An Investigation of the Pederin Family: Total Synthesis of Theopederin D; Synthesis and Determination of the Relative and Absolute Configuration of Psymberic Acid

by

Michael Eric Green

B.S., University of Florida, 2003

Submitted to the Graduate Faculty of

Arts and Sciences in partial fulfillment

of the requirements for the degree of

Doctor of Philosophy

University of Pittsburgh

2008

UNIVERSITY OF PITTSBURGH

FACULTY OF ARTS AND SCIENCES

This dissertation was presented

by

Michael Eric Green

It was defended on

November 11th, 2008

and approved by

Prof. Craig Wilcox

Prof. Peter Wipf

Prof. Jeff Hildebrand

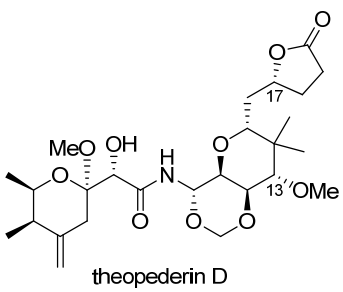
Prof. Paul E. Floreancig: Dissertation Director

An Investigation of the Pederin Family: Total Synthesis of Theopederin D; Synthesis and Determination of the Relative and Absolute Configuration of Psymberic Acid

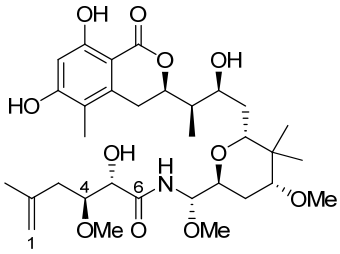
Michael Eric Green, PhD

University of Pittsburgh, 2008

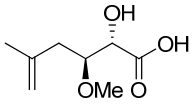
An investigation of the pederin family of natural products has led to the total synthesis of theopederin D, a synthesis of the C1-C6 portion of psymberin (psymberic acid), and the determination of the absolute configuration of C4 and C5 of this fragment.



theopederin D

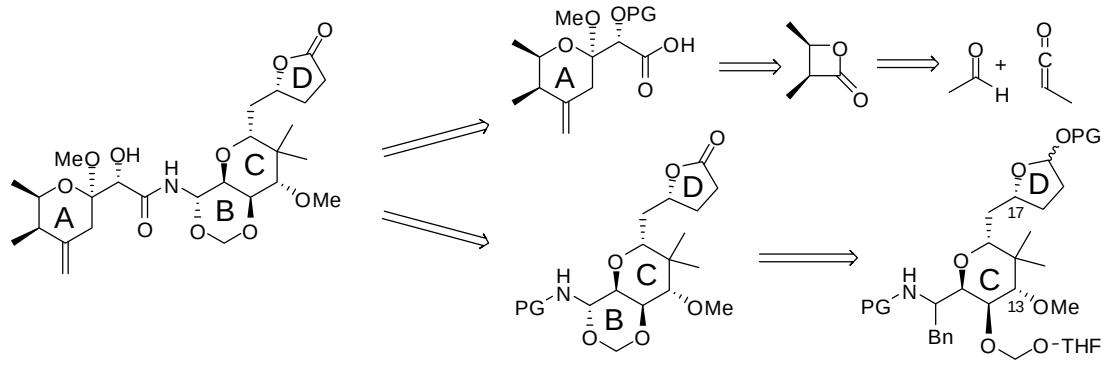


psymberin



psymberic acid

Highlights of our theopederin D synthesis include the use of an asymmetric ketene-aldehyde cycloaddition to synthesize the A ring (or pederic acid subunit), a 1,5-*anti*-boron mediated aldol to construct the C16-C17 bond with high a high level of diastereocontrol, formation of the C and D rings in a one-pot, six reaction sequence, selective differentiation of a tetrahydrofuranol in the presence of a tetrahydropyranol, and elaboration of the C ring using vinylation chemistry developed by Yamamoto and Rainier.



The stereochemically labile B ring of theopederin D was constructed during the late stages of this synthesis using carbon-carbon bond activation via an Electron Transfer Initiated Cyclization (ETIC) method previously developed in the Floreancig research laboratories. This transformation proceeded under essentially neutral conditions and furnished the desired amidotrioxadecalin in high yield. The total synthesis of theopederin D was completed through coupling of pederic acid and an aminotrioxadecalin fragment using a modified diastereoselective strategy initially developed by Rawal.

Our efforts toward the total synthesis of psymberin involved the synthesis of psymberic acid, as its absolute and relative stereochemistry was previously undefined. The use of readily available starting materials (D- or L-serine) and subsequent elaboration using *syn* or *anti* selective methallylation allowed for the efficient construction of all possible stereoisomers of psymberic acid. The absolute configuration of psymberic acid was determined through natural product and model system degradative studies, and analysis of the reaction products using a gas-chromatography/ mass spectrometry apparatus (GC-MS) outfitted with a chiral stationary phase.

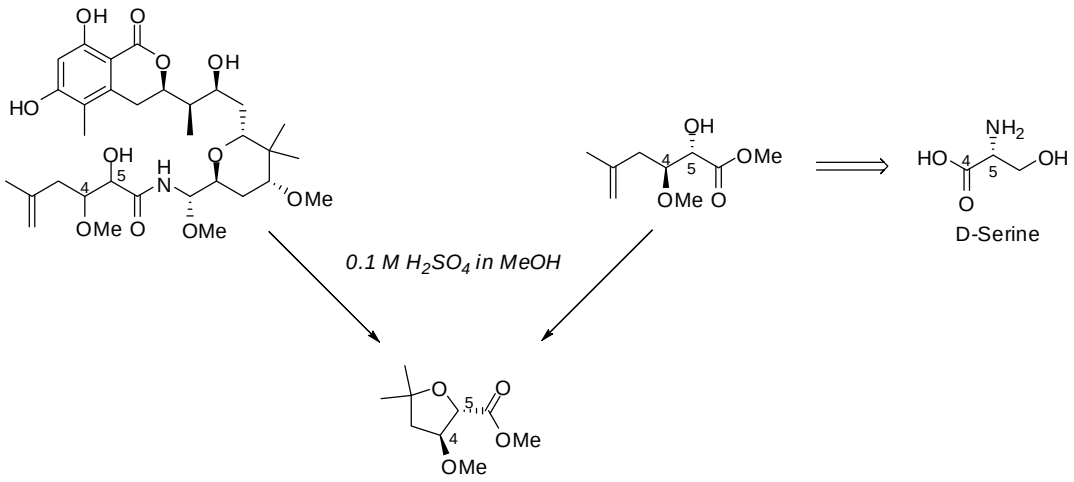

OH
O
HO
O
OH
OH
5
4
H
N
O
OMe
OMe
O
OMe
0.1 M H_2SO_4 in MeOH
OH
4
5
OMe
OMe
O
NH_2
HO
4
5
OH
O
D-Serine
O
5
O
4
OMe
OMe

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF SCHEMES

PREFACE

I entered graduate school wanting to become a better chemist, and hoping to learn as much as possible during my time at the University of Pittsburgh. What I didn't count on, was how much I would learn about myself. My experience during this time has tested my very foundation, pushed me to the brink of failure, and forced me to think "outside the box". For this I am very thankful.

I'd like to thank my advisor Paul Floreancig, for giving me the opportunity to work in your laboratory. Your guidance, patience, and enthusiasm are unparalleled, and I have truly enjoyed the time spent in your lab learning, facing obstacles, and overcoming them.

I would also like to thank my brother George and my sister Yolanda for supporting me during my time in graduate school. You NEVER hesitated to pick up your phone, or to answer your email. You always believed in me, even when I did not believe in myself. I only hope that someday I can repay the favor, but until then I'll spend my days trying to live up to the great examples you have set for me. Additionally, I'd like to thank my parents, for their words of encouragement.

I'd like to thank the Floreancig Research Group for all your help and guidance these past few years, for being good sports about my GREAT taste in music, and for providing a great atmosphere for learning. To the younger students: keep your head up and your hopes high! More

specifically, I'd like to thank Dr. Jason Rech for helping me during my early years, and for trusting me to work on some very difficult projects alongside him. I appreciate your friendship and guidance.

Lastly, I'd like to thank all the friends I've made during my studies in Pittsburgh. I'd list all of your names, but they are to numerous, and I'd probably forget someone on accident. Just know that I value your friendship and support, and that I cannot begin to express how your gratitude has shaped me as a person. Not only are you all great chemists, but you are also great people. Thank you.

1.0 TOTAL SYNTHESIS OF THEOPEDERIN D

1.1 INTRODUCTION

Theopederin D[1] (**1**) is a member of the pederin[2] family of biologically active natural products; a family which also includes mycalamides A-D,[3-6] onnamides A-F,[7-10] psymberin,[11, 12] and theopederins A-L.[1, 13, 14] All members of this family were isolated from marine sponges with the exception of pederin, which was isolated from the *Paederus* beetle.[15, 16] The observance of highly similar compounds from organisms across different phyla has led to hypotheses that these natural products may be derived from bacterial symbionts.[11, 17, 18] Several members of the pederin family display cytotoxicity at nM concentrations, and many have been shown to be potent protein synthesis inhibitors.[19, 20]

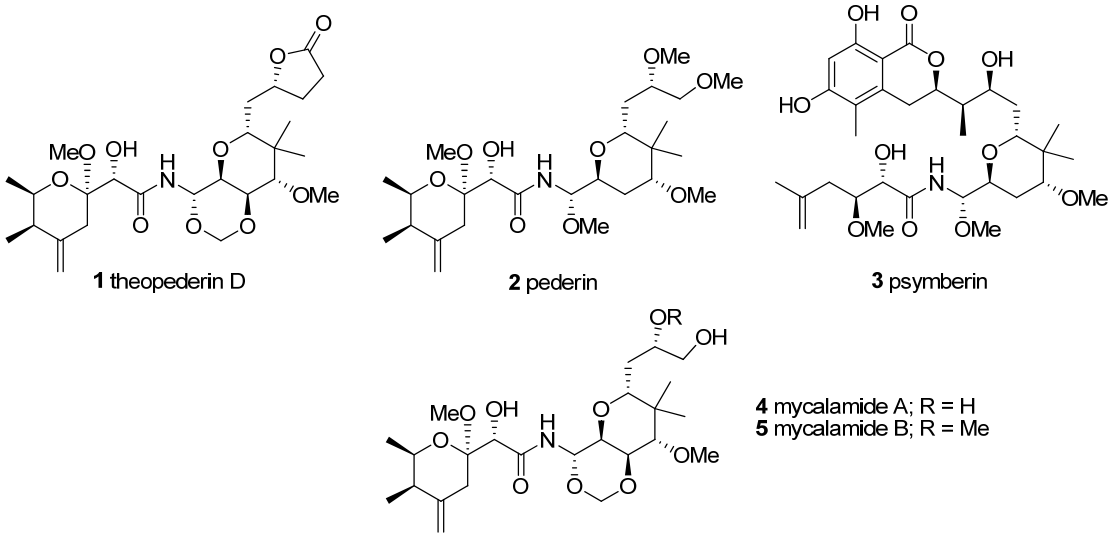


Figure 1. Selected members of the pederin family of natural products

Due to intriguing biological activity, challenging molecular structure, and the lack of natural abundance, this family of natural products has gained the attention of the synthetic community, with total syntheses and fragment syntheses being reported by Matsumoto,[21-24] Meinwald,[25-28] Kishi,[29, 30] Nakata,[31-35] Kocienski,[36-45] Hoffman,[46] Roush,[47, 48] Ihara,[49-52] Trost,[53] Rawal,[54-56] De Brabander,[57, 58] and Williams.[59]

1.1.1 Isolation and Structural Determination of Theopederin D

Theopederins A-E were isolated from the marine sponge genus *Theonella* by Fusetani and coworkers off the coast of Japan in 1992.[1] The frozen specimens (15 kg) were extracted with EtOH, then partitioned between several organic solvents, and subsequently purified via flash chromatography, gel filtration, and reverse-phase HPLC yielding theopederin A (4.8 mg), theopederin B (2.1 mg), theopederin C (0.5 mg), theopederin D (0.8 mg), and theopederin E (0.6 mg) (Figure 2).

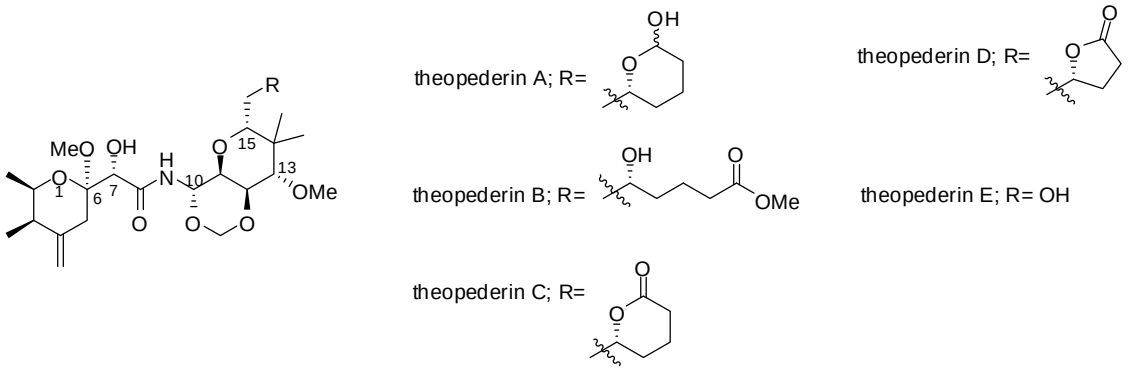


Figure 2. Theopederins A-E

The molecular formula of theopederin D ($C_{26}H_{41}NO_{10}$) was determined using high resolution fast atom bombardment mass spectrometry (HRFABMS). The structure of O1-C16

was initially assigned based upon comparison to spectral data from the mycalamides (see Figure 1), and then confirmed by 2D NMR experiments (COSY, HMQC, and HMBC). The γ-lactone of **1** was assigned based upon HMBC correlations as well as a characteristic IR absorption at 1765 cm^{-1} indicating the presence of a lactone moiety.

1.1.2 Biological Activity of Theopederin D

Theopederin D has demonstrated impressive biological activity, with initial assays performed by Fusetani illustrating that **1** is active at nM concentrations (IC_{50} = 1.0 nM; P388 murine leukemia cell line).[1] Although the mechanism of action has yet to be established, it is believed that members of the pederin family derive their cytotoxicity through the inhibition of protein synthesis.[19] While further biological testing has not been performed with **1**, mycalamide A, mycalamide B, theopederin A, and theopederin B, have all recently been shown to bind to the 60S large subunit of the ribosome. This portion of the ribosome is responsible for protein synthesis in eukaryotic cells.[60]

1.1.3 Structure Activity Relationship (SAR) studies

Several structure activity relationship (SAR) studies of the mycalamide class of compounds have been performed by Munro and Blunt,[61-63] and Nakata.[64] The structures of the pederin family are generally similar, and thus, the conclusions drawn by the SAR studies of the mycalamides are likely to hold true for the family as a whole.

In the pederic acid subunit, research has shown that the exocyclic olefin is not a critical factor in the activity of mycalamides.[63, 64] α-Hydrogenation of the olefin in mycalamide A

afforded **6** (see Table 1) which was more active than mycalamide A (IC_{50} of 0.4 nM compared to 1.0 nM for mycalamide A). α-Hydrogenation of mycalamide B afforded **8**, which gave no significant change in activity. β-Hydrogenation of both mycalamides A and B (compounds **7** and **9**, respectively) resulted in products 4-8 times less biologically active.

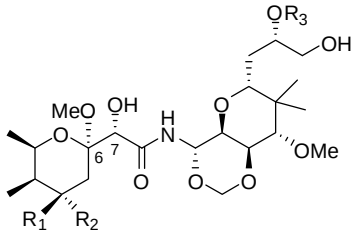


Table 1. mycalamide A and B hydrogenation derivatives

	R_1	R_2	R_3
6	H	Me	H
7	Me	H	H
8	H	Me	Me
9	Me	H	Me

Replacing the C6 methoxy group with an ethoxy group (**10**) (See Table 2) resulted in a 10 fold decrease in activity while incorporation of a hydroxyl group (**11**) at C6 gave a 20-40 fold decrease in activity.[63] Derivatives at C7 (**12-15**) afforded compounds 10-10^3 fold less active than the starting compounds.[61] Analogs of mycalamide A synthesized by Nakata indicate that the stereochemistry at C7 is an important factor in the biological activity of the compound. The C7 epimer of mycalamide A exhibits an approximately 3 fold decrease in biological activity against the HeLa cell line.[64]

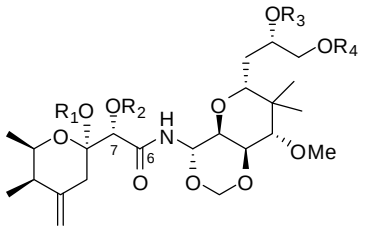
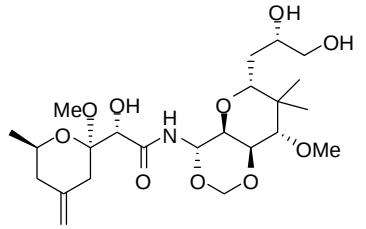


Table 2. Mycalamide A and B alkylated derivatives

	R_1	R_2	R_3	R_4
10	Et	H	H	H
11	H	H	H	H
12	Me	Me	Me	Me
13	Me	Me	H	Me
14	Me	Me	Me	H
15	Me	Me	H	H

Research by Nakata has also shown that the presence of the C3 methyl group is not important to the bioactivity of mycalamide A. Analog **16** (see Figure 3) shares identical bioactivity against the HeLa cell line as mycalamide A.



16

Figure 3. A mycalamide A analog synthesized by Nakata

Structure activity relationship studies have also indicated the importance of the acyl aminal functionality to the biological activity of the mycalamides.[62] For example, the biological activity of mycalamide C (see Figure 4) which lacks the acyl aminal functionality, is significantly less potent than mycalamides A and B (IC_{50} = 230 nM against the P388 leukemia cancer cell line).[65]

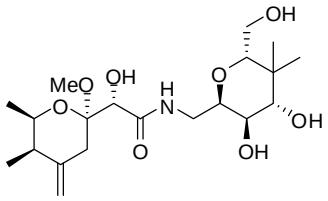


Figure 4. Mycalamide C

The stereochemical configuration of this moiety is also important for the displayed biological activity. Kocienski has reported that the C10 epimer of mycalamide B is 3 times less biologically active than the parent compound.[42]

Lastly, alkylations or silylations of the tetrahydropyran side chain of the mycalamides also changed the biological activity of the molecules (Figure 6).[61] TBDMS ethers of C17 and C18 decreased the biological activity (IC_{50} = 1600 nM), while TMS ethers did not (the researchers speculate that this is likely due to hydrolysis of the TMS ethers in the assay medium). However, methylation of C17 and C18 gave derivatives which were as potent as pederin (IC_{50} = 0.13 nM).

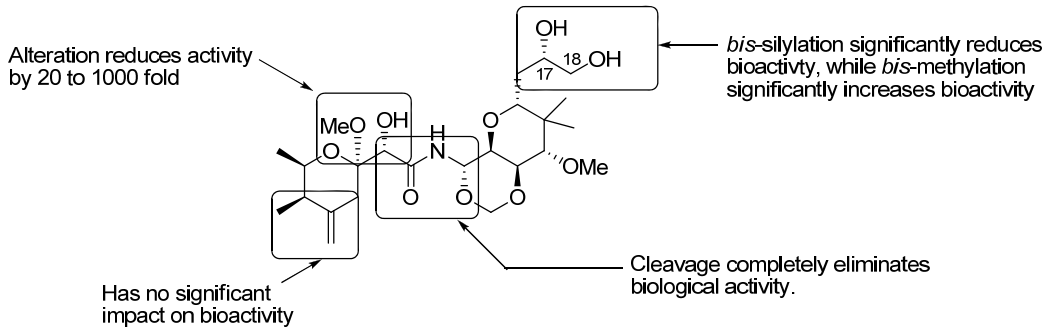


Figure 5. An overview of structure activity relationships

1.2 PREVIOUS SYNTHESES IN THE PEDERIN FAMILY: APPROACHES TO THE MYCALAMIDE AND THEOPEDERIN FAMILIES

To date, there has been one total synthesis of theopederin D, although total and partial syntheses of structurally similar natural products mycalamides A and B have been reported. Generally speaking, convergent approaches involving pederic acid (**18**) and trioxadecalin subunits (**19**) have been used to construct these natural products (Figure 6).

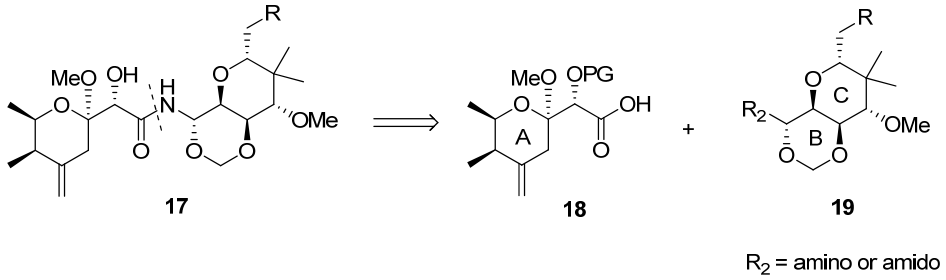


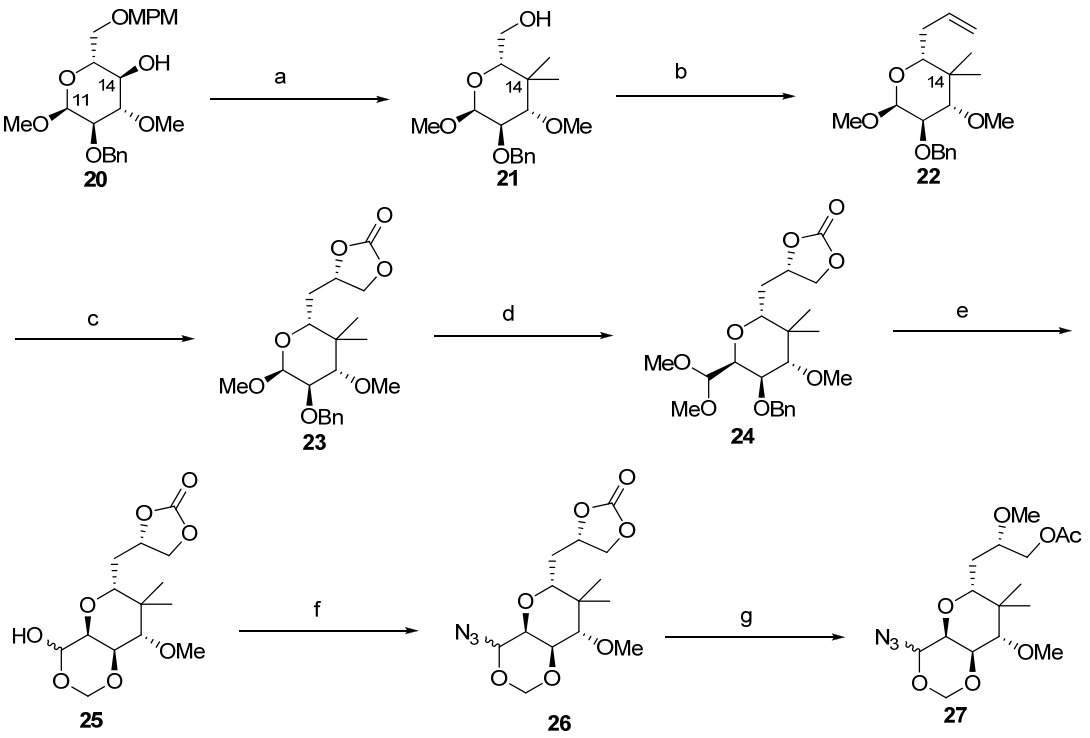
Figure 6. Convergent approach to theopederin and mycalamide families

Several methods have been used in the construction of **18**. Syntheses involving chiral pool starting materials,[25, 26, 28, 36, 40, 53] chiral auxiliaries,[34, 47, 49] transition metal mediated cross couplings,[54] and substrate controlled reactions[25, 26, 28] have all been reported. However, synthesis of the much more complex trioxadecalin scaffold **19** has not varied greatly, and only two general methods for construction of the pivotal *N*-acyl aminal have been investigated: Acylation of a nucleophilic aminotrioxadecalin subunit,[29, 30, 33, 35, 54] or generation of an amidotrioxadecalin fragment via Curtius rearrangement, followed by appendage and elaboration of the pederic acid portion of the molecule.[45, 48, 66] The following sections will briefly describe Kishi's approach for construction of the aminotrioxadecalin ring system, and *N*-acyl aminal functionality in mycalamides A and B, Kocienski's approach to *N*-acyl aminal formation in his synthesis of theopederin D, and Rawal's total synthesis of mycalamide A. Due to the abundance of methods used in preparation of **18**, discussion of the synthesis of this fragment will be mentioned only in

the context of Rawal's efforts toward mycalamide A. Lastly, a discussion of the development of methodology developed in our own research labs directed towards the novel construction of the amidotrioxadecalin scaffold will complete this overview.

1.2.1 Kishi's Syntheses of Mycalamides A and B

Kishi's synthetic efforts towards the mycalamides began with **20**, derived from α-D-glucopyranoside and bearing the requisite stereochemistry at C11, C12, C13, and C15 (see Scheme 1 below).[29] Through a series of fairly straightforward transformations pyranoside **20** was converted to **21**, containing geminal methyl groups at C14, in 7 steps and 62% overall yield. Elaboration of the C15 side chain, asymmetric dihydroxylation, and protection of the diol as carbonate **23** completed the C ring of the mycalamide system. Construction of the B ring commenced with propargyltrimethylsilane addition to **23**, ozonolysis, and acetalization providing **24**. Hydrogenolysis followed by acid mediated cyclization with paraformaldehyde generated hemiacetal **25**. Mesylate formation and displacement with tetrabutylammonium azide afforded azidotrioxadecalin **26** as a 2:1 mixture of inseparable diastereomers in 72% yield.



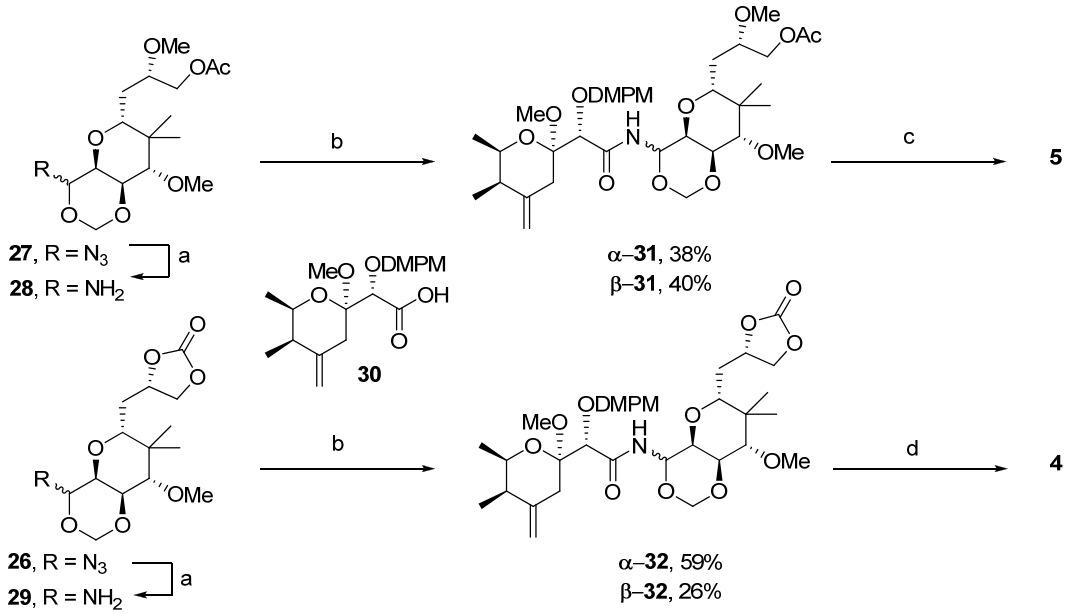
Scheme 1. Kishi's aminotrioxadecalin synthesis

Conditions: a) Swern oxidation; Wittig olefination; CH_2N_2/$Pd(OAc)_2$, Et_2O, 0 °C; H_2, $Pd(OH)_2$/C, EtOAc, rt; H_2/PtO_2, AcOH, rt; TBDPSCl, imidazole, CH_2Cl_2, rt; TBAF, THF, rt, 62% overall yield; b) Swern oxidation; Horner-Emmons olefination; DIBAL-H, CH_2Cl_2, –78 °C; H_2/Rh on Al_2O_3, EtOAc, rt; *o*-$O_2NC_6H_4SeCN$, *n*-Bu_3P, benzene, rt, then *m*-CPBA, 79% overall yield; c) OsO_4, *N*, *N'*-bis(2, 4, 5-trimethylbenzyl)-(*S*,*S*)-1,2-diphenyl-1,2-diaminoethane, CH_2Cl_2, –90 °C, 6:1, 75% d) propargyltrimethylsilane, TMSOTf, CH_3CN, then ozonolysis and acetalization, 60% overall yield; e) H_2/$Pd(OH)_2$ on C, EtOAc, rt; paraformaldehyde, HCl, 0 °C, 86% overall yield; f) MsCl, Et_3N, DMAP, CH_2Cl_2, –60 °C; *n*-Bu_4N^+ N_3^-, CH_2Cl_2, –78 °C to rt, 72% overall yield; g) NaOH, *p*-dioxane (aq), rt; 4-$MeOC_6H_4$-$(C_6H_5)_2CCl$, Hunig's base, CH_2Cl_2, rt; MeI, NaH, DMF, 75 °C; *p*-TsOH, MeOH, rt; Ac_2O, DMAP, CH_2Cl_2, rt, 76% overall yield.

The C15 side chain of azide **26** was elaborated for the synthesis of mycalamide B through a five step sequence providing **27** in 76% yield, and as a 2:1 (desired to undesired) separable mixture of diastereomers.

Hydrogenation of azide **27** furnished amine **28** as a mixture of isomers, configurationally unstable under acidic, basic, and neutral conditions (see Scheme 2). This was also found to be the case for amine **29**, derived from azide **26**. Coupling of amine **28** with pederic acid derivative **30** afforded **α-31** (38%) and **β-31** (40%) as a mixture of separable diastereomers. Coupling of amine **29** and **30** afforded **α-32** (59%) and **β-32** (26%) as a separable mixture of diastereomers.

Undesired isomers **β-31** and **β-32** could be epimerized to the desired natural product configuration at C10 under basic conditions (*t*-BuOK, THF, reflux). However, Kishi notes that while mycalamide A substrate **β-32** could be completely epimerized to the desired configuration at C10, mycalamide B intermediate **β-31** could only be epimerized to a 1:1 mixture of α and β isomers. The syntheses of mycalamides B and A were completed from **α-31** and **α-32**, respectively. The protecting groups were removed in two steps furnishing mycalamide B (**5)** and mycalamide A (**4)** in 69% and 60% yield, respectively.



Scheme 2. Completion of mycalamides A and B by Kishi and coworkers

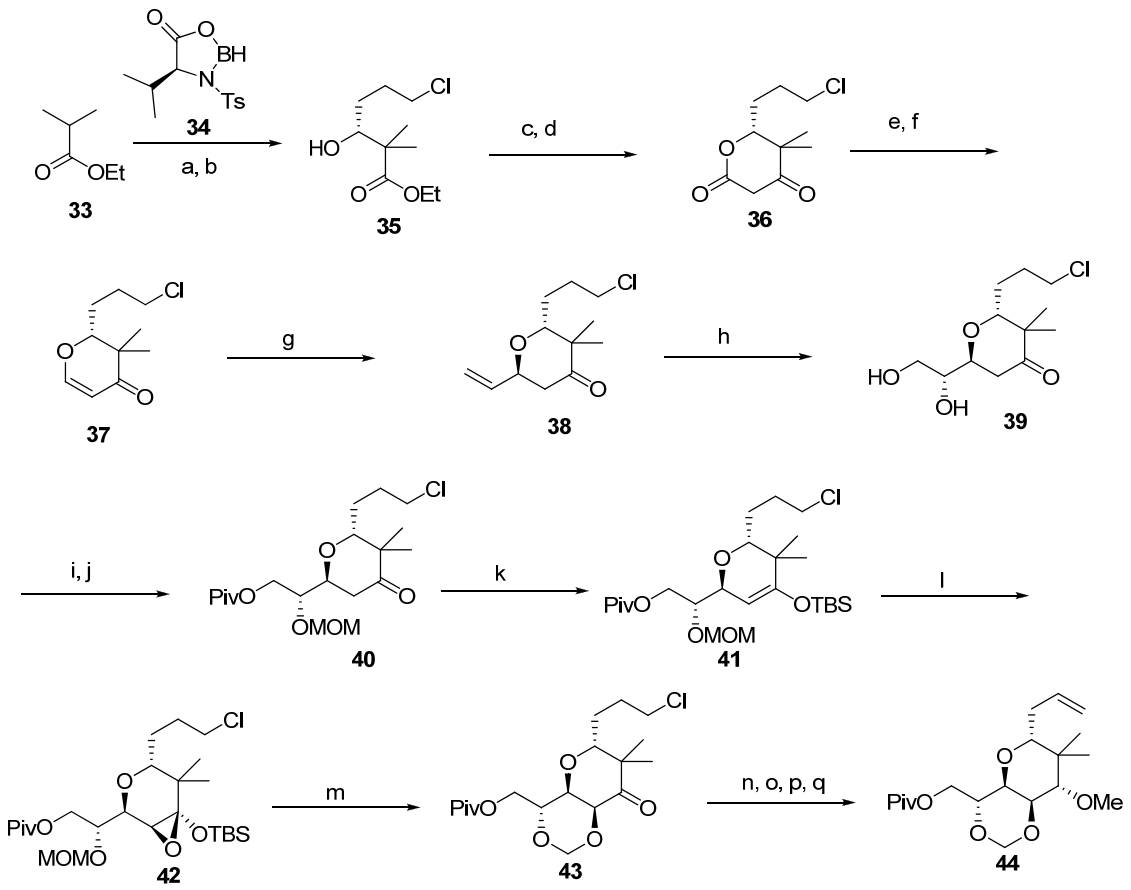
Conditions: a) H_2, Pd/C, EtOAc; b) *p*-TsCl, DMAP, CH_2Cl_2, rt; c) LiOH, MeOH, rt; DDQ, H_2O, CH_2Cl_2, rt, 69%; d) *t*-BuOK, THF, rt; DDQ, H_2O, CH_2Cl_2, rt, 60%.

Kishi's monumental syntheses of mycalamides A and B are significant not only because they were the first reported total syntheses of these molecules, but also because of the valuable insight gained about construction of the *N*-acyl aminal, and the larger implications for synthesis of other pederin family members bearing this sensitive functionality. The conformational lability of **28** and **29** under acidic, basic, and neutral conditions led researchers such as Roush and Kocienski (see Section 1.2.2) to search for alternative methods for construction of the *N*-acyl

aminal without proceeding through an aminotrioxadecalin intermediate. Furthermore, the variable success of Kishi's epimerization of **β-31** and **β-32** is illustrative of the subtle effects of the C15 side chain of these natural products.

1.2.2 Kocienski's Synthesis of Theopederin D

Kocienski's approach to the amidotrioxadecalin framework of theopederin D began with an asymmetric aldol condensation between the silyl ketene acetal derived from **33** and 4-chlorobutanal in the presence of scalemic borane **34**, providing alcohol **35** in 95% yield and 94% *ee* (Scheme 3).[45] Elaboration of the alcohol to the acetate followed by Dieckman condensation afforded keto-lactone **36** in 78% yield. From **36**, enol ether formation followed by DIBAL-H reduction generated dihydropyranone **37** in 85% yield. Copper catalyzed addition of vinyl magnesium bromide to **37**, Sharpless asymmetric dihydroxylation and orthogonal protection of the resulting diol provided **40**. Silyl enol ether formation (85%) followed by epoxidation with *m*-CPBA generated epoxide **42**. Treating epoxide **42** with dimethoxymethane and phosphorous pentoxide afforded trioxadecalin **43** in 77% yield overall yield. Meerwin-Pondorf-Verley reduction of **43** (6:1 d.r.), methylation, selenide formation, oxidation to the selenoxide, and elimination furnished compound **44** in 53% overall yield.

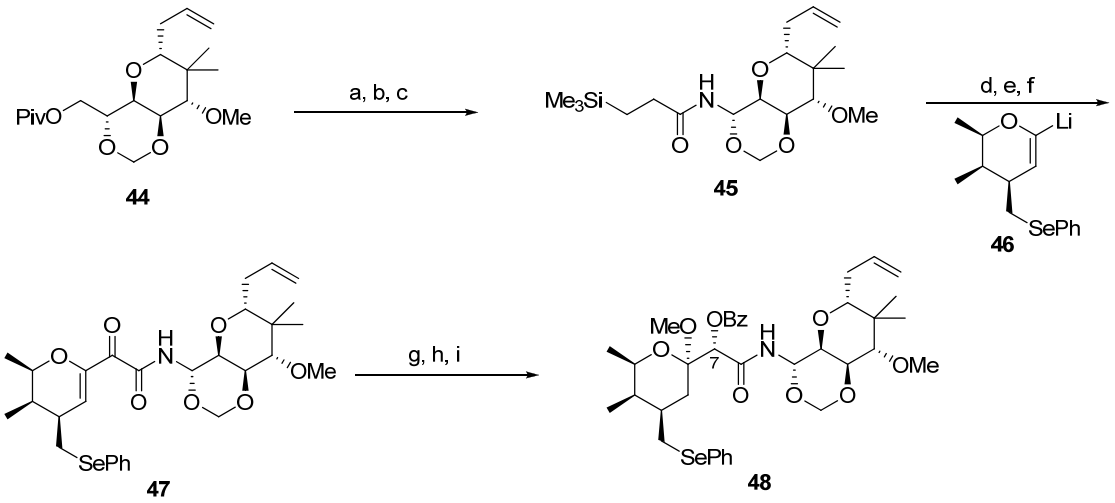


Scheme 3. Kocienski's synthesis of the trioxadecalin framework of Theopederin

Conditions: a) LDA, TMSCl, THF, –78 °C, 91%; b) $Cl(CH_2)_3CHO$, –78 °C, **34**, 95%, 94% *ee*; c) Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt, 76%; d) LDA, THF, –78 °C, 78%; e) Me_2SO_4, K_2CO_3, 18-c-6, CH_2Cl_2, rt, 99%; f) DIBAL-H, CH_2Cl_2, –78 °C, 85%; g) vinyl magnesium bromide, CuI (6 mol%), THF, −90 to −30 °C, 80%; h) Sharpless AD, d.r. >10:1; i) PvCl, pyridine, CH_2Cl_2, 0 °C, 78% from **38**; j) MOMCl, DIPEA, Bu_4NI, PhMe, 90 °C, 97%; k) TBSOTf, Et_3N; CH_2Cl_2, rt, 85%; l) *m*-CPBA, CH_2Cl_2, 0 °C; m) P_2O_5, $CH_2(OMe)_2$, CH_2Cl_2, 0 °C, 77% from **41**; n) Me_3Al, *i*-PrOH, rt, 66% 6:1; o) NaHMDS, MeOTf, THF, –78 °C, 86%; p) PhSeNa, EtOH, 96%, reflux; q) $NaIO_4$, H_2O/MeOH, rt, then PhMe : Me_3N (1:1), reflux, 98%.

With the bulk of the trioxadecalin framework complete, attention was focused on formation of the *N*-acyl aminal functionality. Cleavage of the pivalate protecting group followed by oxidation to the aldehyde, Curtius rearrangement under Shioiri conditions, and thermolysis in the presence of 2-(trimethylsilyl)ethanol afforded **45** in 57% yield over 4 steps (Scheme 4). Treating **45** with methyl-oxalyl chloride followed by TBAF removal of the Teoc-carbamate, and coupling with pederic acid derivative **46** (synthesis not shown) afforded *N*-acyl aminal **47** in 78% yield. Diastereoselective reduction of ketone **47**, methyl acetal formation, and protection of the

secondary alcohol as the benzoyl carbonate furnished **48** in 77% yield as a separable mixture of diastereomers at C7 (~3:1).

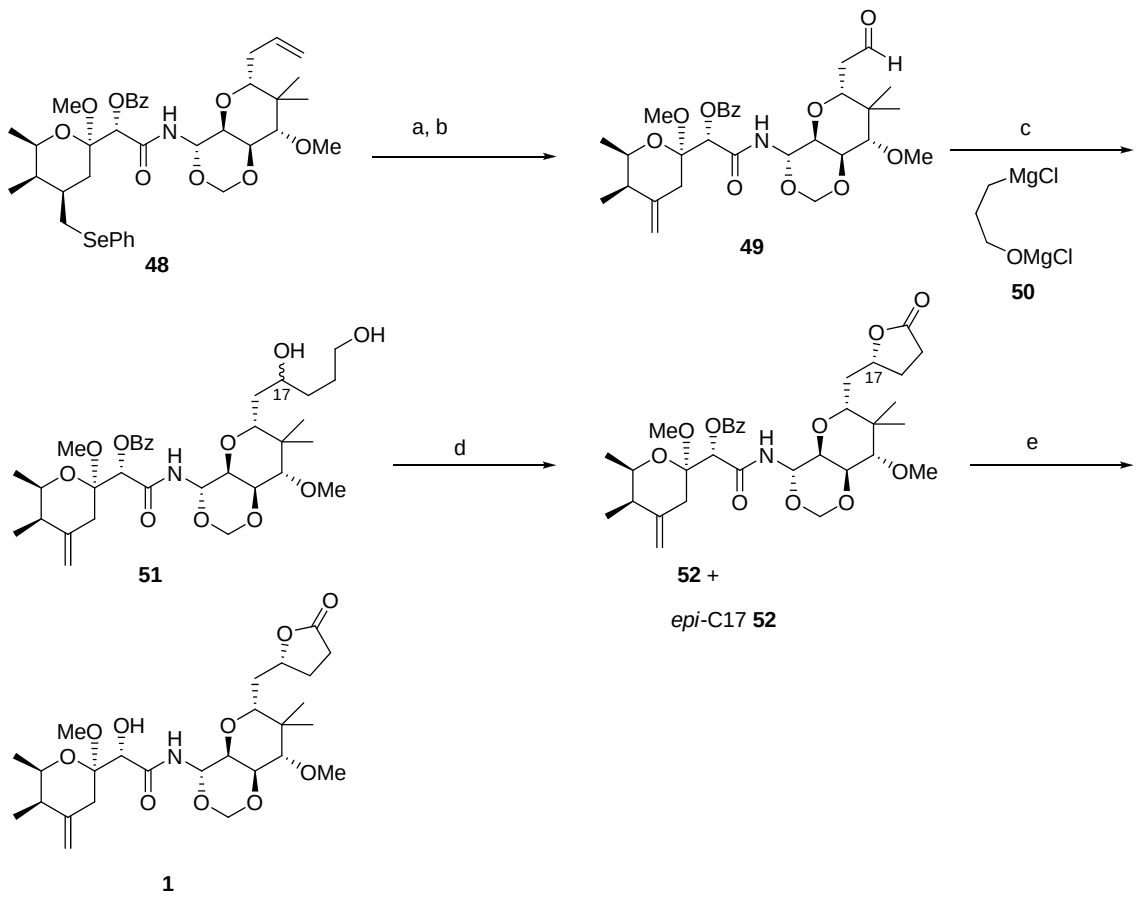


44 **45** **46** **47** **48**

Scheme 4. Kocienski's coupling of trioxadecalin and pederic acid fragments

Conditions: a) Red-Al, THF, –78 °C to 0 °C, 98%; b) PDC, DMF, rt, 24h; c) $(PhO)_2CH_2OH$ $TMSCH_2CH_2OH$, DIPEA, PhMe, 65 °C, 58% (2 steps); d) MeO_2CCOCl, DMAP, CH_2Cl_2, rt, 66%; e) TBAF, THF, 83%; f) **46**, TMEDA, THF, –78 °C, 78%; g) $LiBHBu^s_3$, THF, –95 °C, 6:1 d.r.; h) CSA, MeOH, CH_2Cl_2, rt; i) BzCl, DMAP, CH_2Cl_2, rt, 77%.

With coupling of the two principle fragments complete, attention was turned to unmasking the exocyclic olefin of the pederic acid scaffold, and to the construction of the C17 lactone (Scheme 5). Treating **48** with Sharpless asymmetric dihydroxylation conditions, dual $NaIO_4$ selenide oxidation and diol cleavage, and elimination of the selenoxide furnished **49** in 69% yield over 3 steps. Grignard addition of **50** to aldehyde **49** afforded **51** as a ~1:1 mixture of alcohols at C17. TPAP oxidation of **51** and cyclization afforded a 1:1 mixture of separable lactones at C17. Treatment of the desired isomer **52** with K_2CO_3 in MeOH provided theopederin D (**1**) in 79% yield.



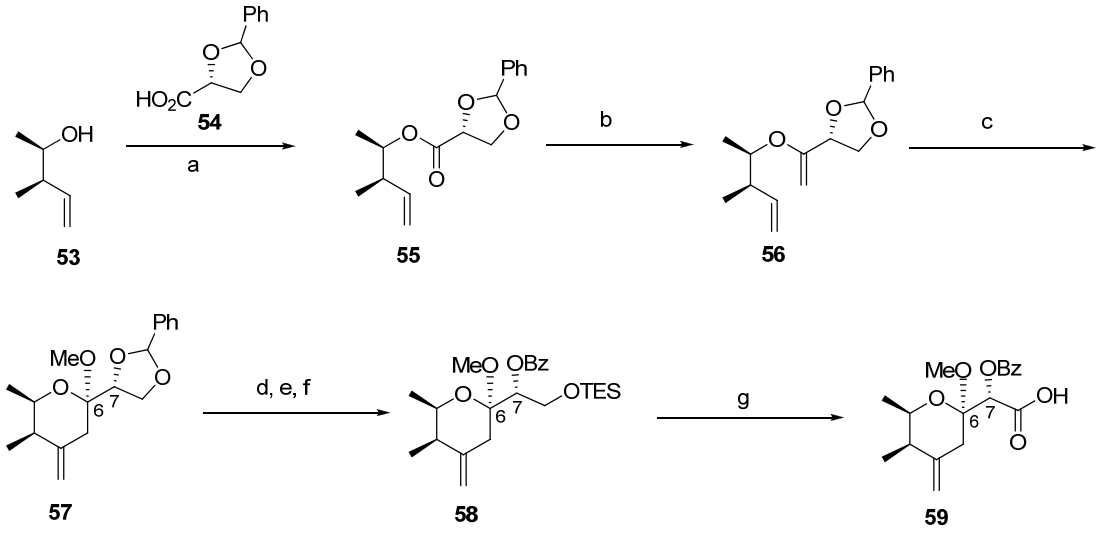
Scheme 5. Kocienski's completion of theopederin D

Conditions: a) Sharpless AD; b) $NaIO_4$, MeOH, CH_2Cl_2, rt; Et_3N/PhMe, reflux, 69% (3 steps); c) **50**, THF, –78 °C, 1:1 d.r.; d) TPAP, NMO, CH_2Cl_2/MeCN; e) K_2CO_3, MeOH, rt, 79%.

Kocienski's synthesis of theopederin D is noteworthy in that the Curtius rearrangement furnished the amidotrioxadecalin subunit as one stereoisomer at C10, thus avoiding the conformationally labile intermediates present in Kishi's synthesis. Furthermore, the "metallated dihydropyran" approach for coupling of the pederic acid core was novel, and high-yielding. However, the synthetic route was lengthy, and the introduction of the C17 stereocenter could not be accomplished diastereoselectively.

1.2.3 Rawal's Synthesis of Mycalamide A

Rawal's total synthesis of mycalamide A began with construction of the pederic acid portion of the molecule.[54] Condensation of homoallylic alcohol **53** (synthesized via Brown crotylation of acetaldehyde) with protected glyceric acid derivative **54** furnished **55** in 91% yield (Scheme 6). Subsequent Petasis-olefination of **55** (85% yield) followed by an intramolecular Heck reaction afforded **57** in 78% yield with a 5.7: 1 ratio of desired to undesired diastereomers at C6. Removal of the benzylidene acetal under dissolving metal conditions, selective protection of the resulting primary alcohol as the triethylsilyl ether (TES), and benzoylation of the secondary alcohol at C7 afforded **58** in 81% overall yield**.** Benzoate **58** was directly converted to carboxylic acid **59** in 83% yield by treatment with pyridinium dichromate.

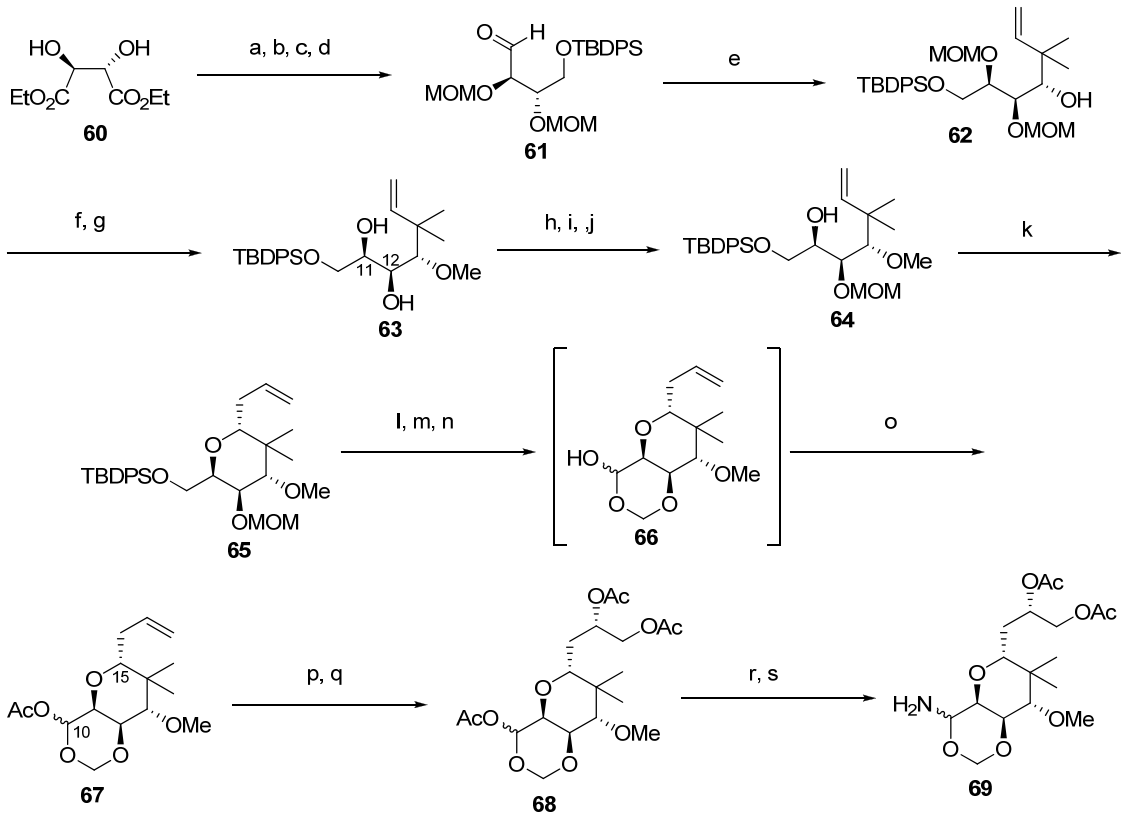


Scheme 6. Rawal's synthesis of pederic acid

Conditions: a) EDC, DMAP, CH_2Cl_2, 91%; b) Cp_2TiMe_2, $PhCH_3$, 80 °C, 85%; c) $PdCl_2$ (0.15 equiv), benzoquinone, MeOH, $CH(OMe)_3$, propylene oxide, THF/DMF (20:1), 78%, 5.7:1.0 desired to undesired diastereomers at C7; d) Na, liq. NH_3, EtOH, 93%; e) TESCl, DIPEA, CH_2Cl_2, 93%; f) BzCl, DMAP, DIPEA, CH_2Cl_2, 94%; g) PDC, DMF, 83%.

Synthesis of the aminotrioxadecalin scaffold began with commercially available diethyl D-tartrate **60** (Scheme 7). Protection of the diol as the bis-methoxy methyl ether (MOM)

followed by $LiAlH_4$ reduction of the ethyl esters, mono-TBDPS protection, and Swern oxidation afforded aldehyde **61** in 77% overall yield. Addition of tri-*n*-butyl prenylstannane under chelation controlled conditions (90%), methylation of resulting alcohol **62** (98%), and MOM deprotection under mild conditions afforded diol **63** in 98% yield.



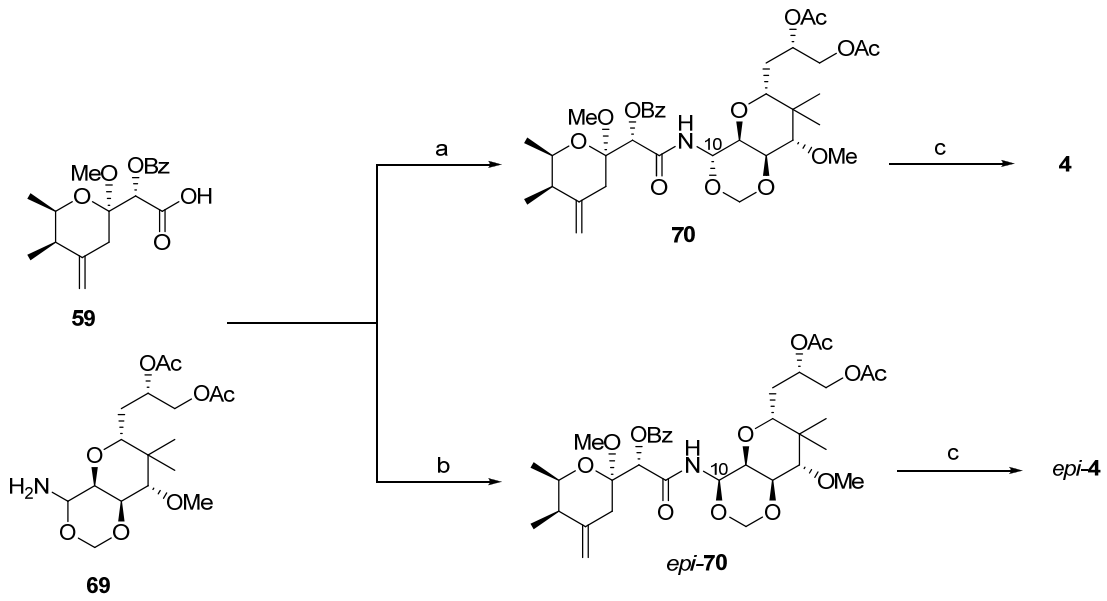
Scheme 7. Rawal's synthesis of the aminotrioxadecalin

Conditions: a) $(MeO)_2CH_2$, P_2O_5, CH_2Cl_2, quant.; b) $LiAlH_4$, Et_2O, 86%; c) *n*-BuLi, TBDPSCl, THF, quant.; d) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 90%; e) $Me_2CCHCH_2SnBu_3$, $ZnBr_2$, CH_2Cl_2, 90%; f) NaH, MeI, THF, 98%; g) $ZnBr_2$ (2.5 equiv.), *n*-BuSH (3.0 equiv.), rt, 8 min, CH_2Cl_2, 98%; h) BzCl, DIPEA, CH_2Cl_2, rt, 11 h, 80%; i) $CH_2(OMe)_2$, P_2O_5, CH_2Cl_2, rt, 3 h, 91%; j) K_2CO_3, MeOH, rt, 3 h, 83%; k) O_3, Me_2S, CH_2Cl_2; Ac_2O, DMAP, pyr; $BF_3{\cdot}OEt_2$, CH_2CHCH_2TMS, CH_2Cl_2, 66%; l) TBAF, THF, 91%; m) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; n) $(CHO)_n$, concd. HCl, THF; o) Ac_2O, DMAP, pyr, 63%, d.r. 5.4:1.0; p) OsO_4, $(DHQ)_2PYR$, K_2CO_3, $K_3Fe(CN)_6$, *t*-BuOH/H_2O, –3 °C, 83%, d.r. 5:1; q) Ac_2O, DIPEA, DMAP, CH_2Cl_2, 92%; r) $TMSN_3$, TMSOTf, CH_3CN, –78 to 0 °C, quant.; s) H_2, Pd/C, EtOAc, 90%.

Selective mono-benzoylation at C11 of diol **63** (80%), MOM-protection of the remaining free alcohol at C12 (91%), and benzoyl group removal afforded alcohol **64** in 83% yield. Ozonolysis of **64**, and acetylation of the resulting lactol followed by $BF_3{\cdot}OEt_2$ mediated allyl

trimethylsilane addition afforded pyran **65** as a single diastereomer in 66% yield. Cleavage of TBDPS ether **66** with TBAF (91%), Swern oxidation, and subjection of the resulting aldehyde to paraformaldehyde and concentrated HCl at –15 to –10 °C resulted in generation of **66**, which without isolation, was acetylated generating acetate **67** in 63% as a 5.4:1 mixture at C10. The C15 side chain was functionalized through asymmetric dihydroxylation (83%, 5:1) and the resulting alcohols were acylated, furnishing **68** in quantitative yield. The trioxadecalin was completed by displacement of the anomeric acetate with $TMSN_3$, providing a 1.8:1.0 mixture of inseparable azide anomers. Hydrogenation of the azidotrioxadecalin mixture afforded aminotrioxadecalin **69** as a mixture of diastereomers.

To complete the synthesis of mycalamide A, **59** and **69** were coupled using DCC and DMAP affording **70** and *epi*-C10-**70** as a favorable 5:1 mixture of separable diastereomers in 56% yield (Scheme 8). Interestingly, coupling fragments **59** and **69** using PyAOP and DIPEA resulted in generation of *epi*-**70** as a single diastereomer in 61% yield. Treatment of **70** with 1N LiOH removed the benzoyl and acetate protecting groups yielding mycalamide A (**4**) in 78% yield. Removal of the protecting groups from *epi*-**70** generated *epi*-**4** (*epi*-mycalamide A) in 75% yield. Attempts to epimerize *epi*-**4** to **4** were unsuccessful.



Scheme 8. Rawal's diastereoselective mycalamide A coupling

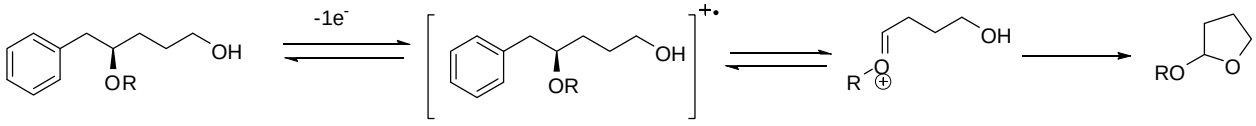
Conditions: a) DCC, DMAP, CH_2Cl_2, rt, 12 h, 56%, 5:1 (**70**:*epi*-**70)**; b) PyAOP, DIPEA, CH_2Cl_2, rt, 24h, 61%, *epi*-**70** sole diastereomer; c) 1N LiOH, THF; 78% (**4**), 75% (*epi*-**4)**.

Rawal's mycalamide A synthesis represents a significant step forward for the synthesis of molecules in the pederin family. Coupling of the pederic acid fragment with a mixture of aminotrioxadecalin epimers to afford a favorable diastereomeric ratio elegantly circumnavigated the task of creating the C10 acyl aminal stereoselectively. Furthermore, the use of an intramolecular Wacker/Heck cyclization as a means for construction of the pederic acid fragment employed a novel disconnection, and eliminated the need for an exocyclic olefin surrogate in the pederic acid subunit.

1.2.4 The Floreancig Approach to the Amidotrioxadecalin Scaffold

Due to the paucity of methods used to synthesize the amidotrioxadecalin ring system, and an interest in pursuing a total synthesis of mycalamide B, Floreancig and coworkers sought to improve upon previous synthetic efforts by employing the Electron Transfer Initiated Cyclization

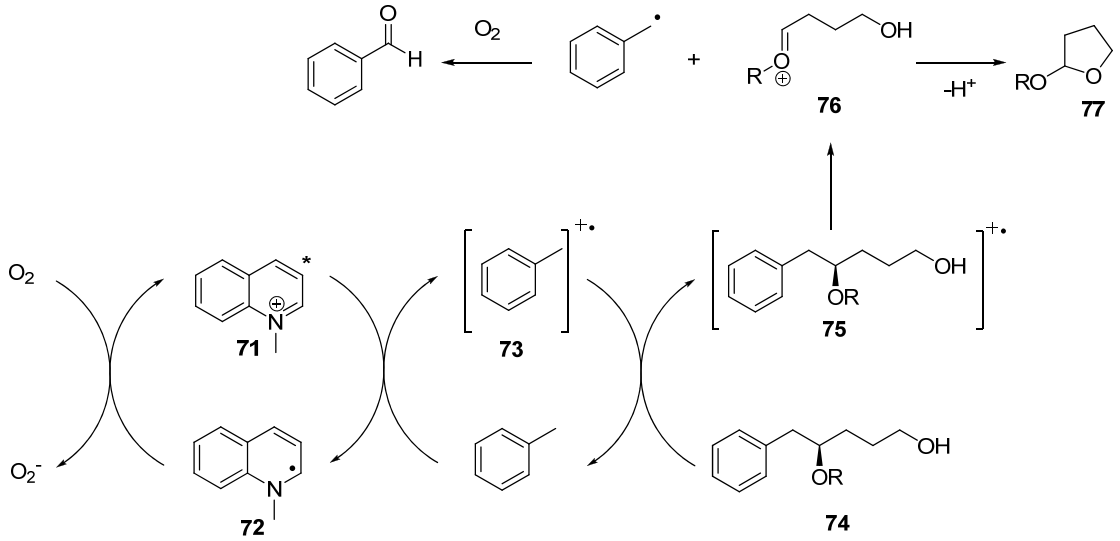
methodology (ETIC) developed in their research labs. Previous reports illustrated that this method allowed for the construction of cyclic ethers and acetals from homobenzylic ethers under mild conditions (Scheme 9).[67, 68]



Scheme 9. Cyclic acetal construction by Floreancig and coworkers

Conditions: *hv*, *N*-methylquinolinium hexafluorophosphate (cat), O_2, toluene, DCE, NaOAc, $Na_2S_2O_3$, 4Å MS.

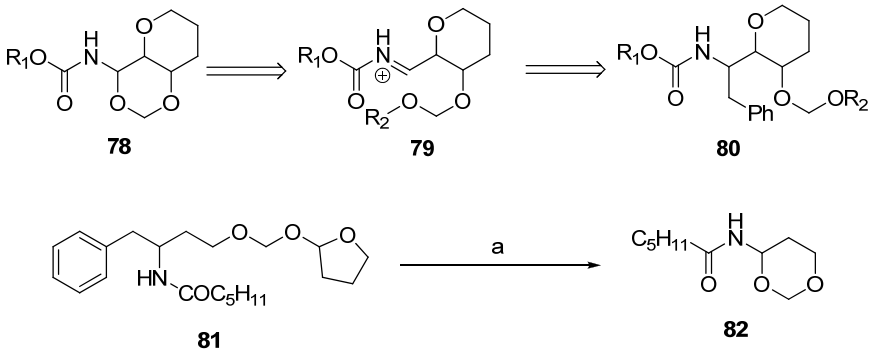
When irradiated, *N*-methylquinolinium hexafluorophosphate ($NMQPF_6$, **71**) becomes photoexcited, and can accept an electron from the co-sensitizer toluene, generating quinolyl radical **72** and the radical cation of toluene (**73**) (Scheme 10). Electron transfer between homobenzylic ether **74** and radical cation **73** regenerates toluene, and affords radical cation **75**. Mesolytic cleavage of **75** generates a benzyl radical and oxocarbenium ion **76**. Cyclization of the tethered nucleophilic alcohol and deprotonation with NaOAc provides the desired product **77**.



Scheme 10. The mechanism of the Electron Transfer Initiated Cyclization (ETIC)

During the reaction, atmospheric oxygen is gently bubbled through the solution. This serves to oxidize the benzylic radical to benzaldehyde, and to regenerate the catalyst by serving as a terminal oxidant (Note: $Na_2S_2O_3$ serves to reduce the superoxide species to H_2O, which is sequestered with molecular sieves).

Based on their cyclic ether work, Floreancig and coworkers reasoned that the amidotrioxadecalin ring system (**78**) could arise via nucleophilic addition of a masked hemiacetal nucleophile into acyliminium ion **79** (Scheme 11).[69] The ETIC conditions would allow for mild generation of such a reactive species from homobenzylic carbamate **80**. After careful optimization of reaction conditions homobenzylic carbamate **81**, bearing a tethered tetrahydrofuranyl protected nucleophile, was synthesized. When treated with standard ETIC conditions this substrate underwent cyclization furnishing acyl aminal **82** in 79% yield (Scheme 11).

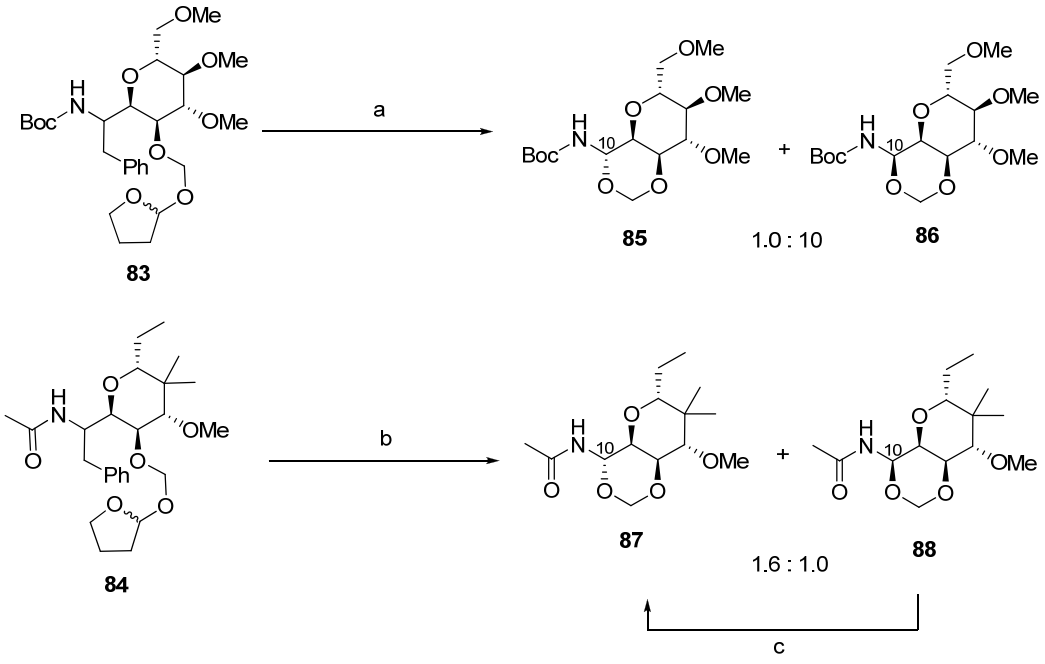


Scheme 11. An electron initiated cyclization forming an *N*-acyl aminal

Conditions: a) *hv*, $NMQPF_6$ (cat), O_2, toluene, DCE, NaOAc, $Na_2S_2O_3$, 4Å MS, 79%.

To test the feasibility of the ETIC methodology in substrates resembling the trioxadecalin ring system, model substrates **83** and **84** were synthesized (Scheme 12). Treatment of **83** with standard ETIC conditions afforded **85** and **86** in 94% yield as 1:10 mixture of separable

diastereomers.[70] Subjection of **84** to identical conditions afforded products **87** and **88** in 94% yield as a 1.6:1.0 mixture of separable diastereomers.[71]



Scheme 12. Construction of a trioxadecalin model system under ETIC conditions

Conditions: a) *hv*, $NMQPF_6$ (cat), O_2, toluene, DCE, NaOAc, $Na_2S_2O_3$, 4Å MS, 94%; b) *hv*, $NMQPF_6$ (cat), O_2, toluene, DCE, NaOAc, $Na_2S_2O_3$, 4Å MS, 94%; c) *p*-TsOH, trifluoroethanol.

The outcome from cyclization of substrate **83** was surprising in that the major product contained the opposite configuration of the natural product at C10 (natural product numbering) (Figure 7). Product **86** has the majority of its substituents in an axial orientation while the configuration of compound **85** (identical to that of the natural product) places all of the ring substituents in an equatorial orientation (Figure 7).

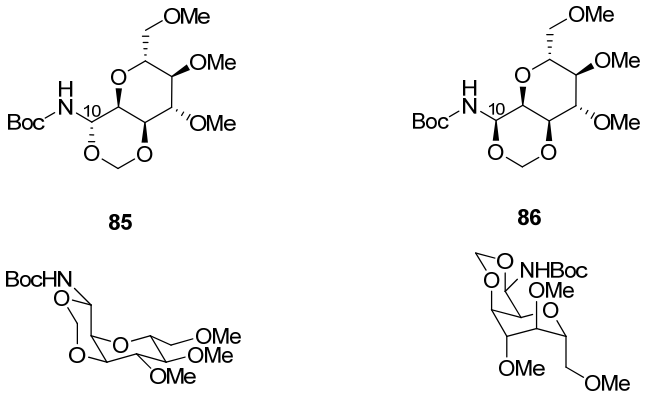


Figure 7. Amidotrioxadecalin diastereomers

From previous experiments, it was noted that ETIC cyclizations of homobenzylic amides likely proceed through late transition states, indicating that the relative energies of the products from these reactions (**85** and **86**) should be comparable to the relative energies of the transition states (**89** and **90**). That is, if product **86** is formed preferentially over **85**, transition state **90** should be lower in energy than transition state **89** (Figure 8).

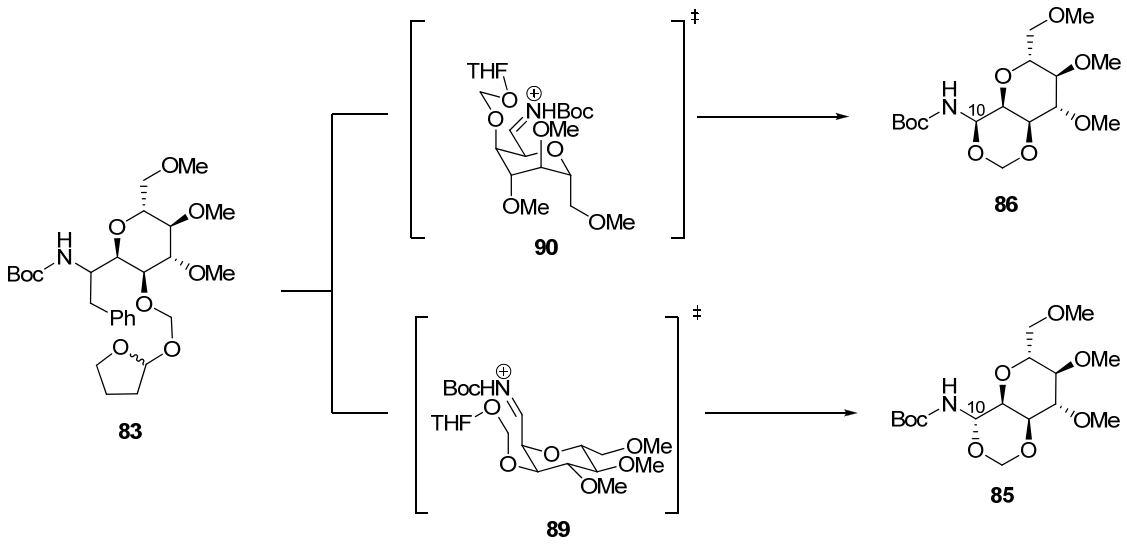


Figure 8. Transition states leading to amidotrioxadecalin model system products

Fuchs and coworkers have performed molecular modeling calculations on the trioxadecalin core structure and have found **91** to be 4.3 kcal/mol lower in energy than **92**, which

has the configuration found in the natural product (Figure 9).[72] This was rationalized by the unfavorable *gauche* COCC bond interactions found in **92**, in comparison to the favorable *anti* COCC bond orientation present in **91**. Molecular modeling calculations (MM3) performed on the product by Floreancig and coworkers indicated a 4.4 kcal/mol difference between products **86** and **85**.[71]

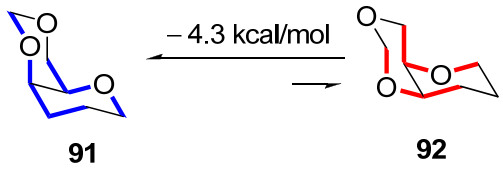


Figure 9. Analysis of the trioxadecalin core

In a reversal of this trend, substrate **84** was found to afford products in a 1.6:1.0 ratio of desired to undesired diastereomers, indicative of how the substituents on the ring system can override the energetic penalty of the developing gauche interactions in the desired amidotrioxadecalin (Scheme 12).

The Floreancig approach offers a novel method for the construction of the amidotrioxadecalin scaffold, with model studies indicating that the transformation is exceptionally high yielding. While the diastereocontrol was modest for substrate **84**, the acyl aminal stereocenter could easily be epimerized under mild conditions (*p*-TsOH, trifluoroethanol). In addition, Rawal's subsequent report of a diastereoselective coupling during his synthesis of mycalamide A illustrates the inconsequentiality of the acyl aminal stereocenter in downstream chemistry. Thus, the ETIC approach offers a powerful method for the construction of highly reactive intermediates under mild conditions, providing products with high levels of molecular complexity, and in high yield.

1.3 PROJECT GOALS

1.3.1 Retrosynthetic Analysis of Theopederin D

With the precedent of construction of *N*-acyl aminals via our electron transfer initiated cyclization (ETIC) method well established, we focused our attention on the application of this method to a natural product total synthesis. We made our initial disconnection of **1** at the C8-N9 bond generating pederic acid (**59**) and aminotrioxadecalin fragments (**3**) (Figure 10). In a forward sense, construction of this pivotal bond could be accomplished through a diastereoselective amide bond formation between **59** and **93**, as reported in Rawal's mycalamide A synthesis (see Scheme 8, page 18).[54]

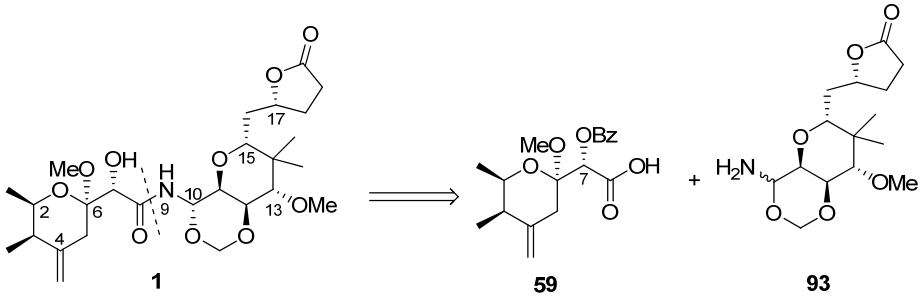


Figure 10. Initial bond disconnection of theopederin D

We anticipated that **59** could be generated via Nakata's diastereoselective Claisen condensation of a suitably protected lactone **94** with glycolate derivative **95** (Figure 11).[34] Lactone **94** could arise from dihydropyranone **96**. We envisioned construction of **96** via an asymmetric hetero-Diels Alder cycloaddition between diene **97** and acetaldehyde.

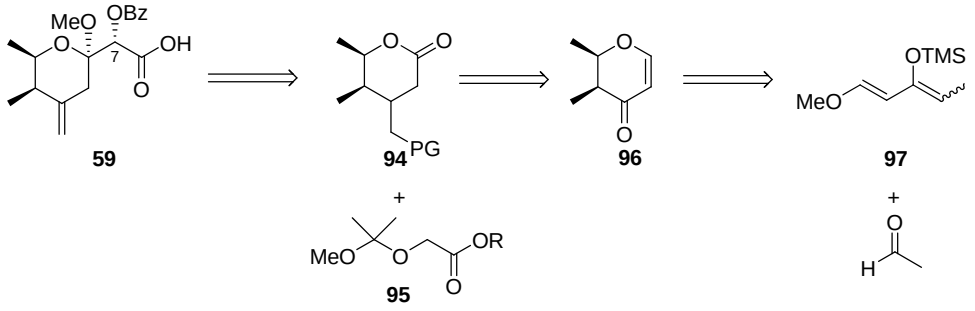


Figure 11. Pederic acid retrosynthesis

Due to the expected lability of **93**,[29] we envisioned late stage formation of this sensitive fragment from deprotection of amidotrioxadecalin **98** under mild hydrogenolytic conditions (Figure 12).

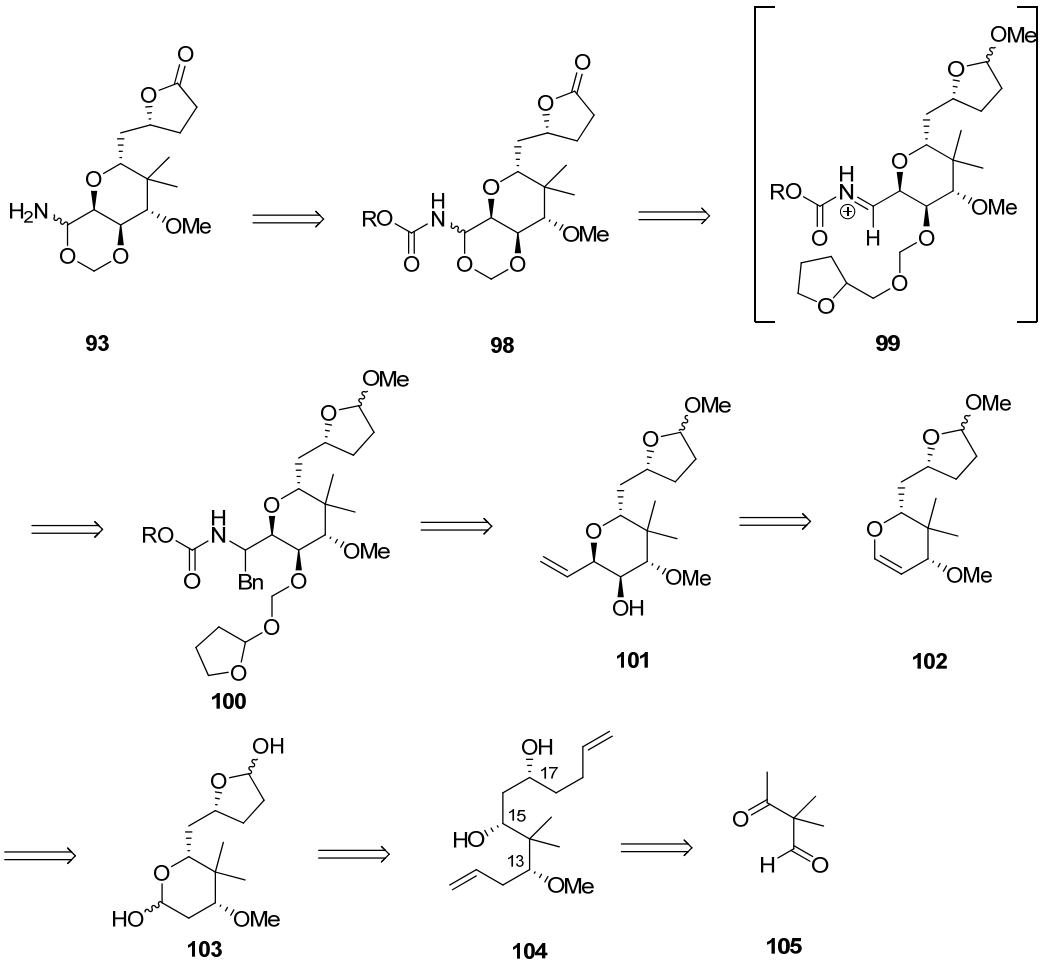


Figure 12. Retrosynthesis of an aminotrioxadecalin fragment

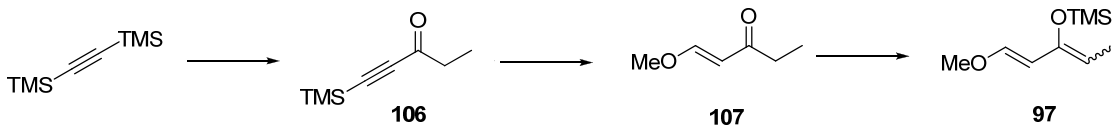
Carbamate **98** could be generated from intermediate **99**, formed in situ via an ETIC reaction of substrate **100**. Homobenzylic carbonate **100** could be obtained from **101** via facile elaboration of

the anomeric vinyl and secondary alcohol functionalities. We envisioned generation of **101** via diastereoselective epoxidation and *syn* vinyl addition to dihydropyran **102**. Dihydropyran **102** could be obtained from bis-lactol **103** via selective tetrahydrofuranol acetal formation, and subsequent tetrahydropyranol dehydration. Intermediate **103** could be obtained from oxidative cleavage and cyclization of diol **104**. Compound **104** could be generated via asymmetric allylation of keto-aldehyde **105**, methylation of the resulting alcohol, followed by a substrate controlled 1, 5-*anti*-boron mediated aldol, and chelation controlled *syn* reduction to construct requisite stereocenters at C13, C15, and C17 (natural product numbering).

1.4 PEDERIC ACID SYNTHESIS

1.4.1 Efforts toward Pederic Acid: Hetero-Diels-Alder Approach

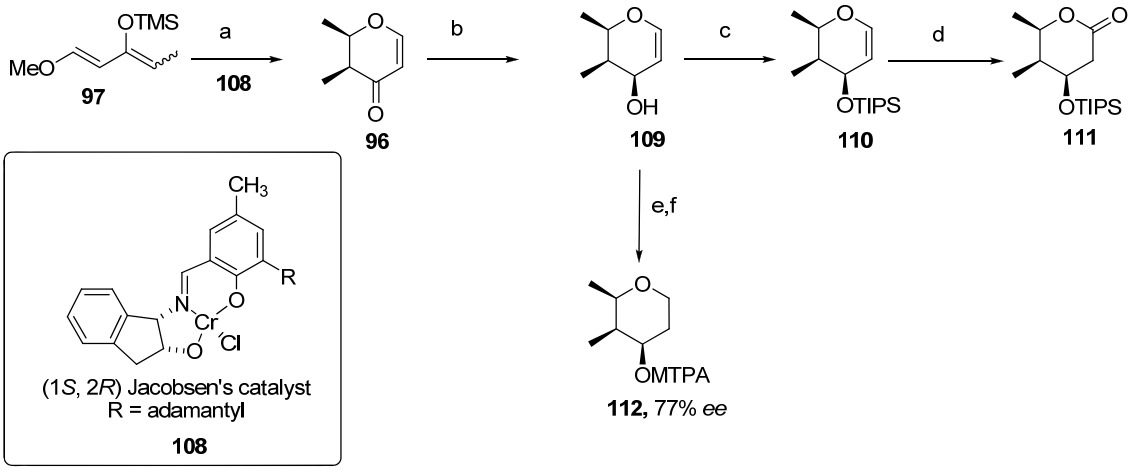
Our synthetic efforts began with synthesis of Danishefsky-type diene **97** (Scheme 13). Acylation of commercially available bis(trimethylsilyl)acetylene with propionyl chloride in the presence of aluminum chloride afforded alkyne **106**, which was used without further purification.[73] Treatment of **106** with methanol and 1,4-diazabicyclo[2.2.2]octane (DABCO)[74] afforded enol ether **107** in 70% yield over 2 steps. Diene formation was achieved by reaction of **107** with Et_3N, TMSOTf, and $ZnCl_2$, generating **97** as a 4:1 ratio of *Z*: *E* isomers in 85% yield.[75]



Scheme 13. Synthesis of a diene for hetero-Diels Alder chemistry

Conditions: a) propionyl chloride, $AlCl_3$, CH_2Cl_2, 0 °C to rt; b) MeOH, DABCO, rt, 70% over 2 steps; c) $ZnCl_2$, Et_3N, TMSCl, toluene, 40 °C, 85%.

Employing chemistry developed by Jacobsen and coworkers,[76, 77] we were able to synthesize dihydropyranone **96** in 82% yield (Scheme 14) via an asymmetric hetero-Diels Alder reaction between **97** and acetaldehyde in the presence of catalyst **108**. Luche reduction[78] of dihydropyranone **96** (87% yield), followed by protection of the resulting alcohol **109** as the triisopropylsilyl ether afforded **110** in 54% yield. Silyl protected dihydropyranol **110** was converted to lactone **111** in 71% yield via oxidation with PCC. The *ee* of pyranone **96** (77%) was established via hydrogenation of dihydropyranol **109** then subsequent treatment with (*S*)-(+)-Mosher's acid chloride to afford **112**. The diastereomers of this compound were sufficiently resolved in the ^{1}H NMR spectrum to permit analysis.



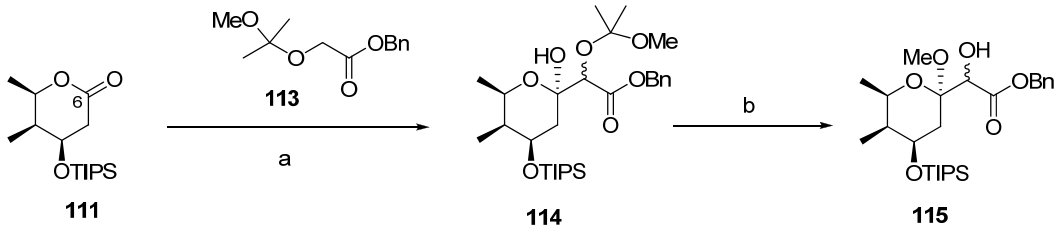
Scheme 14. Synthesis of the pederic acid core via hetero-Diels Alder

Conditions: a) acetaldehyde, 4Å MS, **108**, 40 h, then TFA, 82%, 77% *ee* (see text); b) $NaBH_4$, $CeCl_3$, MeOH, –10 °C to rt, 87%; c) TIPSOTf, 2,6-lutidine, CH_2Cl_2, –10 °C to rt, 54%; d) PCC, DCE, 71%; e) H_2, Pd/C, MeOH; f) (*S*)-(+)-Mosher's acid chloride, pyridine, CH_2Cl_2.

With the core of pederic acid complete, our next task was the synthesis of the C6 side chain using glycolate derivative **113** and lactone **111** following the literature protocol developed by Nakata and co-workers in their synthesis of pederic acid derivatives.[34] Our decision to use protected benzyl glycolate was based on two desires: avoidance of the late stage usage of HMPA in our synthetic route (as reported by Nakata), thus easing the purification of the anticipated

labile final product, and the possibility of employing mild saponification conditions to cleave benzyl ester.

Treatment of lactone **111** and ester **113** under literature conditions afforded acetal **114**, which when treated with acidic $MeOH/CH_2Cl_2$ afforded desired product **115** (Scheme 15).



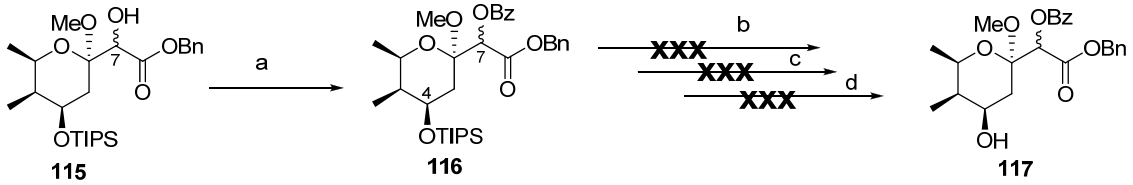
Scheme 15. A diastereoselective Claisen condensation and subsequent acetal deprotection

Conditions: a) LDA (11.3 equiv), **113** (11.3 equiv), THF, HMPA (16.4 equiv), $ZnCl_2$ (1M in Et_2O, 11.3 equiv.), –78 to –40 °C, 17 h; b) CH_2Cl_2/MeOH (1:1), CSA, $CH(OMe)_3$, rt, 10 min, 28% from **111**, 19:81 d.r.

This particular reaction sequence was performed several times with the reaction yields varying from poor to moderate (28%, 40%, and 51%). In addition, the diastereoselectivity for the transformation was extremely variable, ranging from 19:81 to 56:44 ratios of diastereomers at C7 from which neither *syn* nor *anti* products could be assigned from the ^1H NMR spectra. The large quantities of reagents used in this transformation, and the lack of purification of intermediate **114** made analysis and purification of the final products a fairly difficult process.

Although yields were moderate at best, material was moved towards downstream chemistry to determine the viability of our synthetic route (Scheme 16). A 19:81 mixture of diastereomers of substrate **115** was protected at C7 as the benzoate furnishing **116** in 52% yield**.** With **116** in hand, we envisioned that the silyl ether at C4 could be removed to furnish the desired alcohol **117**. An oxidation/olefination route would allow for installation of the C4 exocyclic olefin present in the molecule. Thus, silyl ether **116** was subjected to TBAF in THF in an attempt to obtain alcohol **117**. However, no reaction was observed (even upon heating).

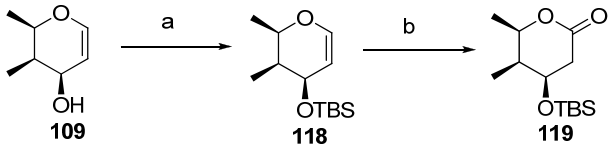
Several other conditions were also employed, but the desired transformation could not be accomplished.



Scheme 16. Protecting group manipulation for pederic acid intermediates

Conditions: a) BzCl, pyridine, DMAP, 52%; b) TBAF, THF, 25 to 40 °C, no reaction; c) TBAT, THF, no reaction; d) HF-pyridine, THF, overnight stirring, no reaction.

In an attempt to avoid C4 silyl deprotection issues, compound **119** bearing the more labile TBS silyl ether was synthesized from **109** in good yield (Scheme 17).



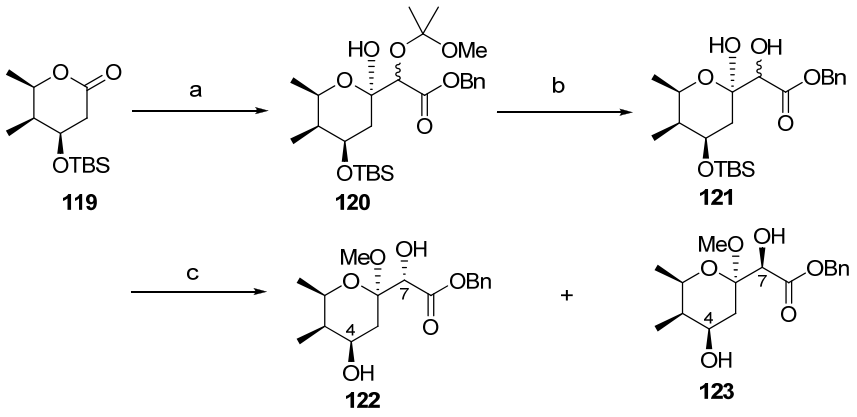
Scheme 17. Synthesis of a TBS lactone substrate

Conditions: a) TBSCl, imidazole, DMF, 72%; b) PCC, DCE, 71%.

TBS protected lactone **119** was subjected to the aforementioned literature Claisen conditions (Scheme 18) but with a few subtle changes in the procedure: Stirring times between the addition of reagents were shortened (see experimental section Appendix A) and the subsequent reaction with camphorsulfonic acid, trimethylorthoformate, and methanol was shortened, due to our belief that our poor yields may have been due to product decomposition under the acidic conditions. Furthermore, commercial LHMDS (1M in THF) rather than LDA was used in an attempt to eliminate variability in preparation of the base. After several attempts at acidic cleavage of the C7 acetal (see experimental), and removal of excess reagents and byproducts from the reaction mixture, diol **121** was isolated. This compound was found to be configurationally unstable in

$CDCl_3$. We hypothesized that this could possibly be an explanation for the variable diastereoselectivities in the preparation of substrate **115**, as all the diastereomeric ratios were determined via analysis of ^1H NMR spectra in $CDCl_3$.

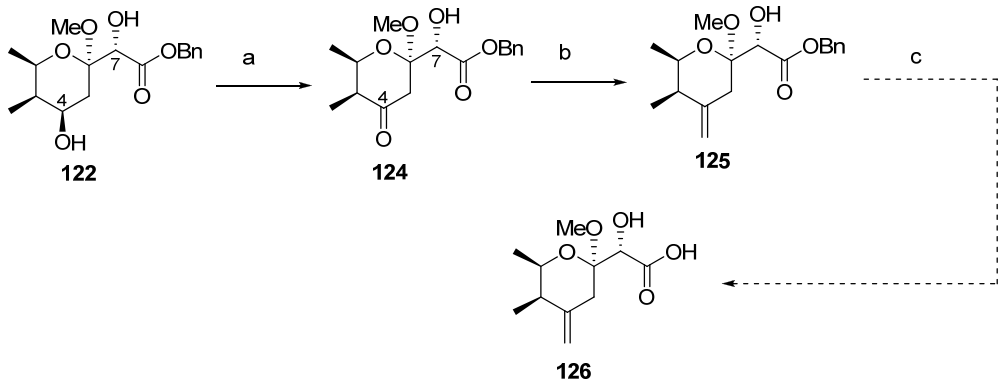
Resubjection of **121** to acidic $MeOH/CH_2Cl_2$ led to formation of the desired acetal as well as C4 silyl-deprotection. The C7 epimers were separable via flash column chromatography, and the structure of the desired diastereomer **122** was confirmed via X-ray crystallography.



Scheme 18. C6 side chain elaboration via a diastereoselective Claisen condensation

Conditions: a) LHMDS (11.3 equiv.), **113** (11.3 equiv.), THF, HMPA (16.4 equiv.), $ZnCl_2$ (1M in Et_2O, 11.3 equiv.), –78 to –40 °C, 17 h; b) CSA, $CH(OMe)_3$, CH_2Cl_2/MeOH (1:1), rt, (see text for a discussion of d.r.); c) CSA, $CH(OMe)_3$, CH_2Cl_2/MeOH (1:1), rt, 2 h.

To determine the viability of this synthetic route, **122** was used for subsequent studies (Scheme 19). Oxidation of the C4 hydroxyl group generating **124** was achieved via PCC oxidation, albeit in a moderate 55% yield. Attempts at other oxidative methods (Parikh-Doering and Dess-Martin oxidations) afforded no reaction or oxidation at C4 and C7, respectively. Takai-Nozaki olefination afforded compound **125** in a 25% unoptimized yield.



Scheme 19. Synthesis of pederic acid

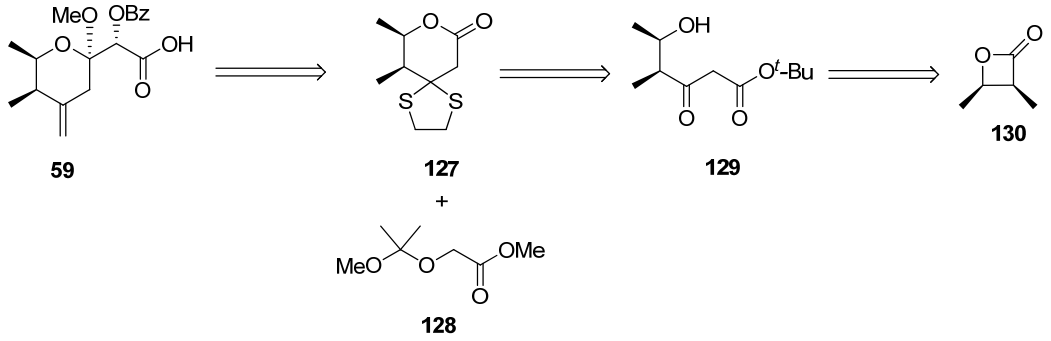
Conditions: a) PCC, CH_2Cl_2, 55%; b) $CH_2I_2ZnTiCl_4$, THF, 25%; c) DMF, NaH, dodecanethiol.

An attempt to cleave the benzyl ester of **125** using sodium dodecanethiolate gave consumption of starting material and formation of one major product which appeared consistent with carboxylic acid formation based upon thin-layer chromatography analysis (i.e. an extremely polar and streaky major product). However, due to the small scale of this reaction (5 mg) and the large excess of reagents used (DMF and dodecanethiol), product formation could not be confirmed with certainty.

From the aforementioned studies we were able to gain significant insight about intermediates in the diastereoselective Claisen reaction as well as a possible explanation of the wildly inconsistent diastereoselectivities. Furthermore, we were also able to isolate our desired Claisen product **122** and determine the relative stereochemistry of this compound via X-ray crystallography. Lastly, we were able to reach the penultimate step in the synthesis of pederic acid.

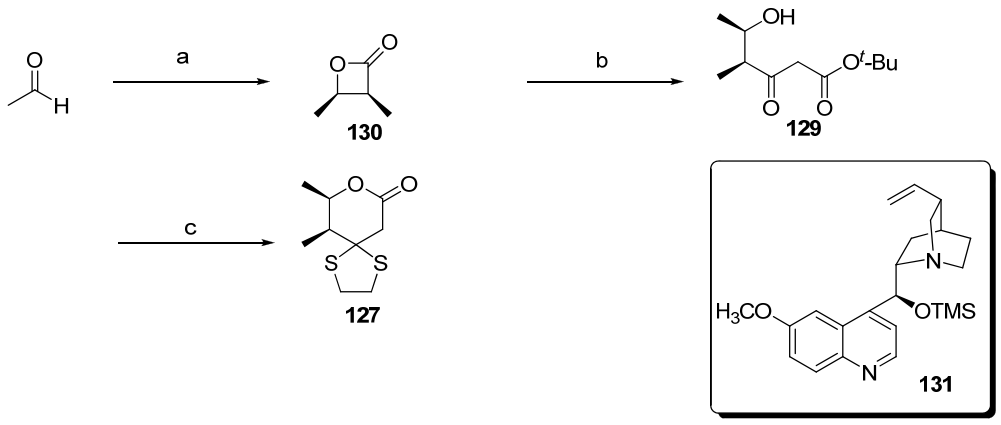
1.4.2 Synthesis of Pederic Acid: Enantioselective Ketene-Aldehyde Cycloaddition Approach

To streamline our synthesis and avoid protecting group issues, we chose to alter our retrosynthetic analysis to construct known key intermediate **127** (Scheme 20).[34] While our forward synthesis would be largely similar to Nakata's work, we were excited about the possibility of construction of the pederic acid core from β-lactone **130**, which we anticipated could be constructed on multi-gram scale and in high enantiopurity through an enantioselective ketene-aldehyde cycloaddition.



Scheme 20. A second generation pederic acid retrosynthesis

Our forward synthesis commenced with the synthesis of **130** using cycloaddition chemistry developed by Nelson and coworkers.[79] Treatment of acetaldehyde with propionyl chloride and DIPEA in the presence of catalytic trimethylsilyl-protected quinidine (**131**) afforded **130** in excellent *ee* (>99%), and a modest 45% isolated yield (Scheme 21).



Scheme 21. Synthesis of lactone substrate for Claisen condensation

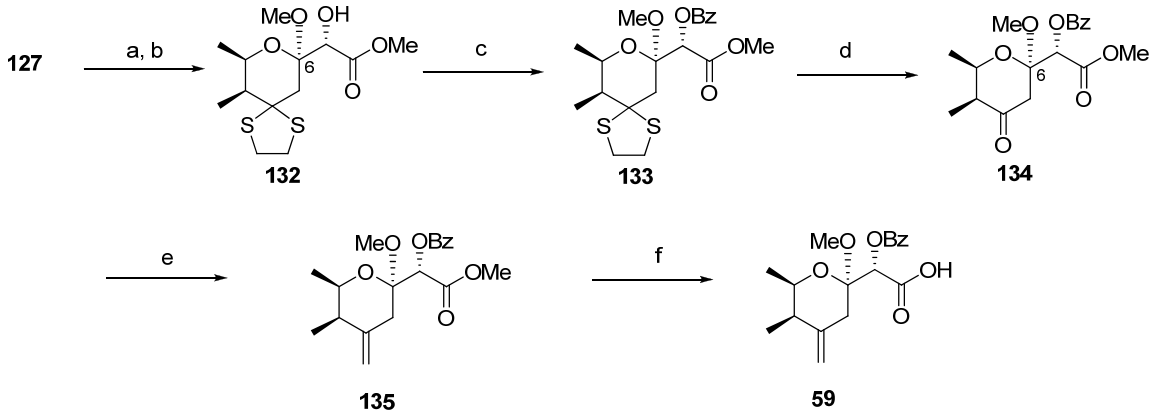
Conditions: a) TMS-quinidine (**131)** (10 mol%), $LiClO_4$ (20 mol %), propionyl chloride (2 equiv.), DIPEA (2.5 equiv.), Et_2O, CH_2Cl_2, –78 °C, 99% *ee*; b) LDA, *t*-BuOAc, THF, –78 °C, 76% (2 steps); c) $BF_3{\cdot}Et_2O$, ethanedithiol, CH_2Cl_2, –40 °C to rt, 3 days, 64%.

Due to the volatility of **130** however, it was more advantageous to avoid purification and isolation of this substrate. Addition of a crude mixture of **130** in CH_2Cl_2/ Et_2O to a solution of the lithium enolate of *tert*-butyl acetate afforded the desired β-keto ester **129** in 76% yield over 2 steps. Subjection of **129** to $BF_3{\cdot}Et_2O$, and ethanedithiol for 3 days afforded the desired product **127** in 64% yield.

With lactone **127** in hand, we were able to carry out the diastereoselective Claisen condensation protocol affording **132** as a single diastereomer in 60% yield (70% brsm) (Scheme 22). While our yields were not as high as those reported by Nakata (83% yield, 88% brsm), it was our observation that this reaction was a consistently difficult undertaking. Rigorous drying of all reagents, the use of deoxygenated solvents, and a painstaking attention to the rates of reagent addition and stirring times was necessary to achieve even moderate yields for this transformation.

Protection of the secondary alcohol **132** with benzoyl chloride, pyridine, and DMAP provided benzoate **133** in 94% yield. Removal of the dithiolane protecting group afforded ketone

134 in 58% yield, which was slightly lower than expected due to unavoidable product decomposition upon purification caused by elimination at C6.



Scheme 22. Completion of C7-*O*-Bz pederic acid

Conditions: a) LDA, *O*-(2-methoxy-2-propyl)-glycolate (**128**), (see Scheme 20), HMPA, $ZnCl_2$ (1M in Et_2O), THF, –78 to –40 °C, 17 h; b) $CH(OMe)_3$, CH_2Cl_2/MeOH (1:1), CSA, 2 h, 60% (70% brsm) (2 steps); c) BzCl, DMAP, pyridine, 94%; d) bis(trifluoroacetoxy)iodo benzene, CH_3CN, H_2O, 58%; e) $CH_2I_2ZnTiCl_4$, THF, 76%; f) $(CH_3)_3SnOH$, 1,2-dichloroethane, 80 °C, 82%.

Subjecting **44** to Takai-Nozaki olefination conditions followed by a fairly rapid purification via flash column chromatography afforded exocyclic olefin **135** in 76% yield. While compound **135** was stable for weeks after isolation and purification, it should be noted that prolonged exposure to silica gel during purification of the crude residue resulted in markedly lower yields. Saponification of methyl ester **135** under conditions developed by Nicoloau[80] afforded our desired product **59** in 82% yield. This material could be stored for several weeks in a benzene matrix at –20 °C without any decomposition.

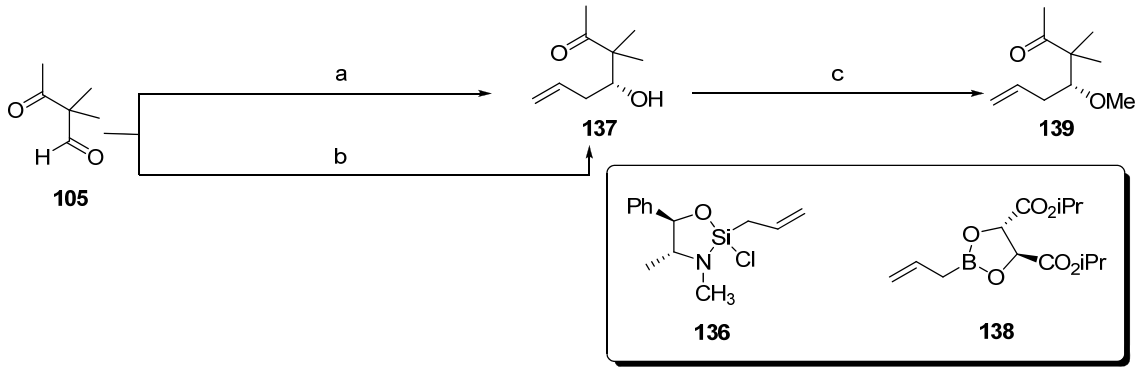
1.4.3 Conclusions

Two methods for construction of the pederic acid core were developed. The initial method utilized an asymmetric hetero-Diels-Alder to construct the core pyran in moderate

enantioselectivity (77% *ee*). Additionally, the pederic acid core was synthesized using an enantioselective ketene-aldehyde cycloaddition furnishing the desired substrate in 99% *ee*. The substrate was functionalized as reported by Nakata. However, a mild tin-mediated saponification was employed to ease purification, affording the desired protected pederic acid fragment in good yield.

1.5 AMIDOTRIOXADECALIN SYNTHESIS

With the pederic acid portion of the molecule complete, we turned our attention to the construction of amidotrioxadecalin fragment **98**. For known keto-aldehyde **105**,[81] several methods for asymmetric allylation were at our disposal. Treatment of **15** with Leighton's pseudoephedrine derived allylsilane[82] **136** afforded homoallylic alcohol **137** in an excellent 94% yield, and 90% *ee* (Scheme 23).[69, 71] This reaction could not be consistently reproduced however, and yields varied by as much as 30%. Furthermore, in our hands preparation of **136** was inefficient and prohibitively expensive on multi-gram scale. Our desire to synthesize large quantities of starting materials efficiently and economically led us to investigate the utility of Roush's diisopropyl tartrate derived allyl borane **138** for this transformation.[83]



Scheme 23. Allylation of keto-aldehyde 15

Conditions: a) **136**, toluene, –15 °C, 60-94%, 90% *ee*; b) **138**, toluene, –78 °C, 71%, 85% *ee*; c) 2,6-di-*tert*-butylpyridine, MeOTf, CH_2Cl_2, 88%.

Although the enantiomeric excess was slightly lower (85% *ee*), the yield of this reaction was consistently reproducible. In addition, allylborane **138** could be prepared easily and relatively inexpensively from D-diisopropyl tartrate. Alcohol **137** was methylated under non-anionic conditions with methyl trifluoromethanesulfonate and 2,6-di-*tert*-butylpyridine to avoid a retro-aldol pathway, generating methyl ether **139** in 88% yield.

With ether **139** in hand we envisioned using 1,5-asymmetric induction via a boron aldol condensation to construct the requisite C17 stereocenter (Scheme 24). This method, initially developed by Masamune[84] and further elaborated by Paterson,[85] has been shown to provide excellent stereocontrol for the aldol reaction of methyl ketones bearing β-*p*-methoxybenzyl (PMB), β-methoxybenzylidene (PMP) acetal, and β-tetrahydropyran (THP) susbstituents.

β-Methoxy ketones have been shown to afford moderate diastereocontrol, while β-silyl ethers show poor 1,5-*anti* diastereocontrol. Although several transition state models have been proposed, a detailed understanding of the root of this induction remains unclear, with empirical results largely serving as the explanation for the selectivity. Recently, Goodman has proposed a

model which invokes a formyl bond between the reactive aldehyde and the oxygen of the β-directing group based upon theoretical calculations (Figure 13).[86]

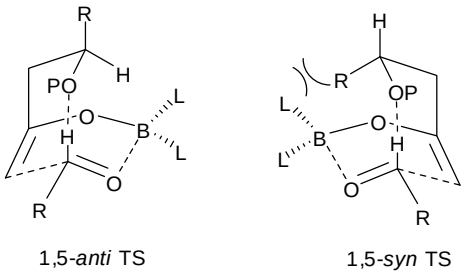
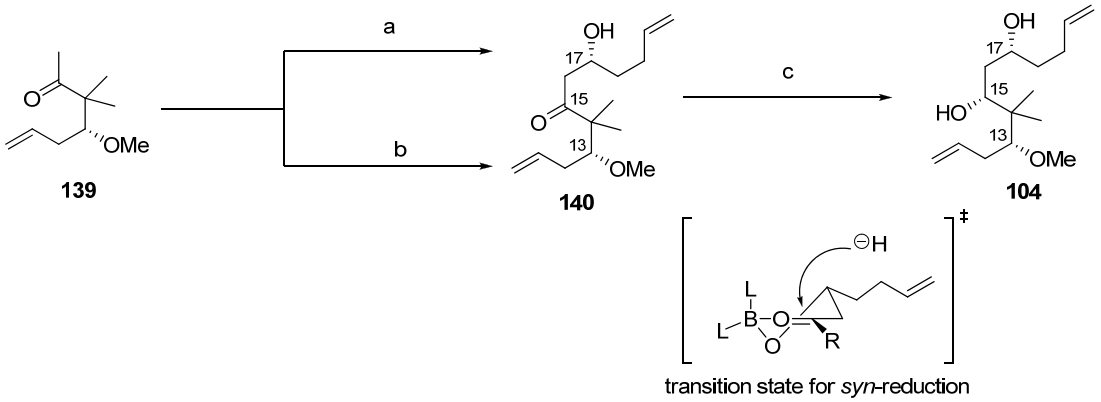


Figure 13. Goodman's transition state model for boron mediated 1,5-asymmetric induction

Treating ketone **139** with diethylboron triflate, and diisopropylethylamine (DIPEA) in Et_2O at –78 °C, followed by addition of 4-pentenal at –78 °C afforded alcohol **140** in excellent yield as a 3:1 (*anti*:*syn*) mixture of inseparable isomers (Scheme 24). To improve upon this result, we chose to generate the boron enolate using (+)-DIP-Cl as our boron source in an attempt to synergistically enhance our diastereoselectivity through matched substrate *and* reagent control.[87, 88]



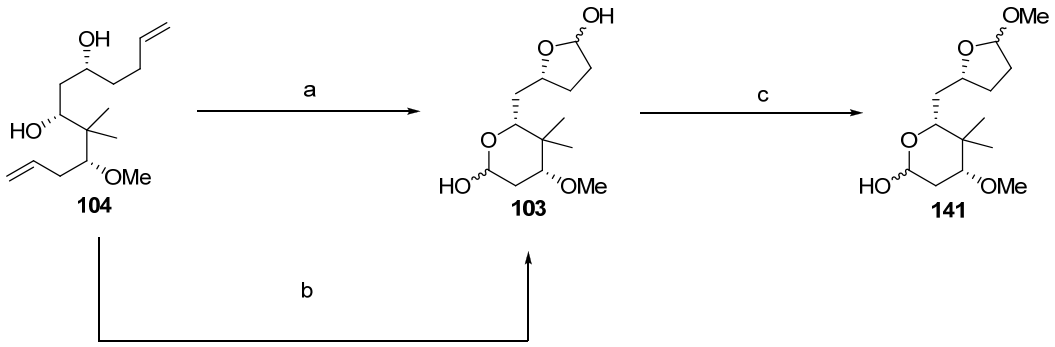
Scheme 24. Synthesis of a diol bearing C13, C15, and C17 stereocenters

Conditions: a) Et_2BOTf, DIPEA, Et_2O, 0 °C, then 4-pentenal, −78 °C, 86%, 3:1 (*anti*:*syn*); b) (+)-DIP-Cl, Et_3N, 0 °C, then 4-pentenal, Et_2O, –78 °C, 62%, 10:1 (*anti:syn*); c) Et_2BOMe, THF:MeOH (10:1), $NaBH_4$, –78 °C, 76%.

Treating **139** with Et_3N and (+)-DIP-Cl in Et_2O at 0 °C, followed by addition of 4-pentenal at –78 °C afforded alcohol **140** in 62% yield and a 10:1 ratio of inseparable isomers. Keto-alcohol

140 was selectively reduced with $NaBH_4$ in the presence of diethylmethoxyborane to *syn*-diol **104** in 76% yield.[89]

With material in hand, we set about construction of the C and D rings of theopederin D (Scheme 25).



Scheme 25. Synthesis of rings C and D of theopederin D

Conditions: a) O_3, CH_2Cl_2, –78 °C, then PPh_3, 30%; b) OsO_4, $NaIO_4$, 2,6-lutidine, *p*-dioxane, H_2O, rt, 82%; c) PPTs, MeOH/THF (1:1), rt, 40 minutes, quantitative (used without purification).

Ozonolysis of **104** afforded bis-lactol **103** in consistently poor yields (~30%). However, subjecting **104** to modified Johnson-Lemieux conditions[90] afforded **103** in an excellent 82% yield. It should be noted that this reaction is essentially a one-pot 6 step transformation consisting of two dihydroxylations, two oxidative cleavages, and two intramolecular cyclizations. Treating **103** with PPTs in MeOH/THF at room temperature selectively furnished tetrahydrofuranyl acetal **141** in quantitative yield. This selectivity can be explained by the differences in ring strain energy of the two possible oxocarbenium ions formed during the acidic methanolysis (**103a** and **103b**, Figure 14). Due to a lower barrier of formation for **103b** relative to **103a** this oxocarbenium ion forms faster, leading to the observed kinetic product **141**. This selective tetrahydrofuranyl ether formation enabled us to selectively mask the D ring lactone of theopederin D until a later point in our synthesis.

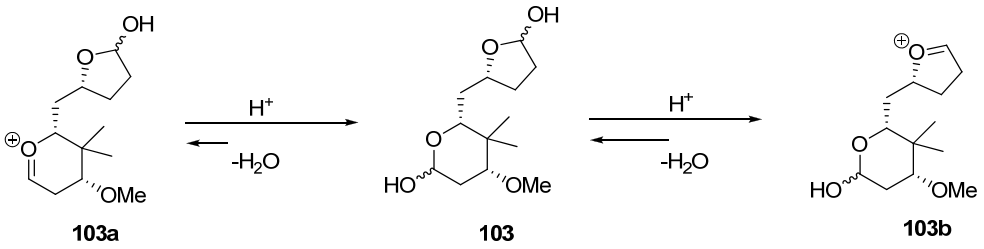
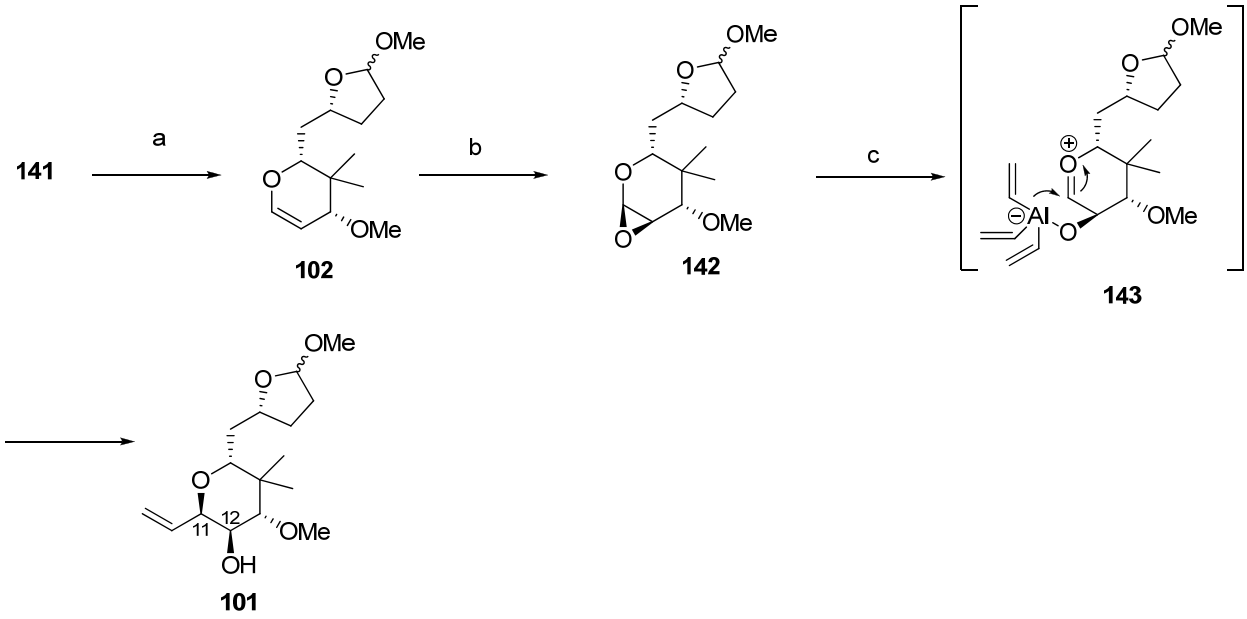


Figure 14. An illustration of the oxocarbenium ions possibly formed during acidic methanolysis of substrate 103

Cyclic acetal **141** was dehydrated under basic conditions using DIPEA, and trifluoroacetic anhydride to afford dihydropyran **102** in 92% yield (2 steps from **103**) (Scheme 26).



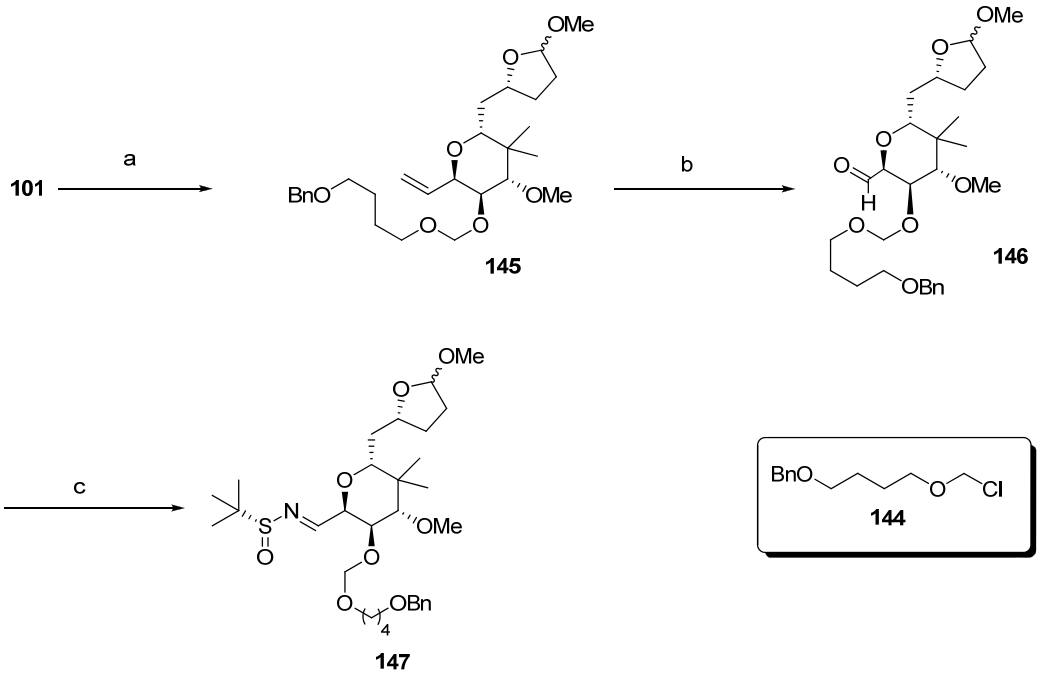
Scheme 26. Towards the synthesis of the aminotrioxadecalin. Elaboration of the theopederin D C ring

Conditions: a) trifluoroacetic anhydride, DIPEA, CH_2Cl_2, 50 °C, 92% (2 steps from **103**); b) DMDO, CH_2Cl_2, 0 °C, then c) trivinylalane, CH_2Cl_2, –78 °C.

Treatment of **102** with dimethyldioxirane (DMDO)[91, 92] afforded labile epoxide **142** which, without purification, was quickly added to a stirring solution of trivinylalane in THF at –78 °C generating *syn* addition product **101**.[93, 94] Interestingly, slow dropwise addition of **142** to

the trivinylalane solution afforded markedly lower yields, with the major product appearing to be oligomerization adduct. Rapid addition of the epoxide however (< 15 min independent of the scale of the reaction), consistently produced the desired product in quantitative yield as one stereoisomer, and without the need for purification.

With stereocenters C11 and C12 constructed, we embarked upon a sequence of functional group interconversions to construct our ETIC substrate. Treatment of **101** with 4-chloromethoxybutoxymethylbenzene[70] (**144**) afforded **145** in 77% yield (over 2 steps from **102**) (Scheme 27).



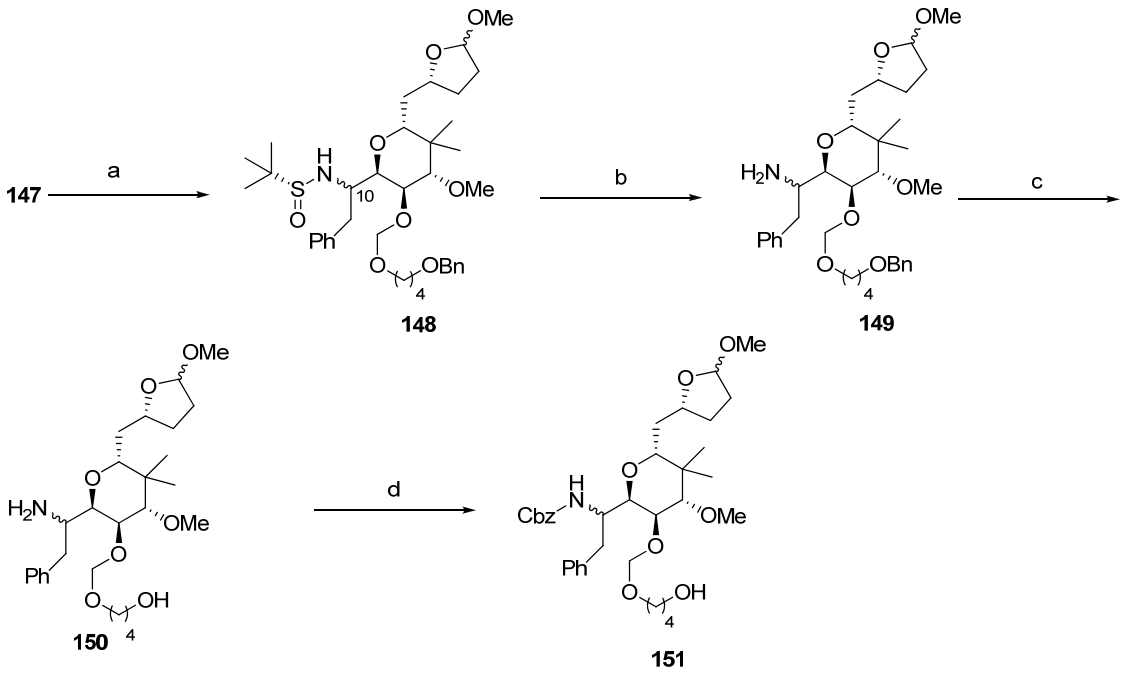
Scheme 27. Tetrahydropyran elaboration towards an ETIC substrate for cyclization

Conditions: a) **144**, KI, CH_2Cl_2, 50 °C, 77% (2 steps); b) O_3, CH_2Cl_2, –78 °C, then c) Ti(O*i*Pr)$_4$, (*R*)-*t*-butyl-sulfinamide, 55% (2 steps).

Ozonolysis of **145** followed by treatment of the resulting labile aldehyde **146** with Ellman's (*R*)-*tert*-butyl sulfonamide and Ti(O*i*Pr)$_4$ afforded **147** in 55% yield over 2 steps.[95] The low yield for this transformation is presumably due to the sensitivity of intermediate aldehyde **146**. Attempts

at purification of aldehyde **146** followed by sulfonamide condensation afforded significantly lower yields.

Sulfinylimine **147** however, was exceptionally stable and addition of benzylmagnesium chloride afforded **148** in 75% yield as 1:1 mixture of diastereomers at C10 (Scheme 28).[96]



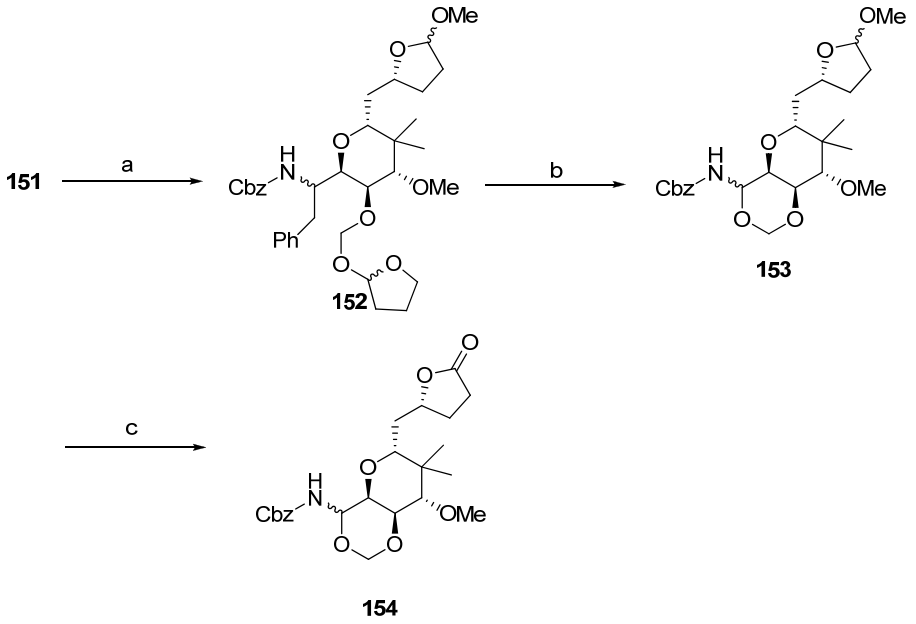
Scheme 28. Completion of the amidotrioxadecalin ring system

Conditions: a) BnMgCl, CH_2Cl_2, 75%, 1:1 d.r.; b) 4M HCl in *p*-dioxane, MeOH, 75%; c) H_2, Pd/C, AcOH, MeOH; d) Cbz chloride, H_2O/THF, $NaHCO_3$, 70% (2 steps).

While the lack of diastereocontrol was surprising, the stereocenter in question had no bearing on the outcome of our synthesis. However, attempts at improving the diastereoselectivity were made in an effort to ease interpretation of spectral data. Adding tetramethylethylenediamine (TMEDA) to the reaction mixture to enhance selectivity[96] also afforded a 1:1 ratio of products. In addition, to determine if the poor diastereocontrol was due to "mismatched" double diastereodifferentiation, the (*S*)-*tert*-butylsulfinylimine was prepared and treated with identical reaction conditions. Again, benzyl addition afforded only a 1:1 ratio of diastereomers.

Cleavage of the chiral sulfur auxiliary with 4M HCl afforded amine **149** in 75% yield as a mixture of diastereomers (Scheme 28). Hydrogenolysis of **149** in the presence of acetic acid afforded amino alcohol **150**. Protection of the amine functionality with CbzCl and $NaHCO_3$ in H_2O/THF afforded carbamate **151** in 70% yield.

Treatment of **151** with oxidative etherification conditions developed by Suarez and coworkers[97] ($PhI(OAc)_2$, iodine, cyclohexane, then *hv*) afforded tetrahydrofuranyl substrate **152** in 80% yield (Scheme 29).[97]



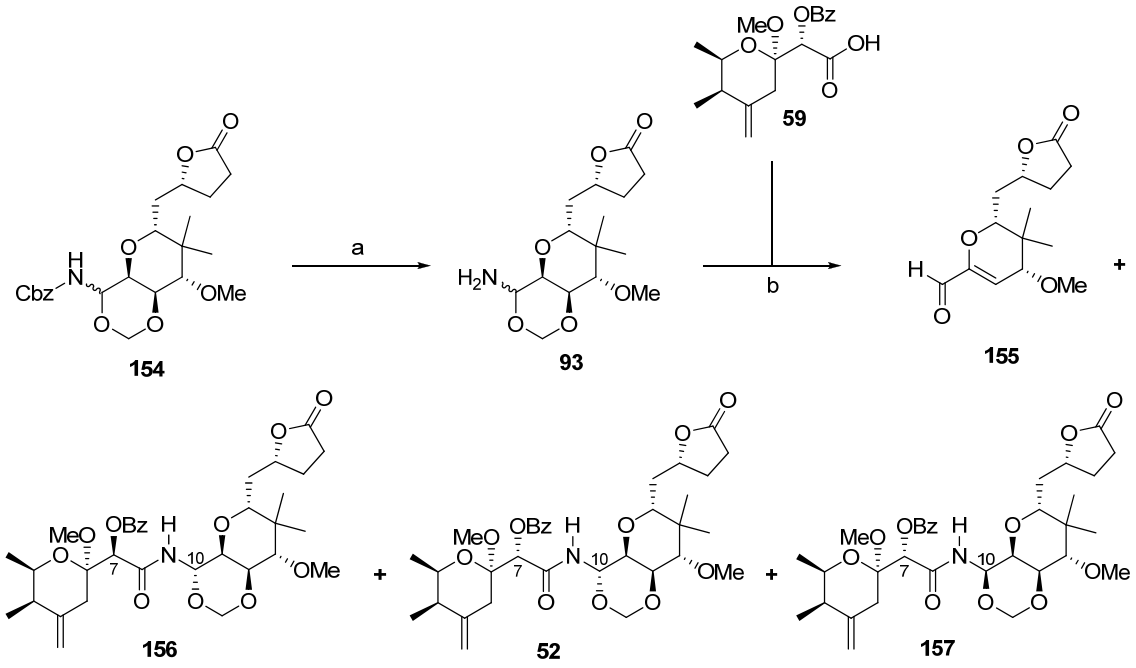
Scheme 29. Completion of the theopederin D amidotrioxadecalin

Conditions: a) DIB, I_2, cyclohexane, 80%, *hv*; b) *hv*, $NMQPF_6$, O_2, NaOAc, $Na_2S_2O_3$, DCE, PhMe, 4Å MS, 76%, 2:1 d.r.; c) Jones oxidation, 64%.

To our delight, subjection of **152** to our ETIC conditions afforded amidotrioxadecalin **153** in 76% yield.[68] Jones oxidation of acetal **153** afforded lactone **154** in 64% yield.

1.6 FRAGMENT COUPLING AND COMPLETION OF THE TOTAL SYNTHESIS OF THEOPEDERIN D

With fragments **59** and **154** in hand our attention turned to coupling of these compounds under conditions developed by Rawal and coworkers (Scheme 30).[54]

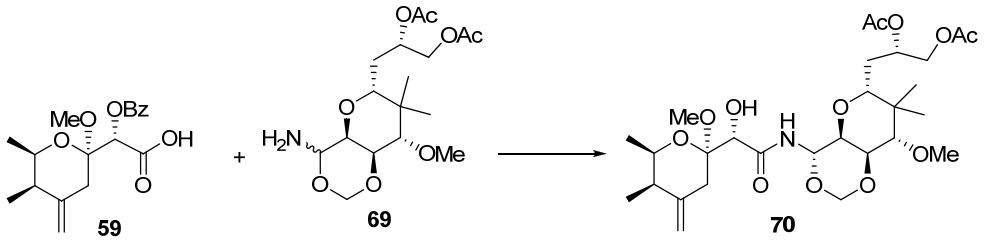


Scheme 30. DCC coupling of C7-*O*Bz-pederic acid and aminotrioxadecalin

Conditions: a) H_2, Pd/C, EtOAc; b) **59**, DMAP, DCC, CH_2Cl_2, rt, mixture of **52, 155-157**, 15%.

Treating carbamate **154** with H_2 and Pd/C in EtOAc furnished aminotrioxadecalin **93**. While Kishi has reported isolation and ^{1}H NMR studies of similar aminotrioxadecalin compounds in his total syntheses of the mycalamides,[29] in our hands **93** was found to decompose fairly rapidly and had to be used within minutes of isolation. Prompt addition of **93** to a solution of freshly prepared **59**, DCC, and DMAP in CH_2Cl_2 at room temperature, followed by stirring for 12 hours afforded products **52**, and **155-157**. From this product mixture α,β-unsaturated aldehyde **155**, the product of aminotrioxadecalin **93** decomposition, was the major product. Coupled products **156**,

52 and **157** were formed in approximately 15% yield in a 1:1:1 ratio. The poor yield and diastereoselectivity for this transformation, in addition to the formation of C7 epimer **156** was perplexing in light of Rawal's elegant mycalamide A synthesis (Scheme 31 below).



Scheme 31. Rawal's mycalamide A fragment coupling

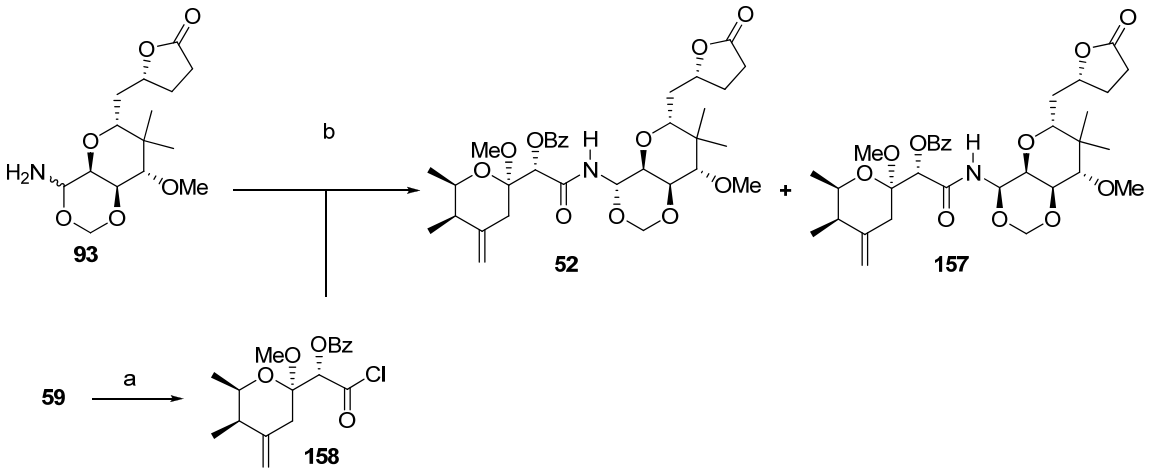
Conditions: DMAP, DCC, CH_2Cl_2, rt, 56%, 5:1 (desired:undesired).

Based upon our unsatisfactory results we hypothesized that the C15 tetrahydrofuranyl side chain could be exerting a remote effect on our substrate. The subtle effects of this side chain on reactivity and diastereocontrol at C10 were initially observed by Kishi in his total syntheses of mycalamides A and B (see Scheme 2, page 10).[29]

Thus, we set about optimization of our coupling reaction. Our intent was to decrease the length of reaction in an effort to suppress decomposition leading to formation of **155**, and to increase the electrophilicity of the pederic acid coupling fragment **59**. To accomplish these objectives, we chose to perform the coupling using C7-*O*Bz-pederic acid chloride **158** (Scheme 32).

Treating **59** with $SOCl_2$ and pyridine in CH_2Cl_2 afforded acid chloride **158**,[98] which was used without further purification (Scheme 32). Treating **158**, with a freshly prepared solution of **93** in CH_2Cl_2 at 0 °C followed by warming to room temperature afforded coupled products **52** and **157** in 40% yield, and in a 1:1 d.r. This reaction was performed several times, and was

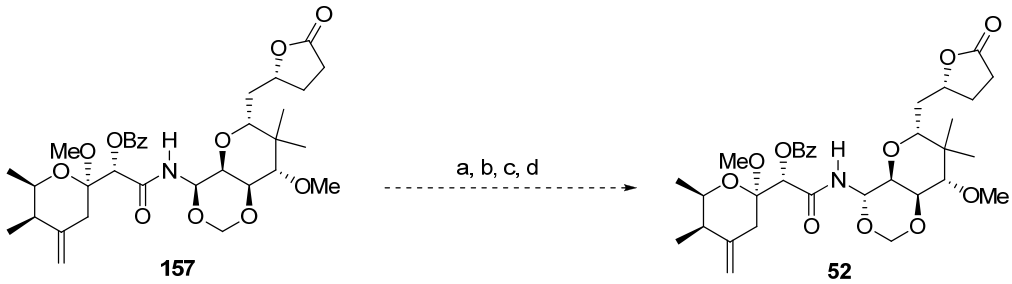
highly reproducible. However, varying amounts of the C7 epimer **156** were also recovered during each coupling.



Scheme 32. Acid chloride coupling conditions

Conditions: a) $SOCl_2$, pyridine, CH_2Cl_2, rt; b) **158**, CH_2Cl_2, 40%.

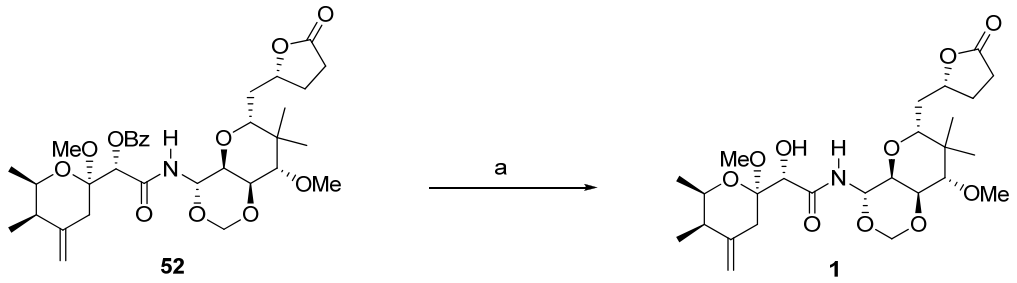
Attempts at epimerization of the *epi*-C10 isomer **157** were unsuccessful. Treating **157** with stoichiometric 2-hydroxypyridine (pyridone) in acetonitrile at room temperature followed by heating to 80 °C for 12 hours afforded only starting material (Scheme 33). Employing DMAP, DMAP hydrochloride salt, and a combination of these two reagents also afforded only starting material, even at elevated temperatures.



Scheme 33. Epimerization studies of *epi*-C10-*O*-Bz-theopederin D

Conditions: a) pyridone, CH_3CN, rt to 80 °C, 12 h, no reaction; b) DMAP, CH_2Cl_2, 4 h no reaction; c) DMAP-HCl, CH_2Cl_2, 4 h, no reaction; d) DMAP, DMAP-HCl, CH_2Cl_2, rt to 50 °C, 1.5 h, no reaction.

To complete our synthesis, C7 *O*-Bz-theopederin D (**52**) was treated with K_2CO_3 in MeOH to afford theopederin D **1**, in 66% yield (Scheme 34).



52 1

Scheme 34. Final protecting group removal to afford theopederin D

Conditions: a) K_2CO_3 in MeOH, rt, 66%.

1.7 CONCLUSION

The amidotrioxadecalin ring system comprising the eastern hemisphere of theopederin D (B, C, and D rings) was successfully synthesized. A 1,5-*anti*-boron aldol was used to establish the required stereochemical relationship between C13 and C17. The C and D rings of theopederin D were constructed in high yield via a one-pot six reaction sequence of dihydroxylation, $NaIO_4$ cleavage, and cyclization. From this bis-lactol substrate, selective tetrahydrofuranyl ether formation in the presence of a tetrahydropyranol allowed for differentiation/protection of the D ring for late stage oxidation to the requisite lactone functionality. The C ring was elaborated using epoxidation/ *syn* vinylation chemistry developed by Yamamoto and Rainier providing functional group handles for preparation of our electron transfer initiated cyclization (ETIC) substrate. After a series of straightforward functional group manipulations, the ETIC substrate was constructed in short order. Treatment of our substrate with mild and essentially neutral ETIC conditions furnished the amidotrioxadecalin ring system

in excellent yield. Lastly, Jones oxidation of the pendant D ring furnished the desired amidotrioxadecalin system with the proper oxidation state.

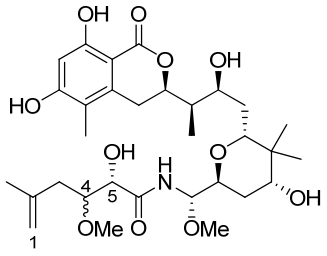
The aminotrioxadecalin and pederic acid subunits were coupled using conditions based upon literature precedent (DCC, DMAP, CH_2Cl_2) affording the desired coupled product, albeit in 15% yield, with the major product being derived from aminotrioxadecalin decomposition. Optimization of the reaction conditions, namely the usage of pederic acid chloride, led to an increase in reaction rate and a significantly higher yield (40% 1:1 d.r.). Lastly, benzoyl protecting group removal furnished the natural product in 66% yield.

Thus the synthesis of theopederin D was completed, with our synthesis furnishing the natural product in 0.8 % overall yield. The longest linear sequence was 16 steps from keto-aldehyde **105**. This material can be easily obtained in multi-gram quantities in two steps from commercially available and inexpensive starting materials.[81] Our usage of a 1,5-*anti* boron aldol to establish the proper C17 stereochemistry on the theopederin side chain should allow for the construction of several other pederin family members, notably mycalamides A and B. Furthermore, our catalytic asymmetric approach to the construction of the pederic acid core allows for rapid construction of this fragment on multi-gram scale.

2.0 SYNTHESIS AND DETERMINATION OF THE ABSOLUTE AND RELATIVE STEREOCHEMISTRY OF PSYMBERIC ACID

2.1 INTRODUCTION

In relation to our interest in the pederin family of natural products, our labs were involved in research towards the total synthesis of psymberin (Figure 15). This distant relative of the theopederin and mycalamide classes of compounds displays *selective* cytotoxicity against several cancer cell lines. In addition to our synthetic studies, we also endeavored to determine the absolute and relative stereochemistry of the C1-C6 side chain (which we have named psymberic acid).



1

Figure 15. Psymberin

Psymberin's unique departure from the structural and biological motifs of the pederin family attracted the interest of several research groups, and many of them were simultaneously working towards the total synthesis of this natural product. The following sections discuss the

isolation and structure elucidation of **1**, as well as its intriguing biological activity. Lastly an overview of the syntheses of psymberic acid (performed concurrently with our own synthetic work) is presented.

2.1.1 Isolation and Elucidation of the Structure of Psymberin

Irciniastatin A was isolated in 2004 from the marine sponge *Ircinia Ramosa* by Pettit[12] and coworkers in Indonesian waters. Also in 2004, Crews and coworkers[11] isolated a compound from the *Psammocinia* sp. sponge off the coast of Papua New Guinea which they named psymberin. Due to their similar biological and structural properties, it was speculated that the two compounds were identical. However, because the spectra of these compounds were reported in different deuterated solvents, this could not be absolutely confirmed.

The planar structure of psymberin (**1**) was elucidated by the two groups in roughly the same manner, with researchers separating the molecule into 3 pieces: The acyclic amide side chain (psymberic acid), the rigid THP ring, and the pendant dihydroisocoumarin (Figure 16). Crews and coworkers established the connectivity of psymberic acid and the THP ring based upon an HMBC correlation between carbonyl C6 and H8. Connectivity to the pendant dihydroisocoumarin was established based upon a COSY correlation between H13 and H15 as well as an HMBC correlation between C14 and H15. Pettit used a somewhat similar HMBC correlation approach in his determination of the connectivity of the molecule.

With the skeletal structure of psymberin established, it was clear that the compound was related to the pederin family. Like other members of the family, psymberin contains acyl aminal functionality as well as an eastern hemisphere THP ring. However, the trioxadecalin ring system

present in the mycalamides, onnamides, and theopederins is absent, and the cyclic pederic acid subunit (seen in all of the 33 other family members) is not present.

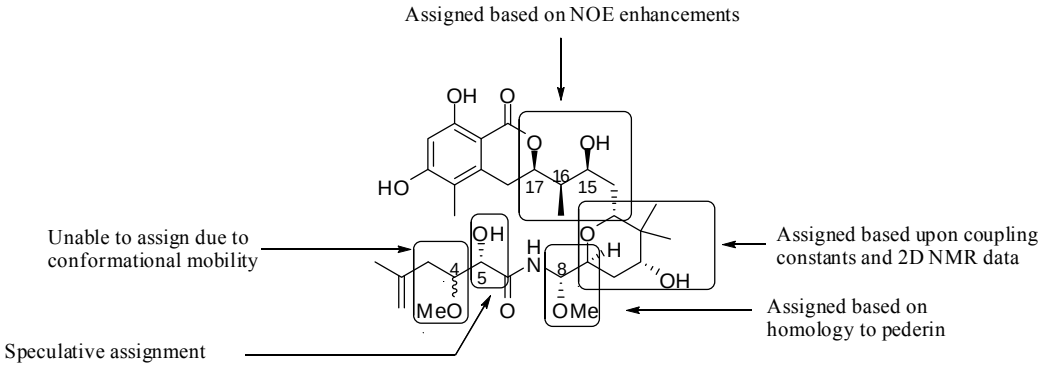


Figure 16. The partially elucidated structure of psymberin/irciniastatin A by Crews

Although both groups arrived at identical planar structures, their assignment of psymberin's stereochemical configuration was not entirely identical. Attempts by both groups to make derivatives or obtain crystal structures of psymberin were unsuccessful.

The Crews group assigned the structure of the psymberic acid side chain using nOe, and HSQMBC data (see Figure 17). However, the C4 stereocenter could not be determined because of the chain's rotational freedom, and assignment of the stereochemistry at C5 (*S**) was speculated based on psymberin's homology to pederin (the same rotamers for the analogous C6 and C7 carbons were reported for mycalamide A). The Pettit group made no attempts at assigning the stereochemical configuration of psymberic acid.

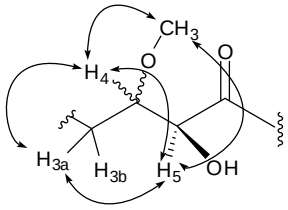


Figure 17. Observed coupling in the determination of psymberic acid stereochemistry

Furthermore, the Crews and Pettit groups reported different stereochemical assignments for the eastern hemisphere THP ring and appended acyl aminal functionality (see Figure 18). The Crews group confirmed the chair structure based on spin-spin couplings and nOe enhancements, with the stereochemistry at C8 being assigned based upon nOe enhancements between H8/H11a, H8/H13a, and 8-OCH_3/H-10e. These enhancements in addition to gauche coupling between H8/C10 (J = 3 Hz) and H8/C9 (J = 6 Hz) confirmed their stereochemical assignment of 8*S**, 9*S**, 11*R**, and 13*R**.

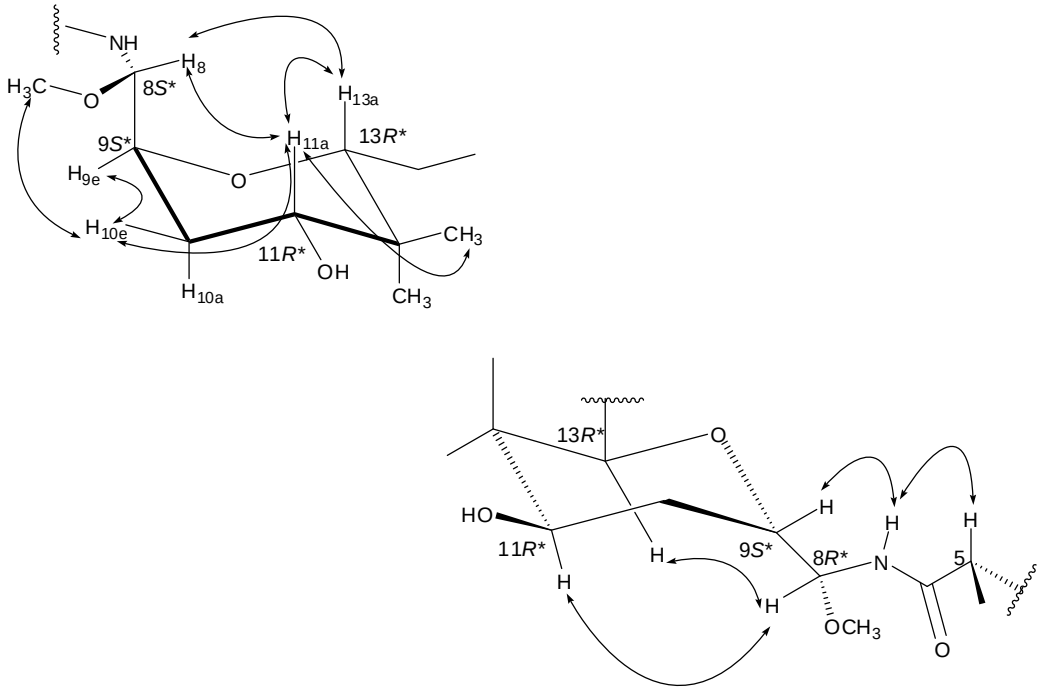


Figure 18. A comparison of Crews (upper) and Pettit (lower) stereochemical assignments using nOe enhancements (arrows) for the THP ring and appended acyl aminal

The Pettit group determined the stereochemistry of the eastern hemisphere tetrahydropyran ring based upon nOe enhancements as well (see Figure 18 above). However, their assignment of C8 differs from that of Crews and co-workers. Their stereochemical configuration is rationalized by enhancements between H5 and the amide proton, and H9 and the

amide proton which led to them to conclude that these protons were all oriented on the same side in space. Further enhancements of H8 to H11 and H13 completed their analysis of the system.

Lastly, Crews and researchers defined the stereochemical configuration of the C15 to C17 system using coupling constants, nOe's (see Figure 19) and the observance of a Cotton effect at the $n \rightarrow \pi^*$ (ca. 270 nm) transition for the chiral dihydroisocoumarin. The Pettit group made no assignment for these stereocenters.

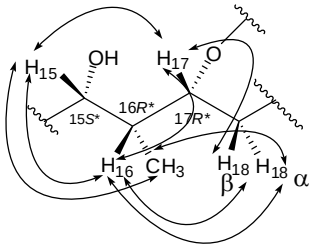


Figure 19. Stereochemical configuration of C15 to C18 of psymberin by Crews and researchers based upon nOe enhancements (arrows)

2.1.2 Biological activity of psymberin

In addition to psymberin's striking structural departures from the class of pederin-like molecules, its biological activity also differs from other family members. Psymberin displays selective in vitro biological activity (see Table 3).[99] For example, for multiple leukemia cell lines (CCRF-CEM, HL-60(TB), K-562) psymberin displayed relatively high LC_{50} values ($>2.5 \times 10^{-5}$ M). However, for other cell lines such as melanoma (MALME-3M) or breast cancer (MDA-MB-435) psymberin is 4 orders of magnitude more potent ($LC_{50} < 2.5 \times 10^{-9}$).

Table 3. In vitro LC50 (M) values for psymberin against various cancer cell lines

cell line	LC50 (M)	cell line	LC50 (M)
Leukemia		**Melanoma**	
CCRF-CEM	>2.5 x 10^{-5}	LOX IMVI	>2.5 x 10^{-5}
HL-60(TB)	>2.5 x 10^{-5}	MALME-3M	<2.5 x 10^{-9}
K-562	>2.5 x 10^{-5}	SK-MEL-2	>2.5 x 10^{-9}
MOLT-4	>2.5 x 10^{-5}	SK-MEL-5	<2.4 x 10^{-9}
RPMI-8226	>2.5 x 10^{-5}	SK-MEL-28	1.41 x 10^{-5}
SR	>2.5 x 10^{-5}	UACC-257	>2.5 x 10^{-5}
		UACC-62	<2.5 x 10^{-9}
breast cancer		**colon cancer**	
MCF7	>2.5 x 10^{-5}	HCC-2998	3.76 x 10^{-7}
HS 578T	>2.5 x 10^{-5}	HCT-116	<2.5 x 10^{-9}
MDA-MB-435	<2.5 x 10^{-9}	HT29	>2.5 x 10^{-5}
NCI/ADR-RES	1.9 x 10^{-5}	SW-620	>2.5 x 10^{-5}
T-47D	1.36 x 10^{-5}		

Psymberin also displays potent growth inhibition against numerous cancer cell lines (GI_{50} values of 10^{-3}-10^{-4} μg/mL) (see Table 4). Initial hypotheses suggested that the psymberic acid and dihydroisocoumarin moieties may have been responsible for psymberin's selective biological activity. However, recent work by De Brabander using psymberin/pederin analogues has illustrated that while the cyclic pederic acid subunit is responsible for the cytotoxicity of pederin and mycalamide, the dihydroisocoumarin is critical to the displayed cytotoxicity of psymberin.[58]

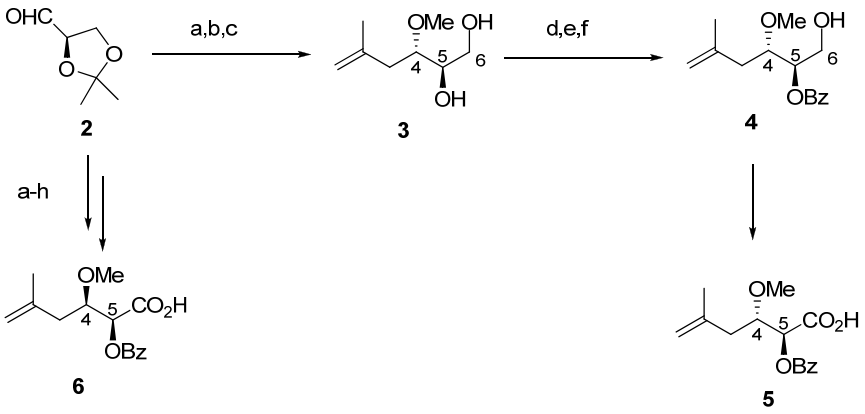
Table 4. Inhibition of cell line growth (GI50, μg/mL) for psymberin

Human cancer cell line		**GI50(μg/mL)**
Pancreas	BXPC-3	0.0038
Breast	MCF-7	0.0032
CNS	SF268	0.0034
Lung	NCI-H460	< 0.0001
colon	KM20L2	0.0027
prostate	DU-145	0.0024
Leukemia (murine)	P388	0.00413

2.2 PREVIOUS SYNTHESES OF PSYMBERIC ACID

2.2.1 Synthesis of Psymberic Acid by De Brabander and Coworkers

Based on the belief that Crews' assignment of the stereochemical configuration of C5was correct, the synthetic route toward psymberic acid pursued by De Brabander involved construction of the two possible stereoisomers at C4 (see Scheme 35).[57] Commercially available acetonide **2** was diastereoselectively methallylated using (–)-$(Ipc)_2$BOMe and methallyllithium to afford an alcohol at C4. The alcohol was subsequently converted to the methyl ether, and the acetonide was removed to afford diol **3** in 62% yield over 3 steps. Substrate **4** was prepared via protection of the C6 hydroxyl group as the TBS ether, benzoylation of the C5 hydroxyl group, and TBS deprotection of the C6 hydroxyl group in 90% yield over 3 steps. Primary alcohol **4** was converted to the aldehyde with Dess Martin-periodinane, followed by a Pinnick oxidation to generate carboxylic acid **5** in 87% yield over 2 steps. *Syn* diastereomer **6** was constructed under identical conditions using (+)-$(Ipc)_2$BOMe.



Scheme 35. De Brabander's synthesis of a protected psymberic acid substrate

Conditions: a) (−)-$(Ipc)_2BOMe$ for the *anti*-series and (+)-$(Ipc)_2BOMe$ for the *syn*-series, CH_2CMeCH_2Li, Et_2O, −78 °C; b) NaH, MeI, THF; c) PPTs, $MeOH/H_2O$, 50 °C, 62% over 3 steps; d) TBSCl, imid., CH_2Cl_2; e) BzCl, pyr.; f) aq. 3 N HCl, 90% over 3 steps; g) DMPI, CH_2Cl_2, Me_2S; h) NaH_2PO_4, $NaClO_2$, 2-methyl-2-butene, *t*-$BuOH/H_2O$, 87% over 2 steps.

The De Brabander group would later determine the correct stereochemical configuration of psymberic acid (4*S*, 5*S*) upon completion of the total synthesis of psymberin and comparison to the natural product's characterization data.

2.2.2 Williams' Model System Approach

In addition to work by the De Brabander group, Williams and coworkers investigated the stereochemical configuration of psymberic acid.[100] Following a similar synthetic route to the De Brabander group, the Williams group was able to synthesize model amides **7** and **8** (see Figure 20).

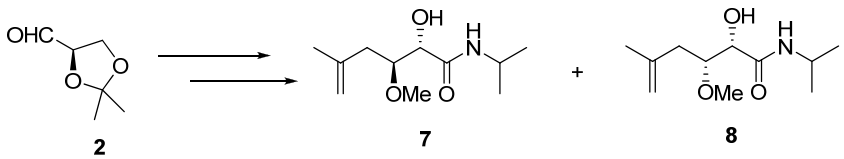


Figure 20. Model substrates for Williams' NMR psymberic acid studies

Comparison of the differences between the ^{1}H NMR and ^{13}C NMR spectra of the natural product with those of the model substrates led to the conclusion that the correct stereochemical configuration was 4*S*, 5*S* (see Figure 21).

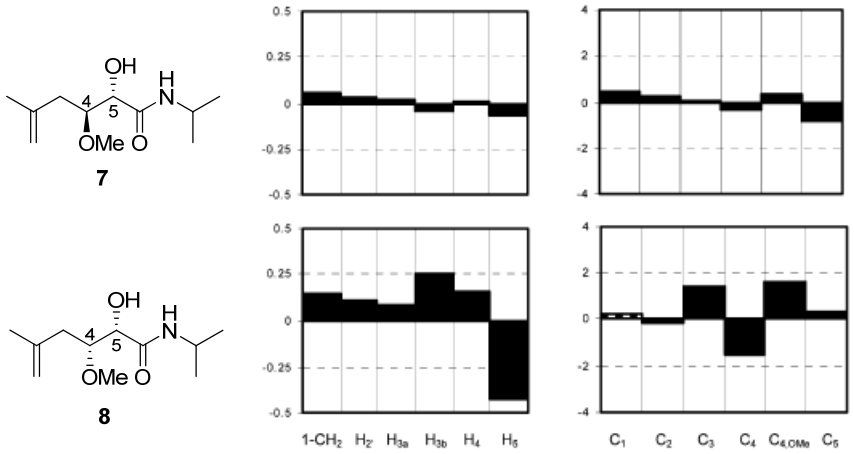


Figure 21. A histogram of the differences between psymberin and psymberic acid model substrates The *x*-axis identifies the appropriate proton/ carbon signals. The *y*-axis is δ(psymberin) - δ(*anti* or *syn* model). Reprinted with permission from Kiren, S; Williams, L.J. "Configuration of the Psymberin Amide Side-chain" *Org. Lett*. 7 (14); 2905-2907.Copyright 2005 American Chemical Society.

2.3 RETROSYNTHESIS OF PSYMBERIC ACID

At the time of our synthesis, the stereochemistry of pederin at C4 was undefined and the configuration at C5 was hypothesized as 5*S** based solely on psymberin's homology to pederin. Thus, we required a synthetic strategy that would allow for generation of all stereoisomers of this side chain for determination of the absolute and relative stereochemistry. Our retrosynthetic analysis began with cleavage of psymberin's amide bond to afford protected psymberic acid derivative **9** (see Figure 22)**.** We envisioned that carboxylic acid **9** could be constructed via diastereoselective methallylation of orthogonally protected dihydroxypropionaldehyde **10**, which

could be generated from known methyl ester **11**. Diol **11** could be obtained from serine, of which both enantiomers are inexpensive and readily available.

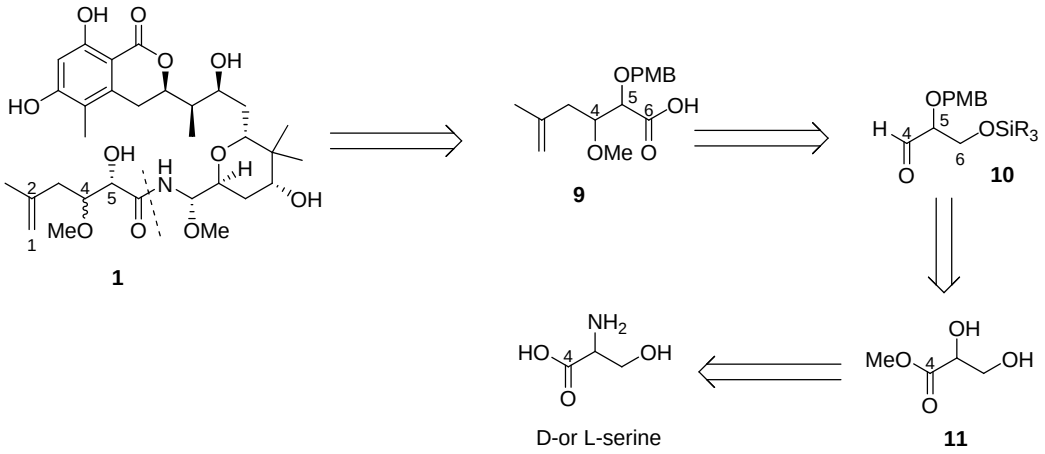
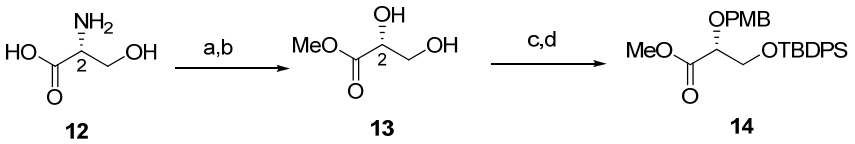


Figure 22. Retrosynthesis of psymberic acid

2.4 SYNTHESIS OF PSYMBERIC ACID

Our synthesis of psymberic acid began with the diazotization of D-serine by treatment with H_2SO_4 and $NaNO_2$ in H_2O for 3 days affording an alcohol at C2, followed by esterification to the methyl ester generating **13** in a modest 41% yield over 2 steps (see Scheme 36). Although our yield of **13** was not comparable to the reported literature yield,[101] the starting materials were inexpensive and the ease of reaction on multi-gram scale, in addition to the high enantiopurity of the product, justified our continued usage of this protocol.



Scheme 36. Synthesis of psymberic acid intermediates

Conditions: a) H_2SO_4, $NaNO_2$, H_2O, 3 days; b) $CH(OMe)_3$, MeOH, 60 °C, 41% over 2 steps; c) TBDPSCl, imidazole, –42 °C, 74%; d) *p*-methoxybenzyltrichloroacetimidate, BF_3·THF, CH_2Cl_2, cyclohexane, 0 °C, 76%.

Mono-protection of the primary alcohol of **13** as the TBDPS ether followed by protection of the secondary alcohol using *p*-methoxybenzyltrichloroacetimidate and catalytic BF_3·THF in CH_2Cl_2/cyclohexane afforded **14**. It should be noted that although many literature procedures call for extended reaction times (i.e. overnight stirring) and catalytic BF_3·Et_2O,[102] overnight stirring resulted in isolation of only starting material, and shorter reaction times with BF_3·Et_2O resulted in yields much lower than reported literature values for this transformation.[103] The use of milder conditions (less than 1 mol% BF_3·THF), shorter reaction times (~3 min) and a "reverse quench" method (see Experimental Appendix B), gave consistently reliable yields on various scales (0.20 g to 9.00 g).

From methyl ester **14**, several choices were available for construction of the C4 stereocenter. A one pot DIBAL-H reduction and methallylation using methallylmagnesium chloride resulted in a 1.8:1.0 ratio of *syn*:*anti* products (**15**) in excellent yield, with our selectivity rationalized by a chelation-controlled transition state (see Figure 23).

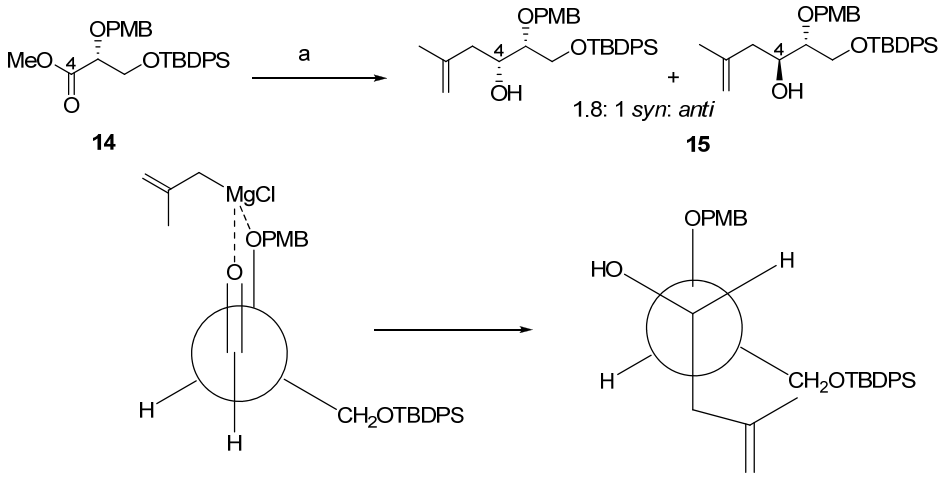
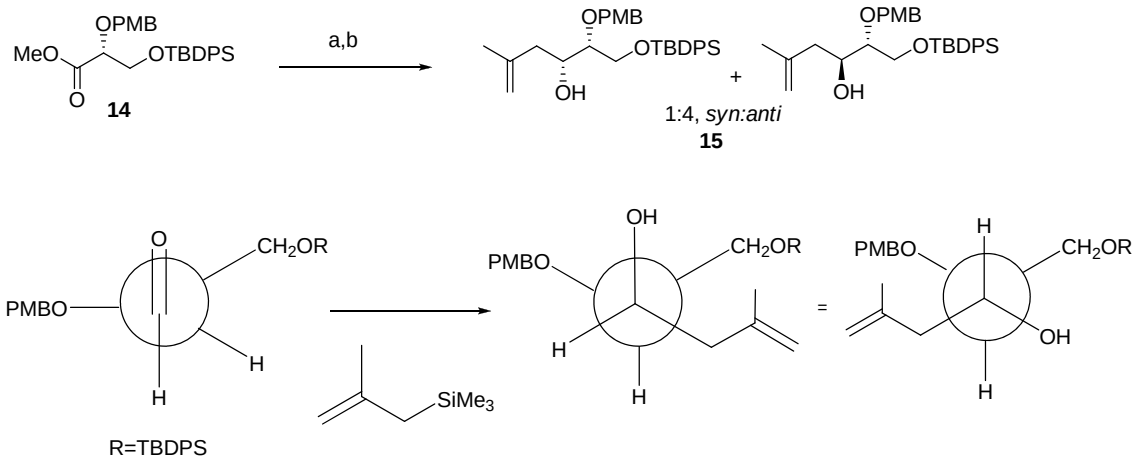


Figure 23. Chelation controlled methallylation

Conditions: a) DIBAL-H, CH_2Cl_2, –78 °C, then methallylmagnesium chloride, –78 °C to rt, 91%.

Due to our need for large quantities of both diastereomers the observed diastereoselectivity was deemed acceptable for our studies. However, research by Mulzer has shown that the addition of $MgBr_2$ to Grignard additions can greatly improve the ratio of *syn* to *anti* products.[104]

Furthermore, we were able to improve our ratio of *syn* to *anti* products by treating the isolated (but crude) aldehyde from DIBAL-H reduction of **14** with $BF_3{\cdot}Et_2O$, and methallyltrimethyl silane at –78 °C to afford **15** in a 1:4 *syn*: *anti* diastereomeric ratio, albeit with much lower yields (typically 30% yield over 2 steps) due to decomposition of the product in the presence of $BF_3{\cdot}Et_2O$. Modification of the reaction conditions by using $BF_3{\cdot}THF$ resulted in a more desirable yield (56% over 2 steps, Scheme 37).

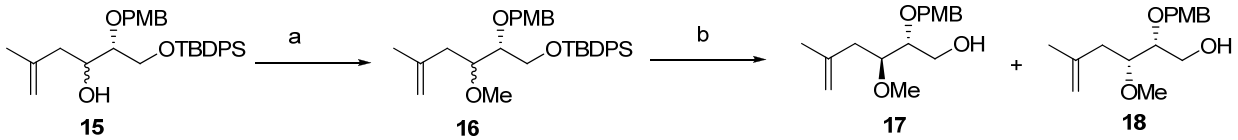


Scheme 37. Felkin-Anh methallylation

Conditions: a) DIBAL-H, CH_2Cl_2, −78 °C; b) Methallyltrimethylsilane, BF_3·THF, CH_2Cl_2, −78 °C, 56% 2 steps.

Attempts to improve upon this yield through the use of other methallylating reagents such as methallyl-tri-*n*-butyltin, resulted in good selectivity (based upon crude ^{1}H NMR). However, removal of the excess tin reagent required for this transformation was difficult.

The diastereomeric mixture of secondary alcohols (**15**) was methylated under non-anionic conditions generating a separable diastereomeric mixture of ethers **16** (see Scheme 38). Although the diastereomers could be separated at this point, material throughput and separation of the diastereomers was improved by delaying separation until removal of the silyl ether protecting group. Treating **16** with TBAF in THF furnished alcohols **17** and **18** in 76% yield.

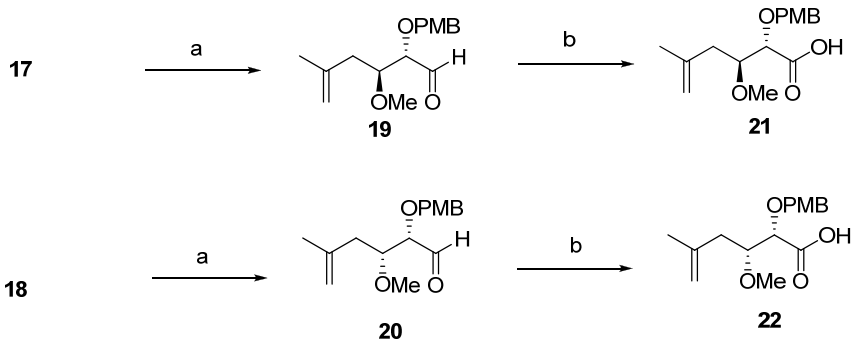


Scheme 38. Methylation and deprotection of a psymberic acid precursor

Conditions: a) MeOTf, 2,6-di-*tert*-butylpyridine, CH_2Cl_2, 0 °C to rt, 87%; b) TBAF, THF, 76%.

From this point, both *anti* and *syn* products (as well as the opposite enantiomeric series) were taken through identical syntheses (Scheme 39). Parikh-Doering oxidation of alcohols **17**

and **18** furnished aldehydes **19** and **20**, respectively. A mild Pinnick oxidation was employed to avoid epimerization at the α-position, providing *anti* and *syn* carboxylic acids **21** and **22**, in 77% and 82% yield, respectively.



Scheme 39. Completion of *anti* and *syn* protected psymberic acid substrates

Conditions: a) SO_3·pyridine complex, Et_3N, DMSO; b) $NaOCl_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH, H_2O, 77% over 2 steps (*anti* series), 82% over 2 steps (*syn* series).

2.5 DETERMINATION OF THE ABSOLUTE AND RELATIVE STEREOCHEMISTRY OF PSYMBERIC ACID: NATURAL PRODUCT DEGRADATION AND ANALYSIS

With the synthesis of all possible stereoisomers of psymberic acid complete, our next task was the determination of the absolute and relative chemistry of the side chain in the natural product. During the late 1960's and early 1970's, Matsumoto and Cardani performed extensive degradation studies of pederin.[105, 106] In their work, they developed conditions for cleavage of the acyl aminal bond (Figure 24). We hypothesized that we could cleave the acyl aminal bond of psymberin in a likewise manner.

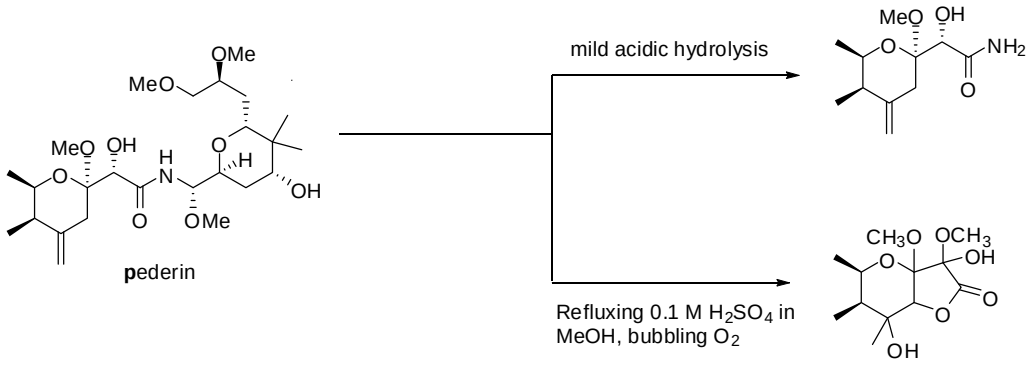
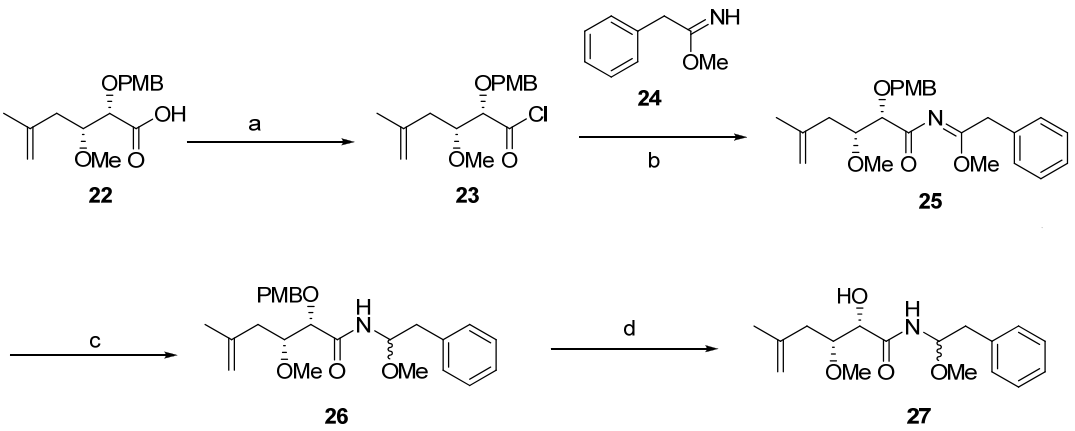


Figure 24. A summary of acyl aminal cleavage conditions and products by Matsumoto (upper) and Cardani (lower)

Due to limited amounts of the natural product at our disposal (0.5 mg were graciously donated to our lab by Prof. Phil Crews), we required an analytical method that would allow for comparison to synthetic material and analysis on a small scale. Thus, we chose to use GC and GC-MS outfitted with chiral stationary phases for analysis of our degradation products.

2.5.1 Construction of a Degradation Model System

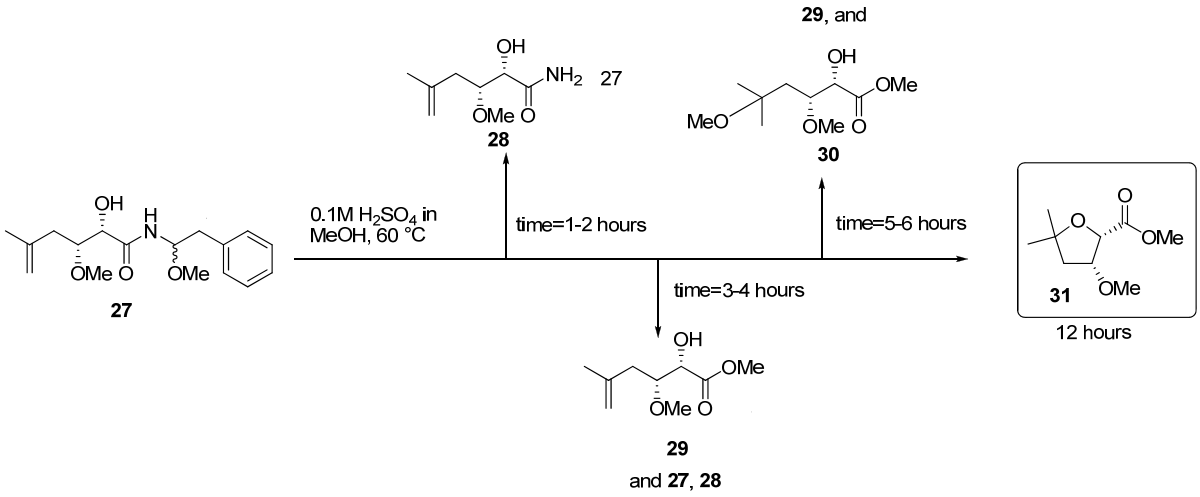
We chose to construct a model system bearing the acyl aminal functionality so that we could develop and optimize the reaction conditions required for cleavage (Scheme 40). Treating protected psymberic acid derivative **22** with Et_3N and thionyl chloride in CH_2Cl_2 generated acid chloride **23**, which was used without purification in subsequent acyl imidate formation with imidate **24**.[107] $NaBH_4$ reduction of acyl imidate **25** afforded acyl aminal **26** in 44% yield over 3 steps, and in a 2:1 ratio of inseparable diastereomers.[107] Deprotection of PMB ether **26** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) afforded our model substrate **27** in a modest 39% yield.



Scheme 40. Synthesis of a model degradation system

Conditions: a) $SOCl_2$, Et_3N, CH_2Cl_2, 0 °C to rt; b) **24**, Et_3N, CH_2Cl_2, 0 °C to rt; c) $NaBH_4$, EtOH, 0 °C, 44% over 3 steps from **22**, 2:1 d.r.; d) DDQ, pH 7 buffer, CH_2Cl_2, 39%.

Treating our model system to modified conditions developed by Cardani[108] afforded several degradation products, depending on the length of reaction. Scheme 41 (see below) provides a timeline of products that can be identified during this reaction based upon ^{1}H NMR analysis.



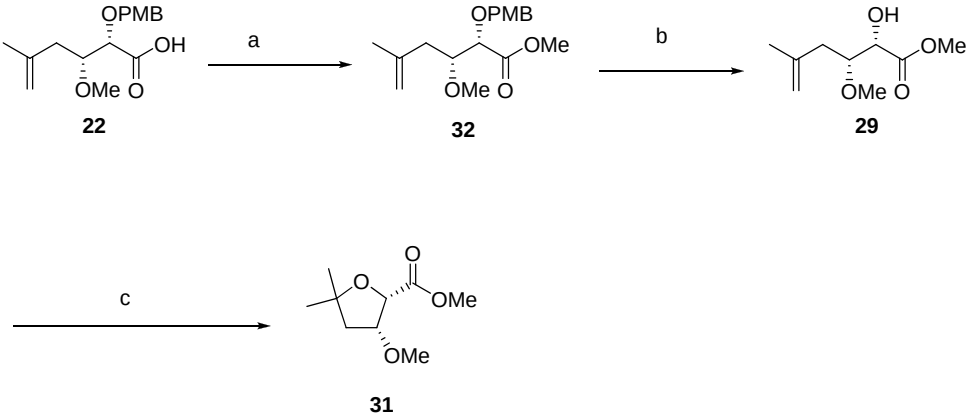
Scheme 41. Degradation products of the acyl aminal model system

After 1 to 2 hours, amide **28** could be detected (based upon ^{1}H NMR), in addition to unreacted starting material. After 3 to 4 hours **27**, **28** and methyl ester **29**, were observed in the

reaction mixture. After 5 to 6 hours, the reaction mixture was composed of methyl ester **29**, and compound **30**, the product of olefin protonation followed by reaction of the resulting carbocation with MeOH. Prolonged reaction (~12 hours) provided **31** as the sole product. No epimerization was seen for this substrate (based initially upon ^{1}H NMR, then upon subsequent research (See following text).

2.5.2 Construction of Tetrahydrofuran Stereoisomers

With knowledge of the degradation products from our model study, we set about synthesizing the final THF degradation products for all of the stereoisomers of psymberic acid (Scheme 42).



Scheme 42. Synthesis of model system degradation products

Conditions: a) $SOCl_2$, Et_3N, CH_2Cl_2, 0 °C to rt, then MeOH at 0 °C, 35%; b) CAN, CH_3CN, H_2O, 96%; c) 0.1 M H_2SO_4 in MeOH, 60 °C, 14 h, quant.

Carboxylic acid **22** was treated with $SOCl_2$ and Et_3N to form the acid chloride which was treated with methanol to afford the methyl ester **32** in 35% yield. The *p*-methoxybenzyl protecting group was subsequently removed to afford alcohol **29** in 96% yield. Treating **29** with 0.1 M H_2SO_4 in MeOH at 60 °C for 14 hours afforded **31** in quantitative yield, as one

stereoisomer and with no signs of epimerization. The *syn* stereochemistry was confirmed by 2D NOESY analysis.

This synthetic sequence was performed for all stereoisomers (with similar yields), and in each case, only one stereoisomer was observed for the final product. Furthermore, each compound was analyzed by GC using a chiral column (Chiraldex G-TA) and only one peak was noted for each substrate. Lastly, conditions were developed that allowed for separation of a mixture of all four stereoisomers (see Figure 25).

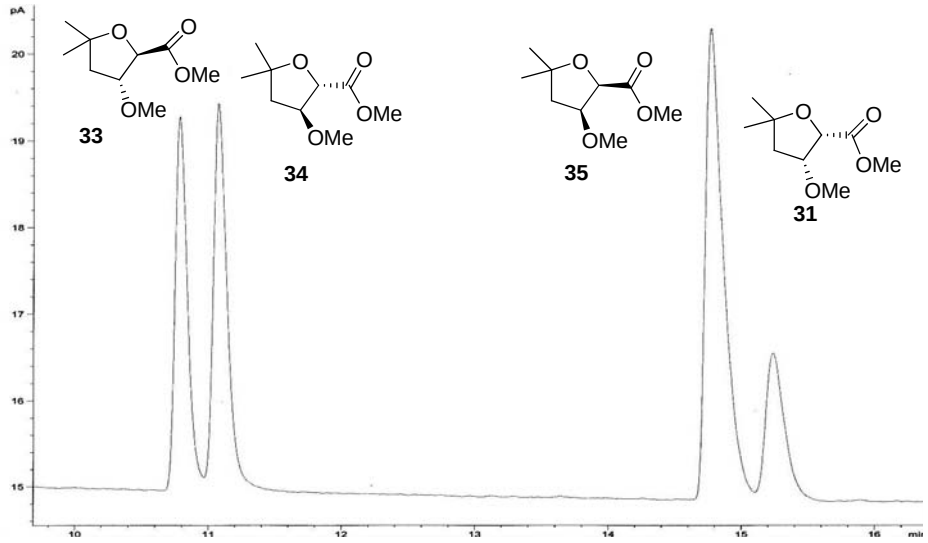


Figure 25. A Chiral GC trace of all possible stereoisomers of psymberic acid degradation products

2.5.3 Determination of the Absolute and Relative Stereochemistry of Psymberic Acid

With the synthesis of all stereoisomers completed and conditions developed to analyze each substrate, we decided to subject psymberin to our acidic methanolysis conditions to determine the absolute and relative stereochemical configuration of the psymberic acid side chain.

Treating 0.1 mg of psymberin with 0.1 M H_2SO_4 in MeOH at 60 °C for 14 hours in a sealed reaction tube provided us with degradation products that we could analyze by GC outfitted with a chiral column (Chiraldex G-TA) (see Figure 26).

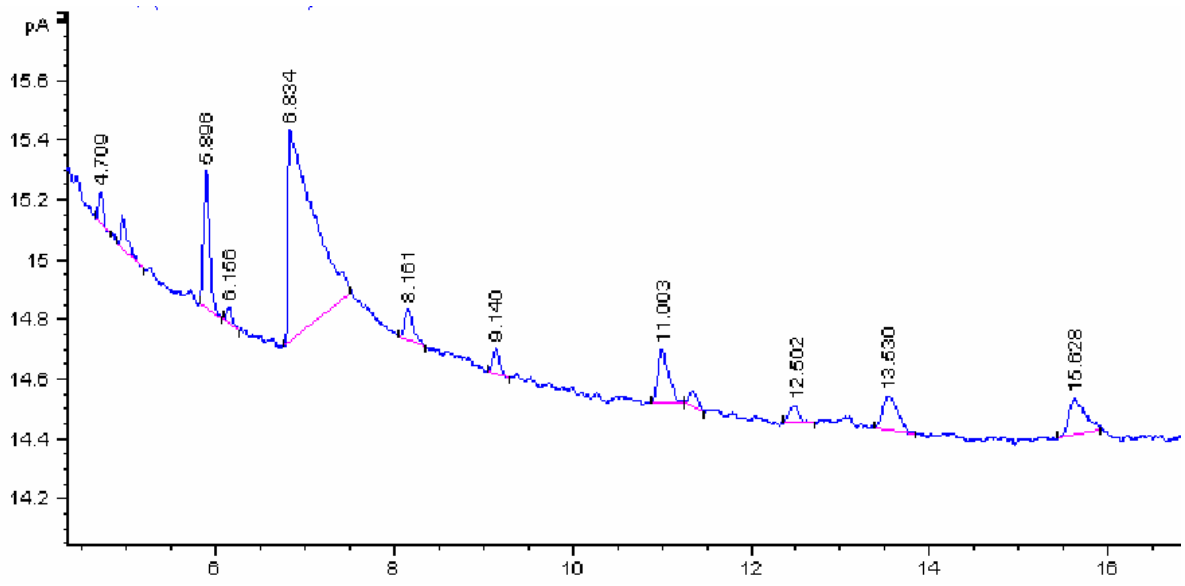


Figure 26. A chiral GC trace of psymberin degradation products

Comparison of the retention times as well as a co-injection of the psymberin degradation mixture with tetrahydrofuran **34** led to our determination that **34** was present in the degradation reaction mixture (see Figure 27).

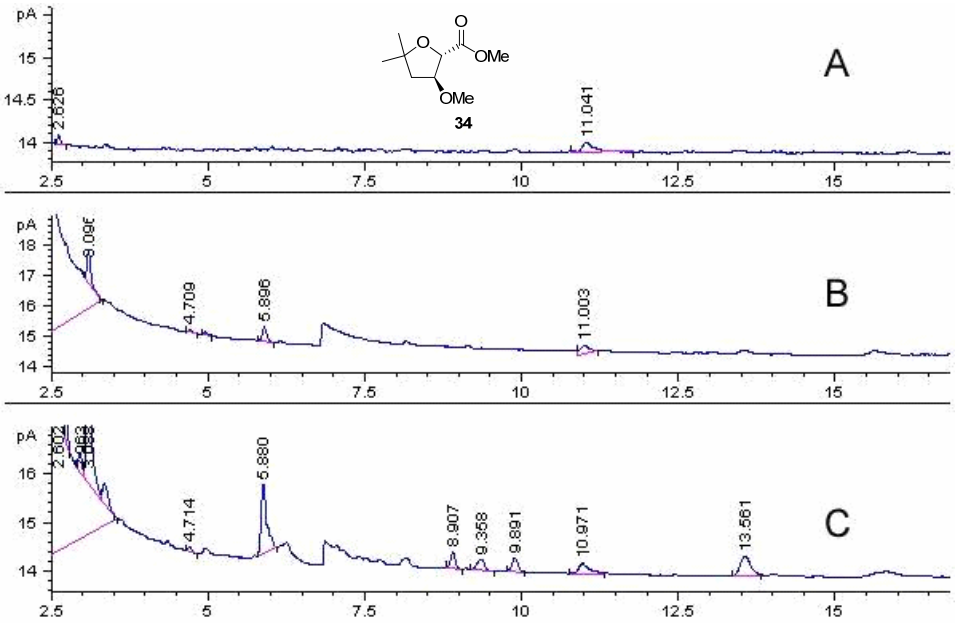


Figure 27. An overlay of degradation products. A: A diluted sample of **34**; B: The psymberin degradation reaction mixture; C: A co-injection of **34** and the psymberin degradation reaction mixture

We also chose to analyze our products by GC-MS using a chiral column. A peak with similar retention time and fragmentation pattern corresponding to **34** was seen in the psymberin degradation mixture (Figure 28). These results led us to conclude that the stereochemical configuration of psymberic acid was 4*S*, 5*S*, which was in agreement with the reports from De Brabander and Williams laboratories.[57, 100]

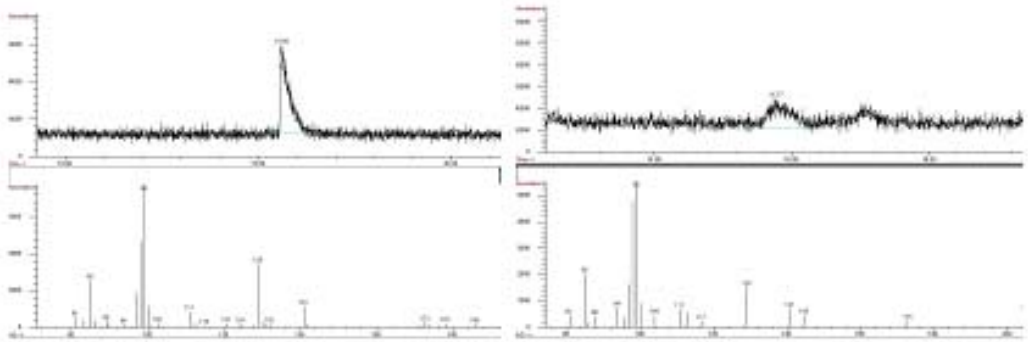


Figure 28. Chiral GC-MS traces of psymberin degradation products Left: A chiral GC-MS trace of **34**. Right: A Chiral GC-MS trace of the psymberin degradation mixture

2.6 CONCLUSION

Starting from the appropriate enantiomer of serine, we were able to construct all possible stereoisomers of the C1-C6 portion of psymberin (psymberic acid). Access to *syn* and *anti* diastereomers was accomplished through chelation controlled or Felkin-Anh methallylations, respectively. Construction of a simple acyl aminal model system and subjection to acidic methanolysis afforded tetrahydropyran degradation products. All possible tetrahydropyran stereoisomers were synthesized and were separable by chiral gas chromatography. Degradation of an authentic sample of psymberin under identical acidic methanolysis conditions afforded one tetrahydrofuran isomer. Comparison of the authentic tetrahydrofuran to synthetic material by GC and GC-MS outfitted with a chiral column (Chiraldex G-TA) enabled assignment of the absolute and relative stereochemistry of psymberin as 4*S*, 5*S*.

APPENDIX A

EXPERIMENTAL: TOTAL SYNTHESIS OF THEOPEDERIN D

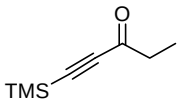
General Experimental

Proton (^{1}H NMR) and carbon (^{13}C NMR) nuclear magnetic resonance spectra were recorded on Bruker Avance 300 spectrometers (300 MHz and 75 MHz, respectively), Bruker Avance 500 spectrometers (500 MHz and 125 MHz, respectively) Bruker Avance 600 spectrometers (600 MHz and 150 MHz, respectively), and a Bruker Avance 600 spectrometer equipped with a 5mm cryoprobe (600 MHz, and 150 MHz, respectively). The chemical shifts are given in parts per million (ppm) on the delta (δ) scale. The solvent peak was used as reference value. For ^{1}H NMR: $CDCl_3$ = 7.27 ppm, C_6D_6 = 7.15. For ^{13}C NMR: $CDCl_3$ = 77.00 ppm, C_6D_6 = 128.00 ppm. For proton data: app = apparent; br = broad; s = singlet; d = doublet; t = triplet; q = quartet; p = pentet; dd = doublet of doublets; dt = doublet of triplets; ddd = doublet of doublet of doublets; dddd = doublet of doublet of doublet of doublets; ddt = doublet of doublet of triplets; ddq = doublet of doublet of quartets; qd = quartet of doublets; m = multiplet. High resolution and low resolution mass spectra were recorded on a VG 7070 spectrometer. Infrared (IR) spectra were

collected on a Mattson Cygnus 100 spectrometer. Samples for IR were prepared as a thin film on NaCl plates. Analytical high performance liquid chromatography (HPLC) was performed on a Hewlett Packard 1100 liquid chromatograph equipped with a variable wavelength UV detector (deuterium lamp, 190-600 nm) using a Daicel Chiralpak^{TM} AD column (250 x 4.6 mm) (Daicel Inc.), and HPLC-grade isopropanol and hexanes were used as the eluting solvents. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Analytical thin layer chromatography (TLC) was performed on E. Merck pre-coated (25 nm) silica gel 60F-254 plates. Visualization was done under UV (254 nm). Flash column chromatography was performed using ICN SiliTech 32-63 60Å silica gel. Preparatory thin layer chromatography (PTLC) was performed on Sorbent Technologies pre-coated (25 nm) silica gel HL UV254 plates. Reagent grade ethyl acetate, hexanes (commercial mixture), ether, dichloromethane, benzene, acetone, and toluene were purchased from EM Science and used as is for chromatography. Reagent grade methylene chloride (CH_2Cl_2) and 1,2-dichloroethane (DCE) were distilled from CaH_2 under N_2. Diethyl ether (Et_2O) was dried by passage through an aluminum drying column. THF was dried by passage through an aluminum drying column, except where noted. In these cases THF, was distilled from sodium benzophenone under N_2. Anhydrous methanol (MeOH) was purchased from Aldrich and used as is. All reactions were conducted under argon or nitrogen atmosphere, in oven or flame dried glassware with magnetic stirring except were noted. "*Careful concentration*" refers to the handling of volatile substrates by concentration under reduced pressure at low temperatures (0 °C to room temperature), or concentration by gently passing a stream of air over the volatile material.

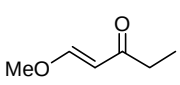
NOTE: *The compounds reported on pages 71-82 are from exploratory work towards the synthesis of the pederic acid subunit of Theopederin D. This route was abandoned after a superior strategy was discovered and thus, the compounds on pages 71-82 were not fully characterized.*

1-Trimethylsilanylpent-1-yn-3-one (106)



To a solution of bis(trimethylsilyl)acetylene (50.0 g, 293 mmol) in CH_2Cl_2 (673 mL) at 0 °C was added propionyl chloride (24.6 g, 266 mmol). After stirring for 10 minutes, $AlCl_3$ (42.6 g, 320 mmol) was added and the reaction mixture was stirred for 2 hours at 0 °C. After 2 hours, the reaction was warmed to room temperature and stirred for an additional 2 hours. After stirring for 2 hours at room temperature, the reaction mixture was poured into an ice/10% HCl (aq) solution (700 mL) and stirred for 10 minutes. The biphasic solution was extracted with CH_2Cl_2 (3 x 250 mL) and the combined organic layers were dried ($MgSO_4$) and filtered. *Careful concentration* under reduced pressure afforded the product as a brown oily residue. The material was taken on crude: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.59 (q, J = 7.5 Hz, 2 H), 1.15 (t, J = 7.3 Hz, 3 H), 0.25 (s, 9 H). *These data are consistent with reported literature values.*[109]

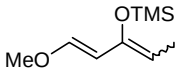
1-Methoxypent-1-en-3-one (107)



To a solution of crude **106** (41.0 g, 266 mmol) in MeOH (216 mL) was slowly added 1,4-diazabicyclo[2.2.2]octane (DABCO) (60.0 g, 533 mmol) at room temperature. After 20 minutes the reaction mixture was concentrated under reduced pressure, and the crude residue was diluted with EtOAc (200 mL), extracted with brine (2 x 100 mL), dried

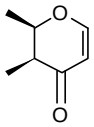
($MgSO_4$), and filtered. After concentration under reduced pressure, the crude material was distilled under vacuum to afford the desired product (2 torr, 45 °C, 21.4 g, 70% yield over 2 steps): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (d, *J* = 12.7 Hz, 1 H), 5.58 (d, *J* = 12.7 Hz, 1 H), 3.69 (s, 3 H), 2.48 (q, *J* = 7.1 Hz, 2 H), 1.09 (t, *J* = 7.2 Hz, 3 H). *These data are consistent with reported literature values.* [110]

1-(2-Methoxyvinyl)propenyloxy]trimethyl-silane (97)



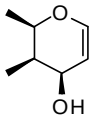
To $ZnCl_2$ (0.29 mg, 2.10 mmol) was added Et_3N (17.9 mL, 0.14 mmol) and the mixture was stirred for 1 hour at room temperature. To this mixture was added a solution of **107** (8.00 g, 7.00 mmol) in toluene (16.5 mL) at room temperature, followed by addition of TMSCl (15.2 g, 140 mmol). A condenser was fitted atop the reaction vessel, and the reaction mixture was heated at 40 °C. After 14 hours, satd. $NaHCO_3$ (aq) was added at room temperature, and the reaction mixture was extracted with Et_2O (3 x 50 mL). The organic layers were combined, washed with brine (50 mL), dried (Na_2SO_4), and filtered. The organic extracts were concentrated under reduced pressure, then distilled (40 °C at 2 torr) to afford the desired product as well as trimethylsilanol. Filtration of the distillate through an oven dried frit containing oven dried Na_2SO_4 (to remove silyl impurities) afforded the desired product as a pale yellow liquid (11.1 g, 4:1 ratio of *Z: E* isomers, 85% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.80 (d, *J* = 12.2 Hz, 0.2 H), 6.65 (d, *J* = 12.4 Hz, 0.8 H), 5.84 (d, *J* = 7.3 Hz, 0.2 Hz), 5.36 (d, *J* = 12.4 Hz, 0.8 H), 4.66-4.45 (m, 1 H), 3.62 (s, 0.6 H), 3.57 (s, 2.4 H), 1.63-1.54 (m, 3 H), 0.23-0.19 (m, 9 H). *These data are consistent with reported literature values values*.[75]

2,3-Dimethyl-2,3-dihydropyran-4-one (96)



To a mixture of **97** (0.16 g, 0.32 mmol) and crushed 3Å molecular sieves (0.40 g) was added acetaldehyde (2.64 g, 53.7 mmol) and the reaction mixture was stirred for 3 hours at room temperature. After 3 hours **108**[76] (2.00 g, 10.7 mmol) was added to the reaction at room temperature, and the reaction was stirred for 40 hours. After 40 hours, the reaction was cooled to 0 °C, CH_2Cl_2 was added (2 ml) followed by 5 drops of trifluoroacetic acid, and the reaction was warmed to room temperature. After stirring for 15 minutes the reaction mixture was filtered through silica on Celite and the filter cake was rinsed with Et_2O. The filtrate was *carefully concentrated* to afford a brown residue which was purified via flash chromatography (20% Et_2O in pentane to 25% Et_2O in pentane) to afford the desired product as a yellow oil (0.66 g, 82% yield based on reactive diene present): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (d, *J* = 5.9 Hz, 1 H), 5.34 (d, *J* = 5.9 Hz, 1 H), 4.57 (qd, *J* = 3.5, 6.6 Hz, 1 H), 2.37 (qd, *J* = 3.5, 7.4 Hz, 1 H), 1.37 (d, *J* = 6.7 Hz, 3 H), 1.09 (d, 1.09, *J* = 7.3 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.5, 162.1, 104.5, 77.5, 43.8, 15.0, 8.6; IR (neat): 2980, 2940, 2249, 1678, 1597, 1454, 1406, 1386, 1225, 1088; HRMS (EI) *m/z* calcd. for $C_7H_{10}O_2$ (M+) 126.0608, found 126.066.

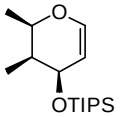
2,3-Dimethyl-3,4-dihydro-2*H*-pyran-4-ol (109)



To a solution of **96** (0.58 g, 4.6 mmol) in MeOH (9.5 mL) was added $CeCl_3 \cdot 7H_2O$ (2.14 g, 5.75 mmol) at room temperature and the reaction mixture was vigorously stirred until all the $CeCl_3 \cdot 7H_2O$ was dissolved. The reaction was cooled to –10 °C and $NaBH_4$ (0.37 g, 9.89 mmol) was added slowly. After addition, the reaction was warmed to room temperature and stirred for 30 minutes. Brine (20 mL) was added and the reaction mixture was extracted with Et_2O (5 x 10 mL). The organic layers were combined, washed with brine (20 mL), dried

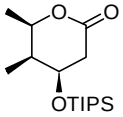
(Na_2SO_4), and filtered. The material was *carefully concentrated* under reduced pressure to afford a brown/yellow oil which was used crude without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.31 (dd, *J* = 1.53, 6.1 Hz, 1 H), 4.61 (ddd, *J* = 2.1, 2.1, 6.2 Hz, 1 H), 4.53-4.52 (m, 1 H), 4.13 (qd, *J* = 2.0, 6.6 Hz, 1 H), 1.99-1.95 (m, 1 H), 1.28 (d, *J* = 6.7 Hz, 3 H), 0.96 (d, *J* = 7 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.1, 103.2, 73.8, 65.8, 36.3, 17.2, 5.1; IR (neat): 3418, 2980, 2882, 2251, 1643, 1383, 1230, 1086.

(2,3-Dimethyl-3,4-dihydro-2H-pyran-4-yloxy)triisopropylsilane (110)



To a stirring solution of **109** (1.13 g, 8.83 mmol) in CH_2Cl_2 (4.00 mL) and cooled to –10 °C was added 2,6-lutidine (1.14 g, 10.6 mmol) followed by triisopropylsilyl-trifluoromethanesulfonate (3.25 g, 10.6 mmol). After 3 hours of stirring at –10 °C, satd. $NaHCO_3$ (aq) was added (2 mL) and the reaction mixture was extracted with CH_2Cl_2 (3 x 3 mL). The combined organic extracts were dried (Na_2SO_4), and filtered. Concentration under reduced pressure, followed by purification via flash column chromatography (5% Et_2O in pentane) afforded the desired compound as a clear oil (1.36 g, 54% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.24 (dd, *J* = 1.6, 6.2 Hz, 1 H), 4.64 (ddd, *J* = 1.8, 1.8, 6.1 Hz, 1 H), 4.57 (ddd, *J* = 1.7, 1.8, 6.3 Hz, 1 H) 4.09 (qd, *J* = 1.9, 6.7 Hz, 1 H), 1.90-1.86 (m, 1 H) 1.26 (d, *J* = 6.6 Hz, 3 H), 1.08 (s, 21 H) 0.97 (d, *J* = 6.9 Hz, 3 H).

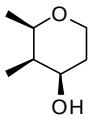
5,6-Dimethyl-4-triisopropylsilanyloxytetrahydropyran-2-one (111)



To a stirring solution of **110** (1.36 g, 4.79 mmol) in 1,2-dichloroethane (53.0 mL) at room temperature was added pyridinium chlorochromate (2.07 g, 9.58 mmol). After 4 hours, the reaction mixture was filtered through a frit of Celite then concentrated under reduced

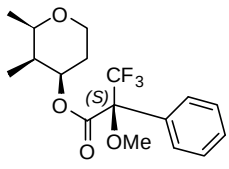
pressure to afford a crude yellow residue. Purification via flash column chromatography (20% EtOAc in hexanes) afforded the desired product as a pale yellow to colorless waxy solid (1.03 g, 71% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.40 (qd, *J* = 2.1, 6.5 Hz, 1 H), 4.24 (ddd, *J* = 4.5, 6.9, 10.2 Hz, 1 H), 2.81 (ddd, *J* = 0.8, 6.9, 18.4 Hz, 1 H), 2.49 (dd, *J* = 10.2, 18.4 Hz, 1 H) 2.05 (m, 1 H), 1.37 (d, *J* = 6.6 Hz, 3 H), 1.06 (s, 21 H), 0.97 (d, *J* = 7.0 Hz, 3 H).

2,3-Dimethyltetrahydropyran-4-ol (159)



To a stirring solution of **109** (336 mg, 2.63 mmol) in MeOH (5.50 mL) was added Pd/C (40.0 mg). A balloon filled with hydrogen gas was attached to a three-way adapter, and the reaction vessel was pumped and purged three times under water aspirator pressure to remove the oxygen atmosphere. After stirring overnight, the reaction mixture was filtered through a frit of Celite, and the filtrate was carefully concentrated. Purification via flash column chromatography (40% Et_2O in pentane to 100% Et_2O) afforded the desired product as a slightly yellow liquid (100 mg, 29% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.95 (ddd, *J* = 1.3, 5.0, 11.6 Hz, 1H), 3.90-3.83 (m, 1 H), 3.51-3.37 (m, 2 H), 1.83-1.63 (m, 3 H), 1.16 (d, *J* = 6.5 Hz, 3 H), 0.90 (d, *J* = 7.0 Hz, 3 H).

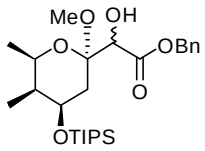
3,3,3-Trifluoro-2-methoxy-2-phenylpropionic acid 2,3-dimethyltetrahydropyran-4-yl ester (112)



To a solution of **159** (25.0 mg, 0.19 mmol) in CH_2Cl_2 was added pyridine (0.30 mL) followed by (*S*)-(+)-alpha-Methoxy-alpha-trifluoromethylphenylacetyl chloride (0.13 μL, 0.67 mmol). After 90

minutes, all starting material was consumed. The reaction mixture was cooled to 0 °C, and H_2O was added (0.10 mL). The reaction mixture was extracted with CH_2Cl_2 (3 x 0.30 mL), and the combined organic layers were dried (Na_2SO_4) and filtered. Concentration under reduced pressure afforded a crude yellow oil which was used without purification for analysis. The diastereomers were sufficiently separated in the ^1H NMR spectrum such that integration could be easily performed. *Peaks used for analysis*: ^1H NMR (300 MHz, $CDCl_3$) δ 0.93 (d, J = 6.9 Hz, 0.98 H), 0.81 (d, J = 6.9 Hz, 0.28 H).

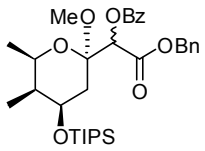
Hydroxy-(2-methoxy-5,6-dimethyl-4-triisopropylsilanyloxytetrahydropyran-2-yl)-acetic acid benzyl ester (115)



To a solution of diisopropylamine (2.63 mL, 18.7 mmol) in THF (37.0 mL) cooled to –78 °C was added *n*-BuLi (11.4 mL, 1.6 M in hexane). After 5 minutes, **113** (4.47 g, 18.8 mmol) was slowly added to the reaction mixture, and the solution was stirred at –78 °C for 1 hour. HMPA (4.74 mL, 27.3 mmol) was subsequently added, and after stirring at –78 °C for 15 minutes, $ZnCl_2$ (18.8 mL, 1 M in Et_2O) was added to the reaction at this same temperature. After 75 minutes, a solution of **111** (0.5 g, 1.66 mmol) in THF (9.50 mL) was slowly added to the reaction mixture. The reaction was allowed to slowly warm to –40 °C. After 18 hours, satd. NH_4Cl (aq) (15 mL) was added to the reaction at –40 °C, and the reaction mixture was extracted with Et_2O (3 x 20 mL). The organic layers were combined and washed with satd. NH_4Cl (aq) (20 mL), satd. $NaHCO_3$ (aq) (20 mL), brine (20 mL), dried ($MgSO_4$), and filtered. The organic material was concentrated under reduced pressure to afford a purple oily residue. To this crude residue at room temperature was added CH_2Cl_2 (6.0 mL) and MeOH (6.0) mL, followed by $CH(OMe)_3$ (1.74 mL, 15.9 mmol),

and 10-camphorsulphonic acid monohydrate (0.12 g, 0.5 mmol). After 10 minutes, the reaction mixture was poured into water (10 mL) and extracted with Et_2O (2 x 10 mL). The organic layers were combined and washed with satd. $NaHCO_3$ (aq) (10 mL) and brine (10 mL), then dried ($MgSO_4$) and filtered. After concentration under reduced pressure, the crude residue was purified via flash column chromatography (10% EtOAc in hexanes) to afford the desired product in a 19:81 mixture of diastereomers (0.22 g, 28% yield over 2 steps). ***Major Diastereomer***: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.35 (m, 5 H), 5.25 (s, 2 H), 4.35 (d, *J* = 6.1 Hz, 1 H), 4.18 (ddd, *J* = 4.9, 4.9, 11.2 Hz, 1 H), 3.80 (qd, *J* = 2.1, 6.6 Hz, 1 H), 3.26 (s, 3 H), 2.88 (d, *J* = 6.1 Hz, 1 H), 1.86 (ddd, *J* = 0.8, 5.0, 13.1 Hz, 1 H), 1.74-1.69 (m, 1 H), 1.46 (dd, *J* = 11.2, 13.1 Hz, 1 H), 1.12 (d, *J* = 6.6 Hz, 3 H), 1.04 (s, 21 H) 0.66 (d, *J* = 6.9 Hz, 3 H).

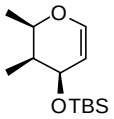
Benzoic acid benzyloxycarbonyl-(2-methoxy-5,6-dimethyl-4-triisopropylsilanyloxytetrahydropyran-2-yl)methyl ester (116)



To a 19:81 diastereomeric mixture of **115** (0.04 g, 0.08 mmol) in pyridine (2.00 mL) and cooled to 0 °C was added benzoyl chloride (0.06 mL, 0.56 mmol) followed by DMAP (0.01 g, 0.08 mmol). The reaction was allowed to warm to room temperature and was stirred overnight. Afterwards, the reaction mixture was cooled to 0 °C and 10% w/v aqueous tartaric acid (1 mL) was added. The reaction mixture was extracted with Et_2O (3 x 2 mL). The organic layers were combined and washed with 10% w/v aqueous tartaric acid (2 mL), satd. $NaHCO_3$ (aq) (2 mL) and brine (2 mL), then dried ($MgSO_4$) and filtered. Concentration under reduced pressure afforded a yellow residue, which after purification via flash chromatography (10% EtOAc in hexanes), afforded the desired product as a colorless oil and as a single diastereomer (0.03 g, 52% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10-8.07 (m, 2

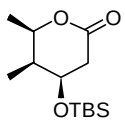
H), 7.60-7.57 (m, 2 H), 7.48-7.33 (m, 6 H), 5.47 (s, 1 H), 5.30 (d, *J* = 12.3 Hz, 1 H), 5.18 (d, *J* = 12.3 Hz, 1 H), 4.2 (app. p. *J* = 4.6 Hz, 1 H), 3.8 (qd, *J* = 3.1, 6.2 Hz, 1 H), 3.27 (s, 3 H), 2.10-1.95 (m, 2 H), 1.75 (m, 1 H), 1.08 (s, 24 H), 0.68 (d, *J* = 6.9 Hz, 3 H).

tert-Butyl-(2,3-dimethyl-3,4-dihydro-2*H*-pyran-4-yloxy)-dimethyl-silane (118)



To a solution of **109** (1.00 g, 7.80 mmol) in DMF (10 mL) cooled to 0 °C was added imidazole (1.06 g, 15.6 mmol) followed by addition of *tert*-butyldimethylsilyl chloride (2.35 g, 15.6 mmol). The reaction was warmed to room temperature and stirred for one hour, then the solution was cooled to 0 °C and satd. $NaHCO_3$ (aq) (5 mL) was added. The reaction mixture was extracted with pentane (3 x 10 mL). The organic layers were combined and washed with H_2O (10 mL). The combined organic layers were dried (Na_2SO_4) and filtered, concentrated under reduced pressure, and purified by flash column chromatography (5% Et_2O in pentane) to afford the desired product as a brown oil (1.31 g, 72% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.25 (dd, *J* = 1.4, 6.2 Hz, 1 H), 4.53 (ddd, *J* = 1.4, 2.2, 6.6 Hz, 1 H), 4.48 (ddd, *J* = 1.7, 1.8, 5.2 Hz, 1 H), 4.1 (qd, *J* = 2.2, 6.7 Hz, 1 H), 1.88-1.83 (m, 1 H), 1.26 (d, *J* = 6.6 Hz, 3 H), 0.94 (d, *J* = 7.0 Hz, 3 H), 0.91 (s, 9 H), 0.08 (s, 6 H).

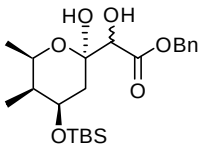
4-(*tert*-Butyldimethylsilanyloxy)-5,6-dimethyltetrahydropyran-2-one (119)



To a solution of **118** (1.05 g, 4.36 mmol) in 1,2-dichloroethane (60 mL) was added pyridinium chlorochromate (2.34 g, 10.9 mmol) at room temperature. After 5 hours the reaction mixture was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure. The crude residue was purified via flash chromatography (20% EtOAc in hexanes) to afford the desired product as a white solid (0.80 g, 71% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.43 (qd, *J* = 2.6, 6.6 Hz, 1 H), 4.13 (ddd, *J* = 4.4, 6.7, 9.6 Hz, 1 H), 2.72 (ddd, *J* = 0.7,

6.8, 18.3 Hz, 1 H), 2.46 (dd, *J* = 9.6, 18.3 Hz, 1 H) 2.05-1.96 (m, 1 H), 1.37 (d, *J* = 6.6 Hz, 3 H), 0.95 (d, *J* = 7.1 Hz, 3 H), 0.90 (s, 9 H) 0.07 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 76.6, 67.7, 38.2, 36.0, 25.6, 18.0, 17.9, 4.5, −4.6, −4.9; IR (neat): 2930, 2254, 1726, 1471, 1384, 1242, 1114, 911, 734; HRMS (EI) *m/z* calcd. for $C_{13}H_{26}O_3Si$ [M+] 258.1651, found 258.1664.

4-(*tert*-Butyldimethylsilanyloxy)-2-hydroxy-5,6-dimethyltetrahydropyran-2-yl]-hydroxy-acetic acid benzyl ester (121)

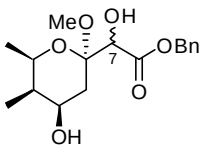


To a solution of LHMDS (18.0 mL, 1 M in THF) in THF (35.0 mL) cooled to -78 °C was added a solution of **113** (4.42 g, 18.6 mmol) in THF (9.00 mL). After 10 minutes HMPA (4.69 mL 27.0 mmol) was added to the reaction mixture. After 15 minutes $ZnCl_2$ (18.0 mL, 1M in Et_2O) was added and the reaction was stirred for an additional 75 minutes at –78 °C. Afterwards, **119** (0.42 mg, 1.64 mmol) in THF (8.50 mL) was slowly added to the reaction mixture at –78 °C and the reaction mixture was allowed to slowly warm to –40 °C overnight. The next day, satd. NH_4Cl (aq) (15 mL) was added to the reaction at –40 °C, and the reaction mixture was extracted with Et_2O (3 x 20 mL). The organic layers were combined and washed with satd. NH_4Cl (aq) (20 mL), satd. $NaHCO_3$ (aq) (20 mL), brine (20 mL), dried ($MgSO_4$), and filtered. The organic material was concentrated under reduced pressure, and this residue was used without further purification.

To this crude residue at room temperature was added CH_2Cl_2 (8.00 mL) and MeOH (8.00 mL), followed by $CH(OMe)_3$ (1.72 mL, 15.8 mmol), and 10-camphorsulphonic acid monohydrate (0.11 g, 0.49 mmol). After 20 minutes, the reaction mixture was poured into water (15 mL) and extracted with Et_2O (3 x 10 mL). The organic layers were combined and washed

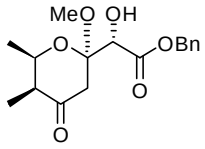
with satd. $NaHCO_3$ (aq) (10 mL), brine (10 mL), then dried ($MgSO_4$) and filtered. The acidic methanol sequence was repeated again with a reaction length of 5 minutes, with an identical workup procedure. Removal of excess reagents and byproducts afforded a crude residue containing the product, as well as a small amount of starting material. This material was used without further purification in subsequent chemistry.

Hydroxy-(4-hydroxy-2-methoxy-5,6-dimethyltetrahydropyran-2-yl)-acetic acid benzyl ester



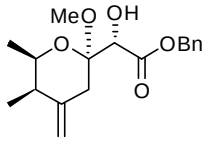
To crude residue **121 (**231 mg, 0.544 mmol) at room temperature was added CH_2Cl_2 (3.00 mL) and MeOH (3.00 mL), followed by $CH(OMe)_3$ (0.57 mL, 5.2 mmol), and 10-camphorsulphonic acid monohydrate (0.04 g, 0.16 mmol). After 2 hours, the reaction mixture was poured into water (15 mL) and extracted with Et_2O (3 x 10 mL). The organic layers were combined, washed with satd. $NaHCO_3$ (aq) (10 mL) and brine (10 mL), then dried ($MgSO_4$), and filtered. Concentration under reduced pressure afforded a crude residue which was purified by flash column chromatography (70% EtOAc in hexanes) to afford the desired product as a separable mixture of diastereomers (56 mg, 32%). ***7R**** **stereoisomer (Faster eluting) 123:** ^{1}H NMR (300 MHz, C_6D_6) δ 7.18-7.02 (m, 5 H), 5.06 (d, *J* = 12.4 Hz, 1 H), 4.90 (d, *J* = 12.4 Hz, 1 H), 4.36 (d, *J* = 6.1 Hz, 1 H), 3.96 (app. p, *J* = 4.3, 11.7 Hz, 1 H), 3.54 (qd, *J* = 4.4, 6.4 Hz, 1 H), 3.12 (s, 3 H), 2.79 (d, *J* = 6.2 Hz, 1 H), 1.94 (app. t, *J* = 12.8 Hz, 1 H), 1.69-1.63 (m, 1 H), 1.48-1.44 (m, 1 H), 0.96 (d, *J* = 6.6 Hz, 3 H), 0.83 (d, *J* = 6.9 Hz, 3 H); **7*S** stereoisomer (slower eluting) 122:** ^{1}H NMR (300 MHz, C_6D_6) δ 7.23-7.06 (m, 5 H), 5.08 (d, *J* = 12.3 Hz, 1 H), 4.92 (d, *J* = 12.3 Hz, 1 H), 4.40 (d, *J* = 6.8 Hz, 1 H), 4.11-4.07 (m, 1 H), 3.58 (qd, *J* = 1.7, 6.5 Hz, 1 H), 3.24 (d, *J* = 7.4 Hz, 1 H), 3.06 (s, 3 H), 2.05 (dd, *J* = 5.0, 12.9 Hz, 1 H), 1.72 (app. t, *J* = 12.3 Hz, 1 H), 0.91 (d, *J* = 6.5 Hz, 3 H), 0.70 (d, *J* = 6.9 Hz, 3 H).

Hydroxy-(2-methoxy-5,6-dimethyl-4-oxo-tetrahydropyran-2-yl)-acetic acid benzyl ester (124)



To a solution of **122** (0.016 g, 0.050 mmol) and 4Å molecular sieves (0.02 g) in CH_2Cl_2 (540 µL) was added pyridinium chlorochromate (PCC) (0.011 g, 0.05 mmol) at room temperature. After 2 hours, the reaction mixture was poured onto Celite and filtered. The filtrate was concentrated under reduced pressure and purified via flash column chromatography (50% EtOAc in hexanes) to afford the desired product as a colorless oil (0.009 g, 55% yield): ^{1}H NMR (300 MHz, C_6D_6) δ 7.07-7.01 (m, 5 H), 5.05 (d, *J* = 12.2 Hz, 1 H), 4.83 (d, *J* = 12.2 Hz, 1 H), 4.29 (d, *J* = 6.7 Hz, 1 H), 3.80 (qd, *J* = 2.9, 6.6 Hz, 1 H), 2.94 (s, 3 H), 2.79 (d, *J* = 15 Hz, 1 H), 2.63-2.59 (m, 2 H), 2.01 (qd, *J* = 3.1, 7.1 Hz, 1 H), 0.74 (d, *J* = 6.5 Hz, 3 H), 0.63 (d, *J* = 7.2 Hz, 3 H).

Hydroxy-(2-methoxy-5,6-dimethyl-4-methylenetetrahydropyran-2-yl)-acetic acid benzyl ester (125)



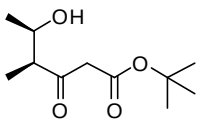
To a solution of **124** (0.02 g, 0.06 mmol) in THF (1.50 mL) was added CH_2I_2-Zn-$TiCl_4$ (1 mL, stock solution as prepared by Nakata[34]) at room temperature. After, 50 minutes, another 0.5 mL of CH_2I_2-Zn-$TiCl_4$ was added. After an additional hour, the reaction mixture was poured into satd. $NaHCO_3$ (aq.) (2 ml), and extracted with EtOAc (3 x 2 mL). The organic layers were combined, washed with satd. $NaHCO_3$ (aq) (2 mL) and brine (2 mL), then dried (Na_2SO_4) and filtered. Concentration under reduced pressure followed by purification via flash column chromatography (30% EtOAc in hexanes) afforded the desired product (5.00 mg, 25.2%): ^{1}H NMR (300 MHz, C_6D_6) δ 7.21-7.48 (m, 5 H), 5.10 (d, *J* =

12.3 Hz, 1 H), 4.90 (d, *J* = 12.2 Hz, 1 H), 4.77 (app. t, *J* = 2.0, 2.1 Hz, 1 H), 4.72 (app. t, *J* = 2.0, 2.1 Hz, 1 H), 4.37 (d, *J* = 5.8 Hz, 1 H), 3.80 (qd, *J* = 2.5, 6.5 Hz, 1 H), 3.06 (s, 3H), 2.52 (d, *J* = 5.7 Hz, 1 H), 2.57 (d, *J* = 14.2 Hz, 1 H), 2.39 (d, *J* = 14.2 Hz, 1 H), 1.9 (qd, *J* = 2.3, 6.9 Hz, 1 H), 0.89 (d, *J* = 6.6 Hz, 3 H), 0.75 (d, *J* = 7 Hz, 3 H).

(3*S* ,4*R*)-3,4-Dimethyloxetan-2-one (130)

To a solution of $LiClO_4$ (1.61 g, 15.1 mmol) in Et_2O (50.0 mL) was added TMS-quinidine[111] (2.00 g, 5.0 mmol) in CH_2Cl_2 (100.0 mL). The reaction was cooled to –78 °C whereupon DIPEA (21.9 mL, 125.8 mmol) and acetaldehyde (3.8 mL, 67.3 mmol) were added. To this reaction mixture was added propionyl chloride (8.8 mL, 100.6 mmol) as a solution in CH_2Cl_2 (25.0 mL), slowly dropwise over 3 hours. After addition, the reaction was stirred at –78 °C overnight. The following morning Et_2O (40.0 mL) was added to the reaction at –78 °C. The reaction mixture was warmed to room temperature then filtered through a short pad of Celite. The filtrate was concentrated to 1/3 its total volume under reduced pressure at 0 °C, and was used crude without further purification. ***Alternatively***, the filtrate can be concentrated under reduced pressure at 0 °C and purified via flash column chromatography (100% pentane to 10% Et_2O in pentane to 20% Et_2O in pentane) to afford the desired product as a low boiling colorless liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.77 (m, 1 H), 3.75 (m, 1 H), 1.46 (d, J = 6.3 Hz, 3 H), 1.28 (d, J = 7.8 Hz, 3 H). *These data are consistent with reported literature values.*[112]

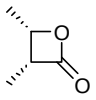
(4*S*, 5*R*)-*tert*-Butyl 5-hydroxy-4-methyl-3-oxohexanoate (129)



To a freshly prepared solution of LDA (150.0 mL, 1 M in THF) cooled to –78 °C was added *t*-butyl acetate slowly dropwise. The reaction mixture was stirred for 10 minutes, before crude **130** in Et_2O/CH_2Cl_2 was slowly added dropwise at –78 °C. After 30 minutes, satd. NH_4Cl (aq) (150 mL) was added, and the reaction was warmed to room temperature. The reaction mixture was extracted with EtOAc (3 x 50 mL), and the combined

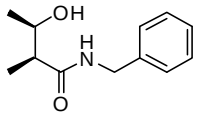
organic layers were washed with brine (50 mL). The organic extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure to afford a crude yellow oil. The crude residue was purified via flash column chromatography (30% EtOAc in hexanes to 70% EtOAc in hexanes to 100% EtOAc to 5% MeOH in EtOAc) to afford the desired product as an 8:1 inseparable mixture with its tautomer (5.15 g, 76%). *Underlined values correspond to assignable tautomer peaks*: ^{1}H (300 MHz, $CDCl_3$) δ 12.4 (br s, 1 H) 4.94 (s, 1 H), 4.21-4.13 (m, 1 H), 3.50 (d, J = 15.3 Hz, 1 H), 3.43 (d, J = 15.6 Hz, 1 H) 2.72 (qd, J = 3.3, 7.2 Hz, 1 H), 2.53 (br s, 1 H), 1.49 (s, 9 H), 1.47 (s, 9 H), 1.18 (d, J = 6.6 Hz, 3 H), 1.17 (d, J = 7.2 Hz, 3 H). *These data are consistent with reported literature values.*[34]

(3*R*, 4*S*)-3,4-Dimethyloxetan-2-one (*ent*-130)



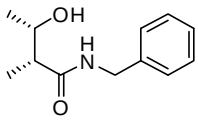
To a solution of $LiClO_4$ (0.64 g, 6.0 mmol) in Et_2O (30.0 mL) was added TMS-quinine[111] (1.19 g, 3.0 mmol) in CH_2Cl_2 (60.0 mL). The reaction was cooled to –78 °C whereupon DIPEA (13.1 mL, 75.0 mmol) and acetaldehyde (4.0 mL, 71.0 mmol) were added. To this reaction mixture was added propionyl chloride (5.2 mL, 60.0 mmol) as a solution in CH_2Cl_2 (15.0 mL) slowly dropwise over 2 hours. After addition, the reaction was stirred at –78 °C overnight. The following morning Et_2O (30.0 mL) was added to the reaction at –78 °C. The reaction mixture was warmed to room temperature then filtered through a short pad of Celite. The filtrate was concentrated under reduced pressure at 0 °C and purified via flash column chromatography (pentane to 10% Et_2O in pentane to 20% Et_2O in pentane) to afford the desired product as a low boiling colorless liquid (0.51 g, 9%).

(2*S*, 3*R*)-*N*-Benzyl-3-hydroxy-2-methylbutanamide (160)



To a solution of **130** (0.15 g, 1.50 mmol) in CH_3CN (5.0 mL) at room temperature was added catalytic DMAP followed by benzylamine (0.16 g, 1.50 mmol). After 4 hours, the reaction was cooled to 0 °C and 3% Et_3N in Et_2O (2 mL) was added to the reaction mixture, followed by addition of H_2O (2 mL). The reaction mixture was extracted with Et_2O (3 x 5 mL), and the organic layers were combined. The combined organic extracts were washed with brine (5 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude residue was purified via flash column chromatography (30 to 60% EtOAc in hexanes) to afford the desired product as a white solid: ^{1}H (300 MHz, $CDCl_3$) δ 7.37-7.25 (m, 5 H), 6.50 (br s, 1 H), 4.43 (s, 1 H), 4.41 (s, 1 H), 4.06 (qd, *J* = 4.1, 6.4 Hz, 1 H), 3.45 (br s, 1 H), 2.32 (qd, *J* = 3.0, 7.1 Hz, 1 H), 1.17 (d, *J* = 7.2 Hz, 3 H), 1.14 (d, *J* = 6.5 Hz, 3 H).

(2*R*, 3*S*)-*N*-Benzyl-3-hydroxy-2-methylbutanamide (*ent*-160)

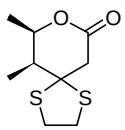


*See procedure for enantiomer (**104**)*. HPLC was performed on a Hewlett Packard 1100 liquid chromatograph equipped with a variable wavelength UV detector (deuterium lamp, 190-600 nm) using a Daicel Chiracel™ OD-H column (250 x 4.6 mm) (Daicel Inc.) and HPLC-grade 8% isopropanol in hexanes as the eluting solvent.

*Undesired derivative **ent-160** retention time*: 10.05 minutes.

*Desired isomer **160** retention time: 11.12* minutes.

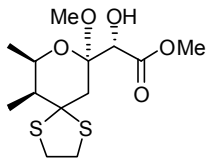
(9*R*, 10*S*)-9,10-Dimethyl-8-oxa-1,4-dithiaspiro[4.5]decan-7-one (127)



To a solution of **129** (2.50 g, 11.6 mmol) in CH_2Cl_2 (69.0 mL) at –40 °C was added 1,2-ethanedithiol (3.00 mL, 34.7 mmol) followed by $BF_3{\cdot}Et_2O$ (7.30 mL, 57.8 mmol) and the reaction was warmed to room temperature. After 48 hours, the reaction mixture was

carefully poured into a 0 °C solution of satd. $NaHCO_3$ (aq) (100 mL). The reaction mixture was extracted with CH_2Cl_2 (3 x 50 mL), and the combined organic layers were washed with satd. $NaHCO_3$ (aq) (20 mL), brine (20 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure to afford a crude orange residue. The material was purified via flash column chromatography (100% hexanes to 20% EtOAc in hexanes) to afford the desired product and its C2 diastereomer (~10:1) as a yellow solid. The solid was recrystallized from 30% EtOAc in hexanes to afford the desired product (1.60 g, 64%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.89 (qd, *J* = 2.7, 6.3, 1 H), 3.45-3.29 (m, 4 H), 3.14 (d, *J* = 19.2 Hz, 1 H), 3.06 (d, 19.2 Hz, 1 H), 2.17 (qd, *J* = 2.7, 6.9, 1 H), 1.38 (d, *J* = 6.3 Hz, 3 H), 1.20 (d, *J* = 6.9 Hz, 3 H), $[\alpha]^{27}_D$ +99.8 (*c* 1.10, $CHCl_3$), lit. $[\alpha]^{27}_D$ +106.7 (*c* 1.10, $CHCl_3$). *These data are consistent with reported literature values.*[34]

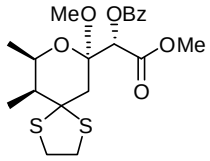
(*S*)-Methyl 2-hydroxy-2-((7*R*, 9*R*, 10*S*)-7-methoxy-9,10-dimethyl-8-oxa-1,4-dithiaspiro[4.5]decan-7-yl)acetate (132)



To a flame dried flask under Ar (g) atmosphere was added diisopropylamine (2.9 mL, 20.7 mmol) and freshly distilled THF (42.0 mL). The flask was evacuated and purged with Ar (g) three times, then cooled to –78 °C, whereupon *n*-BuLi (1.6 M in hexanes, 12.5 mL) was added slowly dropwise. The reaction was warmed to 0 °C for 15 minutes, then cooled to –78 °C. To the reaction mixture was added a solution of **128** (3.36 g, 20.7 mmol) in freshly distilled THF (21.0 mL) (*separately prepared and evacuated/ backfilled with Ar (g)*) slowly dropwise over 10 minutes. The reaction mixture was stirred for 1 hour, then freshly distilled HMPA (5.2 mL, 30.1 mmol, *evacuated and backfilled with Ar (g)*) was added slowly dropwise over 8 minutes. The reaction mixture was stirred for an additional 15 minutes before $ZnCl_2$ (20.7 mL, 1 M in Et_2O) was added slowly dropwise over 15

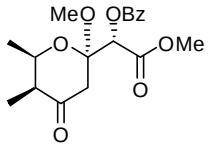
minutes. The reaction mixture was allowed to stir at –78 °C for 2 hours. After 2 hours, **127** (0.40 g, 1.8 mmol) in freshly distilled THF (10.8 mL) (*evacuated and backfilled with Ar (g)*) was added to the reaction mixture slowly dropwise over 4 minutes. The reaction was stirred at –78 °C for 2 hours then warmed to –40 °C. After 12 hours at –40 °C, satd. NH_4Cl (aq) (30 mL) was added, and the reaction mixture was extracted with EtOAc (3 x 20 mL). The organic layers were combined and washed with satd. NH_4Cl (aq) (20 mL), satd. $NaHCO_3$ (aq) (20 mL), and brine (20 mL), then dried (Na_2SO_4), filtered, and concentrated under reduced pressure to afford a crude yellow oil. The crude material was diluted with CH_2Cl_2 (26 mL), MeOH (26 mL). To this reaction mixture was added trimethylorthoformate (10 mL) and camphorsulfonic acid (0.55 g, 2.4 mmol). The solution was stirred at room temperature for 3 hours then poured into a separatory funnel containing ice water (20 mL). The reaction mixture was extracted with Et_2O (3 x 30 mL). The combined organic layers were washed with satd. $NaHCO_3$ (aq) (20 mL), brine (20 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude residue was purified via flash column chromatography (30% EtOAc in hexanes) to afford the desired product as a yellow oil (0.35 g, 60% isolated, 70% brsm) and recovered **127** (0.06 g, 10%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.38 (qd, *J* = 1.8, 6.6 Hz, 1 H), 4.29 (d, *J* = 5.7 Hz, 1 H), 3.82 (s, 3 H), 3.37-3.1 (m, 4 H), 3.33 (s, 3 H), 2.81 (d, *J* = 5.7 Hz, 1 H), 2.33 (d, *J* = 14.7, 1 H), 2.26 (d, *J* = 14.7 Hz, 1 H), 1.69 (br q, *J* = 6 Hz, 1 H), 1.20 (d, *J* = 6.3 Hz, 3 H), 1.00 (d, *J* = 6.9 Hz, 3 H); $[\alpha]^{23}_D$ +63.0 (*c* 0.60, $CHCl_3$), lit. $[\alpha]^{28}_D$ +102.8 (*c* 1.04, $CHCl_3$). *This compound is consistent with literature values.*[34]

(*S*)-2-Methoxy-1-((7*R*,9*R*, 10*S*)-7-methoxy-9,10-dimethyl-8-oxa-1,4-dithiaspiro[4.5]decan-7-yl)-2-oxoethyl benzoate (133)



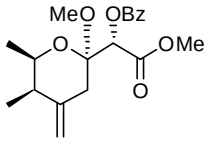
To a solution of **132** (0.13 g, 0.42 mmol) in pyridine (4.50 mL) cooled to 0 °C was added benzoyl chloride (0.35 mL, 3.00 mmol) followed by a few crystals of DMAP (cat). The solution was stirred at 0 °C for 10 minutes then allowed to warm to room temperature. After 17 hours, the reaction was cooled to 0 °C and benzoyl chloride (0.35 mL, 3.00 mmol) followed by a few crystals of DMAP (cat) were added again. The reaction was stirred for 10 minutes at 0 °C then warmed to room temperature and allowed to stir overnight. The following morning the reaction was cooled to 0 °C and 10% tartaric acid (aq., w/v, 10 mL) was added to the reaction mixture, and the reaction was stirred vigorously for 10 minutes at 0 °C. The reaction mixture was extracted with EtOAc (3 x 5 mL). The organic layers were combined, washed with 10% tartaric acid (aq.) (w/v) (10 mL), satd. $NaHCO_3$ (aq) (5 mL), brine (5 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude residue was purified via column chromatography (10% EtOAc in hexanes to 20% EtOAc in hexanes) to afford the desired product as a white solid (0.17 g, 94%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07-8.04 (m, 2 H), 7.61-7.56 (m, 1 H), 7.47-7.40 (m, 2 H), 5.38 (s, 1 H), 4.40 (qd, *J* = 1.9, 6.3 Hz), 3.79 (s, 3 H), 3.34-3.32 (m, 4 H), 3.30 (s, 3 H), 2.84 (d, *J* = 14.7 Hz, 1 H), 2.40 (d, *J* = 14.7 Hz, 1 H), 1.67 (br q, *J* = 6.9 Hz, 1 H), 1.19 (d, *J* = 6.6 Hz, 3 H), 1.01 (d, *J* = 6.9 Hz, 3 H); $[\alpha]^{22}_D$ +84.0 (*c* 0.81, $CHCl_3$), lit. $[\alpha]^{28}_D$ +87.9 (*c* 1.29, $CHCl_3$). *These data are consistent with reported literature values.*[34]

(*S*)-2-Methoxy-1-((2*R*, 5*S*, 6*R*)-2-methoxy-5,6-dimethyl-4-oxotetrahydro-2H-pyran-2-yl)-2-oxoethyl benzoate (134)



To a solution of **133** (0.07 g, 0.16 mmol) in CH_3CN (3.58 mL) and H_2O (0.47 mL) cooled to –5 °C was added bis(trifluoroacetoxy)iodo benzene (0.21 g, 0.49 mmol). The reaction was stirred at –5 °C for 50 minutes then warmed to room temperature. After 20 minutes, the reaction mixture was poured into satd. $NaHCO_3$ (aq) (5 mL) and the mixture was extracted with EtOAc (3 x 5 mL). The organic layers were combined, washed with brine (5 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure to afford a crude yellow oil. The crude residue was purified via flash column chromatography (20% EtOAc in hexanes to 30% EtOAc in hexanes) to afford the desired product. (0.04 g, 63%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07-8.04 (m, 2 H), 7.64-7.58 (m, 1 H), 7.50-7.45 (m, 2 H), 5.49 (s, 1 H), 4.20 (qd, *J* = 3.0, 6.6 Hz, 1 H), 3.84 (s, 3 H), 3.29 (s, 3 H), 3.27 (d, *J* = 15.6 Hz, 1 H), 2.66 (dd, *J* = 0.9, 15.6 Hz, 1 H), 2.36 (br qd, *J* = 2.7, 7.2 Hz, 1 H), 1.26 (d, *J* = 6.6 Hz, 3 H), 1.08 (d, *J* = 7.2 Hz, 3 H); $[\alpha]^{23}_D$ +94.6 (*c* 0.84, $CHCl_3$), lit. $[\alpha]^{28}_D$ +114.4 (*c* 1.23, $CHCl_3$). *These data are consistent with reported literature values.*[34]

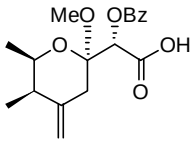
(*S*)-2-Methoxy-1-((2*R*, 5*R*, 6*R*)-2-methoxy-5,6-dimethyl-4-methylenetetrahydro-2H-pyran-2-yl)-2-oxoethyl benzoate (135)



To a solution of **134** (0.12 g, 0.34 mmol) in THF (6.2 mL) at room temperature was added freshly prepared "Stock" Takai-Nozaki olefination reagent[34] slowly dropwise (5.1 mL). After addition was complete, the reaction was poured into 0 °C satd. $NaHCO_3$ (aq) (10 mL), and the reaction mixture was extracted with EtOAc (3 x 10 mL). The organic layers were combined and washed with satd. $NaHCO_3$ (aq) (10 mL), brine (10 mL),

dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude residue was purified via flash column chromatography (30% EtOAc in hexanes) to afford the desired product (0.01 g, 85%) as a colorless oil (**NOTE**: The purification was carried out quickly using a short pad of silica gel to decrease decomposition on the column): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11-8.08 (m, 2 H), 7.63-7.58 (m, 1 H), 7.50-7.49 (m, 2 H) 5.43 (s, 1 H), 4.88 (br t, *J* = 1.8 Hz, 1 H), 4.81 (br t, *J* = 1.8 Hz, 1 H), 3.92 (qd, *J* = 2.4, 6.6 Hz, 1 H), 3.82 (s, 3 H), 3.28 (s, 3 H), 2.91 (d, *J* = 14.4 Hz, 1 H), 2.47 (d, *J* = 14.7 Hz, 1 H), 2.24 (br qd, *J* = 2.4, 7.2 Hz, 1 H), 1.16 (d, *J* = 6.3 Hz, 3 H), 0.961 (d, *J* = 6.9 Hz, 3 H); $[\alpha]^{23}_D$ +104.6 (*c* 2.65, CH_2Cl_2), lit. $[\alpha]^{28}_D$ +112.5 (*c* 0.51, CH_2Cl_2). *These data are consistent with reported literature values.*[34]

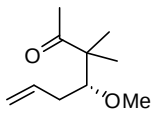
(*S*)-2-(Benzoyloxy)-2-((2*R*, 5*R*, 6*R*)-2-methoxy-5,6-dimethyl-4-methylenetetrahydro-2H-pyran-2-yl)acetic acid (59)



To a solution of **135** (0.08 g, 0.22 mmol) in 1,2-dichloroethane (12.3 mL) was added trimethyltin hydroxide (0.20 g, 1.11 mmol) and the reaction was heated to 80 °C. After 4 hours, the reaction was cooled to room temperature and $NaHSO_4$ (10 mL, 0.01 M in H_2O) was added. The reaction mixture was extracted with EtOAc (3 x mL). The organic layers were combined, washed with brine (10 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude residue was purified via flash column chromatography (30% EtOAc in hexanes to 100% EtOAc to 10% MeOH in EtOAc) to afford the desired product (0.06 g, 82%): ^{1}H (300 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.5 Hz, 2 H), 7.65-7.60 (m, 1 H), 7.51-7.46 (m, 2 H), 5.67 (s, 1 H), 4.94 (s, 1 H), 4.86 (s, 1 H), 4.09 (qd, *J* = 2.7, 6.6 Hz, 1 H), 3.28 (s, 3 H), 2.67 (d, *J* = 14.4 Hz, 1 H), 2.55 (d, *J* = 14.4 Hz, 1 H), 2.36-2.32 (m, 1 H), 1.26 (d, *J*

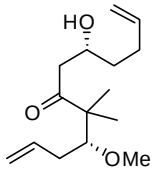
= 6.3 Hz, 3 H), 1.05 (d, J = 7.2 Hz, 3 H); $[\alpha]^{21}_D$ +133.7 (*c* 0.40, CH_2Cl_2), lit. (antipode) $[\alpha]^{25}_D$ – 93.1 (*c* 1.00, CH_2Cl_2).[53] *These data are consistent with reported literature values.*[34]

(*R*)-4-Methoxy-3,3-dimethylhept-6-en-2-one (139)



To a solution of **137**[69, 71] (2.03 g, 13.0 mmol) in CH_2Cl_2 (13.0 mL) cooled to 0 °C was added 2,6-di-*tert*-butyl pyridine (4.3 mL, 19.5 mmol) followed by methyltrifluoromethane sulfonate (1.9 mL, 16.9 mmol), and the reaction was warmed to room temperature. After 12 hours, the reaction was cooled to 0 °C and 2,6-di-*tert*-butyl pyridine (4.3 mL, 19.5 mmol) and methyltrifluoromethane sulfonate (1.9 mL, 16.9 mmol) were added again, and the reaction was subsequently warmed to room temperature. After 12 hours, H_2O (15 mL) was added, and the reaction was extracted with CH_2Cl_2 (3 x 15 mL). The organic layers were combined and washed with satd. $NaHCO_3$ (aq) (20 mL), brine (20 mL), dried (Na_2SO_4), filtered, and *carefully concentrated* under reduced pressure at 0 °C. The crude residue was purified via flash column chromatography (30% Et_2O in pentane) to afford the desired product (2.01 g, 91%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.96-5.82 (m, 1H), 5.15-5.08 (m, 1H), 5.06-5.03 (m, 1H), 3.43 (dd, J = 6.5, 5.5 Hz, 1H), 3.39 (s, 3H), 2.21-2.25 (m, 2H), 2.17 (s, 3H), 1.16 (s, 3H), 1.09 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 212.9, 136.0, 116.4, 86.0, 59.9, 52.4, 36.7, 26.5, 10.9, 20.2; IR (neat) 2977, 2827, 1704, 1469, 1100 cm-^{1}; HRMS (EI) *m/z* calcd. for $C_7H_{13}O_2$ [M-CH_2=CH-CH_2] 129.0915, found 129.0915; $[\alpha]^{24}_D$ −9.72 (*c* 1.19, $CHCl_3$).

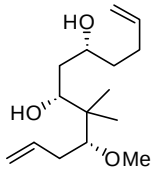
(4*R*, 8*R*)-8-Hydroxy-4-methoxy-5,5-dimethyldodeca-1,11-dien-6-one (140)



To a solution of (+)-DIP-Cl (2.83 g, 8.81 mmol) in Et_2O (6.0 mL) at 0 °C was added Et_3N (1.4 mL, 10.00 mmol), followed by **139** (1.00 g, 5.87 mmol). The

reaction mixture was stirred at 0 °C for 30 minutes then cooled to –78 °C, whereupon 4-pentenal (1.7 mL, 17.61 mmol) was added slowly dropwise. After 15 minutes, pH 7 (phosphate) buffer solution (16 mL), MeOH (8 mL), and hydrogen peroxide solution (aq., 30%, 8 mL) were added to the reaction at –78 °C, and the reaction was warmed to room temperature. After stirring for 20 minutes at room temperature, the reaction mixture was extracted with EtOAc (3 x 20 mL) and the organic layers were combined. The combined organic extracts were washed with brine (20 mL), satd. Na_2SO_3 (aq) (20 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude residue was purified via flash column chromatography (30% EtOAc in hexanes) to afford the desired product as a yellow oil (0.93 g, 62%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.91-5.75 (m, 2 H), 5.15-4.95 (m, 4 H), 4.05-3.97 (m, 1 H), 3.41 (dd, *J* = 5.4, 6.6 Hz, 1 H), 3.35 (s, 3 H), 3.27 (d, *J* = 3 Hz, 1 H), 2.70 (dd, *J* = 2.7, 18 Hz, 1 H), 2.56, (dd, *J* = 9, 18 Hz, 1 H), 2.23-2.12 (m, 4 H), 1.70-1.40 (m, 2 H), 1.16 (s, 3 H), 1.09 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 217.0, 138.3, 136.0, 116.9, 114.8, 86.2, 67.1, 60.0, 52.5, 45.3, 35.6, 35.4, 29.8, 21.4, 19.8; IR (neat): 3526, 3079, 2978, 2936, 1694, 1640 cm^{-1}; HRMS (EI) *m/z* calcd. for $C_{15}H_{25}O_2$ [M-OH] 237.1854, found 237.1843; $[\alpha]^{24}_D$ −21.0 (*c* 0.80, $CHCl_3$).

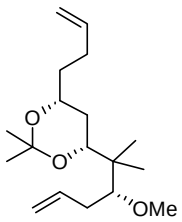
(5*R*, 7*R*, 9*R*)-9-Methoxy-8,8-dimethyldodeca-1,11-diene-5,7-diol (104)



To a solution of **140** (2.09 g, 8.2 mmol) in THF (82.0 mL) and MeOH (8.20 mL) at –78 °C was added Et_2BOMe (1.13 mL, 9.04 mmol). After 1 hour, $NaBH_4$ (0.93 g, 24.7 mmol) was added at –78 °C. After one hour, hydrogen peroxide solution (aq., 30%, 31.0 mL) was added *carefully dropwise* and the reaction was warmed to room temperature. After 3 hours the reaction mixture was extracted with EtOAc (3 x 40 mL), and the combined organic layers were washed with brine (50 mL) and satd. Na_2SO_3 (aq) (40 mL). The reaction

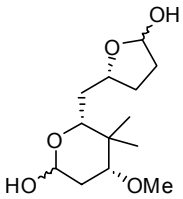
mixture was dried (Na_2SO_4), filtered, and concentrated under reduced pressure to afford a crude residue. The material was purified via flash column chromatography (20% EtOAc in hexanes) to afford the desired product (1.63 g, 77%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.90-5.77 (m, 2 H), 5.17- 4.95 (m, 4 H), 4.46 (d, *J* = 2.3 Hz, 1 H), 4.38 (s, 1 H), 3.87-3.80 (m. 2 H), 3.45 (s, 3 H), 3.17 (dd, *J* = 3.8, 7.6 Hz, 1 H), 2.43-2.13 (m, 4H), 1.66-1.40 (m, 4 H), 0.98 (s, 3 H), 0.86 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.3, 136.0, 116.3, 114.1, 89.6, 77.8, 71.7, 59.9, 41.4, 36.9, 36.6, 34.7, 29.4, 21.2, 20.2; IR (neat): 3440, 2977, 2253, 1641, 1470, 1389 cm^{-1}; HRMS (ES) *m/z* calcd. for $C_{15}H_{28}O_3Na$ [M + Na] 279.1936, found 279.1911; $[\alpha]^{24}_D$ +2.0 (*c* 0.85, $CHCl_3$).

(4*R*, 6*R*)-4-(But-3-enyl)-6-((R)-3-methoxy-2-methylhex-5-en-2-yl)-2,2-dimethyl-1,3-dioxane (161)



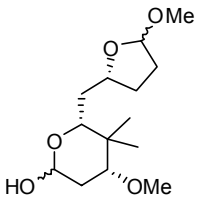
To a solution of **104** (0.05 g, 0.20 mmol) in 2,2-dimethoxypropane (2.79 mL) at room temperature was added *p*-toluenesulfonic acid (5.00 mg, 0.03 mmol). After 3 hours, Et_3N (0.10 mL) was added followed by H_2O (3.00 mL). The reaction mixture was extracted with EtOAc (3 x 2 mL), and the combined organic layers were washed with brine (3 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure to afford an oily yellow residue. The material was purified via flash column chromatography (10% EtOAc in hexanes) to afford the desired product. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.03-5.89 (m, 1 H), 5.89-5.76 (m, 1H), 5.14-4.95 (m, 4 H), 3.95 (dd, *J* = 2.4, 14.4 Hz, 1 H), 3.82 (m, 1 H), 3.40 (s, 3 H), 3.29 (dd, *J* = 3.6, 8.4 Hz, 1 H), 2.36-2.07 (m, 4 H), 1.68-1.15 (m, 4 H), 1.43 (s, 3 H), 1.38 (s, 3H), 0.79 (s, 3H), 0.76 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.4, 137.6, 115.8, 114.6, 98.3, 83.9, 71.2, 68.5, 60.2, 41.7, 35.7, 35.5, 30.9, 30.3, 29.3, 20.0, 18.2, 17.3.

(4*R*, 6*R*)-6-(((*R*)-5-Hydroxytetrahydrofuran-2-yl)methyl)-4-methoxy-5, 5-dimethyltetrahydro-2H-pyran-2-ol (103)



To a solution of **104** (0.92 g, 3.60 mmol) in *p*-dioxane (18.0 mL) and H_2O (18 mL) at room temperature was added 2,6-lutidine (0.77 g, 7.20 mmol), OsO_4 (0.02 g, 0.07 mmol), and $NaIO_4$ (3.08 g, 14.4 mmol). After 4 hours, the chalky reaction mixture was extracted with EtOAc (3 x 50 mL). The aqueous layer was separated and extracted again with EtOAc (2 x 200 mL). The organic layers were combined, dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford a crude residue. The material was purified via flash column chromatography (30% EtOAc in hexanes to 50% EtOAc in hexanes, to 70% EtOAc in hexanes, to 100% EtOAc, to 10% MeOH in EtOAc) to afford the desired product as a viscous oil (0.77 g, 82%): ^{13}C (75 MHz $CDCl_3$) δ 98.6, 98.4, 97.9, 94.6, 94.5, 91.8, 91.6, 83.3, 80.1, 80.0, 79.8, 79.7, 79.3, 78.4, 78.1, 74.7, 73.8, 60.2, 57.1, 57.1, 56.9, 38.8, 38.7, 38.0, 35.7, 34.7, 34.3, 33.6, 33.3, 33.1, 32.2, 32.1, 30.8, 30.6, 30.3, 30.1, 29.3, 22.3, 22.2, 20.8, 14.0, 12.9, 12.0; IR (neat): 3404, 2962, 1737, 1443, 1244 cm^{-1}; HRMS (ES) *m/z* calcd. for $C_{13}H_{24}O_5Na$ [M+Na] 283.1521 found 283.1537; $[\alpha]^{23}_D$ +16.6 (*c* 0.79, MeOH).

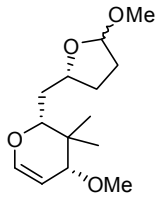
(4*R*, 6*R*)-4-Methoxy-6-(((*R*)-5-methoxytetrahydrofuran-2-yl)methyl)-5, 5-dimethyltetrahydro-2H-pyran-2-ol (141)



To a solution of **103** (0.60 g, 2.31 mmol) in THF (12.0 mL) and MeOH (12.0 mL) at room temperature was added pyridinium *p*-toluenesulfonate (PPTs) (0.17 g, 0.69 mmol). After 40 minutes the reaction was cooled to 0 °C and satd. $NaHCO_3$ (aq) (10 mL) was added. The reaction was subsequently warmed to room temperature then extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine

(10 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure to afford a viscous yellow residue which was used without further purification: ^{13}C NMR (75 MHz, $CDCl_3$) δ 104.8, 104.8, 104.7, 104.6, 94.6, 91.9, 83.6, 83.5, 80.0, 79.9, 79.1, 78.8, 78.12, 78.06, 76.0, 75.7, 72.9, 72.8, 57.2, 57.1, 54.5, 54.4, 54.3, 38.7, 38.6, 37.9, 37.9, 35.5, 35.2, 34.1, 34.1, 34.0, 33.1, 33.0, 31.9, 31.0, 29.0, 28.8, 28.6, 28.5, 22.4, 22.3, 22.3, 22.2, 13.0, 13.0, 12.1, 12.1; IR (neat): 3411, 2962, 2829, 2246, 1733, 1443, 1367, 1244 cm^{-1}; HRMS (EI) *m/z* calcd. for $C_{14}H_{26}O_5Na$ [M + Na] 297.1678 found 297.1705; $[\alpha]^{23}_D$ +30.1 (*c* 0.60, MeOH).

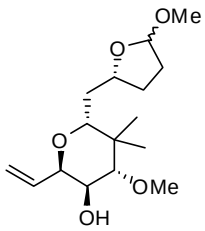
(2*R*, 4*R*)-4-Methoxy-2-(((*R*)-5-methoxytetrahydrofuran-2-yl)methyl)-3,3 -dimethyl-3,4-dihydro-2H-pyran (102)



Crude **141** (0.6 g, 2.31 mmol) was taken up in CH_2Cl_2 (14 mL) and cooled to –78 °C whereupon diisopropylethylamine (2.5 mL, 13.9 mmol) was added followed by trifluoroacetic anhydride (0.69 mL, 4.9 mmol). The reaction mixture was stirred for 10 minutes at –78 °C then warmed to 0 °C and stirred for 1 hour. Afterwards, the reaction was heated to 40 °C. After 2 hours, the reaction was cooled to room temperature and brine was added (10 mL). The reaction mixture was extracted with CH_2Cl_2 (3 x 12 mL), and the combined organic layers were washed with satd. $NaHCO_3$ (aq) (10 mL), brine (15 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude residue was purified via flash column chromatography (the column was washed with 3% Et_3N in hexanes, then eluted with 30% EtOAc in hexanes) to afford the desired product as a mixture of inseparable isomers (0.55 g, 92%): ^1H NMR (300 MHz, $CDCl_3$) δ 6.33 (app. d, *J* = 6.3 Hz, 1 H), 5.04 (dd, *J* = 1.8, 5.1 Hz, 0.5 H), 4.96 (d, *J* = 4.2 Hz, 0.5 H), 4.81 (ddd, *J* = 2.4, 4.8, 6.3 Hz, 1 H), 4.31-4.21 (m, 1 H), 3.61 (d, *J* = 10.8 Hz, 1 H), 3.46 (br s, 1 H), 3.37 (s, 3 H), 3.35 (s, 1.5 H), 3.34 (s, 1.5 H), 2.19-1.80 (m, 4 H), 1.72-1.43 (m, 2 H), 0.96 (s, 3 H), 0.89 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.8, 104.7,

104.6, 100.0, 100.0, 80.3, 80.2, 80.1, 78.1, 75.3, 56.9, 54.4, 54.1, 35.4, 35.2, 35.1, 33.5, 33.0, 31.9, 28.7, 28.4, 23.4, 13.7; IR (neat): 3056, 2979, 2934, 2825, 1648, 1464, 1367, 1266, 1195, 1100, 1042 cm^{-1}; HRMS (EI) *m/z* calcd. for $C_{14}H_{24}O_4$ $[M^+]$ 256.1675, found 256.1675; $[\alpha]^{23}_D$ −30.0 (*c* 1.02, $CHCl_3$).

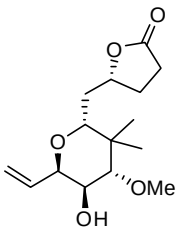
(2*R*, 3*S*, 4*S*, 6*R*)-4-Methoxy-6-(((*R*)-5-methoxytetrahydrofuran-2-yl)methyl)-5, 5-dimethyl-2-vinyltetrahydro-2H-pyran-3-ol (101)



To a solution of **102** (0.47 g, 1.85 mmol) in CH_2Cl_2 (19.0 mL) at 0 °C was slowly added DMDO (0.07 M in CH_2Cl_2, 75.0 mL) in 3 portions. After the final addition was complete, the reaction was concentrated under reduced pressure at 0 °C, (using argon to backfill the rotary evaporator after the vacuum was removed), until approximately 5 mL of solvent remained. The crude solution was diluted in CH_2Cl_2 (31.0 mL) and added dropwise over 15 minutes to a stirring –78 °C solution of trivinyl alane (0.1 M, 111.0 mL). The reaction was stirred for 2 hours at –78 °C, then warmed to room temperature and stirred for an additional 30 minutes. Afterwards, H_2O (30 mL) followed by satd. sodium potassium tartrate (aq) (100 mL) was added and the reaction mixture was stirred for 2 hours at room temperature. The resulting mixture was extracted with CH_2Cl_2 (3 x 40 mL), and the combined organic layers were washed with brine (30 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure to afford the desired product in quantitative yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.21-6.12 (m, 1 H), 5.51-5.41 (m, 1 H), 5.03 (br d, *J* = 3.3 Hz), 4.94 (br d, *J* = 3.9 Hz), 4.56-4.50 (m, 1 H) 4.34-4.19 (m, 1 H), 3.91-3.80 (m, 1 H), 3.60 (s, 3 H), 3.44-3.34 (m, 4 H), 2.82 (d, *J* = 9.9 Hz, 1 H), 2.08-1.62 (m, 6 H), 0.95 (s, 1.5 H), 0.94 (s, 1.5 H), 0.89 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.5, 132.3, 119.3, 119.1, 104.7, 104.5, 87.2, 87.1, 78.2, 75.8, 75.8, 75.7, 74.5, 74.1, 69.4, 67.7, 62.3, 54.3, 54.1, 41.2, 41.1, 36.5, 34.5, 33.0, 31.8, 28.9,

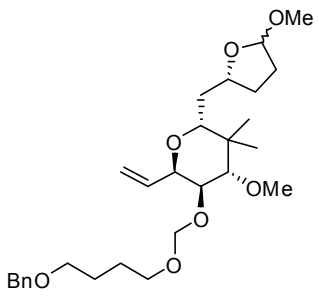
28.5, 25.4, 23.2, 23.1, 13.7, 13.6; HRMS (EI) *m/z* calcd. for $C_{15}H_{25}O_4$ [M-OMe] 269.1752 found 269.1745.

(*R*)-5-(((2*R*,4*S*,5*S*,6*R*)-5-Hydroxy-4-methoxy-3, 3-dimethyl-6-vinyltetrahydro-2H-pyran-2-yl)methyl)dihydrofuran-2(3H)-one (162)



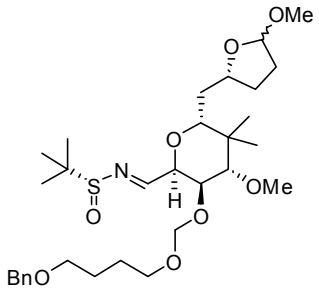
To a solution of **101** (0.02 g, 0.07 mmol) in CH_2Cl_2 (1.34 mL) cooled to 0 °C was added *m*-CPBA (0.02 g, 0.09 mmol) followed by $BF_3{\cdot}Et_2O$ (0.018 mL, 0.15 mmol). After 2 minutes, the reddish-orange reaction mixture was warmed to room temperature. After 20 minutes, the reaction was cooled to 0 °C, and Et_3N (0.050 mL) was added. The reaction was stirred at 0 °C for 10 minutes then concentrated under reduced pressure. The crude residue was purified via flash column chromatography (70% EtOAc in hexanes) to afford the desired product: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.23-6.12 (m, 1 H), 5.47 (app. s, 1 H), 5.42 (d, *J* = 8.7 Hz, 1 H), 4.71-4.65 (m, 1 H), 4.49 (dd, *J* = 5.4, 6.3 Hz, 1 H), 3.89 (dd, 6.6, 9.6 Hz, 1 H), 3.60 (s, 3 H), 3.44 (app. d, *J* = 10.5 Hz, 1 H), 2.85 (d, *J* = 9.9 Hz, 1 H), 2.57-2.52 (m, 2 H), 2.36-2.26 (m, 1 H), 2.09-1.83 (m, 2 H), 1.63-1.59 (m, 2 H), 0.96 (s, 3 H), 0.91 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.0, 132.2, 120.5, 87.1, 78.8, 75.9, 73.0, 69.5, 62.6, 41.2, 34.1, 28.8, 27.3, 23.5, 14.1; HRMS (EI) *m/z* calcd. for $C_{15}H_{24}O_5$ [M^+] 284.1624 found 284.1621.

(2*R*, 4*S*, 5*S*, 6*R*)-5-((4-(Benzyloxy)butoxy)methoxy)-4-methoxy-2-(((R)-5-methoxytetrahydrofuran-2-yl)methyl)-3, 3-dimethyl-6-vinyltetrahydro-2H-pyran (145)



To a solution of **101** (0.042 g, 0.14 mmol) in 1,2-dichloroethane (0.05 mL) was added DIPEA (0.06 mL, 0.35 mmol), and the solution was stirred for 30 minutes. Afterwards, a heterogeneous mixture of BBM-Cl[70] (0.08 g, 0.35 mmol) and KI (0.06 g, 0.35 mmol) in 1,2-dichloroethane (0.05 mL) was added, and the reaction mixture was heated to 50 °C. After stirring overnight the reaction was cooled to room temperature, and H_2O (1 mL) was added to the reaction. The reaction mixture was extracted with EtOAc (3 x 2 mL), and the combined organic layers were washed with brine (2 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude residue was purified via flash column chromatography (10% to 40% EtOAc in hexanes) to afford the desired product (0.053 g, 77%): ^{1}H NMR (300 MHz, $CDCl_3$) 7.25-7.21 (m, 5 H), 6.11-6.05 (m, 1 H), 5.48-5.37 (m, 2 H), 5.04-5.03 (m, 0.5 H), 4.95-4.93 (m, 0.5 H), 4.80 (d, *J* = 6.6 Hz, 1 H), 4.73 (d, *J* = 6.6 Hz, 1 H), 4.60-4.51 (m, 4 H), 4.31-4.15 (m, 1 H), 3.79-3.74 (m, 1 H), 3.56-3.38 (m, 6 H), 3.31-3.24 (m, 4 H), 2.81-2.76 (m, 1 H), 2.03-1.20 (m, 10 H), 0.83 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.5, 133.5, 133.2, 128.2, 127.5, 127.4, 119.1, 119.0, 104.8, 104.6, 95.7, 85.7, 85.6, 78.3, 76.3, 75.8, 74.9, 74.4, 74.0, 72.7, 70.0, 67.8, 61.9, 54.5, 54.2, 41.5, 41.4, 36.8, 34.8, 33.1, 31.9, 29.1, 28.7, 26.4, 26.3, 23.0, 22.9, 13.8, 13.7; IR (neat): 3019, 2400, 1215, 1100, 1040, 757 cm^{-1}; HRMS (ES) *m/z* calcd. for $C_{28}H_{44}O_7Na$ [M + Na] 515.2985 found 515.2963; $[\alpha]^{24}_D$ +32.6 (*c* 1.00, $CHCl_3$).

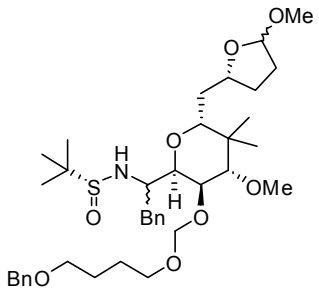
(E)-*N*-(((2*R* ,3*R* ,4*S* ,6*R*)-3-((4-(Benzyloxy)butoxy)methoxy)-4-methoxy-6-(((*R*)-5-methoxytetrahydrofuran-2-yl)methyl)-5, 5-dimethyltetrahydro-2H-pyran-2-yl)methylene)-2-methylpropane-2-sulfinamide (147)



To a solution of **145** (0.50 g, 1.02 mmol) in CH_2Cl_2 (10.00 mL), cooled to –78 °C was bubbled O_3 in 20 second intervals until all starting material was observed to be consumed by TLC (approximately 3 minutes total bubbling time). The solution was placed under N_2 atmosphere for 10 minutes, and PPh_3 (0.80 g, 3.06 mmol) was added to the reaction mixture at –78 °C. The solution was subsequently warmed to room temperature. After stirring for 1 hour at room temperature, the reaction mixture was concentrated under reduced pressure and the residue was dissolved in THF (13.40 mL). To this solution at room temperature was added Ti(*i*-OPr)$_4$ (1.56 mL, 5.20 mmol), followed by (*R*)-*tert*-butylsulfinamide (0.37 g, 3.06 mmol), and the reaction was stirred overnight. The following morning brine (20 mL) was added to the reaction mixture, the heterogeneous mixture was filtered through a short pad of Celite, and the filter cake was washed with EtOAc. The filtrate was washed with brine (10 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude yellow to translucent oil was purified via flash column chromatography (30 to 50% EtOAc in hexanes) to afford the desired product as a pale yellow oil (0.34 g, 55%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.37 (d, *J* = 2.7 Hz, 1 H), 7.38-7.29 (m, 5 H), 5.03-5.00 (m, 0.57 H), 4.93 (app. d, 0.43 H), 4.84 (d, *J* = 6.9 Hz, 1 H), 4.79-4.73 (m, 1 H), 4.77 (d, *J* = 6.9 Hz, 1 H), 4.50 (s, 2 H), 4.65-4.23 (m, 1 H), 4.05-3.98 (m, 1 H), 3.70-3.64 (m, 1 H), 3.55-3.45 (m, 7 H), 3.33-3.32 (m, 3 H), 2.81-2.76 (m, 1 H), 2.2-1.4 (m, 10 H), 1.27-1.22 (m, 9 H), 0.90 (s, 6 H);^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6, 166.5, 138.5, 128.2, 127.4, 127.3, 104.8, 104.7, 96.0, 86.2, 86.2, 78.2, 76.5,

76.3, 76.0, 75.9, 75.4, 70.7, 69.8, 68.1, 62.0, 57.1, 57.1, 54.5, 54.2, 41.4, 41.3, 36.8, 34.8, 33.0, 32.0, 29.6, 29.3, 28.9, 26.4, 26.3, 22.7, 22.5, 22.3, 13.4; IR (neat): 3052, 2933, 2248, 1620, 1454, 1364, 1265, 1100, 1039, 909 cm^{-1}; HRMS (ES) *m/z* calcd. for $C_{31}H_{51}NO_8NaS$ [M + Na] 620.3233 found 620.3267; $[\alpha]^{24}_D$ −10.7 (*c* 0.58, $CHCl_3$).

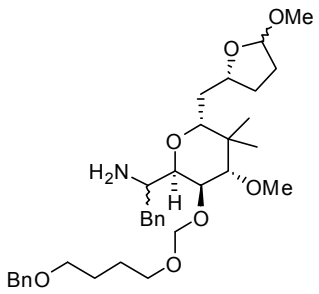
<u>*N*-(1-((2R, 3*R*, 4*S*,6*R*)-3-((4-(Benzyloxy)butoxy)methoxy)-4-methoxy-6-(((R)-5-methoxytetrahydrofuran-2-yl)methyl)-5, 5-dimethyltetrahydro-2H-pyran-2-yl)-2-phenylethyl)-2-methylpropane-2-sulfinamide (148)</u>



To a solution of **147** (0.78 g, 1.31 mmol) in CH_2Cl_2 (33.0 mL) cooled to –78 °C was added benzylmagnesium chloride (18.0 mL, 1 M in Et_2O) slowly dropwise. After addition was complete H_2O (20 mL) was added to the reaction mixture and the solution was warmed to 0 °C. The reaction mixture was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude residue was purified via flash column chromatography (30% EtOAc in hexanes to 100% EtOAc) to afford the desired product as a ~1:1 mixture of inseparable isomers (0.66 g, 73%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34-7.18 (m, 10 H), 5.30-5.19 (m, 1 H), 5.03-4.95 (m, 1 H), 4.77-4.67 (m, 2 H), 4.6-4.5 (m, 1 H), 4.49 (s, 2 H), 4.38-4.22 (m, 1 H), 3.95-3.80 (m, 2 H), 3.54-3.23 (m, 9 H), 3.19-3.03 (m, 2 H), 2.90-2.75 (m, 1 H), 2.38-1.78 (m, 4 H), 1.68-1.26 (m, 7 H), 1.21-0.80 (m, 15 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.4, 138.2, 138.0, 136.8, 136.7, 130.6, 129.6, 129.4, 129.3, 128.1, 127.6, 127.4, 126.2, 126.0, 104.9, 104.7, 104.6, 96.4, 95.3, 84.1, 84.0, 78.8, 78.4, 78.2, 76.4, 75.6, 73.8, 72.7, 72.1, 71.8,

71.0, 69.8, 68.4, 68.3, 68.0, 61.5, 60.5, 59.7, 55.7, 55.5, 55.3, 55.2, 54.5, 54.2, 54.1, 41.2, 41.0, 39.1, 37.3, 37.1, 36.3, 36.1, 35.3, 34.3, 33.8, 33.0, 31.9, 31.8, 29.1, 29.1, 29.0, 25.9, 24.6, 23.8, 23.6, 22.4, 22.1; IR (neat): 3252, 3029, 2947, 2360, 1454, 1364, 1268, 1042, 953 cm^{-1}; HRMS (ES) *m/z* calcd. for $C_{38}H_{59}NO_8NaS$ [M+Na] 712.3859 found 712.2859; $[\alpha]^{25}_D$ −22.6. (*c* 0.53, $CHCl_3$).

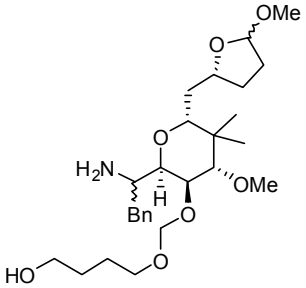
1-((2*R*, 3*R*, 4*S*, 6*R*)-3-((4-(Benzyloxy)butoxy)methoxy)-4-methoxy-6-(((*R*)-5-methoxytetrahydrofuran-2-yl)methyl)-5, 5-dimethyltetrahydro-2H-pyran-2-yl)-2-phenylethanamine (149)



To a solution of **148** (1.60 g, 2.39 mmol) in MeOH (120 mL) at 0 °C was added 4M HCl in *p*-dioxane (6.00 mL, 23.90 mmol). The reaction was stirred for 10 minutes at 0 °C then warmed to room temperature. After 40 minutes the reaction was cooled to 0 °C and 10% NaOH (aq. w/v) was added until precipitation occurred. The reaction mixture was extracted with EtOAc (3 x 40 mL) and the combined organic layers were washed with brine (30 mL). The organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude residue was purified via flash column chromatography (the column was washed in 3% Et_3N in hexanes then eluted with 50% EtOAc in hexanes to 100% EtOAc) to afford the desired product (1.13 g, 80%). ^1H NMR (300 MHz, $CDCl_3$): δ 7.34-7.21 (m, 10 H), 5.03-5.01 (m, 0.64 H), 4.94 (app d, 0.36 H), 4.83 (d, *J* = 6.6 Hz, 1 H), 4.77-4.48 (m, 3 H), 4.49-4.48 (m, 2 H), 4.32-4.28 (m, 1 H), 4.01-3.55 (m, 5 H), 3.49-3.45 (m, 3 H), 3.34-3.29 (m, 3 H), 3.22-3.17 (m, 1 H), 3.08-3.04 (m, 1 H), 2.58-1.41 (m, 12 H), 1.14-1.07 (m, 3 H), 0.95-0.93 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.4, 139.3, 139.2, 139.1, 138.3, 129.5, 129.2, 129.0, 129.0,

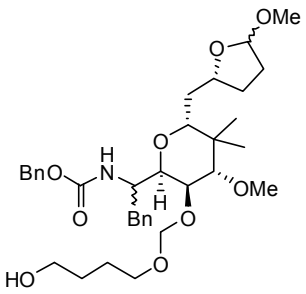
128.2, 128.1, 127.8, 127.3, 127.2, 126.0, 125.6, 104.8, 104.7, 104.6, 104.5, 95.4, 95.3, 95.1, 84.8, 84.3, 84.1, 78.7, 78.2, 77.2, 76.3, 75.7, 74.9, 74.5, 74.2, 73.7, 73.5, 73.3, 72.5, 69.7, 69.7, 68.1, 60.7, 60.4, 60.1, 54.5, 54.3, 54.1, 52.2, 51.0, 50.9, 40.1, 39.9, 39.1, 38.4, 36.4, 34.5, 33.0, 31.7, 29.7, 29.2, 28.9, 28.8, 28.6, 26.3, 26.2, 25.6, 25.1, 24.6; IR (neat): 3364, 2941, 2830, 2525, 1651, 1454, 1098, 1029 cm^{-1}; HRMS (ES) *m/z* calcd. for $C_{34}H_{52}NO_7$ [M+H] 586.3744 found 586.3719; $[\alpha]^{23}_D$ +6.15 (*c* 0.54, $CHCl_3$).

4-(((2*R*, 3*R*, 4*S*, 6*R*)-2-(1-Amino-2-phenylethyl)-4-methoxy-6-(((*R*)-5-methoxytetrahydrofuran-2-yl)methyl)-5, 5-dimethyltetrahydro-2H-pyran-3-yloxy)methoxy)butan-1-ol (150)



To a solution of **149** (0.13 g, 0.22 mmol) in MeOH (20 mL) was added glacial acetic acid (0.10 mL, 1.67 mmol). To the reaction mixture was added Pd/C (0.10 mg, 10 wt. %), the reaction vessel was evacuated, and then placed under H_2 (g) atmosphere. After stirring overnight the reaction mixture was filtered through a pad of Celite, and the filter cake was rinsed copiously with EtOAc. The filtrate was washed with satd. $NaHCO_3$ (aq) (10 mL), followed by brine (20 mL). The aqueous layers were combined and back-extracted with EtOAc (3 x 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude residue was without further purification.

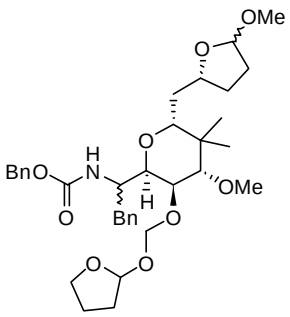
Benzyl 1-((2*R*, 3*R*, 4*S*, 6*R*)-3-((4-hydroxybutoxy)methoxy)-4-methoxy-6-(((R)-5-methoxytetrahydrofuran-2-yl)methyl)-5, 5-dimethyltetrahydro-2H-pyran-2-yl)-2-phenylethylcarbamate (151)



To a solution of crude **150** (0.11 g, 0.22 mmol) in THF/H_2O (1:1, 4.0 mL) was added $NaHCO_3$ (0.22 g, 0.27 mmol) followed by benzylchloroformate (0.05 g, 0.27 mmol). After 2 hours the reaction mixture was diluted with EtOAc (10 mL) and H_2O (3 mL). The reaction mixture was extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (5 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude residue was purified via flash column chromatography (50% EtOAc in hexane to 70% EtOAc in hexanes, to 100% EtOAc) to afford the desired product (0.08 g, 70%, 2 steps): ^{1}H (300 MHz, $CDCl_3$) δ 7.31-7.13 (m, 10 H), 6.42 (br s, 0.32, 1 H), 5.98 (br s, 0.68 H), 5.46 (app d, 0.62 H), 5.35 (app d, 0.38 H), 5.13-5.06 (m, 0.66 H), 5.02-4.91 (m, 2.85 H), 4.82-4.74 (m, 1.22 H), 4.65-4.63 (m, 1.5 H), 4.57-4.42 (m, 1.36 H), 4.40-4.29 (m, 0.41 H), 4.26-4.05 (m, 1.07 H), 3.92-3.77 (m, 1.15 H), 3.67-3.54 (m, 2.53 H), 3.46-3.27 (m, 6.06 H), 3.20-3.00 (m, 1.43 H), 3.00-2.72 (m, 1.76 H), 2.70-2.14 (m, 1.22), 2.12-1.78 (m, 3.15 H), 1.63-1.31 (m, 5.63 H), 1.25 (s, 1.35 H), 1.09 (s, 1.07 H), 1.00 (s, 0.96 H), 0.90-0.85 (m, 2.62 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.2, 156.0, 155.7, 137.6, 137.5, 137.1, 136.8, 130.0, 130.0, 129.6, 129.6, 129.0, 129.0, 129.0, 128.2, 128.1, 127.9, 127.8, 127.7, 127.7, 126.2, 126.1, 104.9, 104.7, 96.1, 96.0, 95.1, 84.4, 84.0, 83.9, 83.7, 80.0, 78.6, 77.1, 75.7, 68.6, 68.1, 66.1, 65.9, 62.3, 62.2, 60.8, 59.9, 59.7, 54.5, 54.2, 54.1, 51.8, 51.2, 39.8, 38.3, 37.7, 37.0, 36.6, 35.1, 34.6, 34.0, 33.1, 32.7, 31.8, 31.5, 29.8, 29.5, 29.4, 29.4, 39.3, 39.3, 29.2, 28.9, 28.8, 26.2, 26.1, 24.5; IR (neat): 3432,

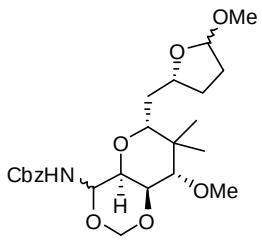
2936, 2360, 1702, 1496, 1453, 1365, 1096, 1038 cm^{-1}; HRMS (ES) *m/z* calcd. for $C_{35}H_{51}NO_9Na$ [M + Na] 652.3462 found 652.3436; $[\alpha]^{21}_D$ +19.6 (*c*, 1.40 $CHCl_3$).

Benzyl 1-((2*R*, 3*R*, 4*S*, 6*R*)-4-methoxy-6-(((*R*)-5-methoxytetrahydrofuran-2-yl)methyl)-5, 5-dimethyl-3-((tetrahydrofuran-2-yloxy)methoxy)tetrahydro-2H-pyran-2-yl)-2-phenylethylcarbamate (152)



To a solution of **151** (0.13 g, 0.21 mmol) in cyclohexane (14.0 mL) at room temperature was added (diacetoxyiodo)benzene (0.150, 0.46 mmol) followed by I_2 (0.04 g, 0.33 mmol). The reaction was stirred vigorously for 20 minutes, and then irradiated using a medium pressure mercury lamp. After 2 hours the reaction mixture was diluted with EtOAc (14.0 mL) and washed with satd. $Na_2S_2O_3$ (aq) (15 mL) followed by brine (15 mL). The aqueous layers were combined then back-extracted with EtOAc (3 x 10 mL). The combined organic layers were dried (Na_2SO_4) filtered, and concentrated under reduced pressure to afford a crude yellow oil. The crude residue was purified via flash column chromatography (the column was washed with 3 % Et_3N in hexanes, then eluted with 30% EtOAc in hexanes to 50% EtOAc in hexanes) to afford the desired product (0.10 g, 80%). The product was used immediately.

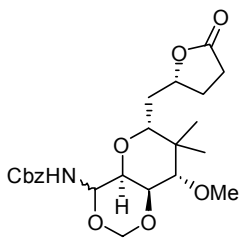
2-((4a*S*, 6*R*, 8*S*, 8a*R*)-8-Methoxy-6-(((*R*)-5-methoxytetrahydrofuran-2-yl)methyl)-7, 7-dimethylhexahydropyrano[3,2-d][1,3]dioxin-4-ylamino)-1-phenylethanone (153)



To a solution of **152** (0.044 g, 70.2 μmol) in 1,2-dichloroethane (9.0 mL) and toluene (1.4 mL) at room temperature was added $NMQPF_6$ (0.001 mg, 4.21 μmol), NaOAc (0.088 mg), $Na_2S_2O_3$ (0.088 mg) and powdered 4Å

mol. sieves (0.088 mg). The reaction mixture was stirred at room temperature for 30 minutes, and then irradiated for 4 hours while air was gently bubbled through the solution. The crude reaction mixture was then filtered through a short pad of Celite, and the filter cake was washed copiously with EtOAc. The filtrate was concentrated under reduced pressure and the crude residue was purified via flash column chromatography (20% EtOAc in hexanes to 50% EtOAc in hexanes) to afford the desired product as a 2:1 mixture of inseparable diastereomers (0.024 g, 73%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.30 (m, 5 H), 6.85 (d, *J* = 7.8 Hz, 0.33 H), 6.73 (d, *J* = 8.1 Hz, 0.67 H), 5.18-5.07 (m, 4.5 H), 4.93 (d, *J* = 3.9 Hz, 0.5 H), 4.85 (d, *J* = 6.6 Hz, 1 H), 4.12-4.02 (m, 1 H), 3.83-3.64 (m, 3 H), 3.39 (s, 3 H), 3.16 (s, 3 H), 2.93 (d, *J* = 2.4 Hz, 1 H), 2.40-1.40 (m, 6 H), 1.24 (s, 3 H), 0.92 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.8, 136.3, 136.1, 128.5, 128.4, 105.1, 105.0, 91.3, 83.8, 83.7, 81.6, 81.5, 80.6, 80.0, 77.7, 77.2, 72.9, 67.1, 66.9, 61.4, 61.3, 59.4, 59.3, 54.4, 54.3, 36.7, 36.6, 34.7, 32.9, 31.6, 29.9, 29.8, 27.7, 27.6; IR (neat): 3054, 2986, 2306, 1729, 1512, 1422, 1265 cm^{-1}; HRMS (ES) *m/z* calcd. for $C_{24}H_{35}NO_8Na$ [M + Na] 488.2260 found 488.2268; $[\alpha]^{23}_{D}$ −8.5 (*c* 0.61, $CHCl_3$).

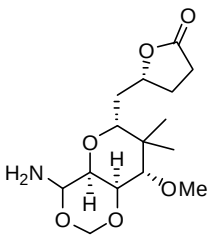
(5*R*)-5-(((4a*S*, 6*R*, 8*S*, 8a*R*)-8-Methoxy-7, 7-dimethyl-4-(2-oxo-2-phenylethylamino)hexahydropyrano[3,2-d][1,3]dioxin-6-yl)methyl)dihydrofuran-2(3H)-one (154)



To a solution of **153** (0.13 g, 0.27 mmol) in acetone (5.00 mL) at 0 °C was added Jones reagent (0.20 mL, 2.67M). After addition, the reaction was complete by TLC analysis. The reaction mixture was loaded directly onto a silica column and purified via flash column chromatography (50% EtOAc in hexanes to 70% EtOAc in hexanes) to afford the desired product as a mixture of inseparable

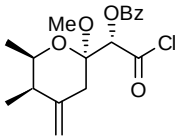
diastereomers (0.08 g, 64%), d.r. = 7.3:1) *Distinguishable peaks assigned to the minor diastereomer are underlined.* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60-7.0 (m, 5 H), 6.16 (d, *J* = 9.0 Hz, 0.88 H), <u>5.95</u> (d, *J* = 10.2 Hz, 0.12), 5.21-5.09 (m, 4 H), <u>4.89</u> (d, *J* = 6.6 Hz, 0.16 H), 4.83 (d, *J* = 6.6 Hz, 0.84 H), 4.54-4.44 (m, 0.74 H), 4.38-4.25 (m, 0.26 H), 3.75 (br s, 2 H), 3.66 (dd, *J* = 2.7, 12.3 Hz, 1 H), 3.39 (s, 2.72 H) <u>2.98</u> (s, 0.27 H), 2.95 (d, *J* = 2.1 Hz, 1 H), 2.65-2.59 (m, 1 H), 2.52-2.47 (m, 2 H), 2.41-2.29 (m, 1 H), 1.93-1.79 (m, 1 H), 1.16-1.58 (m, 1 H), <u>1.26</u> (s, 1.13 H), 1.24 (s, 1.87 H), 0.94 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.6, 155.5, 136.1, 128.7, 128.5, 128.1, 91.4, 83.4, 79.7, 79.5, 79.2, 78.8, 72.6, 67.2, 61.7, 59.3, 36.4, 33.4, 28.6, 28.1, 27.3, 22.5; IR (neat): 3019, 2400, 1771, 1730, 1514, 1423, 1024, 929 cm^{-1}; HRMS (ES) *m/z* calcd. for $C_{23}H_{31}NO_8Na$ [M + Na] 472.1947, found 472.1914; $[\alpha]^{23}_D$ −1.4 (*c* 0.63, $CHCl_3$).

<u>(5R)-5-(((4aS,6R,8S,8aR)-4-Amino-8-methoxy-7,7-dimethylhexahydropyrano[3,2-d][1,3]dioxin-6-yl)methyl)dihydrofuran-2(3H)-one (93)</u>

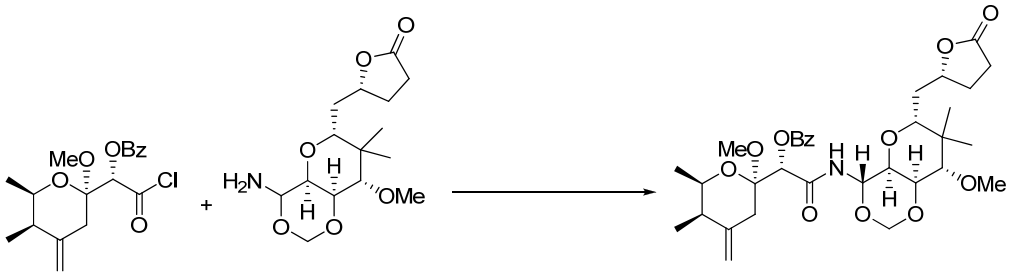


To a solution of **154** (0.016 g, 0.037 mmol) in EtOAc at room temperature was added Pd/C (30 mg, 10 wt%). The reaction vessel was evacuated and backfilled with H_2 (g) 3 times before being left under H_2 (g) atmosphere. After 40 minutes, the reaction was complete by TLC. The reaction mixture was filtered through a short pad of Celite and the filter cake was washed several times with EtOAc. The filtrate was concentrated under reduced pressure to afford a colorless oil which was used immediately without further purification.

(*S*)-2-(Benzyloxy)-2-((2*R*,5*R*,6*R*)-2-methoxy-5,6-dimethyl-4-methylenetetrahydro-2H-pyran-2-yl)acetyl chloride (158)



To a solution of **159** (0.025 g, 0.075 mmol) in CH_2Cl_2 (1.60 mL) was added pyridine (0.31 mL, 0.62 M in CH_2Cl_2, dried over $MgSO_4$) and $SOCl_2$ (0.31 mL, 0.48 M in CH_2Cl_2, dried over $MgSO_4$) at room temperature. The reaction was stirred for 20 minutes then concentrated under reduced pressure. The material was used immediately without further purification.



To a solution of **158** (0.026 g, 0.075 mmol) in CH_2Cl_2 (0.75 mL) cooled to 0 °C was added DMAP (0.009 g, 0.075 mmol), and the reaction was stirred for 5 minutes. Afterwards, a solution of **93** (0.012 g, 0.037 mmol) in CH_2Cl_2 (0.37 mL) was added to the reaction mixture. The reaction was stirred at 0 °C for 5 minutes and then warmed to room temperature. After 4 hours the reaction mixture was directly purified via PTLC (50% EtOAc in hexanes) followed by a second prep plate, (20% EtOAc in benzene, 2 elutions) to afford the desired products (**156** and **52**) as a 1:1 mixture of separable products (0.008 g, 40%).

epi-C_7-*O*-Bz-theopederin D **156** (*Fastest eluting*): ^{1}H NMR (500 MHz, C_6D_6) 8.29-8.28 (m, 2 H), 7.07-6.97 (m, 3 H), 5.93 (s, 1 H), 5.53 (app. t, J = 9.2, 9.4 Hz, 1 H), 4.85 (app t, J = 1.9, 3.7

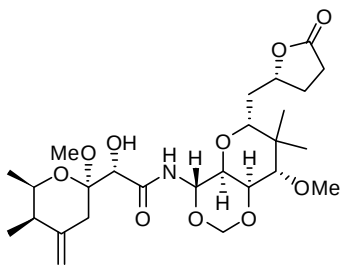
Hz, 1 H), 4.82 (app t, *J* = 2.0, 3.9 Hz, 1 H), 4.72 (d, *J* = 6.6 Hz, 1 H), 4.26-4.22 (m, 1 H), 4.22 (d, *J* = 6.6 Hz, 1 H), 3.97 (qd, *J* = 2.8, 6.5 Hz, 1 H), 3.44 (s, 3 H), 3.31-3.27 (m, 1 H), 3.22 (s, 3 H), 3.1 (dd, *J* = 2.6, 10.3 Hz, 1 H), 3.04-3.02 (m, 1 H), 2.93-2.75 (m, 4 H), 2.56 (d, *J* = 9.5 Hz, 1 H), 2.45-2.37 (m, 1 H), 2.03 (qd, *J* = 2.7, 7 Hz, 1 H), 1.79-1.74 (m, 2 H), 1.43-1.37 (m, 2 H), 1.20 (d, *J* = 6.5 Hz, 3 H), 1.18 (d, *J* = 7.2 Hz, 3 H), 0.84 (s, 3 H), 0.66 (s, 3 H); ^{13}C NMR (125 MHz, C_6D_6) δ 177.5, 167.6, 166.0, 146.1, 133.3, 110.6, 99.7, 92.3, 85.9, 80.9, 80.1, 78.6, 77.1, 76.7, 72.5, 70.0, 61.6, 48.0, 41.9, 41.3, 34.5, 32.0, 30.2, 29.0, 28.0, 22.6, 17.8, 14.5, 12.2, 1.4; IR (neat): 3608, 3359, 2960, 2923, 2852, 1725, 1659, 1632, 1465, 1412, 1378, 1261, 1094, 1021 cm^{-1}; HRMS (ES) *m/z* calcd. for $C_{33}H_{45}NO_{11}Na$ [M + Na] 654.2890 found 654.2870; $[\alpha]^{23}_D$ +9.8 (*c* 0.1, $CHCl_3$).

C_7-*O*-Bz-theopederin D **52** (*faster eluting*): ^{1}H NMR (600 MHz, C_6D_6) δ 8.25 (dd, *J* = 1.5, 8.1 Hz, 2 H), 7.09-7.00 (m, 3 H), 5.84 (s, 1 H), 5.76 (app t, 9.6 Hz, 1 H), 4.82 (br s, 1 H), 4.79 (br s, 1 H), 4.58 (d, *J* = 6.6 Hz, 1 H), 4.56-4.52 (m, 1 H), 4.50 (d, *J* = 6.6 Hz, 1 H), 4.22 (dd, *J* = 6.6, 10.2 Hz, 1 H), 3.81 (qd, *J* = 3.0, 6.0 Hz, 1 H), 3.65 (dd, *J* = 7.2, 10.2 Hz, 1 H), 3.26 (s, 3 H), 3.16 (d, *J* = 10.2 Hz, 1H), 2.93 (d, *J* = 10.2 Hz, 1 H), 2.92 (s, 3 H), 2.77 (br d, *J* = 13.8 Hz, 1 H), 2.71 (d, *J* = 13.8 Hz, 1 H), 2.45-2.37 (m, 1 H), 2.33 (dt, *J* = 11.4, 16.8 Hz, 1 H), 2.14 (ddd, *J* = 3.0, 9.0, 12.6 Hz, 1 H), 1.93-1.85 (m, 1 H), 1.90 (qd, *J* = 2.4, 7.2 Hz, 1 H), 1.21-1.17 (m, 2 H), 1.04 (d, *J* = 7.2 Hz, 3 H), 0.89 (d, *J* = 6.6 Hz, 3 H), 0.75 (s, 3 H), 0.68 (s, 3 H); ^{13}C NMR (150 MHz, C_6D_6) δ 175.9, 167.0, 165.4, 144.9, 133.6, 130.1, 129.8, 127.6, 111.5, 99.8, 86.6, 78.7, 78.0, 75.2, 74.9, 74.1, 73.0, 71.9, 69.9, 61.3, 48.4, 41.4, 41.2, 45.6, 34.6, 28.8, 28.2, , 22.8, 17.6, 12.2; IR (neat): 3354, 2962, 2924, 2854, 2360, 2339, 1770, 1727, 1526, 1453, 1413, 1261 cm^{-1}; HRMS

(ES) *m/z* calcd. for $C_{33}H_{45}NO_{11}Na$ [M+Na] 654.2890 found 654.2877; $[\alpha]^{22}_D$ +29.0 (*c* 0.1, EtOAc); literature[45]: $[\alpha]^{23}_D$ +54.0 (*c* 0.5, EtOAc).

C_7-*O*-Bz-*epi*-C10-theopederin D (**157**) (*slowest eluting*): ^{1}H NMR (300 MHz, C_6D_6) δ 8.36-8.33 (m, 2 H), 8.13 (d, *J* = 9.3 Hz, 1 H), 7.08-6.97 (m, 3 H), 6.20 (s, 1 H), 5.23 (dd, *J* = 1.8, 9.3 Hz, 1 H), 4.87 (br t, *J* = 1.8 Hz, 1 H), 4.84 (d, *J* = 6.3 Hz, 1 H), 4.83 (br t, *J* = 1.8 Hz, 1 H), 4.32 (d, *J* = 6.6 Hz, 1 H), 4.31-4.27 (m, 1 H), 4.11-4.00 (m, 1 H), 4.00 (qd, *J* = 2.7, 6.6 Hz, 1 H), 3.42 (dd, *J* = 2.7, 11.4 Hz, 1 H), 3.17 (s, 3 H), 3.14 (br s , 1 H), 3.05 (br d, *J* = 14.7 Hz, 1 H), 2.90 (s, 3 H), 2.84 (d, *J* = 14.1 Hz, 1 H), 2.66 (d, *J* = 1.8 Hz, 1 H), 2.30 (ddd, *J* = 3.6, 7.5, 15.0 Hz, 2 H), 2.09 (qd, *J* = 2.7, 7.2 Hz, 1 H), 2.00 (d, *J* = 10.2 Hz, 1 H), 1.64-1.54 (m, 1 H) 1.98 (dd, *J* = 1.5, 9.6 Hz, 1 H), 1.39-1.15 (m, 2 H), 1.31-1.29 (m, 6 H), 1.11 (d, *J* = 6.3 Hz, 3 H), 0.76 (s, 3 H); ^{13}C NMR (75 MHz) δ 175.9, 167.3, 166.3, 146.9, 133.4, 130.8, 110.8, 100.3, 91.7, 84.1, 80.2, 79.9, 78.2, 73.2, 72.4, 70.2, 61.7, 59.0, 48.5, 42.5, 36.9, 35.1, 33.4, 32.3, 29.0, 28.5, 28.0, 23.4, 18.5, 14.7, 14.6, 12.6, 1.6; IR (neat): 3608, 3593, 3376, 2924, 1774, 1730, 1703, 1522, 1453, 1270, 1148, 1091, 1027 cm^{-1}; HRMS (ES) *m/z* calcd. for $C_{33}H_{45}NO_{11}Na$ [M+^{23}Na] 654.2890 found 654.2901; $[\alpha]^{23}_D$ +24.5 (*c* 0.22, $CHCl_3$).

Theopederin D (1)



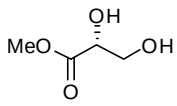
To a solution of **52** (2.0 mg, 0.004 mmol) in MeOH (0.500 mL) at room temperature was added K_2CO_3 (1.0 mg, 0.006 mmol). After 10 minutes, the reaction was complete by TLC analysis. H_2O (1.00 mL) was added and the reaction mixture was extracted with EtOAc (3 x 3 mL). The organic layers were combined, dried (Na_2SO_4), filtered and concentrated under

reduced pressure. The crude residue was purified via flash column chromatography (50% EtOAc in hexanes to 100% EtOAc in hexanes). This material was purified using PTLC (70% EtOAc in hexanes), followed by running an additional prep plate (70% EtOAc in acetone) to afford the desired product as well as an inseparable impurity (1.1 mg, 66%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (d, *J* = 9.6 Hz, 1 H), 5.83 (dd, *J* = 9.3, 9.6 Hz, 1 H), 5.15 (d, *J* = 6.9 Hz, 1 H), 4.89 (d, *J* = 6.9 Hz, 1 H), 4.88 (br s, 1 H), 4.76 (br s, 1 H), 4.50-4.41 (m, 1 H), 4.29 (d, *J* = 3.3 Hz, 1 H), 4.22 (dd, *J* = 6.6, 9.9 Hz, 1 H), 4.16 (d, *J* = 3.3 H, 1 H), 4.04 (qd, *J* = 2.7, 6.3 Hz, 1 H), 3.83 (dd, *J* = 6.3, 9.0 Hz, 1 H), 3.58 (s, 3 H), 3.45 (d, *J* = 9.6 Hz, 1 H), 3.43 (d, *J* = 9.3 Hz, 1 H), 3.32 (s, 3 H), 2.53-2.49 (m, 1 H), 2.46-2.33 (m, 2 H) 2.36 (d, *J* = 13.8 Hz, 1 H); 2.28-2.18 (m, 2 H), 2.05-1.95 (m, 1 H), 1.80-1.60 (m, 2 H), 1.21 (d, *J* = 6.3 Hz, 3 H), 1.03 (s, 3 H), 1.02 (d, *J* = 7.2 Hz, 3 H), 0.89 (s, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.5, 172.3, 145.0, 111.0, 99.8, 86.5, 79.5, 76.1, 74.0, 73.7, 71.6, 69.5, 61.7, 48.5, 41.3, 35.0, 33.3, 28.7, 28.0, 22.7, 18.1, 14.1, 12.0; IR (neat): 3541, 3164, 3060, 2999, 2943, 2292, 2252, 1735, 1627, 1442, 1375, 1270, 1039, 919 cm^{-1}; HRMS (ES) *m/z* calcd. for $C_{26}H_{41}NO_{10}Na$ [M + Na] 550.2528 found 550.2655. $[\alpha]^{21}_{D}$ +7.56 (*c* 0.14, $CHCl_3$); literature[1] $[\alpha]_D$ +80 (*c* 0.04, $CHCl_3$) (*no temperature was reported for the optical rotation*).

APPENDIX B

EXPERIMENTAL: SYNTHESIS AND DETERMINATION OF THE RELATIVE AND ABSOLUTE CONFIGURATION OF PSYMBERIC ACID

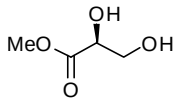
(*R*)-2,3-Dihydroxypropionic acid methyl ester (13)



To a solution of D-serine (25.0 g, 238 mmol) in H_2O (56.0 mL) cooled to 0 °C was added aqueous H_2SO_4 (3.0 M, 126 mL) followed by slow addition of aqueous $NaNO_2$ (6.0 M, 42.0 mL). The reaction was warmed to room temperature and stirred for 5 hours, then subsequently cooled to 0 °C whereupon aqueous H_2SO_4 (3.0 M, 63 mL) and aqueous $NaNO_2$ (6.0 M, 42.0 mL) were added again. The solution was warmed to room temperature and stirred for 2 days after which H_2O was distilled away from the reaction mixture (ca. 250 mL) under water aspirator pressure. The remaining reaction residue was cooled to 0 °C and a solution of NaOH (10.5 g, 263 mol) in H_2O (25.0 mL) was added followed by addition of acetone (25.0 mL) and MeOH (75 mL). The resulting solids were removed via filtration through a frit of Celite, and the filtrate was concentrated under reduced pressure. The above process

(aqueous NaOH addition followed by acetone/MeOH addition, filtration, and concentration) was repeated an additional 3 times. To the partially solvent free residue was added toluene (50.0 mL) and the material was concentrated under reduced pressure. This process was repeated three times. To the crude residue was added MeOH (125 mL) and $CH(OMe)_3$ (25 mL) and the reaction mixture was heated to 60 °C. After 30 minutes, the reaction was cooled to 0 °C and the solution pH was neutralized by addition of solid $NaOCH_3$. The solids were removed via filtration through a frit of Celite, and the filtrate was concentrated under reduced pressure to afford a crude residue which was purified by flash chromatography (20% EtOAc in hexanes to 50% EtOAc in hexanes) to afford the desired product (11.4 g, 41% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.29 (t, J = 3.6 Hz, 1 H), 3.95-3.81 (m, 2 H), 3.84 (s, 3 H); $[\alpha]^{23}_D$ −10.4 (*c* 0.97, $CHCl_3$). *This compound is consistent with literature values.*[113]

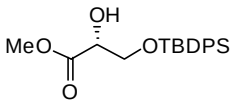
(*S*)-2,3-Dihydroxypropionic acid methyl ester (*ent*-13)



Prepared according to the procedure for the enantiomer.

$[\alpha]^{23}_D$ +8.8 (*c* 0.97, $CHCl_3$).

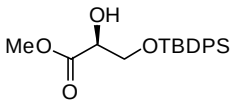
(*R*)-3-(*tert*-Butyldiphenylsilanoxy)-2-hydroxypropionic acid methyl ester (36)



To a solution of (*R*)-methyl 2,3-dihydroxypropanoate (5.00 g, 41.7 mmol) in CH_2Cl_2 (208 mL) at room temperature was added imidazole (5.67 g, 83.3 mmol). After complete dissolution of the solids, the reaction mixture was cooled to −42 °C and *tert*-butyldiphenylsilylchloride (13.7 g, 50.0 mmol) was added. The reaction was stirred at −42 °C for 1 hour then satd. NH_4Cl (aq) (50 mL) was added and the solution was warmed to room temperature. The reaction was extracted with CH_2Cl_2 (3 x 50 mL) and the combined organic

layers were dried ($MgSO_4$) and filtered. The combined organic layers were concentrated under reduced pressure and the crude residue was purified by column chromatography (5% to 20% EtOAc in hexanes) to afford the desired product as a colorless oil (11.0 g, 74% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69-7.62 (m, 4 H), 7.45-7.38 (m, 6 H), 4.27-4.25 (m, 1 H), 3.80 (s, 3 H), 3.14 (d, *J* = 8.1 Hz, 1 H), 1.04 (s, 9 H); $[\alpha]^{23}_D$ –23.9 (*c* 1.5, $CHCl_3$). *The product is consistent with literature values.*[114]

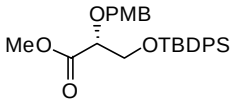
(*S*)-(3-(*tert*-Butyldiphenylsilanoxy)-2-hydroxypropionic acid methyl ester (*ent*-36)



This material was prepared from (*S*)-(+)-methyl 2,3-dihydroxypropanoate through the procedure that was reported for its enantiomer.

$[\alpha]^{23}_D$ +22.8 (*c* 1.91, $CHCl_3$).

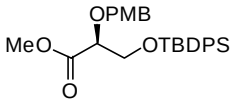
(*R*)-3-(*tert*-Butyldiphenylsilanoxy)-2-(4-methoxybenzyloxy)propionic acid methyl ester (14)



To a stirring solution of *p*-methoxybenzyl trichloroacetimidate (5.26 g, 18.6 mmol) in cyclohexane (30 mL) at room temperature was added a solution of the appropriate secondary alcohol (2.22 g, 6.20 mmol) in CH_2Cl_2 (7.5 mL). The mixture was cooled to 0 °C and BF_3·THF (6.8 μL, 0.062 mmol) was added. An orange/white solid immediately precipitated. The mixture was warmed to room temperature, diluted with CH_2Cl_2 and cyclohexane (1:2, 50 mL), and poured into satd. $NaHCO_3$ (aq) (50 mL). The solution was extracted with a CH_2Cl_2/cyclohexane mixture (1:2, 3 x 20 mL), and the combined organic layers were washed with brine (30 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure to an oily yellow semi-solid. The residue was purified by flash column chromatography (10% EtOAc in hexanes) to afford the desired product as a colorless oil (2.27 g, 76% yield): ^{1}H

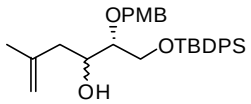
NMR (300 MHz, $CDCl_3$) δ 7.67-7.65 (m, 4 H), 7.43-7.34 (m, 6 H), 7.29-7.26 (m, 2 H), 6.88-6.85 (m, 2 H), 4.67 (d, *J* = 11.5 Hz, 1 H), 4.47 (d, *J* = 11.5 Hz, 1 H) 4.11 (app. t, *J* = 5.1 Hz, 1 H), 3.92 (d, *J* = 5.3 Hz, 2 H), 3.81 (s, 3 H), 3.75 (s, 3 H), 1.03 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 159.3, 135.7, 135.6, 135.5, 135.4, 133.1, 133.0, 129.5, 129.4, 127.6, 113.7, 113.7, 78.8, 72.0, 64.7, 55.1, 51.7, 26.6, 19.2; IR (neat): 1818, 1740, 1423, 1363, 1249, 1202, 1143, 981, 947, 702 cm^{-1}; HRMS(ES) *m/z* calcd. for $C_{28}H_{34}O_5NaSi$ [M + Na] 501.2073, found 501.2052; $[\alpha]^{25}{}_D$ +18.8 (*c* 1.3, $CHCl_3$).

(*S*)-3-(*tert*-Butyldiphenylsilanoxy)-2-(4-methoxybenzyloxy)propionic acid methyl ester (*ent*-*14*)



This material was prepared from the appropriate secondary alcohol through the procedure that was reported for its enantiomer. $[\alpha]^{25}{}_D$ −20.2 (*c* 1.30, $CHCl_3$).

1-(*tert*-Butyl-diphenylsilanoxy)-2-(4-methoxybenzyloxy)-5-methylhex-5-en-3-ol (15)



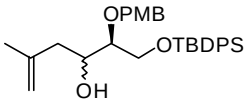
Method A: To a solution of **14** (2.27 g, 4.74 mmol) in CH_2Cl_2 (32 mL) at –78 °C was added DIBAL-H (6.16 mL, 1.00 M in hexanes). The solution was stirred for 1 hour at –78 °C then methallylmagnesium chloride (23.7 mL, 0.80 M in THF) was slowly added. The temperature was held at –78 °C for 15 minutes and then warmed to 0 °C. After 30 minutes H_2O (20 mL) was added at 0 °C, and the reaction mixture was warmed to room temperature. 10% HCl (aq) (20 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (4 x 30 mL). The organic layers were combined, washed with brine (40 mL), dried ($MgSO_4$), and filtered. After concentration under reduced pressure, the crude residue was

purified by flash column chromatography (10% EtOAc in hexanes) to afford the desired product as a colorless oil in a 1.8:1 (*syn:anti*) diastereomeric mixture (2.19 g, 91% yield over 2 steps): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71-7.67 (m, 4 H), 7.47-7.38 (m, 6 H), 7.18-7.13 (m, 2 H), 6.87-6.83 (m, 2 H), 4.86-4.83 (m, 1 H), 4.78 (s, 0.38 H), 4.72 (s, 0.69 H), 4.61 (d, *J* = 11.2 Hz, 1 H), 4.49 (d, *J* = 11.3, 0.43 H), 4.39 (d, *J* = 11.3 Hz, 0.68 H), 4.0-3.94 (m, 1 H), 3.89-3.74 (m, 6 H), 3.49 (dd, *J* = 5.1, 10.2 Hz, 0.40 H), 3.39 (m, 0.69 H), 2.40-2.39 (m, 0.46 H), 2.38 (s, 0.5 H), 2.34-2.12 (m, 2 H) 1.76 (s, 3 H), 1.07 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.24, 159.2, 142.7, 142.6, 135.6, 135.5, 133.3, 133.2, 133.1, 130.7, 130.4, 129.7, 129.6, 129.4, 129.3, 129.26, 127.7, 113.7, 112.9, 112.8, 81.4, 80.4, 72.5, 72.3, 69.7, 68.9, 63.8, 63.2, 55.1, 42.1, 41.2, 26.8, 22.4, 22.3, 19.1; IR (neat): 2875, 2953, 2860, 1612, 1513, 1470, 1462, 1391, 1300, 1250, 1120, 1106, 1079, 1038, 824, 705 cm^{-1}; HRMS (ES) *m/z* calcd. for $C_{31}H_{40}O_4NaSi$ [M + Na] 527.2594, found 527.2596; $[\alpha]^{25}{}_D$ −17.5 (*c* 1.30, $CHCl_3$).

Method B: To solution of **14** (0.52 g, 1.1 mmol) in CH_2Cl_2 (7.2 mL) at –78 °C was added DIBAL-H (1.40 mL, 1.00 M in hexanes). The solution was stirred for 1 hour at –78 °C ,then EtOAc (2.0 mL) was added followed by satd. sodium potassium tartrate (aq) (10 mL) at −78 °C and the reaction mixture was allowed to warm to room temperature over 3 hours. The reaction mixture was extracted with CH_2Cl_2 (3 x 8 mL). The organic layers were combined and washed with brine (15 mL), dried (Na_2SO_4), and filtered. The aldehyde was concentrated under reduced pressure and trace solvent removed under high vacuum. The crude material was dissolved in CH_2Cl_2 (4.5 mL) and cooled to −78 °C. Methallyltrimethylsilane (0.28 g, 2.16 mmol) was added to the solution followed by slow addition of BF_3·THF (121 µL, 1.1 mmol). After 1 hour satd. $NaHCO_3$ (aq) (2 mL) was added at −78 °C and the reaction was warmed to room temperature.

The reaction mixture was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), and filtered. The residue was concentrated under reduced pressure and purified by column chromatography (10% EtOAc in hexanes) to afford the desired product as a colorless oil in 1:4 (*syn:anti*) ratio (303 mg, 56% yield over 2 steps).

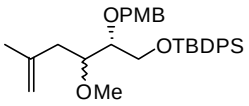
1-(*tert*-Butyl-diphenylsilanoxy)-2-(4-methoxybenzyloxy)-5-methylhex-5-en-3-ol (*ent*-15)



Prepared according to the procedure for the enantiomer.

$[\alpha]^{24}{}_D$ +19.78 (*c* 0.74, $CHCl_3$).

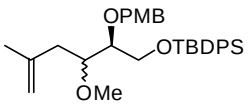
***tert*-Butyl-[3-methoxy-2-(4-methoxybenzyloxy)-5-methylhex-5-enyloxy]-diphenylsilane (16)**



To a mixture of diastereomers of **15** (2.97 g, 5.88 mmol) in CH_2Cl_2 (2.50 mL) was added 2,6-di-*tert*-butylpyridine (1.96 mL, 8.83 mmol) at room temperature. The solution was cooled to 0 °C and methyl triflate was added (1.0 mL, 8.83 mmol). The solution was slowly warmed to room temperature over 12 hours, then H_2O was added (10.0 mL) and the reaction mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with satd. $NaHCO_3$ (aq) (10 mL), brine (10 mL), dried ($MgSO_4$), and filtered. The crude material was concentrated under reduced pressure and purified via flash column chromatography (100% hexanes to 10% EtOAc in hexanes) to afford the desired product as a colorless oil (2.66 g, 87% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70-7.66 (m, 4 H), 7.44-7.36 (m, 6 H), 7.22-7.19 (m, 2 H), 6.85-6.82 (m, 2 H), 4.79-4.78 (m, 1 H), 4.73 (s, 0.48 H), 4.65 (s, 0.61 H), 4.62 (d, *J* = 11.3, 0.75 H), 4.54 (d, *J* = 10.7 Hz, 0.80 H) 4.43 (d, *J* = 11.5 Hz, 0.60 H), 3.90-3.73 (m, 5 H), 3.63-3.56 (m, 1.61 H), 3.53-3.48 (m, 0.79 H) 3.36-3.29 (m, 3 H), 2.34-2.17 (m, 2 H), 1.74 (s, 3 H), 1.07-1.05 (m, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 150.0,

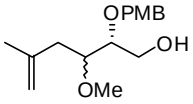
143.2, 142.9, 135.6, 133.6, 133.5, 133.47, 131.0, 130.9, 129.6, 129.5, 129.2, 127.7, 113.6, 112.5, 112.2, 80.3, 79.9, 79.6, 78.7, 77.2, 72.7, 72.3, 63.4, 62.8, 58.3, 58.0, 55.2, 22.2, 38.6, 38.1, 26.9, 22.8, 22.7, 19.2; IR (neat) 3071, 2932, 2858, 1612, 1512, 1248, 1110 cm^{-1}; HRMS (ES) *m/z* calcd. for $C_{32}H_{42}O_4NaSi$ [M + Na] 541.2750, found 541.2774; $[\alpha]^{25}{}_D$ −14.2 (*c* 0.74, $CHCl_3$).

<u>*tert*-Butyl-[3-methoxy-2-(4-methoxybenzyloxy)-5-methylhex-5-enyloxy]-diphenylsilane (*ent*-*16*)</u>



Prepared according to the procedure for the enantiomer. Diastereomeric ratio after column chromatography was 1:1, syn:anti.$[\alpha]^{24}{}_D$ +5.57 (*c* 1.74, $CHCl_3$).

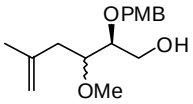
<u>3-Methoxy-2-(4-methoxybenzyloxy)-5-methylhex-5-en-1-ol</u>



To a mixture of diastereomers of **16** (0.28 g, 0.53 mmol) in THF (5.33 mL) was added Bu_4NF (TBAF) (0.21 g) at room temperature. After 3 hours H_2O (5 mL) was added. The solution was extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic layers were dried ($MgSO_4$) and filtered. Concentration of the crude material under reduced pressure, followed by purification via flash column chromatography (30% EtOAc in hexanes) afforded separation of the two diastereomeric products (0.11 g total, 76.2% yield). ***Anti diastereomer* (*17*)** (faster eluting): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28-7.25 (d, *J* = 8.2 Hz, 2 H), 6.90-6.87 (d, *J* = 8.6 Hz, 2 H), 4.82 (s, 1 H), 4.78 (s, 1 H) 4.59 (d, *J* = 11.2 Hz, 1 H), 4.54 (d, *J* = 11.2 Hz, 1 H), 3.80 (s, 3 H), 3.77-3.75 (m, 2 H), 3.58-3.52 (m, 1 H), 3.48-3.44 (m, 4 H), 2.36-2.22 (m, 3 H), 1.76 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.3, 142.5, 130.3, 129.4, 113.8, 112.9, 80.5, 80.2, 71.7, 61.2, 58.6, 55.2, 39.5, 22.8; IR (neat): 3452, 2935, 1612, 1513, 1460, 1513, 1248, 1101,

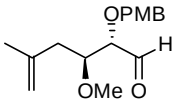
1035 cm^{-1}; HRMS (EI) *m/z* calcd. for $C_{16}H_{24}O_4$ [M^+] 280.1675 found 280.1671; $[\alpha]^{26}{}_D$ +7.6 (*c*, 0.90, $CHCl_3$); ***Syn diastereomer (18)*** (slower eluting): ^1H NMR (300 MHz, $CDCl_3$) δ 7.30-7.26 (d, *J* = 7.4 Hz, 2 H), 6.90-6.87 (d, *J* = 7.4, 2H) 4.80 (s, 1 H), 4.74 (brs, 1 H), 4.59, (s, 2 H) 3.83-3.78 (m, 4 H), 3.67-3.50 (m, 4 H), 3.41 (s, 3 H), 2.35 (dd, *J* = 4.9, 14.3 Hz, 1 H), 2.19 (dd, *J* = 2.19, 14.3 Hz, 1 H) 1.76 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.3, 142.7, 130.4, 129.5, 113.8, 112.6, 80.4, 78.7, 72.4, 61.9, 58.3, 55.2, 37.9, 22.7; IR (neat): 3447, 2934, 1612, 1513, 1461, 1301, 1248, 1088, 1036 cm^{-1}; HRMS (EI) *m/z* calc. for $C_{16}H_{24}O_4$ (M+) 280.1674 found 280.1656; $[\alpha]^{24}{}_D$ −6.5 (*c* 1.06, $CHCl_3$).

3-Methoxy-2-(4-methoxybenzyloxy)-5-methylhex-5-en-1-ol



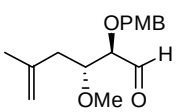
These compounds were prepared in accord with the procedure for their enantiomers. ***Anti diastereomers* (*ent*-17)***:* $[\alpha]^{24}{}_D$ −8.8° (*c* 1.15, $CHCl_3$); ***Syn diastereomers* (*ent*-18)***:* $[\alpha]^{24}{}_D$ +5.8 (*c* 1.29, $CHCl_3$).

3-Methoxy-2-(4-methoxybenzyloxy)-5-methylhex-5-enal (19)



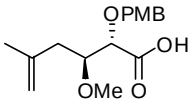
To a solution of **17** (0.15 g, 0.54 mmol) in DMSO (1.1 mL) at room temperature was added Et_3N (0.45 mL, 3.2 mmol) followed by a solution of sulfur trioxide pyridine complex (0.26 g, 1.6 mmol) in DMSO (1.1 mL). After 30 minutes H_2O (2 mL) was added, and the reaction mixture was extracted with Et_2O (3 x 4 mL). The combined organic layers were washed with water (4 mL) and brine (4 mL), dried ($MgSO_4$), and filtered. The material was concentrated under reduced pressure and used without further purification.

3-Methoxy-2-(4-methoxybenzyloxy)-5-methylhex-5-enal (*ent*-19)



This compound was prepared according to the procedure for its enantiomer.

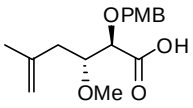
3-Methoxy-2-(4-methoxybenzyloxy)-5-methylhex-5-enoic acid



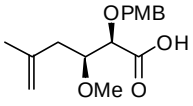
To a solution of crude aldehyde **19** (0.15 mg, 0.54 mmol) in *tert*-butanol (8.5 mL) was added 2-methyl-2-butene (7.2 mL) at room temperature. A solution of 80% $NaClO_2$ (1.35 g, 14.9 mmol) and $NaH_2PO_4 \cdot H_2O$ (1.08 g, 7.80 mmol) in water (8.5 mL) was added and the colorless reaction slowly turned lime green. After 30 minutes the reaction was diluted with water (10 mL) and EtOAc (10 mL), and the organic and aqueous phases separated. The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organic layers were washed with water (20 mL), 10% aq. w/v citric acid (20 ml), and brine (10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to a crude yellow oil. The material was purified via flash chromatography using a short column of silica (20% EtOAc in hexane to 100% EtOAc) to afford the desired product as a clear oil (0.12 g, 77% yield): ***Anti isomer* (*21*):** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32-7.29 (m, 2 H), 6.91-6.84 (m, 2 H), 4.83 (s, 1 H), 4.79 (s, 1 H), 4.71 (d, *J* = 11.4 Hz, 1 H), 4.52 (d, *J* = 11.4 Hz, 1 H), 4.15 (d, *J* = 3.2 Hz, 1 H), 3.81 (s, 3 H), 3.78-3.72 (m, 1 H), 3.41 (s, 3 H), 2.42 (dd, *J* = 7.8, 14.6 Hz,1 H), 2.30 (dd, *J* = 5.4, 14.6 Hz), 1.75 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.9, 159.6, 141.7, 129.7, 128.9, 113.9, 113.3, 80.8, 80.0, 72.6, 58.3, 55.2, 38.5, 22.6; IR (neat): br 2934, 1728, 1613, 1514, 1302, 1250, 1174, 1109 cm^{-1}; HRMS (EI) *m/z* calcd. for $C_{16}H_{22}O_5$ [M^+] 294.1467, found 294.1452; $[\alpha]^{27}{}_D$ −25.9 (*c* 1.08, $CHCl_3$); ***Syn isomer (22):*** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.27 (m, 2 H), 6.90-6.87 (m, 2 H), 4.81 (s, 1 H), 4.71 (d, *J* = 11.2 Hz, 1 H), 4.67 (s, 1 H), 4.43 (d, *J* = 11.2 Hz, 1 H), 4.00 (d, *J* = 2.6 Hz, 1 H), 3.81-3.77 (m, 4 H), 3.39 (s, 3 H), 2.38 (dd, *J* = 6.8, 14.0 Hz, 1 H), 2.33 (dd, *J* = 7.7, 14.2 Hz, 1 H), 1.75 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.3, 159.5, 141.5, 130.1, 128.7, 113.8, 113.6, 80.1, 77.9, 73.1, 58.3, 55.2, 37.7, 22.6; IR (neat): br 2937, 1729, 1612, 1249, 1177,

1093, 1033 cm^{-1}; HRMS (EI) *m/z* calcd. for $C_{16}H_{22}O_5$ [M^+] 294.1467, found 294.1467; $[\alpha]^{27}{}_D$ −20.8 (*c* 0.85, $CHCl_3$).

3-Methoxy-2-(4-methoxybenzyloxy)-5-methylhex-5-enoic acid

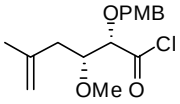


Anti isomer (ent-*21*): *This compound was prepared according to the procedure for its enantiomer.* $[\alpha]^{27}{}_D$ +23.4 (*c* 0.93, $CHCl_3$).



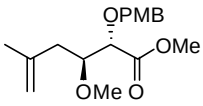
Syn Isomer (ent-*22*): *This compound was prepared according to the procedure for its enantiomer.* $[\alpha]^{27}{}_D$ +26.8 (*c* 1.10, $CHCl_3$).

3-Methoxy-2-(4-methoxybenzyloxy)-5-methylhex-5-enoyl chloride (23)



To a solution of **22** (0.108 g, 0.367 mmol) in CH_2Cl_2 (1.5 mL) at 0 °C was added $SOCl_2$ (54 µL, 0.734 mmol) followed by addition of Et_3N (143 µL, 1.03 mmol). The solution was warmed to room temperature. After 2 hours the reaction was concentrated under reduced pressure, diluted with ether (5 mL) and filtered over Na_2SO_4. The material was concentrated under reduced pressure, and used crude in subsequent reactions.

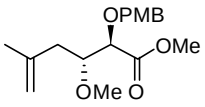
3-Methoxy-2-(4-methoxy-benzyloxy)-5-methylhex-5-enoic acid methyl ester



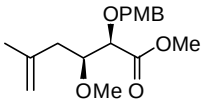
To a solution of **21** (0.122 g, 0.41 mmol) in CH_2Cl_2 (1.50 mL) at 0 °C was added $SOCl_2$ (60.4 µL, 0.83 mmol) followed by addition of Et_3N (162 µL, 1.16 mmol) and the solution was warmed to room temperature. After 2 hours the reaction was cooled to 0 °C and anhydrous MeOH (5 mL) was slowly added. The reaction mixture was concentrated under reduced pressure and purified via flash chromatography (10% to 30% EtOAc in hexanes) to afford the desired product as a colorless oil (70 mg g, 54% yield): ***Anti isomer* (37):** ^{1}H NMR

(300 MHz, $CDCl_3$) δ 7.29 (d, *J* = 9.8 Hz, 2 H), 6.88 (d, *J* = 8.7 Hz, 2 H), 4.81 (s, 1 H), 4.76 (s, 1 H), 4.66 (d, *J* = 11.4 Hz, 1 H), 4.41 (d, *J* = 11.5 Hz), 4.05 (d, *J* = 4.3 Hz), 3.81 (s, 3 H), 3.77 (s, 3 H), 3.66 (m, 1 H), 3.35 (s, 3 H), 2.35-2.28 (m, 2 H), 1.75 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5, 159.4, 142.1, 129.7, 129.3, 113.7, 112.9, 80.7, 78.9, 72.2, 58.1, 55.2, 51.8, 38.9, 22.7; IR (neat): 2935, 1749, 1613, 1514, 1439, 1249, 1173, 1108, 1034 cm^{-1}; HRMS (ES) *m/z* calcd. for $C_{17}H_{24}O_5Na$ [M + Na] 331.1521, found 331.1515; $[\alpha]^{29}{}_D$ −57.0 (*c* 0.73, $CHCl_3$); ***Syn isomer* (32):** ^1H NMR (300 MHz, $CDCl_3$) δ 7.30-7.28 (m, 2 H), 6.90-6.85 (m, 2 H), 4.78 (s, 1 H), 4.74 (d, *J* = 11.3 Hz, 1 H), 4.66 (s, 1 H), 4.35 (d, *J* = 11.3 Hz, 1 H), 3.99 (d, *J* = 3.3 Hz, 1 H), 3.81 (s, 3 H), 3.78-3.73 (m, 4 H), 3.37 (s, 3 H), 2.31 (app. d, 2 H), 1.75 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 159.4, 141.9, 129.9, 129.4, 113.7, 113.2, 80.2, 78.7, 72.7, 58.2, 55.3, 51.9, 38.0, 31.6, 22.7, 14.2; IR (neat): 2951, 1752, 1613, 1438, 1250, 1174, 1097, 1034 cm^{-1}; HRMS (ES) *m/z* calcd. for $C_{17}H_{24}O_5Na$ [M + Na] 331.1521, found 331.1512; $[\alpha]^{29}{}_D$ −38.4 (*c* 0.59, $CHCl_3$).

3-Methoxy-2-(4-methoxy-benzyloxy)-5-methylhex-5-enoic acid methyl ester

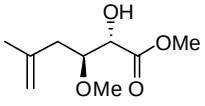


Anti isomer (ent-37): $[\alpha]^{27}{}_D$ +45.9 (*c* 0.63, $CHCl_3$).



Syn isomer (ent-32): $[\alpha]^{27}{}_D$ +41.5 (*c* 1.40, $CHCl_3$).

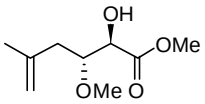
2-Hydroxy-3-methoxy-5-methylhex-5-enoic acid methyl ester



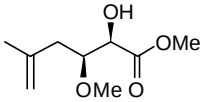
To a solution of **37** (70 m g, 0.22 mmol) in acetonitrile (4 mL) and water (400 μL) was added ceric ammonium nitrate (0.39 g, 0.72 mmol) at room temperature. After 1 hour the reaction mixture was concentrated by *careful evaporation*, and

purified via flash chromatography (10% to 40% Et_2O in pentane) to afford the desired product as a light yellow oil (0.025 mg, 60% yield): ***Anti isomer* (38)**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.85 (s, 1 H), 4.80 (s, 1 H), 4.40 (d, *J* = 2.5 Hz, 1 H), 3.82 (s, 3 H), 3.70-3.66 (m, 1 H), 3.45 (s, 3 H) 3.24-3 (br s, 1 H), 2.37 (dd, *J* = 7.6, 14.5 Hz, 1 H), 2.22 (dd, *J* = 6.2, 14.4 Hz, 1 H), 1.78 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9, 141.7, 113.3, 81.4, 71.9, 58.2, 52.5, 37.9, 22.6; IR (neat): 3424, 3020, 2400, 1736, 1440, 1216, 1107, 929, 756 cm^{-1}; HRMS (EI) *m/z* calcd. for $C_9H_{16}O_4$ (M+) 188.1048, found 188.1043; $[\alpha]^{29}_D$ +26.6 (*c*, 0.37, $CHCl_3$); ***Syn isomer* (29):** ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.89 (s, 1 H), 4.85 (s, 1 H), 4.21 (s, 1 H), 3.85-3.75 (m, 4 H), 3.38 (s, 3 H), 2.46-2.28 (m, 2 H), 1.8 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.9, 141.4, 113.8, 80.3, 71.5, 58.0, 52.4, 37.9, 22.7; IR (neat): 3434, 2953, 1744, 1648, 1440, 1281, 1092; HRMS (EI) *m/z* calcd. for $C_8H_{13}O_4$ [M-CH_3] 173.0813, found 173.0813; $[\alpha]^{29}_D$ +13.1 (*c* 0.19, $CHCl_3$).

2-Hydroxy-3-methoxy-5-methylhex-5-enoic acid methyl ester

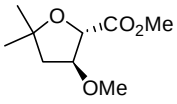


Anti Isomer (ent-38): $[\alpha]^{28}_D$ −30.5 (*c* 0.71, $CHCl_3$).



Syn Isomer (ent-29): $[\alpha]^{29}_D$ −13.0 (*c* 1.13, $CHCl_3$).

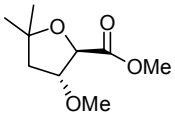
3-Methoxy-5,5-dimethyltetrahydrofuran-2-carboxylic acid methyl ester



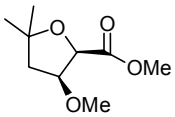
To **38** (33 mg, 0.18 mmol) was added a H_2SO_4 in MeOH (0.1 M, 1 mL) at room temperature. The reaction mixture was heated to 60 °C and stirred for 12 hours. $CaCO_3$ (50 mg) was added and the reaction mixture was filtered to remove the solid. After *careful evaporation* of solvent, the desired product was obtained as a colorless oil in quantitative yield: ***Anti isomer* (34):** ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.53 (d, *J* = 2.9 Hz), 4.12 (app. q, 1 H),

3.78 (s, 3 H), 3.38 (s, 3 H), 2.02-1.90 (m, 2 H), 1.38 (s, 3 H), 1.37 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.5, 85.9, 83.7, 82.3, 57.3, 52.2, 43.8, 29.1, 28.3; IR (neat): 2916, 2848, 1755, 1620, 1439, 1366, 1260, 1107; HRMS: (EI) *m/z* calcd. for $C_8H_{13}O_4$ [M-CH_3] 173.0813, found 173.0802; $[\alpha]^{29}_D$ +2.5 (*c*, 0.13, $CHCl_3$); ***Syn isomer* (31) *prepared from* 29:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.64 (d, *J* = 5.4 Hz, 1 H), 4.25-4.20 (m, 1H), 3.78 (s, 3 H), 3.32 (s, 3 H), 2.05 (dd, *J* = 3.9, 13.2 Hz, 1 H), 1.93 (dd, *J* = 5.8, 13.1 Hz, 1 H), 1.47 (s, 3 H), 1.26 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 83.4, 82.5, 80.5, 57.6, 51.9, 42.8, 28.9, 29.0; IR (neat): 2926, 2850, 1754, 1439, 1367, 1197, 1136, 1098; HRMS (EI) *m/z* calcd. for $C_8H_{13}O_4$ [M-CH_3] 173.0813, found 173.0819; $[\alpha]^{29}_D$ −7.7 (*c* 0.29, $CHCl_3$).

3-Methoxy-5,5-dimethyltetrahydrofuran-2-carboxylic acid methyl ester

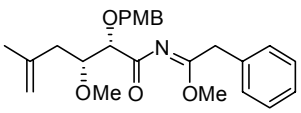


Anti isomer (33, prepared from ent-38): $[\alpha]^{29}_D$ −9.2 (*c* 0.26, $CHCl_3$).



Syn isomer (35, prepared from ent-29): $[\alpha]^{29}_D$ +10.5 (*c* 0.40, $CHCl_3$).

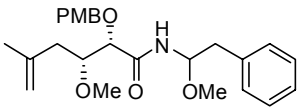
3-Methoxy-2-(4-methoxybenzyloxy)-5-methylhex-5-enoic acid (1-methoxy-2-phenylethylidene)amide (25)



To a solution of **24** (methyl imidate) (56 mg, 0.37 mmol) in CH_2Cl_2 (2 mL) at 0 °C was added Et_3N (208 μL, 1.50 mmol) followed by a solution of crude **23** (0.12 g, 0.37 mmol) in CH_2Cl_2 (2 mL). The reaction was stirred at 0 °C for 1 hour then warmed to room temperature for 3 hours, after which the reaction mixture was

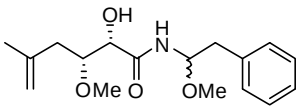
concentrated under reduced pressure, diluted with ether, and filtered over Na_2SO_4. Concentration under reduced pressure afforded a brown oil which was used crude without further purification.

3-Methoxy-2-(4-methoxybenzyloxy)-5-methylhex-5-enoic acid (1-methoxy-2-phenylethyl)amide (26)



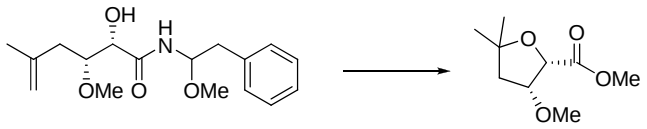
To a solution of crude **25** (0.16 g, 0.374 mmol) in EtOH (5 mL) at 0 °C was added a solution of $NaBH_4$ (350 mg, 9.25 mmol) in EtOH (7 mL). The reaction was stirred for 2 hours at 0 °C then satd. $NaHCO_3$ (aq) was slowly added dropwise. The reaction was warmed to room temperature and the reaction mixture was extracted with CH_2Cl_2 (3 x 5 mL). The organic layers were combined and washed with brine (10 mL), dried (Na_2SO_4) and filtered. The material was concentrated under reduced pressure and purified by flash chromatography (20 to 30% EtOAc in hexanes) to afford the desired product as a slightly yellow oil in a 2:1 ratio of diastereomers (61 mg, 44% over 3 steps): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.11 (m, 8 H), 6.94-6.84 (m, 3 H), 5.51-5.36 (m, 1H), 4.80 (s, 0.72 H), 4.76 (s, 0.33 H), 4.66 (s, 0.81 H), 4.58 (s, 0.33 H), 4.53 (d, *J* = 11.2 Hz, 0.79 H), 4.43 (d, *J* = 11.2 Hz, 0.74 H), 4.33 (d, *J* = 11.3 Hz, 0.31 H), 4.09 (d, *J* = 11.4 Hz, 0.41 H), 3.83-3.65 (m, 4H), 3.35 (d, *J* = 6.1 Hz, 2 H), 3.27 (s, 3 H), 3.18 (s, 2 H) 3.06-2.80 (m, 2 H), 2.34 (dd, *J* = 6.8 Hz, 14.2 Hz, 1 H), 2.21 (dd, *J* = 7.9, 14.0 Hz, 1 H) 1.74-1.72 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 171.8, 159.73, 159.66, 141.8, 141.7, 136.1, 136.0, 130.2, 130.0, 129.5, 129.5, 128.7, 128.6, 128.4, 126.7, 126.6, 114.0, 113.9, 113.5, 81.0, 80.4, 80.2, 80.0, 79.8, 73.9, 73.5, 58.6, 58.3, 55.9, 55.6, 55.2, 41.6, 38.5, 37.9, 22.6; IR (neat): 3400, 3065, 3029, 2933, 2833, 1686, 1612, 1586, 1514, 1454, 1363, 1322, 1302, 1249, 1177, 1089, 1033, 894, 824, 736, 701; HRMS (EI) *m/z* calcd. for $C_{24}H_{30}NO_4$ [M-OCH_3] 396.2175, found 396.2172; $[\alpha]^{29}_D$ −36.4 (*c* 0.79, $CHCl_3$).

2-Hydroxy-3-methoxy-5-methylhex-5-enoic acid (1-methoxy-2-phenylethyl)amide (27)



To a solution of **26** (0.61 g, 0.15 mmol) in CH_2Cl_2 (1 mL) and pH 7 (phosphate) buffer solution (100 μL) was added DDQ (0.38 mg, 0.17 mmol) at room temperature. After 4 hours, the reaction mixture was concentrated under reduced pressure and purified via flash chromatography (20% to 50% EtOAc in hexanes) to afford the desired product as a slightly yellow oil (0.19 g, 39% yield, mixture of diastereomers): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.23 (m, 5 H), 7.06 (d, *J* = 8.9 Hz, 1 H), 5.48-5.39 (m, 1 H), 4.86 (s, 1 H), 4.82 (s, 1 H), 4.0 (br s, 1 H), 3.93-3.84 (m, 1 H), 3.44 (s, 1.15 H), 3.39 (s, 2 H), 3.36 (s, 0.91 H), 3.19 (s, 2 H) 3.14-2.89 (m, 3 H), 2.29 (app. d, *J* = 7.0 Hz, 1 H), 2.22-2.16 (m, 1 H), 1.80 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 172.9, 141.8, 141.7, 135.9, 135.7, 129.7, 129.6, 128.7, 128.4, 126.7, 113.5, 81.1, 80.9, 79.0, 78.8, 71.2, 71.1, 58.2, 56.1, 55.9, 41.6, 41.5, 39.0, 38.2, 22.6; IR (neat): 3403, 2936, 2253, 1678, 1511, 1455, 1379, 1112, 1087, 919, 733, 650 cm^{-1}; HRMS (EI) *m/z* calcd. for $C_{16}H_{21}NO_3$ [M-CH_3OH] 275.1521, found 275.1514; $[\alpha]^{29}_D$ −15.3 (*c* 1.09, $CHCl_3$).

Model System Degradation



Imidate **27** (0.01 g, 0.03 mmol) was diluted in 1 mL of 0.1 M H_2SO_4 in MeOH. The reaction mixture was heated to reflux for 12 hours then cooled to 0 °C. $CaCO_3$ (10 mg) was added and the reaction was filtered. The filtrate was carefully concentrated to afford a yellow residue. The

crude material was purified via flash chromatography to afford the desired product (**31**) as a colorless oil (0.002 g, 34%).

Psymberin Degradation

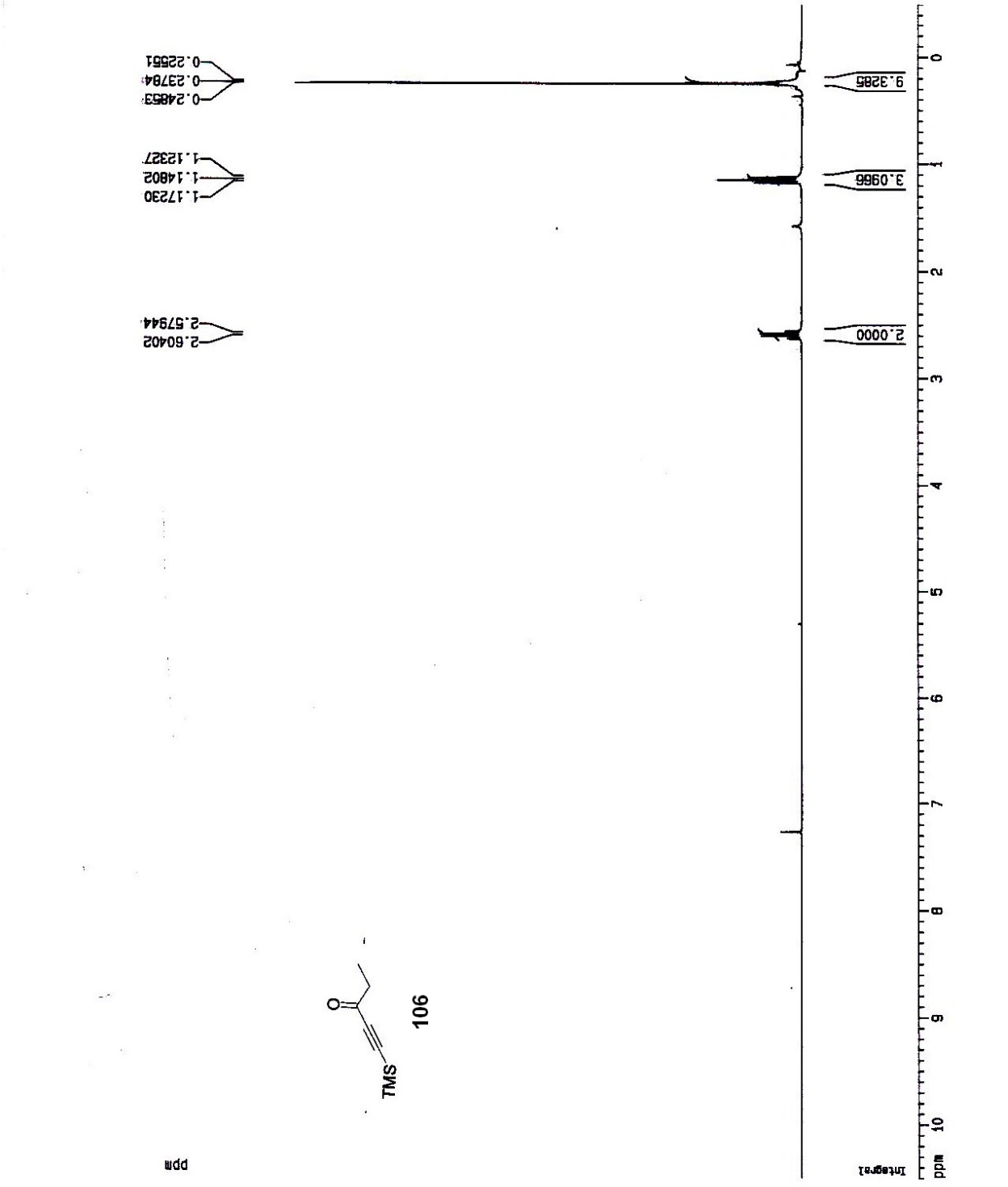
To a sample of psymberin (0.2 mg) in MeOH (250 μL) was added a solution of H_2SO_4 (5.5 μL) in MeOH (750 μL). The reaction mixture was heated at 60 °C for 12 hours in a sealed tube. After 12 hours $CaCO_3$ was added, and the contents of the sealed tube were transferred via syringe into a 3 mL GC vial. The solvent was removed via *careful air evaporation.* The sealed tube as well as the syringe were washed copiously with ether (4 times) and the washings were transferred to the GC vial where the solvent was again carefully evaporated.

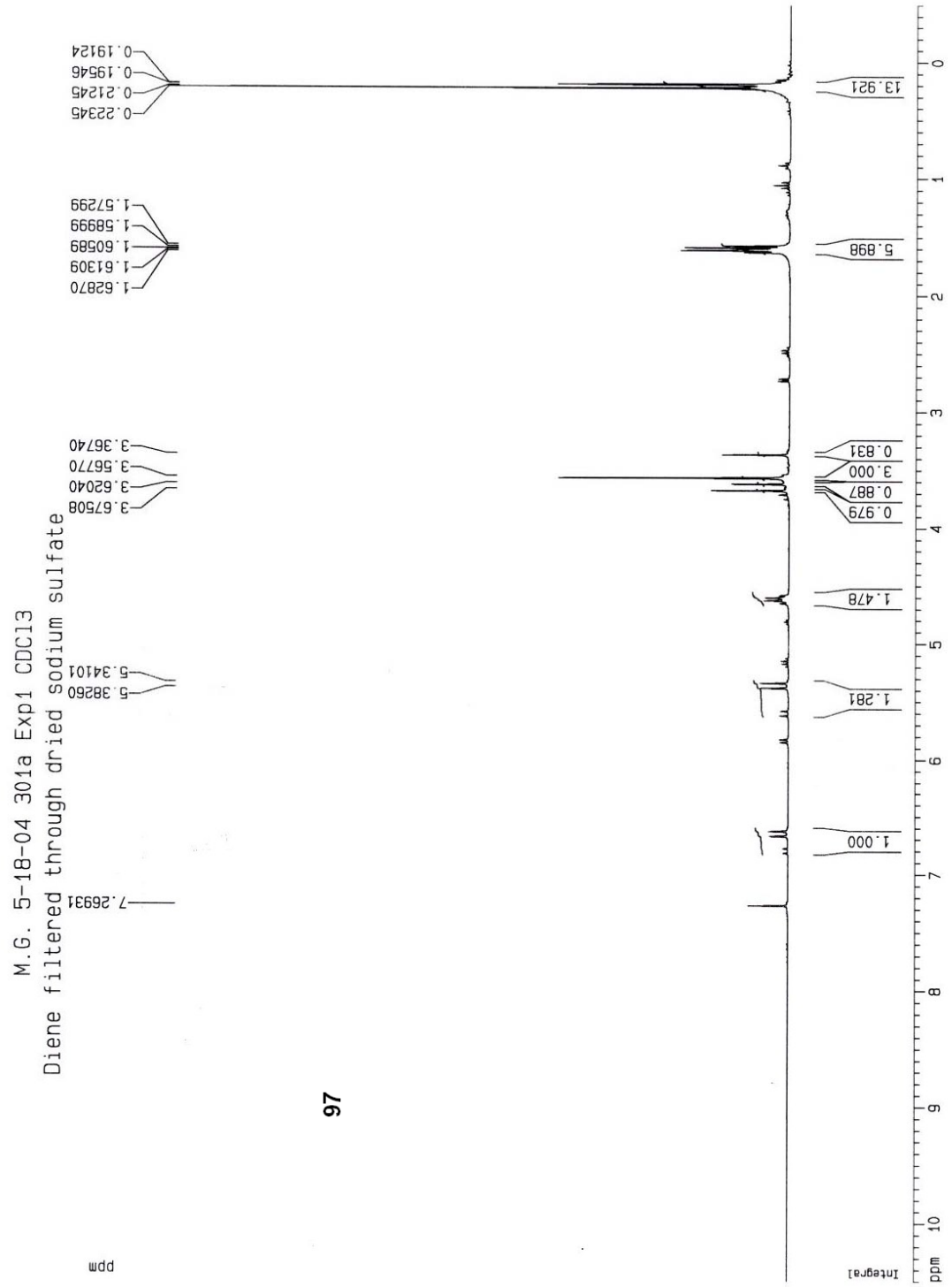
GC Experiments

Studies were conducted using a Hewlett-Packard HP6850 GC System equipped with a Chiraldex G-TA column. For experiments in which **31**, **33**, **34**, and **35** were run either separately or together, the column temperature was held at 100 °C for 25 minutes. Column pressure was 8.7 psi and flow rate was 0.4 mL/min. The psymberin degradation mixture was run independently or with **34,** and the column temperature was held at 100 °C for 25 minutes then warmed to 130 °C for 10 minutes. Column pressure was 8.7 psi and flow rate was 0.4 mL/min.

APPENDIX C

THEOPEDERIN D SPECTRA


0.25551
0.23784
0.24853
1.17230
1.14802
1.12327
2.60402
2.57944
9.3285
3.0966
2.0000
Integral
ppm
TMS
106
ppm


M.G. 5-18-04 301a Exp1 CDC13
Diene filtered through dried sodium sulfate
7.26931
5.38260
5.34101
3.67508
3.62040
3.56770
3.36740
1.62870
1.61309
1.60589
1.58999
1.57299
0.22345
0.21245
0.19546
0.19124
1.000
1.281
1.478
0.979
0.887
3.000
0.831
5.898
13.921
ppm
Integral

97

96
ppm
Integral
1.0000
1.1751
1.1723
1.2358
3.6742
3.6314
7.31340
7.29371
7.26979
5.34682
5.32709
4.59961
4.58910
4.57756
4.56701
4.55539
4.54501
4.53338
2.40396
2.39112
2.37956
2.36572
2.35511
2.34247
2.33085
2.08010
1.42240
1.37719
1.35502
1.33050
1.23872
1.23496
1.20173
1.09832
1.07387

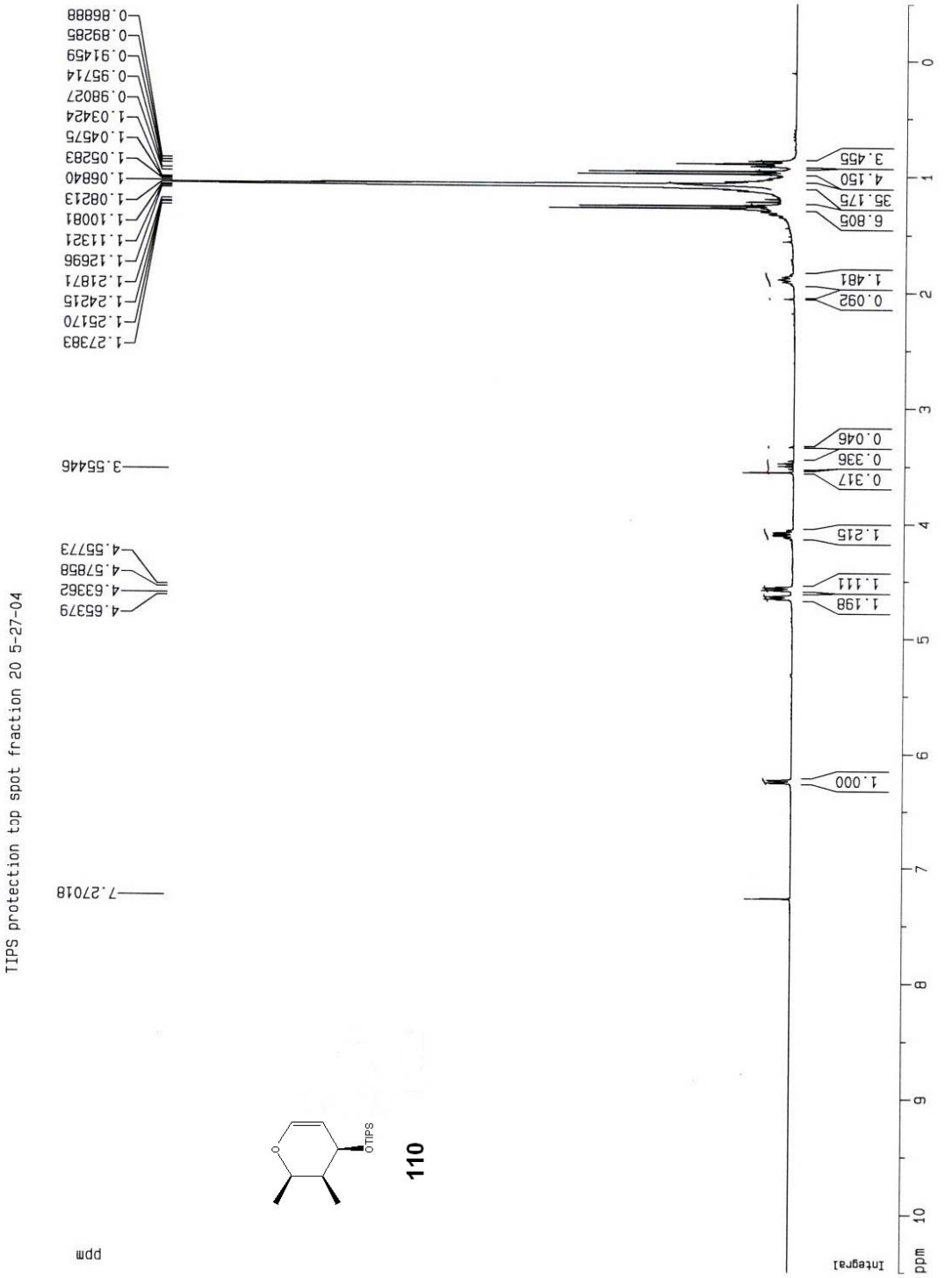

8.583
14.981
43.750
76.577
77.005
77.435
77.508
104.457
162.133
196.466
0
20
40
60
80
100
120
140
160
180
200

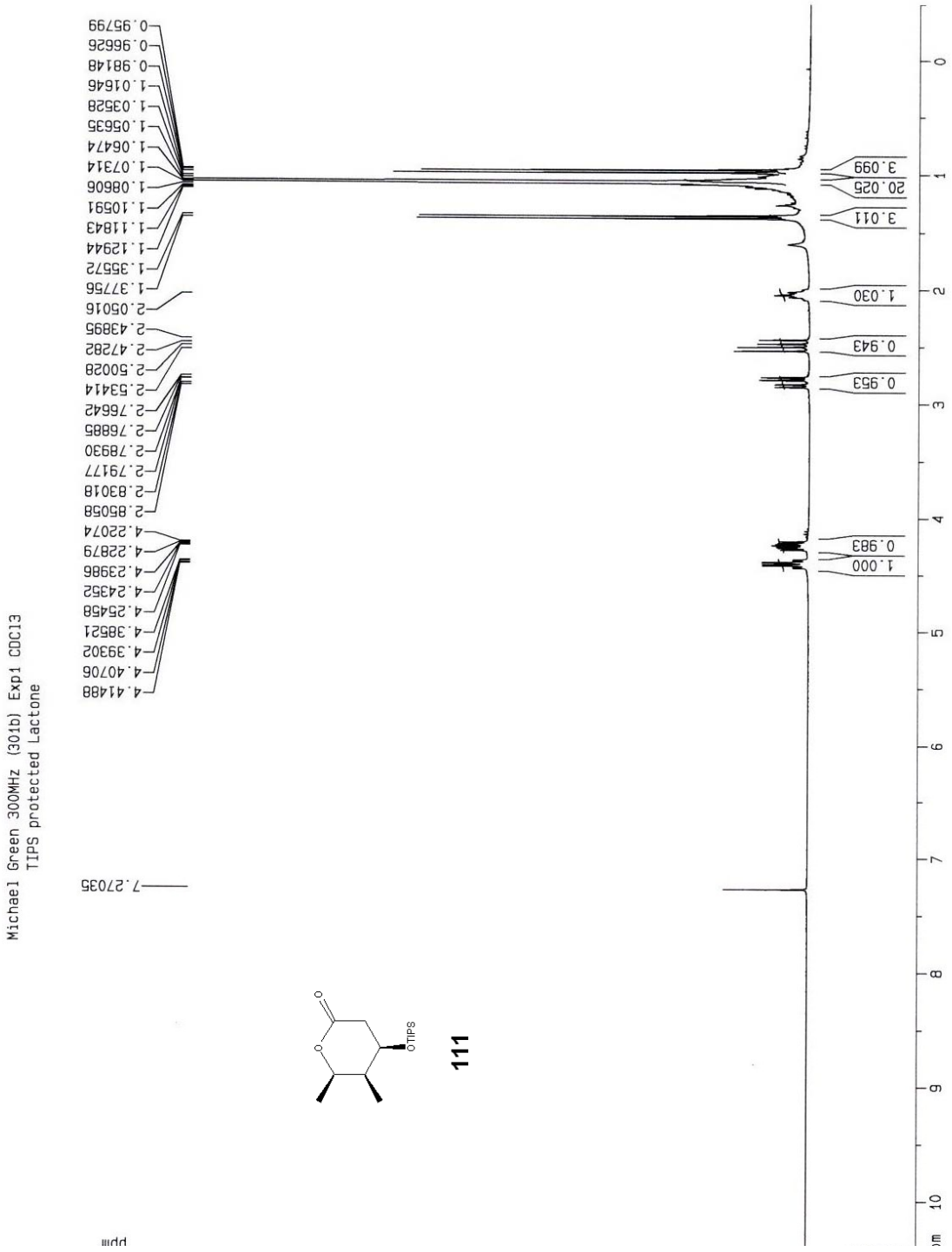
96

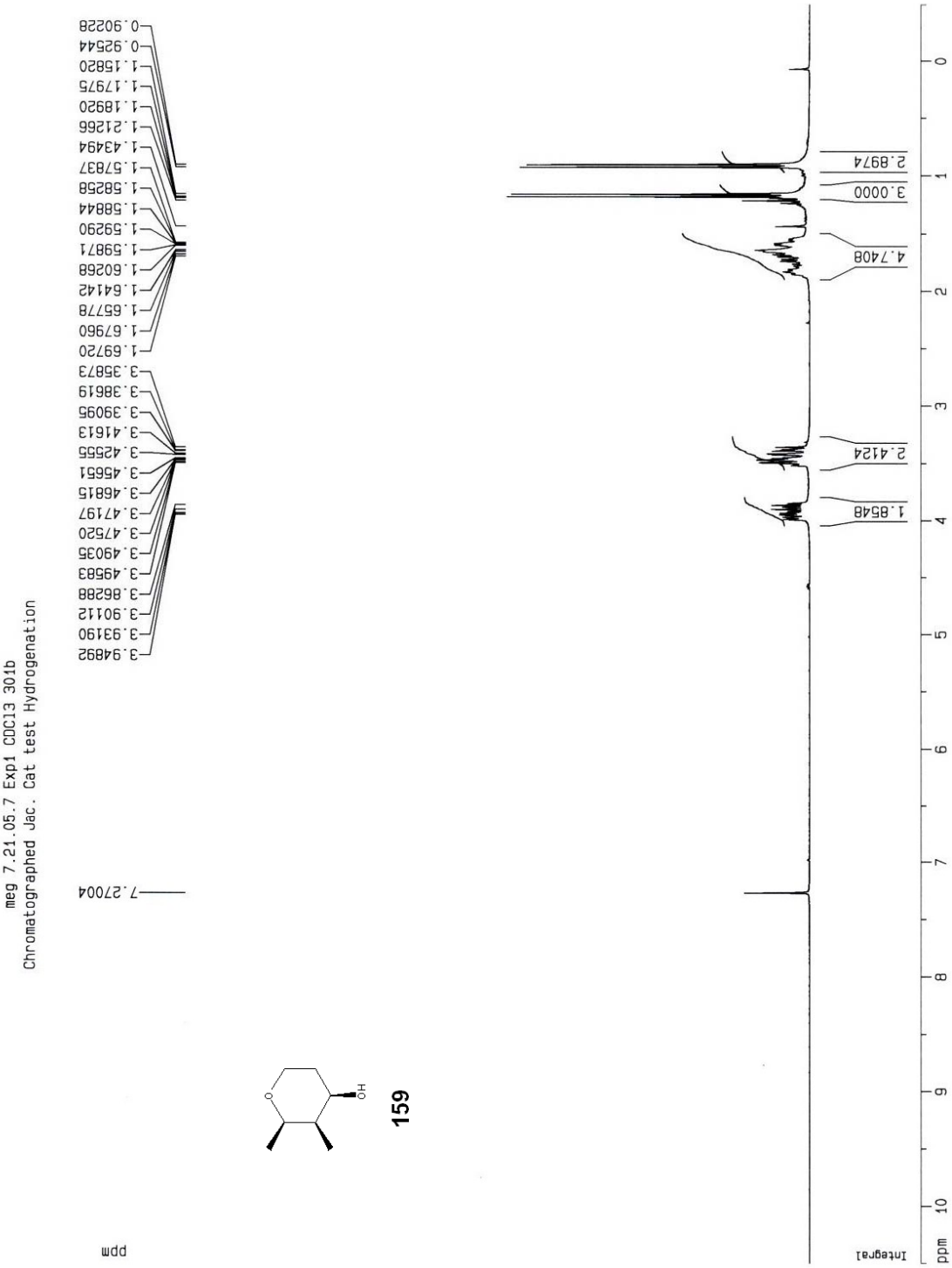
7.27007
1.28678
1.26458
0.97038
0.94703
1.0000
1.2630
1.1296
1.1774
1.3305
4.1668
3.7859
ppm
Integral

109

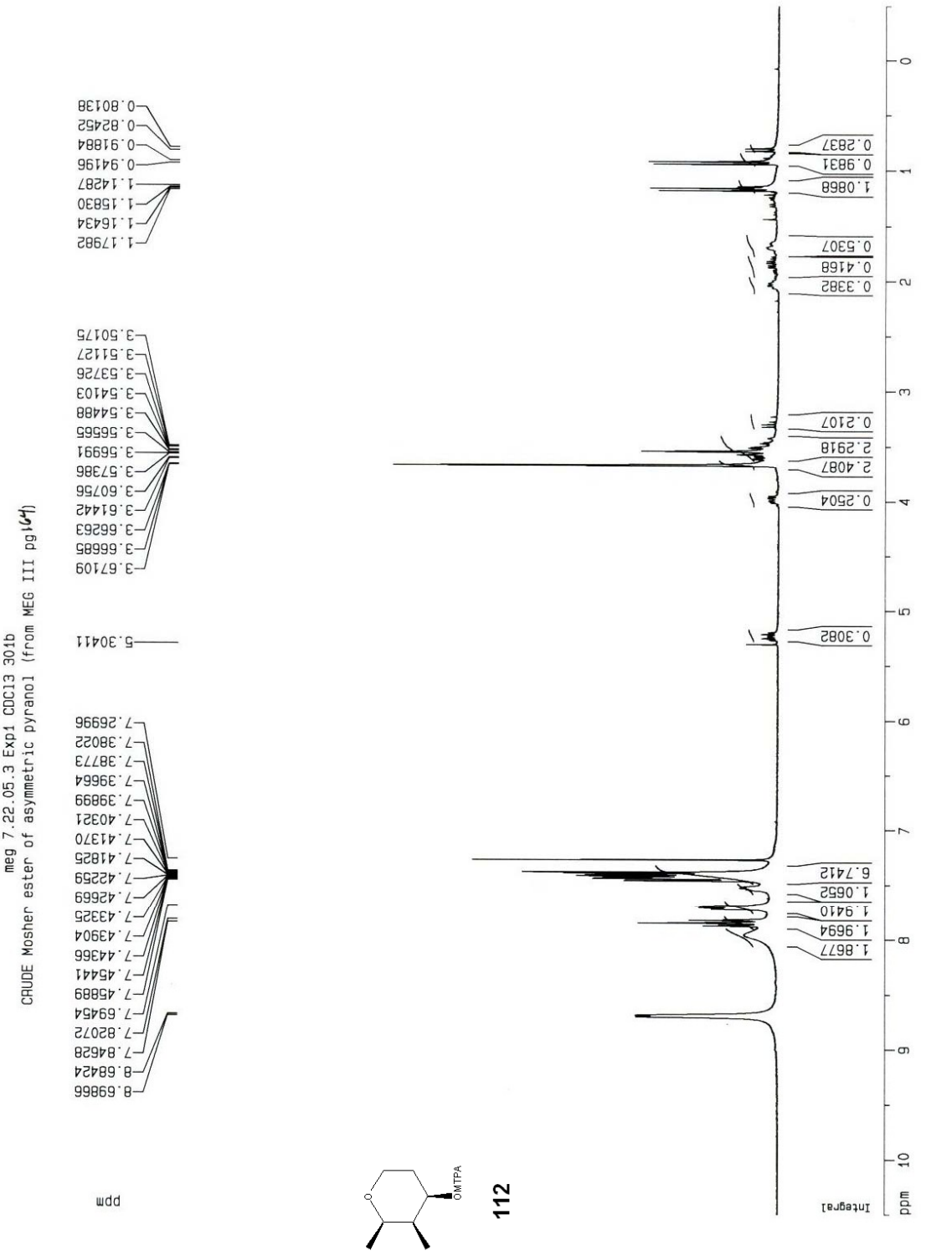
144.071
103.155
77.426
77.001
76.575
73.789
65.802
36.259
17.181
5.115
ppm
109
OH
O
ppm

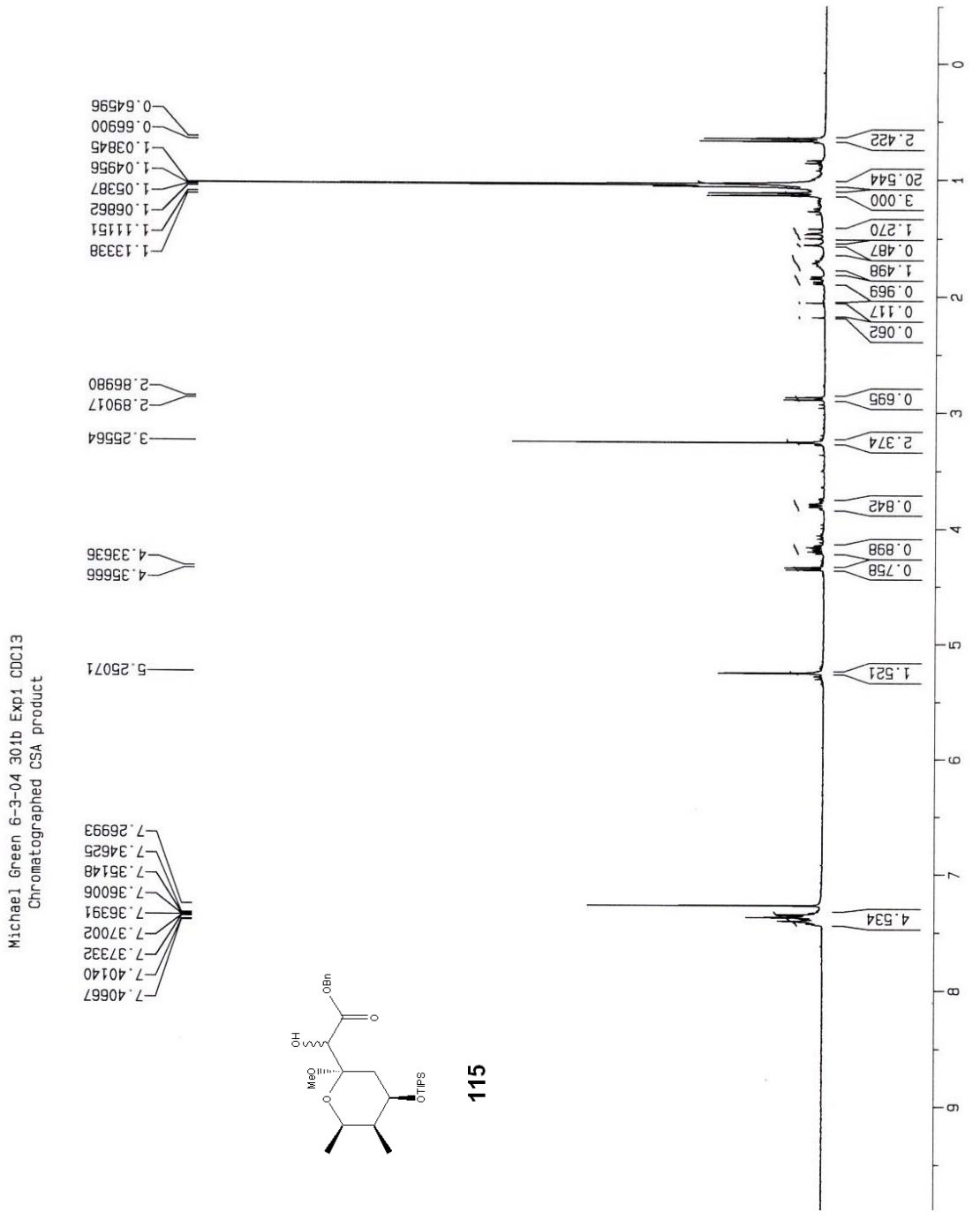

TIPS protection top spot fraction 20 5-27-04
ppm
Integral
7.27018
4.65379
4.63362
4.57858
4.55773
3.55446
1.27383
1.25170
1.24215
1.21871
1.12696
1.11321
1.10081
1.08213
1.06840
1.05283
1.04575
1.03424
0.98027
0.95714
0.91459
0.89285
0.86888
1.000
1.198
1.111
1.215
0.317
0.336
0.046
1.481
0.092
6.805
35.175
4.150
3.455
OTIPS
110


Michael Green 300MHz (301b) Exp1 CDCl3
TIPS protected Lactone
7.27035
4.41488
4.40706
4.39302
4.38521
4.25458
4.24352
4.23986
4.22879
4.22074
2.85058
2.83018
2.79177
2.78930
2.76885
2.76642
2.53414
2.50028
2.47282
2.43895
2.05016
1.37756
1.35572
1.29244
1.18843
1.10591
1.08606
1.07314
1.06474
1.05635
1.03528
1.01646
0.98148
0.96626
0.95799
1.000
0.983
0.953
0.943
1.030
3.011
20.025
3.099
OTIPS
111
ppm

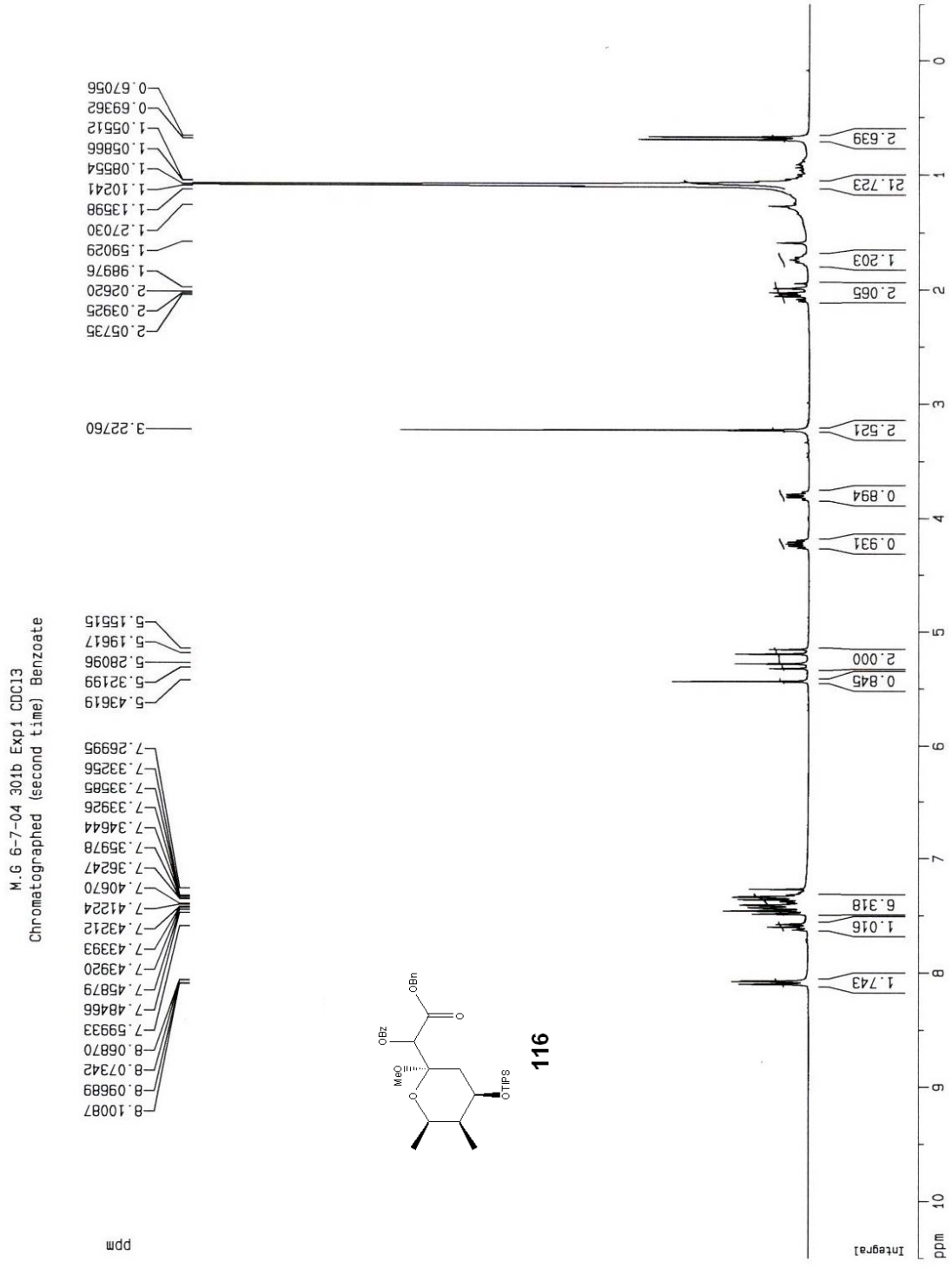

meg 7.21.05.7 Exp1 CDCl3 301b
Chromatographed Jac. Cat test Hydrogenation
ppm
Integral
7.27004
3.94892
3.93190
3.90112
3.86288
3.49583
3.49035
3.47520
3.47197
3.46815
3.45651
3.42555
3.41613
3.39095
3.38619
3.35873
1.69720
1.67960
1.65778
1.64142
1.60268
1.59871
1.59290
1.58844
1.58258
1.57837
1.43494
1.21266
1.18920
1.17975
1.15820
0.92544
0.90228
4.7408
3.0000
2.8974
2.4124
1.8548

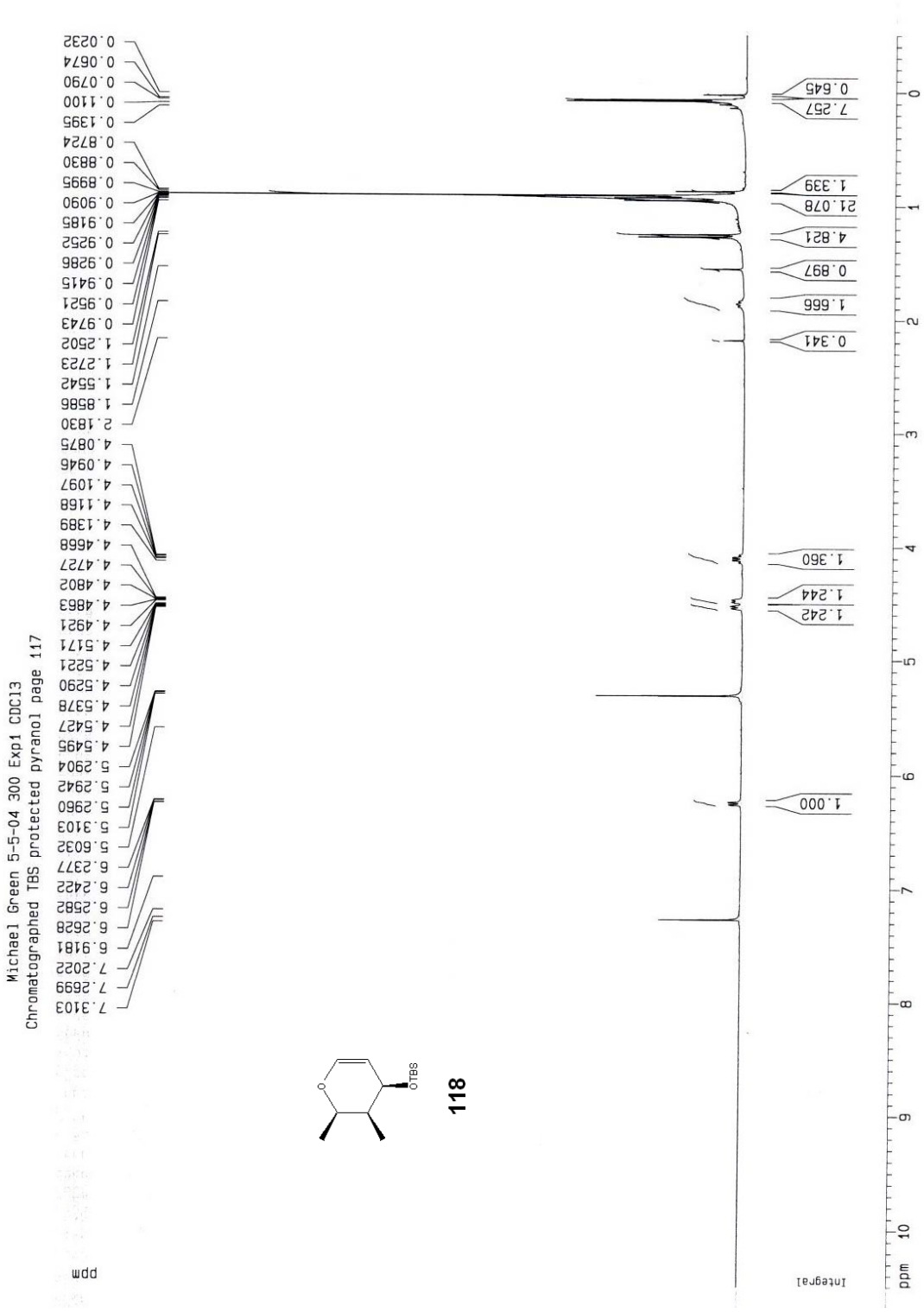
159

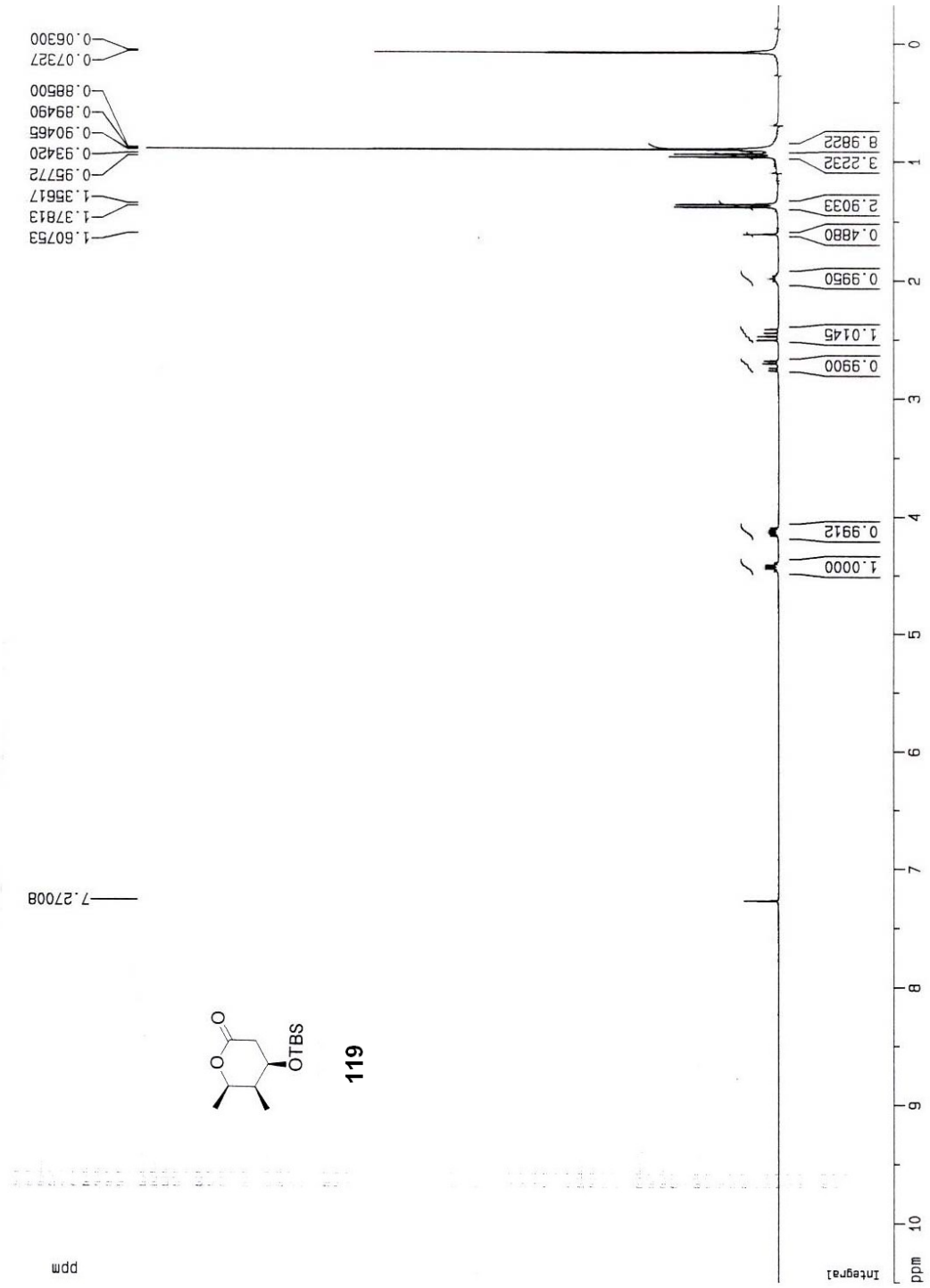

meg 7.22.05.3 Exp1 CDCl3 301b
CRUDE Mosher ester of asymmetric pyranol (from MEG III pg1)
ppm
Integral
OMTPA
112

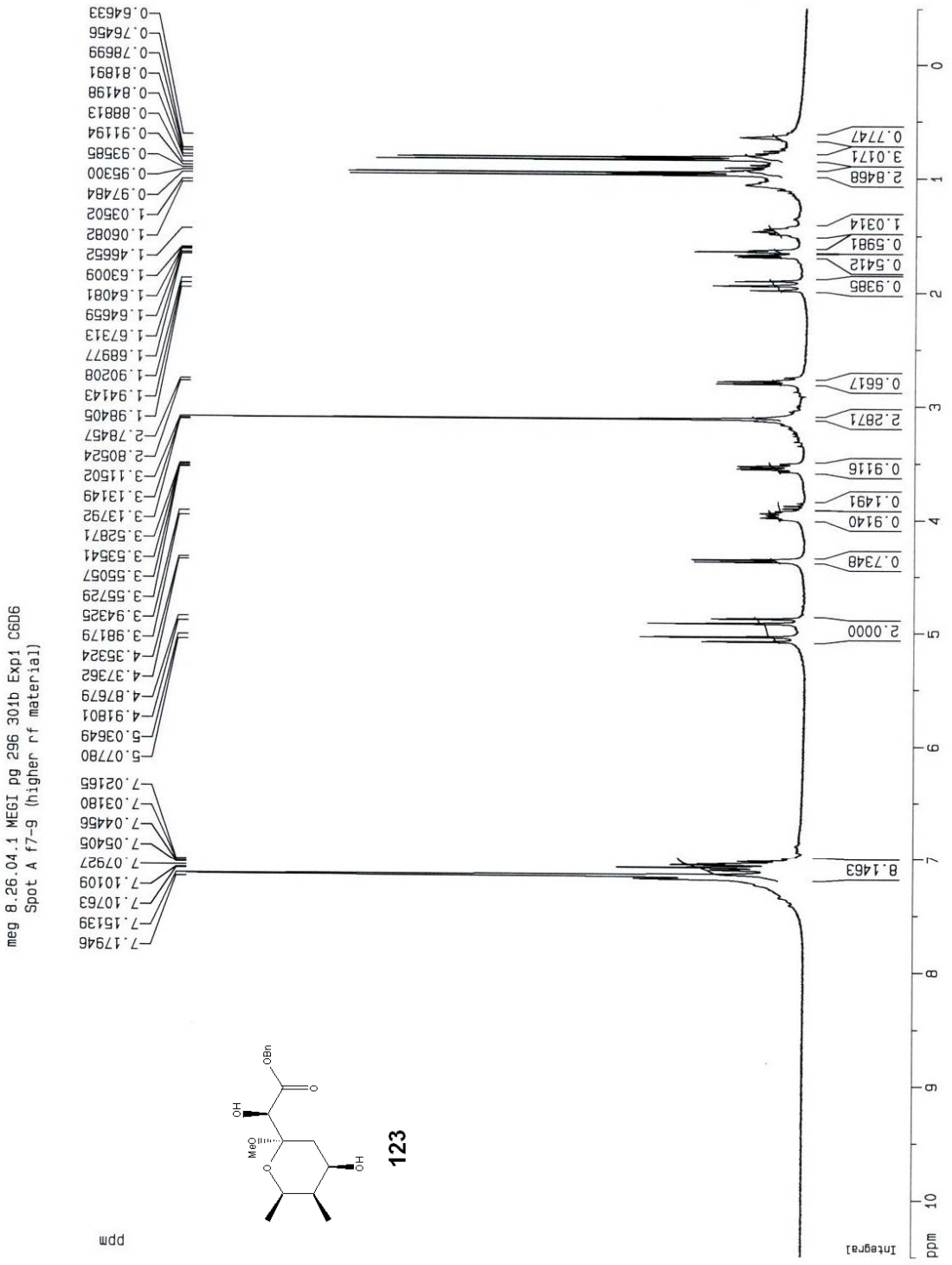

Michael Green 6-3-04 301b Exp1 CDCl3
Chromatographed CSA product
7.40667
7.40140
7.37332
7.37002
7.36391
7.36006
7.35148
7.34625
7.26993
5.25071
4.35666
4.33636
3.25564
2.89017
2.86980
1.13338
1.11151
1.06862
1.05387
1.04956
1.03845
0.66900
0.64596
4.534
1.521
0.758
0.898
0.842
2.374
0.695
0.062
0.117
0.969
1.498
0.487
1.270
3.000
20.544
2.422
OBn
OH
MeO
OTIPS

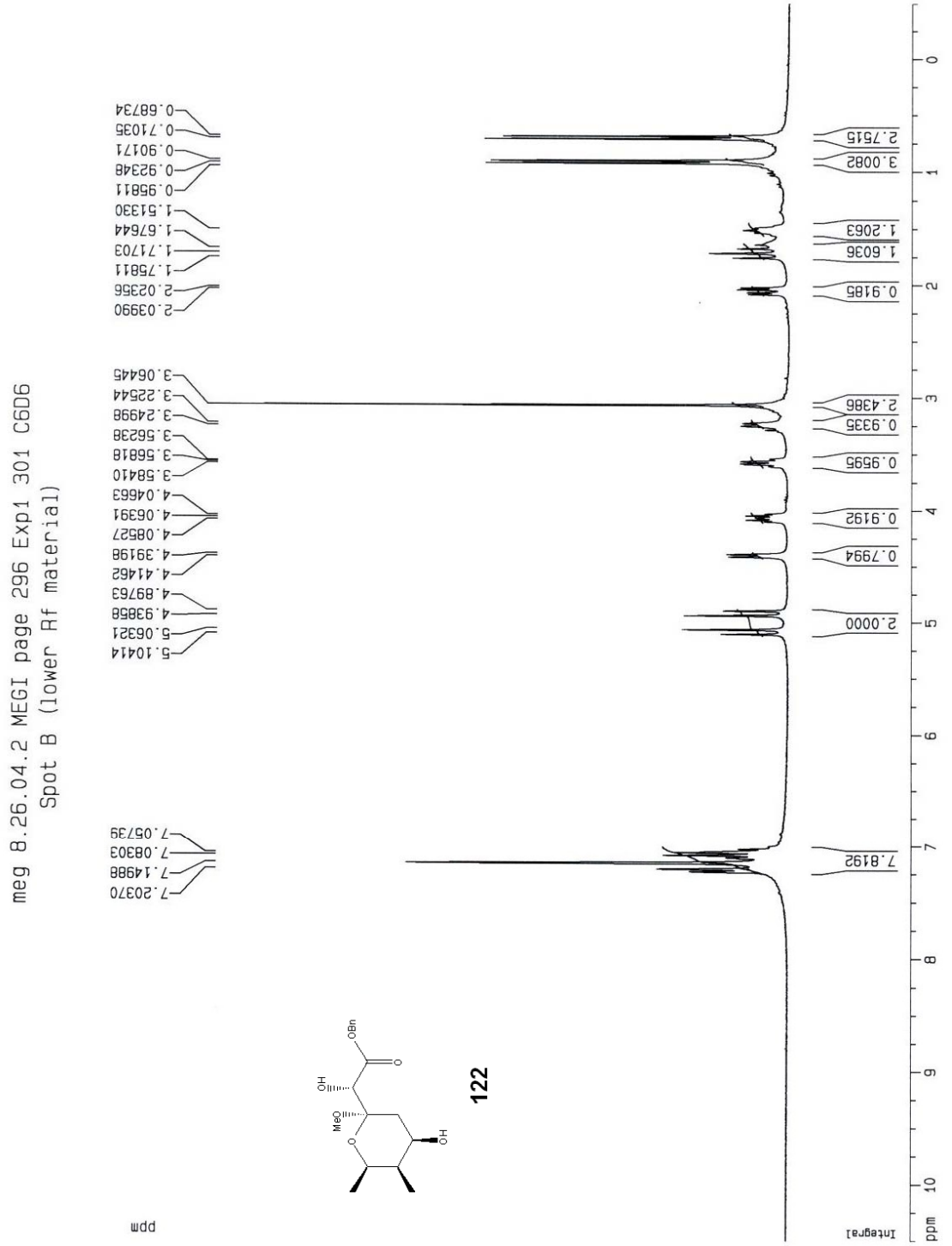
115

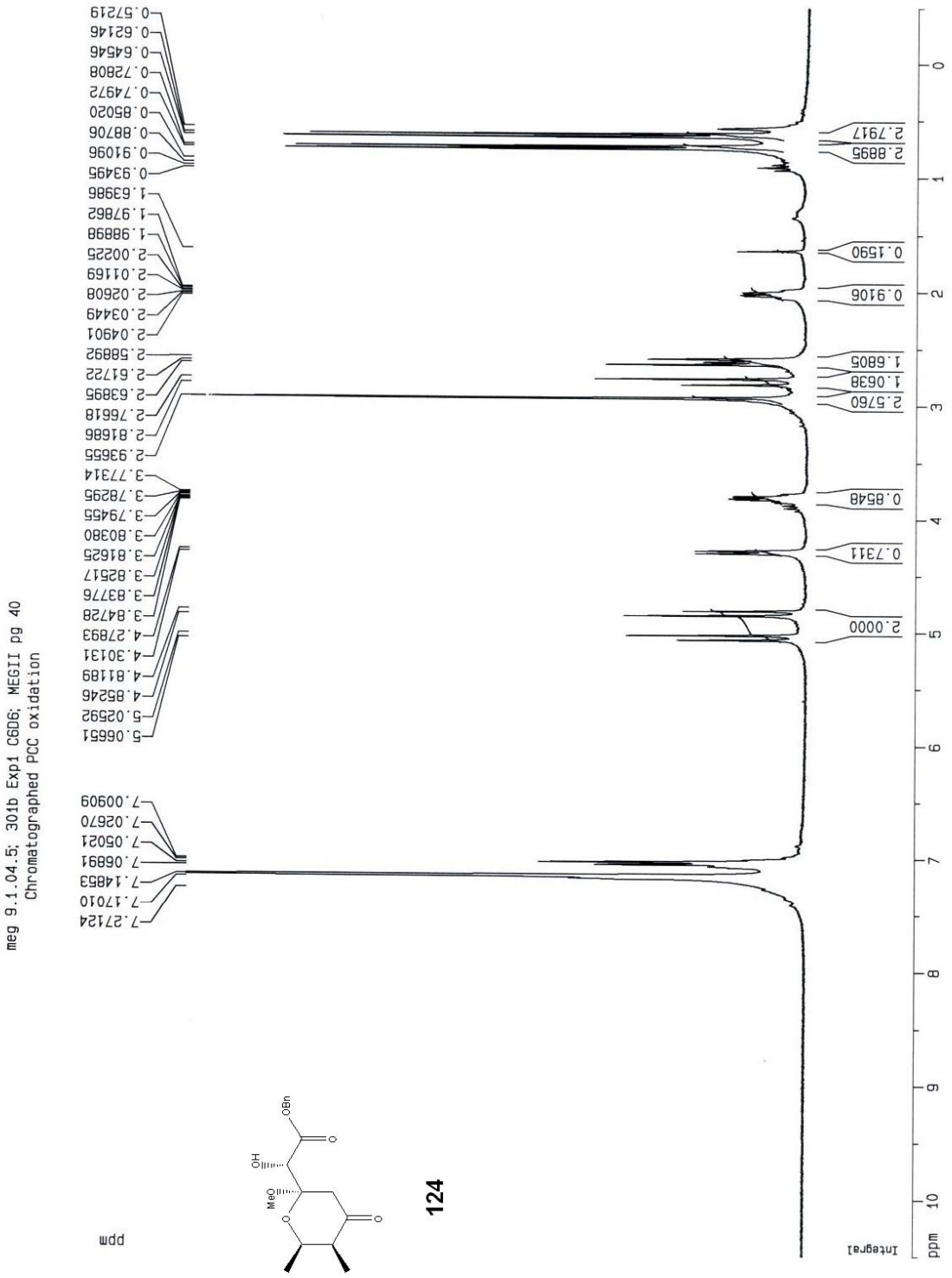

M.G 6-7-04 301b Exp1 CDCl3
Chromatographed (second time) Benzoate
ppm
Integral
116
OBn
OBz
MeO
OTIPS

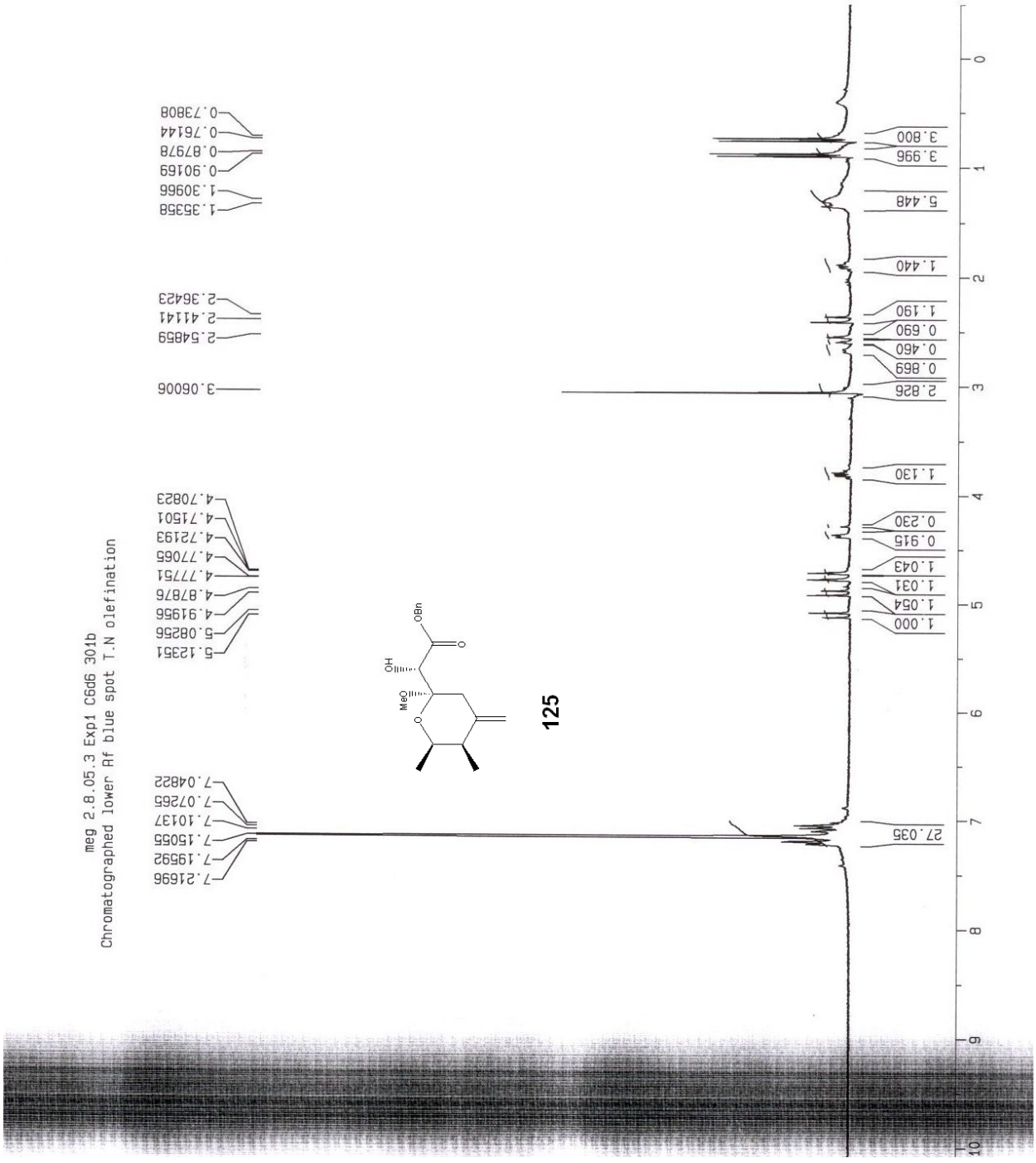

Michael Green 5-5-04 300 Exp1 CDCl3
Chromatographed TBS protected pyranol page 117
ppm
Integral
OTBS
118

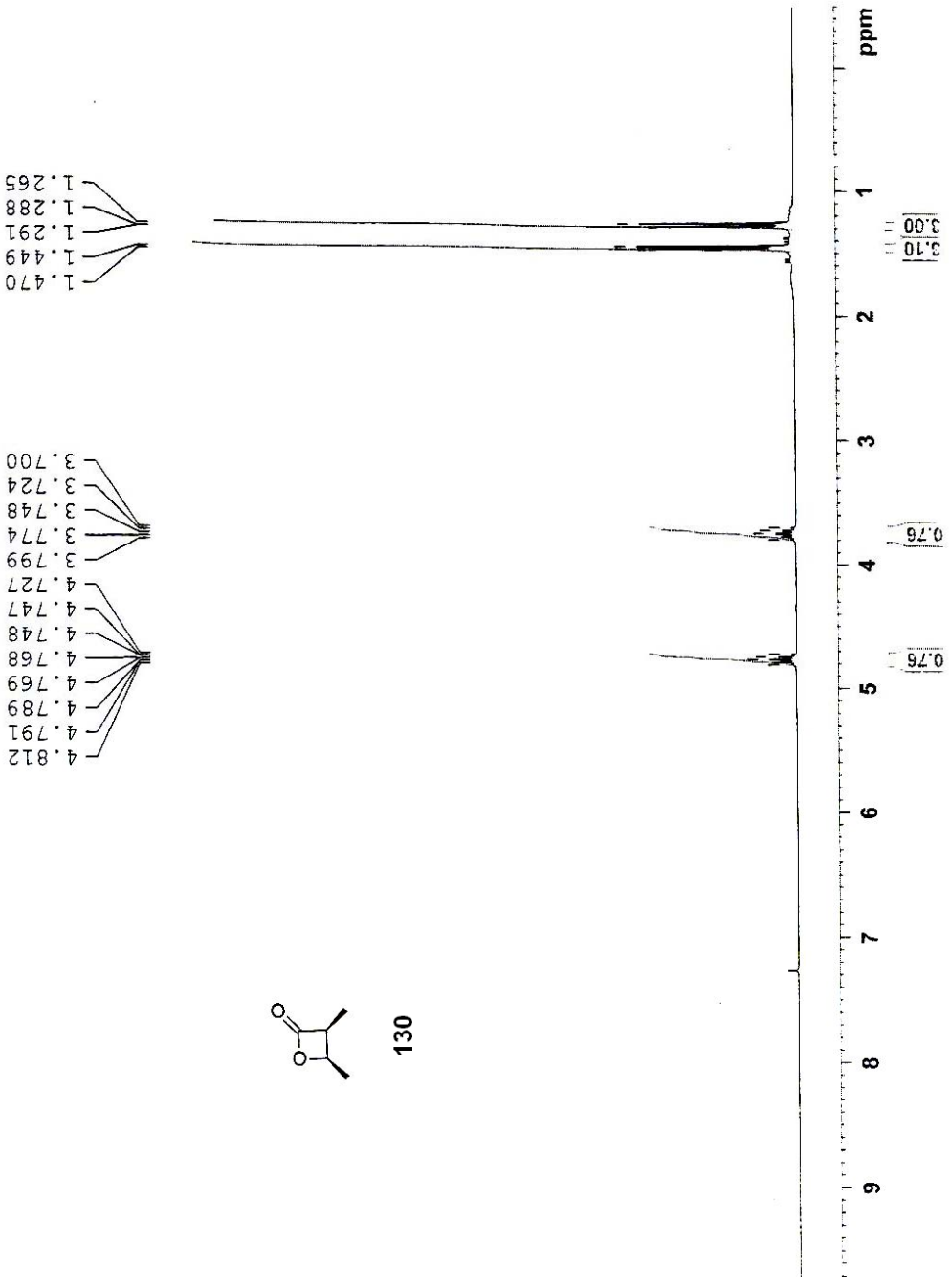

7.2700B
1.6075 3
1.3781 3
1.3561 7
0.9577 2
0.9342 0
0.9046 5
0.8949 0
0.8850 0
0.0732 7
0.0630 0
0.9912
1.0000
0.9900
1.0145
0.9950
0.4880
2.9033
3.2232
8.9822
Integral
ppm
OTBS
O
O
119


meg 8.26.04.1 MEGI pg 296 301b Exp1 C6D6
Spot A f7-9 (higher rf material)
ppm
Integral
123


meg 8.26.04.2 MEGI page 296 Exp1 301 C6D6
Spot B (lower Rf material)
ppm
Integral
122


meg 9.1.04.5; 301b Exp1 C6D6; MEGII pg 40
Chromatographed PCC oxidation
ppm
Integral
124


meg 2.8.05.3 Exp1 C6d6 301b
Chromatographed lower Rf blue spot T.N olefination
7.21696
7.19592
7.15055
7.10137
7.07265
7.04822
5.12351
5.08256
4.91956
4.87876
4.77751
4.77065
4.72193
4.71501
4.70823
3.06006
2.54859
2.41141
2.36423
1.35358
1.30966
0.90169
0.87978
0.76144
0.73808
27.035
1.000
1.054
1.031
1.043
0.915
0.230
1.130
2.826
0.869
0.460
0.690
1.190
1.440
5.448
3.996
3.800
OBn
OH
MeO
125


130
1.265
1.288
1.291
1.449
1.470
3.700
3.724
3.748
3.774
3.799
4.727
4.747
4.748
4.768
4.769
4.789
4.791
4.812
3.10
3.00
0.76
0.76
ppm

12.444
7.270
4.939
4.180
3.521
3.470
3.452
3.400
2.758
2.747
2.734
2.723
2.710
2.699
2.686
2.675
2.534
2.491
2.480
1.499
1.474
1.192
1.180
1.170
1.156
ppm
0.05
0.10
0.72
0.86
1.00
0.76
0.67
1.11
8.74
6.08
OH
O
O
O

129

ppm
7.33505
7.32935
7.32294
7.30710
7.29009
7.28508
7.27053
7.24925
4.42813
4.40909
4.07482
4.06466
4.05352
4.04351
2.33918
2.32908
2.31537
2.30532
1.18287
1.15897
1.15497
1.13878
1.13342
Integral
4.7583
1.0000
2.1258
1.0251
0.9409
1.0303
3.3408
2.4996
ppm
160

```
Closing signal file M:SIGNAL.BNC
RUN#  2591        JUL 30, 2003  03:21:19

SIGNAL FILE: M:SIGNAL.BNC
AREA%

      RT      AREA TYPE  WIDTH      AREA%
   3.367   17647744   PU   .215    9.09522
   3.986   38011118   VB   .183   19.59058
   4.807    4939808   PU  1.022    2.42175
   7.074     352802   VB   .420    1.81829
  10.061   121395936   BB   .496   62.85474
  15.103     8187391   PU   .837    4.21965

TOTAL AREA=1.94035E+07
MUL FACTOR=1.00000E+00

STARRY # 2591      JUL 30, 2003  03:21:19
```

TOTAL AREA=1.1453E+07
MUL FACTOR=1.00000E+00
RT AREA TYPE WIDTH AREA%
3.355 698283 VP .169 6.07066
3.965 2071944 PB .155 18.05116
5.587 448772 BV .953 3.89225
11.049 7378269 VP .696 64.14326
13.388 861534 PV 1.013 7.52248
Closing signal file M:SIGNAL .BNC
RUN# 2590 JUL 30, 2003 03:02:20
SIGNAL FILE: M:SIGNAL.BNC
AREA%
STOP
13.388
11.049
5.587
3.965
3.355
START
* RUN # 2590 JUL 30, 2003 03:02:20
NH
HO
O

Agilent Technologies
PART NUMBER 5181-1219
PRINT THIS SIDE
RUN # 2589 JUL 30, 2003 02:46:37
START
1.855
3.350
3.955
5.210
7.852
10.054
11.122
13.382
STOP
Closing signal file M:SIGNAL .BNC
RUN# 2589 JUL 30, 2003 02:46:37
SIGNAL FILE: M:SIGNAL.BNC
AREA%
RT AREA TYPE WIDTH AREA%
1.855 17593804 PU 1.217 9.16966
3.350 12705556 VV .286 6.62039
3.955 20975902 VB .184 10.92926
5.210 25110533 PB .852 1.30804
7.852 3056534 BV .451 1.59254
10.054 80006772 VV .510 41.66045
11.122 49639805 VP .731 25.89575
13.382 5365776 PV 1.018 2.79569
TOTAL AREA=1.91926E+07
MUL FACTOR=1.00000E+00

4.926
4.917
4.905
4.896
4.883
4.874
4.862
4.852
3.452
3.441
3.425
3.401
3.387
3.382
3.375
3.368
3.362
3.343
3.334
3.330
3.321
3.308
3.299
3.296
3.286
3.168
3.104
3.094
3.033
2.212
2.203
2.189
2.181
2.166
2.158
2.143
2.135
1.388
127
1.00
5.00
1.43
1.17
1.05
3.33
3.32
ppm

7.268
5.307
4.396
4.390
4.374
4.368
4.296
4.277
3.820
3.373
3.334
3.316
3.302
3.296
3.284
3.278
3.272
3.262
3.251
3.244
3.236
3.223
3.214
3.202
3.194
3.169
3.140
3.128
3.123
2.823
2.804
2.356
2.307
2.289
2.287
2.238
1.696
1.676
1.584
1.258

MeO
OH
OMe
O
O
S
S

132

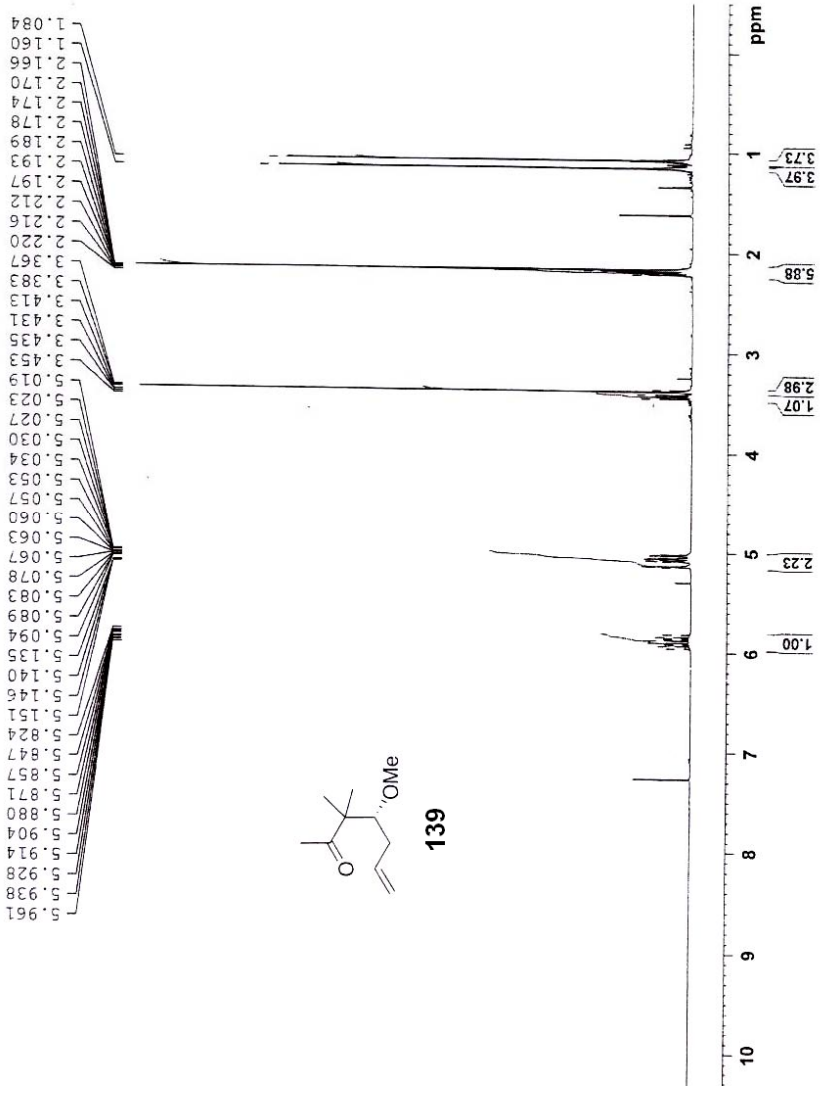
1.04
0.99
3.00
3.40
4.12
0.89
1.12
0.97
1.16
2.84
2.68
ppm

8.084
8.060
7.610
7.587
7.562
7.473
7.448
5.376
4.432
4.411
4.393
4.372
3.790
3.341
3.325
3.303
3.271
3.264
3.241
3.229
3.193
3.164
3.152
2.866
2.817
2.427
2.378
1.706
1.683
1.661
1.644
1.201
1.179
1.018
0.995
MeO
OBz
OMe
O
O
S
S
133
ppm
10
9
8
7
6
5
4
3
2
1
2.12
1.22
2.24
0.72
1.02
3.00
7.28
1.12
1.08
1.52
3.16
3.13

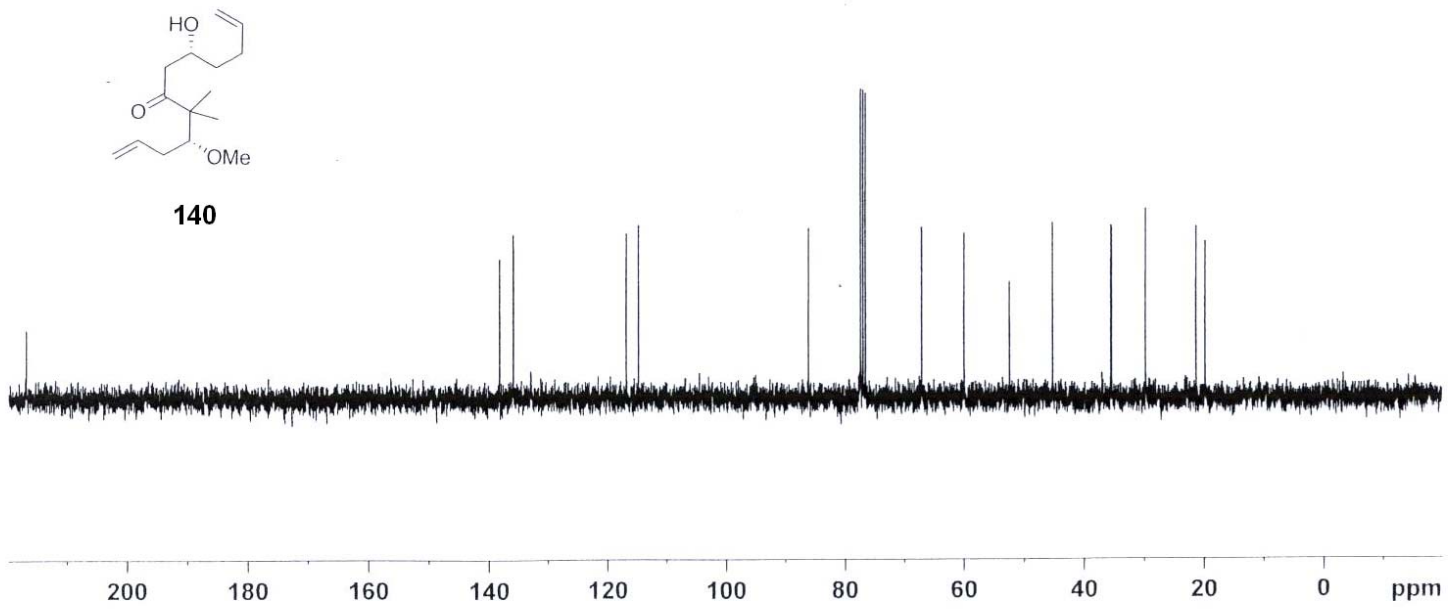
8.071
8.047
8.043
7.641
7.637
7.616
7.595
7.592
7.588
7.497
7.471
7.446
5.493
4.241
4.231
4.219
4.210
4.197
4.188
4.176
4.167
3.841
3.300
3.288
3.248
2.692
2.689
2.640
2.637
2.401
2.392
2.377
2.370
2.353
2.346
2.330
2.322
1.270
1.248
1.087
1.063
MeO
OBz
OMe
O
O
O
134
ppm
1.48
0.80
1.67
0.74
3.84
0.98
2.68
3.78
1.05
0.97
3.35
3.00

0.949
0.972
1.154
1.175
2.204
2.211
2.227
2.234
2.250
2.257
2.273
2.281
2.442
2.491
2.890
2.938
3.275
3.820
3.882
3.890
3.903
3.912
3.925
3.933
3.947
3.955
4.812
4.818
4.874
4.880
5.431
7.269
7.448
7.473
7.499
7.582
7.607
7.632
8.084
8.088
8.112
MeO
OBz
OMe
O
O
135
ppm
1
2
3
4
5
6
7
8
9
10
4.06
4.37
1.37
1.33
1.32
3.69
3.57
1.25
2.71
1.00
2.14
1.13
2.38

8.130
8.106
7.620
7.595
7.510
7.484
7.460
7.268
5.666
4.939
4.856
4.101
4.092
4.079
4.070
3.276
2.698
2.650
2.577
2.529
2.364
2.342
2.319
1.439
1.271
1.250
1.061
1.037
MeO
OBz
OH
O
O
59
ppm
1.78
1.05
2.10
0.90
2.15
1.05
2.91
1.08
1.17
1.57
4.12
3.00


ppm
1.00
2.23
1.07
2.98
5.88
3.97
3.73
OMe
O
139

140
OMe
HO
O
Integral
ppm
2.0000
4.0673
1.1223
1.2498
2.7246
1.0222
1.0642
1.2176
4.2855
4.5523
3.5753
3.4782
7.27030
5.14430
5.08733
5.08237
5.07667
5.07297
5.03314
5.02587
5.01987
4.99759
3.42511
3.42019
3.40319
3.37083
3.35922
3.27100
3.26159
2.68565
2.67695
2.61108
2.58121
2.23232
2.20925
2.18644
1.59670
1.16594
1.09684
1.08328
1.06105



140

2.0000
4.1439
0.9985
0.9240
2.1079
3.2353
1.0730
4.8100
5.2315
0.9950
0.4514
2.5394
2.9501
0 1 2 3 4 5 6 7 8 9
5.88825
5.85414
5.14676
5.14232
5.08979
5.08519
5.06321
5.05850
5.03472
5.00105
4.99613
4.96234
4.95934
4.92851
4.92561
4.46222
4.45441
4.37611
3.83058
3.79493
3.42964
3.41228
3.15566
3.14267
3.13034
2.34599
2.33393
2.31921
2.16763
1.53143
1.52136
1.49517
1.48589
1.45765
1.20609
0.96074
0.90777
0.83694
0.76262
HO
HO
OMe

104

ppm
0
20
40
60
80
100
120
140
160
180
200
138.300
137.785
136.777
136.085
116.278
114.444
114.067
89.594
77.823
77.426
77.001
76.575
71.699
59.868
47.091
41.776
41.441
40.996
36.948
36.647
34.739
29.410
21.244
20.221
13.824
HO
HO
OMe

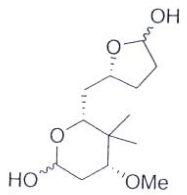
104

7.273
5.976
5.953
5.835
5.813
5.143
5.138
5.086
5.081
5.058
5.053
5.044
5.002
4.984
4.950
3.970
3.962
3.932
3.923
3.401
3.309
3.297
3.281
3.269
2.320
2.314
2.308
2.303
2.298
2.247
2.221
2.195
2.172
2.147
2.123
1.642
1.616
1.595
1.526
1.520
1.514
1.498
1.474
1.432
1.378
1.352
1.344
1.319
1.310
1.302
1.269
1.231
1.192
0.793
0.760
OMe
161
ppm
10
9
8
7
6
5
4
3
2
1
1.00
0.97
4.25
1.00
1.06
2.99
0.96
1.23
3.33
3.00
3.34
3.17
2.81
3.24
2.84

OMe
161

OH
OMe
O
O
HO
103
ppm
10
9
8
7
6
5
4
3
2
1
0.02
0.14
1.49
0.77
0.62
0.40
0.19
0.75
0.61
0.64
0.20
2.82
0.67
0.43
0.33
0.13
1.17
7.72
0.74
3.51
3.00

Dilactol

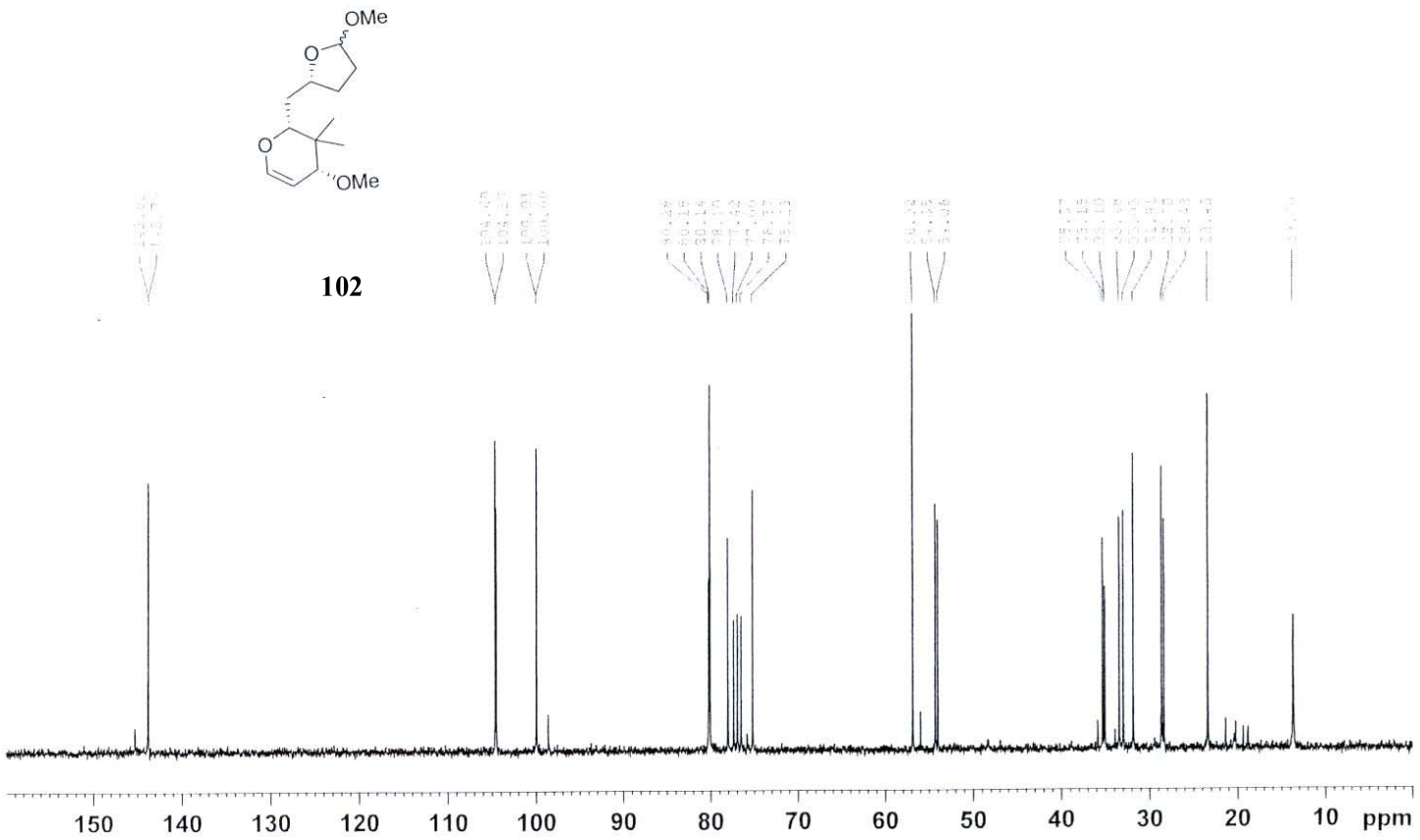


103

141
OMe
OMe
HO
ppm
1.00
0.87
0.70
0.68
1.86
0.55
0.69
9.93
1.09
0.65
0.87
0.66
0.35
0.50
0.77
9.40
6.99
3.30
2.62
2.11
3.19

104.84
104.79
104.70
104.62
94.58
91.90
83.64
83.53
80.03
79.93
79.13
78.77
78.12
78.06
76.00
75.67
72.94
72.78
57.24
57.14
54.50
54.43
54.30
38.68
38.64
37.91
37.86
35.49
35.21
34.14
34.06
34.01
33.08
32.99
31.92
31.00
28.99
28.82
28.58
28.52
22.39
22.32
22.27
22.20
13.01
12.97
12.13
12.08
OMe
OMe
HO
141
ppm

7.269
6.339
6.318
5.053
5.047
5.036
5.031
4.967
4.953
4.834
4.826
4.818
4.813
4.806
4.798
4.281
4.266
4.255
4.247
3.625
3.589
3.464
3.459
3.369
3.348
3.345
2.152
2.148
2.137
2.128
2.119
2.101
2.083
2.073
2.054
2.039
2.021
1.980
1.974
1.959
1.689
1.659
1.651
1.644
1.621
1.614
1.452
1.448
1.430
1.266
1.029
1.007
0.960
0.892
0.837
OMe
OMe
O
O
102
10
9
8
7
6
5
4
3
2
1
ppm
1.00
1.28
1.05
1.28
1.20
1.16
3.07
3.80
5.61
3.48
3.72
3.36

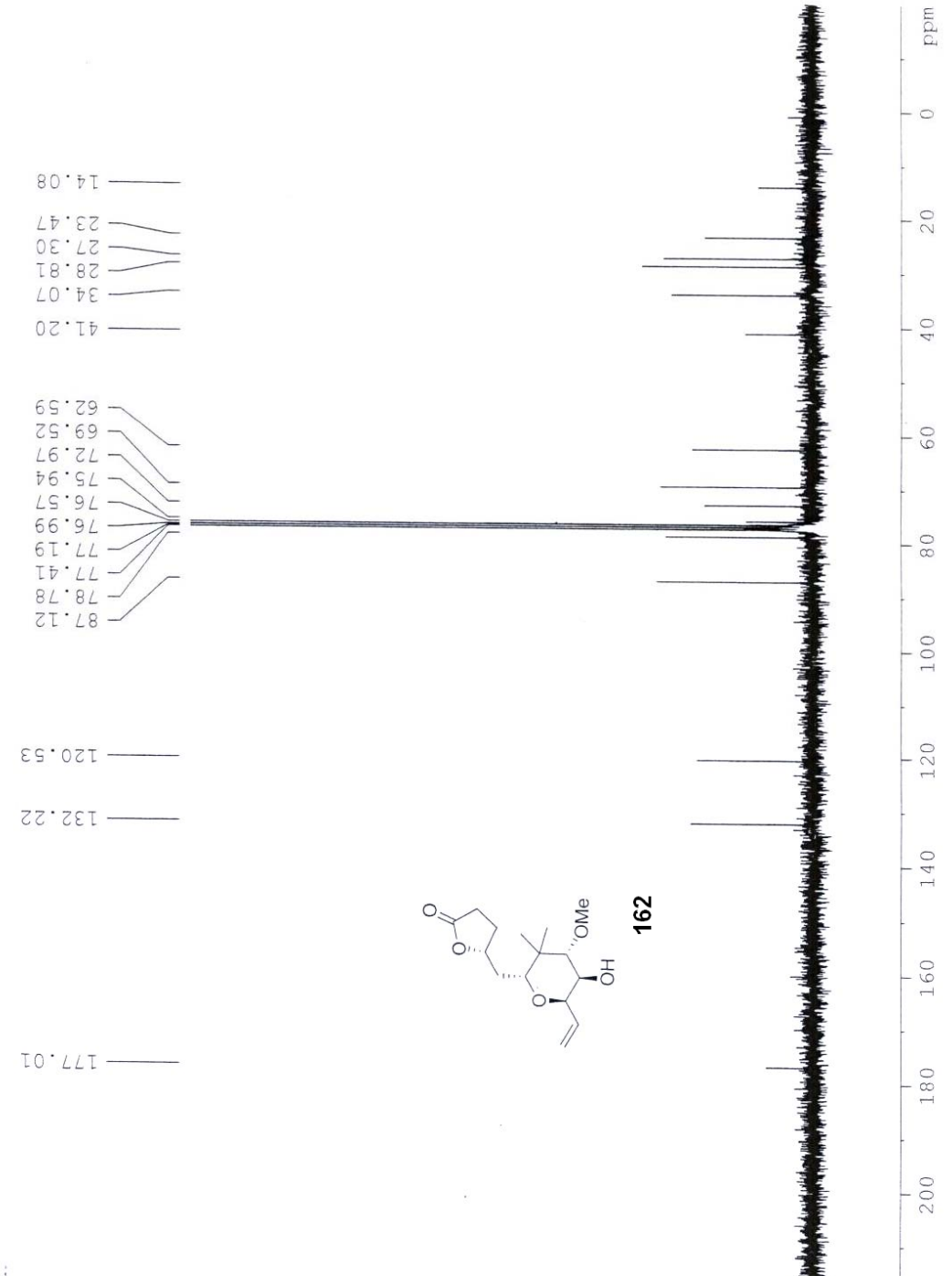


102

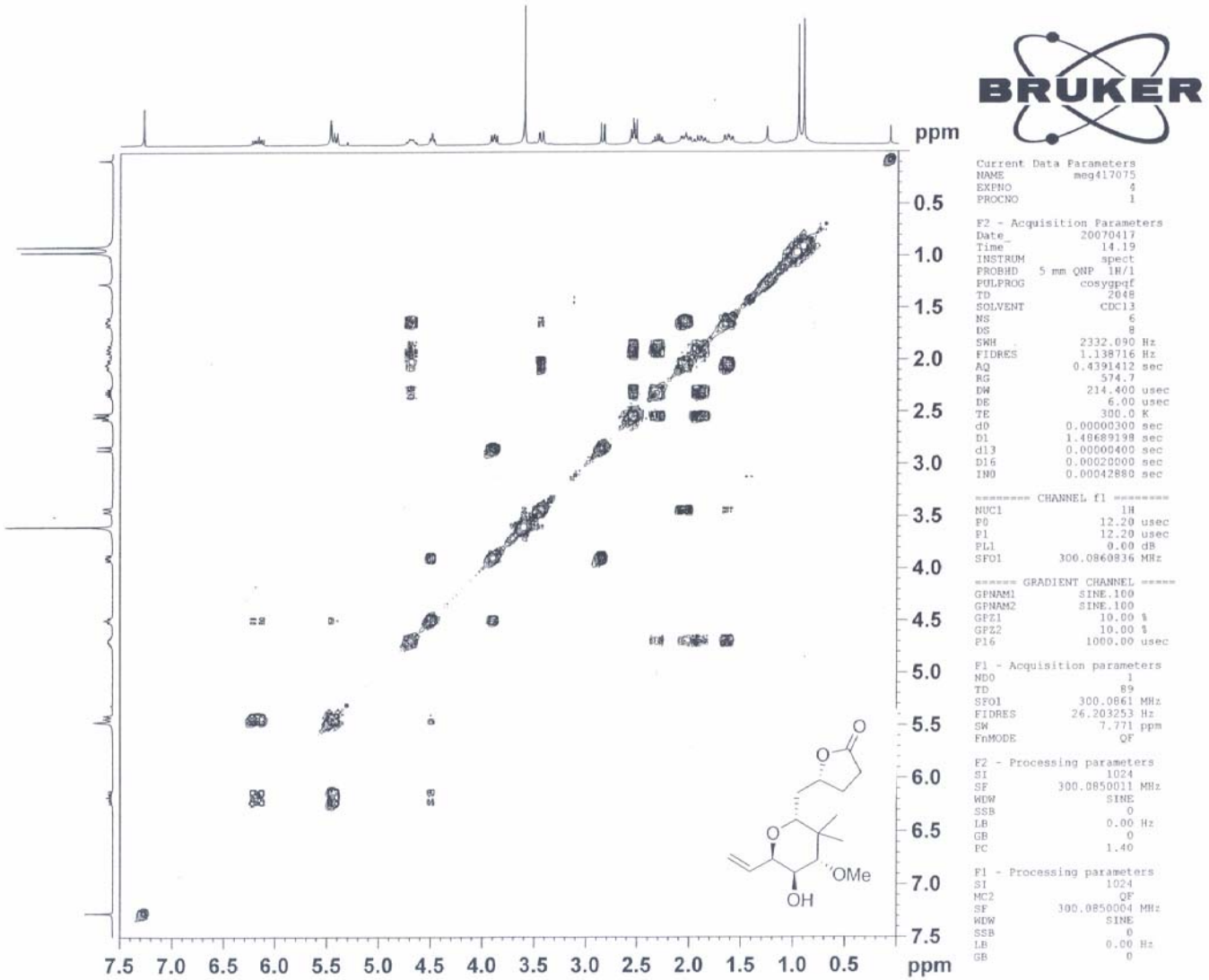
7.271
5.506
5.471
5.447
5.442
5.412
5.408
5.040
5.029
3.776
3.767
3.754
3.734
3.623
3.595
3.565
3.402
3.340
2.837
2.807
2.804
2.103
2.083
2.077
2.059
2.041
2.023
1.957
1.935
1.902
1.886
1.883
1.872
1.860
1.852
1.839
1.807
1.623
1.548
1.521
1.517
1.492
1.476
1.439
1.417
1.392
1.382
1.343
1.262
0.988
0.945
0.938
0.894
0.838
OMe
OMe
OH
O
O
101
ppm
10
9
8
7
6
5
4
3
2
1
1.00
2.37
0.27
1.79
0.96
1.55
1.54
2.04
4.36
1.22
4.28
1.01
10.66
9.33
4.75
5.61

OMe
OMe
OH
O
O
101
200
180
160
140
120
100
80
60
40
20
0
ppm

6.231
6.211
6.195
6.175
6.154
6.138
6.117
5.466
5.434
5.405
4.707
4.689
4.676
4.646
4.513
4.492
4.473
3.921
3.899
3.889
3.867
3.597
3.453
3.418
2.865
2.832
2.570
2.548
2.539
2.517
2.363
2.341
2.320
2.299
2.277
2.257
2.091
2.079
2.044
2.010
1.998
1.962
1.930
1.890
OMe
OH
O
O
O
162
ppm
1
2
3
4
5
6
7
8
9
10
3.67
2.92
1.37
1.81
3.53
1.18
2.11
0.95
1.05
2.97
1.00
1.05
0.95
0.94
0.99
1.00

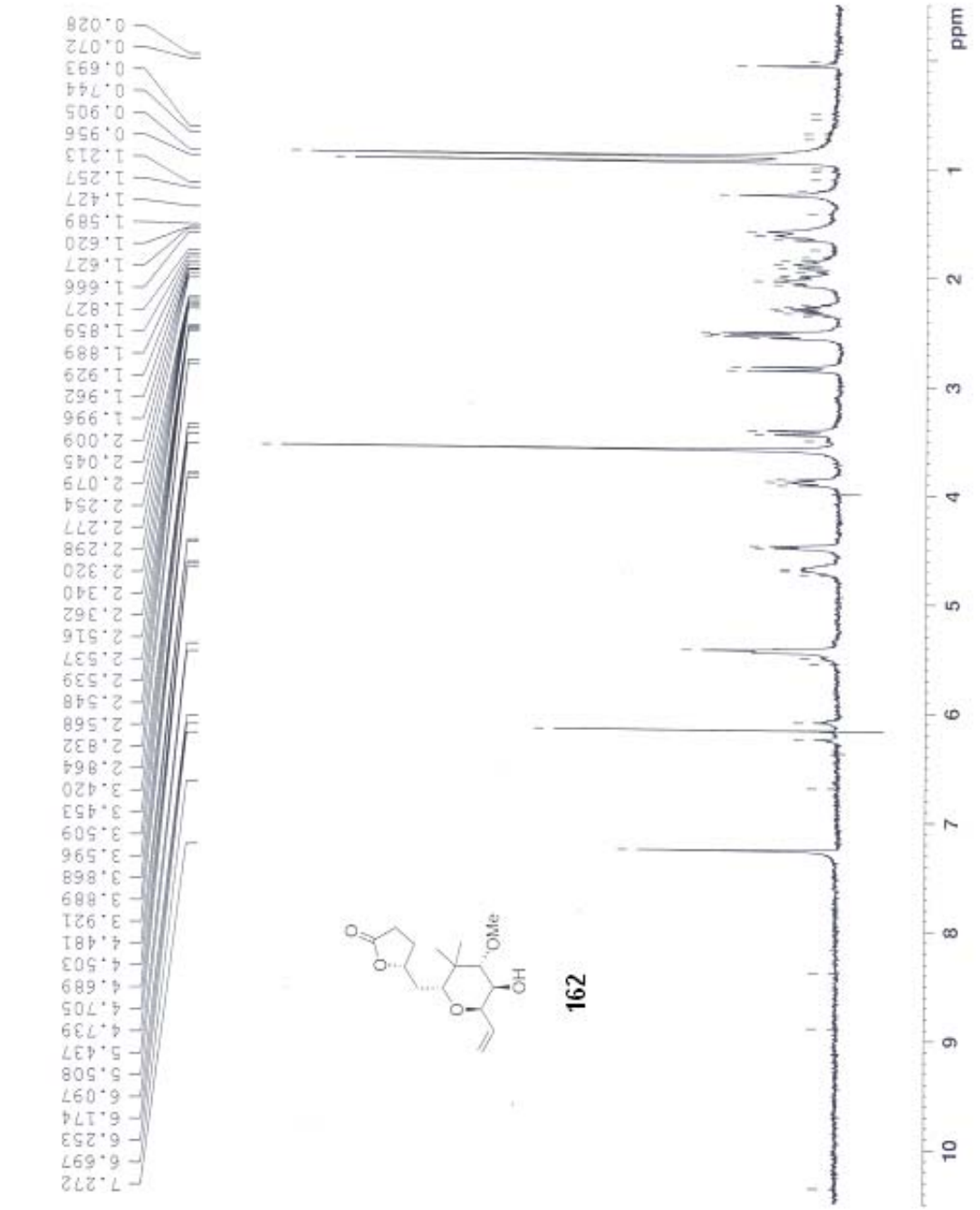

14.08
23.47
27.30
28.81
34.07
41.20
62.59
69.52
72.97
75.94
76.57
76.99
77.19
77.41
78.78
87.12
120.53
132.22
177.01
ppm
0
20
40
60
80
100
120
140
160
180
200
OMe
OH
O
O
O

162



BRUKER

```
Current Data Parameters
NAME              meg417075
EXPNO                     4
PROCNO                    1

F2 - Acquisition Parameters
Date_              20070417
Time                  14.19
INSTRUM                spect
PROBHD    5 mm QNP  1H/1
PULPROG           cosygpqf
TD                    2048
SOLVENT               CDCl3
NS                        6
DS                        8
SWH                2332.090 Hz
FIDRES             1.138716 Hz
AQ                 0.4391412 sec
RG                     574.7
DW                   214.400 usec
DE                     6.00 usec
TE                    300.0 K
d0                 0.00000300 sec
D1                 1.49689198 sec
d13                0.00000400 sec
D16                0.00020000 sec
IN0                0.00042880 sec

======== CHANNEL f1 ========
NUC1                      1H
P0                     12.20 usec
P1                     12.20 usec
PL1                     0.00 dB
SFO1           300.0860836 MHz

====== GRADIENT CHANNEL =====
GPNAM1               SINE.100
GPNAM2               SINE.100
GPZ1                    10.00 %
GPZ2                    10.00 %
P16                   1000.00 usec

F1 - Acquisition parameters
ND0                       1
TD                       89
SFO1           300.0861 MHz
FIDRES          26.203253 Hz
SW                  7.771 ppm
FnMODE                   QF

F2 - Processing parameters
SI                     1024
SF             300.0850011 MHz
WDW                    SINE
SSB                       0
LB                     0.00 Hz
GB                        0
PC                     1.40

F1 - Processing parameters
SI                     1024
MC2                      QF
SF             300.0850004 MHz
WDW                    SINE
SSB                       0
LB                     0.00 Hz
GB                        0
```


0.028
0.072
0.693
0.744
0.905
0.956
1.213
1.257
1.427
1.589
1.620
1.627
1.666
1.827
1.859
1.889
1.929
1.962
1.996
2.009
2.045
2.079
2.254
2.277
2.298
2.320
2.340
2.362
2.516
2.537
2.539
2.548
2.568
2.832
2.864
3.420
3.453
3.509
3.596
3.868
3.889
3.921
4.481
4.503
4.689
4.705
4.739
5.437
5.508
6.097
6.174
6.253
6.697
7.272
OMe
OH
O
O
O
ppm
10
9
8
7
6
5
4
3
2
1

162

7.271
6.187
6.175
6.168
6.152
5.511
5.495
5.488
5.421
5.345
5.328
4.705
4.687
4.672
4.511
4.491
4.470
3.920
3.898
3.888
3.866
3.596
3.452
3.416
2.864
2.832
2.569
2.549
2.538
2.516
2.340
2.319
2.298
2.276
2.255
2.078
2.045
2.033
2.010
1.997
1.961
1.930
1.900
1.888
1.859
1.826
1.666
1.635
1.620
1.590
1.256
0.956
0.905
0.836
0.072
OMe
OH
O
O
O
ppm
10
9
8
7
6
5
4
3
2
1

162

0.072
0.839
0.905
0.956
1.215
1.256
1.589
1.620
1.636
1.666
1.827
1.858
1.897
1.929
1.962
1.996
2.010
2.044
2.078
2.090
2.276
2.298
2.319
2.340
2.361
2.516
2.537
2.548
2.568
2.845
3.417
3.447
3.589
3.661
3.817
3.831
3.896
3.977
4.000
4.489
4.507
4.679
4.710
5.408
5.438
5.470
6.120
6.140
6.157
6.176
6.197
6.213
6.233
7.271
OMe
HO
O
O
O
162
10
9
8
7
6
5
4
3
2
1
ppm

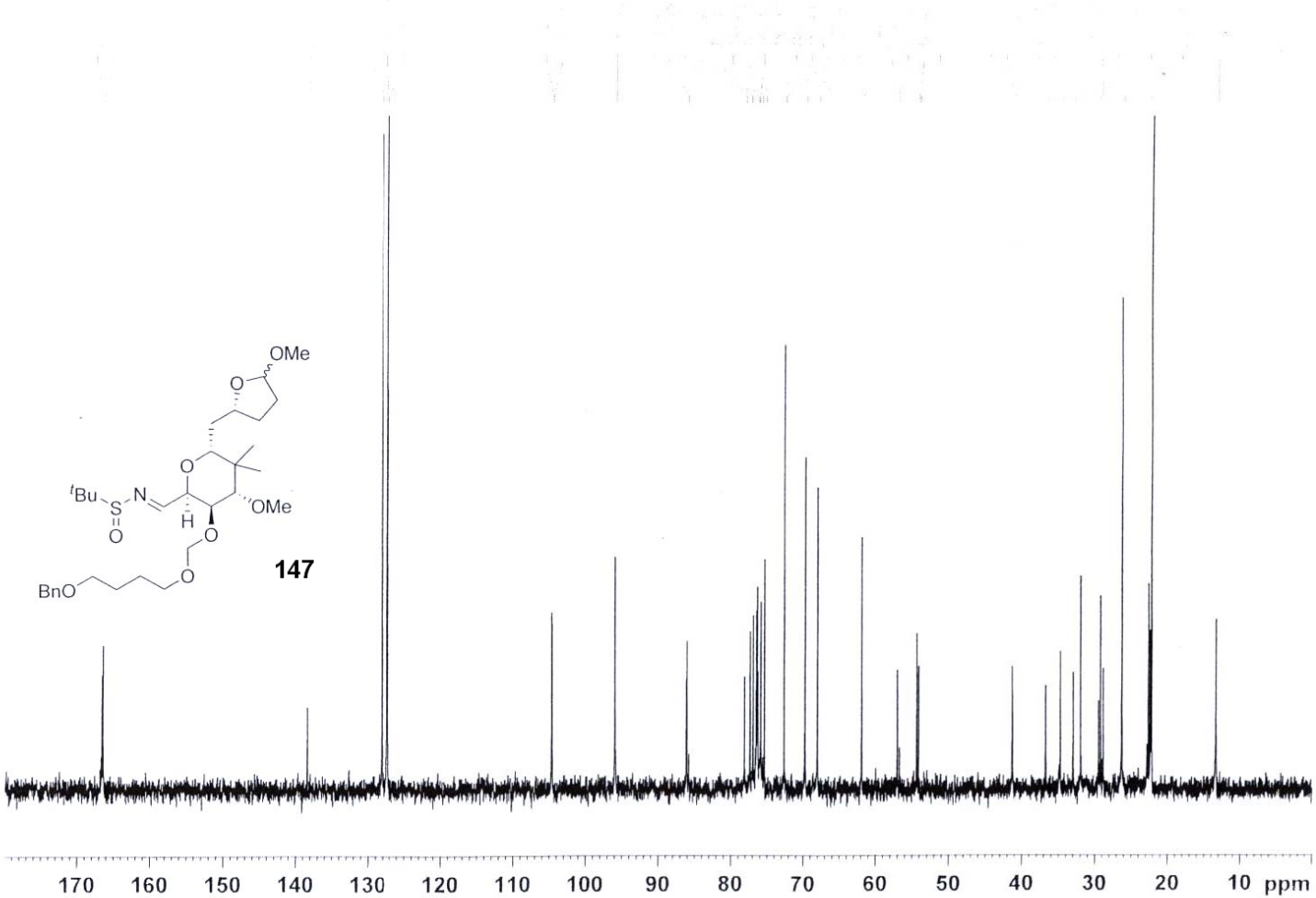
7.270
6.233
6.212
6.196
6.175
6.156
6.139
6.119
5.469
5.437
5.407
4.708
4.677
4.517
4.495
4.474
3.907
3.886
3.602
3.458
3.424
2.927
2.916
2.849
2.772
2.560
2.540
2.530
2.509
2.336
2.316
2.294
2.273
2.088
2.076
2.042
2.030
2.008
1.994
1.959
1.928
1.918
1.896
1.857
1.666
1.634
1.624
1.589
1.256
1.216
0.955
0.905
0.836
0.072
OMe
OH
ppm
10
9
8
7
6
5
4
3
2
1

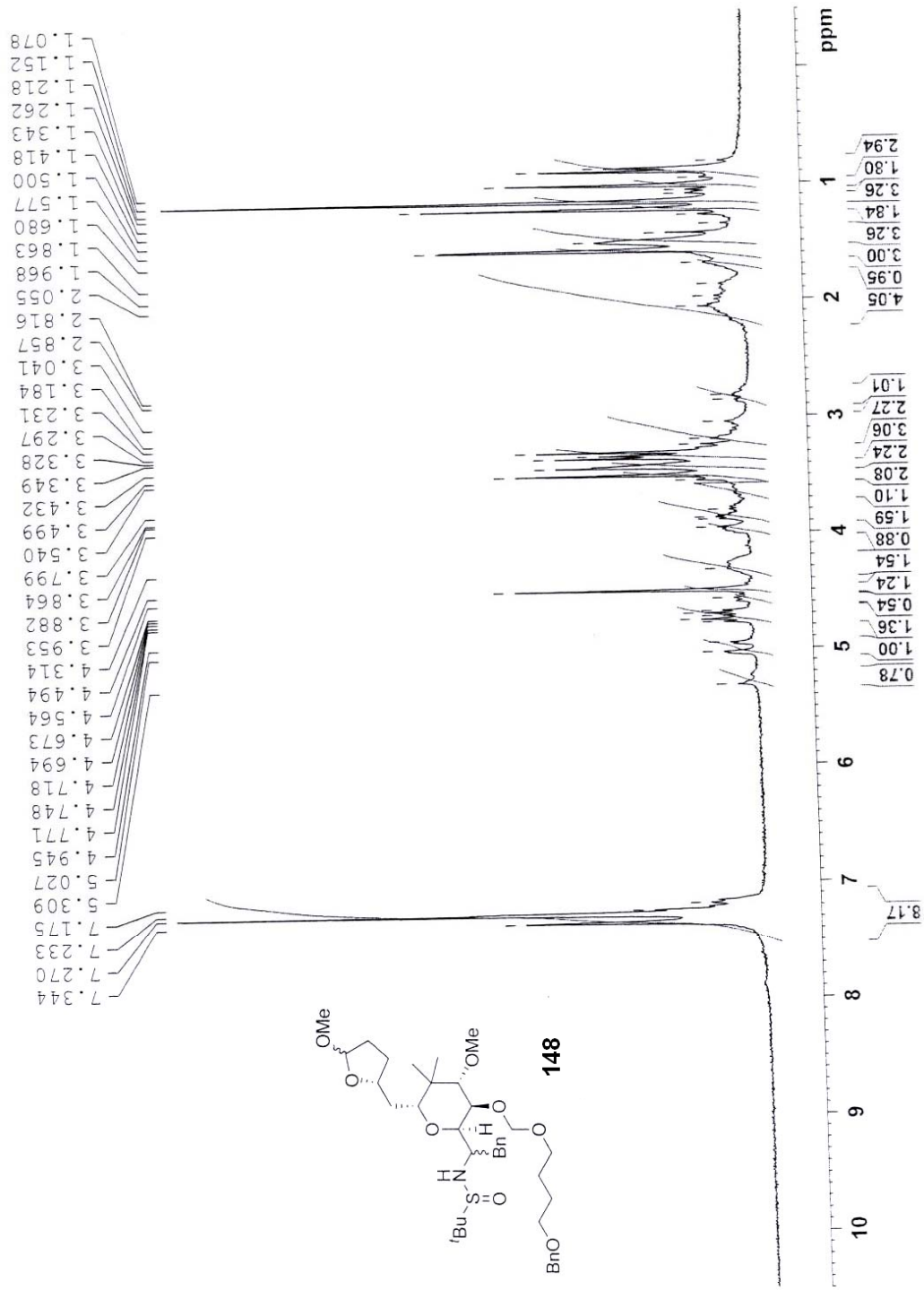
162

145
OMe
OMe
BnO
Integral
ppm
6.0957
0.9722
2.0000
0.5933
0.7275
2.5648
3.5654
1.1927
1.0090
2.3779
7.0865
3.9709
0.9564
4.9385
6.6298
2.2655
5.8330
7.28466
7.27096
7.23985
7.22503
7.20713
5.33882
5.30284
4.74058
4.71818
4.69353
4.66736
4.64512
4.44051
3.53303
3.51005
3.46013
3.44892
3.42739
3.40773
3.27618
3.26635
2.79615
2.76253
1.66714
1.61861
1.60926
1.59958
0.84166
0.83425
0.82535

OMe
OMe
BnO
145
ppm
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

147
OMe
OMe
tBu
BnO
ppm
0.75
0.14
3.77
0.51
0.40
0.93
2.05
2.00
0.97
1.01
1.35
7.19
2.81
0.14
0.82
13.43
11.25
6.54


OMe
O
tBu
S
O
N
O
H
OMe
O
BnO
O
147
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


148
OMe
OMe
Bn
BnO
ppm

138.40
137.94
136.78
136.67
130.63
129.58
128.41
128.06
127.63
126.24
126.04
104.86
104.67
104.55
96.39
95.28
84.06
84.00
78.78
78.43
78.20
77.43
77.00
76.58
76.36
76.04
72.66
72.05
71.75
69.76
68.44
68.25
68.04
61.46
60.48
55.66
55.53
55.34
54.46
54.23
54.14
41.24
37.26
36.28
36.11
35.31
33.04
31.89
31.77
29.20
29.13
29.06
28.97
23.61
22.38
148
OMe
OMe
Bn
BnO
ppm
0
20
40
60
80
100
120
140
160
180
200

7.346
7.300
7.293
7.272
7.253
7.245
7.223
7.213
5.023
5.011
4.944
4.930
4.821
4.772
4.752
4.499
4.488
4.481
4.299
3.696
3.652
3.623
3.607
3.572
3.552
3.494
3.487
3.473
3.463
3.452
3.338
3.316
3.293
3.217
3.194
3.081
3.058
2.066
2.055
2.040
1.680
1.670
1.660
1.606
1.538
1.511
1.494
1.470
1.141
1.115
1.089
1.066
0.953
0.932
OMe
OMe
149
H2N
Bn
BnO
ppm
1
2
3
4
5
6
7
8
9
10
26.86
1.58
0.87
1.00
3.73
5.36
2.51
1.59
0.85
0.85
9.20
16.74
1.17
2.98
2.30
3.63
2.66
1.54
3.11
11.37
13.02
8.85
7.51
8.99

OMe
OMe
H2N
Bn
BnO
149
ppm

7.309
7.282
7.269
7.229
7.219
7.209
7.170
7.152
7.128
5.020
4.986
4.946
4.918
4.735
4.648
4.639
4.628
4.578
4.195
3.873
3.844
3.643
3.622
3.605
3.542
3.461
3.429
3.412
3.390
3.356
3.331
3.299
3.267
3.145
3.095
3.067
3.049
2.888
2.844
2.052
2.026
1.625
1.606
1.576
1.537
1.479
1.436
1.250
1.131
1.092
1.065
0.998
0.898
0.864
0.848
OMe
OMe
BnO
HO
151
ppm
82.82
0.40
0.86
1.60
1.00
3.59
15.55
6.65
8.00
7.43
3.14
9.69
2.08
12.72
27.82
66.75
15.75
19.38
11.83
21.18
9.30
54.48
17.14
13.58
12.22
33.27

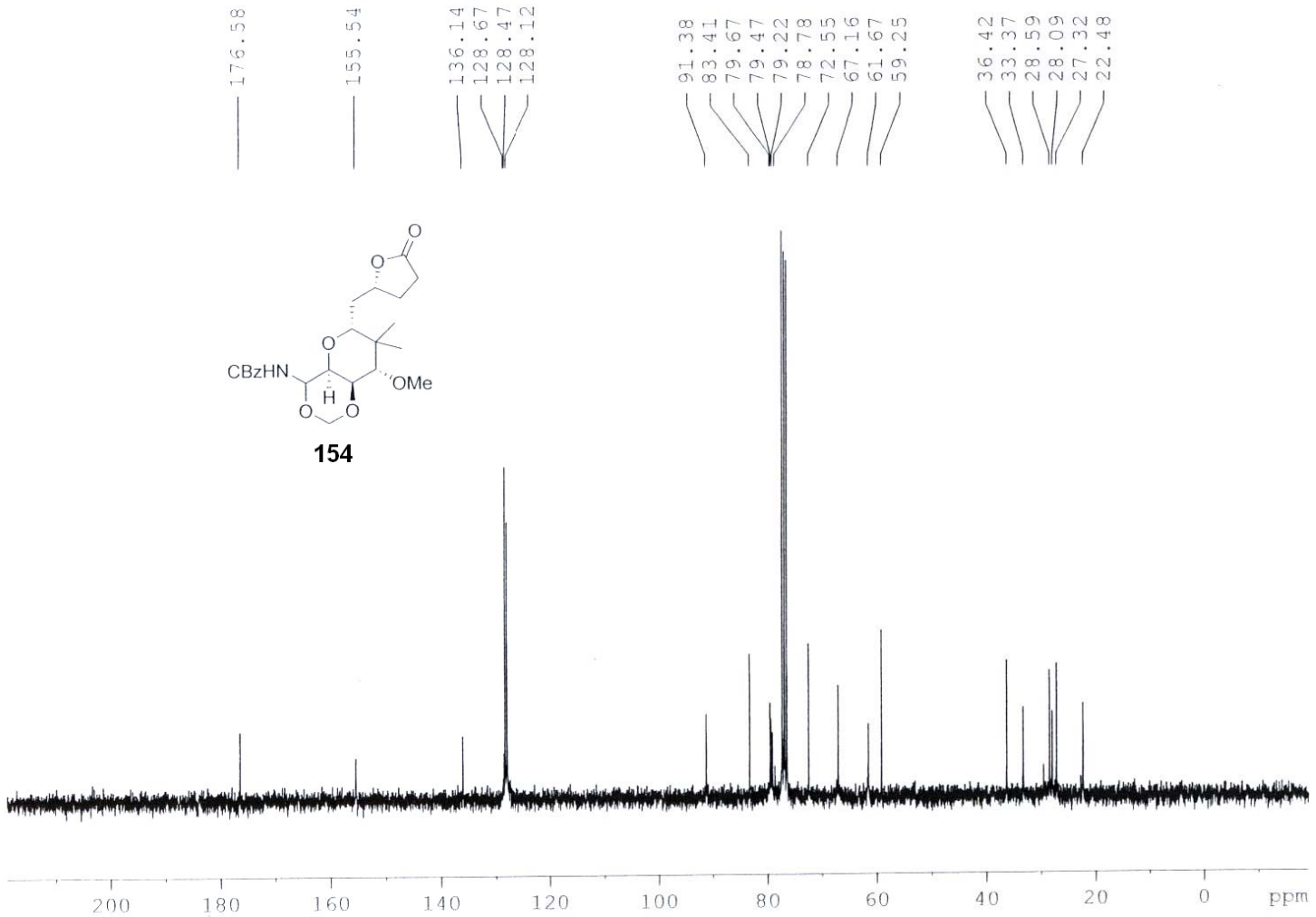
26.11
26.15
28.89
29.21
29.26
29.35
29.44
29.53
29.77
31.48
31.81
33.06
34.01
34.56
38.33
51.75
54.20
54.48
59.69
60.77
62.17
62.27
66.14
68.13
68.63
75.74
76.28
76.59
77.01
77.21
77.43
78.60
83.88
84.36
95.13
96.00
96.14
104.67
104.87
126.09
126.18
127.66
127.71
127.79
127.91
128.11
128.23
129.57
129.64
129.92
130.03
136.81
137.63
155.67
156.16
OMe
OMe
151
BnO
HO
ppm
200
180
160
140
120
100
80
60
40
20
0

7.337
7.316
7.293
7.291
7.288
7.285
7.283
7.280
7.273
7.265
7.262
7.259
7.257
7.254
7.252
7.249
7.247
7.244
7.241
7.239
7.237
7.234
7.231
7.226
7.221
7.206
7.199
7.182
5.021
3.890
3.411
3.396
3.358
3.342
3.335
3.325
3.298
3.276
3.173
3.129
2.863
1.970
1.947
1.922
1.863
1.562
1.410
1.263
1.087
1.072
0.978
0.913
0.875
0.863
OMe
OMe
152
BnO
Bn
ppm
1.00
1.49
0.74
1.74
6.07
11.20
9.10
7.23
6.35
16.01
3.75
26.70
8.25
16.06
36.37
3.21
6.38
4.66
4.20
11.39

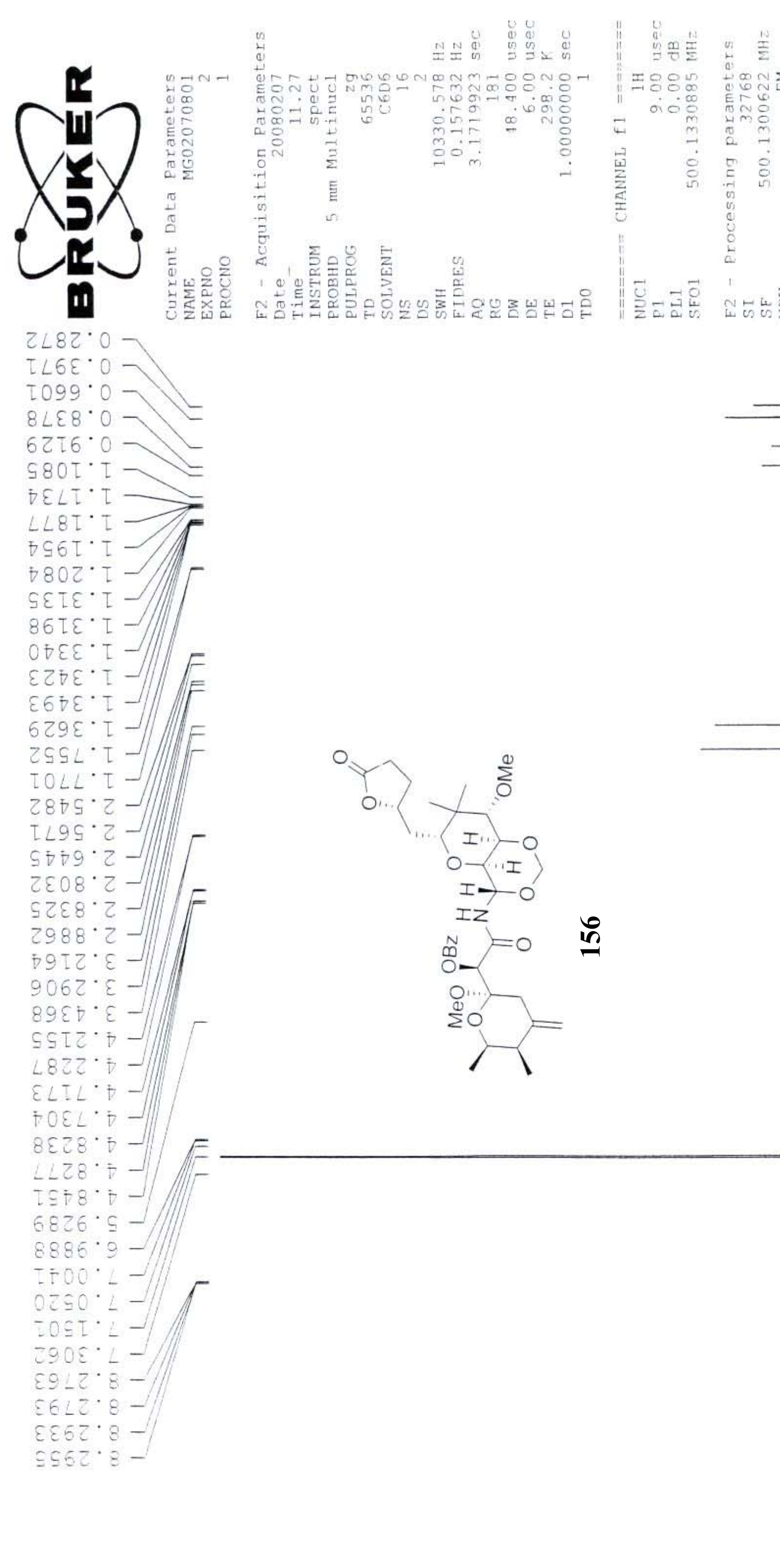
153
OMe
OMe
CBzHN
H
O
O
O
O
ppm
10
9
8
7
6
5
4
3
2
1
4.22
0.19
0.39
3.53
0.57
1.05
0.96
0.99
1.87
2.78
1.84
1.00
0.93
1.13
3.66
2.38
2.99
2.79
7.349
7.331
7.269
6.744
6.717
5.182
5.143
5.129
5.120
5.113
5.073
4.935
4.922
4.858
4.836
4.085
4.071
4.060
4.046
3.827
3.772
3.719
3.683
3.582
3.501
3.389
3.293
3.162
2.939
2.931
2.054
1.987
1.968
1.950
1.928
1.908
1.888
1.870
1.858
1.833
1.811
1.794
1.778
1.764
1.605
1.554
1.545
1.532
1.496
1.480
1.456
1.438
1.239
0.923

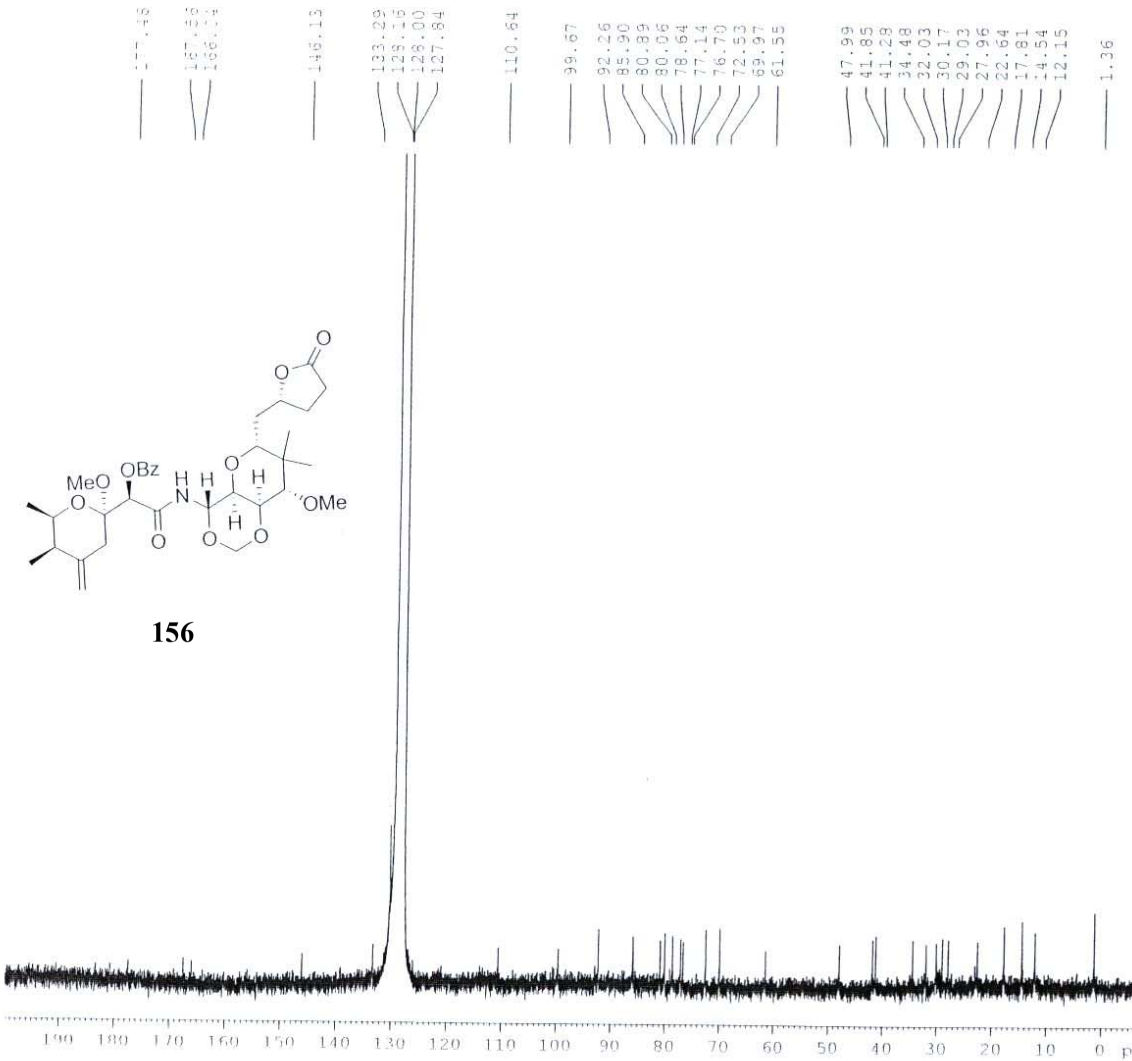
OMe
OMe
CBzHN
153
200
180
160
140
120
100
80
60
40
20
0
ppm

7.354
7.332
7.269
6.179
6.149
5.231
5.211
5.171
5.130
5.115
5.093
4.842
4.820
4.521
4.499
4.473
3.748
3.686
3.677
3.645
3.637
3.578
3.564
3.507
3.391
2.976
2.945
2.682
2.653
2.640
2.612
2.591
2.523
2.501
2.492
2.472
2.413
2.395
2.375
2.354
2.333
1.926
1.897
1.867
1.859
1.827
1.642
1.631
1.593
1.581
1.257
1.236
0.969
0.935
0.874
OMe
CBzHN
154
ppm
1.00
0.13
6.04
0.26
1.33
1.34
0.48
2.49
1.56
0.77
4.07
0.54
0.41
1.34
1.71
2.80
2.25
1.86
2.35
2.44
4.05
0.81
4.20
1.89


176.58
155.54
136.14
128.67
128.47
128.12
91.38
83.41
79.67
79.47
79.22
78.78
72.55
67.16
61.67
59.25
36.42
33.37
28.59
28.09
27.32
22.48
CBzHN
OMe
H
200
180
160
140
120
100
80
60
40
20
0
ppm

154


BRUKER
Current Data Parameters
NAME MG02070801
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20080207
Time_ 11.27
INSTRUM spect
PROBHD 5 mm Multinucl
PULPROG zg
TD 65536
SOLVENT C6D6
NS 16
DS 2
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1719923 sec
RG 181
DW 48.400 usec
DE 6.00 usec
TE 298.2 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 9.00 usec
PL1 0.00 dB
SFO1 500.1330885 MHz
F2 - Processing parameters
SI 32768
SF 500.1300622 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 0.80
ppm
156
MeO
OBz
OMe
H
N
O



156

BRUKER

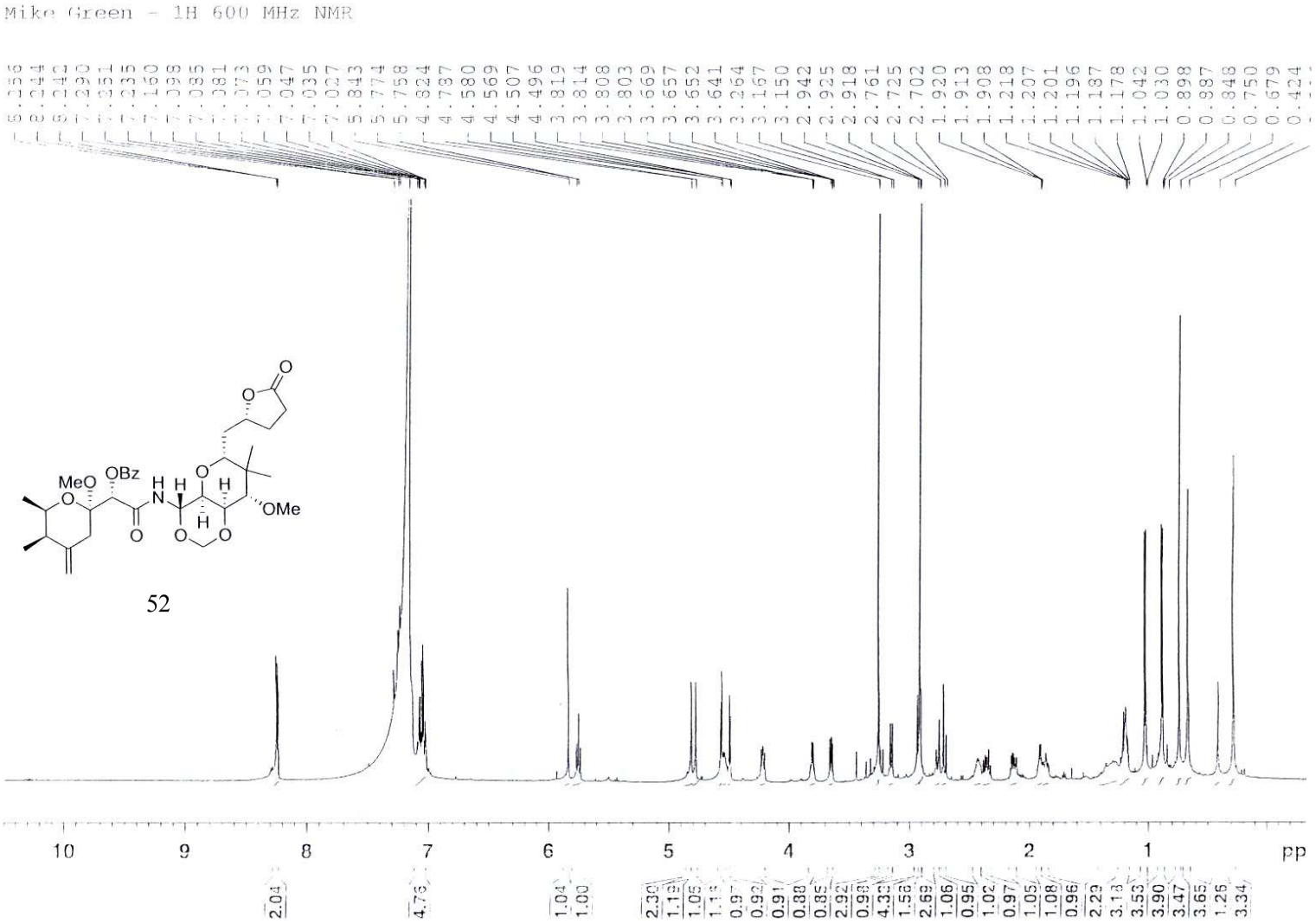
Current Data Parameters
NAME MG02080801
EXPNO 2
PROCNO 1

F2 - Acquisition Parameters
Date_ 20080208
Time 18.20
INSTRUM spect
PROBHD 5 mm TBI 1H-BB
PULPROG zgpg
TD 65536
SOLVENT C6D6
NS 40745
DS 4
SWH 36231.883 Hz
FIDRES 0.552855 Hz
AQ 0.9044606 sec
RG 6502
DW 13.800 usec
DE 6.00 usec
TE 294.2 K
D1 5.00000000 sec
d11 0.03000000 sec
DELTA 4.90000010 sec
TD0 1

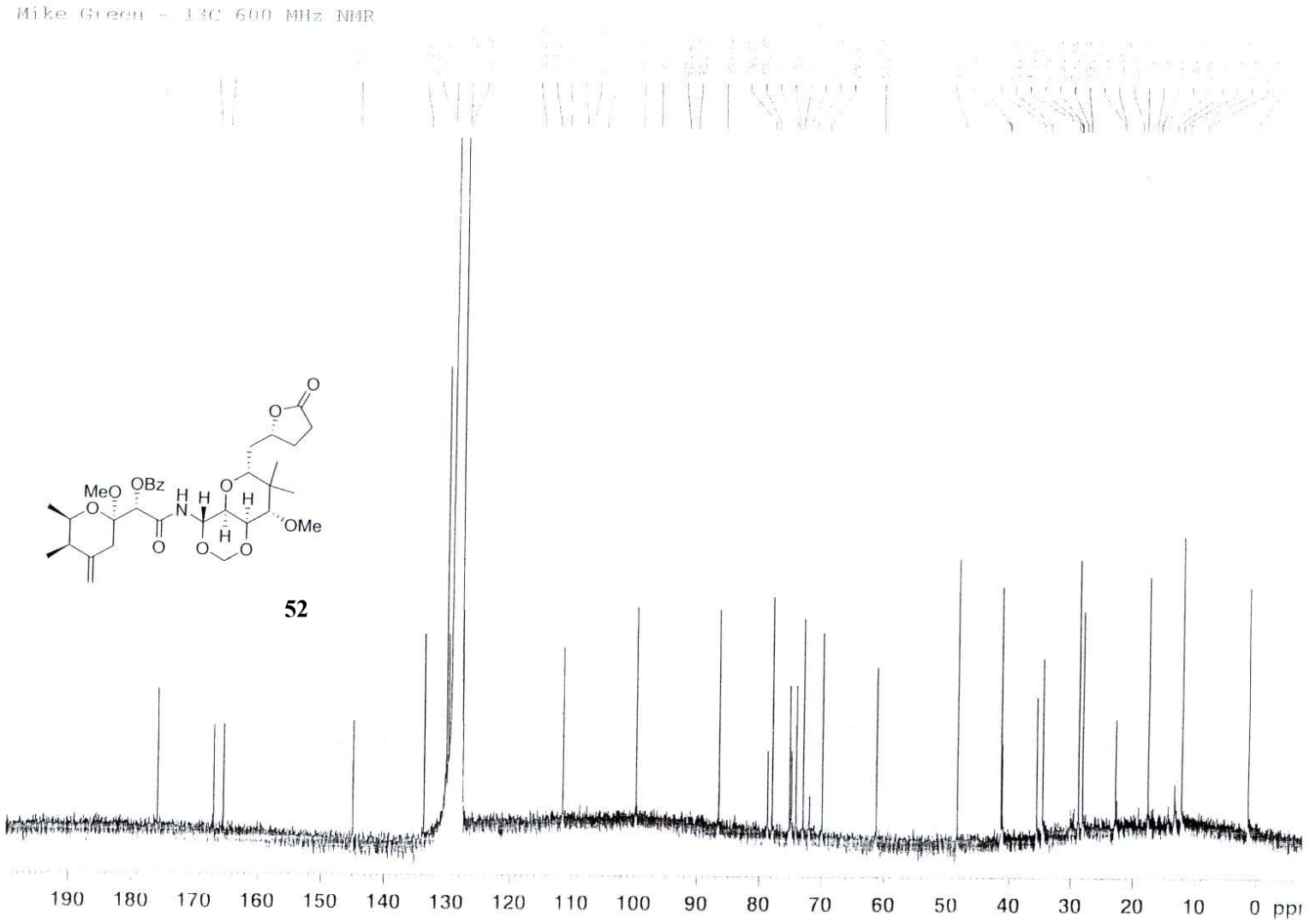
======== CHANNEL f1 ========
NUC1 13C
P1 9.00 usec
PL1 -1.00 dB
SFO1 151.1039906 MHz

======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 8.00 dB
PL12 29.68 dB
PL13 27.10 dB
SFO2 600.8724035 MHz

F2 - Processing parameters
SI 32768
SF 151.0888545 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.00


Mike Green - 1H 600 MHz NMR
MeO
OBz
H
N
H
O
H
H
OMe
O
O
O
O
O
O
O
10
9
8
7
6
5
4
3
2
1
pp

52


Mike Green - 13C 600 MHz NMR
MeO
OBz
H
N
H
O
H
H
OMe
O
O
O
O
O
O
O
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

52

8.363
8.358
8.354
8.336
8.331
8.117
7.082
7.057
7.039
7.034
7.028
7.016
6.992
6.969
6.203
5.252
5.246
5.221
5.215
4.871
4.865
4.848
4.840
4.834
4.827
4.332
4.310
4.017
3.170
3.141
3.096
3.047
2.897
2.868
2.821
2.661
2.655
2.012
1.994
1.989
1.978
1.962
1.955
1.584
1.361
1.316
1.290
1.193
1.161
1.152
1.116
1.095
0.758
0.427
0.289
ppm
1.88
1.01
4.18
1.00
1.07
3.17
1.04
0.57
1.19
1.22
1.26
2.89
1.38
0.55
1.81
3.16
1.51
1.19
1.45
1.52
2.49
1.66
1.25
7.97
2.02
3.90
3.36
2.70
3.19
MeO
OBz
H
N
H
O
O
O
O
O
H
H
O
OMe
O
O
O
157

175.87
167.26
166.27
146.86
133.40
130.83
110.82
100.27
91.77
84.13
80.20
79.88
78.16
73.18
72.38
70.24
61.73
58.98
48.49
42.54
36.85
35.13
33.38
32.30
29.00
28.53
27.95
23.38
18.50
14.68
14.56
12.63
1.75
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
OMe
OBz
MeO
H
N
O

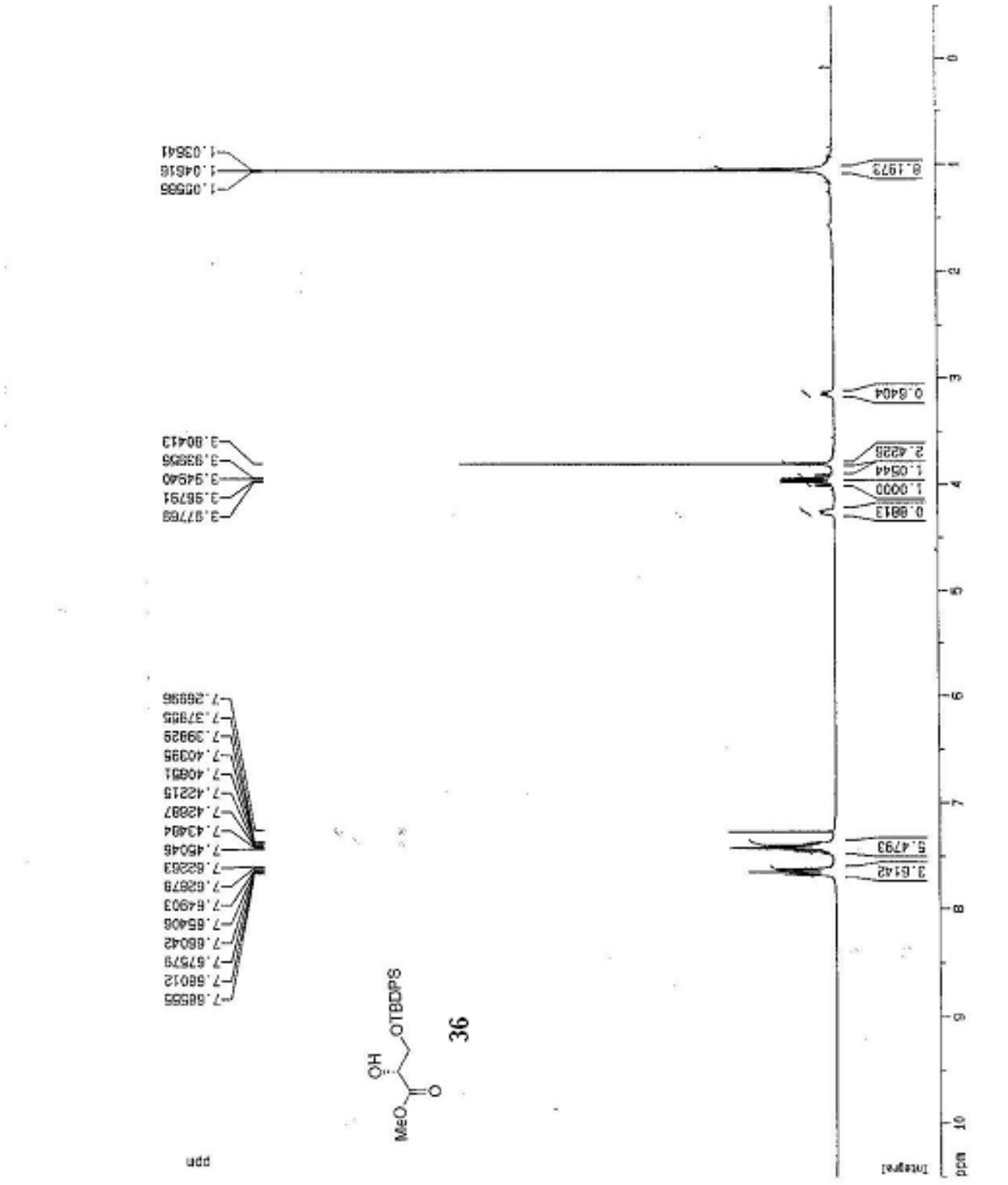
157

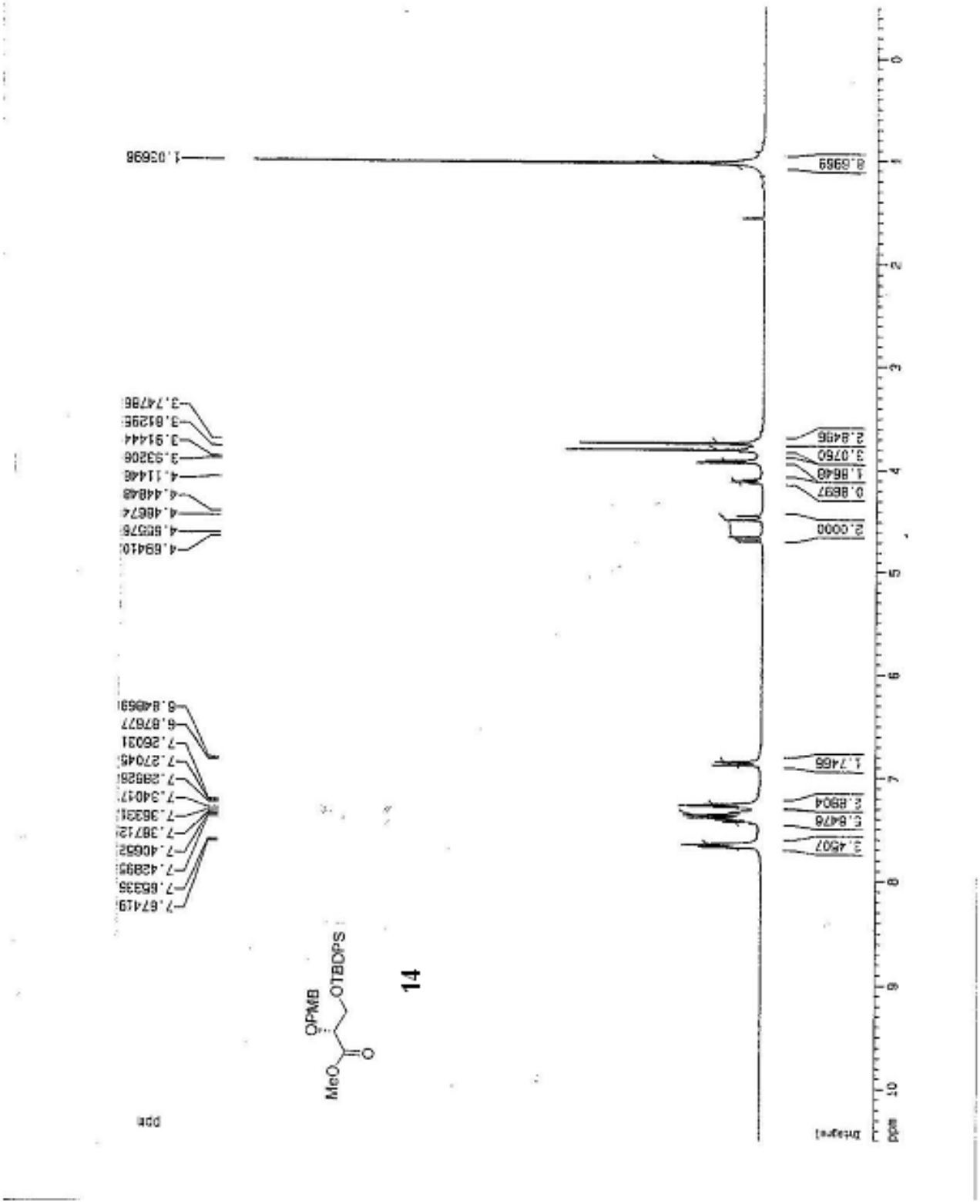
1

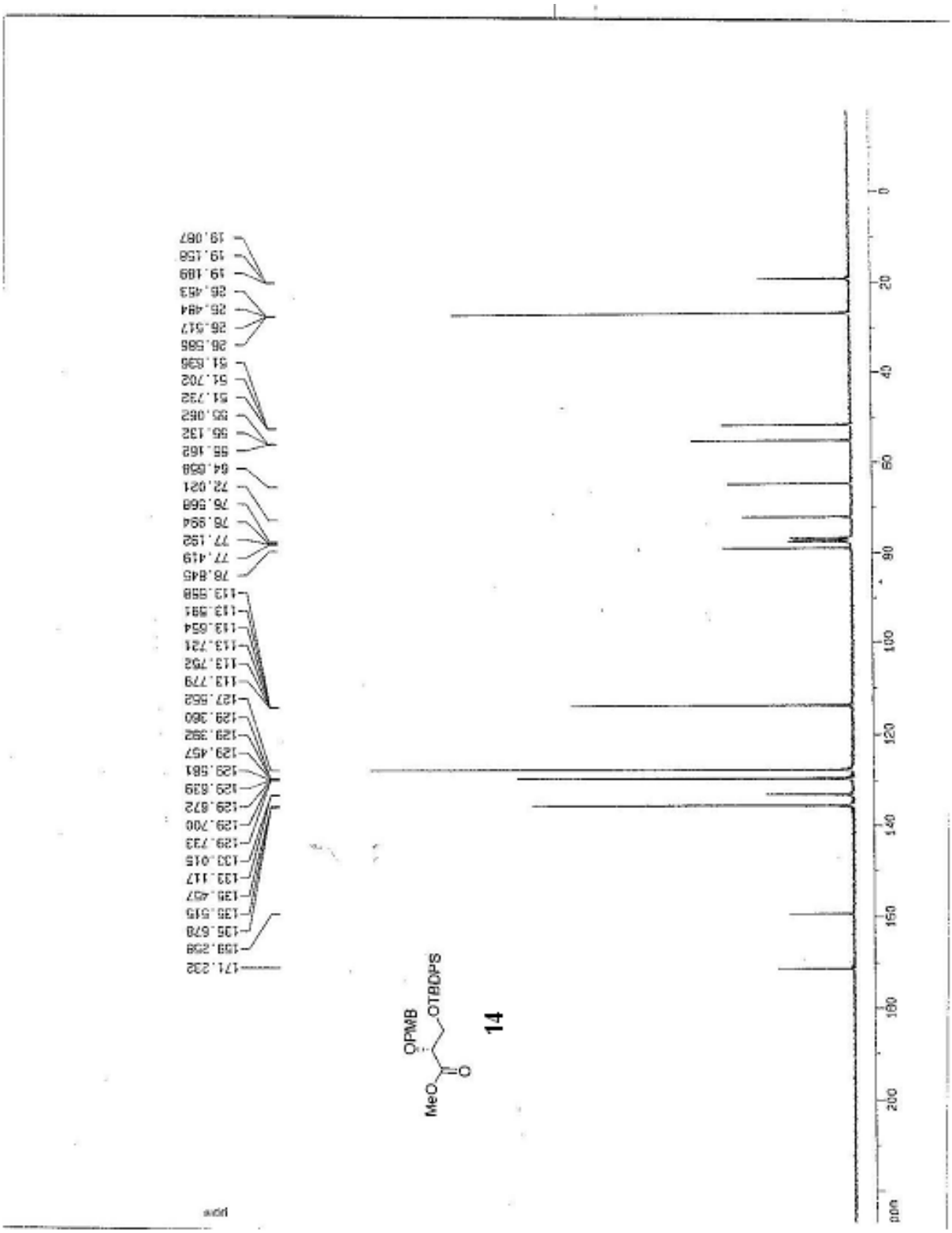
1

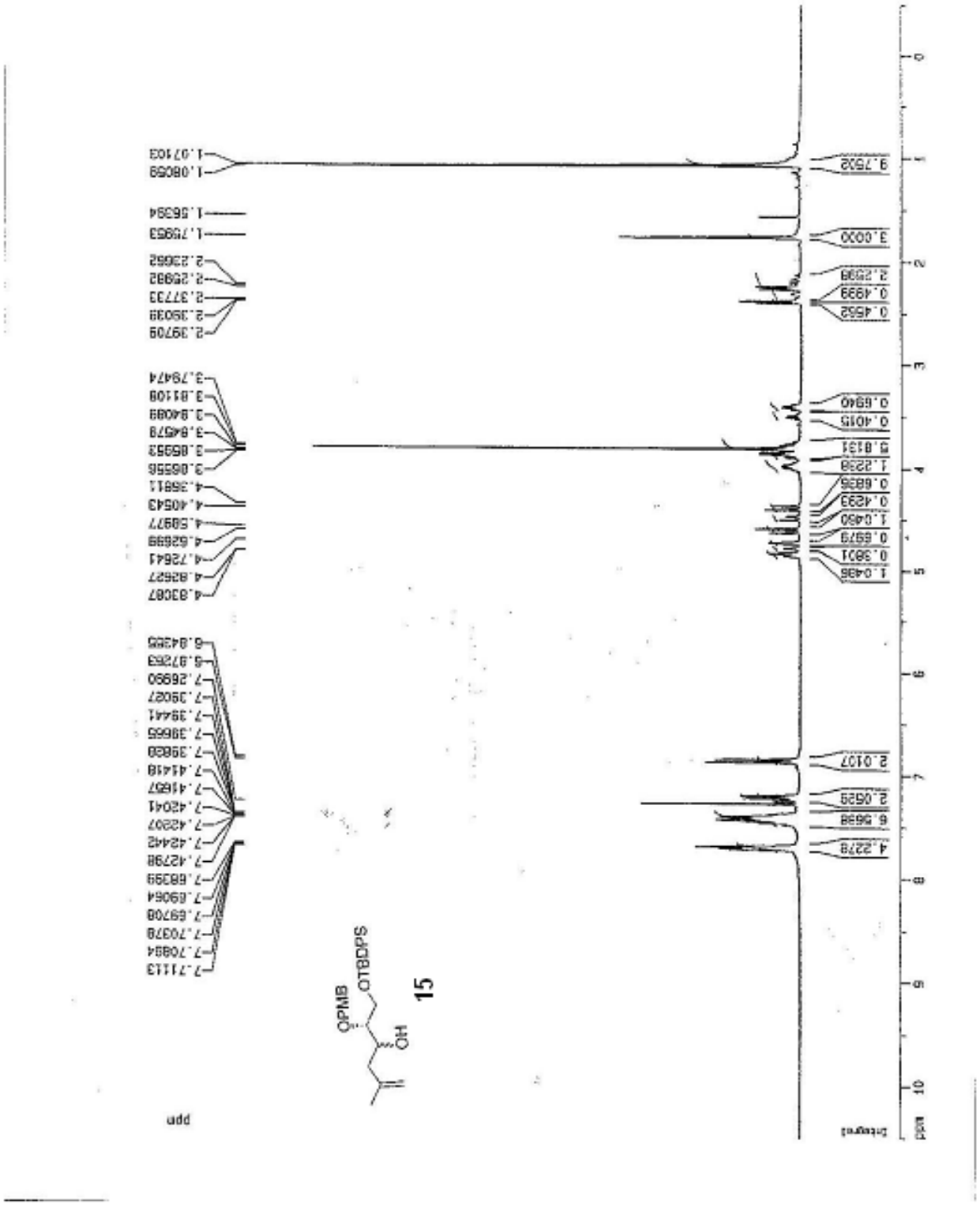
APPENDIX D

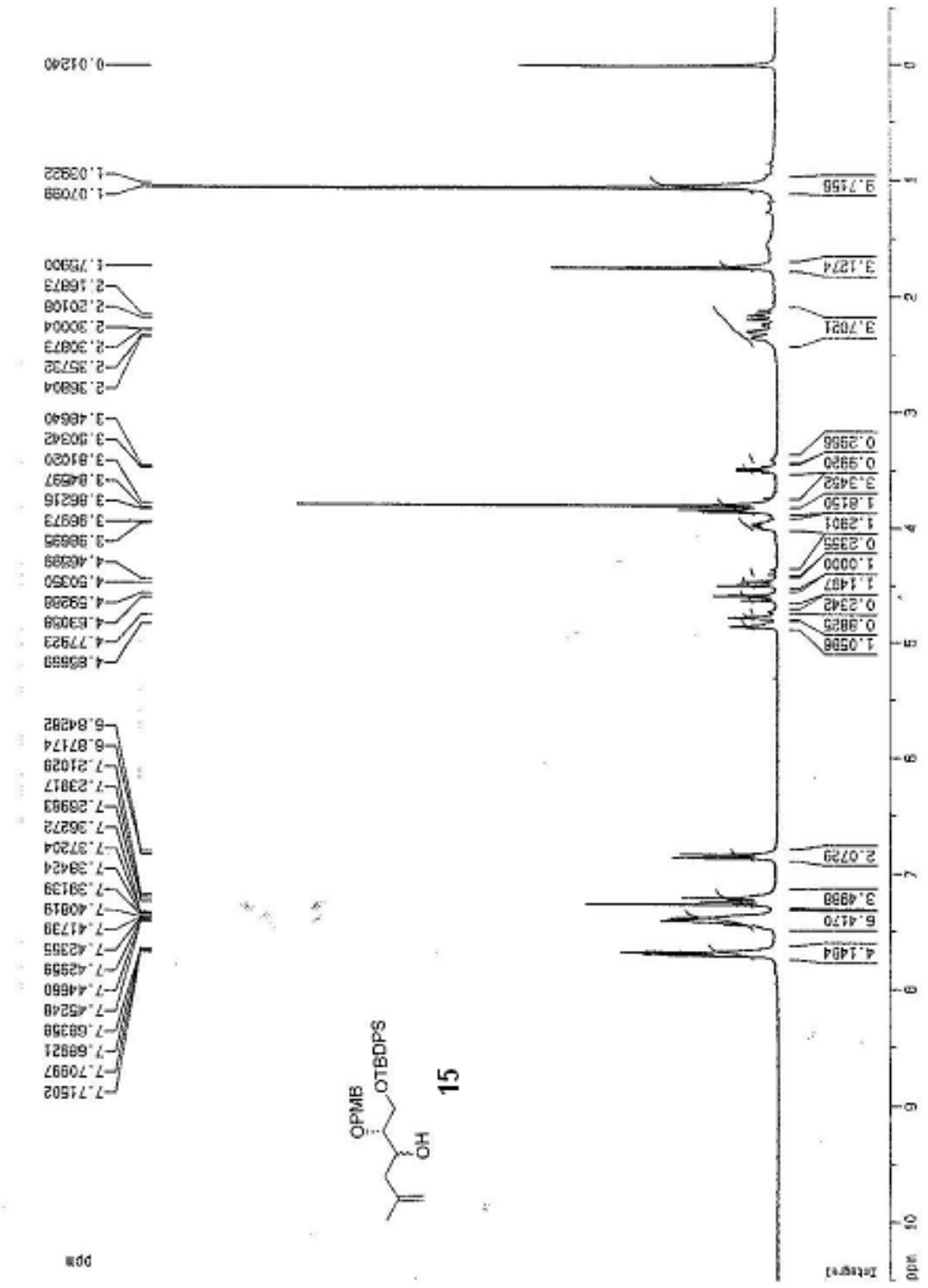
PSYMBERIN SPECTRA

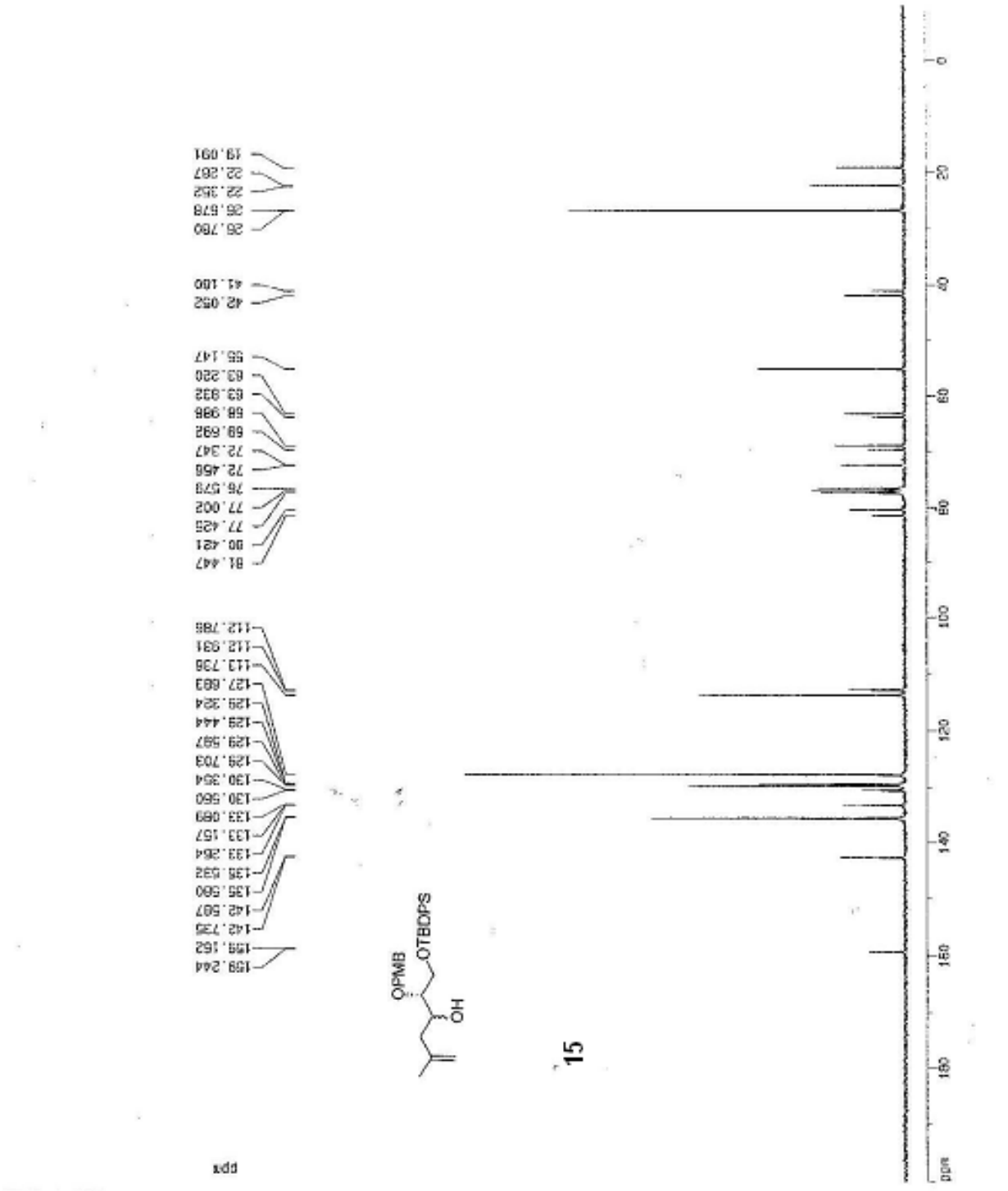

1.03641
1.04516
1.05586
3.80413
3.93806
3.94940
3.96791
3.97769
7.26896
7.37885
7.39829
7.40395
7.40851
7.42215
7.42887
7.43404
7.45046
7.62263
7.62879
7.64903
7.65406
7.66042
7.67579
7.68012
7.68555
0.1973
0.8404
2.4228
1.0544
1.0000
0.8813
5.4793
3.6142
OTBDPS
OH
MeO
O
36
ppm
Integral

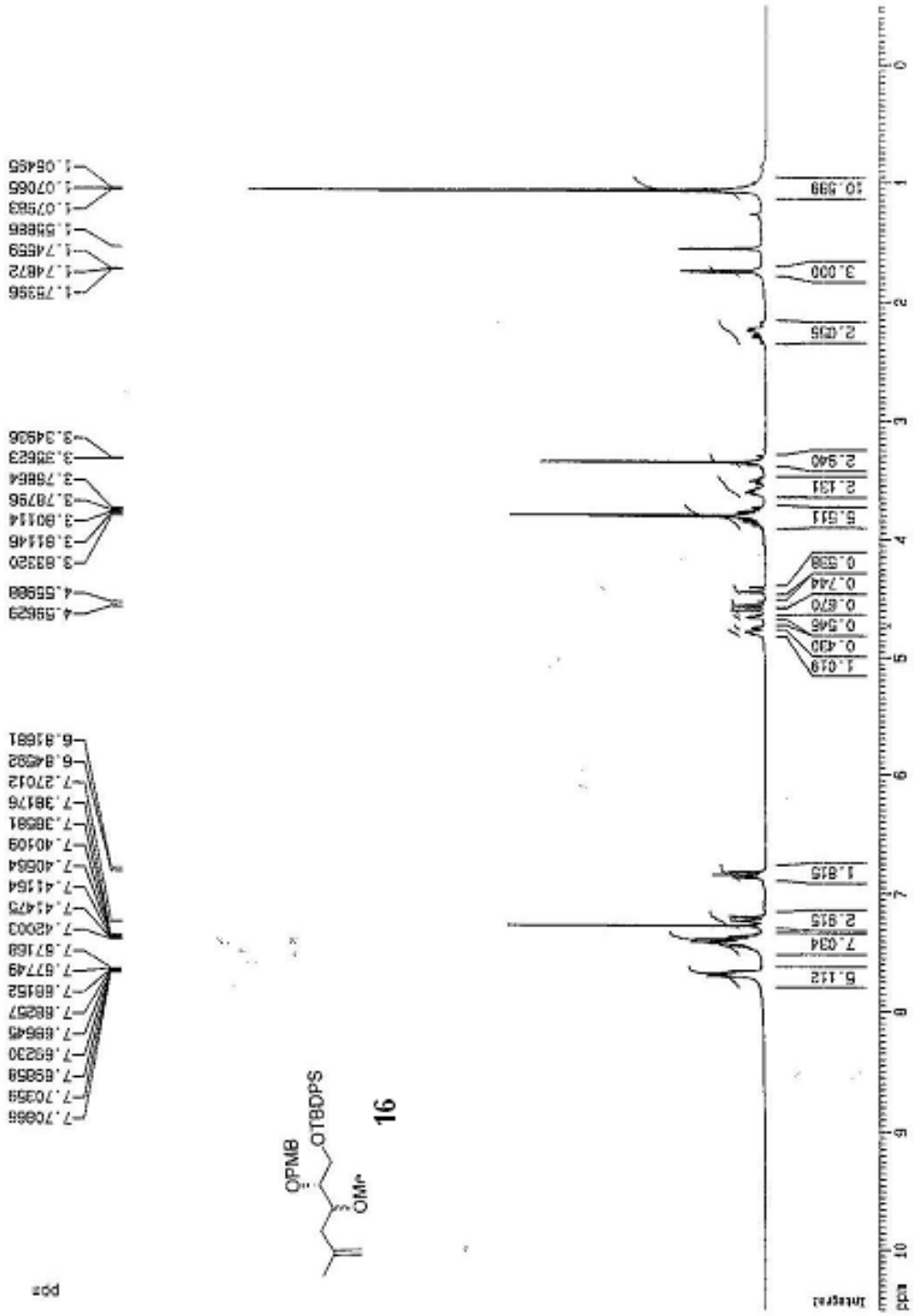

14
OPMB
OTBDPS
MeO
O
O
ppm

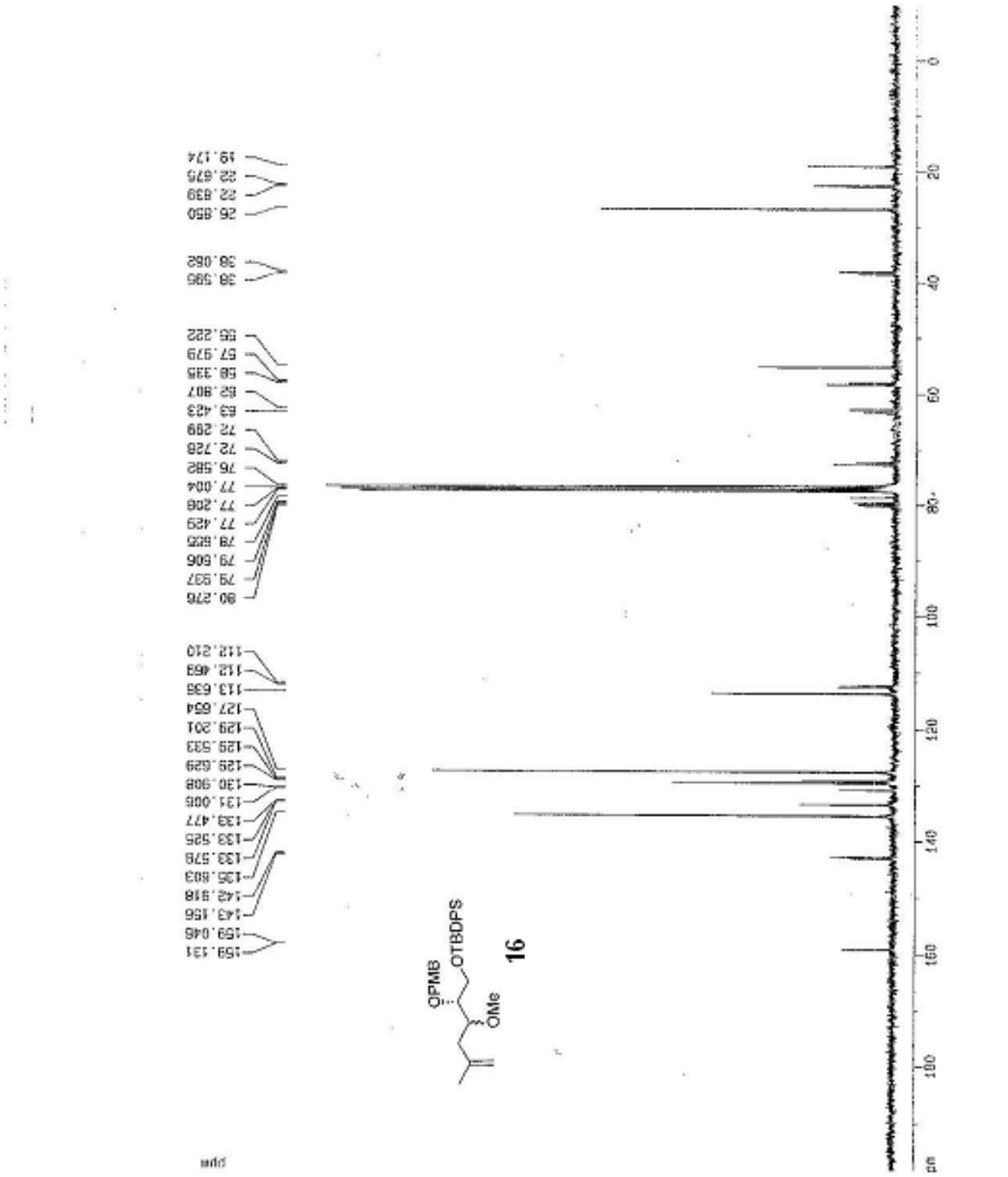

19.087
19.156
19.189
26.453
26.494
26.517
26.586
51.636
51.702
51.732
55.082
55.132
55.162
64.058
72.021
76.568
76.994
77.192
77.419
78.845
113.558
113.591
113.654
113.721
113.752
113.779
127.552
129.360
129.392
129.457
129.581
129.639
129.672
129.700
129.733
133.015
133.117
139.457
135.515
135.578
159.258
171.232
OPMB
OTBDPS
MeO
O
14
0
20
40
60
80
100
120
140
160
180
200
ppm

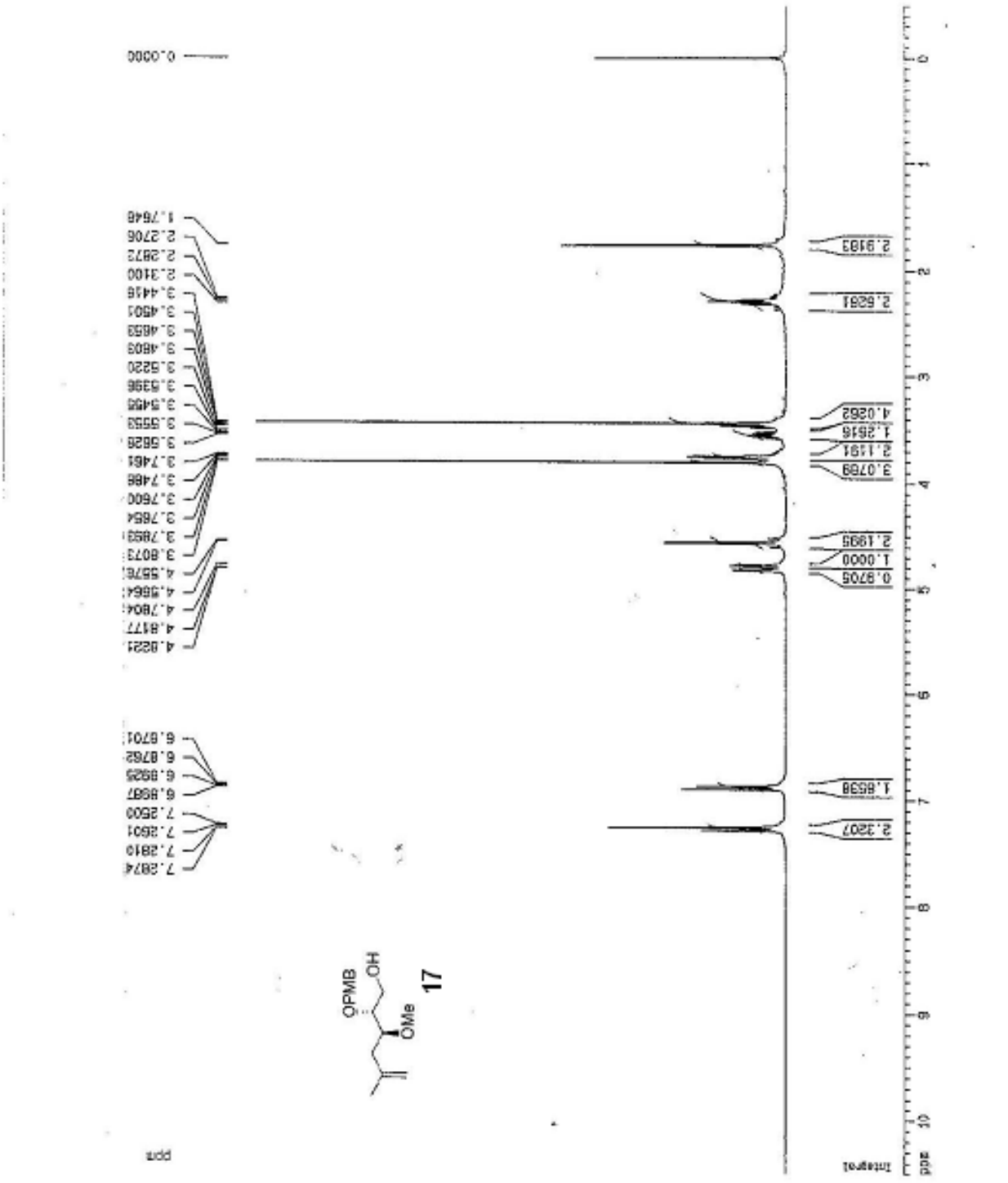

OPMB
OTBDPS
HO
15
ppm

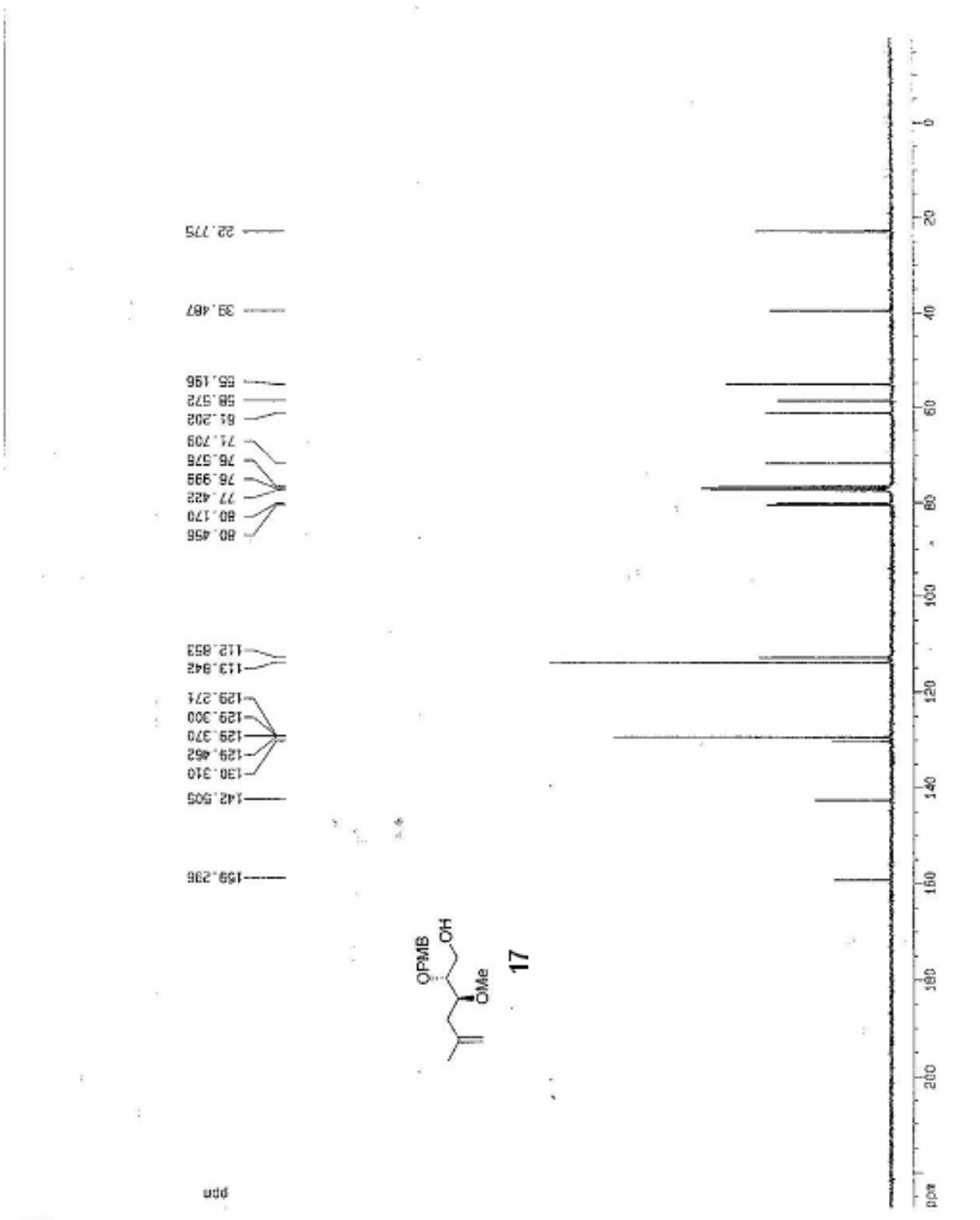

OPMB
OTBDPS
HO
15
ppm

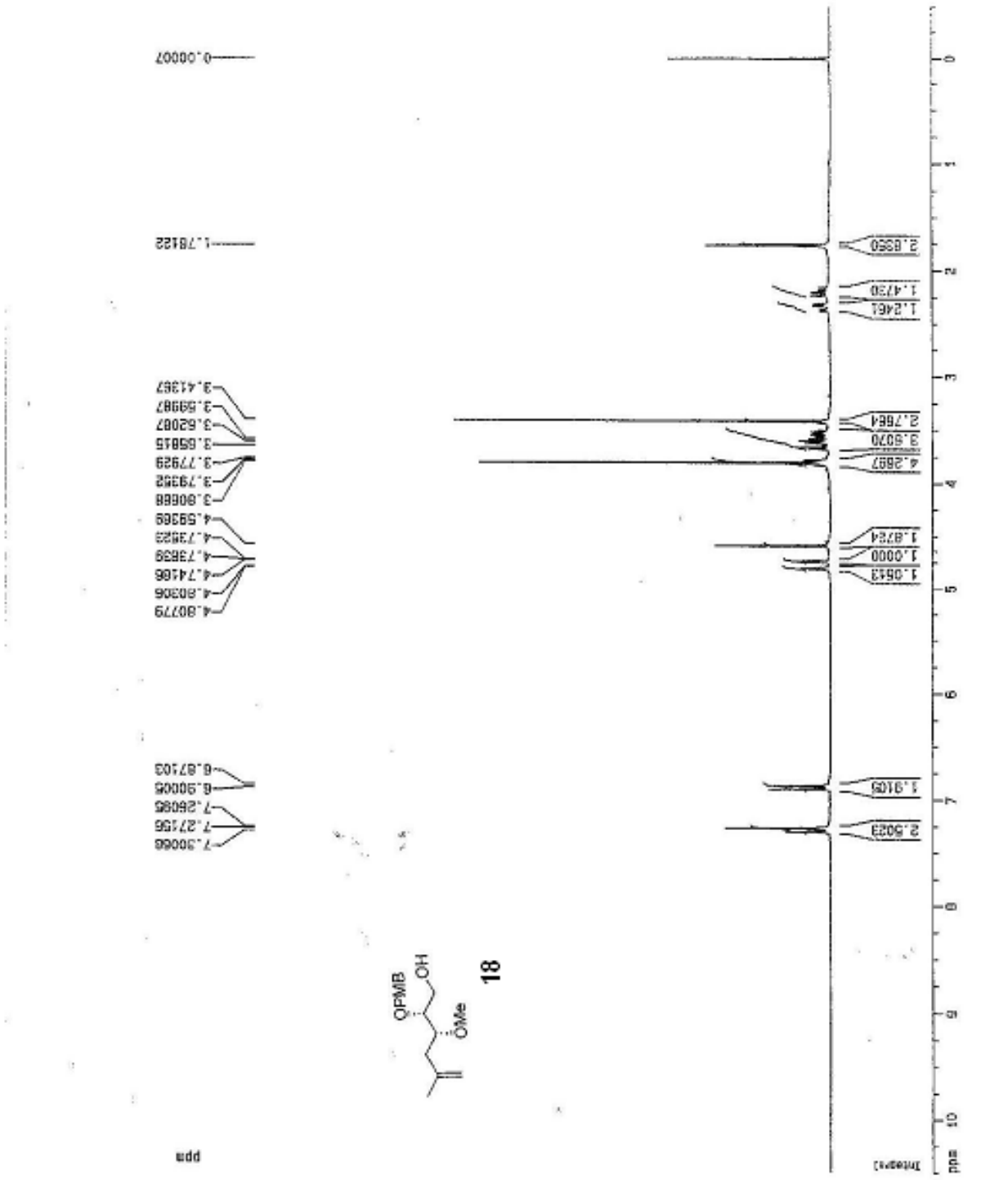

19.091
22.287
22.352
26.678
26.780
41.100
42.052
55.147
63.220
63.832
68.986
68.692
72.347
72.458
76.579
77.002
77.425
80.421
81.447
112.786
113.031
113.736
127.683
129.324
129.444
129.597
129.703
130.364
130.560
133.089
133.157
133.264
135.532
135.560
142.507
142.735
159.162
159.244
OPMB
OTBDPS
OH
15
ppm

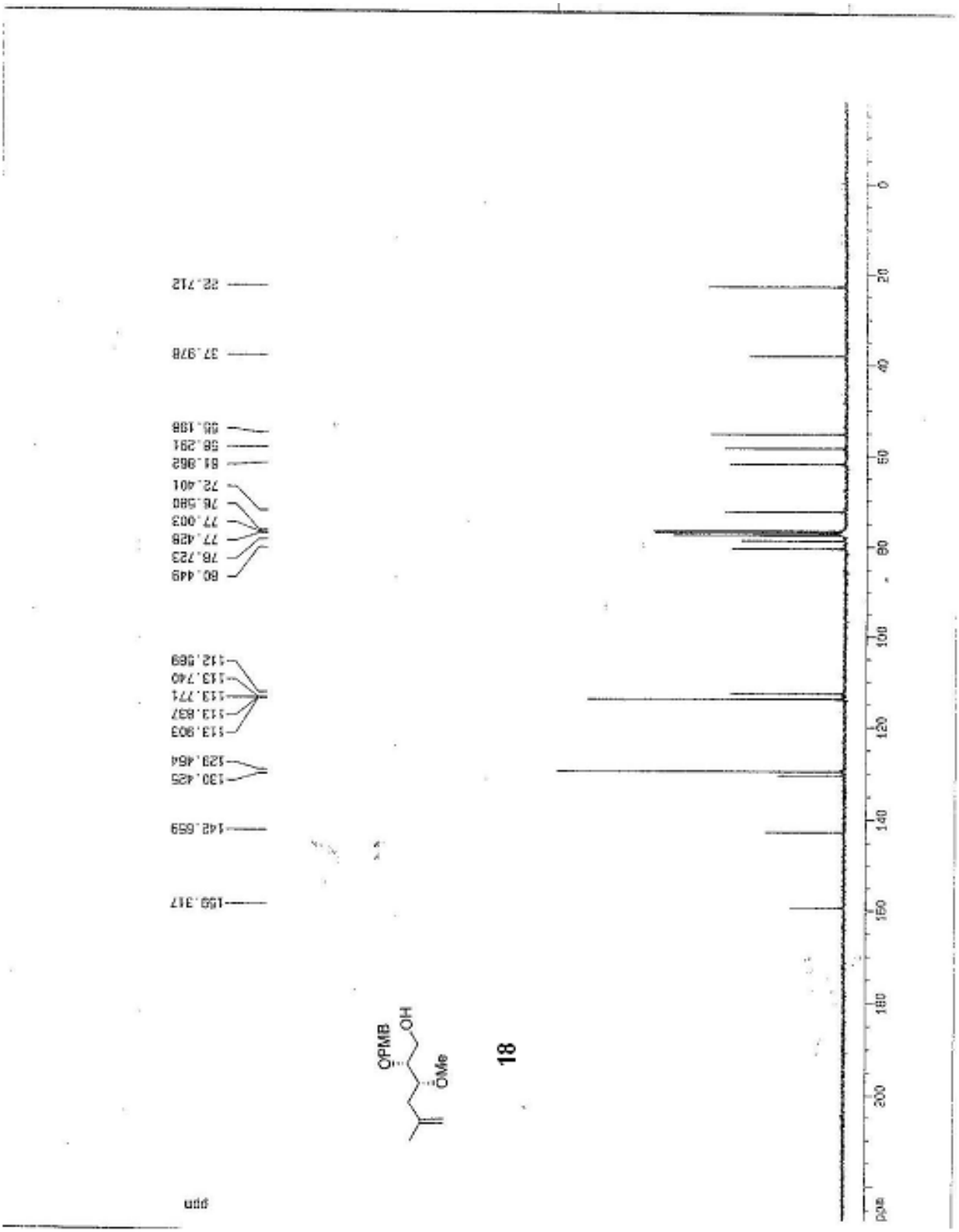

OPMB
OTBDPS
OMe
16
10.000
3.000
2.005
2.940
2.151
5.511
1.019
0.430
0.546
0.670
0.744
0.598
1.845
2.915
7.034
5.112
Integral
ppm


19.174
22.675
22.839
26.850
38.082
38.586
55.222
57.979
58.335
62.807
63.423
72.289
72.728
76.582
77.004
77.208
77.429
78.625
79.606
79.937
80.276
112.210
112.469
113.636
127.654
129.201
129.533
129.629
130.908
131.006
133.477
133.525
133.578
135.803
142.918
143.156
159.046
159.131
OPMB
OTBDPS
OMe
16
ppm

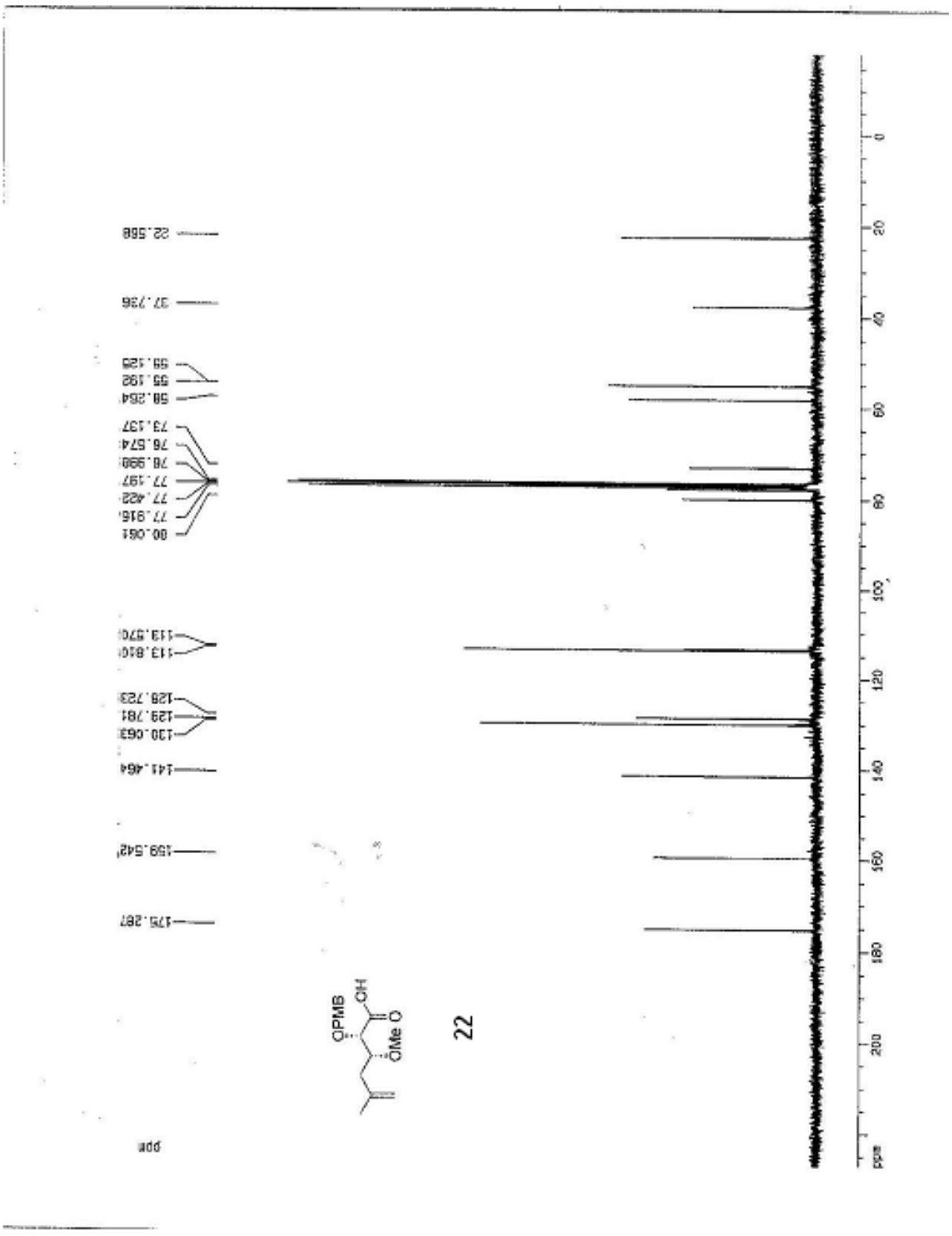

17
OPMB
OH
OMe
ppm
Integral

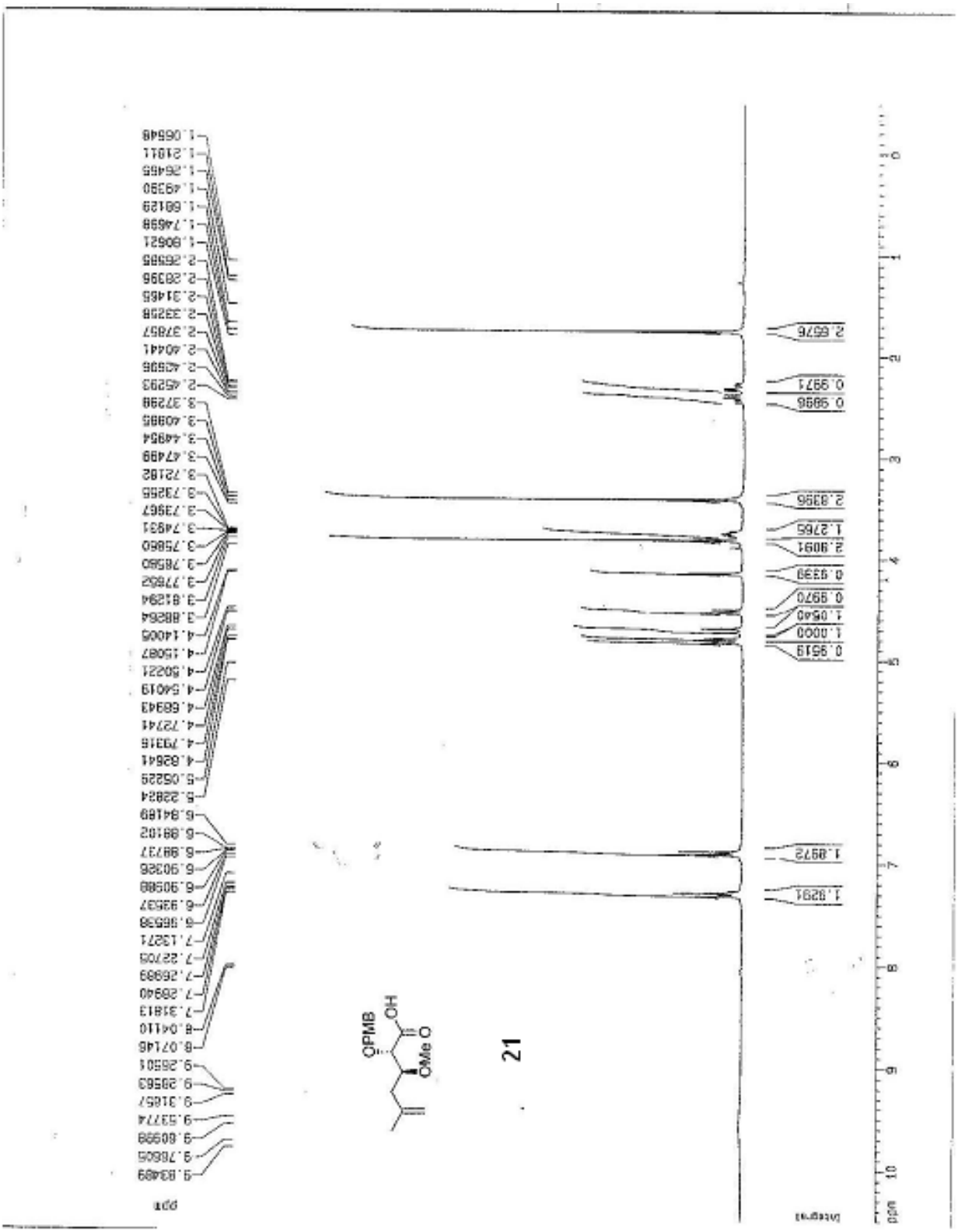

22.775
39.487
55.196
58.572
61.202
71.709
76.576
76.999
77.422
80.170
80.456
112.853
113.842
129.274
129.300
129.370
129.462
130.310
142.505
159.286
OPMB
OH
OMe
17
ppm


PMBO
OH
OMe
18

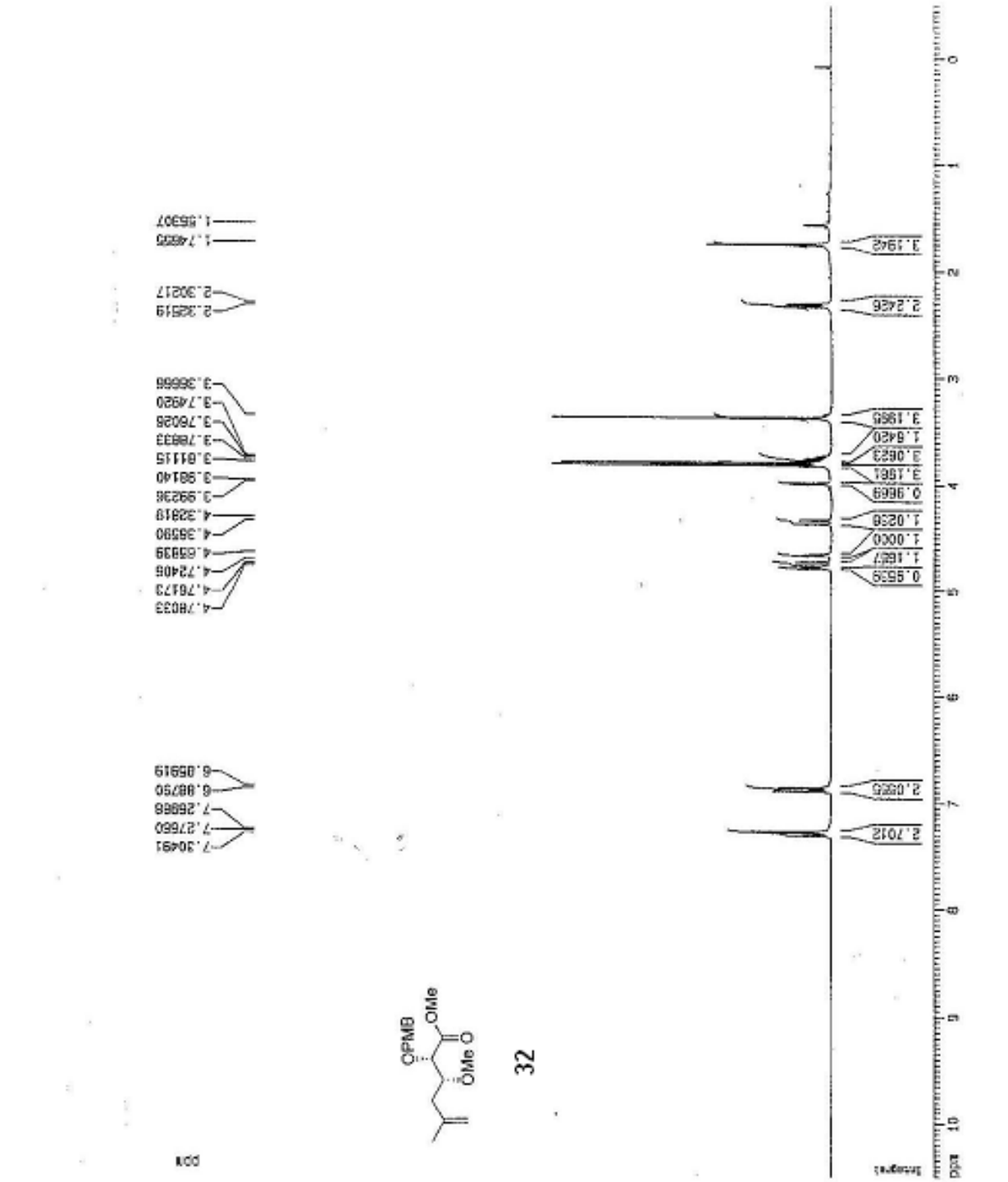

22.712
37.978
55.188
58.291
61.862
72.401
76.580
77.003
77.428
78.723
80.449
112.869
113.740
113.771
113.837
113.903
129.464
130.425
142.659
159.317
ppm
OH
OPMB
OMe
18

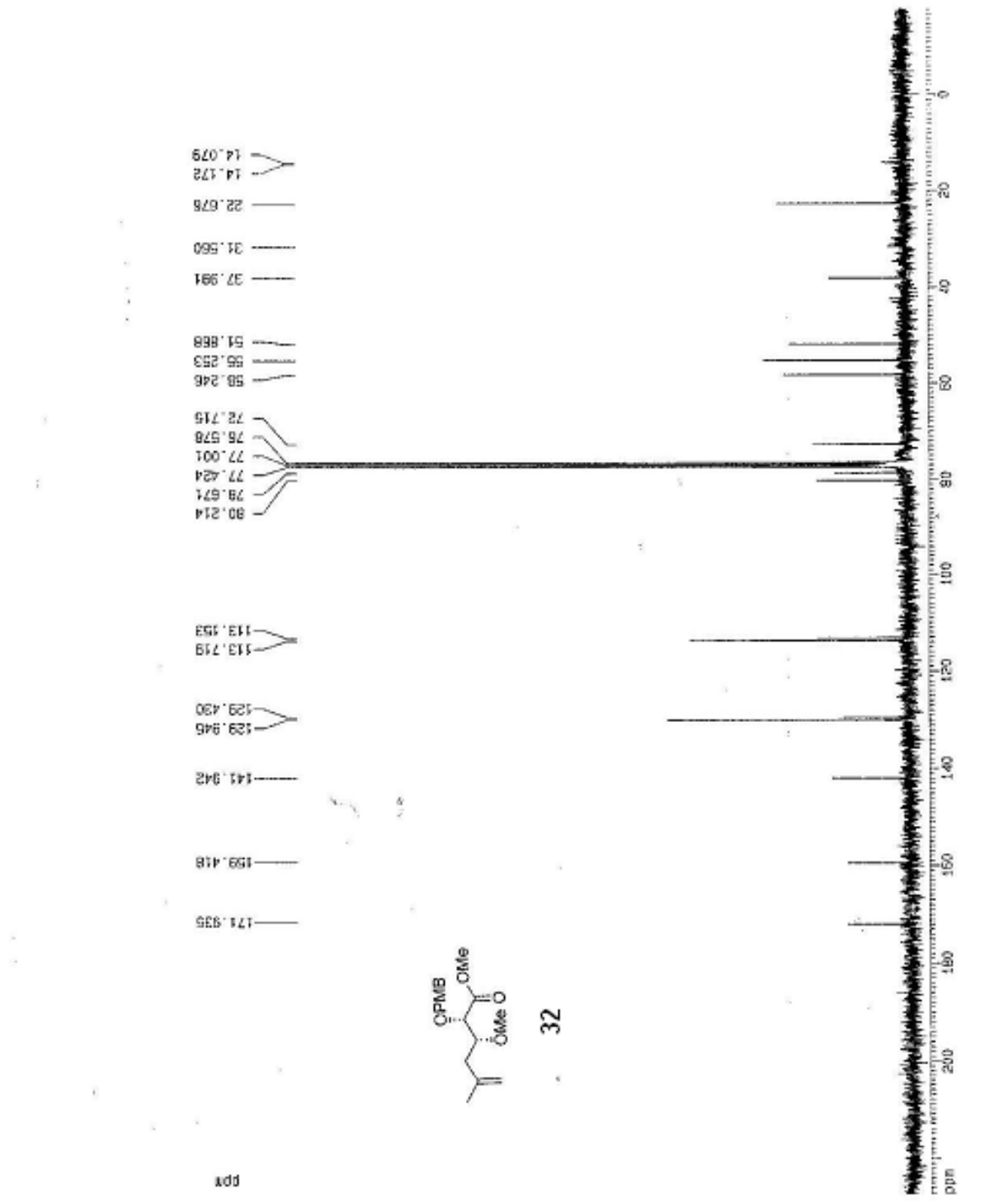
22
OPMB
OH
OMe
O
3.2174
2.3924
3.2763
4.8056
1.0053
1.0376
2.1761
1.0000
2.1080
2.2895
1.79475
2.33815
2.36277
2.37264
3.38089
3.77481
3.78091
3.78321
3.79709
3.80580
3.89988
4.00864
4.44787
4.67681
4.69166
4.72909
4.81422
5.88861
5.89065
6.89706
7.26556
7.26986
7.29338

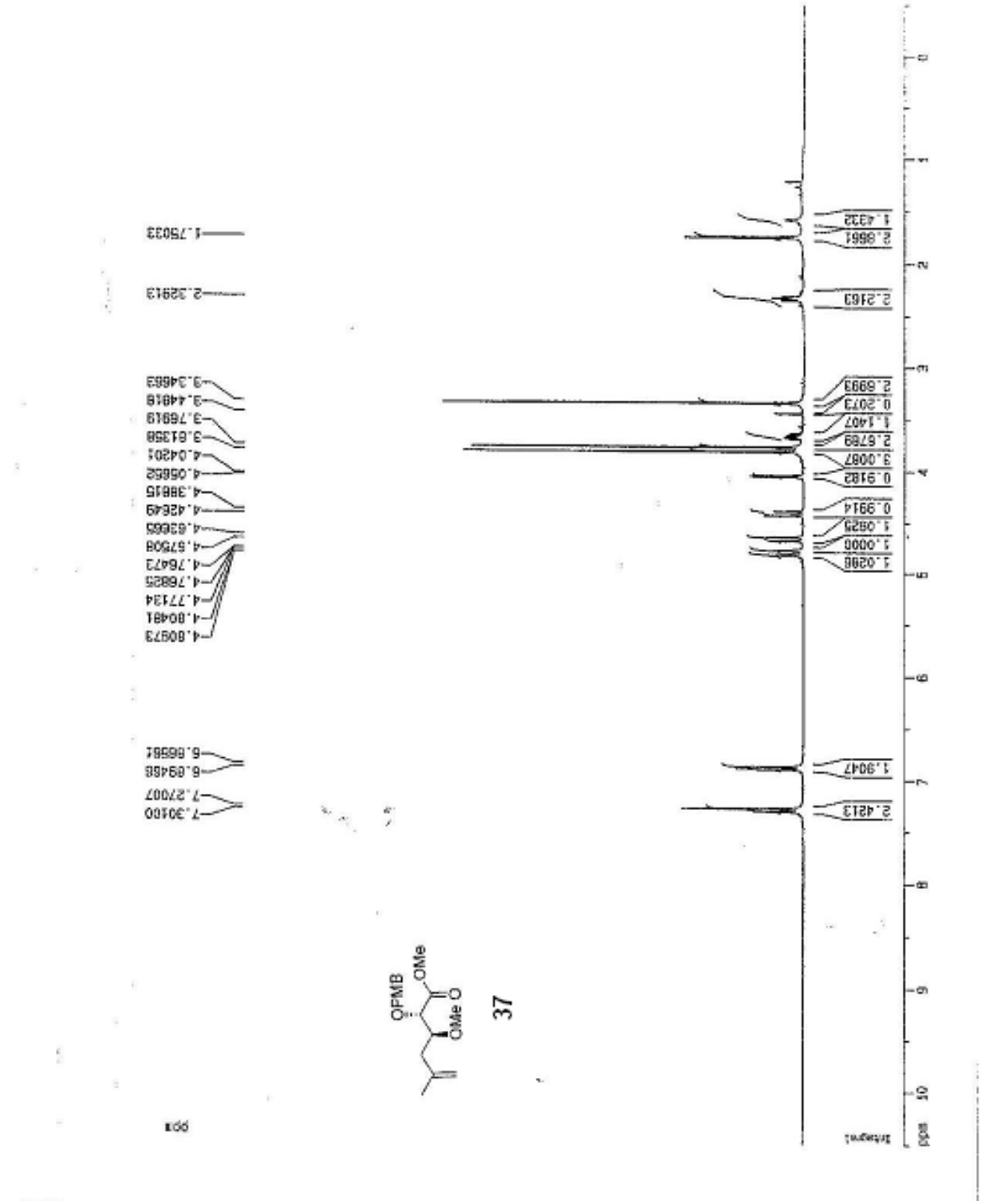

22.568
37.736
59.129
55.192
50.264
73.137
76.574
76.998
77.197
77.422
77.916
80.061
113.970
113.810
128.723
129.781
130.063
141.464
159.542
175.287
OPMB
OH
OMe O
22
ppm

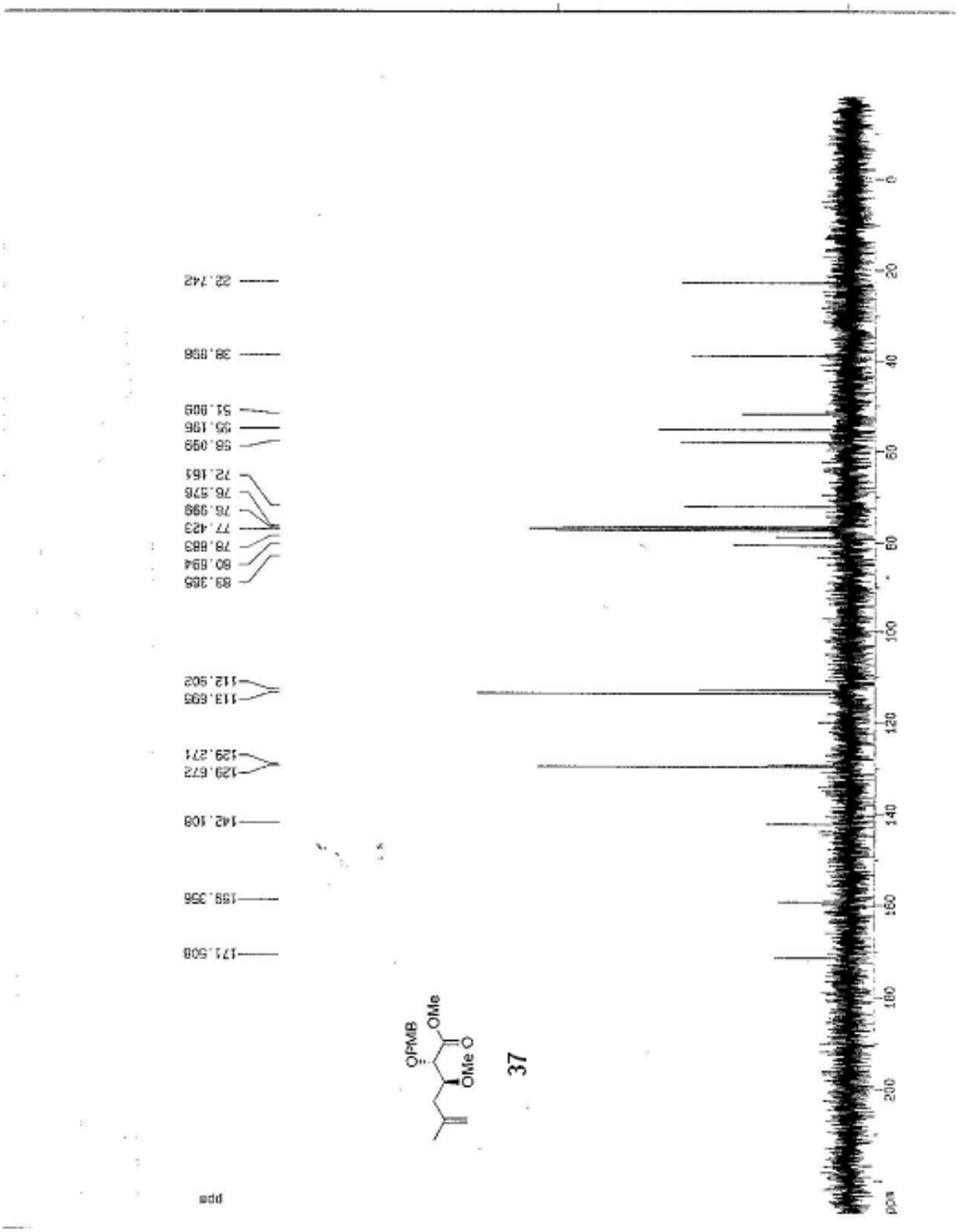

OPMB
OH
OMe O
21

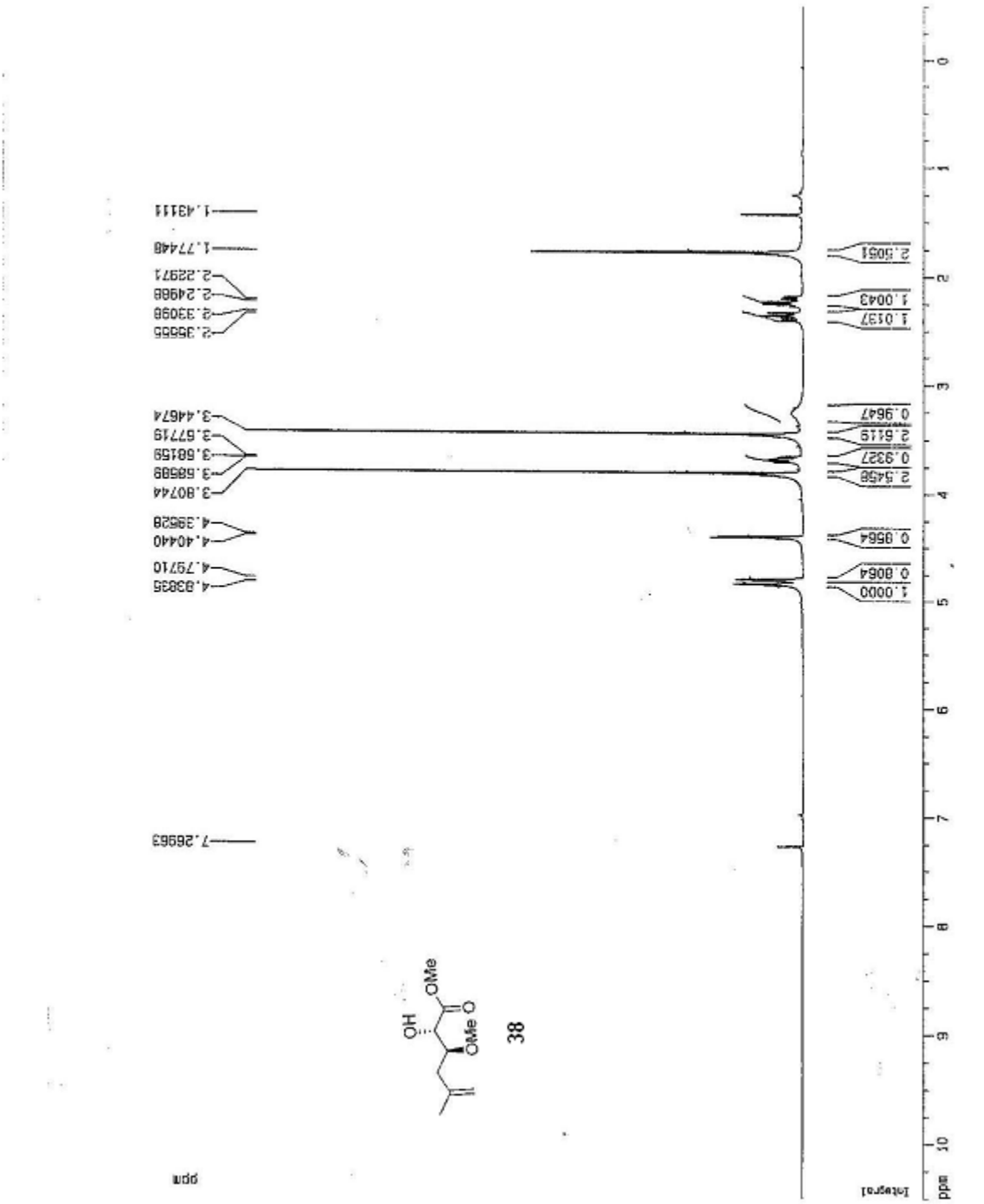
22.536
22.766
39.529
55.238
59.259
59.823
72.645
76.570
76.996
77.204
77.419
78.391
80.024
80.632
113.315
113.892
128.865
129.460
129.673
129.804
141.480
141.670
158.572
173.891
OPMB
OH
OMe O
21
ppm

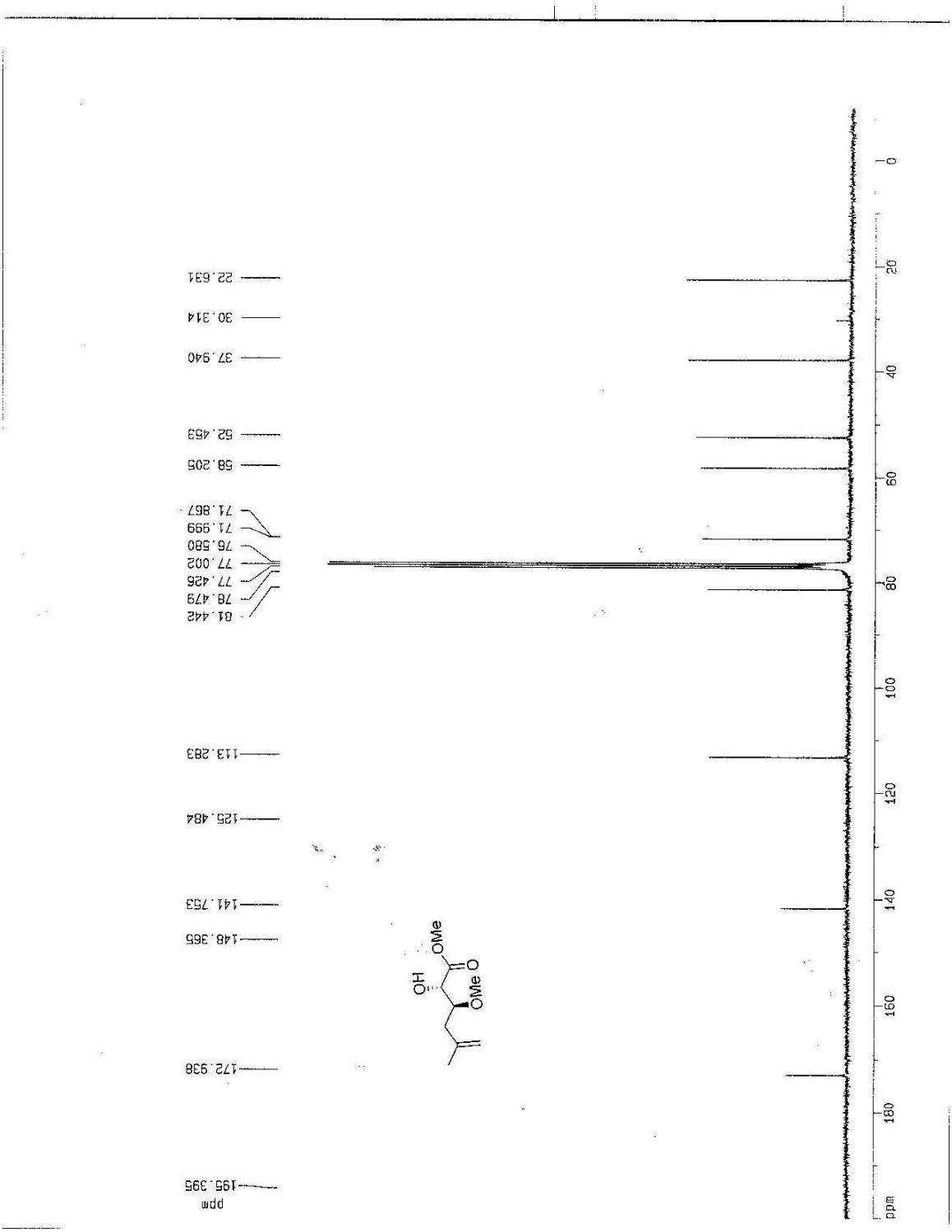

OPMB
OMe
OMe O
32

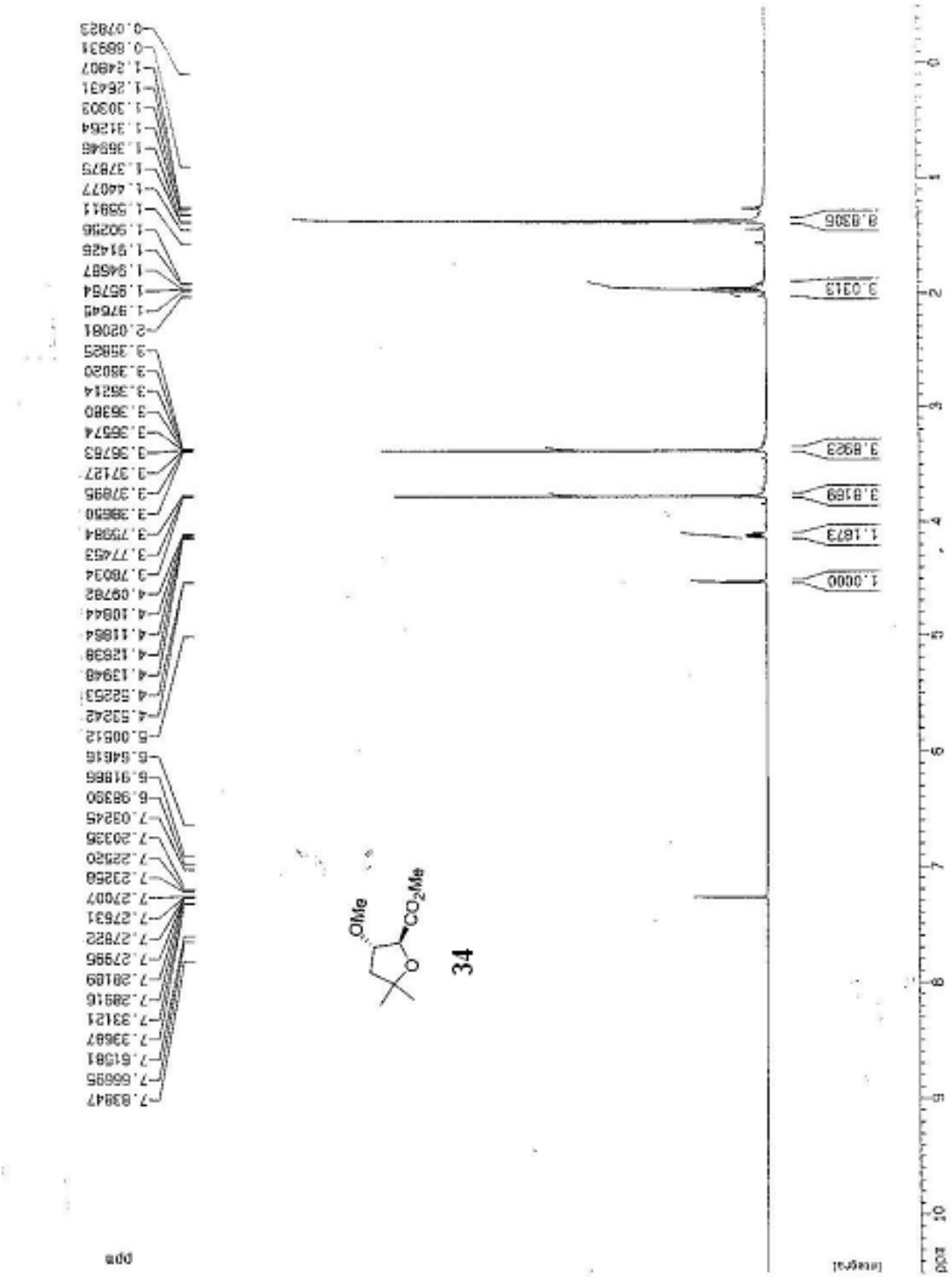

14.079
14.172
22.676
31.560
37.991
51.868
55.253
59.246
72.715
76.578
77.001
77.424
79.671
80.214
113.153
113.719
129.430
129.946
141.942
159.418
171.935
OPMB
OMe
OMe O
32
ppm

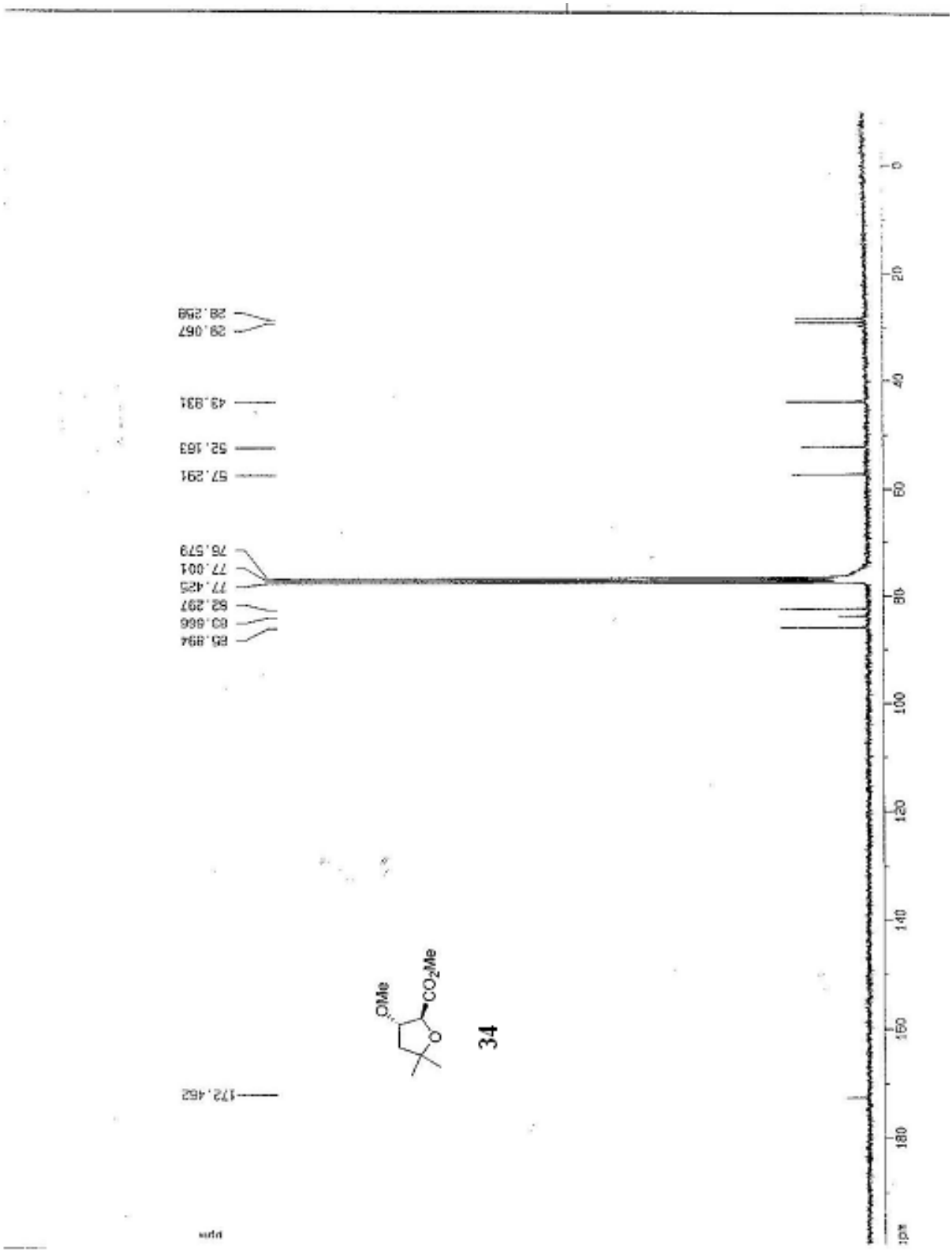

OPMB
OMe
OMe O
37

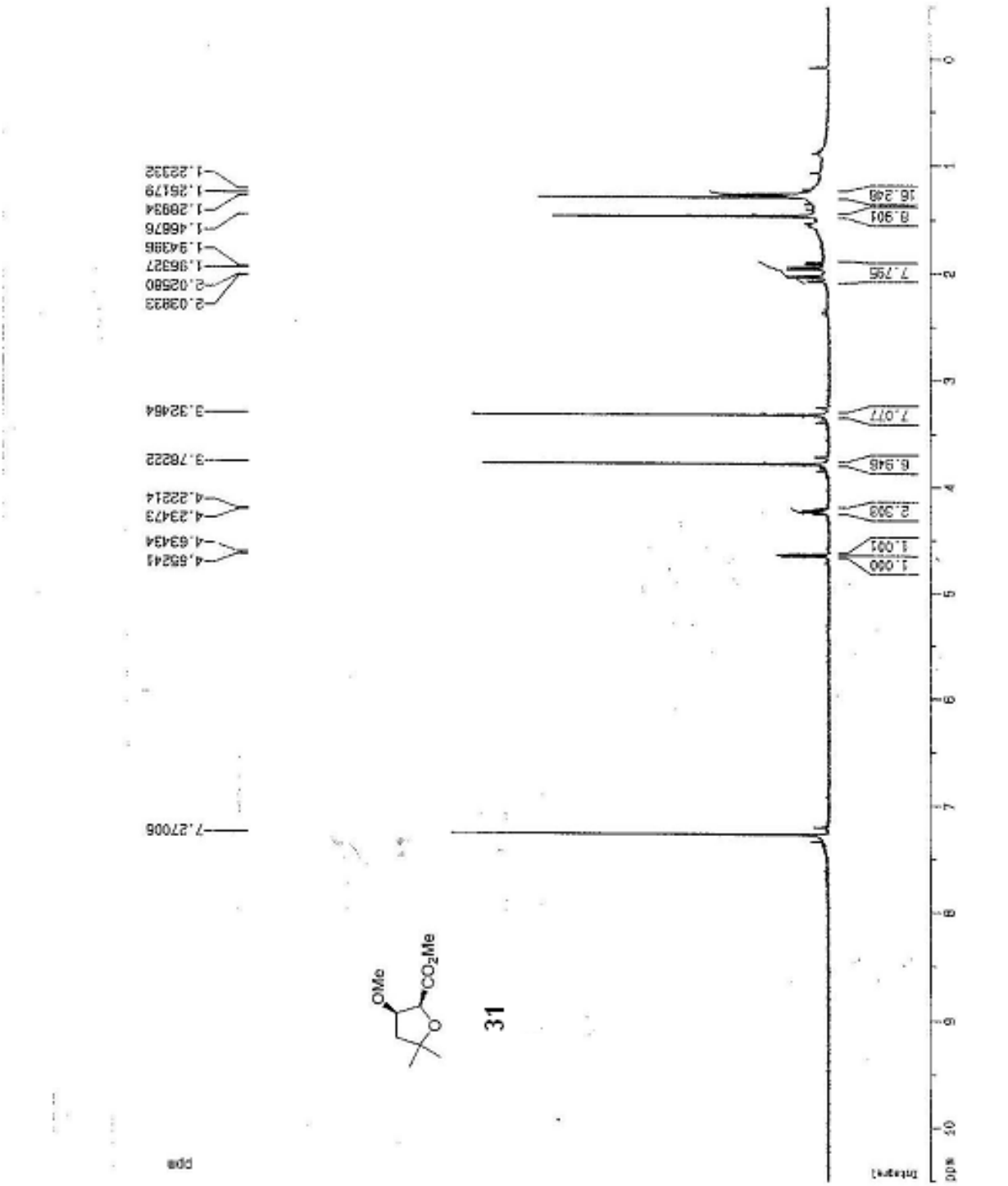

22.742
38.858
51.809
55.186
56.099
72.165
76.576
76.999
77.423
78.883
80.894
89.386
112.502
113.696
129.271
129.672
142.108
159.356
171.508
ppm
OPMB
OMe
OMe O
37

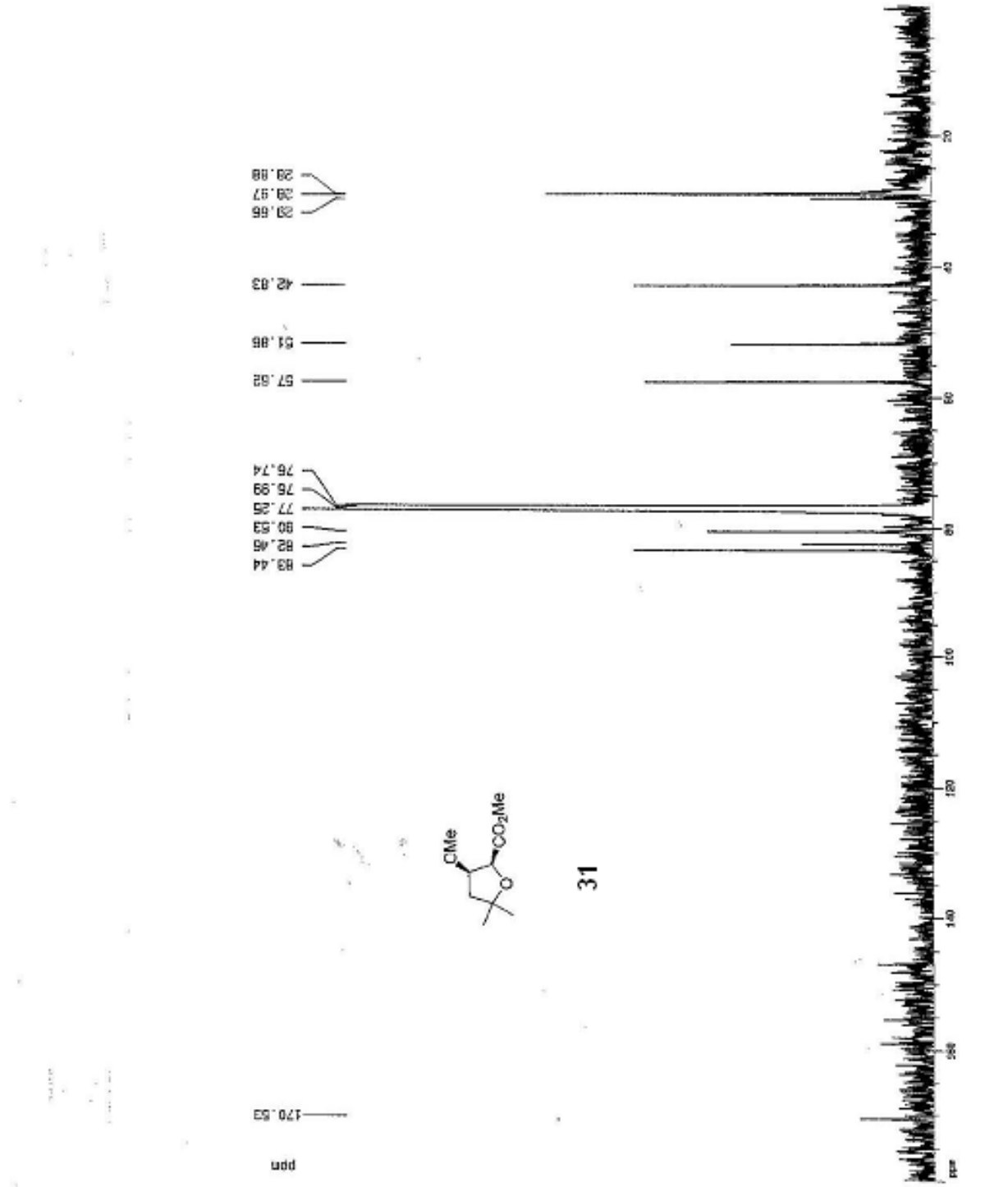

38
OH
OMe
OMe
O
ppm
1.43111
1.77448
2.22971
2.24988
2.33098
2.35555
3.44674
3.67719
3.68159
3.68589
3.80744
4.39528
4.40440
4.79710
4.83835
7.26963
2.5051
1.0043
1.0137
0.9647
2.6119
0.9327
2.5458
0.8564
0.8064
1.0000
[integral]
ppm


22.631
30.314
37.940
52.453
58.205
71.867
71.999
76.580
77.002
77.426
78.479
81.442
113.283
125.484
141.753
148.365
172.938
195.395
ppm
0
20
40
60
80
100
120
140
160
180
ppm
OMe
OH
OMe
O

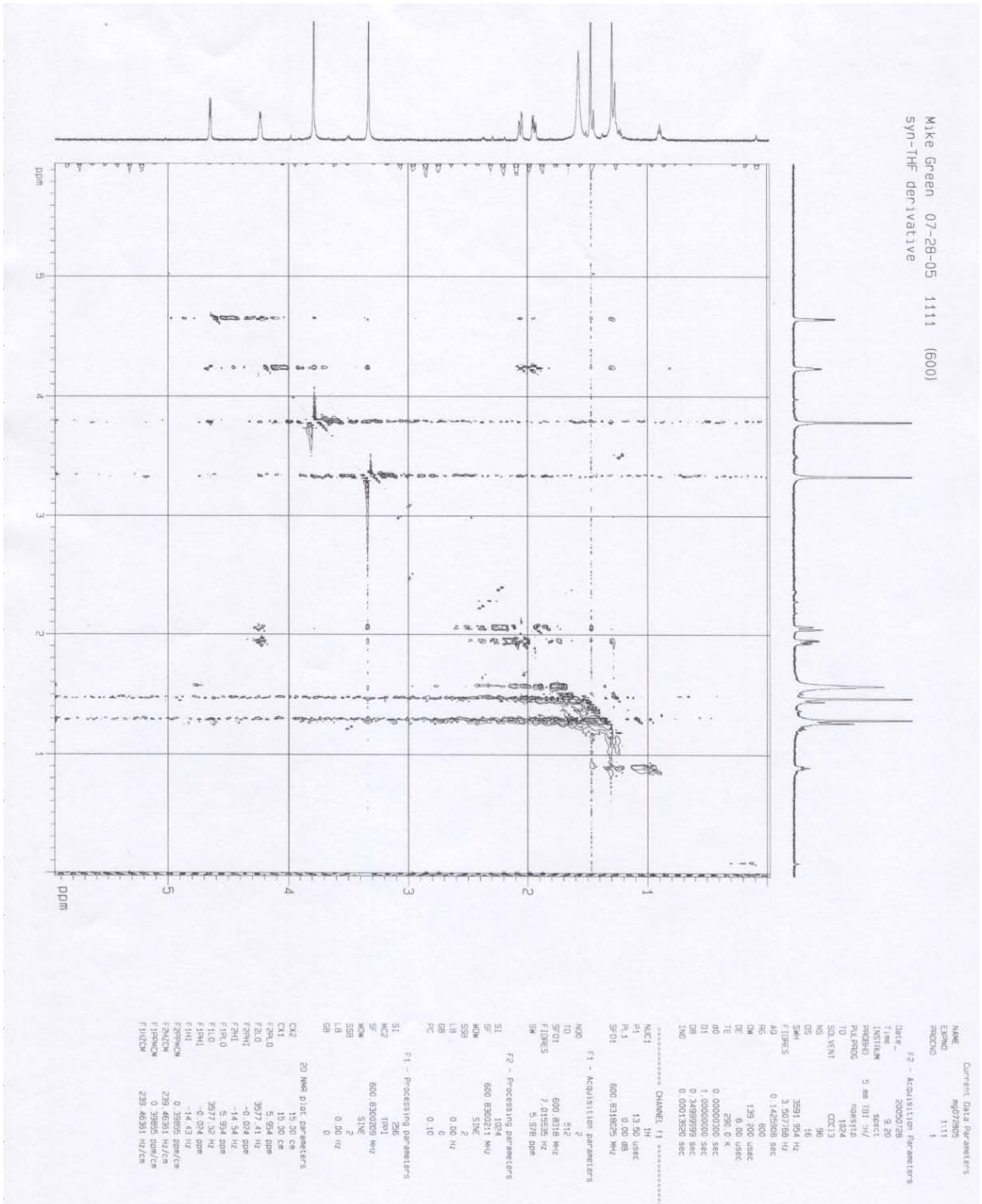

OMe
CO2Me
O
34


28.298
29.067
49.831
52.163
57.291
76.579
77.001
77.425
82.297
83.666
85.894
172.462
OMe
CO2Me
34
ppm

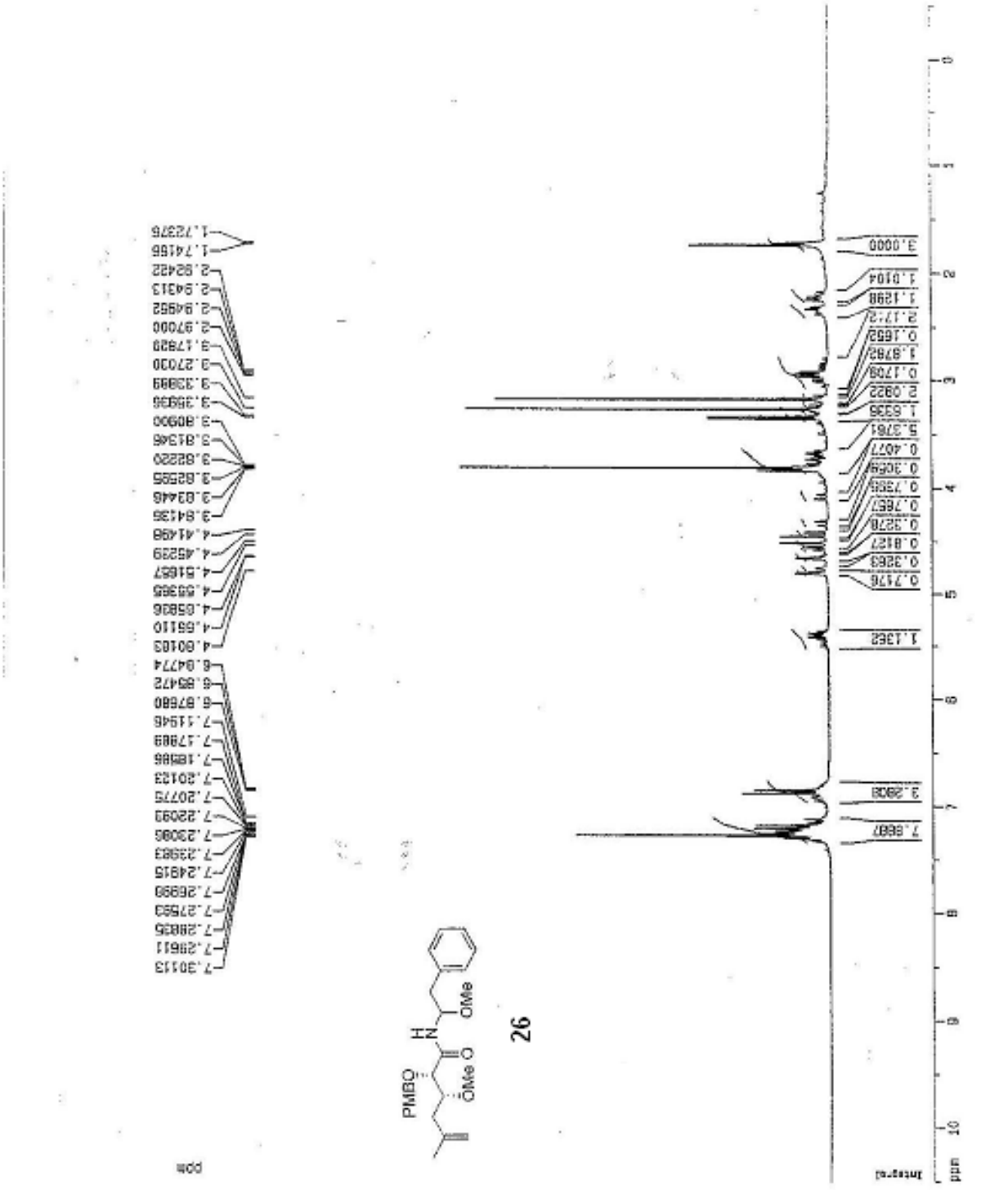

OMe
CO2Me
31

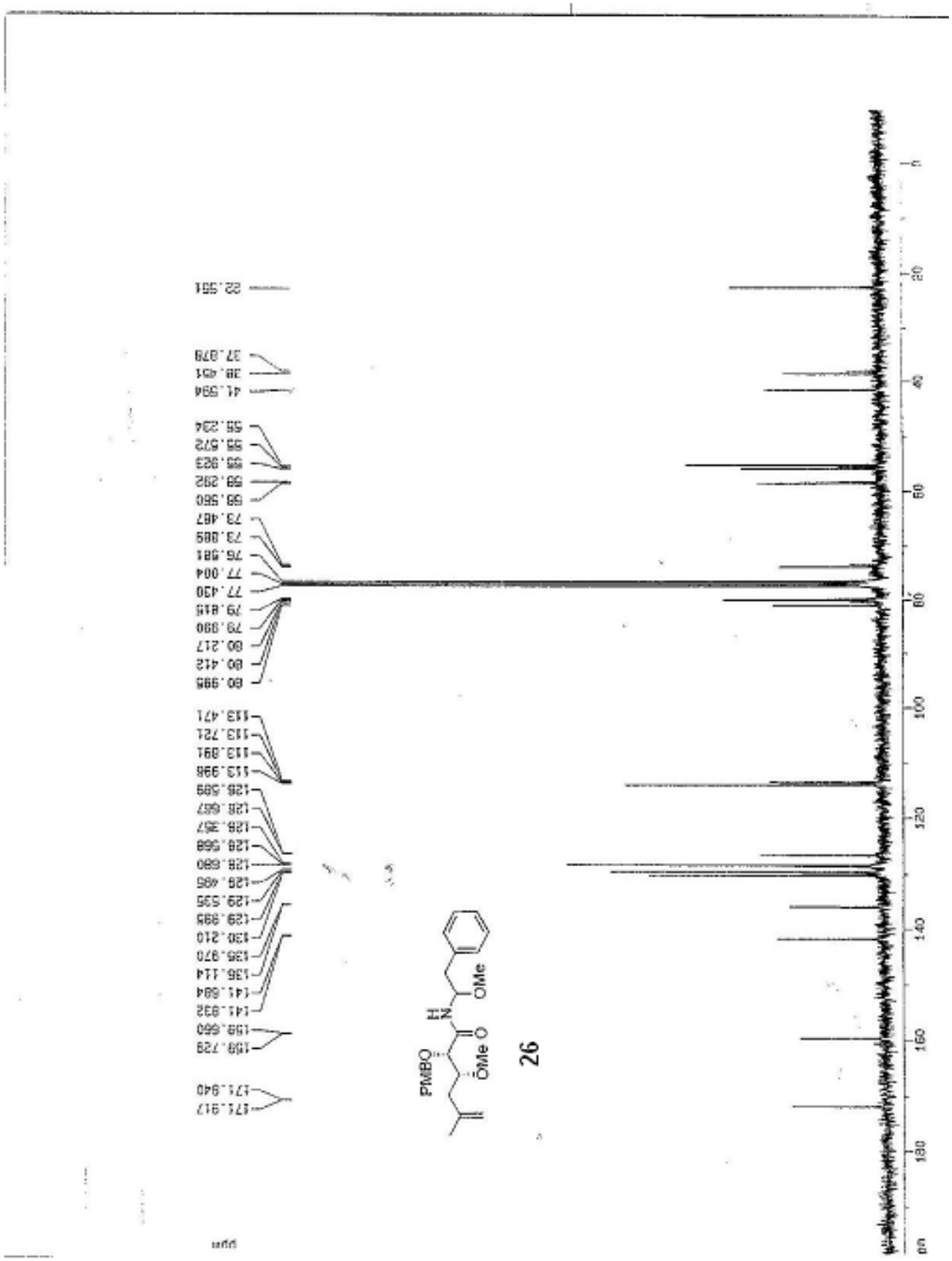

29.88
29.97
29.66
42.83
51.86
57.52
76.74
76.99
77.25
80.53
82.46
83.44
170.53
ppm
CMe
CO2Me
31

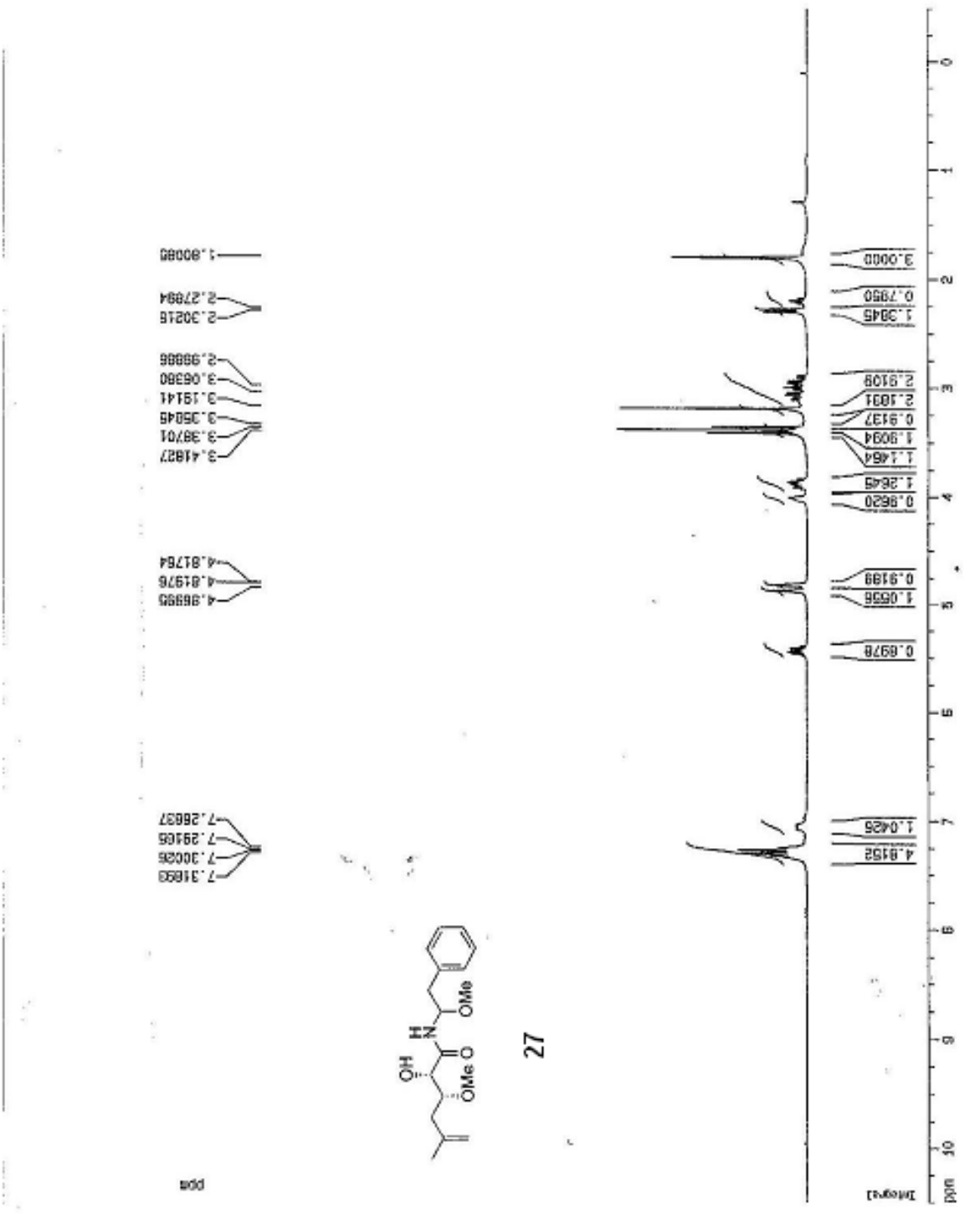
NOESY 31

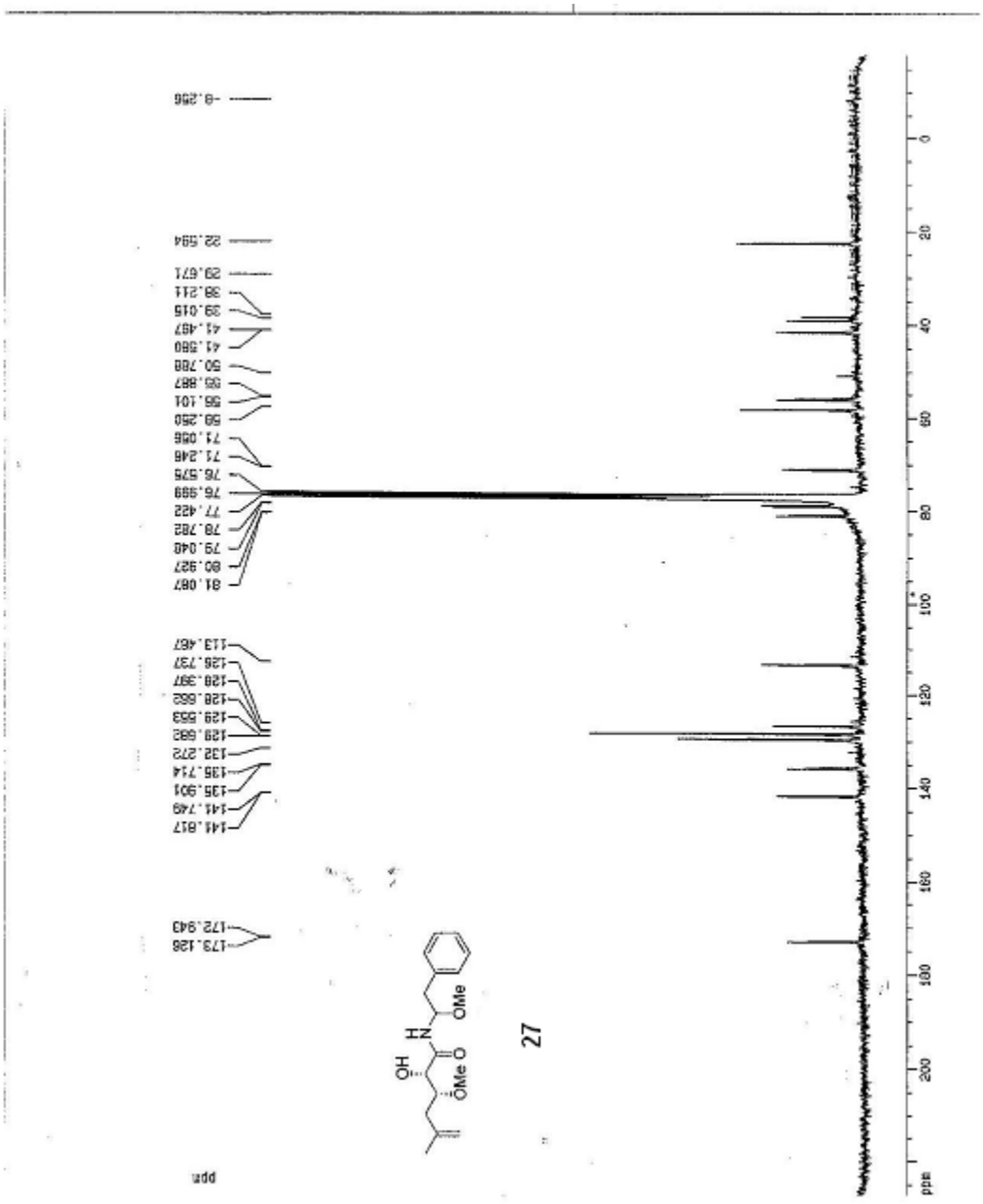


31

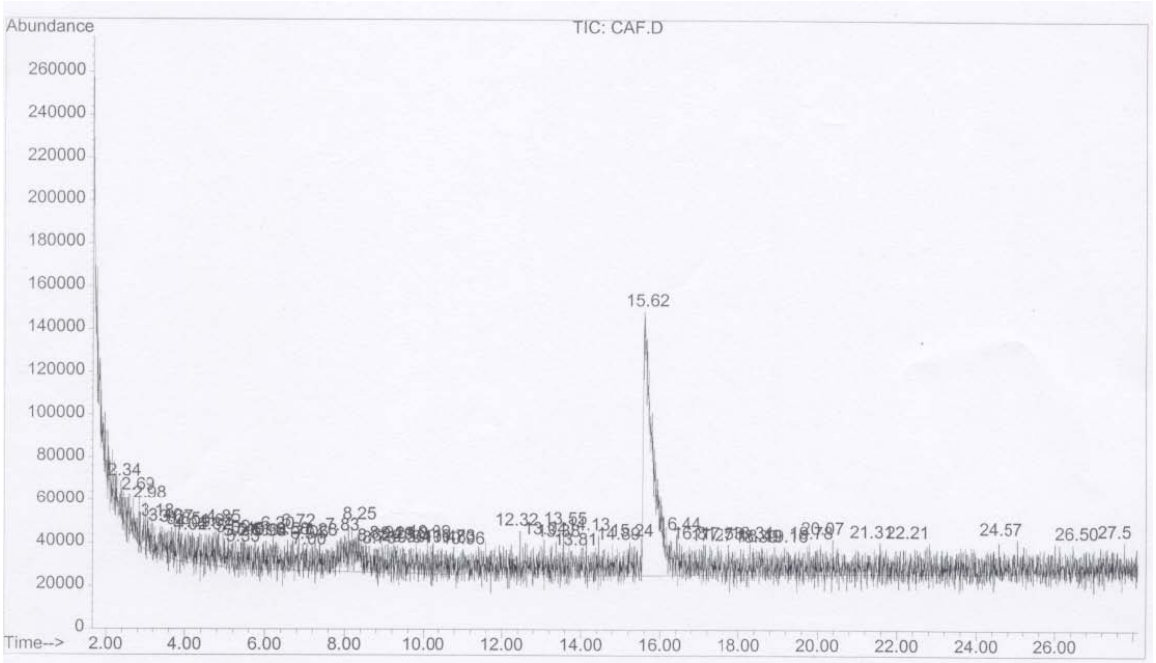

26
PMBO
OMe
OMe
O
H
N
OMe
ppm
Integral

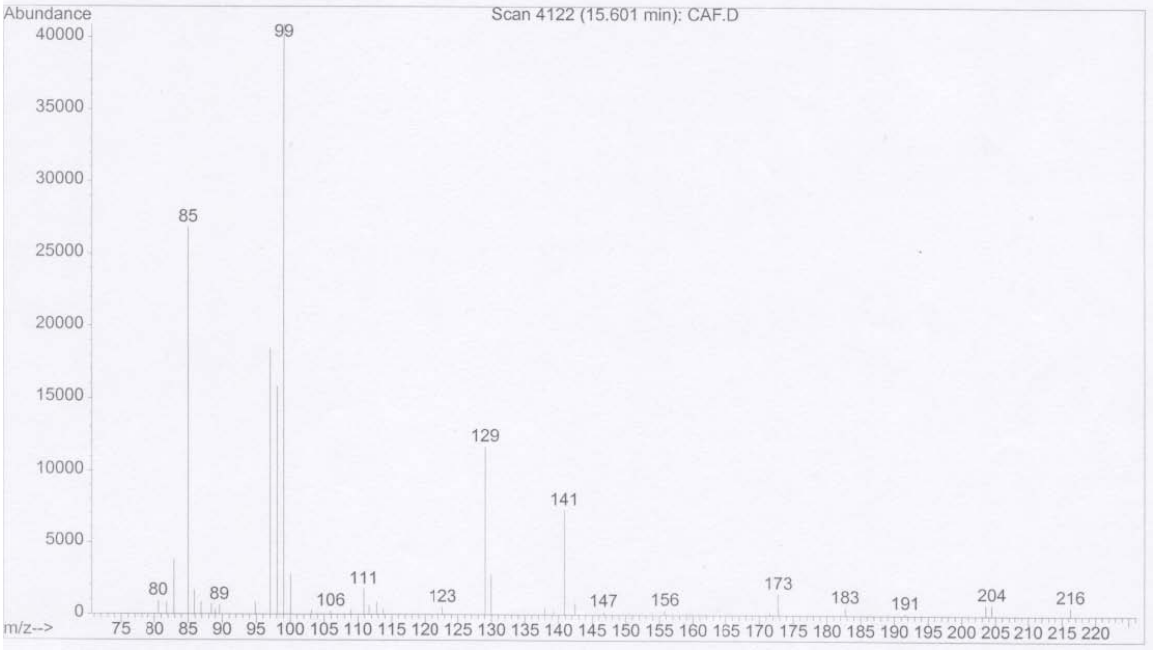

22.551
37.078
38.451
41.594
55.234
55.572
55.823
58.292
58.560
73.487
73.089
76.981
77.004
77.430
79.819
79.890
80.217
80.412
80.985
113.471
113.721
113.891
113.998
128.589
128.667
128.857
128.968
128.680
128.485
129.535
129.889
130.210
135.870
136.114
141.684
141.832
159.660
159.728
171.940
171.917
PMBO
OMe O
OMe
H
N
26

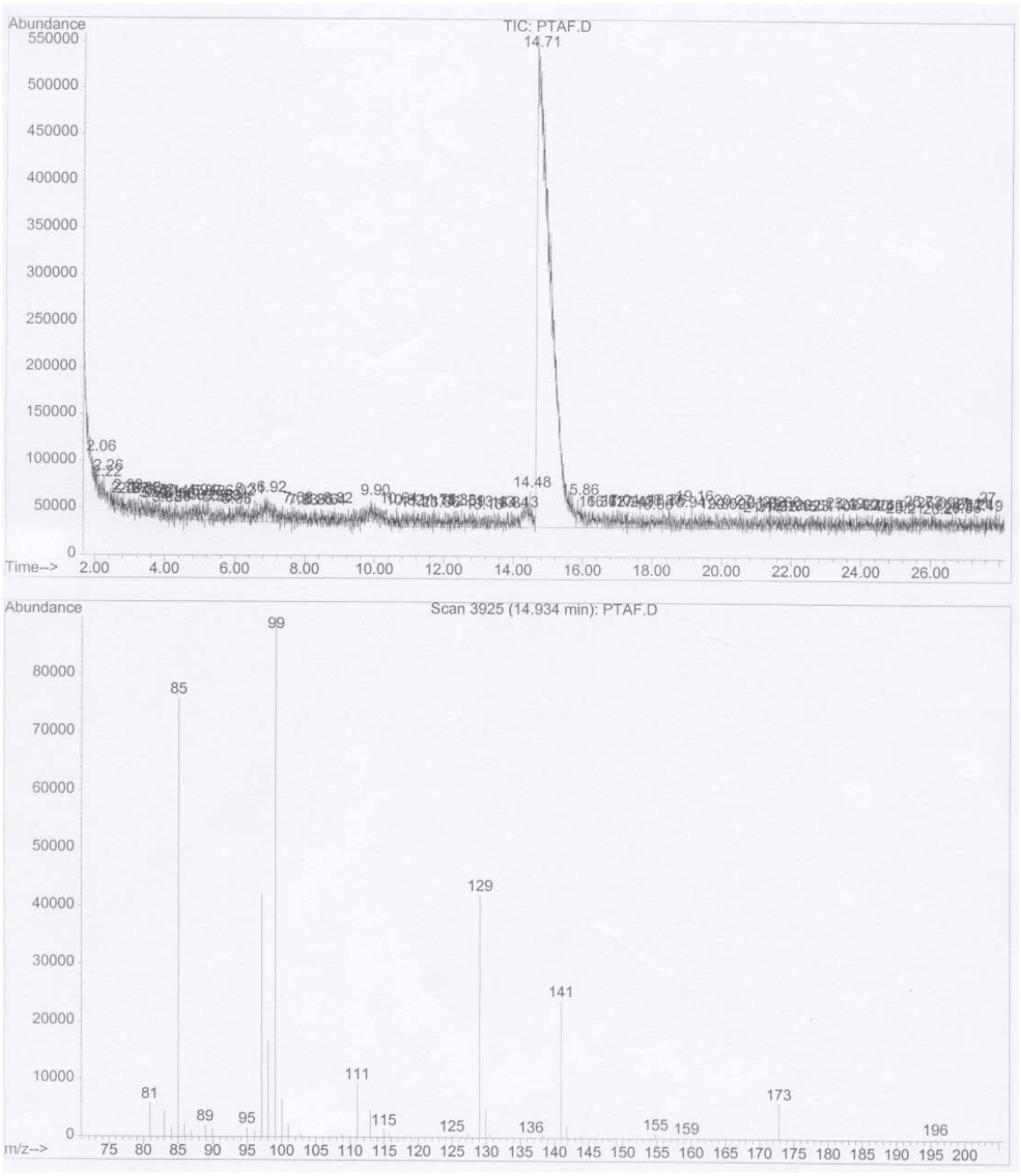

27
OMe
OMe O
OH
H
N
ppm
Integral

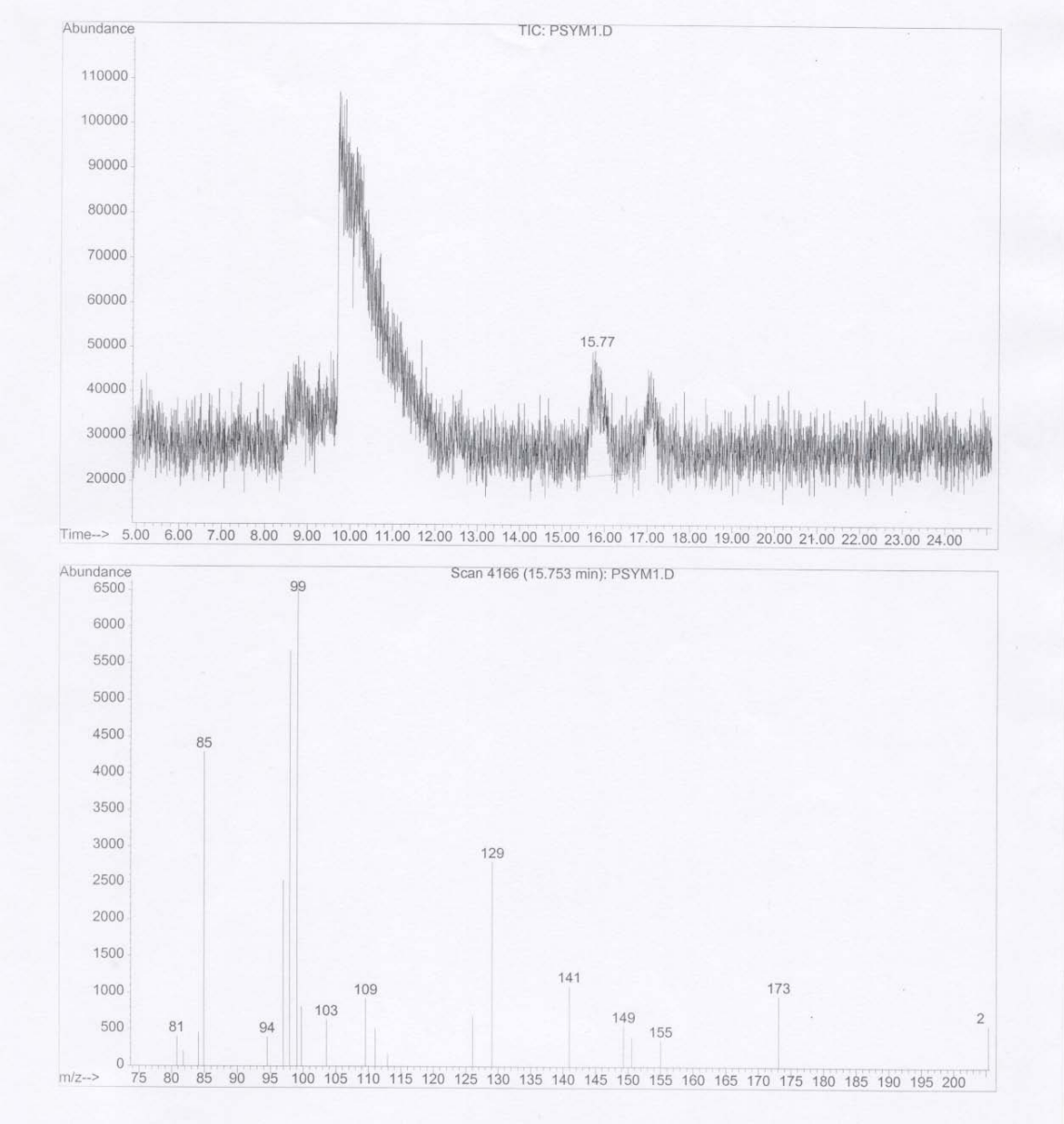

-0.256
22.594
29.671
38.214
39.015
41.487
41.580
50.788
55.887
56.101
69.250
71.086
71.246
76.575
76.999
77.422
78.782
79.040
80.927
81.087
113.467
126.737
128.397
128.662
129.553
129.682
132.272
135.714
135.901
141.749
144.817
172.943
173.128
OH
H
N
OMe
O
OMe
27
ppm

Psymberin degradation co-injection with


Abundance
TIC: CAF.D
15.62
Time-->
2.00 4.00 6.00 8.00 10.00 12.00 14.00 16.00 18.00 20.00 22.00 24.00 26.00


Abundance
Scan 4122 (15.601 min): CAF.D
99
85
129
141
m/z-->
75 80 85 90 95 100 105 110 115 120 125 130 135 140 145 150 155 160 165 170 175 180 185 190 195 200 205 210 215 220


Abundance
TIC: PTAF.D
14.71
2.06
14.48
15.86
Time-->
Abundance
Scan 3925 (14.934 min): PTAF.D
99
85
129
141
111
81
89
95
115
125
136
155
159
173
196
m/z-->


Abundance
TIC: PSYM1.D
110000
100000
90000
80000
70000
60000
50000
40000
30000
20000
15.77
Time--> 5.00 6.00 7.00 8.00 9.00 10.00 11.00 12.00 13.00 14.00 15.00 16.00 17.00 18.00 19.00 20.00 21.00 22.00 23.00 24.00
Abundance
Scan 4166 (15.753 min): PSYM1.D
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
99
85
129
141
109
103
173
81
94
149
155
2
m/z--> 75 80 85 90 95 100 105 110 115 120 125 130 135 140 145 150 155 160 165 170 175 180 185 190 195 200

BIBLIOGRAPHY

1. Fusetani, N.; Sugawara, T.; Matsunaga, S., Bioactive marine metabolites. 41. Theopederins A-E, potent antitumor metabolites from a marine sponge, Theonella sp. *J. Org. Chem.* **1992,** 57, (14), 3828-3832.

2. Cardani, C.; Ghiringhelli, D.; Mondelli, R.; Quilico, A., The structure of Pederin. *Tetrahedron Lett.* **1965,** 6, (29), 2537-2545.

3. Perry, N. B.; Blunt, J. W.; Munro, M. H. G.; Pannell, L. K., Mycalamide A, an antiviral compound from a New Zealand sponge of the genus Mycale. *J. Am. Chem. Soc.* **1988,** 110, (14), 4850-4851.

4. Perry, N. B.; Blunt, J. W.; Munro, M. H. G.; Thompson, A. M., Antiviral and antitumor agents from a New Zealand sponge, Mycale sp. 2. Structures and solution conformations of mycalamides A and B. *J. Org. Chem.* **1990,** 55, (1), 223-227.

5. Simpson, J. S.; Garson, M. J.; Blunt, J. W.; Munro, M. H. G.; Hooper, J. N. A., Mycalamides C and D, Cytotoxic Compounds from the Marine Sponge Stylinos n. Species. *J. Nat. Prod.* **2000,** 63, (5), 704-706.

6. West, L. M.; Northcote, P. T.; Hood, K. A.; Miller, J. H.; Page, M. J., Mycalamide D, a New Cytotoxic Amide from the New Zealand Marine Sponge Mycale Species. *J. Nat. Prod.* **2000,** 63, (5), 707-709.

7. Sakemi, S.; Ichiba, T.; Kohmoto, S.; Saucy, G.; Higa, T., Isolation and structure elucidation of onnamide A, a new bioactive metabolite of a marine sponge, Theonella sp. *J. Am. Chem. Soc.* **1988,** 110, (14), 4851-4853.

8. Matsunaga, S.; Fusetani, N.; Nakao, Y., Eight new cytotoxic metabolites closely related to onnamide A from two marine sponges of the genus Theonella. *Tetrahedron* **1992,** 48, (39), 8369-8376.

9. Kobayashi, J. i.; Itagaki, F.; Shigemori, H.; Sasaki, T., Three New Onnamide Congeners from the Okinawan Marine Sponge Theonella Sp. *J. Nat. Prod.* **1993,** 56, (6), 976-981.

10. Vuong, D.; Capon, R. J.; Lacey, E.; Gill, J. H.; Heiland, K.; Friedel, T., Onnamide F: A New Nematocide from a Southern Australian Marine Sponge, Trachycladus laevispirulifer. *J. Nat. Prod.* **2001,** 64, (5), 640-642.

11. Cichewicz, R. H.; Valeriote, F. A.; Crews, P., Psymberin, A Potent Sponge-Derived Cytotoxin from Psammocinia Distantly Related to the Pederin Family. *Org. Lett.* **2004,** 6, (12), 1951-1954.

12. Pettit, G. R.; Xu, J. P.; Chapuis, J. C.; Pettit, R. K.; Tackett, L. P.; Doubek, D. L.; Hooper, J. N. A.; Schmidt, J. M., Antineoplastic Agents. 520. Isolation and Structure of Irciniastatins A and B from the Indo-Pacific Marine Sponge Ircinia ramosa1. *J. Med. Chem.* **2004,** 47, (5), 1149-1152.

13. Paul, G. K.; Gunasekera, S. P.; Longley, R. E.; Pomponi, S. A., Theopederins K and L. Highly Potent Cytotoxic Metabolites from a Marine Sponge Discodermia Species. *J. Nat. Prod.* **2002,** 65, (1), 59-61.

14. Tsukamoto, S.; Matsunaga, S.; Fusetani, N.; Toh-e, A., Theopederins F-J: Five new antifungal and cytotoxic metabolites from the marine sponge, theonella swinhoei. *Tetrahedron* **1999,** 55, (48), 13697-13702.

15. Pavan, M.; Bo, G., *Memora Soc Entomol Italiana* **1952,** 31, 67.

16. Pavan, M.; Bo, G., *Physiologica Comparata et Oecologia* **1953,** 3, 307.

17. Piel, J., A polyketide synthase-peptide synthetase gene cluster from an uncultured bacterial symbiont of Paederus beetles. *Proc. Natl. Acad. Sci. U.S.A.* **2002,** 99, (22), 14002-14007.

18. Piel, J.; Butzke, D.; Fusetani, N.; Hui, D.; Platzer, M.; Wen, G.; Matsunaga, S., Exploring the Chemistry of Uncultivated Bacterial Symbionts: Antitumor Polyketides of the Pederin Family. *J. Nat. Prod.* **2005,** 68, (3), 472-479.

19. Burres, N. S.; Clement, J. J., Antitumor Activity and Mechanism of Action of the Novel Marine Natural Products Mycalamide-A and -B and Onnamide. *Cancer Res* **1989,** 49, (11), 2935-2940.

20. Brega, A.; Falaschi, A.; De Carli, L.; Pavan, M., Studies on the Mechanism of Action of Pederine. *J. Cell Biol.* **1968,** 36, (3), 485-496.

21. Yanagiya, M.; Matsuda, F.; Hasegawa, K.; Matsumoto, T., Total synthesis of (+)-pedamide. A new, remote controlled asymmetric induction. *Tetrahedron Lett.* **1982,** 23, (39), 4039-4042.

22. Matsuda, F.; Yanagiya, M.; Matsumoto, T., Total synthesis of (+)-pederine. A simple synthetic method for N-(1-methoxyalkyl)amides. *Tetrahedron Lett.* **1982,** 23, (39), 4043-4046.

23. Matsuda, F.; Tomiyoshi, N.; Yanagiya, M.; Matsumoto, T., A new stereocontrolled synthesis of (+)-pederine. Unusual conformation around c-10--c-11 bond in pederine derivatives. *Tetrahedron Lett.* **1983,** 24, (12), 1277-1280.

24. Kodama, M.; Takahashi, T.; Kojima, T.; Ito, S., Synthesis of macrocyclic terpenoids by intramolecular cyclization XIII. : Stereoselective synthesis of (±)-cubitene, a component of defense secretion of termites. *Tetrahedron* **1988,** 44, (23), 7055-7062.

25. Meinwald, J.; Adams, M.; Duggan, A. J., An Advintitious Synthesis of Pederinolactone. *Heterocycles* **1977,** 7, 989-995.

26. Meinwald, J., An Approach to the Synthesis of Pederin. *Pure and Appl. Chem.* **1977,** 49, 1275-1290.

27. Duggan, A. J.; Adams, M. A.; Brynes, P. J.; Meinwald, J., Reaction of enolate anions with lactones. *Tetrahedron Lett.* **1978,** 19, (45), 4323-4326.

28. Adams, M. A.; Duggan, A. J.; Smolanoff, J.; Meinwald, J., Total synthesis of (.+-.)-pederamide. *J. Am. Chem. Soc.* **1979,** 101, (18), 5364-5370.

29. Hong, C. Y.; Kishi, Y., Total synthesis of mycalamides A and B. *J. Org. Chem.* **1990,** 55, (14), 4242-4245.

30. Hong, C. Y.; Kishi, Y., Total synthesis of onnamide A. *J. Am. Chem. Soc.* **1991,** 113, (25), 9693-9694.

31. Nakata, T.; Nagao, S.; Mori, N.; Oishi, T., Total synthesis of (+)-pederin. 1. Stereocontrolled synthesis of (+)-benzoylpedamide. *Tetrahedron Lett.* **1985,** 26, (52), 6461-6464.

32. Nakata, T.; Nagao, S.; Oishi, T., Total synthesis of (+)-pederin. 2. Stereocontrolled synthesis of (+)-benzoylselenopederic acid and total synthesis of (+)-pederin. *Tetrahedron Lett.* **1985,** 26, (52), 6465-6468.

33. Fukui, H.; Tsuchiya, Y.; Fujita, K.; Nakagawa, T.; Koshino, H.; Nakata, T., Synthesis and biological activity of artificial analogs of mycalamide A. *Bioorg. Med. Chem. Lett.* **1997,** 7, (16), 2081-2086.

34. Trotter, N. S.; Takahashi, S.; Nakata, T., Simple and Efficient Synthesis of (+)-Methyl 7-Benzoylpederate, a Key Intermediate toward the Mycalamides. *Org. Lett.* **1999,** 1, (6), 957-959.

35. Takahashi, S. O., A.; Nakata, T, Synthesis of Mycalamide Analagoues. *Heterocycles* **2004,** 63.

36. Isaac, K. K., P.; Campbell, S., Synthetic Approaches to Pederin. A Synthesis of Ethyl Pederate. *J. Chem. Soc., Chem. Commun.* **1983**, 249-250.

37. Kocienski, P. J.; Wilson, T. M., Synthetic Approaches to Pederin. A Synthesis of (+/-) Benzoylpedamide. *J. Chem. Soc., Chem. Commun.* **1984**, 1011-1012.

38. WIlson, T. K., P.; Faller, A.; Campbell, S., Total Synthesis of (+/-) Pederin. *J. Chem. Soc., Chem. Commun.* **1987**, 106-108.

39. Jarowicki, K.; Kocienski, P.; Marczak, S.; Willson, T., A synthesis of (+)-pederin. The metallated dihydropyran approach. *Tetrahedron Lett.* **1990,** 31, (24), 3433-3436.

40. Willson, T. M.; Kocienski, P.; Jarowicki, K.; Isaac, K.; Faller, A.; Campbell, S. F.; Bordner, J., Studies related to the synthesis of (±)-pederin. part 1. Synthesis of ethyl pederate and benzoylselenopederic acid. *Tetrahedron* **1990,** 46, (5), 1757-1766.

41. Willson, T. M.; Kocienski, P.; Jarowicki, K.; Isaac, K.; Hitchcock, P. M.; Faller, A.; Campbell, S. F., Studies related to the synthesis of pederin. part 2. synthesis of pederol dibenzoate and benzoylpedamide. *Tetrahedron* **1990,** 46, (5), 1767-1782.

42. Kocienski, P. R., P.; Davis, J. K.; Boyle, F. T.; Davies, D. E.; Richter, A., Synthesis of 18-O-Methyl Mycalamide B. *J. Chem. Soc., Perkin Trans. I* **1996**, 1797-1808.

43. Kocienski, P. J.; Narquizian, R.; Raubo, P.; Smith, C.; Boyle, F. T., A Synthesis of Mycalamide B. *Synlett* **1998**, (08), 869-872.

44. Kocienski, P. J.; Narquizian, R.; Raubo, P.; Smith, C.; Boyle, F. T., A Synthesis of Theopederin D and a Formal Synthesis of Pederin. *Synlett* **1998**, (12), 1432-1434.

45. Kocienski, P. J.; Narquizian, R.; Raubo, P.; Smith, C.; Farrugia, L. J.; Muir, K.; Boyle, F. T., Synthetic studies on the pederin family of antitumor agents. Synthesis of mycalamide B, theopederin D and pederin. *J. Chem. Soc., Perkin Trans. I* **2000**, (15), 2357-2384.

46. Hoffmann, R. W.; Schlapbach, A., Synthesis of the trioxadecalin-part of mycalamide B. *Tetrahedron Lett.* **1993,** 34, (49), 7903-7906.

47. Roush, W. R.; Marron, T. G.; Pfeifer, L. A., Highly Diastereoselective Synthesis of Pederic Acid Derivatives. *J. Org. Chem.* **1997,** 62, (3), 474-478.

48. Roush, W. R.; Pfeifer, L. A., Total Synthesis of Mycalamide A and 7-epi-Mycalamide A. *Org. Lett.* **2000,** 2, (6), 859-862.

49. Toyota, M.; Hirota, M.; Nishikawa, Y.; Fukumoto, K.; Ihara, M., Palladium-Catalyzed Intramolecular Allylic Alkylation Reaction in Marine Natural Product Synthesis: Enantioselective Synthesis of (+)-Methyl Pederate, a Key Intermediate in Syntheses of Mycalamides. *J. Org. Chem.* **1998,** 63, (17), 5895-5902.

50. Toyota, M.; Hirota, M.; Hirano, H.; Ihara, M., A Stereoselective Synthesis of the C-10 to C-18 (Right-Half) Fragment of Mycalamides Employing Lewis Acid Promoted Intermolecular Aldol Reaction. *Org. Lett.* **2000,** 2, (14), 2031-2034.

51. Kagawa, N.; Ihara, M.; Toyota, M., Total Synthesis of (+)-Mycalamide A. *Org. Lett.* **2006,** 8, (5), 875-878.

52. Kagawa, N.; Ihara, M.; Toyota, M., Convergent Total Synthesis of (+)-Mycalamide A. *J. Org. Chem.* **2006,** 71, (18), 6796-6805.

53. Trost, B. M.; Yang, H.; Probst, G. D., A Formal Synthesis of (-)-Mycalamide A. *J. Am. Chem. Soc.* **2004,** 126, (1), 48-49.

54. Sohn, J. H.; Waizumi, N.; Zhong, H. M.; Rawal, V. H., Total Synthesis of Mycalamide A. *J. Am. Chem. Soc.* **2005,** 127, (20), 7290-7291.

55. John C. Jewett, Viresh H. R., Total Synthesis of Pederin13. *Angew. Chem.* **2007,** 119, (34), 6622-6624.

56. Zhong, H. M.; Sohn, J. H.; Rawal, V. H., Studies toward the Asymmetric Synthesis of the Right Part of the Mycalamides. *J. Org. Chem.* **2007,** 72, (2), 386-397.

57. Jiang, X.; Garcia-Fortanet, J.; DeBrabander, J. K., Synthesis and Complete Stereochemical Assignment of Psymberin/Irciniastatin A. *J. Am. Chem. Soc.* **2005,** 127, (32), 11254-11255.

58. Jiang, X.; Williams, N.; DeBrabander, J. K., Synthesis of Psymberin Analogues: Probing a Functional Correlation with the Pederin/Mycalamide Family of Natural Products. *Org. Lett.* **2007,** 9, (2), 227-230.

59. Shangguan, N.; Kiren, S.; Williams, L. J., A Formal Synthesis of Psymberin. *Org. Lett.* **2007,** 9, (6), 1093-1096.

60. Nishimura, S.; Matsunaga, S.; Yoshida, M.; Hirota, H.; Yokoyama, S.; Fusetani, N., 13-Deoxytedanolide, a marine sponge-derived antitumor macrolide, binds to the 60S large ribosomal subunit. *Bioorg. Med. Chem.* **2005,** 13, (2), 449-454.

61. Thompson, A. M. B., J. W.; Munro, M. H. G.; Perry, N. B.; Pannell, L. K., Chemistry of the Mycalamides, Antiviral and Antitumor Compounds from a Marine Sponge .3. Acyl, Alkyl, and Silyl Derivatives. *J. Chem. Soc., Perkin Trans. I* **1992**, (1335-1342).

62. Thompson, A. M. B., J. W.; Munro, M. H. G.; Perry, N. B., Chemistry of the Mycalamides, Antiviral and Antitumor Compounds from a Marine Sponge .4. Reactions of Mycalamide-a and Alkyl Derivatives with Basic Nucleophiles. *J. Chem. Soc., Perkin Trans. I* **1995**, 1233-1242.

63. Thompson, A. M. B., J. W.; Munro, M. H. G.; Perry, N. B., Chemistry of the Mycalamides, Antiviral and Antitumor Compounds from a Marine Sponge .5. Acid Catalyzed Hydrolysis and Acetal Exchange, Double-Bond Additions and Oxidation Reactions. . *J. Chem. Soc., Perkin Trans. I* **1995,** 10, 1233-1242.

64. Hideo Fuki, Y. T., Keiko Fujita, Tadakiyo Nakagawa, Hiroyuki Koshino, Tadashi Nakata, Synthesis and Biological Activity of Artificial Analogs of Mycalamide A. *Bioorg. Med. Chem. Lett.* **1997,** 7, 2081-2086.

65. Jamie S. Simpson, M. J., Garson, John w. Blunt, Murray H.G. Munro, and John N.A Hooper, Mycalamides C and D, Cytotoxic Compounds from the Marine Sponge *Stylinos* n. Species. *J. Nat. Prod.* **2000,** 63, 704-706.

66. Kocienski*, P. J.; Narquizian, R.; Raubo, P.; Smith, C.; Boyle, F. T., A Synthesis of Theopederin D and a Formal Synthesis of Pederin. *Synlett* **1998**, (12), 1432-1434.

67. Kumar, V. S.; Floreancig, P. E., Electron Transfer Initiated Cyclizations: Cyclic Acetal Synthesis through Carbon-Carbon σ-Bond Activation. *J. Am. Chem. Soc.* **2001,** 123, (16), 3842-3843.

68. Kumar, V. S.; Aubele, D. L.; Floreancig, P. E., Aerobic Organocatalytic Photoinitiated Arene Oxidations: Application to Electron Transfer Initiated Cyclization Reactions. *Org. Lett.* **2001,** 3, (25), 4123-4125.

69. Rech, J. C.; Floreancig, P. E., Concise and Stereoselective Synthesis of the N7-C25 Fragment of Psymberin. *Org. Lett.* **2005,** 7, (23), 5175-5178.

70. Rech, J. C.; Floreancig, P. E., An Oxidative Entry into the Amido Trioxadecalin Ring System. *Org. Lett.* **2003,** 5, (9), 1495-1498.

71. Rech, J. C. The Development of an Electron Transfer Initiated Cyclization Approach Toward the Total Synthesis of Mycalamide B. The Synthesis of N_7-C_{25} fragment of Psymberin. University of Pittsburgh, Pittsburgh, 2005.

72. Golender, L.; Senderowitz, H.; Fuchs, B., Relative stabilities and conformational ring inversion potentials in heterocyclic decalin systems and stereoelectronic implications. *Journal of Molecular Structure: THEOCHEM* **1996,** 370, (2-3), 221-236.

73. Phillips, R. S. H. C. H., Asymmetric Reduction of Ethynyl Ketones and Ethynyl Ketoesters by Secondary Alcohol Dehydrogenase from *Theroanaerobacter ethanolicus*. *J. Chem. Soc., Perkin Trans. I* **2000**, 2821-2825.

74. Bromidge, S. M. E. D. A. G., J.; Orlek, B.S, A Convienient Synthesis of Masked Beta-Ketoaldehydes by the Controlled Addition of Nucleophiles to (Trimethylsilyl)ethynyl Ketones. *Synth. Commun.* **1993,** 23, 487-494.

75. Danishefsky, S.; Yan, C.-F.; Singh, R. K.; Gammill, R. B.; McCurry, P. M.; Fritsch, N.; Clardy, J., Derivatives of 1-methoxy-3-trimethylsilyloxy-1,3-butadiene for Diels-Alder reactions. *J. Am. Chem. Soc.* **1979,** 101, (23), 7001-7008.

76. Alexander G. Dossetter; Jamison, T. F.; Jacobsen, E. N., Highly Enantio- and Diastereoselective Hetero-Diels-Alder Reactions Catalyzed by New Chiral Tridentate Chromium(<FONT SIZE='-2'>III</FONT>) Catalysts. *Angew. Chem., Int. Ed. Engl.* **1999,** 38, (16), 2398-2400.

77. Joly, G. D.; Jacobsen, E. N., Catalyst-Controlled Diastereoselective Hetero-Diels-Alder Reactions. *Org. Lett.* **2002,** 4, (10), 1795-1798.

78. Luche, J. L., Lanthanides in organic chemistry. 1. Selective 1,2 reductions of conjugated ketones. *J. Am. Chem. Soc.* **1978,** 100, (7), 2226-2227.

79. Zhu, C.; Shen, X.; Nelson, S. G., Cinchona Alkaloid-Lewis Acid Catalyst Systems for Enantioselective Ketene-Aldehyde Cycloadditions. *J. Am. Chem. Soc.* **2004,** 126, (17), 5352-5353.

80. K. C. Nicolaou, A. A. E. M. Z. S. H. L. B. S. S., A Mild and Selective Method for the Hydrolysis of Esters with Trimethyltin Hydroxide13. *Angew. Chem., Int. Ed. Engl.* **2005,** 44, (9), 1378-1382.

81. Inukai, T.; Yoshizawa, R., Preparation of .beta.-oxo aldehydes by acylation of aldehyde enamines. *J. Org. Chem.* **1967,** 32, (2), 404-407.

82. Kinnaird, J. W. A.; Ng, P. Y.; Kubota, K.; Wang, X.; Leighton, J. L., Strained Silacycles in Organic Synthesis: A New Reagent for the Enantioselective Allylation of Aldehydes. *J. Am. Chem. Soc.* **2002,** 124, (27), 7920-7921.

83. Roush, W. R.; Hoong, L. K.; Palmer, M. A. J.; Park, J. C., Asymmetric synthesis using tartrate ester modified allylboronates. 1. Factors influencing stereoselectivity. *J. Org. Chem.* **1990,** 55, (13), 4109-4117.

84. Blanchette, M. A.; Malamas, M. S.; Nantz, M. H.; Roberts, J. C.; Somfai, P.; Whritenour, D. C.; Masamune, S.; Kageyama, M.; Tamura, T., Synthesis of bryostatins. 1. Construction of the C(1)-C(16) fragment. *J. Org. Chem.* **1989,** 54, (12), 2817-2825.

85. Paterson, I.; Gibson, K. R.; Oballa, R. M., Remote, 1,5-anti stereoinduction in the boron-mediated aldol reactions of [beta]-oxygenated methyl ketones. *Tetrahedron Lett.* **1996,** 37, (47), 8585-8588.

86. Paton, R. S.; Goodman, J. M., 1,5-Anti Stereocontrol in the Boron-Mediated Aldol Reactions of β-Alkoxy Methyl Ketones: The Role of the Formyl Hydrogen Bond. *J. Org. Chem.* **2008,** 73, (4), 1253-1263.

87. Paterson, I.; Oballa, R. M.; Norcross, R. D., Studies in marine macrolide synthesis: Stereocontrolled synthesis of the AB-spiroacetal subunit of spongistatin 1 (altohyrtin A). *Tetrahedron Lett.* **1996,** 37, (47), 8581-8584.

88. Crimmins, M. T.; Siliphaivanh, P., Enantioselective Total Synthesis of (+)-Leucascandrolide A Macrolactone. *Org. Lett.* **2003,** 5, (24), 4641-4644.

89. Chen, K.-M.; Hardtmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J., 1,3-*syn* diastereoselective reduction of [beta]-hydroxyketones utilizing alkoxydialkylboranes. *Tetrahedron Lett.* **1987,** 28, (2), 155-158.

90. Yu, W.; Mei, Y.; Kang, Y.; Hua, Z.; Jin, Z., Improved Procedure for the Oxidative Cleavage of Olefins by OsO4-NaIO4. *Org. Lett.* **2004,** 6, (19), 3217-3219.

91. Murray, R. W.; Jeyaraman, R., Dioxiranes: synthesis and reactions of methyldioxiranes. *J. Org. Chem.* **1985,** 50, (16), 2847-2853.

92. Halcomb, R. L.; Danishefsky, S. J., On the direct epoxidation of glycals: application of a reiterative strategy for the synthesis of .beta.-linked oligosaccharides. *J. Am. Chem. Soc.* **1989,** 111, (17), 6661-6666.

93. Ishihara, K.; Hanaki, N.; Yamamoto, H., Highly diastereoselective acetal cleavages using novel reagents prepared from organoaluminum and pentafluorophenol. *J. Am. Chem. Soc.* **1993,** 115, (23), 10695-10704.

94. Rainier, J. D.; Cox, J. M., Aluminum- and Boron-Mediated C-Glycoside Synthesis from 1,2-Anhydroglycosides. *Org. Lett.* **2000,** 2, (17), 2707-2709.

95. Ellman, J. A.; Owens, T. D.; Tang, T. P., N-tert-Butanesulfinyl Imines: Versatile Intermediates for the Asymmetric Synthesis of Amines. *Acc. Chem. Res.* **2002,** 35, (11), 984-995.

96. Evans, J. W.; Ellman, J. A., Stereoselective Synthesis of 1,2-Disubstituted β-Amino Alcohols by Nucleophilic Addition to N-tert-Butanesulfinyl α-Alkoxyaldimines. *J. Org. Chem.* **2003,** 68, (26), 9948-9957.

97. De Armas, P.; Concepcion, J. I.; Francisco, C. G.; Hernandez, R.; Salazar, J. A.; Suarez, E., Intramolecular Hydrogen Abstraction. Hypervalent Organoiodine Compounds, Convenient Reagents for Alkoxy Radical Generation. *J. Chem. Soc., Perkin Trans. I* **1998**, 405-411.

98. Matsuda, F.; Tomiyoshi, N.; Yanagiya, M.; Matsumoto, T., Stereocontrolled total synthesis of (+)-pederine. *Tetrahedron* **1988,** 44, (23), 7063-7080.

99. Robert H. Cichewicz, F. A. V., Phillip Crews, Psymberin, A Potent Sponge-Derived Cytotoxin from Psammocinia Distantly Related to the Pederin Family. *Org. Lett* **2004,** 6, 1951-1954.

100. Kiren, S.; Williams, L. J., Configuration of the Psymberin Amide Side Chain. *Org. Lett.* **2005,** 7, (14), 2905-2908.

101. Mukaiyama, T.; Shiina, I.; Iwadare, H.; Saitoh, M.; Nishimura, T.; Ohkawa, N.; SakohHiroki; Nishimura, K.; Tani, Y.-i.; Hasegawa, M.; Yamada, K.; Saitoh, K., Asymmetric Total Synthesis of Taxol. *Chem. Eur J* **1999,** 5, (121-161).

102. Danishefsky, S. J. V., A.; Patten, A. D.; Boisvert, L.; Audia,; E., J., Synthesis of two useful, enantiomerically pure derivatives of (S)-4-hydroxy-2-cyclohexenone. *J. Org. Chem* **1989,** 54, 3738-3740.

103. Andrus, M. B. M., E.L; Soma Sekhar, B.B.V, Synthesis of the Left-Hand Portion of Geldanamycin Using an Anti Glycolate Aldol Reaction. *Org. Lett* **2001,** 3, 259-262.

104. Gaich, T.; Mulzer, J., Synthesis of Epothilones via a Silicon-Tethered RCM Reaction. *Org. Lett.* **2005,** 7, (7), 1311-1313.

105. Matsumoto, T.; Yanagiya, M.; Maeno, S.; Yasuda, S., A revised structure of pederin. *Tetrahedron Lett.* **1968,** 9, (60), 6297-6300.

106. Cardani, C.; Ghiringhelli, D.; Mondelli, R.; Selva, A., On the Methanolysis Products of Pederin. *Gazz. Chim. Italk.* **1973,** 103, 247-255.

107. Wilson, T. M. K., P.; Jarowicki, K.; Isaac, K.; Hitchcock, P.M.; Faller, A.; Campbell, S.F, Studies Related to the Synthesis of Pederin. Part 2. Synthesis of Pederol Dibenzoate and Benzoylpedamide. *Tetrahedron* **1990,** 46, 1767-1782.

108. C. Cardani, D. G., R. Mondelll, A. Selva, On the Methanolysis Products of Pederin. *Gazz. Chim. Ital.* **1973,** 103, 247-255.

109. J.H. Kruithof, K.; F. Schmitz, R.; W. Klumpp, G., Lithiated 2-alkynyl-1,3-dioxanes as fully oxygenated acyl-anion equivalents Synthesis of 1-alkynyl ketones. *Tetrahedron* **1983,** 39, (19), 3073-3081.

110. Li, L. H.; Tius, M. A., Stereospecific Synthesis of Cryptophycin 1. *Org. Lett.* **2002,** 4, (10), 1637-1640.

111. Calter, M. A., Catalytic, Asymmetric Dimerization of Methylketene. *J. Org. Chem.* **1996,** 61, (23), 8006-8007.

112. Viswanath Mahadevan; Y., Y. D.; Getzler, L.; Coates, G. W., Lewis Acid Complexes: A Versatile Class of Catalysts for Carbonylative Ring Expansion of Epoxides and Aziridines13. *Angew. Chem., Int. Ed. Engl.* **2002,** 41, (15), 2781-2784.

113. Shapira, M.; Gutman, A. L., Enzymatic Synthesis of Chiral Monosubstituted Malonate in Organic Solvents. *Tetrahedron: Asymmetry* **1994,** 5, (1689-1700).

114. Van Maarseveen, J. H.; Hermkens, P. H. H.; De Clercq, E.; Balzarini, J.; Scheeren, H. W.; Kruse, C. G., Antiviral and antitumor structure-activity relationship studies on tetracyclic eudistomines. *J. Med. Chem.* **1992,** 35, (17), 3223-3230.