Dissertation

Enantioselective Total Synthesis of (+)-Sieboldine A via Diastereoselective Pauson-Khand Reaction

Graduate School of Medical Sciences
Kanazawa University

Division: Pharmaceutical Sciences
Laboratory: Pharmaceutical and Organic Chemistry

School registration No.: 1429012018
Name: Mohammed Khalifa Abd El-Gaber Khalifa
Primary supervisor name: Prof. Dr. Chisato Mukai

ACKNOWLEDGEMENT

In the name of **ALLAH** Almighty, the Compassionate, the Merciful. Alhamdulillah, to **ALLAH** I extended my heartfelt thanks for giving me a chance to fulfill this research succesfully.

First and foremost, I would first like to thank my supervisor Professor Dr. Chisato Mukai for his innovative ideas, encouragements, endless patient, enthusiasm and guidance during this research over the past few years. It was my highest pleasure to be the member of his brilliant group. Also, I would like to thank gratefully Dr. Fuyuhiko Inagaki and Dr. shigeo Yasuda for their support, motivation, and enormous help during my Ph.D. studies.

I wish to extend my gratitude to all members of the Professor Dr. Chisato Mukai's group, present and past (graduate and undergraduate), for the excellent working atmosphere, the interesting and stimulating discussion about chemistry and the great support I got from them.

I also wish to express my sincere gratitude to the Ministry of Education, Culture, Sports, Science and Technology-Japan for the funded Ph.D scholarship. I wish to thank to the Ministry of the Higher Education of Egypt and Assuit University for their acceptance and support during my Ph.D study at Division of Pharmaceutical Sciences, Graduate School of Natural Science and Technology, Kanazawa University, Japan.

Finally, yet importantly, I would like to express my heartfelt appreciation to my beloved parents, my wife, my sons Omar and Youssef and my friends for their wishes and the loving support that helped me through the tougher times of my graduate studies.

Mohammed Khalifa Abd El-Gaber
Assiut University
Egypt
2017

TABLE OF CONTENTS

		Page
ACKNOWLEDGEMENT		ii
TABLE OF CONTENTS		iv
LIST OF ABBREVIATIONS / SYMBOLS		vi
CHAPTER I	**INTRODUCTION**	1
1.1	**The *Lycopodium* alkaloids**	1
1.1.1	Structure and biological activity of (+)-sieboldine A	2
1.1.2	Strategic comparison of previously reported syntheses of sieboldine A	2
1.1.3	Total synthesis of (+)-sieboldine A by Overman	4
1.1.4	Total synthesis of (+)-sieboldine A by Tu	6
1.2	**Pauson-Khand Reaction (PKR)**	8
1.2.1	The Discovery and Early Evolution of the PKR	8
1.2.2	Mechanism of the PKR	9
1.2.3	Intramolecular PKR	9
1.3	**Total syntheses of *Lycopodium* alkaloids using intramolecular PKR as a key step**	11
1.3.1	Total Syntheses of (+)-Lycoposerramine-C and (-)-phlegmariurine-A by Takayama	11
1.3.2	Total Syntheses of (-)-huperzine-Q, (+)-fawcettimine and (+)-fawcettidine by Takayama	12
1.3.3	Total Syntheses of (-)-magellanine, (+)-magellaninone, and (+)-paniculatine by Mukai	13
1.3.4	Total Syntheses of (+)-fawcettimine and (+)-lycoposerramine B by Mukai	14
1.3.5	Total Syntheses of (±)-fawcettimine, (±)-fawcettidine, (±)-lycoposerramine-Q and (±)-lycoflexine by Mukai	15
1.4	**Research objective**	17
CHAPTER II	**RESULTS AND DISCUSSION**	18
2.1	**Total synthesis of (±)-Sieboldine A**	18
2.1.1	Retrosynthetic analysis of (±)-Sieboldine A	18
2.1.2	Synthesis of PKR precursor Dienyne 105	19
2.1.3	Intramolecular PKR of Dienynes 104 and 105	20
2.1.4	Stereoselective Reduction of indenone 107	21
2.1.5	Construction of the quaternary center and difficulties in removal of benzyl group	22
2.1.6	Attempts for silyl enolization of ketone 119	23
2.1.7	Regioselectivec acetate enolization ketone 119	24
2.1.8	Preparation of Triol 125	25

	2.1.9	Introduction of the nitrogen functionality	26
	2.1.10	Optimized oxidation of Diol 129	27
	2.1.11	Assembly of the azacyclononane ring	29
	2.1.12	Completion of total synthesis of (±)-sieboldine A 1	30
2.2	**Total synthesis of (+)-Sieboldine A**		31
	2.2.1	Retrosynthetic analysis of (+)-Sieboldine A	31
	2.2.2	Keck asymmetric allylation of aldehyde 103	33
	2.2.3	Intramolecular PKR of Dienyne (+)-105	34
	2.2.4	Synthesis of Triol (-)-125	34
	2.2.5	Synthesis of Aminolactol (-)-132	35
	2.2.6	Completion of total synthesis of (+)-sieboldine A	36
2.3	**Conclusion**		37
CHAPTER III	**EXPERIMENTAL**		38
3.1	**General notes**		38
3.2	**Synthetic procedures**		39
3.3	**Determination of the absolute configuration of (+)-144**		59
3.4	**Comparison of synthetic and natural (+)-sieboldine A spectral data**		61
CHAPTER IV	**REFERENCES**		63
CHAPTER V	**APPENDIX**		67

LIST OF ABBREVIATIONS / SYMBOLS

Å	angstrom
Ac	acetyl
AIBN	azobisisobutyronitrile
aq	aqueous
Ar	argon
atm	atmosphere
BINOL	1,1'-Bi-2-naphthol
Bn	benzyl
BOC	*tert*-butyloxycarbonyl
br	broad (in nuclear magnetic resonance)
^{o}C	degree centigrade
calcd	calculate
cat.	catalyst
cm^{-1}	reciprocal centimeters
CO	carbon monoxide
CSA	camphorsulfonic acid
d	doublet
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
dd	doublet of doublet
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
DIPAL-H	diisobutylaluminium hydride
DIPEA	*N,N*-diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMDO	dimethyldioxirane
DMP	Dess–Martin periodinane
DMS	dimethylsulfide
DMSO	dimethylsulfoxide
dpen	1,2-diphenyl-1,2-ethylenediamine
EI	electron impact ionization
equiv.	equivalent
ESI	electron spray ionization
Et	ethyl
EtOAc	ethyl acetate
g	gram
h	hour
HMPA	hexamethylphosphoramide
HR	high resolution
Hz	hertz
IBX	2-iodoxybenzoic acid
Imid.	imidazole
i-Pr	isopropyl
Ipc	isopinocampheyl
IR	infrared
J	coupling constant

KHMDS	potassium bis(trimethylsilyl)amide
LAH	lithium aluminium hydride
m	multiplet
M	metal
M	molar
m-CPBA	*m*-chloroperbenzoic acid
Me	methyl
mg	miligram
MHz	megahertz
min	minute
mL	mililiter
mol%	mole per cent
MOM	methoxymethyl
Ms	methanesulfonyl
MS	molecular sieves, mass spectrometry
MsCl	methanesulfonyl chloride
MTPA	α-methoxy-α-trifluoromethylphenylacetic acid
NMO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
Ph	phenyl
Piv	pivaloyl
PKR	Pauson-Khand reaction
PMB	*p*-methoxybenzyl
ppm	parts per million
PPTS	pyridinium *p*-toluenesulfonate
q	quartet
Rh	rhodium
rt	room temperature
rf	reflux
s	singlet, second
sat	saturated
t	triplet
TBAF	tetra-*n*-butylammonium fluoride
TBAI	tetra-*n*-butylammonium iodide
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl
TMTU	tetramethylthiourea
TPAP	tetrapropylammonium perruthenate
Ts	tosyl
δ	NMR chemical shift in ppm downfield from a standard

CHAPTER I

Introduction

1.1 The *Lycopodium* alkaloids

The *Lycopodium* alkaloids are a large group of natural products characterized by their unique polycyclic frameworks.[1,2] These alkaloids derive their name from the *Lycopodium* species of clubmosses from which they were originally isolated.[3] The *Lycopodium* alkaloids are divided into four distinct structural classes; the fawcettimine class, the lycopodine class, the lycodine class and the miscellaneous class (Figure 1). Hydrindane containing natural products, such as sieboldine A **1**, alopecuridine **2** and fawcettimine **3** are classified in the fawcettimine group. Natural products that contain a pyridine or pyridone ring, such as huperzine A **4**, are classified in the lycodine group. Furthermore, alkaloids that contain four interconnected six-membered rings, such as lycopodine **5**, are members of the lycopodine group. Finally, natural products that are devoid of one of the aforementioned structural features are members of the miscellaneous class, such as phlegmarine **6**.[4]

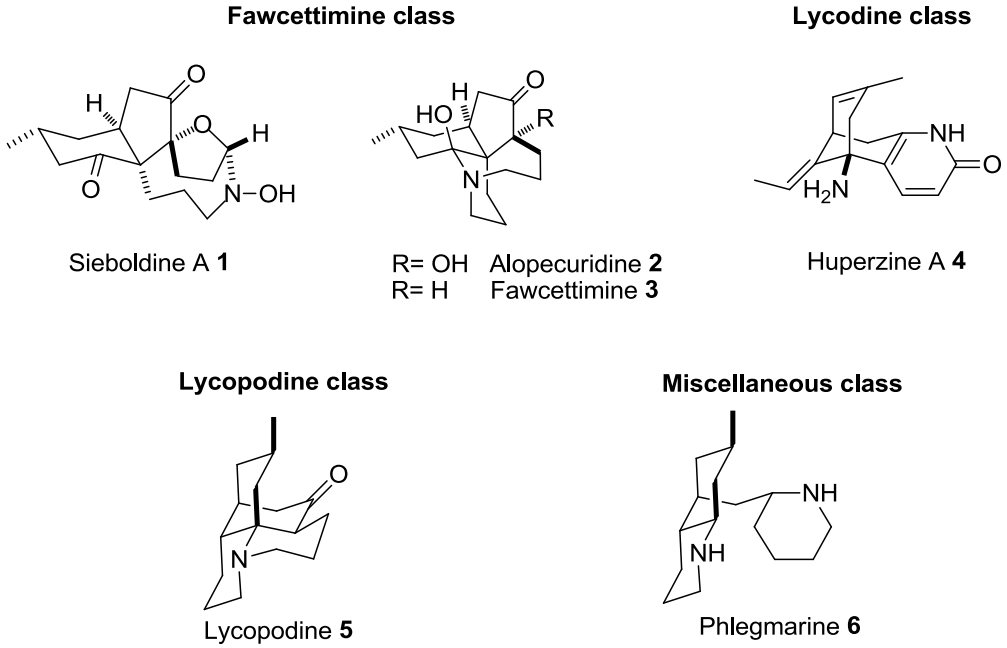
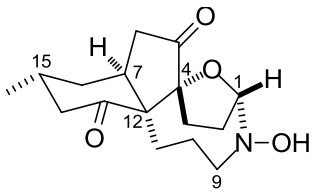


Figure 1. Representative *Lycopodium* Alkaloids.

1.1.1 Structure and biological activity of (+)-sieboldine A

In 2003, Kobayashi and coworkers reported the isolation of (+)-sieboldine A **1** from the clubmoss *Lycopodium sieboldii* in Japan. Structurally, sieboldine A **1** contains unprecedented fused tetracyclic skeleton consisting of *cis*-hydrindane ring system, the distinctive structural feature of fawcettimine-type *Lycopodium* alkaloids and N-hydroxyazacyclononane ring embedded in a bicyclo[5.2.1]decane-N,O-acetal. (+)-Sieboldine A **1** has two contiguous quaternary carbons; one of them is an all-carbon quaternary center (Figure 2).[5]



(+)-Sieboldine A **1**

Figure 2. Structure of (+)-sieboldine A **1**.

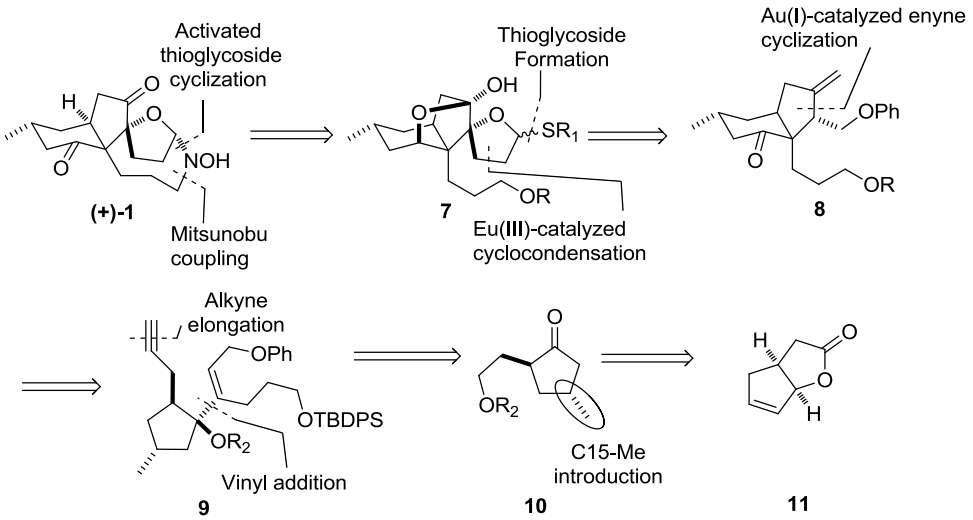
Along with their complex structures, the *Lycopodium* alkaloids generally have interesting biological activities and plants or plant extracts containing these alkaloids have been utilized in traditional folk medicine for decades.[1] Sieboldine A **1** exhibited *in vitro* cytotoxicity against murine lymphoma L1210 cells (IC_{50} 5.1 μg/mL) and inhibited acetylcholinesterase (from electric eel) with an IC_{50} value of 2.0 μM, which was comparable to that of huperzine A **4**.[5] In clinical trials, Huperzine A **4** has been shown to have beneficial effects on cognitive function and memory in patients with Alzheimer's disease.[6,7] The unusual unique skeletons along with the interesting biological activities made the *Lycopodium* alkaloids worthy challenging targets for total synthesis.[8-17]

1.1.2 Strategic comparison of previously reported syntheses of sieboldine A

The completion of the first total synthesis of (+)-sieboldine A **1** was reported in 2010 by Overman.[18,19] Later, Tu and coworkers reported the first total synthesis of alopecuridine **2** and its biomimetic oxidation to sieboldine A **1**.[20,21] Overman and Tu used two completely different strategies to access sieboldine A **1**. The only common

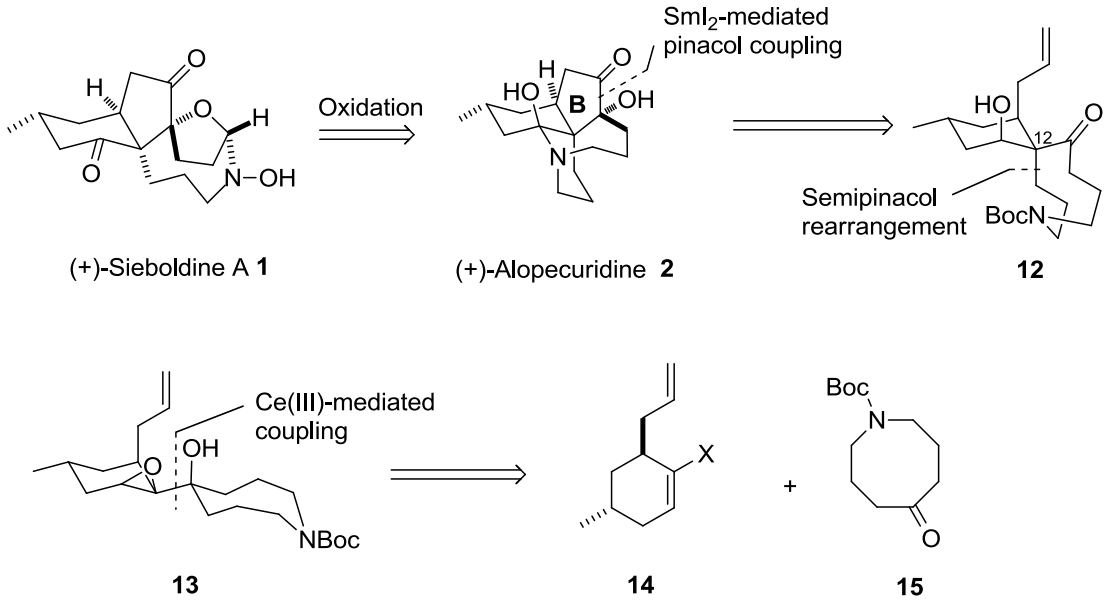
idea shared by the two strategies was the elaboration of the sensitive N,O-acetal moiety at a late stage of the synthesis.

Overman assembled the N,O-acetal via intramolecular coupling of the activated thioglycoside moiety with the tethered hydroxylamine side chain in derivative **7** (Scheme 1**)**. The *cis*-hydrindanone **8** was obtained by a pinacol-terminated Prins cyclization of enyne **9** as a key step. Enyne **9** was prepared from cyclopentanone **10** through vinyl addition and alkyne elongation. Cyclopentanone **10** was readily accessed from previously reported enantiomerically pure bicyclic lactone **11**.



Scheme 1: Overman's retrosynthetic analysis of (+)-sieboldine A **1**.

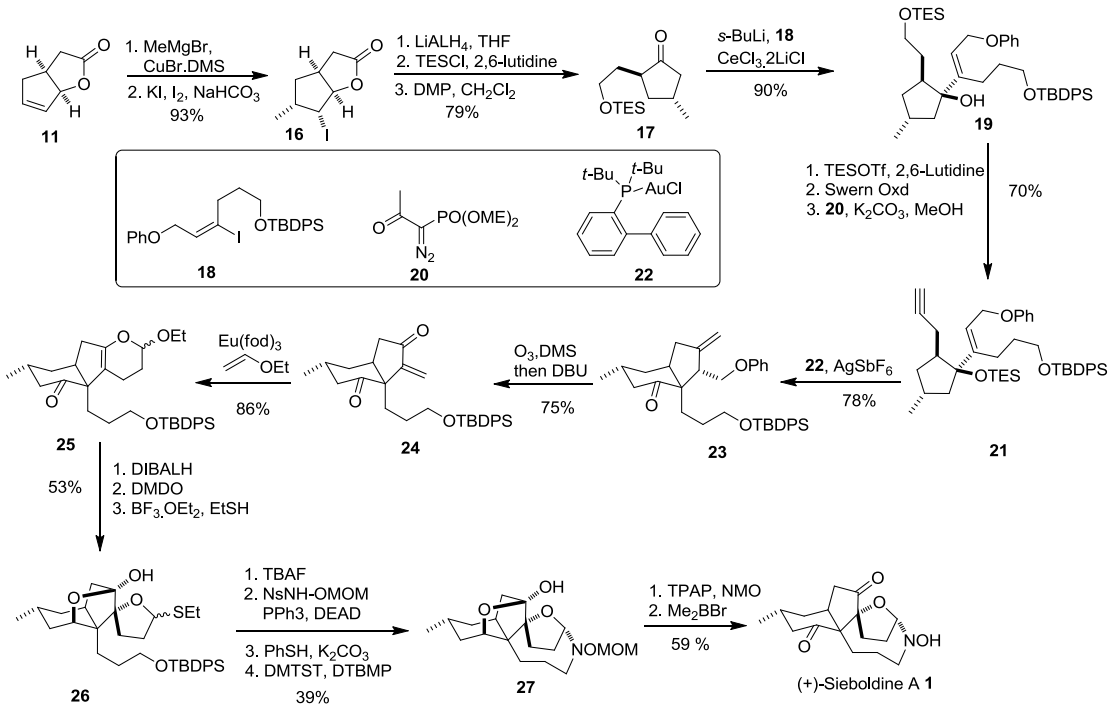
Tu decided to follow Kobayashi's proposed biogenetic pathway and expected that formation of the tetrahydrofuran ring with concomitant formation of the N,O-acetal could be achieved through a two-step oxidation of alopecuridine **2** (Scheme 2). The B-ring of the alkaloid was obtained via SmI_2-mediated pinacol coupling of compound **12**. The all-carbon quaternary center at C12 and the aza-cyclononane ring were constructed through a semipinacol ring expansion of the eight-membered nitrogen-containing ring of **13**. Hydroxy epoxide **13** was prepared from haloalkene **14** and carbamate **15** by coupling and epoxidation.



Scheme 2: Tu's retrosynthetic analysis of (+)-sieboldine A **1**.

1.1.3 Total synthesis of (+)-sieboldine A by Overman

The key step in Overman's preparation of (+)-sieboldine A **1** was a pinacol-terminated cyclization cascade (Scheme 3). The synthetic pathway started with a methyl cuprate-promoted SN2′ alkylation of lactone **11,** followed by iodolactonization to give iodolactone **16** in 93% yield. Next, lithium aluminum hydride (LAH) reduction of **16** led to the corresponding dehalogenated diol, which was selectively monosilylated and oxidized with Dess-Martin periodinane (DMP) to form ketone **17**. Addition of *E*-vinyl iodide derivative **18** to ketone **17** afforded the desired allylic alcohol **19** in 90% yield. Thus, silylation of the allylic hydroxy functionality of **19** followed by Swern oxidation of the primary silyl ether, and subsequent reaction with the Bestmann–Ohira reagent **20** afforded alkyne **21** in 70% yield. Alkyne **21** was subjected to a gold-catalyzed pinacol-type cyclization reaction to deliver *cis*-hydrindanone **23** in 78% yield.



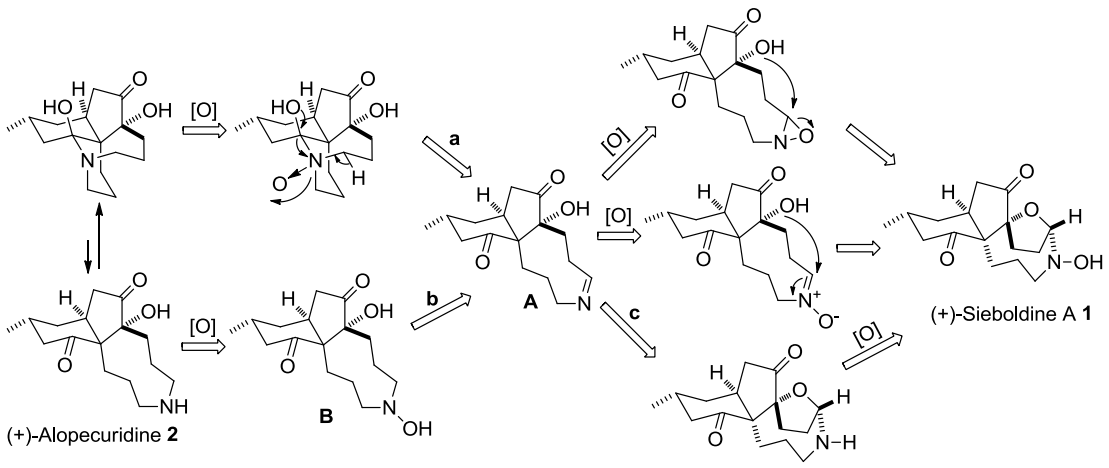
Scheme 3: Overman's total synthesis of (+)-sieboldine A **1**.

The next steps were concerned with the construction of the tetrahydrofuran moiety. Ozonolytic cleavage of the exo-methylene functionality of **23** and subsequent base-promoted elimination of the phenoxide afforded enone **24**. Europium(III)-catalyzed hetero Diels-Alder reaction with ethyl vinyl ether furnished the tricyclic dihydropyran **25**. Reduction of the C13 carbonyl group followed by oxidation with dimethyldioxirane (DMDO) and treatment with $BF_3.OEt_2$ and ethanethiol afforded cyclic hemithioacetal **26** in 53% yield.

Desilylation of **26** was carried out with TBAF and the resulting primary alcohol was subjected to a Mitsunobu coupling with protected hydroxylamine derivative (NsNH-OMOM). Then, the nosyl protecting group was removed with thiophenolate and treatment with dimethyl(methylthio)sulfonium triflate (DMTST) in the presence of 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) afforded the pentacyclic azacyclononane **27** in 39% yield. Final oxidation and MOM deprotection delivered (+)-sieboldine A **1** in 59% yield.[18,19]

1.1.4 Total synthesis of (+)-sieboldine A by Tu

The plausible biogenesis of (+)-sieboldine A **1** was initially proposed by Kobayashi (Scheme 4). Alopecuridine **2** may exist in either an aminoacetal form or an amino ketone form. The aminoacetal form of **2** was confirmed by X-ray analysis. SieboldineA **1** might be generated from alopecuridine **2** as follows. Cleavage of the C13-N1 bond of an N-oxidative product of **2** followed by Polonovski-type reaction (path a) might result in an iminium intermediate **A** with a nine-membered ring system, although an alternative path through a hydroxylamine derivative **B** is also possible (path b). Oxidation of the imine **A** to produce an oxaziridine ring or a nitrone followed by attack of the hydroxy group at C4 to C1 will give (+)-sieboldine A **1**, although an alternative path (path c) is also possible.[5]

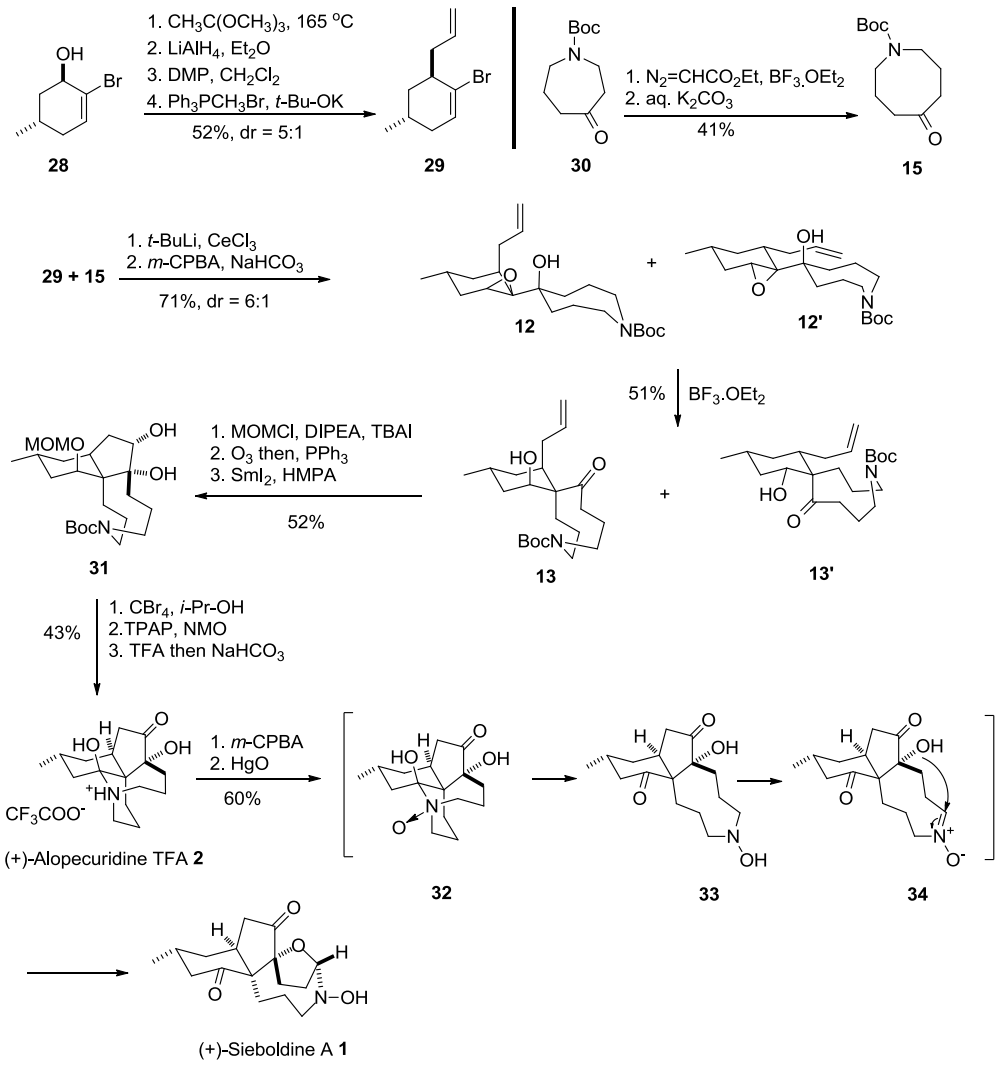


Scheme 4: Kobayashi's proposed biogenesis of (+)-sieboldine A **1**.

Tu and coworkers followed Kobayashi's proposed biogenetic pathway and used alopecuridine **2** as a synthetic scaffold to access sieboldine A **1** (Scheme 5).[20,21] The synthesis was commenced by treatment of *trans*-cyclohexenol **28** with trimethyl orthoester at 165 °C and the generated ester was reduced by LAH followed by Dess-Martin oxidation and Wittig methylenation to produce bromoalkene derivative **29** in 52% yield with a dr of 5:1. The known ketone **15** was prepared from azepine **30** via a Tiffenau–Demjanov-type reaction followed by hydrolysis of the ethyl ester and subsequent decarboxylation. Coupling of **29** with **15** was carried out through the

intermediacy of the vinylcerium species generated from the lithium salt of **29**. To avoid elimination, the generated coupling product was directly epoxidized by *m*-CPBA resulting in formation of epoxides **12** and **12'** as an inseparable mixture in 71% yield with a dr of 6:1. The semipinacol rearrangement of **12** and **12'** promoted by $BF_3.OEt_2$ took place to produce ketones **13** and **13'** in 51% yield. After a three-step sequence involving hydroxyl group protection, ozonolysis, and SmI_2 promoted Intramolecular pinacol coupling, the so obtained tricyclic compound **31** was further subjected to one-pot deprotection, TPAP oxidation and final N-Boc deprotection to deliver (+)-alopecuridine TFA **2** in 23% yield from **13**.

The biomimetic transformation of (+)-alopecuridine TFA **2** to (+)-sieboldine A **1** was realized through a two-step one pot oxidation cascade. Alopecuridine TFA **2** was oxidized to N-oxide **32** by the peroxide agent. The N-oxide **32** might isomerize to N-hydroxide **33** which underwent further oxidation with HgO to give nitrone **34**. The Intramolecular nucleophilic attack of the C4 hydroxy group to C1 led to formation of the tetrahydrofuran ring and afforded (+)-sieboldine A **1** in 60% yield.



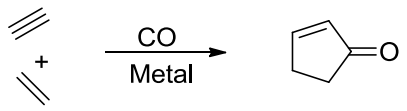
Scheme 5: Tu's total synthesis of (+)-sieboldine A **1**.

1.2 Pauson-Khand Reaction (PKR)

1.2.1 The Discovery and Early Evolution of the PKR

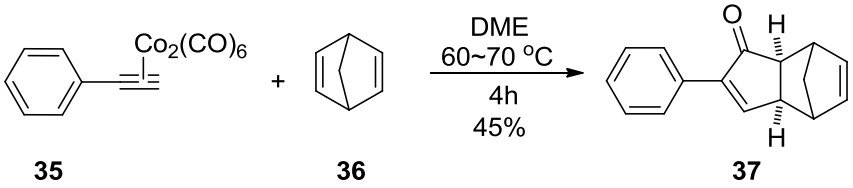
Metal-mediated transformations have changed the profile and enhanced the potential of organic synthesis well beyond that which was previously possible or imaginable. The cycloaddition reaction is one of the most attractive synthetic protocols for accessing a variety of scientifically interesting and pharmaceutically useful ring skeletons from simple starting materials.[22] In 1973, Pauson and Khand reported the formal [2+2+1] cycloaddition reaction between an alkyne, an alkene, and

carbon monoxide that has become one of the most elegant methods for the construction of the cyclopentenone derivatives (Scheme 6).[23,24]



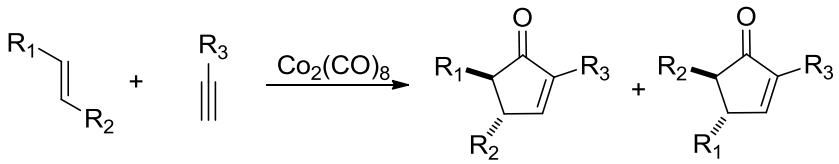
Scheme 6: Pauson-Khand reaction

The first reported example was the reaction of norbornadiene **36** with the phenylacetylene-dicobalthexacarbonyl complex **35** to form the corresponding cyclopentenone **37** in 45% yield (Scheme 7).[24]



Scheme 7: First example of PKR

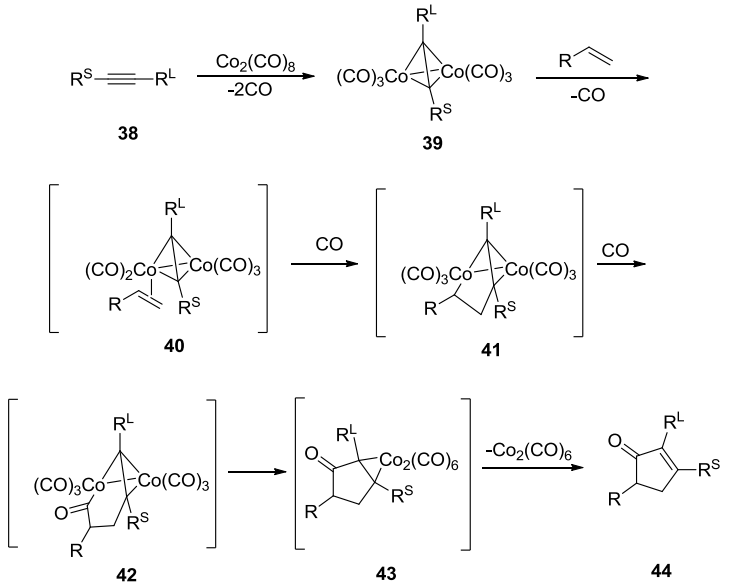
The initial scope and generality of this cyclopentannulation process was established through an extensive series of studies by Pauson and his co-workers.[25-27] However, there were some limitations for the original PKR at that early stage. For example, the stoichiometric amount of catalyst and only strained olefins reacted efficiently under the original reaction conditions. With respect to regiochemistry of PKR, the larger alkyne substituent is being installed in the position α to the cyclopentenone carbonyl unit. Unsymmetrical alkenes usually gave a mixture of regioisomers (Scheme 8).[28]



Scheme 8: Regiochemistry of the PKR

1.2.2 Mechanism of the PKR

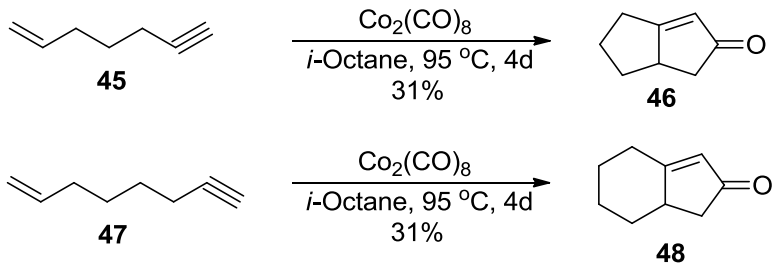
The mechanism of the PKR, initially proposed by Magnus, has now been widely accepted (Scheme 9). In the presence of $Co_2(CO)_8$ the alkyne **38** forms the tetrahedral dicobalt complex **39**. After loss of CO, the alkene is coordinated to give complex **40**, which undergoes insertion of the alkene moiety into the sterically least hindered Co-C bond to give complex **41**. Subsequent CO insertion gives rise to the cobalt acyl complex **42**. Extrusion of one $Co(CO)_3$ fragment yields the cobaltacyclopropene complex **43**, which is finally converted to the cyclopentenone **44** by reductive cleavage of $Co_2(CO)_6$.[29]



Scheme 9: Mechanism of PKR

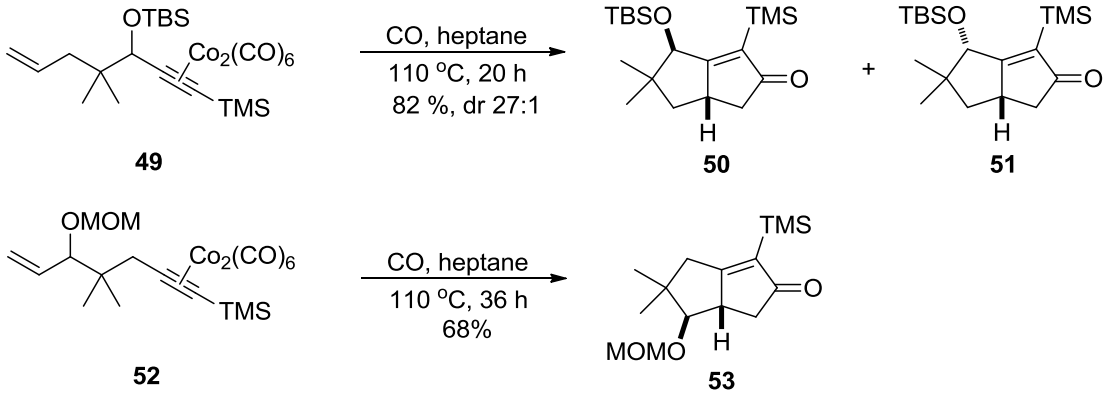
1.2.3 Intramolecular PKR

In 1981, Schore and co-workers reported the first example of an intramolecular PKR.[30] This version provided a powerful methodology for construction of cyclopentenone fused bicyclic frameworks in a straightforward manner. Within the original landmark publication, both hept-6-en-1-ynes **45** and oct-7-en-1-ynes **47** were utilized as substrates in intramolecular PK process to deliver bicyclo[3.3.0]octenones **46** andbicyclo[4.3.0]nonenone **48** (Scheme 10).[30]



Scheme 10: Intramolecular PKR

Later, Magnus further enhanced the efficacy of PKR by showing that appreciable stereoselectivity could be achieved within the intramolecular processes, a feature that proved to be the cornerstone to the application of the PKR in natural product synthesis.[31] Substituents at the propargylic C3 position in **49** and allylic C5 position in **52** have a preference to become situated on the *exo*-face and *syn* to the ring fusion hydrogen in the resulting bicyclic PK products **50** and **53** respectively (Scheme 11). The level of stereoselectivity was further enhanced by bulky substitution at the terminal alkyne carbon.[32]



Scheme 11: Diastereoseletivity of intramolecular PKR.

With the stereochemical reaction outcomes established for a number of substrate substitution patterns, Magnus and co-workers utilized the intramolecular PKR as a key step for the synthesis of the linearly-fused triquinane natural products, coriolin,[31] hirsutic acid[33] and cytotoxic sesquiterpene, quadrone.[34]

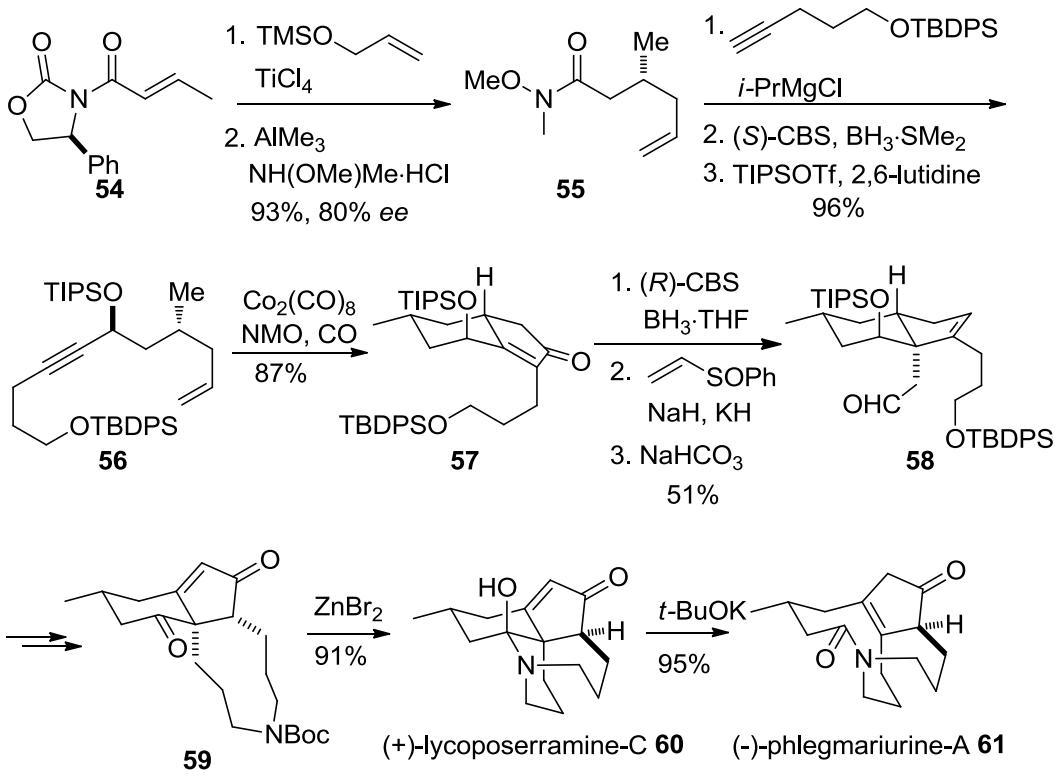
The intramolecular version of the PK annulation has continued to expand in terms of substrate scope and reaction selectivity. The growth in PK potential has been

driven by a range of emerging procedures using a variety of metal complexes and promoters, which have appreciably enhanced the overall efficiency of the cyclization method.[35-44]

1.3 Total syntheses of *Lycopodium* alkaloids using intramolecular PKR as a key step

1.3.1 Total Syntheses of (+)-Lycoposerramine-C and (-)-phlegmariurine-A by Takayama

In 2009, Takayama *et al.* reported the total synthesis of (+)-lycoposerramine-C **60** and (-)-phlegmariurine-A **61** (Scheme 12).[45] Amide **55** was stereoselectively prepared by a diastereoselective Hosomi-Sakurai allylation[46] of **54** and subsequent cleavage of the oxazolidinone ring. Next, introduction of the alkyne chain to **55** followed by a Corey-Bakshi-Shibata (CBS) reduction[47] and TIPS protection of the resulting hydroxyl group afforded enyne **56** in 96% yield. The Intramolecular PKR of enyne **56** proceeded smoothly to form hydrindanone **57** in 87% yield. Construction of the quaternary center was conceived through a stereoselective CBS reduction of **57** followed by sulfoxide formation and Claisen rearrangement to afford the desired aldehyde **58** in 51% yield. The tricyclic dione **59**, obtained from **58** in 12 steps, was treated with $ZnBr_2$ to form (+)-lycoposerramine-C **60** in 32 % yield from **58**. Furthermore, base treatment of (+)-lycoposerramine-C **60** afforded (-)-phlegmariurine-A **61** in 95% yield.

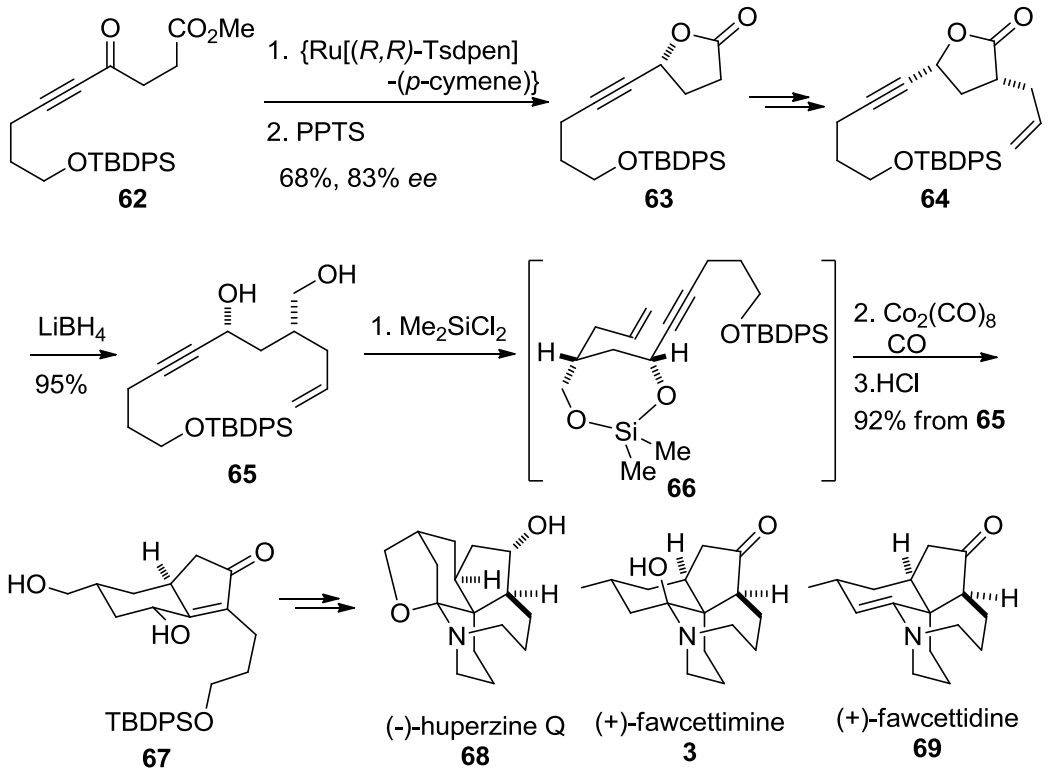


Scheme 12: Takayama's total synthesis of (+)-lycoposerramine-C **60** and (-)-phlegmariurine-A **61**.

1.3.2 Total Syntheses of (-)-huperzine-Q, (+)-fawcettimine and (+)-fawcettidine by Takayama

In 2011, Takayama and coworkers completed the first total synthesis of (-)-huperzine-Q **68** utilizing an intramolecular PKR as a key step (Scheme 13).[48] First, Noyori asymmetric hydrogenation[49] of ketone **62**, followed by acid catalyzed cyclization gave lactone **63** in 68% yield with 83% ee. Allyl lactone **64**, derived from **63** in 2 steps, was reduced by $LiBH_4$ to give enynediol **65** in 95% yield. Direct subjection of enynediol **65** to intramolecular PKR conditions resulted in formation of the undesired C7-epimer. Therefore, Takayama and coworkers decided to install a silicon tether to force the substrate in a chair-like conformation with the C15 side-chain in axial position. With the silyl tether in place, PKR of enyne **66** and subsequent treatment with concentrated hydrochloric acid afforded the desired desilylated bicyclic Pauson-Khand product **67** in excellent yield. With bicyclic intermediate **67** in hand, takayama was able to access (-)-huperzine-Q **68** in 13 synthetic steps from **67**

with an overall yield of 16.4%. In the next year, takayama reported the total synthesis of (+)-fawcettimine **3** and (+)-fawcettidine **69** from **67** as a common synthetic intermediate.[50]

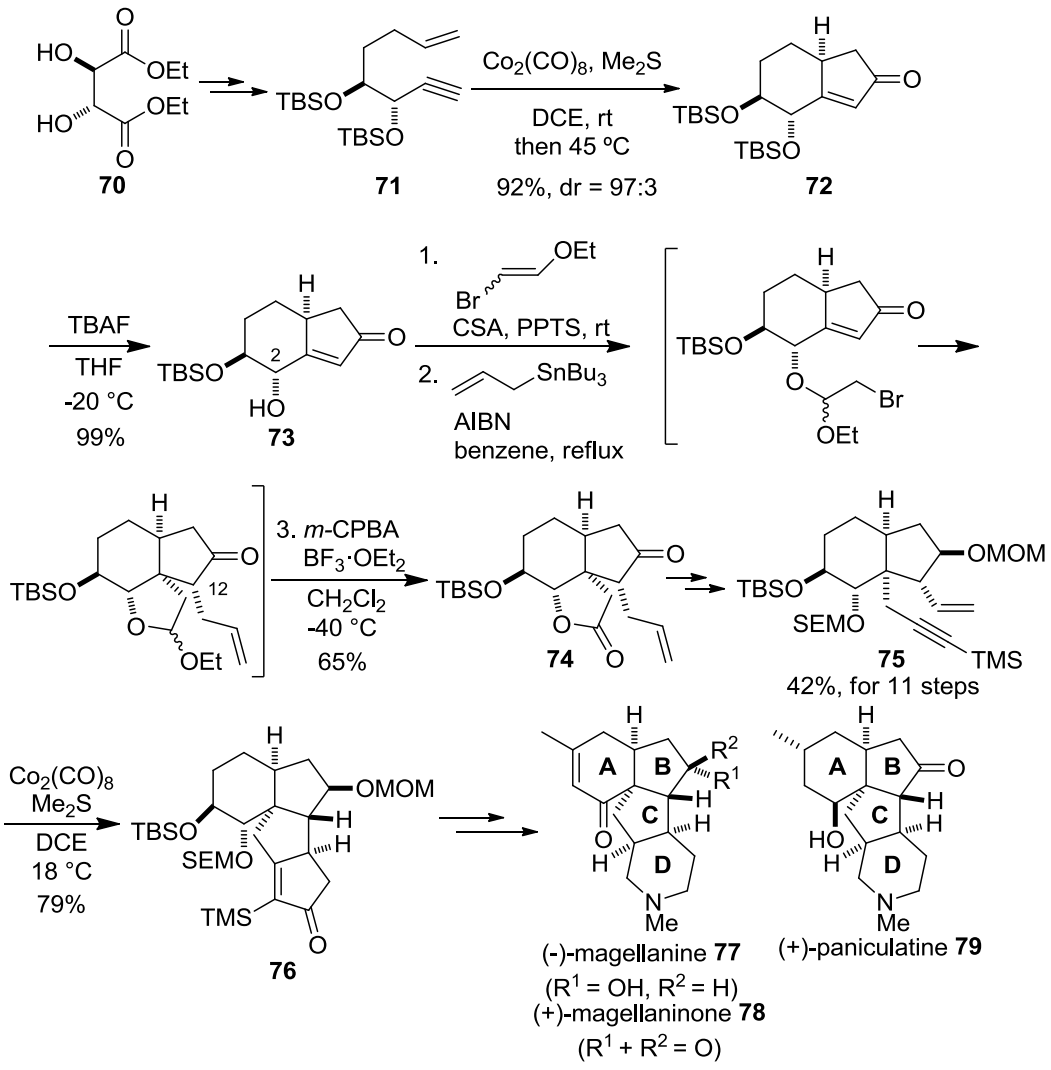


Scheme 13: Takayama's total synthesis of (-)-huperzine Q **68**, (+)-fawcettimine **3**, (+)-fawcettidine **69**.

1.3.3 Total Syntheses of (-)-magellanine, (+)-magellaninone, and (+)-paniculatine by Mukai

In 2007, Mukai reported the total syntheses of (-)-magellanine **77**, (+)-magellaninone **78**, and (+)-paniculatine **79** from diethyl L-tartrate **70** in a stereoselective manner (Scheme 14).[51] The crucial steps in these syntheses involved two intramolecular Pauson-Khand reactions and a Ueno-Stork reaction[52,53] for construction of the quaternary center. Enyne **71**, derived from diethyl L-tartarate **70**, was subjected to an intramolecular PKR according to Sughihara's condition[54] to give preferentially bicyclo[4.3.0]nonenone **72** in 92% yield. Selective deprotection of the C2-siloxy group of **72** with TBAF furnished alcohol **73** in 99% yield. The

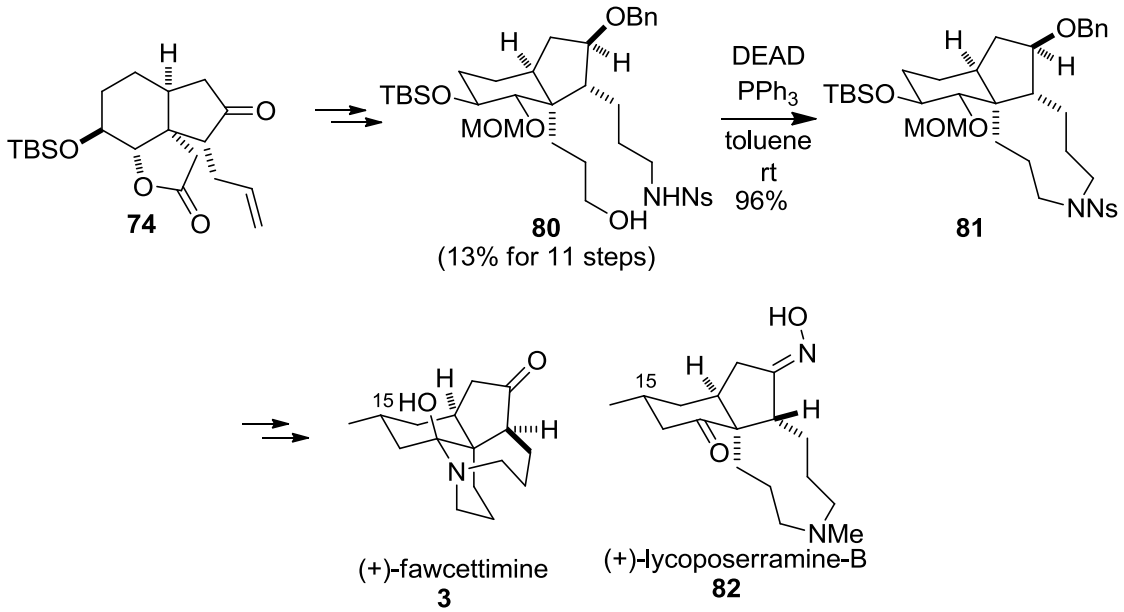
simultaneous and stereoselective introduction of the essential carbon units at the C1 position and the C9 position was realized by the Ueno-Stork reaction. Alcohol **73** was treated with ethyl 2-bromovinyl ether under acidic catalysis, and the resulting bromoacetal derivative was subsequently subjected to AIBN in refluxing benzene in the presence of allyltributyltin to give the tricyclic lactone **74** in 65% yield. The enyne **75**, generated from **74**, was subjected to a second intramolecular PKR to afford tetracyclic derivative **76** which finally converted to (-)-magellanine **61**, (+)-magellaninone **62** and (+)-paniculatine **63** in an overall yield 1.7, 1.9 and 2.8% respectively.



Scheme 14: Mukai's Total Synthesis of (-)-magellanine **77**, (+)-magellaninone **78**, and (+)-paniculatine **79**.

1.3.4 Total Syntheses of (+)-fawcettimine and (+)-lycoposerramine B by Mukai

Three years later, Mukai and coworkers utilized the lactone intermediate **74** for the asymmetric preparation of (+)-fawcettimine **3** and (+)-lycoposerramine B **82** (Scheme 15).[55] The amide alcohol **80**, derived from intermediate **74** in 11 synthetic steps, was subjected to an intramolecular Mitsunobu reaction[56] to give tricyclic derivative **81** in 96% yield. The stereoselective introduction of C15 methyl and final conversions afforded (+)-fawcettimine **3** and (+)-lycoposerramine B **82** from tricyclic **81** in 20 and 6% yield respectively.



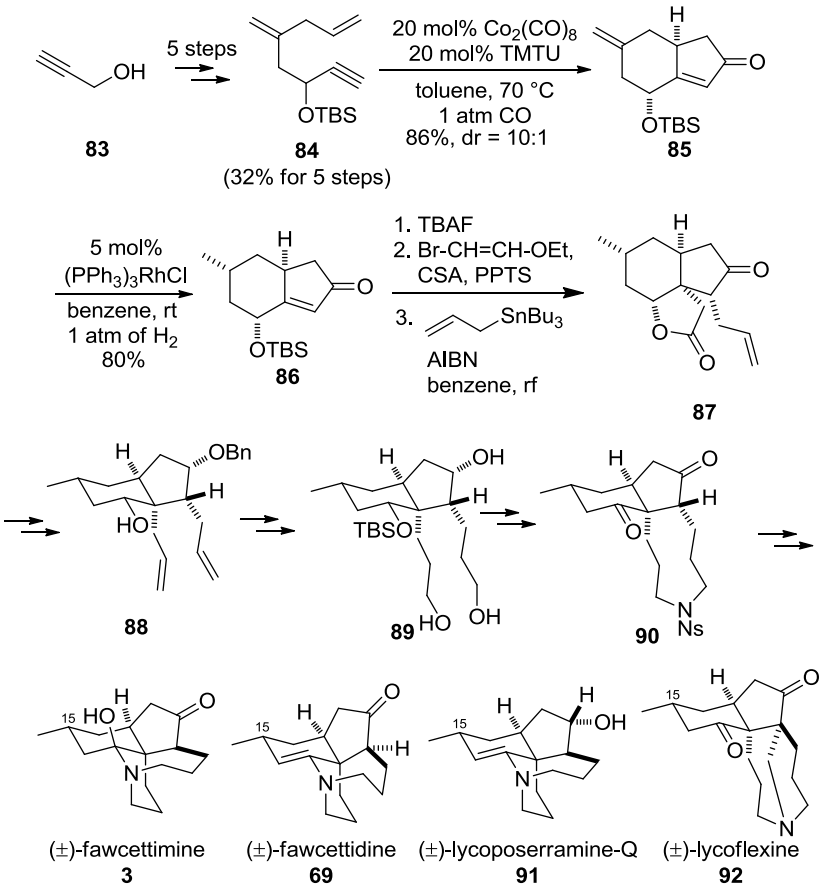
Scheme 15: Mukai's Total Synthesis of of (+)-fawcettimine **3** and (+)-lycoposerramine B **82**.

The high stereoselective intramolecular PKR developed by Mukai for construction of the bicyclo[4.3.0] skeleton applied a nice protocol for the preparation of the *cis*-hydrindane moiety in fawcettimine-type *Lycopodium* alkaloids and enabled the access for several complex natural products from common precursors. However, the approach seemed to have two issues that needed to be improved. First, the conversion of diethyl L-tartrate **54** into the PKR substrate enyne **55** involved 10 synthetic steps. Secondly, the stereoselective introduction of C15 methyl group

needed lengthy functional group manipulations which required several additional steps.

1.3.5 Total Syntheses of (±) -fawcettimine, (±) -fawcettidine, (±) -lycoposerramine-Q and (±)-lycoflexine by Mukai

In 2013, Mukai reported the total synthesis of new *Lycopodium* alkaloids using a more efficient second generation synthetic pathway for preparation of bicyclo[4.3.0]nonenone skeleton.[57] In the improved protocol, Dienyne **84**, generated from commercially available propargyl alcohol **83** in only 5 synthetic steps, was used as a substrate for the PKR. The intramolecular PKR of **84** afforded bicyclo[4.3.0]nonenone **85** in 86% yield with a dr of 10: 1. The exomethylene moiety was stereoselectively reduced by Wilkinson's hydrogenation to give the methyl derivative **86** with the required stereochemistry at C15 in 80% yield. The stereoselective creation of the quaternary center and introduction of allyl group α to the carbonyl group was achieved through the Ueno-Stork reaction to form cyclic acetal **87** in 73% yield. A cascade of reduction, benzyl protection, acid treatment and Wittig olefination gave the diallyl derivative **88** in 48% yield. The diallyl **88** was converted to the tricyclic derivative **90** in 7 synthetic steps with a Mitsunobu coupling reaction of diol **89** as a key step. With the common synthetic intermediate **90** in hand, final manipulations allowed the access of (±)-fawcettimine **3**, (±)-fawcettidine **69**, (±)-lycoposerramine-Q **91** and (±)-lycoflexine **92**.

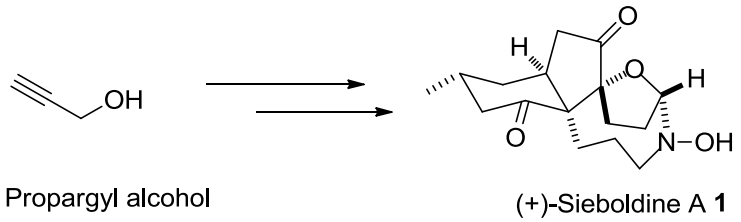


Scheme 16: Mukai's total syntheses of (±)-fawcettimine **3**, (±)-fawcettidine **69**, (±)-lycoposerramine-Q **91** and (±)-lycoflexine **92**.

1.4 Research objective

For the past century, the total synthesis of natural products has served as the flagship of chemical synthesis and the principal driving force for discovering new chemical reactivities, evaluating physical organic theories, testing the power of existing synthetic methods, and enabling biology and medicine to discover new drug candidates. The PKR has become one of the most important stratigies for the synthesis of cyclopentenone containing natural products. The intramolecular PKR of enynes, developed in Mukai's group, enabled the construction of bicyclo[4.3.0]nonenoe skeleton in a highly diastereoselective manner and allowed the access of several fawcettimine-type *Lycopodium* alkaloids. This research is concerned with the enantioselective total synthesis of (+)-sieboldine A **1** using an intramolecular PKR as a key step for construction of the *cis*-hydrindane core. (+)-Sieboldine A has

interesting biological activities and providing a shorter and entatioselective route for its preparation from commercially available starting materials will help to explore its scaffold for the discovery of potential anti-Alzheimer agents.



Scheme 17: Research objective for total synthesis of (+)-sieboldine A **1**.

CHAPTER II

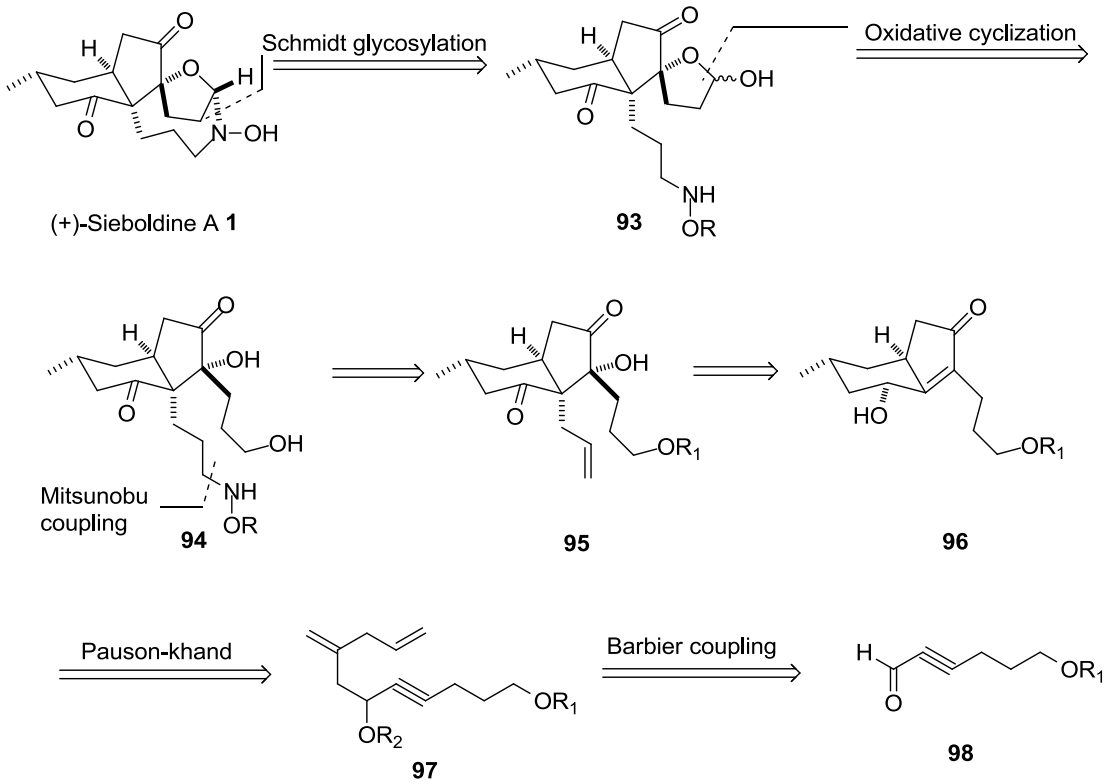
Results and Discussion

2.1 Total synthesis of (±)-Sieboldine A

2.1.1 Retrosynthetic analysis of (±)-Sieboldine A

Our retrosynthetic plan for the preparation of (±)-sieboldine A **1** is presented in Scheme 18. The elaboration of the sensitive N,O-acetal functionality of (±)-**1** was planned to be formed during the late stage of the synthesis via the intramolecular

displacement reaction of the lactol functionality of **93** by the *O*-protected hydroxylamine residue.[58,59] The spirolactol framework of **93** would be formed through oxidative cyclization of the diol **94**. Introduction of the nitrogen functionality could be achieved through the hydroboration−oxidation of the allyl side chain of **95**, followed by a Mitsunobu coupling with the protected hydroxylamine derivative. The *cis*-hydrindanone **95** with all-carbon units required for **1** would be obtained by the consecutive bromoacetalization, Ueno−Stork cyclization, and Wittig olefination of **96**. In our previous studies, we definitely showed that the PKR is a powerful and efficient synthetic tool to assemble bicyclo[4.3.0] frameworks.[55,57,60] Based on our previous results, the PKR of the dienyne **97** would be expected to stereoselectively produce **96**. Dienyne **97** would be available through a Barbier coupling of aldehyde **98** with a suitable allyl derivative.

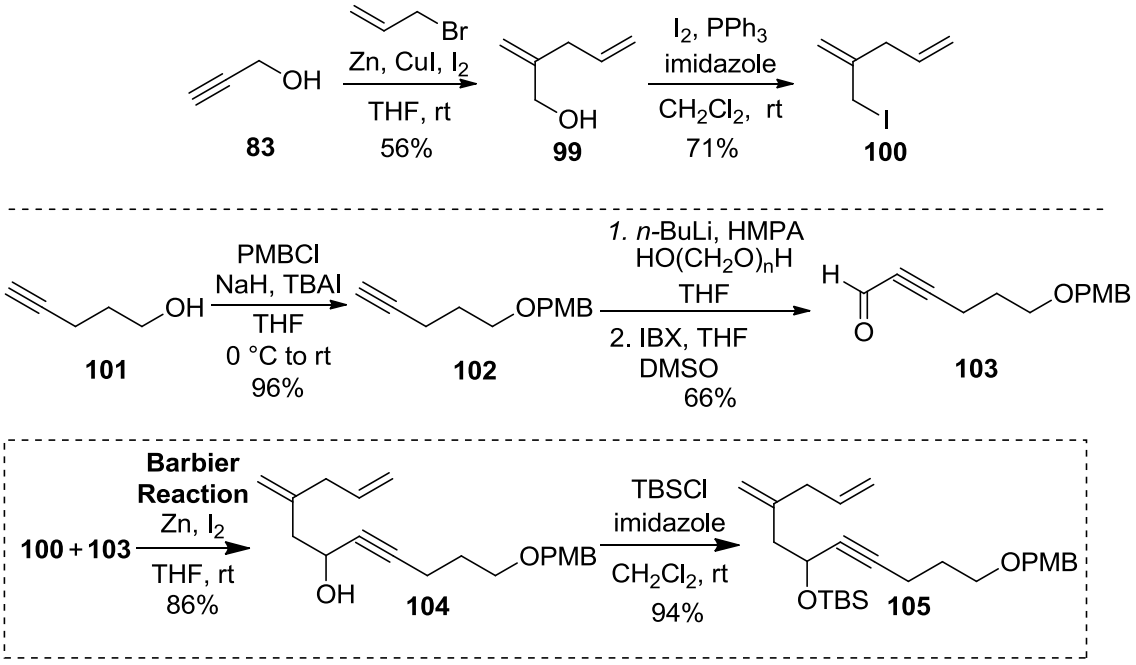


Scheme 18: Retrosynthetic analysis of (±)-Sieboldine A **1**.

2.1.2 Synthesis of PKR precursor Dienyne 105

The synthetic plan towards (±)-sieboldine A **1** started with addition of allyl bromide to propargyl alcohol **83** in the presence of zinc dust and copper(I) iodide to

give alcohol **99** in 56% yield (Scheme 19).[61] The alcohol **99** was subjected to Appel reaction conditions to form iododiene **100** in 71% yield.[57] On the other hand, the hydroxyl group of commercially available 4-pentyn-1-ol **101** was protected with a PMB group to give pentyne **102** in 96% yield. Pentyne **102** was hydroxymethylated with *n*-BuLi and paraformaldehyde and the resulting alcohol was oxidized by 2-iodoxybenzoic acid (IBX) in DMSO/THF mixture to give the desired aldehyde **103** in 66 % yield. The iododiene **100** was entered into a Barbier reaction with aldehyde **103** and the resulting secondary alcohol was protected with TBS group to form dienyne **105**.



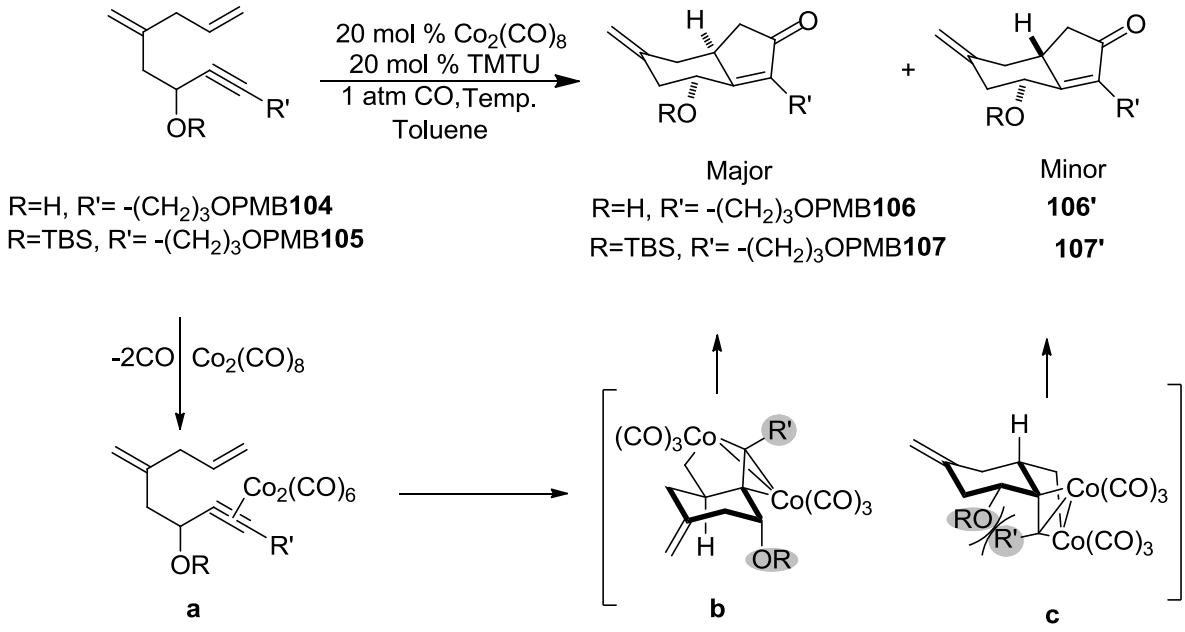
Scheme 19: Preparation of dienyne **105**.

2.1.3 Intramolecular PKR of Dienynes 104 and 105

The intramolecular PKR of dienynes **104** and **105** using a catalytic amount of $Co_2(CO)_8$ in presence of tetramethylthourea (TMTU) under 1 atm of CO afforded indenones **106** and **107** (Table 1).[62-64] An extremely high preferential formation of indenones **106** and **107** over **106'** and **107'** could tentatively be rationalized by considering the steric hindrance between the OR group and the carbon reside having PMB in the possible cobaltacyclic intermediates **b** and **c**. Dienyne **105** showed the best results in terms of diastereoselectivity and yield. The enhanced

diastereoselectivity in PKR of dienyne **105** compared to **104** might be attributed to the more steric repulsion exhibited by the OTBS than the OH group in **104**.

Table 1. Intramolecular PKR of dienynes **104** and **105**.



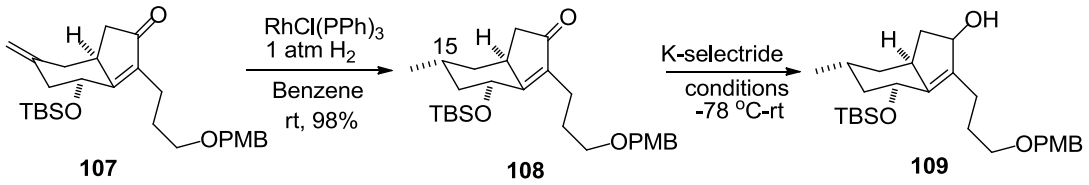
Entry	Substrate	R	Temp (°C)	Yield (%)	Ratio[a] [Major:Minor]
1	**104**	H	70	89	89:11
2	**104**	H	80	86	87:13
3	**105**	TBS	70	96	98:2
4	**105**	TBS	80	92	95:5

[a] *Ratio was calculated from isolated yields after column chromatography*

2.1.4 Stereoselective Reduction of indenone 107

After obtaining indenone **107** with the required stereochemistry, our efforts moved towards the introduction of C15 methyl group and stereoselective reduction of the ketone group (Table 2). Hydrogenation of the exomethylene moiety of **107** in presence of 5 mol% Wilkinson's catalyst proceeded in a highly chemo- and stereoselective manner to form the methyl derivative **108** having the C15-methyl group with the desired stereochemistry in 98% yield.[57] Stereoselective reduction of the ketone group was examined using K-selectride under different conditions, (Table 2). Although the use of [18]-crown 6 as an additive during the reduction process had a beneficial effect on the yield, it decreased the stereoselectivity of the reduction. In addition, oxygenated solvents like Et_2O and THF showed the best results in terms of yield and stereoselectivity over hydrocabon solvents as toluene.

Table 2. Stereoselective reduction of ketone **108**.



107 108 109

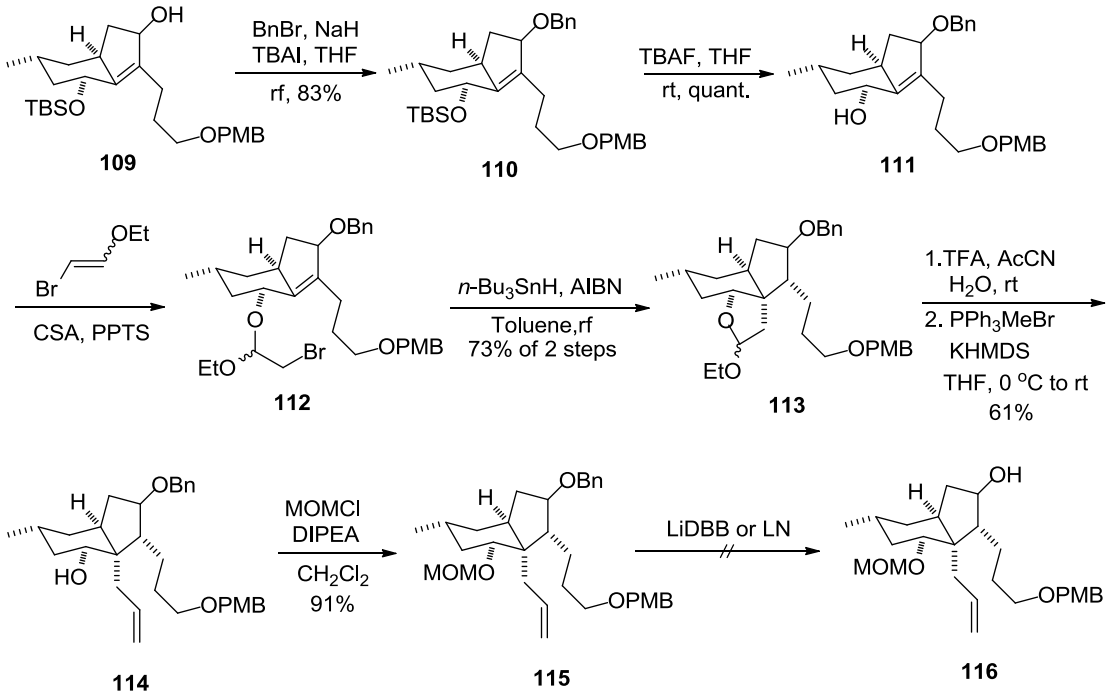
Entry	Solvent	Additive	Yield (%)	dr [a]
1	Toluene	----------	71	88:12
2	THF	----------	87	92:8
3	Et_2O	----------	76	73:27
4	Toluene	[18]-crown-6	77	68:32
5	THF	[18]-crown-6	89	61:39

[a] *Ratio calculated from isolated yields after column chromatography.*

2.1.5 Construction of the quaternary center and difficulties in removal of benzyl group

The next synthetic steps aimed towards the construction of the all-carbon quaternary center by taking the advantage of the Ueno-Stork reaction (Scheme 20).[65-69] First, alcohol **109** was protected with a benzyl group in 83% yield. The TBS group of **110** was removed by TBAF and the resulting alcohol was reacted with ethyl 2-bromovinyl ether in presence of acid catalysis to afford the bromoacetal **112**. Treatment of **112** with tributyltin hydride under conventional radical initiation

conditions (AIBN in toluene) provided the cyclic acetal **113** in 73% yield of 2 steps with a dr of 3:1. The hemiacetal derivative, obtained from **113** by acid treatment, underwent a Wittig olefination reaction with PPh_3MeBr and KHMDS to afford allyl alcohol **114** in 61% yield. Allyl alcohol **114** was protected with a MOM group to provide indene **115** in 91% yield. At this stage, we needed to remove the benzyl protecting group to restore the ketone functionality. Our attempts to obtain alcohol **116** through radical reduction of indene **115** with lithium 4,4'-di-*tert*-butulbiphenylide (LiDBB)[70] or lithium naphthalenide (LN)[71] were unsuccessful. The encountered difficulties in removal of benzyl group through radical reduction may be attributed to the sterically congested environment surrounding the benzyl group. Accordingly, we decided to modify our strategy to form the oxa quaternary center before performing the Wittig olefination.



Scheme 20: Preparation of **115** and attempts for benzyl deprotection.

2.1.6 Attempts for silyl enolization of ketone 119

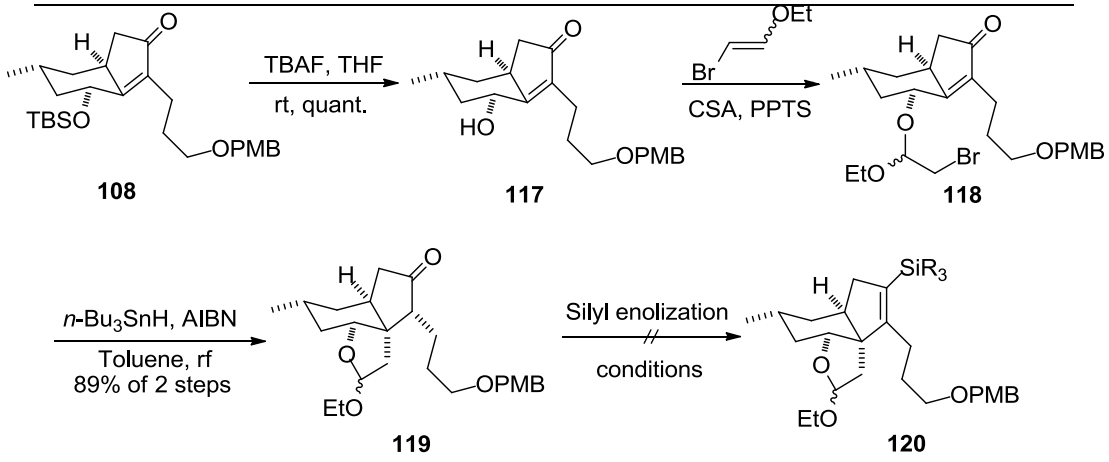
The TBS group of **108** was removed by TBAF and the resulting alcohol **117** was entered into the Ueno-Stork cascade to obtain the cyclic acetal **119** in 89% yield of 2 steps. We conceived that the formation of the oxa quaternary center could be

achieved through a Rubottom oxidation of the silyl enol derivative **120**.[72] We examined different protocols for preparation of the thermodynamically controlled silyl enol isomer **120** but our efforts were unfruitful (Table 3). The chlorosilanes were found to be unreactive enough for the conversion while the silyl triflates leaded to decomposition of the starting material.

Table 3. Attempts for silyl enolization of ketone **119**.

Entry	Conditions	Solvent	Temp.	Time/h	Result
1	TMSCl, Mg	THF	rt to rf	24	No reaction
2	TBSCl, Mg	THF	rt to rf	24	No Reaction
3	TBSCl, Et_3N	DMF	rt	24	No Reaction
4	TBSCl, Et_3N, NaI	CH_3CN	rf	24	No reaction
5	TMSOTf, Et_3N	CH_2Cl_2	0 ^oC to rt	2	Decomposed

6	TBSOTf, Et_3N	CH_2Cl_2	0 °C to rt	2	Decomposed
7	TBSOTf, 2,6-lutidine	CH_2Cl_2	0 °C to rt	2	Decomposed



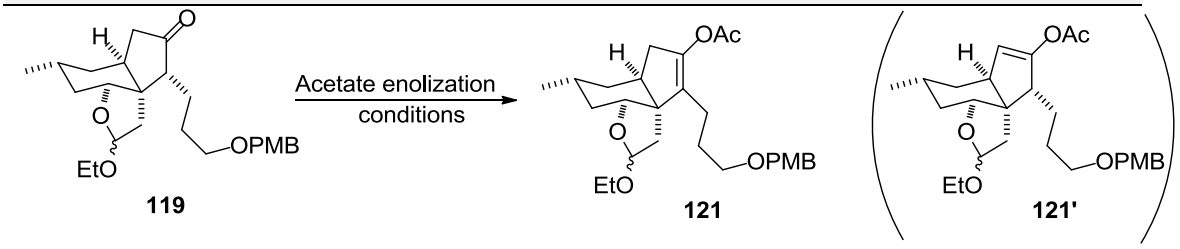
2.1.7 Regioselectivec acetate enolization ketone 119

The acetate enolization of ketone **119** derivative proved to be more successful. we studied the acetate enolization process under weak basic catalysis, high reaction temperatures and long reaction times to favor the formation of the thermodynamically controlled isomer **121** over the kinetically controlled one **121'** (Table 4).

Table 4. Optimization of regioselective acetate enolization ketone **119**.

Entry	Conditions	Temp(°C)	Time/h	Yield(%)

	Reagent (Equiv.)	Additive (Equiv.)	Solvent			
1	Isopropenyl acetate	*P*-TsOH	Neat	110	24	16
2	AcCl	Et_3N,DMAP	CH_2Cl_2	40	12	Complex mixture
3	AcCl	Pyridine, DMAP	CH_2Cl_2	40	12	Complex mixture
4	Ac_2O	Pyridine, DMAP	Neat	40	12	28
5	Ac_2O	Et_3N,DMAP	CH_2Cl_2	40	32	44
6	Ac_2O(45)	Et_3N(60) ,DMAP	Neat	40	8	58
7	Ac_2O (60)	Et_3N(30) ,DMAP	Neat	40	16	85
8	Ac_2O (60)	Et_3N(20) ,DMAP	Neat	40	48	92



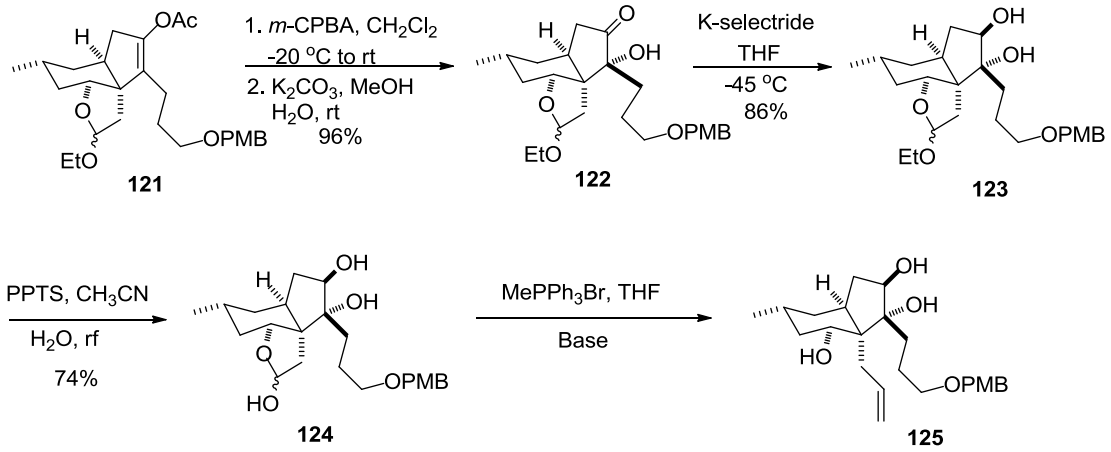
The results showed that acetic anhydride was superior to acetyl chloride for the enolization of ketone **119**. Aliphatic weak basic amines as Et_3N were more successful in catalyzing the enolization process than their aromatic peers. The high regioselectivity was achieved by utilizing Ac_2O and Et_3N and DMAP and performing the reaction neat at 40 ^oC for 48 h to obtain acetate enol **121** in 92% yield.

2.1.8 Preparation of Triol 125

The oxidation of acetate enol **121** with *m*-CPBA occurred from the sterically less hindered α face, and the resulting acetoxy epoxide moiety was hydrolyzed to give the α-hydroxy ketone derivative **122** in 96% yield (Table 5). Ketone **122** was temporarily converted to the *trans*-diol derivative **123** in 86% yield by the stereoselective K-selectride reduction to avoid any side reactions during further

chemical elaboration. The stereoselectivity observed in the K-selectride reduction of **123** might be attributed to the attack of the bulky hydride donor from the sterically less-hindered α face again. Compound **123** was treated with PPTS, and the resulting hemiacetal **124** was subsequently subjected to the Wittig olefination to form the allyltriol **125**. The polar nature of the Wittig olefination substrate triol **124** necessitated the use of base formulated in oxygenated solvent rather than hydrocarbon solvent to optimize the yield of the reaction.

Table 5. Optimization of Wiitig olefination of hemiacetal **124**.

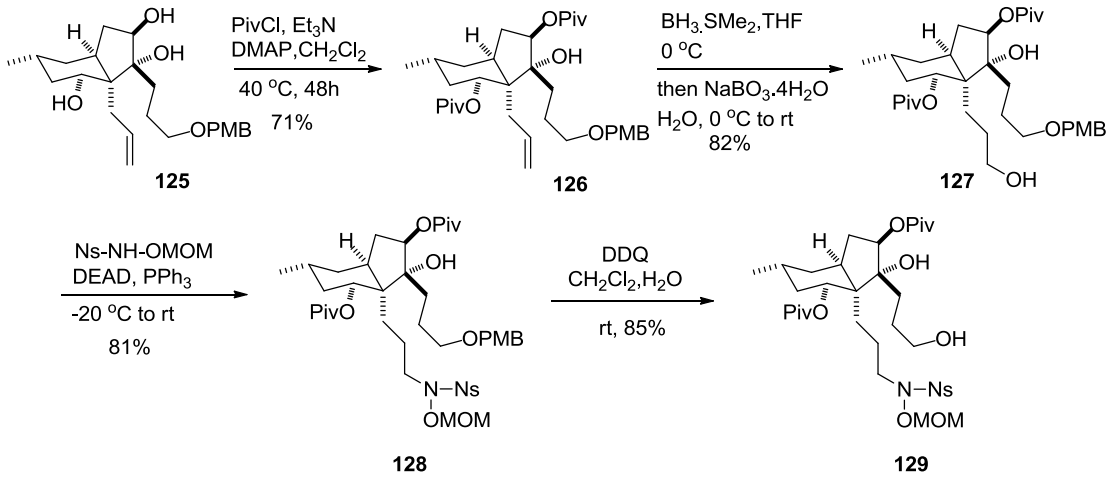


Entry	Base	Temp.	Time/h	Yield
1	*n*-BuLi (1.5 M in hexane)	0 °C to rt	18	18
2	KHMDS (0.5 M in toluene)	0 °C to rt	18	45
3	KHMDS (0.5 M in toluene)	0 °C to rf	8	Decomposed
4	KHMDS (1.0 M in THF)	0 °C to rt	24	74

2.1.9 Introduction of the nitrogen functionality

Having established all the carbon units with the proper stereochemistry, we focused on the introduction of the nitrogen functionality (Scheme 21). The two secondary hydroxyl groups of the triol derivative **125** were protected with pivaloyl group to provide **126** in 71% yield, which was subjected to hydroboration with $BH_3.SMe_2$, followed by oxidation using $NaBO_3.4H_2O$ to afford primary alcohol **127** in 82% yield.[73] The Mitsunobu reaction of **127** with protected hydroxyl amine

derivative Ns-NH-OMOM effected the introduction of the nitrogen atom to give **128** in 88% yield.[74] The PMB group of **128** was then removed with DDQ to afford the diol **129** in 85% yield.



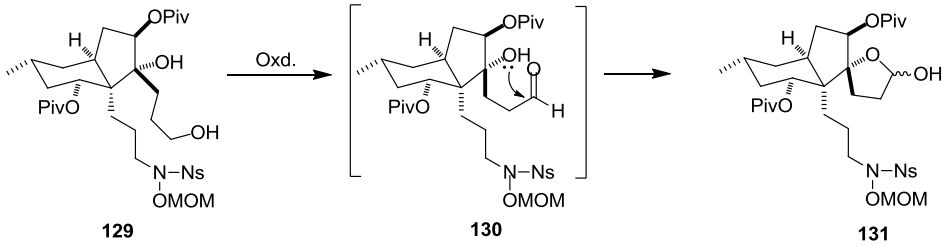
Scheme 21: Preparation of diol **129**.

2.1.10 Optimized oxidation of Diol 129

For the formation of the spirotetrahydrofuran ring, we visualized that a controlled oxidation of diol **129** into aldehyde **130** will be followed by a spontaneous nucleophilic attack of the tertiary hydroxyl to the aldehydic carbonyl and result in formation of the spirolactol derivative **131**. We scanned the oxidation of diol **129** with different oxidant systems and the results are shown in Table 6.

The periodinane reagents showed the best potential for oxidation of diol **129** in terms of yield. Optimization of oxidation of **129** by periodinanes was examined using gradually increasing equivalents of the oxidants to determine the best equivalent that provides the maximum yield of spirolactol **131** with minimum overoxidation to the lactone **131'** (Table 7). We found that the oxidation of the diol **129** with 1.5 equivalent of IBX in THF/DMSO (1:1) at room temperature provided a clean conversion to the spirolactol **131** in 83% yield without overoxidation to the corresponding lactone species.

Table 6. Oxidation of diol **129** with different oxidants.

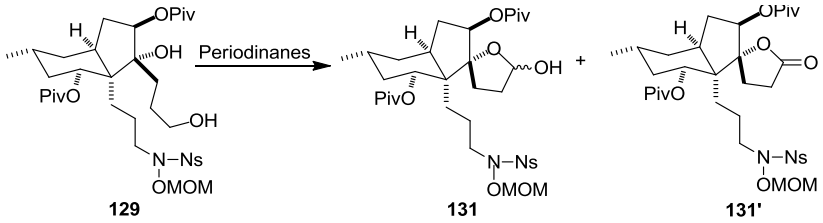


129 130 131

Entry	Oxidant [a]	Solvent	Temp.	Time (h)	Yield (%)[b]
1	Dess-martin	CH_2Cl_2	0 °C to rt	3	45
2	IBX	THF/DMSO	0 °C to rt	6	51
3	PCC	CH_2Cl_2	0 °C	4	29
4	Swern	DMSO	-78 °C to rt	3	33[b]
5	Parikh Doering	DMSO	rt	6	28
6	SeO_2	CH_2Cl_2	0 °C	26	26

[a] *all Oxidants was used in 1.1 equivalent.*
[b] *SM was recovered in varying yields after column chromatography.*

Table 7. Optimization of oxidation of diol **129** with periodinanes.



129 131 131'

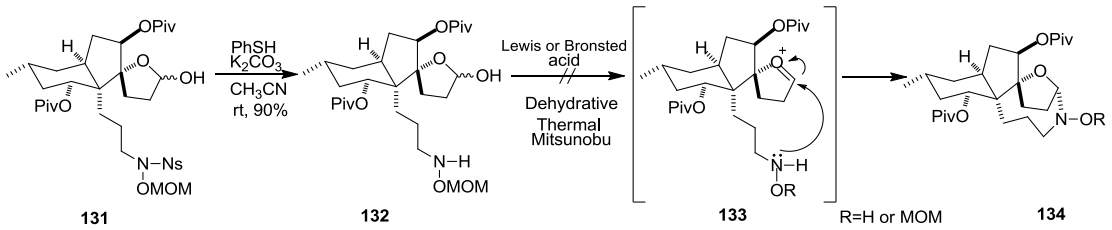
Entry	Oxidant	Equivalent	Yield	
			131%	131'%
1	Dess-martin	1.1	45[a]	---
2		1.3	51[a]	---
3		1.5	58[a]	---
4		1.7	43	12
5		2	33	35
6	IBX	1.1	51[a]	---
7		1.3	64[a]	---
8		1.5	83[b]	---
9		1.7	74	5

[a] *SM was recovered in varying yields after column chromatography.*
[b] *SM was recovered in 5 % yield sfter column chromatography.*

2.1.11 Assembly of the azacyclononane ring

With the spirolactol **131** in hand, we examined the formation of the azacyclononane ring. The denosylation of **131** with thiophenolate smoothly proceeded to afford the aminolactol **132** in 90% yield. Aminolactol **132** possesses all of the necessary functional groups to form tetracyclic derivative **134**. It was envisioned that treatment of **132** with Lewis or Brønsted acids might remove the MOM group from the hydroxylamine, thereby freeing the hydroxylamine to react with oxocarbenium ion **133**, generated under acidic reaction conditions, and assemble the nine-membered ring to form the tetracyclic derivative **134** (Table 8).

Table 8. Attempts for formation of azacyclononane ring.



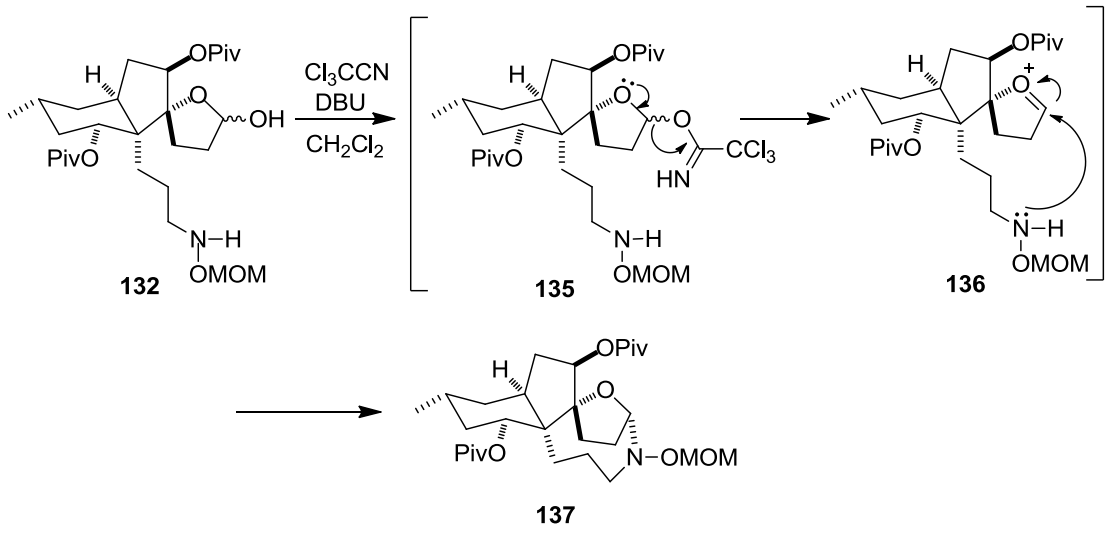
131 132 133 134

Entry	Condition	Solvent	Result
1	$MgSO_4$	CH_2Cl_2	No Reaction
2	PPTS	Pyridine	Complex mixture
2	$ZnBr_2$	CH_2Cl_2	Decomposition
3	TFA	CH_2Cl_2	Decomposition
4	TMSOTf	CH_2Cl_2	Decomposition
5	TMSI	CH_2Cl_2	Decomposition
6	PPh_3,DEAD	Toluene	No Reaction
7	Heat at 80 ^oC	Toluene	No Reaction

Our efforts to induce dehydrative condensation of aminolactol **132** by $MgSO_4$, or a combination of $MgSO_4$ and $ZnCl_2$, were unrewarded. Exposure of **132** to PPTS in pyridine resulted in complex reaction mixture. Moreover, Treatment of aminolactol **132** with a variety of Brønsted and Lewis acids resulted in complete destruction of the starting material (Table 8). We also explored the thermal dehydrative condensation

and Mitsunobu reaction conditions to promote the formation of azacyclononane ring but our attempts were unsuccessful. Our inability to form the *N*-hydroxyazacyclononane ring under variety of conditions necessitated the search for milder reaction conditions to promote the condensation and complete the total synthesis of sieboldine A. We finally reached the conclusion that the Schmidt glycosylation condition was the best one for our purpose.[75-77] Under Schmidt glycosylation conditions, aminolactol **132** would form the trichloroacetamidate **135** which generate the oxocarbenium ion **136**. Intramolecular nucleophilic attack of the N to C1 will assemble the azacyclononane ring. Indeed, treatment of aminolactol **132** with Cl_3CCN and DBU in CH_2Cl_2 at 0 °C to room temperature afforded the desired tetracyclic derivative **137** in 63% yield (Table 9).

Table 9. Optimization of Shmidt glycosylation of aminolactol **132**.

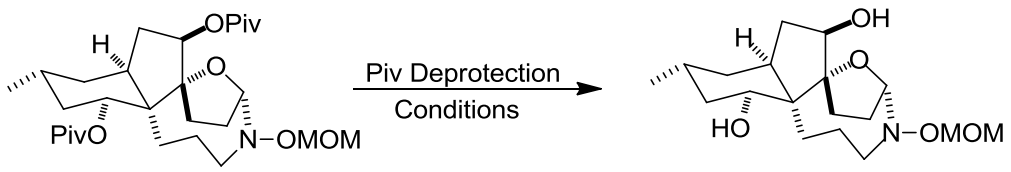


Entry	Cl_3CCN Equivalent	Temp.	Time (h)	Yield (%)
1	3	0 °C to rt	18	31
2	3	rt	18	22
3	5	0 °C to rt	18	55
4	10	0 °C to rt	48	63

2.1.12 Completion of total synthesis of (±)-sieboldine A 1

The final synthetic manipulations included removal of the protecting groups and restoring the ketone functionalities to complete the total synthesis of (±)-sieboldine A **1**. Optimization of the deprotection of Piv groups of **137** under different conditions is shown in table 10. The reductive cleavage with LAH showed the best results and afforded diol **138** in 92% yield.

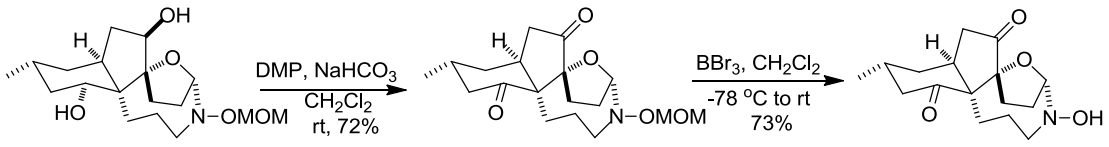
Table 10. Optimization of Piv deprotection of **137**.



137 **138**

Entry	Condition	Solvent	Temp.	Yield (%)
1	DIBAL-H	CH_2Cl_2	-78°C	63
2	K_2CO_3	MeOH	rf	42
3	*t*-BuOK	MeOH/H_2O	rt	45
4	LAH	THF	0 °C to rt	92

Diol **138** was oxidized with DMP to furnish the diketone derivative **139** in 72% yield. Finally, deprotection of the MOM protecting group with BBr_3 delivered (±)-sieboldine A **1** in 73% yield .



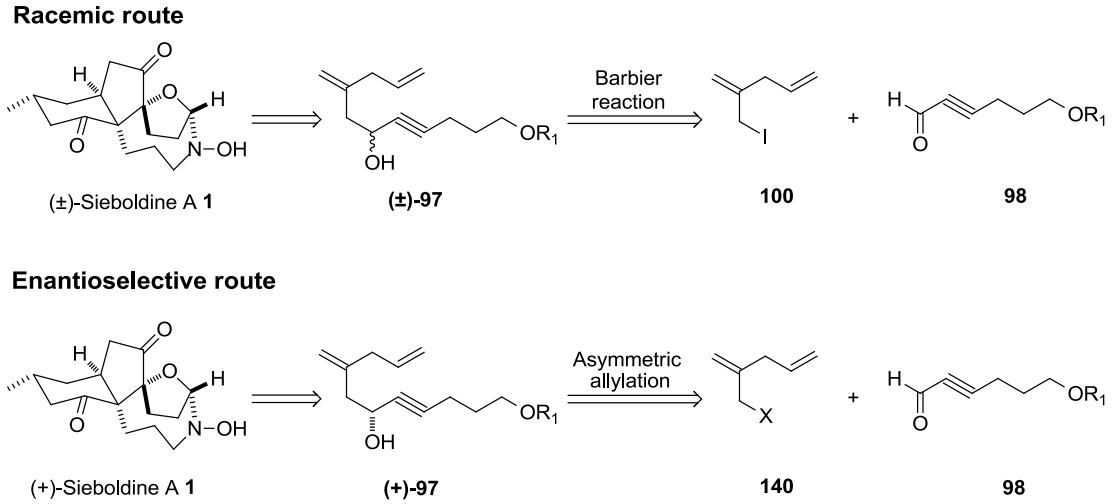
138 139 (±)-Sieboldine A **1**

Scheme 22: Completion of total synthesis of (±)-sieboldine A **1**.

2.2 Total synthesis of (+)-Sieboldine A

2.2.1 Retrosynthetic analysis of (+)-Sieboldine A

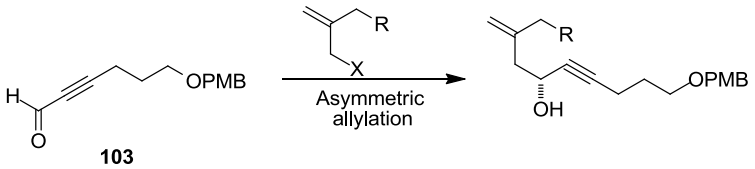
For the preparation of (+)-sieboldine A **1**, we decided to follow the same synthetic steps explored in the racemic route with the exception of employing an optically pure dienyne **97** as a PKR substrate. In the racemic route, we prepared dienyne **97** through a Barbier coupling reaction between aldehyde **98** and iododiene **100**. For induction of chirality, we needed an enantioselective preparation of dienyne (+)-**97** through the asymmetric allylation of aldehyde **98** with a suitable allyl derivative **140**.



Scheme 23: Retrosynthetic analysis of (+)-sieboldine A **1**.

The asymmetric allylation of aldehyde **98** is obviously one of the crucial steps in our synthesis. A parallel research at Mukai's group was concerned with the enantioselective preparation of (+)-**97** through asymmetric allylation of aldehyde **103** (Table 11).[78]

Table 11. Optimization of asymmetric allylation of aldehyde **103**.



Entry[a)]	R	X	Condition	Solvent	Temp.	Yield (%)	ee[b)] (%)
1	-CH=CH$_2$	I	In^0, (+)-Ipc$_2$BCl	THF	-78 °C to rt	7	75

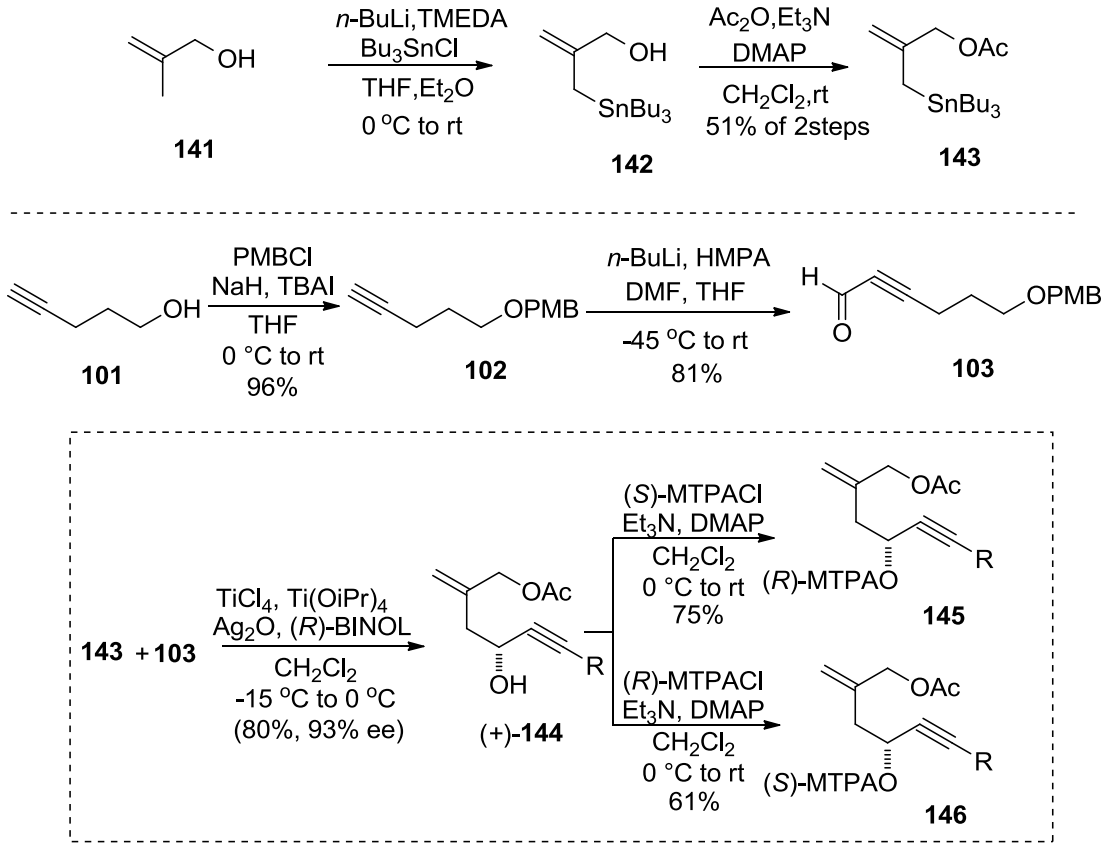
2	-CH=CH_2	I	In^0, (+)-Ipc_2BCl	THF	-98 °C to rt	35	77
3	-OTBDPS	I	In^0, (+)-Ipc_2BCl	THF	-78 °C to rt	15	75
4	-OTBDPS	$SnBu_3$	$TiCl_4$,Ti(O*i*-Pr)$_4$ (*R*)-BINOL	CH_2Cl_2	-15 °C to rt	80	89
5	-OAc	$SnBu_3$	$TiCl_4$,Ti(O*i*-Pr)$_4$ (*R*)-BINOL	CH_2Cl_2	-15 °C to rt	80	93

[a] *Previous work reported by Iida.*[78]
[b] *ee was determined by HPLC analysis (Daicel CHIRALPAK® OD-H).*

Several allyl derivatives and different asymmetric reaction conditions were evaluated to optimize the allylation process in terms of chemical yield and enantiomeric excess (Table 11). The results showed that (+)-**97** could be prepared enantioselectively through a Keck asymmetric allylation of aldehyde **103** with allyl stannate derivatives.[78]

2.2.2 Keck asymmetric allylation of aldehyde 103

Allyl stannate **143** was prepared as described by trost *et al*.[79] 2-Methyl-2-propen-1-ol **141** was reacted with *n*-BuLi, Bu_3SnCl and TMEDA in a mixture of THF/Et_2O and the resulting alcohol **142** was acetylated to afford allyl stannate **143** in 51% yield of two steps. We also optimized the formation of aldehyde **103** from 4-pentyn-1-ol **101** to be conducted in only 2 steps. First, 4-pentyn-1-ol **101** was protected by a PMB group to give pentyne **102** in 96% yield. Second, the direct formylation of **102** under conventional conditions[80] gave the aldehyde **103** in 81% yield.



Scheme 24: Asymmetric allylation of aldehyde **103**.

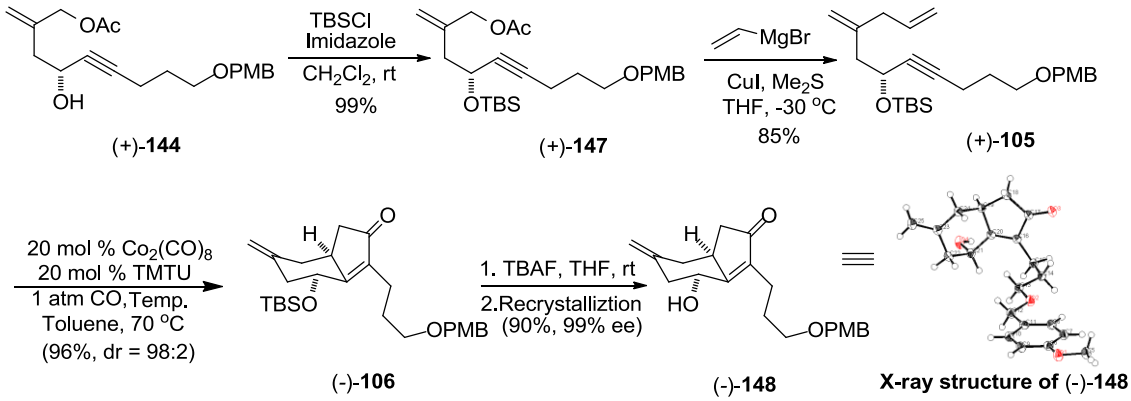
The Keck asymmetric allylation of aldehyde **103** with allyl stannate **143** using the modified Ti(IV) catalyst described by Maruoka *et al.*[81] proceeded smoothly and afforded hydroxyenyne (+)-**144** in 80% yield with 93% ee. The (*R*)-absolute configuration of (+)-**144** was established by NMR spectroscopic considerations based on the differences in chemical shift between the derived Mosher esters **145** and **146**.

2.2.3 Intramolecular PKR of Dienyne (+)-105

The TBS protection of (+)-**144** was followed by treatment with vinyl magnesium bromide to furnish dienyne (+)-**105** in 85% yield of 2 steps. The highly diastereoselective PKR of (+)-**105** was realized under catalytic conditions using 20 mol% of $Co_2(CO)_8$ and 20 mol% of TMTU in toluene at 70 °C under 1 atm of CO to afford the indenone (-)-**106** in 96% yield with dr of 98:2.

Deprotection of the TBS group of (-)-**106** with TBAF provided the alcohol (-)-**148**, which was recrystallized from EtOAc/hexanes to furnish the optically pure (-)-

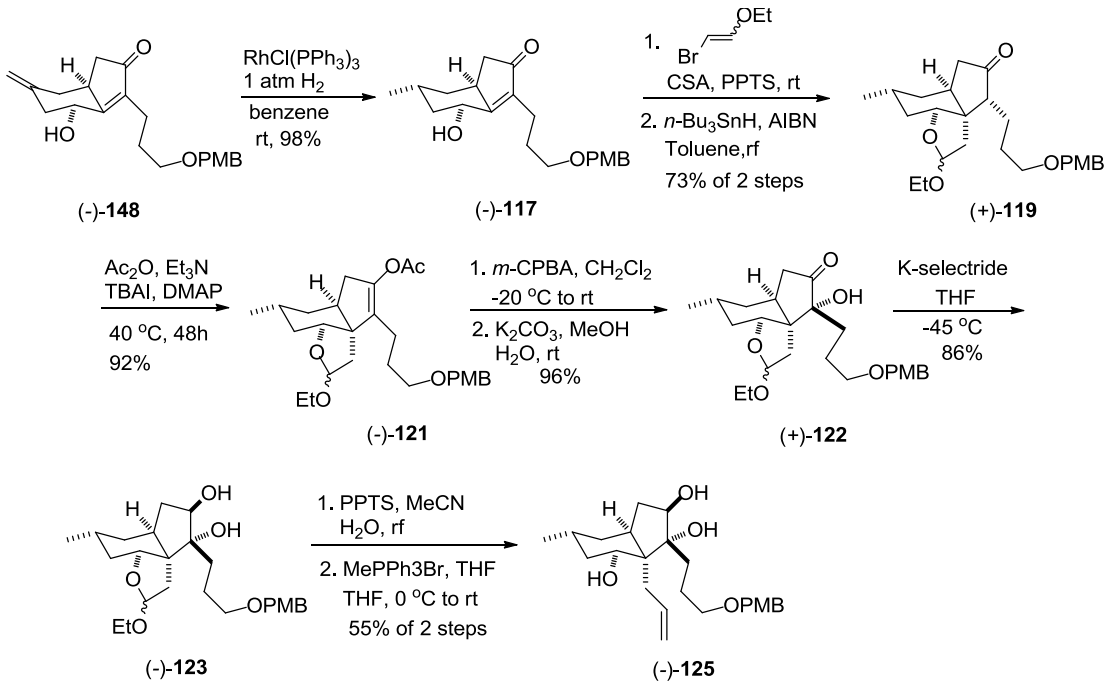
148 in 90% yield (>99% ee). Fortuitously, alcohol (-)-**148** was a crystalline solid and its relative configuration was confirmed by X-ray crystal structure analysis.[82]



Scheme 25: Preparation of alcohol (-)-**148**.

2.2.4 Synthesis of Triol (-)-125

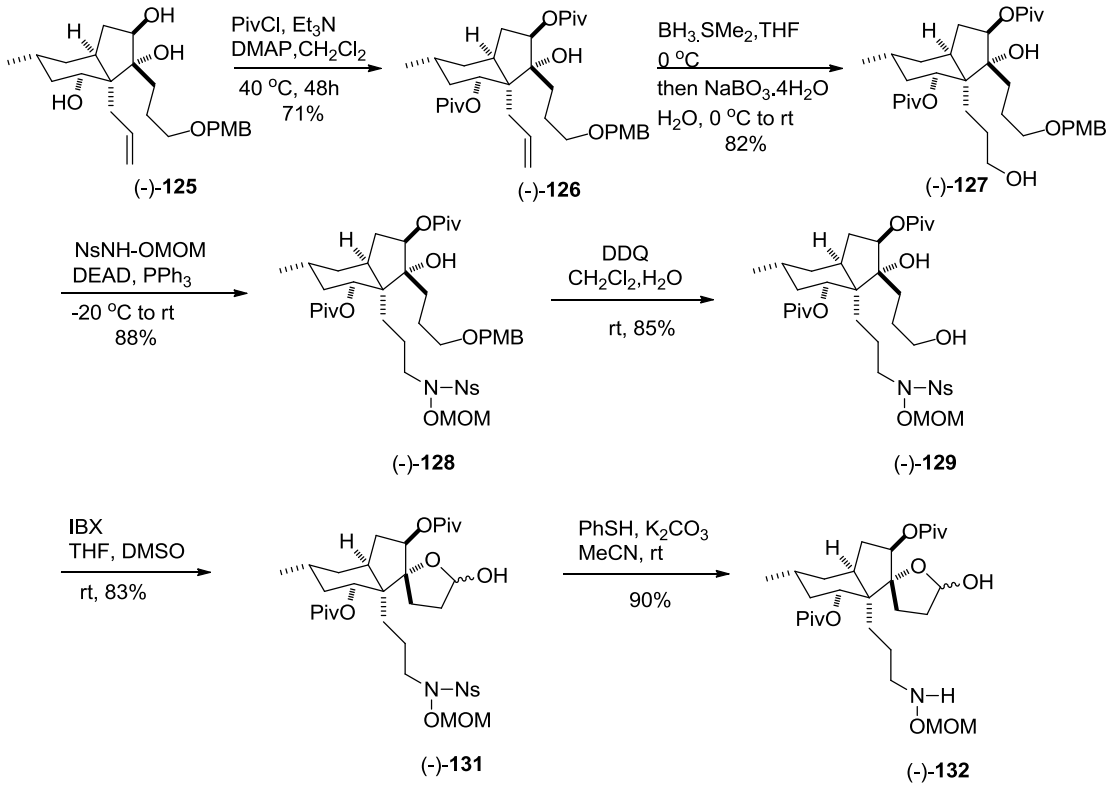
The hydrogenation of (-)-**148** in the presence of Wilkinson's catalyst afforded the methyl derivative (-)-**117** in 98% yield. The Ueno-Stork cascade was applied to (-)-**117** to produce cyclic acetal (+)-**119** in 91% yield with a dr of 3:1. Upon exposure to acetic anhydride in the presence of Et_3N and DMAP at 40 °C, (+)-**119** underwent regioselective acetate enolization to provide the vinyl acetate derivative (-)-**121** in 92% yield. The oxidation of (-)-**121** with *m*-CPBA followed by base promoted hydrolysis gave the α-hydroxy ketone derivative (+)-**122** in 96% yield. The ketone derivative (+)-**122** was temporarily converted to the *trans*-diol derivative (-)-**123** in 86% yield by the stereoselective K-selectride reduction. Compound (+)-**123** was treated with PPTS, and the resulting hemiacetal was subsequently subjected to the Wittig olefination with $MePPh_3Br$ to form the allyltriol (-)-**125** in 55% yield.



Scheme 26: Preparation of triol (-)-**125**.

2.2.5 Synthesis of Aminolactol (-)-132

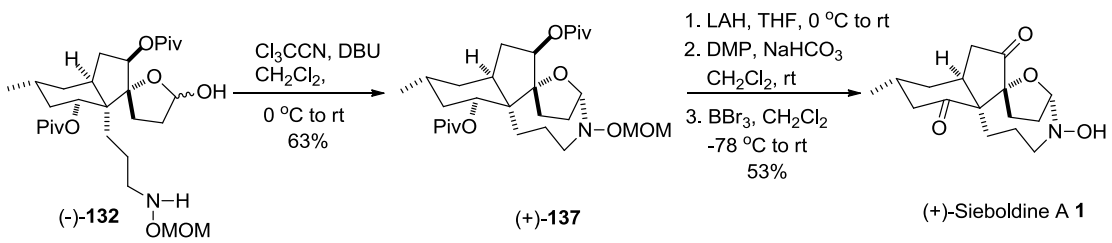
The two secondary hydroxyl groups of triol (-)-**125** were protected with pivaloyl group to provide (-)-**126** in 71% yield, which was subjected to hydroboration followed by oxidation to afford primary alcohol (-)-**127** in 82% yield. The Mitsunobu reaction of (-)-**127** with NsNH-OMOM effected the introduction of the nitrogen atom to give (-)-**128** in 88% yield. The PMB group of (-)-**128** was then removed with DDQ to afford the diol (-)-**129** in 85% yield. Controlled oxidation of (-)-**127** with IBX furnished the spirolactol (-)-**131** in 83% yield. The deprotection of nosyl group of (-)-**131** with thiophenolate produced the aminolactol (-)-**132** in 90% yield.



Scheme 27: synthesis of aminolactol (-)-**132**.

2.2.6 Completion of total synthesis of (+)-sieboldine A

The Schmidt glycosylation of aminolactol (-)-**132** produced the desired tetracyclic derivative (+)-**137** in 63% yield. LAH reduction of (+)-**137** followed by oxidation with DMP furnished the diketone derivative. Finally, the MOM protecting group of the diketone derivative was removed by the commercially available BBr_3, delivering (+)-sieboldine A **1** in 53% yield. The synthetic (+)-**1** exhibited indistinguishable spectral data (^{1}H NMR, ^{13}C NMR, IR, and HRMS) as well as optical rotation (observed $[\alpha]_D$ ^{24} +140, *c* = 0.33, MeOH); lit.$[\alpha]_D$ +139, *c* = 0.3, MeOH) from the natural isolate.[83]



Scheme 28: Completion of total synthesis of (+)-sieboldine A **1**.

2.3 Conclusion

In conclusion, we have completed the highly enantioselective total synthesis of (+)-sieboldine A **1** from 5-(pmethoxybenzyloxy)pentyne in 19 steps with a 1.9% overall yield. The key features of this synthesis include (i) enantioselective Keck allylation to form the optically active enyne (+)-**144**; (ii) PKR to build the bicyclo[4.3.0]nonenone fragment **(-)-106** with a high diastereoselectivity; (iii) Ueno-Stork cyclization to construct the *cis*-hydrindane skeleton with a carbon quaternary center; (iv) regioselective formation of the vinyl acetate moiety followed by oxidation with *m*-CPBA to form the oxa-quaternary center; (v) oxidative cyclization to prepare the spirolactol **(-)-131**; and (vi) Schmidt glycosylation for assembly of the *N*-hydroxyazacyclononane ring. The enantioselective route for construction of the *cis*-hydrindane core is convergent and flexible, thus providing new avenues to access other fawcettimine-type *Lycopodium* alkaloids.

CHAPTER III

Experimental Section

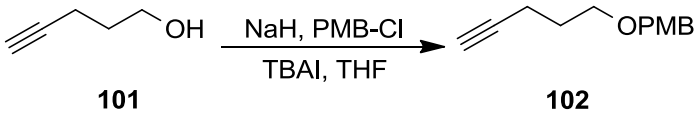
3.1 General notes

All commercially obtained reagents and solvents were used as received unless additional purification is stated in the procedure. All glassware was oven-dried at 150 °C and cooled in desiccator immediately before use. Experiments were conducted under inert atmospheres of Nitrogen or Argon using standard syringe–septa techniques. Reactions performed at room temperature were at approximately 24 °C. Thin layer chromatography (TLC) was performed on Merck analytical glass plates pre-coated with silica gel 60 F254 (0.25 mm thick). Visualization was effected by exposure to UV light (254 nm) and staining with *p*-anisaldehyde or phosphomolybdic acid stains followed by a brief heating on a hot plate. Concentration under reduced pressure was performed by rotary evaporation (~30 mmHg) at 20-40 °C. Flash column chromatography was performed as described by W. C. Still *et al.* (*J. Org. Chem.***1978**, *43*, 2923.) using forced flow of the indicated solvent system on Kanto® Chemical silica gel 60N (spherical, neutral, 40–50 μm,). Melting points were determined on YANAGIMOTO micro melting point apparatus and were uncorrected. Infrared spectra were recorded on a ThermoFisher Nicolet iS5 spectrometer and are reported in terms of frequency of absorption (cm^{-1}). NMR spectra were recorded on JNM-ECS400 or JNM-ECA600 spectrometers. Chemical shift (δ) values are reported in parts per million relative to internal standard tetramethylsilane (δ 0.00 ppm) and residual $CDCl_3$ (δ 7.27 ppm) for proton spectra and to residual $CDCl_3$ (δ 77.23 ppm) for carbon spectra. Coupling constants are reported in Hertz. The following abbreviations were used for spin multiplicity: s, singlet; br s, broad singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublet; ddd, doublet of doublet of doublet; td, triplet of doublet; m, multiplet; br m, broad multiplet. High-resolution mass spectra were measured with JMS-T100TD (DART) mass spectrometer. Optical rotations were

measured with a JASCO P-2200 polarimeter with a sodium lamp and reported as followed: $[\alpha]^{T}_{D}$ (concentration g/100 mL, solvent). Single-crystal X-ray diffraction was measured with R-AXIS RAPID II.

3.2 Synthetic procedures

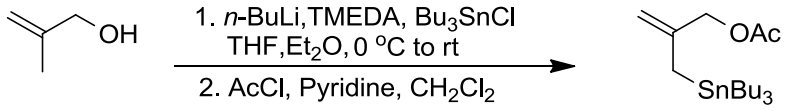
1-Methoxy-4-((pent-4-ynyloxy)methyl)benzene 102



101 **102**

1-Methoxy-4-((pent-4-ynyloxy)methyl)benzene **102** was prepared from 4-pentyn-1-ol **101** according to the method described by Chandrasekhar *et al*.[84]

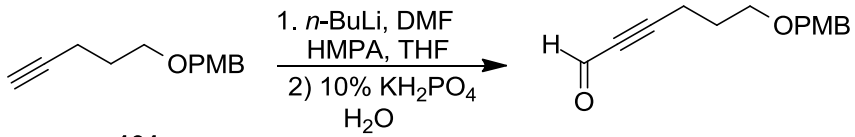
2-((Tributylstannyl)methyl)allyl acetate 143



141 **143**

2-((Tributylstannyl)methyl)allyl acetate **143** was prepared from methallyl alcohol **141** according to the procedure described by Trost and Bonk.[79]

6-((4-Methoxybenzyl)oxy)hex-2-ynal 103

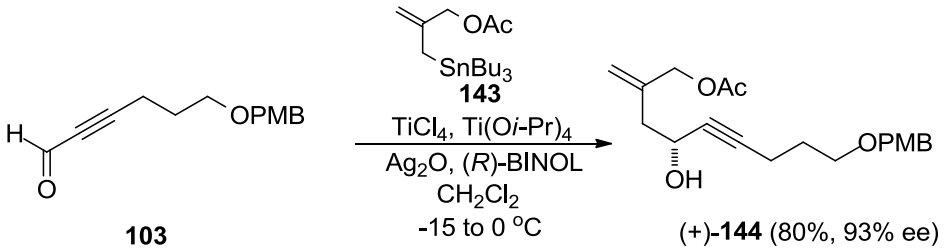


101 **103** (81%)

To a solution of alkyne **101** (10 g, 49 mmol) and hexamethylphosphoramide HMPA (21.5 mL, 122.5 mmol) in THF (100 mL) at -45 °C was added *n*-BuLi (1.43 M in hexane, 51.5 mL, 73.5 mmol). After stirring for 30 min at the same temperature, DMF (15 mL, 196 mmol) was added at once and the reaction mixture was warmed up to room temperature over 1 h. The reaction was quenched with 10% aq KH_2PO_4 (270

mL) and the mixture was partitioned between EtOAc and brine. The layers were separated and the aqueous layer was extracted three times with EtOAc. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography using (hexanes/EtOAc, 6:1) as an eluent to afford aldehyde **103** as pale yellow oil (9.2 g, 81% yield): ^{1}H NMR (600 MHz, $CDCl_3$); δ 9.11 (s, 1H), 7.24 (dd, *J* = 8.2, 4.1, 2H), 6.86 (dd, *J* = 8.6, 4.3, 2H), 4.42 (s, 2H), 3.76 (s, 3H), 3.51 (t, *J* = 6.0, 2H), 2.51 (td, *J* = 7.0, 3.5, 2H), 1.85-1.84 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$); δ 176.9, 159.0, 130.0, 129.0, 113.5, 98.3, 81.5, 72.4, 67.5, 54.9, 27.5, 15.8; IR (thin film, cm^{-1}) 2200, 1664, 1243, 1030; DART HRMS *m/z* $[M+H]^+$ calcd for $C_{14}H_{17}O_3$ 233.1177, found 233.1190.

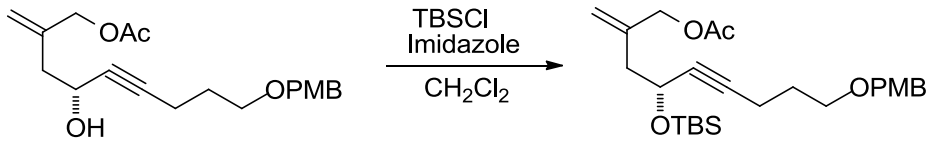
(*R*)-4-Hydroxy-9-((4-methoxybenzyl)oxy)-2-methylenenon-5-yn-1-yl acetate (+)-144



To a stirred solution of $TiCl_4$ (22 μL, 0.2 mmol) in CH_2Cl_2 (3 mL) at 0 °C under argon was added Ti(O*i*-Pr)$_4$ (180 μL, 0.6 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 1 h. Silver(I) oxide Ag_2O (93 mg, 0.4 mmol) was added and the reaction mixture was stirred for 5 h at the same temperature under exclusion of direct light. The reaction mixture was diluted with CH_2Cl_2 (8 mL), and (*R*)-BINOL (229 mg, 0.8 mmol) was added. After stirring for 2 h, the reaction mixture was cooled to -15 °C and a solution of aldehyde **103** (232 mg, 1 mmol) in CH_2Cl_2 (2.5 mL) and a solution of allylstannane **143** (806 mg, 2 mmol) in CH_2Cl_2 (2.5 mL) were added sequentially via cannula. The reaction was allowed to warm to 0 °C and stirred at the same temperature for 10 h. The reaction mixture was quenched with saturated aq $NaHCO_3$ and the heterogeneous suspension was filtered through Celite.® The Celite® was washed thoroughly with Et_2O. The layers were separated and the aqueous layer was extracted three times with Et_2O. The combined

organic extracts were washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography using (hexanes/EtOAc, 2:1) as an eluent to afford alcohol (+)-**144** as colorless oil (277 mg, 80% yield, 93% ee): $[\alpha]^{30}_D$ = +13.2 (*c* 1.1, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$); δ 7.25 (d, *J* = 8.6, 2H), 6.87 (d, *J* = 8.6, 2H), 5.17 (d, *J* = 1.4, 1H), 5.09 (s, 1H), 4.58 (s, 2H), 4.48-4.46 (m, 1H), 4.43 (s, 2H), 3.79 (s, 3H), 3.50 (t, *J* = 6.2, 2H), 2.58 (d, *J* = 5.2, 1H), 2.44 (d, *J* = 10.8, 2H), 2.31 (td, *J* = 7.1, 1.8, 2H), 2.08 (s, 3H), 1.80-1.75 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$); δ 170.6, 159.0, 139.5, 130.3, 129.1, 115.9, 113.6, 85.0, 80.8, 72.4, 68.2, 66.7, 61.0, 55.1, 41.9, 28.5, 20.8, 15.4; IR (thin film, cm^{-1}) 3414, 1696, 1511, 1172; DART HRMS *m/z* $[M+H]^+$ calcd for $C_{20}H_{27}O_5$ 347.1858, found 347.1857; HPLC: Daicel CHIRALPAK® OD-H column; λ = 254 nm; eluent: hexane/isopropanol = 90/10; flow rate: 1.0 mL/min; major enantiomer t_R = 18.0 min, minor enantiomer t_R = 20.2 min; ee = 93%.

(*R*)-4-((*tert*-Butyldimethylsilyl)oxy)-9-((4-methoxybenzyl)oxy)-2-methylenenon-5-yn-1-yl acetate (+)-147

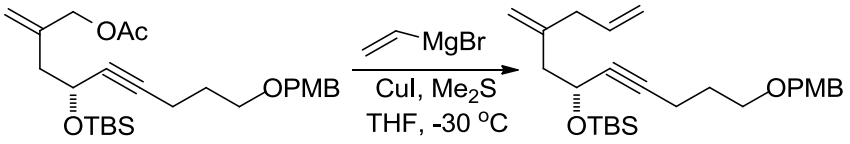


(+)-**144** (+)-**147** (99%)

To a solution of alcohol (+)-**144** (3.1 g, 8.95 mmol) in CH_2Cl_2 (30 mL) were added imidazole (1.8 g, 26.85 mmol) and TBSCl (2.7 g, 17.9 mmol) at room temperature. After stirring for 4 h at the same temperature, the reaction mixture was quenched with water. The layers were separated and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was chromatographed using (hexanes/EtOAc, from 10:1) as an eluent to afford (+)-**147** as colorless oil (4.06 g, 99% yield): $[\alpha]^{30}_D$ = +22.9 (*c* 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$); δ 7.16 (d, *J* = 8.7, 2H), 6.78 (d, *J* = 8.7, 2H), 5.04 (d, *J* = 1.4, 1H), 4.95 (s, 1H), 4.48 (s, 2H), 4.39-4.36 (m, 1H), 4.33 (s, 2H), 3.70 (s, 3H), 3.42 (t, *J* = 6.4, 2H), 2.31 (d, *J* = 6.4, 2H), 2.20 (td, *J* = 7.3, 1.8, 2H), 1.99 (s, 3H), 1.69-1.68 (m, 2H), 0.80 (s, 9H), 0.02 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$);

δ170.5, 159.1, 139.9, 130.5, 129.1, 115.5, 113.7, 84.5, 81.3, 72.6, 68.5, 67.0, 62.4, 55.1, 42.7, 28.7, 25.7, 20.9, 18.1, 15.5, -4.5, -5.1; IR (thin film, cm^{-1}) 1733, 1514, 1249, 1078; DART HRMS *m/z* $[M+H]^+$ calcd for $C_{26}H_{41}O_5Si$ 461.2723, found 461.2730.

(*R*)-*tert*-Butyl((11-((4-methoxybenzyl)oxy)-4-methyleneundec-1-en-7-yn-6-yl)oxy)dimethylsilane (+)-105

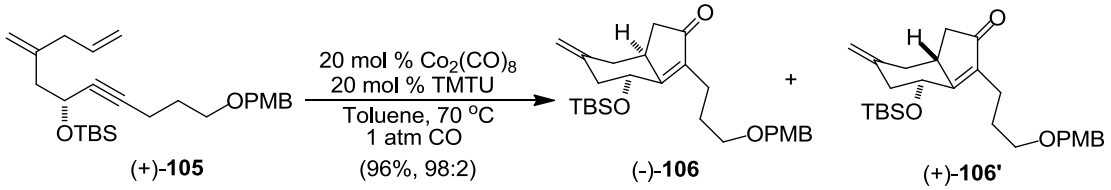


(+)-**147** (+)-**105** (85%)

To a stirred solution of (+)-**147 (**2.3 g, 5 mmol) in THF (18 mL) and dimethylsulfide Me_2S (1.8 mL) at room temperature under argon, was added CuI (190 mg, 1.0 mmol). The reaction mixture was cooled to -30 °C, and vinylmagnesium bromide (10 mL, 10 mmol, 1.0 M in THF) was added slowly over 20 min. After stirring for 30 min at the same temperature, the reaction was quenched with saturated aq $NaHCO_3$ and diluted with Et_2O. The layers were separated and the aqueous layer was extracted three times with Et_2O. The combined organic extracts were washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography using (hexanes/EtOAc, 20:1) as an eluent to afford dienyne (+)-**105** as colorless oil (1.82 g, 85%). $[\alpha]^{30}_D$ = +22.8 (*c* 0.9, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$); δ 7.14 (d, *J* = 8.6, 2H), 6.76 (d, *J* = 8.6, 2H), 5.72-5.67 (m, 1H), 4.96-4.95 (m, 2H), 4.77-4.76 (m, 2H), 4.36-4.35 (m, 1H), 4.32 (s, 2H), 3.66 (s, 3H), 3.41 (t, *J* = 6.4, 2H), 2.71 (d, *J* = 6.9, 2H), 2.27-2.26 (m, 2H), 2.20 (td, *J* = 7.0, 1.7, 2H), 1.69-1.65 (m, 2H), 0.81 (s, 9H), 0.03 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$); δ 159.0, 143.7, 136.0, 130.4, 129.0, 116.1, 113.5, 113.3, 84.0, 81.8, 72.5, 68.4, 62.3, 54.9, 45.1, 40.9, 28.7, 25.7,

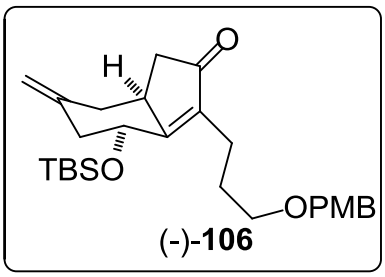
18.1, 15.4, -4.6, -5.1; IR (thin film, cm^{-1}) 2952, 1513, 1248, 1079; DART HRMS *m/z* $[M+H]^+$ calcd for $C_{26}H_{41}O_3Si$ 429.2825, found 429.2827.

(4*R*,7a*S*)-4-((*tert*-Butyldimethylsilyl)oxy)-3-(3-((4-methoxybenzyl)-oxy)propyl)-6-methylene-5,6,7,7a-tetrahydro-1*H*-inden-2(4*H*)-one (-)-106 and (4*R*,7a*R*)-4-((*tert*-butyldimethylsilyl)oxy)-3-(3-((4-methoxybenz-yl)oxy)propyl)-6-methylene-5,6,7,7a-tetrahydro-1*H*-inden-2(4*H*)-one (+)-106'



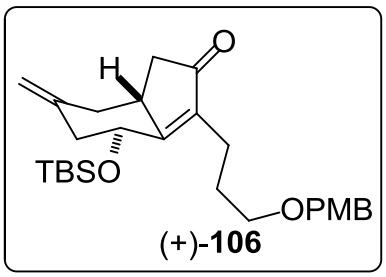
To a stirred solution of dienyne (+)-**105** (4.8 g, 11.2 mmol) in toluene (70 mL) were added $Co_2(CO)_8$ (766 mg, 20 mol %) and tetramethulthiourea TMTU (296 mg, 20 mol %) at room temperature. The reaction was stirred for 4 h at 70 °C under 1 atm CO. The black suspension was concentrated under reduced pressure. The residue was chromatographed with (hexanes/EtOAc, 9:1) eluting first (-)-**106** as colorless oil (4.8 g, 94%) followed by (+)-**106' as** colorless oil (0.1 g, 2%).

(4*R*,7a*S*)-4-((*tert*-Butyldimethylsilyl)oxy)-3-(3-((4-methoxybenzyl)-oxy)propyl)-6-methylene-5,6,7,7a-tetrahydro-1*H*-inden-2(4*H*)-one (-)-106



$[\alpha]^{30}_D$ = -62.1 (*c* 1.0 , $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$); δ 7.18 (d, *J* = 7.6, 2H), 6.79 (d, *J* = 7.6, 2H), 4.82 (s, 2H), 4.71 (s, 1H), 4.34 (s, 2H), 3.72 (s, 3H), 3.36-3.33 (m, 2H), 2.98-2.96 (m, 1H), 2.65 (dd, *J* = 6.5, 3.4, 1H), 2.47 (dd, *J* = 19.2, 6.5, 1H), 2.41 (d, *J* = 13.7, 1H), 2.23-2.22 (m, 2H), 2.09 (d, *J* = 13.7, 1H), 1.88 (d, *J* = 19.2, 1H) 1.71-1.70 (m, 1H), 1.62-1.60 (m, 2H), 0.78 (s, 9H), 0.00 (s, 3H), -0.11 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$); δ 209.1, 173.9, 159.0, 141.8, 136.1, 130.5, 129.0, 113.6, 112.5, 72.3, 69.1, 65.0, 55.1, 43.4, 43.3, 41.1, 36.6, 28.4, 25.5, 19.5, 17.9, -4.8, -4.9; IR (thin film, cm^{-1}) 2928, 1702, 1247, 1071; DART HRMS *m/z* $[M+H]^+$ calcd for $C_{27}H_{41}O_4Si$ 457.2774, found 457.2770.

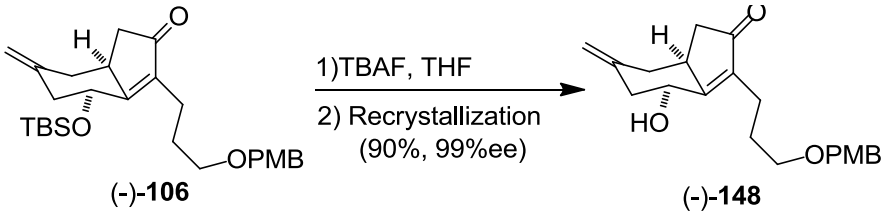
(4*R*,7a*R*)-4-((*tert*-Butyldimethylsilyl)oxy)-3-(3-((4-methoxy-benzyl)oxy)-propyl)-6-methylene-5,6,7,7a-tetrahydro-1*H*-inden-2(4*H*)-one (+)-106'



(+)-**106**

$[\alpha]^{25}_D$ = +21.0 (*c* 3.1 , $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$); δ 7.25-7.23 (m, 2H), 6.85 (d, *J* = 8.6, 2H), 4.83 (s, 2H), 4.47 (dd, *J* = 11.7, 5.5, 1H), 4.41 (d, *J* = 11.6, 1H), 4.39 (d, *J* = 11.6, 1H), 3.79 (s, 3H), 3.42 (t, *J* = 7.0, 2H), 2.64-2.60 (m, 2H), 2.54-2.52 (m, 3H), 2.48-2.45 (m, 1H), 2.24 (t, *J* = 11.9, 1H), 1.96 (d, *J* = 17.2, 1H), 1.77-1.71 (m, 2H), 1.64-1.62 (m, 1H), 0.92 (s, 9H), 0.13 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$); δ 208.4, 173.0, 159.0, 143.2, 138.0, 130.8, 129.3, 113.6, 111.6, 74.3, 72.3, 70.0, 55.2, 45.8, 42.8, 40.5, 39.1, 29.7, 25.9, 19.4, 18.2, -4.6, -5.0; IR (thin film, cm^{-1}) 2952, 1702, 1243, 1093; DART HRMS *m/z* $[M+H]^+$ calcd for $C_{27}H_{41}O_4Si$ 457.2774, found 457.2779.

(4*R*,7a*S*)-4-Hydroxy-3-(3-((4-methoxybenzyl)oxy)propyl)-6-methylene-5,6,7,7a-tetrahydro-1*H*-inden-2(4*H*)-one (-)-148

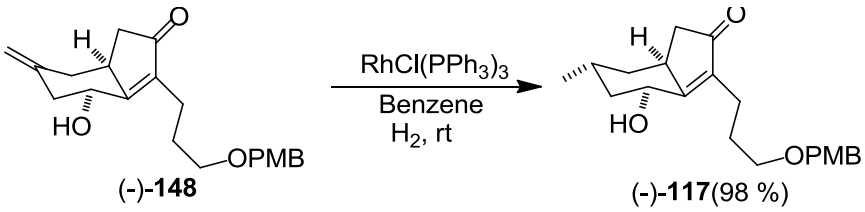


(-)-**106** (-)-**148**

To a solution of indenone (-)-**106** (1.63 g, 3.6 mmol) in THF (36 mL) at room temperature was added tetrabutylammonium fluoride TBAF (5.4 mL, 5.4 mmol, 1.0 M in THF). After stirring for 3 h at the same temperature, the reaction was quenched with saturated aq NH_4Cl and diluted by addition of EtOAc. The layers were separated and the aqueous layer was extracted three times with EtOAc. The combined organic extracts were washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was chromatographed with (hexanes/EtOAc, 2:1) as an eluent. The crude eluted fractions were evaporated and the remaining solid residue was recrystallized from (EtOAc/hexanes) to give (-)-**148** as colorless needles (1.1 g, 90%, 99% ee): $[\alpha]^{30}_D$ = -117.7 (*c* 1.0 , $CHCl_3$); mp = 68-69 °C; ^{1}H NMR (600 MHz, $CDCl_3$); δ 7.23 (d, *J* = 8.6, 2H), 6.86 (d, *J* = 8.6, 2H), 4.98 (brs, 1H), 4.91-4.90 (m, 2H), 4.40 (d, *J* = 11.3, 1H), 4.38 (d, *J* = 11.3, 1H), 3.79 (s, 3H), 3.41 (t, *J* = 6.2, 2H), 3.04-3.00 (m, 1H),

2.79 (d, *J* = 4.8, 1H), 2.73 (dd, *J* = 12.7, 4.5, 1H), 2.60-2.53 (m, 2H), 2.32-2.30 (m, 3H), 1.97 (dd, *J* = 18.7, 1.9, 1H) 1.77-1.72 (m, 3H); ^{13}C NMR (151 MHz, $CDCl_3$); δ 208.7, 172.8, 159.0, 141.6, 137.6, 130.1, 129.2, 113.7, 113.5, 72.0, 68.7, 64.2, 55.1, 42.5, 42.0, 41.0, 36.7, 27.7, 19.2; IR (thin film, cm^{-1}) 3411, 1697, 1512, 1247, 1036; DART HRMS *m/z* $[M+H]^+$ calcd for $C_{21}H_{27}O_4$ 343.1909, found 343.1906; HPLC: Daicel CHIRALPAK® OD-H column; λ = 254 nm; eluent: hexane/isopropanol = 94/6; flow rate: 1.0 mL/min; major enantiomer t_R = 32.9 min; ee = 99%.

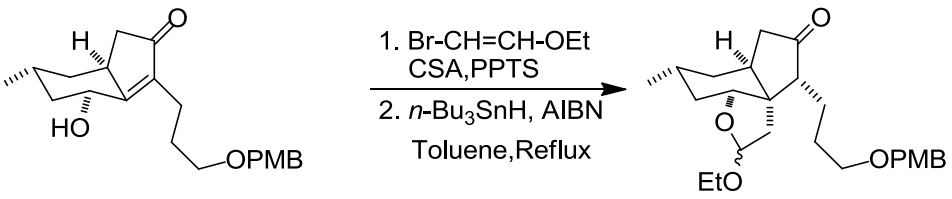
(4*R*,6*R*,7a*S*)-4-Hydroxy-3-(3-((4-methoxybenzyl)oxy)propyl)-6-methyl-5,6,7,7a-tetrahydro-1*H*-inden-2(4*H*)-one (-)-117



(-)-**148** (-)-**117**(98 %)

To a stirred solution of (-)-**148** (5.5 g, 16 mmol) in benzene (60 mL) at room temperature was added $RhCl(PPh_3)_3$ (740 mg, 5 mol %). The reaction was stirred for 6 h at room temperature under 1 atm H_2. The brown mixture was concentrated under reduced pressure and the residue was chromatographed with (hexanes/EtOAc, 1:1) as an eluent to give (-)-**117** as colorless oil (5.4 g, 98%): $[\alpha]^{25}_D$ = -80.4 (*c* 2.2 , $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$); δ 7.22 (d, *J* = 8.6, 2H), 6.87 (d, *J* = 8.6, 2H), 4.83 (brs, 1H), 4.40 (d, *J* = 11.7, 1H), 4.36 (d, *J* = 11.7, 1H), 3.80 (s, 3H), 3.41 (t, *J* = 5.3, 2H), 3.17-3.14 (m, 1H), 3.07 (s, 1H), 2.57 (dd, *J* = 18.9, 6.5, 1H), 2.31 (dd, *J* = 6.8, 6.5, 2H), 2.01-2.00 (m, 1H), 1.95-1.90 (m, 3H), 1.78-1.71 (m, 3H), 1.28-1.27 (m, 4H); ^{13}C NMR (151 MHz, $CDCl_3$); δ 209.6, 175.1, 159.2, 137.4, 129.9, 129.3, 113.7, 71.8, 68.4, 64.2, 55.2, 41.5, 40.2, 37.9, 31.0, 27.0, 26.9, 20.5, 19.1; IR (thin film, cm^{-1}) 3426, 1701, 1512, 1174; DART HRMS *m/z* $[M+H]^+$ calcd for $C_{21}H_{29}O_4$ 345.2065, found 345.2064.

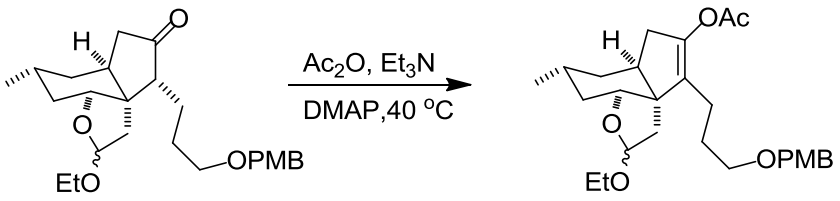
(3a*S*,4R,6a*S*,8*R*,9a*R*)-2-Ethoxy-4-(3-((4-methoxybenzyl)oxy)propyl)-8-methyloctahydroindeno[4,3a-b]furan-5(4*H*)-one (+)-119



(-)-**117** (+)-**119**(91 %)

Pyridinium *p*-toluenesulfonate PPTS (263 mg, 1.05 mmol) and camphorsulfonic acid CSA (244 mg, 1.05 mmol) were added to a solution of alcohol (-)-**117** (1.8 g, 5.23 mmol) and (*Z*/*E*)-2-bromovinyl ethyl ether[85] (3.15 g, 20.9 mmol) at room temperature. After stirring for 2 h, the reaction was diluted by Et_2O and quenched with saturated aq $NaHCO_3$ at 0 °C. The layers were separated and the aqueous layer was extracted three times with Et_2O. The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was passed through a short pad of silica gel using (hexanes/EtOAc, from 10:1 to 3:1) as an eluent. The crude eluted fractions were evaporated and dissolved in toluene. Tributyltin hydride *n*-Bu_3SnH (7.0 mL, 26.15 mmol) and Azobisisobutyronitrile AIBN were added (0.43 g, 2.62 mmol) at room temperature. The reaction was heated under reflux for 4 h. The solvent was evaporated under reduced pressure and the residue was chromatographed with (hexanes/EtOAc, from 6:1 to 2:1) to afford cyclic acetal (+)-**119** as colorless oil (1.97 g, 91%, two diastereomers, 3:1): $[\alpha]^{25}_D$ = +3.4 (*c* 1.9 , $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$, major isomer); δ 7.25-7.24 (m, 2H), 6.87 (d, *J* = 8.6, 2H), 5.12 (dd, *J* = 5.7, 2.6, 1H), 4.41 (s, 2H), 3.95 (t, *J* = 5.3, 1H), 3.80 (s, 3H), 3.75-3.71 (m, 1H), 3.46-3.41 (m, 3H), 2.44 (dd, *J* = 19.2, 8.9, 1H), 2.36-2.35 (m, 1H), 2.26 (dd, *J* = 9.3, 4.8, 1H), 2.00-1.96 (m, 2H), 1.89-1.87 (m, 2H), 1.77-1.73 (m, 2H), 1.68-1.64 (m, 1H), 1.53-1.45 (br m, 3H), 1.39-1.34 (m, 1H), 1.28-1.25 (m, 1H), 1.17 (t, *J* = 7.0, 3H), 1.07 (d, *J* = 6.9, 3H); ^{13}C NMR (151 MHz, $CDCl_3$, major isomer); δ 219.4, 159.1, 130.6, 129.2, 113.7, 102.0, 78.7, 72.4, 69.9, 62.9, 55.2, 52.3, 50.0, 42.1, 38.0, 33.8, 33.6, 33.4, 27.8, 24.9, 23.2, 20.7, 15.3; IR (thin film, cm^{-1}) 2924, 1736, 1513, 1247, 1098; DART HRMS *m/z* $[M+H]^+$ calcd for $C_{25}H_{37}O_5$ 417.2641, found 417.2639.

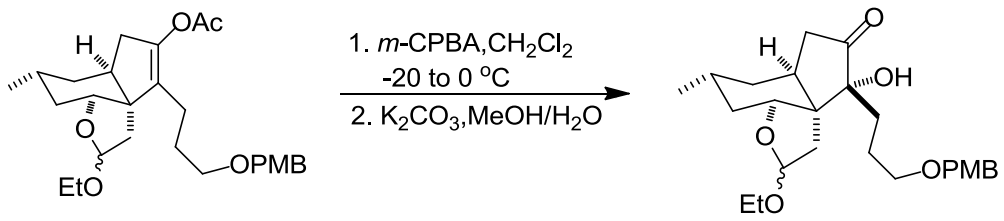
(3a*S*,6a*S*,8*R*,9a*R*)-2-Ethoxy-4-(3-((4-methoxybenzyl)oxy)propyl)-8-methyl-2,3,6,6a,7,8,9,9a-octahydroindeno[4,3a-b]furan-5-yl acetate (-)-121



(+)-**119** (-)-**121** (92%)

Dimethylaminopyridine DMAP (410.5 mg, 3.36 mmol) and Et_3N (11.6 mL, 84 mmol) were added to a solution of (+)-**119** (3.5 g, 8.4 mmol) and acetic anhydride (23.8 mL, 252 mmol) at room temperature. The reaction mixture was stirred at 40 °C for 48 h. The color changed from pale yellow to dark brown during the course of the reaction. The reaction was diluted by EtOAc at 0 °C and quenched with saturated aq $NaHCO_3$. The heterogeneous mixture was filtered through Celite® and the Celite® was washed thoroughly with EtOAc. The layers were separated and the aqueous layer was extracted three times with EtOAc. The combined organic layers were washed with saturated aq copper(II) sulfate and brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography using (hexanes/EtOAc, from 9:1 to 6:1) as an eluent to afford vinyl acetate derivative (-)-**121** as pale yellow oil (3.54 g, 92%, two diastereomers, 3:1): $[\alpha]^{24}_D$ = -13.1 (*c* 1.5, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$, major isomer); δ 7.26 (d, *J* = 8.6, 2H), 6.87 (d, *J* = 8.6, 2H), 5.11 (dd, *J* = 6.0, 3.3, 1H), 4.41 (s, 2H), 4.05 (t, *J* = 4.6, 1H), 3.80 (s, 3H), 3.75-3.73 (m, 1H), 3.45-3.40 (m, 3H), 2.57 (dd, *J* = 15.1, 7.9, 1H), 2.18-2.13 (br m, 5H), 2.08 (s, 3H), 1.92 (dd, *J* = 13.9, 3.3, 1H), 1.77-1.68 (m, 4H), 1.60-1.56 (m, 1H), 1.48-1.46 (m, 1H), 1.39-1.34 (m, 1H), 1.17 (t, *J* = 7.0, 3H), 1.03 (d, *J* = 6.9, 3H); ^{13}C NMR (151 MHz, $CDCl_3$, major isomer); δ 168.7, 159.0, 146.1, 130.7, 129.1, 128.4, 113.7, 102.2, 78.0, 72.3, 69.8, 63.1, 55.2, 54.1, 44.0, 39.0, 35.3, 33.7, 32.7, 28.5, 23.9, 21.7, 20.8, 20.5, 15.3; IR (thin film, cm^{-1}) 3292, 1754, 1512, 1246, 1100; DART HRMS *m/z* $[M+H]^+$ calcd for $C_{27}H_{39}O_6$ 459.2747, found 459.2749.

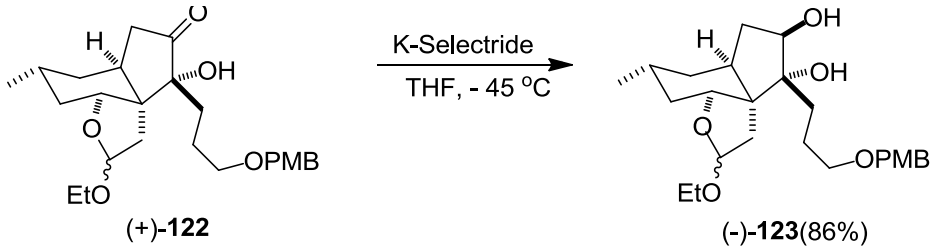
(3a*R*,4*R*,6a*S*,8*R*,9a*R*)-2-Ethoxy-4-hydroxy-4-(3-((4-methoxybenzyl)-oxy)propyl)-8-methyloctahydroindeno[4,3a-b]furan-5(4*H*)-one (+)-122



(-)-**121** (+)-**122** (96%)

To a solution of (-)-**121** (2.0 g, 4.36 mmol) in CH_2Cl_2 (40 mL) at -20 °C was added a solution of *m*-CPBA (2.26 g, 13.0 mmol) in CH_2Cl_2 (25 mL). The reaction mixture was gradually warmed to 0 °C and stirred for 2 h at the same temperature. The reaction was quenched with saturated aq $NaHCO_3$ and $Na_2S_2O_3$. The layers were separated and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was dissolved in MeOH/H_2O (15 mL: 1.5 mL). Potassium carbonate K_2CO_3 (241 mg, 1.74 mmol) was added and the reaction mixture was stirred for 4 h at room temperature. The reaction mixture was partitioned between EtOAc and brine. The layers were separated and the aqueous layer was extracted three times with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography using (hexanes/EtOAc, 4:1) as an eluent to give α-hydroxy ketone (+)-**122** as colorless oil (1.8 g, 96% yield, two diastereomers, 3:1): $[\alpha]^{24}_D$ = +42.5 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, major isomer); δ 7.23 (d, *J* = 8.7, 2H), 6.87 (d, *J* = 8.7, 2H), 5.05 (dd, *J* = 6.4, 4.6, 1H), 4.94 (s, 1H), 4.49 (d, *J* = 11.4, 1H), 4.42 (d, *J* = 11.4, 1H), 3.80 (s, 3H), 3.77-3.74 (m, 1H), 3.55-3.53 (m, 2H), 3.45-3.42 (m, 2H), 2.83-2.80 (m, 1H), 2.71 (dd, *J* = 14.7, 6.4, 1H), 2.63 (dd, *J* = 19.5, 10.3, 1H), 2.15-2.10 (m, 1H), 2.04-1.92 (m, 1H), 1.87-1.84 (m, 4H), 1.51-1.44 (m, 4H), 1.35-1.31 (m, 1H), 1.21 (t, *J* = 7.1, 3H), 0.92 (d, *J* = 5.5, 3H); ^{13}C NMR (151 MHz, $CDCl_3$, major isomer); δ 215.8, 159.3, 129.6, 129.5, 113.8, 104.5, 80.4, 77.4, 72.7, 70.8, 63.5, 56.0, 55.2, 39.5, 39.2, 34.8, 33.6, 32.9, 28.3, 24.0, 22.9, 21.9, 15.4; IR (thin film, cm^{-1}) 3357, 1741, 1246, 1090; DART HRMS *m/z* $[M+H]^+$ calcd for $C_{25}H_{37}O_6$ 433.25901, found 433.25905.

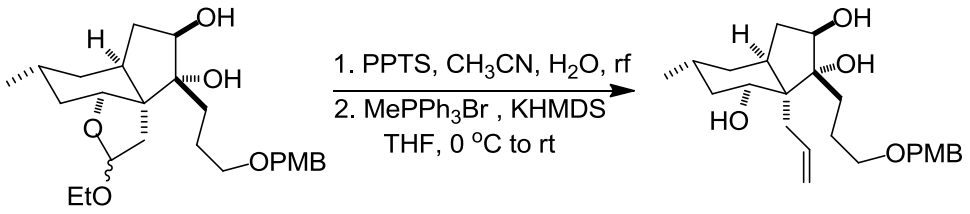
(3a*R*,4*R*,5*R*,6a*S*,8*R*,9a*R*)-2-Ethoxy-4-(3-((4-methoxybenzyl)oxy)-propyl)-8-methyldecahydroindeno[4,3a-b]furan-4,5-diol (-)-123



(+)-**122** (-)-**123**(86%)

K-Selectride (5.5 mL, 5.5 mmol, 1.0M solution in THF) was added dropwise to a solution of (+)-**122** (1.8 g, 4.16 mmol) in THF (40 mL) at -45 °C under argon. After stirring for 6h at the same temperature, the reaction was quenched with 3 M aq NaOH and 30% aq H_2O_2. The mixture was diluted with EtOAc and the layers were separated. The aqueous layer was extracted three times with EtOAc. The combined organic extracts were washed with saturated aq $Na_2S_2O_3$ and brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography using (hexanes/EtOAc, from 2:1 to 1:1) as an eluent to give *trans*-diol (-)-**123** as colorless oil (1.54 g, 86% yield, two diastereomers, 3:1): $[\alpha]^{24}_D$ = -9.3 (*c* 0.8, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$); δ 7.24-7.23 (m, 2H), 6.88-6.87 (m, 2H), 5.12-5.04 (m, 1H), 4.49-4.45 (m, 3H) 4.00-3.98 (m, 1H), 3.80 (d, *J* = 10.0, 3H), 3.77-3.73 (m, 1H), 3.49-3.43 (m, 3H), 2.63-2.62 (m, 1H), 2.54-2.48 (m, 2H), 2.41-2.38 (m, 1H), 2.15-2.08 (m, 2H), 1.83-1.76 (m, 4H), 1.61-1.59 (m, 1H), 1.46-1.44 (m, 1H), 1.34-1.29 (m, 4H), 1.21-1.18 (m, 3H), 0.91-0.89 (m, 3H); ^{13}C NMR (151 MHz, $CDCl_3$); δ 159.2, 129.6, 129.5, 129.4, 113.8, 103.9, 102.4, 86.0, 85.6, 77.9, 77.4, 77.2, 72.9, 72.8, 70.6, 70.3, 63.4, 63.3, 57.3, 55.2, 54.8, 40.0, 39.6, 38.4, 37.8, 37.4, 36.8, 36.2, 34.1, 34.0, 28.8, 27.5, 24.3, 23.9, 23.8, 22.1, 22.0, 15.4; IR (thin film, cm^{-1}) 3430, 1512, 1301, 1091; DART HRMS *m/z* $[M+H]^+$ calcd for $C_{25}H_{39}O_6$ 435.2746, found 435.2742.

(1*R*,2*R*,3a*S*,5*R*,7*R*,7a*R*)-7a-Allyl-1-(3-((4-methoxybenzyl)oxy)-propyl)-5-methyloctahydro-1*H*-indene-1,2,7-triol (-)-125

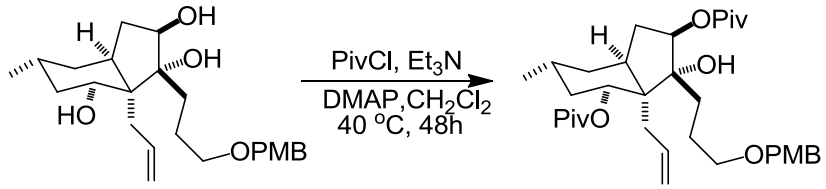


(-)-**123** (-)-**125** (55%)

PPTS (123 mg, 0.49 mmol) was added to a solution of (-)-**123** (1.06 g, 2.44 mmol) in CH_3CN/H_2O (10 mL: 2 mL) at room temperature. The reaction mixture was heated under reflux for 4 h. The reaction was quenched with saturated aq $NaHCO_3$ and the mixture was partitioned between EtOAc and brine. The layers were separated and the aqueous layer was extracted three times with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was passed through a short pad of silica gel using (hexanes/EtOAc, 1:2) as an eluent. The crude eluted fractions were evaporated, dissolved in THF (10 mL) and cooled at 0°C. In a previously prepared second flask, methyltriphenylphosphonium bromide PPh_3MeBr (6.1 g, 17.08 mmol) was dried at 80 °C under vacuum for 3 hours. After the salt has cooled THF (24 mL) was added and the slurry was cooled to 0 °C under argon. Potassium bis(trimehtylsilyl)amide KHMDS (16.8 mL, 16.8 mmol, 1.0 M in THF) was added dropwise at the same temperature resulting in a bright yellow color. After stirring for 30 min at the same temperature, the bright yellow ylide slurry was cannulated to the first reaction flask at 0°C under argon. The reaction mixture was stirred at the same temperature for 2h then warmed gradually to room temperature and stirred overnight. The reaction was quenched with saturated aq NH_4Cl and the mixture was diluted with EtOAc. The layers were separated and the aqueous layer was extracted three times with EtOAc. The combined organic extracts were washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography with (hexanes/EtOAc, 2:1) as eluent to afford triol (-)-**125** as colorless oil (0.54 g, 55% yield): $[\alpha]^{24}_D$ = -13.4 (*c* 0.8, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$); δ 7.26-7.24 (m, 2H), 6.87 (d, *J* = 9.3, 2H), 6.22-6.15 (m, 1H), 5.14 (dd, *J* = 17.2, 1.7, 1H), 5.03 (dd, *J* = 10.0, 1.7, 1H), 4.49 (d, *J* = 11.7, 1H), 4.46 (d, *J* = 11.7, 1H), 4.31-4.27 (m, 1H), 3.94-3.93 (m, 1H), 3.80 (s, 3H), 3.57-3.54 (m, 1H), 3.46 (td, *J* = 8.5, 3.9, 1H), 3.33

(d, *J* = 2.7, 1H) 2.53-2.49 (m, 2H), 2.35-2.31 (m, 1H), 2.29-2.25 (m, 1H), 2.17 (s, 1H), 2.15-2.10 (m, 1H), 1.93-1.88 (m, 1H), 1.84-1.80 (m, 2H), 1.75-1.74 (m, 1H), 1.67-1.64 (m, 1H), 1.49-1.44 (m, 2H), 1.19-1.16 (m, 2H), 1.12-1.09 (m, 1H), 0.92 (d, *J* = 6.5, 3H); ^{13}C NMR (151 MHz, $CDCl_3$); δ 159.3, 139.1, 129.8, 129.5, 116.5, 113.8, 89.3, 77.8, 72.8, 70.1, 69.2, 55.2, 53.0, 41.3, 39.7, 36.0, 32.5, 32.1, 29.4, 25.6, 24.0, 22.1; IR (thin film, cm^{-1}) 3424, 1513, 1247, 1035; DART HRMS *m/z* $[M+H]^+$ calcd for $C_{24}H_{37}O_5$ 405.2641, found 405.2640.

(2*R*,3*R*,3a*R*,4*R*,6*R*,7a*S*)-3a-Allyl-3-hydroxy-3-(3-((4-methoxybenzyl)-oxy)propyl)-6-methyloctahydro-1*H*-indene-2,4-diyl bis(2,2-dimethyl-propanoate) (-)-126

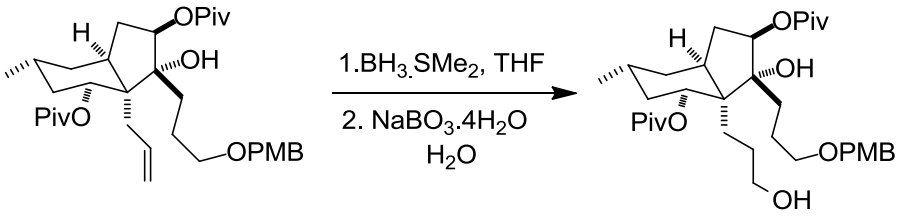


(-)-**125** (-)-**126** (71%)

DMAP (35.5 mg, 0.29 mmol) and Et_3N (8 mL, 58 mmol) were added to a solution of triol (-)-**125** (235 mg, 0.58 mmol) in CH_2Cl_2 (4 mL) at room temperature. The reaction was cooled to 0 °C and pivaloyl chloride (7.1 mL, 58 mmol) was added dropwise. After the addition, the reaction was stirred at 0 °C for 1 h and then warmed to 40 °C and stirred for 48 h. The reaction mixture was diluted with CH_2Cl_2 at 0 °C and quenched with saturated aq $NaHCO_3$. The layers were separated and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic layers were washed with saturated aq copper(II) sulfate and brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography using (hexanes/EtOAc, from 18:1 to 6:1) as an eluent to afford (-)-**126** as colorless oil (234.5 mg, 71% yield)): $[\alpha]^{25}_D$ = -17.8 (*c* 3.3, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$); δ 7.22 (d, *J* = 8.6, 2H), 6.86 (d, *J* = 8.6, 2H), 6.19-6.15 (m, 1H), 5.22 (dd, *J* = 11.5, 4.6, 1H), 5.12 (dd, *J* = 17.0, 1.5, 1H), 5.03 (dd, *J* = 10.1, 1.5, 1H), 4.80 (dd, *J* = 8.2, 3.1, 1H), 4.42 (d, *J* = 11.3, 1H), 4.39 (d, *J* = 11.3, 1H), 3.80 (s, 3H), 3.48-3.44 (m, 1H), 3.39 (br s, 1H), 3.34-3.30 (m, 1H), 2.65-2.63 (m, 1H), 2.55 (dd, *J* = 15.1, 7.2, 1H), 2.50-2.45 (m, 2H), 1.77-1.75 (m, 1H), 1.70-1.66 (m, 3H), 1.62-1.61 (m, 1H), 1.46-1.43 (m, 2H), 1.35-1.31 (m, 2H), 1.21 (s, 9H), 1.17 (s, 9H), 1.11-1.06

(m, 1H), 0.90 (d, J = 6.5, 3H); ^{13}C NMR (151 MHz, $CDCl_3$); δ 177.4, 177.2, 159.2, 138.3, 130.0, 129.3, 116.4, 113.7, 88.1, 79.0, 72.7, 72.4, 70.5, 55.2, 51.8, 40.1, 38.8, 36.5, 35.5, 33.2, 32.6, 30.3, 27.1, 27.0, 26.8, 25.2, 24.0, 21.9; IR (thin film, cm^{-1}) 3443, 2924, 1721, 1158; DART HRMS *m/z* $[M+H]^+$ calcd for $C_{34}H_{53}O_7$ 573.3791, found 573.3794.

(2*R*,3*R*,3a*R*,4*R*,6*R*,7a*S*)-3-Hydroxy-3a-(3-hydroxypropyl)-3-(3-((4-methoxy-benzyl)oxy)propyl)-6-methyloctahydro-1*H*-indene-2,4-diylbis(2,2-dimethyl propanoate) (-)-127

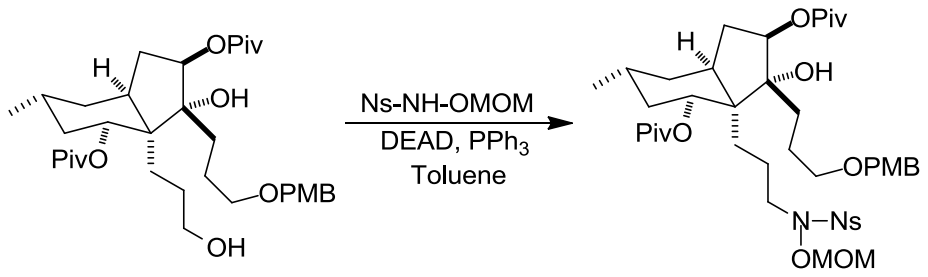


(-)-**126** (-)-**127** (82%)

Borane dimethyl sulfide complex $BH_3.SMe_2$ (0.5 mL, 4.95 mmol) was added to a solution of allyl derivative (-)-**126** (566 mg, 0.99 mmol) in THF (10 mL) at 0 °C under argon. After stirring for 2 h at the same temperature, water H_2O (2 mL) and $NaBO_3.4H_2O$ (762 mg, 4.95 mmol) were added. The reaction was warmed to room temperature and stirred for 4 h. The reaction mixture was partitioned between EtOAc and brine and the layers were separated. The aqueous layer was extracted three times with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was chromatographed using (hexanes/EtOAc, from 2:1 to 1:1) as an eluent to afford primary alcohol (-)-**127** as colorless oil (480 mg, 82% yield): $[\alpha]^{25}_D$ = -19.8 (*c* 3.0, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$); δ 7.23 (d, J = 8.2, 2H), 6.87 (d, J = 8.2, 2H), 5.21 (dd, J = 11.5, 4.6, 1H), 4.81 (dd, J = 8.9, 3.4, 1H), 4.43 (d, J = 11.5, 1H), 4.39 (d, J = 11.5, 1H), 3.81 (s, 3H), 3.64-3.63 (m, 2H), 3.50-3.47 (m, 2H), 3.33-3.31 (m, 1H), 2.65-2.62 (m, 1H), 2.51-2.45 (m, 1H), 1.95-1.93 (m, 1H), 1.77-1.69 (m, 4H), 1.66-1.61 (m, 5H), 1.50-1.48 (m, 2H), 1.32-1.26 (m, 3H), 1.21 (s, 9H), 1.16 (s, 9H), 0.89 (d, J = 6.5, 3H); ^{13}C NMR (151 MHz, $CDCl_3$); δ 177.4, 177.3, 159.3, 129.8, 129.4, 113.8, 87.9, 79.5, 72.8, 72.7, 70.5, 64.3, 55.3, 50.9, 40.4, 38.8, 38.5, 36.6, 35.6, 33.5, 30.2, 29.2, 27.1, 26.8,

25.2, 24.6, 24.1, 21.9; IR (thin film, cm^{-1}) 3426, 1721, 1284, 1156; DART HRMS *m/z* $[M+H]^+$ calcd for $C_{34}H_{55}O_8$ 591.3897, found 591.3890.

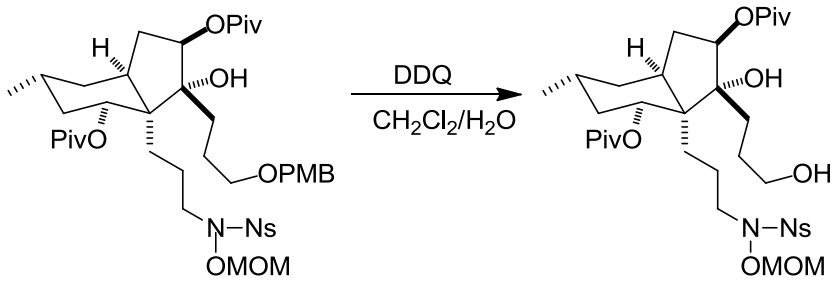
(2*R*,3*R*,3a*R*,4*R*,6*R*,7aS)-3-Hydroxy-3-(3-((4-methoxybenzyl)-oxy)propyl)-3a-(3-(N-(methoxymethoxy)-2-nitrophenylsulfonamido)-propyl)-6-methyloctahydro-1*H*-indene-2,4-diyl bis(2,2-dimethyl-propanoate) (-)-128



(-)-**127** (-)-**128** (88%)

N-(Methoxymethoxy)-2-nitrobenzenesulfonamide[19] Ns-NH-OMOM (47 mg, 0.18 mmol) and triphenylphosphine (168 mg, 0.64 mmol) were added to a solution of primary alcohol (-)-**127** (94 mg, 0.16 mmol) in toluene (3 mL) at -20 °C. Diethyl azodicarboxylate DEAD (348 μL, 0.8 mmol, 40% in toluene) was added dropwise to the reaction mixture at the same temperature. The yellow suspension was warmed gradually to room temperature and stirred for 1 h. The orange suspension was concentrated under reduced pressure and the residue was chromatographed with (hexanes/Et_2O, from 1:1 to 1:2) to afford (-)-**128** as pale yellow oil (114 mg, 88%): $[\alpha]^{25}_D$ = -39.2 (*c* 1.5, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$); δ 8.04 (dd, *J* = 7.9, 1.0, 1H), 7.79-7.72 (m, 2H), 7.59 (dd, *J* = 7.7, 1.2, 1H), 7.20 (d, *J* = 8.6, 2H), 6.86 (d, *J* = 8.6, 2H), 5.19 (dd, *J* = 11.5, 4.6, 1H), 5.02 (d, *J* = 8.3, 1H), 4.99 (d, *J* = 8.3, 1H), 4.79 (dd, *J* = 8.6, 3.1, 1H), 4.40 (d, *J* = 11.0, 1H), 4.38 (d, *J* = 11.0, 1H), 3.80 (s, 3H), 3.49-3.44 (m, 1H), 3.43 (s, 3H), 3.33-3.32 (m, 1H), 3.24-3.23 (m, 2H), 2.62-2.58 (m, 1H), 2.49-2.45 (m, 1H), 2.07-2.04 (m, 1H), 1.78-1.75 (m, 3H), 1.63-1.62 (m, 3H), 1.49-1.43 (m, 2H), 1.29-1.26 (m, 4H), 1.21 (s, 9H), 1.15 (s, 9H), 1.10-1.06 (m, 2H), 0.89 (d, *J* = 6.5, 3H); ^{13}C NMR (151 MHz, $CDCl_3$); δ 177.4, 177.3, 159.2, 149.8, 134.8, 132.3, 130.9, 130.0, 129.2, 126.6, 123.8, 113.7, 102.7, 87.9, 79.3, 72.7, 72.6, 70.5, 57.6, 55.3, 54.5, 51.0, 39.8, 38.8, 36.5, 35.5, 33.3, 30.2, 29.7, 27.1, 26.8, 25.5, 25.2, 24.2, 23.2, 21.8; IR (thin film, cm^{-1}) 3372, 2923, 1722, 1178; DART HRMS *m/z* $[M+H]^+$ calcd for $C_{42}H_{63}N_2O_{13}S$ 835.4051, found 835.4050.

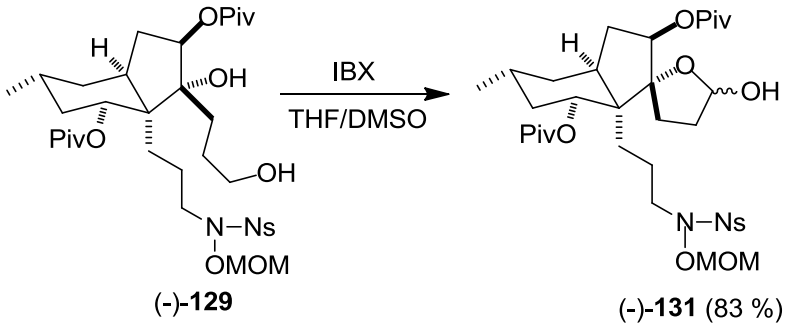
(2*R*,3*R*,3a*R*,4*R*,6*R*,7a*S*)-3-Hydroxy-3-(3-hydroxypropyl)-3a-(3-(N-(methoxymethoxy)-2-nitrophenylsulfonamido)propyl)-6-methyloctahydro-1*H*-indene-2,4-diyl bis(2,2-dimethylpropanoate) (-)-129



(-)-**128** (-)-**129** (85 %)

2,3-Dichloro-5,6-dicyano-1,4-benzoquinone DDQ (102 mg, 0.45 mmol) was added to a solution of (-)-**128** (250 mg, 0.3 mmol) in CH_2Cl_2/H_2O (4 mL: 1 mL) at room temperature. After stirring for 4 h at the same temperature, the reaction was quenched with saturated aq $NaHCO_3$. The layers were separated and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic layers were washed with H_2O and brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography using (hexane/EtOAc, from 1:1 to 1:2) as an eluent to afford diol (-)-**129** as pale yellow oil (182 mg, 85% yield): $[\alpha]^{25}_D$ = -12.2 (*c* 0.22, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$); δ 8.05 (dd, *J* = 7.9, 2.1, 1H), 7.82-7.79 (m, 1H), 7.77-7.76 (m, 1H), 7.60 (d, *J* = 7.9, 1H), 5.21 (dd, *J* = 11.5, 4.6, 1H), 5.06 (d, *J* = 7.9, 1H), 5.01 (d, *J* = 7.9, 1H), 4.82 (dd, *J* = 8.1, 2.9, 1H), 3.70-3.68 (m, 1H), 3.55-3.53 (m, 1H), 3.47 (s, 3H), 3.28-3.21 (m, 3H), 2.62-2.59 (m, 1H), 2.50-2.44 (m, 1H), 2.07-2.05 (m, 1H), 1.84-1.75 (m, 5H), 1.64-1.63 (m, 2H), 1.50-1.44 (m, 2H), 1.34-1.25 (m, 3H), 1.22 (s, 9H), 1.18 (s, 9H), 1.11-1.09 (m, 2H), 0.90 (d, *J* = 6.5, 3H); ^{13}C NMR (151 MHz, $CDCl_3$); δ 177.5, 177.3, 149.8, 134.9, 132.3, 131.0, 126.6, 123.8, 102.7, 87.9, 79.2, 72.6, 63.3, 57.7, 54.5, 51.0, 39.9, 38.9, 38.6, 36.5, 35.5, 33.3, 29.8, 27.1, 26.8, 25.4, 25.2, 23.1, 21.8, 14.2; IR (thin film, cm^{-1}) 3476, 1721, 1711, 1156; DART HRMS *m/z* $[M+H]^+$ calcd for $C_{34}H_{55}N_2O_{12}S$ 715.3476, found 715.3472.

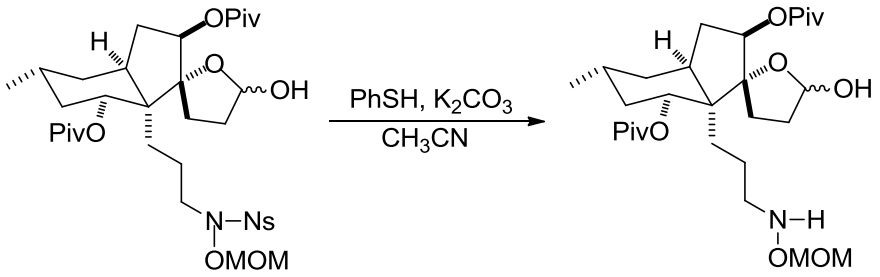
(1'*R*,2'*R*,3a'*S*,5'*R*,7'*R*,7a'*R*)-5-Hydroxy-7a'-(3-(N-(methoxymethoxy)-2-nitrophenylsulfonamido)propyl)-5'-methyldecahydro-3*H*-spiro[furan-2,1'-indene]-2',7'-diyl bis(2,2-dimethylpropanoate) (-)-131



(-)-**129** (-)-**131** (83 %)

2-Iodoxybenzoic acid IBX[86] (29 mg, 0.105 mmol) was added to a solution of diol (-)-**129** (49 mg, 0.07 mmol) in THF/DMSO (1.0 mL: 1.0 mL) at room temperature. After stirring for 6 h at the same temperature, the reaction was quenched with saturated aq $NaHCO_3$ and partitioned between EtOAc and brine. The layers were separated and the aqueous layer was extracted three times with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography using (hexanes/EtOAc, 1:1) as an eluent to afford spirolactol (-)-**131** as colorless oil (41.5 mg, 83% yield, two diastereomers, 3:1): $[\alpha]^{24}_D$ = -8.8 (*c* 0.24, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$); δ 8.08-8.05 (m, 1H), 7.79-7.74 (m, 2H), 7.61-7.60 (m, 1H), 5.46-5.41 (m, 1H), 5.13-5.10 (m, 1H), 5.02-4.97 (m, 2H), 4.80-4.78 (m, 1H), 3.47 (d, *J* = 11.0, 3H), 3.28-3.23 (m, 2H), 2.55-2.48 (m, 1H), 2.42-2.38 (m, 1H), 2.21-2.17 (m, 1H), 2.11-2.03 (m, 1H), 1.81-1.77 (m, 4H), 1.70-1.65 (m, 4H), 1.54-1.50 (m, 2H), 1.44-1.32 (m, 2H), 1.22 (d, *J* = 5.5, 9H), 1.17 (d, *J* = 1.8, 9H), 1.08-1.05 (m, 1H), 0.91-0.89 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$); δ 177.7, 177.3, 158.4, 145.4, 134.8, 132.3, 132.0, 131.1, 123.9, 123.8, 102.3, 100.0, 99.3, 97.0, 78.1, 72.3, 72.1, 57.8, 55.0, 48.8, 39.3, 38.8, 38.6, 36.1, 34.6, 33.2, 32.9, 31.8, 27.2, 27.1, 26.9, 25.0, 24.3, 23.9, 23.4, 21.9; IR (thin film, cm^{-1}) 3492, 1719, 1283, 1158; DART HRMS *m/z* $[M+H]^+$ calcd for $C_{34}H_{53}N_2O_{12}S$ 713.3319, found 713.3313.

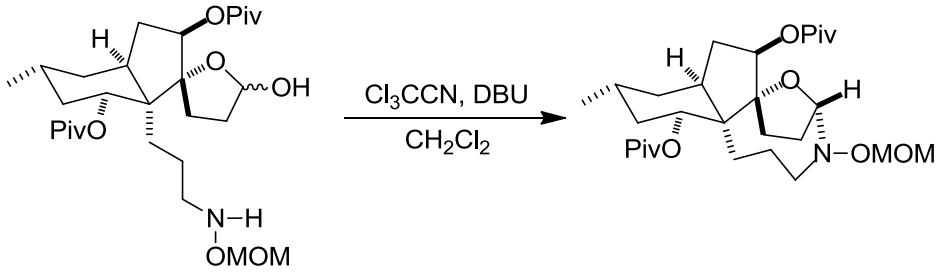
(1'*R*,2'*R*,3a'*S*,5'*R*,7'*R*,7a'*R*)-5-Hydroxy-7a'-(3-((methoxymethoxy)-amino)propyl)-5'-methyldecahydro-3*H*-spiro[furan-2,1'-indene]-2',7'-diyl bis(2,2-dimethylpropanoate) (-)-132



(-)-**131** (-)-**132** (90 %)

K_2CO_3 (29.0 mg, 0.21 mmol) and thiophenol PhSH (140 µL, 0.14 mmol, 1.0M in CH_3CN) were added to a solution of (-)-**131** (50 mg, 0.07 mmol) in CH_3CN (4 mL) at room temperature. After stirring for 6 h at the same temperature, the mixture was partitioned between EtOAc and brine. The layers were separated and the aqueous layer was extracted three times with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography using (hexanes/EtOAc, from 1:1 to 1:2) as an eluent to afford aminolactol (-)-**132** as colorless oil (33.2 mg, 90% yield, two diastereomers, 3:1): $[\alpha]^{24}_D$ = -6.5 (*c* 0.4, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$); δ 5.44-5.43 (m, 1H), 5.11-5.09 (m, 1H), 4.82-4.80 (m, 1H), 4.76 (d, *J* = 2.4, 2H), 3.42 (s, 3H), 3.18-3.16 (m, 1H), 2.92-2.87 (m, 1H), 2.56-2.54 (m, 1H), 2.43-2.38 (m, 1H), 2.13-2.09 (m, 1H), 2.06-2.04 (m, 1H), 1.84-1.75 (m, 5H), 1.70-1.63 (m, 2H), 1.54-1.52 (m, 2H), 1.43-1.38 (m, 1H), 1.27-1.25 (m, 1H), 1.23 (d, *J* = 7.2, 9H), 1.17 (d, *J* = 9.3, 9H), 1.12-1.08 (m, 2H), 0.90-0.89 (m, 4H); ^{13}C NMR (151 MHz, $CDCl_3$); δ 177.6, 177.3, 100.2, 99.2, 98.9, 97.0, 78.3, 72.4, 55.9, 53.1, 48.7, 40.0, 39.3, 38.9, 38.6, 36.4, 34.7, 33.3, 33.2, 27.2, 27.1, 26.9, 25.0, 24.5, 23.9, 23.0, 21.9; IR (thin film, cm^{-1}) 3733, 1723, 1151; DART HRMS *m/z* $[M+H]^+$ calcd for $C_{28}H_{50}NO_8$ 528.3536, found 528.3544.

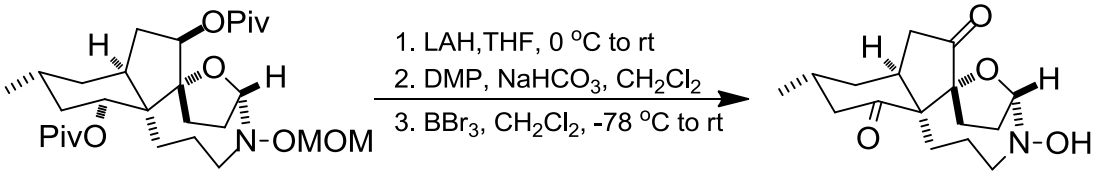
(5*S*,7a*R*,8*R*,9a*S*,11*R*,13*R*,13a*R*)-4-(Methoxymethoxy)-11-methyltetradecahydro-5,7a-epoxyindeno[1,7a-e]azonine-8,13-diyl bis(2,2-dimethylpropanoate) (+)-137



(-)-**132** (+)-**137**(63%)

1,8-Diazabicyclo[5.4.0]undec-7-ene DBU (550 μL, 1.32 mmol, 2.4 M in CH_2Cl_2) was added dropwise to a solution of aminolactol **(-)-132** (32.0 mg, 0.06 mmol) in CH_2Cl_2 (4.0 mL) at 0 °C under argon. Trichloroacetonitrile (660 μL, 3.3 mmol, 5.0 M in CH_2Cl_2) was added dropwise to the reaction mixture at the same temperature. After stirring at 0 °C for 2 h, the reaction mixture was gradually warmed to room temperature and stirred for 36 h. The color changed from pale yellow to dark brown during the course of the reaction. The dark brown solution was concentrated under reduced pressure and the residue was purified by flash chromatography using (hexanes/acetone, 40:3) as an eluent to afford tetracyclic derivative (+)-**137** as a colorless film: (19.4 mg, 63% yield). $[\alpha]^{24}_D$ = +85.5 (*c* 0.33, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$); δ 5.19 (dd, *J* = 11.5, 4.6, 1H), 5.09 (t, *J* = 5.7, 1H), 4.90 (dd, *J* = 8.9, 3.6, 1H), 4.75 (s, 2H), 3.42 (s, 3H), 3.34-3.31 (m, 1H), 3.14-3.12 (m, 1H), 2.73-2.68 (m, 1H), 2.47-2.41 (m, 1H), 2.37-2.33 (m, 1H), 2.21-2.16 (m, 1H), 2.01-1.96 (m, 4H), 1.77-1.70 (m, 3H), 1.55-1.52 (m, 1H), 1.48-1.43 (m, 2H), 1.21 (s, 9H), 1.20 (s, 9H), 1.16-1.15 (m, 2H), 0.89 (d, *J* = 6.2, 3H); ^{13}C NMR (151 MHz, $CDCl_3$); δ 177.8, 177.0, 98.8, 96.5, 95.6, 80.5, 72.1, 56.1, 54.2, 49.5, 38.9, 38.6, 38.4, 35.2, 34.2, 31.3, 29.0, 27.1, 26.9, 26.5, 25.2, 25.0, 21.9, 19.3; IR (thin film, cm^{-1}) 2956, 1723, 1153; DART HRMS *m/z* $[M+H]^+$ calcd for $C_{28}H_{48}NO_7$ 510.3431, found 510.3432.

(+)-Sieboldine A 1



(+)-**137** (+)-Sieboldine A **1** (53%)

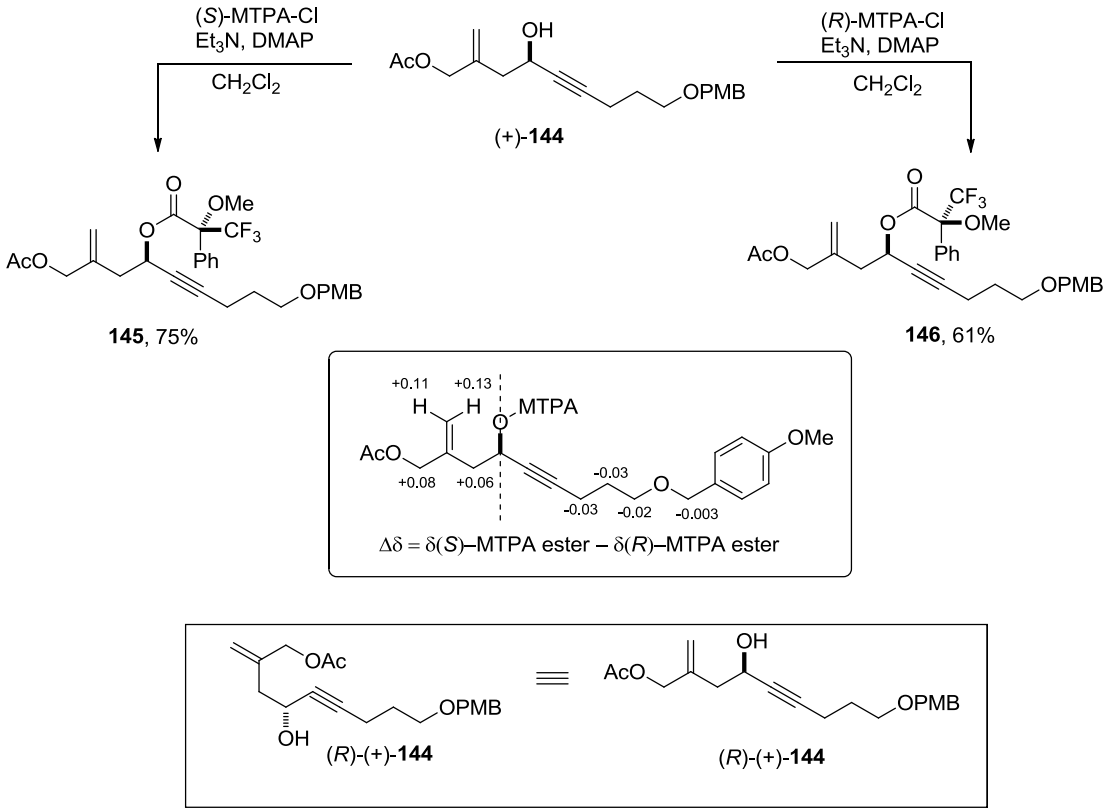
Lithium aluminium hydride LAH (57 mg, 1.5 mmol) was added to a solution of (+)-**137** (11 mg, 0.021 mmol) in THF (3 mL) at 0 °C under argon. After stirring for 2 h at the same temperature, the reaction mixture was gradually warmed to room temperature and stirred for 18 h. The reaction was diluted with EtOAc at 0 °C and a saturated aq solution of Rochelle's salt was added. The mixture was allowed to warm to room temperature and stirred for 2h. The layers were separated and the aqueous layer was extracted three times with EtOAc. The combined organic layers were washed with H_2O and brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure.

The residue was dissolved in CH_2Cl_2 (3 mL). $NaHCO_3$ (13 mg, 0.15 mmol) and Dess martin periodinane DMP (0.5 mL, 0.15 mmol, 0.3 M in CH_2Cl_2) were added to the reaction mixture at room temperature under argon. After stirring for 2 h, the reaction was quenched with saturated aq $NaHCO_3$. The layers were separated and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic layers were washed with H_2O and brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure.

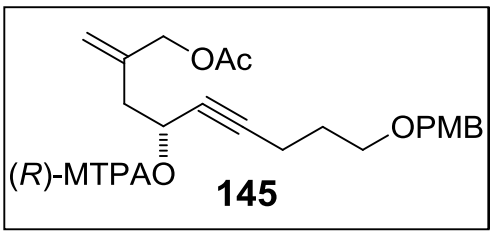
The residue was dissolved in CH_2Cl_2 (3 mL) and cooled to -78 °C under argon. Boron tribromide BBr_3 (105 µL, 0.105 mmol, 1.0 M in CH_2Cl_2) was added dropwise to the reaction mixture at the same temperature. The reaction mixture was gradually warmed to 0 °C and stirred for 2 h and was then warmed to room temperature and stirred for 18h. The reaction was quenched with saturated aq $NaHCO_3$. The layers were separated and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic layers were washed with H_2O and brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified

by flash chromatography using (hexanes/acetone, 1:1) as an eluent to afford (+)-sieboldine A **1** as a colorless powder (3.3 mg, 53% yield): $[\alpha]^{25}_{D}$ = +140.0 (*c* 0.33, CH_3OH); ^{1}H NMR (600 MHz, CD_3OD); δ; 4.89-4.87 (m, 1H), 3.27-3.22 (m, 1H), 3.20-3.18 (m, 1H), 2.90 (ddd, *J* = 14.8, 7.4, 3.7, 1H), 2.57-2.55 (m, 1H), 2.51 (dd, *J* = 12.9, 12.5, 1H), 2.47-2.45 (m, 1H), 2.43 (dd, *J* = 21.3, 10.7, 1H), 2.40-2.38 (m, 1H), 2.11-2.10 (m, 1H), 2.08-2.07 (m, 1H), 2.05-2.04 (m, 1H), 2.03-2.01 (m, 1H), 1.98-1.96 (m, 1H), 1.92 (dd, *J* = 19.6, 10.7, 1H), 1.79-1.77 (m, 2H), 1.76-1.75 (m, 1H), 1.62-1.60 (m, 1H), 1.05 (d, *J* = 6.2, 3H); ^{13}C NMR (151 MHz, CD_3OD); δ 216.5, 212.7, 98.5, 92.8, 62.3, 54.5, 47.6, 38.7, 37.2, 32.5, 31.8, 31.4, 28.3, 26.1, 22.5, 19.4; IR (thin film, cm^{-1}) 3400, 1754, 1698; DART HRMS *m/z* $[M+H]^{+}$ calcd for $C_{16}H_{24}NO_4$ 294.1705, found 294.1701.

3.3 Determination of the absolute configuration of (+)-144



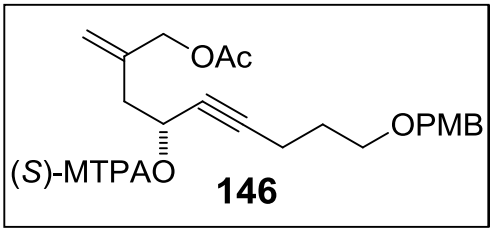
(*R*)-MTPA ester of (+)-144 (145)



To a solution of (+)-**144** (14 mg, 0.040 mmol) in CH_2Cl_2 (0.40 mL) were added Et_3N (50 μL, 0.36 mmol), DMAP (1.0 mg, 8.0 x10^{-3} mmol) and (*S*)-MTPA-Cl (15 mg, 6.0 x10^{-2} mmol) at room temperature. After stirring for 1.5 h at the same temperature, the reaction was quenched with saturated aq NH_4Cl. The layers were separated and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography using (hexanes/EtOAc, 6:1) as an eluent to afford **145** (17 mg, 75%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$); δ 7.55-7.53 (m, 2H), 7.39-7.36 (m, 3H), 7.26-7.23 (m, 2H), 6.88-6.86 (m, 2H), 5.71-5.68 (m, 1H), 5.09 (s, 1H), 4.95 (s, 1H), 4.46-4.45 (m, 2H), 4.41 (s, 2H), 3.80 (s, 3H), 3.58 (s, 3H), 3.49 (t, *J* =

6.2, 2H), 2.58-2.49 (m, 2H), 2.33 (td, *J* = 7.1, 1.8, 2H), 2.07 (s, 3H), 1.81-1.74 (m, 2H).

(*S*)-MTPA ester of (+)-144 (146)

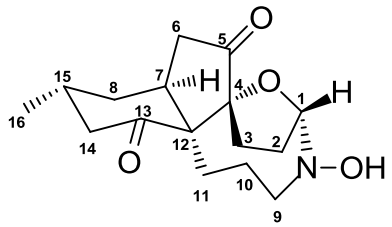


146

In the same manner as that described for preparation of **145**, (+)-**144** (14 mg, 0.040 mmol) with (*R*)-MTPA-Cl (15 mg, 6.0 x 10^{-2} mmol) afforded **146** (14 mg, 61 %) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$); δ 7.53-7.51 (m, 2H), 7.40-7.35 (m, 3H), 7.26-7.23 (m, 2H), 6.89-6.85 (m, 2H), 5.70-5.65 (m, 1H), 5.20 (s, 1H), 5.09 (s, 1H), 4.53 (s, 2H), 4.41 (s, 2H), 3.80 (s, 3H), 3.53 (s, 3H), 3.48 (t, *J* = 6.2, 2H), 2.65-2.53 (m, 2H), 2.30 (td, *J* = 7.1, 1.8, 2H), 2.07 (s, 3H), 1.78-1.72 (m, 2H).

3.4 Comparison of synthetic and natural (+)-sieboldine A spectral data

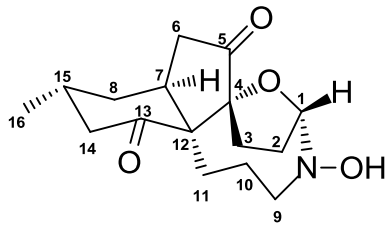
3.4.1 (+)-Sieboldine A ^{13}C spectra comparison:



(+)-Sieboldine A

Position	^{13}C NMR (δ) Natural sample (CD_3OD)	^{13}C NMR (δ) Synthetic sample (151 MHz, CD_3OD)
1	98.5	98.5
2	31.4	31.4
3	26.1	26.1
4	92.8	92.8
5	212.6	212.7
6	37.2	37.2
7	38.7	38.7
8	31.8	31.8
9	54.5	54.5
10	19.4	19.4
11	28.3	28.3
12	62.3	62.3
13	216.5	216.5
14	47.4	47.6
15	32.5	32.5
16	22.5	22.5

3.4.2 (+)-Sieboldine A ^{1}H spectra comparison:



(+)-Sieboldine A

Position	^{1}H NMR (δ) Natural sample (CD_3OD)	^{1}H NMR (δ) Synthetic sample (600 MHz, CD_3OD)
1	4.89 (m, 1H)	4.89-4.87 (m, 1H)
2a	1.98 (m, 1H)	1.98-1.96 (m, 1H)
2b	2.12 (m, 1H)	2.11-2.10 (m, 1H)
3a	2.08 (m, 1H)	2.08-2.07 (m, 1H)
3b	2.40 (m, 1H)	2.40-2.38 (m, 1H)
6a	1.93 (dd, *J* = 19.6, 10.9, 1H)	1.92 (dd, *J* = 19.6, 10.7, 1H)
6b	2.45 (dd, *J* = 19.6, 9.2, 1H)	2.43 (dd, *J* = 21.3, 10.7, 1H)
7	3.25 (m, 1H)	3.27-3.22 (m, 1H)
8a	1.76 (m, 1H)	1.76-1.75 (m, 1H)
8b	1.77 (m, 1H)	1.79-1.77 (m, 1H)
9a	2.91 (ddd, *J* = 14.8, 8.0, 3.7, 1H)	2.90 (ddd, *J* = 14.8, 7.4, 3.7, 1H)
9b	3.19 (m, 1H)	3.20-3.18 (m, 1H)
10a	1.63 (m, 1H)	1.62-1.60 (m, 1H)
10b	2.57 (m, 1H)	2.57-2.55 (m, 1H)
11a	1.77 (m, 1H)	1.79-1.77 (m, 1H)
11b	2.46 (m, 1H)	2.47-2.45 (m, 1H)
14a	2.03 (m, 1H)	2.03-2.01 (m, 1H)
14b	2.54 (dd, *J* = 12.7, 12.7, 1H)	2.51 (dd, *J* = 12.9, 12.5, 1H)
15	2.06 (m, 1H)	2.05-2.04 (m, 1H)

16	1.06 (d, *J* = 6.2, 3H)	1.05 (d, *J* = 6.2, 3H)

CHAPTER IV

REFERENCES

(1) Ma, X.; Gang, D. R. *Nat. Prod. Rep.* **2004**, *21*, 752-772.
(2) Hirasawa, Y.; Kobayashi, J.; Morita, H. *Heterocycles* **2009**, *77*, 679-729.
(3) Kobayashi, J.; Morita, H. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, 2005; Vol. 61, p 1-57.
(4) Siengalewicz, P.; Mulzer, J.; Rinner, U. In *The Alkaloids*; Knölker, H.-J., Ed.; Academic press: New York, 2013; Vol. 72, p 1-151.
(5) Hirasawa, Y.; Morita, H.; Shiro, M.; Kobayashi, J. *Org. Lett.* **2003**, *5*, 3991-3993.
(6) Zheng, W.; Xiang, Y. Q.; Li, X. B.; Ungvari, G. S.; Chiu, H. F.; Sun, F.; D'Arcy, C.; Meng, X.; Xiang, Y. T. *Hum. Psychopharmacol* **2016**, *31*, 286-295.
(7) Yang, G.; Wang, Y.; Tian, J.; Liu, J.-P. *PLoS ONE* **2013**, *8*, e74916.
(8) Wang, F.-X.; Du, J.-Y.; Wang, H.-B.; Zhang, P.-L.; Zhang, G.-B.; Yu, K.-Y.; Zhang, X.-Z.; An, X.-T.; Cao, Y.-X.; Fan, C.-A. *J. Am. Chem. Soc.* **2017**, *139*, 4282-4285.
(9) Ding, R.; Fu, J.-G.; Xu, G.-Q.; Sun, B.-F.; Lin, G.-Q. *J. Org. Chem.***2014**, *79*, 240-250.
(10) Chandra, A.; Pigza, J. A.; Han, J.-S.; Mutnick, D.; Johnston, J. N. *J. Am. Chem. Soc.* **2009**, *131*, 3470-3471.
(11) Fu, J.-G.; Xu, G.-Q.; Ding, R.; Lin, G.-Q.; Sun, B.-F. *Organic Chemistry Frontiers* **2016**, *3*, 62-65.
(12) Lei, X.; Hong, B.; Hu, D.; Wu, J.; Zhang, J.; Li, H. *Chem Asian J* **2017**, *25*, 201700364.
(13) Zhao, L.; Tsukano, C.; Kwon, E.; Shirakawa, H.; Kaneko, S.; Takemoto, Y.; Hirama, M. *Chemistry* **2017**, *23*, 802-812.
(14) Xu, S.; Zhang, J.; Ma, D.; Xu, D.; Xie, X.; She, X. *Org Lett* **2016**, *18*, 4682-4685.
(15) Ochi, Y.; Yokoshima, S.; Fukuyama, T. *Org Lett* **2016**, *18*, 1494-1496.

(16) Azuma, M.; Yoshikawa, T.; Kogure, N.; Kitajima, M.; Takayama, H. *J Am Chem Soc* **2014**, *136*, 11618-11621.
(17) Zaimoku, H.; Taniguchi, T. *Chemistry* **2014**, *20*, 9613-9619.
(18) Canham, S. M.; France, D. J.; Overman, L. E. *J. Org. Chem.* **2013**, *78*, 9-34.
(19) Canham, S. M.; France, D. J.; Overman, L. E. *J. Am. Chem. Soc.* **2010**, *132*, 7876-7877.
(20) Zhang, X.-M.; Shao, H.; Tu, Y.-Q.; Zhang, F.-M.; Wang, S.-H. *J. Org. Chem.* **2012**, *77*, 8174-8181.
(21) Zhang, X. M.; Tu, Y. Q.; Zhang, F. M.; Shao, H.; Meng, X. *Angew. Chem. Int. Ed.* **2011**, *50*, 3916-3919.
(22) Torres, R. R. *The Pauson-Khand Reaction: Scope, Variations and Applications*; Wiley, 2012.
(23) Khand, I. U.; Knox, G. R.; Pauson, P. L. *J. Chem. Soc. Chem. Comm.* **1971**, 36.
(24) U.Khand, I.; Knox, G. R.; L.Pauson, P.; Watts, W. E.; Foreman, M. I. *J. Chem. Soc. Perkin Trans. 1* **1973**, 977–981
(25) Khand, I. U.; Knox, G. R.; Pauson, P. L.; Watts, W. E. *J. Chem. Soc. Perkin Trans. 1* **1973**, 975–977
(26) Pauson, P. L.; Khand, I. U. *Ann. N. Y. Acad. Sci.* **1977**, *295*, 2-14.
(27) Pauson, P. L. *Tetrahedron* **1985**, *41*, 5855–5860.
(28) Blanco-Urgoiti, J.; Anorbe, L.; Perez-Serrano, L.; Dominguez, G.; Perez-Castells, J. *Chem Soc Rev* **2004**, *33*, 32-42.
(29) Magnus, P.; Príncipe, L.-M. *Tetrahedron Lett.* **1985**, *26*, 4851-4854.
(30) Schore, N. E.; Croudace, M. C. *J. Org. Chem.* **1981**, *46*, 5436-5438.
(31) Exon, C.; Magnus, P. *J. Am. Chem. Soc.* **1983**, *105*, 2477-2478.
(32) Magnus, P.; Principe, L. M. *Tetrahedron Lett.* **1985**, *26*.
(33) Magnus, P.; Exon, C.; Albaugh-Robertson, P. *Tetrahedron* **1985**, *41*, 5861–5869.
(34) Magnus, P.; Principe, L. M.; Slater, M. J. *J.Org. Chem.* **1987**, *52*, 1483-1486.
(35) Mukai, C.; Sonobe, H.; Kim, J. S.; Hanaoka, M. *J. Org. Chem.* **2000**, *65*, 6654-6669.
(36) Huang, F.; Yao, Z.-K.; Wang, Y.; Zhang, J.; Yu, Z.-X. *Chem. Asian J.* **2010**, *5*, 1555-1559.
(37) Shibata, T. *Adv. Synth. Catal.* **2006**, *348*, 2328-2336.
(38) Mukai, C.; Nomura, I.; Yamanishi, K.; Hanaoka, M. *Org. Lett.* **2002**, *4*, 1755-1758.
(39) Mukai, C.; Nomura, I.; Kitagaki, S. *J. Org. Chem.* **2003**, *68*, 1376-

1385.
(40) Hirose, T.; Miyakoshi, N.; Mukai, C. *J. Org. Chem.* **2008**, *73*, 1061-1066.
(41) Hayashi, Y.; Ogawa, K.; Inagaki, F.; Mukai, C. *Org. Biomol. Chem.* **2012**, *10*, 4747-4751.
(42) Wender, P. A.; Croatt, M. P.; Descamps, N. M. *J. Am. Chem.Soc.* **2004**, *126*, 5948-5949.
(43) Inagaki, F.; Mukai, C. *Org. Lett.* **2006**, *8*, 1217-1220.
(44) Y., H.; N., M.; Kitagaki, S.; C., M. *Org. Lett.* **2008**, *10*, 2385-2388.
(45) Nakayama, A.; Kogure, N.; Kitajima, M.; Takayama, H. *Org. Lett.* **2009**, *11*, 5554-5557.
(46) Hosomi, A.; Sakurai, H. *Tetrahedron Lett.* **1976**, *17*, 1295-1298.
(47) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551-5553.
(48) Nakayama, A.; Kogure, N.; Kitajima, M.; Takayama, H. *Angew. Chem. Int. Ed.* **2011**, *50*, 8025-8028.
(49) Noyori, R.; Hashiguchi, S. . *Acc. Chem. Res.* **1997**, *30*, 97-102.
(50) Nakayama, A.; Kitajima, M.; Takayama, H. *Synlett* **2012**, 2014-2024.
(51) Kozaka, T.; Miyakoshi, N.; Mukai, C. *J. Org. Chem.* **2007**, *72*, 10147-10154.
(52) Ueno, Y.; Chino, K.; Watanabe, M.; Moriya, O.; Okawara, M. *J. Am. Chem. Soc.* **1982**, *104*, 5564-5566.
(53) Stork, G.; Mook, R.; Biller, S. A.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **1983**, *105*, 3741-3742.
(54) Sugihara, T.; Yamada, M.; Yamaguchi, M.; Nishizawa, M. *Synlett* **1999**, 771-773.
(55) Otsuka, Y.; Inagaki, F.; Mukai, C. *J. Org. Chem.* **2010**, *75*, 3420-3426.
(56) Oyo, M.; Masaaki, Y. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2380-2382.
(57) Itoh, N.; Iwata, T.; Sugihara, H.; Inagaki, F.; Mukai, C. *Chem. Eur. J.* **2013**, *19*, 8665-8672.
(58) Dondoni, A.; Giovannini, P. P.; Perrone, D. *J. Org. Chem.* **2002**, *67*, 7203-7214.
(59) Teze, D.; Dion, M.; Daligault, F.; Tran, V.; Andre-Miral, C.; Tellier, C. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 448-451.
(60) Mukai, C.; Yoshida, T.; Sorimachi, M.; Odani, A. *Org. Lett.* **2006**, *8*, 83-86.
(61) Naruta, Y.; Nishigaichi, Y.; Maruyama, K. *J. Org.Chem.* **1991**, *56*, 2011 –2017.
(62) Tang, Y.; Deng, L.; Zhang, Y.; Dong, G.; Chen, J.; Z. Yang *Org.*

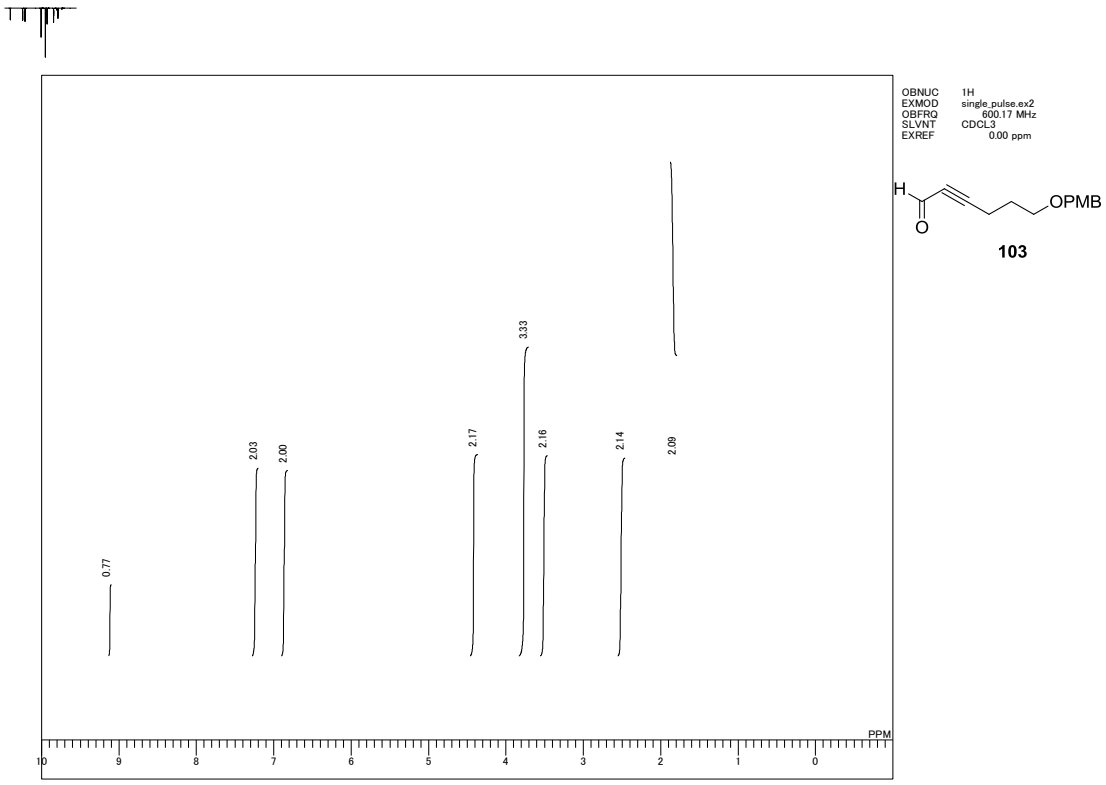
Lett. **2005**, *7*, 593 – 595.
(63) Mukai, C.; Yoshida, T.; Sorimachi, M.; Odani, A. *Org. Lett.* **2006**, *8*, 83-86.
(64) Aburano, D.; Yoshida, T.; Miyakoshi, N.; C. Mukai *J. Org. Chem.* **2007**, *72*, 6878 – 6884.
(65) Ueno, Y.; Moriya, O.; K.Chino; Watanabe, M.; M. Okawara *J. Chem. Soc. Perkin Trans. 1* **1986**, 1351-1356.
(66) Stork, G.; M.Sher, P. *J. Am. Chem. Soc.* **1986**, *108*, 303-304.
(67) Stork, G.; Sher, P. M.; Chen, H.-L. *J. Am. Chem. Soc* **1986**, *108*, 6384 – 6385.
(68) Stork, G. *Bull. Soc. Chim. Fr.* **1990,**, *127*, 675 –680.
(69) Salom-Roig, X. J.; Dénès, F.; Renaud, P. *Synthesis* **2004**, 1903-1928.
(70) Freeman, P. K.; Hutchinson, L. L. *J. Org.Chem.* **1980**, *45*, 1924-1930.
(71) Liu, H. J.; Yip, J.; Shia, K.-S. *Tetrahedron Lett.* **1997**, *38*, 2253-2256.
(72) Davis, F. A.; Chen, B. C. *Chem. Rev.* **1992**, *92*, 919-934.
(73) Kabalka, G. W.; Shoup, T. M.; Goudgaon, N. M. *J. Org. Chem.* **1989**, *54*, 5930 –5933.
(74) Yamashita, T.; Kawai, N.; Tokuyama, H.; Fukuyama, T. *J. Am. Chem. Soc.* **2005**, *127*, 15038-15039.
(75) Schmidt, R. R.; Michel, J. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 731−732.
(76) Nakano, J.; Ichiyanagi, T.; Ohtab, H.; Itoa, Y. *Tetrahedron Lett.* **2003**, *44*, 2853-2856.
(77) Dasgupta, S.; Nitz, M. *J. Org. Chem.* **2011**, *76*, 1918-1921.
(78) Iida, E. *"Asymmetric total synthesis of Fawcettimine-type Lycopodium alkaloids. Synthesis of optically active bicyclo [4.3.0] derivatives"*, Kanazawa University, (Master thesis) 2016.
(79) Trost, B. M.; Bonk, P. J. *J. Am. Chem. Soc.* **1985**, *107*, 1778-1781.
(80) Journet, M.; cai, D.; DiMichele, L. M.; Larsen, R. D. *Tetrahedron Lett.* **1998**, *39*, 6427-6428.
(81) Hanawa, H.; Hashimoto, T.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 1708-1709.
(82) CCDC 1482946 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
(83) The optical rotations of synthetic (+)-sieboldine A **1** reported by Overman and Tu were $[\alpha]_D^{23}$ +141 (*c* = 0.4, MeOH) and

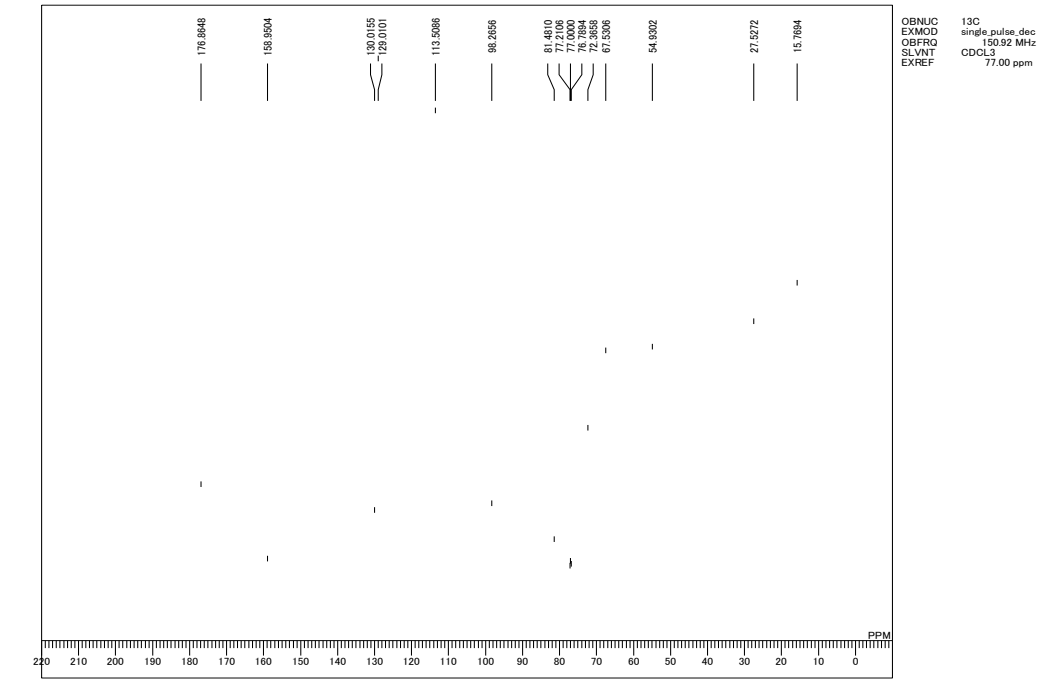
$[\alpha]_D^{20.2}$ +135. 7 (*c* = 0.28, MeOH) respectively.
(84) Chandrasekhar, S.; Rao, C. L.; Seenaiah, M.; Naresh, P.; Jagadeesh, B.; Manjeera, D.; Sarkar, A.; Bhadra, M. P. *J. Org. Chem.* **2009**, *74*, 401-404.
(85) Stalick, W. M.; Khorrami, A.; Hatton, K. S. *J. Org. Chem.* **1986**, *51*, 3577-3581.
(86) Frigerio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem.* **1999**, *64*, 4537-4538.

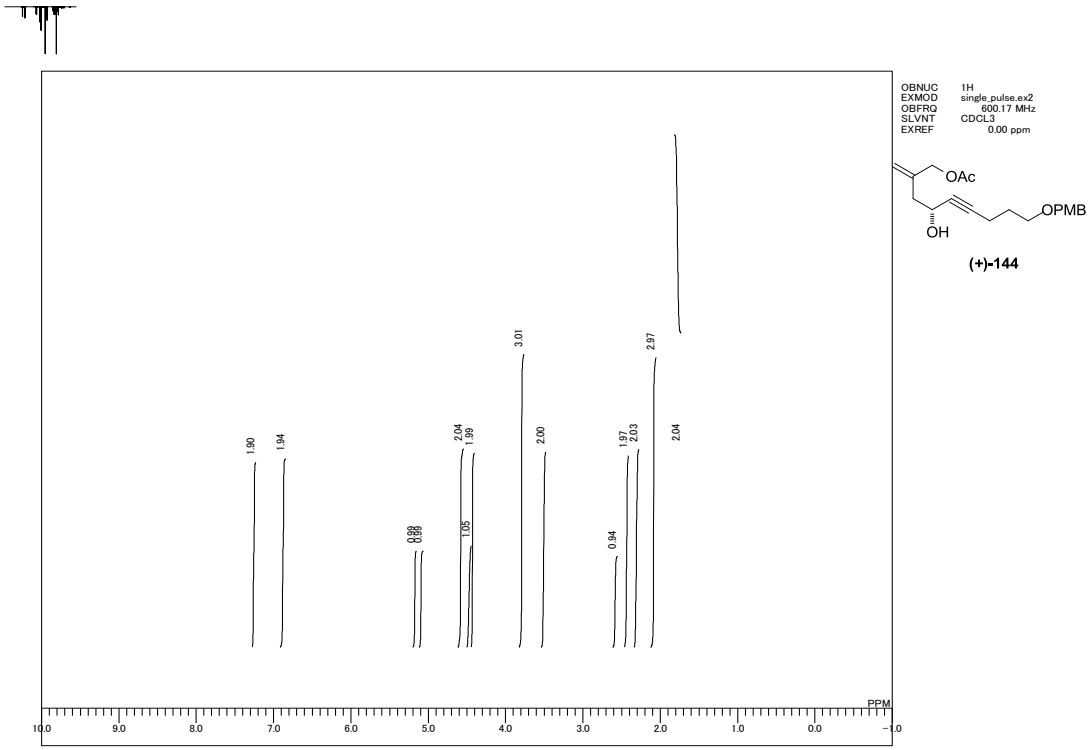
CHAPTER V

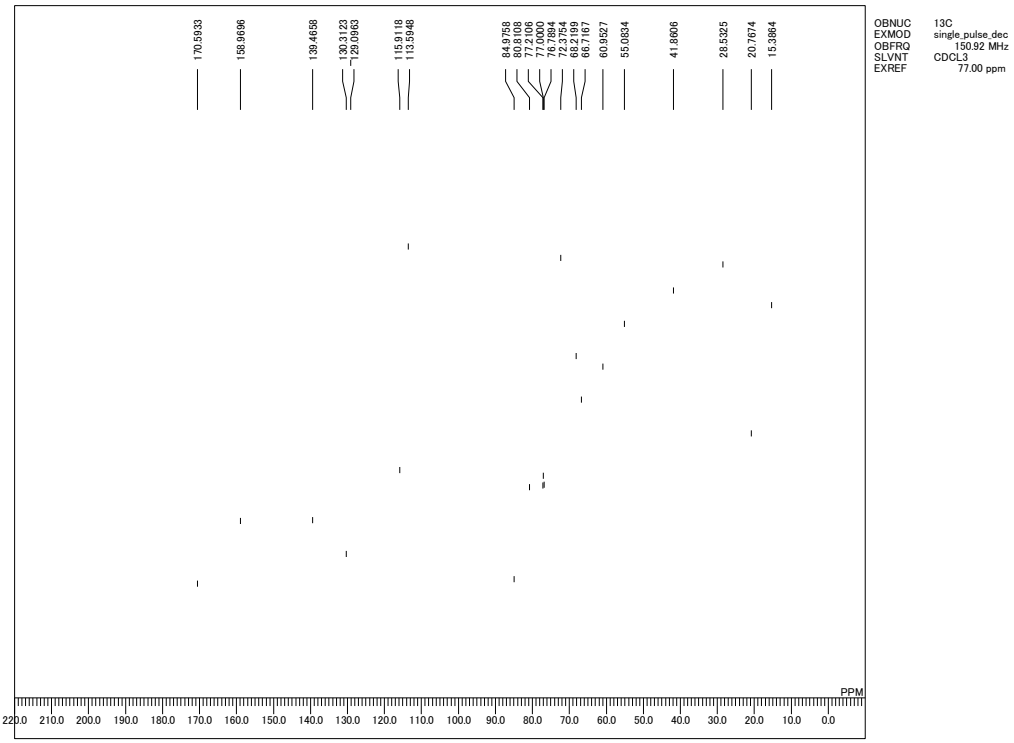
Appendix

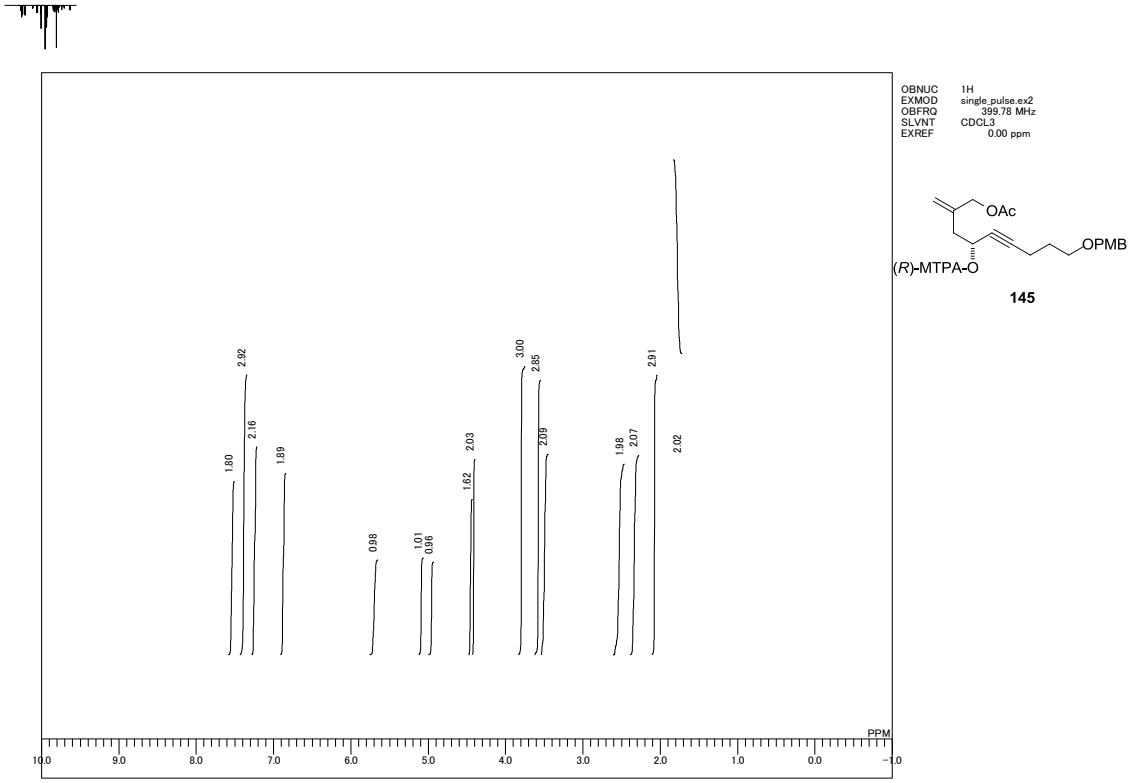
^{1}H and ^{13}C NMR spectra

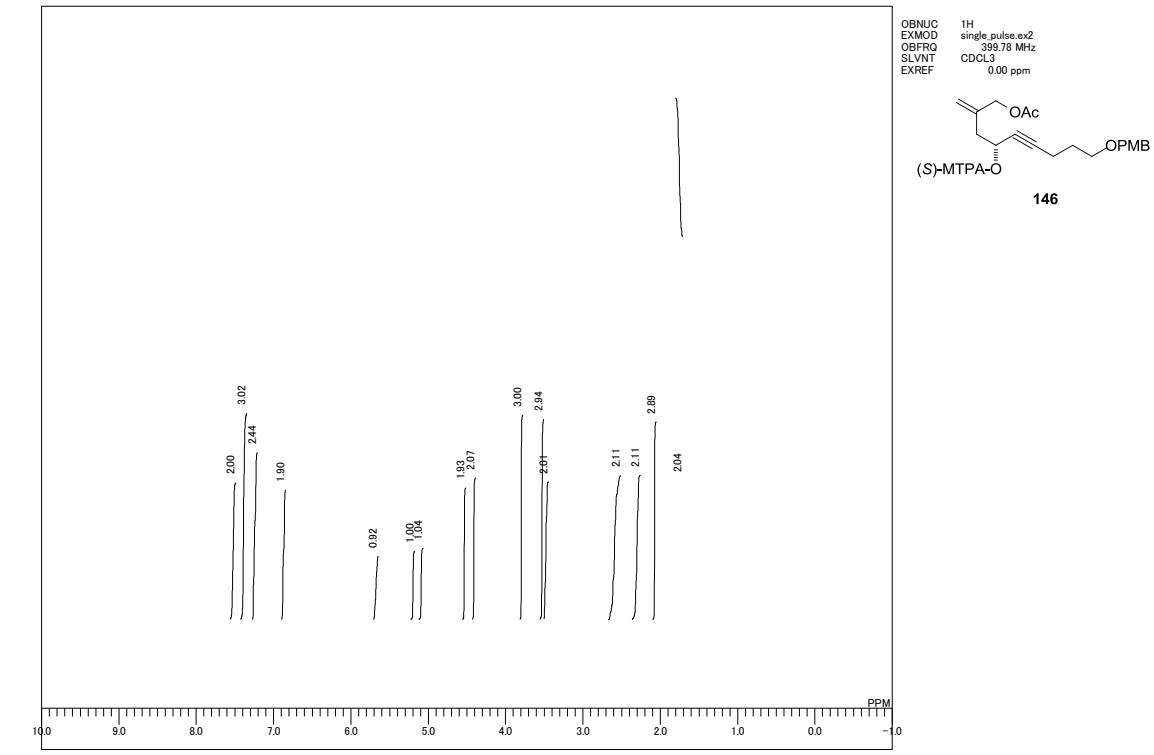


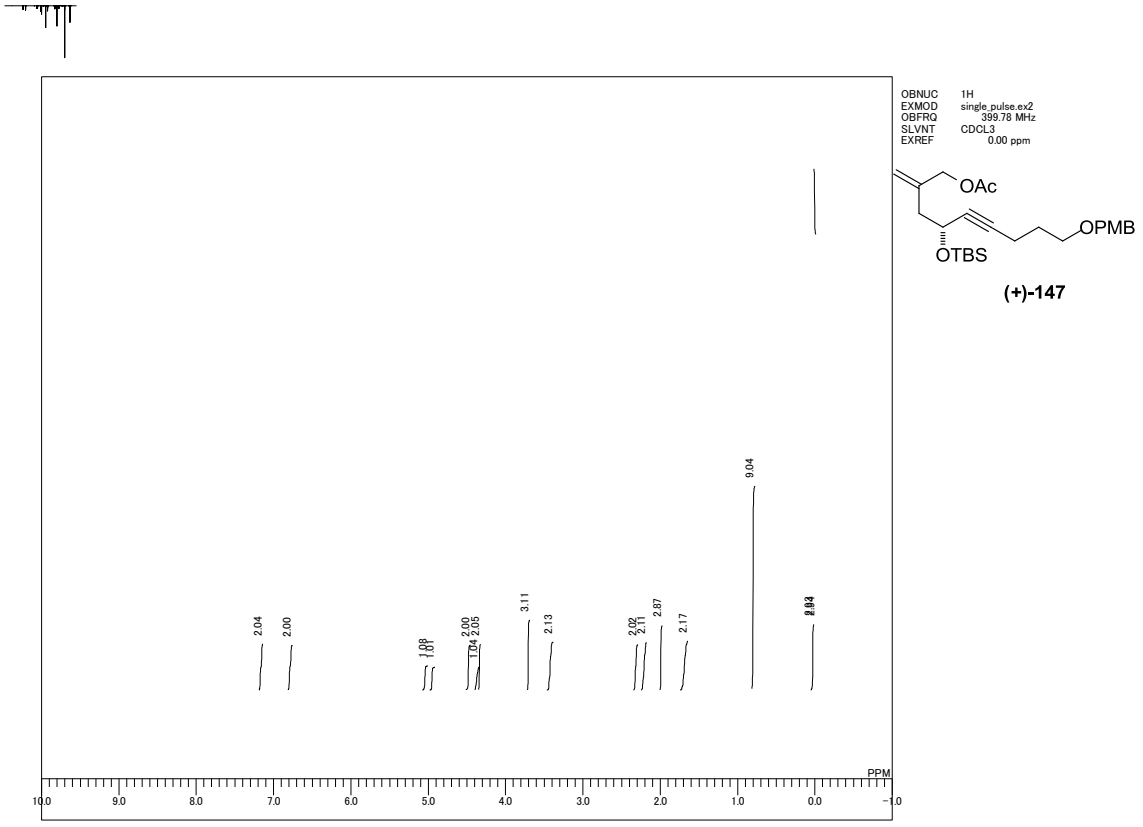

176.8848
158.9504
130.0155
129.0101
113.5086
98.2656
81.4810
77.2056
77.0000
76.7894
72.3658
67.5306
54.9302
27.5272
15.7694
OBNUC 13C
EXMOD single_pulse_dec
OBFRQ 150.92 MHz
SLVNT CDCL3
EXREF 77.00 ppm
PPM
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

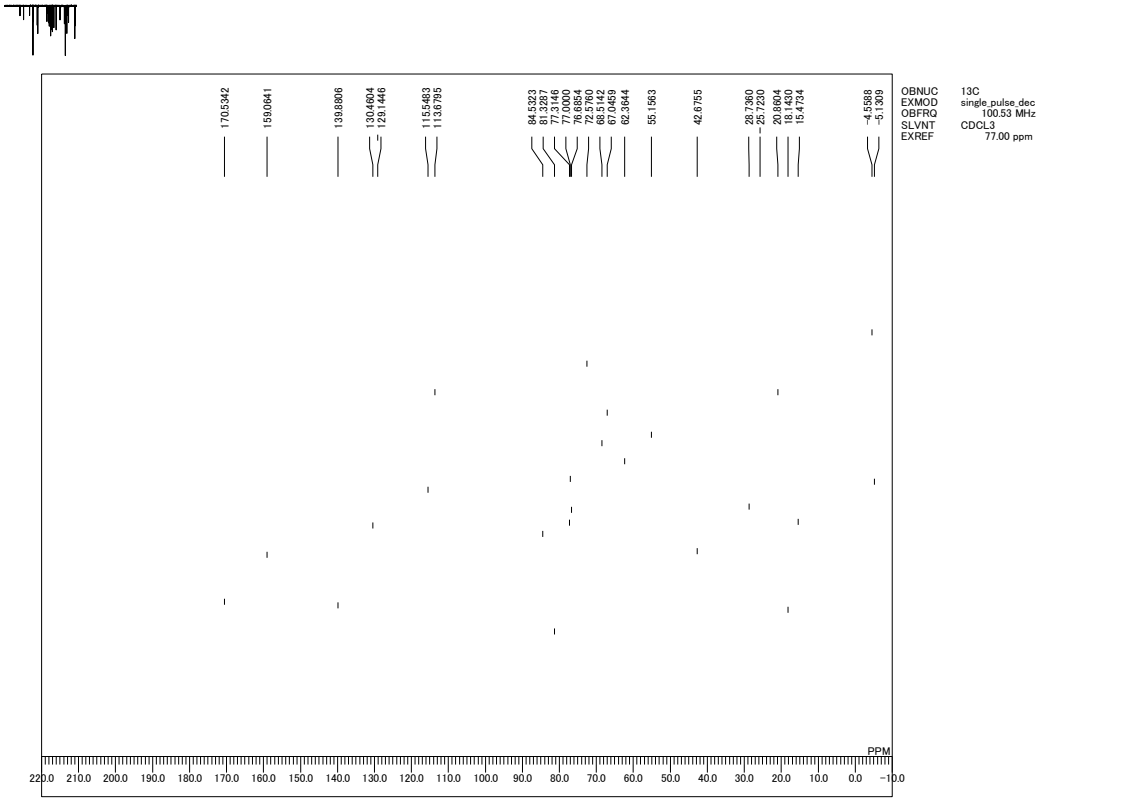

OBNUC 1H
EXMOD single_pulse.ex2
OBFRQ 600.17 MHz
SLVNT CDCL3
EXREF 0.00 ppm
OAc
OPMB
OH
(+)-144
1.90
1.94
0.89
0.89
2.04
1.99
1.05
3.01
2.00
0.94
1.97
2.03
2.97
2.04
PPM
10.0 9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0.0 −1.0

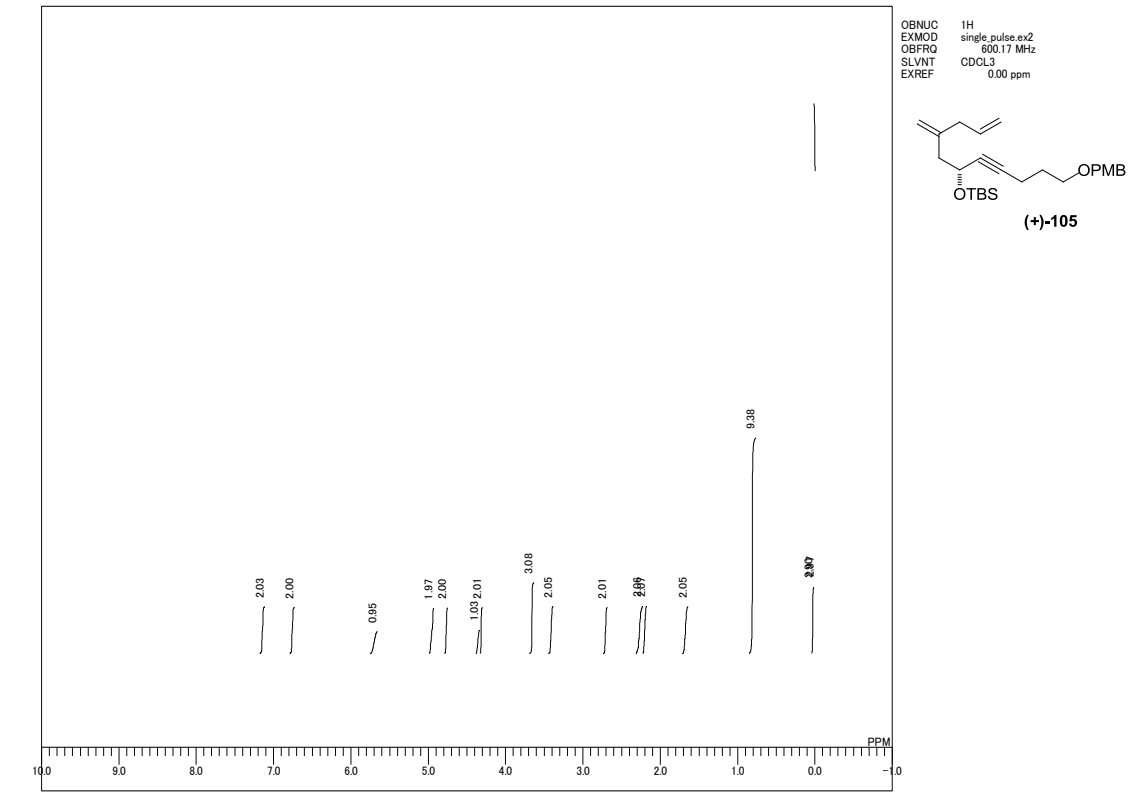

170.5933
158.9696
139.4658
130.3123
129.0963
115.9118
113.5948
84.9758
80.1058
77.2106
77.0000
76.7884
72.3754
68.1939
66.7167
60.9527
55.0834
41.8606
28.5325
20.7674
15.3864
OBNUC 13C
EXMOD single_pulse_dec
OBFRQ 150.92 MHz
SLVNT CDCL3
EXREF 77.00 ppm
PPM
220.0 210.0 200.0 190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0 0.0

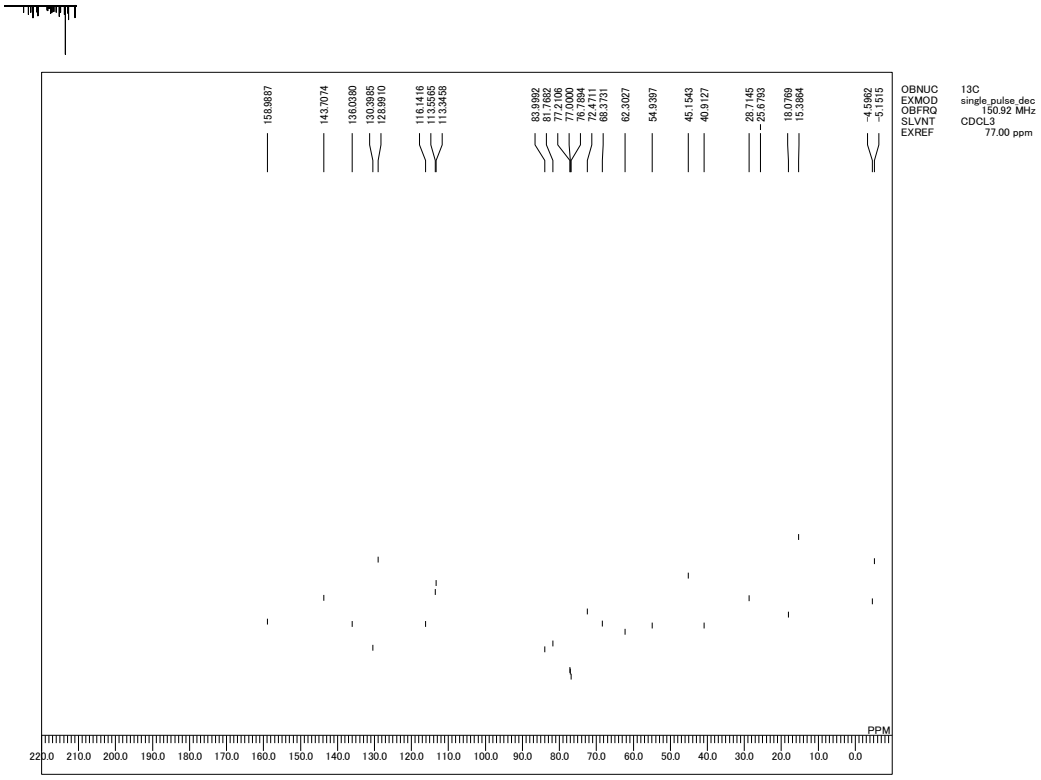

OBNUC 1H
EXMOD single_pulse.ex2
OBFRQ 399.78 MHz
SLVNT CDCL3
EXREF 0.00 ppm
OAc
OPMB
(R)-MTPA-O
145
1.80
2.92
2.16
1.89
0.98
1.01
0.96
1.62
2.03
3.00
2.85
2.09
1.98
2.07
2.91
2.02
PPM
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
−1.0

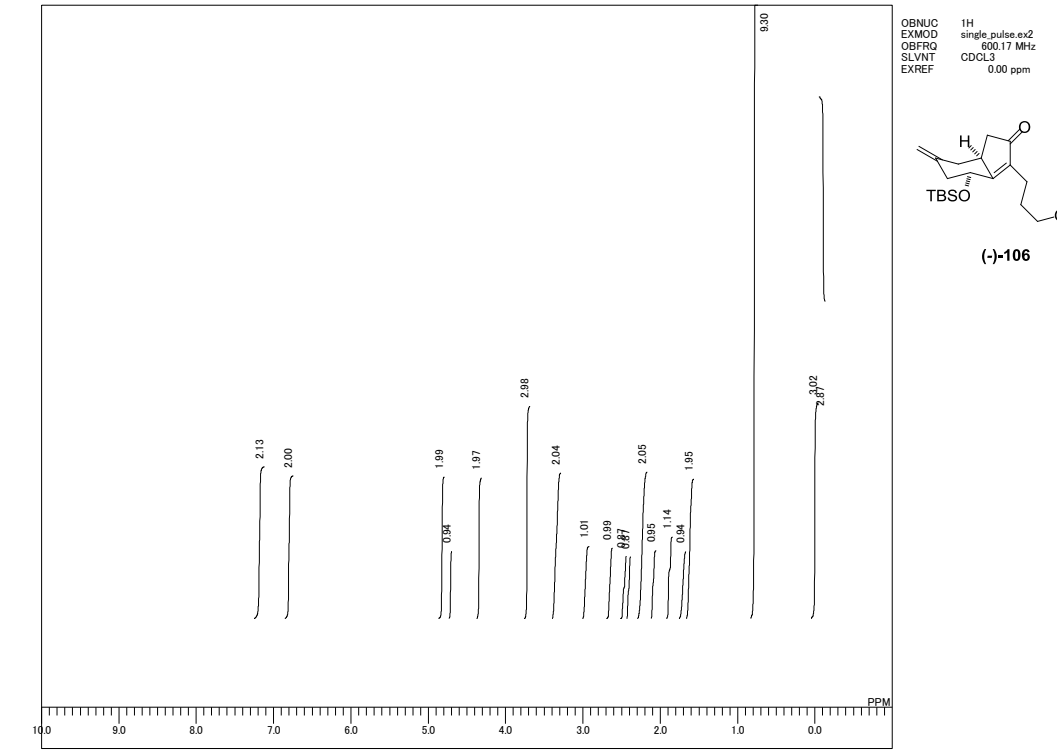

OBNUC 1H
EXMOD single_pulse.ex2
OBFRQ 399.78 MHz
SLVNT CDCL3
EXREF 0.00 ppm
OAc
OPMB
(S)-MTPA-O
146
2.00
3.02
2.44
1.90
0.92
1.00
1.04
1.93
2.07
3.00
2.94
2.01
2.11
2.11
2.89
2.04
PPM
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
−1.0


OBNUC 1H
EXMOD single_pulse.ex2
OBFRQ 399.78 MHz
SLVNT CDCL3
EXREF 0.00 ppm
OAc
OPMB
OTBS
(+)-147
2.04
2.00
1.08
1.01
2.00
2.05
3.11
2.13
2.02
2.11
2.87
2.17
9.04
PPM


OBNUC 13C
EXMOD single_pulse_dec
OBFRQ 100.53 MHz
SLVNT CDCL3
EXREF 77.00 ppm
170.5342
159.0641
139.8806
130.4604
129.1446
115.5483
113.6795
84.5923
83.3927
77.3146
77.0000
76.6854
72.3760
69.5457
67.0459
62.3644
55.1563
42.6755
28.7380
25.7230
20.8804
18.1430
15.4734
-4.5598
-5.1309
PPM

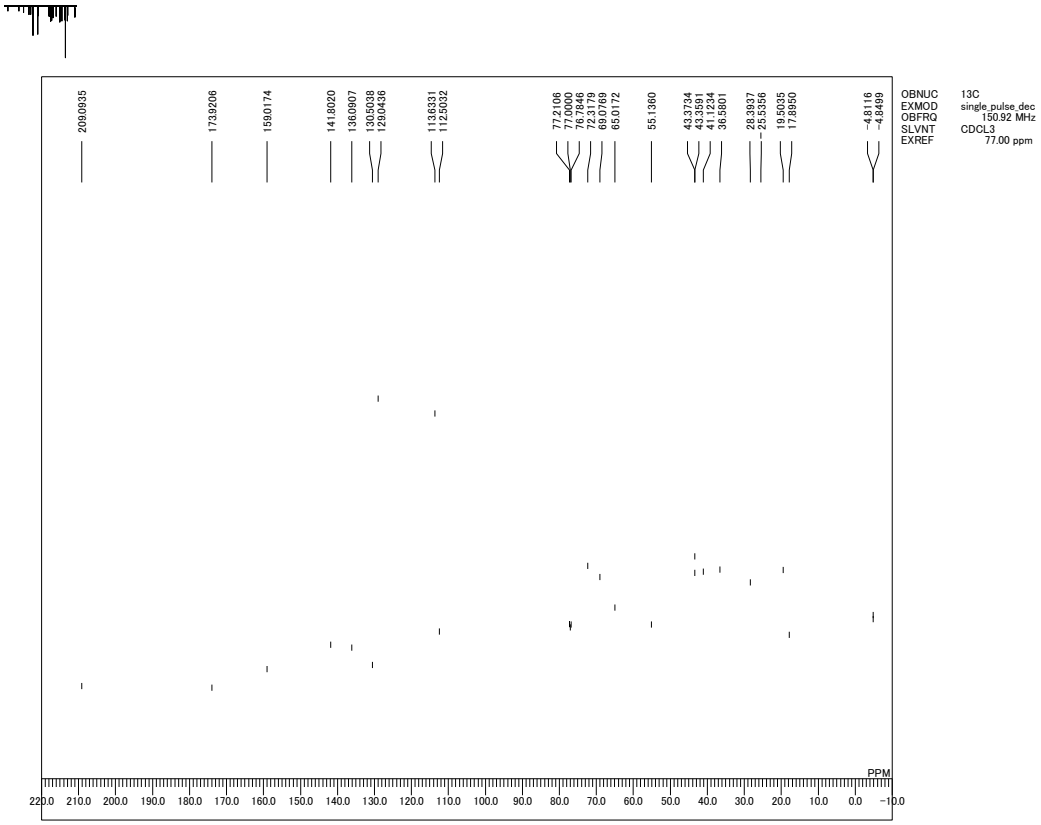

OBNUC 1H
EXMOD single_pulse.ex2
OBFRQ 600.17 MHz
SLVNT CDCL3
EXREF 0.00 ppm
OPMB
OTBS
(+)-105
2.03
2.00
0.95
1.97
2.00
1.03
2.01
3.08
2.05
2.01
2.05
9.38
PPM
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
-1.0

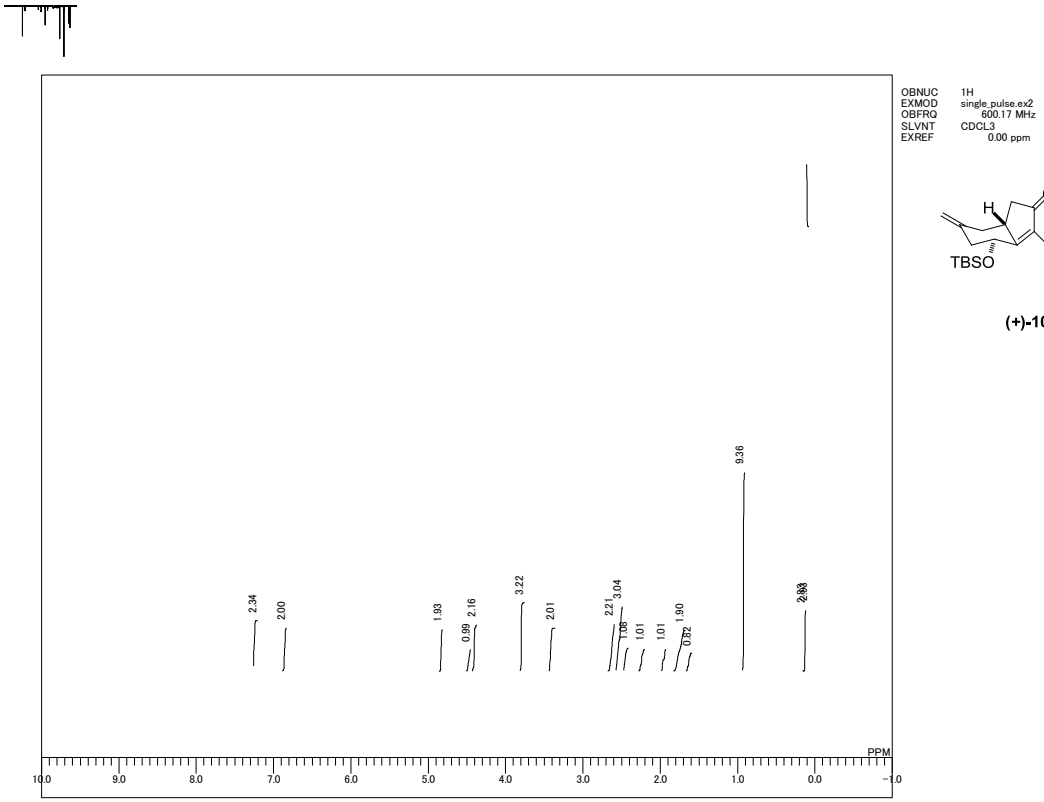

158.9887
143.7074
136.0380
130.3985
128.9910
116.1416
113.5565
113.3458
83.9982
81.7662
77.2495
77.0000
76.7894
72.4711
68.3731
62.3027
54.9397
45.1543
40.9127
28.7145
25.6793
18.0769
15.3864
-4.5962
-5.1515
OBNUC 13C
EXMOD single_pulse_dec
OBFRQ 150.92 MHz
SLVNT CDCL3
EXREF 77.00 ppm
PPM
220.0 210.0 200.0 190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0 0.0


9.30
3.02
2.98
2.13
2.00
1.99
1.97
2.04
2.05
1.95
1.01
0.99
0.94
0.95
1.14
0.94
OBNUC 1H
EXMOD single_pulse.ex2
OBFRQ 600.17 MHz
SLVNT CDCL3
EXREF 0.00 ppm
PPM
10.0 9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0.0

H
O
TBSO
OPMB

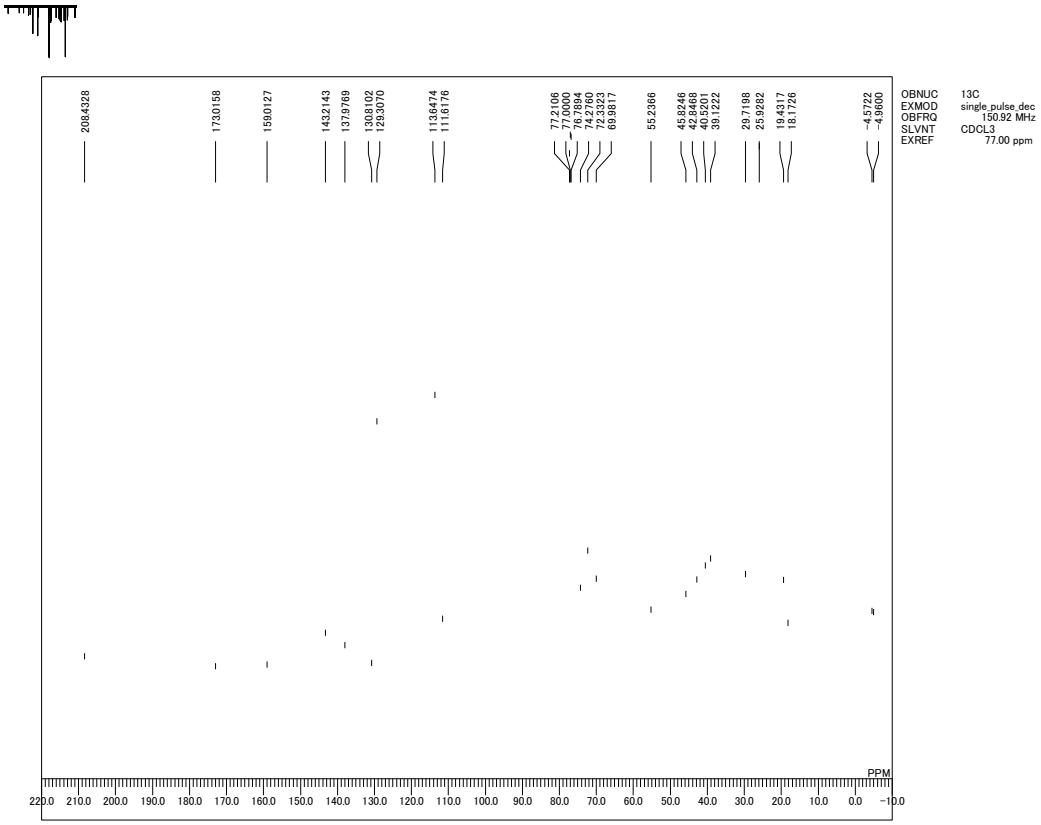
(-)-106

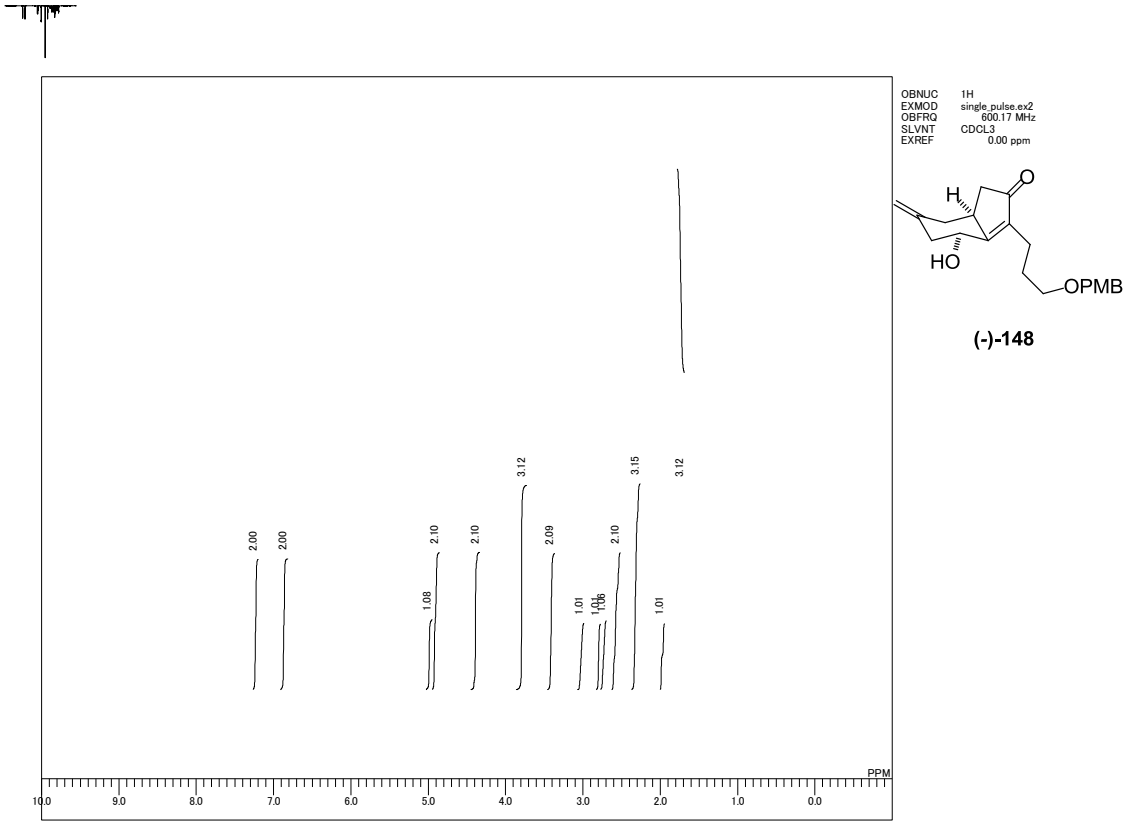

OBNUC 13C
EXMOD single_pulse_dec
OBFRQ 150.92 MHz
SLVNT CDCL3
EXREF 77.00 ppm
209.0935
173.9206
159.0174
141.8020
136.0907
130.5038
129.0436
113.6331
112.5032
77.2106
77.0000
76.7846
72.3179
69.0769
65.0172
55.1380
43.3734
43.1961
41.1234
36.5801
28.3937
25.5356
19.5035
17.8950
-4.8116
-4.8449
PPM


OBNUC 1H
EXMOD single_pulse.ex2
OBFRQ 600.17 MHz
SLVNT CDCL3
EXREF 0.00 ppm
2.34
2.00
1.93
0.99
2.16
3.22
2.01
2.21
3.04
1.08
1.01
1.01
1.90
0.82
9.36
2.83
2.83
PPM

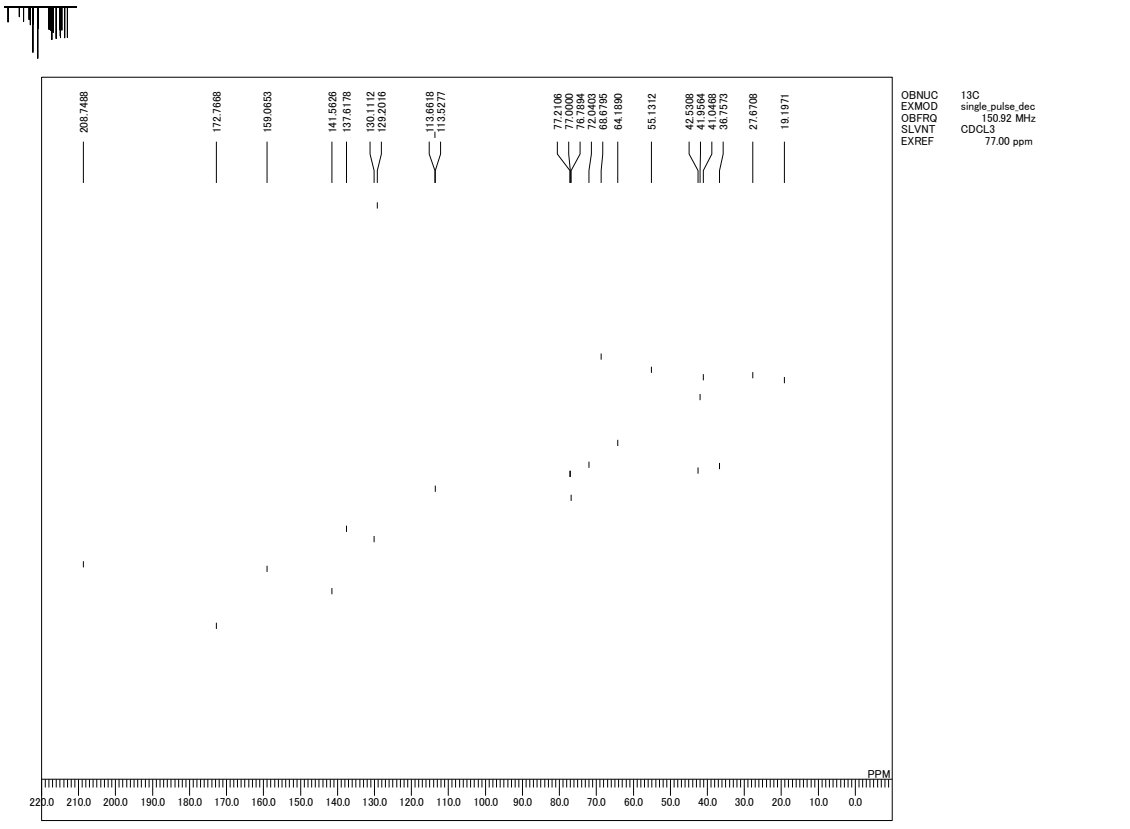
H
O
TBSO
OPMB

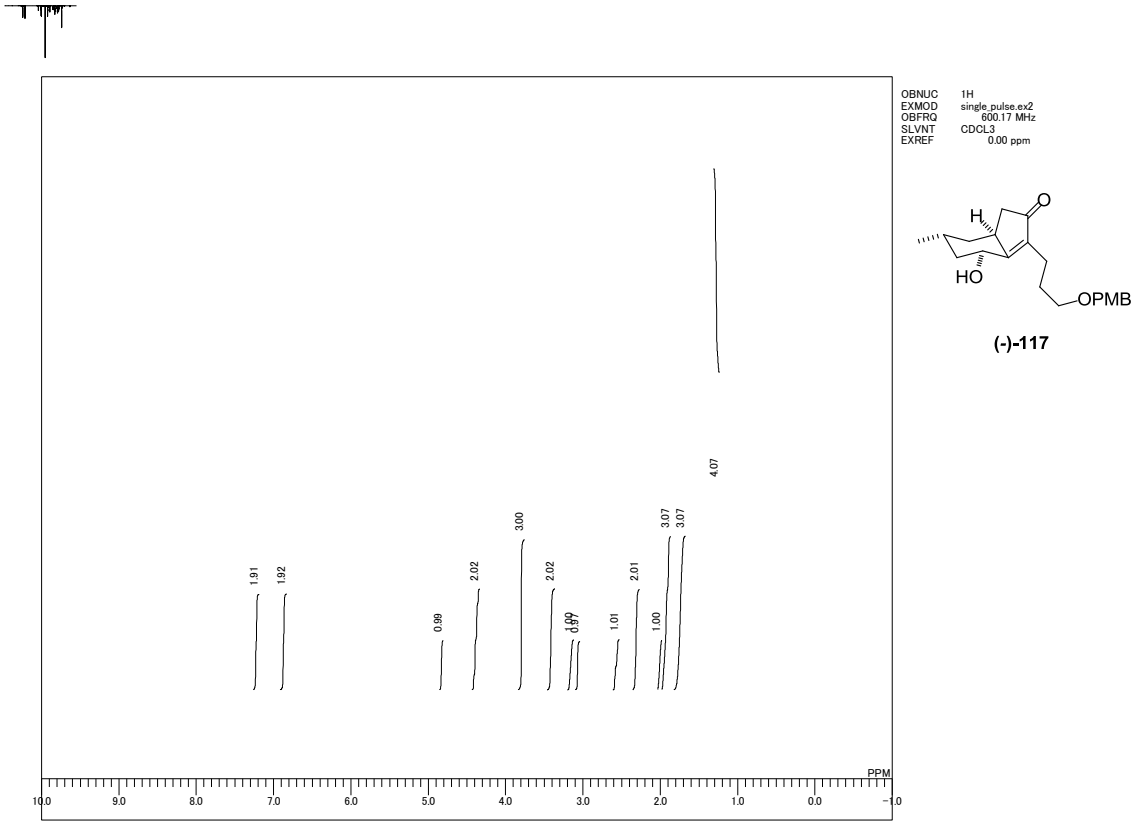
(+)-106'


208.4328
173.0158
159.0127
143.2143
137.9769
130.8102
129.3070
113.6474
111.6178
77.2106
77.0000
76.7894
74.2760
73.2323
69.9817
55.2366
45.8246
42.8468
40.5201
39.1222
29.7198
25.9282
19.4317
18.1726
-4.5722
-4.9600
OBNUC 13C
EXMOD single_pulse_dec
OBFRQ 150.92 MHz
SLVNT CDCL3
EXREF 77.00 ppm
PPM
220.0 210.0 200.0 190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0 0.0 -10.0

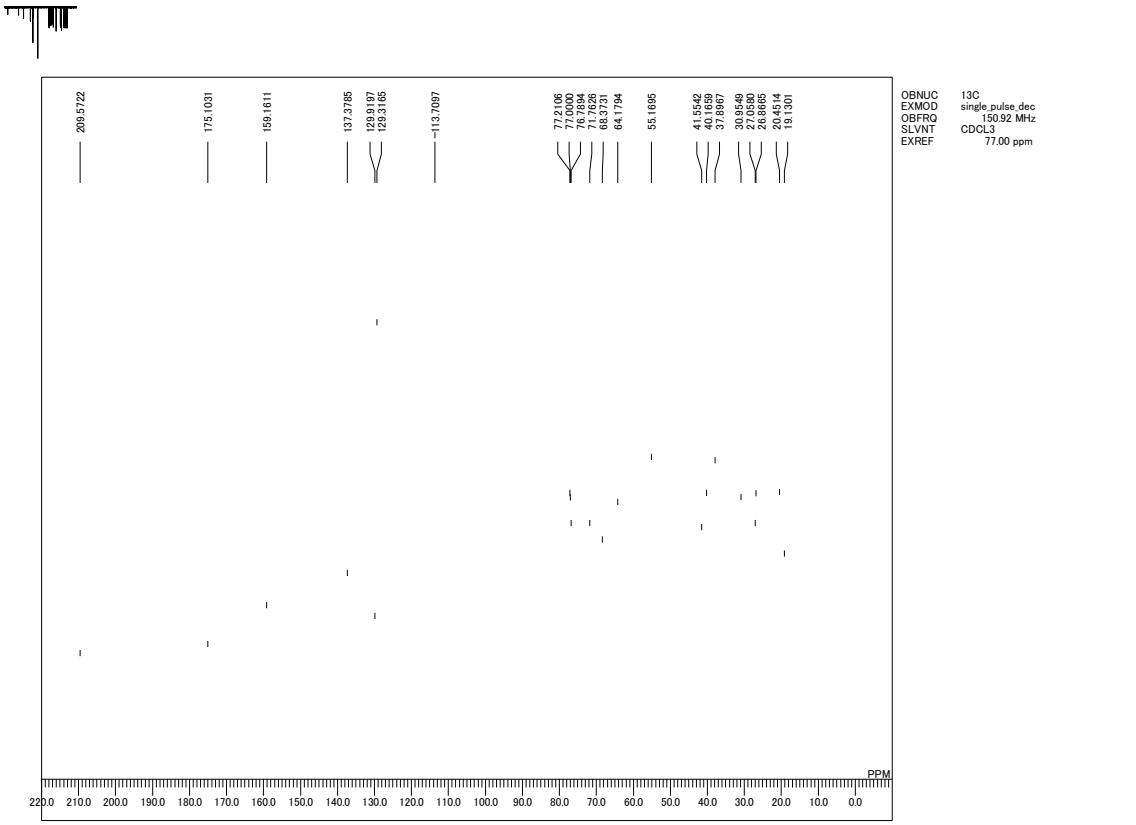

OBNUC 1H
EXMOD single_pulse.ex2
OBFRQ 600.17 MHz
SLVNT CDCL3
EXREF 0.00 ppm
H
O
HO
OPMB
2.00
2.00
1.08
2.10
2.10
3.12
2.09
1.01
1.01
1.06
2.10
3.15
1.01
3.12
PPM
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

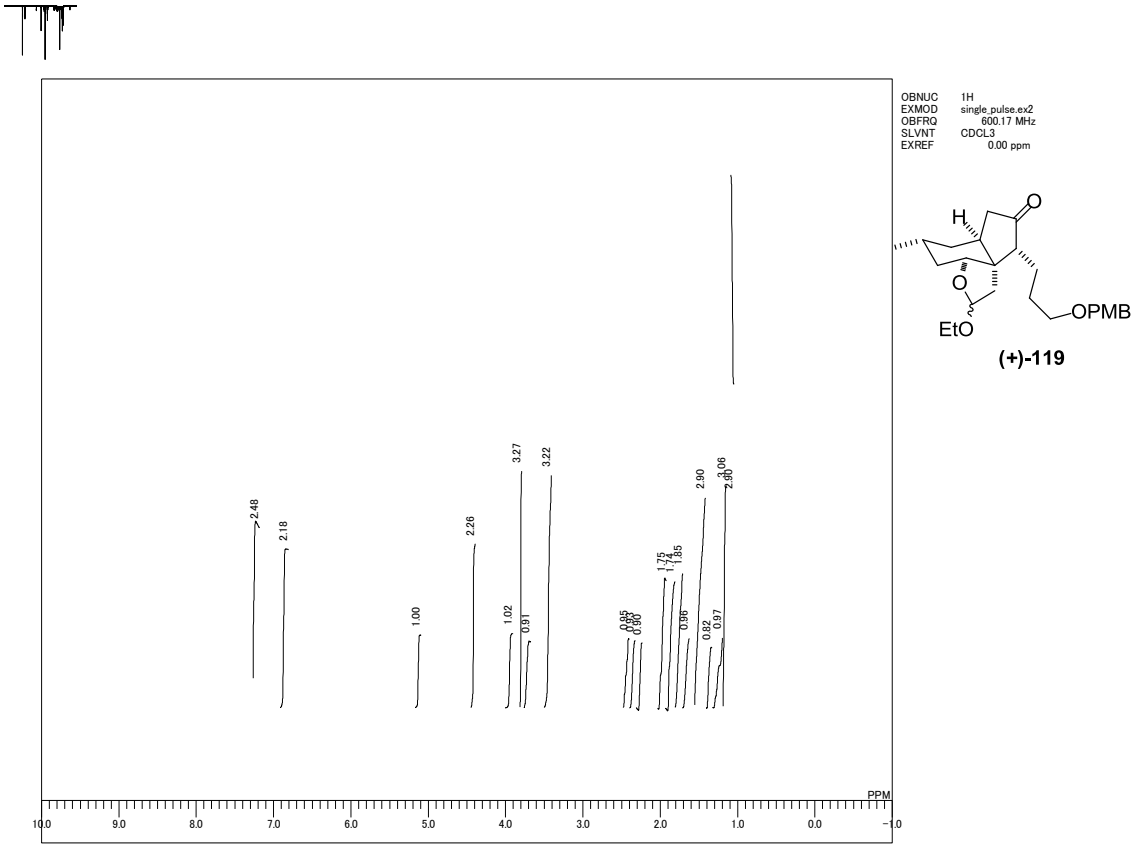
(-)-148

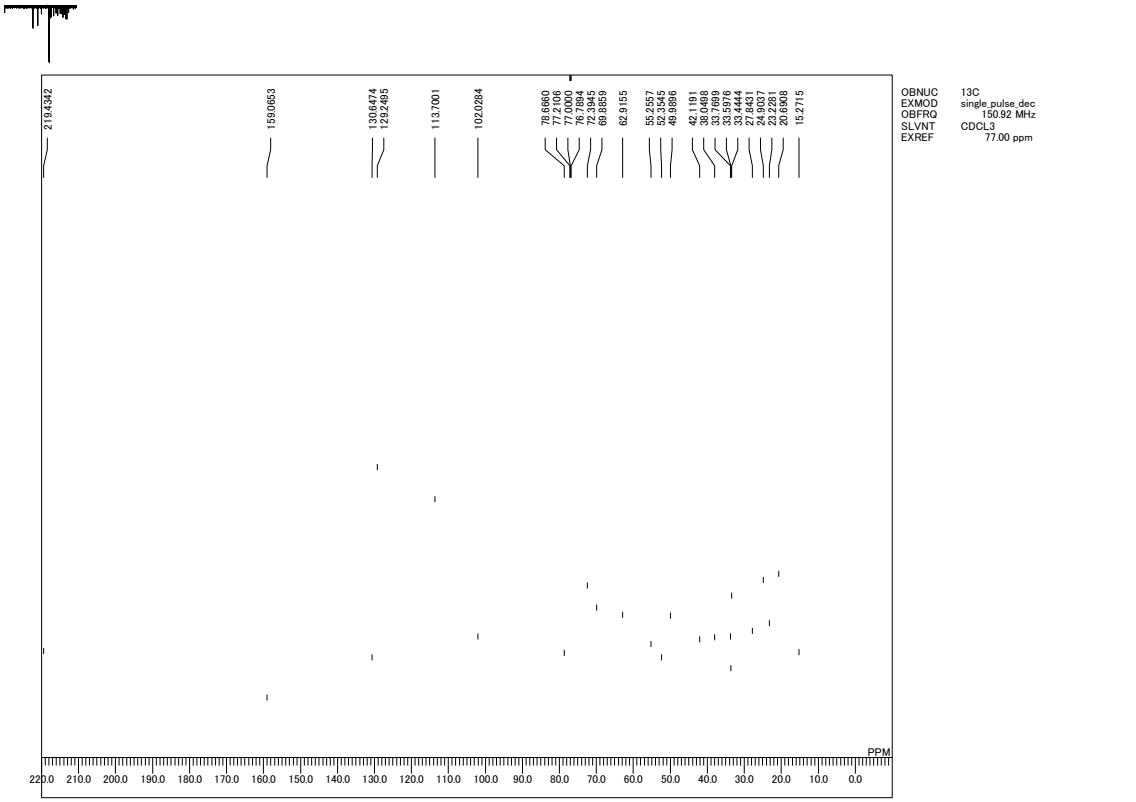

OBNUC 13C
EXMOD single_pulse_dec
OBFRQ 150.92 MHz
SLVNT CDCL3
EXREF 77.00 ppm
208.7488
172.7668
159.0653
141.5626
137.6178
130.1112
129.2016
113.6618
113.5277
77.2106
77.0000
76.7894
72.0403
68.6795
64.1890
55.1312
42.5308
41.9564
41.0668
36.7573
27.6708
19.1971
PPM
220.0
210.0
200.0
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0

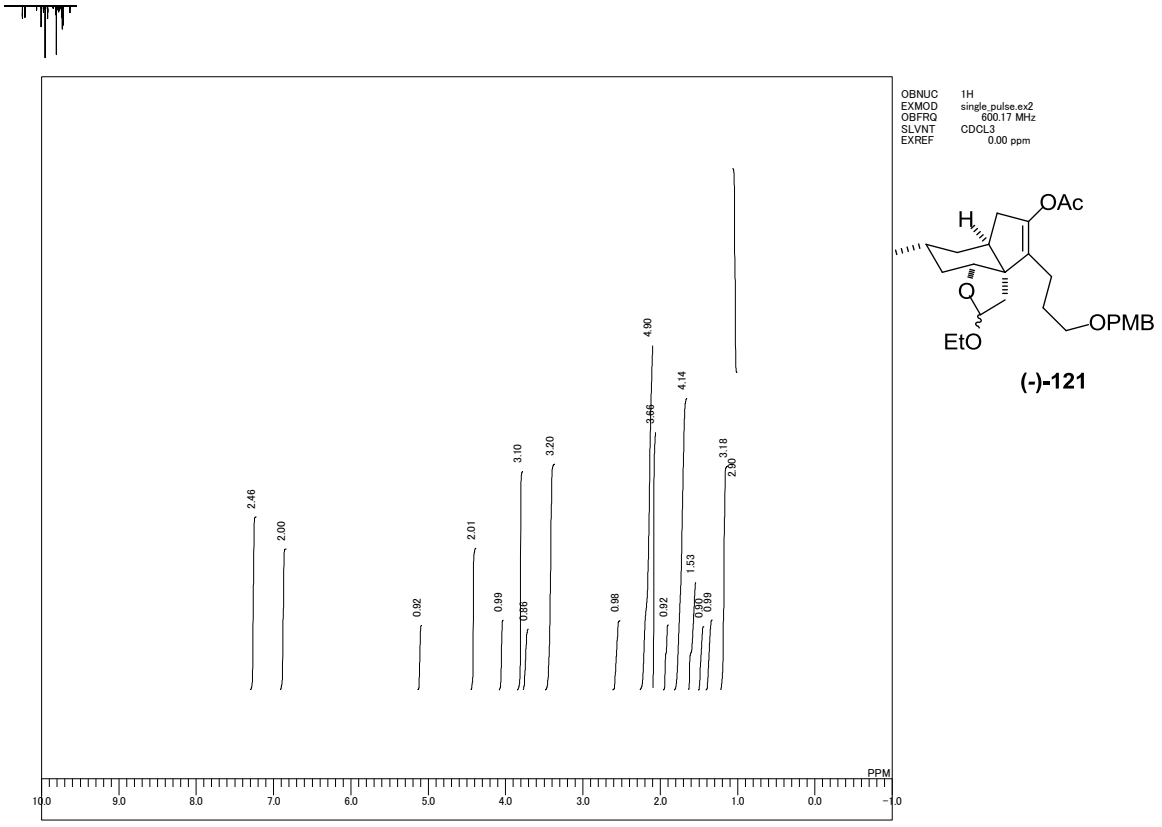

OBNUC 1H
EXMOD single_pulse.ex2
OBFRQ 600.17 MHz
SLVNT CDCL3
EXREF 0.00 ppm
H
O
HO
OPMB
1.91
1.92
0.99
2.02
3.00
2.02
1.01
2.01
1.00
3.07
3.07
4.07
PPM
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
-1.0

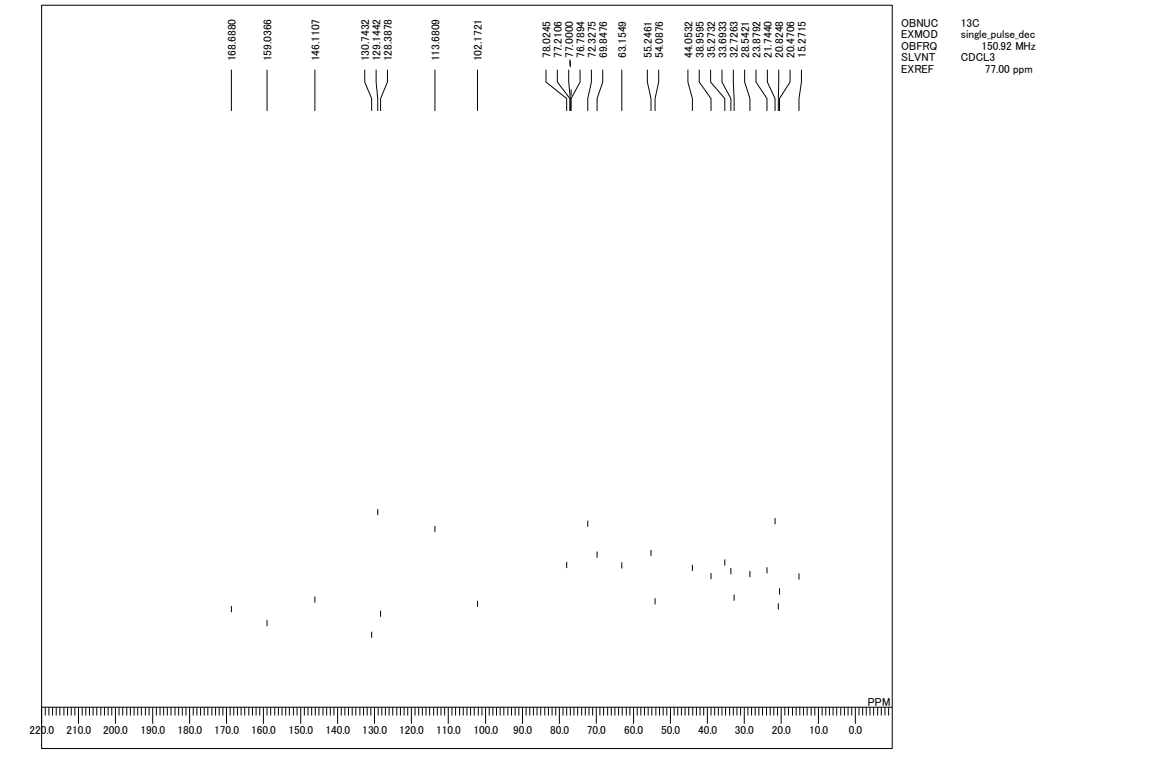
(-)-117

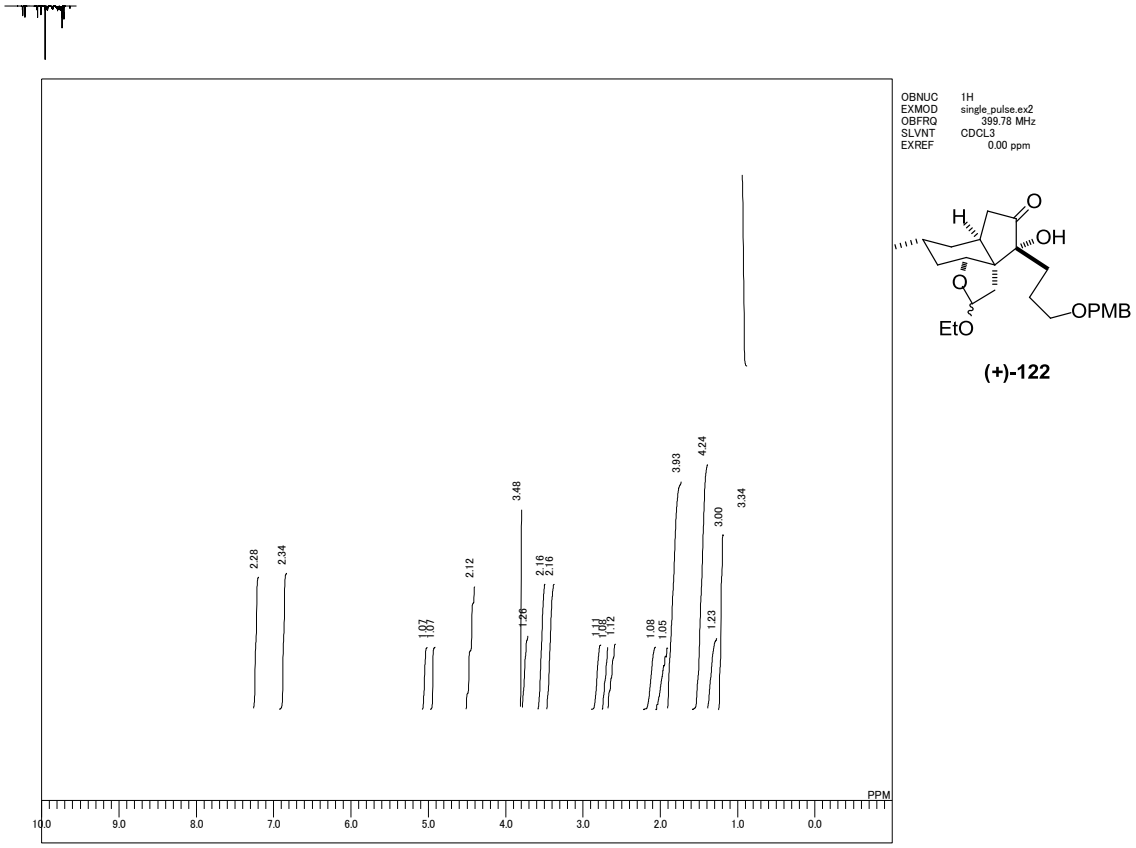

OBNUC 13C
EXMOD single_pulse_dec
OBFRQ 150.92 MHz
SLVNT CDCL3
EXREF 77.00 ppm
209.5722
175.1031
159.1611
137.3785
129.9197
129.3165
113.7097
77.2106
77.0000
76.7894
71.7626
68.3731
64.1794
55.1695
41.5542
40.1659
37.8967
30.9549
27.0580
26.8665
20.4514
19.1301
PPM
220.0
210.0
200.0
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0


OBNUC 1H
EXMOD single_pulse.ex2
OBFRQ 600.17 MHz
SLVNT CDCL3
EXREF 0.00 ppm
H
O
O
EtO
OPMB
(+)-119
2.48
2.18
1.00
2.26
1.02
3.27
0.91
3.22
0.85
0.87
0.90
1.75
1.74
1.85
0.96
2.90
0.82
3.06
3.00
0.97
PPM
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
−1.0

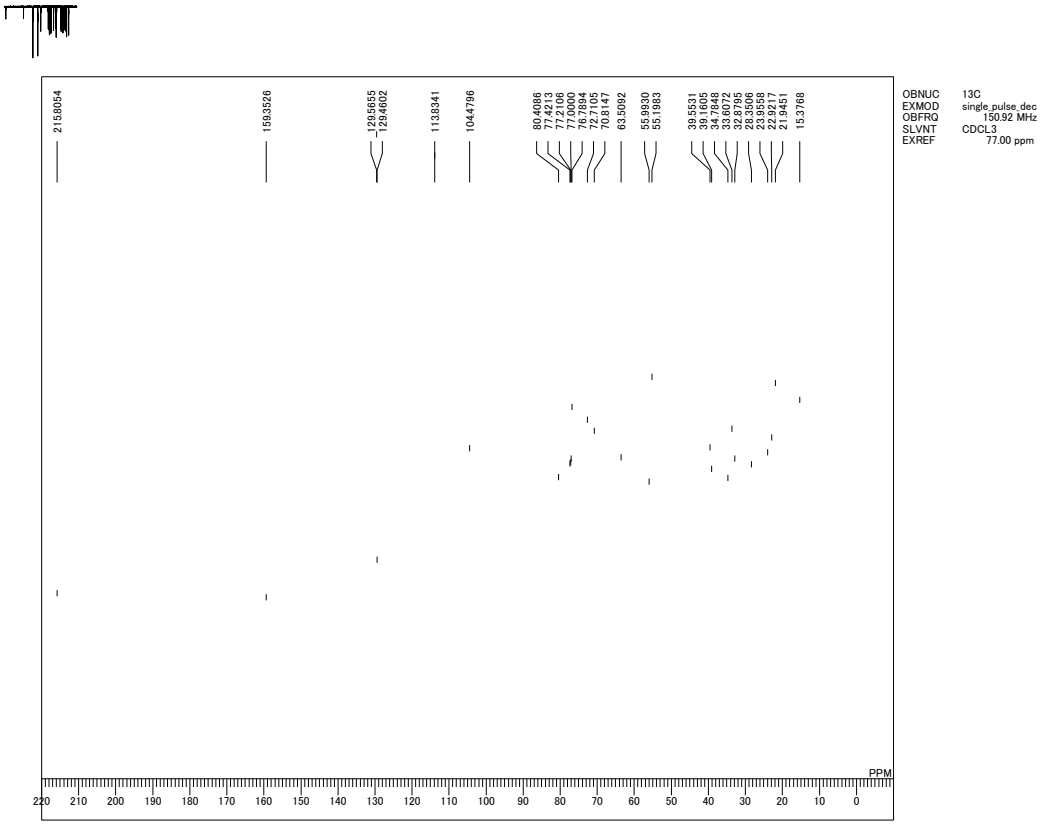

OBNUC 13C
EXMOD single_pulse_dec
OBFRQ 150.92 MHz
SLVNT CDCL3
EXREF 77.00 ppm
2194342
1590053
1306474
1292495
1137001
1020284
78.6660
77.2106
77.0000
76.7894
72.3945
69.8859
62.9155
55.2557
52.3545
49.9896
42.1191
38.0498
33.7689
33.5576
33.4444
27.8431
24.9037
23.2281
20.6908
15.2715
PPM
220.0
210.0
200.0
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0

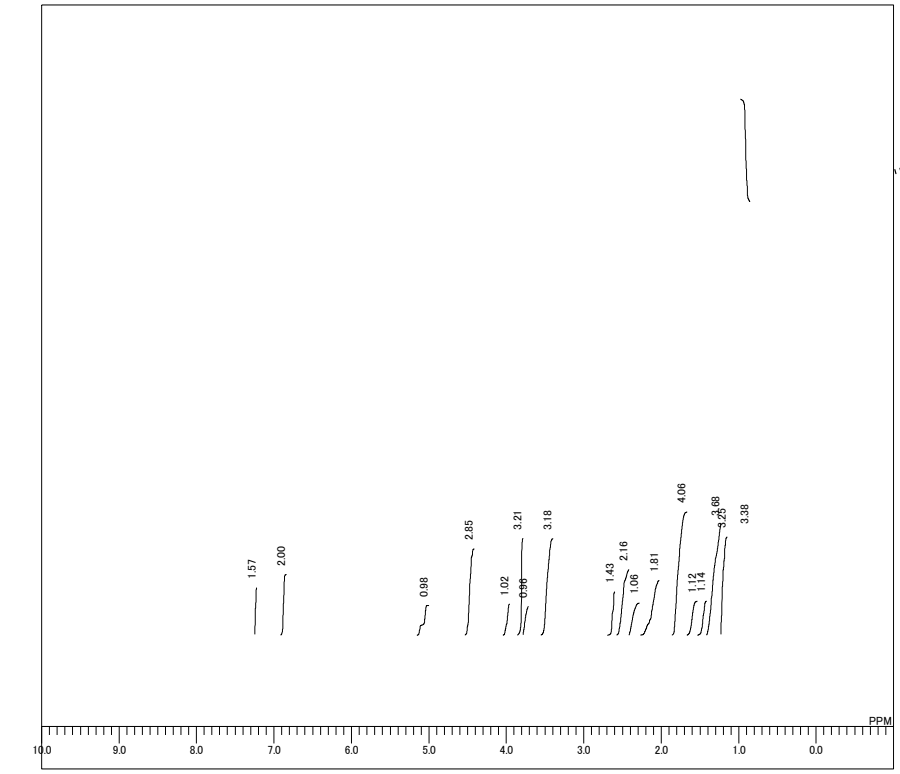

OBNUC 1H
EXMOD single_pulse.ex2
OBFRQ 600.17 MHz
SLVNT CDCL3
EXREF 0.00 ppm
OAc
H
O
EtO
OPMB
(-)-121
2.46
2.00
0.92
2.01
0.99
0.88
3.10
3.20
0.98
4.90
3.66
0.92
4.14
1.53
0.90
0.99
3.18
2.90
PPM

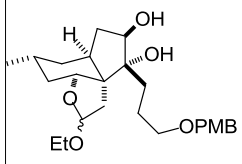

OBNUC 13C
EXMOD single_pulse_dec
OBFRQ 150.92 MHz
SLVNT CDCL3
EXREF 77.00 ppm
168.6880
159.0366
146.1107
130.7432
129.4462
128.3878
113.6809
102.1721
78.9245
77.2166
77.0000
76.7894
72.3275
69.8476
63.1549
55.2461
54.0876
44.0532
38.9395
35.2732
33.6933
32.7263
28.5421
23.8792
21.7144
20.8248
20.4706
15.2715
PPM


OBNUC 1H
EXMOD single_pulse.ex2
OBFRQ 399.78 MHz
SLVNT CDCL3
EXREF 0.00 ppm
H
O
OH
O
EtO
OPMB
2.28
2.34
1.87
1.87
2.12
1.26
3.48
2.16
2.16
1.11
1.02
1.08
1.05
3.93
4.24
1.23
3.00
3.34
PPM
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

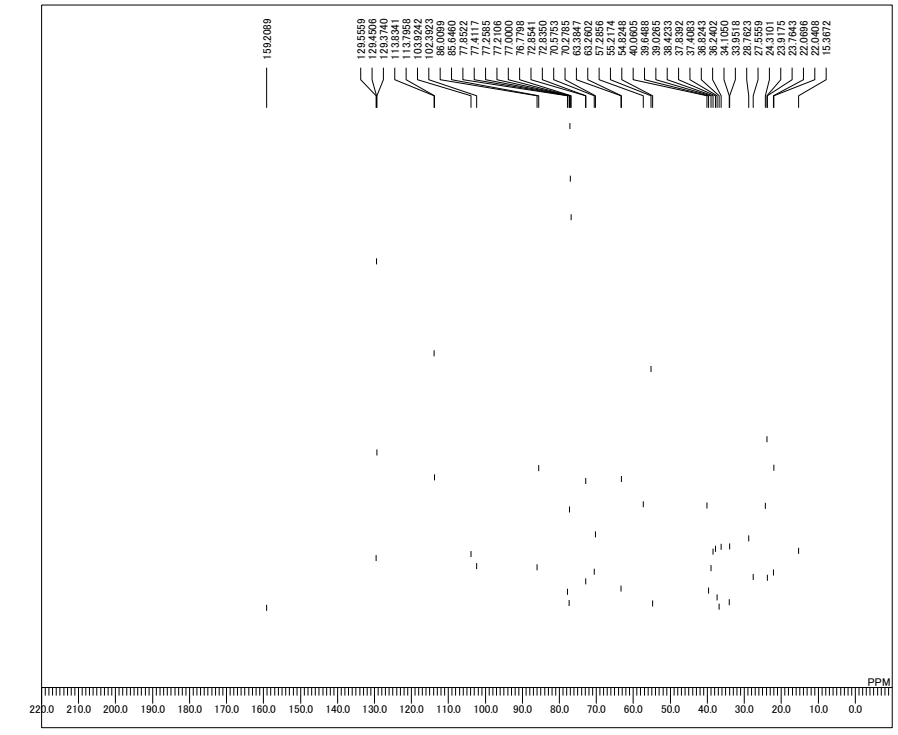
(+)-122

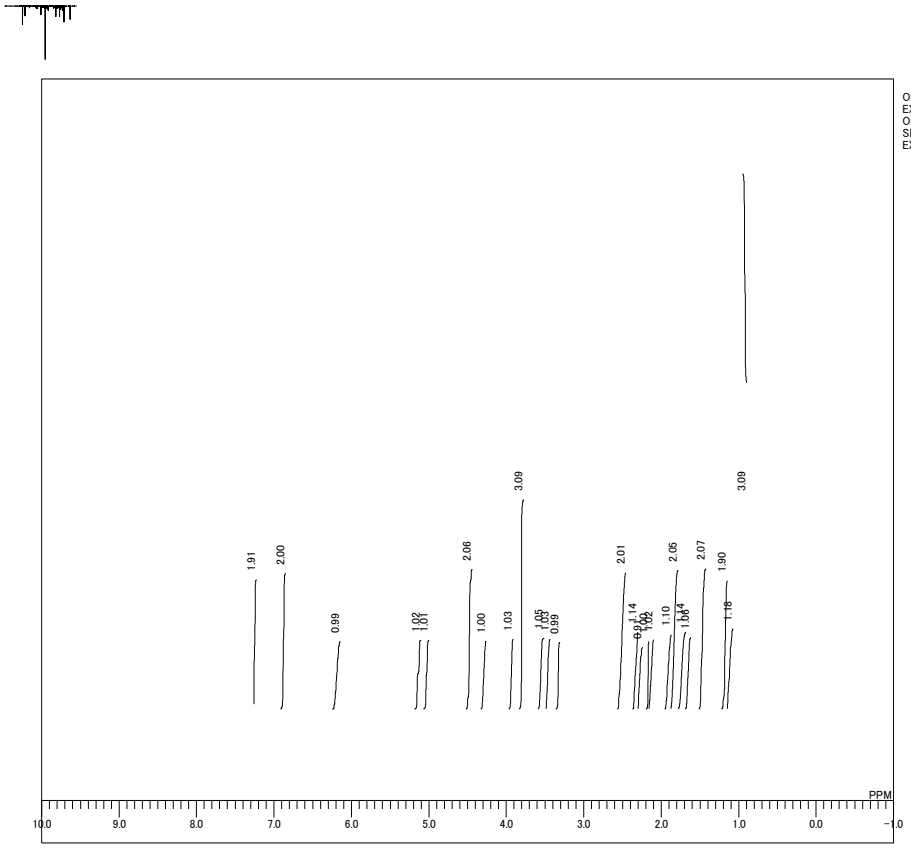

215.8054
159.3526
129.5655
129.4602
113.8341
104.4796
80.4086
77.4213
77.2106
77.0000
76.7894
72.7105
70.8147
63.5092
55.9930
55.1983
39.5531
39.1605
34.7848
33.6972
32.8795
28.3506
23.9558
22.9217
21.9451
15.3768
OBNUC 13C
EXMOD single_pulse_dec
OBFRQ 150.92 MHz
SLVNT CDCL3
EXREF 77.00 ppm
PPM
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

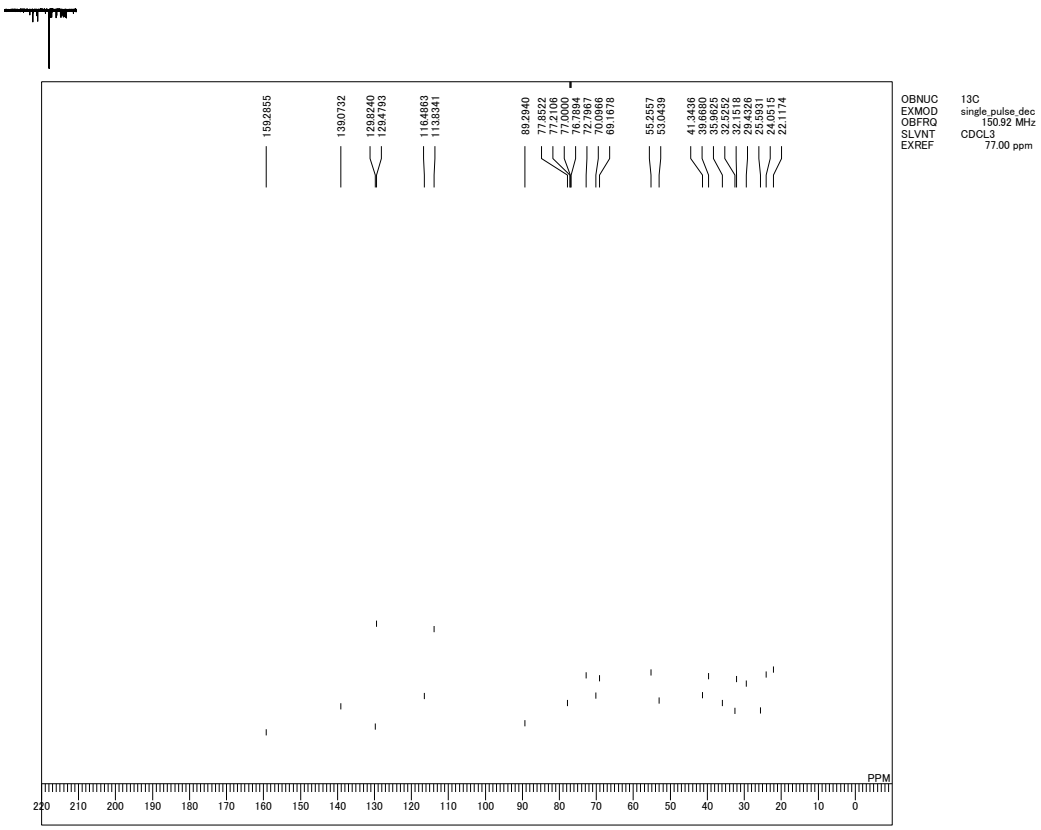

OBNUC 1H
EXMOD single_pulse.ex2
OBFRQ 600.17 MHz
SLVNT CDCL3
EXREF 0.00 ppm
1.57
2.00
0.98
2.85
1.02
0.86
3.21
3.18
1.43
2.16
1.06
1.81
1.12
1.14
4.06
3.88
3.22
3.38
PPM
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

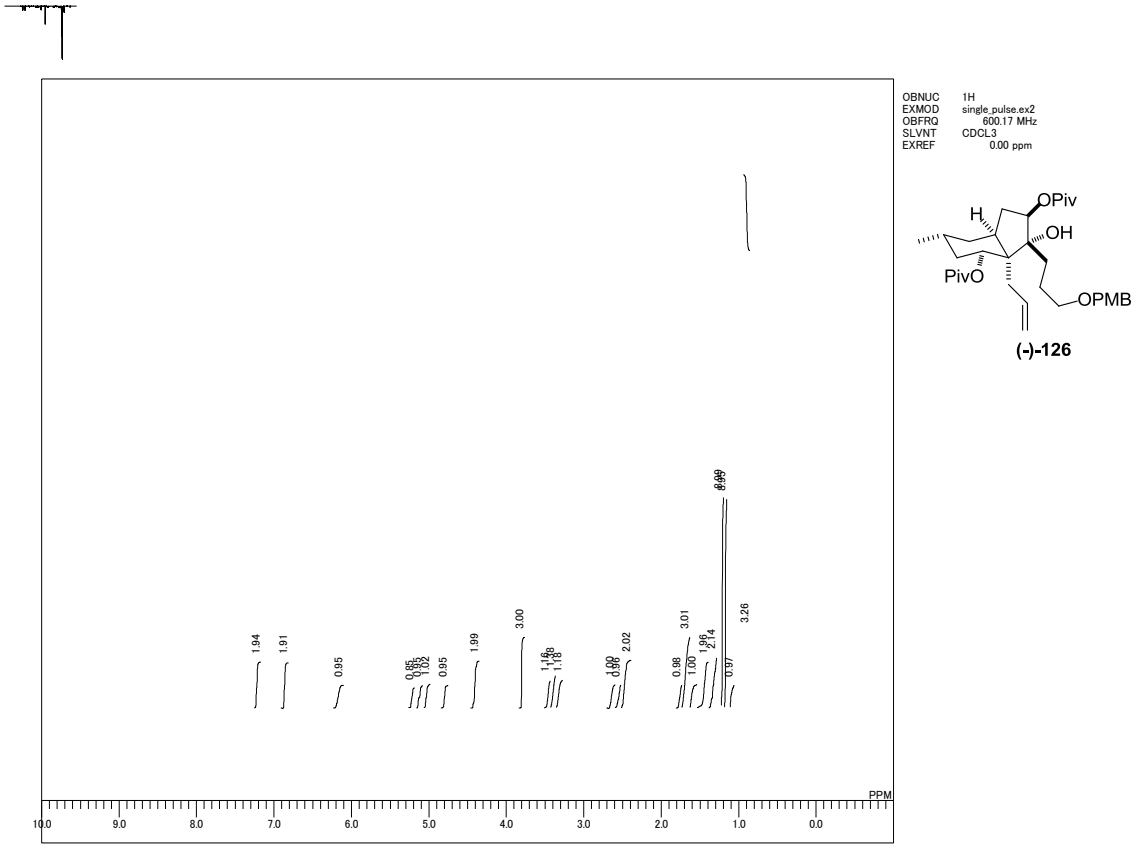

OH
H
OH
O
EtO
OPMB

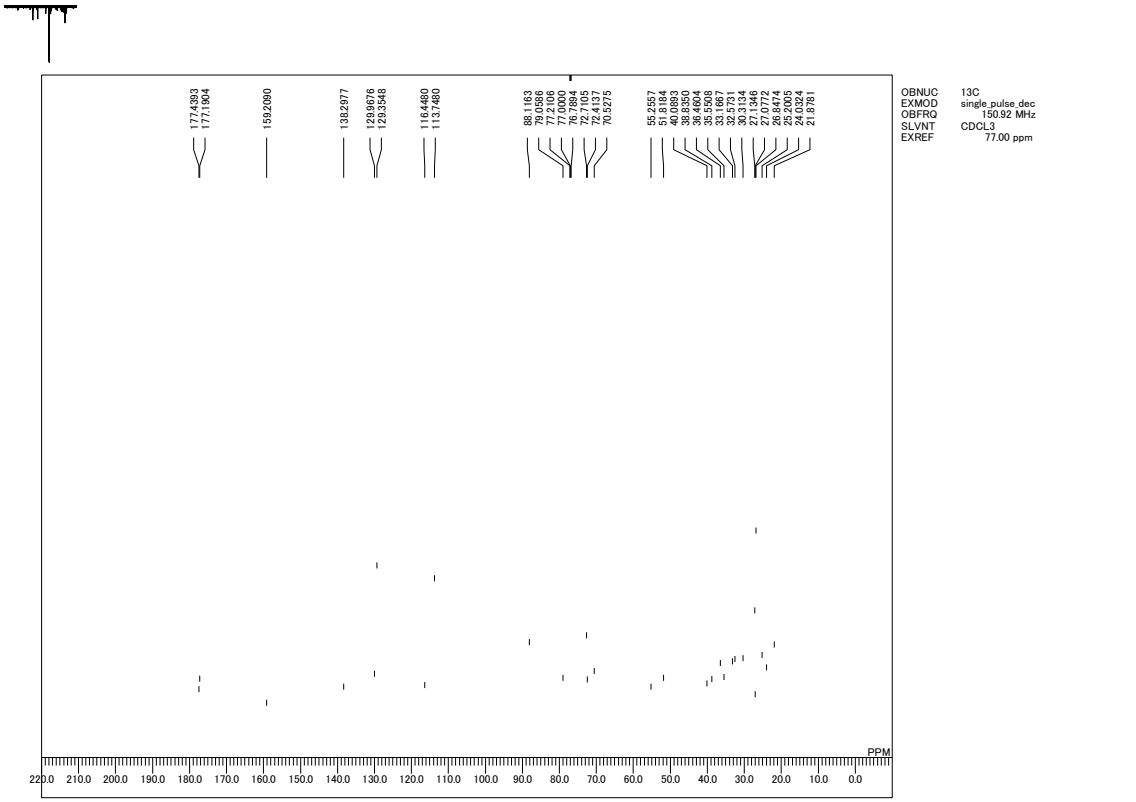
(-)-123

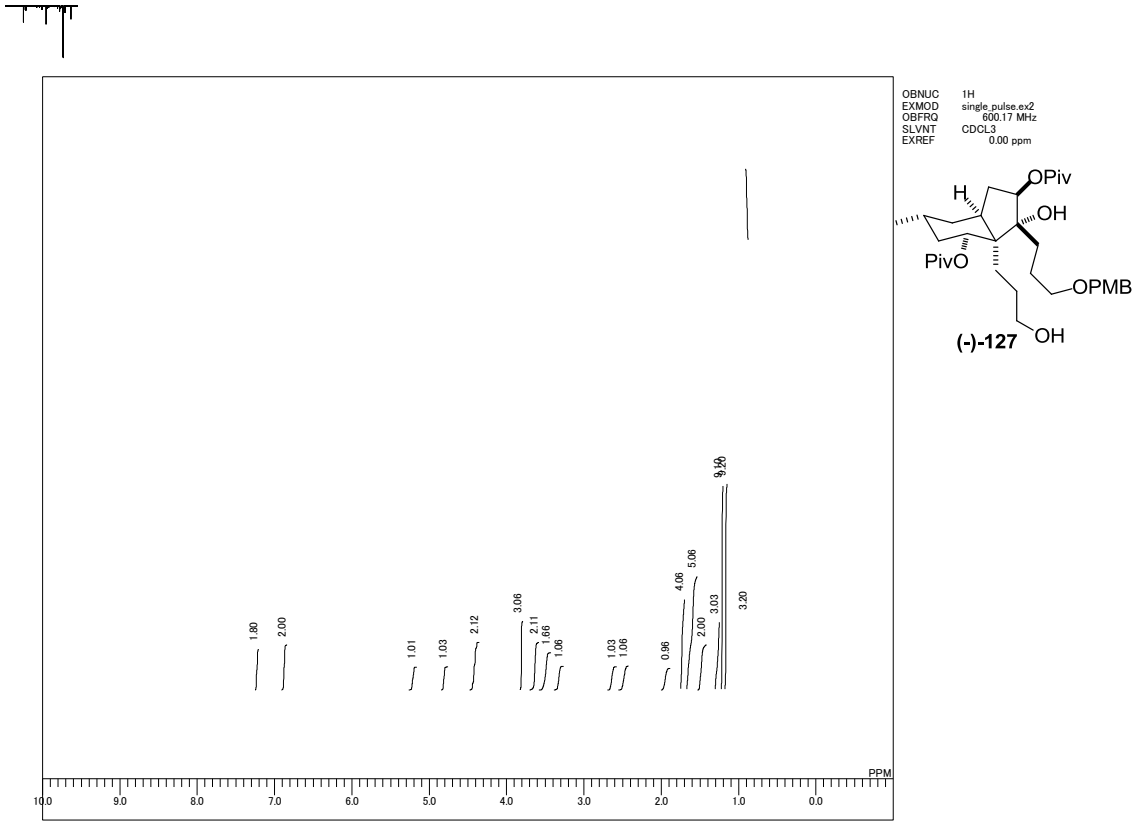

OBNUC 13C
EXMOD single_pulse_dec
OBFRQ 150.92 MHz
SLVNT CDCL3
EXREF 77.00 ppm
159.2089
129.5559
129.4506
129.3740
113.8341
113.7958
103.9844
102.3823
86.0099
85.6460
77.8522
77.4177
77.2585
77.2106
77.0000
76.7798
72.8541
72.8350
70.5753
70.2785
63.3847
63.2862
57.2805
55.2174
54.8248
40.0605
39.6488
39.2055
38.4233
37.8392
37.4083
36.8243
36.4492
34.1060
33.9518
28.7623
27.5559
24.3101
23.3175
23.7643
22.0696
22.0408
15.3672
PPM
220.0
210.0
200.0
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0

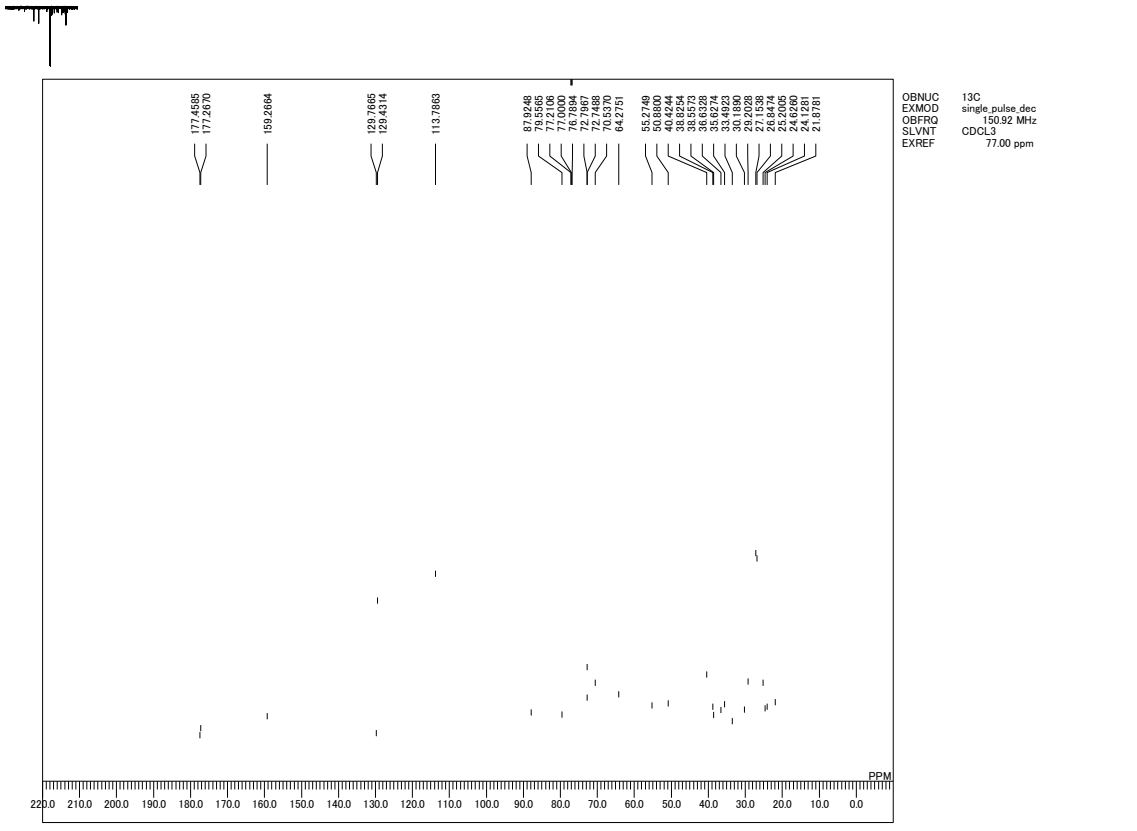

OBNUC 1H
EXMOD single_pulse.ex2
OBFRQ 600.17 MHz
SLVNT CDCL3
EXREF 0.00 ppm
OH
H
OH
HO
OPMB
(-)-125
1.91
2.00
0.99
1.02
1.01
2.06
1.00
1.03
3.09
1.05
1.03
0.99
2.01
1.14
0.97
0.93
1.02
1.10
1.08
1.04
2.05
2.07
1.90
1.16
3.09
PPM
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
-1.0

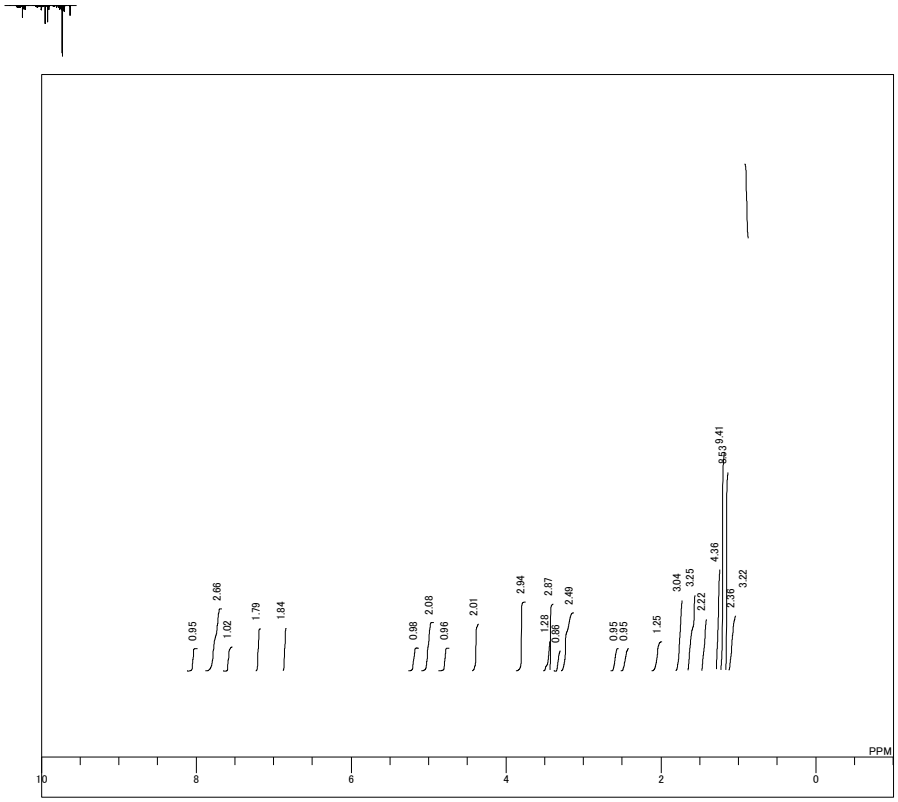

159.2855
139.0732
129.8240
129.4793
116.4863
113.8341
89.2940
77.8522
77.2106
77.0000
76.7894
72.1967
70.0966
69.1678
55.2557
53.0439
41.3436
39.6680
35.8925
33.2032
32.1518
29.4326
25.5931
24.0515
22.1714
OBNUC 13C
EXMOD single_pulse_dec
OBFRQ 150.92 MHz
SLVNT CDCL3
EXREF 77.00 ppm
PPM
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

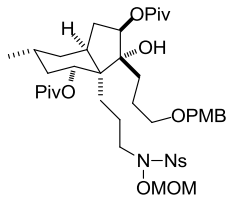

OBNUC 1H
EXMOD single_pulse.ex2
OBFRQ 600.17 MHz
SLVNT CDCL3
EXREF 0.00 ppm
OPiv
H
OH
PivO
OPMB
(-)-126
1.94
1.91
0.95
0.85
0.85
1.02
0.95
1.99
3.00
1.16
1.18
1.18
0.88
0.88
2.02
0.98
3.01
1.00
1.96
2.14
8.99
8.99
0.97
3.26
PPM
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0


OBNUC 13C
EXMOD single_pulse_dec
OBFRQ 150.92 MHz
SLVNT CDCL3
EXREF 77.00 ppm
174.4383
171.1904
159.2090
138.2977
129.9676
129.3548
116.4480
113.7480
88.1163
79.0586
77.2106
77.0000
76.7894
72.7165
72.4137
70.5275
55.2557
51.8184
40.0883
38.4850
36.4464
35.5508
33.1667
32.5731
30.3134
29.7346
27.0772
26.8474
25.2005
24.0324
21.3781
PPM
220.0
210.0
200.0
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0

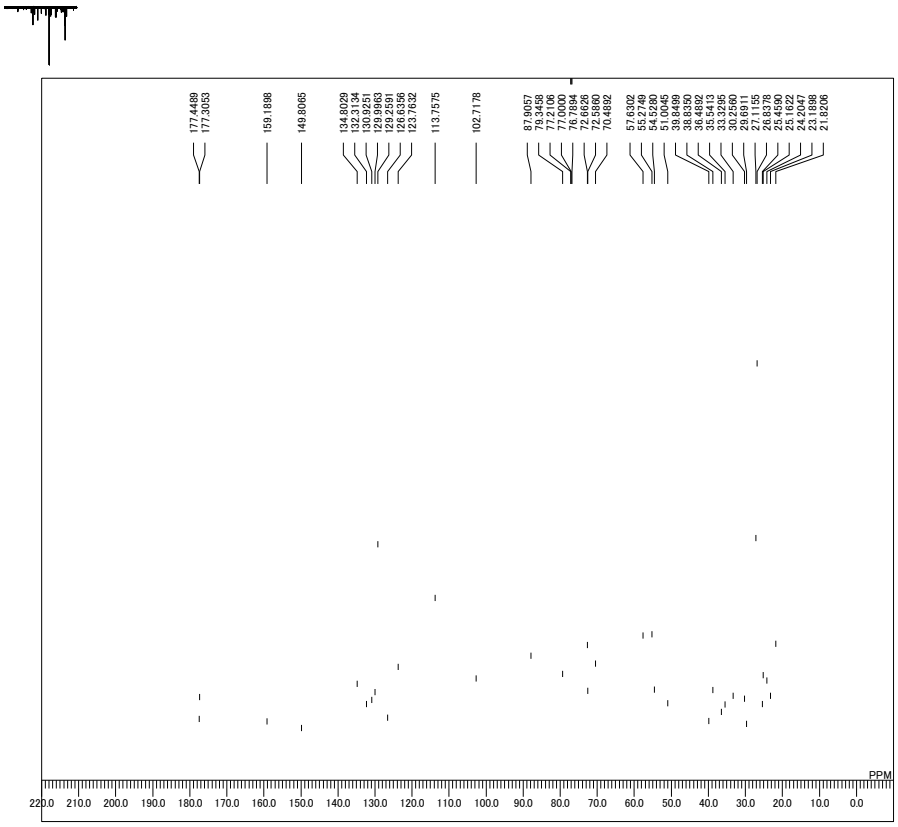

OBNUC 1H
EXMOD single_pulse.ex2
OBFRQ 600.17 MHz
SLVNT CDCL3
EXREF 0.00 ppm
OPiv
H
OH
PivO
OPMB
OH
(-)-127
1.80
2.00
1.01
1.03
2.12
3.06
2.11
1.66
1.06
1.03
1.06
0.96
4.06
5.06
2.00
3.03
9.20
3.20
PPM
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

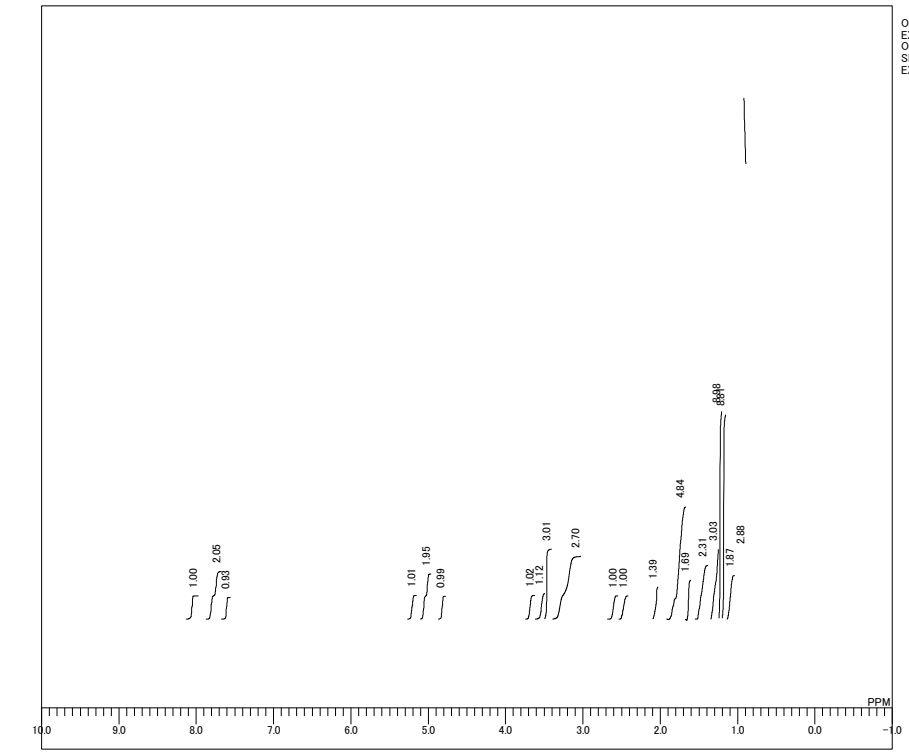

OBNUC 13C
EXMOD single_pulse_dec
OBFRQ 150.92 MHz
SLVNT CDCL3
EXREF 77.00 ppm
177.4585
177.2670
159.2664
129.7665
129.4314
113.7863
87.9248
79.5565
77.2106
77.0000
76.7894
72.7967
72.7488
70.5370
64.2751
55.2749
50.0000
40.4244
38.8254
38.5573
36.6328
35.6724
33.4923
30.1890
29.2028
27.1538
26.8474
26.2005
24.6286
24.1281
21.8781
PPM
220.0
210.0
200.0
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0

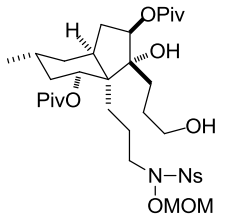

OBNUC 1H
EXMOD single_pulse.ex2
OBFRQ 600.17 MHz
SLVNT CDCL3
EXREF 0.00 ppm
0.95
2.66
1.02
1.79
1.84
0.98
2.08
0.96
2.01
2.94
1.28
2.87
0.86
2.49
0.95
0.95
1.25
3.04
3.25
2.22
4.36
9.53
9.41
2.36
3.22
PPM
10
8
6
4
2
0


OPiv
H
OH
PivO
OPMB
N–Ns
OMOM

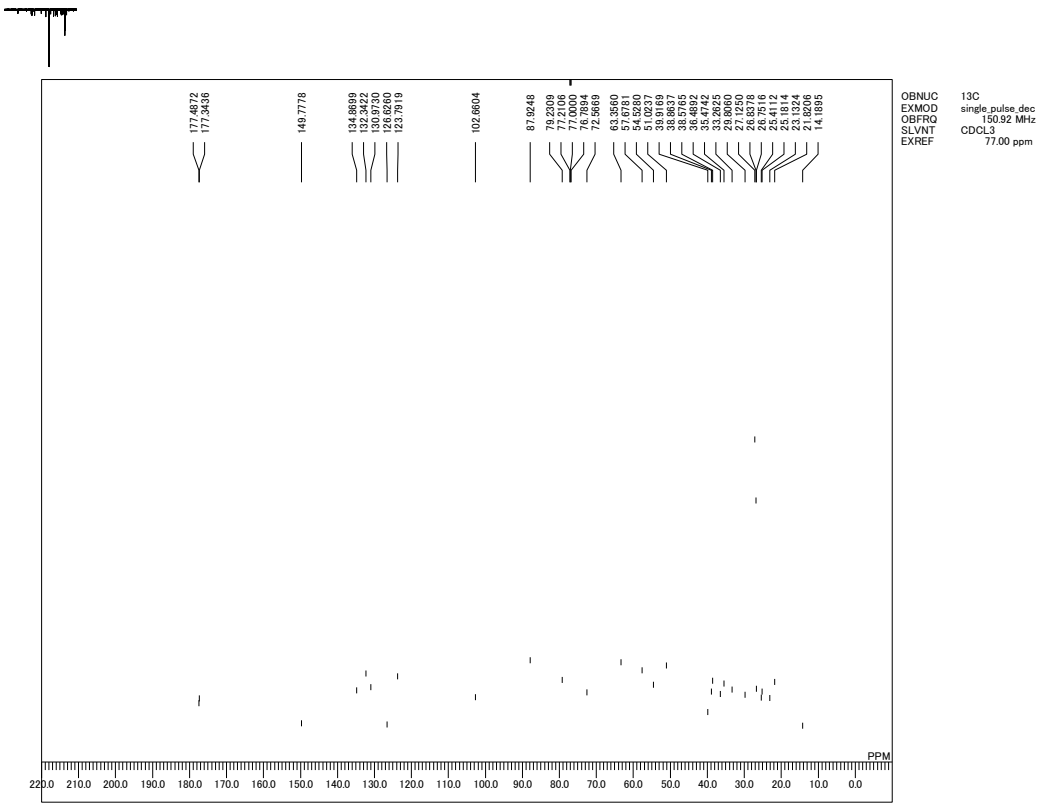
(-)-128

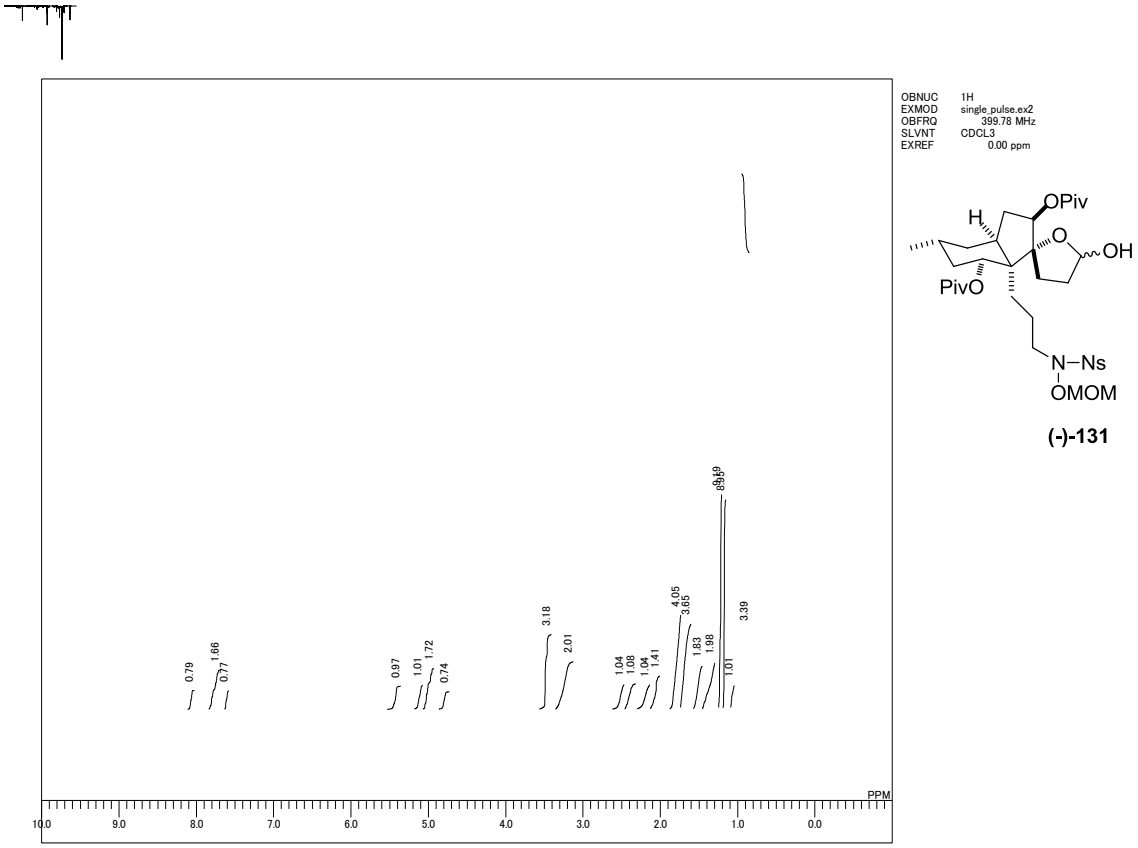

OBNUC 13C
EXMOD single_pulse_dec
OBFRQ 150.92 MHz
SLVNT CDCL3
EXREF 77.00 ppm
177.4489
177.3053
159.1898
149.8065
134.8029
132.3134
130.9251
129.9893
129.2391
126.6356
123.7632
113.7575
102.7178
87.9057
79.3458
77.2106
77.0000
76.7894
72.6628
72.5880
70.4892
57.6302
55.2748
54.5280
51.0045
39.8499
38.8350
38.4492
35.5413
33.3295
30.2560
28.6911
27.1155
26.8378
25.4590
25.1622
24.2047
23.1988
21.8236
PPM
220.0
210.0
200.0
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0

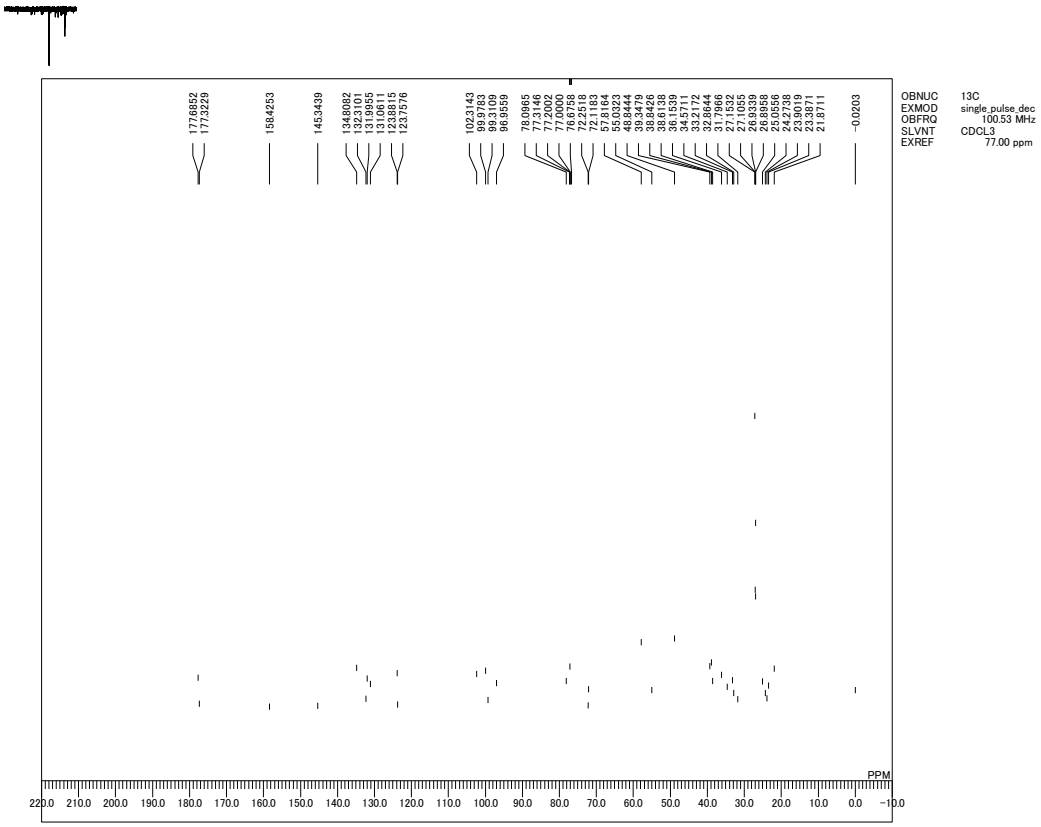

OBNUC 1H
EXMOD single_pulse.ex2
OBFRQ 600.17 MHz
SLVNT CDCL3
EXREF 0.00 ppm
1.00
2.05
0.93
1.01
1.95
0.99
1.02
1.12
3.01
2.70
1.00
1.00
1.39
4.84
1.69
2.31
3.03
1.87
2.88
PPM
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
−1.0

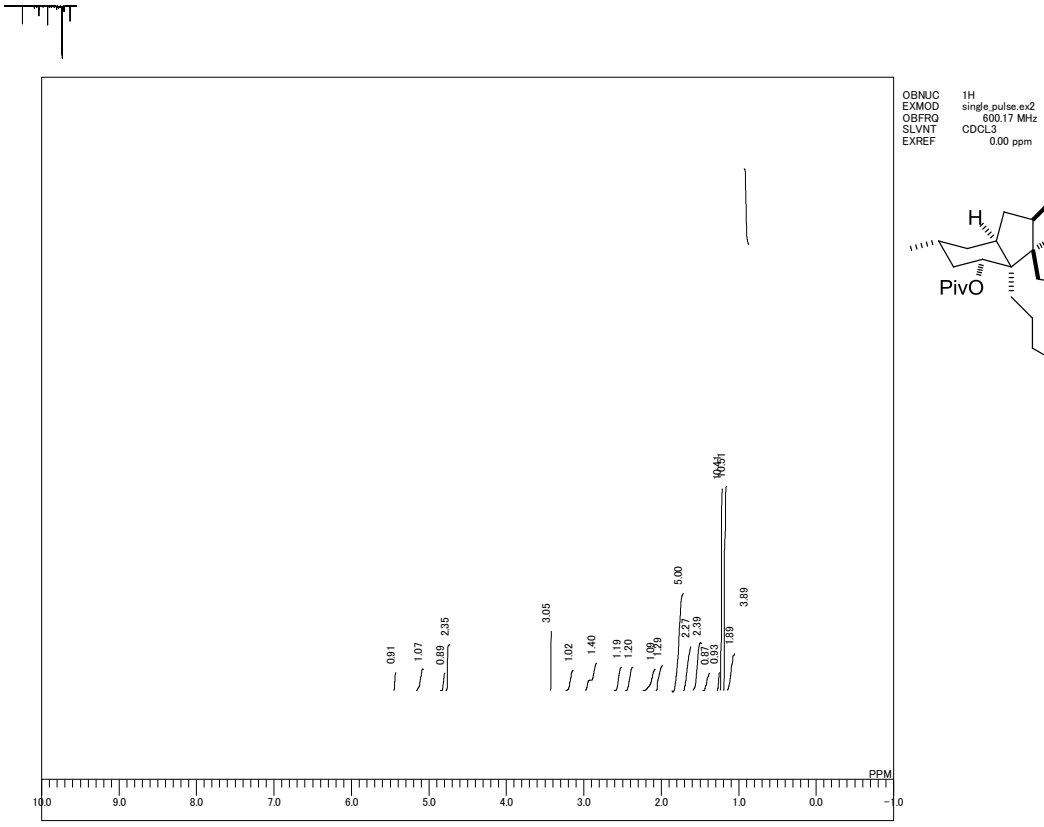

OPiv
H
OH
PivO
OH
N–Ns
OMOM

(-)-129


177.4672
177.3436
149.7778
134.8699
132.3422
130.1730
126.6260
123.7919
102.6604
87.9248
79.2309
77.2106
77.0000
76.7894
72.5669
63.3560
57.6781
54.5280
51.0237
39.9169
39.7487
38.5765
36.4892
35.4742
33.2625
29.8060
27.1270
26.8378
26.7516
25.4112
25.1814
23.1324
21.8206
14.1895
OBNUC 13C
EXMOD single_pulse_dec
OBFRQ 150.92 MHz
SLVNT CDCL3
EXREF 77.00 ppm
PPM
220.0 210.0 200.0 190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0 0.0

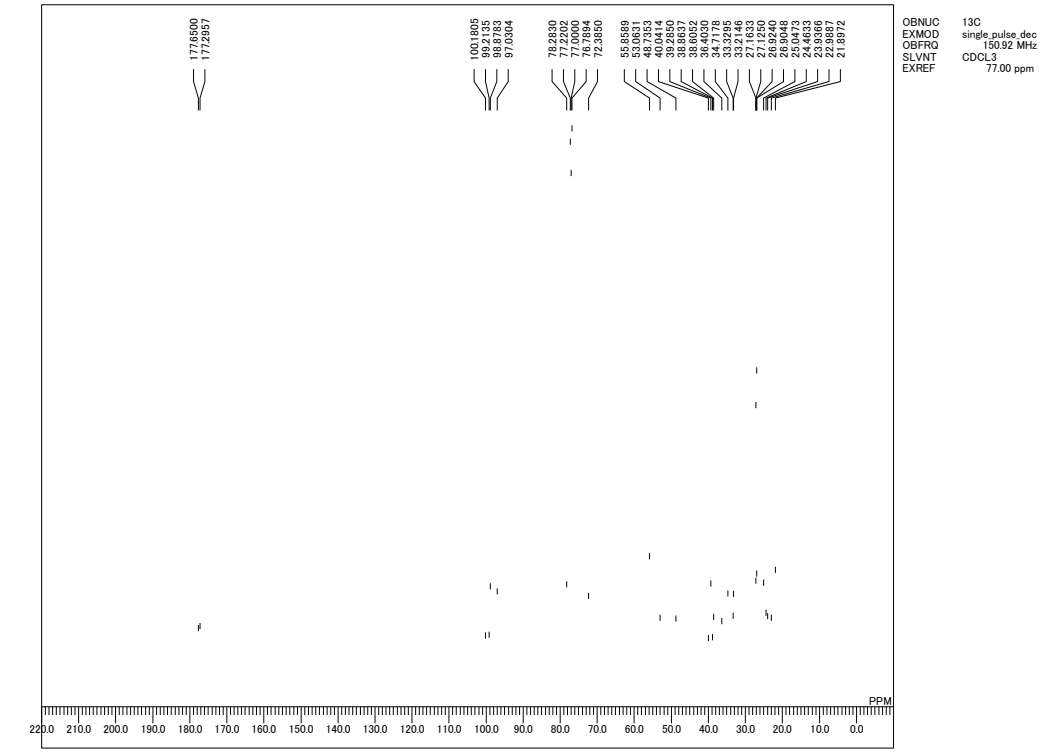

OBNUC 1H
EXMOD single_pulse.ex2
OBFRQ 399.78 MHz
SLVNT CDCL3
EXREF 0.00 ppm
OPiv
H
O
OH
PivO
N–Ns
OMOM
(-)-131
0.79
1.66
0.77
0.97
1.01
1.72
0.74
3.18
2.01
1.04
1.08
1.04
1.41
4.05
3.65
1.83
1.98
8.99
8.97
1.01
3.39
PPM
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

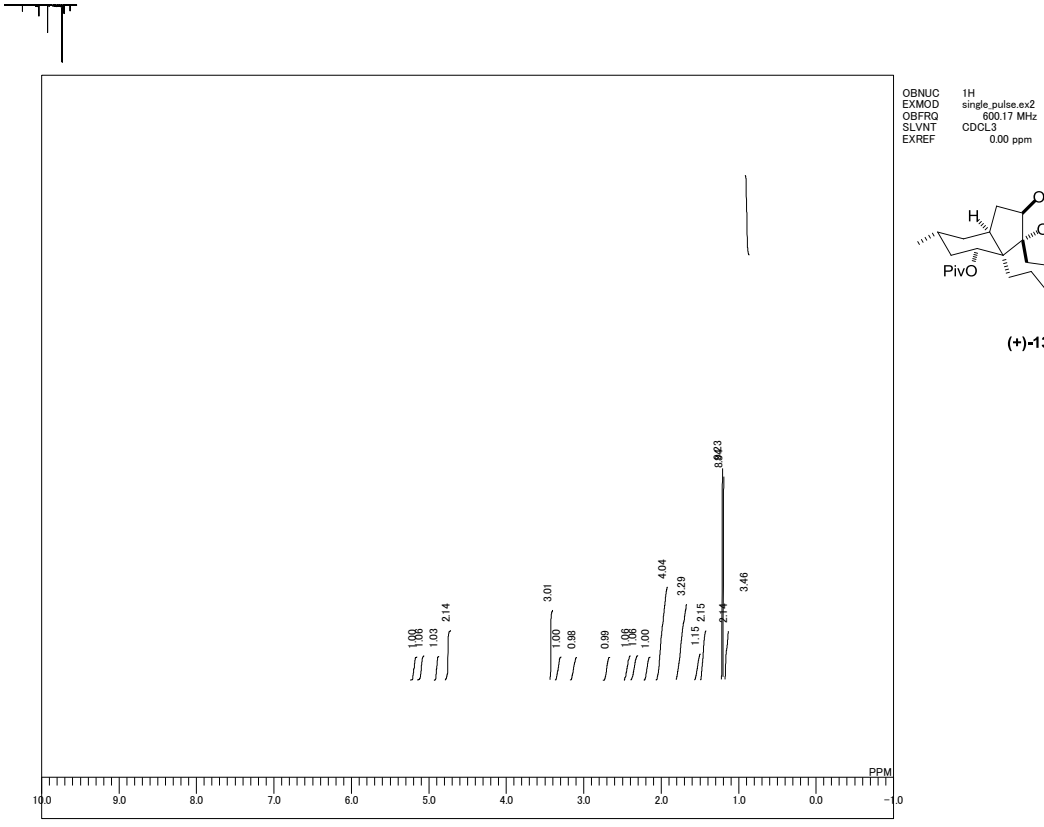

OBNUC 13C
EXMOD single_pulse_dec
OBFRQ 100.53 MHz
SLVNT CDCL3
EXREF 77.00 ppm
PPM


OBNUC 1H
EXMOD single_pulse.ex2
OBFRQ 600.17 MHz
SLVNT CDCL3
EXREF 0.00 ppm
PPM

OPiv
H
O
OH
PivO
N–H
OMOM

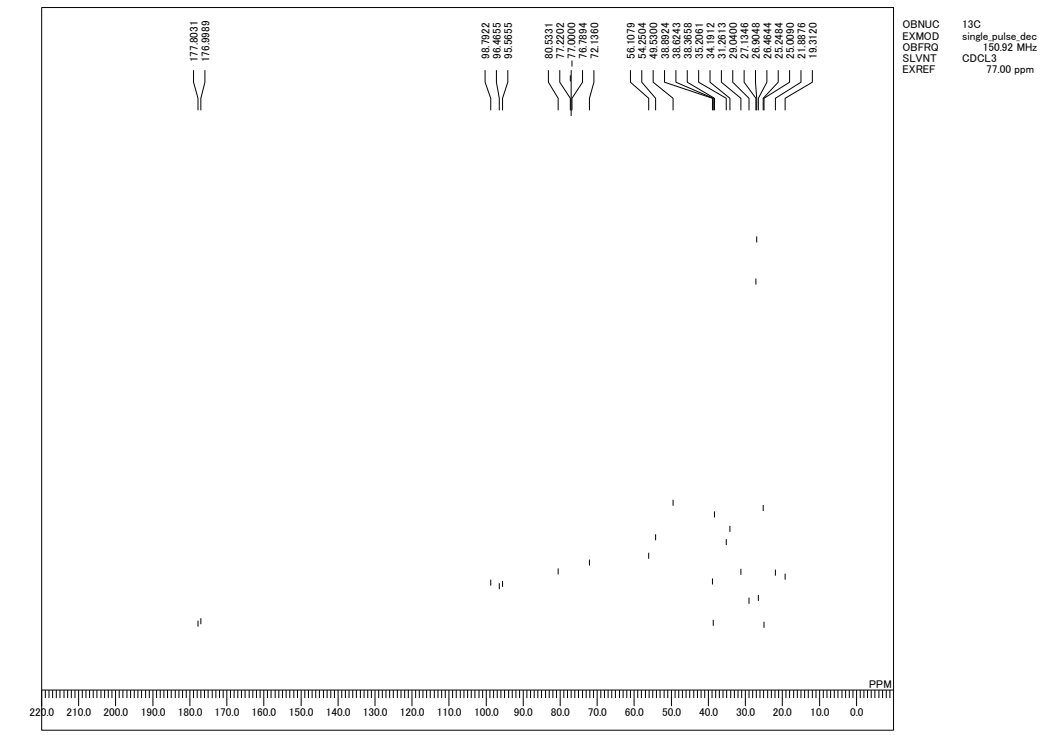
(-)-132

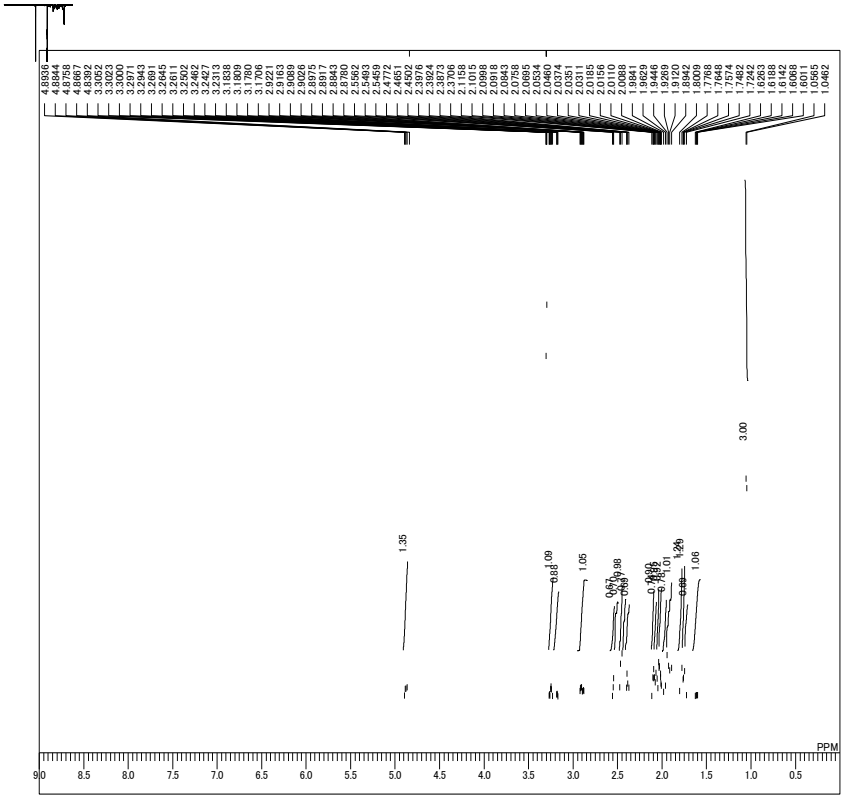

OBNUC 13C
EXMOD single_pulse_dec
OBFRQ 150.92 MHz
SLVNT CDCL3
EXREF 77.00 ppm
PPM

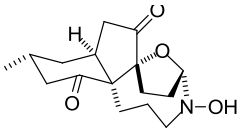

OBNUC 1H
EXMOD single_pulse.ex2
OBFRQ 600.17 MHz
SLVNT CDCL3
EXREF 0.00 ppm
PPM

OPiv
H
O
PivO
N–OMOM

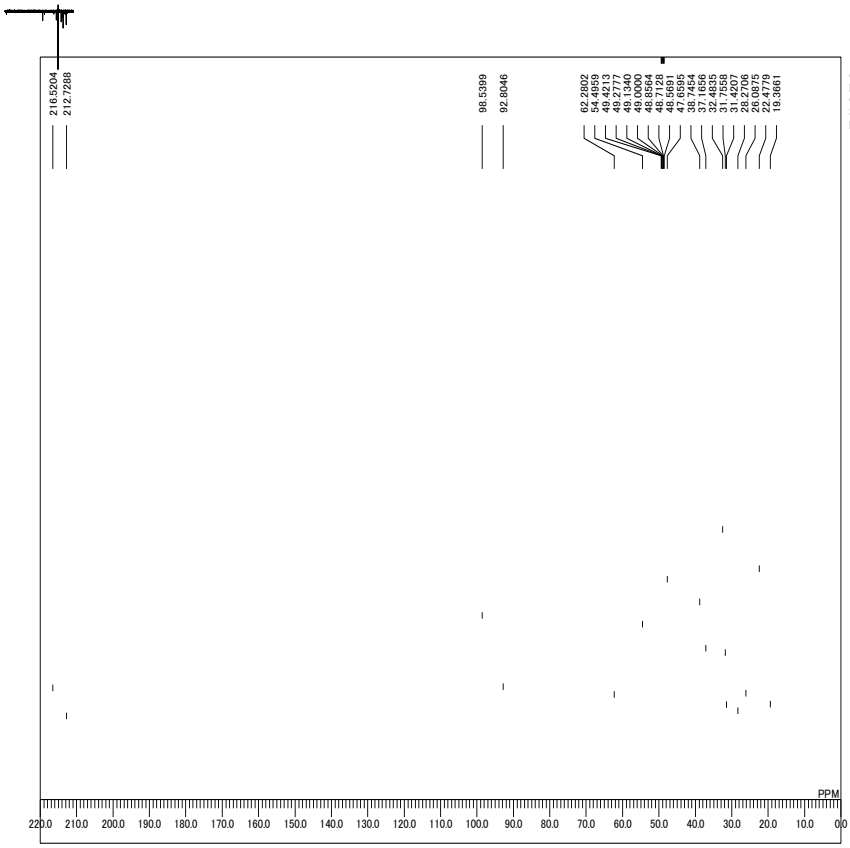
(+)-137

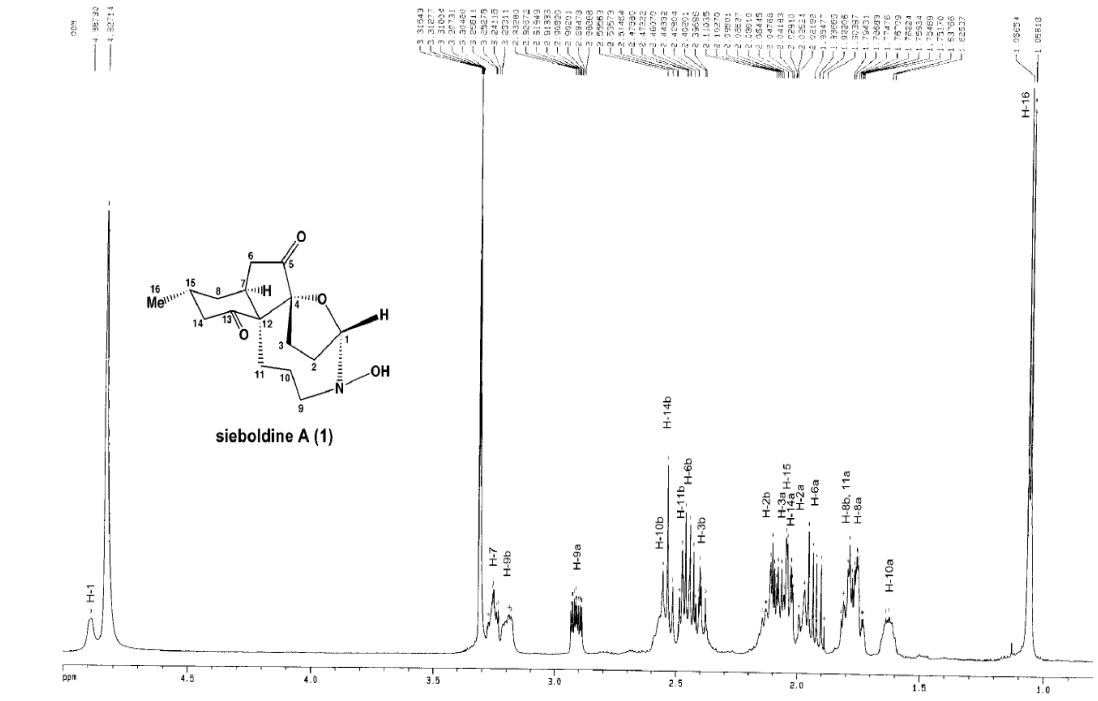

177.8031
176.9989
98.7922
96.4655
95.5655
80.5331
77.2202
77.0000
76.7894
72.1360
56.1079
54.2504
49.5300
38.8924
38.6243
38.3658
35.7071
34.1917
31.2613
29.0400
27.1346
26.9048
26.4644
25.2484
25.0090
21.8876
19.3120
OBNUC 13C
EXMOD single_pulse_dec
OBFRQ 150.92 MHz
SLVNT CDCL3
EXREF 77.00 ppm
PPM
220.0 210.0 200.0 190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0 0.0

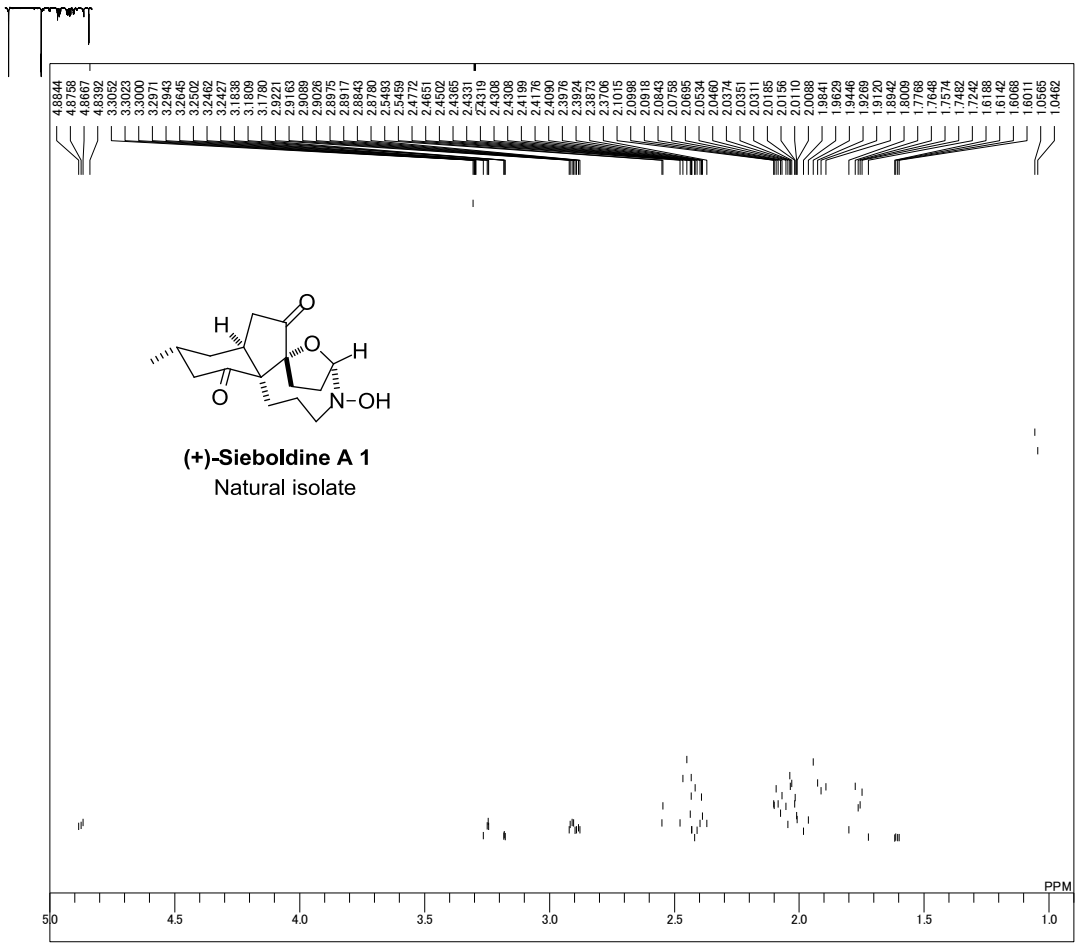


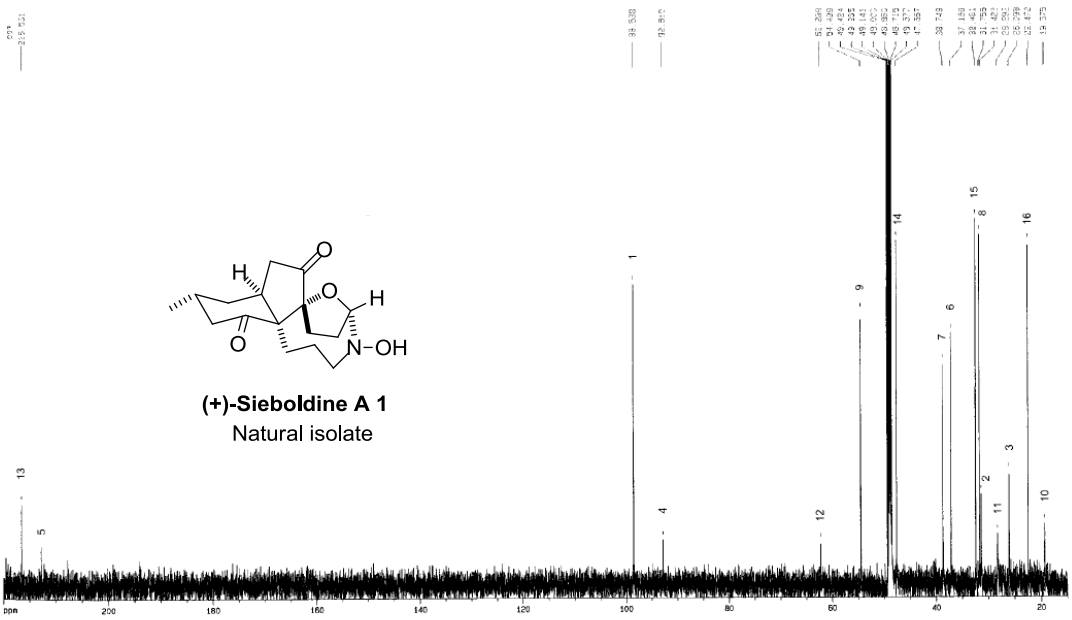


(+)-Sieboldine A **1**

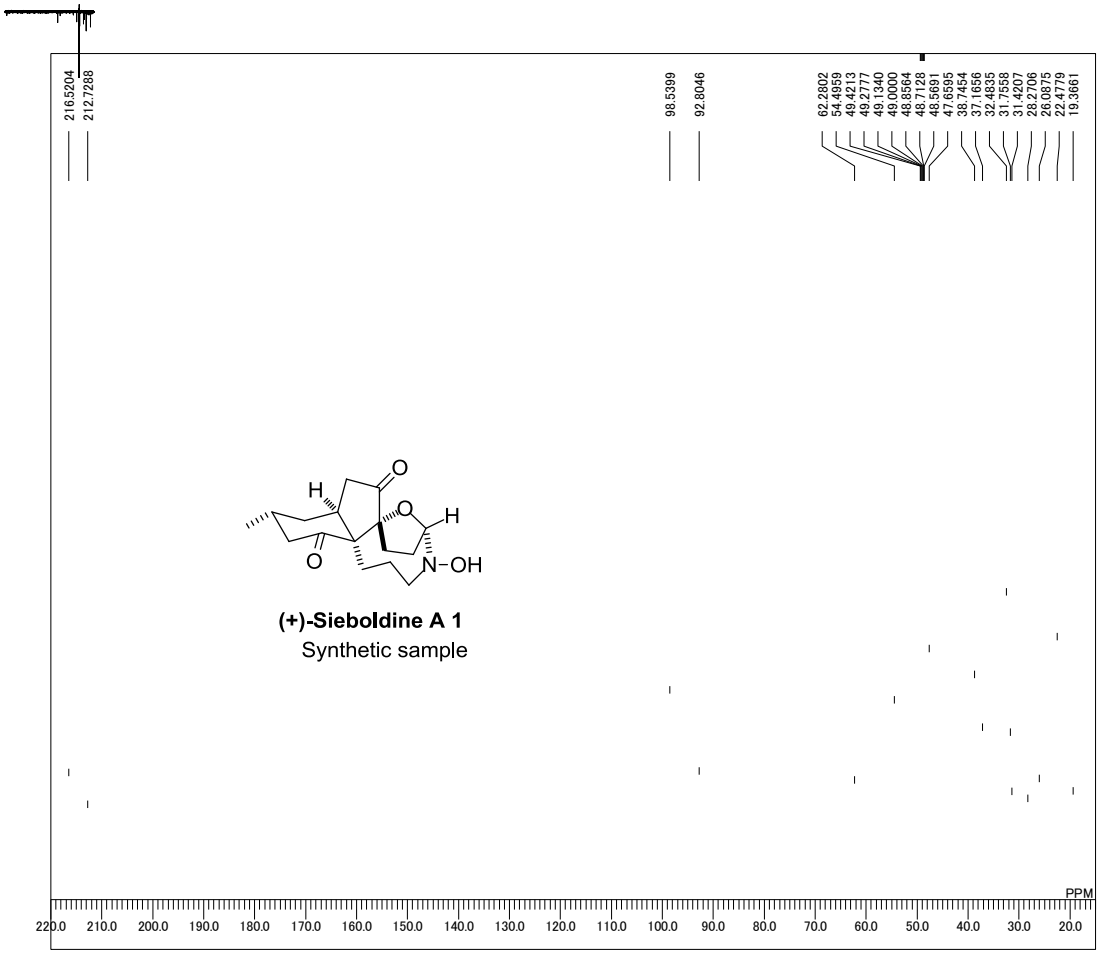



sieboldine A (1)
H-1
H-7
H-9b
H-9a
H-10b
H-14b
H-11b
H-6b
H-3b
H-2b
H-3a
H-15
H-14a
H-2a
H-6a
H-8b, 11a
H-8a
H-10a
H-16
ppm


(+)-Sieboldine A 1
Natural isolate
PPM



(+)-Sieboldine A 1
Natural isolate



(+)-Sieboldine A 1
Synthetic sample