Azapolycyclic Building Blocks for the Synthesis of *Daphniphyllum* Alkaloids: Approaches toward Himalensine A and 2-Deoxymacropodumine A

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Azapolycyclic Building Blocks for the Synthesis of *Daphniphyllum* Alkaloids*:* Approaches toward Himalensine A and 2-Deoxymacropodumine A

Memòria presentada per Clàudia Marquès Garcia per optar al títol de doctor per la Universitat de Barcelona

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List of Abbreviations and Acronyms

^{13}C NMR	carbon-13 nuclear magnetic resonance
^{1}H NMR	proton nuclear magnetic ressonance
9-BBN	9-boracyclo[3.3.1]nonane
AIBN	azobisisobutyronitrile
aq	aqueous
Ar	aryl
atm	atmosphere
ATRC	atom transfer radical cyclization
AZADO or AZADOL	2-azadamantane N oxyl
BHT	dibutylhydroxytoluene
Bn	benzyl
Boc	*tert*-butoxycarbonyl
BOMCl	benzyl chloromethyl ether
bpy or bipy	2,2'-bipyridine
BQ	1,4-benzoquinone
br	broad
brsm	based on recovered starting material
calcd.	calculated
Cbz	benzyloxycarbonyl
COD	1,5-cyclooctadiene
COSY	correlation spectroscopy
Cp	cyclopentadienyl
CSA	camphorsulfonic acid
CuTC	copper (I)-thiophene-2-carboxylate
d	doublet
DBU	1,8-diazabycicloundec-7-ene
dd	doublet of doublets
dddd	doublet of doublets of doublets of doublets
ddddd	doublet of doublets of doublets of doublets of doublets
DDQ or DHDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
DEPT	Distortionless Enhancement by Polarization Transfer
DFT	density functional theory
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminium hydride
DIPEA	*N,N*-Diisopropylethylamine
dm	doublet of multiplets
DMAP	4-Dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMP	Dess-Martin Periodinane or 1,4-Dimethylpiperazine
DMPU	*N,N'*-Dimethylpropyleneurea
DMSO	dimethyl sulfoxide

dppb	1,4-bis(diphenylphosphino)butane
dppf	1,1'-bis(diphenylphosphino)ferrocene
dppp	1,3- bis(diphenylphosphino)propane
dr	diastereomeric ratio
dt	doublet of triplets
DTBPF	1,1'-Bis(di-tert-butylphosphino)ferrocene
EDCI or EDC	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
ee	enantiomeric excess
ent	enantiomer
equiv	equivalent
ESI	electrospray ionization
GC	gas chromatography
HAT	hydrogen atom transfer
HFIP	hexafluoroisopropanol
HGII	second-generation Hoveyda-Grubbs catalyst
HMBC	heteronuclear multiple bond correlation
HMPA	hexamethylphosphoramide
$HONEt_2$	hidroxydiethylamine
HRMS	high resolution mass spectrum
HSQC	hetereonuclear single quantum correlation spectroscopy
HWE	Horner-Wadsworth-Emmons
Im	imidazole
IR	Infrared spectroscopy
J	coupling constant
LAH	lithium aluminium hydride
LCIA	lithium cyclohexyl isopropyl amide
LDA	lithium diisopropylamide
LDCA	lithium dicyclohexylamide
LHMDS or KHMDS	lithiuim or potassium hexamethyldisilylazide
M	molar
m	multiplet
***m*-CPBA**	*m*-chloroperbenzoic acid
m/z	mass to charge ratio
M^+	molecular ion
MHz	megahertz
MOM	methoxymethyl ether
mp	melting point
MS	molecular sieves
Ms	mesyl (methylsulfonyl)
MVK	methyl vinyl ketone
Naph.	naphtalene
NBD	2-(4-nitro-2,1,3-benzoxadiazol-7-yl)aminoethyl]
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide

NIS	*N*-Iodosuccinimide
NMM	*N*-methyl morpholine
NMO	*N*-methyl morpholine oxide
NMP	*N*-methyl-2-pyrrolidine
NOESY	nuclear Overhauser effect spectroscopy
OAc	acetate
***p*-ABSA**	4-acetoimidobenzene-sulfonylazide
***p*-TSA or *p*-TsOH**	*p*-toluenesulfonic acid
Ph	phenyl
PhCN	benzonitrile
PIDA	phenyliodine (III) diacetate
PMB	*p*-methoxy benzyl
ppm	parts per milion
PPTS	pyridinium *p*-toluenesulfonate
py or pyr	pyridine
quant.	quantitative
R	generalized substituent
***rac*-**	racemic
RCM	Ring Closing Metathesis
rfx.	reflux
ROESY	rotating frame nuclear Overhauser effect Spectroscopy
rt	room temperature
s	singlet
SET	single electron transfer
sext.	sextet
sol.	solution
t	triplet
TBAF	tetrabutylammonium fluoride
TBDPS	*tert*-Butyldiphenylsilyl
TBS-	*tert*-Butyldimethylsilyl
TBTH	*tert*-butyltin hydride
TEMPO	2,2,6,6-Tetramethylpiperidin-1-yl
TES-	triethylsilane
Tf	triflate
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TIPS	triisopropylsilane
tm	triplet of multiplets
TMDS or TMDSO	1,1,3,3-Tetramethyldisiloxane
TMP	2,2,6,6-Tetramethylpiperidine
TMPA	Tris(2-pyridylmethyl)amine
TMS	tetramethylsilane
TMS-	trimethylsilyl

TOF	time of flight mass spectrometry
TosMIC	toluenesulfonylmethyl isocyanide
TPP	thiamine pyrophosphate or tetraphenylporphyrin
TS	transition state
Ts	tosyl (*p*-toluenesulfonyl)
TTMSS	tris(trimethylsilyl)silane
wt	weight
δ	chemical shift
μ**W**	microwave

Prologue

Daphniphyllum alkaloids, isolated from various species of the Daphniphyllum genus, constitute a diverse family of natural products containing over 320 distinct members and featuring more than 20 unique polycyclic frameworks. Besides their fascinating architectonic structures, many of these compounds exhibit a wide range of biological activities, including anticancer, anti-HIV, antioxidant, antiviral, vasorelaxation, and nerve growth factor regulation properties. During the last decades, these synthetically challenging molecules have been subject to many studies resulting in the total synthesis of several members. Moreover, this scientific activity has enabled the development of new synthetic methods and strategies for the preparation of advanced intermediates toward their total synthesis.

In the present work, we have investigated the synthesis of the ABC ring core of both himalensine A and 2-deoxymacropodumine A, two members of the *Daphniphyllum* family, establishing a solid groundwork for future endeavors in their total synthesis.

After a brief introduction, where we report the last advances published to date in the total or partial synthesis of these alkaloids, our investigation work is then detailed in three consecutive chapters.

In the first chapter, we present a robust and readily scalable synthetic protocol for the preparation of 3a-methyl- and 3a-methoxycarbonyl octahydroindole moieties found in the calyciphylline A-type *Daphniphyllum* alkaloids. This method is based on the 5-endo-trig radical cyclization of *N*-benzyl-*N*-(2-methylcycloalkenyl)trichloroacetamides and their analogs using Bu_3SnH and AIBN. Our research has also led to the diastereoselective alkylation and methoxycarbonylation of these bicyclic structures through their enelactams. Additionally, enelactam compounds embodying two consecutive stereogenic carbon atoms were also achieved by means of a radical cyclization involving carbo-substituted dichloroacetamides. Upon further reduction, a series of polyfunctionalized *cis*-octahydroindoles was obtained which could serve as valuable building blocks for the synthesis of more complex polycyclic structures *en route* to *Daphniphyllum* alkaloids.

In the next chapter, a concise formal synthesis of himalensine A has been accomplished while providing access to the ABC ring of Calyciphylline A-type alkaloids. The key steps in this synthesis involve a radical cyclization, to form the hydroindole AB ring system, followed by a stereocontrolled aldol cyclization resulting in the closure of the piperidine ring. Additionally, the cyclic alcohol derived from these processes is utilized to introduce the methyl group at C-18 in the bowl-shaped azatricyclic structure, the reaction taking place with configuration retention.

Finally, in the last part of this PhD thesis, we have successfully constructed the azatricyclic ABC ring of 2-deoxymacropodumine A for which no total synthesis has been reported yet. In this part, we have investigated the access to the 7-membered ring through a ring expansion of the cyclohexanone moiety within two ring cores previously synthesized in this thesis. Initially, we have explored several ketone homologation methodologies using diazo derivatives from morphans to homomorphans. The optimized reaction conditions have been applied to the available ABC tricyclic and AC bicyclic scaffolds. From the latter, the reaction has provided regioselectively the corresponding homoindole 3a-methylperhydrocyclohepta[*b*]pyrrole with excellent yield. This outcome has facilitated a further synthesis of the desired azatricyclic [5-6-7] framework. With these promising results, we propose a strategy for achieving the total synthesis of this natural product and several reactions have been explored. These developments represent significant strides in our ongoing quest to comprehend and synthesize intricate natural compounds.

Chapter 1

Introduction and objectives

1.1 Introduction

1.1.1 Daphniphyllum alkaloids

Daphniphyllum alkaloids are a wide family of natural products isolated from trees and shrubs of the genus *Daphniphyllum* located in the eastern and southeastern parts of Asia.[1] In 1909, Yagi was the first to isolate daphnimacrin,[2] but it was not until 1966 that Hirata's work marked a significant breakthrough by elucidating the structure of daphniphylline and yuzurimine, two members of this large family of alkaloids, through X-ray characterization.[3] Since then, over 300 members have been isolated, each featuring intricate azapolycyclic structures with multiple stereocenters. These compounds are categorized into more than 30 subfamilies based on their backbone structures. Moreover, the leaves and the roots of this genus have been used in traditional Chinese medicine and recent studies[1a] show their remarkable range of biological activities including anticancer[4], anti-HIV, antioxidant, antiviral[5], vasorelaxation and nerve growth factor-regulation[6].

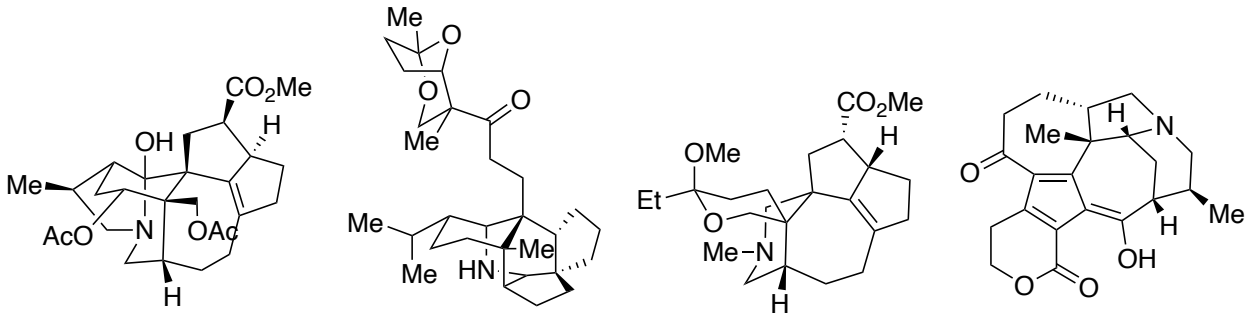


Figure 1. 1 *Structural diversity of Daphniphyllum alkaloids*

[1] For recent reviews: a) Chattopadhyay, A.K.; Hanessian, S. *Chem. Rev.* **2017**, *117*, 4104–4146. b) Kang, B.; Jakubec, P.; Dixon, D.J. *Nat. Prod. Rep.* **2014**, *31*, 550–562.
[2] Yagi, S. *Kyoto Igaku Zasshi*, **1909**, *6*, 208–222.
[3] Irikawa, H.; Sakurai, H.; Sakabe, N.; Hirata, Y. *Tetrahedron Lett.* **1966**, *7*, 5363–5368. b) Sakabe, N.; Irikawa, H.; Sakurai, H.; Hirata, Y. *Tetrahedron Lett.* **1966**, *7*, 963–964.
[4] a) Zhang, H.; Yang, S. P.; Fan, C. Q.; Ding, J.; Yue, J. M. *J. Nat. Prod.* **2006**, *69*, 553–557. b) Zhang, C. R.; Liu, H. B.; Feng, T.; Zhu, J. Y.; Geng, M. Y.; Yue, J. M. *J. Nat. Prod.* **2009**, *72*, 1669–1672. c) Liu, S.; Zhang, J. H.; Di, Y. T.; Dong, J. Y.; Hao, X. *Nat. Prod. Res.* **2018**, *32*, 2165–2170.
[5] Xu, J. B.; Zhang, H.; Gan, L. S.; Han, Y. S.; Wainberg, M. A.; Yue, J. M. *J. Am. Chem. Soc.* **2014**, *136*, 7631–7633.
[6] a) Morita, H.; Ishioka, N.; Takatsu, H.; Shinzato, T.; Obara, Y.; Nakahata, N.; Kobayashi, *J. Org. Lett.* **2005**, *7*, 459–462. b) Saito, S.; Yahata, H.; Kubota, T.; Obara, Y.; Nakahata, N.; Kobayashi, J. *Tetrahedron* **2008**, *64*, 1901–1908.

In 1973, Yamamura and Suzuki,[7] performed feeding experiments with ^{14}C on the leaves of *D. macropodum*. and fruits of *D.* beijmansi to determine the biosynthesis of these alkaloids revealing that they came from mevalonic acid via a squalene intermediate (Figure 1.2).

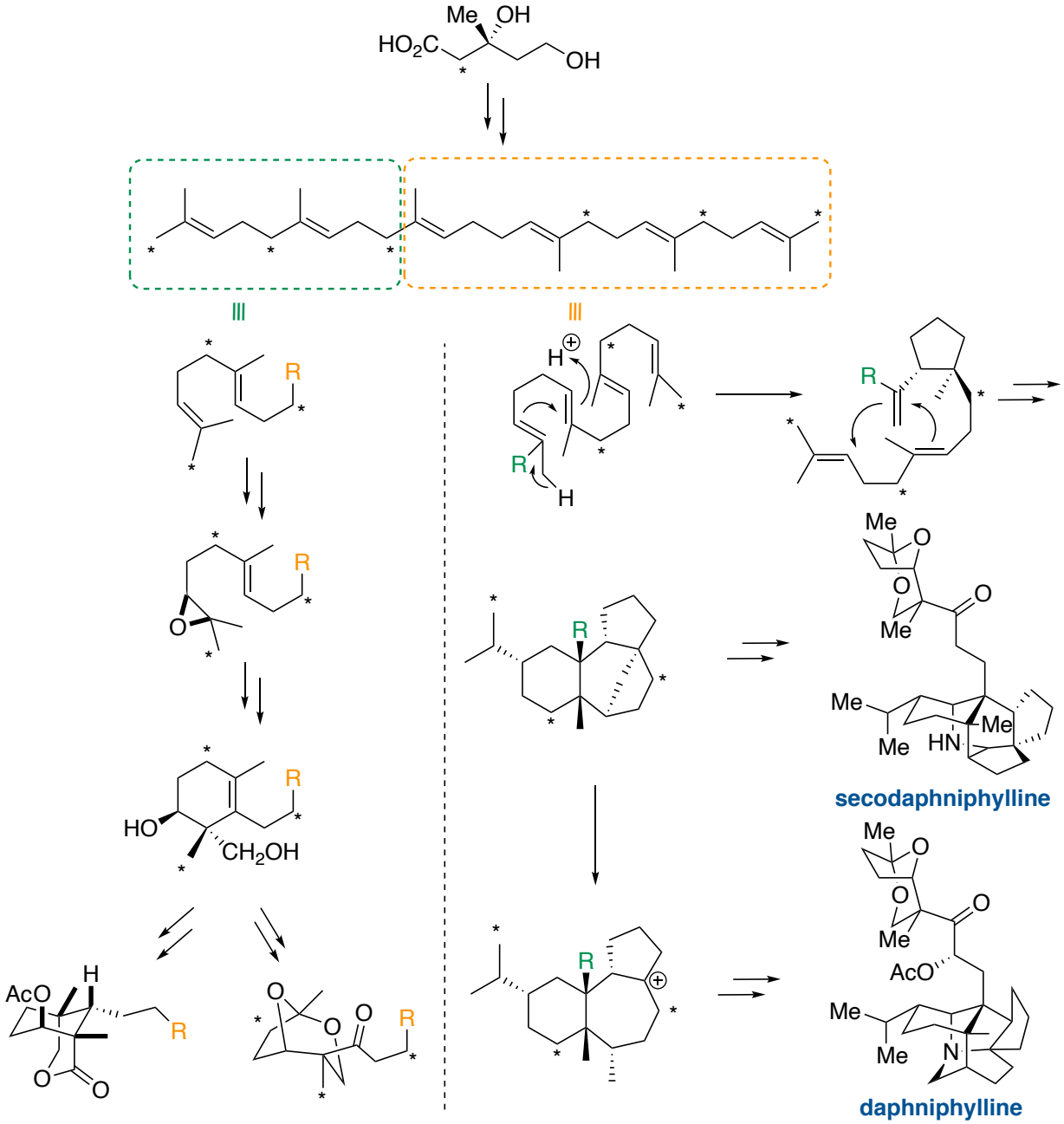


Figure 1. 2 *Proposed biosynthetic origin by Yamamura and Suzuki*[7]

[7] a) Suzuki, K.-T.; Okuda, S.; Niwa, H.; Toda, M.; Hirata, Y.; Yamamura, S. *Tetrahedron Lett.* **1973**, *14*, 799–802. b) Niwa, H.; Hirata, Y.; Suzuki, K.-T.; Yamamura, S. *Tetrahedron Lett.* **1973**, *14*, 2129–2132.

Later, in 1988, Heathcock et al. reported a biomimetic synthesis of *rac*-methyl homo-secodaphniphyllate, which set an important step in *Daphniphyllum* alkaloids obtention.[8] In addition, their experimental work focused on the biosynthetic origin of these alkaloids confirming Yamamura's work.[9]

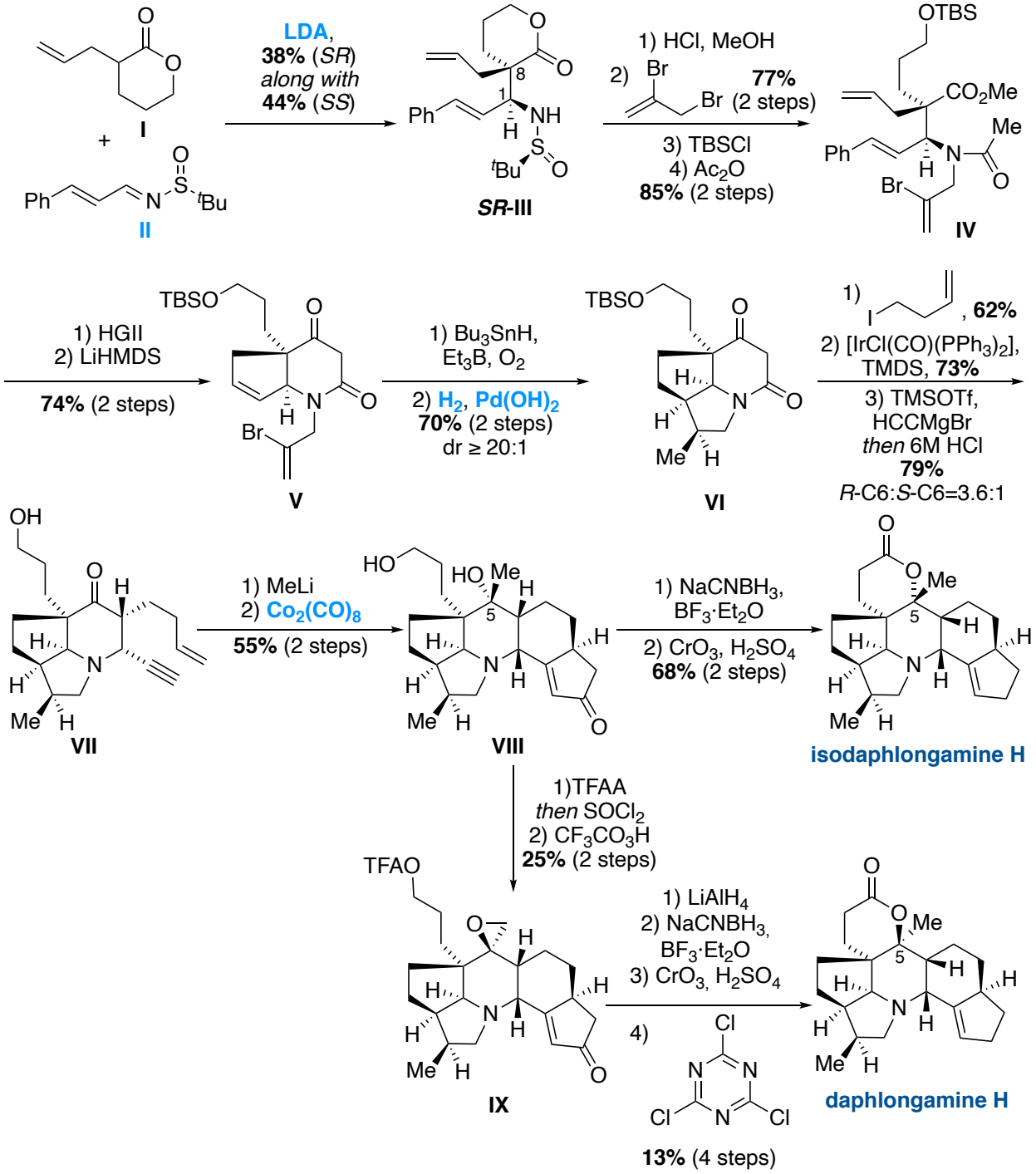
Since then, motivated by their complex architectonic structures and their potential biological activity *Daphniphyllum* alkaloids have been the objective of important research projects leaded by Carreira,[10] Smith,[11] Fukuyama,[12] Hannesian,[13] Li,[14] Zhai,[15] Dixon,[16] Qiu[17] among others.

[8] Ruggeri, R.B.; Hansen, M.M.; Heathcock, C.H. *J. Am. Chem. Soc.* **1988**, *110*, 8734–8736.
[9] a) Ruggeri, R. B.; Heathcock, C. H. *Pure Appl. Chem.* **1989**, *61*, 289–292. b) Piettre, S.; Heathcock, C. H. *Science*, **1990**, *248*, 1532–1534. c) Heathcock, C. H. *Proc. Natl. Acad. Sci. U. S. A.* **1996**, *93*, 14323–14327.
[10] Weiss, M. E.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2011**, *50*, 11501–11505.
[11] a) Shvartsbart, A.; Smith, A. B. III. *J. Am. Chem. Soc.* **2014**, *136*, 870–873. b) Shvartsbart, A.; Smith, A. B. III. *J. Am. Chem. Soc.* **2015**, *137*, 3510–3519.
[12] Yamada, R.; Adachi, Y.; Yokoshima, S.; Fukuyama, T. *Angew. Chem. Int. Ed.* **2016**, *55*, 6067–6070.
[13] Chattopadhay, A. K.; Ly, V. L.; Jakkepally, S.; Berger, G.; Hanessian, S. *Angew. Chem. Int. Ed.* **2016**, *55*, 2577–2581
[14] (a) Lu, Z.; Li, Y.; Deng, J.; Li, A. *Nat. Chem.* **2013**, *5*, 679–684. (b) Li, J.; Zhang, W.; Zhang, F.; Chen, Y.; Li, A. *J. Am. Chem. Soc.* **2017**, *139*, 14893–14896. (c) Zhang, W. H.; Ding, M.; Li, J.; Guo, Z. C.; Lu, M.; Chen, Y.; Liu, L. C.; Shen, Y. H.; Li, A. *J. Am. Chem. Soc.* **2018**, *140*, 4227–4231. (d) Chen, Y.; Zhang, W.; Ren, L.; Li, J.; Li, A. *Angew. Chem., Int. Ed.* **2018**, *57*, 952–956. (e) Xiong, X.; Li, Y.; Lu, Z.; Wan, M.; Deng, J.; Wu, S.; Shao, H.; Li, A. *Chem. Commun.* **2014**, *50*, 5294–5297.
[15] Chen, X.; Zhang, H. J.; Yang, X.; Lv, H.; Shao, X.; Tao, C.; Wang, H.; Cheng, B.; Li, B. Y.; Guo, J.; Zhang, J.; Zhai, H. B. *Angew. Chem., Int. Ed.* **2018**, *57*, 947–951.
[16] a) Sladojevich, F.; Michaelides, I. N.; Darses, B.; Ward, J. W.; Dixon, D. J. *Org. Lett.* **2011**, *13*, 5132–5135. b) Darses, B.; Michaelides, I. N.; Sladojevich, F.; Ward, J. W.; Rzepa, P. R.; Dixon, D. J. *Org. Lett.* **2012**, *14*, 1684–1687.
[17] Xu, B.; Wang, B.; Xun, W.; Qiu, F. G. *Angew. Chem., Int. Ed.* **2019**, *58*, 5754–5757.

1.1.2 Recent total syntheses of *Daphniphyllum* alkaloids

In 2019, Sarpong described the first total synthesis of (-)-daphlongamine H,[18] a member of calyciphylline B-type alkaloids, along with its C-5 epimer (-)-isodaphlongamine H. Both alkaloids contain a hexacyclic ring system with a centered piperidine ring and seven stereocenters. The synthesis started by means of a Mannich reaction between an ester and a chiral Ellman's sulfinamide,[19] followed by the lactone ring opening and oxygen protection. Incorporation of nitrogen substituents allowed a RCM/Dieckmann condensation sequence to build the bicyclic 5,6-system and, subsequent radical cyclization, furnished the tricyclic core in a multigram scale. Next, diastereoselective hydrogenation catalyzed by $Pd(OH)_2$ and subsequent installation of unsaturated chains to the piperidine motif, led to intermediate **VII** which served as a suitable precursor for a Pauson-Khand cyclization, yielding the pentacyclic fragment. Subsequent steps consisted in a carbonyl removal from the cyclopentenone moiety, and oxidation of the primary alcohol, which triggered the closure of the *cis*-lactone ring, completing the synthesis of (-)-isodaphlongamine H. To synthesize (-)-daphlongamine H, a configuration inversion at C-5 was required. Starting from intermediate **VIII**, the tertiary alcohol underwent an elimination process, and the generated double bond was subjected to epoxidation. Treatment with $LiAlH_4$ enabled the reductive opening of the epoxide. The last transformations involved the cyclopentenone carbonyl removal, and the construction of the *trans*-lactone ring in the presence of cyanuric chloride, achieving the synthesis of the natural product in 20 steps.

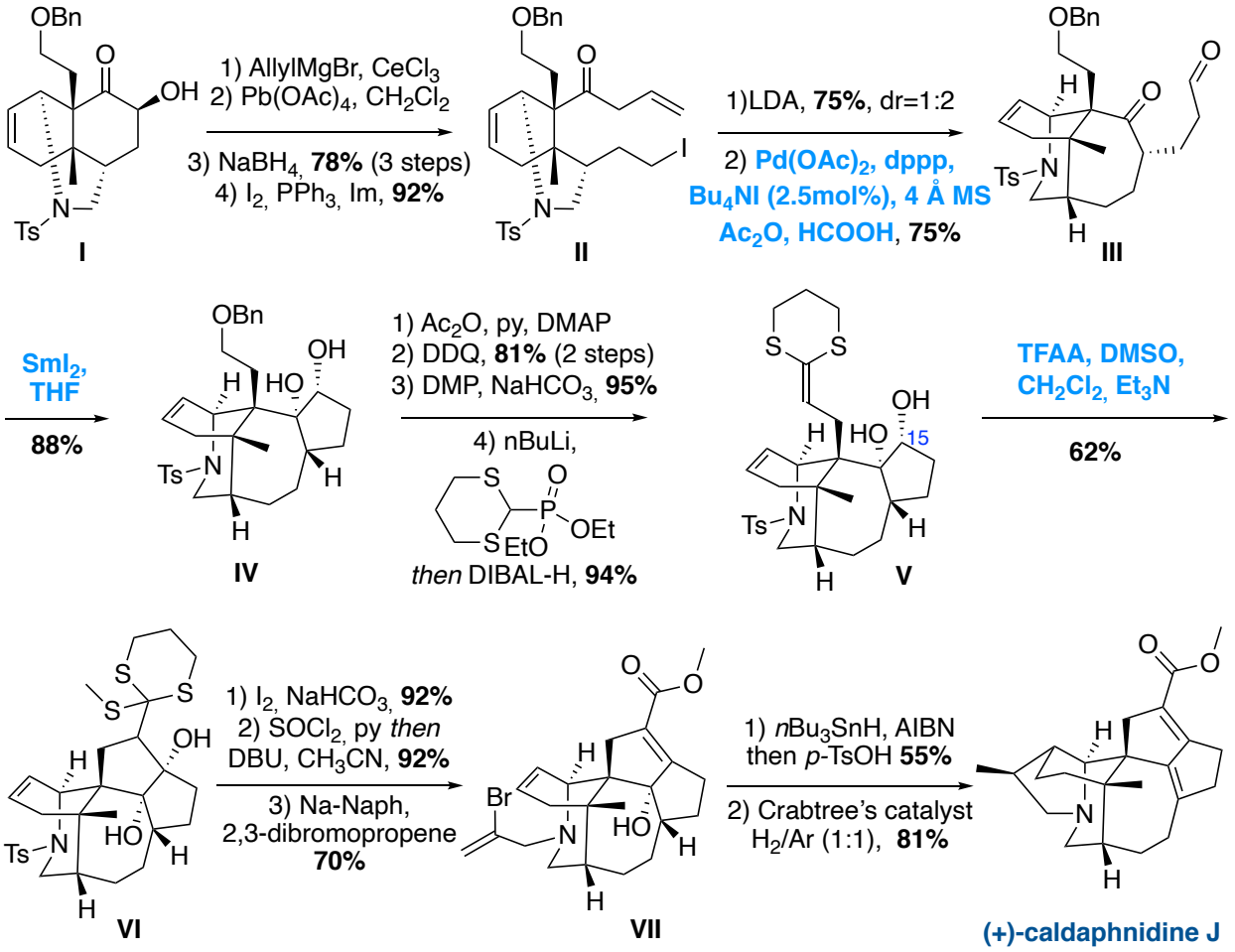
[18] Hugelshofer, C. L.; Palani, V.; Sarpong, R. *J. Am. Chem. Soc.* **2019**, *141*, 8431−8435.
[19] a) Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **2002**, *67*, 7819−7832. b) Robak, M. T.; Herbage, M. A.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 3600−3740.



Scheme 1. 1 *Total synthesis of daphlongamine H and isodaphlongamine H reported by Sarpong et al.*[18]

Although yuzurimine-type alkaloids are one of the largest subfamilies of *Daphniphyllum alkaloids*, no total synthesis of its members had been described until 2020, when Xu *et al*. reported the first total synthesis of (+)-caldaphnidine J.[20] Starting from the previously reported chiral synthon **I**,[21] addition of an allylic chain on the carbonyl was followed by oxidative cleavage of the resulting diol moiety. After hydroxyl iodination and cyclization in the presence of LDA, the double bond was regioselectively hydroformylated using Shi's protocol.[22] Then, a Samarium(II)-mediated pinacol coupling furnished the 5,6-bicyclic system. After a deprotection/oxidation sequence, an aldehyde was installed at the three-carbon chain which was submitted to a Horner-Wadsworth-Emmons reaction to introduce a ketene dithioacetal group. Next, a one-pot procedure involving a Swern oxidation for installation of a ketone at C-15, and a C-C bond formation through an acid-catalyzed ketene dithioacetal Prins reaction provided compound **VI**. After deprotection, alcohol elimination, and vinyl bromide incorporation, intermediate **VII** was submitted to a radical cyclization for the last ring closure. Finally, a diastereoselective hydrogenation was performed in the presence of Crabtree's catalyst to afford (+)-caldaphnidine J in 17 steps.

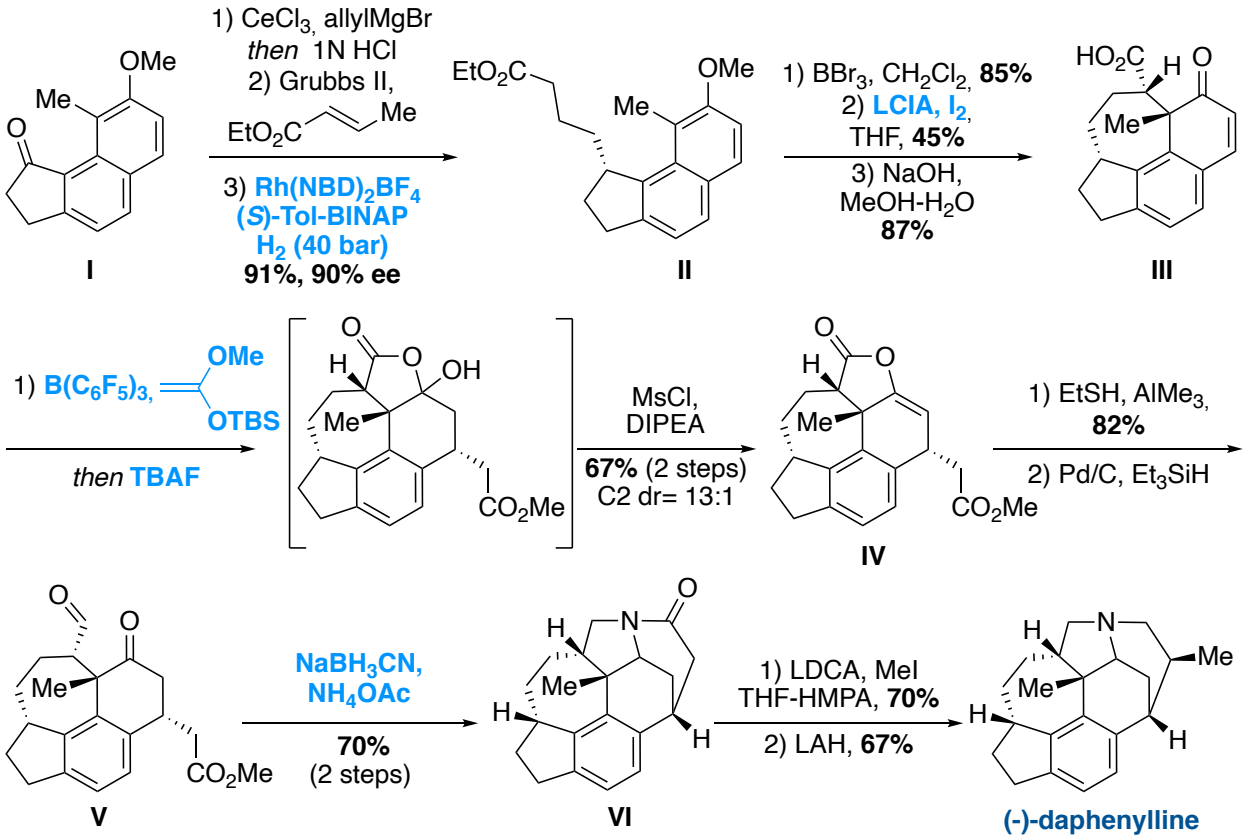
[20] Guo, L.-D.; Zhang, Y.; Hu, J.; Ning, C.; Fu, H.; Chen, Y.; Xu, J. *Nat. Commun.* **2020**, *11*, 3538–3544.
[21] Guo, L.-D.; Hu, J.; Zang, Y.; Tu, W.; Zhang, Y.; Pu, F.; Xu, J. *J. Am. Chem. Soc.* **2019**, *141*, 13043–13048.
[22] Ren, W.; Chang, W.; Dai, J.; Shi, Y.; Li, J.; Shi, Y. *J. Am. Chem. Soc.* **2016**, *138*, 14864–14867.



Scheme 1. 2 *Total synthesis of (+)-caldaphnidine J reported by Xu. et al.* [20]

More recently, Lu's group reported a new synthesis of daphenylline,[23] a natural product with a unique benzene ring with four contiguous substituents. Hitherto, six total syntheses were previously documented, but their approach was based on an innovative intramolecular dearomative cyclization which bypassed the need for protection/deprotection manipulation or functional groups interconversion. Starting from substituted indanone **I**, a four-carbon chain was successfully incorporated through an allylic attack to the carbonyl followed by a cross-metathesis reaction and final enantioselective hydrogenation in the presence of a chiral Rh-catalyst. Next, the removal of the methyl group and further oxidative dearomatization of ester-tethered β-naphtol **II**, in the presence of LCIA and I_2, allowed the challenging 7-membered ring formation. A subsequent Mukaiyama-Michael reaction of **III** resulted in a lactone ring which on opening underwent a tandem reductive amination/amidation double cyclization reaction providing the cage-like scaffold. Finally, methylation and reduction of the carbonyl group afforded (−)-daphenylline.

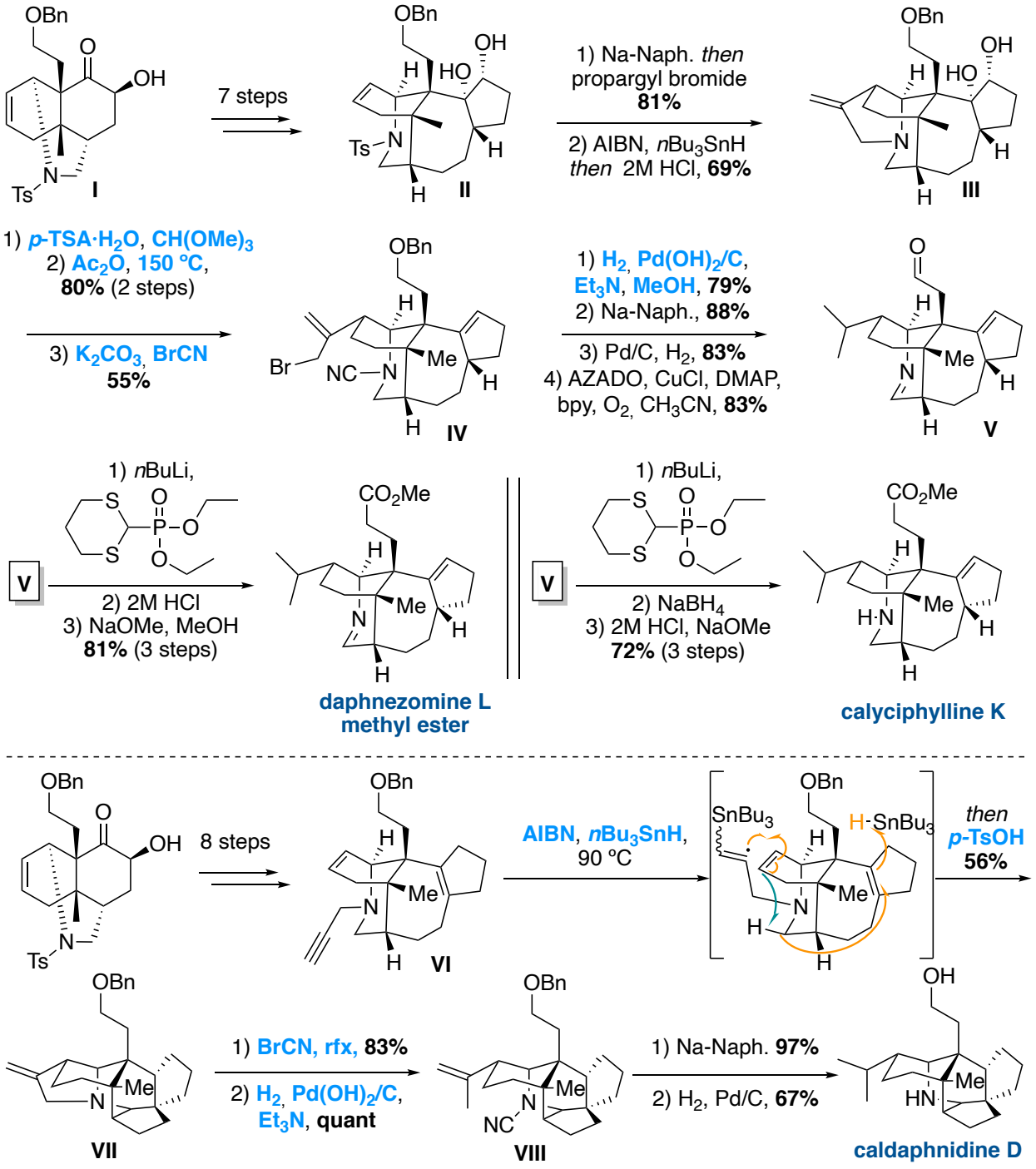
[23] Cao, M.-Y.; Ma, B.-J.; Gu, Q.-X.; Fu, B.; Lu, H.-H. *J. Am. Chem. Soc.* **2022**, 144, 5750−5755.



Scheme 1. 3. *Total synthesis of (-)-daphenylline reported by Lu et al.*[23]

The same year, Xu's group,[24] achieved the first total synthesis of daphnezomine L methyl ester and calcyphilline K, the two representative members of the daphnezomine L-type alkaloid subfamily. Moreover, they described the first total synthesis of caldaphnidine D, a secodaphniphylline type member. Taking into consideration their previous work on the synthesis of yuzurimine-type alkaloids,[20] they envisioned that late-stage C-N bond activations of the involved intermediates would allow a facile access to these alkaloids (Scheme 1.2). Thus, from advanced intermediate **II**, after amine alkylation with propargyl bromide and further radical cyclization, a tetracyclic derivative **III** was isolated with an acceptable yield. Then, diol dehydration through Ando's protocol,[25] led to the corresponding cyclopentene derivative which was submitted to *von Braun* C-N bond cleavage providing intermediate **IV**. Next, hydrogenolysis of the C-Br bond with H_2 and $Pd(OH)_2/C$ in the presence of Et_3N was followed by *N*- and *O*-deprotection and oxidation to obtain aldehyde **V**. Homologation of the aldehyde through a HWE and further deprotection followed by carboxylic acid methylation provided daphnezomine L methyl ester. Additionally, after chain homologation, the imine was reduced and ketene dithioacetal deprotection afforded calyciphylline K. Finally, from compound **I**, intermediate **VI** was prepared with some variations in the chemical sequence which underwent a cascade radical cyclization, involving a 1,5-HAT, generating two new rings. The same *von Braun* C-N bond activation and hydrogenolysis of the C-Br bond sequence was followed by deprotections and the third natural product, caldaphnidine D, was synthesized.

[24] Hu, J.; Guo, L.-D.; Chen, W.; Jiang, Y.; Pu, F.; Ning, C.; Xu, J. *Org. Lett.* **2022**, *24*, 7416–7420
[25] Ando, M.; Ohhara, H.; Takase, K. *Chem. Lett.* **1986**, *15*, 879–882.



Scheme 1. 4. *Total synthesis of daphnezomine L methyl ester, calyciphylline K and caldaphnidine D reported by Xu et al.*[24]

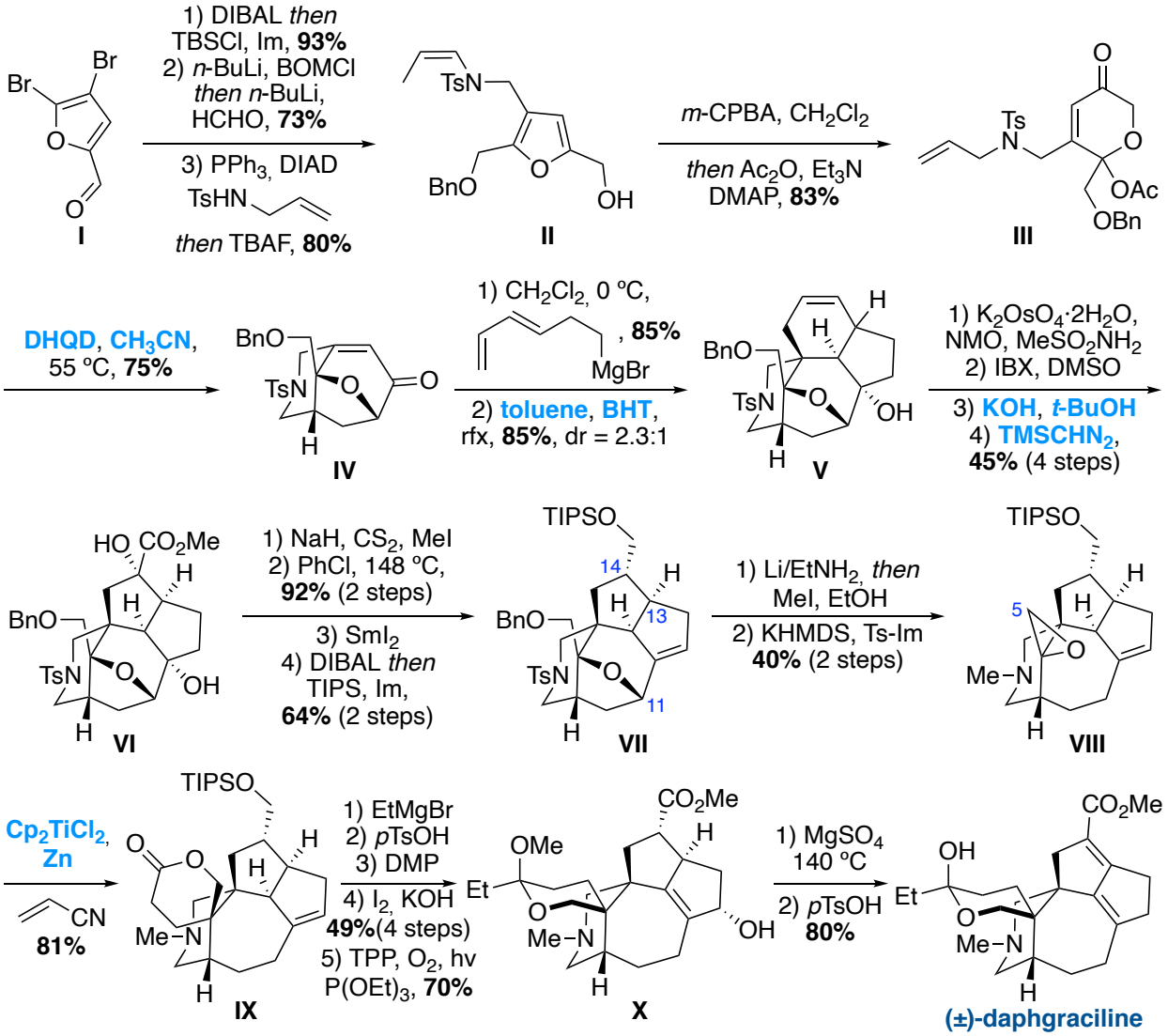
In 2022, Li and Sun described the first total synthesis of *Daphniphyllum* yuzurine-type alkaloid, (±)-daphgraciline.[26] The synthesis started with the preparation of **III** from furan derivative **I** through a three-step sequence followed by an Achmatowicz rearrangement with *m*CPBA. Next, treatment with DHDQ promoted a type II [5+2] cycloaddition to construct, diastereoselectively, the bridged [4.3.1] ring system. 1,2-addition of a Grignard reagent containing a diene moiety was followed by an intramolecular Diels-Alder (IMDA) providing two additional rings. Further olefinic dihydroxylation followed by oxidation, generated a dicarboxylic compound that underwent a ring contraction through a benzylic acid-type 1,2-rearrangement,[27] for the [6-7-5-5] ring core construction. After double Chugaev elimination, a chemo- and diastereoselective conjugated reduction of C13-C14 olefin bond with SmI_2, a one-pot reduction of the ester group with DIBAL, and TIPS protection intermediate **VII** was afforded. Li/$EtNH_2$ system cleaved C11-O bond and triggered both *N*- and *O*-deprotections. The resulting diol, in the presence of KHMDS, furnished the corresponding epoxide **VIII** which was submitted to a Ti-mediated coupling[28] with acrylonitrile generating a spiro tetrahydropyran moiety. Modification in the latter, followed by Schenk ene[29] photooxygenation, provided **X** which after the last dehydration step completed the (±)-daphgraciline synthesis.

[26] Li, L.-X.; Min, L.; Yao, T.-B.; Ji, S.-X.; Qiao, C.; Tian, P.-L.; Sun, J.; Li, C.-C. *J. Am. Chem. Soc.* **2022**, *144*, 18823−18828

[27] Liebig, J. *Ann. Pharm.* **1838**, *25*, 1.

[28] a) RajanBabu, T. V.; Nugent, W. A. *J. Am. Chem. Soc.* **1989**, *111*, 4525−4527. b) Cha, J. Y.; Yeoman, J. T. S.; Reisman, S. *J. Am. Chem. Soc.* **2011**, *133*, 14964−14967.

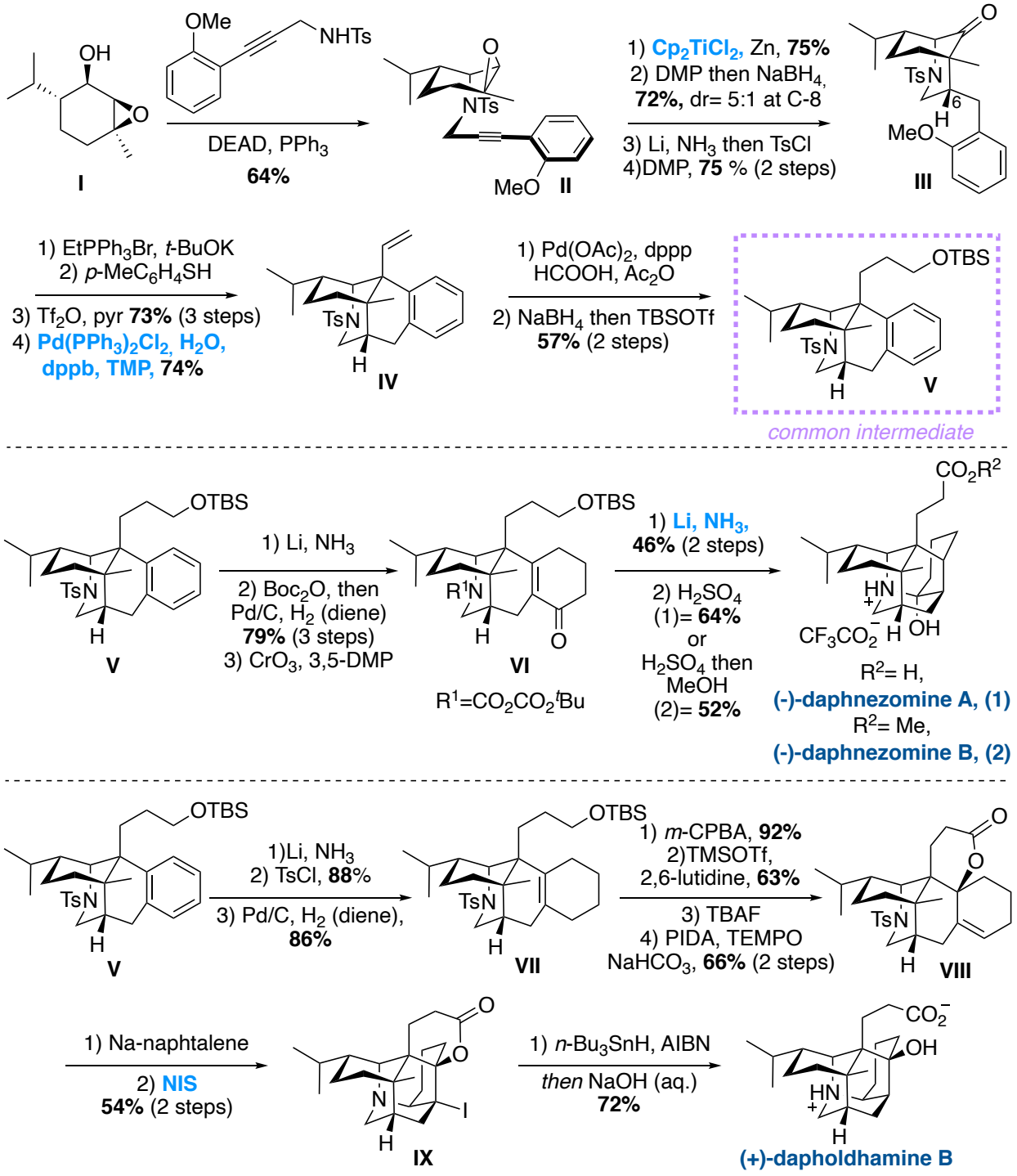
[29] a) Prein, M.; Adam, W. *Angew. Chem. Int. Ed.* **1996**, *35*, 477–494; b) Ghogare, A. A.; Greer, A. *Chem. Rev.* **2016**, *116*, 9994–10034.



Scheme 1. 5. *Total synthesis of (±)-daphgraciline reported by Li et al.*[26]

Recently, Zhai *et al.*[30] reported a divergent total synthesis of the three members of daphnezomine A-type subfamily: (-)-daphnezomines A and B and (+)-dapholdhamine B. The synthesis started with a Mitsunobu substitution between the known chiral alcohol **I**[31] and a sulfonamide to synthesize intermediate **II**. Then, Ti-mediated cyclization was performed to construct the azabicyclo[3.3.1]nonane ring. Next, an epimerization of the resulting hydroxyl was required for a diastereoselective double bond reduction with Li/NH_3. After Wittig reaction and triflate generation at the aromatic ring, a Pd-catalyzed Heck reaction resulted in the tetracyclic ring formation. Additional chemical modifications provided a common intermediate which was used to access the three targeted natural products. Thus, **V** was simultaneously reduced and *N*-deprotected under Birch conditions. Then, protection of the amine as a carbamic-carbonic anhydride followed by an allylic oxidation installed a carbonyl group. Removal of the nitrogen-substituent promoted a conjugate reduction and a ketoamine-carbinolamine tautomerization sequence forming a hemiketal and assembling the aza-adamantane backbone. After Jones oxidation of the primary alcohol, (-)-daphnezomine A was obtained, and the same reaction in the presence of MeOH afforded (-)-daphnezomine B. Finally, for the synthesis of (+)-dapholdhamine B, treatment of **V** with Li/NH_3 promoted Birch reduction of the aromatic ring along with the removal of the nitrogen protecting group. Further treatment with $TsCl/Et_3N$ followed by hydrogenation yielded intermediate **VII**. Next, diastereoselective epoxidation was followed by the opening of the corresponding epoxide with TMSOTf, desilylation with TBAF, and oxidation of the primary alcohol furnishing the lactone ring closure. Finally, removal of the nitrogen protective group followed by NIS promoted a 6-*endo*-trig aminocyclization and the reduction of the iodo derivative provided (+)-dapholdhamine B.

[30] Su, S.; Lin, C.; Zhai, H. *Angew. Chem. Int. Ed.* **2023**, *62*, e202303402.
[31] Cantín, A.; Lull, C.; Primo, J.; Miranda, M. A.; Primo-Yúfera, E. *Tetrahedron: Asymmetry*, **2001**, *12*, 677–683.



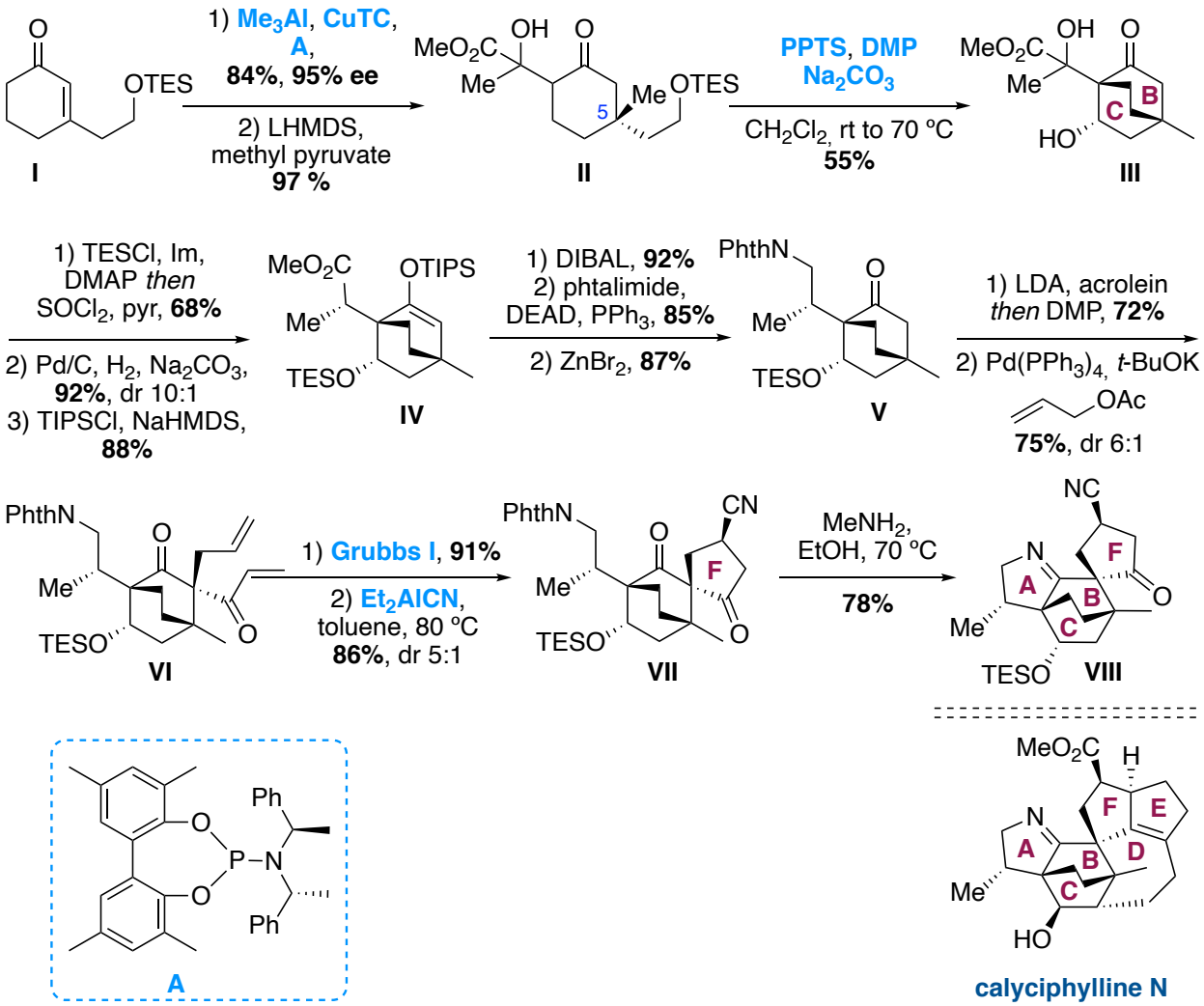
Scheme 1. 6. *Total synthesis of daphnezomine A, (-)-daphnezomine B and (+)-dapholdhamine B reported by Zhai et al.*[30]

1.1.3 Latest syntheses of versatile building blocks

Total syntheses of *Daphniphyllum* alkaloids are quite challenging due to their complex structures. Thus, several investigations leaded to valuable building blocks in which new methodologies were developed to acces advanced intermediates towards these alkaloids.

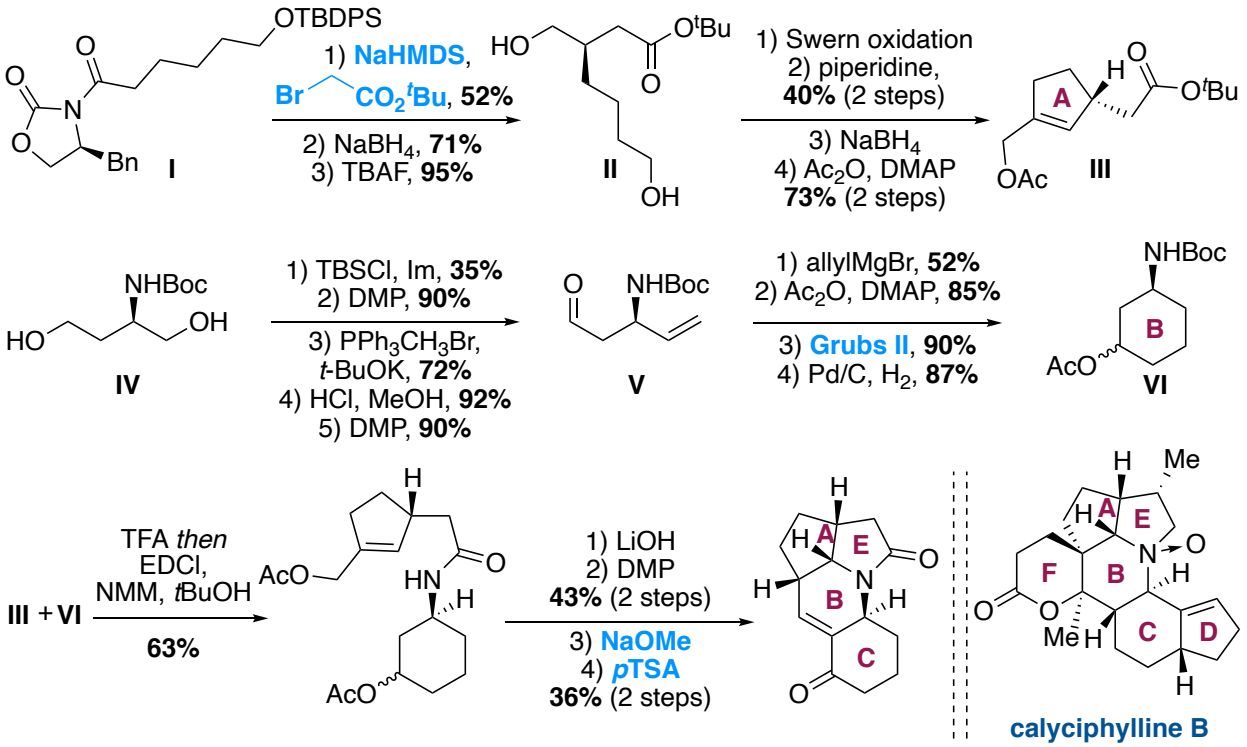
In 2018, Qin *et al.* reported[32] the enantioselective synthesis of the ABCF tetracyclic framework of calyciphylline N, a member of the daphmanidin A type subfamily. The investigation started from enone **I** which underwent a copper-catalyzed asymmetric conjugate addition to install the stereogenic center at C-5. Further α-alkylation of a pyruvate gave **II,** which was submitted to a one-pot sequence that included desilylation, oxidation and aldolic cyclization for the bicyclo[2.2.2]octane construction. Chemoselective protection of the secondary alcohol followed by treatment with $SOCl_2$ provided terminal alkene which, after a diastereoselective hydrogenation, provided ester **IV.** After protection of the carbonyl as a TIPS, the ester was reduced to the corresponding alcohol which underwent a Mitsunobu reaction to introduce the amino group. Aldol condensation with acrolein and Tsuji-Trost[33] allylation furnished the dialkene derivative **VI** to perform a ring closing metathesis for the F-ring closure. Finally, 1,4-hydrocyanation of the enone with Nagata's reagent[34] followed by phthalimide hydrolysis led to a spontaneous cyclization to form the A-ring and, hence, completing the construction of the ABCF-tetracyclic structure present in calyciphylline N.

[32] Li, Y.; Dong, Q.; Xie, Q.; Tang, P.; Zhang, M.; Qin, Y. *Org. Lett.* **2018**, *20*, 5053–5057.
[33] a) Trost, B. M.; Fullerton, T. J. *J. Am. Chem. Soc.* **1973**, *95*, 292–294. b) Tsuji, J.; Takahashi, H.; Morikawa, M. *Tetrahedron Lett.* **1965**, *6*, 4387– 4388.
[34] a) Nagata, W.; Yoshioka, Y. *Org. React.* **1977**, *25*, 255–476. b) Min, S. J.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **2007**, *46*, 2199–2202. c) Murphy, S. K.; Zang, M. S.; Herzon, S. B. *Science*, **2017**, *356*, 956–959. d) Zeng, M. S.; Murphy, S.K.; Herzon, S. B. *J. Am. Chem. Soc.* **2017**, *139*, 16377–16388.



Scheme 1.7. *Synthesis of ABCF-tricyclic framework reported by Qin et al.*[32]

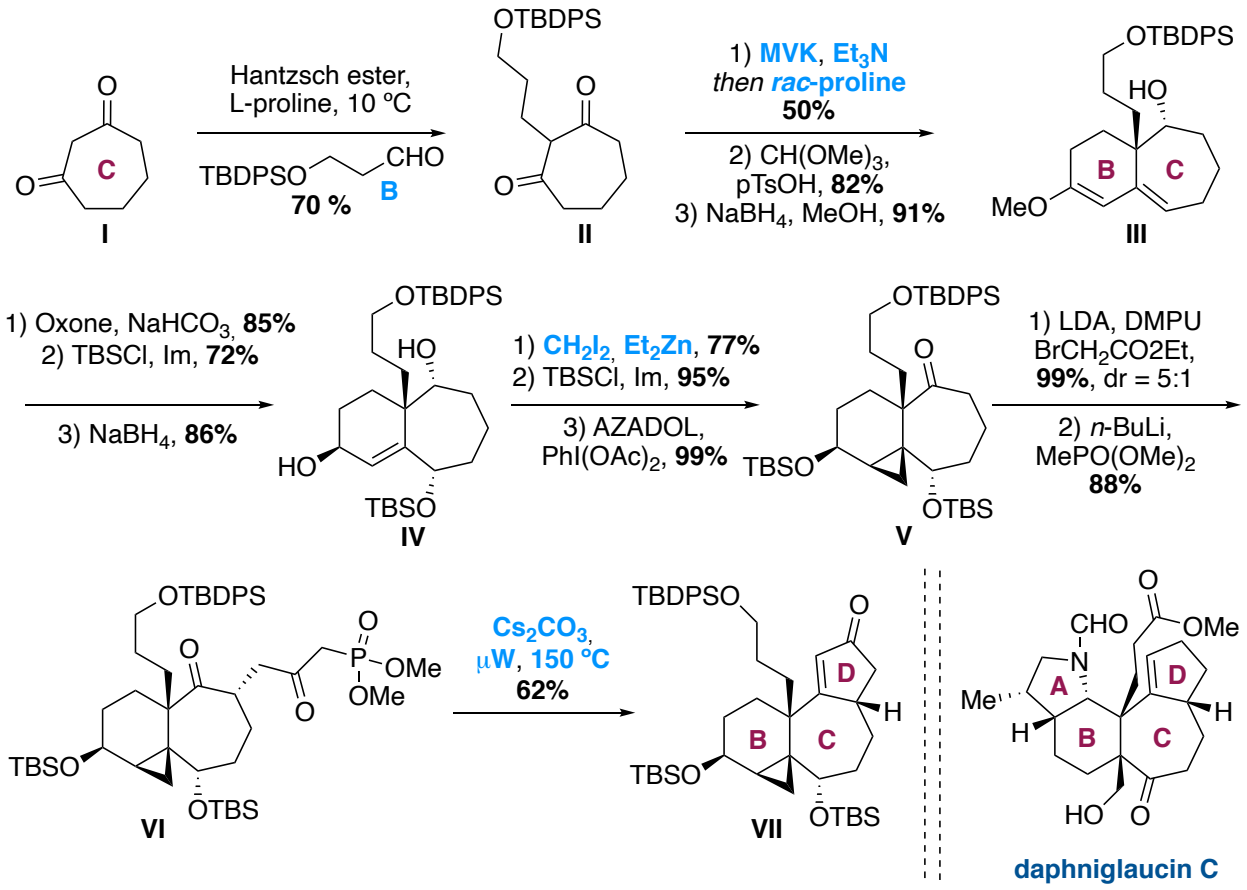
In 2019, She and coworkers[35], reported a synthesis of the ABCE core of calyciphylline B-type alkaloids which allowed them to use it as a platform for the total synthesis of this subfamily members. The work started with the preparation of fragment **III** via enantioselective alkylation of **I**[36] induced by chiral Evans auxiliar. Reductive removal of the auxiliar led to diol **II** which, after oxidation, underwent intramolecular condensation generating the 5-membered A-ring. The second fragment was prepared from chiral diol **IV** which, after oxidation and Wittig reaction, provided aldehyde derivative **V**. Allylic addition to the carbonyl group and further RCM generated the cyclohexene ring and further hydrogenation gave **VI**. Fragments **III** and **VI** condensed thorugh amidation leading to **VII**. After a deprotection step, an intramolecular aza-Michael addition took place followed by an aldolic condensation to afford the ABCE-tetracyclic fragment of calyciphylline B.



Scheme 1. 8. *Synthesis of ABCE-tetracyclic core of calyciphylline B achieved by She et al.*[35]

[35] Du, C.; Fang, J.; Chen, J.; Liu, Z.; Li, H.; Wang, X.; Xie, X.; She, X. *Org. Lett.* **2019**, *211*, 8718–8721
[36] Kobayashi, Y.; Motoyama, Y. *Synlett*, **2006**, *2006*, 2670–2672.

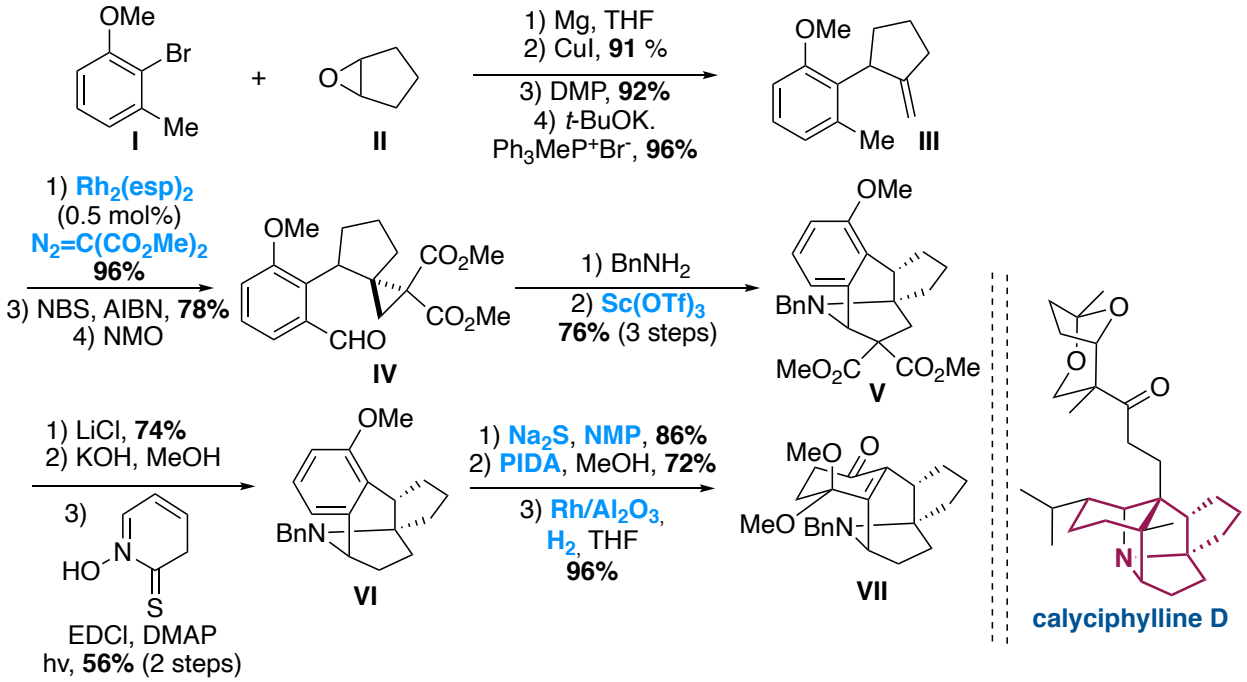
In 2021, Xu and co-workers,[37] in their work toward the synthesis of the daphniglaucin C-type subfamily, described the construction of their BCD-tricyclic core. Hence, reaction of 1,3-cycloheptanedione with aldehyde **B** in the presence of Hantzsch ester provided the reduced substrate **II** which was submitted to a Robinson annulation by reaction with methyl vinyl ketone (MVK). The resulting B,C-bicyclic enone was transformed to enol ether **III** which, after oxone-mediated oxidation and carbonyl reduction, afforded **IV**. Next, Simmons-Smith cyclopropanation with CH_2I_2 installed the quaternary center and an angular carbon. Next, protection and oxidation processes furnished ketone **V**. Incorporation of an ester-containing chain at the α-carbon allowed the preparation of the phosphonate **VI** suitable to undergo a Horner-Wadsworth-Emmons (HWE) reaction for the closure of the 5-membered D-ring of the BCD-tricyclic fragment.



Scheme 1. 9. *Synthesis of BCD tricyclic core of daphniglaucin C reported by Xu et al* [37]

[37] Chen., Y.; Guo, L.-D.; Xu, J. *Tetrahedron Letters,* **2021**, *71*, 153030–153034.

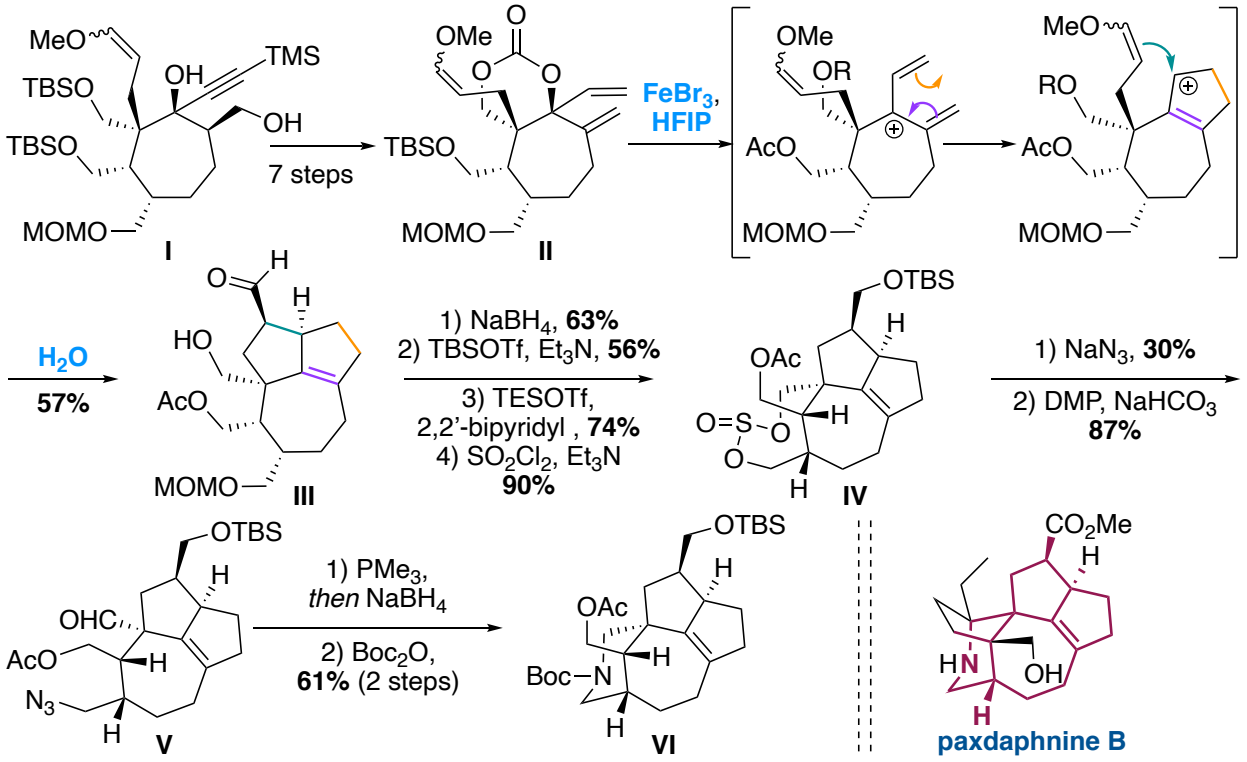
Recently, in 2021, Wang *et. al.*[38] achieved the construction of the aza-[5-6-7-5] tetracyclic core of calyciphylline D with a strategy based on a methodology for Intramolecular Cross Cycloaddition (IMCC) previously developed,[39a,b] and used in some of their total synthesis works.[39c] Reaction of epoxide **II** with Grignard reagent prepared from **I**, and subsequent oxidation and Wittig reaction provided **III**. The terminal methylene was submitted to a Rh-catalyzed diastereoselective cyclopropanation with diazomalonate. Benzylic bromination and subsequent oxidation afforded aldehyde **IV**. In-situ generation of an imine allowed the IMCC catalyzed by $Sc(OTf)_3$ to generate the bridged 8-aza[3.2.1]-octane core. Further modifications to remove the di-carbonylic unit yielded intermediate **VI**. After phenol deprotection using Newman's protocol[40] followed by an oxidative dearomatization[41] and a last selective hydrogenation, the targeted aza-tetracyclic fragment was formed.



Scheme 1.10. *Construction of aza-[5,6,7,5] tetracyclic core of calyciphylline D by Wang et al.* [38]

[38] Cui, Y.; Ren, J.; Lv, J.; Wang, Z. *Org. Lett.* **2021**, *23*, 9198–9193.
[39] a) Xing, S.; Pan, W.; Liu, C.; Ren, J.; Wang, Z. *Angew. Chem. Int. Ed.* **2010**, *49*, 3215–3218. b) Zu, W.; Fang, J.; Liu, Y.; Ren, J.; Wang, Z. *Angew. Chem. Int. Ed.* **2013**, *52*, 2032–2037. c) Wang, Z. *Synlett*, **2012**, *23*, 2311–2327.
[40] Newman, M. S.; Sankaran, V.; Olson, D. R. *J. Am. Chem. Soc.* **1976**, *98*, 3237–3242.
[41] Roy, H. N.; Sarkar, M. S.; Mal, D. *Synth. Commun.* **2005**, *35*, 2183–2188.

Finally, in 2022, Yokoshima *et al.* identified the [7.5.5] fragment present in the major *Daphniphyllum* alkaloids as a key scaffold due to its challenging planar double bond in a bridgehead position of the bicyclo[3.3.0]bowl-shaped system.[42] Cycloheptane **I** was synthesized from MVK and after six synthetic steps, and a final condensation with triphosgene carbonate **II** was formed. Next, an electrocyclic reaction was performed by treatment with $FeBr_3$ to produce a pentadienyl cation that evolved to a cyclopentenyl cation which was intermolecularly trapped to provide the [7.5.5] ring core containing the challenging double bond. The synthesis continued with the reduction of the unstable aldehyde and deprotection of the MOM-group under Fujioka's conditions.[43] The free hydroxyls reacted with $SOCl_2$ to form the corresponding sulfite which was substituted by a N_3 and oxidized to originate aldehyde **V**. The latter was submitted to an aza-Wittig reaction to close the piperidine ring and providing the tetracyclic backbone present in yuzurimine, yuzurine and paxdaphnine B type alkaloids.



***Scheme 1. 11**. Synthesis of the common [7,5,5]- tricyclic ring reported by Yokoshima et al.*[42]

[42] Nakajima, D.; Yokoshima, S. *Org. Lett.* **2022**, *24*, 9520–9524.
[43] a) Fujioka, H.; Kubo, O.; Senami, K.; Minamitsuji, Y.; Maegawa, T. *Chem. Commun.* **2009**, 4429–2231. b) Fujioka, H.; Minamitsuji, Y.; Kubo, O.; Senami, K.; Maegawa, T. *Tetrahedron*, **2011**, *67*, 2949–2960.

1.1.4 Calyciphylline A-type alkaloids

Calyciphylline A-type alkaloids constitute one of the most significant subfamilies within the realm of the *Daphniphyllum* alkaloids. Known since 2003 when Morita and Kobayashi first isolated calyciphylline A,[44] these alkaloids present a common fused [6-6-5-7] ring core with several stereogenic centers. Their structural variation arises from the presence or absence as well as the oxidation state of E and F rings. Heathcock's studies shed light on the possible origin of these alkaloids suggesting that they could be traced back to yuzurimine-type alkaloids.[45]

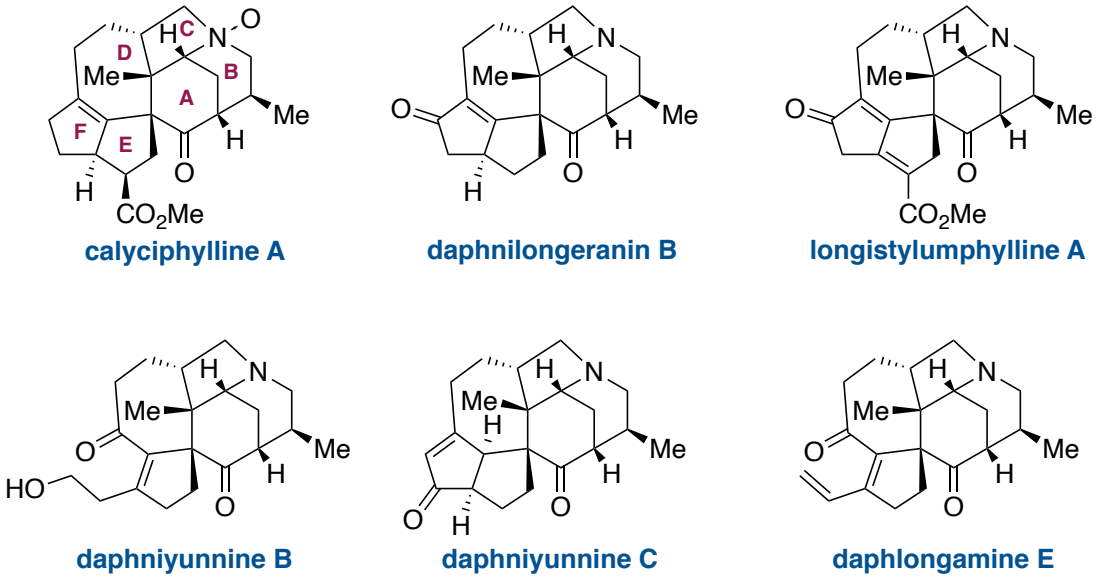


Figure 1. 3. *Representative members of calyciphylline A-type alkaloids*

This group of natural products has been object of considerable investigations. More than fifteen total syntheses of calyciphylline A-type alkaloids have been described and, to date, new approaches are being reported.[46] In our research group, we achieved the first synthesis [47] of the ABC tricyclic core by means of a Pd-catalyzed α-alkenylation and subsequent hydrogenation of the external methylene. Since then, their obtention and methodologies for their core construction have been the context of several group projects.

[44] Morita, H.; Kobayashi, J. *J. Org. Lett.* **2003**, *5*, 2895–2898.
[45] Morita, H.; Kobayashi, J. *Tetrahedron*, **2002**, *67*, 6546–6549
[46] a) Zhang, Y.; Chen, Y.; Song, M.; Tan, B.; Jiang, Y.; Yan, C.; Jiang, Y.; Hu, X.; Zhang, C.; Chen, W.; Xu, J. *J. Am. Chem. Soc.* **2022**, *144*, 16042–16051. b) Chen, Y.; Zhang, W.; Ren, L.; Li, J.; Li, A. *Angew. Chem. Int. Ed.* **2018**, *57*, 952–956.
[47] Solé, D.; Urbaneja, X.; Bonjoch, J. *Org. Lett.* **2005**, *7*, 5461–5464.

1.1.4.1 Himalensine A

Himalensine A is a member of the calyciphylline A-type subfamily. It was isolated in 2016 by Yue and co-workers from the twigs and leaves of *Daphniphyllum himalense*, a plant that grows in the lower regions of Himalaya mountains. [48]

Its molecular formula, $C_{19}H_{25}NO_2$, was assessed by ^{13}C NMR and (+)-HRMS-ESI which revealed eight degrees of insaturation. Moreover, DEPT and HSQC experiments detected the presence of two methyl groups, seven sp^3-methylenes, five sp^3-methynes and five quaternary carbons. IR absorption bands at 1696 and 1641 cm^{-1} indicated the presence of carbonylic and olefinic moieties. Additionally, COSY and HMBC experiments allowed the identification and connection of four fragments. Moreover, NOESY signals showed a cofacial relationship between H-21/H-4/H-6/H-8 with β-orientation. Also, an interaction between H-8/H-3α and H-19β/H-3β revealed a boat-like conformation for the A and B rings. Finally, correlation signals H-2/H-20 plus H-20/H-19β stablished the disposition of the methyl group at C-18.

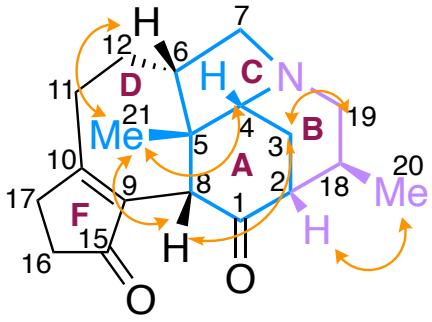


Figure 1. 4. *Himalensine A structure.*
Orange arrows = NOESY interactions

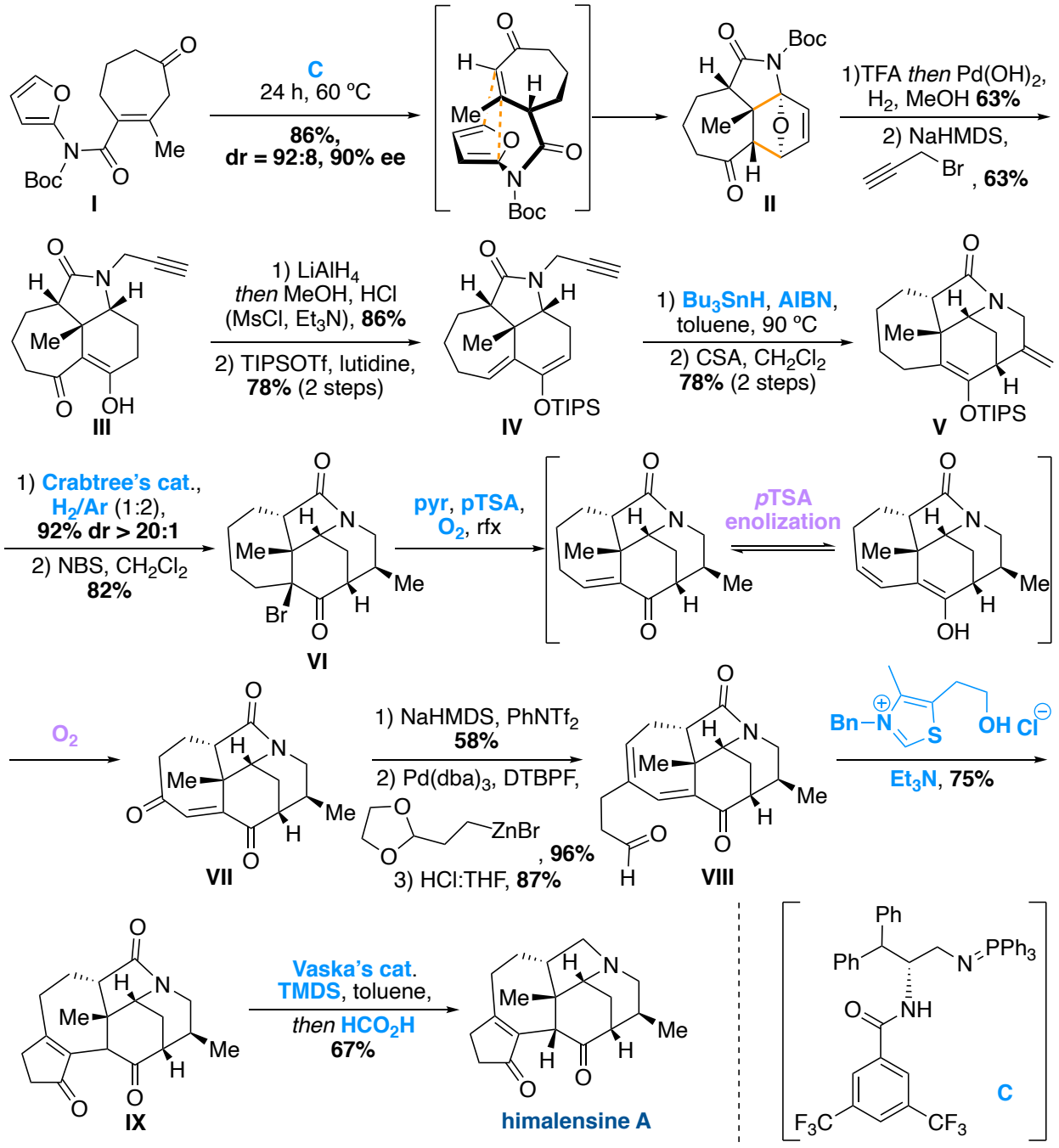
In addition, himalensine A was found to possess a 13,14,22-trinorcalyciphylline A-type skeleton meaning a highly congested pentacyclic ring system with six stereogenic centers and a quaternary carbon. Upon closer examination of himalensine A structure, its tricyclic ABC core is conceived as a fusion of a morphane and an octahydroindole motifs.

[48] Zhang, H.; Shyaula, S.-L.; Li, J.-Y.; Li, J.; Yue, J.-M. *Org. Lett.* **2016**, *18*, 1202–1205.

1.1.4.2 Total syntheses of himalensine A

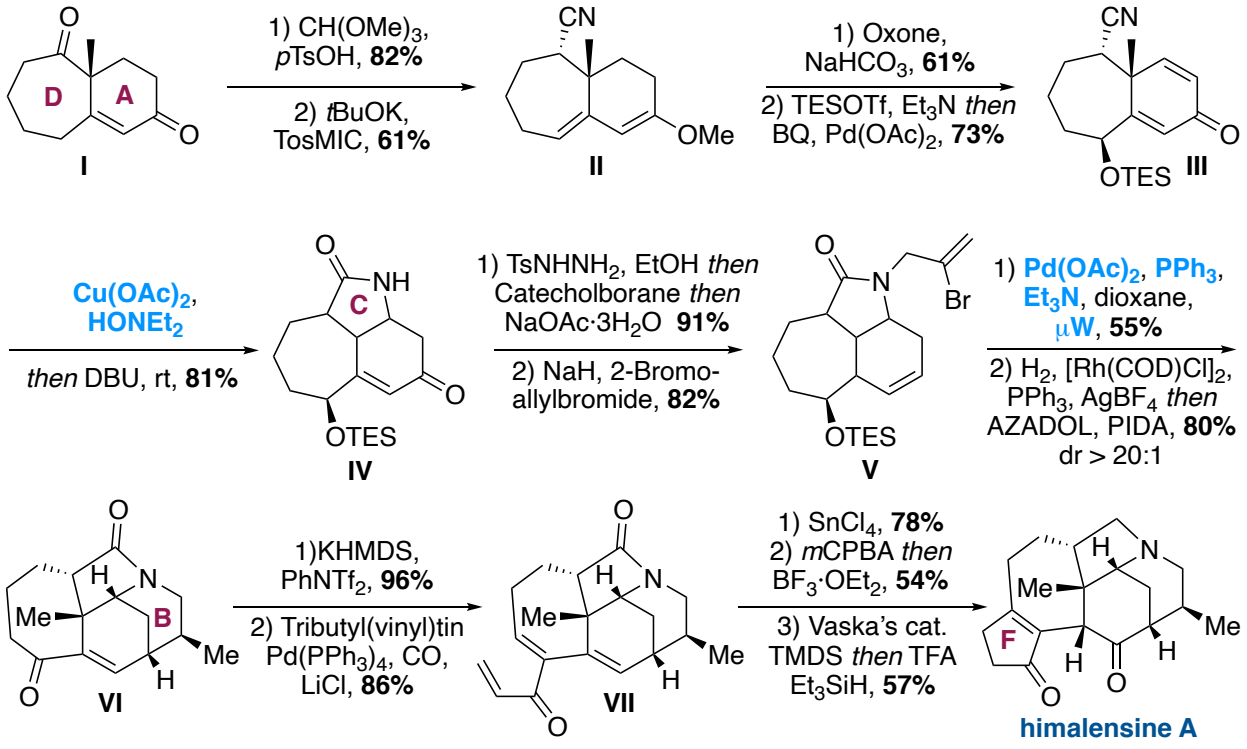
In 2017, Dixon's group, accomplished the first enantioselective synthesis of (-)-himalensine A.[49] The synthesis started with the early construction of the ACD tricyclic fragment from amidofuran **I** through a cascade reaction. Thus, a prototropic shift catalyzed by a chiral Bronsted-base led to the suitable dienophile which underwent an intramolecular amidofuran Diels-Alder reaction (IMDAF).[50] After screening several conditions, they found that the use of iminophosphorane **C** prepared *in situ* gave the best results. Once the tricyclic core containing five stereocenters was obtained, further opening of the aminal ring, hydrogenation, and propylation of the amide led to intermediate **III**. The remaining ketone was submitted to reduction, elimination, and formation of the enol ether providing a suitable compound to undergo a reductive radical cyclization by treatment with Bu_3SnH and AIBN for the ring B closure.[51] Diastereoselective hydrogenation of the external methylene in the presence of Crabtree's catalyst installed the methyl group with the correct configuration and further α-bromination led to tricyclic ketone **VI**. Treatment of the latter with *p*TSA in pyridine triggered an H-Br elimination and further enone enolization promoted an aerobic γ-oxidation under O_2. Regioselective triflate generation allowed a Pd-catalyzed Negishi coupling with a chain containing a protected aldehyde motif which, after deprotection, underwent a Stetter cyclization resulting in the formation of the E-ring. Finally, a chemoselective lactam removal through an Ir-catalyzed (Vaska's catalyst) hydrosilylation in reductive conditions provided (-)-himalensine A in 22 steps.

[49] Shi, H.; Michaelides, I.-N., Darses, B.; Jakubec, P.; Nguyen, Q.-N.-N.; Paton, R.-S.; Dixon, D.-J. *J. Am. Chem. Soc.* **2017**, *139*, 17755–17758.
[50] a) Padwa, A.; Leverett, C. A.; Hong, X.; *Acta. Chim. Slov.* **2009**, *56*, 527–534. b) Leverett, C. A.; Li, G.; France, S.; Padwa, A. *J. Org. Chem.* **2016**, *81*, 10193–10203. c) Padwa, A.; Dimitroff, M.; Liu, B. *Org. Lett.* **2000**, *2*, 3233–3235.
[51] Jansana, S.; Coussanes, G.; Diaba, F.; Bonjoch, J. *Eur. J. Org. Chem.* **2017**, *2017*, 2344–2352.



Scheme 1. 12. *Total synthesis of Himalensine A reported by Dixon et al.*[49]

In 2019, Xu and coworkers described the construction of the 5,6,7-tricyclic fragment present in several *Daphniphyllum* alkaloids and its application toward an asymmetric synthesis of himalensine A.[52] Starting from the known chiral diketone **I**, enolization of the enone was followed by a diastereoselective nitril introduction through a Von-Leusen homologation with TosMIC reagent. After oxidative transformations, intermediate **III** underwent a $Cu(OAc)_2$-catalyzed nitrile-hydration[53] which triggered the closure of the C-ring. Alkene migration via hydrazone intermediate was followed by vinylbromide incorporation. Next, the B-ring was constructed through a Heck-cyclization and Li's carbonyl-directed hydrogenation[14a] installed the methyl group in the required configuration. Triflate preparation allowed a Pd-catalyzed Stille coupling reaction affording **VII** which after Nazarov cyclization provided the last 5-membered ring. Finally, epoxidation and further acidic treatment generated the ketone motif and reduction of the remaining lactam by Vaska's catalyst afforded himalensine A in 14 steps.

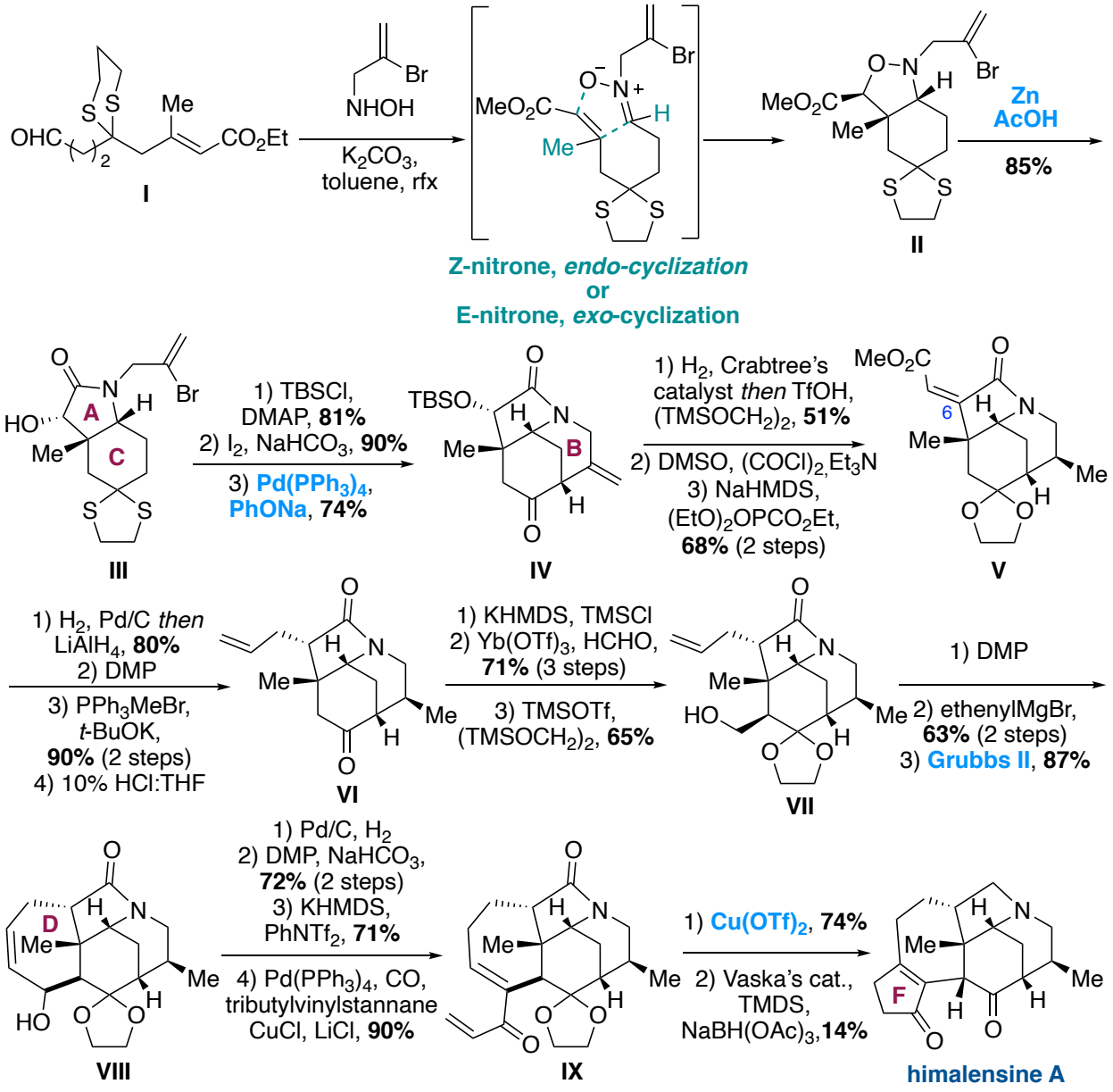


Scheme 1. 13. *Total synthesis of (–)-Himalensine A reported by Xu and co-workers*[52]

[52] Chen, Y.; Hu, J.; Guo, L.-D.; Zhong, W.; Ning, C.; Xu, J. *Angew. Chem. Int. Ed.* **2019**, *58*, 7390–7394.
[53] Marcé, P.; Lynch, J.; Blacker, A. J.; Williams, J. M. J. *Chem. Commun.* **2016**, *52*, 1436–1438.

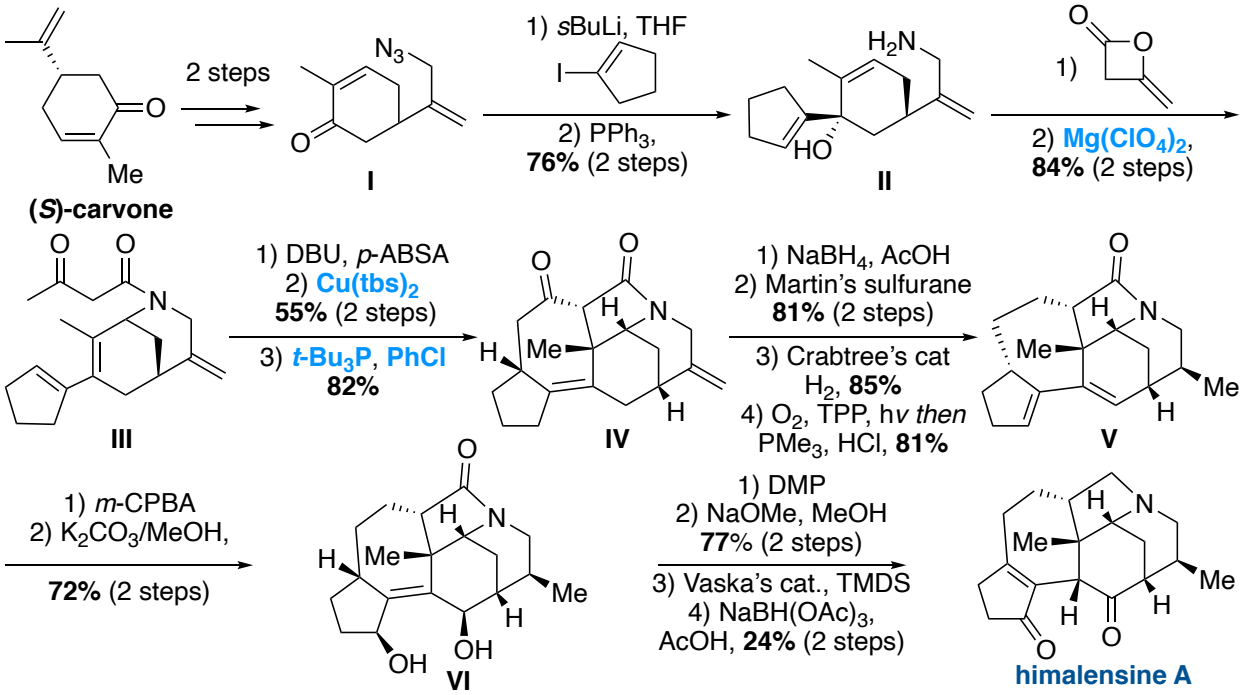
In the same year 2019, Gao *et al.* outlined their strategy for the total synthesis of himalensine A.[54] One of the early key steps was the construction of the A/C scaffold. Starting from the acyclic intermediate **I**, treatment with a hydroxylamine derivative, promoted the generation of a nitrone which underwent a 1,3-dipolar [3+2] cycloaddition. For the obtention of the required *cis*-configuration between C-3a and C-7a two possible TS were proposed, a Z-nitrone through an *endo*-cyclization or an E-nitrone through an *exo*-cyclization. In either case, nitrone **II** was obtained and, after a reductive cleavage and a spontaneous lactamization, octahydroindole moiety **III** was synthesized. Several protection and oxidation processes led to the suitable substrate to perform a Pd-catalyzed enolate alkenylation for the B-ring closure. Incorporation of the methyl group was achieved by a stereoselective hydrogenation in the presence of Crabtree's catalyst. Several chemical transformations at C-6 substituent and ketal hydrolysis provided intermediate **V**. Then, silyl enol ether generation and $Yb(OTf)_3$-mediated Mukaiyama aldol reaction with formaldehyde were performed to incorporate the hydroxylmethane group. After alcohol oxidation and subsequent 1,2-carbonylic addition of an organomagnesian derivative, treatment with Grubbs II catalyst allowed a Ring Closing Metathesis for the 7-membered D-ring construction. Hydrogenation of the double bond and oxidation of the hydroxyl group followed by its transformation to the triflate and subsequent Stille coupling reaction in the presence of carbon dioxide, furnished intermediate **IX**. The latter was submitted to a Nazarov cyclization and finally, the remaining amide group was chemoselectively reduced in the presence of Vaska's catalyst

[54] Zhong, J.; Chen, K.; Qiu, Y.; He, H.; Gao, S. *Org. Lett.* **2019**, *21*, 3741−3745



Scheme 1. 14 *Total synthesis of (-)-himalensine described by Gao et al* [54]

Recently, Qiu and co-workers described a divergent synthesis for (-)- himalensine A and daphenylline. [55] The process commenced with the preparation of azide **I** from (*S*)-carvone following a strategy reported by the same group. The addition of 5-membered ring moiety and Standinger reduction of the azide group led to intermediate **II** which, after acylation, was submitted to an intramolecular amido-cyclization catalyzed by $Mg(ClO_4)_2$. Regitz diazo transfer by treatment with DBU and *p*-ABSA produced a diazo-derivative at the α-carbon which underwent a Cu-catalyzed cyclopropanation.[56] and further treatment with *t*-Bu_3P promoted a Cope-rearrangement[57] for the closure of the 7-membered ring. Alcohol elimination, and diastereoselective hydrogenation in the presence of Crabtree's catalyst, were followed by Schenk-ene[29a] reaction with singlet oxygen and subsequent treatment with PMe_3 produced conjugated diene **V**. Finally, epoxidation and further basic treatment afforded diol **VI** which after oxidation to the dicarbonylic moiety, double bond migration, and amide carbonyl reduction, (-)-himalensine A was obtained in 19 steps.

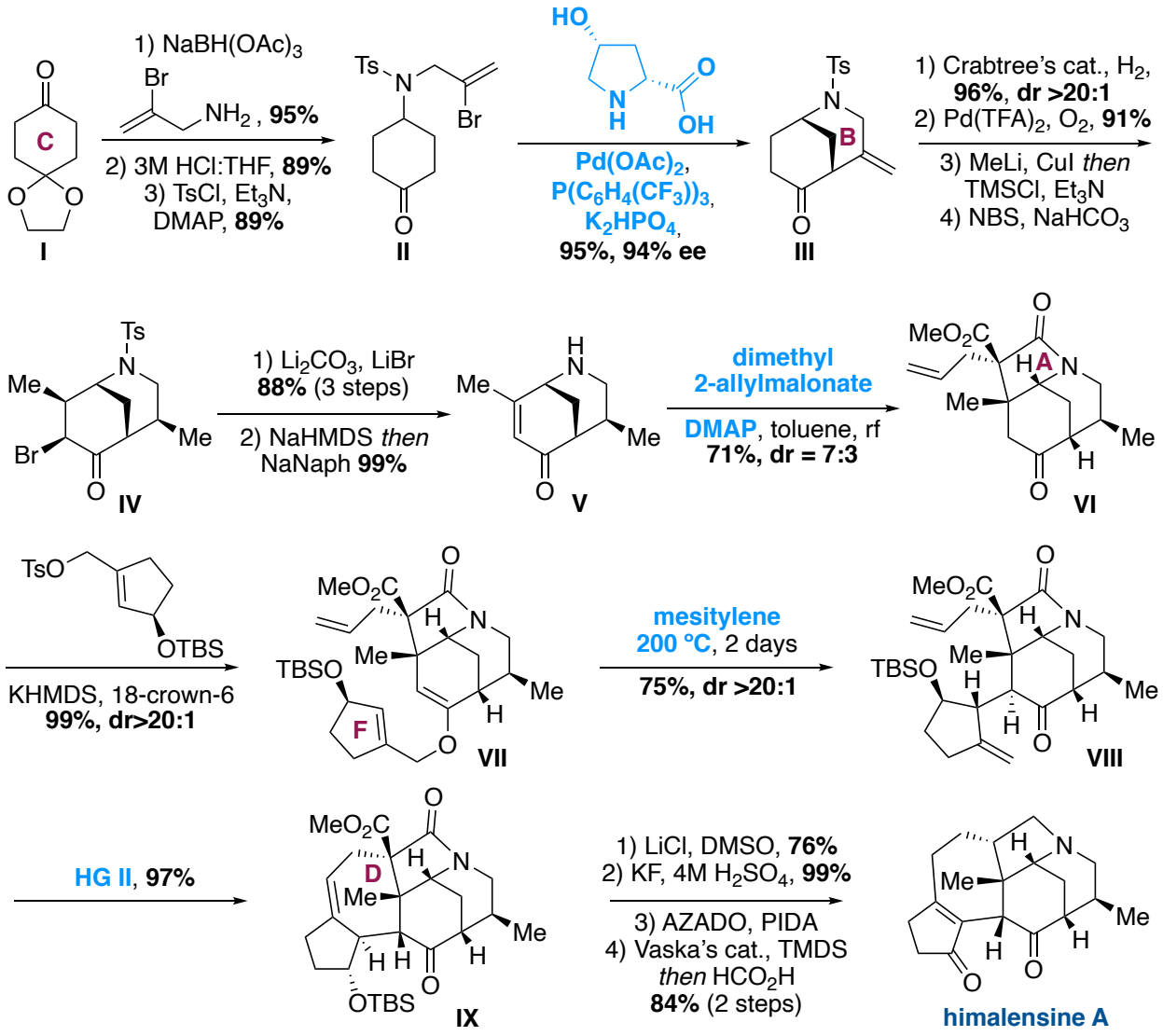


Scheme 1.15. *Total synthesis of (–)-Himalensine A reported by Qiu et al.[55]*

[55] Wang, B.; Xu, B.; Xun, W.; Guo, Y.; Zhang, J.; Qiu, F. G. *Angew. Chem. Int. Ed.* **2021**, *60*, 9439–9443.
[56] Craig II, R. A.; Roizen, J. L.; Smith, R. C.; Jones, A. C.; Virgil, S. C.; Stoltz, B. M. *Chem. Sci.* **2017**, *8*, 507–514.
[57] Wu, J.; Tang, Y.; Wei, W.; Wu, Y.; Li, Y.; Zhang, J.; Zheng, Y.; Xu, S. *Angew. Chem. Int. Ed.* **2018**, *57*, 6284–6288

Finally, in the latest work of Dixon[58] regarding this natural product published in 2023, a desymmetrization strategy for the construction of the morphan core was applied to achieve a more streamlined approach to Himalensine A. Thus, starting from 1,4-ciclohexanedione monoethylene acetal, sulfonamide **II** was synthesized through a reductive amination, hydrolysis, and treatment with TsCl. Next, **II** was submitted to an enantioselective Pd-catalyzed coupling reaction assisted by a chiral secondary amine, providing 2-azabicyclo[3.3.1]nonane **III**. DFT calculations revealed that the enantioselectivity of the Heck reaction arose from the coordination of the carboxylate motif of the enamine intermediate with the vinyl-Pd species. Diastereoselective hydrogenation in the presence of Crabtree's catalyst followed by modifications at the cyclohexanone ring afforded substrate **V**. Next, amide bond formation with dimethyl 2-allylmalonate triggered a Michael addition that furnished the tricyclic core of calyciphylline A-type alkaloids. Ketone **VI** was transformed to enol ether **VII** which, after treatment with mesitylene at 200 ºC for two days, underwent a Claisen rearrangement. Finally, ring-closing metathesis led to the closure of the 7-membered ring and further chemical modifications with the final amide reduction provided himalensine-A in 18 steps.

[58] Kuĉera, R.; Ellis, S.-R.; Yamazaki, K.; Cooke, J.-H.; Checksin, N.; Christensen, K.-E. Hamlin, T.- A.; Dixon, D.-J. *J. Am. Chem. Soc.* **2023**, *145*, 5422−5430.



Scheme 1. 16. *Total synthesis of (-)-himalensine A described by Dixon and co-workers* [58]

1.1.5 2-deoxymacropodumine A

In 2008, Guo and co-workers, [59] isolated 2-dehydroxymacropodumine A from *Daphniphyllum macropodum* Miquel (Euphorbiaceae), a new natural product that they envisioned as a dehydrated derivative from macropodumine A, [60] which presented a unique 11-membered macrolactone ring. Later, in 2019, Hao and Di, [61] isolated both natural products from *Daphniphyllum angustifolium*, and they proposed a structural revision for the above mentioned alkaloids and re-named 2-deoxymacropodumine A, since only an oxygen atom was lost from macropodumine A (Figure 1.5).

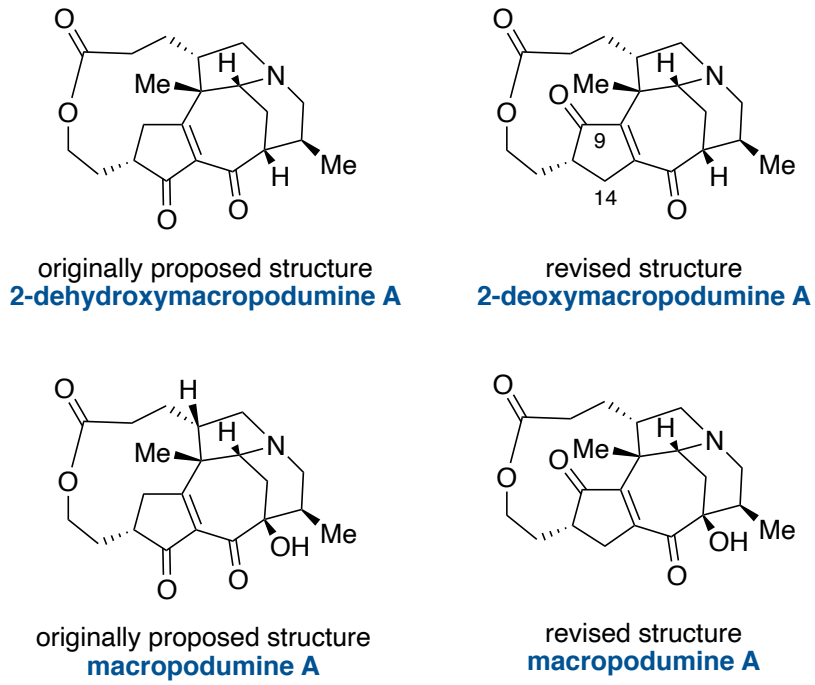


Figure 1. 5. *Structural revision of 2-deoxymacropodumine A and macropodumine A reported by Di and Hao[61]*

[59] Li, Z. Y.; Chen, P.; Xu, H. G.; Peng, S. Y.; Yang, Y. M.; Zhao, Z. Z.; Guo, Y. W. *Chin. J. Chem.* **2008**, *26*, 348–352
[60] Zhang, W.; Guo, Y. W.; Krohn, K. *Chem. - Eur. J.* **2006**, *12*, 5122–5127.
[61] Zhang, J.; Cao, P.; Ma, Y.; Fang, X.; Yang, J.; Zhang, Y.; Chen, D.; Gu, Y.; Di, Y.; Hao, X.; *J. Nat. Prod.* **2019**, *82*, 427−430.

2-deoxymacropodumine A was isolated as a colorless oil. ^{13}C NMR and HSQC experiments determined its molecular formula as $C_{21}H_{27}NO_4$ and the 21-carbons were identified as two methyl groups, eight sp^3-methylenes, five sp^3-methynes, one sp^3-quaternary carbon, two carbonyls along with a carbonyl ester and two non-protonated olefinic carbons. COSY and HSQC revealed three structural fragments that were connected by HMBC experiments. Finally, ROESY signals revealed an interaction between H-14α and H-17a meaning a β-diposition of H-15 and correlation signals between H-2/H-20/H-19α and H-21/H-4/H-19α showed a cofacial relationship between all of them and a β-position of the two methyls.

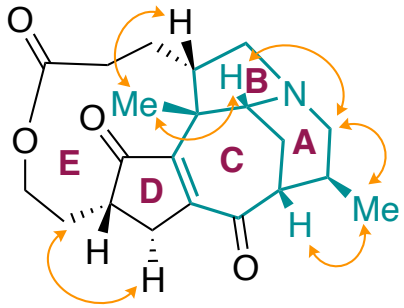
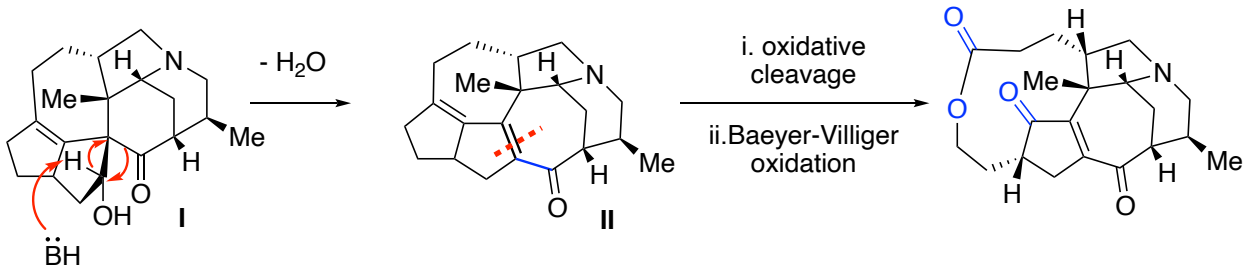


Figure 1. 6. *Structural determination of 2-deoxymacropodumine A. Orange arrows = ROESY interactions.*

Additionally, a plausible biosynthetic mechanism for this alkaloid was proposed suggesting it may derive from 22-nor-calyciphylline A-type alkaloid **I**. Both, cleavage of C1–C8 bond and formation of the C8–C13 resulted in ring C expansion, and further generation of the double bond from the D-ring through a dehydration process would lead to intermediate **II**. Then, an oxidative cleavage of the C1-C13 bond followed by a Baeyer-Villiger oxidation for an oxygen atom insertion would provide the 11-membered macrolactone.



Scheme 1.17 *Biosynthetic mechanism for 2-deoxymacropodumine A origin proposed by Hao and Di.* [61]

1.2 Objectives

The main objective of this thesis is to explore new synthetic routes toward two *Daphniphyllum* alkaloids, namely himalensine A and 2-deoxymacropodumine A. Construction of the adequate functionalized ring cores embedded in their structurally demanding frameworks could lead to advanced and valuable intermediates *en route* to their synthesis.

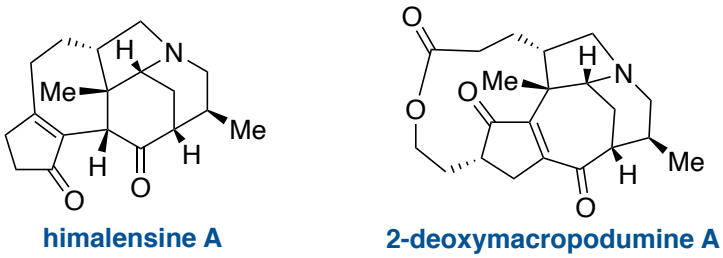
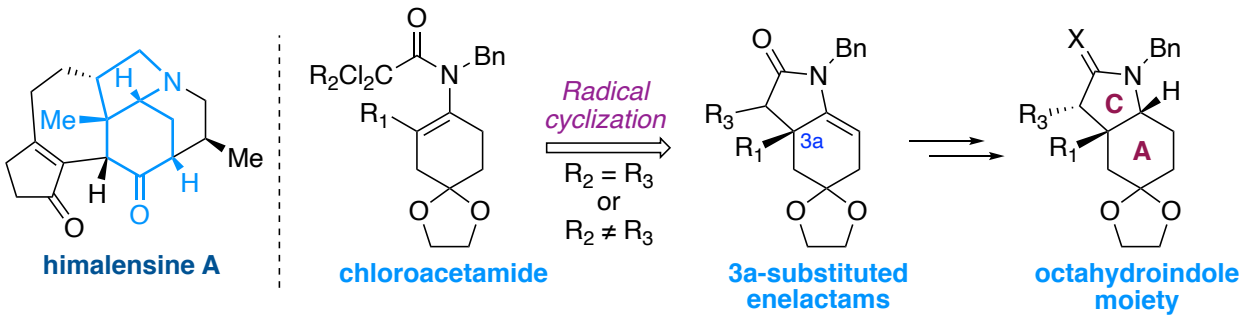


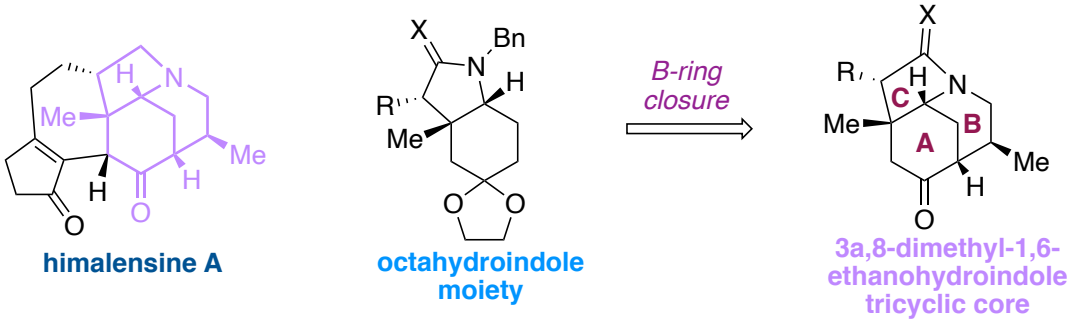
Figure 1.7. *Targeted Daphniphyllum alkaloids*

In the first place, our primary objective is to study in deep the preparation of highly functionalized enelactams and explore their subsequent transformation to octahydroindole compounds. This research is based on the prior work carried out in the research group, particularly the investigation centered on the synthesis of octahydroindole ring employing radical methodologies. These intermediates will be investigated later to obtain more advanced intermediates directed to the synthesis of *Daphniphyllum* alkaloids.



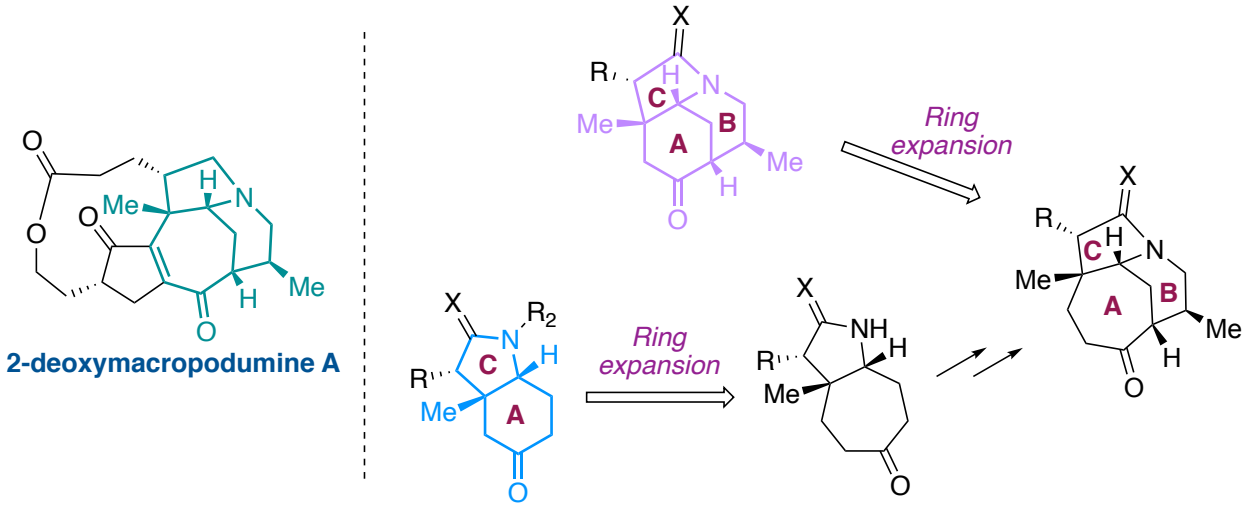
Scheme 1.18. *Objective 1 of the thesis*

In the second place, calyciphylline A-type alkaloids, such as the targeted himalensine A, contain a common ABC tricyclic core embodying the octahydroindole system. Closure of the remaining piperidine ring could afford functionalized tricyclic moieties which will allow the total synthesis of the natural product.



Scheme 1.19. *Objective 2 of the thesis*

Finally, our last target is the azatricyclic [5-6-7] skeleton found in 2-deoximacropodumine A, as a valuable building block to pursue the total synthesis of the natural product, which has not been reported to date. The aforementioned azapolycyclic compounds are potential precursors for the targeted tricyclic system through ring expansion methodologies, either directly from elongation of the cyclohexanone present in the [5-6-6]-tricyclic core or from the homologation of the octahydroindole ring which, after some chemical transformations, could gave the targeted structure.



Scheme 1.20. *Objective 3 of the thesis*

Chapter 2

Synthesis of enelactams leading to densely functionalized octahidroindoles

The octahydroindole moiety can be found in many natural products either in a discrete form or embedded in a more complex structure. (Figure 2.1)

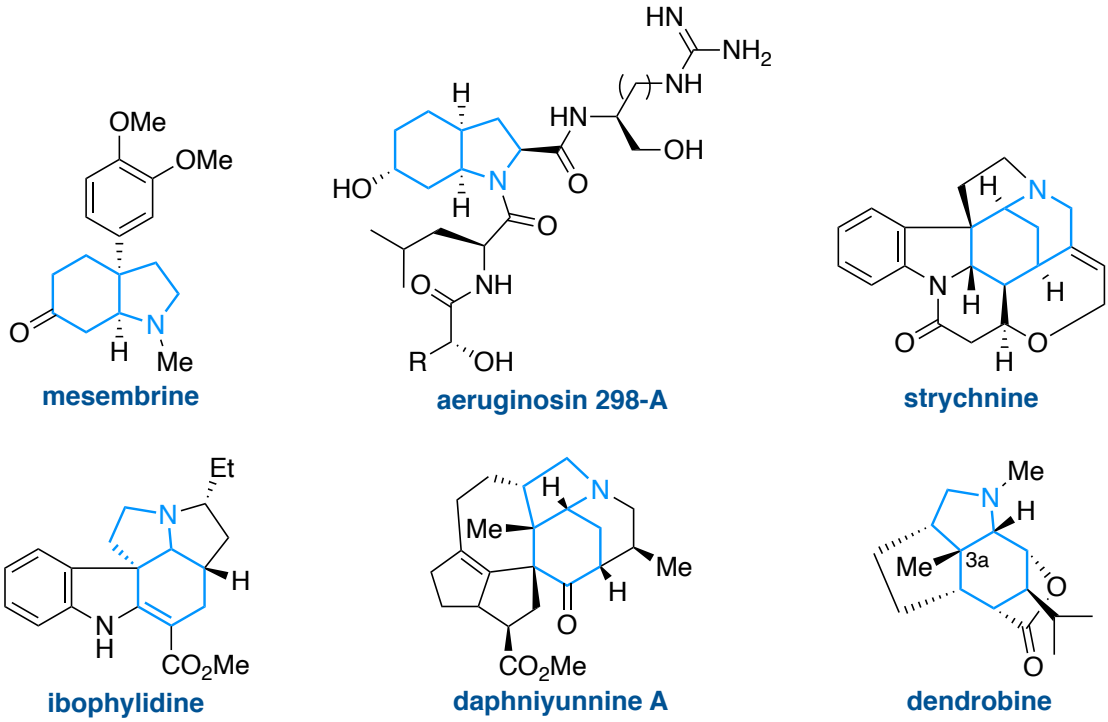


Figure 2. 1 *Natural products with octahydroindole moiety*

Our research group has previously used 3a-functionalized octahydroindoles as scaffolds for the total synthesis of indole alkaloids[62] and aeruginosins[63] along with synthetic works toward *Daphniphyllum* alkaloids.[47,64] In addition, we recently reported a radical cyclization of trichloroacetamide derivatives for the rapid obtention of 3a-substituted tetrahydroindol-2-ones (*i.e.*, enelactams)[64a] which we envisioned as suitable precursors to obtain the octahydroindole ring (Scheme 2.1). Thus, the objective of this chapter is to study in deep the preparation of high functionalized enelactams and their derivatization to octahydroindoles for the synthesis of valuable building blocks *en route* to *Daphniphyllum* alkaloids.

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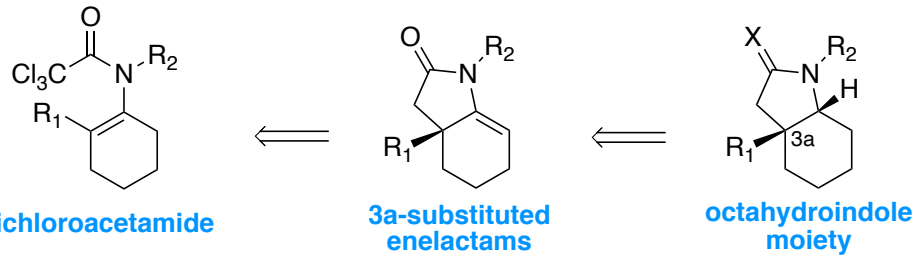
[62] Bonjoch, J.; Catena, J.; Valls, N. *J. Org. Chem.* **1996**, *61*, 7106–7115. b) Bonjoch, J.; Solé, D.; García-Rubio, S.; Bosch, J. *J. Am. Chem. Soc.* **1997**, *119*, 7230–7240. c) Solé, D.; Bonjoch, J.; García-Rubio, S.; Peidró, E.; Bosch, J. *Angew. Chem. Int. Ed.* **1999**, *38*, 395–397.

[63] a) Valls, N.; López-Canet, M.; Vallribera, M.; Bonjoch, J. *J. Am. Chem. Soc.* **2000**, *122*, 11248–11249. b) Valls, N.; Vallribera, M.; Carmeli, S.; Bonjoch, J. *Org. Lett.* **2003**, *4*, 447–450.

[64] a) Coussanes, G.; Bonjoch, J. *Org. Lett.* **2017**, *19*, 878–881. b) Jansana, S.; Diaba, F.; Bonjoch, J. *Org. Lett.* **2019**, *21*, 5757–5761.



Scheme 2. 1. *General overview of the objective of Chapter 2*

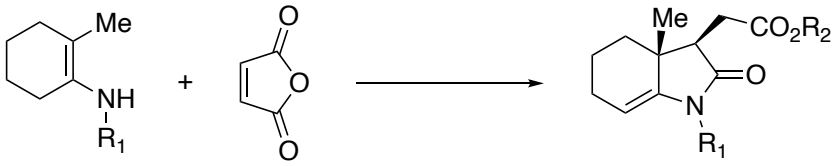
2.1 Precedents

Throughout the literature, several strategies are reported for the synthesis of enelactams based on inter- or intramolecular processes.

2.1.1 Intermolecular processes

Pfau and d'Angelo[65] first reported the obtention of bicyclic lactams through an intermolecular process based on a Michael-type addition between iminoderivatives of 2-methylcyclohexanone and electrophilic olefins (Table 2.1). The enamine tautomer underwent the conjugate addition with maleic anhydride and the resulting imine derivative reacted *in situ* providing the lactam ring. D'Angelo proposal differed in the use of chiral 1-phenylethylamine. Later, other research groups reported examples of this methodology.[66]

Table 2. 1. *Reported examples of enelactam synthesis by Michael addition process*

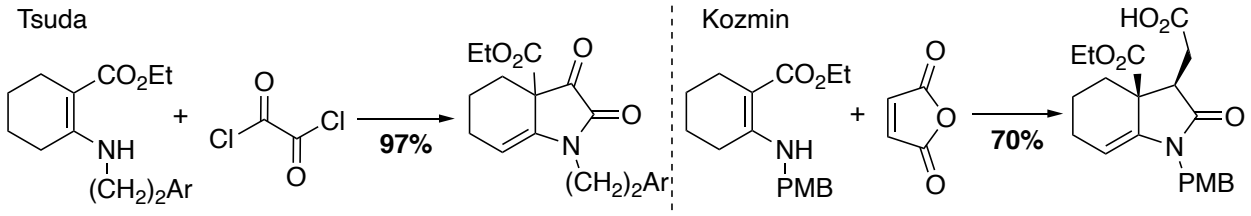


R_1	Yield	Ref.
Bn	63%	Pfau 1995 [4a]
CH(Me)Ph	65%	d'Angelo 1996 [4b]
2-BrBn	48%	Jabin 2001 [5a]
Bn	57%	Bonjoch 2008 [5b]

[65] a) Pfau, M.; Tomas, A.; Lim, S.; Revial, G. *J. Org. Chem.*, **1995**, *60*, 1143–1147. b) Cavé, C.; Desmaële, D.; d'Angelo, J. *J. Org. Chem.*, **1996**, *61*, 4361–4368.

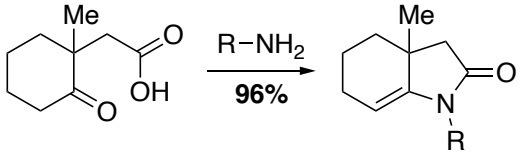
[66] a) Jabin, I.; Netchitaïlo, P. *Tetrahedron Lett.*, **2001**, *42*, 7823–7827. b) Cordero-Vargas, A.; Bradshaw, B.; Bonjoch, J. *Tetrahedron*, **2008**, *64*, 8134–8140.

In addition, several works reported the same methodology from β-ketoesters[67]. In Tsuda's work, α-carbonylated enamine underwent a condensation with oxalyl chloride, and further nitrogen attack to the remaining carbonyl furnished the bicyclic indole formation. In Kozmin's procedure, the enamine condensed with maleic anhydride as the aforementioned works resulting in the same diastereoselectivity observed for the 3a-methyl derivatives.



Scheme 2. 2 *Intermolecular approaches from β-ketoester derivative reported by Tsuda and Kozmin[67]*

A variant for an inter/intramolecular sequence was reported by Padwa and co-workers.[68] 1-methyl-2-oxocyclohexanacetic acid condensed with a primary amine and subsequent spontaneous amido-cyclization gave the desired bicyclic lactam.



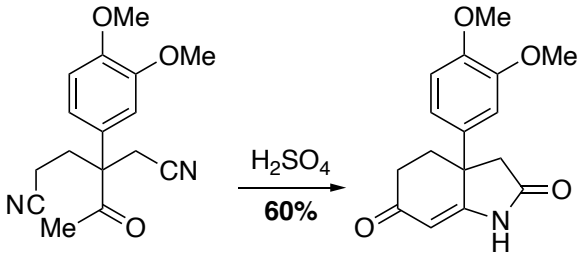
Scheme 2. 3. *Inter/Intramolecular sequence for bicyclic enelactams obtention reported by Padwa et al.[68]*

2.1.2 Intramolecular processes

i. Ionic reactions

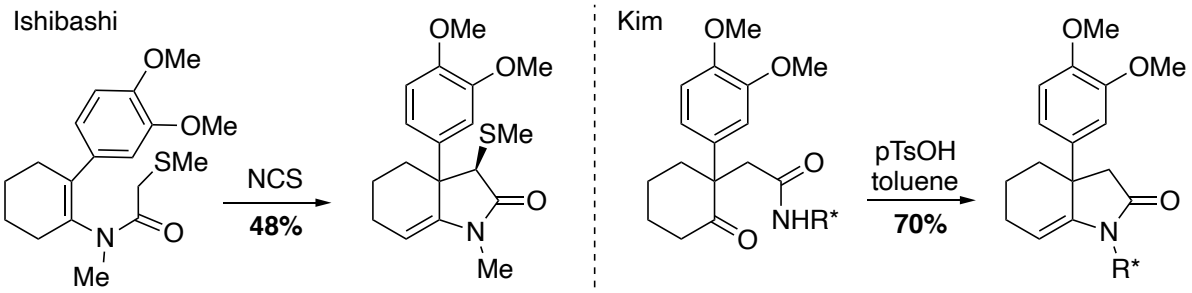
In 1970, Kugita described an intramolecular process for enelactams synthesis (Scheme 2.4).[69] The prepared unsymmetrical dinitrile was treated with H_2SO_4 at 140 ºC for 5 min to underwent a double hydrolytic cyclization furnishing the the bicyclic moiety in one step.

[67] a) Tsuda, Y.; Sakai, Y.; Nakai, A.; Kaneko, M.; Ishiguro, Y.; Isobe, K.; Taga, J.; Sano, Y. *Chem. Pharm. Bull.* **1990**, *38*, 1462–1472. b) Cui, J.; Chai, D. I.; Miller, C.; Hao, J.; Thomas, C.; Wang, J.; Scheidt, K. A.; Kozmin, S. A. *J. Org. Chem.* **2012**, *77*, 7435–7470.
[68] Rashatasakhon, P.; Ozdemir, A. D.; Willis, J. Padwa, A. *Org. Lett.* **2004**, *6*, 917–920.
[69] a) Oh-Ishi, T.; Kugita, H. *Chem. Pharm. Bull.* **1970**, *18*, 291–298. b) Oh-Ishi, T.; Kugita, H. *Chem. Pharm. Bull.* **1970**, *18*, 299–303.



Scheme 2. 4. *Double hydrolitic cyclization sequence reported by Kugita*[69]

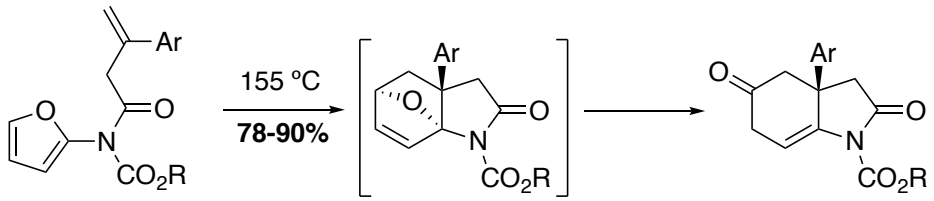
Also, other ionic processes were reported including a NCS-mediated cyclization of *N*-(2-arylcyclohex-en-1-yl)-a-(sulfanyl)acetamides by Ishibashi, [70] and an intramolecular chiral amide-carbonyl condensation in 2,2-disubstituted 1,3- cyclohexanedione by Kim.[71]



Scheme 2. 5. *Other ionic approaches*

ii. Intramolecular furan Diels-Alder of amidofurans

Moreover, Padwa and coworkers,[50,72] described a new strategy for the obtention of the studied scaffolds through a different conceptual approach based on an intramolecular [4+2] cycloaddition/rearrangement cascade. A cycloaddition between a furanyl-carbamate and the double bond motif was followed by a ring opening and a subsequent rearrangement provided the bicyclic enelactam.



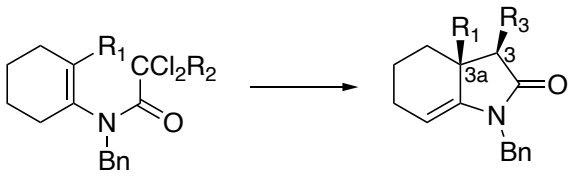
Scheme 2. 6. *[4+2]cycloaddition/rearrangement sequence reported by Padwa*[72]

[70] Saito, M.; Matsuo, J.; Ishibashi, H. *Tetrahedron*, **2007**, *63*, 4865–4973.
[71] a) Tuan, L. A.; Kim, G. *Tetrahedron Lett.,* **2010**, *51*, 2354–2355. b) Park, J.; Kim, Y. K.; Kim, G. *Bull. Korean Chem. Soc.* **2011**, *32*, 3141–3144.
[72] Padwa, A.; Brodney, M. A.; Dimitroff, M.; Liu, B.; Wu, T. *J. Org. Chem.* **2001**, *66*, 3119–3128

iii. Intramolecular radical cyclizations

Finally, several works were reported regarding the formation of C3-C3a bond through radical conditions. Zard and coworkers introduced Ni-based SET cyclization of trichloroacetamides either Me- or Ph-substituted. [73] Later, Parsons used chloroacetamides embodying an ester group under both oxidative procedure with Mn(III), and ATRC conditions promoted by Cu(I). [74] Then, Ph-substituted enamides were employed by Ishibashi [75] for the preparation of the bicyclic lactams under reductive conditions and SET reactions with 1,4-dimethylpiperazine (1,4-DMP). In addition, Clark and Curran[76] described an ATRC process with Cu(I)/TMPA. Finally, our research group described a tin-promoted reductive cyclization leading to 3a-methyl enelactam.[64a]

Table 2. 2. *Radical conditions reported for the enelactams synthesis*



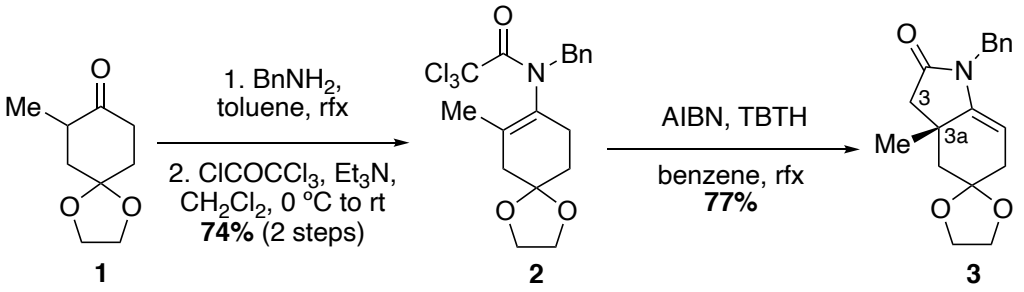
R_1	R_2	R_3	Yield	Method	Author	Year
Me	Cl	Cl	49%	Ni/AcOH	Zard	1998
Ph	Cl	Cl	41%	Ni/AcOH	Zard	1998
Me	CO_2Me	CO_2Me	44%	$Mn(OAc)_3$	Parsons	2000
Me	CO_2Me	CO_2Me	40%	Cu(I)	Parsons	2000
Ph	H	H	63%	Bu_3SnH	Ishibashi	2001
Ph	Cl	Cl	89%	Bu_3SnH	Ishibashi	2001
Ph	Cl	Cl	73%	1,4-DMP	Ishibashi	2006
Ph	Cl	Cl	70%	Cu(I)	Clak/Curran	2016
Me	Cl	H	77%	Bu_3SnH	Bonjoch	2017

[73] Cassayre, J.; Quiclet-Sire, B.; Saunier, J.-B.; Zard, S. Z. *Tetrahedron*, **1998**, *54*, 1029–1040.
[74] Davies, D. T.; Kapur, N.; Parsons, A. F. *Tetrahedron*, **2000**, *56*, 3941–3949.
[75] Ishibashi, H.; Kodama, K.; Higuchi, M.; Muraoka, O.; Tanabe, G.; Takeda, Y. *Tetrahedron*, **2001**, *57*, 7629–7637. b) Ishibashi, H.; Haruki, S.; Uchiyama, M.; Tamura, O.; Matsuo, J. *Tetrahedron Lett.* **2006**, *47*, 6263–6266.
[76] Clark, A.J.; Curran, D. P.; Fox, D. J.; Ghelfi, F.; Guy, C. S.; Hay, B.; James, N.; Phillips, J. M.; Roncaglia, F.; Sellars, P. B.; Wilson, P.; Zhang, H. *J. Org. Chem.* **2016**, *81*, 5547–5565

2.2 Results and discussion

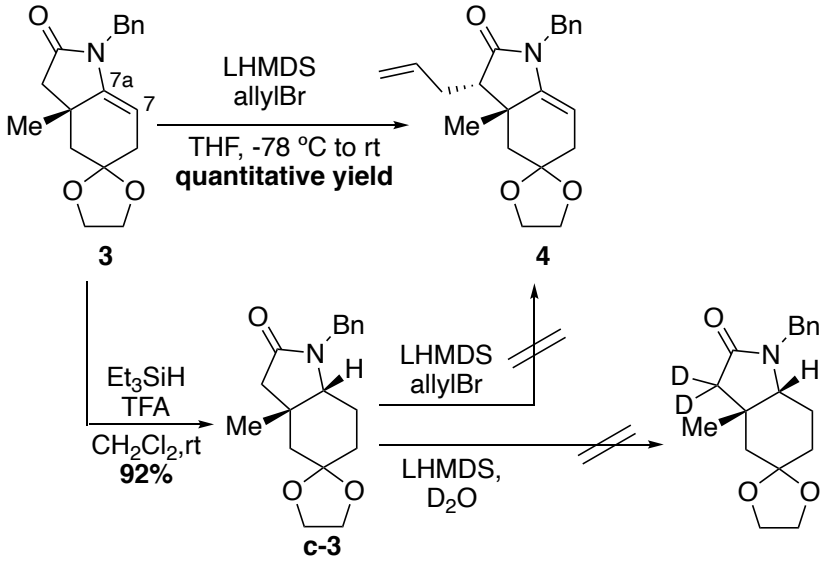
2.2.1 C-C(3) bond formation

In our studies devoted to *Daphniphyllum* alkaloids skeleton,[64a] enelactam **3** was obtained in a multigram scale under reductive radical conditions from trichloroacetamide **2**. The latter was synthesized through a one-pot procedure from 1,4-cyclohexanedione monoethylene acetal **1** (Scheme 2.7).



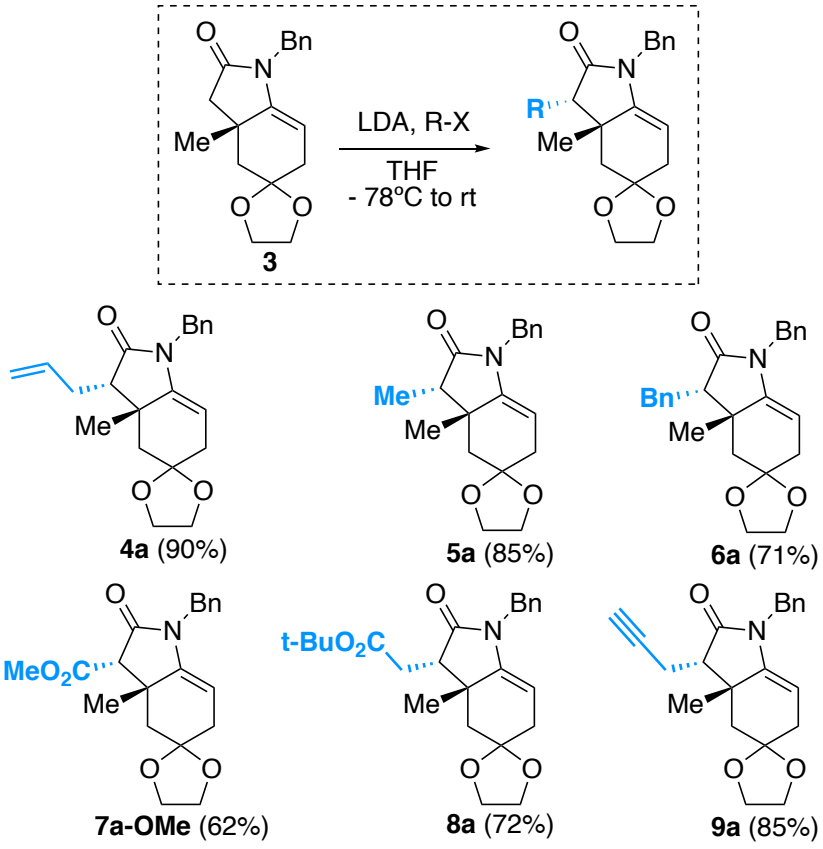
Scheme 2. 7. *Enelactam **3** preparation previosuly reported by our group.*[64a]

Next, an allyl group was introduced diastereoselectively at C-3 by means of enolate alkylation. Noteworthy, the same work showed that unsaturation at C7-C7a was necessary for the substituent introduction since attempts to allylate the reduced compound **c-3** were unsuccessful. In addition, when **c-3** was treated with LHMDS followed by the addition of D_2O, no deuteration was observed. (Scheme 2.8)



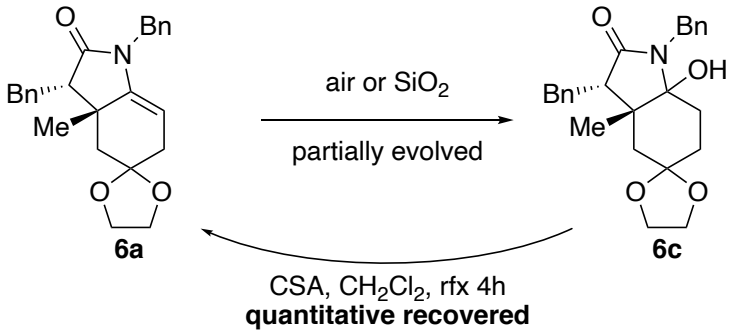
Scheme 2. 8. *Previous studies reported about C-3 bond formation.*[64a]

In this thesis, we examined the capacity of enelactam **3** enolate to form a new C–C bond at C-3 by treatment with a base and several electrophiles (Scheme 2.9). We first tested LDA for the generation of the enolate step, which gave the known product **4a** with good results compared to the previously reported using LHMDS.[64a] We continued using LDA, and alkyl chains (Me, Bn, propargyl) along with carbonylated moieties ($CH_2CO_2{}^tBu$ and CO_2Me) were introduced in good yields. All the reactions took place in excellent diastereoselectivity providing the α-epimer alone. The planar character of the obtained enolate promoted the formation of the new C–C bond from the bottom face avoiding steric interaction with the methyl at C-3a and resulting in an anti-relation between both substituents.



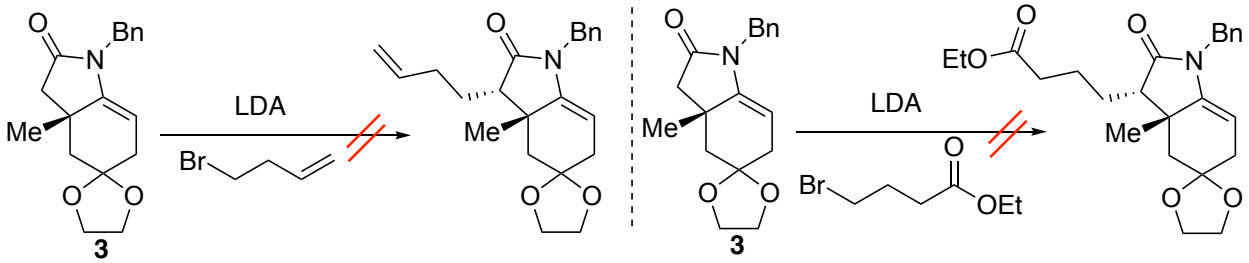
Scheme 2. 9. *C-3 bond formation. R-X = 4a: allyl bromide, 5a: MeI, 6a: BnBr, 7a: $NCCO_2Me$, 8a: $BrCH_2CO_2{}^tBu$, 9a: propargyl bromide.*

The prepared enelactams were isolated as solids or as oils. The latter, when exposed to the air atmosphere or the slightly acidic conditions of chromatographic purification, hydration products were observed (Scheme 2.10).[77] This evolution was reversed by treatment of the hemiaminals with camphorsulphonic acid (CSA) in refluxing CH_2Cl_2 for four hours.[78]



Scheme 2. 10. *Evolution of* ***6a*** *by air or SiO_2 and further recovery by treatment with CSA.*

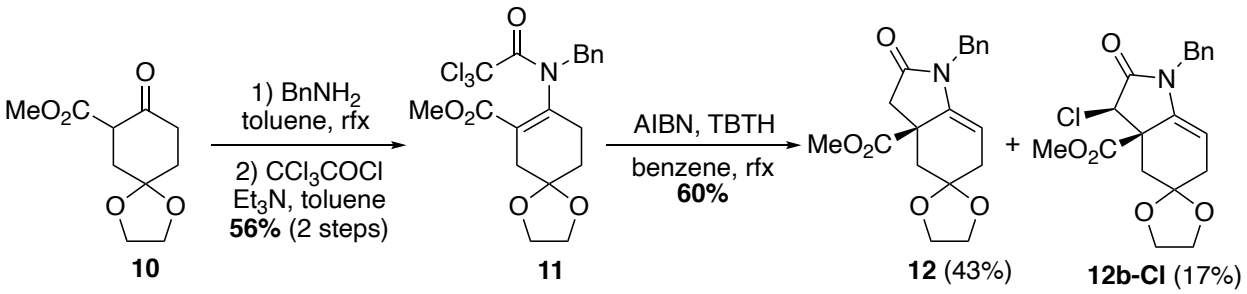
Moreover, we tested the C-3 incorporation of less reactive chains bearing four carbon units. Thus, employing the optimized procedure in Scheme 2.9, enelactam **3** was treated with LDA and the corresponding electrophiles, 4-bromo-1-butene, and ethyl 2-bromobutyrate. Both attempts resulted in the recovery of **3**.



Scheme 2. 11*. Attempts to introduce less reactive chains at C-3*

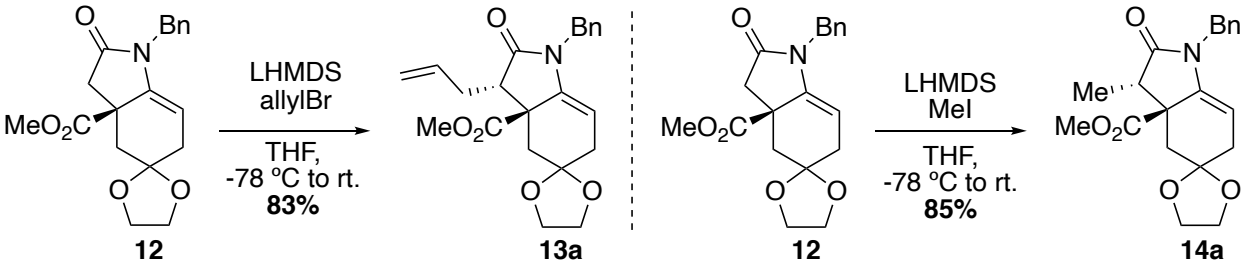
[77] Martín-López, M. J.; Bermejo-González, F. *Tetrahedron Lett.* **1994**, *35*, 8843–8846. b) Watson, R. T.; Gore, V. K.; Chandupatla, K. R.; Dieter, R. K.; Snyder, J. P. *J. Org. Chem.* **2004**, *69*, 6105–6114. c) Padwa, A.; Lee, H. I.; Rashatasakhon, P.; Rose, M. *J. Org. Chem.* **2004**, *69*, 8290–8218..
[78] Gramain, J.-C.; Husson, H.-P.; Troin, Y. *J. Org. Chem.* **1985**, *50*, 5517–5520.

Next, we addressed another set of enelactams bearing an ester group in C-3a position. Hence, 1,4-monoethylene acetal was α-carbonylated following Ducrot's procedure.[79] Then, applying the methodology reported for **3** synthesis, ketone **10** was treated with benzylamine to form an imine which was *in situ* acylated with trichloroacetyl chloride furnishing trichloroacetamide **11** in 56% yield. Afterward, **11** was submitted to the 5-*endo*-trig radical cyclization to afford bicyclic lactam **12** along with chlorinated product **12b-Cl** in 60% overall yield in a 1.4:1 ratio for **12**:**12b-Cl**.



Scheme 2. 12 *Synthesis of enelactam* ***12*** *embodying an ester group at C-3a.*

Finally, the allylation of enelactam **12** enolate under the previously employed conditions (Scheme 2.9) afforded product **13a** in a moderate yield (40%). The lower yield was attributed to the presence of the ester motif. Changing to LHMDS, afforded the bicyclic lactams **13a** and **14a**, with an allyl and methyl respectively, in good yields (Scheme 2.13). Here, the reactions were also completely diastereoselective providing only the α-epimers.

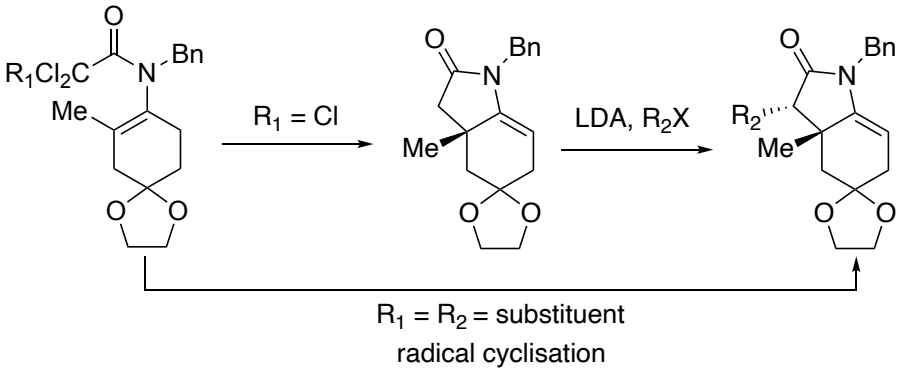


Scheme 2. 13. *Substituent incorporation at C-3 from enelactam* ***12***

[79] Boyer, F.-D.; Descoins, C. L.; Thanh, G. V.; Descoins, C.; Prangé, T.; Ducrot, P.-H. *Eur. J. Org. Chem.* **2003**, 1172–1183.

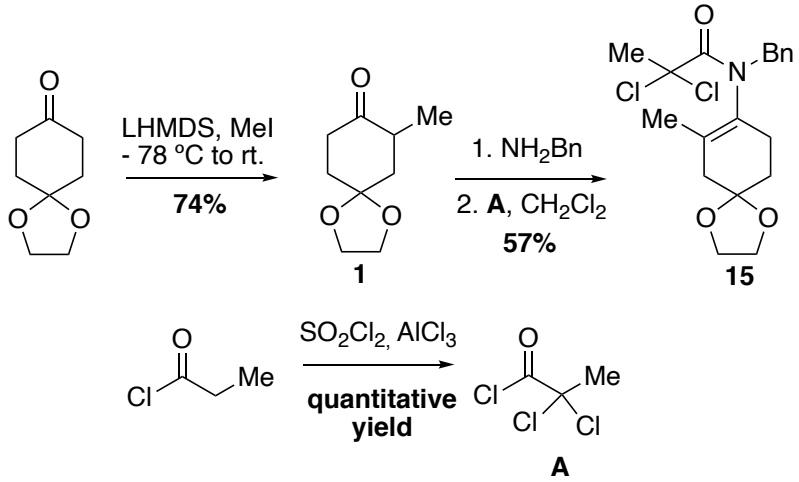
2.2.2 Radical cyclization of α-substituted chloroacetamides

Next, we wanted to study the preparation of C-3 functionalized enelactam hydroindoles through a one-step transformation by means of a radical cyclization of dichloroacetamides already bearing a substituent (Scheme 2.14).



Scheme 2. 14. *Plan for the study of a new one-step synthesis of 3-substituted enelactams*

We started with the preparation of dichloroacetamide **15** from methylated ketone **1** (Scheme 2.15). After treatment of **1** [80] with benzylamine, the generated imine was acylated with chloroderivative **A**, which was previously prepared through an α-chlorination of propionyl chloride.[81]

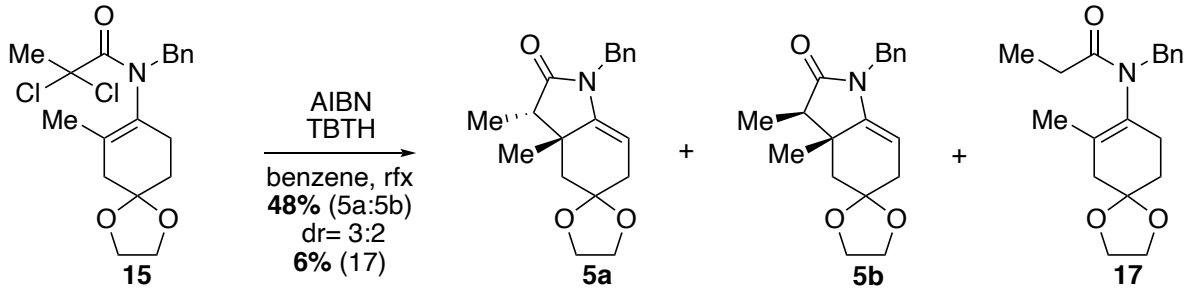


Scheme 2. 15. *Synthesis of dichloroacetamide **15***

[80] Cho, Y. S.; Carcache, D. A.; Tian, Y.; Li, Y.-M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2004**, *126*, 14358–14359

[81] Diaba, F.; Martínez-Laporta, A.; Bonjoch, J. *Eur. J. Org. Chem.* **2014**, 2371–2378.

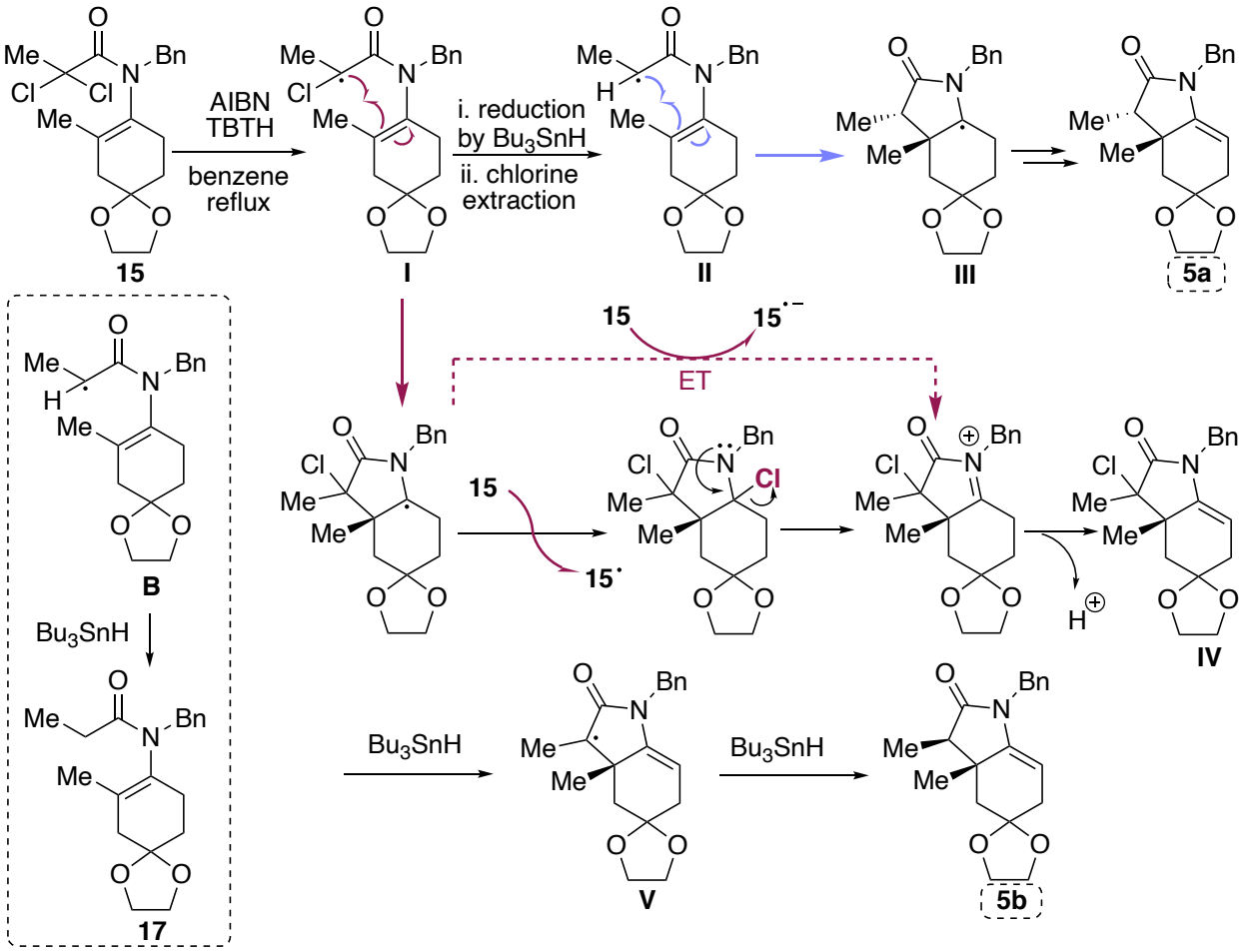
Then, dichloroacetamide **15** was submitted to the reported reductive radical protocol[64a] by treatment with TBTH and AIBN to provide the two possible diastereomers, **5a** as the major epimer and **5b** as the minor one, in 48% overall yield (Scheme 2.16). In addition, amide **17** was isolated in 6% yield as a result of the reduction of **15**. Even if this methodology provided methylated enelactams **5** in one step, the reaction was not diastereoselective and the yields were lower compared with the two-step sequence where only α-epimer was obtained.



Scheme 2. 16. *Radical cyclization of dichloroacetamide* ***15***

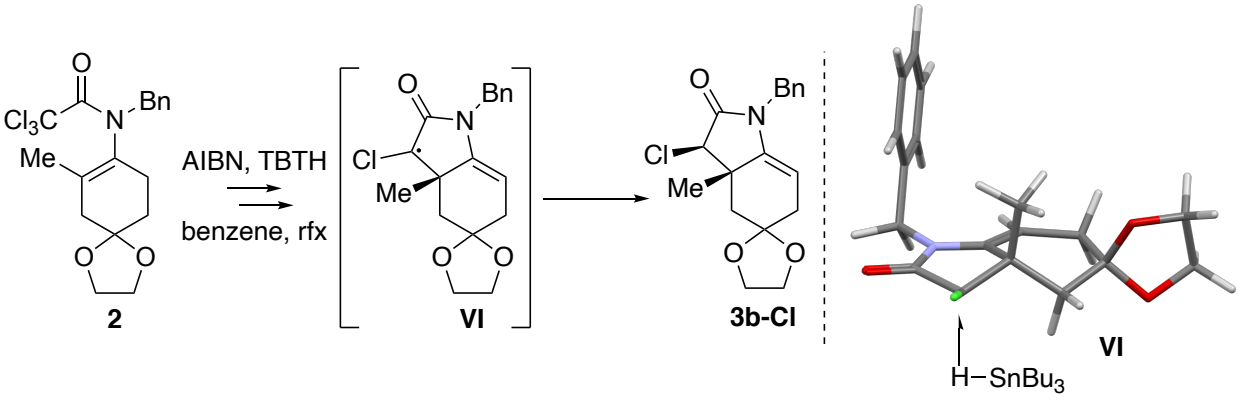
The formation of both epimers could be explained by the existence of two competitive pathways which arose from the two radical intermediates that could undergo a cyclization (**I** and **II**) in which the stereochemical outcome would be controlled by steric factors (Scheme 2.17). On one hand, radical **I** could add to the enamide double bond generating a radical at C-7a that would evolve to the enelactam **IV**, either by electron transfer (ET) or chlorine atom transfer.[82] Further abstraction of the remaining chlorine atom at C-3 would generate the planar radical **V** that, upon H-delivery by Bu_3SnH from the bottom face to avoid steric interaction with 3a-methyl, would provide the *cis*-derivative **5b**. On the other hand, reduction of the radical **I** followed by another chlorine extrusion would lead to intermediate **II**. The stereochemistry is supposed to be set during the cyclization of **II**, since the radical approach to the double bond would take place through an anti-relationship for both methyl groups. Finally, product **17** is the result of a direct reduction of **II**.

[82] Curran, D. P.; Guthrie, D. B.; Geib, S. J. *J. Am. Chem. Soc.* **2008**, *130*, 8437–8445.



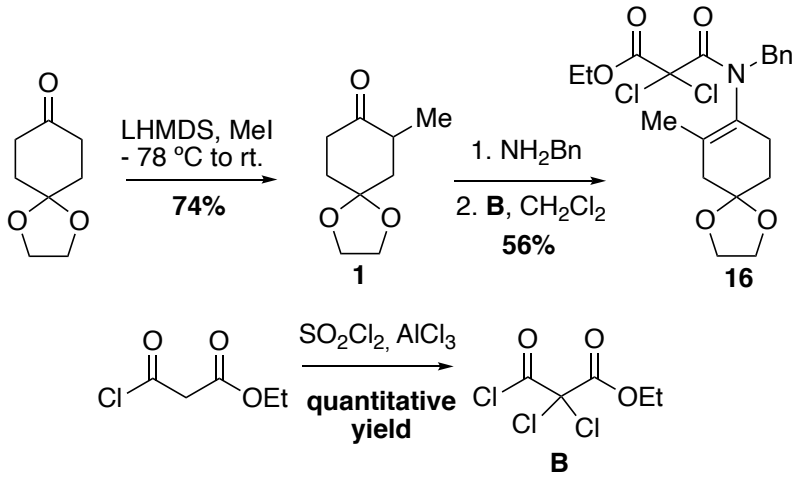
Scheme 2. 17. *Mechanism for* ***5a****,* ***5b*** *and* ***17*** *formation*

The competition between cyclization rates against reduction processes as well as the formation of the double bond had been previously studied.[82] In addition, H-delivery from the less sterically demanding bottom face was also observed in the earlier work of the research group in which the product **3b-Cl** was recovered from reduction of planar radical **VI** (Scheme 2.18).[64a]



Scheme 2. 18. *Recovered chloroderivative* ***3b-Cl*** *from radical cyclization of* ***2*** *reported by the group.*[64a]

Parallely, trichloroacetamide **16** bearing an ester group at the α-carbon was synthesized from condensation of methyl cyclohexanone **1** with benzylamine and further acylation with **B** (Scheme 2.19).[83] Acyl chloride **B** was prepared through α-chlorination of ethyl malonyl chloride in the presence of sulfonyl chloride and a catalytic amount of $AlCl_3$.[81]

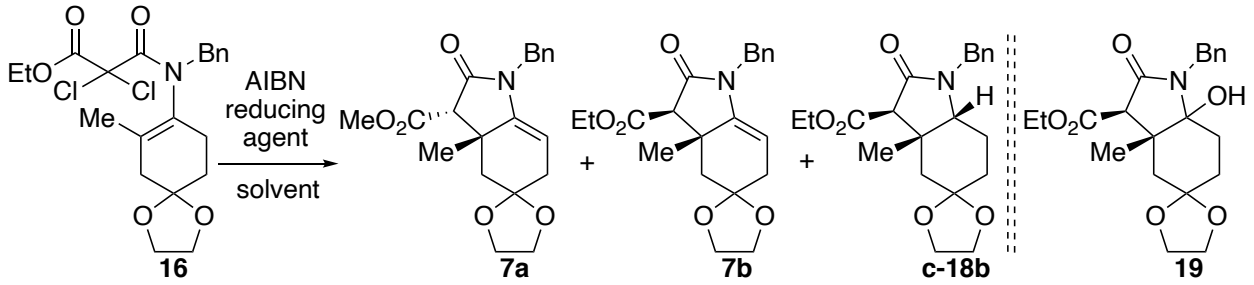


Scheme 2. 19*. Preparation of chloroacetamide* ***16***

Next, trichloroacetamide **16** was submitted to several reductive radical cyclization conditions to study the stereochemical outcome of the new stereogenic center at C-3 (Table 2.3).

[83] For synthesis of enamides by acylation of imines with haloacetyl chlorides, see: ref. 73, and ref. 76 .

Table 2. 3. *Optimization of radical cyclization of dichloroacetamide* ***16***[a]



Entry	AIBN equiv	Hydride source (equiv)	7a	7b	c-18b	Overall yield
1	1.1	TBTH (2.5)	53%	16%	15%	84
2[b]	1.1	TBTH (2.1)	51%	9%	17%	77
3[c]	1.1	TBTH (2.1)	53%	13%[d]	20%[e]	89
4	0.5	TBTH (2.1)	57%	17%	15%	89
5	1.0	TBTH (1.5)	55%	23%[f]	-	78
6[g]	1.1	TBTH (1.5)	63%	1%	-	64
7[h]	1.1	TBTH (2.1)	43%	7%	15%	65
8	0.5	TTMSS (2.0)	43%	12%	-	54
9[c]	0.5	$NaCNBH_3$ (2.0)	-	-	45%[i]	45

[a] *From* ***16*** *(0.4–8.2 mmol scale), reagents were added with a syringe pump over 1 h under benzene reflux and an additional 3 h of reaction time.* [b] *7 g scale. In the NMR of the reaction crude, very low signals attributable to* ***c-18a*** *were observed.* [c] *Only an additional 1 h after the reagents addition.* [d] ***7a*****:*****7b*** *ratio 6:1 by NMR of the crude; ratio 4:1 after chromatography.* [e] ***c-18a*****:*****c-18b*** *ratio 1:3 by NMR of the crude; ratio 1:7 after chromatography.* [f] *Compound* ***7b****, formed by epimerization during* SiO_2 *chromatography, is absent in* ^{1}*H-NMR of the crude.* [g] *Quick chromatographic process.* [h] *In THF as a solvent.* [i] ***c-18a*****:*****c-18b*** *ratio 4:1.*

The first radical cyclization was achieved in a good overall yield from **16** with the slow addition of a solution containing Bu_3SnH (2.5 equiv.) and AIBN (1.1 equiv),[84] although, three bicyclic compounds were obtained (entry 1). The major one was **7a**, followed by the C-3 epimer **7b**, and the additional octahydroindole derivative **c-18b**. A multi-gram scale and a small decrease of the reducing agent amount provided a lower yield (entry 2), but in the same conditions with shorter reaction time, after reagent addition, gave the best overall yield (entry 3). When the amount of AIBN (entry 4) and TBTH (entry 5) were slightly

[84] Diaba, F.; Pujol-Grau, C.; Martínez-Laporta, A.; Fernández, I.; Bonjoch, J. *Org. Lett.* **2015**, *17*, 568–571.

reduced, good yields were obtained, and the latter avoided the formation of the reduced product **c-18b**. A fast purification by column chromatography (entry 6) afforded **7a** almost as the unique product revealing that **7b** could arise from an epimerization process on silica gel. In addition, THF as the solvent, known to act as a H-donor in radical reactions,[85] was tested which gave similar yield results (entry 7 an 8). Switching the hydrogen source to less H-donor TTMSS gave a more moderate yield with no presence of the reduced octahydroindole **c-18b** (entry 9). Finally, applying the recently developed protocol by the research group for radical cyclization of haloacetamides employing $NaCNBH_3$ in AcOH,[86] provided only **c-18b**. Moreover, in some experiments, epimer **7b** partially evolved to compound **19** as previously observed (see Scheme 2.10).

The relative configuration of compounds **7a** and **c-18b**, isolated as solids, were characterized by X-Ray crystallography (Figure 2.2). Reported works described a preferred axial location of the α–ethoxycarbonyl avoiding electronic interactions with the lactam carbonyl.[87] Thus, in epimer **7a**, with an antiplanar relation between substituents at C-3 and C-3a, the 3a-methyl would be axially located and, in epimer **7b**, assuming an axial ester location, the methyl at C-3a would be in an equatorial position.

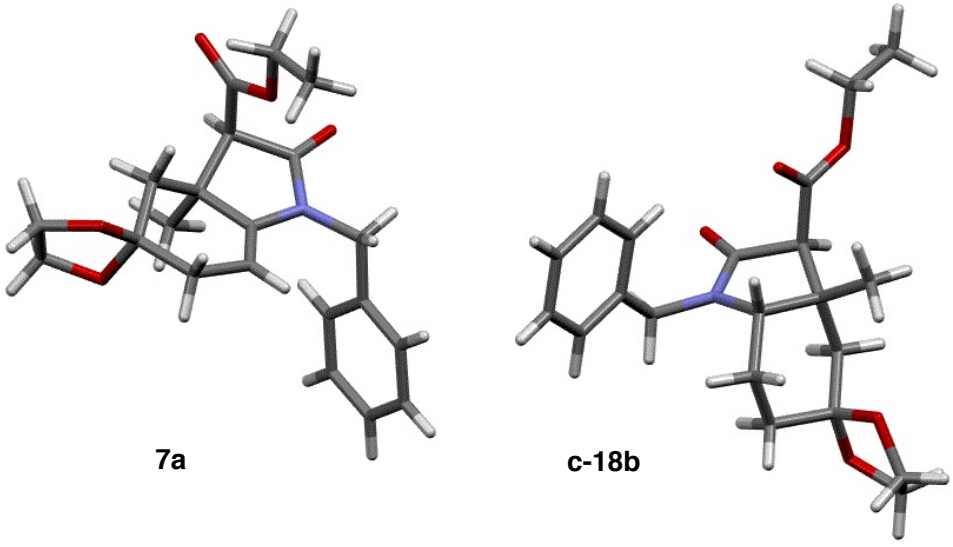


Figure 2. 2. *X-ray for structures* ***7a*** *and* ***c-18b***

[85] Woznica, M.; Chaoui, N.; Taabache, S.; Blechert, S. *Chem.-Eur. J.* **2014**, *20*, 14624–14628.
[86] Coussanes, G.; Jakobi, H.; Lindell, S.; Bonjoch, J. *Chem.-Eur. J.* **2018**, *24*, 8151–8156.
[87] Duchemin, N.; Buccafusca, R.; Daumas, M.; Ferey, V.; Arseniyadis, S. *Org. Lett.* **2019**, *21*, 8205–8210.

The recovery of the epimeric mixtures could form either by epimerization of the α-ethoxycarbonyl group at C-3 [88] or from a low substrate-controlled mechanism. Experimentally, the epimeric ratio observed in the NMR of the crude differed from the recovered after the purification in which **7b** proportion was increased. In addition, a sample of pure **7a** was absorbed in SiO_2 with hexane for 6 hours, and further ^1H NMR analysis showed the appearance of **7b** (Figure 2.3). It is worth noting that H-3 chemical shift differed from **7a** to **7b**, with δ 3.25 and δ 3.35 values respectively. Moreover, when a pure sample of **7a** was treated with KOH in EtOH at reflux overnight, it evolved to an epimeric mixture with dr 2:1 for **7a**:**7b** ratio.

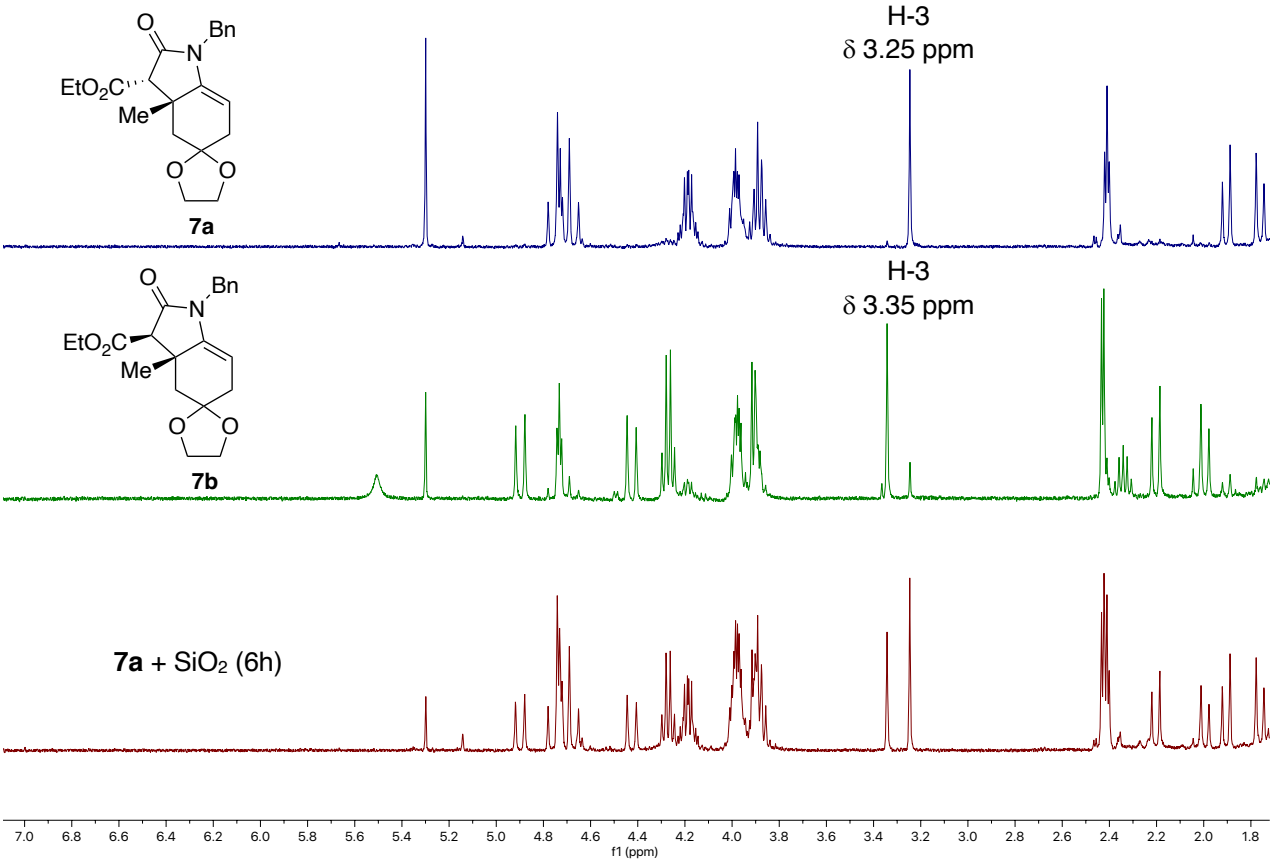


Figure 2. 3. *Epimerization test of 7a to 7b.*

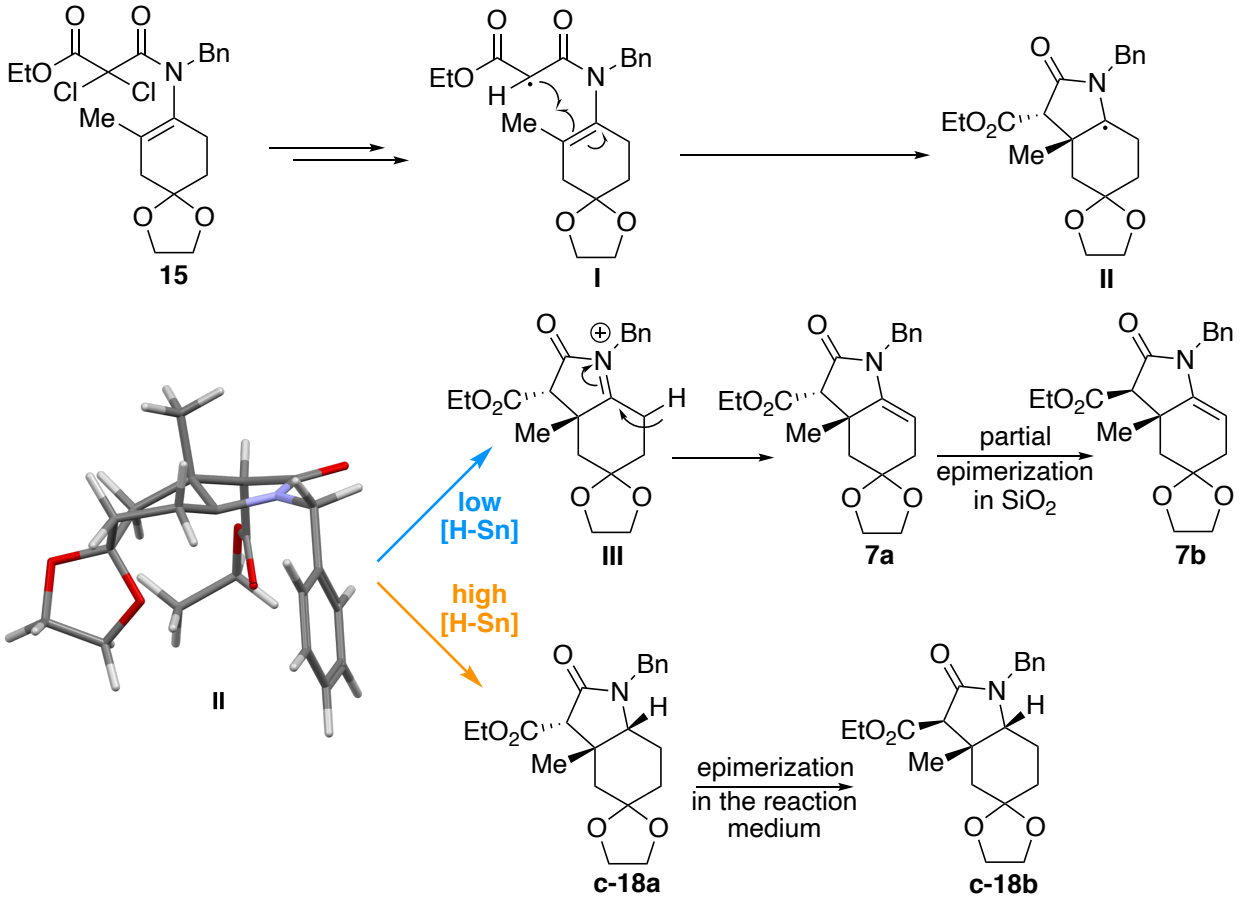
[88] For similar behavior in the δ-lactam series, see: Amat, M.; Pérez, M.; Minaglia, A. T.; Peretto, B.; Bosch, J. *Tetrahedron*, **2007**, *63*, 5839–5848.

From a mechanistic point of view, the major obtention of epimer **7a** could arise from the steric hindrance of the 3a-methyl group (Scheme 2.20). Thus, during the radical cyclization of **I** to form **II**, the ester chain would be located as far as possible from the bulky methyl group. According to Curran's studies,[82] radical **II** could react either directly with **I** through an electron transfer reaction (ET) or with **15** by a chlorine-atom transfer which could gave acylamonium **III** that after proton loss, would form the double bond.

Another interesting point was the formation of reduced products, **c-18b** as the major epimer along with **c-18a** which was detected in less than 1% (Table 2.3, entries 1-4). Previously reported works showed that Bu_3SnH was not capable of reducing enelactams,[89] meaning that the reduction would originate from a radical intermediate. Octahydroindole **c-18b** could be formed from the reduction at C-7a centered radical from **II** giving the epimer **c-18a** followed by an epimerization at C-3 in the reaction medium. When reaction times were shortened (Table 2.3, from entry 1 to entry 4), traces of **c-18a** were recovered in a 1:3 ratio for **c-18a**:**c-18b**, that after chromatography changed to a 1:7 dr. Isomerization at C-3 of these two compounds was observed in further hydrogenation processes (Table 2.4). Radical **II** would adopt a bowl-shaped conformation promoting an axial H-delivery from the convex face that would result in a *cis*-relation between C-3a and C-7 centers. The recovery of compound **c-18b** depended on the amount of reducing agent (Table 2.3, entries 3 and 5 vs. entries 1 and 2). This would be in agreement with Curran's studies,[82] where they pointed out a disappearance of over-reduced products at the expense of enelactams in low tin concentrations, since the ET mechanism is more favored above the reduction.

The radical cyclization could start from the less sterically demanding (ethoxycarbonyl)methyl carbamoyl radical **I**, since in Parson's work,[90] when 3-chloro-3-methoxycarbonyl enelactam was reduced, only the β-epimer was formed differing from the major recovery of the α-epimer in this work.

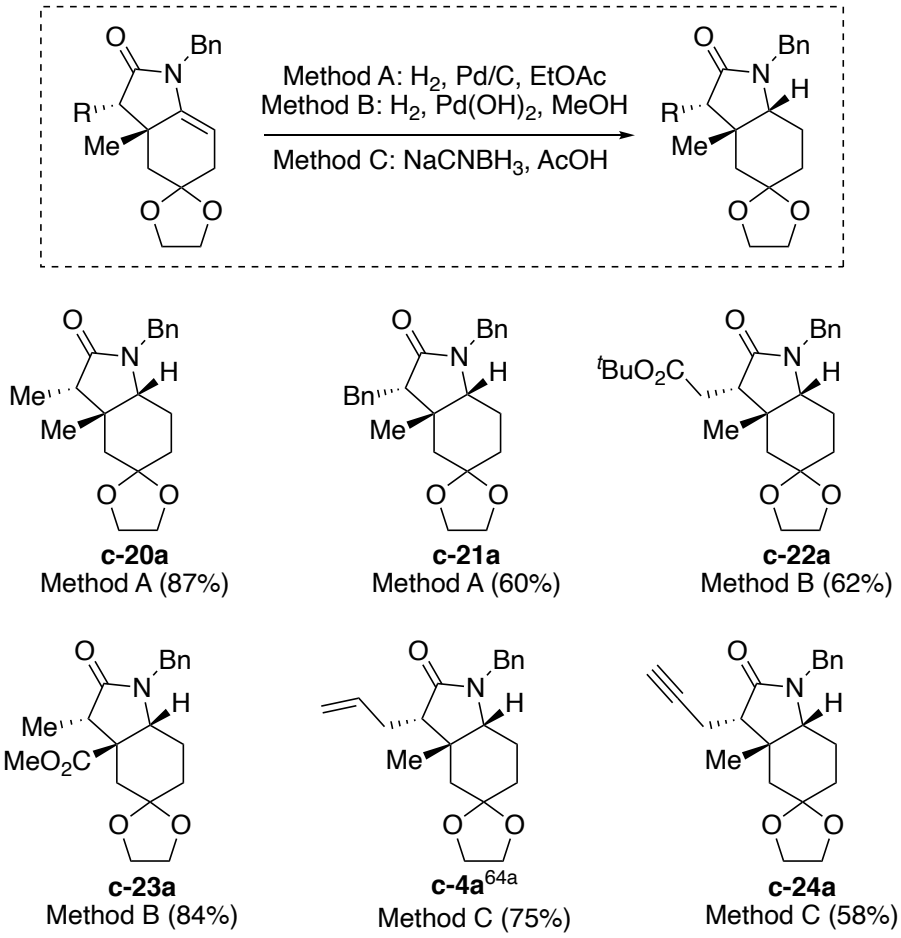
[89] Padwa, A.; Rashatasakhon, P.; Ozdemir, A. D.; Willis, J. *J. Org. Chem.* **2005**, *70*, 519–520.
[90] Identification of the epimer obtained by Parsons (ref 74), was based on the chemical shift of Me-3a (δ_H 1.28 ppm) and C-3 (δ_C 59.2 ppm) which were coincident with those reported for enelactam **7b**.



Scheme 2. 20. *Stereoselectivity of radical cyclization of enelactam* ***16***

2.2.3 Reduction processes: synthesis of octahydroindoles

At this point, we addressed the synthesis of the octahydroindole cores from the obtained functionalized enelactams (Scheme 2.21). Thus, different double bond reduction methodologies were studied. In the first place, the enelactams lacking additional unsaturated substituents, were submitted to hydrogenation processes, either in the presence of catalytic Pd/C or $Pd(OH)_2$, to obtain **c-20a**, **c-21a**, **c-22a** and **c-23a** in good yields. Next, considering the previously reported preparation of **c-4a**, [64a] compound **9a** with an allylic chain at C-3 was treated with $NaCNBH_3$ in AcOH affording octahydroindole **c-24a** in 58% yield. All the reduction process were diastereoselective obtaining only the *cis*-octahydroindole derivatives.



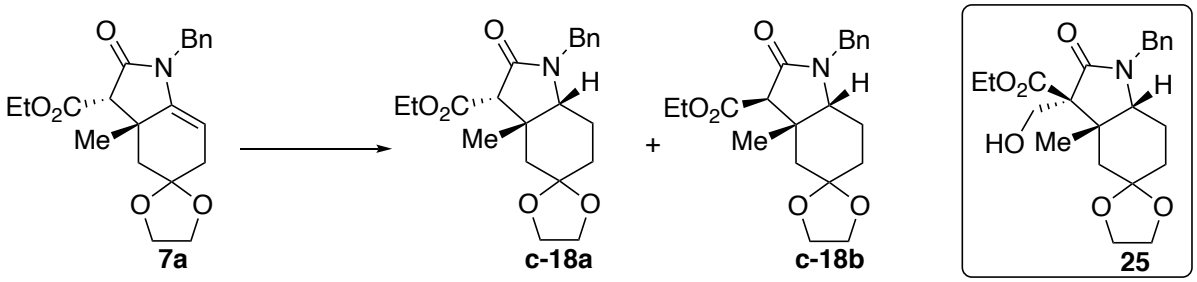
Scheme 2. 21. *Reduction of enelactams for octahydroindole preparation*

Double bond reduction of bicyclic lactams **7a** merits a special mention due to the epimerizable character at C-3 (Table 2.4). When **7a** was submitted to H_2 atmosphere in the presence of Pd/C in EtOAc an epimeric mixture **c-18a**:**c-18b** (dr: 5.6:1) was isolated with an excellent overall yield (entry 1). In another run, under the same reaction conditions, a mixture of **c-18a**:**c-18b** (3.5:1) was observed in the NMR of the crude, and, after chromatographic purification the dr was 1:2.1, hence, epimerization in SiO_2 occurred. Changing the solvent to EtOH, changed the ratio to 1:8 favoring epimer **c-18b** (entry 2). In addition, the yield decreased at the expense of compound **25** formation. Methyl hydroxylated lactam **25** with a new quaternary carbon could arise from a condensation of active C-3 methine with formaldehyde generated *in situ*.[91] Finally,

[91] Precedents of this side reaction: Goyal, V.; Gahtori, J.; Narani, A.; Gupta, P.; Bordoloi, A.; Natte, K. *J. Org. Chem.* **2019**, *84*, 15389−15398.

treatment of **7a** with $NaCNBH_3$ in AcOH afforded the regioselective reduction of the double bond giving mixtures of **c-18a**:**c-18b** (entry 3). Likewise, the reaction was stereoselective providing only the *cis*-isomer.

Table 2. 4. *Reduction of the double bond from enelactam* ***7a***[a]

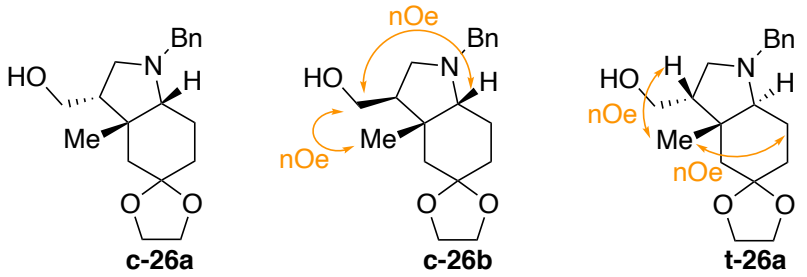


Entry	Reagents	c-18a:c-18b
1	H_2, Pd/C, EtOAc	95% (5.6:1)[b]
2	H_2, Pd/C, MeOH	73% (1:8) + 18% (**25**)[c]
3	$NaCNBH_3$, AcOH	77% (1:1)[b]

[a]*0.08–0.27 mmol scale.* [b]*Observed in the NMR of the crude.* [c]*Isolated yield*

Additionally, the simultaneous reduction of several functional groups present in the 3-carbonylated derivatives was considered (Table 2.5). Thus, lactams **7** were treated with alane generated *in situ* from $LiAlH_4$ and catalytic $AlCl_3$.[84] From enelactam **7a**, **c-26a** was obtained in 41% yield along with product **t-26a** (21%) with a *trans*-junction at bridged positions (entry 1). The latter could arise from anchimeric assistance from the bottom face by the generated alkoxide at C-3 chain. From enelactam **7b** both epimers at C-3 were revered with a *cis*-relation between H-7a and Me-3a (entry 2). Finally, compound **c-26b** was obtained from octahydroindole **c-18b** as a unique product with a good yield (entry 3).

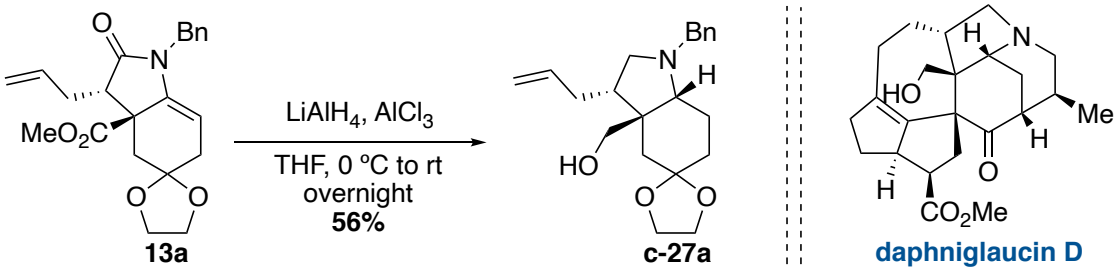
Table 2. 5. *Reduction of enelactam 7a*[a]



Entry	Amido ester	*c*-26a	*c*-26b	*t*-26a
1	7a	41%[b]	--	21% [b]
2	7b	17% [b]	35% [b]	--
3	c-18b	--	79% [b]	--

a. 0.15–0.31 mmol scale. b. Isolated yield.

Finally, lactam **13a** was reduced using the same methodology Scheme 2.22). Thus, the removal of the lactam carbonyl group and the saturation of the double bond were achieved along with the reduction of the ester at the ring junction to give **c-27a** with a hydroxymethyl motif at C-3a. This transformation allowed access to a new functionalized scaffold[47, 92] with great potential for the preparation of advanced intermediates for daphniglaucins D-F synthesis, another group of *Daphniphyllum* alkaloids.[93]



Scheme 2. 22. *Reduction of **13a** with alane methodology.*

[92] Li, S.; Yamamura, S. *Tetrahedron*, **1998**, *54*, 8691–8710.
[93] Takatsu, H.; Morita, H.; Shen, Y.-C.; Kobayashi, J. *Tetrahedron*, **2004**, *60*, 6279–6284.

2.2.4 NMR characterization of the indole derivatives

Having in hand this library of bicyclic compounds, we elaborated a table with ^{13}C NMR data of the studied enelactams as a helpful tool for their faster characterization (Table 2.6).

Table 2. 6. *^{13}C NMR chemical shifts for enelactam products*

	C-2	C-3	C-3a	C-4	C-5	C-6	C-7	C-7a	Me	NCH_2
3[64a]	174.3	47.1	37.5	43.7	108.9	35.4	95.1	145.7	25.9	43.6
3b-Cl[64a]	169.5	67.6	43.9	41.6	107.9	35.4	97.8	141.3	21.1	44.6
4[64a]	176.9	54.4	40.7	38.1	108.9	35.3	95.9	144.5	28.0	43.7
5a	178.4	49.4	40.1	37.5	108.8	35.1	95.9	144.1	27.3	43.4
5b	176.5	49.2	41.0	42.7	108.5	35.3	94.6	144.8	20.2	43.5
6a	176.5	55.1	40.8	38.2	108.6	34.5	95.8	144.2	27.9	43.5
7a	170.3	61.6	41.2	38.4	108.2	35.2	96.5	143.4	27.3	44.1
7b	169.1	59.4	41.1	43.4	108.1	35.1	95.8	142.8	21.5	43.6
8a	176.2	53.4	40.0	37.7	108.6	34.5	96.3	143.9	27.4	44.0
8b	174.3	50.8	43.3	40.9	108.2	35.1	95.6	143.9	20.5	42.8
9a	175.4	53.0	39.9	37.6	108.7	35.1	96.0	144.1	27.9	43.5

Both, ^{1}H-NMR and ^{13}C-NMR spectra of the hexahydroindoles revealed two patterns regarding the configuration at C-3. First, compounds from series **a** showed a chemical shift of δ ~1.92 ppm for H-ax, and δ ~ 37.5–38.4 ppm for C-4, whereas for series **b** products, H-4ax chemical shift was δ ~ 2.00 ppm and δ ~ 41.0–43.4 ppm for C-4. The upfield shift for **a** compounds (3–5 ppm from series **b**) originates from a steric compression of the C-3 side chain to the H-4ax which corresponds to an α-orientation of the substituent and a β-disposition for the epimeric compounds **b**. Another diagnostic signal for the C-3 configuration was the chemical shift for the methyl group at C-3a, showing values of δ 27.6 ($\pm$0.4) for series **a** and δ 20.8 ($\pm$0.6) for series **b** with an antiplanar and a synclinar relationship, respectively, between C-3a and C-3 substituents.

Additionally, the analysis of ^{13}C NMR of the obtained octahydroindoles showed several diagnostic signals (Table 2.7). As mentioned before, the chemical shift at C-4 was a revealing signal to identify epimeric compounds at C-3, when upfield corresponds to α-epimer (δ 38.0±0.5 ppm) and when is more downshielded to β-epimer (δ 42.0±1.0 ppm). Moreover, the 1H NMR and 13C NMR chemical shift of the methyl group at C-3a allowed us to assign the C-3 configuration center. For the α-epimers, the chemical shift for the methyl groups always appears downfield (δ_H 1.36 and δ_c 23.2, for **c-18a**) and upfield for the β-epimers (δ_H 1.16 and δ_c 20.3, for **c-18b**).

Table 2. 7. *C-13 NMR for octahidroindole compounds*

	C-2	C-3	C-3a	C-4	C-5	C-6	C-7	C-7a	Me	CH_2Ph
c-4a[64a]	177.1	55.4	41.8	36.9	108.3	28.8	20.6	59.5	23.2	44.1
c-18a	167.6	61.0	42.0	37.0	107.6	28.5	20.7	59.5	23.2	44.1
c-18b	168.5	60.8	41.2	42.0	107.4	29.1	21.4	59.0	20.3	44.1
c-20a	177.8	50.4	41.1	36.5	108.2	28.7	20.6	59.5	21.9	43.8
c-21a	176.9	53.7	41.8	36.9	108.1	28.5	20.3	59.2	22.7	44.0
c-22a	176.1	52.2	41.1	37.1	107.9	28.7	20.4	59.3	22.4	44.0
c-23a	173.5	46.5	51.2	33.2	107.3	29.4	21.4	54.5	--	44.1
c-24a	175.5	53.8	41.6	36.2	107.9	28.2	20.2	59.3	22.9	44.0
c-26a	55.1	51.0	43.0	36.5	109.6	28.6	21.4	68.5	23.9	57.9
c-26b	55.7	48.4	43.3	44.0	109.3	29.0	21.6	66.7	19.9	57.7
t-26a	56.5	48.4	43.2	41.1	110.1	34.3	21.7	68.6	22.6	58.2
c-27a	57.0	44.8	47.9	35.0	109.8	28.5	23.0	69.6	---	57.9

2.2.5 Atropoisomerism

In previous works of the research group,[94] variable temperature ^{1}H-NMR of trichloroacetamide **2** was recorded. The results showed a broad spectrum at room temperature and, as the sample was cooled, decoalescence occurred revealing two sets of sharp signals with a defined multiplicity (Figure 2.4).

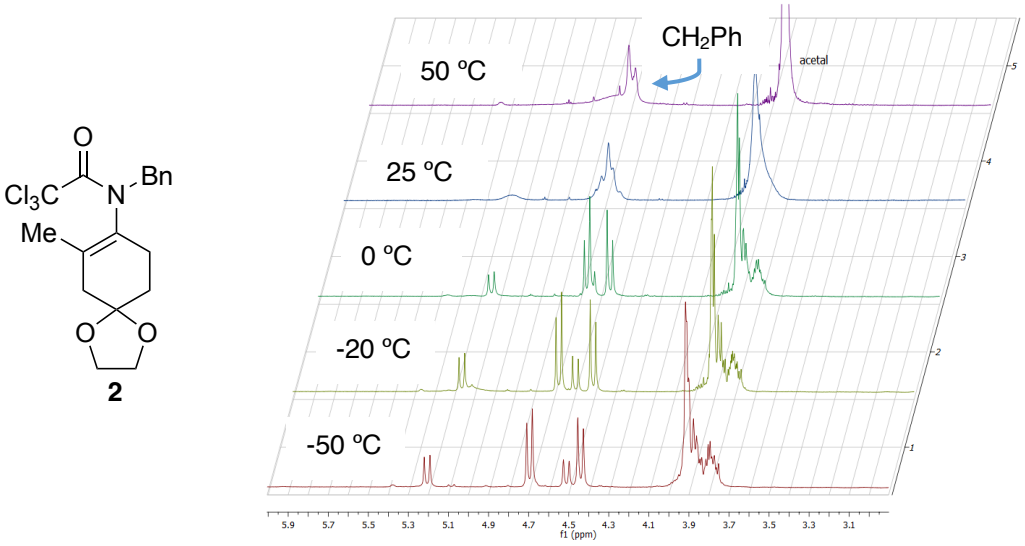


Figure 2. 4. *1H NMR variable temperature of trichloroacetamide **2***

In the case of the prepared chloroacetamides in this thesis, their ^{1}H-NMR at room temperature already revealed two separated sets of signals, in different proportions depending on the substrate, with diastereotopic protons. The characteristic signal for benzylic protons appeared as two doublets for dichloroacetamide **16** (Figure 2.5).

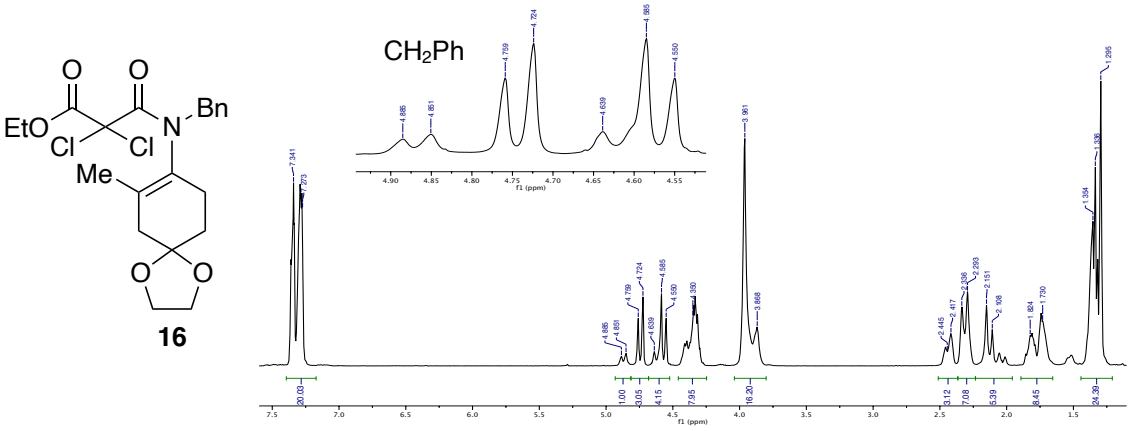
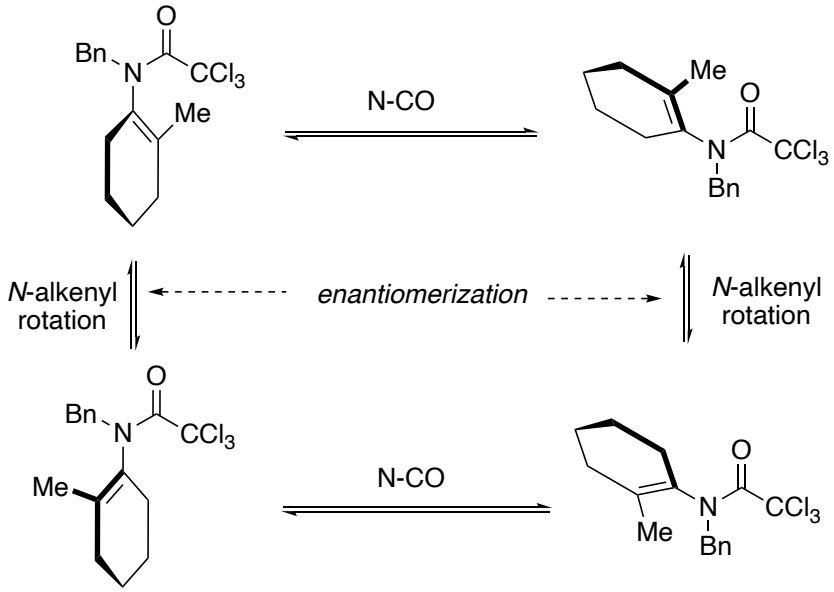


Figure 2. 5. *1H NMR of dichloroacetamide **16** at room temperature*

[94] Coussanes, G. Ph.D. Thesis, Universitat de Barcelona, Barcelona, Spain, 2016.

This well-precedented behaviour,[82,95] is caused by two bond rotations present in these molecules (Scheme 2.23). In the first place, the presence of N-CO bond rotamers causes all signals to be doubled. Moreover, the appearance of diastereotopic geminal protons could be attributed to the slowing down of the *N*-cycloalkenyl bond rotation. Reported X-ray analysis of analogous haloacetamides,[95c] revealed a twisted *N*-cycloalkenyl bond nearly orthogonal with the planes of the amide which makes the molecules axially chiral. Thus, two possible rotamers (*E*,*Z*) are originated from N-CO bond rotation and, in addition, each one exists as a pair of atropoisomers, which are the enantiomers generated by a restricted *N*-alkenyl bond rotation. Clark and Curran,[95c] reported that the factors that influence the restricted rotation were the level of the alkene substitution, followed by the size of the nitrogen substituent and, finally, the size of the acyl substituent.



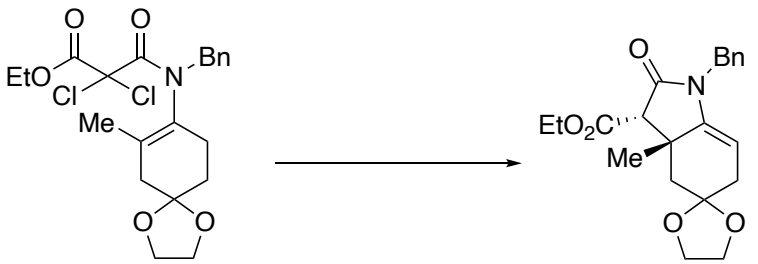
Scheme 2. 23. *Bond rotations of chloroacetamide derivatives*

An interesting application of this substrates would be the chirality transfer from enantiomerically enriched atropoisomeric enamide samples to their cyclization reactions. Hence, reported works of the topic,[95b] showed that *N*-alkenyl bond rotation barriers should

[95] a) Guthrie, D.B.; Damodaran, K.; Curran, D. P.; Wilson, P.; Clark, A. J. *J. Org. Chem.* **2009**, *74*, 4262–4266. b) Clark, A. J.; Curran, D. P.; Geden, J. V.; James, N.; Wilson, P. *J. Org. Chem.* **2011**, *76*, 4546–4551. c) Clark, A. J.; Curran, D. P.; Fox, D. J.; Ghelfi, F.; Guy, C. S.; Hay, B.; James, N.; Phillips, J. M.; Roncaglia, F.; Sellars, P. B.; Wilson, P.; Zhang, H. *J. Org. Chem.* **2016**, *81*, 5547–5565.

be around 25 kcal/mol in order to be separated in the chiral HPLC scale time. Additionally, the reaction should be performed at room temperature or lower. In this thesis, a preliminary work of the radical cyclization at low temperature of dichloroacetamide **16** was investigated (Table 2.8). In the first place, following the protocol employed by Ding *et al.*,[96a] **16** was treated with TBTH in the presence of BEt_3 and air which resulted in the recovery of a complex mixture of non-cyclized products (entry 1). However, the cyclization was achieved when applying the conditions described by Yamashita and Hirama.[96b] First, using TTMSS as H-source and two additions of the reagents BEt_3 and air, produced enelactam **7a** in 40% yield along with the recovery of **16** (entry 2). Then, when three additions of the reagents were carried out lactam **7a** was achieved in 60% yield (entry 3).

Table 2. 8. *Radical cyclization of dichloroacetamide **16** at low temperature*

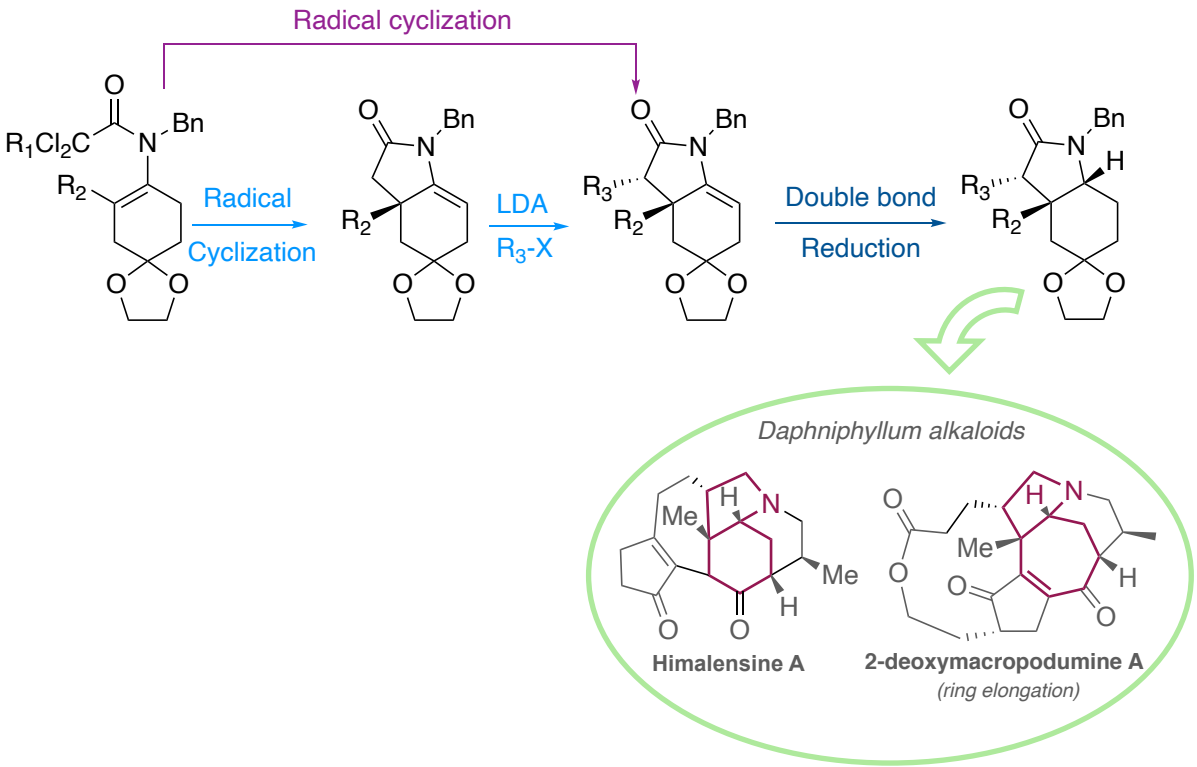


Entry	Reagents and conditions	Product (Yield)
1	TBTH, BEt_3, air, toluene -78 ºC to 0 ºC	Reduced/non-cyclized products
2	1. TTMSS, BEt_3, air, THF, -78 ºC 2. BEt_3, air, –78 ºC to rt	**7a** (40%, 60% brsm)
3	1. TTMSS, BEt_3, air, THF, -78 ºC 2. BEt_3, air, – 78 ºC 3. BEt_3, air – 78ºC to rt	**7a** (60%)

[96] a) Zhu, C.; Liu, Z.; Chen, G.; Zhang, K.; Ding, H. *Angew. Chem. Int. Ed.* **2015**, *54*, 879–882. b) Yamashita, S.; Iso, K.; Hirama, M. *Org. Lett.* **2008**, *10*, 3413–3415.

2.3 Summary and conclusions

In summary, two pathways leading to poly-functionalized cis-octahydroindoles have been described by means of a 5-*endo*-*trig* radical cyclization of tetrasubstituted enamides using Bu_3SnH and AIBN. In the first approach, the resulting 3a-methyl and 3a-methoxycarbonyl enelactams underwent diastereoselective enolate alkylation to provide a set of 3-substituted derivatives (blue route). The synthesis of related building blocks embodying three consecutive stereogenic carbon atoms at C-3 and the ring junction was also achieved through an initial radical cyclization involving carbosubstituted dichloroacetamides and further reduction (purple route). The functionalizations present in the synthesized compounds as well as the diastereoselectivity observed in their transformations make them potential intermediates *en route* to *Daphniphyllum* alkaloids. The results of this chapter were compiled in a publication.[97]



Scheme 2.24. *Conclusions of the Chapter 2*

[97] Marquès, C.; Diaba, F.; Roca, J.; Bonjoch, J. *Org. Biomol. Chem.* **2021**, *19*, 2284–2301.

Chapter 3

Synthesis of the ABC ring of Calyciphylline A-type alkaloids. Formal synthesis of Himalensine A

The azapolycyclic structures of calyciphylline A-type members, one of the largest subfamilies of *Daphniphyllum* alkaloids, possess a common [6-6-5-7] backbone with one or two additional rings.

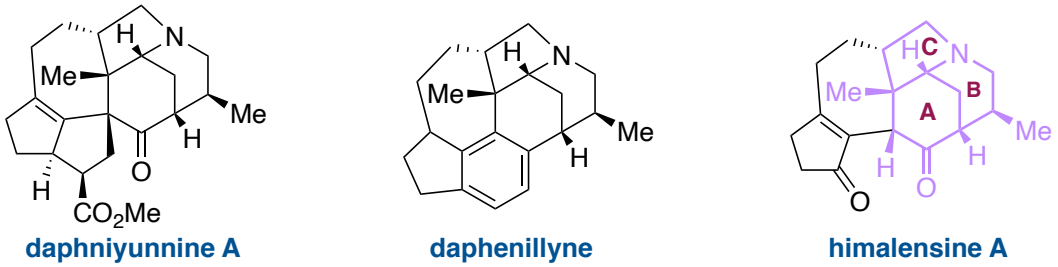
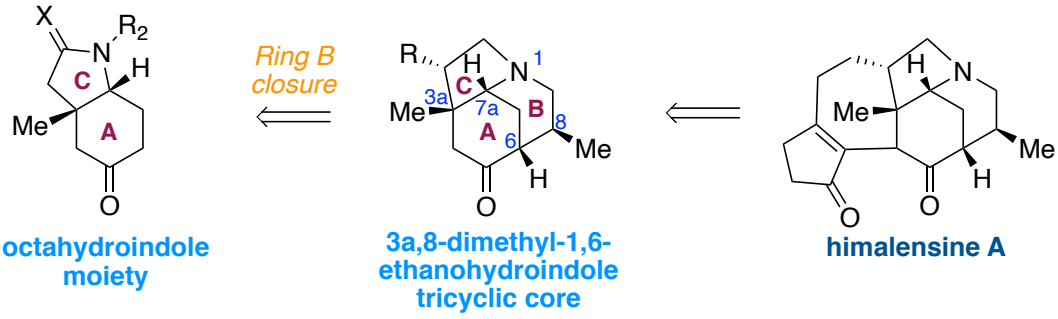


Figure 3. 1. *Daphniphyllum alkaloids embodying azatricyclic [5-6-6]-fragment*

Compounds embodying the compact ABC ring system (Fig. 3.1, depicted in purple) with a quaternary center at C-5 and a methyl group at C-18, would be valuable building blocks for the synthesis of these natural products. Thus, pursuing the total synthesis of himalensine A, this chapter aims to achieve the construction of the 1,6-ethanohydroindole scaffold (ABC) through a process for the ring B closure employing the studied octahydroindole core (AC) (Scheme 3.1). It is worth mentioning that our research group previously reported applications of enelactam hydroindoles in synthetic works toward *Daphniphyllum* alkaloids.[47,64]



Scheme 3. 1. *General overview of the objective of Chapter 3*

3.1 Precedents

Over the literature several syntheses of the targeted ABC-fragment have been reported which could be classified in three different approaches.

Firstly, our research group developed the first access to this tricyclic fragment where the B-ring was closed by means of a Pd-alkenylation of enolizable ketones (Scheme 3.2.a).[47,98] As indicated in Chapter 1, this strategy has been extensively used, naming Xu,[52] Gao,[54] and Dixon,[58] in their works furnishing the total synthesis of himalensine A (Schemes 1.13, 1.14, and 1.16). Moreover, it has also been applied in investigations dedicated to other *Daphniphyllum* alkaloids such as Liang in the synthesis of ABCE rings of daphenylline,[99] and Xue and Qin in the construction of the ring core present in 21-deoxymacropodumine D.[100] In addition, a variation of this strategy was reported by Tang in which a Pd-catalyzed oxidative alkenylation was performed with $Pd(OAc)_2$ and $Yb(OTf)_3$ from an alkene-tethered β-ketoester.[101]

Secondly, Stockdill described a tandem process for the concomitant closure of the B- and C-rings through an aminyl radical and subsequent trapping of the formed carbon-centered radical by an alkyne (Scheme 3.2.b).[102]

Finally, an intramolecular Michael addition from a β-amidoester to an enone was extensively used by Li in his works towards the total synthesis of several *Daphniphyllum* alkaloids (Scheme 3.2.c).[14] Additionally, our research group described a similar process employing a sulfone as the carbanion source for the last ring C formation.[103]

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[98] a) Solé, D.; Urbaneja, X.; Bonjoch, J. *Adv. Synth. Catal.* **2004**, *346*, 1646–1650. b) Jansana, S.; Coussanes, G.; Puig, J.; Diaba, F.; Bonjoch, J. *Helv. Chim. Acta* **2019**, *102*, No. e1900188

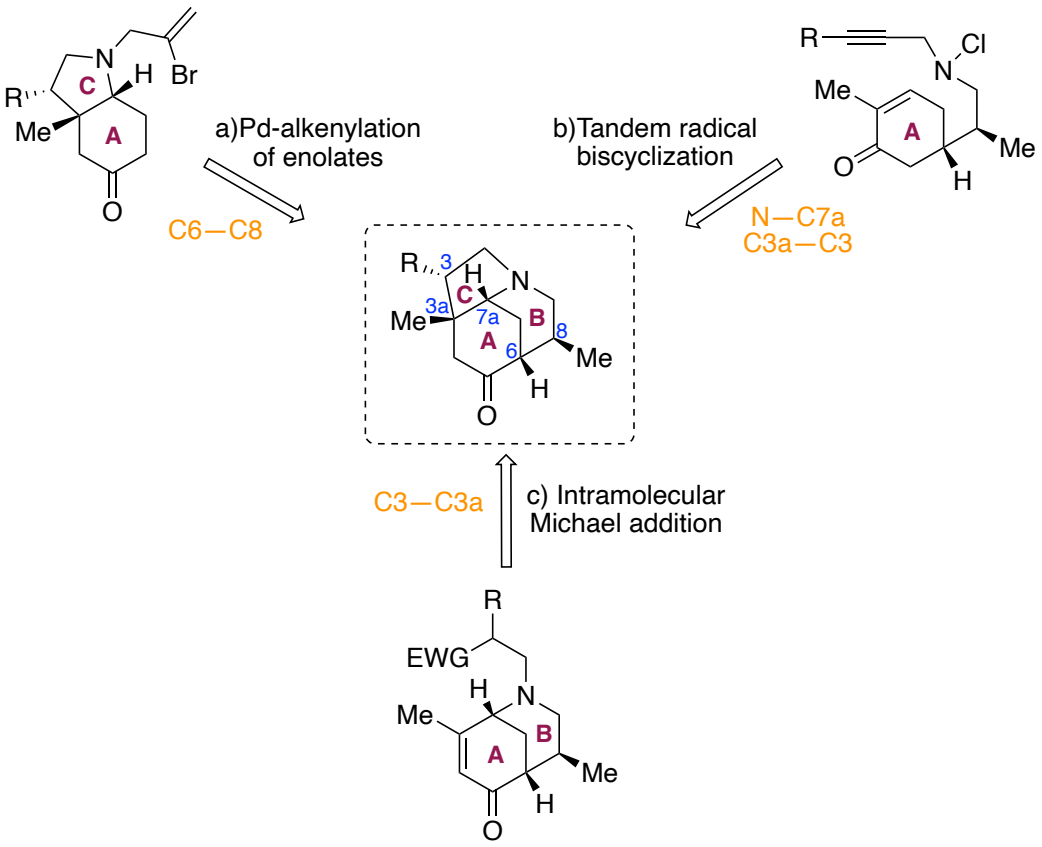
[99] Deng, M.; Yao, Y.; Li, X.; Li, N.; Zhang, X.; Liang, G. *Org. Lett.* **2019**, *21*, 3290–3294.

[100] Mo, X.-F.; Li, Y.-F.; Sun, M.-H.; Dong, Q.-Y.; Xie, Q.-X.; Tang, P.; Xue, F.; Qin, Y. *Tetrahedron Lett.*, **2018**, *59*, 1999–2004.

[101] Wang, H.; Dong, Q.; Xie, Q.; Tang, P. *Chin. Chem. Lett.* **2020**, *31*, 685–688.

[102] a) Ibrahim, A. A.; Golonka, A. N.; Lopez, A. M.; Stockdill, J. L. *Org. Lett.* **2014**, *16*, 1072–1075. b) Stockdill, J. L.; Lopez, A. M.; Ibrahim, A. A. *Tetrahedron Lett.* **2015**, *56*, 3503–3506. c) Lopez, A. M.; Ibrahim, A. A.; Rosenhauer, G. J.; Sirinimal, H. S.; Stockdill, J. L. *Org. Lett.* **2018**, *20*, 2216–2219.

[103] Diaba, F.; Martínez-Laporta, A.; Coussanes, G.; Fernández, I.; Bonjoch, J. *Tetrahedron,* **2015**, *71*, 3642–3651.

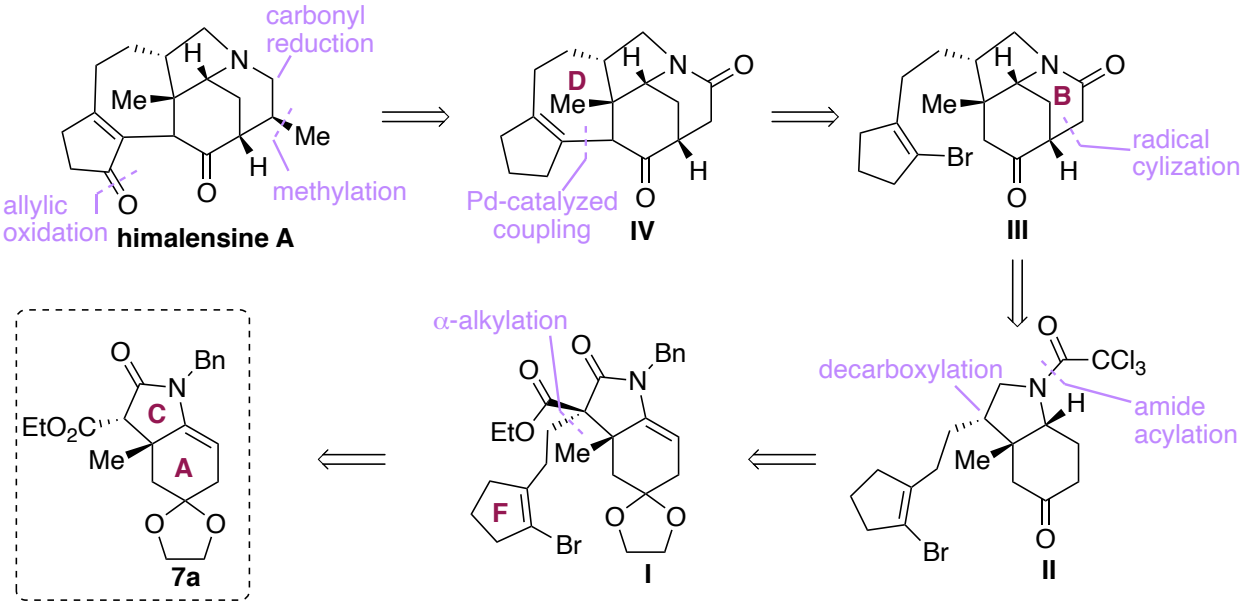


Scheme 3. 2. *Previous approaches to the tricyclic ABC core of the Calyciphylline A-type Alkaloids*

3.2 Results and discussion

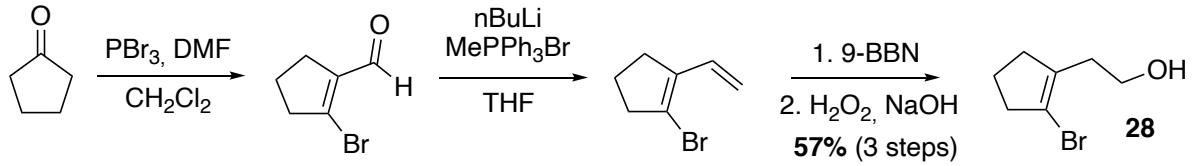
3.2.1 Radical cyclization for the B-ring closure

In the first place, we designed a retrosynthetic analysis for the synthesis of himalensine A featuring the key tricyclic ABC fragment construction from functionalized enelactams prepared in Chapter 2 through a radical closure of the B-ring (Scheme 3.3). Thus, the previously prepared bicyclic lactam **7a**, containing A- and C-rings, would be alkylated to introduce a chain bearing the F-ring. Next, after reduction and decarboxylation processes, a chloroacetamide would be synthesized to perform the key radical cyclization. Then, Pd-catalyzed coupling reactions or radical methodologies could provide the tetracyclic core. Finally, we planned the C-8 methyl installation through an alkylation of the lactam followed by the allylic oxidation and the carbonyl removal to obtain himalensine A.



Scheme 3. 3. *Retrosynthetic plan for himalensine A synthesis starting from enelactam* ***7a***

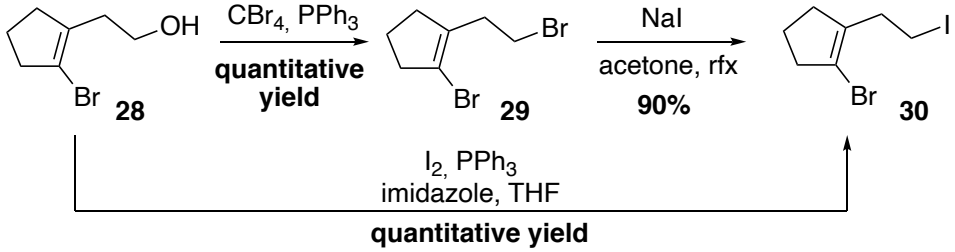
We commenced by synthesizing the alkylating chain bearing the F-ring from cyclopentenone (Scheme 3.4). Firstly, we prepared the bromo aldehyde through a Vilsemeier-Haack type reaction with PBr_3 and DMF.[104] Next, the carbonylic moiety was submitted to Wittig conditions to obtain the conjugated diene derivative.[105] After treatment with 9-BBN and further oxidation with H_2O_2 in a basic medium, alcohol **28** was afforded in 58% over the three steps.[106]



Scheme 3. 4. *Preparation of alcohol* ***28*** *from cyclopentenone*

[104] a) Pawar, S.K.; Wang, C.-D.; Bhunia, S.; Jadhav, A.M.; Liu, R.-S. *Angew. Chem. Int. Ed.* **2013**, *52*, 7559–7563. b) Arnold, Z.; Holy, A. *Collect. Czech. Chem. Commun.* **1961**, *26*, 3059–3073.
[105] Yoshida, K.; Nishii, K.; Kano, Y.; Wada, S.; Yanagisawa, A. *J. Org. Chem.* **2014**, *79*, 4231–4239
[106] Zhan, F.; Liang, G. *Angew. Chem. Int, Ed.* **2013**, *52*, 1266–1269

Alcohol **28** was halogenated to provide better leaving groups for the alkylation reaction (Scheme 3.5). First, bromide derivative **29** was synthesized in a quantitative yield by treatment with CBr_4 in the presence of PPh_3 as described by Liang *et al.*[106] Then, when **29** was treated with NaI under acetone reflux, iododertivatie **30** was obtained. Moreover, **30** could be prepared directly from alcohol **28** by I_2/PPh_3/imidazole using the employed conditions in Shvartsbart and Smith's work.[11a]

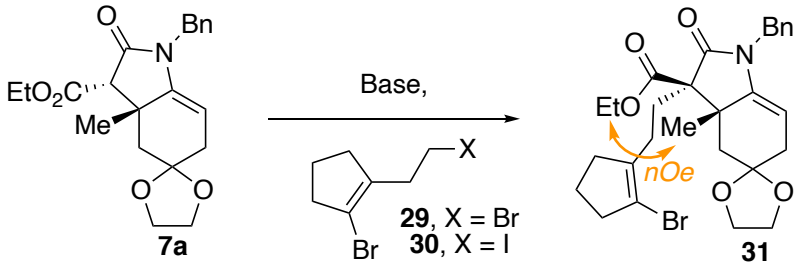


Scheme 3. 5. *Preparation of bromo- and iododerivatives from alcohol **28***

Having prepared both bromo- and iododerivatives, **29** and **30**, the C-3 alkylation of enelactam **7a** was studied (Table 3.1). First, assuming an increase of H-3 acidity due to the presence of the ester group, NaH was used along with iododerivative **30** which was generated *in situ* from bromoderivative **29** and NaI (entry 1).[107] Compound **31** was obtained diastereoselectively with 18% yield. The relative configuration of **31** was confirmed by NOESY experiments. Addition of HMPA at the reaction medium, did not imply a yield improvement (entry 2).[108] Then, when iododerivative **30** was previously prepared and using DMSO as the reaction solvent the product was recovered in 34% (entry 3). Employing the same conditions but changing the base to Cs_2CO_3, the product was isolated in the best yield (entry 4). Additionally, we tested DMF as the solvent but only 31% yield was obtained (entry 5). Finally, a procedure described by Wardrop *et al.*[109] was examined employing K_2CO_3 as the base in the presence of 18-crown-6, but only starting material was recovered (entry 6). The major setback of the process was the side elimination reaction of the alkylating agent to produce the conjugated diene.

[107] Ye, B.; Cramer, N. *Angew. Chem. Int. Ed.* **2014**, *53*, 7896–7899.
[108] a) Shi, S.; Szostak, M. *Org. Lett.* **2015**, *17*, 5144–5147. b) Shi, S.; Lalancette, R.; Szostak, M. *Synthesis*, **2016**, *48*, 1825–1854.
[109] Bhattacharjee, A.; Gerasimov, M. V.; DeJong, S; Wardrop, D. J. *Org. Lett.* **2017**, *19*, 6570–6573.

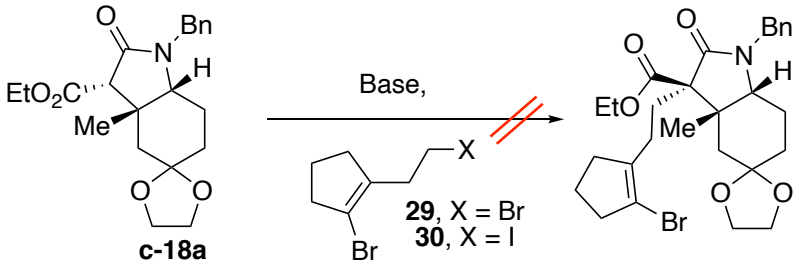
Table 3. 1. *Optimization of the C-3 alkylation of* ***7a***[a]



Entry	Reagents and conditions	Yield[a]
1	1. NaH, THF, rt, 1h 2. **29**, NaI, DMF, 90 ºC, overnight	15%
2	1. NaH, HMPA, THF, rt, 1h 2. **29**, THF, 50 ºC, overnight	13%
3	1. NaH, DMSO, 1h, rt 2. **30**, DMSO, rt, overnight	34%
4	1. Cs_2CO_3, DMSO, 1h, rt 2. **30**, DMSO, rt, overnight	50%
5	1. Cs_2CO_3, DMF, 1h, rt 2. **30**, DMF, rt, overnight	31%
6	K_2CO_3, 18-crown-6, **30**, rt, overnight	SM

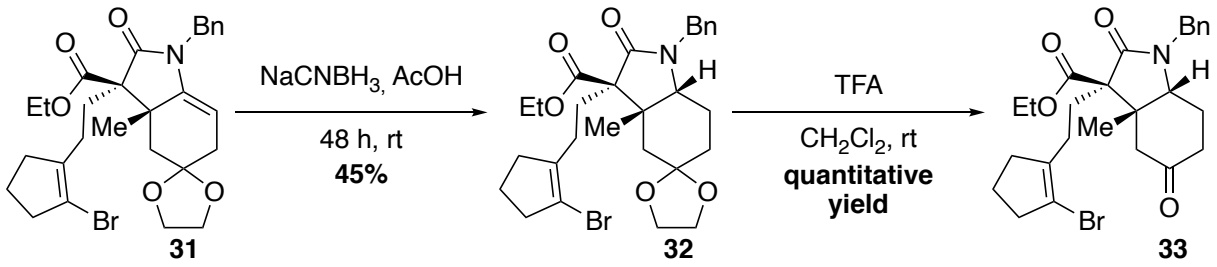
a. 0.14–0.30 mmol scale. b. Isolated yield

Attempts to alkylate octahydroindole **c-18a** resulted in the recovery of starting material (Scheme 3.6). As seen in Chapter 2, the enamide double bond was necessary even with the presence of the ester group to increase the acidity of the α-proton.



Scheme 3. 6. *α-alkylation test of octahydroindole* ***c-18a***

Next, we proceed with the reduction of the enamide double bond from **31**. After screening the reaction conditions, compound **32** was obtained in 45% yield by treatment with $NaCNBH_3$ in AcOH. [64a] Then, ketal hydrolysis with TFA in CH_2Cl_2 provided the bicyclic ketone **33**.

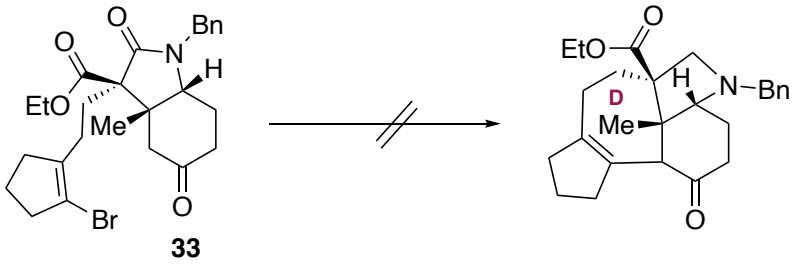


Scheme 3. 7*. Preparation of bicyclic ketone **33***

Due to the moderate yields for the subsequent alkylation and reduction processes, the substrate quantity prevented the execution of the required chemical transformations to perform the radical cyclization of the B-ring. Thus, we decided to address first the closure of the more challenging 7-membered D-ring (Table 3.2). We started by testing the Pd-catalyzed alkenylation conditions, but neither the protocol reported by our research group (entry 1),[47] or the employed by Padwa (entry 2),[50a, 110] were succesful. Next, switching the metal to copper for Ullmann coupling conditions described by Li and co-workers,[111] was tested with Cs_2CO_3 as a base but no cyclization product was obtained (entry 3). Finally, the conditions reported by Ollevier and Taillefer,[112] were applied for a transition-metal-free vinylation of the enolizable ketone **33** obtaining a complex mixture of unidentifiable products (entry 4).

[110] Zhang, C.; Ji, W.; Liu, Y. A.; Song, C.; Liao, X. *J. Nat. Prod.* **2018**, *81*, 1065−1069.
[111] Zhu, L.; Li, C. *Tetrahedron Lett.,* **2015**, *56*, 4331−4333.
[112] Zaid, Y.; Mboyi, C. D.; Drapeau, M. P.; Radal, L.; Chahdi, F. O.; Rodi, Y. K.; Ollevier, T.; Taillefer, M. *Org. Lett.* **2019**, *21*, 1564−1568.

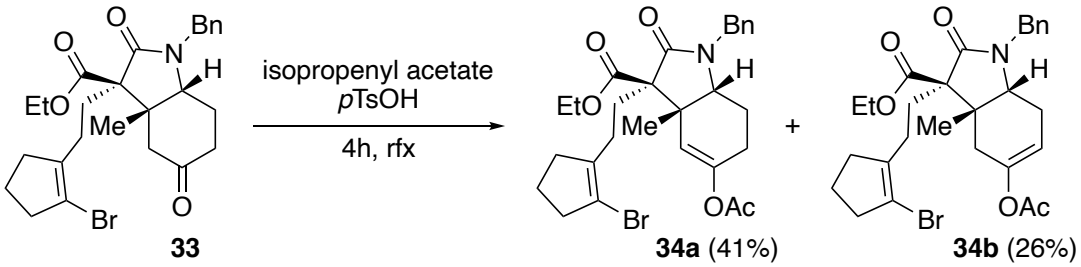
Table 3. 2. *Attempts for the D-ring cyclization*[a]



Entry	Reagents and conditions	Products[b]
1	$PdCl_2(dppf)\cdot DCM$, K_2CO_3, MeOH, 1 h, 70 ºC	SM
2	PhOK, $Pd(PPh_3)_4$ THF, 4 h, 80 ºC	SM
3	CuI, Cs_2CO_3, Ligand, dioxane, overnight, rfx	SM
4	*t*-BuOK, NMP, 70 ºC, 1 h	--

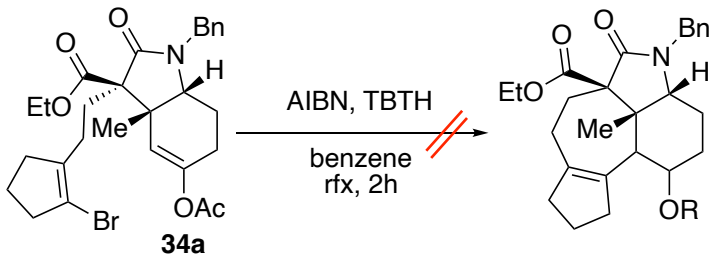
a. 0.02–0.03 mmol scale. b. Observed in the NMR of the crude

Based on the lack of cyclization product employing conditions where the enolate was generated *in situ*, we prepared a substrate already bearing the double bond. Hence, ketone **33** was treated with isopropenyl acetate in the presence of *p*TsOH,[94] to obtain a mixture of both enol acetate regiosiomers, **34a** and **34b** in 67% overall yield (Scheme 3.8).



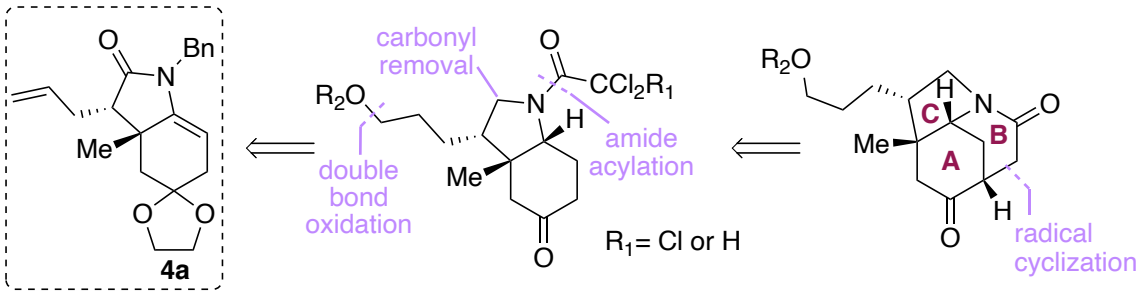
Scheme 3. 8. *Enol acetate preparation*

Next, we examined the ring D cyclization from enol acetate **34a** (Scheme 3.9). However, when the reductive radical conditions described by Ding et al.[96a] were applied, only starting material was recovered. Increasing the equivalents resulted in a complex mixture of compounds and with no evidence of product formation.



Scheme 3. 9. *Reductive radical conditions for radical cyclization*

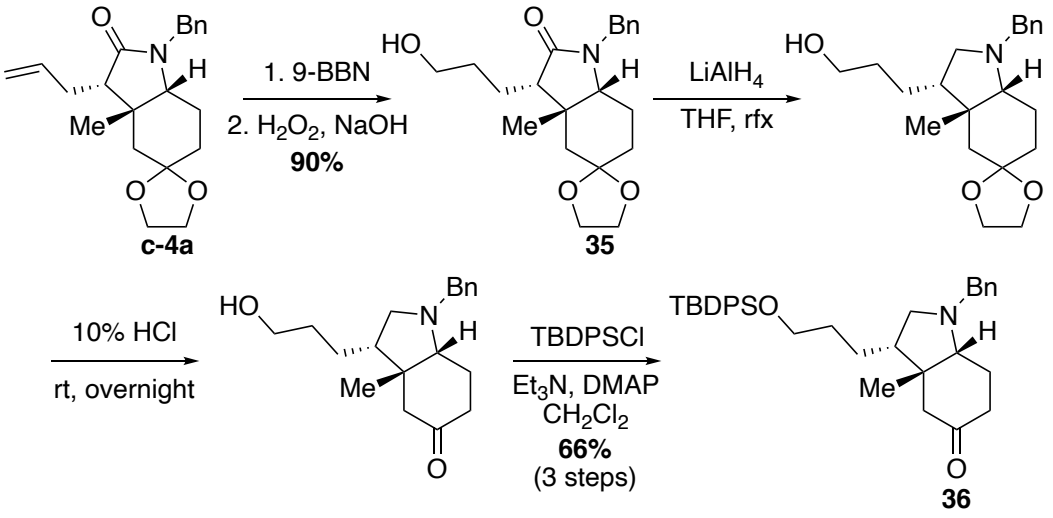
At this point, in which the laborious synthesis of intermediate **33** prevented the study of the radical cyclization for the B-ring, we decided to restart the synthesis from enelactam **4a** which was obtained in excellent yields. Additionally, the allylic C-3 substituent was suitable for the required modifications toward the synthesis of the natural product (Scheme 3.10).



Scheme 3. 10. *Retrosynthetic analysis for ABC ring construction through radical cyclization from* ***4a***

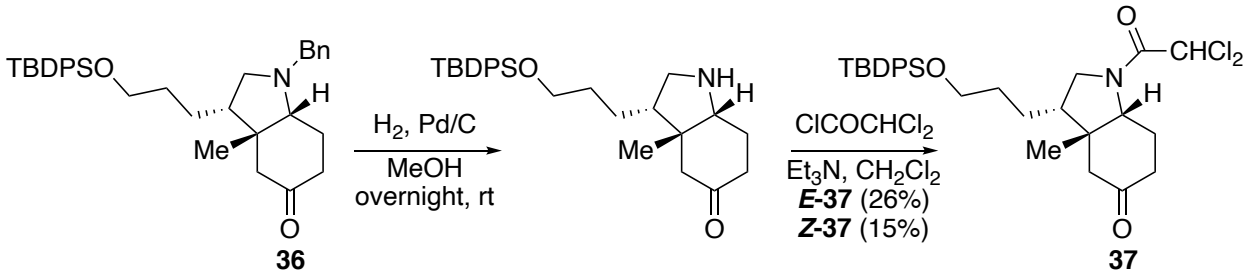
We started with the enamide double bond reduction from enelactam **4a** to obtain octahydroindole **c-4a** as explained in Chapter 2 (Scheme 3.11). Then, the allyl derivative was submitted to hydroboration-oxidation sequence with 9-BBN and H_2O_2,[64b] to provide the bicyclic alcohol **35** in 90% yield. Next, the lactam carbonyl group was reduced by treatment with $LiAlH_4$,[94] followed by ketal hydrolysis in acidic medium. The remaining primary alcohol was protected using TBDPSCl in the presence of Et_3N and DMAP, [113] to afford keto-amine **36** in 66% yield over the 3 steps.

[113] a) Ireland, R. E.; Obrecht, D. M. *Helv. Chim. Acta.* **1986**, *69*, 1273–1286. b) Clode, D. M.; Laurie, W. A.; McHale, D.; Sheridan, J. B. *Carbohydr. Res.* **1985**, *139*, 161–183.



Scheme 3.11. *Preparation of octahydroindole* ***36***

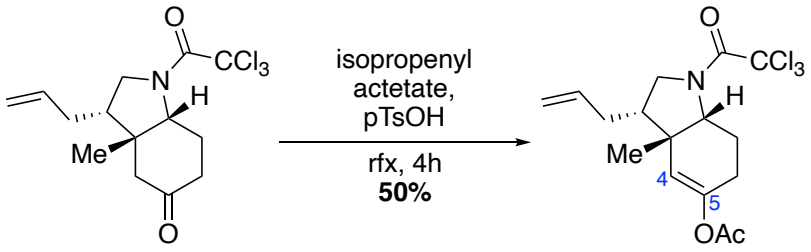
Then, we proceeded with the removal of the benzyl group by hydrogenation conditions and the resulting secondary amine was converted to dichloroacetamide **37** in 41% yield. Interestingly, during the purification process, both *E*- and *Z*-rotamers were separated with 26% and 15% yield respectively.[114]



Scheme 3. 12*. Preparation of dichloroacetamide* ***37***

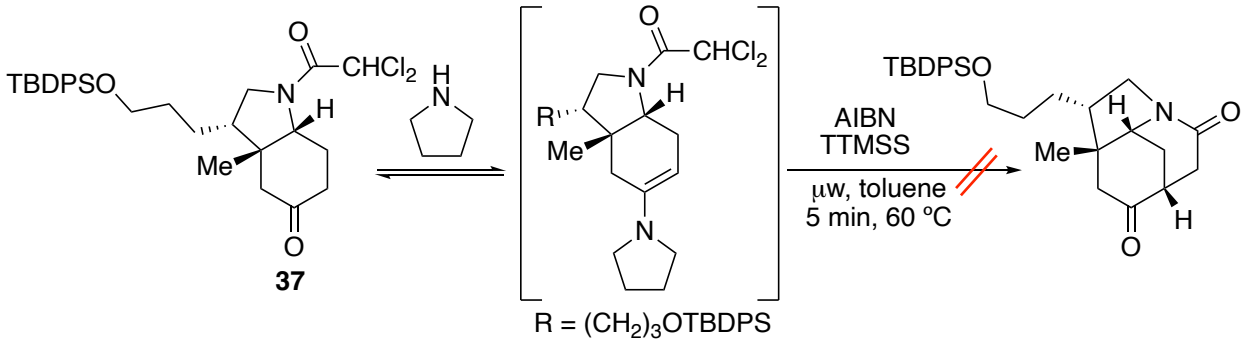
To achieve the radical closure of the B-ring, a double bond at C5-C6 was necessary to act as the radical acceptor. Previous studies in our research group,[64a] supported with calculations,[94] revealed that the preparation of a silyl enol ether from a trichloroacetamide derivative resulted in the thermodynamically more stable position of the electron-rich alkene at the C4-C5 (Scheme 3.13). Moreover, even with different substituents at C-3, the recovered compounds had the same double bond disposition.

[114] Assignation of the rotamers was based in the data reported in the work of the research group: Quirante, J.; Escolano, C.; Merino, A.; Bonjoch, J. *J. Org. Chem.* **1998**, *63*, 968–976.



Scheme 3. 13. *Previous studies of the research group regarding the enolate acetate formation*[64a]

Additionally, in 2016, in our research group a methodology for the radical cyclization of dichloroacetamide-tethered ketone through an enamine intermediate generated *in situ* was reported.[115] This strategy was considered as a suitable process for the present substrate **37** since equilibrium conditions could provide the required enamine for the radical ring closure. However, when dichloroacetamide **37** was submitted to the reported conditions, with AIBN and TTMSS in the presence of pyrrolidine, only chlorine reduction products were recovered in low yields (Scheme 3.14).

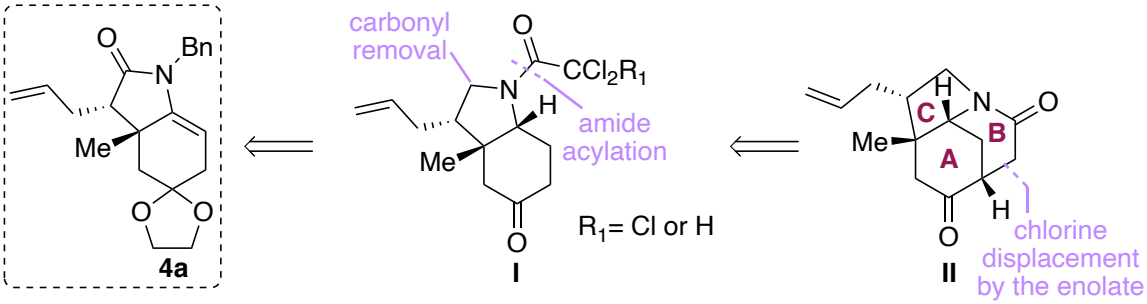


Scheme 3.14*. Attempt for a radical cyclization of* ***37***

3.2.2 Non-radical strategies for the B-ring closure

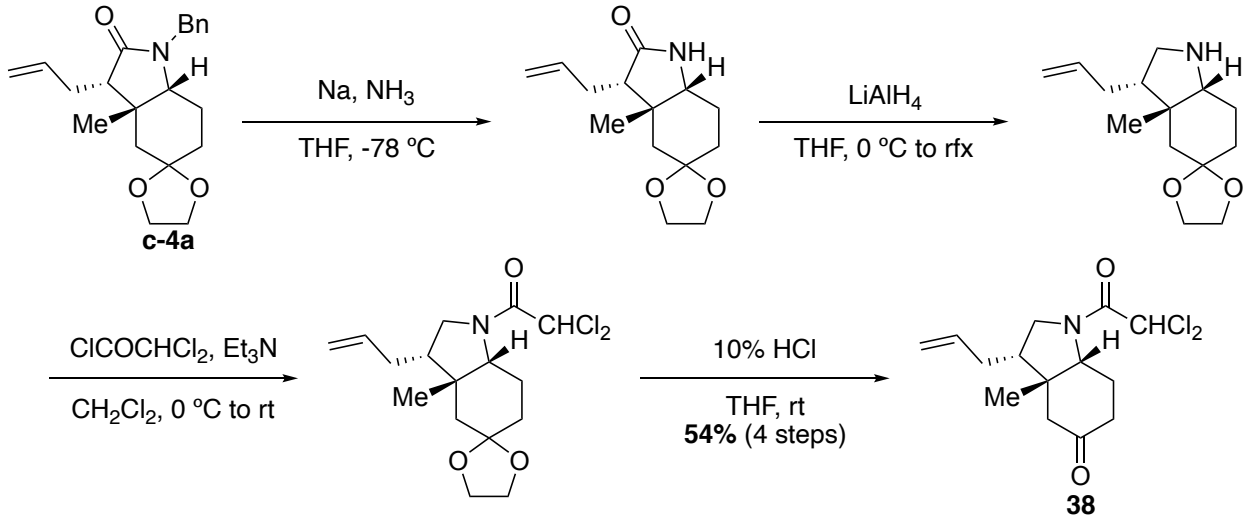
On account of the unsatisfactory results for the B-ring construction through radical processes, alternative approaches were planned. First, taking advantage of chloroacetamide intermediates prepared above, we envisioned an ionic ring closure by means of ketone-enolate attack to the amide α-carbon to displace a chlorine atom (Scheme 3.15).

[115] Diaba, F.; Montiel, J. A.; Bonjoch, J. *Chem. Commun.* **2016**, *52*, 14031–14034.



Scheme 3.15. *Plan for the obtention of tricyclic structure through and enolate.*

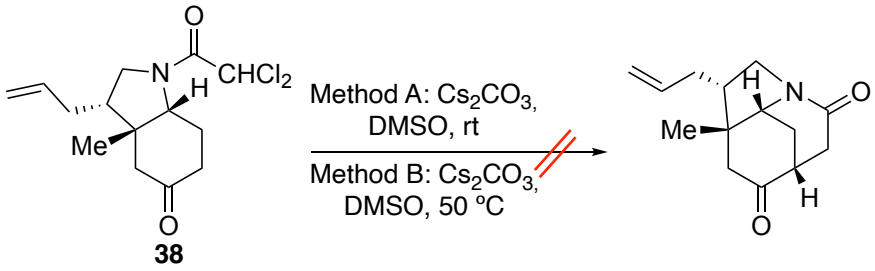
Thus, readily available octahidroindole **c-4a** was treated with Na/NH_3 for benzyl group removal.[94] Subsequent lactam reduction afforded the secondary amine which was acylated with dichloroacetyl chloride in the presence of Et_3N. Final ketal hydrolysis afforded dichloroacetamide **38** in 54% yield over the 4 steps.



Scheme 3.16. *Prepartion of dichloroacetamide **38***

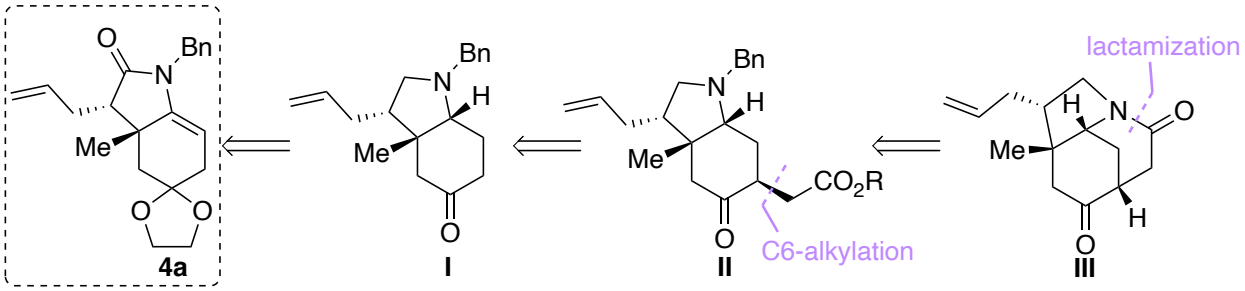
Next, inspired by the work reported by Takiguchi and Inaba,[116] **38** was treated with Cs_2CO_3 in DMSO at room temperature, but no cyclization product was observed. Raising the reaction temperature to 50 ºC also resulted in the recovery of the starting material (Scheme 3.17).

[116] Takiguchi, H.; Higashi, A.; Watanabe, T.; Takeichi, T.; Shimazaki, T.; Inaba, T. *Org. Process Res. Dev.* **2021**, *25*, 342–348



Scheme 3.17. *Attempts for the enolate attack to the α-carbonyl of the lactam moiety.*

Second, an alternative strategy was set out based on the installation of a chain at C6 with a carbonyl moiety capable of undergoing a lactamization reaction with the amino group for the ring B closure. (Scheme 3.18)

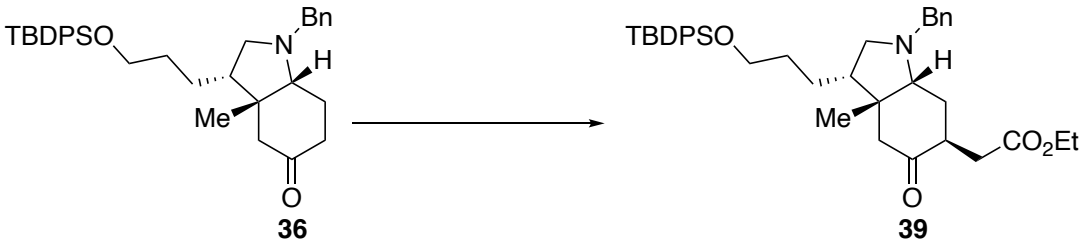


Scheme 3.18. *Ring-B closure through a lactamization process*

Taking advantage of the previously prepared compound **36**, we studied the ketone enolate alkylation reaction with ethylbromoacetate (Table 3.3). First, based on Xu's protocol,[117] LDA was employed in the presence of DMPU, and the alkylated product was isolated in 33% yield (entry 1). Next, a run without DMPU was performed to test its role in the reaction and the yield decreased to 28% (entry 2).[118] Changing the base to KHMDS,[119] provided similar results than LDA recovering the alkylated product in 23% yield (entry 3). Following Thomas *et al*. work,[120] HMPA was tested as an additive to the reaction, and no product formation was observed (entry 4). Finally, we examined the alkylation through an enamine intermediate with pyrrolidine applying the procedure described by Fukuyama,[121] but only starting material (SM) was recovered (entry 5).

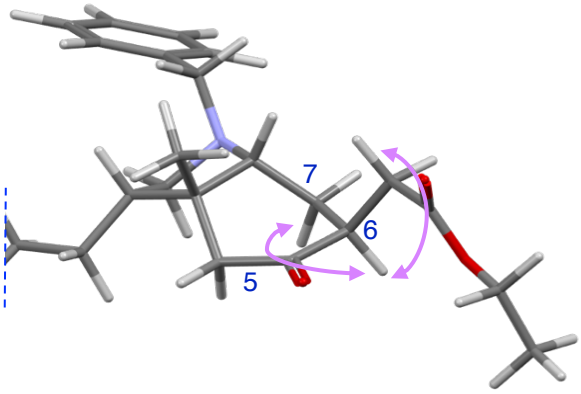
[117] Chen, Y.; Gup, L.-D.; Xu, J. *Tetrahedron Lett.* **2021**, *71*, 153030–153034.
[118] Chen, J.; Xie, Y.; Chen, J.; Zhang, H. *Tetrahedron*, **2015**, *71*, 3747–3755.
[119] Baylis, A. M.; Davies, M. P. H.; Thomas, E. J. *Org. Biomol. Chem.* **2007**, *5*, 3139–3135.
[120] Tang, M.; Fan, C.-A.; Zhang, F.-M.; Tu, Y.-Q. *Tetrahedron*, **2009**, *65*, 5716–5719.
[121] Umihara, H.; Yokoshima, S.; Inoue, M.; Fukuyama, T. *Chem. Eur. J.* **2017**, *23*, 6993–6995.

***Table 3.3**. Attempts for C-6 chain installation*



Entry	Reagents and conditions	Yield[b]
1	LDA, DMPU, ethylbromoacetate, THF, - 78 ºC	33% (45% brsm)
2	LDA, ethylbromoacetate, THF, - 78 ºC	28% (35% brsm)
3	KHMDS, ethylbromoacetate, THF, -78 ºC to rt	23%
4	LHMDS, HMPA, ethylbromoacetate, THF, -78 ºC to rt	SM
5	Pyrrolidine, ethylbromoacetate, benzene/EtOH rfx to rt	SM

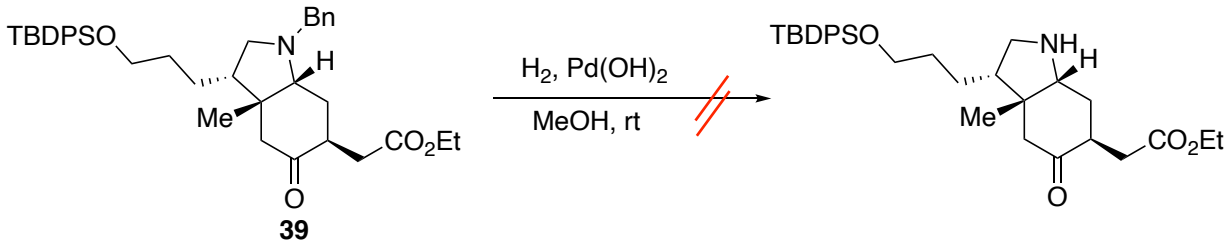
a. 0.1–0.2 mmol scale. b. Isolated yield



The ^{1}H NMR signal for H-6 appeared as a ddddd, which is the result of its coupling with four protons with small coupling constants. This effect would correspond to an equatorial disposition of H-6 and an axial orientation of the introduced chain.

Figure 3. 2.** Structure of the bicyclic core from **39

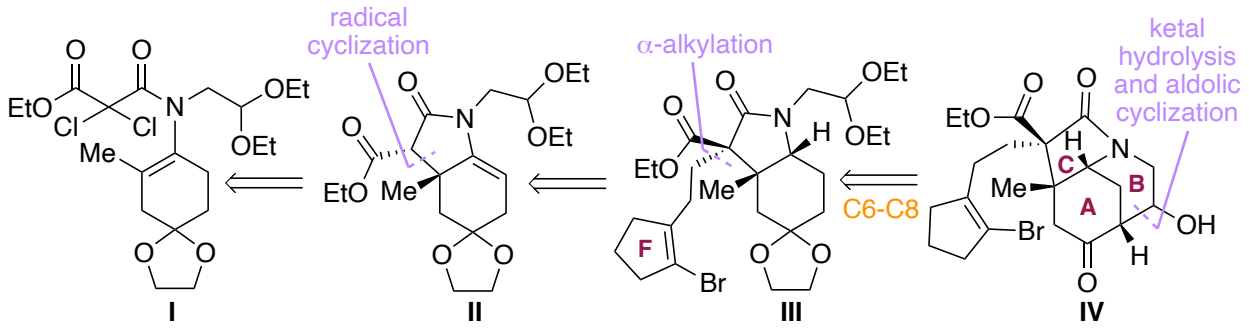
We proceeded with hydrogenation conditions for the debenzylation process in which after the purification process no secondary amine was perceived (Scheme 3.19). Moderate yields for C6-chain installation and no result for the *N*-debenzylation resulted in a non-reliable strategy for the azatricyclic ABC construction.



***Scheme 3.19.** Debenzylation process of **39** by hydrogenation conditions*

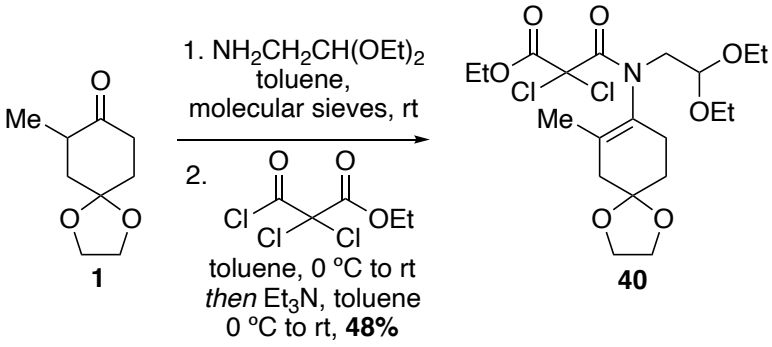
3.2.3 Aldolic strategy for the B-ring closure

Inspired by the previous work of the research group regarding the asymmetric synthesis of 2-azabicyclo[3.3.1]nonanes,[122] we envisioned a new approach for the ring B closure by means of an aldolic cyclization (Scheme 3.20). Hence, we planned to achieve the targeted tricyclic ring core **IV** through aldol reaction of a highly functionalized enelactam **III** containing the protected ketone and aldehyde moieties. Based on the previous studies in this Chapter (3.2.1), we intended to synthesize **III** with a substituent at C-3 bearing the F-ring from enelactam **II** obtained by radical cyclization of **I**. The intermediate **I** could be prepared as the previously reported dichloroacetamide **16** (Chapter 2) differing from the employed primary amine for the imine generation step.



Scheme 3.20. *Strategy for the ABC-tricyclic ring synthesis through an aldol cyclization*

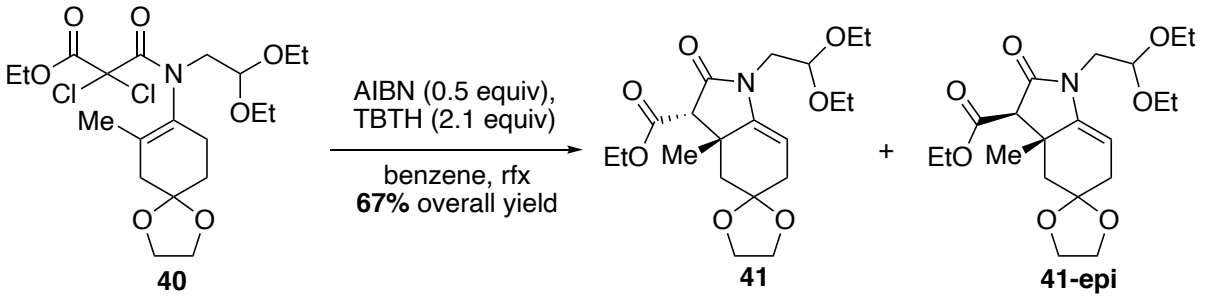
Therefore, methyl cyclohexanone **1** was treated with aminoacetaldehyde diethylacetal, and further acylation with the previously prepared acyl chloride **B** provided trichloroacetamide **40** in 48% yield.



Scheme 3.21. *Preparation of the dichloroacetamide **40**.*

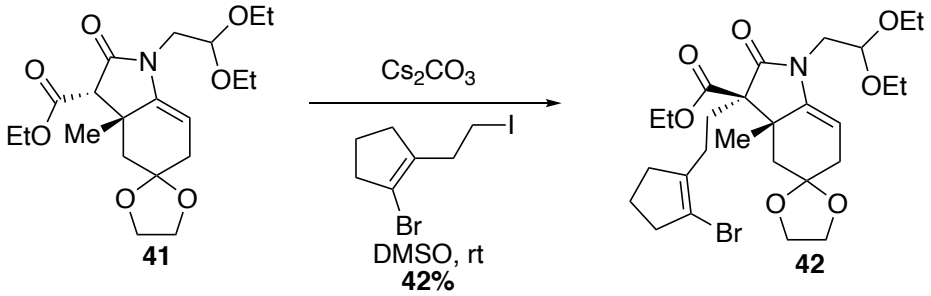
[122] Diaba, F.; Bonjoch, J. *Org. Biomol. Chem.* **2009**, *7*, 2517–2519.

Then, **40** was submitted to the optimized radical conditions applied for dichloroacetamide **16** in Chapter 2 (Table 2.3). Enelactam **40** was obtained in pure samples along with epimeric mixtures of **41** and **41-epi**. NMR yield from the latter allowed to determine that **41** was obtained in 50% yield and **41-epi** in 17% yield.



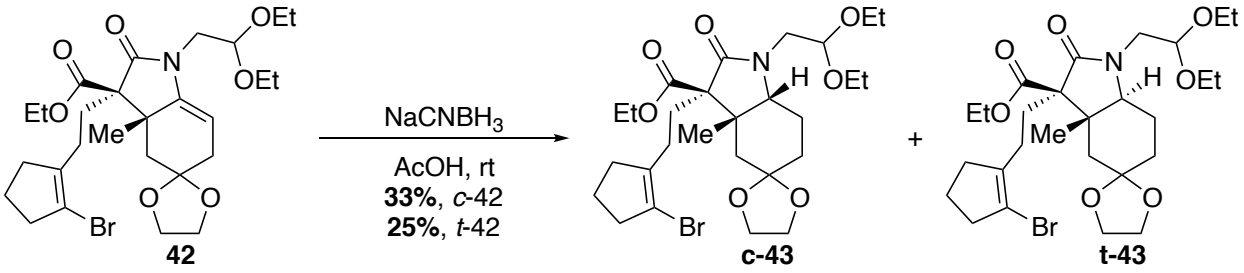
Scheme 3.22. *Radical cyclization of dichloroacetamide **40**.*

Next, the optimized conditions for the previously studied alkylation of enelactam **7a** (Table 3.1) were tested over bicyclic intermediate **41**. Treatment with Cs_2CO_3 and subsequent addition of iododerivative **30** gave alkylated enelactam **42** in 42% yield.



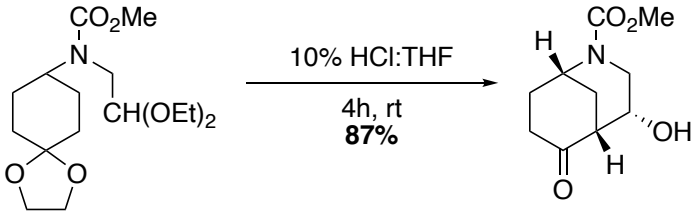
Scheme 3.23. *Alkylation reaction for the incorporation of the chain containing the F-ring.*

Surprisingly, reduction of the enamide double bond with $NaCNBH_3$ in AcOH gave both C-7a diastereoisomers. Recovery of the *trans* junction octahydroindole could arise from an anchimeric assistance by oxygen atoms from the acetal groups.



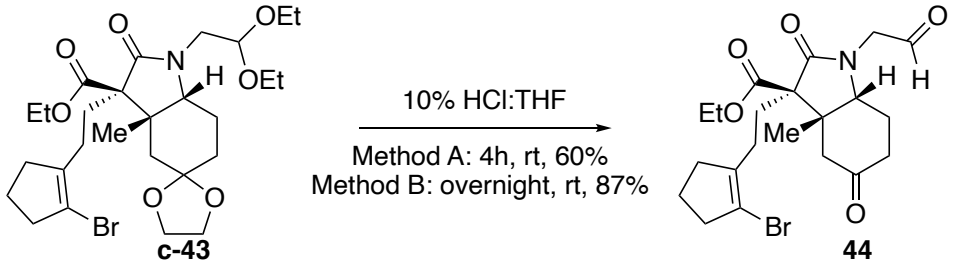
Scheme 3.24. *Reduction of the enelactam double bond*

Regarding the studies from the research group,[122] the racemic formation of 2-azabicyclo-[3.3.1]-nonanes could occur directly from the protected compound. Treatment with 10% HCl:THF promoted concomitant deprotection and aldolic cyclization (Scheme 3.25).



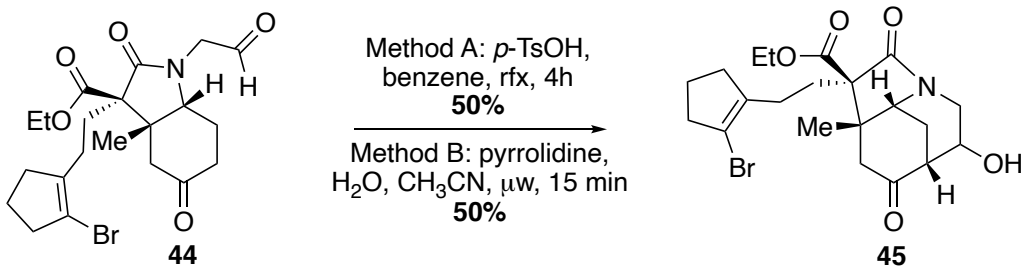
***Scheme 3.25**. Methodology for concomitant deprotection and aldolic cyclization reported by the research group.[122]*

Applying this methodology to the substrate **c-43**, with the desired C-7a configuration, resulted only in the hydrolyzed compound **44**, but no cyclization product was isolated. (Scheme 3.26). Increasing the reaction time also provided **44** in 87% yield.



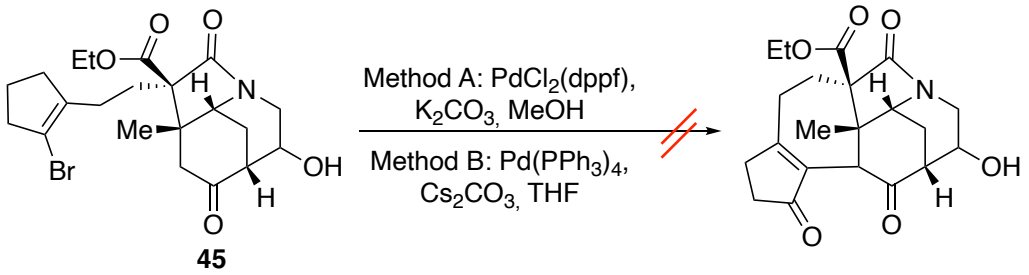
Scheme 3.26.** Application of the reported methodology to **c-43

Since substrate **c-43** did not undergo the aldolic cyclization in the presence of 10% HCl, we investigated more energetic conditions. (Scheme 3.27) Thus, when **44** was treated with *p*-TsOH in refluxing benzene, tricyclic product **45** was obtained in 50% yield.[94] Organocatalyzed conditions for the aldolic cyclization with a racemic protocol were tested by treatment of **44** with pyrrolidine, in the presence of water, which provided tricyclic **45** in 50% yield. This result set the possibility to perform the reaction through an organocatalyzed asymmetric approach by employing chiral proline derivatives as described by the research group for the 2-azabicyclo[3.3.1]-nonanes synthesis.[122]



Scheme 3.27**. Aldolic cyclization of **43** leading to the tricyclic compound **44

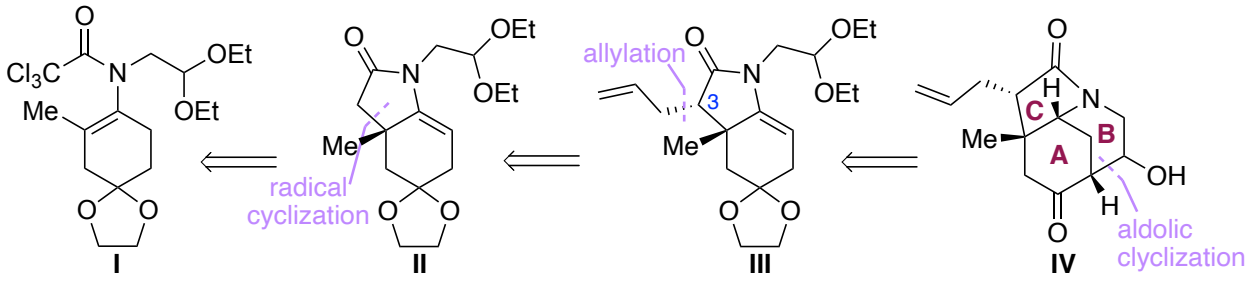
At this point, we addressed the last 7-membered D-ring closure employing methodologies for Pd-alkenylation of enolizable ketones. However, either treatment of **45** with $PdCl_2(dppf)\cdot CH_2Cl_2$ with K_2CO_3 as a base or $Pd(PPh_3)_4$ with Cs_2CO_3[123] as base in THF resulted in complex mixture of unidentifiable products.



***Scheme 3.28**. Attempts for the Pd-catalyzed cyclization of D-ring*

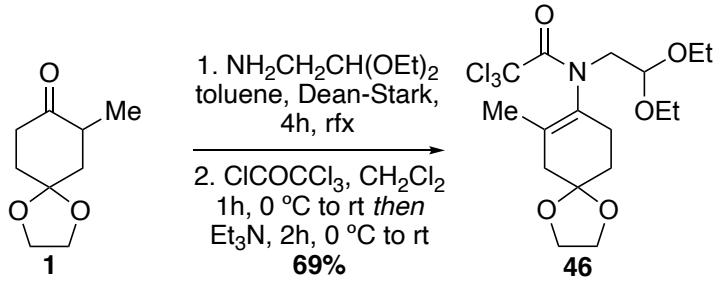
In summary, the synthesis of the tricyclic ABC ring core through an aldolic cyclization for the ring B closure proved to be a reliable methodology. Nonetheless, the obtention of the highly functionalized tricycle **45** gave moderate yields in crucial steps which prevented the study of a further synthetic route. Therefore, we planned a new approach where the tricyclic system would be achieved by cyclization of **III** (Scheme 3.29). We envisaged that enelactam **III** preparation would provide better yields for the C-3 substituent installation by employing the more reactive allyl bromide reagent. Required bicyclic compound **II** could be easily obtained from trichloroacetamide **I** by means of the radical cyclization protocol.

[123] Solé, D.; Diaba, F.; Bonjoch, J. *J. Org. Chem.* **2003**, *68*, 5746–5749.



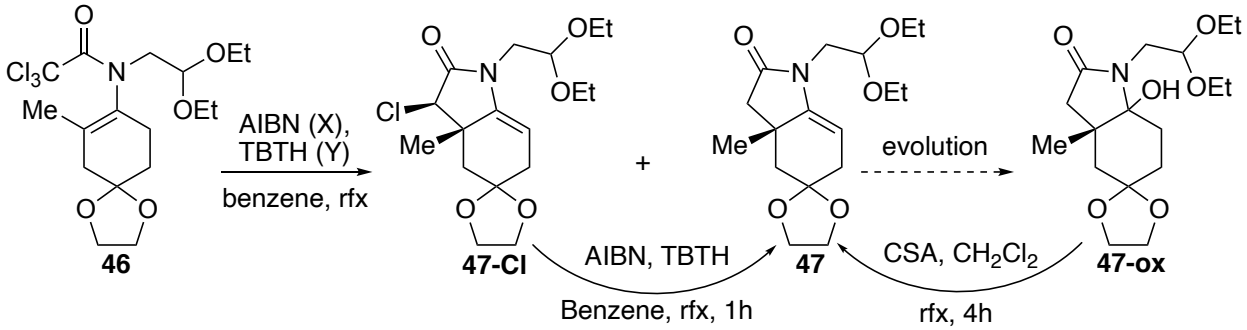
Scheme 3. 29. *New retrosynthetic plan for the tricyclic ABC obtention through an aldolic cyclization*

We commenced as previously, treating methyl ketone **1** with aminoacetaldehyde diethylacetal which generated an imine that was acylated with trichloroacetyl chloride to achieve trichloroacetamide **46** in 69% yield.



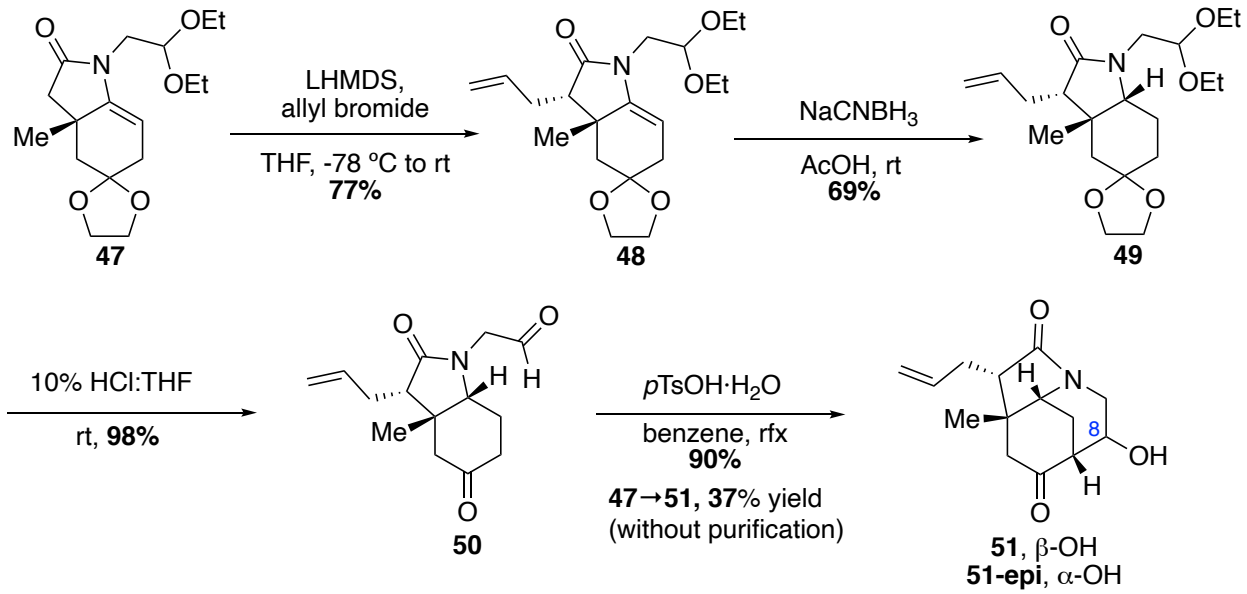
Scheme 3. 30. *Trichloroacetamide **45** preparation.*

Then, trichloroacetamide **46** was submitted to radical cyclization conditions employed for trichloroacetamide **2** (Chapter 2) by treatment with AIBN (0.3 equiv) and TBTH (3.2 equiv) (Scheme 3.31.a).[64a] The bicyclic lactam **47** was obtained in 54% yield along with the C3-chlorinated compound **47-Cl** with 17% yield. The byproduct **47-Cl** could be recycled to provide **47** by an additional hour under the same reductive radical conditions. Increasing TBTH and AIBN equivalents avoided the formation of chlorinated product and enelactam **47** was isolated in 79% yield (Scheme 3.31.b). Moreover, as observed in Chapter 2, product **47** evolved during chromatographic purification to the hemiaminal subproduct **47-ox**. Treatment of the latter with CSA in CH_2Cl_2 reflux recovered compound **47**.



Scheme 3. 31. *Radical cyclization of trichloroacetamide **46**. a) X=0.3 equiv, Y=3.2 equiv, **47**: 54% **47-Cl**: 17%. b) X = 0.5 equiv, Y = 3.5 equiv, **47**:79%.*

Next, treatment of **47** with LHMDS and allyl bromide provided diastereoselectively with C-3 substituted enelactam **48** in 77% yield. Enamide double bond reduction with $NaCNBH_3$ in AcOH achieved the highly functionalized *cis*-octahydroindole **49** with good yields. Then, as observed with product **c-43**, treatment of **49** with 10% HCl in THF resulted in the recovery of the hydrolyzed compound **50**. Thus, further aldolic cyclization was performed in 15 min in the presence of *p*-TsOH·H_2O to construct the tricyclic ABC-core of **51**.[94] A rapid four-step sequence, from **47** to **51**, bypassing purification process was tested, but the overall yield was lower (37% vs. 47%) and did not imply an improved timesaving.



Scheme 3. 32. *Synthesis of tricyclic alcohol **51***

The latter aldolic cyclization process resulted in a separable diastereomeric mixture in 82% yield for the major product and 8% for the minor one. Both were identified as epimers at C-8 but either 2D NMR or the comparison of the ^{13}C NMR values with the reported azabycicle,[122] did not provide conclusive evidence to elucidate the configuration of each one (Figure 3.3). In addition, the well-precedented non-chair conformation in the piperidine ring made it difficult to correlate the coupling constants.

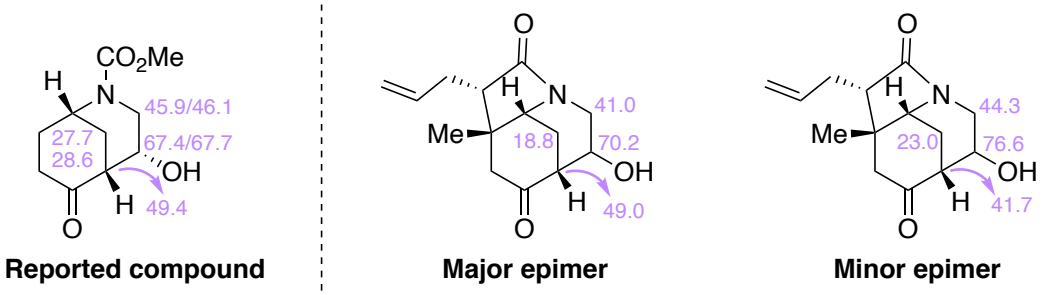


Figure 3.3. *NMR data of both epimers*

Meanwhile, calculations concerning this cyclization step were performed in collaboration with Prof. Enrique Gómez-Bengoa (Figure 3.4). The results revealed a similar energy between the two epimers, meaning that a thermodynamic control of the reaction would lead to an epimeric mixture nearly to 1:1 ratio. Nevertheless, experimentally was observed that only 15 minutes were required for the reaction completion. So, considering a kinetic process, we analyzed the possible transitional states (TS) involving the promoter Brönsted acid (*p*-TsOH). The model showed a preferred disposition that would favor a *Si*-face attack since the corresponding TS1 was 2.3 kcal/mol lower in energy than the *Re*-approach, that could be disfavored by steric and electronic factors. Moreover, the lower energy intermediate originated from the dipole minimized orientation of both carbonyls from the activated aldehyde resulting in an attack of the enol tethered to give majorly **51**. Taking into account the acidic conditions, the reaction would be exothermic by more than 12 kcal/mol which corroborated the non-reversibility of the process (Table 3.4).

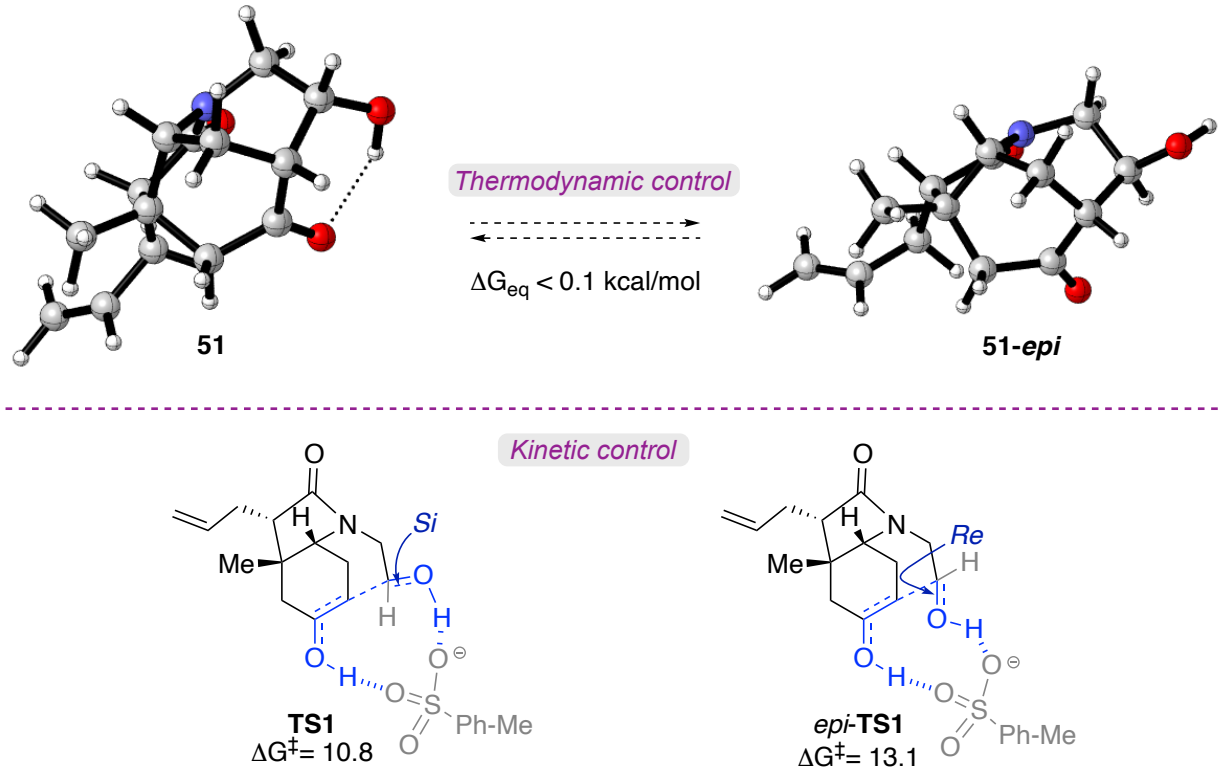


Figure 3. 4. *DFT-calculations performed by Prof. Enrique Gómez-Bengoa.*

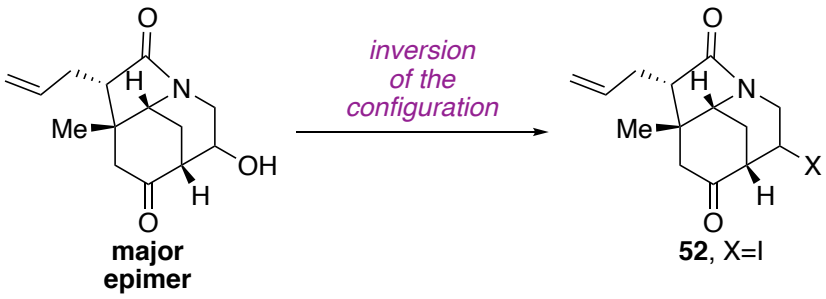
Table 3. 4*. Energies of the compounds from Figure 3.4*[a]

Compound	**G (M06-2X)** (hartree)[b]	**ΔG** (kcal/mol)	**Negative Frequency** (cm^{-1})
51	-824.978625	0	
51-*epi*	-824.978309	0.1	
50-*p*TsOH	-1720.155492	0	
TS1	-1720.138304	10.8	-290.4
***epi*-TS1**	-1720.134628	13.1	-290.9
51-*p*TsOH	-1720.174573	-12.0	
51-*epi*-*p*TsOH	-1720.176310	-13.1	

[a]All structures were optimized using density functional theory (DFT) as implemented in Gaussian 16, with M06-2X as functional, and 6-311++G(d,p) as basis set, introducing solvation factors with the IEF-PCM method, and benzene as solvent, as in the optimized experimental conditions. The stationary points were characterized by frequency calculations in order to verify that they have the right number of imaginary frequencies.[b] 1 hartree = 627.509 kcal/mol.

Parallelly, we attempted to transform the hydroxyl of the major epimer expecting more information about C-8 center. Firstly, substitution conditions implying an inversion of the center configuration were studied (Table 3.5). Bromination either with CBr_4 in the presence of PPh_3 (entry 1), [124] or with NBS,[125] (entry 2) resulted in starting material (SM) recovery. Aiming the hydroxyl substitution for a tosyl group, we employed *p*-TsOH, PPh_3 and DIAD, applying the protocol described by Anderson *et al.*,[126] but no product was observed (entry 3). Chlorine introduction was tested by treatment with $SOCl_2$ but the same previous result was obtained (entry 4).[127] Finally, iodination at C-8 was achieved in 14% yield with I_2/PPh_3/imidazole conditions but, again, no NMR evidence allowed us to establish the center configuration.[128]

Table 3. 5. *Attempts for the group inversión at C-8* [a]



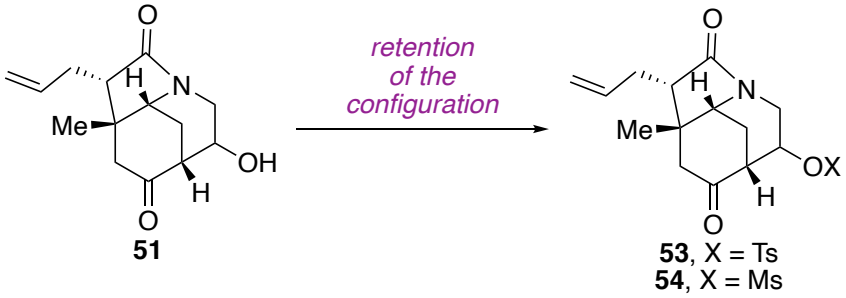
Entry	X	Reagents and conditions	Products (Yield)
1	Br	CBr_4, PPh_3, CH_2Cl_2, 0 ºC to rt	SM
2	Br	NBS, PPh_3, THF, -18 ºC to rt	SM
3	OTs	pTsOH, PPh_3, DIAD, Et_3N, rt to 70 ºC	SM
4	Cl	$SOCl_2$, rt	SM
5	I	I_2, PPh_3, imidazole, toluene, 60 ºC to rfx	**52** (14%)[b]

a. 0.1–0.3 mmol scale. b. Isolated yield

[124] Jansana, S. Ph.D. Thesis, Universitat de Barcelona, Barcelona, Spain, 2019.
[125] Májer, F.; Sharma, R.; Mullins, C.; Keogh, L.; Phipps, S.; Duggna, S.; Kelleher, D.; Keely, S.; Long, A.; Radics, G.; Wang, J.; Gilmer, J. F. *Bioorg. Med. Chem.* **2014**, *22*, 256–258.
[126] Anderson, N. G.; Lust, D. A.; Colapret, K. A.; Simpson, J. H.; Malley, M. F.; Gougoutas, J. Z. *J. Org. Chem.* **1996**, *61*, 7955–7958.
[127] Bansal, R.; Acharya, P. C. *Steroids*, **2012**, *77*, 552–557.
[128] Campbell, J. A.; Lee, W. K.; Rapoport, H. *J. Org. Chem.* **1995**, *60*, 4602–4616.

Since poor results were obtained applying inversion of the configuration conditions, we studied the *O*-derivatization of the hydroxyl over the fractions containing the major epimer (Table 3.6). We started testing *O*-tosylation with *p*-TsCl in pyridine at room temperature but only starting material was recovered (entry 1). Reexamining the bibliography, we observed reported longer reaction times for secondary alcohols with complex tridimensional backbones.[129] Thus, treatment with *p*-TsCl, Et_3N in CH_2Cl_2 for 3 days provided with the tosylate derivative **53** in 70% yield (entry 2). More elaborated methodology adding DMAP to the reaction mixture, used by Mascareñas and Lopez,[130] accelerated the reaction to one overnight and increased the yield to 80% (entry 3). Applying the same optimized procedure using MsCl instead, the mesylate derivative **54** was prepared in 86% (entry 4).

***Table 3. 6**. Attempts for hydroxyl derivatization*[a]



51

53, X = Ts
54, X = Ms

Entry	X	Reagents and conditions	Products (Yield)
1	Ts	pTsCl, pyr, CH_2Cl_2, overnight, rt	SM
2	Ts	pTsCl, pyr, CH_2Cl_2, 3 days, rt	**53** (70%) [b]
3	Ts	pTsCl, Et_3N, DMAP, CH_2Cl_2, overnight, rt	**53** (80%) [b]
4	Ms	MsCl, Et_3N, DMAP, CH_2Cl_2, overnight, rt	**54** (86%) [b]

a. 0.1-3.6 mmol scale. b. Isolated yield

[129] Staas, W. H.; Spurlock, L. A. *J. Org. Chem.* **1974**, *39*, 3822–3828.
[130] Nelson, R.; Gulías, M.; Mascareñas, J. L.; López, F. *Angew. Chem. Int. Ed.* **2016**, *55*, 14359–14363.

Luckily, tosyl derivative **53** was a solid and X-ray crystallography analysis of its enantiomer (***ent*-53**) showed the boat form of the morphan substructure and revealed a *cis* relation between C-6 hydrogen and C-8 tosylate meaning a β-orientation for the latter (Figure 3.4). Assuming, that no inversion at C-8 occurred during tosylation, we established same orientation for C-8 hydroxyl at **51**. Interestingly, the related aldol process for the morphan core, in which the bicyclic system allowed a chair-chair conformation, resulted in reverse diastereoselectivity for the keto-tethered aldehyde cyclization (Figure 3.2).

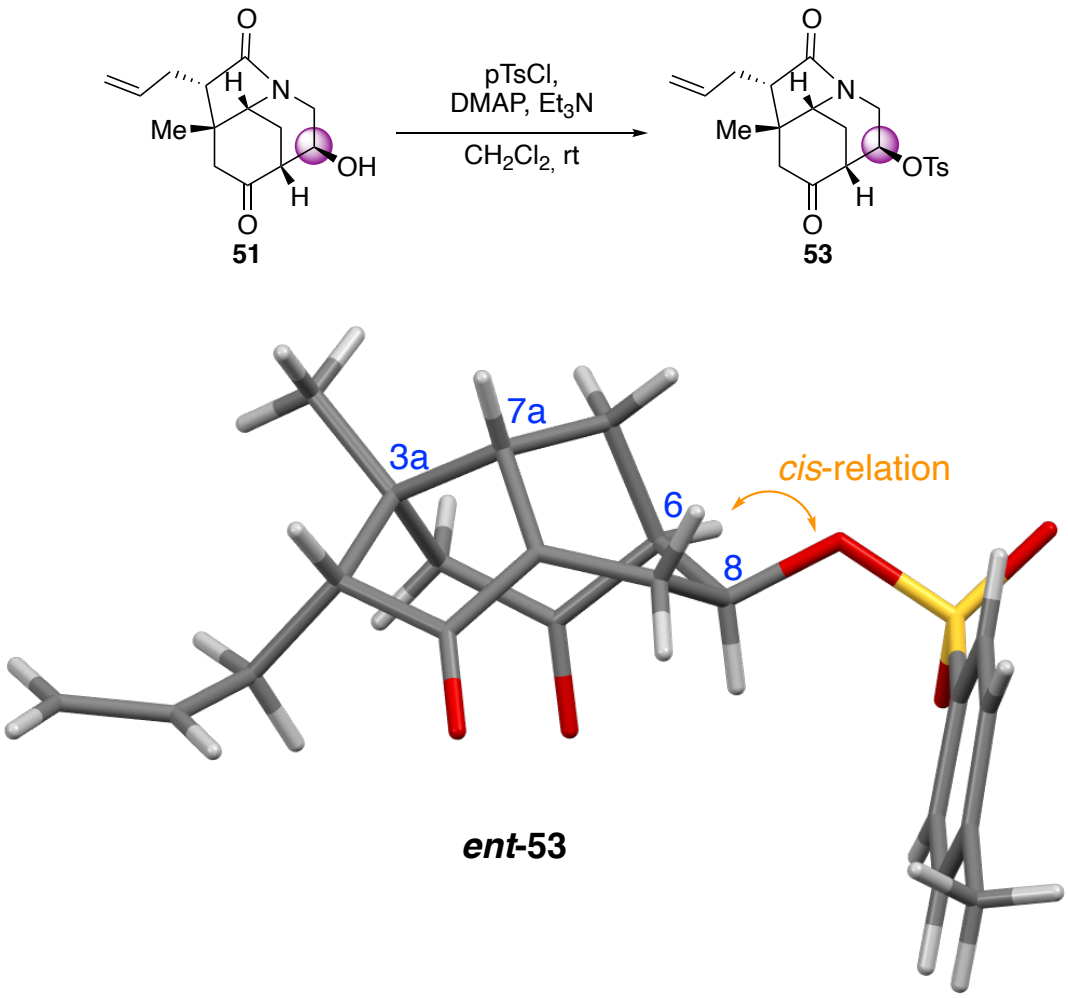
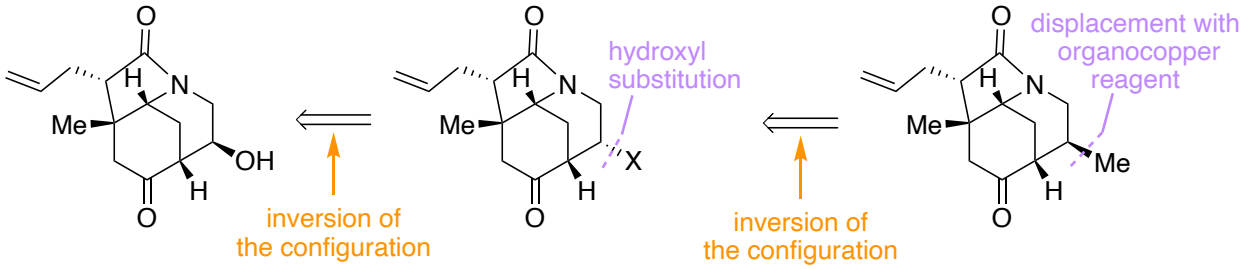


Figure 3.5. *X-ray structure of the enantiomer of tosylate* ***53 (ent-53)***

3.2.3.1 C-8 methyl incorporation

Once we achieved the ABC-tricyclic ring core construction, we proceeded by addressing the next key step for C-8 methyl installation. Both, the desired product and the precursor, had the same C-8 configuration. Thus, we initially planned a two-step sequence based on a double inversion of the configuration through a hydroxyl substitution and subsequent displacement by an organocopper reagent that typically goes through a S_N2 type substitution (Scheme 3.34).

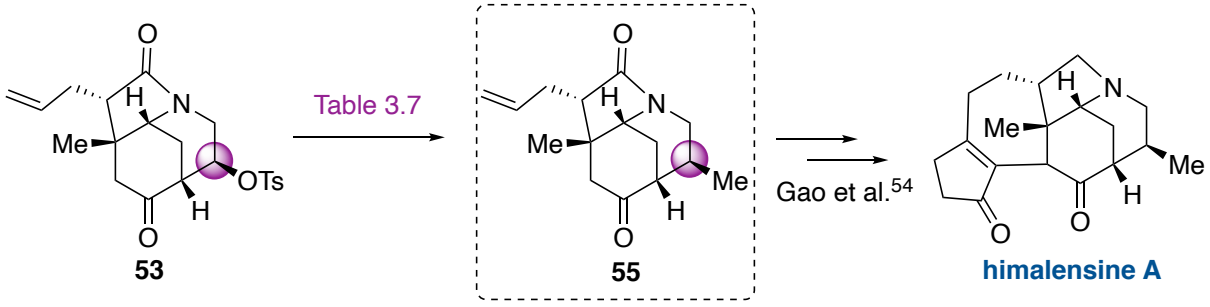


Scheme 3.33. *Inicial plan for C-8 methyl installation*

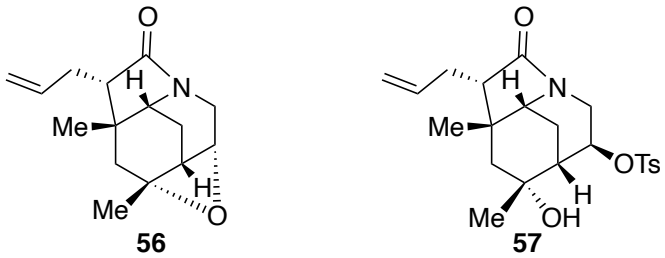
However, hydroxyl substitution conditions for inversion of the configuration gave no successful results (Table 3.4). Prepared tosylate **53** and mesylate **54** had the same β-orientation of both C-8 substituents than the targeted methyl group so, apparently, displacement by organocopper reagent appeared as non-suitable procedure. Even though, we treated tosylate **53** with Gilman's cuprate prepared from CuI and MeLi following the conditions described by Gmeiner,[131] and one major product was recovered in 48% along with a minor one in 21% (Table 3.7, entry 1). The major compound was identified as oxetane **56** originated from a MeLi attack to the carbonyl and subsequent tosylate displacement by the formed alkoxide. Luckily, NMR characterization of the minor product **55** was coincident with the data reported by Gao for the intermediate obtained in his work *en route* to the total synthesis of himalensine A (Chapter 1, Scheme 1.14). [54] Hence, we could assign the desired β-orientation at C-8 for the obtained tricyclic compound **55** which implied a retention of the configuration process from **53**. Moreover, synthesis of **55** represented a formal synthesis of Himalensine A, therefore, we tried to optimize the reaction conditions (Table 3.6).

[131] Heindl, C.; Hübner, H.; Gmeiner, P. *Tetrahedron:Asymmetry*, **2003**, *14*, 3153–3172.

Table 3.7. *Optimization of C-8 methyl installation*[a]



53 **55**



56 **57**

Entry	Reagents	Conditions	Products (Yield)
1	CuI (11), MeLi (22)	Et_2O, -20 ºC → 0 ºC	**55**:**56** (1:2)[b]
2	CuI (10), MeLi (18)	Et_2O, -20 ºC → 0 ºC	**55** (51%), **53** (26%)[c]
3	CuI (15), MeLi (28)	Et_2O, -20 ºC → 0 ºC	**55**:**53** (1:1)[b]
4	CuI (22), MeLi (42)	Et_2O, -20 ºC → 0ºC	--
5	CuI (10), MeLi (18)	Et_2O, -15 ºC → rt	**55** (13%), **56** (48%)[c]
6	CuBr·SMe_2 (10), MeLi (18)	Et_2O, -20 ºC → 0 ºC	**55** (22%)[c]
7	CuBr·SMe_2 (10), MeLi (18)	Et_2O, -15 ºC → rt	**56**[b]
8	CuI (15), MeLi (20), then O_2	Et_2O, -20 ºC → 0 ºC	--
9	CuI (15), MeLi (20), then $CuCl_2$	Et_2O, -20 ºC → 0 ºC	**55** (39%)[c]
10	MeLi (1), HMPA (1)	THF, -78 ºC	**57** (36%)[c]

a. 0.05–0.3 mmol scale. b. NMR of the crude. c.Isolated yield.

We started by adjusting the equivalents of CuI and MeLi for the Gilman's cuprate preparation to avoid the formation of compound **56**. When a small excess of CuI was used to assure the non-presence of free MeLi, the product **55** was obtained in 51% along with starting material in 26% yield, and oxetane derivative was not observed (entry 2). Maintaining reagents ratio, but increasing the equivalents, resulted in a less product **55** formation with 1:1 ratio of **55**:**53** (entry 3). Considerably higher quantities of CuI and MeI

provided a complex mixture of unidentifiable products (entry 4). Then, the reaction temperature was raised and the oxetane compound **56** was recovered as the major product along with a small quantity of the desired **55** (entry 5). Changing the cupper(I) source by employing $CuBr{\cdot}SMe_2$,[130] resulted in the product **55** isolation in 22% yield (entry 6) and, under the same conditions but at room temperature, only **56** was recovered (entry 7). On the first studies of this reaction performed by Whitesides and House, they reported the existence of two competitive processes: coupling reaction and metal-halogen exchange.[132] When the latter occurred, addition of an oxidant to the reaction allowed the obtention of coupled products in high yields. Thus, we added oxygen at -78 ºC to the reaction medium but a complex mixture of products was recovered (entry 8). However, when $CuCl_2$ was used as the oxidant, the product formation occurred in 39% yield (entry 9). Finally, in 2014, Danishefsky reported a bromide displacement at a bridged α-carbon of a ketone directly with MeLi in the presence of HMPA.[133] Even though, when the procedure was applied to **53** only the product **57** was recovered originated from a MeLi attack to the carbonyl but with no further tosylate displacement.

Although nucleophillic displacement of alkyl halides by organocopper reagents typically occurs through a S_N2 process there are few reported examples in which retention of the configuration is the stereochemical outcome.[134] Over the literature, no clear mechanism was established but some speculative proposals were exposed.[135] Firstly, considering a single-electron transfer (SET) process, after the radical formation of the substrate, the retention of the configuration product could originate from the methyl incorporation from the les sterically demanding convex face. Additionally, Ashby described that the reaction could change from polar to SET by varying the reaction factors.[136]

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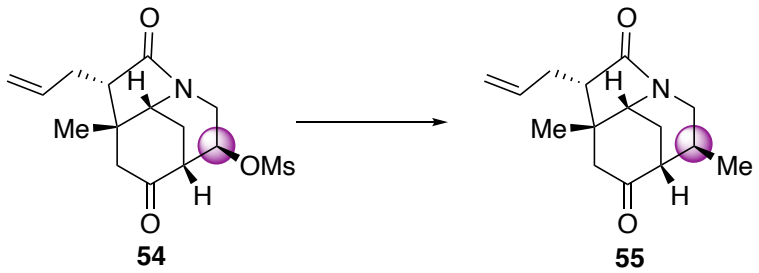
[132] Whitesides, G. M.; Fischer, W. F.; San Filippo, J.; Bashe, R. W.; House, H. O. *J. Am. Chem. Soc.* **1969**, *104*, 4696–4698.
[133] Townsend, S. D.; Ross, A. G.; Liu, K.; Danishefsky, S. J. *PNAS*, **2014**, *111*(22), 7931–7935.
[134] a) Thottathil, K.; Moniot, J. L. *Tetrahedron Lett.* **1986**, *27*, 151–154. b) Hashimoto, K.; Shirahama, H. *Tetrahedron Lett.* **1991**, *32*, 2625–2628. c) Anderson, J. C.; Whitting, M. *J. Org. Chem.* **2003**, *68*, 6160–6163. d) Poisson, J.-F.; Orellana, A.; Greene, A. E. *J. Org. Chem.* **2005**, *70*, 10860–10863.
[135] Johnson, C. R.; Dutra, G. A. *J. Am. Chem. Soc.* **1973**, *95*, 7783–7788
[136] Ashby, E. C. *Acc. Chem. Res.* **1988**, *21*, 414–421.

Another hypothesis could be the participation of a neighboring group such as the amide motif. Staas *et al.*,[137] described a tosylate group substitution by an acetyl moiety with retention of the center configuration which they attributed to an assistance of a vicinal amide and subsequent attack of the nucleophile leaded to a double inversion process. They highlighted that the sterical tension of the intermediate, due to the bulky tosyl group, could slow the reaction. Thus, we tested the best conditions for methylation process in Table 3.8 over the smaller mesylate **54**, and the desired compound **55** was obtained along with starting material in 1:1 ratio. (Table 3.8, entry 1). When a longer reaction time was applied, **55** was isolated in 36% yield (entry 2). Additionally, we tested $AlMe_3$ to act as the nucleophile instead of the Gilman's cupprate but only the oxetane **56** was recovered.[138]

Table 3.8. *Installation of methyl at C-8 from mesylate derivative* ***53***[a]



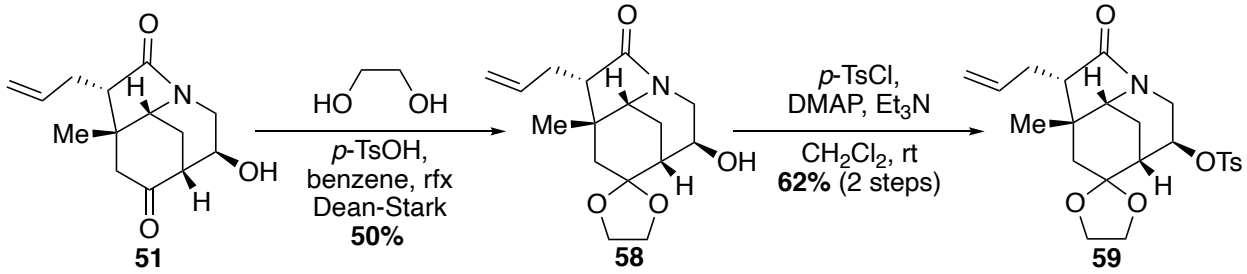
Entry	Reagents (equiv.)	Conditions	Products (Yield)
1	CuI (10), MeLi (18)	Et_2O, -20 ºC → 0 ºC, 2h	**54**:**55** (1:1)[b]
2	CuI (10), MeLi (18)	Et_2O, -20 ºC → 0 ºC, 6h	**55** (36%)[c]
3	$AlMe_3$ (3)	CH_2Cl_2, -78 ºC → rt	**56**[a]

a. 0.2–0.7 mmol scale. b. Observed in the NMR of the crude. c. Isolated yield

Finally, the last proposal was based on an elimination of the tosylate group generating a conjugated enone at the bridgehead position.[139] Further conjugated attack of the Gilman's cuprate to the planar C(sp^2) would lead to a β-orientation of the entering methyl at C-8. To study the importance of the ketone group and to avoid the carbonyl attack side-reaction, the protected tricyclic tosylate **59** was prepared. Protection of the ketone with

[137] Staas, W. H.; Spurlock, L. A. *J. Org. Chem.* **1974**, *39*(26), 3822–3828.
[138] Feng, K.; Quevedo, R. E.; Kohrt, J. T.; Oderinde, M. S.; Reilly, U.; White, M. C. *Nature*, **2020**, *580*, 621–627.
[139] Penny, M.; Willis, C. L. *J. Chem. Soc., Chem. Commun.* **1993**, 1111–1112.

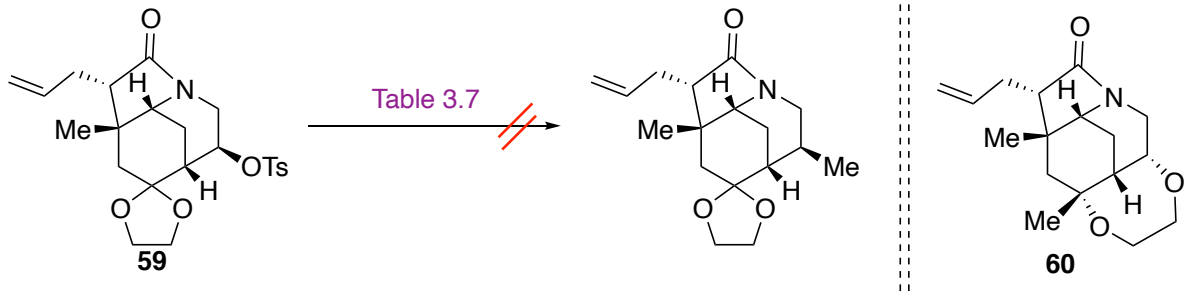
ethylene glycol and catalytic *p*-TsOH, afforded **57** which, after applying the optimized tosylation conditions, **58** was obtained in 62% yield. (Scheme 3.35).



Scheme 3.34. *Prepartion of compound **59***

Next, the protected tosylate **59** was submitted to the studied displacement process by Gilman's cuprate (Table 3.9). When the best conditions were employed, only starting material was recovered (entry 1), and increasing the temperature resulted in the same outcome (entry 2). Then, $AlMe_3$ was tested as the nucleophile and the unexpected compound **60** was obtained in 34% yield. These results allowed us to conclude that the presence of the ketone was required but we could not discern whether the ketal group was blocking the elimination and conjugate addition process, or the structural change prevented the reaction.

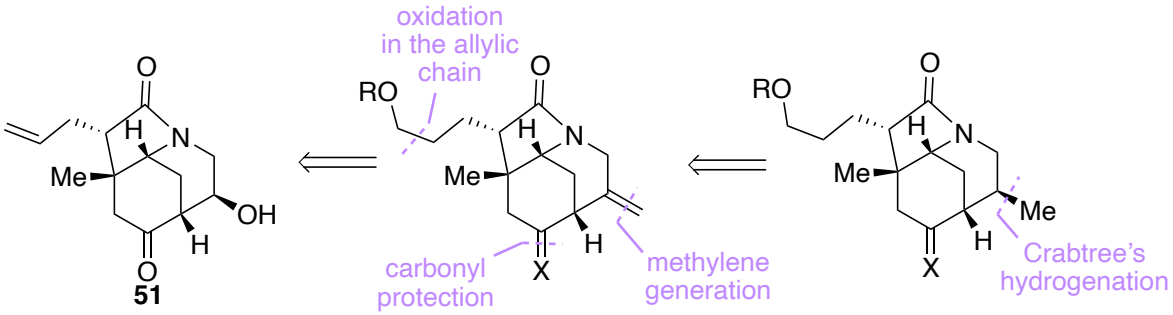
Table 3.9*. C-8 Methyl installation attempts from ketal derivative **59*** [a]



Entry	Reagents (equiv.)	Conditions	Products (Yield)
1	CuI(10), MeLi (18)	Et_2O, -20 °C → 0 °C	SM
2	CuI(10), MeLi (18)	Et_2O, -20 °C → rt	SM
3	$AlMe_3$ (3)	CH_2Cl_2, -78 °C → rt	**59** (34%)[b]

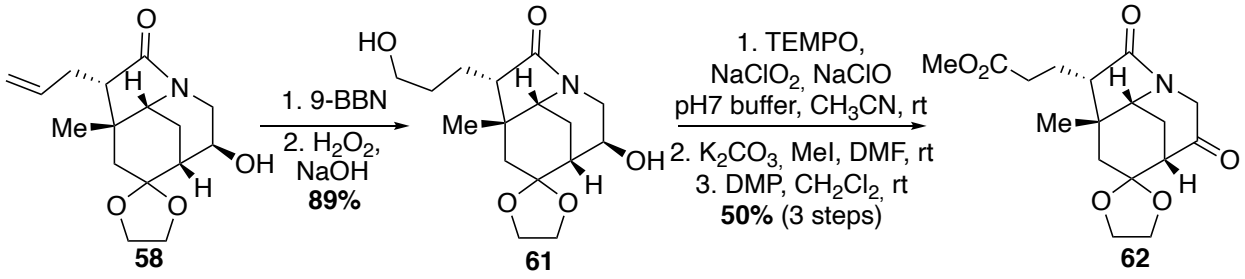
a. 0.1 mmol scale. b. Isolated yield

Parallelly to the organocopper displacement strategy, we investigated the common reported procedure for the C-8 methyl installation from himalensine A through a diastereoselective hydrogenation of an extern methylene in the presence of Crabtree's catalyst (Chapter 1, section 1.1.4.2). We envisioned that, from the obtained tricyclic alcohol **51**, modifications at the allyl group and the carbonyl protection were needed to avoid chemoselectivity problems (Scheme 3.36).



Scheme 3.35. *Methyl installation at C-8 through hydrogenation of an extern methylene*

Thus, the previously prepared compound **58** was submitted to a hydroboration/oxidation process of the allyl group to obtain the diol **61** in 71% yield. Next, we applied a one-pot methodology combining a Pinnick oxidation of the primary alcohol to a carboxylic acid,[64b] esterification of the latter with K_2CO_3 and methyl iodide,[66b] and finally, oxidation with Dess-Martin periodinane of the secondary alcohol,[140] to obtain compound **62** in 50% yield after the 3 steps.

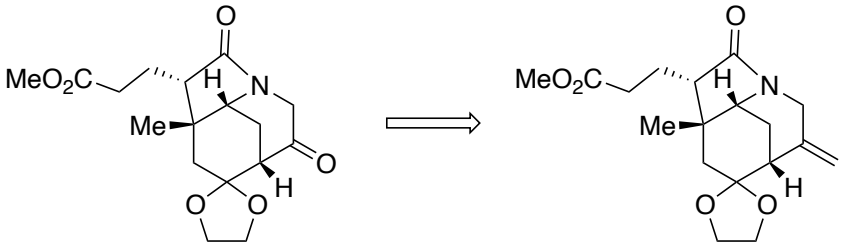


Scheme 3.36*. Dicarbonylic compound **62** preparation*

[140] Corrêa, I. R.; Pilli, R. A. *Angew. Chem. Int. Ed.* **2003**, *42*, 3017–3020.

Next, substrate **62** bearing a ketone moiety was submitted to conditions for the methylene generation. Several procedures were tested from Wittig reaction to Ti-catalyzed conditions (Table 3.10).

***Table 3. 10**. Methylene generation at C-8[a]*



Entry	Reagents	Products
1	$MePPh_3Br$, nBuLi, 0 ºC → rt	--
2	Zn, CH_2I_2, $TiCl_4$ (1.1 equiv), THF, 0 ºC → rt	SM[b]
3	Zn, CH_2I_2, $TiCl_4$ (3.5 equiv), THF, 0 ºC → rt	Unidentified product[b]
4	Zn, CH_2I_2, $TiCl_4$ (1.1 equiv), $PbCl_2$ (0.3 equiv), THF, 0 ºC → rt	--

a. 0.04–0.2 mmol scale. b. Observed in the NMR of the crude.

Firstly, classical Wittig conditions by treatment of **62** with $MePPh_3Br$ and *n*-BuLi resulted in a complex mixture of unidentifiable products (entry 1).[141] Then, we tested the more functional group tolerant Takai-Lombardo reaction.[142] Applying conditions employed by Lautens *et al.*[143] with $Zn/TiCl_4/CH_2I_2$ only starting material was recovered (entry 2). Increasing the reagent equivalents provided a small quantity of an unidentified product but seemed that an interaction at the ester group had occurred (entry 3). According to the literature,[144] presence of $PbCl_2$ in the reaction medium could accelerate the process. However, when tricycle **62** was submitted to conditions reported by Baran *et al.*,[145] a complex mixture of products was obtained (entry 4).

[141] Díaz, S.; Cuesta, J.; González, A.; Bonjoch, J. *J. Org. Chem.* **2003**, *68*, 7400–7406.
[142] a) Hibino, J.; Okazoe, T.; Takai, K.; Nozaki, H. *Tetrahedron Lett.* **1985**, *26*, 5579–5580. b) Lombardo, L. *Tetrahedron Lett.* **1982**, *23*, 4293–4296. c) Takai, K.; Hotta, Y.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1978**, *27*, 2417–2420.
[143] Scott, M. E.; Lautens, M. *Org. Lett.* **2005**, *7*(14), 3045–3047.
[144] Takai, K.; Kakiuchi, T.; Kataoka, Y.; Utimoto, K. *J. Org. Chem.* **1994**, *59*, 2668–2670.
[145] Merchant, R. R.; Oberg, K. M.; Lin, Y.; Novak, A. J. E.; Felding, J.; Baran, P. S. *J. Am. Chem. Soc.* **2018**, *140*, 7462–7465.

3.3 Summary and conclusions

The aim of this chapter was to synthesize the tricyclic ABC ring core of Himalensine A parting from the easily accessible octahydroindoles prepared in Chapter 2, already bearing rings A and C. Hence, several strategies for the ring B closure have been tested (Scheme 3.38.a).

Firstly, a radical approach was studied, but attempts to prepare synthetically advanced intermediates provided with moderate yields. So, parting from more accessible enelactam allowed the dichloroacetamide **I** preparation. However, when radical conditions were applied no cyclization product was recovered.

Taking advantage of previous prepared compounds during the first study we envisioned some ionic approaches. Chlorine displacement by ketone enolate of **I** or a lactamization process of compound **III** between nitrogen atom and a carbonylic chain at C-6 were tested but both resulted in no tricyclic construction.

Finally, based on previous studies of the group towards morphan ring core synthesis, we envisioned an aldolic cyclization for the ABC fragment. Synthesis of high functionalized octahydroindoles **II** allowed the tricyclic ring core construction, but, again, low yields in crucial steps prevent to follow the synthesis towards the natural product. We managed to prepare bicyclic lactams **II** with good yields employing different C-3 substituent and the aldolic procedure resulted in a robust and reliable methodology for the 5,6,6-fragment. Additionally, stereochemical outcome of the process was supported with computational studies performed in collaboration with Prof. Enrique Gómez-Bengoa.

Once the tricyclic core was achieved, we addressed the installation of the methyl at C-8 (Scheme 3.31.b). After screening of several methodologies, compound **55** was accomplished through a displacement of a tosylate group by Gilman's cuprate with a non-expected retention of the C-8 configuration center. NMR data of **55** was coincident with the previously reported by Gao et al. in their work towards the synthesis of Himalensine A, so, obtention of **55** represented a formal synthesis of the targeted natural product. These last results were compiled in a publication.[146]

[146] Marquès, C.; Diaba, F.; Gómez-Bengoa, E.; Bonjoch, J. *J. Org. Chem.* **2021**, *87*(15), 10516−10522

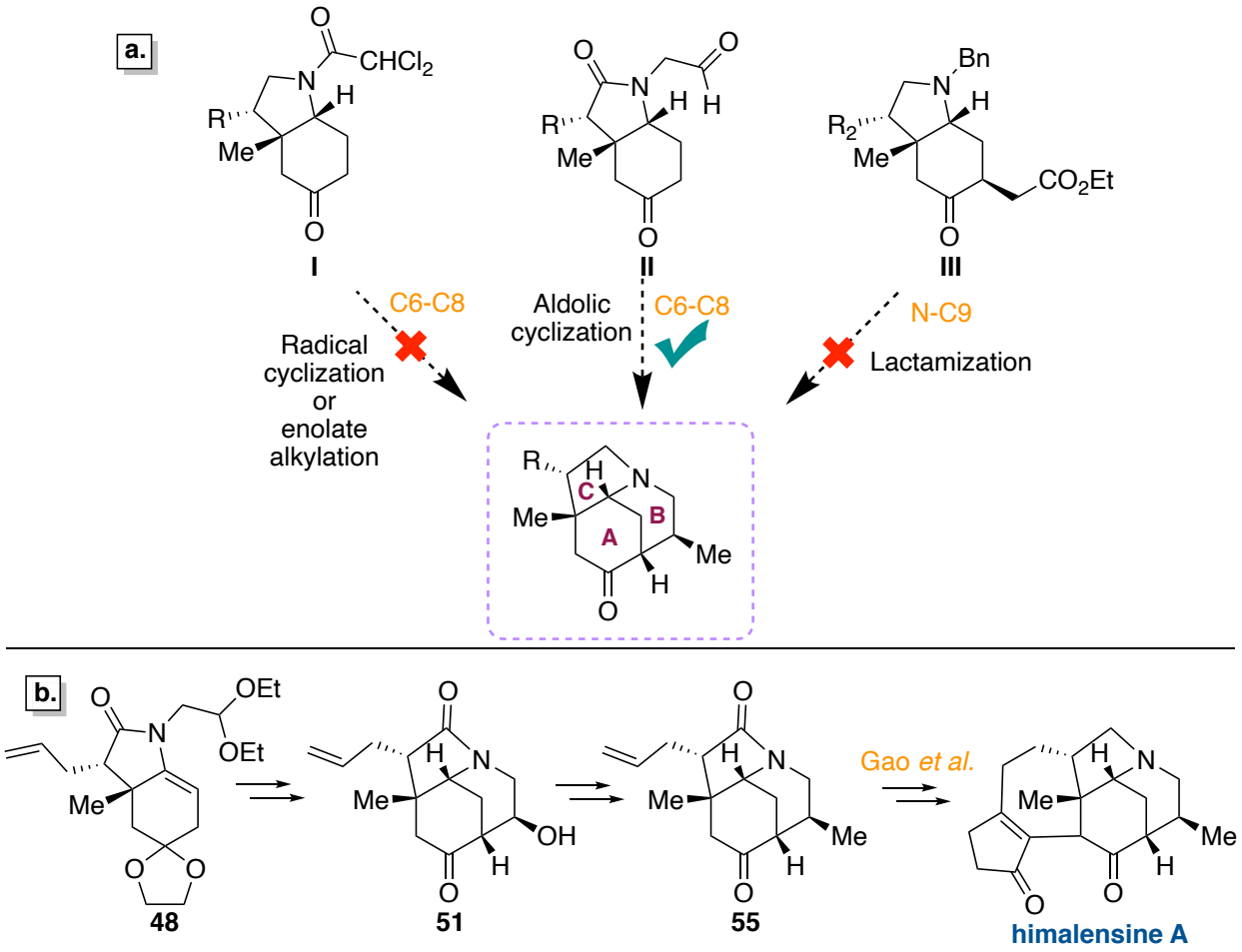


***Figure 3. 6**. Conclusions of the Chapter 3*

Chapter 4

Synthesis of the azatricyclic [5-6-7]-fragment via ring expansion processes: toward the synthesis of 2-deoxymacropodumine A

Among the plethora of Daphniphyllum alkaloids, some have a bridged 7-azabicyclo[4.3.1]decane ring system embedded in their skeleton. Representative alkaloids with this structural feature, *i.e.,* a homoanalog of the morphan nucleus, include daphnicyclidins, [147] daphnillonins, [148] and macropodumines.[59] In these alkaloids, considering the additional fused pyrrolidine ring, a characteristic ABC ring of octahydro-1,7-ethanocyclohepta[*b*]pyrrole (depicted in blue) is found (Figure 4.1).

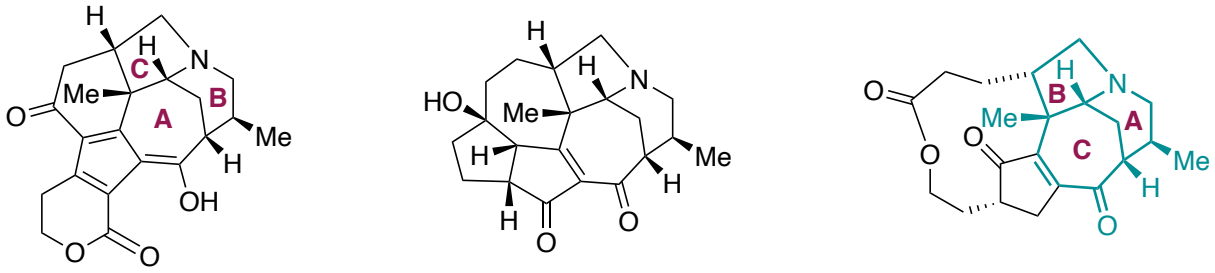
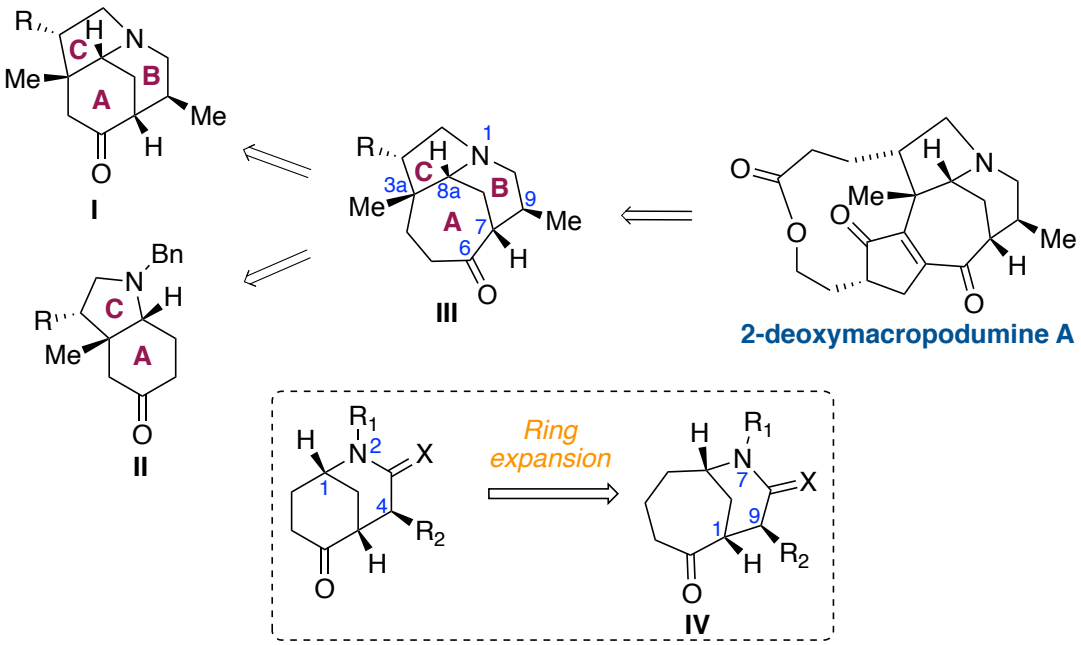


Figure 4. 1. *Daphniphyllum alkaloids containing an azatricyclic-7,6,5-fragment*

Gaining access to building blocks bearing this ABC skeleton through the incorporation of adequate functionalization would constitute a point of departure for exploring new strategies toward these types of alkaloids. Moreover, it would provide a valuable advanced structure for future studies aimed at the first synthesis of 2-deoxymacropodumine A (Scheme 4.1). With this final objective, we planned the synthesis of the functionalized scaffold **III** through two approaches from the two substrates whose preparation is described in the previous chapters of the thesis: azatricyclo **I** (Chapter 3) or azabicyclo **II** (Chapter 2). Both scaffolds could provide access to valuable advanced type **III** intermediates by means of expansion of the cyclohexanone ring to cycloheptanone. In this scenario, additional preliminary ring enlargement studies with easily achieved compounds bearing a basic nitrogen atom in their structure were considered pertinent for evaluating the synthetic protocol. Thus, the ring expansion of morphans to homomorphans was explored.

[147] Kobayashi, J.; Inaba, Y.; Shiro, M.; Yoshida, N.; Morita, H. *J. Am. Chem. Soc.* **2001**, *123*, 11402–11408
[148] Zhang, D-D.; Xu, J-B., Fan, Y.-Y.; Gan, L.-S.; Zhang, H.; Yue, J.-M. *J. Org. Chem.* **2020**, *85*, 3742–3747.



Scheme 4.1. *Objective of Chapter 4*

4.1 Precedents

In spite of the great advances regarding the synthesis of *Daphniphyllum* alkaloids in the last decades, few synthetic studies have been devoted to their complex framework **III**. Moreover, the use of compounds with azatricyclic **I** or azabiyclic **II** structures as building-blocks is unprecedented in this field. Only recently, in 2023, was a first total synthesis achieved in this field, when Li reported the daphnillolin B synthesis.[149]

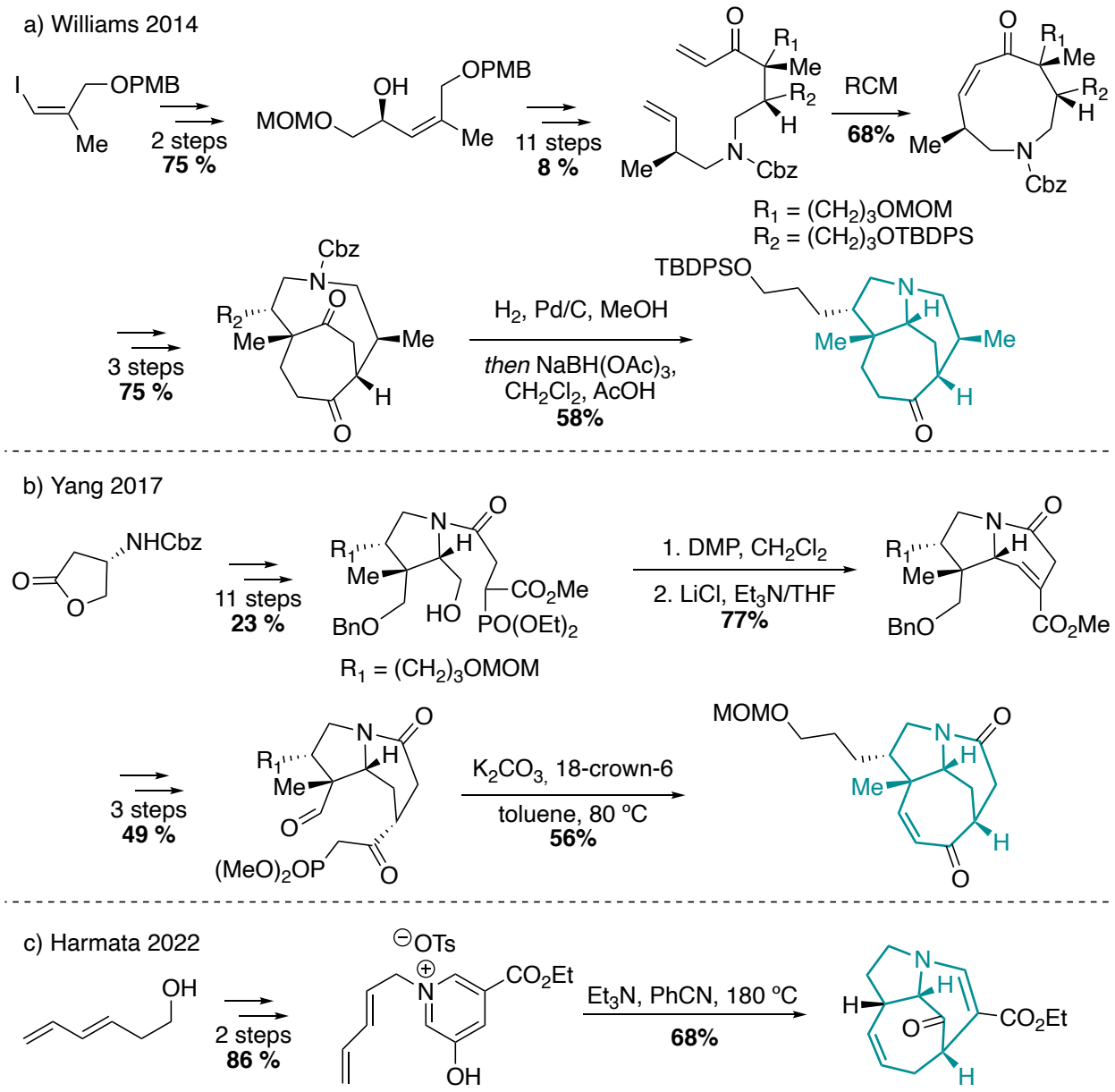
4.1.1 Precedents for azatricyclic [5-6-7] ring synthesis

Previous synthetic approaches to the ABC tricyclic substructure **III** of octahydro-1,7-ethanocyclohepta[*b*]pyrrole have been reported in studies toward daphnicyclidin A synthesis, in all cases involving a long reaction sequence of around twenty steps (Scheme 4.2). Thus, a) Williams transformed a nonacyclic intermediate to an azabicyclic diketone, which was closed through a reductive amination to furnish the target compound;[150] b) the synthesis of Yang involved an advanced intermediate 2,3,4-cis trisubstituted pyrrolidine that allowed the construction of rings A and B by means of two

[149] Zou, Y.-P.; Lai, Z.-L.; Zhang, M.-W.; Peng, J.; Ning, S.; Li, C.-C. *J. Am. Chem. Soc.* **2023**, *145*, 10998–11004

[150] Williams, D. R.; Mondal, P. K.; Bawel, S. A.; Nag, P. P. *Org. Lett.* **2014**, *16*, 1956–1959

intramolecular Horner-Wadsworth-Emmons (HWE) reactions; [151] and c) Harmata described a [4+3] intramolecular cycloaddition of the salt generated from *N*-alkylation with an alkene moiety of 5-hydroxynicotinic acid.[152]



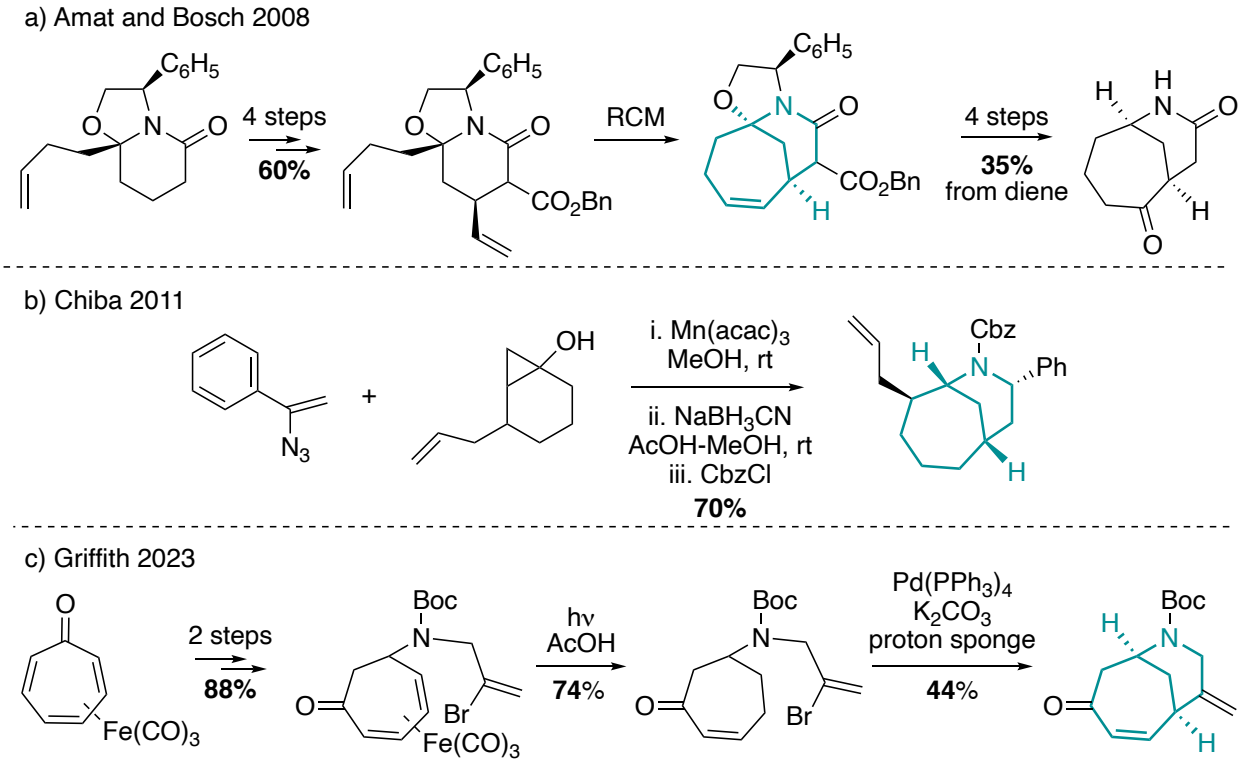
Scheme 4. 2. *Precedents for the tricyclic 7,6,5-ring core*

[151] Li, J. L.; Shi, H. W.; Wang, Q.; Chai, Y. H.; Yang, J. *Org. Lett.* **2017**, *19*, 1497–1499.
[152] Tu, J.; Ripa, R. A.; Kelley, S. P.; Harmata, M. *Chem. Eur. J.* **2022**, *28*, e202200370.

Additionally, other substructures of daphnicyclidin A have also been prepared: an approach to the BCD system with an overall 19-step synthesis[153a] and a route to the ACE substructure proceeding over 19 steps.[153b]

4.1.2 Precedents for homomorphan ring synthesis

Limited research works on the synthesis of homomorphans **IV** are reported in the literature (Scheme 4.3). The first approach was developed by Amat's group based on a ring-closing metathesis (RCM) from a functionalized piperidine compound to provide a potentially valuable keto lactam. [154] Secondly, Chiba reported a Mn(III)-promoted procedure involving a vinyl azide as a radical precursor in a straightforward route to the azabicyclic ring. [155] Recently, Griffith reported the synthesis of the 7-azabicyclo[4.3.1]decane ring system through an intramolecular Heck reaction.[156]



Scheme 4.3. *Precedents for homomorphan ring construction*

[153] a) Ikeda, S.; Shibuya, M.; Kanoh, M.; Iwabuchi, I. *Org. Lett.* **2019**, *11*, 1833–1836. b) Wang, Q.; Zhang, C.; Yang, J. *Chin. Chem. Lett.* **2020**, *31*, 1906–1910.
[154] Amat, M.; Perez, M.; Minaglia, A. T.; Bosch, J. *J. Org. Chem.* **2008**, *73*, 6920–6923
[155] Wang, Y.-F.; Toh, K, K.; Ng, E. P. J.; Chiba, S. *J. Am. Chem. Soc.* **2011**, *133*, 6411–6421.
[156] Shoemaker, A. H.; Foker, E. A.; Uttaro, E. P.; Beitel, S. K.; Griffith, D. R. *Beilstein Org. Chem.* **2023**.

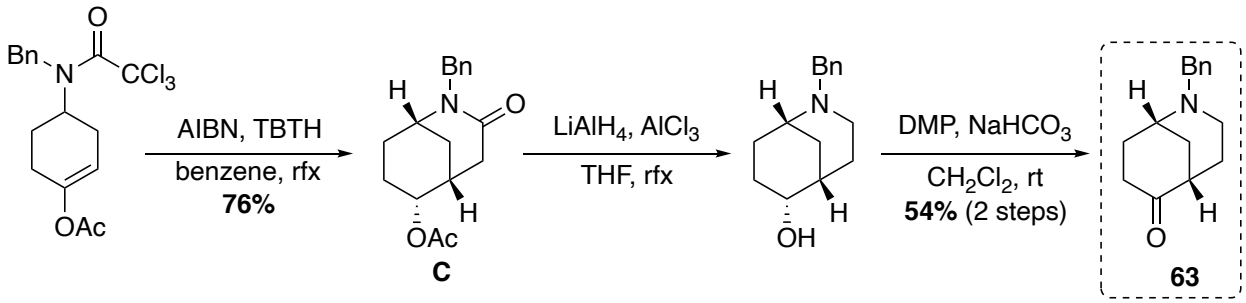
4.2 Results and discussion

4.2.1 Previous studies on morphan ring enlargement

As an initial study, the aim was to develop a synthetic route to 7-azabicyclo[4.3.1]decanes (*i.e.*, homomorphans) by means of carbocyclic ring expansion of morphan compounds obtained by our radical approach.

i. Preparation of the substrates

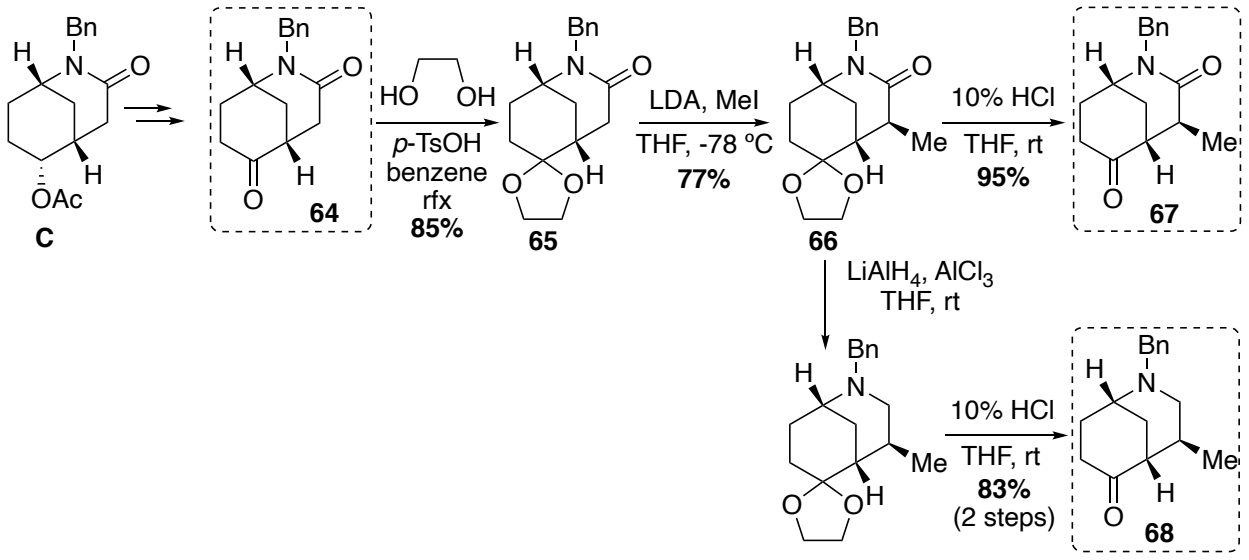
The azabicyclic substrates were functionalized to provide a range of valuable building-blocks for the studies targeting the azatricyclic framework. Thus, employing previously described methodologies, we prepared the known morphan **C** [157] through radical cyclization of the corresponding trichloroacetamide.[158] Then, treatment with $LiAlH_4$ in the presence of $AlCl_3$ reduced the carbonylic functionalities and subsequent hydroxyl oxidation gave the first substrate keto amine **63**.[159]



Scheme 4.4. *Preparation of amino-ketone **63** from reported bicyclic compound **C***

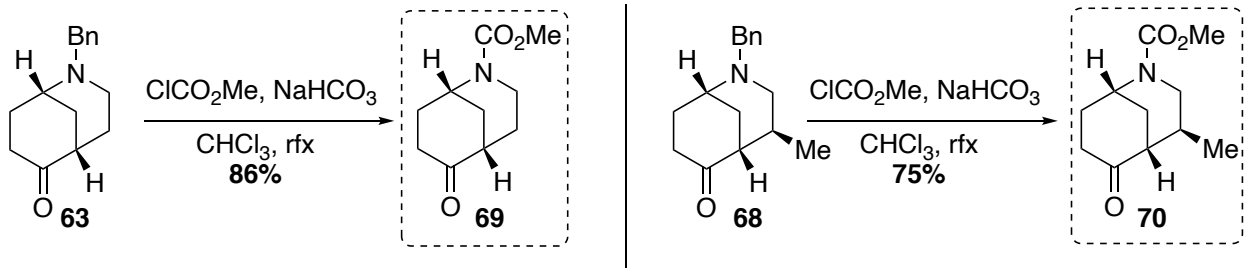
Next, from the same intermediate **C**, we prepared the known bicyclic lactam **64** following the reported procedure (Scheme 4.5).[157] Moreover, to study the effect of the C8-methyl present in the targeted azatrycicle **I**, we prepared the corresponding methylated derivatives. Hence, after ketone protection, the enolate of compound **65** was treated with MeI,[103] and further ketal hydrolysis led to keto lactam **67**. Additionally, lactam reduction of intermediate **66** and final ketal removal afforded methylated keto amine **68**.

[157] Quirante, J.; Escolano, C.; Diaba, F.; Bonjoch, J. *J. Chem. Soc., Perkin Trans., 1.* **1999**, 1157–1162.
[158] Quirante, J.; Escolano, C.; Diaba, F.; Bonjoch, J. *Heterocycles*, **1999**, *50*, 731–738.
[159] Beshore, D. C.; Smith, A. B. III. *J. Am. Chem. Soc.* **2008**, *130*, 13778–13789.



Scheme 4.5**. Preparation of **64**, **67** and **68

Afterwards, an exocyclic carbonylic moiety was introduced by means of an *N*- benzyl group exchange for a carbamate substituent (Scheme 4.6). Hence, *N*-benzyl keto amines **63** and **68** were treated with methyl chloroformate in the presence of $NaHCO_3$ in $CHCl_3$ reflux[160] leading to carbamates **69** and **70** in good yields.



Scheme 4.6**. Preparation of N-carbamate derivatives **69** and **70

[160] Stork, G.; Yamashita, A.; Adams, J.; Schulte, G. R.; Chesworth, R.; Miyazaki, Y.; Farmer, J. J. *J. Am. Chem. Soc.* **2009**, *131*, 11402–11406.

ii. Ring expansion studies

We envisioned performing the ring enlargement process by means of a ketone homologation reaction using diazo compounds.[161] Diazo compounds have an ambiphilic character with a partially negative charge located on the carbon adjacent to the diazo group (Figure 4.2). They carry out a nucleophilic attack on ketones in the presence of a promoter, either a Lewis acid to increase carbonyl electrophilicity, or a base to increase the nucleophilicity of the diazo compound by α-deprotonation. The regioselectivity of the reaction could be attributed to stereoelectronic and conformational effects that would dictate a preferred transitional state for the Tiffeneau-Demjanov-type rearrangement in which the migrating bond is located antiperiplanar to the leaving diazonium group.[162]

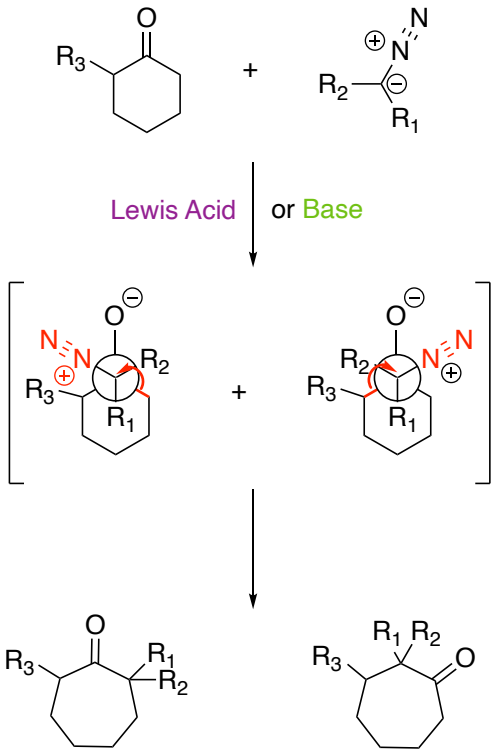
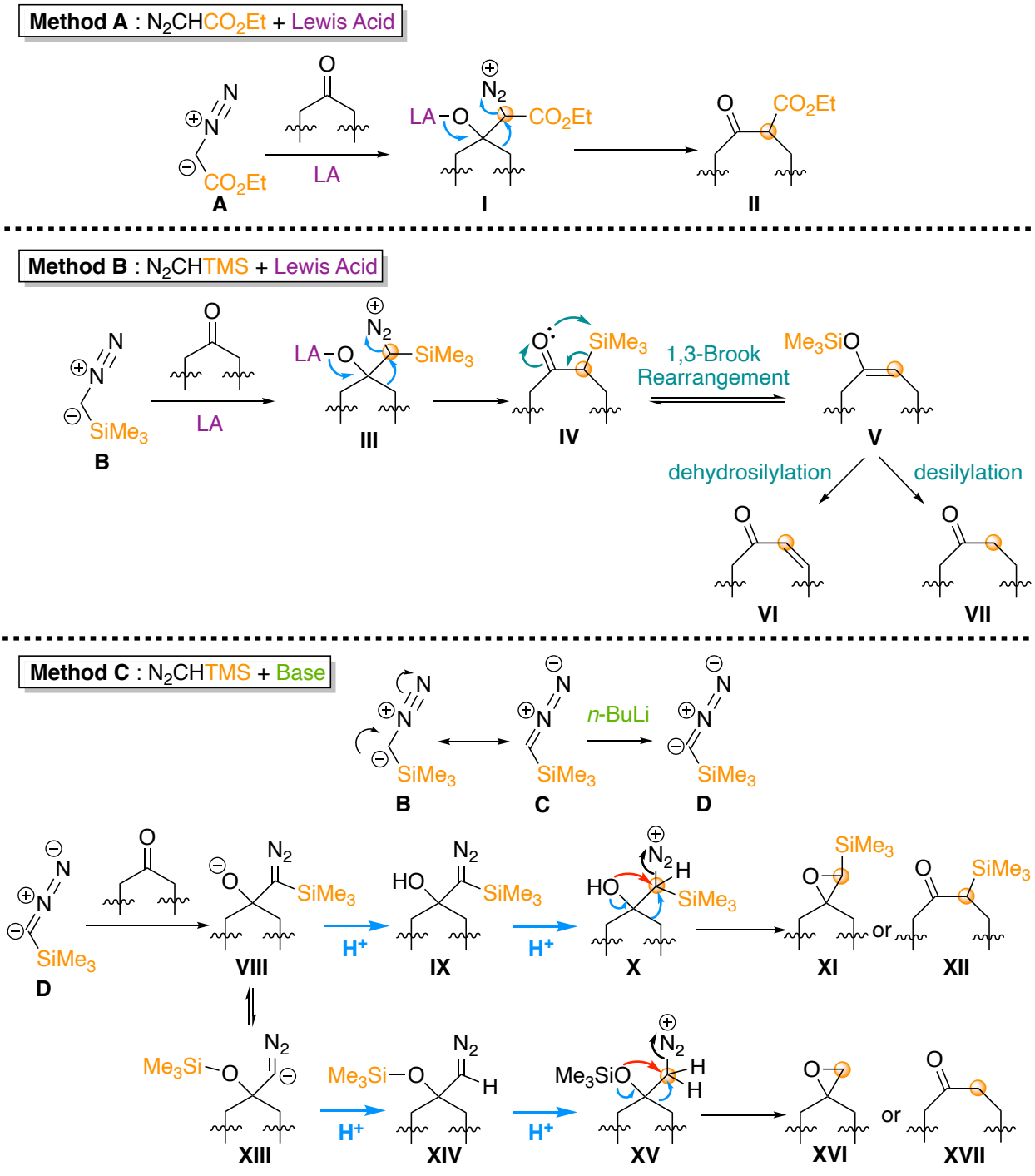


Figure 4.2. *Tiffeneau-Demjanov-type rearrangement in homologation by a diazo compound*

[161] Candeias, N. R.; Paterna, R.; Gois, P. M. P. *Chem. Rev.* **2016**, *116*, 2937–2981.
[162] a) Seto, H.; Fujioka, S.; Koshino, H.; Hayasaka, H.; Shimizu, T.; Yoshida, S.; Watanabe, T. *Tetrahedron Letters*, **1999**, *40*, 2359–2362. b) Coveney, D. J. in *Comprehensive Organic Synthesis*, ed. Trost, B. M.; Fleming, I., Pergamon Press, Oxford, **1991**, vol.3, pp. 777-801; and references cited therein.

In this thesis, three reported ring enlargement methodologies were tested for the formation of B-homomorphan units (Scheme 4.7). First, a procedure previously employed in the group, in which the ketone compound was treated with ethyldiazoacetate in the presence of a Lewis acid (*e.g.*, $BF_3{\cdot}OEt_2$), would lead to an α-carbonylated compound **II** (Method A).[98b] Second, the use of a diazo derivative with TMS as a substituent together with a Lewis acid was explored (Method B). In this case, the obtained compound **IV** could undergo a Brook rearrangement[163] providing the silyl enol ether derivative **V**. This would allow further transformations, such as Pd-catalyzed dehydrosilylation process leading to the corresponding enone **VI**,[164] or acidic desilylation to recover ketone **VII**. [165] Finally, diazo derivatives have a resonance structure (**C**) that could be deprotonated to give more nucleophilic species **D**. Thus, the last methodology consisted of treatment of $TMSCHN_2$ with *n*-BuLi and further addition to the ketone substrate (Method C).[166] Multiple carbon insertions were avoided as the ring expansion occurred after the key protonation step. Moreover, the choice of the protonation source could determine the proportion of the obtained compounds.

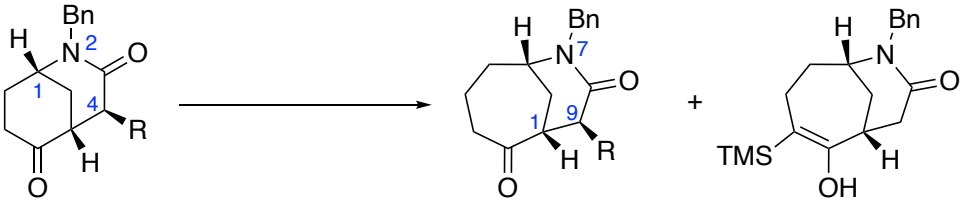
[163] Kang, B. C.; Shim, S. Y.; Ryu, D. H. *Org. Lett.* **2014**, *16*, 2077–2079.
[164] Yang, S.; Hungerhoff, B.; Metz, P. *Tetrahedron Letters,* **1998**, *39*, 2097–2098.
[165] a) Liu, Y.-T.; Li, L.-P.; Xie, J.-H.; Zhou, Q.-L. *Angew. Chem. Int. Ed.* **2017**, *56*, 12708–12711. b) Wegge, T.; Schwarz, S.; Seitz, G. *Tetrahedron: Asymmetry*, **2000**, *11*, 1405–1410.
[166] a) Liu, H.; Sun, C.; Lee, N.-K.; Henry, R. F.; Lee, D. *Chem. Eur. J.* **2012**, *18*, 11889–11893. b) Krüger, S.; Gaich, T. *Eur. J. Org. Chem.* **2016**, 4893–4899. c) Rebmann, H.; Gerlinger, C. K. G.; Gaich, T. *Chem. Eur. J.* **2019**, *25*, 2704–2707.



***Scheme 4.7**. Studied ring enlargement methodologies. Purple = methods using acidic promoters. Green = Methods using basic promoters*

Initially, the unprecedented ring expansion of morphan compounds was studied from ketones **64** and **67** with additional lactam functionalization (Table 4.1).

Table 4.1. *Ring expansion reactions of morphans **64** and **67** bearing amide functionality*



64, R = H
67, R = Me

71, R = H
73, R = Me

72

Entry	SM	Method	Reagents and conditions	Treatment	Products (Yield)[c]
1	**64**[a]	A	EtO_2CCHN_2, $BF_3{\cdot}OEt_2$ Et_2O, 0 °C	--	**SM**
2	**64**[a]	B	$TMSCHN_2$, $BF_3{\cdot}OEt_2$ CH_2Cl_2, rt	TFA/H_2O	**71** (36%)
3	**64**[a]	B	$TMSCHN_2$, $AlMe_3$ CH_2Cl_2, -78 °C to rt	TFA/H_2O	**--**
4	**64**[a]	B	$TMSCHN_2$, $Sn(OTf)_2$ CH_2Cl_2, -40 °C	--	**SM**
5	**64**[a]	C	$TMSCHN_2$, *n*-BuLi Et_2O/THF, -78 °C	1. MeOH 2. 1 M HCl	**71** (26%)
6	**64**[a]	C	$TMSCHN_2$, *n*-BuLi, Et_2O/THF, -78 °C	1. MeOH 2. SiO_2	**71** (27%) **72** (21%)
7	**67**[b]	C	$TMSCHN_2$, *n*-BuLi Et_2O/THF, -78 °C	1. MeOH 2. 1 M HCl	**73** (24%)
8	**67**[b]	C	$TMSCHN_2$, *n*-BuLi Et_2O/THF, -78 °C	1. MeOH 2. SiO_2	**73** (27%)

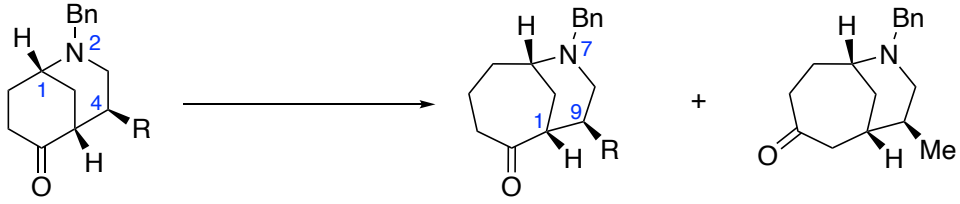
a. 0.20–0.46 mmol scale. b. 0.20 mmol. c. Isolated yield

First, the use of ethyldiazoacetate in the presence of $BF_3{\cdot}OEt_2$ was tested with keto lactam **64**, but only starting material (SM) was recovered (entry 1). Next, treatment with $TMSCHN_2$ and $BF_3{\cdot}OEt_2$ with further acidic desilylation resulted in product formation with 36% yield (entry 2). Other Lewis acids tested were $AlMe_3$, which gave a complex mixture of unidentifiable products (entry 3), and $Sn(OTf)_2$, after which only starting material was recovered (entry 4). Then, employing $TMSCHN_2$ with *n*-BuLi as the basic promoter, and further protonation with MeOH and 1 M HCl gave product **71** in 26% yield (entry 5). Changing the last protonation process by the use of SiO_2 gave **71** with a similar yield but

it was isolated along with compound **72**. The latter might have arisen from the enol tautomer of product **XII** shown in Scheme 4.7 (entry 6). Finally, ketone **67** bearing a methyl at C-4 was submitted to the $TMSCHN_2$ and *n*-BuLi methodology. The final protonation step was performed either by treatment with 1 M HCl, which provided the expanded compound **73** in 24 % yield, or with SiO_2, which gave product **73** with a similar 27% yield.

Next, we proceeded with bicyclic ketones **63** and **68** bearing an amine functionality (Table 4.2). We started by testing ethyldiazoacetate in the presence of a Lewis Acid and only starting material was recovered (entry 1). We then changed the diazo reagent to $TMSCHN_2$ treated with *n*-BuLi and the final protonation treatment with either 1 M HCl or SiO_2 gave the homologated compound **74** in good yields (60% and 67%, respectively) (entries 2 and 3). The same methodology was applied to ketone **68** with a C-4 methyl, leading to the isolation of homomorphan **75**, also in good yields (entry 4). Moreover, when SiO_2 was used for the second protonation step, **75** was isolated along with regioisomer **76** in 17% yield (entry 5).

***Table 4.2**. Ring expansion reactions of morphans **63** and **68** bearing amine functionality*



63, R = H
68, R = Me

74, R = H
75, R = Me

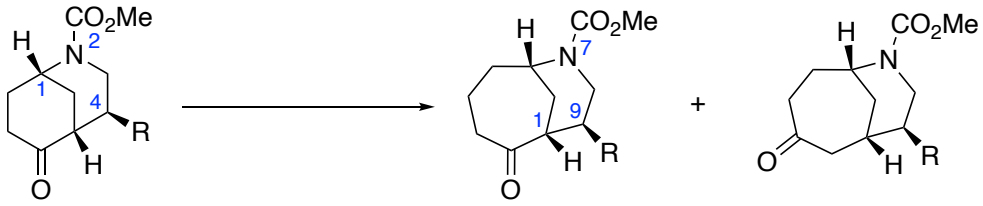
76

Entry	SM	Method	Reagents and conditions	Treatment	Products (Yield)[c]
1	**63**[a]	A	EtO_2CCHN_2, $BF_3{\cdot}OEt_2$ Et_2O, 0 ºC	--	**SM**
2	**63**[a]	C	$TMSCHN_2$, *n*-BuLi Et_2O/THF, -78 ºC	1. MeOH 2. 1 M HCl	**74** (60%)
3	**63**[a]	C	$TMSCHN_2$, *n*-BuLi Et_2O/THF , -78 ºC	1. MeOH 2. SiO_2	**74** (67%)
4	**68**[b]	C	$TMSCHN_2$, *n*-BuLi Et_2O/THF, -78 ºC	1. MeOH 2. 1 M HCl	**75** (43%)
5	**68**[b]	C	$TMSCHN_2$, *n*-BuLi Et_2O/THF, -78 ºC	1. MeOH 2. SiO_2	**75** (63%) **76** (17%)

a. 0.22–2.14 mmol. b. 0.23–0.91 mmol. c. Isolated yield

Finally, the studied methodologies were applied to carbamates **69** and **70** (Table 4.3). When compound **69** was treated with $TMSCHN_2$ in the presence of $BF_3{\cdot}OEt_2$, both regioisomers **77** and **78** were obtained in similar yields (entry 1). Next, methylated compound **70** was treated with a solution of $TMSCHN_2$ and *n*-BuLi and further protonation with MeOH or SiO_2 afforded regioisomers **79** and **80** with 56% and 14% yield, respectively.

Table 4.3. *Ring expansion reactions of morphans **69** and **70** bearing carbamate functionality*



69, R = H
70, R = Me

77, R = H
79, R = Me

78, R = H
80, R = Me

Entry	SM	Method	Reagents and conditions	Treatment	Products (Yield)[c]
1	**69**[a]	B	$TMSCHN_2$, $BF_3{\cdot}OEt_2$ CH_2Cl_2, rt	--	**77** (31%) **78** (38%)
2	**70**[b]	C	$TMSCHN_2$, *n*-BuLi Et_2O/THF, -78 ºC	1. MeOH 2. SiO_2	**79** (56%) **80** (14%)

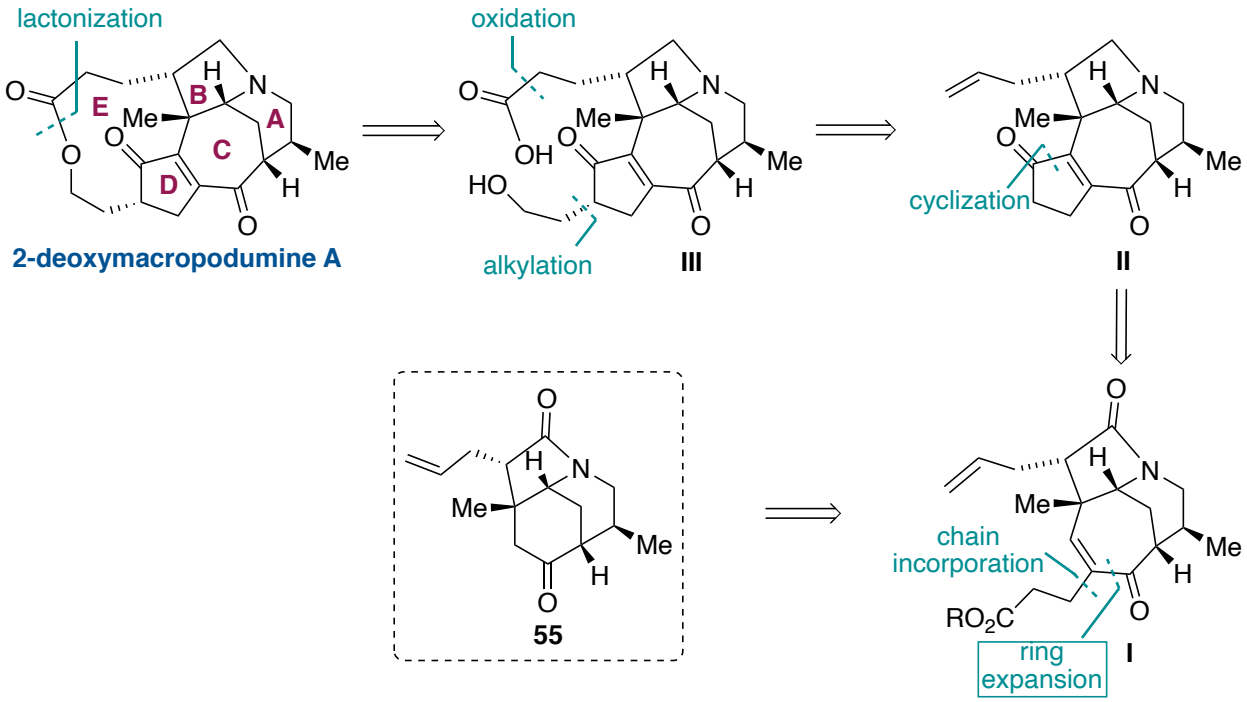
a. 0.45 mmol. b. 0.20 mmol. c. Isolated yield

In summary, the best results were obtained with method C (Scheme 4.7), employing $TMSCHN_2$ with *n*-BuLi. Moreover, ketones **63** and **68** bearing an additional amine functionality gave B-homomorphans in the best yields and regioselectivity.

The overall synthesis constitutes a new route to B-homomorphans and the results were satisfactory considering the observed regioselectivity in the ring-enlargement, with the carbonyl group remaining at the contiguous bridgehead carbon atom as occurs in the aforementioned alkaloids. However, using these homomorphans would require numerous transformations to be useful in a route to the targeted compounds of type **I** (Scheme 4.1).

4.2.2 Synthesis of the azatricyclic [5-6-7]-scaffold by expansion of the carbocyclic [5-6-6]-ring (ABC)

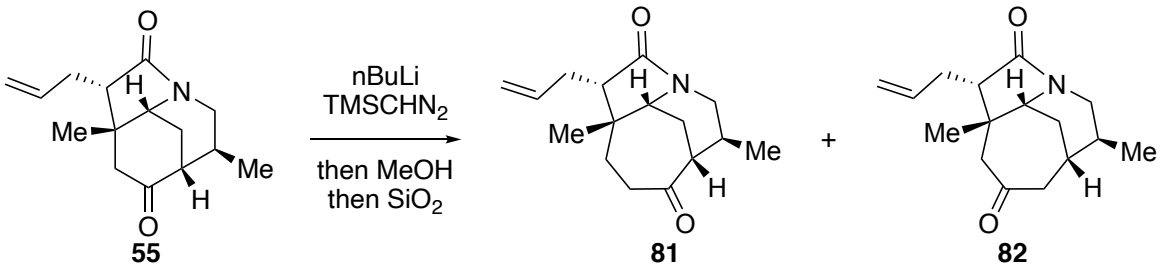
At this point, we decided to test the ring expansion using the more demanding substrate azatricycle **55**, previously prepared in this thesis (Chapter 3). We envisioned the resulting [5,6,7]-scaffold as an advanced intermediate toward the synthesis of 2-deoxymacropodumine A (Scheme 4.8). Hence, the addition of a suitable chain bearing a carbonylic moiety could allow the five-membered ring closure. Further oxidative modifications of the allylic moiety and α-alkylation of the enone at D-ring would provide the appropriate moieties for the macrolactone ring closure.



***Scheme 4.8**. Retrosynthetic plan to obtain 2-deoxymacropodumine A*

The enlargement of the cyclohexanone subunit of azatricycle **55** was explored using the reaction conditions with the best results reported in the morphan series (Table 4.4). Thus, compound **55** was treated with $TMSCHN_2$ and *n*-BuLi and further treatment with MeOH and SiO_2 gave both regioisomers **81**:**82** in a 1:2 ratio. When substituting the second protonation step by the use of 1 M HCl, the ratio changed to 2:1 with a 46% overall yield favoring the desired product **81**.

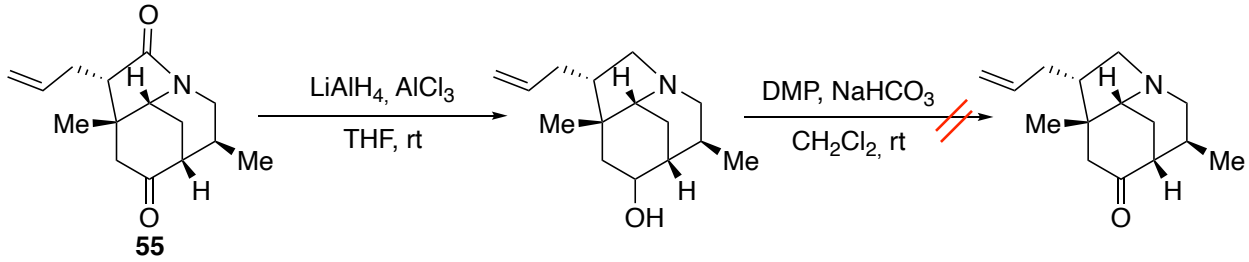
Table 4.4. *Ring enlargement of the tricyclic compound* ***55*** [a]



Entry	Method	Reagents and conditions	Treatment	Product (Yield)[b]
1	C	TMSCHN$_2$, *n*-BuLi Et$_2$O/THF, -78 ºC	1. MeOH 2. SiO$_2$	**81** (15%) **82** (28%)
2	C	TMSCHN$_2$, *n*-BuLi Et$_2$O/THF, -78 ºC	1. MeOH 2. 1 M HCl	**81** (33%) **82** (15%)

a. 0.14–0.18 mmol scale. b. Isolated yield

Taking into account the best results obtained for the morphan series when employing substrates with an amine functionality, we attempted the lactam removal from compound **55** (Scheme 4.9). However, low substrate quantity together with poor reaction yields prevented the preparation of the corresponding amine derivative.

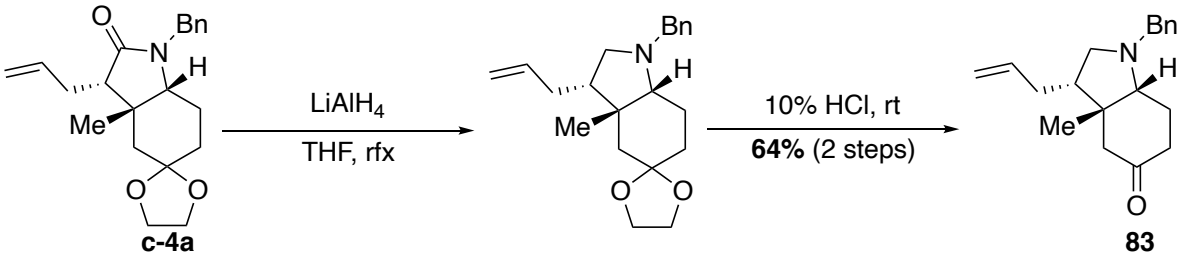


Scheme 4.9. *Attempt to prepare tricyclic-6,5,5-core with amine functionality*

These initial results were not sufficiently satisfactory to continue with this approach to the targeted compound, considering the laborious procedures required for a multigram preparation of azatricyclo **55**.

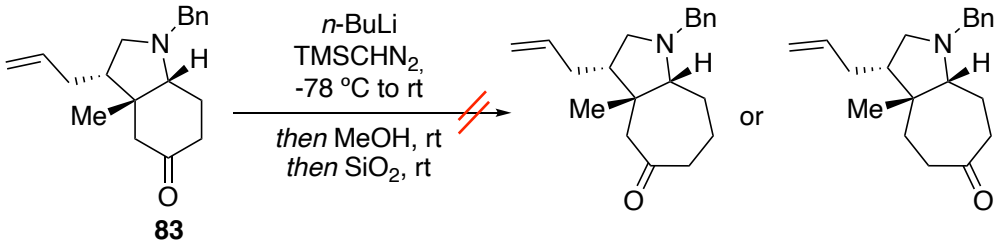
4.2.3 Synthesis of the azatricyclic [5-6-7]-scaffold by ring expansion of the octahydroindole ring (AC)

After these preliminary studies, a more efficient synthetic route to the targeted functionalized 7,6,5-targeted azatricyclic scaffold was aimed. Hence, we focused our efforts on the application of the ring expansion to the octahydroindole scaffold. Based on the best results in the B-homomorphan synthesis, the amine derivative of **c-4a** was prepared (Scheme 4.10). Starting from octahydroindole **c-4a**, the carbonylic moiety was reduced and further ketal hydrolysis provided the amino ketone **83** in 64% over 2 steps.



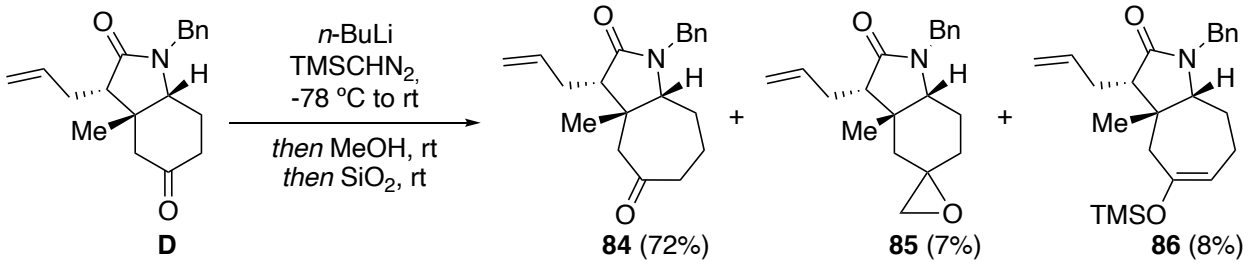
Scheme 4.10. *Octahydroindole **83** preparation*

Next, keto amine **83** was submitted to $TMSCHN_2$ with *n*-BuLi and further treatment with MeOH or SiO_2 but no elongated product was recovered, only complex mixtures of unidentifiable products.



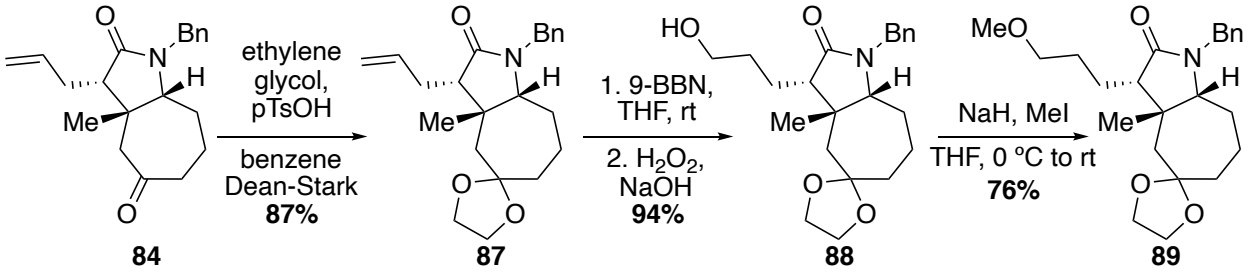
Scheme 4. 11*. Attempts at the ring expansion process in amino octahydroindole **83***

Additionally, we tested the ketone homologation reaction directly on octahydroindole **D** (Scheme 4.12), treating compound **D** with $TMSCHN_2$ and *n*-BuLi, and only the regioisomer **84** was obtained in good yield. Silyl enol ether and epoxide derivatives were also isolated but in low yields. The origin of both subproducts is depicted in Scheme 4.7.



Scheme 4.12. *Expansion of octahydroindole* ***A***

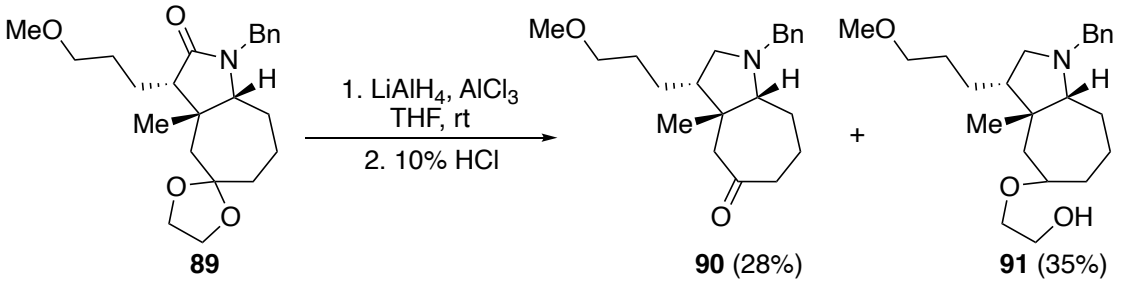
Considering the good yield for the preparation of **84**, a new synthetic route was explored for the construction of the azatricyclic [7-6-5] ring core. Thus, after ketone protection, a hydroboration-oxidation of the allylic moiety gave alcohol **88** in 94% yield. Subsequent hydroxyl protection as a methoxy group by treatment with NaH and iodomethane afforded compound **89** in 76% yield.[167]



Scheme 4.13. *Synthetic steps involving modifications of the allylic chain for the synthesis of* ***89.***

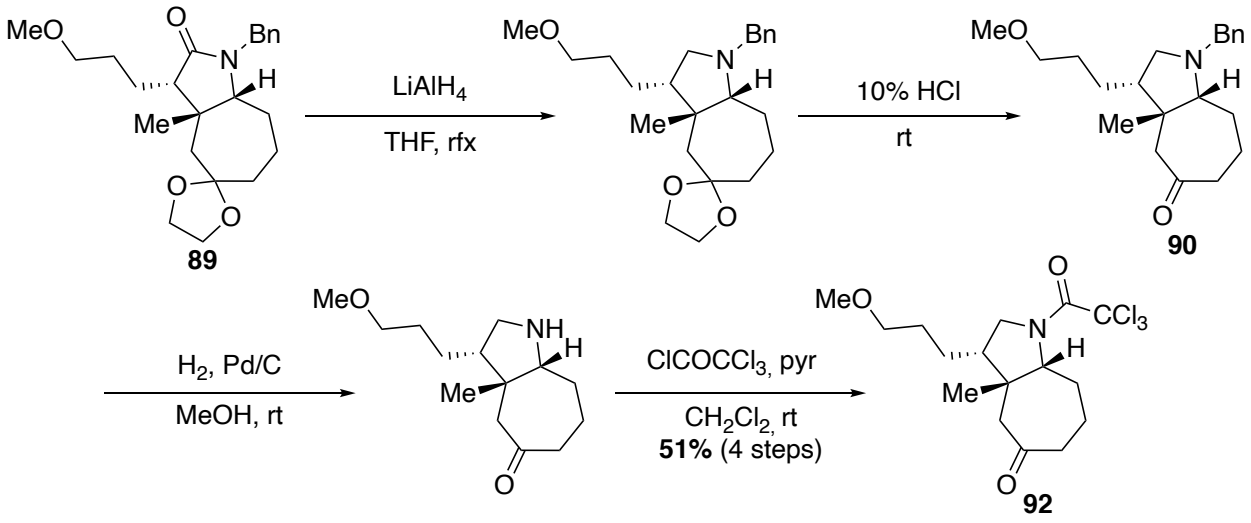
On a first run, bicyclic lactam **89** was treated with alane generated *in situ* with $LiAlH_4$ and $AlCl_3$, for the carbonyl group removal.[84] Subsequent ketal hydrolysis in an acidic medium provided compound **90** in 28% yield, along with undesired compound reduced at position C-5. The isolation of **91** was attributed to the highly reactive alane reagent employed in the first carbonyl reduction step.

[167] Juo, W.-J.; Lee, T.-H.; Liu, W.-C.; Ko, S.; Chittimalla, S. K.; Rao, C. P.; Liao, C.-C. *J. Org. Chem.* **2007**, *72*, 7992–8004.



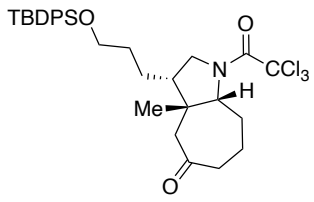
Scheme 4.14. *Attempt at carbonyl reduction of the lactam by treatment with alane*

To avoid **91** formation, the methodology for the carbonyl reduction of **89** was changed, using $LiAlH_4$ in THF, which after ketal hydrolysis provided only product **90** (Scheme 4.15).[94] Bypassing the purification processes, bicyclic amine **90** was submitted to debenzylation under hydrogenation conditions and further treatment with trichloroacetyl chloride, afforded trichloroacetamide **92** in 51% yield over the 4 steps (85% average yield for each step).



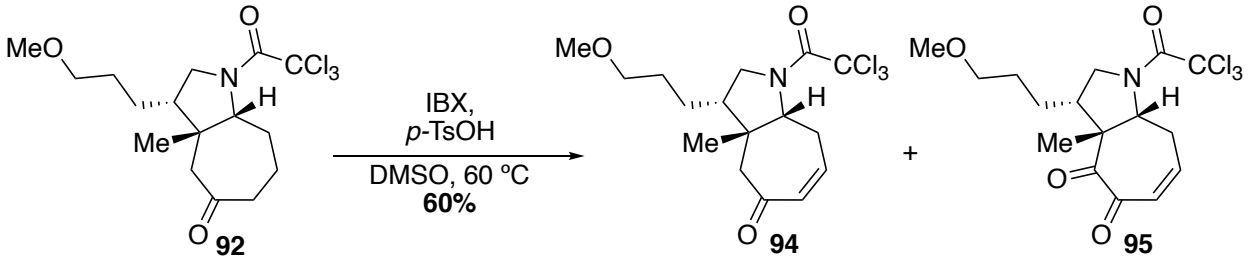
Scheme 4. 15. *Trichloroacetamide **92** synthesis*[168]

[168] Aminolactam **93** was also prepared but with lower yields (see experimental part), which was attributed to interaction of the TBDPS group under hydrogenation conditions. So, the more robust methoxy group was chosen.



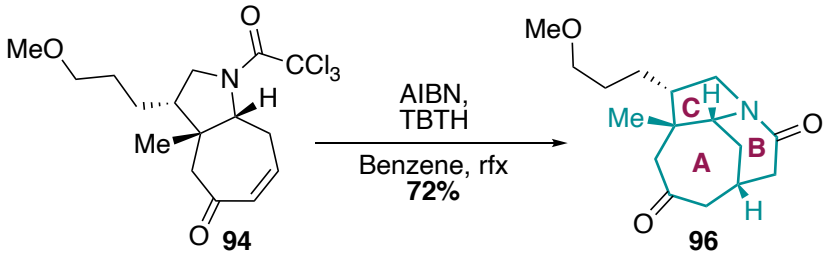
93

Taking advantage of the C-5 carbonyl location, we decided to prepare an enone that would allow the radical closure of the B-ring (Scheme 4.16). Thus, tricholoroacetamide **92** was treated with IBX in the presence of *p*-TsOH.[169] Enone **94** was isolated in 60% yield, along with traces of over-oxidized compound **95**.



Scheme 4.16. *Dehydrogenation reaction of trichloroacetamide* ***92***

Finally, we addressed the final B-ring closure. The enone **94** was submitted to reductive radical conditions by the slow addition of AIBN and TBTH over 4 hours, to obtain product **96** bearing the azatricyclic 5,6,7-fragment in 72% yield.[94]

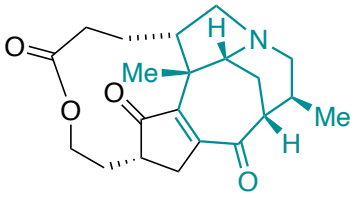


Scheme 4.17. *Radical cyclization for 5,6,7-tricylic core construction*

[169] a) Bradshaw, B.; Etxebarria-Jardí, G.; Bonjoch, J. *J. Am Chem. Soc.* **2010**, *132*, 5966–5967. b) Nicolau, K. C.; Montagnon, T.; Baran, P. S.; Zhong, Y.-L. *J. Am. Chem. Soc.* **2002**, *124*, 2245–2258. *For recent methodologies for carbonyl desaturation reactions, see:* Gnaim, S.; Vantourout, J. C.; Serpier, F.; Echeverria, P.-G.; Baran, P. S. *ACS Catal.* **2021**, *11*, 883–892.

4.3 Toward completion

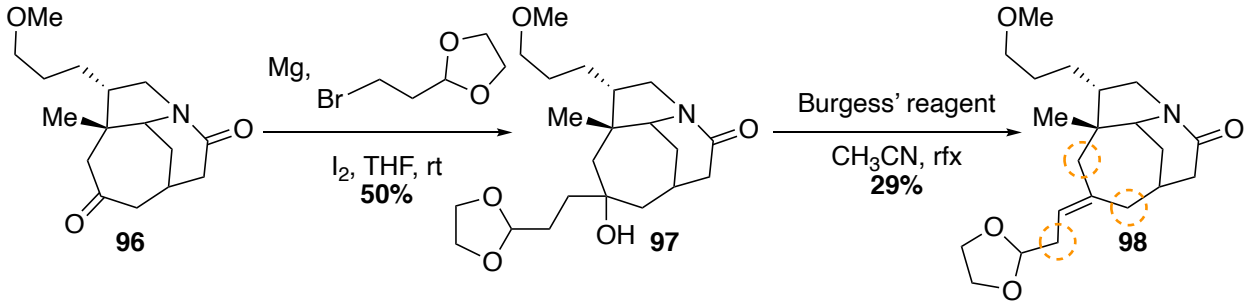
It was envisaged that the synthetic pathway established for the construction of **96** could give access to 2-deoxymacropodumine A. In particular, the ketone functionalization in the seven-membered ring opens several opportunities for future transformation of the building block reported here to more advanced precursors.



2-deoxymacropodumine A

Figure 4. 3. *2-deoxymacropodumine structure. Blue color = azatricyclic[7-6-5] ring core*

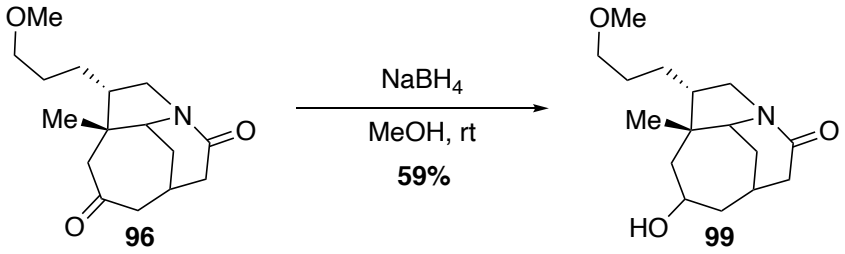
Firstly, we planned to construct the 5-membered ring by means of a Stetter cyclization between an enone and an aldehyde,[170] the latter being incorporated through a 1,2-carbonylic addition of an organomagnesian chain (Scheme 4.18). Therefore, tricyclic scaffold **96** was treated with 2-(2-bromoethyl)-1,3-dioxolane in the presence of Mg turnings to afford intermediate **97** in 50% yield.[171] Next, tertiary alcohol **97** was eliminated with Burgess' reagent and a complex mixture of compounds was recovered, with only the major product **98** being isolated.[172] The location of the obtained olefinic moiety prevented further synthetic steps toward the natural product, as the chemical similarity of three allylic positions (marked in orange) could result in regioselectivity problems.



Scheme 4.18. *1,2-Addition of an organomagnesian chain and further hydroxyl elimination for the synthesis of* ***98****.*

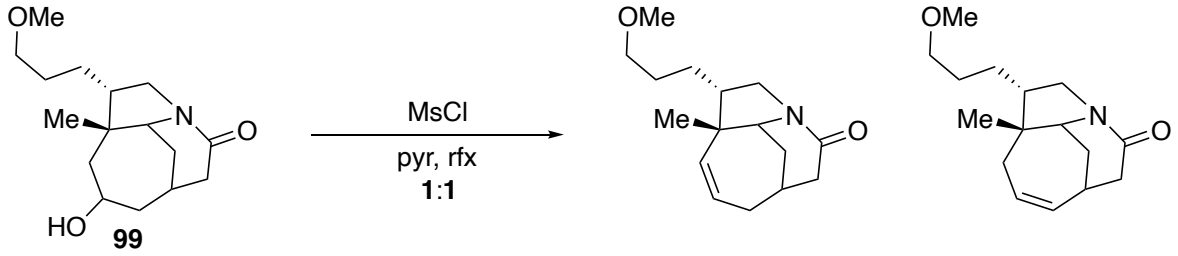
[170] a) Wright, A. C.; Stoltz, B. M. *Chem. Sci.*, **2019**, *10*, 10562–10565 b) Wasnaire, P.; de Merode, T.; Markó, I. E. *Chem. Commun.,* **2007**, 4655–4757.
[171] Seah, K. Y.; Robertson, J. *Tetrahedron*, **2019**, *75*, 130661–130671.
[172] Hjerrild, P.; Tørring, T.; Poulsen, T. B. *Nat. Prod. Rep.,* **2020**, *37*, 1043–1064.

Secondly, the ketone moiety of **96** was reduced by treatment with $NaBH_4$,[124] to afford a C5-epimeric mixture (3:1 ratio) of secondary alcohol **99** in 59% overall yield.



Scheme 4.19**. Reduction of the ketone to obtain alcohol **99.

In the last studies carried out in this thesis, attempts to eliminate the secondary alcohol by treatment with MsCl under pyridine reflux[16b] seemed to provide a 1:1 mixture of the two possible regioisomers. Further purification and characterization processes are required to confirm this result.

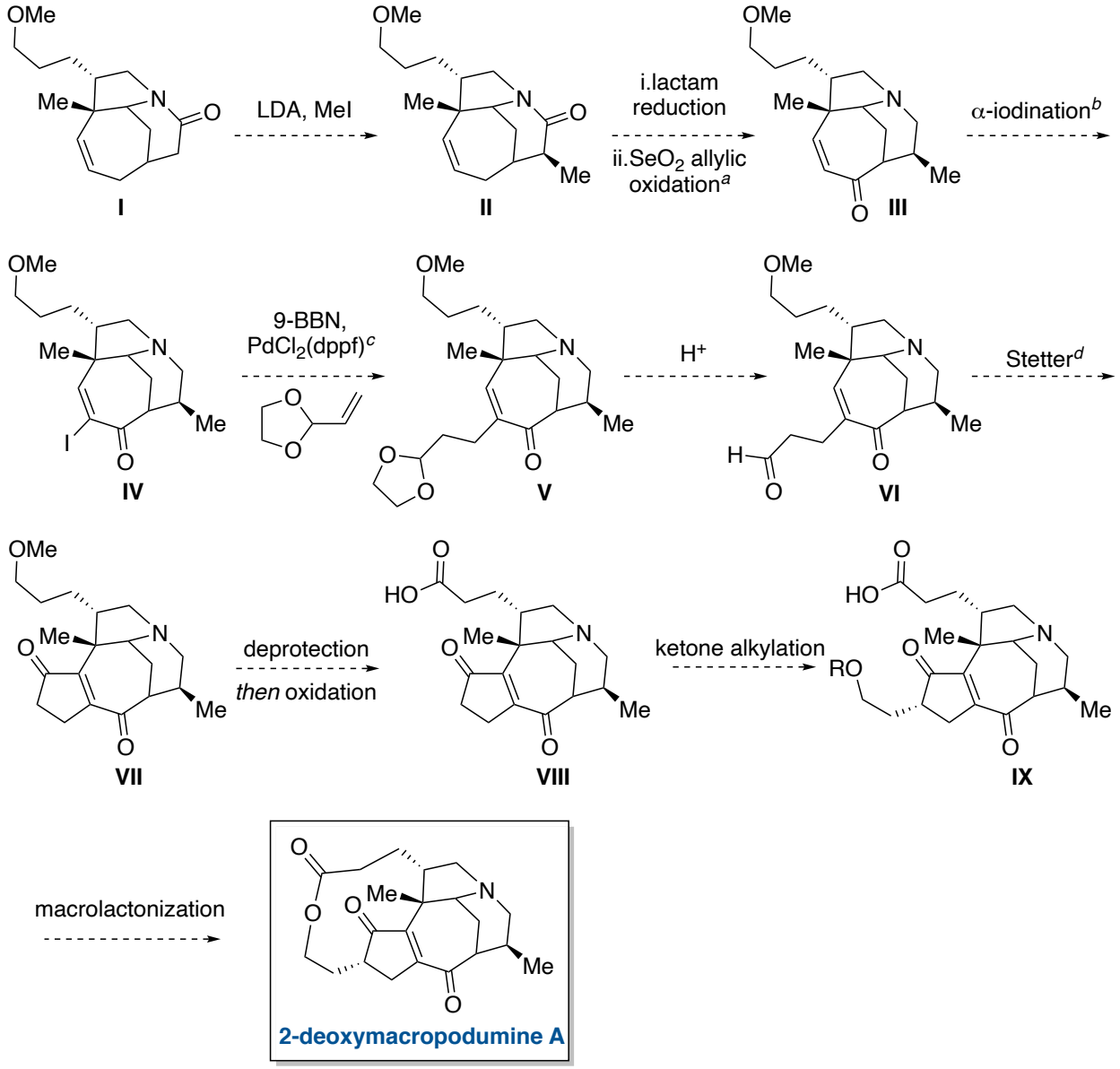


***Scheme 4.20.** Preliminary studies for alcohol elimination.*

Here, briefly described, is one of the possible options for completing the research to achieve the targeted alkaloid using the compounds reported during this doctoral research. A plausible synthetic approach from the available azatricyclic lactam **I** is depicted in Scheme 4.21. After adjustment of the functionalization, followed by an allylic oxidation[173] for ketone installation and subsequent α-iodination,[174] vinyl iodide **IV** would be prepared. Next, coupling of the vinyl iodide moiety with 2-ethyl-1,3-dioxolane[175] could furnish the enone **V**. The formation of the tetracyclic framework in compound **VII** was envisaged by means of a Stetter cyclization from **VI**. After a chemoselective deprotection, adjustment of the oxidation level, and installation of a two-carbon chain, the 11-membered macrolide

[173] Wright, B. J. D.; Chan, C.; Danishefsky, S. J. *J. Nat. Prod.,* **2008**, *71*, 409–414.
[174] Kraft, M. E.; Cran, J.W. *Synlett*, **2005**, *8*, 1263–1266.
[175] a) He, J.; Snapper, M. L. *Tetrahedron*, **2013**, *69*, 7831–7839. b) Amat, M.; Fabregat, R.; Griera, R.; Bosch, J. *J. Org. Chem.,* **2009**, *74*, 1794–1797.

ring of dehydroxymacropodumine A would be assembled at the end by macrolactonization from intermediate **VIII**.



Scheme 4.21. *Proposal for further synthetic studies toward 2-deoxymacropodumine A.*

4.4 Summary and conclusions

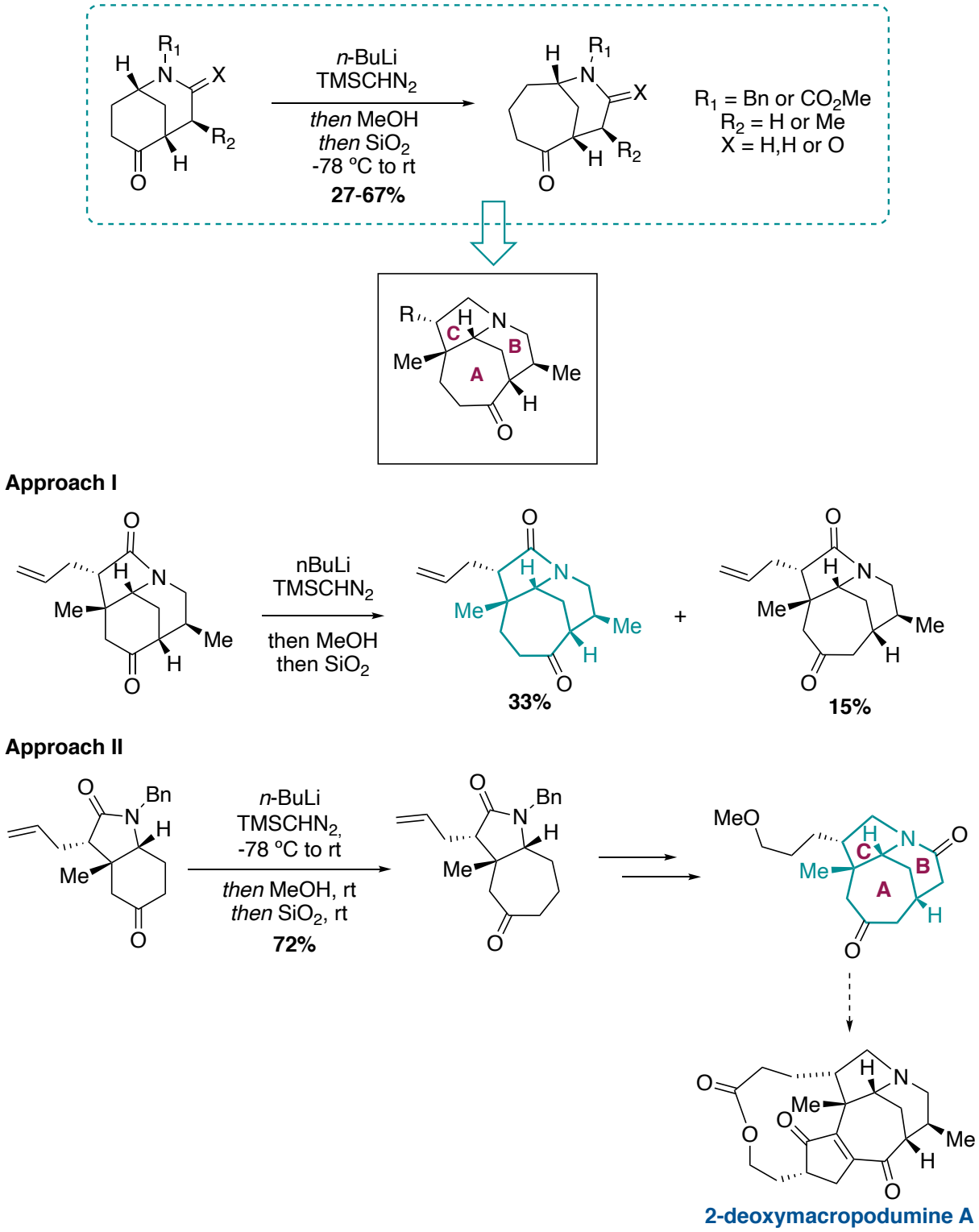
This chapter reports the search for a route to the [5-6-7] ABC ring of *Daphniphyllum* alkaloids by means of ring expansion processes (Scheme 4.22).

Firstly, preliminary studies of a ketone homologation reaction with diazo reagents were performed with a set of easily prepared morphan compounds. After screening several reaction conditions and assessing the influence of the substrate functionalities, the best methodology proved to be the use of $TMSCHN_2$ with *n*-BuLi.

Once the reaction conditions were established, we attempted to obtain the azatricyclic [5,6,7]-ring core. On a first approach, the previously achieved tricyclic 6,6,5-compound **55** was submitted to the ring enlargement methodologies but the reaction was not regioselective and a 2:1 mixture of homologated ketones was obtained.

On a second approach, we tackled the expansion of the octahydroindole ring system, which gave only one regioisomer in good yield. This oppened the possibility for a more efficient synthetic route to the targeted azatricycle. Thus, after several chemical transformations, a trichloroacetamide derivative was prepared, which under reductive radical conditions afforded the tricyclic ABC ring core. Some further synthetic steps were performed following a proposal designed to complete of the synthesis of 2-deoxymacropodumine A.

A manuscript is in preparation for the publication of these results.



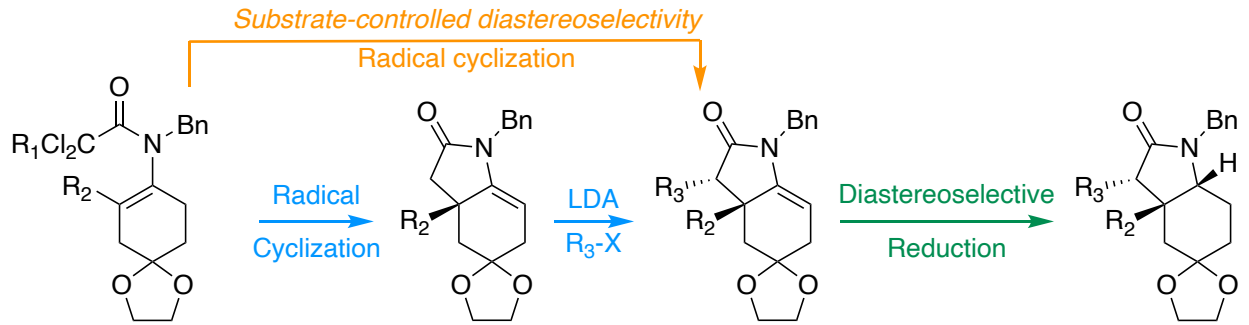
Scheme 4.22. *Conclusions of Chapter 4*

Chapter 5

Conclusions

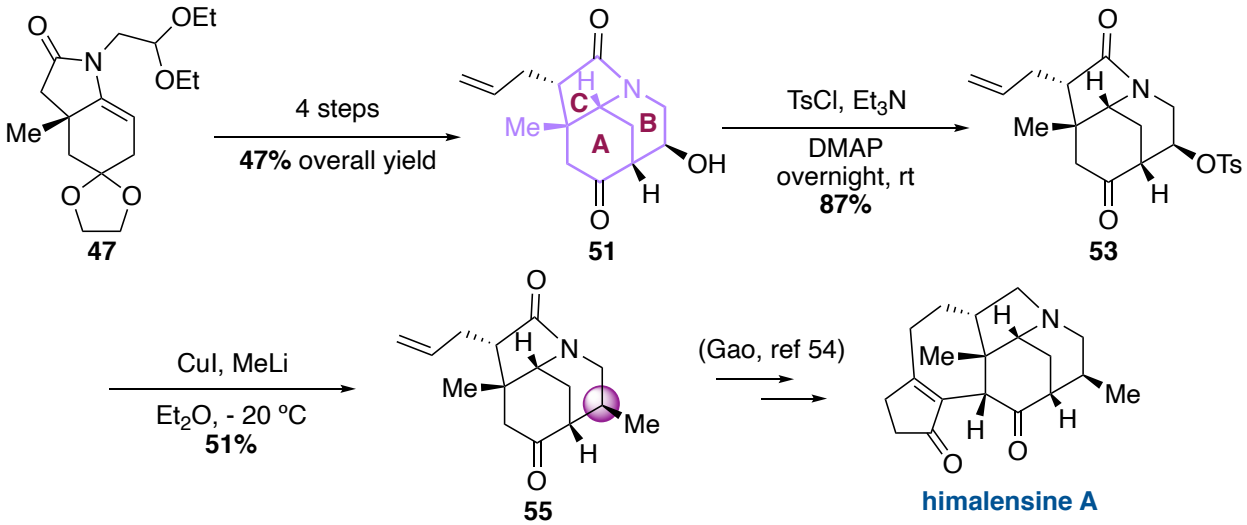
In this thesis, the construction of ABC ring systems embedded in himalensine A and 2-deoxymacropodumine A, two members of *Daphniphyllum* alkaloids family, have been achieved employing highly functionalized octahydroindoles as platform building blocks.

In the first place, a methodology for the synthesis of 3a-methyl and 3a-methoxycarbonyl octahidroindoles was described starting from the 5-*endo*-*trig* radical cyclization of *N*-(2-methylcycloalkenyl)trichloroacetamides and their analogs in the presence of Bu_3SnH and AIBN. The obtained enelactams were diastereoselectively alkylated and methoxycarbonylated providing a set of valuable 3-substituted derivatives. The stereoselectivity of the process arose from the preferential approach of the electrophile reagent to the planar enolate from the opposite face of the methyl group at C-3a. A more direct approach to the 3-functionalized enelactams was achieved by radical cyclization involving carbosubstituted dichloroacetamides in which, depending on the reaction conditions, the resulting γ-lactam radical evolved to an enamide along with over-reduced products. Further reduction processes of the enamide double bond provided octahydroindole derivatives embodying three consecutive stereogenic carbon atoms at C-3, C-3a and C-7a.



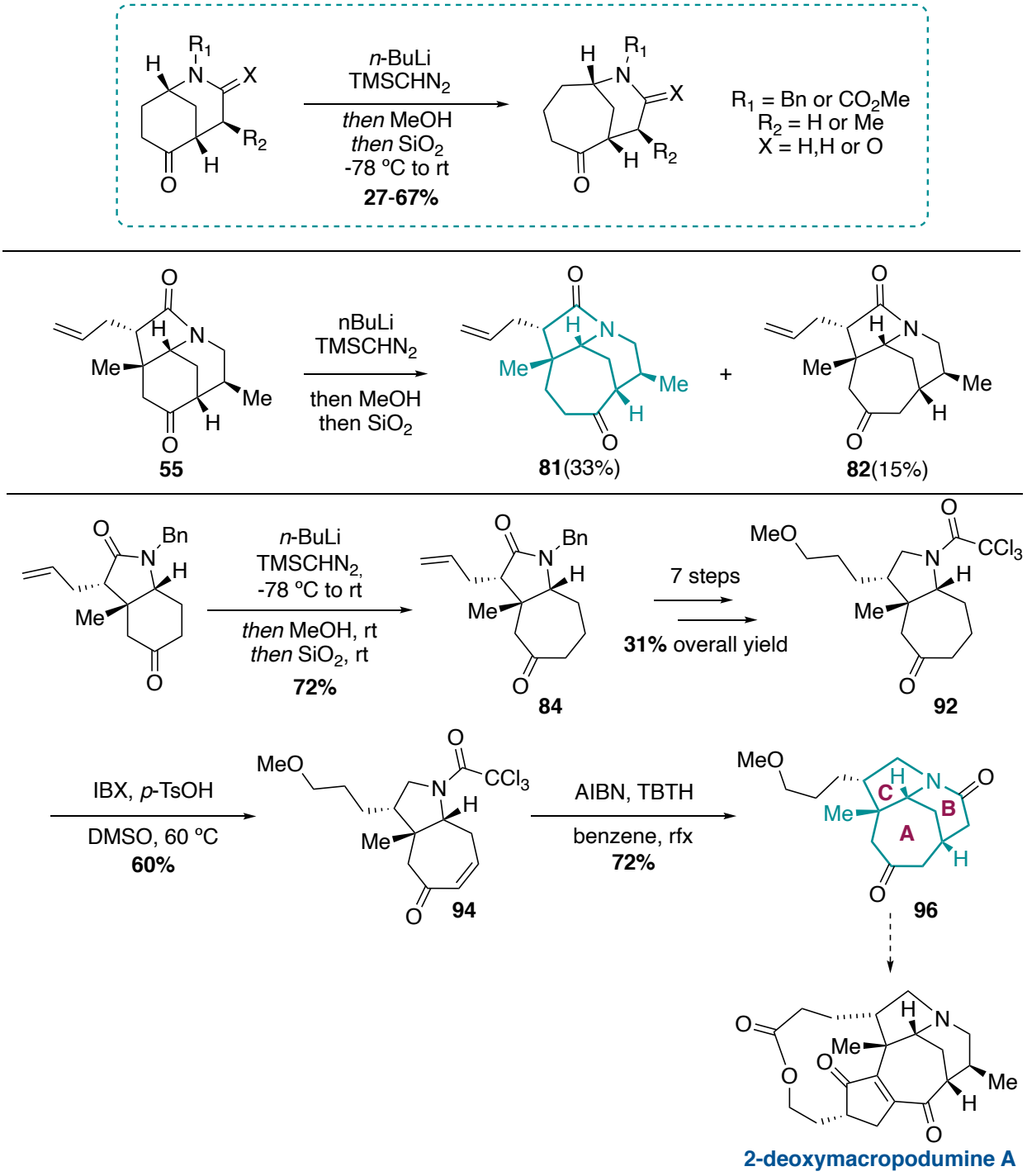
Scheme 5. 1. *Concluding remarks from Chapter 1*

Secondly, the concise access to the tricyclic [5-6-6]-fragment contained in calyciphylline A-type alkaloids was accomplished, resulting in a formal synthesis of himalensine A. The key features of the process commenced with the radical cyclization for the hydroindole ring (AC) construction and after investigation of several methodologies for the closure of the remaining ring B, a new approach to tricyclic ABC ring core was achieved through a diastereoselective aldolic cyclization. The final crucial methyl installation at C-18 was carried out through a tosylate displacement by an organocopper reagent with retention of the center configuration.



Scheme 5. 2. *Concluding remarks from Chapter 2*

Finally, the [5-6-7] tricyclic fragment present in 2-deoxymacropodumine A was furnished via ring enlargement process for the installation of the principal 7-membered ring. Firstly, the ketone homologation methodology was studied employing morphan compounds for the synthesis of B-homomorphans, and the optimized conditions were then applied to the previously studied azatricyclic ABC and azabicyclic AC. Best results were obtained from the latter, which gave regioselectively the nucleus 3a-methylperhydrocyclohepta[b]pyrrole that allowed the preparation of the tricyclic ABC ring core through a radical cyclization. With these promising results, preliminary studies were performed based on a synthetical proposal to obtain 2-deoxymacropodumine A, for which no total synthesis has been reported to date.



***Scheme 5.3**. Concluding remarks from Chapter 3*

Chapter 6

Experimental part

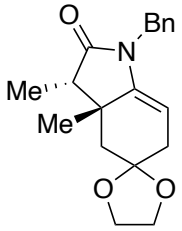
General information

All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions. All product mixtures were analyzed by thin-layer chromatography using TLC silica gel plates with a fluorescent indicator. Analytical thin-layer chromatography was performed on SiO_2 (Merck silica gel 60 F_{254}), and the spots were located by UV light (λ 254 nm) and/or a 1% $KMnO_4$ aqueous solution or anisaldehyde reagent or hexachloroplatinate reagent. Chromatography was carried out on SiO_2 (Carlo Erba silica gel 60A, 35–70 Å), unless otherwise noted. Drying of organic extracts during the reaction workup was performed over anhydrous Na_2SO_4. Solvent evaporation was accomplished with a rotatory evaporator. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution. Chemical shifts of ^1H and ^{13}C NMR spectra are reported in ppm downfield (δ) from Me_4Si. All NMR spectroscopic data assignments are supported by gCOSY and gHSQC experiments. The signal due to residual $CHCl_3$ appearing at δ_H 7.26 and the central resonance of the $CDCl_3$ triplet at δ_C 77.0 were used to reference ^1H and ^{13}C NMR spectra, respectively. Infrared spectra were recorded on a Nicolet 320 FT-IR spectrophotometer. The high-resolution ESI mass spectra were obtained on an Agilent LC/MS-TOF mass spectrometer.

Compounds **1**[80], **2**, **3**, **c-3**, **4a**, **c-4a**,[94] **10**[79], **64**,[156] **A**, **B**,[81] **C**[156], **D**[94] were already described in the literature.

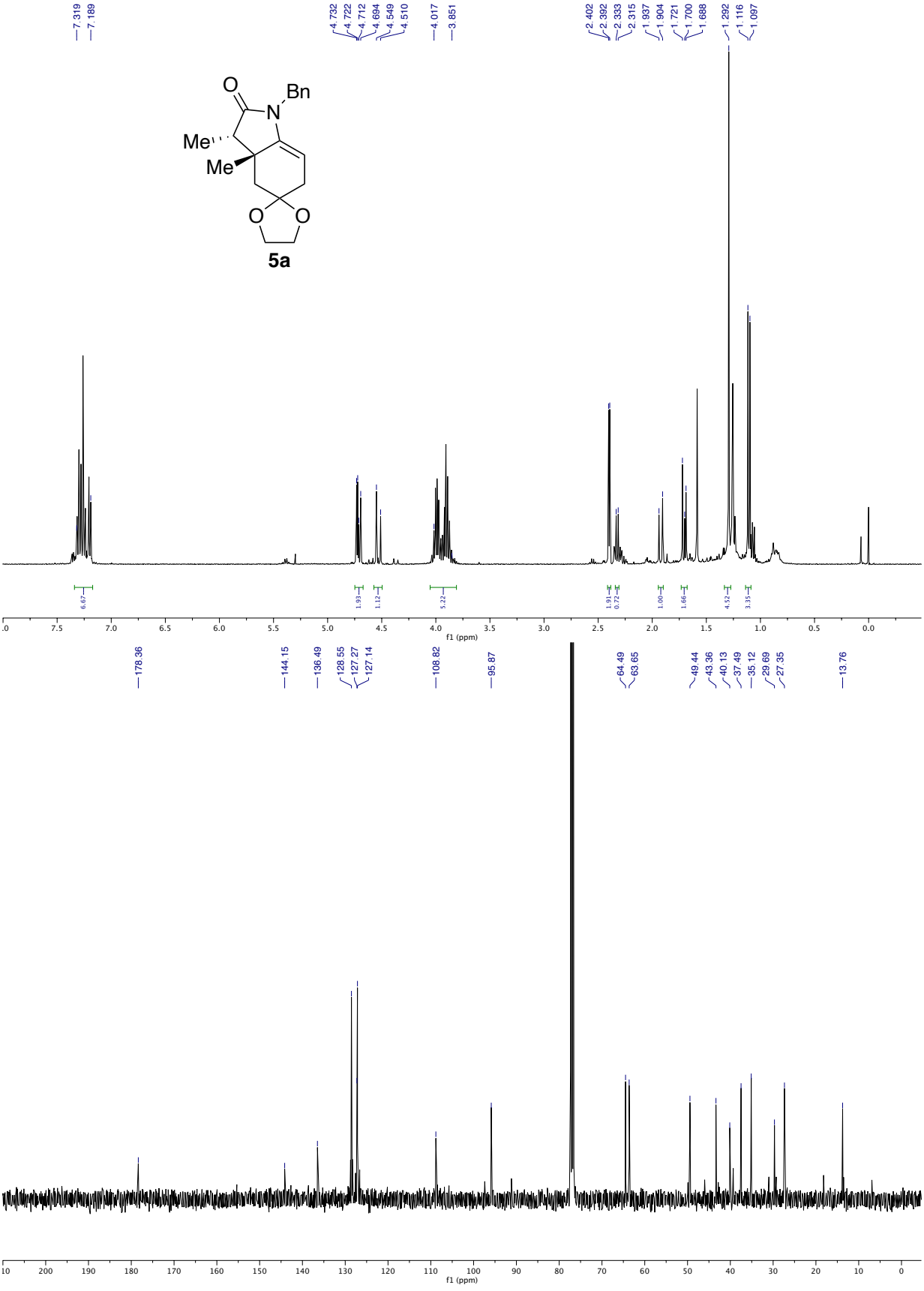
Compounds **34b**, **73**, and **87** were identified after chromatographic purification by their ^1H NMR and ^{13}C NMR spectra but low quantities or the presence of impurities prevented their full characterization.

(3*RS*,3a*SR*)-1-Benzyl-3,3a-dimethyl-1,3a,4,6-tetrahydro-2H-indole-2,5(3H)-dione monoethylene acetal (5a).

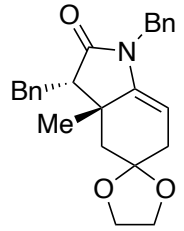


To a solution of **3** (279 mg, 0.93 mmol) in THF (5 mL), cooled to -78 ºC, LDA in THF (1 M, 1.21 mL, 1.3 equiv) was added dropwise. After 30 min at -78 ºC, iodomethane (0.12 mL, 1.86 mmol, 2.0 equiv) was added dropwise. The reaction mixture was allowed to reach room temperature over 2 h, quenched with a saturated solution of NH_4Cl (15 mL), and extracted with ether (3 x 10 mL). The organic extract was dried, concentrated, and purification by chromatography (Al_2O_3, hexane/EtOAc, 9:1 → 1:1) gave **5a** (250 mg, 86%) as a white solid.

mp 96 ºC (hexane). IR (neat) 3020, 2925, 1674, 1455, 1111, 963 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.32–7.17 (m, 5H, Ph), 4.72 (t, J = 4.0 Hz, 1H, H-7), 4.71 and 4.53 (2d, J = 15.4 Hz, 1H each, CH_2Ph), 4.04–3.83 (m, 4H, OCH_2), 2.39 (d, J = 4.0 Hz, 2H, H-6), 2.32 (q, J = 7.4 Hz, 1H, H-3), 1.92 and 1.70 (2 d, J = 13.3 Hz, 1H each, H-4), 1.29 (s, 3H, Me-3a), 1.11 (d, J = 7.4 Hz, 3H, Me-3). ^{13}C NMR ($CDCl_3$,101 MHz): δ 178.4 (C-2), 144.2 (C-7a), 136.5, 128.5, 127.3 and 127.1 (Ph), 108.8 (C-5), 95.9 (C-7), 64.5 and 63.6 (OCH_2), 49.4 (C-3), 43.4 (CH_2Ph), 40.1 (C-3a), 37.5 (C-4), 35.1 (C-6), 27.4 (Me-3a), 13.8 (Me-3). HRMS (ESI-TOF) *m*/*z*: $[M+H]^+$ calcd for $C_{19}H_{24}NO_3$ 314.1751, found 314.1738.


7.319
7.189
4.732
4.722
4.712
4.694
4.549
4.510
4.017
3.851
2.402
2.392
2.333
2.315
1.937
1.904
1.721
1.700
1.688
1.292
1.116
1.097
O
N
Bn
Me
Me
O
O
5a
6.67
1.93
1.12
5.22
1.91
0.72
1.00
1.66
4.52
3.35
f1 (ppm)
178.36
144.15
136.49
128.55
127.27
127.14
108.82
95.87
64.49
63.65
49.44
43.36
40.13
37.49
35.12
29.69
27.35
13.76
f1 (ppm)

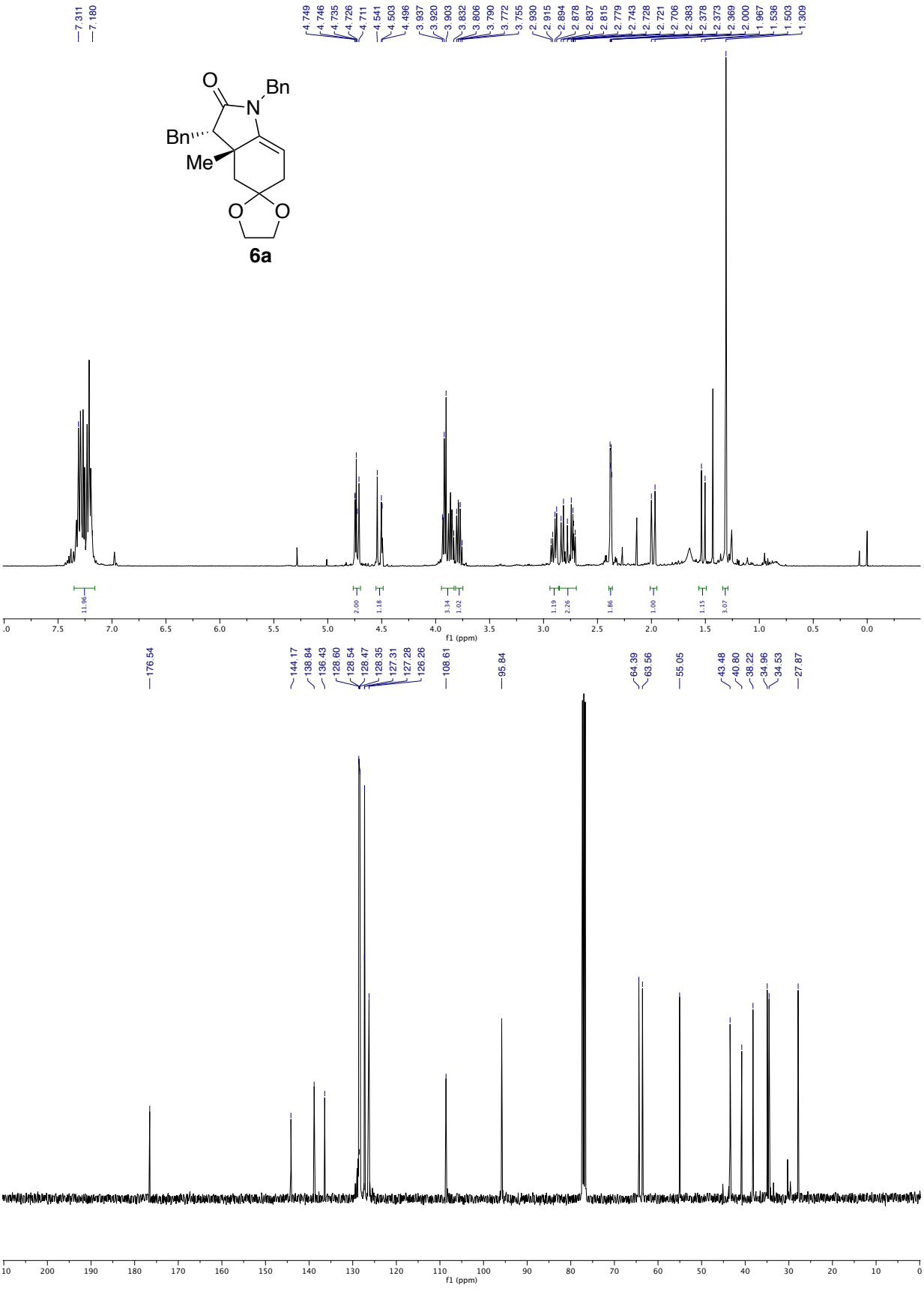
(3*RS*,3a*SR*)-1,3-Dibenzyl-3a-methyl-1,3a,4,6-tetrahydro-2*H*-indole-2,5(3*H*)-dione monoethylene acetal (6a)



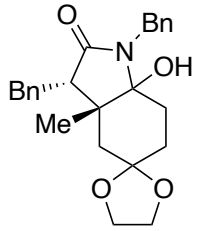
To a solution of **3** (69 mg, 0.23 mmol) in THF (2 mL), cooled to -78 ºC, LDA in THF (1 M, 0.3 mL, 1.3 equiv) was added dropwise. After 30 min at -78 ºC, benzyl bromide (55 mL, 0.46 mmol, 2.0 equiv) was added dropwise. The reaction mixture was allowed to reach room temperature over 2 h, quenched with a saturated solution of NH_4Cl (10 mL), and extracted with ether (3 x 10 mL). The organic extract was dried, concentrated, and purification by chromatography (Al_2O_3, hexane:EtOAc, 9:1 → 3:1) gave **6a** (63 mg, 71%) as a waxy solid.

IR (neat): 3027, 2945, 1681, 1429, 1113, 1066, 700 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.33–7.19 (m, 10H, Ph), 4.74 (t, J = 3.8 Hz, 1H, H-7), 4.73 and 4.52 (2d, J = 15.0 Hz, 1H each, CH_2Ph), 3.95–3.76 (m, 4H, OCH_2), 2.91 (dd, J = 14.4, 6.0 Hz, 1H, CH_2-3), 2.81 (dd, J =14.4, 8.6 Hz, 1H, CH_2-3), 2.73 (dd, J = 8.6, 6.0 Hz, 1H, H-3), 2.38 (2dd, J = 17.4, 3.8 Hz, 2H, H-6), 1.98 and 1.52 (2 d, J = 13.6 Hz, 1H each, H-4), 1.31 (s, 3H, Me). ^{13}C NMR (101 MHz, $CDCl_3$): δ 176.5 (C-2), 144.2 (C-7a), 138.8, 136.5, 128.6, 128.5, 128.4, 127.3, 127.3, 126.3 (Ph), 108.6 (C-5), 95.8 (C-7), 64.4 and 63.6 (OCH_2), 55.0 (C-3), 43.5 (CH_2Ph), 40.8 (C-3a), 38.2 (C-4), 35.0 (C-6), 34.5 (CH_2-3), 27.9 (Me). HRMS (ESI-TOF) *m/z:* $[M + H]^+$ calcd for $C_{25}H_{28}NO_3$ 390.2064, found 390.2058.

When the chromatography was carried out in SiO2, compound 6a partially evolved to the hydrated compound 6c.

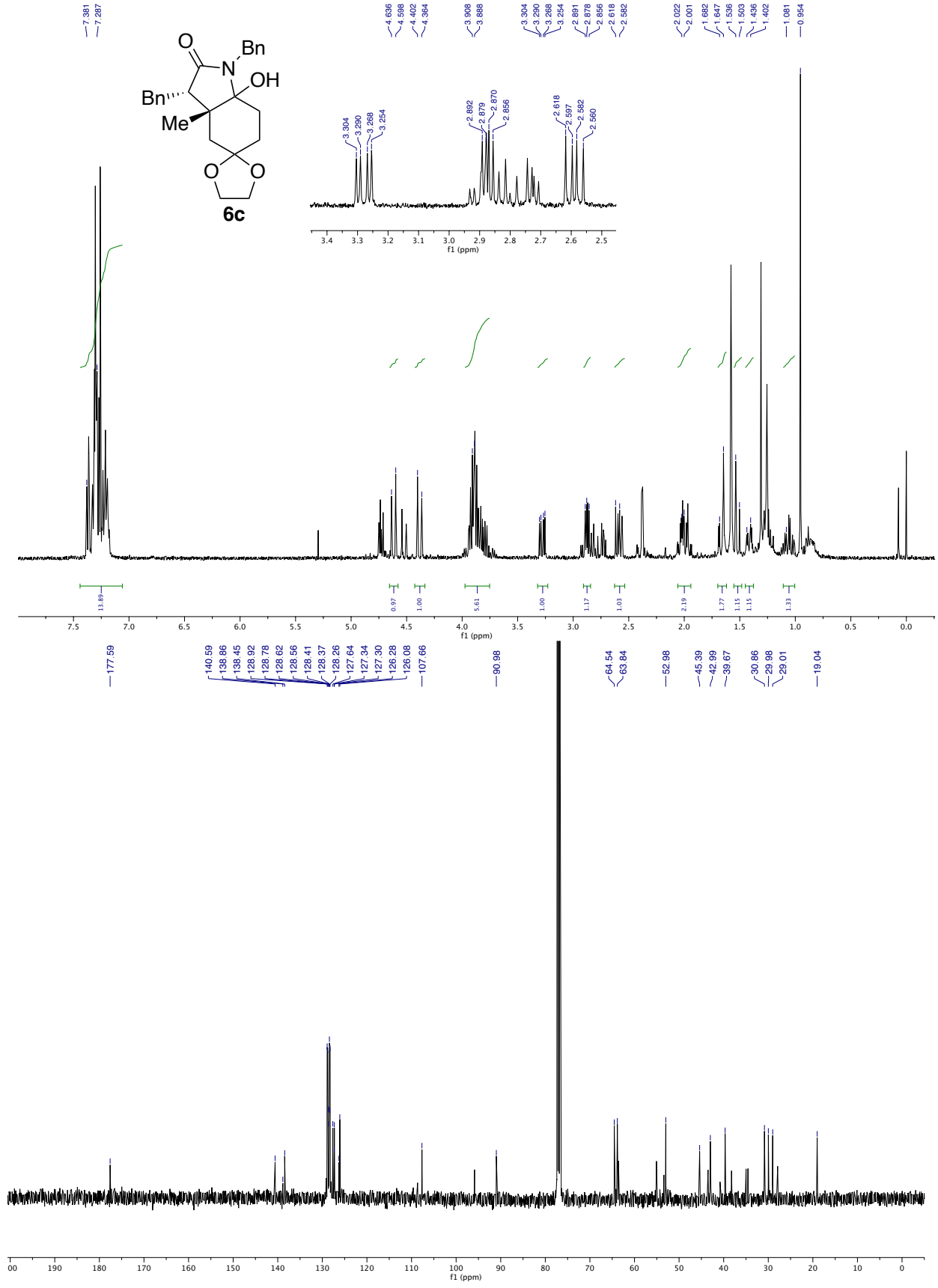

7.311
7.180
4.749
4.746
4.735
4.726
4.711
4.541
4.503
4.496
3.937
3.920
3.903
3.832
3.806
3.790
3.772
3.755
2.930
2.915
2.894
2.878
2.837
2.815
2.779
2.743
2.728
2.721
2.706
2.383
2.378
2.373
2.369
2.000
1.967
1.536
1.503
1.309
O
N
Bn
Bn
Me
O
O
6a
11.96
2.00
1.18
3.34
1.02
1.19
2.26
1.86
1.00
1.15
3.07
f1 (ppm)
176.54
144.17
138.84
136.43
128.60
128.54
128.47
128.35
127.31
127.28
126.26
108.61
95.84
64.39
63.56
55.05
43.48
40.80
38.22
34.96
34.53
27.87
f1 (ppm)

(3RS,3aSR)-1,3-Dibenzyl-7a-hydroxy-3a-methyl-1,3a,4,6,7,7a-hexahydro-2H-indole-2,5(3H)-dione monoethylene acetal (6c).

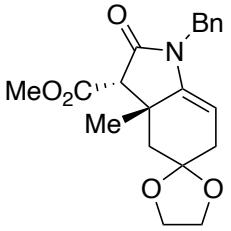


^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38–7.19 (m, 10H, Ph), 4.62 and 4.38 (2 d, *J* = 15.2 Hz, 1H each, CH_2Ph), 3.94–3.81 (m, 4H, OCH_2), 3.28 (dd, *J* = 14.6, 5.6 Hz, 1H, CH_2-3), 2.87 (dd, *J* = 8.4, 5.6 Hz, 1H, H-3), 2.57 (dd, *J* = 14.6, 8.4 Hz, 1H, CH_2-3), 2.07 (m, 2H, H-7), 1.67 and 1.52 (2 d, *J* = 13.6 Hz, 1H each, H-4), 1.49 (ddd, *J* = 13.6, 6.8, 3.4 Hz, 1H, H-6eq.), 1.05 (td, *J* = 13.6, 5.0 Hz, 1H, H-6ax), 0.95 (s, 3H, Me).^{13}C NMR (101 MHz, $CDCl_3$): δ 176.6 (C-2), 140.6 (C-7a), 138.5, 136.5, 128.9, 128.8, 128.4, 128.3, 127.6, 126.1 (Ph), 107.7 (C-5), 91.0 (C-7a), 64.5 and 63.8 (OCH_2), 53.0 (C-3), 45.4 (C-3a), 43.0 (CH_2Ph), 39.7(C-4), 30.9 (C-6), 30.0 (CH_2-3), 29.0 (C-7), 19.0 (Me).

When camphorsulphonic acid (0.04 equiv.) and molecular sieves (5 : 1 in weight) were added to a solution of a 6a/6c mixture in CH_2Cl_2 (0.04 M) and the resulting mixture was heated to reflux for 4 h, pure enamide 6a was recovered.

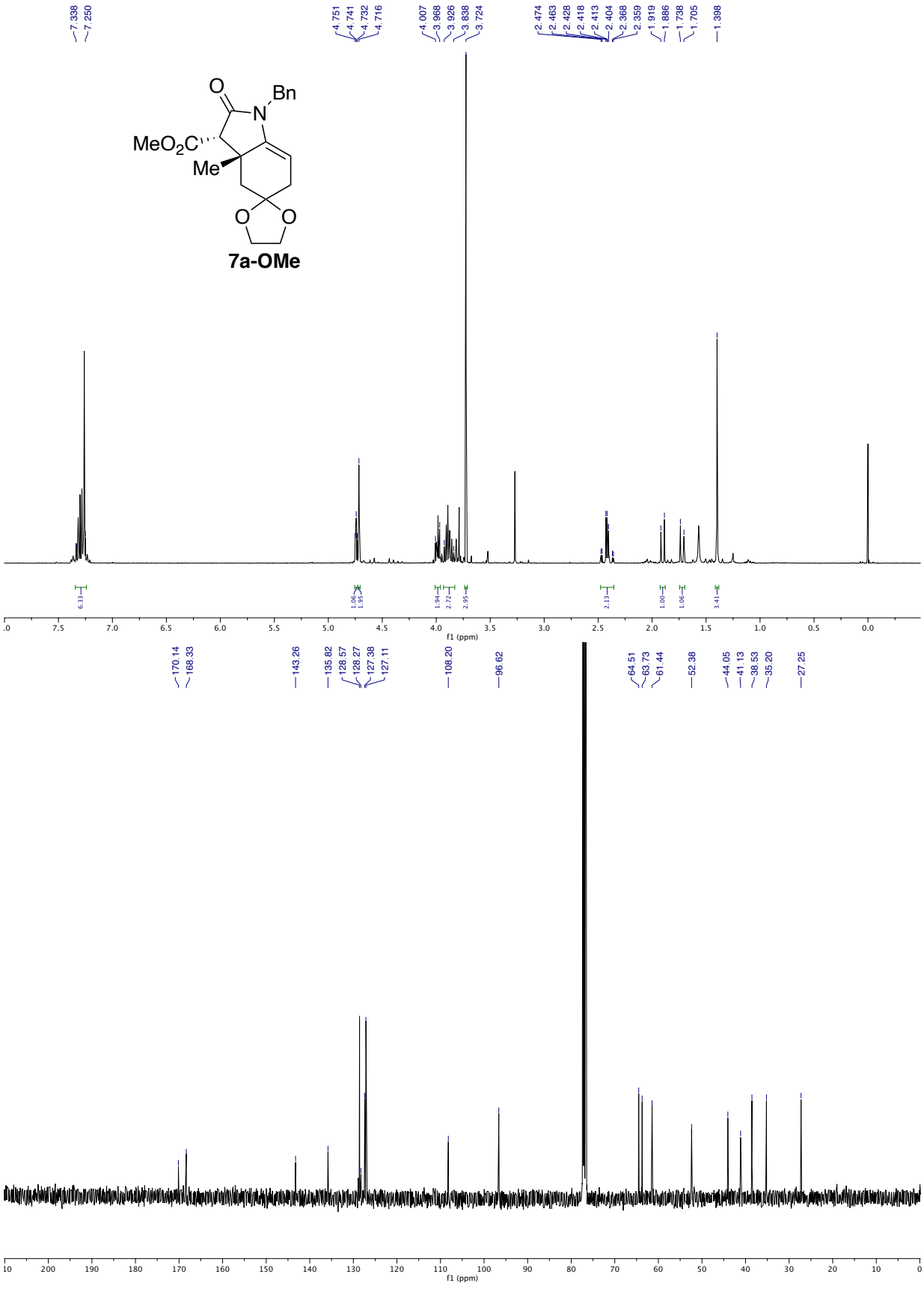

6c

(3*RS*,3a*SR*)-1-Benzyl-3-methoxycarbonyl-3a-methyl-1,3a,4,6-tetrahydro-2*H*-indole-2,5(3*H*)-dione monoethylene acetal (7a-OMe).



To a solution of **3** (100 mg, 0.33 mmol) in THF (1 mL), cooled to -78 ºC, LDA in THF (1 M, 0.43 mL, 1.3 equiv) was added dropwise. After 30 min at -78 ºC, methyl cyanoformate (53 mL, 0.67 mmol, 2.0 equiv) was added dropwise. The reaction mixture was allowed to reach room temperature over 2 h, quenched with a saturated solution of NH_4Cl (10 mL), and extracted with ether (3x 10 mL). The organic extract was dried, concentrated, and purification by chromatography (Al_2O_3, hexane:EtOAc, 9:1 → 3:1) furnished **7a** (73 mg, 61%, dr 9:1) as a waxy solid.

IR (neat): 3026, 2954, 1742, 1686, 1434, 1351, 1170, 1073, 721 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.20 (m, 5 H, Ph), 4.74 (t, J = 3.8 Hz, 1H, H-7), 4.72 (br s, 2H, CH_2Ph), 4.00–3.85 (m, 4 H, OCH_2), 3.72, (s, 3H, OMe), 3.27 (s, 1H, H-3), 2.44–2.40 (m, 2H, H-6), 1.90 and 1.72 (2 d, J = 13.2 Hz, 1H each, H-4), 1.40 (s, 1H, Me). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.1 (CO_2Me), 168.3 (C-2), 143.3 (C-7a), 135.8, 128.6, 127.4, and 127.1 (Ph), 108.2 (C-5), 96.6 (C-7), 64.5 and 63.7 (OCH_2), 61.4 (C-3), 52.4 (OMe), 44.1 (CH_2Ph), 41.1 (C-3a), 38.5 (C-4), 35.2 (C-6), 27.3 (Me). Low peaks derived from its epimer at C-3 were observed. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{20}H_{24}NO_5$ 358.1649, found 358.1647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7.250
4.751
4.741
4.732
4.716
4.007
3.968
3.926
3.838
3.724
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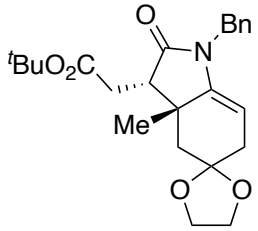
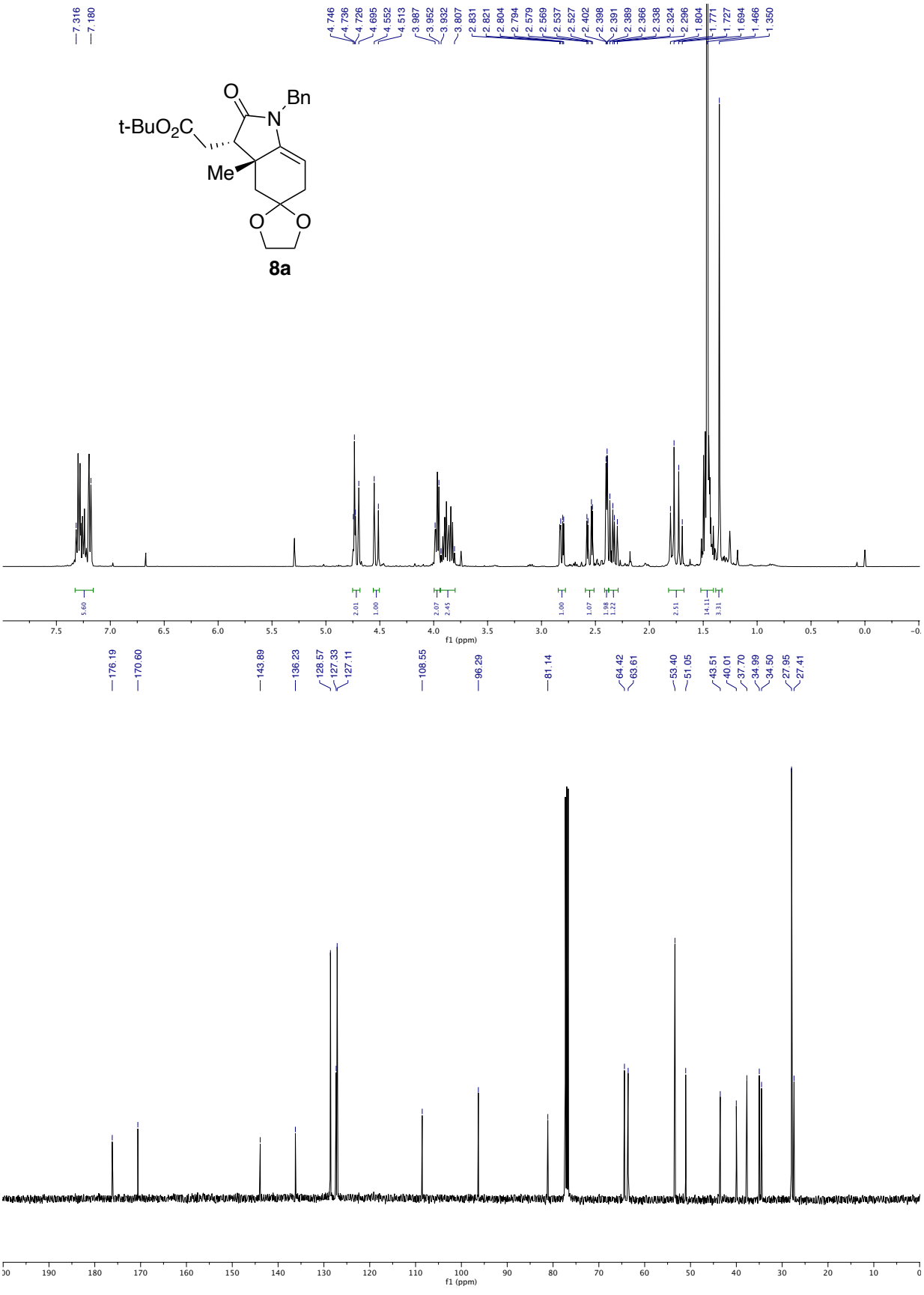
2.463
2.428
2.418
2.413
2.404
2.368
2.359
1.919
1.886
1.738
1.705
1.398
O
N
Bn
MeO2C
Me
O
O
7a-OMe
f1 (ppm)
170.14
168.33
143.26
135.82
128.57
128.27
127.38
127.11
108.20
96.62
64.51
63.73
61.44
52.38
44.05
41.13
38.53
35.20
27.25
f1 (ppm)

(3*RS*,3a*SR*)-1-Benzyl-3-*(tert*-butyloxycarbonyl)methyl-3a-methyl-1,3a,4,6-tetrahydro-2*H*-indole-2,5(3*H*)-dione monoethylene acetal (8a).



To a solution of **3** (105 mg, 0.35 mmol) in THF (1 mL), cooled to -78 ºC, LDA in THF (1 M, 0.46 mL, 1.3 equiv) was added dropwise. After 30 min at -78 ºC, tert-butyl acetate (94 mL, 0.70 mmol, 2.0 equiv) was added dropwise. The reaction mixture was allowed to reach room temperature over 2 h, quenched with a saturated solution of NH_4Cl (10 mL), and extracted with ether (3x 10 mL). The organic extract was dried, concentrated, and purification by chromatography (hexane:EtOAc, 9:1 → 3:1) gave **8a** (120 mg, 83%) as an oil.

IR (neat) 3051, 2976, 2931, 1728, 1687, 1683, 1376, 1150, 1077, 700 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.32–7.18 (m, 5H, Ph), 4.74 (t, *J* = 4.0 Hz, 1H, H-7), 4.72 and 4.53 (2 d, *J* = 15.4 Hz, 1H each, CH_2Ph), 3.99–3.80 (m, 4H, OCH_2), 2.81 (dd, *J* = 11.0, 3.8 Hz, 1H, H-3), 2.55 (dd, *J* = 16.6, 3.8 Hz, 1H, CH_2-3), 2.40 (dd, *J* = 4.0, 1.3 Hz, 2H, H-6), 2.33 (dd, *J* = 16.6, 11.0 Hz, 1H, CH_2-3), 1.79 (dd, *J* = 13.2, 1.3 Hz, H-4eq.), 1.71 (d, *J* = 13.2 Hz, 1H each, H-4ax), 1.47 (s, 9H, Me), 1.35 (s, 3H, Me-3a). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.2 (C-2), 170.6 (CO), 143.9 (C-7a), 136.2, 128.6, 127.3 and 127.1 (Ph), 108.6 (C-5), 96.3 (C-7), 81.1 ($C(CH_3)_3$), 64.4 and 63.6 (OCH_2), 51.1 (C-3), 43.5 (CH_2Ph), 40.0 (C-3a), 37.7 (C-4), 35.0 (C-6), 34.5 (CH_2-3), 28.0 (Me), 27.4 (Me-3a). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{24}H_{32}NO_5$ 414.2275 found 414.2268.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2.324
2.296
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1.727
1.694
1.466
1.350
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Bn
N
t-BuO2C
Me
O
O
8a
5.60
2.01
1.00
2.07
2.45
1.00
1.07
1.98
1.22
2.51
14.11
3.31
f1 (ppm)
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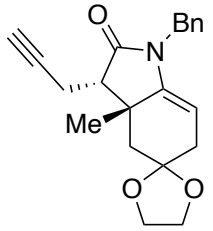
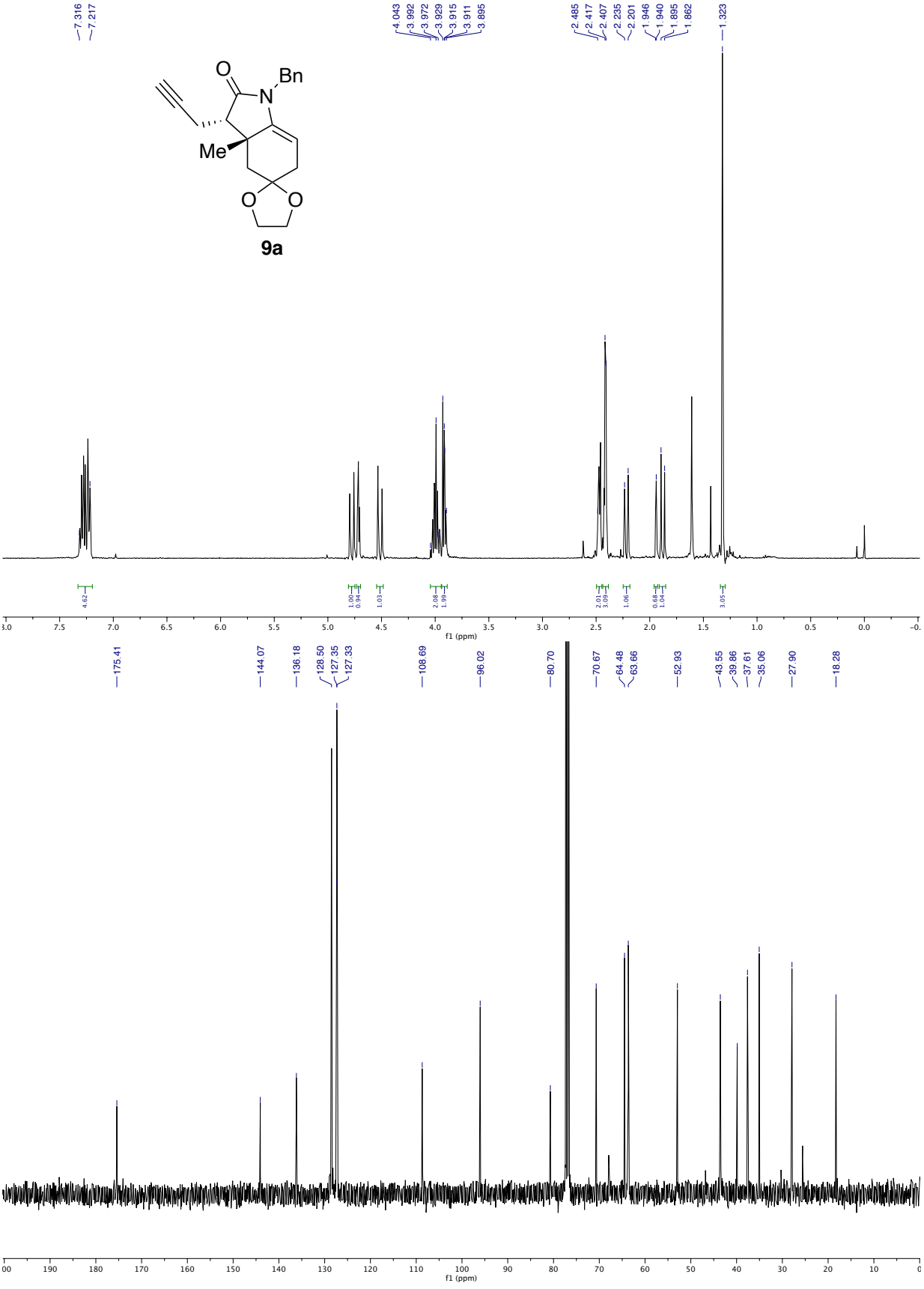
170.60
143.89
136.23
128.57
127.33
127.11
108.55
96.29
81.14
64.42
63.61
53.40
51.05
43.51
40.01
37.70
34.99
34.50
27.95
27.41
f1 (ppm)

(3*RS*,3a*SR*)-1-Benzyl-3a-methyl-3-(prop-2-yn-1-yl)-1,3a,4,6-tetrahydro-2*H*-indole-2,5(3*H*)-dione monoethylene acetal (9a).



To a solution of **3** (107 mg, 0.36 mmol) in THF (1 mL), cooled to -78 ºC, LDA in THF (1 M, 0.46 mL, 1.3 equiv) was added dropwise. After 30 min at -78 ºC, propargyl bromide (80% in toluene, 68 mL, 0.71 mmol, 2.0 equiv) was added dropwise. The reaction mixture was allowed to reach room temperature over 2 h, quenched with a saturated solution of NH_4Cl (10 mL), and extracted with ether (3x 10 mL). After work-up, alkyne **9a** (110 mg, 82%) was obtained essentially pure as a waxy solid.

IR (neat): 3289, 2925, 1723, 1683, 1407, 1077, 991 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.32–7.22 (m, 5H, Ph), 4.78 (d, *J* = 15.2 Hz, 1H, CH_2Ph), 4.72 (t, *J* = 3.8 Hz, 1H, H-7), 4.52 (d, *J* = 15.2 Hz, 1H, CH_2Ph), 4.04–3.90 (m, 4H, OCH_2), 2.49–2.46 (m, 2H, CH_2-3), 2.43–2.40 (m, 3H, H-3 and H-6), 2.22 (d, *J* = 13.2 Hz, 1H, H-4),1.94 (m, 1H, ≡CH), 1.88 (d, *J* = 13.2 Hz, 1H, H-4), 1.32 (s, 3H, Me).^{13}C NMR (101 MHz, $CDCl_3$): δ 175.4 (C-2), 144.1 (C-7a), 136.2, 128.5, 127.4, and 127.3 (Ph), 108.7 (C-5), 96.0 (C-7), 80.7 (≡C), 70.7 (≡CH), 64.5 and 63.7 (OCH_2), 52.9 (C-3), 43.6 (CH_2Ph), 39.9 (C-3a), 37.6 (C-4), 35.1 (C-6), 27.8 (Me), 18.3 (3-CH_2). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{21}H_{24}NO_3$ 338.1751, found 338.1749.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2.485
2.417
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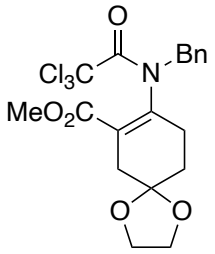
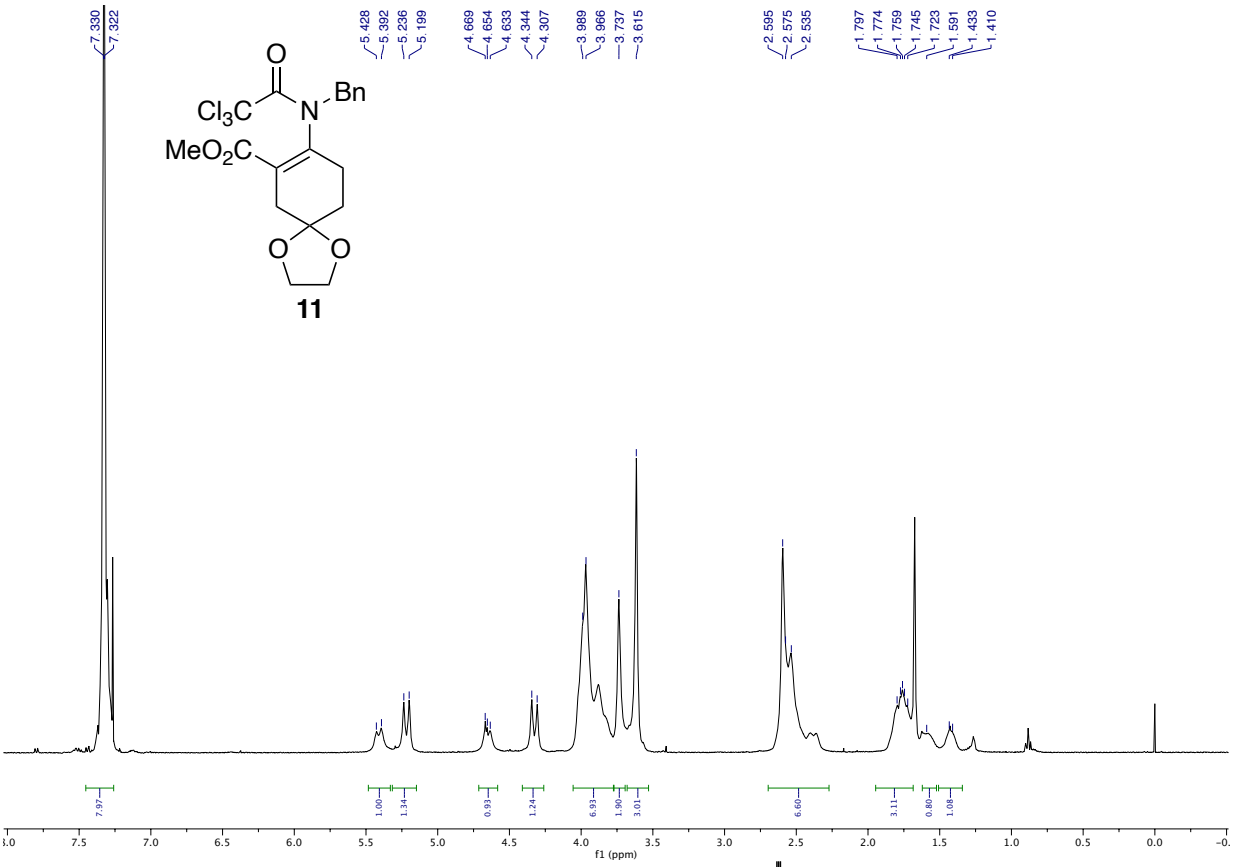
2.235
2.201
1.946
1.940
1.895
1.862
1.323
O
Bn
N
Me
O
O
9a
4.62
1.00
0.94
1.03
2.08
1.99
2.01
3.09
1.06
0.68
1.04
3.05
f1 (ppm)
175.41
144.07
136.18
128.50
127.35
127.33
108.69
96.02
80.70
70.67
64.48
63.66
52.93
43.55
39.86
37.61
35.06
27.90
18.28
f1 (ppm)

_N_-Benzyl-2,2,2-trichloro-_N_-(2-methoxycarbonyl-4-oxocyclohex-1-en-1-yl) acetamide ethylene acetal (11)



Benzylamine (0.74 mL, 6.7 mmol, 1.5 equiv) was added to a solution of 2-methoxycarbonyl-1,4-cyclohexanedione 4-ethylene acetal (**10**, 0.97 g, 4.5 mmol, 1 equiv) in benzene (7 mL) with anhydrous Na_2SO_4 (5:1 by weight). The resulting mixture was stirred at reflux temperature overnight, cooled to room temperature, and $MgSO_4$ was added. The reaction mixture was filtered, concentrated, and redissolved in CH_2Cl_2 (20 mL). A solution of CH_2Cl_2 (2 mL) containing NEt_3 (1.25 mL, 8.9 mmol, 2 equiv) was added dropwise with stirring at room temperature. Afterwards, trichloroacethyl chloride (0.97 mL, 8.7 mmol, 1.9 equiv) was added dropwise. The solution was stirred at reflux for 24 h, washed with HCl (1 M, 10 mL) and brine (10 mL), dried, and concentrated to give a yellow crude material, which was purified by chromatography (hexane:EtOAc 9:1→ 4:1) to give **11** (1.13 g, 56%), as a yellow oil.

IR (neat) 3031, 2950, 2884, 1714, 1675, 1434, 1387, 1244, 1141, 1120, 827, 700 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) 3 : 2 mixture of rotamers δ 7.37–7.28 (br s, 5H) 5.40 and 4.65 (2 br d, 1H each, CH_2Ph minor rotamer), 5.22 and 4.32 (2 d, 1H each, CH_2Ph, J = 15.0 Hz, major rotamer), 4.00–3.75 (m, 4H), 3.74 and 3.62 (2 br s, 3H, minor and major), 2.60–2.30 (m, 4H), 1.80–1.60 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) major rotamer: δ 165.4, 160.6, 145.5, 136.0, 130.1, 128.5, 126.9, 106.1, 64.7, 64.5, 56.5, 52.2, 36.4, 30.9, 30.7; minor rotamer: δ 165.4, 160.6, 146.4, 133.7, 128.7, 127.8, 125.5, 106.2, 64.2, 54.7, 52.2, 36.1, 30.4, 29.1. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{19}H_{21}Cl_3NO_5$ 448.0480, found 448.0459.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7.322
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5.199
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4.654
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4.307
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3.737
3.615
2.595
2.575
2.535
1.797
1.774
1.759
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1.433
1.410
O
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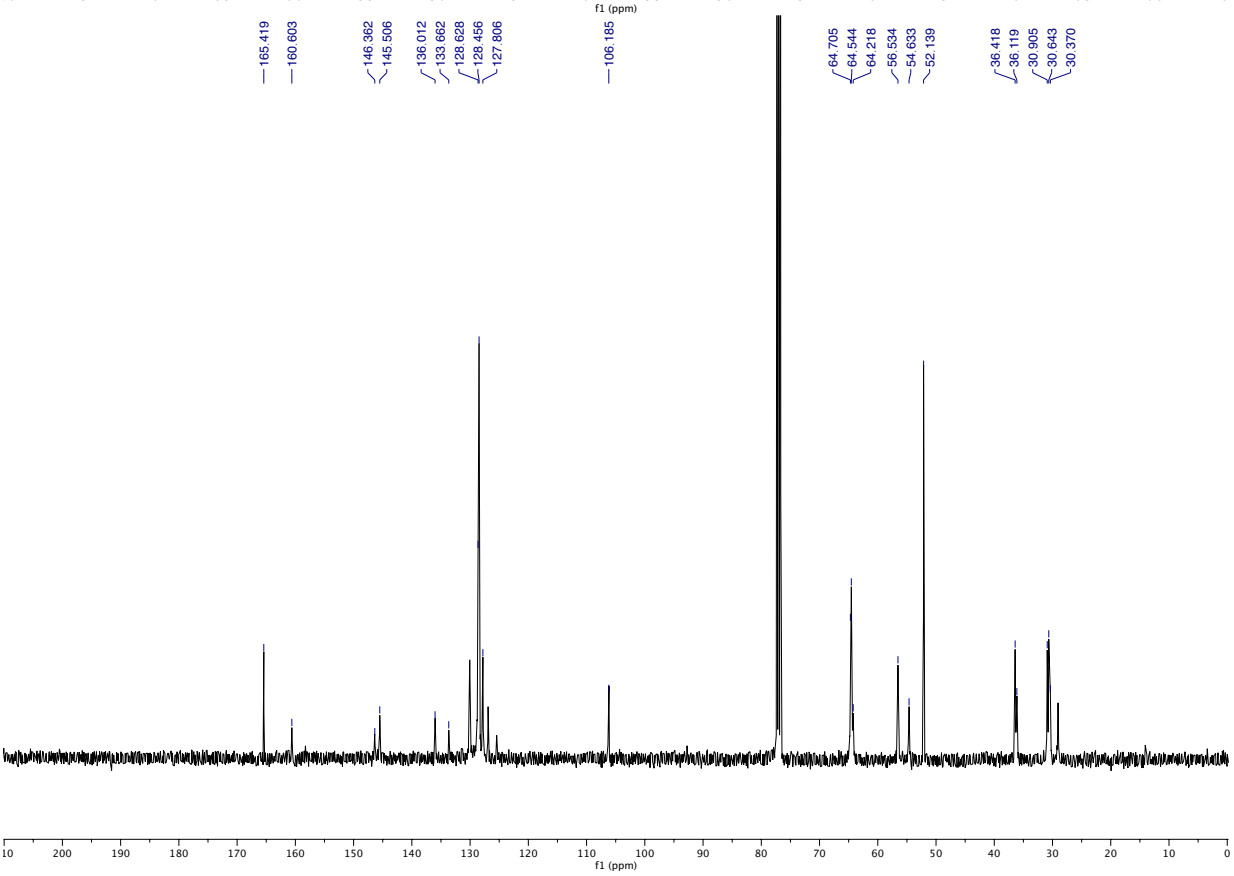
N
Bn
MeO2C
O
O
11
f1 (ppm)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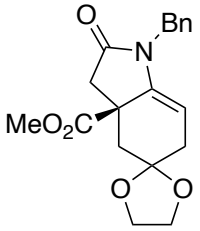
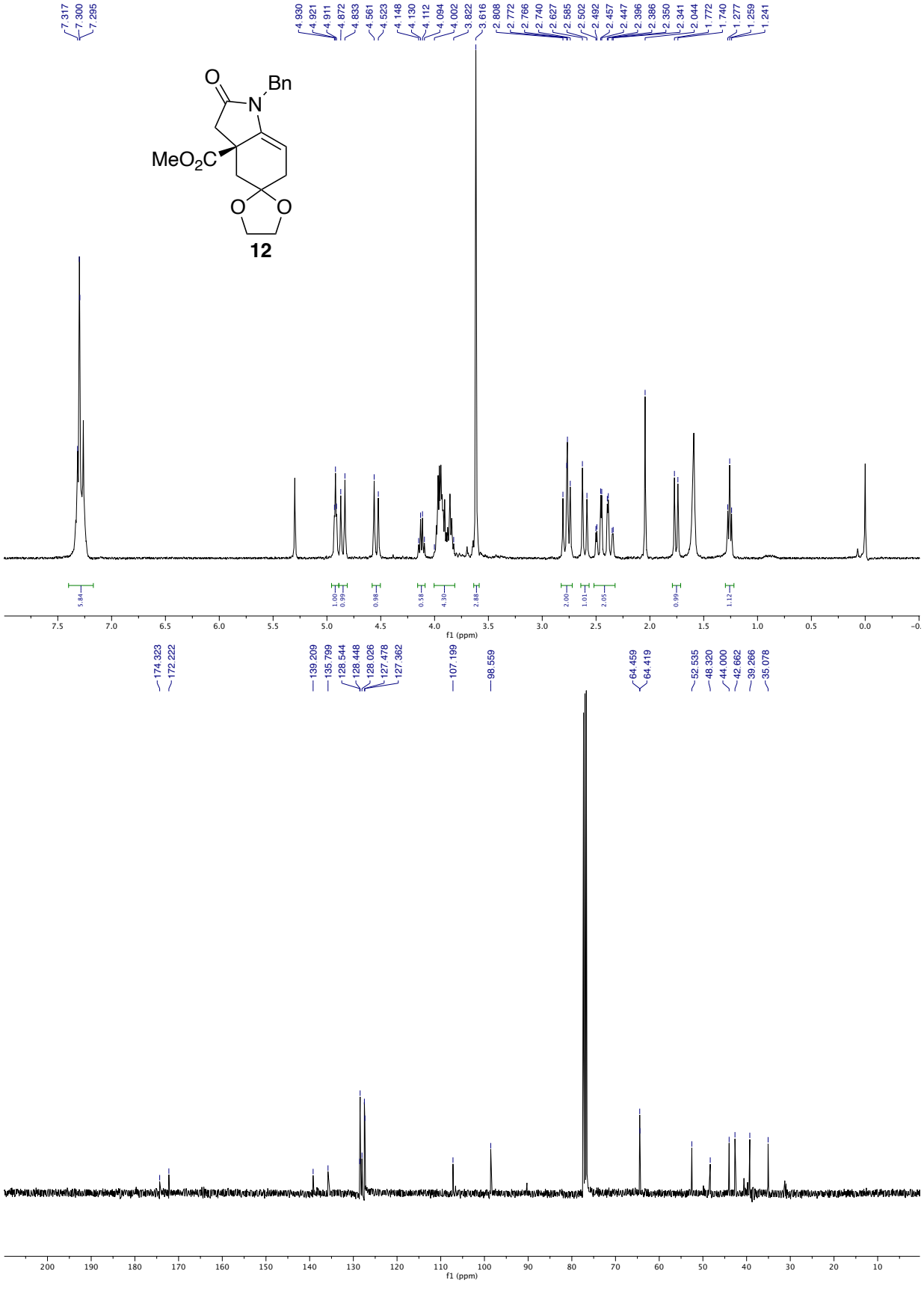
127.806
106.185
64.705
64.544
64.218
56.534
54.633
52.139
36.418
36.119
30.905
30.643
30.370
f1 (ppm)

1-Benzyl-3a-methoxycarbonyl-1,3a,4,6-tetrahydro-2*H*-indole-2,5(3*H*)-dione monoethylene acetal (**12**).



To a solution of **11** (1.13 g, 2.5 mmol, 1 equiv) in benzene (30 mL) at reflux was added a solution of Bu_3SnH (2.17 mL, 8.05 mmol, 3.2 equiv) and AIBN (123 mg, 0.74 mmol, 0.3 equiv) in benzene (30 mL) over 3 h with a syringe pump. After an additional 1 h, the mixture was concentrated and purified by chromatography (hexane:EtOAc, 9.5:0.5→1:1). First, a mixture of **12** and **12b-Cl** was eluted in 1:0.7 ratio (372 mg, 17% for **12b-Cl**) and then a pure sample of **12** was obtained as a white solid (146 mg, 43% for **12**) in a 60% overall yield.

mp 117 °C (hexane). IR (neat): 3030, 2949, 1724, 1679, 1434, 1091, 731 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.34–7.25 (m, 5H, Ph), 4.92 (t, *J* = 3.8 Hz, 1H, H-7), 4.85 and 4.54 (2 d, *J* = 15.6 Hz, 1H each, CH_2Ph), 3.98–3.85 (m, 4H, OCH_2), 3.62 (s, 3H, OMe), 2.79 (d, *J* = 16.8 Hz, 1H, H-3), 2.76 (d, *J* = 12.8 Hz, 1H, H-4), 2.60 (d, *J* = 16.8 Hz, 1H, H-3), 2.47 and 2.37 (2 dd, *J* = 17.8, 3.8 Hz, 1H each, H-6), 1.76 (d, *J* = 12.8 Hz, 1H, H-4); ^{13}C NMR (101 MHz, $CDCl_3$): d 174.3 (C-2), 172.2 (CO_2Me), 139.2 (C-7a), 135.8, 128.4, 127.5, and 127.4 (Ph), 107.2 (C-5), 98.6 (C-7), 64.5 and 64.4 (OCH_2), 52.5 (OMe), 48.3 (C-3a), 44.0 (CH_2Ph), 42.7 (C-3), 39.3 (C-4), 35.1 (C-6). HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{19}H_{22}NO_5$ 344.1492, found 344.1480.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4.112
4.094
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3.822
3.616
2.808
2.772
2.766
2.740
2.627
2.585
2.502
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2.457
2.447
2.396
2.386
2.350
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f1 (ppm)
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98.559
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48.320
44.000
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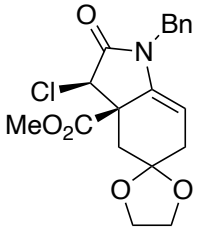
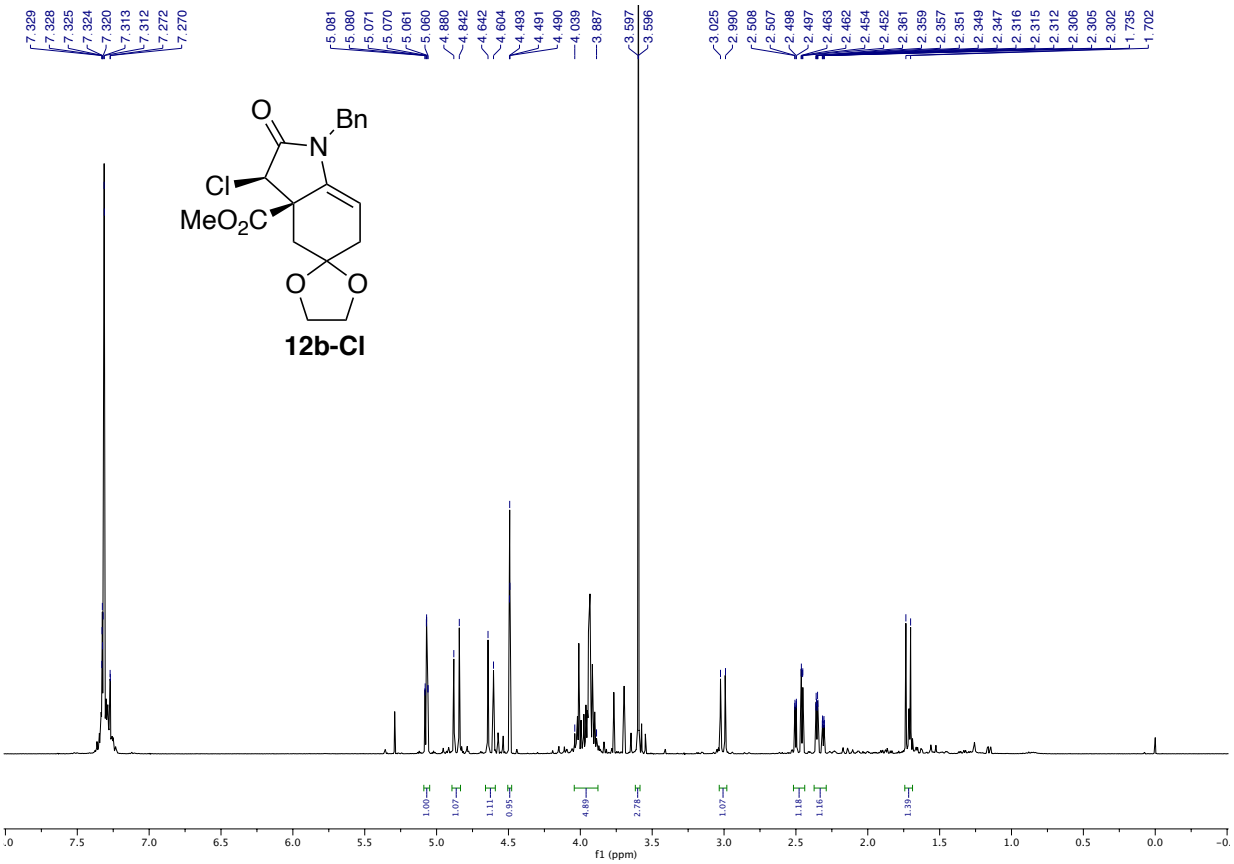
39.266
35.078
f1 (ppm)

(3*RS*, 3a*RS*)-1-Benzyl-3-chloro-3a-methoxycarbonyl-1,3a,4,6-tetrahydro-2*H*-indole-2,5(3*H*)-dione monoethylene acetal (12b-Cl)



IR (neat) 3031, 2949, 1731, 1686, 1403, 1164, 1056, 974, 733, 699 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.34–7.25 (m, 5H, Ph), 5.07 (t, J = 4.0 Hz, 1H, H-7), 4.86 and 4.63 (2 d, J = 15.4 Hz, 1H each, CH_2Ph), 4.49 (s, 1H, H-3), 4.05–3.80 (m, 4H, OCH_2), 3.60 (s, 3H, OMe), 3.01 (dd, J = 13.0, 1.6 Hz, 1H, H-4), 2.48 and 2.34 (2 dd, J = 18.0, 4.0 Hz, 1H each, H-6), 1.72 (d, J = 13.0 Hz, 1H, H-4). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.4 (C-2), 167.8 (CO_2Me), 135.6 (C-7a), 135.1, 128.6, 127.9, and 127.7 (Ph), 106.6 (C-5), 100.8 (C-7), 64.4 and 64.3 (OCH_2), 62.1 (C-3), 55.0 (C-3a), 52.5 (OMe), 45.2 (CH_2Ph), 37.2 (C-4), 35.0 (C-6). HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{19}H_{21}ClNO_5$ 378.1103, found 378.1090.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Bn
Cl
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12b-Cl
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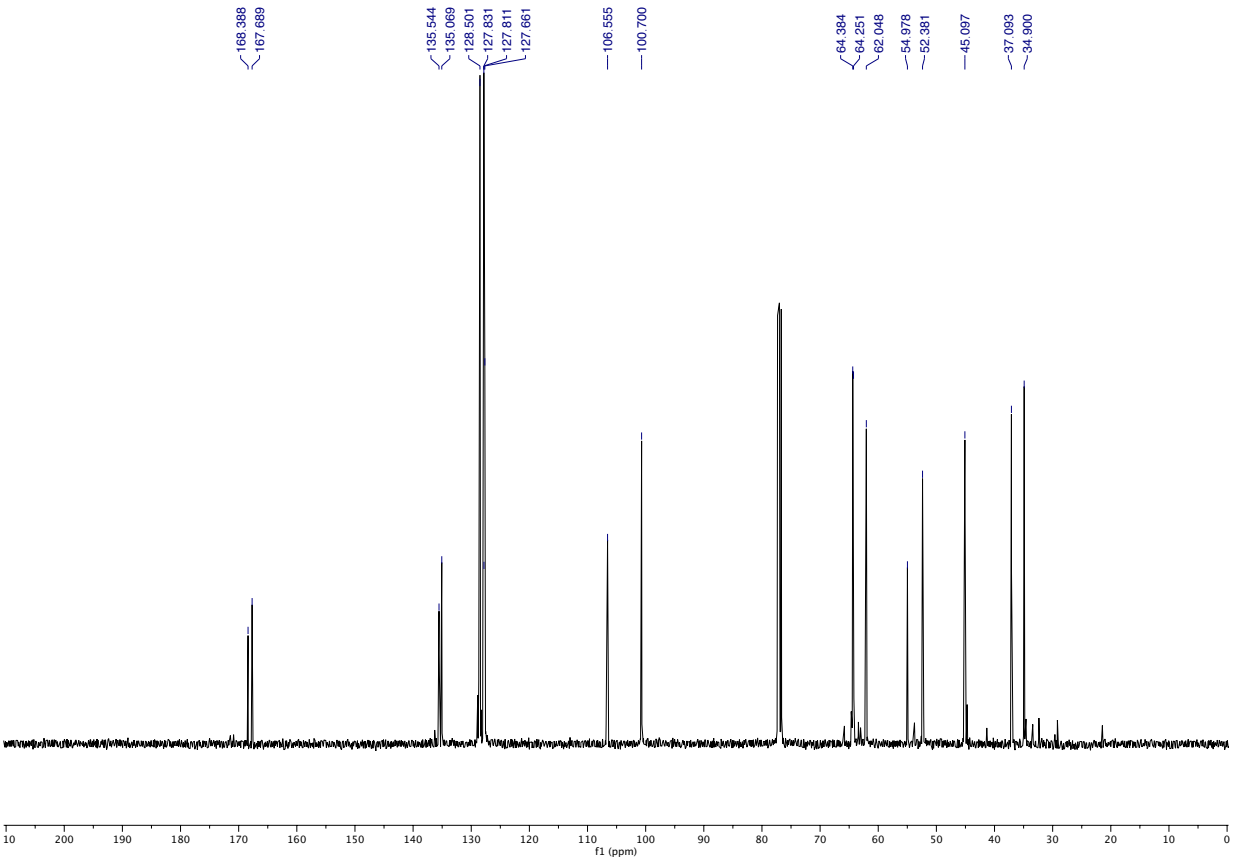
1.39
f1 (ppm)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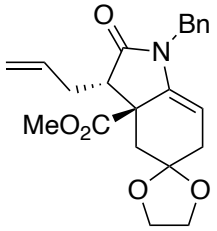
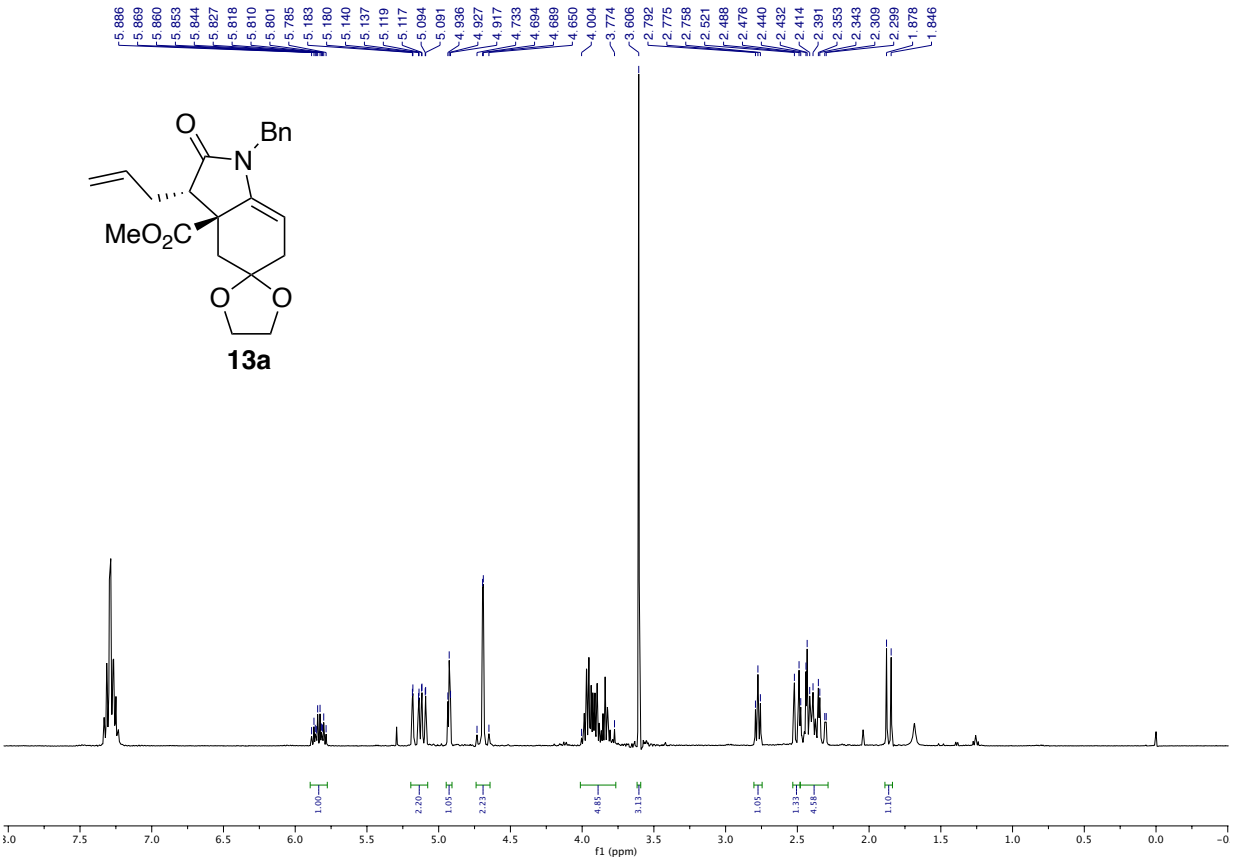
62.048
54.978
52.381
45.097
37.093
34.900
f1 (ppm)

(3*RS*,3a*SR*)-3-Allyl-1-benzyl-3a-methoxycarbonyl-1,3a,4,6-tetrahydro-2*H*-indole-2,5(3*H*)-dione monoethylene acetal (13a).



To a cooled solution (-78 °C) of **12** (70 mg, 0.20 mmol, 1 equiv) in THF (0.6 mL), a solution of LHMDS in THF (1 M, 0.27 mL, 1.3 equiv) was added dropwise. After 30 min at -78 °C, allyl bromide (40 μL, 0.4 mmol, 2.0 equiv) was added dropwise. The reaction mixture was allowed to reach room temperature over 2 h, quenched with a saturated solution of NH_4Cl, and extracted with ether. The organic extract was dried with Na_2SO_4, filtered through silica gel, and concentrated to afford **13a** (65 mg, 83%) as a white solid.

mp 116 ºC (hexane). IR (neat) 3029, 2948, 1721, 1680, 1433, 1236, 1149, 1117, 729, 697 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.35–7.23 (m, 5H, Ph), 5.89–5.79 (m, 1H, =CH), 5.16 (d, J = 16.8 Hz, 1H, =CH_2-*trans*), 5.11 (d, J = 10.2 Hz, 1H, =CH_2-*cis*), 4.93 (t, J = 3.7 Hz, 1H, H-7), 4.72 and 4.67 (2d, J = 14.0 Hz, 1H each, CH_2Ph), 3.99–3.81 (m, 4H, OCH_2), 3.61 (s, 3H, OMe), 2.78 (t, J = 6.9 Hz, 1H, H-3), 2.51 (d, J = 13.2 Hz, 1H, H-4), 2.46 (dd, J = 17.9, 3.2 Hz, 1H, H-6), 2.45–2.37 (m, 2H, CH_2-3), 2.33 (dd, J = 17.9, 4.2 Hz, 1H, H-6), 1.86 (d, J = 13.2 Hz, 1H, H-4). ^{13}C NMR ($CDCl_3$,1011 MHz) δ 174.9, 174.8 (CO and C-2), 138.4 (C-7a), 136.1 (Ph), 134.2 (=CH), 128.5, 127.5, and 127.4 (Ph), 117.7 (=CH_2), 107.4 (C-5), 99.0 (C-7), 64.5 and 64.4 (OCH_2), 52.6 (OMe), 52.0 (C-3a), 50.1 (C-3), 44.2 (CH_2Ph), 35.0 (CH_2-3), 34.2 (C-4), 33.1 (C-6). HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{22}H_{26}NO_5$ 384.1805, found 384.179.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5.119
5.117
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5.091
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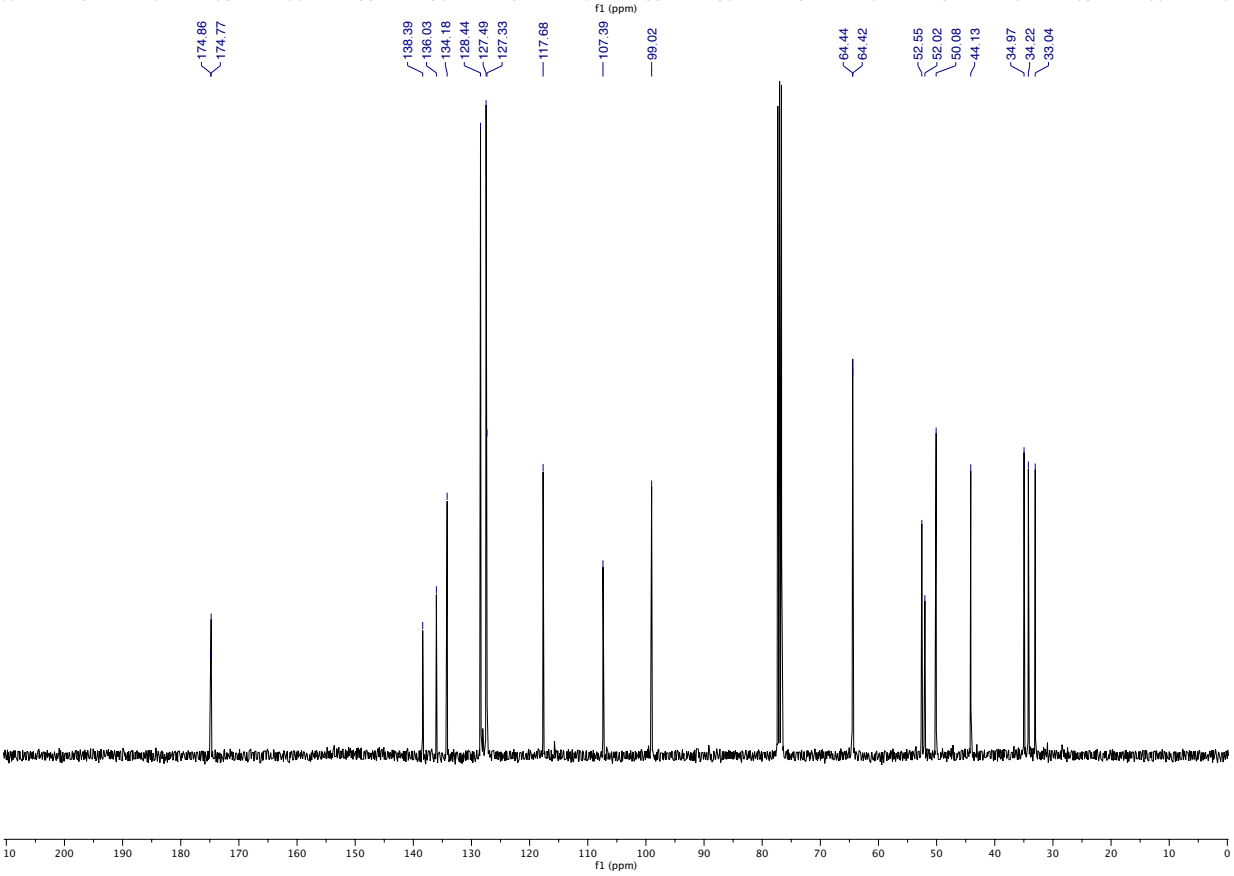
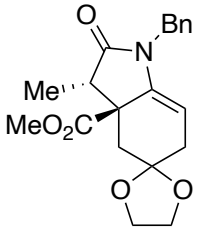
4.917
4.733
4.694
4.689
4.650
4.004
3.774
3.606
2.792
2.775
2.758
2.521
2.488
2.476
2.440
2.432
2.414
2.391
2.353
2.343
2.309
2.299
1.878
1.846
O
N
Bn
MeO2C
O
O
1.00
2.20
1.05
2.23
4.85
3.13
1.05
1.33
4.58
1.10
f1 (ppm)

13a

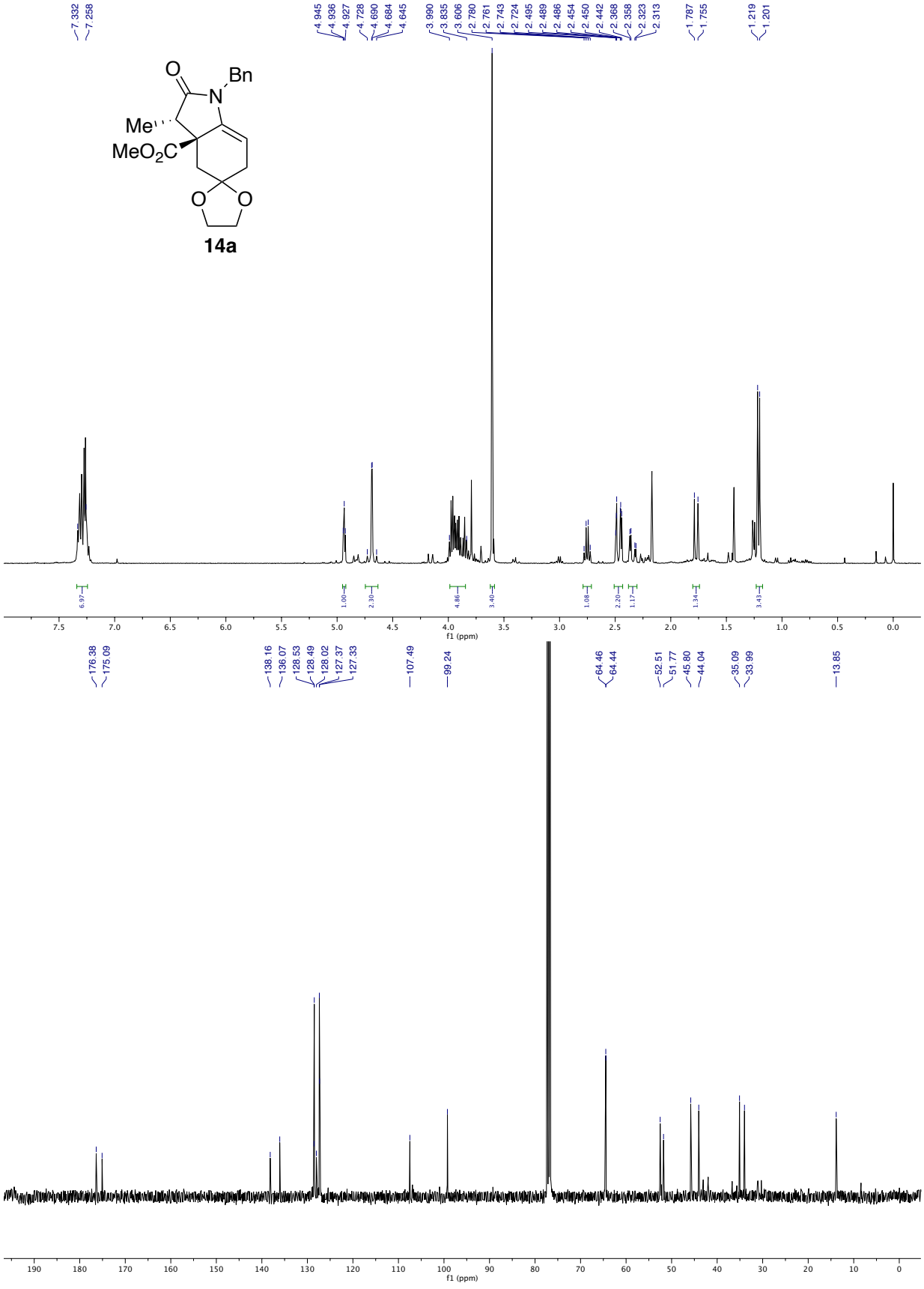

174.86
174.77
138.39
136.03
134.18
128.44
127.49
127.33
117.68
107.39
99.02
64.44
64.42
52.55
52.02
50.08
44.13
34.97
34.22
33.04
f1 (ppm)

(3*RS*,3a*SR*)-1-Benzyl-3a-methoxycarbonyl-3-methyl-1,3a,4,6-tetrahydro-2*H*-indole-2,5(3*H*)-dione monoethylene acetal (14a).

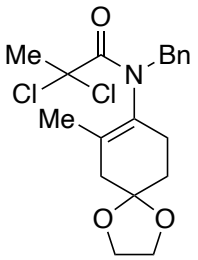


To a cooled (–78 °C) solution of **12** (43 mg, 0.12 mmol, 1 equiv) in THF (0.8 mL), a solution of LHMDS in THF (1 M, 0.16 mL, 1.3 equiv) was added dropwise. After 30 min at -78 °C, methyl iodide (16 μL, 0.24 mmol, 2.0 equiv) was added dropwise. The reaction mixture was allowed to reach room temperature over 2 h. The reaction was quenched by adding an aqueous solution of NH_4Cl, and the solution was extracted with diethyl ether (3 x 10 mL), dried, and concentrated to give **14a** essentially pure (38 mg, 85%) as a white solid.

mp 113 ºC (hexane). IR (neat): 3028, 2922, 1726, 1687, 1441, 1408, 1153, 1117 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.33–7.26 (m, 5H, Ph), 4.94 (t, *J* = 3.6 Hz, 1H, H-7), 4.71 and 4.67 (2 d, *J* = 15.6 Hz, 1H each, CH_2Ph), 3.99–3.84 (m, 4H, OCH_2), 3.61 (s, 3H, OMe), 2.75 (q, *J* = 7.6 Hz, 1H, H-3), 2.47 (d, *J* = 13.1 Hz, 1H, H-4), 2.47 and 2.34 (2 dd, *J* = 18.0, 3.6 Hz, 1H each, H-6), 1.77 (d, *J* = 13.1, 1H, H-4), 1.21 (d, *J* = 7.2 Hz, 3H, Me). ^{13}C NMR ($CDCl_3$,101 MHz) δ 176.4 (CO), 175.1 (CO), 138.2 (C-7a), 136.1, 128.5, 127.4, and 127.3 (Ph), 107.5 (C-5), 99.2 (C-7), 64.5 and 64.4 (OCH_2), 52.5 (OMe), 51.8 (C-3a), 45.8 (C-3), 44.0 (CH_2Ph), 35.1 (C-6), 34.0 (C-4), 13.9 (Me). HRMS (ESI) *m*/*z*: $[M+H]^+$ calcd for $C_{20}H_{24}NO_5$ 358.1649, found 358.1643

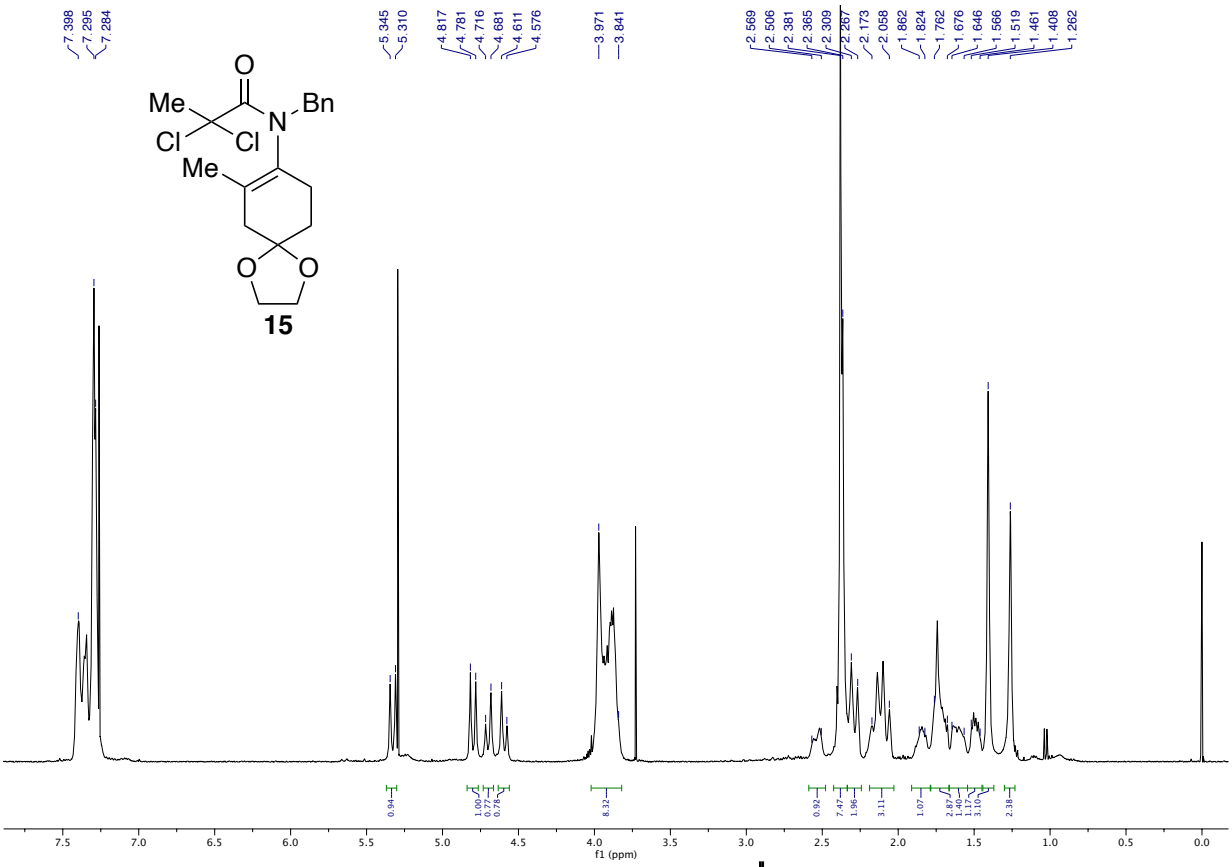

7.332
7.258
4.945
4.936
4.927
4.728
4.690
4.684
4.645
3.990
3.835
3.606
2.780
2.761
2.743
2.724
2.495
2.489
2.486
2.454
2.450
2.442
2.368
2.358
2.323
2.313
1.787
1.755
1.219
1.201
O
N
Bn
Me
MeO2C
O
O
14a
6.97
1.00
2.10
4.86
3.40
1.08
2.20
1.17
1.34
3.43
f1 (ppm)
176.38
175.09
138.16
136.07
128.53
128.49
128.02
127.37
127.33
107.49
99.24
64.46
64.44
52.51
51.77
45.80
44.04
35.09
33.99
13.85
f1 (ppm)

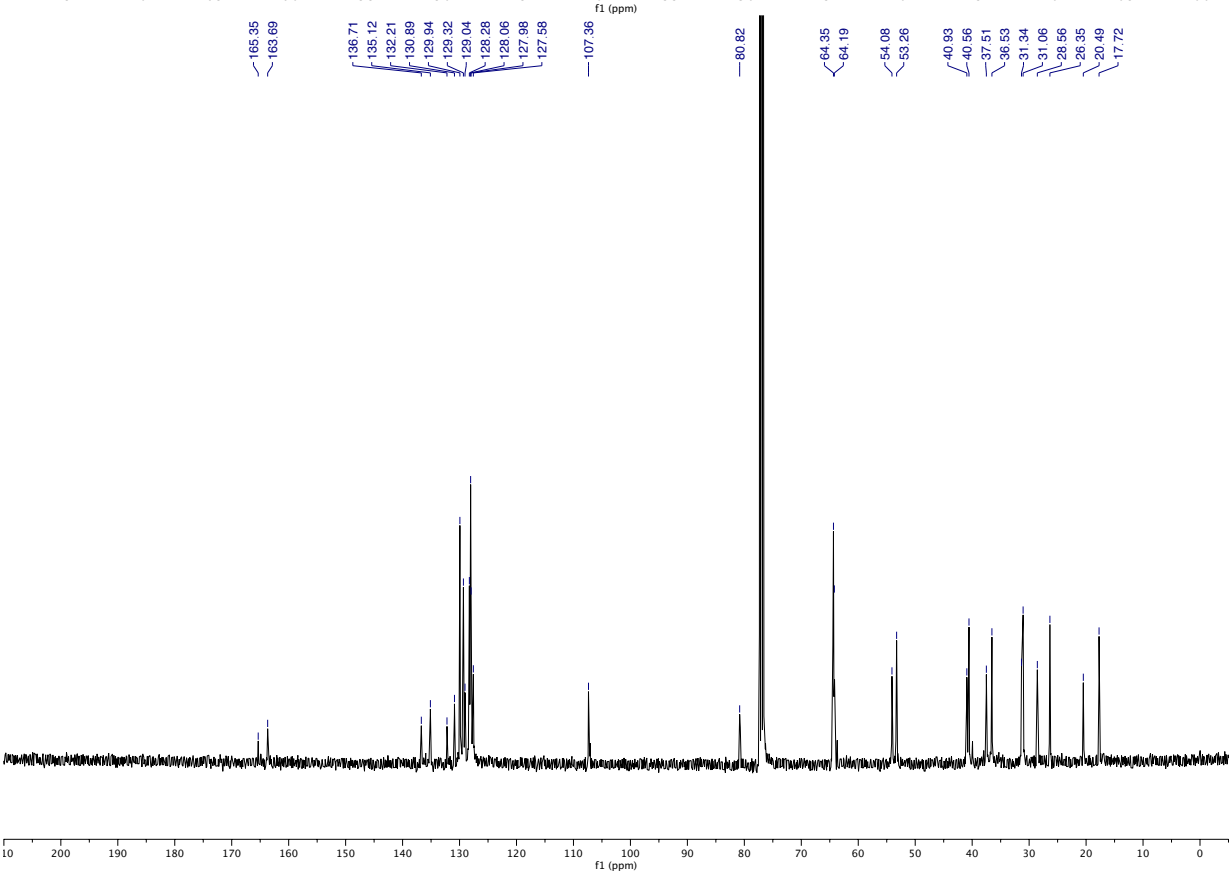
_N_-Benzyl-2-methyl-2,2-dichloro-_N_-(2-methyl-4-oxocyclohex-1-ene-1-yl)acetamide ethylene acetal (15)



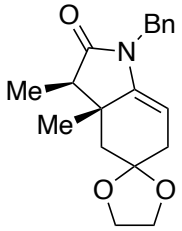
A solution of **1** (0.96 g, 5.6 mmol) and benzylamine (0.6 ml, 5.6 mmol, 1 equiv) in toluene (11 mL) was heated for 4 h using a Dean-Stark apparatus. The mixture was let to reach rt and a part of the imine formed (3.92 mmol, 1 equiv) was added dropwise to a solution of 2,2-dichloropropanoyl chloride **A** (0.70 g, 4.31 mmol, 1.1 equiv) in toluene (5 mL) at 0 ºC. After stirring at rt for 1 h the reaction was cooled to 0 ºC, a solution of triethylamine (1.6 mL, 11.76 mmol, 3 equiv) in toluene (5 mL) was added dropwise and the resulting mixture was stirred at rt for 2 h. Sat. aq. solution of Na_2CO_3 (40 mL) was added and the resulting mixture was stirred for an additional hour. The reaction was extracted with Et_2O (4×30 mL) and the combined organics were dried, concentrated and purified by chromatography (hexane:EtOAc, 95:5) to afford **15** (0.86 g, 57%) as a viscous oil.

IR (neat): 3031, 2939, 1649, 1441, 1255, 1153, 1123, 1091, 700cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): -mixture of rotamers (*M*,*m*)- δ 7.40–7.28 (br s, 5H, Ph) 5.33 and 4.80 (2 br d, 1H each, CH_2Ph, *J* = 14.0 Hz, *M*), 4.70 and 4.59 (2 d, 1H each, CH_2Ph, *J* = 14.0 Hz, *m*), 3.97–3.88 (m, 4H), 2.57–2.52 (m, 1H), 2.38 (s, 3H, Me, *M*), 2.37 (s, 3H, Me, *m*), 2.40–2.27 (m, 2H), 2.19–2.05 (m, 2H), 1.86–1.82 (m, 1H), 1.76–1.68 (m, 2H), 1.64–1.57 (m, 1H), 1.52–1.47 (m, 1H), 1.41 (s, 3H, Me, *M*), 1.26 (s, 3H, *m*). ^{13}C NMR ($CDCl_3$,101 MHz) *M*-rotamer: δ 163.7 (CO), 135.1 (C=), 132.2 (C=), 129.9, 129.3, 128.1, 128.0 (Ph), 107.4 (C-4), 80.8 (C), 64.5 and 64.4 (OCH_2), 53.3 (CH_2Ph), 40.6 (CH_2), 36.5 (Me), 31.0 (CH_2), 26.3 (CH_2), 17.7 (Me). *m*-rotamer: 130.9, 129.1, 128.2, 127.6 (Ph), 107.2 (C-4), 80.7 (C), 64.2 and 64.1 (OCH_2), 54.1 (CH_2Ph), 40.9 (CH_2), 37.5 (Me), 31.3 (CH_2), 28.6 (CH_2), 20.5 (Me). HRMS (ESI) *m*/*z*: $[M+H]^+$ calcd for $C_{19}H_{24}Cl_2NO_3$ 384.1128, found 384.1115.


7.398
7.295
7.284
5.345
5.310
4.817
4.781
4.716
4.681
4.611
4.576
3.971
3.841
2.569
2.506
2.381
2.365
2.309
2.267
2.173
2.058
1.862
1.824
1.762
1.676
1.646
1.566
1.519
1.461
1.408
1.262
O
Me
Cl
Cl
N
Bn
Me
O
O
15
f1 (ppm)

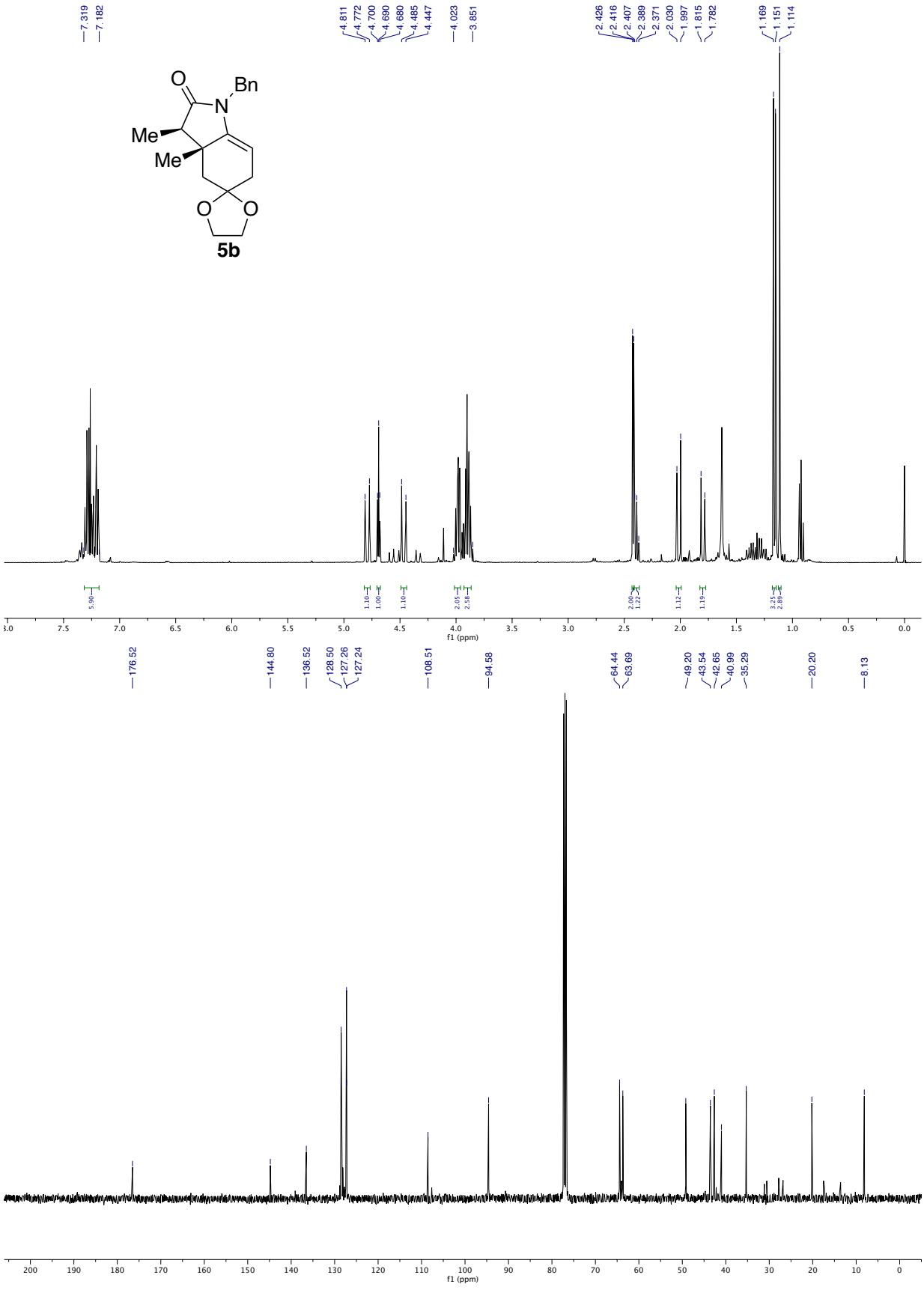

165.35
163.69
136.71
135.12
132.21
130.89
129.94
129.32
129.04
128.28
128.06
127.98
127.58
107.36
80.82
64.35
64.19
54.08
53.26
40.93
40.56
37.51
36.53
31.34
31.06
28.56
26.35
20.49
17.72
f1 (ppm)

(3*SR*,3a*SR*)-1-Benzyl-3,3a-dimethyl-1,3a,4,6-tetrahydro-2H-indole-2,5(3H)-dione monoethylene acetal (5b)



A solution of **15** (250 mg, 0.65 mmol) in benzene (8 mL) was heated to reflux and a solution of AIBN (120 mg, 0.72 mmol, 1.1 equiv) and Bu_3SnH (0.4 mL, 1.37 mmol, 2.1 equiv) in benzene (2 mL) was added over 4 h using a syringe pump. After 1 h of stirring at the same temperature the mixture was concentrated and purified by chromatography (hexane:EtOAc, 9.5:0.5 → 4:1) to afford compounds **5a** (51 mg) and **5b** (34 mg) in 48% overall yield with a dr 3:2. Latterly, Reduced amide **17** (11 mg, 6%) was eluted. The NMR data for **5a** were identical to those recorded when it was obtained by methylation of **3** (see before)

IR (neat) 3029, 2924, 1721, 1679, 1455, 1150, 1102, 1087, 980, 701 cm^{-1}. 1H NMR (400 MHz, $CDCl_3$) δ 7.32–7.17 (m, 5H, Ph), 4.79 (d, *J* = 15.2 Hz, 1H, CH_2Ph), 4.69 (t, *J* = 4.0 Hz, H-7), 4.47 (d, *J* = 15.2 Hz, 1H, CH_2Ph), 4.02–3.85 (m, 4H, OCH_2), 2.42 (d, *J* = 4.0 Hz, 2H, H-6), 2.40 (q, *J* = 7.2 Hz, 1H, H-3), 2.01 and 1.80 (2 d, *J* = 13.3 Hz, 1H each, H-4), 1.16 (d, *J* = 7.2, 3H, Me-3), 1.11 (s, 3H, Me-3a). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.5 (CO), 144.8 (C-7a), 136.5, 128.5, 127.3, and 127.2 (Ph), 108.5 (C-5), 94.6 (C-7), 64.4 and 63.7 (OCH2), 49.2 (C-3), 43.5 (CH_2Ph), 42.7 (C-4), 41.0 (C-3a), 35.3 (C-6), 20.2 (Me-3a), 8.1 (Me-3). HRMS (ESI) *m/z*: [M + H]+ calcd for $C_{19}H_{24}NO_3$ 314.1751, found 314.1738.


7.319
7.182
4.811
4.772
4.700
4.690
4.680
4.485
4.447
4.023
3.851
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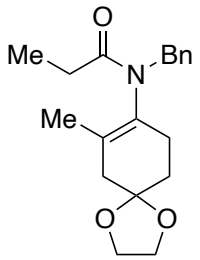
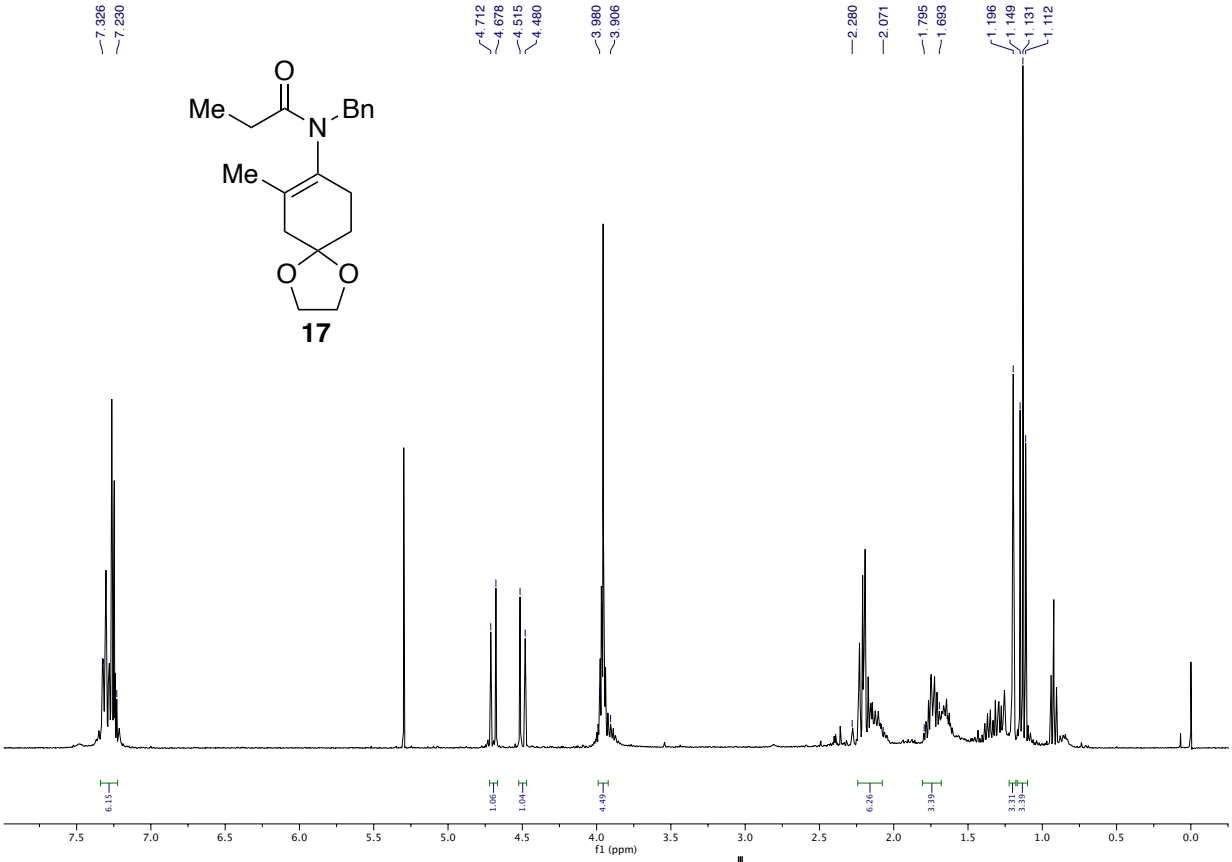
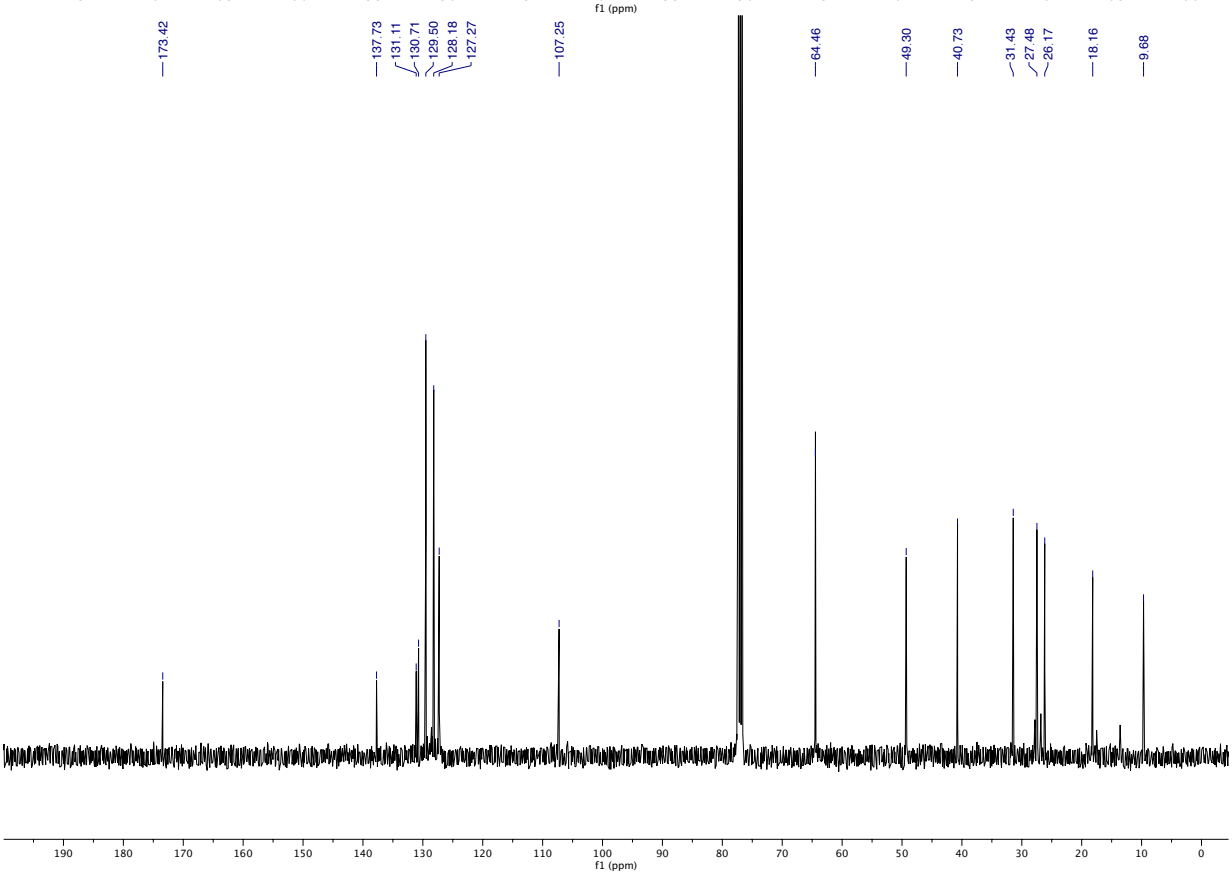
2.416
2.407
2.389
2.371
2.030
1.997
1.815
1.782
1.169
1.151
1.114
O
N
Bn
Me
Me
O
O
5b
f1 (ppm)
176.52
144.80
136.52
128.50
127.26
127.24
108.51
94.58
64.44
63.69
49.20
43.54
42.65
40.99
35.29
20.20
8.13
f1 (ppm)

_N_-benzyl-_N_-(2-methyl-4-oxocyclohex-1-en-1-yl)propionamide (17)

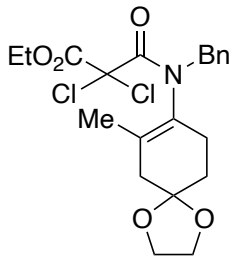


IR (neat): 3030, 2969, 2931, 1661, 1091, 1066, 702 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.19 (m, 5H), 4.69 and 4.50 (2d, J = 13.9 Hz, 1H each), 4.01–3.84 (m, 4H), 2.29–2.02 (m, 6H), 1.81–1.65 (m, 2H), 1.20 (s, 3H), 1.13 (t, J = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.4, 137.7, 131.1, 130.7, 129.5, 128.2, 127.3, 107.3, 64.5, 49.3, 40.7, 31.4, 27.5, 26.2, 18.2, 9.7. HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{19}H_{26}NO_5$ 316.1913; found 315.1916.


7.326
7.230
4.712
4.678
4.515
4.480
3.980
3.906
2.280
2.071
1.795
1.693
1.196
1.149
1.131
1.112
Me
O
N
Bn
Me
O
O
17
6.15
1.06
1.04
4.49
6.26
3.39
3.31
3.39
f1 (ppm)

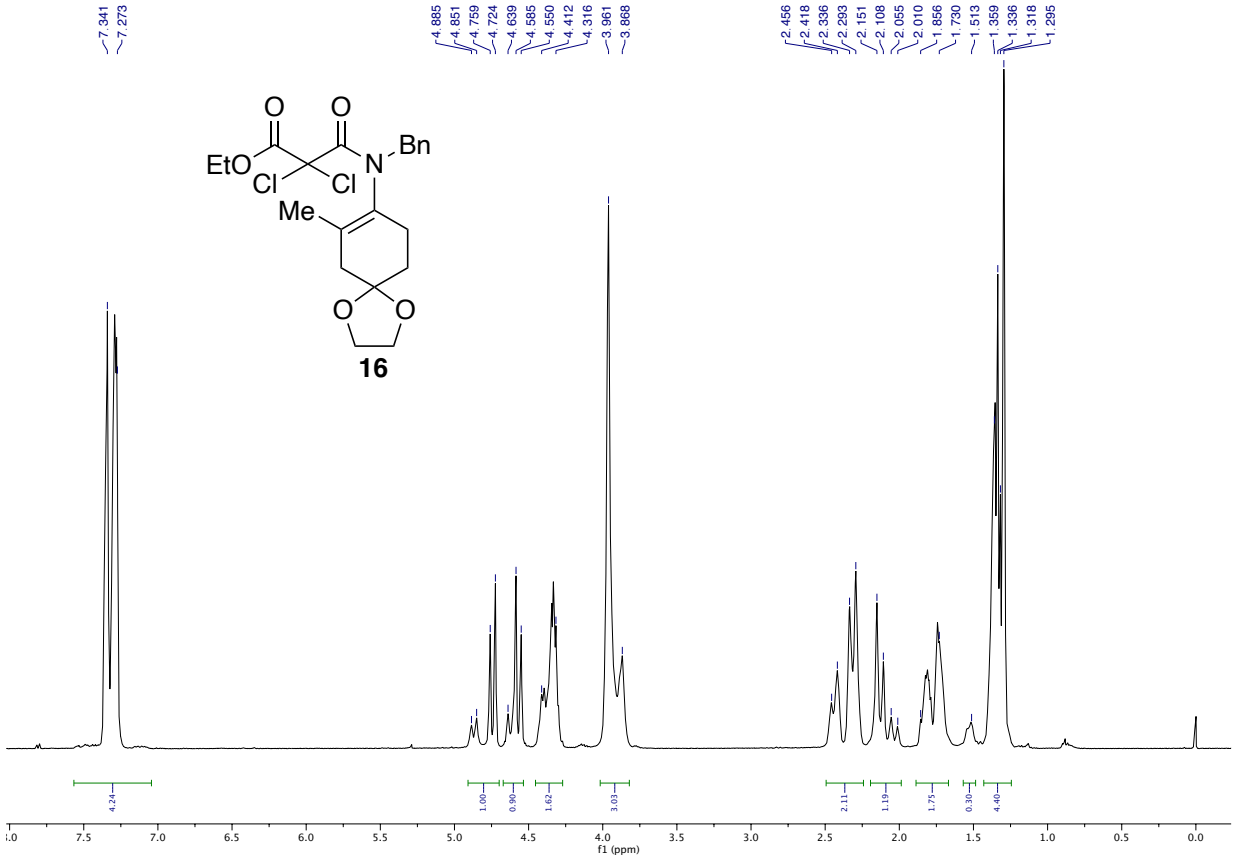

173.42
137.73
131.11
130.71
129.50
128.18
127.27
107.25
64.46
49.30
40.73
31.43
27.48
26.17
18.16
9.68
f1 (ppm)

_N_-Benzyl-2,2-dichloro-2-ethoxycarbonyl-_N_-(2-methyl-4-oxocyclohex-1-ene-1-yl)acetamide ethylene acetal (16)



A solution of ketone **1** (9.8 g, 57.3 mmol, 1 equiv), benzylamine (8.33 ml, 74.6 mmol, 1.3 equiv), and activated sieves (10 g) in CH_2Cl_2 (20 mL) was stirred overnight at room temperature. The mixture was filtered through Celite®, concentrated, dissolved in toluene (120 mL), and added dropwise to a cooled solution (0 °C) of 2,2-dichloro-2-ethoxycarbonylacetyl chloride **B** (13.9 g, 63.1 mmol, 1.1 equiv) in toluene (65 mL). The reaction mixture was stirred at room temperature for 1 h, cooled to 0 °C and a solution of triethylamine (24 mL, 172.1 mmol, 3.0 equiv) in toluene (60 mL) was added dropwise. After stirring at room temperature for 2 h, saturated aqueous Na_2CO_3 (130 mL) was added and the resulting mixture was vigorously stirred for an additional 1 h, extracted with Et_2O (3 x 120 mL) and the combined organics were dried and concentrated. After chromatography (hexane:EtOAc, 1:0 → 9:1), enamide **16** was isolated as a colourless viscous oil (13.9 g, 56%).

IR (neat) 3088, 2983, 1765, 1677, 1605, 1585, 1496 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) 2.2 : 1 rotamer ratio; δ 7.39–7.23 (m, 5H, Ph), 4.86 and 4.74 (2 d, *J* = 14.0 Hz, 1H each m, CH_2Ph), 4.62 and 4.56 (2 d, *J* = 14.0 Hz, 1H each M, CH_2Ph), 4.44–4.26 (m, 2H, OEt), 3.96 and 3.86 (2 br s, 4H, OCH_2), 2.49–2.23 (m, 3H), 2.21–1.97 (m, 1H), 1.80–1.62 and 1.52 (m, 2H), 1.36 and 1.33 (2 br t, *J* = 7.2 Hz, 3H, OEt), 1.29 (br s, 3H, Me). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.6 and 163.5 (CO), 162.1 and 160.4 (CO), 136.1, 134.0, 133.2, 130.0, 129.9, 129.8, 129.3, 128.3, 128.2, 128.1, 127.7 (Ph and C-7a), 107.2 and 106.9 (C), 78.8 (CCl_2), 64.7 and 64.4 (OCH_2), 64.3 (CH_2), 64.2 and 64.1 (CH_2), 53.7 and 52.5 (CH_2), 40.9 and 40.5 (CH_2), 31.1 and 30.9 (CH_2), 28.4 and 26.0 (CH_2), 19.8 and 17.7 (Me), 13.7 and 13.6 (OEt). HRMS (ESI) *m/z*: [M + H]+ calcd for $C_{21}H_{26}Cl_2NO_5$ 442.1188; found 442.1184.


7.341
7.273
4.885
4.851
4.759
4.724
4.639
4.585
4.550
4.412
4.316
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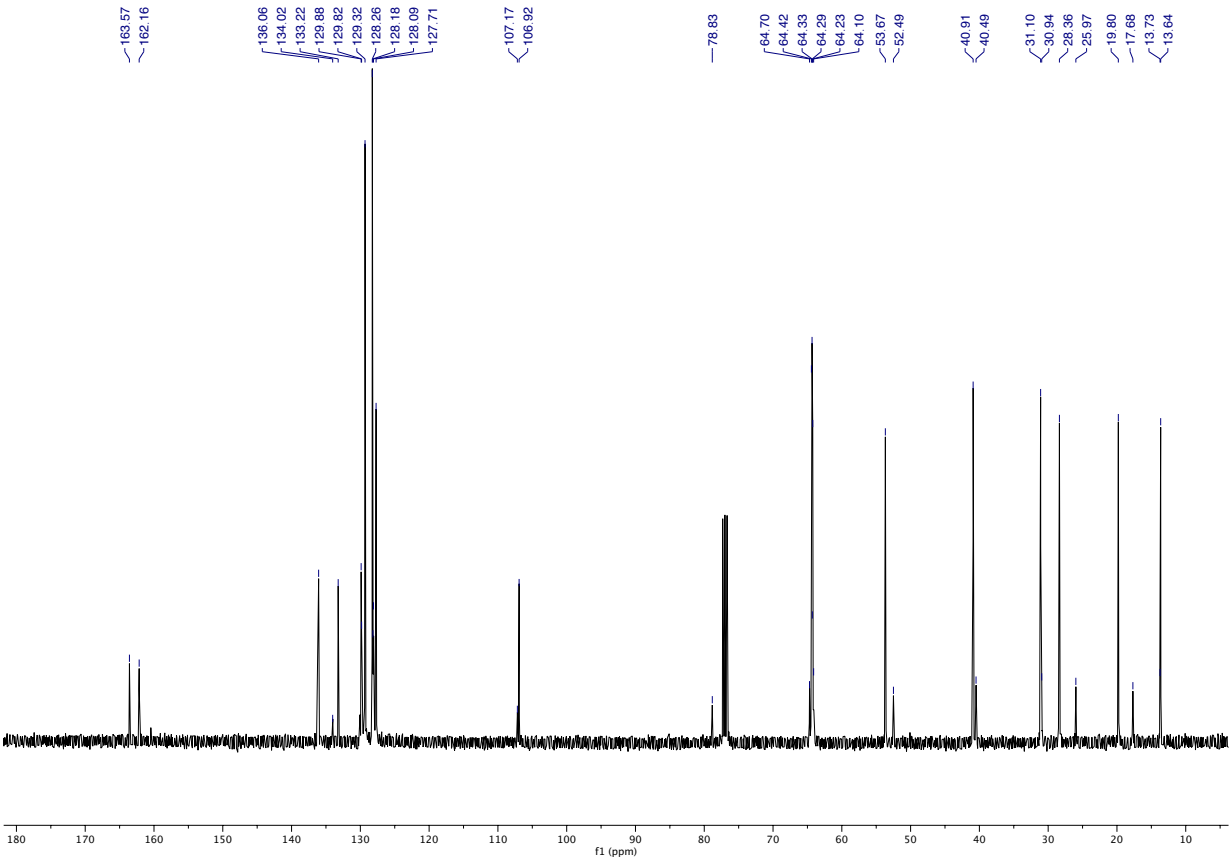
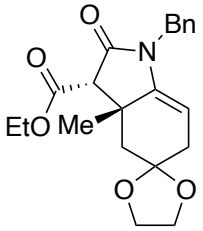
2.456
2.418
2.336
2.293
2.151
2.108
2.055
2.010
1.856
1.730
1.513
1.359
1.336
1.318
1.295
O
O
EtO
N
Bn
Cl
Cl
Me
O
O
16
4.24
1.00
0.90
1.62
3.03
2.11
1.19
1.75
0.30
4.40
f1 (ppm)

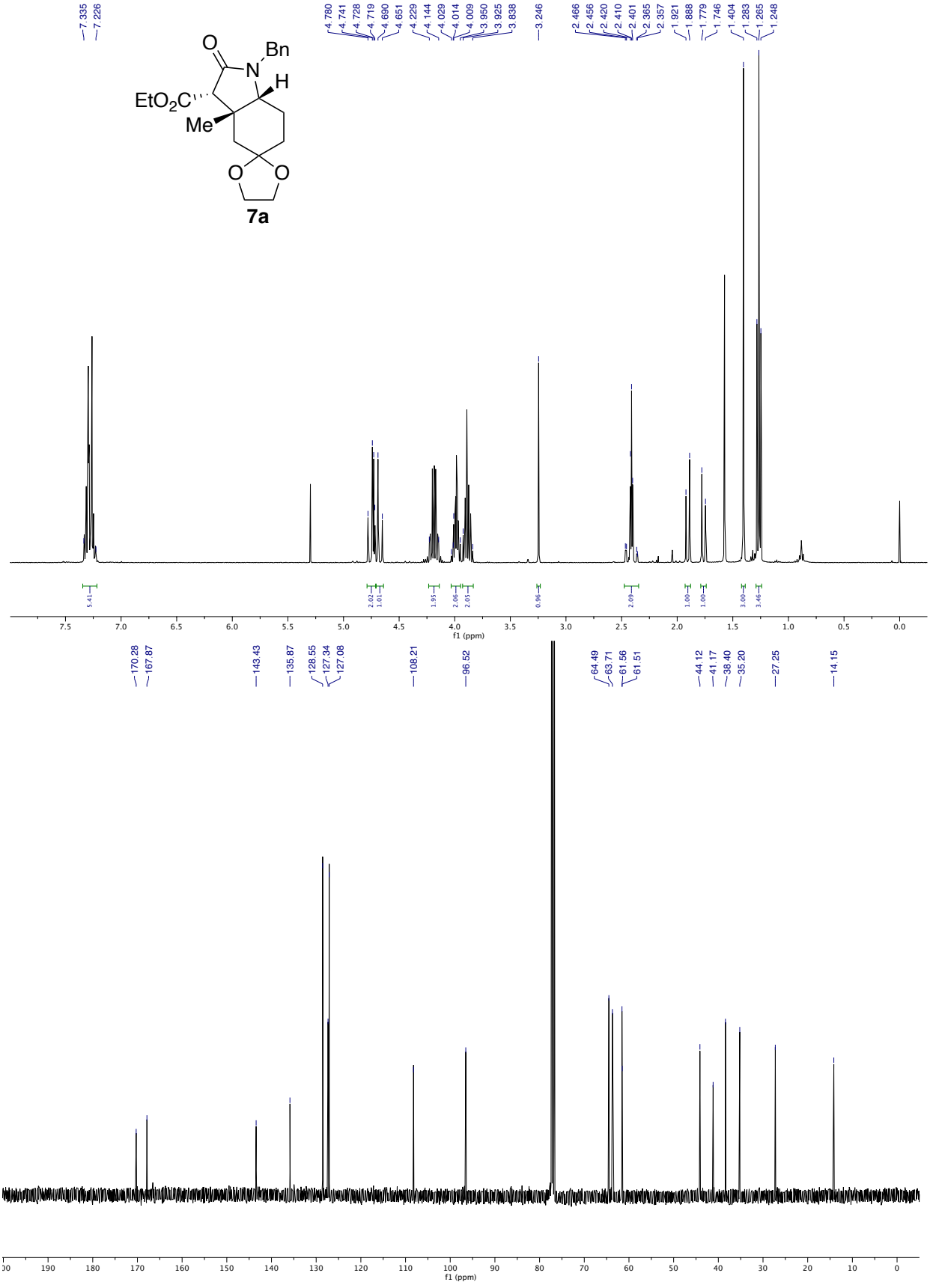

163.57
162.16
136.06
134.02
133.22
129.88
129.82
129.32
128.26
128.18
128.09
127.71
107.17
106.92
78.83
64.70
64.42
64.33
64.29
64.23
64.10
53.67
52.49
40.91
40.49
31.10
30.94
28.36
25.97
19.80
17.68
13.73
13.64
f1 (ppm)

(3*RS*,3a*SR*)-1-Benzyl-3-ethoxycarbonyl-3a-methyl-1,3a,4,6-tetrahydro-2*H*-indole-2,5(3*H*)-dione monoethylene acetal (7a)

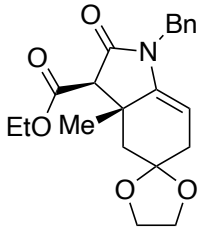


A solution of **16** (850 mg, 1.92 mmol) in benzene (24 mL) was heated to reflux and then a solution of Bu_3SnH (0.77 mL, 2.87 mmol, 2.1 equiv) and AIBN (315 mg, 1.92 mmol, 1.1 equiv) in benzene (5 mL) was added over 1 h using a syringe pump. The mixture was heated under reflux for 3 h and then concentrated. After chromatography (hexane:EtOAc 1:0 → 0:1) **7a** was isolated as a solid (390 mg, 55%) followed by **7b** (170 mg, 23%). The latter epimer **7b** seems to be formed by epimerization in the column chromatography, as its signals in the ^{1}H NMR spectrum of the reaction crude are very small.

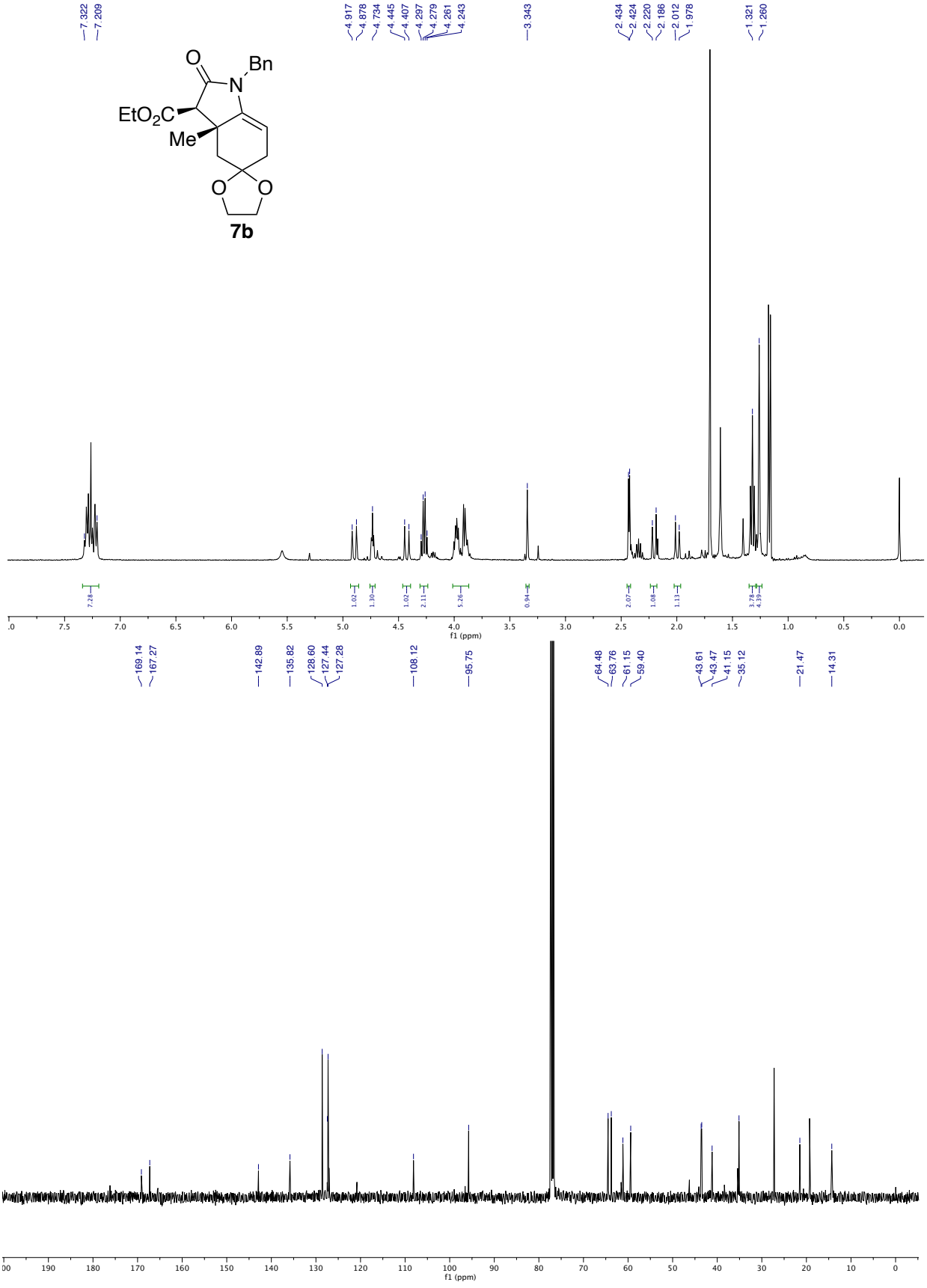
mp 83-86 °C (Et_2O). IR (neat) 3063, 2979, 1738, 1688, 1605 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.34–7.22 (m, 5H, Ph), 4.76 (d, J = 15.5 Hz, 1H, CH_2Ph), 4.73 (t, J = 4.0 Hz, H-7), 4.67 (d, J = 15.5 Hz, 1H, CH_2Ph), 4.24–4.13 (m, 2H, OEt), 4.04–3.94 and 3.93–3.83 (2 m, 2H each, OCH_2), 3.25 (s, 1H, H-3), 2.44 and 2.38 (2 dd, J = 18.2, 4.0 Hz, 1H each, H-6), 1.90 and 1.76 (2 d, J = 13.2 Hz, 1H each, H-4), 1.40 (s, 3H, Me), 1.27 (t, J = 7.2 Hz, 3H, OEt). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.3 (CO), 167.9 (CO), 143.4 (C-7a), 135.9, 128.5, 127.3, and 127.1 (Ph), 108.2 (C-5), 96.5 (C-7), 64.5 and 63.7 (OCH_2), 61.6 (C-3), 61.5 (CH_2), 44.1 (CH_2Ph), 41.2 (C-3a), 38.4 (C-4), 35.2 (C-6), 27.2 (Me), 14.2 (OEt). HRMS (ESI) *m*/*z*: $[M+H]^+$ calcd for $C_{21}H_{26}NO_5$ 372.1805; found 372.1807.


7.335
7.226
4.780
4.741
4.728
4.719
4.690
4.651
4.229
4.144
4.029
4.014
4.009
3.950
3.925
3.838
3.246
2.466
2.456
2.420
2.410
2.401
2.365
2.357
1.921
1.888
1.779
1.746
1.404
1.283
1.265
1.248
O
N
Bn
H
EtO2C
Me
O
O
7a
5.41
2.02
1.01
1.95
2.06
2.05
0.96
2.09
1.00
1.00
3.00
3.46
f1 (ppm)
170.28
167.87
143.43
135.87
128.55
127.34
127.08
108.21
96.52
64.49
63.71
61.56
61.51
44.12
41.17
38.40
35.20
27.25
14.15
f1 (ppm)

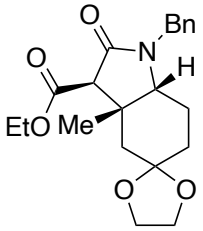
(3*RS*,3a*RS*)-1-Benzyl-3-ethoxycarbonyl-3a-methyl-1,3a,4,6-tetrahydro-2*H*-indole-2,5(3*H*)-dione monoethylene acetal (7b).



^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.34–7.20 (m, 5H, Ph), 4.90 (d, *J* = 15.4 Hz, 1H, CH_2Ph), 4.74 (t, *J* = 4.0 Hz, 1H, H-7), 4.43 (d, *J* = 15.4 Hz, 1H, CH_2Ph), 4.27 (q, *J* = 7.2 Hz, 2H, OEt), 4.01–3.86 (m, 4H, OCH_2), 3.35 (s, 1H, H-3), 2.43 (d, *J* = 4.0 Hz, 2H, H-6), 2.21 and 2.00 (2 d, *J* = 13.5 Hz, 1H each, H-4), 1.32 (t, *J* = 7.2 Hz, 3H, OEt), 1.27 (s, 3H, Me). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.1 (CO), 167.2 (CO), 142.8 (C-7a), 135.9, 128.6, 127.4, and 127.3 (Ph), 108.1 (C-5), 95.8 (C-7), 64.5 and 63.7 (OCH_2), 61.1 (OEt), 59.4 (C-3), 43.6 (CH_2Ph), 43.4 (C-4), 41.1 (C-3a), 35.1 (C-6), 21.5 (Me), 14.3 (OEt).

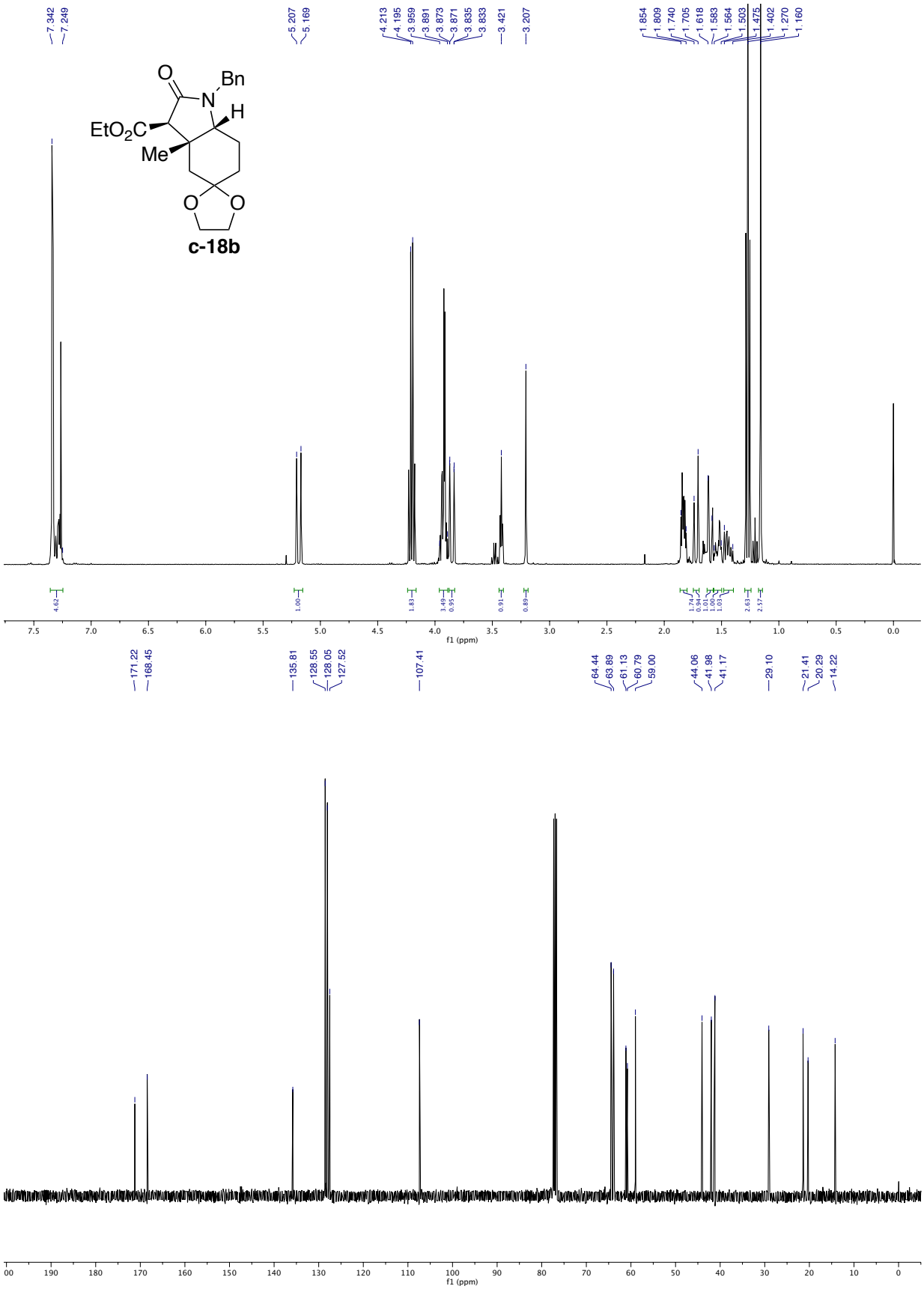

7.322
7.209
4.917
4.878
4.734
4.445
4.407
4.297
4.279
4.261
4.243
3.343
2.434
2.424
2.220
2.186
2.012
1.978
1.321
1.260
O
N
Bn
EtO2C
Me
O
O
7b
7.28
1.02
1.30
1.02
2.11
5.26
0.94
2.07
1.08
1.13
3.78
4.39
f1 (ppm)
169.14
167.27
142.89
135.82
128.60
127.44
127.28
108.12
95.75
64.48
63.76
61.15
59.40
43.61
43.47
41.15
35.12
21.47
14.31
f1 (ppm)

(3*S*,3a*SR*,7a*SR*)-1-Benzyl-3-ethoxycarbonyl-3a-methylhexahydro-2*H*-indole-2,5(3*H*)-dione monoethylene acetal (*c*-18b).

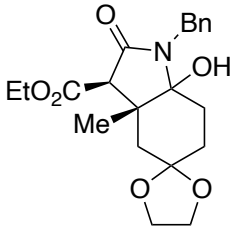


When the radical cyclization was carried out from **16** on 7 g scale (15.8 mmol), after chromatography purification compounds **7a** (3.0 g, 51%), **7b** (530 mg, 9%), and the over-reduced compound ***c*-18b** was isolated in minor quantities as a white solid (1.0 g, 17%).

mp 94–97 °C (Et_2O). IR (neat) 3063, 3030, 2939, 2885, 1731, 1693 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.36–7.23 (m, 5H, Ph), 5.19 (d, J = 15.2 Hz, 1H, CH_2Ph), 4.20 (q, J = 7.2 Hz, 2H, OEt), 3.85 (d, J = 15.2 Hz, 1H, CH_2Ph), 3.98–3.88 (m, 4H, OCH_2), 3.42 (t, J = 4.0 Hz, 1H, H-7a), 3.21 (s, 1H, H-3), 1.87–1.80 (m, 2H, H-7), 1.72 (d, J = 14.4 Hz, 1H, H-4), 1.60 (dd, J = 14.4, 2.1 Hz, 1H, H-4), 1.53 (dtd, J = 13.4, 4.4, 2 Hz, 1H, H-6), 1.44 (ddd, J = 13.4, 9.3, 6.9 Hz, 1H, H-6), 1.27 (t, J = 7.2, 3H, OEt), 1.16 (s, 3H, Me). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.2 (CO), 168.5 (CO), 135.8, 128.6, 128.1, and 127.5 (Ph), 107.4 (C-5), 64.4 and 63.9 (OCH_2), 61.1 (OEt), 60.8 (C-3), 59.0 (C-7a), 44.1 (CH_2Ph), 42.0 (C-4), 41.2 (C-3a), 29.1 (C-6), 21.4 (C-7), 20.3 (Me), 14.2 (OEt). HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{21}H_{28}NO_5$ 374.1962; found 374.1966.

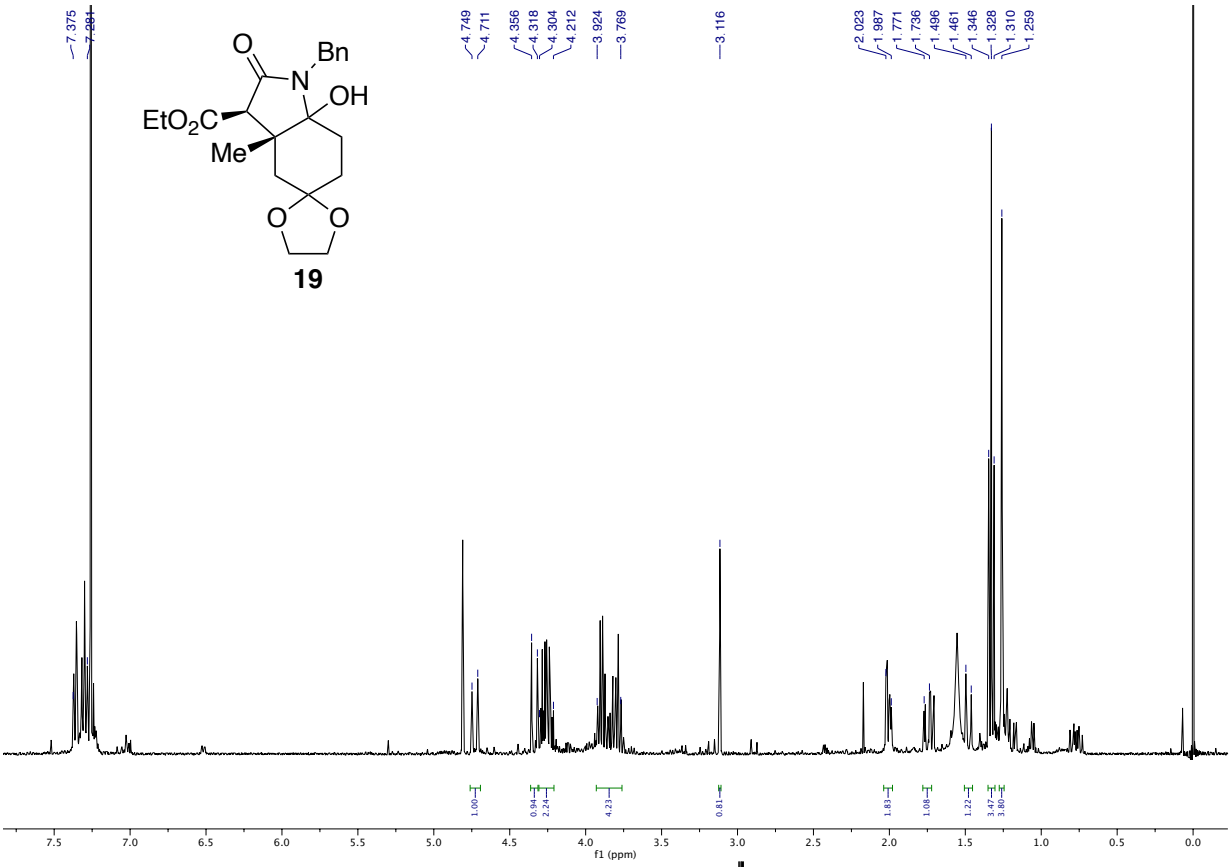

7.342
7.249
5.207
5.169
4.213
4.195
3.959
3.891
3.873
3.871
3.835
3.833
3.421
3.207
1.854
1.809
1.740
1.705
1.618
1.583
1.564
1.503
1.475
1.402
1.270
1.160
O
Bn
N
H
EtO2C
Me
O
O
c-18b
f1 (ppm)
171.22
168.45
135.81
128.55
128.05
127.52
107.41
64.44
63.89
61.13
60.79
59.00
44.06
41.98
41.17
29.10
21.41
20.29
14.22
f1 (ppm)

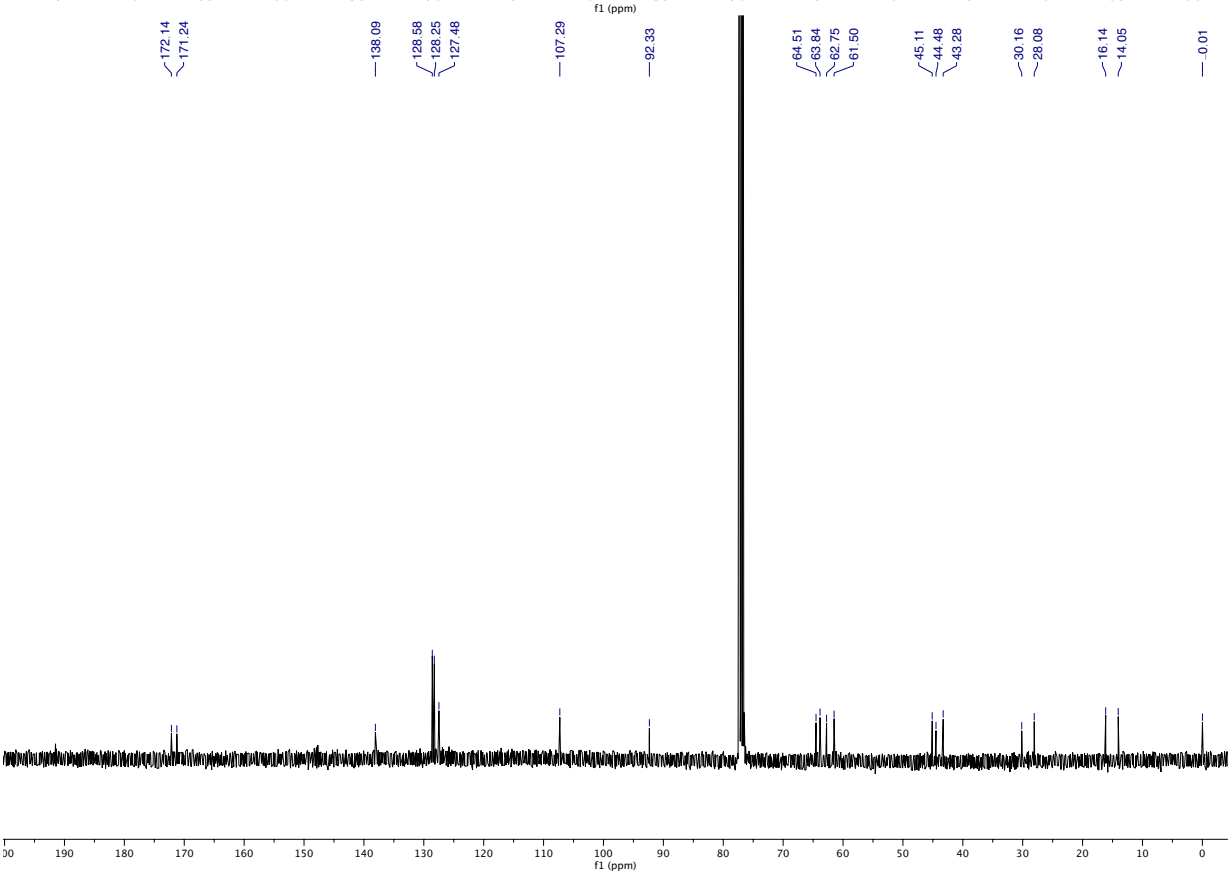
Evolution of 7b to compound 19.



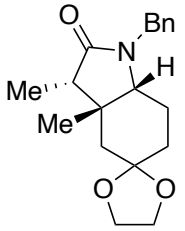
On exposure to air or in the chromatographic column using SiO_2, enlactam **7b** partially evolved to hydroxylated octahydroindole **19**.

IR (neat) 3404, 2978, 2960, 1742, 1694 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.39–7.20 (m, 5H, Ph), 4.81 (s, 1H, OH), 4.73 and 4.34 (2d, *J* = 15.2 Hz, 1H each, CH_2Ph), 4.20–4.32 (m, 2H, OEt), 3.96–3.73 (m, 4H, OCH_2), 3.12 (s, 1H, H-3), 2.02–1.99 (m, 2H, H-7), 1.75 (dd, *J* = 14.0, 3.1 Hz, H-4), 1.48 (d, *J* = 14.0, 1H, H-4), 1.33 (t, *J* = 7.2 Hz, 3H, OEt), 1.26 (s, 3H, Me), 1.24 (m, 1H, H-6eq), 0.77 (m, 1H, H-6ax). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.1 (CO), 171.2 (CO), 138.1, 128.6, 128.3, and 127.5 (Ph), 107.3 (C-5), 92.3 (C-7a), 64.5 and 63.8 (OCH_2), 62.7 (OEt), 61.5 (C-3), 45.1 (C-4), 44.5 (C-3a), 43.3 (CH_2Ph), 30.2 (C-6), 28.1 (C-7), 16.1 (Me), 14.1 (OEt). HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{21}H_{28}NO_6$ 390.1911, found 390.1911.


7.375
7.291
4.749
4.711
4.356
4.318
4.304
4.212
3.924
3.769
3.116
2.023
1.987
1.771
1.736
1.496
1.461
1.346
1.328
1.310
1.259
O
N
Bn
OH
EtO2C
Me
O
O
19
1.00
0.94
2.24
4.23
0.61
1.83
1.08
1.22
3.47
3.80
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

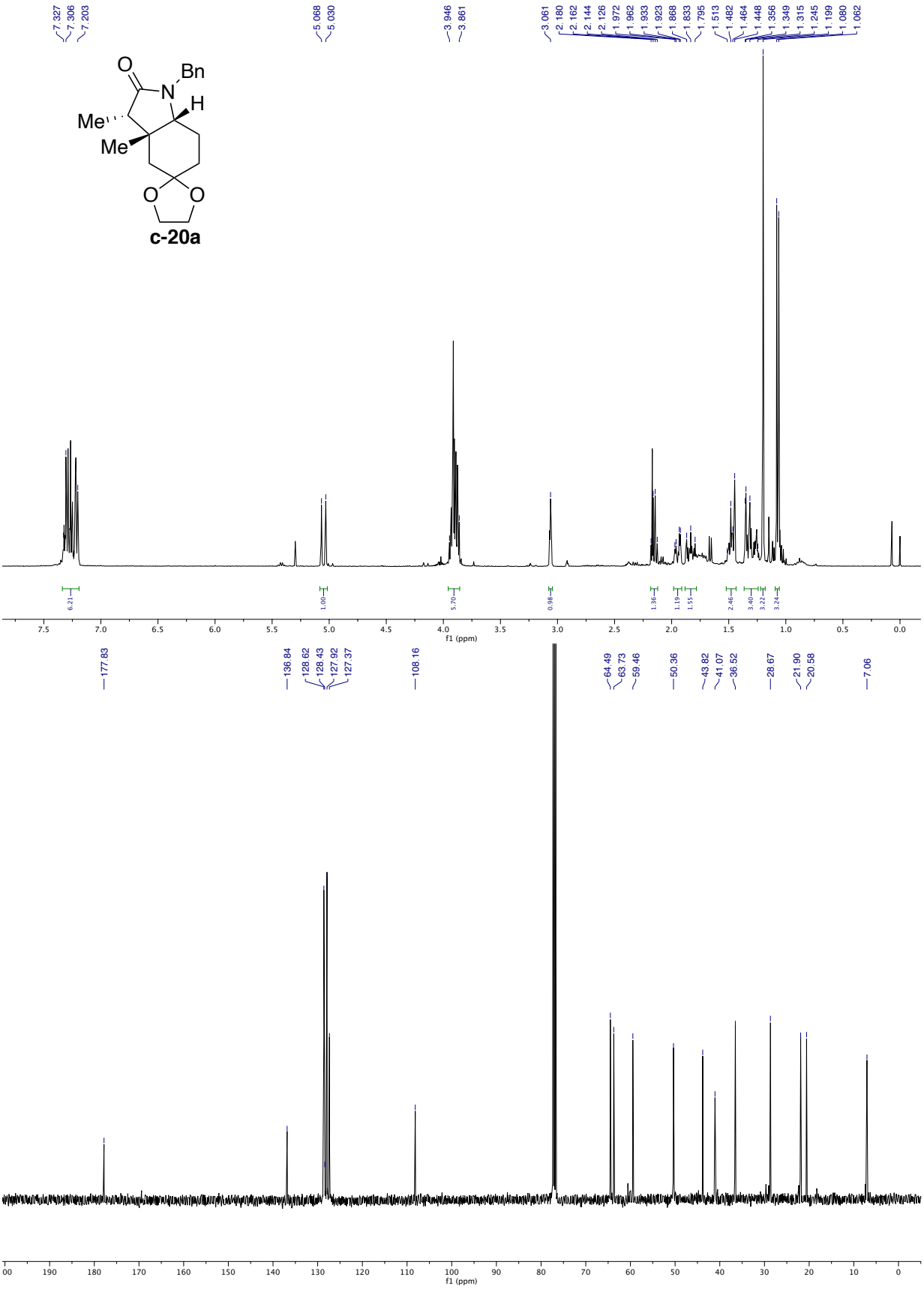

172.14
171.24
138.09
128.58
128.25
127.48
107.29
92.33
64.51
63.84
62.75
61.50
45.11
44.48
43.28
30.16
28.08
16.14
14.05
0.01
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

(3*RS*,3a*SR*,7a*SR*)-1-Benzyl-3,3a-dimethylhexahydro-1*H*-indole-2,5(3*H*,6*H*)-dione ethylene acetal (*c*-20a).



To a solution of **5a** (23 mg, 0.07 mmol) in EtOAc (2 mL) was added Pd/C (8 mg, 40% w/w), and the mixture was stirred under 1 atm of H_2 and at room temperature overnight. The mixture was filtered through a short Celite® pad and concentrated to yield **c-20a** (20 mg, 87%) as a clolorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.20 (m, 5H, Ph), 5.05 (d, J = 15.2 Hz, 1H, CH_2Ph), 3.95–3.86 (m, 5H, OCH_2, CH_2Ph), 3.06 (t, J = 2.8 Hz, 1H, H-7a), 2.15 (q, J = 7.2 Hz, 1H, H-3), 1.95 (dq, J = 14.8, 3.2 Hz, 1H, H-7eq.), 1.83 (tt, J = 14.8, 3.6 Hz, 1H, H-7ax), 1.51–1.45 (m, 1H, H-6), 1.47 and 1.33 (2d, J = 13.6 Hz, 1H each, H-4), 1.36–1.25 (m, 1H, H-6), 1.20 (s, 3H, Me-3a), 1.07 (d, J = 7.2 Hz, 3H, Me-3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.8 (C-2), 136.8, 128.6, 127.9, and 127.4 (Ph), 108.2 (C-5), 64.5 and 63.7 (OCH_2), 59.5 (C-7a), 50.4 (C-3), 43.8 (CH_2Ph), 41.1 (C-3a), 36.5 (C-4), 28.7 (C-6), 21.9 (Me-3a), 20.6 (C-7), 7.1 (Me-3). HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{19}H_{26}NO_3$ 316.1913, found 316.1911.


7.327
7.306
7.203
5.068
5.030
3.946
3.861
3.061
2.180
2.162
2.144
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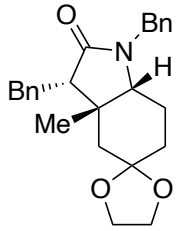
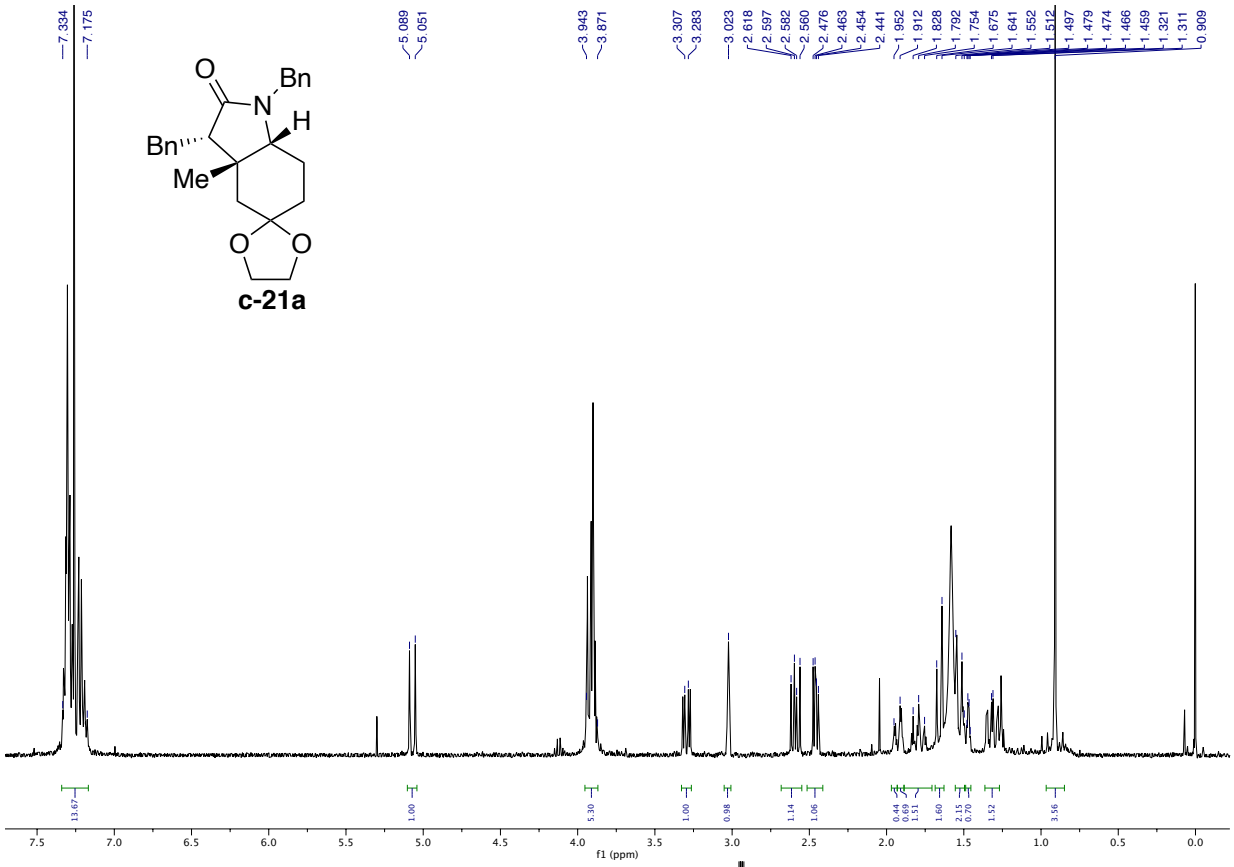
1.972
1.962
1.933
1.923
1.868
1.833
1.795
1.513
1.482
1.464
1.448
1.356
1.349
1.315
1.245
1.199
1.080
1.062
O
N
Bn
H
Me
Me
O
O
c-20a
6.21
1.00
5.70
0.88
1.38
1.19
1.55
2.46
3.40
3.22
3.24
f1 (ppm)
177.83
136.84
128.62
128.43
127.92
127.37
108.16
64.49
63.73
59.46
50.36
43.82
41.07
36.52
28.67
21.90
20.58
7.06
f1 (ppm)

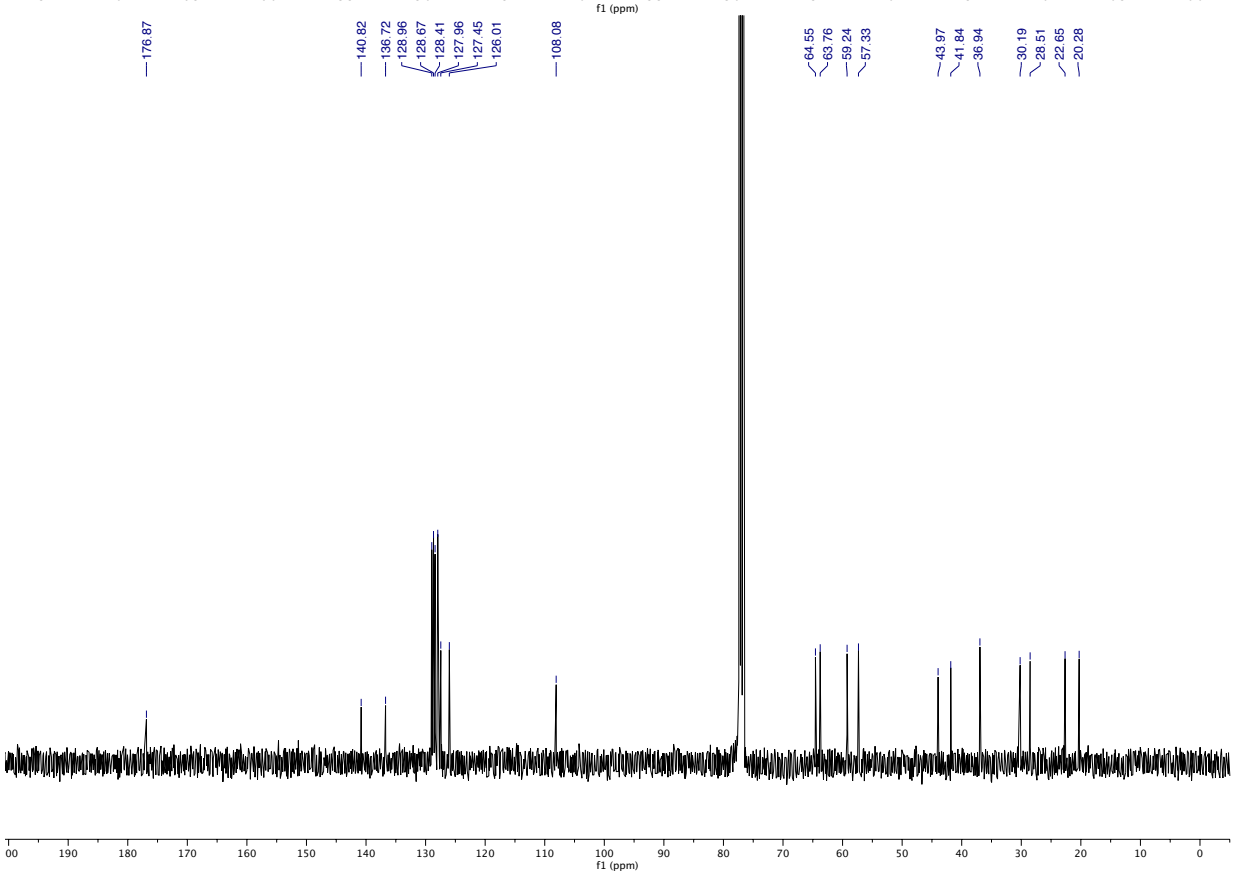
(3*RS*,3a*SR*,7a*SR*)-1,3-Dibenzyl-3a-methylhexahydro-1H-indole-2,5(3*H*,6*H*)-dione ethylene acetal (c-21a).



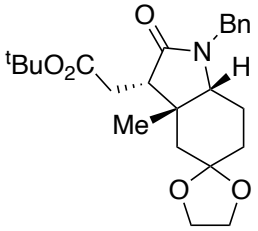
To a solution of **6a** (15 mg, 0.04 mmol) in EtOAc (1 mL) was added Pd/C (6 mg, 40% w/w), and the mixture was stirred under 1 atm of H_2 and at room temperature overnight. The mixture was filtered through a short Celite® pad and concentrated to yield **c-21a** (9 mg, 60%) as a colorless oil.

IR (neat) 3026, 2940, 2160, 1691, 1429, 1119, 1088, 701 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.33–7.18 (m, 10H, Ph), 5.07 (d, J = 15.2 Hz, 1H, CH_2Ph), 3.94–3.87 (m, 5H, CH_2Ph and OCH_2), 3.29 (dd, J = 14.6, 5.0 Hz, 1H, CH_2Ph-3), 3.02 (t, J = 3.0 Hz, 1H, H-7a), 2.59 (dd, J = 14.6, 8.8 Hz, 1H, CH_2Ph-3), 2.46 (dd, J = 8.8, 5.0 Hz, 1H, H-3), 1.92 (dq, J = 14.4, 3.2 Hz, 1H, H-7eq.), 1.79 (tt, J = 14.4, 3.2 Hz, 1H, H-7ax), 1.67 and 1.53 (2d, J = 13.2 Hz, 1H each H-4), 1.48 (ddd, J = 14.4, 6.4, 3.2 Hz, 1H, H-6eq.), 1.32 (td, J = 14.4, 3.2 Hz, 1H, H-6ax), 0.91 (s, 3H, Me). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.9 (C-2), 140.8, 136.7, 129.0, 128.7, 128.4, 128.0, 127.5, 126.0 (Ph), 108.1 (OCH_2), 64.6 and 63.8 (OCH_2), 59.2 (C-7a), 57.3 (C-3), 44.0 (CH_2Ph), 41.8 (C-3a), 36.9 (C-4), 30.2 (CH_2Ph-3), 28.5 (C-6), 22.7 (Me), 20.3 (C-7). HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{25}H_{30}NO_3$ 392.2226, found 392.2230.


7.334
7.175
5.089
5.051
3.943
3.871
3.307
3.283
3.023
2.618
2.597
2.582
2.560
2.476
2.463
2.454
2.441
1.952
1.912
1.828
1.792
1.754
1.675
1.641
1.552
1.512
1.497
1.479
1.474
1.466
1.459
1.321
1.311
0.909
O
Bn
N
H
Bn
Me
O
O
c-21a
13.67
1.00
5.30
1.00
0.98
1.14
1.06
0.44
0.69
1.51
1.60
2.15
0.70
1.52
3.56
f1 (ppm)

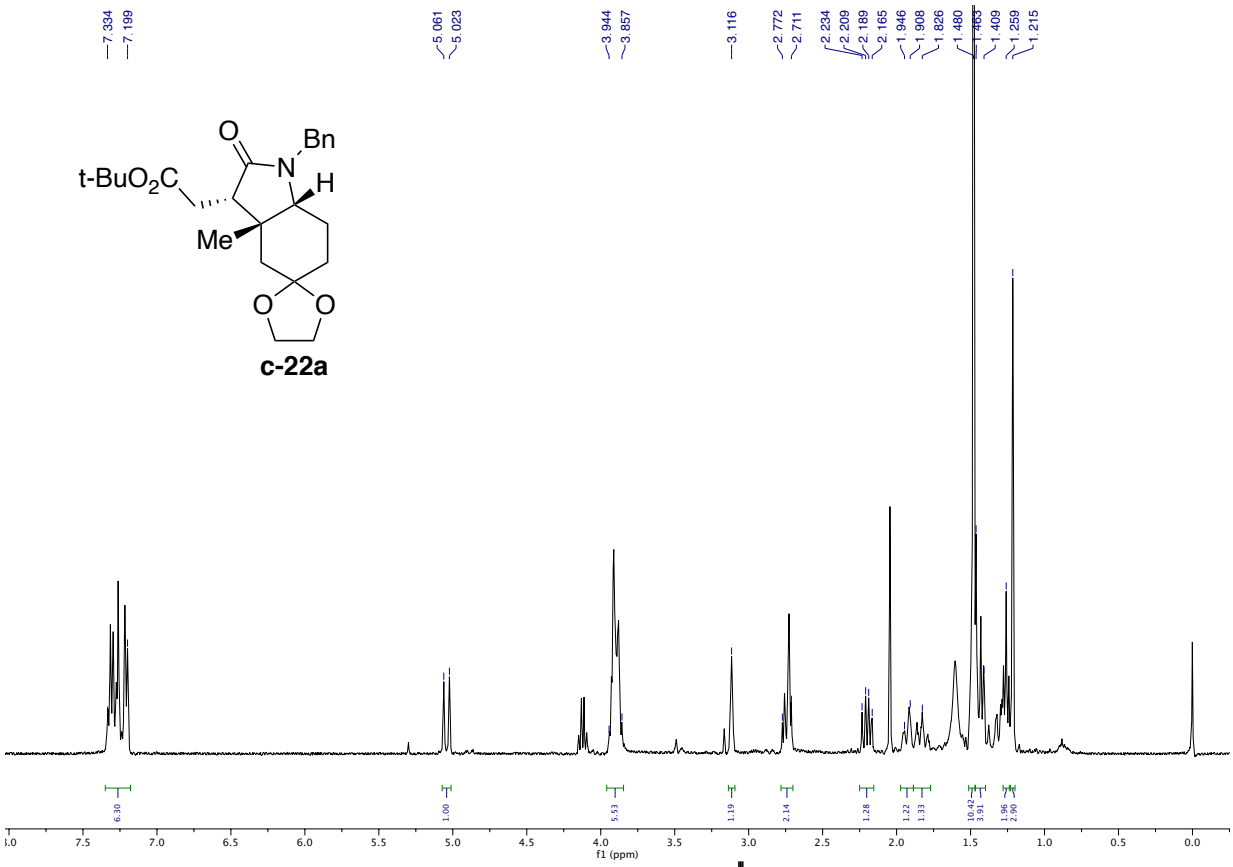

176.87
140.82
136.72
128.96
128.67
128.41
127.96
127.45
126.01
108.08
64.55
63.76
59.24
57.33
43.97
41.84
36.94
30.19
28.51
22.65
20.28
f1 (ppm)

(3RS,3aSR,7aSR)-*tert*-Butyl-1-Benzyl-3a-methyl-2,5-dioxo-3-octahydroindole acetate ethylene acetal (c-22a).



To a solution of **8a** (35 mg, 0.08 mmol) in MeOH (3 mL) was added $Pd(OH)_2$ (19 mg, 60% w/w), and the mixture was stirred under an atmosphere of H_2 at room temperature overnight. The mixture was filtered through a short Celite® pad and concentrated to yield **c-22a** (21 mg, 62%)

IR (neat) 3020, 2779, 1728, 1696, 1412, 1368, 1153, 1088 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.34–7.19 (m, 5H, Ph), 5.04 (d, J = 15.1 Hz, 1H, CH_2Ph), 3.95–3.86 (m, 5H, OCH_2 and CH_2Ph), 3.12 (t, J = 3.0 Hz, 1H, H-7a), 2.77–2.71 (m, 2H, H-3 and CH_2-3), 2.20 (dd, J = 18.0, 9.6 Hz, 1H, 3-CH_2), 1.93 (dq, J = 15.0, 3.6 Hz, 1H, H-7eq.), 1.83 (tt, J = 15.0, 3.6 Hz, 1H, H-7ax), 1.48 (s, 9H, ^{t}Bu), 1.45–1.43 (m, 3H, H-6 and 2H-4), 1.33–1.25 (m, 1H, H-6), 1.22 (s, 3H, Me). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.1 (C-2), 171.9 (CO), 136.6, 128.7, 127.9, and 127.5 (Ph), 107.9 (C-5), 80.7 (C), 64.6 and 63.8 (OCH_2), 59.3 (C-7a), 52.2 (C-3), 44.0 (CH_2Ph), 41.1 (C-3a), 37.1 (C-4), 30.1 (CH_2-3), 28.7 (C-6), 28.1 (^{t}Bu), 22.4 (Me), 20.4 (C-7). HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{24}H_{34}NO_5$ 416.2437; found 416.2441.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7.199
5.061
5.023
3.944
3.857
3.116
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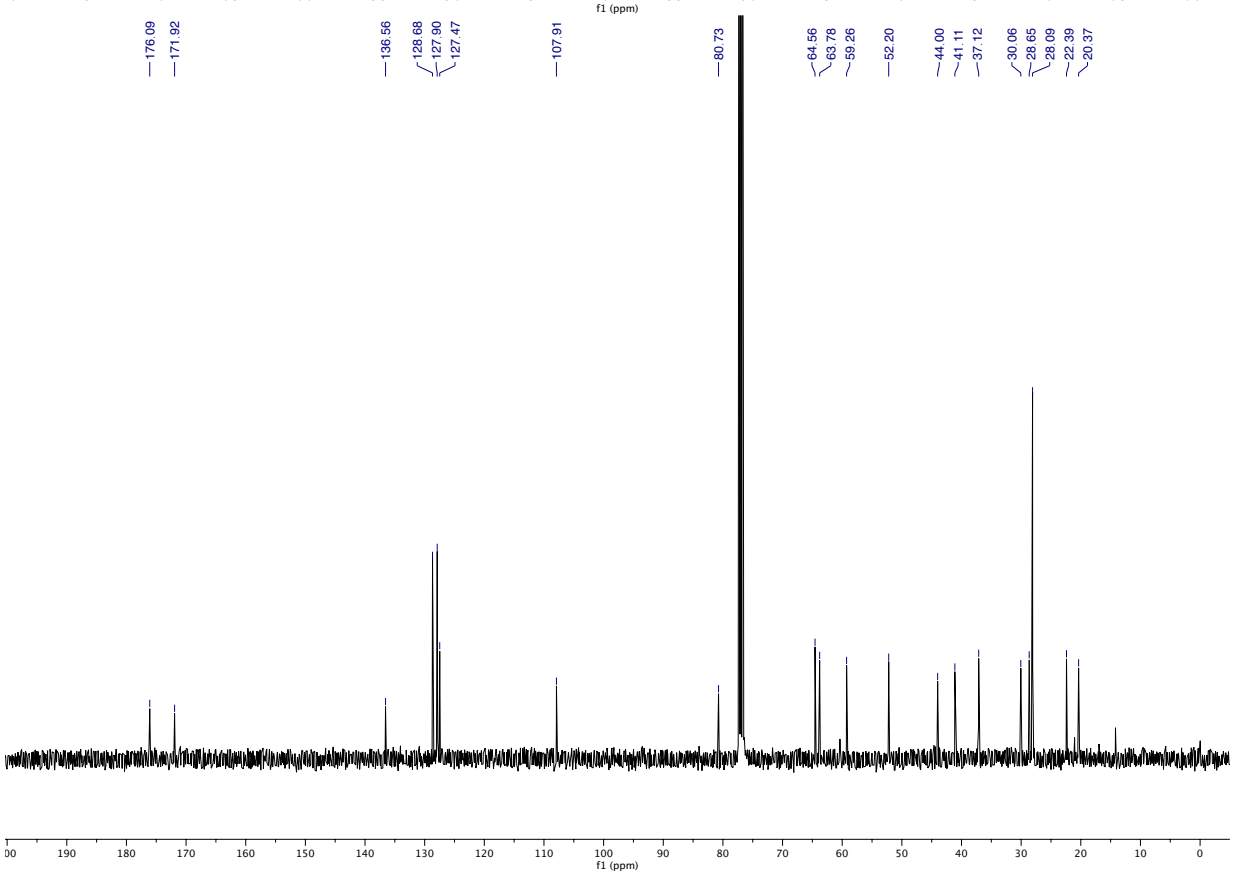
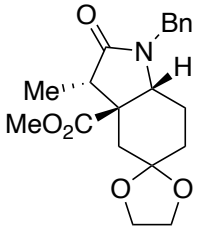
2.711
2.234
2.209
2.189
2.165
1.946
1.908
1.826
1.480
1.463
1.409
1.259
1.215
O
Bn
N
H
t-BuO2C
Me
O
O
6.30
1.00
5.53
1.19
2.14
1.28
1.22
1.33
10.42
3.91
1.06
2.90
f1 (ppm)

c-22a

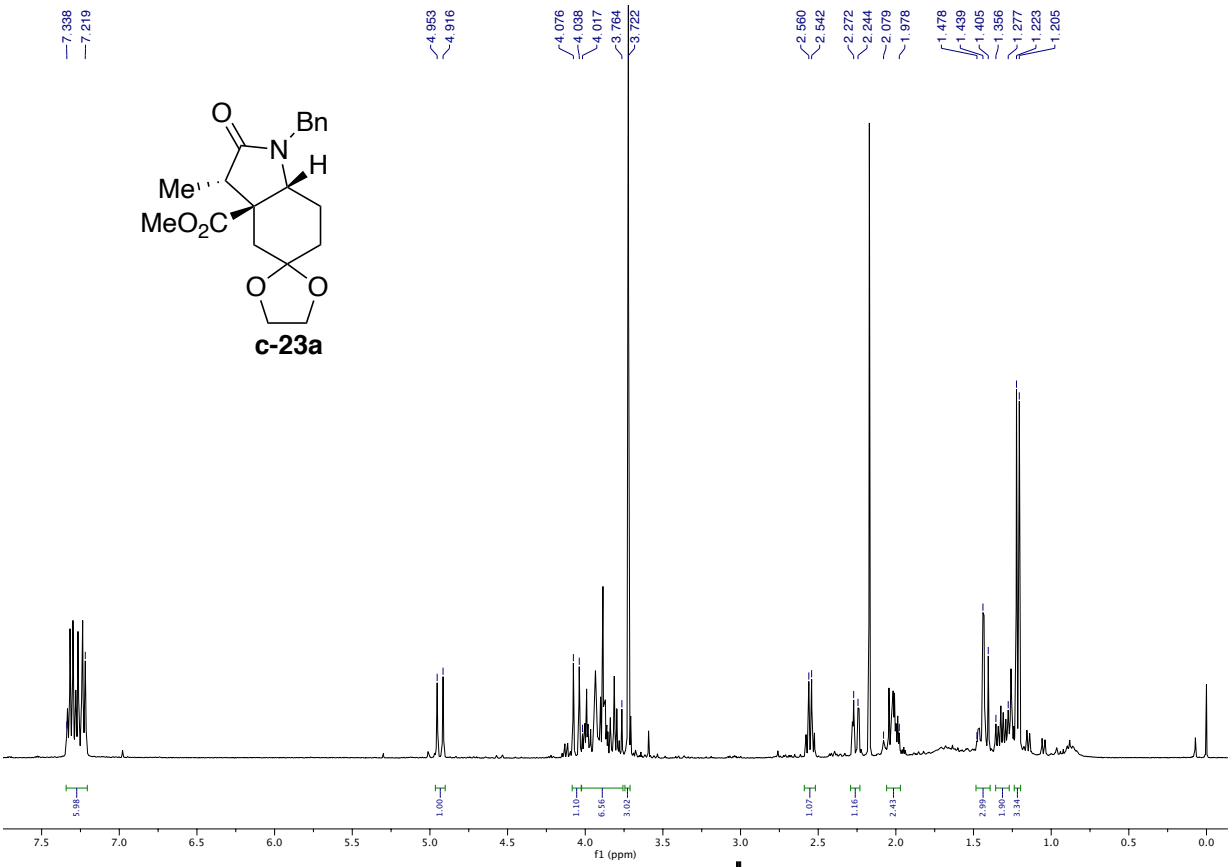

176.09
171.92
136.56
128.68
127.90
127.47
107.91
80.73
64.56
63.78
59.26
52.20
44.00
41.11
37.12
30.06
28.65
28.09
22.39
20.37
f1 (ppm)

(3*RS*,3a*RS*,7a*SR*)-Methyl 1-benzyl-3-methyl-2,5-dioxooctahydro- 1H-indole-3a-carboxylate ethylene acetal (c-23a).



To a solution of **14a** (25 mg, 0.07 mmol) in MeOH (2 mL) was added $Pd(OH)_2$ (15 mg, 60% w/w), and the mixture was stirred under an atmosphere of H_2 at room temperature overnight. The mixture was filtered through a short Celite® pad and concentrated to yield **c-23a** (19 mg, 75%).

IR (neat) 3025, 2885, 1732, 1698, 1448, 1437, 1411, 1235, 1123, 700 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.34–7.22 (m, 5H, Ph), 4.93 and 4.06 (2 d, J = 15.2 Hz, 1H each, CH_2Ph), 4.03–3.76 (m, 4H, OCH_2), 3.93 (t, J = 3.0 Hz, 1H, H-7a), 3.72 (s, 3H, OMe), 2.55 (q, J = 7.2 Hz, 1H, H-3), 2.26 (dd, J = 13.8, 2.7 Hz, 1H, H-4eq.), 2.07–1.98 (m, 2H, H-7), 1.42 (d, J = 13.6 Hz, 1H, H-4ax), 1.47–1.40 and 1.36–1.29 (2 m, 1H each, H-6), 1.21 (d, J = 7.2 Hz, 3H, 3-Me). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.2 (CO), 173.5 (C-2), 136.6, 128.7, 127.9 and 127.6 (Ph), 107.3 (C-5), 64.5 and 64.2 (OCH_2), 54.5 (C-7a), 52.1 (OMe), 51.2 (C-3a), 46.5 (C-3), 44.1 (CH_2Ph), 33.2 (C-4) 29.4 (C-6), 21.4 (C-7), 8.3 (3-Me). HRMS (ESI) *m/z:* $[M + H]^+$ calcd for $C_{20}H_{26}NO_5$ 360.1811; found 360.1813.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3.764
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2.560
2.542
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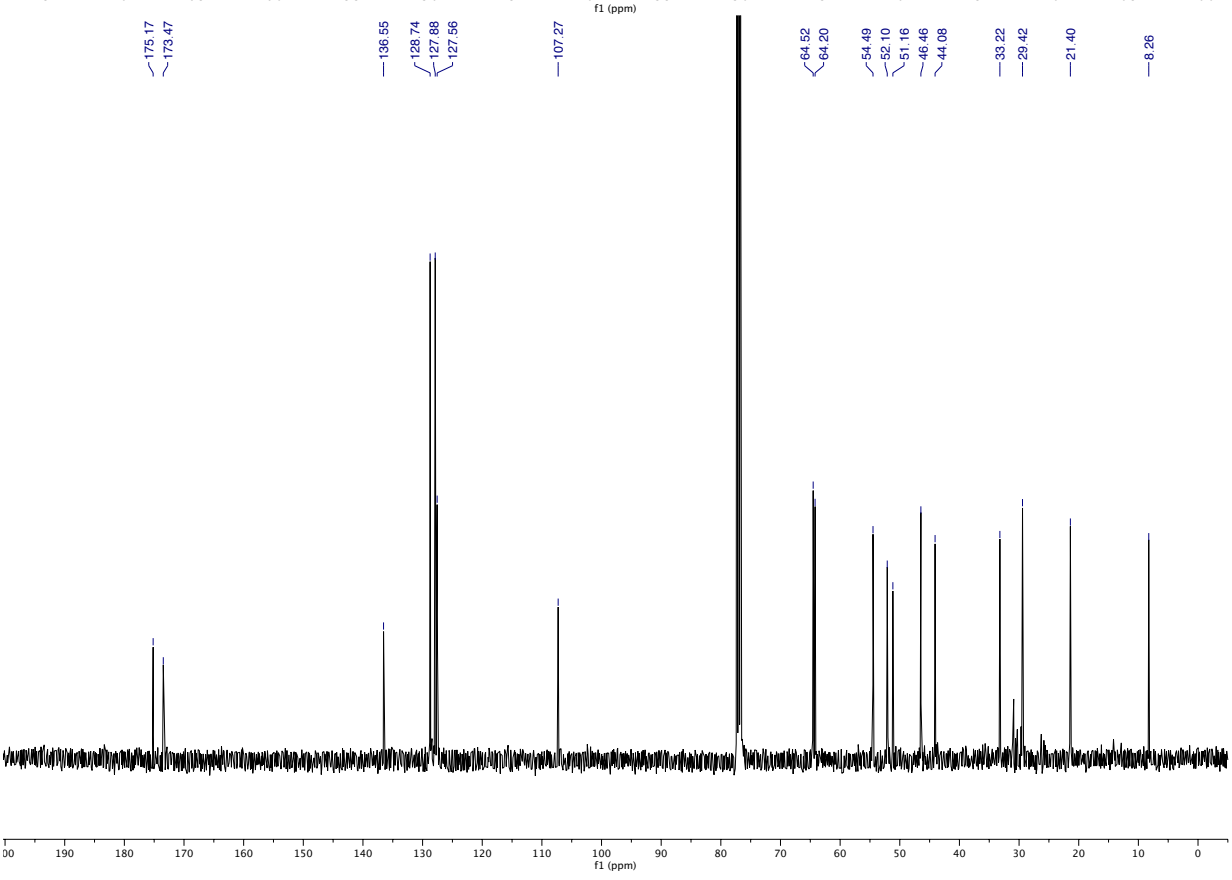
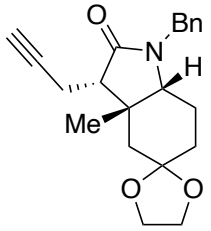
2.079
1.978
1.478
1.439
1.405
1.356
1.277
1.223
1.205
O
Bn
N
H
Me
MeO2C
O
O
c-23a
5.98
1.60
1.10
6.56
3.02
1.07
1.16
2.43
2.99
1.90
3.34
f1 (ppm)

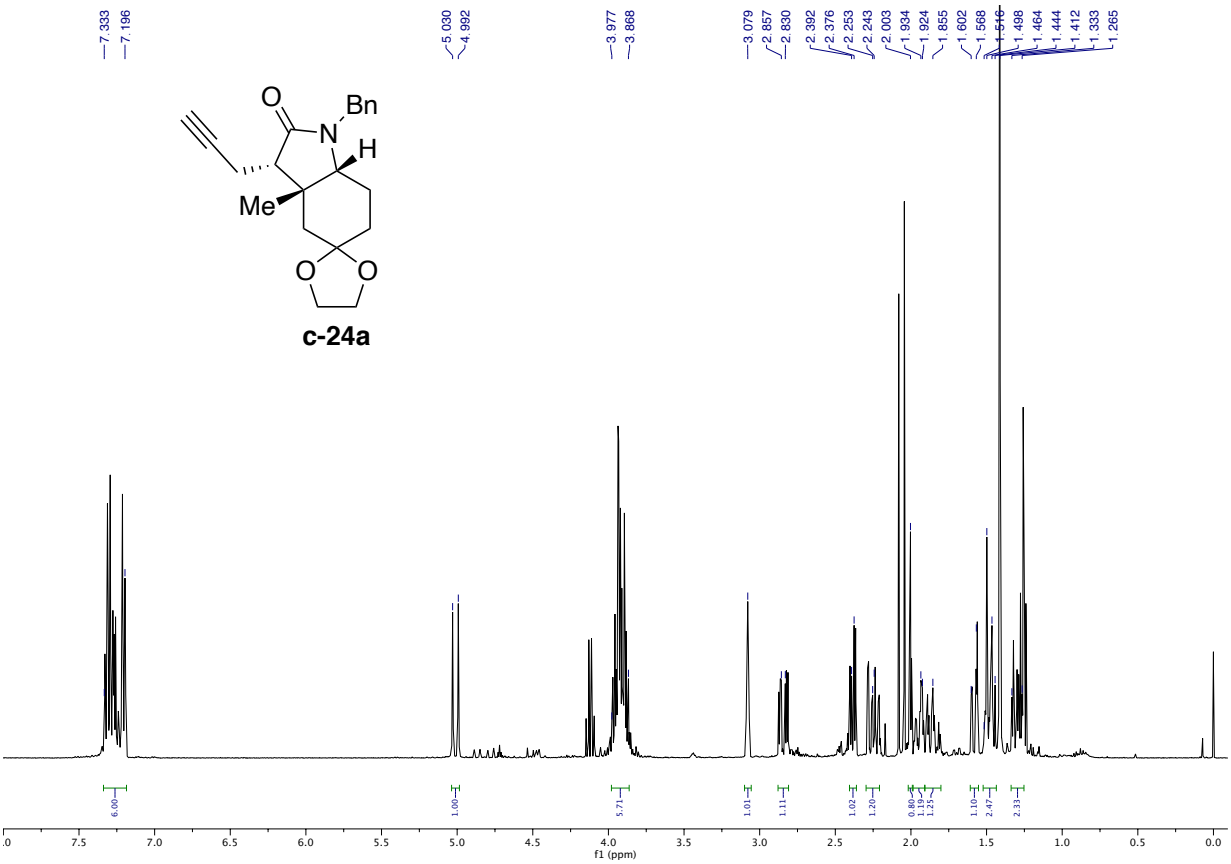

175.17
173.47
136.55
128.74
127.88
127.56
107.27
64.52
64.20
54.49
52.10
51.16
46.46
44.08
33.22
29.42
21.40
8.26
f1 (ppm)

(3*RS*,3a*SR*,7a*SR*)-1-Benzyl-3a-methyl-3-(prop-2-yn-1-yl)hexahydro-indole-2,5-dione ethylene acetal (c-24a).



To a solution of **9a** (59 mg, 0.17 mmol) in AcOH (0.5 mL) was added $NaCNBH_3$ (22 mg, 0.67 mmol), and the reaction mixture was stirred at room temperature for 2 h, quenched with 15% aqueous solution of NaOH and extracted with EtOAc. The dried organic extract was concentrated, and purified by chromatography (hexane:EtOAc, 3 : 1 → 1 : 1) to give **c-24a** (34 mg, 58%) as a colorless oil.

IR (neat) 3028, 2944, 2873, 1693, 1458, 1436, 1419 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.33–7.19 (m, 5H, Ph), 5.01 (d, *J* = 15.2 Hz, 1H, CH_2Ph), 3.95–3.88 (m, 5H, OCH_2 and CH_2Ph), 3.08 (t, *J* = 3.0 Hz, 1H, H-7a), 2.84 (ddd, *J* = 17.0, 4.2, 2.8 Hz, 1H, CH_2-3), 2.38 (dd, *J* = 10.8, 4.4 Hz, 1H, H-3), 2.25 (ddd, *J* = 17.2, 10.8, 2.8 Hz, 1H, CH_2-3), 2.00 (t, *J* = 2.8 Hz, 1H, ≡CH), 1.95 (dq, *J* = 15.1, 3.2 Hz, 1H, H-7eq.), 1.85 (tt, *J* = 15.0, 3.6 Hz, 1H, H-7ax), 1.58 (dd, *J* = 13.6, 2.8 Hz, 1H, H-4), 1.48 (d, *J* = 13.6 Hz, 1H, H-4), 1.52–1.44 (m, 1H, H-6), 1.42 (s, 3H, Me), 1.33–1.24 (m, 1H, H-6). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.5 (C-2), 136.5, 128.7, 127.9 and 127.5 (Ph), 107.9 (C-5), 82.5 (≡C), 69.8 (≡CH), 64.6 and 63.8 (OCH_2), 59.3(C-7a), 53.8 (C-3), 44.0 (CH_2Ph), 41.6 (C-3a), 36.2 (C-4), 28.6 (C-6), 22.9 (Me), 20.2 (C-7), 13.6 (CH_2-3). HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{21}H_{26}NO_3$ 340.1913; found 340.1911.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2.857
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2.392
2.376
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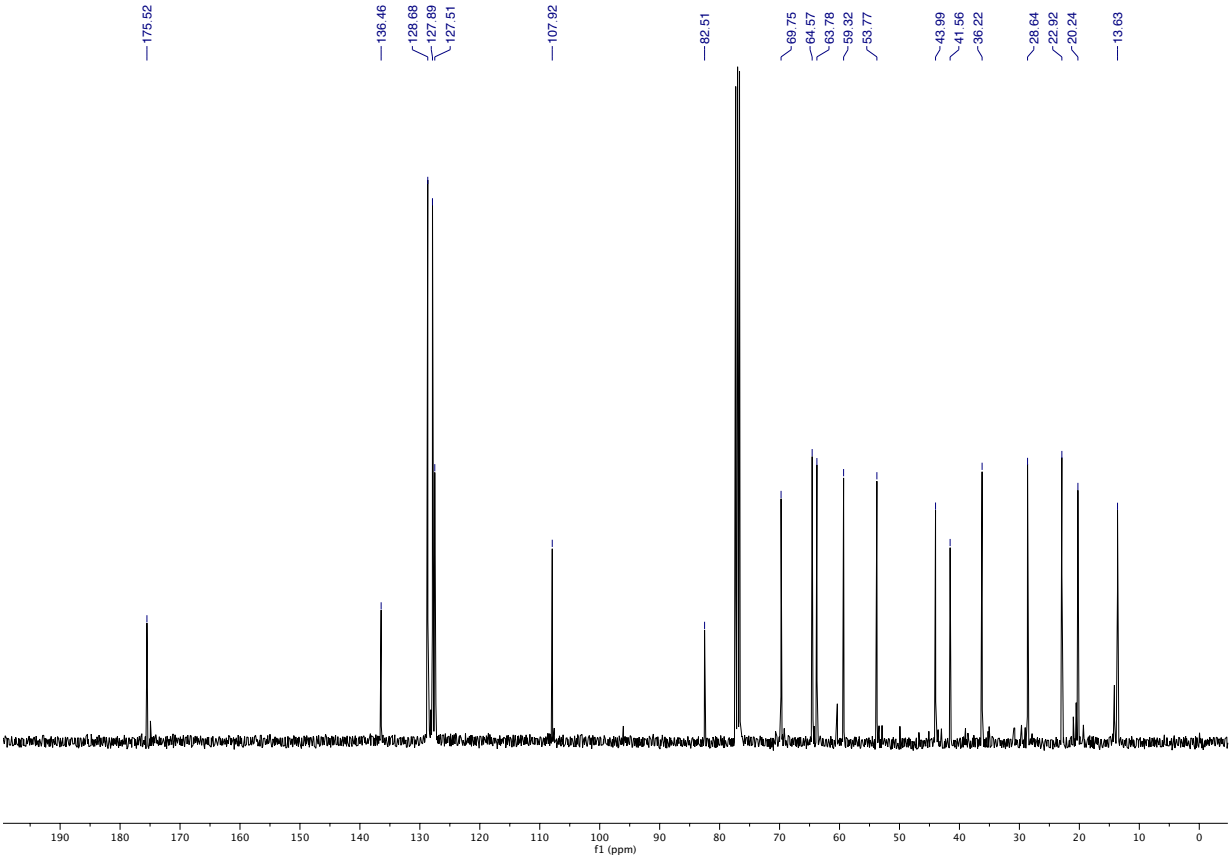
2.003
1.934
1.924
1.855
1.602
1.568
1.516
1.498
1.464
1.444
1.412
1.333
1.265
O
Bn
N
H
Me
O
O
6.00
1.00
5.71
1.01
1.11
1.02
1.20
0.80
1.19
1.25
1.10
2.47
2.33
f1 (ppm)

c-24a


175.52
136.46
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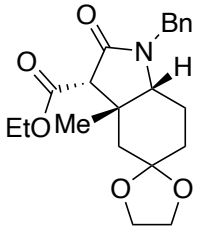
127.89
127.51
107.92
82.51
69.75
64.57
63.78
59.32
53.77
43.99
41.56
36.22
28.64
22.92
20.24
13.63
f1 (ppm)

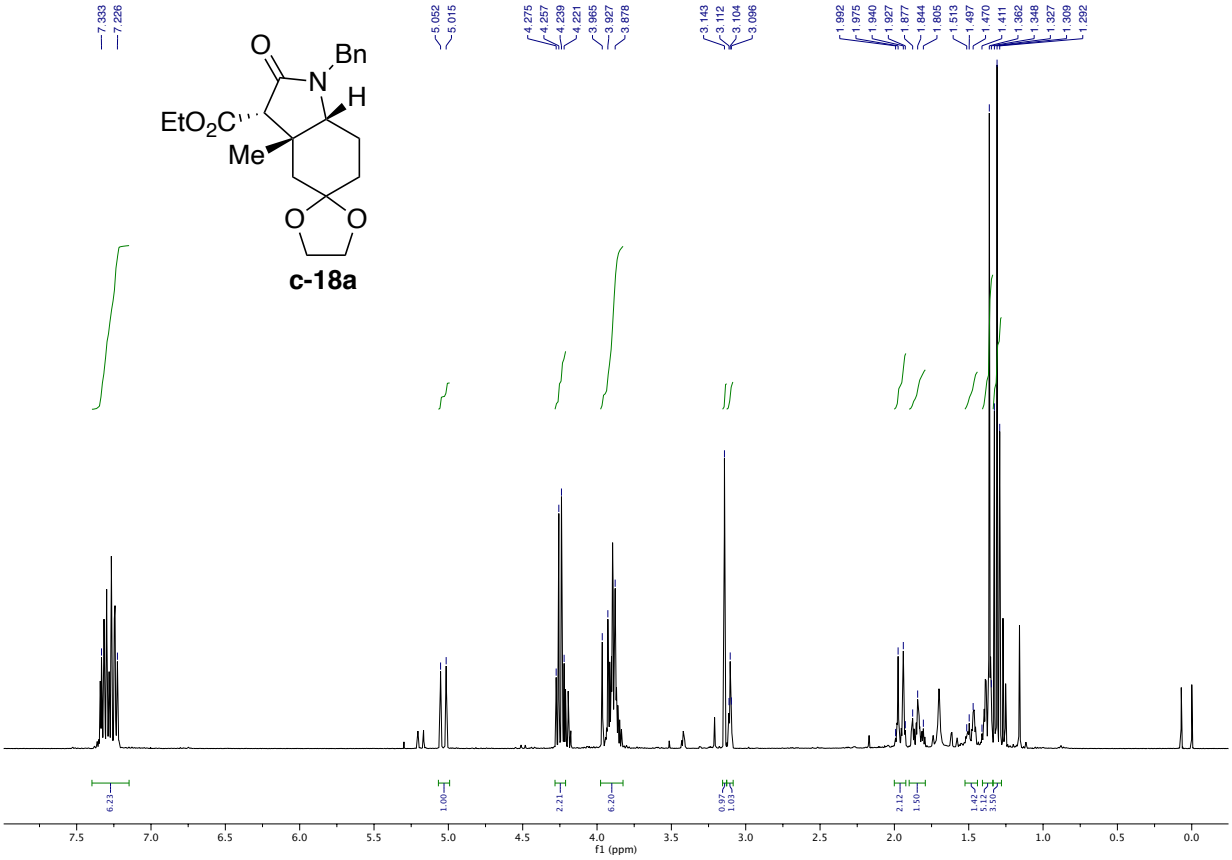
(3*RS*,3a*SR*,7a*SR*)-1-benzyl-3-ethoxycarbonyl-3a-methylhexahydro-1H-indole-2,5(3H,6H)-dione ethylene acetal (c-18a).



Method A: To a solution of **7a** (20 mg, 0.05 mmol) in EtOAc (2 mL) was added Pd/C (8 mg, 40% w/w) and the mixture was stirred under 1 atm of H_2 and at room temperature overnight. The mixture was filtered through a short Celite® pad and concentrated to yield a mixture of **c-18a** and **c-18b** (5.6:1, 18 mg, 98%). In another run, the reduction was performed from **7a** (30 mg, 0.08 mmol) and Pd/C (12 mg, 40% w/w) in EtOAc (2.4 mL) under 1 atm of H_2 at room temperature overnight. After chromatography (hexane:EtOAc, 1:0 → 3:1), a mixture of **c-18a** and **c-18b** (1:2.1) was isolated (27 mg, 84%). However, in the crude reaction a dr of 3.5:1 was observed, and hence an epimerization process took place in the chromatography step.

Method B: To a solution of **7a** (100 mg, 0.27 mmol) in AcOH (1 mL) was added $NaCNBH_3$ (34 mg, 0.54 mmol) portionwise, and the mixture was stirred at room temperature for 62 h. Water was added and the mixture was extracted with CH_2Cl_2 (3 x 15 mL). The organic layer was washed with saturated aqueous Na_2CO_3 (2 x 15 mL), dried, concentrated, and purified by chromatography (hexane:EtOAc, 4:1→ 0:1) to give a 1:1 mixture of **c-18a** and **c-18b** (70 mg, 67%). Finally, **7a** (10 mg) was recovered.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.20 (m, 5H, Ph), 5.03 (d, J = 15.0 Hz, 1H, CH_2Ph), 4.25 (q, J = 7.1 Hz, 2H, OEt), 3.95 (d, J = 15.0 Hz, 1H, CH_2Ph), 3.94–3.82 (m, 4H, OCH_2), 3.14 (s, 1H, H-3), 3.10 (t, J = 3.2 Hz, 1H, H-7a), 1.96 (d, J = 14.0, 1H, H-4), 2.00–1.92 (m, 1H, H-7eq.), 1.84 (tt, J = 13.4, 3.6 Hz, 1H, H-7ax), 1.48 (dm, J = 13.4 Hz, 1H, H-6eq), 1.42–1.34 (m, 2H, H-4 and H-6ax), 1.36 (s, 3H, Me), 1.31 (t, J = 7.1, 3H, OEt). ^{13}C NMR (101 MHz, $CDCl_3$): d 171.1 (CO), 167.6 (C-2), 136.3, 128.7, 128.0, and 127.6 (Ph), 107.6 (C-5), 64.5 and 63.8 (OCH_2), 61.0 (OEt), 61.0 (C-3), 59.5 (C-7a), 44.1 (CH_2Ph), 42.0 (C-3a), 37.0 (C-4), 28.5 (C-6), 23.2 (Me), 20.7 (C-7), 14.3 (OEt)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4.221
3.965
3.927
3.878
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3.104
3.096
1.992
1.975
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1.497
1.470
1.411
1.362
1.348
1.327
1.309
1.292
6.23
1.60
2.21
6.20
0.97
1.03
2.12
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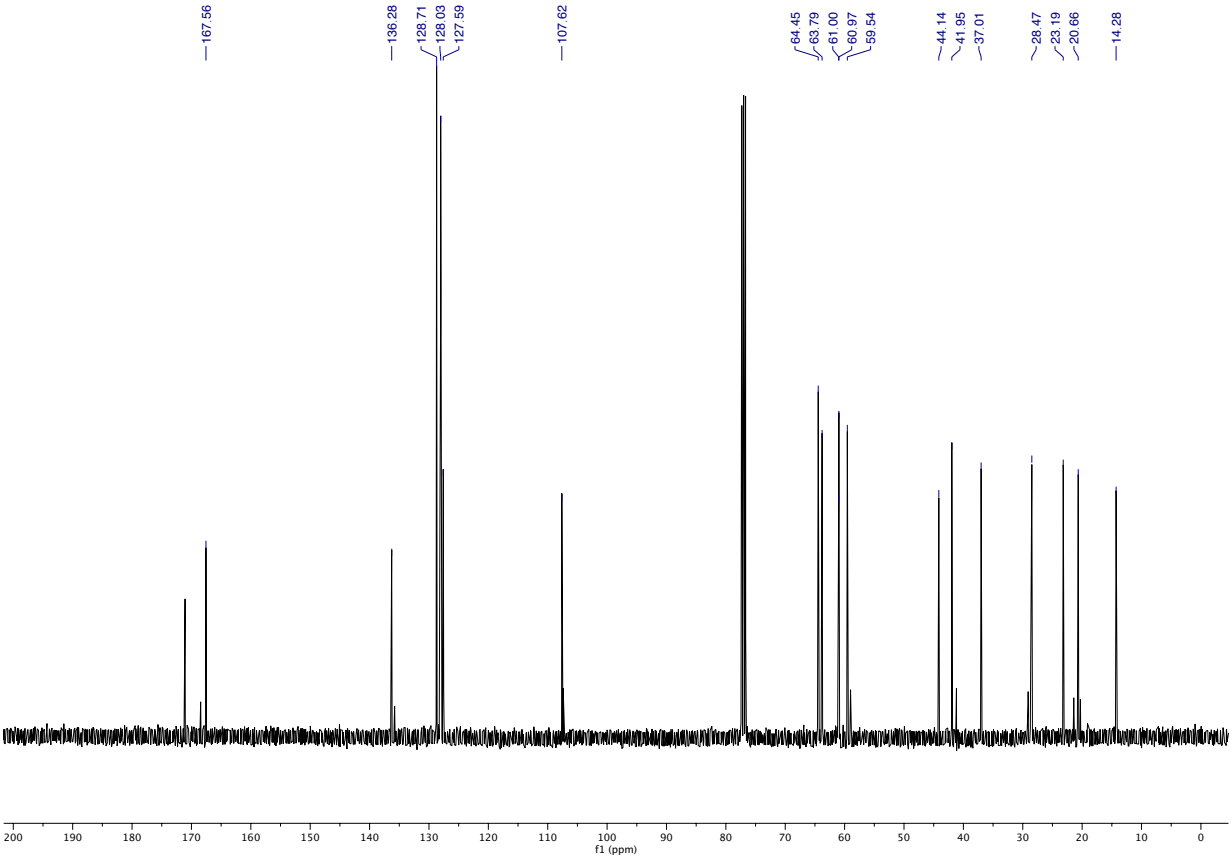
1.42
5.12
3.30
f1 (ppm)

c-18a


167.56
136.28
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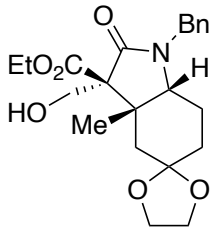
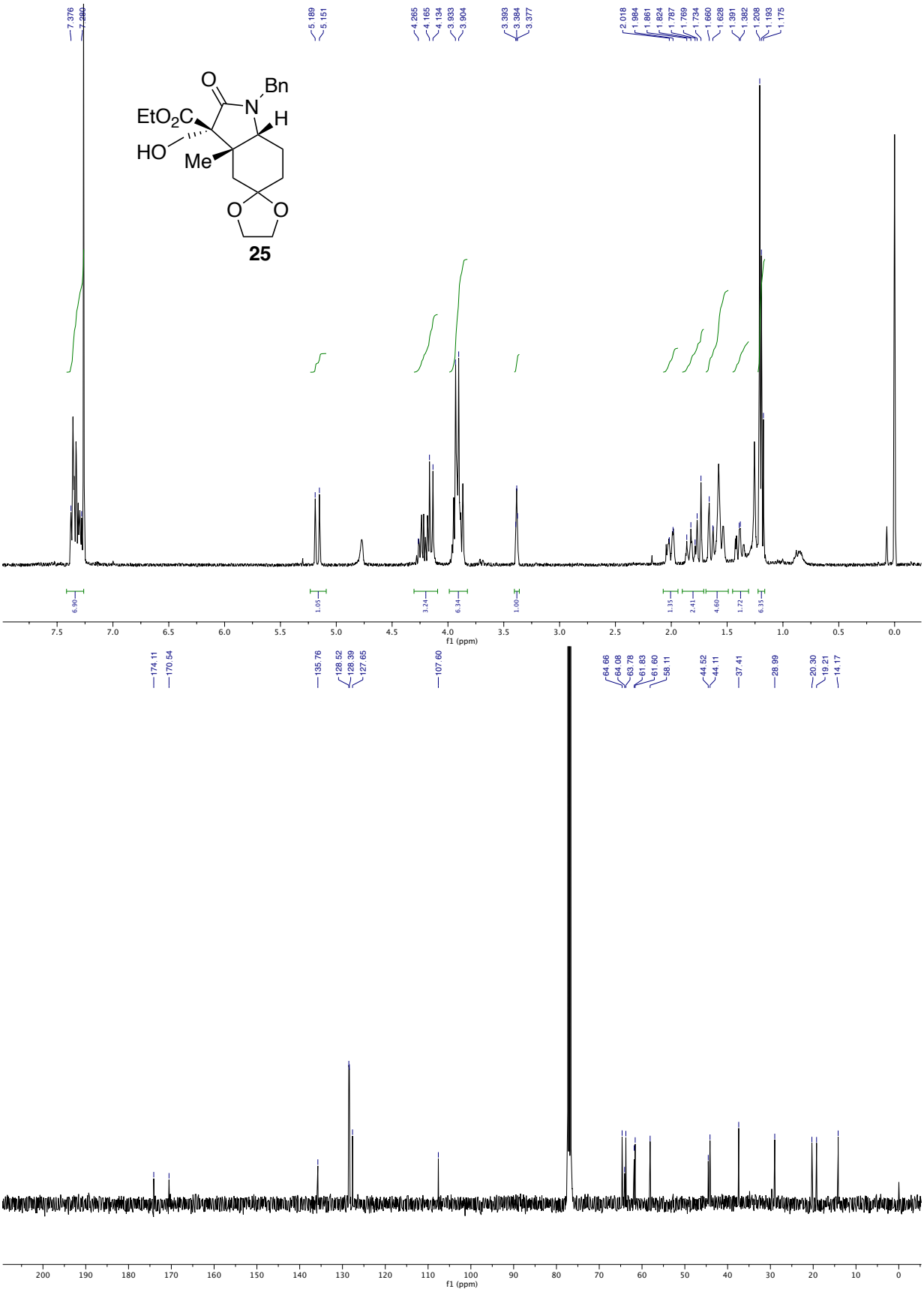
128.03
127.59
107.62
64.45
63.79
61.00
60.97
59.54
44.14
41.95
37.01
28.47
23.19
20.66
14.28
f1 (ppm)

(3*RS*,3a*SR*,7a*SR*)1-Benzyl-3-ethoxycarbonyl-3-hydroxymethyl-3a-methylhexahydro- 1H-indole-2,5(3H,6H)-dione ethylene acetal (25).



To a solution of **7a** (100 mg, 0.27 mmol) in MeOH (10 mL) was added Pd/C (40 mg, 40% w/w) and the mixture was stirred under an atmosphere of H_2 at room temperature overnight. The mixture was filtered through a short celite pad, concentrated and purified by chromatography (hexane:EtOAc, 1:0→ 3:2) to provide a 1:8 mixture of **c-18a** and **c-18b** (74 mg, 73%) and finally **25** (20 mg, 18%).

IR (neat) 3475, 2942, 2889, 1716, 1682 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.39–7.27 (m, 5H, PhH), 5.17 (d, *J* = 15.4 Hz, 1H, CH_2Ph), 4.30–4.12 (m, 3H, CH_2OH, OEt), 3.98–3.88 (m, 5H, 1H-CH_2OH, OCH_2), 3.89 (d, *J* = 14.8 Hz, 1H, CH_2Ph), 3.39 (t, *J* = 3.4 Hz, 1H, H-7a), 2.00 (dq, *J* = 15.2, 3.2 Hz, 1H, H-7eq), 1.82 (tt, *J* = 15.2, 3.6 Hz, 1H, H-7ax), 1.75 and 1.64 (2d, *J* = 13.8 Hz, 1H each, H-4), 1.63–1.54 (m, 1H, H-6), 1.39 (td, *J* = 13.8, 4.1 Hz, 1H, H-6), 1.21 (s, 3H, Me), 1.19 (t, *J* = 7.2 Hz, 3H, OEt). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.1 (CO), 170.5 (C-2), 135.7, 128.5, 128.4, and 127.7 (Ph), 107.6 (C-5), 64.7 (OCH_2), 64.1 (C-3), 63.8 (OCH_2), 61.8 (CH_2OH), 61.6 (CH_2), 58.1 (C-7a), 44.5 (C-3a), 44.1 (CH_2Ph), 37.4 (C-4), 29.0 (C-6), 20.3 (C-7), 19.2 (Me), 14.2 (OEt). HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{22}H_{30}NO_6$ 404.2068; found 404.2073.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1.734
1.660
1.628
1.391
1.382
1.208
1.193
1.175
O
Bn
N
H
EtO2C
HO
Me
O
O
25
6.90
1.05
3.24
6.34
1.00
1.35
2.41
4.60
1.72
6.35
f1 (ppm)
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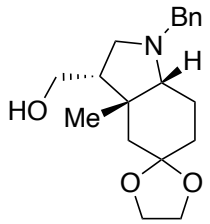
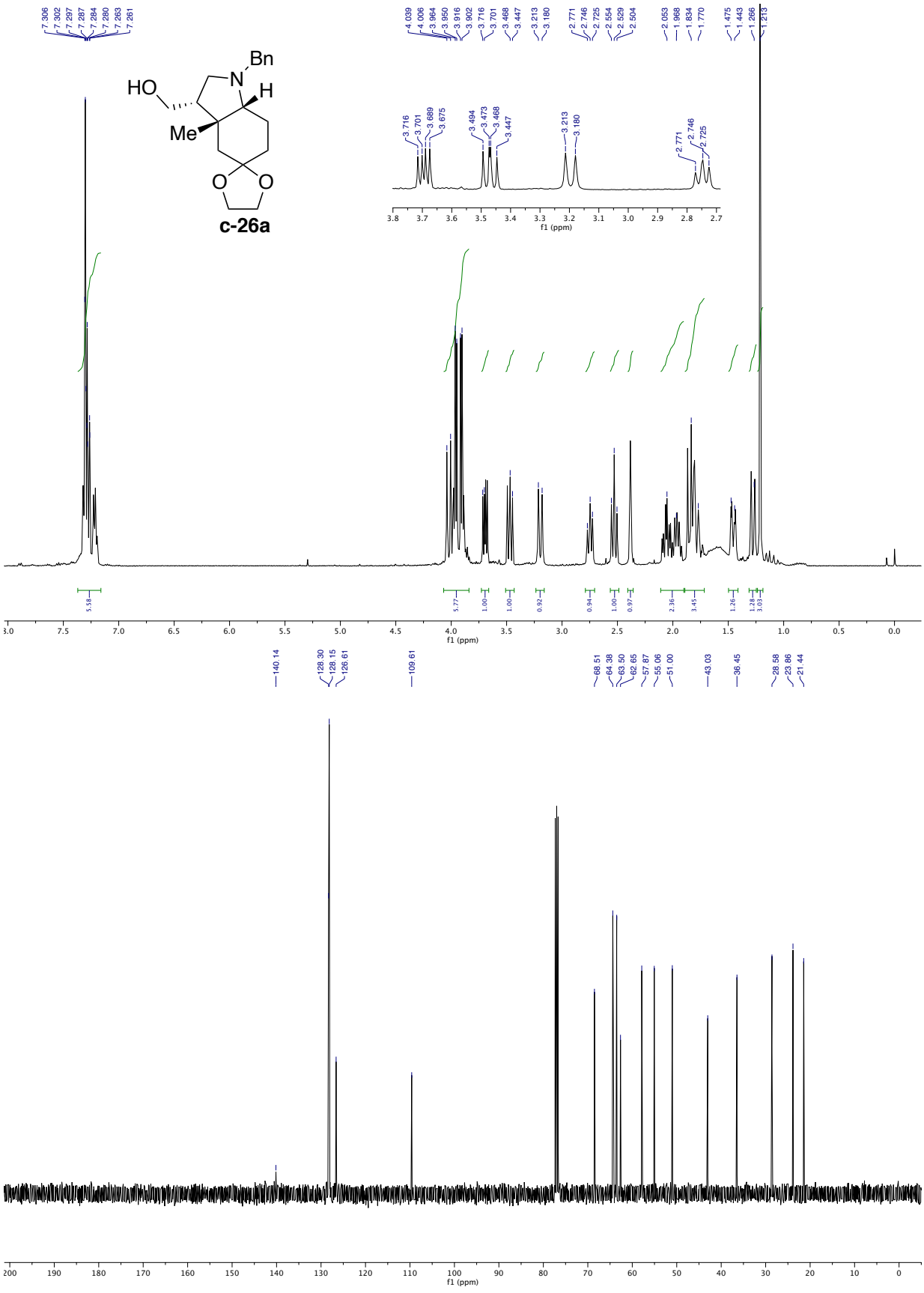
107.60
64.66
64.08
63.78
61.83
61.60
58.11
44.52
44.11
37.41
28.99
20.30
19.21
14.17
f1 (ppm)

(3*RS*,3a*SR*,7a*SR*)-1-Benzyl-3-(hydroxymethyl)-3a-methyloctahydroindol-5-one ethylene acetal (c-26a).

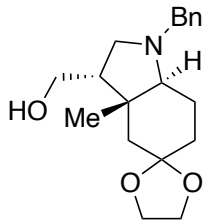


To a solution of $AlCl_3$ (42 mg, 0.31 mmol, 1.5 equiv) in THF (1 mL) was added a 1 M solution of $LiAlH_4$ in THF (0.73 mL, 3.5 equiv) dropwise at room temperature. The mixture was stirred for 20 min, a solution of **7a** (77 mg, 0.21 mmol, 1 equiv) in THF (1 mL) was added and the mixture was stirred at room temperature overnight. The mixture was cooled to 0 °C, quenched with 30% KOH aq. solution (10 mL) and extracted sequentially with CH_2Cl_2 (2 x 10 mL), $CHCl_3$ (2 x 10 mL) and $CHCl_3$:*i*-PrOH (4:1, 2 x 10 mL). The organics were dried, concentrated, and purified by chromatography (CH_2Cl_2:MeOH, 1:0→9.5:0.5) to sequentially give **c-26a** (26 mg, 41%) and **t-26a** (13 mg, 21%).

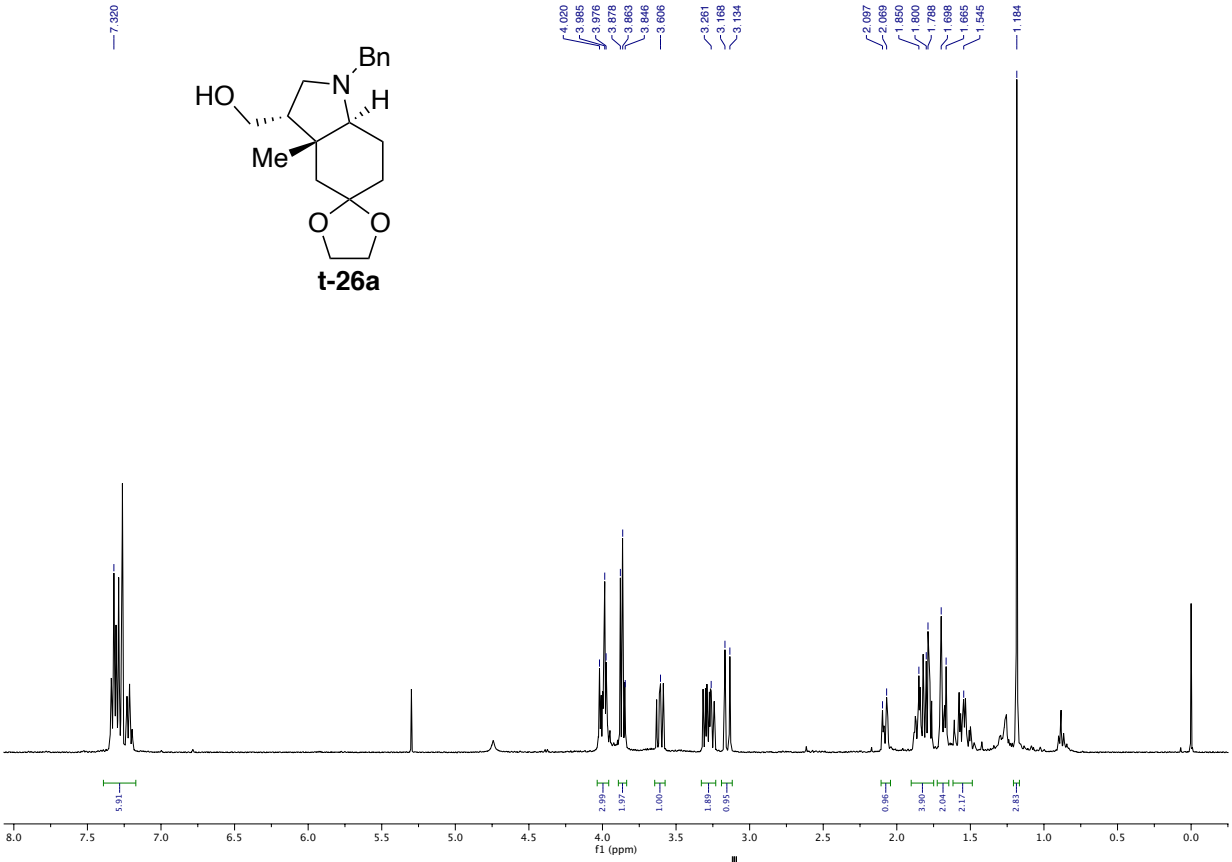
IR (neat) 3409, 3060, 3026, 2952, 2927, 2877, 2789, 1603 cm^{-1}. 1H NMR (400 MHz, $CDCl_3$) δ 7.34–7.18 (m, 5H), 4.02 (d, *J* = 13.5 Hz, 1H, CH_2Ph), 3.99–3.87 (m, 4H, OCH_2), 3.69 (dd, *J* = 10.5, 5.9 Hz, 1H, CH_2OH), 3.47 (dd, *J* = 10.5, 8.5 Hz, 1H, CH_2OH), 3.20 (d, *J* = 13.5 Hz, 1H, CH_2Ph), 2.75 (dd, *J* = 10.1, 8.3 Hz, 1H, H-2), 2.53 (t, *J* = 10.1 Hz, 1H, H-2), 2.38 (br t, *J* = 3.0 Hz, H-7a), 2.06 (td, *J* = 12.8, 4.8 Hz, 1H, H-6ax), 1.96 (m, 1H, H-3), 1.85 (d, *J* = 13.0 Hz, 1H, H-4), 1.85–1.72 (m, 2H, H-7), 1.59 (br s, 1H, OH), 1.46 (dq, *J* = 12.8, 3.0 Hz, 1H, H-6eq.), 1.28 (dd, *J* = 13.0, 2.5 Hz, 1H, H-4), 1.21 (s, 3H, Me). ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.1, 128.3, 128.2, and 126.6 (Ph), 109.6 (C-5), 68.5 (C-7a), 64.4 and 63.5 (OCH_2), 62.7 (CH_2OH), 57.9 (CH_2Ph), 55.1 (C-2), 51.0 (C-3), 43.0 (C-3a), 36.5 (C-4), 28.6 (C-6), 23.9 (Me), 21.4 (C-7). HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{19}H_{28}NO_3$ 318.2064; found 318.2064.


HO
Bn
N
H
Me
O
O
c-26a
f1 (ppm)

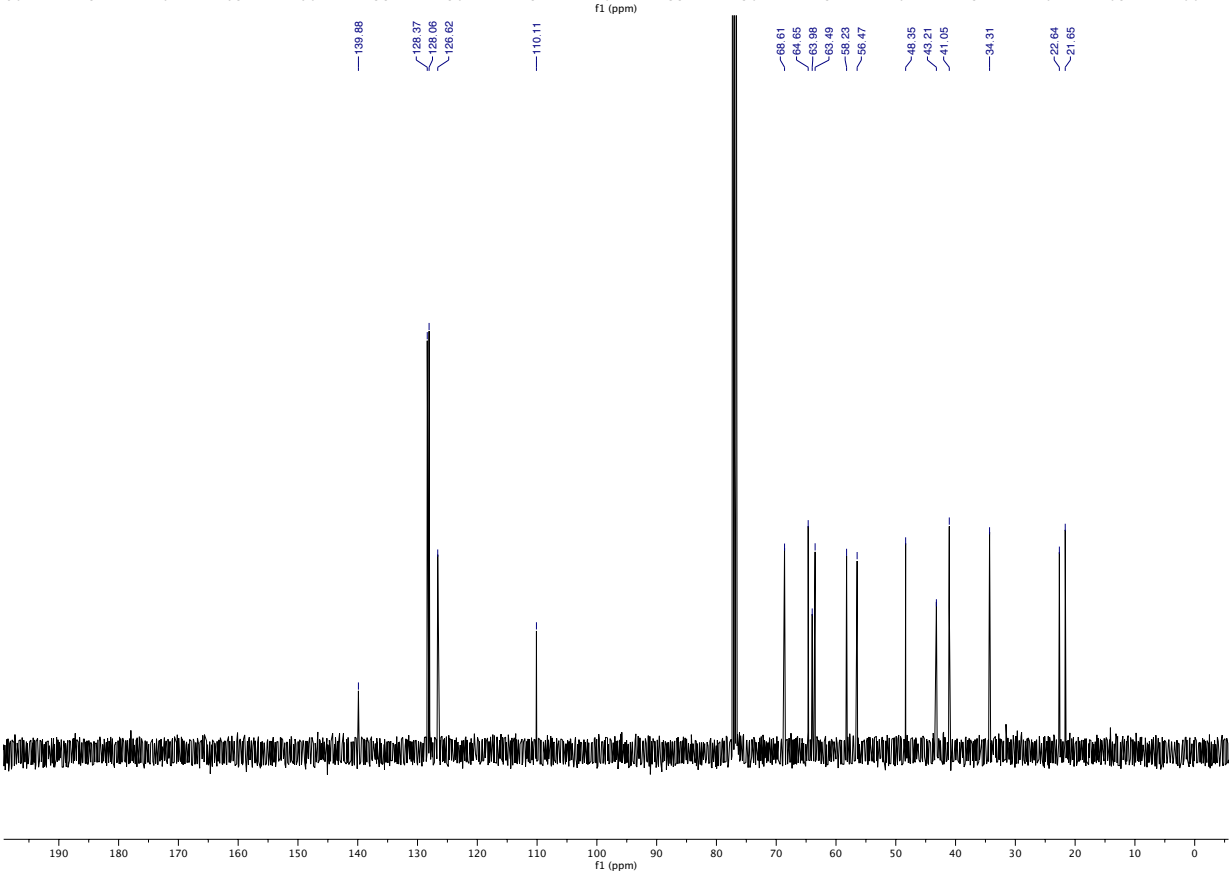
(3*RS*,3a*SR*,7a*RS*)-1-Benzyl-3-(hydroxymethyl)-3a-methyloctahydroindol-5-one ethylene acetal (t-26a).



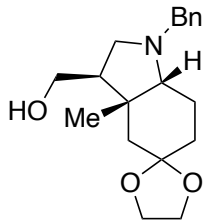
IR (neat) 3412, 3060,3025, 2952, 2924, 2872, 2854, 1604 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.36–7.18 (m, 5H, Ph), 4.04–3.95 (m, 3H, OCH_2 and CH_2Ph), 3.89–3.83 (m, 2H, OCH_2), 3.61 (dd, *J* = 10.4, 7.4 Hz, 1H, CH_2OH), 3.29 (dd, *J* = 10.4,6.6 Hz, 1H, CH_2OH), 3.26 (dd, *J* = 10.3, 8.2, 1H, H-2), 3.15 (d, *J* = 13.3 Hz, 1H, CH_2Ph), 2.08 (dd, *J* = 11.0, 3.2 Hz, 1H, H-7a),1.89–1.75 (m, 4H, H-2, H-3, H-4 and H-6), 1.68 (d, *J* = 13.4 Hz, 1H, H-4), 1.71–1.65 (m, 1H, H-7), 1.62–1.45 (m, 2H, H-6 and H-7), 1.18 (s, 3H, Me); a nOe was observed between Me and H-3 and Me and H-7. ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.9,128.4, 128.1, and 126.6 (Ph), 110.1 (C-5), 68.6 (C-7a), 64.7 (OCH_2), 64.0 (CH_2OH), 63.5 (OCH_2), 58.2 (CH_2Ph), 56.5 (C-2),48.4 (C-3), 43.2 (C-3a), 41.1 (C-4), 34.3 (C-6), 22.6 (Me), 21.7 (C-7). HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{19}H_{28}NO_3$ 318.2064; found 318.2068.


7.320
4.020
3.985
3.976
3.878
3.863
3.846
3.606
3.261
3.168
3.134
2.097
2.069
1.850
1.800
1.788
1.698
1.665
1.545
1.184
Bn
N
H
HO
Me
O
O
5.91
2.99
1.97
1.00
1.89
0.95
0.96
3.90
2.04
2.17
2.83
f1 (ppm)

t-26a

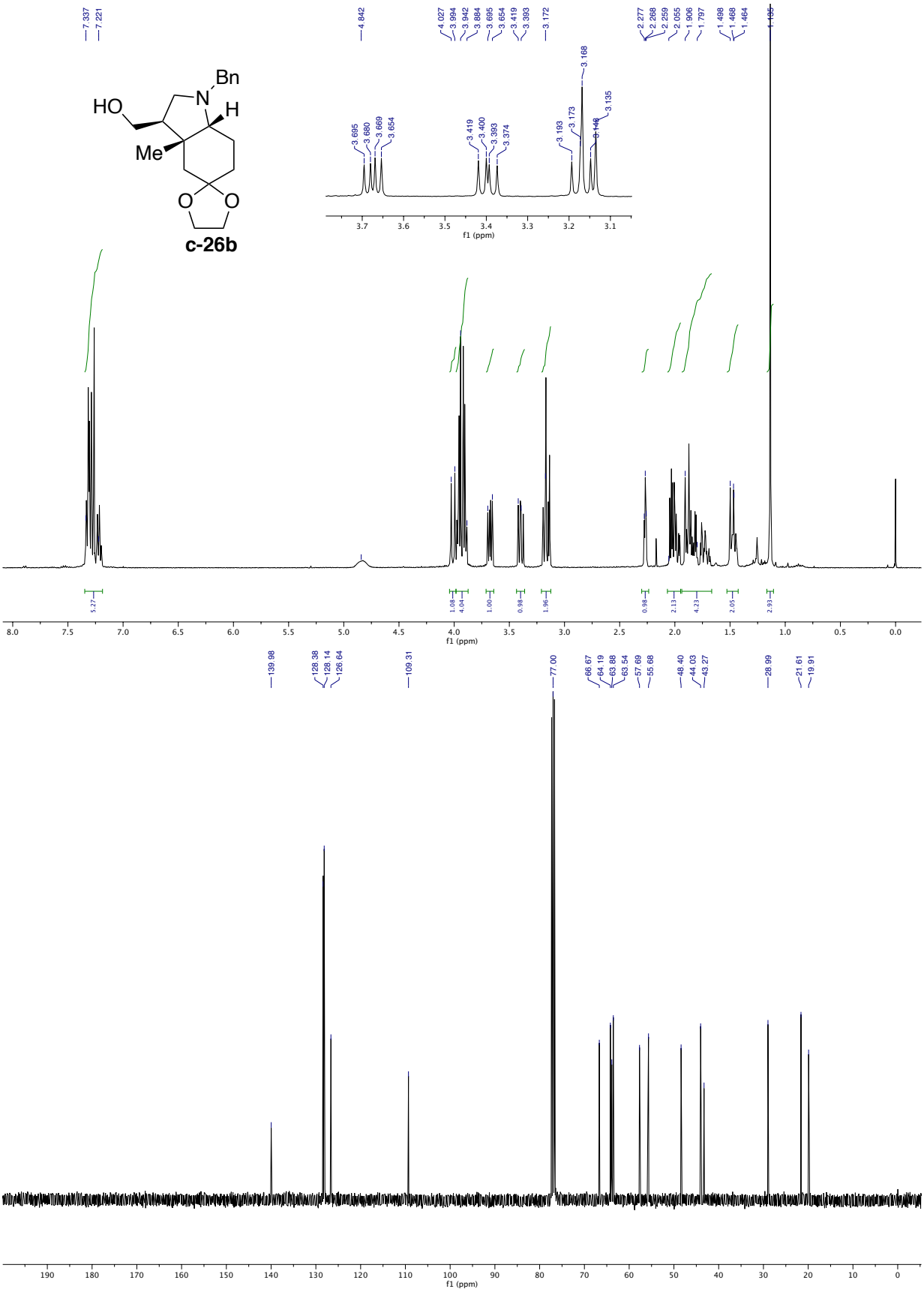

139.88
128.37
128.06
126.62
110.11
68.61
64.65
63.98
63.49
58.23
56.47
48.35
43.21
41.05
34.31
22.64
21.65
f1 (ppm)

(3*SR*,3a*SR*,7a*SR*)-1-Benzyl-3-(hydroxymethyl)-3a-methyloctahydroindol- 5-one ethylene acetal (c-26b).

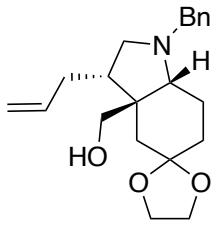


To a solution of $AlCl_3$ (150 mg, 1.1 mmol, 1.5 equiv) in THF (3 mL) was added a 1 M solution of $LiAlH_4$ in THF (1.85 mL, 2.5 equiv) dropwise at room temperature. The mixture was stirred for 20 min, a solution of **c-18b** (270 mg, 0.74 mmol, 1 equiv) in THF (3 mL) was added and the mixture was stirred at room temperature overnight. The mixture was cooled to 0 °C, quenched with 30% KOH aq. Solution and extracted sequentially with CH_2Cl_2 (2 x 5 mL), $CHCl_3$ (2 x 5 mL) and $CHCl_3$:*i*-PrOH (4:1, 2 x 5 mL). The organics were dried, concentrated, and purified by chromatography (CH_2Cl_2:MeOH, 1:0 → 9.5:0.5) to yield **c-26b** (167 mg, 79%) as a colorless oil.

IR (neat) 3416, 3061, 3027, 2954, 2925, 2879, 2787, 1603 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.34–7.18 (m, 5H, Ph), 4.83 (br s, 1H, OH), 4.01 (d, J = 13.2 Hz, 1H, CH_2Ph), 3.98–3.88 (m, 4H, OCH_2), 3.67 (dd, J = 10.5, 6.1 Hz, 1H, CH_2OH), 3.40 (dd, J = 10.5, 7.7 Hz, 1H, CH_2OH), 3.17 (dd, J = 10.0, 8.2, 1H, H-2), 3.15 (d, J = 13.2 Hz, 1H, CH_2Ph), 2.27 (t, J = 3.6 Hz, 1H, H-7a), 2.03 (dd, J = 10.0, 6.0 Hz, 1H, H-2), 1.99 (td, J = 12.7, 4.2 Hz, 1H, H-6ax), 1.89 (d, J = 13.5 Hz, 1H, H-4), 1.86 (m, 1H, H-3), 1.83 (dq, J = 14.6, 4.1 Hz, 1H, H-7eq.), 1.72 (ddt, J = 14.6, 12.7, 3.4 Hz, 1H, H-7ax), 1.51–1.42 (m, 2H, H-4 and H-6), 1.13 (s, 3H, Me); a nOe was observed between Me and CH_2OH and H-7a. ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.0, 128.4, 128.1, and 126.6 (Ph), 109.3 (C-5), 66.7 (C-7a), 64.2 (OCH_2), 63.9 (CH_2OH), 63.5 (OCH_2), 57.7 (CH_2Ph), 55.7 (C-2), 48.4 (C-3), 44.0 (C-4), 43.3 (C-3a), 29.0 (C-6), 21.6 (C-7), 19.9 (Me). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{19}H_{28}NO_3$ 318.2064; found 318.2070.

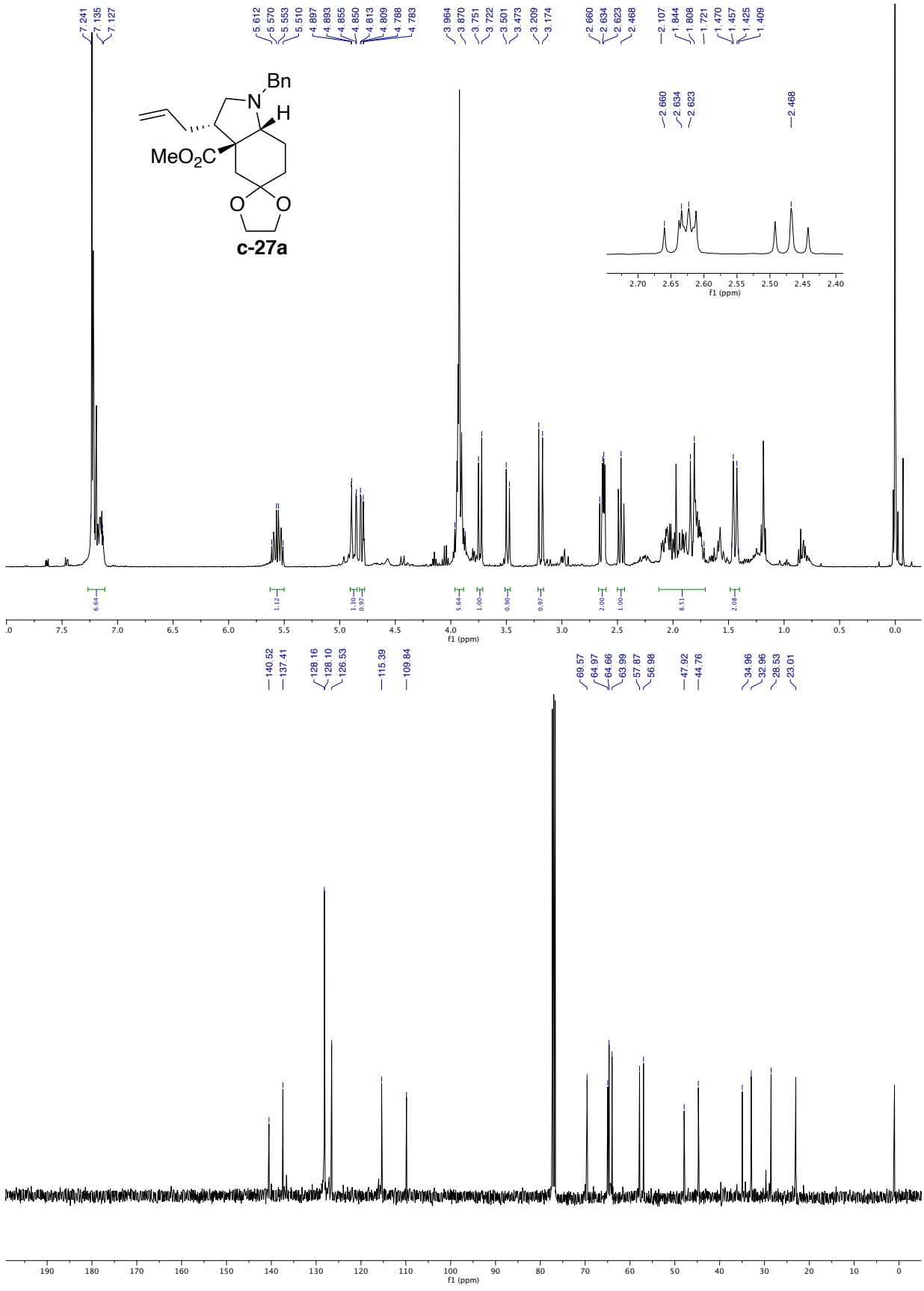

HO
Bn
N
H
Me
O
O
c-26b
f1 (ppm)
f1 (ppm)
f1 (ppm)

(3*RS*,3a*RS*,7a*SR*)-3-Allyl-1-benzyl-3a-(hydroxymethyl)octahydroindol-5-one ethylene acetal (c-27a).

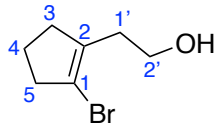


To a solution of $AlCl_3$ (17 mg, 0.13 mmol, 1.5 equiv) in THF (0.6 mL) was added a 1 M solution of $LiAlH_4$ in THF (0.4 mL, 2 equiv) dropwise at room temperature. After stirring the mixture for 15 min, a solution of **13a** (79 mg, 0.2 mmol, 1 equiv) in THF (0.45 mL) was added and the mixture was stirred at room temperature for 5 h. The mixture was cooled to 0 °C, quenched with 30% KOH aq. Solution (10 mL) and extracted sequentially with CH_2Cl_2 (2 x 10 mL), $CHCl_3$ (2 x 10 mL) and $CHCl_3$:*i*-PrOH (4:1, 2 x 10 mL). The organics were dried, concentrated, and purified by chromatography (Al_2O_3, hexane:EtOAc, 9:1 → 3 : 1) to yield c-27a (39 mg, 56%).

IR (neat) 3414, 2959, 1640, 1453, 1360, 1260, 1038, 700, cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.24–7.13 (m, 5H, Ph), 5.56 (ddt, *J* = 17.0, 10.1, 6.9 Hz, =CH), 4.87 (ddt, *J* = 17.0, 1.6, 1.6 Hz, 1H, $=CH_2$-*trans*), 4.80 (ddt, *J* = 10.1, 1.6, 1.2 Hz, 1H, $=CH_2$-*cis*), 3.96–3.87 (m, 5H, OCH_2 and CH_2Ph), 3.74 and 3.49 (2 d, *J* = 11.6 Hz, 1H each, CH_2OH), 3.19 (d, *J* = 13.6 Hz, 1H, CH_2Ph), 2.63 (dd, *J* = 10.4, 8.8 Hz, 1H, H-2eq.), 2.62 (t, *J* = 2.8 Hz, 1H, H-7a), 2.47 (dd, *J* = 10.4, 9.6 Hz, 1H, H-2ax), 2.11–1.72 (m, 6H, CH_2-3, H-3, H-7 and H-6), 1.83 and 1.44 (2d, *J* = 13.6 Hz, 1H each, H-4), 1.47–1.41 (m, 1H, H 6). ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.5 (Ph), 137.4 (=CH), 128.2, 128.1, and 126.5 (Ph), 115.4 ($=CH_2$), 109.8 (C-5), 69.6 (CH_2OH), 65.0 (C-7a), 64.7 and 64.0 (OCH_2), 57.9 (CH_2Ph), 57.0 (C-2), 47.9 (C-3a), 44.8 (C-3), 35.0 (C-4), 33.0 (CH_2-3), 28.5 (C-6), 23.0 (C-7). HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{21}H_{30}NO_3$ 344.2220, found 344.2216

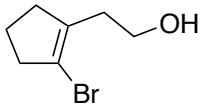

7.241
7.135
7.127
5.612
5.570
5.553
5.510
4.897
4.893
4.855
4.850
4.813
4.809
4.788
4.783
3.964
3.870
3.751
3.722
3.501
3.473
3.209
3.174
2.660
2.634
2.623
2.468
2.107
1.844
1.808
1.721
1.470
1.457
1.425
1.409
Bn
N
H
MeO2C
O
O
c-27a
f1 (ppm)
140.52
137.41
128.16
128.10
126.53
115.39
109.84
69.57
64.97
64.66
63.99
57.87
56.98
47.92
44.76
34.96
32.96
28.53
23.01
f1 (ppm)

2-(2-bromocyclopent-1-en-1-yl)ethan-1-ol (28).



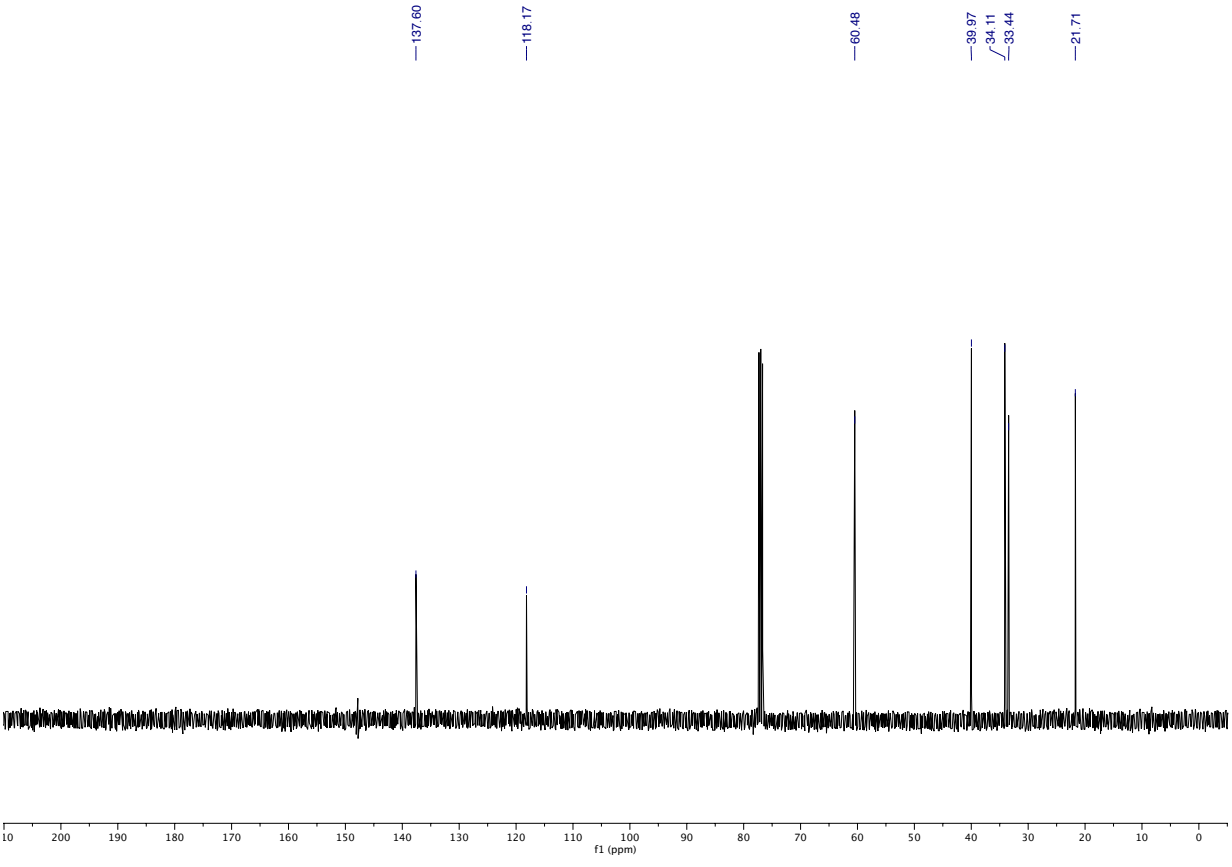
To a solution of 1-bromo-2-vinylcyclopent-1-ene (3.20 g, 18.4 mmol, 1 equiv) in THF (22 mL), a 0.5 M solution of 9-BBN in THF (35 mL, 18.4 mmol, 1 equiv) was added dropwise at room temperature and stirred overnight. Then it was quenched with methanol (10 mL), cooled to 0 ºC, and treated successively with a 3 M solution of NaOH (24 mL), and 30% H_2O_2 (24 mL). The mixture was stirred at room temperature for 8 h. Then, saturated solution of K_2CO_3 was added and the mixture was extracted with Et_2O (3 x 20 mL). The organic extracts were combined, washed with saturated brine (40 mL), dried over Na_2SO_4, and concentrated under vacuum. The crude product was purified by flash column chromatography (CH_2Cl_2:AcOEt, 9.9:0.1) to provide the desired product as a colorless oil (2.49 g, 57% over 3 steps).

IR (neat): 3334, 2951, 2853, 1041 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 3.73 (t, J = 6.6 Hz, 2H, H-2'), 2.65 (tm, J = 6.52 Hz, 2H, H-3), 2.46 (t, J = 6.6 Hz, 2H, H-1'), 2.36 (tm, J = 7.36 Hz, 2H, H-5), 1.99 (m, 2H, H-4). ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.6 (C-2), 118.2 (C-1), 60.4 (C-2'), 40.0 (C-3), 34.1 (C-5), 33.4 (C-1'), 21.7 (C-4). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd 188.9910, found 188.9891.

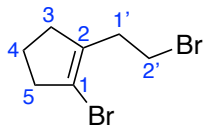

OH
Br

28

3.746
3.729
3.713
2.647
2.455
2.355
1.985
1.947
1.910
1.401
1.00
1.03
1.03
1.00
1.02
0.53
f1 (ppm)

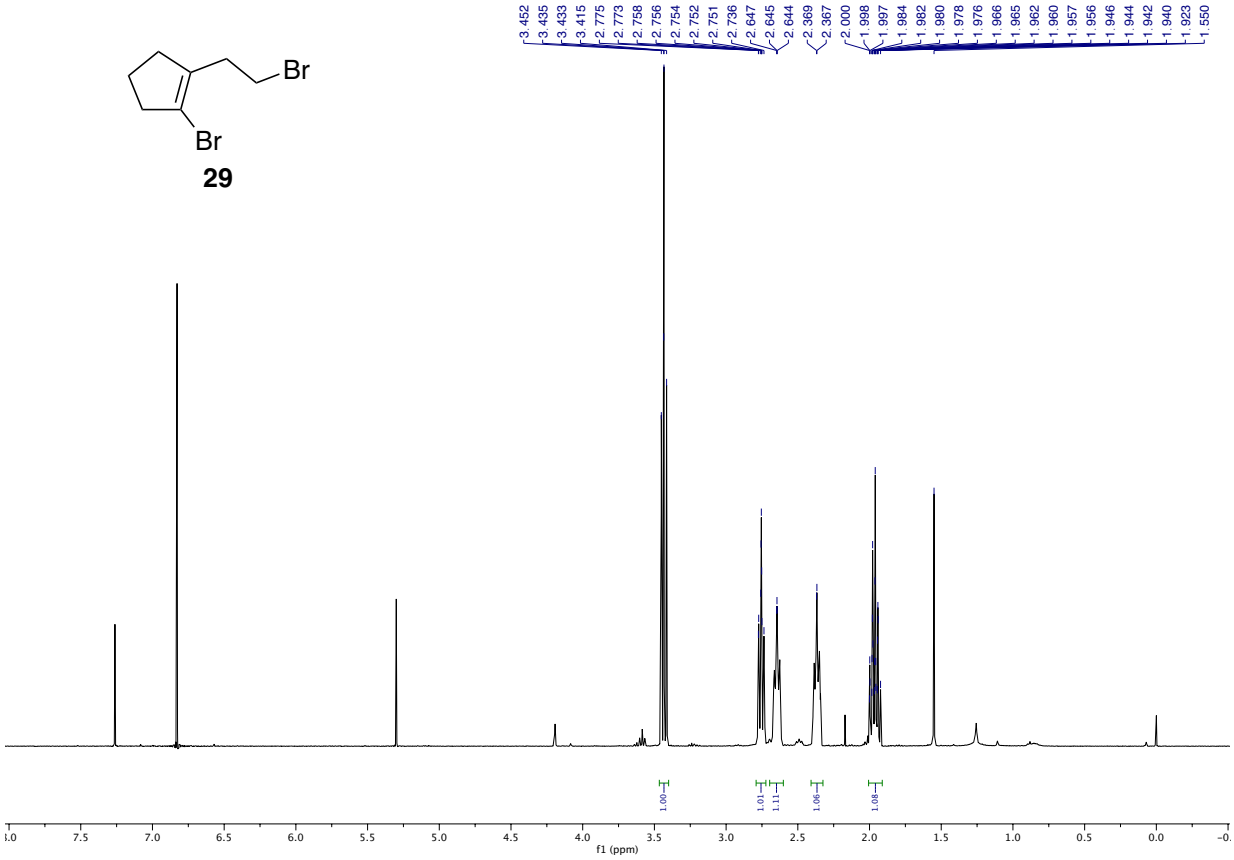

137.60
118.17
60.48
39.97
34.11
33.44
21.71
f1 (ppm)

1-bromo-2-(2'-bromoethyl)cyclopent-1-ene (29).

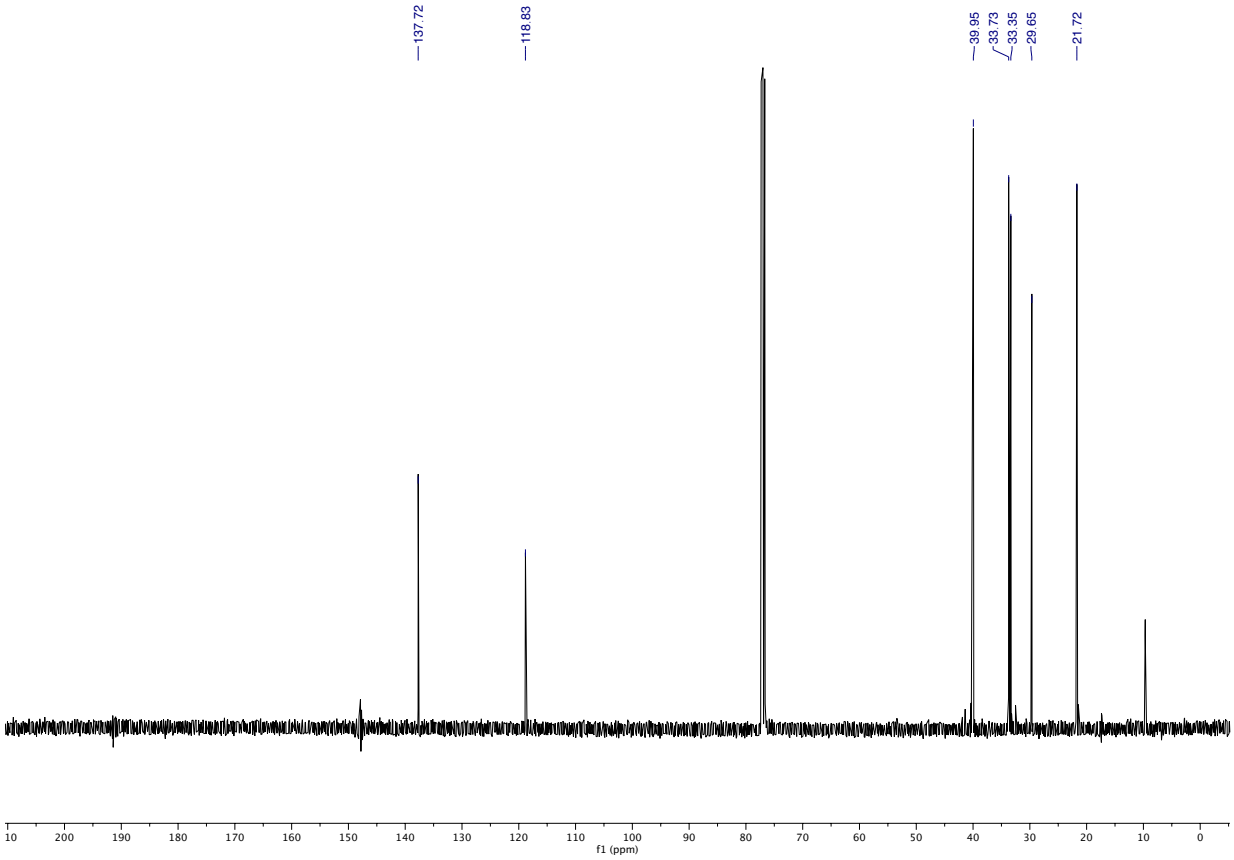


A solution of **28** (0.91g, 4.74 mmols, 1 equiv) and CBr_4 (1.89 g, 5.69 mmols, 1.2 equiv) in CH_2Cl_2 (6.6 mL) was cooled to 0ºC. Then a solution of PPh_3 (1.87 g, 7.12 mmols, 1.5 equiv) in CH_2Cl_2 (3.3 mL) was added and stirred at room temperature for 1 h. The resulting mixture was extracted with CH_2Cl_2 (3 x 20mL) and the combined organic layer was washed with brine (1 x 20 mL), dried over Na_2SO_4, and concentrated under vacuum. The crude product was purified by flash column chromatography (n-Pentane) to provide the desired product **29** as a yellowish oil (1.20 g, quantitative yield).

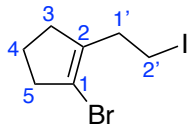
IR (neat): 2968, 2852, 1652, 1444 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 3.43 (t, J = 7.4 Hz, 2H, H-2'), 2.75 (t, J = 7.4 Hz, 2H, H-1'), 2.64 (tm, J = 7.4 Hz, 2H, H-5), 2.37 (tm, J = 7.68 Hz, 2H, H-3), 1.92–2.00 (m, 2H, H-4). ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.7 (C-2), 118.8 (C-1), 39.9 (C-5), 33.7 (C-3), 33.3 (C-1'), 29.6 (C-2'), 21.7 (C-4). MS (GC/EI) *m/z*: calcd for $C_7H_{10}Br_2$ 255.91/253.91/251.91/; found 255.81/253.79/251.81/; calcd for $C_7H_{10}Br$ 174.99/172.99, found 174.93/172.90.


Br
Br
3.452
3.435
3.433
3.415
2.775
2.773
2.758
2.756
2.754
2.752
2.751
2.736
2.647
2.645
2.644
2.369
2.367
2.000
1.998
1.997
1.984
1.982
1.980
1.978
1.976
1.966
1.965
1.962
1.960
1.957
1.956
1.946
1.944
1.942
1.940
1.923
1.550
1.00
1.01
1.11
1.06
1.08
f1 (ppm)

29

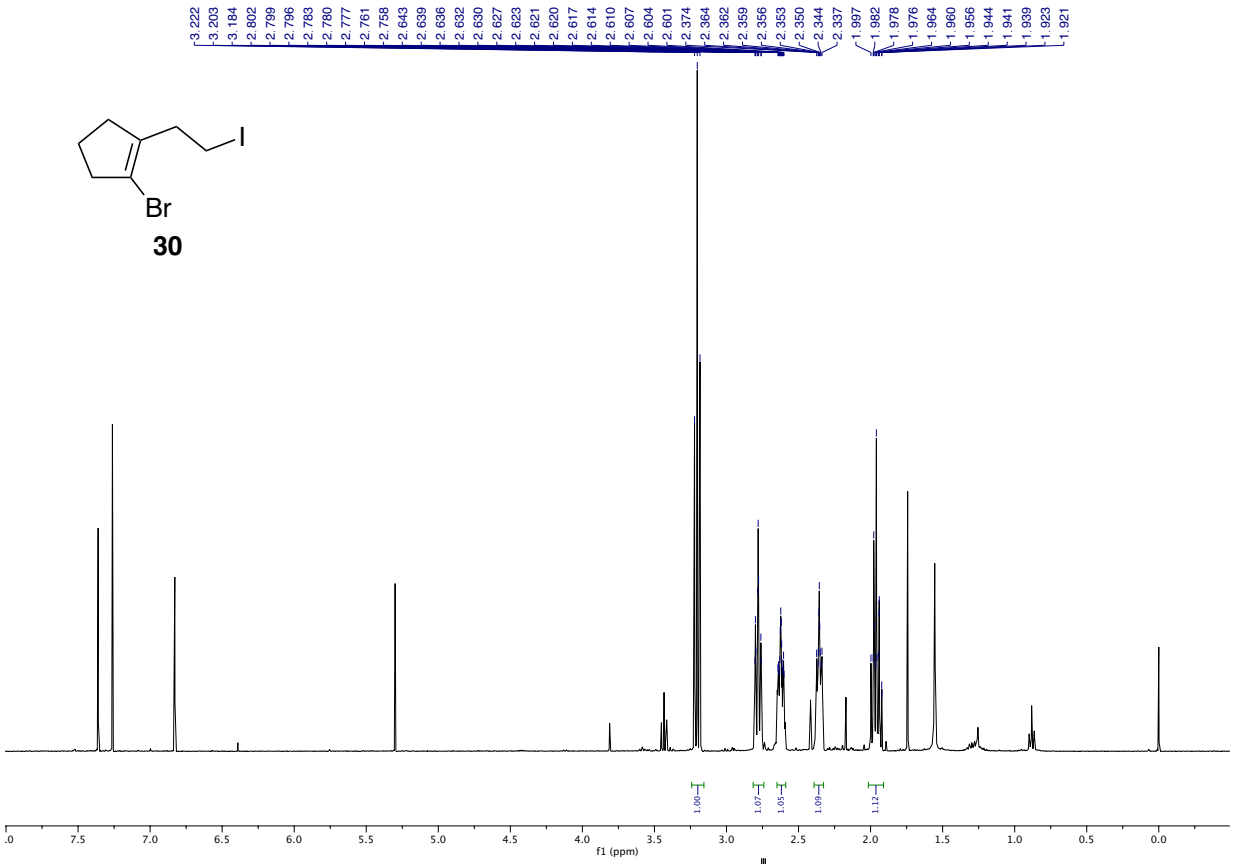

137.72
118.83
39.95
33.73
33.35
29.65
21.72
f1 (ppm)

1-bromo-2-(2'-iodoethyl)cyclopent-1-ene (30).

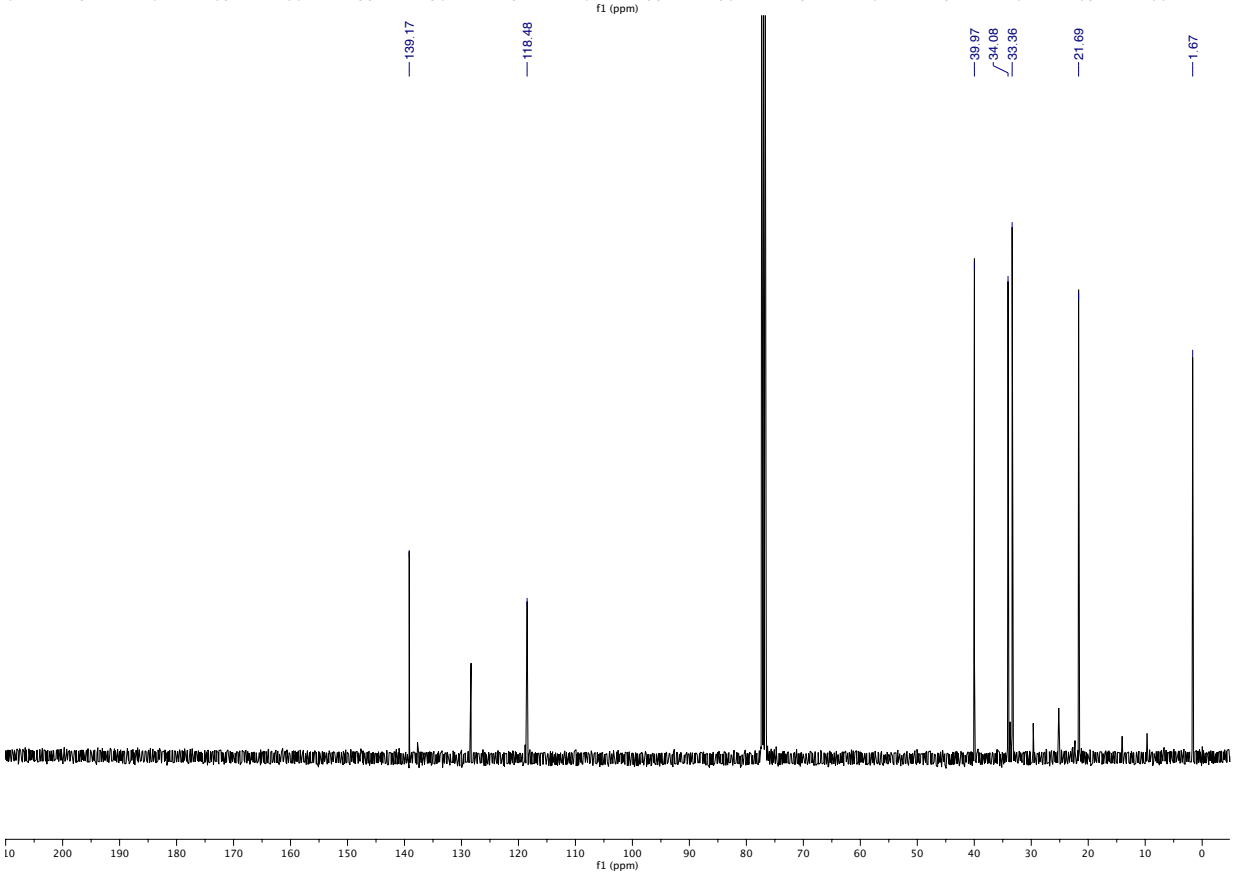


Solution of **28** (0.60 g, 3.15 mmol, 1 equiv) in THF (6 mL) was cooled to 0 ºC and then PPh_3 (0.99 g, 3.78 mmol, 1.2 equiv), imidazole (0.47 g, 6.93 mmol, 2.2 equiv) and I_2 (0.96 g, 3.78 mmol, 1.2 equiv) were added successively and stirred at room temperature for 10 min. Then, the mixture was treated with sat. solution of $Na_2S_2O_3$ and extracted with pentane before being filtered by flash column chromatography (Pentane 100) to obtain product **30** (0.93 g, almost quantitative) as a colored oil.

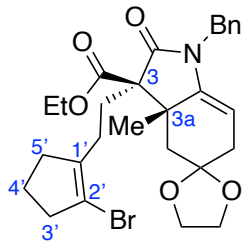
IR (neat): 2959, 2843, 1651, 1440, 1172 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 3.20 (t, J = 7.56, 2H, H-2'), 2.78 (t, J = 7.56 Hz, 2H, H-1'), 2.62 (br t, J = 7.6 Hz, 2H, H-5), 2.36 (br t, J = 7.4 Hz, 2H, H-3),1.92–2.00 (m, 2H, H-4). ^{13}C NMR (101 MHz, $CDCl_3$) δ 1.7 (C-2'), 21.69 (C-4), 33.4 (C-3), 34.1 (C-1'), 40.0 (C-5), 118.5 (C-1), 139.2 (C-2). MS (GC/EI) *m/z*: $[M]^+$ calcd for $C_7H_{10}BrI$ 299.9011/301.8990; found 299.90/301.91; calcd for $C_7H_{10}Br$ 172.9960/174.9940; found 172.99/175.01.


3.222
3.203
3.184
2.802
2.799
2.796
2.783
2.780
2.777
2.761
2.758
2.643
2.639
2.636
2.632
2.630
2.627
2.623
2.621
2.620
2.617
2.614
2.610
2.607
2.604
2.601
2.374
2.364
2.362
2.359
2.356
2.353
2.350
2.344
2.337
1.997
1.982
1.978
1.976
1.964
1.960
1.956
1.944
1.941
1.939
1.923
1.921
I
Br
1.00
1.07
1.05
1.09
1.12
f1 (ppm)

30

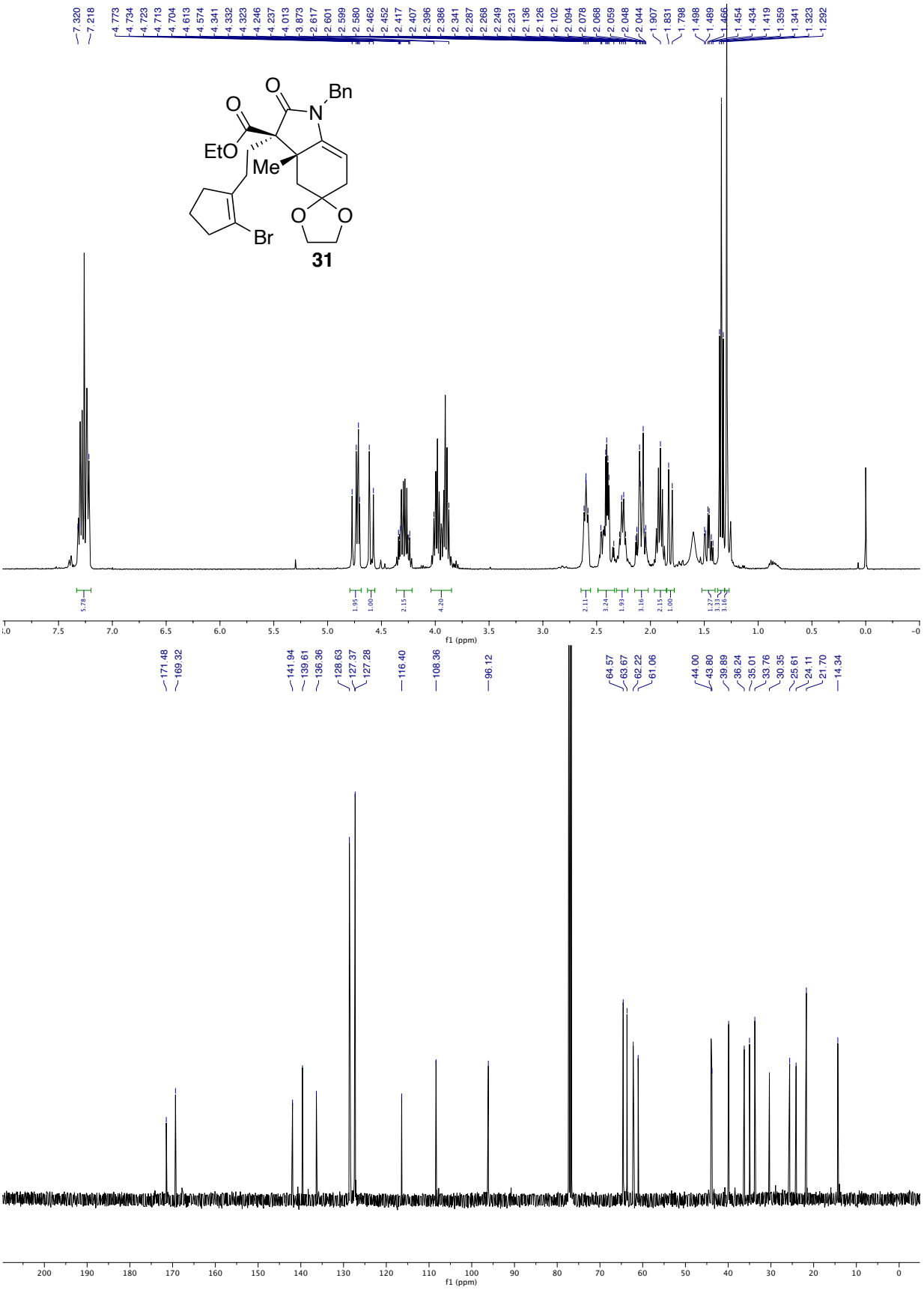

139.17
118.48
39.97
34.08
33.36
21.69
1.67
f1 (ppm)

(3RS,3aSR)-1-Benzyl-3-(2-(2'-bromocyclopent-1'-ene-1'-yl)ehtyl)-3-ethoxycarbonyl-3a-methyl-1,3a,4,6-tetrahydro-2*H*-indole-2,5(3*H*)-dione monoethylene acetal (31).

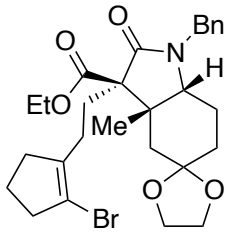


To a solution of **7a** (0.11 g, 0.3 mmol, 1 equiv) in DMSO (1 mL), Cs_2CO_3 (0.12 g, 0.36 mmol, 1.2 equiv) was added and stirred for 15 min. Then **30** was added and the reaction was stirred overnight at room temperature. Water (20 mL) and EtOAc (20 mL) were added, and the mixture was extracted with EtOAc (3 x 20 mL). The organics were combined, washed with brine, and concentrated. The crude was purified by silica gel column chromatography (hexane:EtOAc, 1:0 → 4:1) to provide product **31** (80 mg, 50%) as a colorless oil.

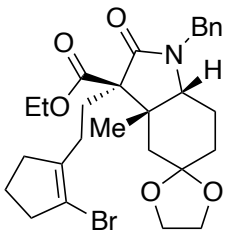
IR (neat) 3063, 2967, 1754, 1728, 1688, 1402, 1099 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.32–7.22 (m, 5H, Ph), 4.75 (d, *J* = 15.4 Hz, 1H, CH_2Ph), 4.71 (t, *J* = 3.8 Hz, 2H, H-7), 4.59 (d, *J* = 15.4 Hz, 1H, CH_2Ph), 4.34–4.23 (m, 2H, OEt), 4.01–3.87 (m, 4H, OCH_2), 2.60 (bt, *J* = 7.4 Hz, 2H, H-3'), 2.40 (dd, *J* = 3.8, 8.4 Hz, 2H, H-6), 2.46–2.34 (m, 1H, CH_2-1'), 2.26 (dt, *J* = 7.4, 7.6 Hz, 2H, H-5'), 2.14–2.04 (m, 2H, CH_2-3, CH_2-1'), 2.08 (d, *J* = 13.5 Hz, 1H, H-4), 1.91 (m, 2H, H-4'), 1.82 (d, *J* = 13.5 Hz, 1H, H-4), 1.46 (td, *J* = 12.8, 3.4 Hz, 1H, CH_2-3), 1.34 (t, *J* = 7.1 Hz, 3H, OEt), 1.29 (s, 3H, Me). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.5 (CO), 169.3 (C-2), 141.9 (C-7a), 139.6 (C-1'), 136.4, 128.6, 127.4, and 127.3 (Ph), 116.4 (C-2'), 108.4 (C-5), 96.1 (C-7), 64.6 and 63.7 (OCH_2), 62.2 (C-3), 61.1 (OEt), 44.0 (C-3a), 43.8 (CH_2Ph), 39.9 (C-3'), 36.2 (C-4), 35.0 (C-6), 33.8 (C-5'), 30.4 (CH_2-3), 25.6 (CH_2-1'), 24.1 (Me), 21.7 (C-4'), 14.3 (OEt). HRMS (ESI) *m/z:* $[M+H]^+$ calcd for $C_{28}H_{35}BrNO_5$ 544.1699/546.1683; found 544.1692/546.1680.


7.320
7.218
4.773
4.734
4.723
4.713
4.704
4.613
4.574
4.341
4.332
4.323
4.246
4.237
4.013
3.873
2.617
2.601
2.599
2.580
2.462
2.452
2.417
2.407
2.396
2.386
2.341
2.287
2.268
2.249
2.231
2.136
2.126
2.102
2.094
2.078
2.068
2.059
2.048
2.044
1.907
1.831
1.798
1.498
1.489
1.466
1.454
1.434
1.419
1.359
1.341
1.323
1.292
O
O
N
Bn
EtO
Me
O
O
Br
31
5.78
1.95
1.00
2.15
4.20
2.11
3.24
1.93
3.16
2.15
1.00
1.27
3.33
3.16
f1 (ppm)
171.48
169.32
141.94
139.61
136.36
128.63
127.37
127.28
116.40
108.36
96.12
64.57
63.67
62.22
61.06
44.00
43.80
39.89
36.24
35.01
33.76
30.35
25.61
24.11
21.70
14.34
f1 (ppm)

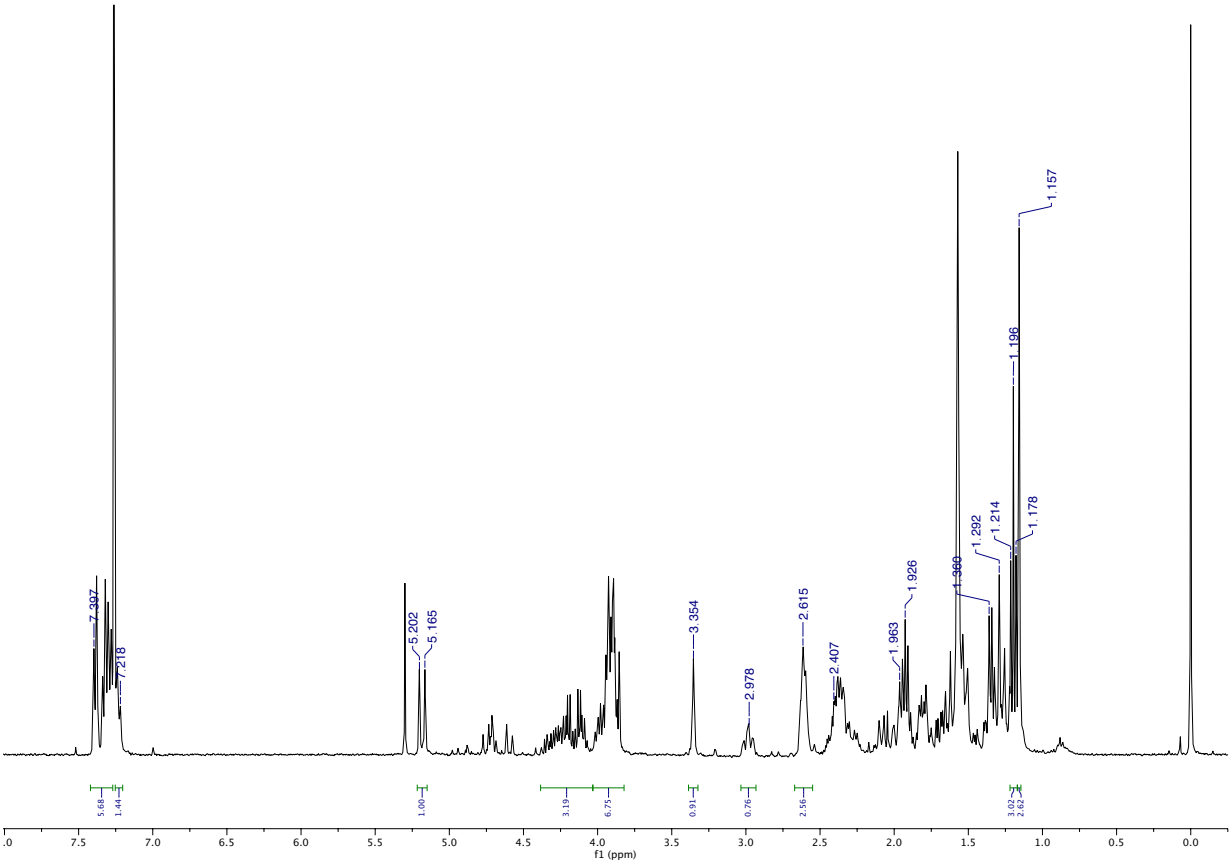
ethyl (3*RS*,3a*RS*,7a*RS*)-1-benzyl-3-(2-(2-bromocyclopent-1-en-1-yl)ethyl)-3a-methyl-2-oxooctahydrospiro[indole-5,2'-[1,3]dioxolane]-3-carboxylate (32).



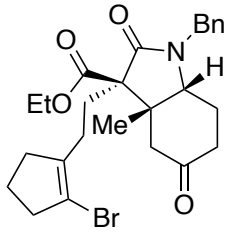
To a solution of **31** (0.1 g, 0.18 mmol, 1 equiv) in AcOH (0.5 mL), $NaCNBH_3$ (0.02 g, 0.37 mmol, 2 equiv) was added portion-wise and stirred over 48 hours. Then water (20 mL) was added and the mixture was extracted with CH_2Cl_2 (4 x 20 mL). The organics were combined, washed with $NaHCO_3$ (1 x 20 mL), brine (1 x 20 mL), dried and concentrated. The crude was purified by silica gel column chromatography (100 hexane → 90:10 hexane:EtOAc) to obtain product **9** (0.045 g, 45 %).


O
O
N
Bn
H
EtO
Me
O
O
Br

32

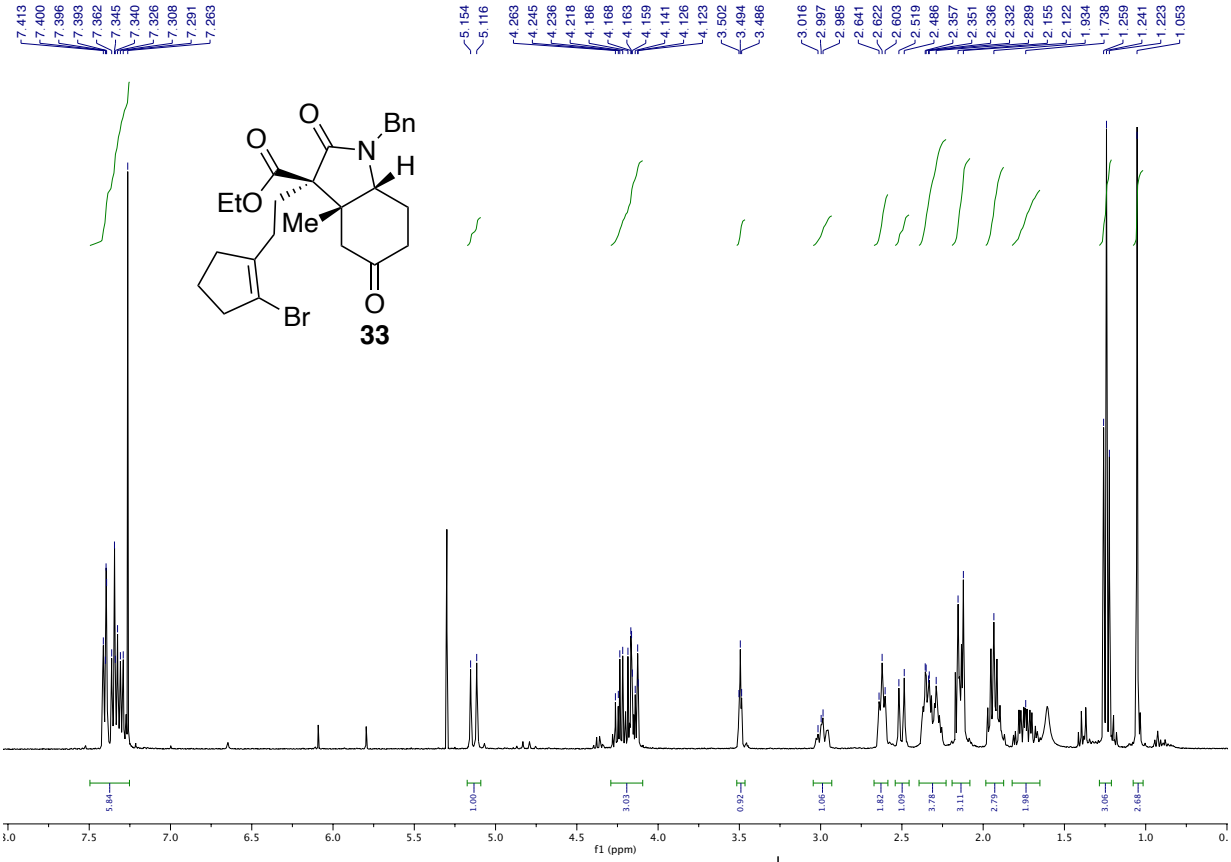

7.397
7.218
5.202
5.165
3.354
2.978
2.615
2.407
1.963
1.926
1.360
1.292
1.214
1.196
1.178
1.157
5.68
1.44
1.00
3.19
6.75
0.91
0.76
2.56
3.02
2.62
f1 (ppm)

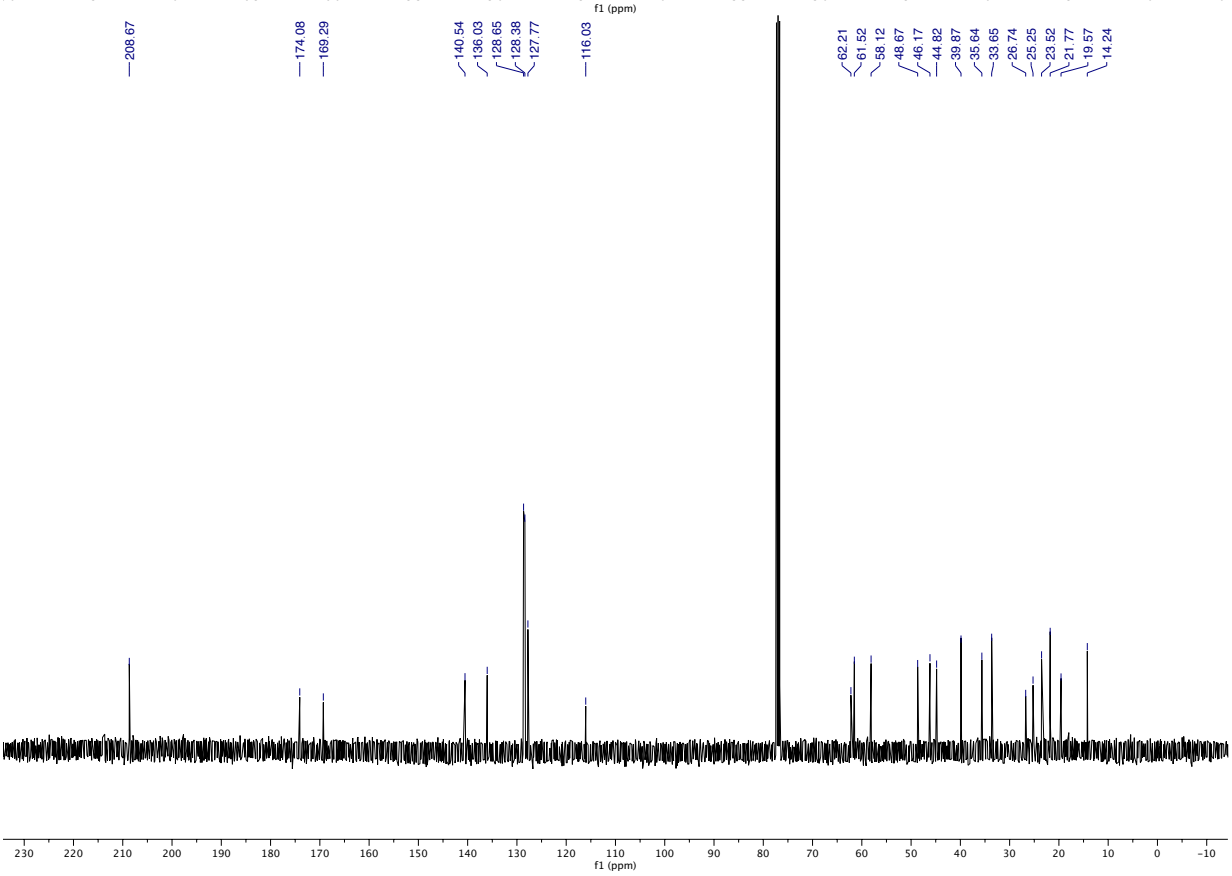
(3*RS*,3a*RS*,7a*RS*)-1-benzyl-3-(2-(2'-bromocyclopent-1'-en-1'-yl)ethyl)-3-ethoxycarbonyl-3a-methylhexahydro-2*H*-indole-2,5(3*H*)-dione (33).



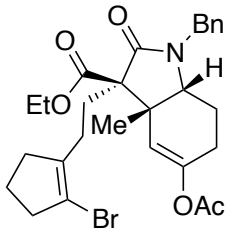
Product **32** (32 mg, 0.06 mmol, 1 equiv) was dissolved in anhydrous CH_2Cl_2 (0.8 mL) and TFA (12 μL, 0.16 mmol, 2.7 equiv) was added and stirred overnight at room temperature. Water (10 mL) and CH_2Cl_2 (10 mL) were added. The mixture was extracted with CH_2Cl_2 (3 x 15 mL), washed with brine, dried, and concentrated under vacuum to obtain crude yellow oil which was purified by chromatography column (hexane:EtOAc, 1:0 → 4:1) to afford product **33** (30 mg, quantitative yield) as a colorless oil.

IR (neat): 3029, 2964, 1717, 1696, 1240, 702 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.41–7.26 (m, 5H,Ph), 5.14 (d, *J* = 15.0 Hz, 1H, CH_2Ph), 4.26–4.13 (m, 2H, OEt), 4.15 (d, *J* = 15.0 Hz, 1H, CH_2Ph), 3.49 (t, *J* = 3.3 Hz, 1H, H-7a), 3.00 (bt, *J* = 12.4 Hz, 1H, CH_2-1'), 2.62 (bt, *J* = 7.5 Hz, 2H, H-3'), 2.51 (d, *J* = 13.2, 1H, H-4), 2.37–2.27 (m, 4H, CH_2-1', H-5', H-7), 2.15–2.12 (m, 3H, H-4, H-6), 1.93 (m, 3H, H-7, H-4'), 1.87–1.67 (m, 2H, CH_2-3), 1.24 (t, *J* = 7.1 Hz, 3H, OEt), 1.05 (s, 3H, Me). ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.7 (C-5), 174.1 (CO), 169.3 (C-2), 140.5 (C-1'), 136.0, 128.6, 128.4, and 127.8 (Ph), 116.0 (C-2'), 62.2 (OEt), 61.5 (C-3), 58.1 (C-7a), 48.7 (C-3a), 46.2 (C-4), 44.9 (CH_2Ph), 39.9 (C-3'), 35.6 (C-6), 33.6 (C-5'), 26.7 (CH_2-3), 25.3 (CH_2-1'), 23.5 (C-7), 21.8 (C-4'), 19.6 (Me), 14.2 (OEt).. HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{26}H_{33}BrNO_4$ 502.1593/504.1576; found 502.1587/504.1591.


7.413
7.400
7.396
7.393
7.362
7.345
7.340
7.326
7.308
7.291
7.263
5.154
5.116
4.263
4.245
4.236
4.218
4.186
4.168
4.163
4.159
4.141
4.126
4.123
3.502
3.494
3.486
3.016
2.997
2.985
2.641
2.622
2.603
2.519
2.486
2.357
2.351
2.336
2.332
2.289
2.155
2.122
1.934
1.738
1.259
1.241
1.223
1.053
O
O
N
Bn
H
EtO
Me
O
Br
33
5.84
1.00
3.03
0.92
1.06
1.82
1.69
3.78
3.11
2.79
1.98
3.06
2.68
f1 (ppm)

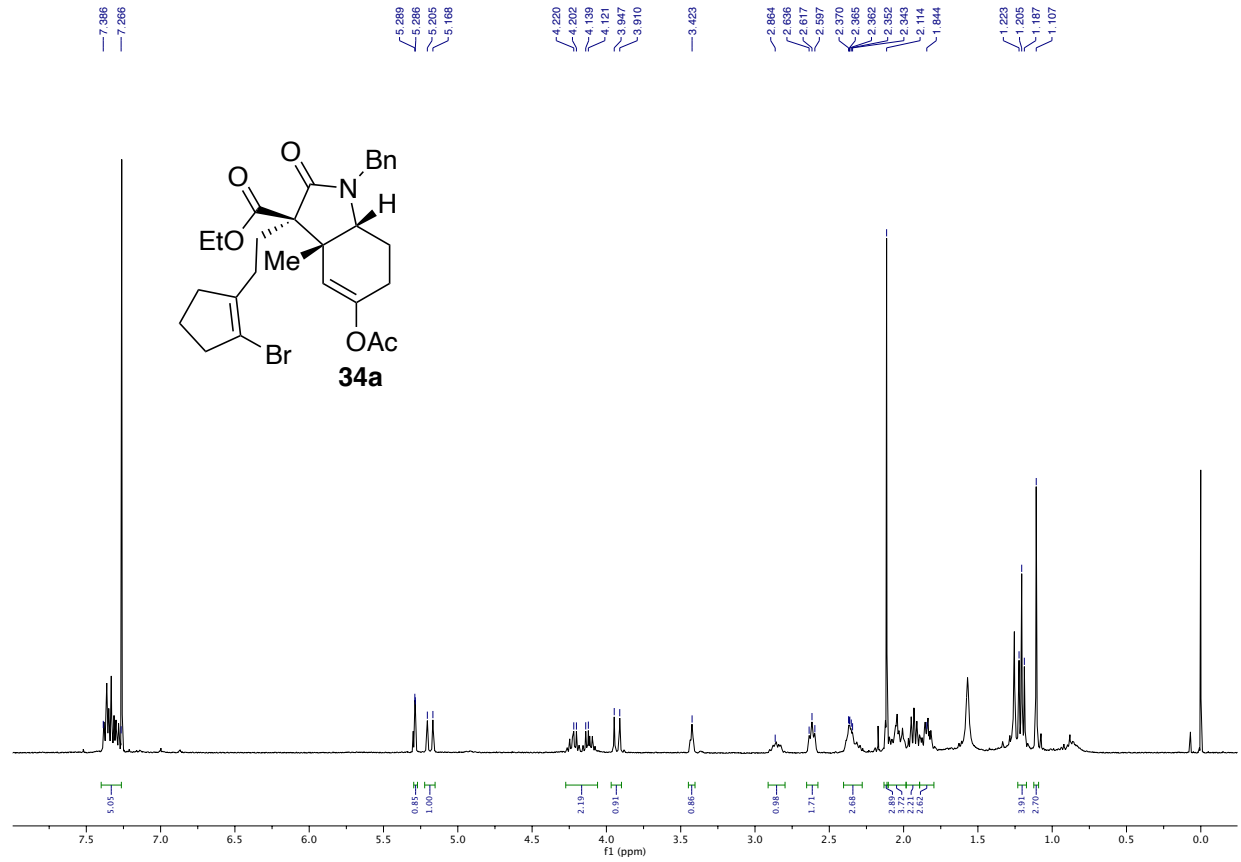

208.67
174.08
169.29
140.54
136.03
128.65
128.38
127.77
116.03
62.21
61.52
58.12
48.67
46.17
44.82
39.87
35.64
33.65
26.74
25.25
23.52
21.77
19.57
14.24
f1 (ppm)

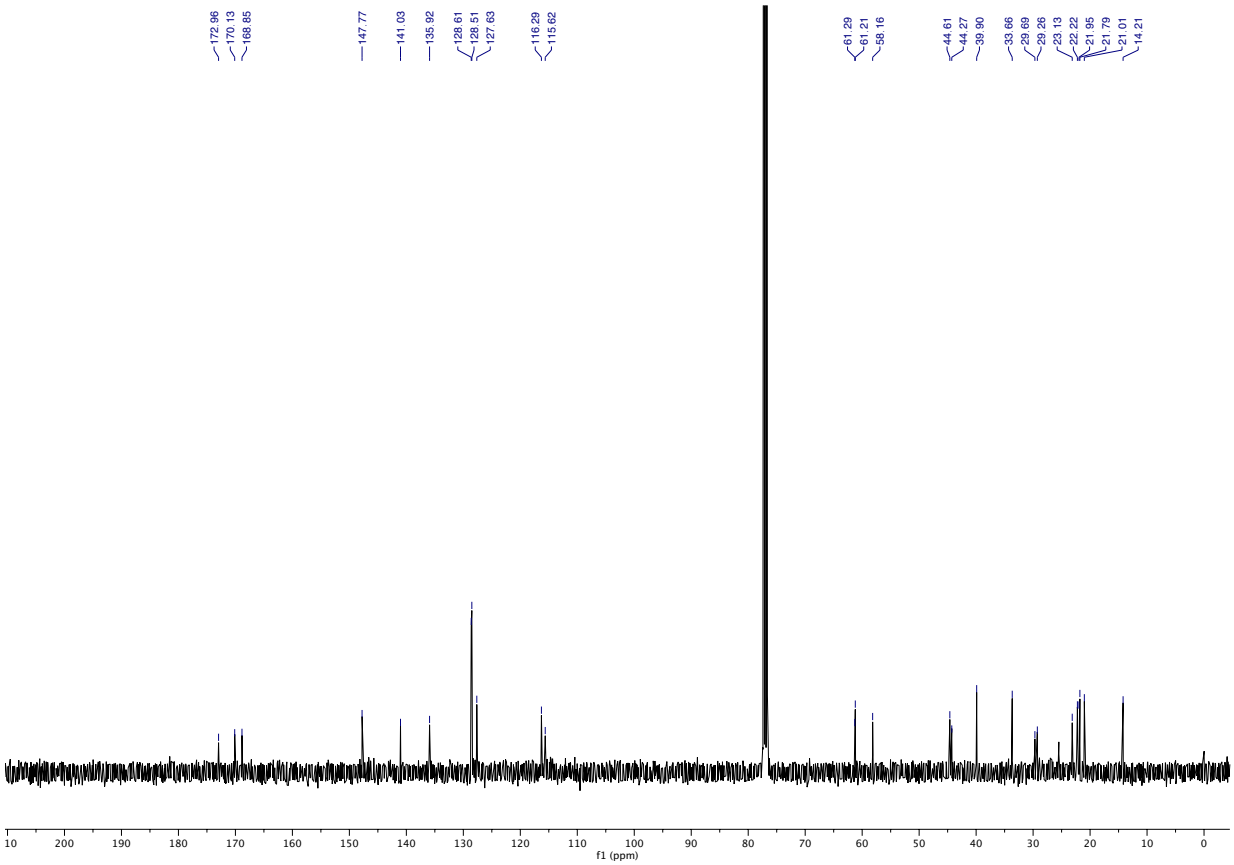
ethyl(3*RS*,3a*RS*,7a*RS*)-5-acetoxy-1-benzyl-3-(2-(2-bromocyclopent-1-en-1-yl)ethyl)-3a-methyl-2-oxo-2,3,3a,6,7,7a-hexahydro-1*H*-indole-3-carboxylate (34a).



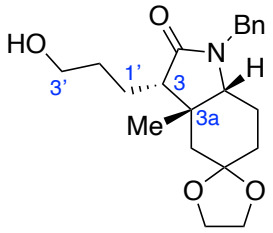
Solution of **33** (30 mg, 0.06 mmol, 1 equiv), *p*-TsOH (11 mg, 0.06 mmol, 1 equiv) in isopropenyl acetate (0.3 mL) was heated to reflux for 4h. The mixture was treated with solid $NaHCO_3$, filtered and concentrated under vacuum. The crude was purified by silica gel column chromatography (hexane:EtOAc, 1:0 → 3:1) to obtain products **34b** (7 mg, 26%) and **34a** (11 mg, 41%).

34a. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.28 (m, 5H, Ph), 5.29 (s, 1H, H-4), 5.19 (d, *J* = 14.9 Hz, 1H, CH_2Ph), 4.09–4.25 (m, 2H, OEt), 3.93 (d, *J* = 14.9 Hz, 1H, CH_2Ph), 3.42 (m, 1H, H-7a), 2.86 (m, 1H, H-6), 2.62 (t, *J* = 7.1 Hz, 2H, H-3'), 2.36 (m, 2H, H-5'), 2.32 (m, 1H, H-6), 2.11 (s, 3H, OAc), 2.04 (m, 2H, CH_2-1'), 2.01 (m, 1H, H-7), 1.93 (m, 2H, H-4'), 1.81–1.88 (m, 3H, H-7, CH_2-3), 1.21 (t, *J* = 7.2 Hz, 3H, OEt), 1.11 (s, 3H, Me). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.9 (CO), 170.1 (CO), 168.4 (C-2), 147.8 (C-5), 141.0 (C-1'), 135.9, 128.6, 128.5, and 127.6 (Ph), 116.3 (C-4), 115.6 (C-2'), 61.3 (C-3), 61.2 (OEt), 58.1 (C-7a), 44.6 (CH_2Ph), 44.3 (C-3a), 39.9 (C-3'), 33.6 (C-5'), 29.2 (CH_2-3), 25.5 (C-6), 23.1 (Me), 22.2 (CH_2-1'), 21.9 (C-7), 21.8 (C-4'), 21.0 (OAc), 14.2 (OEt). HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{28}H_{35}BrNO_5$ 544.1699/546.1683; found 544.1693/546.1700.


7.386
7.266
5.289
5.286
5.205
5.168
4.220
4.202
4.139
4.121
3.947
3.910
3.423
2.864
2.636
2.617
2.597
2.370
2.365
2.362
2.352
2.343
2.114
1.844
1.223
1.205
1.187
1.107
O
O
N
Bn
H
EtO
Me
OAc
Br
34a
f1 (ppm)

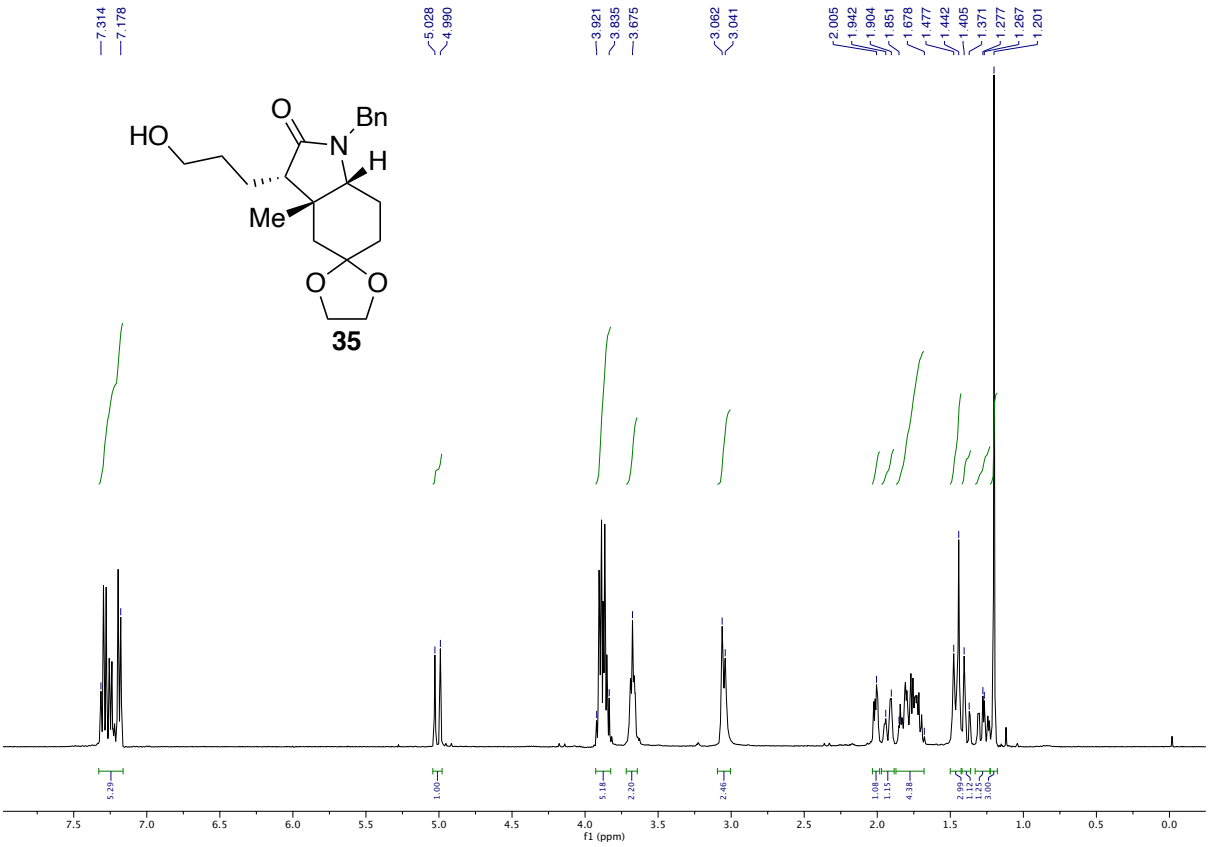

172.96
170.13
168.85
147.77
141.03
135.92
128.61
128.51
127.63
116.29
115.62
61.29
61.21
58.16
44.61
44.27
39.90
33.66
29.69
29.26
23.13
22.22
21.95
21.79
21.01
14.21
f1 (ppm)

(3*SR*,3a*RS*,7a*RS*)-1-benzyl-3-(3'hydroxypropyl)-3a-methylhexahydro-2*H*-indole-2,5(3*H*)-dione monoethylene acetal (35).



A solution of **c-4a** (1.0 g, 2.93 mmol, 1 equiv) and 9-BBN (0.5 M in THF, 11.7 mL, 5.86 mmol, 2 equiv) was stirred at room temperature for 3 h. Then, 2 M NaOH solution (13 mL) and 30% H_2O_2 (11 mL) were added successively at 0 ºC and the reaction was stirred for 4 h at room temperature. Water (20 mL) was added and the mixture was extracted with EtOAc (5 x 20 mL). Combined organics were dried, filtered and concentrated under vacuum to afford the crude. After purification by chromatography (CH_2Cl_2:MeOH, 1:0 → 9:1) compound **35** was obtained (0.95 g, 90%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.20 (m, 5H, Ph), 5.03 (d, *J* = 15.2 Hz, 1H, CH_2Ph), 3.94–3.85 (m, 5H, OCH_2 and CH_2Ph), 3.69 (t, *J* = 5.4 Hz, 2H, CH_2OH), 3.08 (t, *J* = 3.6 Hz, 1H, H-7a), 3.05 (bs, 1H, OH), 2.03 (dd, *J* = 7.4, 3.6 Hz, 1H, H-3), 1.95 (dq, *J* = 15.2, 3.6 Hz, 1H, H-7), 1.87–1.71 (m, 4H, H-7, CH_2-1', CH_2-2') 1.48 (d, *J* = 13.8 Hz, 1H, H-4), 1.51–1.44 (m, 2H, CH_2-2', H-6), 1.40 (dd, *J* = 13.8, 2.4 Hz, H-4), 1.29 (td, *J* = 13.8, 3.6 Hz, H-6), 1.22 (s, 3H, Me). ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.4 (C-2), 136.5, 128.6, 127.8 and 127.4 (Ph), 107.9 (C-5), 64.5 and 63.7 (OCH_2), 61.7 (CH_2OH), 59.4 (C-7a), 55.3 (C-3), 43.8 (CH_2Ph), 41.8 (C-3a), 36.4 (C-4), 32.3 (CH_2-1'), 28.6 (C-6), 22.1 (Me), 20.4 (C-7), 19.3 (CH_2-2').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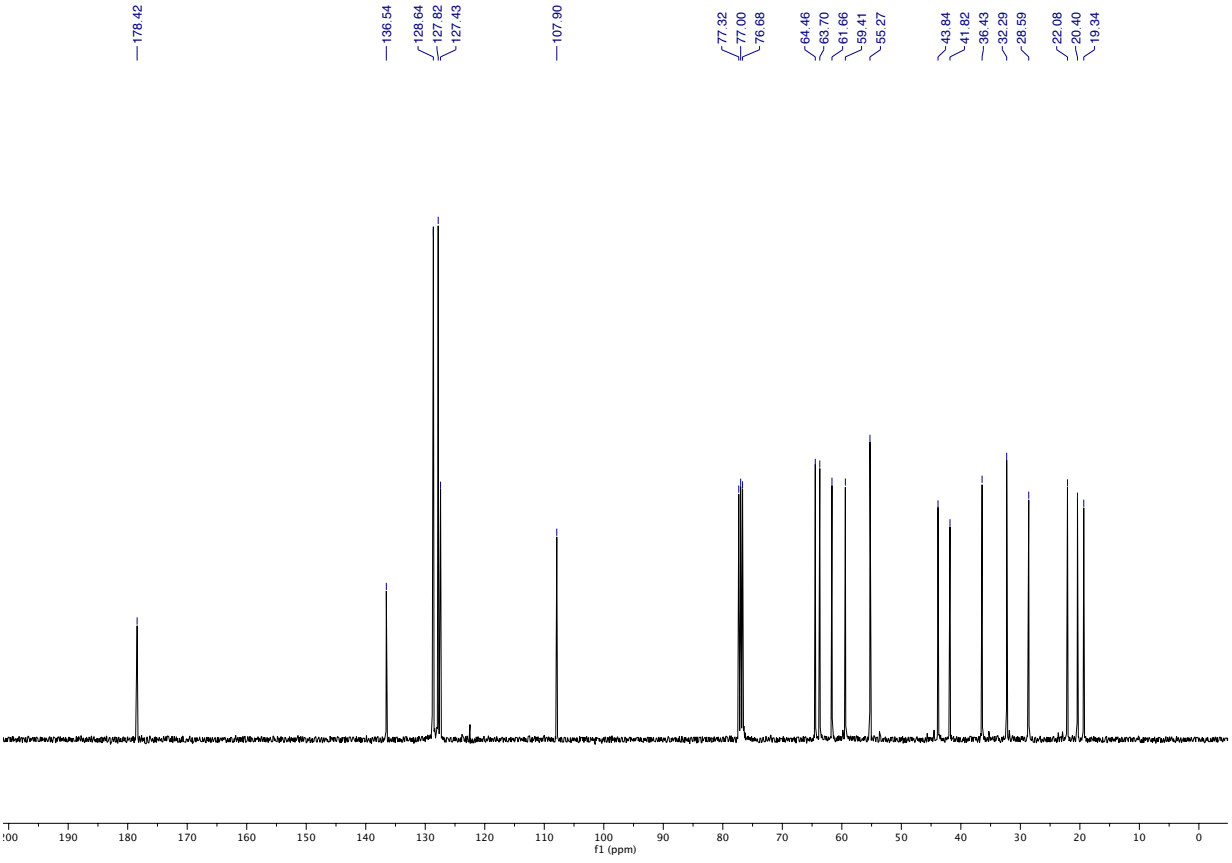
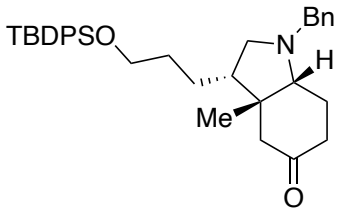
7.178
5.028
4.990
3.921
3.835
3.675
3.062
3.041
2.005
1.942
1.904
1.851
1.678
1.477
1.442
1.405
1.371
1.277
1.267
1.201
HO
O
N
Bn
H
Me
O
O
35
f1 (ppm)

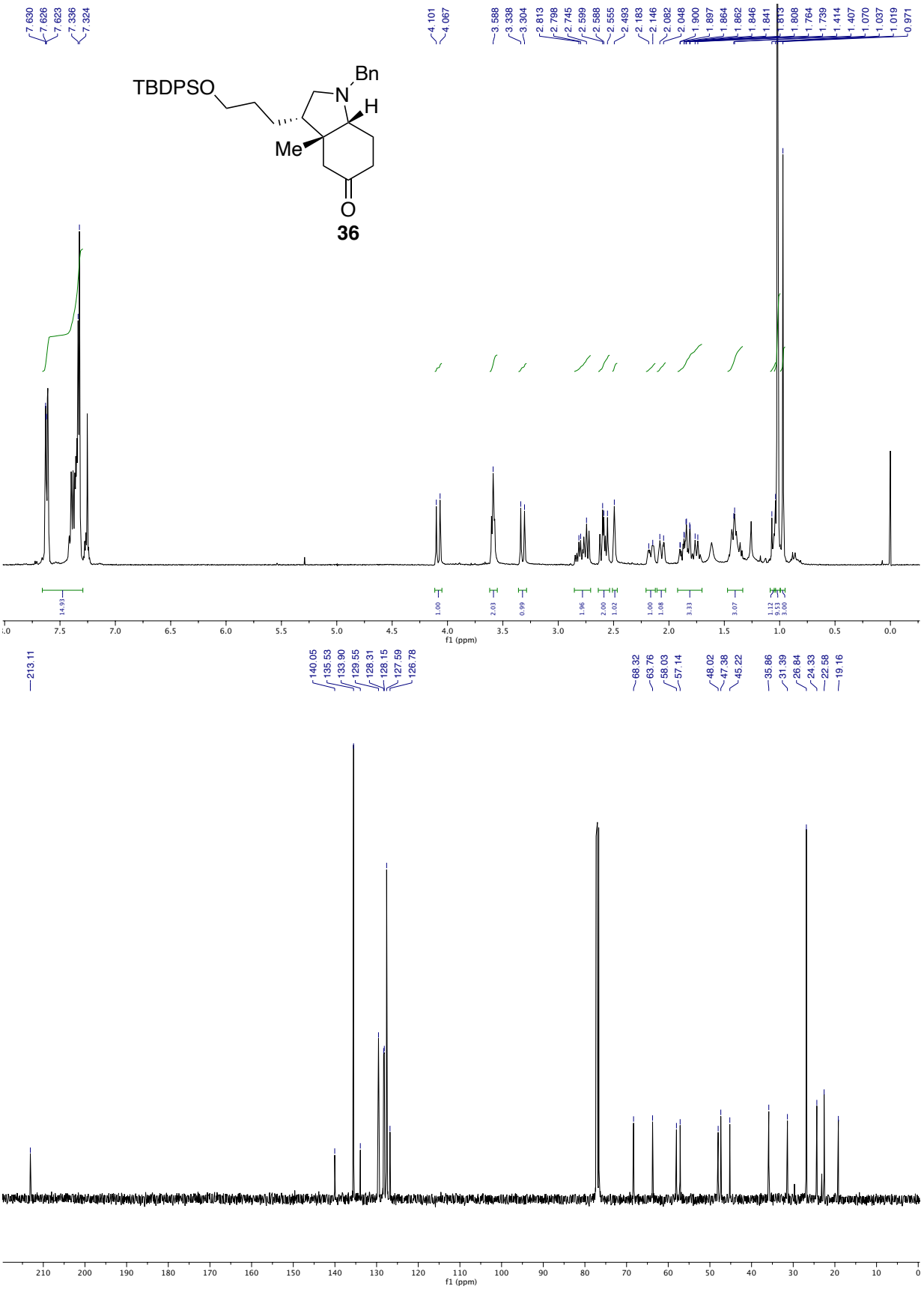

178.42
136.54
128.64
127.82
127.43
107.90
77.32
77.00
76.68
64.46
63.70
61.66
59.41
55.27
43.84
41.82
36.43
32.29
28.59
22.08
20.40
19.34
f1 (ppm)

(3*SR*,3a*RS*,7a*RS*)-1-benzyl-3-(3-((*tert*-butyldiphenylsilyl)oxy)propyl)-3a-methyloctahydro-5*H*-indol-5-one (36).

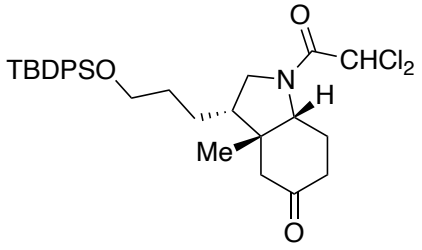


To a 0 ºC cooled solution of **35** (0.53 g, 1.48 mmol, 1 equiv) in THF (16 mL) was added dropwise a solution of $LiAlH_4$ (1M in THF, 5.9 mL, 4 equiv). The reaction was heated to reflux and stirred overnight. After being cooled down, 15 % NaOH solution was added and the resulting mixture was filtered through a celite pad. The filtrated solution was washed with brine and the organic phase was dried, and concentrated. The residue was diluted in 10% HCl (27 mL) and stirred overnight at room temperature. After being quenched with Na_2CO_3 (20 mL) and extracted with CH_2Cl_2 (4 x 20 mL), organics were combined, dried, concentrated and diluted in CH_2Cl_2 (9 mL). TBDPSCl (1.15 mL, 4.44 mmol, 3 equiv), Et_3N (0.25 mL, 1.78 mmol, 1.2 equiv) and DMAP (9 mg, 0.07 mmol, 0.05 equiv) were added. The reaction was stirred at room temperature overnight. Water (15 mL) was added, and the mixture was extracted with CH_2Cl_2 (4 x 20 mL). Combined organics were dried over Na_2SO_4, filtered, and concentrated to afford the crude. Purification by chromatographic column (hexane:EtOAc, 1:0 $\rightarrow$ 9:1) provided with product **36** (0.53 g, 66% 3 steps) as a transparent oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63–7.32 (m, 15H, Ph), 4.08 (d, *J* = 13.6 hz, 1H, CH_2Ph), 3.59 (bt, 2H, CH_2OH), 3.32 (d, *J* = 13.6 Hz, 1H, CH_2Ph), 2.81 (td, *J* = 13.6, 6.0 Hz, 1H, H-6), 2.75 and 2.60 (2t, *J* = 10.0 Hz, 1H each, H-2), 2.57 (d, *J* = 13.2 Hz, 1H, H-4), 2.49 (bs, 1H, H-7a), 2.16 (ddd, *J* = 14.4, 5.4, 2.6 Hz, H-7), 2.06 (ddd, *J* = 13.6, 4.4, 2.2 Hz, 1H, H-6), 1.87 (ddt, *J* = 14.4, 4.2, 3.0 Hz, 1H, H-7), 1.83 (dd, *J* = 13.2, 2.0 Hz, 1H, H-4), 1.75 (dt, *J* = 10.0, 9.6 Hz, 1H, H-3), 1.46–1.34 (m, 3H, CH_2-2' and CH_2-1'), 1.07–1.02 (m, 1H, CH_2-1'), 1.02 (s, 9H, *t*-Bu), 0.97 (s, 3H, Me). ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.1 (C-5), 140.1, 135.5, 133.9, 129.5, 128.3, 128.1, 127.6 and 126.8 (Ph), 68.3 (C-7a), 63.8 (CH_2O), 58.0 (CH_2Ph), 57.1 (C-2), 48.0 (C-3a), 47.4 (C-3), 45.2 (C-4), 35.9 (C-6), 31.4 (CH_2-2'), 26.8 (t-Bu), 24.4 (C-7), 24.3 (CH_2-1'), 22.6 (Me), 19.2 (C).

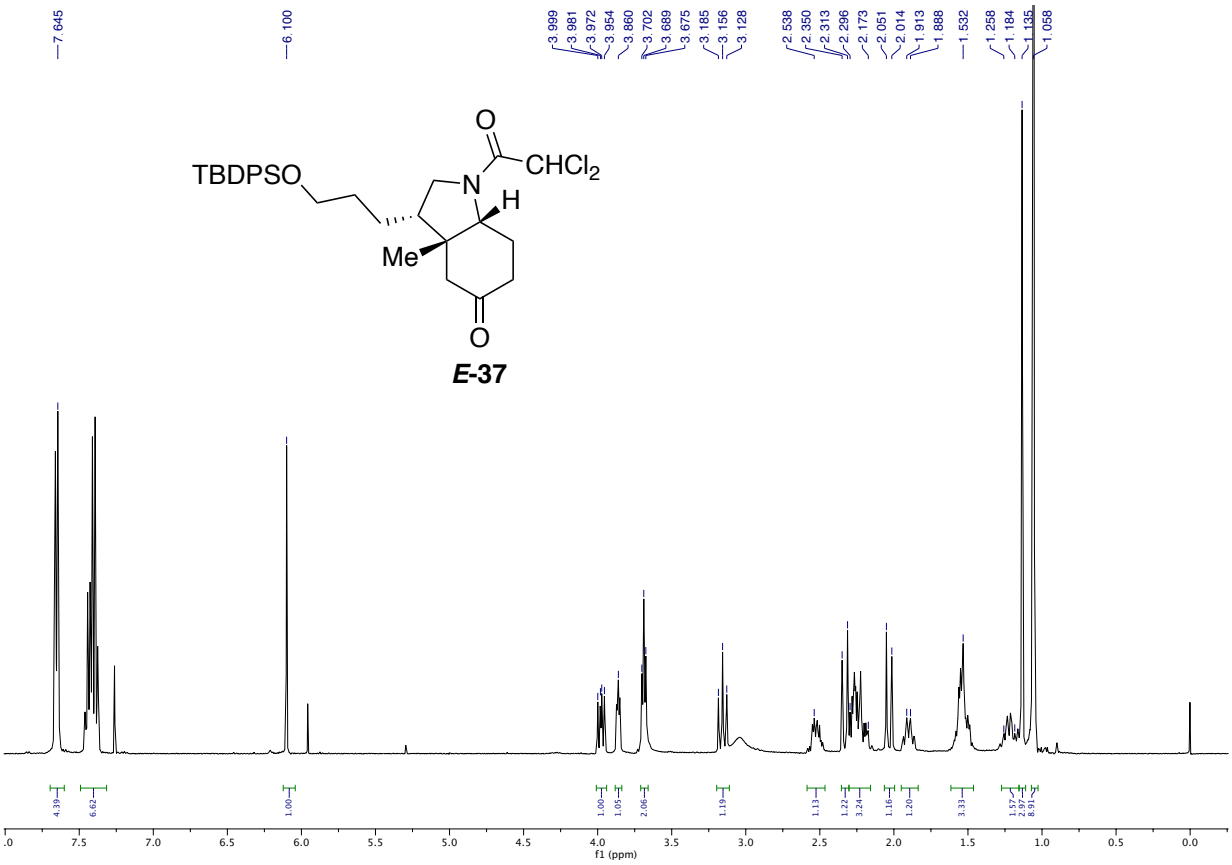

TBDPSO
Bn
N
H
Me
O
36
f1 (ppm)
f1 (ppm)

(3*SR*,3a*RS*,7a*RS*)-3-(3-((*tert*-butyldiphenylsilyl)oxy)propyl)-1-(2,2-dichloroacetyl)-3a-methyloctahydro-5*H*-indol-5-one (37).



A solution of compound **36** (0.15 g, 0.28 mmol, 1 equiv) and Pd/C (30 mg, 20% wt.) in MeOH (2 mL) was stirred under H_2 atmosphere at 1 atm overnight. Then the mixture was filtered through a celite pad and concentrated under. The crude was directly diluted in CH_2Cl_2 (2 mL) cooled to 0 ºC and Et_3N (80 mL, 0.56 mmol, 2 equiv) and dichloroacetyl chloride (32 mL, 0.33 mmol, 1.2 equiv) were added. The reaction was stirred at room temperature for 3 h and after water (10 mL) was added the mixture was extracted with CH_2Cl_2 (4 x 10 mL). Combined organics were dried over Na_2SO_4, filtered and concentrated under vacuum to obtain the crude that was purified by chromatography (hexane:CH_2Cl_2, 1:0 $\rightarrow$ 1:1). Both rotamers of compound **37** were obtained as colorless oils, *E* rotamer (41 mg, 26%) and *Z* rotamer (23 mg, 15 %).

***E*-37**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66–7.64 and 7.44–7.38 (2m, 5H each, Ph), 6.01 (s, 1H, $CHCl_2$), 3.98 (dd, J = 11.0, 7.2 Hz, 1H, H-2), 3.86 (t, J = 4.6 Hz, 1H, H-7a), 3.69 (t, J = 5.2 Hz, 2H, CH_2O), 3.16 (t, J = 11.0 Hz, 1H, H-2), 2.58–2.48 (m, 1H, H-7), 2.33 (d, J = 14.8 Hz, 1H, H-4), 2.30–2.17 (m, 3H, H-6, H-7), 2.03 (d, J = 14.8 Hz, 1H, H-4), 1.90 (qd, J = Hz, 1H, H.3), 1.58–1.49 (m, 3H, CH_2-2', CH_2-1'), 1.26-1.18 (m, 1H, CH_2-2'), 1.14 (s, 3H, Me), 1.06 (s, 9H, *t*-Bu). ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.6 (C-5), 162.4 (CO), 135.6, 133.7, 133.7, 129.8 and 127.7 (Ph), 66.2 ($CHCl_2$), 64.5 (C-7a), 63.3 (CH_2O), 51.4 (C-2), 48.6 (C-3), 44.9 (C-3a), 43.9 (C-4), 34.7 (C-6), 31.3 (CH_2-1'), 26.9 (*t*-Bu), 25.7 (Me), 23.6 (C-7), 22.8 (CH_2-2'), 19.2 (C).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3.860
3.702
3.689
3.675
3.185
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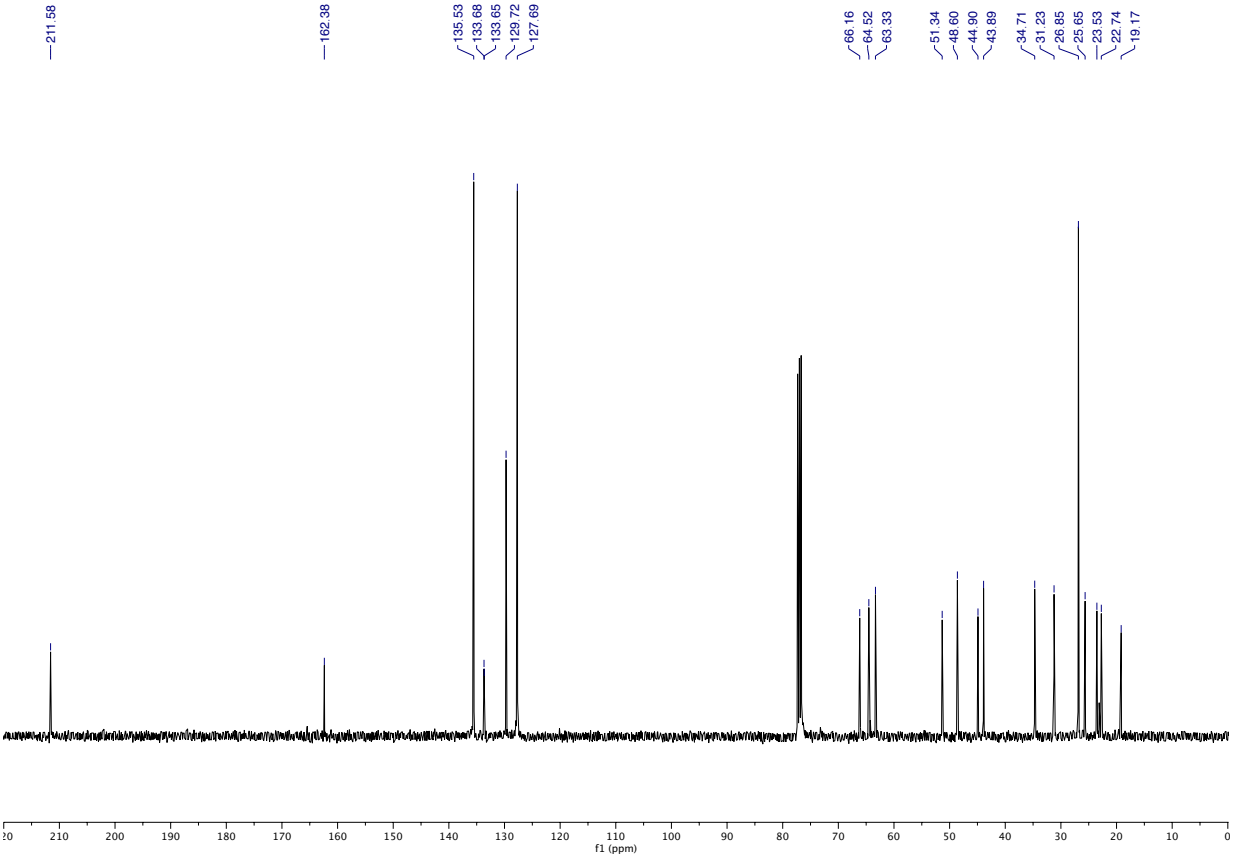
2.538
2.350
2.313
2.296
2.173
2.051
2.014
1.913
1.888
1.532
1.258
1.184
1.135
1.058
O
CHCl2
TBDPSO
N
H
Me
O
f1 (ppm)

***E*-37**


211.58
162.38
135.53
133.68
133.65
129.72
127.69
66.16
64.52
63.33
51.34
48.60
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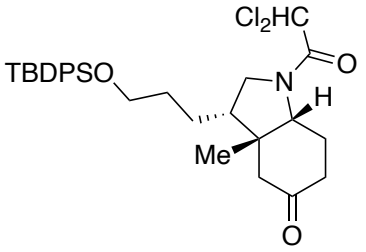
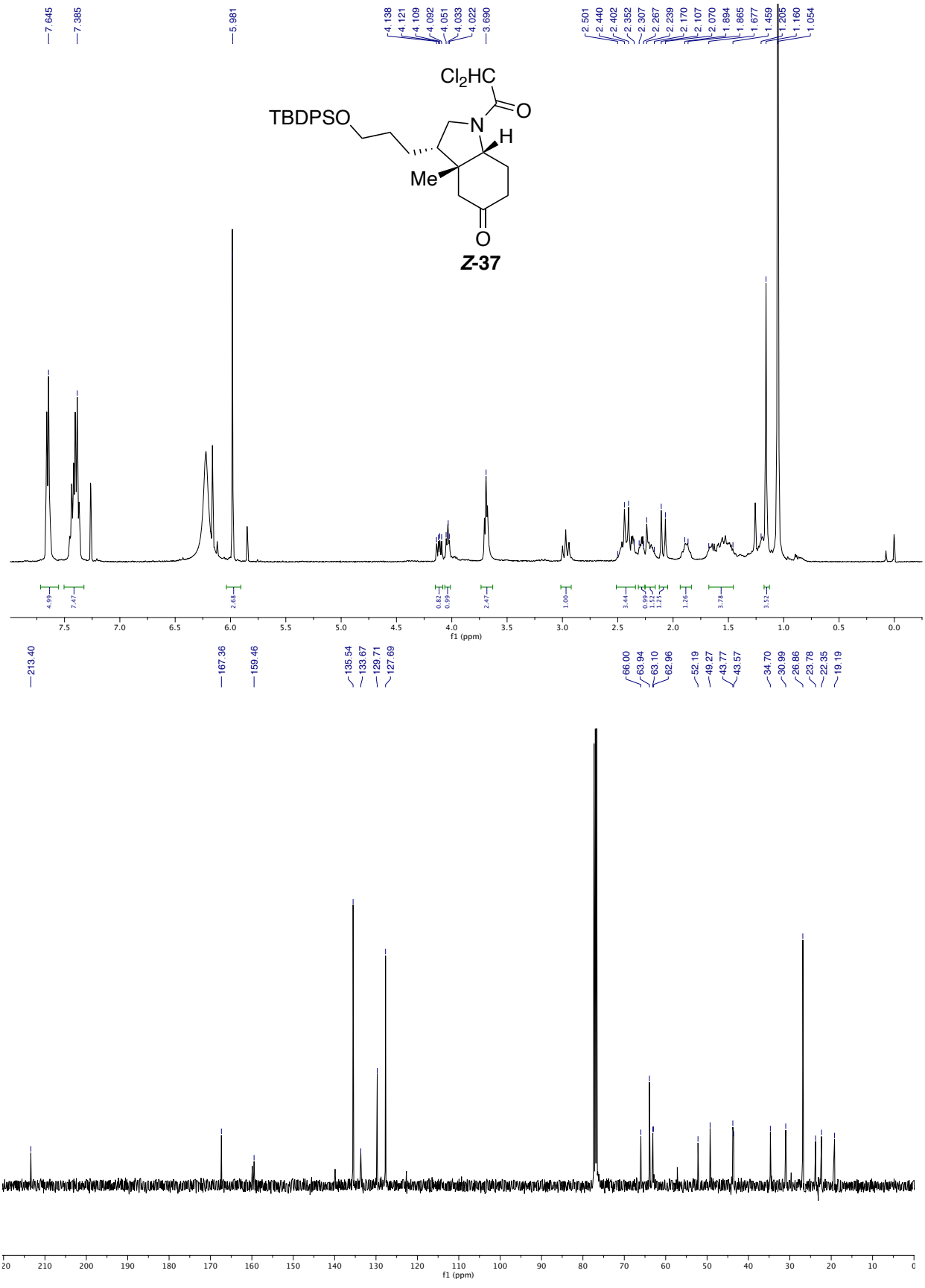
25.65
23.53
22.74
19.17
f1 (ppm)



***Z*-37.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66–7.37 (m, 10H, Ph), 5.98 (s, 1H, $CHCl_2$), 4.11 (d, J = 11.8, 6.6 Hz, 1H, H-2), 4.04 (t, J = 6.0 Hz, 1H, H-7a), 3.69 (t, J = 6.0 Hz, 2H, CH_2O), 2.97 (t, J = 11.6, 1H, H-2), 2.50–2.35 (m, 1H, H-7), 2.42 (d, J = 15.0 Hz, 1H, H-4), 2.37–2.35 and 2.30–2.27 (2 m, 1H each, H-6), 2.24–2.17 (m, 1H, H-7), 2.09 (d, J = 15.0 Hz, 1H, H-4), 1.92–1.84 (m, 1H, H-3), 1.70–1.43 (m, 3H, CH_2-2' and CH_2-1') 1.20 (m, 1H, CH_2-1'), 1.16 (s, 3H, Me), 1.05 (s, 9H, *t*-Bu). ^{13}C NMR (101 MHz, $CDCl_3$) δ 213.4 (C-5), 167.4 (CO), 135.5, 133.7, 129.7 and 127.7 (Ph), 66.0 (C-7a), 63.9 ($CHCl_2$), 63.1 (CH_2O), 52.2 (C-2), 49.3 (C-3), 43.8 (C-4), 43.6 (C-3a), 34.7 (C-6), 31.0 (CH_2-2'), 26.9 and 26.9 (*t*-Bu and Me), 23.8 (C-7), 22.3 (CH_2-1'), 19.2 (C).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7.385
5.981
4.138
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4.109
4.092
4.051
4.033
4.022
3.690
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2.402
2.352
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2.239
2.170
2.107
2.070
1.894
1.865
1.677
1.459
1.205
1.160
1.054
Cl2HC
O
TBDPSO
N
H
Me
O
Z-37
f1 (ppm)
213.40
167.36
159.46
135.54
133.67
129.71
127.69
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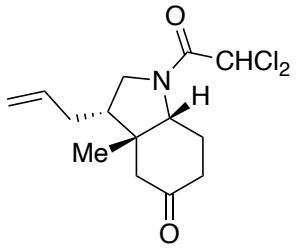
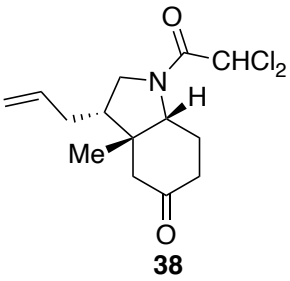
43.77
43.57
34.70
30.99
26.86
23.78
22.35
19.19
f1 (ppm)

(3*SR*,3a*RS*,7a*RS*)-3-allyl-1-(2,2-dichloroacetyl)-3a-methyloctahydro-5*H*-indol-5-one (38)



NH_3 was condensed at – 78 ºC and Na (0.17 g, 7.35 mmol, 5 equiv) was added followed by addition of **c-4a** (0.5 g, 1.47 mmol, 1 equiv) in THF(40 mL). After 5 min at – 78 ºC, the mixture was cautiously quenched with NH_4Cl and warmed to rt. When the bubbling stopped, the mixture was filtered and washed with brine, dried, and concentrated. The residue was suspended in THF (20 mL), cooled to 0 ºC and $LiAlH_4$ (0.2 g, 5.88 mmol, 4 equiv) in THF (10 mL) was added. After being heated to rfx overnight, it was quenched at 0 ºC with 15% NaOH and filtrated through celite, washed with brine, concentrated, and diluted in CH_2Cl_2 (6 mL). Then, Et_3N (0.4 mL, 2.94 mmol, 2 equiv) and trichloroacetyl chloride (0.17 mL, 1.76 mmol, 1.2 equiv) were added at 0 ºC and was stirred for 4 h at rt. Water (30 mL) was added and extracted with CH_2Cl_2 (4 x 20 mL). Combined organics were dried, filtered, and concentrated. Finally, the residue was diluted in a 10% HCl:THF solution (1:4, 12 mL) and stirred at rt overnight. The mixture was quenched with Na_2CO_3 (30 mL) and extracted with CH_2Cl_2 (4 x 20 mL), and the combined organics were dried and filtered to afford the crude. Chromatographic purification (hexane:EtOAc, 9:1 $\rightarrow$ 4:1) provided product **38** as a yellowish oil (0.24 g, 54% over 4 steps).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.14 (s, 1H, CH), 5.80–5.70 (m, 1H, =CH), 5.13 (dq, *J* = 17, 1.6 Hz, 1H, =CH_2), 5.07 (dq, *J* = 10, 1.2 Hz, 1H, =CH_2), 4.01 (dd, *J* = 11.2, 10.6 Hz, 1H, H-2), 3.92 (dd, *J* = 5.6, 3.6 Hz, 1H, H-7a), 3.23 (dd, *J* = 11.2, 11.2 Hz, 1H, H-2), 2.59–2.49 (m, 1H, H-7), 2.40 (d, *J* = 14.4 Hz, 1H, H-4), 2.34–2.16 (m, 4H, 3'-CH_2, H-7, H-6), 2.09 (d, *J* = 14.4 Hz, 1H, H-4), 2.09–2.01 (m, 1H, H-3), 1.99–1.91 (m, 1H, 3'-CH_2).^{13}C NMR (101 MHz, $CDCl_3$) δ 211.2 (C-5), 162.3 (CO), 135.4 (=CH), 117.2 (=CH_2), 66.1 (CH), 64.6 (C-7a), 51.2 (C-2), 48.3 (C-3), 44.6 (C-3a), 44.0 (C-4), 34.7 (C-6), 31.0 (3'-CH_2), 25.9 (Me), 23.5 (C-7).


O
CHCl2
N
H
Me
O

38

6.135
5.801
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5.151
5.147
5.143
5.112
5.108
5.105
5.095
5.092
5.089
5.073
5.070
5.067
5.063
4.038
4.020
4.010
3.993
3.931
3.922
3.917
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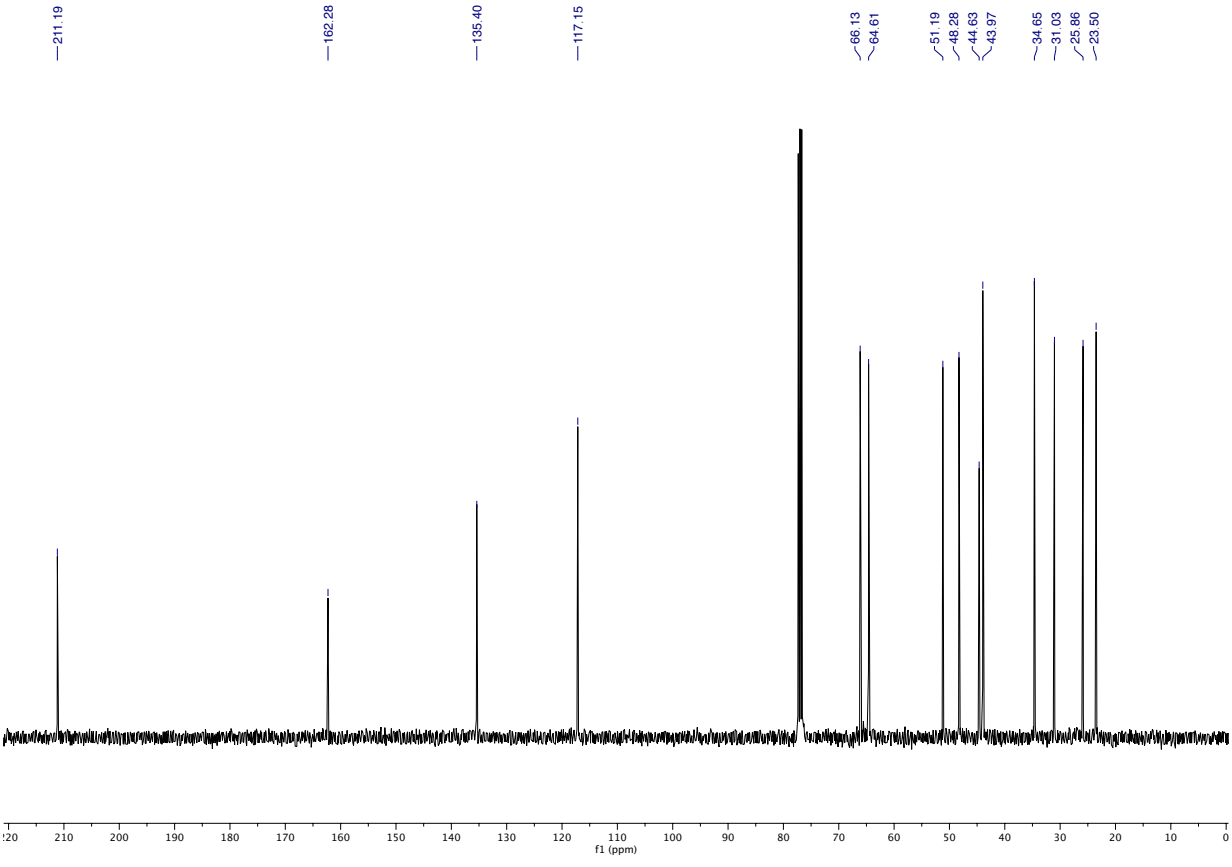
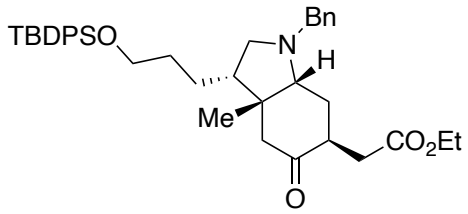
1.11
4.60
2.32
1.18
3.05
f1 (ppm)

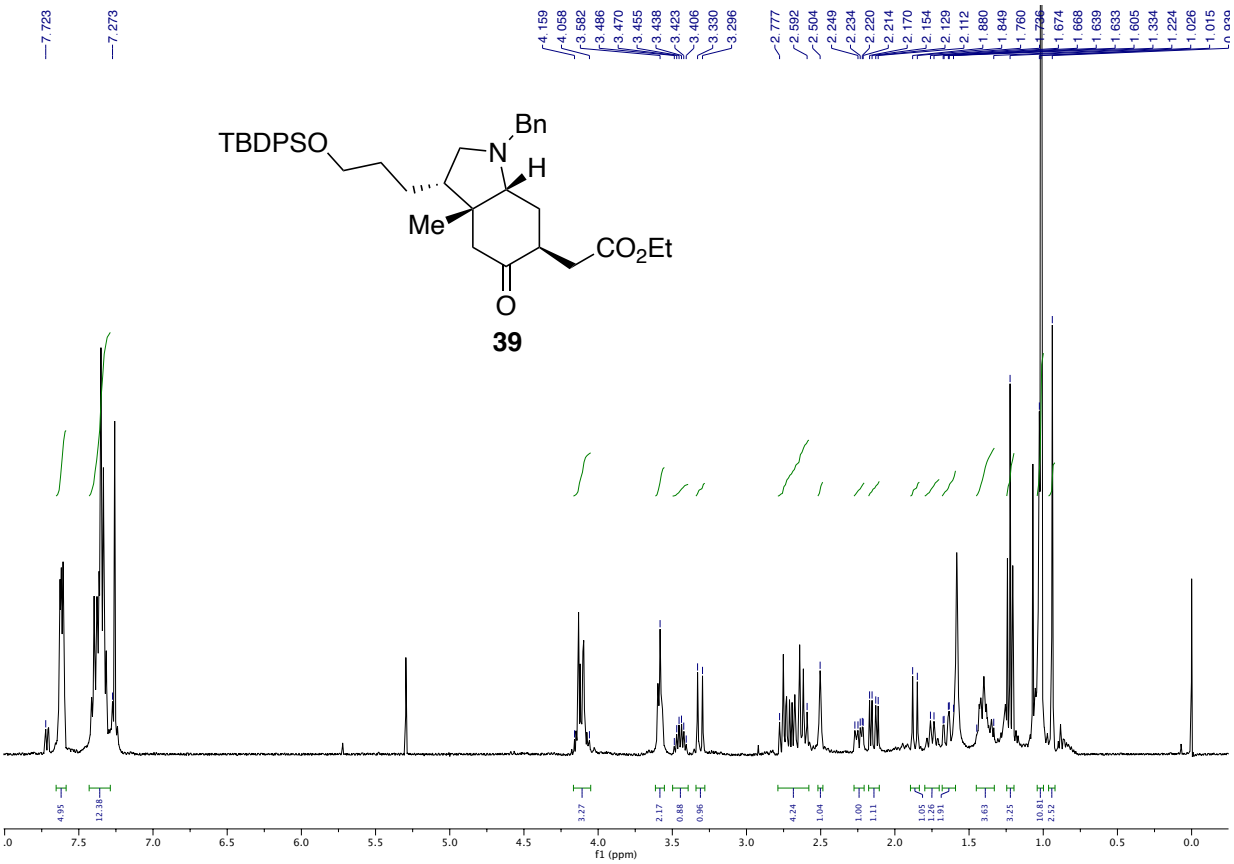

211.19
162.28
135.40
117.15
66.13
64.61
51.19
48.28
44.63
43.97
34.65
31.03
25.86
23.50
f1 (ppm)

(3*SR*,3a*RS*,7a*RS*)-1-benzyl-3-(3-((*tert*-butyldiphenylsilyl)oxy)propyl)-6-ethyl acetate-3a-methyloctahydro-5*H*-indol-5-one (39).



Compound **36** (61 mg, 0.11 mmol, 1 equiv) was diluted in THF (1.3 mL), cooled to -78 ºC, and LDA (1 M in THF,0.17 mL, 0.17 mmol, 1.5 equiv) was added. After stirring at this temperature for 1 h, DMPU (15 mL, 0.12 mmol, 1.1 equiv) and ethyl bromoacetate (25 mL, 0.23 mmol, 2 equiv) were successively added. The stirring was prolonged for 3 h and, then, it was quenched with $NaHCO_3$ (15 mL), warmed up to room temperature and extracted with EtOAc (5 x 20 mL). Combined organics were dried, filtered, and concentrated to afford the reaction crude. After chromatographic purification (hexane:EtOAc, 1.0→ 9:1) compound **39** (23 mg, 33%, 45% brsm) was obtained as a transparent oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72–7.28 (m, 15H, Ph), 4.16–4.06 (m, 3H, OEt and CH_2Ph), 3.60–3.57 (m, 2H, CH_2O), 3.45 (sext, *J* = 6.4 Hz, 1H, H-6), 3.31 (d, *J* = 13.6 Hz, 1H, CH_2Ph), 2.77–2.59 (m, 4H, H-2, H-4 and CH_2CO), 2.50 (bs, 1H, H-7a), 2.24 (ddd, *J* = 14.2, 5.8, 2.4 Hz, 1H, H-7), 2.14 (dd, *J* = 16.6, 6.4 Hz, 1H, CH_2CO), 1.86 (d, *J* = 12.4 Hz, 1H, H-4), 1.75 (dd, *J* = 19.8, 10.2 Hz, 1H, H-3), 1.62 (m, 1H, H-7), 1.45–1.33 (m, 3H, CH_2-2' and CH_2-1'), 1.22 (t, *J* = 7.2 Hz, 3H, OEt), 1.02 (bs, 10H, *t*-Bu and CH_2-1'), 0.94 (s, 3H, Me). ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.8 (C-5), 172.5 (CO), 133.9, 129.6, 128.4, 128.3, 127.6 and 126.8 (Ph), 68.8 (C-7a), 63.7 (CH_2O), 60.4 (OEt), 58.1 (CH_2Ph), 57.1 (C-2), 48.9 (C-3a), 47.3 (C-3), 45.0 (C-4), 40.6 (C-6), 33.8 (CH_2CO), 31.4 (CH_2-2'), 31.3 (C-7), 26.9 (*t*-Bu), 24.4 (CH_2-1'), 22.2 (Me), 19.2 (C), 14.2 (OEt).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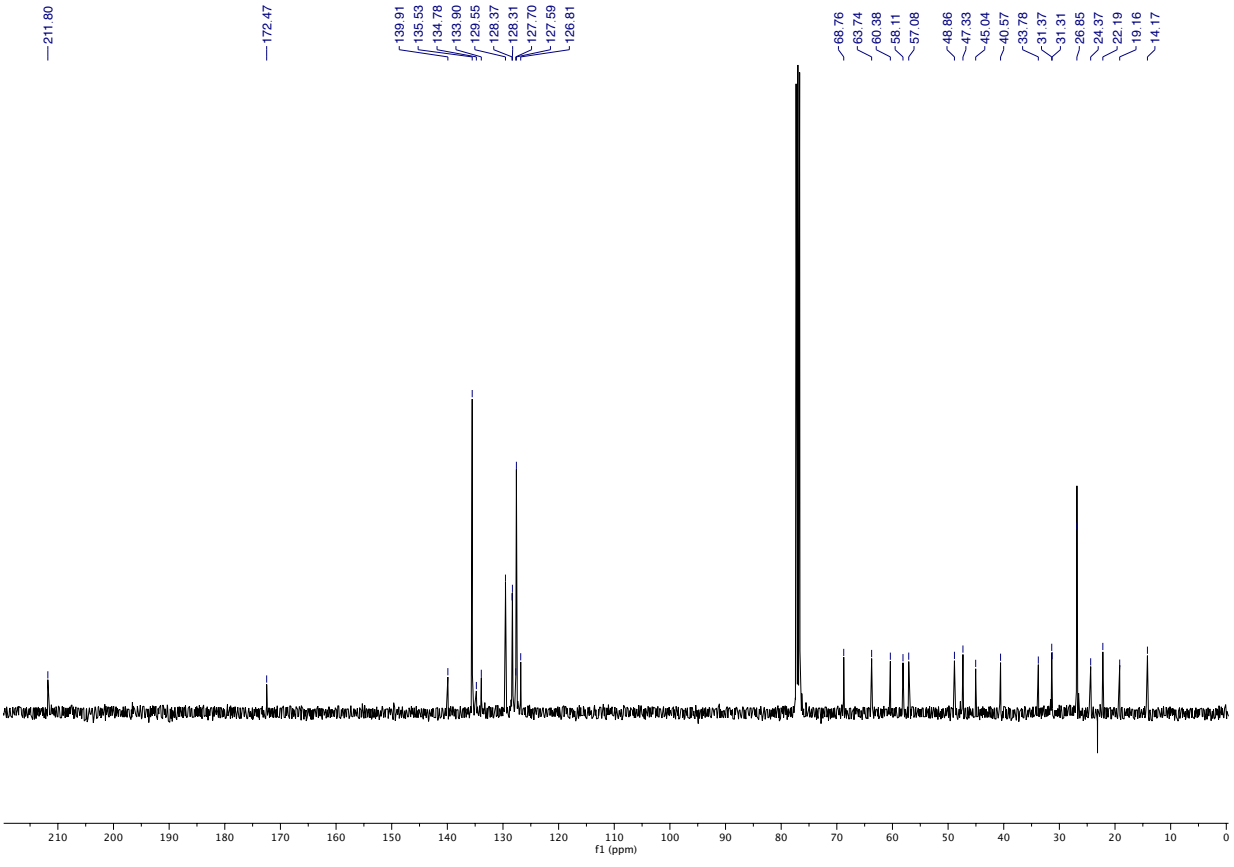
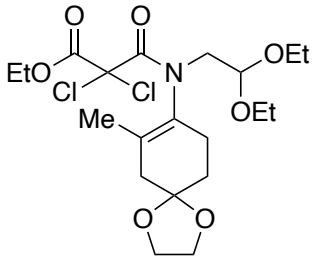
2.777
2.592
2.504
2.249
2.234
2.220
2.214
2.170
2.154
2.129
2.112
1.880
1.849
1.760
1.736
1.674
1.668
1.639
1.633
1.605
1.334
1.224
1.026
1.015
TBDPSO
Bn
N
H
Me
CO2Et
O
39
4.95
12.38
3.27
2.17
0.88
0.96
4.24
1.04
1.00
1.11
1.05
1.26
1.91
3.63
3.25
10.81
2.52
f1 (ppm)

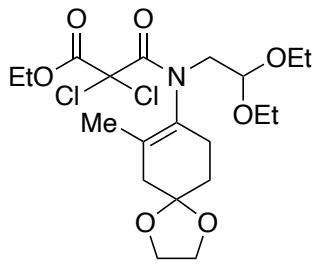

211.80
172.47
139.91
135.53
134.78
133.90
129.55
128.37
128.31
127.70
127.59
126.81
68.76
63.74
60.38
58.11
57.08
48.86
47.33
45.04
40.57
33.78
31.37
31.31
26.85
24.37
22.19
19.16
14.17
f1 (ppm)

2,2-dichloro-*N*-(2,2-diethoxyethyl)-*N*-(2-methyl-4-oxocyclohex-1-enyl) oxapropanoate ethylene acetal (40)



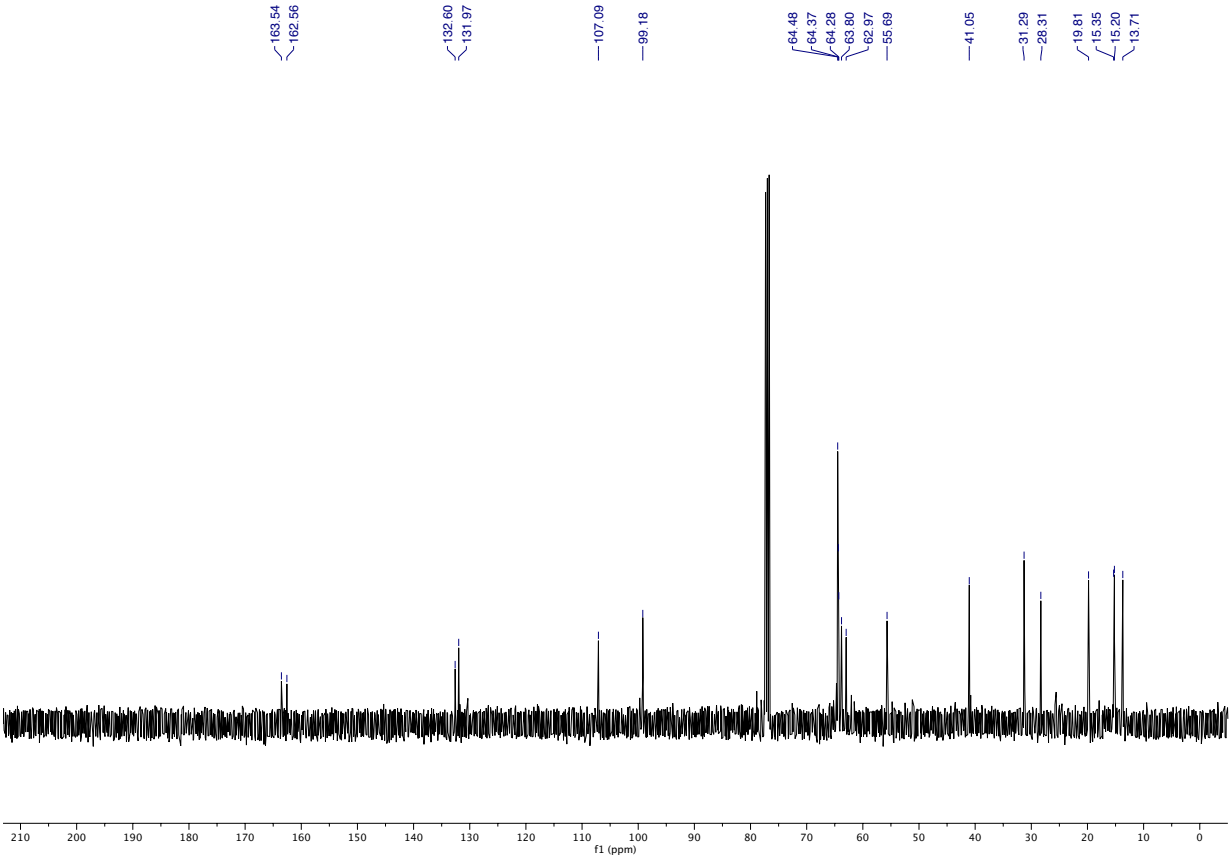
To a solution of 2-methylcyclohexane-1,4-dione monoethylene acetal (3.2 g, 18.7 mmol, 1 equiv) in $CHCl_2$ (7 mL) aminoacetaldehyde diethyl acetal (3.5 mL, 24.2 mmol, 1.3 equiv) and molecular sieves (3 g) were added. After being stirred overnight at room temperature, the mixture was filtered with a celite pad and checked by ^{1}H-NMR. Ethyl 2,2,3-trichloro-3-oxopropanoate (4.52 g, 20.6 mmol, 1.1 equiv) was dissolved in toluene and cooled to 0 ºC. Then, the above imine in toluene (30 mL) was added dropwise and the resulting mixture was stirred for 1 h at room temperature. A solution of NEt_3 (7.8 mL, 56.2 mmol, 3 equiv) in toluene (10 mL) was added at 0 ºC and stirred for two additional hours at room temperature. Sat. solution of Na_2CO_3 (30 mL) was added and after 1 h of stirring the solution was extracted with Et_2O (3 x 40 mL), washed with brine (40 mL), dried, concentrated, and purified by chromatography (hexane:EtOAc, 1:0→ 3:1) to afford **3** as a yellowish oil (4.08 g, 48 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.77 and 4.60 (dd and m, J = 3.4 Hz, 1H, CH), 4.32–4.21 (m, 2H, EtO_2C), 3.92–3.88 (m, 5H, OCH_2 and NCH_2), 3.70–3.39 (m, 4H, OEt), 2.99 (dd, J = 13.6, 7.2 Hz, 1H, NCH_2), 2.64–2.58 and 2.48–2.35 (2m, 2H each, H-6), 2.27 and 2.12 (2d, J = 18.0 Hz, H-3), 1.82–1.70 (m, 2H, H-5), 1.56 and 1.51 (2t, 3H, Me), 1.27 (t, 3H, EtO_2C), 1.31 (t, 6H, OEt). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.5 (CO), 162.6 (CO), 132.6 (=C), 132.0 (=C), 107.1 (C-4), 99.2 (CH), 64.5 and 64.4 (OCH_2), 64.3 (EtO_2C), 63.8 and 63.0 (OEt), 55.7 (NCH_2), 41.2 (C-3), 31.3 (C-5), 28.3 (C-6), 19.8 (Me), 15.4 and 15.2 (OEt), 13.1 (EtO_2C).

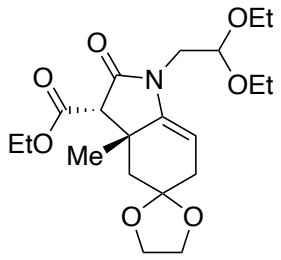

O
O
EtO
Cl
Cl
N
OEt
OEt
Me
O
O

40

4.760
4.602
4.301
4.255
4.235
3.885
3.704
3.451
3.019
3.001
2.985
2.967
2.588
2.474
2.424
2.287
2.242
2.148
2.103
1.732
1.563
1.551
1.514
1.286
1.268
1.250
1.149
1.143
1.135
1.131
1.125
1.114
1.00
0.37
2.77
6.12
6.55
1.08
1.38
1.27
0.58
1.42
1.55
3.18
3.96
3.88
7.60
f1 (ppm)

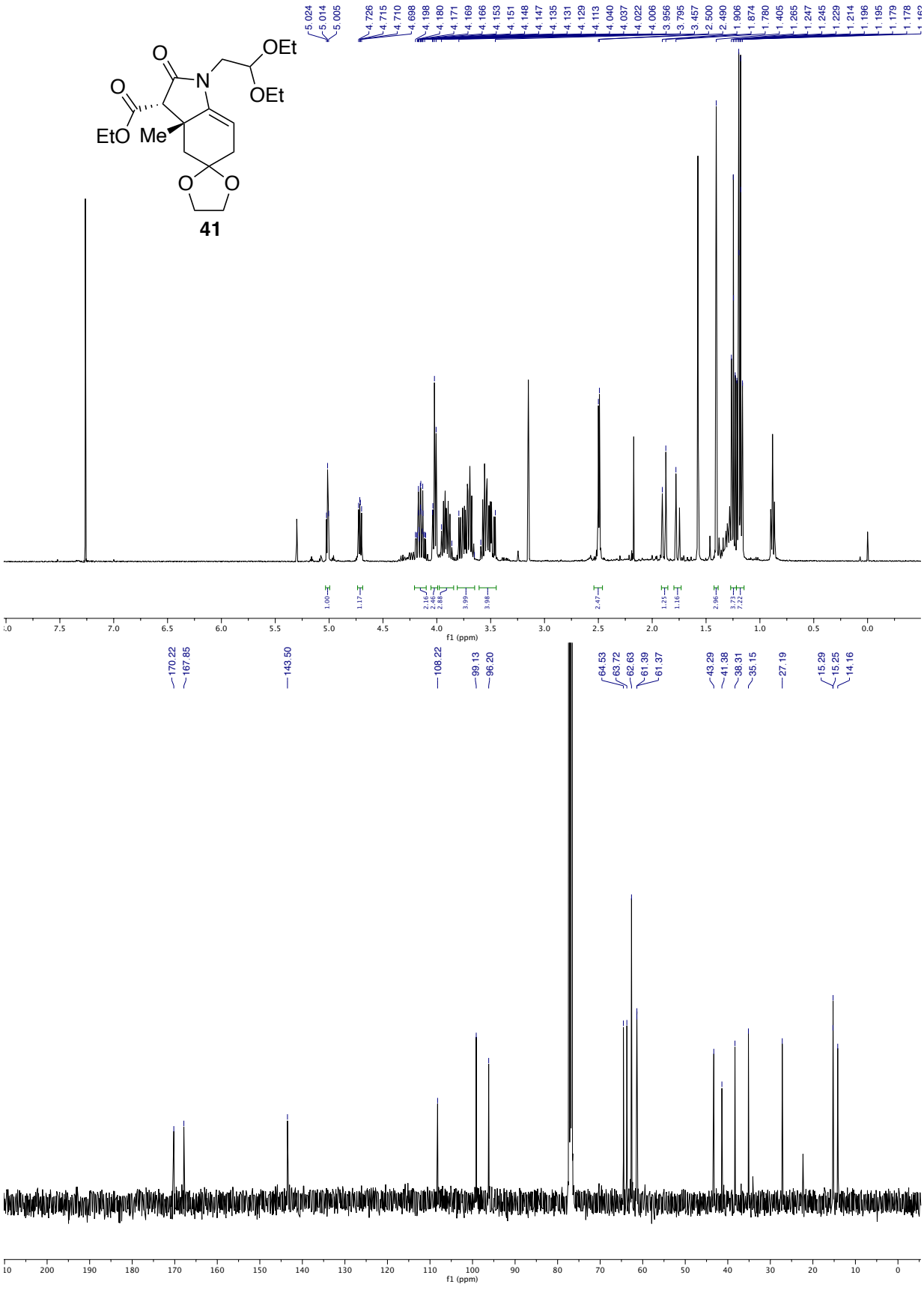

163.54
162.56
132.60
131.97
107.09
99.18
64.48
64.37
64.28
63.80
62.97
55.69
41.05
31.29
28.31
19.81
15.35
15.20
13.71
f1 (ppm)

(3*RS*, 3a*SR*)-1-(2,2-diethoxyethyl)-3-ethoxycarbonyl-3a-methyl-1,3a,4,6-tetrahydro-2*H*-indole-2,5(3*H*)-dione monoethylene acetal (41)



A solution of enamide **40** (1.33 g, 2.84 mmol, 1 equiv) in toluene (24 mL) was heated to 80 ºC. Then, a solution of AIBN (0.23 g, 1.42 mmol, 0.5 equiv), TBTH (1.6 mL, 5.96 mmol, 2.1 equiv) in toluene (11 mL) was added over 1 h with a syringe pump. The mixture was stirred at this temperature for 3 additional hours and concentrated under reduced pressure. The crude was purified by chromatography (hexane:EtOAc, 1:0 → 7:3) to obtain product **41** (0.56 g, 50%), product **41-epi** (0.19 g, 17%) as colorless oils.

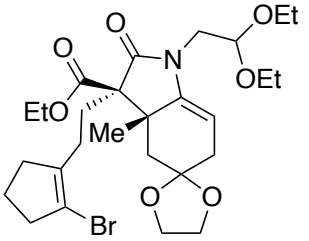
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.01 (t, *J* = 4 Hz, 1H, H-7), 4.71 (dd, *J* = 6.8, 4.8 Hz, 1H, CH), 4.10–4.20 (m, 2H, EtO_2C), 4.01–4.04 and 3.86–3.96 (2m, 2H each, OCH_2), 3.77 (dd, *J* = 14, 6.8 Hz, 1H, NCH_2), 3.66–3.75 and 3.49–3.59 (2m, 2H each, OEt), 3.48 (dd, *J* = 14, 4.8 Hz, 1H, NCH_2), 3.15 (s, 1H, H-3), 2.50 (d, *J* = 4 Hz, 2H, H-6), 1.89 and 1.76 (2d, *J* = 13 Hz, 1H each, H-4), 1.42 (s, 3H, Me), 1.25 (t, *J* = 7.2 Hz, 3H, EtO_2C), 1.20 and 1.18 (2t, *J* = 13.2 Hz, 3H each, OEt). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.2 (CO), 167.8 (C-2), 143.5 (C-7a), 108.2 (C-5), 99.1 (CH), 96.2 (C-7), 64.5 and 63.7 (OCH_2), 62.6 (OEt), 61.4 (C-3), 61.3 (EtO_2C), 43.3 (NCH_2), 41.4 (C-3a), 38.3 (C-4), 35.1 (C-6), 27.2 (Me), 15.3 and 15.2 (OEt), 14.2 (EtO_2C).



O
O
N
OEt
OEt
EtO
Me
O
O

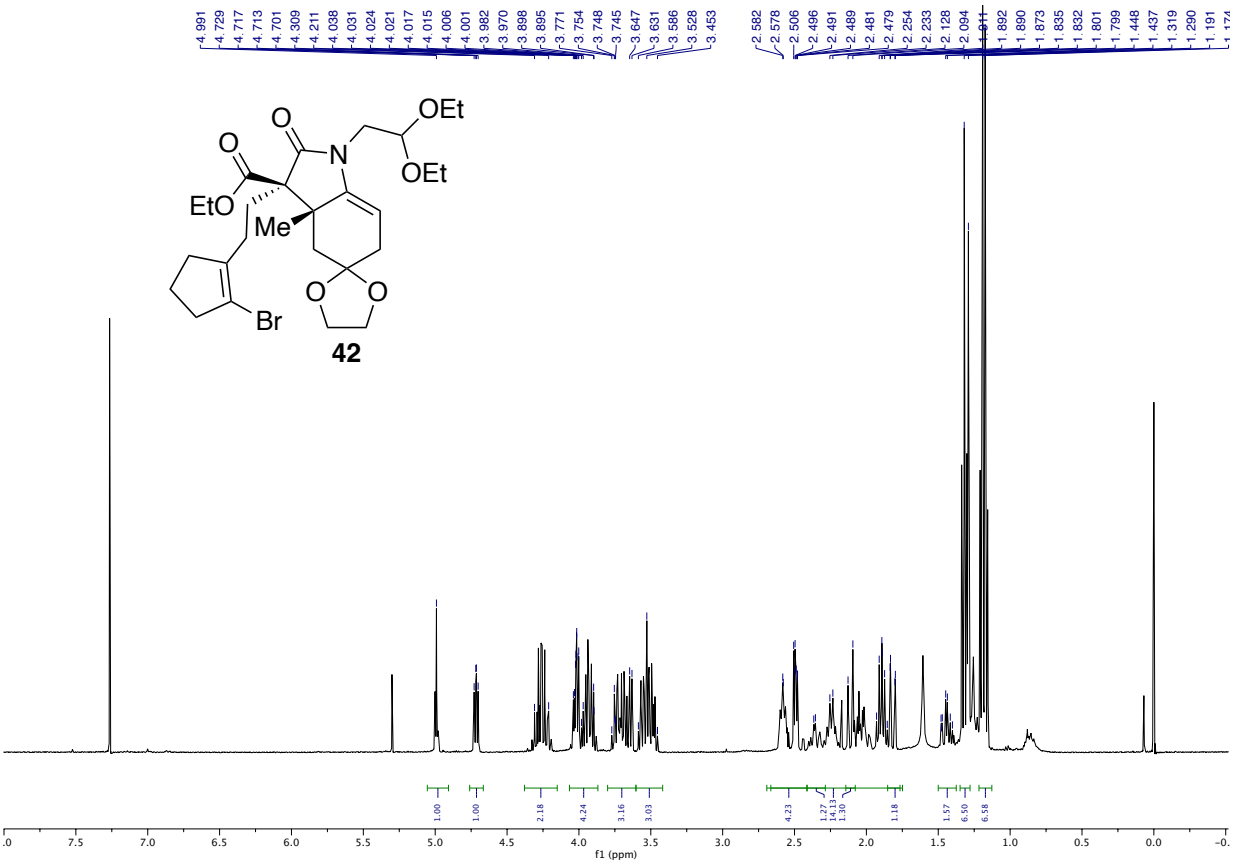
41

(3*RS*,3a*SR*)-1-(2,2-diethoxyethyl)-3-(2-(2'-bromocyclopent-1'-ene-1'-yl)ehtyl)-3-ethoxycarbonyl-3a-methyl-1,3a,4,6-tetrahydro-2*H*-indole-2,5(3*H*)-dione monoethylene acetal (42).

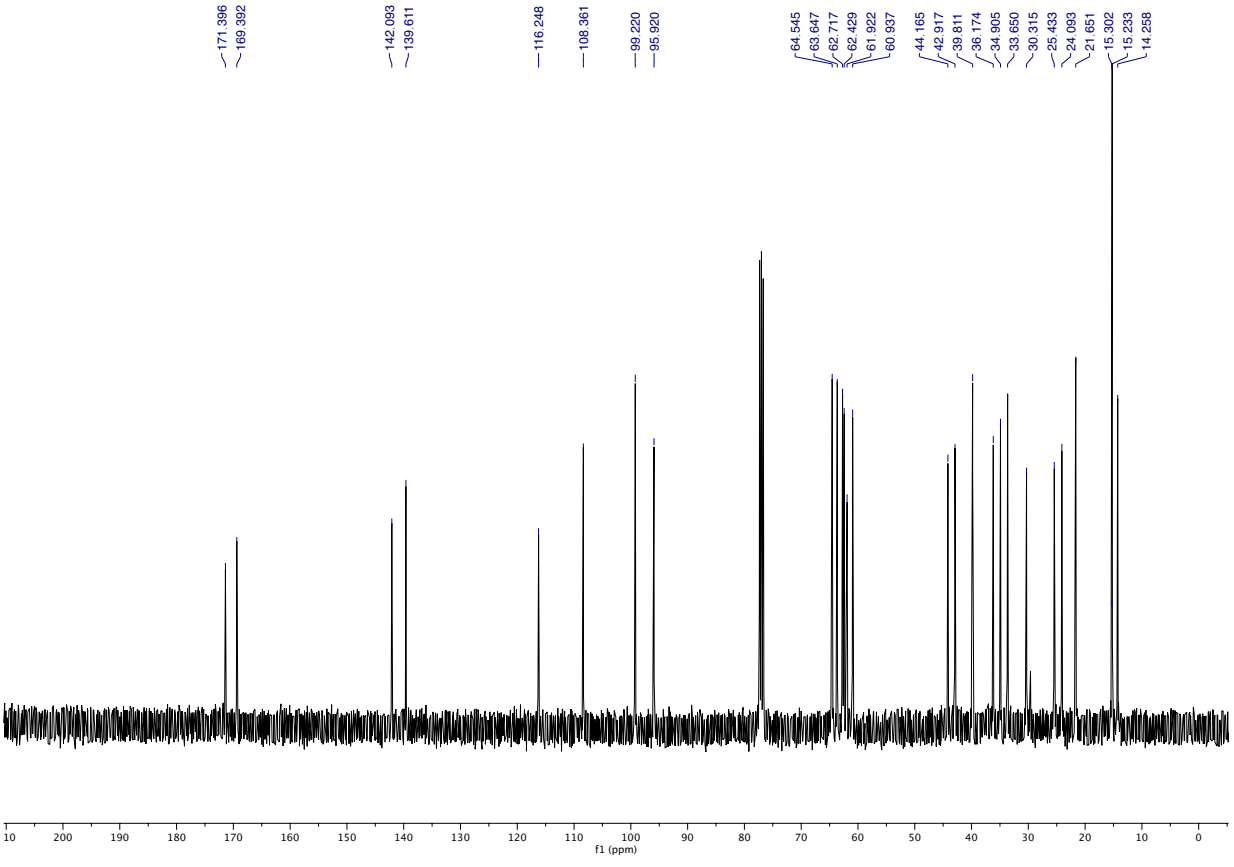


Cs_2CO_3 (0.30 g, 0.91 mmol, 1.1 equiv) was added to a solution of **41** (0.33 g, 0.83 mmol, 1 equiv) in DMSO (3 mL). The mixture was purged with argon and stirred at room temperature for 1h 30 min before **30** (0.50 g, 1.66 mmol, 2 equiv) was added, and then, stirred overnight. The solution was diluted with water and extracted with EtOAc (4 x 20 mL). The organics were combined, dried over Na_2SO_4 and concentrated under vacuum. The brownish crude was purified by silica gel chromatography (hexane:EtOAc, 1:0→1:1) to obtain the product **42** as a colorless oil (0.20 g, 42 %)

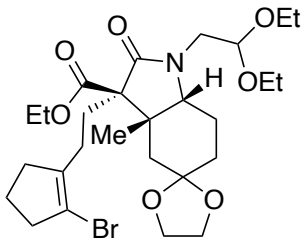
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.99 (t, *J* = 3.8 Hz, 1H, H-7), 4.71 (t, *J* = 6.4 Hz, 1H, CH), 4.25 (m, 2H, EtO_2C), 4.01 and 3.87–3.97 (2m, 2H each, OCH_2), 3.63–3.76 (m, 3H, OEt, NCH_2), 3.45–3.58 (m, 3H, OEt, NCH_2), 2.58 (bt, *J* = 7.4 Hz, 2H, H-3'), 2.49 (dd, *J* = 6.6, 3.8 Hz, 2H, H-6), 2.35 (m, 1H, CH_2-1'), 2.24 (m, 2H, H-5'), 2.11 (d, *J* = 13.2 Hz, 1H, 1H-4), 1.97–2.08 (m, 2H, CH_2-1', CH_2-3), 1.89 (q, *J* = 7.4 Hz, 2H, H-4'), 1.81 (d, *J* = 13.2 Hz, 1H, H-4), 1.43 (m, 1H, CH_2-3), 1.31 (t, *J* = 7 Hz, 3H, EtO_2C), 1.29 (s, 3H, Me), 1.18 (2t, *J* = 6.8 Hz, 6H, OEt). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.4 (CO), 169.4 (C-2), 142.1 (C-1'), 139.6 (C-7a), 116.3 (C-2'), 108.4 (C-5), 99.2 (CH), 95.9 (C-7), 64.6 and 63.7 (OCH_2), 62.7 and 62.5 (OEt), 61.9 (C-3), 61.0 (EtO_2C), 44.2 (C-3a), 42.9 (NCH_2), 39.8 (C-3'), 36.2 (C-4), 34.9 (C-6), 33.7 (C-5'), 30.3 (CH_2-3), 25.5 (CH_2-1'), 24.1 (Me), 21.7 (C-4'), 15.3 and 15.3 (OEt), 14.3 (EtO_2C).



42

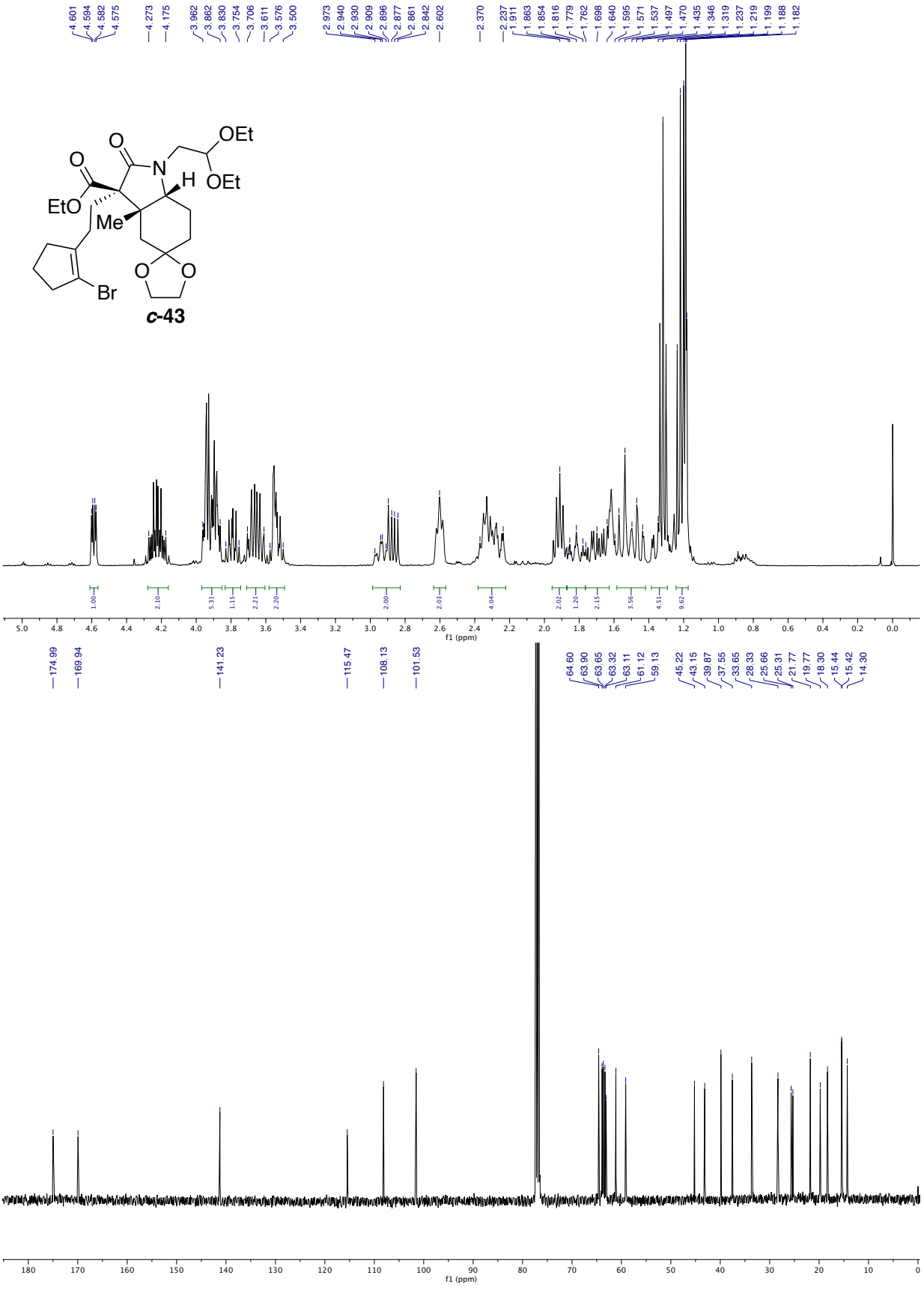


(3*RS*,3a*RS*,7a*RS*)-1-(2,2-diethoxyethyl)-3-(2-(2'-bromocyclopent-1'-ene-1'-yl)ehtyl)-3-ethoxycarbonyl-3a-methylhexahydro-2*H*-indole-2,5(3*H*)-dione monoethylene acetal (*c*-43)



To a solution of **42** (66 mg, 0.11 mmol, 1 equiv) in AcOH (3.5 mL) $NaCNBH_3$ (14 mg, 0.22 mmol, 2 equiv) was added portion-wise, and the reaction was stirred at room temperature overnight. Then, the mixture was diluted with water (20 mL) and extracted with CH_2Cl_2 (5 x 15 mL). The organics were combined, dried, and concentrated. The obtained crude was purified (hexane:EtOAc, 9:1 $\rightarrow$ 4:1) to afford products ***c*-43** (16.9 mg, 33%) and ***t*-43** (13.1 mg, 25%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.59 (dd, *J* = 7.6, 2.8 Hz, 1H, CH), 4.18–4.27 (m, 2H, EtO_2C), 3.86–3.96 (m, 5H, OCH_2, NCH_2), 3.75–3.83 (m, 1H, OEt), 3.61–3.71 (m, 2H, OEt), 3.50–3.58 (m, 2H, OEt, H-7a), 2.94 (td, *J* = 12.5, 4 Hz, 1H, CH_2-1'), 2.87 (dd, *J* = 14, 7.6 Hz, 1H, NCH_2), 2.60 (bt, *J* = 7.2 Hz, 2H, H-3'), 2.24–2.37 (m, 4H, H-7, CH_2-1', H-5'), 1.91 (qt, *J* = 7.4 Hz, 2H, H-4'), 1.82 (m, 1H,H-7), 1.69 (m, 2H, CH_2-3), 1.55 (d, *J* = 13.6 Hz, 1H, H-4), 1.52 (m, 1H, H-6), 1.45 (d, *J* = 13.6 Hz, 1H, H-4), 1.35 (m, 1H, H-6), 1.32 (t, *J* = 7 Hz, 3H, EtO_2C), 1.21 (2t, *J* = 7 Hz, 6H, OEt), 1.19 (s, 3H, Me). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.0 (CO), 169.9 (C-2), 141.2 (C-1'), 115.5 (C-2'), 108.1 (C-5), 101.5 (CH), 64.6 (OCH_2), 63.9 (OEt), 63.6 (OCH_2), 63.3 (OEt), 63.1 (C-3), 61.1 (EtO_2C), 59.1 (C-7a), 45.2 (C-3a), 43.1 (NCH_2), 39.9 (C-3'), 37.5 (C-4), 33.6 (C-5'), 28.3 (C-6), 25.6 (CH_2-3), 25.3 (CH_2-1'), 21.8 (C-4'), 19.8 (C-7), 18.3 (Me), 15.4 and 15.4 (OEt), 14.3 (EtO_2C).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4.575
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4.175
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3.754
3.706
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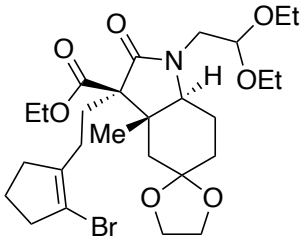
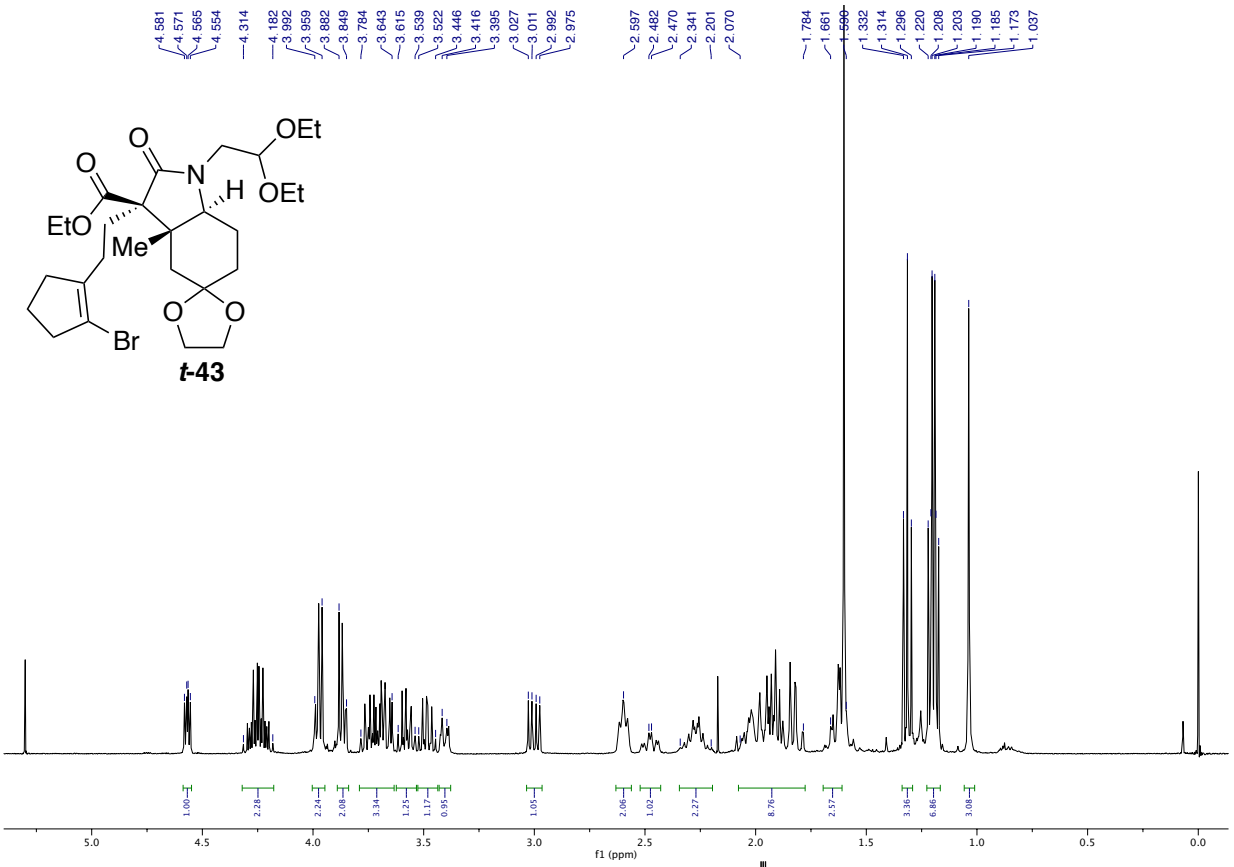
3.500
2.973
2.940
2.930
2.909
2.896
2.877
2.861
2.842
2.602
2.370
2.237
1.911
1.863
1.854
1.816
1.779
1.762
1.698
1.640
1.595
1.571
1.537
1.497
1.470
1.435
1.346
1.319
1.237
1.219
1.199
1.188
1.182
OEt
O
O
N
H
OEt
EtO
Me
O
O
Br
c-43
1.00
2.10
5.31
1.15
2.21
2.20
2.00
2.03
4.04
2.02
1.20
2.15
3.56
4.51
9.62
f1 (ppm)
174.99
169.94
141.23
115.47
108.13
101.53
64.60
63.90
63.65
63.32
63.11
61.12
59.13
45.22
43.15
39.87
37.55
33.65
28.33
25.66
25.31
21.77
19.77
18.30
15.44
15.42
14.30
f1 (ppm)

(3*RS*,3a*RS*,7a*SR*)-1-(2,2-diethoxyethyl)-3-(2-(2'-bromocyclopent-1'-ene-1'-yl)ehtyl)-3-ethoxycarbonyl-3a-methylhexahydro-2*H*-indole-2,5(3*H*)-dione monoethylene acetal (*t*-43).



^{1}H NMR (400 MHz, $CDCl_3$) δ 4.57 (dd, *J* = 6.6, 4.2 Hz, 1H, CH), 4.18–4.31 (m, 2H, EtO_2C), 3.96–3.99 and 3.85–3.88 (2m, 2H each, OCH_2), 3.64–3.78 (m, 3H, OEt, NCH_2), 3.54–3.62 and 3.45–3.52 (2m, 2H each, OEt), 3.40 (dd, *J* = 11.8, 3.4 Hz, 1H, H-7a), 3.00 (dd, *J* = 14.2, 6.6 Hz, 1H, NCH_2), 2.60 (bt, *J* = 7.6 Hz, 2H, H-3'), 2.48 (td, *J* = 13, 4.8 Hz, 1H, CH_2-1'), 2.20–2.34 (m, 2H, H-5'), 1.78–2.07 (m, 8H, H-6, H-7, CH_2-3, CH_2-1', H-4, H-4'), 1.59–1.66 (m, 3H, CH_2-3, H-6, H-7), 1.31 (t, *J* = 7 Hz, 3H, EtO_2C), 1.20 and 1.19 (2t, *J* = 7.2 Hz, 3H each, OEt), 1.04 (s, 3H, Me). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.8 (CO), 170.1 (C-2), 140.0 (C-1'), 116.1 (C-2'), 109.1 (C-5), 101.0 (CH), 64.8 and 63.6 (OCH_2), 63.6 and 63.3 (OEt), 62.0 (C-3), 61.0 (C-7a), 60.8 (EtO_2C), 44.1 (C-3a), 43.3 (NCH_2), 39.9 (C-3'), 38.8 (C-4), 34.6 (C-6), 33.8 (C-5'), 25.8 (CH_2-3), 25.3 (CH_2-1'), 21.7 (C-4'), 20.0 (C-7), 16.9 (Me), 15.5 and 15.4 (OEt), 14.3 (EtO_2C).


4.581
4.571
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3.959
3.882
3.849
3.784
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3.615
3.539
3.522
3.446
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3.011
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2.070
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1.590
1.332
1.314
1.296
1.220
1.208
1.203
1.190
1.185
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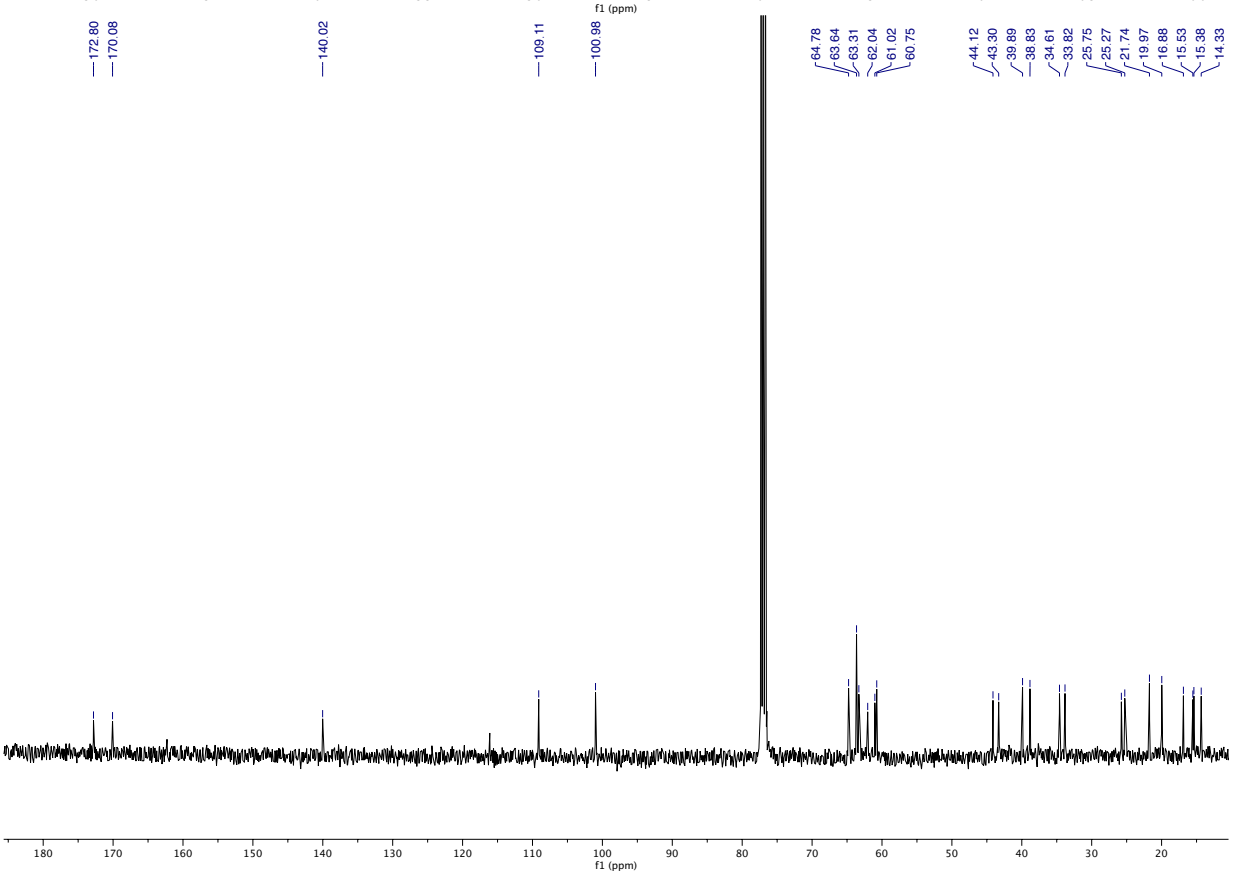
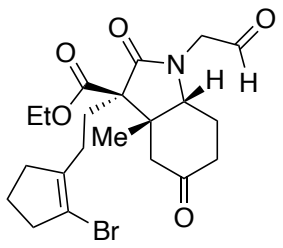
O
O
N
H
OEt
OEt
EtO
Me
O
O
Br
1.00
2.28
2.24
2.08
3.34
1.25
1.17
0.95
1.05
2.06
1.02
2.27
8.76
2.57
3.36
6.66
3.08
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

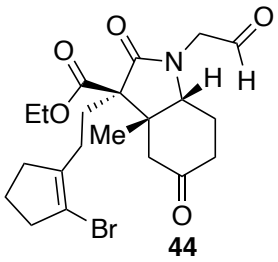
***t*-43**


172.80
170.08
140.02
109.11
100.98
64.78
63.64
63.31
62.04
61.02
60.75
44.12
43.30
39.89
38.83
34.61
33.82
25.75
25.27
21.74
19.97
16.88
15.53
15.38
14.33
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)

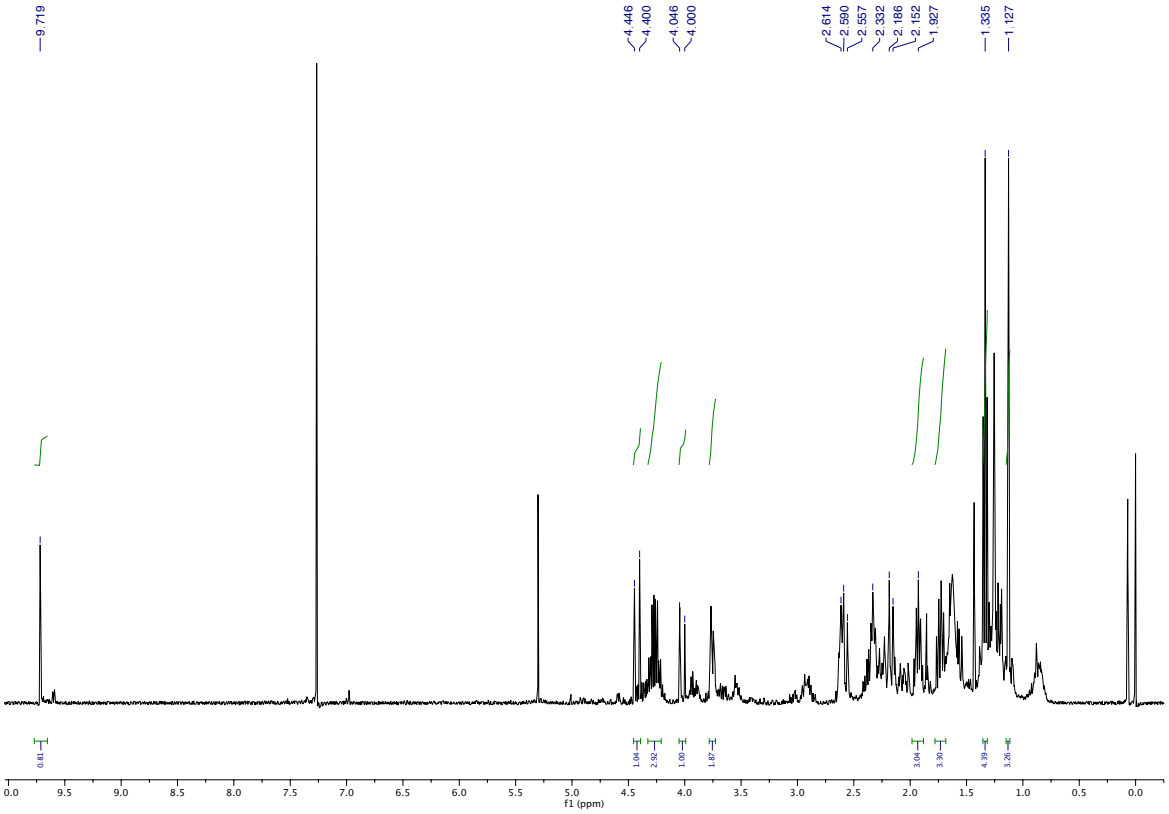
(3*RS*,3a*RS*,7a*RS*)- 3-(2-(2'-bromocyclopent-1'-ene-1'-yl)ehtyl)-3-ethoxycarbonyl-1-(2-oxoethyl)tetrahydro-1*H*-indole-2,5-(3*H*, 6*H*)dione (44).



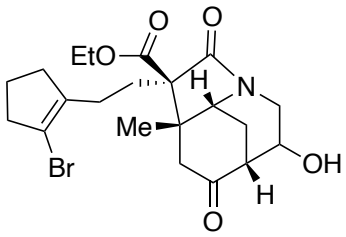
Compound **43** (85 mg, 0.15 mmol) was treated with a mixture of THF:10% HCl (1:2, 2.25 mL) and stirred overnight. The reaction was diluted with water and extracted with CH_2Cl_2 (4 x 20 mL). The organics were combined, dried, and concentrated to afford a yellowish crude that was used directly in the next step without purification.


O
O
N
H
H
O
O
EtO
Me
Br
O

44

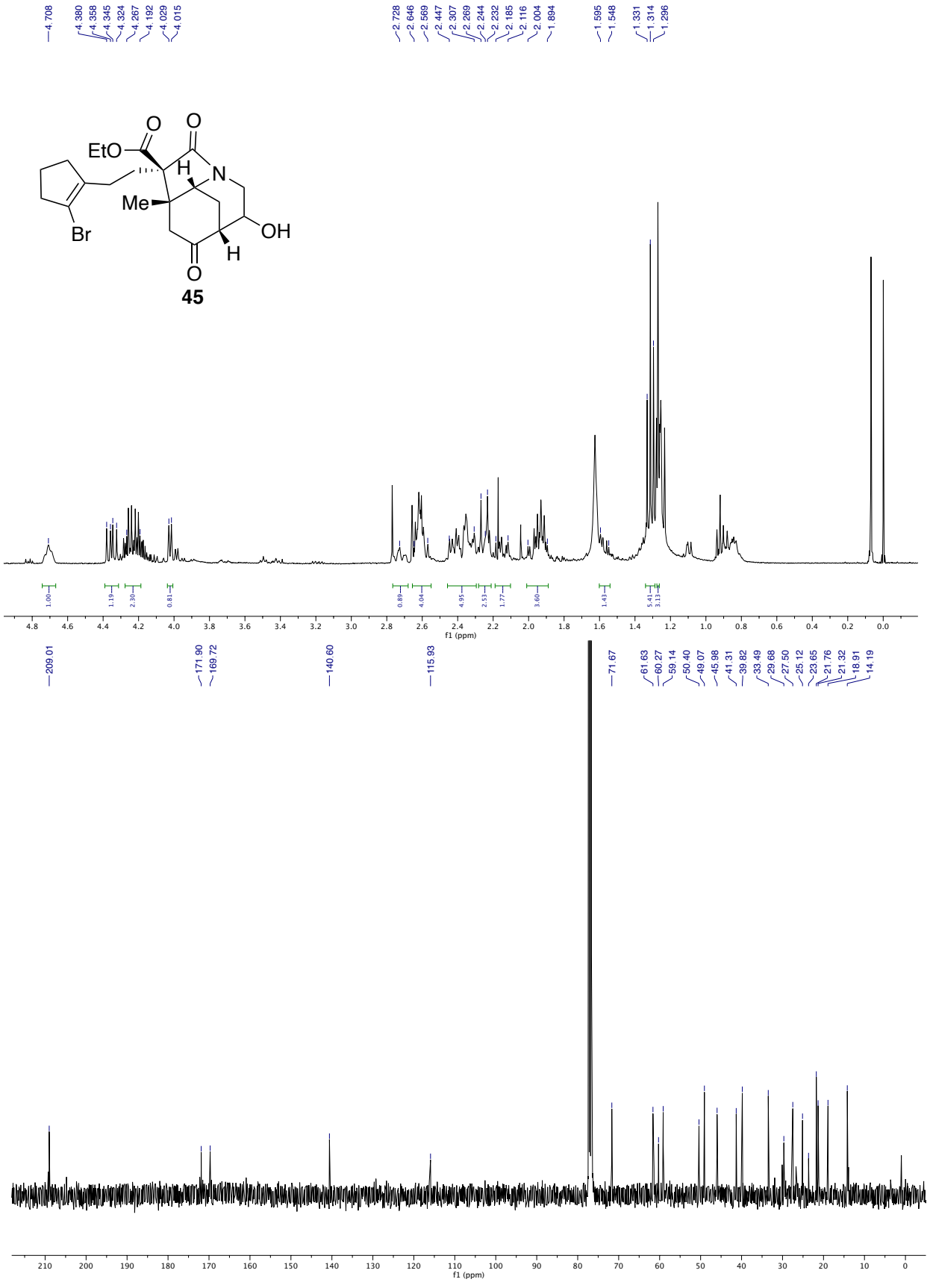

9.719
4.446
4.400
4.046
4.000
2.614
2.590
2.557
2.332
2.186
2.152
1.927
1.335
1.127
0.81
1.04
2.92
1.00
1.87
3.04
3.30
4.39
3.26
f1 (ppm)

(3*SR*,3a*RS*,6*RS*,7a*RS*)-3-3-(2-(2'-bromocyclopent-1'-ene-1'-yl)ehtyl)-3-ethoxycarbonyl -8-hydroxy-3a-methyltetrahydro-6,1-ethanoindole-2,5(3*H*,6*H*)-dione (45).

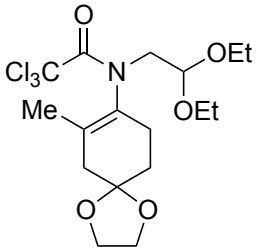


A solution of compound **44** (20 mg, 0.04 mmol, 1 equiv) and *p*-TsOH·H_2O (13 mg, 0.06 mmol, 1.5 equiv) in benzene (1 mL) was heated to reflux and rapidly the color of the mixture went from yellowish to brownish. After 4 h of stirring at this temperature, the reaction was neutralized with Na_2CO_3 sat. solution (15 mL) and extracted with Et_2O (4 x 10 mL). The combined organic phases were dried and concentrated. The crude was purified by chromatography (hexane:EtOAc, 9.5:0.5 → 1:1) to afford compound **45** (10 mg, 50%) as a brownish waxy solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.71 (bt, *J* = 7.0 Hz, 1H, CH), 4.36 (dd, *J* = 13.8 Hz, *J* = 8.6 Hz, 1H, NCH_2), 4.16–4.25 (m, 2H, OEt), 4.02 (d, *J* = 5.6 Hz, 1H, H-7a), 2.73 (td, *J* = 13.0, 4.0 Hz, 1H, CH_2-1'), 2.57–2.65 (m, 4H, H-8, H-3', H-4), 2.31–2.45 (m, 5H, H-5', H-7, CH_2-1', H-7a), 2.22 (m, 1H, H-4), 2.12–2.19 (m, 1H, 1H-7), 1.89–2.00 (m, 1H, CH_2-3), 1.94 (m, 2H, H-4'), 1.55–1.60 (m, 1H, CH_2-3), 1.31 (t, *J* = 7.0 Hz, 3H, OEt), 1.27 (s, 3H, Me). ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.0 (C-5), 171.9 (CO), 169.7 (C-2), 140.6 (C-1'), 115.9 (C-2'), 71.7 (CH), 61.6 (OEt), 60.3 (C-3), 59.1 (C-6), 50.4 (C-3a), 49.1 (C-7a), 46.0 (C-4), 41.3 (NCH_2), 39.8 (C-3'), 33.5 (C-5'), 27.4 (CH_2-3), 25.1 (CH_2-1'), 21.7 (C-4'), 21.3 (Me), 18.9 (C-7), 14.2 (OEt).

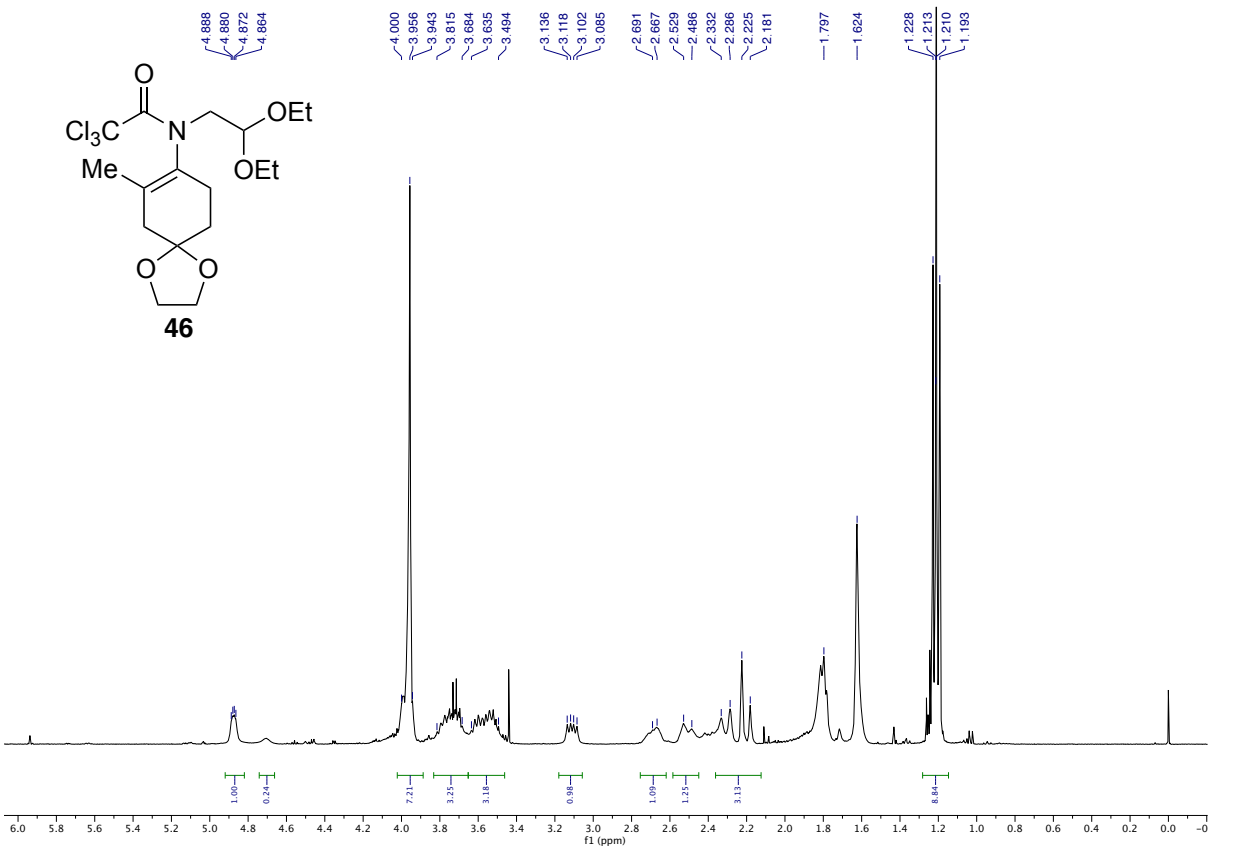

4.708
4.380
4.358
4.345
4.324
4.267
4.192
4.029
4.015
2.728
2.646
2.569
2.447
2.307
2.269
2.244
2.232
2.185
2.116
2.004
1.894
1.595
1.548
1.331
1.314
1.296
EtO
O
O
H
N
Me
Br
OH
H
O
45
f1 (ppm)
209.01
171.90
169.72
140.60
115.93
71.67
61.63
60.27
59.14
50.40
49.07
45.98
41.31
39.82
33.49
29.68
27.50
25.12
23.65
21.76
21.32
18.91
14.19
f1 (ppm)

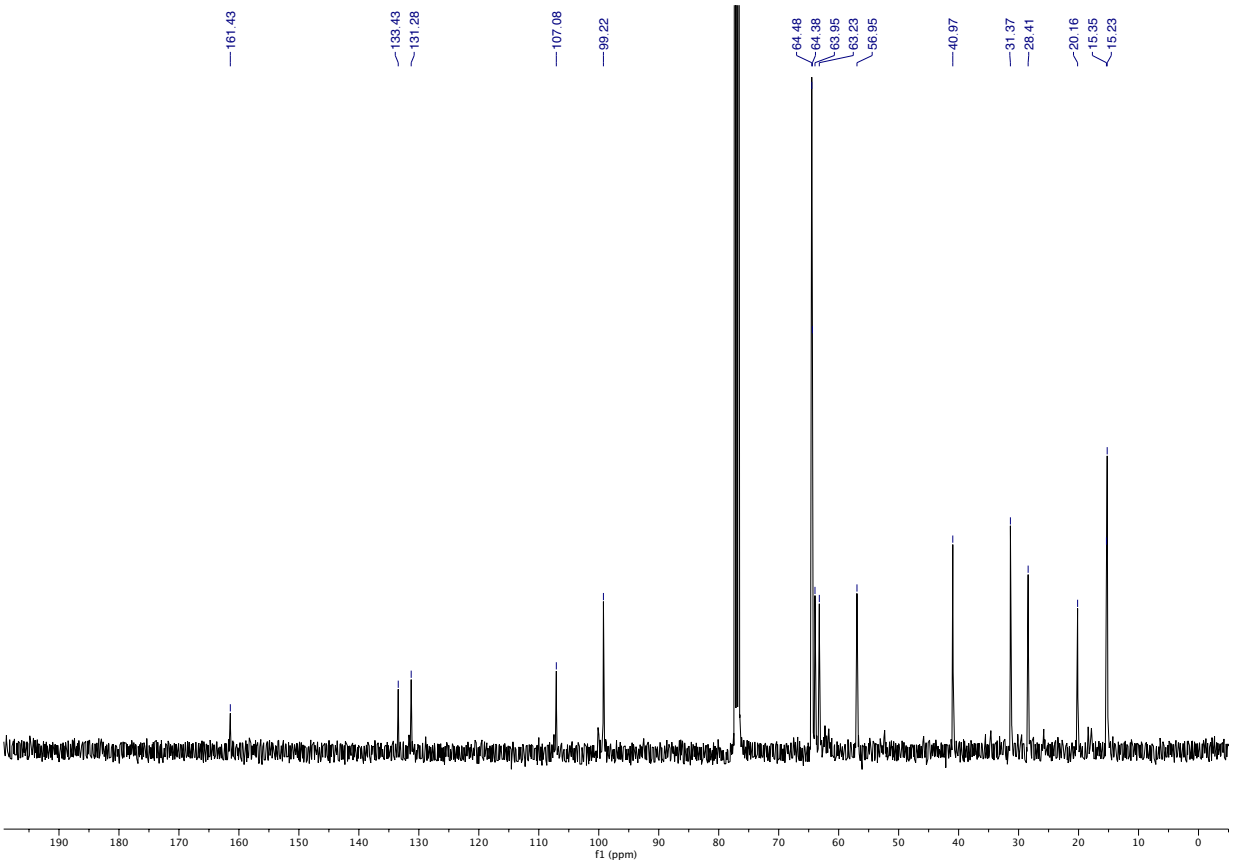
2,2,2-Trichloro-*N*-(2,2-diethoxyethyl)-*N*-(2-methyl-4-oxocyclohex-1-enyl)acetamide ethylene acetal (46)



2-Methylcyclohexane-1,4-dione monoethylene acetal **1** (8.60 g, 50.5 mmol, 1 equiv) and aminoacetaldehyde diethyl acetal (7.4 mL, 50.5 mmol, 1 equiv) were dissolved in toluene (100 mL) and placed under Dean-Stark conditions for 4 h. A solution of trichloroacetyl chloride (6.2 mL, 55.6 mmol, 1.1 equiv) in toluene (64 mL) was cooled to 0 ºC and the above solution containing the imine was added dropwise. The reaction was stirred at room temperature for 1 h, cooled to 0 ºC, and a solution of NEt_3 (21.1 mL, 151.6 mmol, 3 equiv) in toluene (64 mL) was added. After being stirred for 2 h at room temperature, an aqueous Na_2CO_3 saturated solution (100 mL) was added, and the mixture was stirred for 1 h and extracted with Et_2O (3 x 100 mL). The organics were combined, dried, concentrated, and purified by chromatography (hexane:EtOAc, 9.5:0.5 → 1:1) to afford compound **46** (15.0 g, 69%) as a colorless oil.

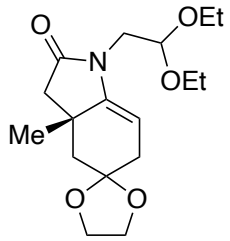
IR (neat): 2975, 2932, 1716, 1672, 1375, 1127, 1060, 822 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 4.88 (dd, *J* = 6.4, 3.2 Hz, 1H, CH), 4.00 (dd, *J* = 13.8, 2.0 Hz, 1H, NCH_2), 4.00–3.94 (m, 4H, OCH_2), 3.82–3.68 and 3.65–3.49 (2 m, 2H each, OCH_2CH_3), 3.11 (dd, *J* = 13.8, 6.6 Hz, 1H, NCH_2), 2.68 (m, 1H, H-5), 2.51 (m, 1H, H-5), 2.31 and 2.20 (2 d, *J* = 18.0 Hz, 1H each, H-3), 1.80 (m, 2H, H-6), 1.62 (s, 3H, Me), 1.21 (t, *J* = 7 Hz, 6H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.4 (CO), 133.4 (C-1), 131.3 (C-2), 107.1 (C-4), 99.2 (CH), 64.5 and 64.4 (OCH_2), 63.9 and 63.2 (OCH_2CH_3), 56.9 (NCH_2), 41.0 (C-3), 31.4 (C-5), 28.4 (C-6), 20.2 (Me), 15.3 and 15.2 (CH_3). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{17}H_{27}Cl_3NO_5$ 430.0955, found 430.0963.


4.888
4.880
4.872
4.864
4.000
3.956
3.943
3.815
3.684
3.635
3.494
3.136
3.118
3.102
3.085
2.691
2.667
2.529
2.486
2.332
2.286
2.225
2.181
1.797
1.624
1.228
1.213
1.210
1.193
1.00
0.24
7.21
3.25
3.18
0.98
1.09
1.25
3.13
8.84
f1 (ppm)


161.43
133.43
131.28
107.08
99.22
64.48
64.38
63.95
63.23
56.95
40.97
31.37
28.41
20.16
15.35
15.23
f1 (ppm)

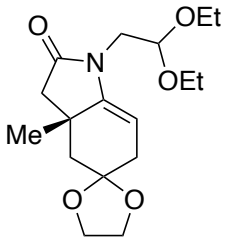
46

1-(2,2-Diethoxyehtyl)-3a-methyl-1,3a,4,6-tetrahydro-2*H*-indole-2,5(3*H*)-dione monoethylene acetal (47)



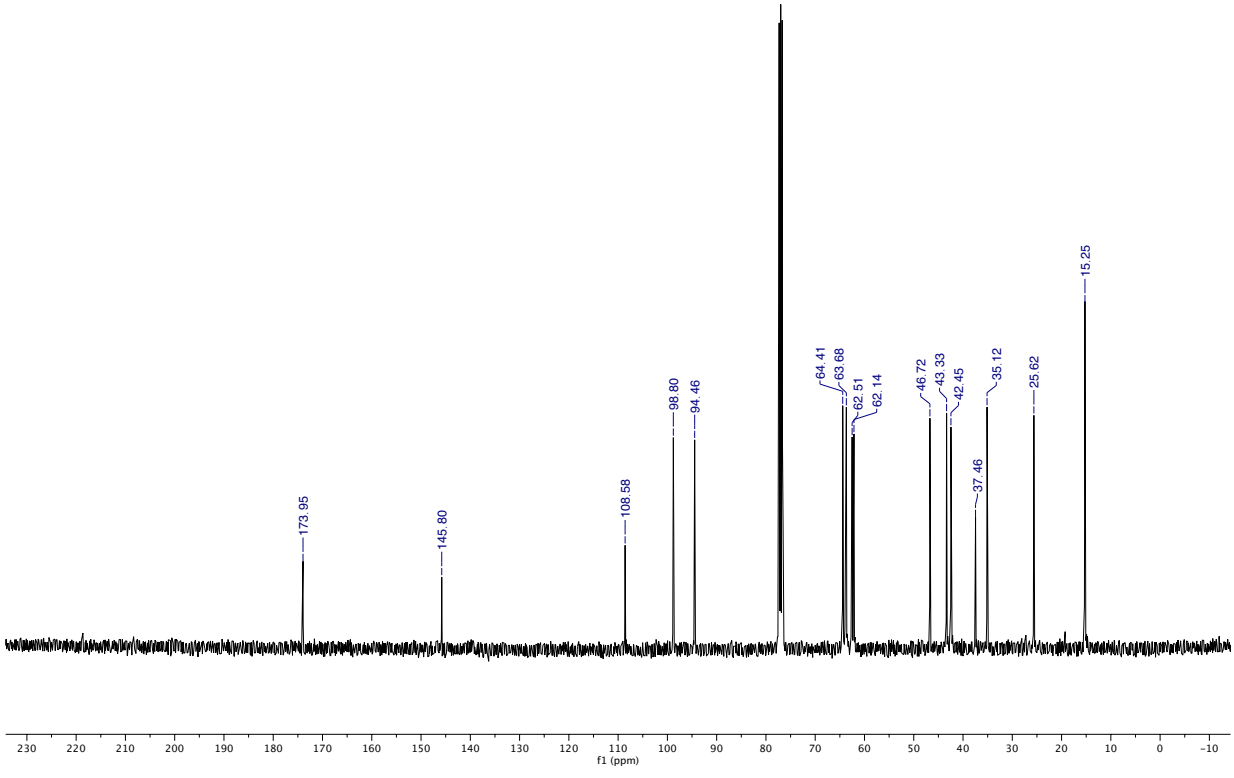
A solution of **46** (15.0 g, 34.9 mmol, 1 equiv) in benzene (400 mL) was heated to reflux with a heating block and a solution of AIBN (2.86 g, 17.4 mmol) and Bu_3SnH (32.9 mL, 122.2 mmol, 3.5 equiv) in benzene (100 mL) was added over 3 h using a syringe pump. The reaction was stirred for an additional hour at this temperature before being cooled and concentrated. The residue was purified by chromatography (hexane:EtOAc, 1:0 → 4:1) to give **47** as a colorless oil (8.9 g, 79%). In some runs, a small quantity of **47-ox** was isolated (less than 5%) as a colorless oil.

IR (neat): 2975, 2885, 1726, 1686, 1118, 1067 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 4.90 (t, J = 4.0 Hz, 1H, H-7), 4.72 (dd, J = 6.2, 5.0 Hz,1H, CH), 4.03–4.00 and 3.95–3.87 (2 m, 2H each, OCH_2), 3.78 (dd, J = 14.0, 6.4 Hz, 1H, NCH_2), 3.74–3.66 and 3.52 (2 m, 2H each, OEt), 3.36 (dd, J = 14.0, 5.0 Hz, 1H, NCH_2), 2.50 (br t, J = 3.7 Hz, 2H, H-6), 2.31 and 2.27 (2d, J = 16.4 Hz, 1H each, H-3), 2.04 and 1.85 (2 d, J = 13.4 Hz, 1H each, H-4), 1.30 (s, 3H, Me), 1.19 and 1.17 (2 t, J = 7.0 Hz, 3H each, OEt). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.0 (C-2), 145.8 (C-7a), 108.6 (C-5), 98.8 (CH), 94.5 (C-7), 64.4 and 63.7 (OCH_2), 62.5 and 62.1 (OEt), 46.7 (C-3), 43.3 (C-4), 42.4 (NCH_2), 37.5 (C-3a), 35.1 (C-6), 25.6 (Me), 15.2 and 15.2 (OEt). HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{17}H_{28}NO_5$ 326.1967, found 326.1975.

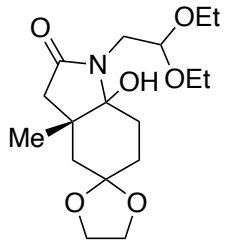

O
N
OEt
OEt
Me
O
O

47

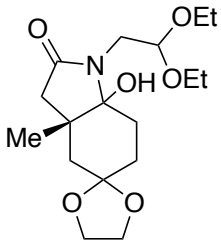
1.297
1.187
1.175
2.292
2.287
2.500
4.001
2.027
1.865
1.705
4.904
4.719
3.515
2.061
1.832
1.711
4.034
3.793
3.774
3.758
3.381
3.369
3.346
3.333
2.333
2.248
1.00
1.01
4.83
1.22
2.37
2.30
1.06
1.82
2.10
1.11
1.06
1.31
3.09
6.42
f1 (ppm)


15.25
64.41
63.68
62.51
62.14
46.72
43.33
42.45
35.12
25.62
98.80
94.46
37.46
173.95
145.80
108.58
f1 (ppm)

Evolution of product 47 (47-ox)

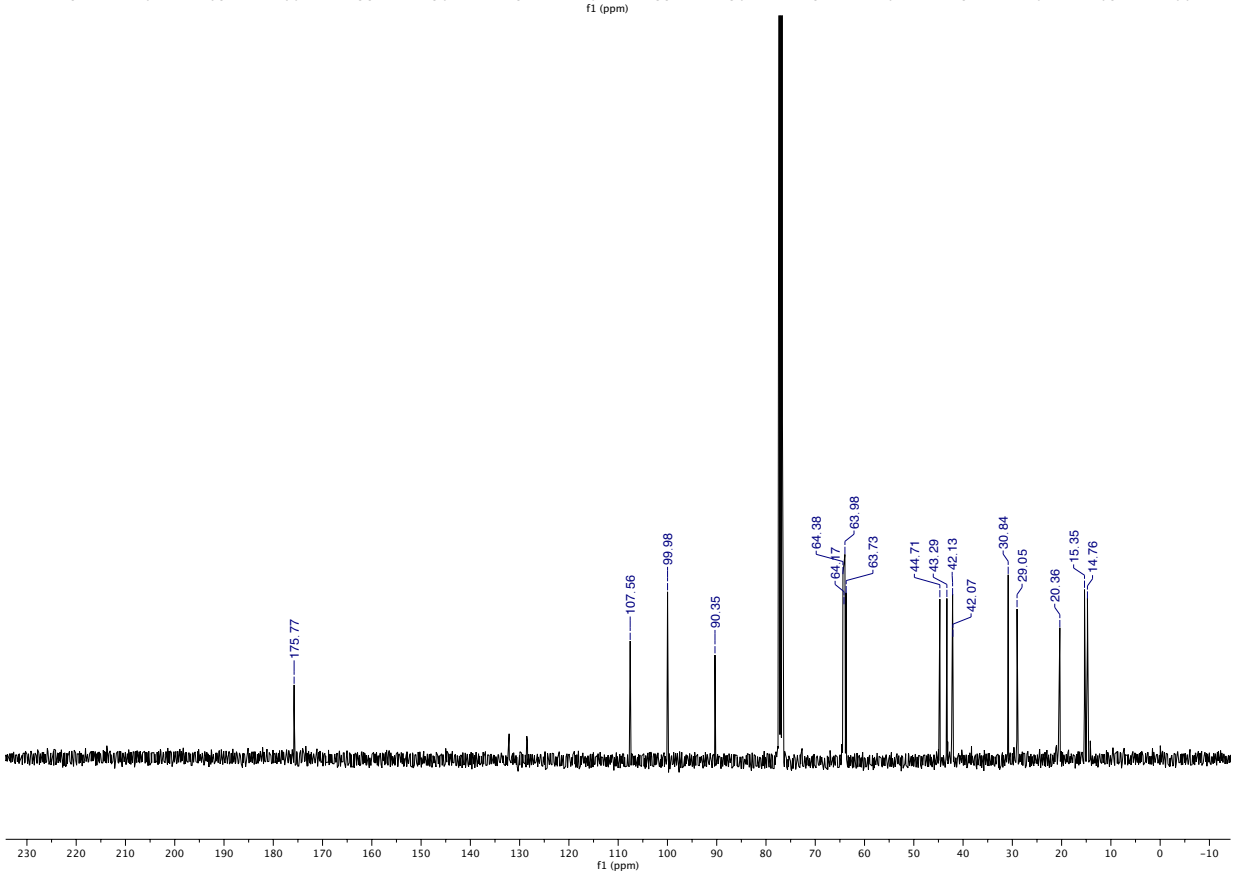


IR (neat): 3405, 2973, 2937, 1705, 1424, 1070 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.63 (dd, J = 7.7, 2.8 Hz, 1H, CH), 3.98–3.85 (m, 5H, OCH_2, NCH_2), 3.76–3.66 and 3.55–3.47 (2m, 2H each, OEt), 2.92 (dd, J = 14.6, 7.7 Hz, 1H, NCH_2), 2.39 and 2.14 (2d, J = 16.0 Hz, 1H each, H-3), 2.10–1.96 (m, 2H, H-7), 1.65 (m, 1H, H-6), 1.66 and 1.55 (2d, J = 14.2 Hz, 1H each, H-4), 1.38 (td, J = 12.8, 4.0 Hz, 1H, 1H-6), 1.25 (t, J =7.1 Hz, 3H, CH_3), 1.24 (s, 3H, Me), 1.23 (t, J = 7.2 Hz, 3H, OEt). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.8 (C-2), 107.6 (C-5), 100.0 (CH), 90.3 (C-7a), 64.4 (OCH_2), 64.2 (OCH_2CH_3), 64.0 (OCH_2), 63.7 (OEt), 44.7 (C-3), 43.3 (C-4), 42.1 (NCH_2 and C-3a), 30.8 (C-6), 29.1 (C-7), 20.4 (Me), 15.4 and 14.8 (OEt). HRMS (ESI-TOF) *m/z*: $[M+H-H_2O]^+$ calcd for $C_{17}H_{28}NO_5$ 326.1967, found 326.1965.

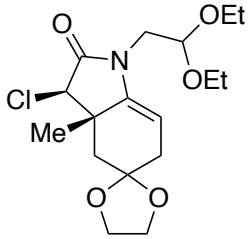

O
N
OH
OEt
OEt
Me
O
O

47-ox

1.247
1.229
4.291
3.940
1.265
1.211
1.645
4.639
4.626
1.568
2.413
2.373
2.163
2.123
1.676
3.968
3.916
3.842
3.659
3.530
3.489
2.949
2.930
2.912
2.893
1.00
8.89
1.59
1.12
1.19
1.16
4.71
1.30
10.22
f1 (ppm)


175.77
107.56
99.98
90.35
64.38
64.17
63.98
63.73
44.71
43.29
42.13
42.07
30.84
29.05
20.36
15.35
14.76
f1 (ppm)

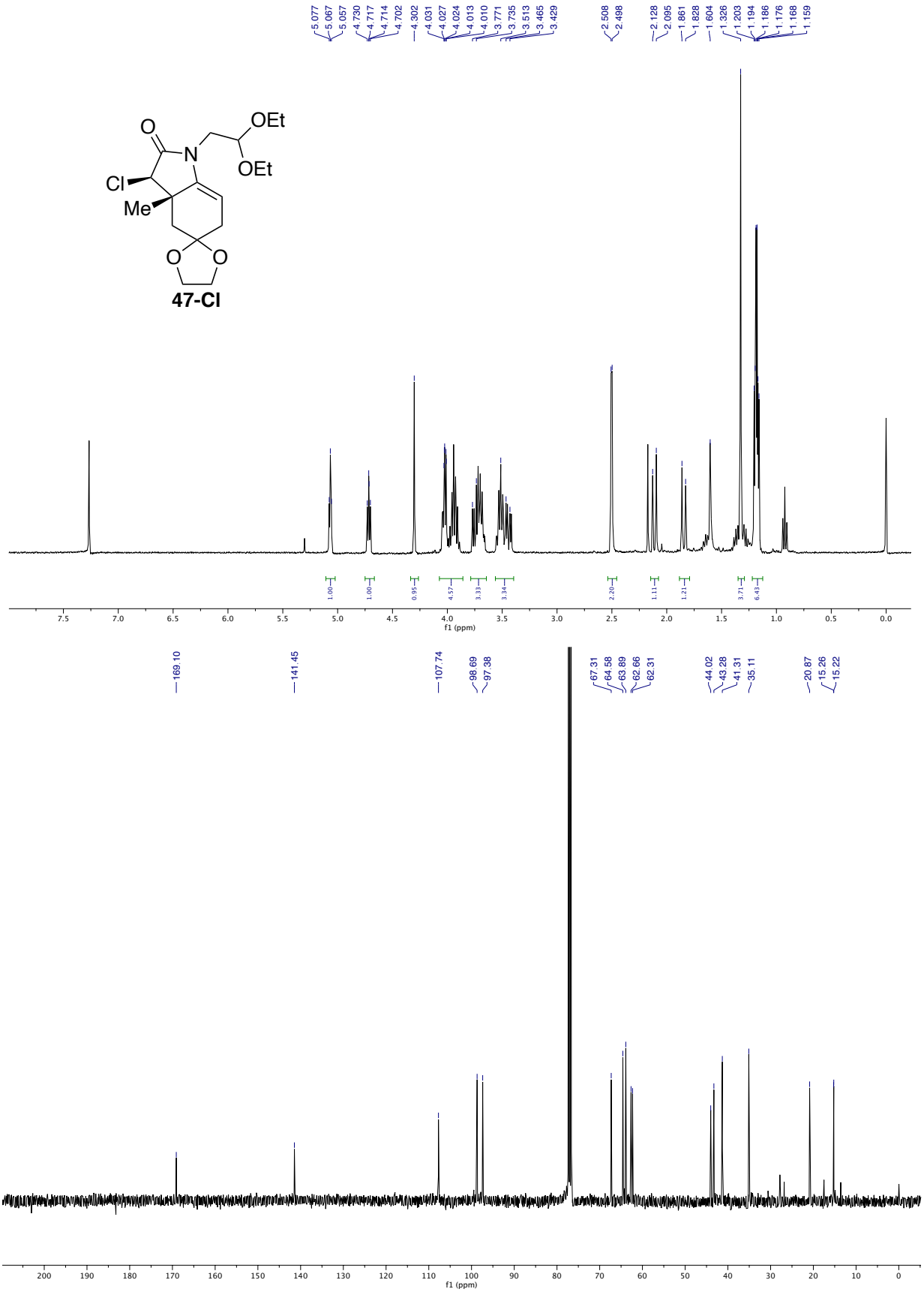
3-chloro-1-(2,2-Diethoxyehtyl)-3a-methyl-1,3a,4,6-tetrahydro-2*H*-indole-2,5(3*H*)-dione monoethylene acetal (47-Cl).



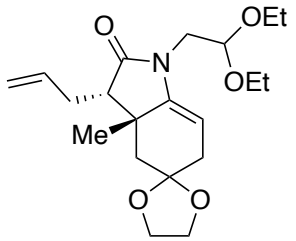
A solution of **46** (7.77 g, 18 mmol, 1 equiv) in benzene (220 mL) was heated to 80 ºC with a heating block and a solution of AIBN (0.89 g, 5.41 mmol, 0.3 equiv) and Bu_3SnH (15.5 mL, 57.7 mmol, 3.2 equiv) in benzene (20 mL) was added over 3 h using a syringe pump. The reaction was stirred for an additional hour at this temperature before being cooled and concentrated. The residue was purified by chromatography (hexane:EtOAc, 1:0 → 4:1) to give **47** as a colorless oil (3.15 g, 54%) along with **47-Cl** (1.02 g, 17 %)

IR (NaCl): 3059, 2977, 1738, 1689, 1407, 1126, 1072, 737 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 5.07 (t, *J* = 4 Hz, 1H, H-7), 4.72 (dd, *J* = 6.3 Hz, *J* = 5 Hz, 1H, CH), 4.30 (s, 1H, H-3), 4.01–4.05 and 3.89–3.98 (m, 2H each, OCH_2), 3.66–3.77 (m, 3H, OCH_2CH_3, NCH_2), 3.47-3.55 (m, 2H, OCH_2CH_3), 3.44 (dd, *J* = 14.4 Hz, *J* = 5.2 Hz, 1H, NCH_2), 2.50 (d, *J* = 4 Hz, 2H, H-6), 2.11 and 1.84 (2 d, *J* = 13.2 Hz, 1H each, H-4), 1.33 (s, 3H, Me), 1.19 and 1.18 (2 t, *J* = 7 Hz, 3H each, OCH_2CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1 (C-2), 141.5 (C-7a), 107.7 (C-5), 98.7 (CH), 97.4 (C-7), 67.3 (C-3), 64.6 and 63.9 (OCH_2), 62.7 and 62.3 (OCH_2CH_3), 44.0 (C-3a), 43.3 (C-4), 41.3 (NCH_2), 35.1 (C-6), 20.9 (Me), 15.3 and 15.2 (OCH_2CH_3).

Recycling procedure: Compound **47-Cl** (731 mg, 2.03 mmol) was diluted in toluene (25 mL) and AIBN (167 mg, 1.02 mmol) and TBTH (0.98 mL, 3.65 mmol) were added to the solution. The reaction was heated to reflux and stirred until consumption of the starting material. After being concentrated under vacuum, the crude was purified by chromatographic column (hexane:EtOAc, 1:0→ 3:1) to recover compound **47** (530 mg, 80%).

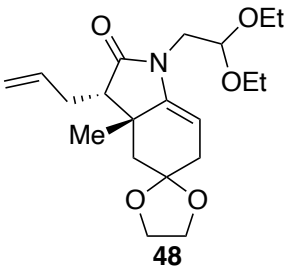

5.077
5.067
5.057
4.730
4.717
4.714
4.702
4.302
4.031
4.027
4.024
4.013
4.010
3.771
3.735
3.513
3.465
3.429
2.508
2.498
2.128
2.095
1.861
1.828
1.604
1.326
1.203
1.194
1.186
1.176
1.168
1.159
O
N
OEt
OEt
Cl
Me
O
O
47-Cl
1.00
1.00
0.95
4.57
3.33
3.34
2.20
1.11
1.21
3.71
6.43
f1 (ppm)
169.10
141.45
107.74
98.69
97.38
67.31
64.58
63.89
62.66
62.31
44.02
43.28
41.31
35.11
20.87
15.26
15.22
f1 (ppm)

(3*RS*,3a*SR*)-3-Allyl-1-(2,2-diethoxyehtyl)-3a-methyl-1,3a,4,6-tetrahydro-2*H*-indole-2,5(3*H*)-dione monoethylene acetal (48)



A solution of lactam **47** (8.92 g, 27.4 mmol, 1 equiv) was cooled to -78 ºC and a solution of LHMDS in THF (1 M, 35.6 mL, 1.3 equiv) was added dropwise. After being stirred for 30 min at -78 ºC, allylbromide (5 mL, 54.8 mmol, 2 equiv) was added. The reaction was let to reach room temperature over 2 h, then it was quenched with NH_4Cl saturated solution (30 mL) and extracted with Et_2O (3 x 20 mL). The crude was purified with a flash chromatographic column (Al_2O_3, hexane:EtOAc 9:1) to obtain compound **48** (7.8 g, 77%) as a transparent oil.

IR (neat): 2975, 1724, 1684, 1406, 1340, 1128, 1069 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 5.87–5.75 (m, 1H, =CH), 5.06 (d, J = 16.4 Hz, 1H, $=CH_2$ H-*trans*), 5.03 (d, J = 9.2 Hz, 1H, $=CH_2$ H-*cis*), 4.93 (t, J = 3.6 Hz, 1H, H-7), 4.71 (dd, J = 6.4, 4.8 Hz, 1H, CH), 4.04–4.01 and 3.99–3.87 (2 m, 2H each, OCH_2), 3.75–3.63 (m, 3H, OEt and NCH_2), 3.58–3.48 (m, 2H, OEt), 3.44 (dd, J = 14.0, 4.8 Hz, 1H, NCH_2), 2.47 (d, J = 3.8 Hz, 2H, H-6), 2.32–2.14 (m, 3H, 3-CH_2 and H-3), 2.01 and 1.74 (2 d, J = 13.6 Hz, 1H each, H-4), 1.32 (s, 3H, Me), 1.18 (2 t, J = 7.0 Hz, 3H each, OEt). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.5 (C-2), 144.5 (C-7a), 135.3 (=CH), 116.7 ($=CH_2$), 108.7 (C-5), 98.8 (CH), 95.4 (C-7), 64.5 and 63.6 (OCH_2), 62.5 and 62.2 (OEt), 54.0 (C-3), 42.6 (NCH_2), 40.6 (C-3a), 37.7 (C-4), 35.0 (C-6), 32.8 (CH_2-3), 27.8 (Me), 15.2 (OEt). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{20}H_{32}NO_5$ 366.2280, found 366.2289.


O
N
OEt
OEt
Me
O
O

48

1.317
1.188
1.174
1.171
1.102
1.206
1.185
1.157
2.472
2.463
2.310
2.270
2.185
2.025
1.991
1.757
1.723
5.853
5.762
5.081
5.040
5.017
4.929
4.920
4.712
4.708
4.696
4.041
3.893
3.693
3.546
3.465
3.453
3.430
3.418
1.00
2.08
1.02
1.03
2.08
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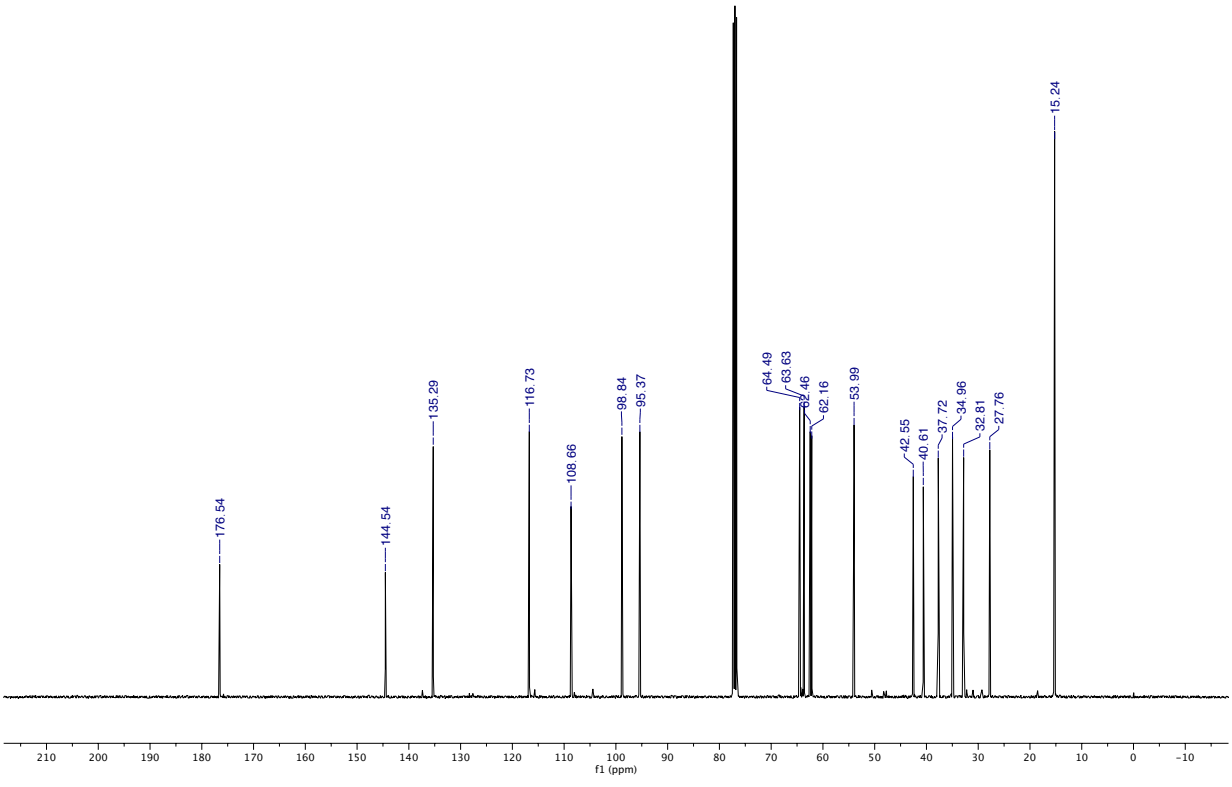
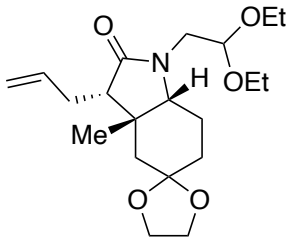
3.14
3.15
2.06
3.18
1.04
1.66
3.15
6.29
f1 (ppm)

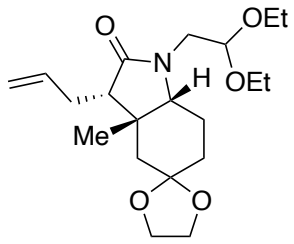

176.54
144.54
135.29
116.73
108.66
98.84
95.37
64.49
63.63
63.46
62.16
53.99
42.55
40.61
37.72
34.96
32.81
27.76
15.24
f1 (ppm)

(3*RS*,3a*SR*,7a*SR*)-3-Allyl-1-(2,2-diethoxyehtyl)-3a-methylhexahydro-2*H*-indole-2,5(3*H*)-dione monoethylene acetal (49).



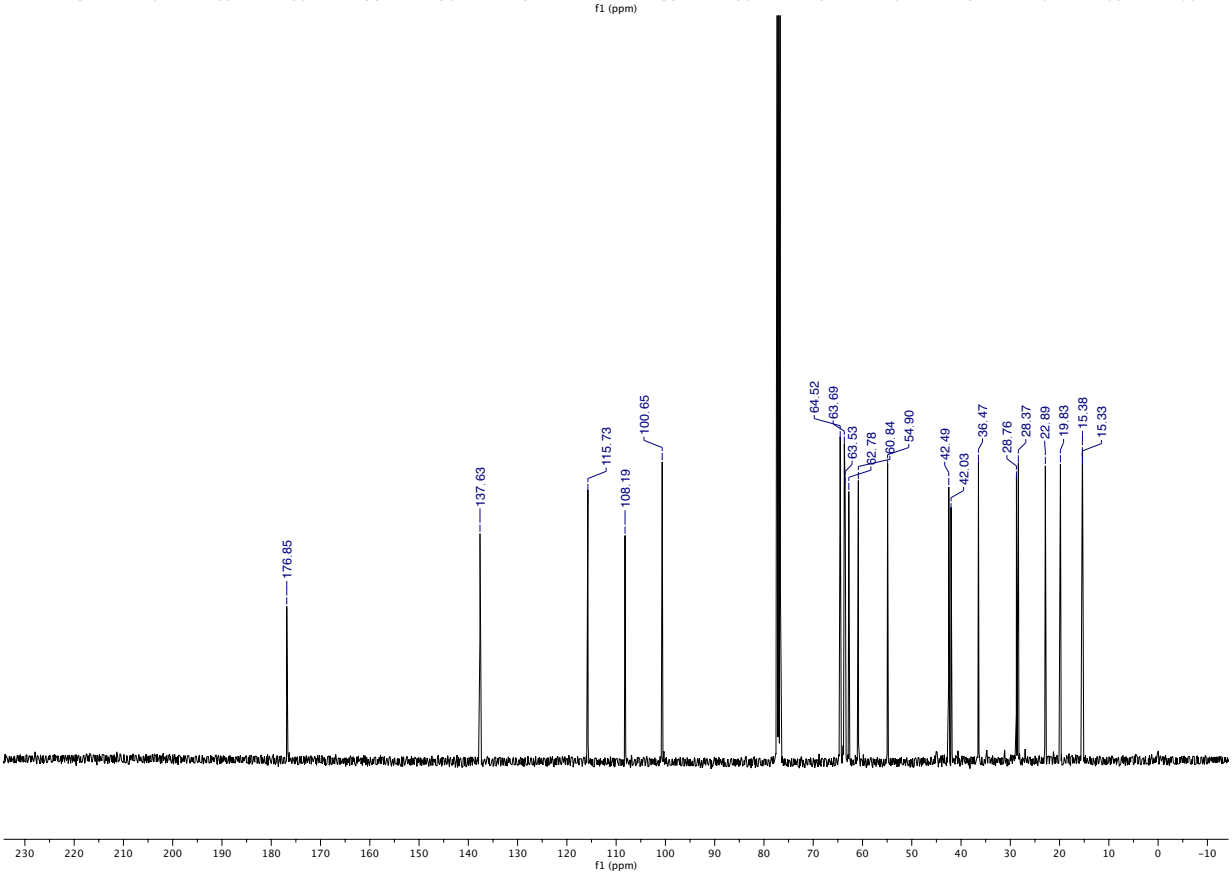
Compound **48** (7.76 g, 21.2 mmol) was diluted in AcOH (35 mL) and $NaCNBH_3$ (2.67 g, 42.5 mmol) was added portionwise. The mixture was stirred at room temperature for 2h 30 min, then MeOH (50 mL) was added and, after being stirred at room temperature for 15 min, the mixture was concentrated. The residue was taken up in CH_2Cl_2, quenched with 15% NaOH and extracted with CH_2Cl_2 (4 x 30 mL). The organics were combined, dried and concentrated. The crude was purified by chromatography (hexane:EtOAc, 1:0 $\rightarrow$ 1:1) to provide with compound **49** (5.32 g, 69%) as a colorless oil.

IR (neat) 2973, 2880, 1692, 1126, 1092, 1063 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 6.01–5.91 (m, 1H, =CH), 5.11 (ddt, *J* = 17, 0.8, 1.6 Hz, 1H, $=CH_2$ H-*trans*), 5.01 (ddt, *J* = 10.4, 1.6, 1.6, 1H, $=CH_2$ H-*cis*), 4.58 (dd, *J* = 6.6, 4.4 Hz, 1H, CH), 3.96–3.85 (m, 5H, NCH_2, OCH_2) 3.72, 3.69, 3.56, and 3.48 (4 dq, *J* = 9.4, 7.0 Hz, 1H each, OEt), 3.30 (t, *J* = 3.0 Hz, 1H, H-7a), 2.85 (dd, *J* = 14.2, 6.4 Hz, 1H, NCH_2), 2.59–2.52 (m, 1H, 3-CH_2), 2.20–2.04 (m, 3H, 3-CH_2, 1H-7, H-3), 1.89 (ddt, *J* = 14.8, 10.3, 3.6 Hz, 1H, H-7), 1.51 (ddt, *J* = 13.4, 3.2, 3.2 Hz, 1H, H-6), 1.48 (d, *J* = 14.8 Hz, 1H, H-4), 1.39 (d, *J* = 14.8 Hz, 1H, H-4), 1.36 (dd, *J* = 13.4, 3.4 Hz, 1H, H-6), 1.27 (s, 3H, Me), 1.20 and 1.18 (2t, *J* = 7 Hz, 3H each, OEt). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.9 (C-2), 137.6 (=CH), 115.7 ($=CH_2$), 108.2 (C-5), 100.7 (CH), 64.5 and 63.7 (OCH_2), 63.5 and 62.8 (OCH_2CH_3), 60.8 (C-7a), 54.9 (C-3), 42.5 (NCH_2), 42.0 (C-3a), 36.5 (C-4), 28.8 (3-CH_2), 28.4 (C-6), 22.9 (Me), 19.8 (C-7), 15.4 and 15.3 (OEt). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{20}H_{34}NO_5$ 368.2437, found 368.2447.

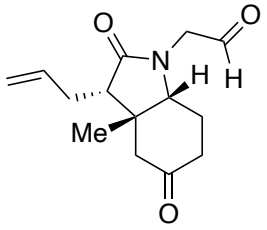

O
N
H
OEt
OEt
Me
O
O

49

6.010
5.907
5.128
5.083
5.026
5.000
4.592
4.581
4.576
4.565
3.949
3.923
3.702
3.563
3.503
3.296
2.879
2.863
2.843
2.828
2.523
2.172
2.111
2.093
1.926
1.889
1.500
1.465
1.407
1.271
1.217
1.200
1.185
1.167
f1 (ppm)

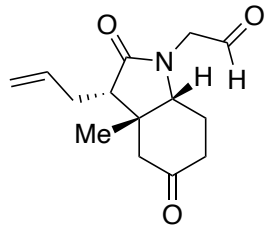

176.85
137.63
115.73
108.19
100.65
64.52
63.69
63.53
62.78
60.84
54.90
42.49
42.03
36.47
28.76
28.37
22.89
19.83
15.38
15.33
f1 (ppm)

(3*RS*,3a*SR*,7a*SR*)-3-Allyl-1-(2-oxoethyl)tetrahydro-1*H*-indole-2,5(3*H*,6*H*)dione (50).



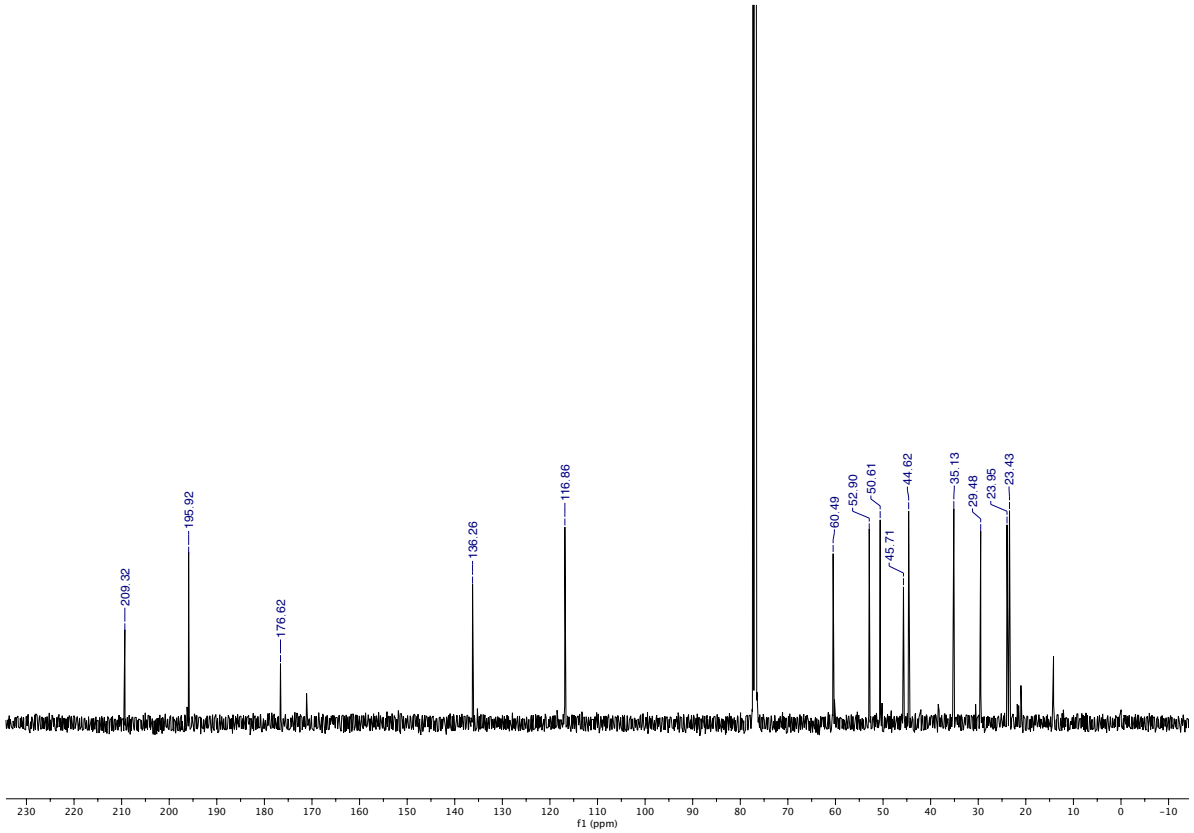
A solution of **49** (3.72 g, 10.1 mmol) in 10% HCl:THF (1:4, 200 mL) was stirred overnight at room temperature. The mixture was diluted with water (100 mL) and extracted with CH_2Cl_2 (3 x 80 mL). The combined organic phases were dried and concentrated and the obtained crude was purified by a flash chromatography (hexane:EtOAc, 3:1) to afford compound **50** (2.47 g, 98%) as a transparent oil.

IR (neat): 3404, 2934, 1716, 1686, 1430, 1059 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 9.65 (s, 1H, CHO), 5.90 (dddd, J = 17.1, 10.1, 8.7, 5.2 Hz, 1H, =CH), 5.14 (d, *J* = 17.1 Hz, 1H, =CH_2 H-*trans*), 5.07 (d, *J* = 10 Hz, 1H, =CH_2 H-*cis*), 4.56 and 3.94 (2 d, *J* = 18.9 Hz, 1H each, NCH_2), 3.57 (t, *J* = 3.6 Hz, 1H, H-7a), 2.66 (dm, *J* = 15.0 Hz, 1H, 3-CH_2), 2.50–2.44 (m, 2H, H-3, H-4), 2.35–2.25 and 2.22–2.20 (m, 1H, H-6), 2.19 (dtd, *J* = 14.6, 4.3, 1.8 Hz, 1H, H-6), 2.17–2.05 (m, 4H, 3-CH_2, H-4, H-7), 1.24 (s, 3H, Me). ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.3 (CHO), 195.9 (C-5), 176.6 (C-2), 136.2 (=CH), 116.8 (=CH_2), 60.5 (C-7a), 52.9 (C-3), 50.6 (NCH_2), 45.7 (C-3a), 44.6 (C-4), 35.1 (C-6), 29.5 (CH_2-3), 23.9 (Me), 23.4 (C-7). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{14}H_{20}NO_3$ 250.1443, found 250.1451.

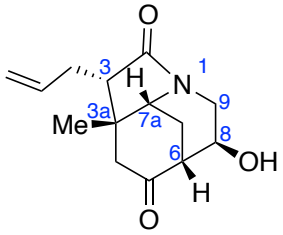

O
O
N
H
H
Me
O

50

9.655
5.955
5.852
5.168
5.125
5.085
5.060
4.584
4.537
3.959
3.912
3.573
2.682
2.645
2.493
2.458
2.273
2.173
2.130
2.095
1.244
1.00
1.89
0.90
0.98
0.85
0.94
1.77
1.33
4.48
2.55
f1 (ppm)

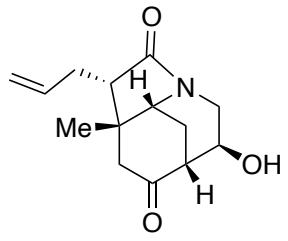

209.32
195.92
176.62
136.26
116.86
60.49
52.90
50.61
45.71
44.62
35.13
29.48
23.95
23.43
f1 (ppm)

(3*SR*,3a*RS*,6*RS*,7a*RS*,8*SR*)-3-allyl-8-hydroxy-3a-methyltetrahydro-6,1-ethanoindole-2,5(3*H*,6*H*)-dione (51)



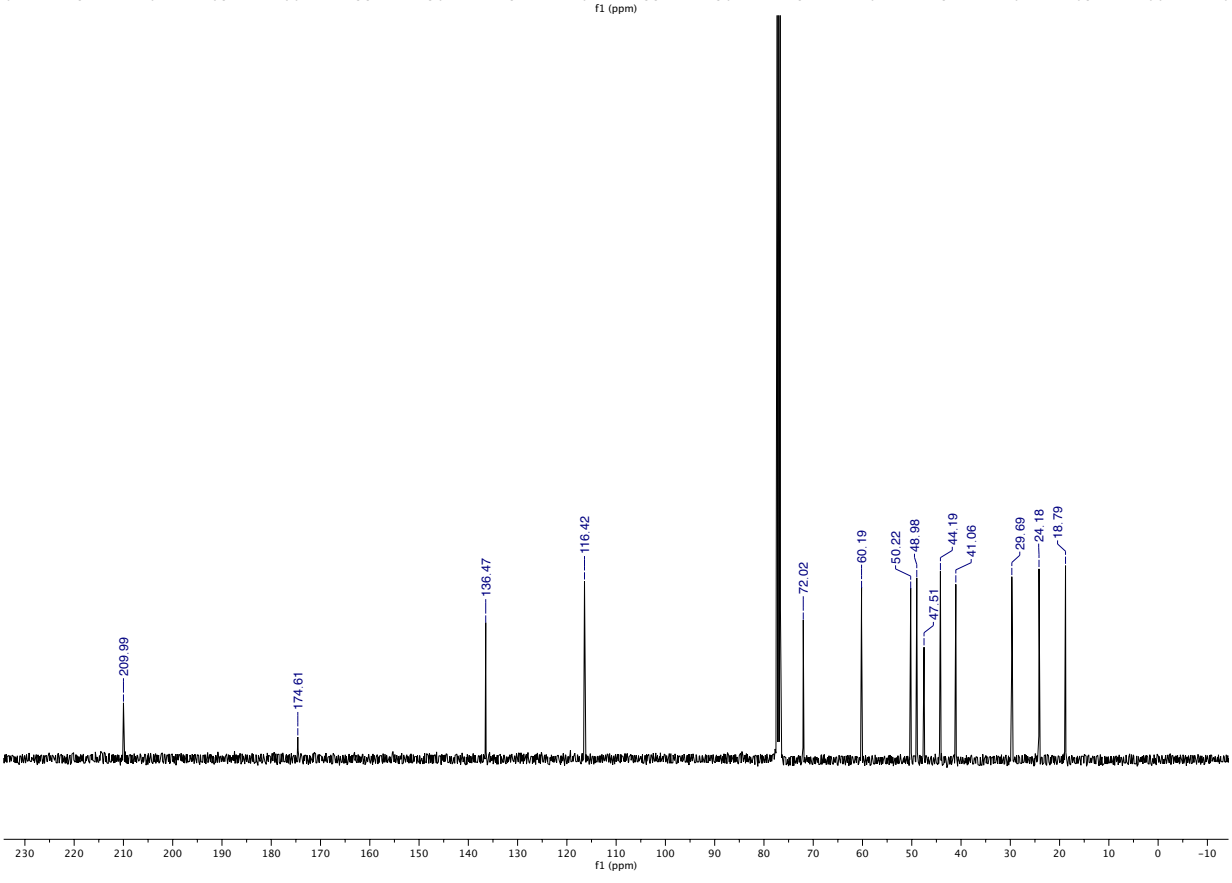
A solution of compound **50** (2.47 g, 9.91 mmol) and *p*TsOH·H_2O (1.88 g, 9.91 mmol) in benzene (170 mL) was heated to reflux with a heating block for 15 min. The mixture was cooled to room temperature and extracted with CH_2Cl_2 (3 x 80 mL) and $CHCl_3$:*i*-PrOH (4:1, 3 x 80 mL). The combined organic extracts were concentrated and purified by chromatography (CH_2Cl_2:EtOAc 9.5:0.5 → 4:1) to obtain **51** as a solid (1.76 g, 82%), and latterly **51-*epi*** (0.17 g, 8%).

mp 100–103 ºC. IR (neat): 3407, 2925, 1705, 1451, 1423, 1125, 1063, 1044 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 5.89 (dddd, *J* = 17.0, 10.1, 8.9, 5.2 Hz, 1H, =CH), 5.14 (ddt, *J* = 17, 0.8, 0.8 Hz, 1H, =CH_2 H-*trans*), 5.04 (ddt, *J* = 10.1, 0.8, 0.8 Hz, 1H =CH_2 H-*cis*), 4.67 (dd, *J* = 8.4, 7.6 Hz, 1H, H-8), 4.30 (dd, *J* = 13.8, 8.6 Hz, 1H, H-9eq), 3.71 (d, *J* = 5.6 Hz, 1H, H-7a), 2.72 (br s, 1H, OH), 2.63–2.53 (m, 1H, CH_2-3) 2.55 (dd, *J* = 13.8, 7.2 Hz, 1H, H-9ax) 2.44 (d, *J* = 14.8 Hz, 1H H-4), 2.40 (ddd, *J* = 14.6, 5.7, 1.3 Hz, 1H, H-7), 2.35–2.30 (m, 2H, H-3, H-6), 2.13 (d, *J* = 14.8 Hz, 1H, H-4), 2.15–2.05 (m, 2H, H-7, CH_2-3), 1.29 (s, 3H, Me). ^{13}C NMR (101 MHz, $CDCl_3$) δ 210.0 (C-5), 174.6 (C-2), 136.5 (=CH), 116.4 (=CH_2), 72.0 (C-8), 60.2 (C-7a), 50.2 (C-3), 49.0 (C-6), 47.5 (C-3a), 44.2 (C-4), 41.0 (C-9), 29.7 (CH_2-3), 24.2 (Me), 18.8 (C-7). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{14}H_{20}NO_3$ 250.1440, found 250.1438.

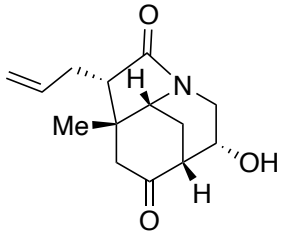

O
H
N
Me
OH
H
O

51

1.289
2.151
2.114
2.416
2.452
2.346
2.339
2.325
2.309
2.581
2.377
2.127
3.719
3.705
4.332
4.298
4.277
4.666
4.646
5.161
5.051
5.049
5.026
5.937
5.833
f1 (ppm)

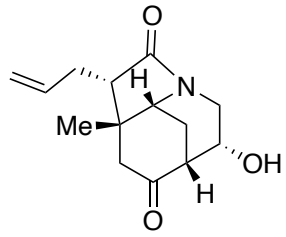

209.99
174.61
136.47
116.42
72.02
60.19
50.22
48.98
47.51
44.19
41.06
29.69
24.18
18.79
f1 (ppm)

(3*SR*,3a*RS*,6*RS*,7a*RS*,8*RS*)-3-allyl-8-hydroxy-3a-methyltetrahydro-6,1-ethanoindole-2,5(3*H*,6*H*)-dione (51-*epi*)



IR (neat): 3420, 2923, 1688, 1423, 1077, 909 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.97–5.87 (m, 1H, =CH), 5.15 (d, *J* = 17.2 Hz, 1H, $=CH_2$ H-*trans*), 5.06 (d, *J* = 10.4 Hz, 1H, $=CH_2$ H-*cis*), 4.22 (t, *J* = 6.4 Hz, 1H, H-8), 4.05 (dd, *J* = 14.8, 1.2 Hz, 1H, H-9eq), 3.52 (d, *J* = 5.6 Hz, 1H, H-7a), 3.11 (dd, *J* = 14.8, 6.6 Hz, 1H, H-9ax), 2.67 (dddt, *J* = 14.8, 6.4, 5.2, 1.2 Hz, 1H, CH_2-3), 2.54 (t, *J* = 6 Hz, 1H, H-6), 2.48 (d, *J* = 14.4 Hz, 1H, H-4), 2.35 (ddd, *J* = 8.2, 6.6, 1.2 Hz, 1H, H-3), 2.28 (dd, *J* = 14.8, 5.2 Hz, 1H, H-7), 2.16 (d, *J* = 14.4 Hz, 1H, H-4), 2.19–2.12 (m, 1H, CH_2-3), 1.75 (ddd, *J* = 14.8, 5.9, 1.2 Hz, 1H, H-7), 1.31 (s, 3H, Me). ^{13}C NMR δ 215.9 (C-5), 174.6 (C-2), 136.4 (=CH), 116.5 ($=CH_2$), 76.6 (C-8), 59.0 (C-7a), 50.4 (C-3), 47.9 (C-3a), 45.0 (C-4), 44.3 (C-9), 41.7 (C-6), 29.9 (CH_2-3), 23.4 (Me), 23.0 (C-7). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{14}H_{20}NO_3$ 250.1440, found 250.1435.

.


O
H
N
Me
OH
H
O

51-*epi*

1.305
2.174
2.138
5.175
5.132
5.064
5.039
4.220
4.205
4.070
4.067
4.033
4.030
3.599
3.585
5.968
5.878
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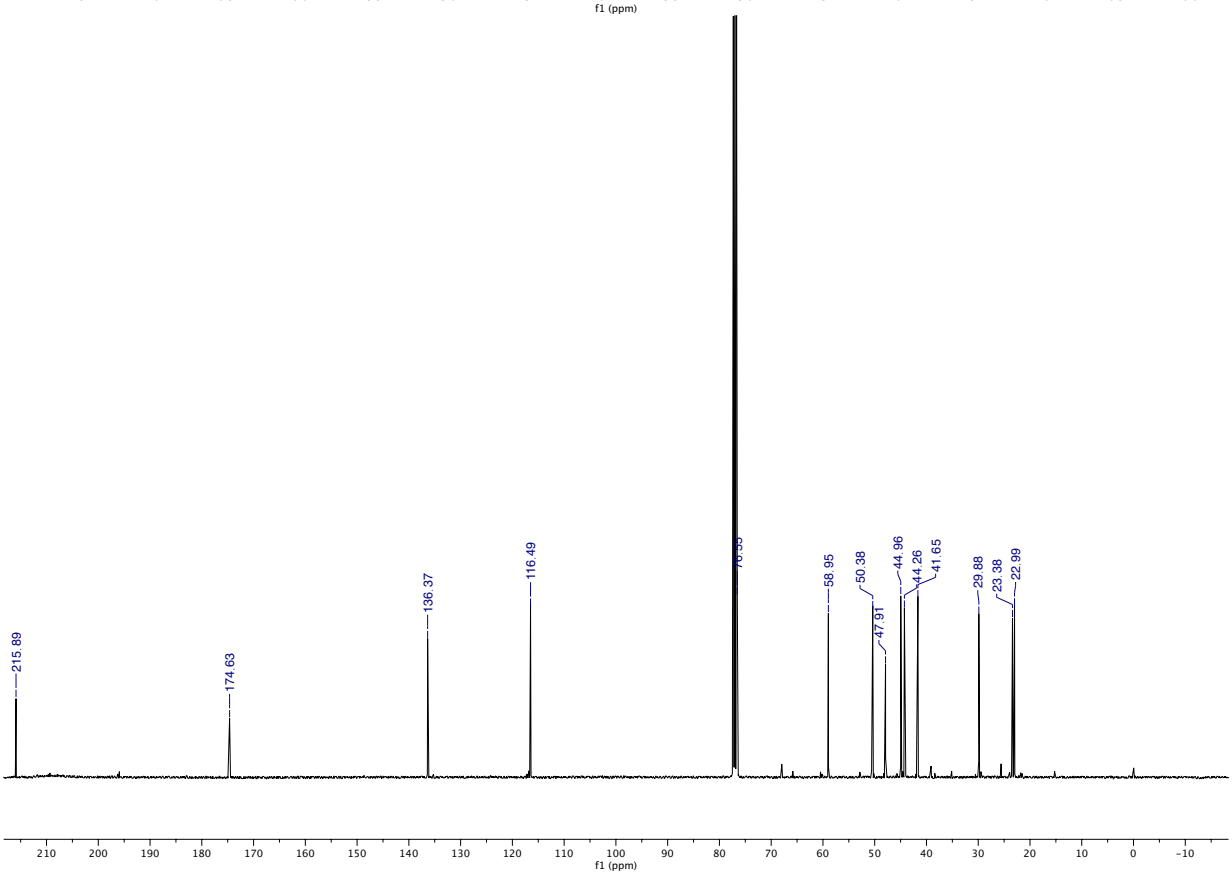
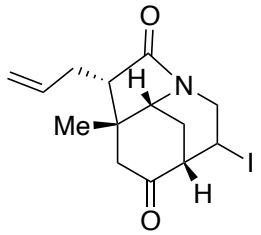
2.270
2.257
1.773
1.771
1.759
f1 (ppm)

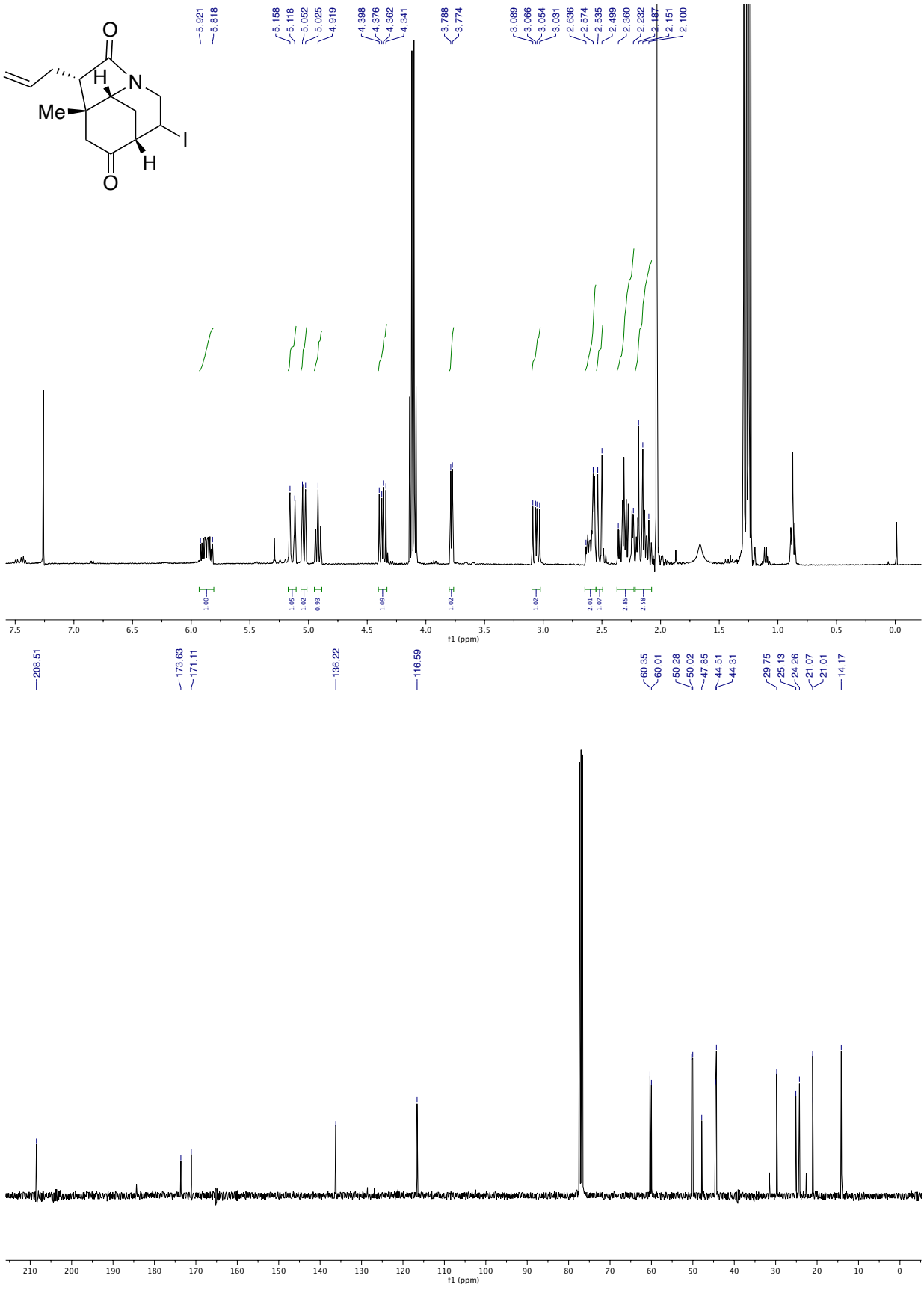

215.89
174.63
136.37
116.49
58.95
50.38
47.91
44.96
44.26
41.65
29.88
23.38
22.99
f1 (ppm)

(3*SR*,3a*RS*,6*RS*,7a*RS*,8*RS*)-3-allyl-8-iodo-3a-methyltetrahydro-6,1-ethanoindole-2,5(3*H*,6*H*)-dione (52)

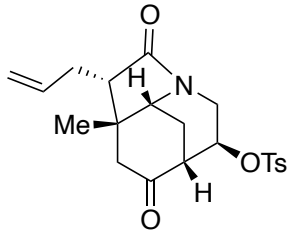


To a suspension of PPh_3 (143 mg, 0.54 mmol, 1.8 equiv and imidazole (102 mg, 1.50 mmol, 5 equiv) in toluene (1.5 mL), iodine was added (138 mg, 0.54 mmol, 1.8 equiv). Then, the reaction was heated at 60 ºC and, after 10 minutes, a soluton of **51** (75 mg, 0.3 mmol, 1 equiv) was added in one portion. After being sitred at the same temperature for 2h 30 min, water (10 mL) was added, phases were separated and the aqueous was extracted with CH_2Cl_2 (4 x 15 mL). Combined organics were washed with $NaHCO_3$ (20 mL) and brine (20 mL), dried and concentrated. The obtained crude was purified by chromatographic column (hexane:EtOAc, 9:1→1:1) to afford iodide compound **52** (15 mg, 14%) as a waxy solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.92–5.82 (m, 1H, =CH), 5.14 (d, *J* = 16.8 Hz, 1H, =CH_2), 5.04 (d, *J* = 10.0 Hz, 1H, =CH_2), 4.92 (t, *J* = 8.8 Hz, 1H, H-8), 4.37 (dd, *J* = 14.0, 8.4 Hz, 1H, H-9), 3.78 (d, *J* = 5.6 Hz, 1H, H-7a), 3.06 (dd, *J* = 14.0, 9.0 Hz, 1H, H-9), 2.64–2.60 (m, 1H, CH_2-3), 2.57 (bd, 1H, H-6), 2.52 (d, *J* = 14.4 Hz, 1H, H-4), 2.36–2.23 (m, 3H, H-7 and H-3), 2.17 (d, *J* = 14.4 Hz, 1H, H-4), 2.11 (m, 1H, CH_2-3), 1.29 (s, 3H, Me). ^{13}C NMR δ 208.5 (C-5), 173.6 (C-2), 136.2 (=CH); 116.6 (=CH_2), 60.0 (C-7a), 50.3 (C-3), 50.0 (C-6), 47.9 (C-3a), 44.5 (C-9), 44.3 (C-4), 29.8 (CH_2-3), 25.1 (C-8), 24.3 (Me), 21.1 (C-7). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{14}H_{19}INO_2$ 360.0455, found 360.0458.

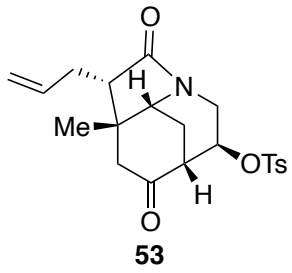

O
H
N
Me
I
H
O
5.921
5.818
5.158
5.118
5.052
5.025
4.919
4.398
4.376
4.362
4.341
3.788
3.774
3.089
3.066
3.054
3.031
2.636
2.574
2.535
2.499
2.360
2.232
2.187
2.151
2.100
1.00
1.05
1.02
0.93
1.09
1.02
1.02
2.01
1.07
2.85
2.58
f1 (ppm)
208.51
173.63
171.11
136.22
116.59
60.35
60.01
50.28
50.02
47.85
44.51
44.31
29.75
25.13
24.26
21.07
21.01
14.17
f1 (ppm)

(3*SR*,3a*RS*,6*RS*,7a*RS*,8*RS*)-3-allyl-3a-methyl-8-tosyloxytetrahydro-6,1-ethanoindole-2,5(3*H*,6*H*)-dione (53)



To a cooled (0 ºC) stirred solution of tricyclic alcohol **51** (0.9 g, 3.62 mmol) in CH_2Cl_2 (25 mL) was sequentially added TsCl (2.1 g, 10.9 mmol), Et_3N (0.76 mL, 5.43 mmol), and DMAP (1.1 g, 9.04 mmol) and the reaction was stirred at room temperature overnight. After quenching with $NaHCO_3$ (40 mL), the mixture was extracted with CH_2Cl_2 (4 x 30 mL), and the combined organics were dried, filtered, concentrated, and chromatographed (CH_2Cl_2:EtOAc, 1:0 → 9.5:0.5) to afford **53** (1.17 g, 80%) as a white solid.

mp. 70-71 ºC (Et_2O). IR (neat) 2959, 1711, 1698, 1415, 1362, 1177, 910 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.81 and 7.37 (2d, *J* = 8.4 Hz, 2H each, Ts), 5.85 (dddd, *J* = 17.0, 10.0, 8.8, 5.2 Hz, 1H, =CH), 5.12 (dm, *J* = 17.0 Hz, 1H, =CH_2-*trans*), 5.06 (ddt, *J* = 8.7, 7.0, 1.5 Hz, 1H, H-8), 5.04 (dm, *J* = 10.0 Hz, 1H, =CH_2-*cis*), 4.23 (dd, *J* = 14.4, 9.0 Hz, H-9), 3.69 (b d, *J* = 5.6 Hz, 1H, H-7a), 2.68 (dd, *J* = 14.4, 7.0 Hz, H-9), 2.59 (br d, *J* = 5.0 Hz, 1H, H-6), 2.57–2.52 (m, 1H, CH_2-3), 2.46 (s, 3H, Ts), 2.41 (d, *J* = 14.4 Hz, 1H, H-4), 2.36 (ddd, *J* = 15.0, 5.8, 1.4 Hz, 1H, H-7), 2.28 (dd, *J* = 8.4, 6.5 Hz, 1H, H-3), 2.17 (ddd, *J* = 15.0, 4.8, 1.4 Hz, H-7), 2.11 (d, *J* = 14.4 Hz, 1H, H-4), 2.09–2.04 (m, 1H, CH_2-3), 1.27 (s, 3H, Me). ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.0 (C-6), 174.6 (C-2), 145.5, 132.6, 130.2 and 128.1 (Ph), 136.2 (=CH), 116.6 (=CH_2), 79.7 (C-8), 59.6 (C-7a), 50.0 (C-3), 47.9 (C-3a), 45.6 (C-6), 43.8 (C-4), 38.7 (C-9), 29.6 (CH_2-3), 24.0 (Me), 21.7 (Ts), 19.1 (C-7). HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{21}H_{26}NO_5S$ 404.1532, found 404.1537.


O
H
N
Me
OTs
H
O

53

7.821
7.800
7.378
7.355
5.906
5.803
5.144
5.101
5.082
5.060
5.042
5.017
4.264
4.242
4.228
4.206
3.694
3.680
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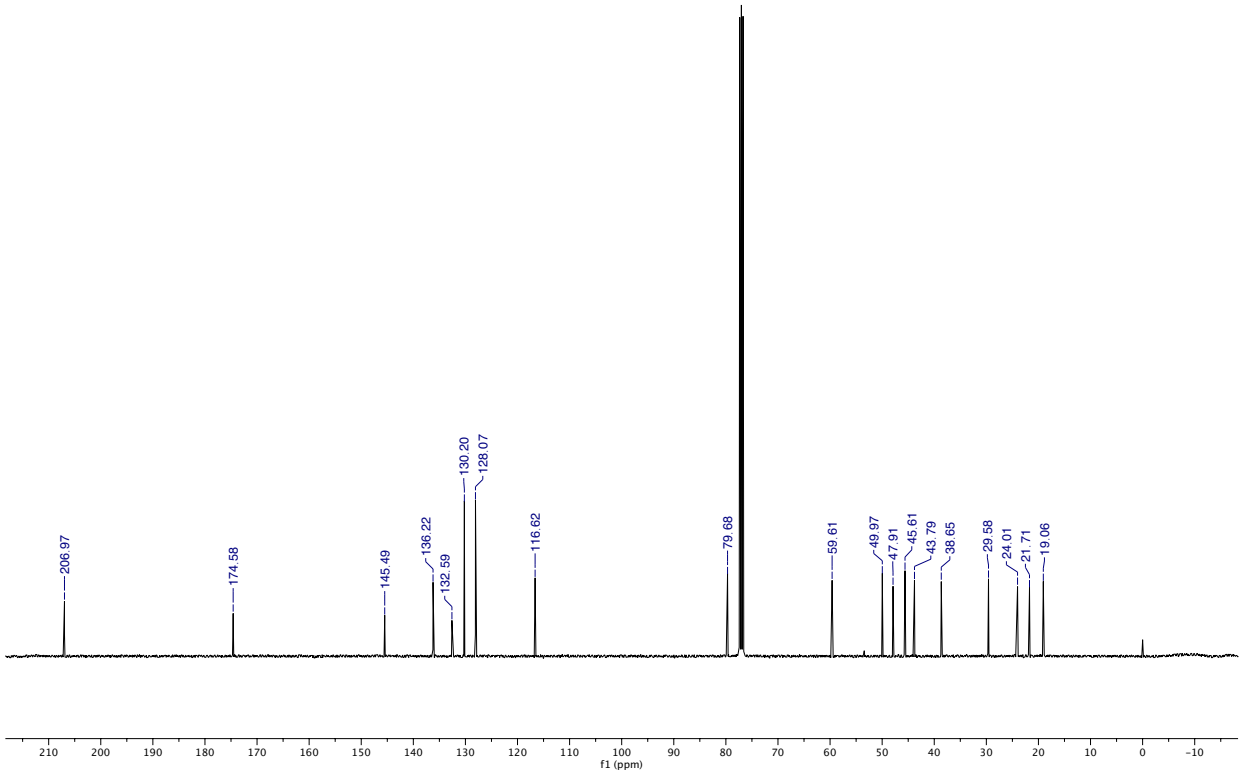
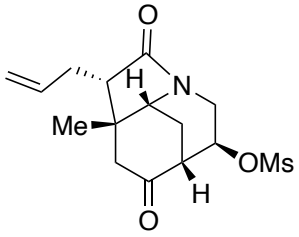
2.348
2.282
2.124
2.088
1.272
f1 (ppm)

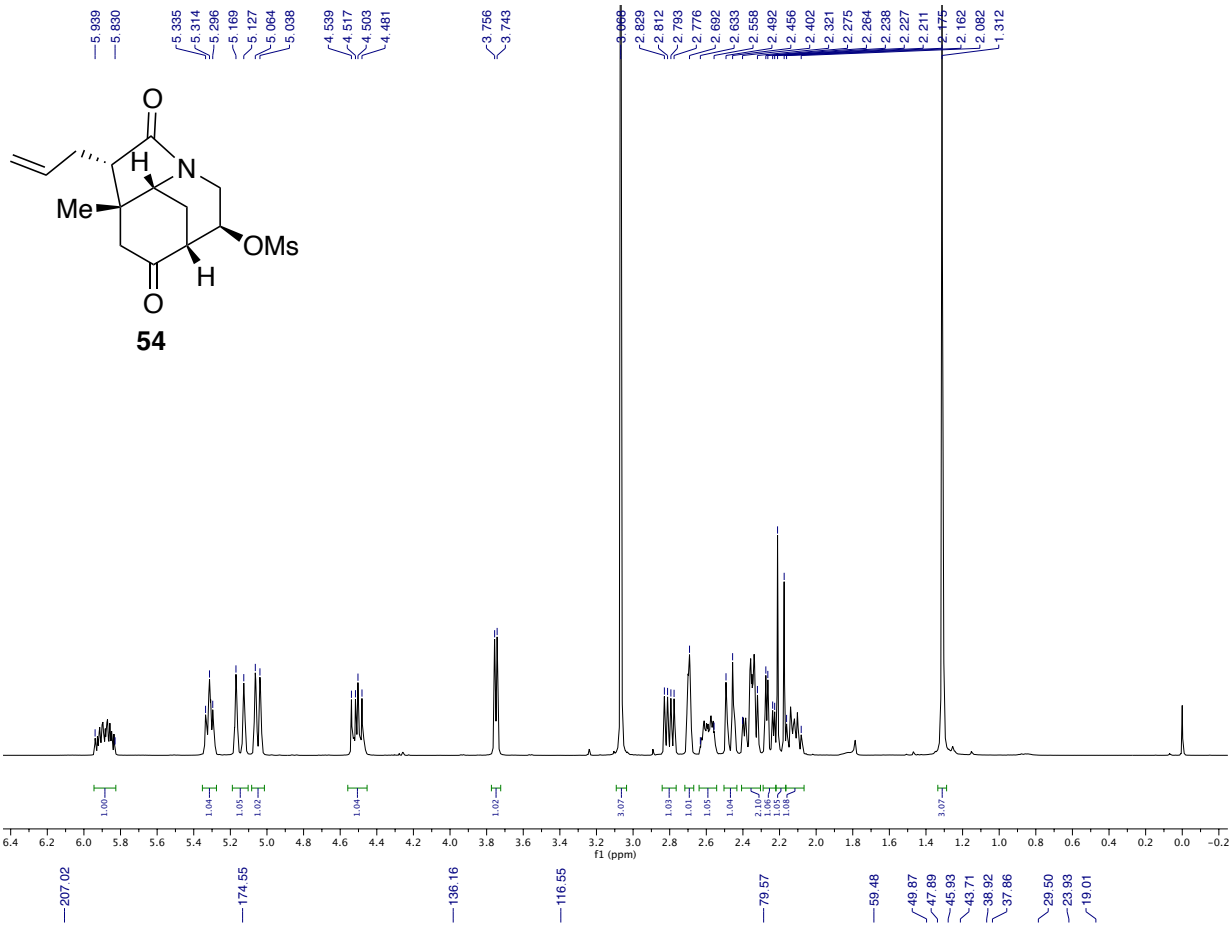

206.97
174.58
145.49
136.22
132.59
130.20
128.07
116.62
79.68
59.61
49.97
47.91
45.61
43.79
38.65
29.58
24.01
21.71
19.06
f1 (ppm)

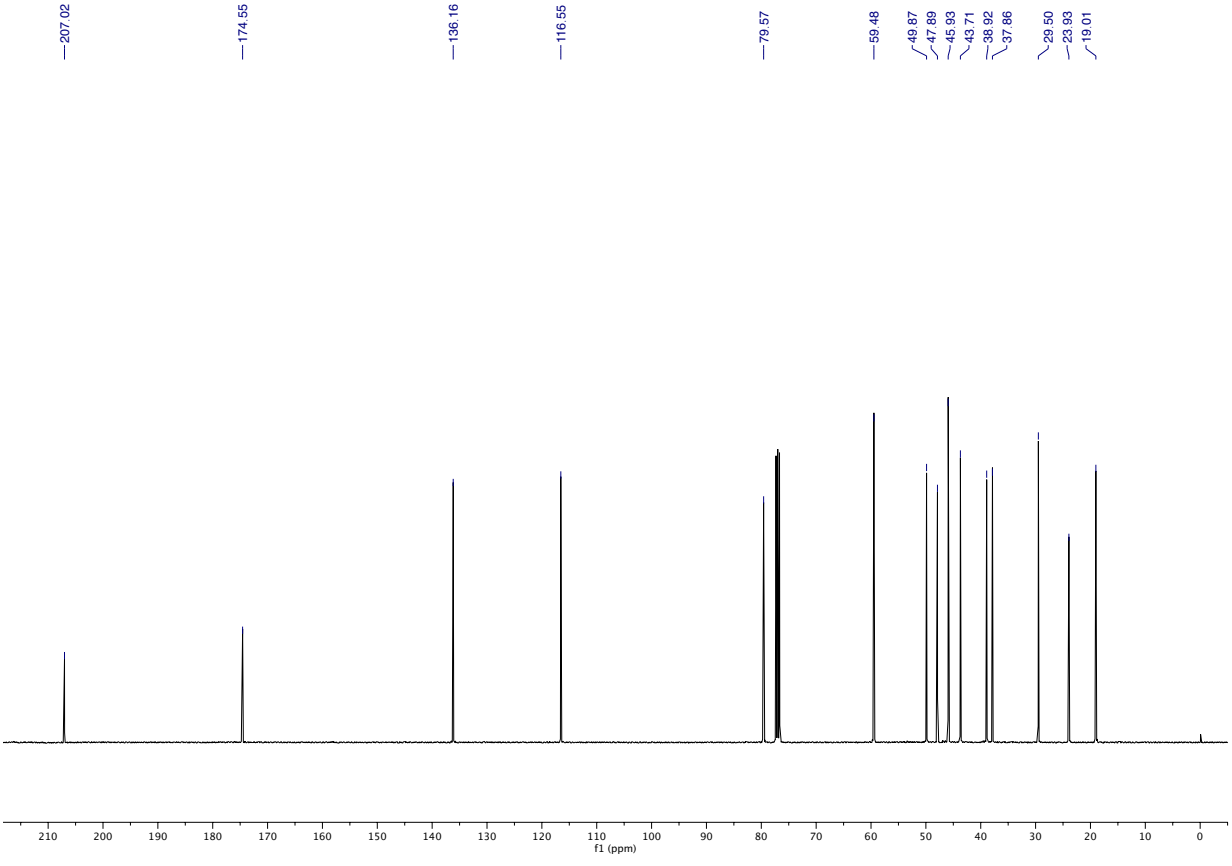
(3*SR*,3a*RS*,6*RS*,7a*RS*,8*RS*)-3-allyl-8-mesyloxy-3a-methyltetrahydro-6,1-ethanoindole-2,5(3*H*,6*H*)-dione (54)



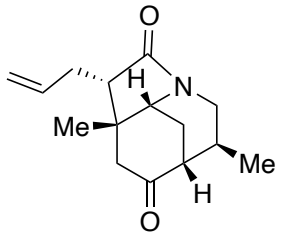
A solution of tricyclic alcohol **51** (0.44 g, 1.78 mmol, 1 equiv) was diluted in CH_2Cl_2 (9 mL) and cooled to 0ºC. Then, MsCl (0.42 mL, 5.34 mmol, 1 equiv), Et_3N (0.37 mL, 2.67 mmol), and DMAP (0.54 g, 4.45 mmol, 2.5 equiv) were added and the reaction was stirred at room temperature overnight. Solution was quenched with $NaHCO_3$ (30 mL), extracted with CH_2Cl_2 (5 x 20 mL) and the combined organics were dried, filtered, and concentrated. The obtained crude was purified by flash chromatographic column (CH_2Cl_2:EtOAc, 9:1) to afford product **54** (0.5 g, 86%) as a white solid.

mp 135 ºC (Et_2O). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.94–5.84 (m, 1H, =CH), 5.31 (br t, *J* = 7.8 Hz, 1H, H-8), 5.15 (dm, *J* =17.2 Hz, 1H, =CH_2-*trans*), 5.05 (dm, *J* = 10.0 Hz, 1H, =CH_2-*cis*), 4.50 (dd, *J* = 14.4, 8.8 Hz, 1H, H-9), 3.75 (d, *J* = 5.6 Hz, 1H, H-7a), 3.07 (s, 3H, Ms), 2.80 (dd, *J* = 14.4, 7.0 Hz, 1H, H-9), 2.70 (d, *J* = 4.0 Hz, 1H, H-6), 2.63–2.55 (m, 1H, CH_2-3), 2.47 (d, *J* = 14.6 Hz, 1H, H-4), 2.40–2.32 (m, 2H, H-3 and H-7), 2.25 (dd, *J* = 14.8, 4.4 Hz, 1H, H-7), 2.20 (d, *J* = 14.6 Hz, 1H, H-4), 2.12 (dt, *J* = 14.8, 8.0 Hz, 1H, CH_2-3), 1.31 (s, 3H, Me). ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.0 (C-5), 174.6 (C-2), 136.2 (=CH), 116.6 (=CH_2), 79.6 (C-8), 59.5 (C-7a), 49.9 (C.3), 47.9 (C-3a), 45.9 (C-6), 43.7 (C-4), 38.9 (C-9), 37.9 (Ms), 29.5 (CH_2-3), 23.9 (Me), 19.0 (C-7).


5.939
5.830
5.335
5.314
5.296
5.169
5.127
5.064
5.038
4.539
4.517
4.503
4.481
3.756
3.743
3.088
2.829
2.812
2.793
2.776
2.692
2.633
2.558
2.492
2.456
2.402
2.321
2.275
2.264
2.238
2.227
2.211
2.175
2.162
2.082
1.312
O
H
N
Me
OMs
H
O
54
f1 (ppm)

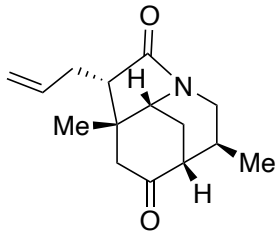

207.02
174.55
136.16
116.55
79.57
59.48
49.87
47.89
45.93
43.71
38.92
37.86
29.50
23.93
19.01
f1 (ppm)

(3*RS*,3a*SR*,6S*R*,7a*SR*,8*RS*)-3-Allyl-3a,8-dimethyltetrahydro-6,1-ethanoindole-2,5(3*H*, 4*H*)-dione (55).



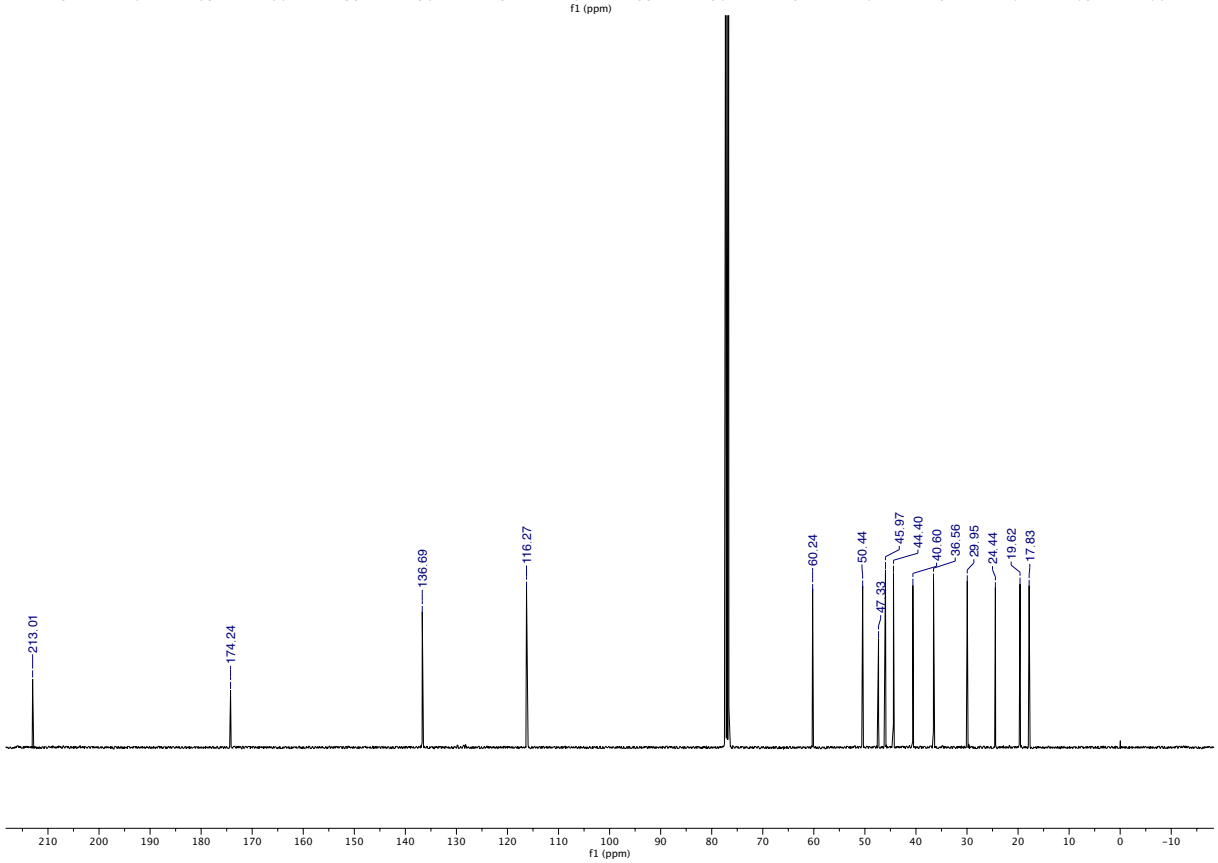
A suspension of CuI (213 mg, 1.11 mmol, 10 equiv) in Et_2O (4.0 mL) was cooled to -20ºC, and MeLi solution (1.6 M in Et_2O, 1.26 mL, 18 equiv) was added dropwise. The reaction was warmed up to 0 ºC and, after stirring for 30 min, a solution of tosylate **53** (45.1 mg, 0.11 mmol) in a 9:1 mixture of Et_2O:THF (5 mL) was added dropwise via cannula. The stirring was prolonged for 1h 30 min before sat. solution of Na_2CO_3 (10 mL) was added and the mixture was extracted with Et_2O (4x10 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated to afford the crude which was purified by chromatography (hexane:EtOAc, 4:1→ 7:3) to obtain tricycle ring **55** (14 mg, 51%) as a white solid along with the recovery of **53** (12 mg, 26%).

mp 95-97 ºC (Et_2O). IR (neat): 2957, 1708, 1691, 1423, 1290, 911 cm^{-1}. The NMR data were identical with those previously reported by Gao[54]: ^1H NMR (400 MHz, $CDCl_3$) δ 5.95–5.85 (m, 1H, =CH), 5.15 (d, *J* = 16.8 Hz, 1H, =CH_2-*trans*) 5.03 (d, *J* = 9.8 Hz, 1H, =CH_2-*cis*), 4.02 (dd, *J* = 13.6, 8.8 Hz, 1H, H-9), 3.66 (t, *J* = 3.0 Hz, 1H, H-7a), 2.91 (tq, *J* = 8.8, 6.4 Hz, 1H, H-8), 2.62 (dm, *J* = 15.0 Hz, 2H, CH_2-3), 2.47 (d, *J* = 14.4 Hz, 1H, H-4), 2.32 (dd, *J* = 8.4, 6.4 Hz, 1H, H-3), 2.21 (dd, *J* = 13.6, 9.0 Hz, 1H, H-9), 2.14 (d, *J* = 14.4 Hz, 1H, H-4), 2.17–2.09 (m, 2H, H-7), 1.93 (t, *J* = 3.1 Hz, 1H, H-6), 1.28 (s, 3H, Me-3a), 1.01 (d, *J* = 6.8 Hz, 3H, Me-8). ^{13}C NMR (101 MHz, $CDCl_3$) δ 213.1 (C-5), 174.2 (C-2), 136.7 (=CH), 116.3 (=CH_2), 60.2 (C-7a), 50.4 (C-3), 47.3 (C-3a), 46.0 (C-6), 44.4 (C-4), 40.6 (C-9), 36.6 (C-8), 30.0 (CH_2-3), 24.4 (Me-3a), 19.6 (C-7), 17.8 (Me-8). HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{15}H_{22}NO_2$ 248.1651, found 248.1661.

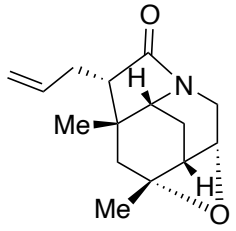

O
H
N
Me
Me
H
O

55

1.280
1.018
1.001
2.157
2.089
2.491
2.454
2.316
5.169
5.124
5.045
5.020
4.051
4.029
4.017
3.995
3.662
3.654
2.936
2.914
2.896
2.874
2.646
5.949
5.846
f1 (ppm)

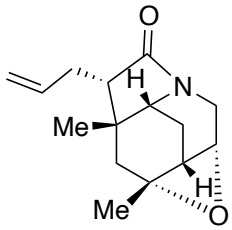

213.01
174.24
136.69
116.27
60.24
50.44
47.33
45.97
44.40
40.60
36.56
29.95
24.44
19.62
17.83
f1 (ppm)

Oxetane derivative (56)



A suspension of CuI (253 mg, 1.3 mmol, 10 equiv) in Et_2O (4.0 mL) was cooled to -20ºC, and MeLi solution (1.6 M in Et_2O, 1.5 mL, 18 equiv) was added dropwise. The reaction was warmed up to 0 ºC and, after stirring for 30 min, a solution of tosylate **53** (54 mg, 0.13 mmol) in a 9:1 mixture of Et_2O:THF (5 mL) was added dropwise via cannula. The stirring was prolonged for 1h 30 min before sat. solution of Na_2CO_3 (10 mL) was added and the mixture was extracted with Et_2O (4x10 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated to afford the crude which was purified by chromatography (hexane:EtOAc, 4:1→ 7:3) to obtain the oxetane derivative **56** (17 mg, 48%) along tricyclic compound **55** (6 mg, 17%).

IR (neat): 2926, 1701, 1393, 1349, 1031, 972 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 6.05–5.95 (m, 1H, =CH), 5.13 (d, *J* = 17.0 Hz, 1H, $=CH_2$-*trans*), 5.02 (d, *J* = 10.0 Hz, 1H, CH_2-*cis*), 4.67 (dd, *J* = 8.0, 3.0 Hz, 1H, H-8), 4.14 (dd, *J* = 14.4, 3.0 Hz, 1H, H-9), 3.60 (d, *J* = 5.2 Hz, 1H, H-7a), 3.06 (d, *J* = 14.4 Hz, 1H, H-9), 2.77–2.70 (m, 1H, CH_2-3), 2.64–2.60 (m, 1H, H-6), 2.52 (dd, *J* = 8.0, 6.4 Hz, 1H, H-3), 2.22 (m, 1H, CH_2-3), 2.07 (d, *J* = 16.4 Hz, 1H, H-4), 1.97 (ddd, *J* = 14.8, 3.4, 2.6 Hz, 1H, H-10), 1.69 (ddd, *J* = 14.8, 3.4, 1.2 Hz, 1H, H-10), 1.39 (s, 3H, Me-5), 1.17 (s, 3H, Me-3a), 1.10 (d, *J* = 16.4 Hz, 1H, H-10). ^{13}C NMR (101 MHz, $CDCl_3$) δ 182.7 (C-2), 137.6 (=CH), 115.6 (CH_2), 82.5 (C-5), 74.2 (C-8), 59.2 (C-7a), 52.9 (C-3), 44.3 (C-3a), 43.8 (C-9), 39.6 (C-4), 34.1 (C-6), 30.5 (CH_2-3), 29.9 (Me-5), 27.6 (Me-3a), 18.0 (C-10); HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{15}H_{22}NO_2$ 248.1645, found 248.1649.


O
H
N
Me
H
Me
O

56

1.387
1.167
6.049
5.945
5.153
5.111
5.035
5.009
4.671
4.659
4.651
4.158
4.151
4.123
4.115
3.608
3.595
3.075
3.039
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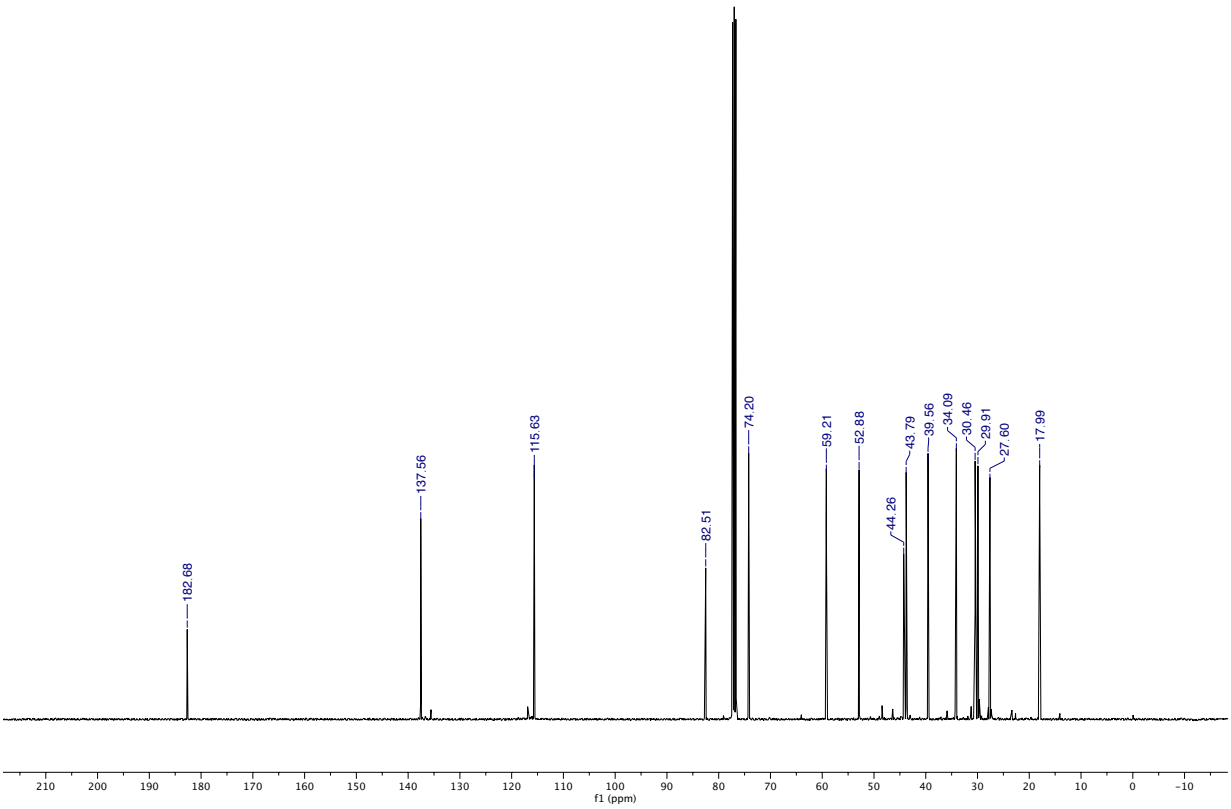
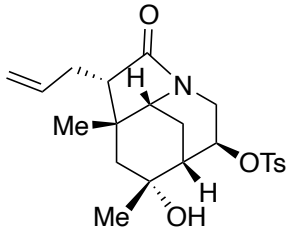
1.938
1.699
1.121
1.080
f1 (ppm)

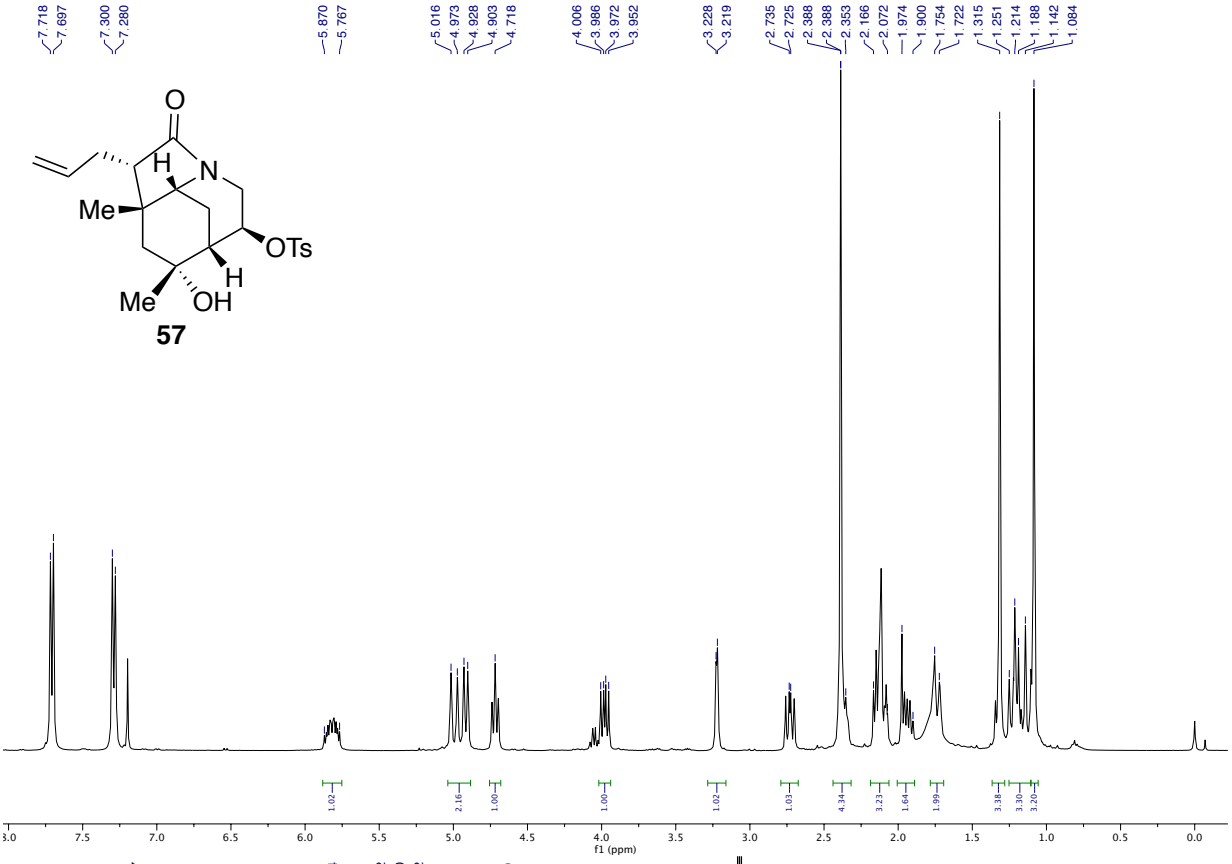

182.68
137.56
115.63
82.51
74.20
59.21
52.88
44.26
43.79
39.56
34.09
30.46
29.91
27.60
17.99
f1 (ppm)

(3*SR*,3a*RS*,5*RS*,6*RS*,7a*R*,8*SR*)-3-allyl-5-hydroxy-8-tosyloxy-3a,5-dimethyltetrahydro-6,1-ethanoindole-2-one (57)



A solution of tosylate **53** (78.7 mg, 0.19 mmol, 1 equiv) in THF (2 mL) was cooled to - 78 ºC. Then HMPA (33 μL, 0.19 mmol, 1 equiv) was added followed by MeLi solution (0.95 M in Et_2O, 0.2 mL, 0.19 mmol, 1 equiv). The reaction was stirred at this temperature for one hour before it was cautiously quenched with sat. solution of NH_4Cl (10 mL). The mixture was extracted with CH_2Cl_2 (5 x 10 mL) and combined organics were dried and concentrated. The residue was purified by flash chromatography (CH_2Cl_2, 100) to obtain product **57** (29.4 mg, 36%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 and 7.29 (2 d, *J* = 8.0 Hz, 2H each, Ts), 5.82 (dddd, *J* =17.0, 10.1, 8.6, 5.3 Hz, 1H, =CH), 4.99 (d, *J* = 17.0 Hz, 1H, =CH_2-*trans*), 4.92 (d, *J* = 10.1 Hz, 1H, =CH_2-*cis*), 4.72 (t, *J* = 8.7 Hz, 1H, H-8), 3.98 (dd, *J* = 13.6, 7.9 Hz, 1H, H-9), 3.22 (d, *J* = 4.1 Hz, 1H, H-7a), 2.73 (dd, *J* = 13.6, 9.6 Hz, 1H, H-9), 2.39 (s, 3H, Ts), 2.38–2.34 (m, 1H, CH_2-3), 2.15 (t, *J* = 6.8 Hz, 1H, H-3), 2.12 (bs, 1H, H-6), 2.12–2.07 (m, 1H, H-7), 1.97–1.90 (m, 1H, CH_2-3), 1.74 (bd, *J* = 14.6 Hz, 1H, H-7), 1.32 (s, 3H, Me-5), 1.25-1.10 (m, 2H, H-4), 1.08 (s, 3H, Me-3a). ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.4 (C-2), 145.3 (Ph), 137.1 (=CH), 132.7, 130.1 and 127.9 (Ph), 115.9 (=CH_2), 73.9 (C-8), 70.5 (C-5), 57.1 (C-7a), 56.2 (C-3), 45.5 (C-6), 45.2 (C-3a), 38.8 (C-4), 38.6 (C-9), 30.9 (5-Me), 28.2 (3-CH_2), 21.7 (Ts), 21.1 (3a-Me), 19.5 (C-7).


7.718
7.697
7.300
7.280
5.870
5.767
5.016
4.973
4.928
4.903
4.718
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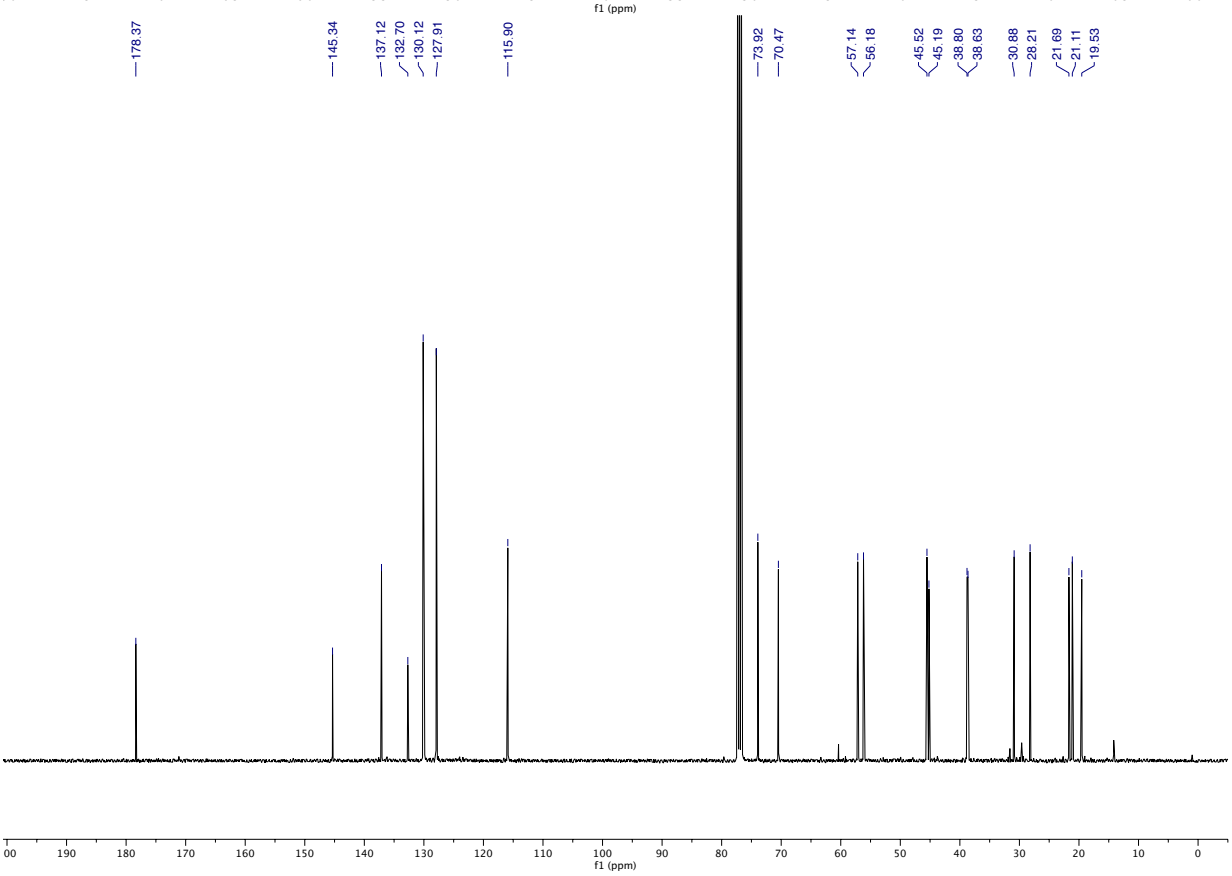
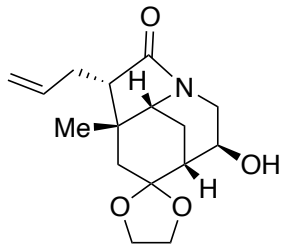
3.986
3.972
3.952
3.228
3.219
2.735
2.725
2.388
2.388
2.353
2.166
2.072
1.974
1.900
1.754
1.722
1.315
1.251
1.214
1.188
1.142
1.084
O
H
N
Me
OTs
H
Me
OH
1.02
2.16
1.00
1.00
1.02
1.03
4.34
3.23
1.64
1.99
3.38
3.30
3.20
f1 (ppm)

57

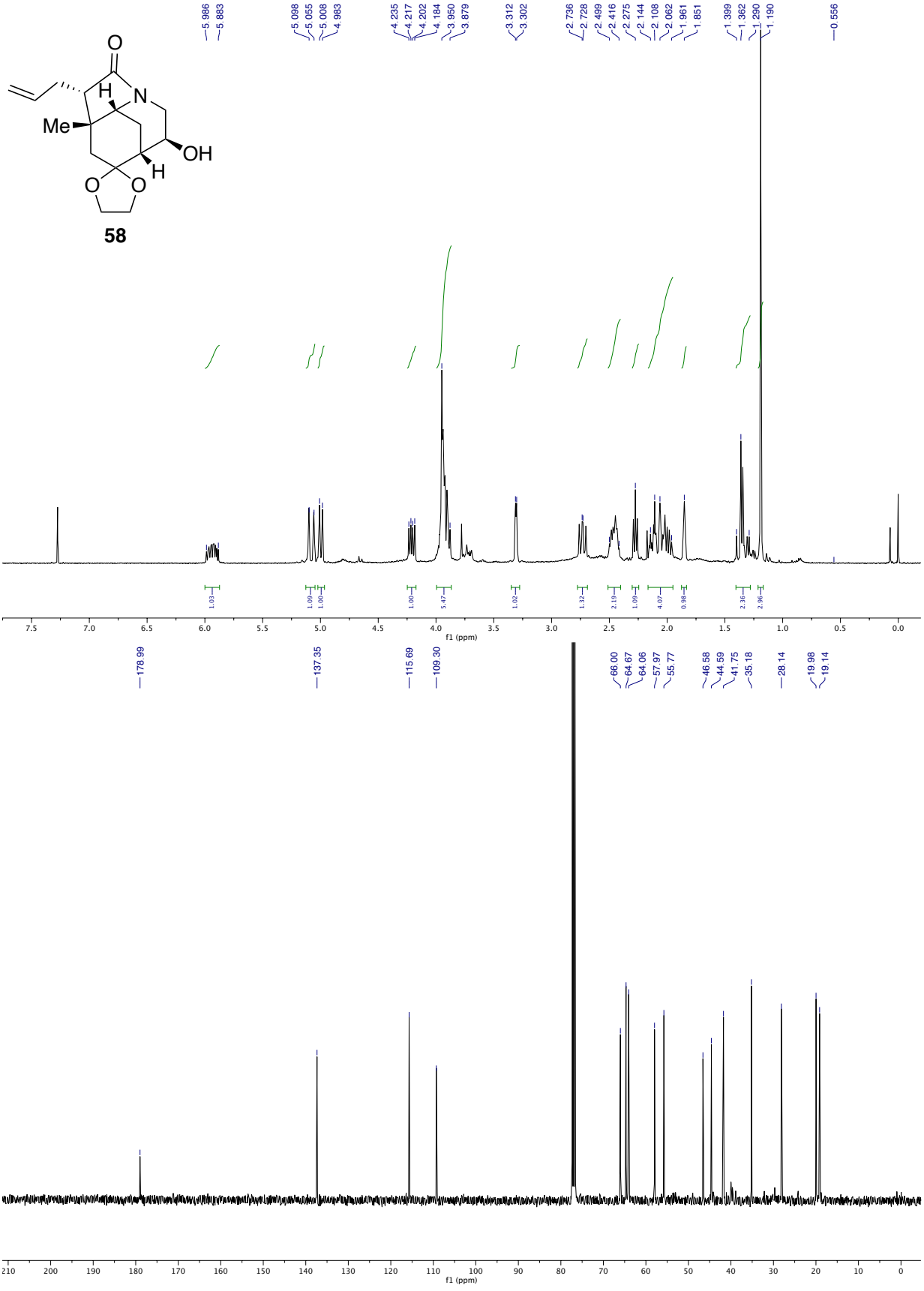

178.37
145.34
137.12
132.70
130.12
127.91
115.90
73.92
70.47
57.14
56.18
45.52
45.19
38.80
38.63
30.88
28.21
21.69
21.11
19.53
f1 (ppm)

(3*SR*,3a*RS*,6*RS*,7a*RS*,8*SR*)-3-allyl-8-hydroxy-3a-methyltetrahydro-6,1-ethanoindole-2,5(3*H*,6*H*)-dione ethylene acetal (58).



Tricyclic alcohol **51** (84 mg, 0.34 mmol, 1 equiv) was dissolved in benzene (5 mL) and ethylene glycol (0.9 mL, 16.8 mmol, 50 equiv) was added followed by a catalytic amount of *p*-TsOH (26 mg, 0.13 mmol, 0.4 equiv). The reaction was placed in a Dean-Stark setup and heated for 4 h. After being cooled to rt, the reaction was diluted with EtOAc (10 mL), and the organic layer was washed with $NaHCO_3$ sat. solution (4x15 mL). Combined organics were dried and concentrated, and the obtained crude was purified by chromatographic column (CH_2Cl_2:EtOAc, 1:0 $\rightarrow$ 1:1) to obtain protected alcohol **58** (49.4 mg, 50%) as a waxy solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.99–5.88 (m, 1H, =CH), 5.08 (dm, *J* = 16.8 Hz, 1H, =CH_2-*trans*), 4.99 (bd, *J* = 10 Hz, =CH_2-*cis*), 4.21 (dd, *J* = 13.2, 7.2 Hz, 1H, H-9), 3.97–3.88 (m, 5H, OCH_2, H-8), 3.31 (d, *J* = 4 Hz, 1H, H-7a), 2.73 (dd, *J* = 13.2, 10 Hz, 1H, H-9), 2.50–2.42 (m, 1H, CH_2-3), 2.28 (t, *J* = 6.8 Hz, 1H, H-3), 2.12 (dt, *J* = 14.4, 4.0 Hz, 1H, H-7), 2.06–2.02 (m, 1H, H-7), 1.99 (dd, *J* = 15.2, 8 Hz, 1H, 3-CH_2), 1.85 (br s, 1H, H-6), 1.40–1.29 (m, 2H, H-4), 1.19 (s, 3H, Me). ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.0 (C-2), 137.4 (=CH), 115.7 (=CH_2), 109.3 (C-5), 66.0 (C-8), 64.7 and 64.1 (OCH_2), 58.0 (C-7a), 55.8 (C-3), 46.6 (C-3a), 44.6 (C-6), 41.8 (C-9), 35.2 (C-4), 28.1 (3-CH_2), 20.0 (Me), 19.1 (C-7).


5.986
5.883
5.098
5.055
5.008
4.983
4.235
4.217
4.202
4.184
3.950
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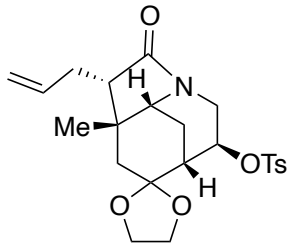
3.312
3.302
2.736
2.728
2.499
2.416
2.275
2.144
2.108
2.062
1.961
1.851
1.399
1.362
1.290
1.190
0.556
1.03
1.09
1.00
1.00
5.47
1.02
1.12
2.19
1.09
4.07
0.98
2.36
2.86
f1 (ppm)
178.99
137.35
115.69
109.30
66.00
64.67
64.06
57.97
55.77
46.58
44.59
41.75
35.18
28.14
19.98
19.14
f1 (ppm)

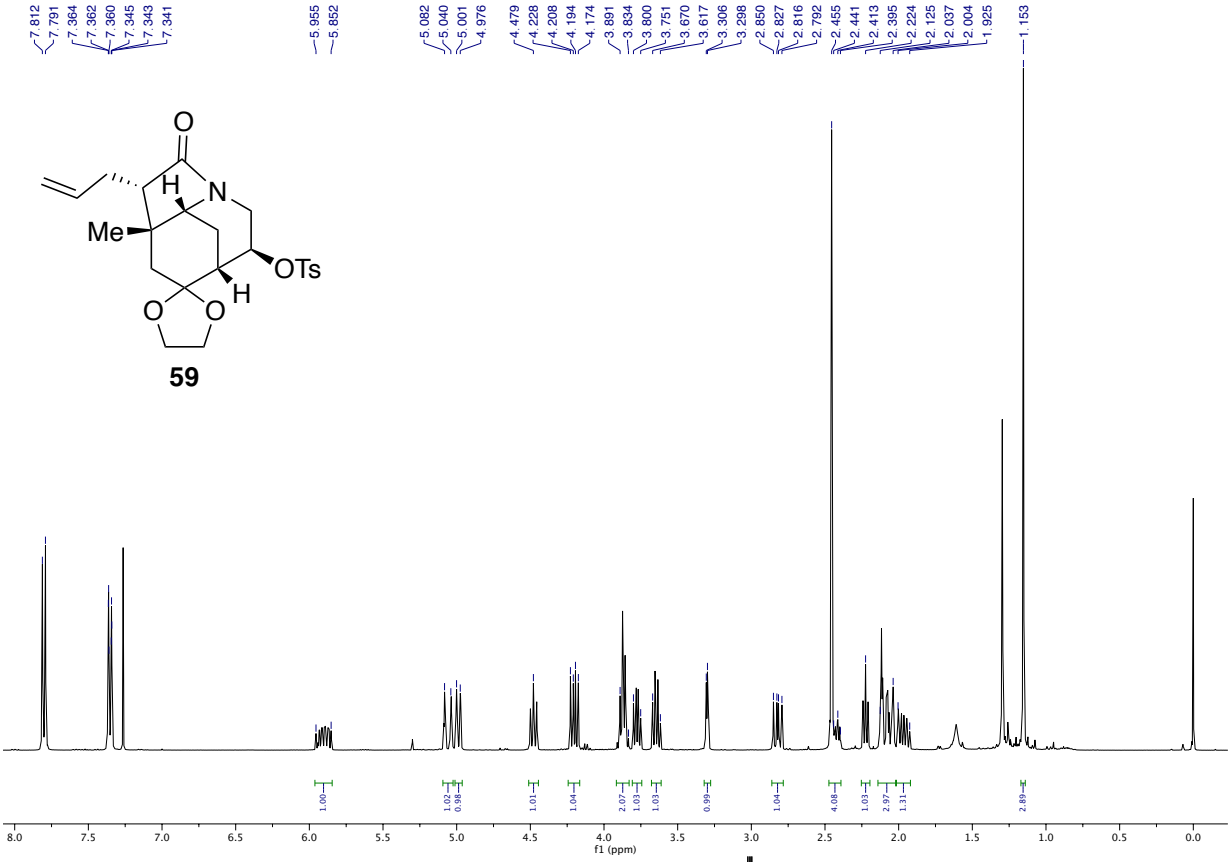
58

(3*SR*,3a*RS*,6*RS*,7a*RS*,8*SR*)-3-allyl-8-tosyloxy-3a-methyltetrahydro-6,1-ethanoindole-2,5(3*H*,6*H*)-dione ethylene acetal (59).

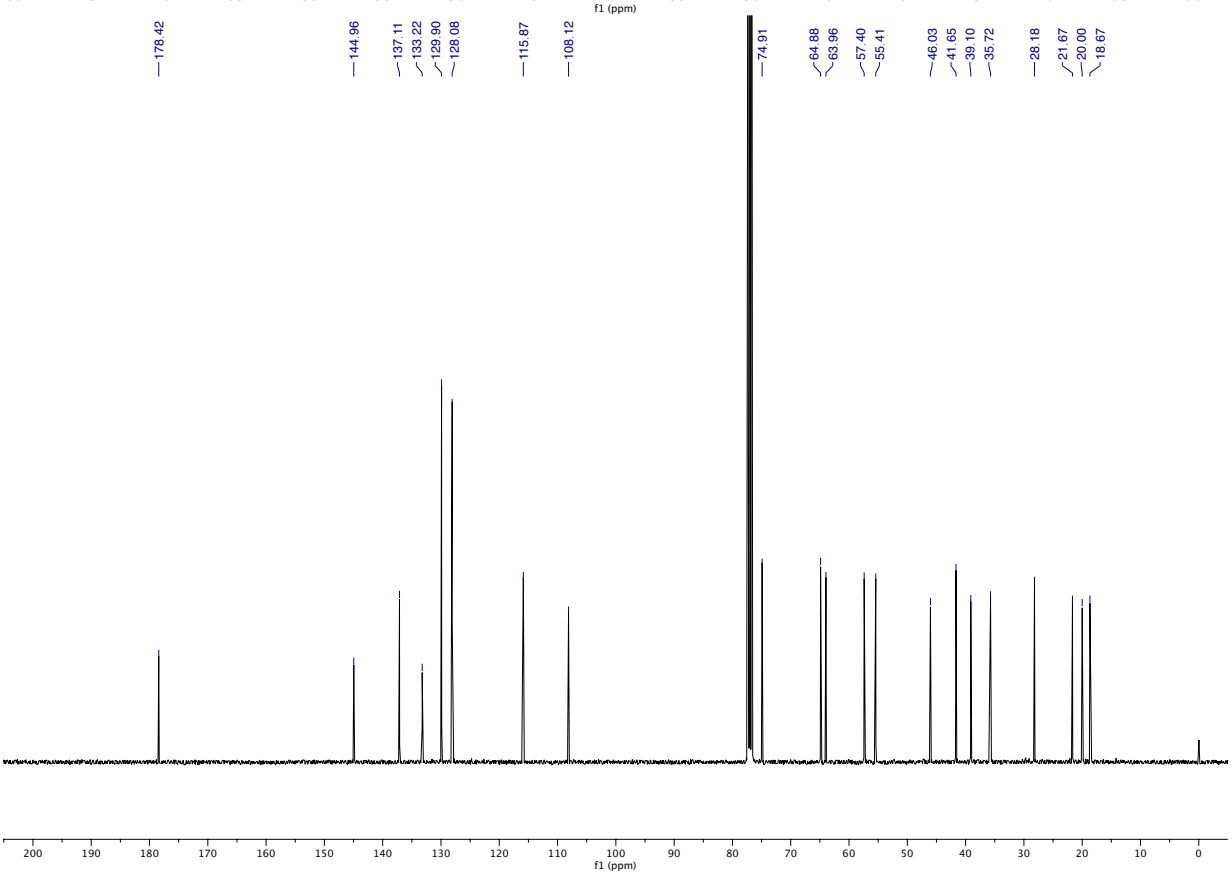


Tricyclic alcohol **58** (49.4 mg, 0.17 mmol, 1 equiv) was dissolved in CH_2Cl_2 (1 mL), and *p*-TsCl (96 mg, 0.51 mmol, 3 equiv), Et_3N (17 μL, 0.25 mmol, 1.5 equiv) and DMAP (51 mg, 0.42 mmol, 2.5 equiv) were added. The reaction was stirred at room temperature overnight before it was quenched with $NaHCO_3$ sat. solution (5 mL) and extracted with CH_2Cl_2 (4 x 10 mL). Combined organics were dried, filtered, concentrated, and the residue was purified by flash chromatography (CH_2Cl_2:EtOAc, 90:10) to obtain protected tosylate **59** (47 mg, 62%) as a waxy solid.

IR (NaCl): 2960, 2884, 1740, 1403, 1362, 1177, 956, 926 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.81–7.79 and 7.36–7.34 (2 d, *J* = 8.0 Hz, 2H each, Ts), 5.96–5.85 (m, 1H, =CH), 5.06 (d, *J* = 16.8 Hz, 1H, $=CH_2$-*trans*), 4.99 (d, *J* = 10.0 Hz, 1H, $=CH_2$-*cis*), 4.48 (t, *J* = 8.6 Hz, 1H, H-8), 4.20 (dd, *J* = 13.8, 8.0 Hz, 1H, H-9), 3.89–3.83 (m, 2H, OCH_2), 3.80–3.75 and 3.67–3.62 (2 m, 1H each, OCH_2), 3.31–3.30 (m, 1H, H-7a), 2.82 (dd, *J* = 13.8, 9.4 Hz, 1H, H-9), 2.46 (s, 3H, Ts), 2.44–2.40 (m, 1H, CH_2-3), 2.22 (t, *J* = 7.2 Hz, 1H, H-6), 2.13–2.04 (m, 3H, H-3 and H-7), 2.00–1.93 (m, 1H, CH_2-3), 1.30 (2d, *J* = 14.8 Hz, 1H each, H-4), 1.15 (s, 3H, Me). ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.4 (C-2), 145.0 (Ph), 137.1 (=CH), 133.2, 129.9, 128.1 (Ph), 115.9 ($=CH_2$), 108.1 (C-5), 74.9 (C-8), 64.9 and 64.0 (OCH_2), 57.4 (C-7a), 55.4 (C-6), 46.0 (C-3a), 41.7 (C-3), 39.1 (C-9), 35.7 (C-4), 28.2 (CH_2-3), 21.7 (Ts), 20.0 (Me), 18.7 (C-7).


7.812
7.791
7.364
7.362
7.360
7.345
7.343
7.341
5.955
5.852
5.082
5.040
5.001
4.976
4.479
4.228
4.208
4.194
4.174
3.891
3.834
3.800
3.751
3.670
3.617
3.306
3.298
2.850
2.827
2.816
2.792
2.455
2.441
2.413
2.395
2.224
2.125
2.037
2.004
1.925
1.153
O
H
N
Me
OTs
H
O
O
1.00
1.02
0.98
1.01
1.04
2.07
1.03
1.03
0.99
1.04
4.08
1.03
2.97
1.31
2.89
f1 (ppm)

59


178.42
144.96
137.11
133.22
129.90
128.08
115.87
108.12
74.91
64.88
63.96
57.40
55.41
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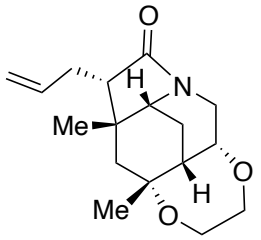
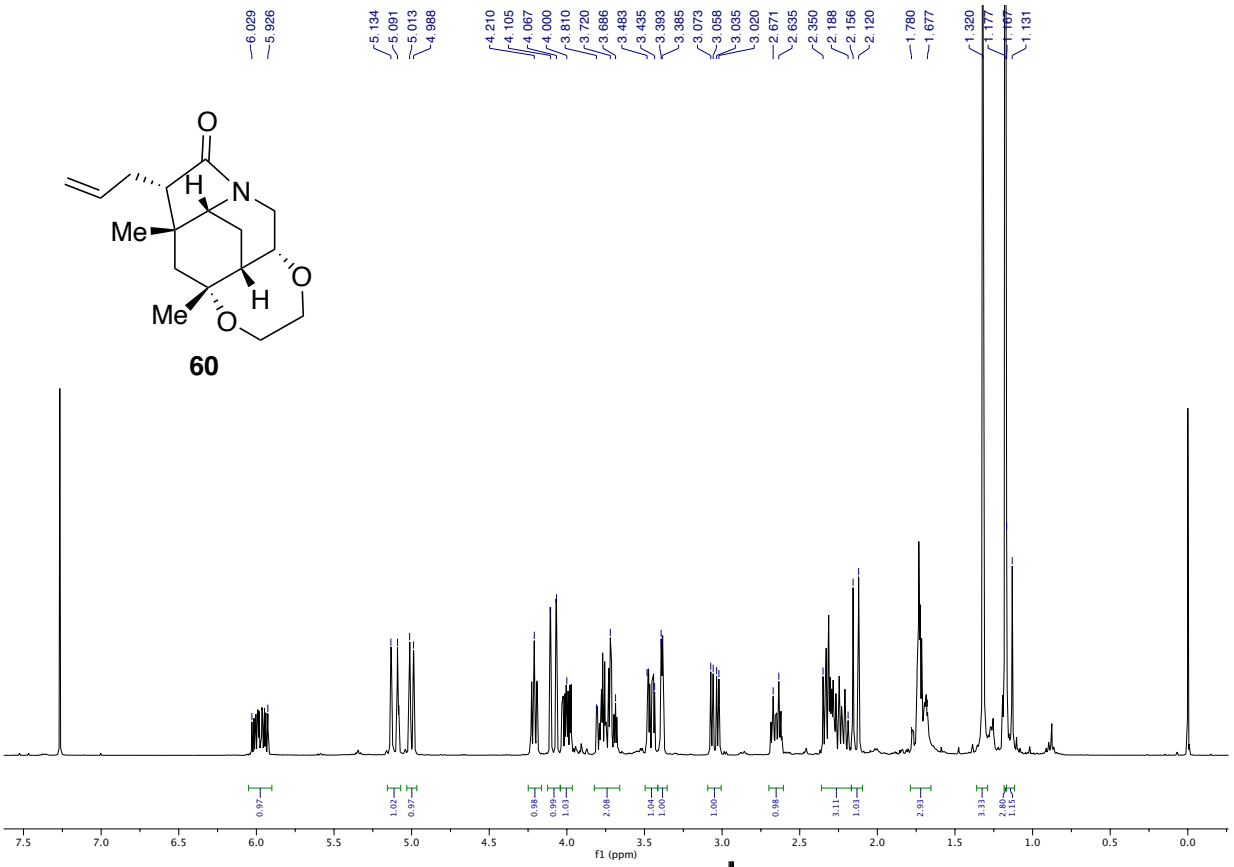
41.65
39.10
35.72
28.18
21.67
20.00
18.67
f1 (ppm)

Compound (60).



To a solution of protected tosylate **59** (46 mg, 0.1 mmol, 1 equiv) in CH_2Cl_2 (0.2 mL), cooled to -78 ºC, a solution of $AlMe_3$ (2M in toluene, 0.15 mL, 0.3 mmol, 3 equiv) was added dropwise. The reaction was stirred at this temperature for 2 hours and an additional hour at room temperature. Then, it was quenched with 2M NaOH and extracted with CH_2Cl_2 (5 x 10 mL). Combined organics were dried, filtered, and concentrated under vacuum to provide the crude that was purified by chromatography (CH_2Cl_2:EtOAc, 1:0 → 0:1) to obtain product **60** (10.2 mg, 34%) as a colorless oil.

IR (neat): 2929, 1697, 1408, 1132, 917 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 5.98 (dddd, *J* = 17.1, 10.1, 8.8, 5.3 Hz, 1H, =CH), 5.11 (dd, *J* = 17.1, 1.1 Hz, 1H, =CH_2-*trans*), 5.00 (dd, *J* = 10.1, 0.8 Hz, 1H, =CH_2-*cis*), 4.21 (ddd, *J* = 7.6, 6.2, 1.2 Hz, 1H, H-8), 4.09 (dd, *J* = 15.2, 1.2 Hz, 1H, H-9), 4.00 (dd, *J* = 12.7, 7.8, 3.2 Hz, 1H, OCH_2), 3.78 (ddd, *J* = 13.4, 8.0, 2.6 Hz, 1H, OCH_2), 3.70 (ddd, *J* = 13.4, 4.2, 3.2 Hz, 1H, OCH_2), 3.46 (ddd, *J* = 12.7, 4.2, 2.6 Hz, 1H, OCH_2), 3.39 (br d, *J* = 4.0 Hz, 1H, H-7a), 3.05 (dd, *J* = 15.2, 6.0 Hz, 1H, H-9), 2.69–2.62 (m, 1H, CH_2-3), 2.35–2.19 (m, 3H, H-3, H-6, CH_2-3), 2.14 (d, *J* = 14.4 Hz, 1H, H-4), 1.72 (m, 2H, H-7), 1.32 (s, 3H, Me-5), 1.18 (s, 3H, Me-3a), 1.15 (d, *J* = 14.4 Hz, 1H, H-4). ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.8 (C-2), 137.9 (=CH), 115.5 (=CH_2), 80.9 (C-8), 78.5 (C-5), 68.3 and 64.8 (OCH_2), 57.9 (C-7a), 54.6 (C-3), 44.1 (C-3a), 43.3 (C-6), 39.8 (C-9), 39.7 (C-4), 30.4 (Me-5), 29.5 (CH_2-3), 24.5 (Me-3a), 23.3 (C-7).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5.926
5.134
5.091
5.013
4.988
4.210
4.105
4.067
4.000
3.810
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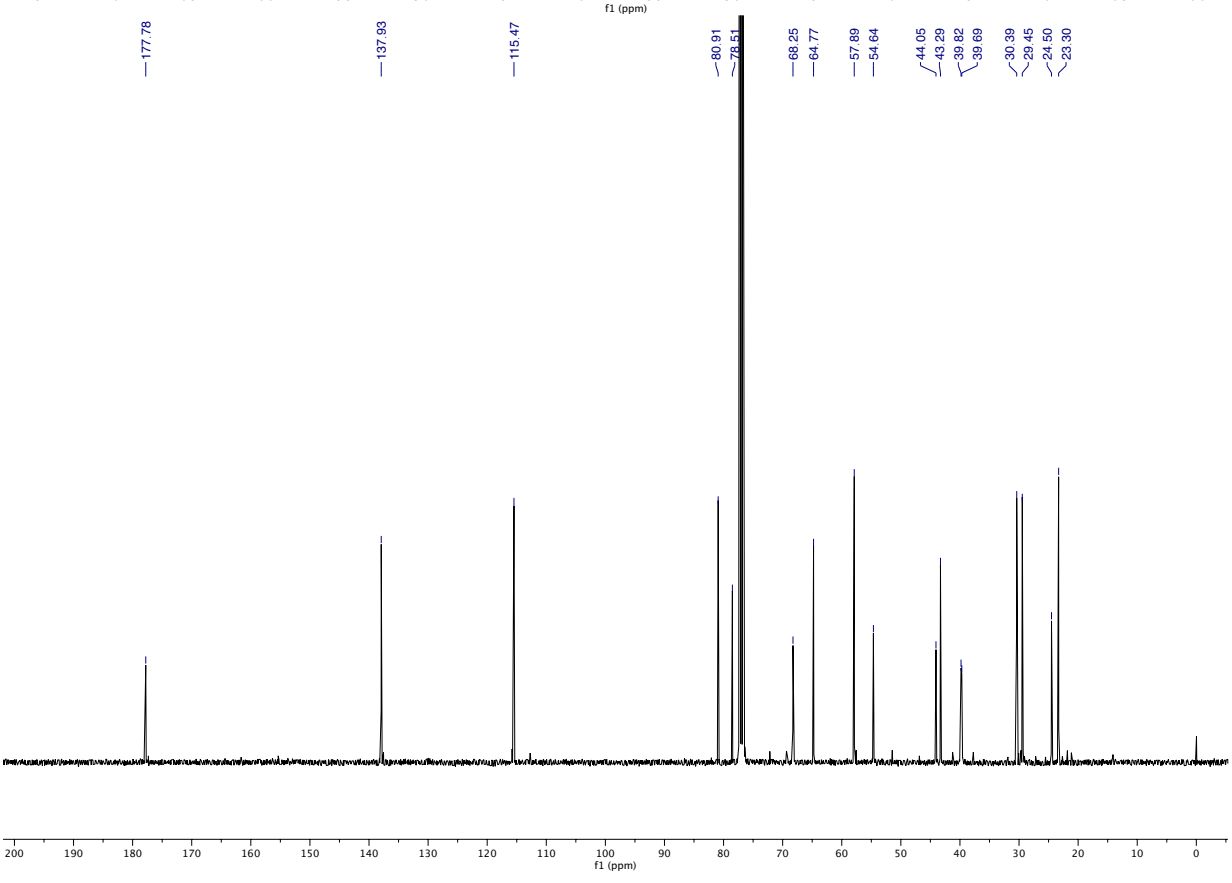
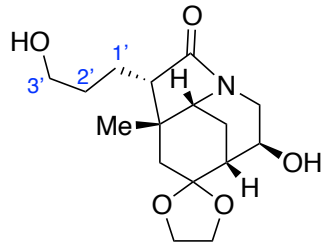
3.686
3.483
3.435
3.393
3.385
3.073
3.058
3.035
3.020
2.671
2.635
2.350
2.188
2.156
2.120
1.780
1.677
1.320
1.177
1.167
1.131
O
H
N
Me
O
H
Me
O
0.97
1.02
0.97
0.98
0.99
1.03
2.08
1.04
1.00
1.00
0.98
3.11
1.03
2.93
3.33
2.80
1.15
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

60

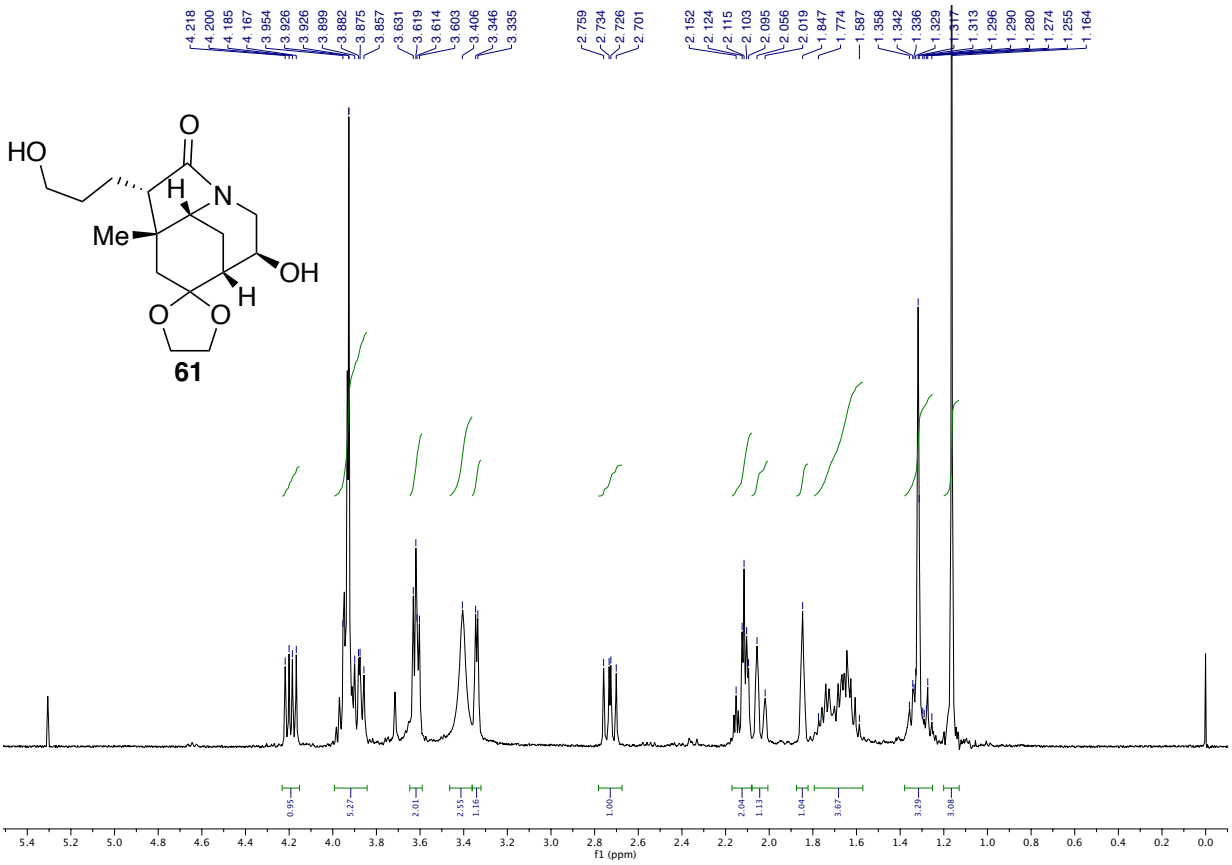

177.78
137.93
115.47
80.91
78.51
68.25
64.77
57.89
54.64
44.05
43.29
39.82
39.69
30.39
29.45
24.50
23.30
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

(3*SR*,3a*RS*,6*RS*,7a*RS*,8*SR*)-8-hydroxy-3-(3'-hydroxypropyl)-3a-methyltetrahydro-6,1-ethanoindole-2,5(3*H*,6*H*)-dione ethylene acetal (61).



A solution of 9-BBN (0.5 M in THF, 2.8 mL, 1.40 mmol, 5 equiv) was added to tricyclic alcohol **58** (0.22 g, 1.06 mmol) and the mixture was stirred at room temperature overnight. Then, the reaction was cooled to 0 ºC and precooled 2M solution of NaOH (1.3 mL, 2.54 mmol, 9 equiv) followed by H_2O_2 (30% wt., 1.1 mL, 10.9 mmol, 39 equiv) were added and stirring was prolonged for 5 h. Then water was added and the mixture was extracted with $CHCl_3$:i-PrOH (4:1, 4x20 mL). The organics were combined, dried, and concentrated to afford the crude which was purified by chromatography (CH_2Cl_2:MeOH, 1:0 → 9.5:0.5) and product **61** (68 mg, 89%) was obtained as a waxy solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.19 (dd, *J* = 13.2, 7.2 Hz, 1H, H-9), 3.95–3.93 (m, 4H, OCH_2), 3.88 (dd, *J* = 9.9, 7.2 Hz, 1H, H-8), 3.62 (br t, *J* = 6.8 Hz, 2H, CH_2OH), 3.34 (d, *J* = 3.2 Hz, 1H, H-7a), 2.73 (dd, *J* = 13.2, 9.9 Hz, 1H, H-9), 2.15–2.10 (m, 2H, H-3 and H-7), 2.04 (br d, *J* = 11.2 Hz, 1H, H-7), 1.85 (br s, 1H, H-6), 1.77–1.59 (m, 3H, 2'-CH_2-3 and 1'-CH_2-3), 1.36–1.26 (m, 1H, 1'-CH_2-3), 1.32 (br s, 2H, H-4) and 1.16 (s, 3H, Me). ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.7 (C-2), 109.2 (C-5), 65.8 (C-8), 64.6 and 64.0 (OCH_2), 61.3 (CH_2OH), 58.2 (C-7a), 56.1 (C-3), 47.0 (C-3a), 44.5 (C-6), 41.8 (C-9), 35.0 (C-4), 32.0 (2'-CH_2-3), 19.3 (C-7), 19.3 (Me), 18.4 (1'-CH_2-3).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4.200
4.185
4.167
3.954
3.926
3.926
3.899
3.882
3.875
3.857
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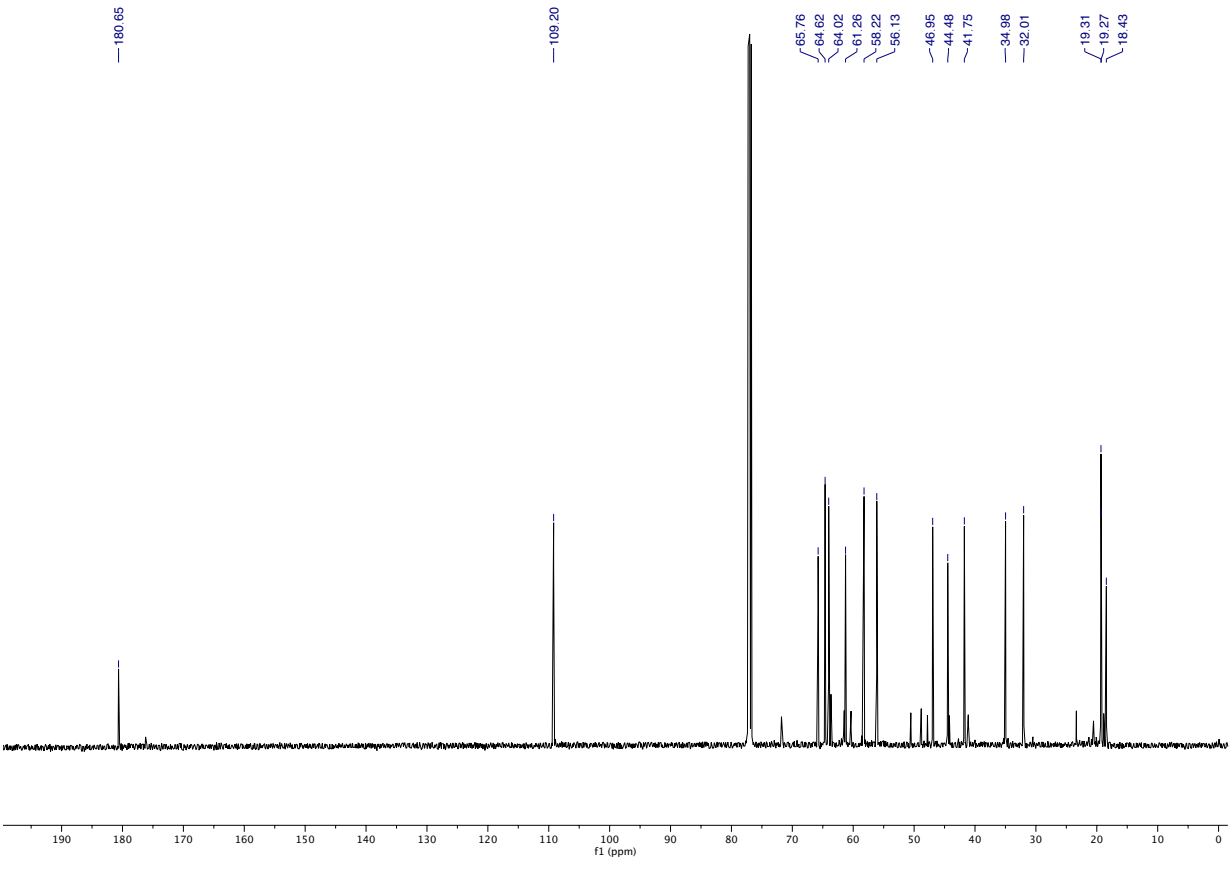
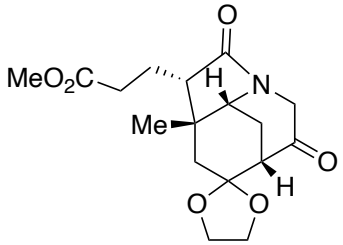
3.619
3.614
3.603
3.406
3.346
3.335
2.759
2.734
2.726
2.701
2.152
2.124
2.115
2.103
2.095
2.056
2.019
1.847
1.774
1.587
1.358
1.342
1.336
1.329
1.317
1.313
1.296
1.290
1.280
1.274
1.255
1.164
HO
O
H
N
Me
OH
H
O
O
61
0.95
5.27
2.01
2.55
1.16
1.00
2.04
1.13
1.04
3.67
3.29
3.08
f1 (ppm)

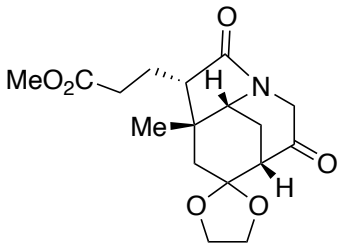

180.65
109.20
65.76
64.62
64.02
61.26
58.22
56.13
46.95
44.48
41.75
34.98
32.01
19.31
19.27
18.43
f1 (ppm)

(3*SR*,3a*RS*,6*RS*,7a*RS*,8*SR*)-3-((3'-methoxycarbonyl)-propyl)-3a-methyltetrahydro-6,1-ethanoindole-2,5,8-trione ethylene acetal (62).

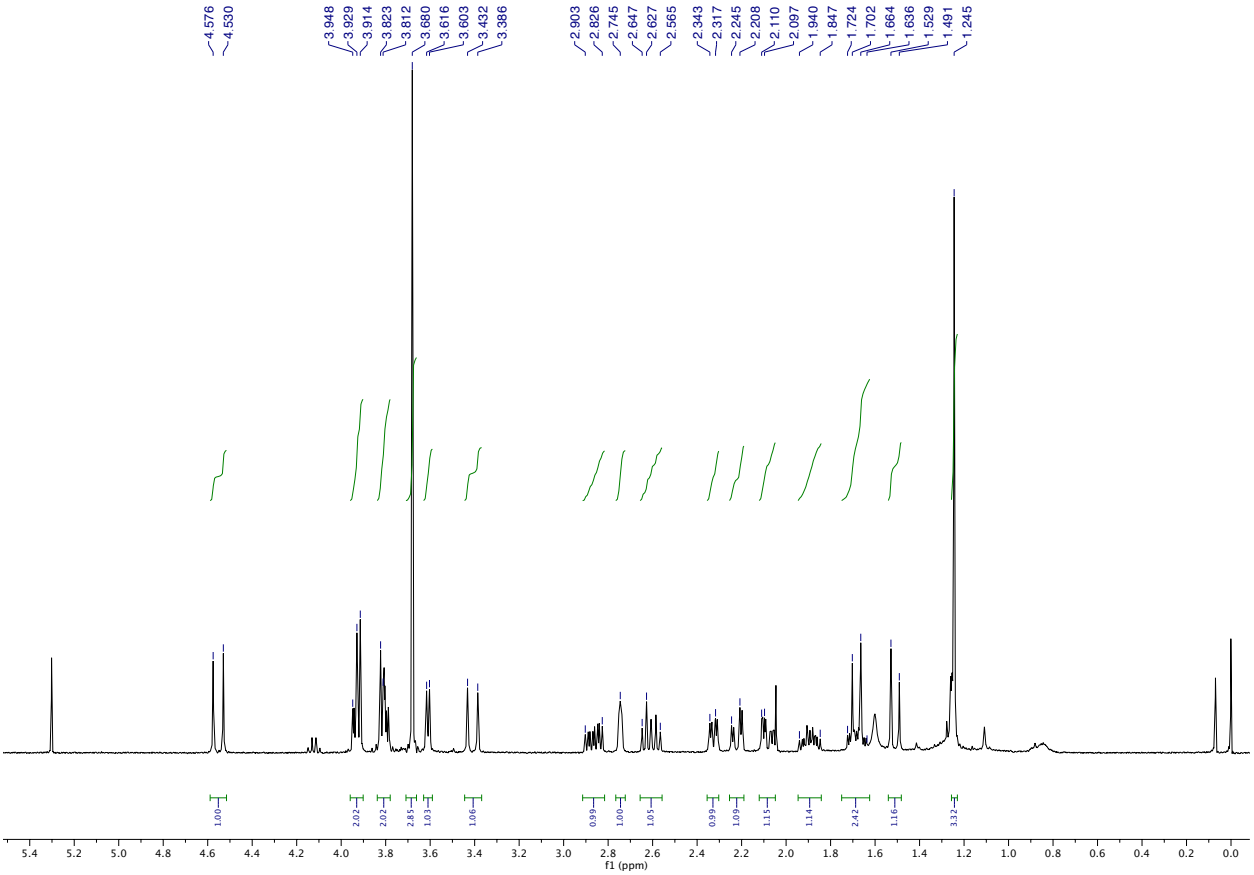


To a solution **61** (97 mg, 0.33 mmol, 1 equiv.) in CH_3CN (3 mL) was added a buffer pH 7 solution (2 mL). Then, TEMPO (15 mg, 0.10 mmol, 0.3 equiv.), $NaClO_2$ (80% in wt., 75 mg, 0.66 mmol, 2 equiv.) and NaClO (10% in wt., 0.25 mL, 0.43 mmol, 1.3 equiv.) were successively added and the reaction was stirred at room temperature for 5 h. The mixture was diluted with sat. solution of Na_2SO_3 (15 mL) and stirred for 10 minutes. Then, it was acidified with 1M HCl solution and extracted with $CHCl_3$:i-PrOH (4:1, 5 x 20 mL). Combined organics were dried, filtered, and concentrated. The residue was diluted in DMF (2 mL) and K_2CO_3 (91 mg, 0.66 mmol, 2 equiv) was added. After stirring for 5 minutes, MeI (50 μL, 0.82 mmol, 2.5 equiv) was added and the reaction was prolonged for 2 hours. Water (20 mL) was added and the solution was extracted with EtOAc (4 x 20 mL). The combined organics were dried, filtered, and concentrated and the obtained crude was diluted in CH_2Cl_2 (3 mL) and DMP (0.17 g, 0.4 mmol, 1.2 equiv) was added. After being stirred for 2h 30 min, the mixture was filtered through a celite pad, and the organics were washed with Na_2SO_4:$NaHCO_3$ (1:1, 2 x 30 mL), dried, filtered and concentrated. The residue was purified by chromatographic column (CH_2Cl_2:EtOAc, 1:0→ 1:1) to afford compound **62** (56 mg, 50%) as a colorless oil.

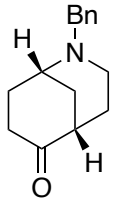
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.55 (d, *J* = 18.4 Hz, 1H), 3.95–3.91 and 3.82–3.81 (2m, 2H each, OCH_2), 3.68 (s, 3H, OMe), 3.61 (d, *J* = 5.2 Hz, 1H), 3.41 (d, *J* = 18.4 Hz, 1H), 2.86 (ddd, *J* = 17.0, 8.2, 5.6 Hz, 1H), 2.75 (br s, 1H), 2.61 (dt, *J* = 17.0, 8.4 Hz, 1H), 2.33 (ddd, *J* = 10.2, 3.6, 1.0 Hz, 1H), 2.23 (dd, *J* = 15.2, 3.6 Hz, 1H), 1.94–1.85 (m, 1H), 1.72–1.64 (m, 1H), 1.68 and 1.51 (2 d, *J* = 15.2 Hz, 1H each), 1.25 (s, 3H).


O
MeO2C
H
N
Me
O
H
O
O

62

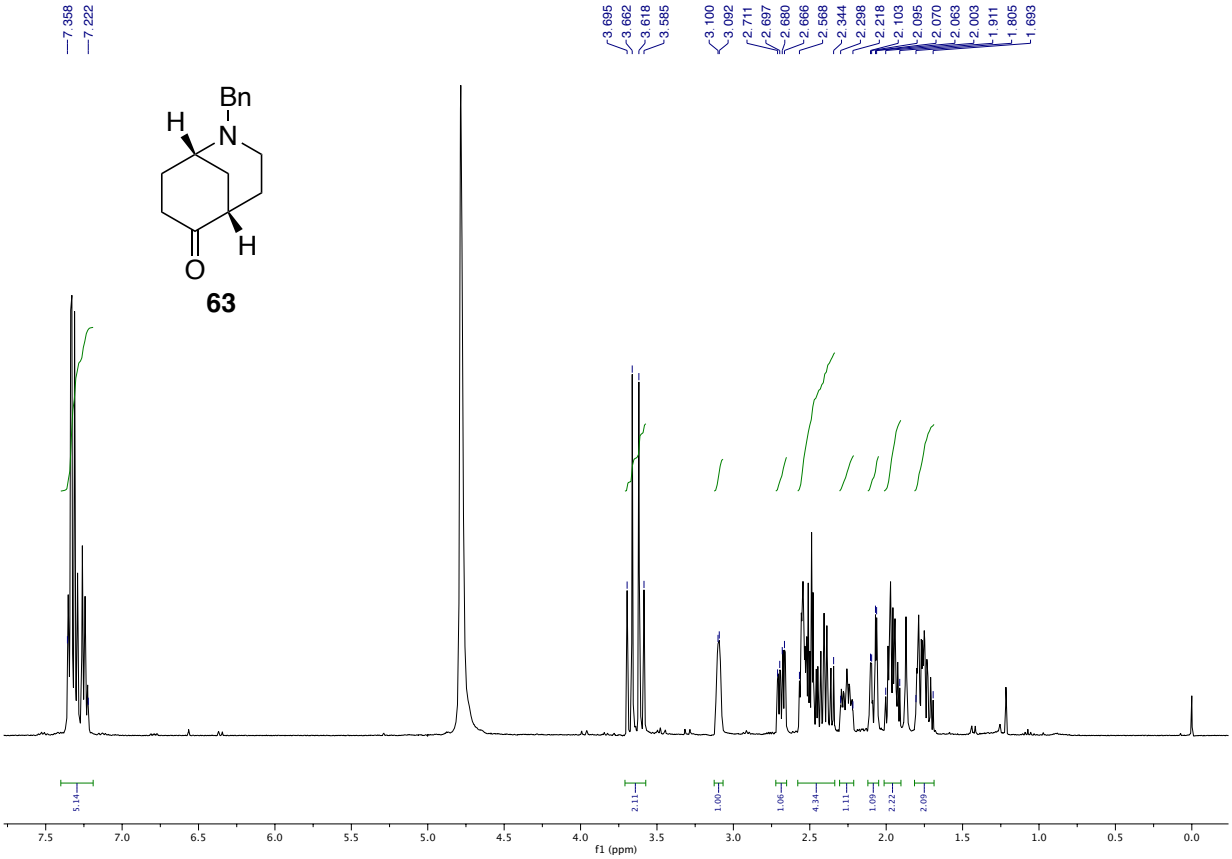

4.576
4.530
3.948
3.929
3.914
3.823
3.812
3.680
3.616
3.603
3.432
3.386
2.903
2.826
2.745
2.647
2.627
2.565
2.343
2.317
2.245
2.208
2.110
2.097
1.940
1.847
1.724
1.702
1.664
1.636
1.529
1.491
1.245
1.00
2.02
2.02
2.85
1.03
1.06
0.99
1.00
1.05
0.99
1.09
1.15
1.14
2.42
1.16
3.32
f1 (ppm)

(1*SR*,5*SR*)-2-benzyl-2-azabicyclo[3.3.1]nonan-6-one (63)



To a solution of $AlCl_3$ (1.36 g, 9.9 mmol, 1.5 equiv) in THF (30 mL) was added a 1 M solution of $LiAlH_4$ in THF (16.6 mL, 16.6 mmol, 2.5 equiv) at 0ºC, and the mixture was stirred for 20 min at rt. Then, a solution of morphan **A** (1.9 g, 6.6 mmol) in THF (70 mL) was added dropwise via cannula and the reaction mixture was stirred overnight at room temperature. The reaction was quenched with 30% KOH solution, and extracted sequentially with CH_2Cl_2 (3 x 30 mL), $CHCl_3$ (3 x 25 mL), and $CHCl_3$:*i*-PrOH (4:1, 2 x 25 mL). The organics were dried and concentrated to yield aminoalcohol pure enough to be used in the next step without further purification. The residue (1.35 g, 5.8 mmol) was diluted in CH_2Cl_2 (100 mL) and $NaHCO_3$ (3.66 g, 43.8 mmol, 7.5 equiv) followed by Dess-Martin periodinane (4.94 g, 11.6 mmol, 2.5 equiv) were added. The reaction was stirred at room temperature for 3 h before it was quenched with a sat. sol. $Na_2S_2O_3$:Na_2CO_3 (1:1, 130 mL). After 30 min of stirring, the mixture was poured into water (100 mL) and extracted with CH_2Cl_2 (3 x 100 mL). Combined organics were dried, filtered and concentrated to obtain a yellow crude. After a flash chromatographic column (Al_2O_3, hexane:EtOAc, 9:1) compound **63** was obtained (0.82 g, 54 % over two steps) as a transparent oil.

IR (NaCl): 2932, 2808, 1705, 1447, 1123 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.36–7.23 (m, 5H, Ph), 3.68 and 3.60 (2d, J = 13.2 Hz, 1H each, CH_2Ph), 3.09 (bs, 1H, H-1), 2.69 (ddd, J = 12.4, 6.0, 2.2 Hz, 1H, H-3), 2.57–2.50 (m, 2H, H-5 and H-7), 2.48 (ddd, J = 12.4, 12.4, 4 Hz, 1H, H-3), 2.38 (dd, J = 18.0, 7.4 Hz, 1H, H-7), 2.30–2.22 (m, 1H, H-8), 2.08 (ddt, J = 13.6, 2.8, 2.8 Hz, 1H, H-9), 2.00–-1.91 (m, 2H, H-9 and H-4), 1.81–1.69 (m, 2H, H-4 and H-8). ^{13}C NMR (101 MHz, $CDCl_3$) δ 216.5 (C-6), 138.9, 128.7, 128.2 and 126.9 (Ph), 59.6 (CH_2Ph), 49.7 (C-1), 46.0 (C-3), 42.8 (C-5), 38.8 (C-7), 31.7 (C-9), 29.2 (C-4), 21.9 (C-8).


7.358
7.222
3.695
3.662
3.618
3.585
3.100
3.092
2.711
2.697
2.680
2.666
2.568
2.344
2.298
2.218
2.103
2.095
2.070
2.063
2.003
1.911
1.805
1.693
Bn
N
H
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O
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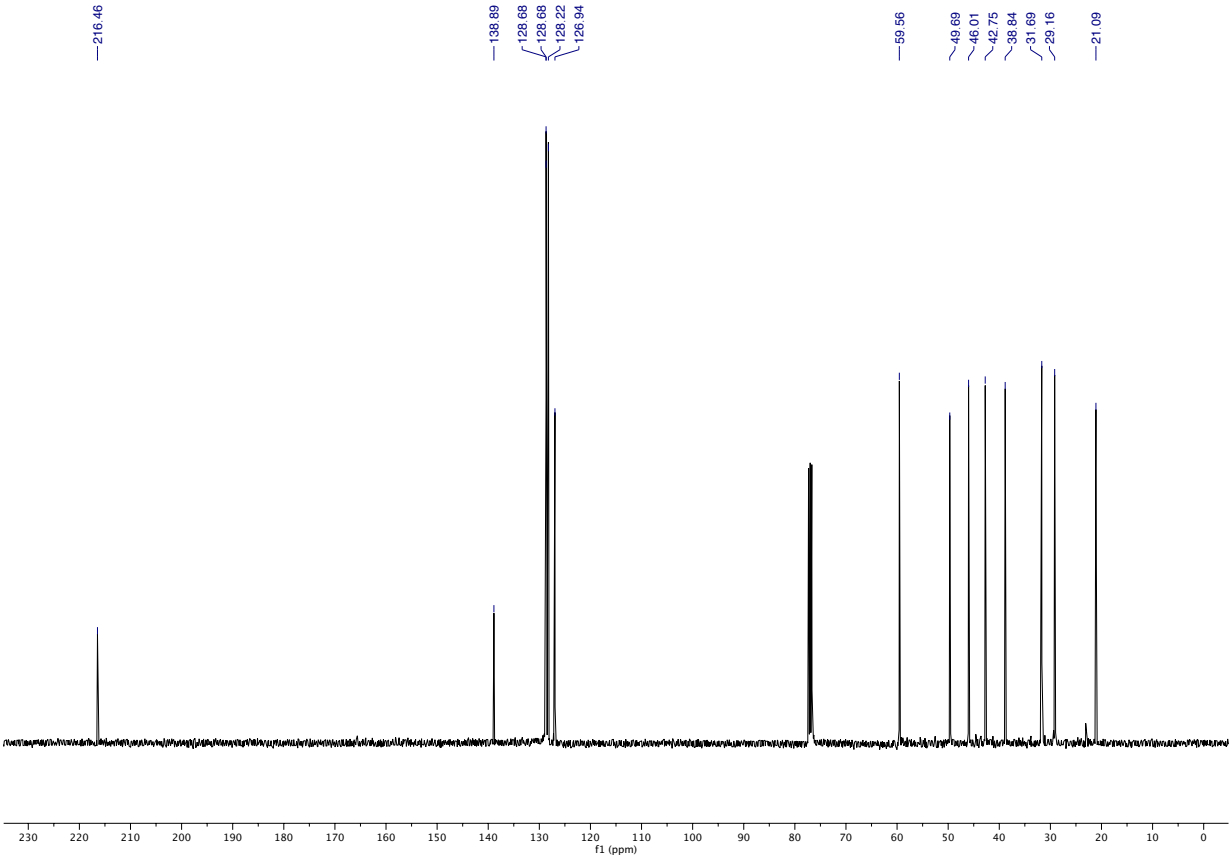
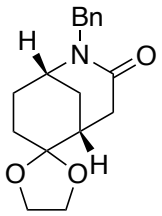
4.34
1.11
1.09
2.22
2.09
f1 (ppm)

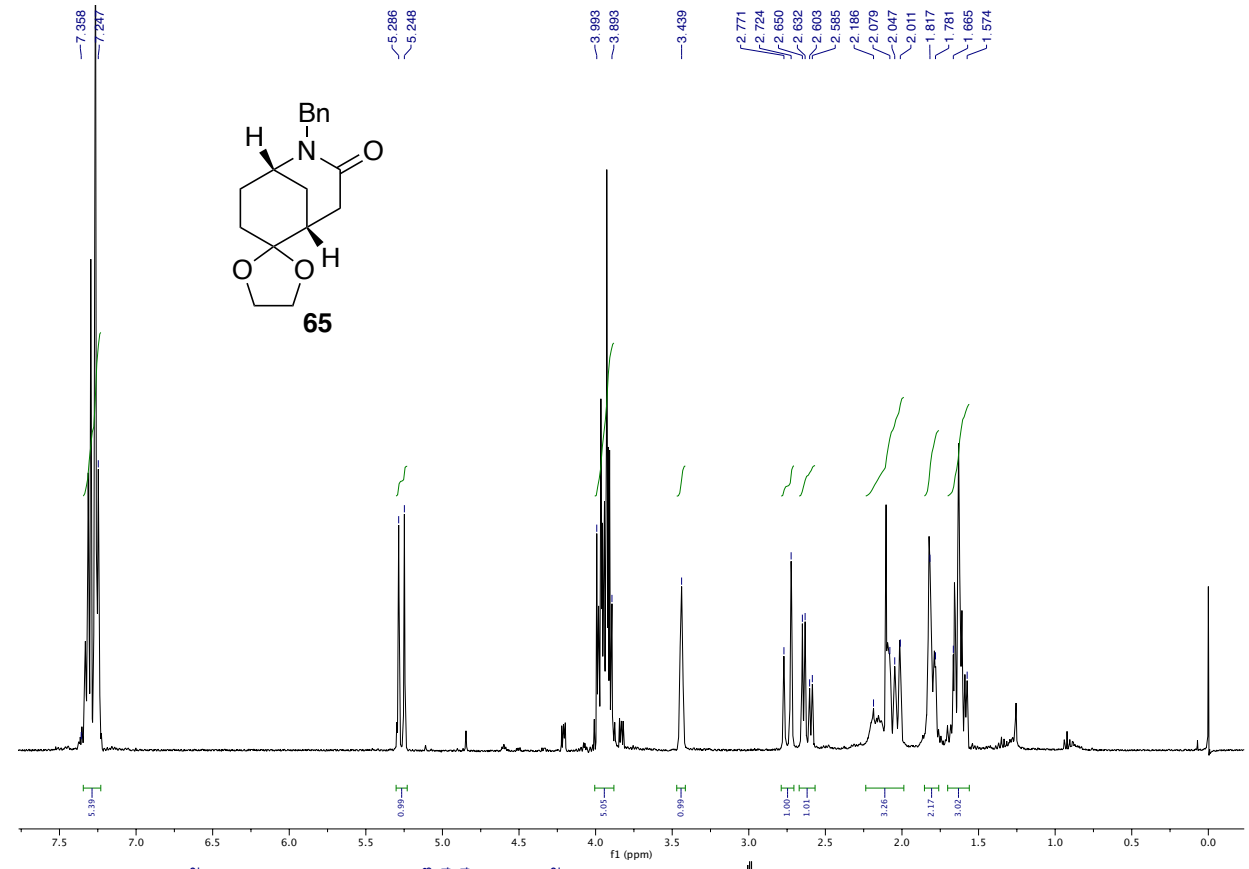

216.46
138.89
128.68
128.68
128.22
126.94
59.56
49.69
46.01
42.75
38.84
31.69
29.16
21.09
f1 (ppm)

(1*SR*,5*RS*)-2-benzyl-2-azabicyclo[3.3.1]nonan-3,6-dione ethylene acetal (65)



A solution of morphan **64** (0.71 g, 2.9 mmol, 1 equiv), *p*-TsOH (0.22 g, 1.16 mmol, 0.4 equiv), and ethylene glycol (8.1 mL, 145 mmol, 50 equiv) in toluene (70 mL) was placed in Dean-Stark set up and heated to reflux for 4 h. After being cooled down, the reaction was quenched with sat. solution of $NaHCO_3$ (50 mL). The aqueous layer was extracted with EtOAc (4 x 20 mL) and combined organics were washed with brine (1 x 40 mL), dried over Na_2SO_4, filtered, and concentrated to obtain a yellow crude. After purification (CH_2Cl_2:EtOAc, 1:0 $\rightarrow$ 3:1) product **65** was obtained (0.71 g, 85 %) as a colorless oil.

IR (NaCl): 2949, 1635, 1452, 1107 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.33–7.25 (m, 5H, Ph), 5.27 (d, *J* = 15.2 Hz, 1H, CH_2Ph), 4.01–3.88 (m, 5H, OCH_2 and CH_2Ph), 3.44 (bs, 1H, H-1), 2.75 (d, *J* = 18.8 Hz, 1H, H-4), 2.62 (dd, *J* =18.8, 7.2 Hz, 1H, H-4), 2.09–2.08 (m, 1H, H-5), 2.03 (bd, 1H, H-9), 1.83–1.78 (m, 2H, H-9 and H-7), 1.67–1.57 (m, 3H, H-7 and H-8). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.1 (C-3), 137.6, 128.6, 127.8 and 127.3 (Ph), 109.6 (C-6), 64.6 and 64.5 (OCH_2), 50.2 (C-1), 48.1 (CH_2Ph), 36.2 (C-5), 34.0 (C-4), 29.9. (C-9), 27.2 (C-7), 26.9 (C-8).


7.358
7.247
5.286
5.248
3.993
3.893
3.439
2.771
2.724
2.650
2.632
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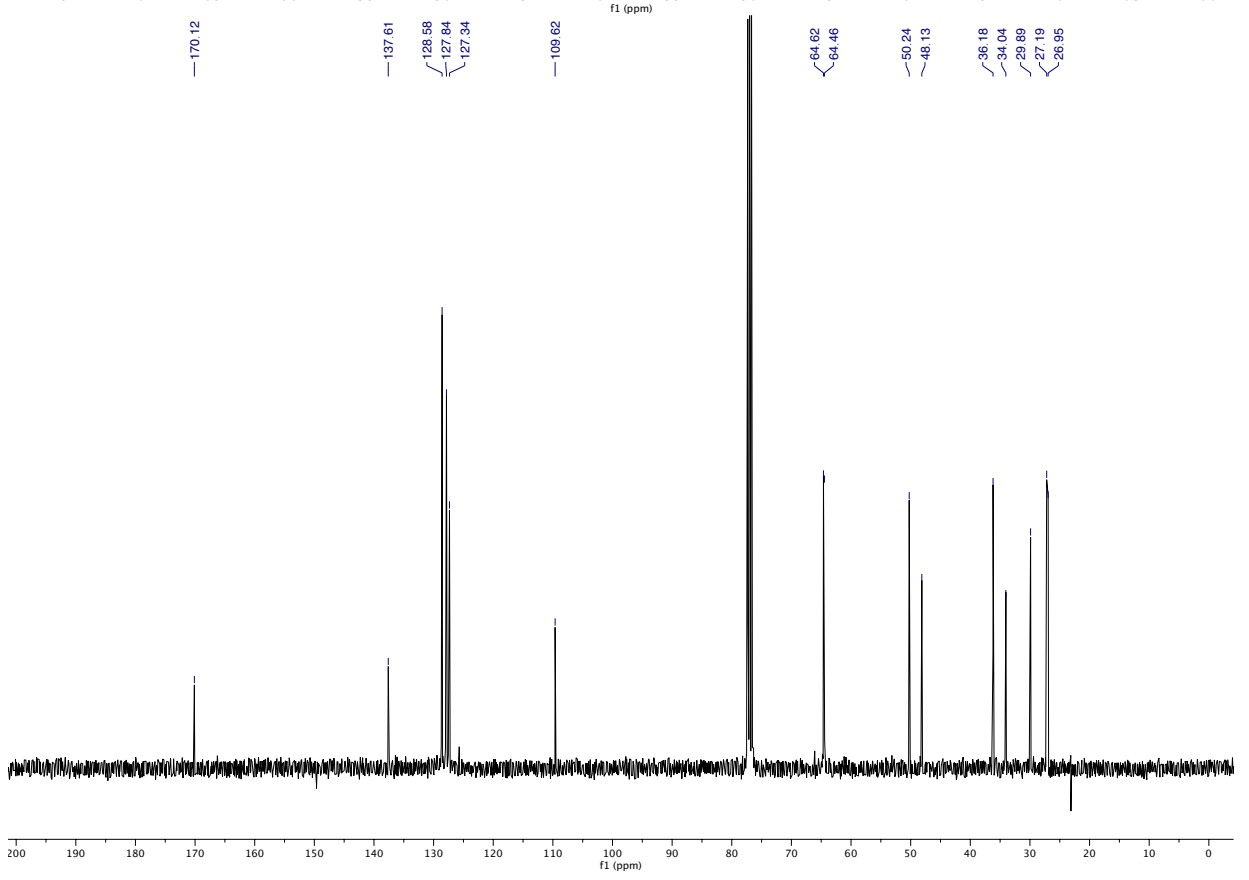
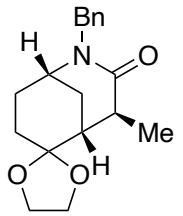
2.585
2.186
2.079
2.047
2.011
1.817
1.781
1.665
1.574
Bn
H
N
O
H
O
O
65
5.39
0.99
5.05
0.99
1.00
1.01
3.26
2.17
3.02
f1 (ppm)

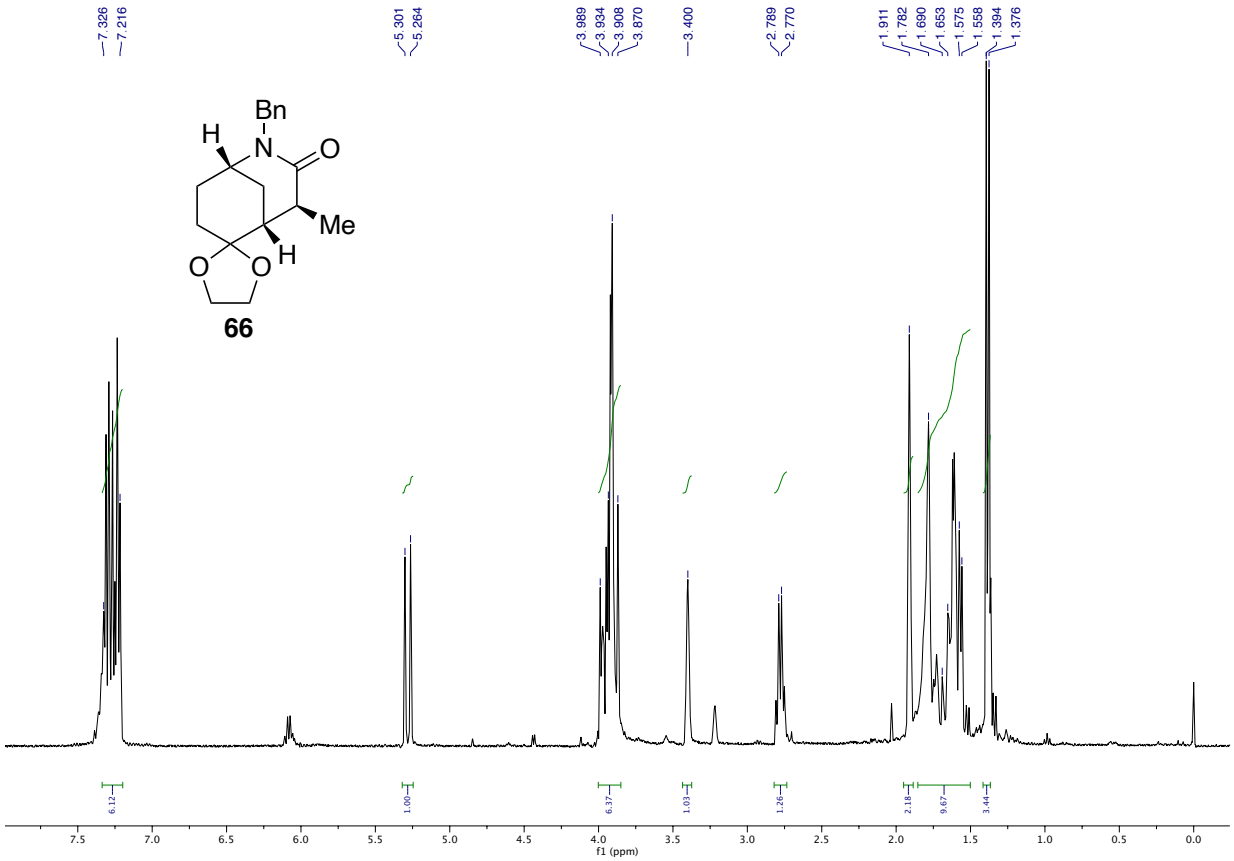

170.12
137.61
128.58
127.84
127.34
109.62
64.62
64.46
50.24
48.13
36.18
34.04
29.89
27.19
26.95
f1 (ppm)

(1*SR*,4*SR*,5*RS*)-2-benzyl-4-methyl-2-azabicyclo[3.3.1]nonan-3,6-dione ethylene acetal (66)

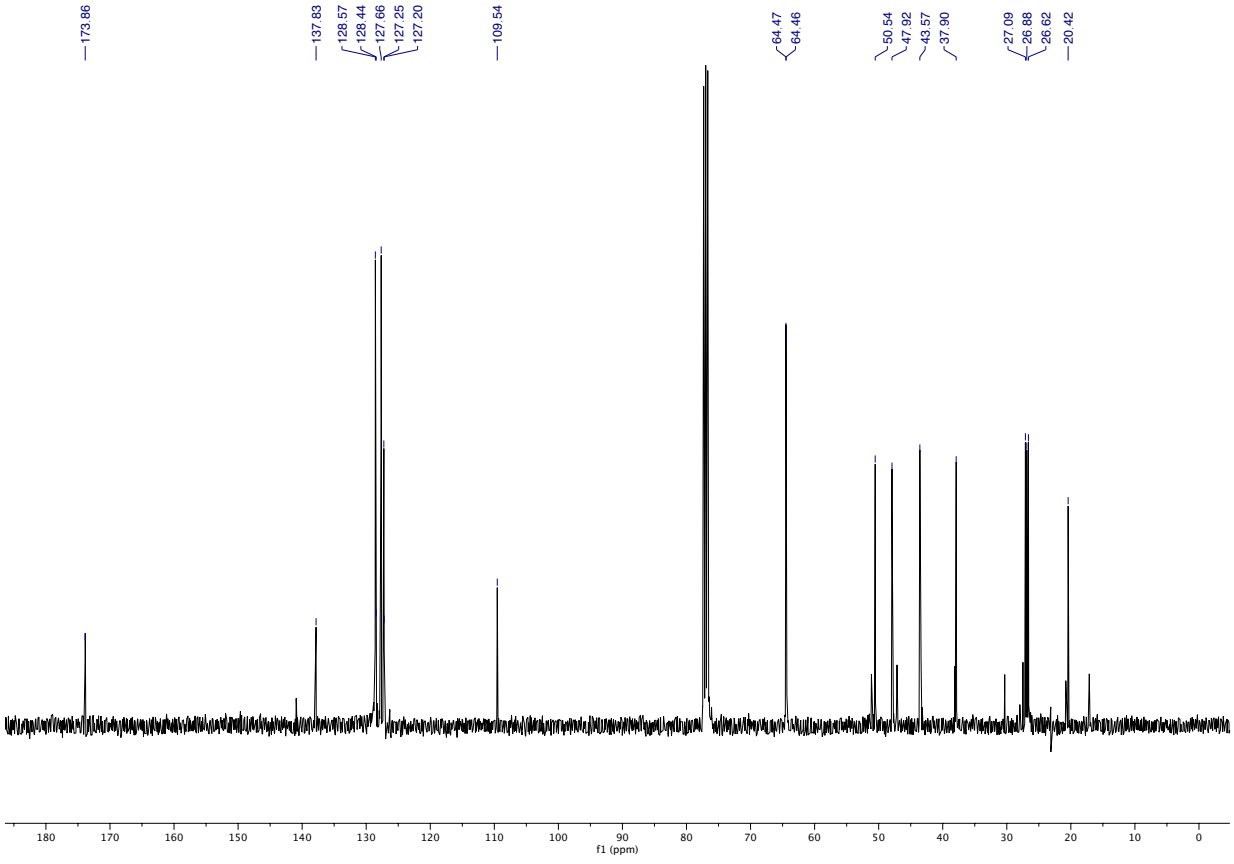


Lactam **65** (0.62 g, 2.19 mmol, 1 equiv) was diluted in THF (24 mL), cooled to -78 ºC and LDA solution (1M in THF, 4.4 mL, 2 equiv) was added dropwise. After stirring for 1 h, iodomethane (0.4 mL, 5.9 mmol, 2.7 equiv) was added to the reaction, and the stirring was prolonged for 3h. Sat. solution of NH_4Cl (20 mL) was added and the mixture was extracted with EtOAc (4x20 mL). Combined organics were dried over Na_2SO_4, filtered, and concentrated under vacuum. The obtained crude was purified by chromatography (CH_2Cl_2:EtOAc, 1:0 $\rightarrow$ 4:1) and compound **66** was obtained (0.50 g, 77%) as a transparent oil.

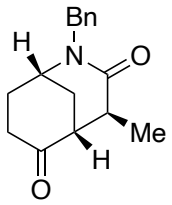
IR (NaCl): 2937, 1634, 1449, 1113 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.22 (m, 5H, Ph), 5.28 (d, *J* = 14.8 Hz, 1H, CH_2Ph), 3.99–3.87 (m, 5H, OCH_2 and CH_2Ph), 3.40 (bs, 1H, H-1), 2.78 (q, *J* = 7.4 Hz, 1H, H-4), 1.91 (bs, 2H, H-9), 1.81–1.69 (m, 3H, H-5 and H-8), 1.65–1.56 (m, 2H, H-7), 1.39 (d, *J* = 7.4 Hz, 3H, Me). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.9 (C-3), 137.8, 128.6, 127.7 and 127.2 (Ph), 109.5 (C-6), 64.5 and 64.5 (OCH_2), 50.5 (C-1), 47.9 (CH_2Ph), 43.6 (C-5), 37.9 (C-4), 27.1 (C-7), 26.9 (C-8), 26.6 (C-9), 20.4 (Me).


7.326
7.216
5.301
5.264
3.989
3.934
3.908
3.870
3.400
2.789
2.770
1.911
1.782
1.690
1.653
1.575
1.558
1.394
1.376
Bn
H
N
O
Me
H
O
O
6.12
1.00
6.17
1.03
1.26
2.18
9.67
3.44
f1 (ppm)

66

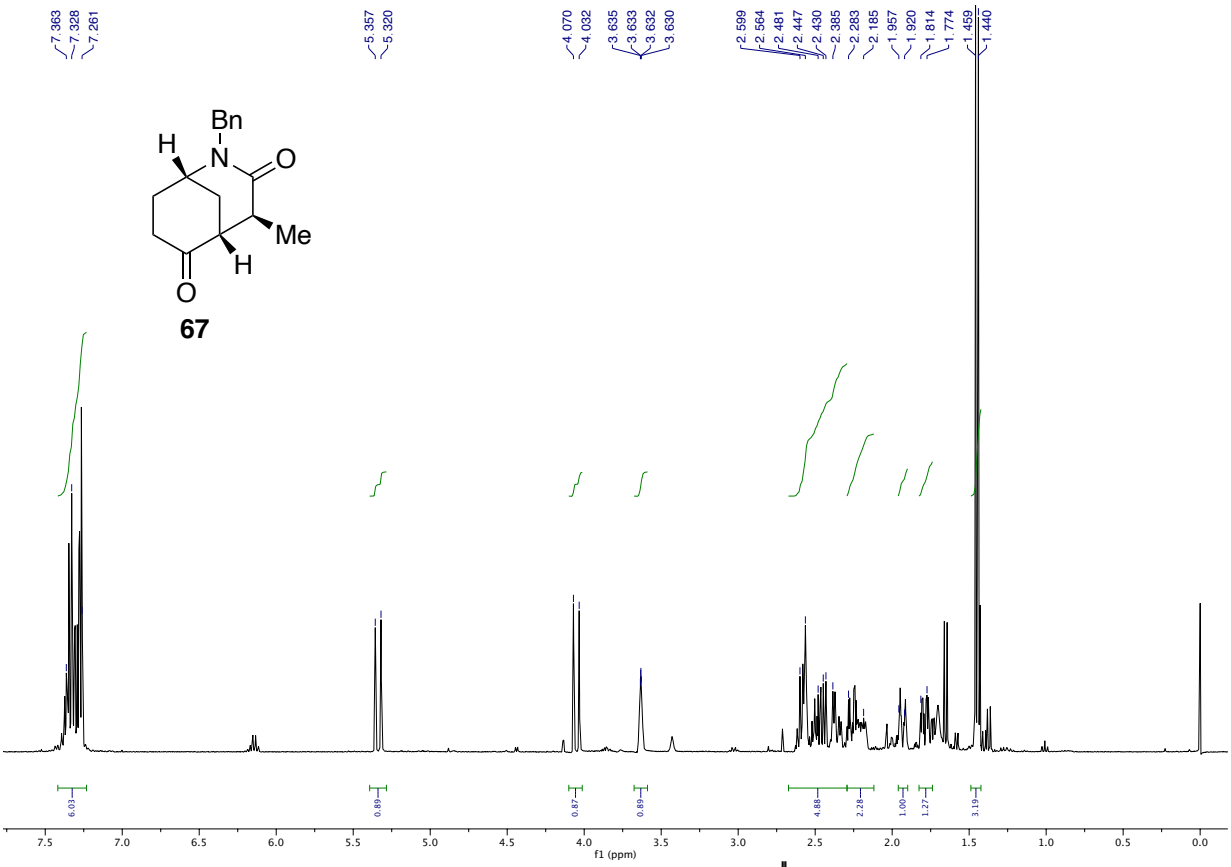

173.86
137.83
128.57
128.44
127.66
127.25
127.20
109.54
64.47
64.46
50.54
47.92
43.57
37.90
27.09
26.88
26.62
20.42
f1 (ppm)

(1*SR*,4*SR*,5*RS*)-2-benzyl-4-methyl-2-azabicyclo[3.3.1]nonan-3,6-dione (67).



Methylated lactam **66** (113 mg, 0.38 mmol) was diluted in THF (4 mL) and 10% HCl solution was added (8 mL). After stirring overnight at room temperature, Na_2CO_3 (20 mL) was added, and the mixture was extracted with CH_2Cl_2 (4 x 10 mL). The organics were dried over Na_2SO_4, filtered and concentrated under vacuum to provide with a crude that was purified by chromatography (CH_2Cl_2:EtOAc, 1:0 $\rightarrow$ 9:1). Compound **67** was obtained as a transparent oil (92 mg, 95%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.26 (Ph), 5.34 and 4.05 (2d, J = 15.0 Hz, 1H each, CH_2Ph), 3.63 (bs, 1H, H-1), 2.59 (q, J = 7.6 Hz, 1H, H-4), 2.56 (bs, 1H, H-5), 2.46 (dd, J = 13.4, 7.2 Hz, 1H, H-7), 2.36–2.33 (m, 1H, H-7), 2.26 (dq, J = 13.6, 3.6 Hz, 1H, H-9), 2.23–2.16 (m, 1H, H-8), 1.93 (dm, J = 13.6 Hz, 1H, H-9), 1.77 (tdd, J = 13.6, 5.4, 2.6 Hz, 1H, H-8), 1.45 (d, J = 7.6 Hz, 3H, Me). ^{13}C NMR (101 MHz, $CDCl_3$) δ 210.8 (C-6), 172.2 (C-3), 137.3, 128.8, 127.8 and 127.2 (Ph), 51.2 (C-5), 50.3 (C-1), 48.3 (CH_2Ph), 39.2 (C-4), 34.2 (C-7), 29.5 (C-8), 28.5 (C-9), 19.8 (Me).


7.363
7.328
7.261
5.357
5.320
4.070
4.032
3.635
3.633
3.632
3.630
2.599
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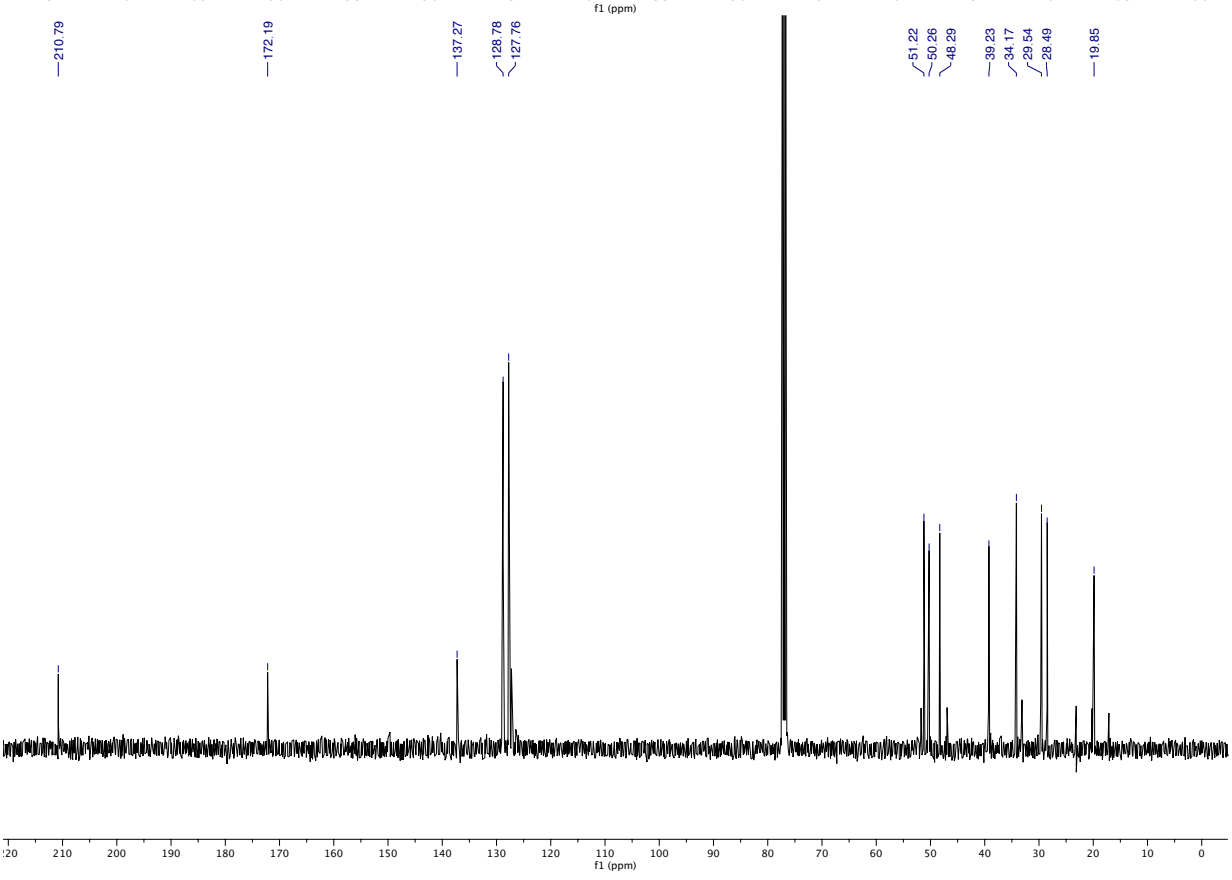
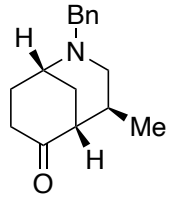
2.481
2.447
2.430
2.385
2.283
2.185
1.957
1.920
1.814
1.774
1.459
1.440
Bn
H
N
O
Me
H
O
6.03
0.89
0.87
0.89
4.68
2.28
1.00
1.27
3.19
f1 (ppm)

67

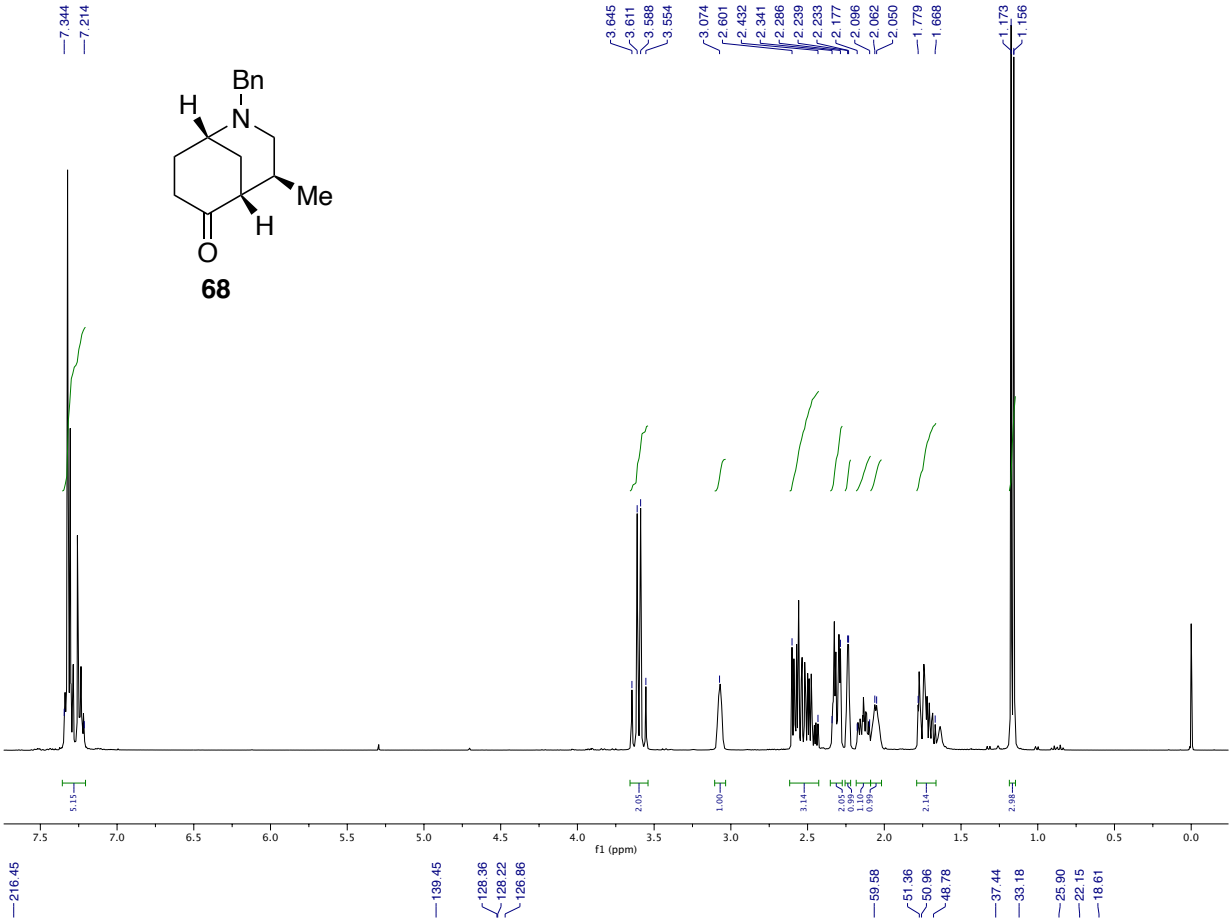

210.79
172.19
137.27
128.78
127.76
51.22
50.26
48.29
39.23
34.17
29.54
28.49
19.85
f1 (ppm)

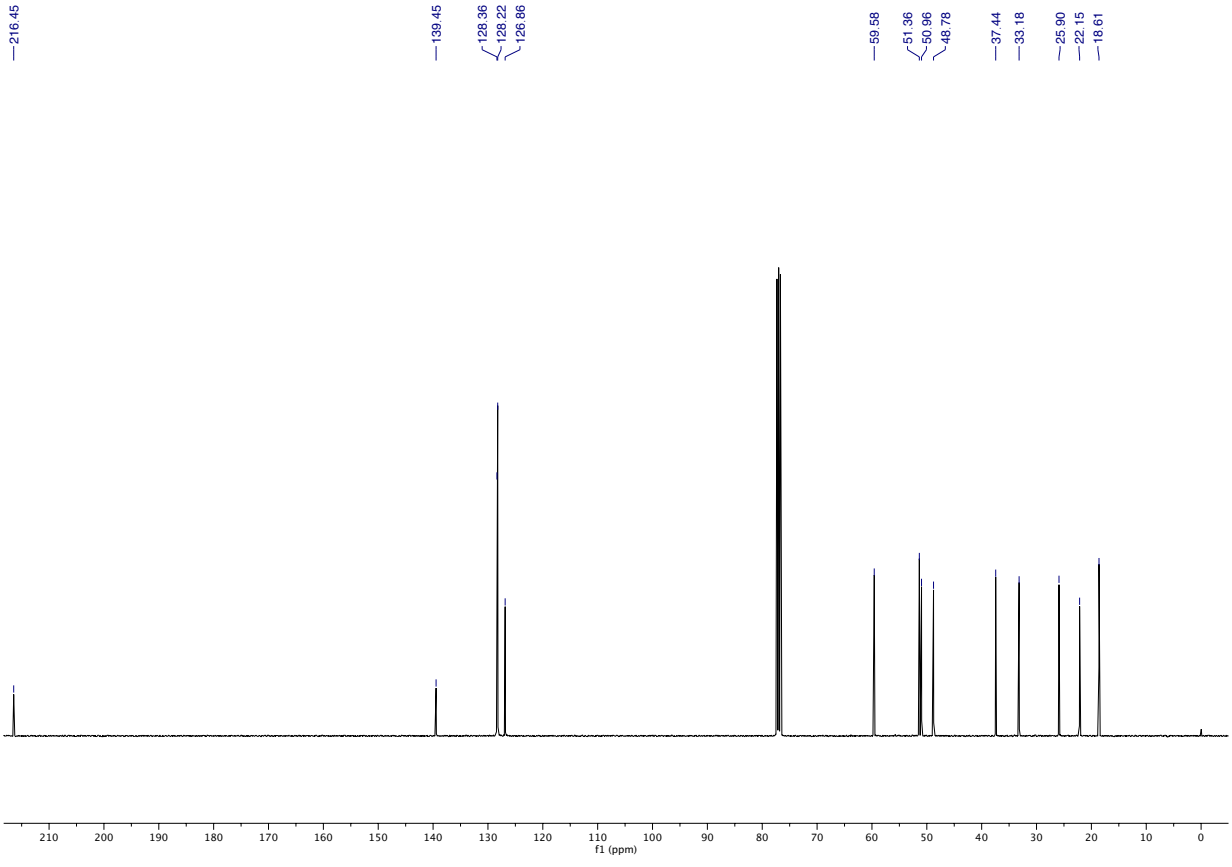
(1*SR*,4*SR*, 5*RS*)-2-benzyl-4-methyl-2-azabicyclo[3.3.1]nonan-6-one (68)



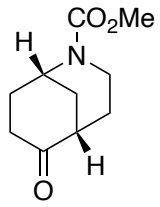
To a solution of $AlCl_3$ (0.18 g, 1.35 mmol, 1.5 equiv) in THF (4 mL), a solution of $LiAlH_4$ (1M in THF, 1.8 mL, 2 equiv) was added dropwise at room temperature. After being stirred for 30 min, a solution of lactam **66** (0.27 g, 0.9 mmol, 1 equiv) was added dropwise via cannula. The reaction was stirred overnight and, after being cooled to 0 ºC, it was quenched with 30% KOH aqueous solution. The mixture was extracted with CH_2Cl_2 (4 x 15 mL) and the combined organic phases were dried over Na_2SO_4, filtered, and concentrated. The obtained protected amine was diluted in 10% HCl aqueous solution (5 mL) and the reaction was stirred overnight at room temperature. Then it was quenched with 15% NaOH, and the mixture was extracted with CH_2Cl_2 (5x10 mL). The organic phases were dried over Na_2SO_4, filtered, and concentrated to afford the crude that was purified by a flash chromatographic column (Al_2O_3, hexane:EtOAc, 98.2). Aminoketone **68** was obtained as a transparent oil. (0.18 g, 83% over two steps).

IR (NaCl): 2926, 1704, 1425 cm^{-1} . ^1H NMR (400 MHz, $CDCl_3$) δ 7.34–7.21 (m, 5H, Ph), 3.63 and 3.57 (2d, J = 13.6 Hz, 1H each, CH_2Ph), 3.07 (bs, 1H, H-1), 2.58 (dd, J = 12.2, 5.6 Hz, 1H, H-3), 2.54 (dd, J = 8.8, 5.6 Hz, 1H, H-7), 2.49 (dd, J = 8.8, 5.6 Hz, 1H, H-7), 2.34–2.29 (m, 1H, H-9), 2.30 (dd, J = 12.2, 3.8 Hz, 1H, H-3), 2.24 (bd, J = 2.4 Hz, 1H, H-5), 2.17–2.10 (m, 1H, H-8), 2.06–2.05 (m, 1H, H-4), 1.78–1.68 (m, 1H, H-8), 1.16 (d, J = 6.8 Hz, 3H, Me). ^{13}C NMR (101 MHz, $CDCl_3$) δ 216.5 (C-6), 139.5, 128.4, 128.2 and 126.9 (Ph), 59.6 (CH_2Ph), 51.4 (C-3), 51.0 (C-1), 48.8 (C-5), 37.4 (C-7), 33.2 (C-4), 25.9 (C-9), 22.3 (C-8), 18.6 (Me).


7.344
7.214
3.645
3.611
3.588
3.554
3.074
2.601
2.432
2.341
2.286
2.239
2.233
2.177
2.096
2.062
2.050
1.779
1.668
1.173
1.156
Bn
H
N
Me
H
O
68
f1 (ppm)

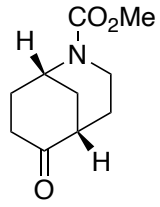

216.45
139.45
128.36
128.22
126.86
59.58
51.36
50.96
48.78
37.44
33.18
25.90
22.15
18.61
f1 (ppm)

(1*SR*,5*SR*)-2-methoxycarbonyl-2-azabicyclo[3.3.1]nonan-6-one (69)



To a solution of compound **63** (0.12 g, 0.52 mmol, 1 equiv) in dry $CHCl_3$ (2 mL), were added $NaHCO_3$ (0.66 g, 7.9 mmol,15 equiv) and methyl chloroformate (0.84 g, 0.69 mL, 8.9 mmol, 17 equiv). The reaction mixture was placed in a sealed tube and stirred at reflux overnight. Then, the mixture was cooled to room temperature and diluted with CH_2Cl_2 (10 mL) and the organic layer was washed with water, dried, and concentrated. The crude was purified by chromatography (hexane:EtOAc, 1:0 → 3:1) providing **69** as a transparent oil (89 mg, 86 %).

IR (neat): 2942, 1695, 1450, 1215 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.59 and 4.44 (2 bs, 1H, H-1), 4.02–3.91 (m, 1H, H-3), 3.74 (s, 3H, OMe), 3.22 (dd, *J* = 13.6, 1H, H-3), 2.66 (m, 2H, H-5), 2.54–2.48 (m, 2H, H-7) 2.11 (bs, 2H, H-8), 2.01 (bs, 2H, H-9), 1.90–1.88 (m, 2H, H-4). ^{13}C NMR (101 MHz, $CDCl_3$) δ 214 and 213.6 (C-6),156.3 (CO_2Me), 52.6 (OMe), 44.8 and 44.6 (C-1), 42.2 (C-5), 38.9 (C-3), 37.7(C-7), 31.0 and 30.8 (C-9), 29.4 and 28.7 (C-8), 27.9 and 27.6 (C-4).


CO2Me
H
N
H
O

69

4.593
4.444
4.017
3.905
3.728
3.240
3.226
3.206
3.191
2.657
2.536
2.478
2.105
2.012
1.896
1.865
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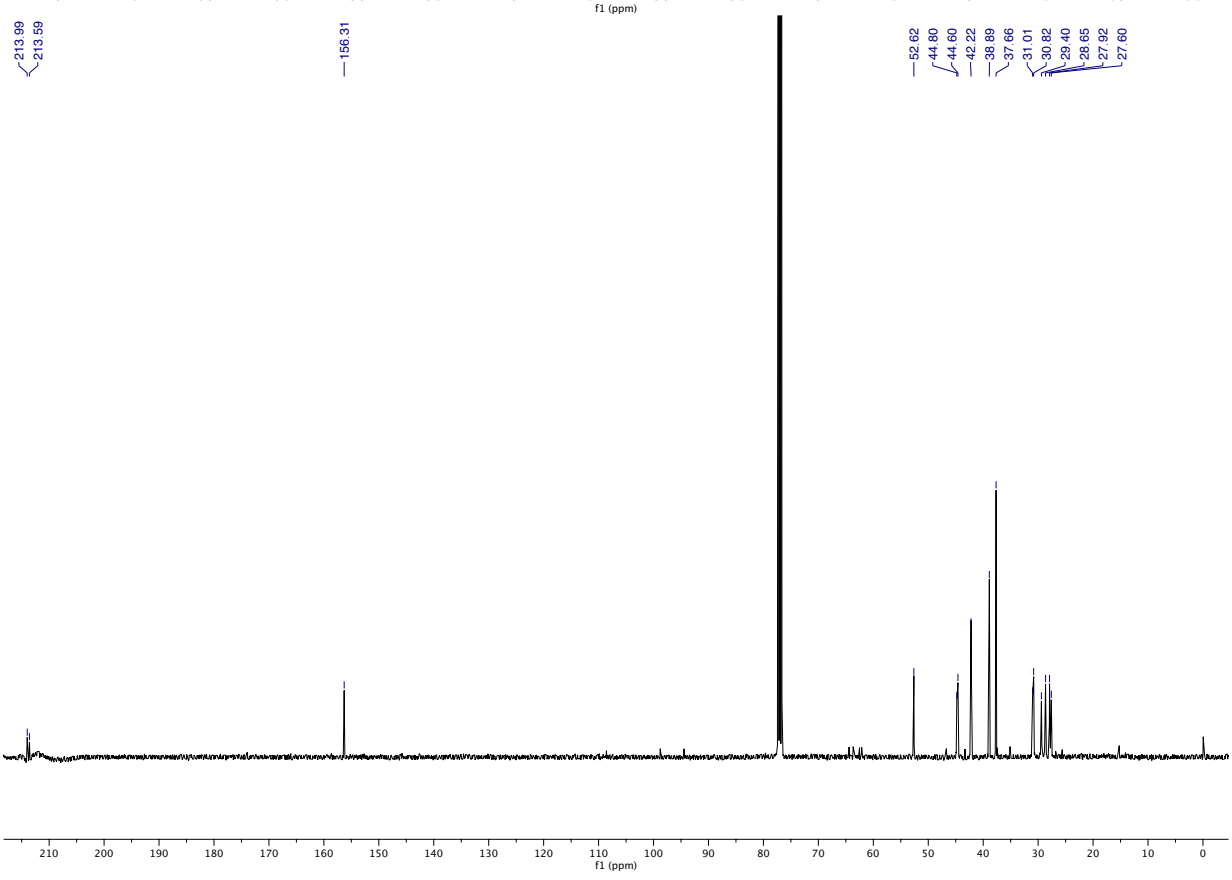
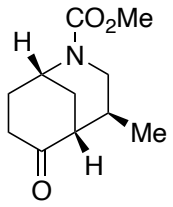
1.13
3.13
1.06
1.03
2.15
2.12
2.28
2.08
f1 (ppm)

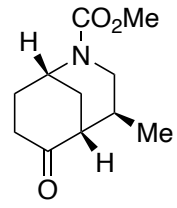

213.99
213.59
156.31
52.62
44.80
44.60
42.22
38.89
37.66
31.01
30.82
29.40
28.65
27.92
27.60
f1 (ppm)

(1*SR*,5*SR*)-2-methoxycarbonyl-2-azabicyclo[3.3.1]nonan-6-one (70)



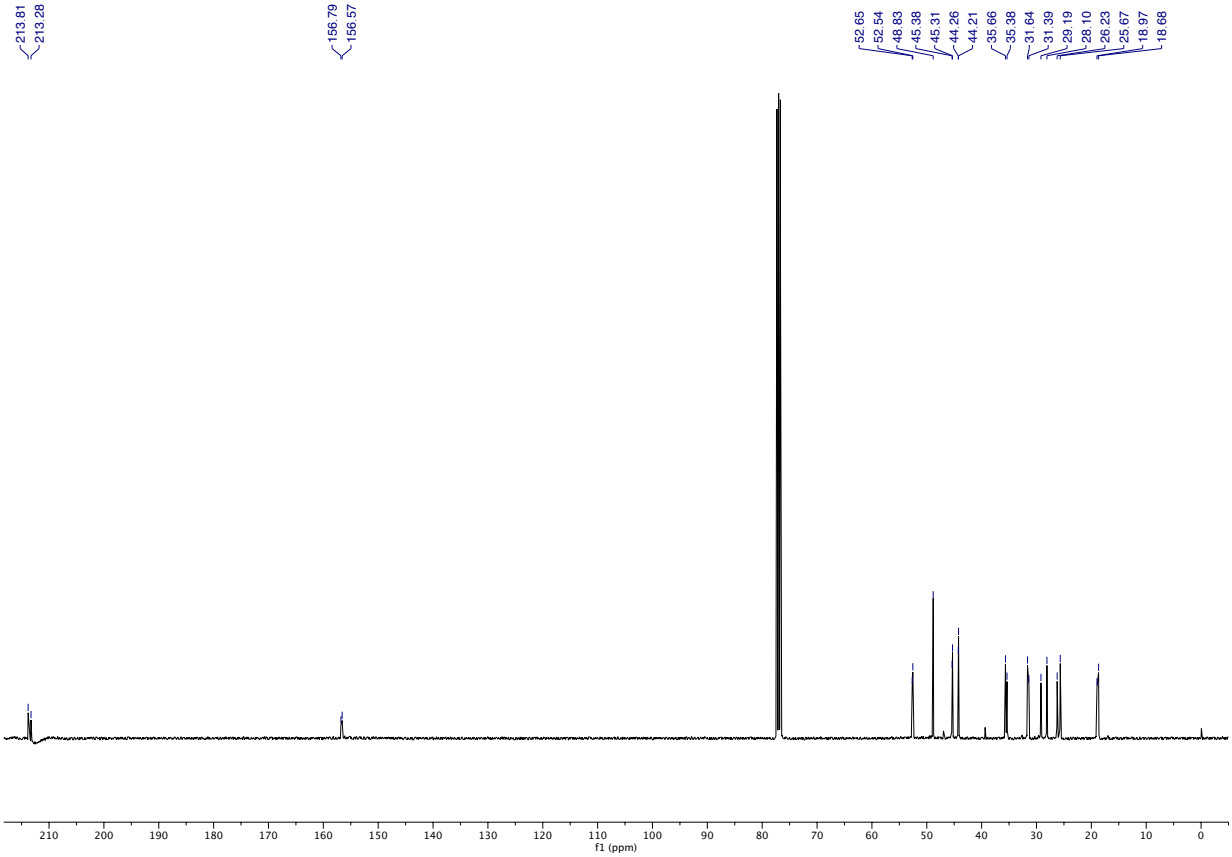
To a solution of compound **68** (105 mg, 0.43 mmol, 1 equiv) in dry $CHCl_3$ (1.5 mL), $NaHCO_3$ (0.54 g, 6.47 mmol, 15 equiv) and methyl chloroformate (0.69 g, 0.57 mL, 7.3 mmol, 17 equiv) were added. The reaction mixture was placed in a sealed tube and stirred at reflux overnight. Then, the mixture was cooled to room temperature, diluted with CH_2Cl_2 (10 mL), and the organic layer was washed with water, dried over Na_2SO_4 and concentrated. The crude was purified by chromatography (hexane:EtOAc, 1:0 $\rightarrow$ 3:1) providing **70** as a transparent oil (69 mg, 75 %).

IR (neat): 2956, 2873, 1699, 1447, 1230 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 4.43–4.28 (2 s, 1H, H-1), 3.71 (s, 3H, OMe), 3.58–3.48 (m, 1H, H-3), 3.31 (dm, *J* = 13.6 Hz, 1H, H-3), 2.61 and 2.40 (2m, 1H each, H-7), 2.31 (s, 1H, H-5), 2.24 (m, 1H, H-9), 2.17 (m, 1H, H-8), 2.03 (s, 1H, H-4), 1.95 (m, 1H, H-8), 1.78 (m, 1H, H-9), 1.09 (s, 3H, Me). ^{13}C NMR (101 MHz, $CDCl_3$) δ 213.8 and 213.3 (C-6),156.8 and 156.7 (CO_2Me), 52.7 and 52.5 (OMe), 48.8 (C-5), 44.4 and 45.3 (C-3), 35.7 and 35.4 (C-7), 31.6 and 31.4 (C-4), 29.1 and 28.1 (C-8), 26.3 and 25.7 (C-9), 19.0 and 18.7 (Me).

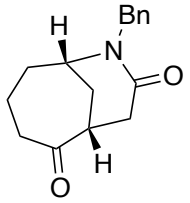

CO2Me
H
N
Me
H
O

70

4.433
4.276
3.723
3.576
3.475
3.329
3.295
2.612
2.402
2.306
2.244
2.168
2.033
1.784
1.088
f1 (ppm)

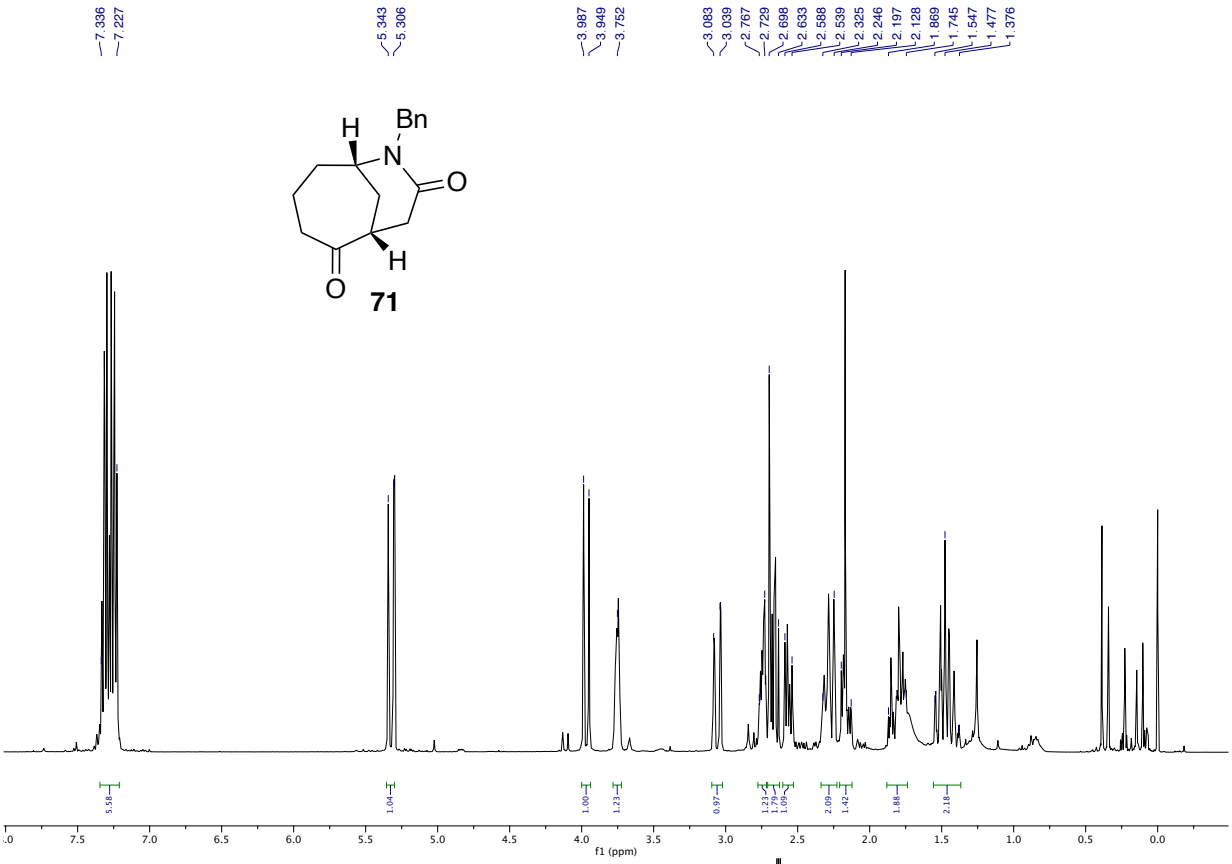

213.81
213.28
156.79
156.57
52.65
52.54
48.83
45.38
45.31
44.26
44.21
35.66
35.38
31.64
31.39
29.19
28.10
26.23
25.67
18.97
18.68
f1 (ppm)

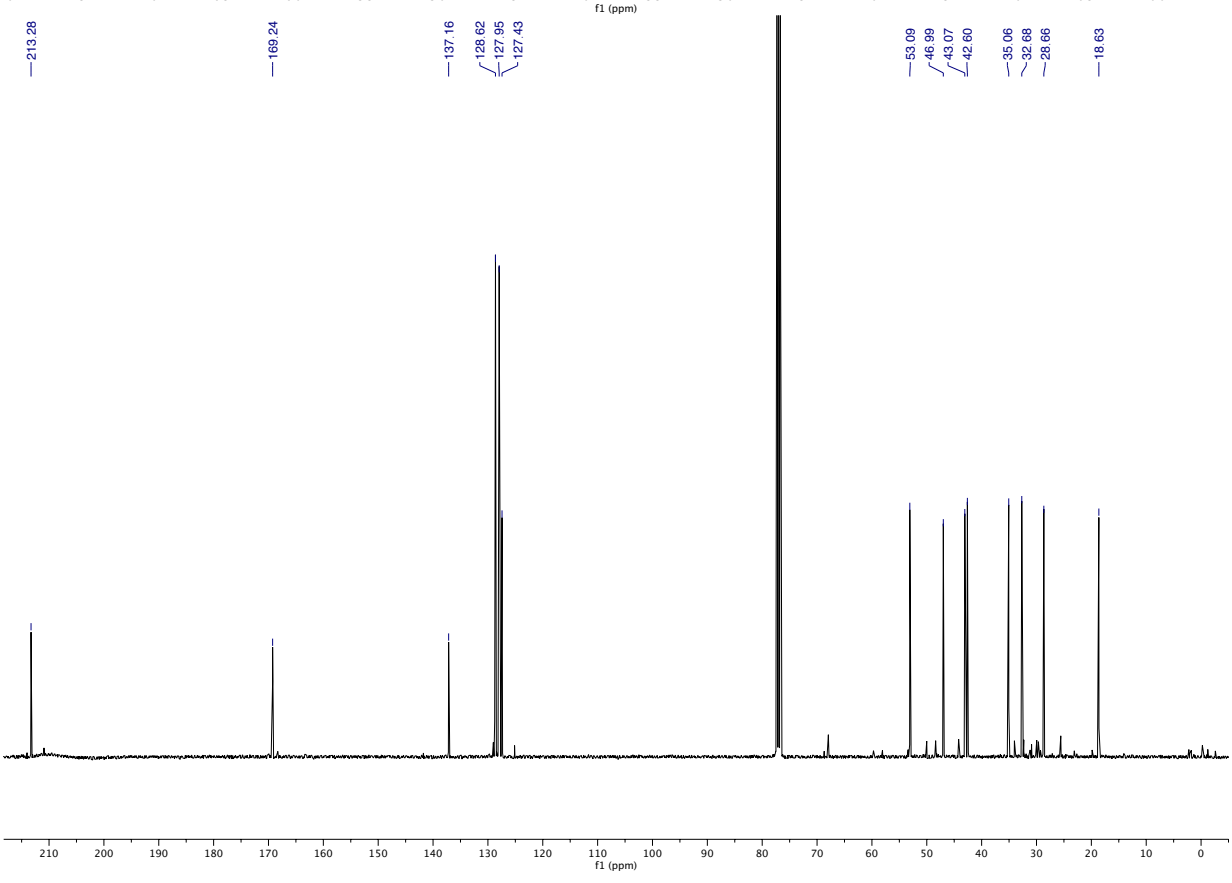
(1*RS*,6*SR*)-7-Benzyl-7-azabicyclo[4.3.1]decane-2,8-dione (71)



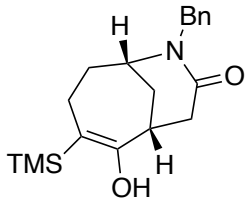
Method C: To a solution of *n*-BuLi (2.5 M in hexanes, 0.4 mL, 0.98 mmol, 2.25 equiv.) in Et_2O (10 mL) at -78 ºC $TMSCHN_2$ (0.6 M in hexanes, 0.44 mL, 0.98 mmol, 2.25 equiv.) was added. After being stirred for 40 min a solution of **64** (0.10 g ,0.44 mmol) in THF (11 mL) was added slowly over 20 min via syringe pump. The reaction was stirred at -78 ºC for 2 h, then, a solution of MeOH/THF (1:9, 10 mL) was added, and the mixture was stirred at room temperature for 30 min. A solution of 2 M NaOH was added, phases were separated, and the aqueous layer was extracted sequentially with CH_2Cl_2 (2 x 30 mL), $CHCl_3$ (2 x 20 mL), and $CHCl_3$: iPrOH (4:1) (2 x 15 mL). To the combined organics were added SiO_2 and Na_2SO_4 and it was stirred at room temperature for 40 min, observing a tonality variation and an effervescence due to nitrogen gas generation. The reaction mixture was filtered through a celite pad and concentrated to obtain the crude which was purified by chromatography (CH_2Cl_2:EtOAc, 1:0 → 98:2) providing **71** as solid (30 mg, 27%) along with undesired product **72** (24.5 mg, 21% yield).

IR (NaCl): 2930, 1698, 1638, 1450 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.33–7.23 (m, 5H, Ph), 5.32 and 3.97 (2 d, *J* = 15.0 Hz, 1H each, CH_2Ph), 3.77–3.73 (m, 1H, H-6), 3.06 (d, *J* = 18.0 Hz, 1H, H-9), 2.76–2.72 (m, 1H, H-1), 2.70–2.63 (m, 2H, H-9 and H-3), 2.59–2.54 (m, 1H, H-3), 2.29–2.25 (m, 2H, H-5 and H-10), 2.21–2.13 (m, 1H, H-10), 1.87–1.74 (m, 1H, H-4), 1.55–1.38 (m, 2H, H-4 and H-5) . ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.3 (C-2), 169.2 (C-8), 137.2, 128.6, 127.9 and 127.4 (Ph), 53.1 (C-6), 47.0 (CH_2Ph), 43.1 (C-3), 42.6 (C-1), 35.1 (C-9), 32.7 (C-5), 28.7 (C-10), 18.6 (C-4).

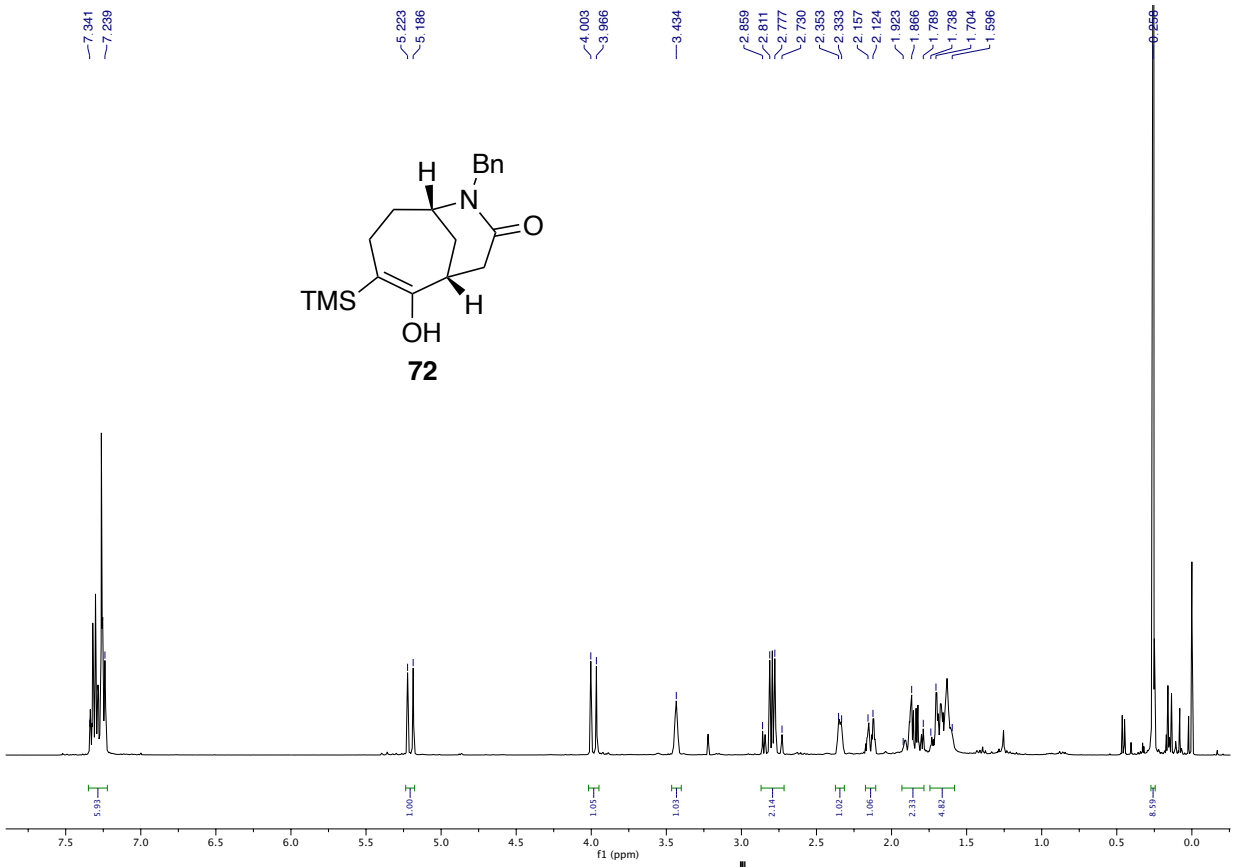

7.336
7.227
5.343
5.306
3.987
3.949
3.752
3.083
3.039
2.767
2.729
2.698
2.633
2.588
2.539
2.325
2.246
2.197
2.128
1.869
1.745
1.547
1.477
1.376
H
Bn
N
O
O
H
71
f1 (ppm)


213.28
169.24
137.16
128.62
127.95
127.43
53.09
46.99
43.07
42.60
35.06
32.68
28.66
18.63
f1 (ppm)

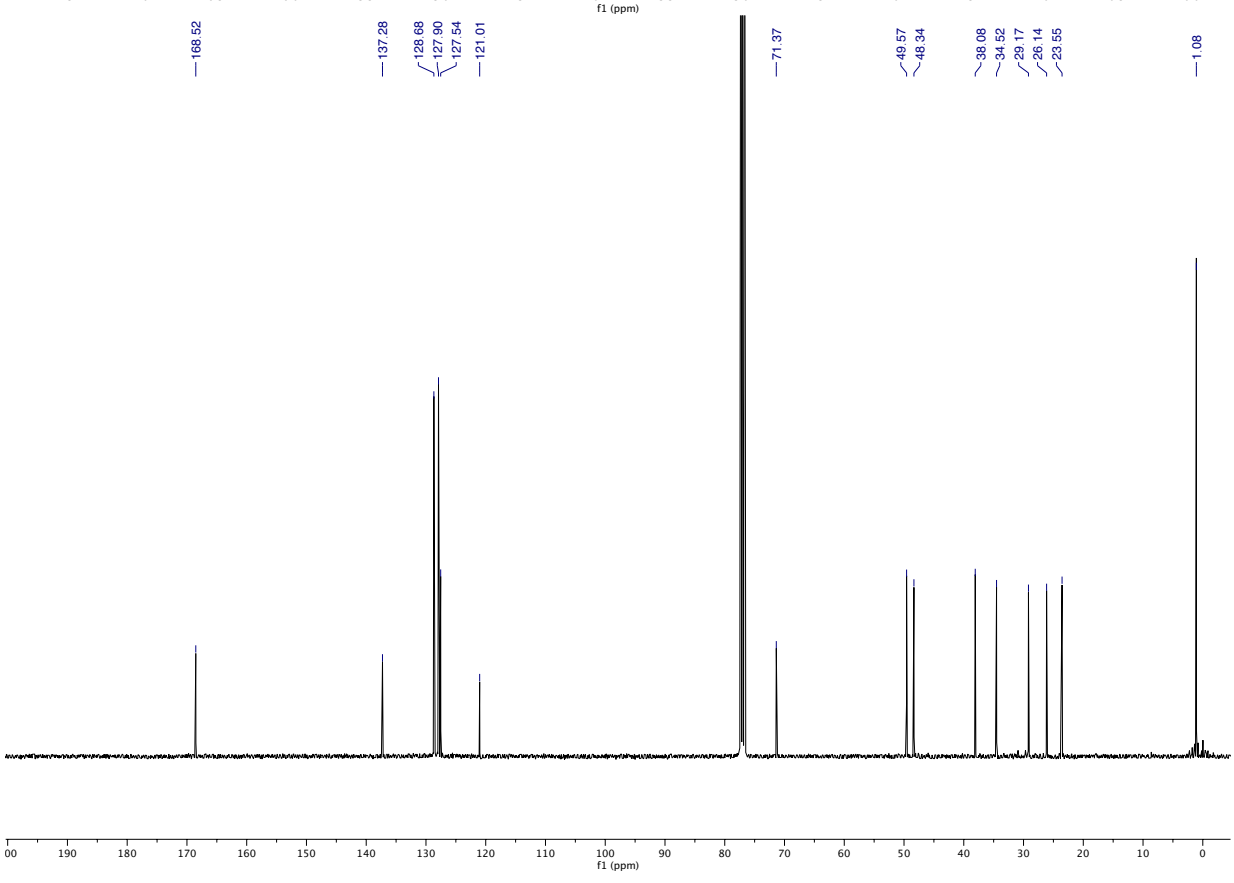
(1*RS*,6*SR*)-7-Benzyl-2-hydroxy-3-(trimethylsilyl)-7-azabicyclo[4.3.1]dec-2-en-8-one (72)



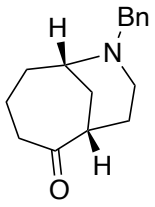
IR (neat): 2954, 1644, 1452, 1254, 849 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.24 (m, 5H, Ph), 5.20 and 3.98 (2d, J = 14.8 Hz, 1H, CH_2Ph), 3.43 (bs, 1H, H-6), 2.83 (dd, J = 19.0, 6.8 Hz, 1H, H-9), 2.75 (dm, J = 19.0 Hz, 1H, H-9) 2.35–2.33 (m, 1H, H-1), 2.14 (dq, J = 13.2, 2.8 Hz, 1H, H-10), 1.92–1.79 (m, 2H, H-4), 1.70–1.60 (m, 3H, H-10 and H-5), 0.26 (s, 9H, TMS). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.7 (C-8), 137.3, 128.7, 127.9 and 127.5 (Ph), 121.2 (C-2), 71.4 (C-3), 49.6 (C-6), 48.3 (CH_2Ph), 38.1 (C-1), 34.5 (C-9), 29.2 (C-4), 26.1 (C-10), 23.6 (C-5), 1.24 (TMS).


7.341
7.239
5.223
5.186
4.003
3.966
3.434
2.859
2.811
2.777
2.730
2.353
2.333
2.157
2.124
1.923
1.866
1.789
1.738
1.704
1.596
0.256
H
Bn
N
O
TMS
H
OH
5.93
1.00
1.05
1.03
2.14
1.02
1.06
2.33
4.82
8.59
f1 (ppm)

72

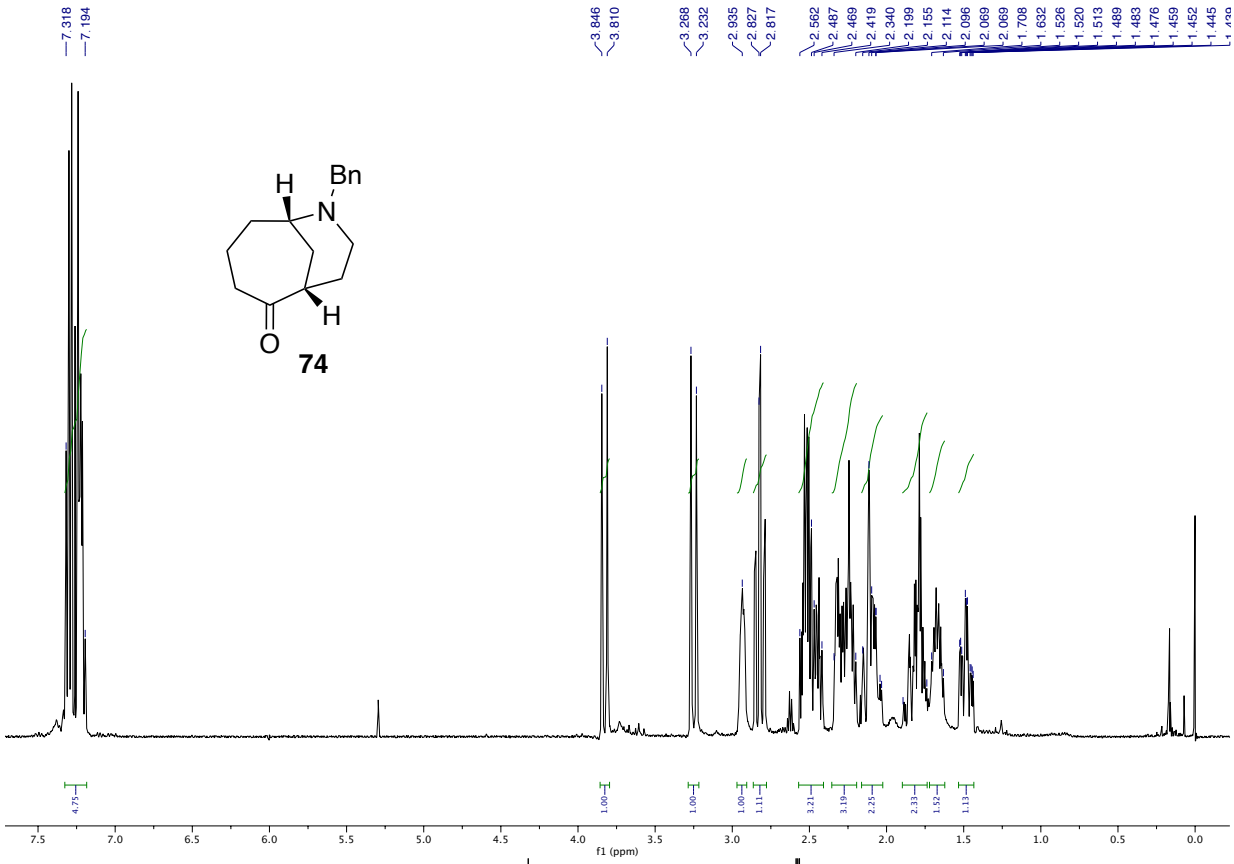

168.52
137.28
128.68
127.90
127.54
121.01
71.37
49.57
48.34
38.08
34.52
29.17
26.14
23.55
1.08
f1 (ppm)

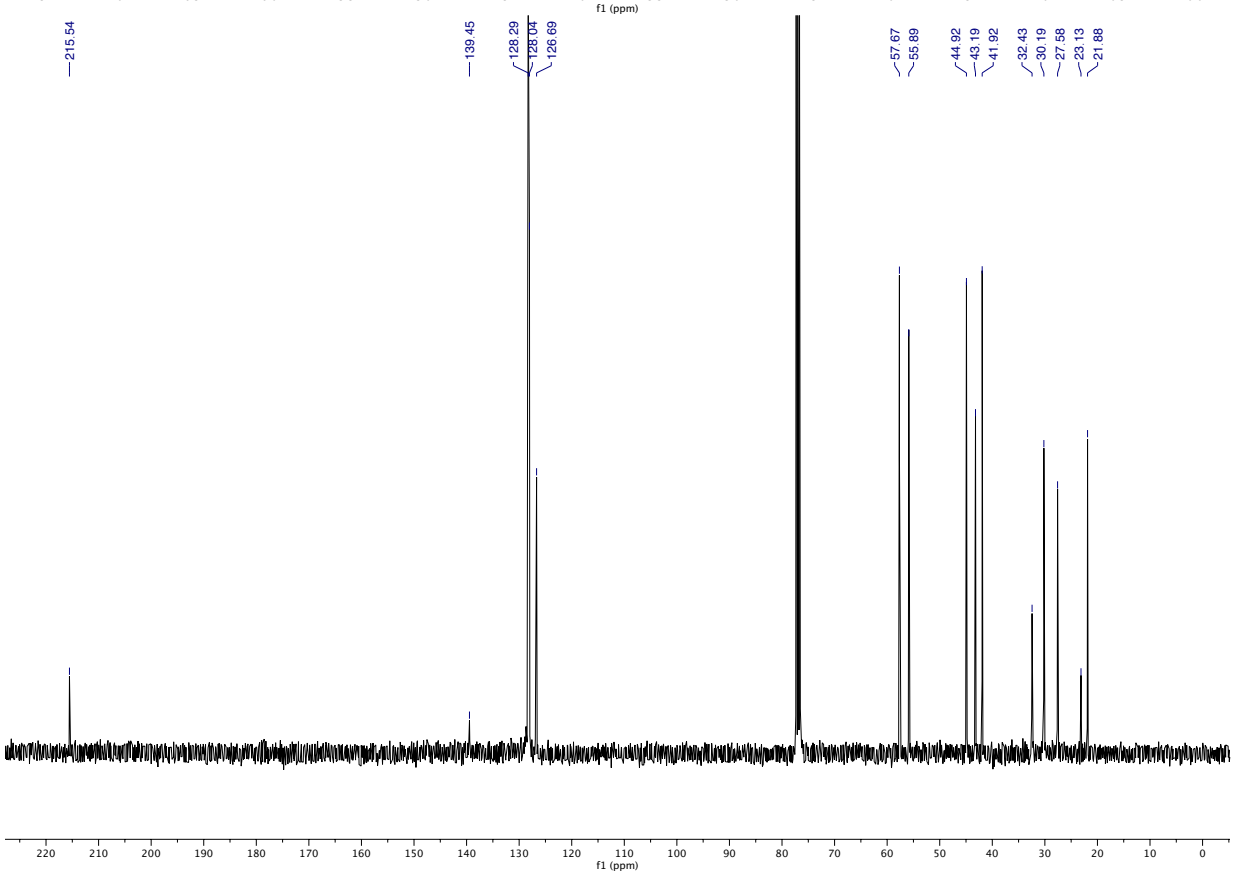
(1*SR*, 6*SR*)-7-Benzyl-7-azabicylo[4.3.1]decan-2-one (74)



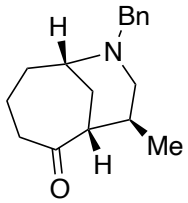
n-BuLi (2.5 M in hexanes, 1.92 mL, 4.8 mmol, 2.25 equiv) was added to Et_2O at -78 ºC followed by the addition of $TMSCHN_2$ (0.6 M in hexanes, 8 mL, 4.8 mmol, 2.25 equiv). After being stirred for 40 min a solution of **63** (0.49 g, 2.1 mmol) in THF (53 mL) was added slowly over 20 min with a syringe pump. The reaction was stirred at -78 ºC for 2 h, then, a solution of MeOH/THF (1:9, 20 mL) was added, and the mixture was stirred at room temperature for 30 min. A solution of 2 M NaOH was added, the phases were separated, and the aqueous layer was extracted sequentially with CH_2Cl_2 (2 x 50 mL), $CHCl_3$ (3 x 50 mL) and $CHCl_3$: iPrOH (4:1, 2 x 25 mL). To the combined organics were added SiO_2 and Na_2SO_4 and it was stirred at room temperature for 40 min. The reaction mixture was filtered through celite pad and concentrated to obtain the crude which was purified by chromatography (Al_2O_3, hexane:EtOAc, 1:0 → 9.8:0.2) providing **74** as white solid (0.35 g, 67%).

mp: 78-81 (ºC). IR (NaCl): 2952, 2360, 2342, 1696, 1446 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 3.83 and 3.25 (2d, *J* = 14.4 Hz, 1H each, CH_2Ph), 2.94 (bt, 1H, H-6), 2.82 (td, *J* = 12, 4 Hz, 1H, H-3), 2.56–2.47 (m, 2H, H-3, H-8), 2.45 (ddt, *J* = 14.4, 7.6, 2 Hz, 1H, H-9), 2.32 (dtd, *J* = 7.6, 3.6, 1.6 Hz, H-1), 2.29–2.20 (m, 2H, H-5, H-8), 2.13 (ddd, *J* = 14.4, 3.6, 1.8 Hz, 1H, H-10), 2.06 (ddd, *J* = 14.4, 7.6, 3.6 Hz, 1H, H-10), 1.86–1.74 (m, 2H, H-4), 1.71-1.63 (m, 1H, H-9), 1.48 (dddd, *J* = 14.8, 12.4, 5.4, 2.8 Hz, 1H, H-5). ^{13}C NMR (101 MHz, $CDCl_3$) δ 215.5 (C-2), 139.5, 128.3, 128.0 and 126.7 (Ph), 57.7 (CH_2Ph), 55.9 (C-6), 44.9 (C-8), 43.2 (C-3), 41.9 (C-1), 32.4 (C-5), 30.2 (C-10), 27.6 (C-9), 21.9 (C-4).


7.318
7.194
3.846
3.810
3.268
3.232
2.935
2.827
2.817
2.562
2.487
2.469
2.419
2.340
2.199
2.155
2.114
2.096
2.069
2.069
1.708
1.632
1.526
1.520
1.513
1.489
1.483
1.476
1.459
1.452
1.445
H
Bn
N
H
O
74
4.75
1.00
1.00
1.00
1.11
3.21
3.19
2.25
2.33
1.52
1.13
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

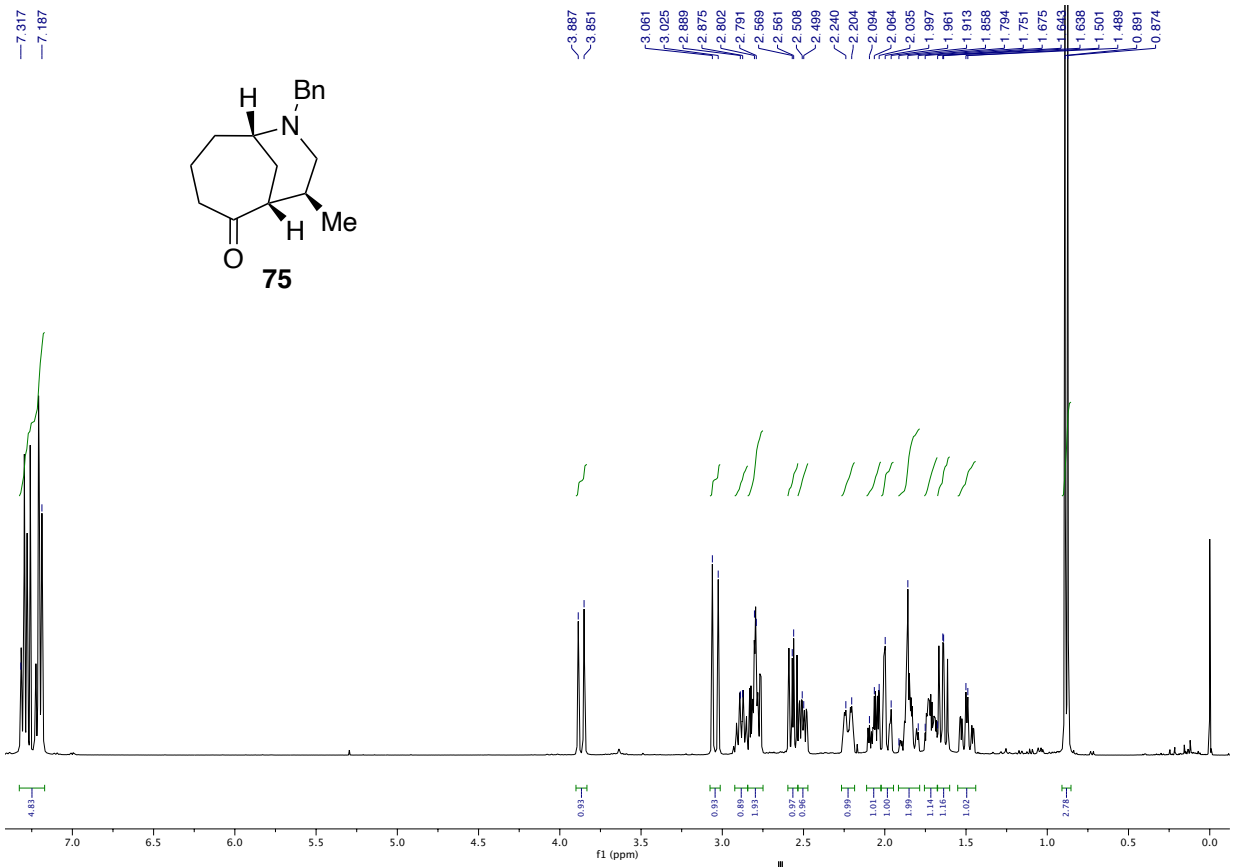

215.54
139.45
128.29
128.04
126.69
57.67
55.89
44.92
43.19
41.92
32.43
30.19
27.58
23.13
21.88
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

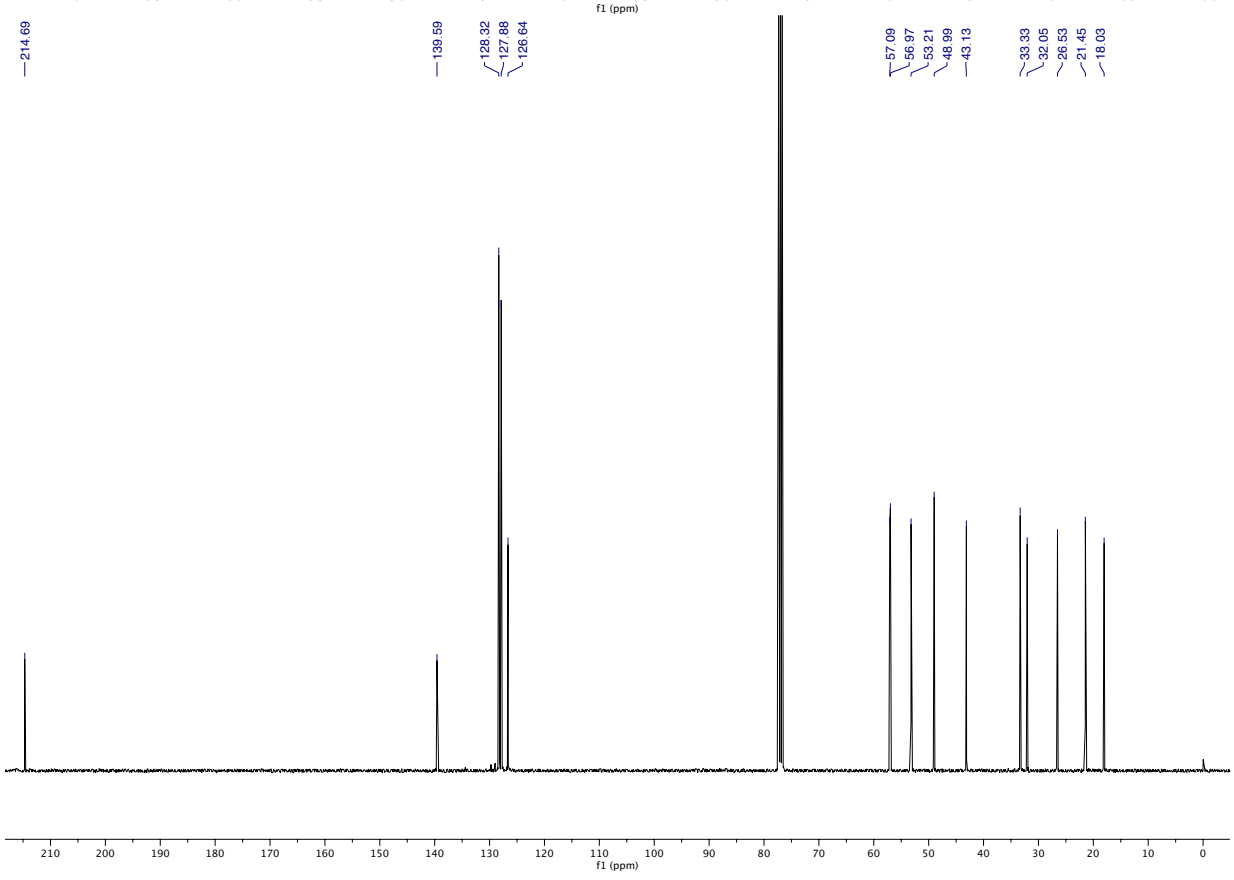
(1*RS*, 6*SR*, 9*SR*)-7-Benzyl-9-methyl-7-azabicyclo[4.3.1]decan-2-one (75)



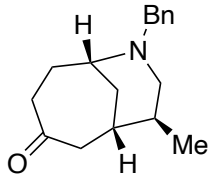
n-BuLi (2.5 M in hexanes, 0.82 mL, 2.05 mmol, 2.25 equiv) was added to Et_2O at -78 ºC followed by the addition of $TMSCHN_2$ (2 M in Et_2O , 1.04 mL, 2.05 mmol, 2.25 equiv) and the mixture was stirred for 40 min. A solution of amine **68** (0.22 g, 0.91 mmol, 1 equiv) in THF (22.8 mL) was added slowly for 20 min and the reaction mixture was stirred at -78 ºC for 2 h. Then, the reaction was quenched by the addition of dry MeOH/THF (1:9, 15 mL) solution, and the mixture was stirred at room temperature for 30 min before a 2M NaOH (25 mL) solution was added. The phases were separated and the aqueous was extracted sequentially with CH_2Cl_2 (3 x 40 mL), $CHCl_3$ (2 x 40 mL), and $CHCl_3$ / iPrOH (4:1, 2 x 25 mL). To the combined organics were added sodium sulfate and a SiO_2 (silica gel) and it was stirred at room temperature for 40 min. The reaction mixture was filtered through celite, and concentrated obtaining a yellow crude which was purified by chromatography (Al_2O_3, hexane:EtOAc, 1:0 → 9.8:0.2), providing **75** as solid (0.154 g, 66% yield) along with **76** (31 mg, 13%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.19 (m, 5H, Ph), 3.87 and 3.04 (2d, *J* = 14.4 Hz, 1H each, CH_2Ph), 2.98–2.89 (m, 1H, H-9), 2.83–2.76 (m, 2H, H-6 and H-3), 2.57 (dd, *J* = 11.6, 8.4 Hz, 1H, H-8), 2.50 (ddd, *J* = 11.6, 6.4, 1.6 Hz, 1H, H-3), 2.23 (ddd, *J* = 14.4, 7.8, 4.0 Hz, 1H, H-5), 2.07 (dddd, *J* = 15.0, 8.4, 3.6, 0.8 Hz, 1H, H-10), 1.98 (dd, *J* = 15.0, 3.4 Hz, 1H, H-10), 1.91–1.79 (m, 2H, H-1 and H-4), 1.75–1.68 (m, 1H, H-4), 1.64 (dd, *J* = 11.6, 9.6 Hz, 1H, H-8), 1.50 (dddd, *J* = 14.4, 13.2, 4.8, 1.2 Hz, 1H, H-5), 0.88 (d, *J* = 6.8 Hz, 3H, Me). ^{13}C NMR (101 MHz, $CDCl_3$) δ 214.7 (C-2), 139.6, 128.3, 127.9, 126.6 (Ph), 57.1 (CH_2Ph), 57.0 (C-6), 53.2 (C-8), 49.0 (C-1), 43.1 (C-3), 33.3 (C-5), 32.1 (C-9), 26.5 (C-10), 21.5 (C-4), 18.0 (Me).

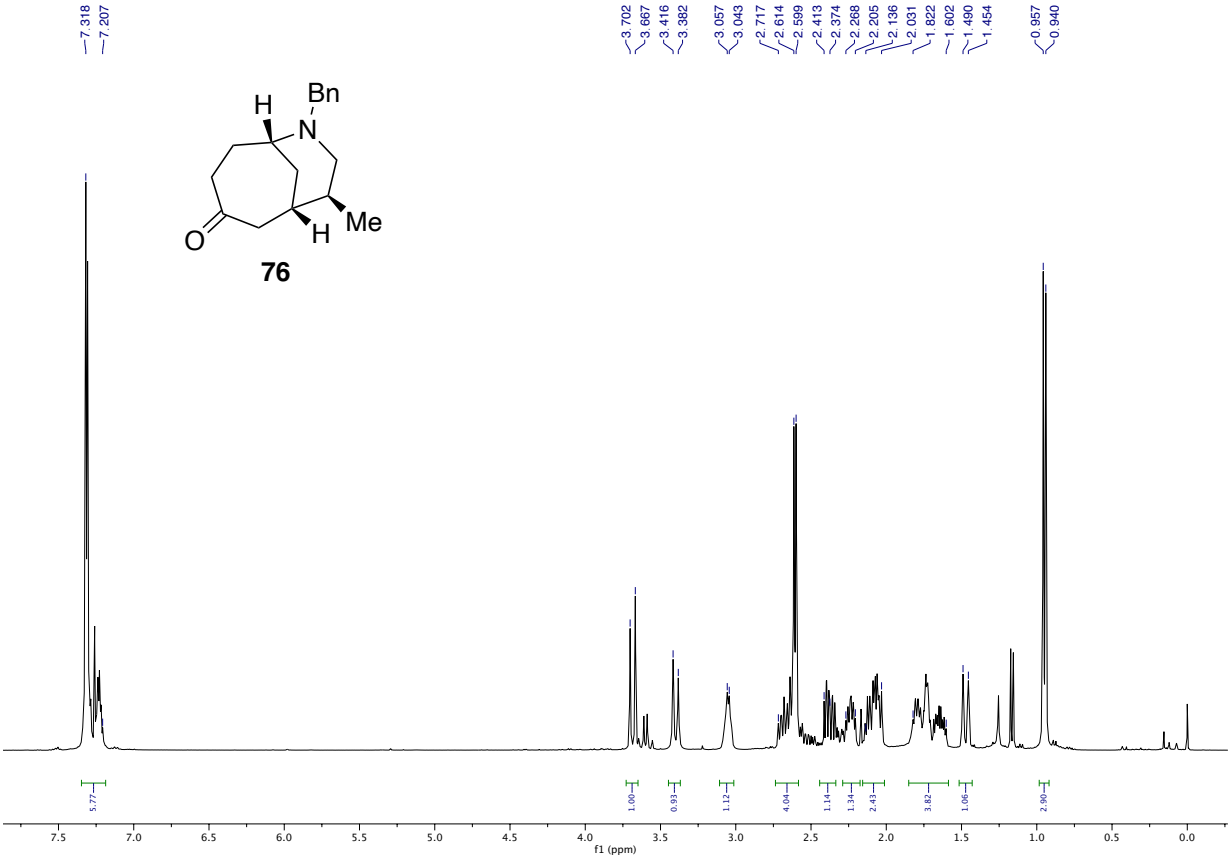

7.317
7.187
3.887
3.851
3.061
3.025
2.889
2.875
2.802
2.791
2.569
2.561
2.508
2.499
2.240
2.204
2.094
2.064
2.035
1.997
1.961
1.913
1.858
1.794
1.751
1.675
1.643
1.638
1.501
1.489
0.891
0.874
H
Bn
N
Me
H
O
75
4.83
0.93
0.93
0.89
1.93
0.97
0.96
0.99
1.01
1.00
1.99
1.14
1.16
1.02
2.78
f1 (ppm)

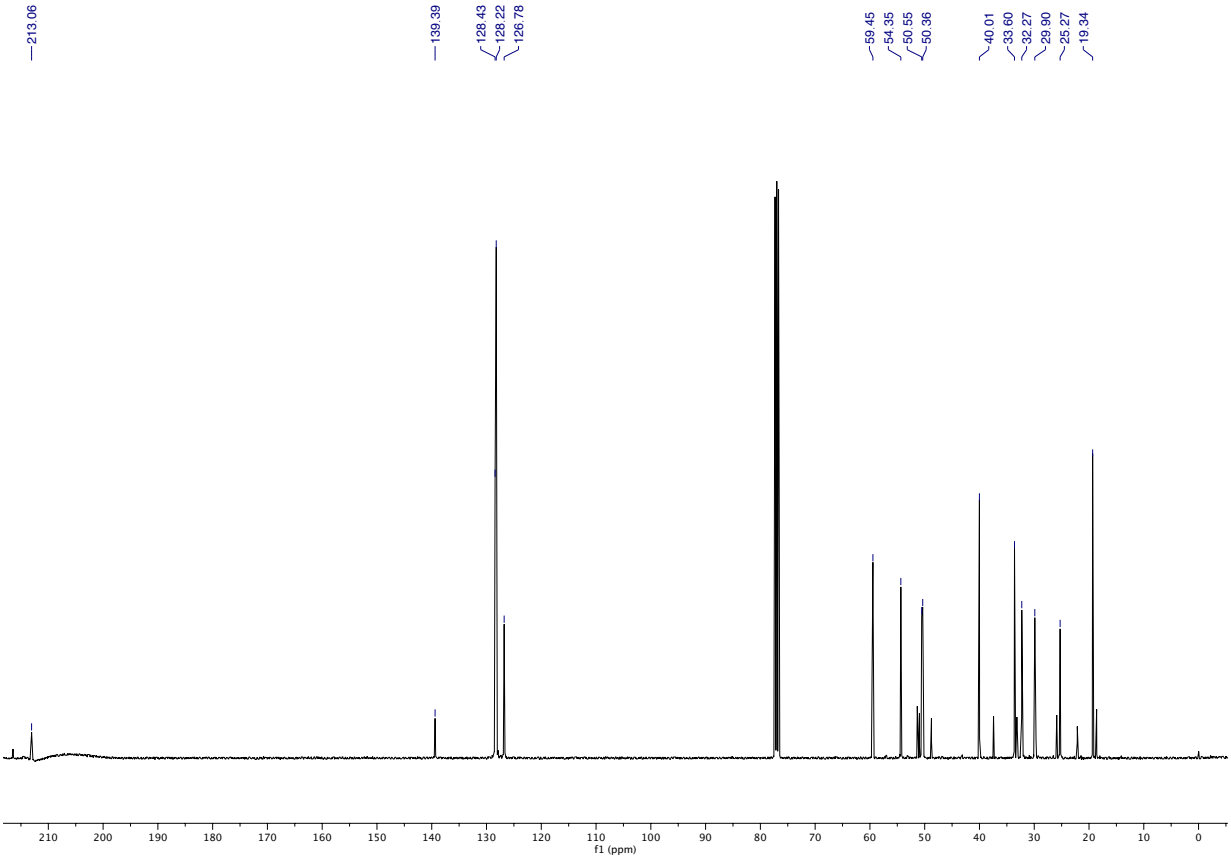

214.69
139.59
128.32
127.88
126.64
57.09
56.97
53.21
48.99
43.13
33.33
32.05
26.53
21.45
18.03
f1 (ppm)

(1*SR*,6*SR*,9*SR*)-7-Benzyl-9-methyl-7-azabicyclo[4.3.1]decan-3-one (76)

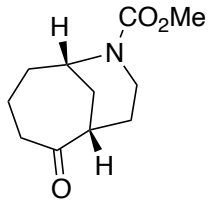


^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−7.21 (m, 5H, Ph), 3.68 and 3.40 (2d, J = 13.8 Hz, 1H each, CH_2Ph), 3.05 (bq, J = 5.6 Hz, 1H, H-6), 2.68 (ddd, J = 15.6, 8.8, 6.8 Hz, 1H, H-4), 2.64−2.60 (m, 1H, H-8), 2.61 (d, J = 6.0 Hz, 2H, H-2), 2.38 (ddd, J = 15.6, 6.8, 6.0 Hz, 1H, H-4), 2.27–2.21 (m, 1H, H-10), 2.14–2.03 (m, 2H, H-8 and H-5), 1.82–1.77 (m, 1H, H-9), 1.76–1.71 (m, 1H, H-1), 1.69–1.60 (m, 1H, H-5), 1.47 (bd, J = 14. 4 Hz, 1H, H-10), 0.95 (d, J = 6.8 Hz, 1H, Me). ^{13}C NMR (101 MHz, $CDCl_3$) δ 213.1 (C-3), 139.4, 128.4, 128.2 and 126.8 (Ph), 59.5 (CH_2Ph), 54.4 (C-6), 50.6 (C-8), 50.4 (C-2), 40.0 (C-4), 33.6 (C-9), 32.3 (C-1), 29.9 (C- 10), 25.3 (C-5), 19.4 (Me).


7.318
7.207
3.702
3.667
3.416
3.382
3.057
3.043
2.717
2.614
2.599
2.413
2.374
2.268
2.205
2.136
2.031
1.822
1.602
1.490
1.454
0.957
0.940
H
Bn
N
O
H
Me
76
5.77
1.00
0.93
1.12
4.04
1.14
1.34
2.43
3.82
1.06
2.90
f1 (ppm)

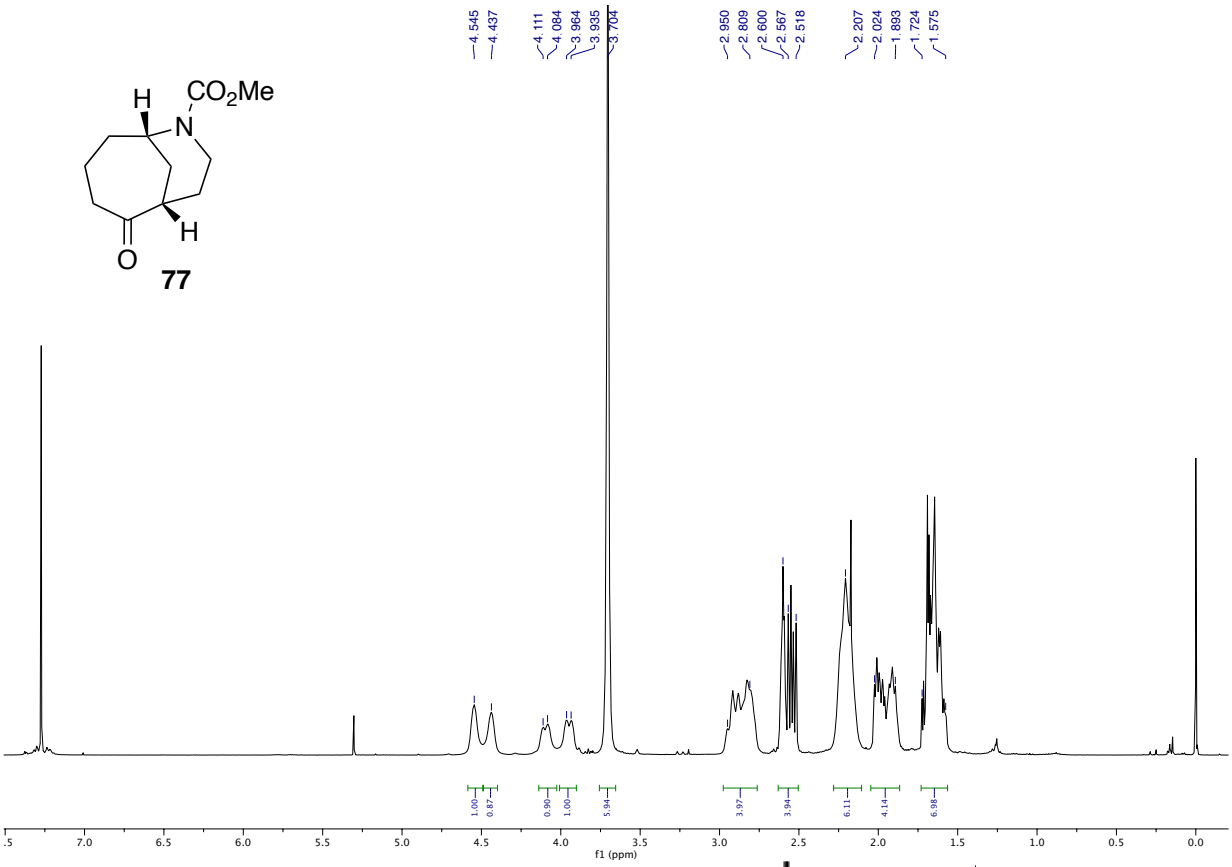

213.06
139.39
128.43
128.22
126.78
59.45
54.35
50.55
50.36
40.01
33.60
32.27
29.90
25.27
19.34
f1 (ppm)

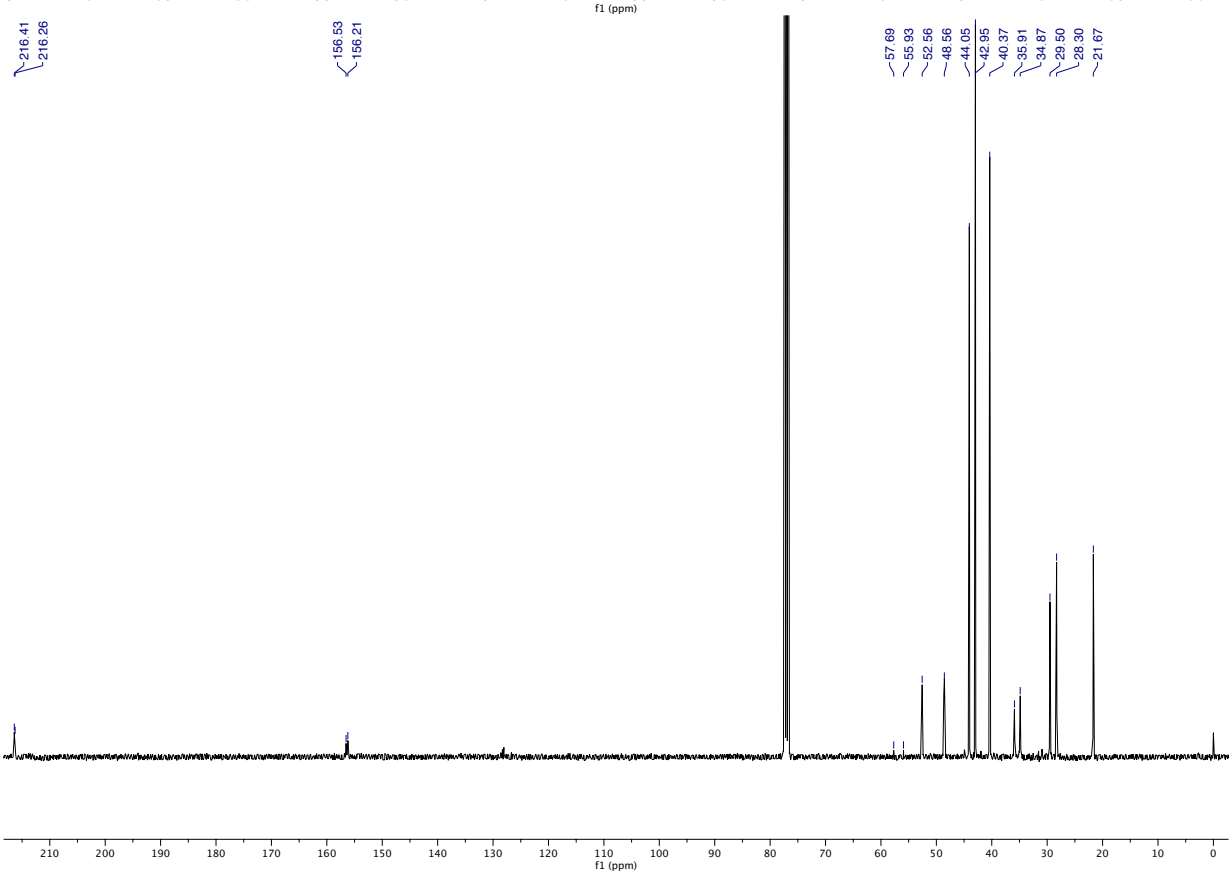
(1*SR*,6*SR*)- 7-methoxycarbonyl-7-azabicyclo[4.3.1]decan-2-one (77)



To a solution of $BF_3{\cdot}OEt_2$ (0.07 mL, 0.58 mmol, 1.3 equiv) in dry CH_2Cl_2, a solution of carbamate **69** (88 mg, 0.45 mmol, 1 equiv) in dry CH_2Cl_2 (1.5 mL) was added dropwise at -78 ºC. Subsequently, $TMSCHN_2$ (0.27 mL, 0.58 mmol, 1.3 equiv) was added slowly at - 78 ºC, and the reaction mixture was stirred at room temperature overnight. Then, the reaction mixture was diluted with diethyl ether and the organic layer was treated with ice-cooled solution of $NaHCO_3$ 2.5 % at 0 ºC. The mixture was stirred for 5 min, phases were separated and the organic layer was washed rapidly with ice-cooled solution of $NaHCO_3$ 2.5 % and water, dried, filtered, and concentrated obtaining a yellowish oil as crude. This crude was purified by chromatography (CH_2Cl_2:EtOAc 1:0 → 9:1) providing two products as oils, **77** (28.9 mg, 31%) and **78** (36.2 mg, 38%).

IR (neat): 2952, 1697, 1447 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 4.55 and 4.44 (2 s, 1H, H-6), 4.10 and 3.95 (2d, J = 11.6 Hz, 1H, H-8) 3.70 (s, 3H, OMe), 2.95–2.78 (m, 2H, H-8 and H-3), 2.62–2.58 (m, 1H, H-1), 2.54 (dd, J = 13.0, 6.6 Hz, 1H, H-3), 2.21–2.17 (m, 3H, H-10, H-9 and H-5), 2.03–1.89 (m, 2H, H-10 and H-4), 1.72–1.58 (m, 3H, H-9, H-5 and H-4). ^{13}C NMR (101 MHz, $CDCl_3$) δ 216.4 and 216.2 (C-2), 156.5 and 156.2 (CO_2Me), 52.5 (OMe), 48.5 (C-6), 44.0 (C-3), 42.9 (C-1), 40.3 (C-8), 35.9 and 34.8 (C-5), 29.5 (C-10), 28.3 (C-9), 21.6 (C-4).

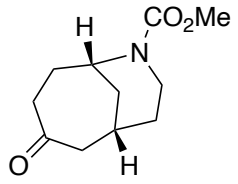

4.545
4.437
4.111
4.084
3.964
3.935
3.704
2.950
2.809
2.600
2.567
2.518
2.207
2.024
1.893
1.724
1.575
1.00
0.87
0.90
1.00
5.94
3.97
3.94
6.11
4.14
6.88
f1 (ppm)


216.41
216.26
156.53
156.21
57.69
55.93
52.56
48.56
44.05
42.95
40.37
35.91
34.87
29.50
28.30
21.67
f1 (ppm)

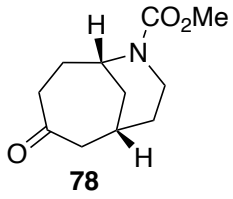
H
CO2Me
N
H
O

77

(1*SR*,6*SR*)- 7-methoxycarbonyl-7-azabicyclo[4.3.1]decan-3-one (78)

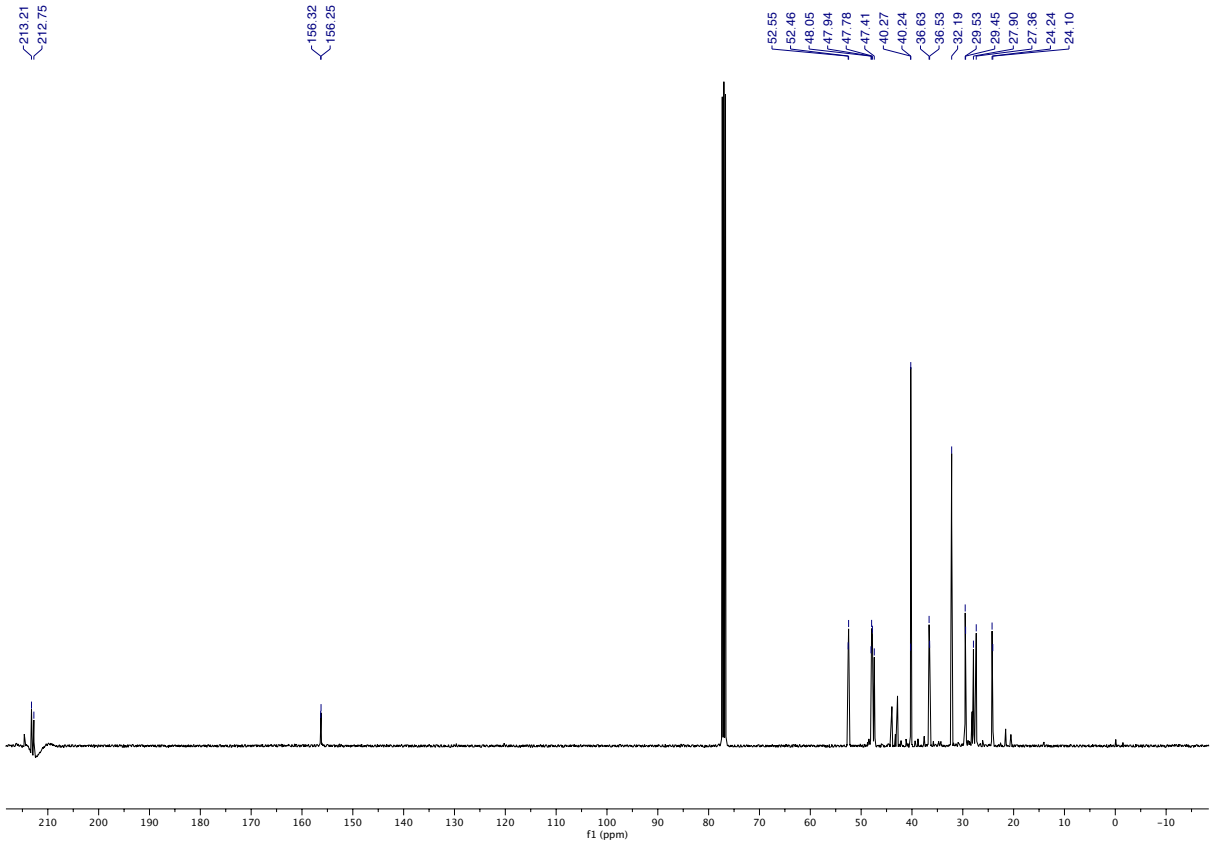


IR (neat): 2932, 1697, 1448 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.59 and 4.46 (2d, *J* = 6.2 Hz, 1H, H-6)), 3.86 (dd, 1H, *J* = H-8, (of each rotamer), *J* = 14.88, 14.32, 4.90 and 4.36 Hz), 3.70 (s, 3H, OMe), 3.21 (t, 1H, H-8, *J* = 12.8 Hz), 2.65 (d, 2H, H-2, *J* = 6.4 Hz), 2.58–2.42 (m, 2H, H-4), 2.28 (m, 1H, H-1), 2.02–1.96 (m, 3H, H-5 and H-10), 1.82–1.72 (m, 2H, H-9 and H-10), 1.65–1.59 (m, 1H, H-9). ^{13}C NMR (101 MHz, $CDCl_3$) δ 213.3 and 212.8 (C-3), 156.3 and 156.3 (CO_2Me), 52.6 and 52.5 (OMe), 48.1 and 47.9 (C-6), 47.8 and 47.4 (C-2), 40.3 and 40.2 (C-4), 36.6 and 36.5 (C-8), 32.2 (C-10), 29.5 and 29.9 (C-9), 27.9 and 27.4 (C-5), 24.2 and 24.1 (C-1).

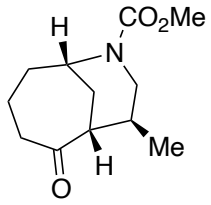

H
CO2Me
N
O
H

78

4.597
4.585
4.467
4.456
3.948
3.913
3.803
3.758
3.238
3.206
3.174
2.660
2.644
2.584
2.418
2.277
2.015
1.962
1.815
1.718
1.651
1.587
1.00
1.04
3.32
1.98
2.09
1.02
3.28
2.08
1.30
f1 (ppm)

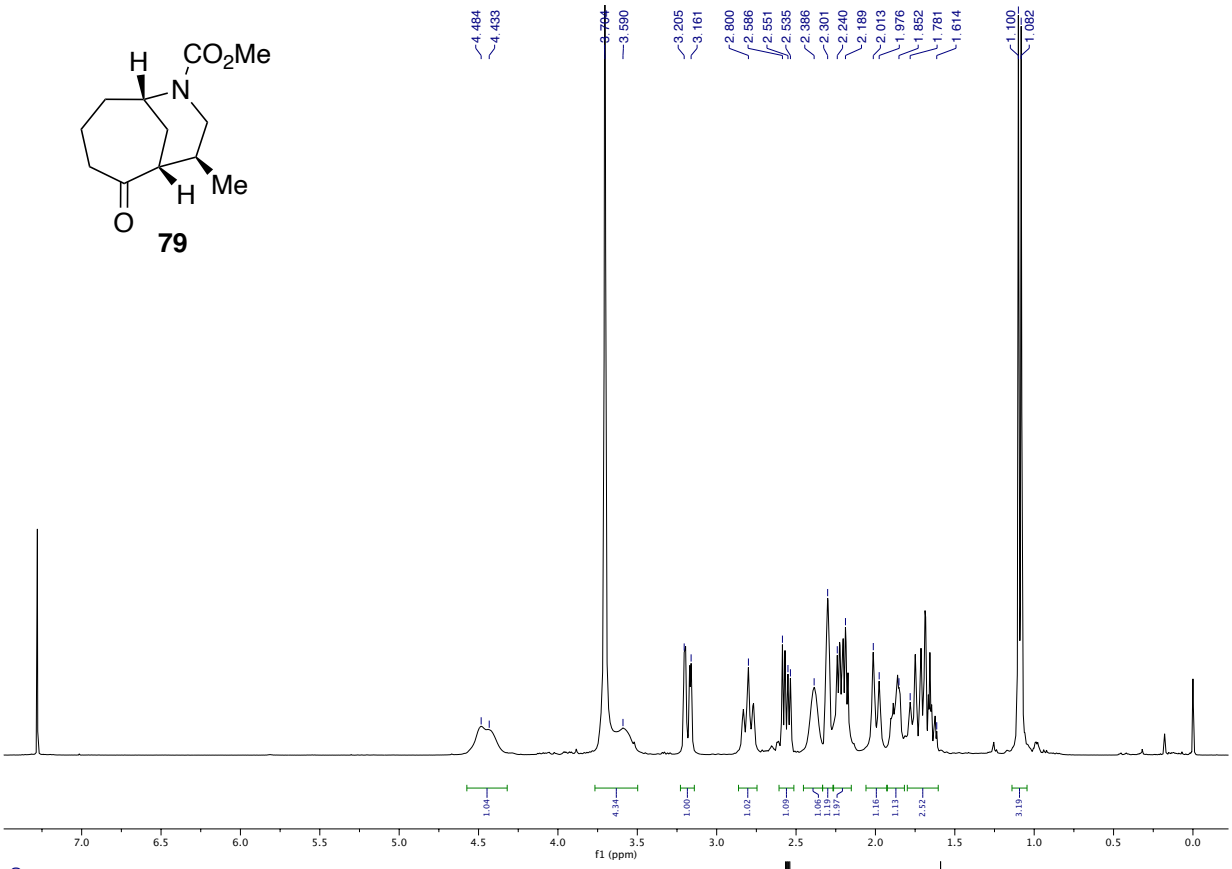

213.21
212.75
156.32
156.25
52.55
52.46
48.05
47.94
47.78
47.41
40.27
40.24
36.63
36.53
32.19
29.53
29.45
27.90
27.36
24.24
24.10
f1 (ppm)

(1*RS*,6*SR*,9*SR*)-7-methoxycarbonyl-9-methyl-7-azabicyclo[4.3.1]decan-2-one (79)



To a solution of *n*-BuLi (1.8 M in hexanes, 0.30 mL, 0.54 mmol, 2.25 equiv.) in Et_2O (10 mL) at -78 ºC $TMSCHN_2$ (0.6 M in hexanes, 0.44 mL, 0.98 mmol, 2.25 equiv.) was added. After being stirred for 40 min a solution of **70** (50 mg ,0.24 mmol) in THF (4.8 mL) was added slowly over 20 min with a syringe pump. The reaction was stirred at −78 ºC for 2 h, then, a solution of MeOH/THF (1:9, 10 mL) was added, and the mixture was stirred at room temperature for 30 min. After the addition of a solution of 2 M NaOH, the phases were separated. The aqueous layer was extracted sequentially with CH_2Cl_2 (2 x 15 mL), $CHCl_3$ (2 x 15 mL) and $CHCl_3$: *i*-PrOH (4:1, 2 x 15 mL). To the combined organics were added SiO_2 and Na_2SO_4 and it was stirred at room temperature for 40 min. The reaction mixture was filtered through a Celite® pad and concentrated to obtain the crude as a yellowish oil. Then, the crude was purified by chromatography (CH_2Cl_2:EtOAc, 1:0 → 9:1), providing the carbamate **79** in 56% yield and compound **80** in 14%.

IR (neat): 2954, 2874, 1697, 1448 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 4.48 and 4.43 (2 s, 1H, H-6), 3.70 (s, 3H, OMe), 3.59 (br s, 1H, H-8), 3.18 (dd, *J* = 14.0, 3.6 Hz, 1H, H-8), 2.80 (dd, *J* = 13.6, 4.8 Hz, 1H, H-3), 2.56 (dd, *J* = 13.6, 6.6 Hz, 1H, H-3), 2.39 (br s, 1H, H-9), 2.30 (br s, 1H, H-1), 2.24–2.19 (m, 2H, H-10 and H-5), 1.99 (d, *J* = 14.8 Hz, 1H, H-10), 1.90–1.85 (m, 1H, H-4), 1.78–1.61 (m, 2H, H-5 and H-4), 1.09 (d, *J* = 7.2 Hz, 3H, Me). ^{13}C NMR (101 MHz, $CDCl_3$) δ 216.1 (C-2), 156.9 (CO), 52.5 (OMe), 49.5 (C-1), 48.6 (C-6), 45.4 (C-8), 43.8 (C-3), 31.1 (C-9), 24.1 (C-10), 21.6 (C-4), 17.7 (Me); the signal for C-5 was not observed.


H
CO2Me
N
Me
H
O
4.484
4.433
3.784
3.590
3.205
3.161
2.800
2.586
2.551
2.535
2.386
2.301
2.240
2.189
2.013
1.976
1.852
1.781
1.614
1.100
1.082
1.04
4.34
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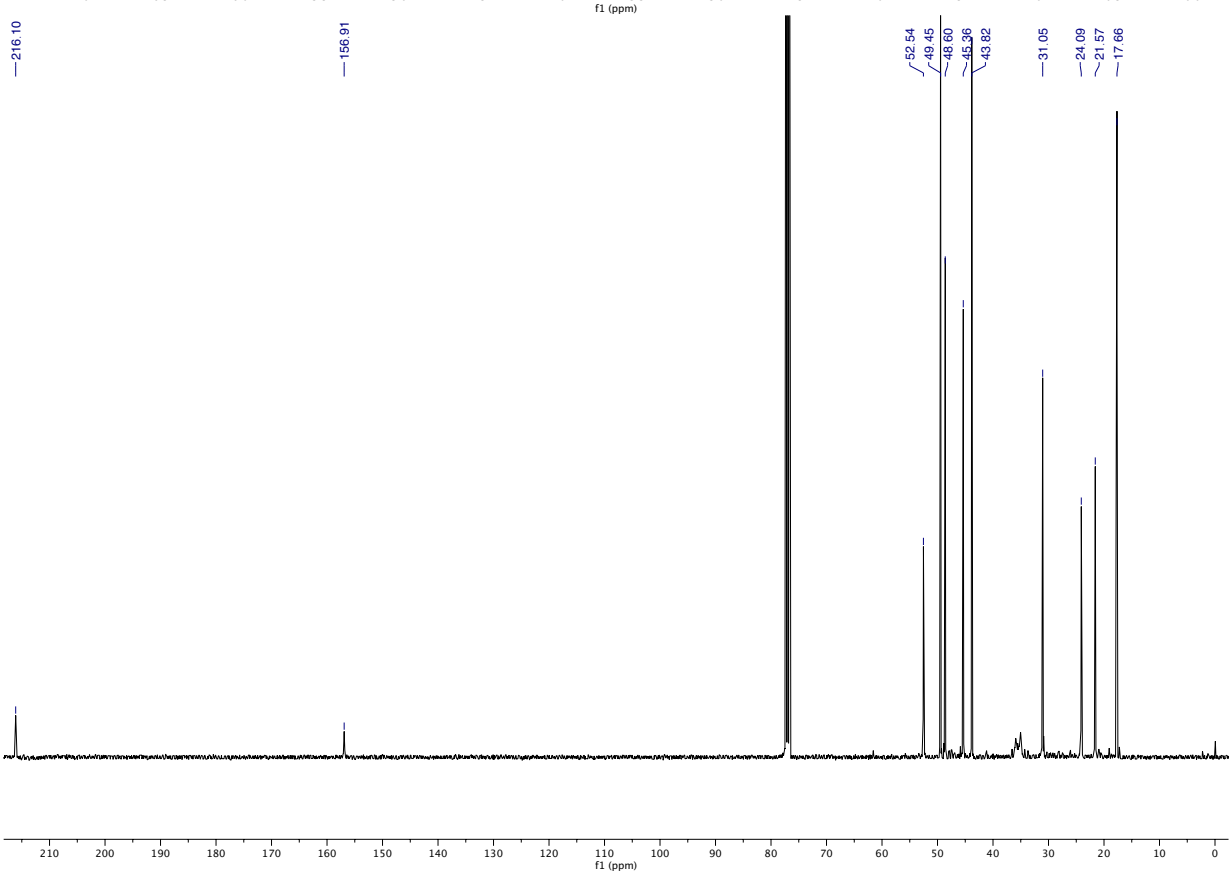
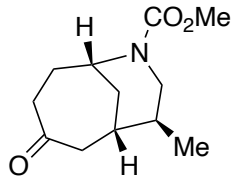
1.06
1.19
1.97
1.16
1.13
2.52
3.19
f1 (ppm)

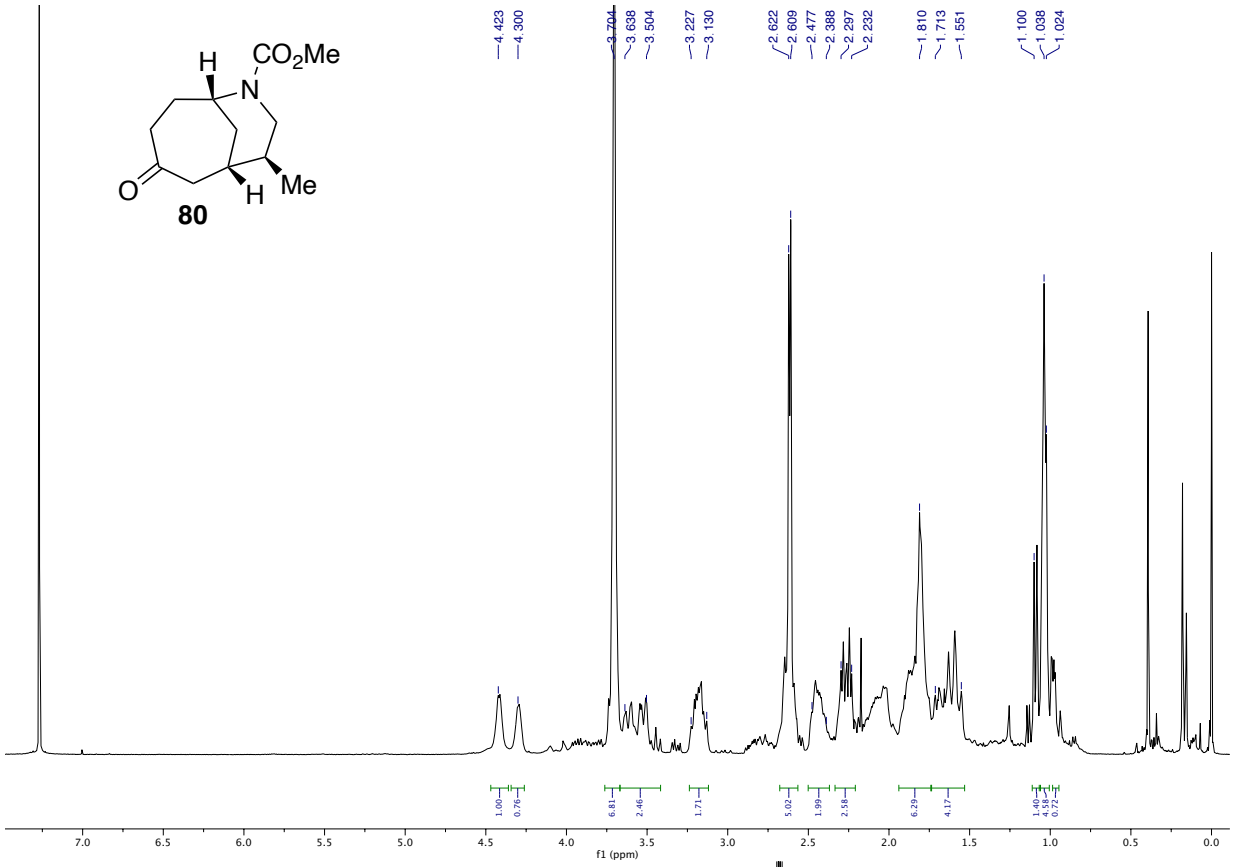
79


216.10
156.91
52.54
49.45
48.60
45.36
43.82
31.05
24.09
21.57
17.66
f1 (ppm)

(1*SR*,6*SR*,9*SR*)-7-methoxycarbonyl-9-methyl-7-azabicyclo[4.3.1]decan-3-one (80)



IR (neat): 2955, 1697, 1448 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.42 and 4.30 (2 br s, 1H, H-6), 3.70 (s, 3H, OMe), 3.64 -3.50 and 3.23–3.13 (2 m, 1H each, H-8), 2.65-2.59 (m, 1H, H-4), 2.66 (d, J = 5.2 Hz, 2H, H-2), 2.48–2.39 (m, 1H, H-4), 2.30-2.23 (m, 1H, H-10), 2.14–2.02 (m,1H, H-5), 1.93–1.75 (m, 3H, H-5, H-1 and H-9), 1.71–1.55 (m, 1H, H-10), 1.09 and 1.03 (2 d, J = 6.8 Hz, 3H, Me). ^{13}C NMR (101 MHz, $CDCl_3$) δ 213.5 and 213.2 (C-3), 156.9 and 156.7 (CO_2Me), 52.6 and 52.5 (OMe), 49.4 and 49.1 (C-2), 48.9 (C-6), 43.9 and 43.8 (C-8), 40.0 and 40.0 (C-4), 33.7 (C-1) 31.3 and 31.3 (C-9), 29.3 and 29.0 (C-10), 28.9 and 28.1 (C-5), 19.1 and 17.7 (Me).


H
CO2Me
N
O
H
Me
80
4.423
4.300
3.704
3.638
3.504
3.227
3.130
2.622
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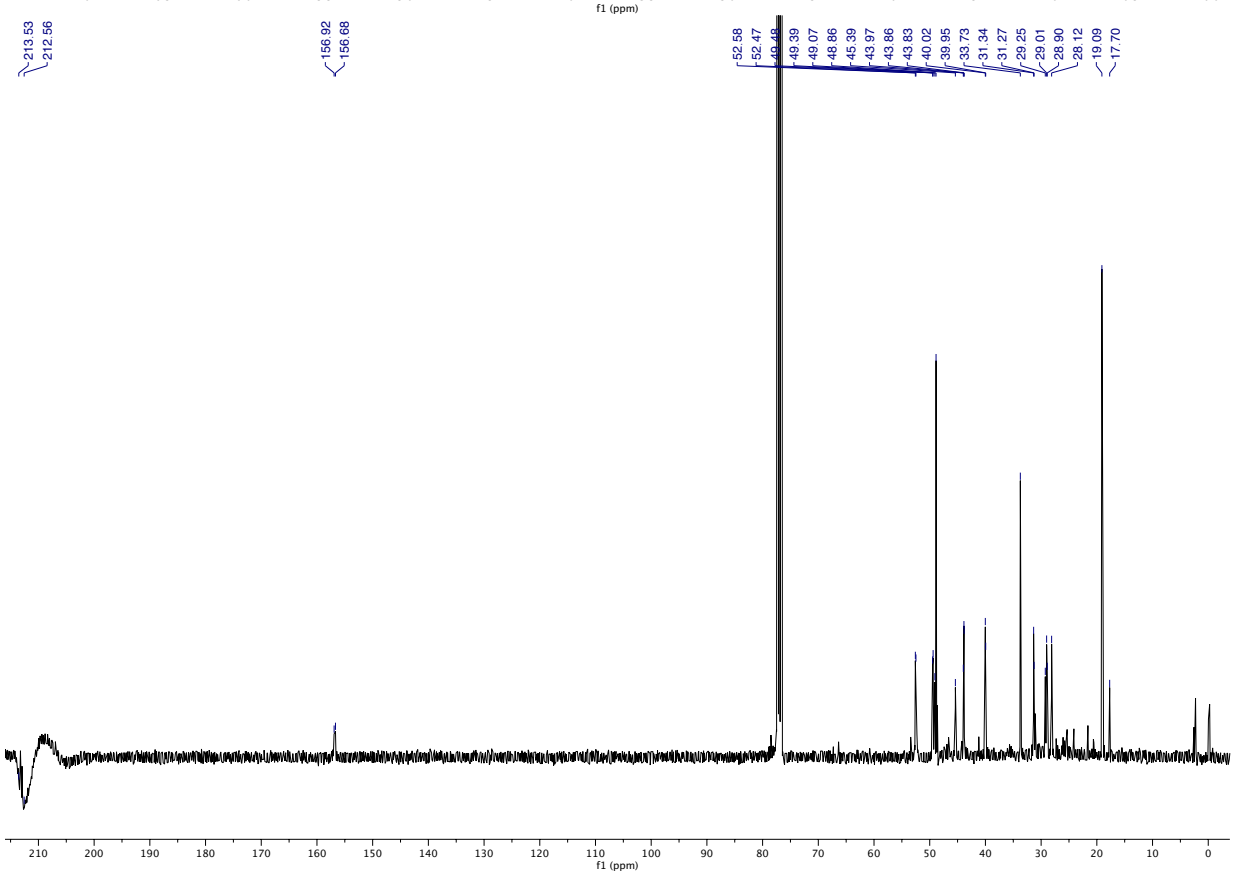
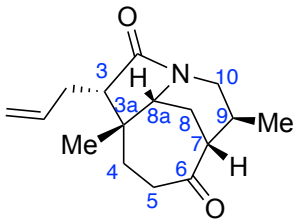
1.713
1.551
1.100
1.038
1.024
f1 (ppm)

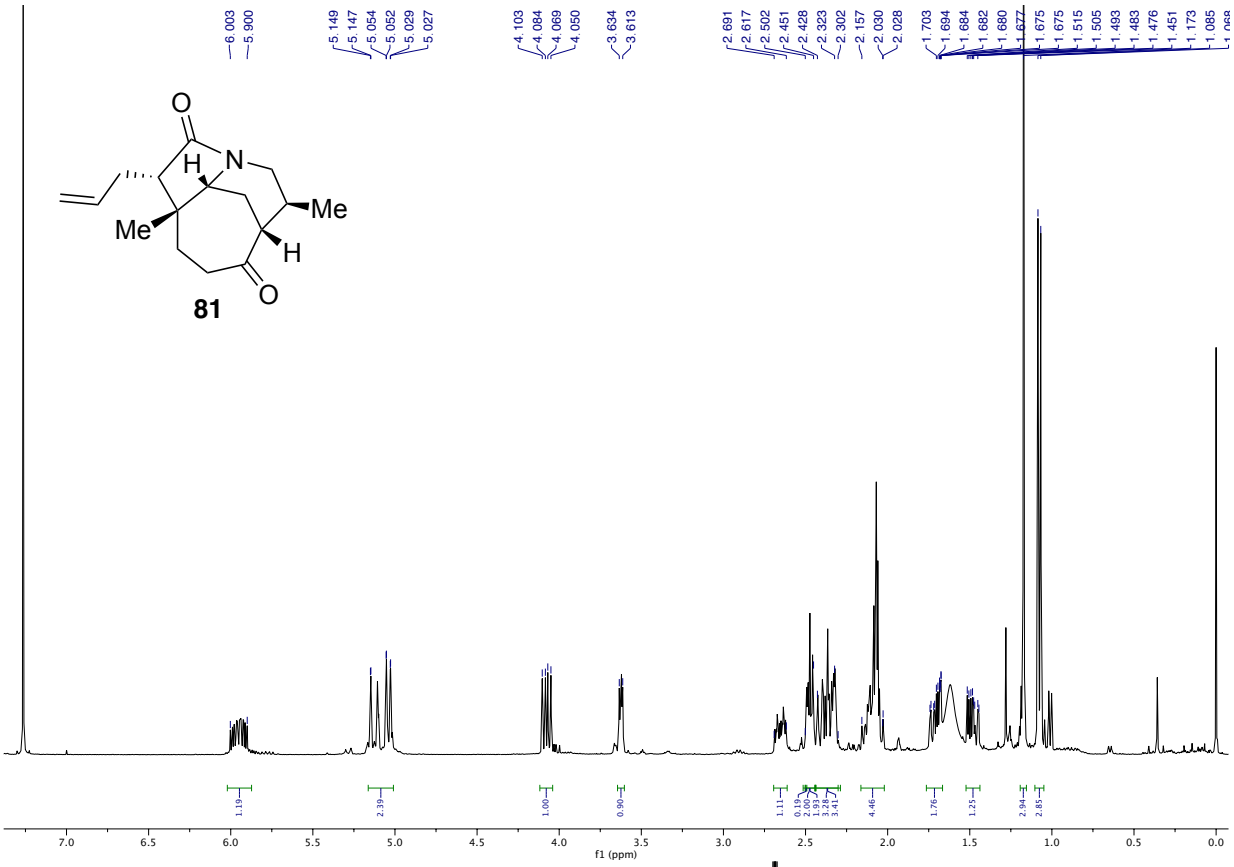

213.53
212.56
156.92
156.68
52.58
52.47
49.39
49.07
48.86
45.39
43.97
43.86
43.83
40.02
39.95
33.73
31.34
31.27
29.25
29.01
28.90
28.12
19.09
17.70
f1 (ppm)

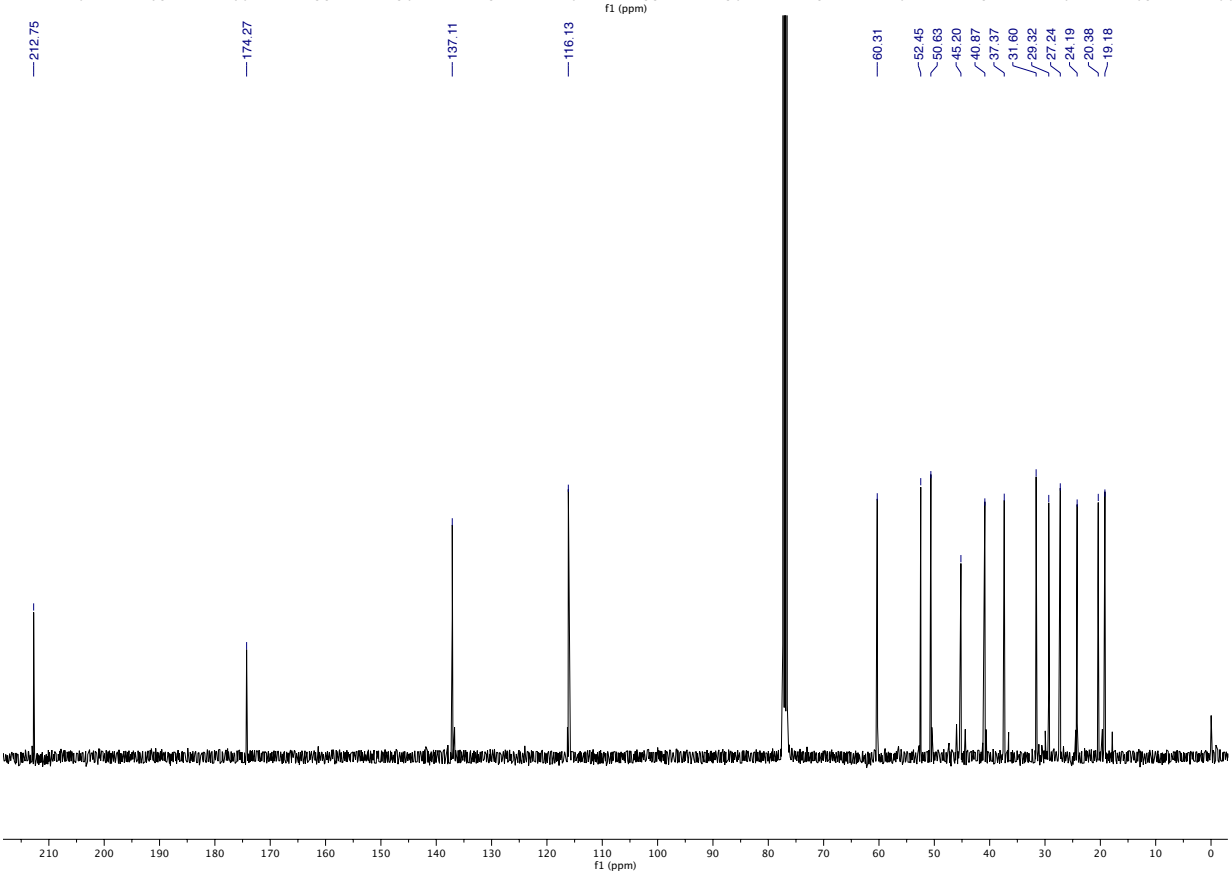
(3*SR*,3a*RS*,7*RS*,8a*RS*,9*SR*)-3-allyl-3a,9-dimethylhexahydro-2*H*-7,1-ethanocyclohepta[*b*]pyrrole-2,6(3*H*)-dione (81)



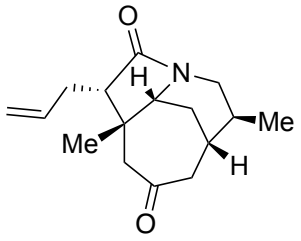
Diethyl ether (4 mL) was cooled to -78 ºC and *n*BuLi (1.8 M in THF, 0.12 mL, 0.31 mmol, 2.25 equiv) and $TMSCHN_2$ (2 M in Et_2O, 0.23 mL, 0.42 mmol, 3.0 equiv) were added. After being stirred at this temperature for 30 min, a solution of tricycle **55** (34 mg, 0.14 mmol) in THF (2 mL) was added over 15 min and the stirring was prolonged for 2h 30 min. Then, a solution of anhydrous MeOH:THF (1:9, v:v, 5 mL) was added dropwise and the mixture was let to reach room temperature over 30 min. 2 M NaOH solution (10 mL) was added, the phases were separated and the aqueous layer was extracted with $CHCl_3$:*i*-PrOH (4:1, 4 x 20 mL). The organics were combined, treated with SiO_2 and Na_2SO_4 and stirred at room temperature for 45 min. The mixture was filtered and concentrated to afford the crude which was purified (hexane:EtOAc, 1:0 → 3:2) to obtain compound **81** (11.7 mg, 33%) along with compound **82** (5.4 mg, 15%).

IR (NaCl): 2955, 1694, 1456, 1434, 912 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 6.00–5.90 (m, 1H, =CH), 5.13 (d, *J* = 16.8 Hz, 1H, $=CH_2$-*trans*), 5.04 (d, *J* = 10.0 Hz, 1H, $=CH_2$-*cis*), 4.08 (dd, *J* = 13.6, 7.6 Hz, 1H, H-10), 3.63–3.61 (m, 1H, H-8a), 2.69–2.62 (m, 1H, CH_2-3), 2.50–2.45 (m, 2H, H-5), 2.43–2.30 (m, 3H, H-10, H-3 and H-7), 2.16–2.03 (m, 4H, H-8, CH_2-3 and H-9), 1.71 (ddd, *J* = 15.5, 8.8, 2.4 Hz, 1H, H-4), 1.48 (ddd, *J* = 15.5, 9.6, 4.0 Hz, 1H, H-4), 1.17 (s, 3H, Me-3a), 1.08 (d, *J* = 6.8 Hz, 3H, Me-9). ^{13}C NMR (101 MHz, $CDCl_3$) δ 212.7 (C-6), 174.3 (C-2), 137.1 ($=CH_2$), 116.1 (=CH), 60.3 (C-8a), 52.5 (C-3), 50.6 (C-7), 45.2 (C-3a), 40.9 (C-10), 37.4 (C-5), 31.6 (C-9), 29.3 (CH_2-3), 27.2 (C-4), 24.2 (Me-3a), 20.4 (Me-9), 19.2 (C-8).

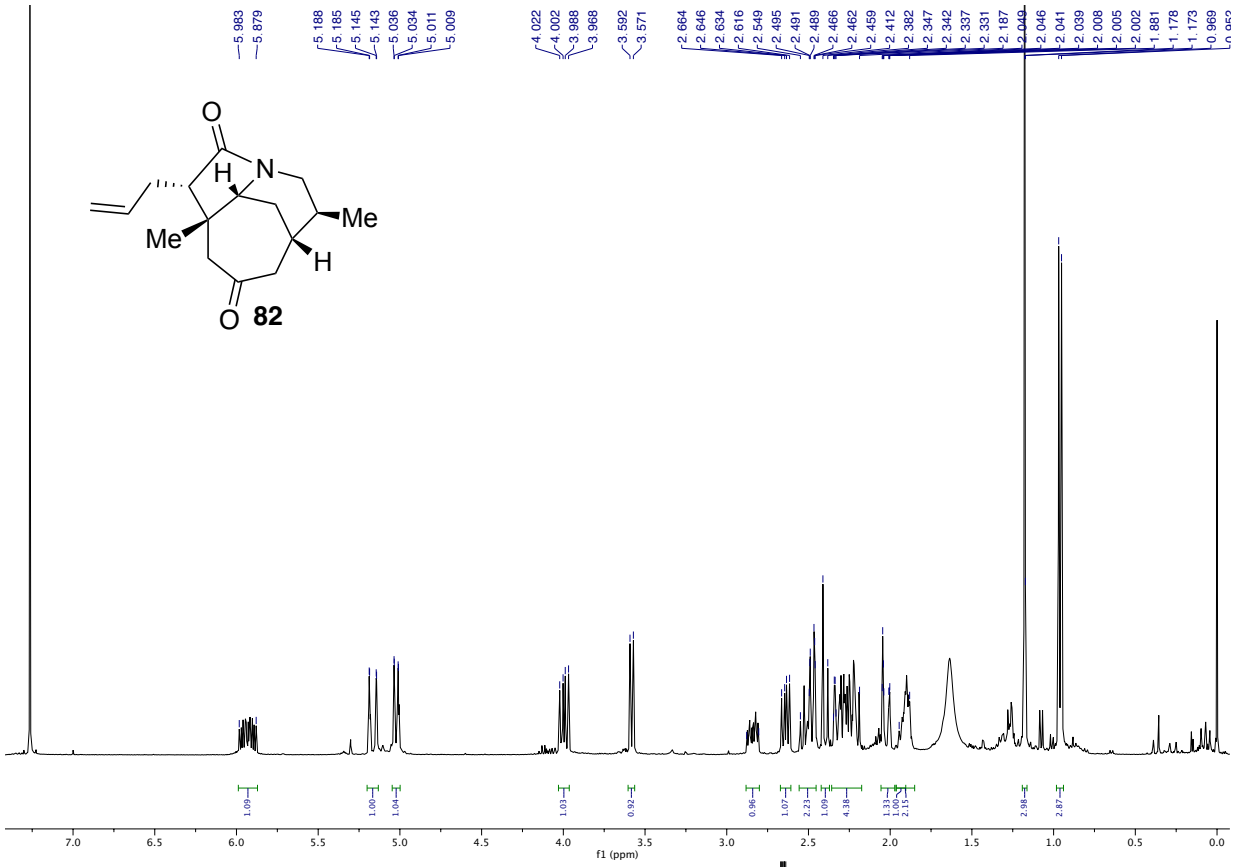

6.003
5.900
5.149
5.147
5.054
5.052
5.029
5.027
4.103
4.084
4.069
4.050
3.634
3.613
2.691
2.617
2.502
2.451
2.428
2.323
2.302
2.157
2.030
2.028
1.703
1.694
1.684
1.682
1.680
1.677
1.675
1.675
1.515
1.505
1.493
1.483
1.476
1.451
1.173
1.085
O
H
N
Me
Me
H
O
81
1.19
2.39
1.00
0.90
1.11
0.18
2.00
1.93
3.28
3.41
4.46
1.76
1.25
2.94
2.85
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

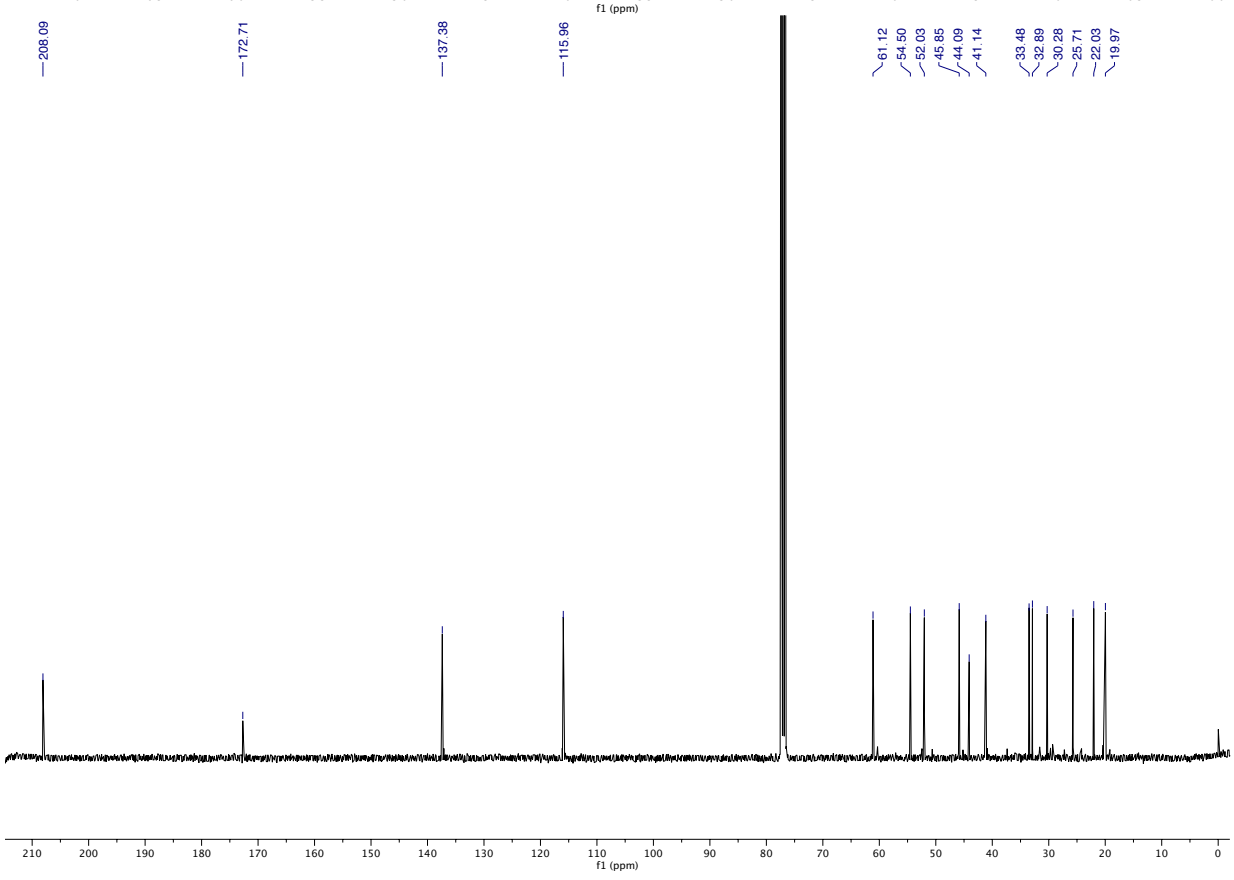

212.75
174.27
137.11
116.13
60.31
52.45
50.63
45.20
40.87
37.37
31.60
29.32
27.24
24.19
20.38
19.18
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

(3*SR*,3a*RS*,7*SR*,8a*RS*,9*SR*)-3-allyl-3a,9-dimethylhexahydro-2*H*-7,1-ethanocyclohepta[*b*]pyrrole-2,5(3*H*)-dione (82)

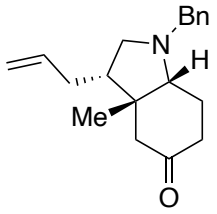


IR (NaCl): 2957, 1699, 1459, 903 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 5.98–5.88 (m, 1H, =CH), 5.17 (br d, J = 17 Hz, 1H, $=CH_2$-*trans*), 5.02 (br d, J = 10 Hz, 1H, $=CH_2$-*cis*), 4.00 (dd, J = 13.6, 8.0 Hz, 1H, H-10), 3.58 (d, J = 8.4 Hz, 1H, H-8a), 2.88–2.80 (m, 1H, CH_2-3), 2.64 (dd, J = 12.0, 7.2 Hz, 1H, H-6), 2.55–2.50 (m, 1H, CH_2-3), 2.48 and 2.40 (2d, J = 11.8 Hz, 1H each, H-4), 2.35–2.19 (m, 4H, H-6, H-10, H-3 and H-8), 2.02 (dd, J = 15.4, 2.2 Hz, H-8), 1.95–1.88 (m, 2H, H-7 and H-9), 1.18 (s, 3H, Me-3a), 0.96 (d, J = 6.8 Hz, Me-9). ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.1 (C-5), 172.7 (C-2), 137.4 (=CH), 116.0 ($=CH_2$), 61.1 (C-8a), 54.5 (C-6), 52.0 (C-3), 45.9 (C-4), 44.1 (C-3a), 41.1 (C-10), 33.5 (C-9), 32.9 (C-7), 30.3 (CH_2-3), 25.7 (Me-3a), 22.0 (C-8), 20.0 (Me-9).


5.983
5.879
5.188
5.185
5.145
5.143
5.036
5.034
5.011
5.009
4.022
4.002
3.988
3.968
3.592
3.571
2.664
2.646
2.634
2.616
2.549
2.495
2.491
2.489
2.466
2.462
2.459
2.412
2.382
2.347
2.342
2.337
2.331
2.187
2.049
2.046
2.041
2.039
2.008
2.005
2.002
1.881
1.178
1.173
0.969
O
H
N
Me
Me
H
O
82
1.09
1.00
1.04
1.03
0.92
0.96
1.07
2.23
1.09
4.38
1.33
1.00
2.15
2.98
2.87
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

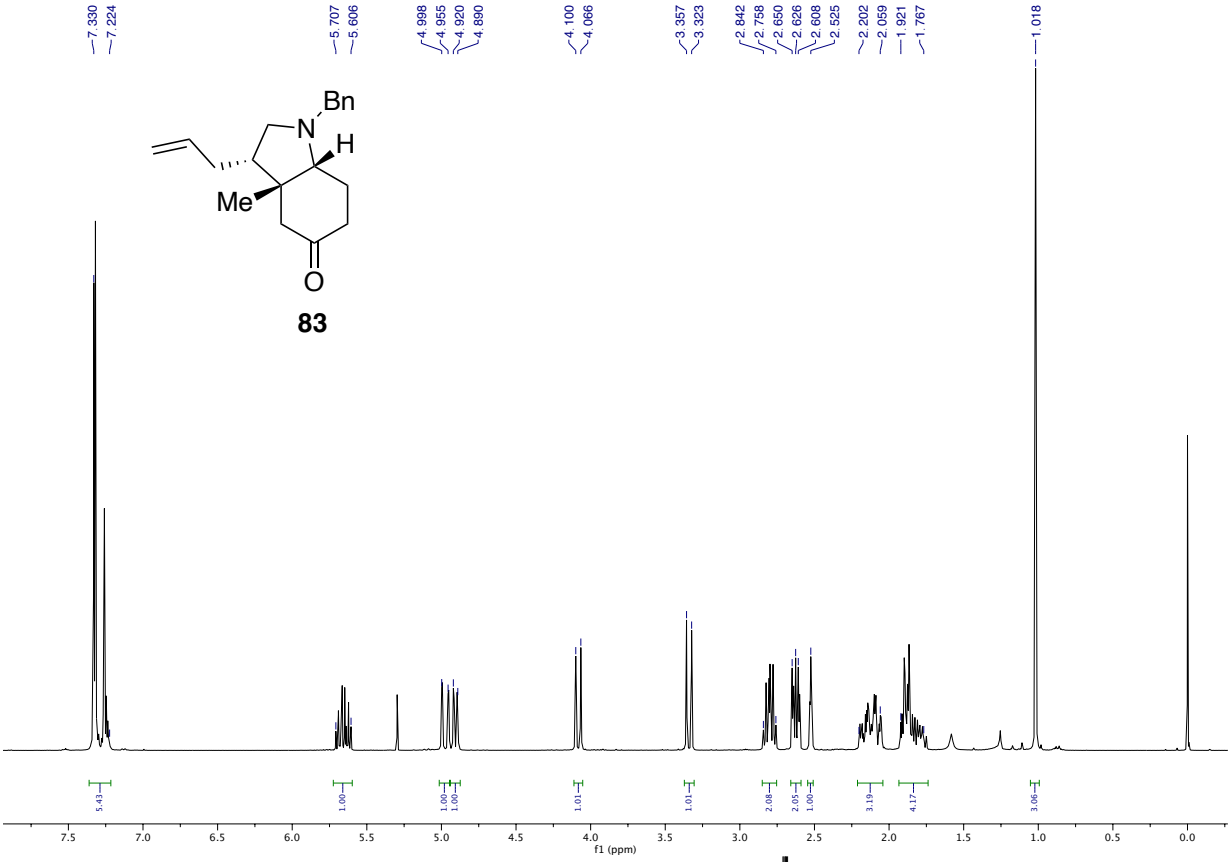

208.09
172.71
137.38
115.96
61.12
54.50
52.03
45.85
44.09
41.14
33.48
32.89
30.28
25.71
22.03
19.97
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

(3*SR*,3a*RS*,7a*RS*)-3-allyl-1-benzyl-3a-methyloctahydro-5*H*-indol-5-one (83)



A suspension of $AlCl_3$ (0.29 g, 2.18 mmol, 1.5 equiv) in THF (7 mL) was cooled to 0 ºC and solution of $LiAlH_4$ (1 M in THF, 2.9 mL, 2 equiv) was added. After being stirred at this temperature for 20 min, a solution of octahydroindole **c-4a** (0.50g, 1.45 mmol, 1 equiv) in THF (14 mL) was added via cannula, and the reaction was stirred at room temperature overnight. Next, it was quenched with 30% KOH solution (20 mL) and extracted with $CHCl_3$:*i*-PrOH (4:1, 4 x 20 mL). The combined organics were dried, filtered, and concentrated to afford the crude which was diluted in 10% HCl (30 mL) and stirred overnight. After being basified with 15% NaOH solution (40 mL), the mixture was extracted with CH_2Cl_2 (4 x 30 mL) and the combined organics were dried, filtered, and concentrated. The obtained crude was purified by chromatographic column (hexane:EtOAc, 9.5:0.5 $\rightarrow$ 4:1) to provide compound **83** (0.26 g, 64%) as a waxy solid.

IR (NaCl): 3027, 2954, 1712, 1452, 912, 739, 699 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 5.66 (ddt, *J* = 17.0, 10.2, 6.8 Hz, 1H, =CH), 4.97 (dq, *J* = 17.0 Hz, 1H, =CH_2-*trans*), 4.91 (ddt, *J* = 10.2, 2.1, 1.1 Hz, 1H, =CH_2-*cis*), 4.08 and 3.34 (2d, *J* = 13.6 Hz, 1H each, CH_2Ph), 2.80 (dd, *J* = 19.8, 13.8 Hz, 1H, H-6), 2.80 (dd, *J* = 10.4, 8.2 Hz, 1H, H-2), 2.63 (dd, *J* = 10.4, 9.6 Hz, 1H, H-2), 2.62 (d, *J* = 13.0 Hz, 1H, H-4), 2.53 (t, *J* = 2.6 Hz, 1H, H-7a), 2.20–2.05 (m, 3H, CH_2-3, H-7 and H-6), 1.88 (d, *J* = 13.0 Hz, 1H, H-4), 1.92–1.75 (m, 3H, H-3, H-7 and CH_2-3), 1.02 (s, 3H, Me). ^{13}C NMR (101 MHz, $CDCl_3$) δ 212.9 (C-5), 139.9 (Ph), 137.1 (=CH), 128.3, 128.1 and 126.8 (Ph), 115.6 (=CH_2), 68.3 (C-7a), 58.0 (CH_2Ph), 56.8 (C-2), 47.8 (C-3a), 47.1 (C-3), 45.3 (C-4), 35.8 (C-6), 32.8 (C-7), 24.2 (CH_2-3), 22.9 (Me).


7.330
7.224
5.707
5.606
4.998
4.955
4.920
4.890
4.100
4.066
3.357
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2.842
2.758
2.650
2.626
2.608
2.525
2.202
2.059
1.921
1.767
1.018
Bn
N
H
Me
O
5.43
1.00
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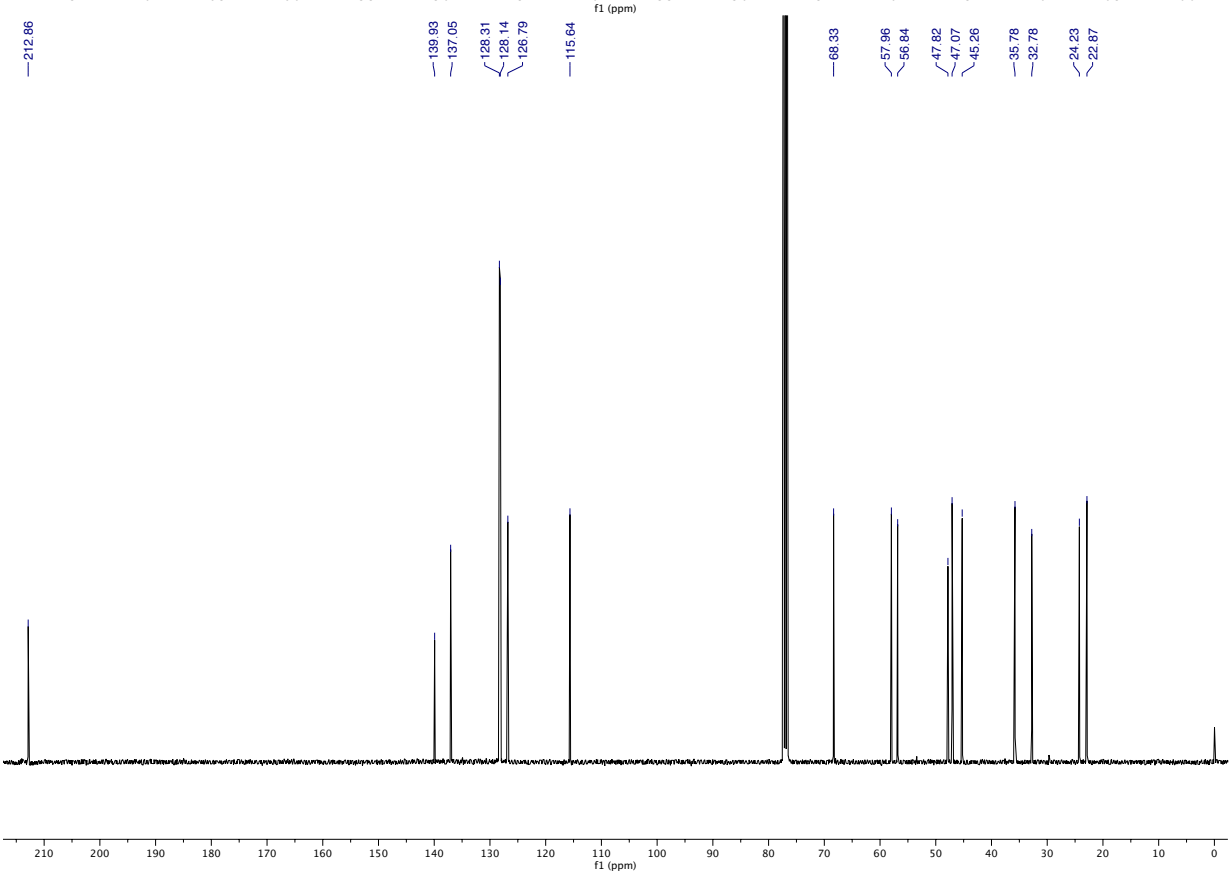
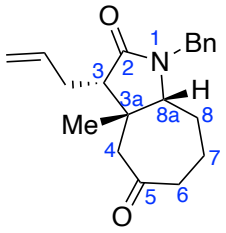
2.05
1.00
3.19
4.17
3.06
f1 (ppm)

83

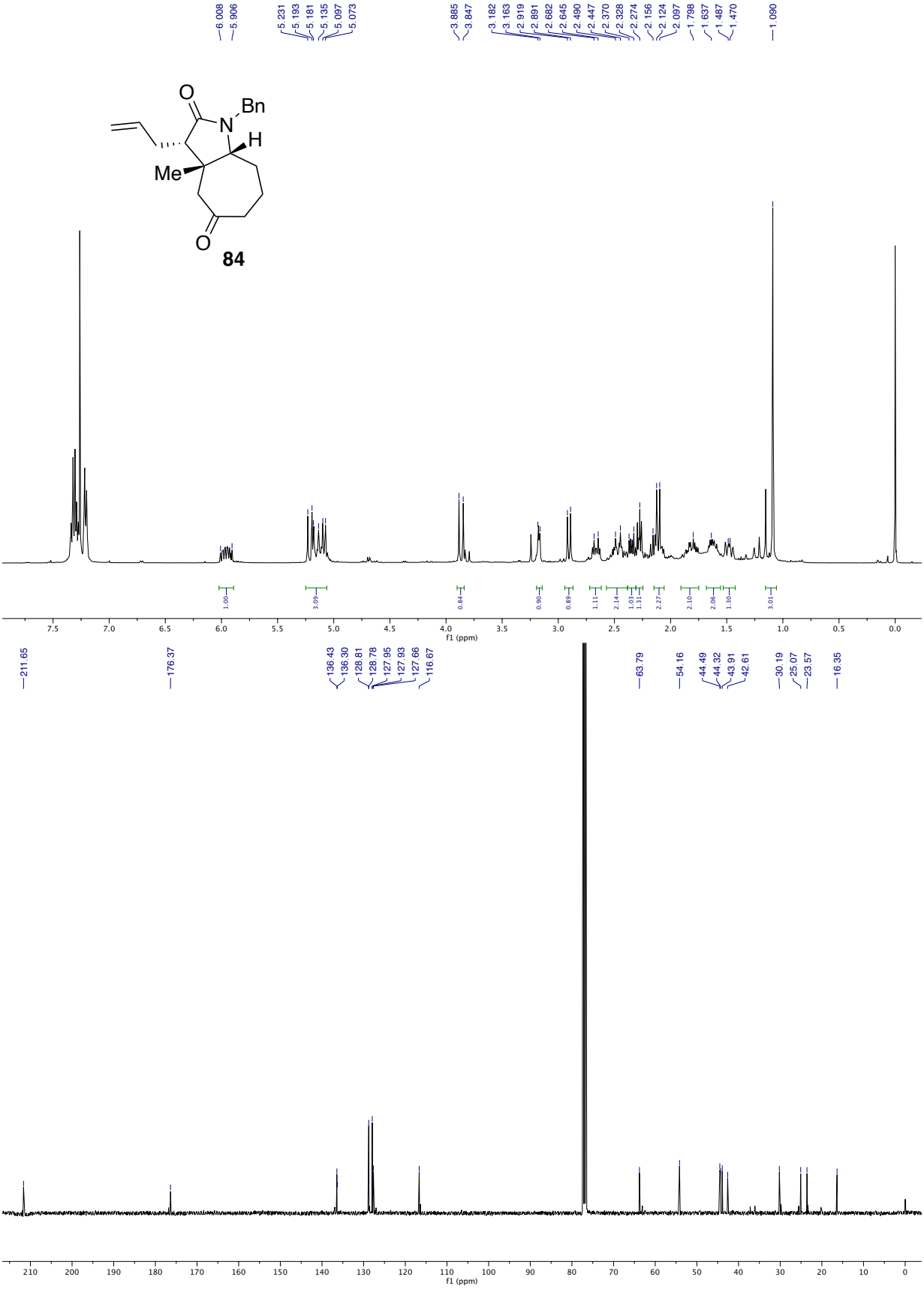

212.86
139.93
137.05
128.31
128.14
126.79
115.64
68.33
57.96
56.84
47.82
47.07
45.26
35.78
32.78
24.23
22.87
f1 (ppm)

(3*RS*,3a*SR*,8a*SR*)-1-Benzyl-3a-methyl-3-(prop-2-en-1-yl)hexahydrocyclohepta[b] pyrrole-2,5(1H,3H)-dione ethylene acetal (84)



Diethyl ether (70 mL) was cooled to -78 ºC and a solution of $TMSCHN_2$ (1.8 M in Et_2O, 4.1 mL, 7.8 mmol, 2.25 equiv) followed by *n*-BuLi solution (1.9 M in THF, 4.3 mL, 7.8 mmol 2.25 equiv) were added. After being stirred for 30 min at this temperature, a solution of bicyclic lactam **D** (1.03 g, 3.46 mmol) was added over 15 min via syringe pump. The reaction was stirred for 2h 30 min before a solution of MeOH:THF (1:9, v:v, 50 mL) was added dropwise and let to reach room temperature over 1h. The mixture was quenched with 2M NaOH (100 mL), phases were separated and the aqueous was extracted with CH_2Cl_2 (2 x 80 mL) and $CHCl_3$:i-PrOH (4:1, 4 x 80 mL). Combined organics were treated with SiO_2 and Na_2SO_4 and stirred at room temperature for 30 minutes. Then, it was filtered through a celite pad, concentrated under vacuum and the obtained crude was purified by chromatographic column (hexane:EtOAc, 9:1 $\rightarrow$ 4:1) to provide with the expanded product **84** (0.79 g, 73%) as a waxy solid along with subproduct **85** (0.07 g, 7%) and silyl enol ether **86** (0.11 g, 8%).

The NMR data were identical with those previously reported by our research group [98b]


6.008
5.906
5.231
5.193
5.181
5.135
5.097
5.073
3.885
3.847
3.182
3.163
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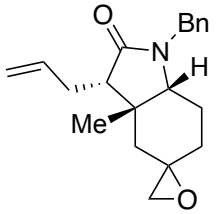
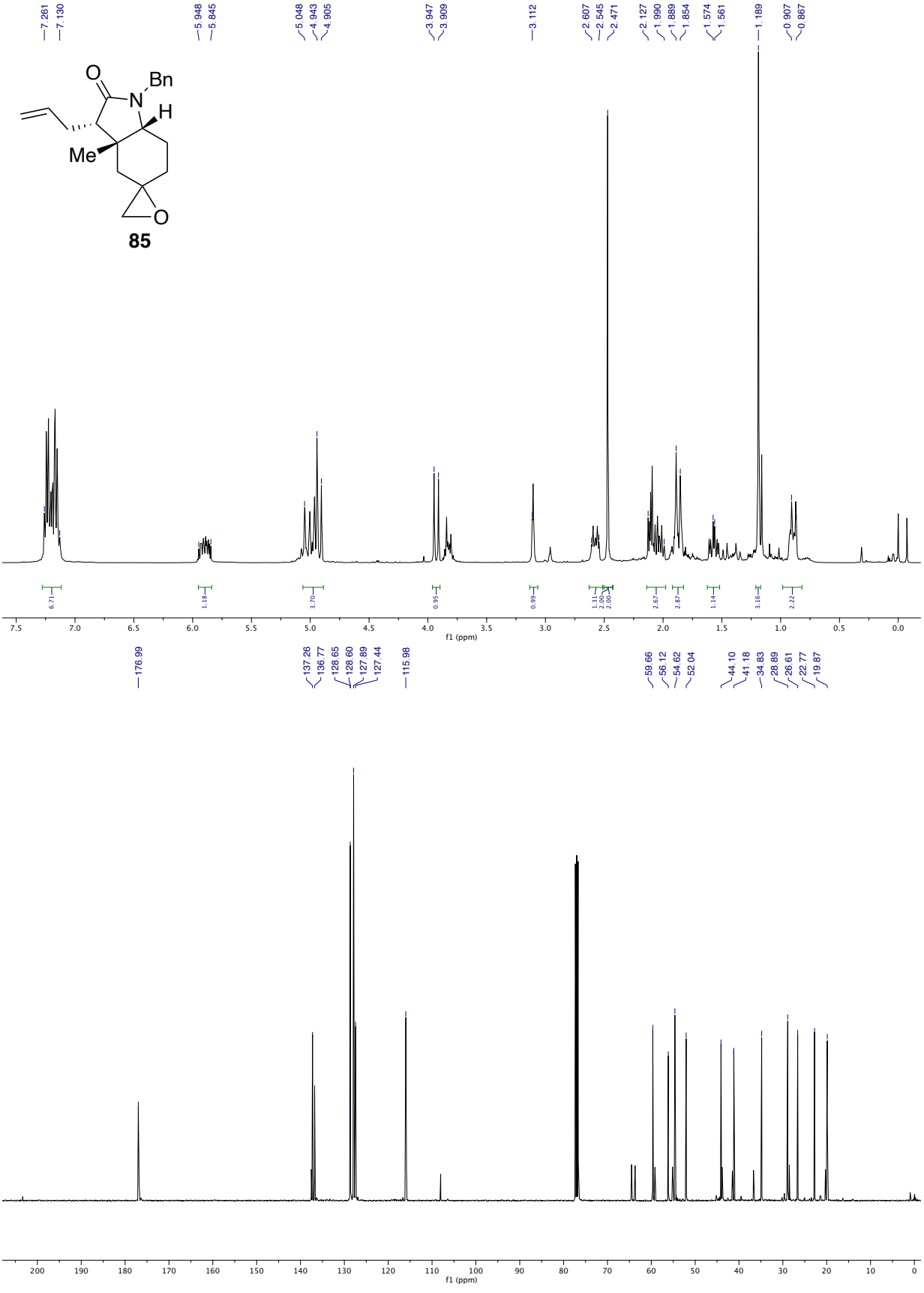
2.891
2.682
2.645
2.490
2.447
2.370
2.328
2.274
2.156
2.124
2.097
1.798
1.637
1.487
1.470
1.090
O
N
Bn
H
Me
O
84
f1 (ppm)
211.65
176.37
136.43
136.30
128.81
128.78
127.95
127.93
127.66
116.67
63.79
54.16
44.49
44.32
43.91
42.61
30.19
25.07
23.57
16.35
f1 (ppm)

Epoxide (85)



IR (NaCl) : 3065, 2938, 1690, 1432, 1411, 914, 732 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26–7.13 (m, 5H, Ph), 5.95–5.85 (m, 1H, =CH), 5.05–4.91 (m, 3H, $=CH_2$ and CH_2Ph), 3.93 (d, *J* = 15.0 Hz, 1H, CH_2Ph), 3.11 (t, *J* = 3.1 Hz, 1H, H-7a), 2.60–2.54 (m, 1H, CH_2-3), 2.47 (s, 2H, OCH_2), 2.10 (dd, *J* = 8.6, 5.2 Hz, 1H, H-3), 2.08–1.99 (m, 1H, 3-CH_2), 1.94–1.80 (m, 3H, H-7 and H-4), 1.57 (td, *J* = 13.5, 5.2 Hz, 1H, H-6), 1.19 (s, 3H, Me), 0.93-0.87 (m, 2H, H-6 and H-4). ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.0 (C-2), 137.3 (=CH), 136.8, 128.6, 127.9 and 127.4 (Ph), 116.0 ($=CH_2$), 59.7 (C-7a), 56.1 (C-5), 54.6 (C-3), 52.0 (OCH_2), 44.1 (CH_2Ph), 41.2 (C-3a), 34.8 (C-4), 28.9 (CH_2-3), 26.6 (C-6), 22.8 (Me), 19.9 (C-7).


7.261
7.130
5.948
5.845
5.048
4.943
4.905
3.947
3.909
3.112
2.607
2.545
2.471
2.127
1.990
1.889
1.854
1.574
1.561
1.189
0.907
0.867
O
Bn
N
H
Me
O
85
6.71
1.18
3.70
0.95
0.99
1.11
2.03
2.00
2.67
2.87
1.14
3.16
2.22
f1 (ppm)
176.99
137.26
136.77
128.65
128.60
127.89
127.44
115.98
59.66
56.12
54.62
52.04
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41.18
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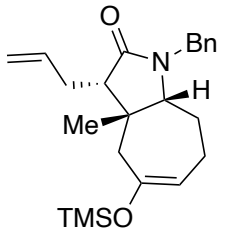
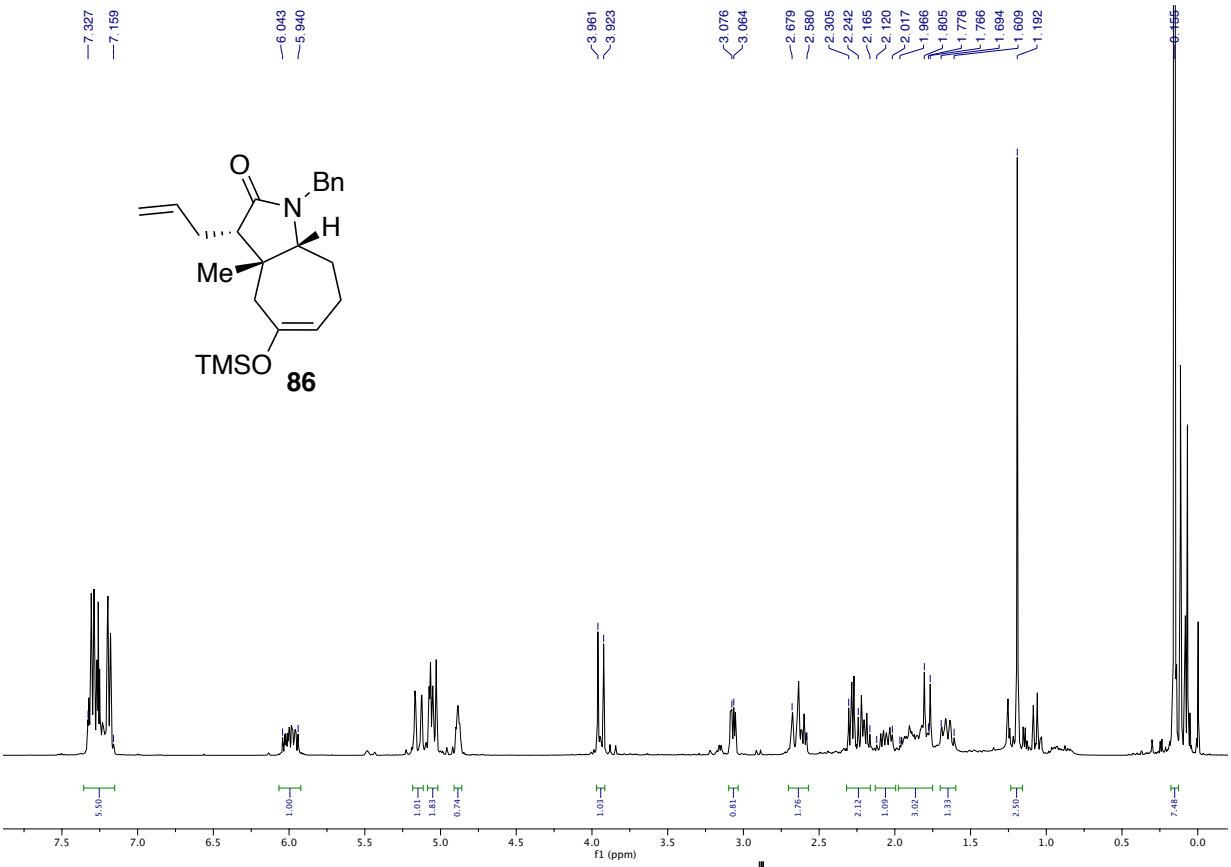
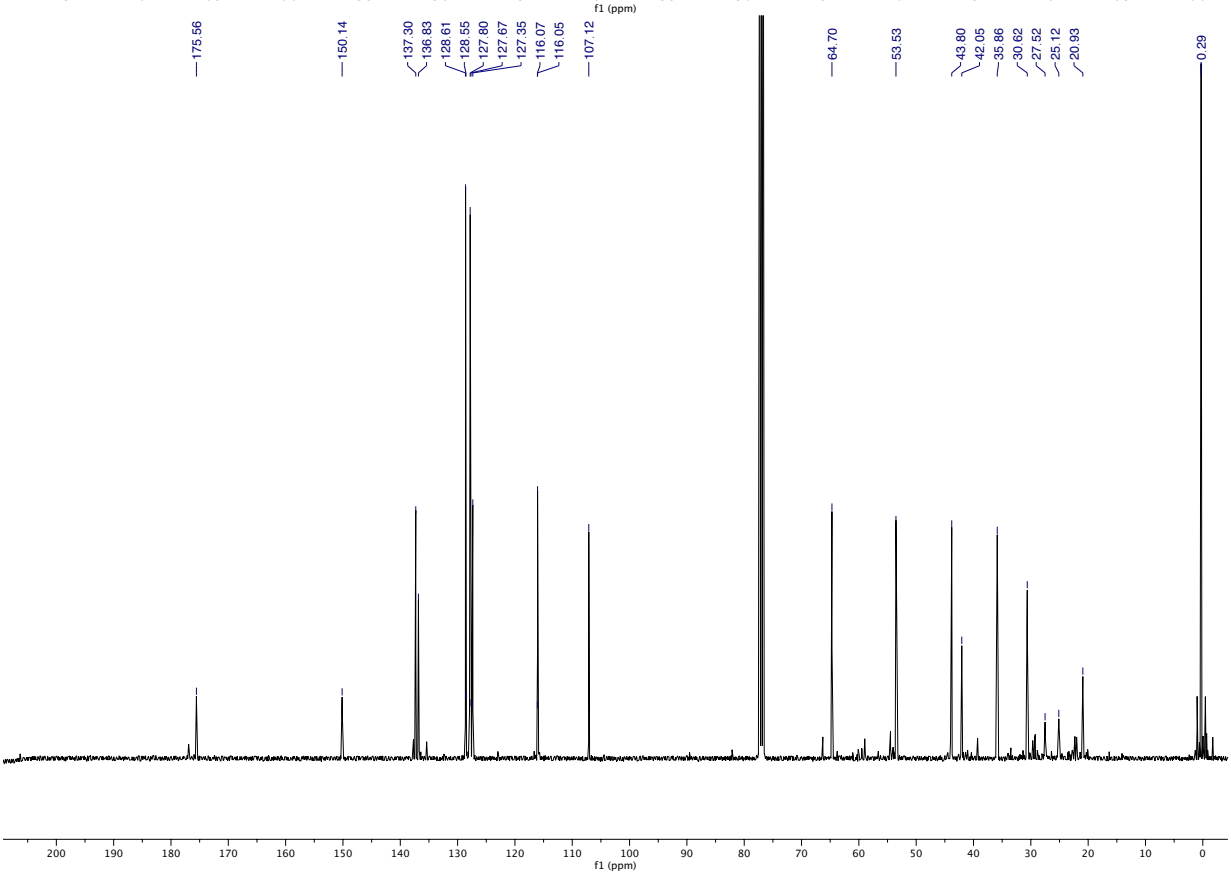
28.89
26.61
22.77
19.87
f1 (ppm)

Silyl enol ether (86)

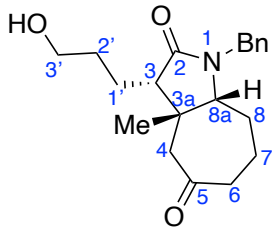


IR (NaCl): 3066, 2957, 1690, 1433, 1251, 845, 733 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.18 (m, 5H, Ph), 5.99 (dddd, *J* = 17.0, 9.8, 8.0, 5.6 Hz, 1H, =CH), 5.15 (dd, *J* = 17.0 Hz, 1H, $=CH_2$trans), 5.06 (d, *J* = 9.8 Hz, 1H, $=CH_2$cis), 5.05 (d, *J* = 15.2 Hz, 1H, CH_2Ph), 4.88 (bt, 1H, H-6), 3.94 (d, *J* = 15.2 Hz, 1H, CH_2Ph), 3.07 (dd, *J* = 9.2, 4.2 Hz, 1H, H-8a), 2.66 (d, *J* = 15.8 Hz, 1H, H-4), 2.65–2.58 (m, 1H, CH_2-3), 2.29 (dd, *J* = 8.2, 5.8, 1H, H-3), 2.20 (dt, *J* = 14.0, 8.0 Hz, 1H, CH_2-3), 2.06 (dt, *J* = 15.8, 7.0 Hz, 1H, H-7), 1.95–1.78 (m, 2H, H-7 and H-8), 1.78 (d, *J* = 15.8 Hz, 1H, H-4), 1.69–1.61 (m, 1H, H-8), 1.19 (s, 3H, Me), 0.16 (s, 9H, TMS). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.6 (C-2), 150.1 (C-5), 137.3 (=CH), 136.8, 128.6, 127.8 and 127.3 (Ph), 116.1 ($=CH_2$), 107.1 (C-6), 64.7 (C-8a), 53.5 (C-3), 43.8 (NCH_2), 42.0 (C-3a), 35.9 (C-4), 30.6 (CH_2-3), 27.5 (C-8), 25.1 (Me), 20.9 (C-7), 0.3 (TMS).


7.327
7.159
6.043
5.940
3.961
3.923
3.076
3.064
2.679
2.580
2.305
2.242
2.165
2.120
2.017
1.966
1.805
1.778
1.766
1.694
1.609
1.192
0.166
O
Bn
N
H
Me
TMSO
86
f1 (ppm)

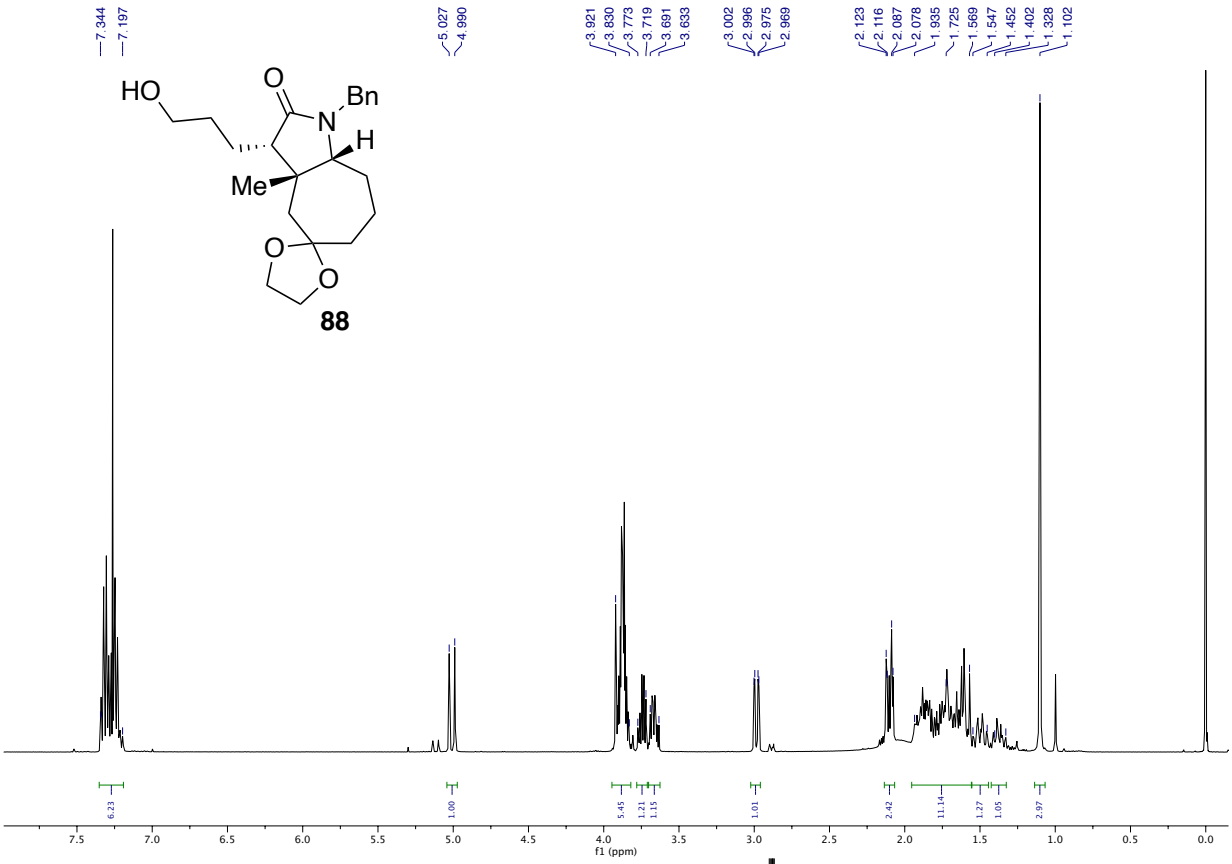

175.56
150.14
137.30
136.83
128.61
128.55
127.80
127.67
127.35
116.07
116.05
107.12
64.70
53.53
43.80
42.05
35.86
30.62
27.52
25.12
20.93
0.29
f1 (ppm)

(3*RS*,3a*SR*,8a*SR*)-1-Benzyl-3a-methyl-3-(3'-hydroxypropyl)-hexahydrocyclohepta [b] pyrrole-2,5(1*H*,3*H*)-dione ethylene acetal (88)



Product **87** (0.73 g, 2.04 mmol) and 9-BBN solution (0.5 M in THF, 8.2 mL, 4.1 mmol) were stirred for 5 h at room temperature. Then, at 0 ºC, 2M NaOH (9.1 mL) and H_2O_2 (8.2 mL) were added, and the reaction was stirred at room temperature overnight. Water was added (15 mL) and the mixture was extracted with EtOAc (5 x 15 mL) and CH_2Cl_2 (3 x 10 mL). Combined organics were dried, filtered and concentrated under vacuum to obtain a crude that was purified by chromatographic column (CH_2Cl_2:MeOH, 9.9:0.1→ 9.5:0.5) to achieve alcohol **88** (0.72 g, 1.92 mmol, 94%) as a waxy solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.20 (m, 5H, Ph), 5.01 (d, *J* = 14.8 Hz, 1H, CH_2Ph), 3.92–3.83 (m, 5H, CH_2Ph and OCH_2), 3.77–3.72 and 3.69–3.63 (2m, 1H each, CH_2OH), 2.98 (dd, *J* = 10.8, 2.4 Hz, 1H, H-8a), 2.12–2.08 (m, 2H, H-4 and H-3), 1.94–1.57 (m, 9H, H-4, H-6, 1'-CH_2-3, H-7, 2'-CH_2-3, H-8), 1.55–1.45 (m, 1H, H-8), 1.40–1.33 (m, 1H, H-7), 1.10 (s, 3H, Me). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.4 (C-2), 136.6, 128.6, 128.3, 127.5 (Ph), 111.2 (C-5), 67.1 (C-8a), 64.9 and 63.5 (OCH_2), 62.6 (CH_2OH), 54.4 (C-3), 44.3 (CH_2Ph), 40.5 (C-4), 39.7 (C-3a), 39.0 (C-6), 31.2 (2'-CH_2-3), 29.8 (Me), 28.2 (C-8), 26.5 (1'-CH_2-3), 20.8 (C-7).


7.344
7.197
5.027
4.990
3.921
3.830
3.773
3.719
3.691
3.633
3.002
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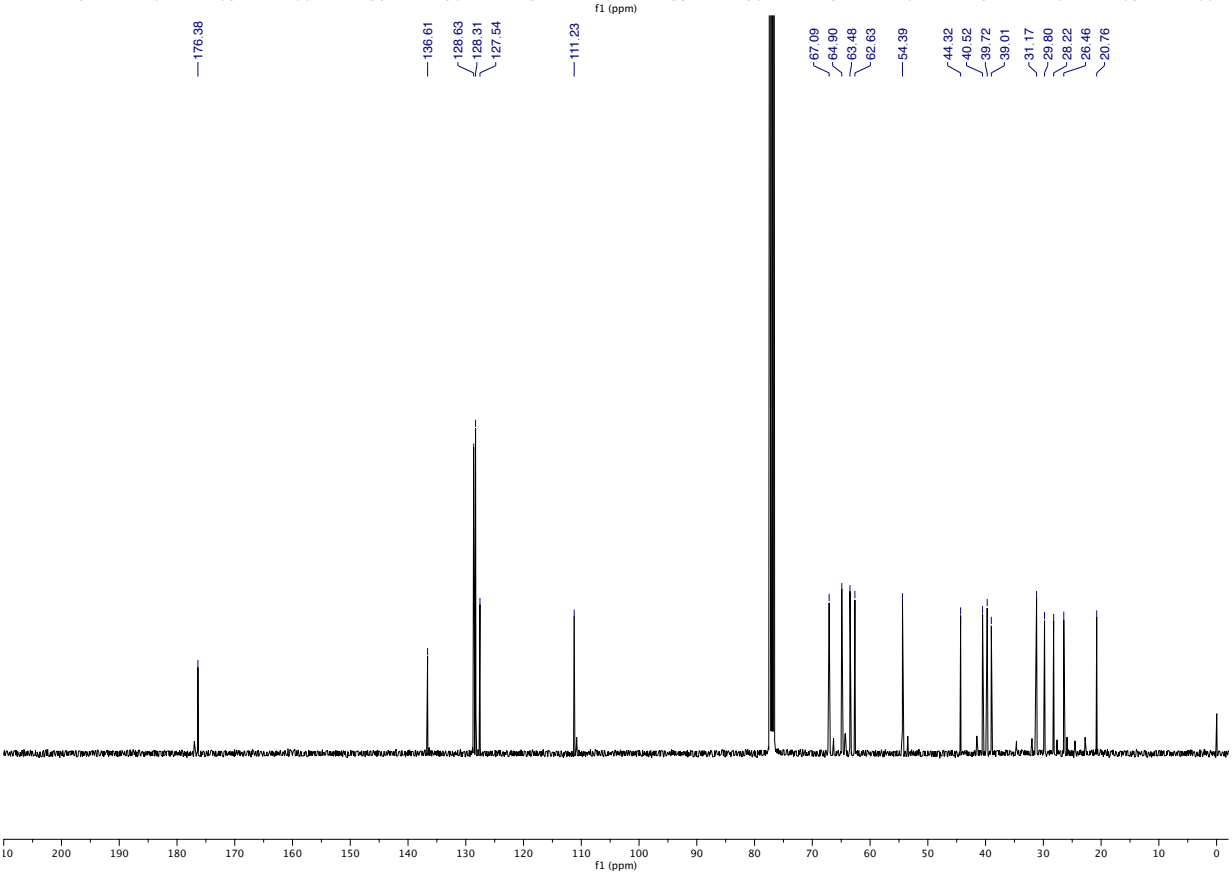
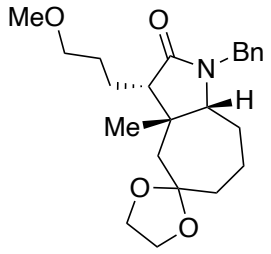
2.975
2.969
2.123
2.116
2.087
2.078
1.935
1.725
1.569
1.547
1.452
1.402
1.328
1.102
HO
O
N
Bn
H
Me
O
O
88
6.23
1.00
5.45
1.21
1.15
1.01
2.42
11.14
1.27
1.05
2.97
f1 (ppm)

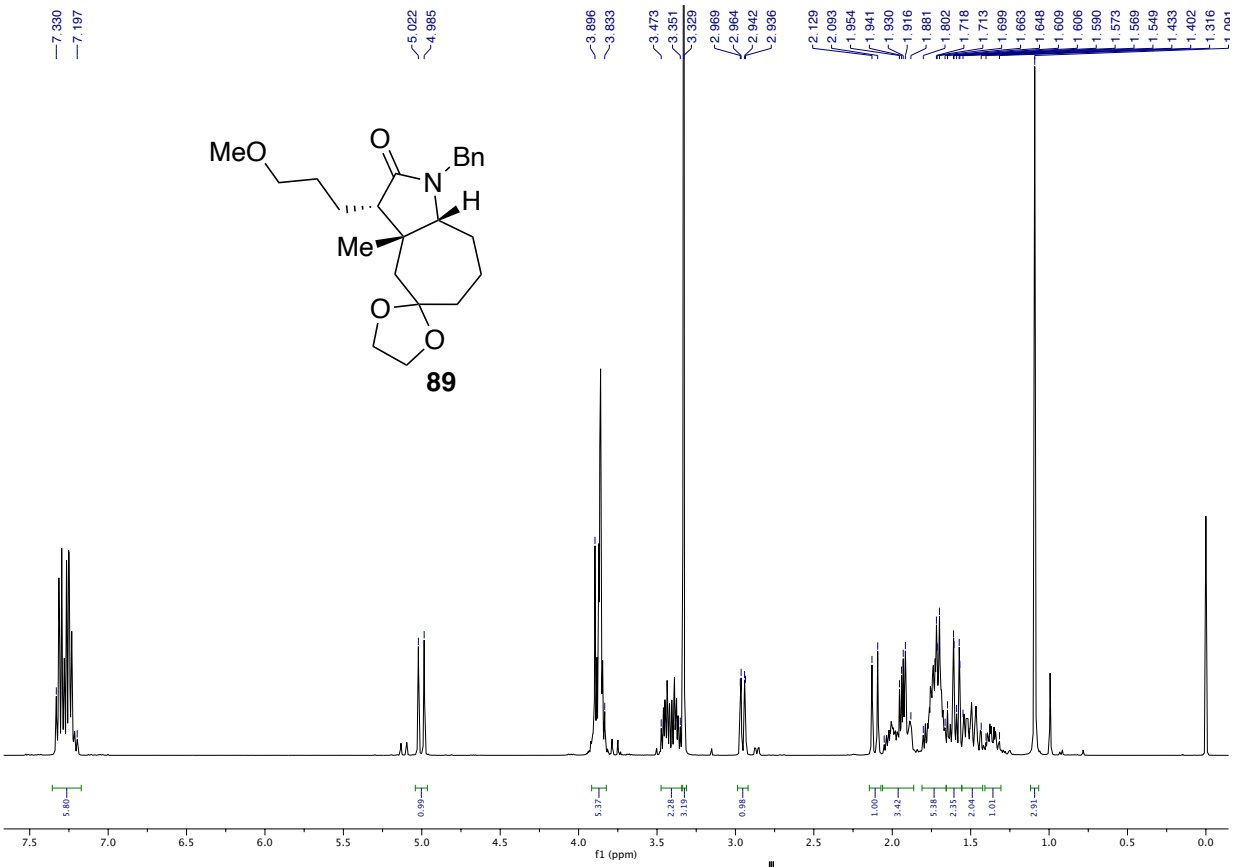

176.38
136.61
128.63
128.31
127.54
111.23
67.09
64.90
63.48
62.63
54.39
44.32
40.52
39.72
39.01
31.17
29.80
28.22
26.46
20.76
f1 (ppm)

(3*RS*,3a*SR*,8a*SR*)-1-Benzyl-3a-methyl-3-(3'-methoxypropyl)-hexahydrocyclohepta [b]pyrrole-2,5(1*H*,3*H*)-dione ethylene acetal (89)



A suspension of NaH (0.11 g, 2.77 mmol, 3 equiv) in THF (7 mL) was cooled to 0 ºC and a solution of alcohol **88** (0.34 g, 0.92 mmol, 1 equiv) in THF (9 mL) was added dropwise via cannula. After being stirred at this temperature for 30 min, iodomethane (0.17 mL, 2.77 mmol, 3 equiv) was added and the reaction was stirred at room temperature overnight. Then, it was cautiously quenched with NH_4Cl sat. solution and extracted with CH_2Cl_2 (4 x 20 mL). Combined organics were dried, filtered and concentrated under vacuum to obtain the crude that was purified by chromatographic column (CH_2Cl_2:MeOH, 9.9:0.1 $\rightarrow$ 9.5:0.5) to provide the desired protected alcohol **89** (0.27 g, 0.70 mmol, 76%)

IR (NaCl): 2933, 1680, 1448, 1118, 1074, 731, 702 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.33–7.20 (m, 5H, Ph), 5.00 (d, *J* = 14.8 Hz, 1H, CH_2Ph), 3.90–3.83 (m, 4H, OCH_2 and CH_2Ph), 3.47–3.35 (m, 2H, CH_2OMe), 3.33 (s, 3H, OMe), 2.95 (dd, *J* = 11.0, 2.2 Hz, 1H, H-8a), 2.11 (d, *J* = 14.6, 1H, H-4), 1.94 (dd, *J* = 9.7, 5.4 Hz, 1H, H-3), 2.05–1.88 (m, 2H, 2'-CH_2-3 and H-8), 1.80–1.66 (m, 4H, 2'-CH_2-3, 1'-CH_2-3, H-6 and H-7), 1.64–1.59 (m, 1H, H-6), 1.59 (d, *J* = 14.6 Hz, 1H, H-4), 1.55–1.43 (m, 2H, 1'-CH_2-3 and H-8), 1.40–1.32 (m, 1H, H-7), 1.09 (s, 3H, Me). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.8 (C-2), 136.8, 128.6, 128.3 and 127.4 (Ph), 111.3 (C-5), 72.6 (CH_2OMe), 67.0 (C-8a), 64.9 and 63.4 (OCH_2), 58.5 (OMe), 54.9 (C-3), 44.2 (CH_2Ph), 40.7 (C-4), 39.4 (C-3a), 38.9 (C.6), 30.0 (Me), 28.5 (2'-CH_2-3), 28.1 (C-8), 26.7 (1'-CH_2-3), 20.9 (C-7).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7.197
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4.985
3.896
3.833
3.473
3.351
3.329
2.969
2.964
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2.936
2.129
2.093
1.954
1.941
1.930
1.916
1.881
1.802
1.718
1.713
1.699
1.663
1.648
1.609
1.606
1.590
1.573
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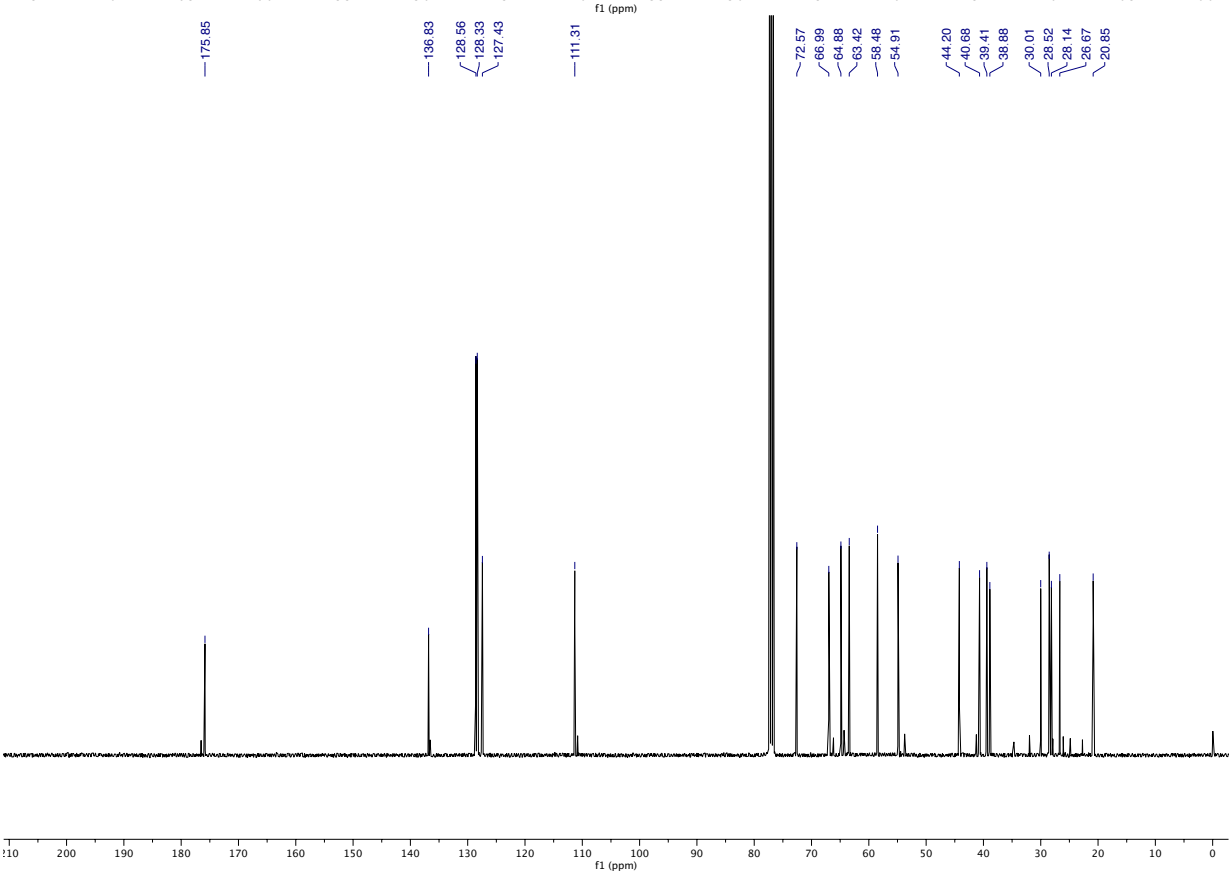
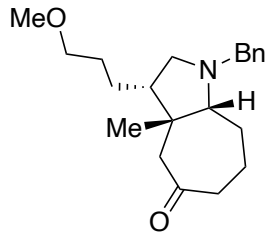
MeO
O
N
Bn
H
Me
O
O
89
f1 (ppm)

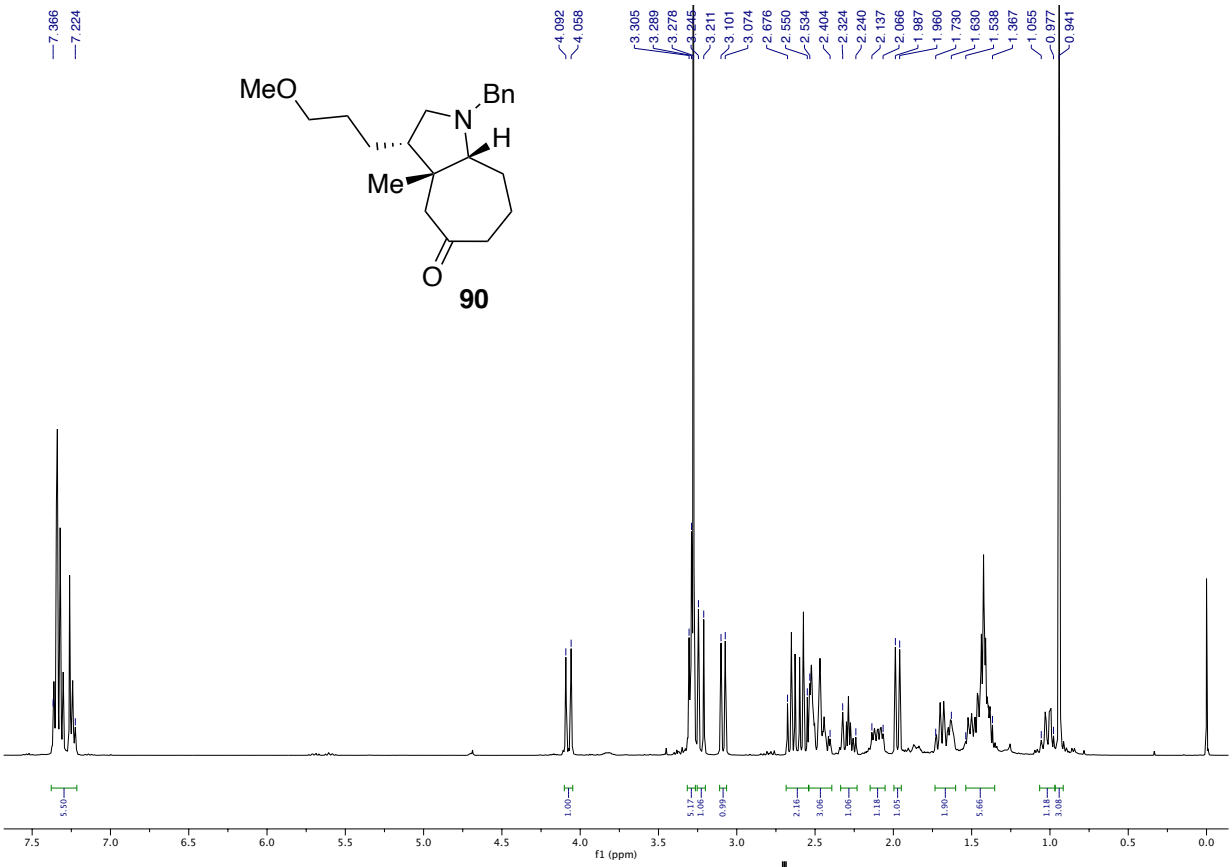

175.85
136.83
128.56
128.33
127.43
111.31
72.57
66.99
64.88
63.42
58.48
54.91
44.20
40.68
39.41
38.88
30.01
28.52
28.14
26.67
20.85
f1 (ppm)

(3*RS*,3a*SR*,8a*SR*)-1-Benzyl-3-(3'-methoxypropyl)- 3a-methyloctahydrocyclohepta [*b*]pyrrol-5(1*H*)-one (90)



A suspension of $AlCl_3$ (0.29 g, 2.20 mmmol) in THF (11 mL) was cooled to 0 ºC and a solution of $LiAlH_4$ (1M in THF, 2.9 mL) was added dropwise. After being stirred for 30 min at this temperature, a solution of compound **89** (0.57 g, 1.47 mmol) was added dropwise via cannula. The reaction was stirred at room temperature overnight before it was quenched with 30% KOH solution. The obtained mixture was extracted sequentially with CH_2Cl_2 (3 x 20 mL) and $CHCl_3$:*i*-PrOH (3 x 20 mL) and the combined organic phases were dried, filtered, and concentrated. The obtained crude containing the protected bicyclic compound (0.54 g, 1.65 mmol) was diluted in 10% HCl and the mixture was stirred at room temperature overnight. After that, the reaction was quenched with 15% NaOH solution and extracted with CH_2Cl_2 (3x10 mL) combined with CH_3Cl_3:i-PrOH (4:1, 4 x 20 mL). The organic phases were dried, filtered, and concentrated and the obtained crude was purified by chromatographic column (CH_2Cl_2:MeOH, 1:0→ 9.5:0.5) to obtain product **90** (0.14 g, 28%) along with a subproduct **91** (0.17 g, 35%).

IR (NaCl): 2932, 2864, 1697, 1452, 1117, 736, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37–7.22 (m, 5H, Ph), 4.08 (d, *J* = 13.6 Hz, 1H, CH_2Ph), 3.31–3.28 (m, 2H, CH_2OMe), 3.28 (s, 3H, OMe), 3.23 (d, *J* = 13.6 Hz, 1H, CH_2Ph), 3.09 (d, *J* = 10.8 Hz, 1H, H-4), 2.65 and 2.57 (2 t, *J* = 9.8 Hz, 1H each, H-2), 2.53–2.40 (m, 3H, H-8a, H-6 and H-7), 2.34–2.24 (m, 1H, H-6), 2.14–2.07 (m, 1H, 1'-CH_2-3), 1.97 (d, *J* = 10.8 Hz, 1H, H-4), 1.73–1.63 (m, 1H, H-3), 1.54–1.34 (m, 5H, H-7, H-8 and 2'-CH_2-3), 1.06–0.98 (m, 1H, 1'-CH_2-3), 0.94 (s, 3H, Me). ^{13}C NMR (101 MHz, $CDCl_3$) δ 215.0 (C-5), 140.2, 128.2, 128.2 and 126.7 (Ph), 72.8 (CH_2OMe), 71.9 (C-8a), 58.6 (OMe), 57.5 (CH_2Ph), 56.7 (C-2), 48.7 (C-3), 44.7 (C-4), 44.4 (C-3a), 44.3 (C-6), 28.8 (3-CH_2-2'), 26.2 (3-CH_2-1'), 25.8 (C-8), 22.4 (Me), 15.2 (C-7).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7.224
4.092
4.058
3.305
3.289
3.278
3.245
3.211
3.101
3.074
2.676
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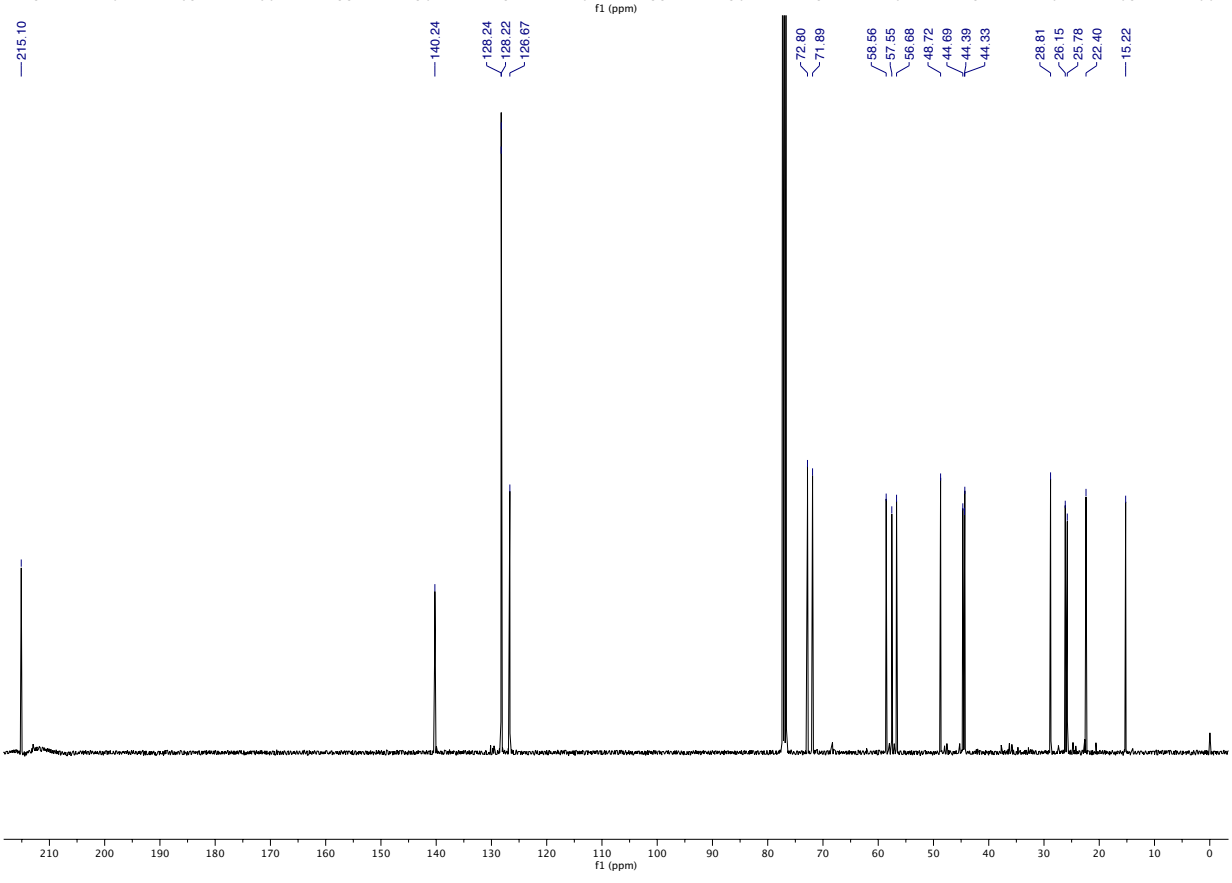
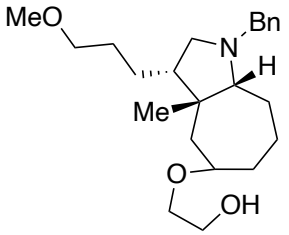
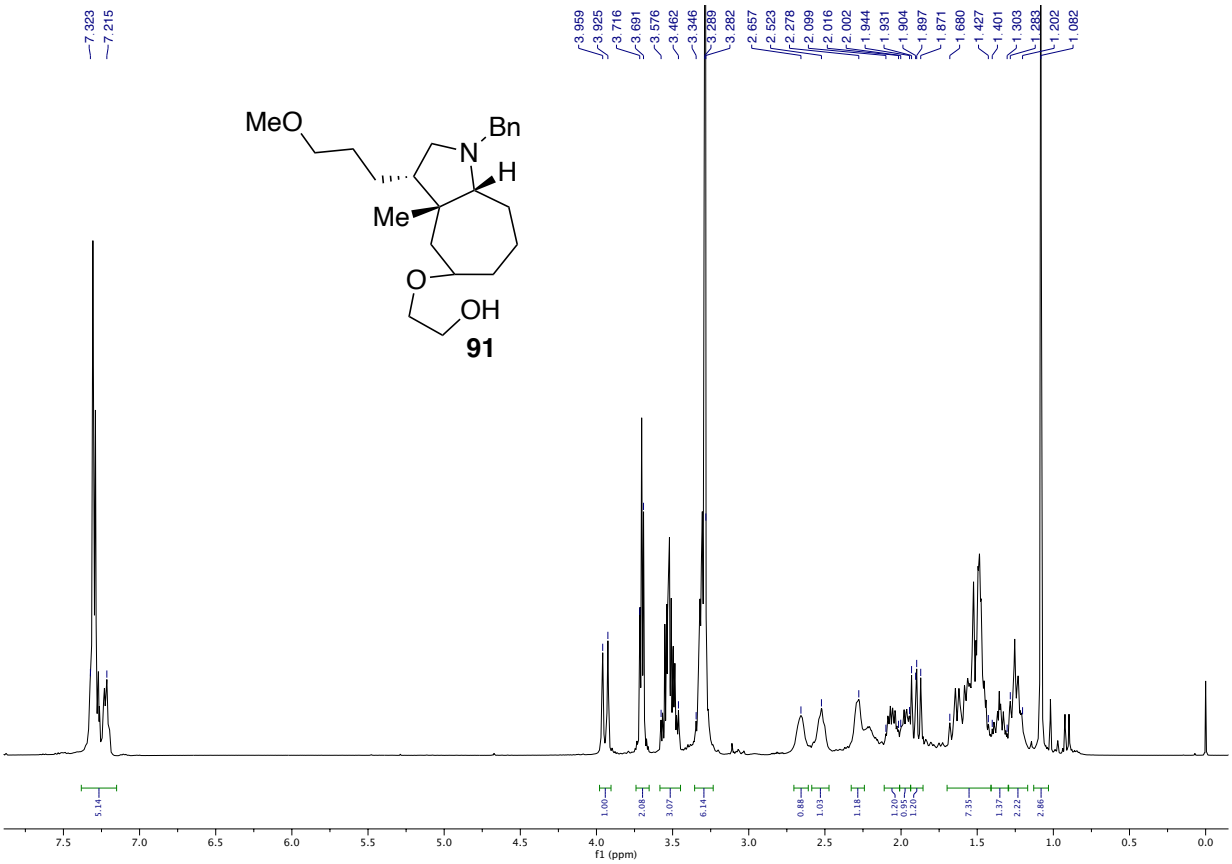
2.534
2.404
2.324
2.240
2.137
2.066
1.987
1.960
1.730
1.630
1.538
1.367
1.055
0.977
0.941
MeO
Bn
N
H
Me
O
90
f1 (ppm)

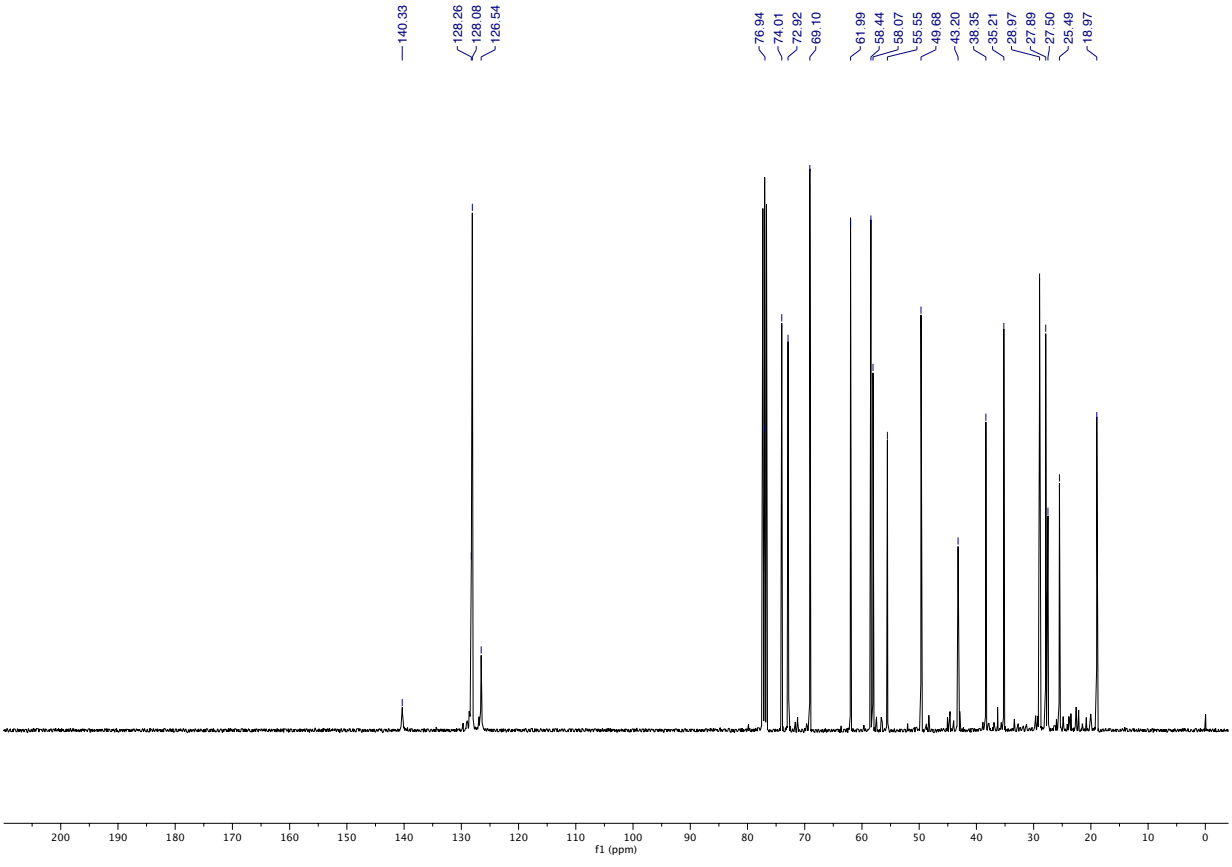

215.10
140.24
128.24
128.22
126.67
72.80
71.89
58.56
57.55
56.68
48.72
44.69
44.39
44.33
28.81
26.15
25.78
22.40
15.22
f1 (ppm)

Reduced derivative (91)

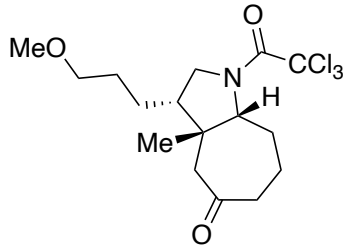


IR (NaCl): 3455, 2928, 2864, 1454, 1116, 699 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.22 (m, 5H, Ph), 3.94 (d, *J* = 13.6 Hz, 1H, CH_2Ph), 3.72–3.62 (m, 2H, CH_2O), 3.58–3.46 (m, 3H, H-5 and CH_2OH), 3.35–3.28 (m, 3H, CH_2Ph and CH_2OMe), 3.29 (s, 3H, OMe), 2.66 and 2.52 (2m, 1H each, H-2), 2.28 (m, 1H, H-8a), 2.10–2.02 (m, 1H, H-6), 2.00–1.94 (m, 1H, H-7), 1.90 (dd, *J* = 13.4, 10.6 Hz, 1H, H-4), 1.68–1.43 (m, 7H, H-3, H-4, H-6, 2'-CH_2-3, 1'-CH_2-3 and H-8), 1.40–1.30 (m, 1H, 2'-CH_2-3), 1.28–1.20 (m, 2H, 3-CH_2-1' and H-7), 1.08 (s, 3H, Me). ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.3, 128.3, 128.1 and 126.5 (Ph), 76.9 (C-5), 74.0 (C-8a), 72.9 (CH_2OMe), 69.1 (CH_2OH), 62.0 (CH_2O), 58.4 (OMe), 58.1 (CH_2Ph), 55.6 (C-2), 49.7 (C-3), 43.2 (C-3a), 38.3 (C-4), 35.2 (C-6), 29.0 (2'-CH_2-3), 27.9 (C-8), 27.5 (Me), 25.5 (1'-CH_2-3), 19.0 (C-7).


7.323
7.215
3.959
3.925
3.716
3.691
3.576
3.462
3.346
3.289
3.282
2.657
2.523
2.278
2.099
2.016
2.002
1.944
1.931
1.904
1.897
1.871
1.680
1.427
1.401
1.303
1.283
1.202
1.082
MeO
Bn
N
H
Me
O
OH
91
f1 (ppm)

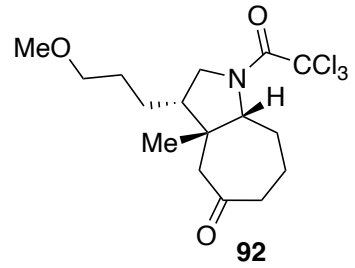

140.33
128.26
128.08
126.54
76.94
74.01
72.92
69.10
61.99
58.44
58.07
55.55
49.68
43.20
38.35
35.21
28.97
27.89
27.50
25.49
18.97
f1 (ppm)

(3*SR*,3a*RS*,8a*RS*)-3-(3-methoxypropyl)-3a-methyl-1-(2,2,2-trichloroacetyl) octahydrocyclohepta[*b*]pyrrol-5(1*H*)-one (92)



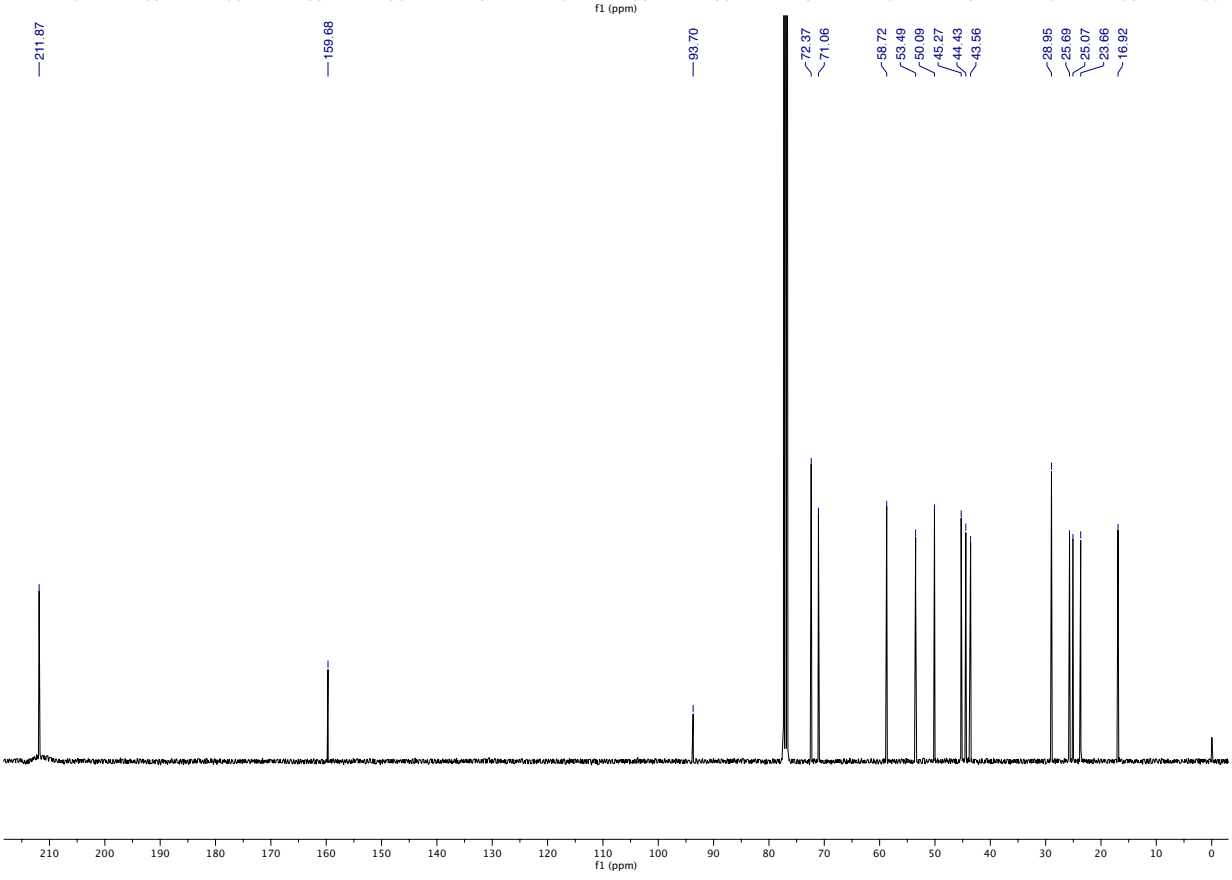
A suspension of $LiAlH_4$ (0.19 g, 4.9 mmol, 4 equiv) in THF (5 mL) was cooled to 0 ºC and a solution of bicyclic lactam **89** (0.48 g, 1.23 mmol, 1 equiv) was added and stirred at reflux overnight. After being quenched with 15% NaOH solution (20 mL) the mixture was filtered through a celite pad and washed with brine (20 mL), dried and concentrated. The obtained crude was diluted in MeOH (11 mL), added Pd/C (0.2 g, 50% in wt.) and stirred overnight at rt under H_2 atmosphere. Then, it was filtered through a celite pad, concentrated, and the obtained secondary amine was diluted in CH_2Cl_2 (5 mL). Trichloroacetyl chloride (0.2 mL, 1.84 mmol, 1.5 equiv) and pyridine (0.2 mL, 2.58 mmol, 2.1 equiv) were added and the reaction was stirred at rt overnight. Then, sat. sol. of Na_2CO_3 (20 mL) was added and extracted with CH_2Cl_2 (3 x 20 mL) and $CHCl_3$:i-PrOH (4:1, 5 x 20 mL). The organic layer were dried, filtered, and concentrated. The residue was diluted in THF:10% HCl (1:2, 12 mL) and stirred overnight at rt. Sat. sol. of Na_2CO_3 (20 mL) was added. The mixture was extracted with CH_2Cl_2 (5 x 20 mL), and the organics were dried, filtered, concentrated and purified by chromatographic column (hexane:EtOAc, 9:1 $\rightarrow$ 1:1) to provide trichloroactemide **92** (0.24 g, 51%).

IR (NaCl): 2934, 2870, 1703, 1679, 1453, 1389, 1116, 811, 699 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 4.37 (dd, *J* = 11.2, 6.8 Hz, 1H, H-2), 3.90 (dd, *J* = 7.0, 6.2 Hz, 1H, H-8a), 3.41–3.33 (m, 3H, H-2 and CH_2OMe), 3.34 (s, 3H, OMe), 2.73 (d, *J* = 11.4 Hz, 1H, H-4), 2.66–2.58 (m, 1H, H-8), 2.40 (bt, *J* = 6.0 Hz, 2H, H-6), 2.14 (d, *J* = 11.4 Hz, 1H, H-4), 1.87–1.52 (m, 7H, H-3, H-8, 2'-CH_2-3, H-7, 1'-CH_2-3), 1.36–1.27 (m, 1H, 1'-CH_2-3), 1.13 (s, 3H, Me). ^{13}C NMR (101 MHz, $CDCl_3$) δ. 211.9 (C-5), 159.7 (CO), 93.7 (C), 72.4 (CH_2OMe), 71.1 (C-8a), 58.7 (OMe), 53.5 (C-2), 50.1 (C-3), 45.3 (C-6), 44.4 (C-4), 43.6 (C-3a), 28.9 (2'-CH_2-3), 25.7 (C-8), 25.1 (Me), 23.7 (1'-CH_2-3), 16.9 (C-7).

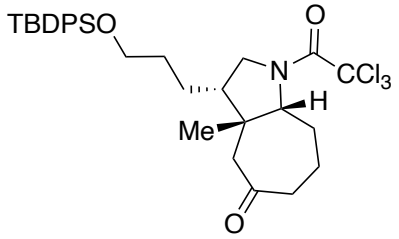

MeO
O
N
CCl3
H
Me
O

92

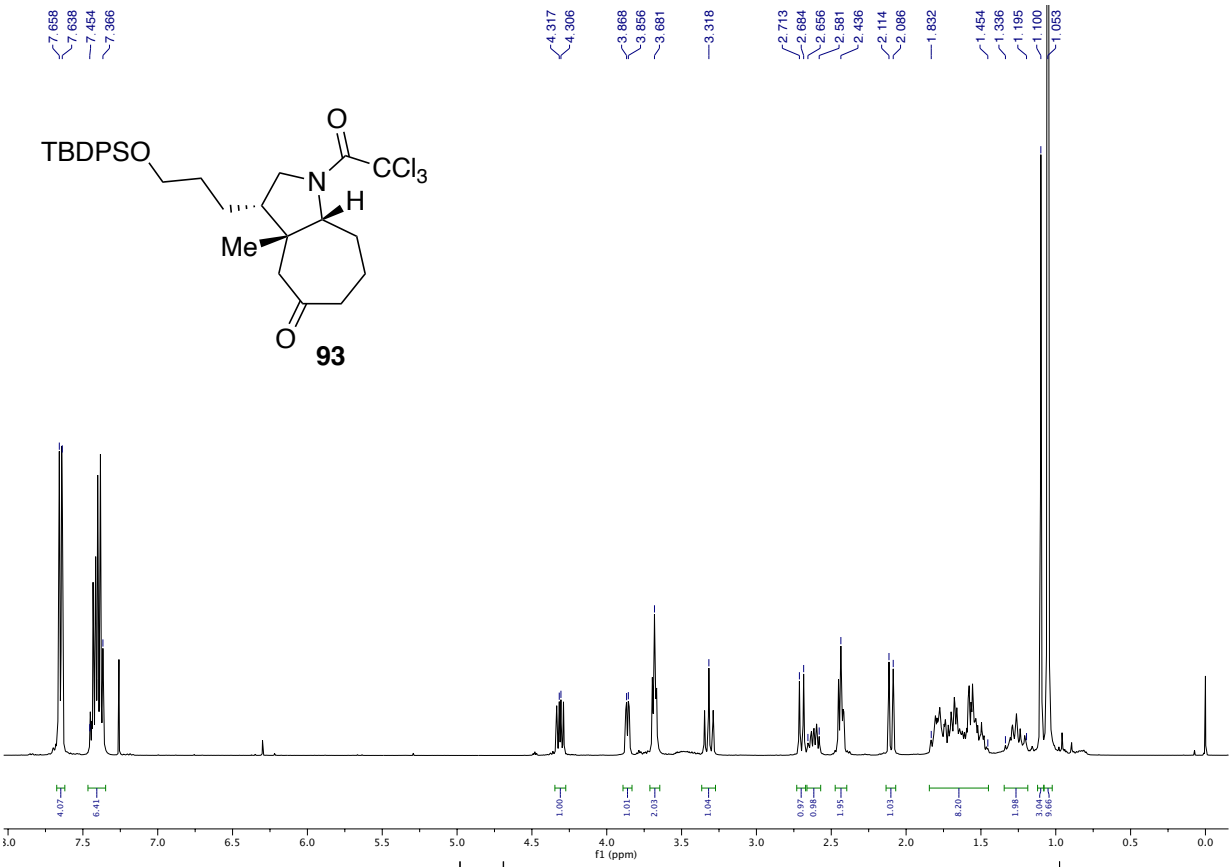
4.397
4.380
4.369
4.352
3.902
3.891
3.405
3.395
2.744
2.716
2.658
2.581
2.439
2.159
2.130
1.870
1.517
1.356
1.276
1.133
1.00
0.98
6.14
1.00
1.02
1.98
1.02
7.85
1.06
2.99
f1 (ppm)


211.87
159.68
93.70
72.37
71.06
58.72
53.49
50.09
45.27
44.43
43.56
28.95
25.69
25.07
23.66
16.92
f1 (ppm)

(3*S*,3a*R*,8a*R*)-3-(3-((*tert*-butyldiphenylsilyl)oxy)propyl)-3a-methyl-1-(2,2,2-trichloroacetyl)octahydrocyclohepta[*b*]pyrrol-5(1*H*)-one (93)



A solution of $LiAlH_4$ (1 M in THF, 5.9 mL, 4 equiv) was cooled to 0 ºC and a solution of bicyclic lactam **88** (0.53 g, 1.48 mmol, 1 equiv) was added and stirred at rfx overnight. After being quenched with 15% NaOH solution (20 mL) the mixture was filtered through a celite pad, washed with brine (20 mL). The residue was diluted in 10% HCl sol.(27 mL) and stirred at rt overnight. Then, 15 % NaOH sol. (20 mL) was added, extracted with CH_2Cl_2 (3 x 20 mL). The residue was diluted in CH_2Cl_2 (9 mL), and DMAP (9 mg, 0.07 mmol, 0.06 equiv), TBDPSCl (1.15 mL, 4.44 mmol, 3.5 equiv) and Et_3N (0.25 mL, 1.78 mmol, 1.4 equiv) were added and stirred overnight at rt. Next, the mixture was extracted with CH_2Cl_2. A portion of the amine (0.17 g, 0.4 mmol, 1 equiv) was diluted in MeOH, added Pd/C (90 mg, 50% wt.), and stirred at rt overnight under H_2 atm. After being filtered and concentrated, it was diluted in CH_2Cl_2 (3 mL). Trichloroacetyl chloride (70 μL, 0.6 mmol) and Et_3N (0.1 mL, 0.8 mmol) were added and the reaction was stirred at rt overnight. Then, sat. sol. of Na_2CO_3 (20 mL) was added and extracted with CH_2Cl_2 (3 x 20 mL). Purification by chromatography (hexane:EtOAc, 9:1 → 4:1) provided **93** (97 mg, 40%). IR (NaCl) : 4049, 2932, 1971, 1691, 1428, 733, cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.66–7.64 (m, 4H, Ph), 7.36 (m, 6H, Ph), 4.31 (dd, *J* = 11.2, 6.8 Hz, 1H, H-2), 3.86 (dd, *J* = 6.8, 2.4 Hz, 1H, H-8a), 3.68 (br t, 2H, OCH_2), 3.32 (t, *J* = 11.2 Hz, 1H, H-2), 2.70 (d, *J* = 11.4 Hz, 1H, H-4), 2.66–2.58 (m, 1H, H-8), 2.45–2.42 (m, 2H, H-6), 2.10 (d, *J* = 11.4 Hz, 1H, H-4), 1.83–1.46 (m, 7H, H-3, 2'-CH_2-3, H-8, 1'-CH_2-3, H-7), 1.34–1.17 (m, 1H, 1'-CH_2-3), 1.10 (s, 3H, Me), 1.05 (s, 3H, ^{t}Bu). ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.8 (C-5), 159.7 (CO), 135.5, 133.7, 133.7, 129.7, 129.7, 127.7 (Ph), 93.7 (CCl_3), 71.1 (C-8a), 63.4 (OCH_2), 53.5 (C-2), 49.8 (C-3), 45.2 (C-6), 44.4 (C-4), 43.5 (C-3a), 31.5 (2'-CH_2-3), 26.9 (^{t}Bu), 25.6 (C-8), 25.0 (Me), 23.1 (1'-CH_2-3), 19.2 (C), 16.9 (C-7).


7.658
7.638
7.454
7.366
4.317
4.306
3.868
3.856
3.681
3.318
2.713
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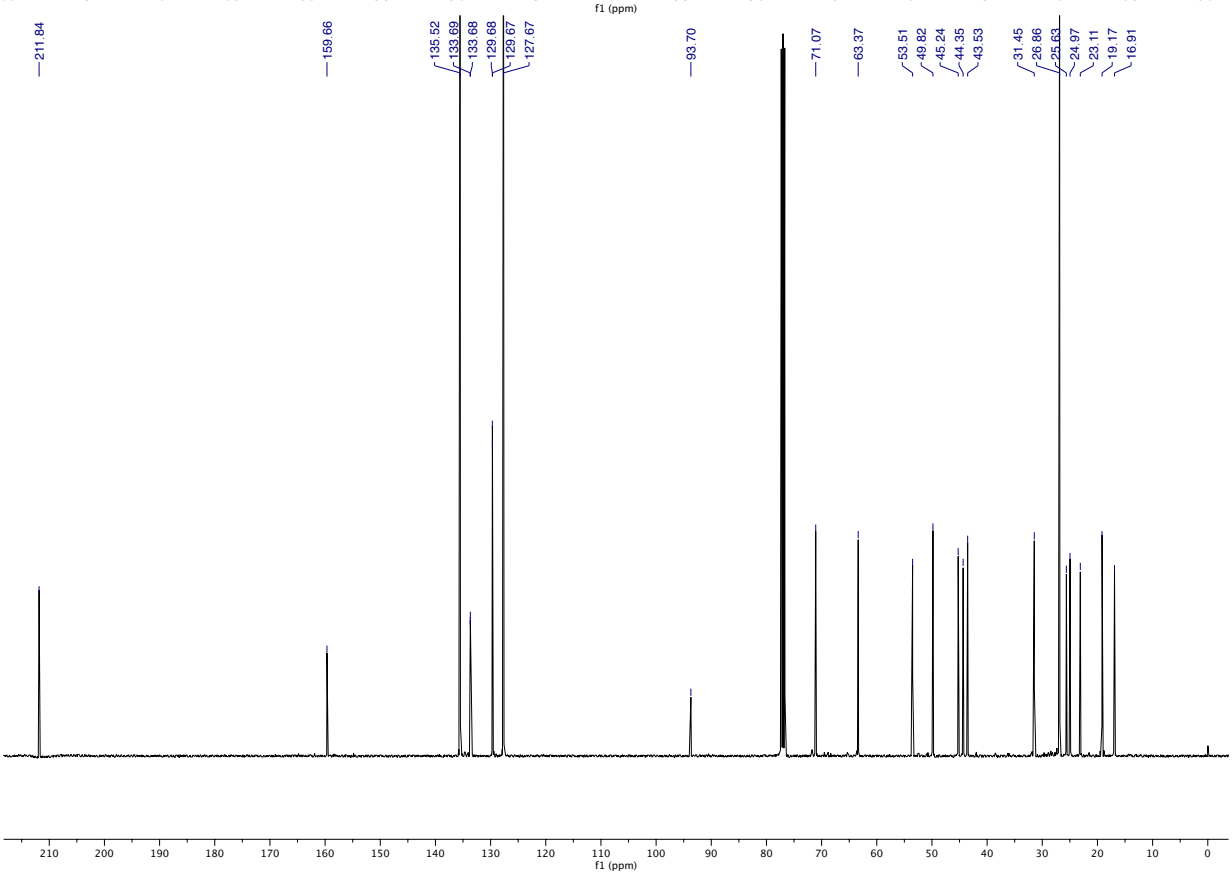
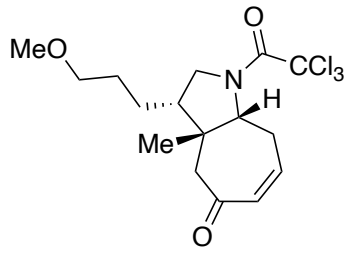
2.656
2.581
2.436
2.114
2.086
1.832
1.454
1.336
1.195
1.100
1.053
TBDPSO
O
N
CCl3
H
Me
O
93
f1 (ppm)

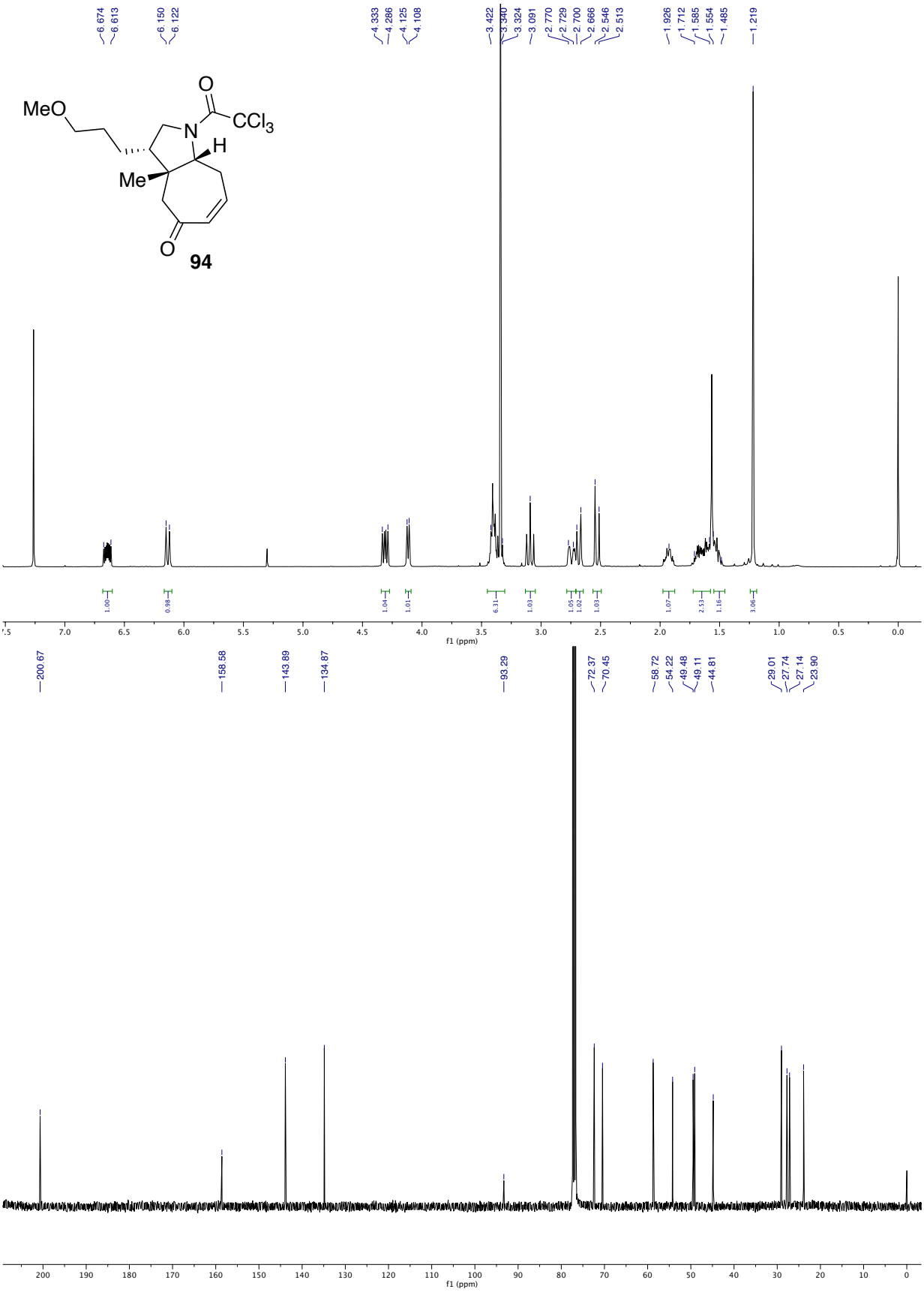

211.84
159.66
135.52
133.69
133.68
129.68
129.67
127.67
93.70
71.07
63.37
53.51
49.82
45.24
44.35
43.53
31.45
26.86
25.63
24.97
23.11
19.17
16.91
f1 (ppm)

(3*SR*,3a*RS*,8a*RS*)-3-(3-methoxypropyl)-3a-methyl-1-(2,2,2-trichloroacetyl)-2,3,3a,4,8,8a-hexahydrocyclohepta[*b*]pyrrol-5(1*H*)-one (94)

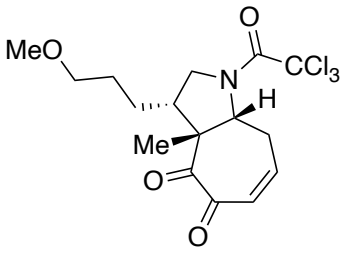


A solution of trichloroacetamide **92** (45 mg, 0.09 mmol), IBX (41 mg, 0.15 mmol, 2.5 equiv) and pTsOH (7 mg, 0.04 mmol, 0.3 equiv) in DMSO (1 mL) was heated to 70 ºC and stirred overnight. After being cooled down to rt, the mixture was diluted with EtOAc (10 mL) and water (10 mL) was added. Phases were separated and the aqueous was extracted with EtOAc (5 x 10 mL). Combined organics were dried, filtered and concentrated to afford the crude that was purified by chromatographic column (CH_2Cl_2:MeOH, 1:0 $\rightarrow$ 9.5:0.5) and the enone **94** (27 mg, 60%) was obtained along with traces of over-oxidized product **95**.

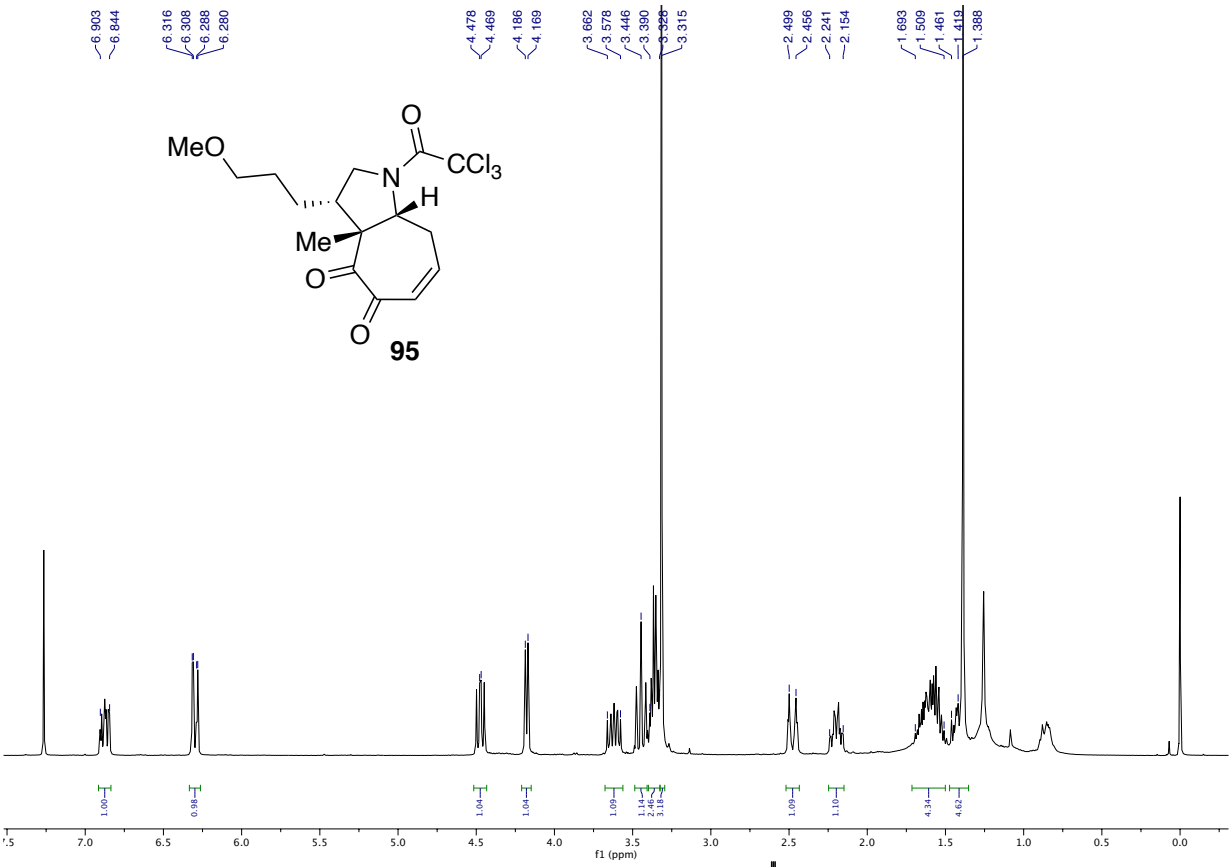
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.64 (ddd, *J* = 11.2, 8.2, 4 .6 Hz, 1H, H-7), 6.14 (dd, *J* = 11.2, 2.0 Hz, 1H, H-6), 4.31 (dd, *J* = 11.6, 7.2 Hz, 1H, H-2), 4.12 (d, *J* = 7.2 Hz, 1H, H-8a), 3.43–3.32 (m, 3H, CH_2OMe and H-8), 3.34 (s, 3H, OMe), 3.09 (t, *J* = 11.6 Hz, 1H, H-2), 2.74 (dddd, *J* = 16.4, 4.6, 2.2, 2.0 Hz, 1H, H-8), 2.68 and 2.53 (2d, *J* = 13.2 Hz, 1H each, H-4), 1.97–1.89 (m, 1H, H-3), 1.71–1.48 (m, 4H, 1'-CH_2-3 and 2'-CH_2-3), 1.22 (s, 3H, Me). ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.7 (C-5), 158.6 (CO), 143.9 (C-7), 134.9 (C-6), 93.3 (C), 72.4 (CH_2OMe), 70.5 (C-8a), 58.7 (OMe), 54.2 (C-2), 49.5 (C-4), 49.1 (C-3), 44.8 (C-3a), 29.0 (2'-CH_2-3), 27.7 (C-8), 27.1 (Me), 23.9 (1'-CH_2-3).

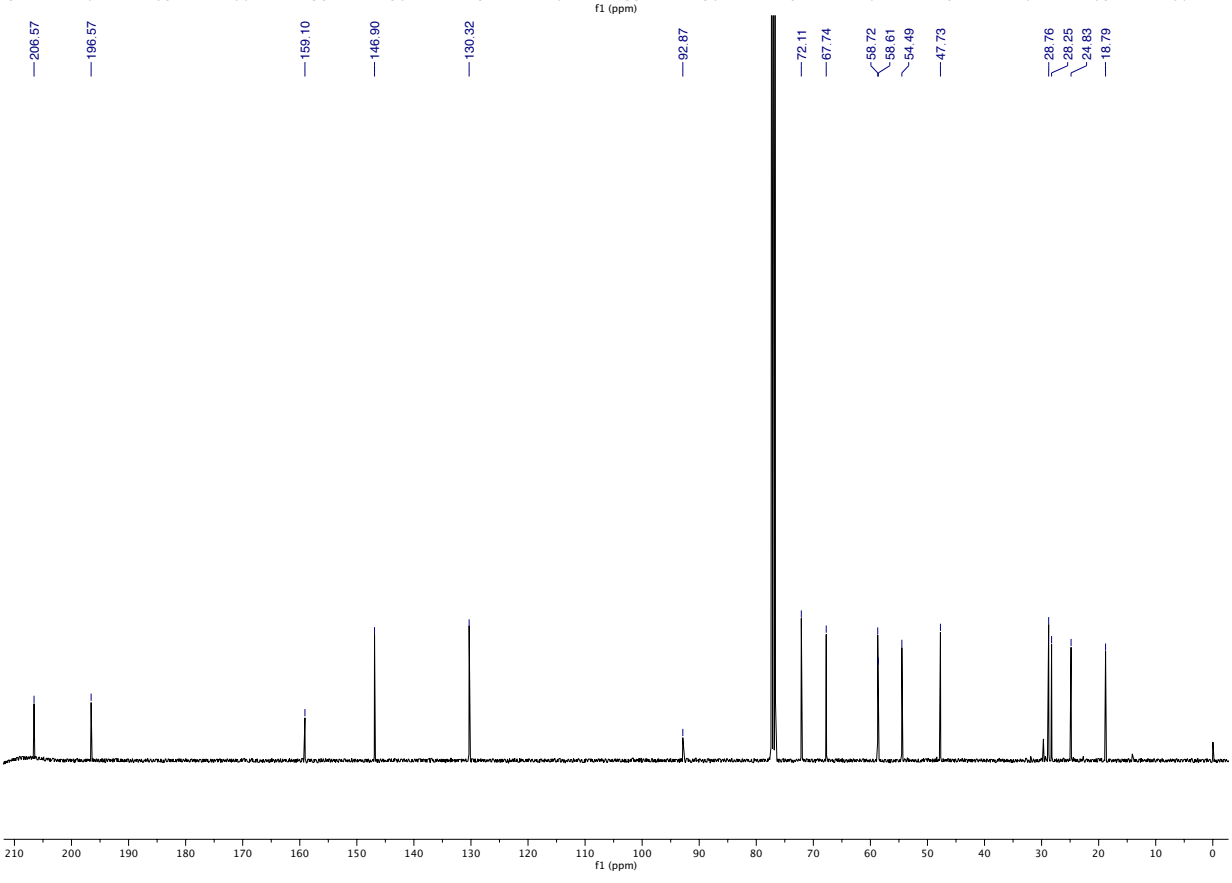

6.674
6.613
6.150
6.122
4.333
4.286
4.125
4.108
3.422
3.340
3.324
3.091
2.770
2.729
2.700
2.666
2.546
2.513
1.926
1.712
1.585
1.554
1.485
1.219
MeO
O
CCl3
N
H
Me
O
94
f1 (ppm)
200.67
158.58
143.89
134.87
93.29
72.37
70.45
58.72
54.22
49.48
49.11
44.81
29.01
27.74
27.14
23.90
f1 (ppm)

Over-oxidized compound (95)

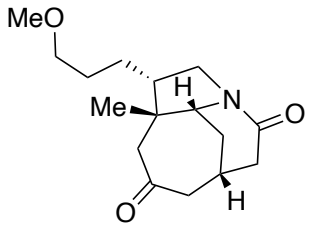


IR (NaCl): 2927, 2868, 1702, 1677, 1459, 1390, 1116, 843 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.87 (ddd, *J* = 11.2, 9.0, 3.0 Hz, 1H, H-7), 6.30 (dd, *J* = 11.2, 3.2 Hz, 1H, H-6), 4.47 (dd, *J* = 11.8, 8.0 Hz, 1H, H-2), 4.18 (d, *J* = 6.8 Hz, 1H, H-8a), 3.62 (ddd, *J* = 17.2, 9.2, 7.2 Hz, 1H, H-8), 3.45 (t, *J* = 11.8 Hz, 1H, H-2), 3.39–3.33 (m, 2H, CH_2OMe), 3.32 (s, 3H, OMe), 2.46 (dt, *J* = 17.2, 2.8 Hz, 1H, H-8), 2.24–2.15 (m, 1H, H-3), 1.69–1.51 (m, 3H, 2'-CH_2-3 and 1'-CH_2-3), 1.46–1.42 (m, 1H, 3-CH_2-1'), 1.39 (s, 3H, Me). ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.6 (C-4), 196.6 (C-5), 159.1 (CO), 146.9 (C-7), 130.3 (C-6), 92.9 (C), 72.1 (CH_2OMe), 67.7 (C-8a), 58.7 (OMe), 58.6 (C-3a), 54.5 (C-2), 47.7 (C-3), 28.8 (2'-CH_2-3), 28.2 (C-8), 24.8 (1'-CH_2-3), 18.8 (Me).


6.903
6.844
6.316
6.308
6.288
6.280
4.478
4.469
4.186
4.169
3.662
3.578
3.446
3.390
3.328
3.315
2.499
2.456
2.241
2.154
1.693
1.509
1.461
1.419
1.388
MeO
O
CCl3
N
H
Me
O
O
95
f1 (ppm)

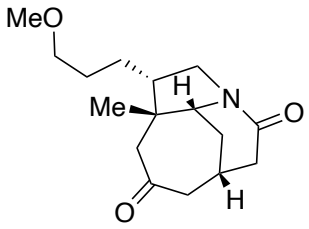

206.57
196.57
159.10
146.90
130.32
92.87
72.11
67.74
58.72
58.61
54.49
47.73
28.76
28.25
24.83
18.79
f1 (ppm)

(3*SR*,3a*RS*,7*SR*,8a*RS*)-3-(3-methoxypropyl)-3a-methyloctahydro-5*H*-1,7-ethanocyclohepta[*b*]pyrrole-5,10-dione (96)



A solution of trichloroacetamide **94** (68 mg, 0.18 mmol, 1 equiv) in benzene (6 mL) was heated to reflux. Then, a solution of AIBN (16 mg, 0.1 mmol, 0.5 equiv) and TBTH (0.21 mL, 0.76 mmol, 4.2 equiv) in benzene (1.5 mL) was added over 4h via syringe pump. The reaction was stirred for an additional hour before it was cooled down and concentrated under vacuum. The obtained crude was purified by chromatographic column (CH_2Cl_2:MeOH, 1:0 $\rightarrow$ 9.9:0.1) and tricyclic compound **96** was obtained (32 mg, 65%).

IR (NaCl): 2926, 2870, 1695, 1645, 1455, 1117 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 3.45–3.37 (m, 4H, 3-CH_2-3', H-2 and H-8a), 3.33 (s, 3H, OMe), 3.12 (dd, *J* = 12.0, 10.0 Hz, 1H, H-2), 2.64 (dd, *J* = 13.0, 8.2 Hz, 1H, H-6), 2.50 (m, 1H, H-7), 2.44–2.31 (m, 4H, H-6, H-4 and H-9), 2.25–2.21 (m, 3H, H-4 and H-8), 1.84 (ddd, *J* = 20.0, 10.0, 1.8 Hz, 1H, H-3), 1.67–1.62 (m, 2H, 2'-CH_2-3 and 1'-CH_2-3), 1.56–1.49 (m, 2H, 2'-CH_2-3 and 1'-CH_2-3), 1.06 (s, 3H, Me). ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.9 (C-5), 168.2 (C-10), 72.6 (3-CH_2-3), 64.8 (C-8a), 58.6 (OMe), 50.2 (C-6), 48.2 (C-2), 46.8 (C-3a), 46.7 (C-3), 45.1 (C-4), 39.7 (C-9), 28.6 (2'-CH_2-3), 26.1 (1'-CH_2-3), 25.9 (C-7), 25.3 (C-8), 24.3 (Me).


MeO
H
N
Me
O
O
H

96

3.454
3.352
3.332
3.126
3.121
2.650
2.638
2.500
2.401
2.354
2.306
2.247
2.218
1.850
1.821
1.674
1.619
1.542
1.502
1.059
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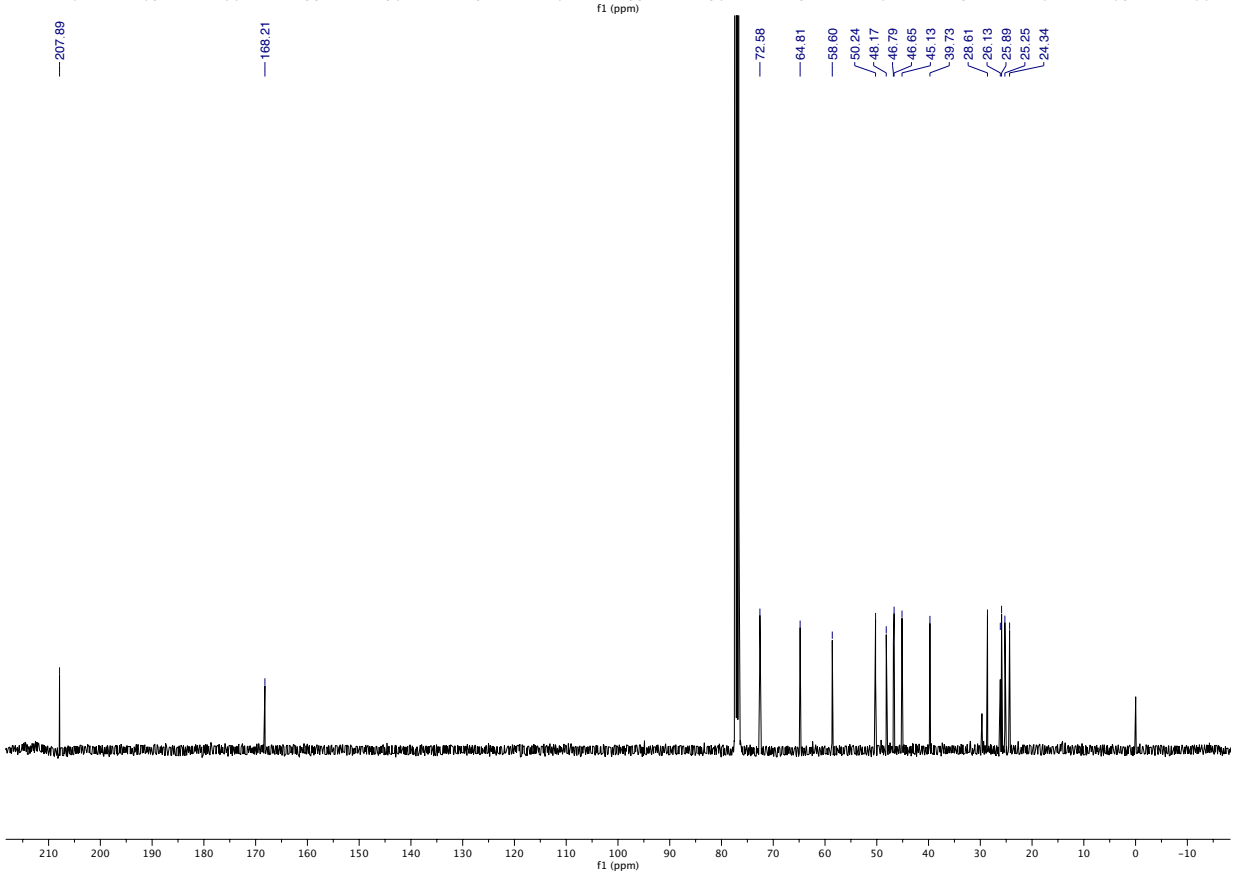
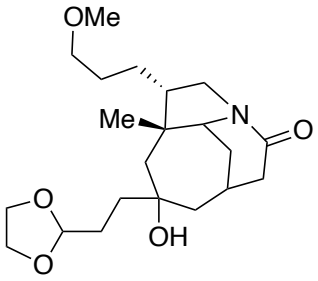
4.40
2.84
1.21
2.74
2.75
3.70
f1 (ppm)

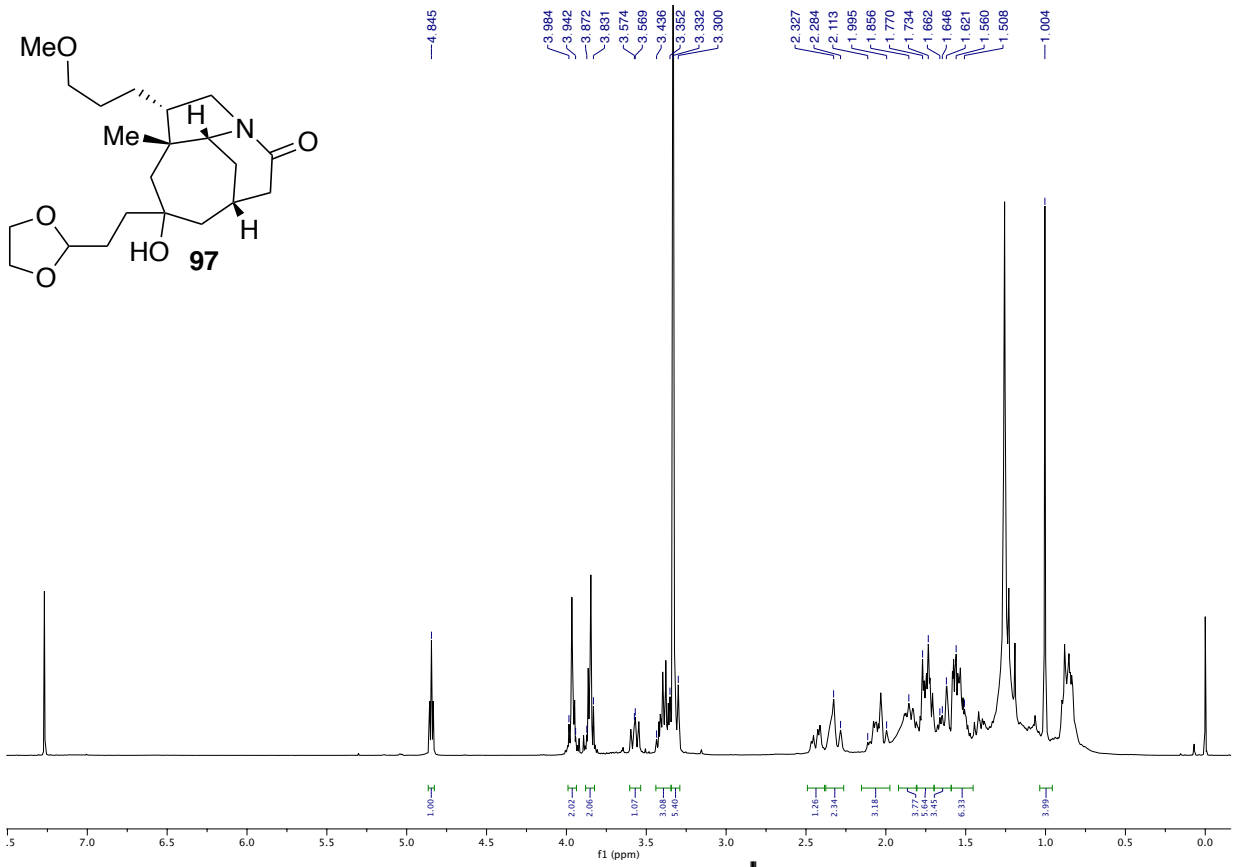

207.89
168.21
72.58
64.81
58.60
50.24
48.17
46.79
46.65
45.13
39.73
28.61
26.13
25.89
25.25
24.34
f1 (ppm)

(3*S*,3a*R*,7*S*,8a*R*)-5-(2-(1,3-dioxolan-2-yl)ethyl)-5-hydroxy-3-(3-methoxypropyl)-3a-methyloctahydro-2*H*-1,7-ethanocyclohepta[*b*]pyrrol-10-one (97)



In an oven-dried flask Mg turnings (20 mg, 0.83 mmol) were added and diluted in THF (1 mL). Then, 2-(2-bromoethyl)-1,3-dioxolane (90 mL, 0.75 mmol) was added followed by a small crystal of I_2 and the mixture was stirred at room temperature for 45 min. A solution of tricyclic compound **96** (20 mg, 0.07 mmol) in THF (0.7 mL) was cooled to 0 ºC and the above solution (0.75 M, 0.12 mL, 0.09 mmol) was added dropwise. The reaction was stirred at room temperature for 4 h before it was quenched with sat. sol. NH_4Cl (5 mL) and extracted with CH_2Cl_2 (4 x 10 mL). Combined organics were dried, filtered, and concentrated under vacuum to obtain the crude that was purified by chromatographic column (CH_2Cl_2:MeOH, 1:0 → 9.5:0.5), and tricycle **97** was isolated (14 mg, 50%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.85 (t, *J* = 4.4 Hz, 1H, $CHOCH_2$), 3.98–3.94 and 3.87–3.83 (2m, 2H each, OCH_2), 3.57 (dd, *J* = 11.0, 9.0 Hz, 1H, H-2), 3.33 (s, 3H, OMe), 3.44–3.30 (m, 4H, H-2, H-8a and CH_2OMe), 2.44 (dd, *J* = 16.4, 5.8 Hz, 1H, H-9), 2.35–2.28 (m, 2H, H-9 and H-7), 2.08 (ddd, *J* = 14.8, 7.2, 4.4 Hz, 1H, H-8), 2.01 (d, *J* = 14.8 Hz, 1H, H-8), 1.88–1.83 (m, 1H, H-3), 1.78–1.71 (m, 4H, 2'-CH_2-5, H-4 and 1'-CH_2-5), 1.69–1.65 (m, 1H, 2'-CH_2-3), 1.62 (m, 1H, 2'-CH_2-5), 1.58–1.47 (m, 5H, 2'-CH_2-3, H-6 and 1'-CH_2-3), 1.20 (d, *J* = 19.2 Hz, 1H, H-4), 1.00 (s, 3H, Me). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.9 (C-10), 104.4 ($CHOCH_2$), 73.4 (C-5), 72.8 (CH_2OMe), 65.5 (C-8a), 64.9 and 64.9 (OCH_2), 58.5 (OMe), 49.9 (C-2), 47.8 (C-3), 47.3 (2'-CH_2-5), 44.7 (C-3a), 43.2 (C-4), 39.7 (C-6), 39.6 (C-9), 28.8 (Me), 28.8 (2'-CH_2-3), 28.0 (1'-CH_2-5), 27.7 (C-7), 26.5 (1'-CH_2-3), 25.2 (C-8).


MeO
Me
H
N
O
O
O
HO
H
97
4.845
3.984
3.942
3.872
3.831
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3.569
3.436
3.352
3.332
3.300
2.327
2.284
2.113
1.995
1.856
1.770
1.734
1.662
1.646
1.621
1.560
1.508
1.004
1.00
2.02
2.06
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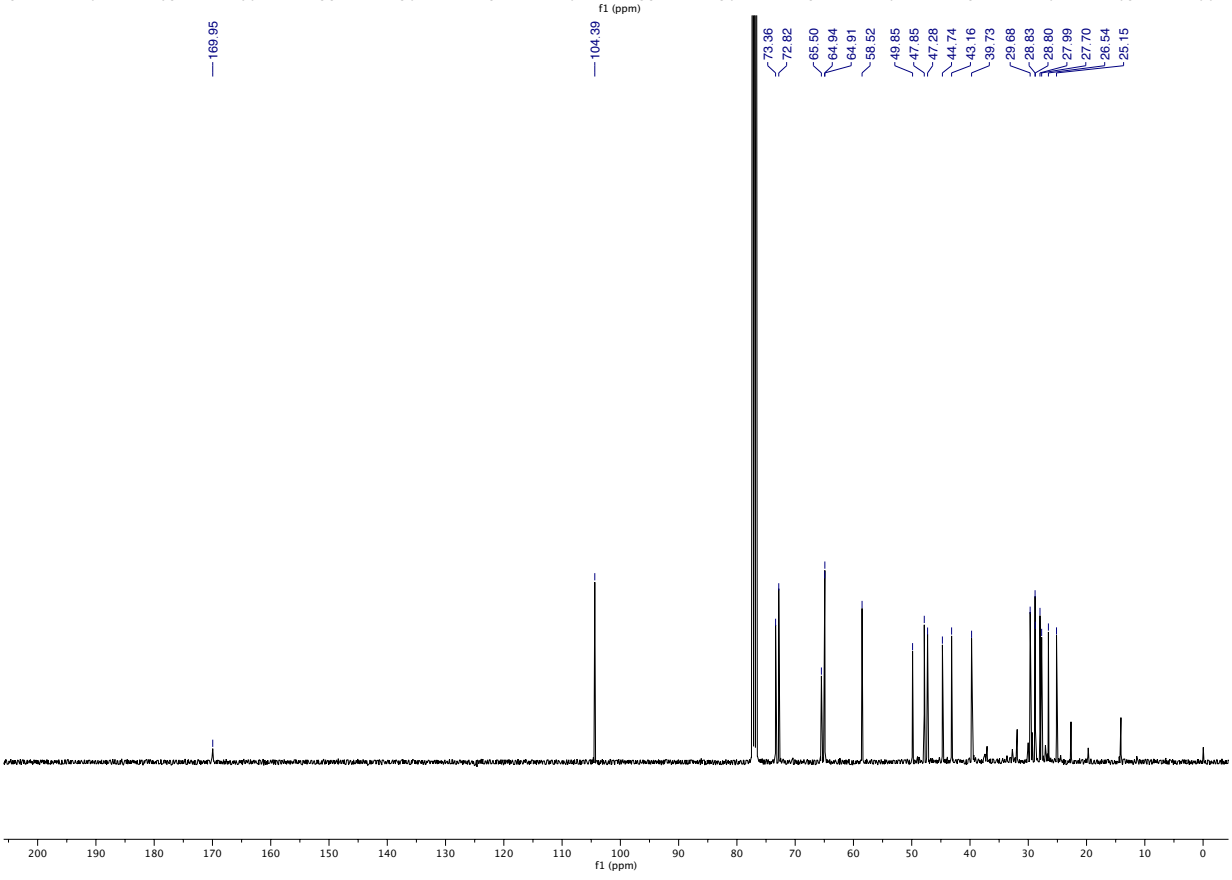
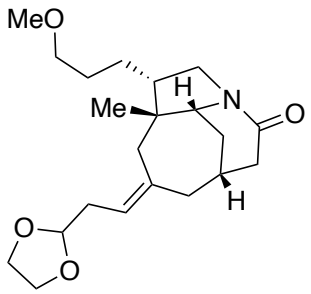
3.77
5.64
3.45
6.33
3.99
f1 (ppm)

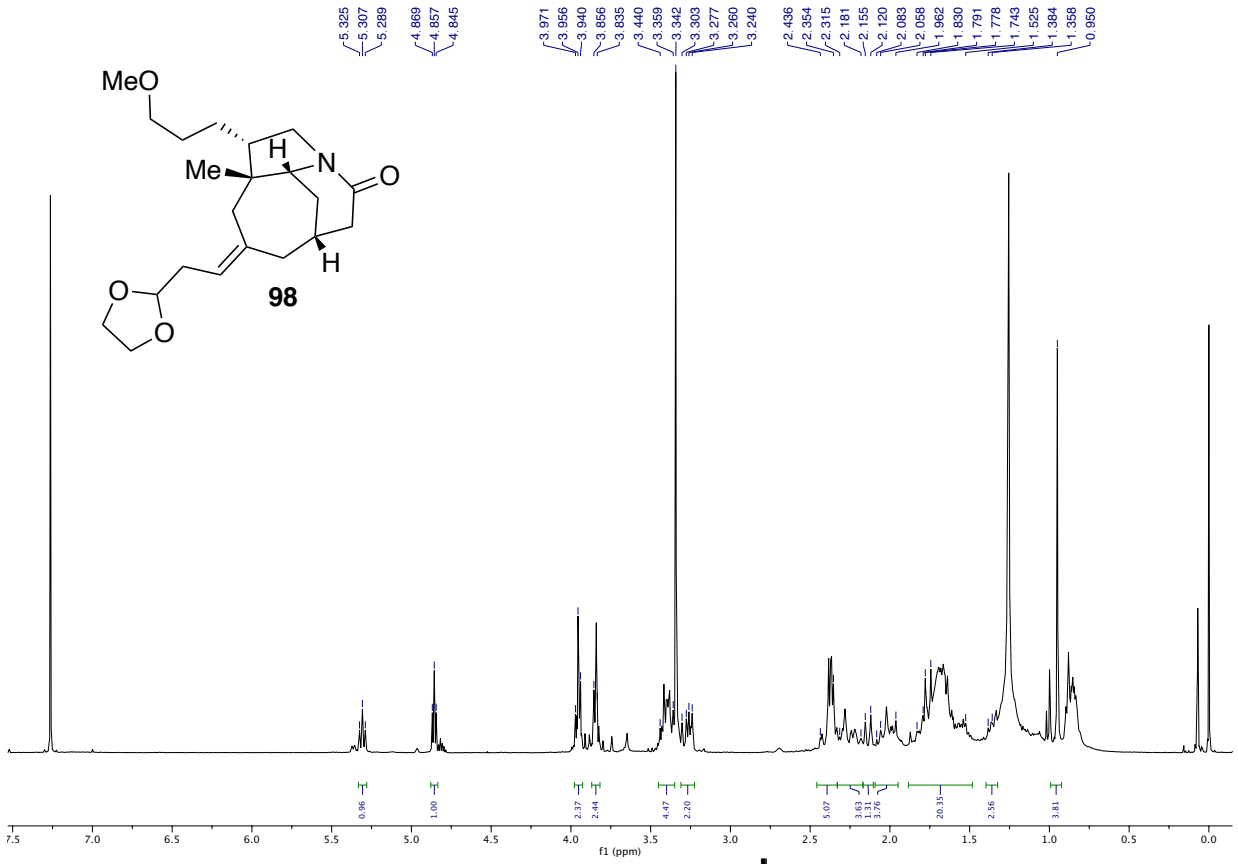

169.95
104.39
73.36
72.82
65.50
64.94
64.91
58.52
49.85
47.85
47.28
44.74
43.16
39.73
29.68
28.83
28.80
27.99
27.70
26.54
25.15
f1 (ppm)

(3*SR*,3a*RS*,7*RS*,8a*RS*)-5-(2-(1,3-dioxolan-2-yl)ethylidene)-3-(3-methoxypropyl)-3a-methyloctahydro-2*H*-1,7-ethanocyclohepta[*b*]pyrrol-10-one (98)



Tricyclic ketone **97** (14 mg, 0.04 mmol, 1 equiv) was diluted in CH_3CN (0.5 mL) and Burgess reagent (26 mg, 0.11 mmol, 3 equiv) was added. The reaction was stirred at reflux overnight and concentrated under vacuum. The residue was diluted with water and extracted with EtOAc (1 x 20 mL) and CH_2Cl_2 (4 x 10 mL). Combined organics were dried filtered and concentrated under vacuum and further chromatographic purification (CH_2Cl_2:MeOH, 1:0 $\rightarrow$ 9.5:0.5) afforded compound **98** (3.9 mg, 29%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.31 (t, *J* = 7.2 Hz, 1H, =CH), 4.86 (t, *J* = 4.8 Hz, CH), 3.97–3.94 and 3.86–3.84 (2m, 2H each, OCH_2), 3.44–3.36 (m, 3H, CH_2OMe and H-2), 3.34 (s, 3H, OMe), 3.30–3.24 (m, 2H, H-2 and H-8a), 2.44–2.35 (m, 4H, H-9, CH_2CH=, and H-7), 2.32–2.18 (m, 3H, H-6 and H-9), 2.14 (d, *J* = 14.0 Hz, H-4), 2.08–1.96 (m, 2H, H-8), 1.53–1.83 (m, 4H, H-3, 1'-CH_2-3, 2'-CH_2-3), 1.76 (d, *J* = 14.0 Hz, 1H, H-4), 1.38–1.36 (m, 1H, 1'-CH_2-3), 0.95 (s, 3H, Me). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.3 (C-10), 136.9 (C-5), 122.1 (=CH); 103.9 (CH), 72.7 (CH_2OMe), 66.0 (C-8a), 64.9 and 64.9 (OCH_2), 58.6 (OMe), 48.9 (C-2), 47.3 (C-3), 44.4 (C-3a), 42.2 (C-4), 39.6 (C-9), 36.8 (C-6), 33.3 (CH_2CH=), 28.8 (2'-CH_2-3), 27.7 (C-7), 25.8 (1'-CH_2-3), 25.3 (C-8), 23.8 (Me).


MeO
Me
H
N
O
H
O
O
98
5.325
5.307
5.289
4.869
4.857
4.845
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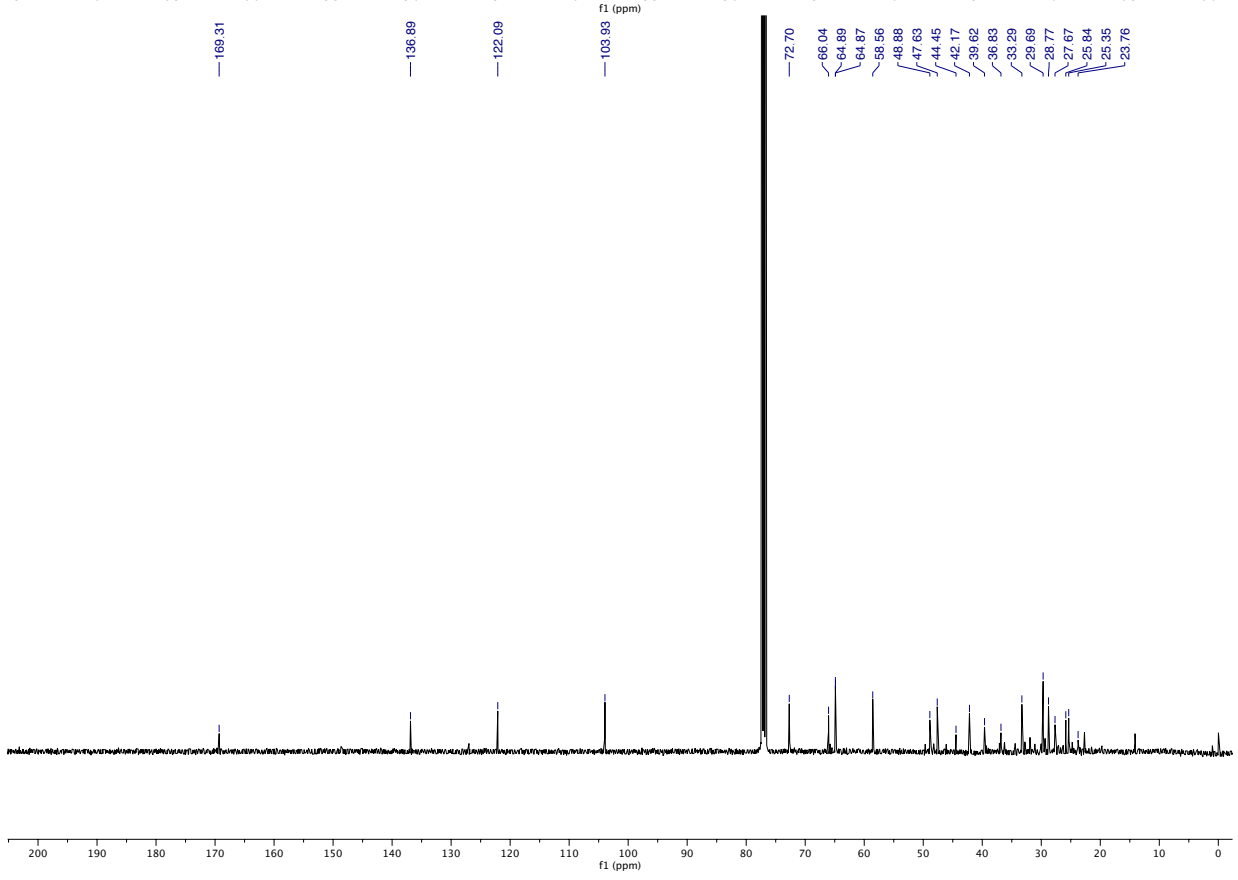
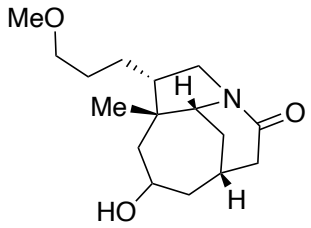
3.956
3.940
3.856
3.835
3.440
3.359
3.342
3.303
3.277
3.260
3.240
2.436
2.354
2.315
2.181
2.155
2.120
2.083
2.058
1.962
1.830
1.791
1.778
1.743
1.525
1.384
1.358
0.950
0.96
1.00
2.37
2.44
4.47
2.20
5.07
3.83
3.33
3.76
20.35
2.56
3.81
f1 (ppm)

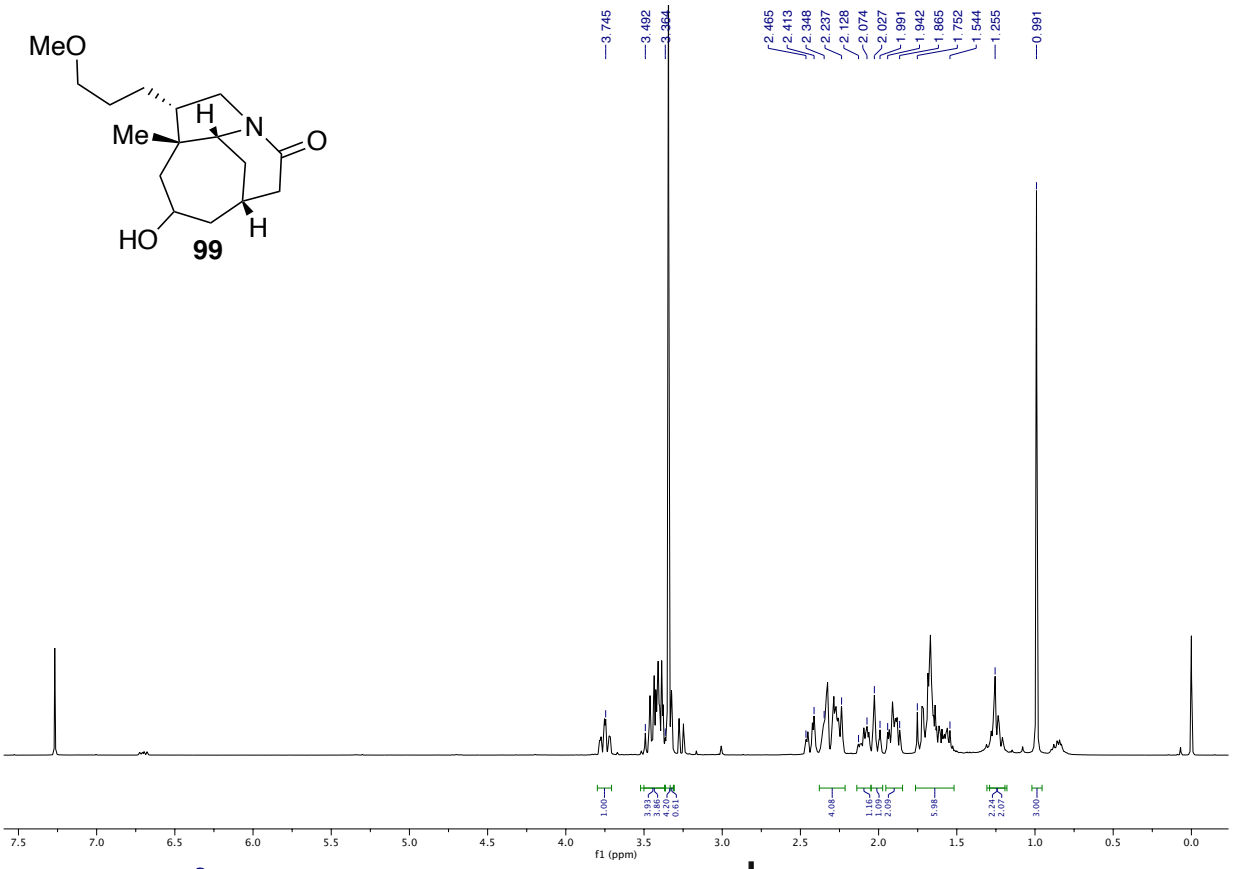

169.31
136.89
122.09
103.93
72.70
66.04
64.89
64.87
58.56
48.88
47.63
44.45
42.17
39.62
36.83
33.29
29.69
28.77
27.67
25.84
25.35
23.76
f1 (ppm)

(3*SR*,3a*RS*,7*SR*,8a*RS*)-5-hydroxy-3-(3-methoxypropyl)-3a-methyloctahydro-2*H*-1,7-ethanocyclohepta[*b*]pyrrol-10-one (99)



Tricyclic compound **96** (33 mg, 0.12 mmol) was diluted in MeOH:CH_2Cl_2 (1.2:0.3 mL) and $NaBH_4$ (22 mg, 0.58 mmol) was added. The reaction was stirred at room temperature for 3h before it was quenched 1M HCl and extracted with $CHCl_3$:i-PrOH (4 x 10 mL). Combined organics were dried, filtered and concentrated under vacuum and the obtained crude was purified by chromatographic column (CH_2Cl_2:MeOH, 1:0 $\rightarrow$ 9.5:0.5) to provide with tricyclic alcohol **99** (10 mg, 31%) along with the other epimer (5.6 mg, 18%).

Maj. Epimer. IR (NaCl): 3472, 2930, 1642, 1461, 1118 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 3.75 (ddd, *J* = 11.7, 11.7, 3.0 Hz, 1H, H-5), 3.49–3.36 (m, 4H, CH_2OMe and H-2), 3.34 (s, 3H, OMe), 3.36–3.32 (m, 1H, H-8a), 2.44 (dd, *J* = 16.2, 4.4 Hz, 1H, H-9), 2.37–2.24 (m, 4H, H-7, H-9, H-6 and H-4), 2.13–2.06 (m, 1H, H-8), 2.01 (dt, *J* = 14.4, 2.8 Hz, 1H, H-8), 1.94–1.87 (m, 2H, H-6 and, H-3), 1.75–1.53 (m, 4H, 2'-CH_2-3, H-4 and 1'-CH_2-3), 1.28–1.20 (m, 1H, 1'-CH_2-3), 0.99 (s, 3H, Me) ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.1 (C-10), 72.5 (CH_2OMe), 65.0 (C-8a), 58.6 (OMe), 56.3 (C-5), 49.6 (C-2), 47.3 (C-6), 46.6 (C-3), 45.5 (C-3a), 45.1 (C-4), 39.0 (C-9), 28.7 (2'-CH_2-3), 28.6 (C-7), 27.1 (1'-CH_2-3), 26.4 (Me), 24.9 (C-8).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Me
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N
O
HO
H
99
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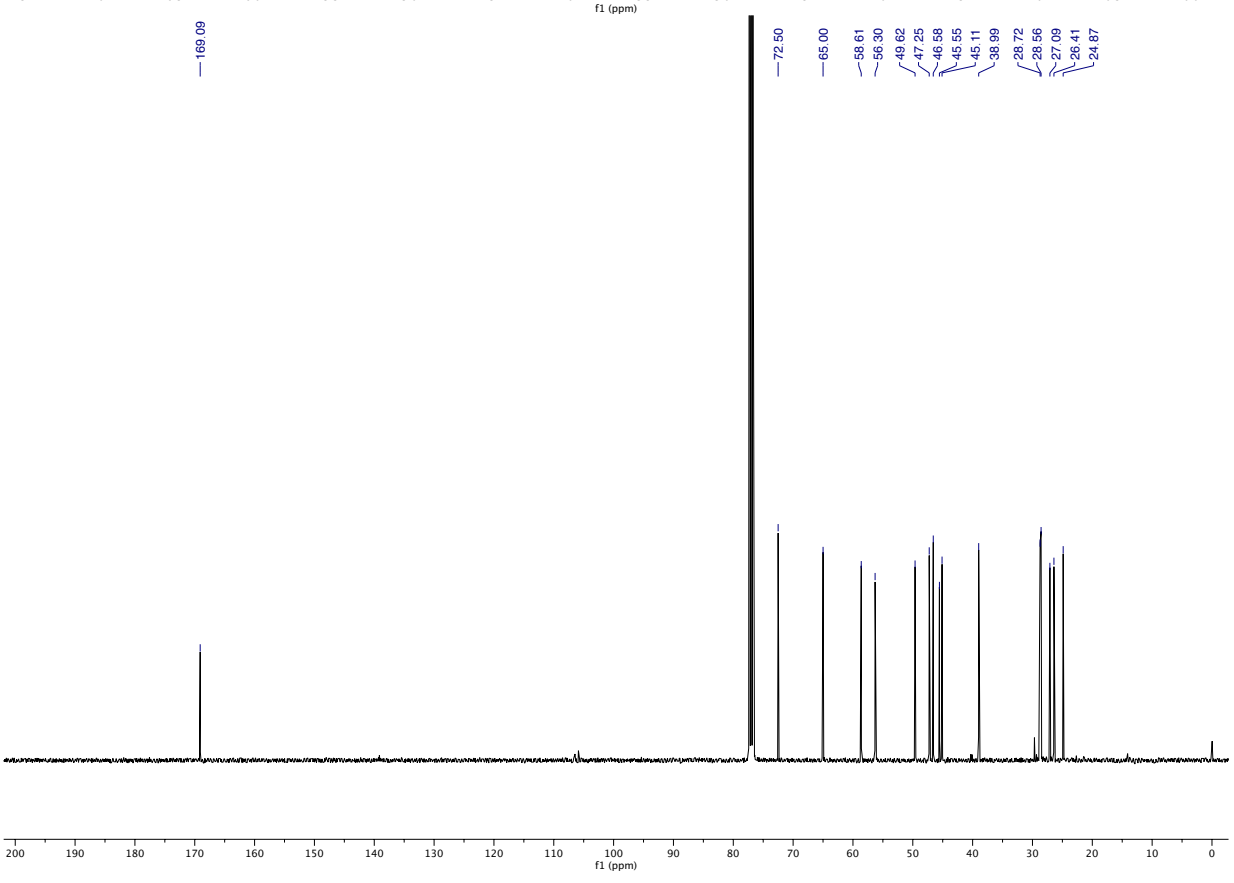
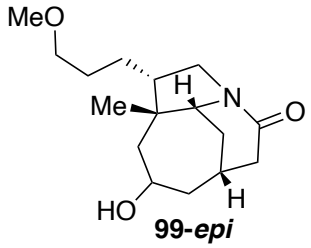
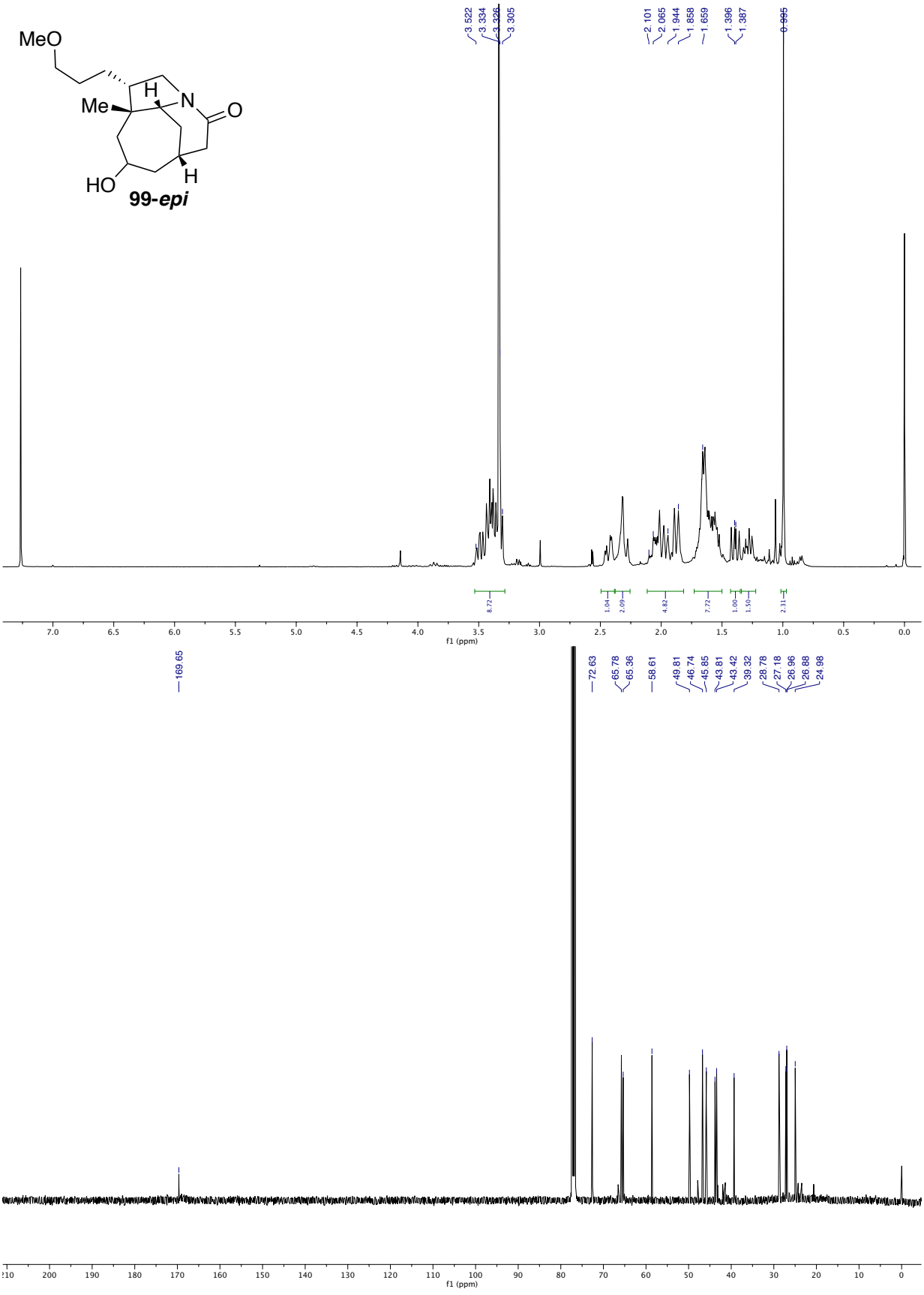
2.413
2.348
2.237
2.128
2.074
2.027
1.991
1.942
1.865
1.752
1.544
1.255
0.991
f1 (ppm)


169.09
72.50
65.00
58.61
56.30
49.62
47.25
46.58
45.55
45.11
38.99
28.72
28.56
27.09
26.41
24.87
f1 (ppm)



99-*epi*

Min. Epimer. IR (NaCl): 3401, 2930, 1625, 1466, 1117 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.52–3.31 (m, 6H, CH_2OMe, H-5, H-8a, H-2), 3.33 (s, 3H, OMe), 2.43 (dd, *J* = 16.0, 5.0 Hz, 1H, H-9), 2.33–2.28 (m, 2H, H-9 and H-7), 2.10–1.94 (m, 3H, H-8 and H-6), 1.92–1.84 (m, 2H, H-4 and H-3), 1.68–1.52 (m, 4H, 1'-CH_2-3, H-6, 2'-CH_2-3), 1.39 (dd, *J* = 15.0, 11.0 Hz, 1H, H-4), 1.32–1.25 (m, 1H, 1'-CH_2-3), 1.00 (s, 3H, Me). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.6 (C-10), 72.6 (CH_2OMe), 65.8 (C-5), 65.4 (C-8a), 58.6 (OMe), 49.8 (C-2), 46.7 (C-3), 45.8 (C-6), 43.8 (C-3a), 43.4 (C-4), 39.3 (C-9), 28.8 (2'-CH_2-3), 27.2 (1'-CH_2-3), 27.0 (Me), 26.9 (C-7), 25.0 (C-8).


MeO
Me
H
N
O
HO
H
99-epi
3.522
3.334
3.326
3.305
2.101
2.065
1.944
1.858
1.659
1.396
1.387
0.995
8.72
1.04
2.09
4.82
7.72
1.00
1.50
2.31
f1 (ppm)
169.65
72.63
65.78
65.36
58.61
49.81
46.74
45.85
43.81
43.42
39.32
28.78
27.18
26.96
26.88
24.98
f1 (ppm)