TOTAL SYNTHESIS OF THE UNIQUE PEDERIN FAMILY MEMBER PSYMBERIN

&

CHEMICAL STUDIES TOWARD SALINIKETAL FAMILY MEMBERS:
SALINIKETAL A, SALINISPORAMYCIN AND RIFSALINIKETAL

APPROVED BY SUPERVISORY COMMITTEE

Jef K. DeBrabander, Ph.D.

Uttam Tambar, Ph.D.

Joseph M. Ready, Ph.D.

Chuo Chen, Ph.D.

Total Synthesis of the Unique Pederin Family Member Psymberin

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Saliniketal A, Salinisporamycin and Rifsaliniketal

By

Yu Feng

DISSERTATION

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For the Degree of

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The University of Texas Southwestern Medical Center at Dallas

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To my family

ACKNOWLEDGEMENTS

Time flies. It's so fast that I have been a graduate student at UT Southwestern for 5 years. The graduation is approaching. I would like to take this opportunity to thank all those people who made the completion of this work possible. Firstly, I would like to thank my mentor, Prof. Jef K. De Brabander, for his guidance, support, and patience. His insight of chemistry, creativity and wittiness provides us a stimulating and friendly environment allowing independent thought and soul to pursue the cutting edge of science in his laboratory. I feel extremely fortunate to have him as my Ph.D. mentor. Secondly, I would like to thank my thesis committee members: Prof. Chuo Chen, Prof. Joseph M. Ready and Prof. Uttam Tambar for their support during my graduate study and critiquing this dissertation. Thirdly, I enjoyed being a member of the De Brabander group, with many friendly, knowledgeable and helpful colleagues. I would like to thank Dr. Bo Liu, Dr. Xin Jiang, Dr. Chris Bender, Dr. Jun Liu and Mr. Chris Paradise for their help during my senior undergraduate and junior graduate study. I would also like to thank Dr. Wei Li, Mr. Xueliang Yu, Dr. Casey Cosner, Dr. Qiren Liang, Dr. Hua-Yu Wang and Dr. Jose Garcia Rodriguiz for their friendship and discussion of chemistry over the years. Fourthly, I would appreciate the collaborations with Prof. Michael Roth, Dr. Cheng-Yang Wu, Prof. John Macmillan and Ms. Yazmin Carrasco. They provided me solid support to complete my projects. Finally, I would like to express my deep appreciate to my family. This thesis certainly would not be possible without the love and encouragement of my family. Thanks to my parents for the education and support provided to me throughout my life. I would have had a hard time to pass through the life abroad without their caring.

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The University of Texas Southwestern Medical Center at Dallas, 2013

Jef K. De Brabander, Ph.D.

Abstract

This manuscript consists of six chapters. The first four chapters involve the psymberin/ irciniastatin A project. Psymberin was isolated from a *psammoncinal* sponge possessing an unprecedented differential cytotoxicity profile, whereas irciniasatin A was isolated from the marine sponge *Ircinia ramose* showing potent growth-inhibitory properties against solid human tumor cell lines. The first chapter provides the background information, i.e. isolations, biosynthesis and preliminary biological activities of psymberin/irciniastatin A. The second chapter reviews all the total syntheses and formal syntheses from the chemistry community. In the third chapter, we detail our chemical studies toward the unique pederin family member

psymberin. The De Brabander laboratory had previously demonstrated that psymberin and irciniastatin A are identical. Subsequently, a highly convergent second generation of psymberin was finished, and the synthetic highlights were including the Iridium-catalyzed *bis*-allylation of 2,2-dimethylpropane-1,3-diol, and a stepwise Sonogashira coupling/cycloisomerization/ reduction sequence to construct the dihydroisocoumarin unit. The total synthesis of psymberin and its analogs would provide sufficient material for mode-of-action and SAR studies. The fourth chapter describes the biological studies toward psymberin. Structural modifications of psymberin helped to elucidate that protein translation can be uncoupled from cytotoxicity, suggesting that psymberin has more than one bioactivity. The Roth laboratory developed a forward genetic screen in *C. elegans* to identify the molecular target(s) of psymberin. Finally, our analogs aided in demonstrating the blistering activity associated with pederin and other members of the family is not due to their protein synthesis inhibiting activity. Unlike pederin and mycalamide, psymberin does not display irritant or blistering activity.

The last two chapters involve the saliniketal family members: saliniketal A, salinisporamycin and rifsaliniketal. Saliniketal A, salinisporamycin and rifsaliniketal are three novel secondary metabolites from the marine actinomycete *Salinispora arenicola*. The fifth chapter reveals the isolation of the molecules, biological activities and their biorelationship with rifamycin. In the final chapter, we review the previous synthetic efforts toward saliniketals, followed by our studies including the synthesis of the three members via a highly convergent route. These studies were aimed at enabling future structure-function and mode of action studies. The synthetic highlights for saliniketal A includes: Pt(II)-catalyzed cycloisomerization to construct the dioxabicyclo[3.2.1] ring system, a highly diastereoselective aldol coupling whose stereochemical outcome was influenced by the γ-stereogenic methyl group and an unique dihydropyranone

fragmentation/amidation sequence. For salinisporamycin and rifsaliniketal, the 1,4-naphthoquinone skeleton was assembled via Diels-Alder cycloaddition or benzyne cycloaddition. A peptide coupling or Buchwald C-N bond coupling at a late stage between saliniketal A and the 1,4-naphtholene fragments followed by radical oxidation afforded salinisporamycin and rifsaliniketal, respectively.

TABLE OF CONTENTS

Prior Publications

Feng, Y.; Jiang, X.; De Brabander, J. K. Studies toward the Unique Pederin Family Member Psymberin: Full Structure Elucidation, Two Alternative Total Syntheses, and Analogs. *J. Am. Chem. Soc.* **2012**, *134*, 17083;

Wu, C.-Y.; Feng, Y.; Cardenas, E. R.; Williams, N.; Floreancig, P. E.; De Brabander, J. K.; Roth, M. SAR, Biochemical Studies and Genetics Identify Features Unique to Psymberin and Common to the Pederin Family. *J. Am. Chem. Soc.* **2012**, *134*, 18998;

List of Schemes

List of Tables

List of Figures

LIST OF DEFINITIONS

Ac	acetyl
acac	acetylacetonyl
AD	asymmetric dihydroxylation
anhyd.	anhydrous
APCI	atmospheric pressure chemical ionization
aq.	Aqueous
Ar	aryl (substituted aromatic ring)
BBN (9-BBN)	9-borabicyclo[3.3.1]nonane (9-BBN)
Bn	benzyl
Boc	*tert*-butoxycarbonyl
br	broad
t-Bu	*tert*-butyl
BuLi	butyl lithium
Bz	benzoyl
calc'd	calculated
cat.	Catalytic
ca	cerca (approximately)
^{o}C	degrees Celsius
conc.	concentrated
Cp	cyclopentadienide
Cp*	pentamethyl cyclopentadienide
Cy	cyclohexyl
δ	chemical shift downfield from $(CH_3)_4Si$
d	doublet
dd	doublet of doublets
ddd	doublet of doublet of doublets
dba	dibenzylideneacetone
DBU	1, 8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DCE	dichloroethane
DDQ	2, 3-dichloro-5, 6-dicyano-benzoquinone
DIAD	diisopropyl azodicarboxylate

DIBAL	diisobutylaluminum hydride
DIPEA	diisopropylethylamine
DMDO	dimethyldioxirane
DMAP	*N*,*N*-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMPM	3,4-dimethoxybenzyl
DMPMCl	3,4-dimethoxybenzyl chloride
DMSO	dimethylsulfoxide
DMS	dimethylsulfide
DMP	Dess-Martin periodinane
dr	diastereomeric ratio
dt	doublet of triplets
E^+	electrophile (denotes any electrophile in general)
ee	enantiomeric excess
eq.	equation
equiv	equivalent
ES^+	electrospray, positive ionization mode
Et	ethyl
Et_3N	triethylamine
Et_2O	diethyl ether
EtOAc	ethyl acetate
E-X	electrophile (denotes any electrophile in general)
FT-IR	Fourier transform infrared
g	gram
GC	gas chromatography
h	hour
[H]	reductant
Hg mm	millimeter of mercury (760 Hg mm = 1 atm = 760 Torr)
HMBC	heteronuclear multiple bond correlation
HMPA	hexamethylphosphoramide
HOMO	highest occupied molecular orbital
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectrometry
HSQC	heteronuclear Single quantum coherence

hν	light
Hz	hertz
IPA	isopropyl alcohol
i-Pr	isopropyl
IR	infrared
J	coupling constant
L	ligand
LA	Lewis acid
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LHMDS	lithium bis(trimethylsilyl)amide
liq.	liquid
LTBP	lithium *tert*-butyl peroxide
LUMO	lowest unoccupied molecular orbital
M	molar
m	multiplet or medium
[M]	metal
MAO	methylaluminoxane
m-CPBA	*m*-chloroperoxybenzoic acid
MDR	multiple drug resistance
Me	methyl
MeCN	acetonitrile
Mes	mesityl
mg	milligram
MHz	megahertz
min	minutes
mL	milliliter
mmol	millimole
MOM	methoxymethyl
m/z	mass / charge
Ms	methane sulfonyl
MS	molecular sieves
N	normal
NBS	*N*-bromosuccinimide

NCS	*N*-chlorosuccinimide
NIS	*N*-iodosuccinimide
NMO	*N*-methylmorpholine oxide
NMR	nuclear magnetic resonance
n-Pr	propyl
Nu	nucleophile
o-	ortho
[O]	oxidant
OAc	acetate
OMs	mesylate
OTf	triflate
p-	para
Ph	phenyl
PCC	pyridinium chlorochromate
PhH	benzene
PhMe	toluene
PMB (MPM)	*p*-methoxybenzyl
PMBTCA	PMB-acetimidate
PPh3	triphenylphosphine
ppm	part per million
PPTS	pyridinium *p*-toluenesulfonate
pyr	pyridine
q	quarter
rac	racemic
Rf	retention factor in chromatography
ROESY	rotating-frame overhauser effect spectroscopy
rt	room temperature
Salen	*N,N'*-ethylenebis(salicylideneiminato)bis (salicylidene)
s	singlet or strong
t	triplet
TBAF	tetrabutylammonium fluoride
TBHP	*tert*-butyl hydroperoxide
TBS	*tert*-butyldimethylsilyl
Tf	trifluoromethanesulfonyl

TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMEDA	*N,N,N',N'*-tetramethylenediamine
TMS	trimethylsilyl
tol	toluene
Tr	retention time
p-TsOH	*p*-toluenesulfonic acid
Ts	toluenesulfonyl
UV	ultraviolet
w	weak
y	yield

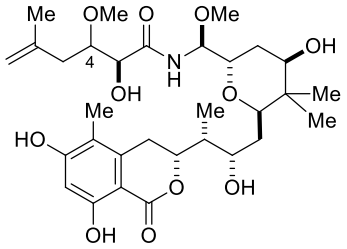
Chapter 1

Introduction: Psymberin and Pederin Family

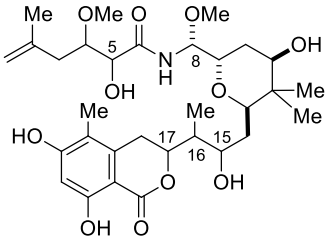
1.1 Isolations and Structural Elucidations

In 2004, the Crews and Pettit groups independently reported the isolation of structurally novel, constitutionally identical polyketides, named psymberin (**1.1**)[1] and irciniastatin A (**1.2**)[2] respectively. Psymberin (**1.1**) was discovered from the marine sponge *Psammocinia sp*.,[1] whereas irciniastatin A (**1.2**) was isolated from the *Ircinia ramosa* sp.[2] Comprehensive NMR studies substantiated the assigned relative configuration for psymberin as shown in **1.1** (Figure 1), save for the undefined configuration at C_4. The absolute configuration was confirmed by observation of a well-defined positive Cotton effect at the n → π* transition (280 nm) of the dihydroisocoumarin unit. On the other hand, the relative stereochemistry of irciniastatin A (**1.2**) was only assured for the C_8−C_{13} aminal fragment. Interestingly, the C_8-aminal configuration in ircinastatin A (nOe data) was opposite to the corresponding center assigned for psymberin. Given the differing relative configuration (C_8−C_9), producing organisms, and NMR spectra (acquired in different NMR solvents), the structures formulated for irciniastatin and psymberin thus define two different natural products. Psymberin is the latest member in the pederin family, however, it is uniquely extended with a dihydroisocoumarin unit not found in any of the other ~35 members of the pederin family isolated to date and lacks this family's signature acetal-containing pederate side chain.

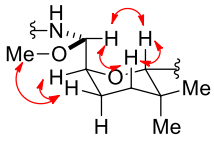
Figure 1. Psymberin and Irciniastatin A, the Structures Proposed by Crews and Pettit, Respectively



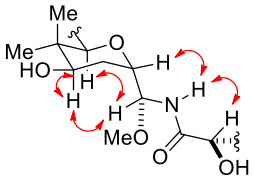
psymberin, **1.1**
from psammocinia sp.



irciniastatin A, **1.2**
from irciniaramose sp.



nOe correlations
by Crews



nOe correlations
by Pettits

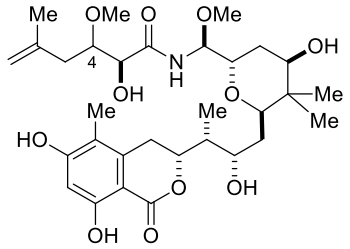
1.2 A Brief Review of the Pederin Family

Pederin (**1.3a**, Figure 2),[3] a potent toxic amide with irritant (vesicant) activity, was isolated from the haemolymph of the Paederus genus of beetles in 1949. The structure of pederin was determined by X-ray crystallography in 1968.[3e, f] Due to structural resemblance, several other biological active natural products containing exactly the same left tetrahydropyran ring were classified as members of the pederin family (Figure 2), including icadamides A (**1.4a**) and B (**1.4b**),[4] myclamides A-E (**1.5a-e**),[5] onnamides A-F (**1.6a-m**),[6] and theopederins A-L (**1.7a-l**),[7] which were all discovered from marine sponges over thirty years, and most of them have garnered considerable interest as potential anticancer agents. Pederin (**1.3a**) inhibits mitosis at low concentrations (~ 1 ng/mL) by blocking protein and DNA synthesis.[8] It does not affect

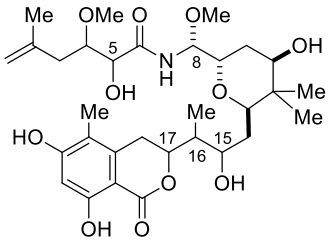
RNA synthesis, but does prevent cell division. It has also been shown to extend the life of mice bearing a variety of tumors. Another member of the pederin family is myclamide A (**1.5a**), which was obtained from a marine sponge, genus *Mycale,* native to the Otago Harbor of New Zealand in 1988. It has a potential to be used as inhibitor of tumor cell proliferation and possesses immunosuppressive activity. In the same year, Higa and co-workers screened the bioactive marine organisms which were obtained from Okinawan waters, and identified an active constituent, namely onnamide A (**1.6a**).[6a] It has antiviral activity against herpes simplex virus type-1, vesicular stomatitis virus, and coronavirus A-59. Another member in the pederin family is theopederin A (**1.7a**),[7a] isolated from a sponge of the *Theonella* genus off the coast of Japan. Like the mycalamides, it contains an unusual amido trioxadecalin unit, an acid-labile cyclic *β, γ*-unsaturated acetal, and has an IC_{50} value of approximately 2 nM against murine P388 leukemia cells.

All members of the pederin family except psymberin contain an identical left-hand fragment, known as pederic segment. Another striking similarity is that both fragments are connected via an *O*-methyl carbinolamide. Psymberin (**1.1**) is considered as a new member of the pederin family due to the highly substituted tetrahydropyran ring and the *O*-methyl carbinolamide. However, the novel dihydroisocoumarin and lack of the exocyclic olefin containing tetrahydropyran of psymberin distinguishes it from other pederin members. In this context, the biosynthesis of psymberin became of interest, and was finally elucidated by Piel and coworkers.[8]

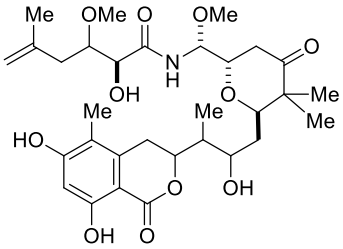
Figure 2. Structures of All Members of the Pederin Family



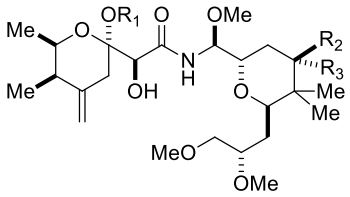
psymberin, **1.1**



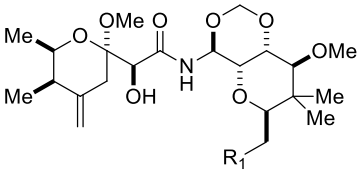
irciniastatin A, **1.2**

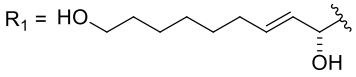


irciniastatin B, **1.2a**
(proposed structure by Pettit, et al)

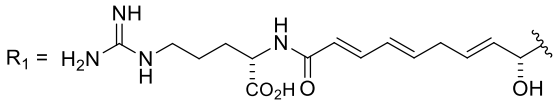


R_1 = Me, R_2 = OH, R_3 = H, pederin, **1.3a**
R_1 = H, R_2 = OH, R_3 = H, pseduopederin, **1.3b**
R_1 = H, R_2 = O, R_3 = O, pederone, **1.3c**

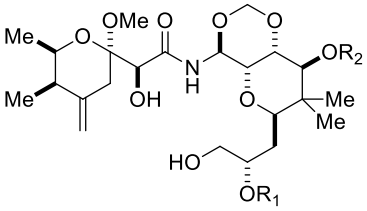




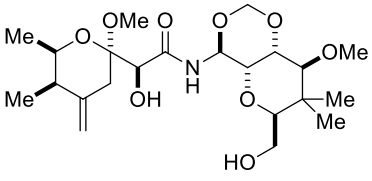
icadamide A, **1.4a**



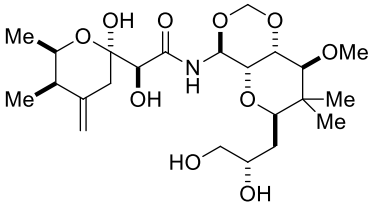
icadamide B, **1.4b**



R_1 = H, R_2 = Me, mycalamide A, **1.5a**
R_1 = Me, R_2 = Me, mycalamide B, **1.5b**
R_1 = H, R_2 = H, mycalamide D, **1.5d**

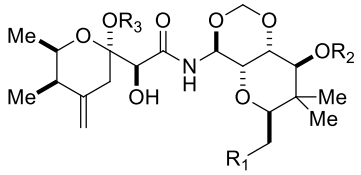


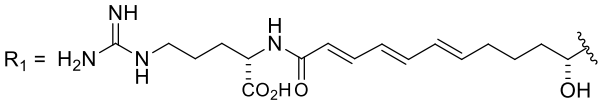
mycalamide C, **1.5c**



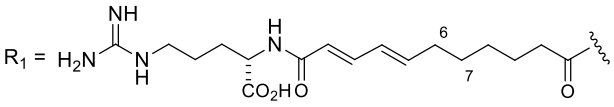
mycalamide E, **1.5e**

Figure 2. Continued

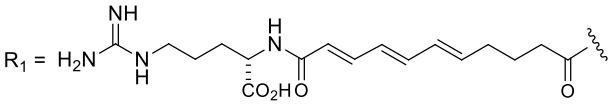




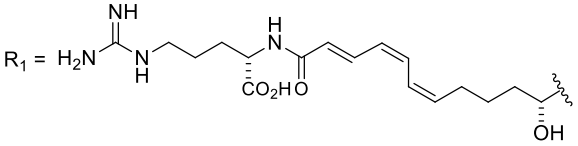
R_2 = Me, R_3 = Me — onnamide A, **1.6a**



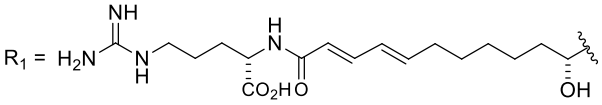
R_2 = Me, R_3 = Me — 6,7-dihydro-11-oxo-onnamide A, **1.6b**



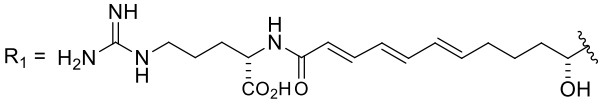
R_2 = Me, R_3 = Me — 11-oxo-onnamide A, **1.6c**



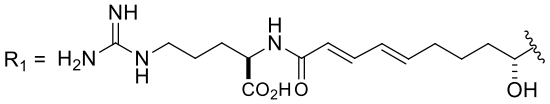
R_2 = Me, R_3 = Me — 4*Z*-onnamide A, **1.6d**



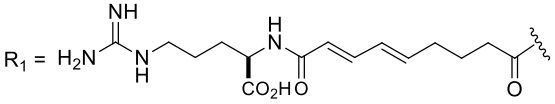
R_2 = Me, R_3 = Me — dihydroonnamide A, **1.6e**



R_2 = H, R_3 = Me — 13-*Des*-*O*-methyl onnamide A, **1.6f**



R_2 = Me, R_3 = Me — onnamide B, **1.6g**



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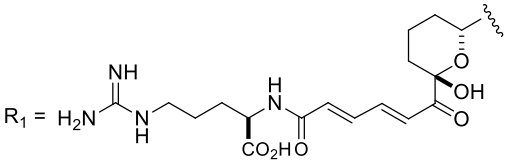
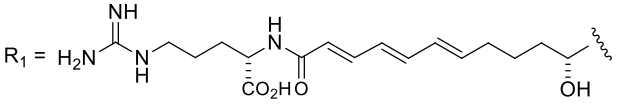
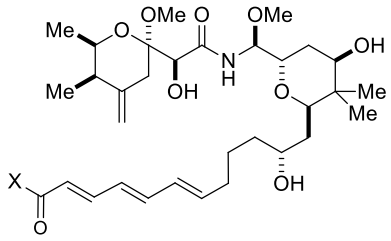


R_2 = Me, R_3 = Me — onnamide C, **1.6i**

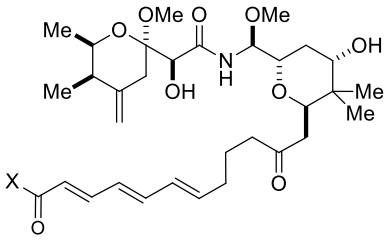


R_2 = Me, R_3 = H — pseudoonnamide A, **1.6j**

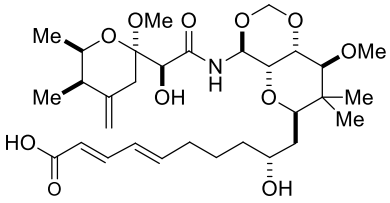
Figure 2. Continued



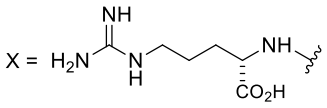
onnamide D, **1.6k**

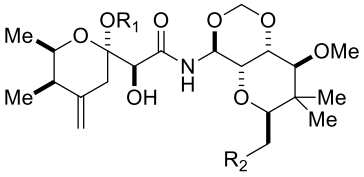


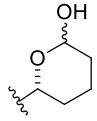
onnamide E, **1.6l**

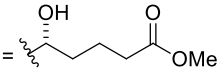


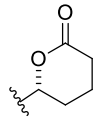
onnamide F, **1.6m**

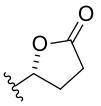




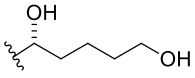
R_1 = Me, R_2 =  theopederin A, **1.7a**

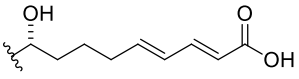
R_1 = Me, R_2 =  theopederin B, **1.7b**

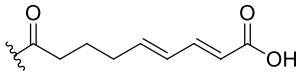
R_1 = Me, R_2 =  theopederin C, **1.7c**

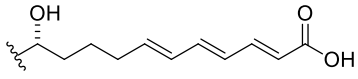
R_1 = Me, R_2 =  theopederin D, **1.7d**

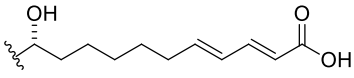
R_1 = Me, R_2 = OH theopederin E, **1.7e**

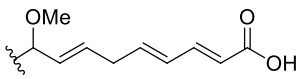
R_1 = Me, R_2 =  theopederin F, **1.7f**

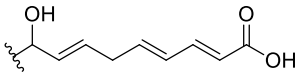
R_1 = H, R_2 =  theopederin G, **1.7g**

R_1 = H, R_2 =  theopederin H, **1.7h**

R_1 = H, R_2 =  theopederin I, **1.7i**

R_1 = H, R_2 =  theopederin J, **1.7j**

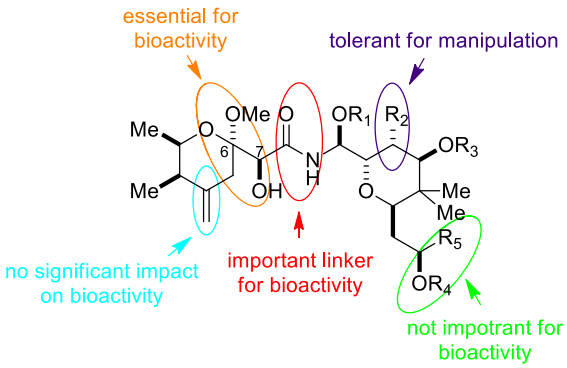
R_1 = H, R_2 =  theopederin K, **1.7k**

R_1 = H, R_2 =  theopederin L, **1.7l**

1.3 Biological Studies

Pederin (**1.3a**), mycalamide (**1.5a**), and other members of the family are potent eukaryotic protein synthesis inhibitors and cytotoxic agents,[9, 10] which exhibit strong blistering activity upon contact with the skin. Several examinations of the structural-activity relationship of mycalamides (**1.5**) have been done (Figure 3).

Figure 3. An Overview of Structure-Activity Relationships for Pederin Family Members



Since the pederin family members have similar structures, the conclusions drawn by the SAR studies of mycalamides are likely consistent for the entire family. α-Hydrogenation and β-hydrogenation of the exocyclic alkene in the pederic acid fragment didn't result in significant changes of biological activies.[11] In contrast, the C_6 methoxy group was essential for the bioactivity.[12] Replacing it with an ethoxy or incorporation of a hydroxyl group at C_6 decreased the activity (10-40 fold, data not shown). Modification at C_7 or inversion of the stereocenter at C_7 resulted in loss of bioactivity. The acyl aminal functionality also plays an important role for the biological activity.[13] Mycalamide C (**1.5c**), which lacks the acyl group, is significantly less potent than mycalamide A (**1.5a**) and B (**1.5b**). (IC_{50} = 230 nM against the

P388 leukemia cancer cell line). Comparing the structure of pederin (**1.3a**) and mycalamide A (**1.5a**) indicates that the methylene dioxy structure at C_{10}-C_{12} is not important for the toxicity.[14]

Both irciniastatins (**1.2**) and psymberin (**1.1**) were isolated based on their potent activity in human tumor cell assays. Interestingly, the unique structures of irciniastatin A/psymberin and remarkable specific cell line cytotoxicities that are not shown by other pederin family members suggest another mode of action. Initially reported by the Pettit group,[2] irciniastatins A (**1.2**) and B (**1.2a**) are able to inhibit the growth of human tumor cell lines with values ranging from 0.1 to 6.2 nM (GI_{50}).[2] A powerful antivascular activity for irciniastatin was noted by the strong inhibition of human umbilical vein endothelial cells (HUVEC, 0.5 nM) and corresponding inhibition of tube formation (Matrigel assay).

Psymberin (**1.1**),[1] on the other hand, was evaluated in the NCI Development Therapeutics in Vitro Screening Program (Table 1) where it exhibited an unprecedented differential cytotoxicity profile – three of the melanoma (MALME-3M, SKMEL-5, UACC-62), one breast (MDAMB-435) and one colon cancer cell line (HCT-116) were sensitive to psymberin concentrations below 2.5 nM (LC_{50}), whereas most other cancer cell lines did not respond to concentrations up to 25 μM. Such data, supporting a $>10^4$ differential activity for psymberin (**1.1**), was exceptional and might indicate a novel mode-of action.

Table 1. Psymberin/Irciniasatin A Biological Activities against the NCI 60 Cell Human Tumor Cell Line Panel

Cell line	LC_{50} (M)	Cell Line	LC_{50} (M)
Leukemia		**Melanoma**	
CCRF-CEM	$>2.5 \times 10^{-5}$	LOX IMVI	$>2.5 \times 10^{-5}$
HL-60 (TB)	$>2.5 \times 10^{-5}$	MALME-3M	$<2.5 \times 10^{-9}$
K-562	$>2.5 \times 10^{-5}$	SK-MEL-2	$>2.5 \times 10^{-9}$
MOLT-4	$>2.5 \times 10^{-5}$	SK-MEL-5	$<2.4 \times 10^{-9}$
RPMI-8226	$>2.5 \times 10^{-5}$	SK-MEL-28	1.41×10^{-5}
SR	$>2.5 \times 10^{-5}$	UACC-257	$>2.5 \times 10^{-5}$
		UACC-62	$<2.5 \times 10^{-9}$
Breast cancer		**Colon cancer**	
MCF7	$>2.5 \times 10^{-5}$	HCC-2998	3.76×10^{-7}
HS 578T	$>2.5 \times 10^{-5}$	HCT-116	$<2.5 \times 10^{-9}$
MDA-MB-435	$<2.5 \times 10^{-9}$	HT29	$>2.5 \times 10^{-5}$
NCI/ADR-RES	1.9×10^{-5}	SW620	$>2.5 \times 10^{-5}$
T-47D	1.36×10^{-5}		

In a quest to discover the mode of action and an interest in a more comprehensive preclinical evaluation of psymberin, the first project of my Ph.D. studies was to continue our study of this fascinating natural product. In this thesis, I will describe a full account of the total synthesis, an improved second generation total synthesis developed by myself during the course of my Ph.D. studies, and the synthesis of strategically designed analogs of psymberin. In addition, I will detail our biological investigations (collaboration with Prof. Roth and Dr. Cheng-Yang Wu, UT Southwestern) that led to the target identification of psymberin and attributes that distinguish it from the pederin/mycalamide family of natural products.

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Chapter 2

Synthetic Efforts towards Psymberin: A Historic Review

Due to uncertainties regarding the structural relation between psymberin (**1.1**) and irciniastatin (**1.2**), significant structural divergence from the pederin family of natural products, low natural abundance, and impressive biological activities, psymberin/irciniastatin has been an attractive target for synthetic pursuit. Through the total synthesis of several diastereoisomers consistent with partially assigned structures of **1.1** and **1.2**, the De Brabander group concluded that psymberin and irciniastatin are actually identical compounds.[1] Several other total syntheses,[2] formal syntheses,[3] fragment syntheses,[4] as well as analog syntheses,[5] have appeared during recent years.

In this chapter, the synthetic efforts from other laboratories, including all of the completed syntheses and formal syntheses to date, will be described. The first synthesis of psymberin done by the De Brabander group will be detailed together with my second generation synthesis and analogs in the chapter 3.

2.1 Floreancig's Synthesis

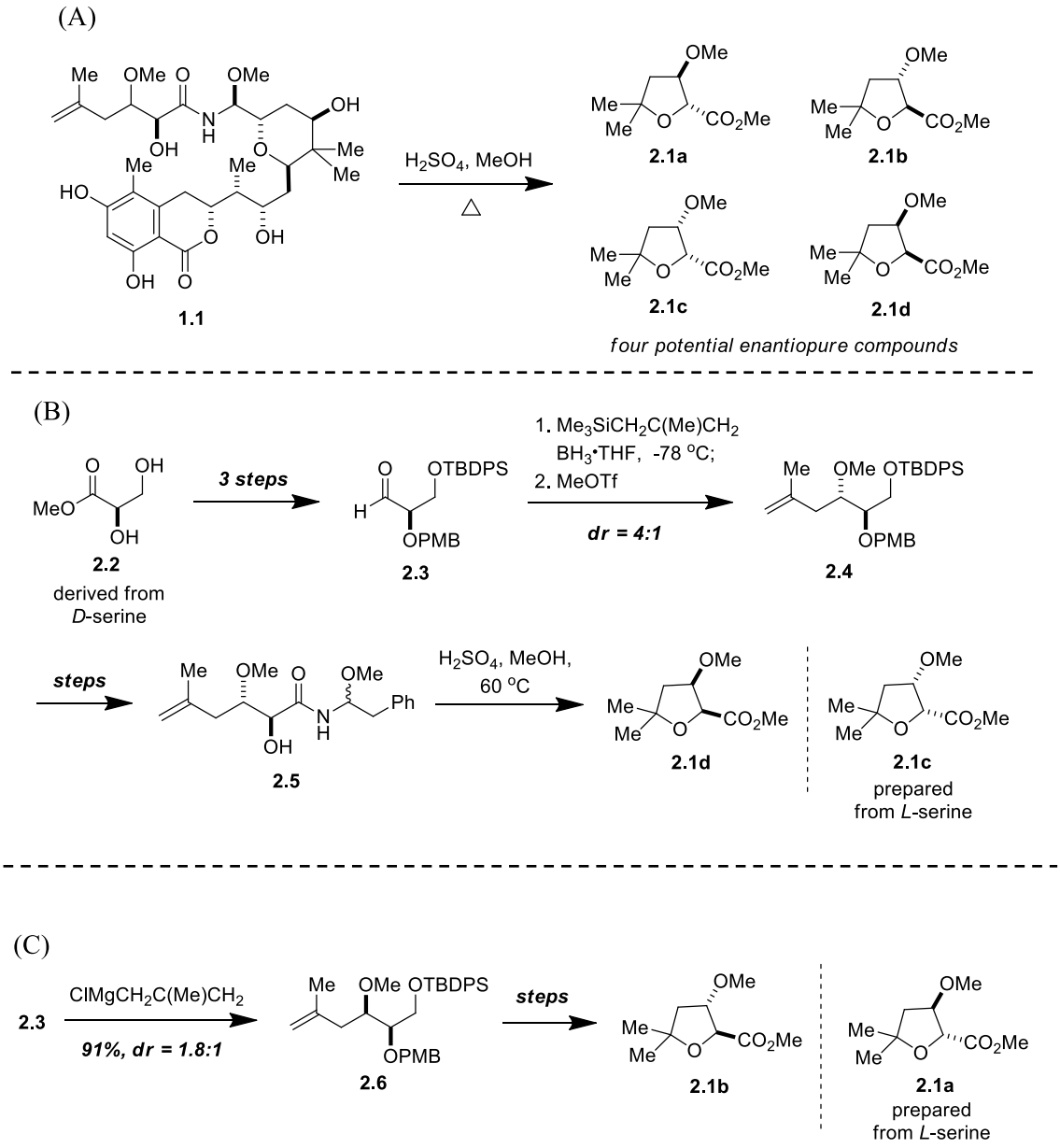
After the first total synthesis and full structure assignments of psymberin/irciniastatin A was reported by De Brabander and co-workers, Floreancig and co-workers published two papers[4b,4c] regarding fragment syntheses and supporting analysis of the configuration of the C_4 and C_5 stereocenters through degradation studies. Floreancig found that acidic

methanolysis of psymberin provided a tetrahydrofuran (**2.1)** of unknown absolute and relative configuration. To establish the configuration, four enantiopure compounds **(2.1a-d)** were synthesized from both D-serine and L-serine[6] (Scheme 1). In three steps, alcohol **2.2** obtained from D-serine, was transformed to aldehyde **2.3**. Reagent controlled methallylation followed by methylation provided *anti*-methyl ether **2.4** via a Felkin-Anh controlled addition[7] (*dr* 4:1) whereas the *syn*-methyl ether **2.6** was obtained from chelation controlled methallylation with poor selectivity (*dr* 1.8:1).[8] Further elaborations of *anti*-methyl ether **2.4** then provided a synthetic psymberate-containing acyl aminal **2.5**. Acidic methanolysis (H_2SO_4, MeOH) of the acyl aminal **2.5** then yielded tetrahydrofuran **2.1d**.

Tetrahydrofuranyl ether **2.1b** was obtained via similar transformations from *syn*-methyl ether **2.6**, whereas the enantiomers **2.1a** and **2.1c** were started from antipodal L-serine.

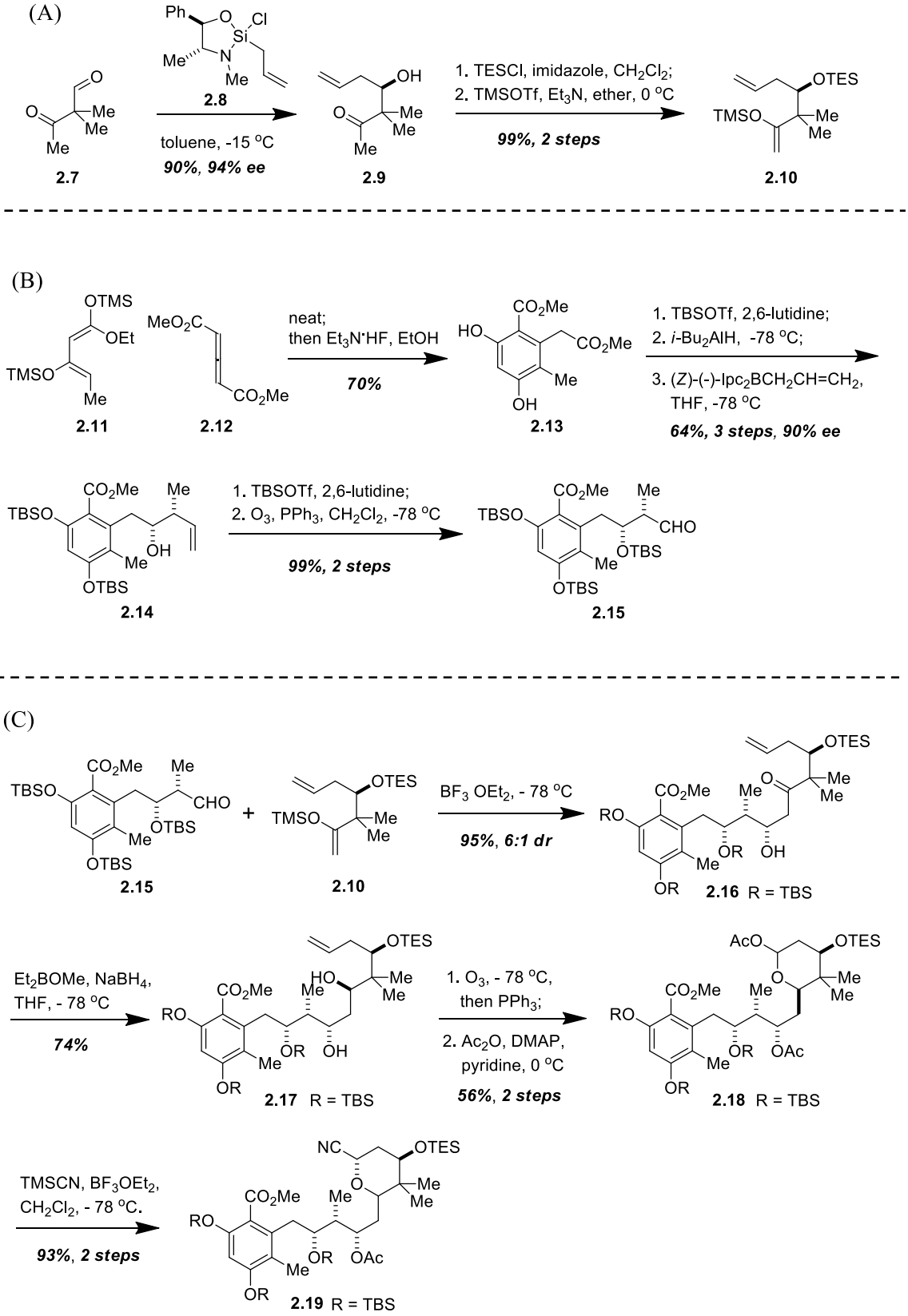
With all four tetrahydrofuran diastereomers in hand, an analytic method was established using a chiral GC method. The same GC retention time and identical GC-MS fragmentation pattern between degradation product and **2.1d** indicated the psymberate side chain has the C_4-*S* and C_5-*S* configurations. This result was also supported by the NMR correlation study conducted by Williams (vide infra).[4a]

Scheme 1. Floreancig Strategies for Psymberate Side Chain and Determination the Configurations



Floreancig's approach to the N_7-C_{25} fragment of psymberin is outlined in scheme 2. For C_9-C_{14} fragment **2.10** (panel A), the aldehyde **2.7** was subjected to Leighton allylation providing allylic alcohol **2.9**. Protection followed by silyl-enonlization then gave silyl enol ether **2.10**.

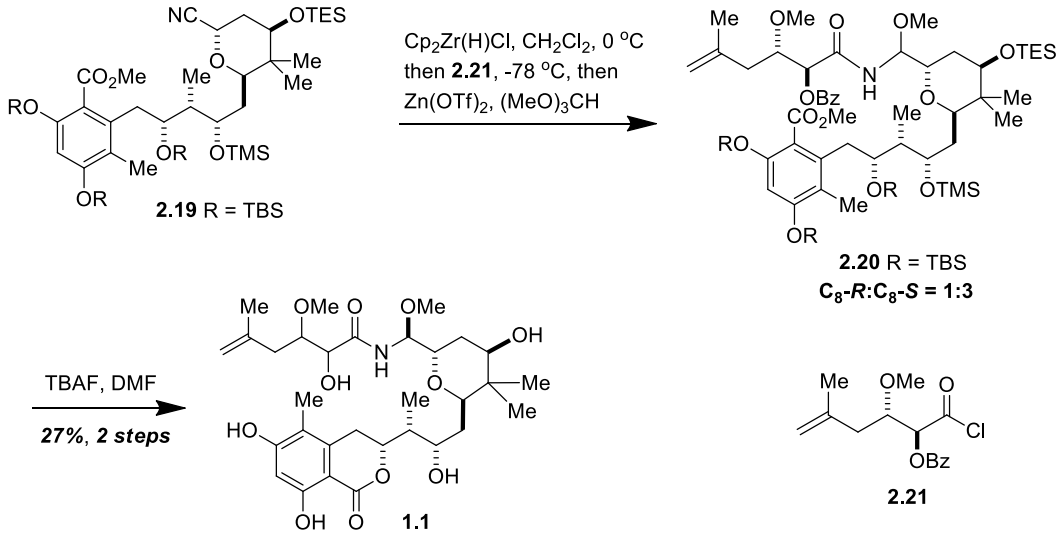
Scheme 2. Floreancig Strategies for N_7-C_{25} fragment



For the aromatic portion (panel B), the Langer cycloaddition[9] between allene **2.12** and diene **2.11** yielded the *penta*-substituted benzene **2.13** on a large scale (12 g). After silylation, chemselective *semi*-reduction of the benzylic ester followed by an enantioselective Brown crotylation gave the homoallylic alcohol **2.14** in 64% overall yield and 90% *ee*.[10] Silylation followed by ozonolysis of the terminal alkene then gave the aldehyde **2.15** for the Mukaiyama aldol coupling.

The Mukaiyama aldol reaction (panel C) between enolsilyl ether **2.10** and aldehyde **2.15** afforded two diastereomers with modest selectivity (*dr* 6:1). At this point, a *syn*-selective reduction (Et_2BOMe, $NaBH_4$) of the major isomer **2.16** furnished a single stereoisomer **2.17**. Ozonolysis of the terminal alkene and concomitant ring formation gave a lactol that was trapped as a stable diacetate **2.18**. The $BF_3{\cdot}OEt_2$ mediated acetate displacement with TMSCN completed the synthesis of N_7-C_{25} fragment (**2.19**).

Scheme 3. Floreancig's Completion of Psymberin[2e]

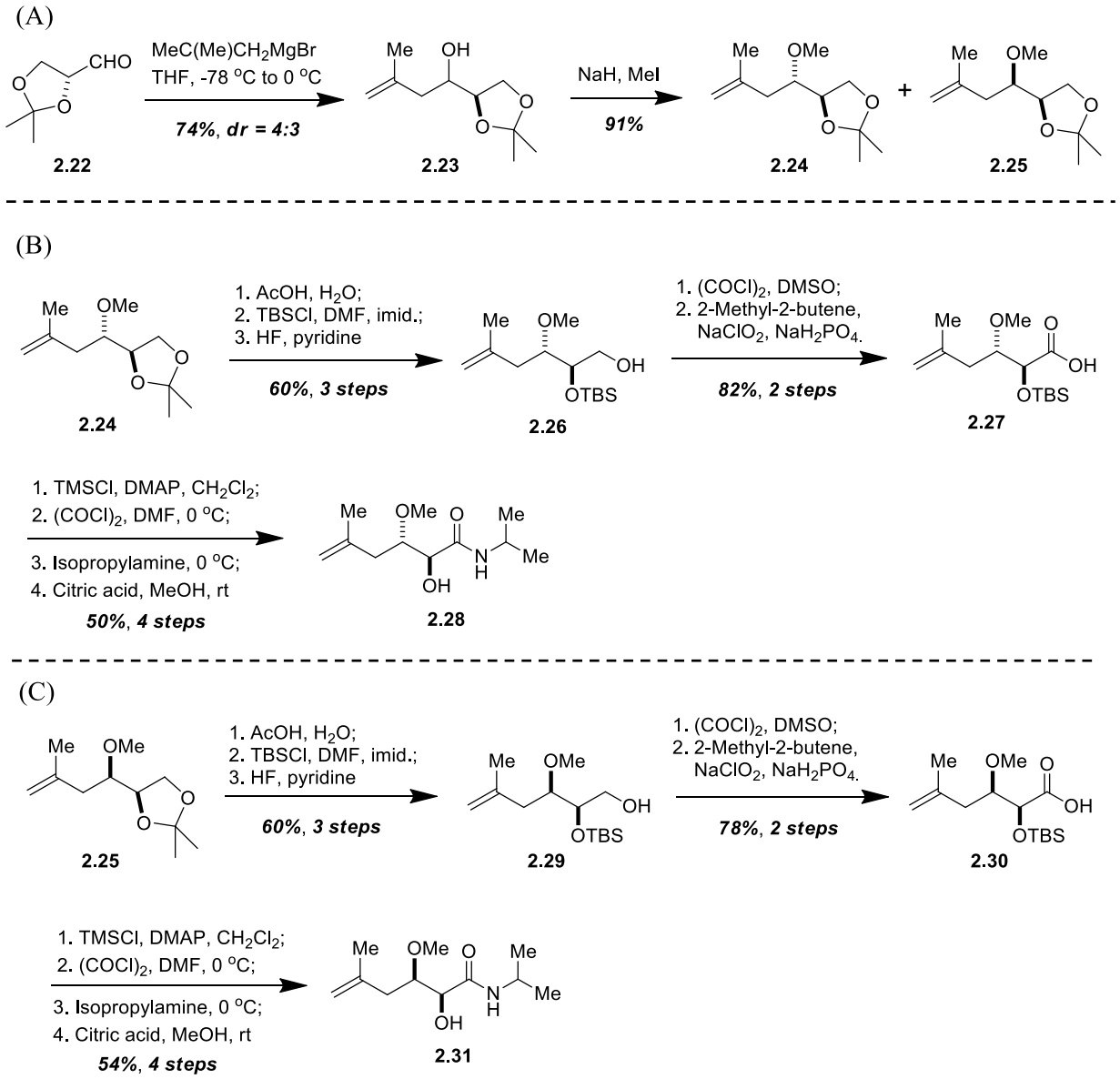


To install the psymberate side chain, Floreancig and co-workers developed a creative novel approach for *N*-acyl aminial synthesis from nitriles. Hydrozirconation ($Cp_2Zr(H)Cl$, CH_2Cl_2) of nitrile **2.19** followed by acylation with acid chloride **2.21** provided an acylimine intermediate that in the presence of Zinc triflate and $(MeO)_3CH$ provided a mixture of diastereomeric aminols **2.20** at C_8. Unfortunately, the undesired diastereomer dominated with a 3:1 ratio. Exposing the acyl aminal mixture to Bu_4NF in DMF induced formation of the dihydroisocoumarin and removal of the benzoate protection group produced psymberin in 27% yield from nitrile **2.19**. In conclusion, this route provided psymberin from commercially available materials in 14 longest linear sequence and 4.4% overall yield.

2.2 Williams' Formal Synthesis

In 2005, Williams[4a] reported the synthesis of the psymberic acid side chain in both *syn*- and *anti*-relative configurations (Scheme 4). Starting with methallylation of mannitol derived aldehyde **2.22**, alcohol **2.23** was obtained as a disatereomeric mixture. The isomers would be separated after formation of methyl ethers **2.24** and **2.25**. Removal of the acetonide of the *anti*-isomer **2.24,** followed by *bis*-silylation and selective deprotection of the primary silyl ether, carbinol **2.26** was obtained. It was subjected to a stepwise oxidation to give the corresponding acid **2.27**. The glycoamide **2.28** was formed in a further 4-steps sequence. The *syn* glycoamide diastereomer **2.31** was prepared via the same sequence from the corresponding *syn*-methyl ether **2.25** in 9 linear steps. Based on the hypothesis that the ^1H and ^{13}C NMR signatures of stereoclusters are inherent to the specific arrangement of the

Scheme 4. Williams Synthesis of the Psymberate Side Chain



stereogenic carbons and are virtually context independent, Williams compared the NMR spectral data between the original psymberin and synthesized psymberate side chain. The differences of the chemical shift between *anti*-isomer and psymberin are less than 0.05 ppm for ^{1}H NMR and less than 0.10 ppm for ^{13}C NMR, indicating an excellent correlation. In addition, only the *anti*-isomer has a good coupling constant correlation with the psymberate

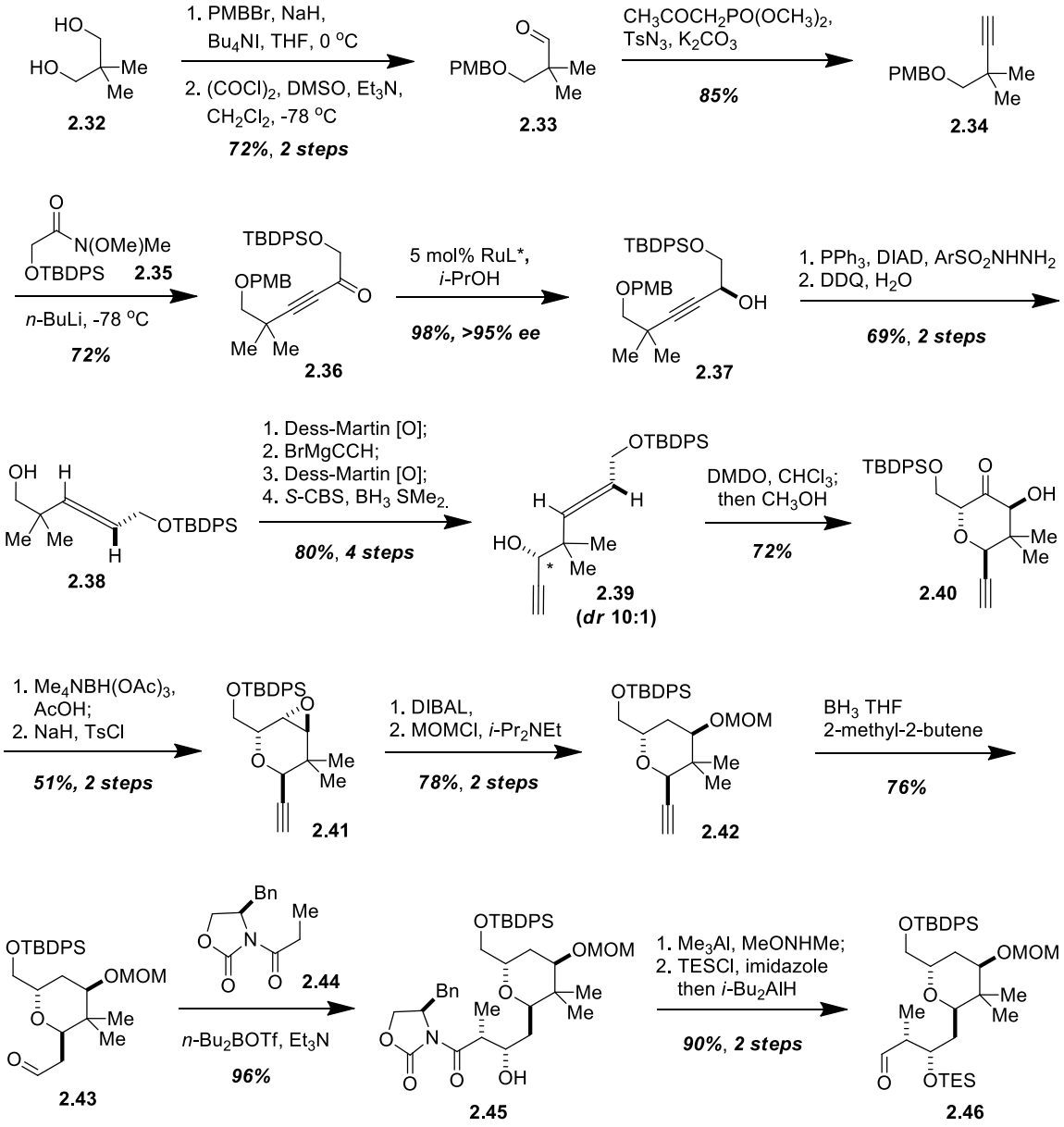
fragment in psymberin (**1.1**). Therefore, Williams concluded that psymberin has the C_4-*S*, and C_5-*S* configuration.[13]

In 2006, Williams and co-workers reported an interesting formal synthesis of psymberin.[3] The central tetrahydropyran (Scheme 5) was synthesized starting from neopentyl glycol **2.32** that was monoprotected and oxidized to aldehyde **2.33**. Transformation of the aldehyde to terminal alkyne **2.34** was achieved via an Ohira-Bestmann[14] reaction. Treating the triple bond with *n*-BuLi, followed by the addition of Weinreb amide **2.35**, afforded the alkynone **2.36** which was then reduced under Noyori conditions[15]. The resultant propargylic alcohol **2.37** was converted to the chiral allene **2.38** through a protocol developed by Myers,[16] after oxidative removal of the PMB with DDQ. An oxidation/acetylenic addition/oxidation sequence followed by an enantioselective CBS reduction gave the alkynone **2.39** (*dr* 10:1). Subsequently, the DMDO induced *bis*-epoxide formation followed by addition of methanol (cosolvent) gave *trans*-pyran **2.40** as a single isomer. Stereoselective reduction of **2.40** followed by epoxide formation in the presence of sodium hydride and toluenesulfonyl chloride gave terminal alkyne **2.41**. A regio-selective epoxide reduction[17] and protection afforded the advanced tetrahydropyran **2.42**. Hydroboration of **2.42** in the presence of 2-methyl-2-butene produced the aldehyde **2.43**, which was engaged in a *syn*-selective aldol reaction (→ **2.45**). Weinreb amide formation, silylation and *semi*-reduction yielded aldehyde **2.46** (90% from **2.45**).

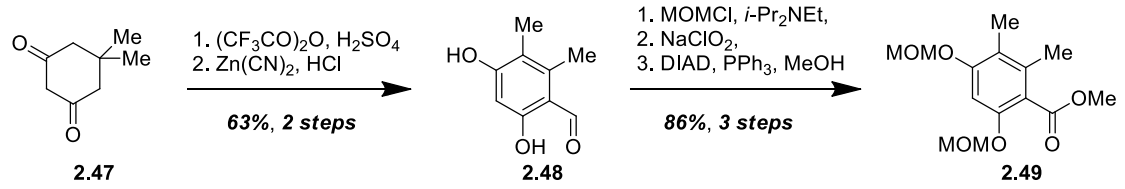
Williams' concise synthesis of the aromatic segment (Scheme 6) began with aromatization[18] of the *C2*-symmetry diketone **2.47** in the presence of trifluoroacetic anhydride followed by formylation to give aryl aldehyde **2.48**, which then was converted to methyl ester **2.49** in a

three-steps sequence.

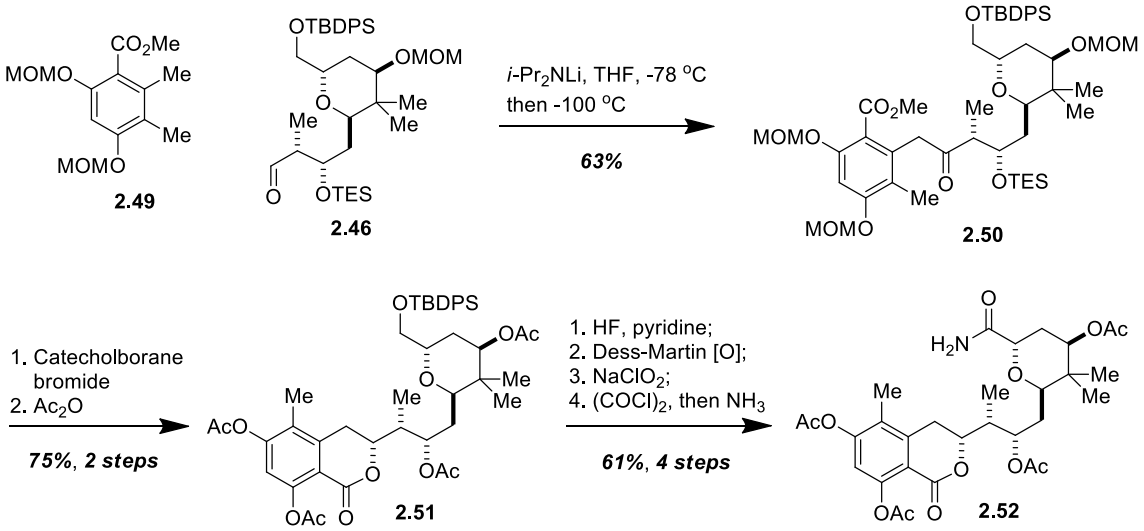
Scheme 5. Williams Tetrahydropyran Synthesis



Scheme 6. Williams Synthesis of the Arene Subunit of Psymberin



Scheme 7. Williams Formal Synthesis of pysmberin

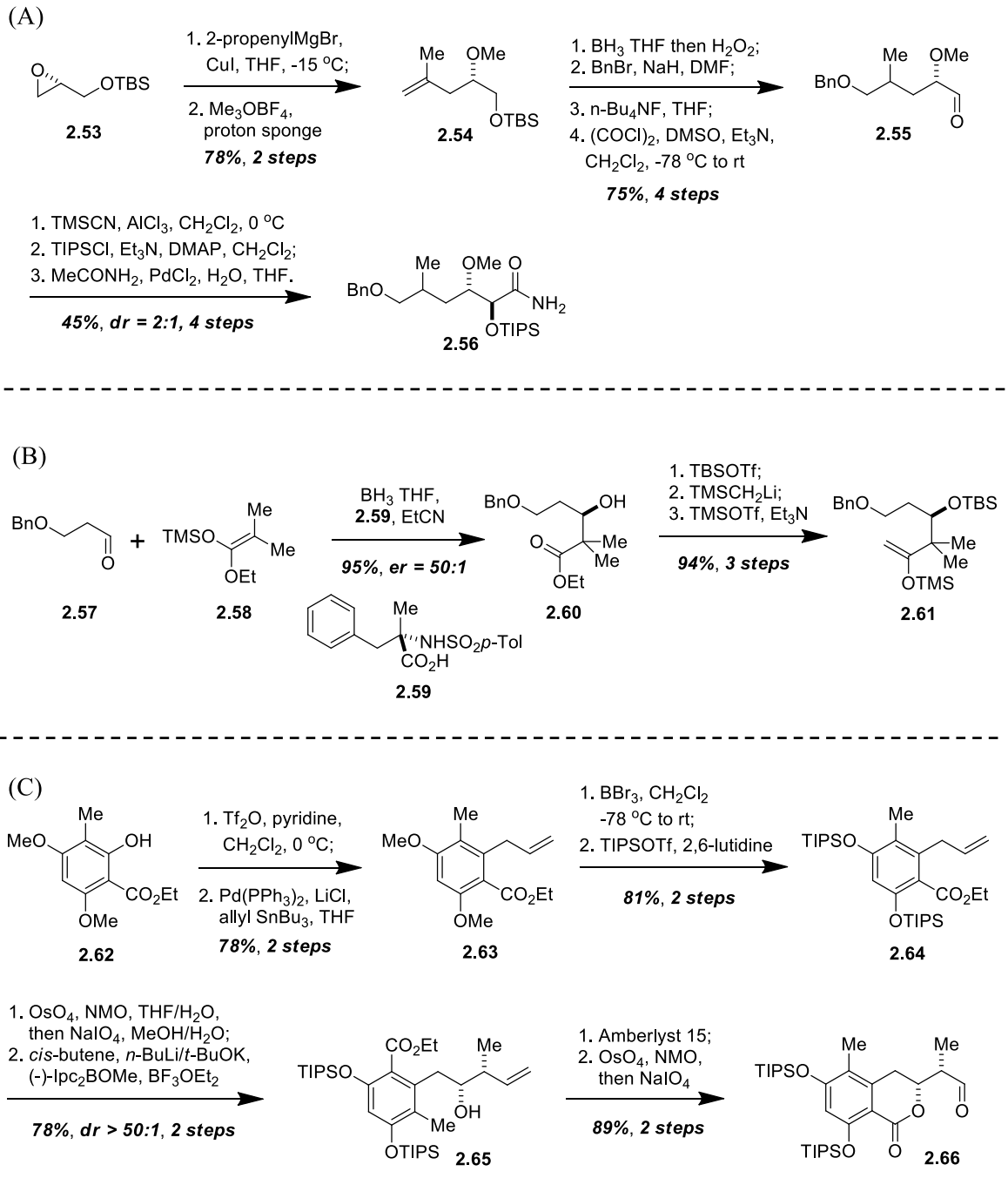


With the two segments in hand, addition of the enolate of **2.49** to aldehyde **2.46** gave the aldol adduct **2.50** in 63% yield with 3:1 *dr* (Scheme 7). The dihydroisocoumarin **2.51** was generated after catecholborane reduction and a global acylation. Desilylation of tetraacetate **2.51** with HF followed by a two-step oxidation sequence to form the acid, and amidation yielded amide **2.52**. The compound **2.52** is the same as our advanced intermediate for psymberin (**1.1**) synthesis. In summary, Williams and co-workers achieved a formal synthesis of psymberin (**1.1**) in a 27 longest linear sequence and 1.44% overall yield.

2.3 Schering Plough Total Synthesis

A research group from Schering Plough[2a] completed the third total synthesis of psymberin,

Scheme 8. Schering Plough Fragments Syntheses



which was significantly different from earlier work by our group. For the synthesis of the psymberate side chain, the Schering Plough Group employed a chiral pool strategy. Using epoxide **2.53** as the starting material (Scheme 8, panel A), a regio-selective epoxide opening in the presence of isopropenylmagnesium bromide afforded a secondary alcohol, which was trapped as the methyl ether **2.54**. Hydroboration and protection of the resultant alcohol was followed by removal of the silyl group and Swern oxidation to furnish aldehyde **2.55**. $AlCl_3$ mediated TMSCN addition installed a secondary alcohol mixture with poor diastereoselectivity (*dr* 2:1), of which the C_5-*S* carbinol isomer was separated and silylated. The hydrolysis[19] of the resultant nitrile in the presence of $MeCONH_2$ and $PdCl_2$ provided the amide **2.56**.

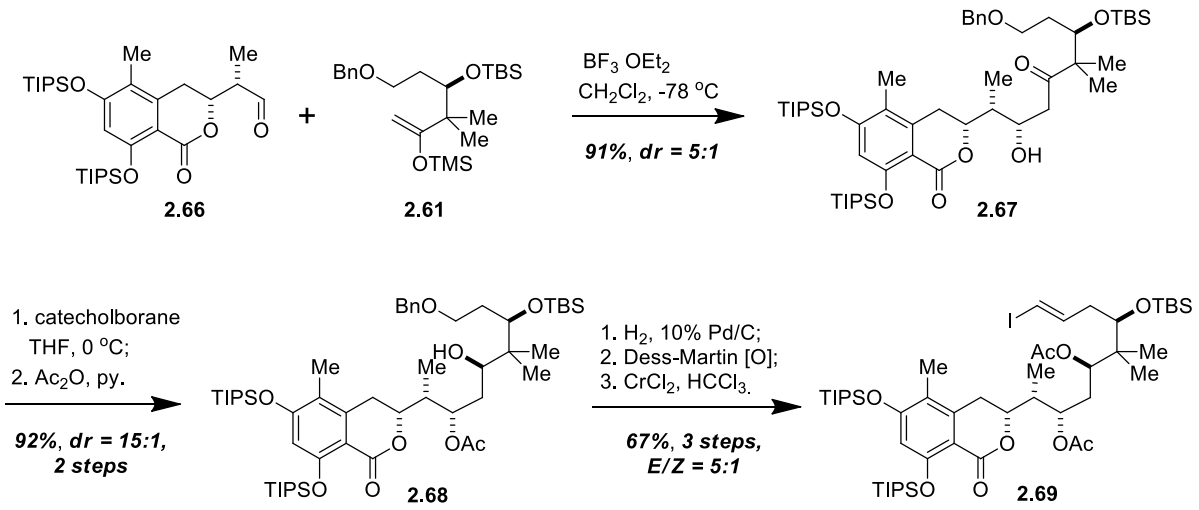
The late stage formation of the tetrahydropyran sought by Schering Plough group resulted in a concise synthesis of C_9-C_{13} fragment (Scheme 8, panel B). The enantioselective Masamune aldol coupling between silyl enolate **2.58** and aldehyde **2.57** set the single stereocenter[20] (*er* 50:1) of compound **2.60**. Protection of the resultant alcohol **2.60** followed by enol ether formation (2 steps) gave the enolsilane **2.61**.

Like our strategy to access the dihydroisocumarin, the Schering group explored a synthetic route by elaborating a commercially available aromatic ring **2.62** as starting material (panel C). It was converted to the aryl triflate followed by a Stille coupling to give alkene **2.63**. A protection group switch delivered compound **2.64**. Next, the terminal alkene **2.64** was oxidized to the aldehyde followed by a Brown crotylation that afforded the *syn*-secondary alcohol **2.65** with excellent diastereoselectivity (*dr* >50:1). Under the acidic hydrolysis conditions, the dihydroisocoumarin was formed smoothly, which was converted to the

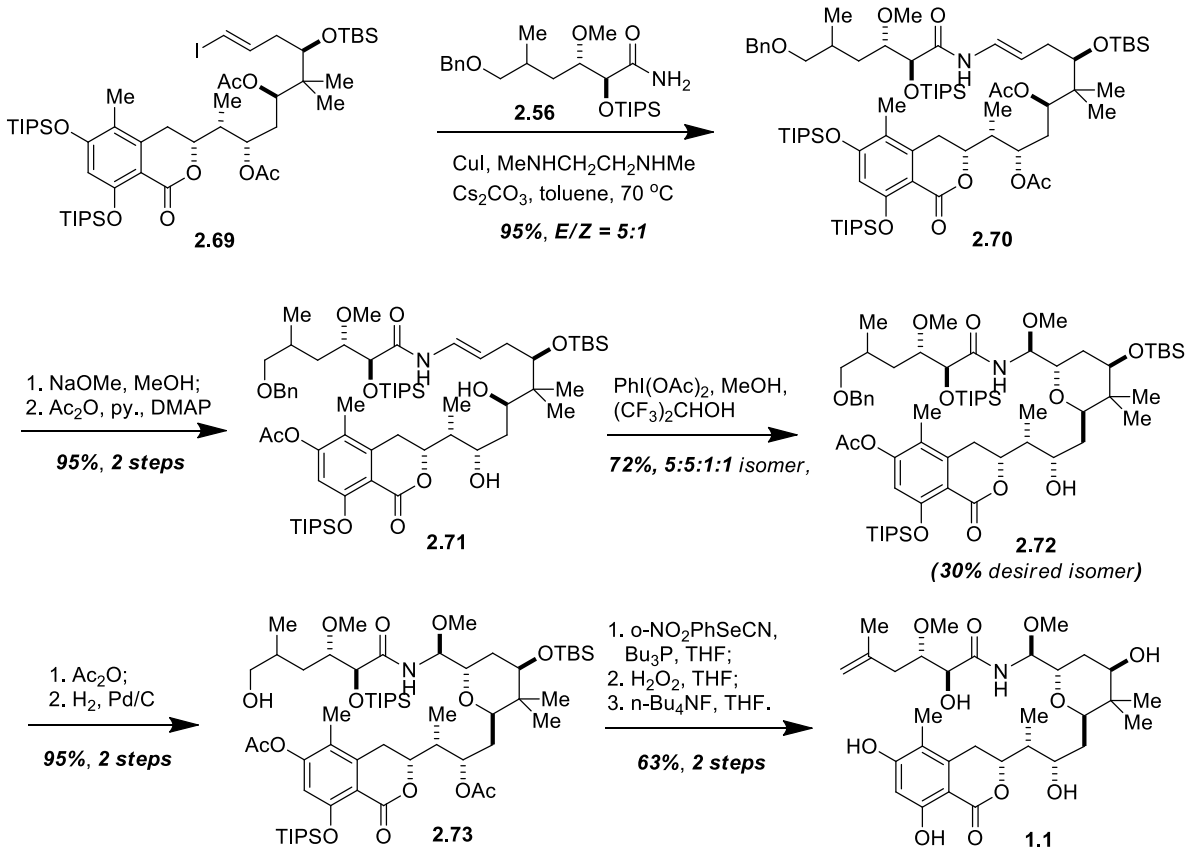
corresponding aldehyde **2.66** by oxidative cleavage.

With all fragments in hand, the Schering group employed a substrate controlled Mukaiyama aldol coupling[21] (Scheme 9) to construct β-hydroxyl ketone **2.67** with a 91% yield and 5:1 *dr*. A 1, 3-*syn* selective reduction (catecholborane, THF) gave the *S* configuration at C_{13}, which was then trapped as acetate **2.68**. Removal of the benzyl group, Dess-Martin oxidation and homologation via a Takai olefination [22] provided vinyl iodide **2.69** (*E/Z* = 5:1).

Scheme 9. Schering Plough Strategy for the Union of the Aryl Fragment and the Tetrahydropyran Precursor



Scheme 10. Schering Plough Total Synthesis of Psymberin



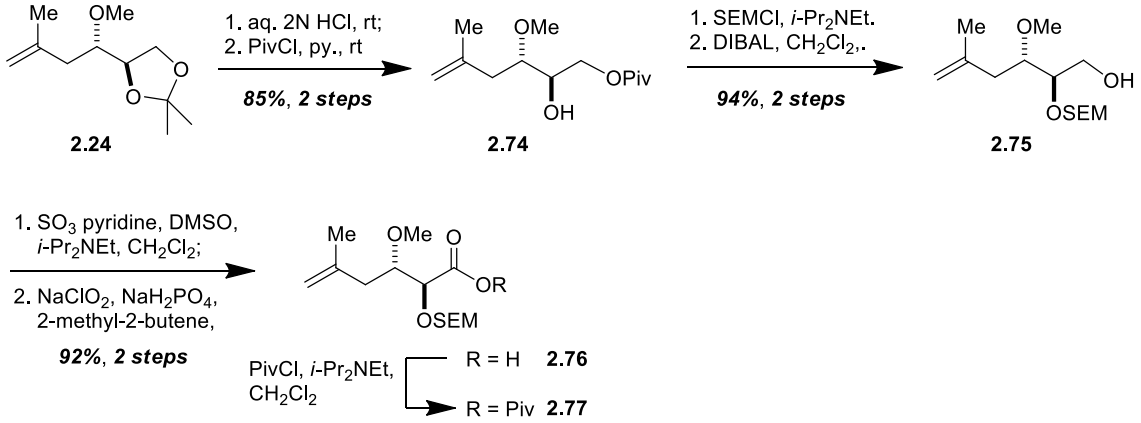
Once the vinyl iodide had been prepared successfully, they investigated a novel strategy for the installation of the signature *N*-acyl aminal unit (Scheme 10). The Buchwald coupling of vinyl iodide **2.69** and amide **2.56** produced the protected *N*-acyl enamine **2.70** under Copper(I)-catalyzed conditions.[23] Removal of the O_{13} acetate was accompanied by desilylation at O_{21}, which was subsequently reacetylated as compound **2.71**. Iodophenzyl diacetate mediated oxidative cyclization[24] gave a separable mixture of tetrahydropyrans in modest yield (30% isolated yield for desired product **2.72**). Compound **2.72** was acetylated followed by hydrogenlytic removal of the benzyl ether. The resultant primary alcohol **2.73** was converted into an olefin via a selenium-mediated dehydration. Finally, a

fluoride-mediated global deprotection afforded psymberin (**1.1**, 21 longest linear steps, 8% overall yield).

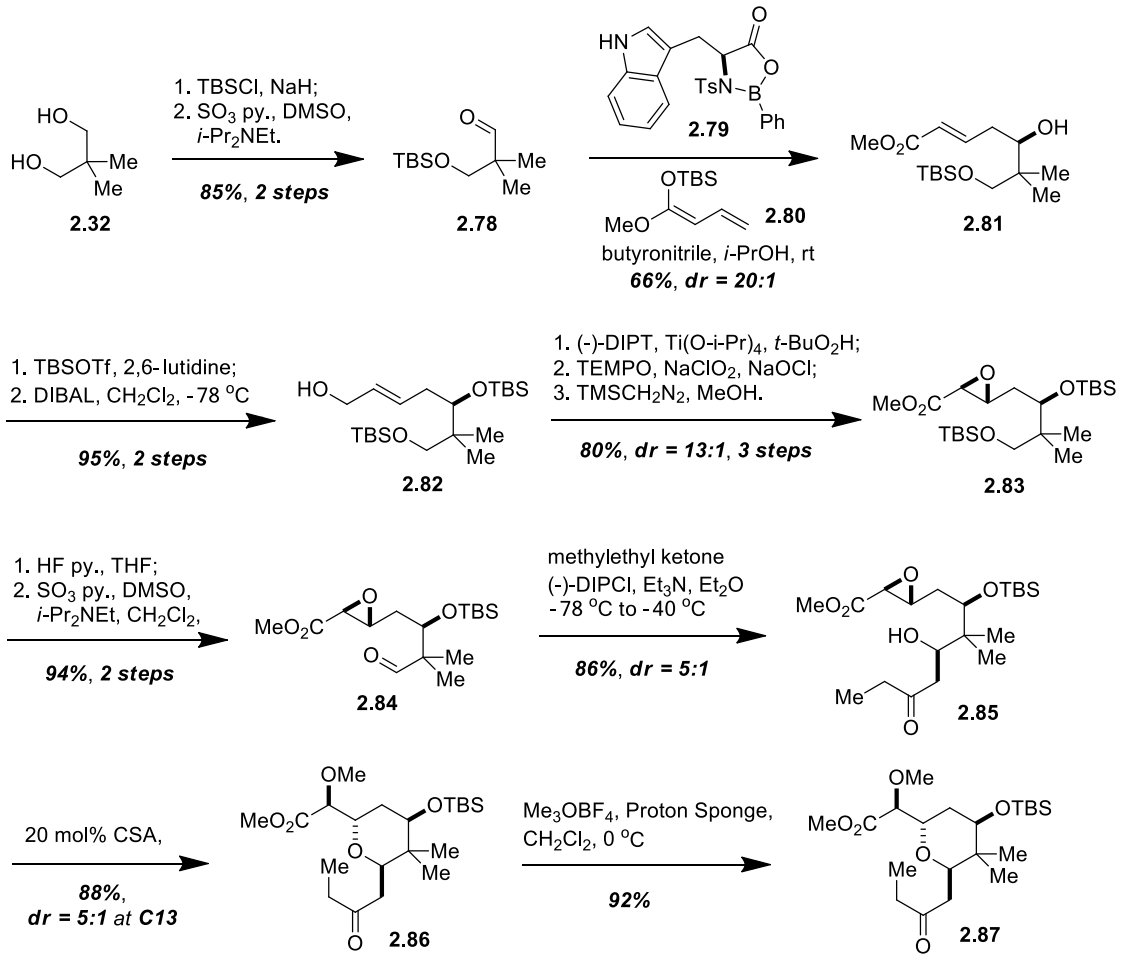
2.4 Smith's Total Synthesis

Subsequently, the Smith group[2b] completed the fourth total synthesis of psymberin (**1.1**) in 2008. For the psymberate side chain (Scheme 11), Smith employed a nearly identical strategy to our and Williams' approach. The 1,2-diol acetonide in **2.24** was removed and the resultant primary alcohol was protected to form pivalate ester **2.74**. After the secondary alcohol was masked as a SEM ether, a reductive deprotection released the primary alcohol **2.75**. A standard two-step oxidation sequence furnished the carboxylic acid **2.76**, which was converted to the mixed pivalate anhydride **2.77** for further side chain installation.

Scheme 11. Smith Synthesis of Psymberate Side Chain



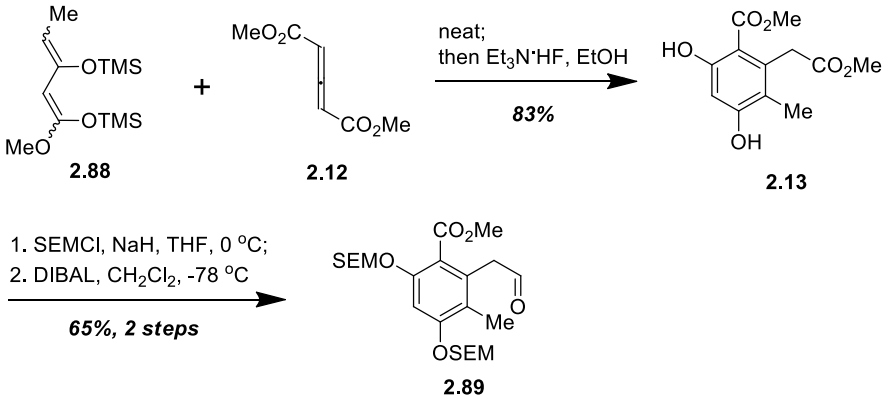
Scheme 12. Smith Synthesis of Central Tetrahydropyran Core



The commercial available neopentyl glycol **2.32** was used as starting material for synthesis of the central tetrahydropyran fragment (scheme 12). It was subjected to mono silylation and oxidation to afford aldehyde **2.78**. Employing the oxazaborolidinone **2.79** as the promoter, the vinylogous Mukaiyama aldol reaction with silyl ketene acetal **2.80** delivered carbinol **2.81** as a single optical-active isomer in 66% yield. Silylation of the resultant alcohol and reduction of the methyl ester released the allylic alcohol **2.82**, which was epoxidized under Sharpless asymmetric epoxidation[25] conditions in 88% yield and 13:1 *dr*. Subsequently, the

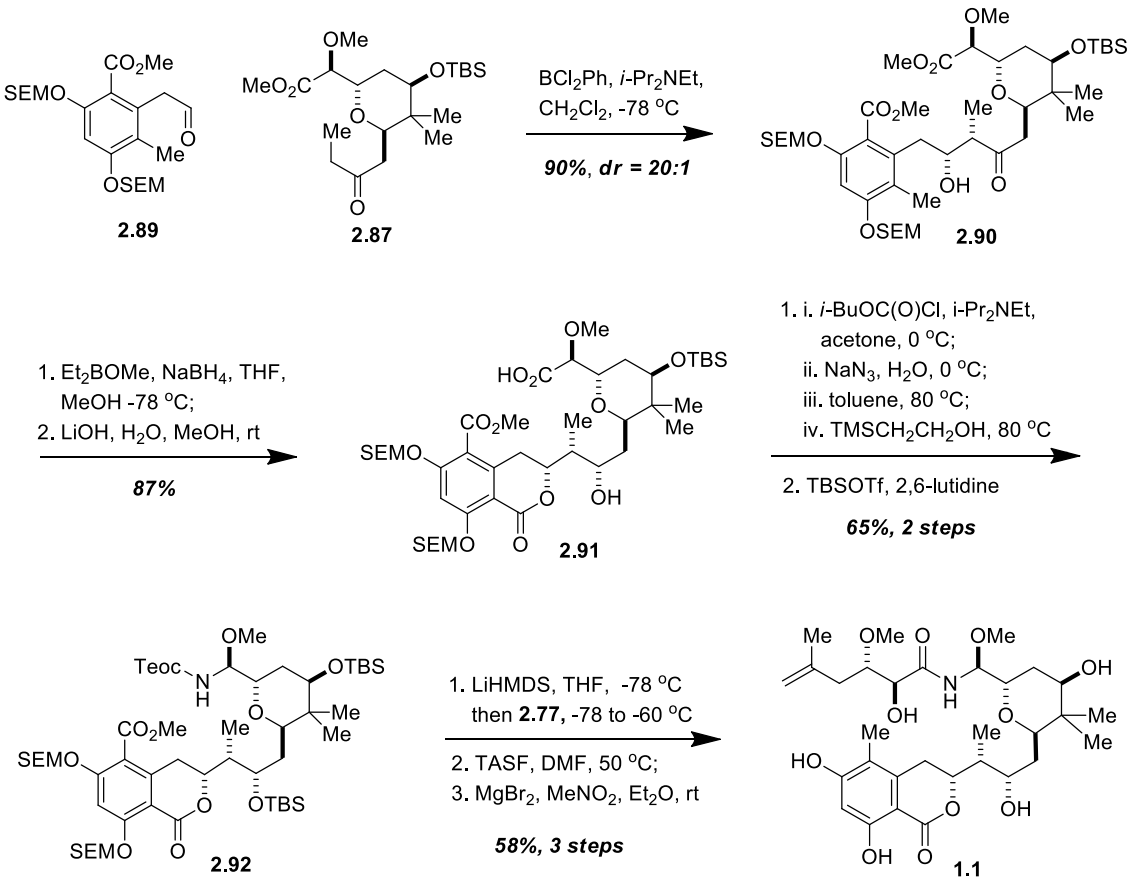
TEMPO-mediated oxidation of the primary alcohol gave the corresponding carboxylic acid, which was methylated to methyl ester **2.83** using $TMSCH_2N_2$. Selective removal of the primary silyl group followed by Parikh-Doering oxidation of the resultant alcohol made the aldehyde **2.84**. According to the Paterson's method,[26] aldehyde **2.84** was treated with the boron enolate derived from 2-butanone to form the ethyl ketone **2.85** in 88% yield and 5.3:1 *dr* at C_{13}. Treatment with catalytic amount of acid induced an intramolecular epoxide opening to form the six-membered pyran ring **2.86**. Methylation of the resultant secondary alcohol completed the synthesis of central segment **2.87**.

Scheme 13. Smith Synthesis of Aryl Fragment



In a manner similar to Floreancig, the Langer [4+2] cycloaddition between 1, 3-*bis*(trimethylsiloxy)-1,3-diene **2.88**[27] and allene **2.12** formed the poly-substituted benzene **2.13** in 83% yield (Scheme 13). Protection and *semi*-reduction yielded the desired aldehyde **2.89** in two steps with 65% yield.

Scheme 14. Smith Synthesis of Psymberin



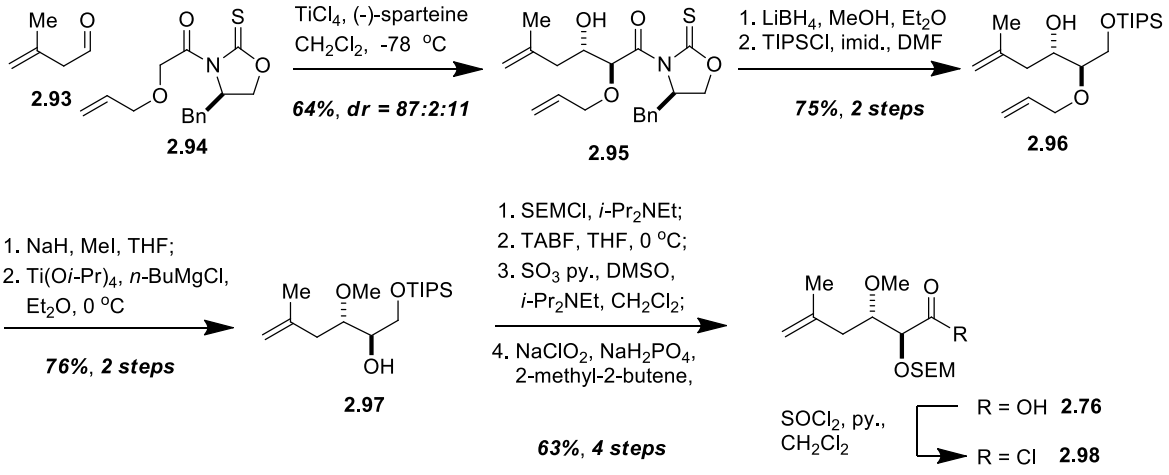
After the three key fragments had been prepared, Smith launched an investigation to couple tetrahydropyran fragment **2.87** and aryl fragment **2.89** (Scheme 14). Addition of the (*Z*)-chlorophenylboryl enolate derived from ketone **2.87** to aldehyde **2.89** gave a substrate controlled *syn*-aldol product **2.90** in 20:1 *dr*[28], a strategy first employed by De Brabander and co-workers.[1] 1,3-*Syn* reduction (Et_2BOMe, $NaBH_4$)[29] followed by hydrolysis with concomitant lactonization provided the dihydroisocoumarin **2.91**. A Curitus rearrangement strategy was employed to provide Teoc-protected hemiaminal **2.92**. Using carefully optimized conditions, they found that LiHMDS could be used as the base to execute the coupling between **2.92** and **2.77**. Final deprotection then provided synthetic psymberin (**1.1**,

21 longest linear steps from commercially available 2,2-dimethyl-1,3-propanediol, 5.3% overall yield). This strategy represents a significant improvement for the selective installation of the C_8 hemiaminal.

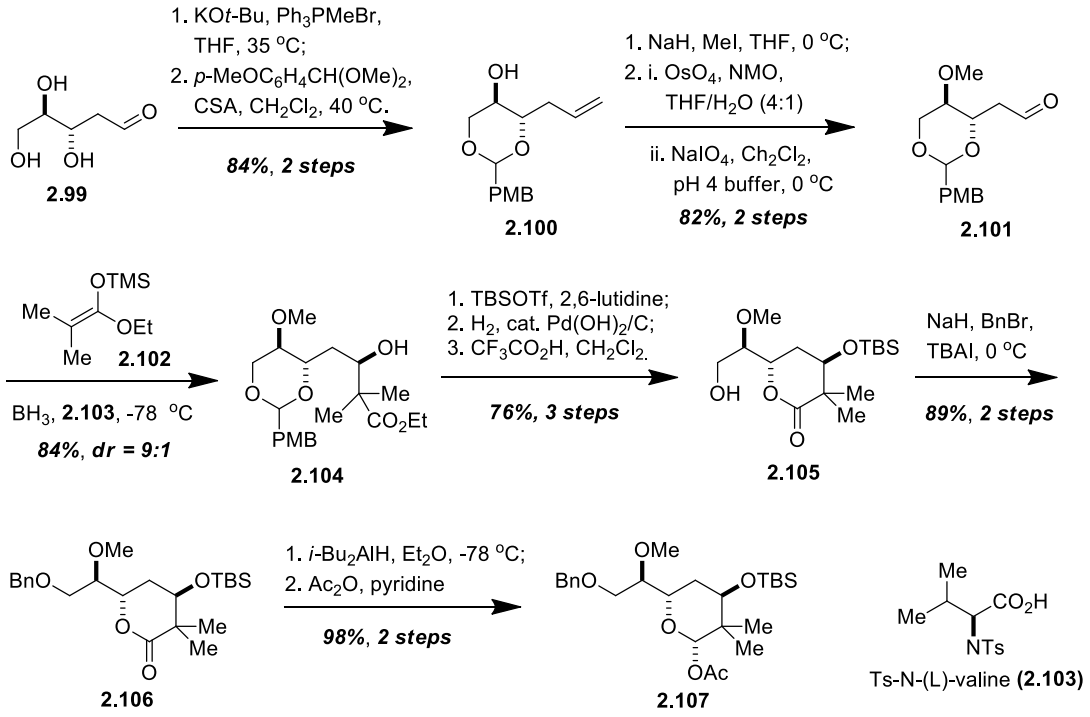
2.5 Crimmins Total Synthesis

Crimmins reported the fifth total synthesis of psymberin in 2010.[2c] They employed a different strategy for the psymberate side chain synthesis (Scheme 15). Unlike the previous chiral pool approaches, they utilized an asymmetric glycolate aldol[30] reaction, which allowed accessing the enantioenriched product **2.95** from the non-chiral starting material **2.93**. Removal of the chiral auxiliary and silylation yielded the allylic ether **2.96**. Subsequent methylation followed by Lewis acid catalytic deprotection (Kulinkovich conditions[31]) afforded the secondary alcohol **2.97**. Another four steps then provided the Smith psymberic acid **2.76**.

Scheme 15. Crimmins Synthesis of Psymberate side chain

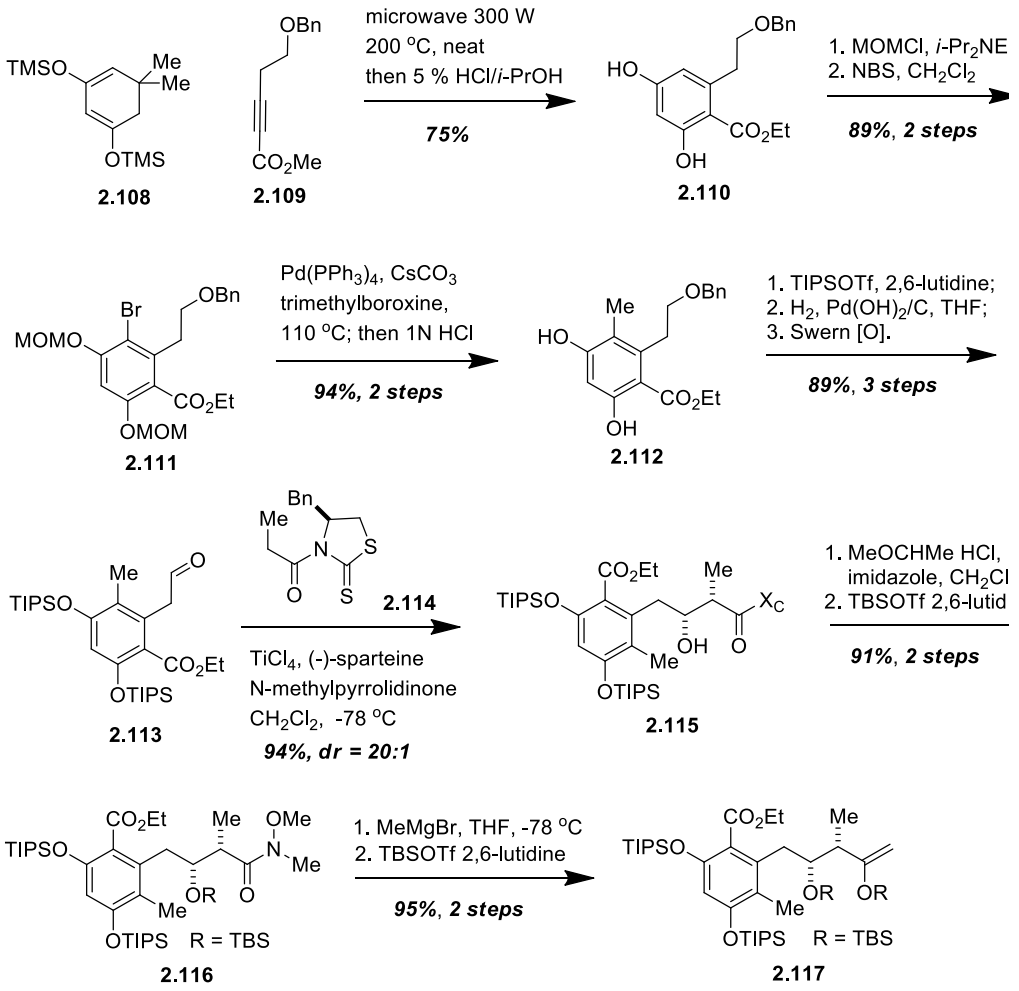


Scheme 16. Crimmins Synthesis of Central Tetrahydropyran Core



Employing the commercially available 2-deoxy-D-ribose **2.99** as starting material[32] (Scheme 16), olefination followed by 1,3-protection gave the acetonide **2.100**. Methylation followed by dihydroxylation-oxidative cleavage unmasked the aldehyde **2.101**, which was engaged in a catalytic Kiyooka aldol reaction[33] with enolsilane **2.102** to provide carbinol **2.104** in 84% yield and 9:1 *dr*. Silylation, hydrogenation and acid promoted lactonization then delivered the lactone **2.105** in three steps. The primary alcohol was masked as benzyl ether **2.106**, which after careful *semi*-reduction of the lactone with DIBAL-H, followed by acetylation led to acetate **2.107**.

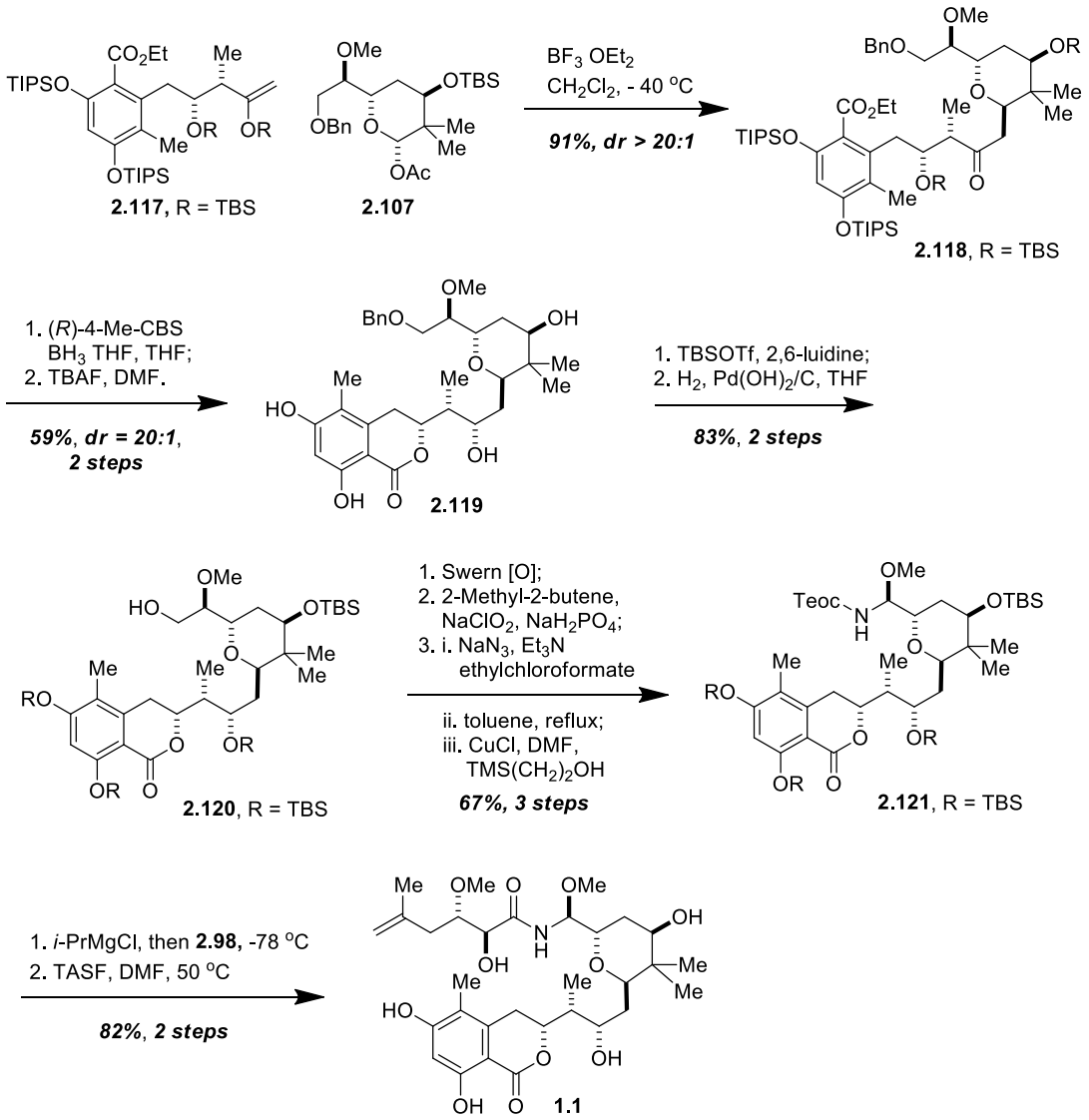
Scheme 17. Crimmins Synthesis of Aryl Fragment



For the aryl portion, the synthesis commenced with a microwave-induced Diels-Alder reaction between diene **2.108**[34] and alkynoate **2.109**[35] (Scheme 17). Protection of the aryl product **2.110** as a *bis*-MOM ether and regio-selective bromination provided aryl bromide **2.111**. The methyl group at C_{20} was introduced (→ **2.112**) via a sp^2-sp^3 Suzuki coupling[36] with trimethylboroxine. After switching the MOM ethers to TIPS ethers, standard hydrogenation conditions removed the benzyl group followed by oxidation of the resultant alcohol to aldehyde **2.113**. The aldol reaction between aldehyde **2.113** and propionyl thiazolodinethione **2.114** provided the *syn* aldol adduct **2.115** in 94% yield and 20:1 *dr*. The

chiral auxiliary was replaced by a Weinreb amide, and followed by silylation to give amide **2.116**. Grignard addition provided a methyl ketone, which was converted to TMS enolsilane **2.117** for further coupling.

Scheme 18. Crimmins Synthesis of Psymberin



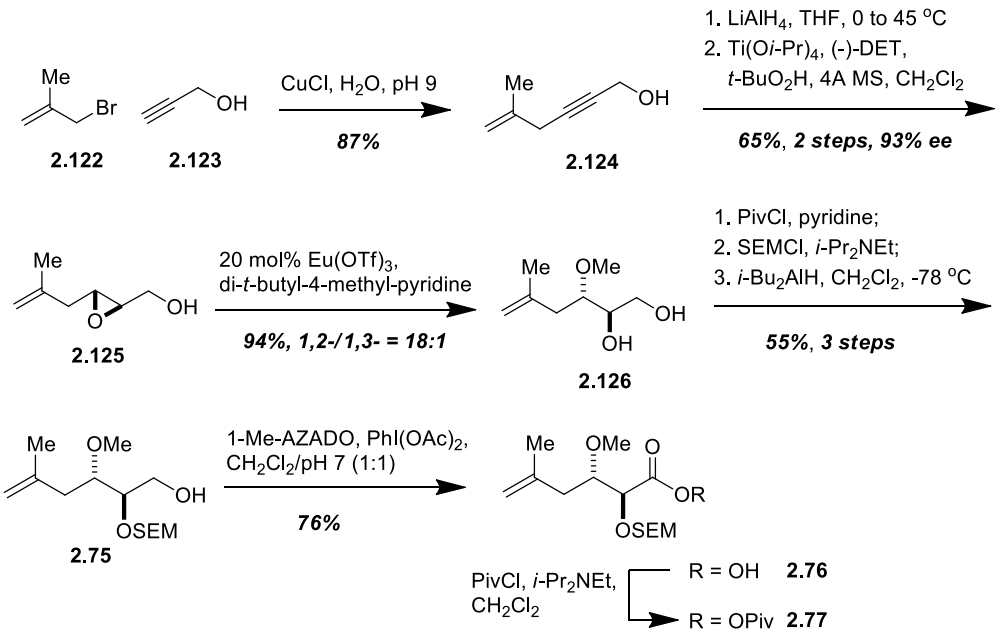
It was observed that the Mukaiyama aldol reaction[37] was most efficiently performed via addition of enolsilane **2.117** to a performed solution of **2.108** and $BF_3 \cdot OEt_2$ at -40 °C,

producing the desired aldol adduct **2.118** in 91% yield and 20:1 *dr* (Scheme 18). The (*R*)-4-Me-CBS mediated 1,3-*syn* reduction afforded the desired alcohol as the major isomer (*dr* 20:1). At this point, a fluoride mediated global deprotection led to concomitant dihydroisocoumarin formation (→ **2.119**). Reprotection of all the free hydroxyl groups as TBS ethers, followed by removal of the benzyl group by hydrogenation generated the primary alcohol **2.120**, which was oxidized to corresponding carboxylic acid and transformed to *N*-Teoc hemiaminal **2.121**. After installing the psymberate side chain, a global deprotection with TASF in DMF delivered the psymberin (**1.1**) in 94% yield. In conclusion, Crimmins and co-workers completed the total synthesis of psymberin in a 19 longest linear sequence with a 6% overall yield from 2-deoxy-D-ribose (**2.99**).

2.6 Watanabe Total Synthesis

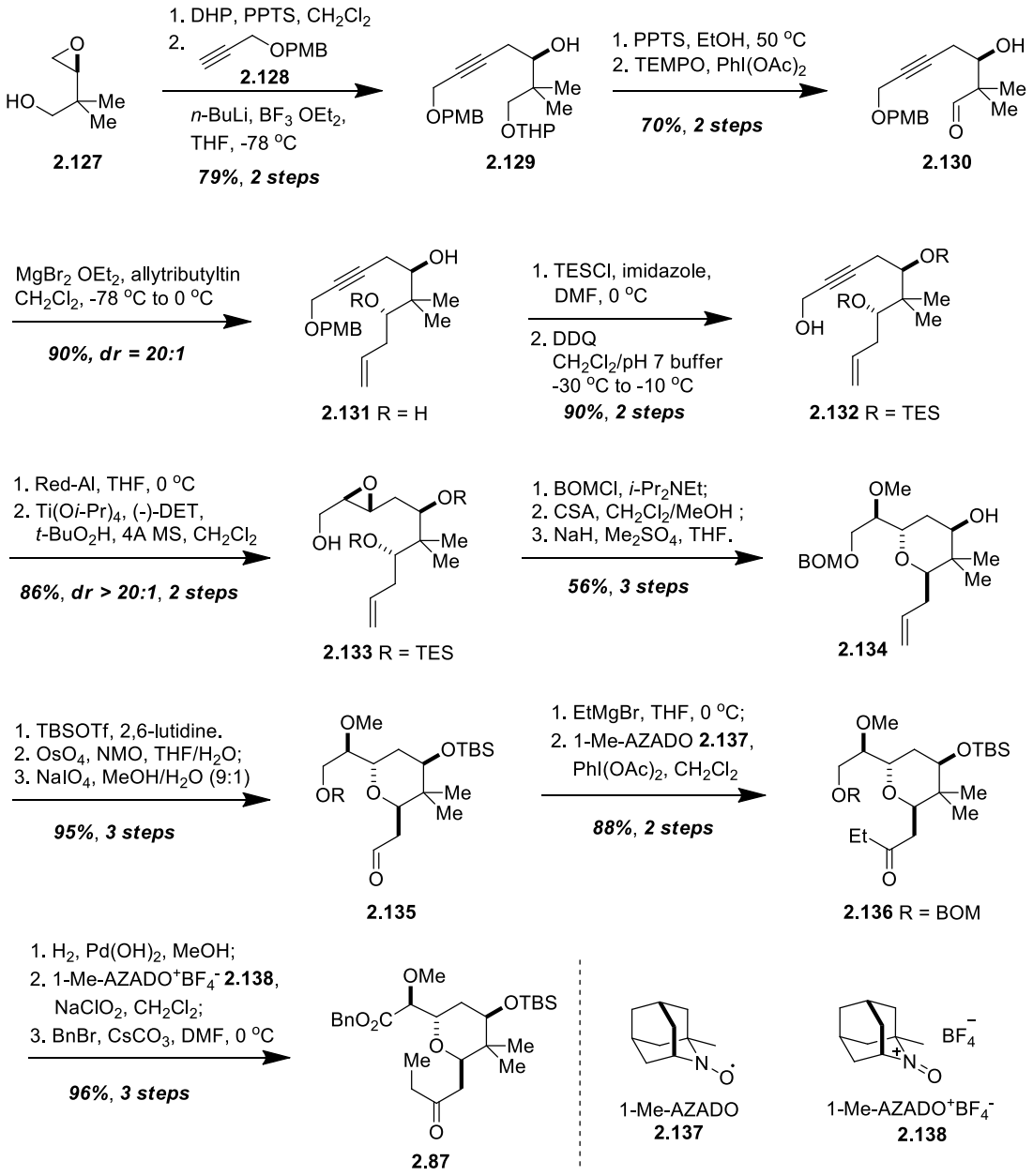
In 2010, Watanabe and co-workers completed the sixth synthesis of psymberin **1**.[2d] For the psymberate side chain, Watanabe developed a concise and scalable approach, starting from non-chiral materials (Scheme 19). Copper(I)-catalyzed coupling between methallylbromide **2.122** and propargyl alcohol **2.123** generated the terminal olefin **2.124**,[38] which was then reduced to an allylic alcohol. Under Sharpless conditions,[39] a enantioselective epoxidation afforded the epoxide **2.125** in 65% yield over two steps and 99% *ee*. The Lewis acid catalyzed ring opening reaction delivered the 1,2-diol **2.126** regioselectively, after selective methylation of the C_3 hydroxyl group. Further transformation to anhydride **2.77** followed the route previously exploited by Smith.[2b]

Scheme 19. Watanabe Synthesis of Psymberate Side Chain



Watanabe and co-workers developed a long route for the central tetrahydropyran fragment synthesis (Scheme 20). Starting from the known epoxide **2.127**,[41] protection of the free alcohol and subsequent acetylide addition[42] to the epoxide delivered propargylic alcohol **2.128**. Removal of the THP protection group followed by oxidation generated the aldehyde **2.130** in 70% yield over two steps. A diastereoselective allylation[43] (→**2.131**) set the desired configuration at C_{13} with a 20:1 *dr*. Silylation of **2.131** followed by oxidative cleavage of the PMB group yielded the primary alcohol **2.132**. Red-Al mediated reduction of the alkyne to alkene allowed by Sharpless epoxidation furnished epoxide **2.133** with a > 20:1 *dr*. After the primary alcohol of **2.133** had been protected, it was treated with CSA to induce a cyclization to give the tetrahydropyran **2.134**, after methylation of the secondary alcohol.

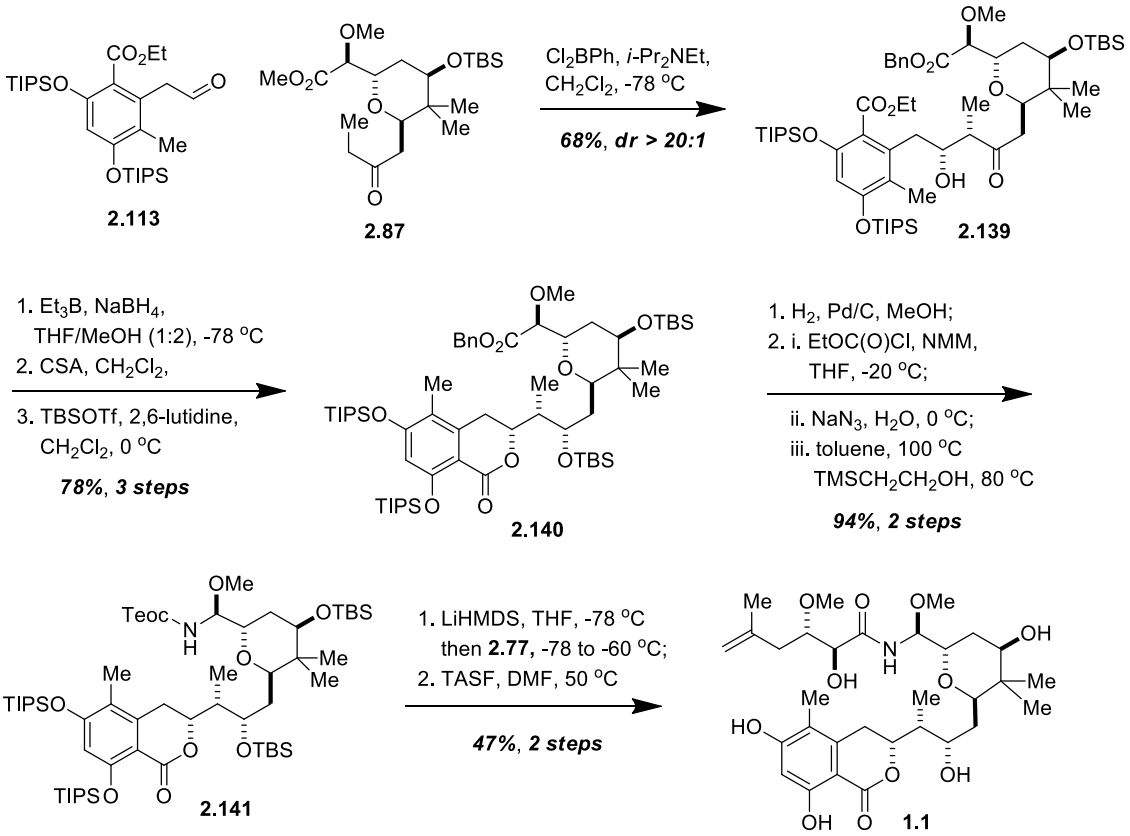
Scheme 20. Watanabe Synthesis of Tetrahydropyran



Having constructed the key tetrahydronpyran, they moved their attention to convert the terminal alkene to the requisite ethyl ketone. Reprotection of the silyl ether that was lost during the cyclization process, followed by dihydroxylation and oxidative cleavage revealed the aldehyde **2.135**. The ethyl ketone **2.136** was installed through Grignard addition and an

ensuing oxidation catalyzed by salt **2.137**. Hydrogenolysis of the BOM ether followed by oxidation and benzylation provided target coupling partner **2.87**, identical to the Smith fragment. Starting from epoxide **2.127**, the central fragment **2.87** was accomplished in a 20 longest linear sequence and 16% overall yield.

Scheme 21. Watanabe Synthesis of Psymberin



The synthesis of the aromatic fragment **2.113** was borrowed from work published by De Brabander,[1] whereas the aldol coupling with ethyl ketone **2.87** and further elaboration to psymberin (Scheme 21) heavily relied on works from the De Brabander and Smith

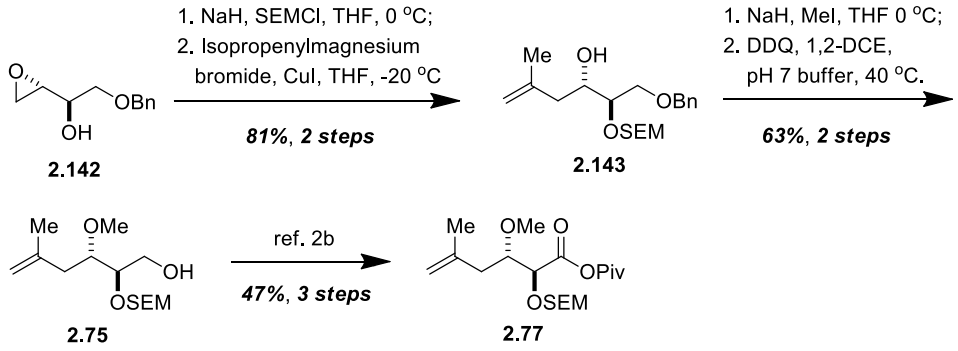
laboratories.[1, 2b]

2.7 Hong Total Synthesis

To date, the Hong group[2f] reported the seventh synthesis of psymberin (**1.1**) employing chiral epoxides to prepare two of the three subunits in the natural product. The highlight of this work was a highly stereoselective organocatalytic *oxa*-conjugate addition to an α, β-unsaturated ketone for the synthesis of the 2,6-*trans*-tetrahydropyran embedded in psymberin.

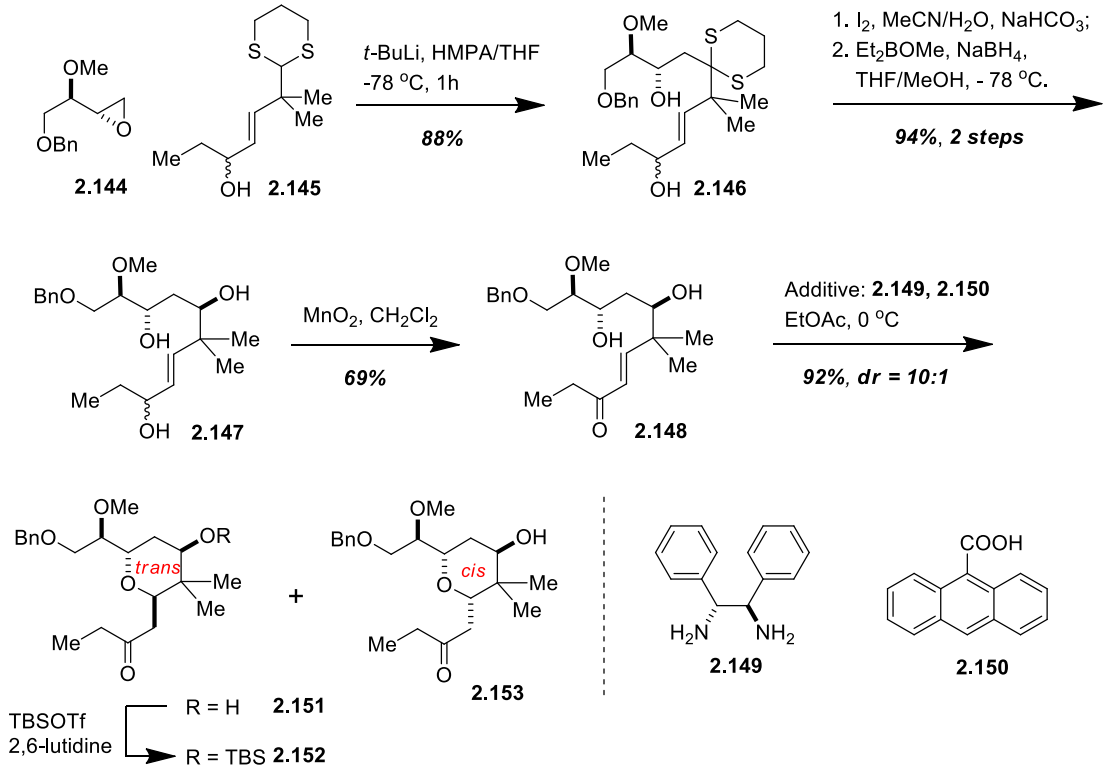
The pivalate mixed anhydride **2.77** of psymberic acid, which had been synthesized by the Smith[2b] and Crimmins[2c] groups, was prepared from a significantly different starting material **2.142** (Scheme 22). Protection of the secondary alcohol **2.142** as a SEM ether followed by epoxide opening with isopropenyl magnesium bromide delivered secondary alcohol **2.143**. Methylation and oxidative removal of the benzyl ether proceeded smoothly to afford the known primary alcohol **2.75**, which was converted to the pivalate mixed anhydride **2.77**

Scheme 22. Hong Synthesis of Psymberated Side Chain



employing the Smith protocol in literature [2b].

Scheme 23. Hong Synthesis of Central Tetrahydropyran Core

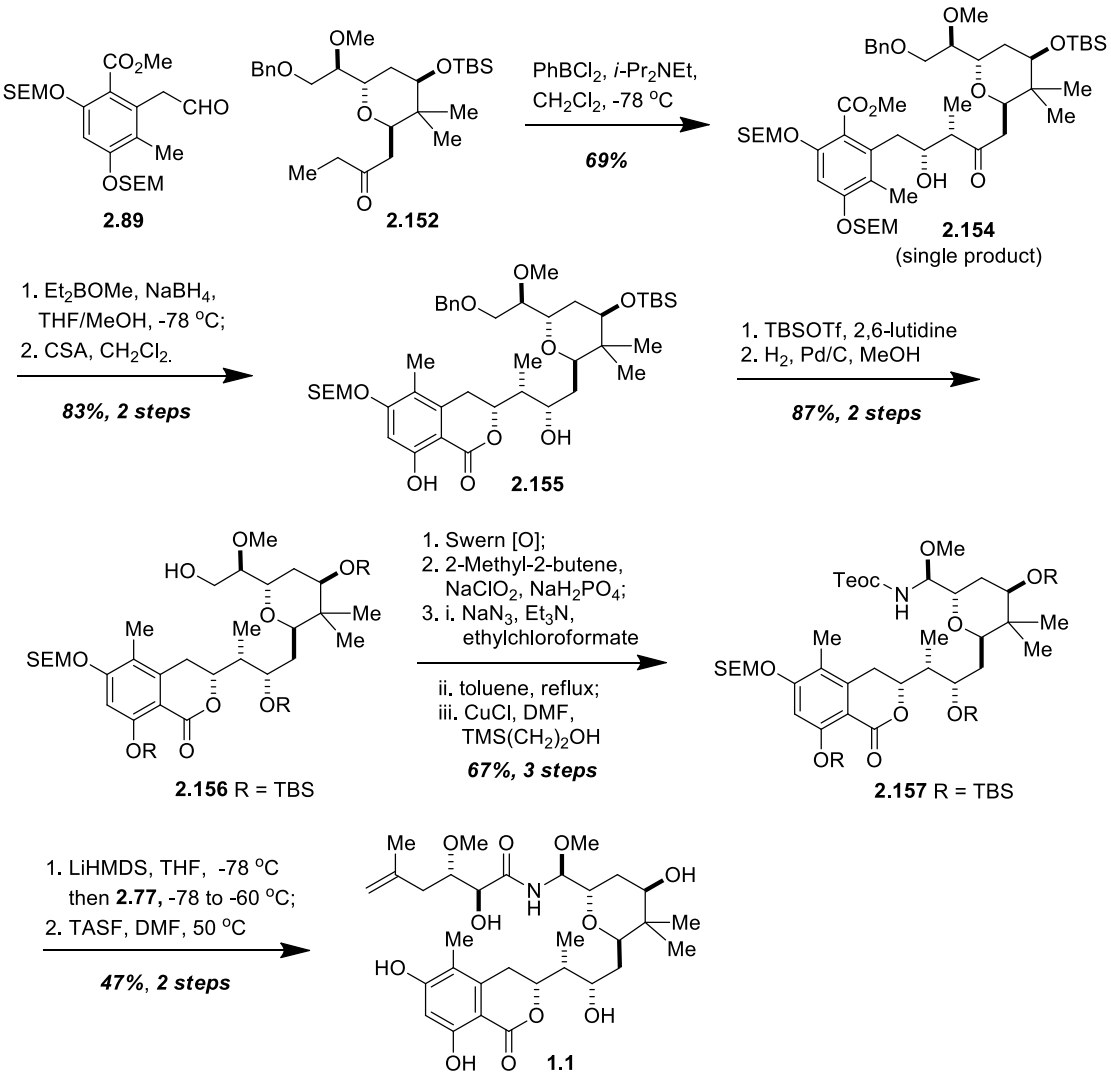


The synthesis of the central tetrahydropyran fragment (Scheme 23) started from the union of chiral epoxide **2.144** (prepared from (*S*)-(+)-glycidyl benzyl ether[46] in 3 steps) and vinyl alcohol **2.145** (prepared from 2,2-dimethyl-1,3-propanediol in 8 steps). Treatment of dithiane **2.145** with *t*-BuLi followed by addition of epoxide **2.144** delivered **2.146**. In the event, dithiane groups in **2.146** were removed and 1,3-*syn* reduction afforded the triol **2.147**. MnO_2-oxidation of the secondary alcohol set the stage for the organo-catalytic cyclization. The Hong group screened a wide range of conditions for this key organocatalytic oxaconjugate addition reaction.[47-49] Due to the steric congestion of the iminium intermediate,

the diamine mediated addition provided the tetrahydropyran with both *anti*- and *syn*- manners. Finally, they found that in the presence of the 9-anthracenecarboxylic acid **2.150**, the (1*R*,2*R*)-1,2-diphenylethane-1,2-diamine **2.149** catalyzed *oxa*-conjugate addition yielded the 2,6-*trans*-3,3-dimethyl tetrahydropyran **2.151** smoothly with 92% yield and 10:1 *dr*. The major product was subsequently masked as silyl ether **2.152**.

With the three key subunits in hand, they investigated the *syn*-aldol coupling between the tetrahydropyran **2.152** and aldehyde **2.89** (Scheme 24), using conditions first explored by De Brabander.[1] The aldehyde **2.89** was added into the solution of enolate derived from **2.152** ($PhBCl_2$, *i*-Pr_2NEt) in CH_2Cl_2 at -78 ^oC, which constructed the desired *β*-hydroxy ketone **2.154** as a single diastereomer. 1,3 *Syn*-reduction (Et_2BOMe, $NaBH_4$) followed by lactone formation under acidic condition afforded the dihydroisocoumarin **2.155**. However, the process resulted in loss of the C_{22} SEM group. Silylation and benzyl deprotection delivered the primary alcohol **2.156**. Curtius rearrangement following the procedure previously reported by Smith group smoothly proceeded to give hemiaminal **2.157**. Coupling of **2.77** with **2.157** followed by exhaustive deprotection of the silyl protecting groups completed the synthesis of **1.1**. In summary, the total synthesis of psymberin was accomplished in 24 steps (in the longest sequence from 2, 2-dimethyl-1, 3-propanediol) and 3.7% overall yield.

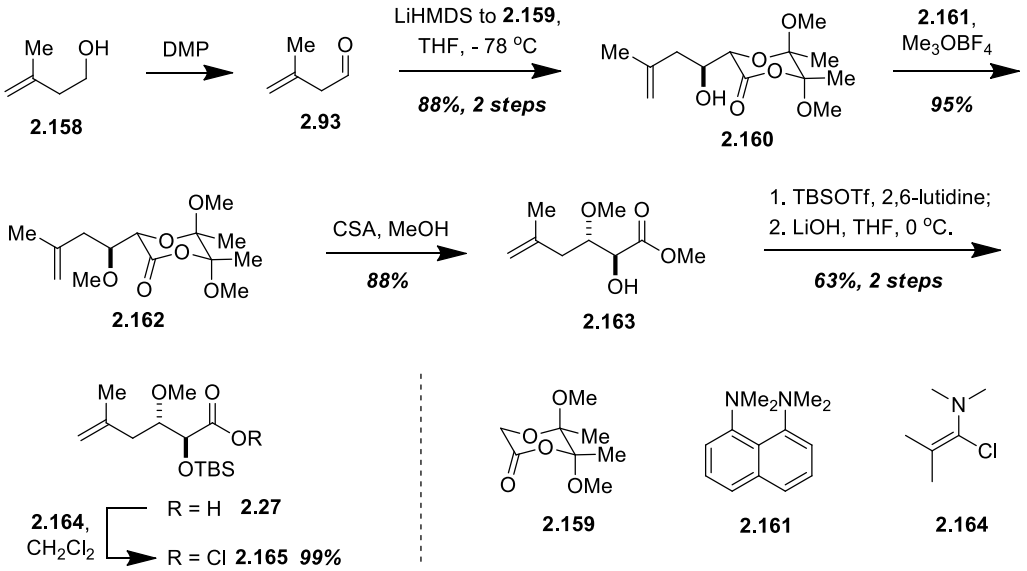
Scheme 24. Hong Completion Synthesis of Psymberin



2.8 Pietruszka Formal Synthesis[50]

In 2013, Pietruszka completed a formal synthesis of psymberin **1.1**. For the psymberate side chain[51] (Scheme 25), the commercial available primary alcohol **2.158** was chosen as starting material. After Dess-Martin oxidation, the unstable crude aldehyde **2.93** was added to the enolate of protected glycolic acid **2.159** at –78 °C. It exclusively led to the formation of the

Scheme 25. Pietruszka Synthesis of Psymberated Side Chain

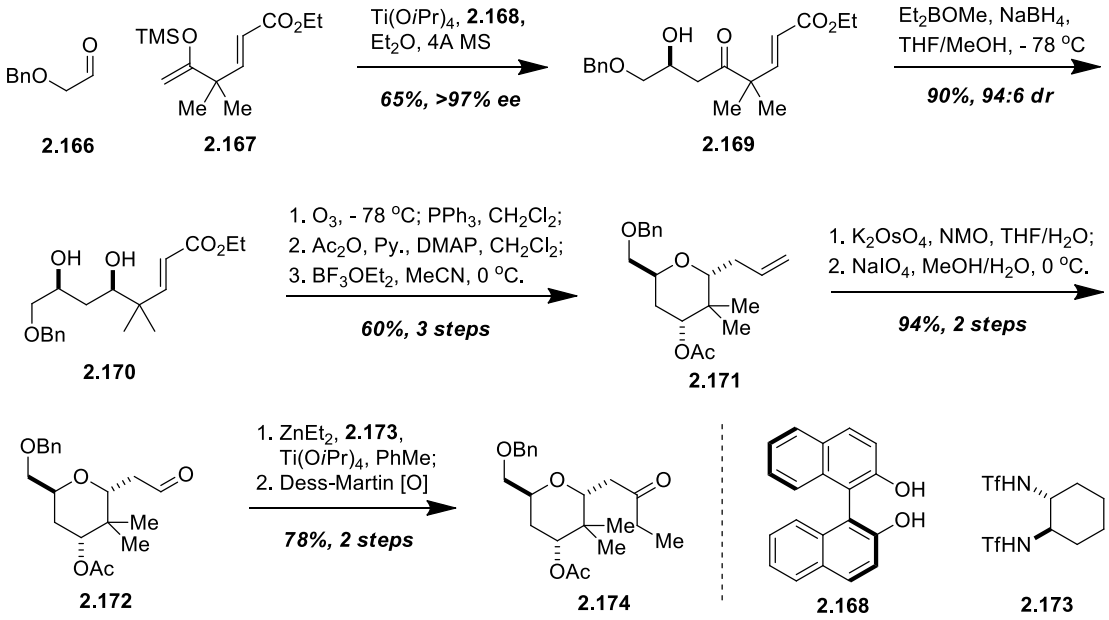


anti-aldol product **2.160** in 88% yield over two steps. Treatment of **2.160** with proton sponge **2.161** and Meerwein salt masked the secondary alcohol as the methyl ether **2.162**. Removal of the protecting group of **2.162** in the presence of camphorsulfonic acid released the methyl ester **2.163**. Silylation followed by hydrolysis with LiOH afforded carboxylic acid **2.27**, which was converted to acid chloride **2.165** using Ghosez's reagent **2.164**.[52]

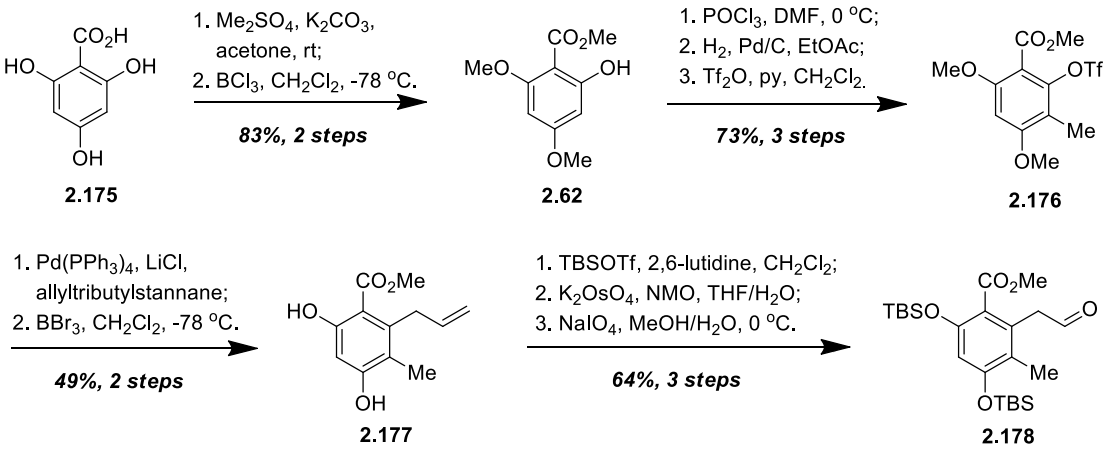
For the central tetrahydropyran fragment (Scheme 26), the silyl enol ether **2.167** that was prepared from *iso*-butyraldehyde in four steps. The titanium(IV)-BINOL catalyzed enantioselective Mukaiyama aldol coupling[53] between the enolate **2.167** and aldehyde **2.166** gave the desired adduct **2.169** in 65% yield and >97% *ee*. Under Prasad conditions[54] using diethylmethoxyborane and sodium borohydride, the 1, 3-*syn* diol **2.170** was obtained in 90% yield and 94:6 *dr*. Ozonolysis and double acylation of diol **2.170** followed by a diastereoselective allylation employing allyltrimethylsilane and $BF_3 \cdot OEt_2$ smoothly produced the THP-core **2.171** in 60% yield over 3 steps. The terminal olefin of **2.171** was then

converted into aldehyde **2.172** via oxidative double bond cleavage. Diethylzinc addition using the Kobayashi conditions, followed by Dess-Martin oxidation completed the synthesis of fragment **2.174**.[55]

Scheme 26. Pietruszka Synthesis of Tetrahydropyran Fragment

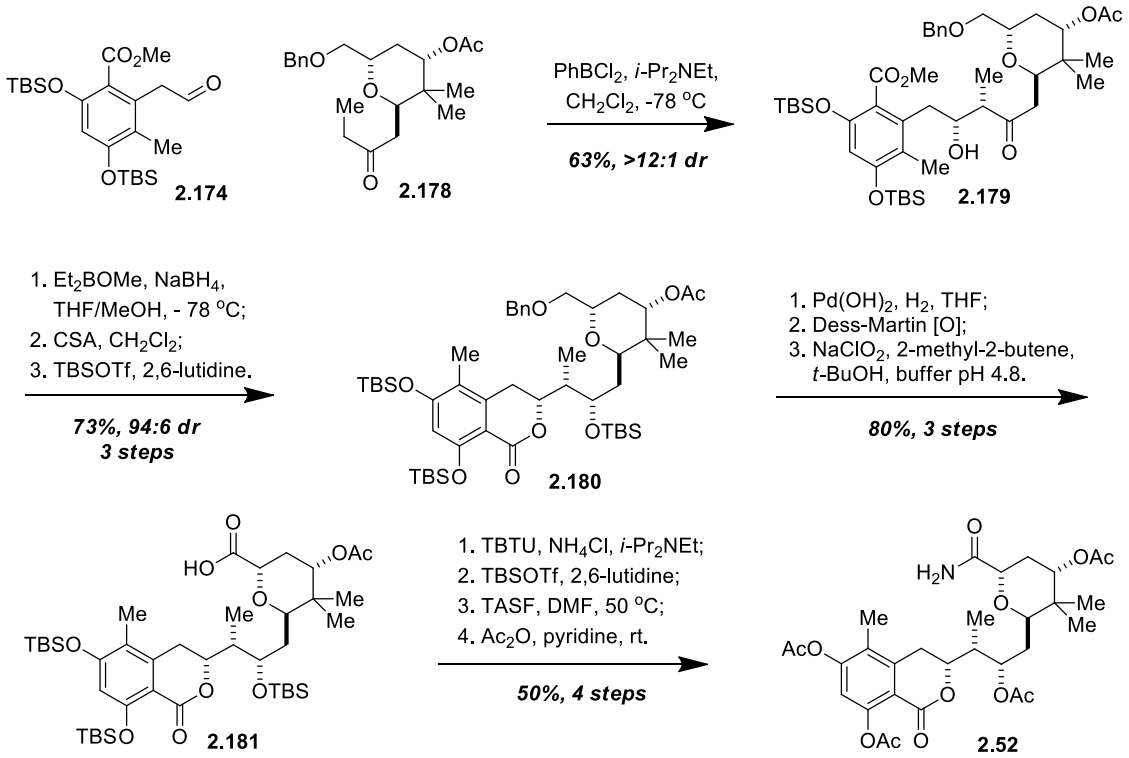


Scheme 27. Pietruszka Synthesis of Aryl Fragment



The synthesis of the aryl fragment started from the phloroglucinol **2.175** (Scheme 27). Global methylation followed by regioselective deprotection gave the phenol **2.62**, an identical intermediate from the Schering Plough's approach.[2a] It was then subjected to Vilsmeier-Haack[56] formylation and hydrogenation to install a methyl group at C3, after which the phenol was converted into aryl triflate **2.176**. Stille coupling between **2.176** and allyltributylstannane followed by deprotection afforded the *penta*-substituted aryl compound **2.177**. After silylation, the terminal double bond was oxidatively cleaved to deliver aldehyde **2.178**.

Scheme 28. Pietruszka Formal Synthesis of Psymberin



With the three fragments in hand, the aldol coupling between ethyl ketone **2.178** and aryl aldehyde **2.174** was investigated (Scheme 28). In analogy to De Brabander's strategy, the dichlorophenyl boron mediated coupling between the enolate derived from ketone **2.178** and aldehyde **2.174** delivered the adduct **2.179** with modest yield (63%) and good diasrereoselectivity (12:1 *dr*). After 1,3-*syn* reduction of the *β*-hydroxyl ketone **2.179**, the dihydroisocoumarin was installed in the presence of a catalytic amount of camphorsulfonic acid, followed by silylation to give **2.180** in 73% yield over three steps. For the conversion of the alcohol functionality to the corresponding primary amide, the benzyl group of **2.180** was removed using Pearlman's[57] catalyst, and the resulting primary alcohol was oxidized to acid **2.181** in a two-steps sequence. Amidation under peptide coupling conditions followed by reprotection with TBSOTf afforded a fully protected amide. To complete the formal synthesis, all the silyl groups were switched to acetate to give the peracetylated amide **2.52**. All the spectra data of **2.52** are in agreement with those reported by De Brabander.[1]

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Chapter 3

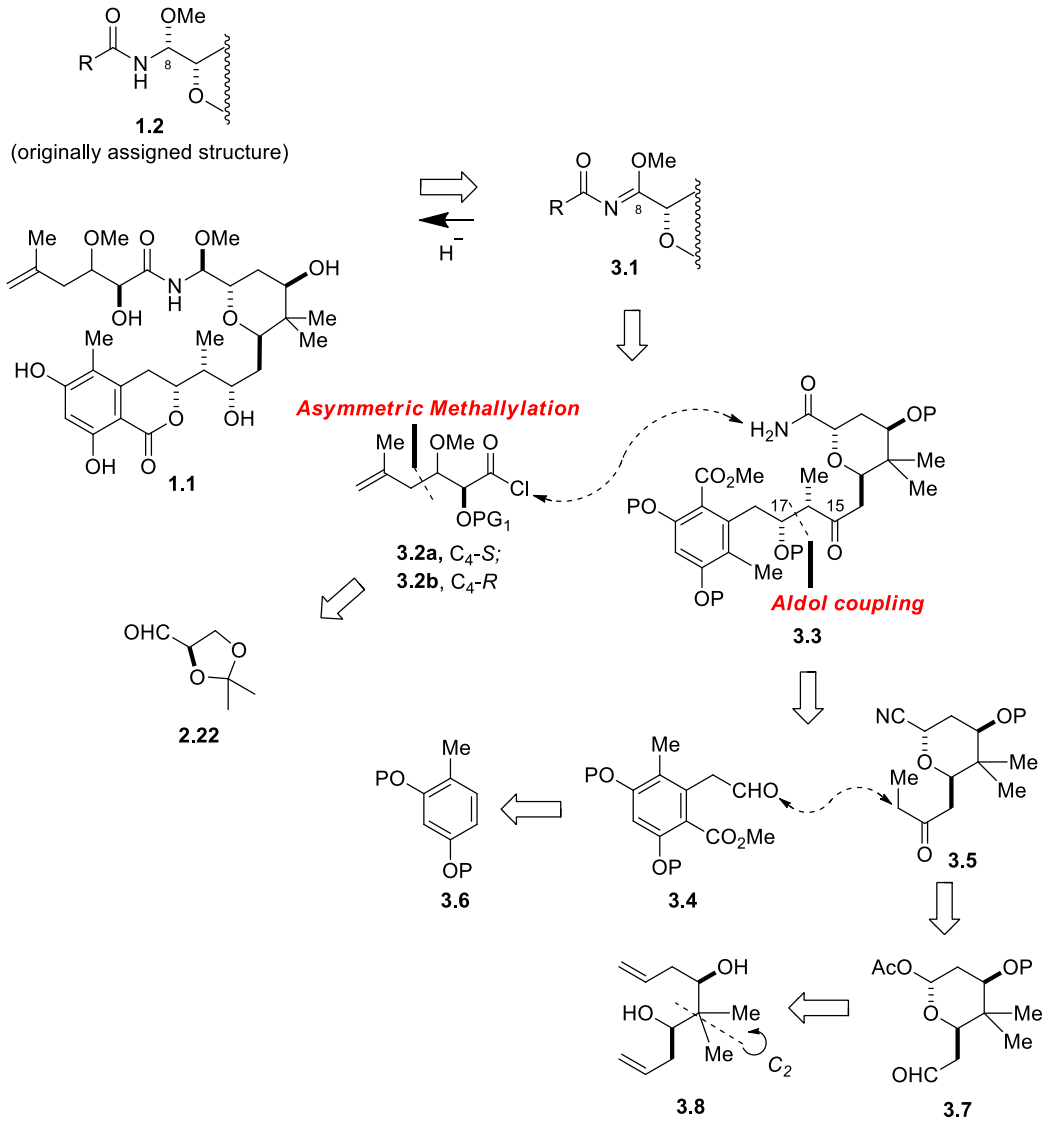
Chemical Studies toward the Unique Pederin Family Member Psymberin

Psymberin (**1.1**) is a complex polyketide comprising nine stereocenters, a geminal dimethyl, and a dihydroisocoumarin fragment. Its tetrahydropyranyl core is appended with a 2-hydroxy-3-methoxy-5-methyl-hex-5-enoic acid (psymberic acid) through an *N*-acylaminal linkage. In 2005, the De Barbander group completed the first total synthesis of psymberin,[1] of which proved that psymberin[2] and irciniastatin A[3] were identical and the structure proposed by Crews[2] for psymberin was correct. Due to the novel structure, significant biological activity, and unknown mode-of-action, we launched a second generation synthesis of psymberin and analogs for SAR studies. This second generation synthesis of psymberin and analogs was done by me as part of this Ph.D. thesis. Since I relied on the work previously performed by Drs. Xin Jiang and Jorge García-Fortanet in the De Brabander lab,[1] I have incorporated their results within this chapter. To be clear, the work described in section 3.1 was the previous work from the lab, whereas sections 3.2 second generation and 3.3 experimental procedures recorded my research.

3.1 First Generation

After the two initial independent isolation reports,[2,3] it remained unclear if psymberin (**1.1**) and irciniastatin A (**1.2**) were stereochemically identical. Therefore, in the first design, our lab previously planned a flexible route to access both *R* and *S* configurations of the uncertain

Scheme 29. Retrosynthetic Analysis for the First Generation Approach

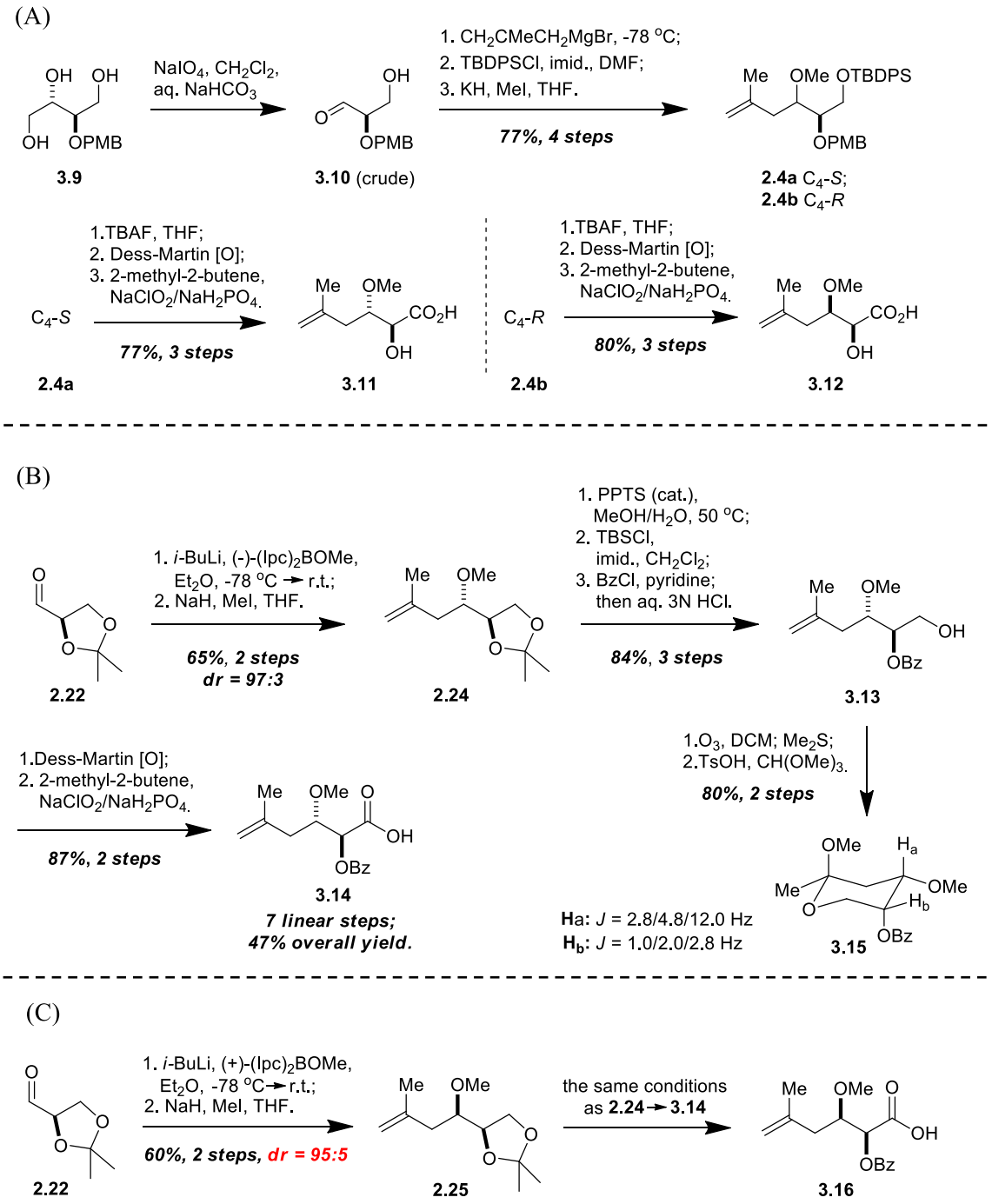


stereocenter at C_4.[1] As outlined in Scheme 29, it was anticipated that an intermediate *N*-acyl-methoxyimidate **3.1** could be intercepted with a reducing agent to provide the C_8-*S* and C_8-*R* *N*-acyl aminals corresponding to the assigned structures of psymberin and irciniastatin, respectively. Given the unknown configuration at C_4, both *syn*- and *anti*- acid chlorides **3.2a** and **3.2b** could be independently coupled with amide **3.3**. Both epimeric acid chlorides in turn will be accessible from common intermediate **2.22**, derived from *D*-mannitol

via a stereocontrolled methallylation. The approach to **3.3** hinged on combing aryl aldehyde **3.4**, obtained from commercially available 2,4-dimethoxy-1-methylbenzene **3.6** and ethyl ketone **3.5** via a substrate-controlled aldol coupling to set the correct stereochemistry of the C_{15}-C_{17} stereotriad. Ethyl ketone **3.5** was envisioned to be derived from aldehyde **3.7**, in turn accessible through an oxidative cleavage of C_2-symmetric *bis*-homoallyl alcohol **3.8**.

Given the unknown configuration at C_4, both diastereomers of the psymberic acid side chain were prepared (cf. **3.11**, **3.12**, **3.14**, and **3.16**, Scheme 30). Panel A delineates the previous first generation approach starting from known triol **3.9**, prepared in two steps from *D*-tartaric[4] acid. Oxidative diol-cleavage[5] of this material, followed by treatment of (2-methylallyl)magnesium bromide with the crude aldehyde **3.10**, delivered an inseparable mixture of homoallylic alcohols. Selective protection of the primary alcohol and methylation of the secondary alcohol provided compounds **2.4a** and **2.4b**, which could be separated at this stage (ratio = ~1:1.4). Independent processing via desilylation and a two-step oxidation then provided protected psymberic acids **3.11** and **3.12**. In panel B, an alternative and fully stereoselective synthesis of benzoyl-protected psymberic acids **3.14** and **3.16** is shown. Starting from protected glyceraldehyde **2.22**, asymmetric methallylation with a borane reagent derived from isobutenyllithium and (-)-Ipc_2BOMe,[7] followed by methylation delivered methyl ether **2.24** in 65% yield (2 steps) and 97:3 *dr*, a significant improvement over the 4:3 ratio obtained by Williams[8] using the corresponding Grignard reagent. Acetonide hydrolysis, silylation of the primary alcohol and benzoylation of the secondary alcohol, followed by an acidic aqueous work-up provided alcohol **3.13** over a three steps sequence from **2.24**. Finally, a two-step oxidation sequence yielded psymberic acid **3.14** (7 steps from

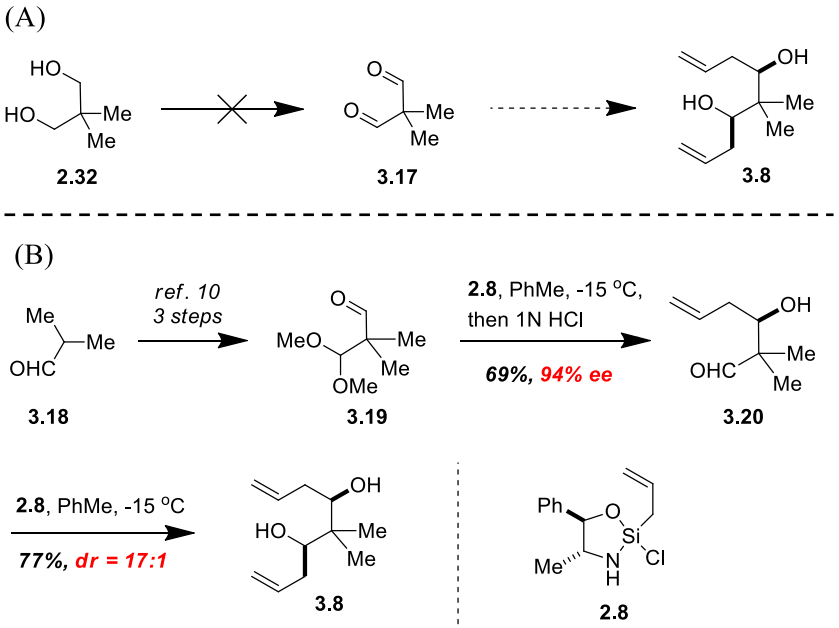
Scheme 30. Synthesis of Psymberic Acids



aldehyde **2.22**; 47% yield). The relative stereochemistry set during the methallylation step was ascertained through ^{1}H-NMR analysis of acetal **3.15**, obtained via ozonolysis of the terminal olefin followed by acetal formation. Diastereomeric acid **3.16** was synthesized as

outlined for acid **3.14**, except that methallylation of aldehyde **2.22** exploited the antipodal borane reagent.

Scheme 31. Attempts for Synthesis of *Bis*-homoallyl Alcohol **3.8**



The synthesis of the central tetrahydropyranyl core of psymberin was inspired by the possibility to engage C_2-symmetrical *bis*-homoallyl alcohol **2.32** in an oxidative desymmetrization reaction (Scheme 31). On paper, this compound should be available from an enantioselective *bis*-allylation of dialdehyde **3.17**[9] (panel A). A practical problem arises when one considers that malondialdehydes are unstable, sensitive to hydrate formation, self-condensation and oligomerization. In fact, all attempts to generate pure dialdehyde **3.17** from neopentyl glycol **2.32** met with failure. In light of this, De Brabander and co-workers originally settled for a slightly longer approach starting from *iso*-butyraldehyde (**3.18**, panel B). According to a known literature procedure,[10] this material was converted in three steps to

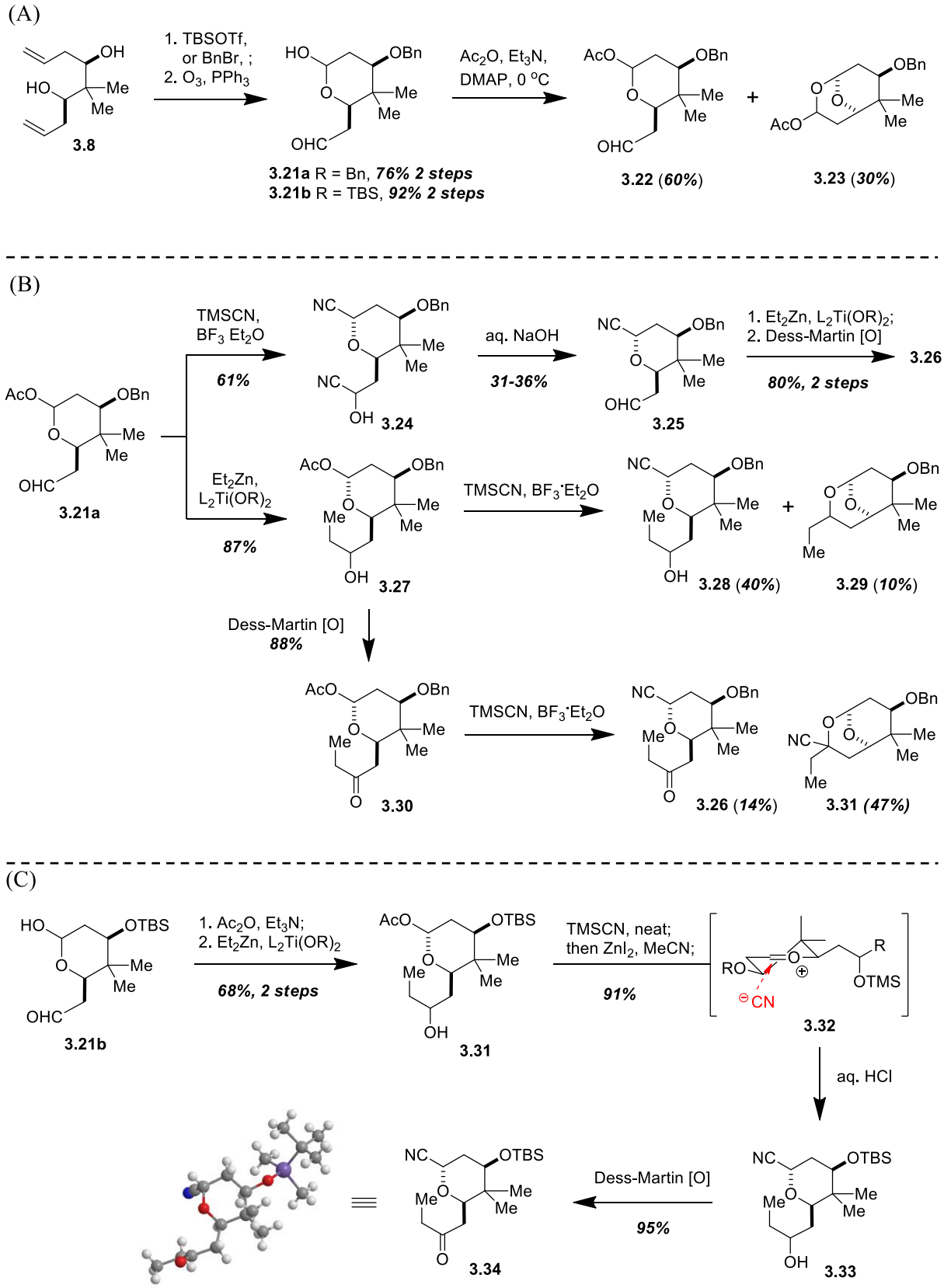
3,3-dimethoxy-2,2-dimethylpropanal **3.19**, a mono-protected version of the corresponding malondialdehyde **3.17**. An enantioselective allylation of aldehyde **3.19** using Leighton's silane reagent **2.8**[11] provided homoallyl alcohol **3.20** in 69% yield and 94% *ee*. Noteworthy, the dimethyl acetal was unmasked during the work-up conditions, enabling for a subsequent allylation under the same reaction conditions. The corresponding *bis*-homoallyl alcohol **3.8** was thus obtained in 77% yield and >17:1 *dr*.

At this point, it was envisioned that the termini of diene **3.8** could be differentiated via an oxidative cleavage of the terminal olefins, after which one of the resulting aldehydes would be trapped as a lactol. As shown in Scheme 32 (panel A), this concept was best put to practice after monoprotection of diol **3.8** (silyl or benzyl), followed by ozonolytic cleavage of both double bonds to yield lactols **3.21a** (76%) and **3.21b** (92%), respectively. At this point, they needed to homologate the aldehyde to an ethyl ketone and activate the lactol for introduction of the cyano group as a masked primary amide. In the event, acylation of the benzylated lactol **3.21a** provided acetate **3.22** in 60% yield. Under the reaction conditions, dioxabicyclononane byproduct **3.23** was formed in 30% yield. Lewis acid-catalyzed acetate (**3.21a**) displacement with trimethylsilyl cyanide[12] (panel B) yielded cyano acetal **3.24**, wherein the aldehyde was trapped as a cyanohydrin (60% yield).[13] Hydrolysis of the cyanohydrin **3.24** was more difficult than anticipated and provided aldehyde **3.25** in modest yields (31−36%). Treatment of this material with diethylzinc in the presence of a diaminocyclohexane-ligated titanium(IV) catalyst[14] was followed by Dess−Martin oxidation[15] to yield the corresponding ethyl ketone **3.26** in 80% yield for this two-step procedure.

To avoid cyanohydrin formation, the order of events was changed. The diethylzinc addition to aldehyde **3.21a** was employed to yield carbinol **3.27** in 87% yield. Unfortunately, cyanide displacement of acetate **3.27** was now accompanied by the formation of dioxabicyclononane byproduct **3.29** (10%), resulting from intramolecular acetate displacement with the secondary alcohol. Preventing alcohol participation via oxidation of **3.27** to ethyl ketone **3.30**, obtained in 88% yield, now led to dehydrative dioxabicyclononane formation upon treatment with trimethylsilyl cyanide[12] and boron trifluoride etherate to yield bicycle **3.31** as the major product isolated in 47% yield, together with 14% of the desired ethyl ketone **3.26**.

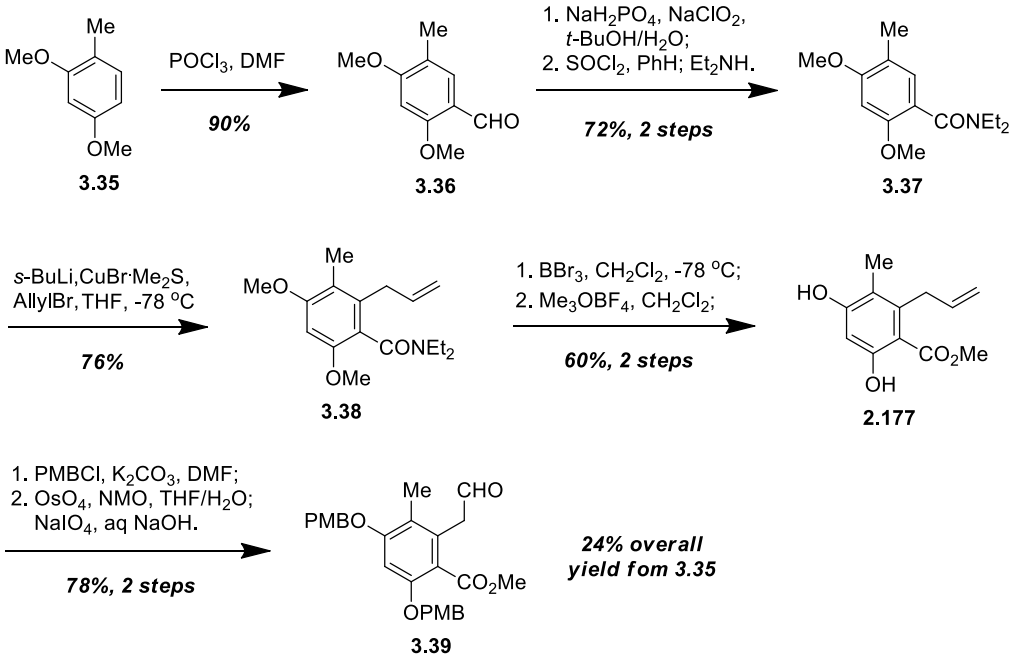
So far, from the above synthetic exercises, they learned that activation of the anomeric acetate with boron trifluoride etherate not only enables cyanide introduction but also leads to a facile formation of dioxabicyclononane and cyanohydrin byproducts in the presence of an aldehyde or ketone. Ultimately, a solution was formulated that started with the silylated lactol **3.21b** (Scheme 32, panel C). Acylation of this material was not accompanied by dioxabicyclononane ring formation (cfr. **3.23**), presumably because of the larger steric hindrance of the TBS protecting group. Ethyl ketone formation with diethylzinc using the Kobayashi[14] conditions also proceeded with higher yield, providing ethyl carbinol **3.31** in 68% yield (two steps). To avoid formation of potential bicyclic ring products, the conditions were modified by introduction of the cyano group. In a one-pot procedure, trimethylsilyl cyanide[22] was added to alcohol **3.31** (neat) in the absence of Lewis acid to allow protection of the secondary alcohol as a silyl ether, followed by addition of a solution of zinc iodide in acetonitrile to initiate oxonium formation (**3.32**), followed by axial cyanide attack. After

Scheme 32. Synthesis of Ethyl Ketone through Desymmetrization of *Bis*-homoallylic Alcohol **3.8**



acidic aqueous workup, compound **3.33** was obtained in 91% yield and further oxidized[15] to target ethyl ketone **3.34** in 95% yield. Crystallographic analysis of **3.34** fully confirmed the assigned structure and the relative stereochemistry. Using this optimized sequence, ethyl ketone **3.34** was obtained in seven steps from *bis*-homoallylic alcohol **3.8** in 54% overall yield, versus ~7% overall yield (6−7 steps) for the synthesis of the corresponding benzylated ethyl ketone **3.26**.

Scheme 33. Synthesis of the Aryl Fragment **3.39**



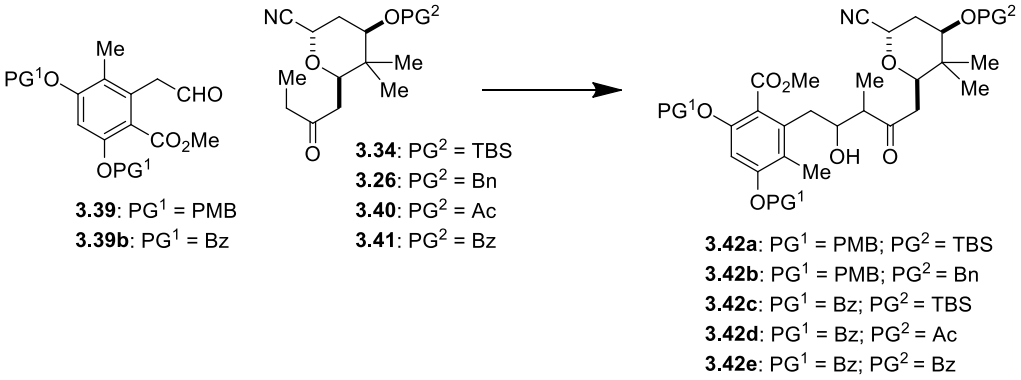
The synthesis of the aryl fragment **3.39** is shown in Scheme 33. Starting from the commercially available 2,4-dimethoxy-1-methylbenzene **3.35**, formylation (→**3.36**),[16] oxidation to the corresponding carboxylic acid, and amidation afforded diethylamide **3.37** in 66% yield for the three-step sequence. *Ortho*-directed allylation[17] of this material (→**3.38**) was followed by deprotection of the phenolic methyl ethers with boron tribromide. Formation

of the methyl ester **2.177** was best executed according to a protocol developed by Keck and coworkers,[18] i.e. treatment of the amide with trimethyloxonium tetrafluoroborate followed by aqueous hydrolysis of the incipient methylimidate. The overall yield for this three-step sequence was 45%. Subsequent protection of the phenols and a two-step oxidative cleavage of the double bond (dihydroxylation; diol-cleavage) delivered coupling partner aldehyde **3.39** in an eight-step sequence and 24% overall yield from the commercially available starting material **3.35**.

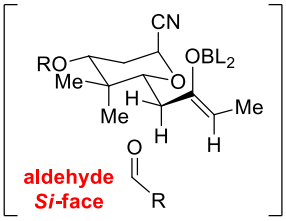
Having accessed the psymberin fragments in high yield and enantiomerically pure form enabled the exploration of convergent coupling strategies. First, a stereoselective aldol coupling between ethyl ketones (**3.26**, **3.34**, **3.40**, and **3.41**) and aryl aldehydes (**3.39**, and **3.39b**) were explored. In table 2, the results obtained from the aldol reaction between aryl aldehyde fragments **3.39** and **3.39b**, and various ethyl ketone fragments **3.26, 3.34**, **3.40**, and **3.41** are described. Initial explorations with titanium enolates ($TiCl_4$, iPr_2NEt, entry 1)[19] only delivered mixtures of diastereoisomers (~1:1 ratio). The addition of the *Z* chlorophenylboryl enolate[20] derived from **3.26** added to aldehyde **3.39** (entry 2) gave the *syn*-aldol product **3.42b** in 77% yield and 6:1 *dr*. Interestingly, it was found that the *Z* chlorophenylboryl enolate[20] derived from **3.34** added to aldehyde **3.39** (entry 3) with high facial selectivity producing the *syn*-aldol product **3.42a** in 88% yield and 12:1 *dr*.[21] The stereochemical outcome was predicted based on the inherent facial bias of enolate when combined with aldehyde **3.39** (*Si*-face) through a chair-like transition state.[20] Under the same aldol coupling conditions, the additions of *Z*-enolates derived from ethyl ketones **3.34**, **3.40** and **3.41** to aldehyde **3.39b** (entries 4-6) respectively, did not produce the corresponding aldol adduct

with satisfying yields or excellent diastereoselectivity.

Table 2. Investigation of Aldol Coupling between Ethyl Ketone and Aldehyde

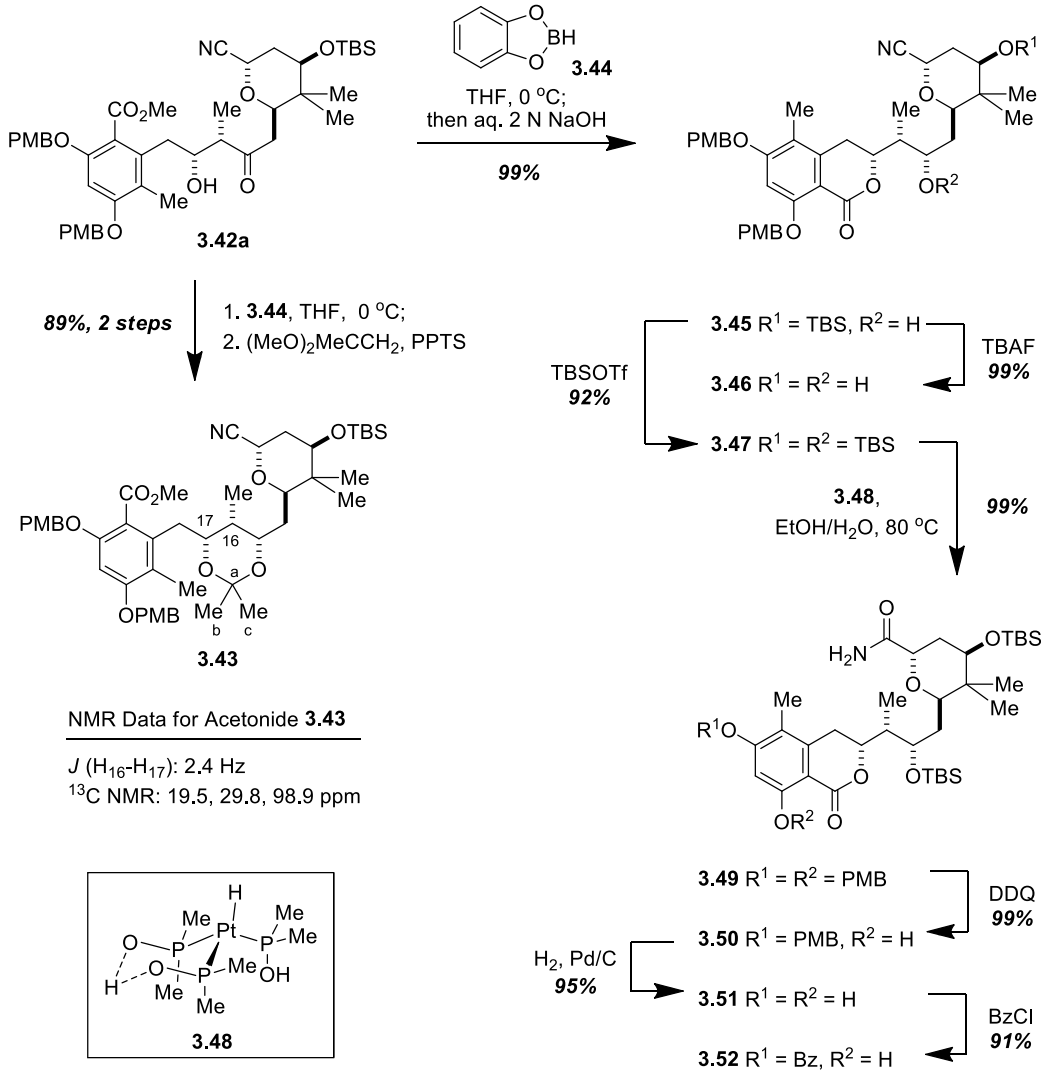


Entry	PG^1	PG^2	Lewis Acid	*dr*	Yield (BRSM)	Pdt.
1	PMB (**3.39**)	Bn (**3.26**)	$TiCl_4$ (1.1 eq.)	1 : 1	84%	**3.42b**
2	PMB (**3.39**)	Bn (**3.26**)	$PhBCl_2$ (1.2 eq.)	6 : 1	77%	**3.42b**
3	PMB (**3.39**)	TBS (**3.34**)	$PhBCl_2$ (1.2 eq.)	12 : 1	88%	**3.42a**
4	Bz (**3.39b**)	TBS (**3.34**)	$PhBCl_2$ (1.2 eq.)	5 : 1	47% (90 %)	**3.42c**
5	Bz (**3.39b**)	Ac (**3.40**)	$PhBCl_2$ (1.2 eq.)	7 : 1	10% (22 %)	**3.42d**
6	Bz (**3.39b**)	Bz (**3.41**)	$PhBCl_2$ (1.2 eq.)	5 : 1	< 10 (80 %)	**3.42e**



Transition State of the Aldol Coupling for Entry 3

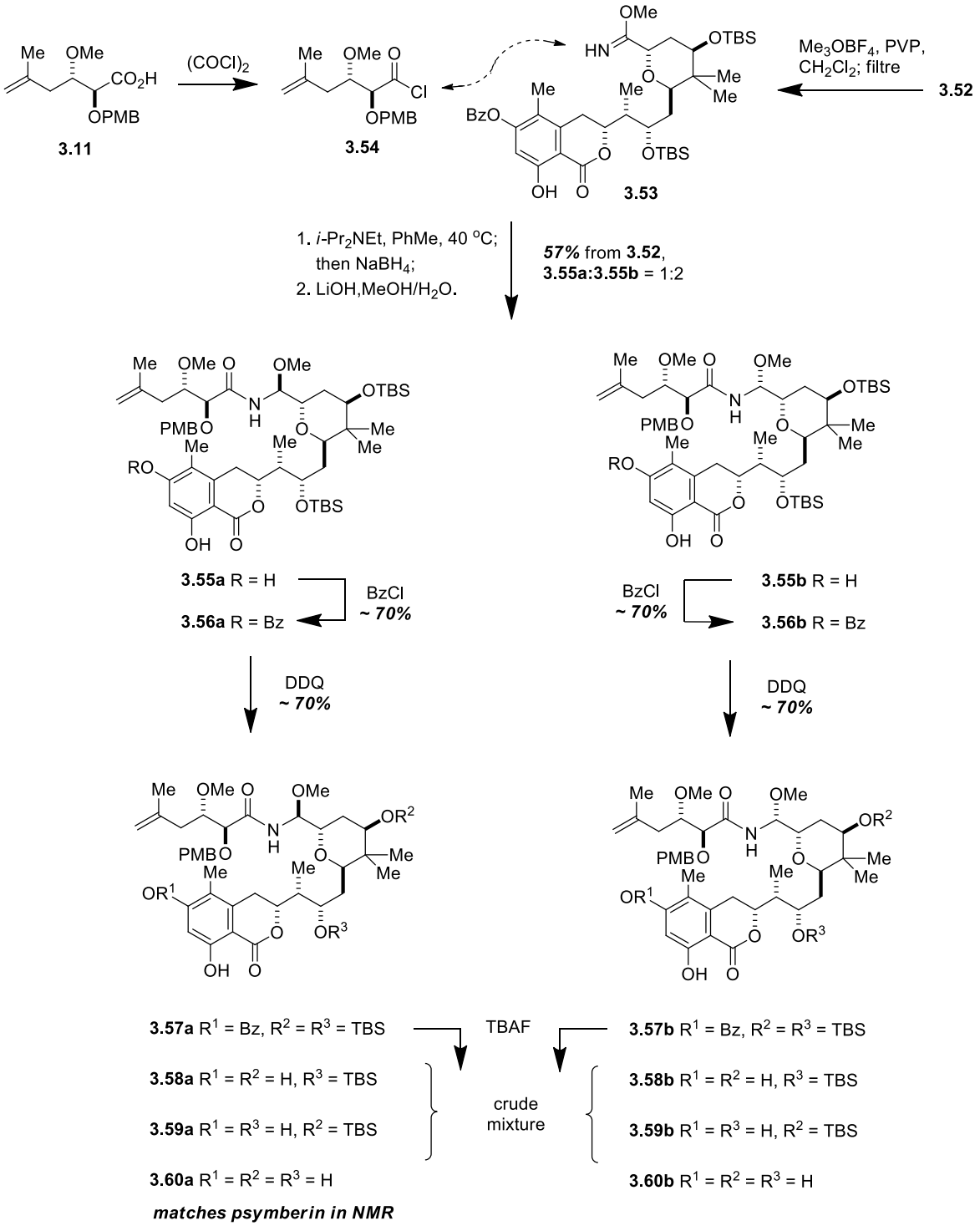
Scheme 34. Synthesis of Dihydroisocoumarin Fragments



Stereoselective reduction (Scheme 34) of *β*-hydroxyketone **3.42a** with catecholborane **3.44**[22] provided lactone **3.45** after basic workup (99%). Quenching the reducing mixture with aqueous Na, K-tartrate permitted isolation of the 1,3-*syn*-diol for derivatization as acetonide **3.43**.[23] ^{1}H and ^{13}C NMR analysis of this derivative confirmed the 1,3-*syn* configuration.[23] Silylation of the secondary alcohol (→ **3.47**, 92%) set the stage for a mild nitrile hydrolysis exploiting a platinum(II)-catalyst (**3.48**) developed by Ghaffar and Parkins (99%),[24] which was followed by oxidative removal of the *ortho*-phenolic *p*-methoxybenzyl protecting group

in 99% yield. The second *p*-methoxybenzyl group was then replaced with a benzoate via hydrogenolysis (→ **3.51**, 95%) followed by benzoylation (→ **3.52**, 91%).

Scheme 35. Initial Attempts toward Psymberin



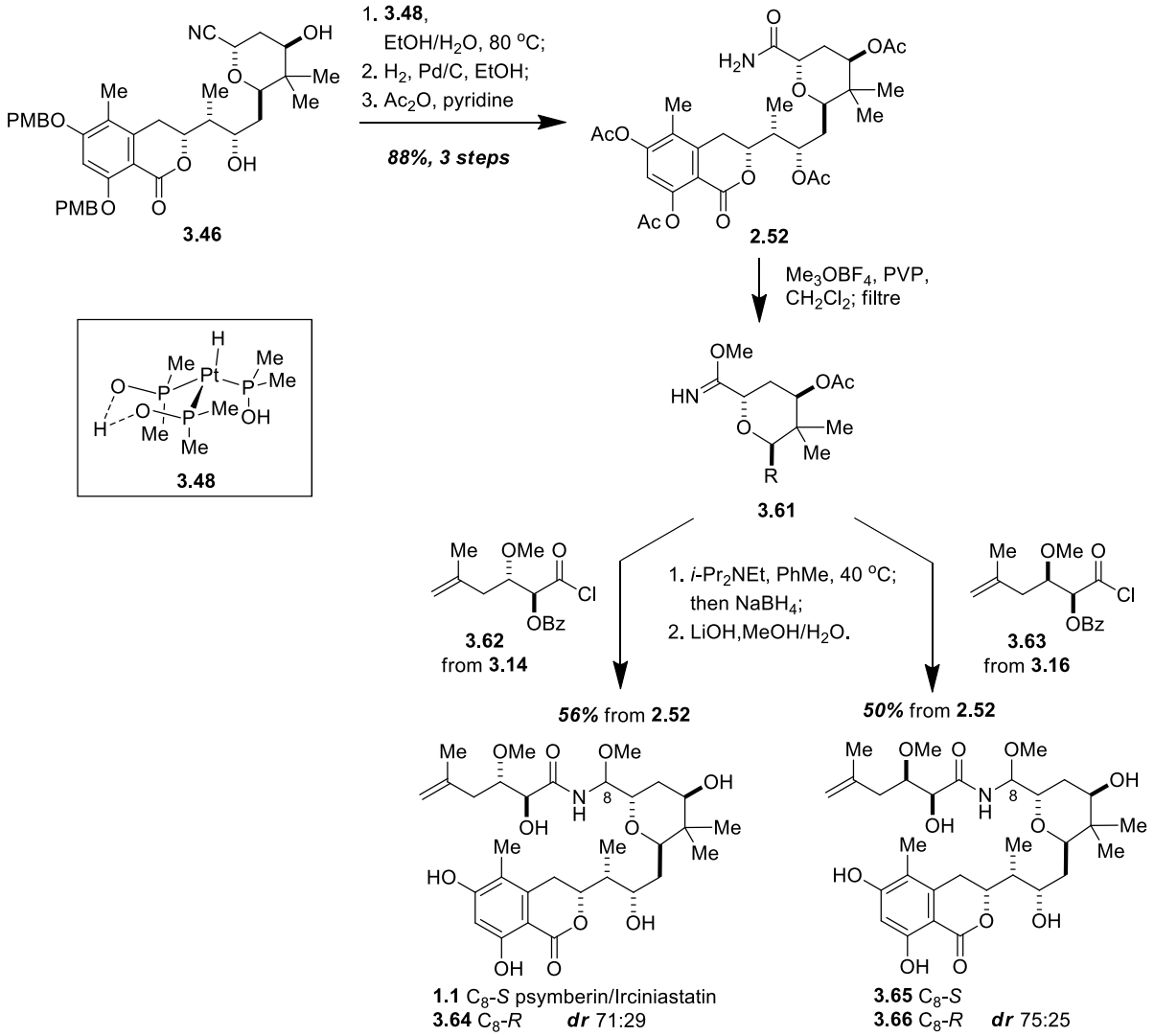
The stage was now set to execute a reductive fragment coupling (*N*-acylaminal) of dihydroisocoumarin **3.52** with the psymberic acid side chain. The plan was to acylate imidate **3.53** with acid chloride **3.54** (from acid **3.11**) and intercept the incipient acylimidate with a reducing agent (Scheme 35), a tactic employed for the synthesis of the structural relative pederin (**1.3a**).[25] However, the preparation and handling of imidate **3.53** using Me_3OBF_4 as reported proved unproductive.[35] Treatment of **3.52** with Me_3OBF_4 resulted in decomposition, methyl ester formation, and *N*-methylation. Reasoning that the acidity of Meerwein's salt and water are potential culprits, additives including Et_3N, $NaHCO_3$, proton sponge, molecular sieves, and pyridine were screened to no avail. Extensive experimentation identified a uniquely beneficial effect of adding poly(4-vinylpyridine) (25% cross-linked) during the imidate formation with Me_3OBF_4 (CH_2Cl_2). After stirring at room temperature, the crude imidate reaction mixture was filtered and concentrated, followed by dissolving the crude imidate **3.53** in toluene, addition of Hunig's base and acid chloride **3.54**. The mixture was heated to 40 ^oC for 2 h, cooled to 0 ^oC and treated with an ethanolic sodium borohydride solution. After workup, the crude compounds were saponified to afford a separable mixture of **3.55a** and **3.55b** (~1:2 ratio) in 57% yield from **3.52**. This saponification step was necessary because some acylation of the free phenol occurred during the acylation step with acid chloride **3.54**. Since *bis*-phenols **3.55a** and **3.55b** were unstable towards the oxidative conditions to remove the *p*-methoxybenzyl protecting group present in the psymberate side chain, and hydrogenolytic conditions resulted in saturation of the terminal 1,1-disubstituted olefin, these compounds were benzoylated to afford benzoates **3.56a** and **3.56b** respectively (70%). Oxidative removal of the *p*-methoxybenzyl protecting group now smoothly yielded

alcohols **3.57a** and **3.57b**. Treatment of **3.57a** and **3.57b** with tetrabutylammonium fluoride first removed the phenolic benzoate, followed by a slow but partial desilylation of one of the silyl ethers (crude NMR). Only a small amount of fully deprotected material was observed, even when a large excess of fluoride was added. Moreover, the crude mixture of compounds **3.57a**-**3.60a** or **3.57a**-**3.60b** could not be converted, nor purified to a globally deprotected material. However, thorough analysis of the crude ^{1}H-NMR spectra hinted that the mixture containing **3.60a** provided a spectral fingerprint congruent with that reported for psymberin. Although these studies had defined an endgame strategy toward psymberin, it was clear that protecting group issues were plaguing an efficient execution. From the above described initial forays toward psymberin, it became obvious that the *p*-methoxybenzyl protecting groups needed to be removed before installing the olefin-containing psymberic acid side chain, and that a more easily removable replacements for the silylether protecting groups was added.

Toward this end, diol **3.46** was obtained from silylether **3.45** via fluoride-mediated deprotection (TBAF, 99%, Scheme 34). As shown in Scheme 36, nitrile **3.46** was hydrolyzed with the Ghaffar-Parkins catalyst (**3.48**),[24, 26] followed by hydrogenolytic removal of the *p*-methoxybenzyl protecting groups and peracylation with acetic anhydride. The corresponding amide **2.52** was obtained in 88% yield (3 steps).

As tactic used in scheme 35, stirring a solution of amide **2.52** (in CH_2Cl_2) with Me_3OBF_4 in the presence of poly(4-vinylpyridine) yielded a crude imidate mixture (→ **3.61**) that was filtered, concentrated, and resuspended in toluene. After addition of Hunig's base, acid chloride **3.62** or **3.63** was added, followed by heating to 40 ^{o}C for 2 h. The reaction mixture was then cooled to 0 ^{o}C and treated with an ethanolic sodium borohydride solution, providing

Scheme 36. Completion of the First Generation of Psymberin



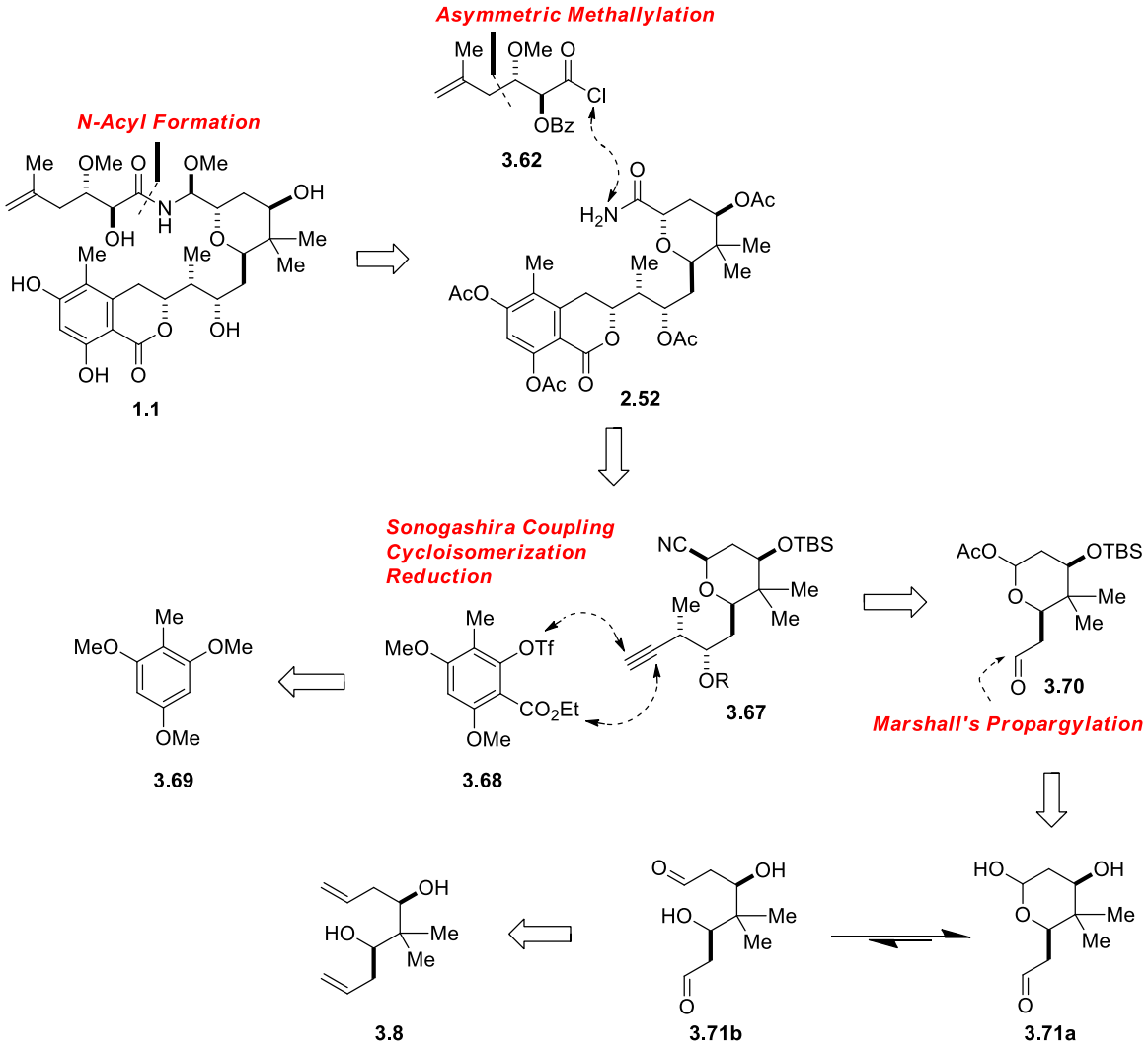
after workup and saponification of the acetate protecting groups with a methanolic LiOH solution a separable mixture of **1.1** and **3.64** (71:29 ratio) in 56% yield from **2.52** and an inseparable mixture of **3.65** and **3.66** (75:25 ratio) in 50% yield from **2.52**. As noted in the introduction, a constitutional identical natural product termed irciniastatin was isolated by the Pettit group.[3] Although the relative stereochemistry of irciniastatin was only partly resolved, the assignment dictated it to be a different compound than psymberin. Because the NMR

spectra of psymberin and irciniastatin were recorded in different solvents, we recorded the spectra of psymberin/irciniastatin diastereoisomers **1.1**, **3.64**-**3.66** in both solvents reported for psymberin and irciniastatin respectively. Careful analysis of all the spectral data obtained for the four synthetic diastereoisomers indicated that **1.1** represents the true structure of natural psymberin as well as irciniastatin; i.e psymberin and irciniastatin are identical compounds.

3.2 Second Generation

Although the above described first generation synthesis reported by De Barbander and co-workers led to a full structural assignment of psymberin/irciniastatin, introduction of the dihydroisocoumarin fragment required an eight-step synthesis of aromatic aldehyde **3.39**, followed by a stereoselective aldol coupling and reductive lactonization. As part of my Ph.D. work, I decided to design and execute a more flexible alternative approach that could facilitate aromatic fragment SAR studies via analog syntheses, and mode-of-action studies. This approach that would rely on a late-stage introduction of an aromatic electrophile such as triflate **3.68** via Sonogashira cross coupling with an alkynyl partner, such as **3.67** (see Scheme 37). The resulting alkyne-substituted benzoic acid derivative would enable dihydroisocoumarin formation (**2.52**) via cycloisomerization followed by hydrogenation of the resulting isocoumarin. This approach has the advantage that many functionalized aromatic halides and triflates (from the phenol) are commercially available. For the synthesis of psymberin, aromatic triflate **3.68** is a known compound available in three steps from

Scheme 37. Retrosynthetic Analysis for the Second Generation Approach



commercial trimethoxytoluene (**3.69**).[27] Alkynyl fragment **3.67** in turn would be accessible from lactol **3.70** via a Marshall propargylation.[28] Like the first generation developed by the De Brabander group, the lactol **3.71a** could be formed via desymmetrization of *bis*-homoallylic alcohol **3.8**.

For the psymberic acid fragment (**3.14**), I followed the first generation synthesis. After optimizing the reaction conditions, a stereoselective synthesis of benzoyl-protected psymberic acid **3.14** was accumulated on a 4.5 g scale, which was ready for coupling with

amide **2.52**. Therefore, the attention was turned to explore a new approach to dihydroisocoumarin **2.52**.

Since our original route to the diol **3.8**, Krische and coworkers developed a creative two-directional carbonyl allylation[29] from the alcohol oxidation level to circumvent the use of difficult to handle malondialdehydes. As reported by Krische (Scheme 38, panel A), treatment of diol **2.32** with allyl acetate employing a cyclometallated catalyst formed *in situ* from $[Ir(cod)Cl]_2$, (*R*)-Cl-MeO-BIPHEP **3.72**, 4-chloro-3-nitrobenzoic acid and Cs_2CO_3 in degassed dioxane, furnished diol **3.8** in 42% yield (>99% *ee*, 20:1 *dr*) on a 4 gram scale. Although not reported by Krische, a mono-allylated intermediate **3.73** was isolated in 24-30% yield. This material could be allylated under the same reaction conditions to obtain additional *bi*- allylated product **3.8** in 30% yield (51% combined yield from **2.32**).

To continue the synthesis of the THP fragment (Scheme 38, panel B), the diol **3.8** was efficiently monosilylated (TBSOTf, 2,6-lutidine), followed by ozonolysis and *in situ* reduction with triphenylphosphine to yield a clean lactol, which was trapped as stable acetate **3.70** in 74% yield over three steps. Aldehyde **3.70** was converted to *anti*-propargylic alcohol **3.75** via treatment with an *in situ* prepared allenylindium species derived from mesylate **3.74** according to Marshall and co-workers in good yield (70%) and excellent diastereoselectivity (*dr* > 10:1, separable). The corresponding reaction ($Pd(OAc)_2$, PPh_3, Et_2Zn in THF) with the allenylzinc species derived from **3.74** led to decomposition.[28b] Acetate displacement with TMSCN,[14] under the conditions described for the corresponding reaction leading to give cyanotetrahydropyran **3.76** in 81% yield. Making both of the *R*- and *S*- Mosher ester[30] of the secondary alcohol **3.76** confirmed that the absolute configuration of C_4 is *R* (1,2-*anti*) based

Scheme 38. Attempts for Construction of the Tetrahydropyran Core

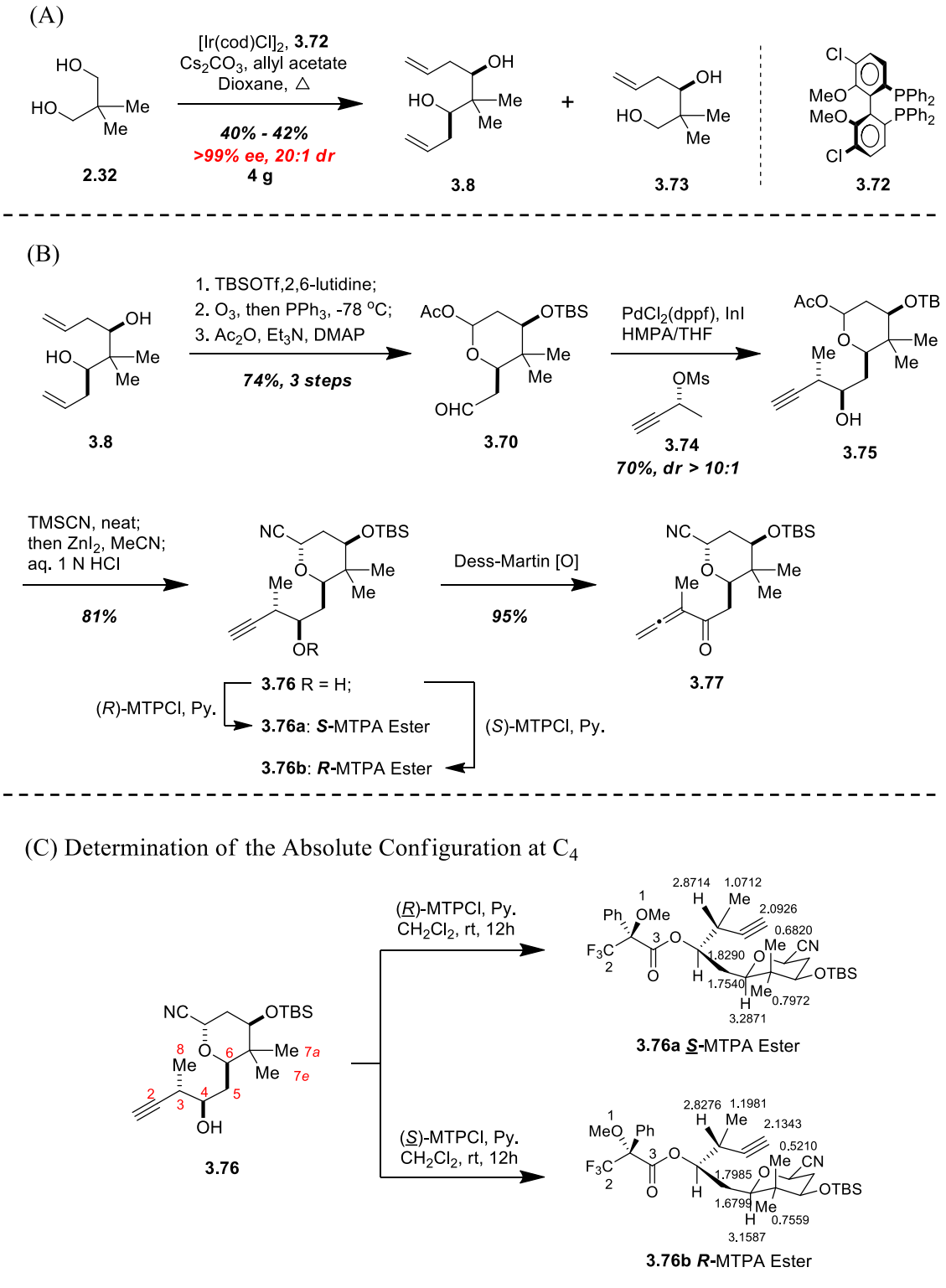
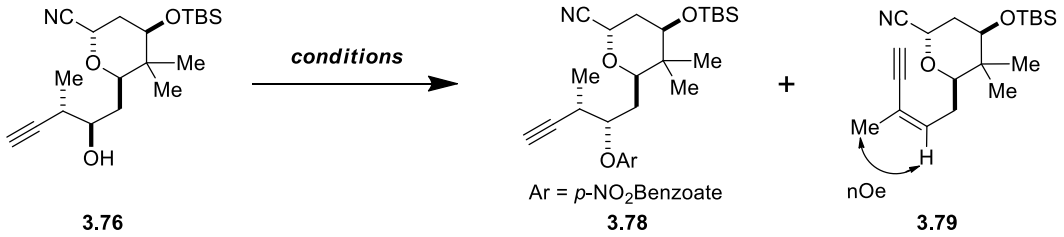


Table 3. Mitsunobu Reaction with *anti*-alcohol **3.76**[a]



3.76 **3.78** **3.79**

Entry	Conditions[b]	Conversion (%)	**3.78:3.79**	Yield (%)[c]
1	DEAD, PPh_3, 4-NO_2BzOH, THF, rt	0	-	0
2	DEAD, PPh_3, 4-NO_2BzOH, THF, 60 ^oC	100	0:100	83
3	DIAD, PPh_3, 4-NO_2BzOH, THF, rt	0	-	0
4	DIAD, PPh_3, 4-NO_2BzOH, THF, 60 ^oC	100	0:100	79
5	TMAD, PBu_3, 4-MeOBzOH, Benzene, 50 ^oC	100	<1:20	92
6	TMAD, PBu_3, 4-NO_2BzOH, Benzene, 60 ^oC	100	1:1	88
7	TMAD, PBu_3, 4-NO_2BzOH, Benzene, 50 ^oC	100	100:0	90

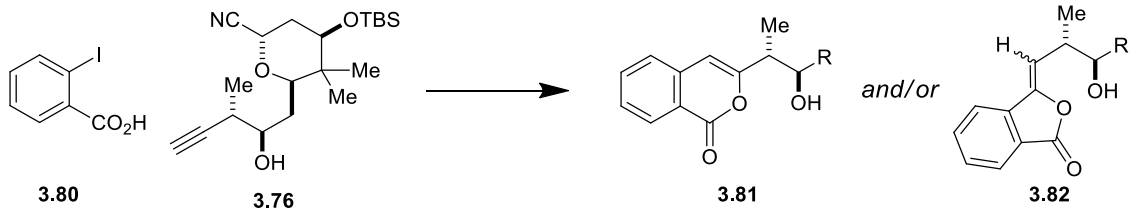
[a]All reactions were performed with 1.0 mmol **3.76**. [b] 2.0 mmol DEAD, PIAD or TMAD was used; 2.0 mmol PPh_3 or PBu_3 was used; and 2.0 mmol 4-NO_2BzOH or 4-MeOBzOH was used. [c]isolated yields.

on their ^{1}H NMR data (Scheme 38, panel C, detailed calculation see 6.4 experimental procedure). At this point, the attention was turned to invert the hydroxyl stereocenter. An oxidation/reduction plan failed due to the formation of allenone **3.77** under Dess-Martin conditions. Initial efforts to invert the stereochemistry of *anti*-alcohol **3.76** using contemporary Mitsunobu conditions[31] (diethyl azodicarboxylate or diisopropyl azodicarboxylate, PPh_3, in THF, table 3, and entries 1-4) failed and led to elimination (→enyne **3.79**) or recovered starting material. At this point, we decided to explore a protocol

originally reported by Tsunoda.[32] They found that in the presence of TMAD (*N,N,N′,N′*-tetramethylazodicarboxamide), *p*-NO_2BzOH provided poor inversion ratio of the stereocenter. Of special merit was the combination of the TMAD/Bu_3P system with *p*-methoxybenzoic acid to achieve complete inversion of sterically congested secondary alcohols. However, in our case, combination of 4-MeOBzOH/TMAD/Bu_3P resulted in a complete elimination (→ enyne **3.79**, entry 5). After extensive experiments, it was found that switching to *p*-NO_2BzOH did deliver the desired product **3.78**. If the reaction temperature was elevated to 60 ^oC, we isolated the desired product **3.78** and elimination compound **3.79** with ~ 1:1 ratio (entry 6). A final experiment (entry 7) revealed that it efficiently provided inverted *p*-nitrobenzoate **3.78** as the major product (90% yield) after heating at 50 ^oC overnight. The configuration of the C_4 stereocenter of **3.78** was confirmed by a corresponding crystallographic analysis of compound **2.52** (scheme 39). The geometry of the enyne **3.79** was confirmed by 1D NOE experiments.

At this point, we were ready to investigate the coupling of alkyne **3.76** with aromatic fragment **3.80**. Initial model studies to construct the isocoumarin via a one-pot Pd-catalyzed heteroannulation between alkyne **3.76** and *o*-iodobenzoic acid **3.80** indicated low conversion and significant amounts of phthalide **3.82** formation. As shown in table 4, known conditions[33] (entries 1, 2, and 5) only led to decomposition of the starting material **3.76**. Modifying the base or solvent (entries 3, 4, and 6) did provide some product formation albeit in low yields and poor regioselectivity.

Table 4. Attempts for Construction of the Isocoumarin[a]



Entry	Catalysts[b]	Base[c]	Solvent	Time (h)	T (^oC)	Yield (%)[d]	**3.81:3.82**
1	$Pd(PPh_3)_2Cl_2$, CuI	Et_3N	DMF	12	60	Decomposition	-
2	$Pd(PPh_3)_4$, CuI	*i*-Pr_2NH	DMF	10	60	Decomposition	-
3	Pd/C, CuI	*i*-Pr_2NH	DMF	16	60	15	3:2
4	Pd/C, CuI	Et_3N	EtOH	16	60	16	1:1
5	$ZnCl_2$, $Pd(PPh_3)_4$	Et_3N	DMF	16	50	Decomposition	-
6	$ZnCl_2$, $Pd(PPh_3)_4$	Et_3N	DMSO	16	60	20	1:3

[a]All reactions were performed with 50 µmol **3.76** and 60 µmol **3.80**. [b]5.0 mol% Pd catalysts, 10.0 mol% CuI and 10 mol% $ZnCl_2$ were used. [c]0.25 mmol bases. [d]isolated yields.

Our revised plan for the installation of the dihyroisocoumarin fragment centered on isocoumarin formation of the arylated alkyne via cycloisomerization followed by a reduction. Therefore, a stepwise construction of the isocoumarin was investigated (Scheme 39). Sonogashira coupling of alkyne **3.78** with penta-substituted aryl triflate **3.68**, obtained in three steps according to known literature, followed by saponification yielded benzoic

acid-substituted alkyne **3.83** in 83% yield.[34] As shown in table 5, extensive experimentation was required to obtain the desired isocoumarin **3.85**. Besides solving the issue of

Scheme 39. Synthesis of Dihydroisocoumarin **2.52**

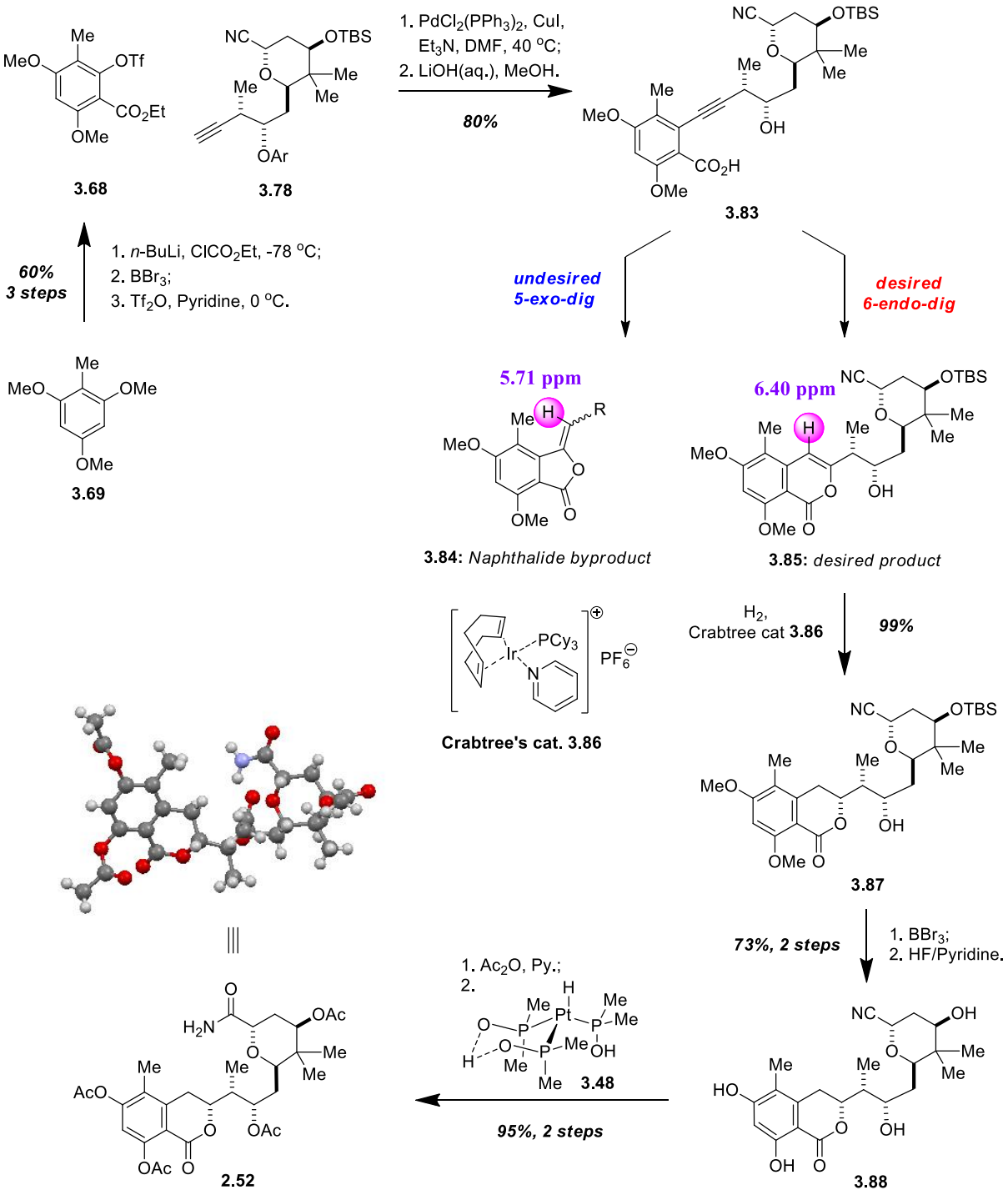
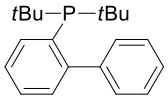


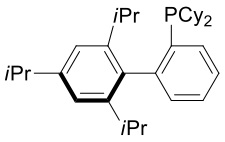
Table 5. Cycloisomerization of Alkynyl Benzoic Acid **3.83**[a]

Entry	Reagent	Solvent	Time	Temp	**3.85**:**3.84**[d]
1	pTsOH[b]	EtOH	0.1	100 °C	-
2	TFA[b]	THF	3	Δ	-
3	$InBr_3$[b]	THF	1	Δ	-
4	$AuCl_3$[c]	MeCN	2	50 °C	-
5	$AgSbF_6$[c]	DMF	4	60 °C	1:1
6	$[Pt(C_2H_4)Cl_2]_2$	DMF	0.5	rt	3:7
7	$ClAuL_1$[c]	CH_2Cl_2	1	rt	2:5
8	Ph_3PAuCl[c]	CH_2Cl_2	1	rt	2:1
9	$Ph_3PAuNTf_2$[c]	CH_2Cl_2	1	rt	4:1
10	Tf_2NAuL_2[c]	CH_2Cl_2	1	rt	>95:5

[a]All reactions were performed with 50 μmol **3.83**. [b]20 mol %. [c]5 mol%. [d]Ratios were determined by ^1H NMR.



L_1



L_2

regioselectivity (5-exo to **3.84** *vs* 6-endo to **3.85**), the presence of the homopropargylic alcohol also could create issues with competing hydroalkoxylation and elimination to the enyne. Furthermore, the isocoumarin **3.85** and isomeric alkylideneisobenzofuran-1(3H)-one **3.84** were unstable to chromatography. Various cycloisomerization conditions[35] including Brønsted acid[36] (entries 1, 2), $InBr_3$[37] (entry 3), and $AuCl_3$ (entry 4) gave complex mixtures from which no characterizable compounds could be observed by crude NMR.

Silver(I)-mediated cycloisomerization proceeded more smoothly but afforded an equimolar mixture of 5-exo and 6-endo products (entry 5, ~70% mass balance) similar to results reported in the literature.[38]

Inspired by the cycloisomerization methodology developed by our group, we explored Zeise's dimer ([Pt-(CH_2CH_2)Cl_2]$_2$).[39] Although 5 mol % of this catalyst now promoted the cycloisomerization at room temperature, the undesired 5-exo product dominated (3:7 ratio of **3.85**:**3.84**, ~50% mass balance, entry 6). Switching to Johnphos-ligated AuCl[40] provided a slight improvement but still favored the undesired 5-exo product **3.84** (entry 7).[41] In the end, we could overturn the regioselectivity favoring the desired 6-endo product when cationic Au(I) (PPh_3PAuCl, $AgSbF_6$) was engaged as the catalyst (2:1 ratio of **3.85**:**3.84**, ~60% mass balance, entry 8). The use of (Ph_3P)$AuNTf_2$[42] further improved the selectivity for the isocoumarin product **3.85** (4:1 ratio, 75% mass balance, entry 9).

Finally, dihydroisocoumarin **3.85** was obtained in 79% isolated yield and >95:5 regioselectivity by stirring a room temperature solution of alkyne **3.83** with 5 mol % of Xphos ligated $AuNTf_2$[43] (entry 10, ~80% mass balance), followed by hydrogenation of **3.85** with Crabtree's catalyst (>99%) to yield dihyroisocourmarin **3.87**. Alternatively, hydrogenation of **3.85** over Pd/C at 0 ^oC provided dihydroisocoumarin **3.87** with similar yield. Both methods yielded the desired stereoisomer exclusively, which was confirmed later via X-ray crystallography (see Scheme 39).

Continuing with the psymberin synthesis, a two-step methyl (BBr_3) and silyl ether (HF/py) deprotection provided dihydroisocoumarin **3.88** in 73% yield for the two-step sequence. Ghaffar-Parkins[24] nitrile hydrolysis followed by peracetylation provided a material

(compound **2.52**) that was identical to that obtained via the route outlined in Scheme 36. Single crystal X-ray analysis of compound **2.52** obtained via this route further confirmed the stereochemistry as assigned.

Based on the previous method developed by the De Brabander group, the *N*-acyl aminal formation was executed with the same procedure to yield psymberin (**1.1**) and C-8 epimer **3.64** (Scheme 36).

Overall, this synthetic approach to psymberin entails an 18 steps longest linear sequence from three fragments each prepared in 3, 7, and 8 steps, respectively. Although the overall yields using the two alternative synthetic approaches are similar, this second generation approach offers an attractive late stage introduction of aromatic fragments for SAR around the dihydroisocoumarinn structure.

3.3 Experimental Procedures

(*R*)-3-hydroxy-2-((4-methoxybenzyl)oxy)propanal (3.10)

To a solution of **3.9** (726 mg, 3.0 mmol) in CH_2Cl_2 (30 mL) was added saturated $NaHCO_3$ solution (0.4 mL) followed by $NaIO_4$ (1.28 g, 6.0 mmol) at 0 °C. The mixture was allowed to stir for 2h at ambient temperature. After filtered with a short pad of celite® and concentration, it gave a crude compound **3.10** (R_f = 0.58, hexanes:EtOAc = 1:1) as a pale yellow liquid (605 mg, 96%) without further purification. This reaction was repeated three times (same scale) with yields ranging from 92-96%.

tert-butyl(((2_R_)-3-methoxy-2-((4-methoxybenzyl)oxy)-5-methylhex-5-en-1-yl)oxy)diphenylsilane (2.4a/b)

Compound **3.10** (420 mg, 2.0 mmol) was dissolved in ether (20 mL) and (2-methylallyl)magnesium bromide (0.5 M in THF, 12 mL) was added and stirred at 0 °C for 30 min. Saturated NH_4Cl solution (20 mL) was added to quench the reaction. After extraction with EtOAc (40 mL), the combined organic phase was washed with brine (30 mL) and dried over Na_2SO_4. The solvent was removed under vacuum and the residue obtained was dissolved in CH_2Cl_2 (15 mL), imidazole (190 mg), TBDPSCl (0.6 mL, 2.33 mmol), and DMAP (30 mg) was added at 0 °C and stirred for 30 min. Then, saturated NH_4Cl solution (20 mL) was added to quench the reaction. After extraction with EtOAc (40 mL), the combined organic phase was washed with brine (30 mL) and dried over Na_2SO_4. The solvent was removed under vacuum and the residue obtained was dissolved in THF (25 mL), KH (81 mg, 2.03 mmol) was added at 0 °C during several portions over 30 min. Then, MeI (0.2 mL) was added and stirred at ambient temperature for overnight. Saturated NH_4Cl solution (20 mL) was added to quench the reaction. After extraction with EtOAc (40 mL), the combined organic phase was washed with brine (30 mL) and dried over Na_2SO_4. The solvent was removed under vacuum and the residue obtained was purified by FC (silica gel; hexanes:EtOAc = 20:1) to give **2.4a** as a pale yellow liquid (1,2-*anti*, 332 mg, 32% over 3 steps) and **2.4b** as a pale yellow liquid (1,2-*syn*, 445-465 mg, over 3 steps). These reactions were repeated 3 times (1.0-2.2 mmol scale) to provide **2.4a** and **2.4b** with yields ranging from 30% to 32%, and 43-45% respectively.

The compound **2.4a** has R_f = 0.80, hexanes: EtOAc = 5:1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (m, 4H), 7.38 (m, 6H), 7.23 (m, 2H), 6.82 (m, 2H), 4.76 (dd, *J* = 19.6, 2.0 Hz, 2H), 4.57 (dd, *J*

= 15.6, 13.2 Hz, 2H), 3.79 (s, 3H), 3.78 (dt, *J* = 7.2, 6.0, 2.8 Hz, 2H), 3.60 (m, 2H), 3.35 (s, 3H), 2.24 (m, 2H), 1.77 (s, 3H), 1.06 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 143.1, 135.6, 135.5, 133.4, 133.4, 130.9, 129.6, 129.2, 127.6, 113.6, 112.2, 80.1, 79.8, 72.3, 63.3, 58.0, 55.2, 38.5, 26.8, 22.8, 19.2; MS (ES) calculated for $C_{32}H_{42}O_4SiNa$ 518.3, found $[M+Na]^+$: 541.3.

The compound **2.4b** has ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (m, 4H), 7.40 (m, 6H), 7.20 (d, *J* = 6.4 Hz, 2H), 6.82 (d, *J* = 6.4 Hz, 2H), 4.77 (s, 1H), 4.64 (s, 1H), 4.57 (d, *J* = 14.8 Hz, 1H), 4.42 (d, *J* = 14.8 Hz, 1H), 3.85 (dd, *J* = 8.0, 3.2 Hz, 1H), 3.77 (s, 3H), 3.72 (dd, *J* = 8.0, 3.2 Hz, 1H), 3.58 (m, 1H), 3.49 (s, 1H), 3.34 (s, 3H), 2.25 (dq, *J* = 8.0, 10.0, 21.6 Hz, 2H), 1.73 (s, 3H), 1.04 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 142.9, 135.6, 135.5, 133.5, 133.4, 130.8, 129.6, 129.5, 127.7, 113.6, 112.5, 79.4, 78.5, 72.7, 62.7, 58.3, 55.2, 38.0, 26.8, 22.7, 19.1; MS (ES) calculated for $C_{32}H_{42}O_4SiNa$ 518.3, found $[M+ Na]^+$: 541.3.

(2*S*, 3*S*)-3-methoxy-2-((4-methoxybenzyl)oxy)-5-methylhex-5-enoic acid (3.11)

To a solution of **2.4a** (259 mg, 0.5 mmol) in THF (5 mL), TBAF (1M in THF, 1.0 mL) was added at ambient temperature. After 2 h, TLC indicated that all the starting material was consumed. Saturated $NaHCO_3$ solution (10 mL) was added and the crude was extracted with EtOAc. The combined organic extracts were washed with water, dried over $MgSO_4$ and concentrated. The residue obtained was purified by column chromatography (silica gel; hexanes/EtOAc, 10:1) to give primary alcohol (R_f = 0.35, hexanes: EtOAc = 4:1) as a colorless liquid (100-112 mg, 72-80%).

The primary alcohol has ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (m, 2H), 6.88 (d, 2H), 4.79 (dd, *J* = 12.8, 1.6 Hz, 2H), 4.55 (dd, *J* = 16.8, 1.6 Hz, 2H), 3.79 (s, 3H), 3.74 (t, *J* = 6.8 Hz, 2H),

3.54 (m, 1H), 3.45 (m, 1H), 3.43 (s, 3H), 2.40 (m, 1H), 2.28 (t, *J* = 8.0 Hz, 2H), 1.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 142.5, 130.2, 129.4, 113.8, 112.9, 80.4, 80.1, 71.7, 61.1, 58.6, 55.2, 39.4, 22.8; MS (ES) calculated for $C_{16}H_{24}O_4$ 280.2, found $[M+Na]^+$: 303.3.

To a mixture of primary alcohol (112 mg, 0.4 mmol) and $NaHCO_3$ (67 mg, 0.8 mmol) in CH_2Cl_2 (6 mL) was added Dess-Martin periodinane (339 mg, 0.8 mmol) at 0 □C. After stirring 1 h at room temperature, ether (20 mL) and 10% $Na_2S_2O_3$ (10 mL) was added. After 5 min, the organic layer was separated and washed thoroughly with sat. $NaHCO_3$ and water and dried over $MgSO_4$. Filtration and concentration afforded the crude aldehyde. To a mixture of the crude aldehyde, *t*-BuOH (12 mL), water (3.0 mL) and 2-methyl-2-butene (3.0 mL) was added NaH_2PO_4 (165 mg, 1.2 mmol) and $NaClO_2$ (181 mg, 1.6 mmol) at 0 □C. After stirring at room temperature for 1.5 h, EtOAc (30 mL) and 0.05 N $NaHSO_4$ (30 mL) was added. After 5 min, the crude was extracted with EtOAc and the combined organic extracts were washed with water and dried over $MgSO_4$. After concentration, the residue was purified by column chromatography (silica gel, MeOH/CH_2Cl_2, 1:5) to give **3.11** (R_f = 0.30, CH_2Cl_2: MeOH = 10:1; 99-107 mg, 84-91% over two steps) as a viscous oil.

The compound **3.11** has ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (m, 2H), 6.88 (m, 2H), 4.80 (m, 2H), 4.69 (d, *J* = 15.2 Hz, 1H), 4.14 (d, *J* = 4.4 Hz, 1H), 3.79 (s, 3H), 3.74 (m, 1H), 3.41 (s, 3H), 2.34 (m, 2H), 1.74 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.7, 141.6, 130.2, 129.8, 128.8, 113.9, 113.4, 80.8, 78.3, 72.7, 58.3, 55.3, 38.5, 22.6; MS (ES) calculated for $C_{16}H_{24}O_5Na$ $[M+Na]^+$ 317.2, found 317.2.

(2*S*, 3*R*)-3-methoxy-2-((4-methoxybenzyl)oxy)-5-methylhex-5-enoic acid (3.12)

To a solution of **2.4b** (259 mg, 0.5 mmol) in THF (5 mL), TBAF (1M in THF, 1.0 mL) was added at ambient temperature. After 1.5 h, TLC indicated that all the starting material was consumed. Saturated $NaHCO_3$ solution (10 mL) was added and the crude was extracted with EtOAc. The combined ether extracts were washed with water, dried over $MgSO_4$ and concentrated. The residue obtained was purified by column chromatography (silica gel; hexanes/EtOAc, 10:1) to give primary alcohol (R_f = 0.30, hexanes: EtOAc = 4:1; 104-119 mg, 74-85%).

This compound has ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (m, 2H), 6.88 (m, 2H), 4.81 (m, 1H), 4.74 (m, 1H), 4.60 (s, 2H), 3.78 (s, 3H), 3.76 (m, 1H), 3.67 (m, 1H), 3.59 (m, 1H), 3.51 (m, 1H), 3.42 (s, 3H), 2.35 (dd, *J* = 5.6, 13.2 Hz, 1H), 2.22 (d, *J* = 10.4 Hz, 1H), 2.20 (dd, *J* = 5.6, 13.2 Hz, 1H), 1.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 142.6, 130.3, 129.5, 113.8, 112.6, 80.4, 78.5, 72.3, 61.8, 58.3, 55.2, 37.9, 22.7; MS (ES) calculated for $C_{16}H_{24}O_4$ 280.2, found $[M+Na]^+$: 303.3.

To a mixture of primary alcohol (112 mg, 0.4 mmol) and $NaHCO_3$ (67 mg, 0.8 mmol) in CH_2Cl_2 (6 mL) was added Dess-Martin periodinane (339 mg, 0.8 mmol) at 0 ^{o}C. After stirring 1 h at room temperature, ether (20 mL) and 10% $Na_2S_2O_3$ (10 mL) was added. After 5 min, the organic layer was separated and washed thoroughly with sat. $NaHCO_3$ and water and dried over $MgSO_4$. Filtration and concentration afforded the crude aldehyde. To a mixture of the crude aldehyde, *t*-BuOH (12 mL), water (3.0 mL) and 2-methyl-2-butene (3.0 mL) was added NaH_2PO_4 (165 mg, 1.2 mmol) and $NaClO_2$ (181 mg, 1.6 mmol) at 0 □C. After stirring at room temperature for 1.5 h, EtOAc (30 mL) and 0.05 N $NaHSO_4$ (30 mL) was added. After 5 min, the crude was extracted with EtOAc and the combined organic extracts were washed with

water and dried over $MgSO_4$. After concentration, the residue was purified by column chromatography (silica gel, MeOH/CH_2Cl_2, 1:5) to give **3.12** (R_f = 0.25, CH_2Cl_2: MeOH = 10:1; 102-111 mg, 86-94% over two steps) as a viscous oil.

The compound **3.12** has ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (m, 2H), 6.85 (m, 2H), 4.76 (m, 2H), 4.63 (s, 1H), 4.40 (d, *J* = 11.2 Hz, 1H), 4.00 (d, *J* = 2.6 Hz, 1H), 3.79 (s, 3H), 3.78 (m, 1H), 3.39 (s, 3H), 2.35 (m, 2H), 1.74 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.2, 159.6, 141.6, 130.2, 128.7, 113.9, 113.7, 80.2, 78.0, 73.2, 58.3, 55.2, 37.8, 22.6; MS (ES) calculated for $C_{16}H_{24}O_5Na$ $[M+Na]^+$ 317.2, found 317.2.

(*R*)-4-((*S*)-1-methoxy-3-methylbut-3-en-1-yl)-2,2-dimethyl-1,3-dioxolane (2.24)

To a round bottom flask containing TMEDA (11.7 mL, 76.9 mmol) and *n*-BuLi (2.5 M in hexane, 30.8 mL, 76.9 mmol) in Et_2O (45 mL) was added 2-methylpropene (13.3 g, 230.7 mmol) under N_2 at −78 ^{o}C. The reaction was allowed to stir at −78 ^{o}C for 1 h and at room temperature overnight. The mixture obtained was added to a stirred solution of (−)-$(Ipc)_2$BOMe (24.7 g, 76.9 mmol) in Et_2O (75 mL) at −78 ^{o}C. After stirring at −78 ^{o}C for 1 h and at room temperature for 1 h, the reaction was cooled to −78 ^{o}C and a solution of aldehyde (10.0 g, 76.9 mmol) in Et_2O (130 mL) was added dropwise. After 1 h, the reaction was quenched by adding pH 7 buffer (400 mL), MeOH (400 mL) and 30% H_2O_2 (200 mL), and stirred at room temperature for 30 min. The crude was extracted with Et_2O and the combined organic phases were washed with water and dried over $MgSO_4$. After concentration, the residue obtained was purified by FC (silica gel; EtOAc/hexanes 1:4) to give allylic alcohol (R_f = 0.25, hexanes: EtOAc = 4:1, ~ 14.0-14.5 g containing

isopinocampheol, *dr* 95:5) as a colorless oil, and was used without further purification. To a suspension of NaH (60% in mineral oil, 620 mg, 15.4 mmol) in THF (70 mL) was added a solution of all above allylic alcohol in THF (60 mL) at 0 ^{o}C. After stirring at 0 ^{o}C for 30 min, MeI (3.53 mL, 56.4 mmol) was added and the reaction was allowed to stir at ambient temperature overnight. The crude was extracted with Et_2O and the combined organic phases were dried over $MgSO_4$, filtered and concentrated. The residue obtained was purified by FC (silica gel, Et_2O/Hexanes 1:1) to afford methyl ether **2.24** (R_f = 0.75, hexanes: EtOAc = 5:1; 9.8-10.0 g, 64-65% over two steps) as a colorless volatile oil.

The compound **2.24** has $[\alpha]^D$ = +16.38 ($CHCl_3$, *c* = 1.0); ^{1}H NMR ($CDCl_3$) δ 1.37 (s, 3H), 1.44 (s, 3H), 1.78 (s, 3H), 2.01 (d, 1H, *J* = 2.4 Hz), 2.11 (dd, 1H, *J* = 9.4, 14.2 Hz), 2.30 (dd, 1H, *J* = 4.0, 14.2 Hz), 3.85 (m, 1H), 4.00 (m, 3H), 4.82 (s, 1H), 4.89 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 22.3, 25.3, 26.6, 41.7, 65.4, 68.8, 78.4, 109.1, 113.7, 141.9; IR ν_{max} 3477, 1219, 1066 cm^{-1}; MS (ES) calculated for $C_{10}H_{18}O_3Na$ $[M + Na]^+$ 209.12, found 209.5.

(2*R*,3*S*)-1-hydroxy-3-methoxy-5-methylhex-5-en-2-yl benzoate (3.13)

A mixture of the methyl ether **2.24** (6.6 g, 33.0 mmol), PPTS (1.76 mg, 7.0 mmol), and water (11 mL) in MeOH (200 mL) was stirred at 50 ^{o}C overnight and then brought to room temperature. $NaHCO_3$ (2.0 g) was added and solvent was removed under reduced pressure. The residue obtained was dissolved in EtOAc (150 mL), dried with $MgSO_4$, filtered and concentrated. The residue obtained was purified by FC (silica gel, EtOAc) to afford 4.78-4.87 g (91-93%) of diol (R_f = 0.20, hexanes: EtOAc = 1:1) as a colorless oil.

To a solution of diol (4.87 g, 30.4 mmol) and imidazole (2.48 g, 36.6 mmol) in CH_2Cl_2 (150

mL) was added TBSCl (5.52 g, 36.6 mmol) in CH_2Cl_2 (10 mL) at 0 ^oC. After 30 min, the reaction mixture was washed with sat. $NaHCO_3$ and water and dried over $MgSO_4$. After concentration, the residue was purified by FC (silica gel, hexanes/EtOAc, 10:1) to give the desired product (R_f = 0.55, hexanes: EtOAc = 1:1; 7.79-7.92 g, 93-95%) as a colorless oil.

To a solution of the alcohol (7.92 g, 25.88 mmol) in pyridine (40 mL) was added benzoyl chloride (6.99 mL, 38.82 mmol). After 30 min at room temperature, benzoyl chloride (2.8 mL, 12.15 mmol) was added again and stirred for another 30 min. Sat. $NaHCO_3$ solution was added and the crude was extracted with EtOAc. The combined organic extracts were washed with 1 N HCl and water and concentrated. 3N HCl (30 mL) was added to a solution of the crude benzoate in THF (150 mL). After stirring at room temperature for 2 h, $NaHCO_3$ (10.0 g) was added and the solvent was removed under reduced pressure. The residue obtained was extracted with CH_2Cl_2 and the combined organic extracts were washed with water and dried over $MgSO_4$. After removal of solvent, the residue was purified by FC (silica gel, hexanes/EtOAc, 3:1) to give compound **3.13** (R_f = 0.15, hexanes: EtOAc = 4:1; 6.30-6.49 g, 92-95%) as colorless oil.

Compound **3.13** has $[\alpha]^{24}_D = -26.4$ (EtOAc, *c* = 0.55); ^{1}H NMR ($CDCl_3$) δ 1.81 (s, 3H), 2.30 (dd, 1H, *J* = 6.0, 14.4 Hz), 2.42 (dd, 1H, *J* = 7.5, 14.4 Hz), 3.49 (s, 3H), 3.80 (ddd, 1H, *J* = 3.9, 6.0, 7.5 Hz), 3.92 (dd, 1H, *J* = 3.9, 12.0 Hz), 3.97 (dd, *J* = 4.8, 12.0 Hz), 4.80 (m, 1H), 4.84 (m, 1H), 5.13 (ddd, 1H, *J* = 3.9, 3.9, 4.8 Hz), 7.45 (m, 2H), 7.58 (m, 1H), 8.07 (m, 2H); 13C NMR (CDCl3) δ 22.6, 39.6, 58.9, 61.8, 76.2, 80.2, 113.5, 128.4, 129.7, 129.9, 133.2, 141.6, 166.3; IR ν_{max} 3439, 2918, 1715, 1250, 1272, 1114 cm^{-1}; MS (ES) calculated for $C_{15}H_{20}O_4Na$ $[M + Na]^+$ 287.13, found 287.00.

(3*R*, 4*S*, 6*R*)-4, 6-dimethoxy-6-methyltetrahydro-2H-pyran-3-yl benzoate (3.15)

Ozone was bubbled through a solution of compound **3.13** (30 mg, 114 μmol) in CH_2Cl_2 (10 mL) at –78 ºC until the solution became slightly blue. Me_2S (1 mL) was added and the resultant solution was stirred at room temperature overnight. After removal of solvent, the residue obtained was purified by FC (silica gel; hexanes/EtOAc, 1:1) to give a mixture of four hemiketals (24 mg, 89%) as viscous oil. To a solution of hemiketals (24 mg, 90 μmol) in MeOH (3 mL) was added $HC(OMe)_3$ (0.2 mL) and a catalytic amount of *p*-TsOH. After stirring at room temperature for 1 h, Et3N (50 μL) was added and stirred for 5 min. The solvent was removed under reduced pressure and the residue obtained was purified by FC (silica gel; hexanes/EtOAc, 3:1) to give compound **3.13 (**20 mg, 80%) as a colorless oil.

^{1}H NMR ($CDCl_3$) δ 1.42 (s, 3H), 1.96 (dd, 1H, *J* = 12.0, 12.4 Hz), 2.06 (dd, 1H, *J* = 4.8, 12.4 Hz), 3.23 (s, 3H), 3.37 (s, 3H), 3.75 (dd, 1H, *J* = 1.0, 12.8 Hz), 3.81 (ddd, 1H, *J* = 2.8, 4.8, 12.0 Hz), 3.92 (dd, 1H, *J* = 2.0, 12.8 Hz), 5.44 (ddd, 1H, *J* = 1.0, 2.0, 2.8 Hz), 7.44 (t, 2H, *J* = 7.6 Hz), 7.56 (t, 1H, *J* = 7.6 Hz), 8.08 (d, 2H, *J* = 7.6 Hz); ^{13}C NMR ($CDCl_3$) δ 23.3, 37.2, 48.2, 56.1, 62.3, 66.5, 73.3, 99.7, 128.3, 129.8, 133.0, 166.2; MS (ES) calculated for $C_{15}H_{20}O_5Na$ $[M + Na]^+$ 303.12, found 303.00.

(2*S*,3*R*)-2-(benzoyloxy)-3-methoxy-5-methylhex-5-enoic acid (3.16)

Compound **3.16** was synthesized form aldehyde **2.22** using the similar procedure as the synthesis of **3.14**, but starting with enantiomeric borane ((+)-$(Ipc)_2$BOMe). To a mixture of **2.25** (4.5 g, 17.0 mmol) and $NaHCO_3$ (2.85 g, 34.0 mmol) in CH_2Cl_2 (150 mL) was added

Dess-Martin periodinane (14.42 g, 34.0 mmol) at 0 □C. After stirring 1 h at room temperature, ether (200 mL) and 10% $Na_2S_2O_3$ (100 mL) was added. After 5 min, the organic layer was separated and washed thoroughly with sat. $NaHCO_3$ and water and dried over $MgSO_4$. Filtration and concentration afforded the crude aldehyde. To a mixture of the crude aldehyde, *t*-BuOH (500 mL), water (125 mL) and 2-methyl-2-butene (125 mL) was added NaH_2PO_4 (7.71 g, 68.0 mmol) and $NaClO_2$ (7.71 g, 68.0 mmol) at 0 ^oC. After stirring at room temperature for 1.5 h, EtOAc (300 mL) and 0.05 N $NaHSO_4$ (300 mL) was added. After 5 min, the crude was extracted with EtOAc and the combined organic extracts were washed with water and dried over $MgSO_4$. After concentration, the residue was purified by column chromatography (silica gel, MeOH/CH_2Cl_2, 1:5) to give **3.16** (R_f = 0.25, CH_2Cl_2: MeOH = 10:1; 3.9-4.1 g, 84-87%) as a viscous oil.

Compound **3.16** has ^{1}H NMR ($CDCl_3$) δ 1.75 (s, 3H), 2.33 (dd, 1H, *J* = 7.8, 13.8 Hz), 2.45 (dd, 1H, *J* = 6.6, 13.8 Hz), 3.42 (s, 3H), 4.04 (ddd, 1H, *J* = 2.1, 6.6, 7.8 Hz), 4.68 (bs, 1H), 4.79 (t, 1H, *J* = 1.5 Hz), 5.25 (d, 1H, *J* = 2.1 Hz), 7.42 (m, 2H), 7.55 (m, 1H), 8.09 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 22.5, 38.2, 58.2, 73.3, 78.8, 114.1, 128.4, 129.2, 129.9, 133.3, 140.9, 166.1, 172.9; IR ν_{max} 3446, 2938, 1726, 1602, 1266, 1107, 1072 cm^{-1}; MS (ES) calculated for C15H18O5Na $[M + Na]^+$ 301.11, found 301.00.

(*R*)-3-hydroxy-2, 2-dimethylhex-5-enal (3.20)

To a solution of **3.19** (Johnson, P. R.; White, J. D. *J. Org. Chem*. **1984**, *49*, 4424) (2.0 g, 14.1 mmol) in toluene (20 mL) was added allylsilane **2.8** (5.69 g, 21.1 mmol) at −15 ºC. After 48 h at −10 ºC, 0.5 N HCl (20 mL) was added to the reaction mixture and stirred at room

temperature for 30 min. The crude was extracted with ether and combined organic extracts were washed with water, sat. NaHCO3, brine and dried over MgSO4. After concentration, the residue was purified by FC (silica gel; hexanes/EtOAc, 15:1) to give **3.20** (1.38 g, 69%, 94% *ee*) as a colorless oil.

Compound **3.20** has $[\alpha]^{23}_{D}$ = +3.73 (CH_2Cl_2, *c* = 2.0); 1H NMR ($CDCl_3$) δ 1.08 (s, 3H), 1.11 (s, 3H), 2.07 (m, 1H), 2.15 (d, 1H, *J* = 3.6 Hz), 2.32 (m, 1H), 3.78 (dt, 1H, *J* = 3.6, 10.4 Hz), 5.17 (m, 2H), 5.85 (m, 1H), 9.57 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 16.5, 19.0, 36.2, 50.0, 73.8, 118.6, 134.9, 206.2; IR ν_{max} 3417, 3077, 2977, 1724, 1642 cm^{-1}. MS (ES) calculated for C16H28O4Na [M2Na]+ 307.19, found 307.10. The enantiomeric excess was determined from the H NMR spectrum of the Mosher ester derivative prepared with (*S*)-(−)-MTPA: major isomer has Me-resonances at 1.064 and 1.067 ppm; the minor isomer has Me-resonances at 1.094 and 1.100 ppm. Integration of the Me-resonances was used to calculate an *ee* of 94%.

(4*R*, 6*R*)-5, 5-dimethylnona-1, 8-diene-4, 6-diol (3.8)

Method A: To a solution of 3.20 (1.30 g, 9.15 mmol) in toluene (15 mL) was added allylsilane **2.8** (4.93 g, 18.3 mmol) at −15 ºC. After kept at this temperature for 20 h, 0.5 N HCl (15 mL) was added to the reaction mixture and stirred at room temperature for 15 min. The crude was extracted with ether and the combined organic extracts were washed with water, sat. $NaHCO_3$, brine and dried over $MgSO_4$. After concentration, the residue was purified by FC (silica gel; hexanes/EtOAc, 15:1) to give **3.8** (1.33 g, 79%, *dr* = 17:1) as a colorless oil.

Method B: To an oven-dried sealed tube under one atmosphere of argon gas charged with $[Ir(cod)Cl]_2$ (1.34 g, 2.0 mmol, 5 mol%), (*R*)-Cl,MeO-BIPHEP (**3.59**, 2.61 g, 4.0 mmol, 10 mol%), Cs_2CO_3 (5.2 g, 16.0 mmol, 40 mol%) and 4-chloro-3-nitrobenzoic acid (1.61 g, 8.0 mmol, 20 mol%) was added 1,4-dioxane (100 mL) followed by allyl acetate (40 g, 400 mmol). The reaction mixture was allowed to stir at 90 ^oC for 30 min and was then allowed to cool to room temperature. Neopentyl glycol **2.32** (4.17 g, 40.0 mmol) in 1,4-dioxane (60 mL) was added to the reaction mixture and the reaction mixture was allowed to stir at 100 ^oC for 3 days, at which point the reaction mixture was filtered. The organic phase was evaporated onto silica gel. Purification of the product by column chromatography (SiO_2; ethyl acetate: hexanes, 1:8 to 1:4) provided **3.8** (R_f = 0.25, hexanes: EtOAc = 5:1; 3.10-3.25 g, 16.8 mmol, 42%-45% yield, *dr* = 20:1) as a colorless oil.

Compound **3.8** has $[\alpha]^{22}_D$ = +21.5 ($CHCl_3$, *c* = 1.45); ^1H NMR (400 MHz, $CDCl_3$) δ 5.87 (m, 2H), 5.15 (m, 4H), 3.54 (ddd, *J* = 10.5, 3.5, 2.0 Hz, 2H), 3.01 (s, 2H), 2.29 (m, 2H), 2.14 (m, 2H), 0.91 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.3, 117.9, 77.3, 40.2, 36.6, 21.0. **IR** (neat): 3369, 3077, 2973, 2915, 2878, 1717, 1641, 1475, 1431, 1370, 1269, 1054, 994, 912, 867 cm^{-1}; MS (ES) calculated for $C_{11}H_{20}O_2Na$ $[M + Na]^+$ 207.14, found 207.05. HPLC: Enantiomeric excess was determined by HPLC analysis of bis-4-nitro-benzoate derivative of the product. (Chiralpak AD-H column, hexanes: *i*-PrOH = 95:5, 1.0 mL/min, 254 nm), t_{major} = 20.7 min, t_{minor} = 16.3 min; *dr* >20:1. HPLC analysis was determined as literature reported and the NMR and IR data match the reported data for **203**.

Besides **3.8**, a minor product (**(*R*)-2, 2-dimethylhex-5-ene-1, 3-diol**, **3.60**) was isolated according method B. Additionally, we also isolated the monoallyl alcohol that was not

mentioned in the previous literature (R_f = 0.15, hexanes: EtOAc = 4:1).

The compound **3.60** has $[\alpha]^{23}_D$ = +4.86 (CH_2Cl_2, *c* = 2.0); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.85 (m, 1H), 5.12 (m, 2H), 3.51 (dd, *J* = 10.4, 3.5 Hz, 2H), 3.27 (d, *J* = 3.6 Hz, 1H), 2.31 (m, 1H), 2.06 (m, 1H), 0.85 (s, 3H), 0.85 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.3, 118.0, 78.0, 72.2, 38.4, 36.8, 22.8, 18.9. IR: 3368, 3077, 2962, 2876, 1827, 1641, 1475, 1432, 1393, 1367, 1322, 1276, 1193, 1066, 1041, 991, 912, 864 cm^{-1}; MS (ES) calculated for $C_{16}H_{32}O_4Na$ [M_2 + Na]$^+$ 311.24, found 311.10.

2-((2*R*, 4*R*)-4-((*tert*-butyldimethylsilyl)oxy)-6-hydroxy-3, 3-dimethyltetrahydro-2H-pyran-2-yl)acetaldehyde (3.21b)

To a solution of **3.8** (465 mg, 2.53 mmol) and 2, 6-lutidine (0.44 mL, 3.80 mmol) in CH_2Cl_2 (20 mL) was added TBSOTf (0.64 mL, 2.78 mmol) at 0 ºC. After stirring for 10 min, MeOH (1mL) was added and stirred for 10 min. The solvent was removed under vacuo and the residue obtained was purified by FC (silica gel; hexanes/EtOAc, 50:1) to give monosilylated intermediate (692 mg, 92%) as an colorless oil: $[\alpha]^{23}_D$ = +29.2 (EtOAc, *c* = 1.05); ^{1}H NMR ($CDCl_3$) δ 0.09 (s, 3H), 0.10 (s, 3H), 0.80 (s, 3H), 0.90 (s, 9H), 1.00 (s, 3H), 2.13 (m, 2H), 2.33 (m, 1H), 2.52 (m, 1H), 3.57 (dd, 1H, *J* = 4.6, 6.4 Hz), 3.87 (dd, 1H, *J* = 4.1, 8.7 Hz), 5.10 (m, 4H), 5.91 (m, 2H); ^{13}C NMR ($CDCl_3$) δ −4.2, −3.8, 18.1, 20.4, 23.3, 26.0, 36.4, 37.7, 41.2, 75.0, 83.2, 116.3, 116.8, 136.5, 136.8; IR ν_{max} 3494, 3077, 2955, 1641, 1470, 1255 cm^{-1}; MS (ES) calculated for $C_{17}H_{35}O_2Si$ [M + H]$^+$ 299.24, found 299.15; calculated for $C_{17}H_{34}O_2SiNa$ [M + Na]$^+$ 321.22, found 321.15.

Ozone was bubbled through a solution of monosilylated intermediate (692 mg, 2.32 mmol) in

CH_2Cl_2 (50 mL) at –78 ºC until the solution became slightly blue. Ph_3P (2.43 g, 9.28 mmol) was added and the resultant solution was stirred at room temperature overnight. After concentration, the residue obtained was purified by FC (silica gel; hexanes/EtOAc, 10:1 to 3:1) to give hemiacetal **3.21b** (692 mg, 99%) as viscous oil.

(4*R*, 6*R*)-4-((*tert*-butyldimethylsilyl)oxy)-5, 5-dimethyl-6-(2-oxoethyl)tetrahydro-2H-pyran-2-yl acetate (3.57)

To a solution of **3.21b** in CH_2Cl_2 (18 mL) was added Et_3N (1.27 mL, 9.19 mmol), DMAP (50 mg) and Ac_2O (431 μL, 4.59 mmol) successively at 0 ºC. After 10 min, sat $NaHCO_3$ (20 mL) was added and the crude was extracted with ether. The combined ether extracts were washed with water, dried over $MgSO_4$ and concentrated. The residue obtained was purified by column chromatography (silica gel; hexanes/EtOAc, 6:1) to give **3.57** (633 mg, 81%) as a mixture of two epimers and was used without further separation. The compound with axial OAc has ^{1}H NMR ($CDCl_3$) δ 2.13 (s, 3H), 3.75 (dd, 1H, *J* = 5.2, 11.3 Hz), 4.13 (dd, 1H, *J* = 2.9, 10.1 Hz), 6.12 (dd, 1H, *J* = 0.9, 3.7 Hz), 9.71 (t, 1H, *J* = 1.5 Hz); The compound with equatorial OAc has ^{1}H NMR ($CDCl_3$) δ 2.09 (s, 3H), 3.49 (dd, 1H, *J* = 4.9, 11.6 Hz), 3.71 (dd, 1H, *J* = 3.1, 9.8 Hz), 5.68 (dd, 1H, *J* = 2.8, 10.1 Hz), 9.74 (t, 1H, *J* = 2.1 Hz); IR ν_{max} 2929, 2856, 1727, 1367, 1235, 1076, 833 cm^{-1}; MS (ES) calculated for $C_{18}H_{36}O_6SiNa$ [MNa + MeOH]$^+$ 399.22, found 399.15.

(4*R*, 6*R*)-4-((*tert*-butyldimethylsilyl)oxy)-6-(2-hydroxybutyl)-5, 5-dimethyltetrahydro -2H-pyran-2-yl acetate (3.31)

To a suspension of (*R, R*)-1,2-*bis*(trifluoromethanesul-fonamido) cyclohexane in anhydrous toluene (500 mL) was added Ti(O-*i*Pr)$_4$ (14.36 mL, 48.68 mmol) at room temperature. After stirring at 45 ^{o}C for 40 min, the reaction was cooled to –78 ^{o}C and $ZnEt_2$ (1.0 M in hexanes, 48.68 mL, 48.68 mmol) was added dropwise. After 10 min, a solution of compound acetate **221** (4.60 g, 15.43 mmol) in toluene (70 mL) was added. After stirring for 8 h at −10 ^{o}C, sat NH_4Cl (30 mL) was added and the reaction mixture was filtered through a pad of celite®. The crude was extracted with EtOAc and the combined organic phases were washed with water and brine, dried over $MgSO_4$ and concentrated. The residue obtained was purified by column chromatography (silica gel; hexanes/EtOAc, 20:1) to give **3.31** (R_f = 0.40-0.55, CH_2Cl_2: EtOAc = 20:1; 3.51-3.78 g, 78-84%) as a mixture of four diastereomers and was used without further separation.

(2*S*,4*R*,6*R*)-4-((tert-butyldimethylsilyl)oxy)-6-(2-hydroxybutyl)-5,5-dimethyltetrahydro-2H-pyran-2-carbonitrile (3.33)

TMSCN (5.39 mL, 40.50 mmol) was added to **3.31** (3.78 g, 10.17 mmol) and stirred at room temperature for 15 min. After cooled to 0 ^{o}C, MeCN (120 mL), TMSCN (2.73 mL, 19.95 mmol) and ZnI_2 (758 mg, 2.39 mmol) were added successively and stirred for 40 min. Sat. $NaHCO_3$ solution (120 mL) was added and the reaction was extracted with EtOAc. The combined organic extracts were shaken with 1N HCl for 20 min and washed with aq. $NaHCO_3$ and water and dried over $MgSO_4$. After concentration, the residue obtained was purified by FC (silica gel; hexanes/EtOAc, 8:1) to give compound **3.33** (R_f = 0.90, hexanes: EtOAc = 4:1; 3.10-3.16 g, 89-93%) as a mixture of two alcohol epimers in the ratio of 3:1.

The major isomer is a color less oil.

The major isomer has $[\alpha]^{24}{}_{D}$ = +67.6 (EtOAc, *c* = 0.55); ^{1}H NMR ($CDCl_3$) δ 0.05 (s, 3H), 0.06 (s, 3H), 0.81 (s, 3H), 0.87 (s, 9H), 0.89 (s, 3H), 0.93 (t, 3H, *J* = 7.4 Hz), 1.49 (m, 4H), 1.76 (ddd, 1H, *J* = 1.2, 4.5, 13.8 Hz), 1.97 (ddd, 1H, *J* = 6.0, 11.7, 13.8 Hz), 2.10 (s, 1H), 3.65 (m, 2H), 3.76 (dd, 1H, *J* = 5.1, 6.6 Hz), 4.83 (dd, 1H, *J* = 1.2, 6.0 Hz); ^{13}C NMR ($CDCl_3$) δ −5.1, −4.3, 10.1, 12.3, 17.9, 22.5, 25.6, 30.4, 33.5, 35.4, 39.5, 63.7, 69.7, 72.3, 78.5, 117.8; IR νmax 3436, 2959, 1472, 1258, 1104, 1082, 880 cm^{-1}; MS (ES) calculated for $C_{18}H_{35}O_3NSiNa$ [M + Na]+ 364.23, found 364.20. The minor is a colorless oil: $[\alpha]^{25}{}_{D}$ = + 50.2 (EtOAc, *c* = 0.69); ^{1}H NMR ($CDCl_3$) δ 0.06 (s, 3H), 0.07 (s, 3H), 0.85 (s, 3H), 0.88 (s, 9H), 0.89 (s, 3H), 0.94 (t, 3H, *J* = 7.4 Hz), 1.49 (m, 2H), 1.60 (dd, 1H, *J* = 7.5, 10.2 Hz), 1.68 (ddd, 1H, *J* = 2.7, 3.3, 11.4 Hz), 1.75 (ddd, 1H, *J* = 1.2, 4.5, 13.5 Hz), 1.99 (ddd, 1H, *J* = 6.0, 11.4, 13.5 Hz), 2.03 (s, 1H), 3.69 (m, 3H), 4.88 (dd, 1H, 1.2, 6.0 Hz); ^{13}C NMR ($CDCl_3$) δ −5.02, −4.22, 9.66, 12.35, 17.90, 22.60, 25.66, 29.76, 33.41, 35.11, 39.88, 63.81, 71.99, 72.65, 82.85, 117.35; IR ν_{max} 3306, 2857, 1461, 1082, 884 cm^{-1}; MS (ES) calculated for $C_{18}H_{35}O_3NSiNa$ $[M + Na]^+$ 364.23, found 364.20.

(2*S*, 4*R*, 6*R*)-4-((*tert*-butyldimethylsilyl)oxy)-5, 5-dimethyl-6-(2-oxobutyl)tetrahydro-2H -pyran-2-carbonitrile (3.34)

To a solution of **3.33** (3.13 g, 9.24 mmol) in CH_2Cl_2 (200 mL) was added Dess-Martin periodinane (13.38 g, 31.58 mmol) at 0 ^{o}C. After stirring at ambient temperature for 3 h, 10% $Na_2S_2O_3$ solution (120 mL) was added and stirred for 10 min. The reaction was extracted with CH_2Cl_2 and the combined extracts were washed with $NaHCO_3$, water and dried over

$MgSO_4$. After concentration, the residue obtained was purified by FC (silica gel; hexanes/EtOAc, 10:1) to give compound **3.34** (R_f = 0.70, hexanes: EtOAc = 4:1; 2.87-2.95 g, 93-96%) as white solid.

Compound **3.34** has $[\alpha]^{24}_D$ = +40.6 (EtOAc, *c* = 0.16); ^{1}H NMR ($CDCl_3$) δ 0.08 (s, 3H), 0.09 (s, 3H), 0.85 (s, 3H), 0.90 (s, 9H), 0.91 (s, 3H), 1.07 (t, 3H, *J* = 7.3 Hz), 1.79 (ddd, 1H, *J* = 1.5, 4.6, 13.7 Hz), 1.98 (ddd, 1H, *J* = 6.1, 11.3, 13.7 Hz), 2.52 (m, 4H), 3.74 (dd, 1H, *J* = 4.6, 11.3 Hz), 4.07 (dd, 1H, *J* = 2.8, 9.8 Hz), 4.80 (dd, 1H, *J* = 1.5, 6.1 Hz). ^{13}C NMR ($CDCl_3$) δ −5.0, −4.2, 7.5, 12.5, 17.9, 22.7, 25.7, 33.6, 36.1, 39.4, 42.4, 63.7, 72.1, 77.8, 117.2, 208.4; IR ν_{max} 3402, 2958, 1716, 1462, 1256, 1099, 885 cm^{-1}. A crystal structure of **3.34** was obtained from a **3.34** solution in hexanes/EtOAc.

2, 4-dimethoxy-5-methylbenzaldehyde (3.36)

To a solution of $POCl_3$ (4.07 mL, 43.65 mmol) in DMF (200 mL), compound **3.35** (4.43 g, 29.10 mmol) in DMF (20 ml) was added dropwise at 0 ^oC. The resulting solution was stirred for additional 6 h at ambient temperature. Water (200 mL) and EtOAc (200 mL) was added. After 5 min, the organic layer was separated and washed thoroughly with sat. $NaHCO_3$ and water and dried over $MgSO_4$. The combined organic solvent was removed on vacuum, and the crude oil was purified by FC (silica gel, EtOAc/Hexanes 5:1) to afford compound **3.36** (4.19-4.30 g, 80-82%),

***N, N*-diethyl-2,4-dimethoxy-5-methylbenzamide (3.37)**

To a solution of benzaldehyde **3.36** (4.19 g, 23.28 mmol) in DMSO (67 mL) were added

NaH_2PO_4 (8.03 g, 58.20 mmol) in H_2O (9 mL) and $NaClO_2$ (5.26 g, 46.56 mmol) in H_2O (33 mL) at 10 ^oC. After stirring overnight at room temperature, saturated Na_2CO_3 solution (200 mL) was added. After 5 min, the crude was extracted with EtOAc (100 mL) and the aqueous phase was acidified with *conc.* HCl to pH 2. The white precipitate that formed was collected by filtration to give 2, 4-dimethoxy-5-methylbenzoic acid (R_f = 0.15, CH_2Cl_2: MeOH = 10:1; 3.80-3.90 g, 83-85%).

2,4-dimethoxy-5-methylbenzoic acid has ^1H NMR ($CDCl_3$) δ 2.16 (s, 3H), 3.92 (s, 3H), 4.07 (s, 3H), 6.46 (s, 1H), 7.91 (1H, d, *J* = 0.8 Hz), 10.61 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 15.1, 55.6, 56.7, 94.1, 108.8, 120.6, 134.7, 158.2, 162.9, 165.6,; IR ν_{max} 3242, 1725, 1621, 1280, 1021, 828 cm^{-1}; MS calculated for $C_{10}H_{13}O_4$ $[M + H]^+$ 197.08, found 197.05; calculated for $C_{10}H_{12}O_4Na$ $[M + Na]^+$ 219.06, found, 219.00.

To a solution of 2, 4-dimethoxy-5-methylbenzoic acid (3.88 g, 19.79 mmol) in benzene (110 mL) was added dropwise thionyl chloride (8.52 mL, 77 mmol) at room temperature. The reaction mixture was cooled down after refluxing for 2 h. The solvent and excess of thionyl chloride were removed under reduce pressure to give crude acid chloride. To a solution of crude acid chloride in benzene (56 mL) was added dropwise diethylamine (6.14 mL, 59.38 mmol) at 0 □C. After stirring 2 h at 0 ^oC and overnight at room temperature, the reaction was concentrated and the crude oil was purified by FC (silica gel, EtOAc/Hexanes/NEt_3 9:1:0.05) to afford compound **3.37** (R_f = 0.40, hexanes: EtOAc = 2:1; 4.60- 4.85 g, 93-97%) as a white solid.

Compound **3.37** has ^1H NMR ($CDCl_3$) δ 1.03 (t, 3H, *J* = 7.2 Hz), 1.23 (t, 3H, *J* = 7.2 Hz), 2.13 (s, 3H), 3.17 (q, 2H, *J* = 7.2 Hz), 3.55 (q, 2H, *J* = 7.2 Hz), 3.81 (s, 3H), 3.85 (s, 3H),

6.41 (s, 1H), 6.95 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 12.9, 14.0, 15.2, 38.8, 42.8, 55.4, 55.9, 95.0, 118.5, 118.6, 129.2, 154.5, 158.7, 169.0; IR ν_{max} 1614, 1462, 1207, 1143, 1033 cm^{-1}; MS (ES) calculated for $C_{14}H_{22}NO_3$ $[M + H]^+$ 252.16, found 252.10.

2-allyl-*N*, *N*-diethyl-4,6-dimethoxy-3-methylbenzamide (3.38)

To a solution of amide **3.37** (1.61 g, 6.40 mmol) in THF (16 mL) was added *sec*-BuLi (1.4 M in cyclohexane, 10.06 mL, 14.09 mmol) at −78 ºC dropwise. After 1 h at −78 ºC, $CuBr{\cdot}Me_2S$ (2.63 g, 12.81 mmol) was added and the reaction was allowed to warm to −15 ºC. After 30 min, allylbromide (1.12 mL, 12.81 mmol) was added at −78 ºC and kept at this temperature for 1 h. The reaction was warmed to room temperature, filtered through a pad of silica gel and washed with EtOAc. The filtrate was dried over $MgSO_4$, concentrated and purified by FC (silica gel, EtOAc/Hexanes/NEt_3 85:15:0.5) to give (1.41 g, 76%) of compound **3.38**.

^{1}H NMR ($CDCl_3$) δ 1.02 (t, 3H, *J* = 6.8 Hz), 1.23 (t, 3H, *J* = 7.2 Hz), 2.09 (s, 3H), 3.04 (dt, 1H, *J* = 7.6 Hz), 3.15 (dt, 1H, *J* = 7.6 Hz), 3.24-3.40 (3H, m), 3.79 (s, 3H), 3.84 (s, 3H), 4.97 (m, 2H), 5.84 (m, 1H), 6.36 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 10.8, 12.5, 13.5, 34.7, 38.1, 42.7, 55.4, 55.5, 93.2, 115.3, 117.9, 119.2, 135.4, 136.1, 154.0, 158.3, 168.5; IR (film) 1626, 1594, 1460, 1436, 1318, 1207, 1140, 1094 cm^{-1}; MS (ES) calculated for $C_{17}H_{26}NO_3$ $[M + H]^+$ 292.19, found 292.10

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Methyl 2-allyl-4,6-dihydroxy-3-methylbenzoate (2.177)

To a solution of **3.38** (1.00 g, 3.61 mmol) in CH_2Cl_2 (60 mL) was added a solution of BBr_3 (2.05 mL, 21.7 mmol) in CH_2Cl_2 (20 mL) at –78 ºC. After stirring at −78 ºC for 30 min, 0 ºC

for 4 h and 25 ºC for 1 h, water was added at 0 ºC and the crude was extracted with CH_2Cl_2. The combined extracts were washed with water, dried over $MgSO_4$ and concentrated. The residue obtained was purified by FC (silica gel; CH_2Cl_2/EtOAc, 20:1) to give 2-allyl-*N*,*N*-diethyl-4,6-dihydroxy-3-methylbenzamide (730 mg, 81%) as white solid. 2-allyl-*N*,*N*-diethyl-4,6-dihydroxy-3-methylbenzamide has ^{1}H NMR (CD_3OD) δ 1.07 (t, 3H, *J* = 6.9 Hz), 1.22 (t, 3H, *J* = 6.9 Hz), 2.04 (s, 3H), 3.11-3.45 (m, 5H), 3.65 (m, 1H), 4.98 (m, 2H), 5.82 (m, 1H), 6.28 (s, 1H); ^{13}C NMR (CD_3OD) δ 11.3, 13.1, 14.1, 36.0, 40.2, 45.0, 101.6, 116.0, 116.3, 117.5, 137.1, 137.3, 153.1, 157.8, 172.3; IR ν_{max} 3307, 1600, 1577, 1439, 1144 cm^{-1}; MS (ES) calculated for $C_{15}H_{22}NO_3$ $[M + H]^+$ 264.16, found 264.10; calculated for $C_{15}H_{21}NO_3Na$ $[M + Na]^+$ 286.14, found 286.05.

To a solution of 2-allyl-*N*,*N*-diethyl-4,6-dihydroxy-3-methylbenzamide (845 mg, 3.21 mmol) in CH_2Cl_2 (25 mL) was added Me_3OBF_4 (590 mg, 3.99 mmol) at room temperature. After 20 h, the reaction was concentrated and mixed with MeOH (9 mL) and saturated Na_2CO_3 solution (9 mL). After stirring at room temperature for 6 h, ether (50 mL) was added and the aqueous phase was adjusted to pH 2 using 0.5 N HCl. The crude was extracted with ether, and the combined ether extracts were washed with water and dried over $MgSO_4$. After concentration, the residue obtained was purified by FC (silica gel; Hexanes/EtOAc, 6:1) to give **2.177** (520 mg, 73%) as white solid: ^{1}H NMR ($CDCl_3$) δ 2.11 (s, 3H), 3.70 (dt, 2H, *J* = 1.7, 5.8 Hz), 3.91 (s, 3H), 4.95 (m, 2H), 5.52 (s, 1H), 5.91 (m, 1H), 6.33 (s, 1H), 11.30 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 10.9, 35.6, 52.0, 101.5, 106.1, 114.9, 117.2, 136.2, 142.1, 159.2, 161.6, 171.9; IR ν_{max} 3330, 1654, 1597, 1439, 1329, 1262, 1159 cm^{-1}; MS (ES) calculated for $C_{14}H_{17}NO_4Na$ $[MNa + MeCN]^+$ 286.11, found 286.05.

Methyl 4,6-*bis*((4-methoxybenzyl)oxy)-3-methyl-2-(2-oxoethyl)benzoate (3.39)

The mixture of compound **2.177** (1.56 g, 7.02 mmol), K_2CO_3 (2.91 g, 21.06 mmol), PMBCl (2.86 mL, 21.06 mmol), Bu_4NI (519 mg, 1.41 mmol) and DMF (90 mL) was heated at 80 ^oC for 20 h. Remove DMF under vacuum (5 mmHg) at 50 ^oC, add water and the crude was extracted with CH_2Cl_2. The combined organic extracts were washed with water, dried over $MgSO_4$ and concentrated. The residue obtained was purified by FC (silica gel; Hexanes/EtOAc, 9:1) to give methyl 2-allyl-4,6-*bis*((4-methoxybenzyl)oxy)-3-methylbenzoate (R_f = 0.50, hexanes: EtOAc = 4:1; 2.75-2.97 g, 85-92 %) as white solid.

2-allyl-4,6-*bis*((4-methoxybenzyl)oxy)- 3-methylbenzoate has ^1H NMR ($CDCl_3$) δ 2.12 (s, 3H), 3.35 (m, 2H), 3.78 (s, 3H), 3.80 (s, 3H), 3.82 (s, 3H), 4.93 (s, 2H), 4.97 (s, 2H), 4.99 (m, 2H), 5.85 (m, 1H), 6.46 (s, 1H), 6.91 (m, 4H), 7.27 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 11.0, 35.0, 51.9, 55.15, 55.18, 70.1, 70.6, 97.1, 113.8, 113.9, 115.6, 117.7, 118.6, 128.6, 128.8, 128.8, 128.9, 135.4, 136.9, 154.4, 158.1, 159.2, 159.3, 169.2; IR ν_{max} 2949, 1725, 1593, 1515, 1250, 1155 cm^{-1}; MS (ES) calculated for $C_{28}H_{30}O_6Na$ $[M + Na]^+$ 485.19, found 485.10.

To a solution of 2-allyl-4,6-*bis*((4-methoxybenzyl)oxy)-3-methylbenzoate (2.97 mg, 6.43 mmol) in THF (35 mL) and H_2O (6 mL) were added 4-methyl-morpholine-*N*-oxide (1.50 g, 12.86 mmol) and OsO_4 (0.1 M solution in *t*-BuOH, 5.14 mL, 0.51 mmol) at 0 ^oC. After stirring at ambient temperature for 12 h, 10% $Na_2S_2O_3$ solution was added. After 30 min, the crude was extracted with EtOAc and the combined organic extracts were washed with water and dried over $MgSO_4$. After concentration, the residue obtained was filtered through a short column (silica gel) and washed with EtOAc. Removal of the solvent from the combined filtrate gave the crude diol. $NaIO_4$ (2.06 g, 9.65 mmol) was added to a solution of crude diol

in 90% MeOH (150 mL). After stirring at room temperature for 1 h, EtOAc (250 mL) was added and the reaction mixture was washed with water and dried over $MgSO_4$. After concentration, the residue obtained was purified by FC (silica gel; CH_2Cl_2/EtOAc, 20:1) to give compound **3.39** (R_f = 0.40, hexanes: EtOAc = 4:1; 2.50-2.62 g, 84-88%) as white crystals.

Compound **3.39** has ^{1}H NMR ($CDCl_3$) δ 2.08 (s, 3H), 3.68 (d, 2H, *J* = 1.8 Hz), 3.81 (s, 3H), 3.82 (s, 3H), 3.83 (s, 3H), 4.97 (s, 2H), 5.01 (s, 2H), 6.53 (s, 1H), 6.91 (m, 4H), 7.30 (m, 4H), 9.64 (t, 1H, *J* = 1.8 Hz); ^{13}C NMR ($CDCl_3$) δ 11.6, 45.8, 52.1, 55.2, 55.2, 70.1, 70.8, 98.2, 113.9, 114.0, 117.6, 119.5, 128.5, 128.6, 128.7, 128.8, 130.7, 155.3, 158.6, 159.3, 159.4, 168.6, 198.6; IR ν_{max} 3000, 2951, 1722, 1594, 1515, 1250, 1156 cm^{-1}; MS (ES) calculated for $C_{27}H_{28}O_7Na$ $[M + Na]^+$ 487.17, found 487.10.

(2*S*, 4*R*, 6*R*)-6-((2*S*, 3*R*)-3-((*R*)-6,8-*bis*((4-methoxybenzyl)oxy)-5-methyl-1-oxoisochroman-3-yl)-2-hydroxybutyl)-4-((*tert*-butyldimethylsilyl)oxy)-5,5-dimethyltetrahydro-2H-pyran-2-carbonitrile (3.45)

To a solution of **3.42a** (3.0 g, 3.75 mmol) in anhydrous THF (300 mL) was added catecholborane (1.0 M in THF, 112.2 mL, 112.2 mmol) at –78 ^{o}C. After stirring at 0 ^{o}C for 20 h, 2 N NaOH (360 mL) was added and the resultant reaction mixture was stirred at ambient temperature for 0.5 h. The reaction was extracted by CH_2Cl_2 and the combined organic extracts were washed with 1 N NaOH solution until the aqueous phase is colorless and then washed with water. The extracts were dried over $MgSO_4$ and concentrated to give a white solid in quantitative yield, which is an 8:1 mixture of compound **3.45** and its diastereomer.

Pure compound **3.45** was obtained through recrystallization from CH_2Cl_2/acetone.

Compound **3.45** has $[\alpha]^{22}_D$ = 39.4 (CH_2Cl_2, *c* = 0.20); ^{1}H NMR ($CDCl_3$) δ 0.08 (s, 3H), 0.10 (s, 3H), 0.88 (s, 3H), 0.90 (s, 9H), 0.93 (s, 3H), 1.12 (d, 3H, *J* = 7.2 Hz), 1.74 (t, 2H, *J* = 6.0 Hz), 1.79 (dd, 1H, *J* = 4.6, 13.7 Hz), 1.91 (m, 1H), 2.01 (ddd, 1H, *J* = 6.2, 11.9, 13.7 Hz), 2.10 (s, 3H), 2.83 (dd, 1H, *J* = 12.0, 16.3 Hz), 2.96 (dd, 1H, *J* = 2.6, 16.3 Hz), 3.68 (m, 2H), 3.80 (s, 3H), 3.82 (s, 3H), 4.07 (m, 1H), 4.41 (ddd, 1H, *J* = 2.7, 4.9, 12.0 Hz), 4.87 (d, 1H, *J* = 5.3 Hz), 4.98 (s, 2H), 5.09 (d, 1H, *J* = 12.0 Hz), 5.16 (d, 1H, *J* = 12.0 Hz), 6.49 (s, 1H), 6.90 (m, 4H), 7.30 (d, 2H, *J* = 8.6 Hz), 7.44 (d, 2H, *J* = 8.6 Hz); ^{13}C NMR ($CDCl_3$) δ −5.0, −4.2, 8.8, 11.1, 12.4, 17.9, 22.7, 25.7, 29.6, 32.9, 33.4, 40.0, 41.5, 55.2, 55.3, 63.8, 69.9, 70.9, 71.97, 72.0, 78.7, 83.0, 98.2, 107.5, 113.9, 114.0, 116.0, 117.4, 128.3, 128.5, 128.8, 141.4, 159.2, 159.5, 160.2, 161.0, 163.1; IR ν_{max} 3364, 1671, 1588, 1515, 1249, 1098 cm^{-1}; MS (ES) calculated for $C_{44}H_{59}O_9NSiNa$ $[M + Na]^+$ 796.39, found 796.50; calculated for $C_{44}H_{59}NO_9SiK$ [M + K]+ 812.36, found 812.45.

Methyl 2-(((4*R*, 5*S*, 6*S*)-6-(((2*R*, 4*R*, 6*S*)-4-((*tert*-butyldimethylsilyl)oxy)-6-cyano-3, 3-dimethyltetrahydro-2H-pyran-2-yl)methyl)-2, 2, 5-trimethyl-1, 3-dioxan-4-yl)methyl)-4, 6-*bis*((4-methoxybenzyl)oxy)-3-methylbenzoate (3.43)

The acetonide-derivative **i** of the diol obtained from **3.42a** by omitting a basic workup (Na,K-tartrate workup instead), was prepared for determination of the relative stereochemistry. ^{13}C NMR ($CDCl_3$) resonances of the acetonide Me peaks and quaternary carbon (19.5, 29.8, and 98.9 ppm) confirm the C_{15},C_{17}-*syn* configuration (Rychnovsky, S. D.; Rogers, B.; Yang, G. *J. Org. Chem.* **1993**, *58*, 3511); the ^{1}H NMR H_{16}-H_{17} coupling constant

of 2.4 Hz (δ 4.02 ppm) is in agreement with an equatorial disposition of H_{16}, confirming the C_{16},C_{17}-*anti* configuration. ^{1}H NMR (CD_3OD) δ 0.11 (s, 3H), 0.12 (s, 3H), 0.87 (s, 3H), 0.92 (s, 9H), 0.95 (d, 3H, *J* = 6.4 Hz), 0.96 (s, 3H), 1.22 (s, 3H), 1.29 (s, 3H), 1.58 (m, 1H), 1.62 (m, 1H), 1.67 (m, 1H), 1.80 (ddd, 1H, *J* = 1.2, 4.4, 14.0 Hz), 2.00 (ddd, 1H, *J* = 5.6, 11.6, 14.0 Hz), 2.14 (s, 3H), 2.54 (dd, 1H, *J* = 2.4, 14.4 Hz), 3.01 (dd, 1H, *J* = 8.8, 14.4 Hz), 3.44 (dd, 1H, *J* = 2.0, 11.8 Hz), 3.69 (dd, 1H, *J* = 8.4, 11.6 Hz), 3.79 (s, 3H), 3.80 (s, 3H), 3.82 (s, 3H), 4.02 (ddd, 1H, *J* = 2.4, 2.4, 8.8 Hz), 4.07 (ddd, 1H, *J* = 1.6, 4.8, 13.2 Hz), 4.99 (bs, 4H), 6.60 (s, 1H), 6.90 (m, 4H), 7.30 (m, 4H); ^{13}C NMR ($CDCl_3$) δ −5.0, −4.2, 4.8, 11.8, 12.3, 17.9, 19.5, 22.6, 25.7, 29.8, 31.2, 33.5, 33.8, 34.2, 39.8, 52.1, 55.2, 55.3, 63.7, 70.1, 70.6, 70.8, 72.4, 74.8, 77.8, 97.3, 98.9, 113.8, 113.9, 117.6, 118.2, 119.6, 128.6, 128.8, 129.0, 129.1, 137.8, 154.3, 158.0, 159.2, 159.3, 169.3; MS (ES) calculated for $C_{48}H_{67}O_{10}NSiNa$ [M + Na]$^+$ 868.44, found 868.45.

(2*S*,4*R*,6*R*)-6-((2*S*,3*R*)-3-((*R*)-6,8-*bis*((4-methoxybenzyl)oxy)-5-methyl-1-oxoisochroman-3-yl)-2-hydroxybutyl)-4-hydroxy-5,5-dimethyltetrahydro-2H-pyran-2-carbonitrile (3.46)

To a solution of **3.45** (2.5 g, 2.25 mmol) in THF (500 mL) was added TBAF (1.0 M in THF, 5.0 mL, 5.0 mmol) at room temperature. After 2 h, the reaction was concentrated and the residue was purified by FC (silica gel; hexanes/EtOAc, 1:2 to EtOAc) to give **3.46** (2.03-2.15 g, 94-99%) as a viscous oil.

Compound **3.46** has $[\alpha]^{26}_D$ = +33.6 (EtOAc, *c* = 0.60); ^{1}H NMR ($CDCl_3$) δ 0.91 (s, 3H), 1.02 (s, 3H), 1.11 (d, 3H, *J* = 6.8 Hz), 1.76 (m, 2H), 1.89-2.06 (m, 3H), 2.10 (s, 3H), 2.84 (dd, 1H, *J* = 12.0, 16.0 Hz), 2.94 (dd, 1H, *J* = 2.8, 16.0 Hz), 3.68 (dd, 1H, *J* = 4.6, 7.8 Hz), 3.76 (dd,

1H, *J* = 4.8, 11.6 Hz), 3.80 (s, 3H), 3.83 (s, 3H), 4.07 (m, 1H), 4.43 (ddd, 1H, *J* = 2.8, 4.4, 11.6 Hz), 4.91 (d, 1H, *J* = 4.8 Hz), 4.98 (s, 2H), 5.10 (d, 1H, *J* = 12.2 Hz), 5.16 (d, 1H, *J* = 12.2 Hz), 6.49 (s, 1H), 6.90 (t, 4H, *J* = 8.4 Hz), 7.29 (d, 2H, *J* = 8.4 Hz), 7.43 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR ($CDCl_3$) δ 8.8, 11.1, 12.1, 22.2, 29.6, 32.5, 32.6, 39.5, 41.4, 55.2, 55.3, 64.0, 69.9, 70.9, 71.5, 72.0, 78.6, 82.7, 98.1, 107.4, 113.9, 114.0, 116.0, 117.2, 128.2, 128.5, 128.7, 128.8, 141.4, 159.2, 159.5, 160.2, 161.1, 163.2; IR ν_{max} 3394, 2966, 1674, 1588, 1514, 1248, 1097 cm^{-1}; MS (ES) calculated for $C_{38}H_{45}O_9NNa$ $[M + Na]^+$ 682.30, found 682.35.

(2*S*,4*R*,6*R*)-6-((2*S*,3*S*)-3-((*R*)-6,8-*bis*((4-methoxybenzyl)oxy)-5-methyl-1-oxoisochroman-3-yl)-2-((*tert*-butyldimethylsilyl)oxy)butyl)-4-((*tert*-butyldimethylsilyl)oxy)-5,5-dimethyltetrahydro-2H-pyran-2-carbonitrile (3.47)

To a solution of **3.46** (100 mg, 0.129 mmol) and 2,6-lutidine (0.10 mL) in CH_2Cl_2 (5 mL) was added TBSOTf (0.16 mL) at 0 ^oC. After stirring for 1 h, MeOH (1 mL) was added and stirred for 10 min. The solvent was removed under vacuum and the residue obtained was purified by FC (silica gel; hexanes/EtOAc, 50:1) to give **3.47** (R_f = 0.85, hexanes: EtOAc = 4:1, 97-105 mg, 85-92%).

The compound **3.47** has ^{1}H NMR ($CDCl_3$, 400 MHz): 7.47 (d, *J* = 8.6 Hz, 2H), 7.32 (d, *J* = 8.6 Hz, 2H), 6.91 (m, 4H), 6.51 (s, 1H), 5.13 (dd, *J* = 19.6, 6.8 Hz, 2H), 5.00 (s, 2H), 4.77 (d, *J* = 5.3 Hz, 1H), 4.29 (ddd, *J* = 2.6, 11.3 Hz, 1H), 4.06 (m, 1H), 3.83 (s, 3H), 3.80 (s, 3H), 3.64 (dd, *J* = 4.6, 11.8 Hz, 1H), 3.48 (d, *J* = 9.9 Hz, 1H), 2.97 (dd, *J* = 2.6, 16.3 Hz, 1H), 2.74 (dd, *J* = 11.3, 16.3 Hz, 1H), 1.94 (m, 2H), 1.81 (dd, *J* = 9.3, 14.1 Hz, 1H), 1.74 (ddd, *J* = 1.1, 3.7, 12.6 Hz, 1H), 1.61 (ddd, *J* = 3.1, 10.4, 14.0 Hz, 1H), 1.11 (d, *J* = 6.8 Hz, 3H), 0.91 (s,

3H), 0.89 (s, 9H), 0.84 (s, 9H), 0.82 (s, 3H), 0.09 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H), 0.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 163.2, 160.9, 160.2, 159.5, 150.1, 141.1, 128.9, 128.4, 128.3, 117.5, 115.3, 114.0, 113.9, 107.8, 98.0, 78.4, 78.2, 72.3, 70.8, 69.9, 69.1, 63.6, 55.3, 55.2, 40.4, 39.7, 33.5, 32.4, 29.8, 25.8, 25.6, 22.7, 17.9, 17.9, 12.2, 9.0, -3.7, -4.2, -4.8, -5.0; MS (ES) calculated for $C_{50}H_{73}NO_9Si_2$: 887.5, found $[M + Na]^+$: 910.6.

(2*S*,4*R*,6*R*)-6-((2*S*,3*S*)-3-((*R*)-6,8-*bis*((4-methoxybenzyl)oxy)-5-methyl-1-oxoisochroman-3-yl)-2-((*tert*-butyldimethylsilyl)oxy)butyl)-4-((*tert*-butyldimethylsilyl)oxy)-5,5-dimethyltetrahydro-2H-pyran-2-carboxamide (3.49)

To a suspension of **3.47** (105 mg, 118 μmol) in 80% ethanol (8 mL) was added [PtH(PMe_2OH) (PMe_2O)$_2$H] (**3.48**, 13 mg, 30 μmol). After refluxing in air for 80 min, the reaction was cooled to room temperature. Water was added and the crude was extracted with EtOAc. The combined organic extracts were washed with water, dried over MgSO4 and concentrated to give a residue which was purified by FC (silica gel; CH_2Cl_2/MeOH 20:1) to give **3.49** (R_f = 0.45, hexanes: EtOAc = 4:1; 100-107 mg, 93-99%).

The compound **3.49** has ^{1}H NMR ($CDCl_3$, 400 MHz): 7.43 (d, *J* = 8.6 Hz, 2H), 7.30 (d, *J* = 8.6 Hz, 2H), 6.92 (m, 4H), 6.79 (bs, 1H), 6.50 (s, 1H), 5.84 (bs, 1H), 5.14 (dd, *J* = 19.6, 6.8 Hz, 2H), 4.99 (s, 2H), 4.40 (m, 1H), 4.40 (m, 1H), 4.37 (dd, *J* = 1.6, 6.2 Hz, 1H), 4.29 (m, 1H), 3.83 (s, 3H), 3.81 (s, 3H), 3.37 (dd, *J* = 4.4, 11.0 Hz, 1H), 3.25 (dd, *J* = 3.1, 8.8 Hz, 1H), 2.86 (m, 2H), 2.35 (ddd, *J* = 2.0, 4.2, 13.2 Hz, 1H), 2.15 (m, 1H), 2.07 (s, 3H), 1.75(m, 3H), 1.02 (d, *J* = 7.1 Hz, 3H), 0.91 (s, 9H), 0.89 (s, 9H), 0.85 (s, 3H), 0.84 (s, 3H), 0.14 (s, 3H), 0.11 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 173.63, 163.2, 161.2,

160.5, 159.5, 159.3, 141.8, 128.9, 128.6, 128.4, 128.2, 115.9, 114.1, 114.0, 107.2, 97.8, 79.3, 73.2, 72.6, 70.8, 69.9, 67.6, 55.3, 39.4, 38.6, 34.6, 29.8, 29.7, 28.3, 26.0, 25.8, 23.3, 18.1, 18.0, 13.1, 11.0, 8.9, -3.0, -4.1, -4.3, -5.1; MS (ES) calculated for $C_{50}H_{73}NO_9Si_2$: 905.5, found $[M+Na]^+$: 928.5.

(2*S*,4*R*,6*R*)-4-((*tert*-butyldimethylsilyl)oxy)-6-((2*S*,3*S*)-2-((*tert*-butyldimethylsilyl)oxy)-3-((*R*)-8-hydroxy-6-((4-methoxybenzyl)oxy)-5-methyl-1-oxoisochroman-3-yl)butyl)-5,5-dimethyltetrahydro-2H-pyran-2-carboxamide (3.50)

To a solution of **3.49** (107 mg, 118 μmol) in CH_2Cl_2/H_2O (8 mL/0.4 mL) was added DDQ (31 mg, 0.14 mmol). After stirring at RT for 1 h, the solution poured into saturated aqueous $NaHCO_3$ (10 mL) and extracted with DCM (3 × 10 mL) and the combined organic phase was washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The crude was purified by FC (silica gel Hexanes/EtOAc 2:1) to give compound **3.50** (R_f = 0.40, hexanes: EtOAc = 2.5:1; 85-92 mg, 92-99%).

Compound **3.50** has ^{1}H NMR ($CDCl_3$, 400 MHz): 11.2 (s, 1H), 7.35 (d, *J* = 8.4 Hz, 2H), 6.93 (d, *J* = 8.4 Hz, 2H), 6.66 (bs, 1H), 6.46 (s, 1H), 5.60 (s, 1H), 5.30 (bs, 1H), 5.02 (s, 2H), 4.49 (m, 1H), 4.33 (m, 2H), 3.83 (s, 3H), 3.37 (dd, *J* = 4.0, 6.4 Hz, 1H), 3.28 (dd, *J* = 3.6, 8.0 Hz, 1H), 2.91 (m, 2H), 2.31 (ddd, *J* = 2.4, 4.0, 10.2 Hz, 1H), 2.18 (m, 1H), 2.06 (s, 3H), 1.77 (m, 3H), 1.02 (d, *J* = 6.8 Hz, 3H), 0.90 (s, 9H), 0.89 (s, 9H), 0.85 (s, 3H), 0.84 (s, 3H), 0.13 (s, 3H), 0.11 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H).

(2*S*,4*R*,6*R*)-4-((*tert*-butyldimethylsilyl)oxy)-6-((2*S*,3*S*)-2-((*tert*-butyldimethylsilyl)oxy)-3-((*R*)-6,8-dihydroxy-5-methyl-1-oxoisochroman-3-yl)butyl)-5,5-dimethyltetrahydro-2H-pyran-2-carboxamide (3.51)

10% Pd/C (20 mg) was added to a solution of **3.50** (92 mg, 118 μmol) in ethanol (10 mL) and hydrogenated (H_2, 1 atm) for 24 h. The catalyst was filtered and ethanol was removed under reduced pressure. The residue obtained was purified by FC (silica gel; CH_2Cl_2/MeOH 10:1) to give **3.51** (R_f = 0.30, hexanes: EtOAc = 2.5:1; 70-74 mg, 90-95%) as colorless foam.

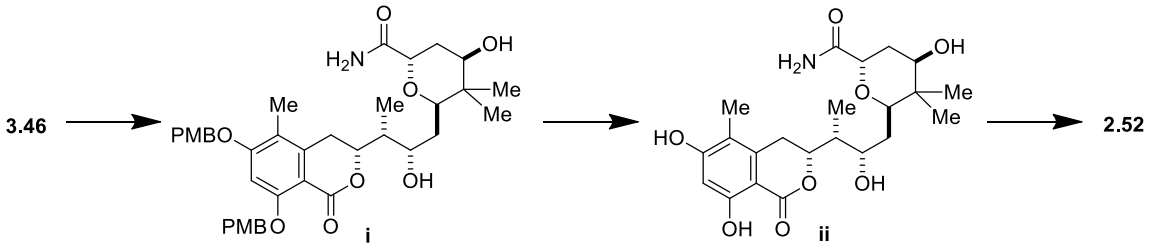
Compound **3.51** has ^{1}H NMR (400 MHz, Chloroform-d) δ 11.2 (s, 1H), 6.66 (s, 1H), 6.32 (s, 1H), 5.72 (s, 1H), 4.49 (dt, *J* = 10.0, 5.4 Hz, 1H), 4.36 (dd, *J* = 2.7, 3.4 Hz, 2H), 4.28 (dt, *J* = 2.8, 6.0, 12.8 Hz, 1H), 3.38 (dd, *J* = 6.2, 4.2 Hz, 1H), 3.28 (d, *J* = 8.6 Hz, 1H), 2.91 (m, 2H), 2.30 (dt, *J* = 13.2, 3.7 Hz, 1H), 2.16 (ddd, *J* = 7.3, 4.8, 2.8 Hz, 1H), 2.06 (s, 3H), 1.78 (m, 3H), 1.06 (d, *J* = 7.0 Hz, 3H), 0.95 (s, 9H), 0.93 (s, 9H), 0.89 (s, 3H), 0.84 (s, 3H), 0.13 (s, 3H), 0.10 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H).

(*R*)-3-((2*S*,3*S*)-3-((*tert*-butyldimethylsilyl)oxy)-4-((2*R*,4*R*,6*S*)-4-((*tert*-butyldimethylsilyl)oxy)-6-carbamoyl-3,3-dimethyltetrahydro-2H-pyran-2-yl)butan-2-yl)-8-hydroxy-5-methyl-1-oxoisochroman-6-yl benzoate (3.52)

To a solution of **3.52** (40 mg, 60 μmol) in toluene (10 mL), DIPEA (200 μL) and BzCl (35 μL) was added successively at ambient temperature. After stirring for 30 min, MeOH (1 mL) was added. The solution was removed under reduced pressure. The residue obtained was purified by FC (silica gel; CH_2Cl_2/MeOH 10:1) to give **3.52** (R_f = 0.45, hexanes: EtOAc = 2.5:1; 38-42 mg, 82-91%) as a white foam.

The compound **3.52** has ^{1}H NMR (400 MHz, Chloroform-d) δ 11.15 (s, 1H), 8.20 (d, *J* = 7.0 Hz, 2H), 7.67 (t, *J* = 7.4 Hz, 1H), 7.54 (t, *J* = 7.7 Hz, 2H), 6.77 (s, 1H), 6.66 (s, 1H), 5.60 (s, 1H), 4.61 (dt, *J* = 12.0, 4.0 Hz, 1H), 4.38 (dd, *J* = 6.4, 4.0 Hz, 1H), 4.29 (m, 1H), 3.38 (dd, *J* = 4.0, 10.4 Hz, 1H), 3.33 (d, *J* = 9.2 Hz, 1H), 2.97 (m, 2H), 2.32 (dt, *J* = 4.0, 6.8, 9.2 Hz, 1H), 2.24 (m ,1H), 2.05 (s, 3H), 1.80 (m, 3H), 1.08 (d, *J* = 7.0 Hz, 3H), 0.91 (s, 9H), 0.90 (s, 9H), 0.87 (s, 3H), 0.86 (s, 3H), 0.14 (s, 3H), 0.11 (s, 3H), 0.08 (s, 3H), 0.06 (s, 3H).

(*R*)-3-((2*S*,3*S*)-3-acetoxy-4-((2*R*,4*R*,6*S*)-4-acetoxy-6-carbamoyl-3,3-dimethyltetrahydro-2H-pyran-2-yl)butan-2-yl)-5-methyl-1-oxoisochroman-6,8-diyl diacetate (2.52)



To a suspension of **3.46** (42 mg, 64 μmol) in 80% ethanol (8 mL) was added [PtH(PMe_2OH)(PMe_2O)$_2$H] (**3.38**, 7 mg, 16 μmol). After refluxing in air for 80 min, the reaction was cooled to room temperature. Water was added and the crude was extracted with EtOAc. The combined organic extracts were washed with water, dried over $MgSO_4$ and concentrated to give a residue which was purified by FC (silica gel; CH_2Cl_2/MeOH 20:1) to give **i (**42 mg, 97%) as a viscous oil. Compound **i** has $[\alpha]^{27}_D$ = +37.5 (EtOAc, *c* = 0.43); ^{1}H NMR ($CDCl_3$) δ 0.89 (s, 3H), 0.91 (s, 3H), 1.13 (d, 3H, *J* = 7.2 Hz), 1.67 (m, 2H), 1.79 (m, 1H), 1.88 (m, 1H), 2.09 (s, 3H), 2.46 (dd, 1H, *J* = 3.8, 13.0 Hz), 2.82 (dd, 1H, *J* = 3.2, 16.4 Hz), 2.89 (dd, 1H, *J* = 12.0, 16.4 Hz), 3.37 (d, 1H, *J* = 8.0 Hz), 3.41 (dd, 1H, *J* = 4.4, 11.6 Hz), 3.80 (s, 3H), 3.83

(s, 3H), 4.11 (bd, 1H, *J* = 7.6 Hz), 4.42 (ddd, 1H, *J* = 3.2, 3.6, 11.6 Hz), 4.45 (d, 1H, *J* = 6.4 Hz), 4.99 (s, 2H), 5.08 (d, 1H, *J* = 12.0 Hz), 5.16 (d, 1H, *J* = 12.0 Hz), 5.59 (bs, 1H), 6.51 (s, 1H), 6.91 (t, 4H, *J* = 8.0 Hz), 7.29 (d, 2H, *J* = 8.8 Hz), 7.42 (d, 2H, *J* = 8.8 Hz), 7.75 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 7.9, 11.1, 11.9, 22.5, 29.2, 29.2, 34.2, 38.6, 41.7, 55.3, 55.3, 70.0, 70.9, 71.9, 73.8, 74.1, 80.0, 81.2, 98.0, 107.0, 114.0, 114.1, 115.9, 128.1, 128.5, 128.6, 128.9, 141.3, 159.3, 159.6, 160.5, 161.3, 162.7, 174.0; IR ν_{max} 3402, 2965, 1682, 1596, 1515, 1247, 1157, 1081 cm^{-1}; MS (ES) calculated for $C_{38}H_{47}O_{10}NNa$ $[M + Na]^+$ 700.31, found 700.35.

10% Pd/C (10 mg) was added to a solution of **i** (40 mg, 59 mmol) in ethanol (10 mL) and hydrogenated (H_2, 1 atm) for 24 h. The catalyst was filtered and ethanol was removed under reduced pressure. The residue obtained was purified by FC (silica gel; CH_2Cl_2/MeOH 10:1) to give **ii** (26 mg) in quantitative yield as viscous oil.

Compound **ii** has$[\alpha]^{22}_D$ = +34.0 (EtOAc, *c* = 0.20); ^{1}H NMR ($CDCl_3/CD_3OD$, 10/1) δ 0.85 (s, 3H), 0.88 (s, 3H), 1.09 (d, 3H, *J* = 6.8 Hz), 1.67 (m, 2H), 1.78 (ddd, 1H, *J* = 6.8, 12.0, 13.2 Hz), 1.88 (m, 1H), 2.01 (s, 3H), 2.30 (ddd, 1H, *J* = 1.4, 4.6, 9.0 Hz), 2.88 (m, 2H), 3.30 (dd, 1H, *J* = 4.4, 11.6 Hz), 3.34 (m, 1H), 4.01 (ddd, 1H, *J* = 2.4, 7.8, 7.8 Hz), 4.39 (dd, 1H, *J* = 6.0 Hz), 4.52 (ddd, 1H, *J* = 4.4, 6.0, 10.0 Hz), 5.97 (bs, 1H), 6.25 (s, 1H), 7.78 (bs, 1H); 13C NMR δ 8.2, 10.3, 11.9, 22.4, 27.9, 28.9, 33.7, 38.4, 42.0, 71.3, 73.1, 73.3, 81.0, 81.1, 100.5, 114.1, 139.1, 161.8, 162.0, 162.9, 170.6, 175.1; IR ν_{max} 3401, 2967, 1659, 1651, 1376, 1254 cm^{-1}; MS (ES) calculated for $C_{22}H_{31}O_8NNa$ $[M + Na]^+$ 460.19, found 460.20.

To a solution of **ii** (25 mg, 57 μmol) was dissolved in pyridine (2.5 mL) was added Ac_2O (1.25 mL) at room temperature. After 20 h, EtOAc (20 mL) and sat. $NaHCO_3$ (10 mL) was added at 0 ºC and stirred at room temperature for 15 min. The organic phase was separated,

washed with water, 1N HCl and water, and dried over $MgSO_4$. After concentration, the residue obtained was purified by FC (silica gel; EtOAc/hexanes 2:1) to give compound **2.52 (**32 mg, 92%) as a viscous oil.

Compound **2.52** has $[\alpha]^{22}_D$ = +48.4 (CH_2Cl_2, *c* = 0.80); ^{1}H NMR ($CDCl_3$) δ 0.94 (s, 3H), 0.95 (s, 3H), 1.17 (d, 3H, *J* = 7.2 Hz), 1.79 (ddd, 1H, *J* = 2.4, 4.8, 15.2 Hz), 1.91 (ddd, 1H, *J* = 5.2, 9.2, 13.6 Hz), 2.06 (s, 3H), 2.08 (s, 3H), 2.10 (s, 3H), 2.12 (m, 1H), 2.26 (m, 2H), 2.33 (s, 3H), 2.35 (s, 3H), 2.78 (dd, 1H, *J* = 12.0, 16.4 Hz), 3.04 (dd, 1H, *J* = 2.8, 16.4 Hz), 3.46 (dd, 1H, *J* = 2.4, 11.6 Hz), 4.38 (m, 2H), 4.83 (dd, 1H, *J* = 4.0, 8.4 Hz), 5.29 (m, 1H), 5.48 (bs, 1H), 6.82 (bs, 1H), 6.84 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 9.4, 12.1, 14.2, 16.7, 20.8, 21.0, 21.1, 21.4, 24.2, 27.4, 28.7, 30.6, 37.0, 40.5, 72.2, 73.4, 78.3, 79.6, 115.7, 117.0, 125.7, 141.1, 150.5, 153.1, 161.5, 168.3, 169.5, 170.0, 171.0, 173.4; IR ν_{max} 3466, 2975, 1771, 1727, 1693, 1598, 1371, 1241, 1192, 1060 cm−1; MS (ES) calculated for $C_{30}H_{39}O_{12}NNa$ $[M + Na]^+$ 628.24, found 628.15.

Psymberin (1.1) and C_8 epimer (3.51)

To a solution of acid **3.14** (1.20 g, 4.34 mmol) in CH_2Cl_2 (65 mL) was added oxalyl chloride (1.54 mL, 17.36 mmol) and a catalytic amount of DMF at 0 ^oC. After stirring at room temperature for 2 h, solvent was removed by N_2 flushing. The acid chloride obtained was dried on vacuum pump for 5 min and dissolved in CH_2Cl_2 (20 mL) to give a 0.2 M solution of compound **3.49**.

To a mixture of compound **2.52** (0.41 g, 0.47 mmol) and poly(4-vinylpyridine) (0.84 g, 7.98 mmol) in CH_2Cl_2 (45 mL) was added Me_3OBF_4 (0.50 g, 3.06 mmol) at room temperature.

After 2 h, ether (80 mL) was added and allowed to stir for 5 min to precipitate the excess Me_3OBF_4. The reaction mixture was filtered and the solvent was removed by N_2 flushing. The residue obtained was dissolved in anhydrous toluene (60 mL) and cooled to 0 ^oC. DIPEA (2.32 mL, 13.44 mmol) and **3.49** (0.2 M solution prepared in situ, 10.08 mL) was added at 0 ^oC and the reaction mixture was stirred at 40 ^oC for 2 h. **3.49** (0.2 M solution in CH_2Cl_2, 3.60 mL) was added again and stirred for another 40 min and cooled to 0 ^oC. $NaBH_4$ (1.26 g) and ethanol (70 mL) was added and the reaction mixture was stirred at 0 ^oC for 2 h. EtOAc was added and the crude was washed with water and dried over $MgSO_4$. After concentration, the residue was roughly purified by FC (silica gel, EtOAc/hexanes, 1.5:1) to give a mixture of peracetylated compounds. This mixture was dissolved in MeOH (250 mL) and 1 N LiOH (50 mL) was added. After stirring at room temperature for 6 h, EtOAc was added and the aqueous phase was adjusted to pH 6 using 0.05 N $NaHSO_4$. The crude was extracted with EtOAc and the combined organic extracts were washed with sat. $NaHCO_3$, water and dried over $MgSO_4$. After concentration, the residue was purified by FC (silica gel, CH_2Cl_2/MeOH, 20:1) to give psymberin **1.1** (R_f = 0.45, hexanes: EtOAc = 1:4, 155-168 mg) and **3.51** (R_f = 0.25, hexanes: EtOAc = 1:4, 52-58 mg) in 51-56% total yield from **2.52** (ratio determined by ^1H NMR of crude mixture: 7:3). This reaction was repeated three times to prepare more than 500 mg psymberin.

Psymberin (**1.1**): $[\alpha]^{23}_D$= +21.8 (MeOH, *c* = 0.10); IR ν_{max} 3368, 2932, 1660, 1652, 1622, 1506, 1456, 1378, 1253, 1174, 1108, 1069, 973, 896 cm^{-1}; MS (ES) calculated for $C_{31}H_{47}O_{11}Na$ $[M + Na]^+$ 632.30, found 632.25. ^1H NMR (400MHz, CD_3OD): 6.23 (s, 1H), 5.37 (d, *J* = 8.2 Hz, 1H), 4.70 (m, 2H), 4.47 (ddd, *J* = 12.3, 6.0, 3.0 Hz, 1H), 4.34 (d, *J* = 2.6

Hz, 1H), 3.92 (m, 2H), 3.65 (ddd, *J* = 9.6, 2.5, 3.4 Hz, 1H), 3.58 (dd, *J* = 11.2, 4.7 Hz, 1H), 3.47 (dd, *J* = 10.2, 1.0 Hz, 1H), 3.34 (s, 3H), 3.18 (s, 3H), 3.10 (dd, *J* = 18.0, 3.0 Hz, 1H), 2.82 (dd, *J* = 16.8, 12.3 Hz, 1H), 2.33 (dd, *J* = 14.7, 9.3 Hz, 1H), 2.09 (s, 3H), 2.08 (m, 1H), 1.99 (ddd, *J* = 13.2, 4.5, 2.4 Hz, 1H), 1.87 (m, 1H), 1.75 (m, 3H), 1.69 (s, 3H), 1.08 (d, *J* = 6.9 Hz, 3H), 0.96 (s, 3H), 0.88 (s, 3H). ^{13}C NMR (125 MHz, CD_3OD): 174.7, 170.9, 163.1, 162.2, 142.4, 139.7, 113.8, 111.6, 99.95, 99.89, 81.2, 80.7, 80.5 78.3, 72.3, 72.0, 71.8, 70.5, 56.2, 55.1, 41.8, 38.3, 37.2, 32.9, 29.0, 28.0, 22.2, 21.5, 12.7, 9.4, 7.7. ^{1}H NMR (400 MHz, $CDCl_3$): 11.12 (s, 1H), 7.08 (d, *J* = 10.0 Hz, 1H), 6.32 (s, 1H), 5.44 (dd, *J* = 10.2, 8.3 Hz, 1H) 4.80 (bs, 2H), 4.54 (dt, *J* = 11.9, 4.1 Hz, 1H), 4.38 (d, *J* = 3.1 Hz, 1H), 4.13 (d, *J* = 2.6 Hz, 1H), 3.95 (m, 1H), 3.89 (m, 1H), 3.73 (m, 1H), 3.73 (m, 1H), 3.54 (d, *J* = 10.8 Hz, 1H), 3.38 (s, 3H), 3.38 (s, 3H), 2.90 (m, 1H), 2.83 (m, 1H), 2.36 (dd, *J* = 15.0, 4.6 Hz, 2H), 2.18 (m, 1H), 2.06 (m, 1H), 2.03 (s, 3H), 1.84 (m, 1H), 1.80 (m, 1H), 1.78 (s, 3H), 1.62 (m, 2H), 1.0 (d, *J* = 7.0 Hz, 3H), 0.98 (s, 3H), 0.92 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): 173.5, 170.6, 162.2, 160.9, 142.1, 139.5, 113.4, 113.0, 101.3, 101.1, 81.9, 80.6, 79.6, 78.4, 74.0, 73.3, 73.0, 71.3, 58.1, 56.2, 42.6, 38.7, 37.5, 32.2, 29.7, 28.4, 23.0, 22.7, 13.7, 10.4, 9.2.

3.51: [α]D= −19.2 (MeOH, *c* = 0.12); 1H NMR (CD3OD) δ 0.89 (s, 3H), 0.97 (s, 3H), 1.13 (d, 3H, *J* = 6.8 Hz), 1.73 (m, 4H), 1.77 (s, 3H), 2.00 (m, 1H), 2.06 (s, 3H), 2.14 (dd, 1H, *J* = 3.2, 14.6 Hz), 2.34 (dd, 1H, *J* = 9.2, 14.6 Hz), 2.85 (dd, 1H, *J* = 12.4, 16.8 Hz), 3.17 (dd, 1H, *J* = 3.0, 16.8 Hz), 3.38 (s, 3H), 3.41 (s, 3H), 3.53 (dd, 1H, *J* = 4.0, 8.0 Hz), 3.58 (dd, 1H, *J* = 6.0, 10.0 Hz), 3.69 (ddd, 1H, *J* = 3.2, 3.6, 9.2 Hz), 3.93 (m, 1H), 4.11 (m, 1H), 4.35 (d, 1H, *J* = 3.2 Hz), 4.49 (ddd, 1H, *J* = 3.0, 6.8, 12.4 Hz), 4.77 (bs, 1H), 4.79 (bs, 1H), 5.48 (d, 1H, *J* = 8.8 Hz), 6.25 (s, 1H); 1H NMR (CDCl3) δ 0.92 (s, 3H), 0.99 (s, 3H), 1.15 (d, 3H, *J* = 7.2 Hz),

1.76 (s, 3H), 1.77 (m, 1H), 1.88 (m, 1H), 1.94 (m, 1H), 2.05 (s, 3H), 2.11 (dd, 1H, *J* = 3.0, 14.4 Hz), 2.29 (dd, 1H, *J* = 8.8, 14.4 Hz), 2.91 (dd, 1H, *J* = 12.0, 16.4 Hz), 3.02 (dd, 1H, *J* = 2.8, 16.4 Hz), 3.14 (bs, 1H), 3.41 (s, 3H), 3.42 (s, 3H), 3.63 (d, 1H, *J* = 10.4 Hz), 3.73 (m, 2H), 3.90 (m, 1H), 4.07 (m, 2H), 4.41 (bs, 1H), 4.58 (ddd, 1H, *J* = 3.0, 5.2, 12.0 Hz), 4.80 (bs, 1H), 4.83 (bs, 1H), 5.35 (dd, 1H, *J* = 7.6, 9.6 Hz), 6.00 (bs, 1H), 6.30 (s, 1H), 7.17 (d, 1H, *J* = 9.6 Hz), 11.2 (s, 1H); 13C NMR (CD3OD) δ 9.9, 10.8, 13.6, 23.2, 23.5, 29.5, 30.5, 34.2, 38.9, 40.1, 42.9, 56.2, 58.1, 72.5, 72.7, 73.2, 74.5, 79.9, 80.1, 82.5, 83.1, 101.4, 101.6, 113.4, 115.2, 141.2, 144.0, 163.8, 164.9, 172.6, 176.2; IR νmax 3396, 2931, 1652, 1511, 1462, 1376, 1254, 1173, 1108, 1067 cm-1; MS (ES) calculated for C31H47O11Na [MNa]+ 632.30, found 632.25.

(4*R*,6*R*)-4-((*tert*-butyldimethylsilyl)oxy)-6-((2*R*,3*S*)-2-hydroxy-3-methylpent-4-yn-1-yl)-5,5-dimethyltetrahydro-2H-pyran-2-yl acetate (3.70)

An oven-dried, 100-ml flask is charged with **3.57** (3.44 g, 10.0 mmol) and the (*R*)-3-Butyn-2-yl methanesulfonate (**3.74**, 1.64 g, 11.0 mmol) under Argon. THF (35 mL) and HMPA (9.0 mL) are added via syringe. To the solution was added $PdCl_2$(dppf) (364 mg, 0.5 mmol), immediately followed by indium(I) iodide (2.90 g, 12.0 mmol). The resultant dark suspension is stirred vigorously for 1 hr. The reaction mixture is quenched by the addition of H_2O (40 mL) and ether (30 mL) is added. The aqueous layer is extracted with EtOAc (3 × 30 mL) and the combined extracts are dried over anhydrous $MgSO_4$. Filtration of the solution and concentration of the filtrate under reduced pressure followed by purification of the crude product by flash chromatography on silica gel provide 2.65-2.80 g (66-70%) of **3.70** (R_f =

0.35, hexanes: EtOAc = 4:1) as colorless oil of a mixture of two epimers and used without further separation.

The compound with axial OAc has ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.07 (dd, *J* = 3.8, 1.3 Hz, 1H), 3.80 (m, 1H), 3.68 (m, 1H), 2.46 (m, 1H), 2.11 (s, 1H), 2.06 (s, 3H); the compound with equatorial OAc has ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.09 (dd, *J* = 4.0, 1.2 Hz, 1H), 3.71 (m, 1H), 3.54 (m, 1H) 2.46 (m, 1H), 2.08 (s, 1H), 2.04 (s, 3H); IR: 3500, 3311, 2883, 2858, 1749, 1472, 1371, 1252, 1215, 1157, 1134, 1118, 1083, 1047, 1013, 960, 890, 837 cm^{-1}.

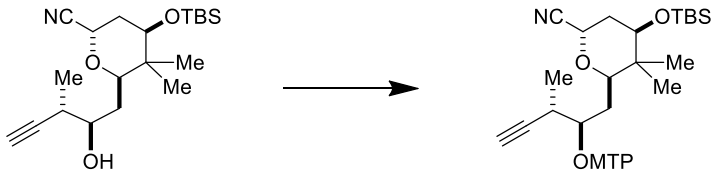
(2*S*,4*R*,6*R*)-4-((*tert*-butyldimethylsilyl)oxy)-6-((2*R*,3*S*)-2-hydroxy-3-methylpent-4-yn-1-yl)-5,5-dimethyltetrahydro-2H-pyran-2-carbonitrile (3.75)

TMSCN (3.72 mL, 28.0 mmol) was added to **3.70** (2.79 g, 7.0 mmol) and stirred at room temperature for 15 min. After cooled to 0 ^oC, MeCN (80 mL), TMSCN (1.86 mL, 14.0 mmol) and ZnI_2 (443 mg, 0.36 mmol) were added successively and stirred for 40 min. Sat. $NaHCO_3$ solution (100 mL) was added and the reaction was extracted with EtOAc (3 × 60 mL). The combined organic extracts were shaken with 1 N HCl (60 mL) for 20 min and washed with aq. $NaHCO_3$ and water and dried over $MgSO_4$. After concentration, the residue obtained was purified by FC (silica gel; hexanes/EtOAc, 8:1 to 4:1) to give compound **3.75** (R_f = 0.45, hexanes: EtOAc = 4:1, 2.00-2.07 g, 78-81%) as a colorless oil.

The compound **3.75** has $[\alpha]^{24}_D$ = +47.1 ($CDCl_3$, *c* = 0.17); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.84 (dd, *J* = 6.0, 1.5 Hz, 1H), 3.78 (dd, *J* = 10.4, 1.8 Hz, 1H), 3.72 (m, 1H), 2.50 (qdd, *J* = 7.1, 4.6, 2.3 Hz, 1H), 2.14 (s, 1H), 1.97 (m, 2H), 1.77 (ddd, *J* = 13.6, 4.6, 1.6 Hz, 1H), 1.79 (m, 1H), 1.56 (m, 1H), 1.23 (d, *J* = 1.2 Hz, 3H), 0.91 (s, 3H), 0.88 (s, 9H), 0.82 (s, 3H), 0.08

(s, 3H), 0.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ118.0, 85.3, 78.5, 72.6, 71.3, 70.7, 64.0, 60.2, 39.8, 34.7, 33.9, 26.0, 22.8, 21.3, 18.2, 17.6, 14.6, 12.3, -4.0, -4.7. IR: 3522, 3311, 2957, 2932, 2858, 1732, 1652, 1472, 1372, 1258, 1162, 1083, 1028, 963, 878, 838, 776 cm^{-1}; MS (ES) calculated for $C_{20}H_{35}NO_3SiNa$ $[M + Na]^+$ 388.2, found 388.30.

Determination of the Absolute Configuration of the Secondary Alcohol in 3.66

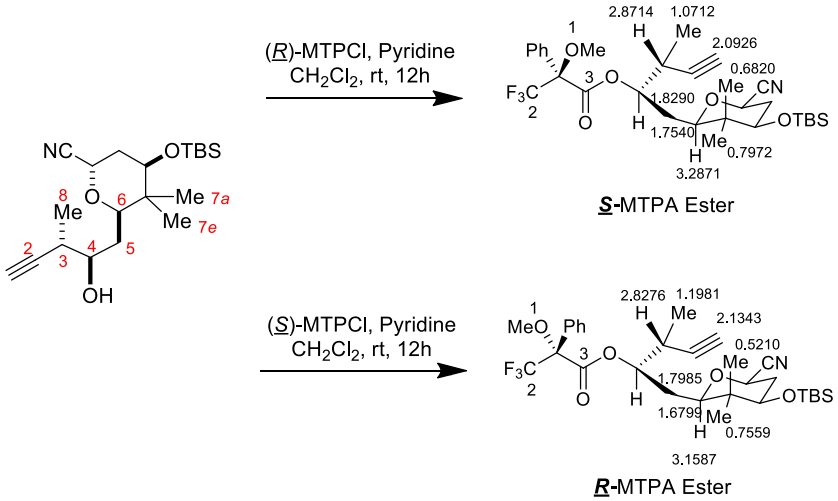


According to the literature[7], preparation of *S*-MTPA ester **3.76a** was from **3.76** with the *R*-acid chloride, and preparation of R-MTPA ester **3.76b** was from **3.76** with the *S*-acid chloride.

The compound **3.76a**: To a solution of **3.76** (10 mg, 0.027 mmol) in dry CH_2Cl_2 (2 mL), was added dry pyridine (22 μL, 0.27 mmol) and *R*-acid chloride (52μL, 0.27 mmol). The resultant solution was stirred for 12h at that point the TLC plate indicated all the **3.76** was consumed. EtOAc (10 mL) and sat. $NaHCO_3$ solution (10 mL) was added and the reaction was extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried over $MgSO_4$. After concentration, the crude **3.76a** was clean enough for characterization.

The compound **3.76b** was made by the same procedure with *S*-acid chloride.

The ^{1}H NMR data of the Mosher's Ester (400MHz, $CDCl_3$):



Terminal alkyne side chain:

Δδ(C1) = δS-ester – δR-ester = 2.0926 – 2.1343 = -0.0417

Δδ(C3) = δS-ester – δR-ester = 2.8714 – 2.8276 = 0.0438

Δδ(C8) = δS-ester – δR-ester = 1.0712 – 1.1981 = -0.1269

THP side chain

Δδ(C5a) = δS-ester – δR-ester = 1.8290 – 1.7985 = 0.0305

Δδ(C5b) = δS-ester – δR-ester = 1.7540 – 1.6799 = 0.0741

Δδ(C6) = δS-ester – δR-ester = 3.2871 – 3.1587 = 0.1284

Δδ(C7*a*) = δS-ester – δR-ester = 0.6820 – 0.5210 = 0.1610

Δδ(C7*e*) = δS-ester – δR-ester = 0.7972 – 0.7559 = 0.0413

Conclusion: According to the ^{1}H NMR data, the absolute configuration is *R* (1, 2-*anti*).

(2*S*,3*S*)-1-((2*R*,4*R*,6*S*)-4-((*tert*-butyldimethylsilyl)oxy)-6-cyano-3,3-dimethyltetrahydro-2H-pyran-2-yl)-3-methylpent-4-yn-2-yl 4-nitrobenzoate (3.78)

The Mitsunobu conversion of the hindered secondary alcohol **376** was difficult. The initial

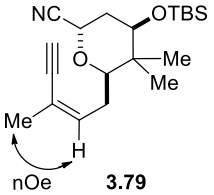
efforts with regular conditions[8] (table 3, entry 1-4) resulted in either recovering starting material at room temperature or leading to elimination at 60 ^{o}C. According to the literature,[32] the combination of TMAD and 4-MeOBzOH was a good choice for conversion of the hindered secondary alcohol. However, with our substrate (entry 5), it only led to elimination. Finally, we figured out the condition (entry 6, TMAD, 4-NO_2BzOH) could convert the configuration.

Procedure: Under dry Ar atmosphere, solid TMAD (1.05 g, 6.0 mmol) was added in one portion to the dry benzene solution (15 mL) of **3.76** (1.10 g, 3.0 mmol), TBP (1.5 mL, 6.0 mmol) and a carboxylic acid (1.0 g, 6.0 mmol) at 0 ^{o}C with stirring. After 10 min, the reaction mixture was heated at 60 ^{o}C for 24 h with stirring, EtOAc (100 mL) and sat. $NaHCO_3$ solution (100 mL) was added and the reaction was extracted with EtOAc (3 × 60 mL). The combined organic extracts were dried over $MgSO_4$. After concentration, the residue obtained was purified by FC (silica gel; hexanes/EtOAc, 8:1 to 4:1) to give compound **3.78** (R_f = 0.45, hexanes: EtOAc = 4:1, 1.30-1.35 g, 87-90%) as a colorless oil.

Compound **3.78** has $[\alpha]_{24}^{D}$ = +36.8 ($CDCl_3$, *c* = 0.15); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (m, 4H), 5.40 (dt, *J* = 10.6, 3.4 Hz, 1H), 4.83 (d, *J* = 3.2 Hz, 1H), 3.58 (dd, *J* = 11.5, 4.6 Hz, 1H), 3.45 (dd, *J* = 10.8, 1.8 Hz, 1H), 2.85 (ddd, *J* = 9.6, 4.5, 2.6 Hz, 1H), 2.16 (s, 1H), 2.10 (m, 1H), 1.91 (m, 2H), 1.71 (dd, *J* = 4.5, 1.7 Hz, 1H), 1.24 (d, *J* = 3.2 Hz, 3H), 0.92 (s, 3H), 0.90 (s, 9H), 0.86 (s, 3H), 0.08 (s, 3H), 0.08 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.2, 150.8, 135.8, 131.1, 123.8, 117.4, 84.1, 77.7, 73.2, 72.5, 71.1, 64.0, 39.8, 33.8, 31.7, 31.3, 25.9, 22.8, 18.2, 17.3, 12.6, -4.0, -4.8. IR: 3294, 2956, 2933, 2858, 1731, 1608, 1529, 14712, 1350, 1319, 1162, 1103, 1083, 1014, 959, 903, 875 840, 777 cm^{-1}. MS (ES) calculated for $C_{27}H_{39}O_6N_2Si$

$[M + H]^+$ 515.3, found 515.4.

(2*S*,4*R*,6*R*)-4-((*tert*-butyldimethylsilyl)oxy)-5,5-dimethyl-6-((*Z*)-3-methylpent-2-en-4-yn-1-yl)tetrahydro-2H-pyran-2-carbonitrile (3.79)



3.79

The compound **3.79** was formed under the conditions in entry 2, 4 or 5.

Compound **3.79** has ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.80 (dt, *J* = 7.2, 2.0 Hz, 1H), 4.86 (m, 1H), 3.66 (dd, *J* = 11.5, 4.6 Hz, 1H), 3.49 (dd, *J* = 10.0, 2.4 Hz, 1H), 3.12 (s, 1H), 2.61 (m, 1H), 2.31 (m, 1H), 1.98 (m, 1H), 1.86 (s, 3H), 1.78 (m, 1H), 0.95 (s, 3H), 0.89 (s, 9H), 0.86 (s, 3H), 0.07 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.1, 118.7, 117.8, 82.8, 81.8, 81.4, 72.4, 63.8, 55.4, 39.8, 33.6, 30.8, 25.7, 22.9, 17.9, 12.4, -4.2, -5.0; MS (ES) calculated for $C_{20}H_{34}O_2NSi$ $[M + H]^+$ 348.23, found 348.30.

Note: the 1D-NOE interaction between Me and H in the olefin was observed.

Ethyl 2-((3*S*,4*S*)-5-((2*R*,4*R*,6*S*)-4-((*tert*-butyldimethylsilyl)oxy)-6-cyano-3,3-dimethyl tetrahydro-2H-pyran-2-yl)-3-methyl-4-((4-nitrobenzoyl)oxy)pent-1-yn-1-yl)-4,6-dimethoxy-3-methylbenzoate

To a solution of **3.78** (514 mg, 1.0 mmol) and aryl trifilate **3.68** (409 mg, 1.1 mmol) in dry DMF (10 mL) , $PdCl_2(PPh_3)_2$ (35 mg, 0.05 mmol) and CuI (19 mg, 0.1 mmol) was added in one protion and followed by Et_3N (505 mg, 5.0 mmol). The resulting mixture was stirred at

40 ^{o}C for 12 h under Ar. EtOAc (20 mL) and $NaHCO_3$ (20 mL) was added to quench the reaction after TLC indicates all starting matrials were consumed. The aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried over $MgSO_4$. After concentration, the residue obtained was purified by FC (silica gel; hexanes/EtOAc, 6:1 to 3:1) to give compound **i** (R_f = 0.40, hexanes: EtOAc = 4:1, 581-603 mg, 80-83%) as a colorless oil.

This compound has $[\alpha]_{24}^{D}$ = +22.6 ($CDCl_3$, *c* = 0.1). IR: 3935, 2858, 2359, 1728, 1587, 1529, 1471, 1438, 1334, 1202, 1152, 1102, 1083, 1028, 1014, 876, 838, 777, 720 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (m, 4H), 6.43 (s, 1H), 5.47 (dt, *J* = 10.2, 3.0 Hz, 1H), 4.83 (d, *J* = 5.9 Hz, 1H), 4.32 (qd, *J* = 8.2, 7.0, 2.3 Hz, 2H), 3.85 (s, 3H), 3.82 (s, 3H), 3.58 (dd, *J* = 11.6, 4.6 Hz, 1H), 3.45 (d, *J* = 10.7 Hz, 1H), 3.07 (dd, *J* = 6.9, 3.3 Hz, 1H), 2.25 (s, 3H), 2.23 (m, 1H), 1.93 (m, 2H), 1.72 (m, 1H), 1.33 (t, *J* =7.2 Hz, 3H), 1.30 (d, *J* = 7.8 Hz, 3H), 0.97 (s, 3H), 0.94 (s, 9H), 0.92 (s, 3H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.9, 164.4, 159.4, 155.6, 150.8, 135.8, 131.3, 123.8, 122.4, 121.5, 118.8, 117.4, 97.0, 95.8, 79.4, 77.3, 77.0, 73.5, 72.5, 64.1, 64.0, 61.5, 56.6, 56.0, 39.8, 33.9, 32.6, 26.0, 22.8, 18.2, 17.8, 14.9, 14.55, 13.5, 12.5, -3.9, -4.7; MS (ES) calculated for $C_{39}H_{52}O_{10}N_2SiK$ $[M + K]^+$ 775.3, found 775.5.

(2*S*,4*R*,6*R*)-4-((*tert*-butyldimethylsilyl)oxy)-6-((2*S*,3*R*)-3-((*R*)-6,8-dimethoxy-5-methyl-1-oxoisochroman-3-yl)-2-hydroxybutyl)-5,5-dimethyltetrahydro-2H-pyran-2-carbonitrile (3.87)

To a solution of **i** (298 mg, 0.41 mmol) in MeOH (10 mL) was added aq. LiOH (1 M, 4 mL) at 0 ^{o}C. The resulting solution was stirred at 0 ^{o}C for overnight. Then EtOAc (20 mL) and NH_4Cl

(20 mL) was added. The organic phase was seperated. The aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried over $MgSO_4$. After concentration, the residue obtained **3.83** (227 mg, 99%) was used without purification.

To a solution of **3.83** (150 mg, 0.55 mmol) in CH_2Cl_2 (5 mL), the $AuNTf_2$(xPhos) (14 mg, 0.014 mmol) was added in one portion under Ar. The resultant solution was stirred at room temperature and the reaction was monitored by TLC plate. After 1 h, all the starting material was consumed. The additional CH_2Cl_2 (15 mL) was added followed by H_2O (15 mL). After 5 min, the crude was extracted with EtOAc and the combined organic extracts were washed with water and dried over $MgSO_4$. After concentration, the residue (**3.85**, unstable) was used for next step intermediately without further purification.

The crude residue was dissolved in CH_2Cl_2 (4 mL), the carbtree's catalyst (**3.86**, 22 mg, 0.027 mmol) was added under H_2 (1 atm). The reaction was stirred for 24 h at room temperature. The additional CH_2Cl_2 (10 mL) was added followed by H_2O (15 mL). After 5 min, the crude was extracted with EtOAc and the combined organic extracts were washed with water and dried over $MgSO_4$. The residue obtained was purified by FC (silica gel; CH_2Cl_2/MeOH 10:1) to give **3.87** (R_f = 0.25, hexanes: EtOAc = 4:1, 112-119 mg) in a 74-79% overall yield.

The compound **3.87** has $[\alpha]_{22}^{D}$ = +18.4 ($CDCl_3$, *c* = 0.11); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.51 (s, 1H), 4.84 (dd, *J* = 6.3, 1.4 Hz, 1H), 4.43 (ddd, *J* = 11.8, 5.2, 1.8 Hz, 1H), 4.06 (br, 1H), 3.85 (s, 3H), 3.81 (s, 3H), 3.66 (m, 2H), 2.84 (m, 2H), 2.20 (s, 3H), 1.96 (m, 2H), 1.78 (m, 3H), 1.10 (d, *J* = 6.9 Hz, 3H), 0.90 (s, 3H), 0.85 (s, 9H), 0.82 (s, 3H), 0.12 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5, 161.1, 160.0, 141.7, 117.5, 116.1, 107.5, 96.1,

82.9, 78.7, 73.6, 71.1, 63.8, 55.0, 54.1, 41.5, 40.1, 31.8, 31.5, 30.0, 25.1, 22.5, 18.0, 12.7, 11.0, 8.9, -6.1, -5.3; MS (ES) calculated for $C_{30}H_{47}O_7NSiNa$ $[M + Na]^+$ 584.3, found 584.3.

(2*S*,4*R*,6*R*)-6-((2*S*,3*R*)-3-((*R*)-6,8-dihydroxy-5-methyl-1-oxoisochroman-3-yl)-2-hydroxy butyl)-4-hydroxy-5,5-dimethyltetrahydro-2H-pyran-2-carbonitrile (3.88)

To a solution of **3.87** (100 mg, 0.18 mmol) in CH_2Cl_2 (5 mL) was added a solution of BBr_3 (1.07 mL, 1 M in CH_2Cl_2, 1.07 mmol) at –78 ^oC. After stirring at −78 ^oC for 30 min, 0 ^oC for 4 h and 25 ^oC for 1 h, water was added at 0 ^oC and the crude was extracted with CH_2Cl_2. The combined extracts were washed with water, dried over $MgSO_4$ and concentrated. The residue obtained was dissolved in THF (10 mL), added TBAF (1.0 M in THF, 50 μL, 0.05 mmol) at room temperature. After 2 h, the reaction was concentrated and the residue was purified by FC (silica gel; hexanes/EtOAc, 1:2 to EtOAc) to give **3.88** (R_f = 0.15, CH_2Cl_2: MeOH = 10:1; 53-55 mg, 72-73%).

Compound **3.88** has $[\alpha]_{22}^D$ = +32.1 ($CDCl_3$, *c* = 0.19); ^1H NMR (500 MHz, $CDCl_3$) δ 11.24 (s, 1H), 6.32 (s, 1H), 5.63 (s, 1H), 4.97 (dd, *J* = 6.0, 1.6 Hz, 1H), 4.62 (ddd, *J* = 12.0, 5.2, 3.5 Hz, 1H), 4.14 (m, 2H), 3.78 (m, 2H), 3.52 (s, 3H), 2.97 (m, 3H), 2.14 – 1.95 (m, 8H), 1.82 – 1.72 (m, 3H), 1.32 – 1.25 (m, 4H), 1.20 – 1.13 (d, *J* = 6.9 Hz, 3H), 1.05 (s, 3H), 0.97 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 162.6, 161.0, 140.0, 117.7, 113.2, 104.8, 101.6, 83.4, 80.4, 77.0, 72.1, 71.8, 64.3, 42.1, 39.8, 33.0, 32.8, 28.5, 22.5, 12.4, 9.3; MS (ES) calculated for $C_{22}H_{30}O_7N$ $[M + H]^+$ 420.19, found 420.20.

Psymberin (1.1)

This reaction was conducted at a 50 μmol scale, 55% yield (*dr* ~ 3:1). The second synthetic psymberin was fully characterized by proton and carbon NMR (in $CDCl_3$ and CD_3OD, respectively), rotation, IR and LC-MS. All the data are matched with natural and first synthetic psymberin.

$[\alpha]^{23}_D$= +21.8 (MeOH, *c* = 0.10);

IR ν_{max} 3368, 2932, 1660, 1652, 1622, 1506, 1456, 1378, 1253, 1174, 1108, 1069, 973, 896 cm^{-1};

MS (ES) calculated for $C_{31}H_{47}O_{11}Na$ $[M+Na]^+$ 632.30, found 632.25.

^1H NMR (400MHz, CD_3OD): 6.23 (s, 1H), 5.37 (d, *J* = 8.2 Hz, 1H), 4.70 (m, 2H), 4.47 (ddd, *J* = 12.3, 6.0, 3.0 Hz, 1H), 4.34 (d, *J* = 2.6 Hz, 1H), 3.92 (m, 2H), 3.65 (ddd, *J* = 9.6, 2.5, 3.4 Hz, 1H), 3.58 (dd, *J* = 11.2, 4.7 Hz, 1H), 3.47 (dd, *J* = 10.2, 1.0 Hz, 1H), 3.34 (s, 3H), 3.18 (s, 3H), 3.10 (dd, *J* = 18.0, 3.0 Hz, 1H), 2.82 (dd, *J* = 16.8, 12.3 Hz, 1H), 2.33 (dd, *J* = 14.7, 9.3 Hz, 1H), 2.09 (s, 3H), 2.08 (m, 1H), 1.99 (ddd, *J* = 13.2, 4.5, 2.4 Hz, 1H), 1.87 (m, 1H), 1.75 (m, 3H), 1.69 (s, 3H), 1.08 (d, *J* = 6.9 Hz, 3H), 0.96 (s, 3H), 0.88 (s, 3H).

^{13}C NMR (125 MHz, CD_3OD): 174.7, 170.9, 163.1, 162.2, 142.4, 139.7, 113.8, 111.6, 99.95, 99.89, 81.2, 80.7, 80.5 78.3, 72.3, 72.0, 71.8, 70.5, 56.2, 55.1, 41.8, 38.3, 37.2, 32.9, 29.0, 28.0, 22.2, 21.5, 12.7, 9.4, 7.7.

^1H NMR (400 MHz, $CDCl_3$): 11.12 (s, 1H), 7.08 (d, *J* = 10.0 Hz, 1H), 6.32 (s, 1H), 5.44 (dd, *J* = 10.2, 8.3 Hz, 1H) 4.80 (bs, 2H), 4.54 (dt, *J* = 11.9, 4.1 Hz, 1H), 4.38 (d, *J* = 3.1 Hz, 1H), 4.13 (d, *J* = 2.6 Hz, 1H), 3.95 (m, 1H), 3.89 (m, 1H), 3.73 (m, 1H), 3.73 (m, 1H), 3.54 (d, *J* = 10.8 Hz, 1H), 3.38 (s, 3H), 3.38 (s, 3H), 2.90 (m, 1H), 2.83 (m, 1H), 2.36 (dd, *J* = 15.0, 4.6 Hz, 2H), 2.18 (m, 1H), 2.06 (m, 1H), 2.03 (s, 3H), 1.84 (m, 1H), 1.80 (m, 1H), 1.78 (s, 3H),

1.62 (m, 2H), 1.0 (d, J = 7.0 Hz, 3H), 0.98 (s, 3H), 0.92 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): 173.5, 170.6, 162.2, 160.9, 142.1, 139.5, 113.4, 113.0, 101.3, 101.1, 81.9, 80.6, 79.6, 78.4, 74.0, 73.3, 73.0, 71.3, 58.1, 56.2, 42.6, 38.7, 37.5, 32.2, 29.7, 28.4, 23.0, 22.7, 13.7, 10.4, 9.2.

Table 6. Comparisons of the ^{1}H NMR spectra (in CD_3OD) of natural, first and second generation synthetic psymberin

Entry	Natural	1st Synthetic	2nd Synthetic
1	6.22 (s, 1H)	6.25 (s, 1H)	6.23 (s)
2	5.36 (d, J=8.0 Hz) 1H	5.38 (d, 1H, *J* = 8.0 Hz)	5.37 (d, *J* = 8.2 Hz, 1H)
3	4.71 (s, 1H), 4.69 (s, 1H)	4.72 (bs, 1H), 4.74 (bs, 1H)	4.70 (m, 2H)
4	4.46 (ddd, *J* = 3.0, 6.0, 12.0 Hz, 1H)	4.49 (ddd, 1H, *J* = 3.2, 6.0, 12.2 Hz),	4.47 (ddd, *J* = 12.3, 6.0, 3.0 Hz, 1H)
5	4.33 (d, *J* = 2.5 Hz, 1H)	4.35 (d, 1H, *J* = 2.4 Hz)	4.34 (d, *J* = 2.6 Hz, 1H)
6	3.91 (ddd, *J* = 3.0, 6.0, 8.0 Hz, 1H) + 3.91 (m, 1H)	3.94 (m, 2H)	3.92 (m, 2H)
7	3.65 (ddd, *J* = 2.5, 3.5, 9.5 Hz, 1H)	3.67 (ddd, 1H, *J* = 2.8, 3.2, 9.4 Hz)	3.65 (ddd, *J* = 9.6, 2.5, 3.4 Hz, 1H)
8	3.57 (dd, *J* = 4.5, 11.0 Hz, 1H)	3.59 (dd, 1H, *J* = 4.2, 11.0 Hz)	3.58 (dd, *J* = 11.2, 4.7 Hz, 1H)
9	3.47 (dd, *J* = 1.0, 11.0 Hz, 1H)	3.50 (dd, 1H, *J* = 1.6, 11.2 Hz)	3.47 (dd, *J* = 10.2, 1.0 Hz, 1H)
10	3.33 (s, 3H)	3.35 (s, 3H)	3.34 (s, 3H)
11	3.18 (s, 3H)	3.21 (s, 3H)	3.18 (s, 3H)
12	3.11 (dd, *J* = 3.0, 17.0 Hz, 1H)	3.13 (dd, 1H, *J* = 3.2, 16.6 Hz)	3.10 (dd, *J* = 18.0, 3.0 Hz, 1H)
13	2.83 (dd, *J* = 12.0, 17.0 Hz, 1H)	2.85 (dd, 1H, *J* = 12.2, 16.6 Hz)	2.82 (dd, *J* = 16.8, 12.3 Hz, 1H)
14	2.32 (dd, *J* = 9.5, 14.5 Hz, 1H)	2.35 (dd, 1H, *J* = 9.4, 14.4 Hz)	2.33 (dd, *J* = 14.7, 9.3 Hz, 1H)
15	2.08 (s, 3H)	2.10 (s, 3H)	2.09 (s, 3H)
16	2.06 (dd, *J* = 3.5, 14.5 Hz,	2.08 (dd, 1H, *J* = 3.2, 14.4	2.08 (m, 1H)

	1H)	Hz)	
17	1.98 (ddd, *J* = 2.5, 4.5, 13.5 Hz, 1H)	2.01 (ddd, 1H, *J* = 2.8, 4.2, 13.2 Hz)	1.99 (ddd, *J* = 13.2, 4.5, 2.4 Hz, 1H)
18	1.87 (ddq, *J* = 2.0, 6.0, 6.0, 1H)	1.91 (ddq, 1H, *J* = 2.4, 6.0, 6.8 Hz)	1.87 (m, 1H)
19	1.75 (ddd, *J* = 6.0, 11.0, 13.5 Hz, 1H) + 1.75 (m, 2H)	1.77 (ddd, 1H, *J* = 6.4, 11.0, 13.2 Hz) + 1.74 (m, 2H)	1.75 (m, 3H)
20	1.69 (s, 3H)	1.71 (s, 3H)	1.69 (s, 3H)
21	1.07 (d, *J* = 6.5 Hz, 3H)	1.09 (d, 3H, *J* = 6.8 Hz)	1.08 (d, *J* = 6.9 Hz, 3H)
22	0.95 (s, 3H)	0.97 (s, 3H)	0.96 (s, 3H)
23	0.87 (s, 3H)	0.89 (s, 3H)	0.88 (s, 3H)

Table 7. Comparisons of the ^{1}H NMR spectra (in $CDCl_3$) of natural, first and second generation synthetic psymberin

Entry	Natural	1st Synthetic	2nd Synthetic
1	11.13 (s)	11.15 (bs, 1H)	11.12 (s, 1H)
2	7.09 (d)	7.09 (d, 1H, *J* = 10.0 Hz)	7.08 (d, *J* = 10.0 Hz, 1H)
3	6.31 (s)	6.30 (s, 1H)	6.32 (s, 1H)
4	5.45 (t, J = 4.5)	5.45 (dd, 1H, *J* = 8.8, 10.0 Hz)	5.44 (dd, *J* = 10.2, 8.3 Hz, 1H)
5	4.80 (s)	4.80 (bs, 2H)	4.80 (bs, 2H)
6	4.53 (m)	4.54 (ddd, 1H, *J* = 4.0, 4.8, 12.0 Hz)	4.54 (dt, *J* = 11.9, 4.1 Hz, 1H)
7	4.36 (s)	4.40 (d, 1H, *J* = 3.2 Hz)	4.38 (d, *J* = 3.1 Hz, 1H)
8	4.11 (d, J = 2.5)	4.12 (d, *J* = 2.8, 1H)	4.13 (d, J = 2.6 Hz, 1H)
9	3.96 (m)	3.95 (dm, 1H, *J* = 8.8 Hz)	3.95 (m, 1H)
10	3.89 (m)	3.88 (ddd, 1H, *J* = 2.4, 6.4, 8.0 Hz)	3.89 (m, 1H)
11	3.74 (m)	3.74 (ddd, 1H, *J* = 3.2, 4.0, 8.8 Hz)	3.73 (m, 1H)
12	3.67 (dd, J = 4.0, 10.5)	3.67 (dd, 1H, *J* = 4.4, 11.8 Hz)	3.73 (m, 1H),
13	3.53 (d, J = 10.5 Hz)	3.53 (d, 1H, *J* = 10.0 Hz),	3.54 (d, *J* = 10.8 Hz, 1H)
14	3.38 (s)	3.38 (s, 3H)	3.38 (s, 3H)
15	3.38 (s)	3.38 (s, 3H),	3.38 (s, 3H)
16	2.89 (m)	2.91(dd, 1H, *J* = 4.0, 16.8 Hz)	2.90 (m, 1H)
17	2.82 (m)	2.82 (dd, 1H, *J* = 12.0, 16.8 Hz)	2.83 (m, 1H)
18	2.38 (dd, J = 4.0, 15 Hz)	2.37 (dd, 1H, *J* = 8.8, 14.6 Hz)	2.36 (dd, J= 15.0, 4.6 Hz, 2H)
19	2.18 (m)	2.18 (dd, 1H, *J* = 4.0, 14.6 Hz)	2.18 (m, 1H)

20	2.06 (m)	2.07 (m, 1H)	2.06 (m, 1H)
21	2.02 (s)	2.04 (s, 3H)	2.03 (s, 3H)
22	1.84 (m)	1.88 (m, 1H)	1.84 (m, 1H)
23	1.81 (m)	1.80 (m, 1H)	1.80 (m, 1H)
24	1.76 (s)	1.76 (s, 3H)	1.78 (s, 3H)
25	1.62 (m)	1.62 (m, 2H)	1.62 (m, 2H)
26	1.1 (d, J = 6.0 Hz)	1.09 (d, 3H, *J* = 7.2 Hz)	1.0 (d, *J* = 7.0 Hz, 3H)
27	0.97 (s)	0.98 (s, 3H)	0.98 (s, 3H)
28	0.92 (s)	0.92 (s, 3H)	0.92 (s, 3H)

Table 8. Comparisons of the ^{13}C NMR spectra (in CD_3OD) of natural, first and second generation synthetic psymberin

Entry	Natural	1st Synthetic	2nd Synthetic
1	174.6	174.9	174.7
2	170.9	171.0	170.9
3	163.1	163.1	163.1
4	162.2	162.3	162.2
5	142.4	142.2	142.4
6	139.6	139.7	139.7
7	113.8	113.8	113.8
8	111.5	111.6	111.6
9	99.98	99.9	99.95
10	99.92	99.9	99.89
11	81.2	81.2	81.2
12	80.7	80.8	80.7
13	80.5	80.5	80.5
14	78.4	78.4	78.3
15	72.6	72.8	72.3
16	72.0	72.0	72.0
17	71.9	71.7	71.8
18	70.6	70.6	70.5
19	56.2	56.1	56.2
20	55.0	55.1	55.1
21	41.8	41.8	41.8
22	38.3	38.4	38.3
23	37.2	37.2	37.2
24	32.9	32.9	32.9
25	29.0	29.0	29.0

26	28.0	28.1	28.0
27	22.2	22.2	22.2
28	21.4	21.5	21.5
29	12.6	12.5	12.7
30	9.3	9.4	9.4
31	7.7	7.7	7.7

Table 9. Comparisons of the ^{13}C NMR spectra (in $CDCl_3$) of natural, first and second generation synthetic psymberin

Entry	Natural	1st Synthetic	2nd Synthetic
1	173.5	173.6	173.5
2	170.4	170.5	170.6
3	162.3	162.3	162.2
4	160.1	161.1	160.9
5	142.0	142.0	142.1
6	139.7	139.6	139.5
7	113.2	113.3	113.4
8	113.1	113.0	113.0
9	101.6	101.4	101.3
10	101.3	101.3	101.1
11	81.9	81.9	81.9
12	80.5	80.5	80.6
13	79.4	79.5	79.6
14	78.3	78.2	78.4
15	73.8	73.9	74.0
16	73.1	73.0	73.3
17	73.1	73.0	73.0
18	71.4	71.4	71.3
19	57.9	57.9	58.1
20	56.3	56.2	56.2
21	42.6	42.6	42.6
22	38.8	38.7	38.7
23	37.6	37.5	37.5
24	32.1	32.1	32.2
25	29.7	29.6	29.7

26	28.4	28.4	28.4
27	23.1	23.0	23.0
28	22.7	22.7	22.7
29	13.7	13.5	13.7
30	10.4	10.4	10.4
31	9.4	9.2	9.2

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Chapter 4

Biological Studies toward Psymberin: Structure-Activity Relationships, Biochemical Studies and Genetics Identify the Mode-of-Action of Psymberin

In chapter 3, we described the full structural elucidation and two alternative total syntheses of psymberin (**1.1**),[1] the latest member and a structural outlier of the pederin family of natural products.[2] Our enthusiasm to initiate a comprehensive synthetic and biological evaluation of psymberin was initially dampened by the notion that psymberin shares a common *N*-acyl aminal-substituted tetrahydropyranyl core with all pederin family members, several of which exhibit dermatotoxicity (blistering activity) and pharmacologically act as protein synthesis inhibitors.[3] Our motivation to press forward was based on the following notions. First, without exception, all 36 members of the pederin family,[4] isolated from various sources around the globe, display an identical cyclic pederate side chain – a structural (and evolutionary) conservation which we postulated to be functionally relevant. In contrast, psymberin uniquely possesses a less complex acyclic side chain (psymberate). Second, the dihydroisocoumarin fragment is unique to psymberin, indicating divergent biosynthetic machinery not found in any of the other pederin-type producing organisms.[5] Finally, psymberin was described to exhibit an unprecedented differential cytotoxicity profile,[2] whereas pederin-like compounds display much more uniform cytotoxicity profiles.[6] In light of these observations, we hypothesized that psymberin could be endowed with unique biological activities.

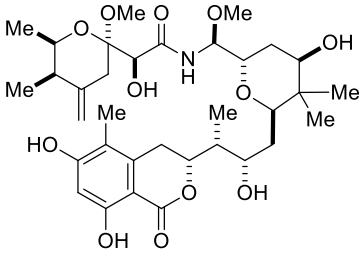
In this chapter, we describe the analogs synthesized by the chemistry community and our, detailed mode-of-action studies through a combination of structure-activity relationships, biochemical studies, and a forward genetic screen in the nematode worm *C. elegans.*

4.1 Psymberin Analogs

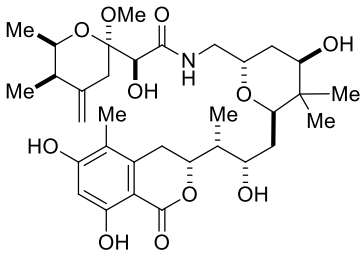
4.1.1 Analogs from other laboratories

To probe the structure-activity relationship for this natural product, a number of analogs have been prepared by the groups of De Brabander,[1, 7] Floreancig,[8] Schering-Plough,[9] Watanabe,[10] Smith,[11] and Pietruszka.[12]

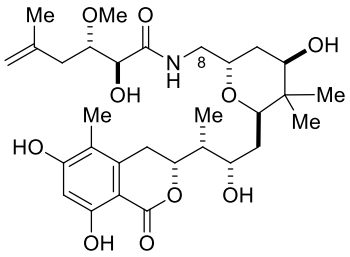
Figure 4. Analogs from Other Laboratories



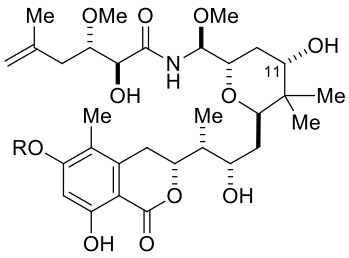
pedestatin **4.1**
(Floreancig, 2011)
GI_{50} 0.004 nM



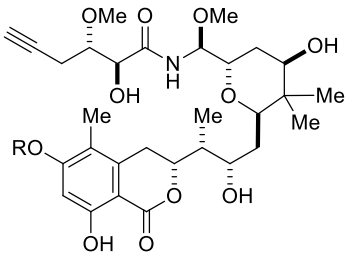
10-desmethoxy pedestatin **4.2**
(Floreancig, 2011)
GI_{50} 0.068 nM



C8-desmethoxy psymberin **4.3**
(Floreancig, 2011, Pietruszka, 2013)
GI_{50} 0.83 nM

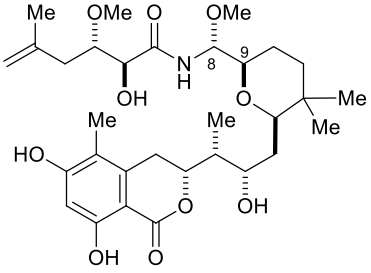


epi-C(11)-psymberin **4.4**
(Smith, 2013)
n.r.

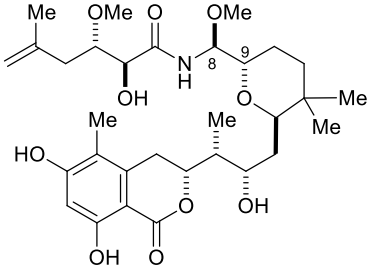


C1-C2 Alkyne Analogue **4.5**
(Watanabe, 2010)
GI_{50} 1.2 nM

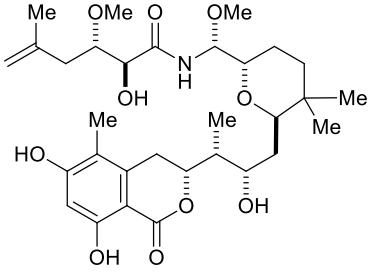
Figure 4. Continued



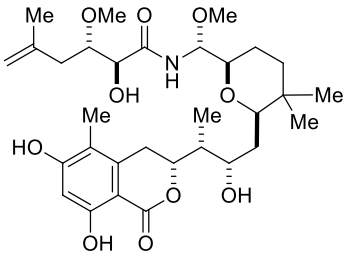
C8,C9-epimer of psymberin **4.6**
(Schering-Plough, 2008)
IC_{50} 4600 nM



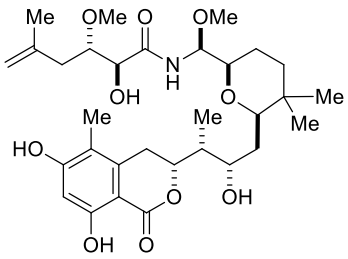
C8*S*, C9*S*, C11-deoxy psymberin **4.6a**
(Schering-Plough, 2008)
IC_{50} 0,055 nM



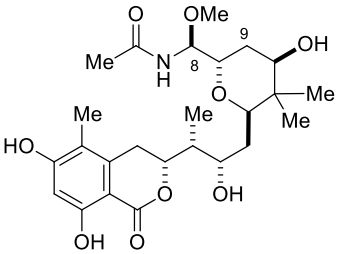
C8*R*, C9*S*, C11-deoxy psymberin **4.6b**
(Schering-Plough, 2008)
IC_{50} 46 nM



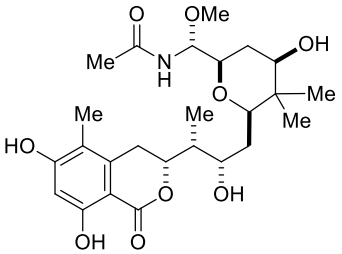
C8*R*, C9*R*, C11-deoxy psymberin **4.6c**
(Schering-Plough, 2008)
IC_{50} 177 nM



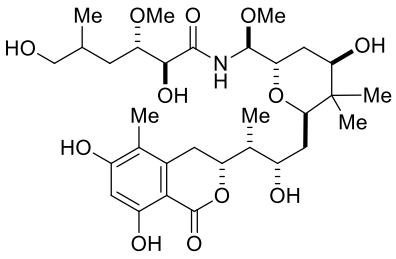
C8*S*, C9*R*, C11-deoxy psymberin **4.6d**
(Schering-Plough, 2008)
IC_{50} 3.0 nM



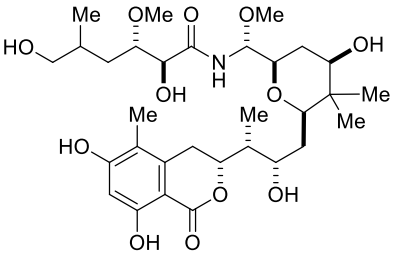
4.7a
(Schering-Plough, 2008)
IC_{50} > 10000 nM



4.7b
(Schering-Plough, 2008)
IC_{50} > 10000 nM

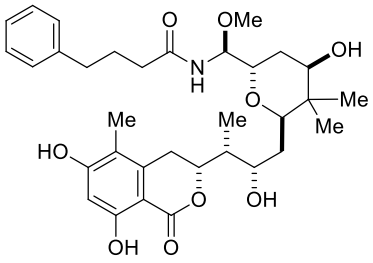


4.8a
(Schering-Plough, 2008)
IC_{50} 260 nM

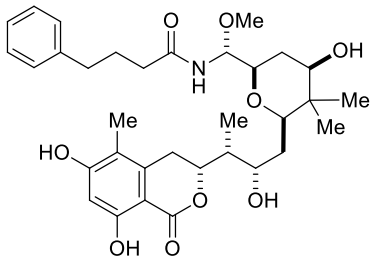


4.8b
(Schering-Plough, 2008)
IC_{50} > 10000 nM

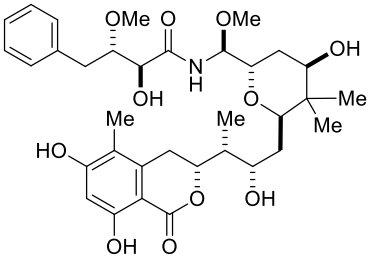
Figure 4. Continued



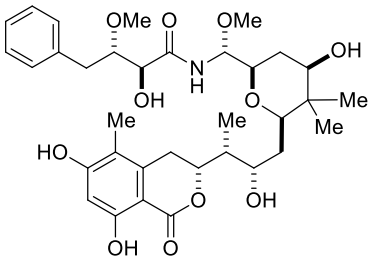
4.9a
(Schering-Plough, 2008)
IC_{50} > 10000 nM



4.9b
(Schering-Plough, 2008)
IC_{50} > 10000 nM



4.10a
(Schering-Plough, 2008)
IC_{50} 32 nM



4.10b
(Schering-Plough, 2008)
IC_{50} 615 nM

It was determined by Floreancig[8] that pedestatin (**4.1**, pederin + irciniastatin) showed extremely strong cytotoxicity (GI_{50} = 0.004 nM) against HCT 116 cells. The test results for the potency of C10-desmethoxy pedestatin **4.2** and C8-desmethoxy psymberin **4.3** against HCT 116 cells (GI_{50} = 0.068 nM for **4.2** and GI_{50} = 0.83 nM for **4.3**) demonstrated that pedestatin and psymberin cores have the ability to provide sufficient cytotoxicity even in the absence of the *N*-acyl aminal motif. It was determined by Watanabe[10] that if the alkene is replaced by an alkyne (**4.5**), the activity is slightly diminished (GI_{50} = 1.2 nM). The C11-deoxypsymberin (**4.6a**) and its three epimers (**4.6b**-**4.6d**) were prepared by the Schering-Plough group.[9] When the four analogs above were subjected to cell proliferation studies in the HOP62 human lung cancer line, the activity of C11-deoxypsymberin (**4.6a**, IC_{50} = 0.055 nM) is consistently more potent than psymberin (**1.1**, IC_{50} = 0.42 nM), and its

epimers (**4.6b**-**4.6d**) also showed activities (IC_{50} = 46, 177 and 3.0 nM, respectively) whereas the C8-C9 epimer of psymberin (**4.6**) produces a remarkable drop in cytotoxicity (IC_{50} = 4200 nM). In addition, to further probe the side chain function, analogs **4.7a/b**-**4.10a/b** were evaluated in the HOP62 human lung cancer line. When the psymberate side chain was truncated to a methyl group, both **4.7a** and **4.7b** lost activity dramatically. The importance of the terminal olefin was then investigated. The activity of hydroxyl terminated psymberin analog **4.8a** (IC_{50} = 260 nM) was 650 folder less than that of psymberin (**1.1**, IC_{50} = 0.42 nM), whereas its C8, C9-epimer **4.8b** was completely devoid of cytotoxic activity. These results indicate that the terminal alkene plays an important role for the activity of pysmberin. To mimic the electronic effect of the double bond, a phenyl ring was installed as the termini. The compounds without substituents at C4 and C5 (**4.9a** and **4.9b**) lost all activity, whereas analog **4.10a** with substituents at C4 and C5, regained its potency (IC_{50} = 32 nM), in contrast, to epimer **4.10b** which showed moderate activity (IC_{50} = 615 nM).

4.1.2 De Brabander's Analogs

As noted in the introduction, psymberin (**1.1**) is structurally distinct from other pederin family members in two important aspects: (1) It lacks the typical cyclic pederate side chain present in all other family members; and (2) psymberin is the only member containing a dihydroisocoumarin side chain.

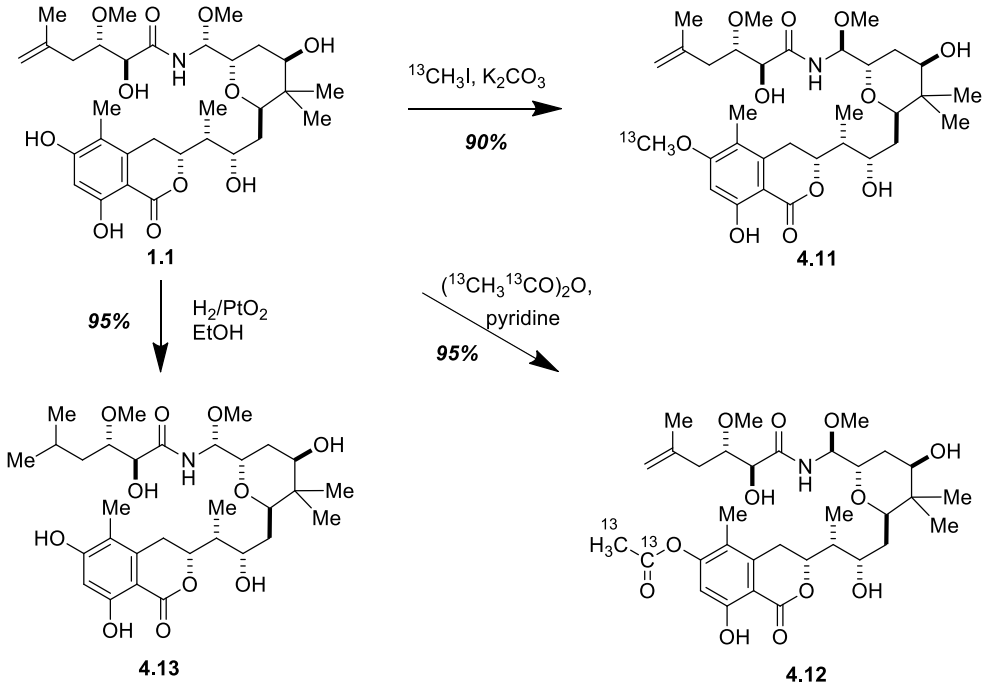
To study meaningful structure-activity relationships of psymberin, several analogs were synthesized[1, 7] to probe the influence of the individual psymberate and dihydroisocoumarin

side chains on biological output as compared to pederin/mycalamide structures containing a cyclic pederate side-chain.

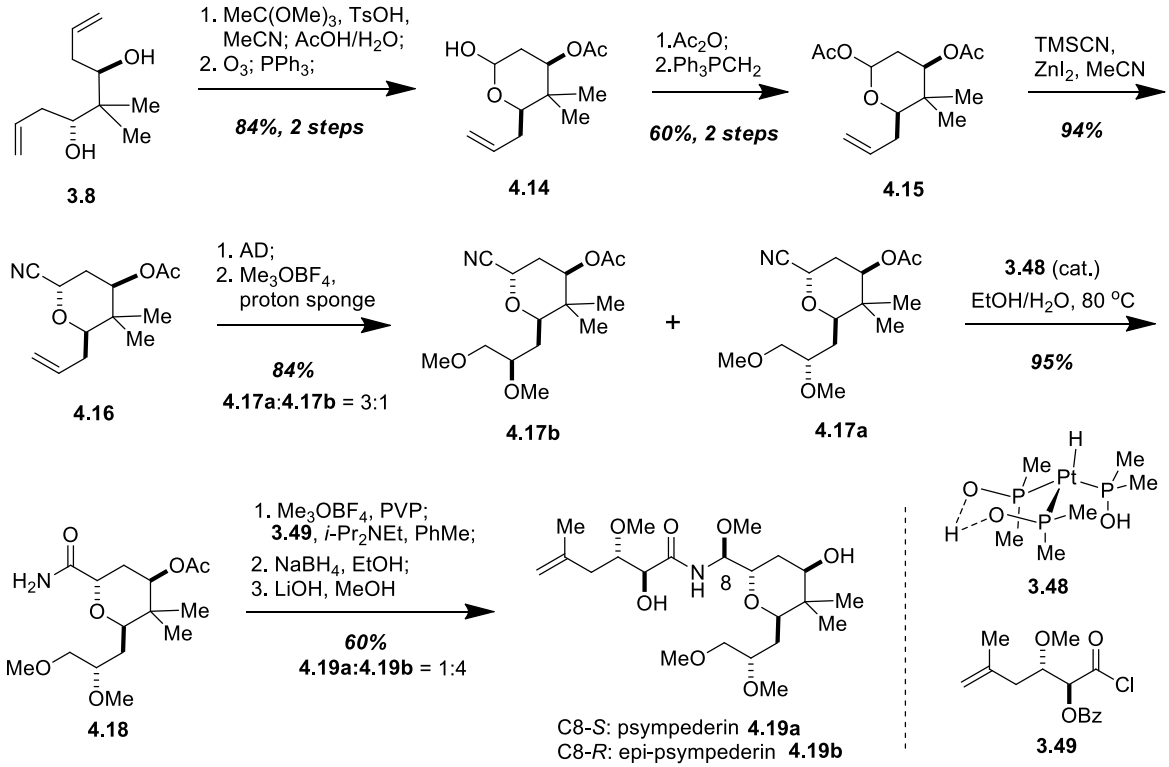
The analogs described in Scheme 40 below (**4.11**-**4.13**) were prepared by me as part of my Ph.D. work. The psymberin analogs **4.19a/b** (psympederins) were prepared preciously by Dr. Xin Jiang in the De Brabander lab.

Initially, ^{13}C phenolic methyl ether **4.11** or acetate **4.12** was prepared via methylation or acetylation of psymberin **1.1** (90−95% yield, Scheme 40). Second, the terminal olefin of **1.1** is distinct from the exocyclic double bond present in other pederin family members. Hydrogenation of the terminal olefin of psymberin would allow for the preparation of a radiolabeled variant for biological studies. Thus, hydrogenation of psymberin (**1.1**) over platinum provides 95% of the corresponding dihydropsymberin **4.13**.

Scheme 40. Synthesis of Methyl-, Acetyl-, and Dihydropsymberin



Scheme 41. Synthesis of Psympederin, a Psymberin-Pederin Hybrid



As mentioned above, to fully assess the importance of psymberin's unique dihydroisocoumarin moiety, De Brabander designed a truncated psymberin analog **4.19a** (Scheme 41) that lacks this fragment, which is in essence also an analog of pederin with the acyclic "psymberate" (C1−C6) side chain substituting for the cyclic "pederate" fragment reminiscent of the pederin/ mycalamide natural products. The synthesis of this analog, termed psympederin, commenced from the C_2-symmetrical *bis*-homoallylic alcohol **3.8**, which was monoacetylated via cyclic orthoacetate formation and hydrolysis under acidic conditions, followed by ozonolytic double-bond cleavage to yield the desymmetrized lactol **4.14** in 84% yield for the two step process. Acylation of lactol **4.14** then permitted olefination of the aldehyde, after which anomeric acetate **4.15** (mixture of anomers) was treated with

trimethylsilyl cyanide[14] in the presence of ZnI_2 to yield a single axial nitrile **4.16** in 94% yield. The dihydroxylation of terminal olefin **4.16** required extensive experimentation to yield an acceptable diastereoselectivity. Dihydroxylation using the UpJohn process[15] (cat. OsO_4, Nmethylmorpholine) revealed an intrinsic facial bias slightly favoring the undesired diastereomer **4.17b** (**4.17a**:**4.17b** = 1:1.4), whereas Sharpless asymmetric dihydroxylation[16] using the $(DHQ)_2PYR$ or $(DHQ)_2PHAL$ ligand was nonselective (1:1 ratio). After some experimentation, it was found that hydroxyquinine 9-phenanthryl ether (HQP ether) was the optimal ligand for the asymmetric dihydroxylation of **4.16**,[17] providing a ~3:1 mixture favoring the desired C_{15}-*S* configuration (**4.17a**). Kocienski and co-workers had previously screened various ligands for the asymmetric dihydroxylation of a closely related substrate (TBS-protected version of **4.16**) and found HQP ether also to be optimal, although selectivity for the desired diastereomer was lower (1.5:1) with their substrate.[18] This inseparable mixture[19] of epimers was treated with Meerwein's salt and proton sponge to afford a separable mixture of methyl ethers **4.17a** and **4.17b**. The stereochemistry was determined by chemical correlation of acetate **4.16** to the corresponding known TBS-ether. Nitrile hydrolysis of the major methyl ether **4.17** with use of the Ghaffar−Parkins catalyst (**3.48**)[20] provided acetylpedamide **4.18** in 95% yield. The final introduction of the C1−C6 "psymberate" side chain was accomplished via the protocol outlined for the synthesis of psymberin (Scheme 30). Thus, acylation of the imidate derived from **4.18** with the acid chloride **3.49** derived from carboxylic acid **3.14** followed by reduction and saponification yielded a separable 1:4 mixture of psympederin **4.19a** and epi-psympederin **4.19b** in 60% yield from acetylpedamide **4.18**.[21] This result is in sharp contrast with the corresponding

psymberin result where the natural methoxyaminal epimer dominated (3:1) and indicates that diastereoselectivity associated with the *N*-acyl imidate reduction is highly dependent on the presence or absence of the dihydroisocoumarin fragment.

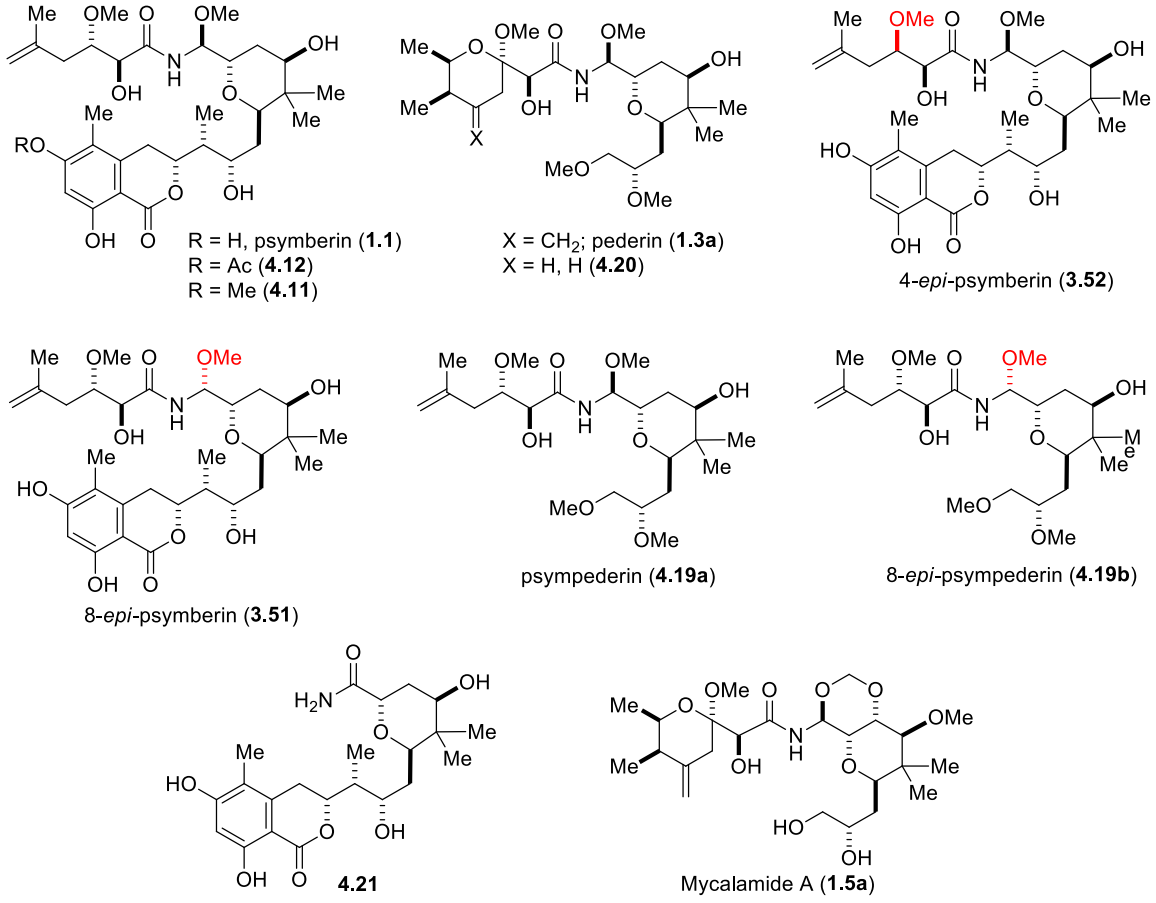
In sections 4.2-4.4 described below, we review the biological studies involving psymberin and related compounds. A full account of the biological studies can be found in the Ph.D. thesis of Dr. Cheng-Yang Wu (title: Using *C. Elegans* as Model Organism to Study the Mode of Action of a Natural Toxin, Psymberin, **2011**). The biological experiments were performed by Dr. Cheng-Yang Wu in the Roth lab (department of biochemistry, UT Southwestern). Analogs and probe reagents were prepared by the De Brabander lab. The data analysis and interpretation were performed between Dr. Cheng-Yang Wu, Prof. Michael Roth, Prof. Jef De Brabander and me. This work was attributed to "Studies Toward the Unique Pederin Family Member Psymberin: Structure-Activity Relationships, Biochemical Studies, and Genetics Identify the Mode of Action of Psymberin" (Wu, C.-Y.; Feng, Y.; Cardenas, E. R.; Williams, N.; Floreancig, P. E.; De Brabander, J. K. *J. Am. Chem. Soc.* **2012**, *134*, 18998-19003).

4.2 Cytotoxicity and Translation Inhibition of Psymberin and Related Compounds

A selection of analogs relevant to this biological study is depicted in Figure 5 and includes: psymberin (**1.1**) and its 4-*epi* and 8-*epi* diastereomers **3.52** and **3.51**; methylated psymberin **4.11** and acylated psymberin **4.12**; a psymberate-truncated analog **4.21**; a

dihydroisocoumarin-truncated psymberin analog which also represents a pederin analog in which the cyclic pederate side chain is substituted with psymberin's acyclic psymberate side chain and termed psympederin **4.19a** (basically a hybrid between pederin and psymberin), and the corresponding 8-*epi* psympederin diastereomer **4.19b**; pederin (**1.3a**) and the corresponding desmethylene pederin analog **4.20**;[22] and mycalamide A (**1.5a**) which serves as a representative of the pederin family.[23] Compounds 4.20 and 1.5a were kindly provided by Profs. P. Floreancig (University of Pittsburgh) and P. Northcote (University of Wellington), respectively.

Figure 5. Psymberin and Related Compounds Used for Biological Studies.



4.2.1 Cytotoxicity of psymberin and related compounds.

As noted in the introduction, psymberin was reported to exhibit a highly differential cytotoxicity profile (>10,000-fold differences among cancer cell lines in the NCI 60 cell line panel). We were therefore surprised to see that in our hands, synthetic psymberin was highly cytotoxic to every human cancer cell line tested. For example, psymberin inhibited the PC3 prostate and SK-MEL-5 melanoma cancer cell lines with an IC_{50} of 0.98 and 0.27 nM respectively,[13] whereas the same two cance cell lines were reported to respond highly differentially to natural psymberin (>25 M for PC3 and <2.5 nM for SKMEL- 5).[2] Additional data regarding cytotoxicity in HeLa, SK-MEL-5, KM12, PC3, and T98G human tumor cell lines were obtained and listed in Table 10. As shown in Table 10, synthetic psymberin exhibited very potent antiproliferative activity against a selection of human tumor cell lines (KM12, PC3, SK-MEL-5, T98G) with IC_{50} values in the single digit to subnanomolar range (0.45-2.29 nM), about 2-fold more active than mycalamide A (0.95-3.79 nM).[24] Albeit less active, the 8-*epi*- and 4-*epi*-psymberin variants **3.51** and **3.52** were still able to prevent the proliferation of these cancer lines in the submicromolar range (37-763 nM). Similar structural changes (methoxyaminal epimer) in the pederin/mycalamide series resulted in >3 orders of magnitude reduction in cytotoxic activity.

Compared to psymberin (**1.1**), mycalamide A (**1.5a**) was nearly equipotent against the same cell lines. Because mycalamide is a known eukaryotic protein translation inhibitor,[25] we also included cycloheximide, a compound with a similar mode-of-action, namely inhibition of elongation-translocation via binding to the large 60S ribosomal subunit.[26] In the HeLa cell

line, cycloheximide was over a 1,000-fold less potent as a cytotoxic agent (Table 10). Removal of the psymberate side chain as in compound **4.21** also completely abolished cytotoxic activity. Moving to the dihydroisocoumarin side chain, acetylation of one of the phenols as in compound **4.12** resulted in similar cytotoxicity as psymberin (Table 10).

Table 10. Cytotoxicity[a] of psymberin and related compounds against Human Tumor Cell Lines

	Cytotoxicity (IC_{50}, nM)				
compound	Hela[b]	SK-MEL-5[c]	KM12	PC3	T98G
cycloheximide	2242 ± 1515	3116 ± 754	n.d.[d]	n.d.	n.d.
1.1	0.64 ± 0.14	0.27 ± 0.04	0.45 ± 0.01	0.98 ± 0.12	1.37 ± 0.06
4.12	0.54 ± 0.01	0.35 ± 0.07	n.d.	n.d.	n.d.
4.11	2.34 ± 0.53	1.58 ± 0.42	n.d.	n.d.	n.d.
1.5a	2.52 ± 1.39	3.79 ± 0.04	0.95 ± 0.02	2.5 ± 0.2	2.87 ± 0.07
3.52	6.18.6 ± 267.0	352.0 ± 12.1	126.08 ± 8.6	346.5 ± 102.8	186.7 ± 51.3
3.51	>1000	762.8 ± 70.0	37.1 ± 5.5	200.2 ± 27.6	85.8 ± 48.4
4.19a	>1000	>1000	710.9 ± 35.8	>1000	>1000
4.19b	>1000	>1000	>1000	>1000	>1000
4.21	>1000	>1000	n.d.	n.d.	n.d.

[a] A CellTiter-Glo® luminescent assay, which measures cellular ATP concentrations, was used to measure cell viabilitywith and without compound treatment. IC_{50} values were calculated by fitting the luminescence data to an equation representing the doseresponse of inhibiting luminescence. [b]R^2 values range from 0.931 to 0.994. [c]R^2 values range from 0.90 to 0.995. [d]n.d. means not determine. KM12: colon tumor. PC3: prostate tumor. SK-MEL-5: melanoma. T98G: glioblastoma.

The antiproliferative activity of the psymberin-pederin hybrid (psympederin **4.19a**) provided the most informative piece of structure-function information: this compound, and its diastereomer **4.19b**, was devoid of activity up to 1 μM concentrations, a loss of >1,000-fold compared to psymberin or mycalamide. If pederin/mycalamide and psymberin share the same mode-of-action, then the dihydroisocoumarin side chain in psymberin should not be critically important given the absence of this fragment in the potent cytotoxin mycalamide. Moreover, we also know that a cyclic pederate side chain is not critical for activity given the potent cytotoxicity associated with psymberin. Thus the inactivity of psympederin **4.19a** strongly suggests that the dihydroisocoumarin fragment is vitally important for psymberin cytotoxicity, and at the same time reveals that the cyclic pederate side chain is critically important for the cytotoxic phenotype of pederin/mycalamide family members.[29]

4.2.2 Inhibition of protein translation in cell-based and in vitro assays.

Given the structural relationship between psymberin and pederin, we tested the ability of psymberin and analogs to inhibit protein synthesis. Two assays were used to measure the inhibition of translation induced by psymberin and analogs.

Table 11. Translation Inhibition[a] of psymberin and related compounds

compound	Translation inhibition (EC_{50}, nM)[b]		
	in vitro assay	cell-based assay	
		Hela	SK-MEL-5
cycloheximide	3150 ± 2152	3325 ± 834	2670
1.1	28 ± 7	2.2 ± 1.4	11 ± 10
4.12	142 ± 21	5.8 ± 1.7	4.2 ± 3.2
4.11	120 ± 47	9.6 ± 8.9	9.3 ± 8.5
1.5a	238 ± 44	59 ± 32	64
3.52	346 ± 64	4950 ± 4870	496
3.51	318 ± 182	2200 ± 1410	843
4.19a	641 ± 262	1650 ± 1060	578
4.19b	>10000	>10000	>10000
4.21	>10000	>10000	>10000

[a]Data are means ± standard deviation from at least two independent experiments conducted in triplicate. [b]R^2 ranges from 0.90 to 0.995.

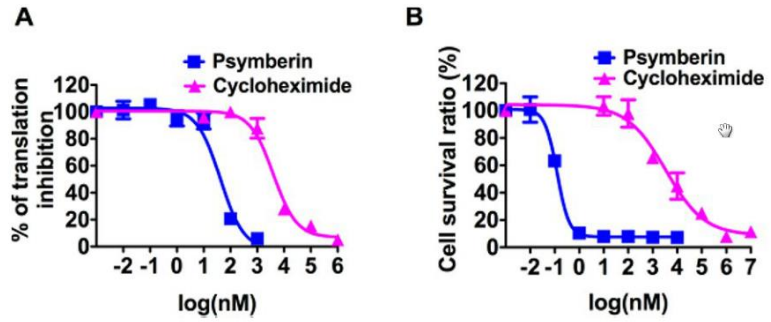
The first assay measured total protein translation in HeLa or SK-MEL-5 cells through incorporation of radioactive ^{35}S-methionine into TCA-precipitable counts in the presence or absence of the compounds. As shown in Table 11, psymberin (**1.1**) and mycalamide (**1.5a**) potently inhibited translation in HeLa (EC_{50} = 2.2 and 59 nM) and SK-MEL-5 cells (EC_{50} = 11 and 64 nM) as compared to the positive control cycloheximide with micromolar potency. The extremely potent cytotoxic psymberin acetate **4.12** exhibited nanomolar activity in the cell-based protein translation inhibition assay (EC_{50} 5.8 nM), whereas the EC_{50} concentrations of psymberin epimers **3.51** and **3.52**, and psympederin (**4.19a**) increased 700 to 2000 fold compared to psymberin. Psympederin diastereomer **4.19b** and

psymberate-truncated analog **4.21** lost all activity. Thus it appears that the SAR data obtained in the cellbased protein translation inhibition assay mirrored those observed in the cytotoxicity assay (Table 10).

Compounds were also evaluated in a cell-free *in vitro* translation assay using rabbit reticulocyte extracts, where translation of firefly luciferase was measured as a function of compound concentration. Surprisingly, in this assay the psymberin analogs **3.52, 3.51, 4.19a** were only about 10-fold to 25 fold less potent than psymberin.

We also observed that the EC_{50} values for the natural products psymberin and mycalamide were higher in the *in vitro* assay than the cell based translation inhibition assay, unlike the analogs **3.52, 3.51, 4.19a** which were more potent in the *in vitro* assay. This data suggests that stereochemical changes (**3.52** and **3.51**) or the elimination of the dihydroisocoumarin side chain (psympederin **4.19a**) must affect processes in the cell-based assays other than those occurring on the ribosome. Indeed, psympederin **4.19a** gave no more than a 23-fold change in inhibition of protein synthesis *in vitro* compared to psymberin, but more than a 1,000 fold change in cell-based cytotoxicity assay. Thus, the dihydroisocoumarin side chain of psymberin appears to be important for inducing cytotoxicity but not for inhibiting protein translation. This significant result was surprising given the generally accepted notion that protein synthesis inhibition fully accounts for the cytotoxic effects of the pederin/mycalamide family of natural products. However, we note that the majority of pederin/mycalamide analogs have been tested for cytotoxic effects only, and not for protein synthesis inhibition. The similar IC_{50} and EC_{50} values of cycloheximide suggest that its cytotoxicity may originate entirely from inhibiting translation.

Figure 6. (A) Representative translation – inhibition curves from a cell based assay. (B) Representative cycotoxicity curves from the cell based CellTiter – Glo assay. Means with standard deviations are plotted for each treatment condition.



4.2.3 Differential accumulation of analogs in cells

Based on our observation that cytotoxic effects and protein synthesis inhibition did not coincide for some analogs tested (most notably psympederin **4.19a**), we argued that the dihydroisocoumarin side chain was key to psymberin's cytotoxic activity, but not for translation inhibition. However, as we will describe later, the genetics does indicate that the ribsome is the main target for inducing toxicity, at least in worms. To explain the discrepancies between the in vitro and cell-based potency of compounds **3.52**, **3.51**, **4.19a**, their intracellular concentrations were measured. As shown in Table 12, after incubating HeLa cells for two hours with 100 nM of each compound, the intracellular concentration of the two psymberin epimers **3.52** and **3.51** was about 20 fold less than psymberin. The intracellular concentration of psympederin **4.19a** was below the limit of detection. This difference could be due to a change in cellular uptake of compounds, a change in efflux, or a

change in metabolism of the compounds. Thus, structural and stereochemical features of psymberin are important for its intracellular concentration and should be taken into account when interpreting data from cell-based assays.

Table 12. Intracellular Concentration of Different Psymberin Analogs in HeLa Cells[a]

compound	intracellular concentration (μM)
1.1	7.14 ± 2.93
3.52	0.21 ± 0.08
3.51	0.31 ± 0.11
4.19a	<LD

[a]Data shown are means ± standard deviation from at least two independent experiments conducted in duplicate. LD is limit of detection.

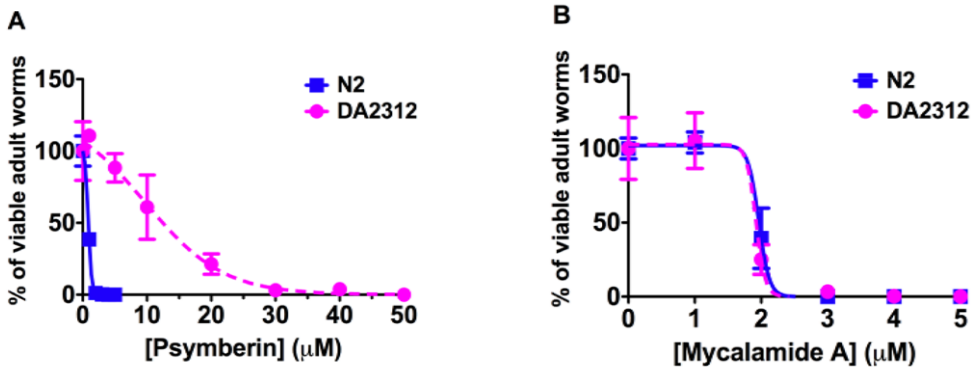
4.3 Forward Genetic Screen in *C. elegans*.

Parallel to the SAR study, we also searched for targets of psymberin responsible for toxicity in an unbiased fashion. Using a forward genetic screen in the model organism *C. elegans*,[30] Dr. Cheng-Yang Wu performed two forward genetic screens from which a mutant strain (DA2312) was identified that conferred 20-fold resistant to psymberin compared to wild-type worms (Figure 7). The drug-resistant mutation, a proline to leucine, is in the ribosomal large subunit protein, RPL41, which is the ortholog of human RPL36a and RPL36al and of archaeal protein L44e. The amino acid sequence surrounding this proline is highly conserved in eukaryotic organisms and forms a loop of protein between the P and E sites on the ribosome.[31] During the course of our studies, Steitz and co-workers published the crystal

structure of mycalamide A bound to an archaeal ribosome.[32] Their data suggest that there is interaction between mycalamide A and the two conserved lysines in the ribosomal protein L44e (the homologue of RPL41). To determine if the mutation in rpl-41 would confer cross-resistance to mycalamide, wild-type N2 and psymberin-resistant DA2312 worms were treated with various concentrations of mycalamide A (**4**). Interestingly, DA2312 showed the same sensitivity to mycalamide A as the wild-type N2 worms (Figure 7). Thus, the mutation in rpl-41 is psymberin-specific.

Figure 7. Psymberin-Resistant Mutation Does not Confer Resistance to Mycalamide A.

The toxicity curves for psymberin on DA2312 and N2 worms (A), and the toxicity curves for mycalamide A on DA2312 and N2 worms (B) are presented.



Note: Blue squares indicate data from N2 samples, pink solid circle the data from DA2312. The concentration of compound is indicated on the X-axis. The Y-axis is the ratio of survived worms. Means with standard deviations are plotted for each treatment condition.

Although we had expected to find multiple psymberin resistant mutants in *C. elegans*, we repeatedly found the same single point mutation in RPL-41, suggesting that relatively few

changes on the ribosome allow it to remain active in the presence of psymberin. The change from a rigid proline to a relatively flexible leucine may cause structural changes in the pocket where psymberin binds to the ribosome. If so, these changes do not affect the binding of the structurally similar toxin, mycalamide A, and this suggests that the changes induced by the P65L mutation must be rather local. A comparison of the binding pocket between archeal[35] and mammalian ribosomes[36] reveals that the conformations of the rRNA surrounding the binding pocket are totally different in the two ribosomes. The proline that was mutated to produce resistance to psymberin is in a small loop of sequence absent from the archaeal ribosome. Thus, the binding conformation of mycalamide A on the archaeal ribosome may suggest one of several types of interactions that can stabilize binding but not necessarily indicate the interactions on the eukaryotic ribosome. The answers to these arguments will have to come from higher resolution structures of mammalian ribosomes with these inhibitors bound.

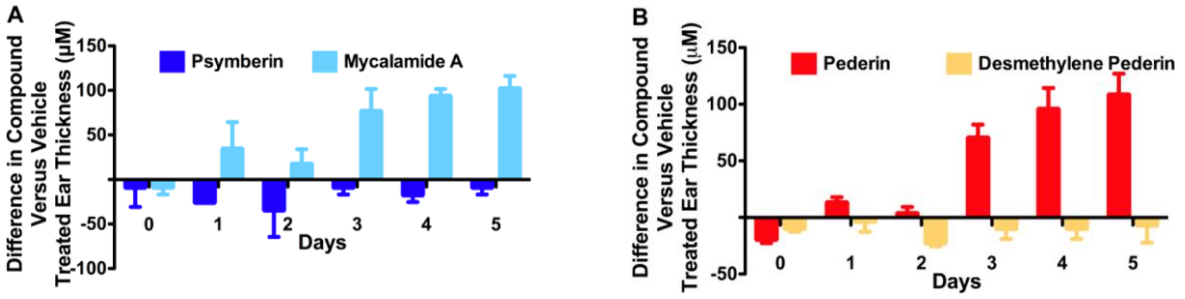
4.4 Vesicant activity.

One of the earliest described effects of pederin (**1.3a**) is a vesicant activity causing severe dermatitis.[3] Many related compounds, such as mycalamide and the onnamide family, are also known to share this activity. The structural features of the pederin family of compounds responsible for this activity are unknown. To determine if psymberin is also a vesicant, a mouse ear-swelling test (MEST)[37] was established by Dr. N. Williams (Department of Biochemistry, UT Southwestern) and psymberin vesicant activity evaluated in comparison to that shown by mycalamide (**1.5a**), pederin (**1.3a**), and a synthetic variant of pederin,

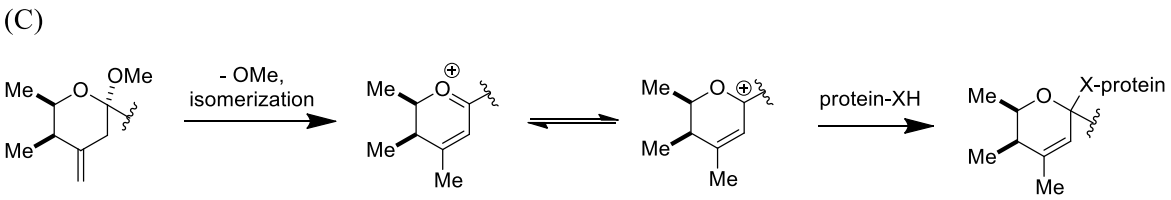
desmethylene pederin **4.20**.[7] The left and right ears of C57BL/6 mice were painted with either vehicle or compound and ear thickness was monitored daily with a modified Mitutoyo micrometer by an investigator blinded to the treatment. Both acute vesicant and delayed contact hypersensitivity were monitored by pre-treatment of the mice on their abdomen with vehicle or compound. As shown in Figure 8, mycalamide (**1.5a**), but not psymberin (**1.1**), clearly induces swelling of the ear treated with compound relative to the vehicle treated ear. Pretreatment of the abdomen of mice with mycalamide but not psymberin resulted in a blistering effect on the abdominal skin but did not consistently or significantly increased swelling of subsequently treated ears (data not shown), suggesting the effect was acute and not due to an immune mediated delayed type hypersensitivity reaction. As expected, pederin (**1.3a**) also showed significant vesicant activity as measured in the MEST (Figure 8, panel B). Significantly, a synthetic variant of pederin in which a methylene group has been removed (desmethylene pederin **4.20**) showed no activity in this assay. A hydrogenated derivative of pederin (dihydropederin) was reported to have lost its vesicant activity though it remained a potent inhibitor of protein synthesis.[3] This uncoupling of vesicant activity and protein translation inhibition in desmethylene pederin (**4.20**), psymberin (**1.1**), and dihydropederin[3] suggests that the homoallylic acetal present in pederin (**1.3a**) and related natural products might function as a site of reactivity via formation of a stabilized oxocarbenium species (alkylating agent) and responsible for the blistering/ vesicant activity. The absence of an acetal in psymberin and stabilization of the acetal in pederin/mycalamide relatives via removal of the *exo*-methylene double bond eliminates this liability and consequently the blistering/vesicant activity of these compounds (Figure 8, panel C).

Figure 8. Vesicant Activity of Pederin, Mycalamide, and Psymberin Differ.

(A) Pederin or its synthetic analog, demethylene pederin (B), prepared in the same vehicle was applied to either the right or left ear of the treated mice.



(C) Hypothesis for Pederin/Mycalamide Showing Vesicant Activity



Note: The abdomen of C57BL/6 mice was shaved using an electrical razor and 100 mL of vehicle solution (5% ethanol in 3:1 acetone:olive oil) was applied. Seven days later, 25 mL of a 0.00125% w/v solution of psymberin or mycalamide A. The opposing ear was treated with vehicle only. Prior to the ear application and then each day thereafter for 5 days, the thickness of both ears was measured by an investigator blinded to the treatment using a modified Mitutoyo micrometer. The differences in ear thickness between compound and vehicle treated ears in mm are plotted.

4.5 Conclusion

With its dihydroisocoumarin and acyclic *N*-acyl side chains, psymberin represents a structural outlier of the pederin/ mycalamide family of natural products. Founded on a comprehensive synthetic footing, we were able to study the chemical biology of this family in more detail. Initial observations that cytotoxic activity and protein synthesis inhibition did not track for all analogs suggested that psymberin might differ from other pederin family members in it cellular targets. However, forward genetic studies with C. elegans indicated that the primary target of psymberin is the ribosome.[23] Drug-resistant worms were not cross-resistant to mycalamide, and this could indicate subtle binding differences of these two compounds for the same target. We also demonstrated that psymberin is not a blistering agent and determined the chemical features responsible for vesicant activity in other pederin family members. In the end, dramatic differences in intracellular concentrations explained discrepancies between pharmacological and cellular activity of structurally related analogs with similar physicochemical properties, a characteristic that is often not measured in SAR studies of natural products.

4.6 Experimental Procedures

(*R*)-8-hydroxy-3-((2*R*,3*S*)-3-hydroxy-4-((2*R*,4*R*,6*S*)-4-hydroxy-6-((*S*)-((2*S*,3*S*)-2-hydroxy-3-methoxy-5-methylhex-5-enamido)(methoxy)methyl)-3,3-dimethyltetrahydro-2H-pyran-2-yl)butan-2-yl)-5-methyl-1-oxoisochroman-6-yl acetate (4.12)

To a solution of psymberin (**1.1**, 2 mg, 3.28 μmol) in DCM (0.2 mL), was added ($^{13}CH_3{}^{13}CO)_2O$ (0.82 μL, 3.4 μmol) followed by pyridine (0.77 μL, 3.4 μmol) at 0 ^oC. After removing the cooling bath, the solution was allowed to stir at room temperature for overnight. The resulting solution was diluted with EtOAc (2 mL) and quenched by sat. aq. $NaHCO_3$ (2 mL). The aqueous phase was extracted with EtOAc (2 mL) three times. The combined organic phase was dried over $MgSO_4$. After removing the solvents in vacuum, the residue was purified by column (silica gel, EtOAC:Hexanes 1:1) to give product **4.12** (R_f = 0.15, hexanes: EtOAc = 1:1; 2.0 mg, 95%) as a white solid.

Compound **4.12** has ^1H NMR (400 MHz, $CDCl_3$) δ 11. 29 (s, 1H), 7.01 (d, *J* = 10.3 Hz, 1H), 6.35 (s, 1H), 5.43 (t, *J* = 9.5 Hz, 1H), 4.77 (s, 2H), 4.55 (dt, *J* = 12.3, 3.9 Hz, 1H), 4.33 (m, 2H), 4.16 (bs, 1H), 4.02 (s, 2H), 3.93 (m, 1H), 3.85 (m, 1H), 3.67 (m, 4H), 3.56 (d, *J* = 9.3 Hz, 1H), 3.36 (s, 3H), 3.33 (s, 3H), 2.95 (m, 1H), 2.84 (m, 1H), 2.35 (dd, *J* = 14.5, 8.8 Hz, 1H), 2.27 (dd, *J* = 14.6, 4.6 Hz, 1H), 2.04 (m, 4H), 1.74 (m, 2H), 1.65 (s, 3H), 1.09 (d, *J* = 7.0 Hz, 3H), 0.98 (s, 3H), 0.85 (s, 3H); ^{13}C NMR (100MHz, $CDCl_3$) δ 184.1, 173.0, 170.8, 164.3, 163.2, 142.1, 137.8, 115.1, 113.2, 100.5, 98.8, 83.1, 82.0, 80.5, 79.8, 75.1, 73.7, 71.8, 58.2, 56.0, 55.5, 42.9, 39.6, 38.0, 32.2, 30.1, 28.7, 22.7, 22.4, 10.7, 9.5, 0.2; MS calcd. for $C_{31}{}^{13}C_2H_{49}NO_{12}$ 653.3, found $[M + Na]^+$ 676.3.

(2*S*,3*S*)-2-hydroxy-*N*-((*S*)-((2*S*,4*R*,6*R*)-4-hydroxy-6-((2*S*,3*R*)-2-hydroxy-3-((*R*)-8-hydroxy-6-methoxy-5-methyl-1-oxoisochroman-3-yl)butyl)-5,5-dimethyltetrahydro-2H-pyran-2-yl)(methoxy)methyl)-3-methoxy-5-methylhex-5-enamide (4.11)

To a solution of psymberin (**1.1**, 3 mg, 4.92 μmol) in acetone (0.3 mL), was added $^{13}CH_3$ iodide (0.32 μL, 5.2 μmol) followed by K_2CO_3 (0.82 mg, 5.9 μmol) at room temperature. The solution was allowed to stir at 50 □C for overnight. The resulting solution was diluted with EtOAc (2 mL) and quenched by sat. aq. NH_4Cl (2 mL). The aqueous phase was extracted with EtOAc (2 mL) three times. The combined organic phase was dried over $MgSO_4$. After removing the solvents in vacuum, the residue was purified by column (silica gel, EtOAC: Hexanes 1:1) to give product **4.11** (R_f = 0.20, hexanes: EtOAc = 1:1; 2.7 mg, 90%) as a white solid.

Compound **4.11** has ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.11 (d, *J* = 0.9 Hz, 1 H), 7.01 (d, *J* = 10.2 Hz, 1H), 6.62 (s, 1H), 5.43 (t, *J* = 9.3 Hz, 1H), 4.79 (m, 2H), 4.63 (dt, *J* = 9.9, 4.5 Hz, 1H), 4.35 (m, 2H), 3.94 (dd, *J* = 27.6, 17.7 Hz, 2H), 3.70 (m, 2H), 3.53 (d, *J* = 10.4 Hz, 1H), 3.38 (s, 3H), 3.37 (s, 3H), 2.97 (m, 1H), 2.50-2.18 (dd, *J* = 6.9, 0.9 Hz, 3H), 2.36 (dd, *J* = 14.6, 8.8 Hz, 1H), 2.04 (m, 4H), 1.90 (m, 1H), 1.76 (m, 4H), 1.56 (m, 1H), 1.11 (d, *J* = 7.2Hz, 3H), 0.98 (s, 3H), 0.92 (s, 3H); ^{13}C NMR (100MHz, $CDCl_3$) δ 173.5, 171.1, 169.2, 168.6, 161.8, 142.5, 140.2, 113.5, 110.1, 82.4, 80.9, 79.9, 78.7, 74.0, 73.6, 71.9, 58.4, 56.7, 43.1, 39.2, 38.0, 32.3, 30.2, 28.9, 23.6, 22.8, 22.3, 21.6, 20.9, 14.7, 11.2, 9.9; MS calcd. for $C_{31}{}^{13}C_1H_{49}NO_{11}$ 624.3, found $[M + H]^+$ 625.3.

(2*S*,3*S*)-*N*-((*S*)-((2*S*,4*R*,6*R*)-6-((2*S*,3*R*)-3-((*R*)-6,8-dihydroxy-5-methyl-1-oxoisochroman-3-yl)-2-hydroxybutyl)-4-hydroxy-5,5-dimethyltetrahydro-2H-pyran-2-yl)(methoxy)methyl)-2-hydroxy-3-methoxy-5-methylhexanamide (4.13)

To a solution of psymberin (**1.1**, 5 mg, 8.21 μmol) in EtOH (2 mL), was added PtO_2 (1 mg). The solution was stirred for overnight under H_2 (1 atm) at room temperature. The catalyst was filtered and ethanol was removed under reduced pressure. The residue obtained was purified by FC (silica gel; CH_2Cl_2/MeOH 10:1) to give **4.13** (R_f = 0.40, hexanes: EtOAc = 1:4; 4.7 mg, 95%) as white soild.

Compound **4.13** has ^{1}H NMR (400 MHz, $CDCl_3$) $[\alpha]^{22}_D$ = +19.9 ($CDCl_3$, *c* = 0.09); ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.07 (s, 1H), 8.10 (bs, 1H), 7.20 (d, *J* = 10.2 Hz, 1H), 6.31 (s, 1H), 5.42 (t, *J* = 9.3 Hz, 1H), 4.48 (dt, *J* = 12.3, 4.1 Hz, 1H), 4.42 (d, *J* = 2.8 Hz, 1H), 4.34 (s, 1H), 3.92 (td, *J* = 21.6, 19.8, 8.9 Hz, 2H), 3.63 (m, 2H), 3.50 (d, *J* = 10.2 Hz, 1H), 3.37 (s, 3H), 3.32 (s, 3H), 2.81 (m, 2H), 2.05 (m, 2H), 2.01 (s, 3H), 1.83 (m, 4H), 1.63 (m, 2H), 1.09 (d, *J* = 4.0 Hz, 3H), 0.96 (s, 3H), 0.92 (s, 6H), 0.75 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.3, 170.9, 162.4, 162.0, 139.8, 113.8, 101.4, 101.2, 82.2, 80.5, 80.4, 79.77, 78.6, 74.4, 73.0, 71.6, 57.8, 56.6, 42.8, 39.0, 38.6, 32.3, 29.9, 28.7, 24.7, 23.8, 23.3, 22.1, 14.4 10.8, 10.7, 9.5. IR (cm $^{-1}$): 3370.16, 2956.59, 1658.81, 1620.23, 1519.64, 1464.16, 1375, 1252.5, 1172.83, 1111.09, 1069.36, 846.03, 797.33. MS (ES) calculated for $C_{31}H_{50}O_{11}Na$ $[M + H]^+$ 611.30, found 611.2.

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Chapter 5

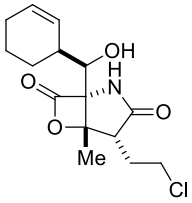
Isolation, Structure Elucidation and Biological Activity of Saliniketal Family Members: Saliniketals A and B, Salinisporamycin and Rifsaliniketal

5.1 Saliniketals and Salinisporamycin

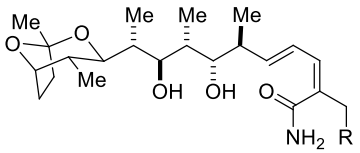
Throughout history, secondary metabolites have provided a fundamental source of drugs for fighting infection, inflammation and cancer in humans. Marine-derived microorganisms, more specifically actinomycetes, have become the frontier of natural product research over the last 10 years, providing a vast number of novel natural products. The genus *Salinispora* has been a prolific source of secondary metabolites. Currently, there are three species that belong to this genus: *Salinispora tropica, Salinispora arenicola* and *Salinispora pacifica*.[2] The potent proteasome inhibitor salinosporamide A (**5.1**, Figure 9) represents the first natural product isolated from the obligate marine bacteria *S. tropica*,[3] which is currently in clinical trials for the treatment of cancer. In 2007 the genome of *S. tropica* was sequenced to provide insight into their biosynthetic potential. It was shown that a large percentage of its genome is devoted to the assembly of natural products,[4] suggesting that there is still a large chemical diversity to explore within this genus. Another example of natural products isolated from *Salinispora* are saliniketals A (**5.2**, Figure 9) and B (**5.3**), which were isolated from *S. arenicola* by Fenical and co-workers.[5] Surprisingly, saliniketals possess similar structural characteristics to the *ansa* side chain of rifamycin (**5.4**), which co-occurs in the fermentation media. Unlike rifamycin (**5.4**), which has

antitumor and antibacterial activity, saliniketals were found to be devoid of cytotoxic and antibacterial activity. They were found to inhibit the phorbol ester-mediated induction of ornithine decarboxylase (ODC), an enzyme responsible for polyamine synthesis.[6] Polyamines are organic cations derived from amino acids and are important components in the development of mice.[7] In addition, ODC is a direct target of the *MYC* oncogene, and it has been shown to be overexpressed in different tumor cells. [8] Due to their inhibitory properties against ODC, saliniketals may be utilized as chemopreventive agents.[6,9] 2D NMR spectroscopic methods were used to solve the structure of **5.2** and **5.3**. The absolute stereochemistry of the compounds was assigned by Mosher's analysis. The unique structural characteristics of the saliniketals along with its interesting biological activity have resulted in three total syntheses of these molecules.[11-13] On the other hand, salinisporamycin (**5.5**), which shares the exacted same side chain with saliniketals, was recently isolated from *Salinispora arenicora* YM23-082 by Matsuda and co-workers (Figure 9). Unlike rifamycins, salinisporamycin showed moderate cytotoxic activity against A549 cells with an IC_{50} value of 3.0 μg/ml. The antimicrobial activity of salinisporamycin was tested against six microorganisms and showed moderated activity against two microorgansims (Table 13), which was weaker than that of rifamycin S (**5.4**).

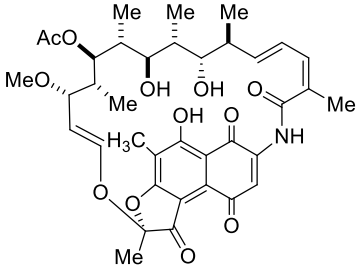
Figure 9. Saliniketals and Related Natural Products



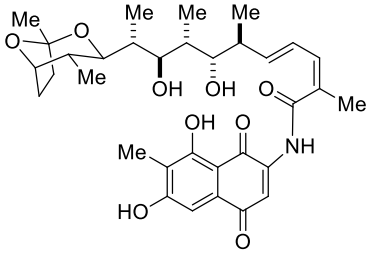
Salinosporamide A **(5.1)**



R=H, Saliniketal A **(5.2)**
R=OH, Saliniketal B **(5.3)**



Rifamycin S **(5.4)**



Salinisporamycin **(5.5)**

Table 13. Antimicrobial activity properties of Saliniketal A, Salinisporamycin and Rifamycin

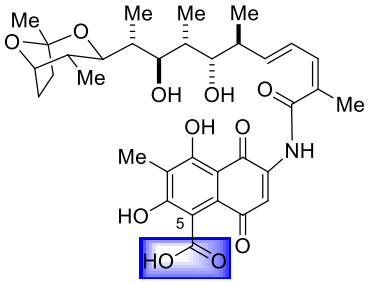
Taxin	Strain	Saliniketal	Salinisporamycin	Rifamycin
Firmicutes	Staphylococcus aureus	37	0.46	0.0056
Firmicutes	Bacillus subtilis	111	4.1	1.4
Bacteroidetes	Cytophaga marinoflava	>200	>200	12.3
Gammaproteobacteria	Escherichia coli	>200	>200	>200
Gammaproteobacteria	Pseudomonas aeruginosa	>200	>200	>200
Yeast	Candida albicans	>200	>200	>200

Antimicrobial activity (MIC, μg ml^{-1})

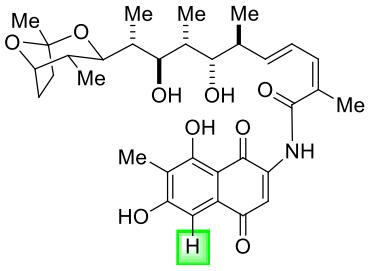
5.2 Isolation of Rifsaliniketal

MacMillan and co-workers at UT Southwestern Medical Center are also working on the isolation and structural elucidation of novel secondary metabolites from actinomycetes. The marine bacteria SNB-003 was isolated from a marine sediment sample collected in the Bahamas. Analysis of the strain by 16s rRNA revealed high sequence identity to *S. arenicola*. Crude extracts from SNB-003 revealed cytotoxic activity. In an attempt to purify a pure bioactive constituent, a 20 L fermentation of SNB-003 led to the isolation of 1.79 mg of rifsaliniketal (**5.6**, Figure 10) as a yellow powder. However, this purified compound did not show activity. The structure was determined by 1D and 2D NMR spectroscopy (NMR data in Table 14), which showed it to be structurally similar to salinisporamycin, differing only by the presence of a carboxylate at C5 (Figure 10).

Figure 10. Structure of Rifsaliniketal and Comparison with Salinispoamycin



Rifsaliniketal **(5.6)**



Salinisporamycin **(5.5)**

Figure 11. Key Correlations Used to Assemble Rifsaliniketal.

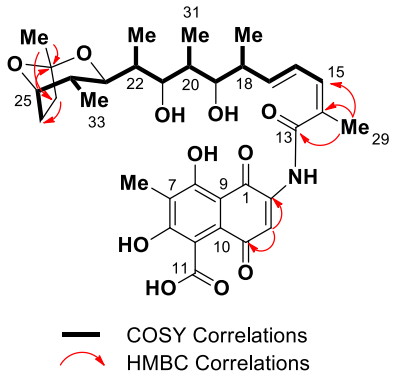


Table 14. 1D and 2D NMR Data of Rifsaliniketal in CD_3OD

No.	δ_H, mult. (J in Hz)	δ_C	COSY	HMBC
1		209.8		12
2		141.3		3
3	7.66, s	117.6		2,4,10
4		184.0		3
5				
6		162.8		12
7				
8				
9				
10		128.8		3
11				
12	2.16, s	8.0		1,3,6,10
13		169.7		15,29
14		129.2		29
15	6.46, d (11.2)	138.2	16,29	13,17,29
16	6.78, dd (11.2,15.2)	127.4	15,17,29	14,15,18
17	6.02, dd (8.0,15.2)	145.4	16,18,29	15,18,19,30
18	2.42, ddq (9.1,8.0,6.9)	41.9	17,19,30	16,17,19,30
19	3.77,dd (9.1,1.4)	75.4	18,20,26b	17,18,20,21,30,31
20	1.86-1.89 m	35.9	19,21,31	21,31

21	3.51, dd (8.3,4.3)	77.9	20,22	19,22
22	1.83-1.86 m	36.7	21,23,32	21,32
23	3.95, dd (10.6,1.1)	74.7	22,24	21,22,32,33
24	1.97-2.01,m	34.9	23,25,33	
25	4.22, dd (6.7,3.4)	81.3	24,26a,26b	23,28
26a	1.89-1.93, m	24.6	25	24,25
26b	1.93-1.97, m			
27a	1.78-1.83, m	34.8		26
27b	2.01-2.05, m			
28		106.1		25,34
29	2.08, s	20.2	15,16,17	13,14,15,16,17
30	0.99, d (6.9)	16.8	18	17,18,19
31	1.01, d (7.2)	10.9	20	18,19,20,21
32	0.89, d (7.0)	10.1	22	21,22,23
33	0.73, d (6.9)	12.6	24	23,24,25
34	1.39, s	24.0		27,28

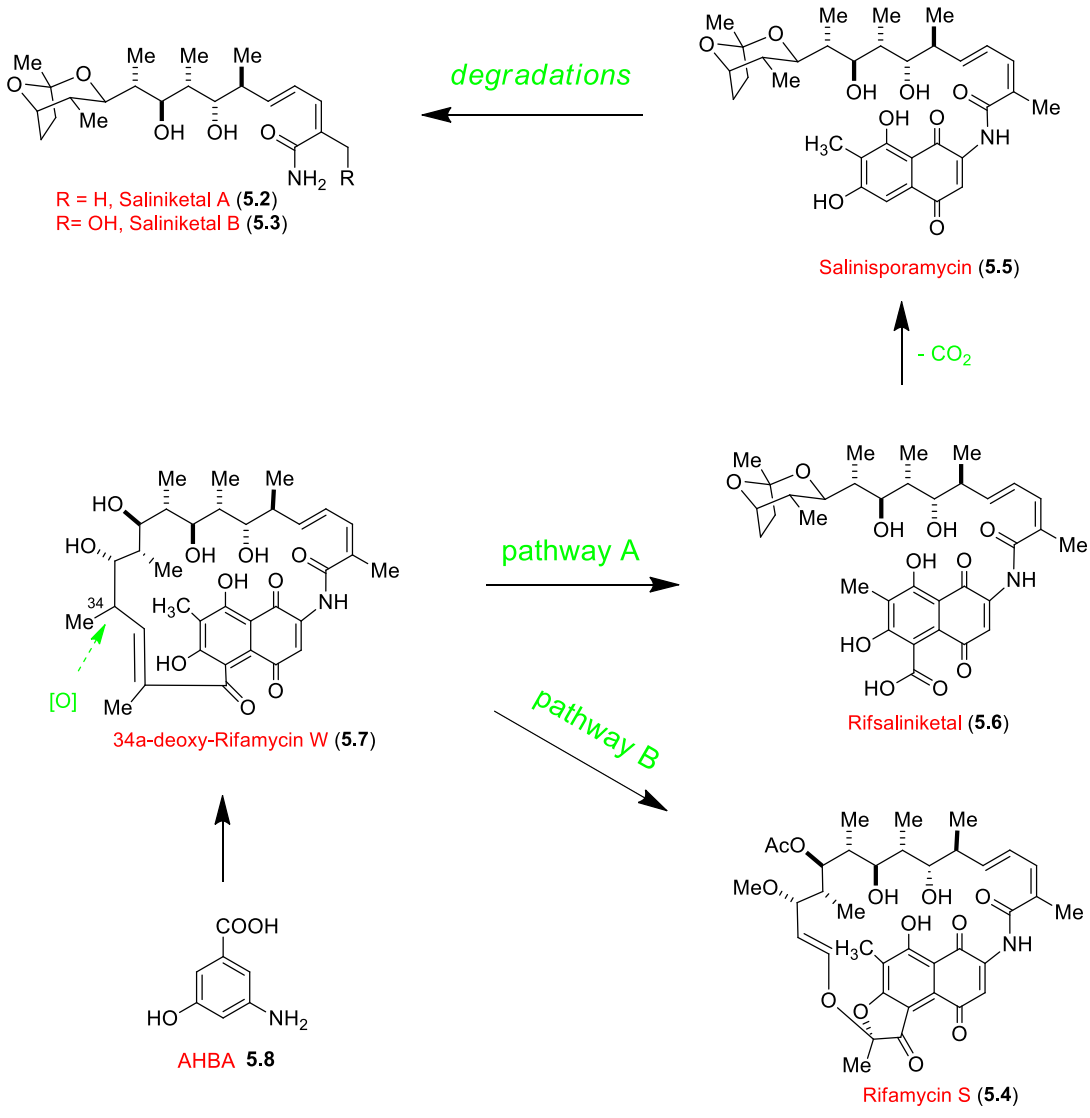
The antimicrobial activity of **5.6** and its methyl ester derivative were investigated by disk diffusion assay against two strains of bacteria, *Pseudomonas aeruginosa* and *Bacillus subtilis,* gram-negative and gram-positive bacteria, respectively. Despite the similar structural characteristics with rifamycin, no antimicrobial activity of **5.6** or of its methyl ester derivative was detectable against these two bacterial strains.

5.3 Biosynthetic Relationship of Saliniketal Family Members

Saliniketals (**5.2** and **5.3**), salinisporamycin (**5.5**) and rifsaliniketal (**5.6**) possess structural similarities to rifamycin, which co-occured in the fermentation media that produced saliniketals and salinisporamycin.[5] The elegant work done by Moore and co-workers provided evidence that

saliniketals are byproducts of rifamycin biosynthesis.[10] Using PCR-directed mutagenesis, chemical complementation studies, and isotope feeding experiments, they were able to demonstrate that the enzyme cytochrome P450 monoxygenase, encoded by the biosynthetic gene *sare1259* is involved in multiple oxidative rearrangement reactions of 34a-deoxyrifamycin W (**5.7**) to afford the saliniketals, salinisporamycin, rifsaliniketal and rifamycin (Scheme 42).

Scheme 42. Biosynthetic Relationship between Saliniketal Family Members and Rifamycin



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Chapter 6

Total Syntheses of Saliniketal Family Members: Saliniketal A, Salinisporamycin and Rifsaliniketal

Due to their unusual chemical structures and interesting biological activities, the saliniketals have drawn attention from the synthetic community. The Paterson group[1] finished the first total synthesis of saliniketals A (**5.2**) and B (**5.3**), and confirmed the absolute configuration. Subsequently, our group[2] completed a synthesis of saliniketal B. The Yadav group[3] claimed a formal synthesis of saliniketals later. To date, no total synthesis of salinisporamycin (**5.5**) and rifsaliniketal (**5.6**) has been reported.

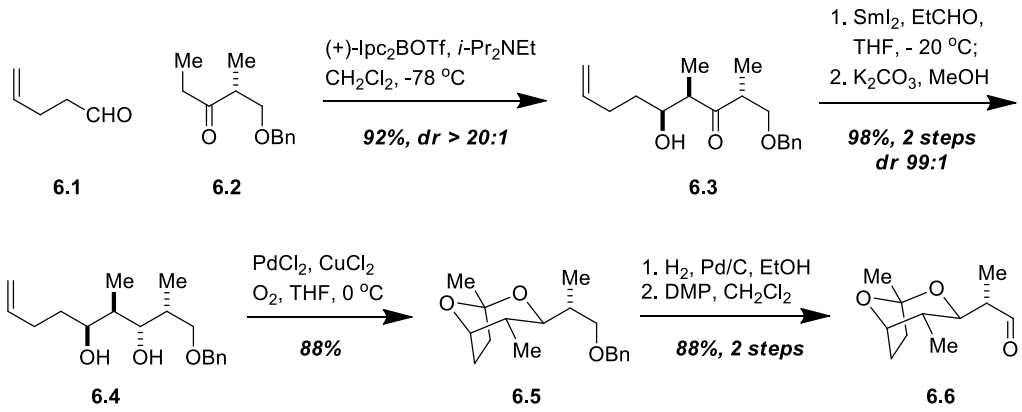
In this chapter, we will review the Paterson and Yadav syntheses, followed by the De Brabander synthesis of saliniketal B, which laid the foundation to my Ph.D. studies described in sections 6.2 and 6.3.

6.1 Previous Synthetic Work

6.1.1 Paterson Total Synthesis of Saliniketals A and B

In 2008, Paterson and co-workers claimed the first syntheses of Saliniketals A and B[1]. The key feature of this work included the use of two boron aldol reactions to set six of the nine stereocenters, an intramolecular Wacker-type cyclization to install the bicyclic ring system, and a late stage Stille coupling to append the *E*,*Z* dienamide.

Scheme 43. Paterson's Synthesis of the Aldehyde **6.6**

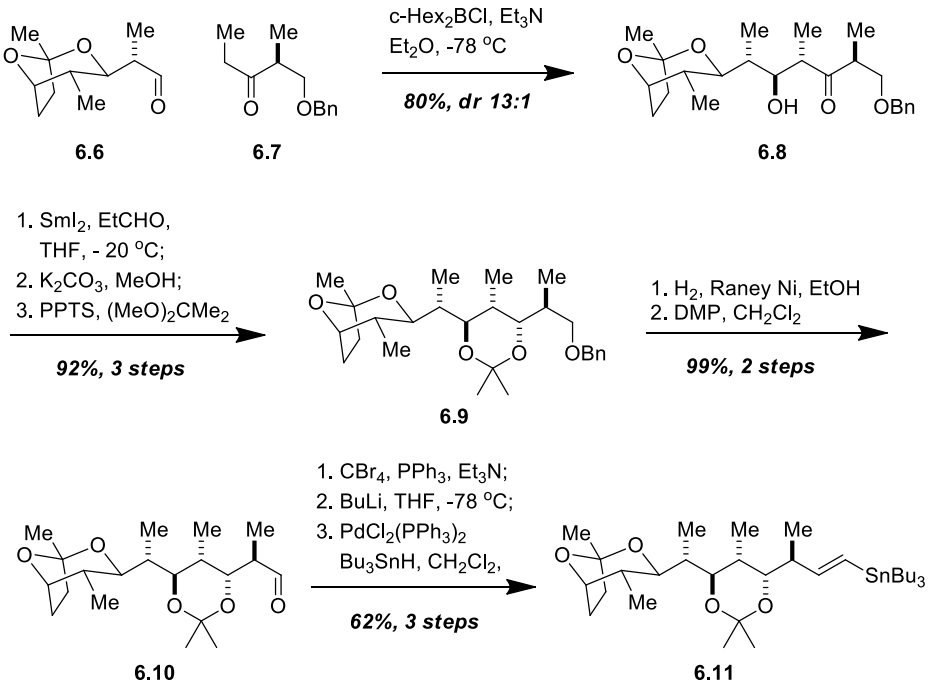


Their synthetic adventure started from a classical reagent-controlled aldol reaction of (*R*)-**6.2**[4] (Scheme 43). Formation of the *Z* boron enolate followed by addition of aldehyde **6.1**, afforded the *syn* adduct **6.3** in 92% yield and >20:1 diastereoselectivity. Under Evans-Tishchenko condition,[5] a 1,3-*anti* reduction to diol **6.4** was accomplished after the base-mediated hydrolysis of the resultant ether. Inspired by Grigg and coworkers,[6] treatment of **6.4** with catalytic amounts of $PdCl_2$ and $CuCl_2$ under oxygen atmosphere in THF at 0 ^oC, an intramolecular Wacker-type cyclization was achieved to give the desired [3.2.1]dioxabicycle **6.5**. Subsequently, the reductive cleavage of the benzyl ether followed by oxidation delivered the aldehyde **6.6**, which set the stage for a second boron-mediated aldol coupling.

Enolization of **6.7** (*c*-Hex_2BCl, Et_3N), followed by addition of aldehyde **6.6** (Scheme 44) furnished the *anti*-adduct **6.8** in 80% yield and excellent diasetreoselectivity (*dr* 13:1). Then, Evans-Tishchenko[5] reduction of *β*-hydroxy ketone **6.8**, hydrolysis and acetonide formation gave **6.9**. This material was subjected to a debenzylation /oxidation sequence to deliver the aldehyde **6.10** smoothly, which was then converted into a terminal alkyne using the procedure developed

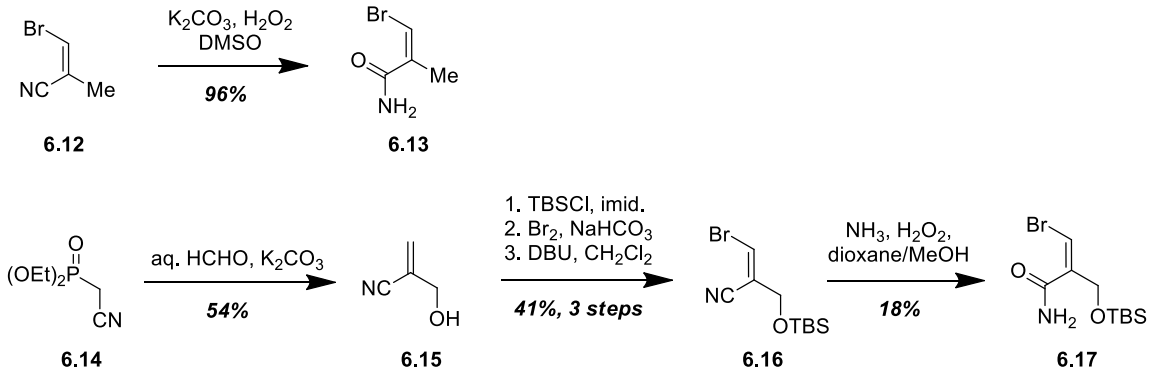
by Corey[7] and Fuchs. Pd-catalyzed *syn*-hydrostannation[8] provided the vinyl stannane **6.11** that served as the precursor for a Stille coupling.

Scheme 44. Paterson's Synthesis of the Vinyl Stannane **6.11**



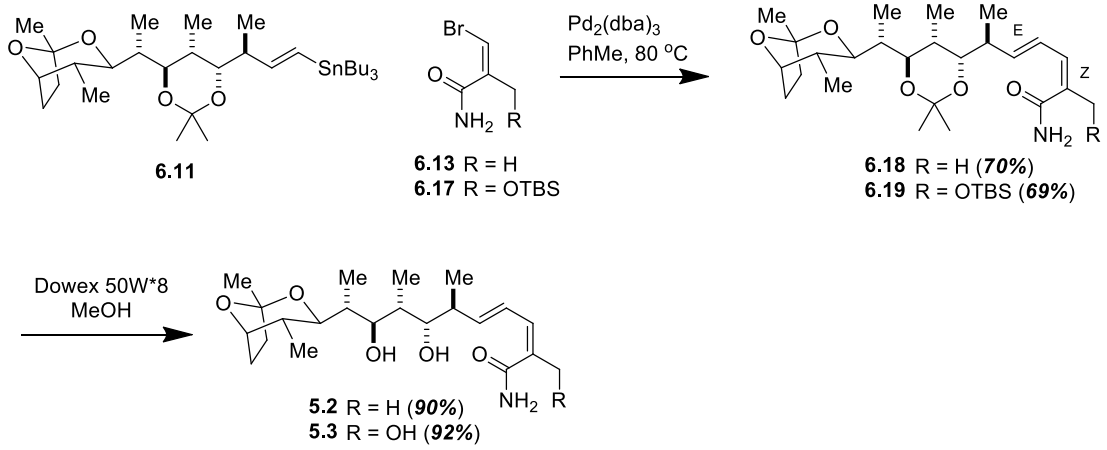
A straightforward route to the Stille coupling partners, i.e. vinyl bromides **6.13** and **6.17,** was explored (Scheme 45). The known *Z* alkene **6.12**[9] was hydrolyzed under oxidative conditions[10] (K_2CO_3, H_2O_2) to give the corresponding primary amide **6.13**. Treatment of phosphonate **6.14** with formaldehyde and K_2CO_3 furnished allylic alcohol **6.15** via an addition-elimination sequence. Silylation, bromination and elimination allowed formation of vinyl bromide **6.16**. Finally, a low yielding hydrolysis delivered the amide **6.17** which retained the *E*- configuration.

Scheme 45. Paterson's Syntheses of Vinyl Bromides **6.13** and **6.17**



With all three fragments (**6.11**, **6.13**, and **6.17**) in hand, they turned their attention to the Stille coupling (Scheme 46).[11] For both saliniketals A and B, this proceeded well with catalytic amount of $Pd_2(dba)_3$ in toluene at 80 ^oC. The final cleavage of the acetonide was then performed with Dowex resin in MeOH, which accomplished saliniketals A (**5.2**) and B (**5.3**), respectively. In summary, Paterson and co-workers completed the total syntheses of saliniketal A in 17 longest linear sequence in 20% overall yield, and saliniketal B in an identical 17 longest linear sequence and 19.5% overall yield.

Scheme 46. Paterson's Syntheses of Saliniketals A and B

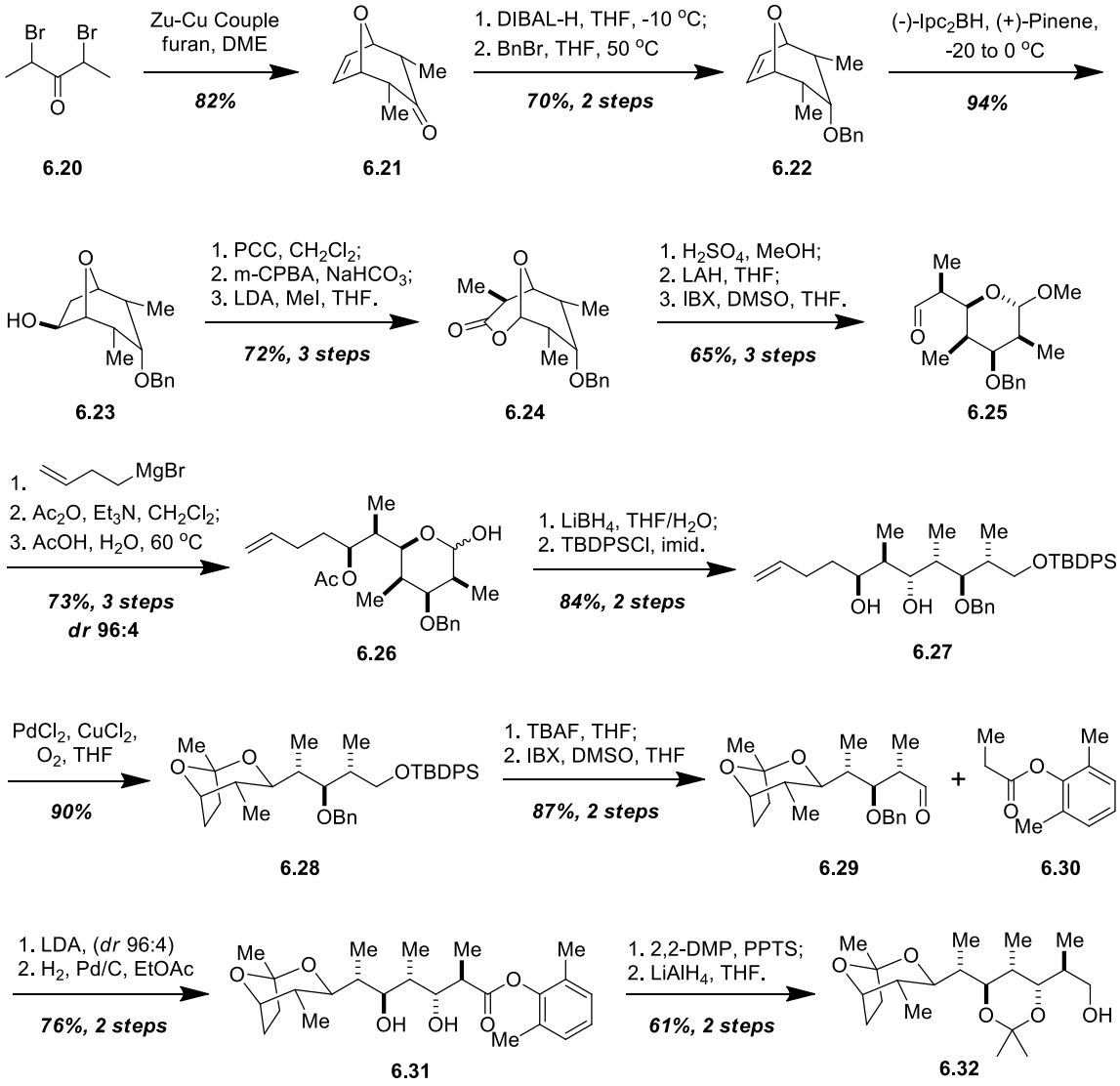


6.1.2 Yadav Formal Synthesis

In 2009, Yadav and co-workers reported a stereoselective formal synthesis of saliniketals A (**5.2**) and B (**5.3**).[3]

Their synthetic work started from a Cu-Zn couple mediated [4+3] cycloaddition[12] between dibromoketone **6.20** and furan to give bicyclic compound **6.21** (Scheme 47). DIBAL-H reduction followed by benzylation yielded benzyl ether **6.22** in 70% yield over two steps. An asymmetric hydroboration of alkene **6.22** afforded alcohol **6.23**. Then, oxidation by PCC, Bayer-Villiger oxidation[13] and alkylation formed *exo*-alkylated lactone **6.24**. Acid-methanolysis[14] of the lactone **6.24**, LAH reduction followed by oxidation (IBX, DMSO)[15] gave the aldehyde **6.25** (65% yield, 3 steps). After a substrate controlled Grignard addition[16] of **6.25** with 1-butenylmagnesium bromide (90% yield and 96:4 *dr*) and acylation, this material was subjected to aqueous acetic acid to deliver a mixture of lactol **6.26**. $LiBH_4$ mediated reduction then cleaved the lactol **6.26**, which was selectively silylate as compound **6.27**. Like the strategy used by Paterson,[1] an intramolecular Wacker-type cyclization of diol **6.27** in the presence of a catalytic amount of $PdCl_2$ and $CuCl_2$ under oxygen atmosphere yielded dioxabicycle **6.28** (90%). A subsequent fluoride mediated deprotection followed by oxidation furnished the aldehyde **6.29**. According to Pirung-Heathcock conditions,[17] the aldol coupling between the ketone **6.30** and aldehyde **6.29** gave the *anti*-adduct with excellent diastereoselectivity (*dr* 96:4), which afforded diol **6.31** via debenzylation. Acetonide formation of diol **6.31** followed by reduction yielded the Paterson intermediate **6.32**. The ^{1}H NMR and ^{13}C NMR data of alcohol **6.32** were in good agreement with the data reported by Paterson. In summary, Yadav and co-workers finished a formal synthesis of saliniketals in a 22 longest linear sequence with 10% overall yield.

Scheme 47. Yadav Formal Synthesis of Saliniketals

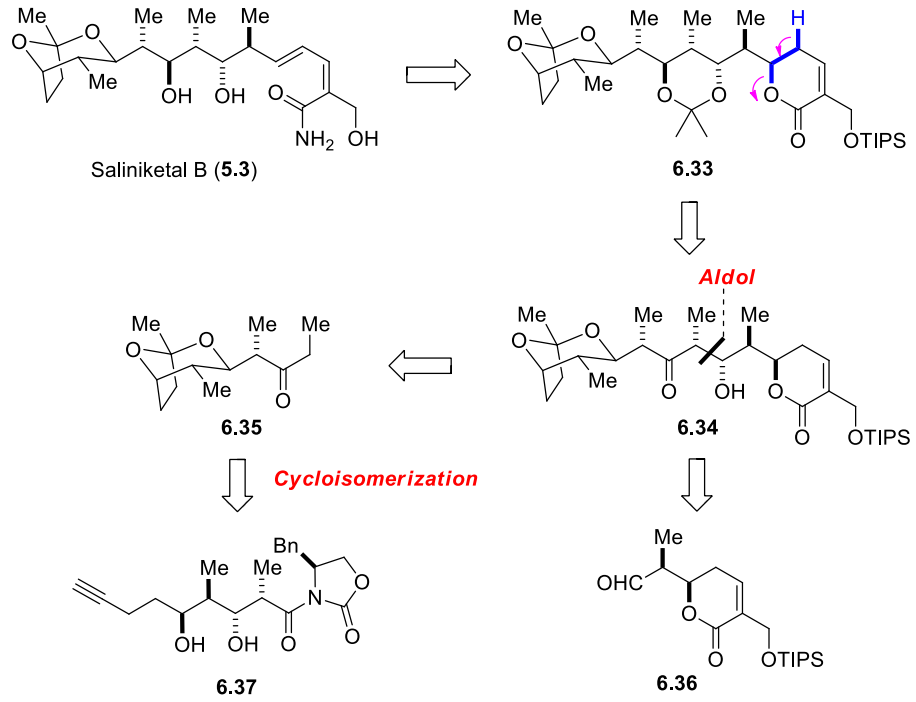


6.1.3 De Brabander Synthesis of Saliniketal B

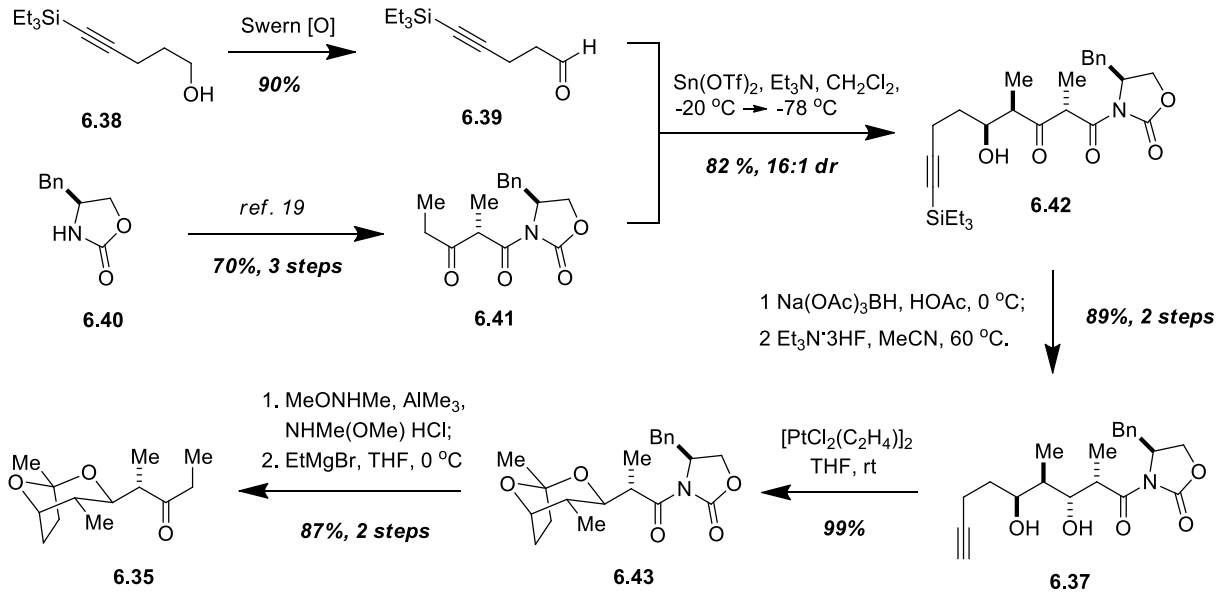
Before I started the synthetic study towards the saliniketal family, our group had already completed the synthesis of saliniketal B[2] that features a strategy aimed at enabling future structure-function and mode-of-action studies, which provided me a solid foundation to this project.

This synthetic strategy (Scheme 48) was based on a convergent aldol coupling of fragments **6.35** and **6.36** following an *anti*-selective reduction of *β*-hydroxyketone **6.34**. They envisioned a late-stage installation of the *E,Z* dienamide via a fragmentation of a dihydropyranone. The unusual 2,8-dioxabicylo[3.2.1]octane moiety was achieved via cycloisomerization of alkynediol **6.37** by exploiting methodology[18] developed by the De Brabander group.

Scheme 48. Retrosynthetic Analysis for De Brabander's Synthesis of Saliniketal B

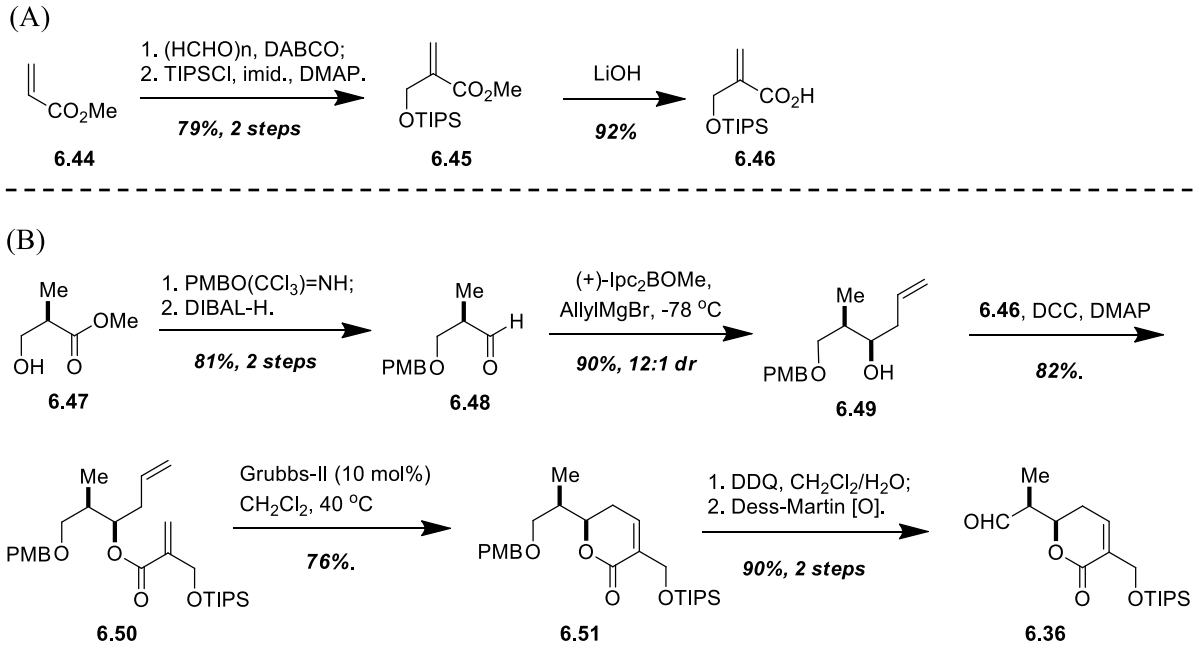


Scheme 49. De Brabander's Synthesis of the Ethyl Ketone **6.35**



According to Evans's protocol, oxazolidinone **6.41**[19] was achieved from (*S*)-4-benzyl-2-oxazolidinone **6.40** in three steps (Scheme 49). The reagent-controlled aldol reaction of the stannyl enolate derived from **6.41** with aldehyde **6.39**, obtained from oxidation of commercially available alkynol **6.38** (95% yield), produced aldol product **6.42** in 82% yield and 16:1 *dr*. *Anti*-selective reduction with $Na(OAc)_3BH$[20] (preparing from $NaBH_4$ and HOAc *in situ*, >20:1 *dr*) followed by desilylation (89% yield, 2 steps) set the stage for a cycloisomerization of alkynediol **6.37**. Use of 5 mol % Zeise's dimer[18] afforded 2, 8-dioxabicyclo[3.2.1]octane **6.43** in 99% yield. This compound was processed to ethyl ketone **6.35** via Weinreb amide[21] formation and Grignard reaction with EtMgBr (87%, two steps). From the known ethyl ketone **6.41**, the ethyl ketone **6.35** was accomplished in 7 linear steps with 56% overall yield.

Scheme 50. De BraBander's Synthesis of the Aldehyde **6.36**

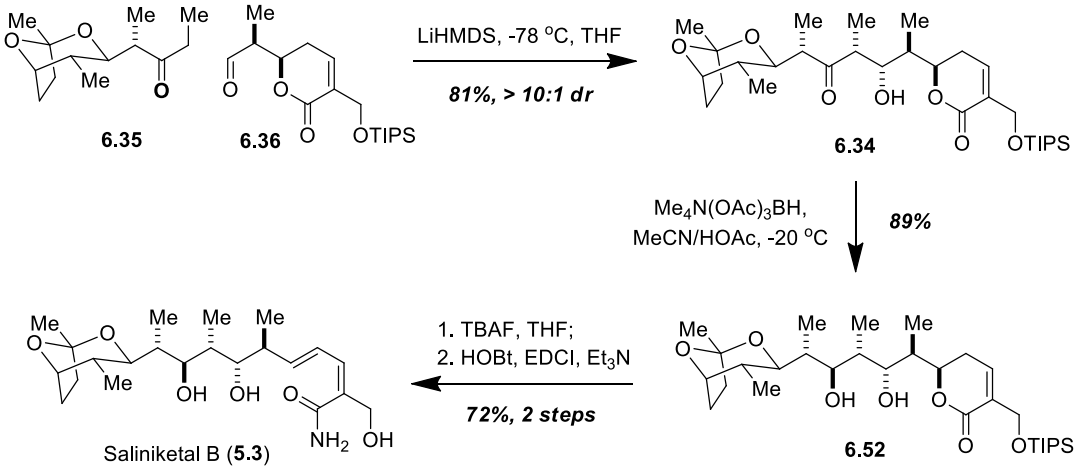


For the aldehyde **6.36**, the synthesis started from the commercial available Roche ester **6.47**[22] (Scheme 50, panel B). According to a sequence reported by Nicolaou[23] and co-workers, *p*-methoxybenzyl ether formation (87%) was followed by semi-reduction to aldehyde **6.48** (93%) and asymmetric allylation with Brown's reagent[24] (90%, 12:1 *dr*). The resulting *syn*-homoallylic alcohol **6.49**, was esterified with acid **6.46**, which was prepared from methyl acrylate **6.44** via Baylis-Hillman reaction,[25] silylation, and saponification (73%, three steps, scheme 50, Panel A). Dihydropyranone formation to give **6.51** was accomplished in 80% yield via ring-closing metathesis with Grubbs' second-generation catalyst[26] under high dilution conditions. Final oxidative deprotection (DDQ) and oxidation with Dess-Martin periodinane delivered aldehyde **6.36** in seven steps with 36% overall yield.

The aldol coupling (Scheme 51) between ethyl ketone **6.35** and aldehyde **6.36** yielded the *anti*-Felkin adduct **6.34** with high selectivity (>10:1 *dr*) in 81% yield. Next, reduction of *β*-hydroxy

ketone **6.34** delivered *anti*-diol **6.52** (89%). Finally, fluoride-mediated desilylation and concomitant fragmentation of the dihydropyranone[27] followed by in situ amidation of the liberated carboxylic acid provided saliniketal B (**5.3**) with a 72% yield for this one-pot operation. In summary, the De Brabander group[2] achieved a short, highly efficient synthesis of saliniketal B in 11 steps (longest linear sequence) and 23% overall yield.

Scheme 51. De Brabander's Synthesis of Saliniketal B



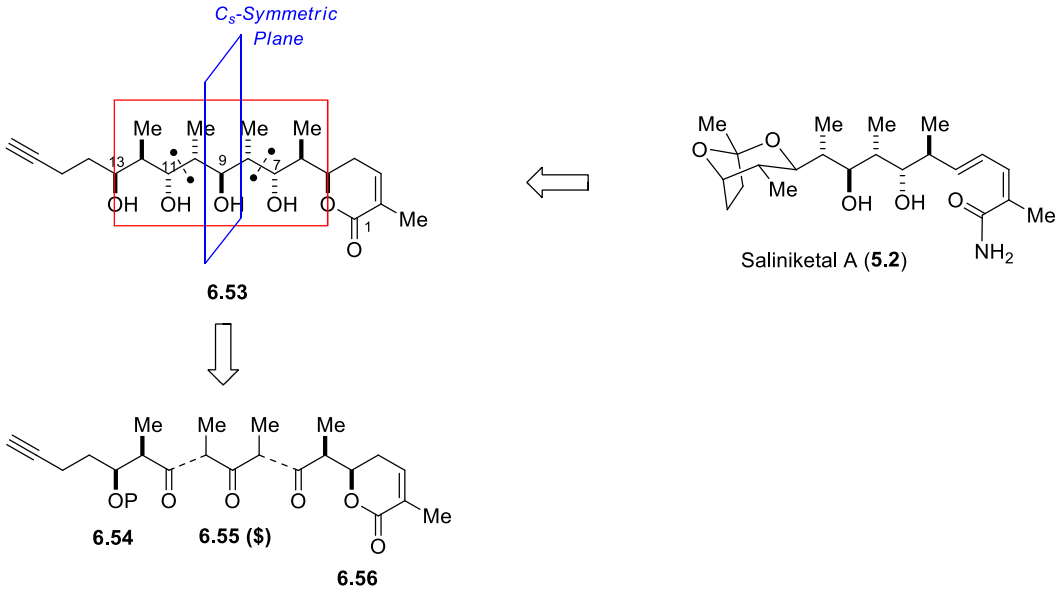
6.2 Total Synthesis of Saliniketal A

Although the previous synthesis of saliniketal B proved to be rather efficient and in principle could be easily adapted for the synthesis of saliniketal A (**5.2**), I decided to explore alternative pathways toward saliniketals.

6.2.1 Synthetic Plan towards Saliniketal A

The initial retrosynthetic analysis, as shown in scheme 52, was envisioned to install the *E*,*Z* dienamide via a base-mediated fragmentation[27, 28] of a dihydroxypyranone ring as before (see **6.53**). I recognized a hidden *Cs*-symmetry element when unraveling the dioxabicyclo ring system to alkyne **6.53**. This would lead to a strategy where 3-pentanone **6.55** would form the linkage to couple aldehydes **6.54** and **6.56**. The stereochemical requirements for both aldol reactions (**6.55** + **6.54** and **6.55** + **6.56**) would be the same, namely a 1,2-*syn*/1,3-*anti* relation in the product. Given that the aldol reaction of aldehyde **6.36** and ethyl ketone **6.35** gave good yield with excellent diasteroselectivity (see Scheme 48) found by the De Brabander group previously, we were hopeful that we could couple 3-pentanone **6.55** and aldehyde **6.56** with a similar stereochemical outcome.

Scheme 52. Initial Plan for the Synthesis of Saliniketal A



6.2.2 Aldol Studies

Keeping this in mind, we explored the synthetic route shown in scheme 53. After one step oxidation from commercial available alkynol **6.57**, the aldehyde **6.58** was subjected to asymmetrical croylation[29] with a borane reagent derived from *n*-BuLi and (-)-Ipc_2OMe, which generated the *syn*-olefin **6.59** with excellent yield (87%) and good diastereoselectivity (*dr* >10:1). Silylation followed by oxidative cleavage ($NaIO_4$, OsO_4) of the terminal alkene **6.59** delivered the aldehyde **6.60**. Next, we carefully investigated the aldol coupling between the aldehyde **6.60** and ketone **6.55** (see Table 15 for conditions). The *Z*-lithium enolate has been documented[30] to preferentially afford the *anti*-Felkin adduct with an *anti* Me-Me configuration. In our case, however, the addition of the *Z*-lithium[31] enolate derived from **6.55** (Table 15, entry 1) to chiral aldehyde **6.60** afforded an inseparable mixture of *syn*-aldol products with poor yield (27%) and diastereoselectivity (*dr* 2:1), favoring the undesired isomer **6.61**. Switching to the boron enolate[32] (entry 2), only complex mixtures were observed, whereas the titanium enolate[33] (entry 3), provided Felkin adduct **6.61** with a *syn* Me-Me relationship as a single diastereomer (53% yield) when 1 equivalent $TiCl_4$ and tributyl amine were used. In case when two equivalents of $TiCl_4$ and corresponding amounts of base were added (entry 4), only eliminated and cyclized compound **6.63** was obtained. In addition, we also found that when the diisopropylethyl amine was used along with $TiCl_4$ (entry 5), the yield and selectivity for undesired **6.61** could be improved to 73% and > 20:1 *dr*.

At this point, we do not understand these results in light of current models for asymmetric induction. Roush had provided a general model to explain the stereochemical outcome of the aldol reaction between *Z*-(O)-enolates[30] and α-methyl chiral aldehydes. To avoid the *syn*-pentane

interaction, the *anti*-Felkin adduct would be preferentially formed via the transition state (as shown in eq. 6.1A) to give the 2,3-*syn*-3,4-*anti* configuration. Perhaps the alkyne was the culprit. In this context, Danishefsky and coworkers have observed an unusual influence of an olefin to the aldehyde in aldol reactions with α-methyl substituted alkenals.

(6.1A)

Scheme 53. Initial Synthetic Efforts

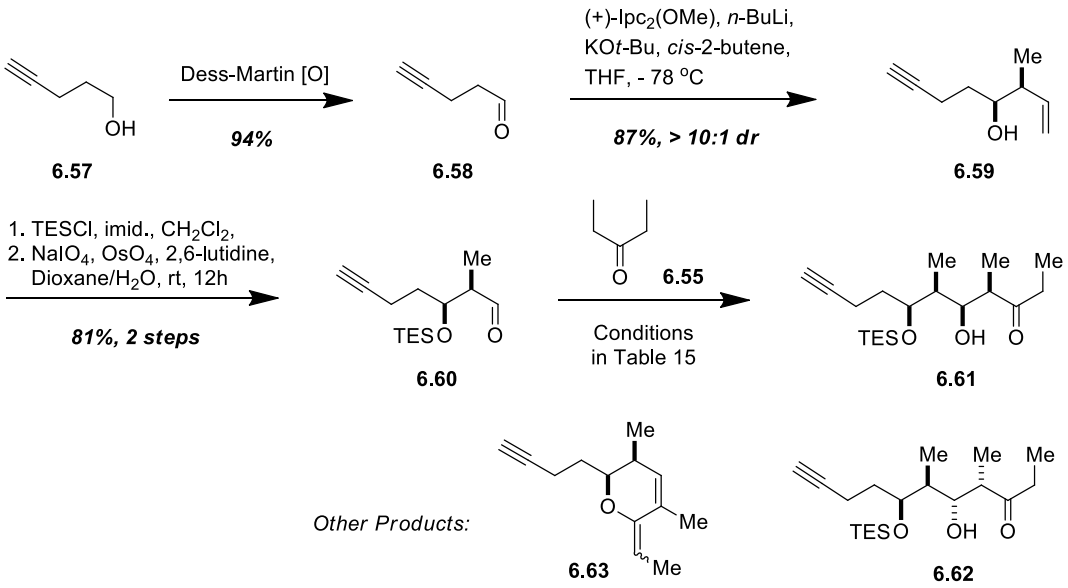


Table 15.[a] Investigation of Aldol Coupling between **6.60** and **6.55**

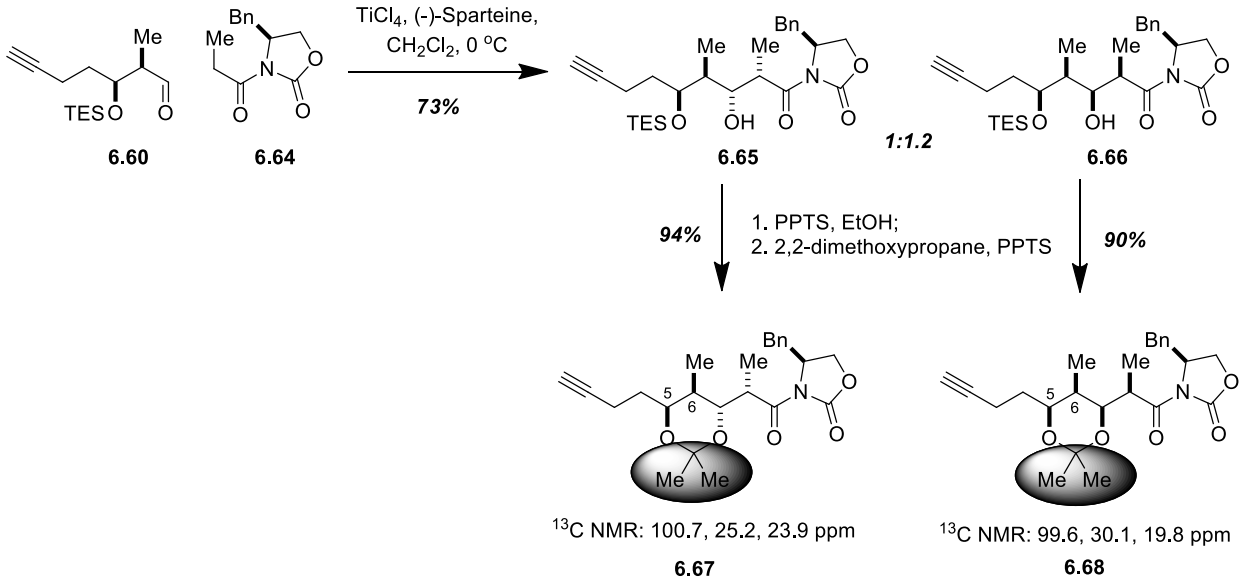
Entry	Conditions[b]	Major Product	Results[c]
1	LiHMDS, CH_2Cl_2, - 78°C	**6.61**	27%, 2:1 *dr*
2	Bu_2BOTf, *i*-Pr_2NEt, Et_2O, -78 °C	-	Complex mixtures
3	$TiCl_4$, Bu_3N, CH_2Cl_2, - 78 °C	**6.61**	53%, single pdt
4	2.0 eq $TiCl_4$, 2.2 eq. Bu_3N, THF, - 78 to - 50 °C	**6.63**	45%
5	$TiCl_4$, *i*-Pr_2NEt, CH_2Cl_2, - 78°C	**6.61**	73%, >20:1 *dr*

[a]All reactions were performed with 0.1 mmol ethyl ketone **6.55** and aldehyde **6.60**. [b]Unless otherwise noted, 1.0 equivalent metal reagent and 1.1 equivalents of base were used. [c]Isolated yields.

Unable to construct the C_{10}-C_{11} bond with desired configuration, we resorted to auxiliary aldol approaches. At first, we turned to the aldol coupling between **6.60** and **6.64** based on Evans's procedure[34] (Scheme 54). However, the facial selectivity was poor (1:1.2) and the undesired all *cis* adduct **6.66** was the major product. Desilylation of **6.65** and **6.66** followed by acetonide formation produced the compounds **6.67** and **6.68**, respectively. The ^{13}C NMR data confirmed the relative configurations[35] of **6.67** and **6.68**.

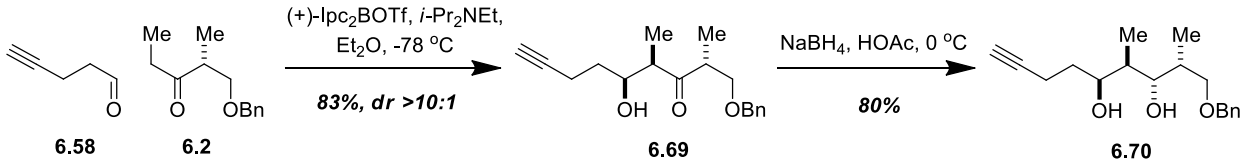
Next, we explored the aldol coupling between Paterson's ethyl ketone **6.2**[4] and aldehyde **6.58** (Scheme 55). The reagent controlled aldol reaction between *Z*-boron enolate derived from **6.2** and commercial available aldehyde **6.58** accomplished the 1,2-*syn* adduct **6.69** in 83% yield and high diastereoselectivity (> 10:1 *dr*) in favor of the desired stereocenter. This result is similar to that has been observed by Paterson in a similar aldol reaction with 4-pentenal (see Scheme 43). 1,3-*Anti*-selective reduction ($NaBH_4$ in HOAc) of **6.69** set the stage for a cycloisomerization of alkynediol **6.70**, which will be described later.

Scheme 54. Aldol Reaction between Ethyl Ketone **6.64** and Aldehyde **6.60**



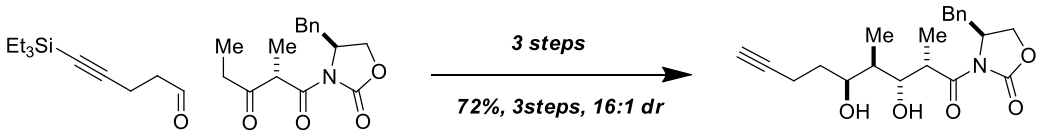
6.60 **6.64** **6.65** **6.66** **6.67** **6.68**

Scheme 55. Aldol Reaction between Ethyl Ketone **6.2** and Aldehyde **6.58**



6.58 **6.2** **6.69** **6.70**

Scheme 56. Aldol Reaction between Ethyl Ketone **6.41** and Aldehyde **6.39**



6.39 **6.41** **6.37**

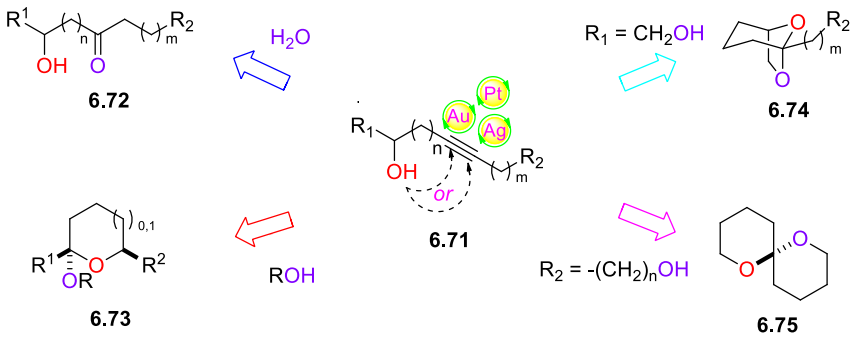
Finally, we also resorted to our previous aldol strategy explored for saliniketal B (Scheme 56). The reagent-controlled aldol reaction of the stannyl enolate derived from **6.41** with aldehyde

6.39 produced aldol product in 82% yield and 16:1 *dr*. *Anti*-selective reduction with $Na(OAc)_3BH$[20] (preparing from $NaBH_4$ and HOAc *in situ*, >20:1 *dr*) followed by desilylation (89% yield, 2 steps) set the stage for a cycloisomerization of alkyediol **6.37**, which will be described in the following paragraph.

6.2.3 Cycloisomerization Studies

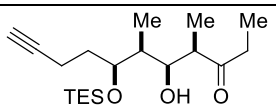
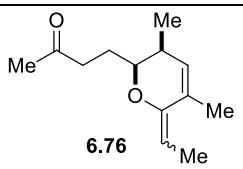
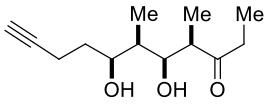
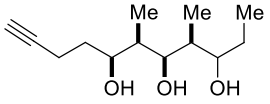
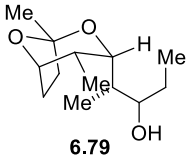
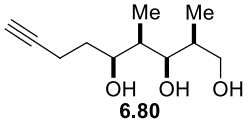
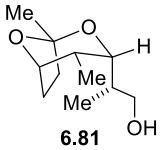
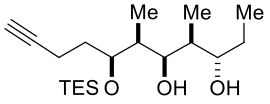
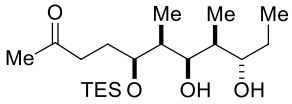
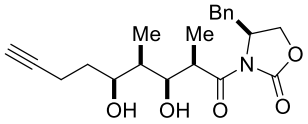
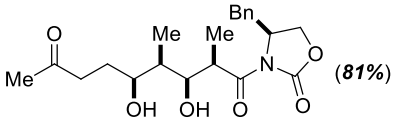
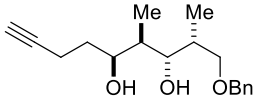
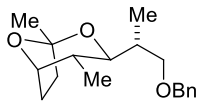
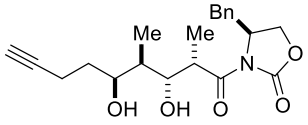
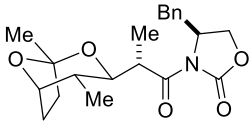
Several years ago, the De Brabander group developed a room temperature cycloisomerization[18] of unactivated alkynols (Scheme 57). Under the appropriate conditions, different types of scaffolds could be accomplished depending on substrates, catalysts and reaction conditions. Typically, *β*-hydroxyl ketones (**6.72**), acetals (**6.73**), bridged ketals (**6.74**), and spiroketals (**6.75**), were all available. The unique 2, 8-dioxabicyclo[3.2.1]octane structure in the saliniketal family provides a prefect testing ground for this synthetic methodology.

Scheme 57. Metal-Catalyzed Regioselective Oxy-Functionalization of Alkynes



With a limited set of alkynediol sbustrates available (see above sections 6.2.1 and 6.2.2), we investigated them as substrates for Pt(II)-catalyzed cycloisomerzation. As shown in table 16, treatment of the substrate **6.61** (entry 1) with our standard catalytic conditions (5 mol% Zeise's dimer, THF, ambient temperature) led to the diene **6.76**. Presumably, this product was formed via alkyne hydration, *β*-hydroxy elimination, desilylation, and final lactolizaton/dehydration. Surprisingly, without TES group, the same substrate was not reactive even after 1.5 hours and all the starting material **6.77** (entry 2) was recovered. When the carbonyl group was reduced (→ **6.78**), the desired cycloisomerization was observed (**6.79**, entry 3). A similar result (→ **6.81**) was obtained with truncated triol substrate **6.80** (entry 4). If the hydroxyl group at C5 was protected (entry 5), alkyne hydration to ketone **6.83** was observed. Interestingly, in the case of substrate **6.84** (entry 6), ketone formation (→ **6.85**) was observed without bicyclic ring formation. Compared to entry 4, this result indicates that additional steric bulk associated with the oxazolidinone or H-bond formation with the *β*-carbonyl could prevent ring formation. In contrast, diastereomeric alkynediol **6.37** (entry 8) smoothly provided dioxabicyclo[3.2.1]octane product **6.43** in 99% yield. In addition, cycloisomerization of alkynediol **6.70** afforded the desired compound **6.5** (entry 7, 95% yield), which was identical with Paterson's intermediate synthesized from **6.2** (Scheme 43). The ^{1}H NMR and ^{13}C NMR data for **6.5** were in good agreement with the data reported by Paterson.[1]

Table 16.[a] Substrates Scope for Zeise's dimer Catalyzed Cycloisomerization[b]

Entry	Substrates	Products
1	 **6.61**	 **6.76** (***65%***)
2	 **6.77**	**n. r.**
3	 **6.78**	 **6.79** (***97%***)
4	 **6.80**	 **6.81** (***94%***)
5	 **6.82**	 **6.83** (***78%***)
6	 **6.84**	 **6.85** (***81%***)
7	 **6.70**	 **6.5** (***95%***)
8	 **6.37**	 **6.43** (***99%***)

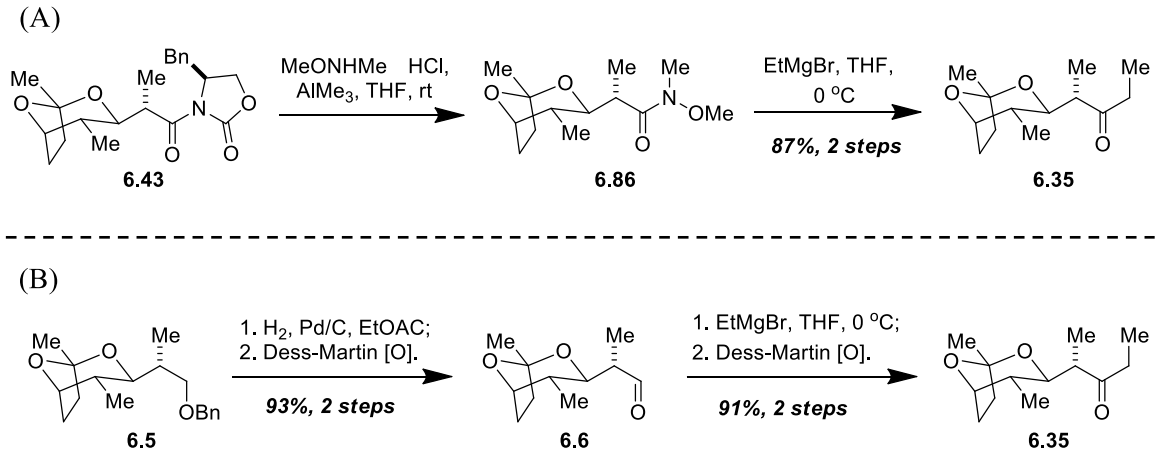
[a]All reactions were performed in 0.1 mmol scale. [b]In all cases, 5 mol% of Zeise's dimer were used and THF were used as the solvent without any inert atmosphere protection in ambient temperature. The reaction times were range from 5 minutes to 1.5 hours and details see 6.4 experimental procedures. [c]Only the major products are shown. [d]All the yields are isolated yields.

6.2.3 Synthesis of Saliniketals A

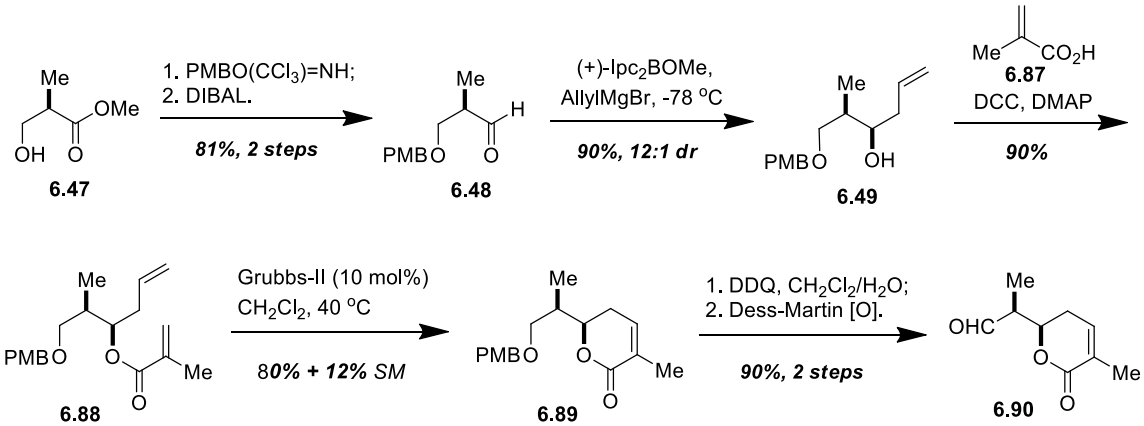
With the cycloisomerization accomplished, oxazolidinone **6.43** (Scheme 58, panel A) was processed to ethyl ketone **6.35** via Weinreb amide formation[21] (→ **6.86**) and Grignard reaction with EtMgBr (87%, 2 steps). Alternatively, ethyl ketone **6.35** was obtained from **6.5** via debenzylation/Dess-Martin oxidation (→ **6.6**, Scheme 58, panel B), followed by Grignard addition and another Dess-Martin oxidation.

In conclusion, ethyl ketone **6.35** was obtained via two alternative routes, each with 7 linear steps and 56% and 49% overall yield, respectively.

Scheme 58. Two Alternative Routes to Synthesis of the Ethyl Ketone **6.35**



Scheme 59. Synthesis of the Dihydropyranone **6.90**

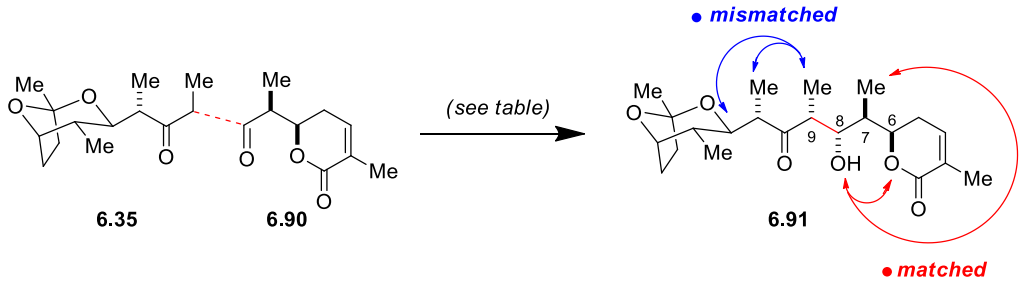


The synthesis of dihydropyranone fragment **6.90** started from the commercial available Roche ester **6.47**[22] (Scheme 59) as described previously for saliniketal B in Scheme 50. Thus, *p*-methoxybenzyl ether formation (87%) was followed by semireduction to aldehyde **6.48** (93%) and asymmetric allylation with Brown's reagent[24] (→ **6.49**, 90%, 12:1 *dr*). The resulting *syn*-homoallylic alcohol **6.49**, was esterified with methacrylic acid **6.87**. Dihydropyranone formation to give **6.89** was accomplished in 80% via ring-closing metathesis with Grubbs' second-generation catalyst[26] under high dilution conditions. Final oxidative deprotection (DDQ) and oxidation with Dess-Martin periodinane delivered aldehyde **6.90** in seven steps and 39% overall yield.

With both fragments in hand, we turned our attention to the coupling between ethyl ketone **6.35** and aldehyde **6.90** (table 17). For this double stererodifferenating aldol reaction,[31] the relative *syn*-relationship between the methyl at C_9 and hydroxyl at C_8 would be enforced through a cyclic transition state with a *Z*-enolate. Based on the literature precedent,[28] the diastereofacial bias of the chiral aldehyde would favor production of the *anti*-Felkin adduct with an *anti*-relationship between the hydroxyl at C_8 and methyl at C_7, by minimizing the *syn* pentane interactions

according to Roush's model[30, 36] (model 6.2-A, eq. 6.2), and also favor the *anti*-relationship between the hydroxyl at C_8 and *β*-alkoxy group at C_6 by minimizing dipole-dipole interactions[37] (model 2-B, eq. 6.2) according to Evan's model, a fully matched situation. Although the stereochemistry of the *β*-alkoxy is not important for the final product (will be destroyed during the dihydropyranone fragmentation), it was engendered to favor the desired stereochemical outcome for this aldol reaction. On the other hand, the diastereofacial bias of chiral enolates depend on the *α*-methyl and *β*-alkoxy stereocenters. The predicted bias for enolates of this type would preferentially afford the *anti*-Me, Me relationship via minimization of $A^{1,3}$ –strain (eq. 6.2A), a mismatched situation.

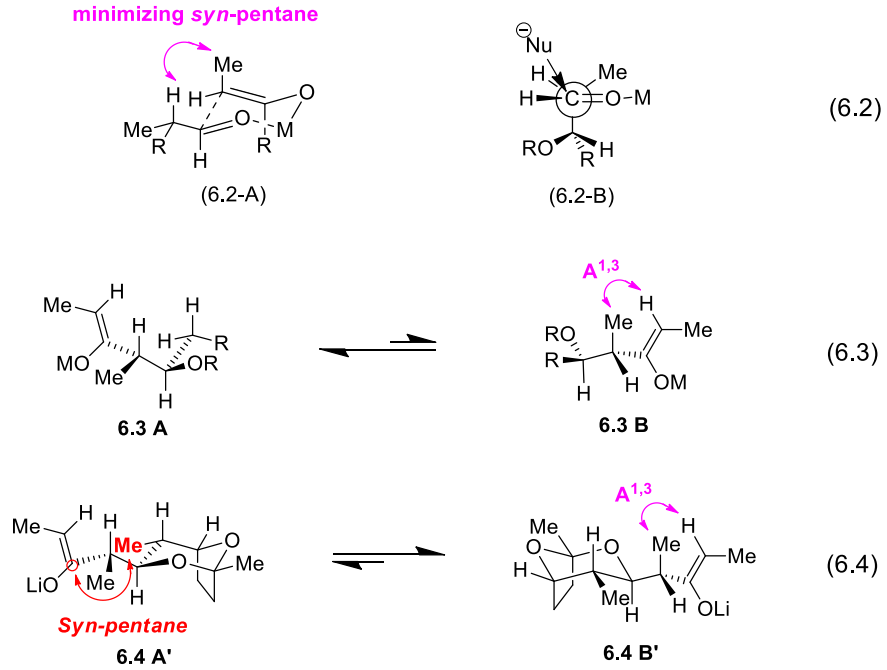
Table 17.[a] Investigation of the Aldol Coupling between Ethyl Ketone **6.35** and Aldehyde **6.90**



Entry	Conditions	Results
1	$TiCl_4$, Bu_3N, CH_2Cl_2, - 78°C	recovered **6.90**
2	$TiCl_4$, *i*-Pr_2NEt, CH_2Cl_2, - 78°C	recovered **6.90**
3	LiHMDS, THF, -78 °C	77%[b], >10:1 *dr*[c]

[a]All the reactions were performed in 0.1 mmol scale of ethyl ketone **6.35** and 1.1 equivalents of aldehyde **6.90**. [b]isolated yield. [c]The relative configuration was confirmed by further preparation of the corresponding acetonide.

In the event, treatment of the titanium *Z*(O)-enolate derived from **6.35** with aldehyde **6.90** led to complete decomposition of **6.35** and recovered aldehyde **6.90** (Table 17, entries 1 and 2). Fortunately, we found that treatment of **6.35** with LiHMDS followed by addition of aldehyde **6.90** delivered the desired *anti*-Felkin adduct **6.91** with good yield (entry 3, 77%) and highly selectivity (*dr* 10:1). Based on this unexpected result, we postulated that the observed excellent diastereoselectivity for this reaction can be attributed to the presence of the additional γ-Me stereocenter. As shown in eq. 6.3, normally, the *Si*-enolate face is exposed via conformation A, minimizing $A^{1,3}$-strain in the transition state, whereas the additional γ-Me group disfavors this conformation as a result of unfavorable *syn*-pentane interactions (eq. 6.4). This exposes the enolate *Re*-face via B′ for a matched reaction with aldehyde **6.90**. We are currently testing this hypothesis by preparing the corresponding γ-desmethyl and epimeric analogs of ketone **6.35**, which are expected to give a lower selectivity, according to this analysis.



Having achieved a highly stereoselective aldol coupling, we turned our attention to complete the synthesis of saliniketal A (**5.2**, Scheme 60). A stereoselective reduction[38] of *β*-hydroxyl ketone **6.91** followed by protection delivered the corresponding acetonide **6.92**[35] (81% over two steps). ^{1}H and ^{13}C NMR analysis of this derivative confirmed the 1, 3-*anti* configuration.

Scheme 60. Completion of the Synthesis of Saliniketal A

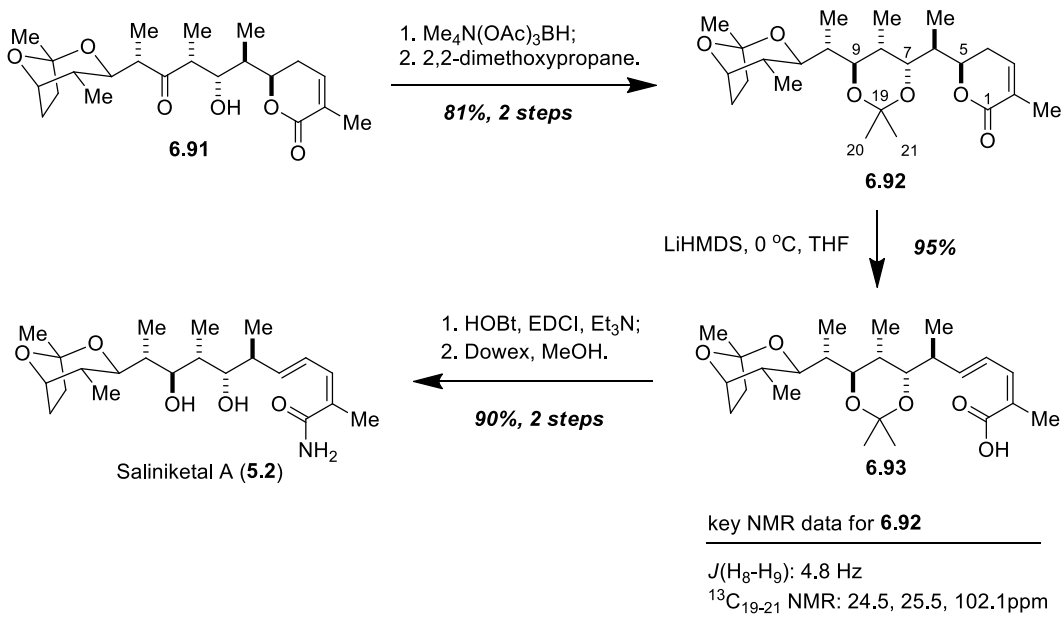


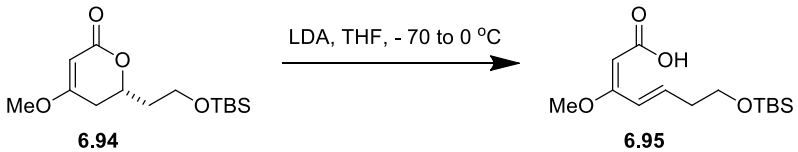
Table 18.[a] Investigation of the Elimination of Tetahydropyranone **6.92**

Entry	Conditions	Results[b]
1	*t*-BuOK, THF, 0 °C, 24 h	13% **6.93** + 60% sm
2	DBU, THF, rt, 48 h	20% **6.93** + 65% sm
3	LiHMDS (10 eq.), THF, 0 °C , 1 h	95% **6.93**
4	TBAF (10 eq.), THF, rt, 24 h	40% **6.93** + 55% sm

[a]All the reactions were performed on 0.1 mmol scale. [b]Isolated yields.

At this point, we could execute the fragmentation of dihydropyranone **6.92**. During the course of our previous synthetic study towards saliniketal B, we found that the TBAF-mediated desilylation[27] of the primary alcohol present in saliniketal B, induced concomitant elimination. Applying the same reaction conditions to furnish the *E,Z*-dienoic acid **6.93**, however, only led to recovered starting material **6.92**. When ten equivalents of TBAF (1.0 M solution in THF) were added, only ~ half the amount of starting material was converted into the desired *E,Z*-dienoic Acid **6.93** (Scheme 18, entry 4), and any further efforts, i.e. heating or prolonging reaction time, resulted in decomposition of **6.92**. These results indicate that the corresponding process for saliniketal B would be one occurring via an intramolecular alkoxide-mediated fragmentation (in situ obtained via desilyation). Next, we tried some inorganic bases, such as *t*-BuOK[39] (entry 1) and 1,8-diazabicycloundec-7-ene[40] (DBU, entry 2) which only led to low conversion along with recovered the dihydropyranone **6.92**. Fortunately, we found that if LiHMDS (entry 3) was added at 0 ^{o}C, it formed the desired conjugated acid **6.93** in 95% yield. Earlier this year, Donner[41] reported a similar LDA mediated fragmentation of dihydropyranone (Scheme 61). Finally, amidation[42] (1.0 M NH_3 in dioxane, HOBt, EDC in THF) and deprotection provided saliniketal A (**5.2**). Here, we have achieved a short, highly efficient synthesis of saliniketal A in totally 12 steps, and 23.5 overall yield, comparing favorably to the Paterson's synthesis (17 steps, 18.4% overall yield).[1]

Scheme 61. LDA Mediated Fragmentation of Dihydropyranone Reported By Donner



6.94 **6.95**

6.3 Total Synthesis of Salinisporamycin and Rifsaliniketal

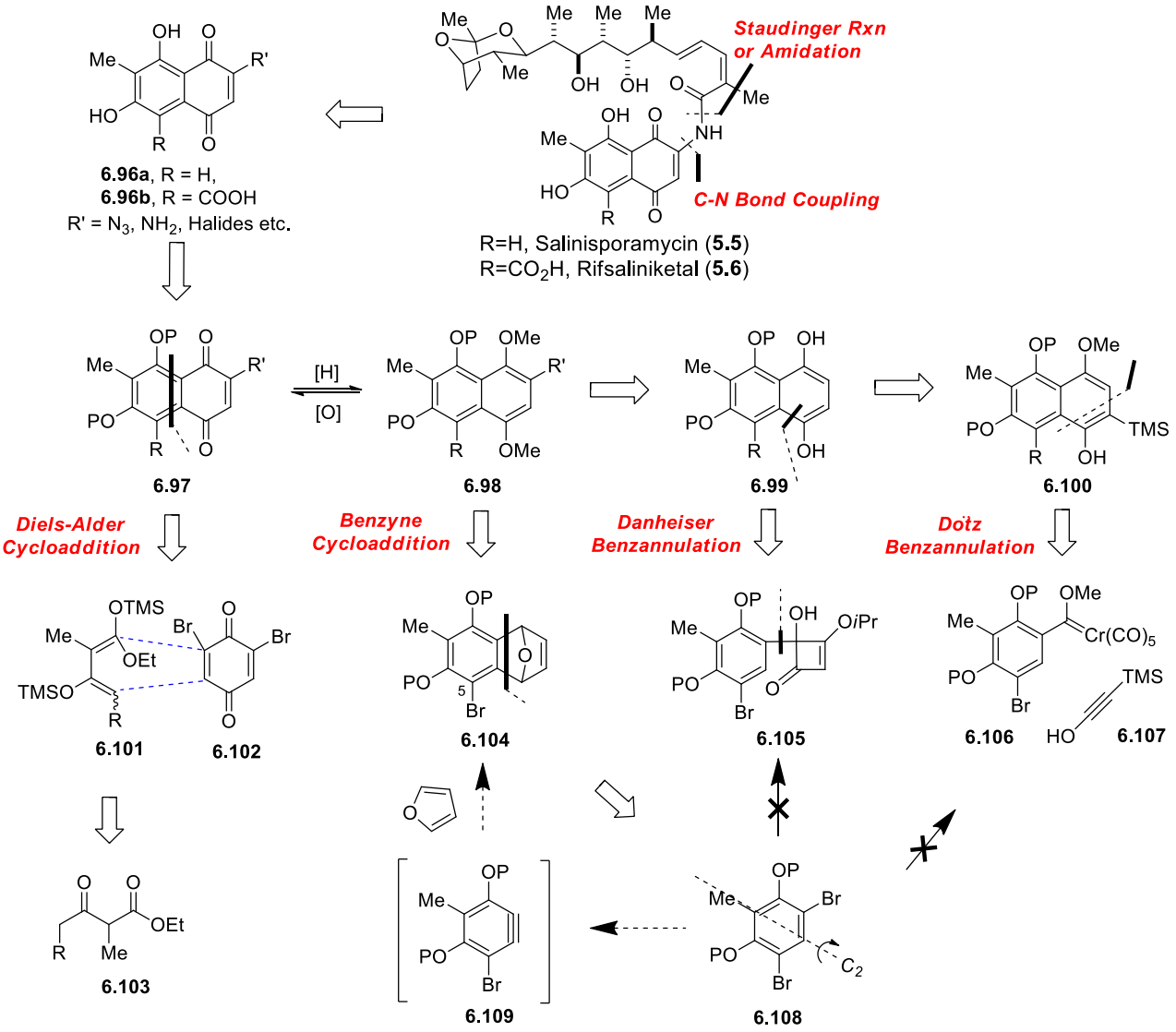
During the course of my Ph.D. studies, two new natural products related to saliniketals were isolated. Salinisporamycin (**5.5**) was disclosed in 2009 by Mastuda,[43] and rifsaliniketal (**5.6**) was recently isolated by John MacMillan and coworkers[44] at UT Southwestern. Salinisporamycin and rifsaliniketal share the same side chain with saliniketals, connected through an amide motif to a naphthoquinone. We envisioned three possible methods (Scheme 62) to connect the two subunits: (a) a Staudinger ligation[45] between saliniketal acid and naphthoquinone/quinol azide, (b) peptide coupling[42] between saliniketal acid and naphthoquinone/quinol aryl amine, or (c) transition metal catalyzed C-N bond coupling between saliniketal and naphthoquinone/quinol halide. Before executing the fragment coupling, we moved our attention to explore synthetic routes towards many functionalized naphthoquinone/quinol fragments (Scheme 62).

Considering a potential facile redox interconversion between naphthoquinones and naphthoquinols, we envisioned various approaches towards fragments **6.97** and/or **6.98**.

The naphthoquinone **6.97** could either be obtained from naphthalene **6.98** or synthesized from a Diels-Alder reaction[46] between 2,6-dibromobenzoquinone **6.102** and silylated diene **6.101**. For the reduced naphthalene **6.98**, we envisioned a benzyne cycloaddition[47] between a benzyne (**6.109**) generated from *C2*-symmetical dibromozenzene **6.108** and furan to yield intermediate **6.104**. Reductive *O*-ring opening of **6.104** and transmetalation at the C_5 position could allow access to many functionalized naphthoquinols (**6.98)**. The Danheiser benzannulation[48] and Dotz benzannulation[49] provide two alternative possible routes to access the naphthalene **6.98** from intermediates **6.105** and **6.106**, respectively. In practice, however, efforts to prepare both of the necessary key intermediates **6.105** (Danheiser benzannulation), and **6.106** (Dotz benzannulation)

failed. In what follows, we therefore focused on the Diels-Alder and benzyne cycloaddition approaches.

Scheme 62. Retrosynthetic Plan for Aryl Fragments

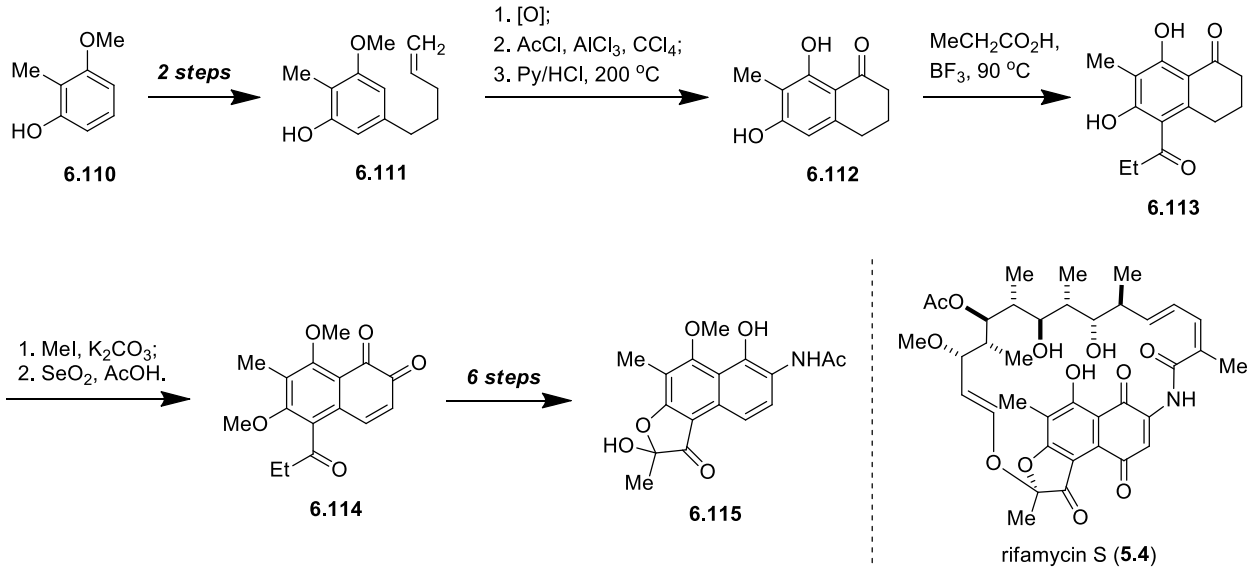


Rifsaliniketal (**5.6**) and salinisporamycin (**5.5**) contain a polysubstituted naphthoquinone fragment reminiscent of that found in ansamycins. Given previous efforts toward the ansamycin synthetic problem, a body of literature regarding synthetic approaches towards the challenging naphthoquinone fragment is available. Some classical examples are listed in scheme 63.

During the course of a synthetic study of rifamycin S (**5.4**, panel A), Kishi[50] and co-workers applied a Friedel-Craft benzannulation to yield ketone **6.112**, which after Friedel-Craft acylation and oxidation provided an *ortho*-naphthoquinone **6.114** that was processed to key intermediate **6.115** in an additional 6 steps.

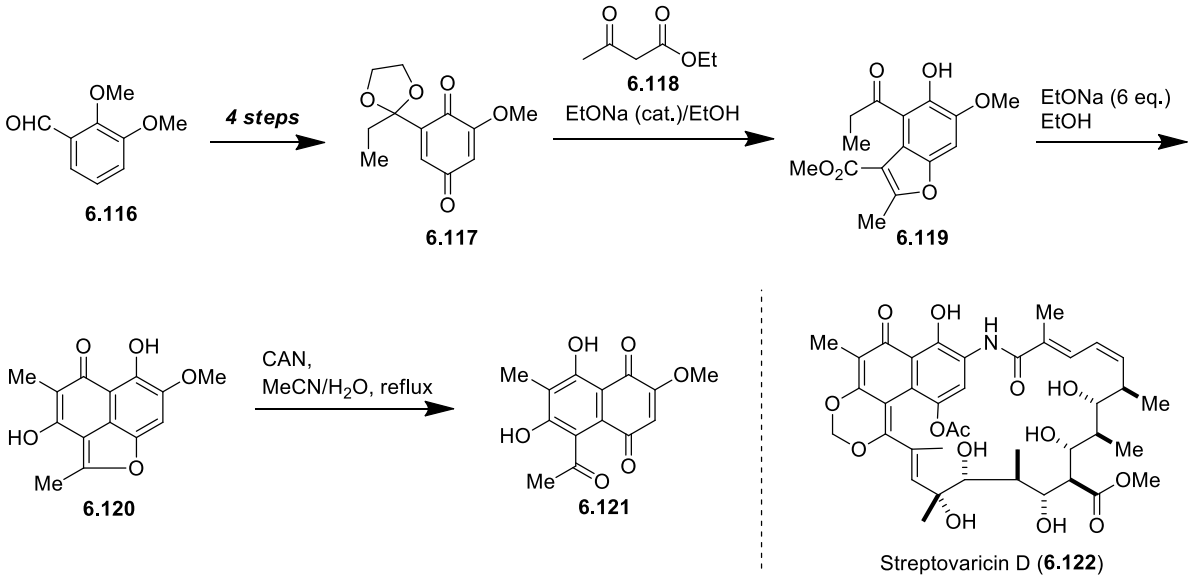
Scheme 63. Successful Routes to Related Naphthalenes or Naphthaquinones

A. Kishi's Approach

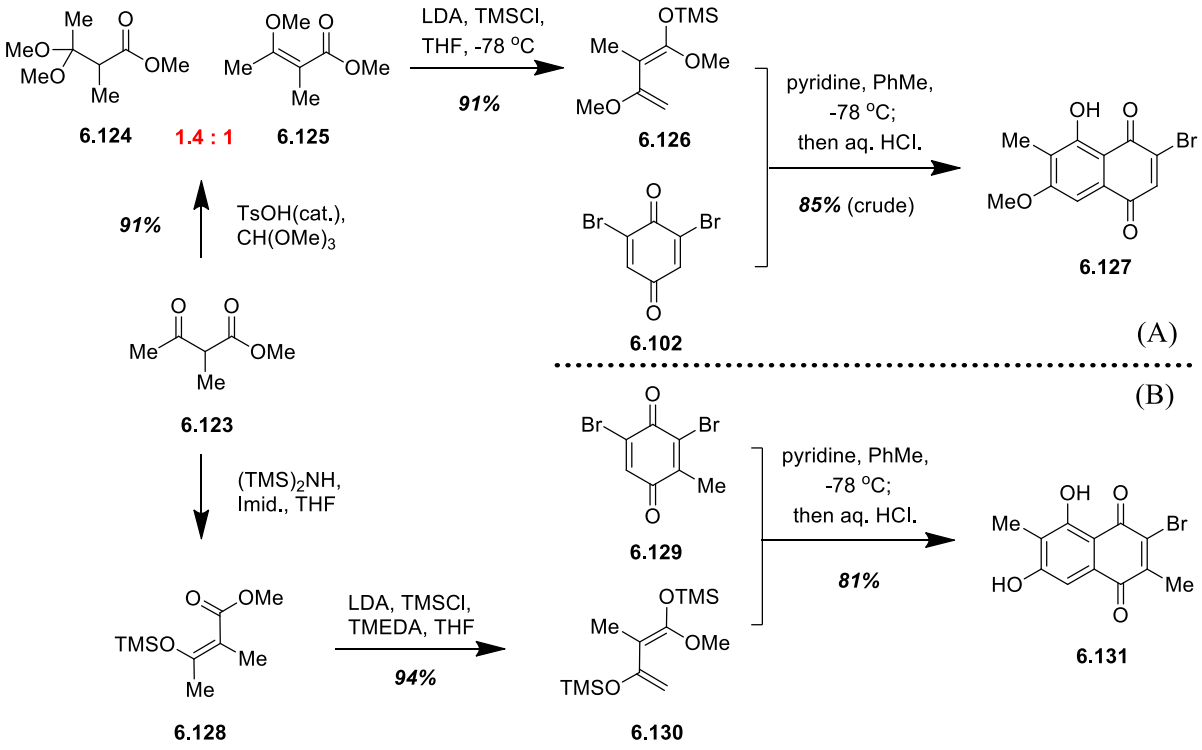


Scheme 63. Continued

B. Parker's Approach

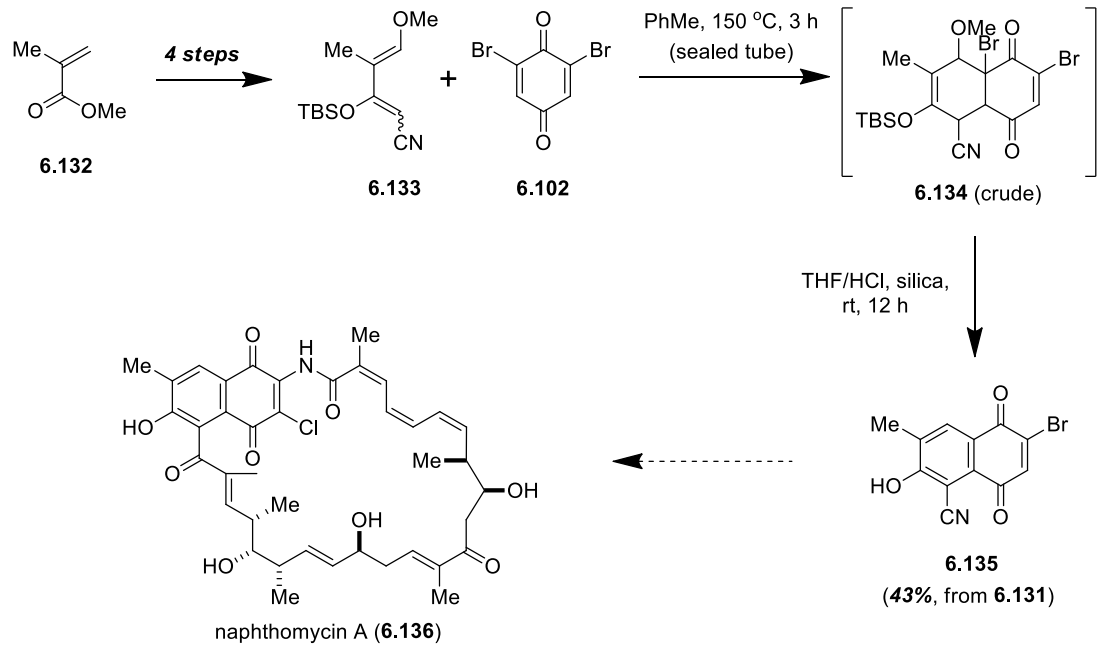


C. Roush's Approach

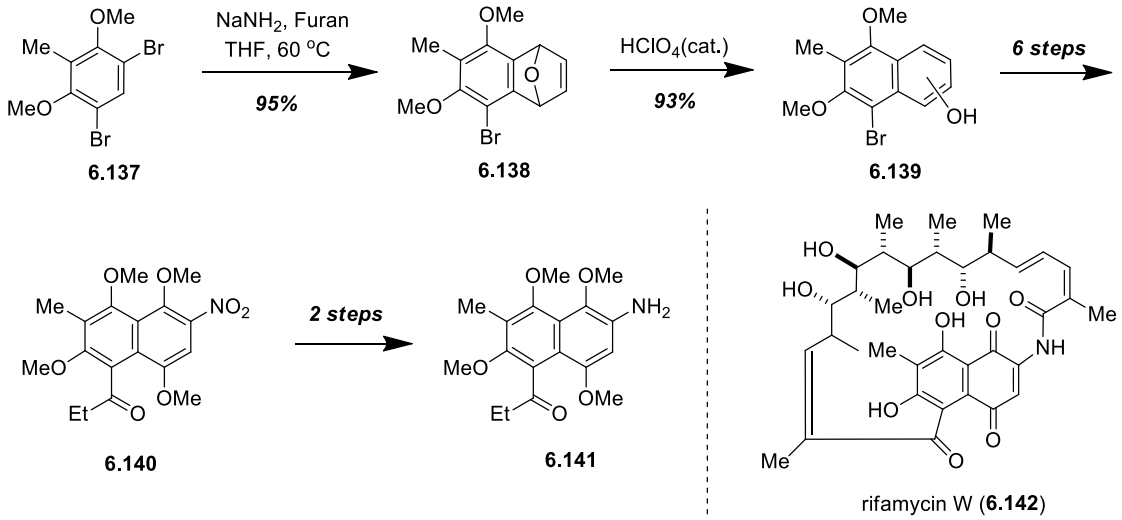


Scheme 63. Continued

D. Trauner's Approach



E. Kinishita's Approach



Parker and co-workers reported a route to access the naphthoquinone **6.121**, which served as the key intermediate to streptovaricin D (**6.122**, panel B).[51] Their approach involved a Michael addition of ethyl acetoacetate **6.118** to **6.117** followed by acidic quenching, which resulted in deketalization and dehydration to afford the benzofuran **6.119**. An intramolecular Claisen condensation gave the tricyclic compound **6.120** in the presence of sodium ethoxide in ethanol. Finally, an oxidative cleavage of the hydroquinone monoether moiety of **6.120** delivered the target naphthoquione **6.121** smoothly.

In Roush's approach (panel C)[52] to streptovaricins, methyl methylacetoacetate **6.123** was subjected to trimethyl orthoformate and a catalytic amount of TsOH, which afforded a 1.4:1 mixture of dimethyl ketal **6.124** and methyl enol ether **6.125**. Treating this mixture with LDA and excess TMSCl delivered the thermally unstable diene **6.126**, which was used directly for the next cycloaddition without further purification. Cyclocondensation (in pyridine and toluene, -78 ^{o}C) between diene **6.126** and quinone **6.102** afforded the desired naththoquinone **6.127** after an acidic quenching operation. For the synthesis of the similar naphthoquinone **6.131**, Roush borrowed a route developed by Trost and co-workers.[53] Treating methyl methylacetoacetate **6.123** with $(TMS)_2NH$ and imidazole afforded enol ether **6.128** as single product in 94%, which was converted to the requisite diene **6.130** in the presence of fresh prepared LDA and TMEDA. The subsequent Diels-Alder addition (pyridine, toluene, -78 ^{o}C; then workup with aq. HCl) between diene **6.130** and 2,6-dibromo-3-methylbenzoquinone **6.129** yielded cycloadduct **6.131**.

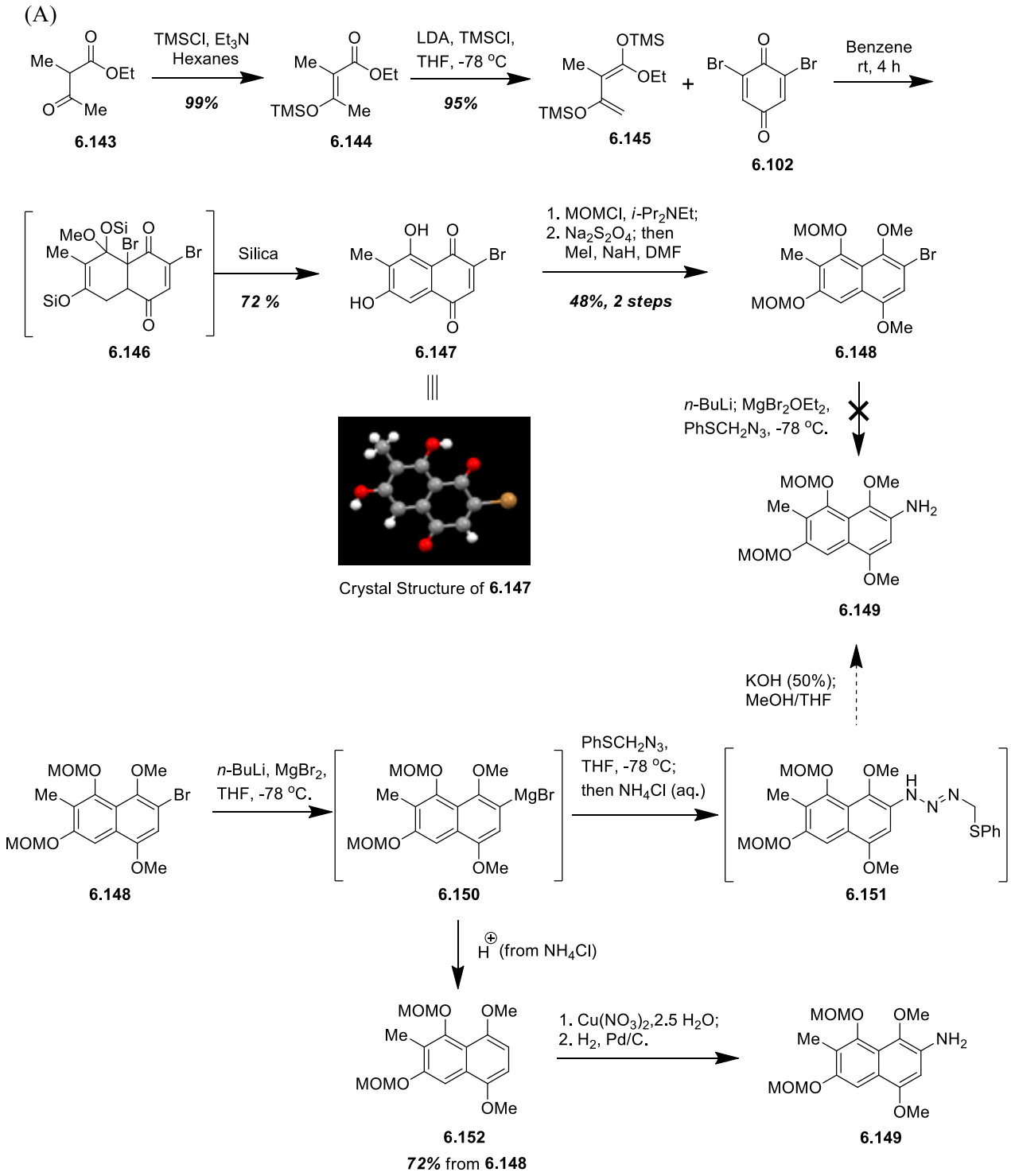
Recently, during the course of a synthesis of naphthomycin A (**6.136**, panel D), Trauner[54] and co-workers reported an approach to aminonaphthoquinone using a modified Danishefsky diene **6.133**, obtained from commercial available methyl methacrylate **6.132** in 4 steps. Diels-Alder reaction between **6.133** and the known benzoquinone derivative **6.109** formed intermdediary

adduct **6.134** as a mixture of stereoisomers, which was directly treated with oven-dried silica gel in HCl/THF to yield naphthoquinone **6.135** via desilylation and aromatization in 43% overall yield from **6.133**.

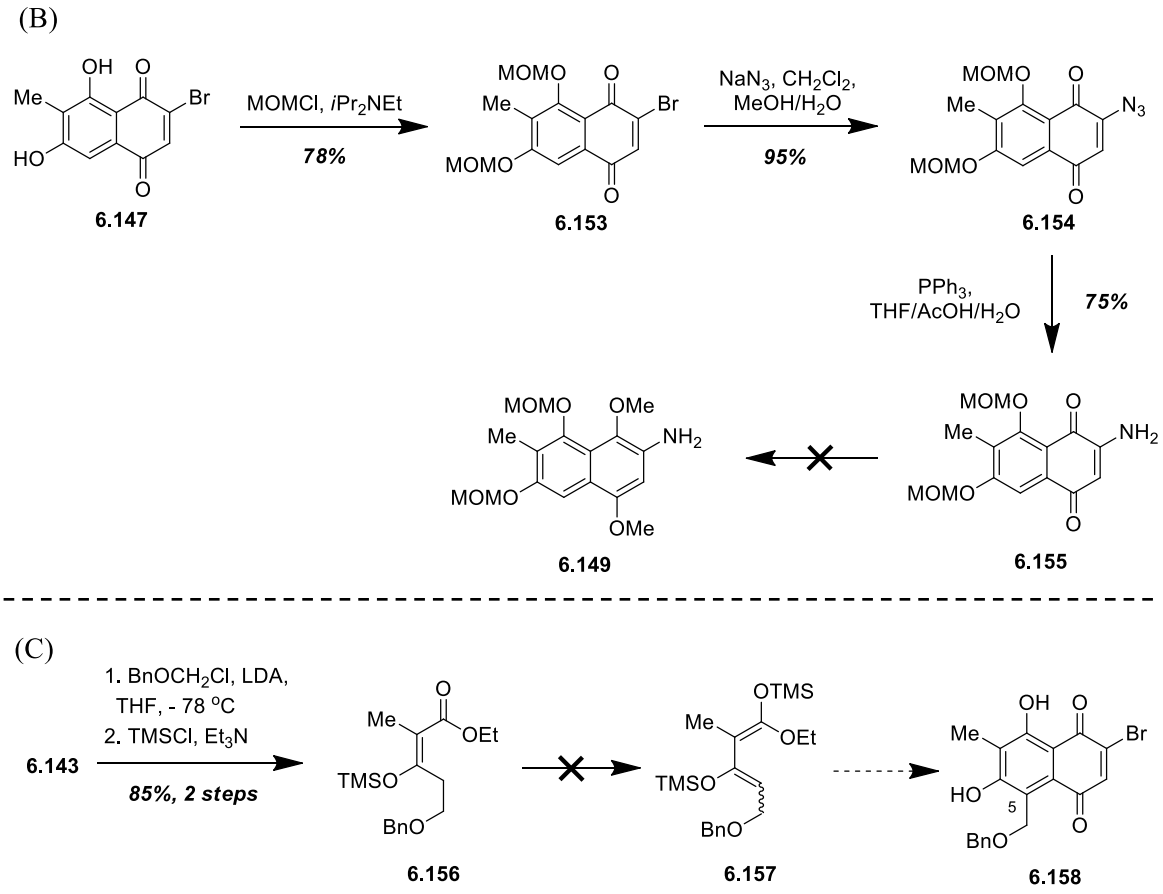
Finally, Kinishita[55] and co-workers provided a route to access the naphthalene amine **6.141**, which served as the intermediate to rifamycin W (**6.142**, panel E). They utilized the C_2-symmetrical *penta*-subtsituted benzene **6.137** as the starting material for a base induced formation of benzyne, which was quenched *in situ* by addition of furan to generate oxa-tricycle compound **6.138.** The regioselective *O*-ring opening by a catalytic amount of perchloric acid formed the naphtol **6.139**, which was converted to the naphthalene **6.141** in an additional eight steps sequence.

Since Roush[52, 56] already established an efficient method to construct the naphthalene, we decided to explore a similar strategy to our target. The synthesis of 2-bromo-1,4-naphthoquinone **6.147** (Scheme 64, panel A) commenced with a known Diels-Alder reaction between the diene **6.145** and 2,6-dibromobenzoquinone **6.102** (obtained in one step from oxidation of available tribromophenol). The diene **6.145**[57] was synthesized from commercial available ethyl 2-methyl-3-oxobutanoate **6.143** via silylenolization. The enol **6.144** (single product from enolization of **6.143**) was stable to air, but **6.145** was thermally unstable and used without further purification. Interestingly, the performance of this Diels-Alder cycloaddition depended on the workup conditions. The HCl(aq.)/THF workup protocol reported by Roush[52] caused full decomposition. After significant experimentation, we found that after stirring the mixture of **6.102** and **6.145** in dry benzene overnight at ambient temperature, TLC and crude ^{1}H NMR indicated the formation of a single product, which was lost during column chromatography (low yield after purification). Through parallel experiments, we found that if the silica gel was added as an additive during the

Scheme 64. Diels-Alder Cycloaddition Approach to Naphthoquinone



Scheme 64. Continued



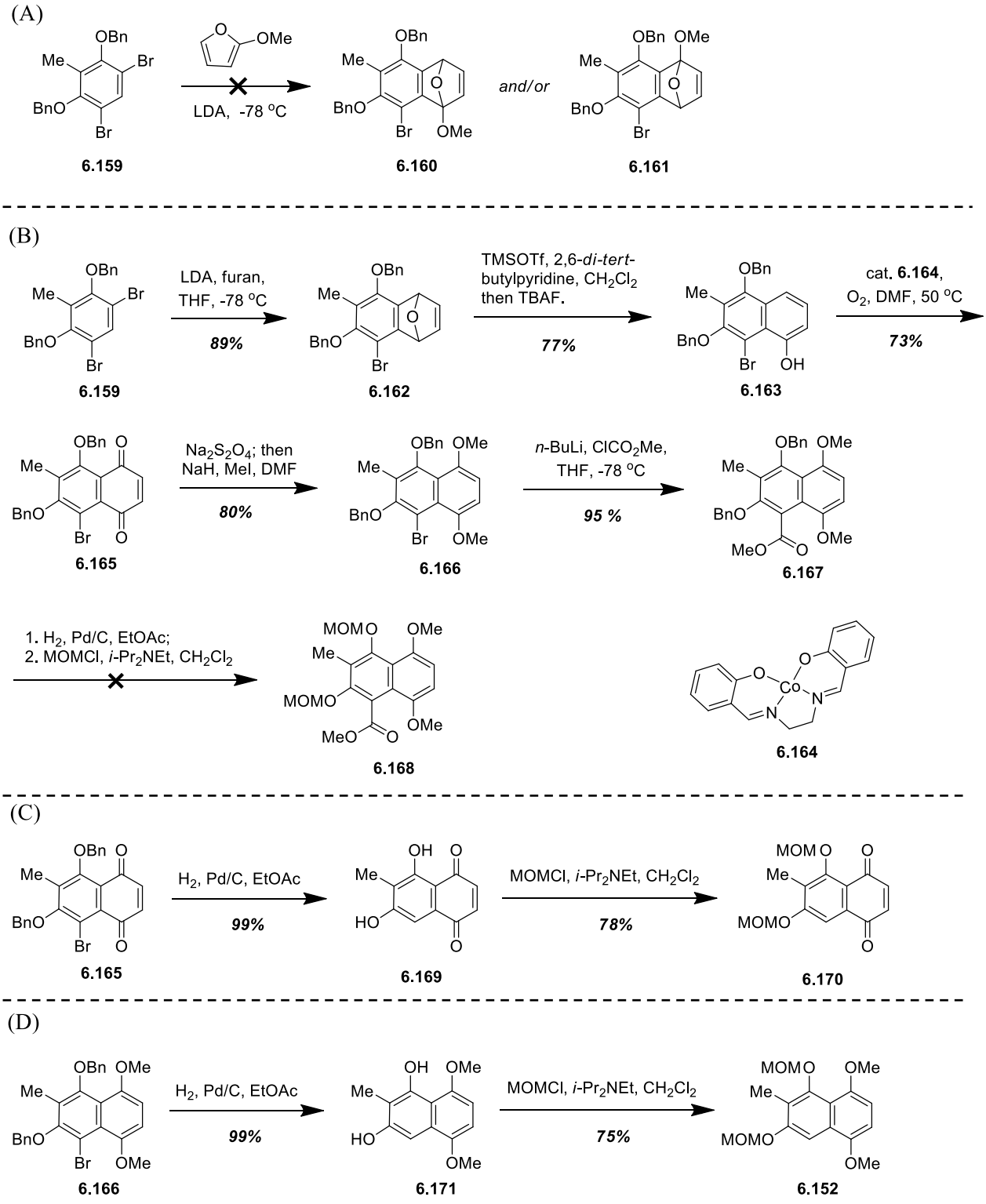
reaction, the isolated yield of **6.147** could be increased from 30-40% to 72%. We surmised the mild acidic SiO_2[58, 59] promoted desilylation and aromatization to give **6.147** as a stable compound. The crystal structure of **6.147** confirmed its structure. Interestingly, Trauner observed similar benefic effect of SiO_2 as shown in Scheme 63, panel D; results which were published[54] during the course of our own work. Treatment of **6.147** with excess MOMCl and *i*-Pr_2NEt in CH_2Cl_2 delivered *bis*-MOM protected napathoquinone, which was further reduced by using $Na_2S_2O_4$[60] in ether/H_2O to give naphthalene **6.148**. At this point, we tried to transform bromide **6.148** to amine **6.149**. One-step procedures to transform the bromide **6.148** to amine **6.149**

proved to be very difficult. Regular amination or azide displacement methods lead to either low conversions or recovered starting materials. Hoping to achieve a direct amination using conditions developed by Trost,[61] we treated bromide **6.148** with 2.0 eq *n*-BuLi at -78 ^{o}C followed by $MgBr_2 \cdot OEt_2$ to prepare an aryl magnesium **6.150** *in situ*. Dropwise addition of $PhSCH_2N_3$ in dry THF at -78 ^{o}C, followed by hydrolysis of the triazene intermediate with KOH in MeOH/THF/H_2O should then lead to amine **6.149**. Instead of the desired amine **6.149**, only elimination product **6.152** was obtained, presumably via quenching of Grignard intermediate **6.150**. We were hopeful that a regioselective nitration of **6.152** would provide a solution. However, nitration of **6.152** with copper(II) nitrate in acetic anhydride at -40 ^{o}C failed. We attributed this failure to residual water in commercial $Cu(NO_3)_2$ (2.5 H_2O, Aldrich). All attempts to dehydrate the $Cu(NO_3)_2$ failed, only leading to decomposition to CuO. In the end, addition of anhydrous $CaCl_2$[62] to the mixture proved to be an efficient solution to achieve regiospecifically nitronaphthalene (65% yield) formation, which was reduced under a hydrogen atmosphere in the presence of a catalytic amount of Pd/C to give amine **6.149**.

Alternatively, conversion of bromide **6.153** to amine **6.155** was accomplished in a two-step sequence (Scheme 64, panel B) employing the protocol contributed by Boger[63] with modification. Carefully controlled conditions for azide displacement, a reaction which is sensitive to the presence of excess azide, provided the azide intermediate **6.154** cleanly and subsequent utilization of triphenylphosphine in THF/H_2O afforded amine **6.155**. Unfortunately, all attempts to transform **6.155** to the reduced naphthoquinol **6.149** failed under various conditions, i.e. Luche conditions,[64] or hydrogenations with different catalysts.

The only difference between salinisporamycin (**5.5**) and rifsaliniketal (**5.6**) is the substituent at the C_5 position of the naphthoquinone ring. To introduce functionality at C_5, we tried to

Scheme 65. Initial Benzyne Cycloaddition Approach to Naphthalene

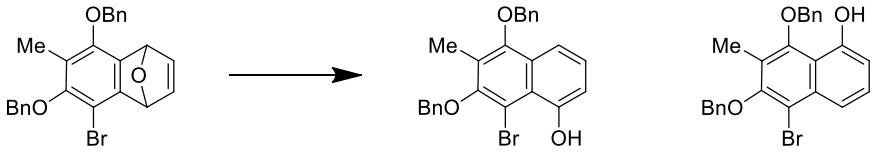


synthesize the advanced diene partner **6.157** (panel C), which could in principle be further debenzylated and oxidized to a carboxylic acid at C_5. A number of methods[65] were tried; however, the extremely unstable diene **6.157** could not be isolated and trapped for the cycloaddtion. In conclusion, this Diels-Alder route has enabled the synthesis of brominated, or aminated protected naphthoquinol coupling partners **6.148** and **6.149**, respectively; and an aminated naphthoquinone **6.155**.

We also sought an alternative route to synthesize C_5-substituted naphthoquinones/quinols via a benzyne cycloaddition approach (Scheme 65). Initially, we envisioned the cycloaddition[66] between the dibromobenzene **6.159** and 2-methoxyfuran to generate the tricyclic compounds **6.160** and/or **6.161** (panel A). In fact, complex mixtures were obtained due to this mismatched inverse electron demand Diels-Alder reaction. Furan was therefore chosen instead of 2-methoxyfuran as the diene. Thus, a solution of 2,6-*bis*(benzyloxy)-3,5-dibromotoluene **6.159**, obtained from 2,6-dihydroxytoluene in two steps and furan in THF was added to a fresh prepared LDA[67] solution in THF at –78 ^{o}C to afford Diels-Alder adduct **6.162** in 89% yield (panel B).

The approach to this *bis*-*O*-benzylated compound was similar to the Kinishita synthesis of *bis*-O-methyl analog **6.139**. However, the subsequent ring-opening of **6.162** prove to be more difficult than for 6.139 as described by Kinishita.[55] A wide range of Lewis and Brønsted acids were screened for the *O*-ring opening reaction of **6.162** (Table 19). Mild acidic conditions[67] (entry 1) provided naphtol **6.163** in 23% yield, together with an unstable regiosiomer **6.163a** that was decomposed during the column purification. The use of *p*-toluenesulfonic acid[68] (pTSA in DCM, entry 2) catalyzed reaction resulted in recovered starting material, whereas trifluoroacetic acid in DCM provided **6.163** in a modest yield (17%, entry 3). The yield was highly improved to 34% with perchloric acid[47] in THF (34%, entry 4), whereas other Brønsted acids lead to Ru(II)[71]

Table 19.[a] Acid Promoted *O*-Ring Opening



6.162 **6.163** **6.163a** (unstable)

Entry	Conditions	Yield[b]
1	2,2-Dimethylpropane-1,3-diol, $(MeO)_3CH$, pTSA (5 mol%), CH_2Cl_2, 40 ^oC, 12h	23%
2	pTSA (10 mol%), CH_2Cl_2, 40 ^oC, 6h	n.r.[c]
3	CF_3COOH (10 mol%), CH_2Cl_2, 40 ^oC, 6h	17%
4	$HClO_4$ (5 mol%), THF	34%
5	H_2SO_4 (5 mol%), MeOH/H_2O (5:1), 60 ^oC	n.r.
6	HCl (12 M, 20 mol%), MeOH, rt, 12h	n.r.[c]
7	PPTS (20 mol%), THF/MeOH (10:1), 40 ^oC, 20h	n.r.[c]
8	$HClO_4$ (5 mol%), $PhI(OTf)_2$ (10 mol%), THF	decomposition
9	TMSOTf (1.0 eq.), CH_2Cl_2, rt, 1h	decomposition
10	TMSOTf (1.0 eq.), pyridine (1.0 eq) CH_2Cl_2, rt, 1h	decomposition
11	TMSI (2.0 eq.), CH_2Cl_2, 0 ^oC, 1h	decomposition
12	TBSOTf (5.0 eq), 2,6-lutidine (20 eq.),	n.r.[c]
13	Cp*Ru(cod)Cl (10 mol%), $ClCH_2CH_2Cl$, 60 ^oC, 12h	n.r.[c]
14	CH_2Cl_2, TMSOTf (5.0 eq.), 2,6-*di*-*tert*-butyl pyridine (6.0 eq), THF, rt, 3h, then TBAF (3.0 eq)	77%

[a]All the reactions were performed on 0.1 mmol scale. [b]Isolated yields. [c]n.r. means no reaction.

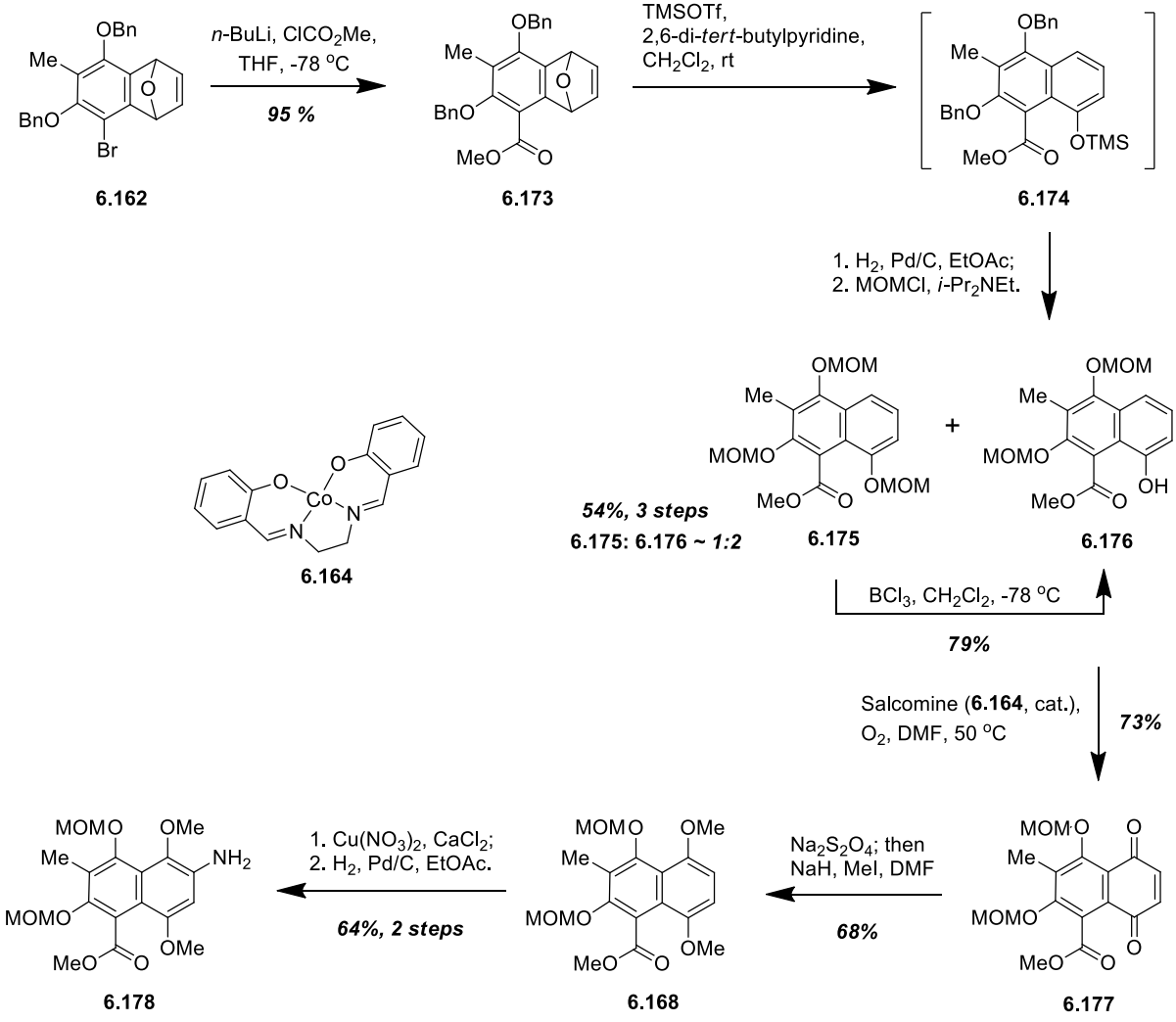
(entry 13) decomposition (H_2SO_4 or HCl, entries 5-6) or recovered starting material (entry 7, PPTS). Oxidative ring-opening (entry 8) or TMSOTf or TMSI mediated conditions (entries 9-11) led to full decomposition of starting material **6.162**. On the other hand, TBSOTf[69, 70] (entry 12) or mediated ring-opening led to recovered starting material. Finally, we found that addition of

2,6-*di*-*tert*-butylpyridine dampened the reactivity of TMSOTf just enough such that in the presence of six equivalents of base (entry 14), the bridged ether was cleaved regioselectively, forming naphthol **6.163** in 77 % yield, after removal of the intermediate silyl ether by addition of TBAF.

With a successful ring-opening reaction established, we returned to the further elaboration of **6.163** into a fully functionalized naphthoquinone/quinol (Scheme 65, panel B). The oxidation of naphtol **6.163** proved to be quite challenging. Neither Jones reagent,[72] Ag_2O (in dioxane/HNO_3),[70] NBS (in HOAc/H_2O)[73] nor Ferric(III) salts,[74] produced the desired naphthoquinone **6.165**. Finally, treating naphthol **6.163** with a catalytic amount of salcomine[75] (Co(Salen), **6.164**) in DMF, and bubbling oxygen at 50 ^oC for overnight, afforded the pure naphthaquinone **6.165**, which was then reduced to dimethyl ether **6.166** (80% yield). To introduce a carboxyl group at C_5 of **6.166**, transmetalation with *n*-BuLi was followed by trapping with methyl chloroformate to install the methyl ester **6.167** in 95% yield. An attempt to switch the benzyl groups to MOM ethers met with failure. Hydrogenation of **6.167** was successful, but we could not introduce MOM ethers (→ **6.168**). In addition, both hydrogenations of **6.165** (panel C) and **6.166** (panel D) resulted in debromination products (→ **6.169**, **6.171**, respectively) even with a $ZnBr_2$ poisoned palladium on carbon catalyst.

To solve many of the problems that we faced, we launched a new synthesis starting with benzyne cycloadduct **6.162** (Scheme 66). Transmetalation of bromide **6.162** with *n*-BuLi followed by trapping with methyl chloroformate yielded methyl ester **6.173** in 95% yield. Then, *O*-ring cleavage with TMSOTf in the presence of 2,6-*di*-*tert*-butylpyridine, according to the conditions in talbe 19 (entry 14), lead to a stable intermediate **6.174**. After removing the solvent, the silyated naphtol **6.174** was reduced with hydrogen over Pd on carbon and subsequently trapped

Scheme 66. The Successful Benzyne Cycloaddition Approach to Naphthalene



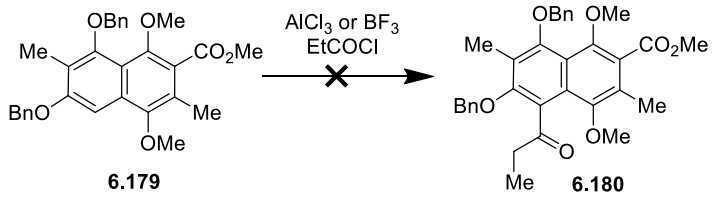
with MOMCl. After column purification, we isolated two products **6.176** and **6.175** in a 2:1 ratio in 54% total yield (from **6.173**). Regioselective deprotection of **6.175** with BCl_3 at -78 ^oC was successful in transofrming *tris*-MOM product **6.175** to *bis*-MOM ether **6.176**. Then, a Co(salen) catalyzed oxidation converted the naphtol **6.176** to naphthoquinone **6.177**, which was then reduced to **6.168**. As shown before, for the nitration of **6.152** (Scheme 64, panel A), a regioselective nitration of **6.168** with copper(II) nitrate in acetic anhydride at -40 ^oC in the

presence of anhydrous $CaCl_2$ introduced a nitro group at the C_2 position, which was reduced to amine **6.178** in 64% yield over the two steps.

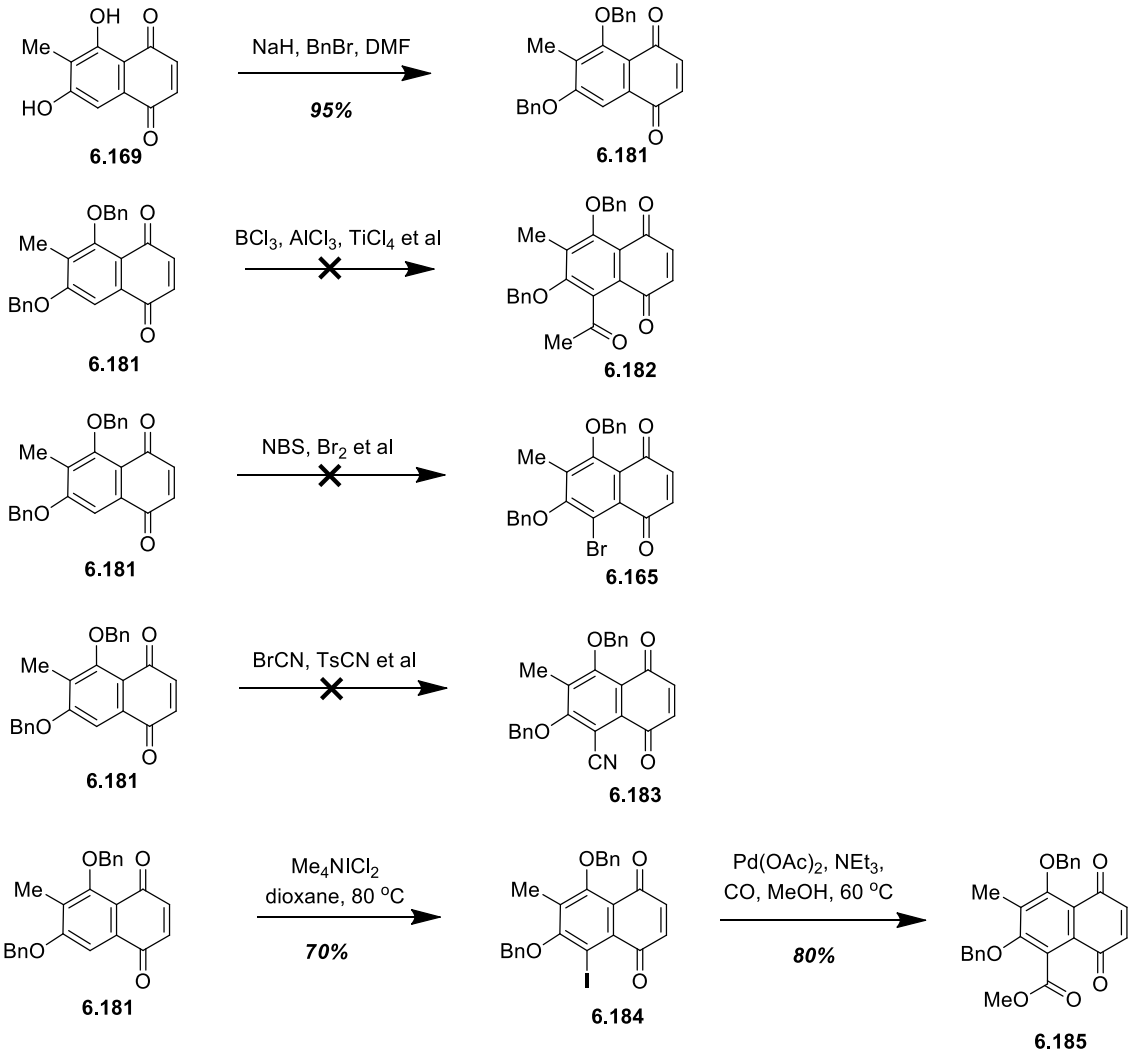
As an alternative, we also sought to functionalize the C_5-position of naphthoquinones/quinols obtained via the Diels-Alder route. Due to the base sensitive nature of the naphthoquinone,[76] conventional methods of C_5 position functionalization, i.e., formylation, carboxylation or iodination, were difficult. Roush[52] had shown the difficulty to introduce the ethyl ketone at the C_5 position of **6.179** (Scheme 67, panel A) via Friedel-Crafts reaction or Fries rearrangement. Indeed, with our less electron rich model substrate **6.181**, obtained by benzylation of **6.169** in 95% yield, routine methods using $AlCl_3$ or BCl_3 as Lewis acid and $NCCO_2Me$ or $ClCO_2Me$ as acylating agent, were unproductive (Scheme 67, panel B). Another idea was to introduce a cyanide[77] to C_5 (→ **6.183**), which would serve as the precursor to a carboxylic acid, or bromination[78] (→ **6.165**) as a handle for a metallation/acylation sequence. None of the explored conditions were fruitful. Direct iodination also proved to be challenging. Regular conditions[79] using $I_2/Hg(OTf)_2$, $I_2/PhI(OAc)_2$ or NIS either decomposed or recovered starting material. However, the reagent Me_4NICl_2[80] provided an efficient source of electrophilic iodine, affording iodide **6.184** as the sole product after reflux for 4 hours in 70% yield. Subsequently, a Pd(II)-catalyzed alkoxycarbonylation[81] of aryl iodide **6.184** installed a methyl ester (→ **6.185**) at the C_5 position. Thus, it provided us a successful route to access C_5 functioned naphthoquinones via the Diels-Alder cycloaddition approach.

Scheme 67. Functionalization of Naphthoquinone

(A) *Roush et al.,*



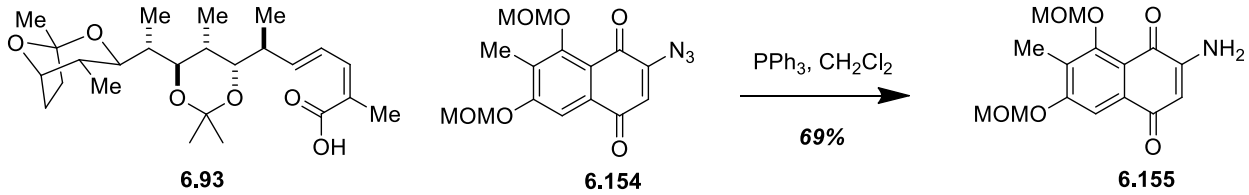
(B) *Our Work*



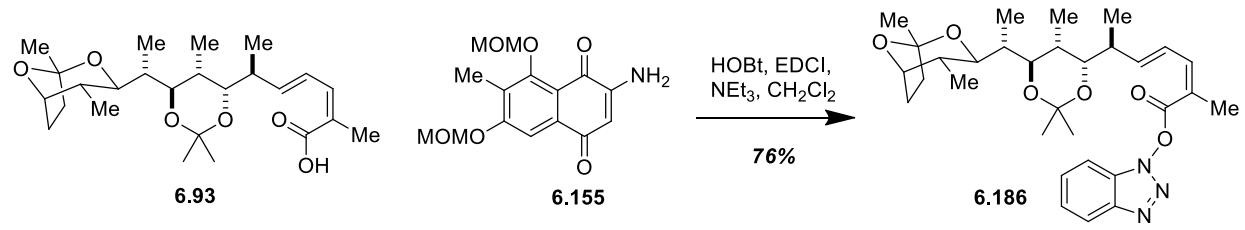
With various functionalized (-NH_2, -N_3, -Br) naphthoquinone/quinol fragments in hand, we turned our attention to the exploration of various coupling methods. First, we explored the Staudinger ligation between naphthoqunione azide **6.154** and protected acid **6.93** (Scheme 68, panel A). However, contemporary Staudinger ligation conditions[45] only reduced the azide to amine **6.155**. This material allowed us to investigate a peptide coupling between saliniketal acid **6.93** and amine **6.155**. However, several chemical methods failed by using **6.155** as the amine source. In a representative example (Scheme 68, panel B), peptide coupling conditions (HOBt, EDCI) provided activated ester **6.186** as the sole product in addition to recovered amine **6.155**. Reasoning that the amide-like character may the reason for the poor reactivity[76] of naphthoquinone amide **6.155**, the more electron-rich dimethyl ether **6.149** was investigated. Due to the instability of amine **6.149**, it was prepared freshly before use (Scheme 64, panel A) and subjected to the peptide coupling conditions as above (Scheme 68, panel C). This time an acceptable yield of coupled amide **6.187** (67%) was obtained. Alternatively, we explored a C-N bond formation strategy to couple the two key fragments. Again, the more electron-deficient coupling partner naphthoquinone bromide **6.153**, proved to be unresponsive (panel D) when treated with saliniketal amide **6.188**, obtained from amidation of saliniketal acid **6.93** in the presence of a wide variety of Pd-[82] or Cu-[83] based catalysts. Again, the more electron-rich coupling partner, naphtyl bromide **6.148**, provided a solution. Indeed, in the presence of copper(I) iodide[83] as the catalyst and *N,N'*-dimethylethylenediamine as the ligand, the Buchwald type *C-N* bond coupling (panel E) between amide **6.188** and naphtyl bromide **6.148** afforded the desired product **6.187** in 57% yield.

Scheme 68. Investigation of Coupling between Saliniketal and Aryl Fragments

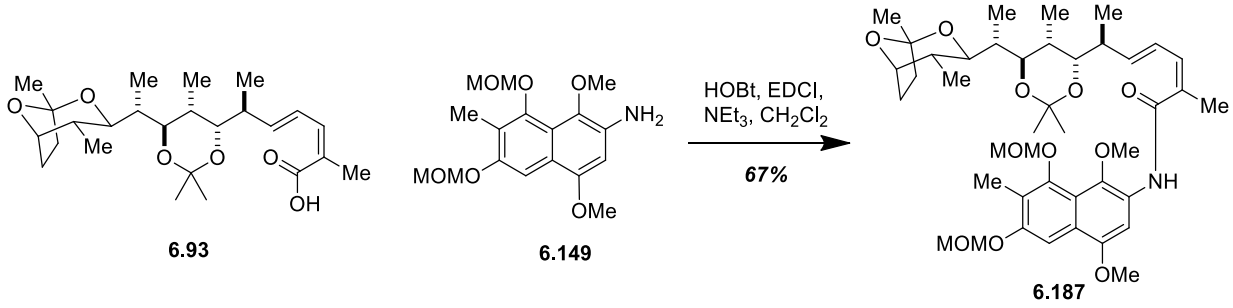
(A) *Staudinger Ligation:*



(B) *Initially Peptide Coupling:*

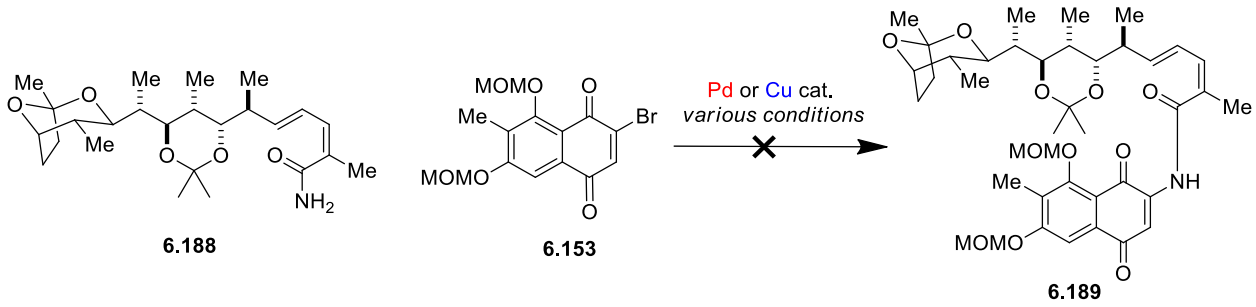


(C) *Modified Peptide Coupling:*

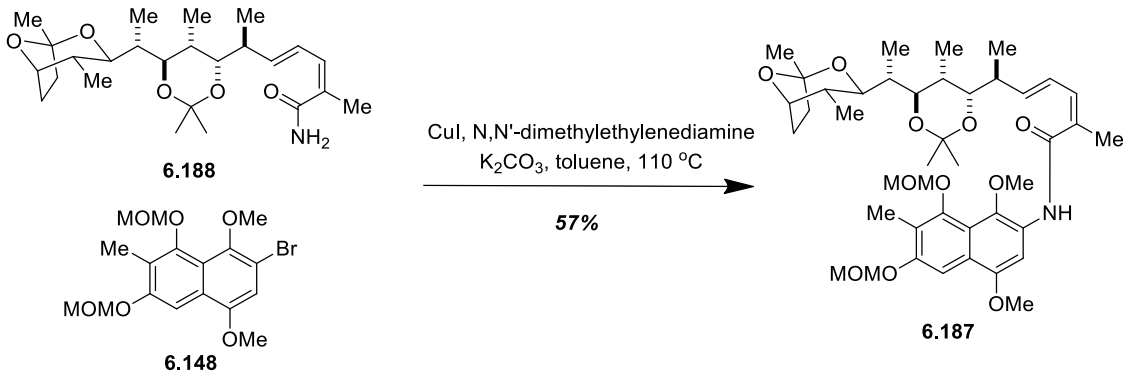


Scheme 68. Continued

(D) *Initially C-N bond coupling:*

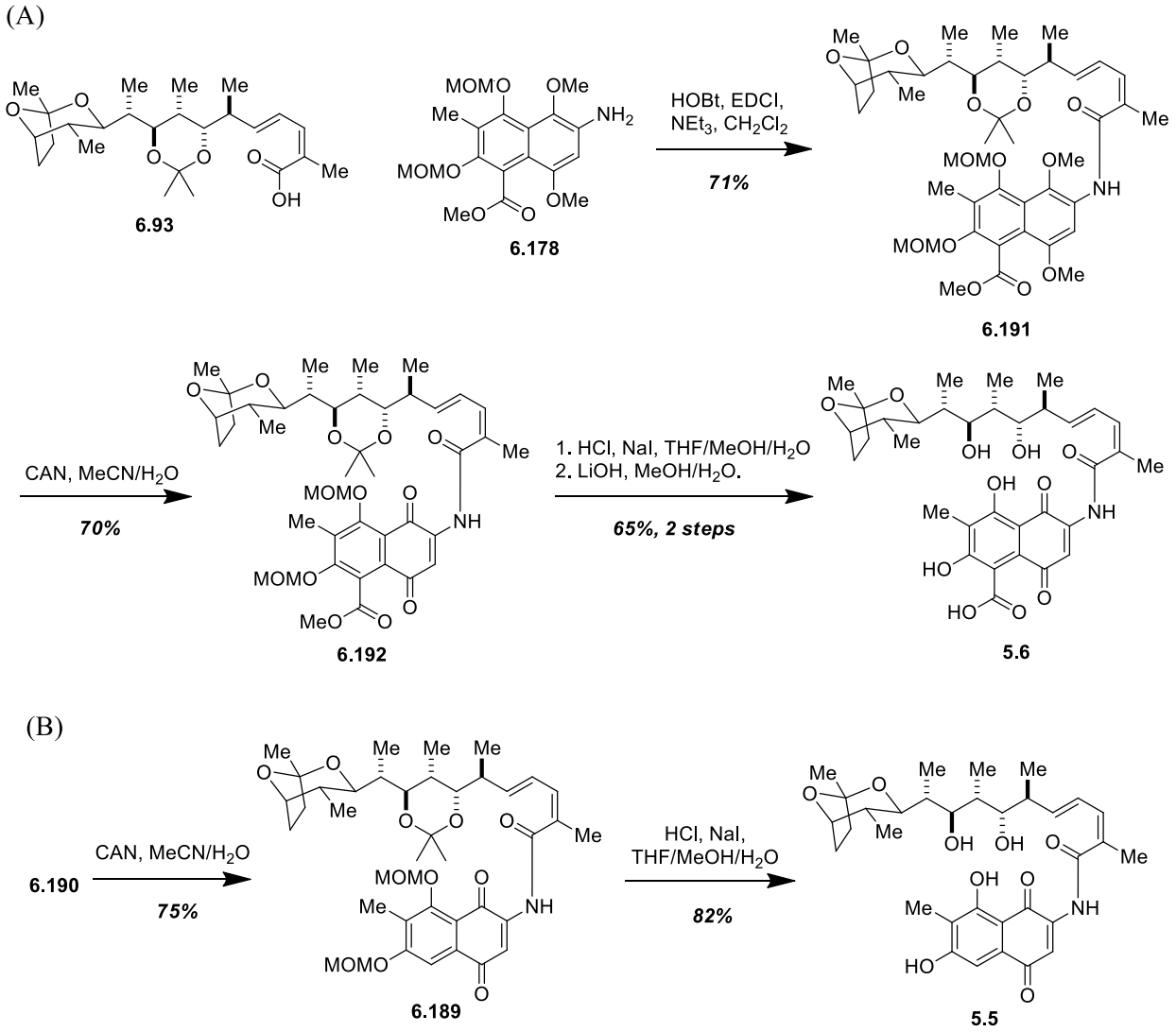


(E) *Modified C-N bond coupling:*



Because the peptide coupling strategy was slightly higher yielding, we opted for those conditions to couple the fragments required for rifsaliniketal precursor **6.191** (Scheme 69, panel A). As such, the amidation between amine **6.178** and saliniketal **6.93** afforded amide **6.191** smoothly in 71% yield. A mild radical oxidation of **6.191** with ceric ammonium nitrate[56] (CAN) delivered the naphthoquinone derivative **6.192** in 70% yield. We next extensively explored conditions for the simultaneous deprotection of the acetonide and phenolic MON-protecting groups. Whereas the

Scheme 69. Completion of Syntheses of Salinisporamycin and Rifsaliniketal



acetonide could be removed under a variety of acidic conditions, the MOM protecting groups proved to be much more reluctant. For example, the mildly acidic Dowex only removed the acetonide whereas a variety of Lewis acidic conditions led to decomposition. According to the literature,[56] aqueous HCl in THF should be able to remove both acetonide and MOM-protecting groups. However, even after screening a variety of parameters including concentration, solvent

and temperature, we were unable to remove all protection groups simultaneously. Finally, we found that NaI could serve as a key additive to facilitate this transformation. In the event, treating naphthoquinone **6.192** with two equivalents of sodium iodide[84] in the presence of aqueous HCl (10%) in THF and methanol, delivered the rifsaliniketal methyl ester, which was converted to rifsaliniketal (**5.6**) via saponification in 65% overall yield (from **6.192**). The completion of salinisporamycin (**5.5**) was accomplished using a similar sequence, save for the saponification (Scheme 69, panel B). It was obtained after reaction with CAN (→ **6.189**, 75%), followed by the optimized protecting group cleavage with HCl in THF/MeOH in the presence of NaI (82%).

In summary, saliniketal A (**5.2**), salinisporamycin (**5.5**) and rifsaliniketal (**5.6**) are three novel secondary metabolites from the marine actinomycete *Salinispora arenicola*. Total syntheses of these three molecules were completed via a highly convergent route. These studies were aimed at enabling future structure-function and mode of action studies. The synthetic highlights for saliniketal A includes: Pt(II)-catalyzed cycloisomerization to construct the dioxabicyclo[3.2.1] ring system, a highly diastereoselective aldol coupling whose stereochemical outcome was influenced by the γ-stereogenic methyl group and an unique dihydropyranone fragmentation/amidation sequence. For salinisporamycin and rifsaliniketal, the 1,4-naphthoquinone skeleton was assembled via Diels-Alder cycloaddition or benzyne cycloaddition. A peptide coupling or Buchwald C-N bond coupling at a late stage between saliniketal A and the 1,4-naphthalene fragments followed by radical oxidation afforded salinisporamycin and rifsaliniketal, respectively.

6.4 Experimental Section

Pent-4-ynal (6.58)

To a solution of pent-4-yn-1-ol (**6.57**, 1.68 g, 20 mmol) in CH_2Cl_2 (160 mL) was added $NaHCO_3$ (3.36g, 40 mmol) and dess-martin periodinane (17.68 g, 40 mmol) in one portion. The resultant mixture was allowed to stir for 2 h at ambient temperature. After removing the solvent on vacuum, the residue was resolved in EtOAc (150 mL) and $Na_2S_2O_3$ (sat. solution, 100 mL) and $NaHCO_3$ (sat. solution, 50 mL) were added. After stirring for 3 h, the biphasic solution was separated. The aqueous phase was then washed with ether (2 × 100 mL) and the combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, filtered, and concentrated in vacuum. Short flash chromatography on silica gel, using ethyl acetate-hexanes (1:50) as eluant, provided desired aldehyde **6.58** as colorless oil (1.54 g, 94%).

Rf: 0.7, (Ethyl acetate/Hexanes 1:8); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (t, *J* = 1.3 Hz, 1H), 2.66 (m, 2H), 2.56 (ddd, *J* = 7.7, 6.6, 1.0 Hz, 2H), 0.96 (m, 9H), 0.56 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.8, 106.1, 83.4, 43.0, 13.5, 7.7, 4.7; MS (ES) calculated for $C_9H_{14}O_6$ $[M + H]^+$ 197.1, found 197.1.

(3*S*, 4*S*)-3-methyloct-1-en-7-yn-4-ol (6.59)

The potassium *tert*-butoxide (2.9 g, 26.0 mmol, 2.0 equiv) was heated at 80 ^{o}C under high vacuum overnight to dry. Then, THF (10 mL) was added and the suspension was cooled to –78 ^{o}C. *Cis*-2-butene (3.3 mL) was then added via cannula, followed by *n*-BuLi (1.6 M in hexane, 17.0 mL, 2.1 equiv) dropwise to produce an orange suspension. After 10 min at –45 ^{o}C, the reaction mixture was cooled to –78 ^{o}C and treated with (+)-Ipc_2BOMe (8.54 g, 27 mmol, 2.05

equiv) in THF (30 mL) dropwise over 15 min. After an additional 30 min at –78 ^{o}C, the colorless slurry was treated with BF_3•OEt_2 (3.7 mL, 29 mmol, 2.1 equiv) dropwise over 10 min, followed by aldehyde (**6.58**, 1.07 g, 13.0 mmol) over 20 min and 2 × 5 mL THF rinses. After an additional 3 h, the pale yellow slurry was charged with 3N NaOH (20 mL) and allowed to slowly warm to ambient temperature. During this time, H_2O_2 (30% aq., 6 mL) was added in 1 mL portions to control bubbling and the resulting mixture was heated at reflux for 1 h. The biphasic solution was then cooled to ambient temperature and diluted with water (30 mL). The aqueous phase was then washed with ether (2 × 30 mL) and the combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuum. After short flash chromatography on silica gel, using ethyl acetate-hexanes (1:10) as eluent, it was provided an >20:1 diastereomeric mixture of homoallyllic alcohol **6.59** (1.56 g, 11.3 mmol, 87% yield).

Rf 0.50 (hexanes/ethyl acetate 3/1); $[a]^{20}_{D}$ = –22.3 (c = 2.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.77 (m, 1H), 5.10 (m, 2H), 3.62 (dtd, *J* = 10.3, 5.3, 2.8 Hz, 1H), 2.32 (m, 3H), 1.96 (t, *J* = 2.7 Hz, 1H), 1.75 (m, 1H), 1.58 (m, 2H), 1.04 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.7, 115.9, 84.5, 73.8, 68.9, 43.9, 32.8, 15.6, 14.7; MS (ES) calculated for $C_9H_{14}O_6$ $[M + H]^+$ 139.1, found 139.1.

(2*R*, 3*S*)-2-methyl-3-((triethylsilyl)oxy)hept-6-ynal (6.60)

To a solution of homoallylic alcohol **6.59** (1.38 g, 10 mmol) in CH_2Cl_2 (25 mL), was added triethylsilyl chloride (20 mmol), imidazole (30 mmol) and DMAP (5 mmol) in one portion at 0 oC. After stirring 2 hours at ambient temperature, $NaHCO_3$ solution (10 mL) was added. The biphasic solution was then separated. The aqueous phase was washed with ether acteate (3 × 10 mL) and the combined organic layers were washed with brine (20 mL), dried over $MgSO_4$,

filtered, and concentrated in vacuo. The flash chromatography on silica gel, using ethyl acetate-hexanes (1:25) as eluant, provided the desired alkene (2.4 g, 9.5 mmol, 95% yield).

R_f: 0.4 hexanes/ethyl acetate 20/1); $[a]^{20}_D$ = –19.5 (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85 (m, 1H), 5.00 (m, 2H), 3.67 (dt, *J* = 7.4, 4.7 Hz, 1H), 2.24 (m, 4H), 1.91 (t, *J* = 2.6 Hz, 1H), 1.60 (m, 2H), 0.96 (m, 9H), 0.61 (q, *J* = 8.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.7, 114.6, 84.8, 74.8, 68.4, 43.2, 32.5, 15.4, 14.7, 7.2, 5.3; MS (ES) calculated for $C_{15}H_{28}OSi$ $[M + H]^+$ 253.2, found 253.1.

To a solution of alkene (8.0 mmol) in acetone/H_2O (40 mL, v/v = 10:1) was added OsO_4 (0.4 mmol, 4 mL, 0.1 M in *t*-BuOH) and NMO (16.0 mmol) in ambient temperature. The mixture solution was stirred for 2 hours, the solvents were removed by vacuum. The crude residue was resolved in CH_2Cl_2 (40 mL), and $Pd(OAc)_4$ (1.5 eq) and pyridine (3.0 eq) was added in 0 ^oC. After stirring for overnight at ambient temperature, $CuSO_4$ solution (20 mL) was added. The biphasic solution was then separated. The aqueous phase was washed with ether acteate (3 × 10 mL) and the combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The flash chromatography on silica gel, using ethyl acetate-hexanes (1:15) as eluant, provided the desired product **6.60** (1.73 g, 6.8 mmol, 85% yield).

R_f: 0.35 hexanes/ethyl acetate 2/1); $[a]_{20}{}^D$ = –24.8 (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.81 (s, 1H), 4.26 (ddd, *J* = 7.5, 5.5, 3.8 Hz, 1H), 2.50 (qd, *J* = 7.0, 6.6, 3.5 Hz, 1H), 2.24 (td, *J* = 7.1, 2.7 Hz, 2H), 1.97 (t, *J* = 2.7 Hz, 1H), 1.70 (m, 2H), 1.06 (d, *J* = 7.0 Hz, 3H), 0.94 (t, *J* = 7.9 Hz, 9H), 0.61 (q, *J* = 8.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.9, 83.8, 70.9, 69.1, 51.4, 32.9, 14.9, 8.0, 6.9, 5.0; MS (ES) calculated for $C_{14}H_{26}O_2Si$ $[M + H]^+$ 255.2, found 255.2.

(4*R*, 5*S*, 6*S*, 7*S*)-5-hydroxy-4, 6-dimethyl-7-((triethylsilyl)oxy)undec-10-yn-3-one (6.61)

$TiCl_4$ (1.0 M in CH_2Cl_2; 1.2 mL) and Bu_3N (185mg, 1.4 mmol) were successively added to a stirred solution of propiophenone (134 mg, 1.0 mmol) in CH_2Cl_2 (2.0 mL) at -78 ^oC under an Ar atmosphere. After 30 min, aldehyde **6.60** (1.2 mmol) was added to the mixture, which was stirred at -78 ^oC for 2h. The reaction mixture was quenched with water and was extracted twice with ether. The organic phase was washed with water, brine, dried with $MgSO_4$ and concentrated. The obtained crude oil was purified by SiO_2-column chromatography (hexane-EtOAc, 9:1) to give the adduct **6.61** as single product (192 mg, 53%). If *i*-Pr_2NEt was used to instead of Bu_3N, the yield was promoted to 73% (264mg, >20:1 *dr*).

Rf; 0.30 (Hexanes : EtOAc = 5:1); ^1H NMR (400 MHz, $CDCl_3$) δ 3.93 (m, 2H), 3.08 (d, *J* = 2.0 Hz, 1H), 2.82 (p, *J* = 7.0 Hz, 1H), 2.48 (m, 2H), 2.13 (qt, *J* = 9.6, 4.8 Hz, 2H), 1.95 (t, *J* = 2.6 Hz, 1H), 1.71 (m, 2H), 1.58 (m, 1H), 1.17 (d, *J* = 7.0 Hz, 3H), 1.04 (t, *J* = 7.6 Hz, 3H), 0.95 (t, *J* = 7.9 Hz, 9H), 0.90 (d, *J* = 6.8 Hz, 3H), 0.62 (q, *J* = 7.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.8, 83.5, 75.3, 74.5, 69.1, 49.2, 38.2, 35.4, 32.7, 15.1, 12.7, 7.9, 7.6, 7.1, 5.5; MS (ES) calculated for $C_{19}H_{36}O_3SiNa$ $[M + H]^+$ 363.3, found 363.2.

(2*S*, 3*S*)-2-(but-3-yn-1-yl)-6-ethylidene-3, 5-dimethyl-3, 6-dihydro-2H-pyran (6.63)

The procedure was the same as the preparation of **6.61**. Only two equivalents of $TiCl_4$ and 2.2 equivalents of Bu_3N were added.

The compound **6.63**: Rf 0.80 (Hexanes : EtOAc = 5:1); ^1H NMR (400 MHz, $CDCl_3$) δ 5.58 (d, *J* = 5.7 Hz, 1H), 4.69 (q, *J* = 6.9 Hz, 1H), 3.91 (dt, *J* = 10.1, 3.4 Hz, 1H), 2.38 (m, 2H), 2.21 (m, 1H), 1.94 (t, *J* = 2.8 Hz, 1H), 1.90 (m, 1H), 1.74 (s, 3H), 1.68 (d, *J* = 7.2 Hz, 3H), 1.60 (m, 1H), 0.84 (d, *J* = 6.8 Hz, 3H). MS calcd. for $C_{13}H_{18}ONa$ $[M + Na]^+$ 213.2, found 213.2.

Aldol Coupling: $TiCl_4$ was added dropwise to the solution of **6.64** (142 mg, 0.61 mmol) in CH_2Cl_2 (3 mL) at 0 ^oC. After stirring for 5 min, (-)-sparteine (350 uL, 1.53 mmol) was added for stirring an additional 20 min. Then the solution of aldehyde **6.60** (170 mg, 0.67 mmol) in CH_2Cl_2 (3 mL) was added and stirred for 1 h at 0 ^oC. The mixture was quenched with sat. NH_4Cl solution (10 mL) and CH_2Cl_2 (10 mL). The aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic phase was dried over $MgSO_4$. After concentration by vacuum, the crude residue was purified by FC (silica gel, Hexanes/EtOAc 12:1) to give compound **6.65** (100 mg, 34%) and **6.66** (120 mg, 40%).

(*S*)-4-benzyl-3-((2*S*,3*R*,4*S*,5*S*)-3-hydroxy-2,4-dimethyl-5-((triethylsilyl)oxy)non-8-ynoyl)oxazolidin-2-one (6.65)

Rf: 0.50 (Hexanes : EtOAc 3:1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.26 (m, 5H), 4.67 (ddt, *J* = 10.1, 7.5, 2.8 Hz, 1H), 4.34 (s, 1H), 4.18 (m, 2H), 4.01 (ddd, *J* = 9.6, 4.6, 2.3 Hz, 2H), 3.86 (qd, *J* = 6.9, 2.4 Hz, 1H), 3.35 (dd, *J* = 13.3, 3.2 Hz, 1H), 2.75 (m, 1H), 2.33 (m, 1H), 2.17 (m, 1H), 1.95 (t, *J* = 4.8 Hz, 1H), 1.85 (m, 1H), 1.74 (m, 2H), 1.21 (d, *J* = 6.8 Hz, 3H), 0.96 (m, 9H), 0.85 (d, *J* = 6.0 Hz, 3H), 0.64 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.2, 153.5, 135.7, 129.6, 129.1, 127.5, 84.0, 75.6, 73.3, 69.1, 66.4, 56.1, 41.0, 39.9, 37.9, 30.8, 15.6, 12.5, 8.6, 7.0, 5.1; MS calcd. for $C_{27}H_{42}NO_5Si$ $[M + H]^+$ 488.3, found 488.3.

(*S*)-4-benzyl-3-((2*R*, 3*S*, 4*S*, 5*S*)-3-hydroxy-2,4-dimethyl-5-((triethylsilyl)oxy)non-8-ynoyl)oxazolidin-2-one (6.66)

Rf: 0.35 (Hexanes : EtOAc 3:1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.28 (m, 5H), 4.65 (ddt, *J* = 10.3, 6.8, 3.2 Hz, 1H), 4.18 (m, 2H), 4.07 (q, *J* = 6.9, 3.2 Hz, 1H), 4.01 (dt, *J* = 6.9, 4.0, 2.2 Hz, 1H),

3.32 (dd, *J* = 13.3, 3.4 Hz, 1H), 3.19 (s, 1H), 2.66 (dd, *J* = 13.2, 10.0 Hz, 1H), 2.14 (m, 2H), 1.94 (t, *J* = 2.6 Hz, 1H), 1.74 (t, *J* = 7.1, 7.0 Hz, 3H), 1.68 (m, 1H), 1.28 (d, *J* = 6.2 Hz, 3H), 0.96 (m, 9H), 0.94 (d, *J* = 8.0 Hz, 3H), 0.63 (q, *J* = 7.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.3, 153.0, 135.4, 129.5, 129.2, 127.6, 83.4, 74.9, 74.6, 69.2, 66.1, 55.5, 41.0, 38.4, 38.2, 32.7, 15.0, 13.5, 7.6, 7.1, 5.4; MS calcd. for $C_{27}H_{42}NO_5Si$ $[M + H]^+$ 488.3, found 488.3.

Acetonide Formation Procedure: To a solution of Aldol adduct in EtOH, PPTS (5 mol%) was added. The mixture was stirred at room temperature; when TLC plate was indicated the reaction was completed, filter the mixture and remove the solvent. After concentration by vacuum, the crude residue was resolve in acetone and in dimethoxypropane / acetone (2.0 mL/2.0 mL) was added 2 mg PPTS. This mixture was stirred at room temperature for 30 min; then concentrated under vacuum. The crude was purified by FC (silica gel, Hexanes/EtOAc 5:1) to give compound **6.67** or **6.68**.

Compound **6.67**: Rf: 0.55 (Hexanes : EtOAc 3:1); $[\alpha]^{20}_D$ = 46.2 (*c* = 1.43 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.34-7.18 (m, 5H), 4.62 (dq, *J* = 6.4, 3.2, 1H), 4.18-4.11 (m, 2H), 4.04-3.98 (m, 1H), 3.92 (dt, *J* = 10.4, 3.2, 1H), 3.60 (dd, *J* = 7.2, 4.8, 1H), 3.33 (dd, *J* = 13.2, 3.2, 1H), 2.76 (dd, *J* = 13.2, 9.6, 1H), 2.34-2.17 (m, 2H), 1.93 (t, *J* = 2.4, 1H), 1.91-1.84 (m, 1H), 1.68-1.61 (m, 1H), 1.53-1.43 (m, 1H), 1.32 (s, 3H), 1.28 (s, 3H), 1.26 (d, *J* = 6.8, 3H), 0.89 (d, *J* = 6.8, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 175.0, 153.4, 135.5, 129.7, 129.1, 127.5, 100.7, 84.2, 75.4, 68.7, 68.0, 66.3, 56.1, 41.2, 38.0, 37.0, 30.0, 25.2, 23.9, 15.3, 12.3, 11.8; IR (film, cm^{-1}): 3290, 2936, 1781, 1698, 1382, 1210; MS calcd. for $C_{24}H_{31}NO_5$, 413.22; found: 436.70 $[M + Na]^+$.

Compound **6.68**: Rf: 0.60 (Hexanes : EtOAc 3:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (m, 5H), 4.68 (m, 1H), 4.15 (m, 3H), 4.03 (m, 2H), 3.27 (dd, *J* = 13.3, 3.6 Hz, 1H), 2.71 (dd, *J* = 13.4, 9.6

Hz, 1H), 2.24 (m, 3H), 2.14 (s, 1H), 1.90 (t, *J* = 2.6 Hz, 1H), 1.73 (dddd, *J* = 13.5, 9.4, 6.8, 5.5 Hz, 1H), 1.45 (s, 3H), 1.38 (s, 3H), 1.25 (d, *J* = 6.7 Hz, 3H), 0.87 (d, *J* = 13.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5, 152.9, 135.2, 129.6, 129.2, 127.6, 99.6, 84.2, 75.2, 71.3, 68.6, 66.1, 55.4, 39.9, 38.4, 33.4, 31.8, 30.1, 19.8, 15.9, 15.0, 6.0; MS calcd. for $C_{24}H_{32}NO_5$, 414.2; found: 414.3 $[M + H]^+$.

General Procedure for the Cycloisomerization of Alkynediols

A solution of alkynediol (0.1 mmol) in fresh distilled THF (0.5 mL) was added dropwise a solution of Zeise's dimer ($[Cl_2(CH_2CH_2)Pt]_2$, 5.0 μmol, 5% mmol) in fresh distilled THF (0.5 ml) at room temperature under N_2. The resultant solution was stirred at room temperature. When the reaction was completed, it was quenched with 300 μL NEt_3. The mixture was concentrated under vacuum and purified by FC (silica gel, Hexanes/EtOAc 2:1 or 4:1) to give compound.

4-((2*S*, 3*S*)-6-ethylidene-3,5-dimethyl-3,6-dihydro-2H-pyran-2-yl)butan-2-one (6.76)

Rf: 0.55 (Hexanes : EtOAc = 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.57 (d, *J* = 5.7 Hz, 1H), 4.67 (q, *J* = 6.9 Hz, 1H), 3.74 (dt, *J* = 10.4, 3.3 Hz, 1H), 2.72 (ddd, *J* = 17.6, 8.8, 5.4 Hz, 1H), 2.58 (ddd, *J* = 17.6, 8.6, 6.6 Hz, 1H), 2.20 (m, 1H), 2.17 (s, 3H), 1.87 (m, 1H), 1.72 (s, 3H), 1.67 (d, *J* = 7.3, 4.5 Hz, 3H), 0.91 (d, *J* = 8.4 Hz, 3H); MS calcd. for $C_{13}H_{21}O_2$ $[M + H]^+$ 209.1, found 209.1.

(2*S*)-2-((1*S*, 3*R*, 4*R*, 5*S*)-1, 4-dimethyl-2,8-dioxabicyclo[3.2.1]octan-3-yl)pentan-3-ol (6.79)

Rf: 0.15 (Hexanes: EtOAc = 1:2); Inseparable 1:1 mixture. The one has ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.62 (m, 1H), 4.34 (dt, *J* = 7.1, 6.8, 2.8 Hz, 1H), 4.14 (dt, *J* = 9.9, 4.8 Hz, 1H),

2.85(ddd, J = 19.2, 14.0, 2.8 Hz, 1H), 1.07 (dd, *J* = 6.9, 1.6 Hz, 2H); The other has ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.57 (m, 1H), 4.29 (dt, *J* = 7.1, 6.8, 2.8 Hz, 1H), 4.06 (ddd, *J* = 9.9, 5.3, 3.7 Hz, 1H), 2.53 (ddd, *J* = 52.6, 25.1, 5.2 Hz, 1H); MS calcd. for $C_{13}H_{25}O_3$ $[M + H]^+$ 229.2, found 229.2.

(*S*)-2-((1*S*, 3*R*, 4*R*, 5*S*)-1, 4-dimethyl-2, 8-dioxabicyclo [3.2.1]octan-3-yl)propan-1-ol (6.81)

Rf: 0.50 (Hexanes: EtOAc = 1:2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.05 (td, *J* = 9.3, 6.0 Hz, 1H), 3.56 (t, *J* = 8.7 Hz, 1H), 3.49 (dd, *J* = 10.2, 3.2 Hz, 1H), 3.28 (dd, *J* = 10.1, 2.8 Hz, 1H), 2.05 (m, 2H), 1.75 (m, 5H), 1.41 (s, 3H), 1.10 (d, *J* = 6.8 Hz, 3H), 1.02 (d, *J* = 6.8 Hz, 3H); MS calcd. for $C_{11}H_{20}O_3Na$ $[M + Na]^+$ 223.1, found 223.2.

(2*R*, 3*S*, 4*R*, 5*S*)-1-((*S*)-4-benzyl-2-oxooxazolidin-3-yl)-3, 5-dihydroxy-2, 4-dimethylnonane-1, 8-dione (6.83)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (m, 5H), 4.69 (dddt, *J* = 17.9, 10.7, 6.9, 3.3 Hz, 1H), 4.16 (m, 1H), 4.09 (m, 1H), 4.04 (q, *J* = 6.0, 4.0 Hz, 2H), 3.78 (dq, *J* = 9.2, 2.8 Hz, 1H), 3.26 (dt, *J* = 13.4, 4.4 Hz, 1H), 3.03 (d, *J* = 3.6 Hz, 1H), 2.75 (m, 1H), 2.67 (d, *J* = 3.2 Hz, 1H), 2.62 (q, *J* = 7.2, 6.8 Hz, 2H), 2.16 (s, 3H), 1.80 (m, 1H), 1.59 (m, 2H), 1.24 (d, J = 6.4 Hz, 3H), 1.01 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.0, 176.1, 153.6, 135.2, 129.6, 129.2, 127.7, 75.8, 74.0, 66.5, 55.4, 41.1, 40.9, 38.3, 30.3, 29.0, 12.1, 7.1; MS calcd. for $C_{21}H_{30}NO_6$ $[M + H]^+$ 392.2, found 392.2.

5-(triethylsilyl)pent-4-ynal (6.39)

To a solution of oxalyl chloride (5.6 mL, 65 mmol) in dry CH_2Cl_2 (150 mL) was added DMSO (9.3 mL, 0.13 mol) dropwise at -78 °C. After stirring for 30 min at -78 °C, alcohol **6.38** (11.65 g,

58.8 mmol) in CH_2Cl_2 (8 mL) was added and the reaction was stirred at -78 °C for another 30 min. Then NEt_3 (41 mL, 0.30 mol) was added and the mixture was allowed to warm to RT. The reaction was stirred for 30 min at RT, then poured into 5% HCl (200 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 150 mL) and the combined organic phase was washed with aqueous $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated under vacuum. The crude was purified by FC (silica gel, Hexanes/EtOAc 12:1) to give compound **6.39** (10.6 g, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.79 (s, 1H), 2.66 (t, J = 7.2 Hz, 2H), 2.55 (t, J = 7.2 Hz, 2H), 0.95 (q, J = 8.0 Hz, 9H), 0.55 (t, J = 8.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.8, 106.0, 83.4, 43.0, 13.5, 7.7, 4.7; IR (film, cm^{-1}): 2954, 2874, 2175, 1729, 1413, 1017, 726; MS calcd. for $C_{11}H_{20}OSi$, 196.13; found: 197.05 $[M + Na]^+$.

(*S*)-1-((*S*)-4-benzyl-2-oxooxazolidin-3-yl)-2-methylpentane-1, 3-dione (6.41)

The procedure of preparation of **6.41** from **6.40** was according Evans's Procedure. Compound **6.41**: Rf: 0.55 (Hexanes : EtOAc 2:1); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.37 – 7.14 (m, 26H), 4.79 – 4.68 (m, 5H), 4.59 (qd, J = 7.3, 0.8 Hz, 5H), 4.28 – 4.06 (m, 11H), 3.30 (dd, J = 13.4, 3.4 Hz, 5H), 2.81 – 2.53 (m, 16H), 1.58 (s, 1H), 1.43 (dd, J = 7.2, 0.8 Hz, 15H), 1.31 – 1.20 (m, 1H), 1.06 (td, J = 7.2, 0.8 Hz, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.5, 170.4, 135.4, 129.6, 129.2, 127.6, 66.7, 55.5, 53.0, 38.2, 34.2, 13.1, 7.8; MS calcd. for $C_{16}H_{20}NO_4$, 290.1; found: 290.2 $[M + H]^+$.

(2*S*, 4*R*, 5*S*)-1-((*S*)-4-benzyl-2-oxooxazolidin-3-yl)-5-hydroxy-2, 4-dimethyl-9-(triethylsilyl) non-8-yne-1, 3-dione (6.42)

To a stirred suspension of anhydrous, acid-free $Sn(OTf)_2$ (634 mg, 1.52 mmol) in dry CH_2Cl_2 (6 mL) was added triethylamine (0.212 mL, 1.52 mmol) and then immediately cooled to -20 °C under N_2. After 5 min, a solution of diketone **6.41** (400 mg in 3 mL dry CH_2Cl_2, 1.38mmol) was added dropwise over 5 min. The mixture was stirred for 1 h at -20 °C and then cooled to -78 °C, followed by the addition of aldehyde **6.39** (541 mg in 2 mL CH_2Cl_2, 2.76 mmol). The reaction mixture was stirred at -78 °C for 30 min and then quenched rapidly with a cool and vigorously stirred 1:1 mixture of CH_2Cl_2/1 N aqueous $NaHSO_4$ (20mL / 20mL). After stirring at 0°C for 10 min, the mixture was diluted with additional CH_2Cl_2/1 N aqueous $NaHSO_4$ (20mL / 20mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 40 mL) and the combined organic phase was washed with aqueous $NaHCO_3$, brine, dried over Na_2SO_4 and concentrated under vacuum. The crude was purified by FC (silica gel, Hexanes/EtOAc 3:1) to give compound **6.42** (549 mg, 82%). $[\alpha]^{22}_D$ = 28.4 (*c* = 0.50 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.34-7.20 (m, 5H), 4.85 (q, *J* = 7.2, 1H), 4.79-4.71 (m, 1H), 4.24 (t, *J* = 8.8, 1H), 4.18-4.15 (m, 1H), 4.06 (dt, *J* = 8.4, 3.6, 1H), 3.30 (dd, *J* = 13.2, 3.2, 1H), 2.87 (dq, *J* =7.2, 2.8, 1H), 2.77 (dd, *J* = 13.6, 9.6, 1H), 2.37 (dt, *J* = 7.2, 3.2, 2H), 1.78-1.67 (m, 1H), 1.60-1.52 (m, 1H), 1.47 (d, *J* = 7.6, 3H), 1.22 (d, *J* = 7.2, 3H), 0.95 (q, *J* = 8.0, 9H), 0.55 (t, *J* = 8.0, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.2, 170.4, 153.8, 135.2, 129.6, 129.2, 127.6, 107.8, 82.7, 70.7, 66.7, 55.5, 52.3, 48.4, 38.1, 32.9, 17.0, 13.1, 10.5, 7.7, 4.6; IR (film, cm^{-1}): 2954, 1779, 1714, 1358, 1214, 1007, 736; MS calcd. for $C_{27}H_{39}NO_5Si$, 485.26; found: 508.50 $[M + Na]^+$.

(*S*)-4-benzyl-3-((2*S*, 3*R*, 4*R*, 5*S*)-3, 5-dihydroxy-2, 4-dimethylnon-8-ynoyl)oxazolidin-2-one (6.37)

To 5 mL of acetic acid at 0°C was added portionwise $NaBH_4$ (293 mg, 7.7 mmol). After completion of gas evolution (about 10 min), the reaction was allowed to warm to RT and stirred for 1 h. To this solution was added a solution of **6.42** (373 mg in 2.5 mL acetic acid, 0.77 mmol). After 70 min, the reaction was concentrated under vacuum. The residue was poured into saturated aqueous $NaHCO_3$ (25mL, **caution!**). The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic phase was washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The crude was purified by FC (silica gel, Hexanes/EtOAc 1:1) to give intermediate (296 mg, 79%). $[\alpha]^{22}_D$ = 23.4 (*c* = 0.93 in CH_2Cl_2); ^{1}H NMR (400 MHz, CDCl3) *δ*: 7.35-7.18 (m, 5H), 4.73-4.68 (m, 1H), 4.26-4.18 (m, 2H), 3.98 (d, *J* = 9.6, 1H), 3.85 (dq, *J* = 7.2, 1.6, 1H), 3.80 (d, *J* = 1.6, 1H), 3.24 (dd, *J* = 13.2, 3.2, 1H), 3.16 (d, *J* = 6.4, 1H), 2.78 (dd, *J* = 13.2, 9.6, 1H), 2.52-2.34 (m, 2H), 1.97-1.89 (m, 1H), 1.80-1.63 (m, 3H), 1.26 (d, *J* = 6.8, 3H), 0.98 (q, *J* = 8.0, 9H), 0.84 (d, *J* = 7.2, 3H), 0.57 (t, *J* = 8.0, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 178.1, 153.0, 135.1, 129.6, 129.2, 127.6, 108.5, 82.3, 74.2 73.7, 66.4, 55.3, 39.6, 39.4, 37.9, 31.9, 17.5, 12.4, 9.8, 7.6, 4.7; IR (film, cm^{-1}): 3436 (br), 2953, 2170, 1781, 1698, 1387, 1210, 736; MS calcd. For $C_{27}H_{39}NO_5Si$, 487.28; found: 510.50 $[M + Na]^+$.

To a solution of intermediate (317 mg, 0.65 mmol) in dry THF (15 mL) was added TBAF (0.72 mL, 1 M in THF) dropwise at 0 °C. After stirring for 3 min at 0 °C, sat. NH_4Cl solution (20 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (2 × 25 mL) and the combined organic phase was washed with aqueous $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated under vacuum. The crude was purified by FC (silica gel, Hexanes/EtOAc 1:1) to give compound **6.37** (228 mg, 94%). $[\alpha]^{20}_D$ = 29.5 (*c* = 1.12 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.34-7.18 (m, 5H), 4.71-4.67 (m, 1H), 4.26-4.17 (m, 2H), 3.98 (dt, *J* = 9.2, 2.4, 1H), 3.91-3.84 (m, 2H), 3.74 (d,

J = 2.4, 1H), 3.24 (dd, *J* = 13.6, 3.2, 1H), 3.10 (d, *J* = 7.2, 1H), 2.78 (dd, *J* = 13.6, 9.2, 1H), 2.52-2.24 (m, 2H), 1.95 (t, *J* = 2.4, 1H), 1.92-1.84 (m, 1H), 1.78-1.71 (m, 1H), 1.67-1.59 (m, 1H), 1.27 (d, *J* = 6.8, 3H), 0.85 (d, *J* = 7.2, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.1, 153.0, 135.1, 129.6, 129.2, 127.7, 84.6, 74.0 73.4, 68.8, 66.4, 55.2, 39.7, 39.2, 37.9, 31.8, 15.9, 12.3, 10.2; IR (film, cm^{-1}): 3296, 2937, 1778, 1693, 1386, 1211, 972; MS calcd. for $C_{21}H_{27}NO_5$, 373.19; found: 373.75 $[M + H]^+$.

The relative 1,3-*anti* diol stereochemistry of **6.37** was established by ^{13}C NMR analysis of acetonide **6.67** using Rychnovsky's method: relevant ^{13}C NMR signals (75 MHz, $CDCl_3$): 100.7, 25.2, 23.9 ppm.

(*S*)-4-benzyl-3-((*S*)-2-((4*R*, 5*R*, 6*S*)-6-(but-3-yn-1-yl)-2, 2, 5- trimethyl-1,3-dioxan-4-yl)propanoyl)oxazolidin-2-one (6.67)

To a stirred solution of **6.35** (16 mg, 0.043 mmol) in dimethoxypropane / acetone (1.0 mL/1.0 mL) was added 2 mg PPTS. This mixture was stirred at room temperature for 30 min, then concentrated under vacuum. The crude was purified by FC (silica gel, Hexanes/EtOAc 5:1) to give compound **6.67** (15 mg, 87%). $[\alpha]^{20}_D$ = 46.2 (*c* = 1.43 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.34-7.18 (m, 5H), 4.62 (dq, *J* = 6.4, 3.2, 1H), 4.18-4.11 (m, 2H), 4.04-3.98 (m, 1H), 3.92 (dt, *J* = 10.4, 3.2, 1H), 3.60 (dd, *J* = 7.2, 4.8, 1H), 3.33 (dd, *J* = 13.2, 3.2, 1H), 2.76 (dd, *J* = 13.2, 9.6, 1H), 2.34-2.17 (m, 2H), 1.93 (t, *J* = 2.4, 1H), 1.91-1.84 (m, 1H), 1.68-1.61 (m, 1H), 1.53-1.43 (m, 1H), 1.32 (s, 3H), 1.28 (s, 3H), 1.26 (d, *J* = 6.8, 3H), 0.89 (d, *J* = 6.8, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.0, 153.4, 135.5, 129.7, 129.1, 127.5, 100.7, 84.2, 75.4, 68.7, 68.0, 66.3, 56.1, 41.2, 38.0, 37.0, 30.0, 25.2, 23.9, 15.3, 12.3, 11.8; IR (film, cm^{-1}): 3290, 2936, 1781,

1698, 1382, 1210;MS calcd. for $C_{24}H_{31}NO_5$, 413.22; found: 436.70 $[M + Na]^+$. The spectra of this compound is fully matched the spectra of **6.67** synthesized from **6.65**.

(*S*)-4-benzyl-3-((*S*)-2-((1*S*, 3*R*, 4*R*, 5*S*)-1, 4-dimethyl-2, 8-dioxabicyclo[3.2.1]octan-3-yl)propanoyl)oxazolidin-2-one (6.43)

A solution of **6.37** (69 mg, 0.185 mmol) in fresh distilled THF (1 mL) was added dropwise a solution of Zeise's dimer ($[Cl_2(CH_2CH_2)Pt]_2$, 9.25 μmol, 5% eq) in fresh distilled THF (1.5 ml) at room temperature under N_2. The resultant solution was stirred at room temperature for 5 min; then was quenched with 300 μL NEt_3. The mixture was concentrated under vacuum and purified by FC (silica gel, Hexanes/EtOAc 2:1) to give compound **6.43** (68 mg, 99%). $[\alpha]^{20}{}_D$ = 38.3 (*c* = 0.60 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.34-7.20 (m, 5H), 4.66-4.60 (m, 1H), 4.20-4.14 (m, 3H), 3.93 (dq, *J* = 6.8, 2.8, 1H), 3.77 (dd, *J* = 6.8, 2.8, 1H), 3.35 (dd, *J* = 13.2, 3.2, 1H), 2.75 (dd, *J* = 13.6, 9.6, 1H), 2.03-1.95 (m, 1H), 1.92-1.78 (m, 4H), 1.45 (s, 3H), 1.23 (d, *J* = 6.8, 3H), 0.78 (d, *J* = 6.8, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.8, 153.5, 135.6, 129.7, 129.1, 127.5, 105.3, 80.1, 74.8, 66.4, 56.2, 40.0, 37.8, 35.0, 34.5, 24.2, 24.1, 12.9, 9.9; IR (film, cm^{-1}): 2961, 1778, 1705, 1454, 1385, 1194, 973; MS calcd. for $C_{21}H_{27}NO_5$, 373.19; found: 396.10 $[M + Na]^+$.

(*S*)-2-((1*S*, 3*R*, 4*R*, 5*S*)-1, 4-dimethyl-2, 8-dioxabicyclo[3.2.1]octan-3-yl)pentan-3-one (6.35)

To a stirred suspension of Weinreb salt (45 mg, 0.46 mmol) in dry CH_2Cl_2 (8 mL) was added $AlMe_3$ (2.0 M in toluene, 0.23 mL, 0.46 mmol) dropwise at -10 °C under N_2. After gas evolution was evident, the solution was stirred at ambient temperature for 45 min before it was cooled to -10 °C and a solution of **376** (57 mg, 0.153 mmol) in 2 mL of $CH_2Cl_2$was added. The resultant solution was warmed to RT and allowed to sit for 5 h before it was quenched by the addition of

10 mL of a saturated aqueous solution of Rochelle's salt. The mixture was stirred vigorously until the phases became clear. The aqueous layer was then extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The crude amide was used for next step without further purification.

To a solution of crude Weinreb amide in 5 mL of dry THF at 0 °C was added ethyl Grignard (2.0 M in THF, 0.23 mL, 0.46 mmol). After 30 min the solution was warmed to ambient temperature and allowed to stir for 2 additional hours. The reaction was recooled to 0 °C and quenched with 10 mL of a saturated aqueous solution of NH_4Cl and 10 mL of Et_2O. The aqueous layer was extracted with ether (3 × 10 mL) and the combined organic phase was washed with brine, dried over $MgSO_4$ and concentrated under vacuum. The crude was purified by FC (silica gel, Hexanes/EtOAc 5:1) to give compound **6.35** (30 mg, 87% for 2 steps).

$[\alpha]^{20}_D$ = -7.8 (*c* = 1.0 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.20 (dd, *J* = 6.0, 3.6, 1H), 3.84 (dd, *J* = 10.4, 3.2, 1H), 2.54-2.46 (m, 3H), 1.98-1.76 (m, 5H), 1.41 (s, 3H), 1.12 (d, *J* = 7.2, 3H), 1.02 (t, *J* = 7.2, 3H), 0.72 (d, *J* = 7.2, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.6, 105.2, 80.1, 75.6, 48.1, 34.8, 34.4, 33.9, 24.2, 24.0, 13.0, 9.5, 7.9.; IR (film, cm^{-1}): 2960, 1713, 1459, 1389, 1155, 1021, 970; MS calcd. for $C_{13}H_{22}O_3$, 226.16; found: 227.00 $[M + H]^+$.

(2*R*, 4*R*, 5*S*)-1-(benzyloxy)-5-hydroxy-2, 4-dimethylnon-8-yn-3-one (6.69)

To a solution of (+)-di*iso*pinocampheylboron triflate (5.1 mmol) in CH_2Cl_2 (5 mL) at –78 °C was added *i*-Pr_2NEt (1.76 mL, 10.2 mmol) dropwise and the solution was stirred for 5 min. A solution of ketone **6.2** (700 mg, 3.4 mmol) in CH_2Cl_2 (2 mL + 1 mL washing) was added to the cold triflate and amine base solution. The reaction was stirred at –78 °C for 15 min, then warmed

to 0 °C and stirred for 2 h. The enolate solution was recooled to –78 °C and aldehyde **6.58** (10.2 mmol) was added. The reaction was stirred at –78 °C for 3 h before being placed in the freezer (–23 °C) for 16 h. The reaction was then warmed to 0 °C and quenched with excess MeOH (7 mL) and pH 7 phosphate buffer (7 mL). Hydrogen peroxide solution (30% aqueous, 3.5 mL, 31 mmol) was then added dropwise and the reaction stirred for 1 h, with warming to RT. The mixture was extracted with CH_2Cl_2 (4 x 10 mL) and the combined organic fractions were washed with saturated aqueous NaHCO3, dried ($MgSO_4$), filtered and concentrated *in vacuum* to remove residual solvent. The crude material was purified by flash chromatography utilizing a gradient of 5-10% EtOAc/hexane as the mobile phase to give the aldol adduct **6.69** (813 mg, 83%) as pale yellow oil; R*f* 0.30 (30% EtOAc/hexane); MS calcd. for $C_{18}H_{25}O_3$, 289.2; found: 289.2 $[M + H]^+$.

(1*S*, 3*S*, 4*R*, 5*S*)-3-((*R*)-1-(benzyloxy)propan-2-yl)-1, 4-dimethyl-2, 8-dioxabicyclo[3.2.1]octane (6.5)

To 5 mL of acetic acid at 0°C was added portionwise $NaBH_4$ (293 mg, 7.7 mmol). After completion of gas evolution (about 10 min), the reaction was allowed to warm to RT and stirred for 1 h. To this solution was added a solution of **6.69** (373 mg in 2.5 mL acetic acid, 0.77 mmol). After 70 min, the reaction was concentrated under vacuum. The residue was poured into saturated aqueous $NaHCO_3$ (25mL, **caution!**). The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic phase was washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The crude residue was purified by a short column. The pure compound was resolved in THF; and was added dropwise a solution of zeise's dimer ($[Cl_2(CH_2CH_2)Pt]_2$, 9.25 μmol, 5% mmol) in fresh distilled THF (1.5 ml) at room temperature under N_2. The resultant solution was stirred at room temperature for 5 min; then was quenched

with 300 μL NEt_3. The mixture was concentrated under vacuum and purified by FC (silica gel, Hexanes/EtOAc 2:1) to give compound **6.5** as pale yellow oil.

The compound **6.5**: R*f* 0.25 (10% EtOAc/hexane); ^{1}H NMR (500 MHz, CD_3OD) δH 7.34-7.26 (5H, m), 4.53 (1H, d, *J*= 12.0 Hz,), 4.46 (1H, d, *J*= 12.0 Hz,), 4.19 (1H, br dd, *J*= 5.8, 3.3 Hz,), 3.65 (1H, dd, *J*= 10.5, 1.8 Hz), 3.48 (1H, m), 3.31 (1H, m), 1.96-1.78 (6H, m,), 1.38 (3H, s,), 0.86 (3H, d, *J*= 6.9 Hz), 0.72 (3H, d, *J*= 6.9 Hz); ^{13}C NMR (125 MHz, CD_3OD) δC 140.0, 129.4, 128.8, 128.6, 106.3, 81.5, 74.8, 74.0, 73.8, 35.2, 35.1, 34.9, 24.9, 24.2, 12.7, 10.0; $[\alpha]^{20}_{D}$ –48.5 (*c* 0.13, $CHCl_3$); MS calc. for $C_{18}H_{26}O_3Na$ $[M + Na]^+$ 313.2, found 313.2.

(*S*)-2-((1*S*, 3*R*, 4*R*, 5*S*)-1, 4-dimethyl-2, 8-dioxabicyclo[3.2.1]octan-3-yl)propanal (6.6)

To a solution of benzyl ether **6.5** (65 mg, 0.22 mmol) in absolute EtOH (0.5 mL) at ambient temperature was added Pd/C (5% by weight, 15 mg) in one portion. The slurry was degassed, purged with H_2 three times and stirred vigorously for 1 h. The slurry was filtered through celite, eluting with EtOAc and concentrated *in vacuo* to give alcohol (43 mg, 96%) which was used without further purification.

R*f* 0.20 (30% EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.22 (1H, dd, *J*= 6.9, 3.6 Hz), 3.72 (1H, dd, *J*= 10.9, 3.6 Hz), 3.68-3.61 (2H, m), 2.42 (1H, m), 2.07-1.76 (6H, m), 1.46 (3H, s), 1.00 (3H, d, *J*= 7.1 Hz), 0.71 (3H, d, *J*= 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 105.0, 80.1, 77.6, 67.6, 35.1, 34.5, 34.1, 24.0, 23.9, 12.6, 9.4; $[\alpha]^{20}_{D}$ = –20.7 (*c* 1., $CDCl_3$); MS calc. for $C_{11}H_{20}O_3$ [M + H]+ 201.1, found 201.1.

A slurry of Dess-Martin periodinane (865 mg, 2.04 mmol) and $NaHCO_3$ (344 mg, 4.1 mmol) in CH_2Cl_2 (6.5 mL) was stirred at ambient temperature for 20 min before being cooled to 0 °C. To

the cold slurry was added alcohol (137 mg, 0.68 mmol) in CH_2Cl_2 (1 + 0.5 mL) dropwise. The reaction was warmed to RT and stirred for 20 min. The reaction was recooled to 0 °C and quenched by the addition of saturated aqueous NaHCO3 (2 mL) and saturated aqueous $Na_2S_2O_3$ (4 mL). The reaction was stirred for 1 h while warming to RT. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (4 x 5 mL). The combined organic fractions were dried (Na_2SO_4), filtered and concentrated to dryness *in vacuo*. The resulting oil was purified by flash chromatography on silica, utilizing 20% EtOAc/hexane as the mobile phase to give aldehyde **6.6** as a colorless oil (125 mg, 92%).

R*f* 0.37 (30% EtOAc/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.66 (1H, d, *J*= 0.7 Hz), 4.24 (1H, dd, *J*= 6.3, 3.3 Hz), 3.98 (1H, dd, *J*= 10.5, 2.3 Hz), 2.37 (1H, qd, *J*= 6.9, 2.4 Hz), 2.07-1.79 (5H, m), 1.40 (3H, s), 1.14 (3H, d, *J*= 7.1 Hz), 0.75 (3H, d, *J*= 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.9, 105.3, 79.9, 74.1, 47.3, 34.4, 34.9, 24.0, 23.8, 12.7, 6.7;

$[\alpha]^{20}_D$ = +9.3 (*c* 1.0, $CDCl_3$); MS calc. for $C_{11}H_{18}O_3$ [M + Na]+ 221.1, found 221.1.

Note: The preparation of **6.35** from **6.6** was achieved in two steps including standard Grignard addition and Dess-Martin oxidation manipulations. The spectra of **6.35** obtained from this method were identical with the spectra of **6.35** that prepared from **6.86** over two steps.

(2*R*, 3*R*)-1-((4-methoxybenzyl)oxy)-2-methylhex-5-en-3-ol (6.49)

To a solution of (+)-diisopinocampheylallylborane in ether (36.8 mmol in 80 mL ether) was added **6.48** (7.2 g, 35 mmol in 10 mL ether) at - 98°C. The solution was stirred at – 98 °C for 2 h and then warmed to 0 °C. The mixture was treated with 1N NaOH (50 mL) and 30% H_2O_2 (20 mL) and heated under reflux for 1 h. After allowed to reach ambient temperature, the aqueous

layer was extracted with ether (3 × 50 mL). The combined organic phase was washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The crude was purified by FC (silica gel, Hexanes/EtOAc 5:1) to give compound **6.49** (7.79 g, 90%). R*f* 0.30 (15% EtOAc/hexane); $[\alpha]^{22}_D$ = 5.71 (*c* = 0.88 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.25-7.21 (m, 2H), 6.89-6.85 (m, 2H), 5.88-5.78 (m, 1H), 5.13-5.05 (m, 2H), 4.43 (s, 2H), 3.83-3.77 (m, 1H), 3.80 (s, 3H), 3.49 (d, *J* = 5.3, 2H), 2.55 (d, *J* = 4.0, 1H, OH), 2.23-2.17 (m, 2H), 1.94-1.84 (m, 1H), 0.94 (d, *J* = 6.8, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 159.4, 135.9, 130.4, 129.5, 117.4, 114.0, 74.4, 73.2, 55.5, 39.1, 37.7, 11.0; IR (film, cm^{-1}): 3462(br), 1640, 1513, 1456, 1247, 1173, 1090, 984, 818; MS calcd. for $C_{15}H_{22}O_3$: 250.16; found: 251.05 $[M + H]^+$.

(2*R*, 3*R*)-1-((4-methoxybenzyl)oxy)-2-methylhex-5-en-3-yl methacrylate (6.88)

To a solution of acid **6.87** (0.8 mmol) and alcohol **6.49** (100 mg, 0.4 mmol) in dry CH_2Cl_2 (10 mL) was added CH_2Cl_2 (412 mg, 2.0 mmol) and DMAP (25 mg, 0.2 mmol) at 0 °C under N_2. After stirring at 0 °C for 30 min, the solution was warmed to room temperature and stirred for 12 h, then poured into saturated aqueous $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic phase was washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The crude was purified by FC (silica gel, Hexanes/EtOAc 9:1) to give compound **6.88** (114 mg, 90%; 160 mg, 82%).

Compound **6.88:** Rf: 0.50 (Hexanes : EtOAc = 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.18 (m, 2H), 6.91 – 6.81 (m, 2H), 6.05 (dq, *J* = 1.8, 0.9 Hz, 1H), 5.73 (ddt, *J* = 17.2, 10.2, 7.1 Hz, 1H), 5.50 (p, *J* = 1.6 Hz, 1H), 5.19 – 4.96 (m, 3H), 4.38 (s, 2H), 3.79 (s, 3H), 3.28 (m, 2H), 2.47 – 2.26 (m, 2H), 2.12 – 1.97 (qt, *J* = 6.8, 3.5 Hz, 1H), 1.90 (s, 3H), 0.96 (d, *J* = 6.9 Hz, 3H); ^{13}C

NMR (125 MHz, $CDCl_3$) δ 167.1, 159.3, 144.2, 136.9, 134.2, 130.7, 129.3, 125.3, 125.3, 117.8, 114.0, 73.8, 72.3, 55.5, 36.7, 18.6, 11.70; MS calcd. for $C_{19}H_{27}O_4$: 319.2; found: 319.2 $[M + H]^+$.

(*R*)-6-((*R*)-1-((4-methoxybenzyl)oxy)propan-2-yl)-3-methyl-5,6-dihydro-2H-pyran-2-one (6.89)

Grubbs' second generation catalyst (1,3-*Bis*-(2,4,6-trimethylphenyl)-2-(imidazolidinylidene)-(dichlorophenylmethylene)(tricyclohexylphosphine)ruthenium, 28 mg, 0.033 mmol) was added to a solution of **6.88** (0.33 mmol) in dry CH_2Cl_2 (120 mL). The reaction was refluxed for 14 h under N_2. The solution was concentrated and purified by FC (silica gel, Hexanes/EtOAc 6:1) to give compound **6.89** (62 mg, 64%) and recover **386a** (19 mg, 20%).

The compound **6.89**: Rf: 0.20 (Hexanes : EtOAc = 5:1); δ 7.27 – 7.18 (m, 2H), 6.91 – 6.80 (m, 2H), 6.57 (dt, *J* = 6.4, 2.0 Hz, 1H), 4.51(dt, *J*= 13.2, 4.0, 3.6 Hz, 1 H), 4.14 (q, *J* = 11.2, 9.2, 2H), 3.79 (s, 3H), 3.50 (dd, *J*= 7.2, 9.2 Hz, 1H), 3.40 (dd, *J* = 5.2, 9.2 Hz, 1H), 2.44 (ddp, *J* = 18.1, 13.0, 2.6 Hz, 1H), 2.16 (m, 1H), 1.99 (m, 1H), 1.91(s, 3H), 1.02 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 159.4, 139.7, 130.5, 130.1, 129.5, 114.0, 82.10, 73.1, 71.5, 55.5, 37.7, 27.8, 17.2, 12.1; MS calcd. for $C_{17}H_{22}O_4Na$, 312.7; found: 312.9 $[M + Na]^+$.

(*S*)-2-((*R*)-5-methyl-6-oxo-3, 6-dihydro-2H-pyran-2-yl)propanal (6.90)

To a solution of **6.89** (0.14 mmol) in CH_2Cl_2/H_2O (8 mL/ 0.4 mL) was added DDQ (38 mg, 0.17 mmol). After stirring at RT for 1 h, the solution poured into saturated aqueous $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic phase was washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The crude was purified by FC (silica gel, Hexanes/EtOAc 2:1) to give intermediate.

The alcohol intermediate: Rf 0.23 (Hexanes : EtOAc 1:1); $[\alpha]^{22}_D$ = 35.0 (*c* = 0.65 in $CDCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.62 (m, 1H), 4.57 (dt, *J* = 13.0, 3.7 Hz, 1H), 3.73 (dd, *J* = 10.8, 7.4 Hz, 1H), 3.62 (dd, *J* = 10.8, 5.3 Hz, 1H), 2.48 (ddp, *J* = 18.2, 13.1, 2.6 Hz, 1H), 2.19 (m, 1H), 2.06 (s, 1H), 1.98 – 1.85 (m, 4H), 1.01 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.5, 139.8, 128.5, 78.7, 64.4, 39.3, 27.5, 17.3, 11.5; MS calcd. for $C_9H_{15}O_3$, 171.1; found: 171.1 $[M + H]^+$.

To a solution of intermediate (80 mg, 0.234 mmol) in dry CH_2Cl_2 (10 mL) was added Dess-Martin reagent (198 mg, 0.47 mmol) and solid $NaHCO_3$ (79 mg, 0.94 mmol). The reaction was stirred for 30 min at RT, then poured into aqueous $NaHCO_3$ (15 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic phase was washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The crude was purified by FC (silica gel, Hexanes/EtOAc 3:1) to give compound **6.90** (95%).

The compound **6.90**: Rf 0.35 (Hexanes : EtOAc 1:1); $[\alpha]^{22}_D$ = -25.7 (*c* = 0.50 in $CDCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 9.79 (s, 1H), 6.64 (tdd, *J* = 4.3, 2.7, 1.4 Hz, 1H), 4.78 (ddd, *J* = 12.0, 5.4, 4.4 Hz, 1H), 2.73 (m, 1H), 2.41 (m, 2H), 1.94 (s, 3H), 1.28 (d, *J* = 5.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.2, 165.6, 139.0, 128.8, 77.1, 49.9, 27.6, 17.3, 9.9; MS calcd. for $C_9H_{13}O_3$, 169.1; found: 169.1 $[M + H]^+$.

(*R*)-6-((2*R*, 3*S*, 4*R*, 6*S*)-6-((1*S*, 3*R*, 4*R*, 5*S*)-1, 4-dimethyl-2,8-dioxabicyclo[3.2.1]octan-3-yl)-3-hydroxy-4-methyl-5-oxoheptan-2-yl)-3-methyl-5,6-dihydro-2H-pyran-2-one (6.91)

To a solution of ketone **6.35** (56.5 mg, 0.25 mmol) in dry THF (5 mL) at -78 °C was added a solution of lithium bis(trimethylsilyl)amide (1 M in THF, 0.3 mL, 0.3 mmol) dropwise. The resulting yellow solution was stirred at -78 °C for 2 h and then a solution of aldehyde **6.90** (119

mg, 0.35 mmol) in 1 mL THF was added. The resulting solution was stirred at -78 °C for another 2 h. The reaction was quenched by the addition of pH 7 phosphate buffer solution (6 mL). The aqueous layer was extracted with ether (3 × 10 mL) and the combined organic phase was washed with brine, dried over $MgSO_4$ and concentrated under vacuum. The crude was purified by FC (silica gel, Hexanes/EtOAc 3:1) to give compound **6.91** (112 mg, 81%).

Rf: 0.20 (hexanes : EtOAc 4:1); $[\alpha]^{22}_D$ = -14.2 (*c* = 0.27 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.60 (m, 1H), 4.96 (ddd, *J* = 13.4, 3.6, 1.7 Hz, 1H), 4.20 (dd, *J* = 6.2, 3.4 Hz, 1H), 4.01 (dt, *J* = 9.9, 1.7 Hz, 1H), 3.82 (dd, *J* = 10.3, 3.1 Hz, 1H), 3.54 (d, *J* = 2.0 Hz, 1H), 3.03 (qd, *J* = 7.0, 1.5 Hz, 1H), 2.77 (qd, *J* = 7.0, 3.1 Hz, 1H), 2.51 (ddp, *J* = 18.3, 13.5, 2.5 Hz, 1H), 2.15- 2.05 (m, 2 H), 2.00 – 1.81 (m, 8H), 1.42 (s, 3H), 1.12 (d, *J* =7.2 Hz, 3H), 1.06 (d, *J* = 7.2 HZ, 3H), 0.94 (d, *J* = 7.2Hz, 3H), 077 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, $cdcl_3$) δ 218.62, 166.51, 139.72, 128.53, 105.47, 80.13, 76.55, 75.78, 69.83, 47.32, 43.36, 39.22, 34.75, 34.42, 28.12, 24.03, 24.00, 17.35, 13.14, 9.89, 9.34, 8.90; IR (film, cm^{-1}): 326, 2937,1778, 1693, 1386, 1211, 972; MS calcd. for $C_{22}H_{35}O_6$, 395.2; found: 395.2 $[M + H]^+$.

(*R*)-6-((*S*)-1-((4*S*, 5*R*, 6*R*)-6-((*R*)-1-((1*S*, 3*R*, 4*R*, 5*S*)-1, 4-dimethyl-2, 8-dioxabicyclo[3.2.1]octan-3-yl)ethyl)-2,2,5-trimethyl-1,3-dioxan-4-yl)ethyl)-3-methyl-5,6-dihydro-2H-pyran-2-one (6.92)

Tetramethylammonium triacetoxyborohydride (345 mg, 1.31 mmol) was added to CH_3CN/acetic acid (3 mL / 3 mL), and the resulting solution was stirred for 30 min at RT and cooled to -20 °C before ketone **6.91** (93 mg, 0.164 mmol) was added. After 48 h at -20 °C, the reaction was quenched by the addition of 20 mL of a saturated aqueous solution of Rochelle's salt. The aqueous layer was then extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were

washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by FC (silica gel, Hexanes/EtOAc 2:1) to give diol compound (83 mg, 89%).

To a stirred solution of diol (16 mg, 0.043 mmol) in dimethoxypropane / acetone (1.0 mL/1.0 mL) was added 2 mg PPTS. This mixture was stirred at room temperature for 30 min; then concentrated under vacuum. The crude was purified by FC (silica gel, Hexanes/EtOAc 5:1) to give compound **6.92** (15 mg, 87%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.65 – 6.59 (m, 0H), 4.86 – 4.78 (m, 0H), 4.21 (dd, *J* = 6.1, 3.2 Hz, 0H), 4.13 (q, *J* = 7.2 Hz, 0H), 3.98 (dd, *J* = 11.0, 3.6 Hz, 0H), 3.76 (dd, *J* = 10.5, 2.0 Hz, 0H), 3.38 – 3.25 (m, 0H), 2.53 (dddd, *J* = 18.4, 15.9, 5.1, 2.5 Hz, 0H), 2.39 – 2.28 (m, 0H), 2.06 (q, *J* = 8.6, 7.9 Hz, 0H), 2.01 – 1.56 (m, 1H), 1.50 – 1.15 (m, 1H), 1.05 (s, 0H), 1.04 – 0.97 (m, 0H), 0.97 – 0.79 (m, 1H), 0.70 (d, *J* = 6.9 Hz, 0H), 0.08 (s, 0H).

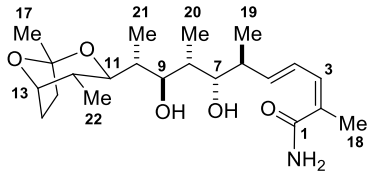
(*S*, 2*Z*, 4*E*)-6-((4*S*, 5*R*, 6*R*)-6-((*R*)-1-((1*S*, 3*R*, 4*R*, 5*S*)-1, 4-dimethyl-2, 8-dioxabicyclo[3.2.1]octan-3-yl)ethyl)-2,2,5-trimethyl-1,3-dioxan-4-yl)-2-methylhepta-2,4-dienoic acid (6.93)

Saliniketal A (5.2)

To the solution of **6.93** (9.7 mg, 0.024 mmol) in THF (0.2 mL), was added HOBt (7.3 mg, 0.054 mmol) and EDCI (10.4 mg, 0.054 mmol) for 10 h. The mixture was filtered with Celite and washed twice with THF. The combined organic phase was concentrated under vacuum and the crude residue was dissolved in MeOH (0.5 mL), Dowex (5 mg) was added. The mixture was

stirred for 6 h and was filtered and purified by FC (silica gel, DCM/MeOH 20:1) to give Saliniketal A as a white amorphous solid (8.4 mg, 90%). All spectral details match those reported by Fenical.

$[\alpha]^{22}_{D}$ = -7.2 (*c* = 0.10 in CD_3OD) ^{1}H NMR (400 MHz, Methanol-d_4) δ 6.59 (dd, *J* = 15.2, 11.1 Hz, 1H), 6.17 (dd, *J* = 11.2, 1.8 Hz, 1H), 5.78 (dd, *J* = 14.9, 8.3 Hz, 1H), 4.23 (dd, *J* = 6.3, 3.3 Hz, 1H), 3.96 (d, *J* = 11.2, 1.2 Hz, 1H); 3.72 (dd, *J* = 9.2, 1.8 Hz, 1H); 3.52 (dd, *J* = 8.6, 4.0 Hz, 1H), 2.36 (q, *J* = 8.0 Hz, 1H), 2.05 (m, 2H), 2.02 (dqd, *J* = 17.3, 6.9, 3.6 Hz, 1H), 1.90 (m, 3H), 1.40 (s, 3H), 1.31 (d, *J* = 17.7 Hz, 3H), 1.02 (d, *J* = 7.0 Hz, 3H), 0.96 (d, *J* = 6.8 Hz, 3H), 0.88 (d, *J* = 6.8 Hz, 3H), 0.74 (dd, *J* = 6.9, 1.4 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 175.1, 142.0, 134.0, 131.4, 128.3, 106.6, 81.6, 78.1, 75.7, 74.9, 42.3, 37.1, 35.8, 35.2, 35.1, 24.9, 24.3, 21.0, 17.1, 12.8, 11.1, 10.3; MS calcd. for $C_{22}H_{38}NO_5$, 396.3; found: 396.3 $[M + H]^+$.



Saliniketal A (5.2)

Table 20. Comparison of ^{1}H NMR data of natural and synthetic Saliniketal A

No.	Natural	Synthetic
1		
2		
3	6.17, br d (11.1, 1.2)	6.17; d, *J* = 11.2, 1.6 Hz
4	6.60, dd (15.3, 11.1)	6.60; dd, *J* = 15.3, 11.1Hz
5	5.78, dd (15.3, 8.4)	5.78; dd, *J* = 14.9, 8.3 Hz
6	2.35, m (9.3, 8.4, 6.8)	2.36; q, *J* = 8.0 Hz
7	3.71, dd (9.3, 1.8)	3.72; dd, *J* = 9.2, 1.8 Hz
8	1.88, m (7.4, 4.9, 1.8)	1.87; m
9	3.52, dd (8.3, 4.9)	3.52; dd, *J* = 8.6, 4.0 Hz
10	1.84, br dq (8.3, 7.2, 1.4)	1.83; m
11	3.97, br d (10.8, 1.4)	3.96; d, *J* = 11.2, 1.2 Hz
12	2.00, dqd (10.8, 7.3, 3.4)	2.02; dqd, *J* = 12.3, 6.9, 3.6 Hz
13	4.23, br dd (6.3, 3.4)	4.23; dd, *J* = 6.3, 3.3 Hz
14a	1.94, m	1.93; m
14b	1.90, m	1.90; m
15	2.05, m	2.07; m
15b	1.80, m	1.82; m
16		
17	1.39, s	1.40; s
18	1.94, d (1.2)	1.94; d, *J* = 1.2 Hz
19	0.96, d (6.8)	0.96; d, *J* = 6.8 Hz
20	1.02, d (7.3)	1.02; d, *J* = 7.0 Hz
21	0.89, d (7.2)	0.88; d, *J* = 6.8 Hz
22	0.76, d (7.3)	0.74; d, *J* = 6.8 Hz

Table 21. Comparison of ^{13}C NMR data of natural and synthetic Saliniketal A

No.	Natural	Synthetic
1	175.1	175.1
2	131.4	131.4
3	134.1	134.0
4	128.3	128.3
5	142.0	142.0
6	42.3	42.3
7	75.8	75.7
8	35.7	35.8
9	78.2	78.1
10	37.1	37.1
11	74.9	74.9
12	35.2	35.2
13	81.6	81.6
14a	24.9	24.9
15	35.1	35.1
16	106.4	106.6
17	24.2	24.3
18	20.9	21.0
19	17.1	17.1
20	11.1	11.1
21	10.2	10.3
22	12.8	12.8

(*E*)-Ethyl 2-methyl-3-((trimethylsilyl)oxy)but-2-enoate (6.144)

To a solution of ethyl 2-methyl-3-oxobutanoate **6.143** (1.44g, 10.0 mmol) in hexanes (30 mL) was added NEt_3 (2.09 mL, 15.0 mmol) followed by TMSCl (1.26 mL, 15.0mmol). After stirring for 24 hrs at ambient temperature, the white mixture was filtered by Celite® and washed by hexanes three times. The combined organic phase was concentrated under vacuum. The crude residue **6.144** (2.14g, 99%) was used for next step without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.15 (q, *J* = 7.2 Hz, 2H), 2.26 (q, *J* = 1.2 Hz, 3H), 1.76 (q, *J* = 1.2 Hz, 3H), 1.28 (t, *J* = 7.2 Hz, 3H), 0.24 (s, 9H); IR (film, cm^{-1}): 3296, 2937, 1778, 1693, 1386, 1211, 972; MS calcd. for $C_{10}H_{20}O_3Si$, 216.12; found: $[M + H]^+$.

2, 6-dibromocyclohexa-2, 5-diene-1, 4-dione (6.102)

To a solution of 2, 4, 6-tribromophenol (3.98g, 12.0 mmol) in acetic acid (50 mL) was added the mixture of $HClO_4$ (155 mL) in acetic acid (50 mL) followed by PbO_2 (5.54g, 24.0 mmol). After stirring at ambient temperature for 10 minutes, the dark red mixture was filtered by Celite® and washed by ethyl ether three times. The combined red solution was concentrated under vacuum to remove most of the acid. Then the solution was dilute with EtOAc (100 mL) and neutralized by sat $NaHCO_3$ (100 mL). The separated aqueous phase was extracted with EtOAc (40 mL) for three times. The combined organic phase was dried over $MgSO_4$ and concentrated. The residue was purified by FC (silica gel; Hexanes/EtOAc 12:1) to give pure compound **6.102** as gold solid (2.56g, 81%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.33 (s, 2H); MS calcd. for $C_6H_2Br_2O_2$, 263.84; found: $[M + H]^+$.

2-bromo-6, 8-dihydroxy-7-methylnaphthalene-1,4-dione (6.147)

To a solution of Diisopropylamine (1.54 mL, 10.89 mmol) in THF (30 mL) was added *n*-BuLi (2.5M in hexanes, 4.75 ml, 11.88 mmol) at -78°C, and stirred for 10 minutes. The resulting solution was warmed to 0 °C and stirring for additional 15 minutes, and cooled back to -78 °C. The compound **6.144** (2.14 g, 5.95 mmol) in THF (10 ml) was added dropwise over 10 minutes. After stirring for 15 minutes at -78 °C, the TMSCl (1.88 ml) was added in one portion and stirred for an additional 15 min. The resulting yellow mixture was warm to room temperature over 1 h. After filtered by Celite® and washed by hexanes three times, the combined organic phase was concentrated under vacuum. The crude residue (**6.145,** 2.45g, 86%) was used to next step without further purification.

To a solution of **6.102** (2.24 g, 8.5 mol) in benzene (15 mL) was added compound **6.145** (2.45 g, 8.5 mol) in benzene (10 mL) dropwise over 10 min under Ar. The resulting green solution was stirred for 4 h at ambient temperature and silica gel (5 g) was added. Then the mixture was stirred for additional 10 h at room temperature. After filtered by cotton, the solution was concentrated under vacuum. The residue was purified by FC (silica gel; Hexanes/EtOAc 4:1) to give pure compound **6.147** (1.73 g, 72%).

^{1}H NMR (400 MHz, CDCl3) δ: ;

^{13}C NMR (75 MHz, CDCl3) δ: ;

IR (film, cm^{-1}): 3296, 2937, 1778, 1693, 1386, 1211, 972;

MS calcd. for; found: [M + H] +.

2-Bromo-6, 8-*bis*(methoxymethoxy)-7-methylnaphthalene-1, 4-dione (6.153)

To a solution of compound **6.147** (1.73 g, 6.1 mmol) in dry CH_2Cl_2 (100 mL), was added MOMCl (1.39 mL, 18.3 mmol) and Diisopropyietheramine (4.25 mL, 24.4 mmol) under Ar

atmosphere. The resulting dark green solution was allowed to stir for 24h at ambient temperature. Sat. $NaHCO_3$ (100 mL) was added and the aqueous phase was extracted with EtOAc (50 mL) for three times. The combined organic phase was dried over $MgSO_4$ and concentrated. The residue was purified by FC (silica gel; Hexanes/EtOAc 6:1) to give pure compound **6.153** (1.73 g, 76%). Rf: 0.50 (Hexanes: EtOAc = 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (s, 1H), 7.41 (s, 1H), 5.34 (s, 2H), 5.09 (s, 2H), 3.63 (s, 3H), 3.49 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 182.2, 176.0, 160.6, 158.7, 142.4, 138.7, 132.7, 129.8, 117.2, 108.3, 102.0, 94.5, 58.1, 56.9, 10.5; IR (film, cm^{-1}): 3296, 2937,1778, 1693, 1386, 1211, 972; MS calcd. for $C_{15}H_{16}BrO_6$, 371.0 ; found: 371.1 $[M + H]^+$.

7-bromo-5, 8-dimethoxy-1, 3-*bis*(methoxymethoxy)-2-methylnaphthalene (6.148)

To a solution of compound **6.147** (370 mg, 1mmol) in ether (15 mL) was added $Na_2S_2O_4$ (1.39 g, 8 mmol) in H_2O (2 mL) at ambient temperature. After 30 min, water (10 mL) was added. The crude was extracted with ether (10 mL) three times. And the combined organic phase was dried over $MgSO_4$ and concentrated. The residue was dissolved in DMF (10 mL) and NaH (76 mg, 1 mmol) was added under Ar. After the mixture was stirred for 15 min at ambient temperature, MeI (220 µL, 4 mmol) was added. The resulting solution was allowed to stir for 12 h at ambient temperature. Water (10 mL) and EtOAc (10 mL) were added. The crude was extracted with EtOAc (10 mL) three times. The combined organic phase was dried over $MgSO_4$ and concentrated. The residue was purified by FC (silica gel; Hexanes/EtOAc 7:1) to give pure compound **6.148** as pale yellow oil (312mg, 78%).

Rf 0.55 (Hexanes: EtOAc 5:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (s, 1H), 6.86 (s, 1H), 5.35 (s, 2H), 5.06 (s, 2H), 3.94 (s, 3H), 3.81 (s, 3H), 3.63 (s, 3H), 3.54 (s, 3H), 2.43 (s, 3H); ^{13}C NMR

(125 MHz, $CDCl_3$): δ 154.4, 151.6, 150.8, 145.3, 126.7, 124.0, 119.0, 112.3, 108.2, 101.9, 100.4, 94.6, 61.8, 58.1, 56.6, 56.1, 10.7; MS calcd. for $C_{17}H_{21}BrO_6Na$, 423.1; found: 423.1 $[M + H]^+$.

5, 8-dimethoxy-1, 3-*bis*(methoxymethoxy)-2-methylnaphthalene (6.152)

To a solution of dimethyl ether **6.148** (212 mg, 0.5 mmol) was added *n*-BuLi (2.5 M in Hexanes, 220 μL) in THF (2 mL) at – 78 ^oC. After stirring for 30 min at that temperature, the solution was transferred into the solution of azidomethyl phenyl sulfide (78 μL, 0.55 mmol) and magnesium bromide (92 mg, 0.5 mmol) in THF (2 mL) at 78 ^oC. After 1 h, the mixture was warmed to – 20 ^oC and then quenched with saturated aqueous ammonium chloride (10 mL). The resulting triazene was dissolved in degassed THF (0.5 mL) and methanol (0.5 mL) and 50% aqueous potassium hydroxide solution (0.5 mL) was added slowly. After stirring for overnight, aqueous workup followed by column purification (silica gel; Hexanes/EtOAc 10:1) gave the pure **6.143** (116 mg, 72%) as a yellow oil.

2-amino-6, 8-*bis*(methoxymethoxy)-7-methylnaphthalene-1,4-dione (6.155)

To a solution of compound **6.153** (200 mg, 0.54 mmol) in CH_2Cl_2/H_2O/MeOH (6 mL/0.6 mL/0.6 mL) was added NaN_3 (38 mg, 0.59 mmol) at room temperature. The resulting mixture was allowed to stir for overnight and quenched by sat $NaHCO_3$. The aqueous phase was extracted with EtOAc three times and the combined organic phase was dried over $MgSO_4$ and concentrated. The residue **6.154** was dissolved in THF/H_2O (5 mL/0.5 mL) and PPh3 (200 mg) was added. After stirring for 1 h, aqueous workup followed by column purification (silica gel; Hexanes/EtOAc 10:1) to give the pure **6.155** (124 mg, 75%) as a yellow solid.

Rf: 0.25 (Hexanes: EtOAc = 4:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (s, 1H), 5.92 (s, 1H), 5.37 (s, 2H), 5.30 (br, 2H), 5.10 (s, 2H), 3.66 (s, 3H), 3.52 (s, 3H), 2.30 (s, 3H); MS calcd. for $C_{15}H_{18}NO_6$, 308.1; found: 308.2 $[M + H]^+$.

(*E*)-Methyl 5-(benzyloxy)-2-methyl-3-((trimethylsilyl)oxy)pent-2-enoate (6.156)

To a solution of Diisopropylamine (1.54 mL, 10.89 mmol) in THF (30 mL) was added *n*-BuLi (2.5M in hexanes, 4.75 ml, 11.88 mmol) at -78°C, and stirred for 10 minutes. The resulting solution was warmed to 0 °C and stirring for additional 15 minutes, and cooled back to -78 °C. The compound **6.143** (1.44 g, 10 mmol) in THF (50 mL) was added and allowed to stirred for 30 min. Then benzyl chloromethyl ether (1.61 mL, 10.5 mmol) was added. After warming the mixture to ambient temperature over 1 h, it was quenched by saturated NH_4Cl solution (50 mL). After combing the organic phase and removing the solvent by vacuum, it was dissolved in hexanes (45 mL). Then it was added Et_3N (2.5 mL) and TMSCl (2.1 mL). After stirred for overnight at ambient temperature, it was filtered and concentrated. Compound **6.156**: Rf: 0.35 (Hexanes : EtOAc, 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (m, 5H), 4.51 (s, 2H), 4.16 (m, 2H), 3.64 (dd, *J* = 7.7, 6.9 Hz, 2H), 2.99 (t, *J* = 7.4, 1.1 Hz, 2H), 1.76 (s, 3H), 1.27 (m, 3H), 0.22 (s, 9H); MS calcd. for $C_{18}H_{29}O_4Si$, 337.2; found: 337.3 $[M + H]^+$.

5, 7-*bis*(benzyloxy)-8-iodo-6-methylnaphthalene-1,4-dione (6.184)

To a solution of naphthaquinone **6.181** (192 mg, 0.5 mmol) in dioxane (4 mL) was added Me_4NICl_2 (163 mg, 0.6 mmol). The mixture was allowed to stir for 4 h at 80 ^oC. Then, it was removed the solvent by vacuum and purified by column (silica gel; Hexanes/EtOAc 10:1) to give pure **6.184** as a red solid.

Rf: 0.30 (Hexanes: EtOAc 4:1), ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.47 – 7.32 (m, 11H), 5.17 (s, 2H), 4.90 (s, 2H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.2, 175.3, 160.3, 155.5, 149.2, 135.7, 135.2, 130.4, 129.7, 129.1, 128.9, 128.7, 128.6, 128.4, 127.3, 123.1, 109.5, 77.0, 76.7, 70.8, 10.6; MS calcd. for $C_{25}H_{20}IO_4$, 511.0; found: 511.1 $[M + H]^+$.

5,7-*bis*(benzyloxy)-8-bromo-6-methyl-1,4-dihydro-1,4-epoxynaphthalene (6.162)

To a solution of *di*-isopropylamine (1.2 mL, 8.6 mmol) in THF (15 mL) was added *n*-BuLi (2.5M in hexanes, 3.13 mL, 7.8 mmol) at -78°C, and stirred for 10 minutes. The resulting solution was warmed to 0 °C and stirring for additional 15 minutes, and cooled back to -78 °C. The compound **6.159** (3.0 g, 6.5 mmol) and furan (5 mL) in THF (30 mL) was added over 1 h. The resulting mixture was allowed to stir for overnight. The reaction was quenched by the addition of pH 7 phosphate buffer solution (50 mL). The aqueous layer was extracted with ether (3 × 30 mL) and the combined organic phase was washed with brine, dried over $MgSO_4$ and concentrated under vacuum. The crude was purified by FC (silica gel, Hexanes/EtOAc 8:1) to give compound **6.162** (2.6 g, 89%) as yellow oil.

Rf: 0.7 (Hexanes: EtOAc 4:1), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (m, 2H), 7.39 (m, 8H), 7.03 (dd, *J* = 5.6, 1.9 Hz, 1H), 6.73 (dd, *J* = 5.5, 1.8 Hz, 1H), 5.93 (dd, *J* = 1.9, 1.0 Hz, 1H), 5.78 (dd, *J* = 1.9, 1.0 Hz, 1H), 5.06 (t, *J* = 21.0, 12.2 Hz, 2H), 4.88 (t, *J* = 21.0, 12.2 Hz, 2H), 2.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.8, 150.6, 149.6, 143.2, 142.3, 137.1, 133.8, 129.0, 128.7, 128.6, 128.5, 128.5, 128.4, 127.8, 123.2, 105.0, 83.4, 82.8, 75.2, 74.7, 14.4; MS calcd. for $C_{25}H_{22}BrO_3$, 449.1; found: 449.1 $[M + H]^+$.

5, 7-*bis*(benzyloxy)-8-bromo-6-methylnaphthalen-1-ol (6.163)

To a solution of **6.162** (610 mg, 1.36 mmol) and 2, 6-*di*-*tert*-butylpridine (1.89 mL, 8.54 mmol) in CH_2Cl_2 (14 mL) was added TMSOTf (1.29 mL, 7.12 mmol) at 0 ^oC and stirred for 5min before moved to rt. The resulting mixture was stirred at rt for 3h and then TBAF (1.0 M in THF, 2.8 mL) was added at 0 ^oC. After stirring for an additional 15 min, it was quenched with sat.$NaHCO_3$, extracted with EtOAc, dried with $MgSO_4$ and concentrated in vacuum to get the crude product (orange oil). The crude product was directly used in next step.

Rf: 0.5 (Hexanes: EtOAc 4:1),

5, 7-*bis*(benzyloxy)-8-bromo-6-methylnaphthalene-1, 4-dione (6.165)

To a solution of phenol **6.163** (76 mg, 0.17 mmol) in DMF (2.0 mL) was added salcomine catalyst (**6.164**, 7.6 mg, 10% wt). The resulting mixture was stirred under O_2 at 50 ^oC overnight. The reaction was quenched with quenched with water, extracted with EtOAc, dried with $MgSO_4$ and concentrated in vacuum to get the crude product. The crude was purified by prepared TLC (50% EtOAc/Hexane) to get the pure product **6.165** as a yellow-red solid (58 mg, 73%).

R_f=0.3 (50% EtOAc in Hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 10.5Hz, 1H), 7.50 (m, 2H), 7.39 (m, 8H), 6.30 (d, *J* = 10.5Hz, 1H), 4.98 (s, 2H), 4.87 (s, 2H), 2.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.0, 178.3, 158.3, 155.8, 139.4, 135.7, 135.6, 135.2, 129.2, 129.0, 128.9, 128.8, 128.7, 128.4, 128.2, 127.0, 126.1, 118.7, 76.7, 75.0, 11.6; MS calcd. for $C_{25}H_{20}BrO_4$, 463.1; found: 463.1 $[M + H]^+$.

1,3-*bis*(benzyloxy)-4-bromo-5, 8-dimethoxy-2-methylnaphthalene (6.166)

To a solution of **6.165** (58 mg, 0.126 mmol) in ether (1.5 mL) and water (0.5 mL) was added $Na_2S_2O_4$ (175 mg, 1.0 mmol). The resulting mixture was stirred at ambient temperature for 15

min and then quenched with water, extracted with ether, dried with $MgSO_4$ and concentrated in vacuum. The crude product was dissolved in DMF (1 mL) was added NaH (9.5 mg, 0.38 mmol) and MeI (50 μL). The resulting mixture was stirred at ambient temperature overnight. The reaction was quenched with quenched with water, extracted with EtOAc, dried with $MgSO_4$ and concentrated in vacuo to get the crude product. The crude was purified by prepared TLC (40% EtOAc/Hexane) to get the product **6.166** (50 mg, 80 %).

Rf = 0.65 (20 % EtOAc in Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 9.3 Hz, 1H), 7.46 (m, 10H), 7.26 (d, *J* = 9.2 Hz, 1H), 5.01 (s, 2H), 4.93 (s, 2H), 3.98 (s, 3H), 3.93 (s, 2H), 2.35 (s, 3H); MS calcd. for $C_{27}H_{25}BrO_4Na$, 515.1; found: 515.2 $[M + Na]^+$.

5, 8-dimethoxy-1, 3-*bis*(methoxymethoxy)-2-methylnaphthalene (6.152)

To a solution of **6.166** (20 mg, 0.041 mmol) in EtOAc (5 mL) was added Pd/C (10 mg). The reaction mixture was bubbled into hydrogen for 2h at ambient temperature. The mixture was filtered through a pale of celite® to remove the catalyst. After concentrated in vacuum, the crude residue was dissolved in the CH_2Cl_2 (2 mL) and was added *i*-Pr_2NEt (29 μL, 0.16 mmol) and MOMCl (20 μL). After stirring for 4 h, the reaction was quenched with water (20 mL); the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers was washed with brine, dried with $MgSO_4$ and concentrated in vacuum. The crude was purified by flash column (0 to 20% EtOAc/Hexane) to get the pure compound **6.152** (9.8 mg, 74%) as yellow oil.

Rf 0.60 (Hexanes: EtOac 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.8 Hz, 1H), 7.38 (s, 1H), 7.13 (d, *J* = 9.3 Hz, 1H), 5.34 (s, 2H), 5.11 (s, 2H), 3.96 (s, 3H), 3.93 (s, 3H), 3.66 (s, 3H), 3.52 (s, 3H), 2.33 (s, 3H); MS calcd. for $C_{17}H_{22}O_6Na$, 345.1; found: 345.1 $[M + Na]^+$.

Methyl 6,8-*bis*(benzyloxy)-7-methyl-1,4-dihydro-1,4-epoxynaphthalene-5-carboxylate (6.173)

To a solution of **6.162** (910 mg, 2.02mmol) in THF (20 mL) was added *n*-BuLi (1.65 mL, 2.63 mmol, 1.6M in THF) dropwise at -78 ^{o}C for 10min. The solution was stirred for 10 min before the addition of $ClCO_2Me$ (313 μL, 4.05 mmol). The resulting orange reaction solution was stirred at -78 ^{o}C for at least 3h and then slowly warmed to rt overnight. The reaction was quenched with water (20 mL), the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers was washed with brine, dried with $MgSO_4$ and concentrated in vacuum. The crude was purified by flash column (0 to 20% EtOAc/Hexane) to get the product **6.173** (828 mg, 95%); R_f=0.3 (25% EtOAc in Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (m, 10H), 7.05 (dd, *J* = 5.5, 1.9 Hz, 1H), 6.75 (dd, *J* = 5.5, 1.7 Hz, 1H), 6.10 (dd, *J* = 1.9, 1.0 Hz, 1H), 5.96 (dd, *J* = 1.8, 1.0 Hz, 1H), 5.21 (d, *J* = 11.7 Hz, 1H), 5.10 (d, *J* = 11.8 Hz, 1H), 4.96 (d, *J* = 10.5 Hz, 1H), 4.79 (d, *J* = 10.6 Hz, 1H), 3.87 (s, 3H), 2.15 (s, 3H); MS calcd. for $C_{27}H_{25}O5$, 429.2; found: 429.3 $[M + H]^+$.

Methyl 8-hydroxy-2, 4-*bis*(methoxymethoxy)-3-methyl-1-naphthoate (6.176)

& methyl 2,4,8-tris(methoxymethoxy)-3-methyl-1-naphthoate (6.175)

To a solution of **6.173** (610 mg, 1.42 mmol) and 2, 6-^{t}*di*-butylpridine (1.89 mL, 8.54 mmol) in CH_2Cl_2 (14 mL) was added TMSOTf (1.29 mL, 7.12 mmol) at 0 ^{o}C and stirred for 5min before moved to ambient temperature. The resulting mixture was stirred at ambient temperature for 3h and then quenched with sat.$NaHCO_3$ (20 mL), extracted with EtOAc (3 × 20 mL), dried with $MgSO_4$ and concentrated in vacuum to get the crude product (orange oil), which was directly used in next step. The crude residue was dissolved in EtOAc (14 mL) was added Pd/C (50 mg).

The reaction mixture was stirred under H_2 for 2h at ambient temperature. The mixture was filtered through a pale of celite® to remove the catalyst. After concentrated in vacuum, the crude product of last step was dissolved in CH_2Cl_2 (14 mL). The *i*-Pr_2NEt (735 μL) and MOMCl (315 μL) were added to the solution at 0 °C. The resulting solution was stirred at ambient temperature overnight. The reaction was quenched with quenched with water (10 mL), extracted with EtOAc (3 × 20 mL), dried with $MgSO_4$ and concentrated in vacuum to get the crude product. The crude was purified by flash column (0 to 50% EtOAc/Hexane) to get the compounds **6.176** (172 mg, 36% for 3 steps) and **6.175** (97 mg, 18% for 3 steps).

Compound **6.176**: R_f=0.2 (50% EtOAc in Hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 7.64 (dd, *J* = 8.5, 1.0 Hz, 1H), 7.25 (dd, *J* = 8.5, 7.5 Hz, 1H), 6.84 – 6.77 (m, 1H), 6.00 (s, 1H), 5.11 (d, *J* = 10.0 Hz, 4H), 3.95 (s, 3H), 3.64 (d, *J* = 17.4 Hz, 7H), 2.44 (s, 3H), 1.26 (t, *J* = 7.1 Hz, 1H); MS calcd. for $C_{17}H_{21}O_7$, 337.2; found: 337.3 $[M + H]^+$.

Compound **6.175**: R_f=0.30 (50% EtOAc in Hexane); MS calcd. for $C_{19}H_{25}O_8$, 381.2; found: 381.2 $[M + H]^+$.

Methyl 2, 4-*bis*(methoxymethoxy)-3-methyl-5, 8-dioxo-5, 8-dihydronaphthalene-1-carboxylate (6.177)

To a solution of **6.175** (76 mg, 0.226mmol) in DMF (2.5 mL) was added salcomine catalyst (**6.164**, 7.6 mg, 0.1 eq). The resulting mixture was stirred under O_2 at 50 °C overnight. The reaction was quenched with quenched with water, extracted with EtOAc (10 mL), dried with $MgSO_4$ and concentrated in vacuum to get the crude product. The crude was purified by prepared TLC (50% EtOAc/Hexane) to get the pure compound **6.177** (54 mg, 68%) as yellow oil.

R_f = 0.3 (50% EtOAc in Hexane); ^{1}H NMR (400 MHz, $CDCl_3$): 7.82 (d, *J* = 10.5 Hz, 1H), 6.40 (d, *J* = 10.4 Hz, 1H), 5.06 (s, 2H), 5.05 (s, 2H), 3.98 (s, 3H), 3.64 (s, 3H), 3.58 (s, 3H), 2.35 (s, 3H); MS calcd. for $C_{17}H_{18}O_8Na$, 373.1; found: 373.2 $[M + Na]^+$.

Methyl 5, 8-dimethoxy-2, 4-*bis*(methoxymethoxy)-3-methyl-1-naphthoate (6.168)

To a solution of **6.167** (20 mg, 0.057 mmol) in ether (1 mL) and water (0.2 mL) was added $Na_2S_2O_4$ (99 mg, 0.46 mmol). The resulting mixture was stirred at ambient temperature for 15 min and then quenched with water, extracted with ether, dried with $MgSO_4$ and concentrated in vacuum. The crude product was dissolved in DMF (1 mL) was added NaH (4.2 mg) and MeI (20 μL). The resulting mixture was stirred at ambient temperature overnight. The reaction was quenched with quenched with water, extracted with EtOAc (10 mL), dried with $MgSO_4$ and concentrated in vacuum to get the crude product. The crude was purified by prepared TLC (40% EtOAc/Hexane) to get the pure compound **6.168** (54 mg, 68%) as yellow oil.

R_f = 0.4 (40% EtOAc in Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 9.4 Hz, 1H), 7.25(d, *J* = 9.4 Hz, 1H), 5.11 (s, 2H), 5.10 (s, 2H), 3.97 (s, 3H), 3.94 (s, 3H), 3.84 (s, 3H), 3.66 (s, 3H), 3.62 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (101 MHz, $cdcl_3$) δ 169.5, 153.4, 149.3, 141.8, 125.6, 122.4, 121.1, 118.8, 118.1, 114.3, 110.0, 100.9, 100.1, 61.2, 57.9, 57.6, 56.4, 52.2, 11.1; MS calcd. for $C_{19}H_{25}O_8$, 381.2; found: 381.2 $[M + H]^+$.

(*S*, 2Z, 4E)-1H-benzo[d][1, 2, 3]triazol-1-yl 6-((4S, 5R, 6R)-6-((R)-1-((1S, 3R, 4R, 5S)-1,4-dimethyl-2, 8-dioxabicyclo[3.2.1]octan-3-yl)ethyl)-2, 2, 5-trimethyl-1, 3-dioxan-4-yl)-2-methylhepta-2, 4-dienoate (6.186)

To a solution of acid **6.93** (1.0 mg) and amine **6.155** (2.5 mg) in CH_2Cl_2 (150 μL) was added HOBt (1 mg), EDCI (1.0 mg), and triethyl amine (1 μL). And the resulting solution was stirred for 2 h at ambient temperature. After removing the solvent by vacuum, the crude residue was purified by PTLC (Hexanes: EtOAc 4:1). It provided the compound **6.186** (1.1 mg) as white solid and recovered amine **6.155** (2.0 mg).

Compound **469**: Rf: 0.25 (Hexanes: EtOAc 4:1);

(S, 2Z, 4E)-N-(1, 4-dimethoxy-6, 8-bis(methoxymethoxy)-7-methylnaphthalen-2-yl)-6-((4S, 5R, 6R)-6-((R)-1-((1S, 3R, 4R, 5S)-1,4-dimethyl-2,8-dioxabicyclo[3.2.1]octan-3-yl)ethyl)-2, 2, 5-trimethyl-1, 3-dioxan-4-yl)-2-methylhepta-2, 4-dienamide (6.187)

Method A: To a solution of **6.93** (5.4 mg, 12.4 μmol) in CH_2Cl_2 (100 μL) was added HOBt (3.34 mg, 24.7 μmol), EDCI (3.8 mg, 24.7 μmol), and triethyl amine (3.5 μL, 24.7 μmol). After stirring for 20 min at ambient temperature, the amine **6.149** (8.5 mg, 24.7 μmol) in CH_2Cl_2 (100 μL) was added. The yellow solution was stirred for 6 h under Ar atmosphere. After removing the solvent by vacuum, the crude residue was purified by PTLC (Hexanes: EtOAc 4:1). It provided the compound **6.187** (6.3 mg, 67%) as pale yellow foam.

Method B: Using the general amidation procedure Cu(I)I (0.25 mg, 10 mol%), amide **6.188** (5.8 mg, 13.3 μmol), bromide **6.148** (6.4 mg, 15.6 μmol), and K_3PO_4 (5.6 mg, 26.6 μmol), *N', N'*-dimethylethylenediamine (0.5 μL) and toluene (150 μL) were reacted at 100 ^oC for overnight. After removing the solvent by vacuum, the crude residue was purified by PTLC (Hexanes: EtOAc 4:1). It provided the compound **6.187** (5.7 mg, 57%) as pale yellow foam.

Compound **6.187**: Rf: 0.25 (Hexanes: EtOAc 3:1); MS calcd. for $C_{42}H_{62}NO_{11}$, 756.4; found: 756.4 $[M + H]^+$.

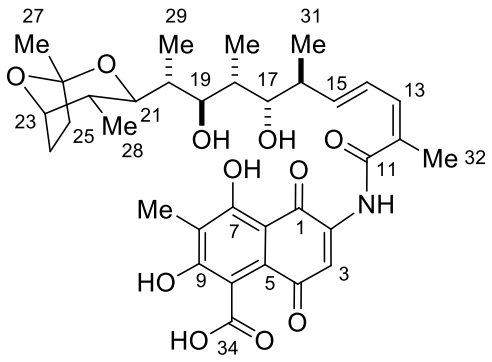
Rifsaliniketal (5.6)

To a solution of ceric ammonium nitrate (15.6 mg, 29 μmol) in 1:1 CH_3CN/H_2O (100 μL) was added to a 0 ^oC solution of **6.190** (7.9 mg, 9.7 μmol) in CH_3CN (300 μL) and H_2O (10 μL). The resulting solution was stirred at 0 ^oC for 15 min and then was poured into H_2O (1 mL). The aqueous phase was extracted with CH_2Cl_2 (3 times, 1 mL each time). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuum to give bright yellow oil. The crude residue was purified by a short column and the collected phase was removed by vacuum. The residue was dissolved in THF/MeOH/ H_2O (140 μL/40 μL/20 μL) and NaI (2.9 mg, 20 μmol), 3N HCl (20 μL) were added. The resulting mixture was stirred for 24 h at ambient temperature. After removing the solvent by vaccum, the residue was dissolve in MeOH (200 μL), and LiOH solution (1.0 M, 50 μL) was added. After stirring for overnight at 0 ^oC, the crude residue was purified by PTLC (CH_2Cl_2: MeOH 5 :1) to give rifsaliniketal as a yellow foam (2.9 mg, 47% over 3 steps).

^1H NMR (600 MHz, Methanol-d_4) δ 7.66 (s, 1H), 6.79 (dd, *J* = 15.1, 10.8 Hz, 1H), 6.46 (dd, *J* = 11.3, 1.6 Hz, 1H), 6.01 (dd, *J* = 15.1, 8.0 Hz, 1H), 4.24 (dd, *J* = 7.2, 3.3 Hz, 1H), 3.97 (dd, *J* = 10.5, 1.8 Hz, 1H), 3.77 (dd, *J* = 9.1, 1.9 Hz, 1H), 3.51 (dd, *J* = 8.4, 4.2 Hz, 1H), 2.43 (ddq, *J* = 9.2, 7.6, 6.8 Hz, 1H), 2.16 (s, 3H), 2.08 (s, 3H), 2.03 (m, 1H), 1.99 (m, 1H), 1.95 (m, 1H), 1.92 (m, 1H), 1.88 (ddt, *J* = 7.4, 4.9, 2.4 Hz, 1H), 1.84 (m, 1H), 1.81 (m, 1H), 1.39 (s, 3H), 1.01 (d, *J* = 7.0 Hz, 3H), 0.99 (d, *J* = 6.8 Hz, 3H), 0.89 (d, *J* = 6.9 Hz, 3H), 0.72 (d, *J* = 6.9 Hz, 3H);

^{13}C NMR (125 MHz, DMSO) δ 209.8, 170.0, 145.5, 138.2, 129.5, 127.5, 106.2, 81.4, 77.9, 75.5, 74.7, 42.0, 36.7, 36.0, 35.20, 34.9, 24.6, 24.0, 20.3, 16.8, 12.7, 10.9, 10.1, 8.0;

MS calcd. for $C_{34}H_{44}NO_{11}$, 642.3; found: 642.3 $[M + H]^+$.



Rifsaliniketal (5.6)

Table 22. Comparison of ^{1}H NMR Data of Natural and Synthetic Rifsaliniketal

No.	Natural	Synthetic
3	7.66 (s, 1H)	7.66 (s, 1H)
13	6.46 (d, *J* = 11.2 Hz, 1H)	6.46 (dd, *J* = 11.3, 1.6 Hz, 1H)
14	6.78 (dd, *J* = 15.2, 11.2 Hz, 1H)	6.79 (dd, *J* = 15.1, 10.8 Hz, 1H)
15	6.02 (dd, *J* = 15.2, 8.0 Hz, 1H)	6.01 (dd, *J* = 15.1, 8.0 Hz, 1H)
16	2.42 (ddq, *J* = 9.1, 8.0, 6.9 Hz, 1H)	2.43 (ddq, *J* = 9.2, 7.6, 6.8 Hz, 1H)
17	3.77 (dd, *J* = 9.1, 1.4 Hz, 1H)	3.77 (dd, *J* = 9.1, 1.9 Hz, 1H)
18	1.86-1.89 (m, 1H)	1.88 (ddt, *J* = 7.4, 4.9, 2.4 Hz, 1H)
19	3.51 (dd, *J* = 8.3, 4.3 Hz, 1H)	3.51 (dd, *J* = 8.4, 4.2 Hz, 1H)
20	1.83-1.89 (m, 1H)	1.84 (m, 1H)
21	3.95 (dd, *J* = 10.6, 1.1 Hz, 1H)	3.97 (dd, *J* = 10.5, 1.8 Hz, 1H),
22	1.97-2.01 (m, 1H)	1.95 (m, 1H)
23	4.22 (dd, *J* = 6.7, 3.4 Hz, 1H)	4.24 (dd, *J* = 7.2, 3.3 Hz, 1H)
24a	1.89-1.93 (m, 1H)	1.92 (m, 1H)
24b	1.93-1.97 (m, 1H)	1.95 (m, 1H)
25a	1.78-1.83 (m, 1H)	1.81 (m, 1H)
25b	2.01-2.05 (m, 1H)	2.03 (m, 1H)
27	1.39 (s, 3H)	1.39 (s, 3H)
28	0.73 (d, *J* = 6.9 Hz, 3H)	0.72 (d, *J* = 6.9 Hz, 3H)
29	0.89 (d, *J* = 7.0 Hz, 3H)	0.89 (d, *J* = 6.9 Hz, 3H)
30	1.01 (d, *J* = 7.2 Hz, 3H)	1.01 (d, *J* = 7.0 Hz, 3H)
31	0.99 (d, *J* = 6.9 Hz, 3H)	0.99 (d, *J* = 6.8 Hz, 3H)
32	2.08 (s, 3H)	2.08 (s, 3H)
33	2.16 (s, 3H)	2.16 (s, 3H)

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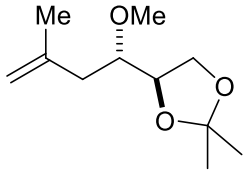
Appendix A: Characterization Spectra Relevant to Chapters 3 and 6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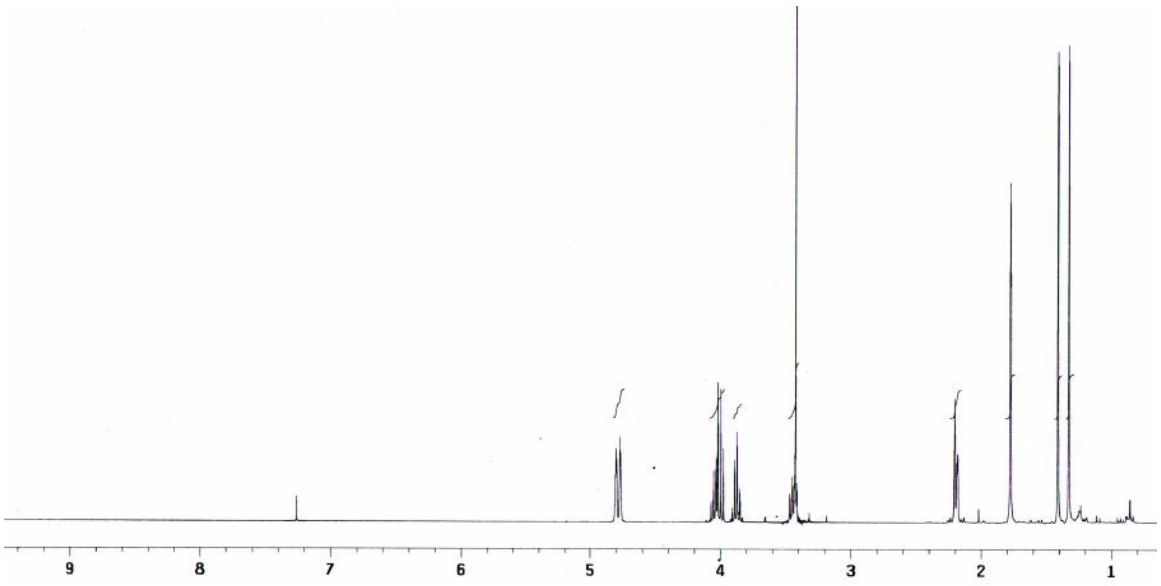
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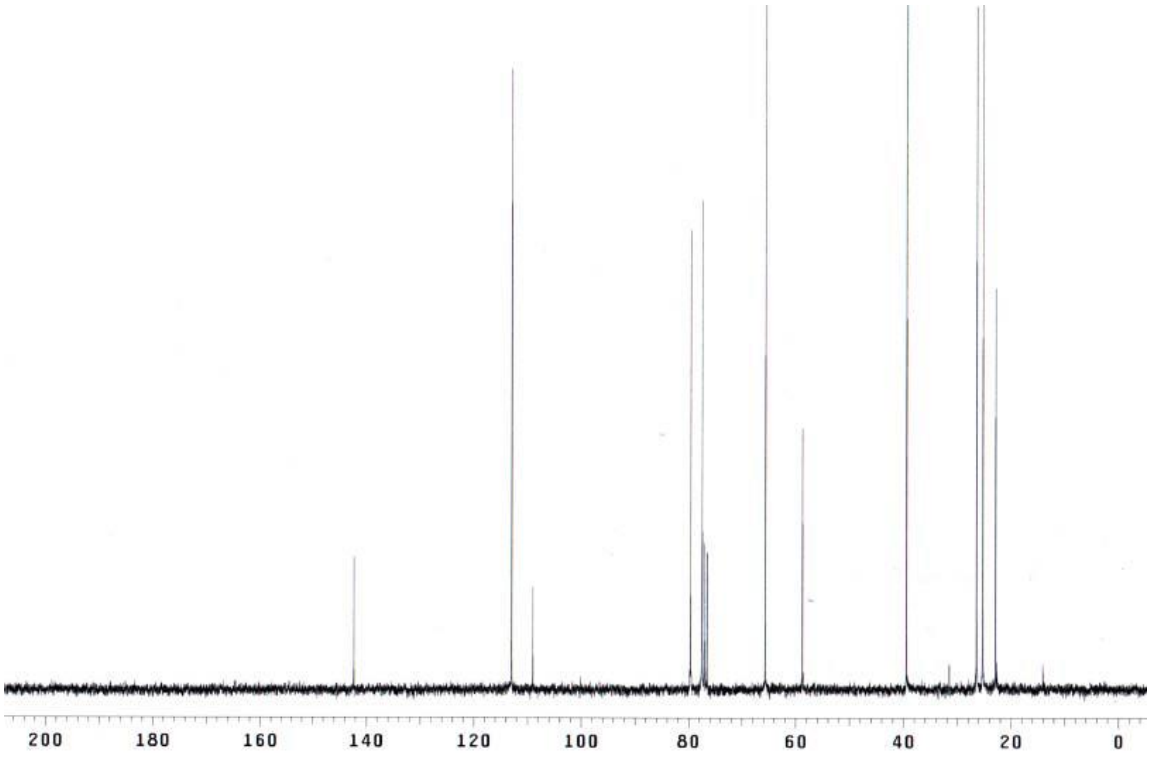
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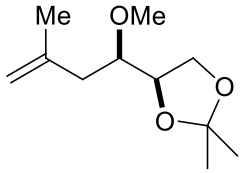
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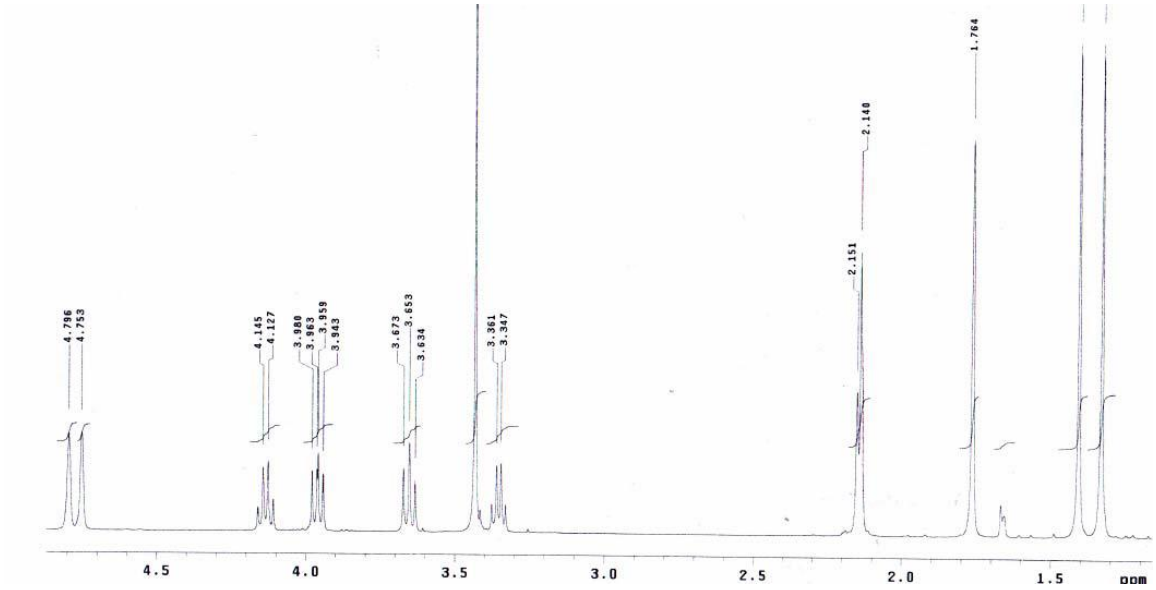
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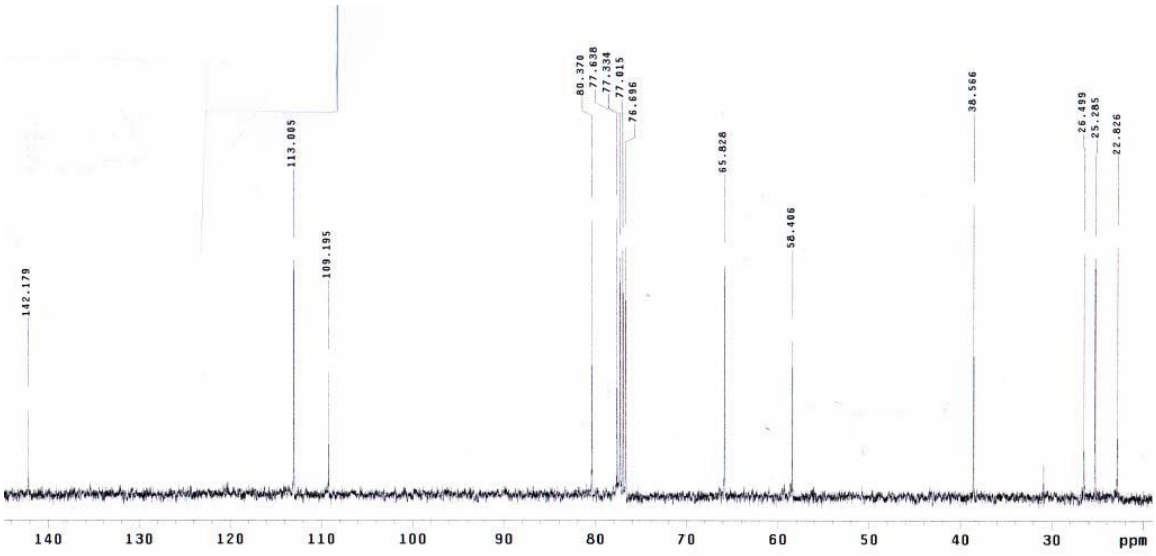
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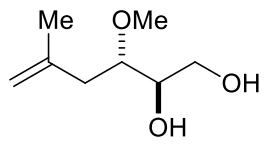
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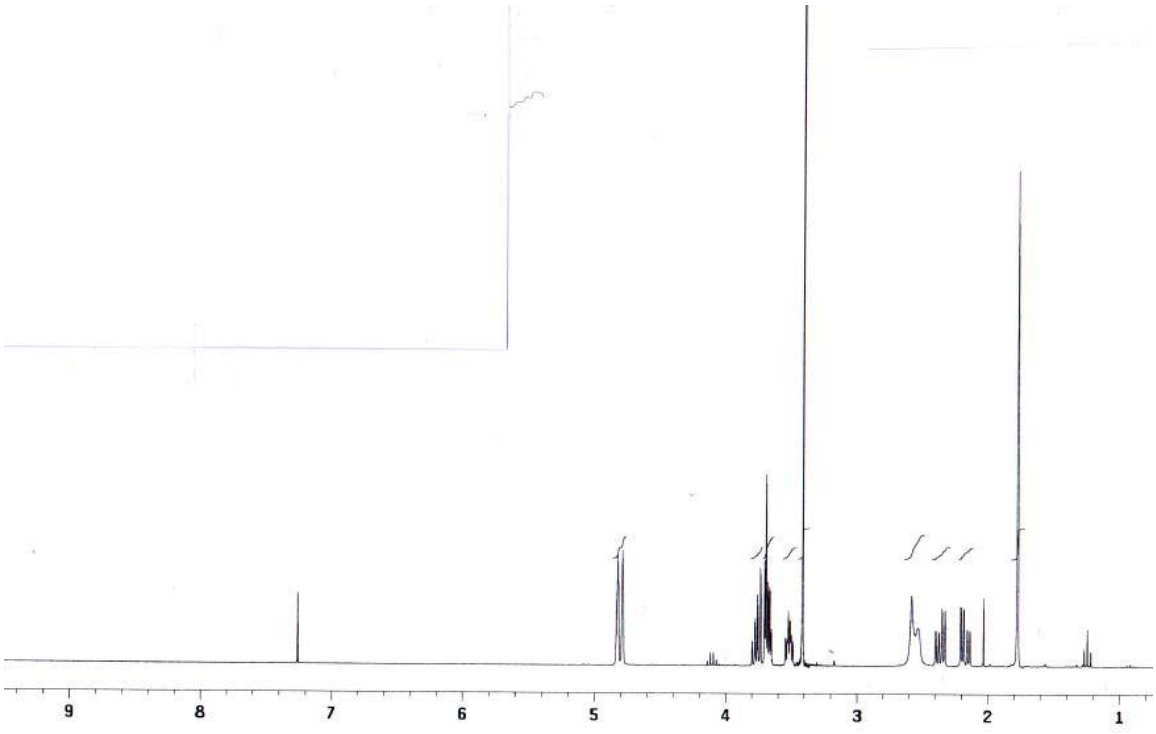
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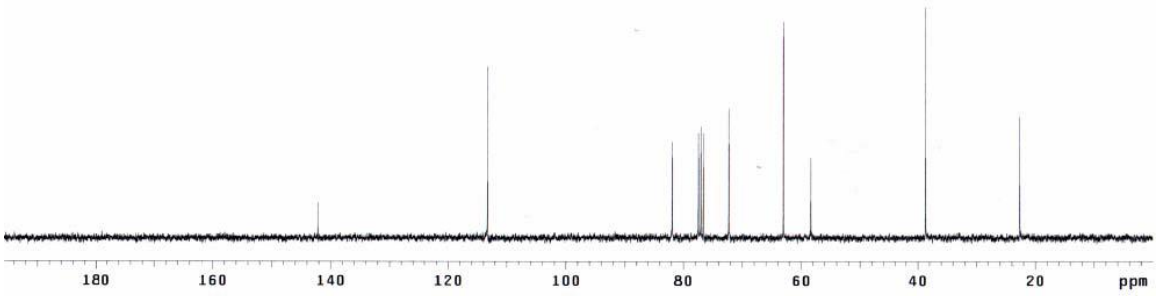
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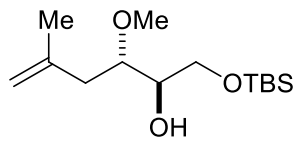
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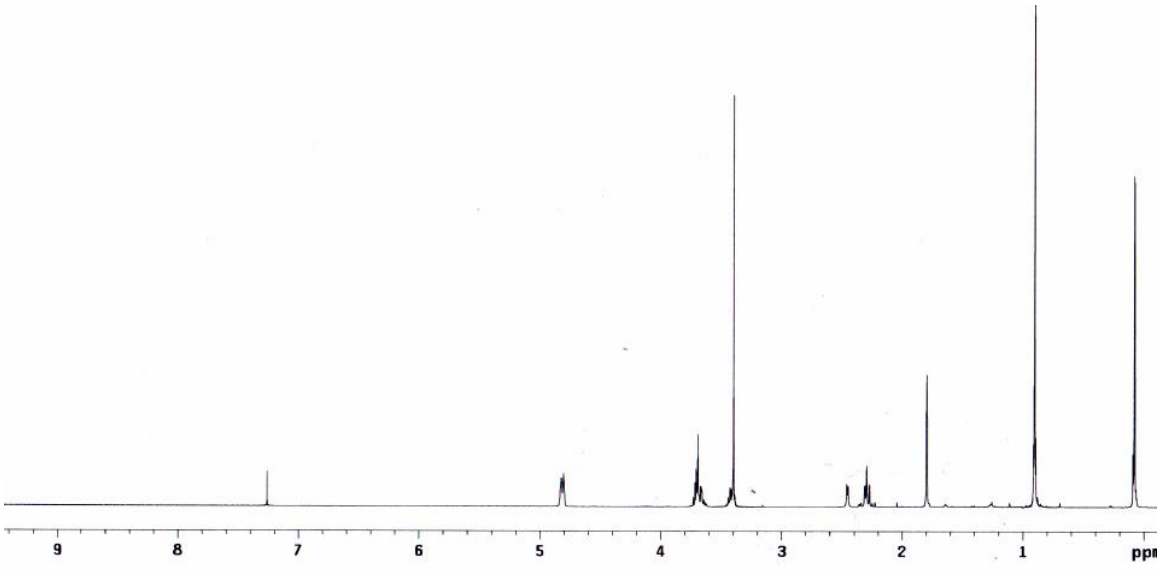
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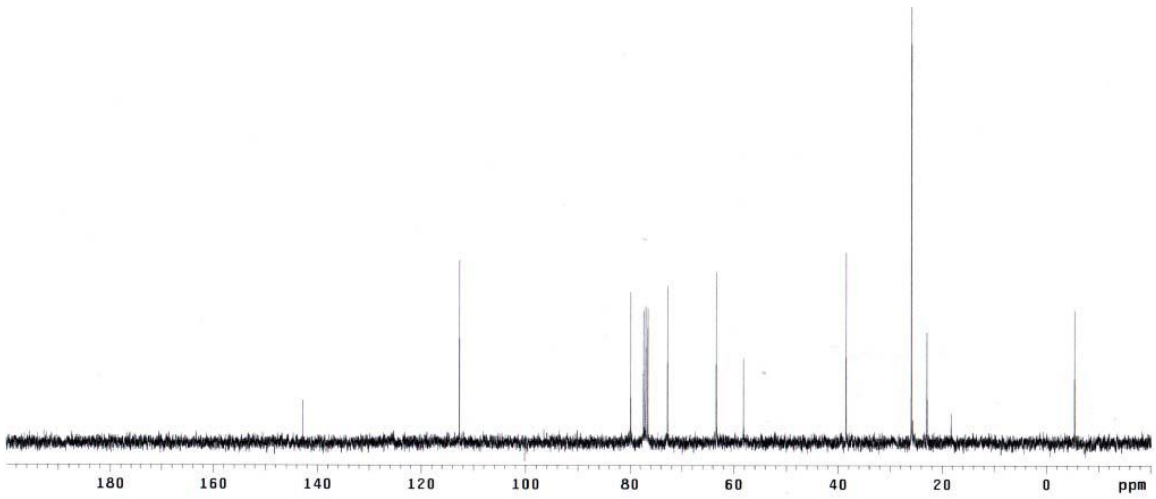
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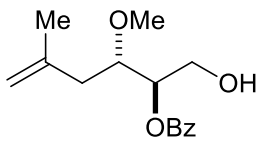
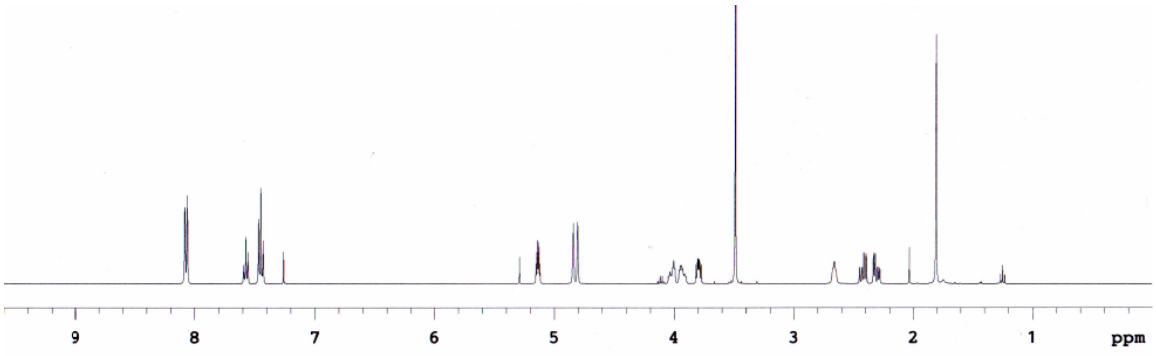
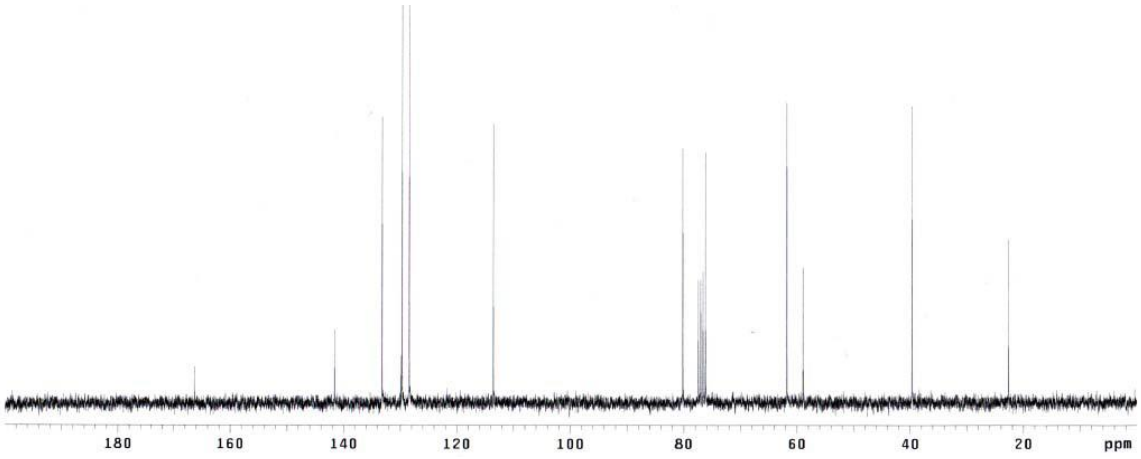
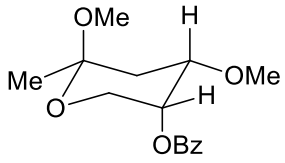
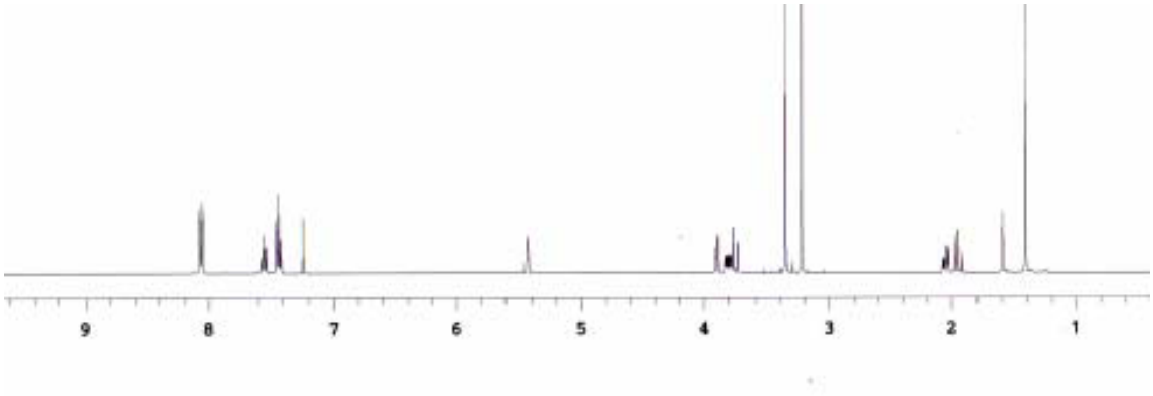

Me
OMe
OH
OBz


9
8
7
6
5
4
3
2
1
ppm


180
160
140
120
100
80
60
40
20
ppm


OMe
H
Me
OMe
O
H
OBz


9
8
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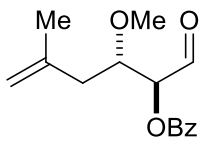
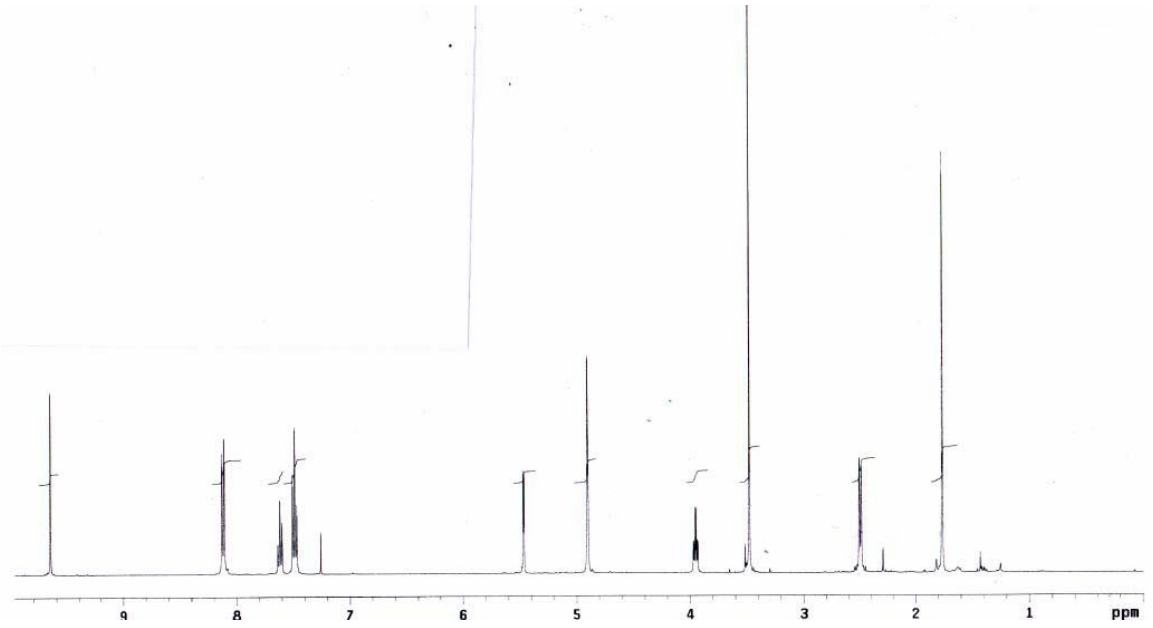
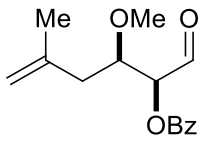
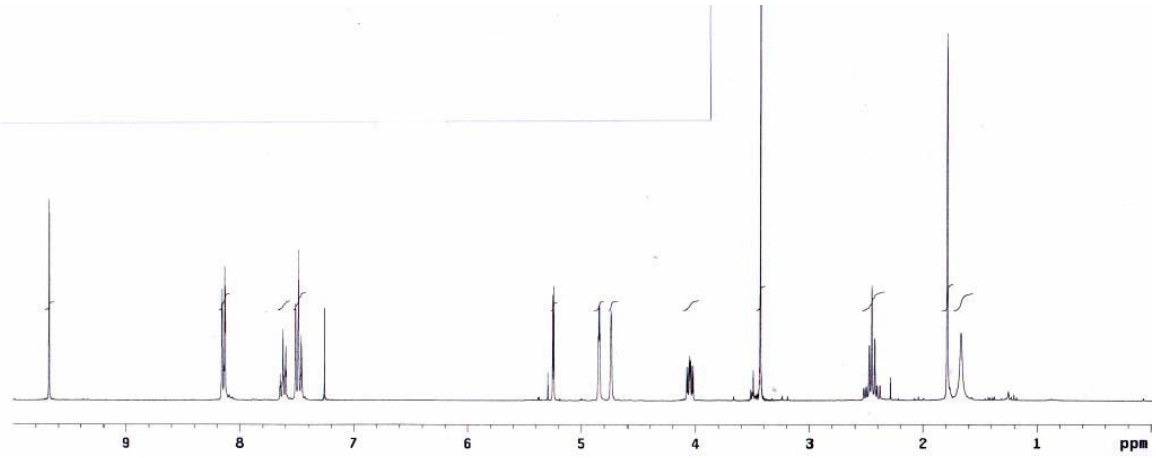
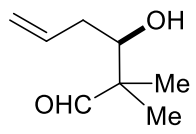
6
5
4
3
2
1

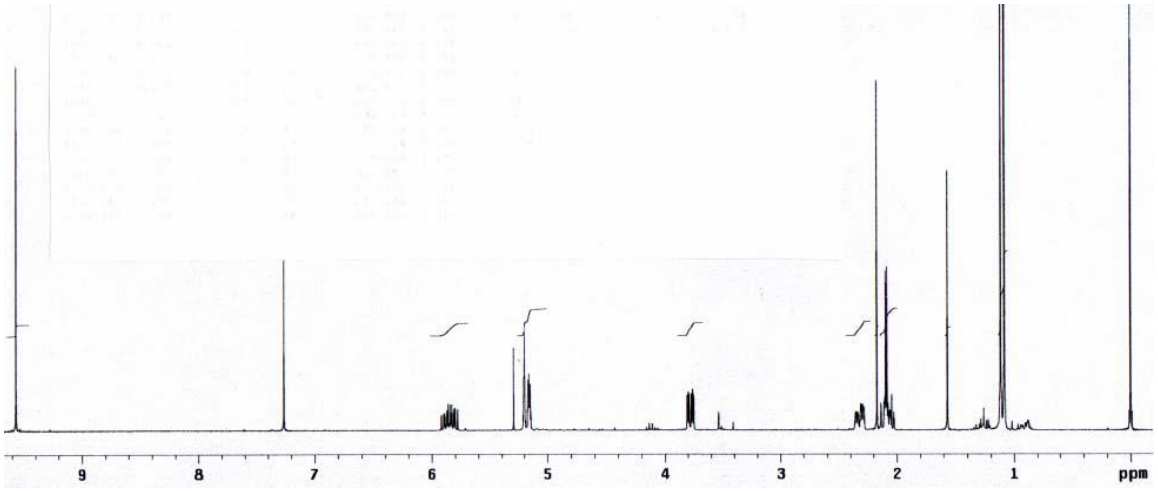

Me
OMe
O
OBz

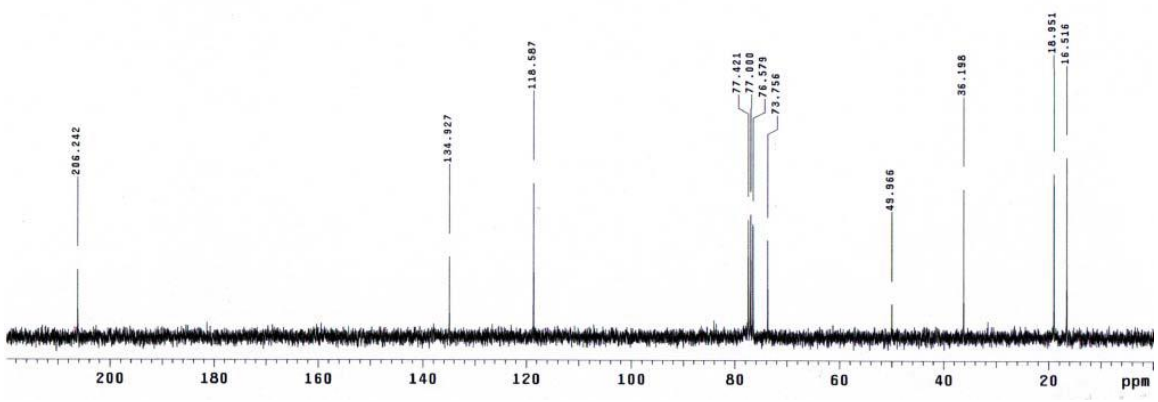

9
8
7
6
5
4
3
2
1
ppm


Me
OMe
O
OBz

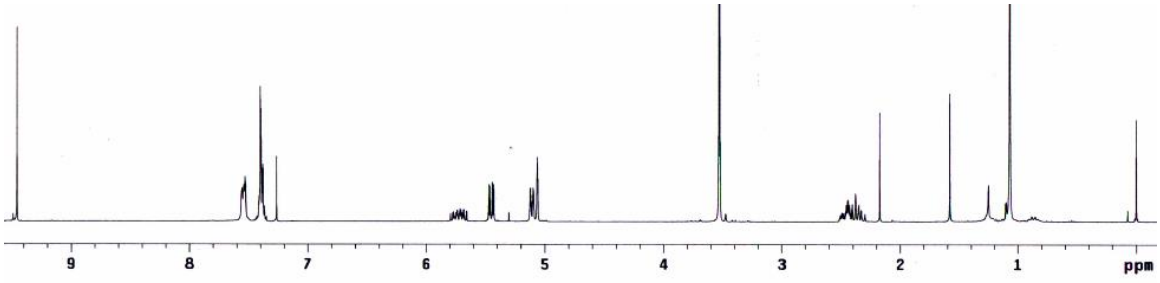

9
8
7
6
5
4
3
2
1
ppm


OH
Me
OHC
Me

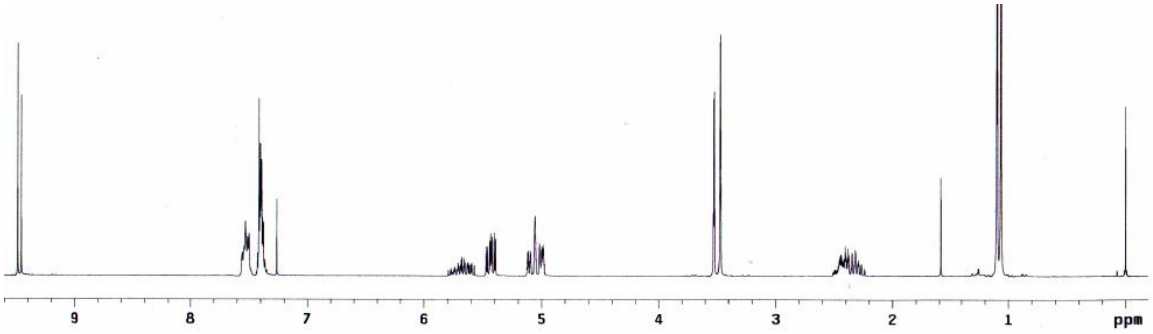

9
8
7
6
5
4
3
2
1
ppm


206.242
134.927
118.587
77.421
77.000
76.579
73.756
49.966
36.198
18.951
16.516
200
180
160
140
120
100
80
60
40
20
ppm

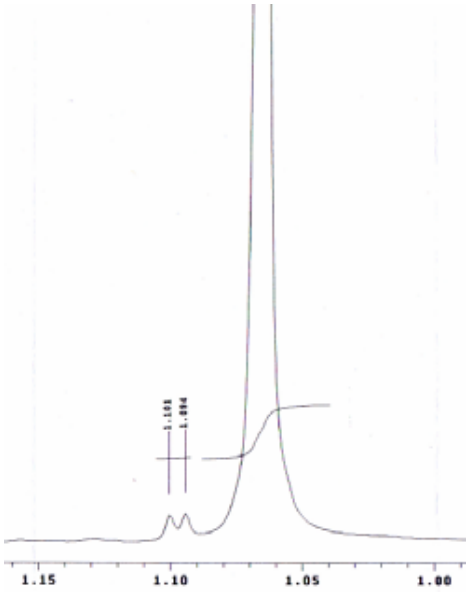
(*S*)-(−)-MTPA-ester of **216**



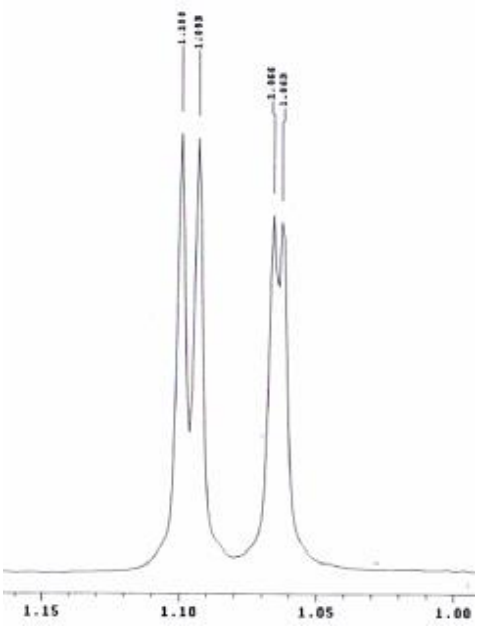
(*S*)-(−)-MTPA-ester of *rac*-**216**

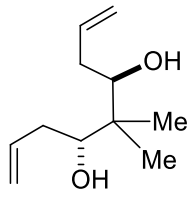


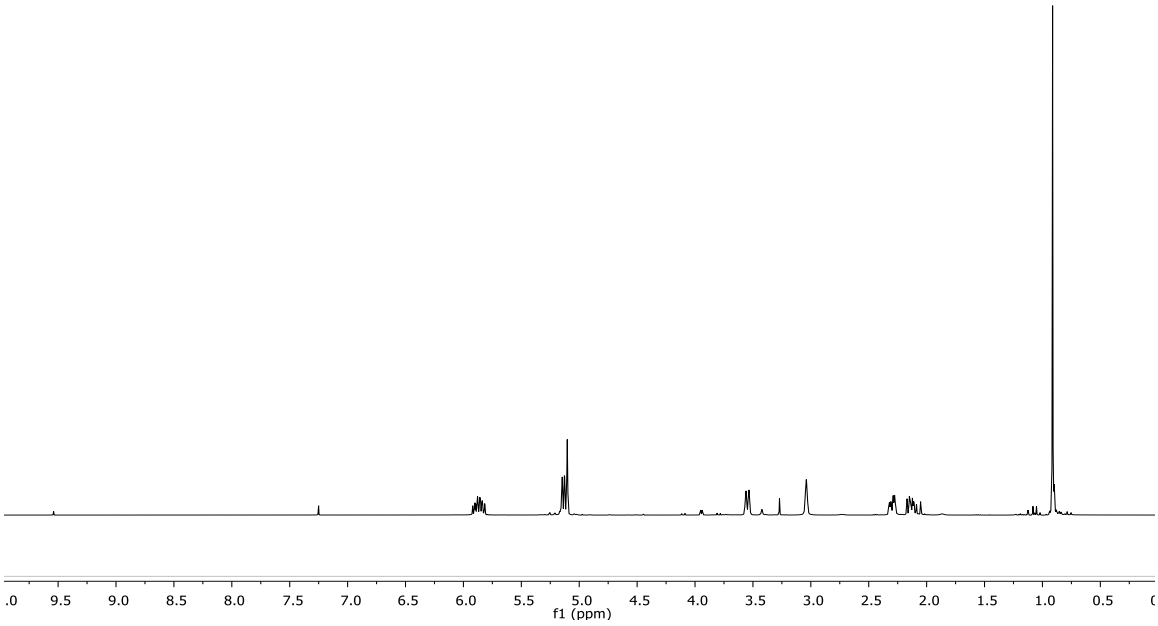
(*S*)-(−)-MTPA-ester of **216**

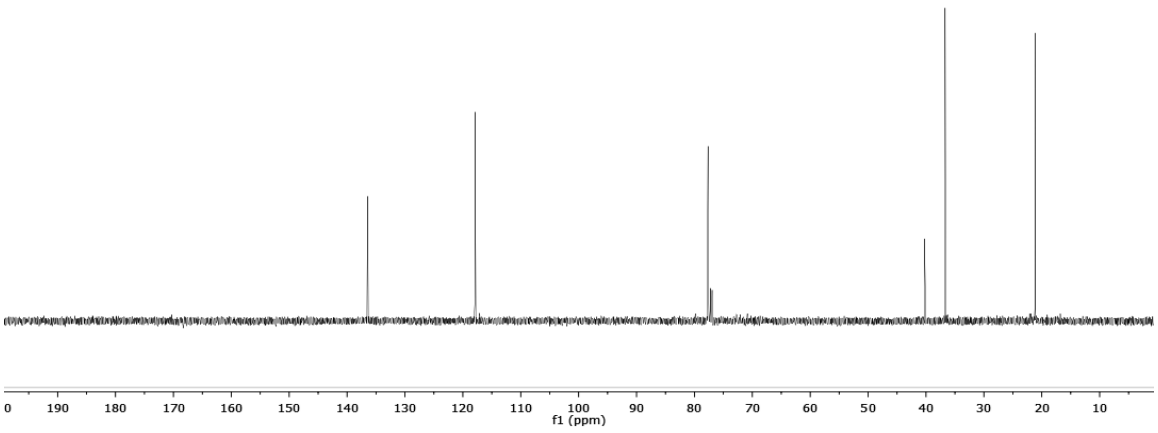


(*S*)-(−)-MTPA-ester of *rac*-**216**

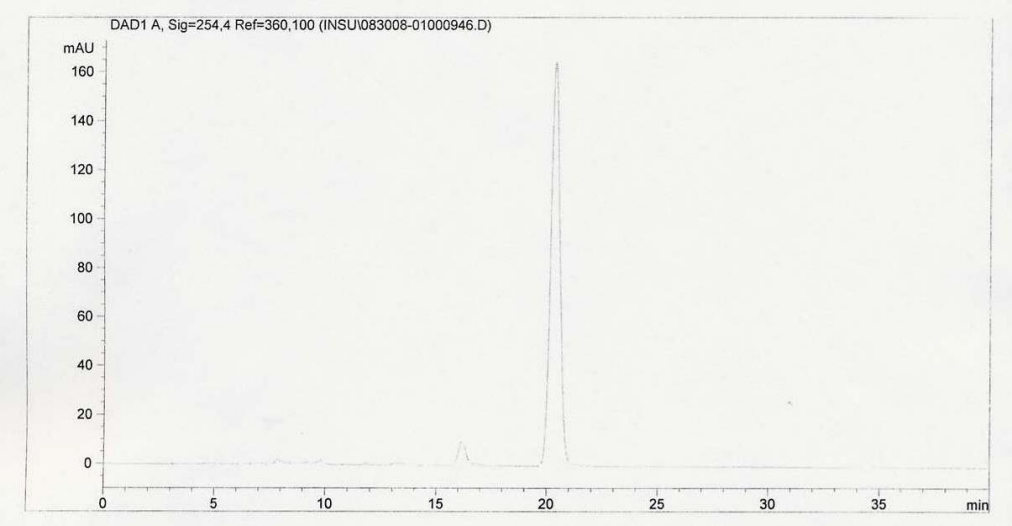



OH
Me
Me
OH

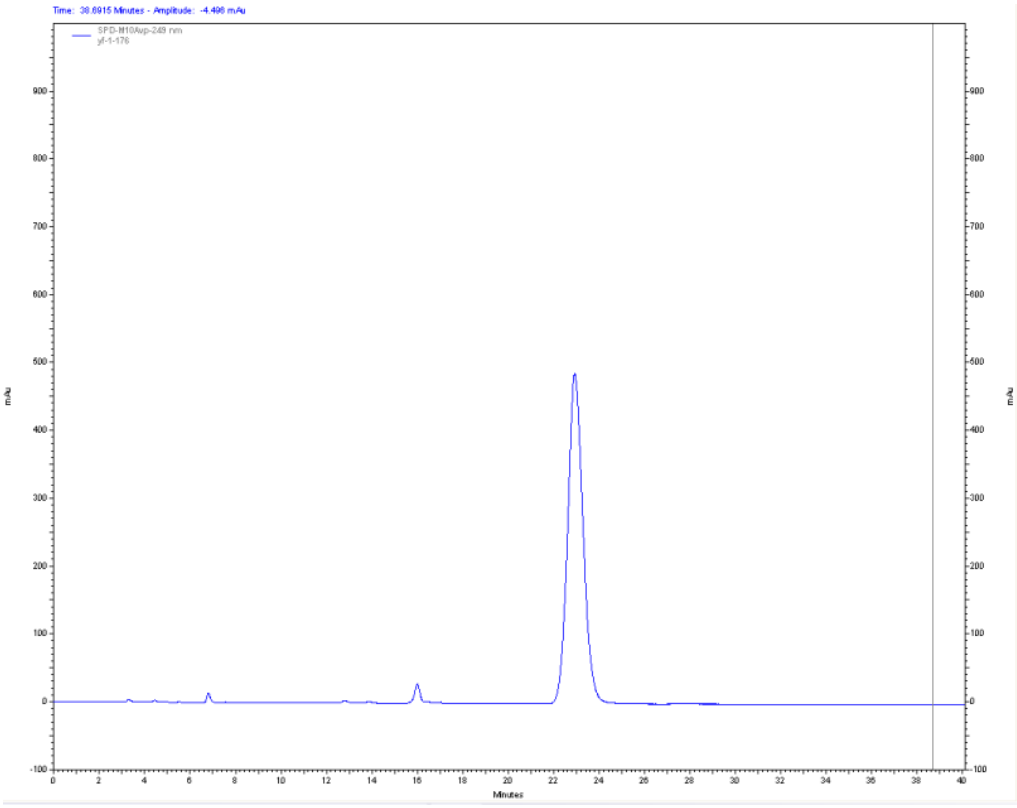

.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

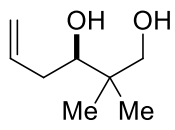

0 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

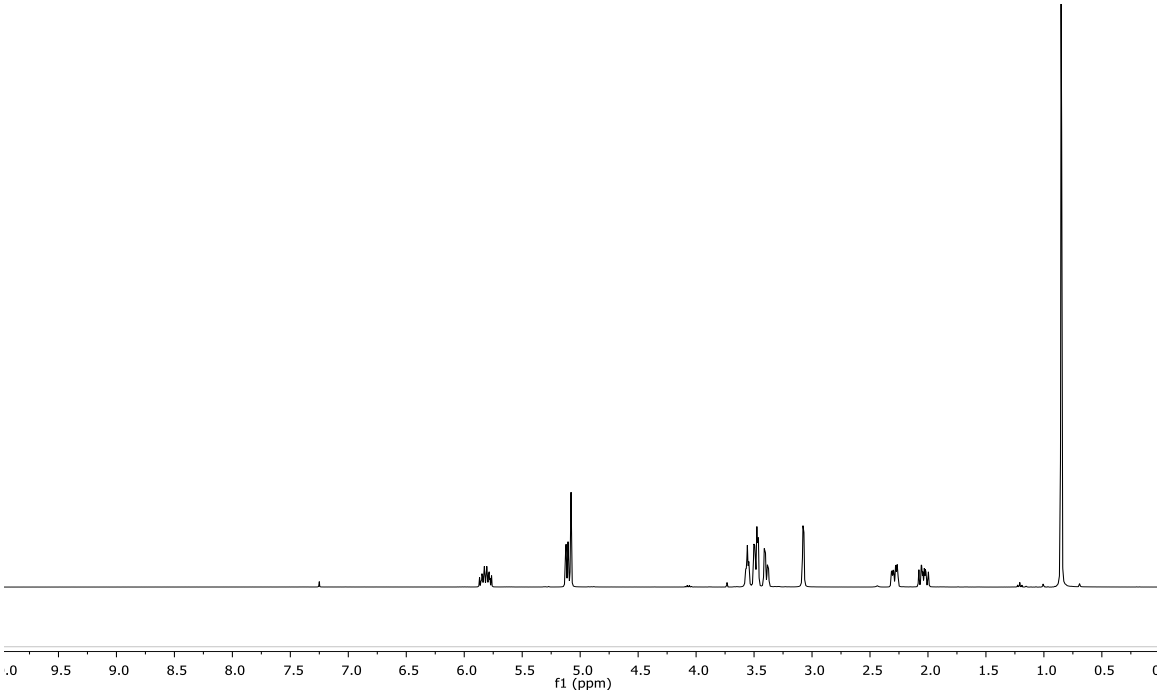
Reference HPLC:

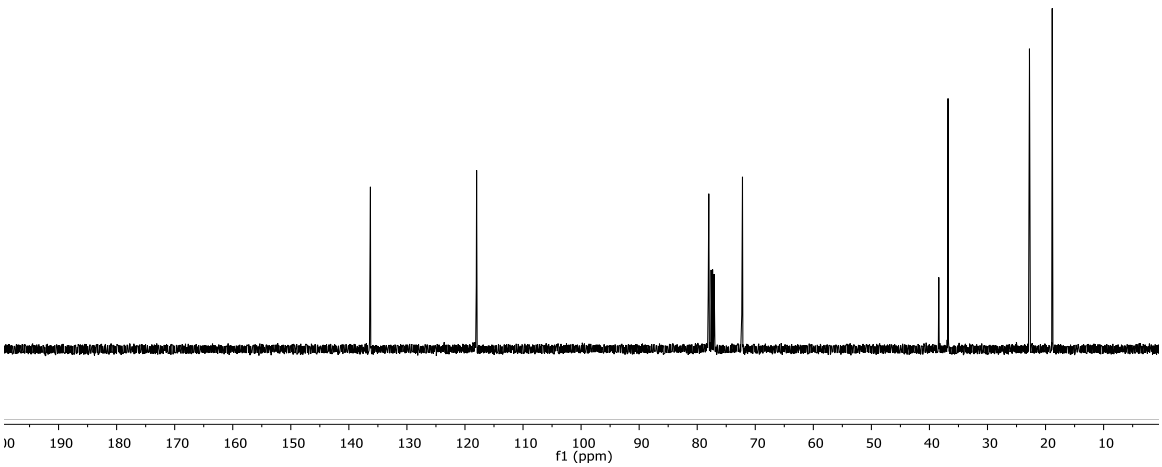


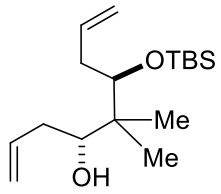
Synthetic sample HPLC:

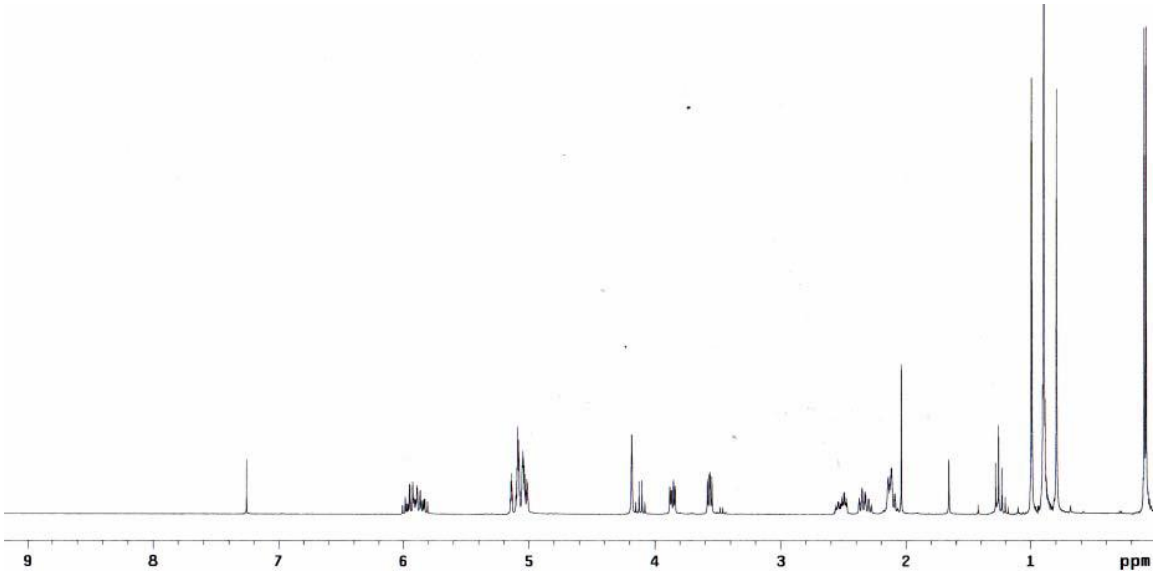


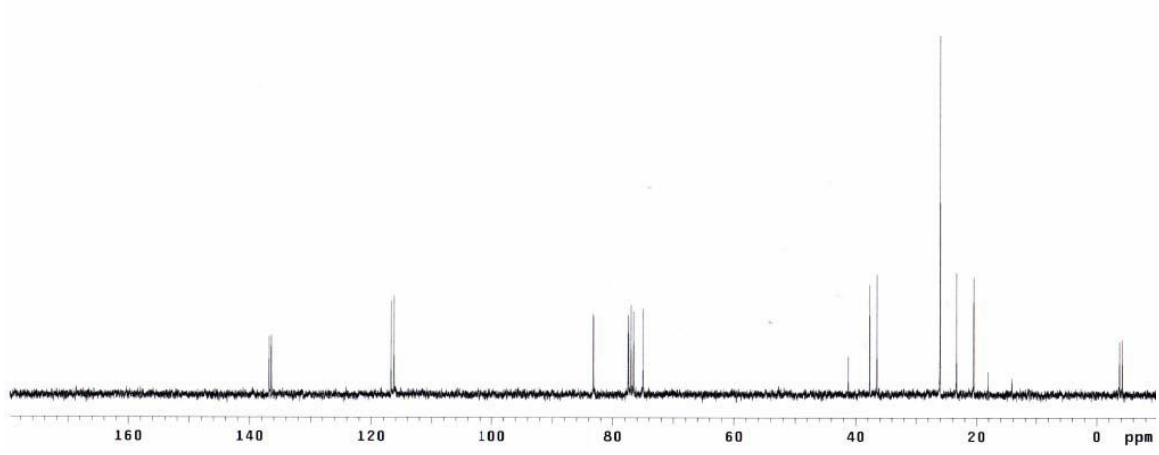

OH
OH
Me
Me

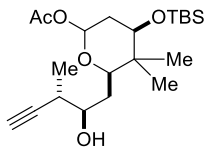

9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

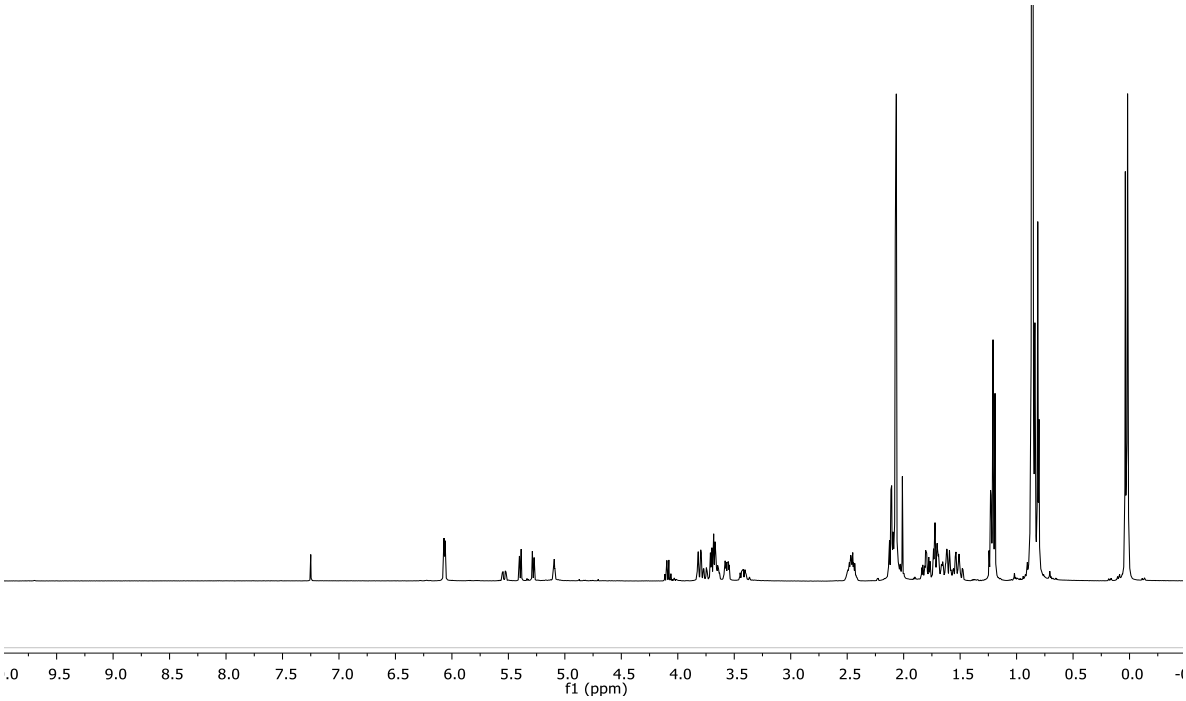

190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

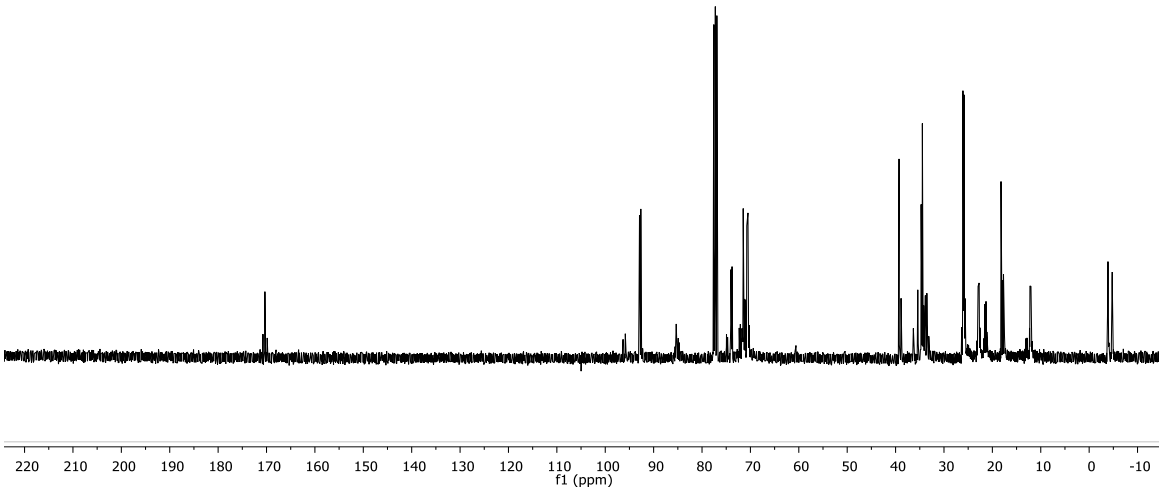

OTBS
Me
Me
OH

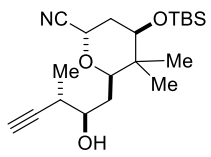

9
8
7
6
5
4
3
2
1
ppm


160
140
120
100
80
60
40
20
0
ppm

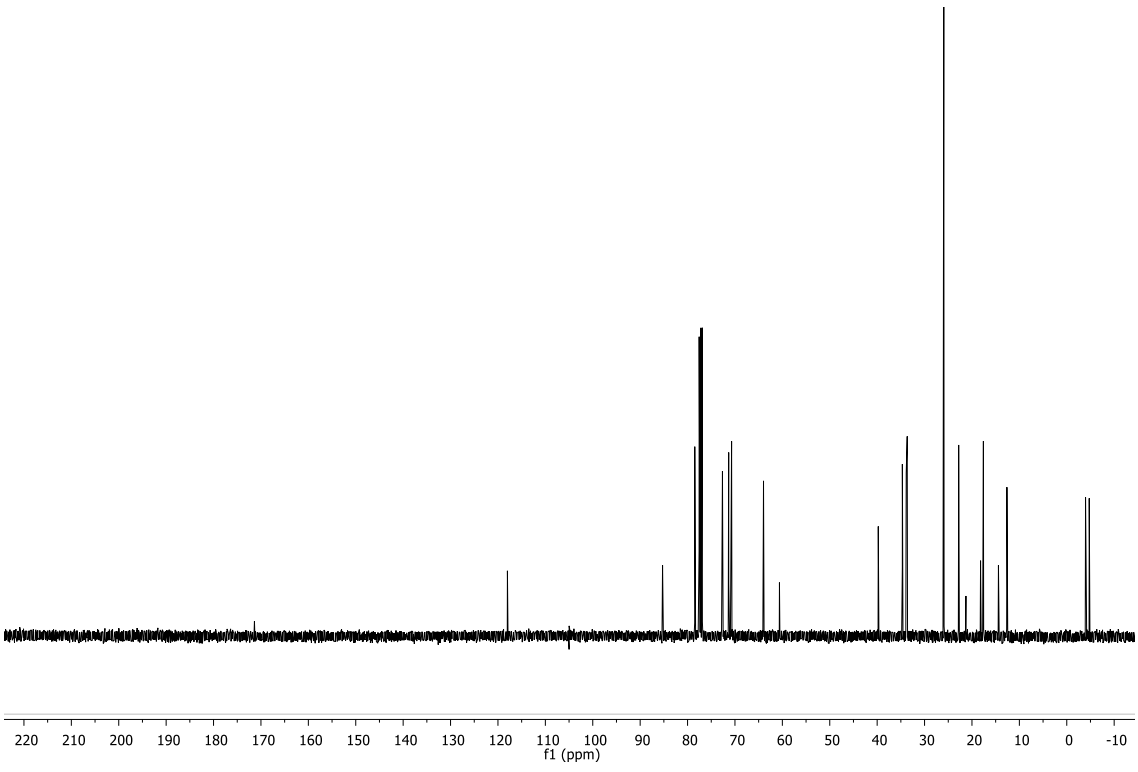

AcO
OTBS
O
Me
Me
Me
OH

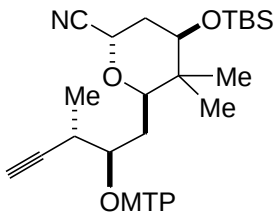

.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

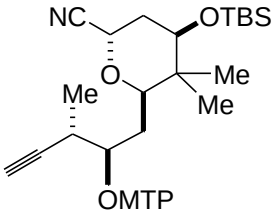

NC
OTBS
O
Me
Me
Me
OH

.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

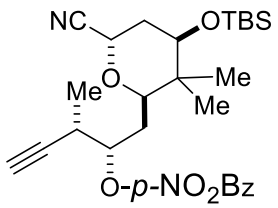

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

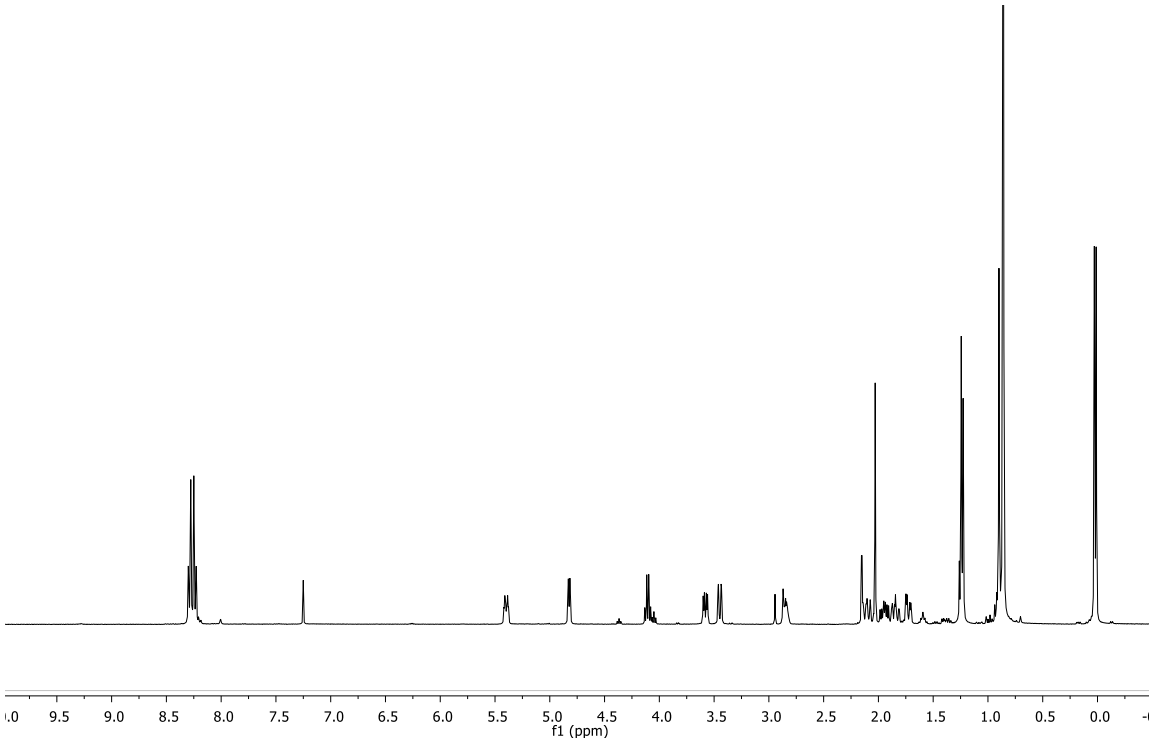


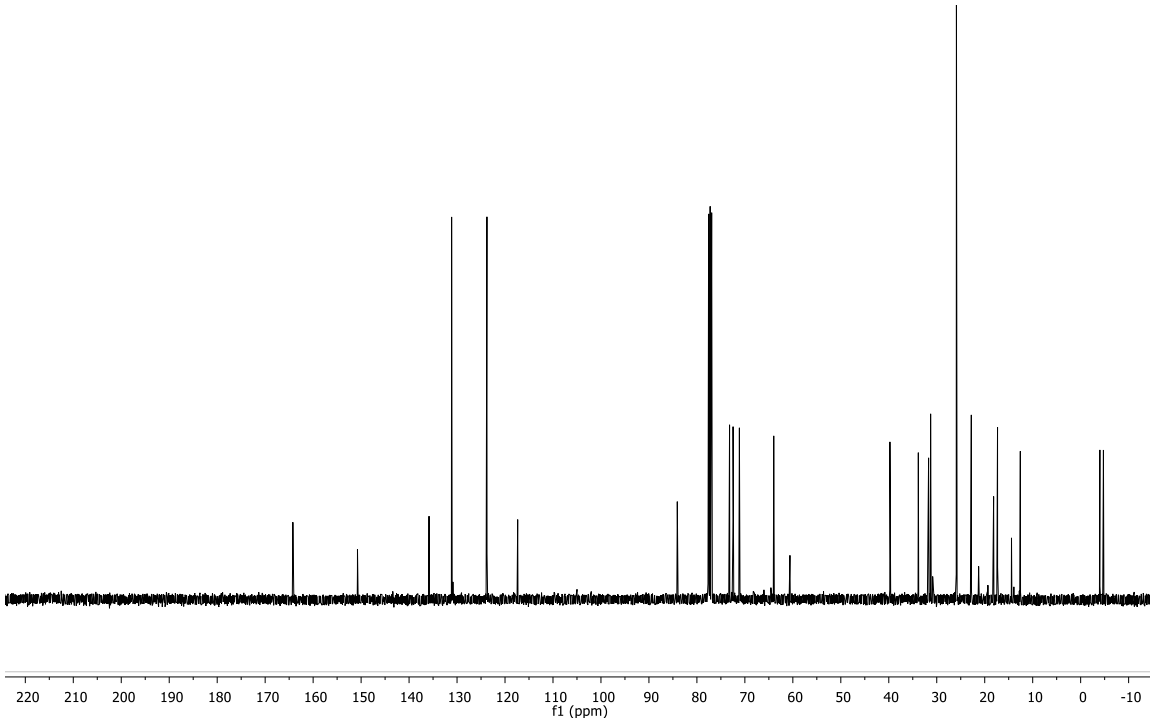
***S*-MTPA Ester**

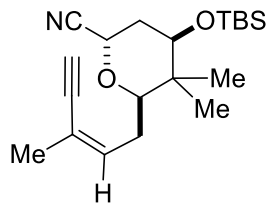


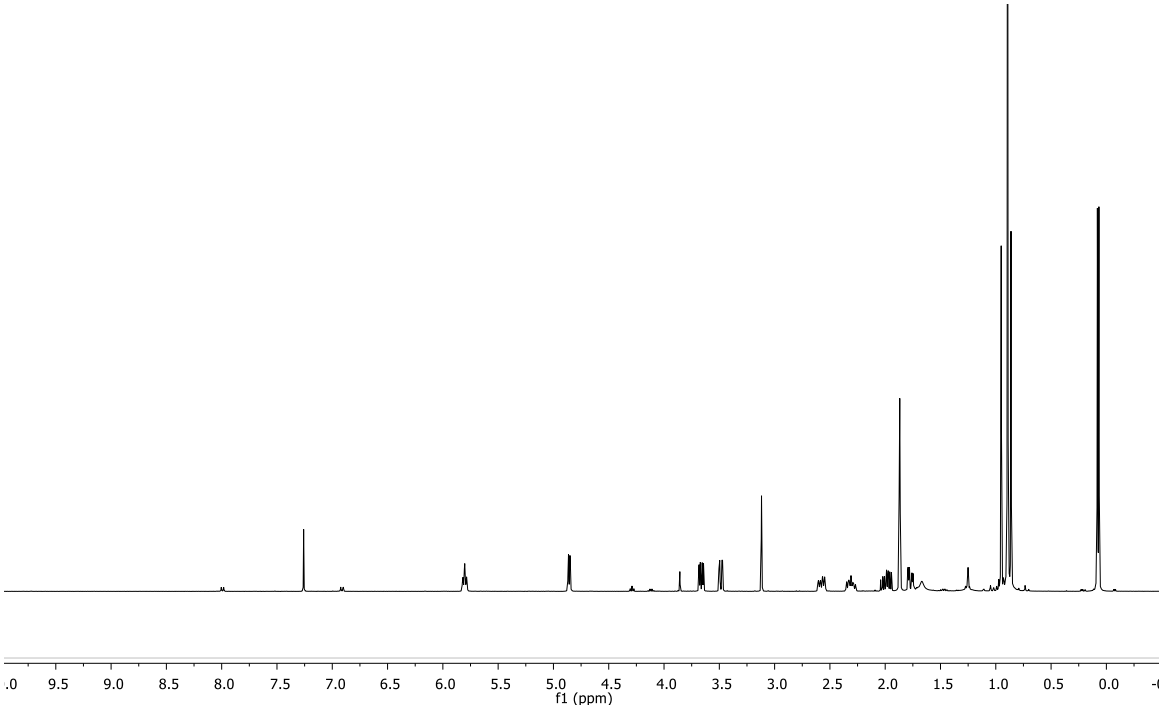
***R*-MTPA Ester**

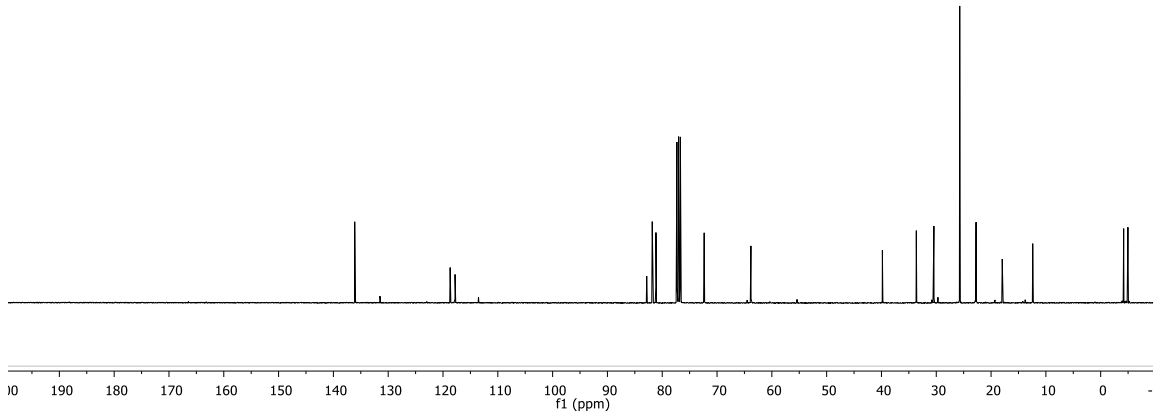

NC
OTBS
Me
O
Me
Me
O-p-NO2Bz

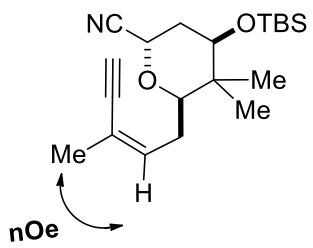

9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

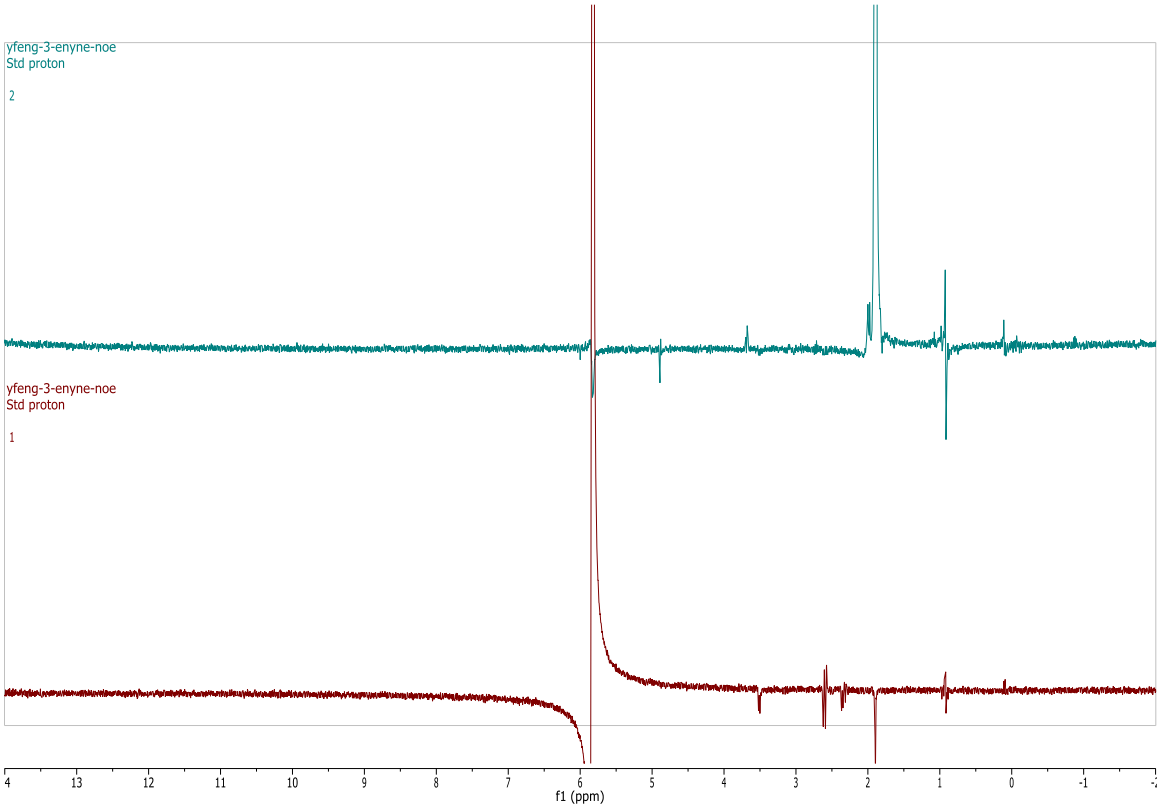

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

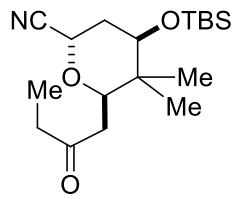

NC
OTBS
O
Me
Me
Me
H

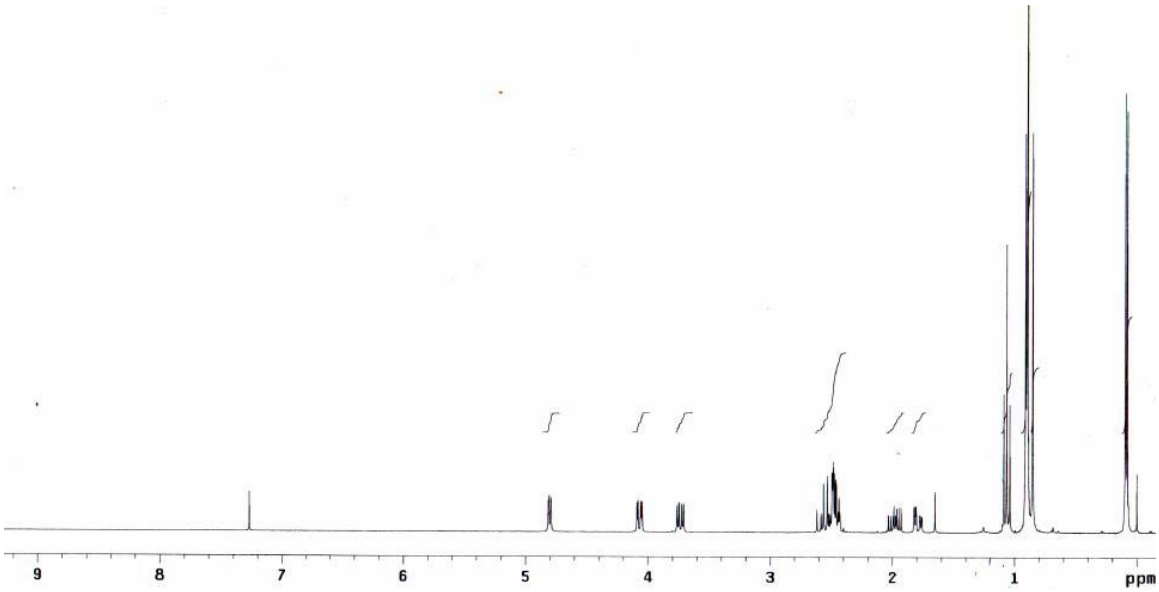

9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

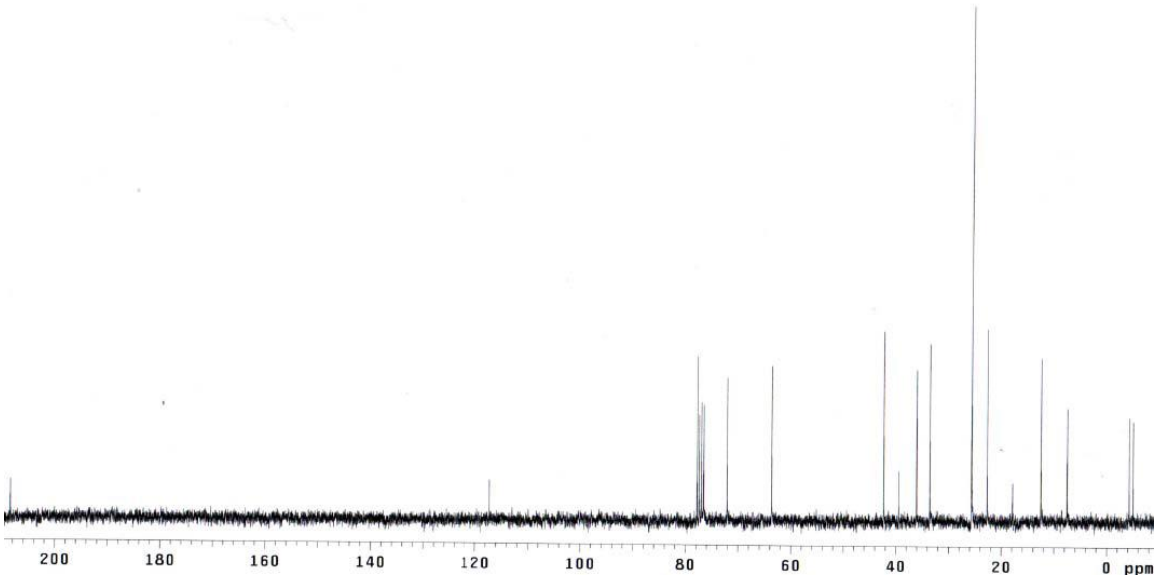

190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

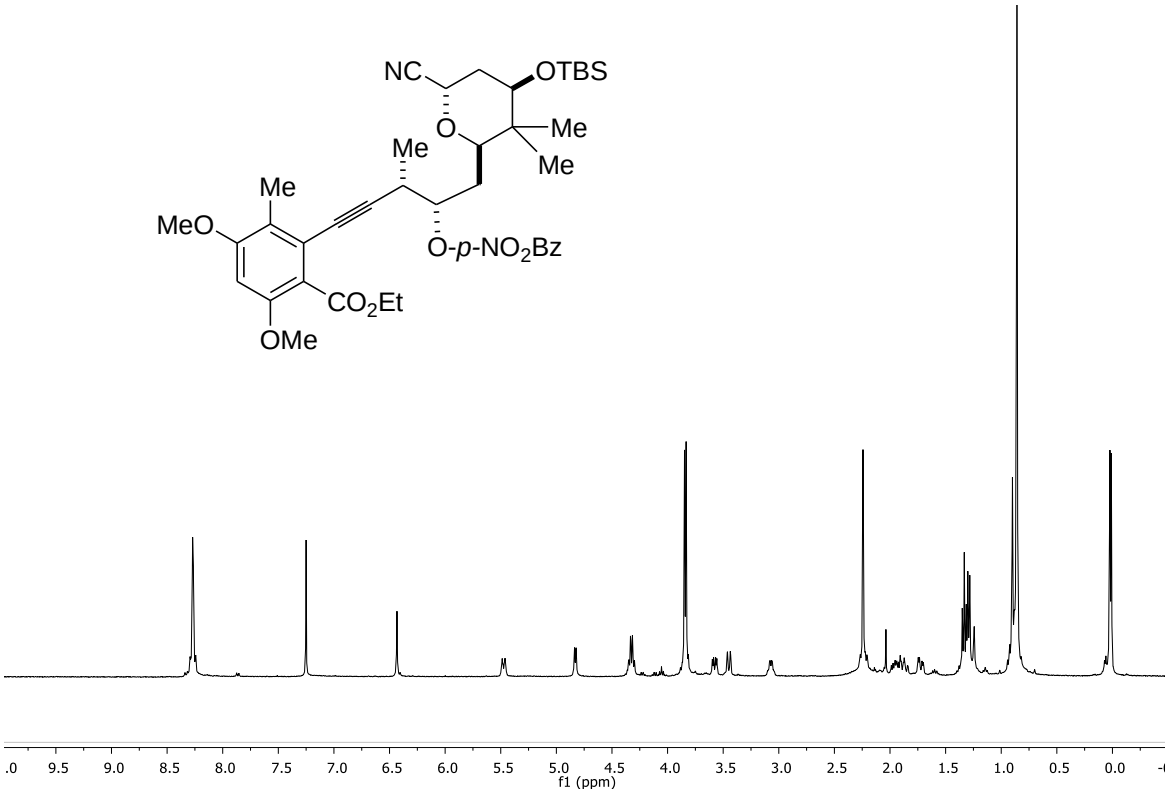

NC
OTBS
O
Me
Me
Me
H
nOe

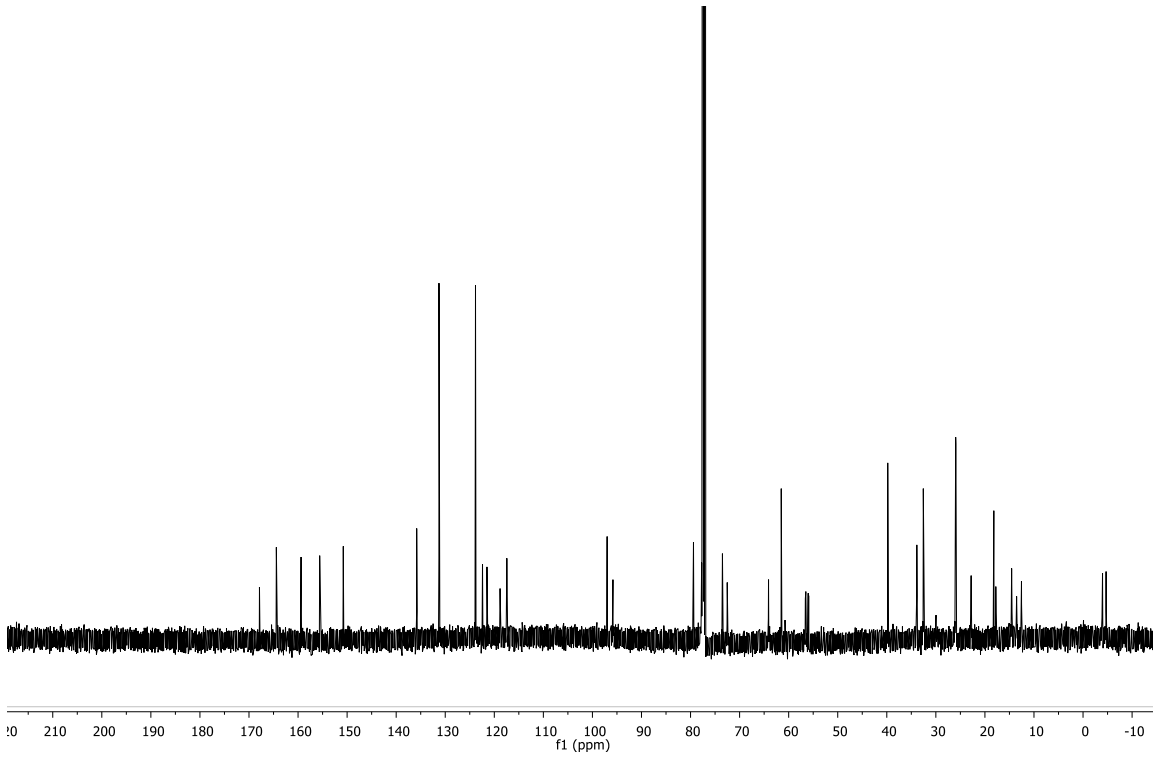

yfeng-3-enyne-noe
Std proton
2
yfeng-3-enyne-noe
Std proton
1
f1 (ppm)

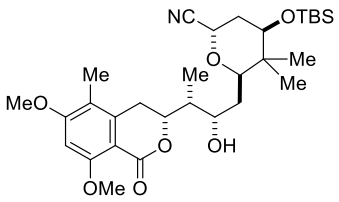

NC
OTBS
Me
O
Me
Me
O

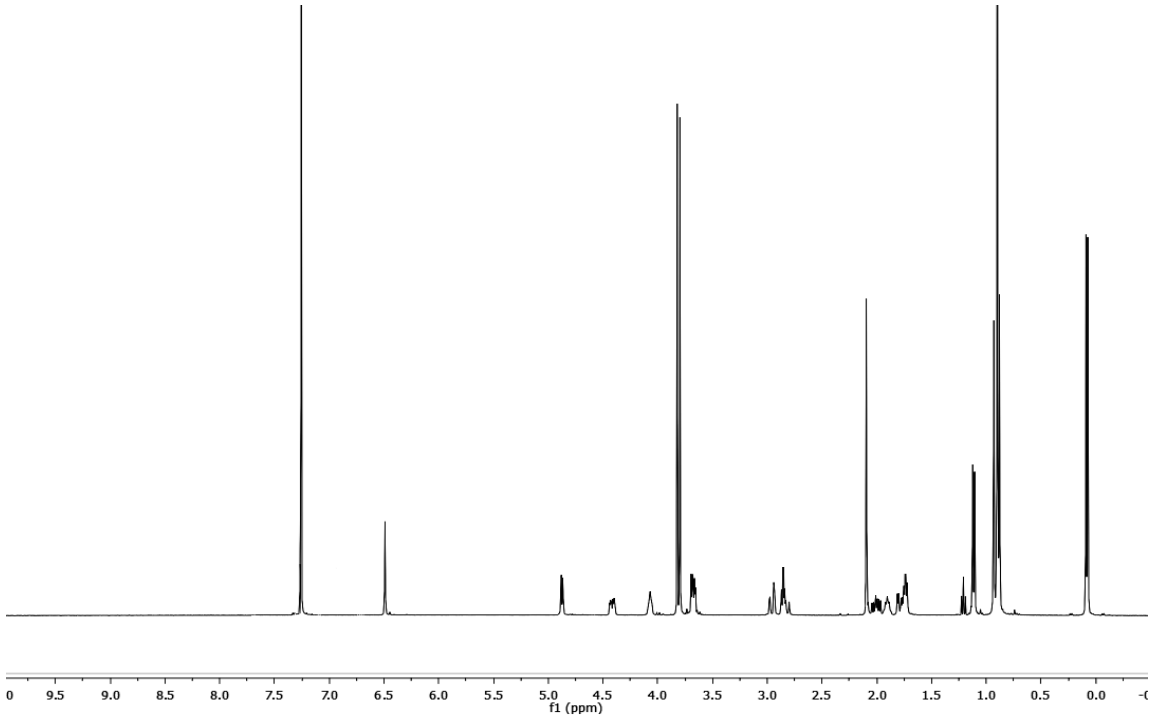

9
8
7
6
5
4
3
2
1
ppm

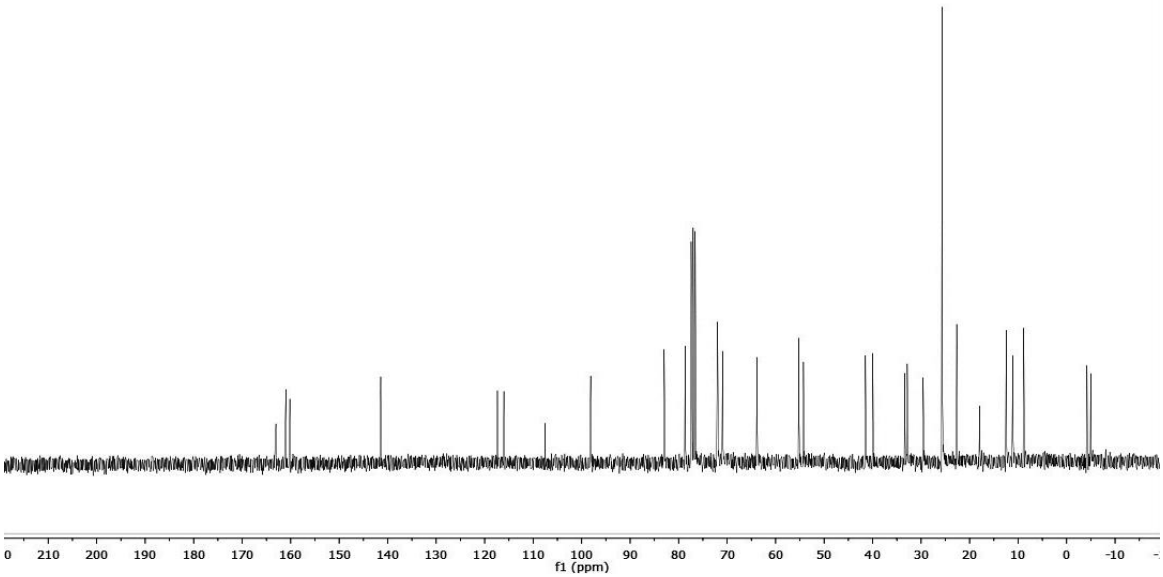

200
180
160
140
120
100
80
60
40
20
0 ppm

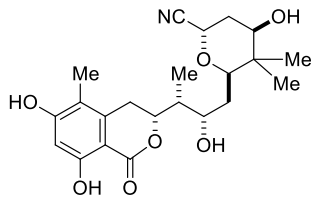

NC
OTBS
O
Me
Me
Me
Me
MeO
O-p-NO2Bz
CO2Et
OMe
f1 (ppm)

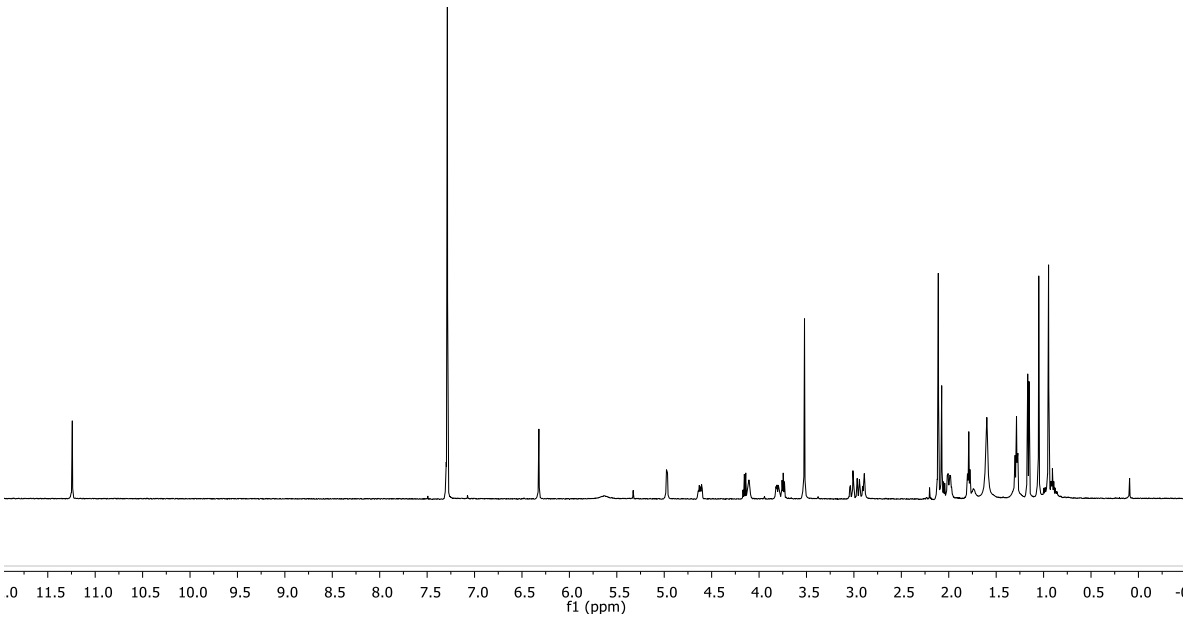

f1 (ppm)

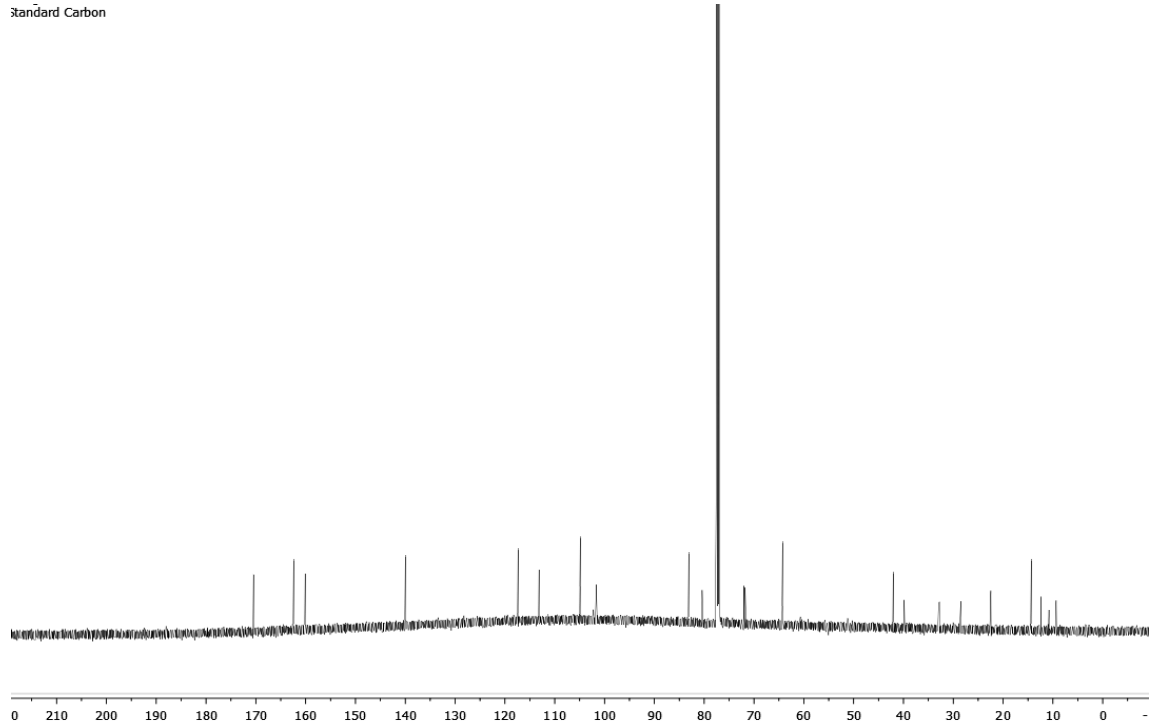

NC
OTBS
O
Me
Me
Me
Me
MeO
O
OH
OMe
O

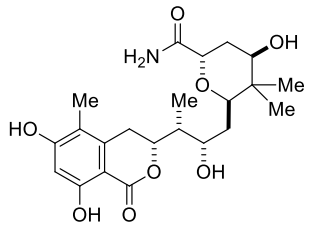

0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

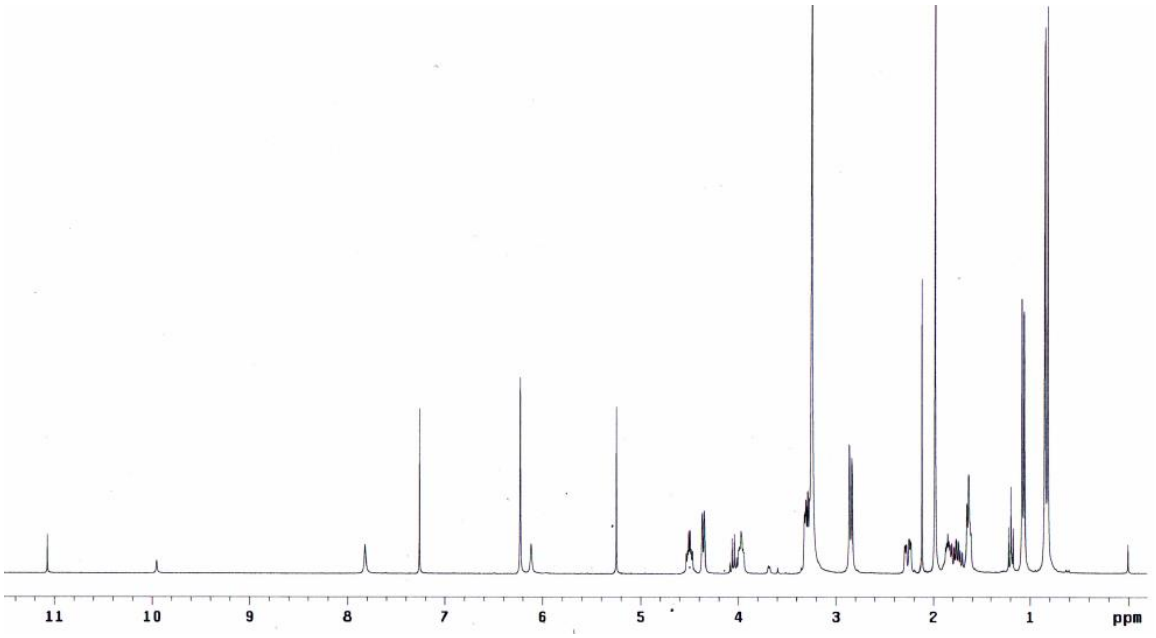

0
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

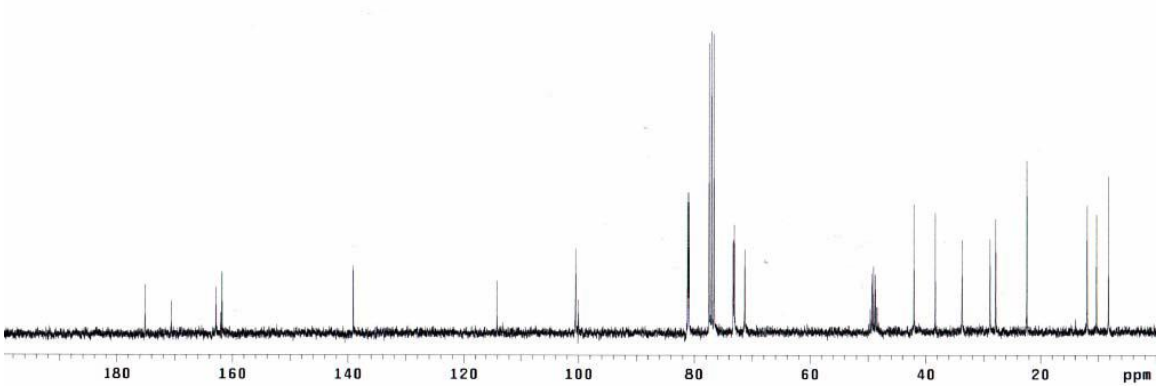

NC
OH
O
Me
Me
Me
HO
O
OH
OH
O

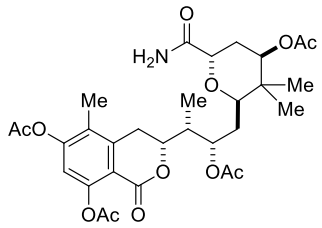

.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

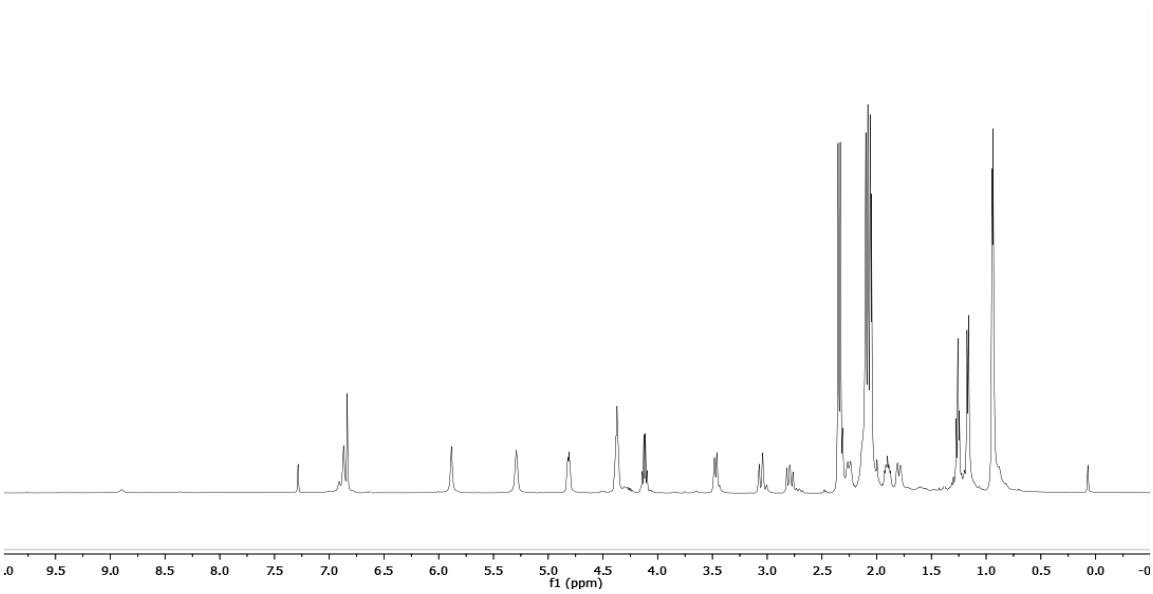

Standard Carbon
0 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

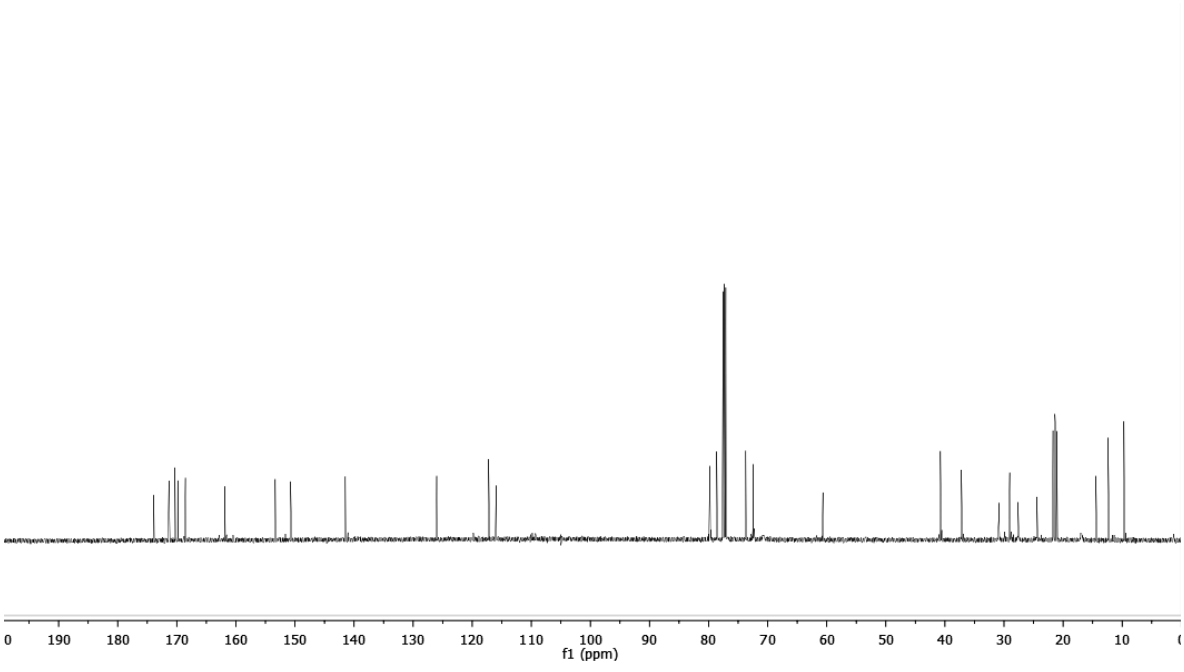

O
H2N
OH
O
Me
Me
Me
HO
O
OH
OH
O


11
10
9
8
7
6
5
4
3
2
1
ppm


180
160
140
120
100
80
60
40
20
ppm


O
H2N
OAc
O
Me
Me
Me
AcO
O
OAc
OAc
O


9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


190
180
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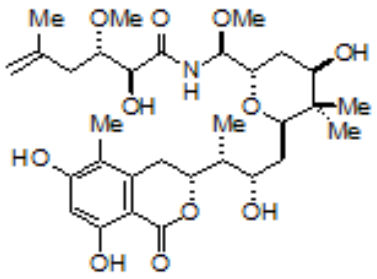
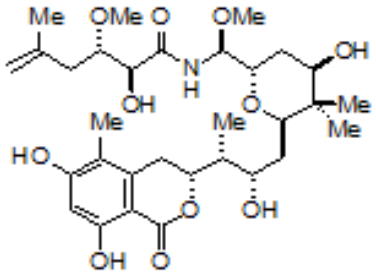
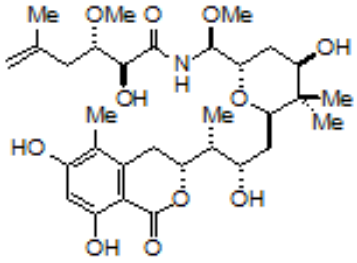
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)



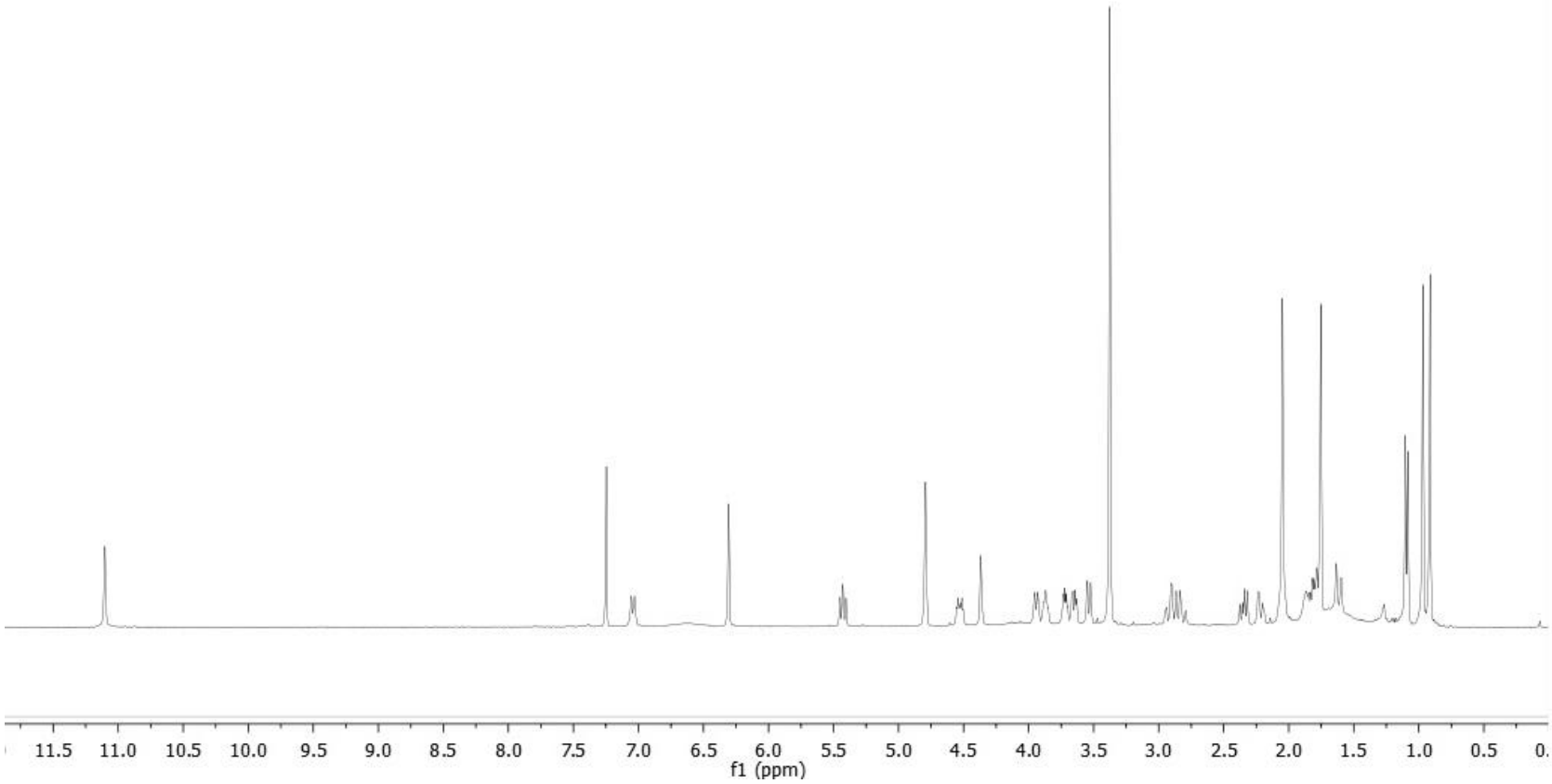
Psymberin (in CD_3OD)

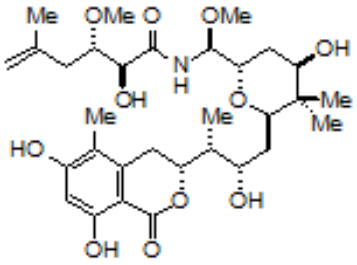


Psymberin (in CD_3OD)

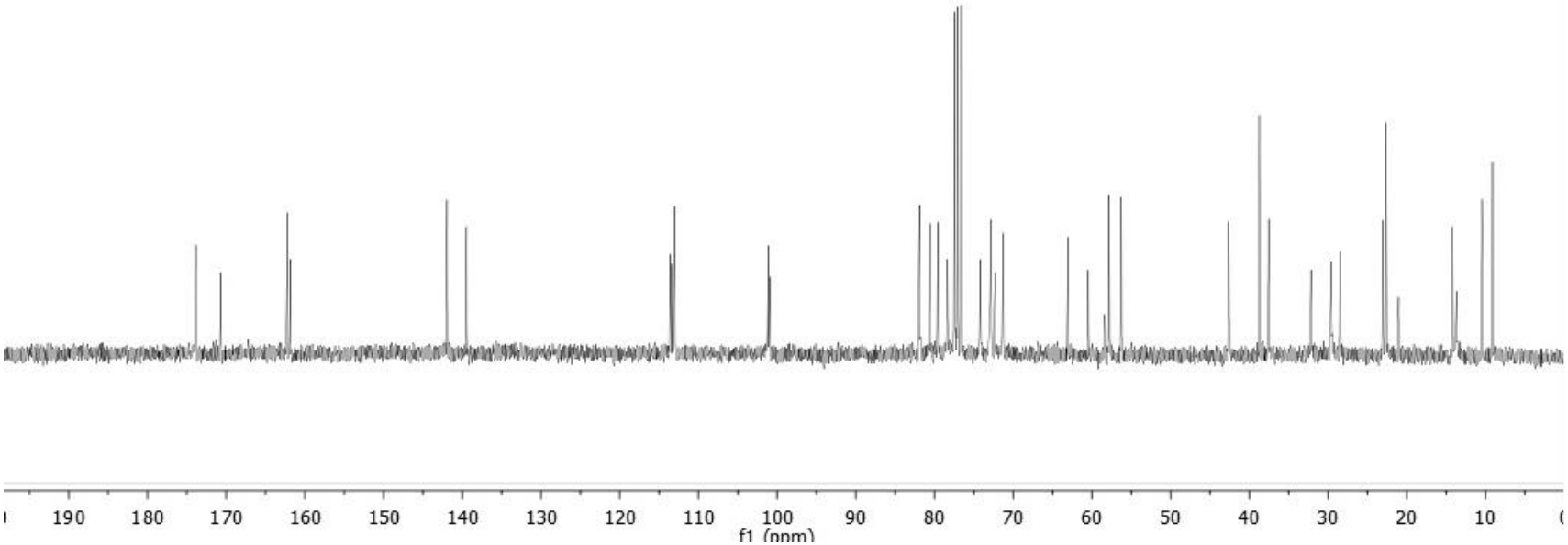


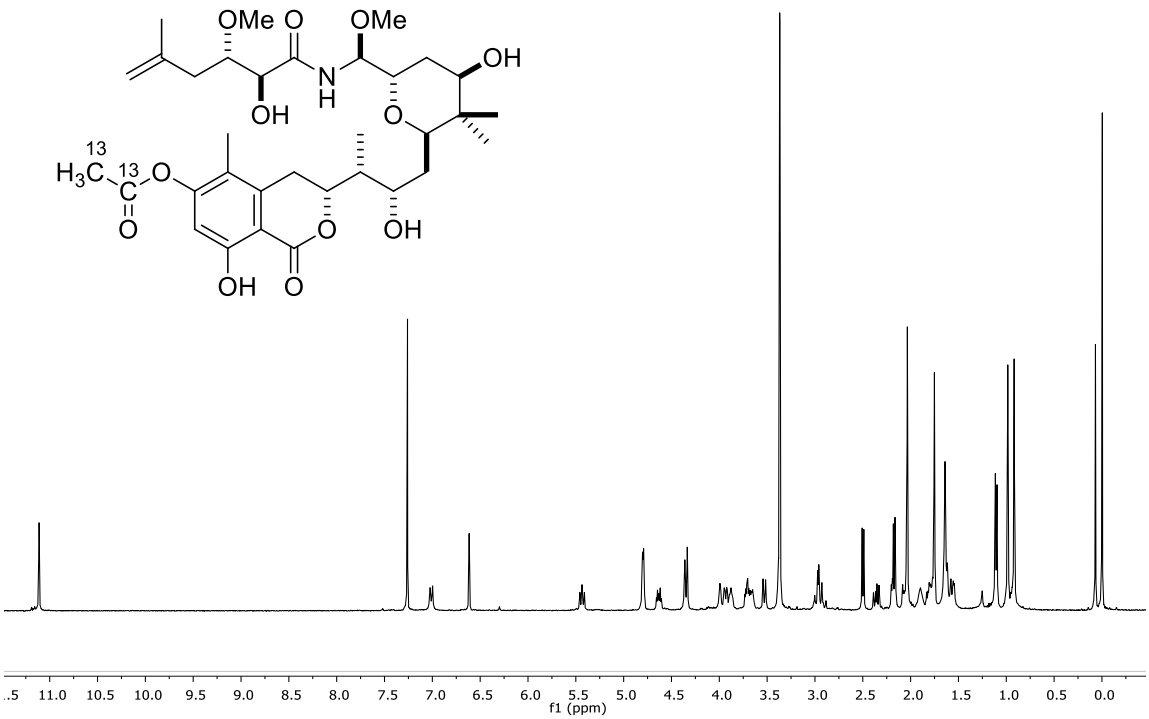
Psymberin (in $CDCl_3$)

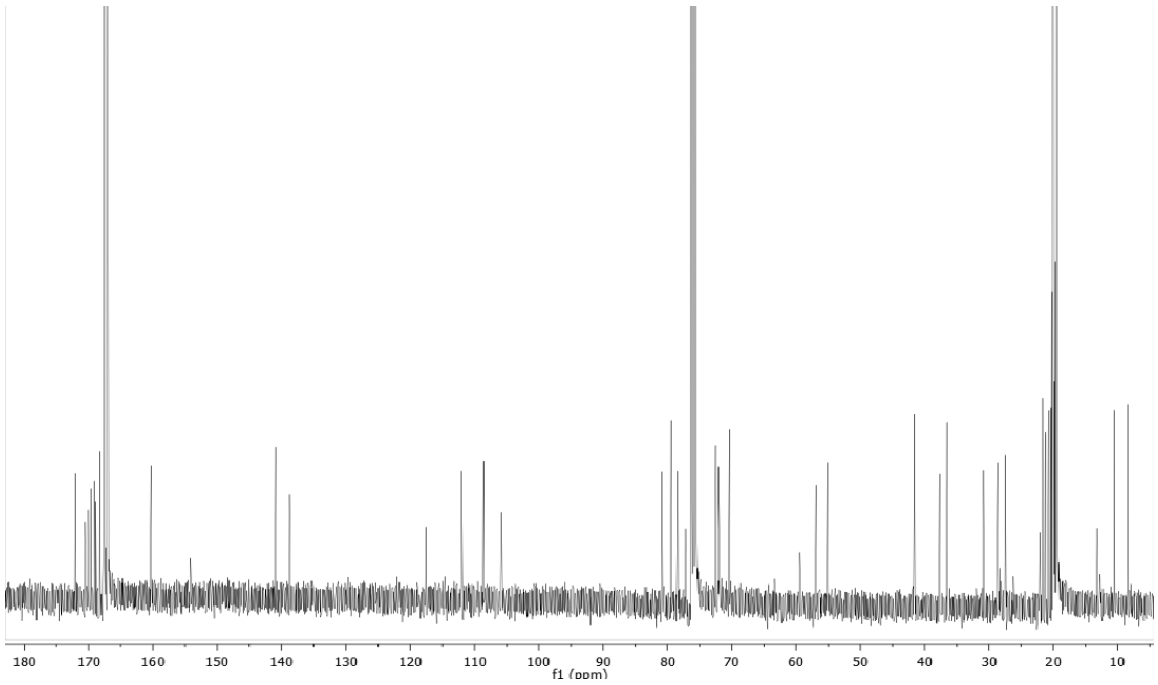




Psymberin (in $CDCl_3$)




OMe
O
OMe
OH
N
H
OH
O
13
H_3C
13
C
O
O
O
OH
OH
O
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


180
170
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150
140
130
120
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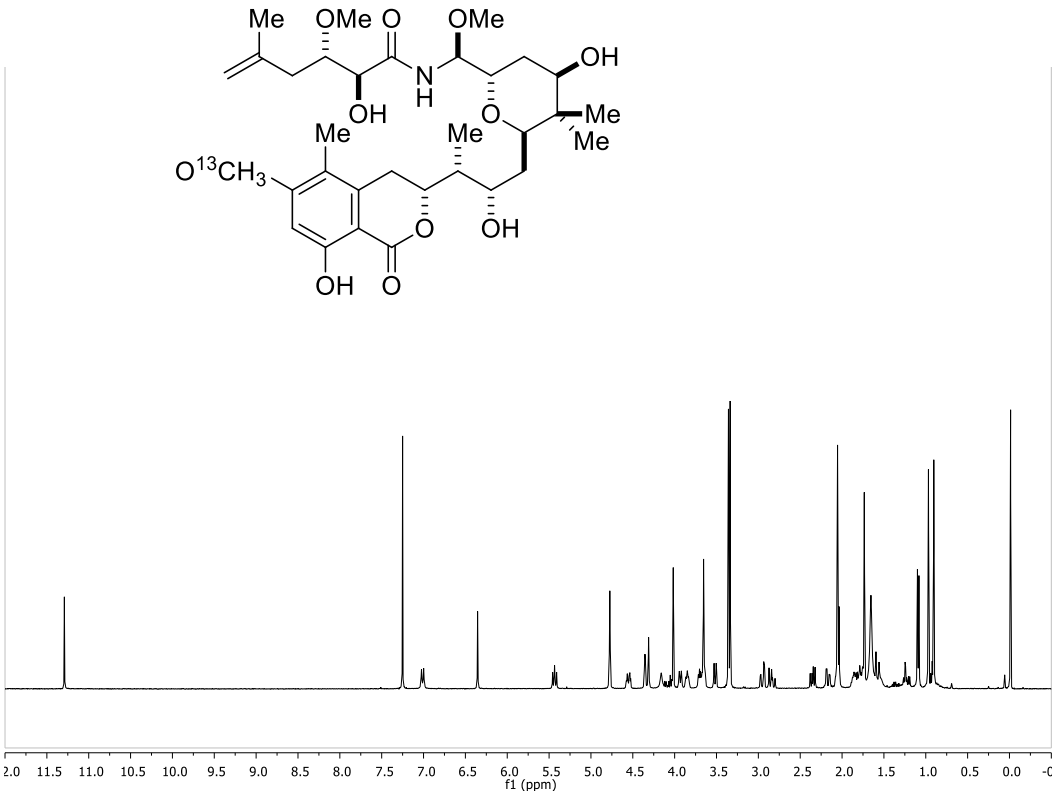
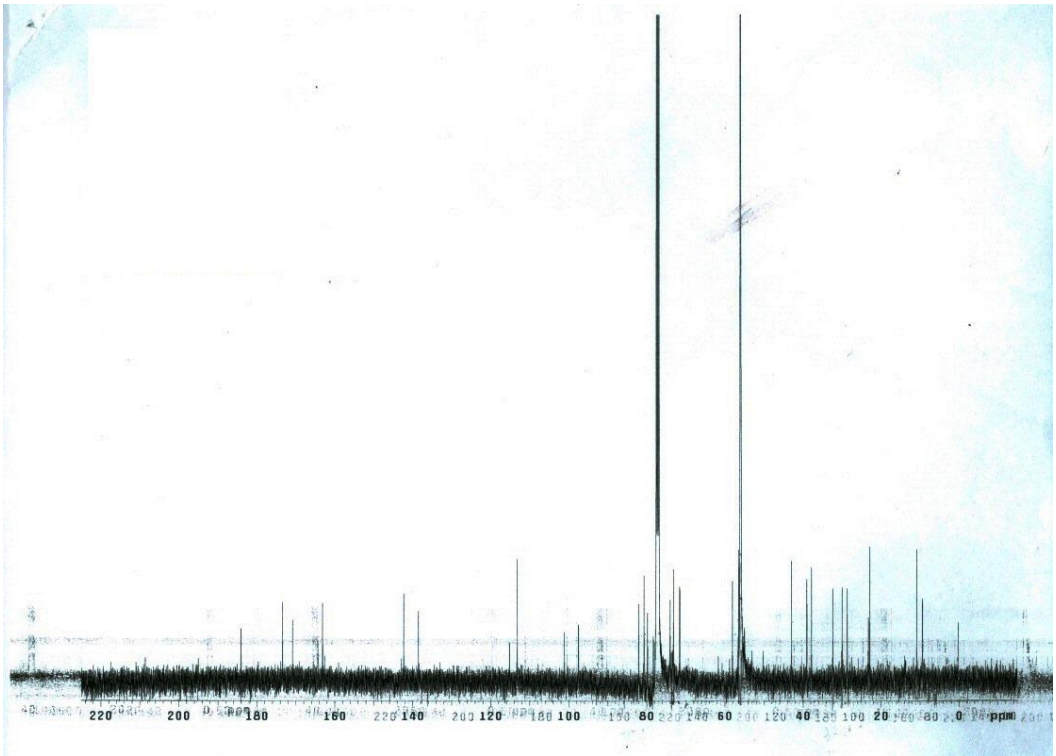
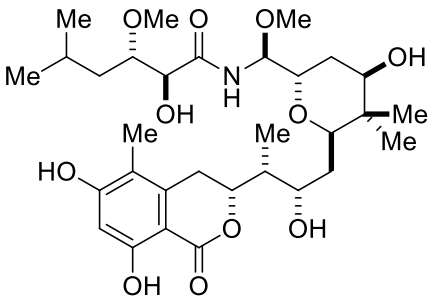
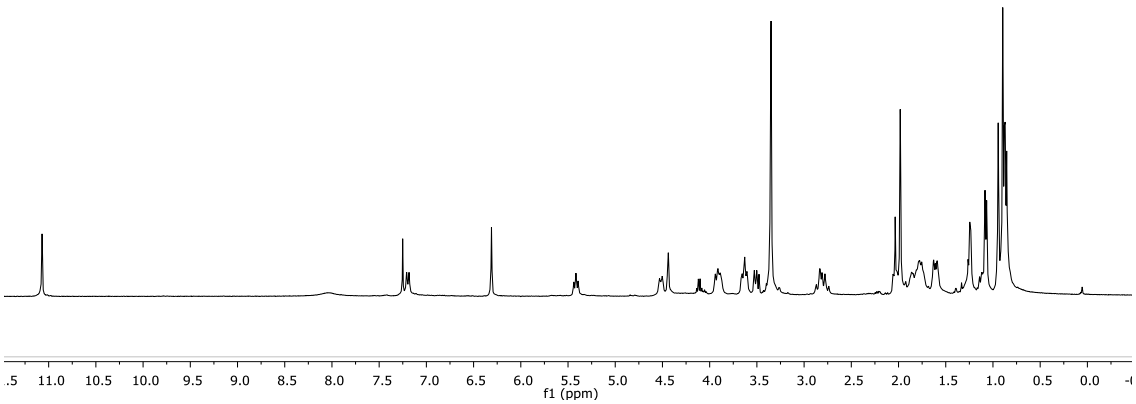
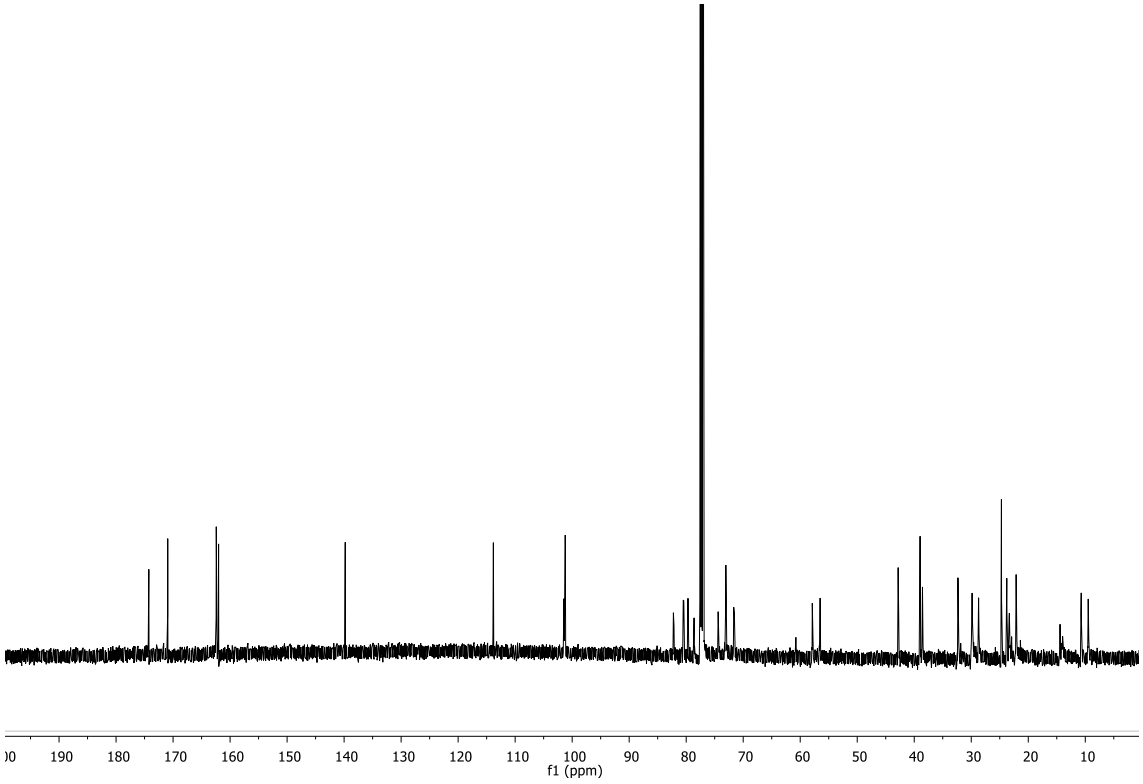
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


Me
OMe
O
OMe
OH
N
H
OH
O
Me
Me
Me
$O^{13}CH_3$
O
OH
OH
O
f1 (ppm)




Me
OMe
O
OMe
Me
N
H
OH
OH
O
Me
Me
Me
Me
HO
O
OH
OH
O


11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


190
180
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140
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120
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100
90
80
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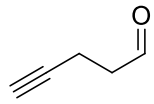
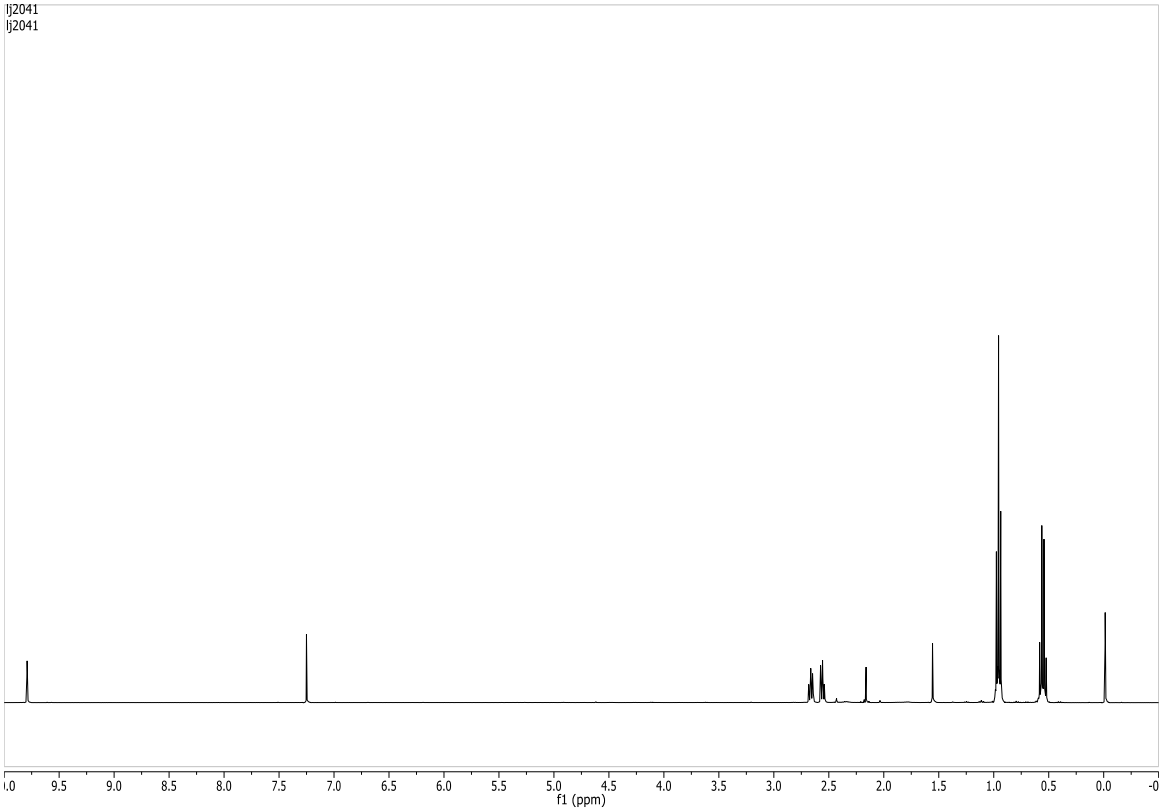
60
50
40
30
20
10
f1 (ppm)




lj2041
lj2041
9.5
9.0
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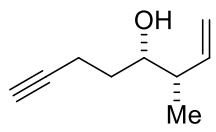
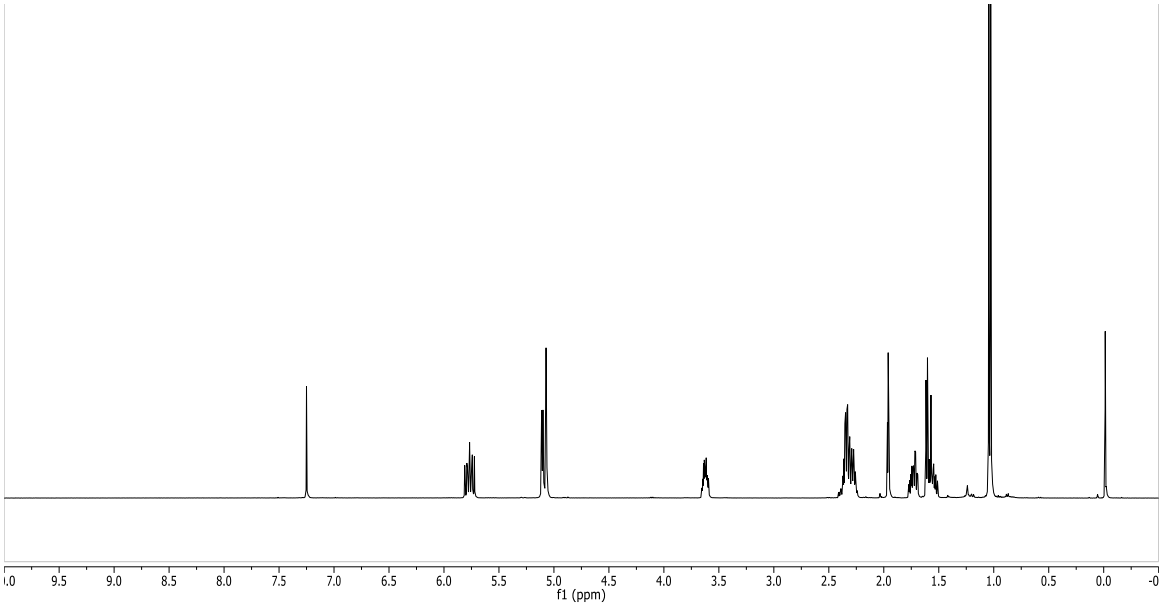
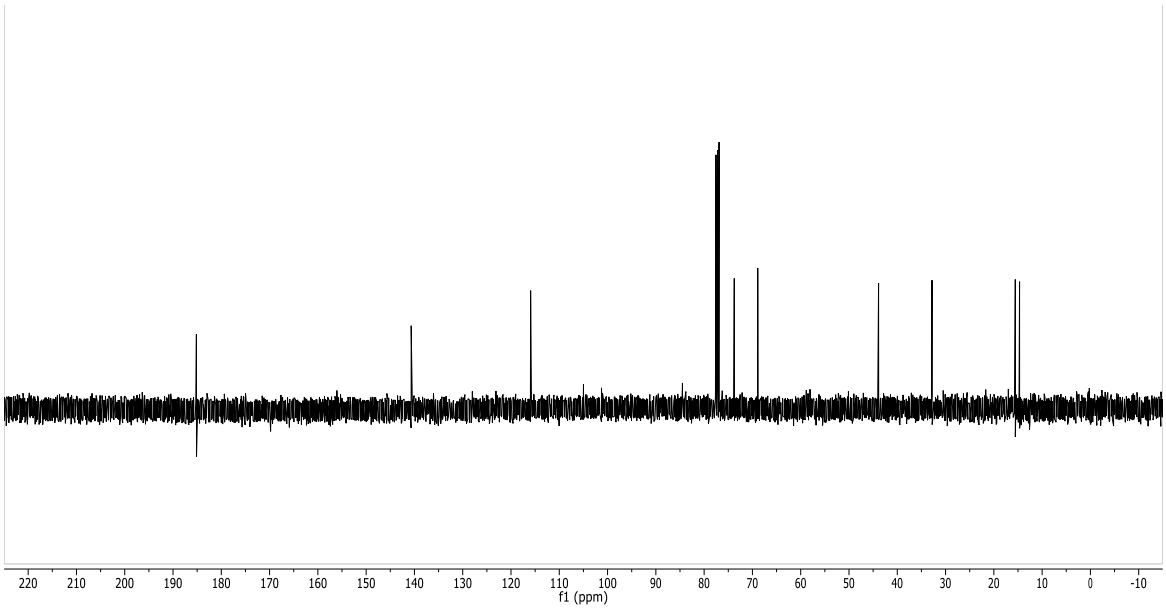
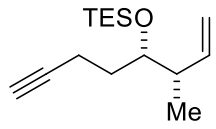
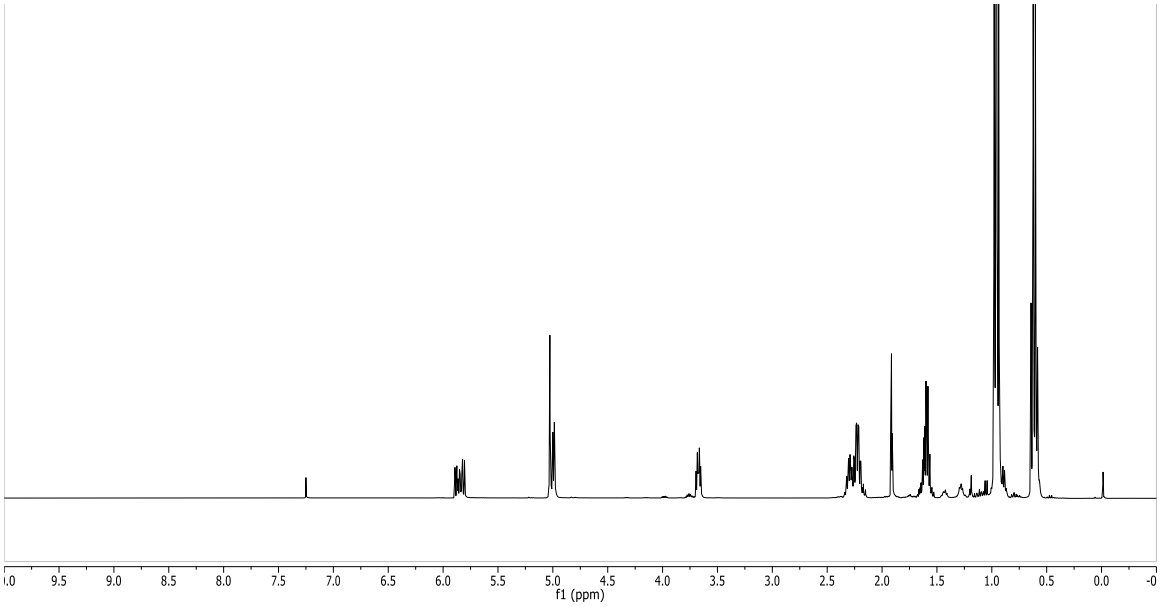
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

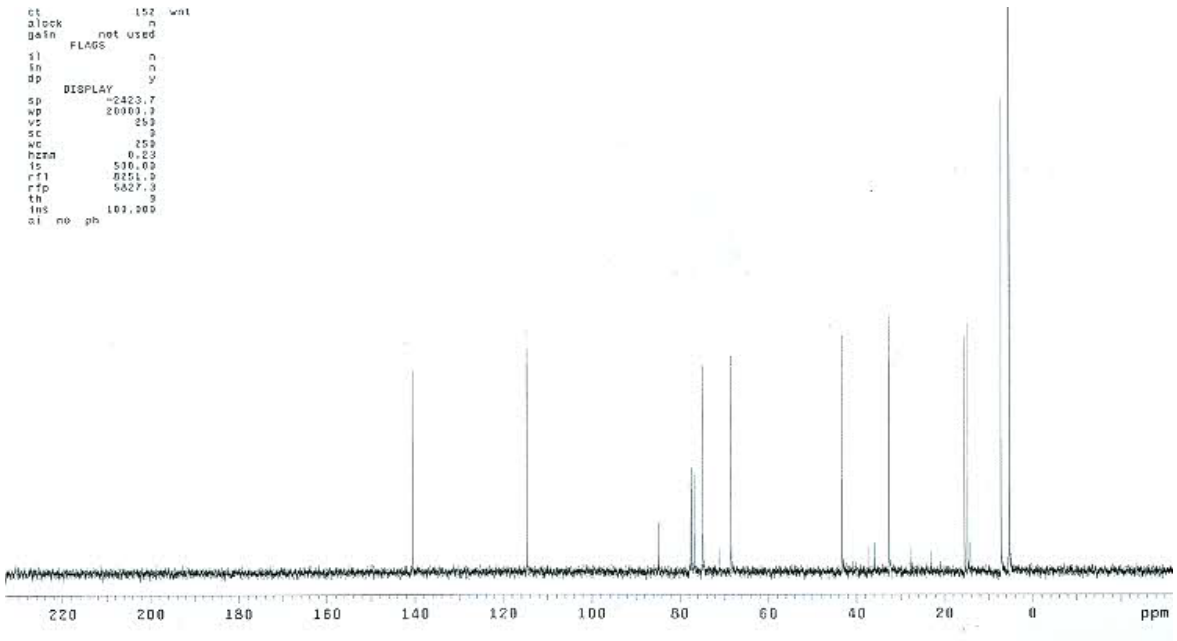

OH
Me

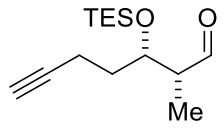

f1 (ppm)

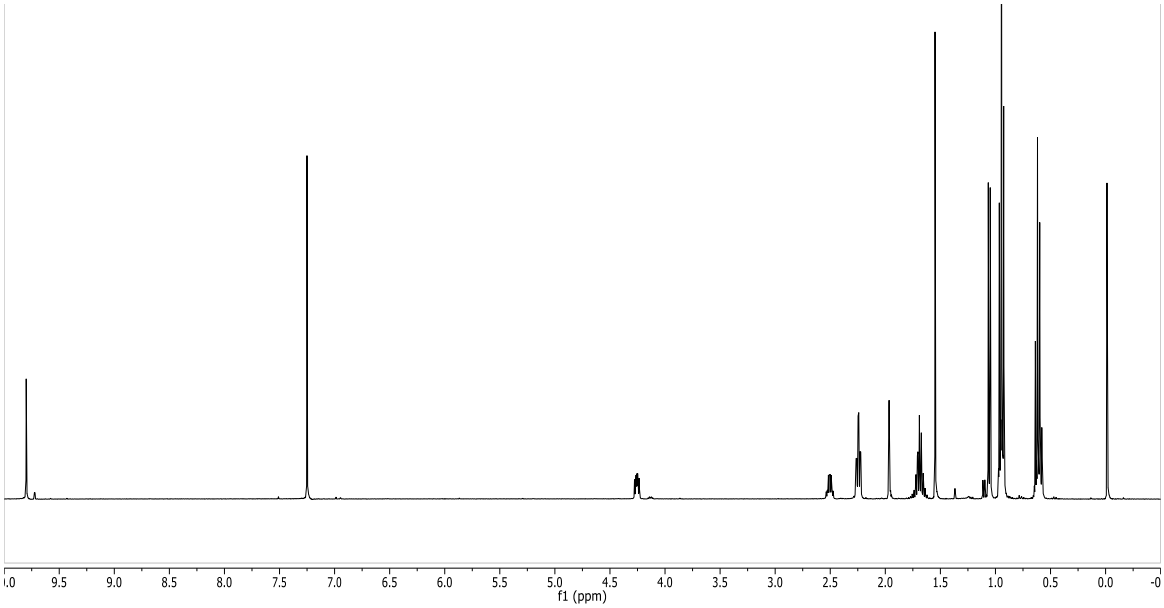

f1 (ppm)

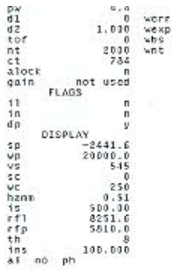

TESO
Me


f1 (ppm)

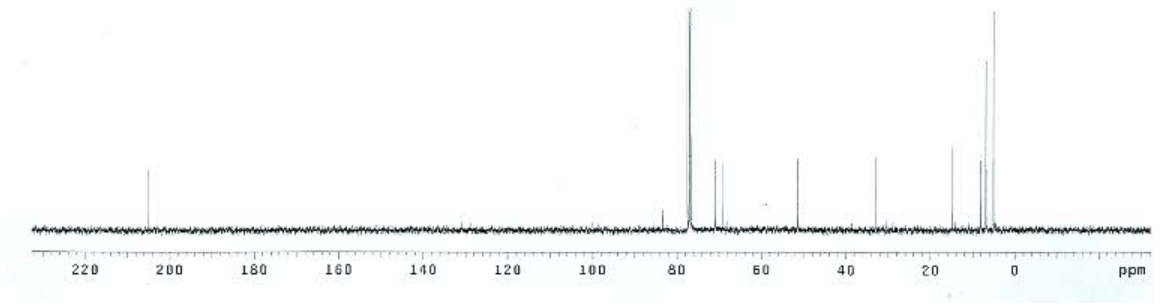

ppm

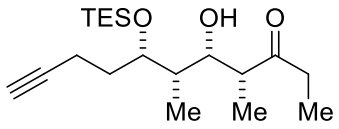


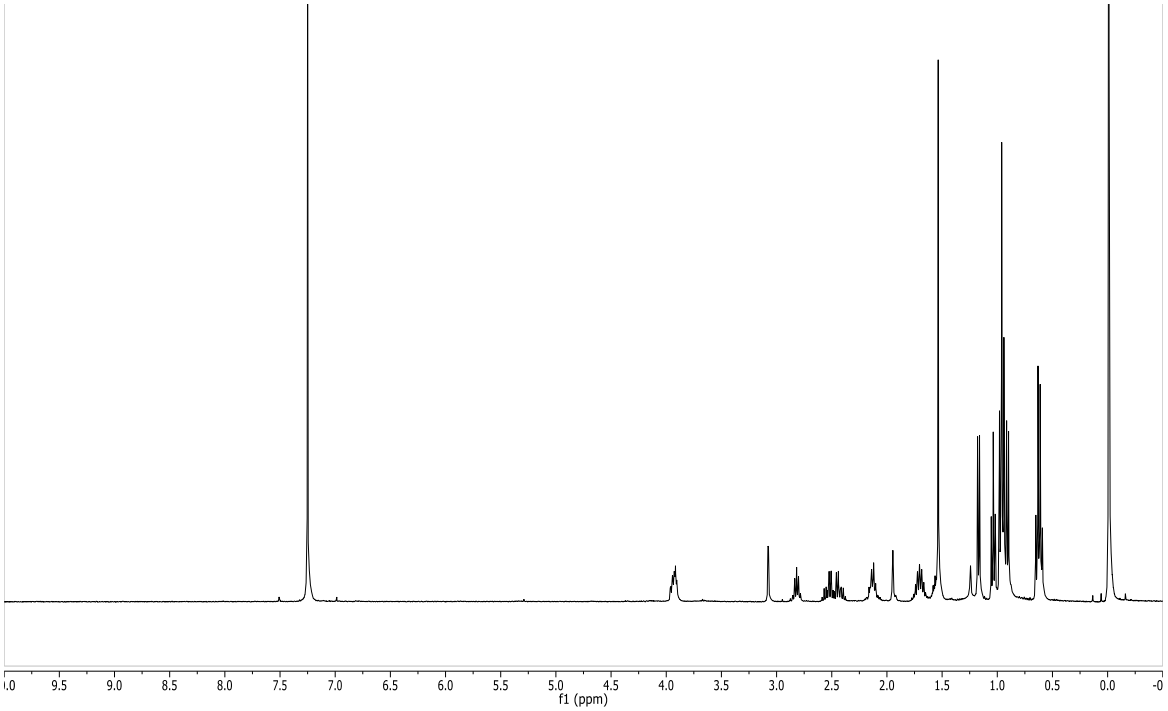


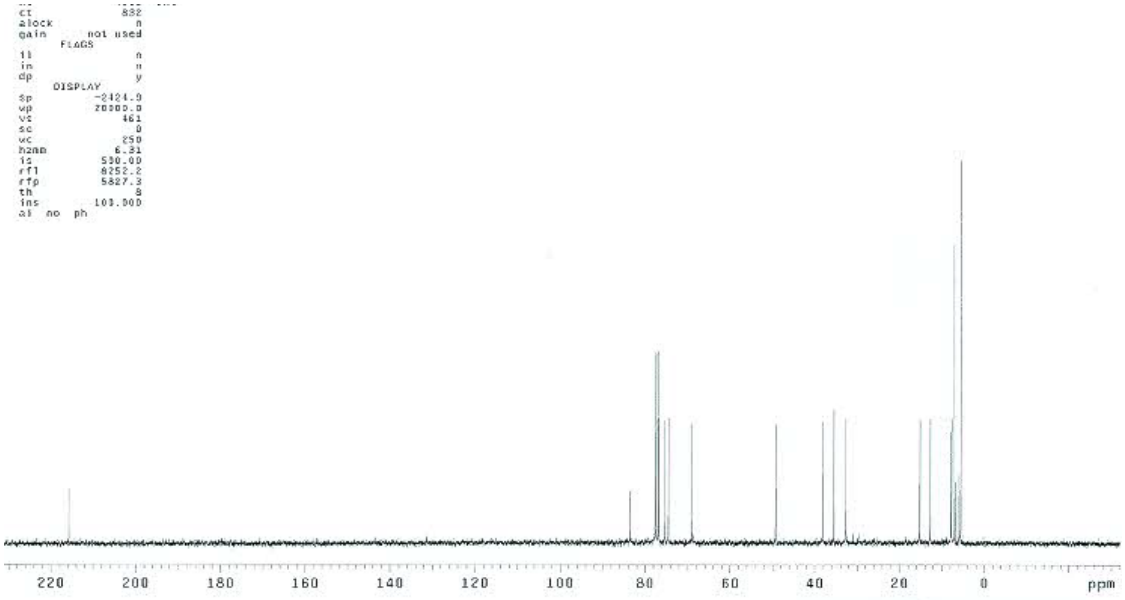


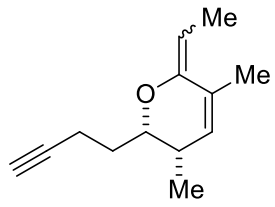
```
pw              6.6
d1                0  werr
d2            1.000  wexp
tof               0  wbs
nt             2030  wnt
ct              734
alock             n
gain      not used
      FLAGS
il                n
in                n
dp                y
    DISPLAY
sp          -2441.6
wp          20000.0
vs              545
sc                0
wc              250
hzmm           0.51
is           500.30
rf1          8251.6
rfp          5810.0
th                8
ins         100.000
al  no  ph
```

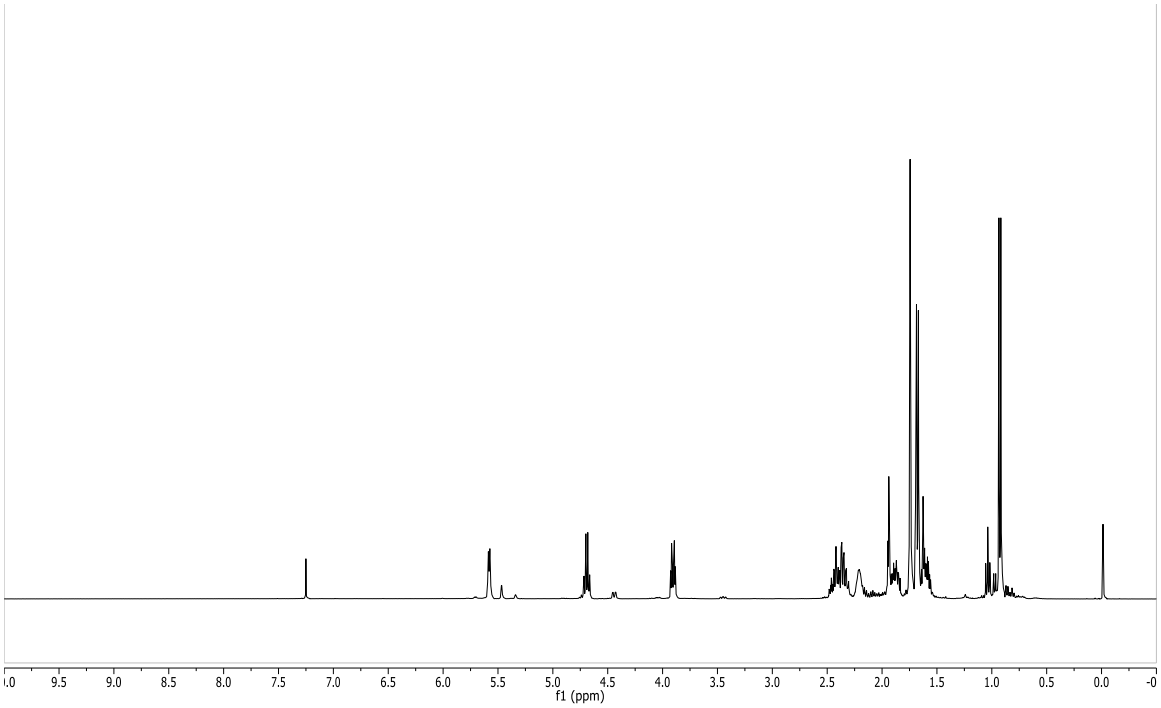


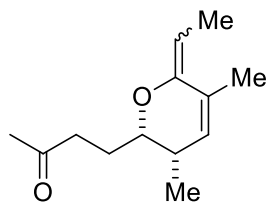

TESO
OH
O
Me
Me
Me

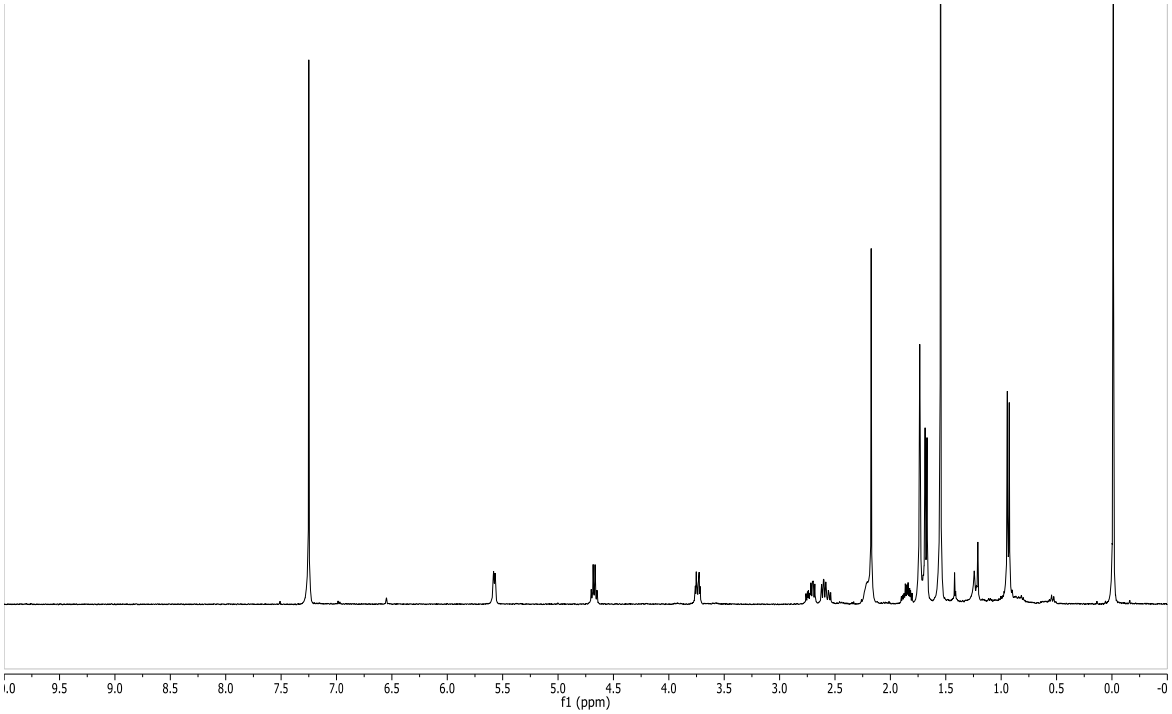

f1 (ppm)

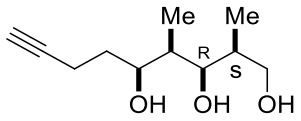

ct 832
alock n
gain not used
FLAGS
ii n
in n
dp y
DISPLAY
sp -2424.9
wp 20000.0
vs 461
sc 0
vc 250
hzmm 6.31
is 530.09
rf1 8252.2
rfp 5827.3
th 8
ins 101.000
ai no ph
ppm

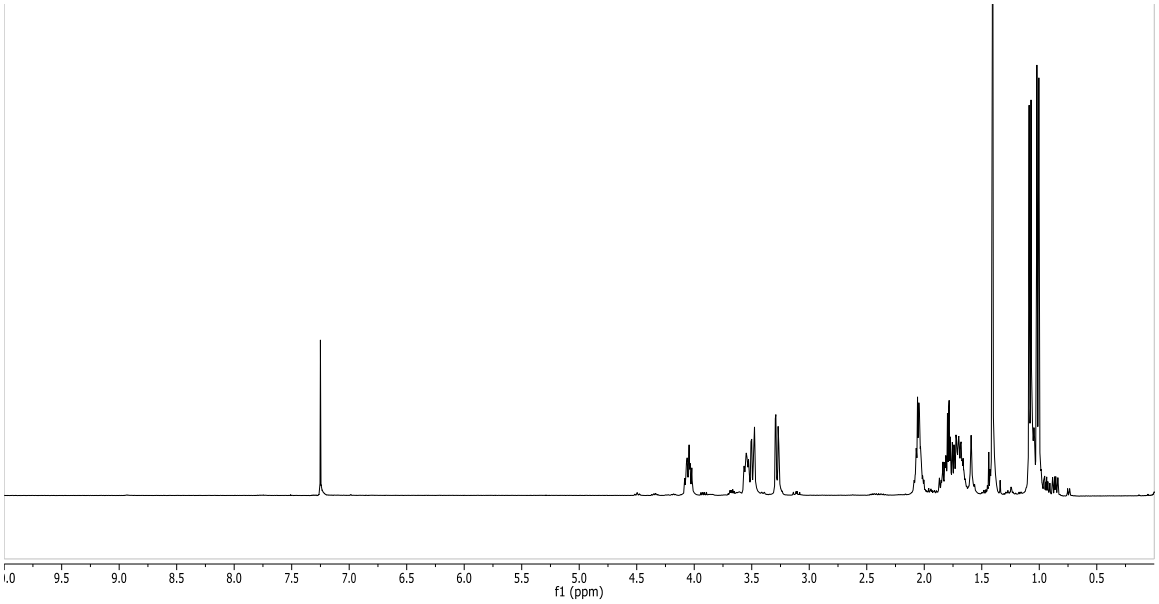

Me
Me
O
Me

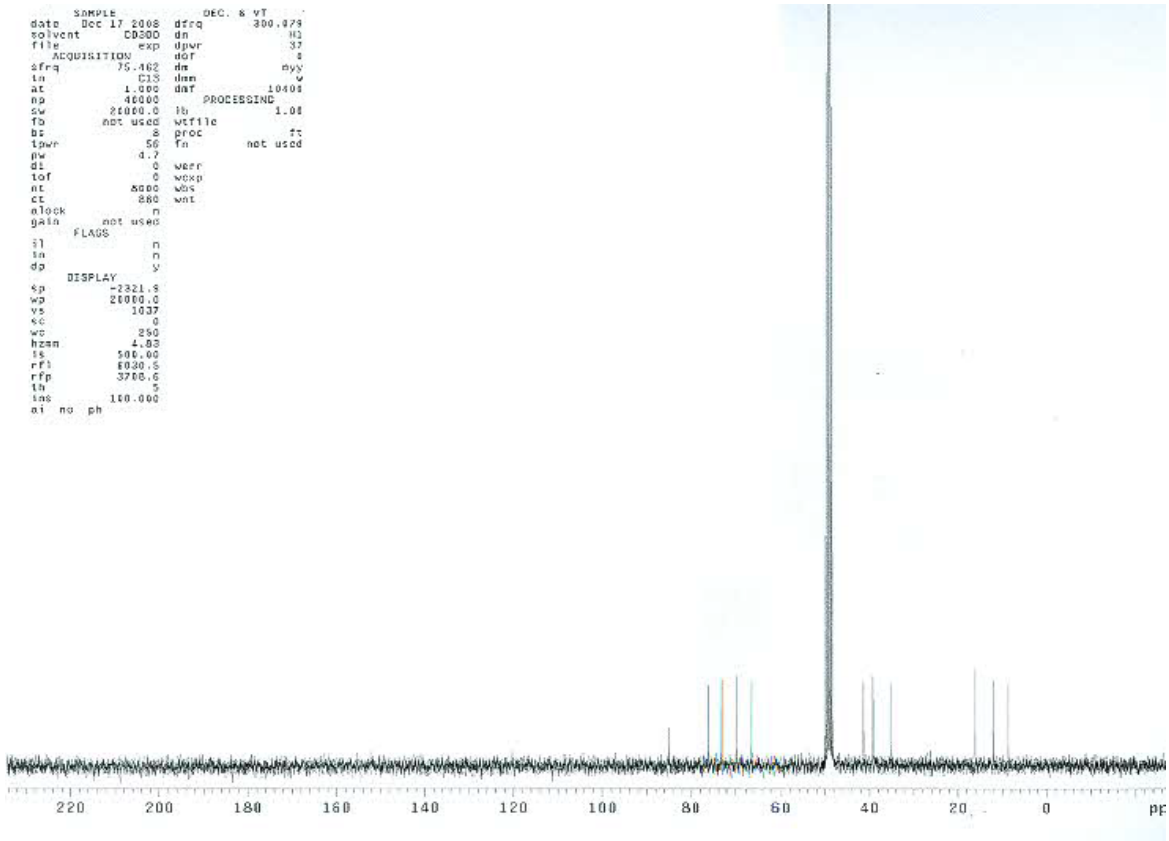

9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


Me
Me
O
O
Me


9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


Me
Me
R
S
OH
OH
OH


f1 (ppm)


SAMPLE
date Dec 17 2008
solvent CD3OD
file exp
ACQUISITION
sfrq 75.462
tn C13
at 1.000
np 40000
sw 21000.0
fb not used
bs 8
tpwr 56
pw 4.7
dl 0
tof 0
nt 5000
ct 880
alock n
gain not used
FLAGS
il n
in n
dp y
DISPLAY
sp -2321.9
wp 20000.0
vs 1037
sc 0
wc 250
hzmm 4.83
ss 500.00
rfl 8030.5
rfp 3706.6
th 5
ins 100.000
ai no ph
DEC. & VT
dfrq 300.079
dn H1
dpwr 37
dof 0
dm nyy
dmm w
dmf 10408
PROCESSING
lb 1.00
wtfile
proc ft
fn not used
werr
wexp
wbs
wnt
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200
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120
100
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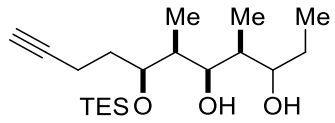
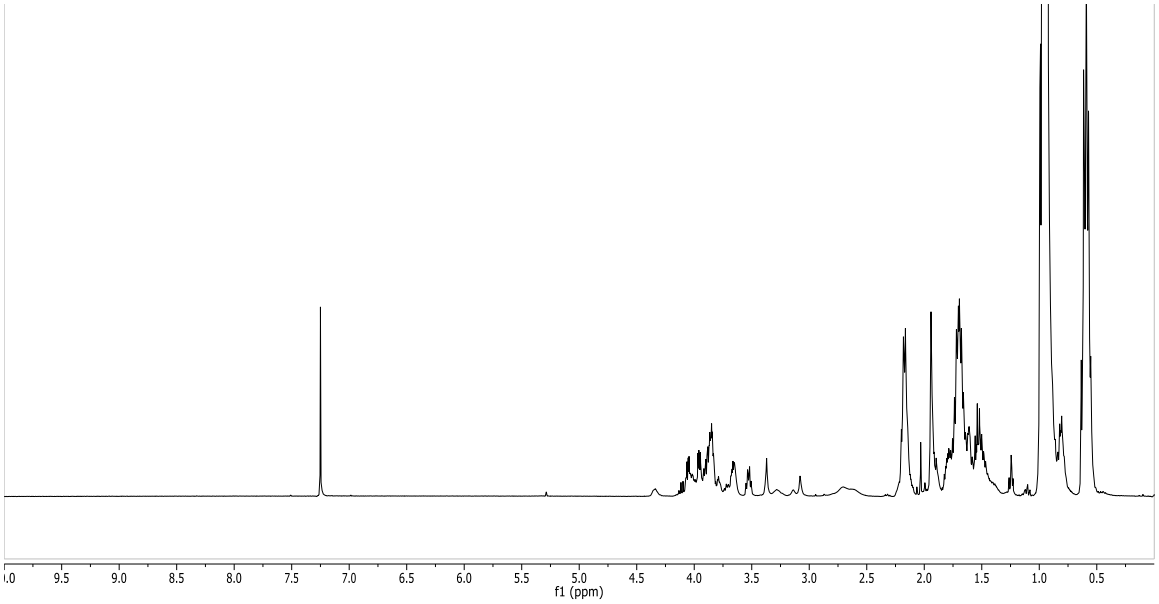
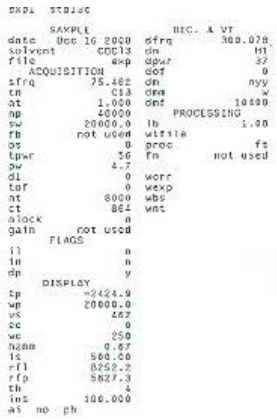
60
40
20
0
pp

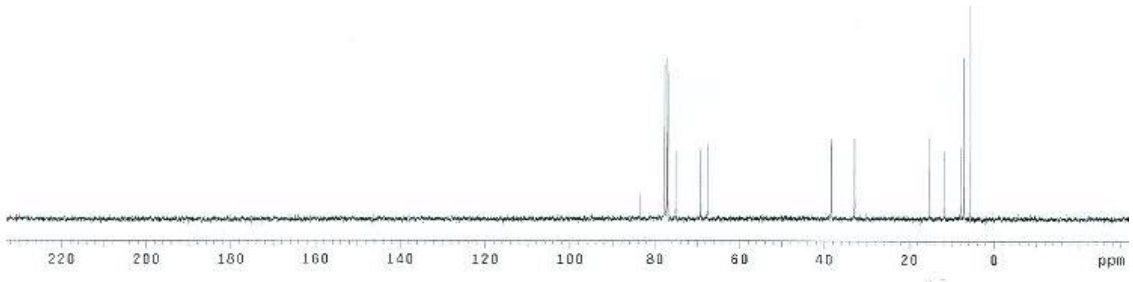


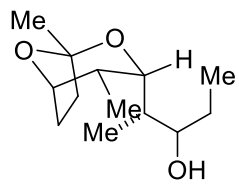


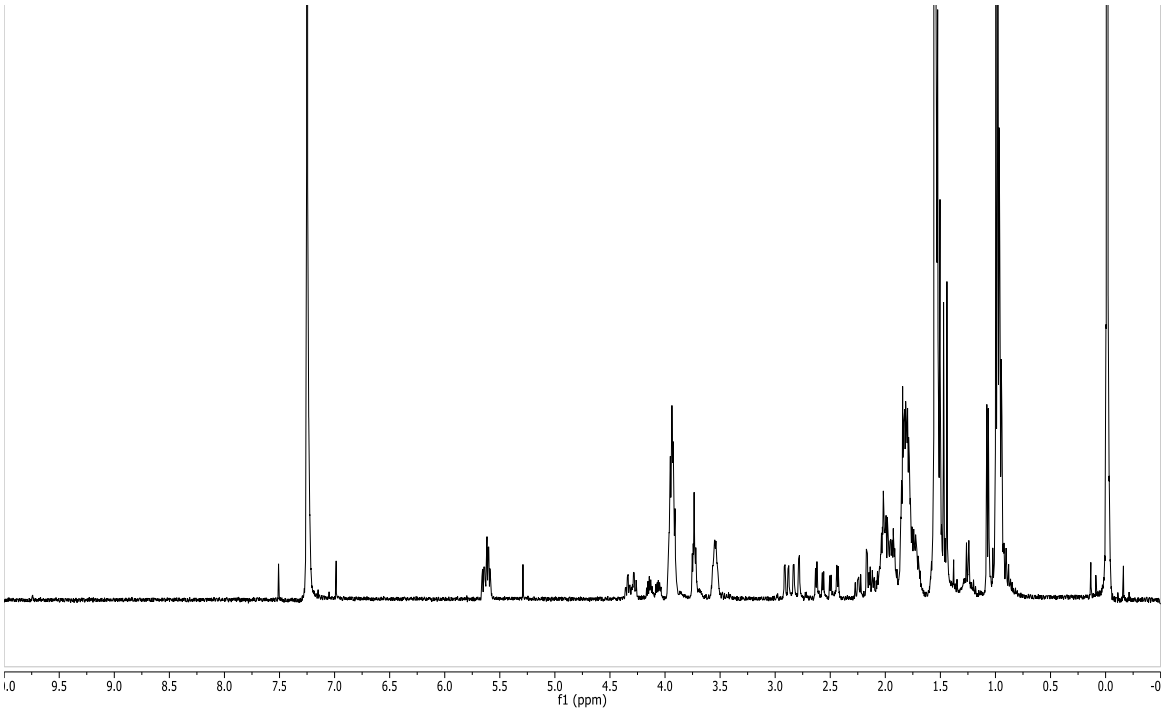


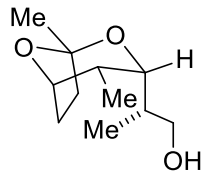
SAMPLE		DEC. & VT	
date	Dec 16 2008	dfrq	300.078
solvent	CDCl3	dn	H1
file	exp	dpwr	37
ACQUISITION		dof	0
sfrq	75.462	dm	nyy
tn	C13	dmm	w
at	1.000	dmf	10000
np	40000	PROCESSING	
sw	20000.0	lb	1.00
fb	not used	wtfile	
bs	8	proc	ft
tpwr	56	fn	not used
pw	4.7		
dl	0	werr	
tof	0	wexp	
nt	8000	wbs	
ct	861	wnt	
alock	n		
gain	not used		
FLAGS			
il	n		
in	n		
dp	y		
DISPLAY			
sp	-2424.9		
wp	20000.0		
vs	462		
sc	0		
wc	250		
hzcm	0.67		
is	500.00		
rfl	8252.2		
rfp	5827.3		
th	4		
ins	100.000		

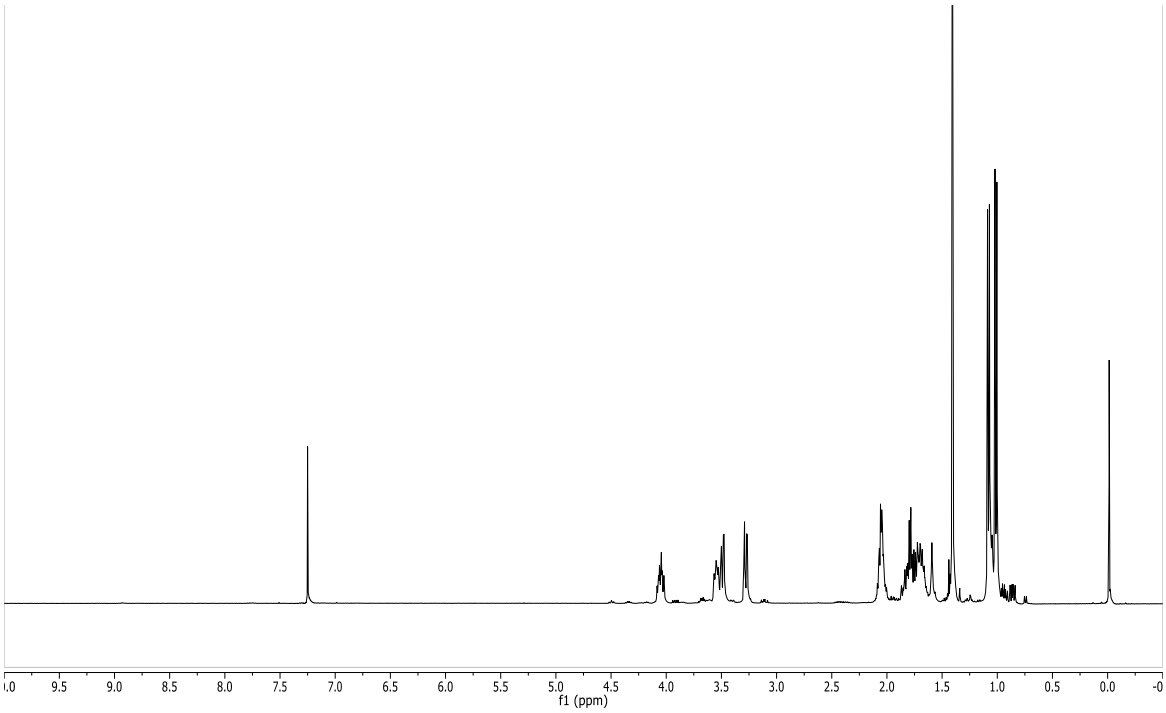
as mp ph

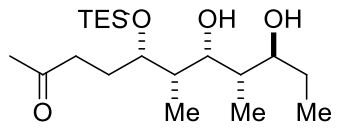


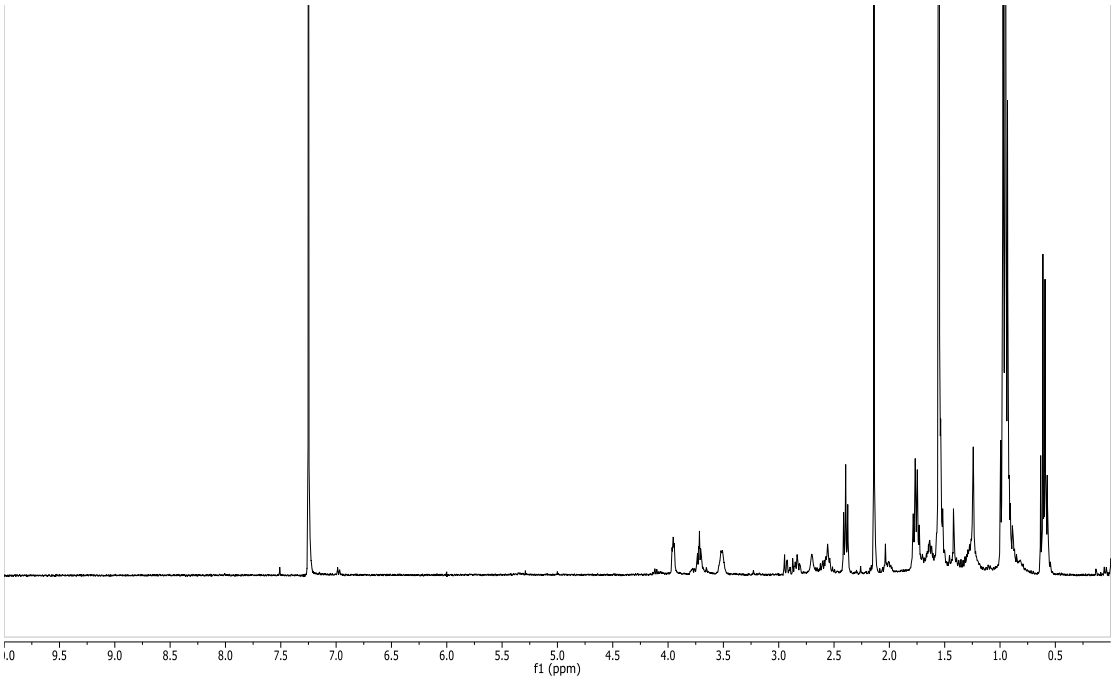

Me
O
O
H
Me
Me
Me
OH

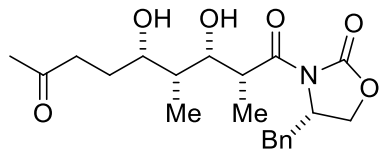

10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0
f1 (ppm)

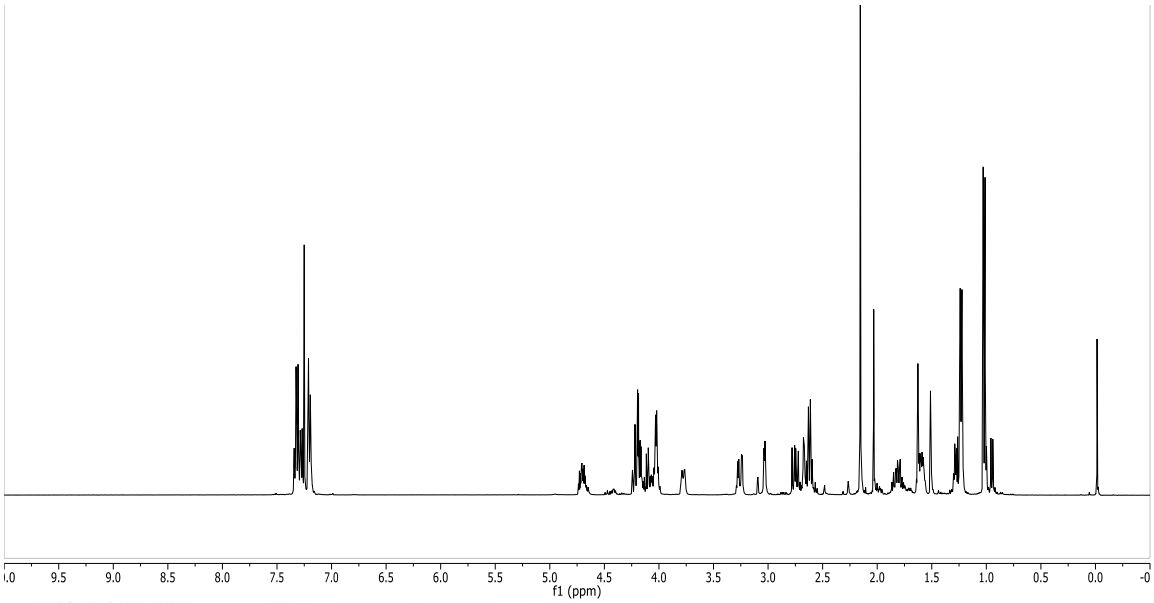

Me
O
O
H
Me
Me
OH

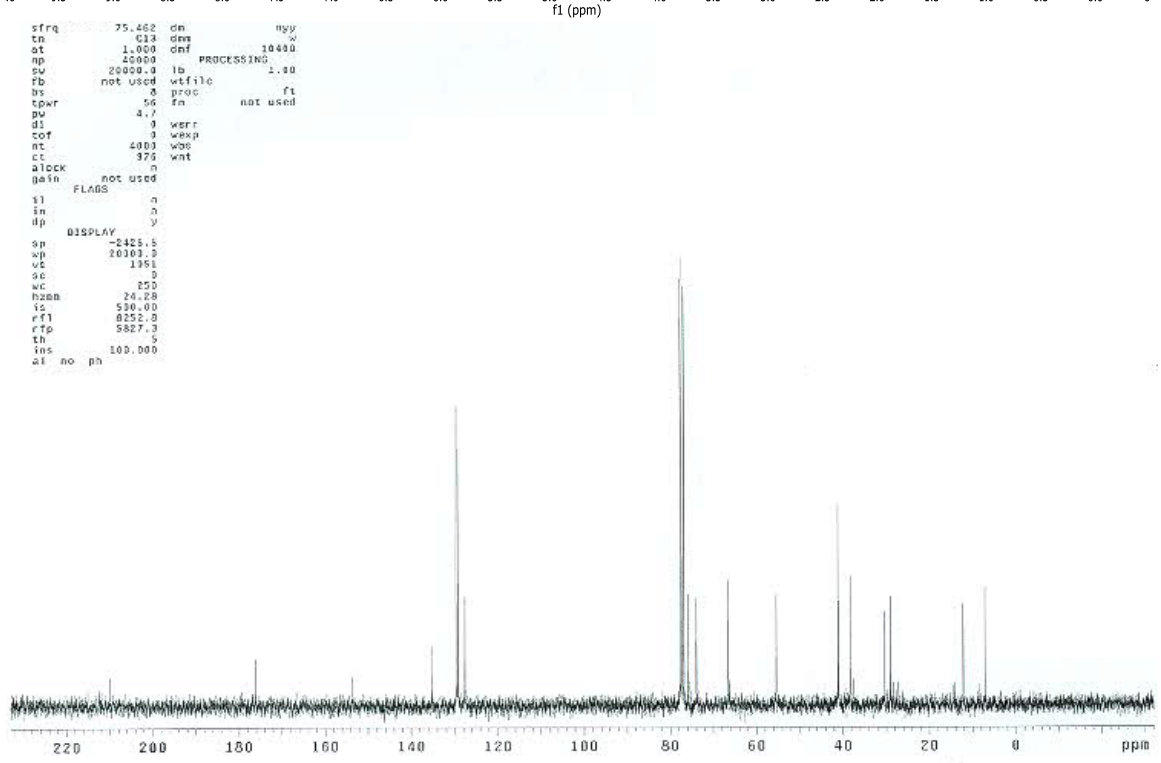

f1 (ppm)

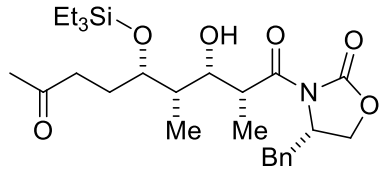

TESO
OH
OH
O
Me
Me
Me

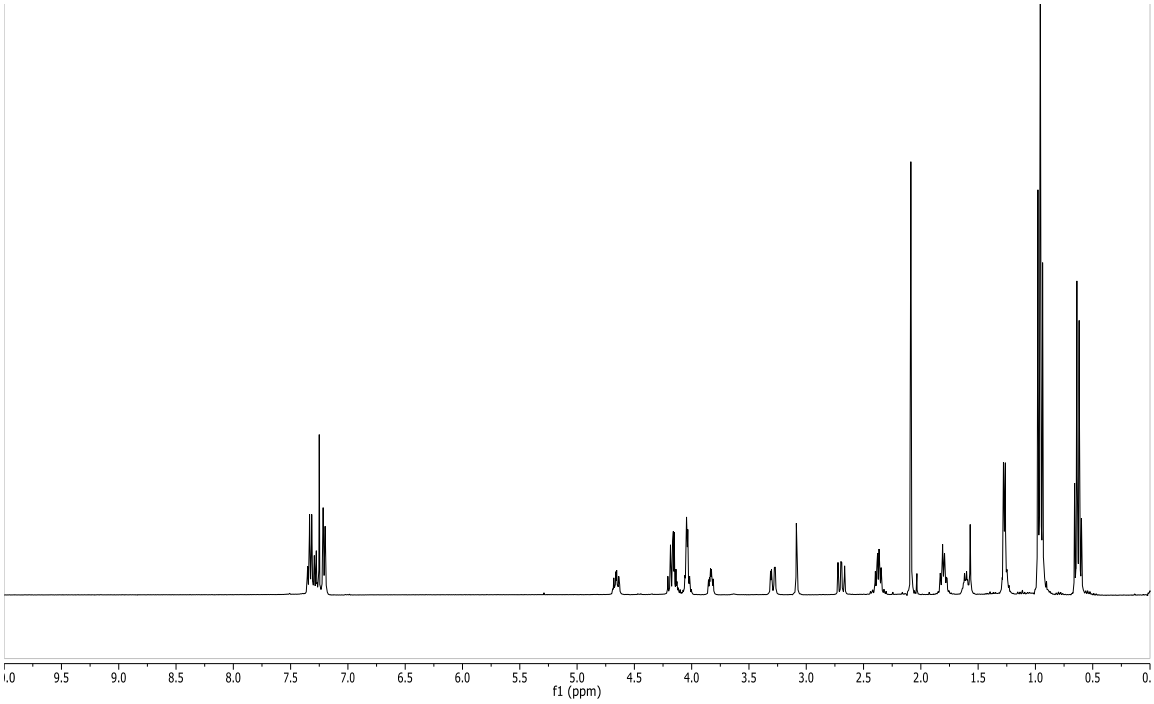

9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

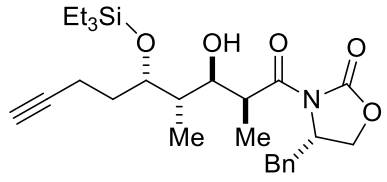

OH
OH
O
O
N
O
O
Me
Me
Bn

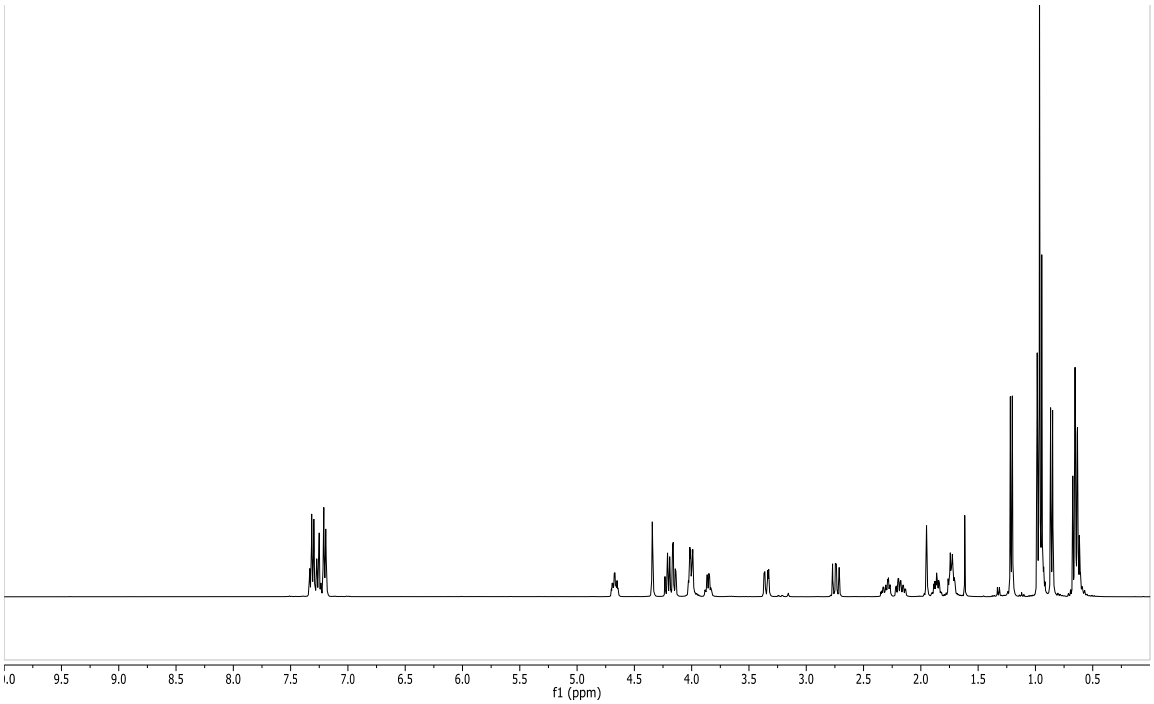

f1 (ppm)

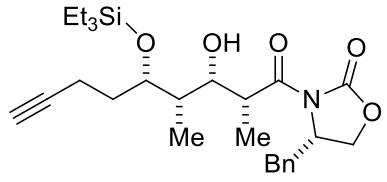

ppm

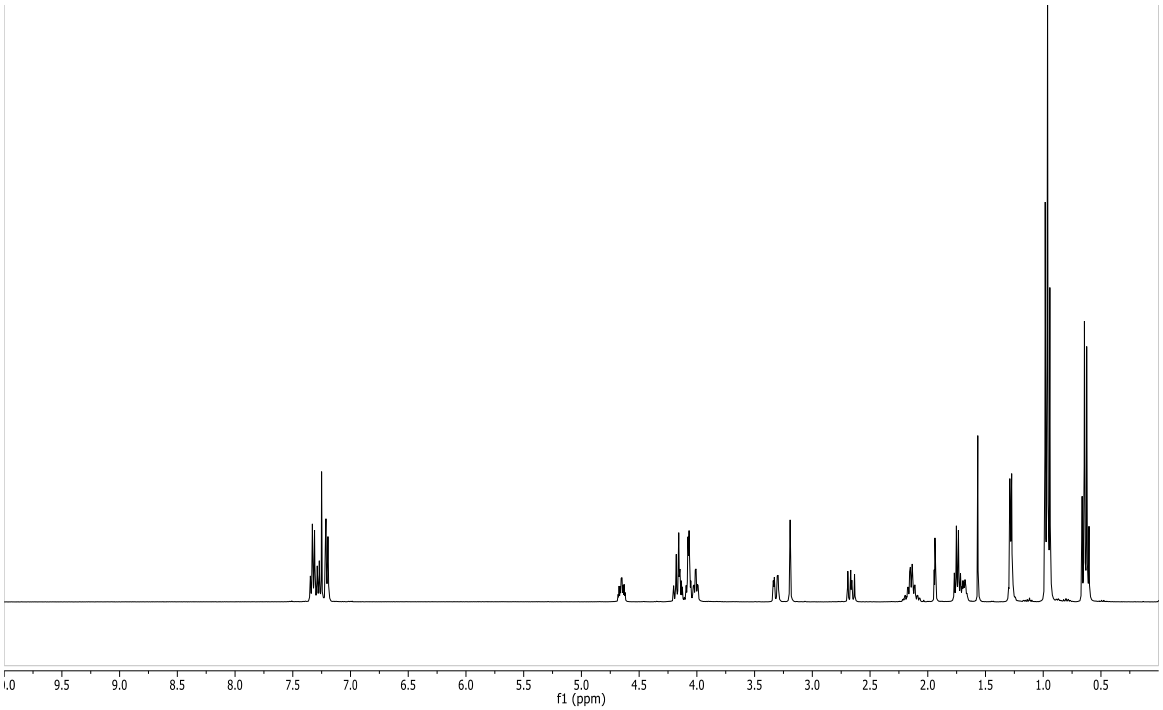

Et3Si
O
OH
O
O
N
O
O
Me
Me
Bn

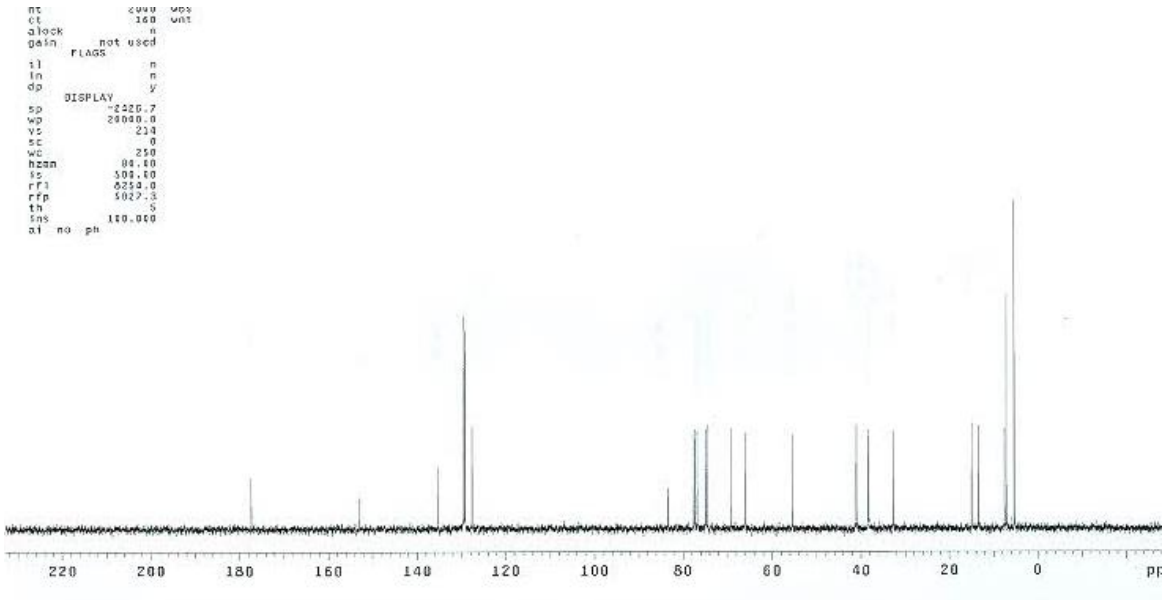

9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


Et3Si
O
OH
O
O
N
O
Me
Me
Bn


10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


Et3Si
O
OH
O
O
N
O
Me
Me
Bn


f1 (ppm)


220
200
180
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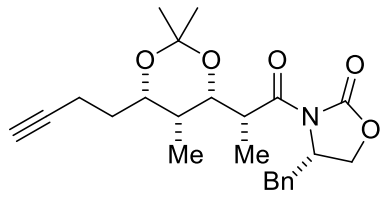
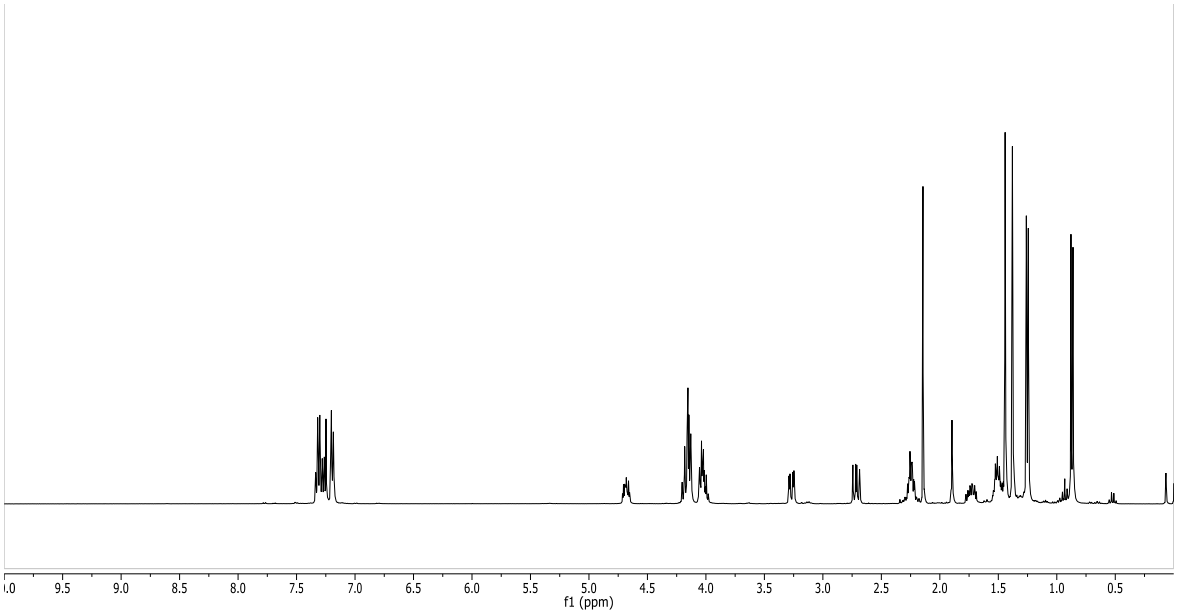
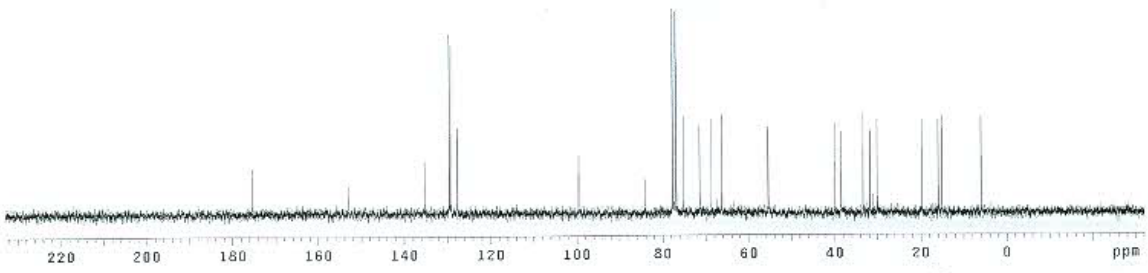
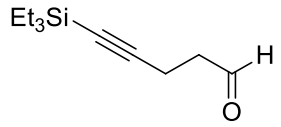
140
120
100
80
60
40
20
0

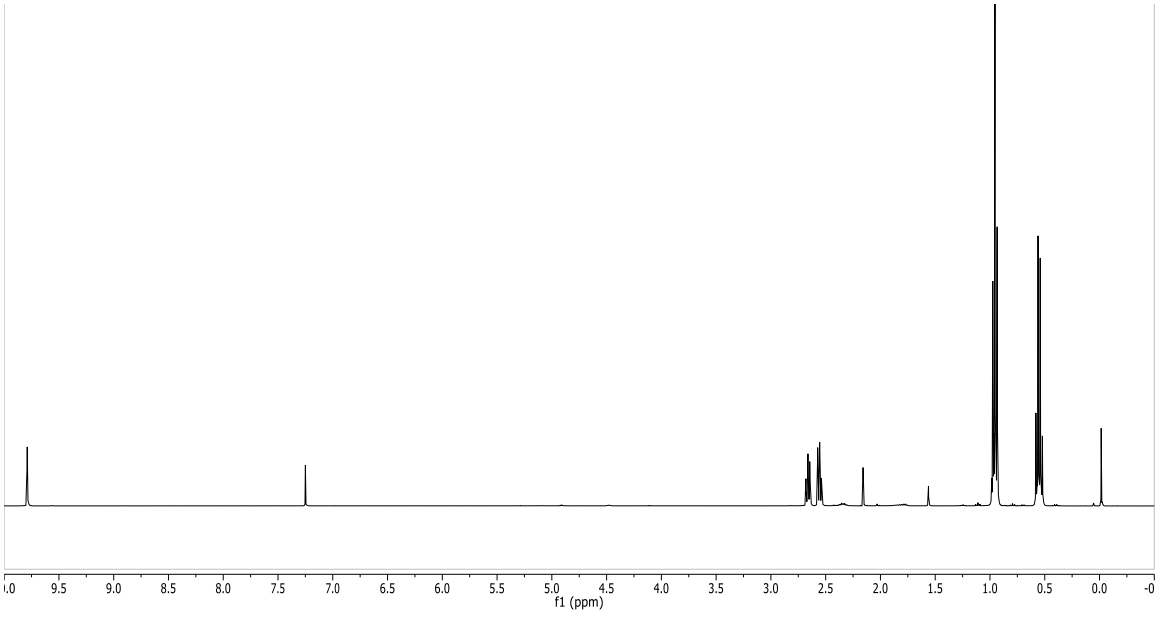

O
O
O
O
N
O
Me
Me
Bn

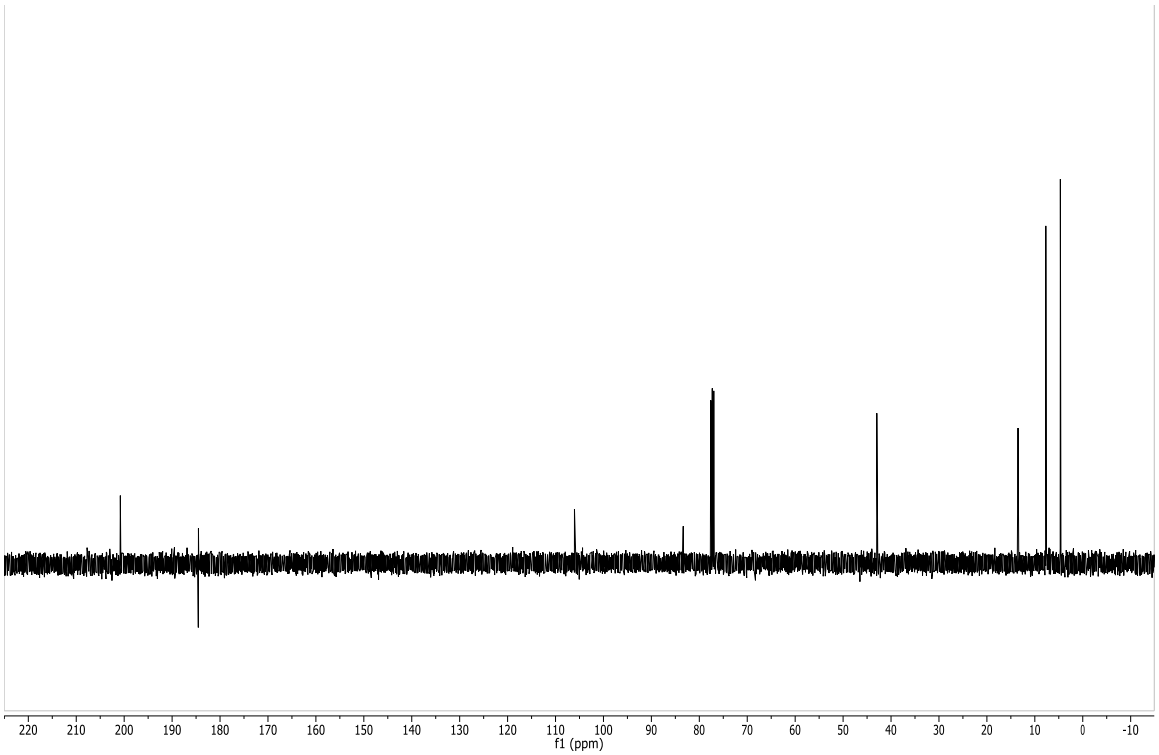

f1 (ppm)

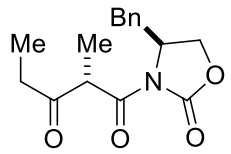

solvent CDCl3
file exp
ACQUISITION
sfrq 75.462
ta 0.13
at 1.090
np 32030
sw 20000.0
fb not used
bs 8
tdwr 56
pw 4.7
d1 0
tof 0
nt 2000
ct 400
alock n
gain not used
FLAGS
il n
in n
dp y
DISPLAY
sp -2426.1
wp 20000.0
vs 559
sc 0
wc 250
hzpp 1.73
ts 503.38
rfl 8253.4
rfp 9827.3
th 5
ins 130.000
al no ph
dn N4
dpwr 37
dof 0
dm nyy
dmm w
dmf 10400
PROCESSING
lb 1.00
wtfile
proc ft
fn not used

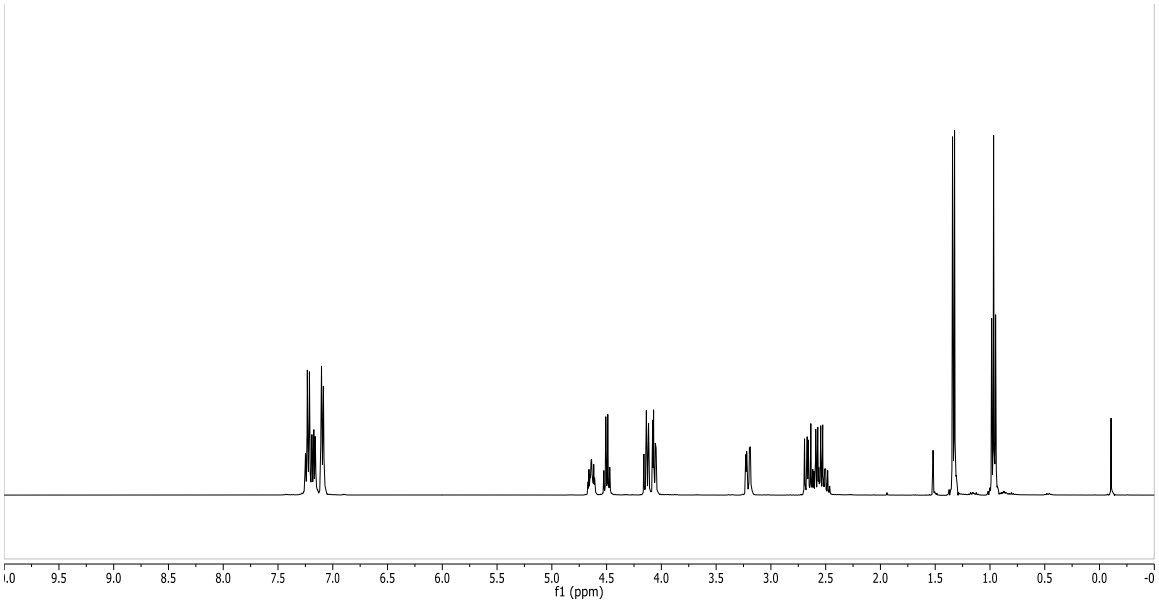

ppm

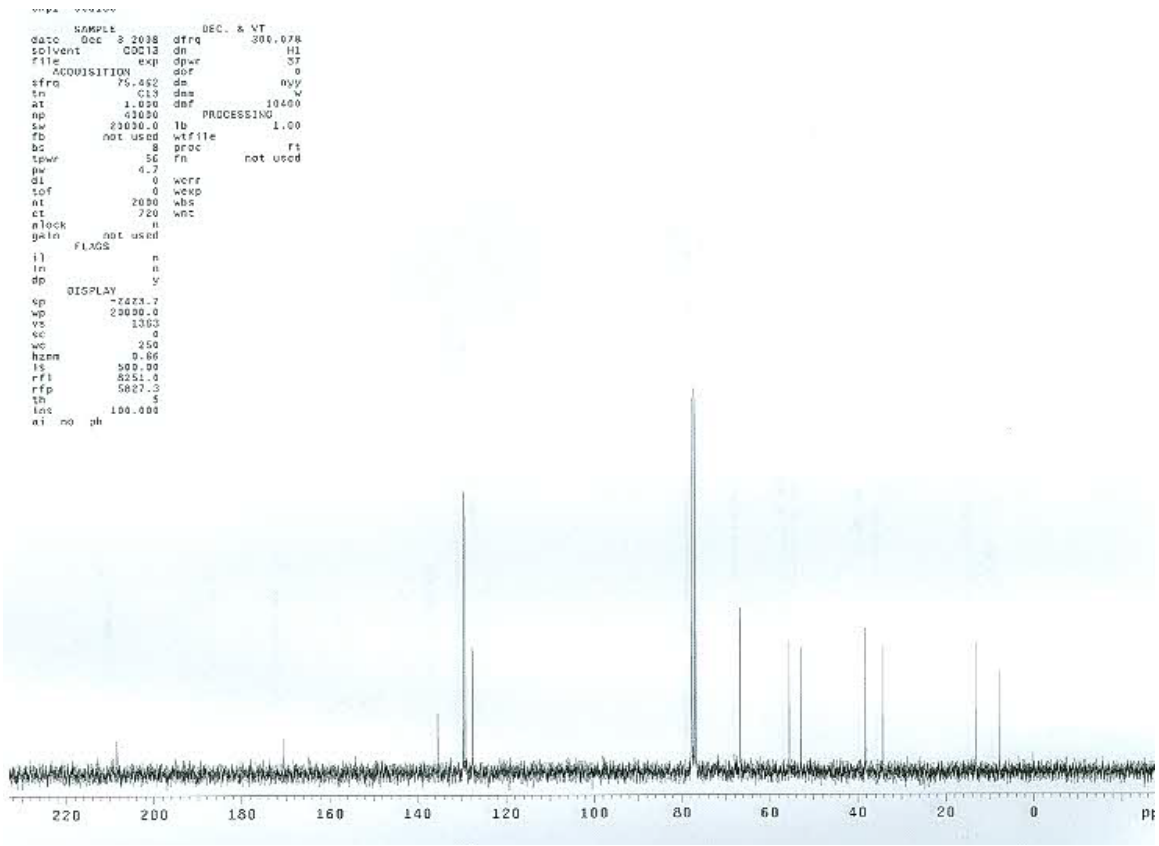

Et3Si
H
O


9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


Bn
Me
Me
N
O
O
O
O


f1 (ppm)


SAMPLE
date Dec 8 2038
solvent CDCl3
file exp
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sfrq 75.462
tn C13
at 1.090
np 43030
sw 23030.0
fb not used
bs 8
tpwr 56
pw 4.7
dl 0
tof 0
nt 2880
ct 720
alock n
gain not used
FLAGS
il n
in n
dp y
DISPLAY
sp -2423.7
wp 23000.0
vs 1363
sc 0
wc 250
hzmm 0.86
is 500.00
rfl 8251.0
rfp 5827.3
th 5
lsfrq 100.600
DEC. & VT
dfrq 300.078
dn H1
dpwr 57
dof 0
dm nyy
dmm w
dmf 10400
PROCESSING
lb 1.00
wtfile
proc ft
fn not used
werr
wexp
wbs
wnt
220
200
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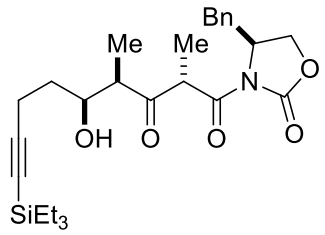
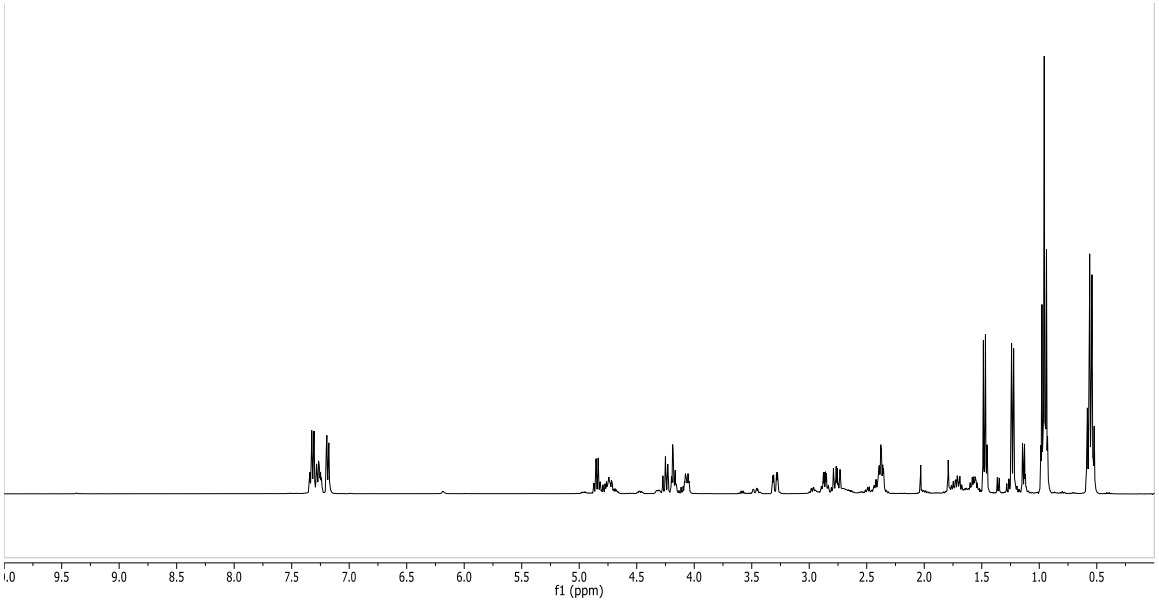
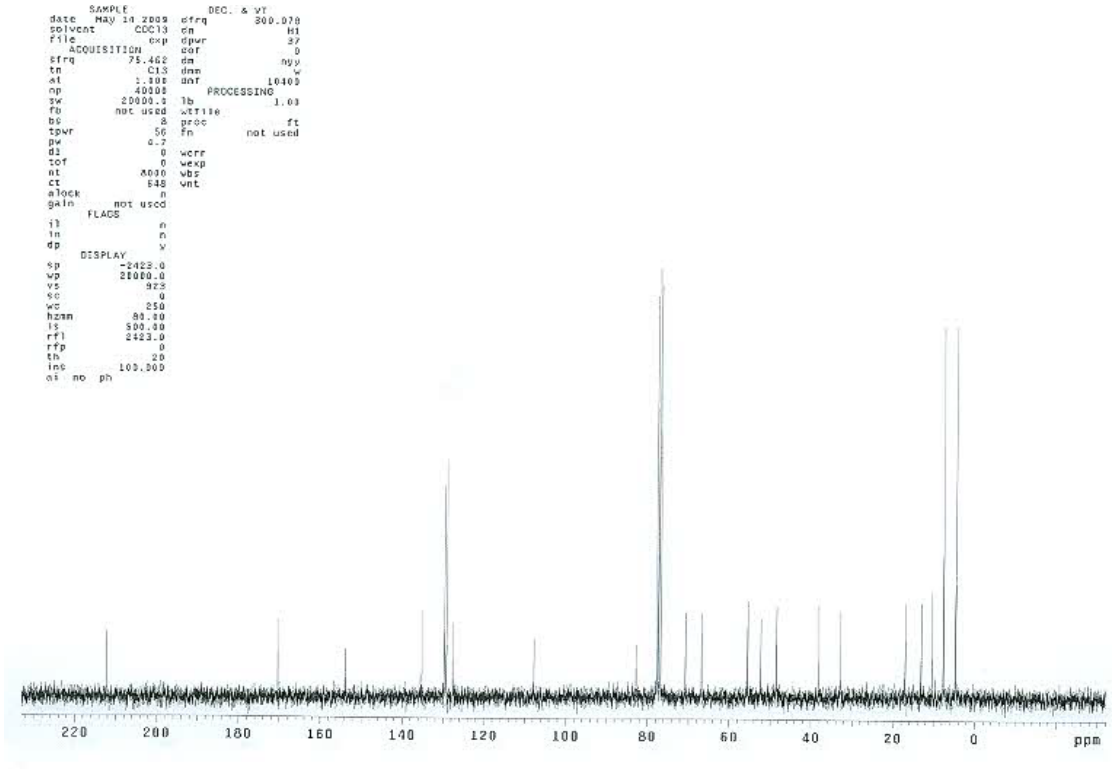
60
40
20
0


Bn
Me
Me
N
O
O
OH
O
O
O
SiEt3


f1 (ppm)


SAMPLE
date May 14 2009
solvent CDCl3
file exp
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sw 20000.3
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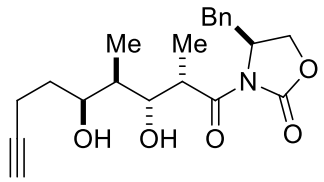
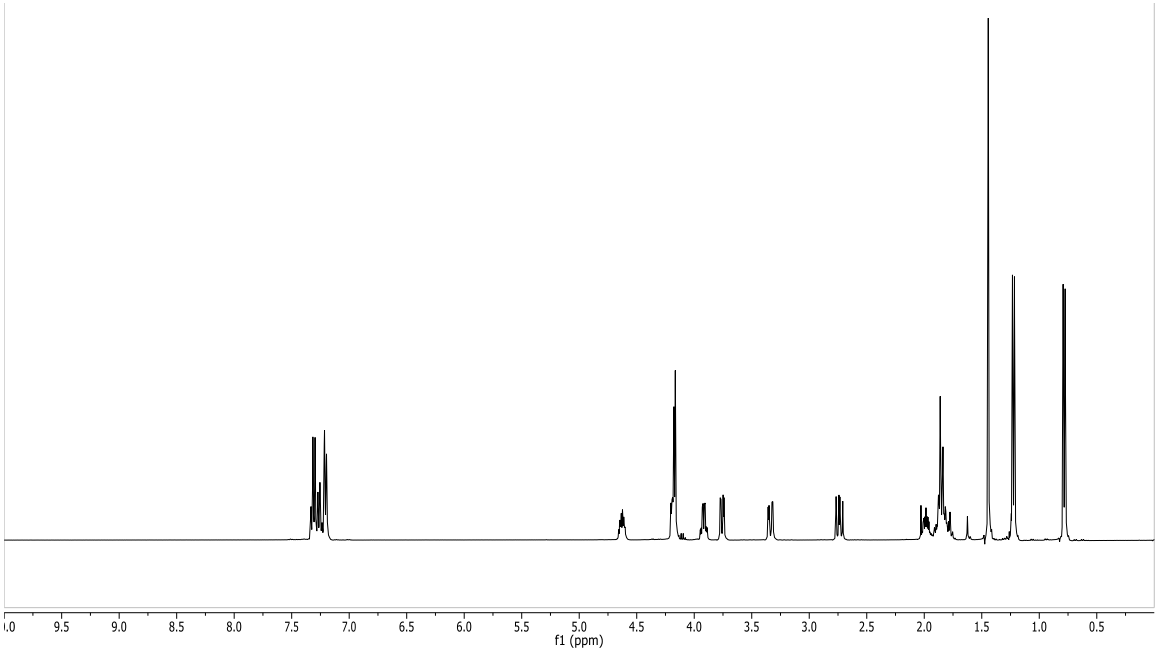
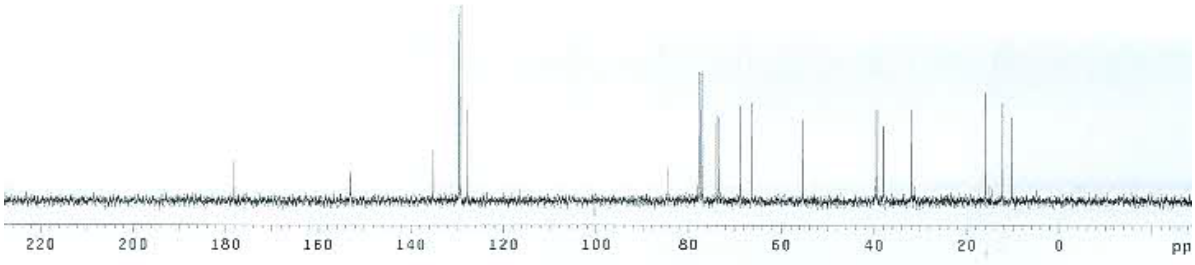
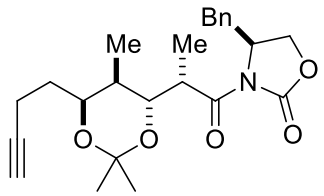
pw 6.7
dl 0
tof 0
nt 4030
ct 648
alock n
gain not used
FLAGS
il n
in n
dp y
DISPLAY
sp -2423.0
wp 20080.0
vs 925
sc 0
wc 250
hzmm 80.30
is 500.00
rfl 2423.0
rfp 0
th 20
ins 100.000
ai no ph
DEC. & VT
sfrq 300.078
tn H1
dpwr 37
dof 0
dm nyy
dmm w
dmf 10409
PROCESSING
lb 1.00
wtfile
proc ft
fn not used
werr
wexp
wbs
wnt
220
200
180
160
140
120
100
80
60
40
20
0
ppm

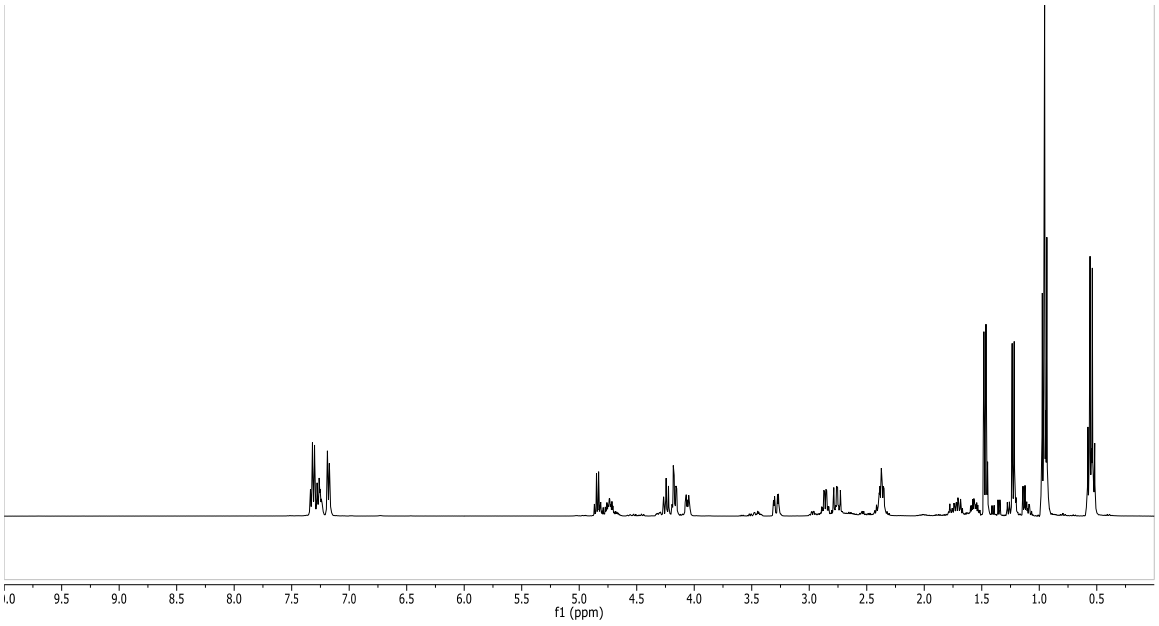




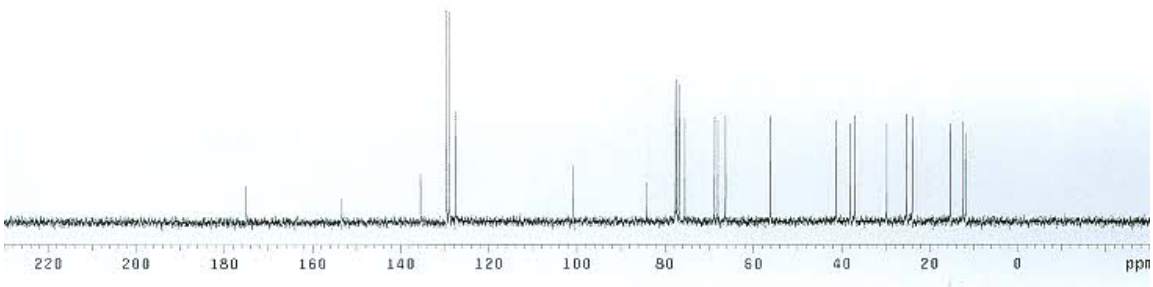

```
tpwr          58  fn       not used
pw           4.7
d1             0  werr
tof            0  wexp
nt          8000  wbs
ct           208  wnt
alock          n
gain     not used
     FLAGS
il             n
in             n
dp             y
    DISPLAY
sp       -2426.1
wp       20000.0
vs           288
sc             0
wc           250
hzcm        0.59
is        500.00
rfl       8253.4
rfp       5827.3
th             5
lns       101.000
al  ne  ph
```

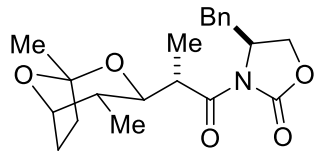


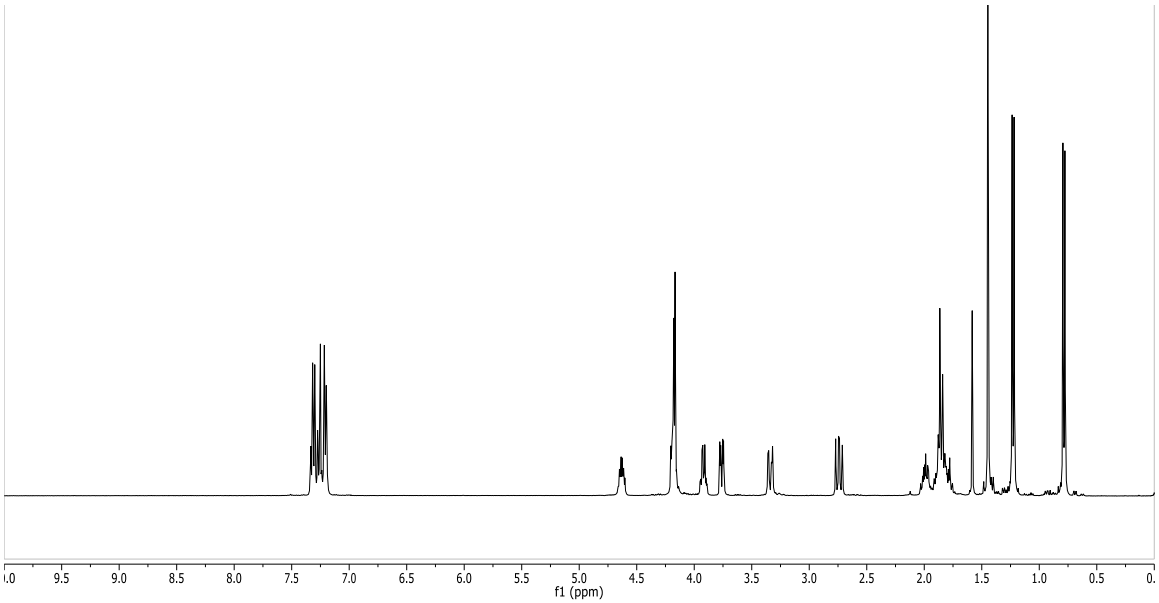


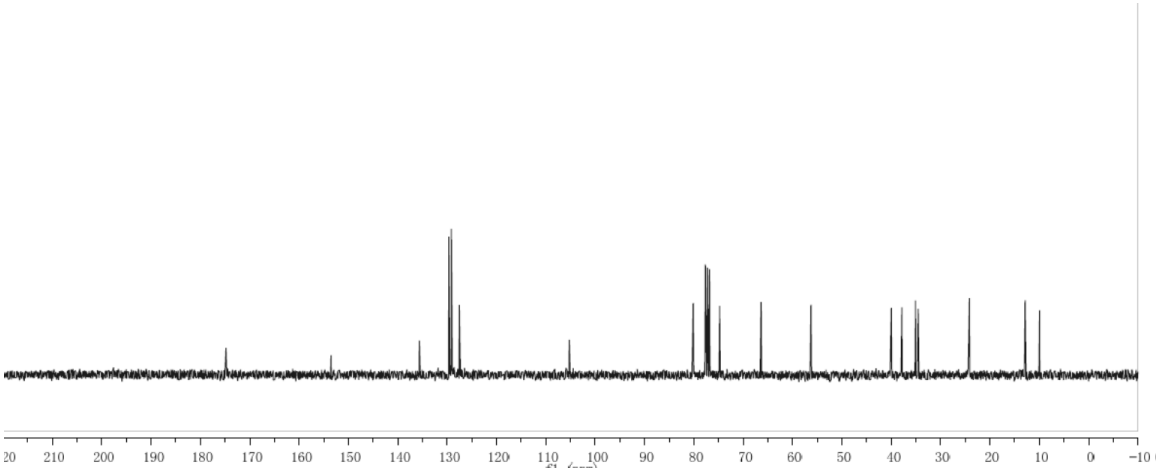


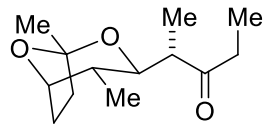

```
      SAMPLE                  DEC. & VT
date    Dec 10 2008   dfrq        301.67B
solvent       CDCl3   dn               H1
file            exp   dpwr             57
   ACQUISITION        dof               0
sfrq         75.462   dm              nyy
tn              C13   dmm              W
at            1.000   dmf          10400
np            40000       PROCESSING
sw         20000.0    lb            1.00
fb        not used    wtfile
bs                0   proc             ft
tpwr             56   fn        not used
pw              4.7
d1                1   werr
tof               0   wexp
nt             8000   wbs
ct              584   wnt
alock             n
gain      not used
      FLAGS
ii                n
in                n
dp                y
      DISPLAY
sp         -2426.1
wp         20000.0
vs             802
sc               0
wc             250
hzmm          0.50
is          500.00
rfl         8253.4
rfp         5827.3
th                5
ins         100.000
as  nn  ph
```

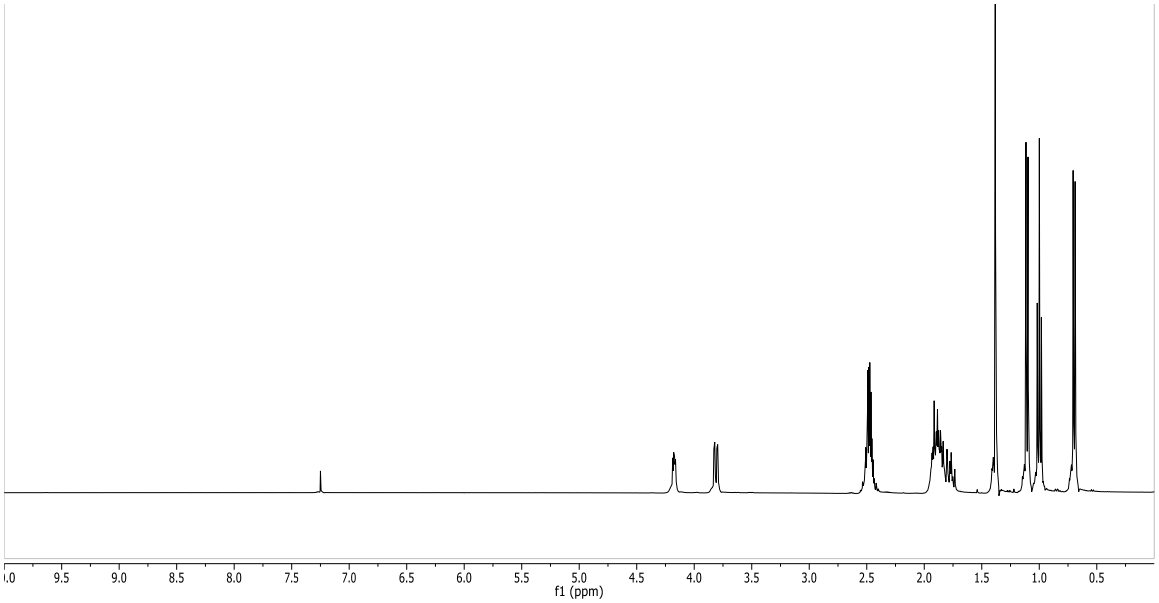


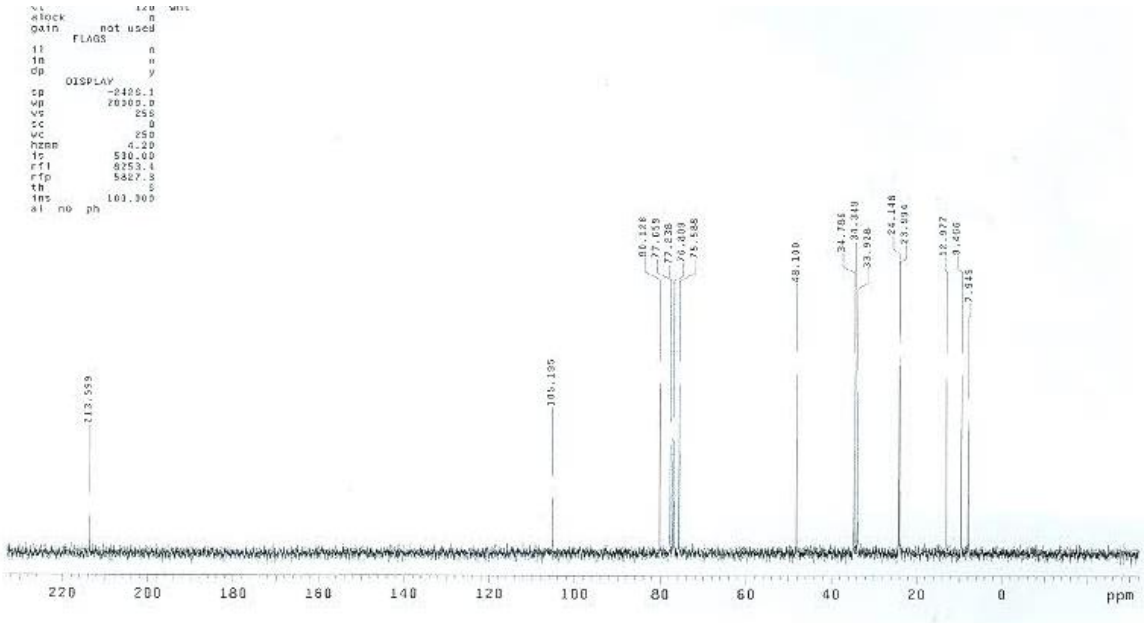

Bn
Me
Me
O
O
N
O
Me
O
O

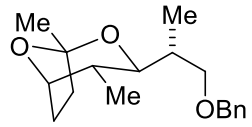

f1 (ppm)

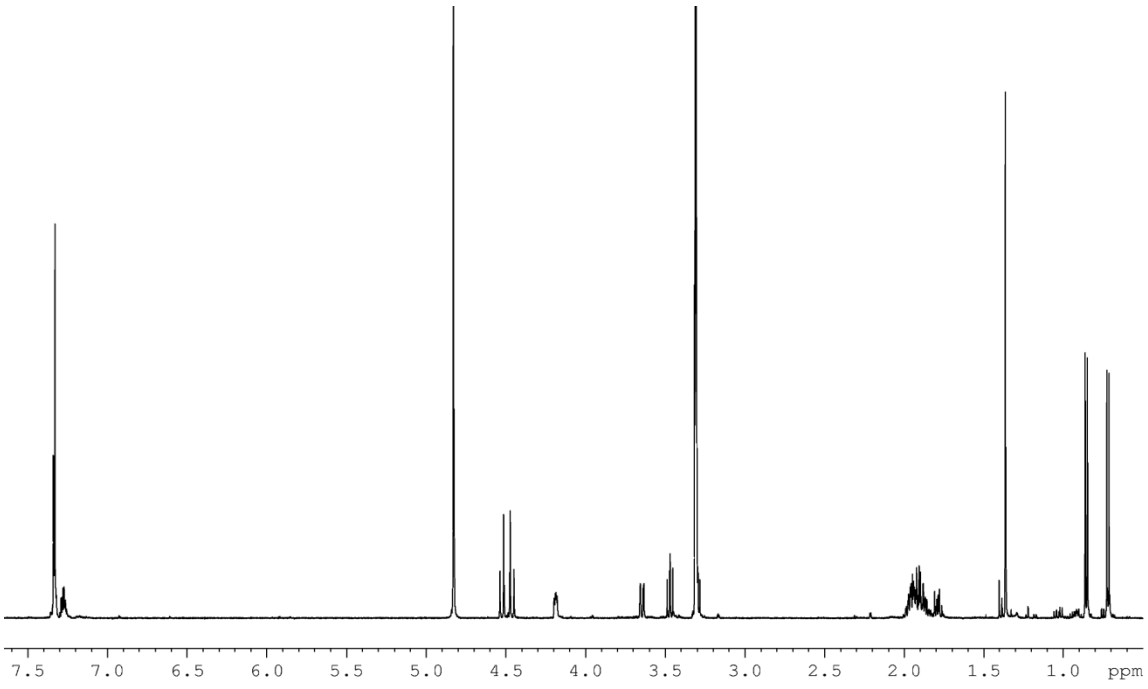


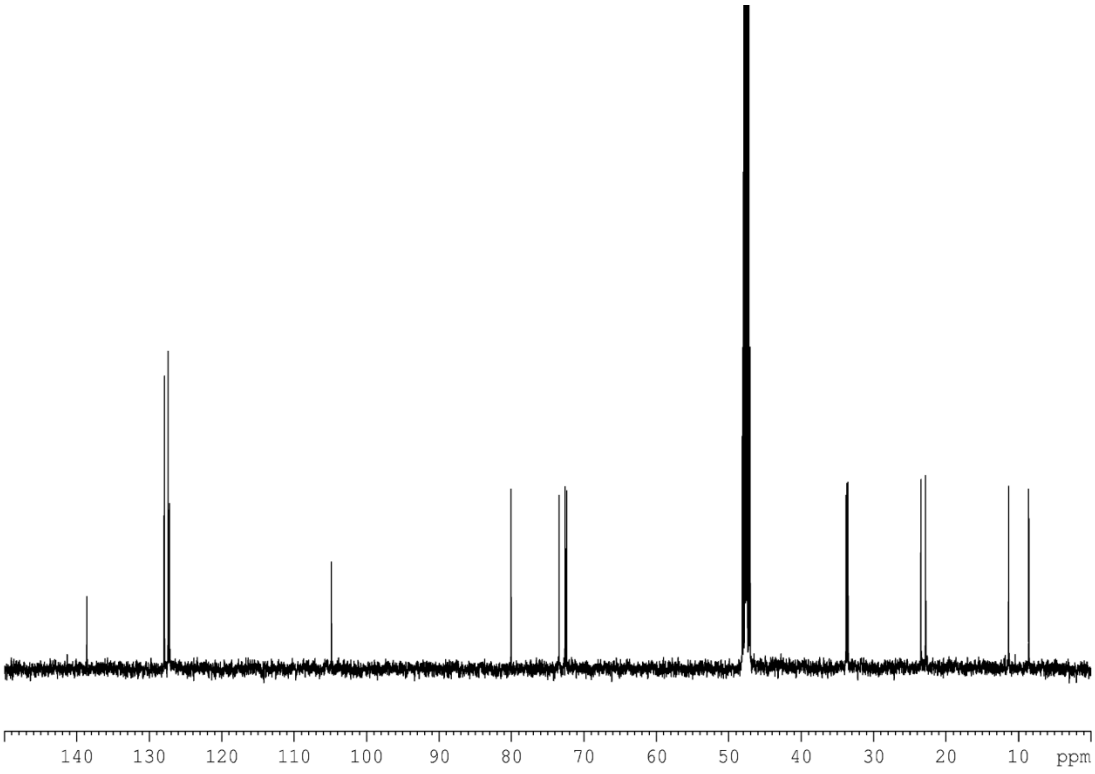

Me
O
O
Me
Me
Me
O

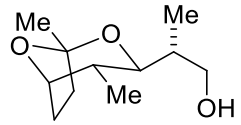

f1 (ppm)

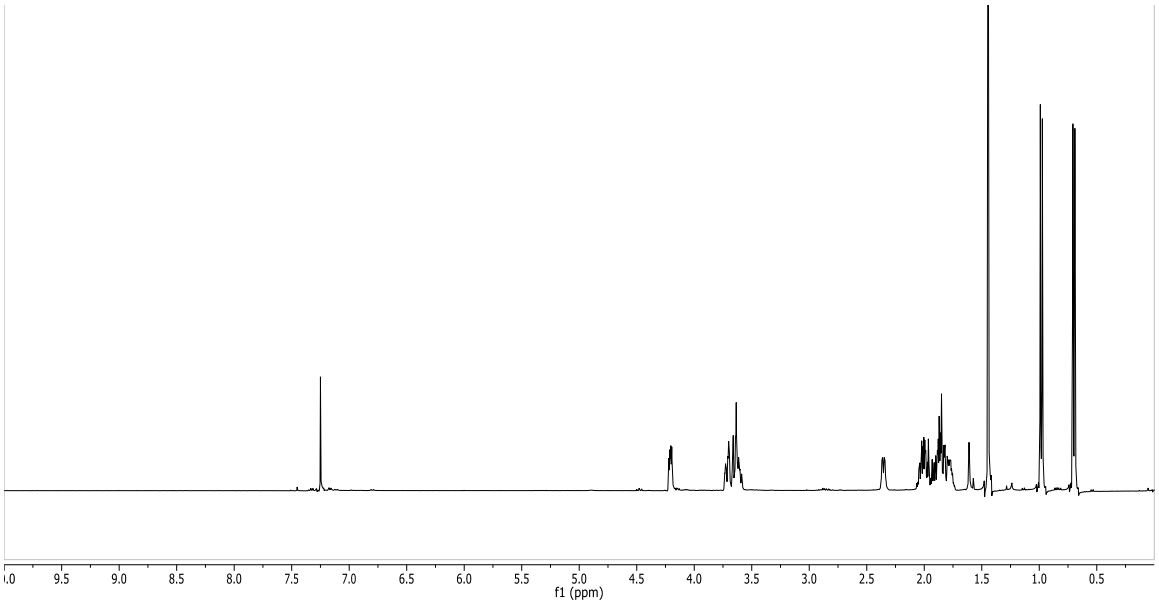

213.559
105.195
77.659
77.238
76.809
48.130
34.786
33.928
24.148
23.596
12.977
9.466
ppm

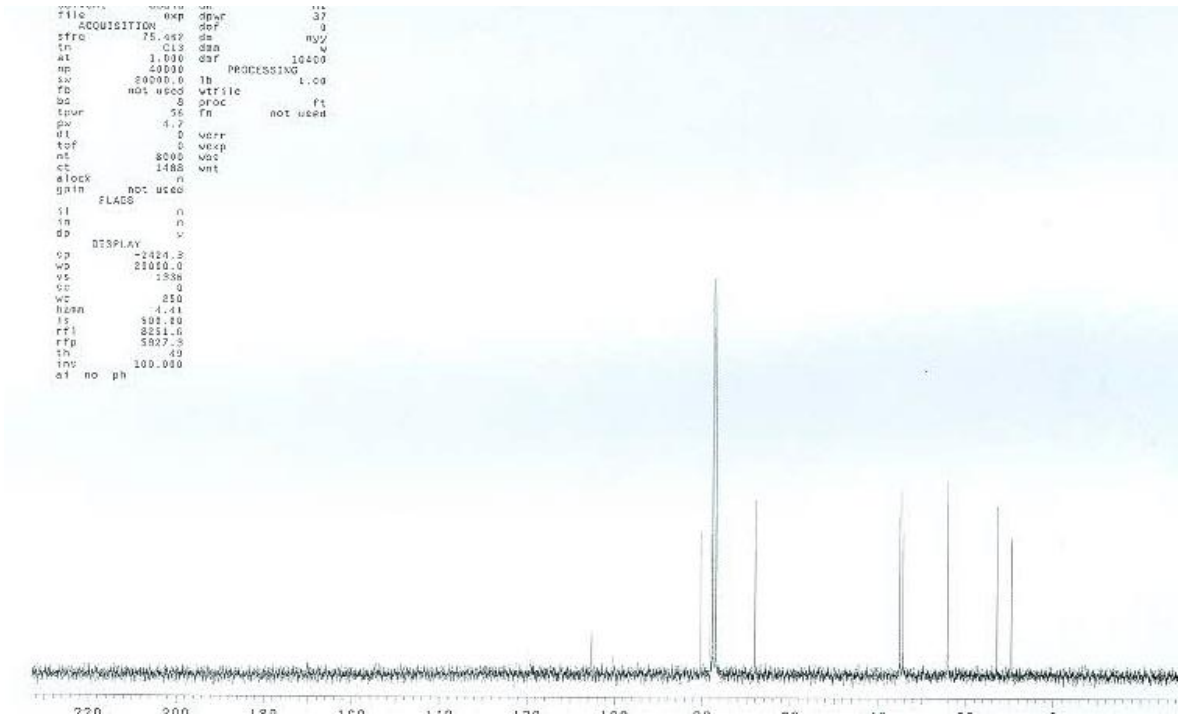

Me
O
O
Me
Me
OBn

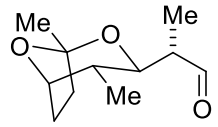

7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

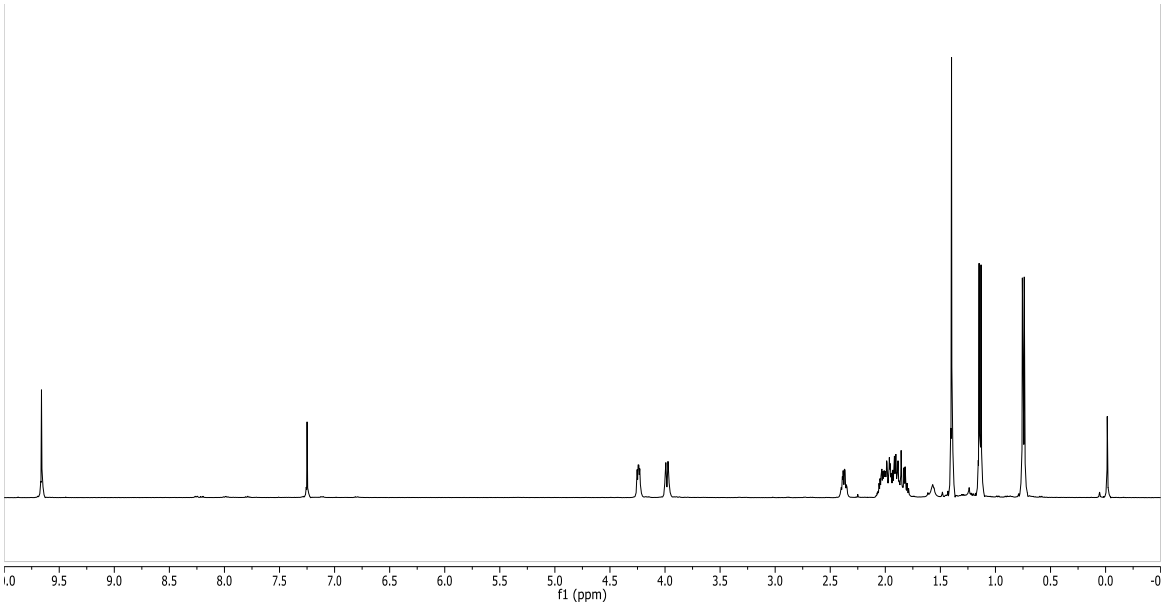

140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


Me
O
O
Me
Me
OH

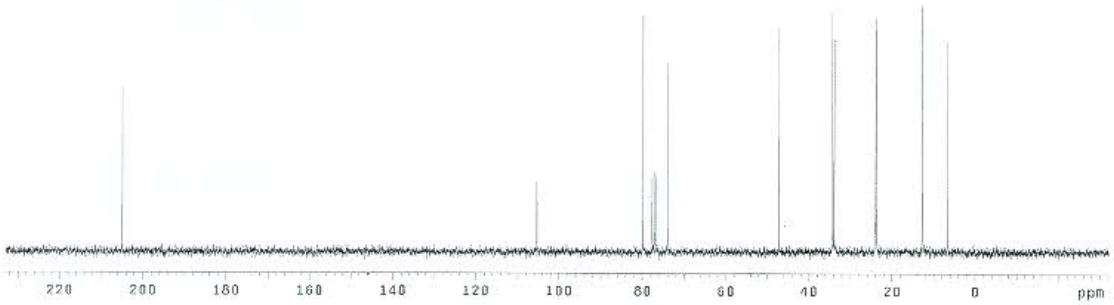

f1 (ppm)

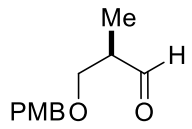


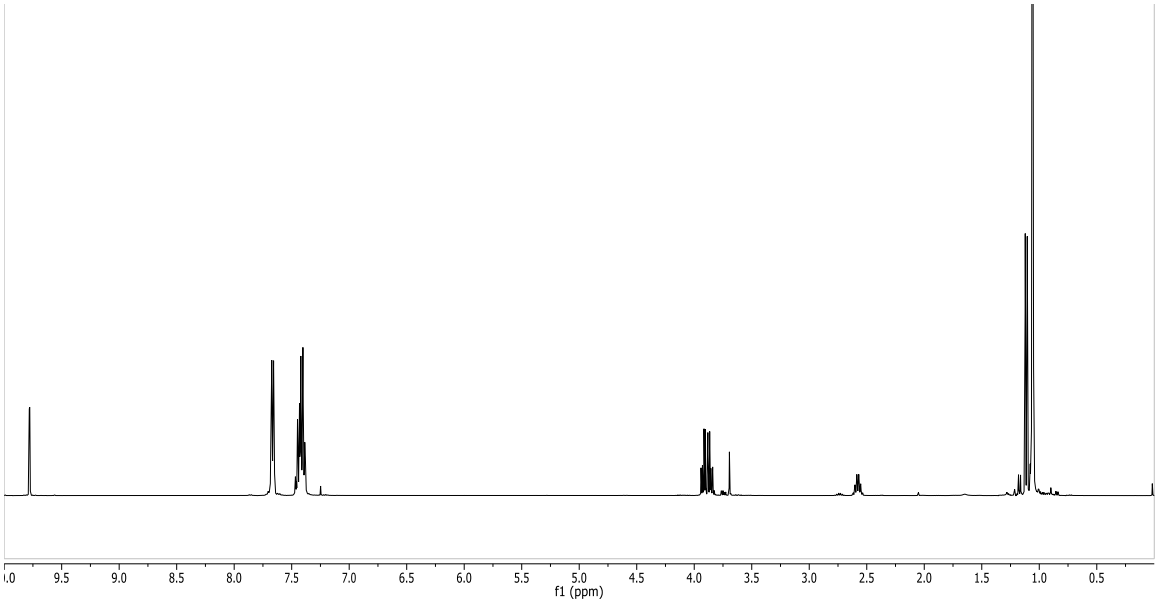


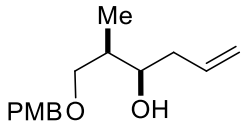


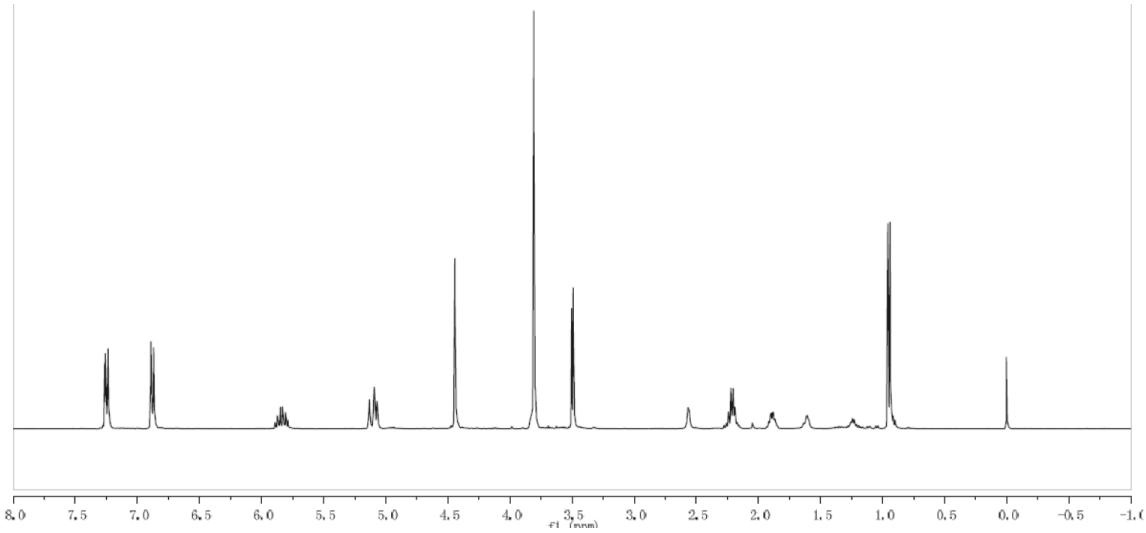

```
expl  std13c
        SAMPLE              DEC. & VT
date   Jan  7 2003  dfrq          300.078
solvent       CDCl3  dn               H1
file             exp  dpwr             37
    ACQUISITION       dof               0
sfrq         75.467  dm              nyy
tn             C13  dmm               w
at           1.303  dmf           10400
np          40000      PROCESSING
sw        20000.3  lb              1.00
fb        not used  wtfile
bs              8  proc              ft
tpwr           55  fn          not used
pw            4.7
d1              1  werr
tof             1  wexp
nt           5001  wbs
ct             80  wnt
block           n
gain       not used
      FLAGS
sl              n
sh              n
dp              y
     DISPLAY
sp         -2428.5
wp         20000.0
vs             166
sc               0
wc             250
hzcm          1.26
is          500.00
rfl         5255.9
rfp         5827.3
th               11
ins         100.000
al  no  ph
```

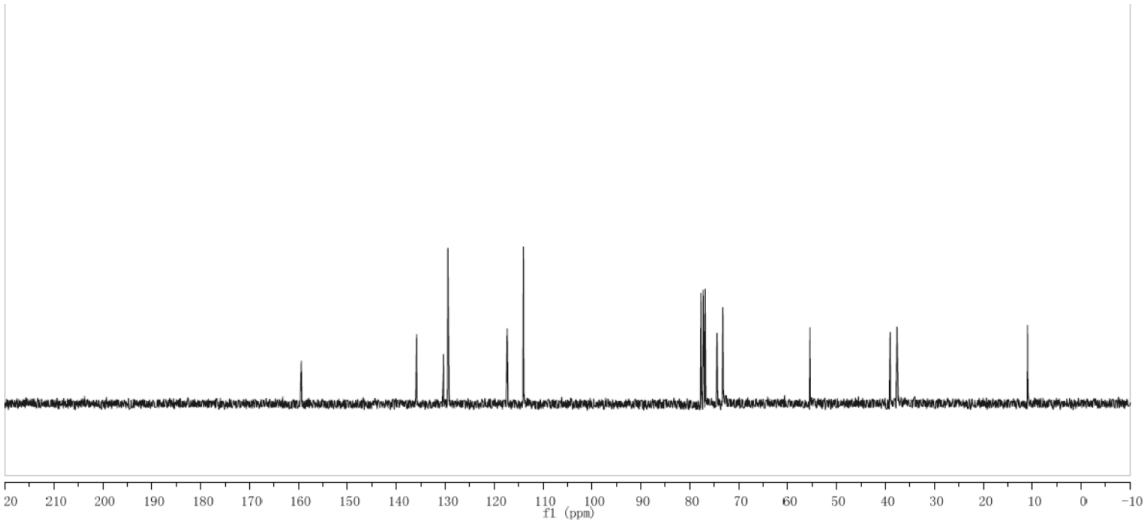


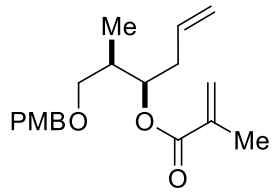

Me
H
PMBO
O

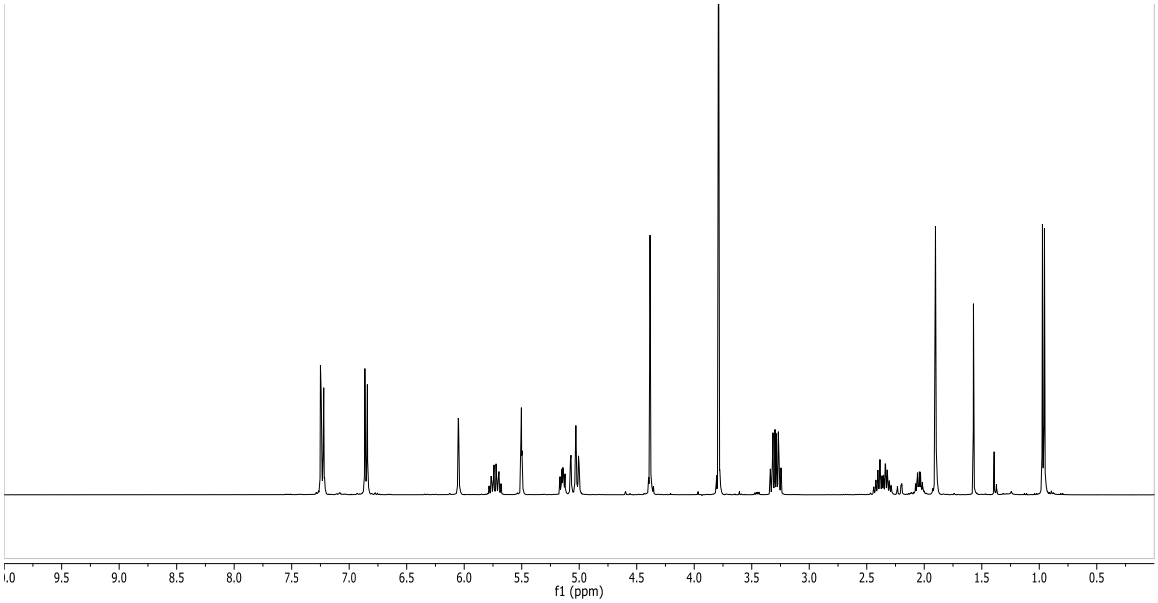

9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

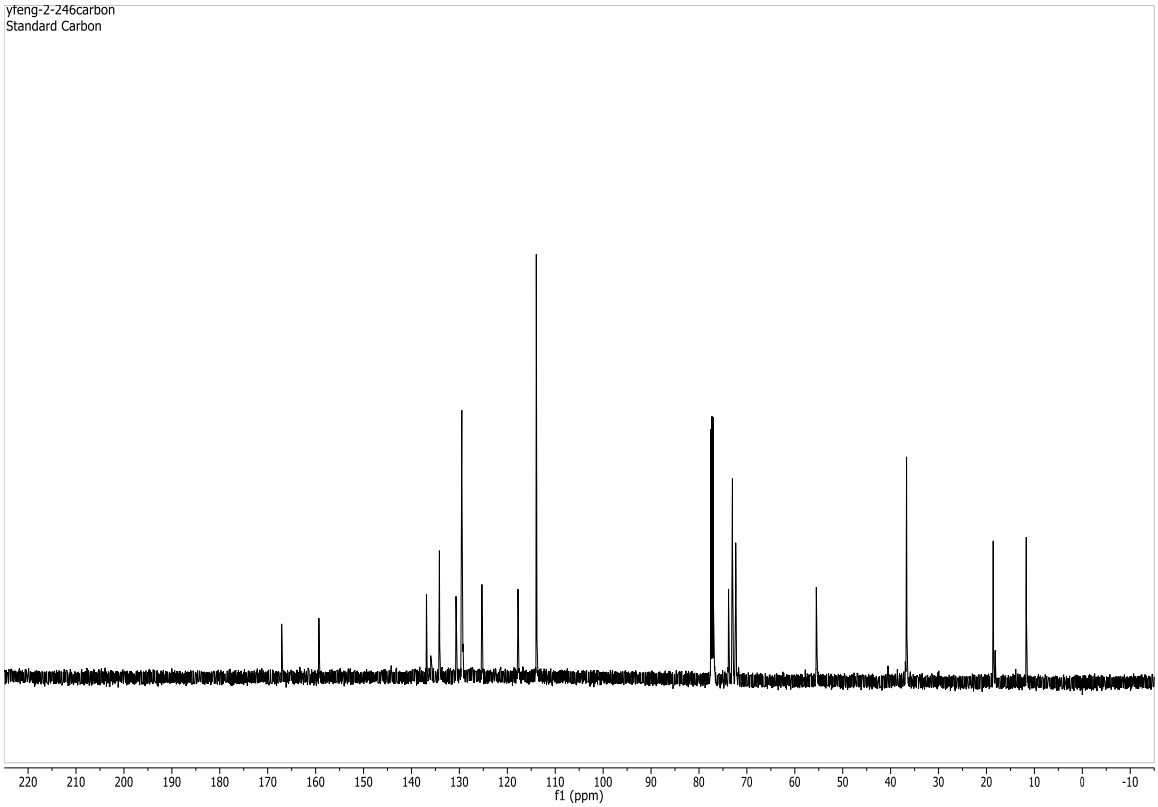

Me
PMBO
OH

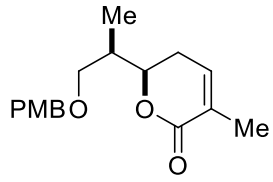

8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5

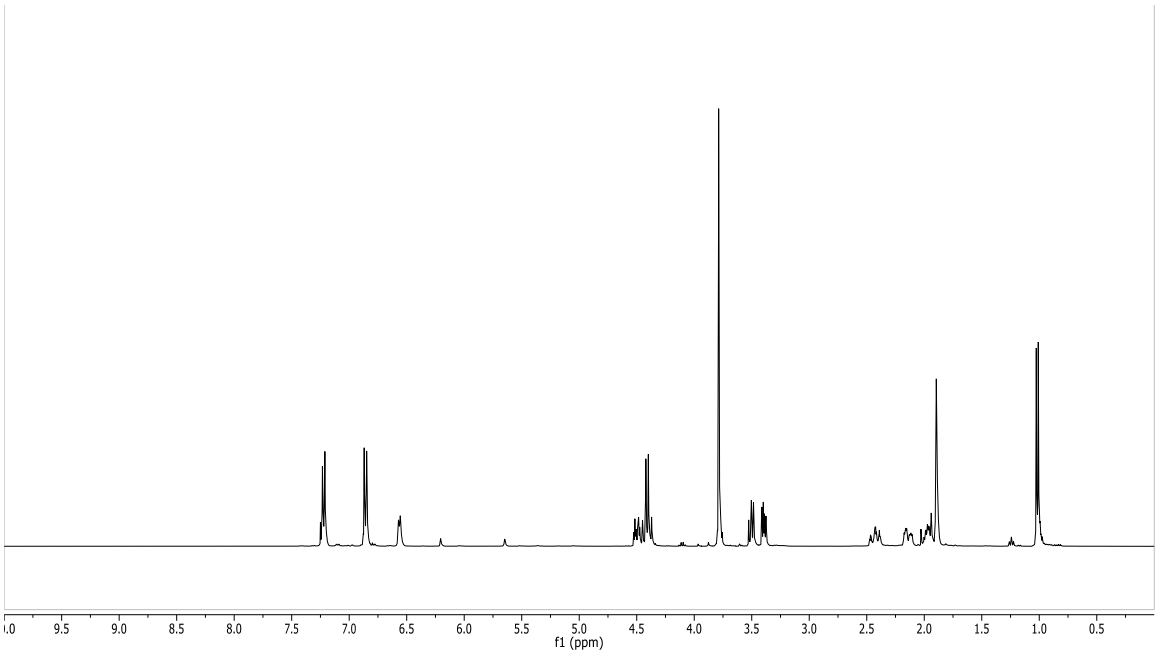

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

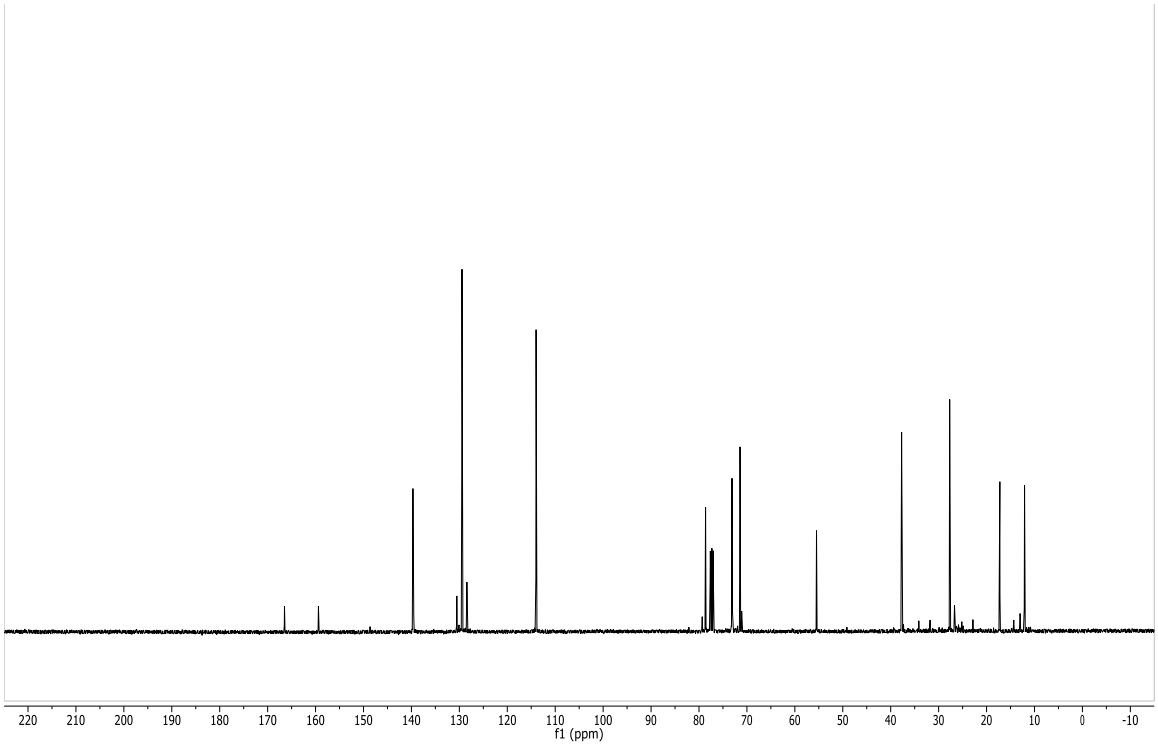

Me
PMBO
O
Me
O

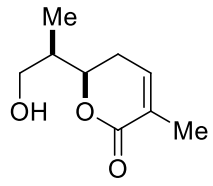

9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

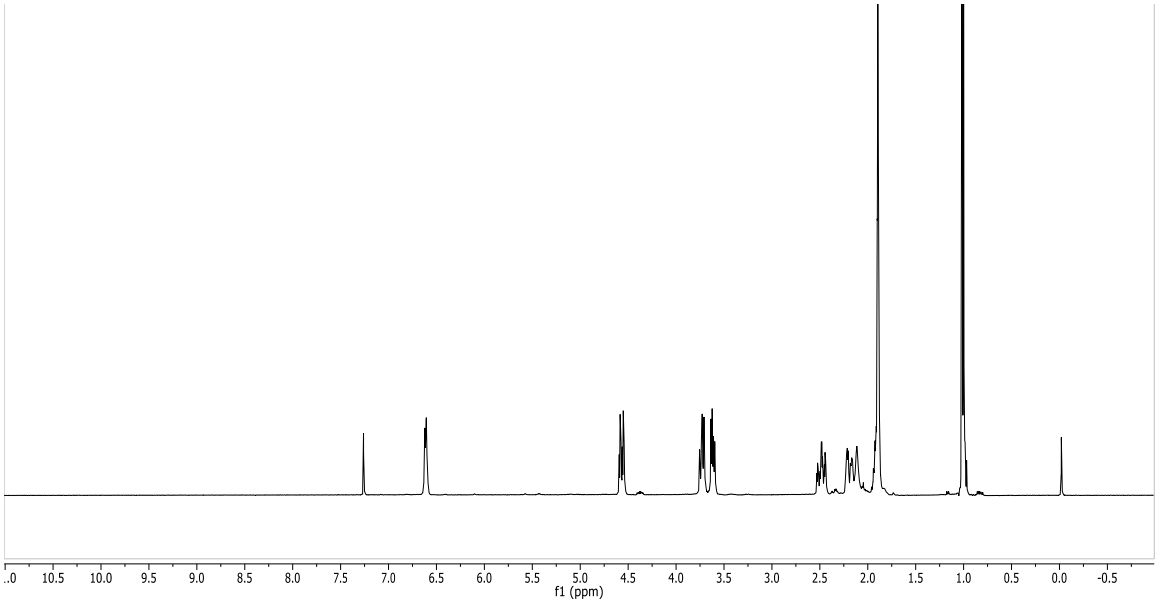

yfeng-2-246carbon
Standard Carbon
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

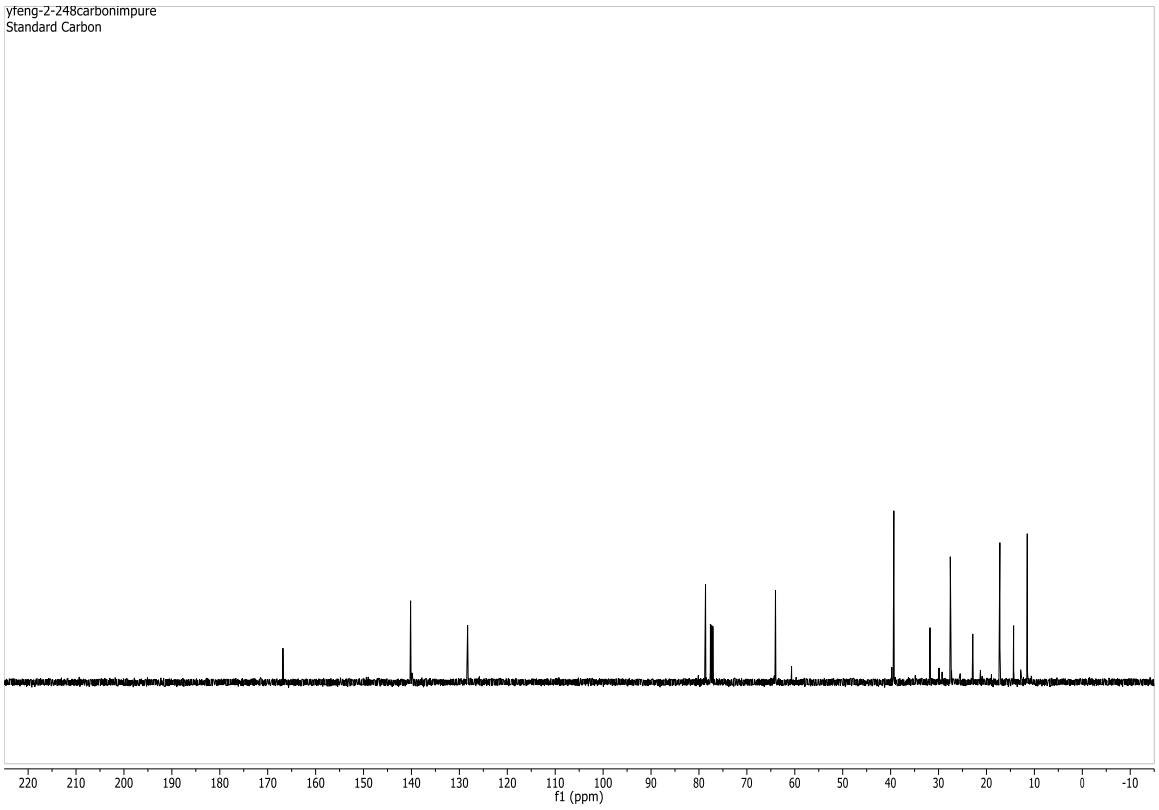

Me
PMBO
O
Me
O

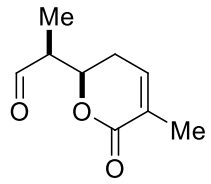

f1 (ppm)

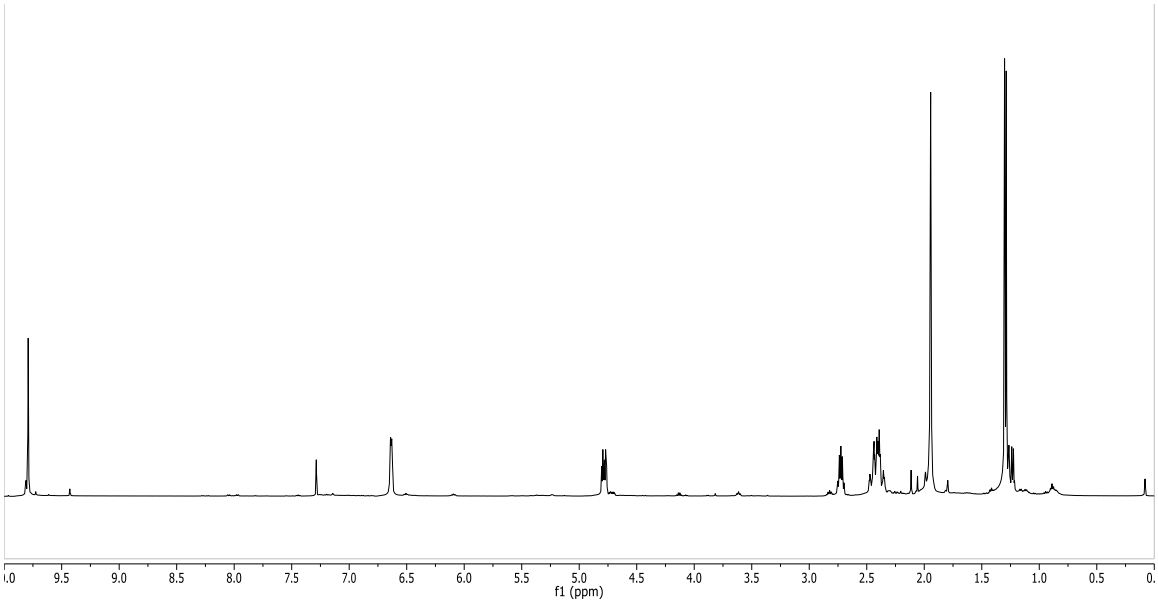

f1 (ppm)

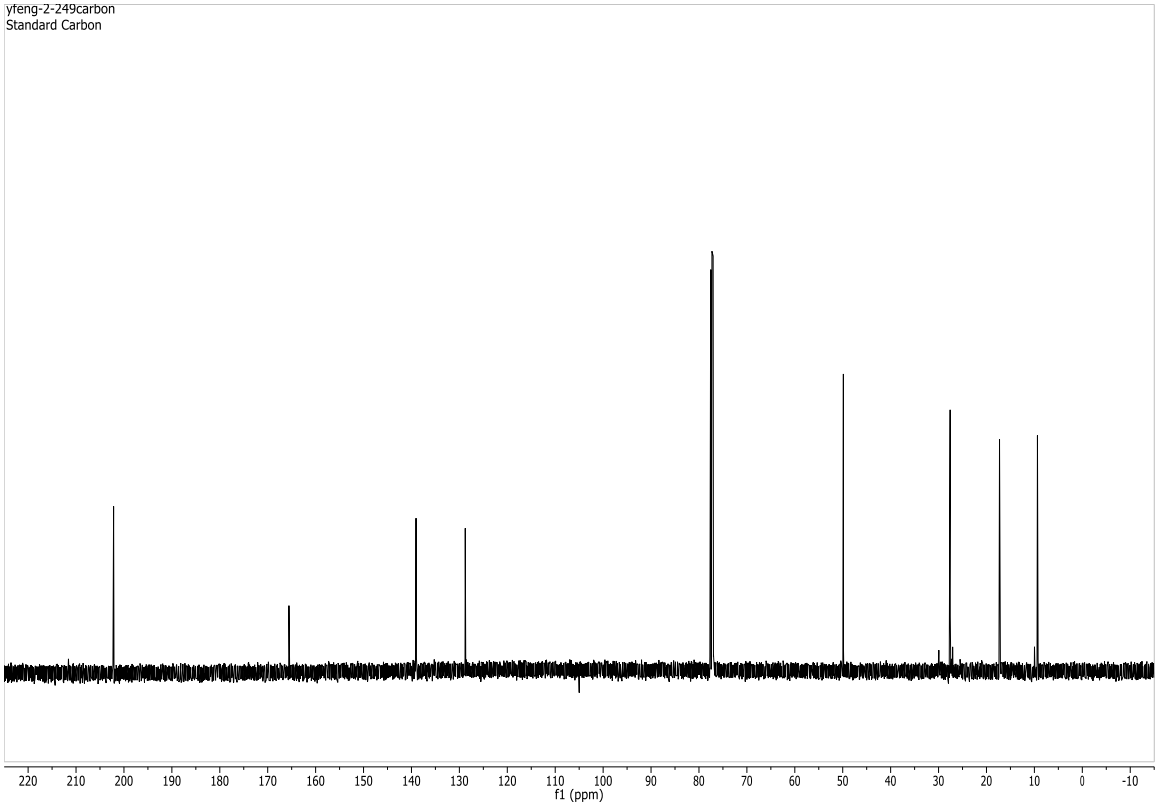

Me
OH
O
Me
O

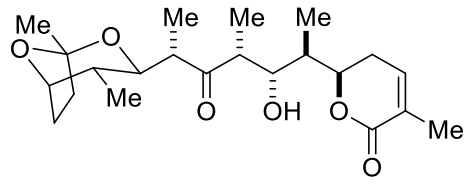

..0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

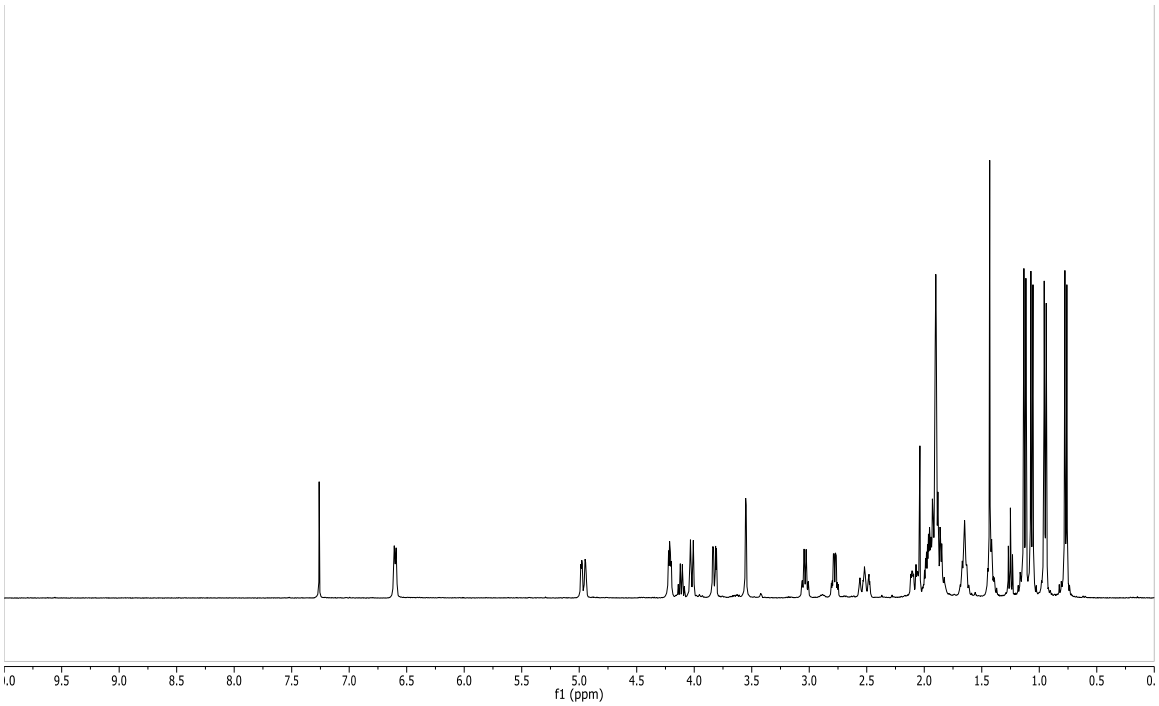

yfeng-2-248carbonimpure
Standard Carbon
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

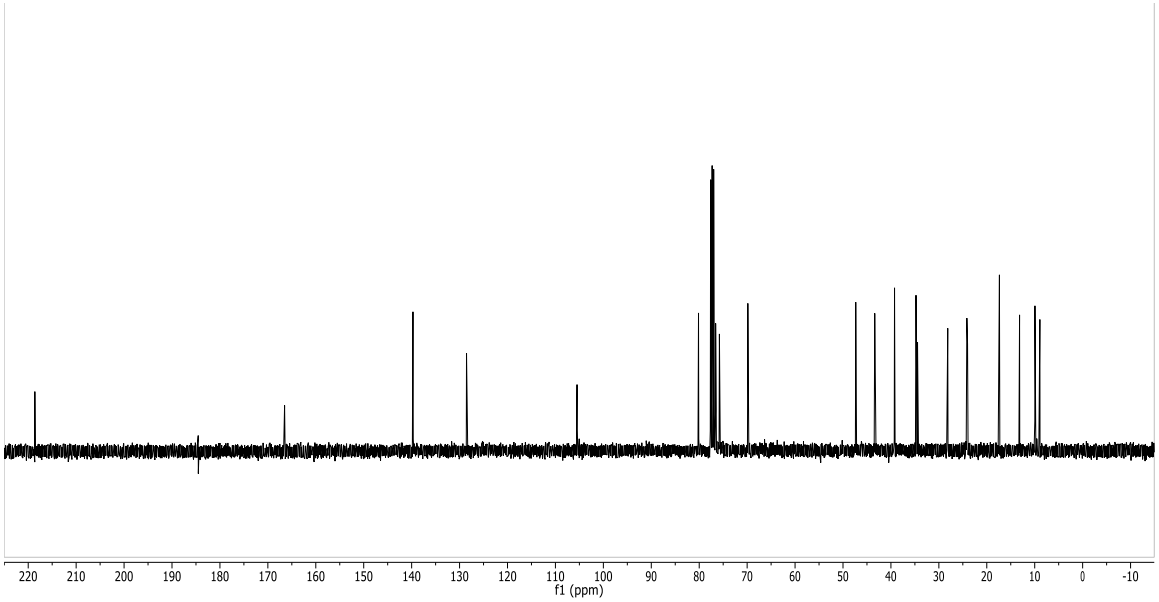

Me
O
O
Me
O

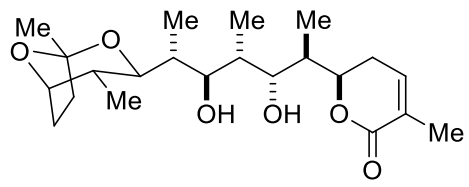

f1 (ppm)

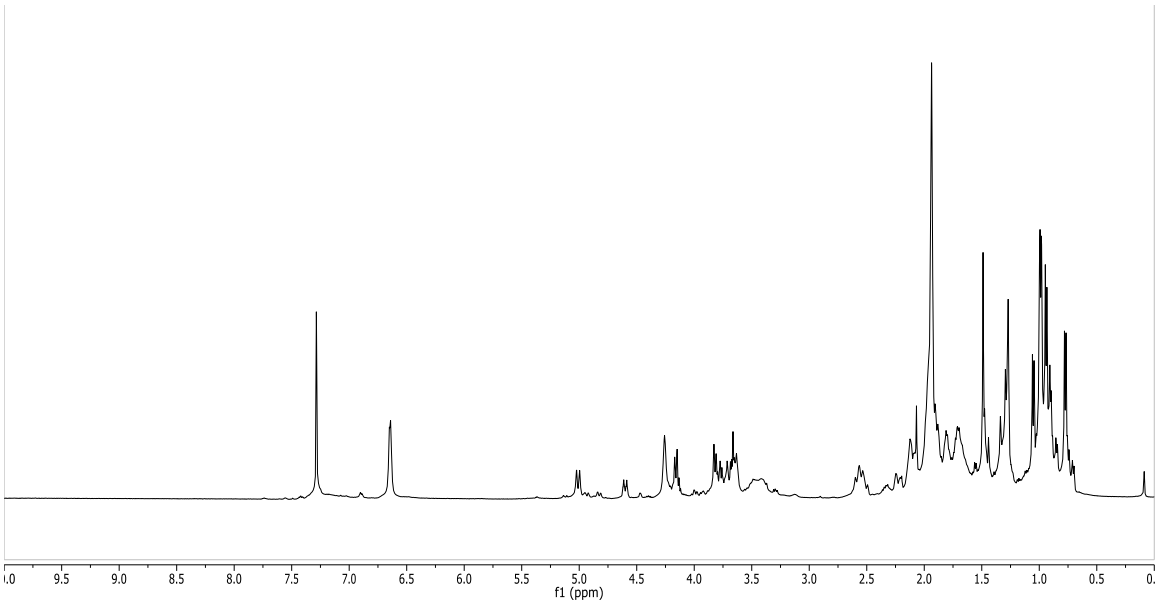

yfeng-2-249carbon
Standard Carbon
f1 (ppm)

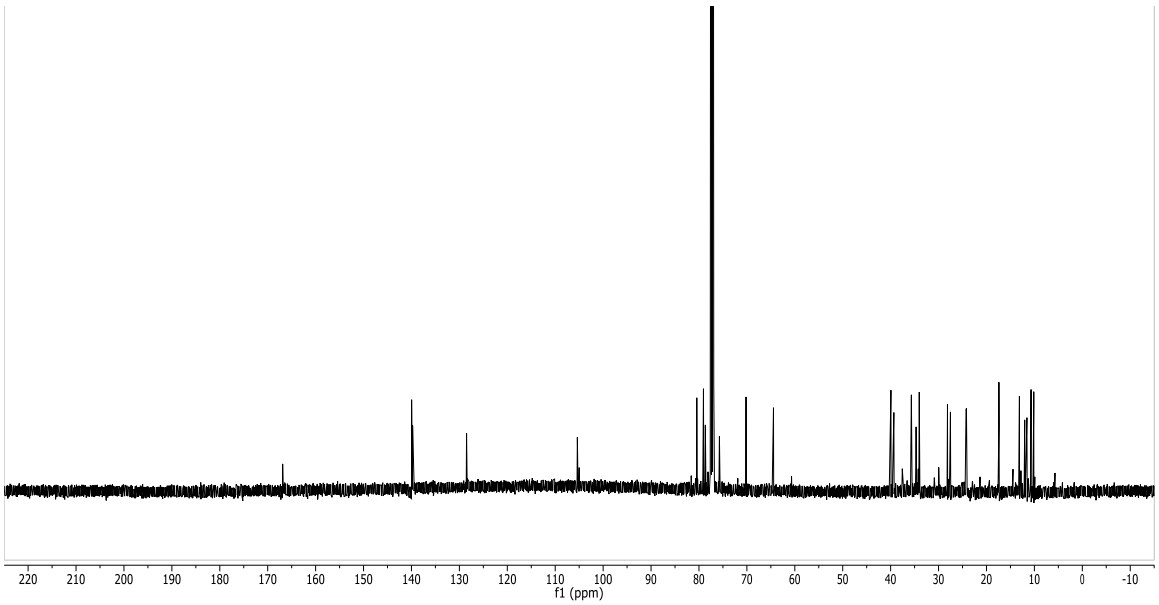

Me
O
O
Me
Me
Me
Me
O
OH
O
Me
O

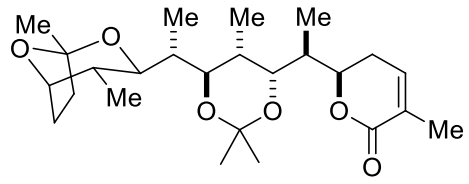

9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

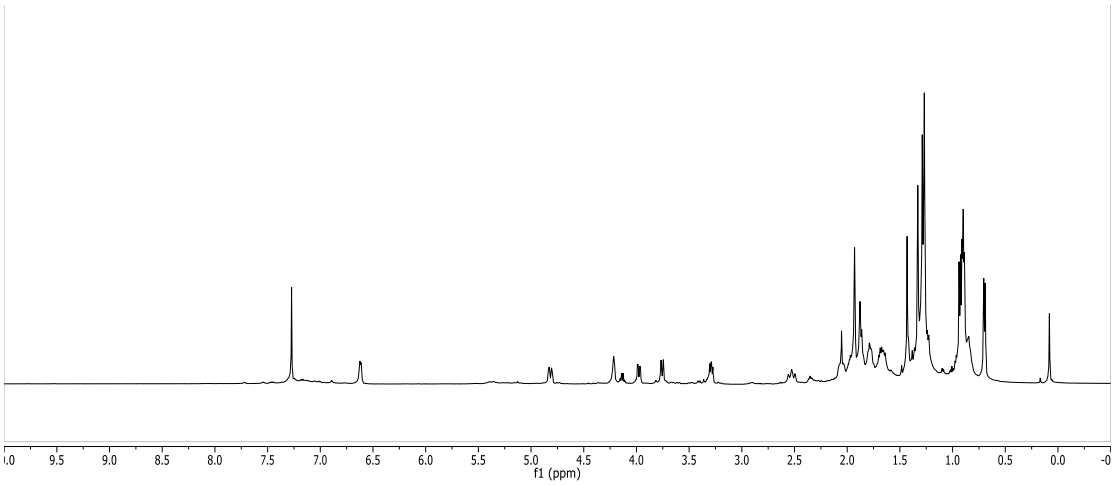

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

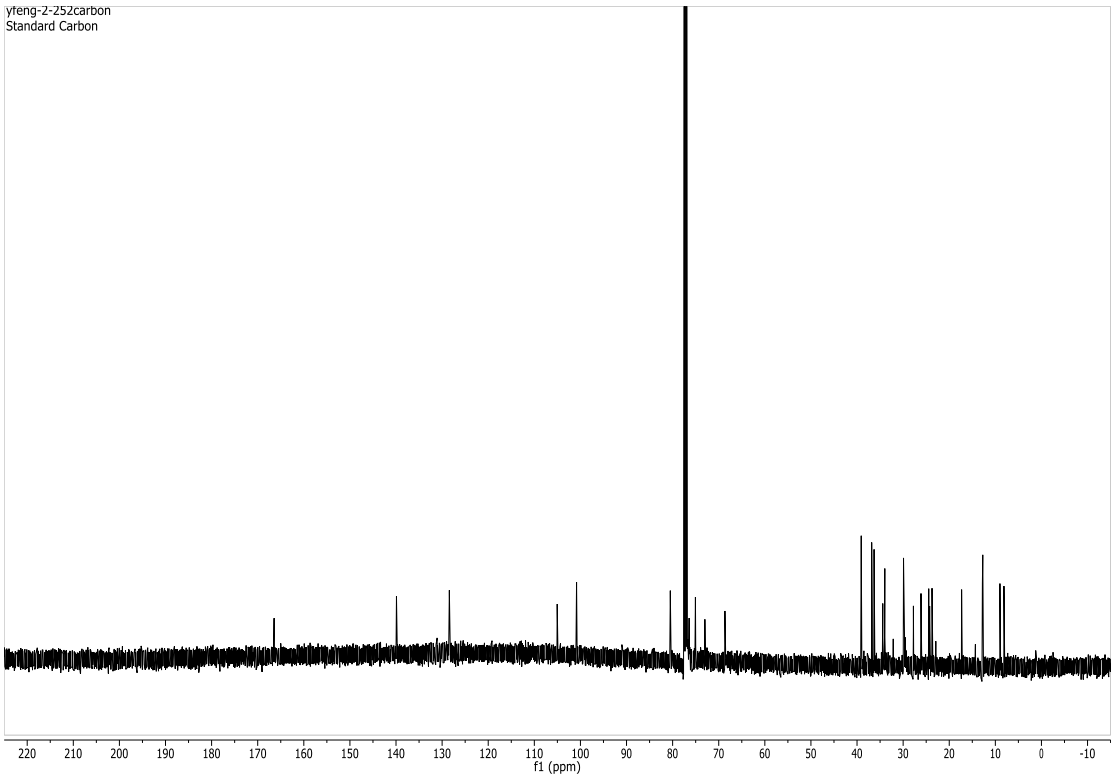

Me
O
O
Me
Me
Me
Me
OH
OH
O
Me
O

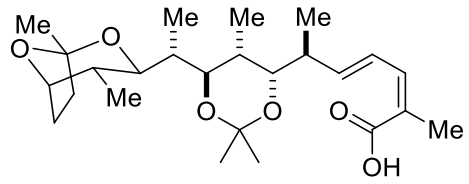

9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

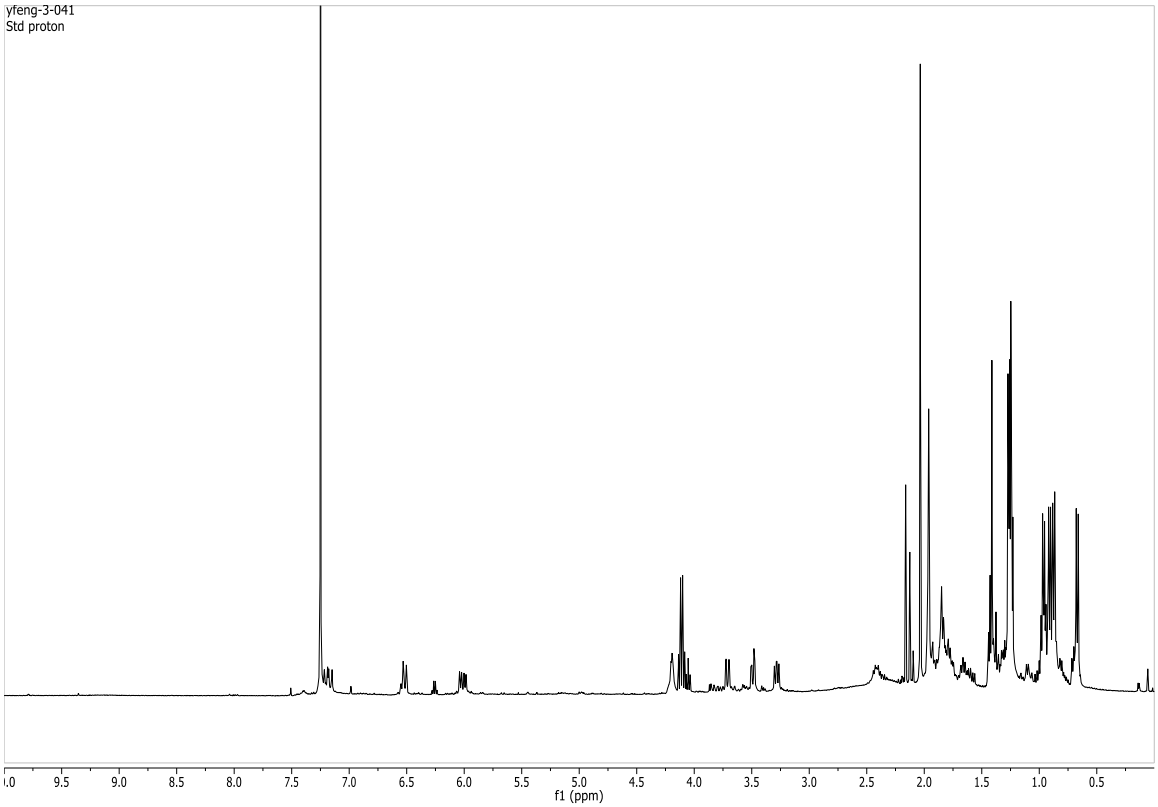

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

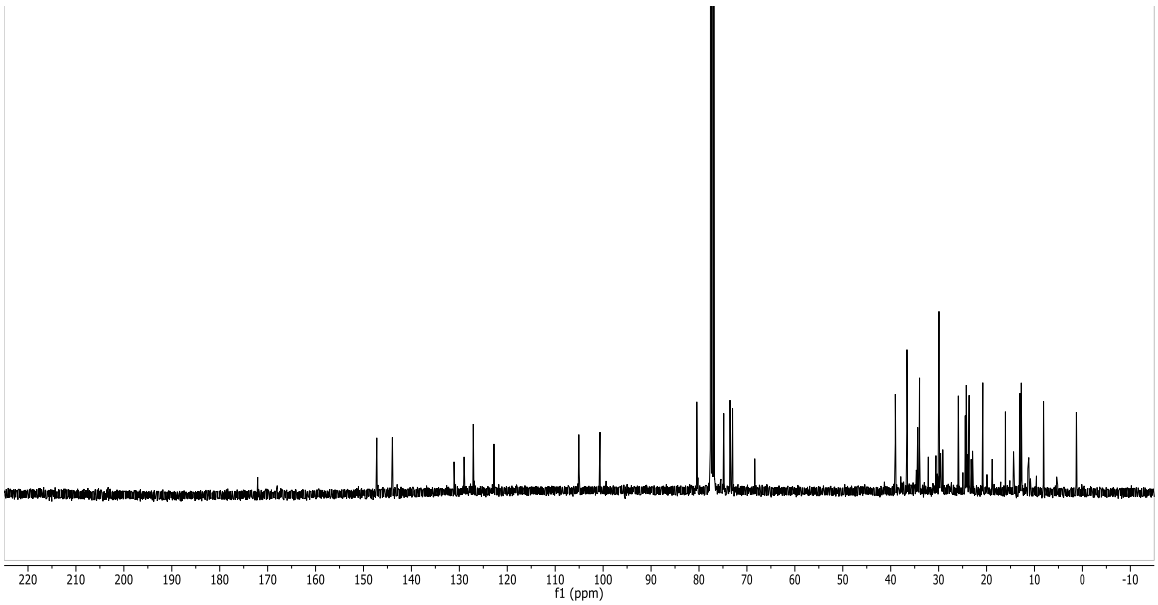

Me
O
O
Me
Me
Me
Me
O
O
O
Me
O

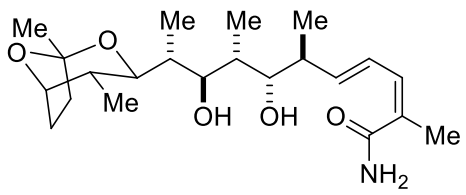

9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

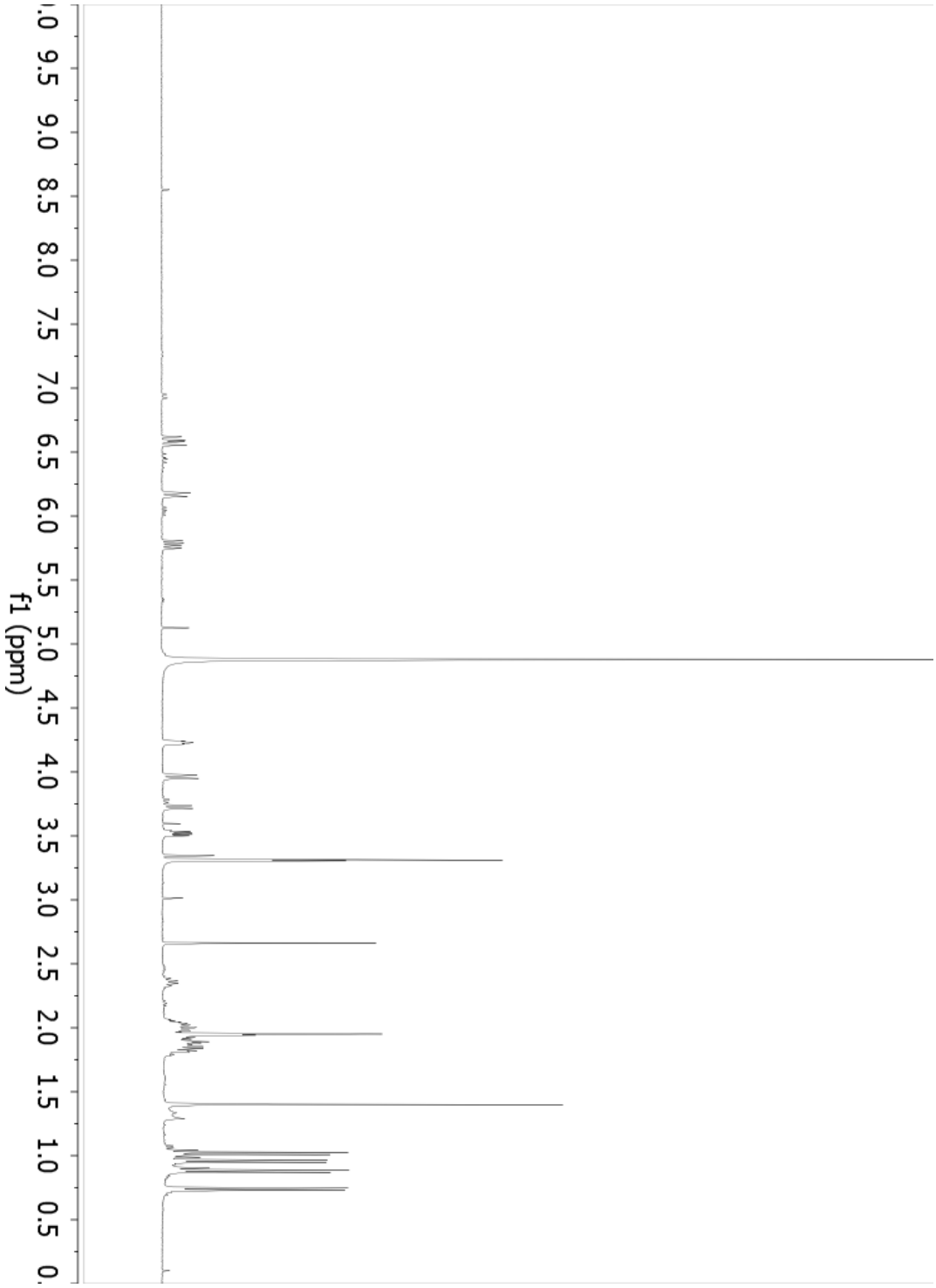

yfeng-2-252carbon
Standard Carbon
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

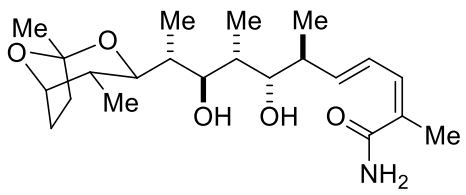

Me
O
O
Me
Me
Me
Me
O
O
O
Me
OH

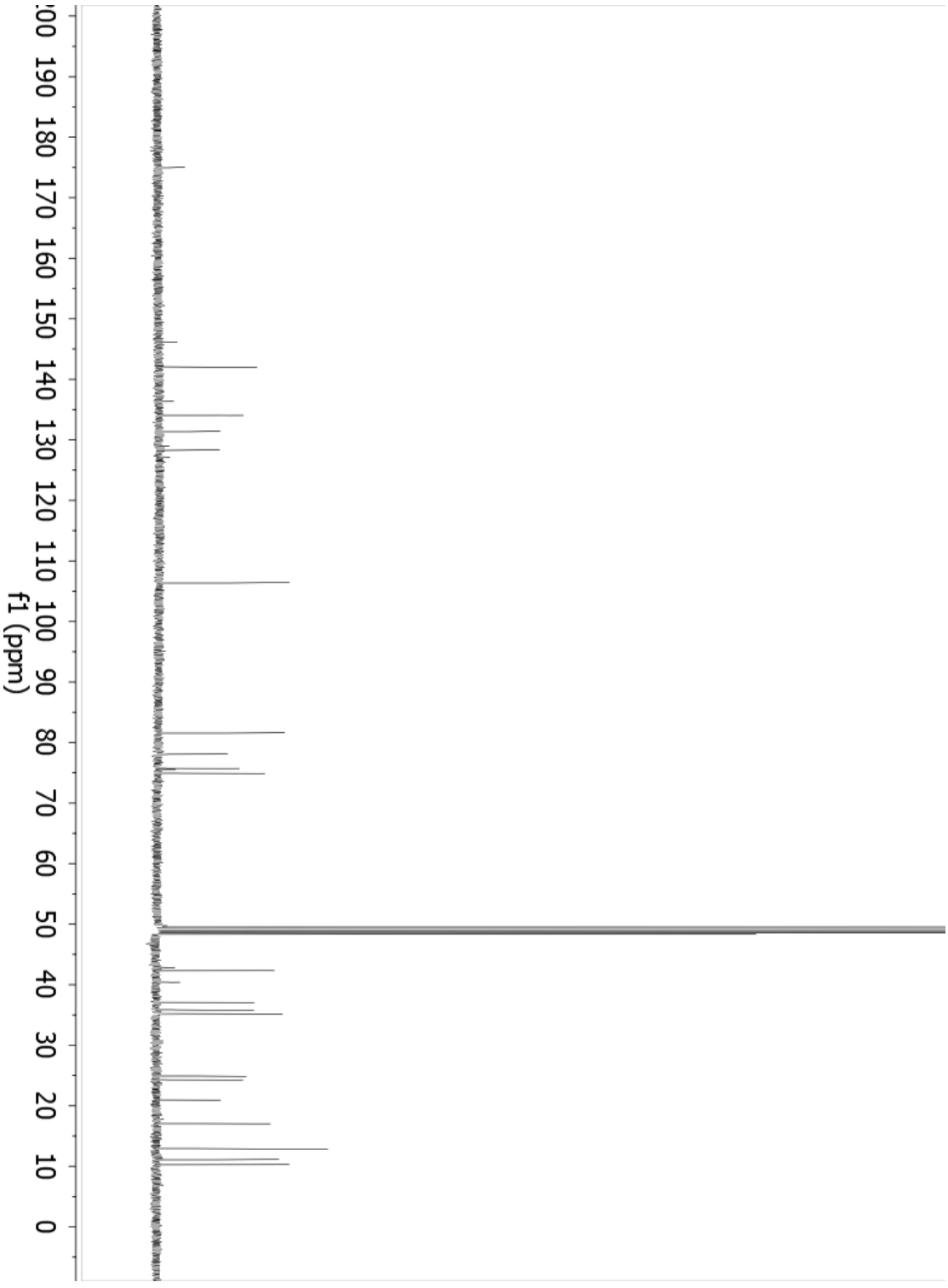

yfeng-3-041
Std proton
f1 (ppm)

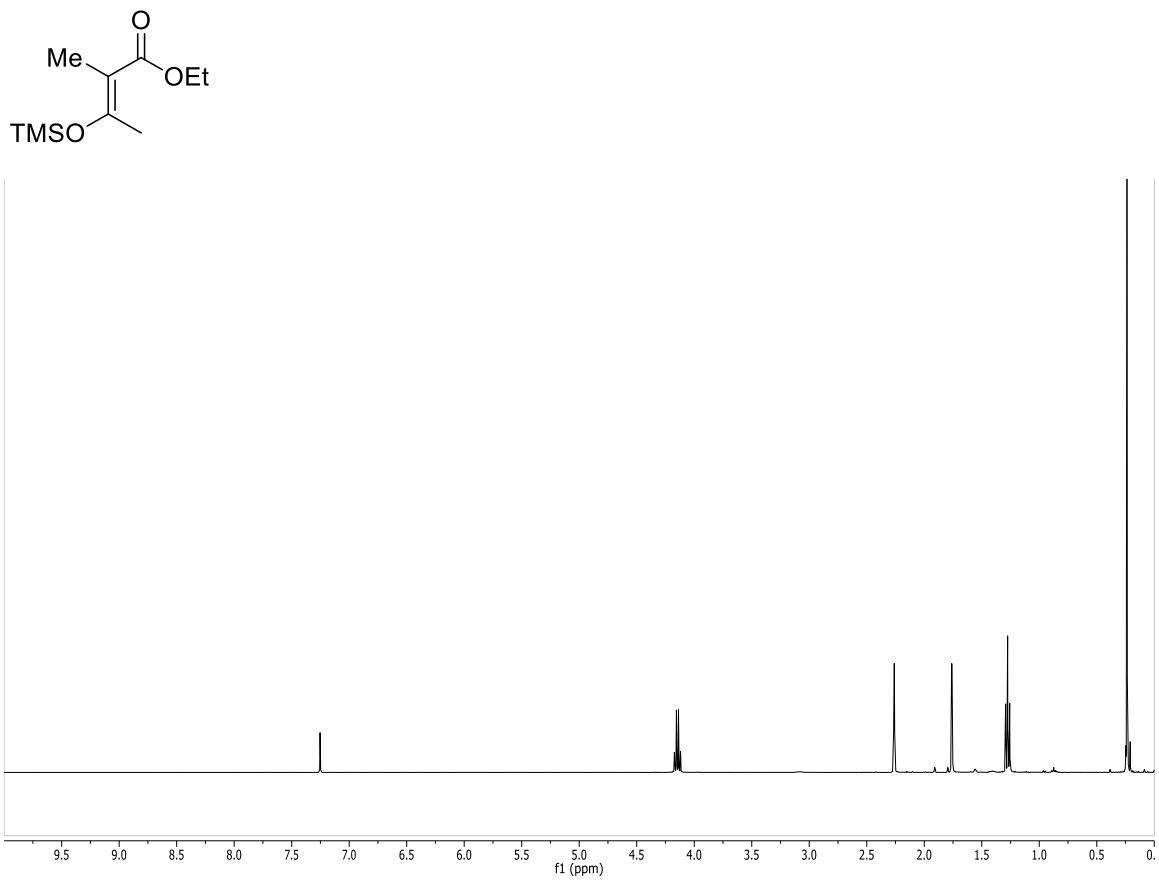

f1 (ppm)

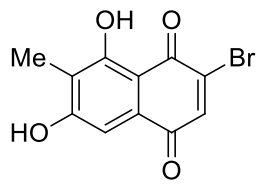

Me
O
O
Me
Me
Me
Me
OH
OH
O
Me
NH2

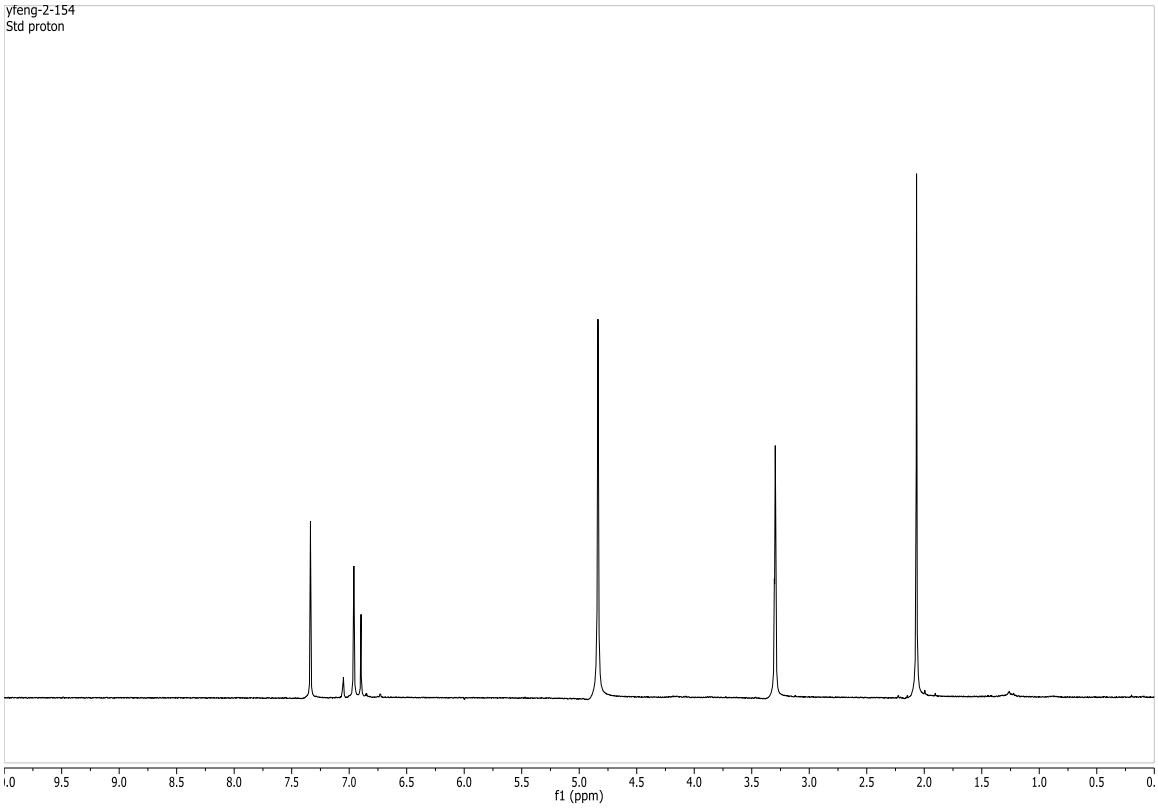

f1 (ppm)
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

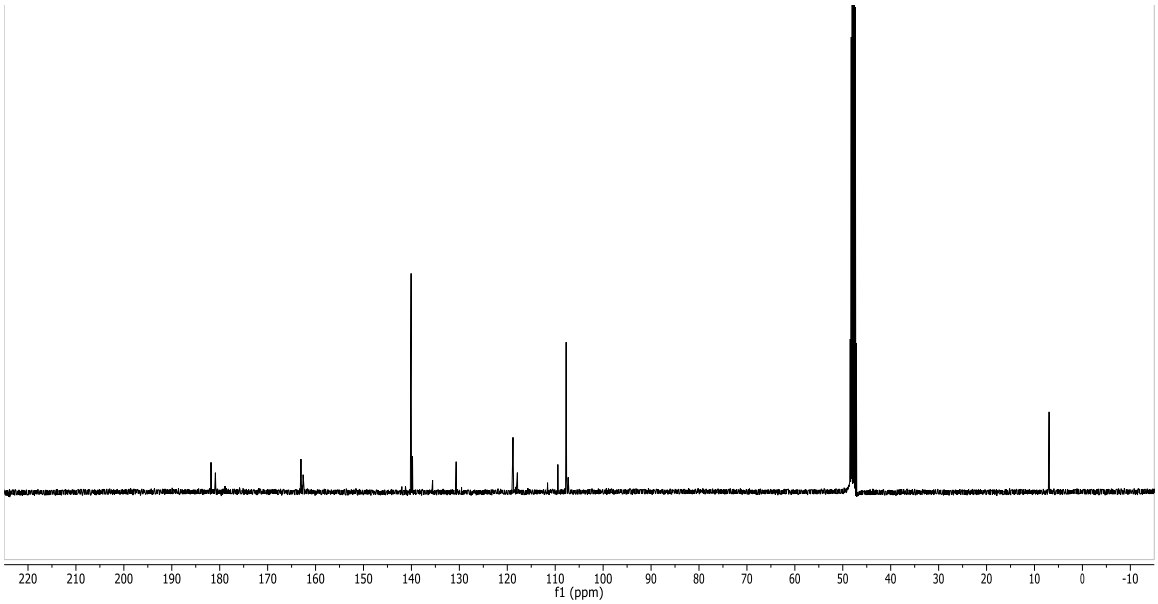

Me
O
O
Me
Me
Me
Me
OH
OH
O
Me
NH2

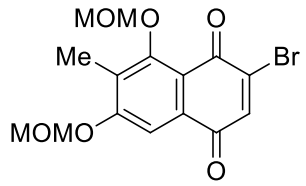

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

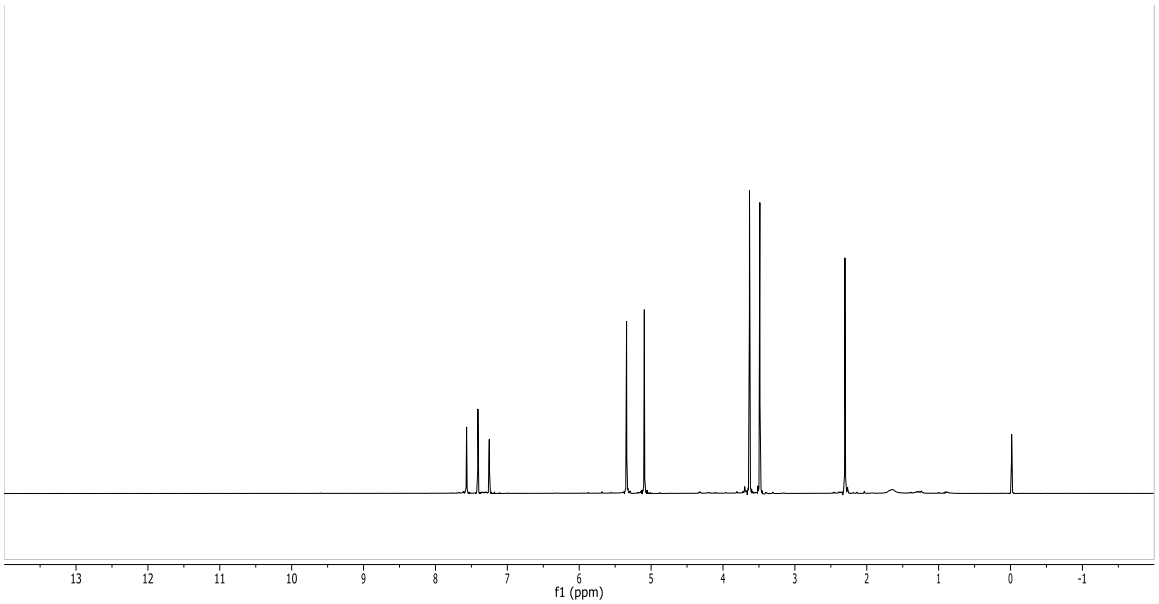

O
Me
OEt
TMSO
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

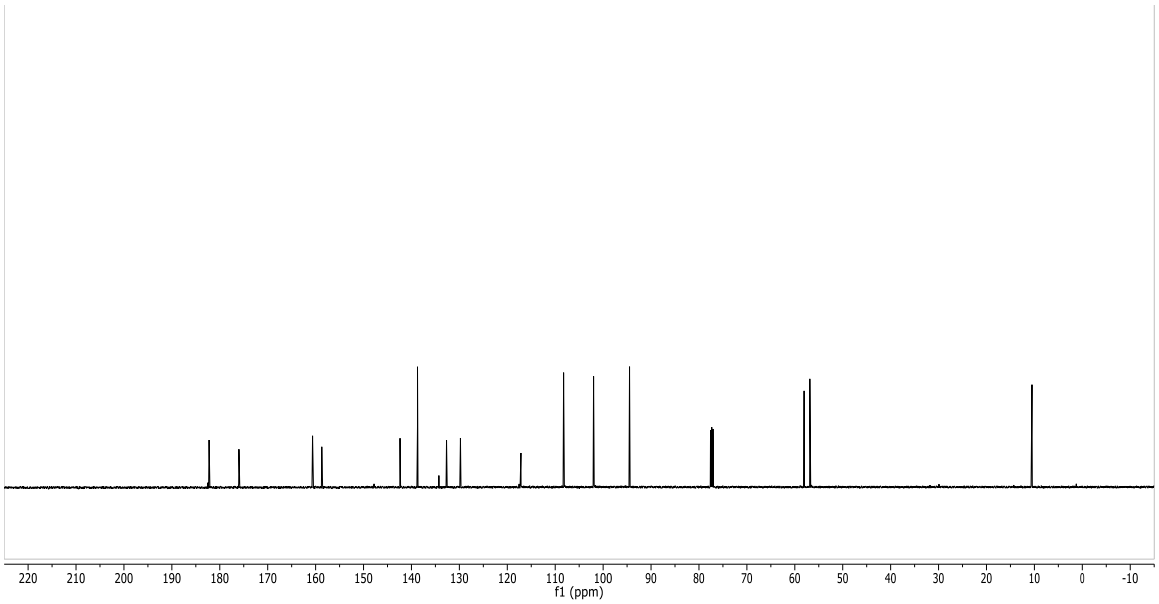

OH
O
Me
Br
HO
O

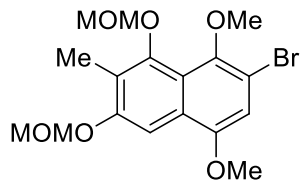

yfeng-2-154
Std proton
f1 (ppm)

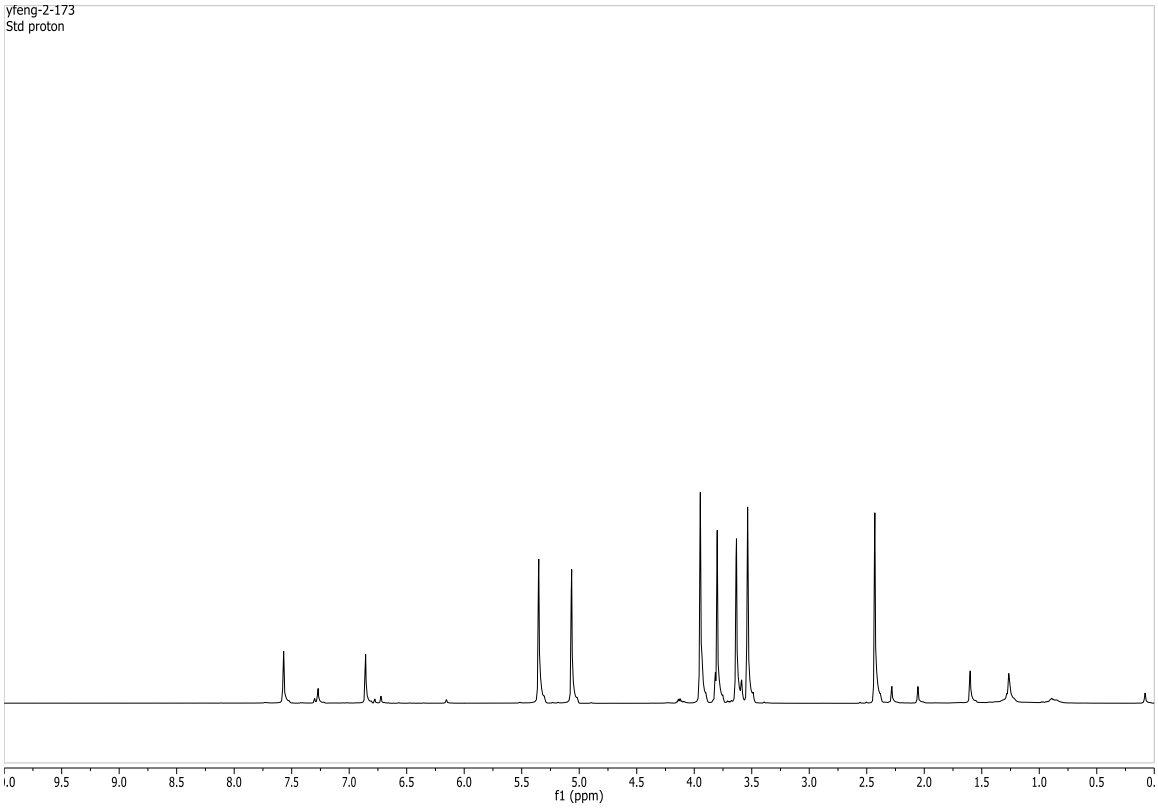

f1 (ppm)

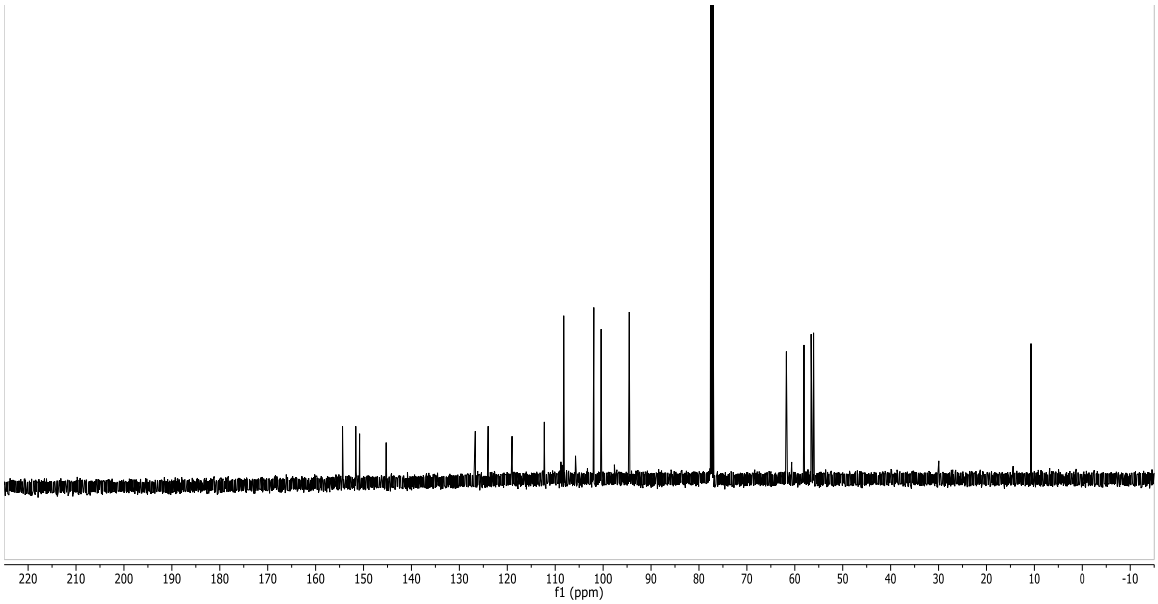

MOMO
O
Me
Br
MOMO
O

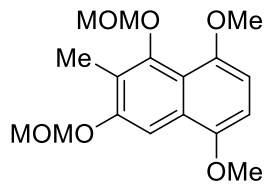

13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

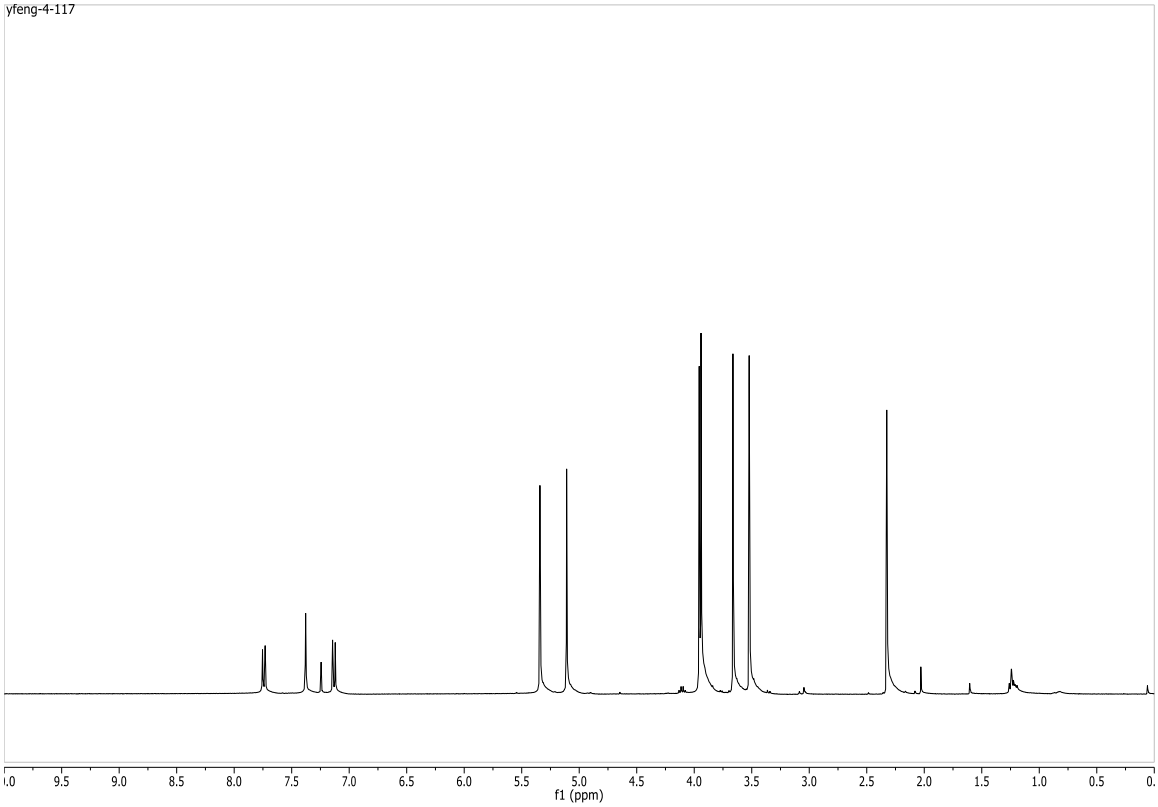

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

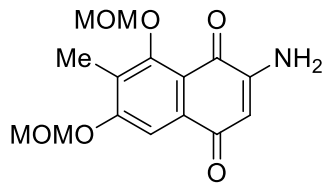

MOMO
OMe
Me
Br
MOMO
OMe

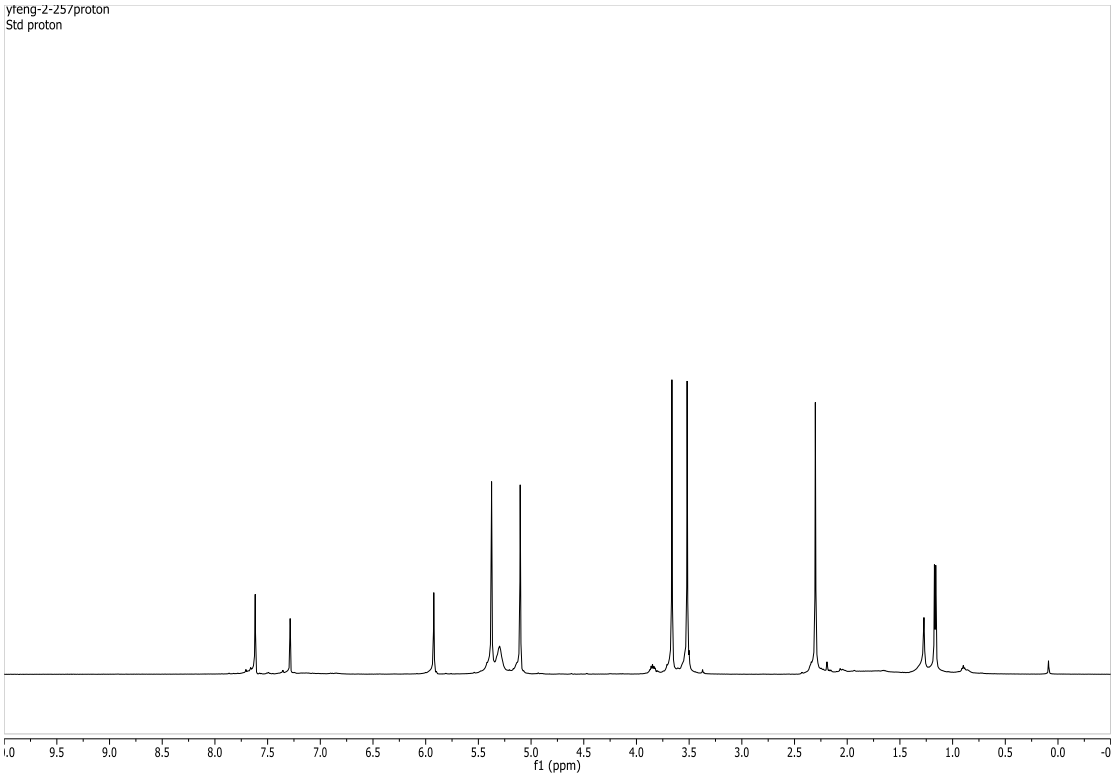

yfeng-2-173
Std proton
f1 (ppm)

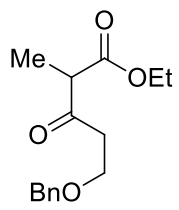

f1 (ppm)

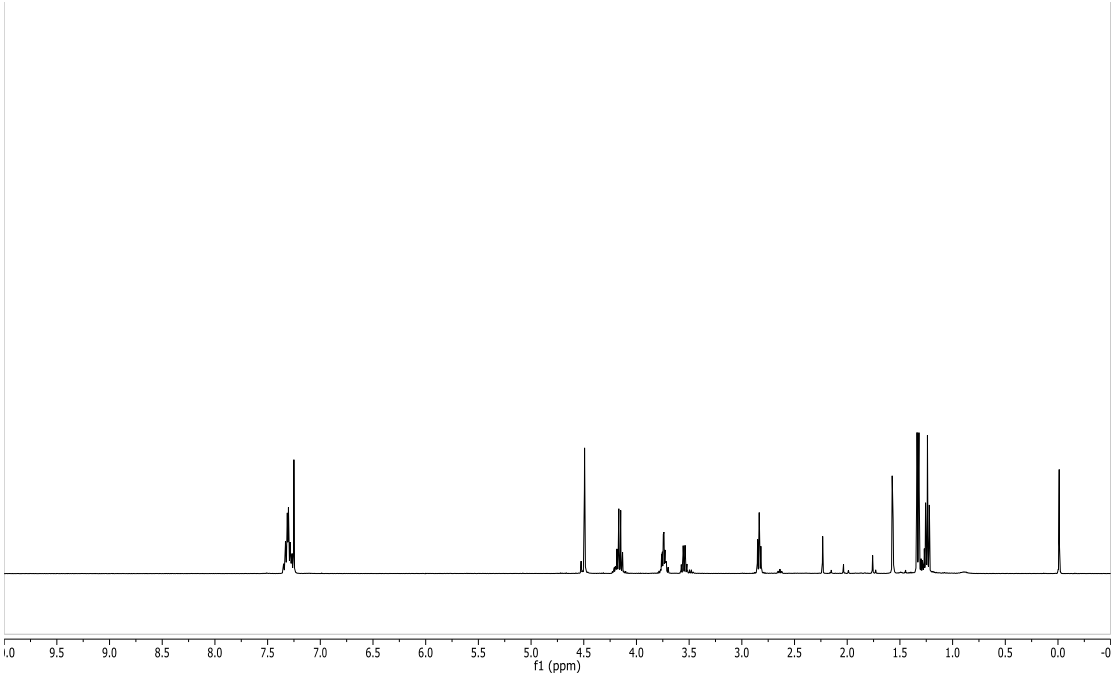

MOMO
OMe
Me
MOMO
OMe

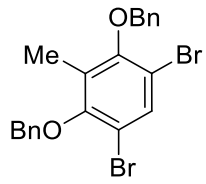

yfeng-4-117
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

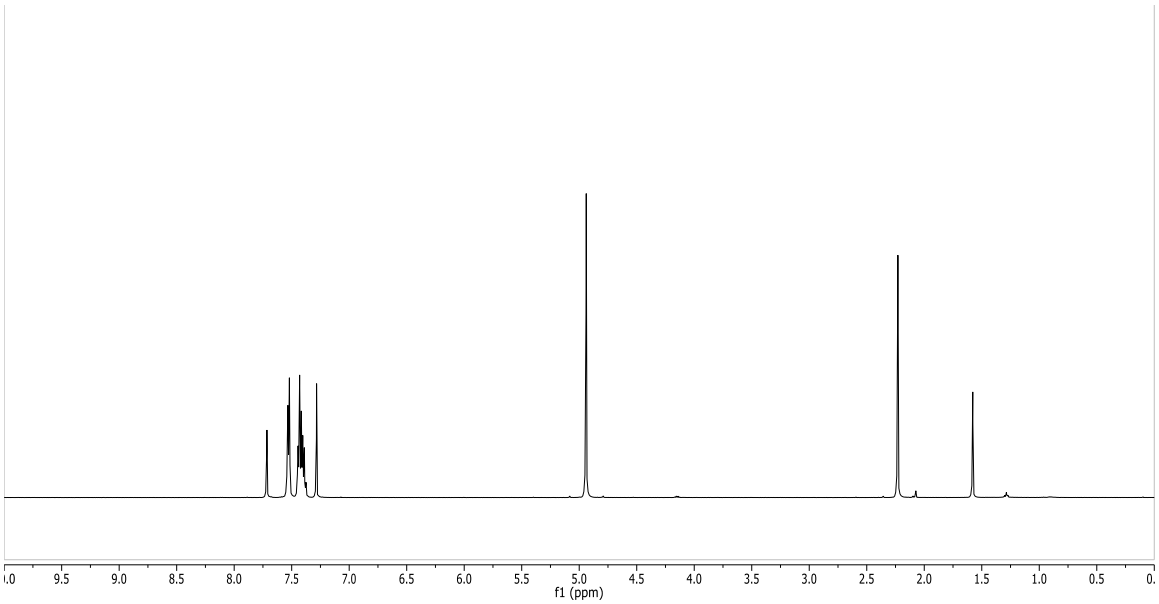

MOMO
O
Me
NH2
MOMO
O

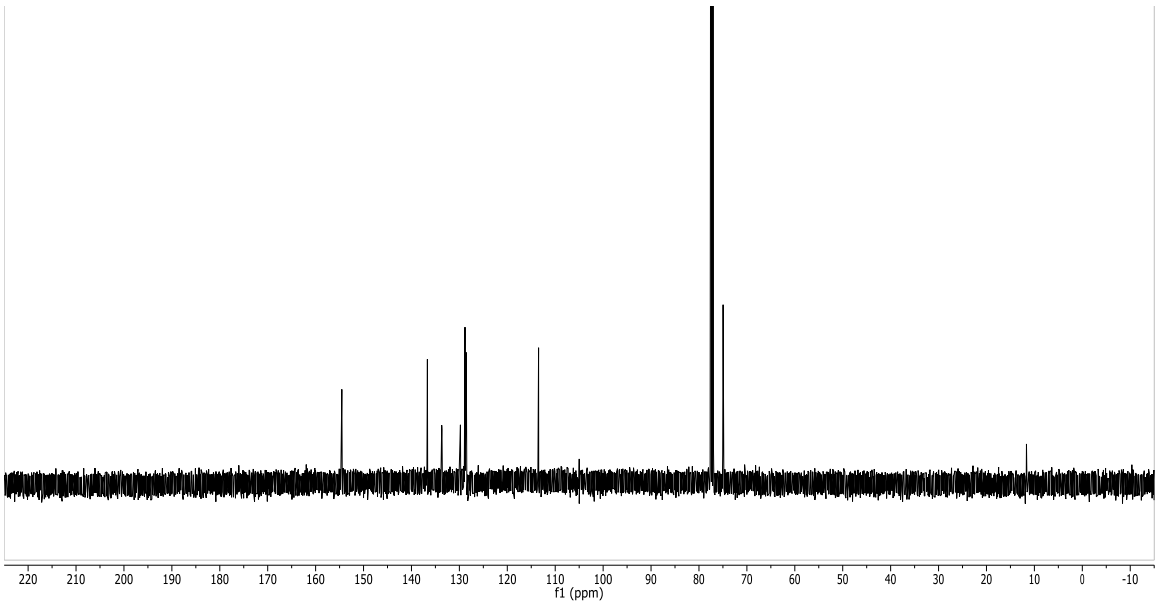

yteng-z-257proton
Std proton
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

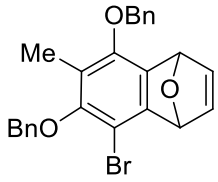

O
Me
OEt
O
BnO

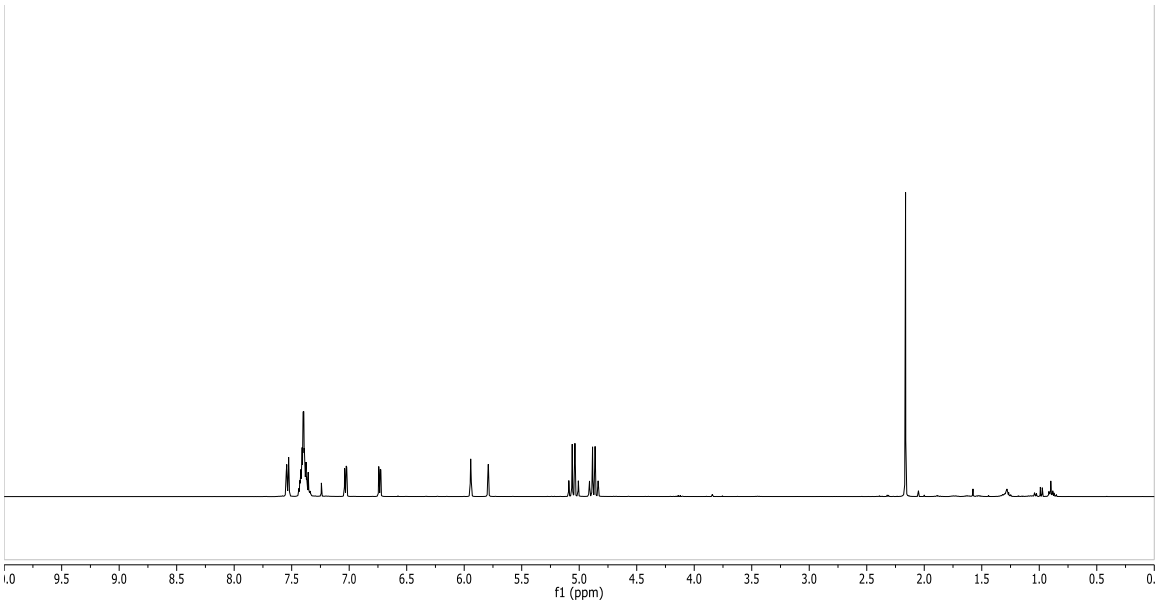

9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

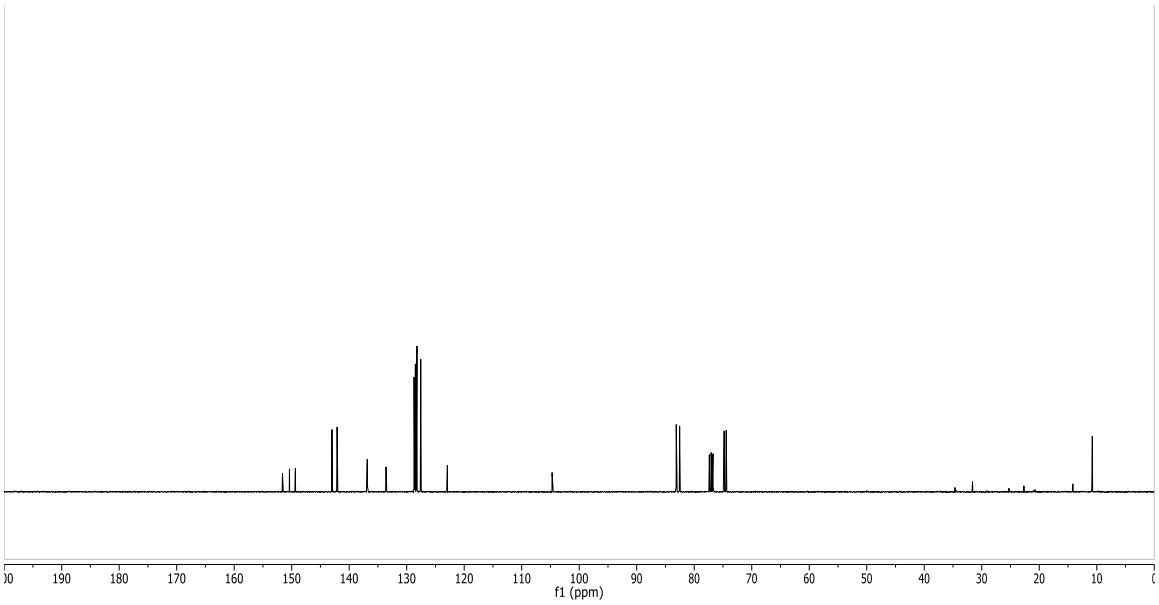

OBn
Me
Br
BnO
Br

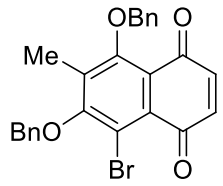

f1 (ppm)

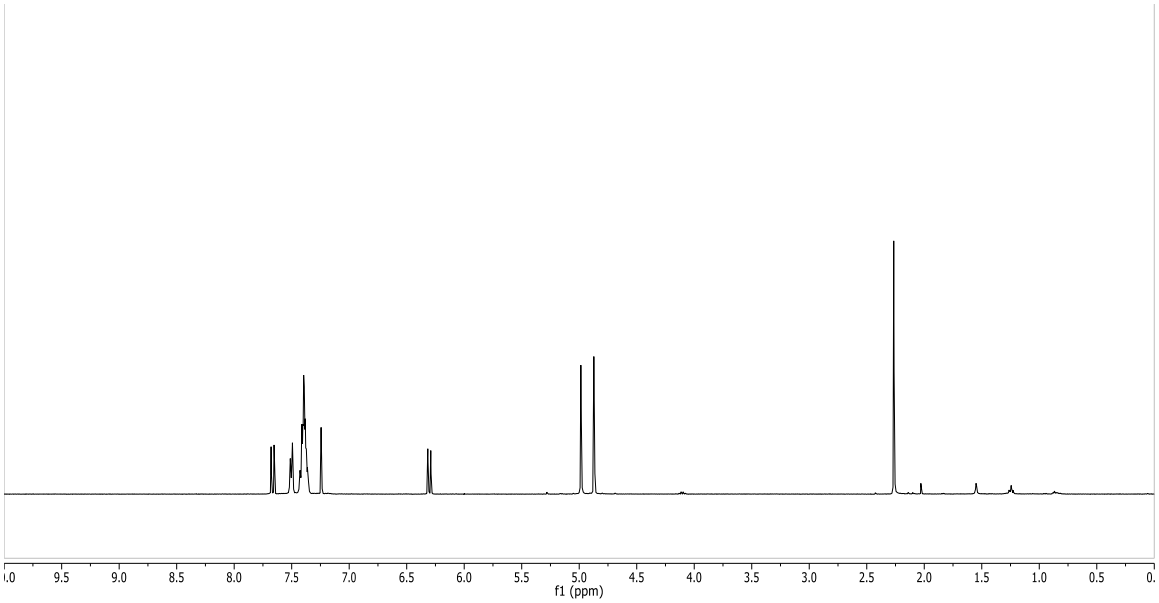

f1 (ppm)

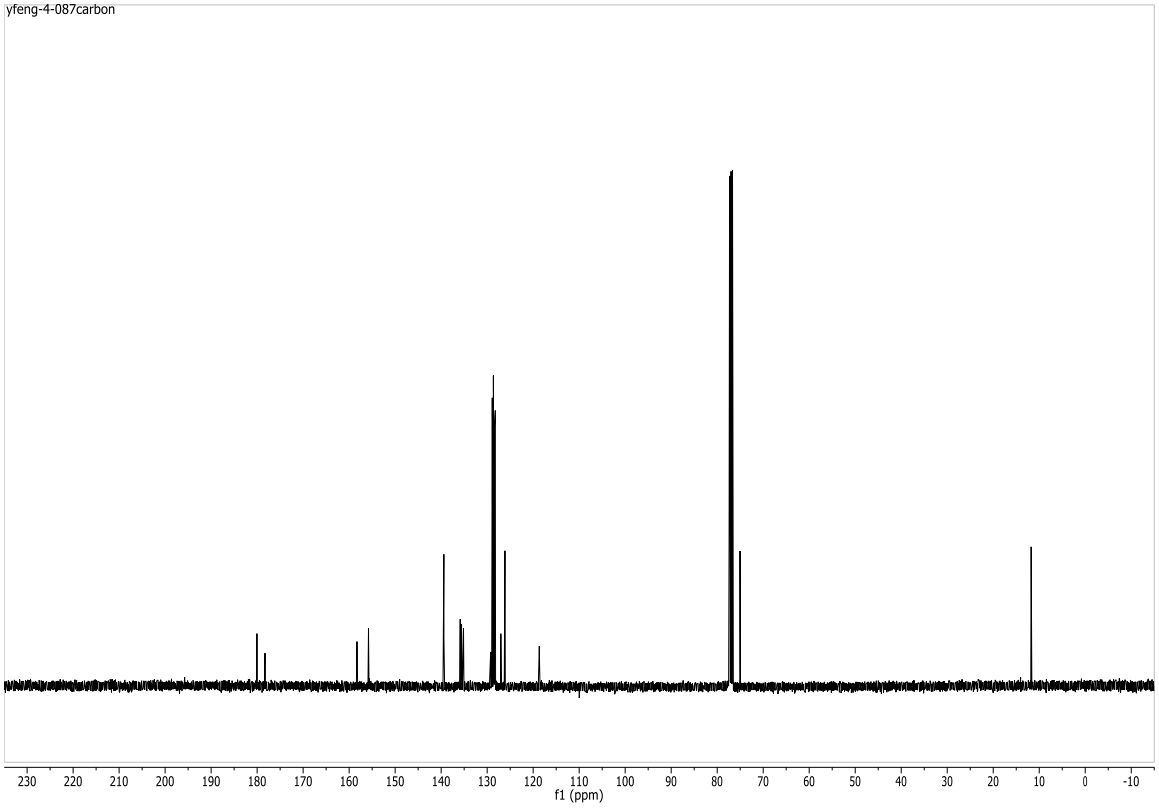

OBn
Me
O
BnO
Br

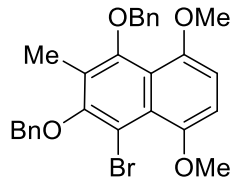

f1 (ppm)

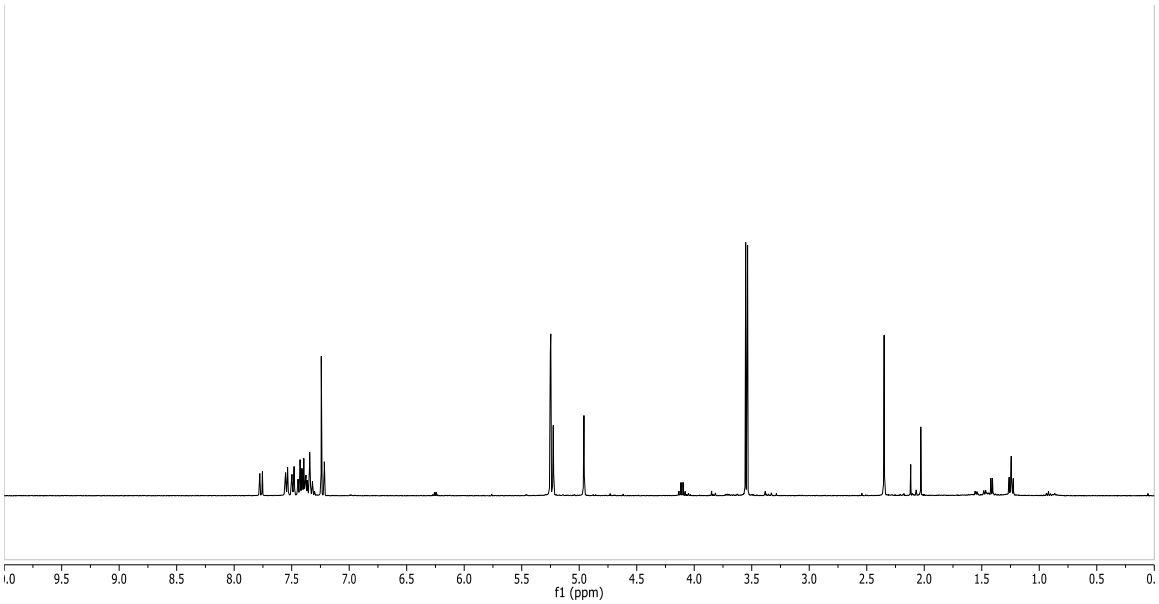

f1 (ppm)

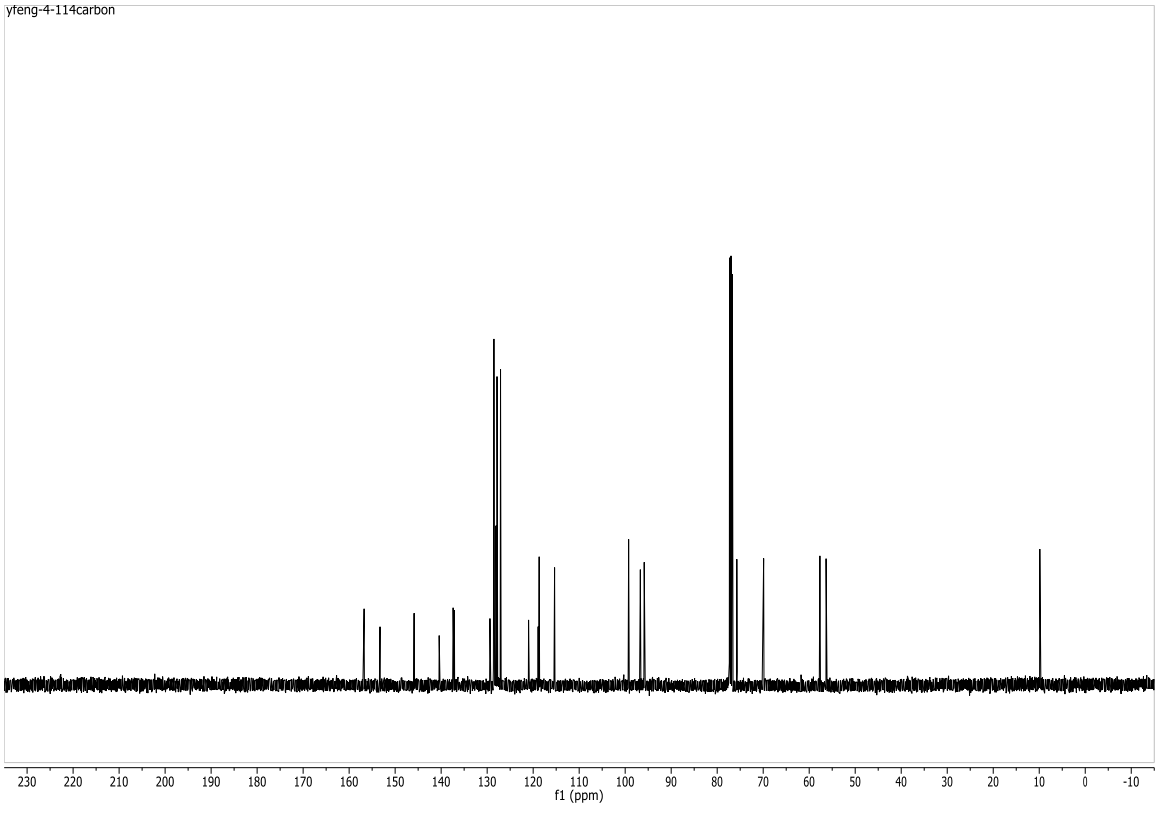

OBn
O
Me
BnO
Br
O

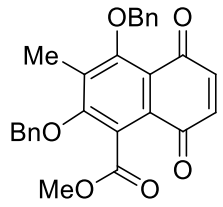

f1 (ppm)

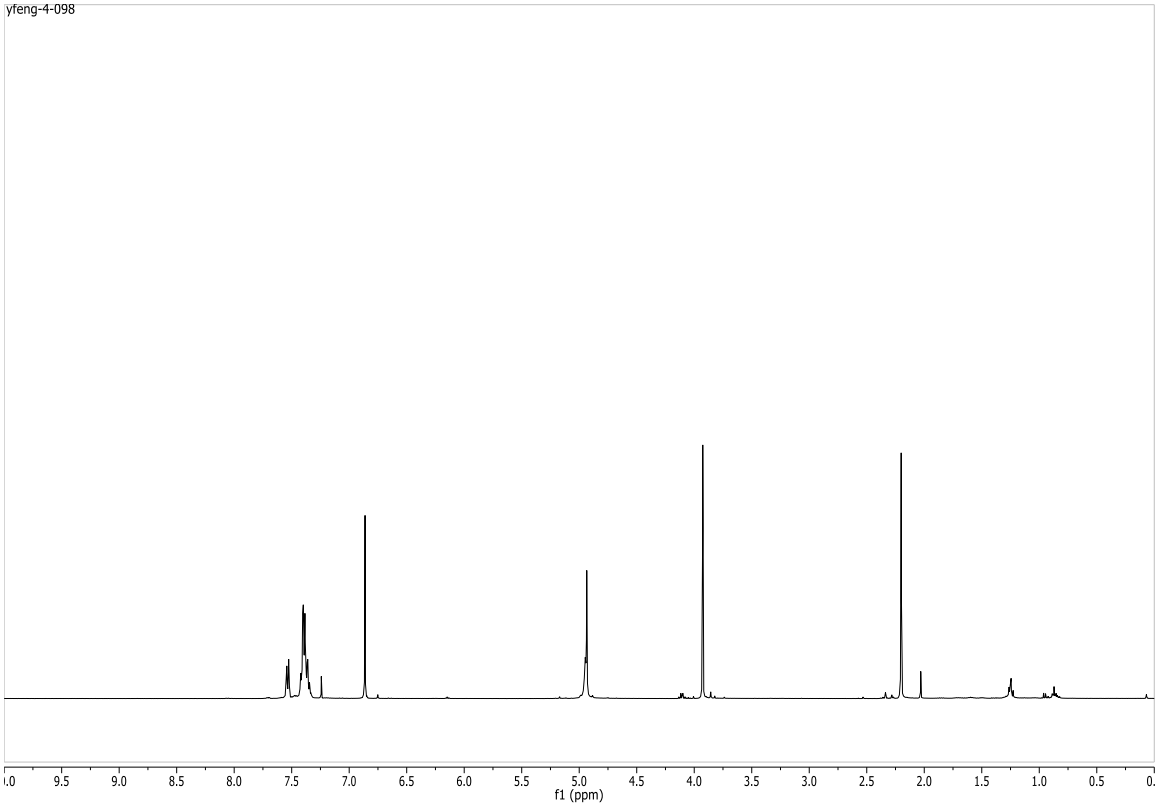

yfeng-4-087carbon
f1 (ppm)

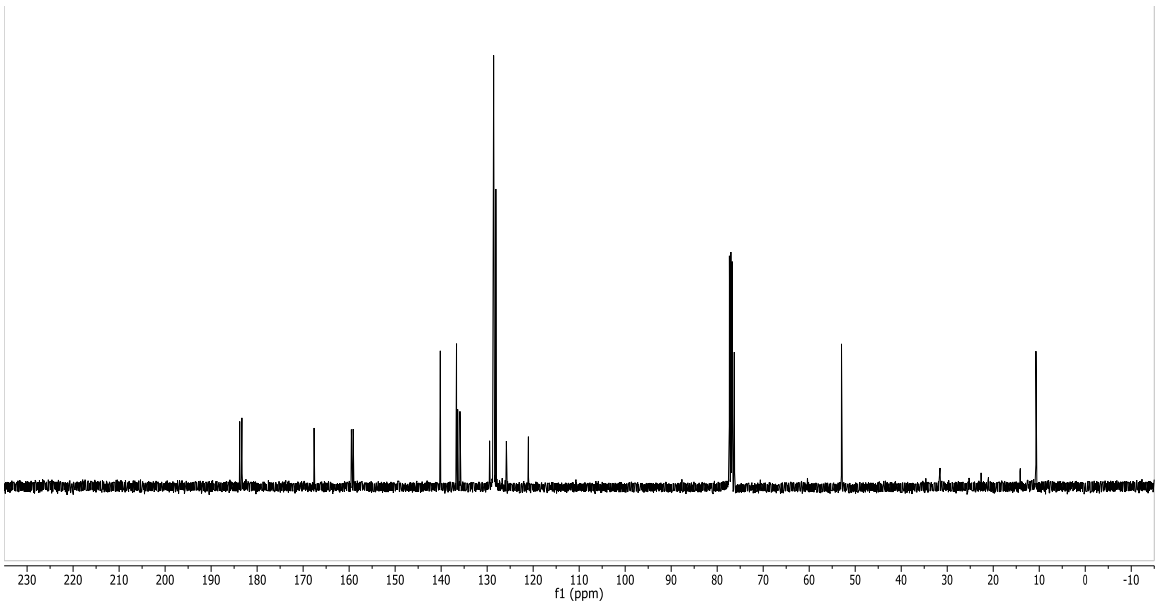

OBn
OMe
Me
BnO
Br
OMe

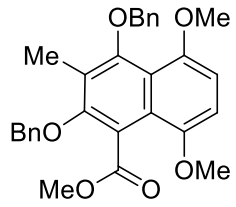

f1 (ppm)

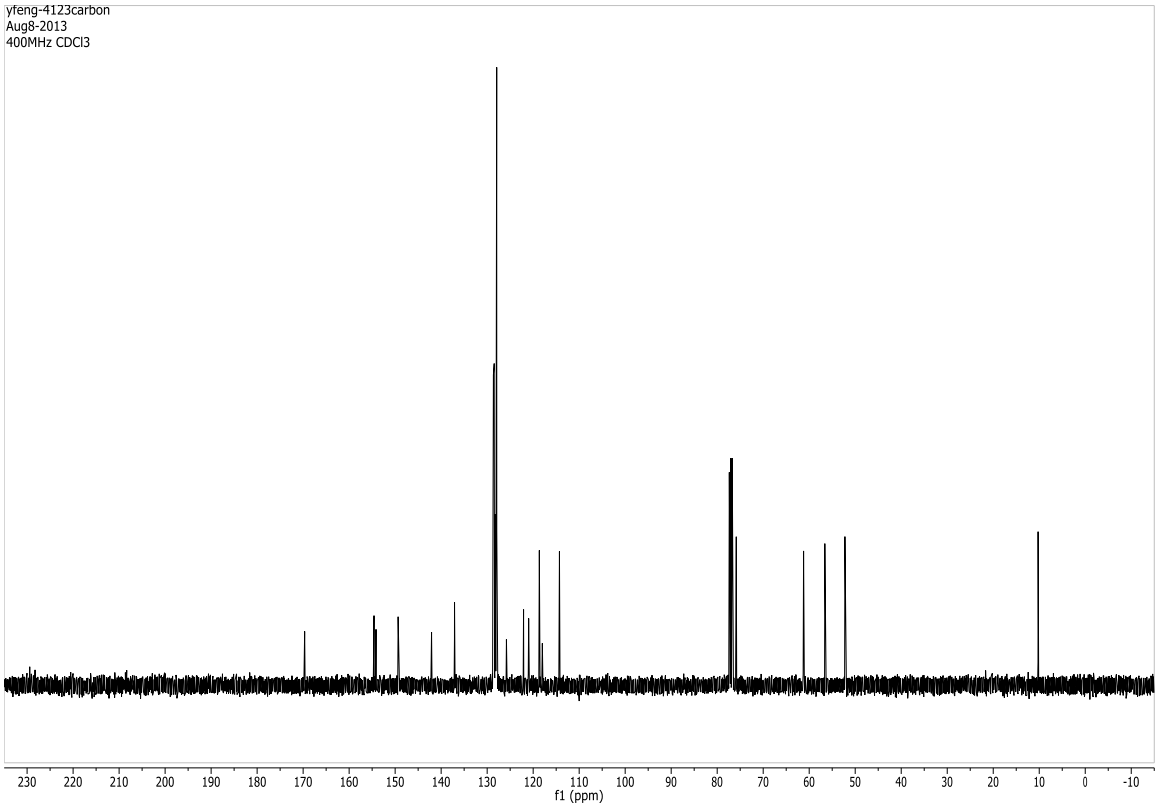

yfeng-4-114carbon
f1 (ppm)


OBn
O
Me
BnO
O
MeO
O


yfeng-4-098
f1 (ppm)


f1 (ppm)


OBn
OMe
Me
BnO
OMe
MeO
O


yfeng-4123carbon
Aug8-2013
400MHz CDCl3
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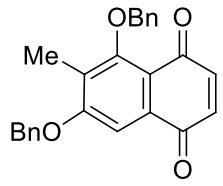
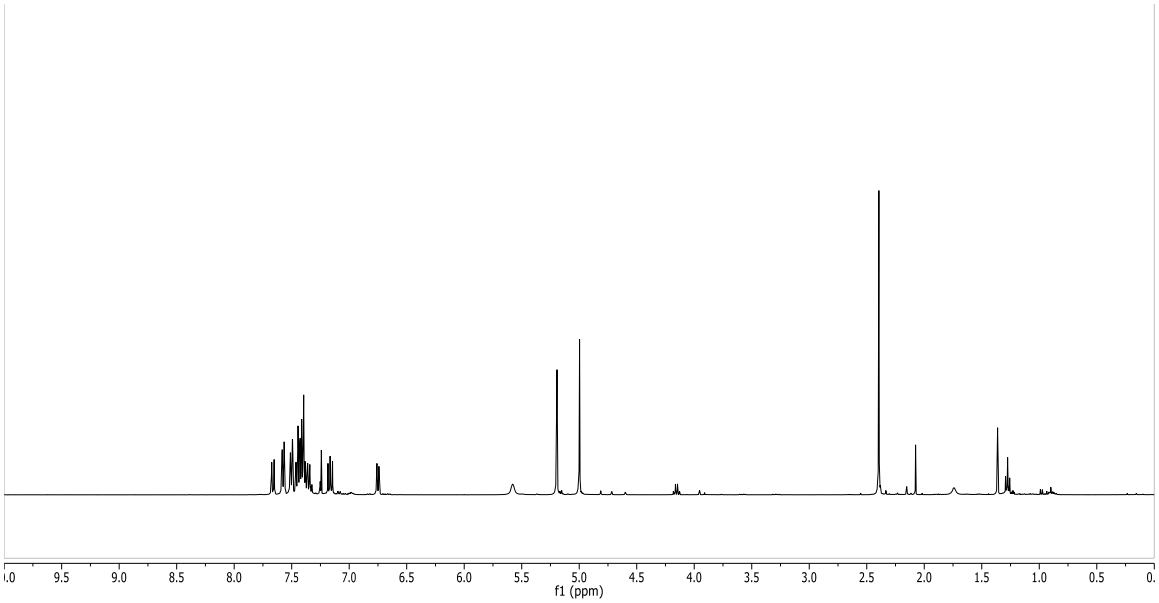
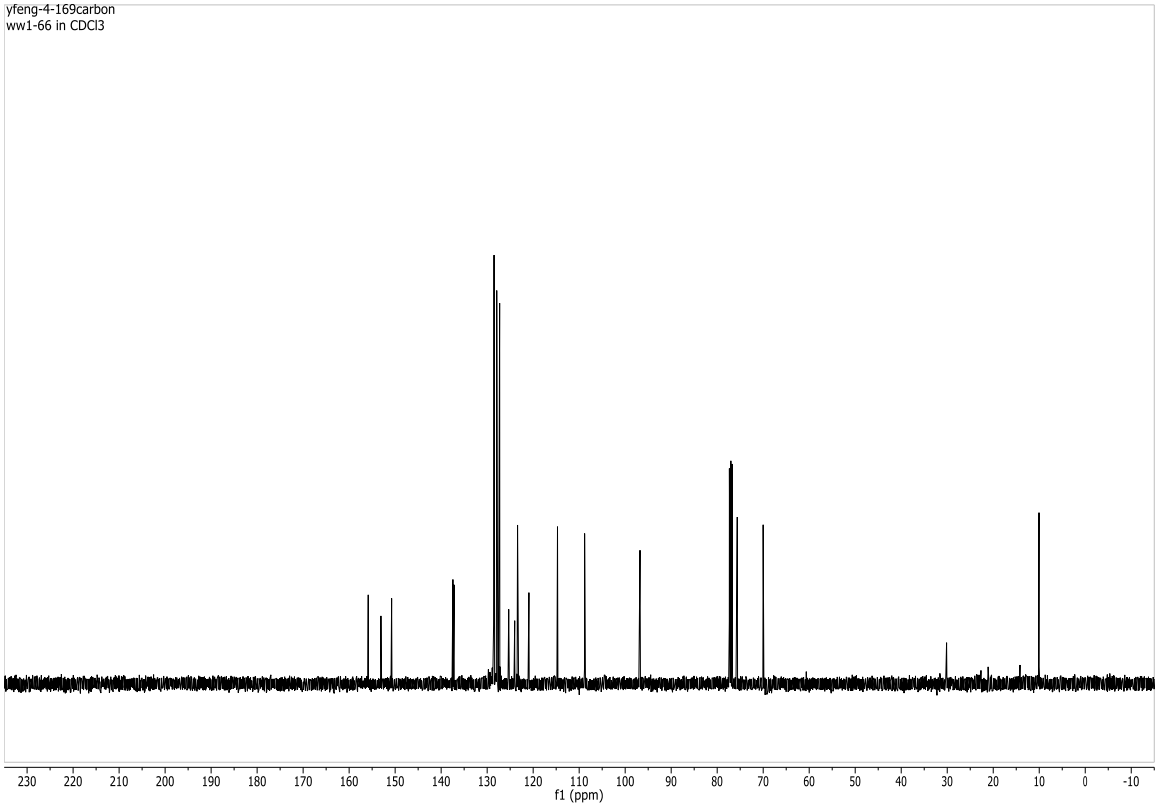
f1 (ppm)


OBn
O
Me
BnO
O


f1 (ppm)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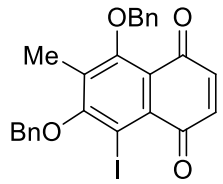
ww1-66 in CDCl3
f1 (ppm)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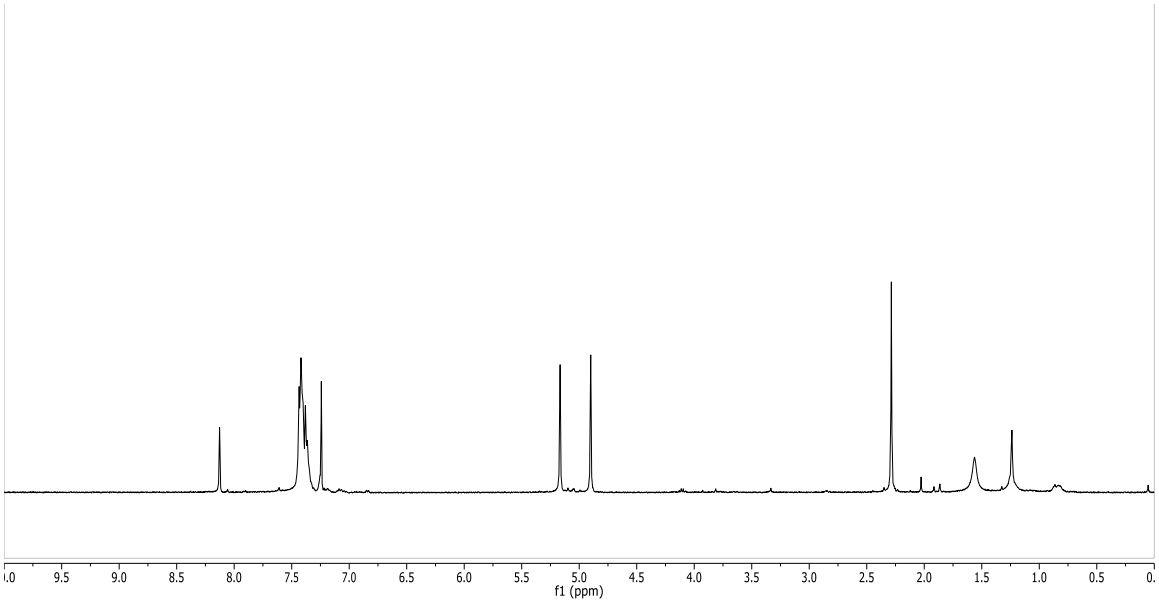
O
Me
BnO
I
O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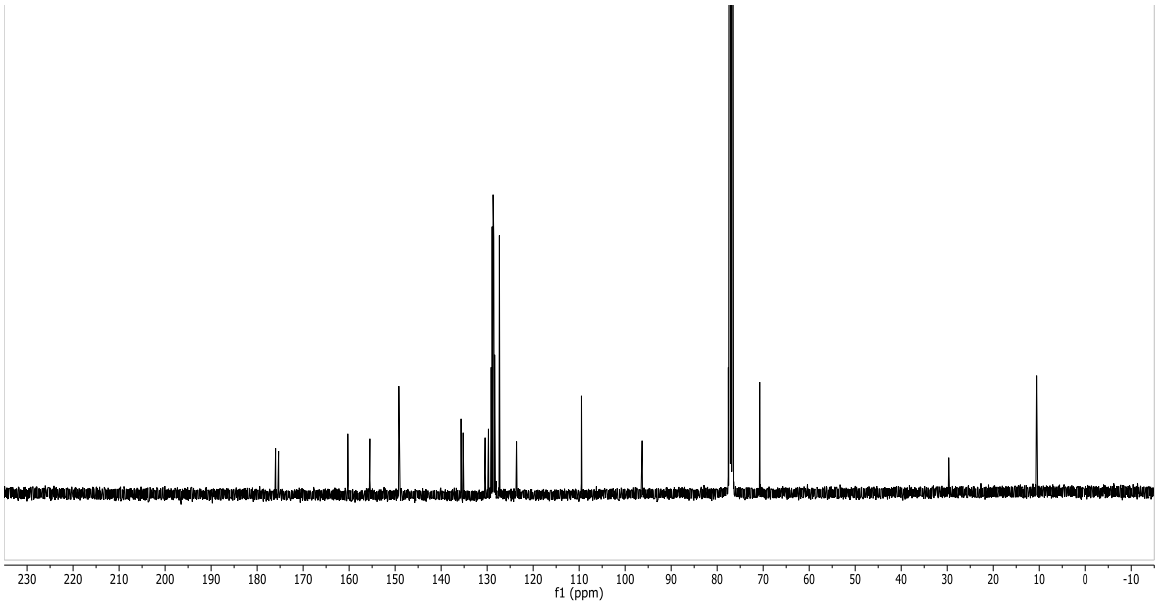
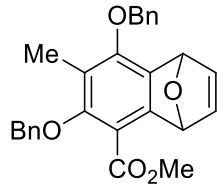

f1 (ppm)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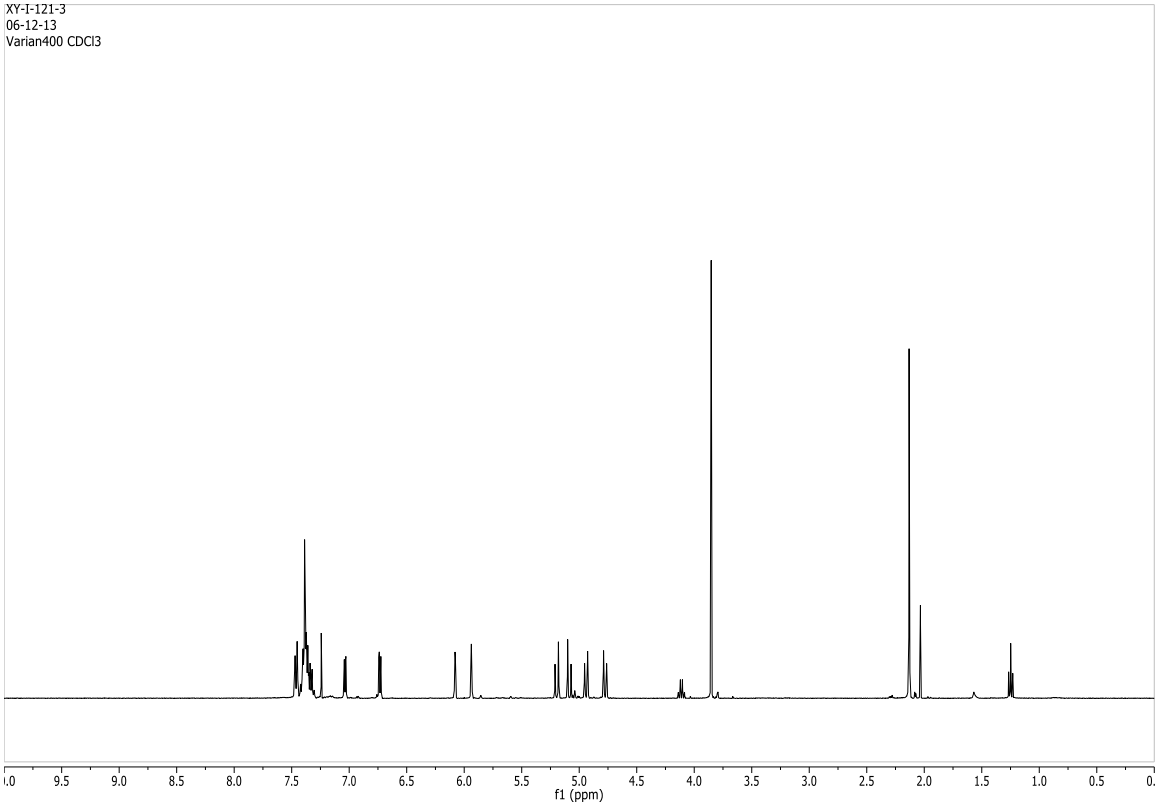
Me
O
BnO
CO2Me


XY-I-121-3
06-12-13
Varian400 CDCl3
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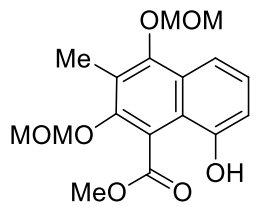
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)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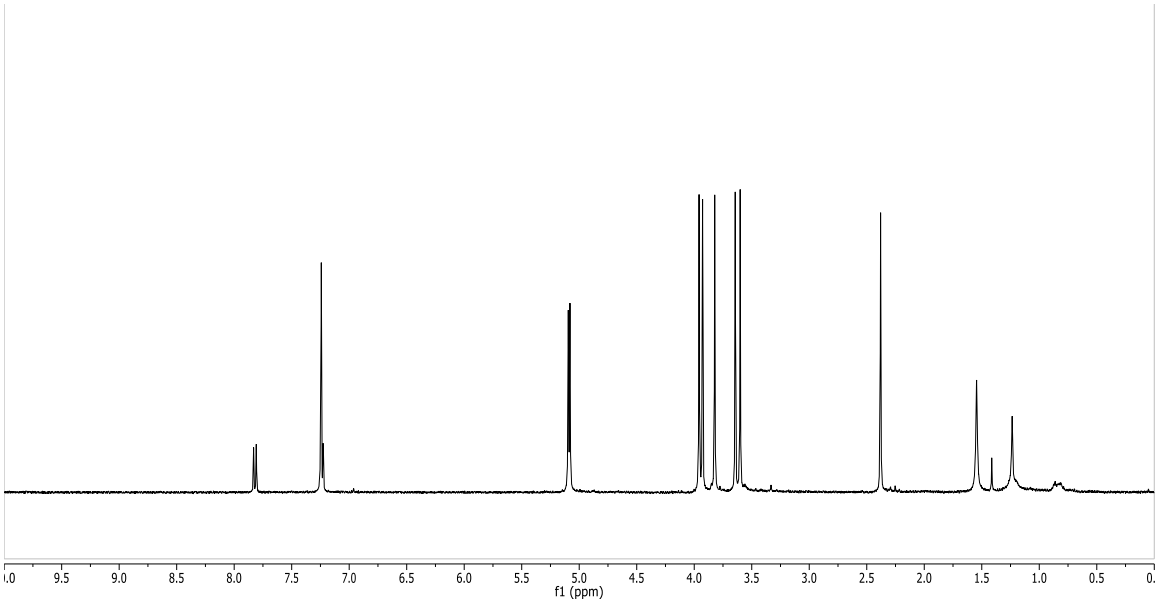
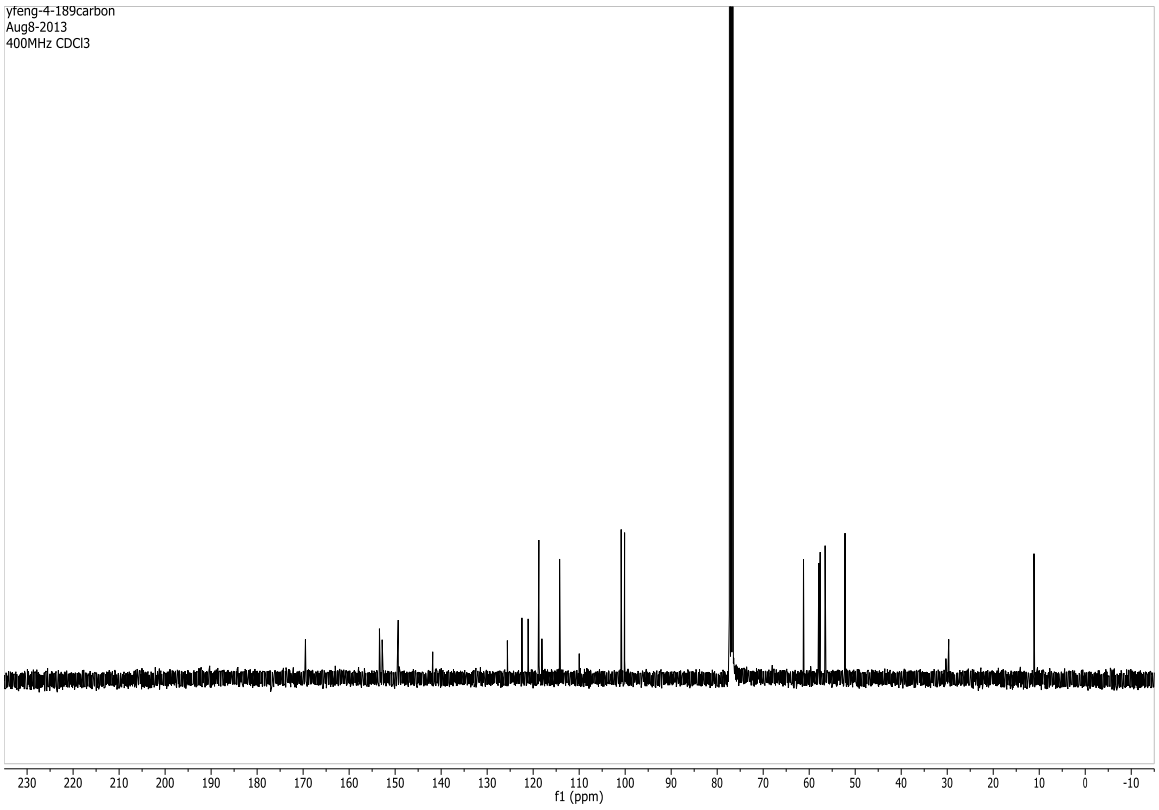
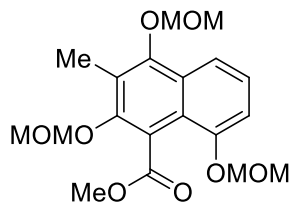
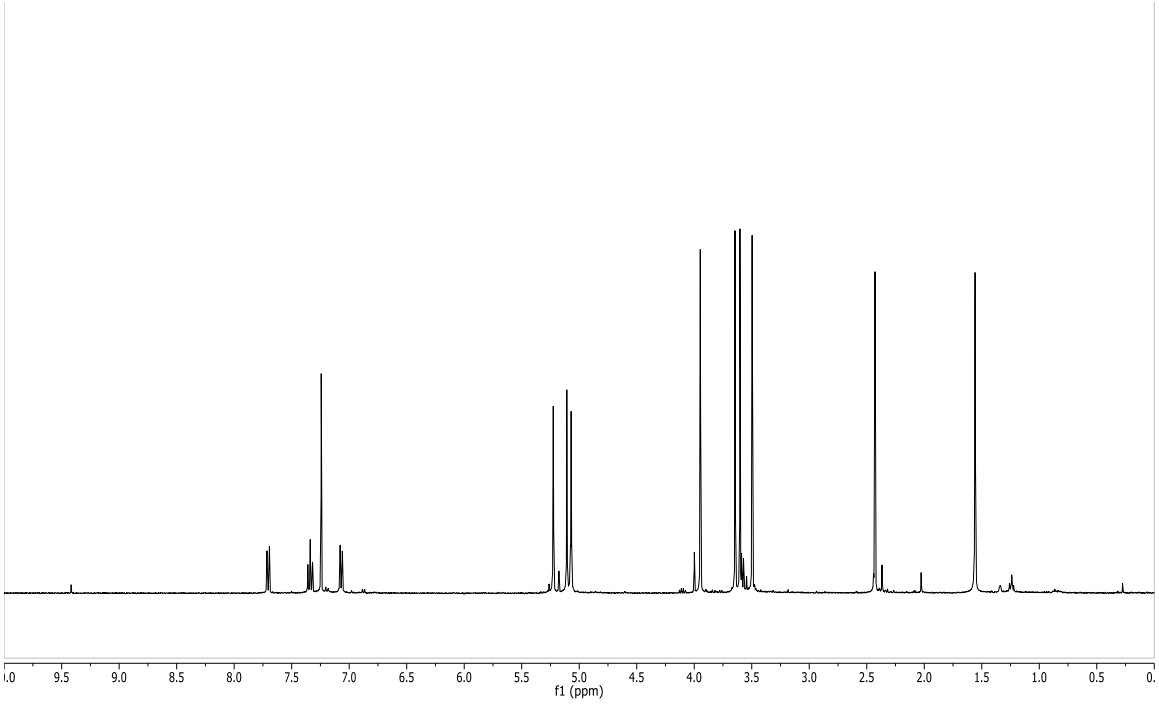
Me
MOMO
OH
MeO
O


f1 (ppm)


yfeng-4-189carbon
Aug8-2013
400MHz CDCl3
f1 (ppm)


OMOM
Me
MOMO
OMOM
MeO
O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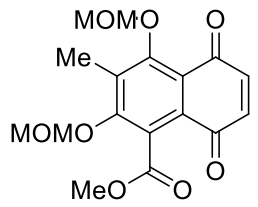
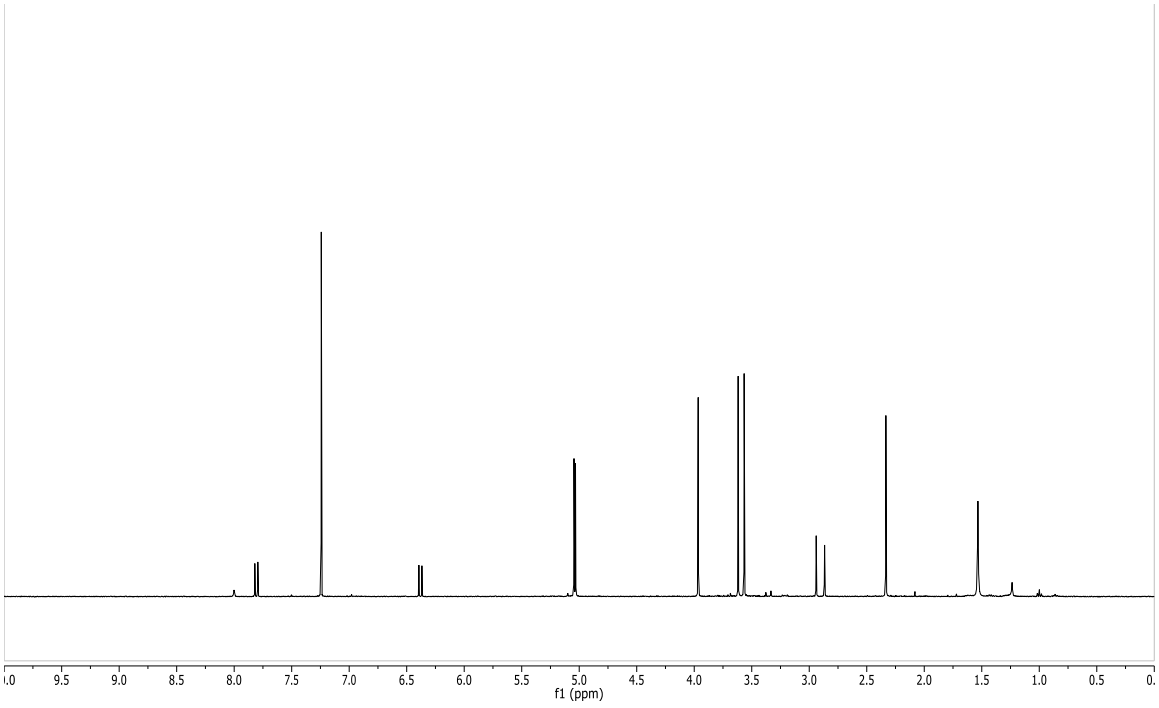
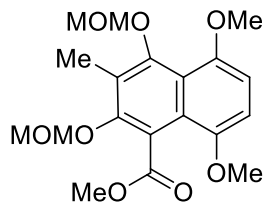
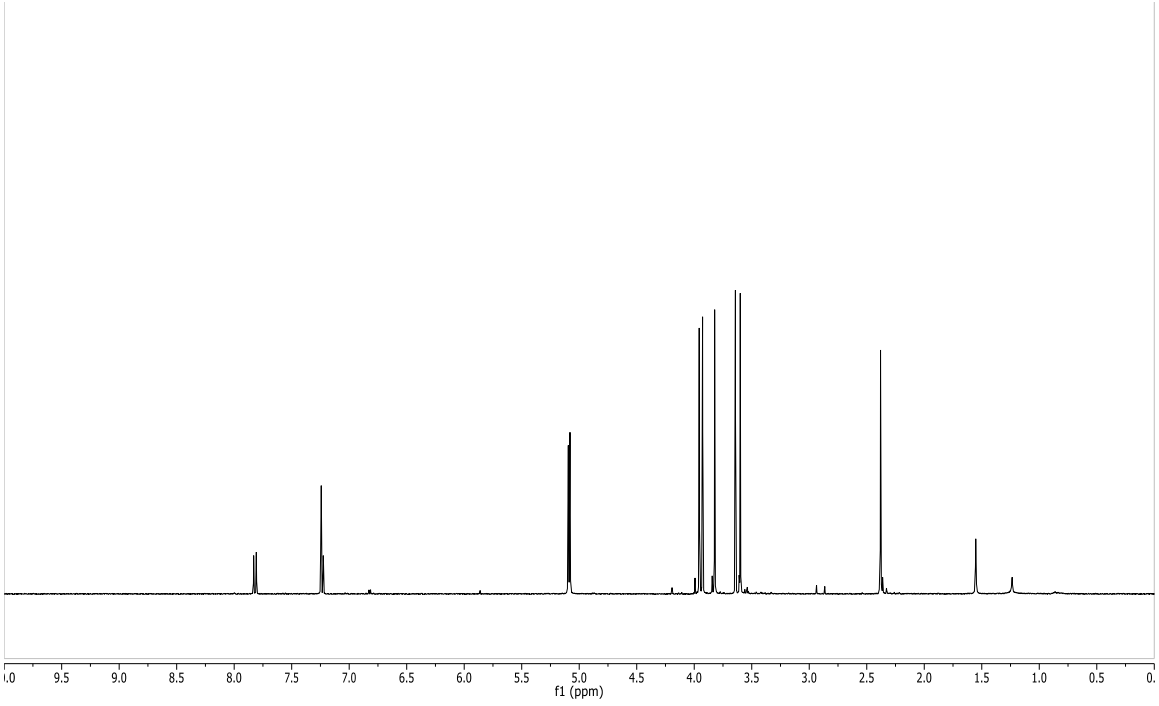
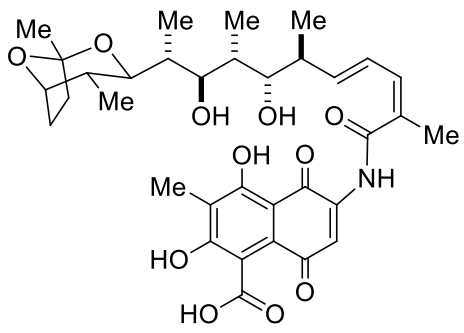
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

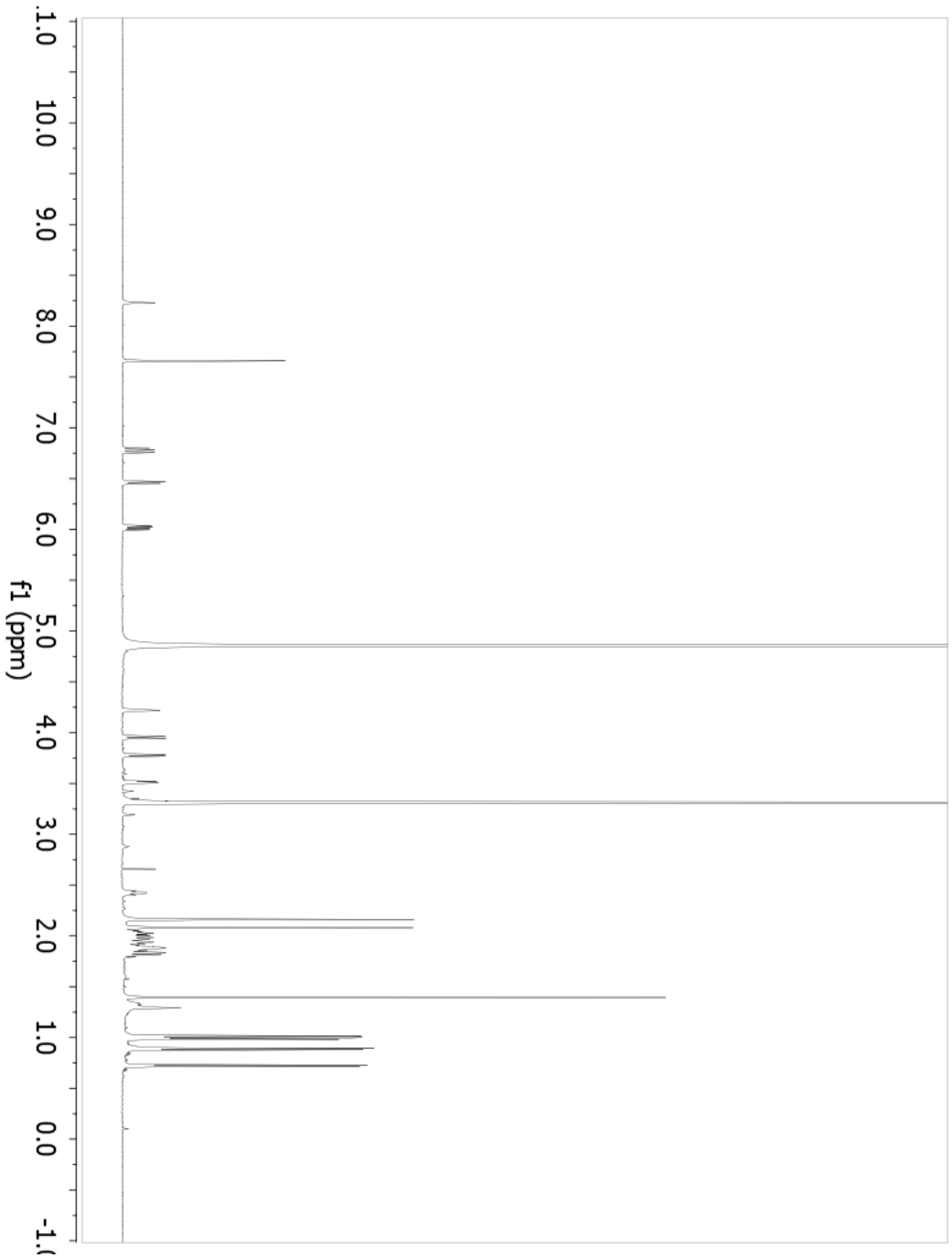

MOMO
O
Me
MOMO
O
MeO
O

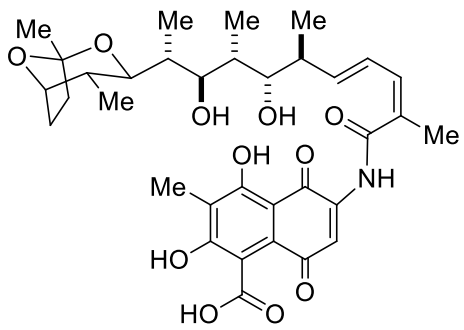

9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

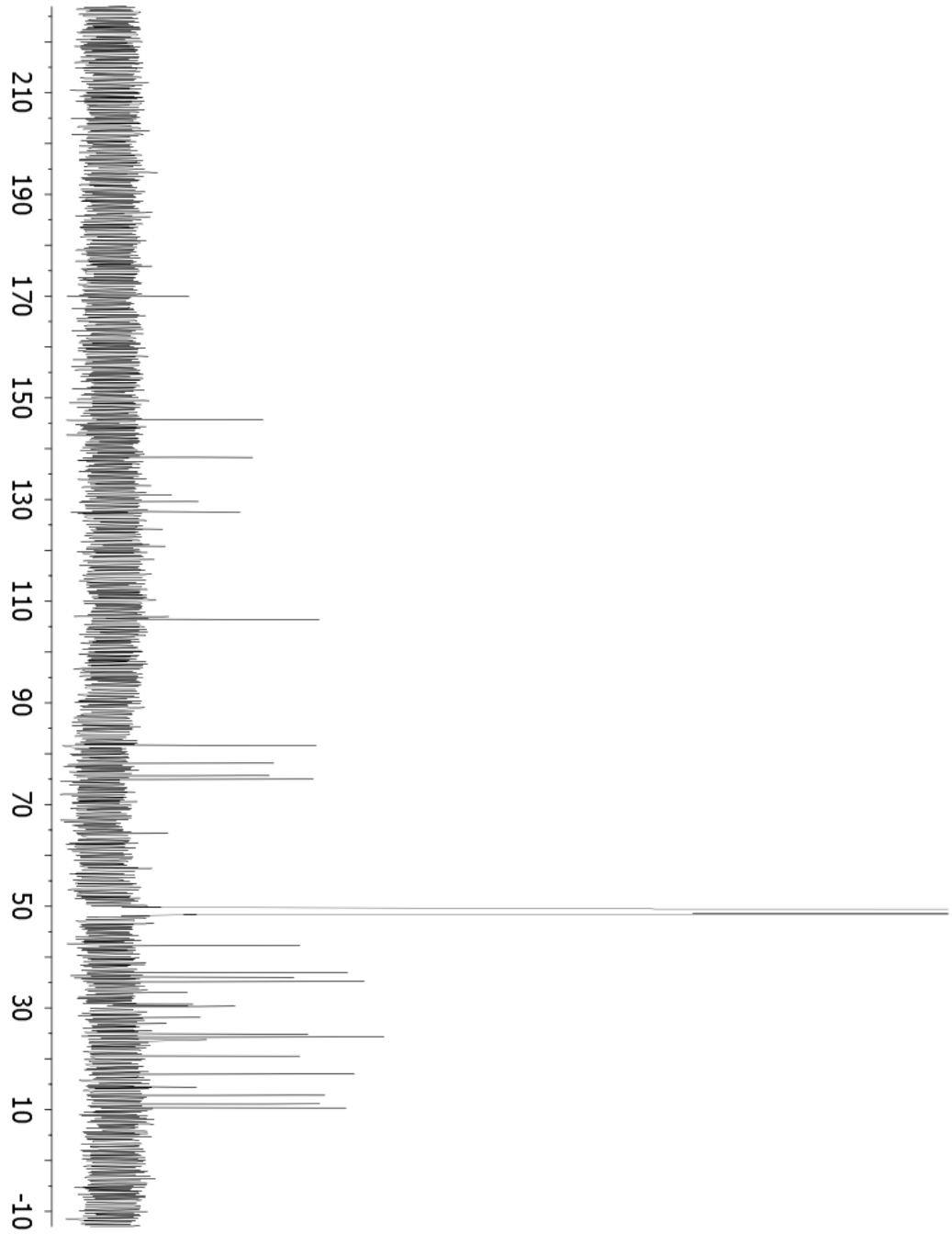

MOMO
OMe
Me
MOMO
OMe
MeO
O


f1 (ppm)


Me
O
O
Me
Me
Me
Me
OH
OH
O
Me
NH
OH
O
Me
HO
O
HO
O


f1 (ppm)
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0


Me
O
O
Me
Me
Me
Me
Me
OH
OH
O
Me
OH
O
NH
Me
HO
O
HO
O


210
190
170
150
130
110
90
70
50
30
10
-10

Appendix B: Crystal Structures Relevant to Chapters 3 and 6

1 X-ray Crystal Structure of 231

Crystals of **231** for X-ray analysis were obtained by slow evaporation from Hexanes and EtOAc (colorless needles). X-ray data were collected using Bruker Kappa CCD (charge couple device) based diffractometer. A suitable crystal (0.2 mm x 0.2 mm x 0.8 mm) was mounted on a glass fiber. The crystal was stable during data collection.

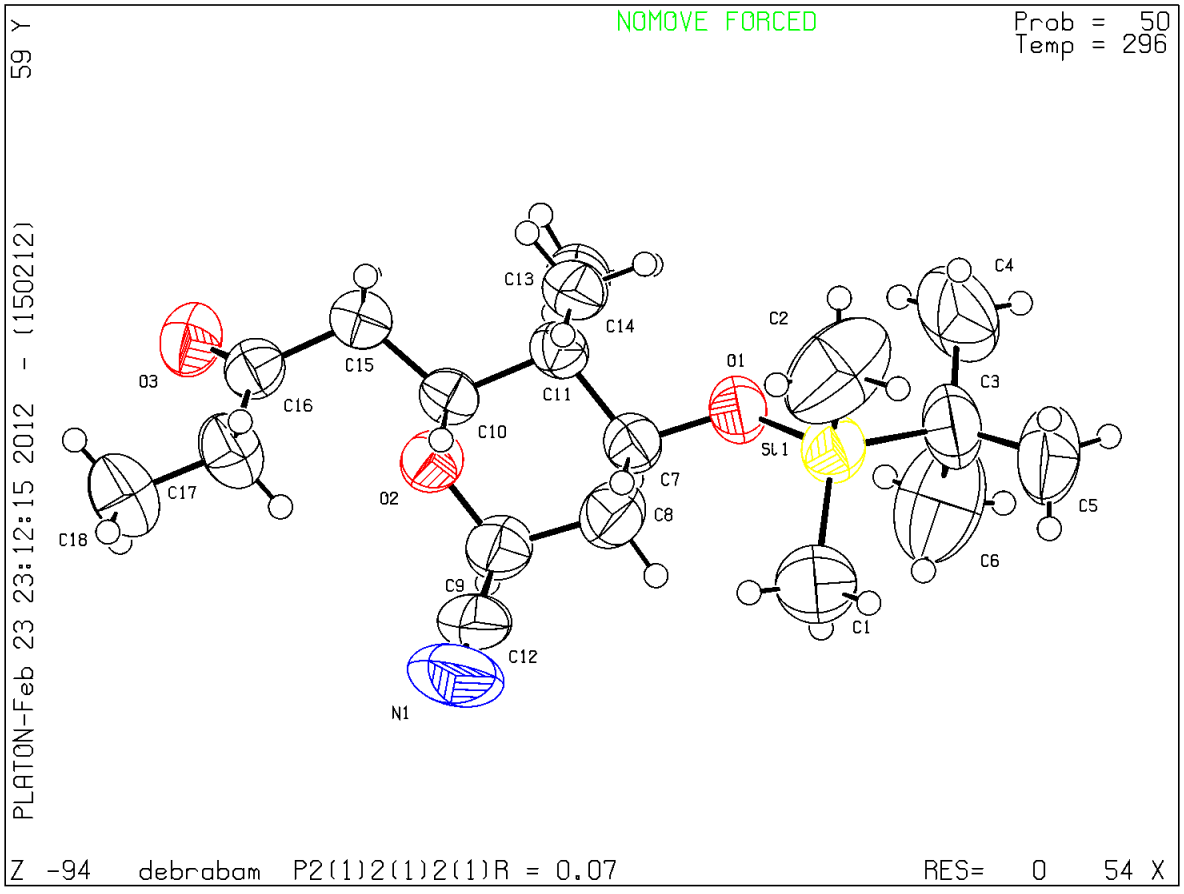


Figure B1. X-ray Crystal Structure of **231**

Table B1. Crystal data and structure refinement for **231**

Identifer	**231**
Literature Reference	unknown
Formula	$C_{18}H_{33}NO_3Si$
Space Group	P 2_1 2_1 2_1
Cell Lengths	a 7.818(2) b 9.973 (3) c 27.516(8)
Cell Angles	α90.00 β 90.00 γ 90.00
Cell Volume	2145.61
Z, Z'	Z: 4 Z':0
R-Factor (%)	6.51

Table B2. Bond lengths [Å] for **231**.

Number	Atom1	Atom 2	Type	Polymeric	Length	SybylType
1	Si1	O1	Unknown	no	1.650(2)	1
2	Si1	C1	Unknown	no	1.826(4)	1
3	Si1	C2	Unknown	no	1.872(5)	1
4	Si1	C3	Unknown	no	1.849(3)	1
5	N1	C12	Unknown	no	1.127(5)	un
6	O1	C7	Unknown	no	1.428(3)	1
7	O2	C9	Unknown	no	1.413(3)	1
8	O2	C10	Unknown	no	1.446(3)	1
9	O3	C16	Unknown	no	1.216(3)	2
10	C1	H1A	Unknown	no	0.959(4)	1
11	C1	H1B	Unknown	no	0.960(4)	1
12	C1	H1C	Unknown	no	0.960(6)	1
13	C2	H2A	Unknown	no	0.960(5)	1
14	C2	H2B	Unknown	no	0.960(5)	1
15	C2	H2C	Unknown	no	0.959(5)	1
16	C3	C4	Unknown	no	1.516(6)	1
17	C3	C5	Unknown	no	1.516(6)	1
18	C3	C6	Unknown	no	1.609(7)	1
19	C4	H4A	Unknown	no	0.961(7)	1
20	C4	H4B	Unknown	no	0.960(5)	1
21	C4	H4C	Unknown	no	0.959(5)	1
22	C5	H5A	Unknown	no	0.960(5)	1
23	C5	H5B	Unknown	no	0.959(5)	1
24	C5	H5C	Unknown	no	0.960(6)	1
25	C6	H6A	Unknown	no	0.960(6)	1
26	C6	H6B	Unknown	no	0.960(6)	1
27	C6	H6C	Unknown	no	0.959(6)	1

28	C7	H7	Unknown	no	0.980(2)	1
29	C7	C8	Unknown	no	1.511(4)	1
30	C7	C11	Unknown	no	1.528(3)	1
31	C8	H8A	Unknown	no	0.970(3)	1
32	C8	H8B	Unknown	no	0.971(3)	1
33	C8	C9	Unknown	no	1.525(4)	1
34	C9	H9	Unknown	no	0.980(2)	1
35	C9	C12	Unknown	no	1.501(4)	1
36	C10	H10	Unknown	no	0.980(2)	1
37	C10	C11	Unknown	no	1.542(3)	1
38	C10	C15	Unknown	no	1.507(3)	1
39	C11	C13	Unknown	no	1.550(3)	1
40	C11	C14	Unknown	no	1.512(4)	1
41	C13	H13A	Unknown	no	0.960(3)	1
42	C13	H13B	Unknown	no	0.960(3)	1
43	C13	H13C	Unknown	no	0.961(3)	1
44	C14	H14A	Unknown	no	0.960(3)	1
45	C14	H14B	Unknown	no	0.960(3)	1
46	C14	H14C	Unknown	no	0.960(3)	1
47	C15	H15A	Unknown	no	0.970(2)	1
48	C15	H15B	Unknown	no	0.970(2)	1
49	C15	C16	Unknown	no	1.511(4)	1
50	C16	C17	Unknown	no	1.499(4)	1
51	C17	H17A	Unknown	no	0.971(3)	1
52	C17	H17B	Unknown	no	0.970(3)	1
53	C17	C18	Unknown	no	1.499(4)	1
54	C18	H18A	Unknown	no	0.960(4)	1
55	C18	H18B	Unknown	no	0.960(4)	1
56	C18	H18C	Unknown	no	0.960(4)	1

Table B3. Bond angles [deg] for **231**

Number	Atom1	Atom2	Atom3	Angle
1	O1	Si1	C1	111.2(2)
2	O1	Si1	C2	110.7(2)
3	O1	Si1	C3	104.5(1)
4	C1	Si1	C2	106.9(2)
5	C1	Si1	C3	113.4(2)
6	C2	Si1	C3	110.3(2)
7	Si1	O1	C7	127.1(1)
8	C9	O2	C10	114.0(2)
9	Si1	C1	H1A	109.4(4)
10	Si1	C1	H1B	109.5(4)
11	Si1	C1	H1C	109.4(4)
12	H1A	C1	H1B	109.4(4)
13	H1A	C1	H1C	109.6(4)
14	H1B	C1	H1C	109.5(4)
15	Si1	C2	H2A	109.5(4)
16	Si1	C2	H2B	109.5(4)
17	Si1	C2	H2C	109.5(4)
18	H2A	C2	H2B	109.5(5)
19	H2A	C2	H2C	109.4(5)
20	H2B	C2	H2C	109.4(5)
21	Si1	C3	C4	110.2(3)
22	Si1	C3	C5	111.6(3)
23	Si1	C3	C6	104.6(3)
24	C4	C3	C5	109.6(4)
25	C4	C3	C6	111.1(4)
26	C5	C3	C6	109.8(3)
27	C3	C4	H4A	109.5(5)
28	C3	C4	H4B	109.5(5)

29	C3	C4	H4C	109.5(5)
30	H4A	C4	H4B	109.5(5)
31	H4A	C4	H4C	109.4(5)
32	H4B	C4	H4C	109.5(5)
33	C3	C5	H5A	109.5(4)
34	C3	C5	H5B	109.5(4)
35	C3	C5	H5C	109.5(4)
36	H5A	C5	H5B	109.5(5)
37	H5A	C5	H5C	109.4(5)
38	H5B	C5	H5C	109.5(5)
39	C3	C6	H6A	109.5(5)
40	C3	C6	H6B	109.5(5)
41	C3	C6	H6C	109.5(5)
42	H6A	C6	H6B	109.3(6)
43	H6A	C6	H6C	109.5(6)
44	H6B	C6	H6C	109.5(6)
45	O1	C7	H7	108.1(2)
46	O1	C7	C8	109.0(2)
47	O1	C7	C11	110.8(2)
48	H7	C7	C8	108.2(2)
49	H7	C7	C11	108.2(2)
50	C8	C7	C11	112.4(2)
51	C7	C8	H8A	109.3(3)
52	C7	C8	H8B	109.2(3)
53	C7	C8	C9	111.7(2)
54	H8A	C8	H8B	108.0(3)
55	H8A	C8	C9	109.2(3)
56	H8B	C8	C9	109.3(3)
57	O2	C9	C8	111.5(2)
58	O2	C9	H9	108.6(2)
59	O2	C9	C12	109.3(2)

60	C8	C9	H9	108.6(2)
61	C8	C9	C12	110.3(2)
62	H9	C9	C12	108.6(3)
63	O2	C10	H10	108.0(2)
64	O2	C10	C11	112.0(2)
65	O2	C10	C15	104.6(2)
66	H10	C10	C11	107.9(2)
67	H10	C10	C15	108.0(2)
68	C11	C10	C15	116.0(2)
69	C7	C11	C10	105.5(2)
70	C7	C11	C13	111.0(2)
71	C7	C11	C14	109.2(2)
72	C10	C11	C13	111.3(2)
73	C10	C11	C14	109.5(2)
74	C13	C11	C14	110.2(2)
75	N1	C12	C9	178.3(4)
76	C11	C13	H13A	109.5(2)
77	C11	C13	H13B	109.5(2)
78	C11	C13	H13C	109.5(2)
79	H13A	C13	H13B	109.4(3)
80	H13A	C13	H13C	109.5(3)
81	H13B	C13	H13C	109.4(3)
82	C11	C14	H14A	109.5(2)
83	C11	C14	H14B	109.5(2)
84	C11	C14	H14C	109.4(2)
85	H14A	C14	H14B	109.5(3)
86	H14A	C14	H14C	109.6(3)
87	H14B	C14	H14C	109.4(3)
88	C10	C15	H15A	108.7(2)
89	C10	C15	H15B	108.7(2)
90	C10	C15	C16	114.2(2)

91	H15A	C15	H15B	107.6(2)
92	H15A	C15	C16	108.7(2)
93	H15B	C15	C16	108.8(2)
94	O3	C16	C15	120.3(2)
95	O3	C16	C17	122.3(2)
96	C15	C16	C17	117.4(2)
97	C16	C17	H17A	108.6(2)
98	C16	C17	H17B	108.7(2)
99	C16	C17	C18	114.6(3)
100	H17A	C17	H17B	107.6(3)
101	H17A	C17	C18	108.6(3)
102	H17B	C17	C18	108.6(3)
103	C17	C18	H18A	109.5(3)
104	C17	C18	H18B	109.4(3)
105	C17	C18	H18C	109.5(3)
106	H18A	C18	H18B	109.4(4)
107	H18A	C18	H18C	109.5(4)
108	H18B	C18	H18C	109.5(4)

Table B4. Atoms Information for **231**

Number	Label	Charge	SybylType	Xfrac + ESD	Yfrac + ESD	Zfrac + ESD	Symm. op.
1	Si1	0	Si	0.31079(13)	0.13620(8)	0.32964(3)	x,y,z
2	N1	0	N.1	0.1178(6)	0.2700(4)	0.52282(13)	x,y,z
3	O1	0	O.3	0.2441(2)	0.28899(17)	0.34267(6)	x,y,z
4	O2	0	O.3	0.0973(2)	0.54726(18)	0.45380(6)	x,y,z
5	O3	0	O.2	0.2476(2)	0.8361(2)	0.51145(7)	x,y,z
6	C1	0	C.3	0.2499(8)	0.0174(4)	0.37710(13)	x,y,z
7	H1A	0	H	0.2910	0.0488	0.4079	x,y,z
8	H1B	0	H	0.2992	-0.0687	0.3702	x,y,z
9	H1C	0	H	0.1276	0.0096	0.3781	x,y,z
10	C2	0	C.3	0.5496(6)	0.1314(5)	0.3252(2)	x,y,z
11	H2A	0	H	0.5877	0.1991	0.3029	x,y,z
12	H2B	0	H	0.5852	0.0448	0.3138	x,y,z
13	H2C	0	H	0.5985	0.1478	0.3566	x,y,z
14	C3	0	C.3	0.2135(5)	0.0987(4)	0.26991(11)	x,y,z
15	C4	0	C.3	0.2630(9)	0.2052(5)	0.23319(15)	x,y,z
16	H4A	0	H	0.3853	0.2078	0.2300	x,y,z
17	H4B	0	H	0.2224	0.2910	0.2440	x,y,z
18	H4C	0	H	0.2128	0.1842	0.2023	x,y,z
19	C5	0	C.3	0.2672(8)	-0.0381(4)	0.25134(16)	x,y,z
20	H5A	0	H	0.2239	-0.0508	0.2190	x,y,z
21	H5B	0	H	0.2220	-0.1063	0.2723	x,y,z
22	H5C	0	H	0.3898	-0.0438	0.2509	x,y,z
23	C6	0	C.3	0.0107(7)	0.1001(6)	0.2799(2)	x,y,z
24	H6A	0	H	-0.0257	0.1901	0.2867	x,y,z
25	H6B	0	H	-0.0148	0.0439	0.3073	x,y,z
26	H6C	0	H	-0.0484	0.0672	0.2518	x,y,z
27	C7	0	C.3	0.2264(3)	0.3471(2)	0.38982(8)	x,y,z
28	H7	0	H	0.2832	0.2881	0.4133	x,y,z
29	C8	0	C.3	0.0388(4)	0.3539(3)	0.40275(10)	x,y,z
30	H8A	0	H	-0.0075	0.2638	0.4042	x,y,z

31	H8B	0	H	-0.0220	0.4024	0.3775	x,y,z
32	C9	0	C.3	0.0101(3)	0.4233(3)	0.45145(11)	x,y,z
33	H9	0	H	-0.1126	0.4400	0.4554	x,y,z
34	C10	0	C.3	0.2783(3)	0.5378(2)	0.44357(7)	x,y,z
35	H10	0	H	0.3287	0.4747	0.4668	x,y,z
36	C11	0	C.3	0.3131(3)	0.4843(2)	0.39193(7)	x,y,z
37	C12	0	C.1	0.0693(4)	0.3351(3)	0.49232(12)	x,y,z
38	C13	0	C.3	0.2394(4)	0.5797(3)	0.35269(9)	x,y,z
39	H13A	0	H	0.3096	0.6584	0.3505	x,y,z
40	H13B	0	H	0.1250	0.6051	0.3614	x,y,z
41	H13C	0	H	0.2378	0.5347	0.3218	x,y,z
42	C14	0	C.3	0.5035(4)	0.4669(3)	0.38476(9)	x,y,z
43	H14A	0	H	0.5477	0.4079	0.4093	x,y,z
44	H14B	0	H	0.5589	0.5525	0.3872	x,y,z
45	H14C	0	H	0.5247	0.4294	0.3532	x,y,z
46	C15	0	C.3	0.3474(3)	0.6755(2)	0.45469(9)	x,y,z
47	H15A	0	H	0.3004	0.7385	0.4314	x,y,z
48	H15B	0	H	0.4705	0.6744	0.4504	x,y,z
49	C16	0	C.2	0.3073(3)	0.7248(3)	0.50535(9)	x,y,z
50	C17	0	C.3	0.3492(4)	0.6334(3)	0.54694(9)	x,y,z
51	H17A	0	H	0.2868	0.5501	0.5427	x,y,z
52	H17B	0	H	0.4703	0.6124	0.5458	x,y,z
53	C18	0	C.3	0.3082(5)	0.6893(4)	0.59615(11)	x,y,z
54	H18A	0	H	0.3454	0.7809	0.5979	x,y,z
55	H18B	0	H	0.3660	0.6377	0.6206	x,y,z
56	H18C	0	H	0.1870	0.6850	0.6015	x,y,z

2 X-ray Crystal Structure of 257

Crystals of **257** for X-ray analysis were obtained by slow evaporation from Hexanes and EtOAc (colorless needles). X-ray data were collected using Bruker Kappa CCD (charge couple device) based diffractometer. A suitable crystal (0.2 mm x 0.2 mm x 0.6 mm) was mounted on a glass fiber. The crystal was stable during data collection.

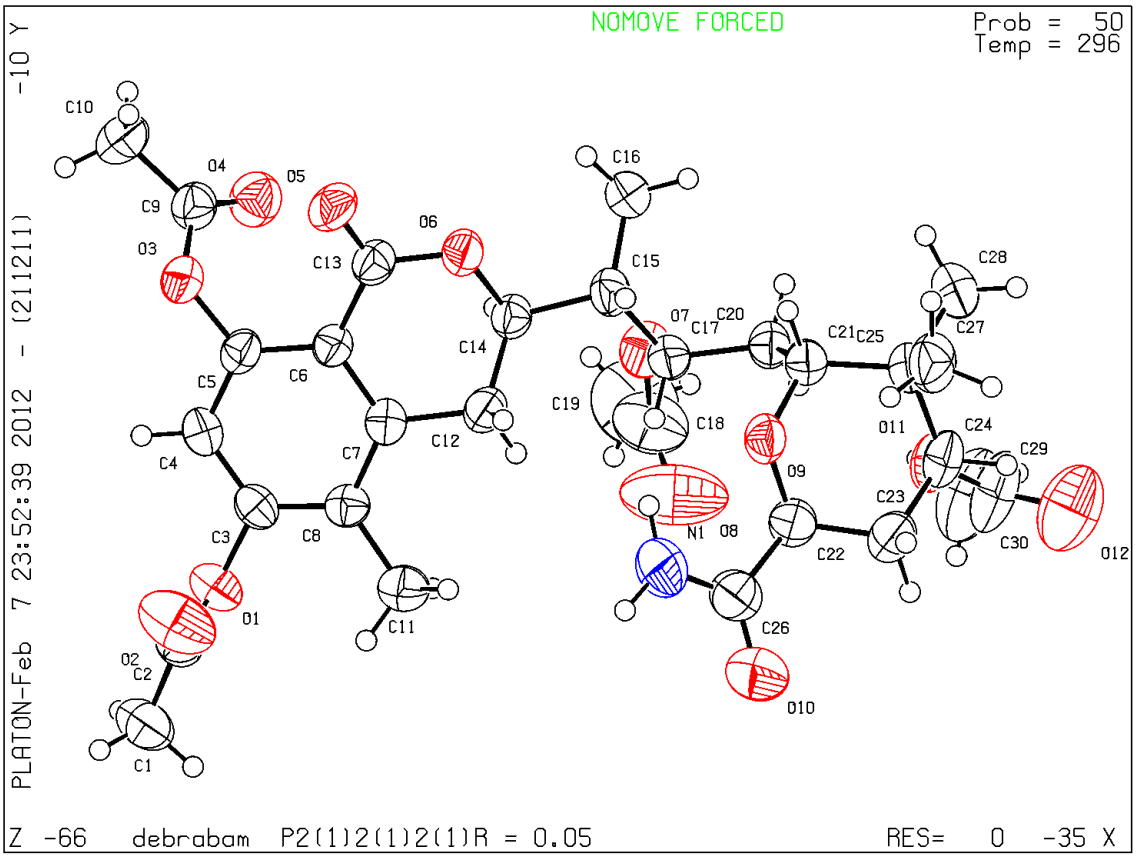


Figure B2. X-ray Crystal Structure of **257**

Table B5. Crystal data and structure refinement for **257**

Identifer	**257**
Literature Reference	unknown
Formula	$C_{30}H_{39}NO_{12}$
Space Group	P 2_1 2_1 2_1
Cell Lengths	a 10.6173(16) b 15.033 (2) c 20.101(3)
Cell Angles	α90.00 β 90.00 γ 90.00
Cell Volume	3208.32
Z, Z'	Z: 4 Z':0
R-Factor (%)	4.92

Table B6. Bond lengths [Å] for **257**.

Number	Atom1	Atom2	Type	Polymeric	Length	SybylType
1	O1	C2	Unknown	no	1.341(4)	1
2	O1	C3	Unknown	no	1.414(4)	1
3	O2	C2	Unknown	no	1.197(5)	2
4	O3	C5	Unknown	no	1.393(4)	1
5	O3	C9	Unknown	no	1.365(4)	1
6	O4	C9	Unknown	no	1.202(4)	2
7	O5	C13	Unknown	no	1.206(4)	2
8	O6	C13	Unknown	no	1.342(4)	1
9	O6	C14	Unknown	no	1.467(3)	1
10	O7	C17	Unknown	no	1.450(4)	1
11	O7	C18	Unknown	no	1.335(5)	1
12	O8	C18	Unknown	no	1.217(7)	2
13	O9	C21	Unknown	no	1.429(4)	1
14	O9	C22	Unknown	no	1.439(4)	1
15	O10	C26	Unknown	no	1.225(5)	2
16	O11	C24	Unknown	no	1.440(4)	1
17	O11	C29	Unknown	no	1.298(5)	1
18	O12	C29	Unknown	no	1.232(5)	2
19	N1	H1N1	Unknown	no	0.86(4)	1
20	N1	H2N1	Unknown	no	0.96(4)	1
21	N1	C26	Unknown	no	1.338(6)	un
22	C1	H1A	Unknown	no	0.960(4)	1
23	C1	H1B	Unknown	no	0.960(4)	1
24	C1	H1C	Unknown	no	0.961(4)	1
25	C1	C2	Unknown	no	1.472(5)	1
26	C3	C4	Unknown	no	1.382(4)	un
27	C3	C8	Unknown	no	1.375(4)	un
28	C4	H4	Unknown	no	0.931(3)	1

29	C4	C5	Unknown	no	1.371(4)	un
30	C5	C6	Unknown	no	1.396(4)	un
31	C6	C7	Unknown	no	1.400(4)	un
32	C6	C13	Unknown	no	1.486(4)	un
33	C7	C8	Unknown	no	1.410(4)	un
34	C7	C12	Unknown	no	1.501(4)	1
35	C8	C11	Unknown	no	1.499(4)	1
36	C9	C10	Unknown	no	1.486(4)	1
37	C10	H10A	Unknown	no	0.960(4)	1
38	C10	H10B	Unknown	no	0.960(4)	1
39	C10	H10C	Unknown	no	0.960(4)	1
40	C11	H11A	Unknown	no	0.961(3)	1
41	C11	H11B	Unknown	no	0.959(3)	1
42	C11	H11C	Unknown	no	0.960(3)	1
43	C12	H12A	Unknown	no	0.971(3)	1
44	C12	H12B	Unknown	no	0.970(3)	1
45	C12	C14	Unknown	no	1.505(5)	1
46	C14	H14	Unknown	no	0.981(3)	1
47	C14	C15	Unknown	no	1.525(4)	1
48	C15	H15	Unknown	no	0.980(3)	1
49	C15	C16	Unknown	no	1.531(5)	1
50	C15	C17	Unknown	no	1.526(4)	1
51	C16	H16A	Unknown	no	0.960(4)	1
52	C16	H16B	Unknown	no	0.960(4)	1
53	C16	H16C	Unknown	no	0.961(3)	1
54	C17	H17	Unknown	no	0.980(3)	1
55	C17	C20	Unknown	no	1.515(4)	1
56	C18	C19	Unknown	no	1.474(8)	1
57	C19	H19A	Unknown	no	0.959(6)	1
58	C19	H19B	Unknown	no	0.961(6)	1
59	C19	H19C	Unknown	no	0.960(6)	1

60	C20	H20A	Unknown	no	0.969(3)	1
61	C20	H20B	Unknown	no	0.971(3)	1
62	C20	C21	Unknown	no	1.529(4)	1
63	C21	H21	Unknown	no	0.981(3)	1
64	C21	C25	Unknown	no	1.548(4)	1
65	C22	H22	Unknown	no	0.980(3)	1
66	C22	C23	Unknown	no	1.511(5)	1
67	C22	C26	Unknown	no	1.505(5)	1
68	C23	H23A	Unknown	no	0.970(3)	1
69	C23	H23B	Unknown	no	0.969(4)	1
70	C23	C24	Unknown	no	1.512(4)	1
71	C24	H24	Unknown	no	0.979(3)	1
72	C24	C25	Unknown	no	1.540(4)	1
73	C25	C27	Unknown	no	1.539(5)	1
74	C25	C28	Unknown	no	1.533(5)	1
75	C27	H27A	Unknown	no	0.959(4)	1
76	C27	H27B	Unknown	no	0.961(4)	1
77	C27	H27C	Unknown	no	0.960(4)	1
78	C28	H28A	Unknown	no	0.960(4)	1
79	C28	H28B	Unknown	no	0.962(4)	1
80	C28	H28C	Unknown	no	0.959(4)	1
81	C29	C30	Unknown	no	1.463(6)	1
82	C30	H30A	Unknown	no	0.960(6)	1
83	C30	H30B	Unknown	no	0.960(6)	1
84	C30	H30C	Unknown	no	0.960(4)	1

Table B7 Bond angles [deg] for **257**

Number	Atom1	Atom2	Atom3	Angle
1	C2	O1	C3	118.6(2)
2	C5	O3	C9	118.6(2)
3	C13	O6	C14	118.8(2)
4	C17	O7	C18	117.9(3)
5	C21	O9	C22	113.9(2)
6	C24	O11	C29	122.0(3)
7	H1N1	N1	H2N1	124(4)
8	H1N1	N1	C26	114(3)
9	H2N1	N1	C26	122(3)
10	H1A	C1	H1B	109.5(4)
11	H1A	C1	H1C	109.4(4)
12	H1A	C1	C2	109.5(3)
13	H1B	C1	H1C	109.5(4)
14	H1B	C1	C2	109.5(3)
15	H1C	C1	C2	109.5(3)
16	O1	C2	O2	121.3(3)
17	O1	C2	C1	111.6(3)
18	O2	C2	C1	127.0(3)
19	O1	C3	C4	117.3(3)
20	O1	C3	C8	118.4(3)
21	C4	C3	C8	124.0(3)
22	C3	C4	H4	120.7(3)
23	C3	C4	C5	118.7(3)
24	H4	C4	C5	120.6(3)
25	O3	C5	C4	115.8(3)
26	O3	C5	C6	123.7(3)
27	C4	C5	C6	120.4(3)
28	C5	C6	C7	119.3(3)

29	C5	C6	C13	121.4(3)
30	C7	C6	C13	119.0(3)
31	C6	C7	C8	121.0(3)
32	C6	C7	C12	117.0(3)
33	C8	C7	C12	122.0(3)
34	C3	C8	C7	116.3(3)
35	C3	C8	C11	122.2(3)
36	C7	C8	C11	121.4(3)
37	O3	C9	O4	122.7(3)
38	O3	C9	C10	110.9(3)
39	O4	C9	C10	126.5(3)
40	C9	C10	H10A	109.5(3)
41	C9	C10	H10B	109.5(3)
42	C9	C10	H10C	109.5(3)
43	H10A	C10	H10B	109.4(4)
44	H10A	C10	H10C	109.5(4)
45	H10B	C10	H10C	109.4(4)
46	C8	C11	H11A	109.4(3)
47	C8	C11	H11B	109.5(3)
48	C8	C11	H11C	109.5(3)
49	H11A	C11	H11B	109.5(3)
50	H11A	C11	H11C	109.4(3)
51	H11B	C11	H11C	109.5(3)
52	C7	C12	H12A	109.6(3)
53	C7	C12	H12B	109.7(3)
54	C7	C12	C14	110.2(2)
55	H12A	C12	H12B	108.1(3)
56	H12A	C12	C14	109.6(3)
57	H12B	C12	C14	109.6(3)
58	O5	C13	O6	118.8(3)
59	O5	C13	C6	123.3(3)

60	O6	C13	C6	117.7(3)
61	O6	C14	C12	108.4(2)
62	O6	C14	H14	108.7(3)
63	O6	C14	C15	105.6(2)
64	C12	C14	H14	108.7(3)
65	C12	C14	C15	116.5(3)
66	H14	C14	C15	108.7(3)
67	C14	C15	H15	107.4(3)
68	C14	C15	C16	111.6(3)
69	C14	C15	C17	110.7(2)
70	H15	C15	C16	107.4(3)
71	H15	C15	C17	107.4(3)
72	C16	C15	C17	112.0(3)
73	C15	C16	H16A	109.5(3)
74	C15	C16	H16B	109.5(3)
75	C15	C16	H16C	109.5(3)
76	H16A	C16	H16B	109.6(3)
77	H16A	C16	H16C	109.4(3)
78	H16B	C16	H16C	109.4(3)
79	O7	C17	C15	107.3(2)
80	O7	C17	H17	108.1(3)
81	O7	C17	C20	107.9(2)
82	C15	C17	H17	108.1(3)
83	C15	C17	C20	116.9(3)
84	H17	C17	C20	108.1(3)
85	O7	C18	O8	121.5(5)
86	O7	C18	C19	112.1(4)
87	O8	C18	C19	126.1(5)
88	C18	C19	H19A	109.5(5)
89	C18	C19	H19B	109.4(5)
90	C18	C19	H19C	109.5(5)

91	H19A	C19	H19B	109.4(6)
92	H19A	C19	H19C	109.5(6)
93	H19B	C19	H19C	109.4(6)
94	C17	C20	H20A	108.8(3)
95	C17	C20	H20B	108.8(3)
96	C17	C20	C21	114.0(3)
97	H20A	C20	H20B	107.6(3)
98	H20A	C20	C21	108.8(3)
99	H20B	C20	C21	108.7(3)
100	O9	C21	C20	111.5(2)
101	O9	C21	H21	105.9(3)
102	O9	C21	C25	110.3(2)
103	C20	C21	H21	105.8(3)
104	C20	C21	C25	116.6(3)
105	H21	C21	C25	105.9(3)
106	O9	C22	H22	107.9(3)
107	O9	C22	C23	110.9(3)
108	O9	C22	C26	107.8(3)
109	H22	C22	C23	108.0(3)
110	H22	C22	C26	107.9(3)
111	C23	C22	C26	114.1(3)
112	C22	C23	H23A	109.6(3)
113	C22	C23	H23B	109.7(3)
114	C22	C23	C24	110.0(3)
115	H23A	C23	H23B	108.2(3)
116	H23A	C23	C24	109.7(3)
117	H23B	C23	C24	109.7(3)
118	O11	C24	C23	107.5(3)
119	O11	C24	H24	109.2(3)
120	O11	C24	C25	109.2(2)
121	C23	C24	H24	109.3(3)

122	C23	C24	C25	112.5(3)
123	H24	C24	C25	109.1(3)
124	C21	C25	C24	110.3(3)
125	C21	C25	C27	108.0(3)
126	C21	C25	C28	111.1(3)
127	C24	C25	C27	107.2(3)
128	C24	C25	C28	110.6(3)
129	C27	C25	C28	109.5(3)
130	O10	C26	N1	124.3(4)
131	O10	C26	C22	120.0(4)
132	N1	C26	C22	115.7(4)
133	C25	C27	H27A	109.4(3)
134	C25	C27	H27B	109.4(3)
135	C25	C27	H27C	109.5(3)
136	H27A	C27	H27B	109.5(4)
137	H27A	C27	H27C	109.6(4)
138	H27B	C27	H27C	109.4(4)
139	C25	C28	H28A	109.5(3)
140	C25	C28	H28B	109.4(3)
141	C25	C28	H28C	109.5(3)
142	H28A	C28	H28B	109.4(4)
143	H28A	C28	H28C	109.5(4)
144	H28B	C28	H28C	109.5(4)
145	O11	C29	O12	120.6(4)
146	O11	C29	C30	113.9(4)
147	O12	C29	C30	125.2(4)
148	C29	C30	H30A	109.4(4)
149	C29	C30	H30B	109.5(4)
150	C29	C30	H30C	109.6(4)
151	H30A	C30	H30B	109.5(5)
152	H30A	C30	H30C	109.5(5)

153	H30B	C30	H30C	109.4(5)

Table B8. Atoms Information for **257**

Number	Label	Charge	SybylType	Xfrac + ESD	Yfrac + ESD	Zfrac + ESD	Symm. op.
1	O1	0	O.3	0.2900(2)	0.21672(14)	0.80918(11)	x,y,z
2	O2	0	O.2	0.1910(2)	0.3074(2)	0.87840(15)	x,y,z
3	O3	0	O.3	0.6447(2)	0.40683(13)	0.81058(10)	x,y,z
4	O4	0	O.2	0.8125(2)	0.32997(16)	0.77308(12)	x,y,z
5	O5	0	O.2	0.8015(2)	0.37793(14)	0.92030(11)	x,y,z
6	O6	0	O.3	0.82914(19)	0.23844(13)	0.94897(10)	x,y,z
7	O7	0	O.3	0.8542(2)	-0.03847(14)	0.92053(11)	x,y,z
8	O8	0	O.2	0.6913(4)	-0.1305(3)	0.9324(2)	x,y,z
9	O9	0	O.3	0.75286(19)	-0.02813(13)	1.12076(10)	x,y,z
10	O10	0	O.2	0.4519(3)	-0.1249(2)	1.13157(15)	x,y,z
11	O11	0	O.3	0.8554(2)	-0.24663(14)	1.09769(11)	x,y,z
12	O12	0	O.2	0.8807(4)	-0.3760(2)	1.14692(18)	x,y,z
13	N1	0	N.am	0.5207(4)	0.0155(3)	1.1125(2)	x,y,z
14	H1N1	0	H	0.443(4)	0.031(3)	1.108(2)	x,y,z
15	H2N1	0	H	0.590(4)	0.056(3)	1.108(2)	x,y,z
16	C1	0	C.3	0.0713(3)	0.2206(3)	0.8013(2)	x,y,z
17	H1A	0	H	0.0046	0.2632	0.8064	x,y,z
18	H1B	0	H	0.0465	0.1651	0.8210	x,y,z
19	H1C	0	H	0.0881	0.2119	0.7548	x,y,z
20	C2	0	C.2	0.1856(3)	0.2538(2)	0.83447(19)	x,y,z
21	C3	0	C.2	0.4076(3)	0.2384(2)	0.83795(14)	x,y,z
22	C4	0	C.2	0.4711(3)	0.3108(2)	0.81208(15)	x,y,z
23	H4	0	H	0.4346	0.3458	0.7791	x,y,z
24	C5	0	C.2	0.5889(3)	0.33013(19)	0.83592(15)	x,y,z
25	C6	0	C.2	0.6444(3)	0.27641(17)	0.88436(14)	x,y,z
26	C7	0	C.2	0.5803(3)	0.20073(19)	0.90681(14)	x,y,z
27	C8	0	C.2	0.4568(3)	0.18205(18)	0.88516(14)	x,y,z

28	C9	0	C.2	0.7572(3)	0.3994(2)	0.77822(16)	x,y,z
29	C10	0	C.3	0.7982(4)	0.4869(2)	0.75148(19)	x,y,z
30	H10A	0	H	0.8713	0.4789	0.7240	x,y,z
31	H10B	0	H	0.8184	0.5260	0.7877	x,y,z
32	H10C	0	H	0.7315	0.5124	0.7255	x,y,z
33	C11	0	C.3	0.3860(3)	0.1026(2)	0.91027(17)	x,y,z
34	H11A	0	H	0.3987	0.0969	0.9574	x,y,z
35	H11B	0	H	0.4161	0.0501	0.8883	x,y,z
36	H11C	0	H	0.2978	0.1100	0.9013	x,y,z
37	C12	0	C.3	0.6493(3)	0.1408(2)	0.95416(15)	x,y,z
38	H12A	0	H	0.6205	0.0800	0.9484	x,y,z
39	H12B	0	H	0.6316	0.1586	0.9996	x,y,z
40	C13	0	C.2	0.7644(3)	0.3022(2)	0.91717(14)	x,y,z
41	C14	0	C.3	0.7889(3)	0.14564(18)	0.94154(15)	x,y,z
42	H14	0	H	0.8055	0.1266	0.8957	x,y,z
43	C15	0	C.3	0.8728(3)	0.0921(2)	0.98836(15)	x,y,z
44	H15	0	H	0.8585	0.1145	1.0335	x,y,z
45	C16	0	C.3	1.0126(3)	0.1053(2)	0.97243(19)	x,y,z
46	H16A	0	H	1.0319	0.0774	0.9307	x,y,z
47	H16B	0	H	1.0628	0.0791	1.0070	x,y,z
48	H16C	0	H	1.0307	0.1678	0.9696	x,y,z
49	C17	0	C.3	0.8355(3)	-0.00596(19)	0.98770(14)	x,y,z
50	H17	0	H	0.7455	-0.0100	0.9981	x,y,z
51	C18	0	C.2	0.7763(5)	-0.1014(3)	0.8981(3)	x,y,z
52	C19	0	C.3	0.8151(6)	-0.1355(4)	0.8325(3)	x,y,z
53	H19A	0	H	0.7432	-0.1594	0.8098	x,y,z
54	H19B	0	H	0.8770	-0.1815	0.8383	x,y,z
55	H19C	0	H	0.8506	-0.0880	0.8067	x,y,z
56	C20	0	C.3	0.9060(3)	-0.0671(2)	1.03467(15)	x,y,z
57	H20A	0	H	0.9955	-0.0620	1.0259	x,y,z
58	H20B	0	H	0.8815	-0.1281	1.0255	x,y,z
59	C21	0	C.3	0.8824(3)	-0.0477(2)	1.10829(15)	x,y,z
60	H21	0	H	0.9287	0.0072	1.1181	x,y,z

61	C22	0	C.3	0.6712(3)	-0.1043(2)	1.11613(17)	x,y,z
62	H22	0	H	0.6823	-0.1306	1.0719	x,y,z
63	C23	0	C.3	0.7062(3)	-0.1737(2)	1.16728(18)	x,y,z
64	H23A	0	H	0.6536	-0.2259	1.1615	x,y,z
65	H23B	0	H	0.6918	-0.1504	1.2116	x,y,z
66	C24	0	C.3	0.8432(3)	-0.1992(2)	1.15959(17)	x,y,z
67	H24	0	H	0.8676	-0.2384	1.1963	x,y,z
68	C25	0	C.3	0.9311(3)	-0.1177(2)	1.15861(17)	x,y,z
69	C26	0	C.2	0.5374(4)	-0.0719(3)	1.12137(17)	x,y,z
70	C27	0	C.3	0.9271(4)	-0.0759(3)	1.22847(17)	x,y,z
71	H27A	0	H	0.9994	-0.0385	1.2345	x,y,z
72	H27B	0	H	0.9275	-0.1222	1.2614	x,y,z
73	H27C	0	H	0.8518	-0.0411	1.2331	x,y,z
74	C28	0	C.3	1.0665(3)	-0.1457(3)	1.1423(2)	x,y,z
75	H28A	0	H	1.0664	-0.1833	1.1037	x,y,z
76	H28B	0	H	1.1014	-0.1777	1.1794	x,y,z
77	H28C	0	H	1.1165	-0.0938	1.1337	x,y,z
78	C29	0	C.2	0.8659(5)	-0.3326(3)	1.0955(2)	x,y,z
79	C30	0	C.3	0.8697(6)	-0.3689(3)	1.0280(2)	x,y,z
80	H30A	0	H	0.7893	-0.3944	1.0173	x,y,z
81	H30B	0	H	0.9335	-0.4140	1.0254	x,y,z
82	H30C	0	H	0.8887	-0.3222	0.9970	x,y,z

3 X-ray Crystal Structure of 433

Crystals of **433** for X-ray analysis were obtained by slow evaporation from Hexanes and EtOAc (colorless needles). X-ray data were collected using Bruker Kappa CCD (charge couple device) based diffractometer. A suitable crystal (0.2 mm x 0.2 mm x 0.8 mm) was mounted on a glass fiber. The crystal was stable during data collection.

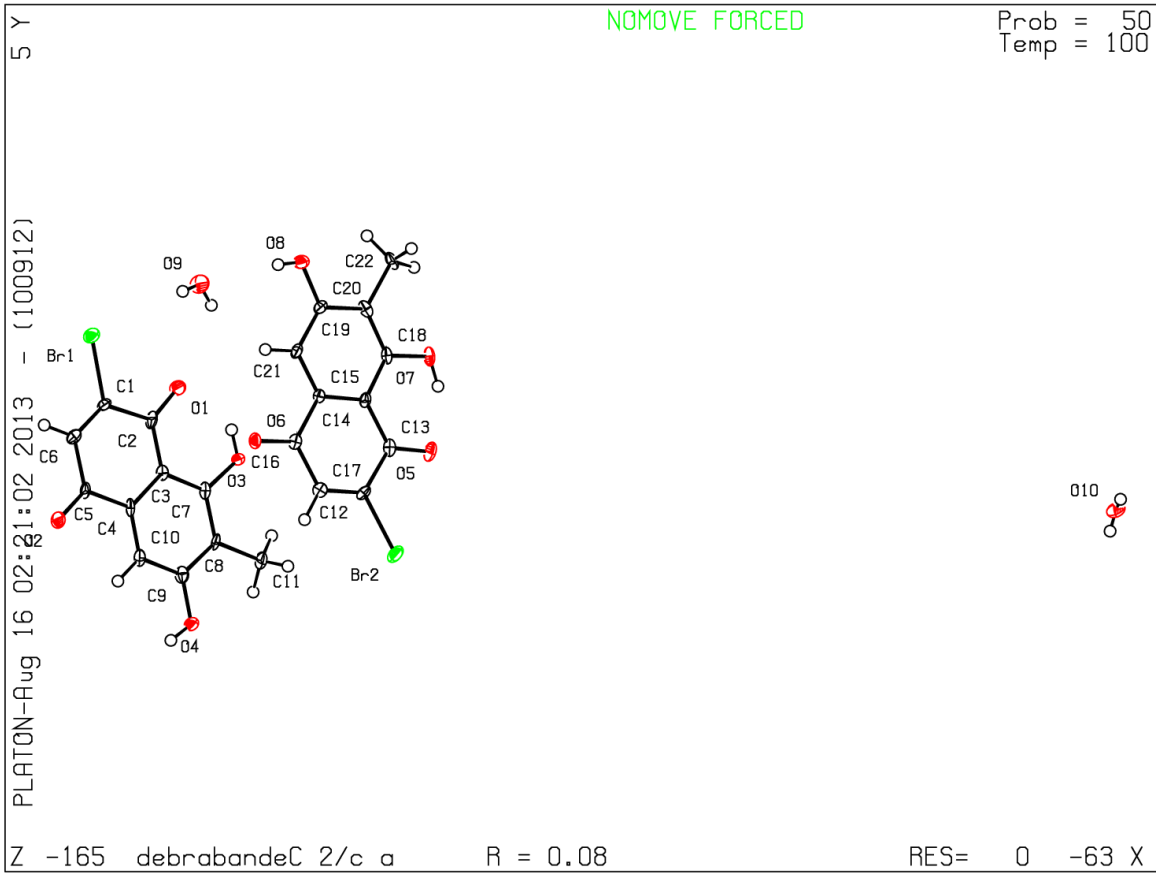


Figure B3 Crystal structure of **433**

Table B9. Crystal data and structure refinement for **433**

Identifer	**433**
Literature Reference	unknown
Formula	$C_{11}H_{7.}BrO_4$
Space Group	C 2/c
Cell Lengths	a 24.919(3) b 4.6867 (2) c 36.199(5)
Cell Angles	α 90.00 β 96.463 γ 90.00
Cell Volume	4200.74
Z, Z'	Z: 16 Z':0
R-Factor (%)	7.6

Table B10. Bond angles [deg] for **433**

Number	Atom1	Atom2	Atom3	Angle
1	H3	O3	C7	109.5(6)
2	H4	O4	C9	109.5(6)
3	Br1	C1	C2	114.8(5)
4	Br1	C1	C6	122.2(6)
5	C2	C1	C6	123.0(7)
6	O1	C2	C1	120.0(7)
7	O1	C2	C3	123.4(7)
8	C1	C2	C3	116.6(6)
9	C2	C3	C4	120.7(7)
10	C2	C3	C7	120.8(7)
11	C4	C3	C7	118.4(7)
12	C3	C4	C5	120.4(7)
13	C3	C4	C10	121.0(7)
14	C5	C4	C10	118.7(7)
15	O2	C5	C4	121.3(7)
16	O2	C5	C6	120.7(7)
17	C4	C5	C6	118.0(7)
18	C1	C6	C5	121.2(7)
19	C1	C6	H6	119.2(8)
20	C5	C6	H6	119.6(7)
21	O3	C7	C3	121.8(7)
22	O3	C7	C8	116.3(7)
23	C3	C7	C8	121.9(7)
24	C7	C8	C9	117.1(7)
25	C7	C8	C11	121.5(7)
26	C9	C8	C11	121.4(7)
27	O4	C9	C8	117.3(7)
28	O4	C9	C10	120.7(7)

29	C8	C9	C10	122.0(7)
30	C4	C10	C9	119.5(7)
31	C4	C10	H10	120.3(8)
32	C9	C10	H10	120.2(7)
33	C8	C11	H11A	109.6(7)
34	C8	C11	H11B	109.5(7)
35	C8	C11	H11C	109.5(7)
36	H11A	C11	H11B	109.6(8)
37	H11A	C11	H11C	109.5(8)
38	H11B	C11	H11C	109.2(8)
39	H7	O7	C18	109.4(6)
40	H8	O8	C20	109.5(6)
41	Br2	C12	C13	116.1(5)
42	Br2	C12	C17	121.4(6)
43	C13	C12	C17	122.5(7)
44	O5	C13	C12	120.7(7)
45	O5	C13	C14	122.1(7)
46	C12	C13	C14	117.1(6)
47	C13	C14	C15	121.4(7)
48	C13	C14	C18	121.4(7)
49	C15	C14	C18	117.2(7)
50	C14	C15	C16	119.4(7)
51	C14	C15	C21	122.1(7)
52	C16	C15	C21	118.4(7)
53	O6	C16	C15	122.8(7)
54	O6	C16	C17	118.6(7)
55	C15	C16	C17	118.6(6)
56	C12	C17	C16	121.0(7)
57	C12	C17	H17	119.6(8)
58	C16	C17	H17	119.4(7)
59	O7	C18	C14	120.9(7)

60	O7	C18	C19	117.1(7)
61	C14	C18	C19	122.0(7)
62	C18	C19	C20	118.2(7)
63	C18	C19	C22	121.6(7)
64	C20	C19	C22	120.0(7)
65	O8	C20	C19	117.5(7)
66	O8	C20	C21	121.5(7)
67	C19	C20	C21	121.0(7)
68	C15	C21	C20	119.3(7)
69	C15	C21	H21	120.4(7)
70	C20	C21	H21	120.4(7)
71	C19	C22	H22A	109.4(7)
72	C19	C22	H22B	109.6(7)
73	C19	C22	H22C	109.5(7)
74	H22A	C22	H22B	109.4(7)
75	H22A	C22	H22C	109.5(7)
76	H22B	C22	H22C	109.5(7)
77	H1O9	O9	H2O9	117(14)
78	H1O1	O10	H1O1	118(12)

Table B11 Atoms Information for **433**

Number	Label	Charge	SybylType	Xfrac + ESD	Yfrac + ESD	Zfrac + ESD	Symm. op.
1	Br1	0	Br	1.09650(3)	0.6793(2)	0.66045(2)	x,y,z
2	O1	0	O.2	0.9833(2)	0.5483(12)	0.62807(15)	x,y,z
3	O2	0	O.2	1.0655(2)	1.3836(12)	0.55098(15)	x,y,z
4	O3	0	O.3	0.8914(2)	0.5744(12)	0.58520(14)	x,y,z
5	H3	0	H	0.9104	0.5407	0.6054	x,y,z
6	O4	0	O.3	0.8805(2)	1.2006(13)	0.48360(15)	x,y,z
7	H4	0	H	0.8974	1.3359	0.4751	x,y,z
8	C1	0	C.3	1.0573(3)	0.8536(17)	0.6189(2)	x,y,z
9	C2	0	C.2	1.0002(3)	0.7425(17)	0.6095(2)	x,y,z
10	C3	0	C.2	0.9689(3)	0.8676(15)	0.5774(2)	x,y,z
11	C4	0	C.2	0.9910(3)	1.0805(17)	0.5566(2)	x,y,z
12	C5	0	C.2	1.0465(3)	1.1859(17)	0.5676(2)	x,y,z
13	C6	0	C.2	1.0783(3)	1.0486(17)	0.5995(2)	x,y,z
14	H6	0	H	1.1148	1.1038	0.6061	x,y,z
15	C7	0	C.2	0.9158(3)	0.7754(17)	0.5661(2)	x,y,z
16	C8	0	C.2	0.8850(3)	0.8889(16)	0.5345(2)	x,y,z
17	C9	0	C.2	0.9095(3)	1.0955(17)	0.5144(2)	x,y,z
18	C10	0	C.2	0.9619(3)	1.1954(18)	0.5256(2)	x,y,z
19	H10	0	H	0.9772	1.3412	0.5118	x,y,z
20	C11	0	C.3	0.8286(3)	0.788(2)	0.5226(2)	x,y,z
21	H11A	0	H	0.8028	0.9167	0.5324	x,y,z
22	H11B	0	H	0.8240	0.5946	0.5321	x,y,z
23	H11C	0	H	0.8222	0.7853	0.4953	x,y,z
24	Br2	0	Br	0.70551(3)	1.0752(2)	0.57608(2)	x,y,z
25	O5	0	O.2	0.7052(2)	0.6357(12)	0.63710(15)	x,y,z
26	O6	0	O.2	0.8986(2)	1.1421(12)	0.64167(14)	x,y,z
27	O7	0	O.3	0.7399(2)	0.2985(12)	0.69142(15)	x,y,z

28	H7	0	H	0.7192	0.3491	0.6726	x,y,z
29	O8	0	O.3	0.9147(2)	0.4522(13)	0.75028(15)	x,y,z
30	H8	0	H	0.9398	0.5730	0.7511	x,y,z
31	C12	0	C.3	0.7622(3)	0.9761(16)	0.6121(2)	x,y,z
32	C13	0	C.2	0.7504(3)	0.7434(16)	0.6387(2)	x,y,z
33	C14	0	C.2	0.7939(3)	0.6588(16)	0.6663(2)	x,y,z
34	C15	0	C.2	0.8452(3)	0.7878(16)	0.6681(2)	x,y,z
35	C16	0	C.2	0.8548(3)	1.0161(16)	0.6412(2)	x,y,z
36	C17	0	C.2	0.8103(3)	1.0978(17)	0.6130(2)	x,y,z
37	H17	0	H	0.8162	1.2400	0.5952	x,y,z
38	C18	0	C.2	0.7867(3)	0.4453(17)	0.6927(2)	x,y,z
39	C19	0	C.2	0.8270(3)	0.3766(16)	0.7212(2)	x,y,z
40	C20	0	C.2	0.8767(3)	0.5166(17)	0.7222(2)	x,y,z
41	C21	0	C.2	0.8861(3)	0.7189(17)	0.6950(2)	x,y,z
42	H21	0	H	0.9205	0.8066	0.6953	x,y,z
43	C22	0	C.3	0.8170(3)	0.1679(18)	0.7518(2)	x,y,z
44	H22A	0	H	0.8060	0.2732	0.7731	x,y,z
45	H22B	0	H	0.8502	0.0615	0.7596	x,y,z
46	H22C	0	H	0.7883	0.0346	0.7425	x,y,z
47	O9	0	O.3	0.9980(3)	0.1630(17)	0.6910(2)	x,y,z
48	H1O9	0	H	0.976(4)	0.14(2)	0.675(3)	x,y,z
49	H2O9	0	H	1.015(6)	0.29(3)	0.690(4)	x,y,z
50	O10	0	O.3	0.0000	0.805(2)	0.7500	x,y,z
51	H1O1	0	H	0.002(4)	0.87(2)	0.764(2)	x,y,z
52	H1O1	0	H	-0.002(4)	0.87(2)	0.736(2)	-x,y,1.5-z

Table B12. Bond lengths [Å] for **433**.

Number	Atom1	Atom2	Type	Polymeric	Length	SybylType
1	Br1	C1	Unknown	no	1.885(7)	1
2	O1	C2	Unknown	no	1.23(1)	2
3	O2	C5	Unknown	no	1.23(1)	2
4	O3	H3	Unknown	no	0.840(5)	1
5	O3	C7	Unknown	no	1.35(1)	1
6	O4	H4	Unknown	no	0.839(6)	1
7	O4	C9	Unknown	no	1.351(9)	1
8	C1	C2	Unknown	no	1.52(1)	1
9	C1	C6	Unknown	no	1.30(1)	1
10	C2	C3	Unknown	no	1.45(1)	un
11	C3	C4	Unknown	no	1.40(1)	un
12	C3	C7	Unknown	no	1.41(1)	un
13	C4	C5	Unknown	no	1.48(1)	un
14	C4	C10	Unknown	no	1.38(1)	un
15	C5	C6	Unknown	no	1.47(1)	un
16	C6	H6	Unknown	no	0.950(7)	1
17	C7	C8	Unknown	no	1.41(1)	un
18	C8	C9	Unknown	no	1.39(1)	un
19	C8	C11	Unknown	no	1.50(1)	1
20	C9	C10	Unknown	no	1.40(1)	un
21	C10	H10	Unknown	no	0.951(8)	1
22	C11	H11A	Unknown	no	0.977(8)	1
23	C11	H11B	Unknown	no	0.981(9)	1
24	C11	H11C	Unknown	no	0.983(7)	1
25	Br2	C12	Unknown	no	1.870(7)	1
26	O5	C13	Unknown	no	1.230(9)	2
27	O6	C16	Unknown	no	1.239(9)	2
28	O7	H7	Unknown	no	0.841(5)	1

29	O7	C18	Unknown	no	1.350(9)	1
30	O8	H8	Unknown	no	0.842(6)	1
31	O8	C20	Unknown	no	1.343(9)	1
32	C12	C13	Unknown	no	1.51(1)	1
33	C12	C17	Unknown	no	1.32(1)	1
34	C13	C14	Unknown	no	1.44(1)	un
35	C14	C15	Unknown	no	1.41(1)	un
36	C14	C18	Unknown	no	1.41(1)	un
37	C15	C16	Unknown	no	1.48(1)	un
38	C15	C21	Unknown	no	1.37(1)	un
39	C16	C17	Unknown	no	1.47(1)	un
40	C17	H17	Unknown	no	0.950(8)	1
41	C18	C19	Unknown	no	1.39(1)	un
42	C19	C20	Unknown	no	1.40(1)	un
43	C19	C22	Unknown	no	1.52(1)	1
44	C20	C21	Unknown	no	1.41(1)	un
45	C21	H21	Unknown	no	0.950(8)	1
46	C22	H22A	Unknown	no	0.980(8)	1
47	C22	H22B	Unknown	no	0.980(8)	1
48	C22	H22C	Unknown	no	0.980(8)	1
49	O9	H1O9	Unknown	no	0.8(1)	1
50	O9	H2O9	Unknown	no	0.7(1)	1
51	O10	H1O1	Unknown	no	0.59(8)	1
52	O10	H1O1	Unknown	no	0.59(8)	1