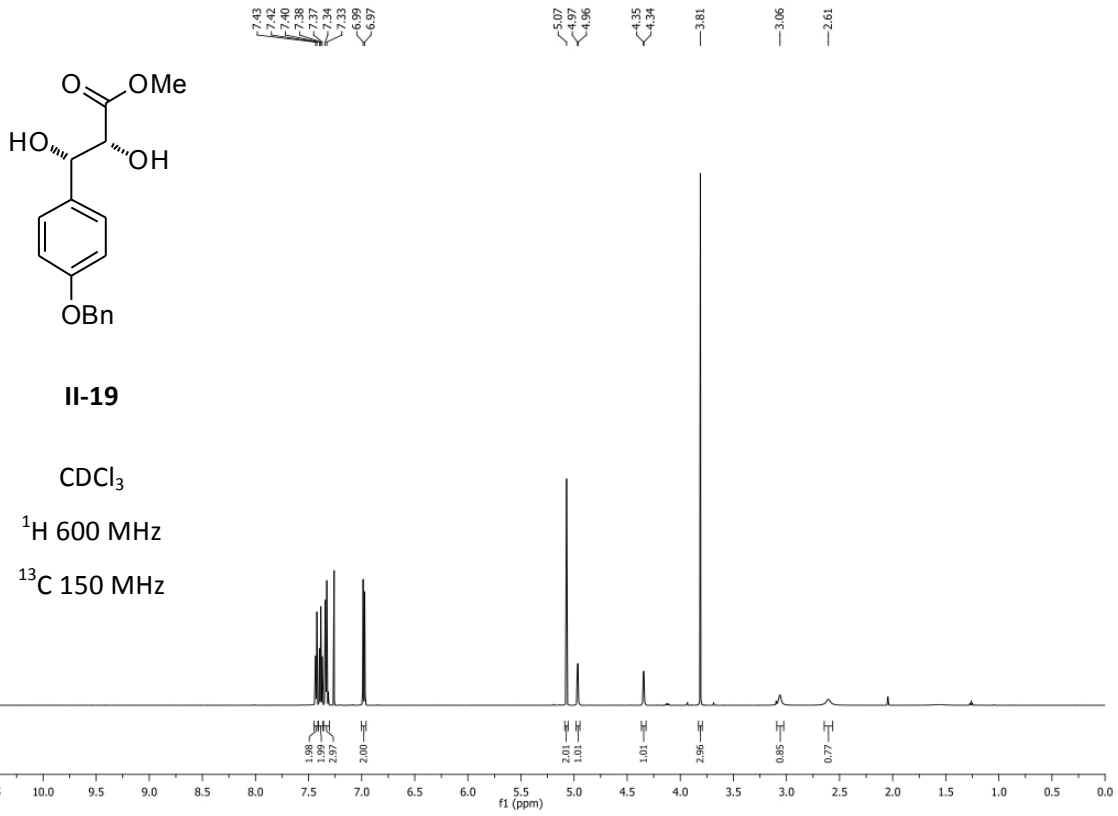
II-18

CD_3OD

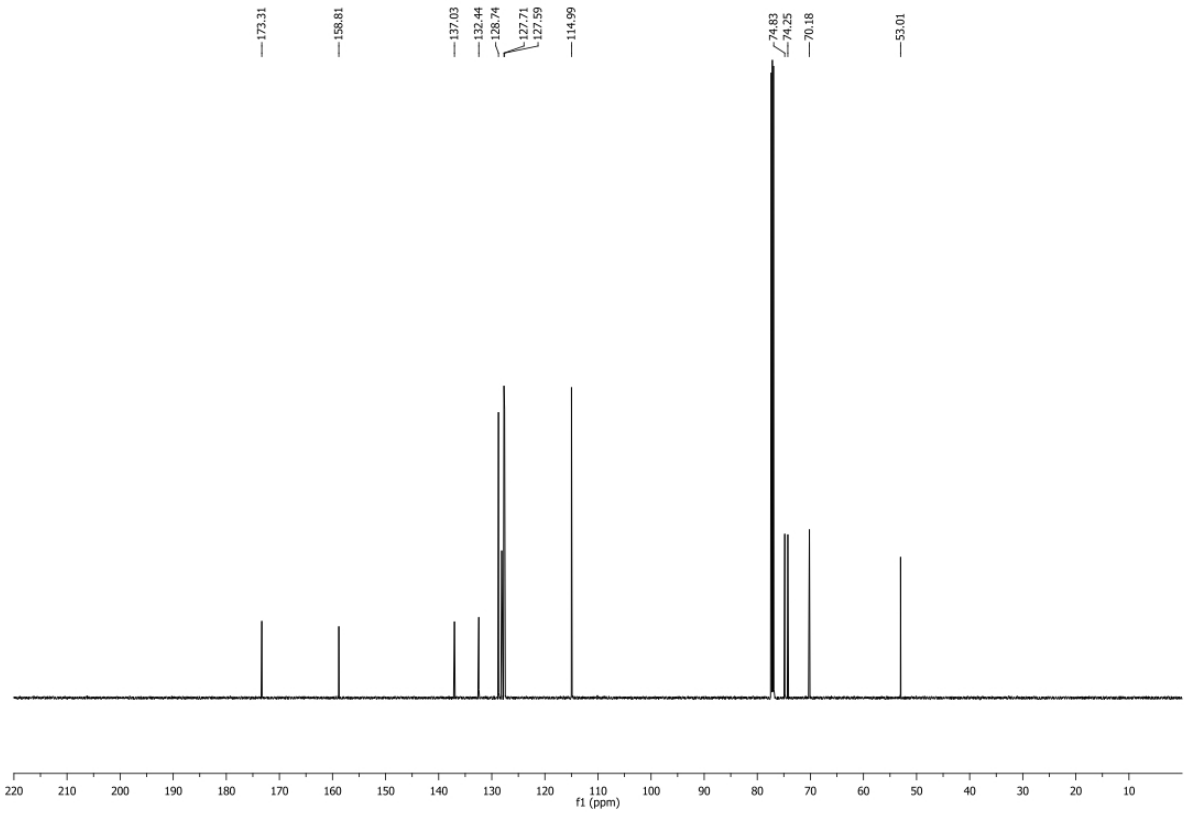
^{1}H 400 MHz

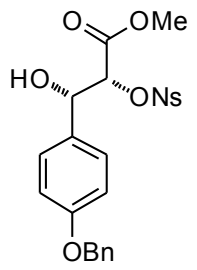
^{13}C 100 MHz




7.43
7.42
7.40
7.38
7.37
7.34
7.33
6.99
6.97
5.07
4.97
4.96
4.35
4.34
3.81
3.06
2.61
O
OMe
HO
OH
OBn
CDCl3
1H 600 MHz
13C 150 MHz
1.98
1.99
2.97
2.00
2.01
1.01
1.01
2.96
0.85
0.77
f1 (ppm)

II-19


173.31
158.81
137.03
132.44
128.74
127.71
127.59
114.99
74.83
74.25
70.18
53.01
f1 (ppm)

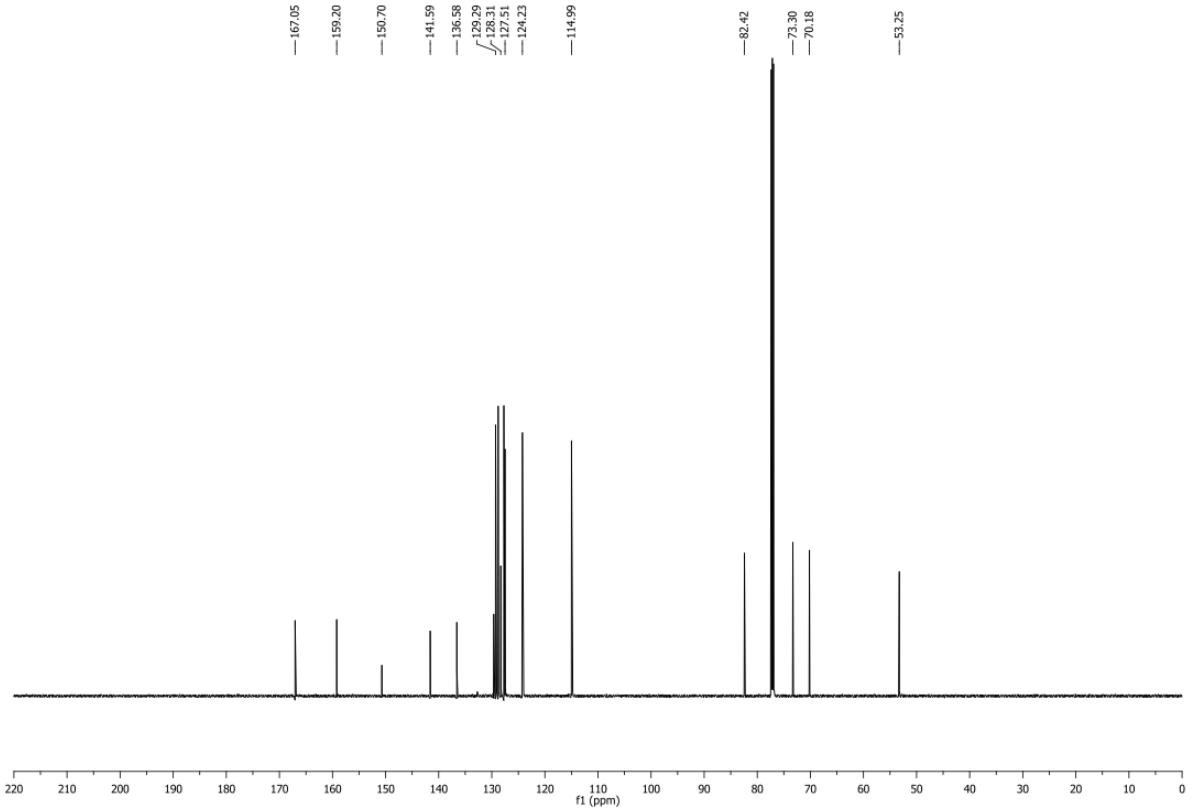


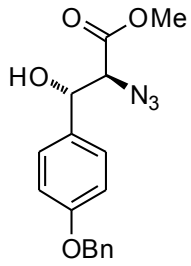
II-20

$CDCl_3$

^{1}H 600 MHz

^{13}C 150 MHz



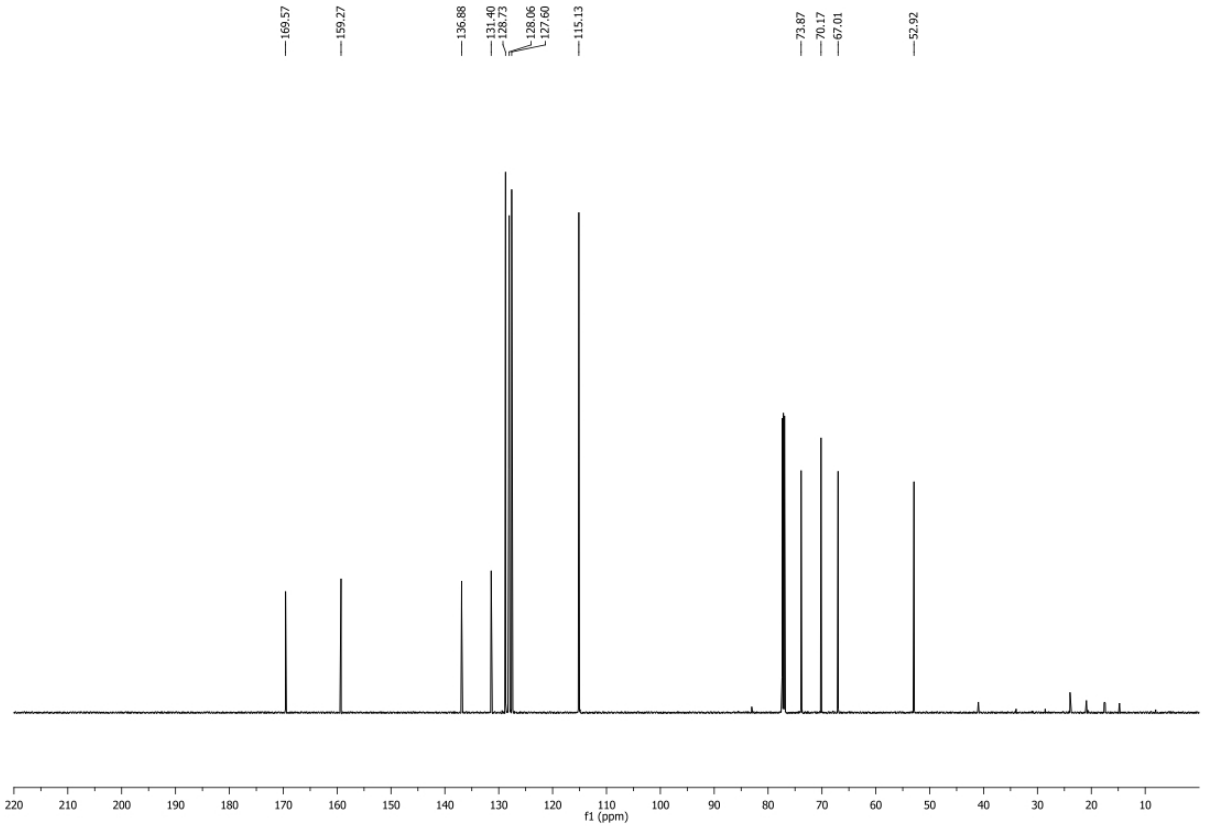


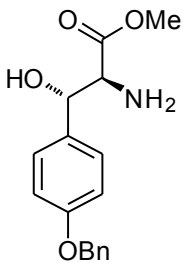
II-21

$CDCl_3$

^{1}H 600 MHz

^{13}C 150 MHz



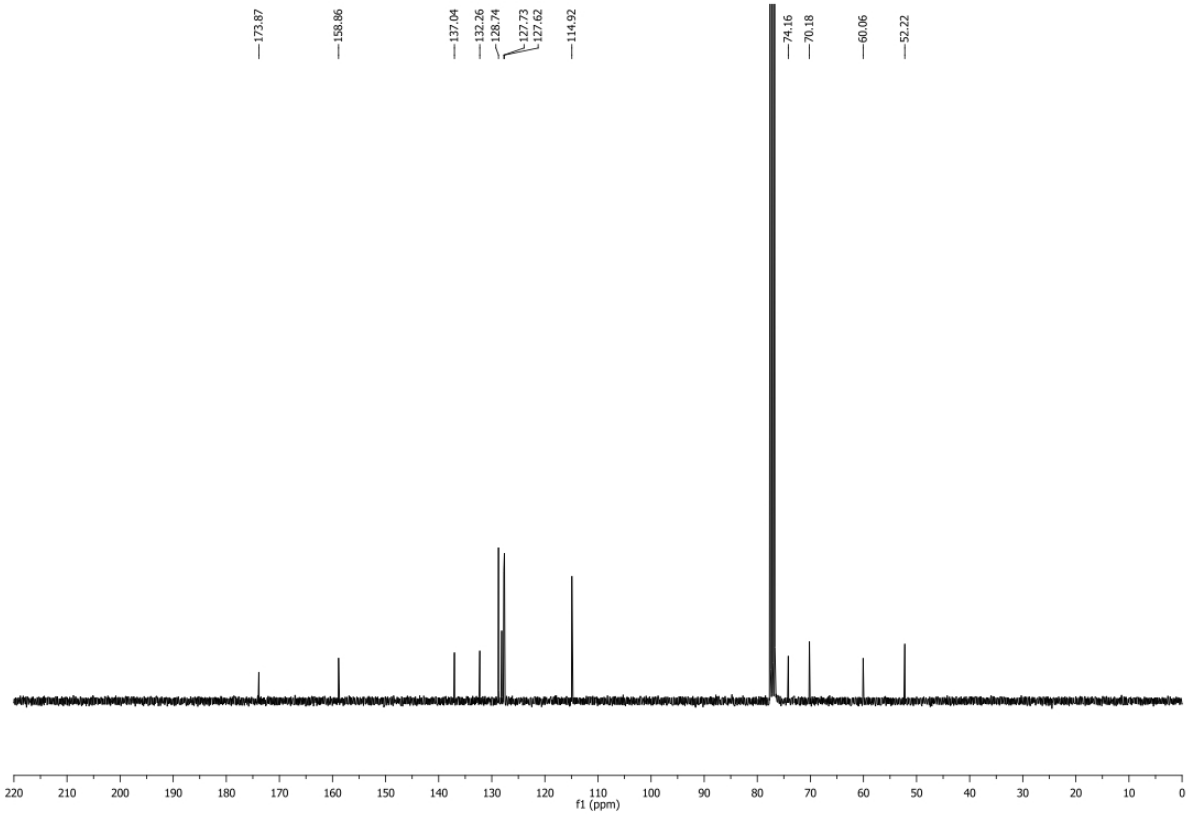


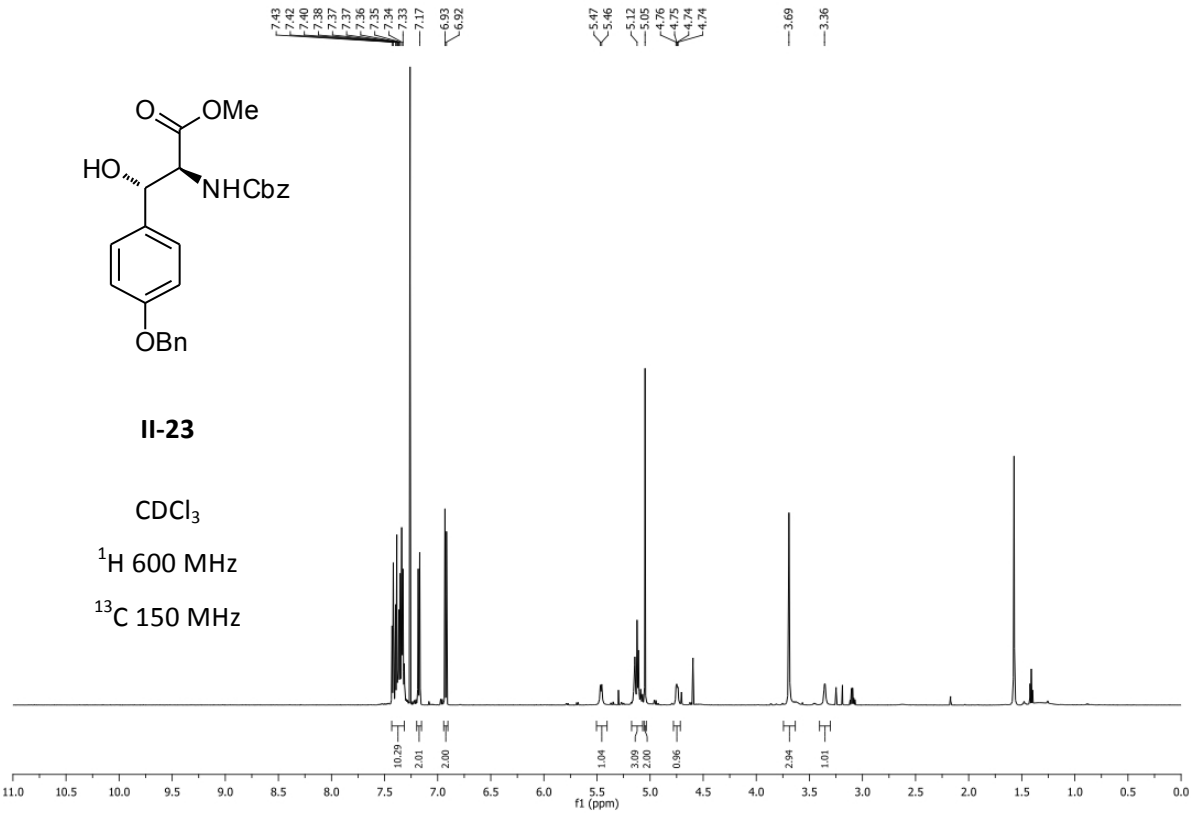
II-21

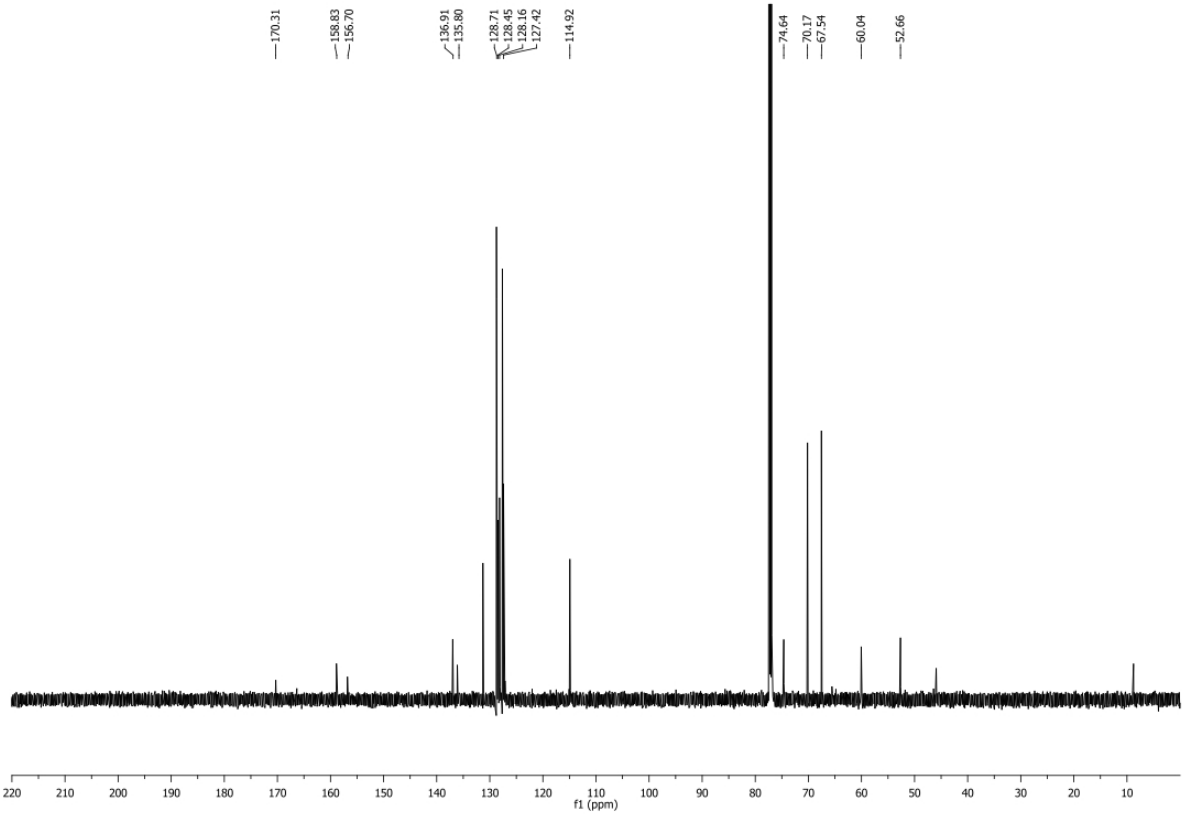
$CDCl_3$

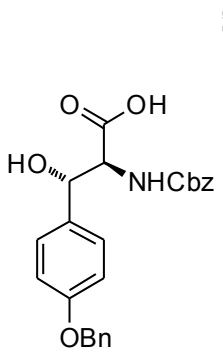
^{1}H 300 MHz

^{13}C 75 MHz




7.43
7.42
7.40
7.38
7.37
7.37
7.36
7.35
7.34
7.33
7.17
6.93
6.92
5.47
5.46
5.12
5.05
4.76
4.75
4.74
4.74
3.69
3.36
O
OMe
HO
NHCbz
OBn
II-23
CDCl3
1H 600 MHz
13C 150 MHz
10.29
2.01
2.00
1.04
3.09
2.00
0.96
2.94
1.01
f1 (ppm)


170.31
158.83
156.70
136.91
135.80
128.71
128.45
128.16
127.42
114.92
74.64
70.17
67.54
60.04
52.66
f1 (ppm)

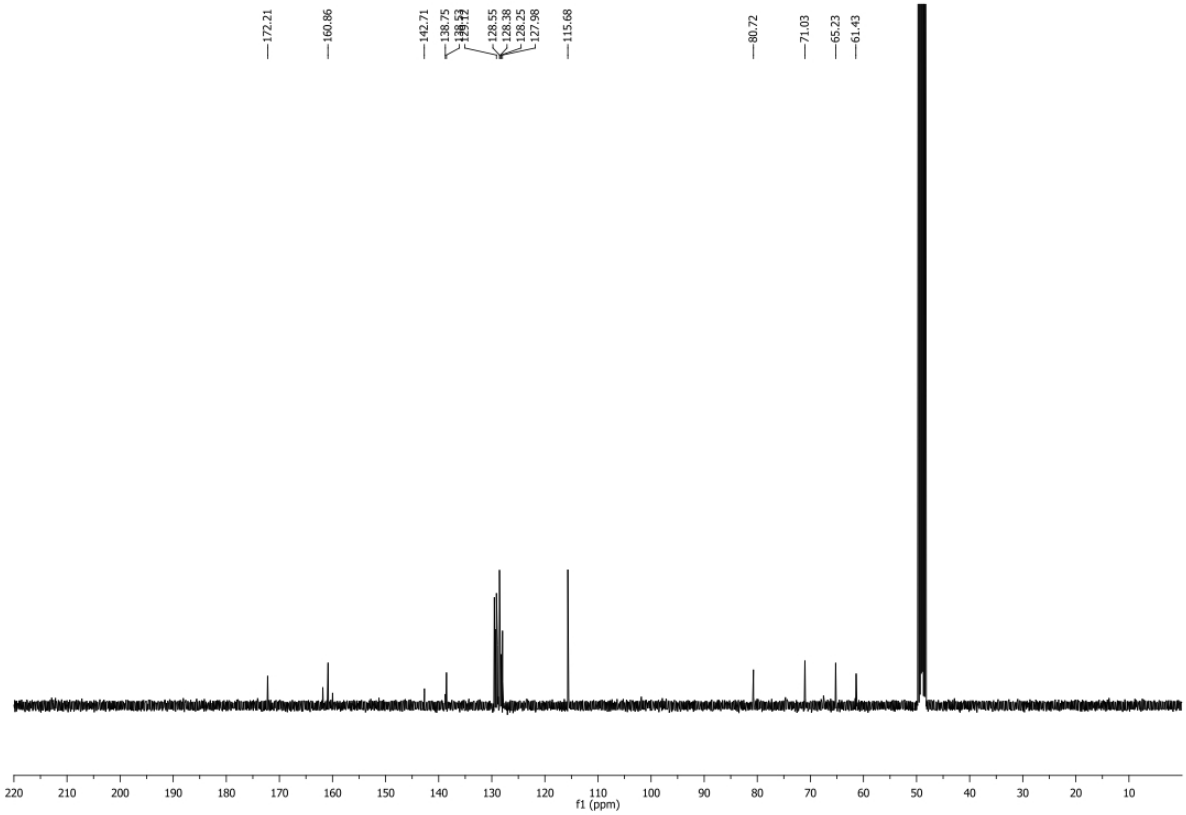


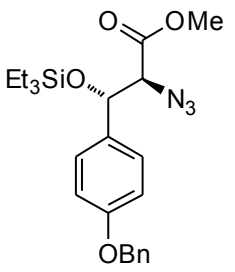
II-24

CD_3OD

^{1}H 400 MHz

^{13}C 100 MHz



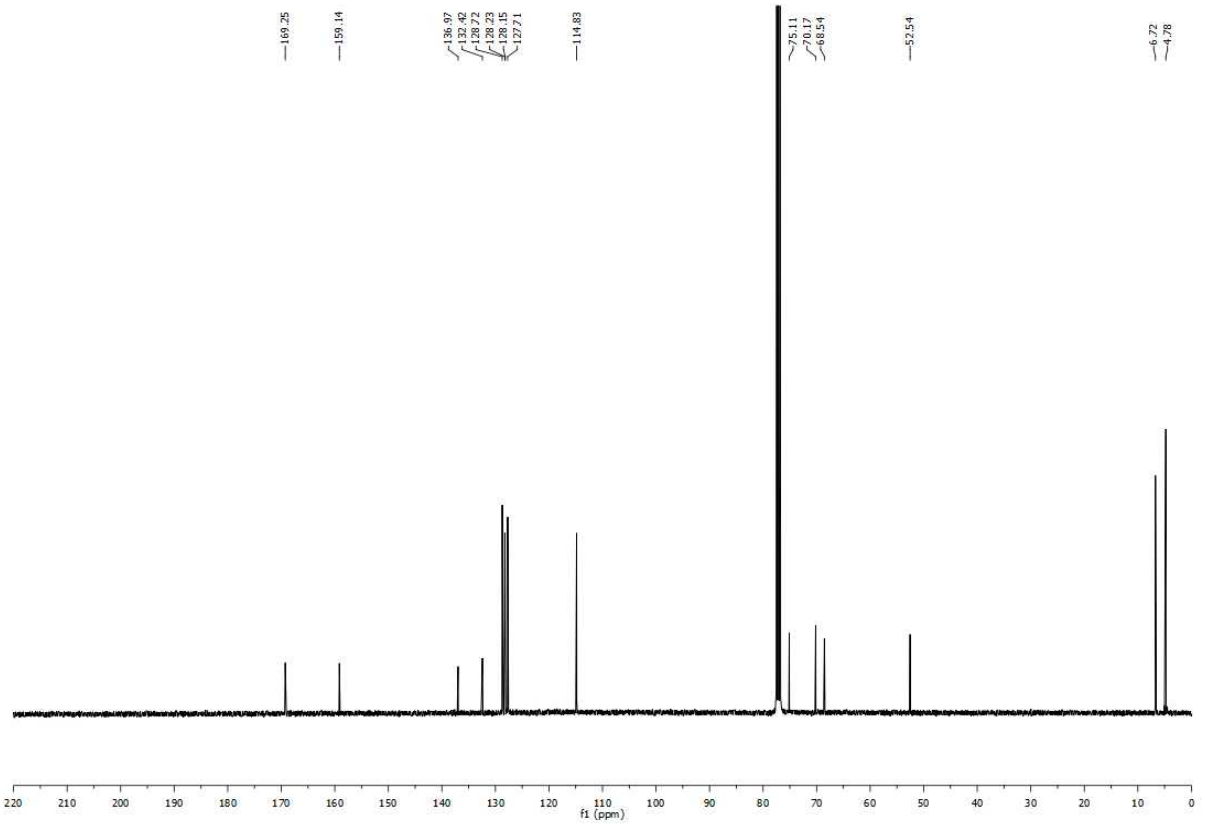


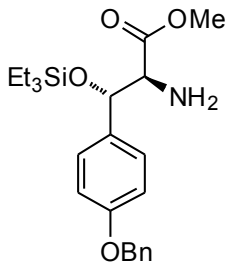
II-25

$CDCl_3$

^{1}H 400 MHz

^{13}C 100 MHz



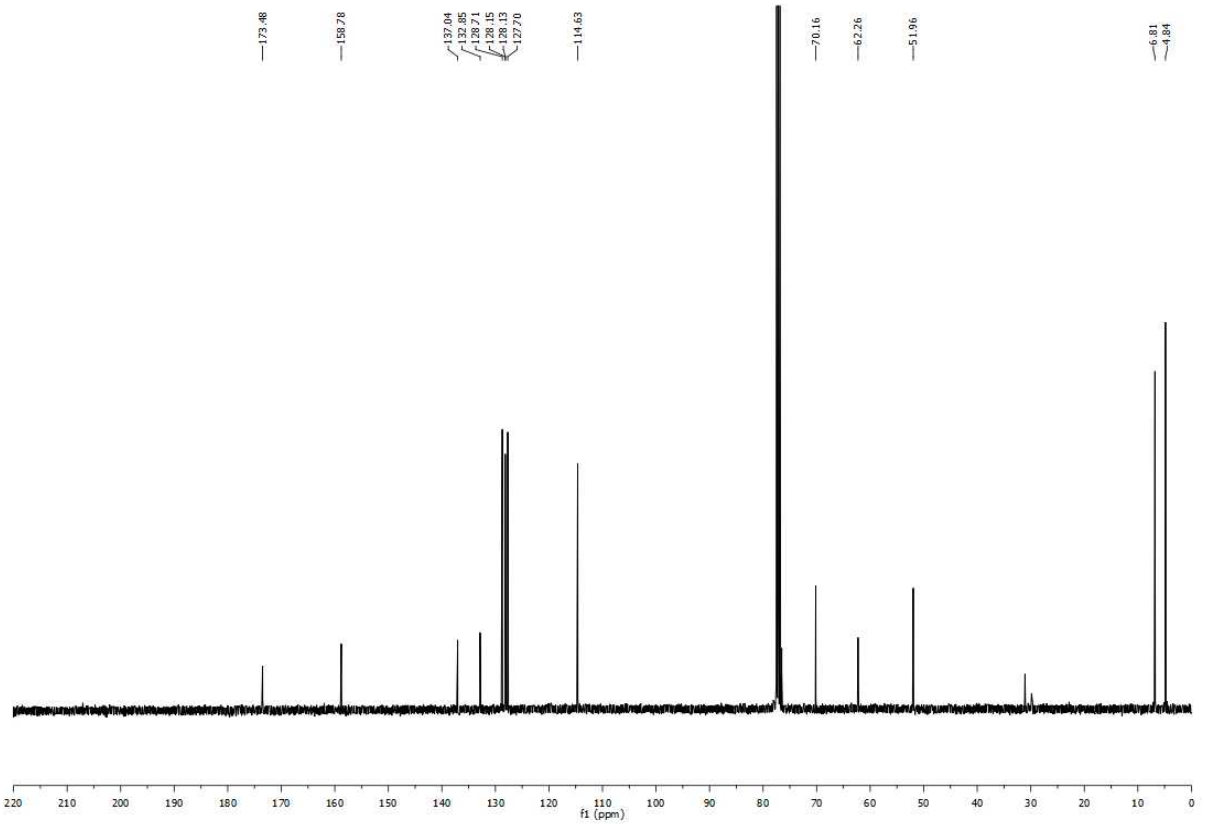


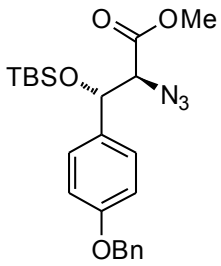
II-26

$CDCl_3$

^{1}H 400 MHz

^{13}C 100 MHz



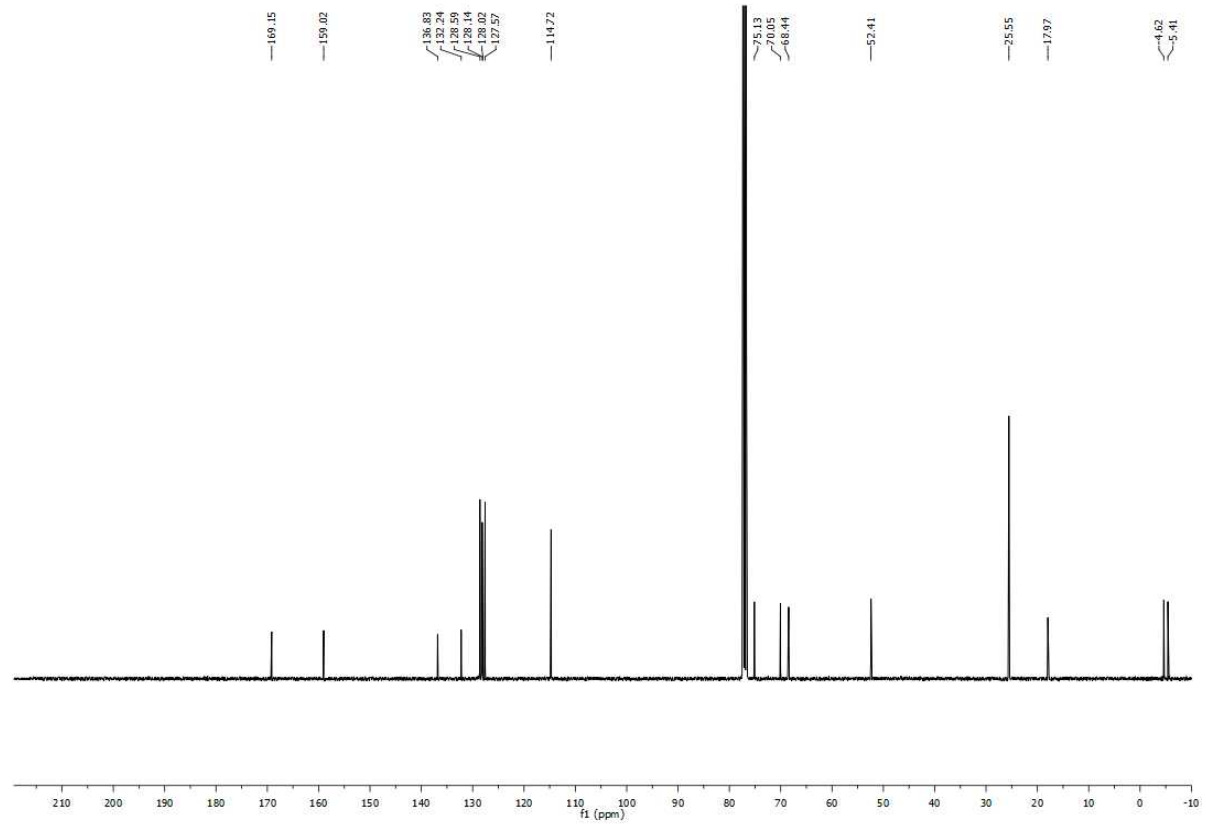


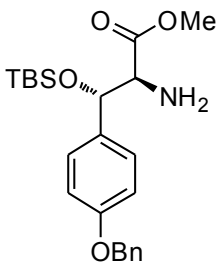
II-27

$CDCl_3$

^{1}H 400 MHz

^{13}C 100 MHz



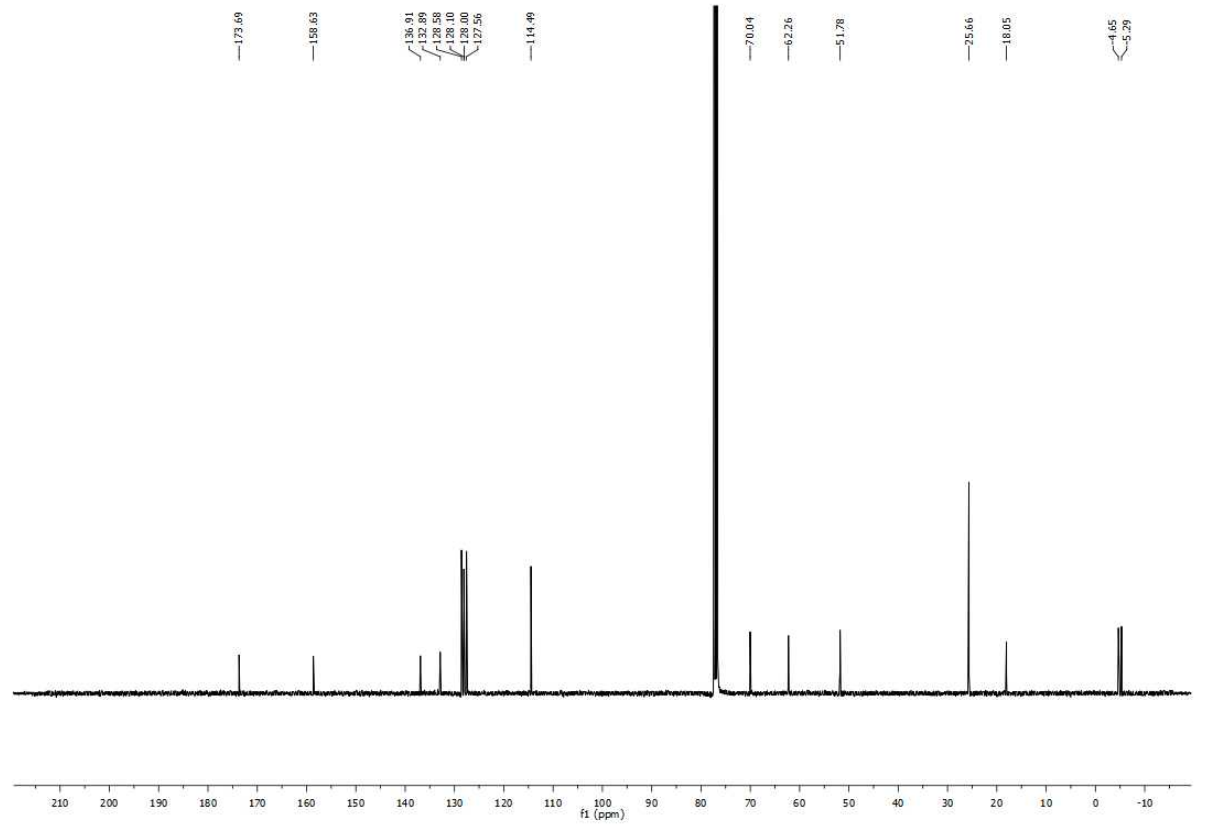


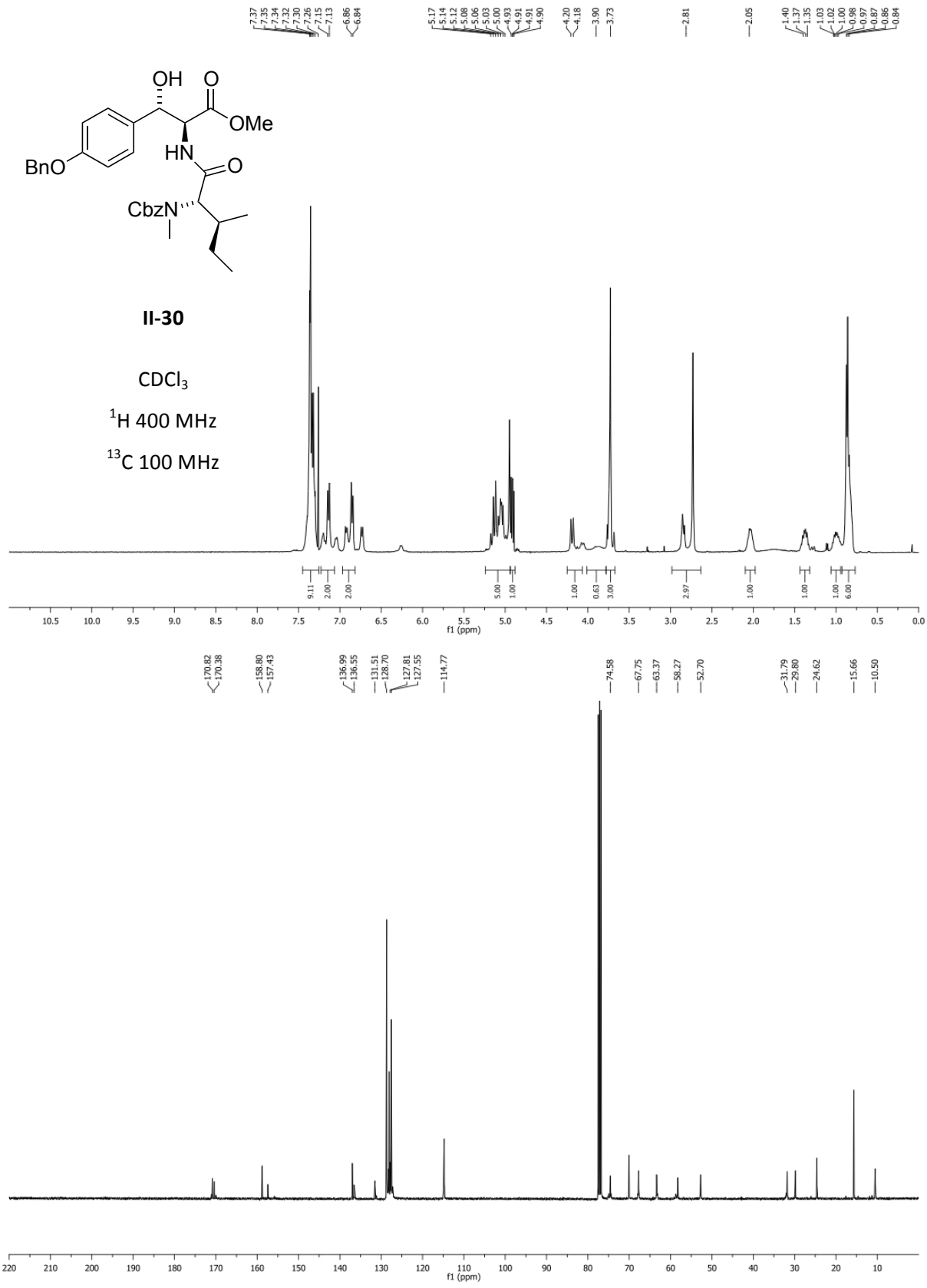
II-28

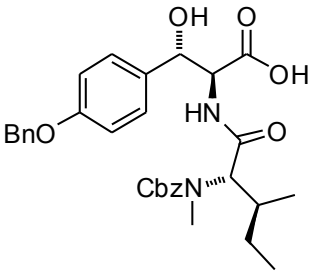
$CDCl_3$

^{1}H 400 MHz

^{13}C 100 MHz




OH
O
OMe
HN
O
BnO
CbzN
II-30
CDCl3
1H 400 MHz
13C 100 MHz
f1 (ppm)
f1 (ppm)

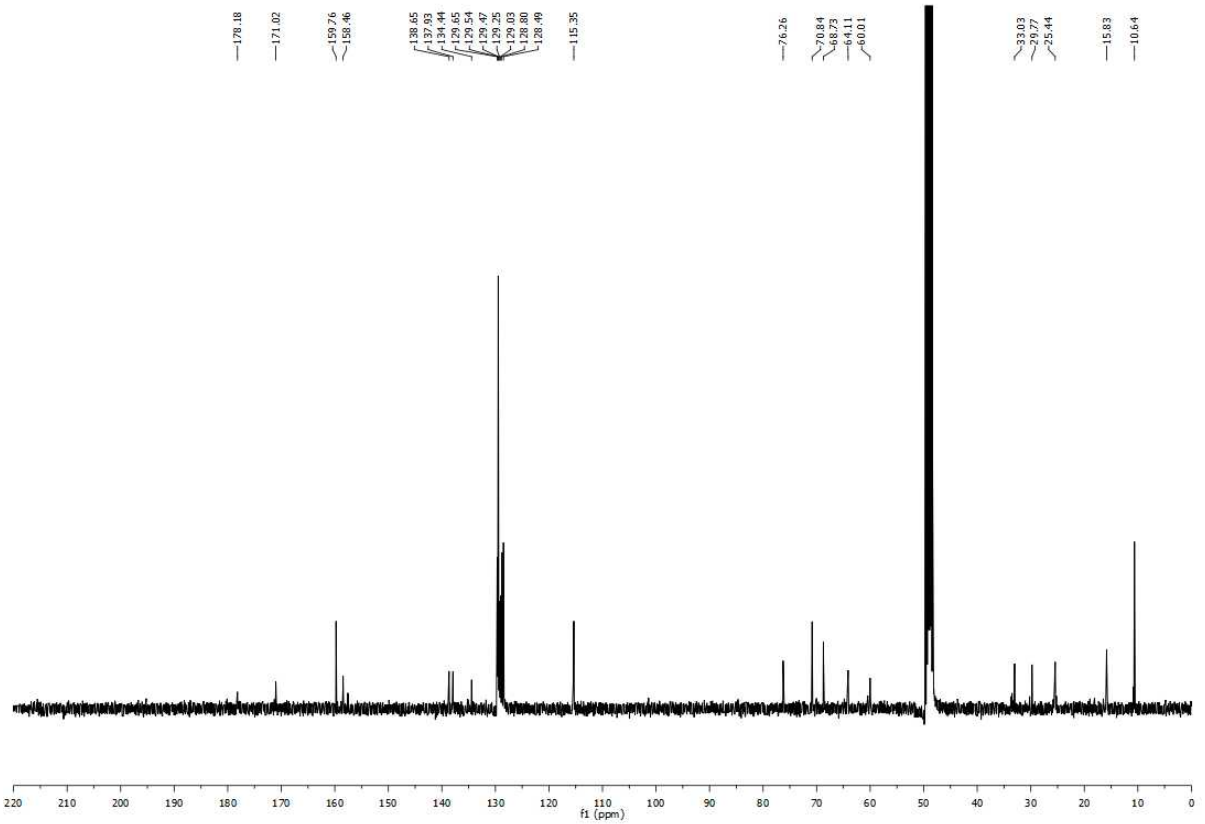


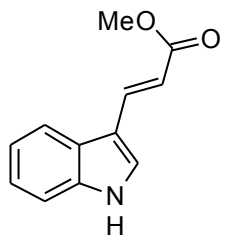
II-31

CD_3OD

^{1}H 400 MHz

^{13}C 100 MHz



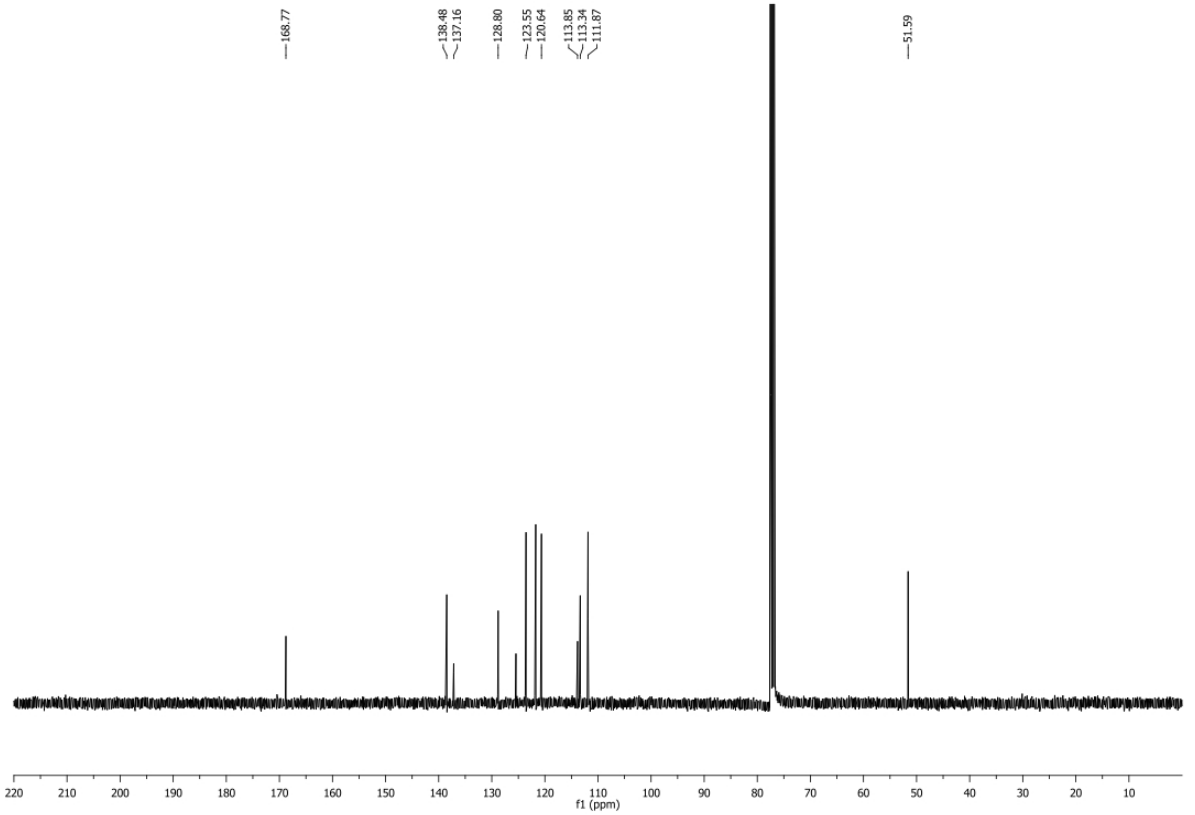


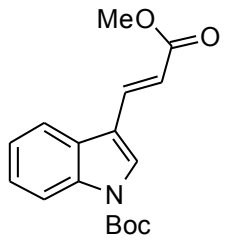
II-33

$CDCl_3$

^{1}H 400 MHz

^{13}C 100 MHz



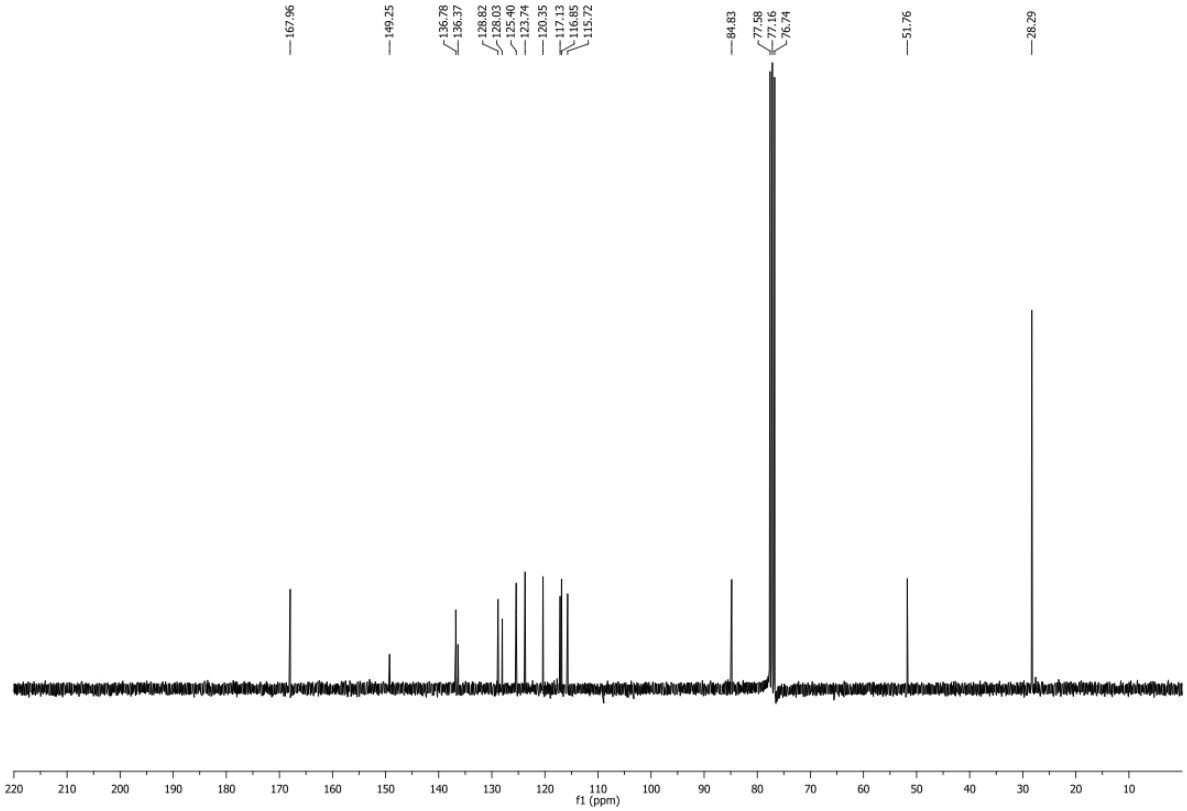


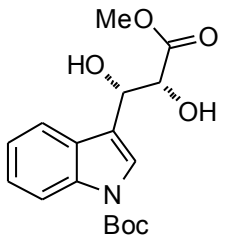
II-34

$CDCl_3$

^{1}H 300 MHz

^{13}C 75 MHz



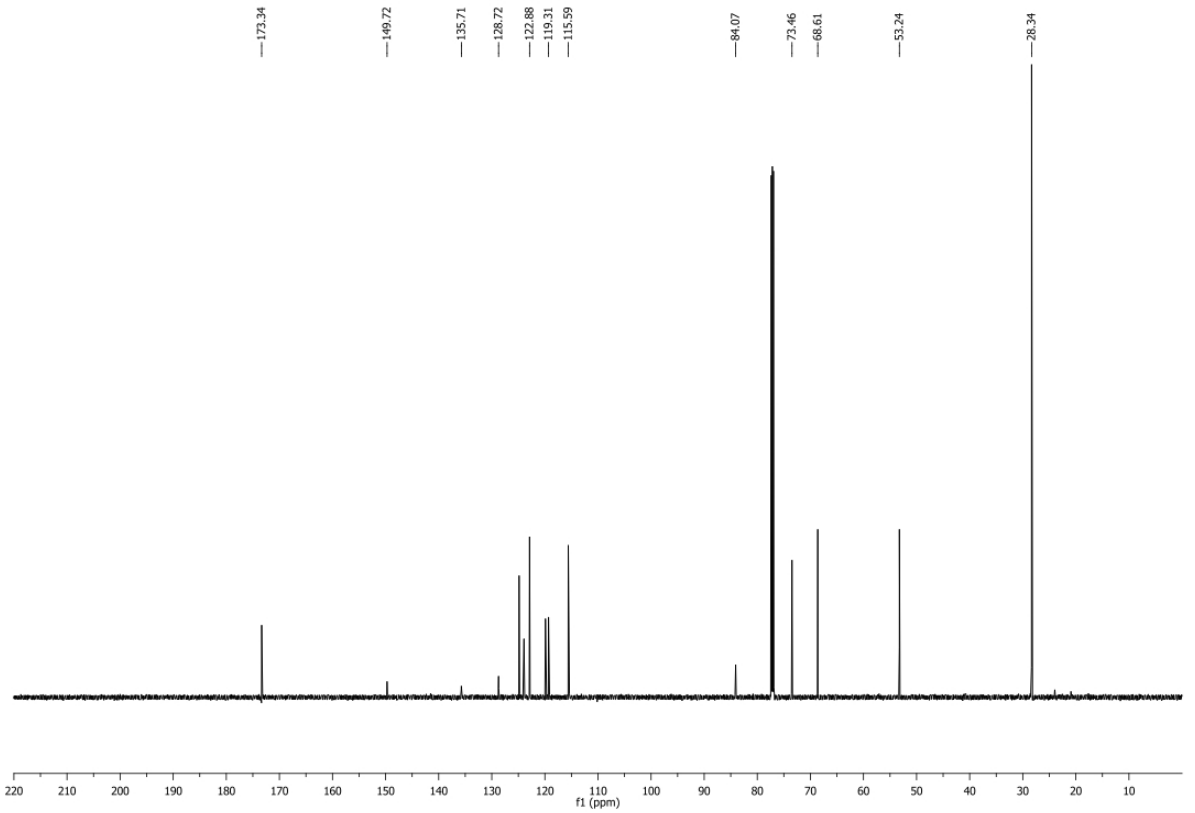


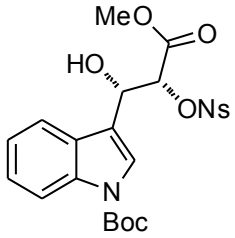
II-35

$CDCl_3$

^{1}H 600 MHz

^{13}C 150 MHz



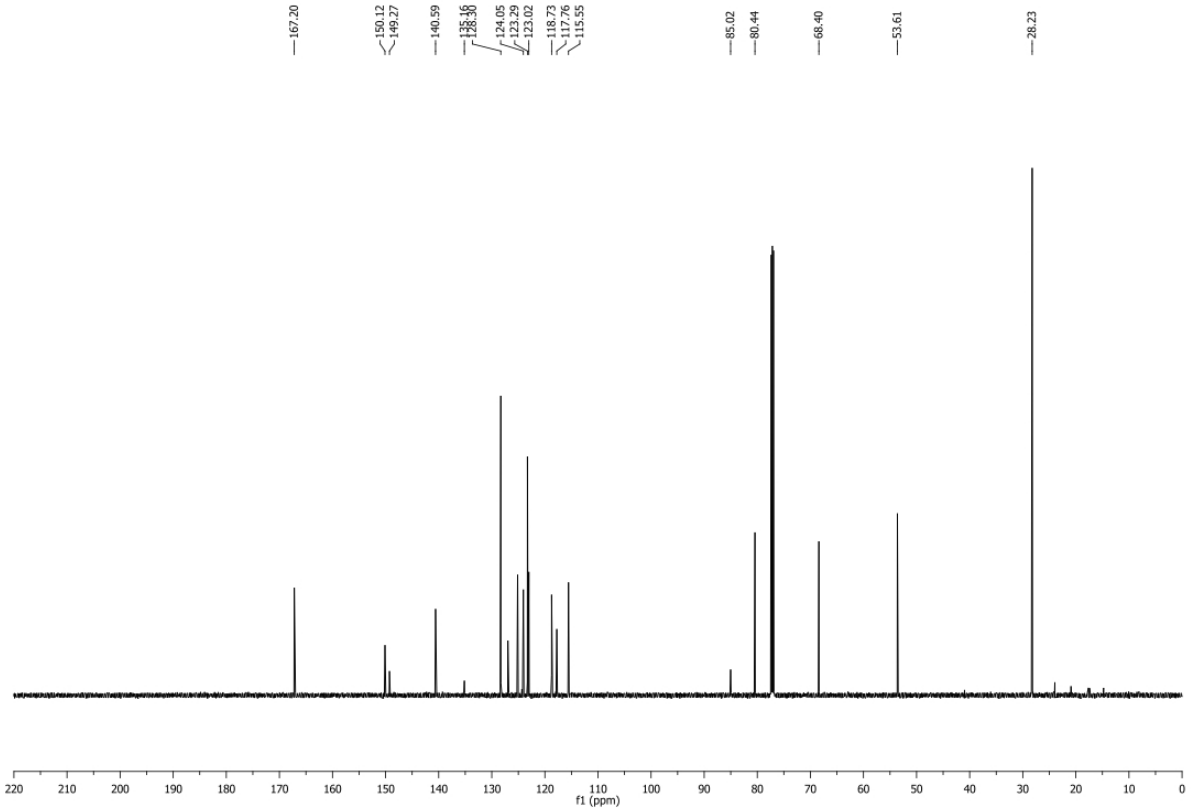


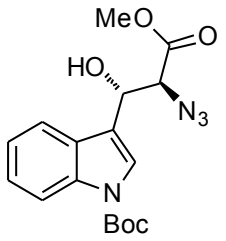
II-36

$CDCl_3$

^{1}H 600 MHz

^{13}C 150 MHz



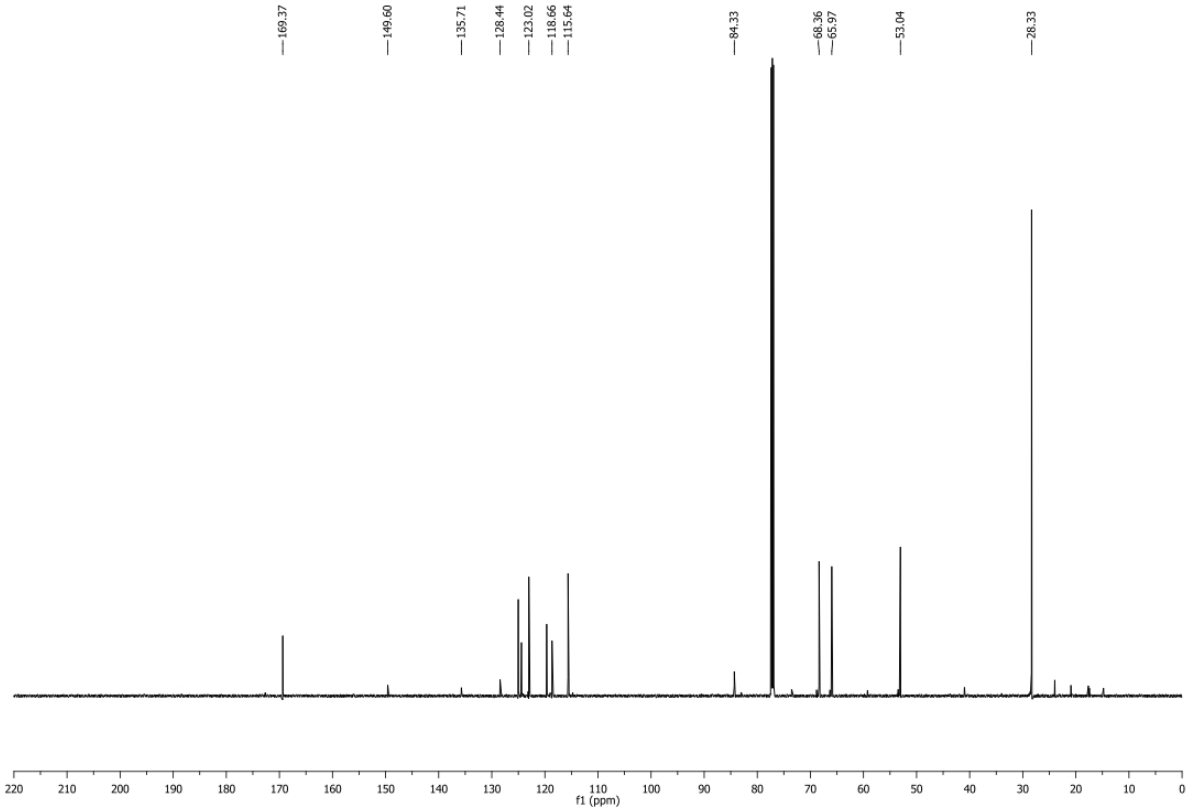


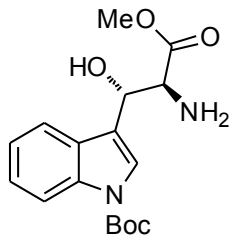
II-37

$CDCl_3$

^{1}H 600 MHz

^{13}C 150 MHz



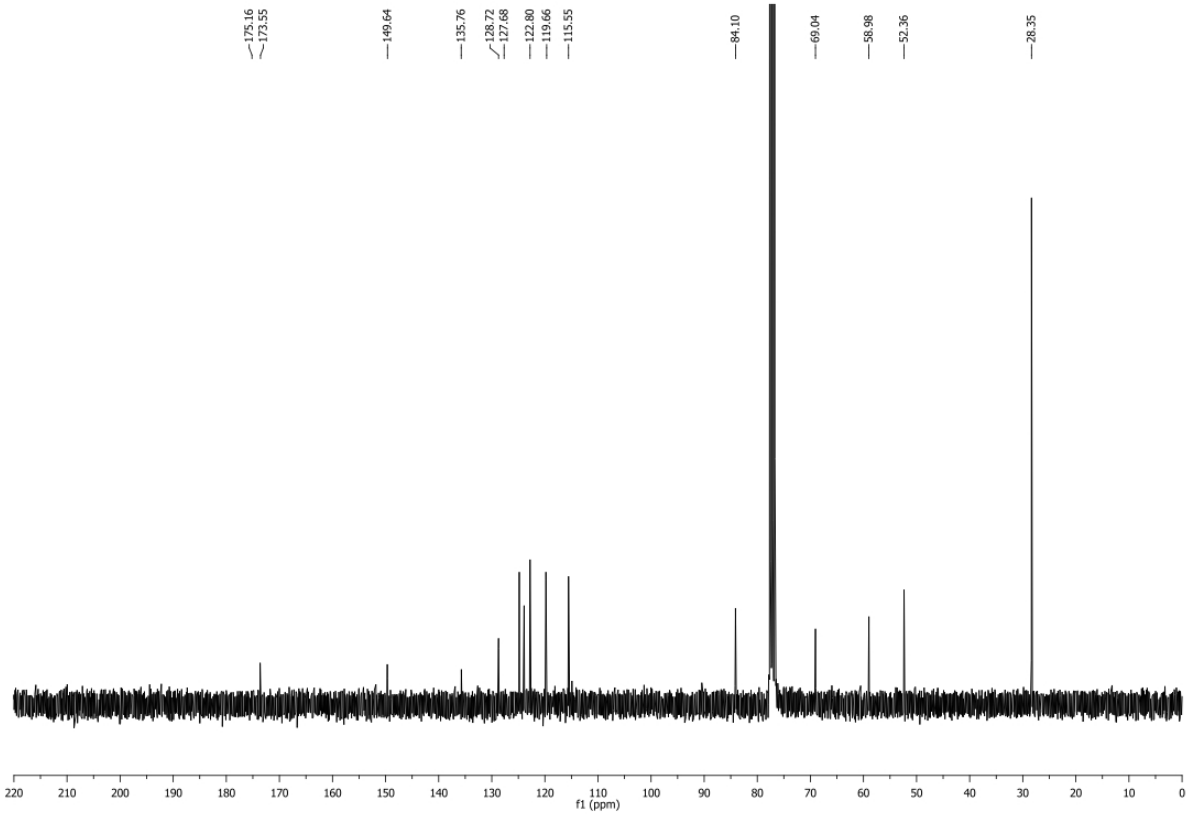


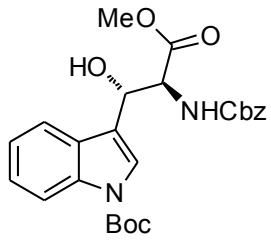
II-38

$CDCl_3$

^{1}H 300 MHz

^{13}C 75 MHz



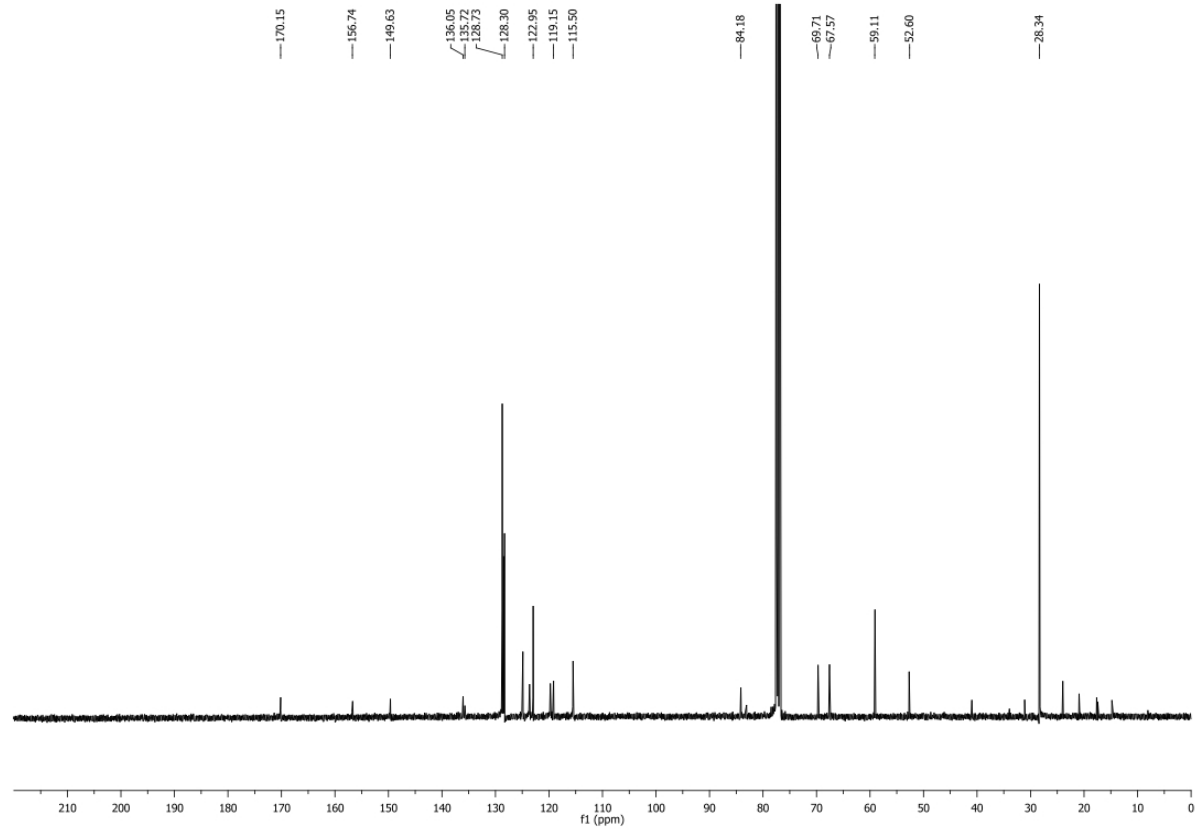


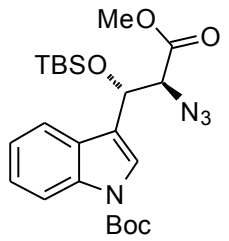
II-39

$CDCl_3$

^{1}H 600 MHz

^{13}C 100 MHz



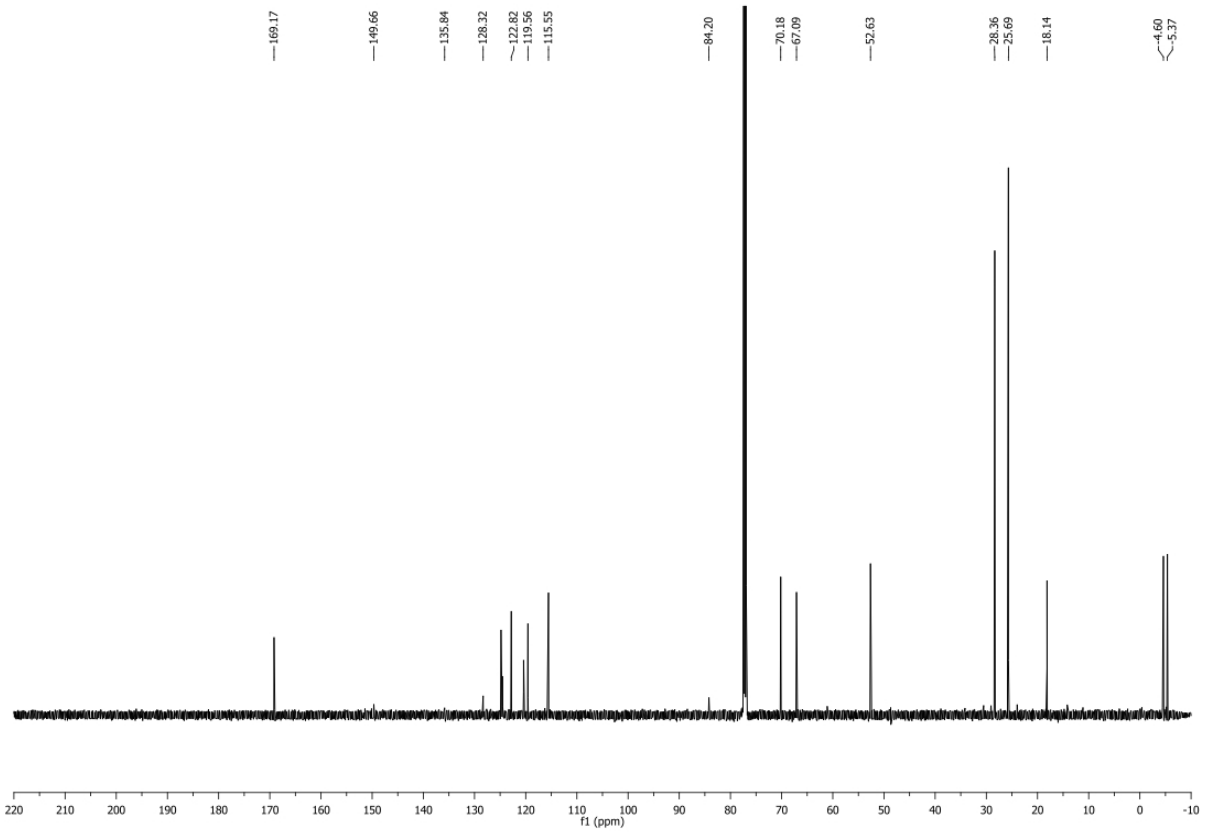


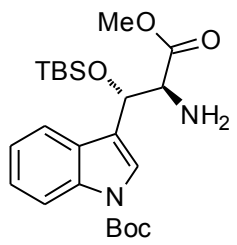
II-40

$CDCl_3$

^{1}H 600 MHz

^{13}C 150 MHz



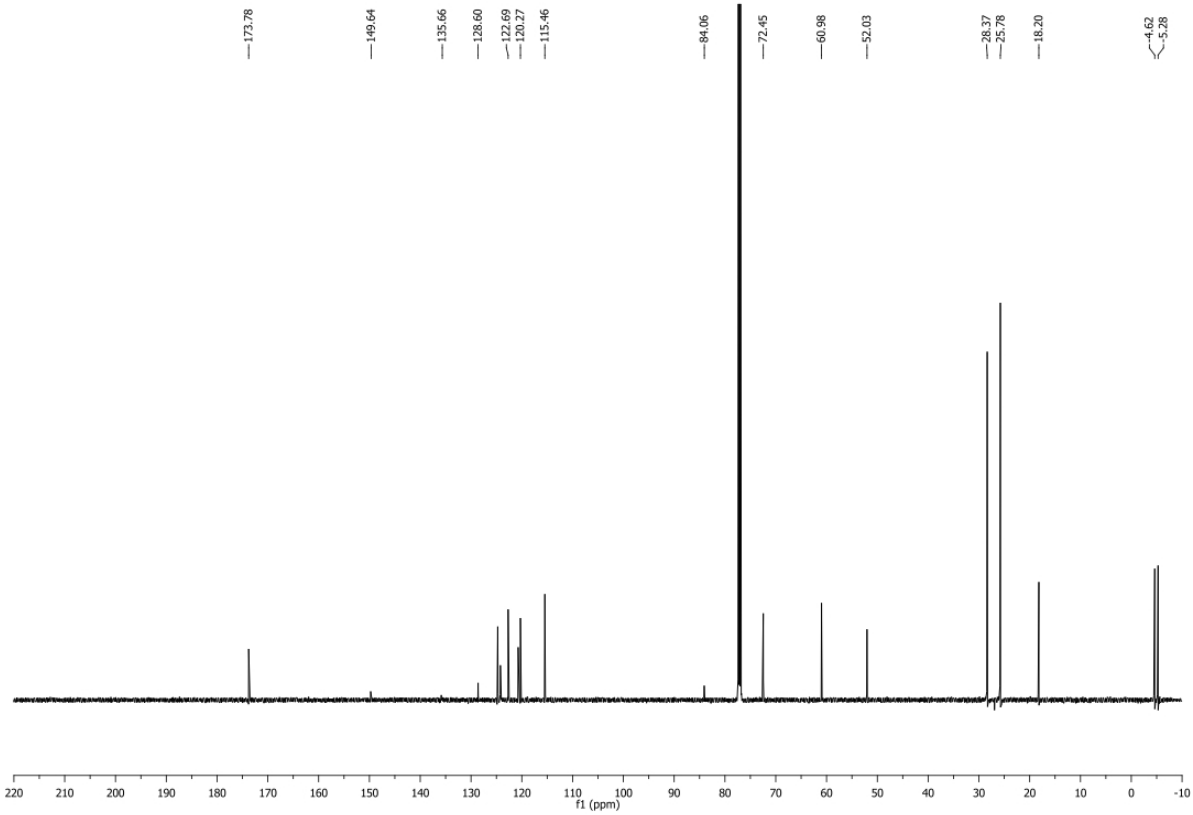


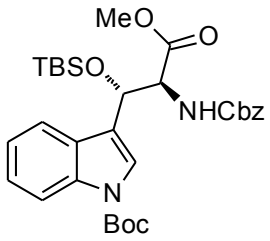
II-41

$CDCl_3$

^{1}H 600 MHz

^{13}C 150 MHz



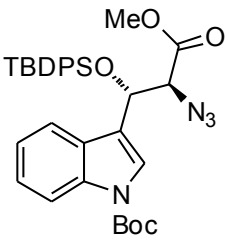


II-42

$CDCl_3$

^{1}H 400 MHz

^{13}C 150 MHz

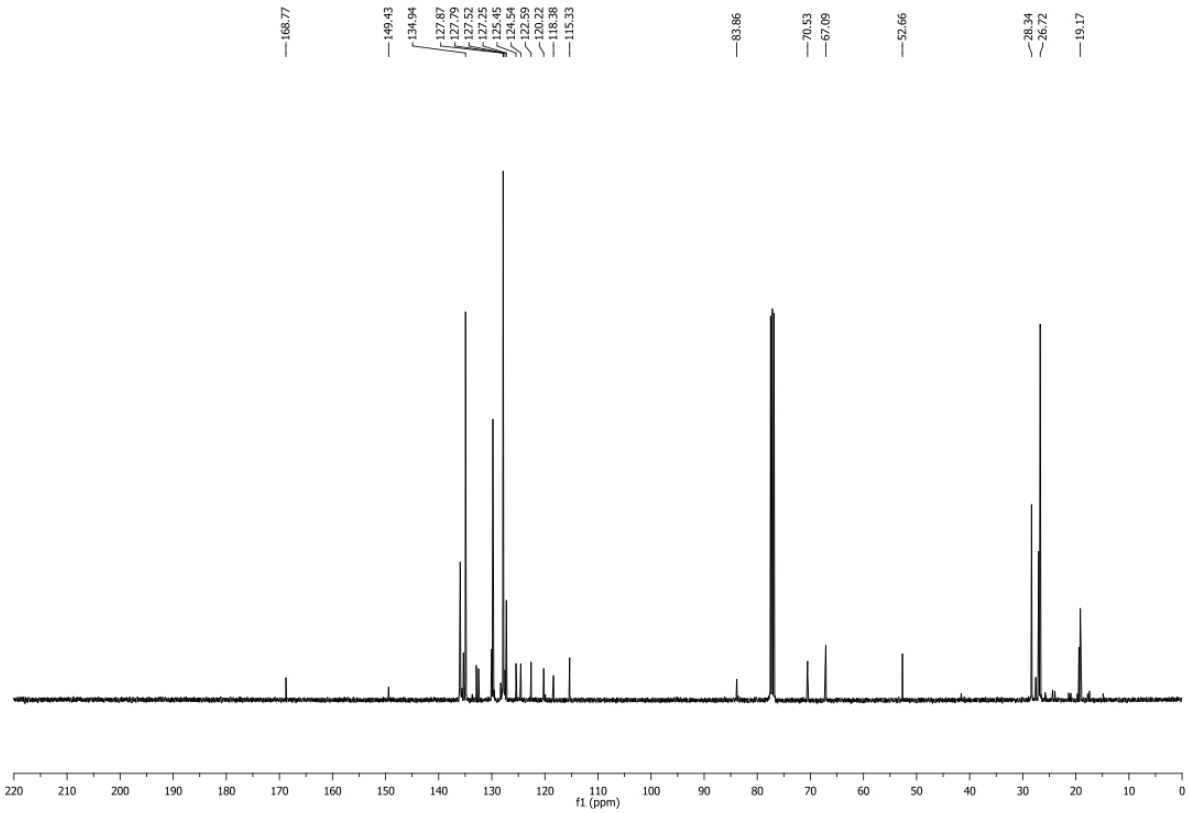


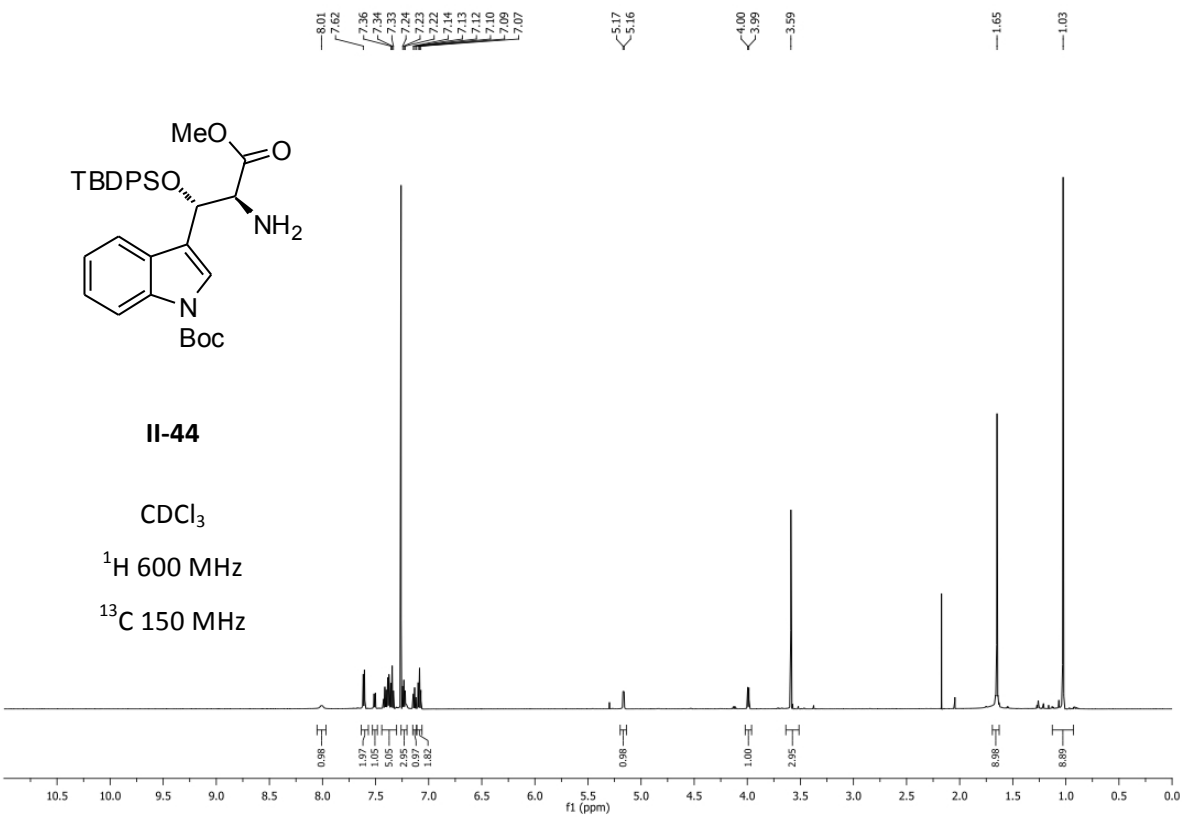
II-43

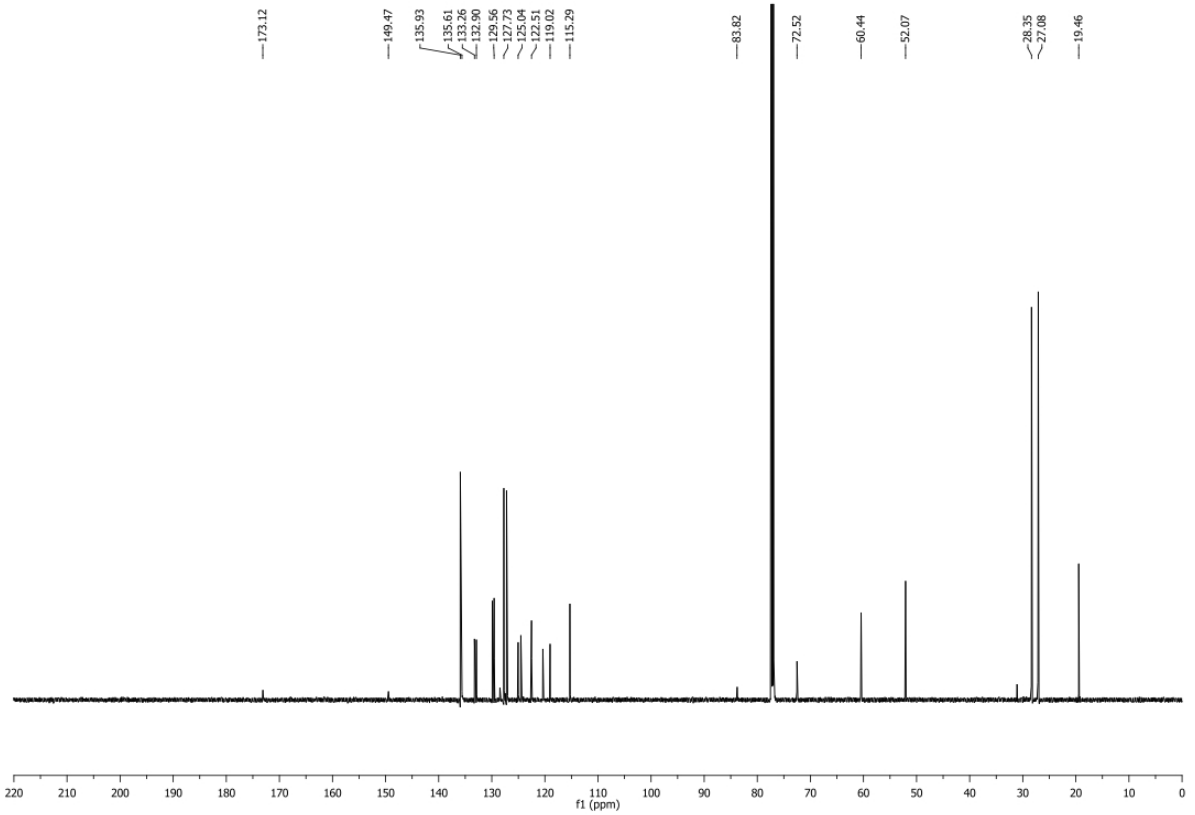
$CDCl_3$

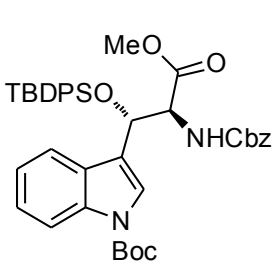
^{1}H 400 MHz

^{13}C 100 MHz




MeO
O
TBDPSO
NH2
N
Boc
II-44
CDCl3
1H 600 MHz
13C 150 MHz
f1 (ppm)


f1 (ppm)

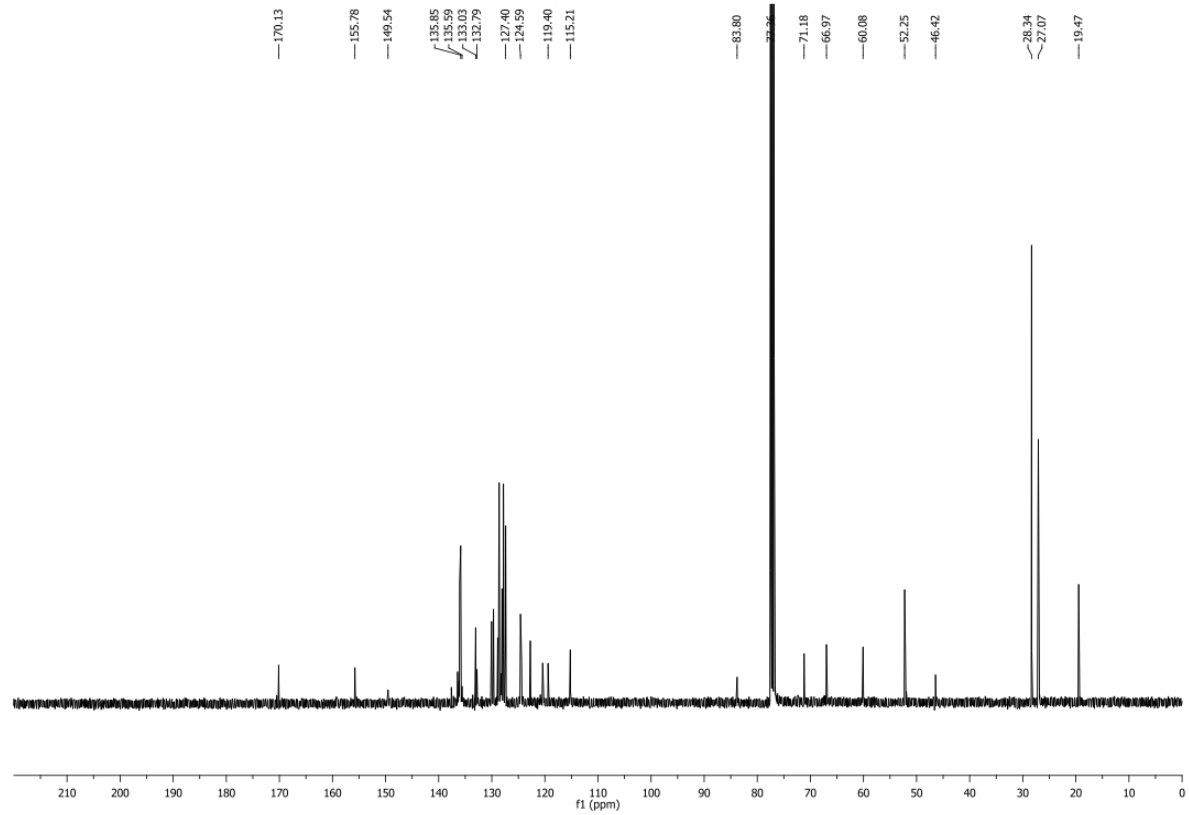


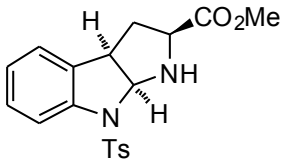
II-44

$CDCl_3$

^{1}H 400 MHz

^{13}C 100 MHz



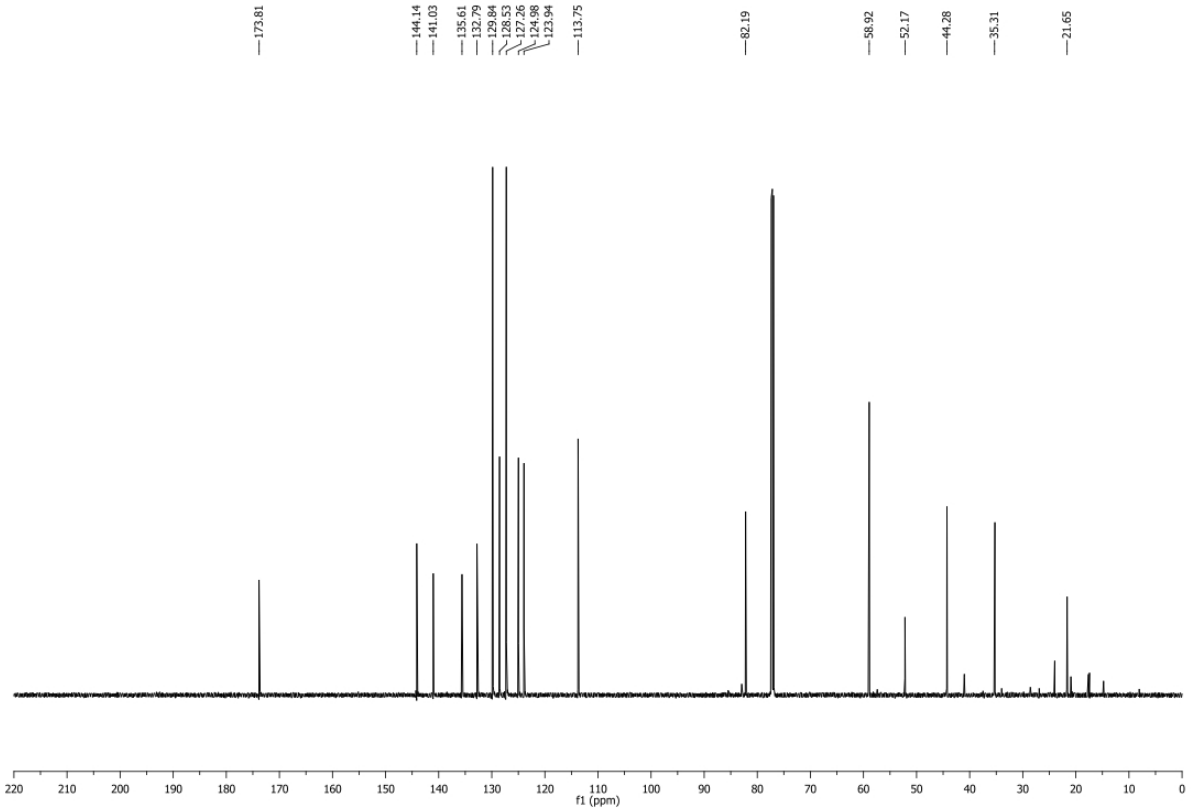


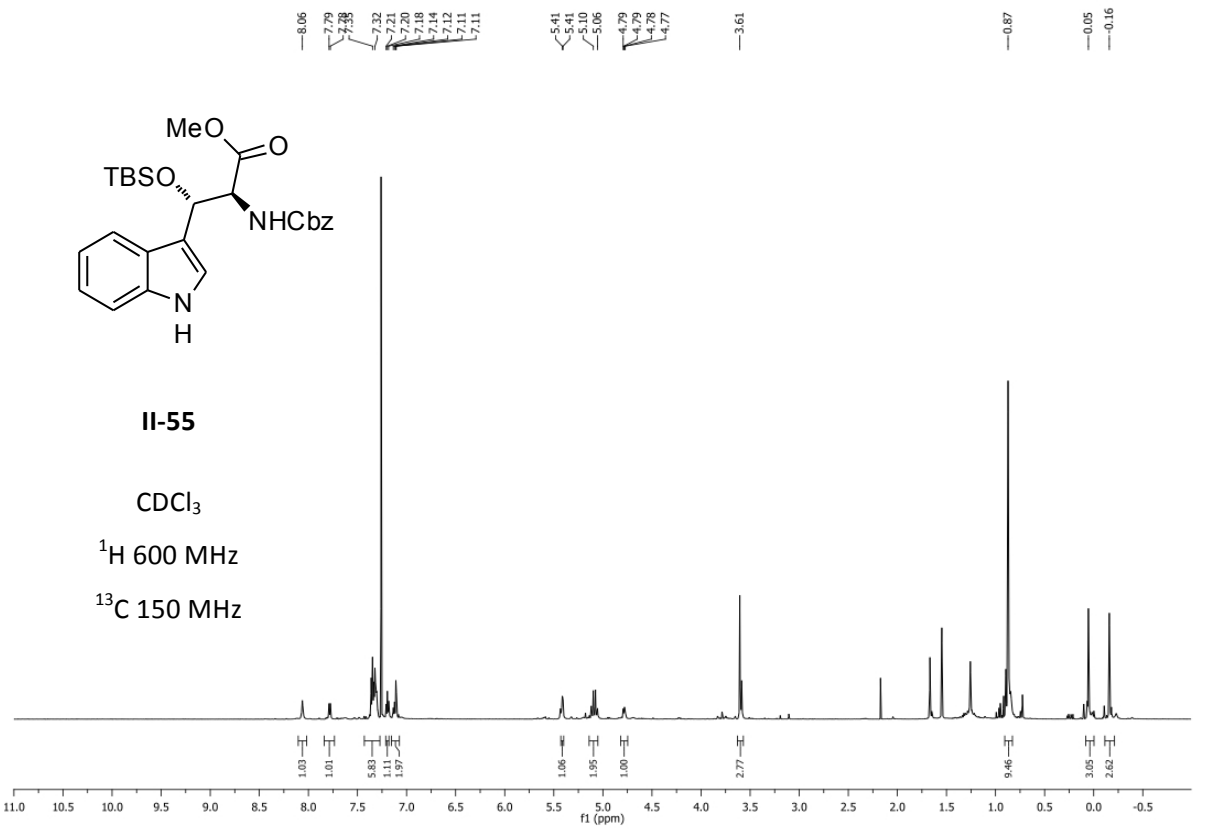
II-127 endo

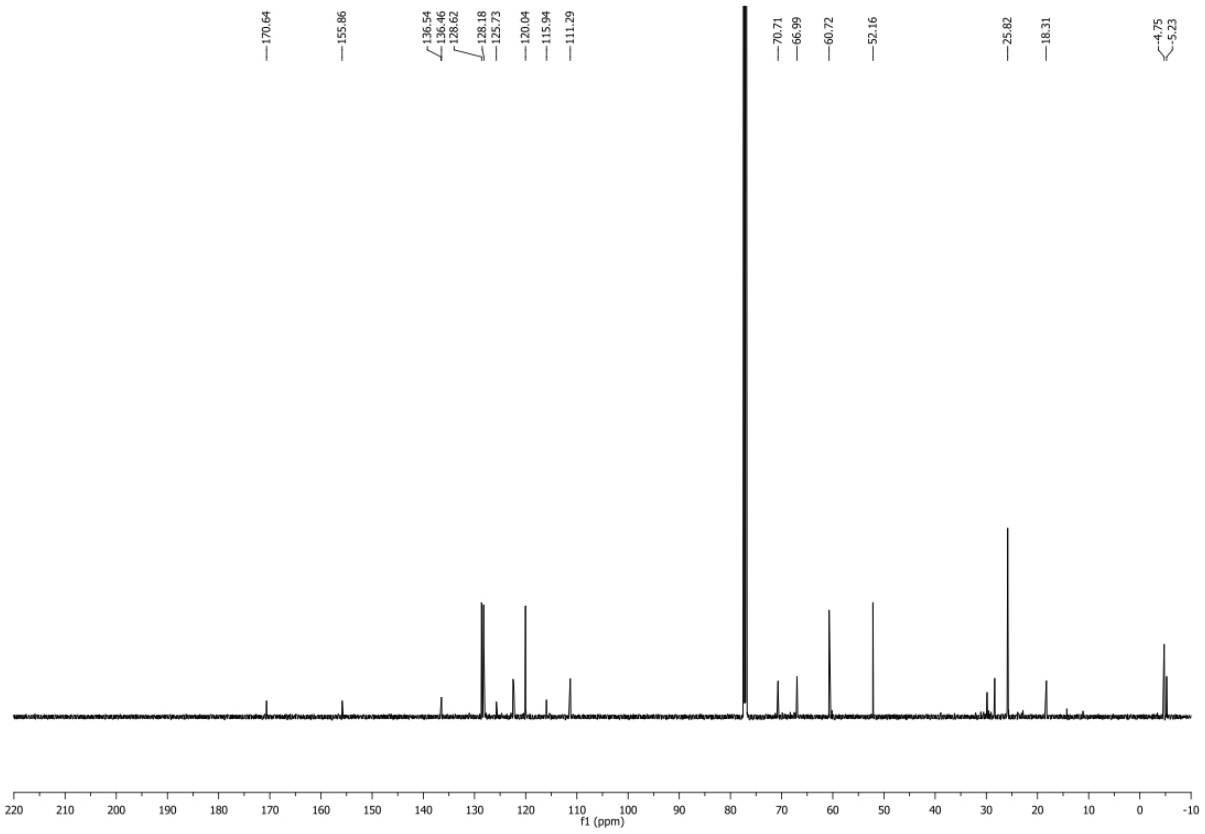
$CDCl_3$

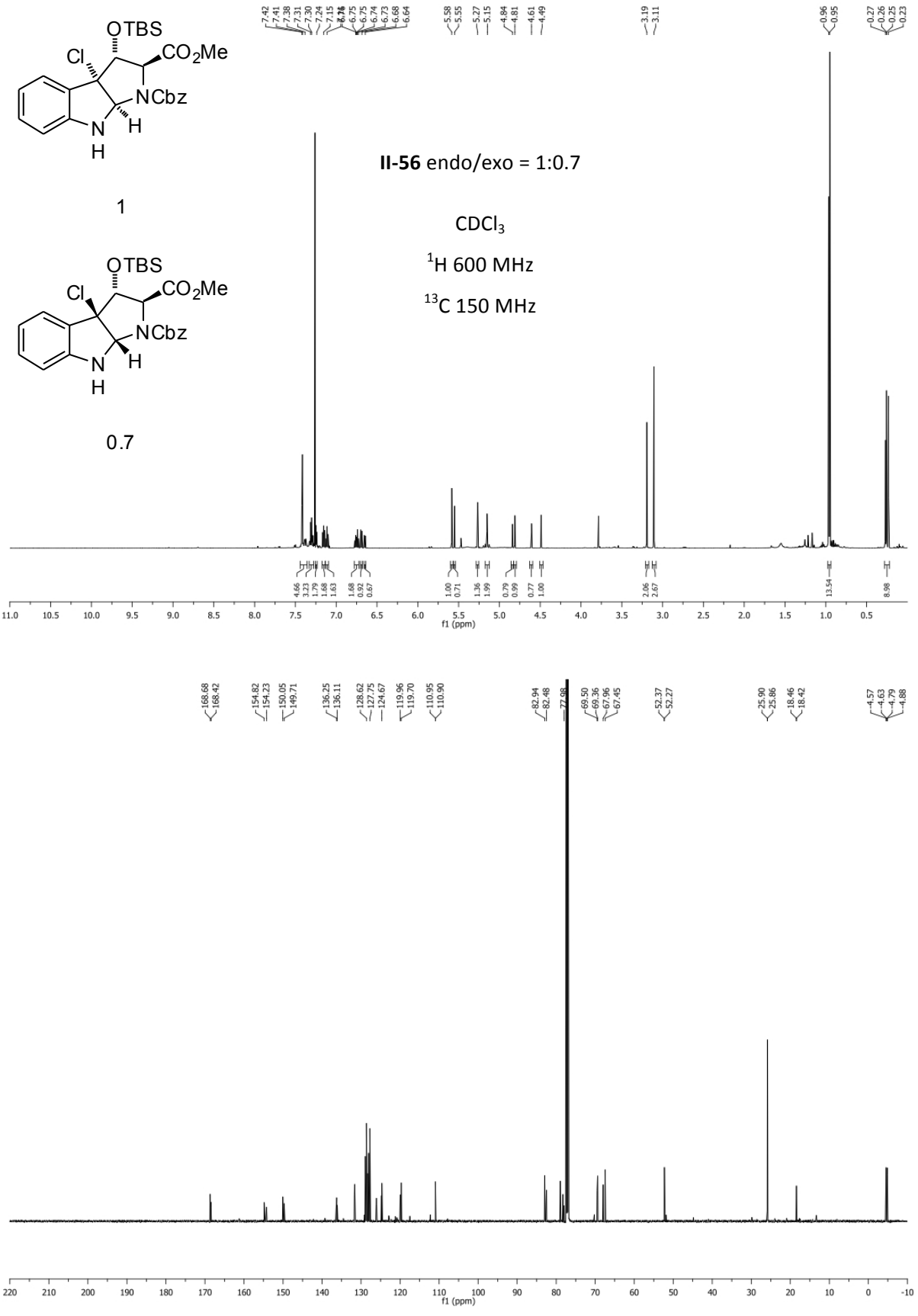
^{1}H 600 MHz

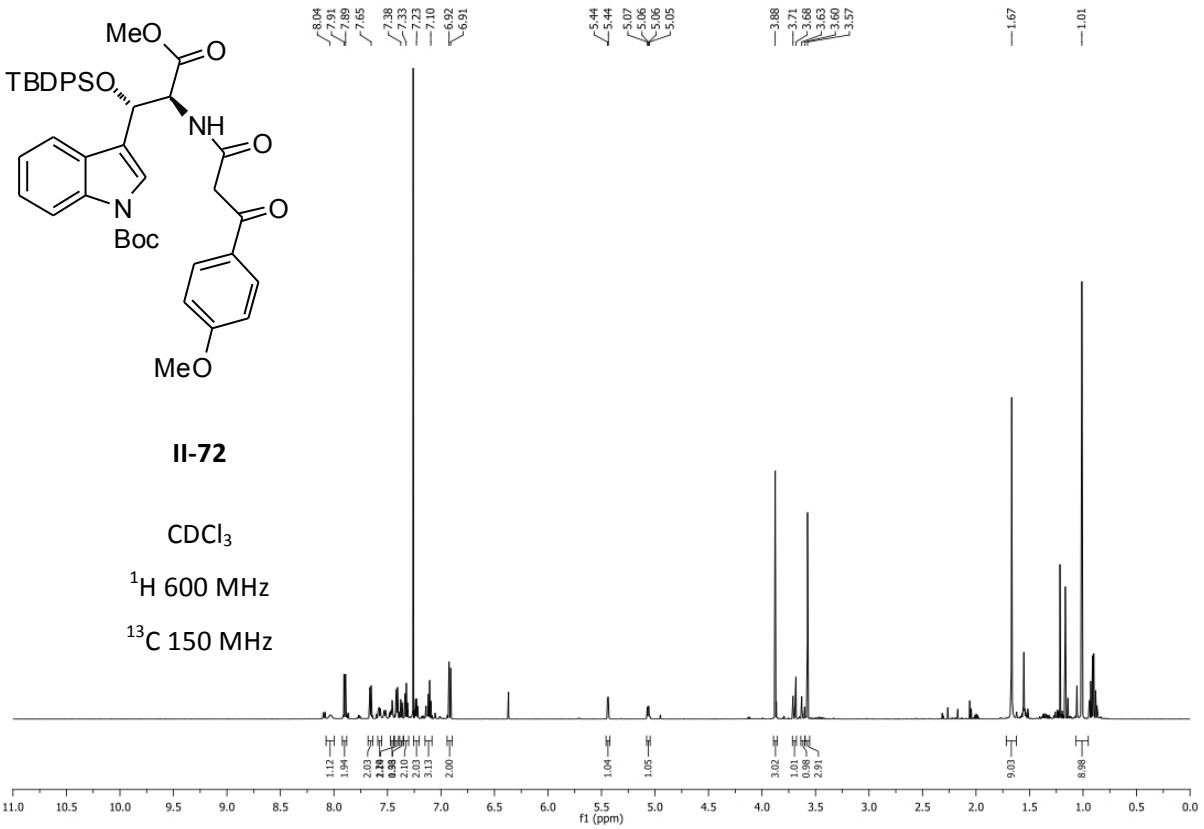
^{13}C 150 MHz

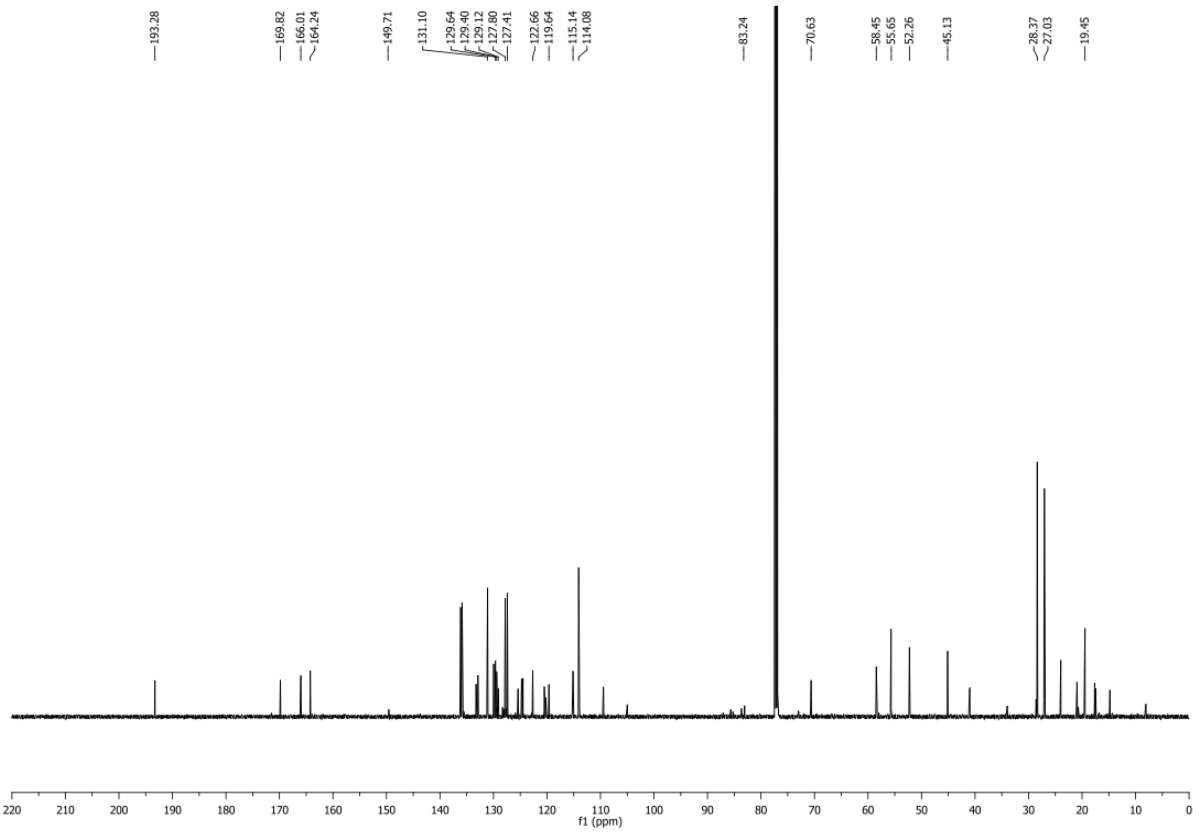


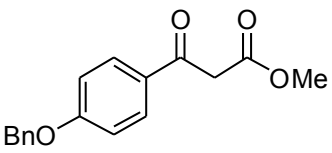

MeO
O
TBSO
NHCbz
N
H
II-55
CDCl3
1H 600 MHz
13C 150 MHz
f1 (ppm)


f1 (ppm)


OTBS
Cl
CO2Me
NCbz
N
H
H
1
OTBS
Cl
CO2Me
NCbz
N
H
H
0.7
II-56 endo/exo = 1:0.7
CDCl3
1H 600 MHz
13C 150 MHz
f1 (ppm)
f1 (ppm)


MeO
O
TBDPSO
NH
O
N
Boc
O
MeO
II-72
CDCl3
1H 600 MHz
13C 150 MHz
f1 (ppm)


f1 (ppm)

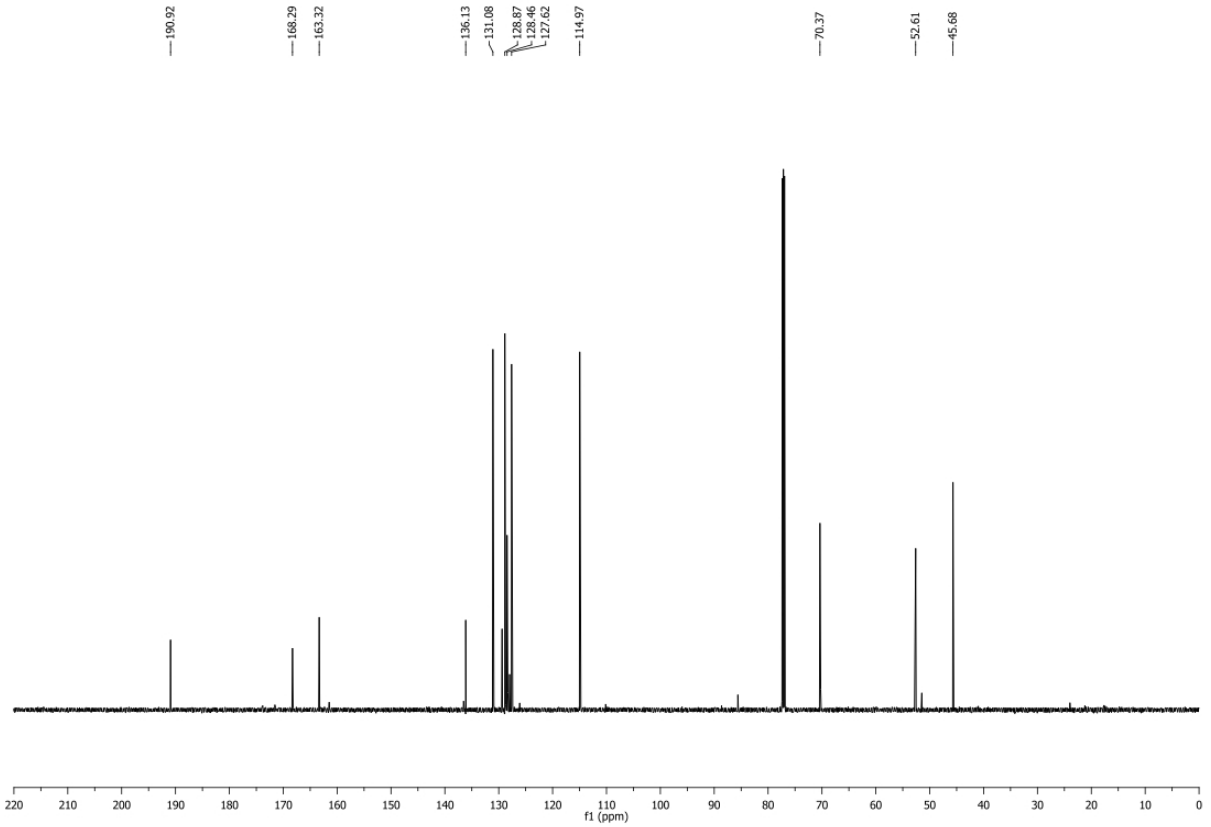


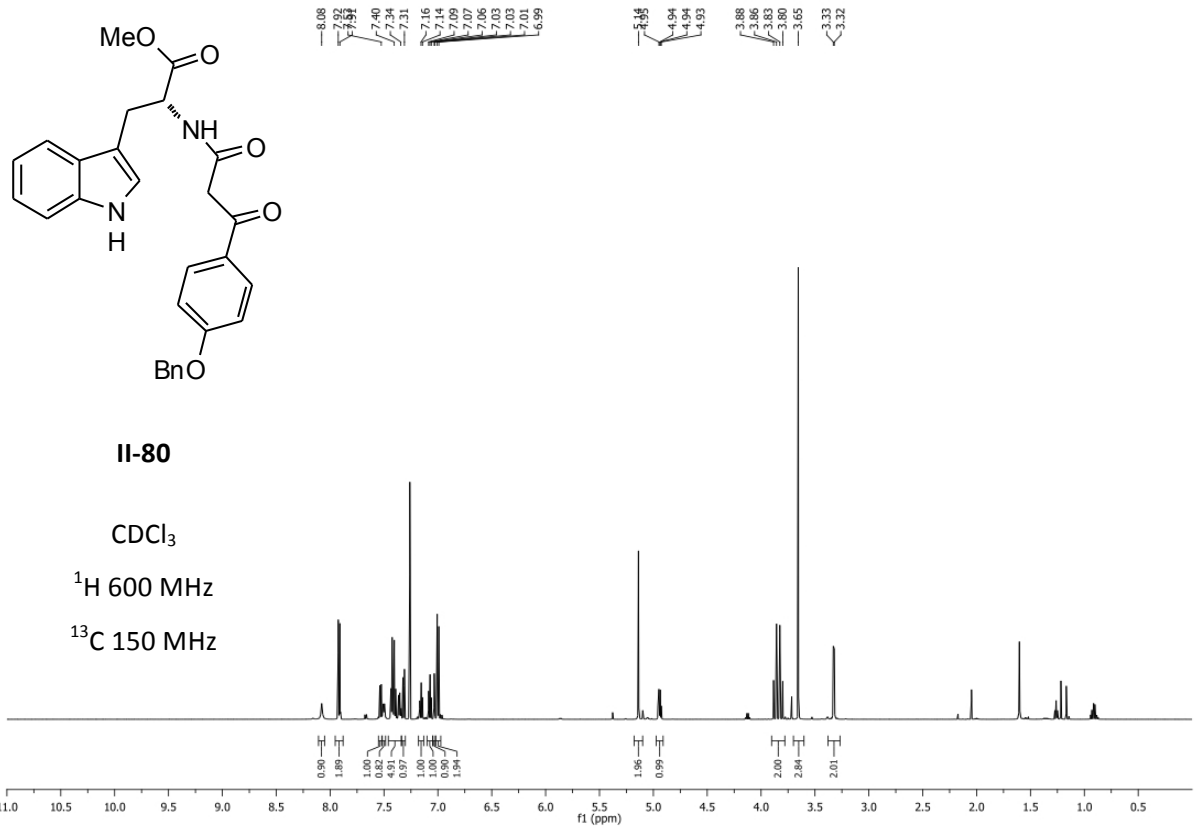
II-82

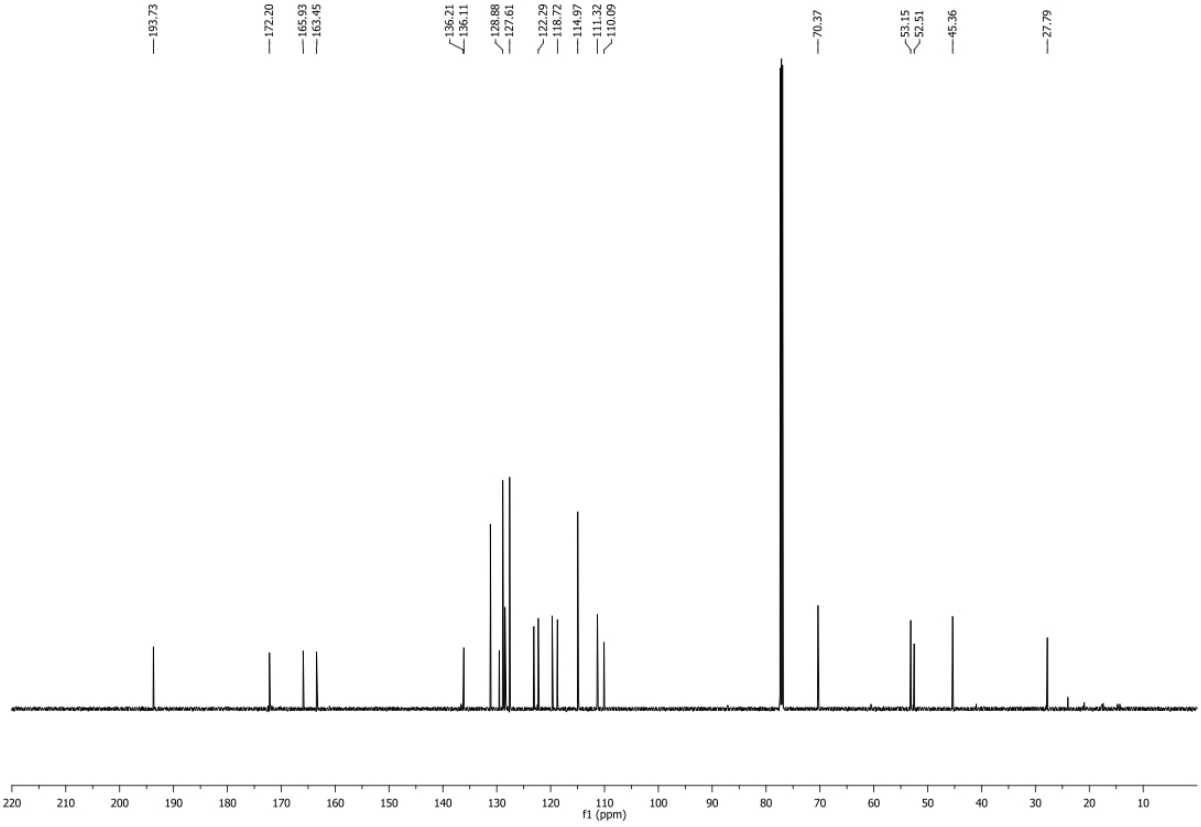
$CDCl_3$

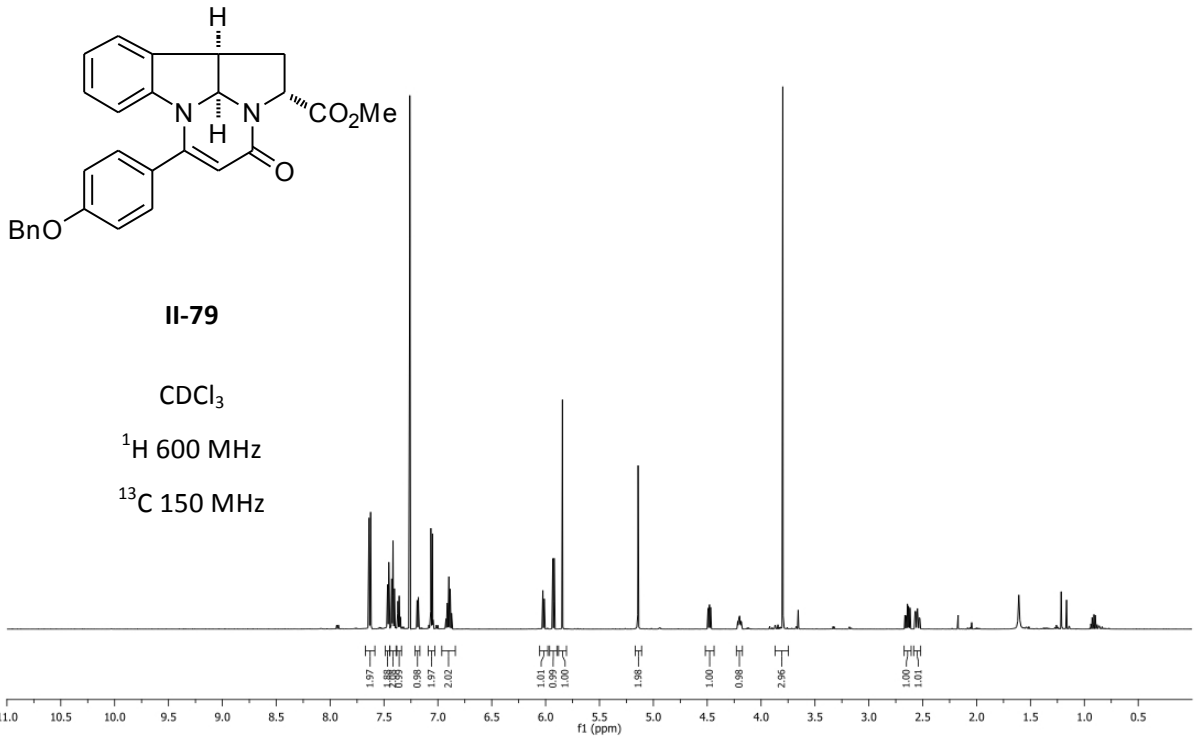
^{1}H 600 MHz

^{13}C 150 MHz




MeO
O
NH
O
O
N
H
BnO
II-80
CDCl3
1H 600 MHz
13C 150 MHz
f1 (ppm)


193.73
172.20
165.93
163.45
136.21
136.11
128.88
127.61
122.29
118.72
114.97
111.32
110.09
70.37
53.15
52.51
45.36
27.79
f1 (ppm)

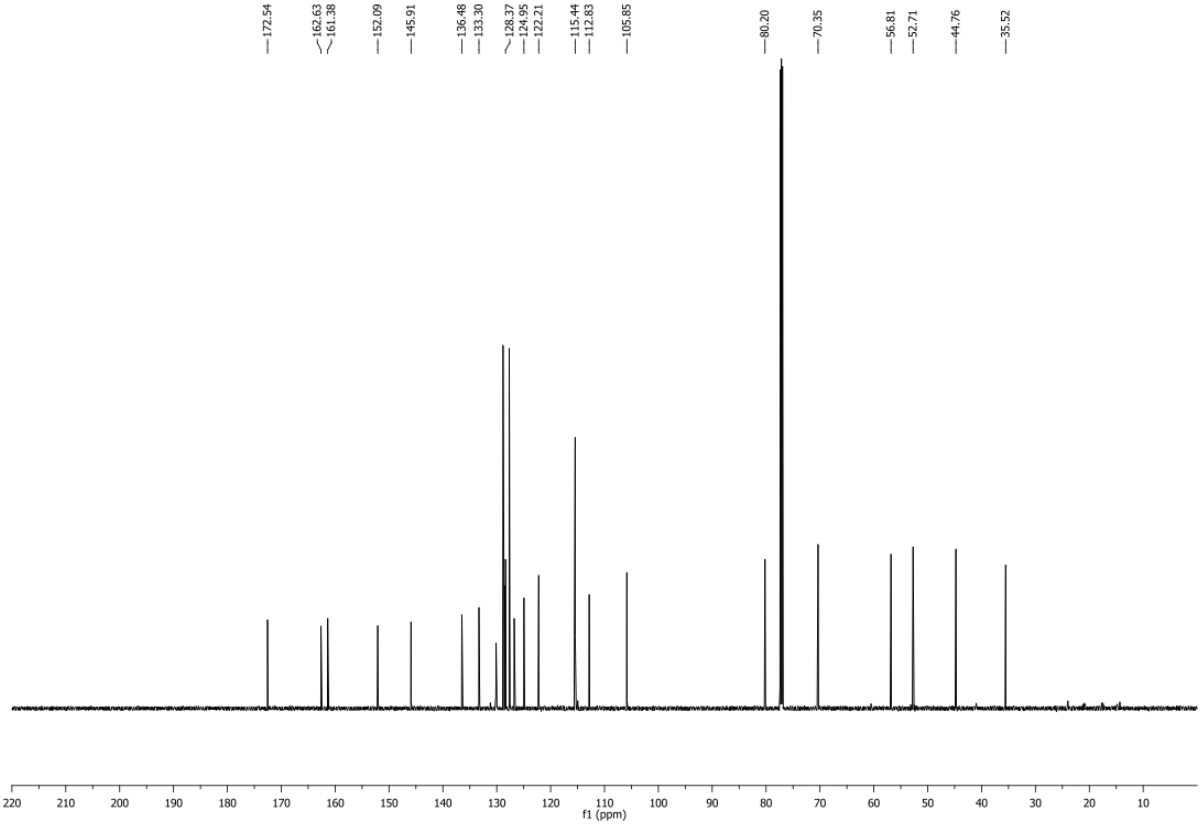


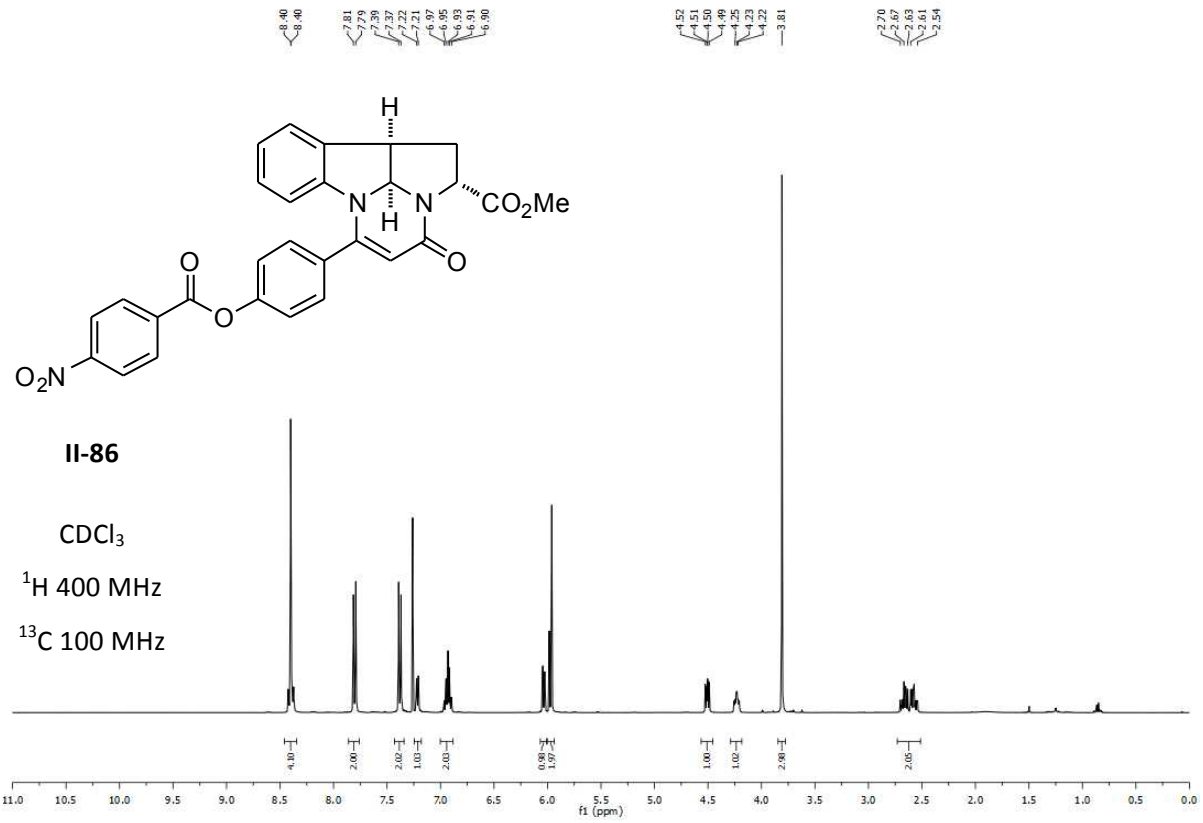
II-79

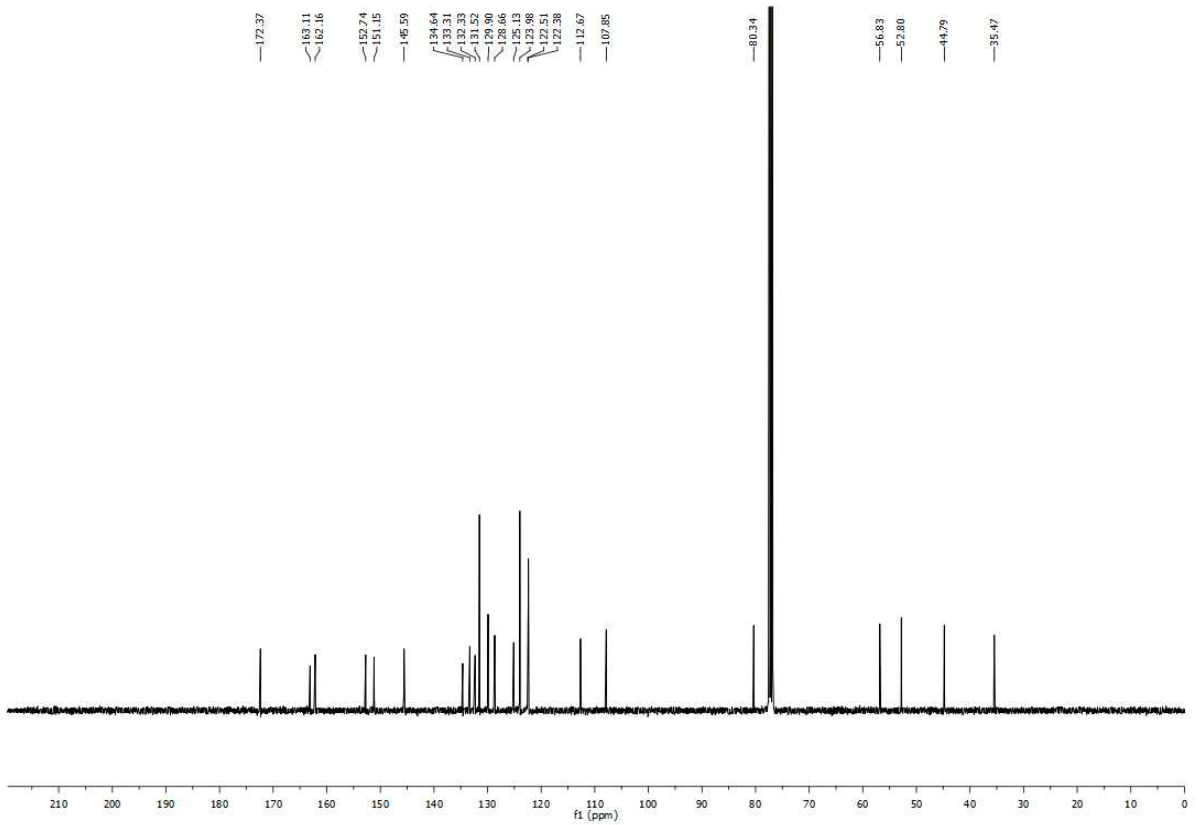
$CDCl_3$

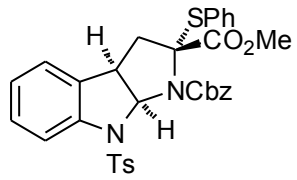
^{1}H 600 MHz

^{13}C 150 MHz




II-86
CDCl3
1H 400 MHz
13C 100 MHz
f1 (ppm)


f1 (ppm)

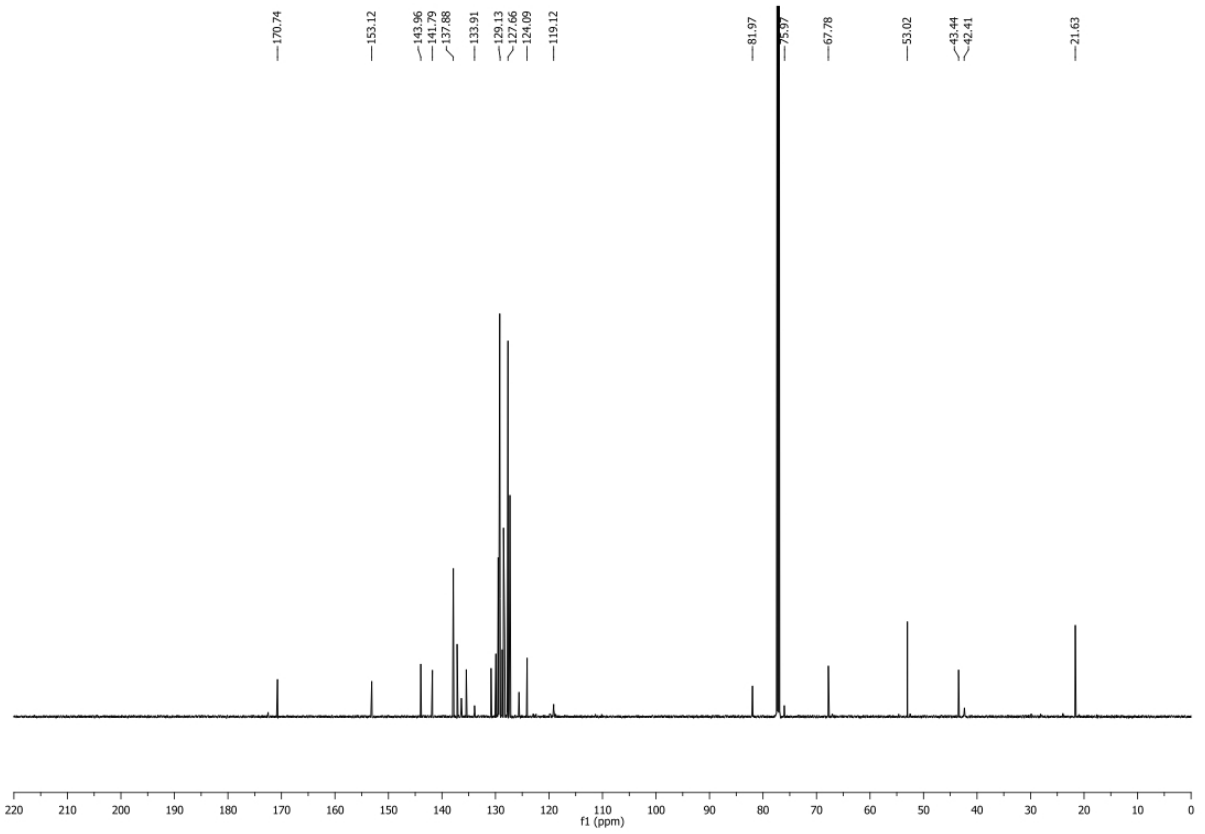


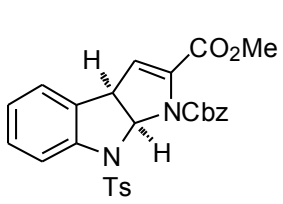
II-128

$CDCl_3$

^{1}H 600 MHz

^{13}C 150 MHz



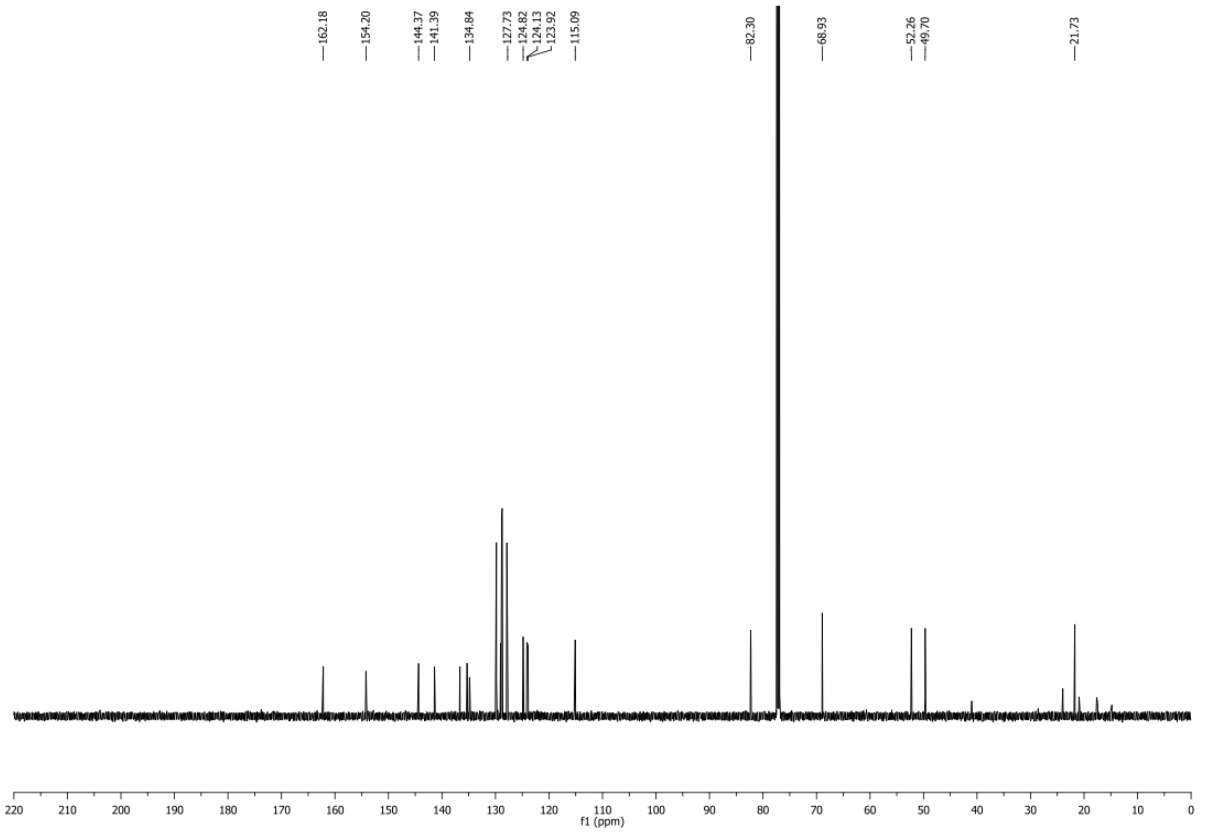


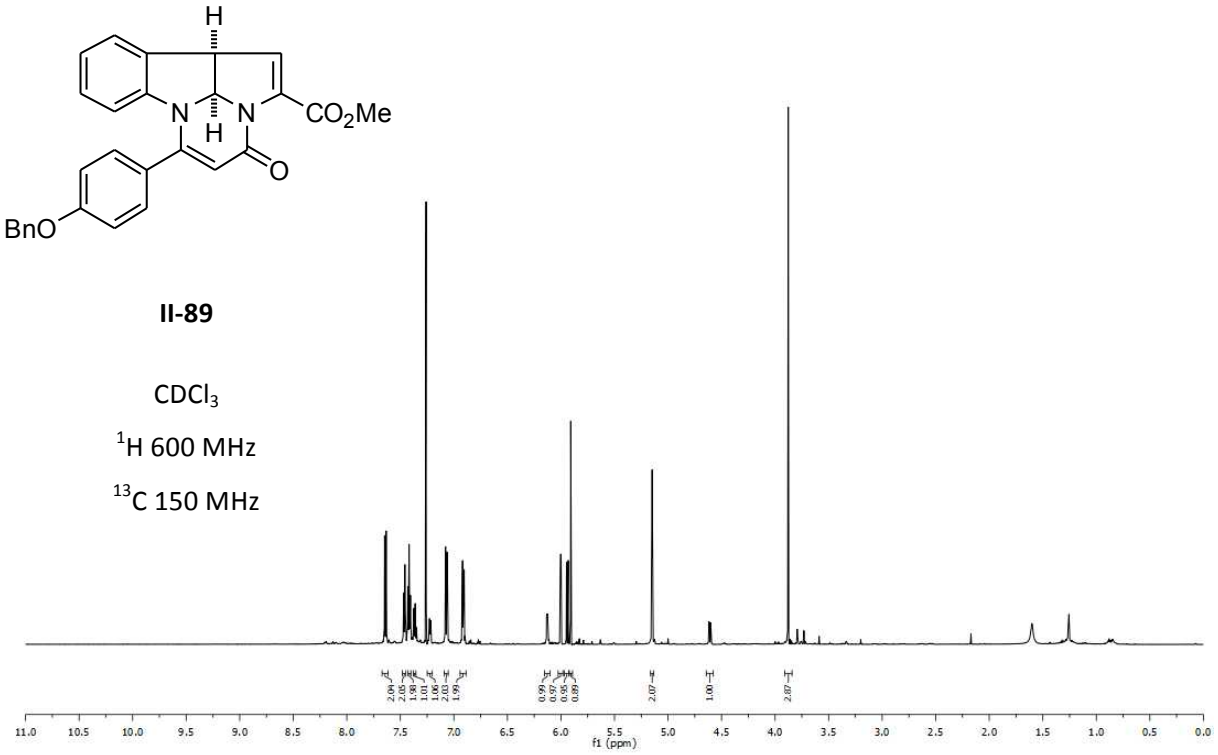
II-129

$CDCl_3$

^{1}H 600 MHz

^{13}C 150 MHz



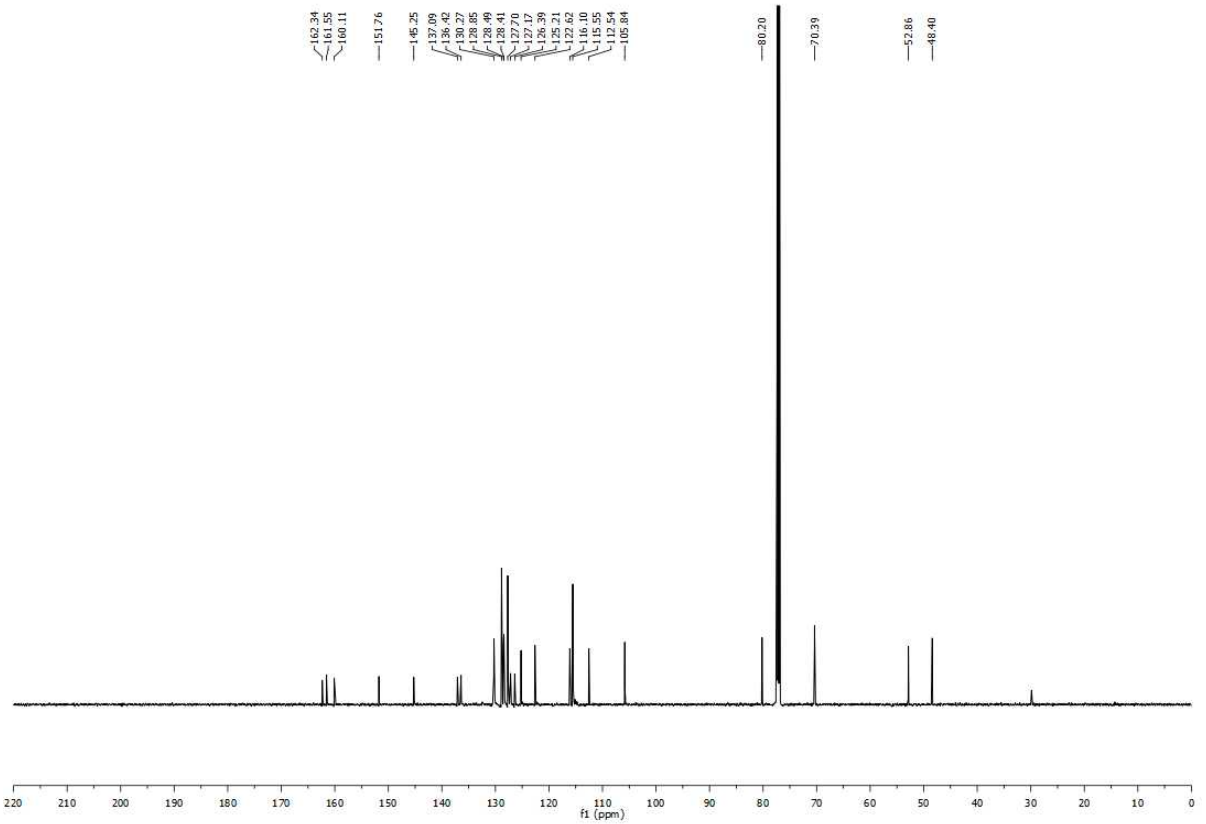


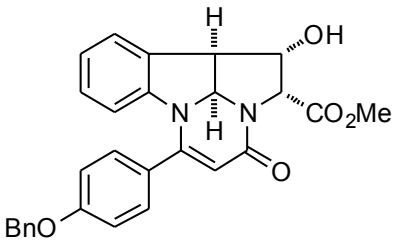
II-89

$CDCl_3$

^{1}H 600 MHz

^{13}C 150 MHz



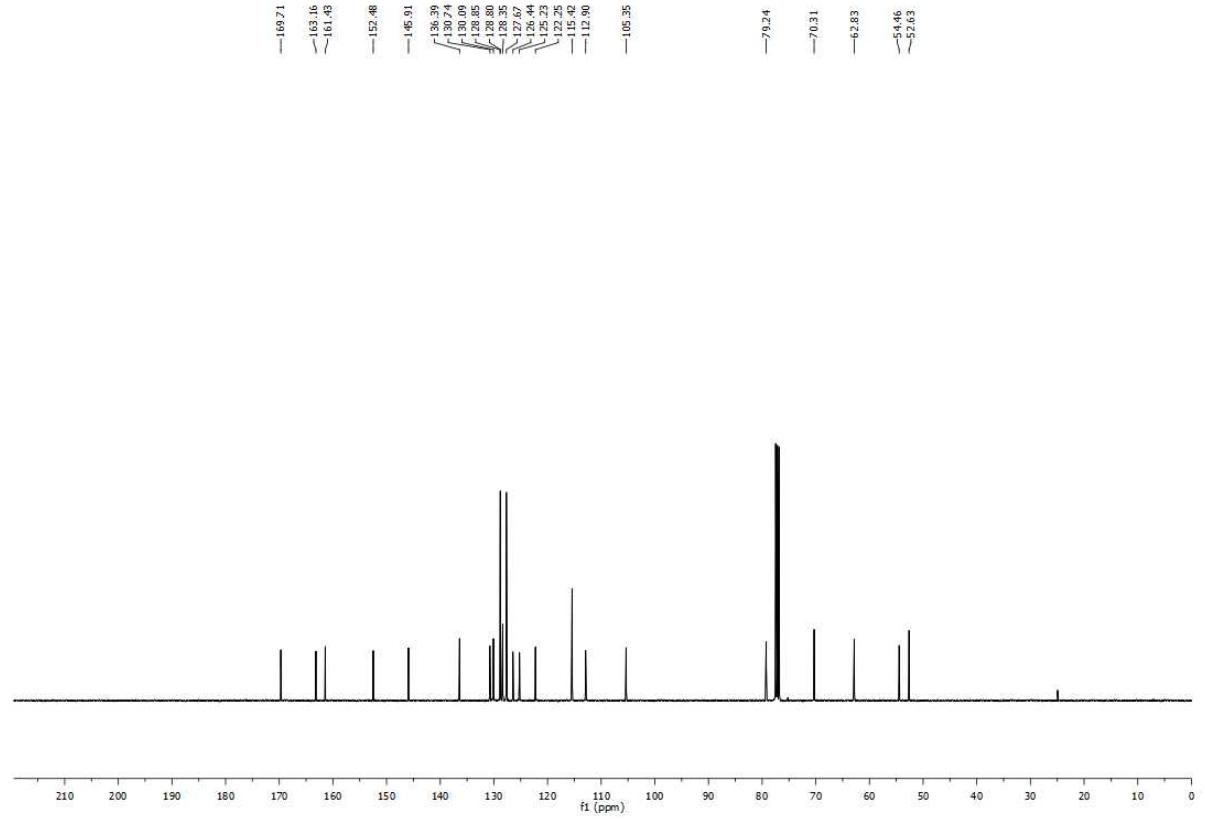


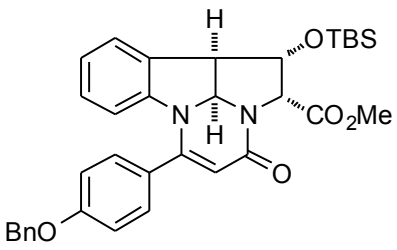
II-90

$CDCl_3$

^{1}H 400 MHz

^{13}C 100 MHz



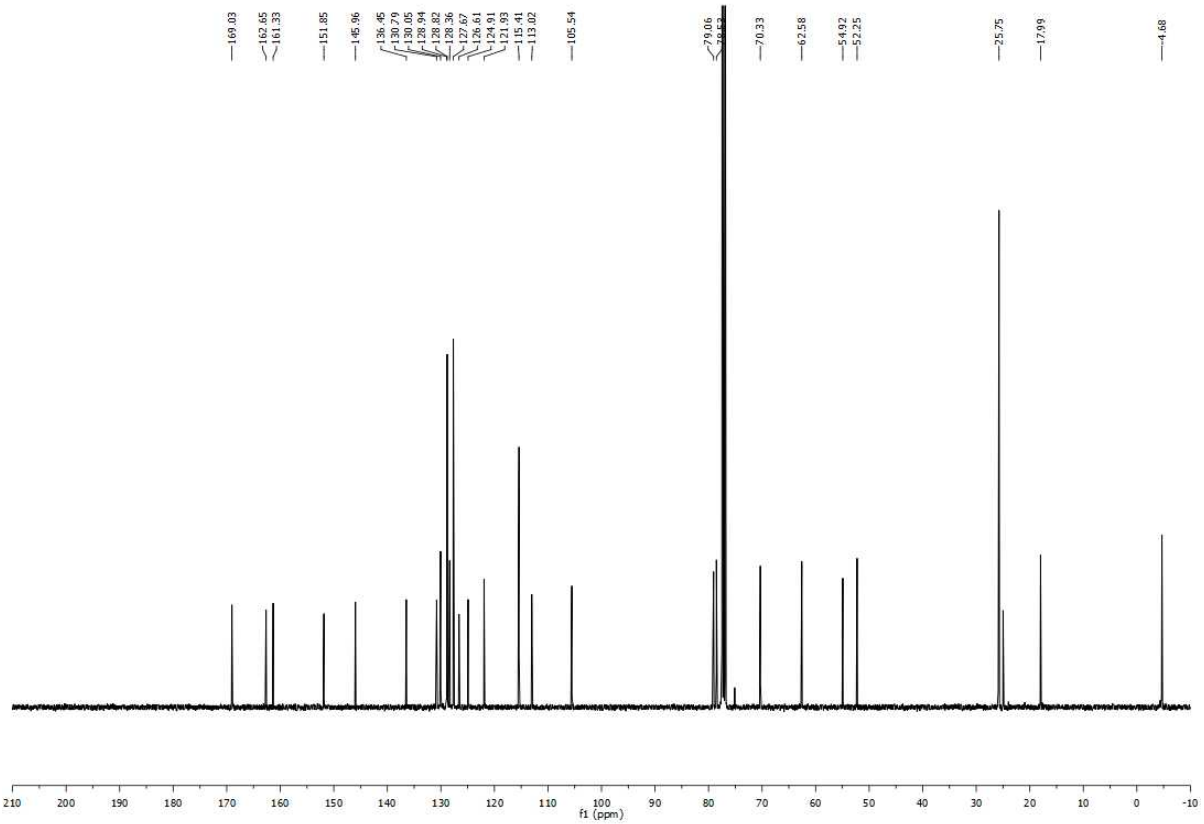


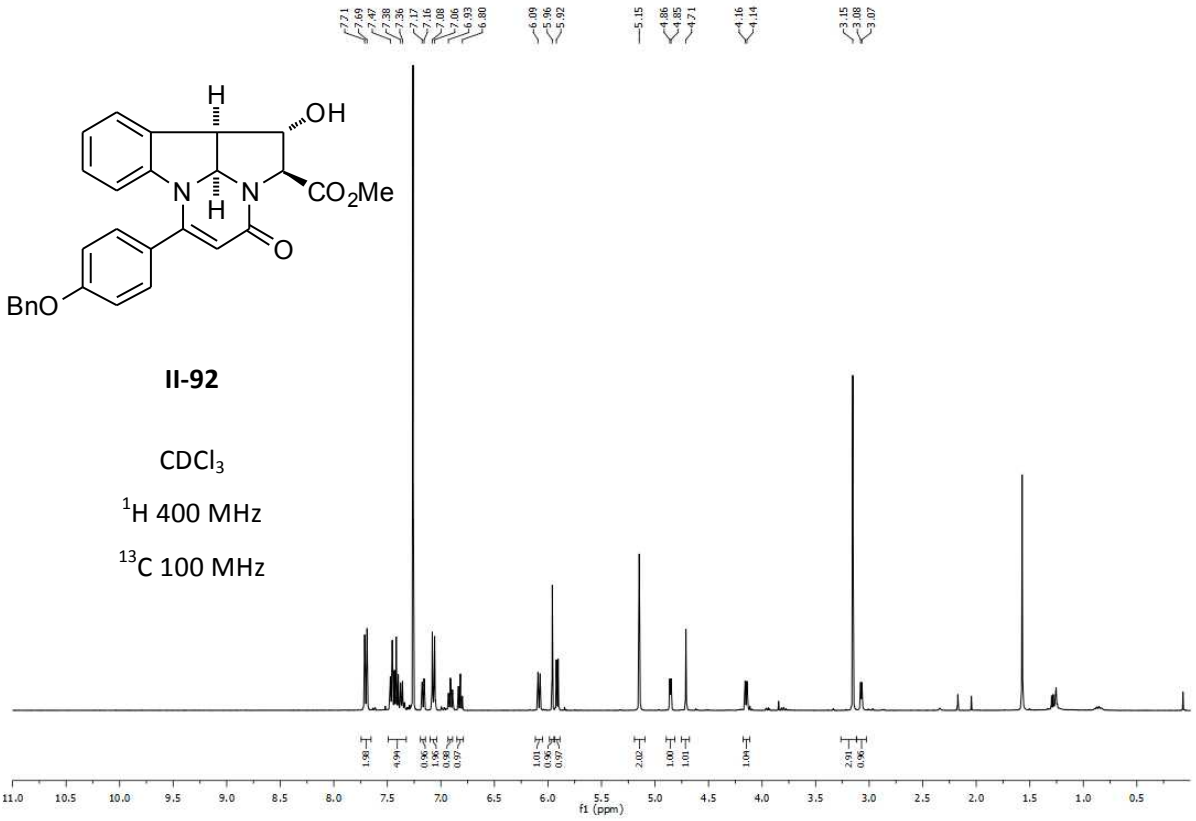
II-91

$CDCl_3$

^{1}H 400 MHz

^{13}C 100 MHz



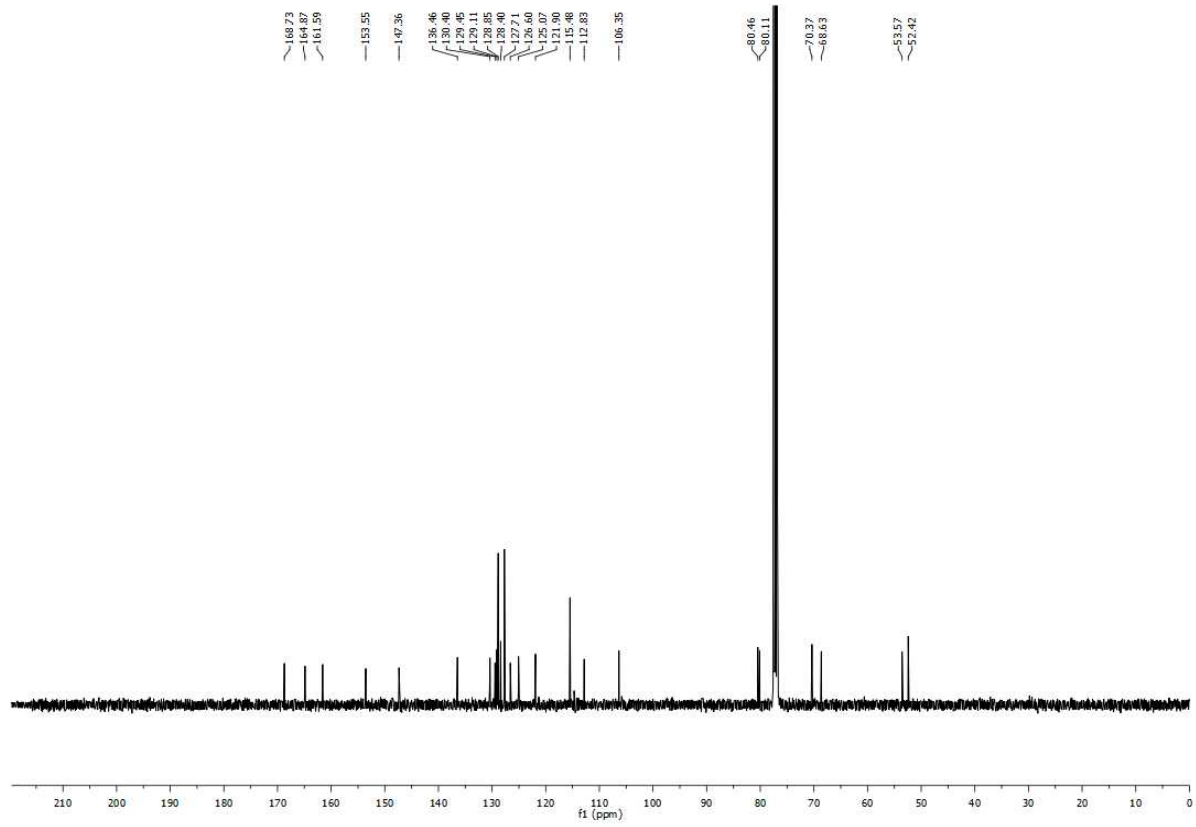


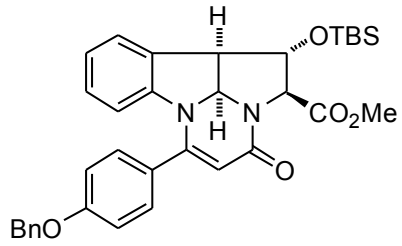
II-92

$CDCl_3$

^{1}H 400 MHz

^{13}C 100 MHz



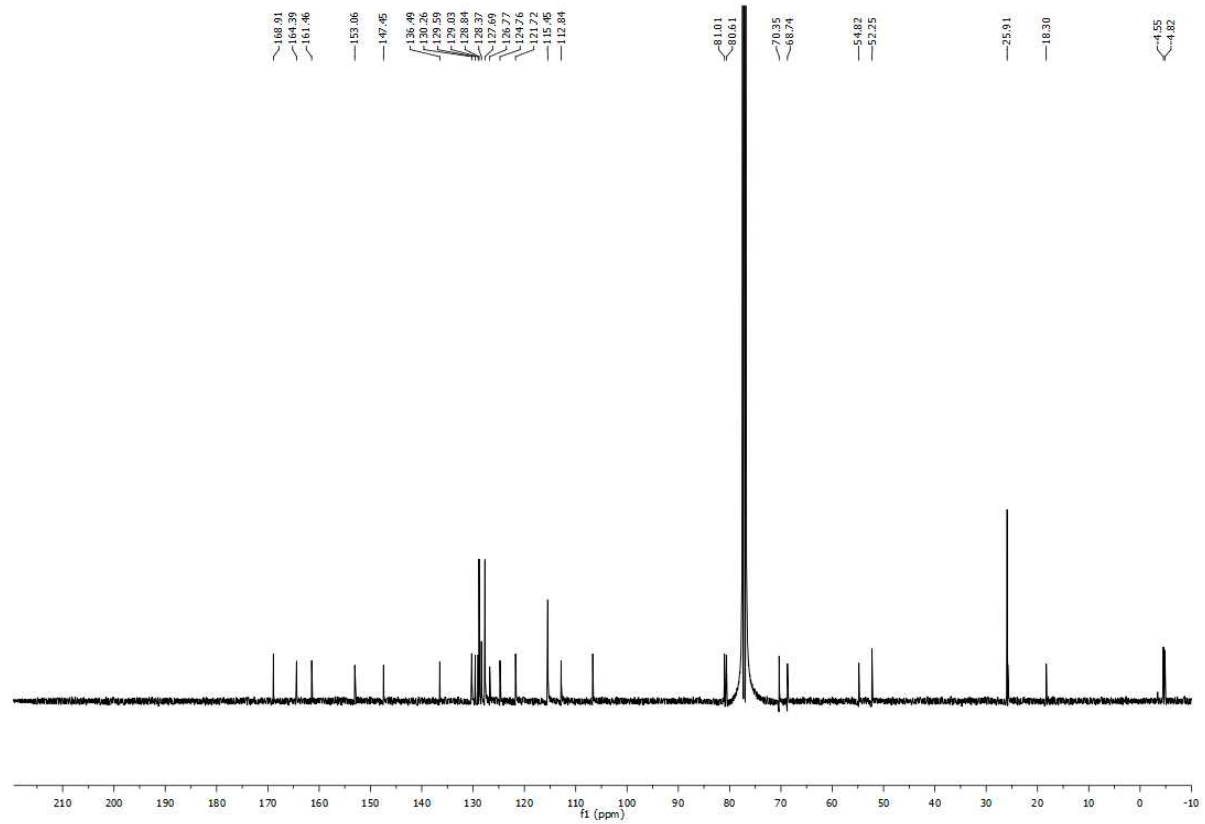


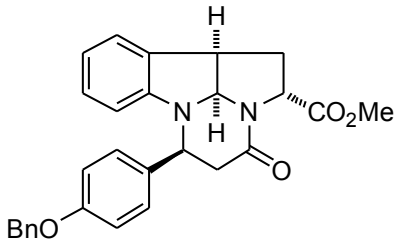
II-78

$CDCl_3$

^{1}H 400 MHz

^{13}C 100 MHz



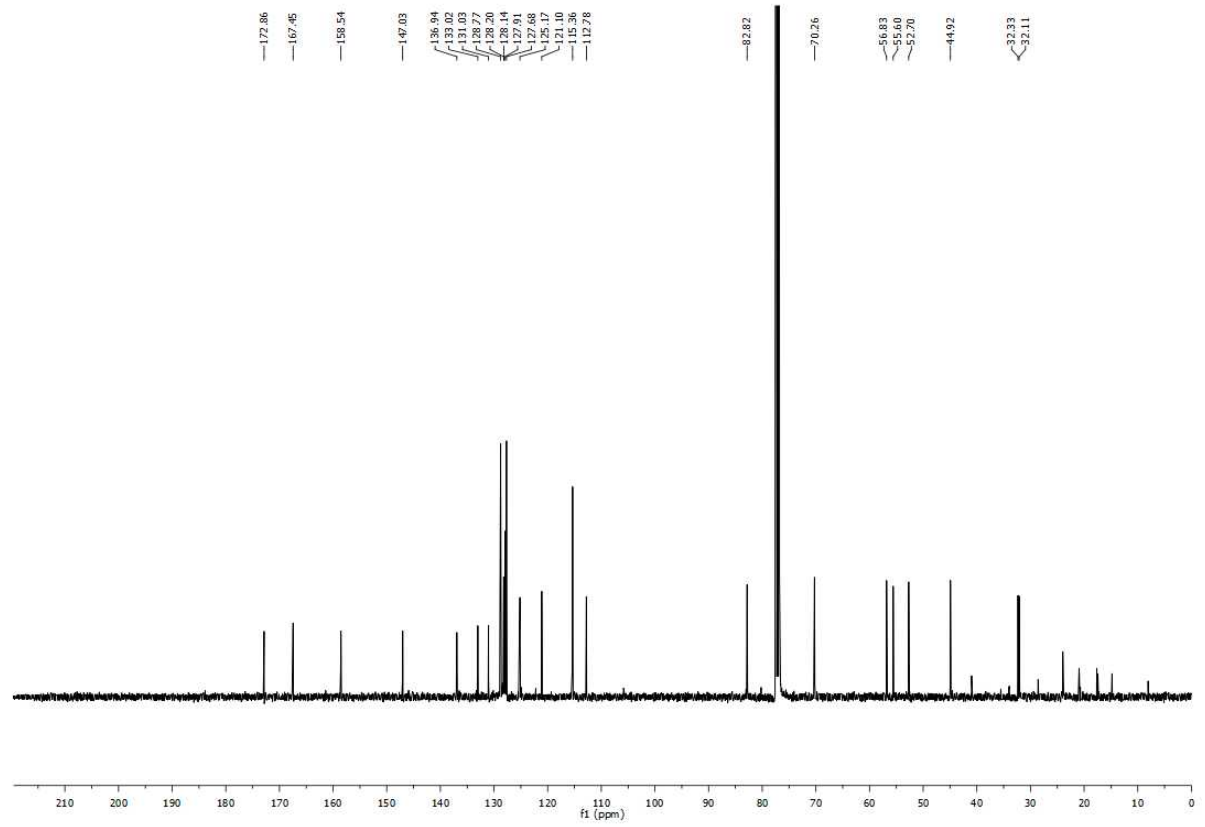


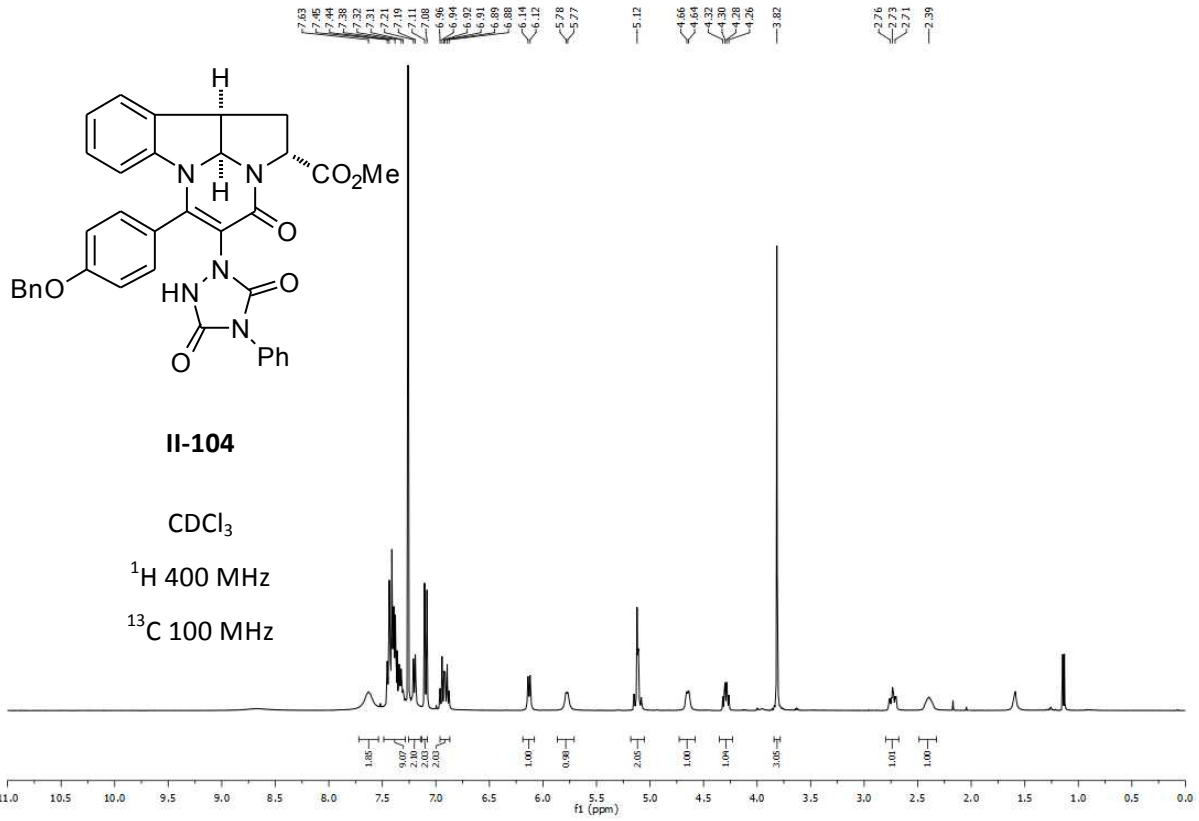
II-99

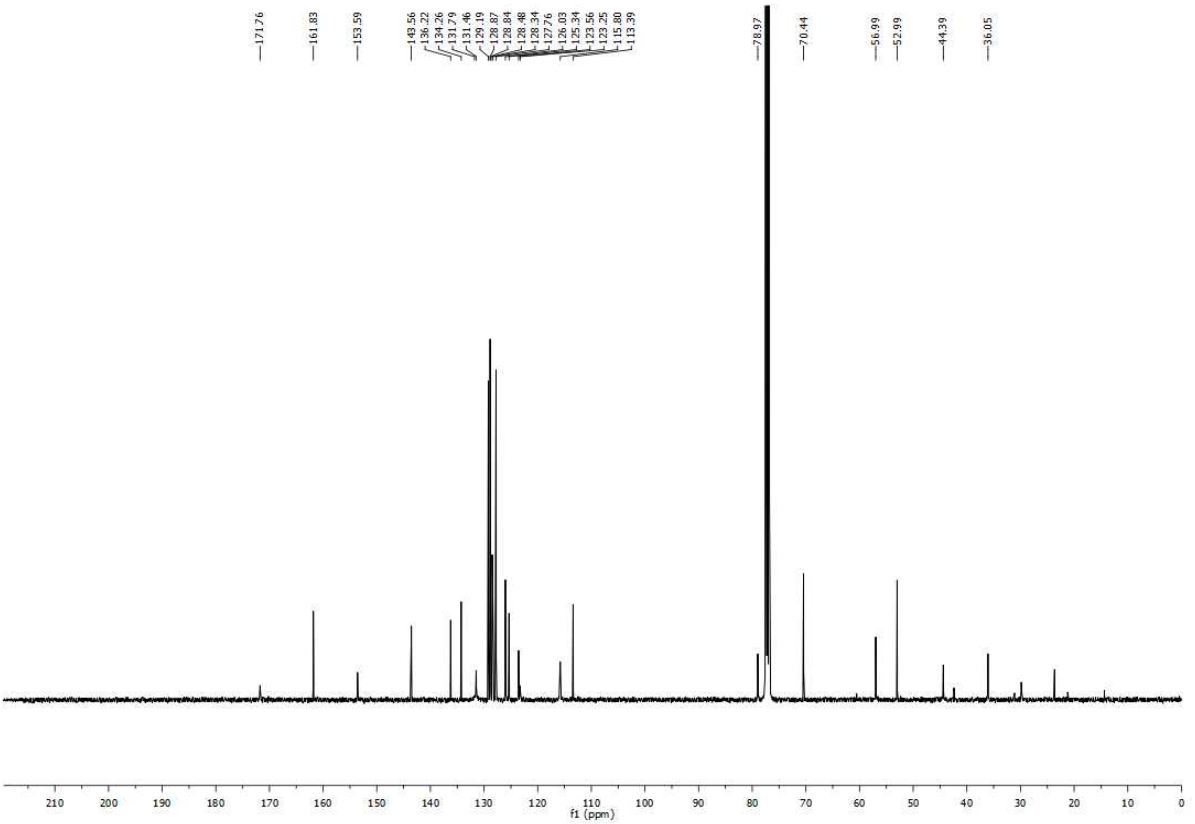
$CDCl_3$

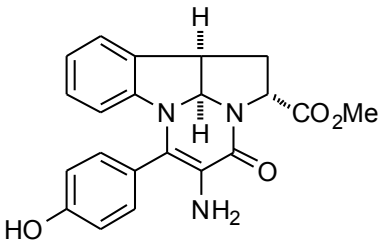
^{1}H 400 MHz

^{13}C 100 MHz




H
N
H
N
CO2Me
O
N
HN
O
O
N
Ph
BnO
II-104
CDCl3
1H 400 MHz
13C 100 MHz
f1 (ppm)


f1 (ppm)

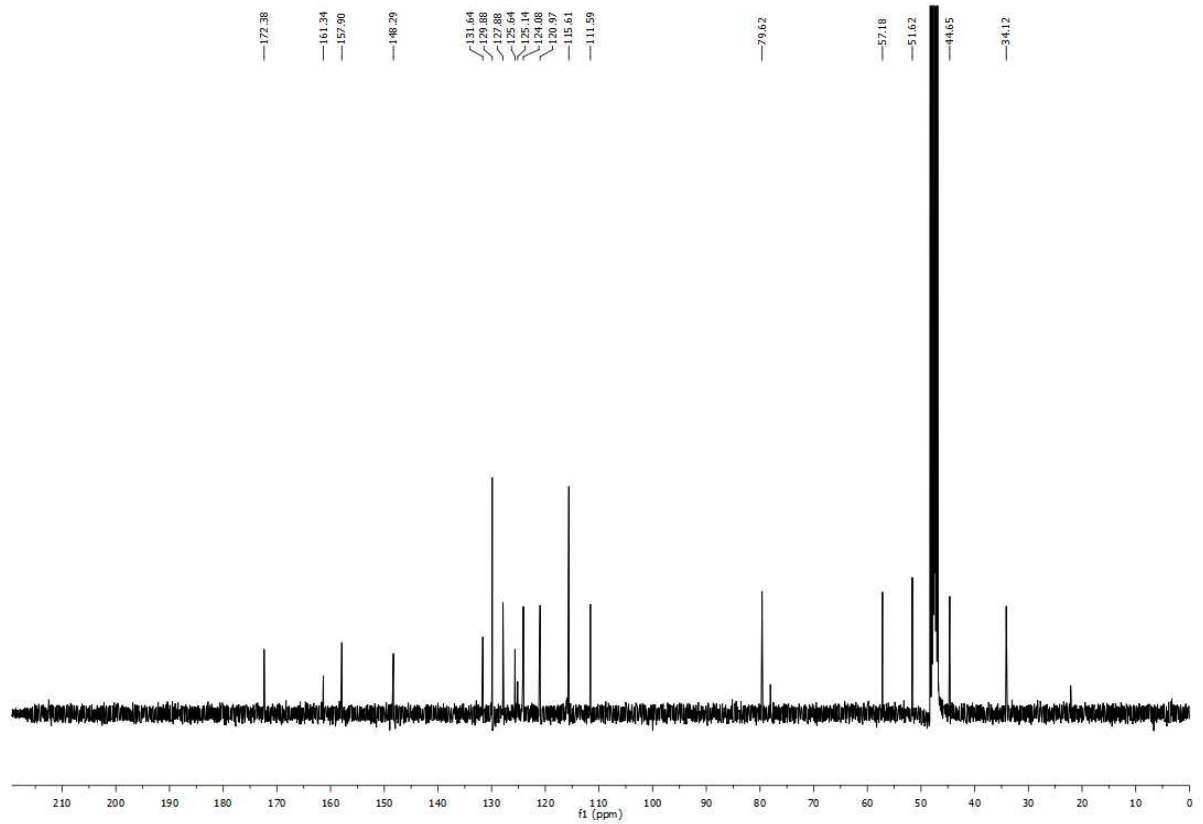


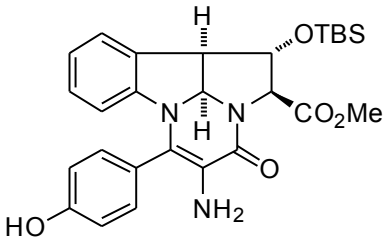
II-106

CD_3OD

^{1}H 400 MHz

^{13}C 100 MHz



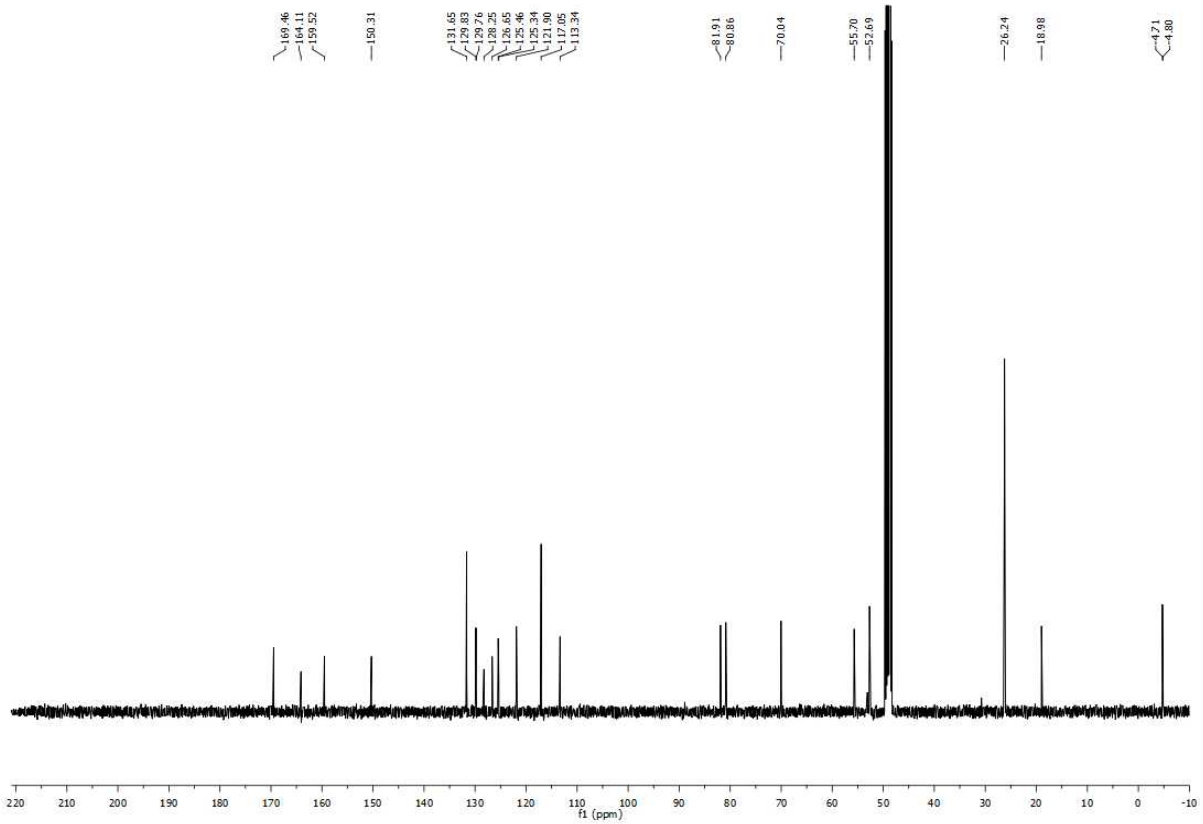


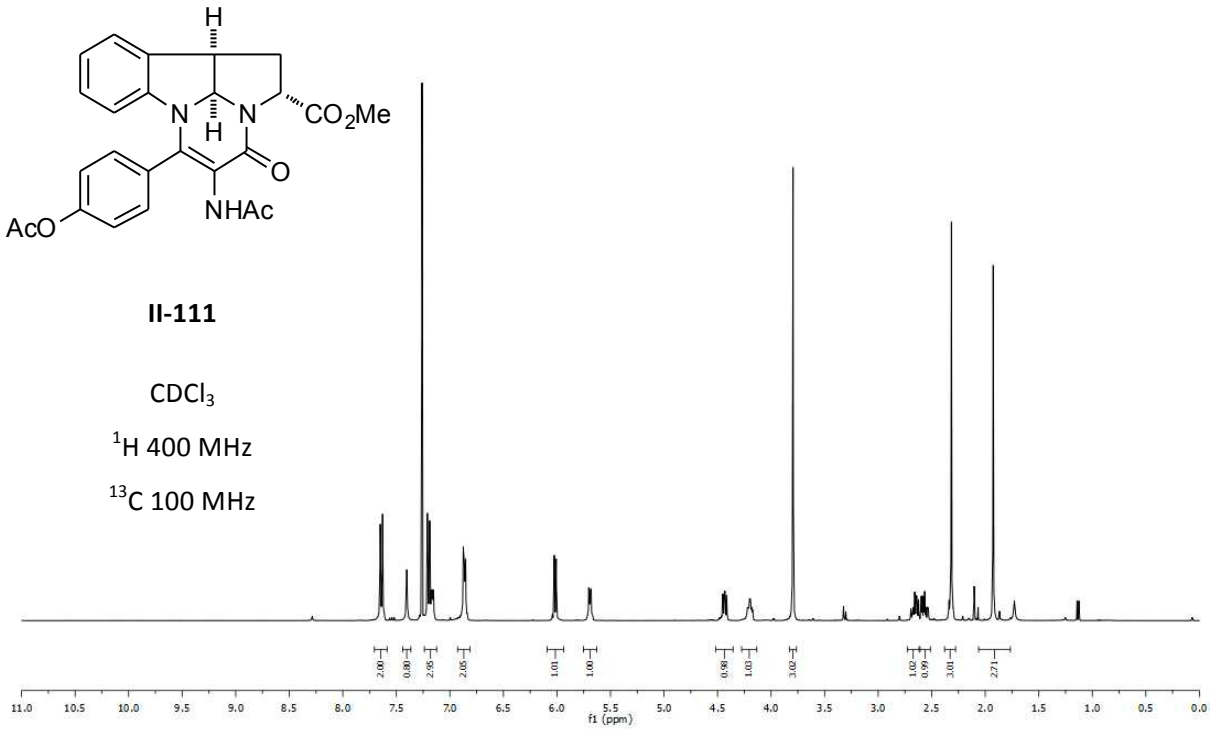
II-108

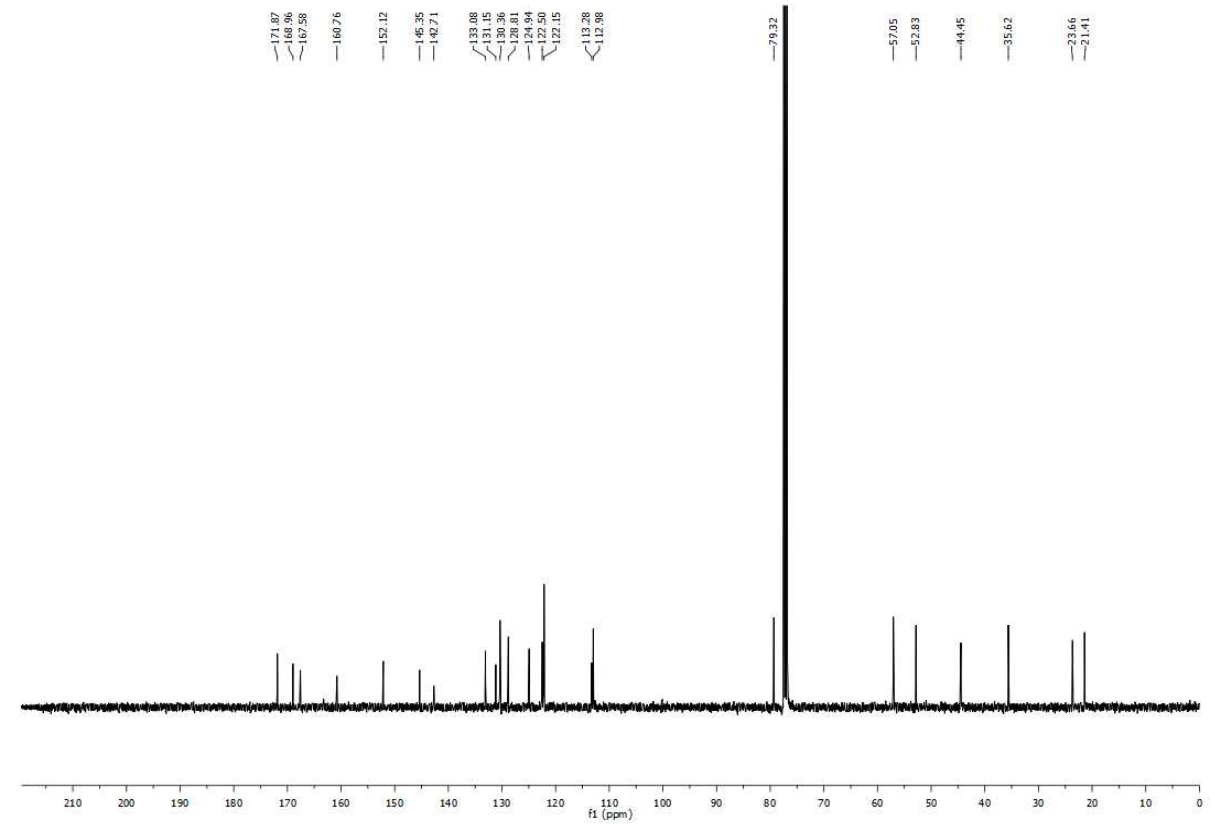
CD_3OD

^{1}H 400 MHz

^{13}C 100 MHz





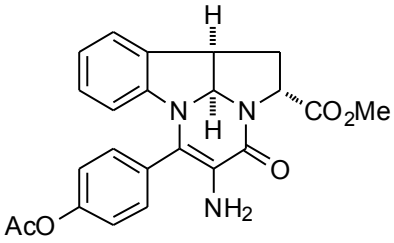


II-111

$CDCl_3$

^{1}H 400 MHz

^{13}C 100 MHz

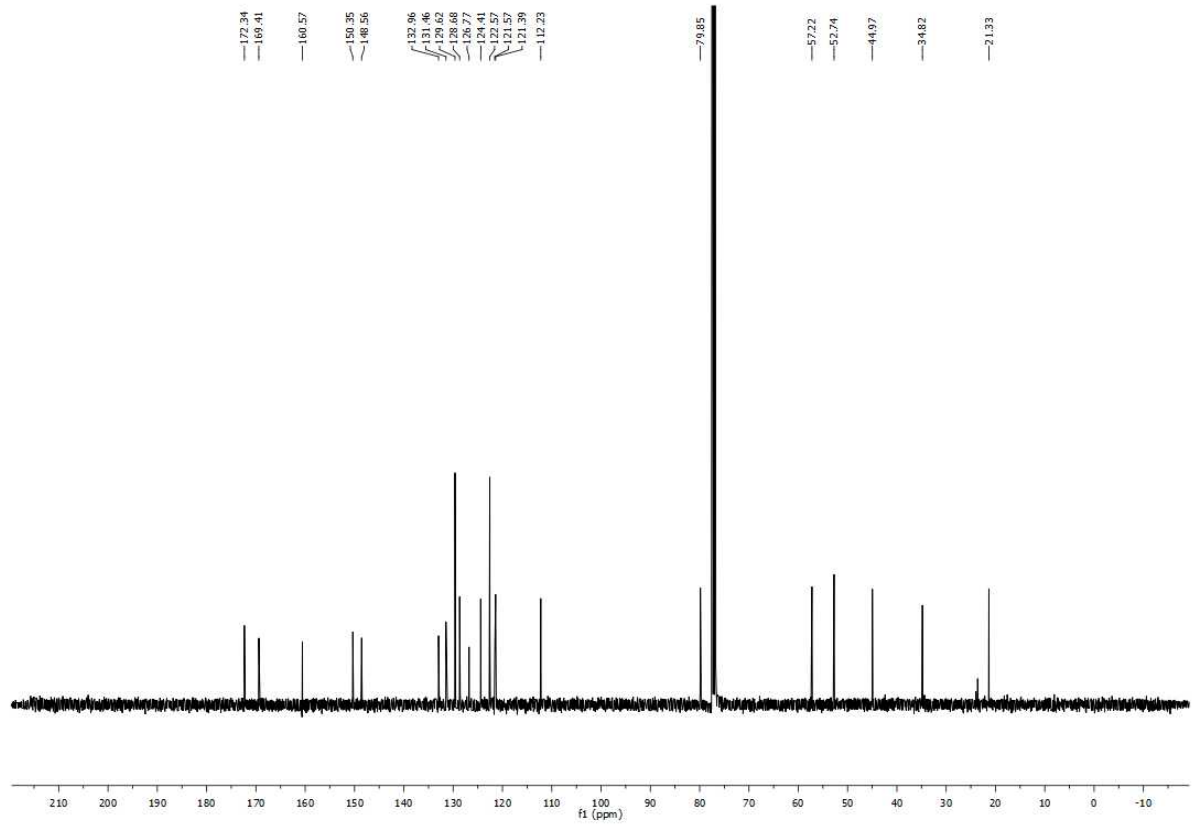


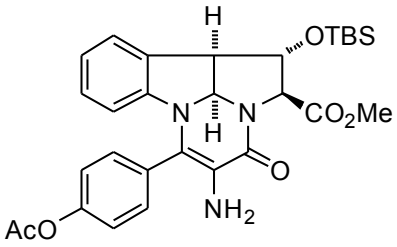
II-110

$CDCl_3$

^{1}H 400 MHz

^{13}C 100 MHz



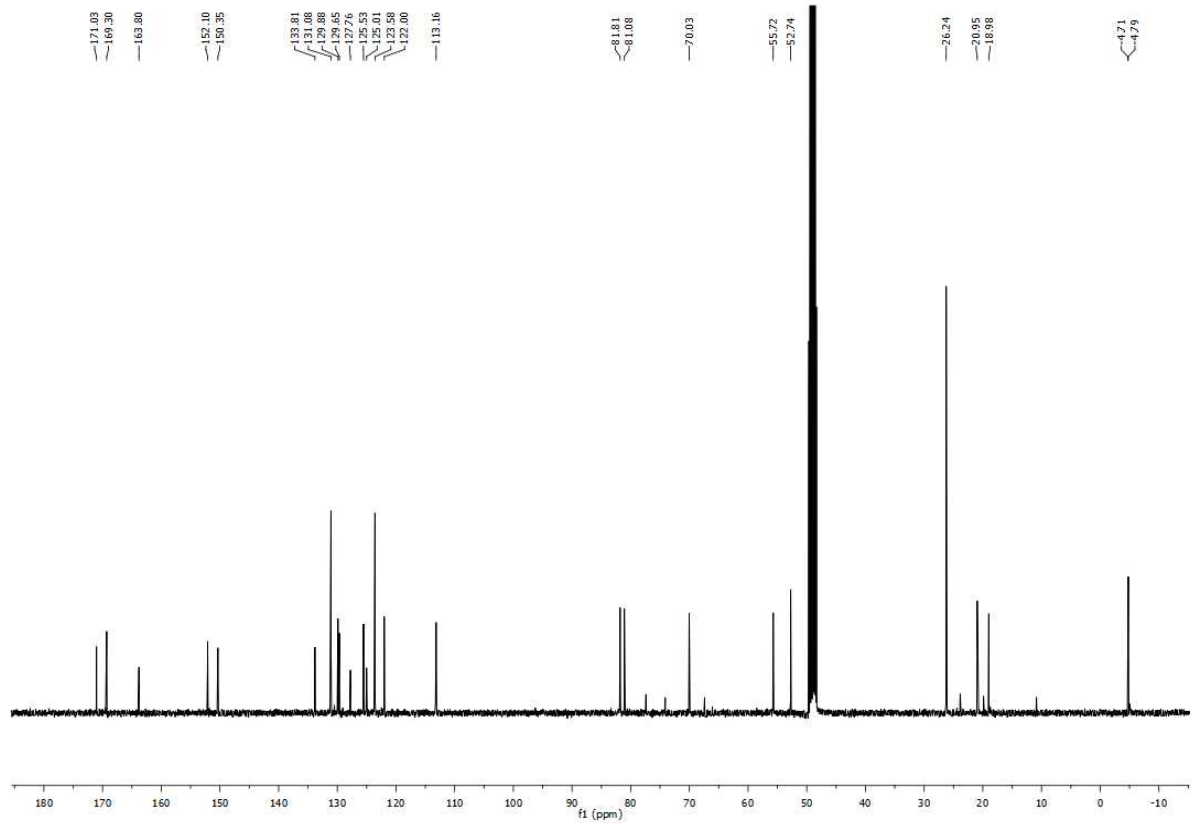


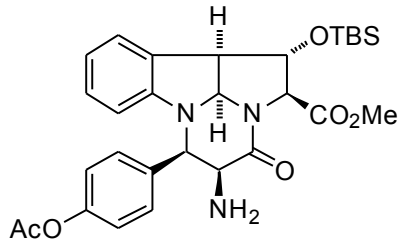
II-116

CD_3OD

^{1}H 400 MHz

^{13}C 100 MHz



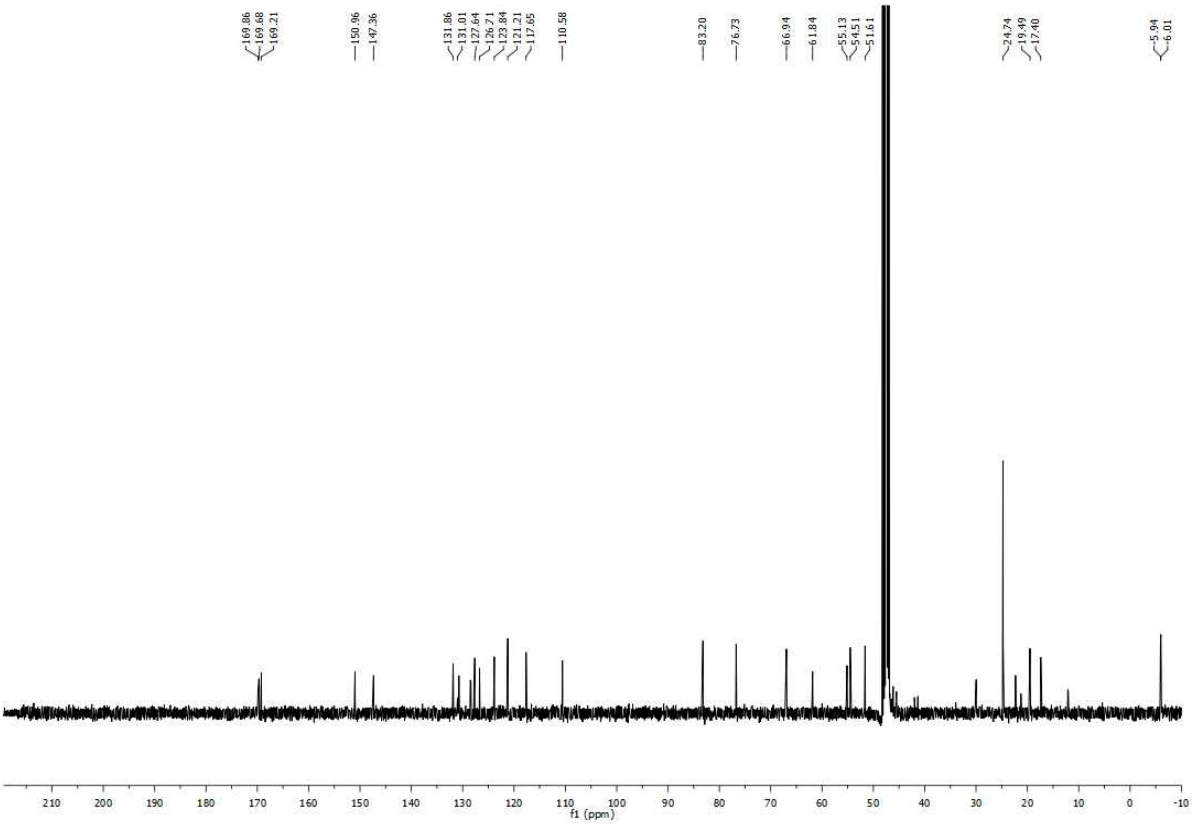


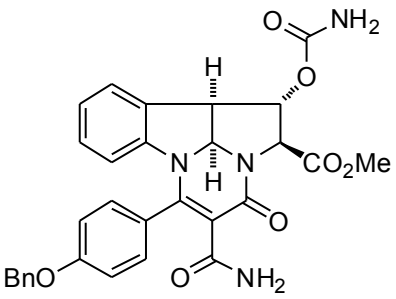
II-77

CD_3OD

^{1}H 400 MHz

^{13}C 100 MHz



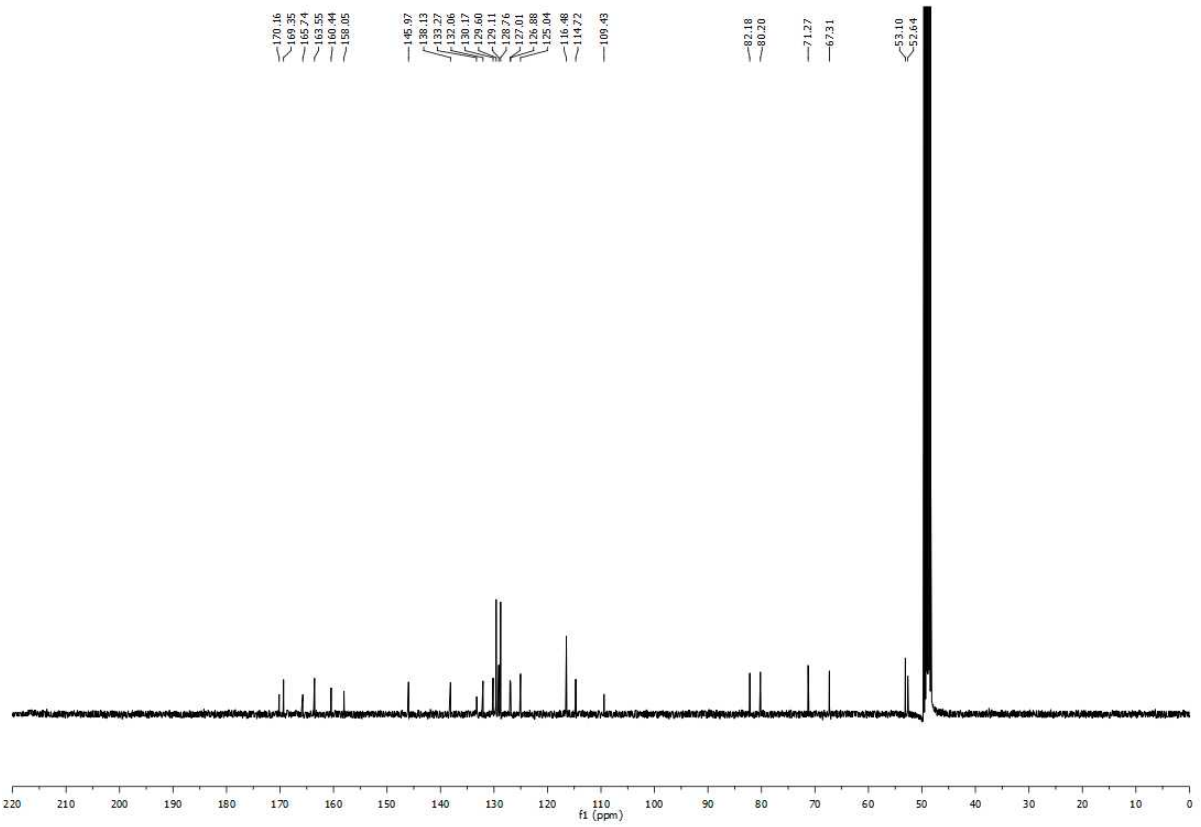


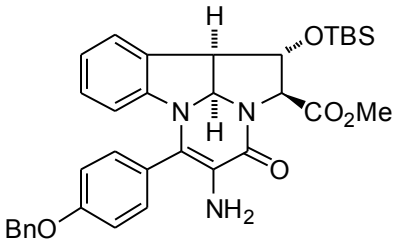
II-120

CD_3OD

^{1}H 400 MHz

^{13}C 100 MHz



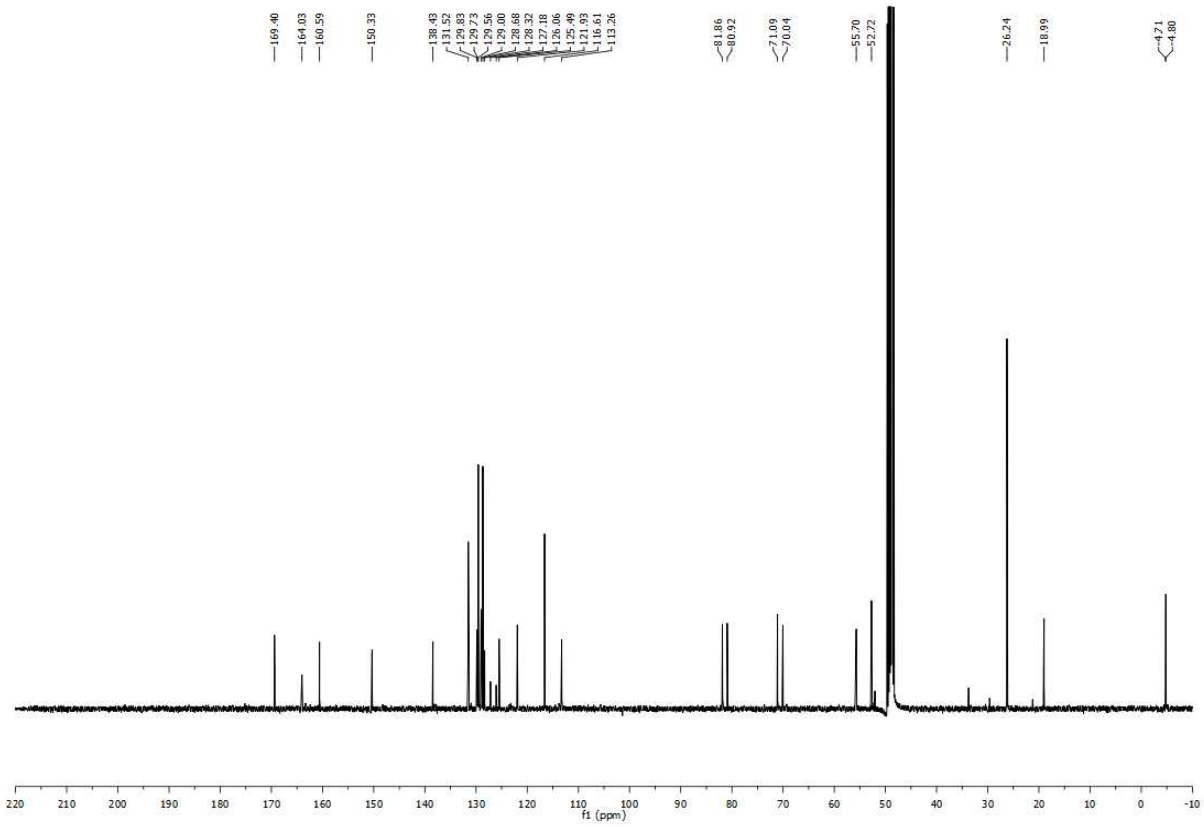


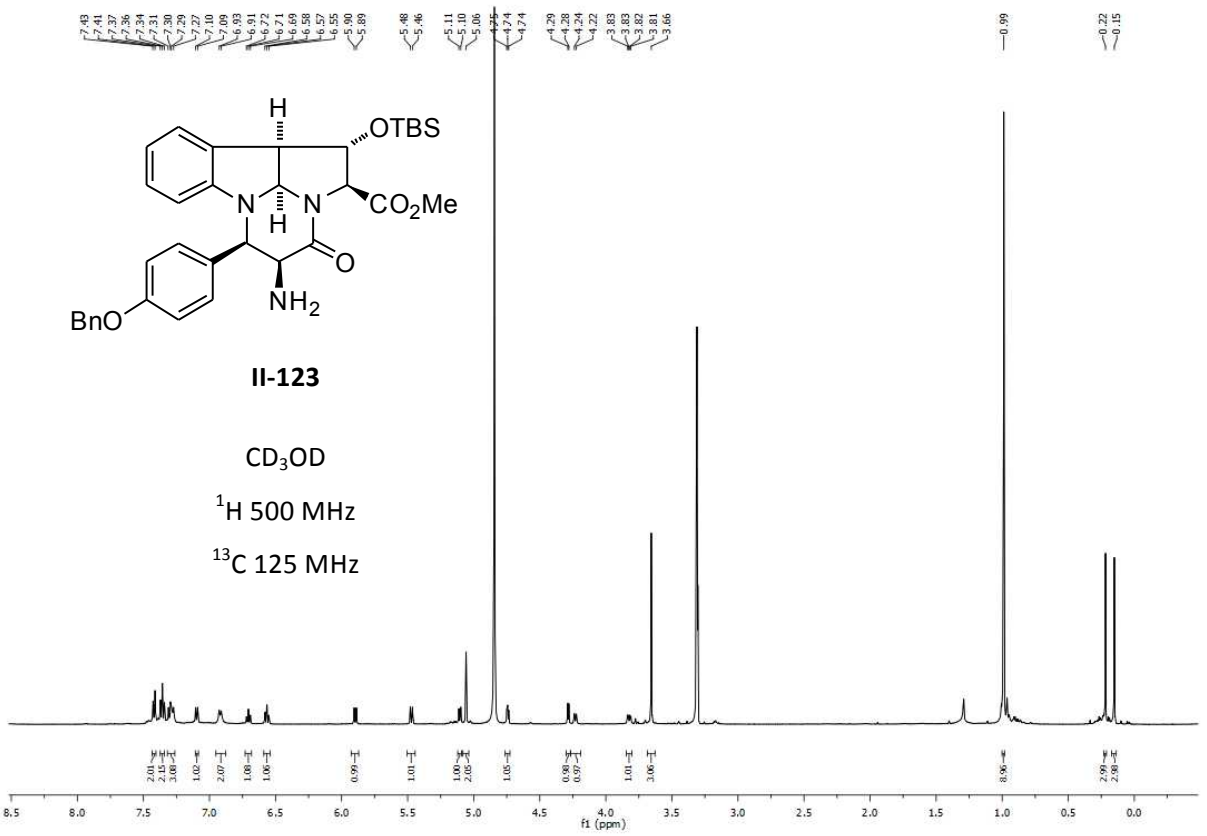
II-122

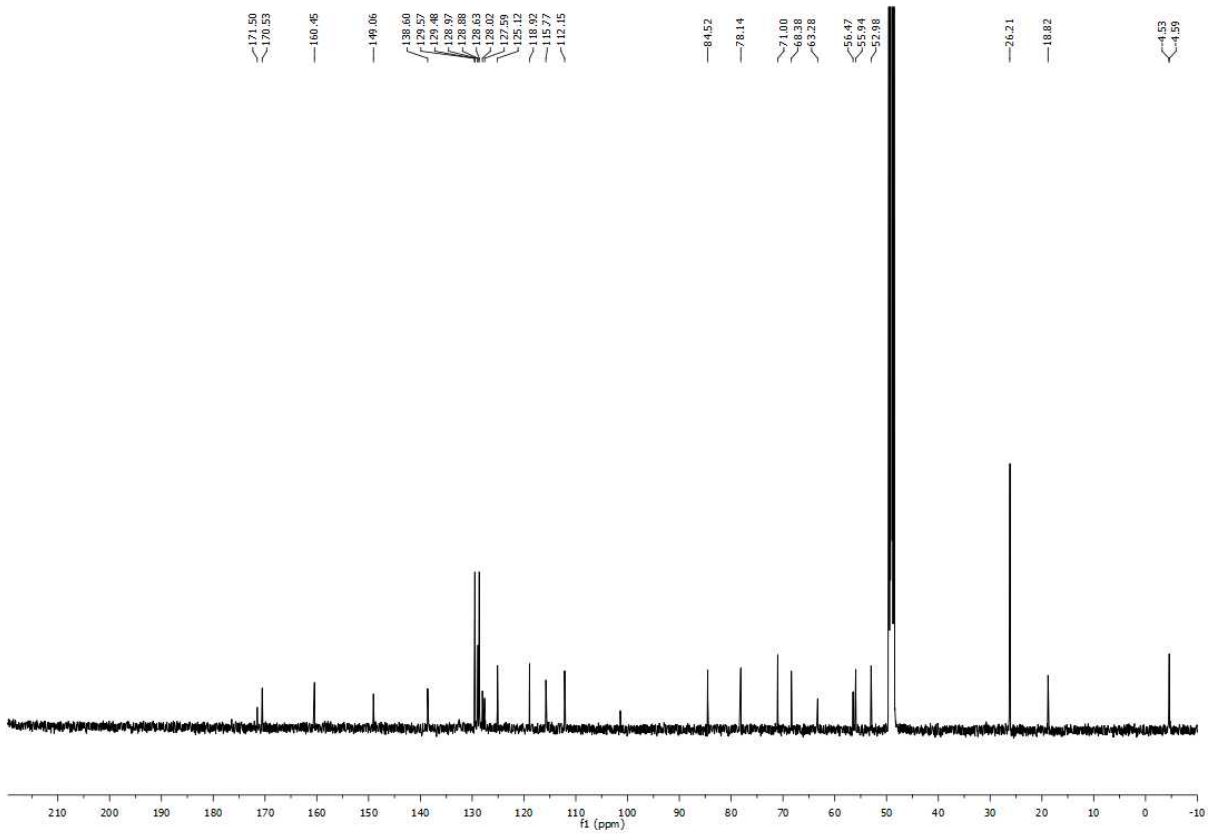
CD_3OD

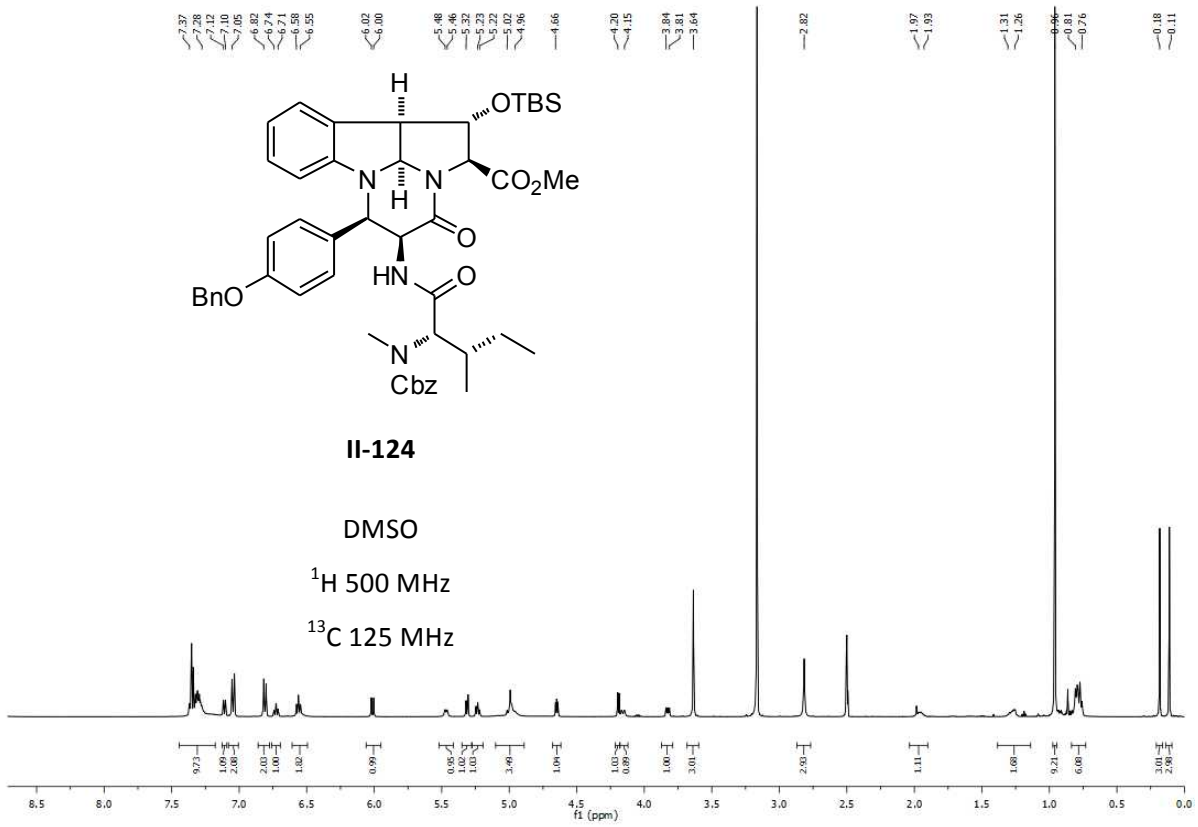
^{1}H 400 MHz

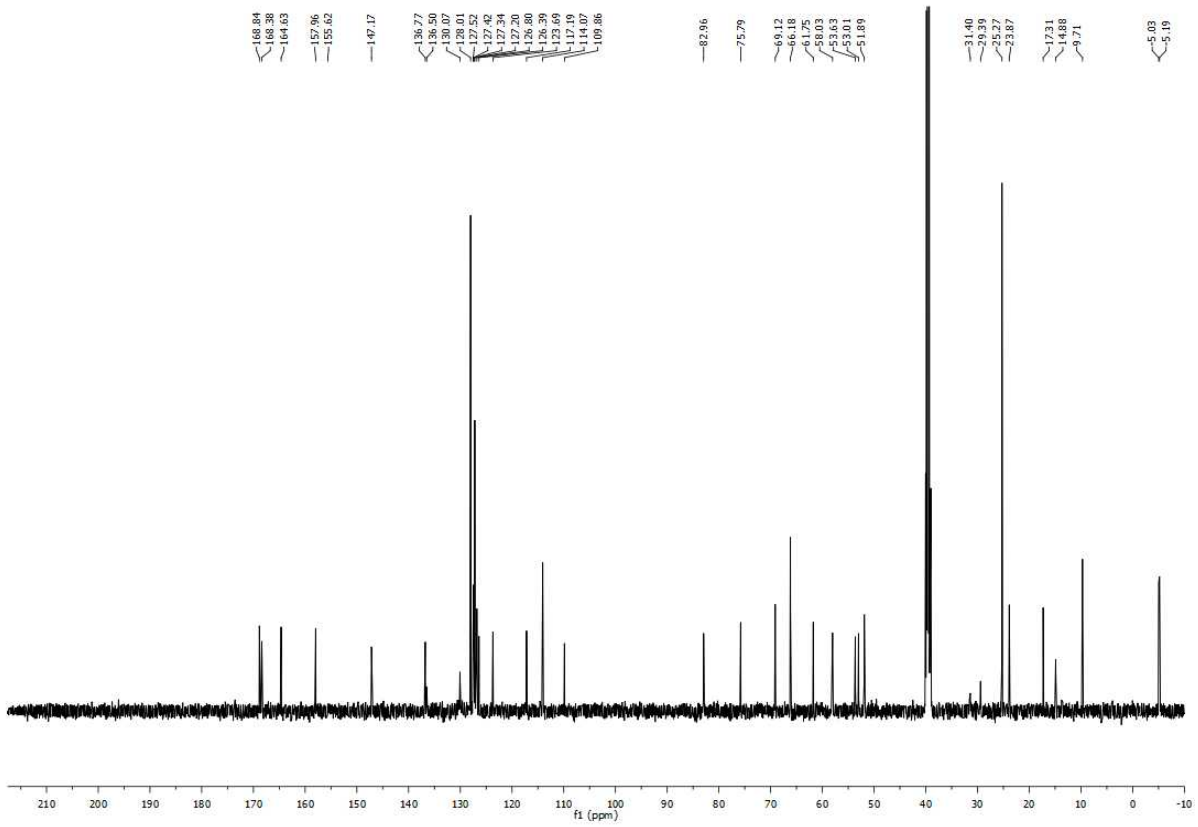
^{13}C 100 MHz

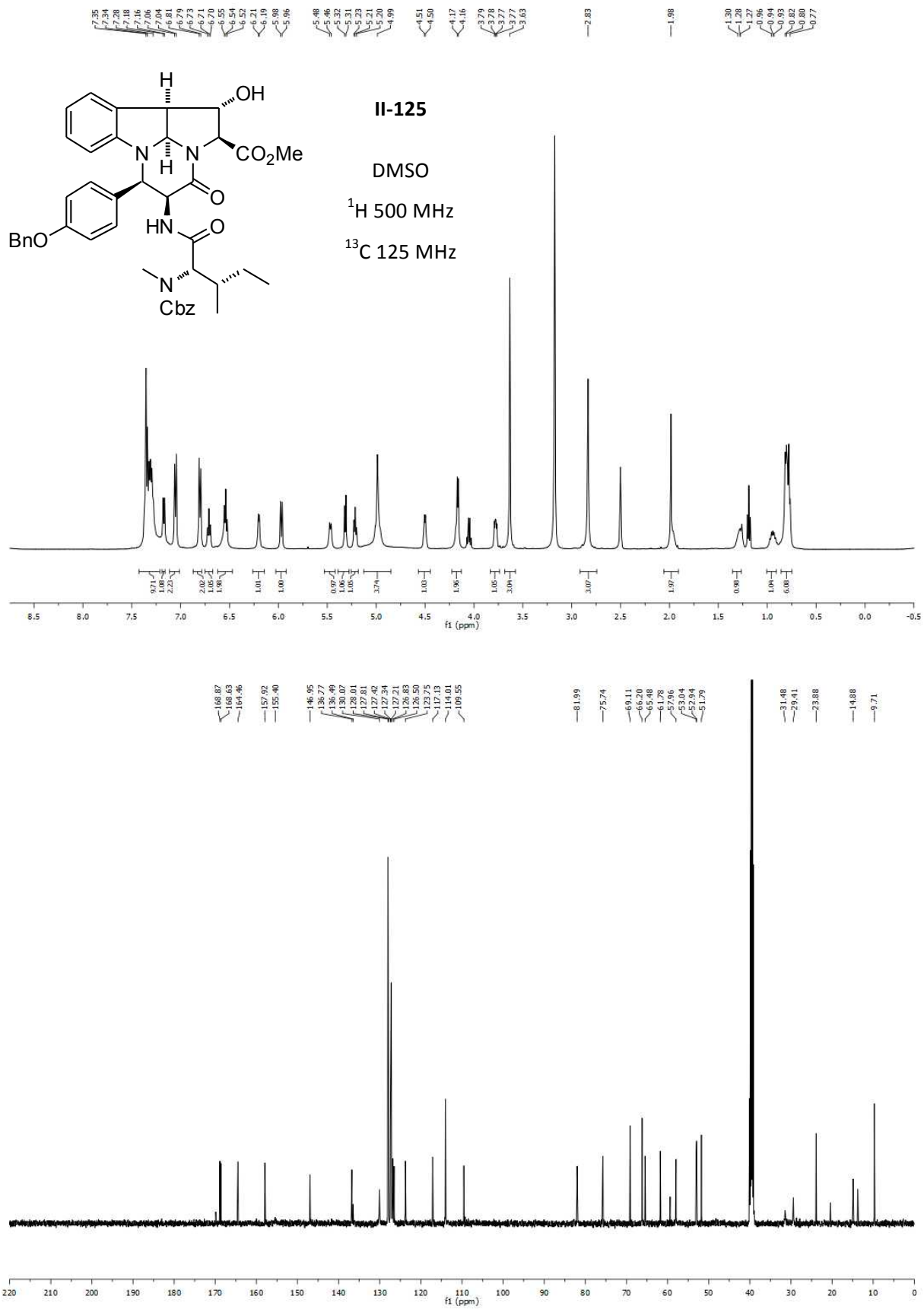



OTBS
CO2Me
NH2
BnO
II-123
CD3OD
1H 500 MHz
13C 125 MHz
f1 (ppm)

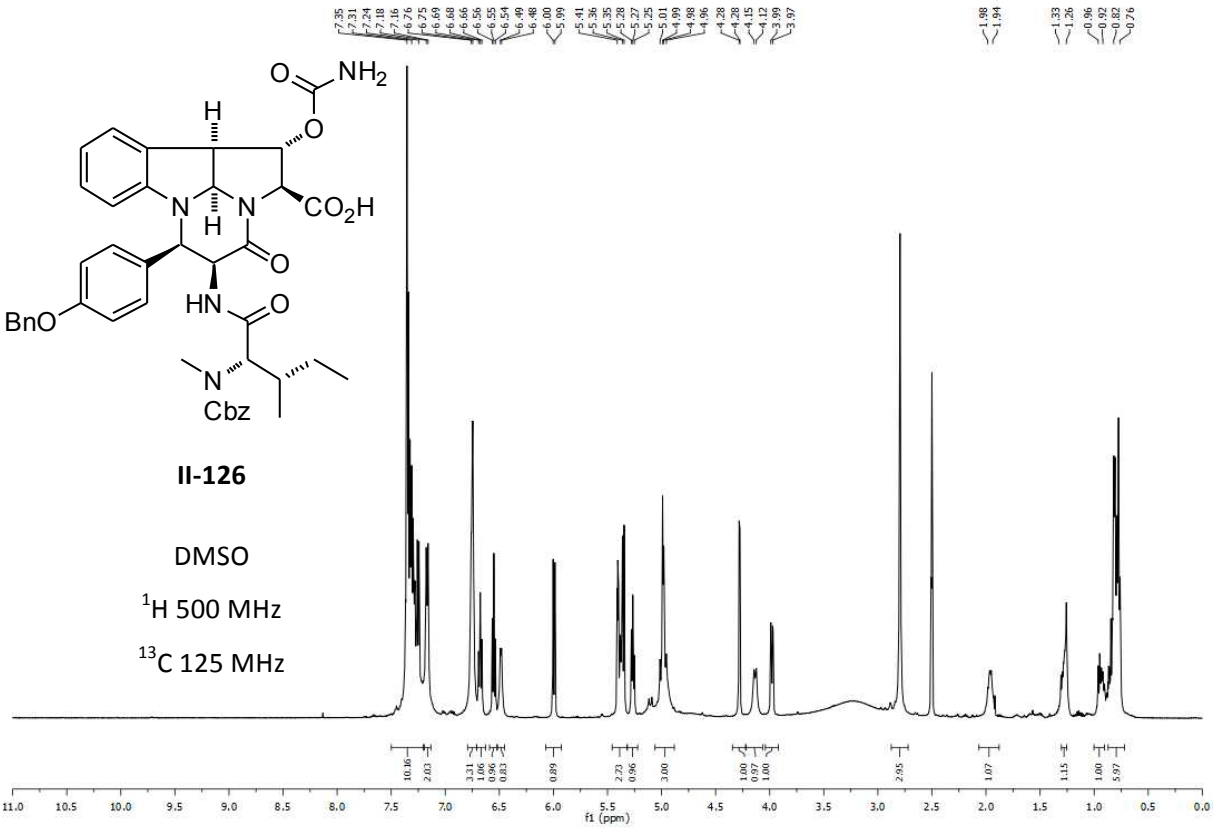

f1 (ppm)

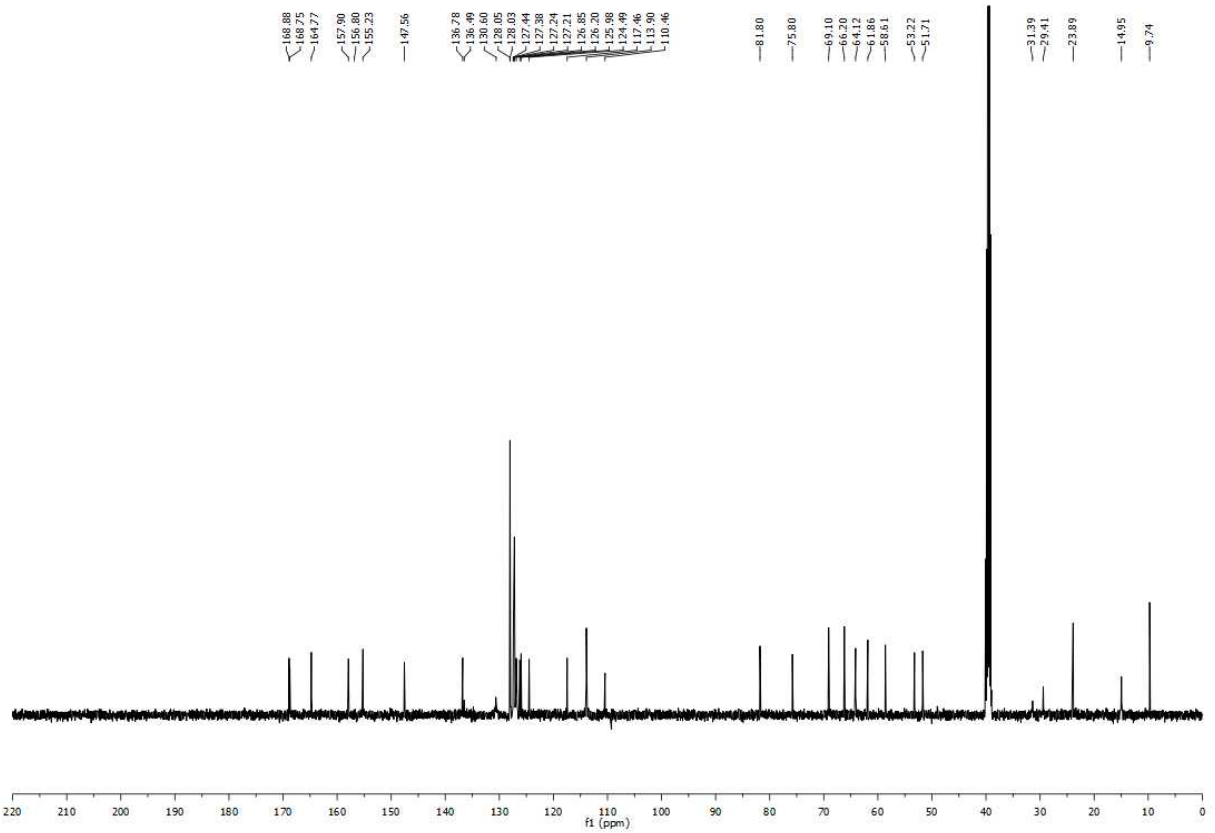

OTBS
CO2Me
BnO
HN
N
Cbz
II-124
DMSO
1H 500 MHz
13C 125 MHz
f1 (ppm)

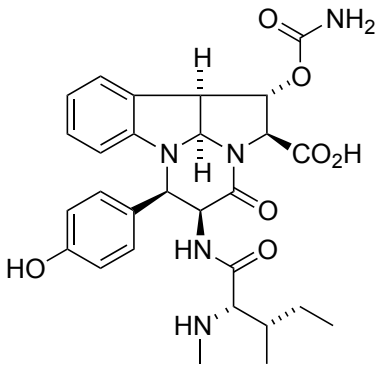

f1 (ppm)



Inseparable from EtOAc, even after 2 days under vacuum of 10^{-3} mbar and coevaporation with toluene.


II-126
DMSO
1H 500 MHz
13C 125 MHz
f1 (ppm)


f1 (ppm)

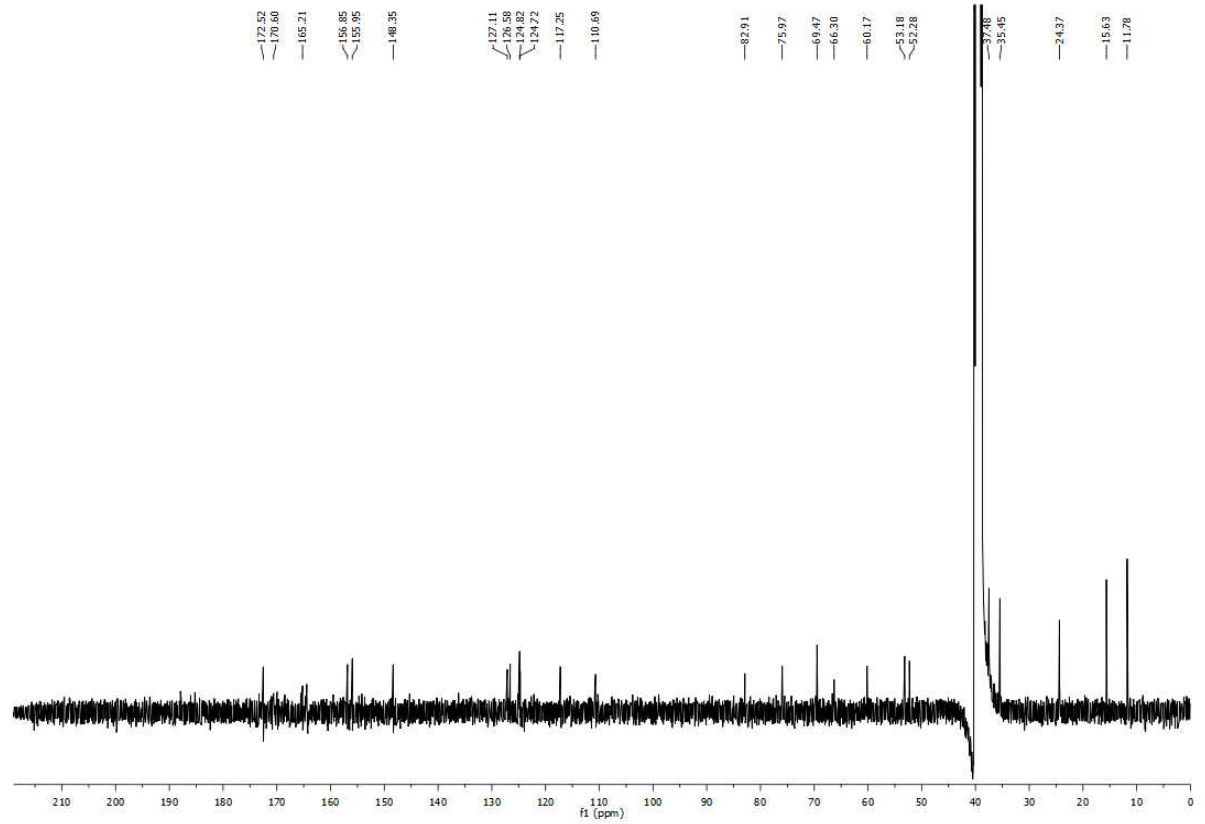


II-7

DMSO

^{1}H 400 MHz

^{13}C 100 MHz



5.2 Crystallographic Data

Single-Crystal X-ray Analysis of Dess-Martin-Periodinane (I-41)

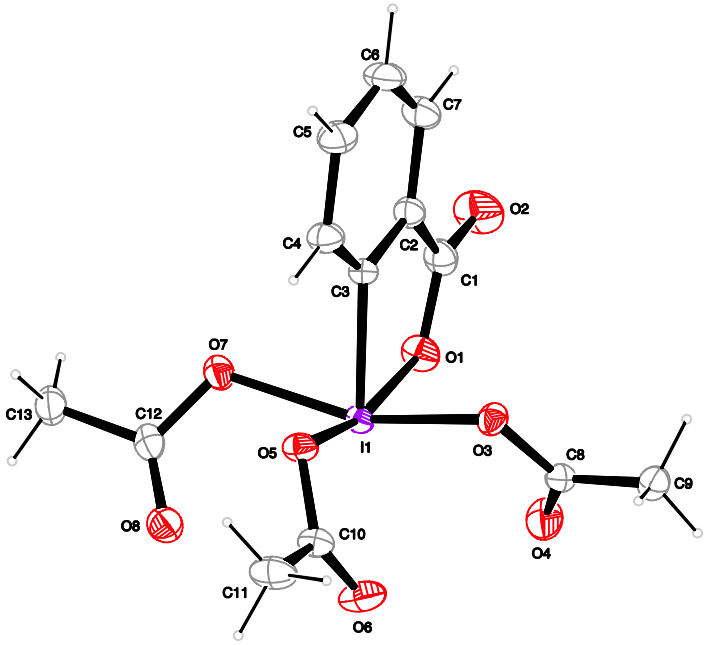


Figure 5.1 Molecular structure of **I-41** (one molecule out of assymetric unit).

Table 5.1 Crystallographic data for **I-41**.

	I-41
net formula	$C_{13}H_{13}IO_8$
M_r/g mol^{-1}	424.142
crystal size/mm	0.30 × 0.21 × 0.15
T/K	173(2)
radiation	MoKα
diffractometer	'Oxford XCalibur'
crystal system	triclinic
space group	*P*1bar
a/Å	8.3829(4)
b/Å	8.4906(6)
c/Å	11.6195(8)
α/°	100.659(6)
β/°	99.289(5)
γ/°	111.040(5)
V/Å^3	734.80(8)
Z	2
calc. density/g cm^{-3}	1.9170(2)
μ/mm^{-1}	2.218
absorption correction	'multi-scan'
transmission factor range	0.611–0.717

refls. measured	6431
R_{int}	0.0141
mean σ(*I*)/*I*	0.0263
θ range	4.29–30.50
observed refls.	4154
x, y (weighting scheme)	0.0244, 0.0931
hydrogen refinement	constr
refls in refinement	4411
parameters	202
restraints	0
$R(F_{obs})$	0.0187
$R_w(F^2)$	0.0479
S	1.060
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.548
min electron density/e Å^{-3}	−0.590

Single-Crystal X-ray Analysis of dihydroxy tyrosine II-19

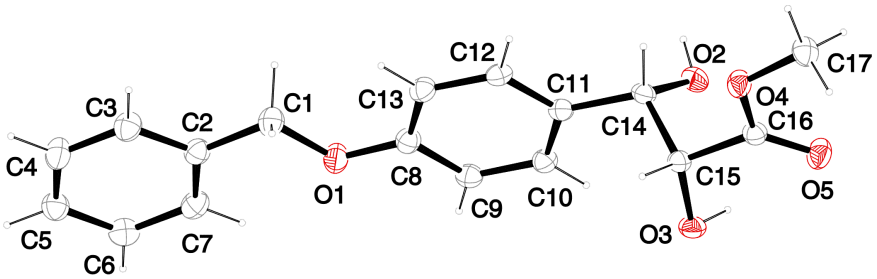


Figure 5.2 Molecular structure of **II-19** (one molecule out of assymetric unit).

Table 5.2 Crystallographic data for **II-19**.

	II-19
net formula	$C_{17}H_{18}O_5$
M_r/g mol^{-1}	302.322
crystal size/mm	0.22 × 0.18 × 0.06
T/K	200(2)
radiation	MoKα
diffractometer	'KappaCCD'
crystal system	monoclinic
space group	$P2_1$
a/Å	7.7926(3)
b/Å	5.6941(2)
c/Å	17.0116(6)
α/°	90
β/°	101.0379(18)
γ/°	90
V/Å^3	740.87(5)

Z	2
calc. density/g cm^{-3}	1.35523(9)
μ/mm^{-1}	0.100
absorption correction	none
refls. measured	6035
R_{int}	0.0292
mean σ(I)/I	0.0414
θ range	3.13–27.43
observed refls.	2921
x, y (weighting scheme)	0.0539, 0.4750
hydrogen refinement	mixed
Flack parameter	−0.5(14)
refls in refinement	3358
parameters	208
restraints	1
$R(F_{obs})$	0.0513
$R_w(F^2)$	0.1382
S	1.068
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.219
min electron density/e Å^{-3}	−0.190

Single-Crystal X-ray Analysis of hydroxy/amino tyrosine II-22

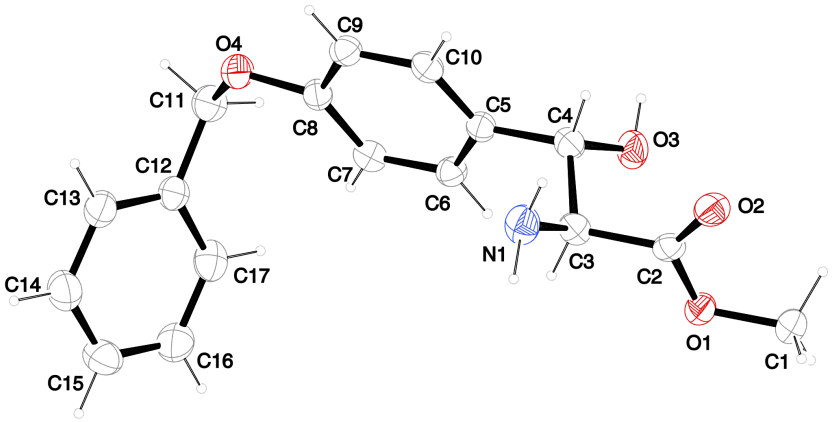


Figure 5.3 Molecular structure of **II-22** (one molecule out of asymmetric unit).

Table 5.3 Crystallographic data for **II-22**.

	II-22
net formula	$C_{17}H_{19}NO_4$
M_r/g mol^{-1}	301.337
crystal size/mm	0.46 × 0.09 × 0.04
T/K	173(2)
radiation	MoKα

diffractometer	'Oxford XCalibur'
crystal system	monoclinic
space group	$P2_1$
a/Å	8.4148(9)
b/Å	5.5238(6)
c/Å	16.2161(16)
α/°	90
β/°	102.302(12)
γ/°	90
V/Å^3	736.44(13)
Z	2
calc. density/g cm^{-3}	1.3589(2)
μ/mm^{-1}	0.097
absorption correction	'multi-scan'
transmission factor range	0.30515–1.00000
refls. measured	2651
R_{int}	0.0198
mean σ(I)/I	0.0478
θ range	4.44–26.36
observed refls.	2033
x, y (weighting scheme)	0.0562, 0
hydrogen refinement	mixed
Flack parameter	−0.1(14)
refls in refinement	2273
parameters	212
restraints	1
$R(F_{obs})$	0.0436
$R_w(F^2)$	0.1113
S	1.058
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.173
min electron density/e Å^{-3}	−0.230

Single-Crystal X-ray Analysis of tetracyclic compound II-86

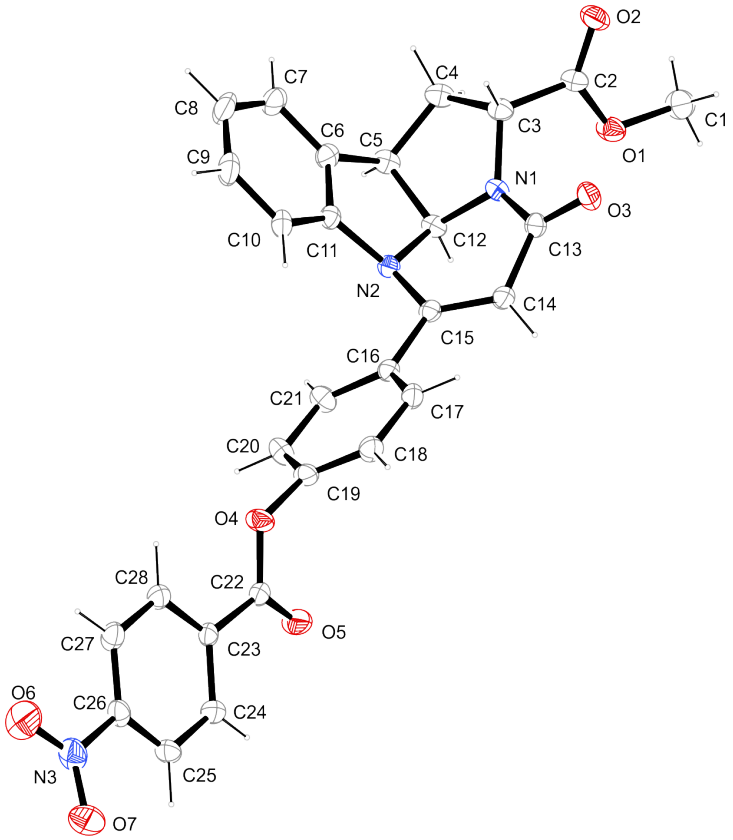


Figure 5.4 Molecular structure of **II-86** (one molecule out of asymmetric unit).

Table 5.4 Crystallographic data for II-86.

	II-86
net formula	$C_{28}H_{21}N_3O_7$
M_r/g mol^{-1}	511.482
crystal size/mm	0.120 × 0.100 × 0.080
T/K	173(2)
radiation	'Mo Kα
diffractometer	'Bruker D8Venture'
crystal system	orthorhombic
space group	$P2_12_12_1$
a/Å	4.7688(2)
b/Å	20.4417(11)
c/Å	24.2942(11)
α/°	90
β/°	90
γ/°	90
V/Å^3	2368.26(19)
Z	4
calc. density/g cm^{-3}	1.43455(12)
μ/mm^{-1}	0.105

absorption correction	multi-scan
transmission factor range	0.9231–0.9580
refls. measured	12832
R_{int}	0.0307
mean σ(I)/I	0.0367
θ range	3.10–25.38
observed refls.	3658
x, y (weighting scheme)	0.0371, 0.4195
hydrogen refinement	constr
Flack parameter	0.7(9)
refls in refinement	4290
parameters	344
restraints	0
$R(F_{obs})$	0.0342
$R_w(F^2)$	0.0792
S	1.021
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.188
min electron density/e Å^{-3}	−0.127

Single-Crystal X-ray Analysis of tetracyclic compound II-109

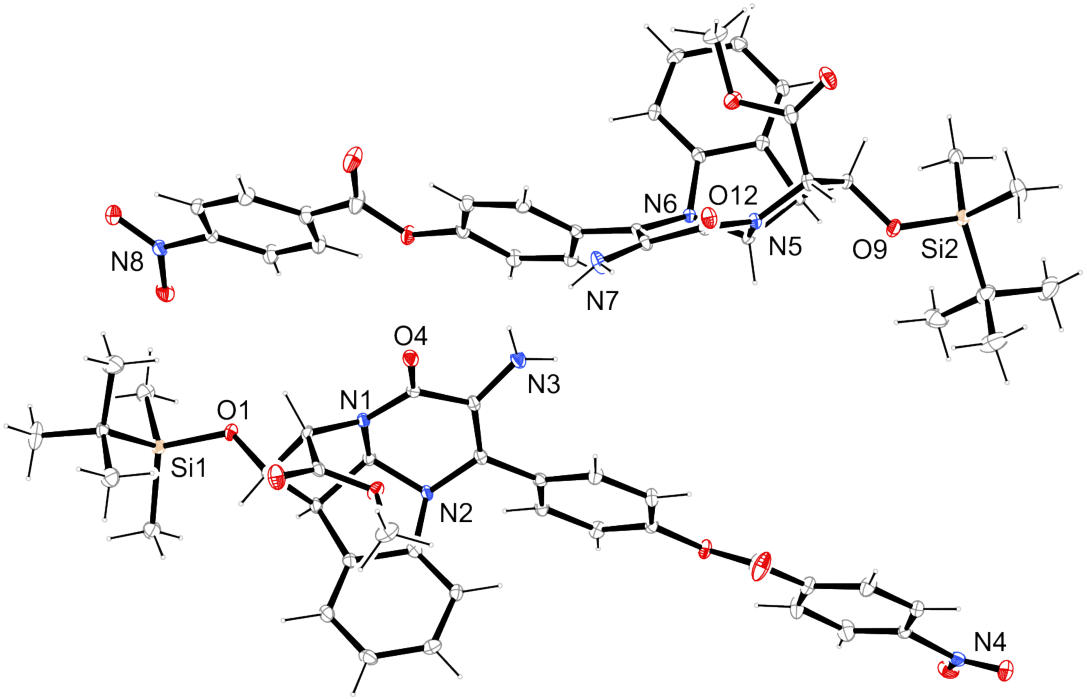


Figure 5.5 Molecular structure of **II-109** (two molecules out of assymetric unit).

Table 5.5 Crystallographic data for **II-109**.

	II-109
net formula	$C_{34}H_{36}N_4O_8Si$
M_r/g mol^{-1}	656.757
crystal size/mm	0.200 × 0.050 × 0.020
T/K	100(2)
radiation	'Mo Kα
diffractometer	'Bruker D8Venture'
crystal system	triclinic
space group	P1
a/Å	7.0977(6)
b/Å	12.5914(11)
c/Å	19.2902(16)
α/°	76.810(2)
β/°	86.395(2)
γ/°	75.068(2)
V/Å^3	1621.8(2)
Z	2
calc. density/g cm^{-3}	1.34491(17)
μ/mm^{-1}	0.131
absorption correction	multi-scan
transmission factor range	0.8145–0.9585
refls. measured	59648
R_{int}	0.0717
mean σ(I)/I	0.0687
θ range	3.04–26.37
observed refls.	10470
x, y (weighting scheme)	0.0407, 0.4337
hydrogen refinement	mixed
Flack parameter	0.07(9)
refls in refinement	13003
parameters	885
restraints	7
$R(F_{obs})$	0.0450
$R_w(F^2)$	0.0972
S	1.032
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.492
min electron density/e Å^{-3}	−0.268

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