

TOTAL SYNTHESIS OF DICTYOSTATIN ANALOGS FOR ANTICANCER AGENTS

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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
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(-)-Dictyostatin, isolated from a marine sponge, shows potent cancer cell antiproliferative activity by stabilizing microtubules. Following the structure proof of dictyostatin, efforts have focused on the design and synthesis of analogs on the basis of the structural similarities between dictyostatin and discodermolide. To this end, the C15 *Z*-alkene was introduced in dictyostatin and the C16 methyl group was removed to simplify the structure, which gave 16-normethyl-15,16-dehydrodictyostatin. The macrolactone was disconnected into three main fragments, each of which had a full carbon skeleton. The C1–C9 fragment was synthesized via Brown crotylation and cross metathesis as key reactions. The C10–C15 fragment was synthesized via Roush crotylation of the (*S*)-Roche ester and diimide reduction. The C16–C26 fragment was synthesized via Evans aldol reaction of the (*S*)-Roche ester, *syn* 1,3-reduction and Nozaki–Hiyama reaction. The C10–C15 and C16–C26 fragments were coupled via a Wittig reaction, and the C1–C9 fragment was coupled with the lithium reagent derived from the C10–C26 vinyl iodide. Yamaguchi macrolactonization and global deprotection produced 16-normethyl-15,16-dehydrodictyostatin, along with C2*E*-, C9 isomers and an isomeric lactone. 16-Normethyl-15,16-dehydrodictyostatin showed a low nanomolar cancer cell antiproliferative activity and effectively competed with paclitaxel for binding to tubulin polymer.

6-*epi*-Dictyostatin showed potent cancer cell antiproliferative activity in preliminary results. Further biological evaluation of 6-*epi*-dictyostatin required the preparation of a large

quantity. A common intermediate was made to reduce the number of reaction steps for constructing both the C11'–C17 and C18–C26 fragments. The C1–C10' and C11'–C17 fragments were coupled via a silicon-tethered ring-closing metathesis reaction. The C1–C17 and C18–C26 fragments were united via a HWE reaction. The Stryker and *syn* 1,3-reductions converted the C19 enone into the saturated alcohol regio- and diastereoselectively. A Shiina reagent used for macrolactonization suppressed the isomerization of the C2 *Z*-unsaturated ester. A mild global deprotection method was developed to complete the synthesis. As an effort to validate the routes for the large-scale synthesis, 33 mg of 6-*epi*-dictyostatin was synthesized.

TABLE OF CONTENTS

1.0	INTRODUCTION.....	1
1.1	MICROTUBULE STABILIZERS AND CANCER.....	1
1.2	DICTYOSTATIN	3
2.0	TOTAL SYNTHESIS OF 16-NORMETHYL-15,16-DEHYDRODICTYOSTATIN	6
2.1	DESIGN OF A CONFORMATIONALLY RESTRICTED ANALOG OF DICTYOSTATIN	6
2.2	RETROSYNTHETIC ANALYSIS	9
2.3	SYNTHESIS OF THE C16–C26 FRAGMENT 20.....	11
2.4	SYNTHESIS OF THE C1–C9 FRAGMENT 22.....	15
2.5	SYNTHESIS OF THE C10–C15 FRAGMENT 21.....	20
2.6	COUPLING OF THE FRAGMENTS 21 AND 22.....	21
2.7	REVISED COUPLING STRATEGY	25
2.8	COMPLETION OF THE SYNTHESIS	29
2.9	SYNTHESIS OF THE 9-EPIMER.....	31
2.10	BIOLOGICAL EVALUATION	33
2.11	SUMMARY AND CONCLUSIONS	36
3.0	IMPROVED SYNTHESIS OF 6-EPI-DICTYOSTATIN	40

3.1	FIRST SYNTHESIS OF 6- <i>EPI</i> -DICTYOSTATIN	40
3.2	ATTEMPTED SYNTHESIS OF 6- <i>EPI</i> -DICTYOSTATIN.....	42
3.2.1	Background	42
3.2.2	The initial synthetic plan for a large-scale synthesis of 6- <i>epi</i> -dictyostatin	44
3.2.3	Attempted large-scale synthesis of 6- <i>epi</i> -dictyostatin.....	45
3.3	REVISED PLAN FOR THE SYNTHESIS OF 6- <i>EPI</i> -DICTYOSTATIN....	50
3.4	SYNTHESIS OF THE COMMON INTERMEDIATE 132.....	51
3.5	SYNTHESIS OF THE C18–C26 FRAGMENT 99.....	53
3.6	SYNTHESIS OF THE C11'–C17 FRAGMENT 128.....	54
3.7	SYNTHESIS OF THE C1–C10' FRAGMENT 127.....	55
3.8	FRAGMENT COUPLINGS	57
3.8.1	Coupling of the C1–C10' and C11'–C17 fragments	57
3.8.2	RCM reactions of the silylketals.....	58
3.8.3	Coupling of the C1–C17 and C18–C26 fragments	62
3.9	COMPLETION OF THE SYNTHESIS	63
3.9.1	Selective reduction reactions of the C17–C19 region	63
3.9.2	Completion of the synthesis of 6- <i>epi</i> -dictyostatin 101	65
3.10	SUMMARY AND CONCLUSIONS	68
4.0	EXPERIMENTAL	71
4.1	GENERAL INFORMATION.....	71
4.2	PROCEDURES AND DATA.....	72
	BIBLIOGRAPHY	150
	APPENDIX.....	157

LIST OF TABLES

Table 1. Comparison of the strategies for synthesizing the fragment the C1–C9 fragment 22 ...	20
Table 2. Biological activities of 9 , 92 , 94 and 95	34
Table 3. Potencies of 9 , 92 , 94 and 95 on HeLa cells	35
Table 4. Biological activities of 5 , 101 , 102 and 103	42
Table 5. Reaction of the lithium reagent derived from the vinyl iodide 111 with the aldehyde 112	49
Table 6. Macrolactonization of the <i>seco</i> -acid 169	67

LIST OF FIGURES

Figure 1. Structures of representative natural microtubule stabilizers.....	2
Figure 2. Structures 4 and 5 for dictyostatin.....	3
Figure 3. Conformers of acetylcholine and 2-tropanyl ethanoate methiodides.....	7
Figure 4. Structural comparison of discodermolide 2 and dictyostatin 5	8
Figure 5. 16-Normethyl-15,16-dehydrodictyostatin 9 and other simplified analogs.....	8
Figure 6. Summary of the synthetic strategy for dictyostatin 5	10
Figure 7. Retrosynthetic analysis for 16-normethyl-15,16-dehydrodictyostatin 9	11
Figure 8. Synthesis of the diol 31	12
Figure 9. Preparation of the C19 diastereomeric mixture.....	12
Figure 10. Synthesis of the diene 37	13
Figure 11. Synthesis of the C16–C26 fragment 20	14
Figure 12. Synthesis of the trityl ether 45	15
Figure 13. Synthesis of the Weinreb amide 18	16
Figure 14. Attempted cross metathesis reaction between the TBS ether 43 and the trityl ether 48	17
Figure 15. Cross metathesis reaction between the alcohol 42 and the trityl ether 48	18
Figure 16. Synthesis of the C1–C9 fragment 22	18
Figure 17. Cross metathesis strategy for synthesizing the C1–C9 fragment 22	19

Figure 18. Synthesis of the fragment 21	21
Figure 19. Coupling of the alkyne 21 and the Weinreb amide 22	22
Figure 20. Proposed mechanism for the isomerization of the C2 <i>Z</i> -unsaturated ester	22
Figure 21. Synthesis of the dienyl ether 70	23
Figure 22. Attempted partial reduction reaction of the dienyl ether 73	23
Figure 23. Attempted partial reduction reactions of the dienolate 66	24
Figure 24. Revised retrosynthetic analysis for 16-normethyl-15,16-dehydrodictyostatin 9	25
Figure 25. Wittig reaction of the aldehyde 78 and the phosphonium salt 79 done by Dr. Y. Shin	26
Figure 26. Synthesis of the C10–C15 fragment 77	26
Figure 27. Coupling of the C10–C15 fragment 77 and the C16–C26 fragment 20	27
Figure 28. Coupling of the aldehyde 70 and the vinyl iodide 76	28
Figure 29. Structures of the <i>seco</i> -acids 85α , 86 , 87 and 88	28
Figure 30. Completion of the synthesis of 16-normethy-15,16-dehydrodictyostatin 9	30
Figure 31. HMBC spectrum of 16-normethyl-15,16-dehydrodictyostatin 9	31
Figure 32. Completion of the synthesis of 9- <i>epi</i> -16-normethyl-15,16-dehydrodictyostatin 94 ..	32
Figure 33. Summary of the FMS of dictyostatin and three 6,7-epimers.....	41
Figure 34. Fragment coupling strategies for dictyostatin analogs by the Curran group. (a) Wittig reaction; (b) alkynyllithium addition; (c) RCM; (d) vinylolithium addition	43
Figure 35. Initial plan for a large-scale synthesis of 6- <i>epi</i> -dictyostatin.....	45
Figure 36. Synthesis of the C10–C17 fragment 113	46
Figure 37. Synthesis of the C10–C26 vinyl iodide 111	47
Figure 38. Coupling of the vinyl iodide 111 and the aldehyde 112	48

Figure 39. Structures of the TBS ether 123α and the fluoros TIPS ether 124	49
Figure 40. Retrosynthetic analysis of <i>6-epi</i> -dictyostatin	50
Figure 41. Synthesis of the fragments 97 and 99 in the attempted synthesis of <i>6-epi</i> -dictyostatin	51
Figure 42. Structural analysis of the C11–C14 and C20–23 regions.....	52
Figure 43. Synthesis of the common intermediate 132	52
Figure 44. Synthesis of the C18–C26 fragment 99	54
Figure 45. Synthesis of the C11'–C17 fragment 128	55
Figure 46. Synthesis of the C1–C10' fragment 127	56
Figure 47. Synthesis of the silylketals 126 and 147	57
Figure 48. Two reaction pathways in the RCM reaction of the silylketals 126 and 147	58
Figure 49. Synthesis of the new C1–C10' fragment (151 and 152).....	60
Figure 50. Synthesis of a mixture of the acetonides 153 and 154	60
Figure 51. Selected resonances of the acetonide mixture (153 and 154) on the ¹³ C NMR spectrum.....	60
Figure 52. Synthesis of the 8-membered disiloxanes 148 and 149	61
Figure 53. Construction of the full C1–C26 carbon skeleton	62
Figure 54. Model study on the selective reduction of the enone	63
Figure 55. Regioselective reduction of the C17–C18 olefin of the enone 164	63
Figure 56. Model study on the selective reduction of the ketone	64
Figure 57. Diastereoselective reduction of the C19 ketone 164	65
Figure 58. Completion of the synthesis of <i>6-epi</i> -dictyostatin 101	66
Figure 59. Comparison of ¹ H NMR spectra of the TBS-protected macrolactones.....	67

LIST OF SCHEMES

Scheme 1. Summary of the synthesis of 16-normethyl-15,16-dehydrodictyostatin 9	37
Scheme 2. Summary of the synthesis of 6- <i>epi</i> -dictyostatin 101	69

PREFACE

My foremost thank goes to my advisor Professor Dennis Curran. Without him, this dissertation would not have been possible. I thank him for his patience and suggestions that carried me on through difficult times of research. His considerate help and valuable feedback contributed greatly to this dissertation.

I thank Dr. Gustavo Moura-Letts and Dr. Christian Harrison who worked together to synthesize 6-*epi*-dictyostatin. I also thank Dr. Yoshikazu Fukui and Dr. Youseung Shin for their beautiful chemistry serving as a reference. They are best synthetic chemists I have ever seen.

I thank Lynne Clemente and all the Curran group (Xiaoyuan Ding, Claude Ogoe, Sabrina Guyenne, Jared Moretti, Kai Zhang, Bin Sui, Elliot Wang, Venugopal Gudipati, Concepción Riesco-Fagundo, Jean-Hugues Fournier, Arndt M. Brückner, Qianli Chu, Reena Bajpai, David Guthrie, Edmund Yeh, Maria del Sol Hopkins and Wei Zhu).

I thank the rest of my thesis committee members: Professor Billy Day, Professor Kazunori Koide and Professor Paul Floreancig. Their valuable feedback helped me to improve the dissertation in many ways.

Last, I thank my wife Jaehyun Cho for being patient and encouraging me through all these years.

LIST OF ABBREVIATIONS

9-BBN	9-Borabicyclo[3.3.1]nonane
Bu ₂ OTf	Dibutylboron triflate
COSY	Correlated spectroscopy
DCC	Dicyclohexylcarbodiimide
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL-H	Diisobutylaluminum hydride
DIPEA	Diisopropylethylamine
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
DMAP	4-Dimethylaminopyridine
HMBC	Heteronuclear multiple-bond correlation spectroscopy
HMQC	Heteronuclear multiple quantum correlation
K-Selectride	Potassium tri- <i>sec</i> -butylborohydride
KHMDS	Potassium hexamethyldisilazine
LDA	Lithium diisopropylamine
NaHMDS	Sodium hexamethyldisilazine
NBSH	<i>o</i> -Nitrobenzenesulfonyl hydrazide
PMB	<i>p</i> -Methoxybenzyl
PMP	<i>p</i> -Methoxyphenyl
PPTS	Pyridinium <i>p</i> -toluenesulfonate
SO ₃ •pyr	Sulfur trioxide pyridine complex
TCBC	2,4,6-Trichlorobenzoyl chloride
TES	Triethylsilyl
TESOTf	Triethylsilyl triflate

TBS	<i>tert</i> -Butyldimethylsilyl
TBSOTf	<i>tert</i> -Butyldimethylsilyl triflate
TEA	Triethylamine
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TrCl	Triphenylmethyl chloride

1.0 INTRODUCTION

1.1 MICROTUBULE STABILIZERS AND CANCER

Microtubules are protein structures found within cells and one of the components of the cytoskeleton. They have a diameter of about 25 nm and varying length from 200 nm to 20 μm . Microtubules are polymers of α - and β -tubulin dimers. The tubulin dimers polymerize end-to-end to form protofilaments. The protofilaments are arranged by lateral contacts into hollow cylindrical filaments to complete the microtubules.¹

Microtubules are dynamic structures and grow and shrink mainly through addition and loss of the tubulin dimers at their ends. This process is called microtubule dynamics and plays critical roles in the assembly and function of the mitotic spindle. Microtubule dynamics can be altered by drugs. For example, paclitaxel **1** (Figure 1) suppresses the dynamics by binding β -tubulin and stabilizing the microtubule. This alteration of microtubule dynamics causes cell cycle arrest and cell death by apoptosis. Natural products (paclitaxel **1**, discodermolide **2** and epothilone B **3** in Figure 1) that stabilize microtubules (called microtubule stabilizers) are recognized as cancer chemotherapy agents.²

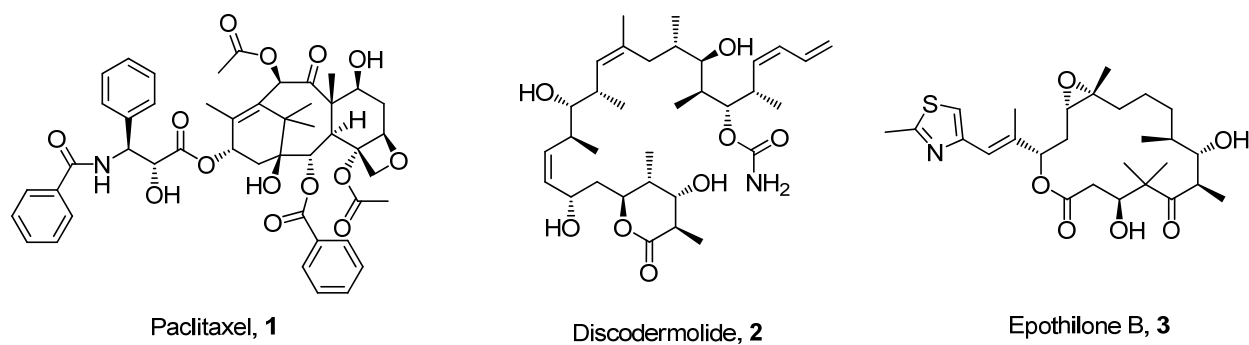


Figure 1. Structures of representative natural microtubule stabilizers

Paclitaxel **1**, isolated from the Pacific yew *Taxus brevifolia*, has demonstrated clinical success in the treatment of breast, lung and ovarian cancers.³ However, the use of this compound has been limited by poor solubility, undesirable side effects and partial effectiveness towards multidrug-resistant or recurrent cancers. As a result, new microtubule stabilizers are being developed with antiproliferative activity against paclitaxel-resistant cells and in the hopes that they will have fewer side effects.⁴

(+)-Discodermolide **2**, a marine sponge-derived polyketide, was isolated and characterized by Gunasekera *et al.* in 1990.⁵ It was initially reported to have strong *in vitro* and *in vivo* immunosuppressive activities.⁶ Later, (+)-discodermolide was shown to have microtubule stabilizing properties similar to those of paclitaxel **1**⁷ and to also retain antiproliferative activity against paclitaxel-resistant cells.⁸ Total syntheses of (+)-discodermolide **2** have been reported to date by Schreiber,⁹ Smith,¹⁰ Paterson,¹¹ Marshall,¹² Myles,¹³ Panek¹⁴ and Ardisson.¹⁵ Other efforts have focused on the design and synthesis of structurally simplified analogs of (+)-discodermolide.¹⁶ In addition, the Novartis pharmaceutical company synthesized about 60 g of

this natural product for clinical trials. The phase II clinical trial of (+)-discodermolide was halted.¹⁷ This increases the need for discovery of the new microtubule stabilizers.

Epothilone B **3** was isolated and characterized by Hofle *et al.* from the myxobacterium *Sorangium cellulosum* and was shown to have cancer cell antiproliferative activity by stabilizing microtubule.¹⁸ Epothilone analogs are undergoing clinical development for treatment of various cancers.

1.2 DICTYOSTATIN

In 1994, the Pettit group reported the isolation of a macrocyclic lactone, (-)-dictyostatin, from a marine sponge of the genus *Spongia* in the Republic of Maldives. They assigned it the structure **4** (Figure 2) on the basis of 2D NMR spectroscopic data.¹⁹ (-)-Dictyostatin strongly inhibited the growth of a selection of human cancer cell lines ($GI_{50} = 0.05\text{--}1\text{ nM}$), as well as murine P388 lymphocytic leukemia cells ($ED_{50} = 0.38\text{ nM}$).

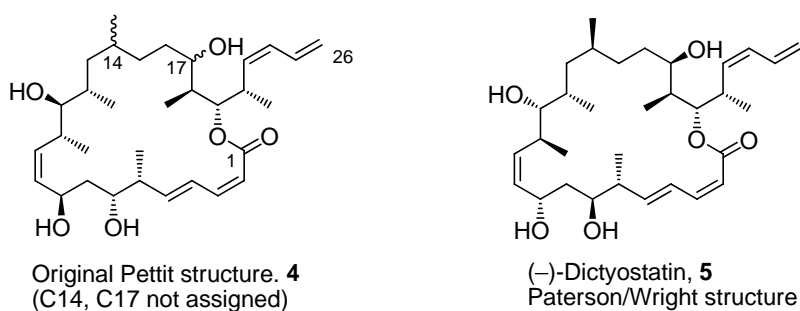


Figure 2. Structures **4** and **5** for dictyostatin

In 2003, the Wright group again isolated (–)-dictyostatin from a Lithistida sponge of the family *Corallistidae* collected off the north Jamaican coast.²⁰ They reported that its mechanism of cytotoxic activity was similar to that of paclitaxel, and that dictyostatin induced the polymerization of purified bovine brain tubulin *in vitro*. Dictyostatin was highly potent toward two paclitaxel-resistant human cancer cell lines expressing P-glycoprotein.

In 2004, Paterson and Wright proposed the structure **5** for dictyostatin, as shown in Figure 2, on the basis of a combination of high field NMR studies and molecular modeling.²¹ The first total syntheses of dictyostatin **5** and the confirmation of its structure were simultaneously reported by the groups of Curran and Paterson.²² Additional total syntheses of dictyostatin **5** by the groups of Phillips and Ramachandran,²³ as well as synthesis of analogs,²⁴ were reported.

Detailed studies of biological activities were conducted with synthetic dictyostatin **5** by the Day group.²⁵ The 50% growth inhibitory concentration (GI₅₀, against 1A9 cells) of dictyostatin was comparable to those of paclitaxel **1** and discodermolide **2** (0.69, 0.71 and 1.7 nM, respectively). Like discodermolide, dictyostatin retained antiproliferative activity against cells resistant to paclitaxel (3.2 nM against 1A9PTX10 cells, 1.3 nM against 1A9PTX22 cells) and inhibited the paclitaxel binding to tubulin polymer (61% inhibition at 1 μM concentration). The competitive binding implies that dictyostatin and paclitaxel bind at the same site on tubulin polymers.

Since proving the structure of dictyostatin, the dictyostatin project in the Curran group has been centered on two goals.^{24b–e} The first goal is the synthesis of analogs designed to investigate the structure-activity relationship as well as to define the important structural

elements required for anticancer activity. The second goal is the exploration of various strategies to develop a practical synthesis of drug candidates.

2.0 TOTAL SYNTHESIS OF 16-NORMETHYL-15,16-DEHYDRODICTYOSTATIN

2.1 DESIGN OF A CONFORMATIONALLY RESTRICTED ANALOG OF DICTYOSTATIN

Acetylcholine (**6a**, **6b**) shows a nicotinic activity as well as a muscarinic activity. Archer suggested that the nicotinic activity arose from the *syn*-conformer **6a** and that the muscarinic activity was due to the *anti*-conformation **6b** (Figure 3).²⁶ This was based on the observation that the β -conformer (key bonds highlighted in bold) of 2-tropanyl ethanoate methiodide **7a** binds preferentially to nicotinic receptors, whereas the α -conformer **7b** (key bonds highlighted in bold) prefers binding to muscarinic receptors. This study suggests that conformationally restricted analogs could result in the selective binding of drugs to target sites with reduced binding to unwanted sites.

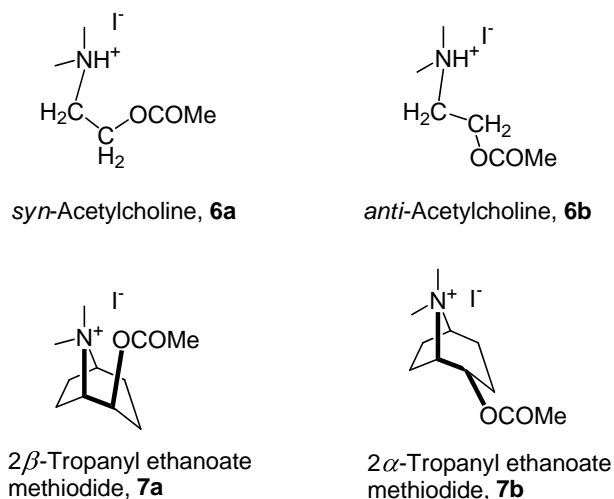


Figure 3. Conformers of acetylcholine and 2-tropanyl ethanoate methiodides

While designing analogs of dictyostatin, we focused on the structural differences between dictyostatin **5** and discodermolide **2**. This was because dictyostatin **5** shares identical configurations at all common stereocenters with discodermolide **2**.^{24a} The key differences in the structures of discodermolide and dictyostatin are highlighted in dashed boxes in Figure 4. Discodermolide has an open chain carbamate (in box A), a double bond at C13–C14 (in box B), and a C1–C5 six-membered lactone (in box C). In an attempt to design a hybrid of dictyostatin/discodermolide, the C15 *Z*-alkene was envisioned in dictyostatin to give 15,16-dehydrodictyostatin **8** (Figure 5). (Note that the carbon skeleton of dictyostatin is two atoms longer than that of discodermolide, so C14 of discodermolide **2** corresponds to C16 of dictyostatin **5**.)

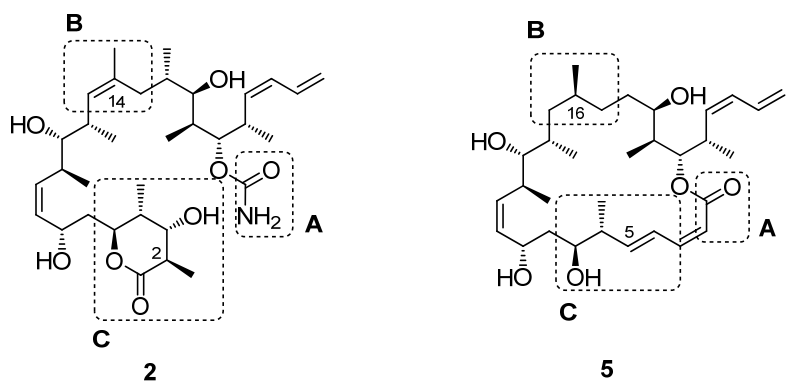


Figure 4. Structural comparison of discodermolide **2** and dictyostatin **5**

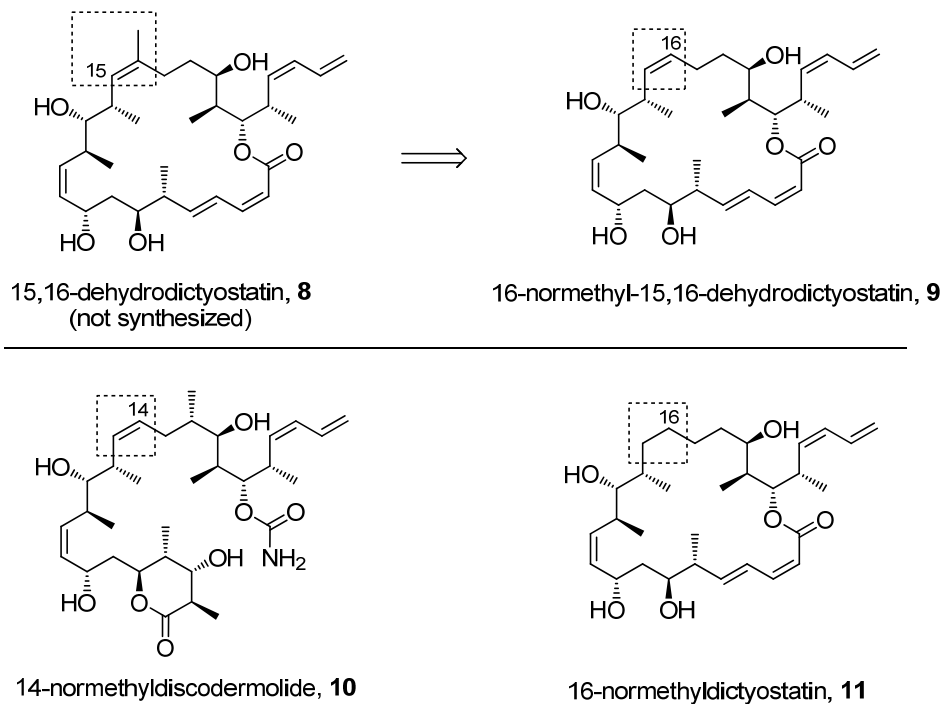


Figure 5. 16-Normethyl-15,16-dehydrodictyostatin **9** and other simplified analogs

The C16 methyl group of 15,16-dehydrodictyostatin **8** was removed to simplify the structure, because 14-normethyldiscodermolide **10** retains much of antiproliferative activity as its

parent discodermolide ($IC_{50} = 46, 28 \text{ nM}$, respectively).²⁷ This led us to 16-normethyl-15,16-dehydrodictyostatin **9** as a target compound (Figure 5). In the course of synthesizing 16-normethyl-15,16-dehydrodictyostatin **9**, 16-normethyl-15,16-dehydrodictyostatin **11** was synthesized and showed the antiproliferative activity similar to that of dictyostatin ($GI_{50} = 0.41, 0.69 \text{ nM}$, respectively).^{24b}

2.2 RETROSYNTHETIC ANALYSIS

In the original synthesis of dictyostatin **5** by the Curran group (Figure 6), primary disconnections were made across the C1–O21, C9–C10 and C17–C18 bonds to give three main fragments (the phosphonate **16**, the alkyne **17** and the Weinreb amide **18**).^{22b} The C3–C17 fragment was first constructed via addition of the alkynyllithium derived from the alkyne **17** to the Weinreb amide **18**. The resulting ynone (not shown) was subjected to Noyori and Lindlar reductions to give the C9 α -hydroxy group and the C10 *Z*-alkene. Next, the C3–C17 aldehyde **15** was united with the C18–C23 phosphonate **16** via a Horner–Wadsworth–Emmons (HWE) olefination reaction. After fragment couplings were done, the C24–C26 bonds were constructed with the allyl bromide **13**, and the C1–C2 unsaturated ester with the phosphonate **14**.

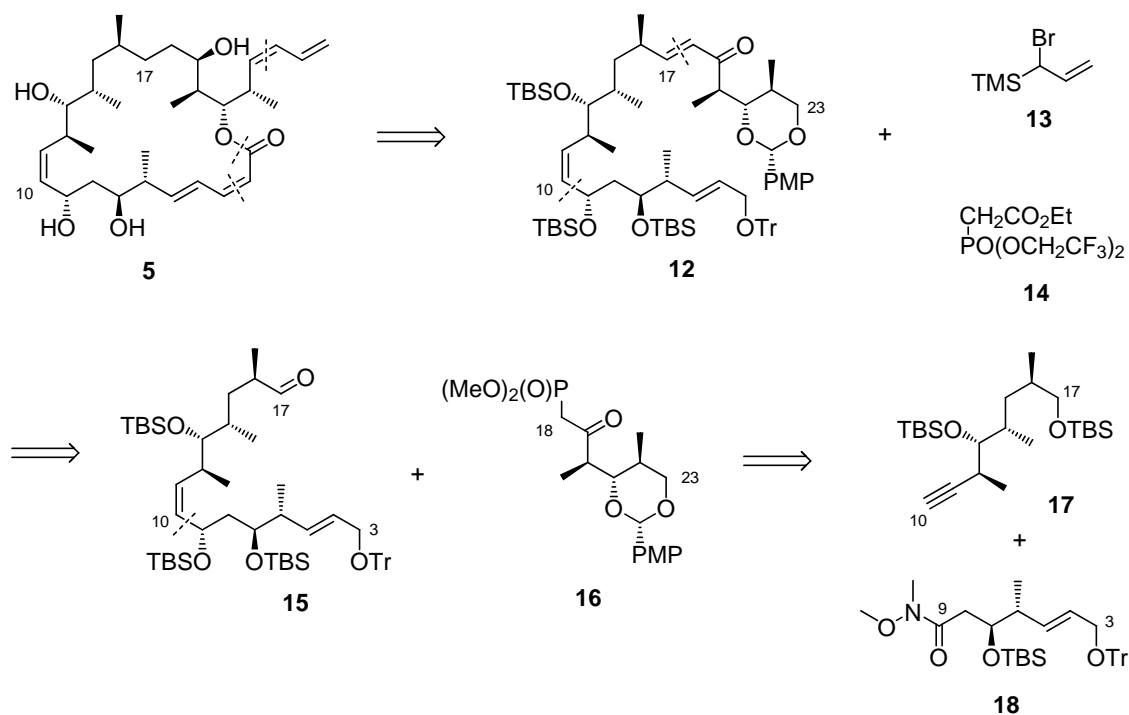


Figure 6. Summary of the Curran's synthetic strategy for dictyostatin **5**

The plan for the synthesis of 16-normethyl-15,16-dehydrodictyostatin **9** is outlined in Figure 7. The C15–C16 *Z*-alkene was envisioned to be made by a Wittig olefination reaction to give the aldehyde **19** and the phosphonium salt **20**. Further disconnection of the C1–C15 fragment **19** across the C9–C10 bond gave the alkyne **21** and the Weinreb amide **22**. They were envisioned to be united by addition of the alkynyllithium derived from the alkyne **15** to the Weinreb amide **16**. This is similar to the strategy for constructing the C9–C11 region of dictyostatin **5**. In addition, each of three fragments (**20**, **21** and **22**) had a full carbon skeleton so as to increase convergency of the synthesis of 16-normethyl-15,16-dehydrodictyostatin **9**.

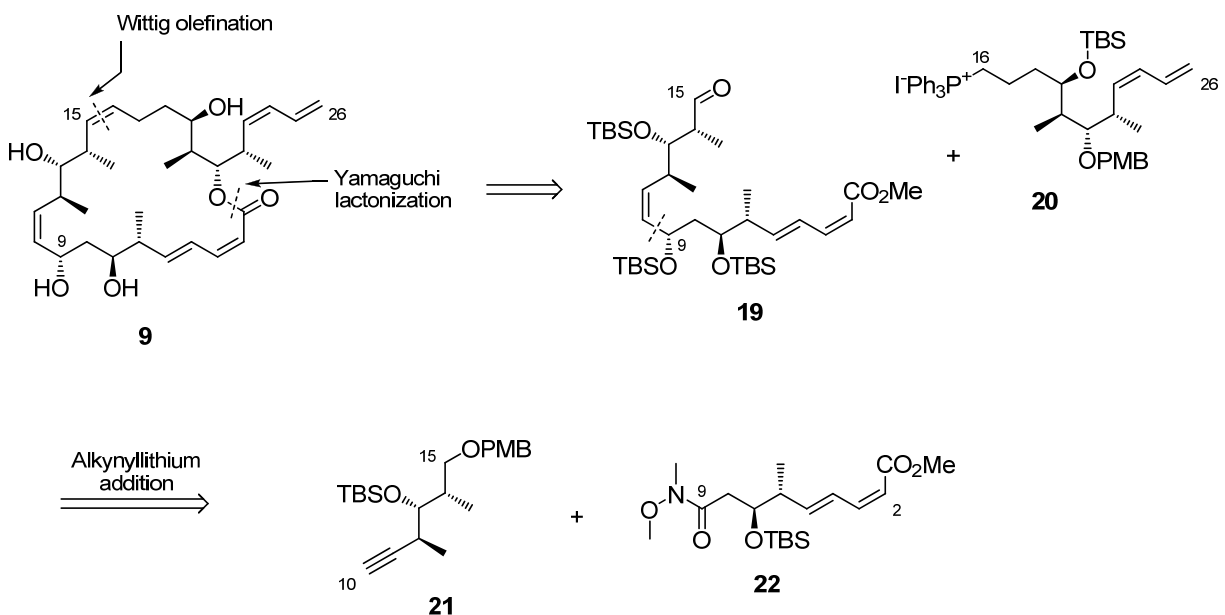


Figure 7. Retrosynthetic analysis for 16-normethyl-15,16-dehydrodictyostatin **9**

2.3 SYNTHESIS OF THE C16–C26 FRAGMENT **20**

The Weinreb amide **28** was synthesized from the (*S*)-Roche ester **23** by following the procedures established by Smith^{10c} (Figure 9). Commercially available (*S*)-Roche ester **23** was protected by using trichloroimidate **24**²⁸ to give a 4-methoxybenzyl (PMB) ether **25** in 87% yield. The ester group of **25** was reduced with lithium borohydride to give an alcohol, which was oxidized via a Swern reaction²⁹ to provide the crude aldehyde. The aldehyde was subjected to the Evans *syn*-aldol reaction³⁰ to give the aldol product **27** in 89% yield over three steps. Transamidation of the aldol product **27** by using trimethylaluminum^{10c} produced the Weinreb amide **28** in 96% yield.

Next, the alkyl iodide **29** (3.0 equiv) was treated with *t*-BuLi (6.5 equiv), then the Weinreb amide **28** was added to give a β -hydroxyketone **30** in 84% yield. The ketone **30** was reduced with NaBH₄ and Et₂BOMe³¹ to give a *syn*-1,3-diol **31** in 85% yield. To measure the diastereoselectivity of the reaction, a mixture of two C19 isomers (**31** and **32**) was synthesized by reduction of the ketone **30** with NaBH₄ (Figure 9). The two C19 isomers were resolved by LC-MS and the ratio was 1.7:1 (**31**/**32**). Next, the diol **31** from the NaBH₄/Et₂BOMe reduction was analyzed by LC-MS under the same conditions. The ratio was 127:1(**31**/**32**).

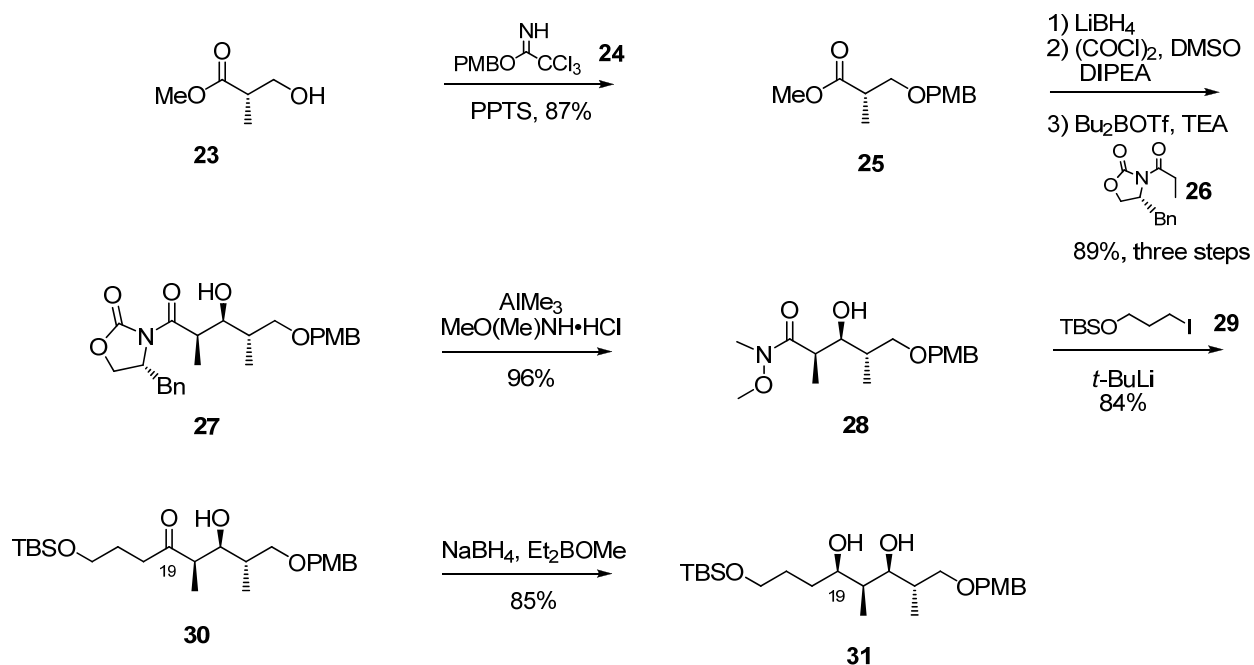


Figure 8. Synthesis of the diol **31**

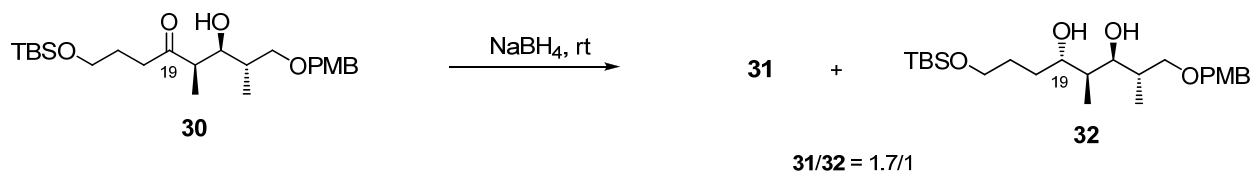


Figure 9. Preparation of the C19 diastereomeric mixture

As shown in Figure 10, the diol **31** was treated with DDQ in the presence of 4 Å molecular sieves³² to provide a *p*-methoxybenzylidene (PMB) acetal **33** in 60% yield. The C19 hydroxyl group of the acetal **33** was protected with TBSOTf to give a TBS ether **34** in 99% yield. Treatment of the ether **34** with DIBAL-H³³ at -45 °C gave the expected alcohol **35** resulting from the PMB acetal opening, and the diol **36** in which the C16 TBS group was also removed. They were separated by silica gel chromatography (41% yield for the alcohol **35** and 55% yield for the diol **36**). The diol **36** was then converted to the desired alcohol **35** by treatment with TBSCl and imidazole in 55% yield.

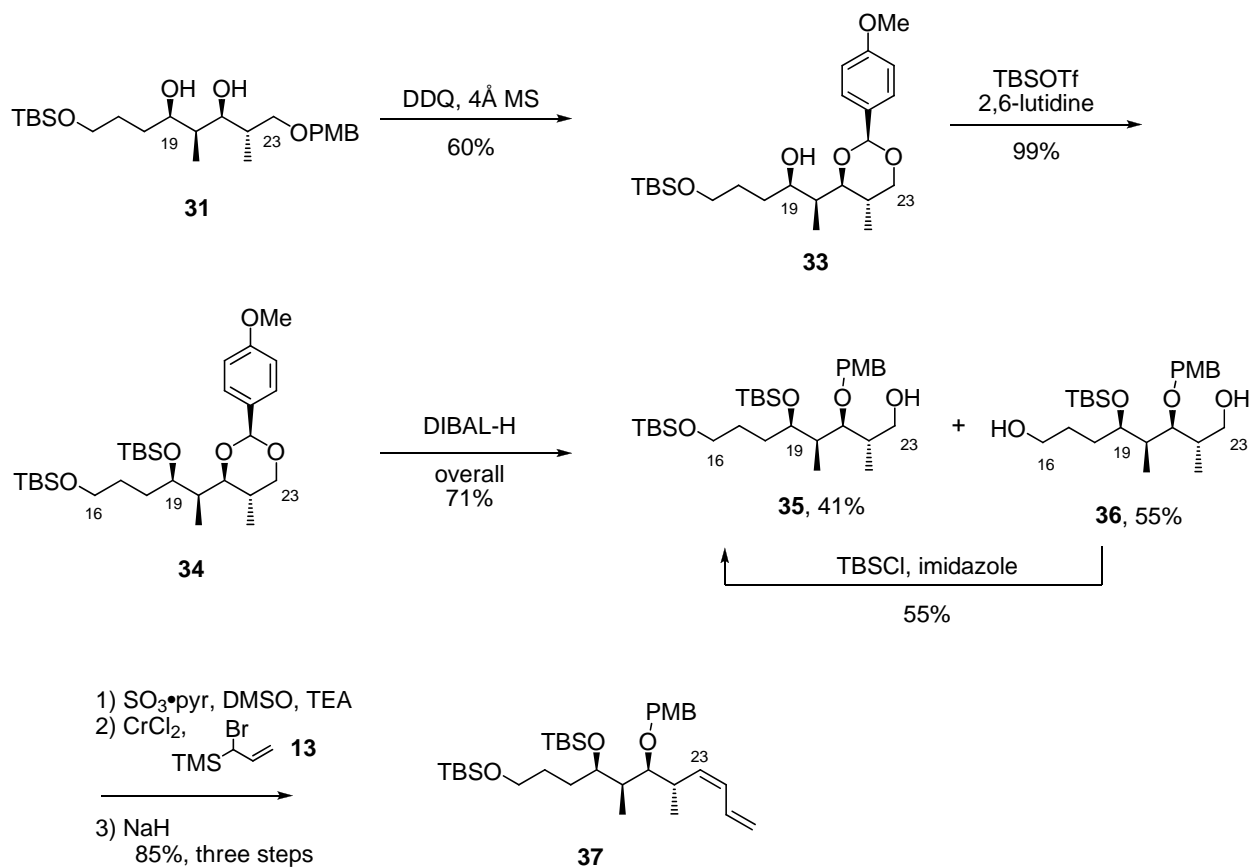


Figure 10. Synthesis of the diene **37**

Next, a Paterson protocol (Nozaki–Hiyama reaction followed by Peterson elimination)³⁴ was used to install the C23–C26 diene, as shown in Figure 10. To this end, oxidation of the alcohol **35** under Parikh–Doering conditions ($\text{SO}_3 \cdot \text{pyr}$, DMSO and Et_3N)³⁵ gave the crude aldehyde, which reacted with the allyl bromide **13** in the presence of CrCl_2 to give the crude β -hydroxysilane (not shown). Next, this silane was treated with sodium hydride to provide the C23–C24 *Z*-diene **37** after silica gel chromatography in 85% yield over three steps.

Completion of the synthesis of the C16–C26 fragment **20** is summarized in Figure 11. The C16 TBS protecting group of **37** was removed with $\text{HF} \cdot \text{pyr}$ to give the primary alcohol **38** in 75% yield. The alcohol **38** was converted into the iodide **39** by using PPh_3 , I_2 and imidazole in 93% yield. The iodide **39** was treated with PPh_3 to produce the phosphonium salt **20** in 78% yield.³⁶

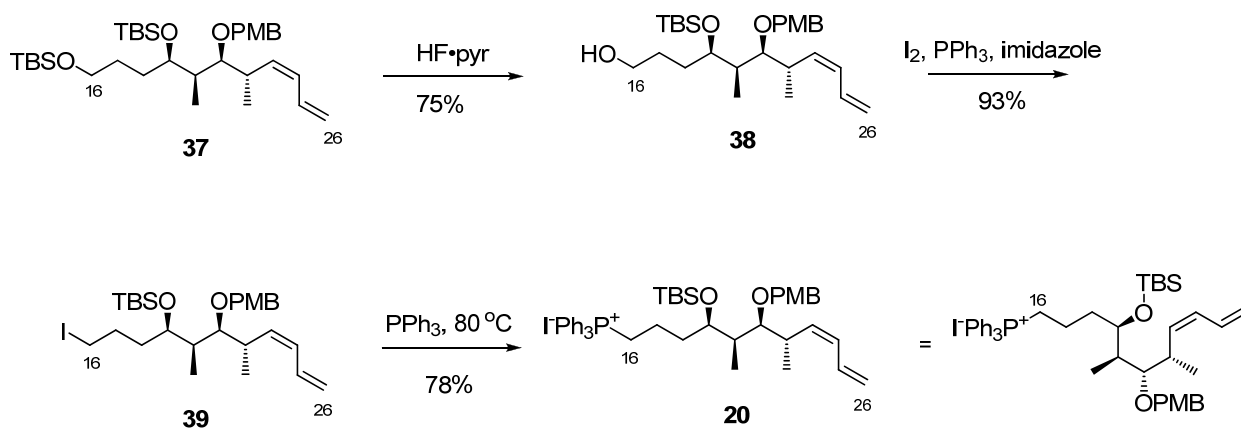


Figure 11. Synthesis of the C16–C26 fragment **20**

Overall, the C16–C26 fragment **20** (2.0 g) was synthesized from the (*S*)-Roche ester **23** in 16 steps and 12% yield.

2.4 SYNTHESIS OF THE C1–C9 FRAGMENT 22

The Weinreb amide **18** was synthesized by following procedures used for synthesis of dictyostatin **5**.^{22b} This began with mono-protection of 1,3-propanediol **40** using TBSCl and NaH (Figure 12).³⁷ The resulting alcohol was oxidized with TEMPO and bleach to provide the aldehyde **41** after silica gel chromatography (76% yield, two steps). A Brown (*E*)-crotylboration³⁸ of the aldehyde **41** with (+)-(ipc)₂-B-crotyl gave the *anti*-homoallylic alcohol **42** after silica gel chromatography (69% yield). The alcohol **42** was protected with TBSCl to provide the TBS ether **43** (95% yield), which was oxidatively cleaved with OsO₄/NaIO₄ to give the crude aldehyde. The aldehyde was treated with ethyl 2-(diethoxyphosphoryl)acetate and NaH to give the *E*-unsaturated ester **44** after silica gel chromatography (83% yield, three steps).³⁹ The ester **44** was reduced with DIBAL-H at 0 °C to give an allyl alcohol, which was protected with TrCl to give the trityl ether **45** after silica gel chromatography (70% yield, two steps).

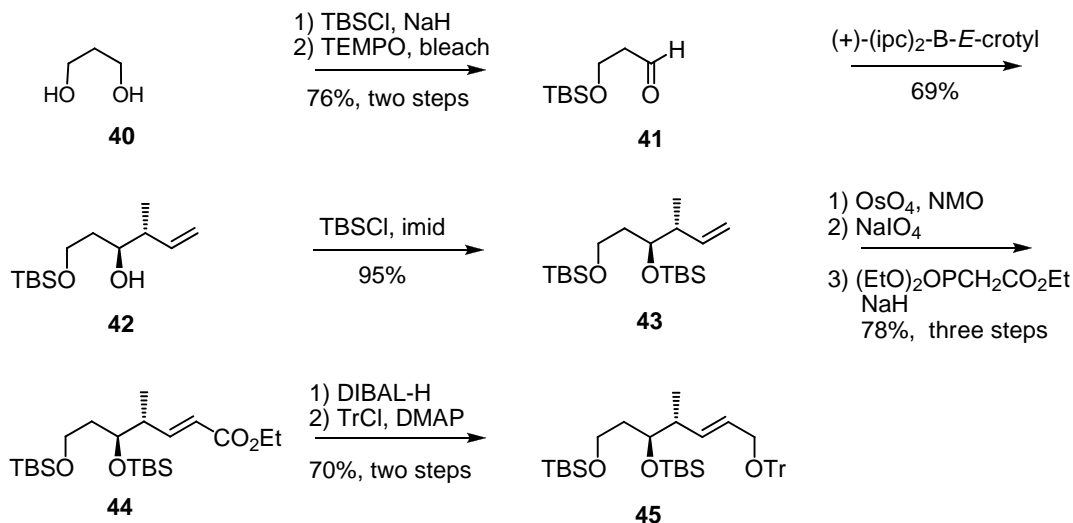


Figure 12. Synthesis of the trityl ether **45**

As summarized in Figure 13, the TBS ether **45** was treated with HF•pyr at room temperature to provide the alcohol **46** after silica gel chromatography in 74% yield. The primary alcohol **46** was oxidized by using SO₃•pyr, DMSO and Et₃N³⁵ to give the corresponding aldehyde **47**, which was further oxidized with sodium chlorite to give a carboxylic acid.⁴⁰ The crude carboxylic acid was coupled with *N,O*-dimethylhydroxylamine by using DCC to give the Weinreb amide **18** after silica gel chromatography in 78% yield for two steps.^{22b}

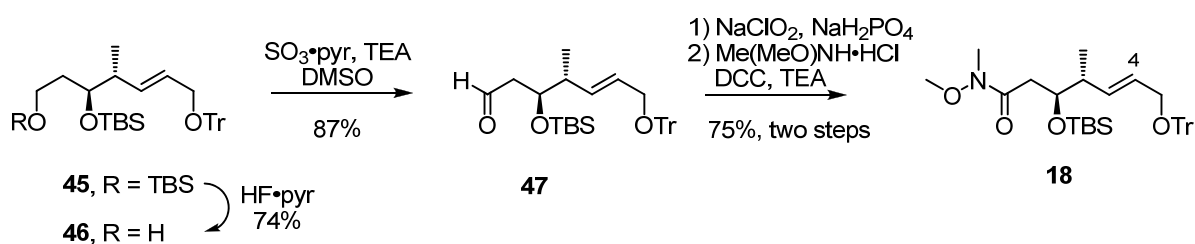


Figure 13. Synthesis of the Weinreb amide **18**

To reduce the number of reaction steps for synthesizing the Weinreb amide **18**, a cross metathesis reaction⁴¹ was attempted to construct the C4 *E*-alkene. A mixture of the homoallylic alcohol **43** and an allyl ether **48** was treated with a Grubbs second-generation (Grubb II) catalyst **49** or a Blechert–Grubbs catalyst **50**⁴² (Figure 14) in methylene chloride at 40°C. This gave the dimer (not shown) of the ether **48** without formation of the coupled product **45**. It was hypothesized that the C7 TBS group of **43** might prevent the cross coupling by steric hindrance.

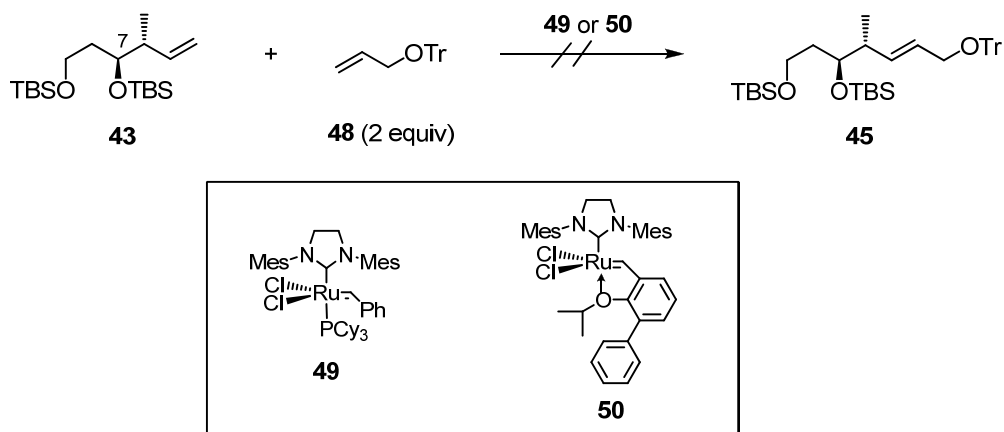


Figure 14. Attempted cross metathesis reaction between the TBS ether **43** and the trityl ether **48**

Next, the metathesis reaction between the unprotected alcohol **42** and the allyl ether **48** in methylene chloride was tried. This provided an inseparable mixture of the coupled product **51** and two isomerized alcohols **52** and **53** in a 2:1:1 ratio (Figure 15).⁴³ This mixture was protected to give the corresponding TBS ethers (**45**, **54** and **55**). They were then separated by silica gel chromatography to give the TBS ether **45** in 40% yield over two steps. In contrast, the use of degassed methylene chloride gave a mixture of the coupled product **51** and the two isomerized alcohols **52** and **53** in a 9:1:1 ratio. The TBS ether **45** was isolated after protection (0.5 g, 55% yield over two steps). This cross metathesis approach could reduce the number of reaction steps from the homoallylic alcohol **42** to the trityl ether **45** from six to two with the similar overall yield.

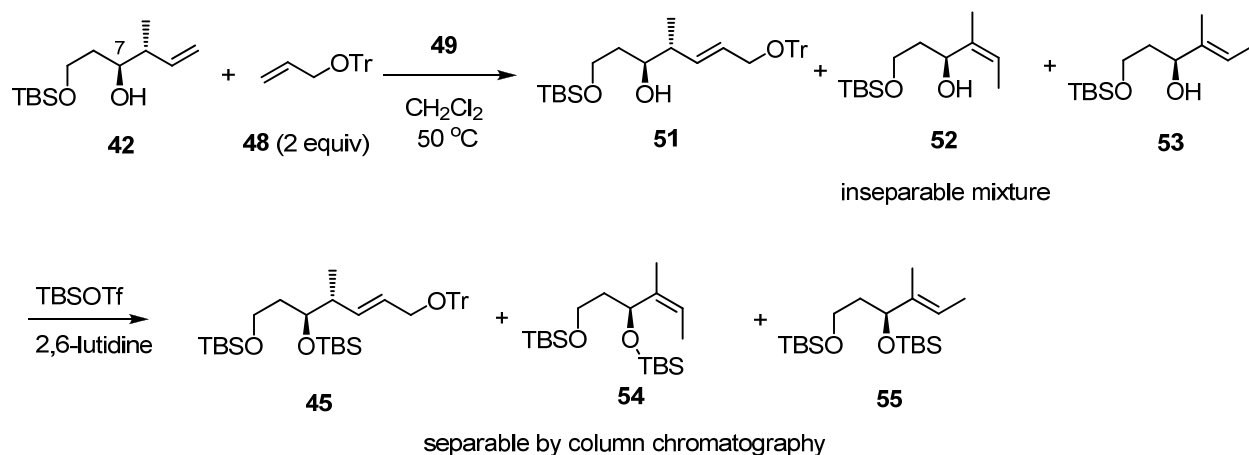


Figure 15. Cross metathesis reaction between the alcohol **42** and the trityl ether **48**

To complete the synthesis of the C1–C9 fragment **22**, the trityl group of **18** was removed with zinc bromide to provide the alcohol **56** in 91% yield (Figure 16).^{22b} Next, oxidation of the alcohol by using $\text{SO}_3 \cdot \text{pyr}$, DMSO and DIPEA gave the aldehyde, which was submitted to Still–Gennari olefination conditions (**14**, KHMDS and 18-crown-6)⁴⁴ to produce the C1–C9 fragment **22** (3.0 g, 70% yield over two steps). The C2 Z-geometry of **22** was confirmed in the ^1H NMR spectrum by the coupling constant between H2 and H3 ($J = 11.5$ Hz).

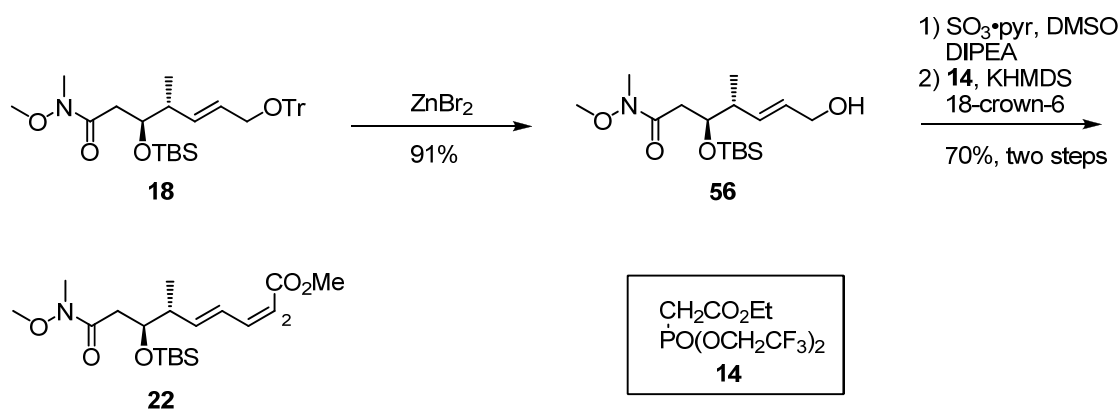


Figure 16. Synthesis of the C1–C9 fragment **22**

For an alternative approach to synthesizing the C1–C9 fragment **22** (Figure 17), the cross metathesis reaction between crotonaldehyde and the alkene **43** was tried. The reaction proceeded in the presence of the Grubb II catalyst **49** to provide the unsaturated aldehyde **57** in 77% yield. Carrying out seven reactions used for constructing the C9 Weinreb amide and the C1 unsaturated ester provided the C1–C9 fragment **22** (0.4 g). This cross metathesis approach could reduce the number of reaction steps from the homoallylic alcohol **42** to the C1–C9 fragment **22** from 13 to 7 in comparison to the strategy using no cross metathesis (Route 1), as shown in Table 1.

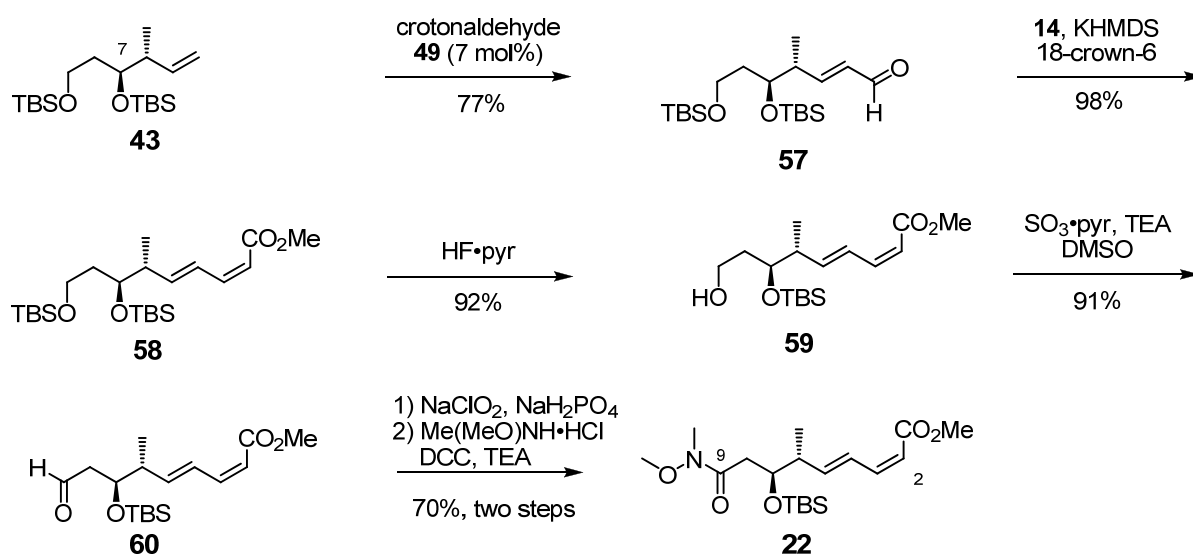


Figure 17. Cross metathesis strategy for synthesizing the C1–C9 fragment **22**

Table 1. Comparison of the strategies for synthesizing the fragment the C1–C9 fragment **22**

Route	Strategy	Reaction steps from the alcohol 42 to the C1–C9 fragment 22
1	No cross metathesis via HWE reaction and Tr protection	13
2	Cross metathesis with allyl ether 48	9
3	Cross metathesis with crotonaldehyde	7

2.5 SYNTHESIS OF THE C10–C15 FRAGMENT **21**

The synthesis of the C10–C15 fragment **21** is summarized in Figure 18. The alcohol **61** derived from the (*S*)-Roche ester **23** was oxidized with SO₃•pyr, DMSO and DIPEA. The resulting crude aldehyde was reacted with the Roush reagent **62**⁴⁵ at –78 °C for 8 h to provide the alcohol **63** in 67% yield over two steps. This alcohol was protected with TBSOTf and 2,6-lutidine to give the TBS ether **64** (82% yield), which was oxidatively cleaved by using a Jin one-pot protocol (OsO₄, NaIO₄, 2,6-lutidine)⁴⁶ to provide the aldehyde. The crude aldehyde was submitted to Corey–Fuchs olefination conditions (CBr₄, PPh₃)⁴⁷ with 2,6-lutidine to give the vinyl dibromide **65** in 74% yield over two steps. Next, the dibromide **65** was treated with BuLi (4 equiv) to produce the alkyne **21** in 96% yield.^{22b} Overall, 4.3 g of the C10–C15 fragment **21** was synthesized from the alcohol **61** in 39% yield over 6 steps.

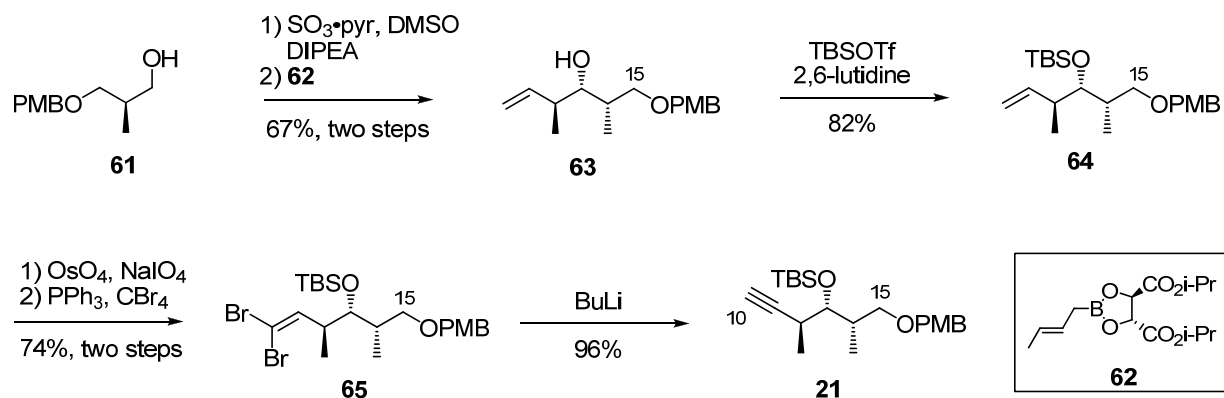


Figure 18. Synthesis of the fragment **21**

2.6 COUPLING OF THE FRAGMENTS **21** AND **22**

The plan for construction of the C9–C11 region was to use the three-step sequence of alkynyllithium addition, Noyori reduction then Lindlar reduction as was used for the synthesis of dictyostatin **5**.^{22b,28} First, the alkyne **21** was deprotonated with BuLi, and then addition of the Weinreb amide **22** gave a 1:1 mixture of the C2 *Z*-isomer **66** and the C2 *E*-isomer **67** (Figure 19). The mixture was separated by silica gel chromatography to give each pure isomer. The C2 geometries were confirmed in the ^1H NMR spectrum by the coupling constant between H2 and H3. It was presumed that the C2 isomerization originated from the addition of the C9 alkoxy anion to the C5 position of the intermediate **68** (Figure 20). This produced the tetrahydropyran ring **69**, which broke down to a mixture of the C2 *Z*-isomer **66** and the C2 *E*-isomer **67** during acidic workup.

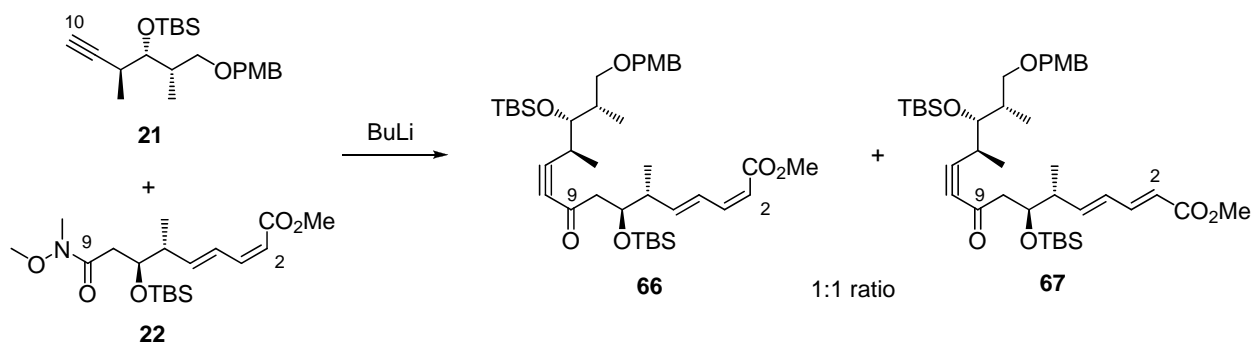


Figure 19. Coupling of the alkyne **21** and the Weinreb amide **22**

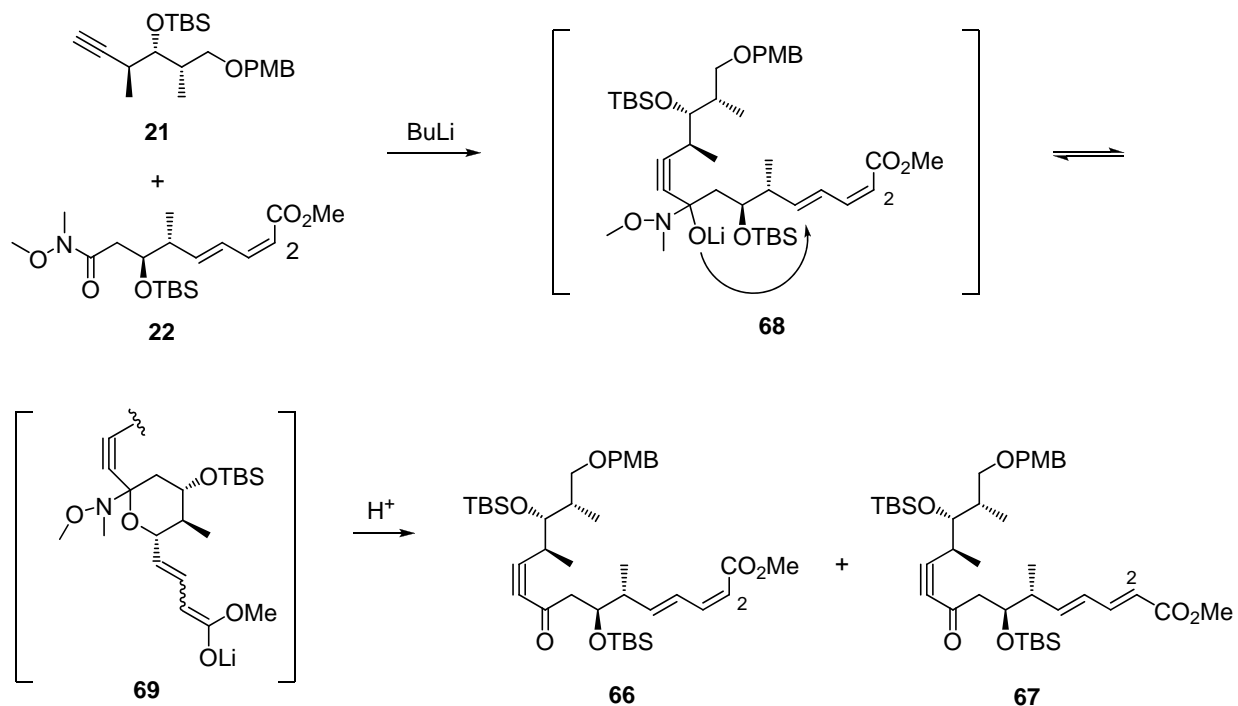


Figure 20. Proposed mechanism for the isomerization of the C2 Z-unsaturated ester

To prevent the 1,6-conjugate addition of the C9 alkoxy anion, the ester group of the C1–C9 fragment **22** with DIBAL-H was reduced. Next, the crude alcohol was treated with TBSOTf to produce the TBS ether **70** in 96% yield over two steps (Figure 21). The addition of the

alkynyllithium derived from the alkyne **21** to the aldehyde **70** provided a mixture of two C9 epimers, which was oxidized without purification to the ynone **71** in 55% yield over two steps (Figure 22). The ynone **71** was reduced with the (*S,S*)-Noyori catalyst **72**⁴⁸ to give the alcohol **73** in 81% yield. The C9 configuration of the alcohol **73** was assigned by analogy to dictyostatin **5**, because the same method was used to establish the C9 configuration. The stereoselectivity of the reaction was not determined.

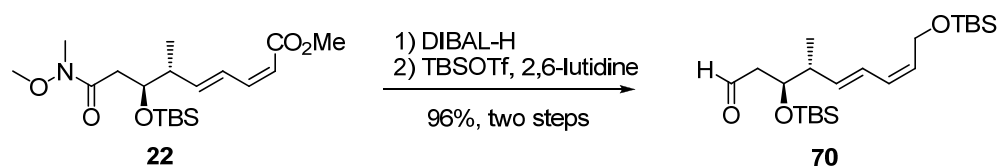


Figure 21. Synthesis of the dienyl ether **70**

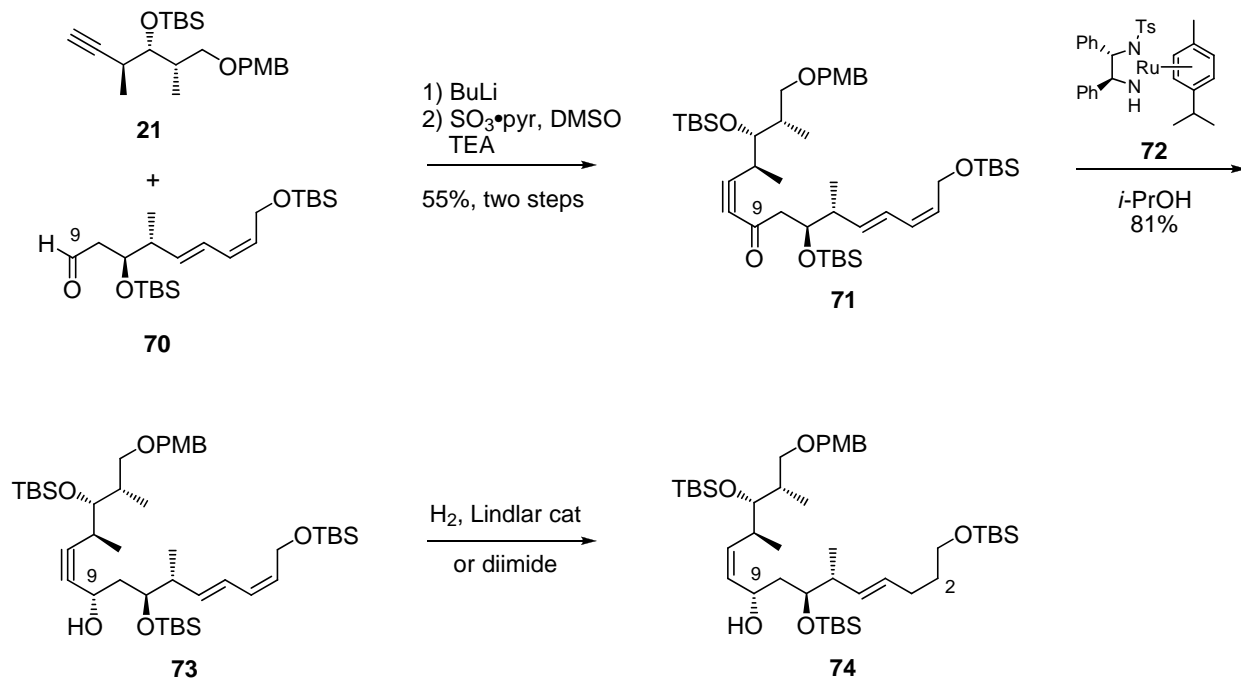


Figure 22. Attempted partial reduction reaction of the dienyl ether **73**

Next, the partial reduction of the C10–C11 alkyne of the dienyl ether **73** in the presence of the C2–C4 diene was attempted by using H₂ and Lindlar catalyst.⁴⁹ However, this saturated the C2–C3 alkene in addition to partial reduction of the C10–C11 alkyne to give the ether **74** (Figure 22). Likewise, treatment of the ether **73** with the diimide generated from *o*-nitrobenzenesulfonyl hydrazide (NBSH)⁵⁰ and Et₃N gave the same product, **74**. It was presumed that the C1–C5 dienyl ether of **73** is too electron-rich to be differentiated from the C10–C11 alkyne.

Thus, the reduction of the C10 alkyne possessing a C1–C5 dienoate was attempted because the dienoate is less electron-rich than the dienyl ester. To this end, the C9 ketone of the ynone **66** was reduced with the Noyori catalyst **72** to give the C9 alcohol, which was subjected to hydrogenation using Lindlar catalyst poisoned with quinoline, as well as diimide reduction. These reduction reactions gave the C4–C5 saturated ester **75** (Figure 23).

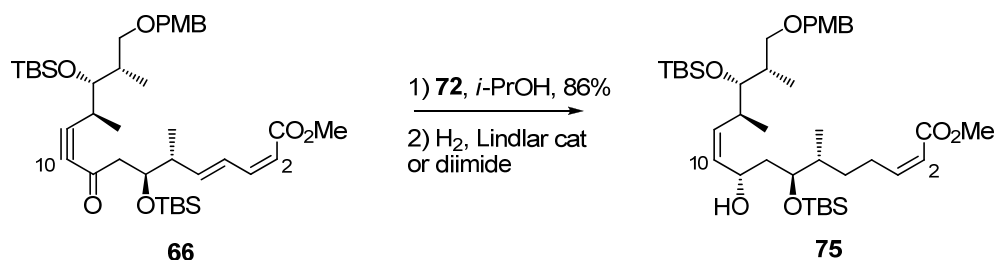


Figure 23. Attempted partial reduction reactions of the dienoate **66**

Overall, the hydrogenation or diimide reduction of the C10–C11 alkyne of the dienoate **66** or the dienyl ether **73** in the presence of the C2–C4 diene partially saturated the C2–C5 region as well as the C10 alkyne. It was concluded that the reactivity of the C10 alkyne and C2–C4 diene toward the reduction seems to be too similar to be differentiated from each other. Thus, the

coupling strategy was revised with a vinyl iodide **76**, which requires no reduction reaction of the C10–C11 bond.

2.7 REVISED COUPLING STRATEGY

In the revised strategy, it was decided to first couple the aldehyde **77** and the phosphonium salt **20** via a Wittig olefination, and then to add the lithium reagent derived from the vinyl iodide **76** to the aldehyde **70**, as shown in Figure 24. The Wittig olefination between the aldehyde **78** and the phosphonium salt **79** gave a 29% yield (previously done by Dr. Y. Shin, Figure 25).⁵¹ Thus, it was decided to first do the Wittig reaction with the relatively small fragments **20** and **77**.

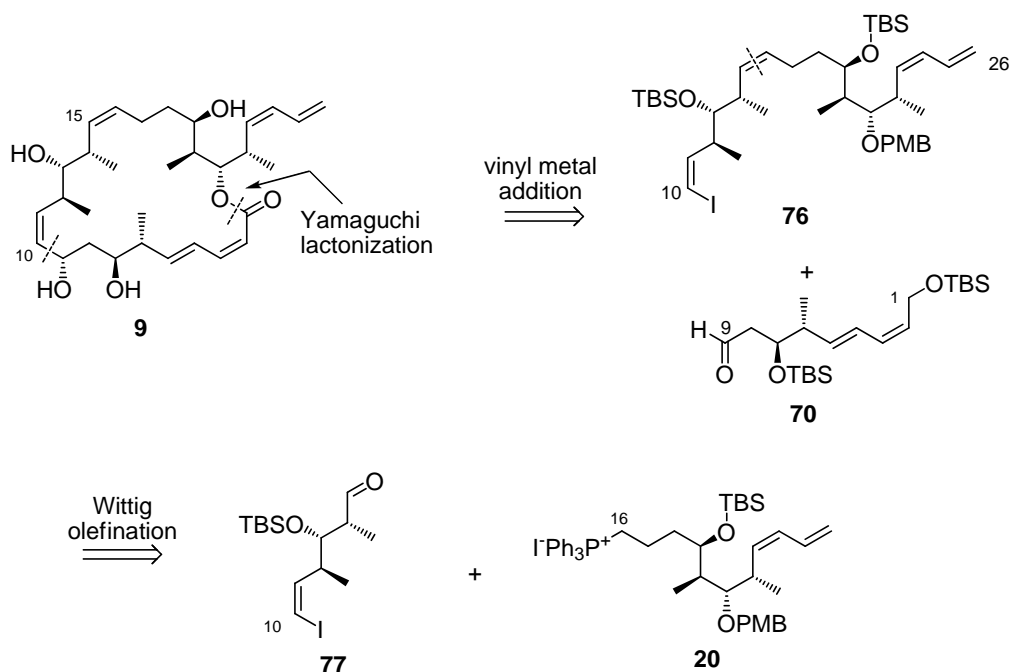


Figure 24. Revised retrosynthetic analysis for 16-normethyl-15,16-dehydrodictyostatin **9**

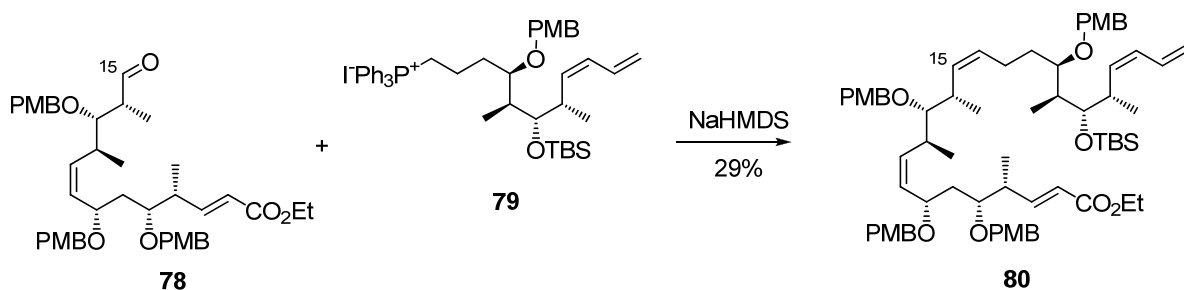


Figure 25. Wittig reaction of the aldehyde **78** and the phosphonium salt **79** done by Dr. Y. Shin

The conversion of the alkyne **21** to the vinyl iodide **77** is summarized in Figure 26. First, the alkyne **21** was deprotonated with BuLi and quenched with iodine to produce the iodoalkyne **81** in 99% yield. Diimide generated from *o*-nitrobenzenesulfonyl hydrazide (NBSH) and Et₃N smoothly reduced the iodoalkyne **81** to the *Z*-vinyl iodide **82** without overreduced products in 95% yield. Removal of the PMB group with DDQ followed by a Dess–Martin oxidation⁵² provided the aldehyde **77**, which was used for the Wittig reaction without purification.

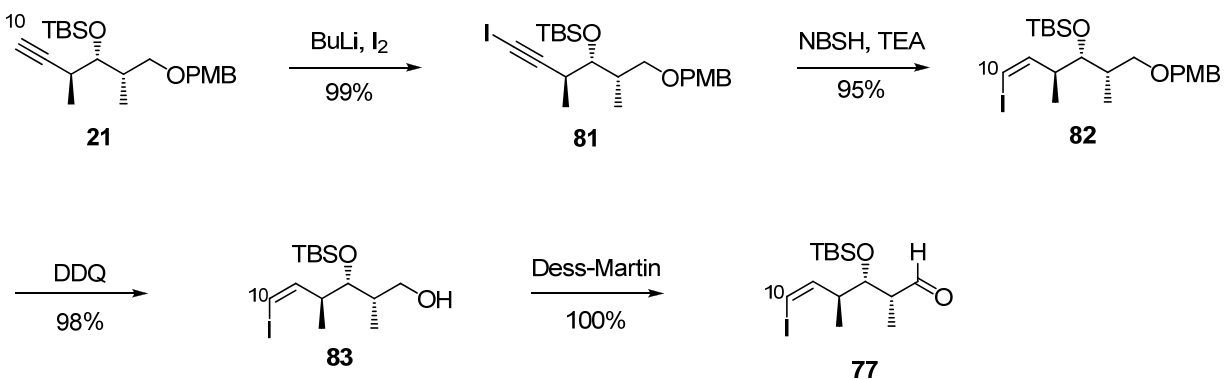


Figure 26. Synthesis of the C10–C15 fragment **77**

To construct the C10–C26 fragment **76** (Figure 27), the phosphonium salt **20** (0.64 g) that was dried azeotropically with benzene was deprotonated with NaHMDS to give a reddish

solution of the ylide, and then the aldehyde **77** (0.38 g) was added. This produced 0.47 g of the C10–C26 fragment **76** after silica gel chromatography in 82% yield. The C15 *Z*-geometry of the Wittig product **76** was confirmed by the coupling constant between H15 and H16 ($J = 10.7$ Hz) in the ^1H NMR spectrum. This reaction was repeated with 1.50 g of the phosphonium salt **20** and 0.90 g of the aldehyde **77** to give 1.05 g of the Wittig product **76** (72% yield).

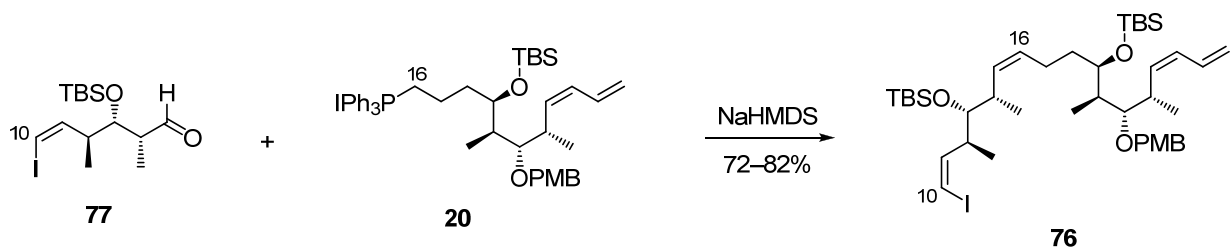


Figure 27. Coupling of the C10–C15 fragment **77** and the C16–C26 fragment **20**

Next, methods for the addition of the vinyl iodide **76** to the aldehyde **70** were studied. A Nozaki–Hiyama–Kishi reaction⁵³ of **76** and **70** using CrCl_2 and NiCl_2 gave two C9 epimers **84 α** and **84 β** in 32% yield. In contrast, lithium-halogen exchange with *tert*-BuLi gave a 60% yield in a test reaction. Thus, this method was used with the vinyl iodide **76** (0.76 g, 0.94 mmol) and the aldehyde **70** (0.37 g, 0.88 mmol) to give a mixture of two epimers **84 α** and **84 β** . They were separated by silica gel chromatography to provide the C9 α -epimer **84 α** (more polar, 0.26 g, 27% yield) and the C9 β -epimer **84 β** (0.42 g, 43% yield), as shown in Figure 28.

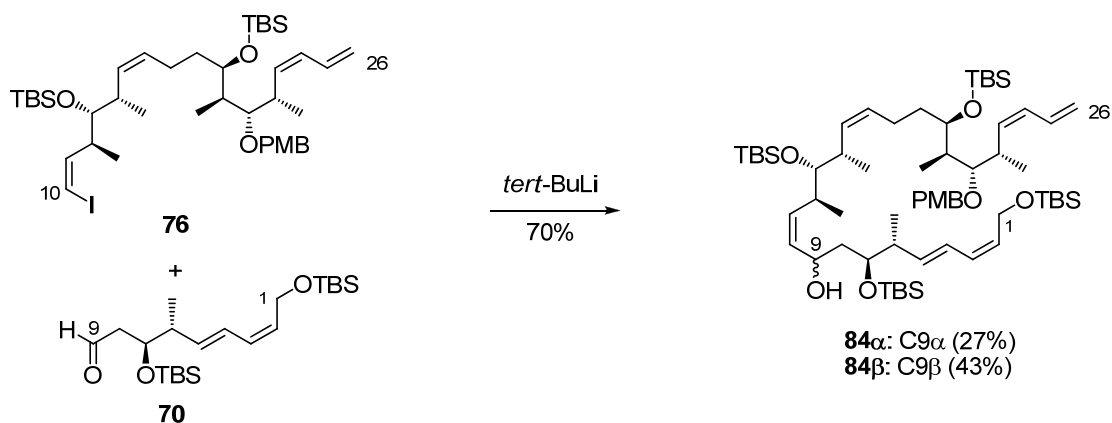


Figure 28. Coupling of the aldehyde **70** and the vinyl iodide **76**

The assignment of the C9 configurations of two C9 epimers (**84α** and **84β**) was based on ¹H NMR similarities between a *seco*-acid **85α** and analogous **86**, **87** and **88**. The *seco*-acid **86** is the intermediate for 16-normethyldictyostatin,^{24b} **87** for 16-*epi*-dictyostatin^{24d} and **88** for dictyostatin,^{22b} and they differ only in the C15–C16 region (Figure 29). The H9 signal of **85α** was at δ 4.48 ppm (dd, $J = 7.6, 12.4$ Hz). For **86**, **87** and **88**, dd's with similar chemical shifts and J -values were observed for the H9. In contrast, the H9 signal of a *seco*-acid **85β** of the C9 β -alcohol **84β** was a triplet ($J = 8.1$ Hz) at δ 4.41 ppm.

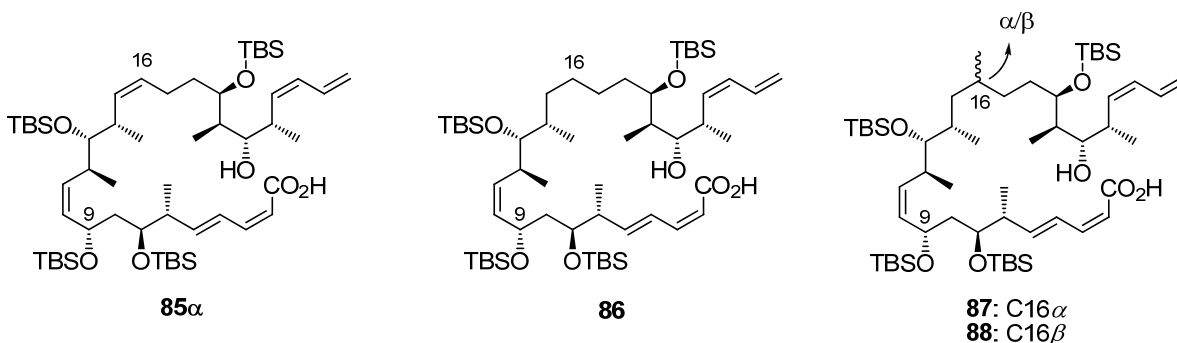


Figure 29. Structures of the *seco*-acids **85α**, **86**, **87** and **88**

2.8 COMPLETION OF THE SYNTHESIS

The completion of the synthesis of 16-normethyl-15,16-dehydrodictyostatin **9** is shown in Figure 30. The C9 hydroxyl group of the coupled product **84 α** was protected with TBSOTf, and then the C1 TBS group was removed with HF•pyr to provide the alcohol **89 α** in 85% yield over two steps. The alcohol **89 α** was oxidized with Dess–Martin periodinane to give the aldehyde, which was converted without purification into a carboxylic acid by using NaClO₂. Next, the C21 PMB group of the resulting acid was removed with DDQ to provide a *seco*-acid **85 α** after silica gel chromatography in 31% yield over three steps.

In turn, the *seco*-acid **85 α** was submitted to Yamaguchi conditions (2,4,6-trichlorobenzoyl chloride (TCBC), Et₃N, DMAP)⁵⁴ to give an inseparable mixture of the C2 *Z*-macrolactone and the C2 *E*-isomer **91** (less polar, 5% by ¹H-NMR analysis) in 71% yield. Finally, global deprotection of the TBS-protected macrolactones with HCl produced 16-normethyl-15,16-dehydrodictyostatin **9** in 42% yield and the more polar C2 *E*-isomer **92**⁵⁵ in 3% yield after silica gel chromatography. The C2 geometries of the macrolactones were confirmed by the coupling constants of the H2–H3 in the ¹H NMR spectra ($J = 11.5$ Hz for 16-normethyl-15,16-dehydrodictyostatin **9** and 15.3 Hz for the C2 *E*-isomer **92**).

Overall, 16-normethyl-15,16-dehydrodictyostatin **9** was synthesized from the (*S*)-Roche ester in total 44 steps and 25 steps (longest linear sequence) and in 0.013% overall yield.

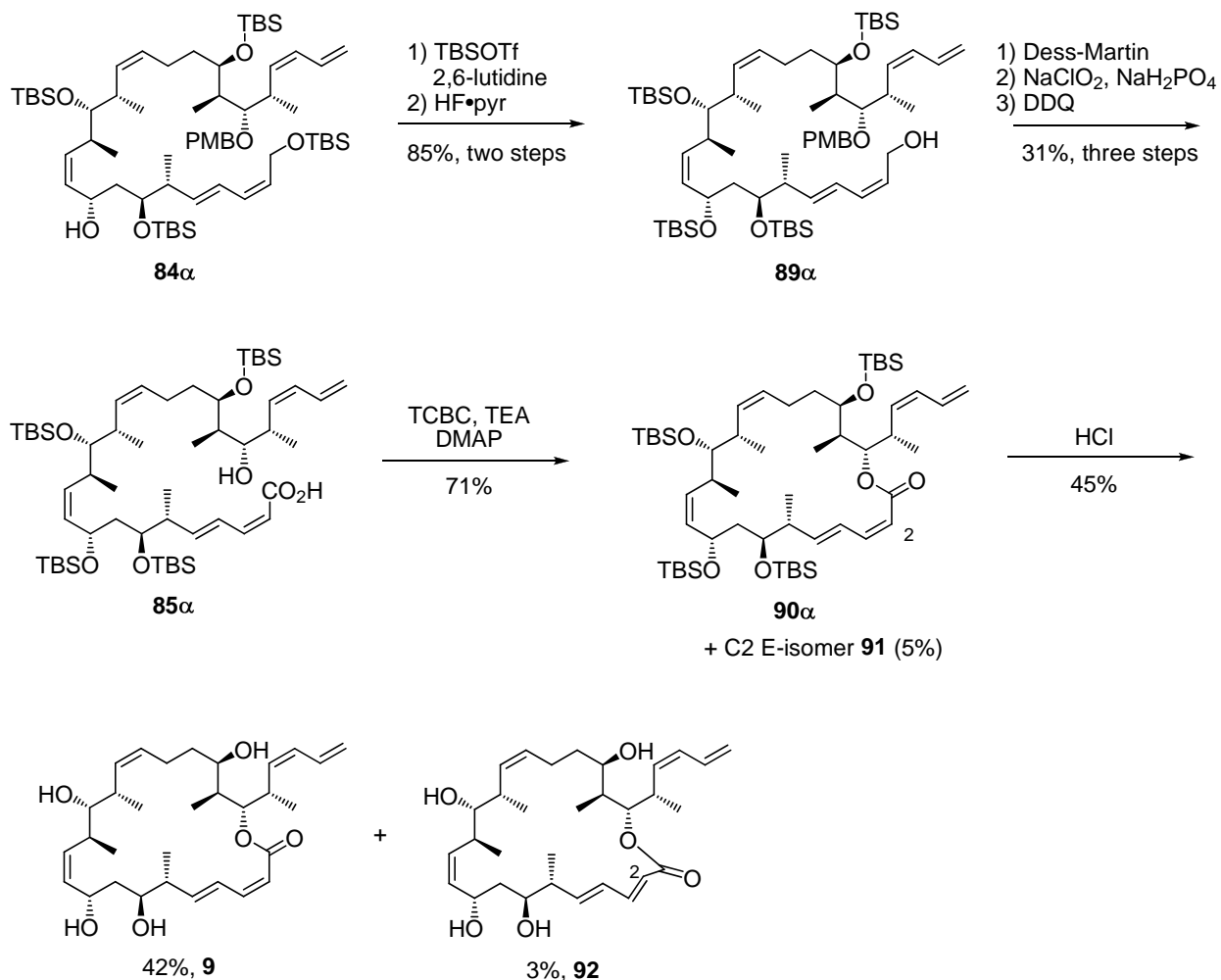


Figure 30. Completion of the synthesis of 16-normethyl-15,16-dehydrodictyostatin **9**

All proton resonances of 16-normethyl-15,16-dehydrodictyostatin **9** were assigned by ¹H and ¹H-¹H COSY spectroscopies and the carbon atoms were assigned by HMQC and HMBC NMR studies. The coupling constants measured ($J = 10.8$ Hz for H10–H11, 11.0 Hz for H15–H16) confirmed the *Z*-olefins at C10–C11 and C15–C16. In addition, the correlation between C1 and H21 in the HMBC spectrum (boxed in Figure 31) confirmed the connectivity of the C1 carbonyl to the C21 hydroxy group.

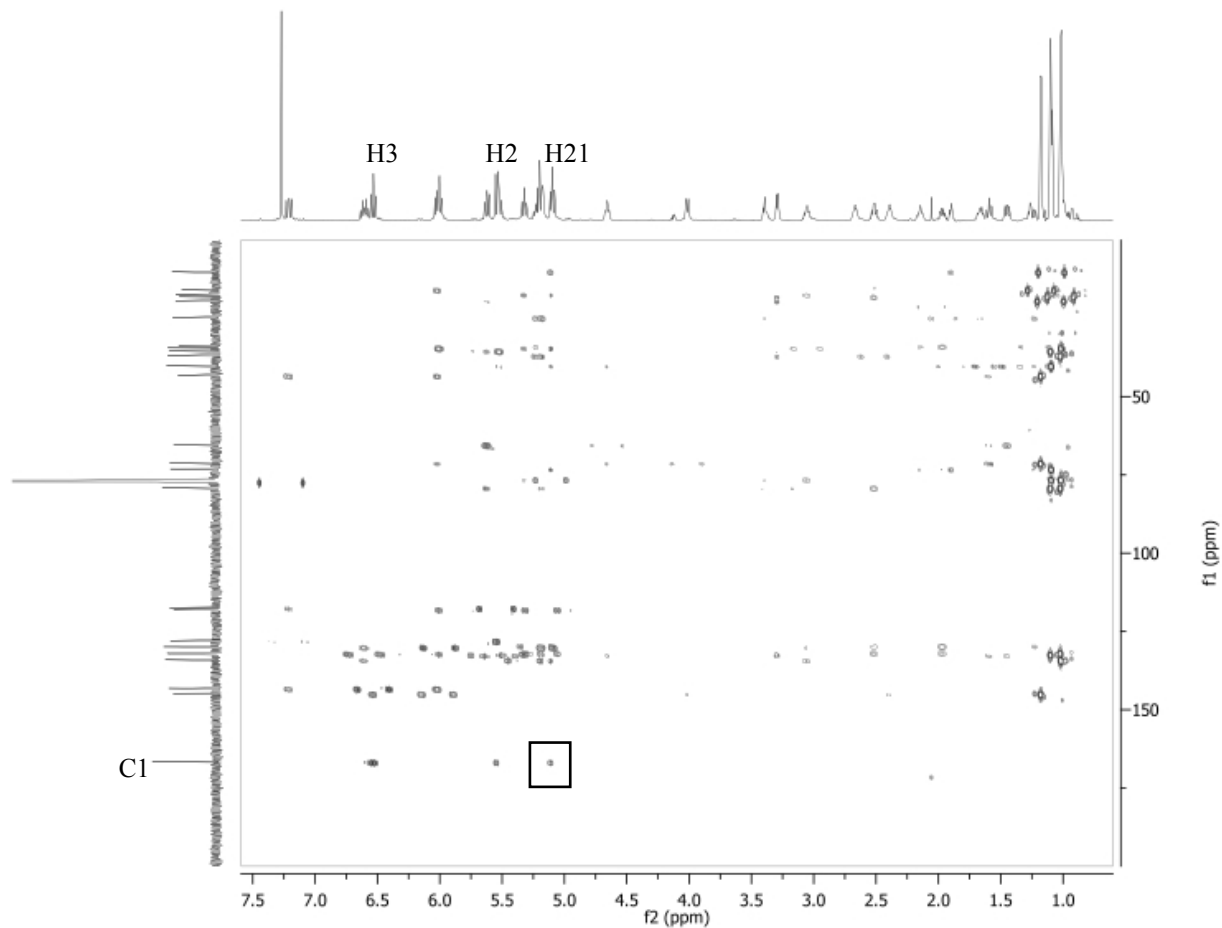


Figure 31. HMBC spectrum of 16-normethyl-15,16-dehydrodictyostatin **9**

2.9 SYNTHESIS OF THE 9-EPIMER

The synthesis of *9-epi*-16-normethyl-15,16-dehydrodictyostatin **94** was achieved by following the same seven-step sequence starting from the C9 β -epimer **84 β** , as summarized in Figure 32. The TBS-protection of the C9 hydroxy group of the alcohol **84 β** and the removal of the C1 TBS group provided a primary alcohol **89 β** in 60% yield over two steps. The alcohol **89 β**

was converted into the corresponding carboxylic acid via two successive oxidations. The C21 PMB group of the carboxylic acid was then removed to provide a *seco*-acid **85 β** in 47% yield over three steps.

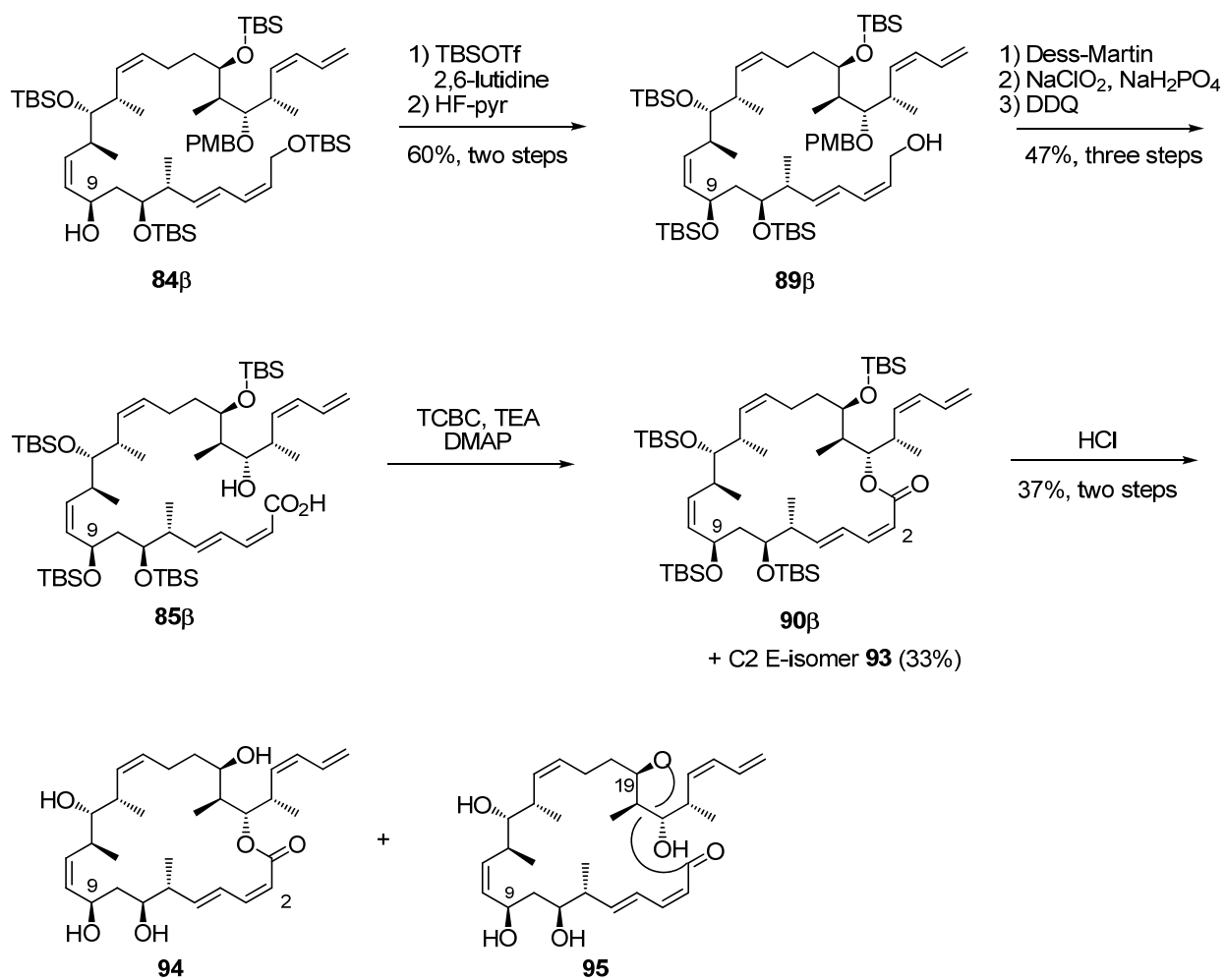


Figure 32. Completion of the synthesis of 9-*epi*-16-normethyl-15,16-dehydrodictyostatin **94**

Next, the *seco*-acid **85 β** was cyclized to the macrolactone **90 β** under Yamaguchi conditions, which contained an inseparable C2 *E*-isomer **93** (1:2 *E/Z* ratio). The global deprotection of the TBS-protected macrolactones produced 9-*epi*-16-normethyl-15,16-

dehydrodictyostatin **94** and a C19 lactone **95** in 37% yield over two steps, as well as the impure C2 *E*-isomer (5%). The structure of the C19 lactone **95** was determined by observing the three-bond coupling between H19 (δ 5.07 ppm) and C1 (δ 166.3 ppm) in the HMBC spectrum.⁵⁶

2.10 BIOLOGICAL EVALUATION

16-Normethyl-15,16-dehydrodictyostatin **9**, its C2*E*-isomer **92**, its C9-epimer **94** and the C19 lactone **95** were tested for cellular and biochemical activity in comparison to paclitaxel **1**, dictyostatin **5** and 16-normethyldictyostatin **11** by the groups of Day and Vogt.^{24d,57}

The minimum detectable effective concentrations (MDECs) for the chemicals to cause increases in cellular tubulin polymer mass in HeLa cells are given in Table 2.^{24d} 16-Normethyl-15,16-dehydro-dictyostatin **9** caused tubulin polymer increase at a low nanomolar concentration, which was comparable to paclitaxel **1**, dictyostatin **5** and 16-normethyldictyostatin **11**. The C2*E*-isomer **92** was less active, and the C9-epimer **94** and the C19 lactone **95** were not potent.

The 50% growth inhibitory concentrations (GI₅₀s) were determined against human ovarian carcinoma 1A9, 1A9/Ptx10 and 1A9/Ptx22 cells (Table 2).^{24d} The 1A9/Ptx10 and 1A9/Ptx22 cells are mutant β -tubulin-expressing, paclitaxel resistant clones of the 1A9 cells (Phe270 \rightarrow Val and Ala364 \rightarrow Thr, respectively). The GI₅₀ of 16-normethyl-15,16-dehydrodictyostatin **9** against 1A9 cells was 10- to 20-fold less than dictyostatin **5** and 16-normethyldictyostatin **11**. For 1A9/Ptx10 cells, 16-normethyl-15,16-dehydrodictyostatin **9** was comparable to 16-normethyldictyostatin **11**, but 300-fold less active than dictyostatin **5**. For 1A9/Ptx22 cells, 16-normethyl-15,16-dehydrodictyostatin **9** was 10- to 50-fold less potent than

dictyostatin **5** and 16-normethyl dictyostatin **11**. The large cross resistance of 1A9/Ptx10 cells (as compared to the parental 1A9 cells) toward 16-normethyl analogs **9** and **11**, indicates that the C-16 region of **9** and **11** interacts with or is positioned near the Phe270 region of the binding pocket of β -tubulin.

Table 2. Biological activities of **9**, **92**, **94** and **95**

Test agent	Cellular			In vitro		
	MDEC ^a for tubulin polymer increase, nM \pm SD (<i>N</i>)	GI ₅₀ ^b nM (<i>N</i> = 4)			% tubulin polymerized by 10 μ M test agent relative to 10 μ M paclitaxel ^c	% inhibition of binding of [³ H]paclitax- el to tubulin polymer ^d (<i>N</i> \geq 3)
		1A9	1A9/Ptx10	1A9/Ptx22		
9	11 \pm 2 (3)	8.3 \pm 0.8	942 \pm 250	62 \pm 5	107	38 \pm 9 (3)
92 (2 <i>E</i>)	674 \pm 106 (4)	210 \pm 110	23680 \pm 1090	847 \pm 140	10	5 \pm 2 (3)
94 (9- <i>epi</i>)	>5000 (1)	4260 \pm 400	19300 \pm 530	4600 \pm 500	1	11 \pm 1 (3)
95 (19-lactone)	>5000 (1)	>50000	32700 \pm 510	>50000	6	7 \pm 2
11 (16-normethyl)	25 \pm 9 (3)	0.41 \pm 0.52	470 \pm 70	5.6 \pm 4.7	91	48 \pm 3 (3)
5 (dictyostatin)	5.4 \pm 1.9 (4)	0.69 \pm 0.80	3.2 \pm 2.4	1.3 \pm 1.0	157	75 \pm 5 (6)
1 (paclitaxel)	5.2 \pm 0.4 (4)	0.71 \pm 0.11	64 \pm 8	51 \pm 9	100	

^a Minimum detectable effective concentration of the test agent in HeLa cells after 21 h of continuous exposure.

^b Fifty percent growth inhibitory concentration after 72 h of continuous exposure to the test agent.

^c Bovine brain tubulin (10 μ M) in 0.2 M monosodium glutamate was treated at 0 $^{\circ}$ C with the test agent (predissolved in DMSO). The mixture was transferred to a cuvette in a 6-channel, temperature-controlled spectrophotometer, and the temperature was rapidly raised to 30 $^{\circ}$ C. Tubulin assembly was monitored by turbidity development at 350 nm, and the percent assembly reported is relative to that caused by 10 μ M paclitaxel, analyzed in the same experiment in one of the six cuvettes, after 20 min at 30 $^{\circ}$ C.

^d Percent competition at 37 $^{\circ}$ C by 4 μ M test agent with 2 μ M [³H]paclitaxel for binding to microtubules formed from 2 μ M bovine brain tubulin and 20 μ M dideoxyGTP.

The potencies of inducing polymer assembly of isolated bovine brain tubulin were evaluated (Table 2).^{24d} 16-Normethyl-15,16-dehydrodictyostatin **9** was equipotent with paclitaxel **1** and 16-normethyldictyostatin **11**. In addition, 16-normethyl-15,16-dehydrodictyostatin **9** effectively competed with [³H]-paclitaxel for binding to tubulin polymer, but the potency was half of that of dictyostatin **5**.

Table 3. Potencies of **9**, **92**, **94** and **95** on HeLa cells

Compound	EC ₅₀ (nM) ^a		MDEC (nM) ^{a,b}	
	Cell density	Nuclear condensation	Mitotic index ^c	Microtubule Mass
9	23.9 ± 15.5	12.6 ± 5.2	9.3 ± 0.2	8 ± 9 (3)
92 (2 <i>E</i>)	896 ± 135	738 ± 214	520 ± 95	649 ± 2 (3)
94 (9- <i>epi</i>)	>5000	>5000	>5000	>5000
95 (19-lactone)	>5000	>5000	>5000	>5000
11 (16- normethyl)	37.4 ± 6.2	23.7 ± 8.8	24.1 ± 5.4	25.0 ± 9.0
5 (dictyostatin)	9.2 ± 6.6	3.9 ± 1.0	5.8 ± 1.5	5.4 ± 1.9
1 (paclitaxel)	10.4 ± 1.9	3.9 ± 2.0	3.5 ± 1.2	5.2 ± 0.4

^aAverage of at three independent experiments ± S.D.

^bMinimal detectable effective concentration.

^cPercentage of phosphohistone H3 positive cells.

The cellular effects of 16-normethyl-15,16-dehydrodictyostatin **9**, its C2*E*-isomer **92**, its C9-epimer **94** and the C19 lactone **95** are shown in Table 3.⁵⁷ The EC₅₀s were measured for cell density (cytotoxicity) and nuclear condensation. In addition, the effects on histone H3 phosphorylation (mitotic index), and changes in microtubule morphology (microtubule mass)

were evaluated. The overall cellular effects of 16-normethyl-15,16-dehydrodictyostatin **9** were slightly better than 16-normethyl-15,16-dehydrodictyostatin **11**, but 2- to 3-fold worse than paclitaxel **1** and dictyostatin **5**.

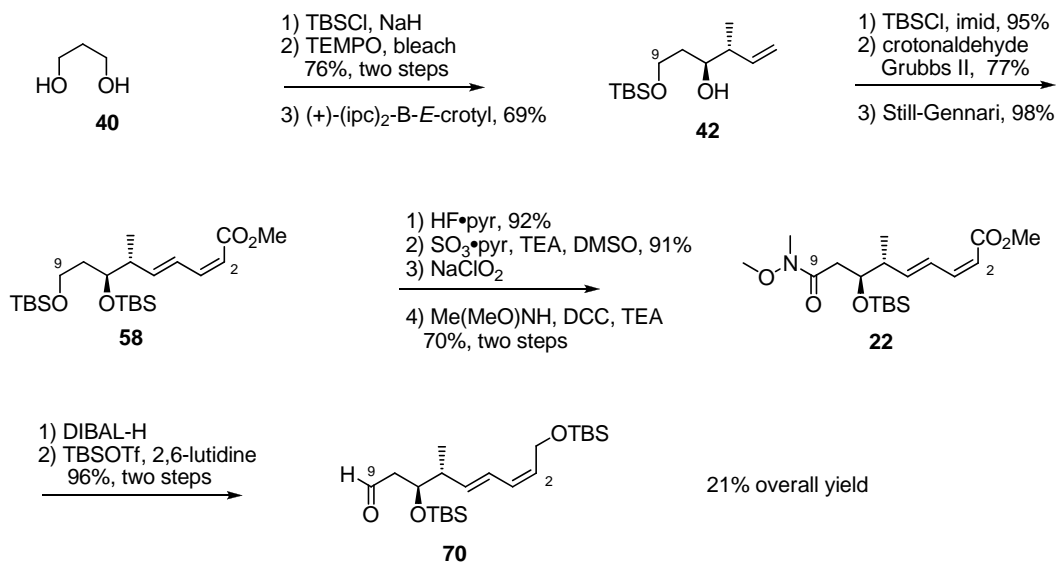
2.11 SUMMARY AND CONCLUSIONS

16-Normethyl-15,16-dehydrodictyostatin, a hybrid of dictyostatin/discodermolide, was designed and synthesized along with three related analogs. Synthesis of 16-normethyl-15,16-dehydrodictyostatin was achieved in a convergent manner from three main fragments, each of which has a full carbon skeleton. Fragments were coupled via a Wittig olefination and a vinylolithium addition to an aldehyde. This addition reaction gave two C9-epimers (1.6:1, β/α) favoring the undesired C9 β -epimer. Thus, improved selectivity of the addition reaction is still needed. Otherwise, the development of methods for converting the C9 α -isomer into the β -isomer is needed. This synthesis proceeded in total 44 steps and 25 steps (longest linear sequence) from the (*S*)-Roche ester and in 0.013% overall yield (Scheme 1).

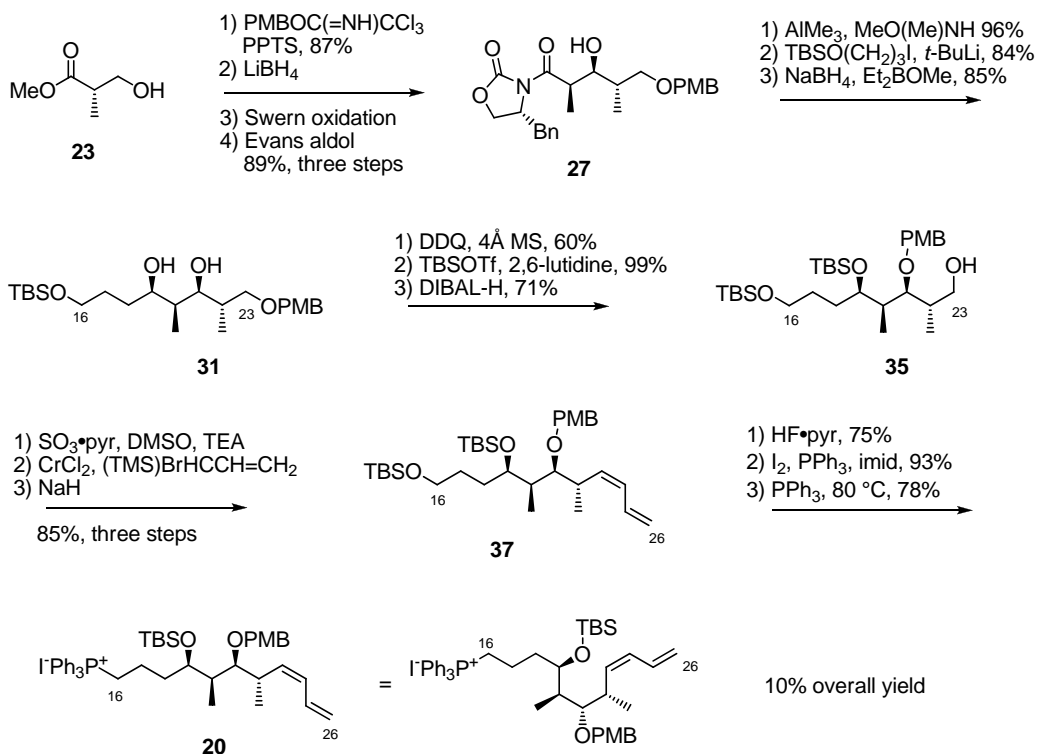
16-Normethyl-15,16-dehydrodictyostatin, C2*E*-isomer, C9-epimer and the C19 lactone were evaluated for anticancer activity. 16-Normethyl-15,16-dehydrodictyostatin was, overall, equipotent with 16-normethyl-15,16-dehydrodictyostatin, but 2- to 10-fold less active toward several cancer cell lines than dictyostatin. To date, 16-normethyl-15,16-dehydro-dictyostatin is one of the most potent hybrids of dictyostatin/discodermolide.

Scheme 1. Summary of the synthesis of 16-normethyl-15,16-dehydrodictyostatin **9**

Synthesis of the C1-C9 fragment

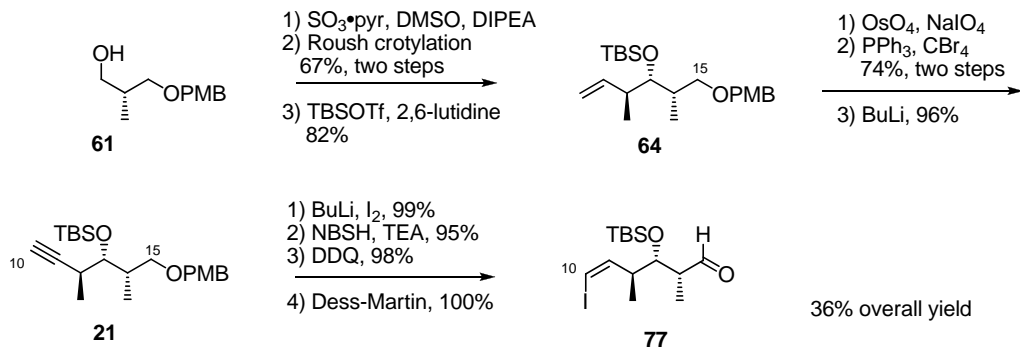


Synthesis of the C16-C26 fragment

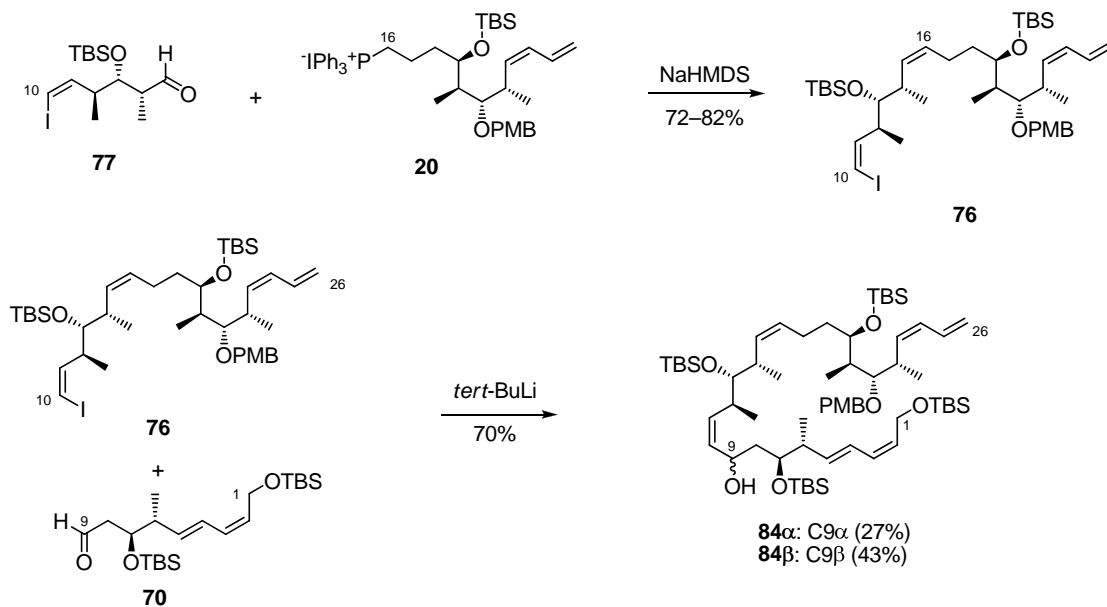


Scheme 1. Summary of the synthesis of 16-normethyl-15,16-dehydrodictyostatin **9** (*continued*)

Synthesis of the C10-C15 fragment

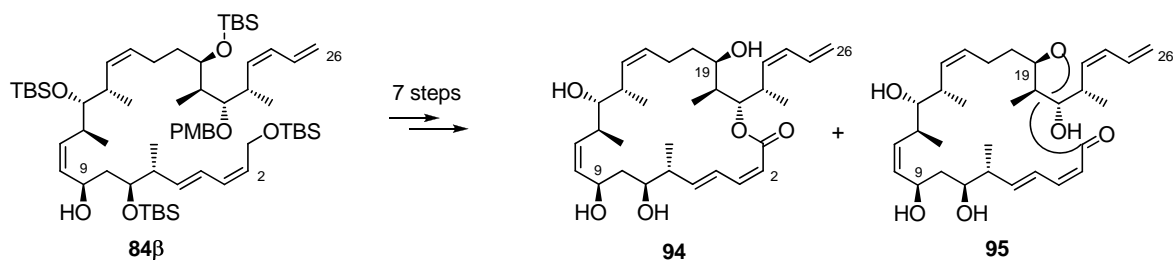
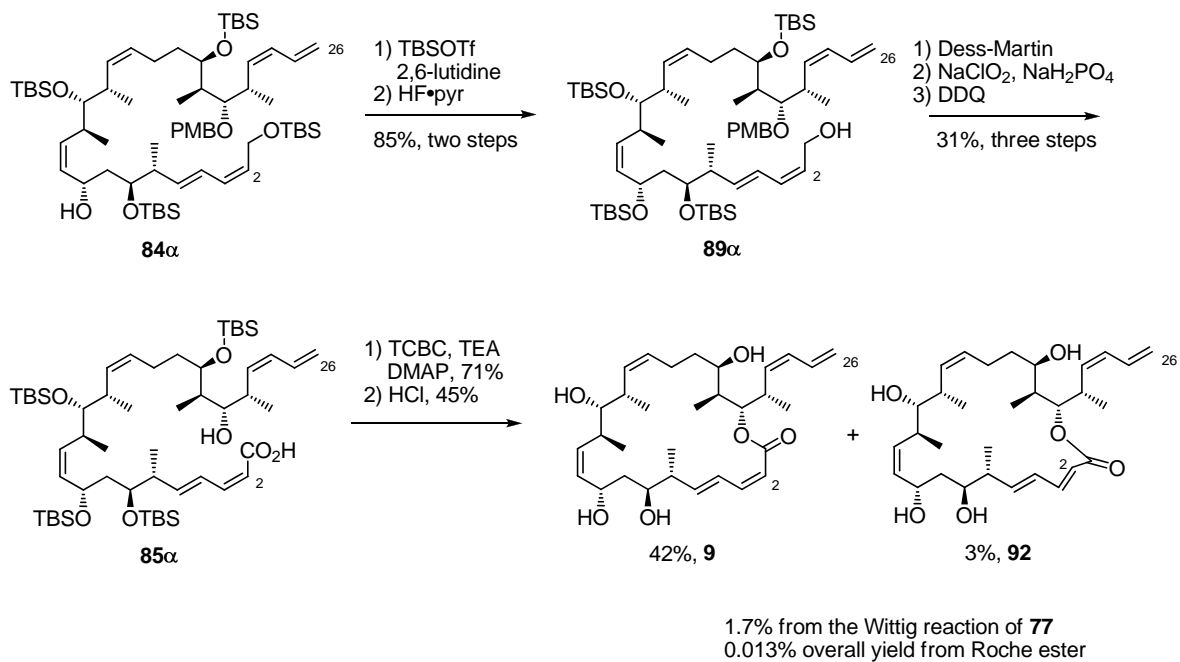


Fragment couplings



Scheme 1. Summary of the synthesis of 16-normethyl-15,16-dehydrodictyostatin **9** (*continued*)

Completion of the synthesis



3.0 IMPROVED SYNTHESIS OF 6-*EPI*-DICTYOSTATIN

3.1 FIRST SYNTHESIS OF 6-*EPI*-DICTYOSTATIN

In the course of studying the structure-activity relationship of dictyostatin through the total synthesis of analogs, dictyostatin **5** and three 6,7-epimers (*6-epi* **101**, *7-epi* **102**, *6,7-bis-epi* **103**)^{24c} were prepared via a fluorous mixture synthesis (FMS)⁵⁸ by the Curran group. As summarized in Figure 34, four 6,7-isomers coded with fluorous silyl groups were synthesized separately and mixed to give a mixture **96**. Lithium acetylide generated from the alkyne **97** was added to the Weinreb amide **96** to give an ynone (not shown). Next, carrying out the 5-step sequence used for synthesis of dictyostatin **5** provided the C3–C17 fragment **98**. In turn, the C3–C17 aldehyde **98** was coupled with the C18–C26 phosphonate **99** via a Horner–Wadsworth–Emmons (HWE) reaction to give the enone **100**. Carrying out 10 steps further and demixing provided dictyostatin **5** and three 6,7-epimers (**101**, **102**, **103**).

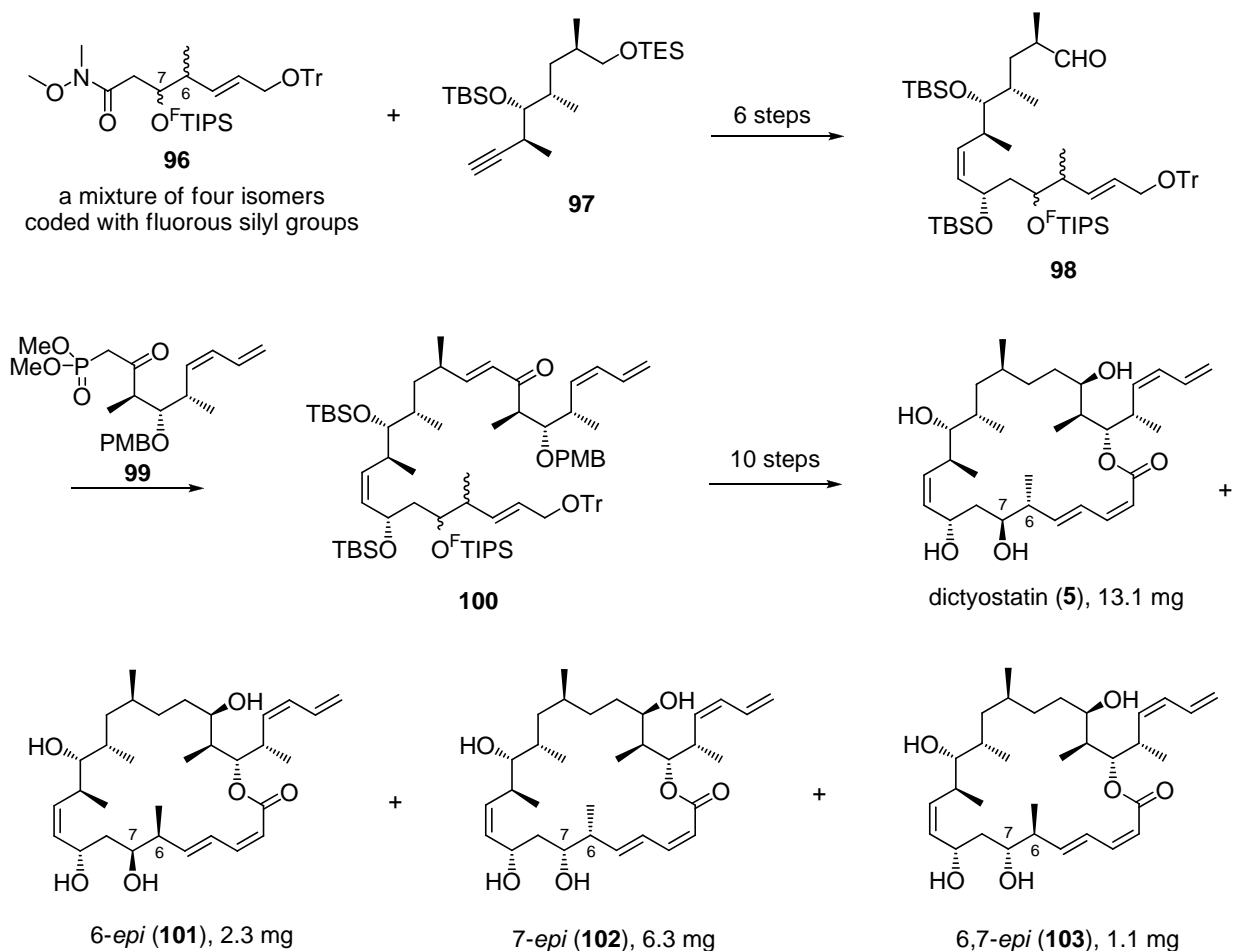


Figure 33. Summary of the FMS of dictyostatin and three 6,7-epimers

Preliminary antiproliferative assays^{24c} against human ovarian carcinoma 1A9/Ptx22 cells showed that *6-epi*-dictyostatin **101** was 4-fold more potent than dictyostatin **5** ($GI_{50} = 0.81$ and 3.4 nM, respectively), as shown in Table 4. The fact that *6-epi*-dictyostatin **101** showed the high potency and dictyostatin will be off patent before if it could be commercialized, led us to further evaluate biological activity of *6-epi*-dictyostatin for the treatment of cancer. This required the preparation of a large quantity of the material. The large-scale synthesis of *6-epi*-dictyostatin,

aimed at increasing the convergency of the original synthesis of 6-*epi*-dictyostatin **101** and developing practical methods for a large-scale synthesis, was therefore pursued.

Table 4. Biological activities of **5**, **101**, **102** and **103**^{24c,57}

Compound	GI ₅₀ ± S.D. (nM) ^a	EC ₅₀ ± S.D. (nM) ^b
	1A9/Ptx22	Cell density
Dictyostatin (5)	3.4 ± 0.7	9.2 ± 6.6
6- <i>epi</i> (101)	0.81 ± 0.17	8.9 ± 2.7
7- <i>epi</i> (102)	4.7 ± 0.6	17.5 ± 1.9
6,7- <i>epi</i> (103)	123 ± 25	ND
Paclitaxel (1)	5.2 ± 0.4	10.4 ± 1.9

^aFifty percent growth inhibitory concentration after 72 h of continuous exposure of human ovarian cancer cells to the test agent. ^bAverage of at three independent experiments on human cervical cancer HeLa cells.

3.2 ATTEMPTED SYNTHESIS OF 6-EPI-DICTYOSTATIN

3.2.1 Background

In the course of synthesizing dictyostatin analogs, the Curran group had at this point developed four synthetic strategies for constructing the C9–C11 region as summarized in Figure 35. The first-generation approach, introduced in the synthesis of 6,16-*bis-epi*-dictyostatin,^{24e} used the Wittig olefination between the phosphonium salt **104** and the aldehyde **105** possessing the C9 β -hydroxy group to provide the C10–C11 *Z*-olefin ((a) in Figure 34). The second-

generation approach developed for the synthesis of dictyostatin included the three-step sequence of alkynyllithium addition, Noyori reduction, and Lindlar reduction ((b) in Figure 34).^{22b}

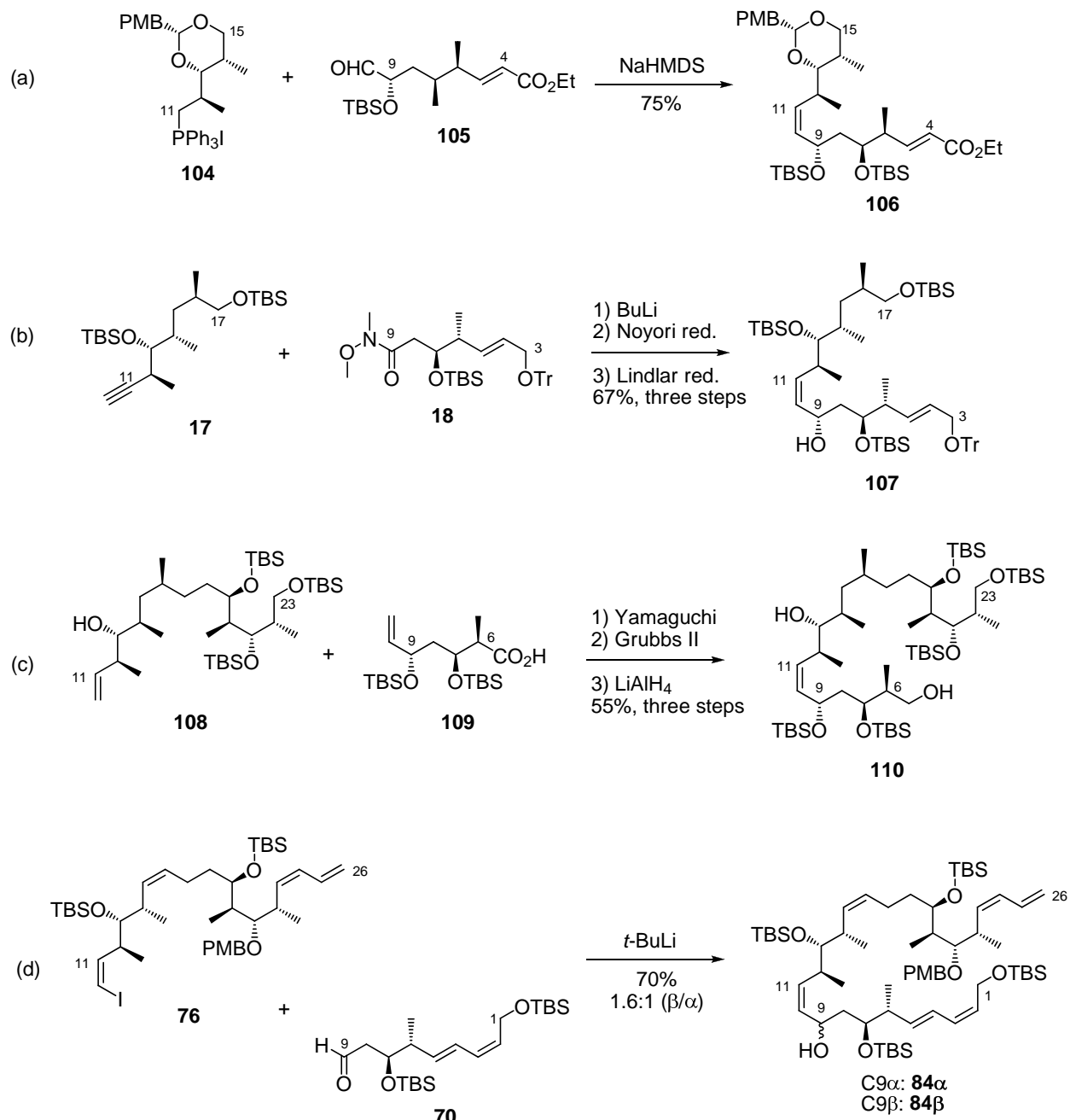


Figure 34. Fragment coupling strategies for dictyostatin analogs by the Curran group. (a) Wittig reaction; (b) alkynyllithium addition; (c) RCM; (d) vinyl lithium addition

The third attempt toward forming the C10–C11 *Z*-olefin utilized the RCM reaction of the ester derived from the alcohol **108** and the carboxylic acid **109**, followed by LiAlH₄ reduction to give the C5–C23 fragment **110** possessing the C10 *Z*-alkene ((c) in Figure 34).⁵⁹ All of the above-mentioned methods had truncated bottom fragments (the C1–C2 for the aldehyde **105** and the Weinreb amide **18** or the C1–C4 for the alkene **109** were absent).

In the fourth-generation strategy used for the synthesis of 16-normethyl-15,16-dehydrodictyostatin **9**, the bottom fragment **70** possessed the full carbon skeleton. This strategy used the addition reaction of the lithium reagent derived from the vinyl iodide **76** to the aldehyde **70**, which directly generated the C9 β -hydroxy group of the coupled product **84 α** ((d) in Figure 34).^{24d}

3.2.2 The initial synthetic plan for a large-scale synthesis of 6-*epi*-dictyostatin

To synthesize 6-*epi*-dictyostatin on a large scale, it was decided to use the strategy of a vinylolithium addition to an aldehyde to maximize the synthetic convergency (Figure 35). To this end, the macrolactone **101** was divided into three fragments of roughly equal complexity. The disconnection across the C9–C10 bond leads to the C10–C26 vinyl iodide **111** and the C1–C9 aldehyde **112**. Further disconnection of **111** across the C17–C18 bond by a HWE olefination reaction reveals the aldehyde **113** and the phosphonate **99**, the C18–C26 fragment in the initial FMS.^{24c}

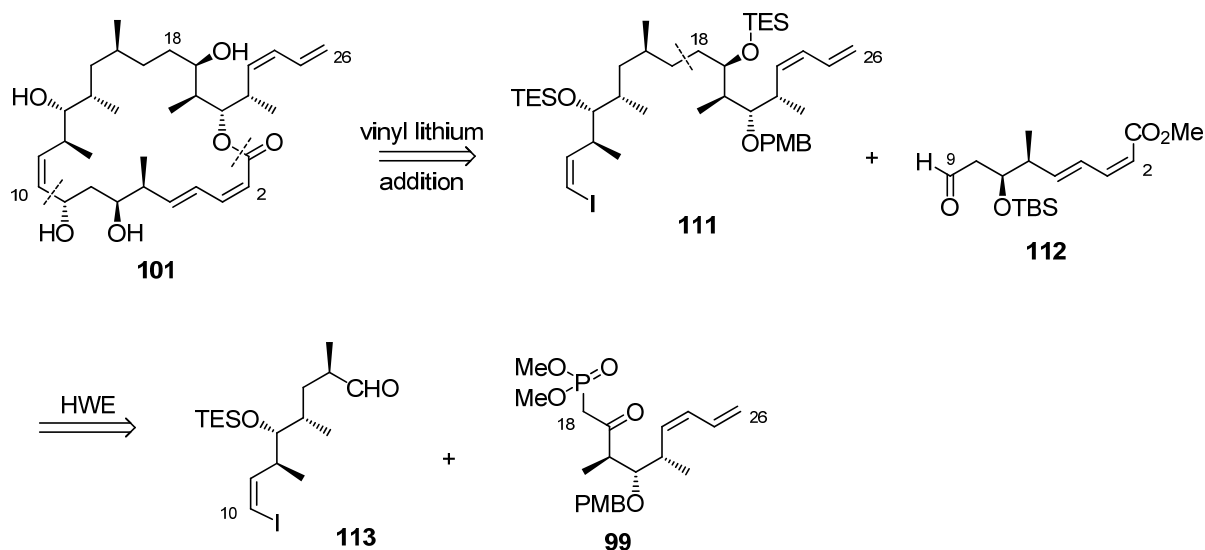


Figure 35. Initial plan for a large-scale synthesis of 6-*epi*-dictyostatin

3.2.3 Attempted large-scale synthesis of 6-*epi*-dictyostatin

The new approach needed the C10–C17 fragment **113** possessing both vinyl iodide and aldehyde functional groups. Its synthesis started with the known intermediate **114** used for the synthesis of dictyostatin.^{22b} As shown in Figure 36, the TBS ether **114** was deprotected with HCl to give a diol, which was protected as a TES ether **115** (86% yield, two steps). Removal of the PMB group of the ether **115** with DDQ gave the alcohol **116** (90% yield), which was oxidized with $\text{SO}_3 \cdot \text{pyr}$, DMSO and Et_3N to provide the aldehyde **117** (80% yield). Next, the aldehyde **117** was submitted to Wittig olefination conditions (ICH_3PPh_3 , I_2 , BuLi and NaHMDS)⁶⁰ to give the *Z*-vinyl iodide, which was used for the next reaction without further purification. The crude vinyl iodide was treated with dichloroacetic acid to give a primary alcohol **118** (48% yield, two steps). The C10 *Z*-geometry of **118** was confirmed by the coupling constant between H10 and H11 ($J = 7.5$ Hz) in the ^1H NMR spectrum. The alcohol **118** was then oxidized under Parikh–Doering

conditions to provide the C10–C17 aldehyde **113** (70% yield). Overall, 6 g of the C10–C17 fragment **113** was synthesized from the known intermediate **114** in 7 steps and 21% overall yield.

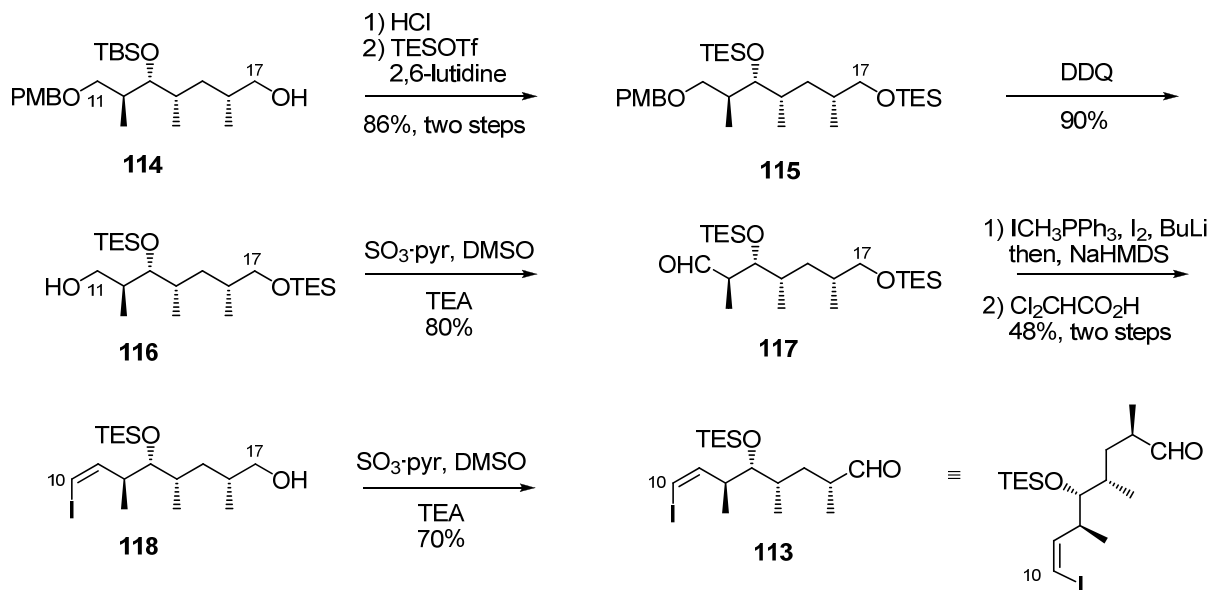


Figure 36. Synthesis of the C10–C17 fragment **113**

Next, the C18–C26 phosphonate **99**⁶¹ (synthesized by Dr. C. Harrison) was coupled with the C10–C17 aldehyde **113**. By following the procedure used for dictyostatin **5**, the phosphonate **99** was deprotonated with Ba(OH)₂, and then the aldehyde was added (Figure 37). The reaction mixture was stirred at room temperature for 18 h. This produced the enone **119** after silica gel chromatography (11.9 g, 88% yield). The C17 *E*-geometry of **119** was confirmed by the coupling constant of the H17–H18 ($J = 15.7$ Hz) in the ¹H NMR spectrum. The C17 *Z*-isomer of the enone **119** was not observed in the spectrum.

The C17–C18 alkene of the enone **119** was then saturated with a Stryker reagent ([Ph₃PCuH]₆, red powder)⁶² to give the ketone **120** (9.1 g, 77% yield). The ketone **120** was

reduced with $\text{LiAlH}(\text{O}t\text{-Bu})_3$ to give two C19 epimers in a 3.5:1 ratio favoring the C19 β -epimer. The less polar C19 β -epimer was separated by silica gel chromatography to give the alcohol **121** (6.0 g, 70%). The C19 configuration of **121** was assigned by analogy to the 6,7-epimers of dictyostatin.^{24c} Next, the alcohol **121** was protected with TESOTf to give the TES ether **111** (6.9 g, 99%).

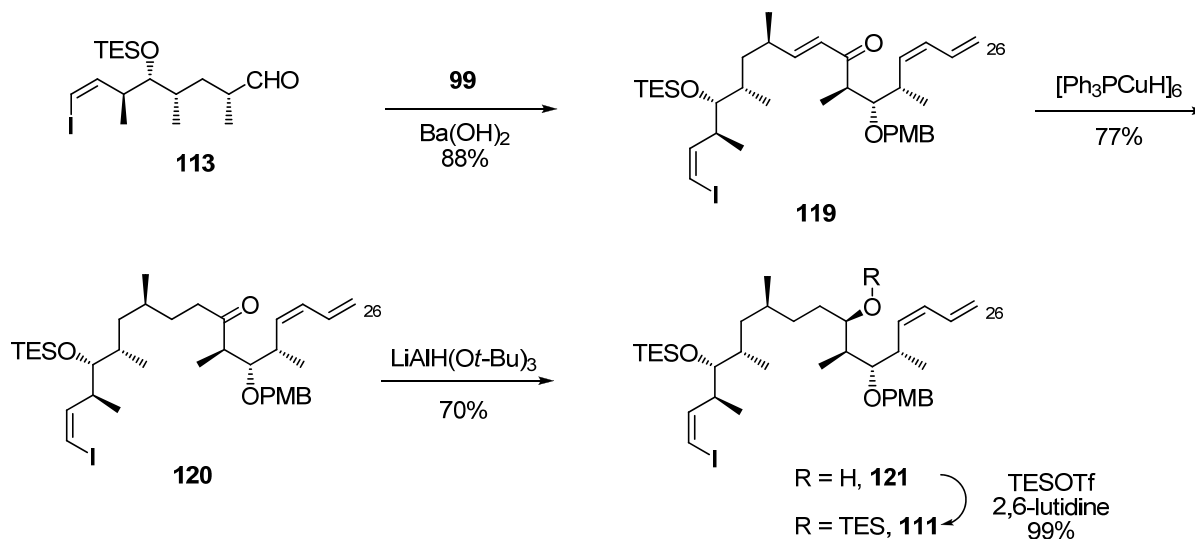


Figure 37. Synthesis of the C10–C26 vinyl iodide **111**

The addition of the lithium reagent derived from the vinyl iodide **76** to the aldehyde **70** was previously used for the synthesis of 16-normethyl-15,16-dehydrodictyostatin **9** (Figure 28). This gave two C9 epimers of **84 α** (desired) and **84 β** in a 1:1.6 ratio favoring **84 β** . Likewise, the initial test reaction with the vinyl iodide **111** and the aldehyde **112** (synthesized by Dr. G. Moura-Letts) gave two C9 epimers of **122 α** (desired) and **122 β** in a 1:1.9 ratio favoring **122 β** (Figure 38). The ratio was determined by chiral HPLC analysis.

The asymmetric addition of a vinylzinc reagent to the aldehyde **112** was tried with (+)- or (-)-methylephedrine (Oppolzer reaction).⁶³ The vinyl iodide **111** was treated with *tert*-BuLi, and then a solution of zinc reagents (ZnBr₂, ZnCl₂ or ZnEt₂) and (+) or (-)-methylephedrine were added. However, the use of zinc reagents and methylephedrines gave the unreacted aldehyde and the C10 deiodinated alkene of the vinyl iodide **111**.

Chiral additives were added to the vinyl lithium reagent to increase the formation of the desired epimer **122α** (Figure 38 and Table 5). Use of (+)- or (-)-methylephedrine as an additive did not improve ratio (1.7:1, favoring **122β**). In contrast, addition of (-)-sparteine (1.3 equiv) gave a 1.2:1 ratio (β/α). More (-)-sparteine (3.6 equiv) was not helpful (1.7:1 ratio (β/α)). Then, the reaction was scaled up with 1 g of the vinyl iodide **111** and (-)-sparteine (1.3 equiv) to give two C9-epimers **122α** (0.32 g, 26% yield) and **122β** (0.32 g). This reaction was repeated with 4.9 g of the vinyl iodide **111**, which gave **122α** (0.45 g, 8% yield) and **122β** (0.70 g, 12% yield). It seemed that the reactive vinyl lithium reagent derived from **111** decomposed over the long time period required for *tert*-BuLi addition in the reaction of large scale.

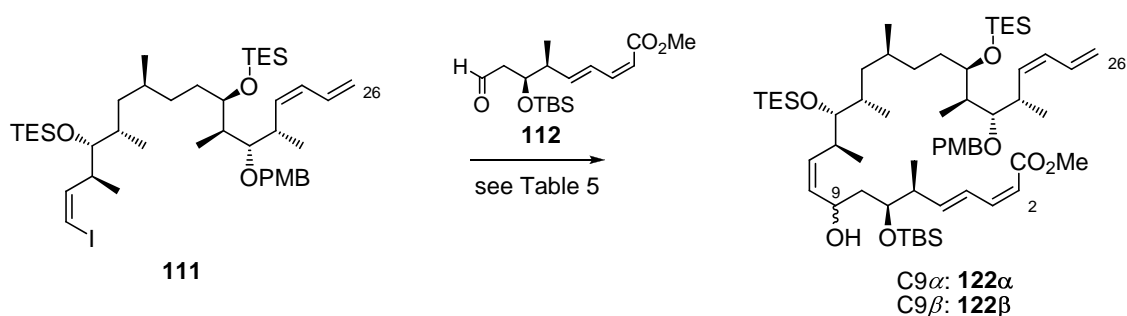


Figure 38. Coupling of the vinyl iodide **111** and the aldehyde **112**

Table 5. Reaction of the lithium reagent derived from the vinyl iodide **111** with the aldehyde **112**

vinyl iodide 111	additive	122α (yield)	122β (yield)
30 mg	no additive		1:1.9 ratio ^a
30 mg	(+) or (-)-methylephedrine		1:1.7 ratio ^a
30 mg	(-)-sparteine (1.3 equiv)		1:1.2 ratio ^a
30 mg	(-)-sparteine (3.6 equiv)		1:1.7 ratio ^a
70 mg	(-)-sparteine (1.3 equiv)	20 mg (23%)	20 mg (23%)
1 g	(-)-sparteine (1.3 equiv)	0.32 g (26%)	0.32 g (26%)
4.9 g	(-)-sparteine (1.3 equiv)	0.45 g (8%)	0.70 g (12%)

^a by chiral HPLC analysis

The assignment of the C9 configuration of the coupled product **122 α** was based on ¹H NMR similarities between the TBS ether **123 α** and the fluoros TIPS ether **124** previously synthesized in the FMS of 6,7-epimers (Figure 39).^{24c}

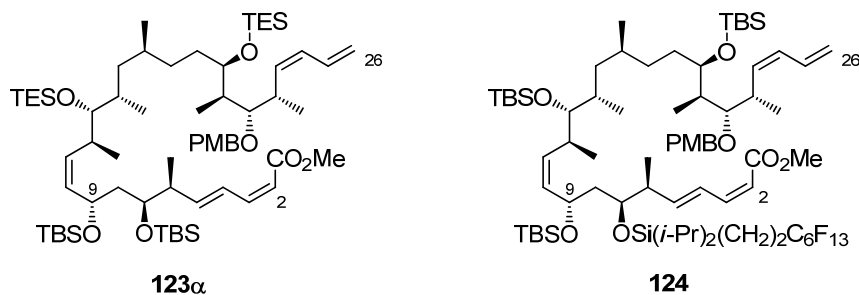


Figure 39. Structures of the TBS ether **123 α** and the fluoros TIPS ether **124**

At this time, a more scalable synthetic route was sought to provide coupling of two main fragments. Thus, a ring-closing metathesis reaction with two silicon-tethered alkenes was tried.

3.3 REVISED PLAN FOR THE SYNTHESIS OF 6-EPI-DICTYOSTATIN

The revised plan for the large-scale synthesis of 6-*epi*-dictyostatin **101** is outlined in Figure 40. The macrolactone **101** was again divided into three fragments. The disconnection across the C17–C18 bond by a HWE olefination reaction reveals the C1–C17 aldehyde **125** and the C18–C26 ketophosphonate **99**.^{24c} Further disconnection of the C1–C17 fragment **125** across the C10–C11 bond leads to the C1–C10' fragment **127** and the C11'–C17 fragment **128**, which can be united via a silicon-tethered ring-closing metathesis (RCM) reaction.

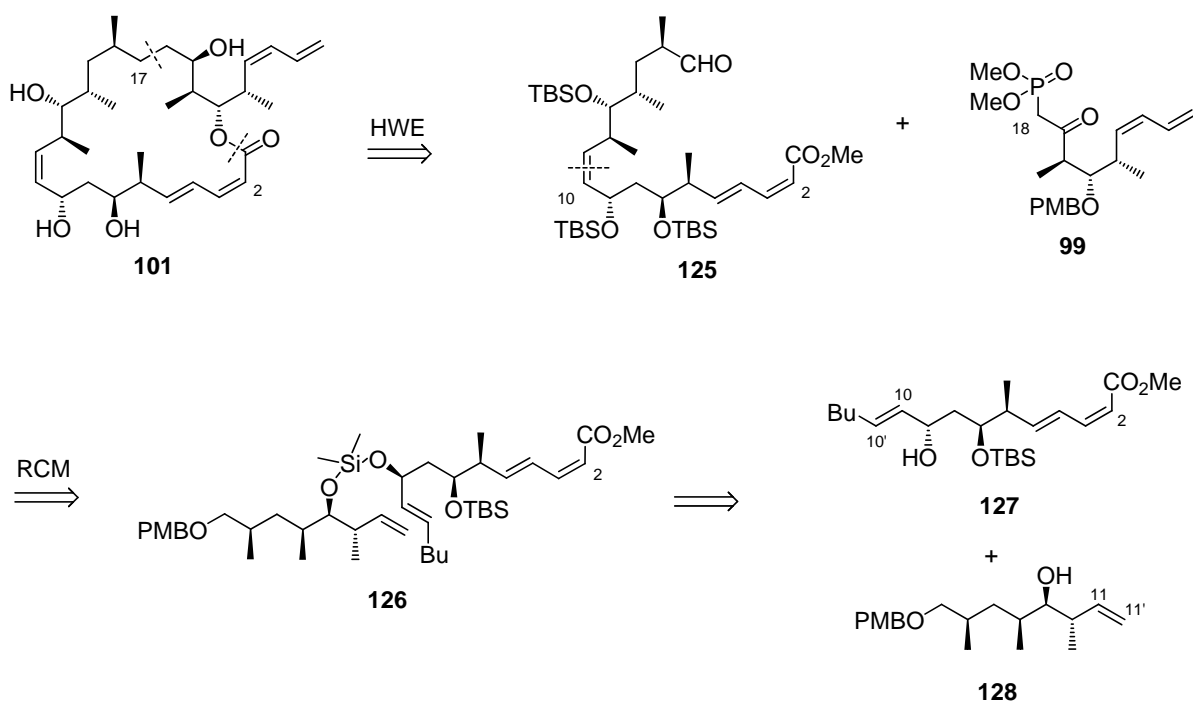


Figure 40. Retrosynthetic analysis of 6-*epi*-dictyostatin

3.4 SYNTHESIS OF THE COMMON INTERMEDIATE 132

In the initial synthesis of 6,7-epimers of dictyostatin,^{24c} each of the TBS- and PMB-protected aldehydes (**129** and **131**) was submitted to the Evans *syn*-aldol reaction to provide the C18–C26 fragment **99** or the C10–C17 fragment **97**, respectively (Figure 41). In contrast, a common intermediate **132** was selected to develop a practical method for synthesizing both the C18–C26 phosphonate **99** and the C11'–C17 alkene **128**.⁶⁴ As shown in Figure 42, the structural analysis of the fragments **99** and **128** showed that a triad of contiguous stereogenic centers with a *syn,anti*-relationship was present at both the C20→C22 of **99** and the C14→C12 of **128**. In addition, both fragments have the alkenes at the C23 or C11, respectively. Thus the synthesis of these C11'–C17 and C18–C26 fragments from **132**^{9a,b} as the common intermediate could reduce the number of steps required to prepare both main fragments from 24 to 19.

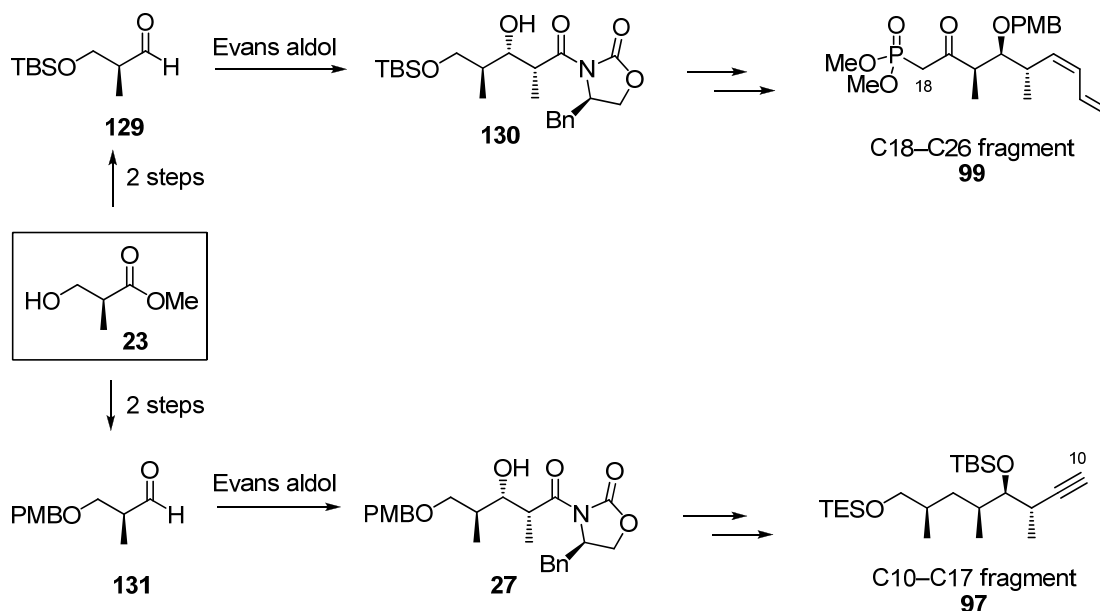


Figure 41. Synthesis of the fragments **97** and **99** in the attempted synthesis of 6-*epi*-dictyostatin

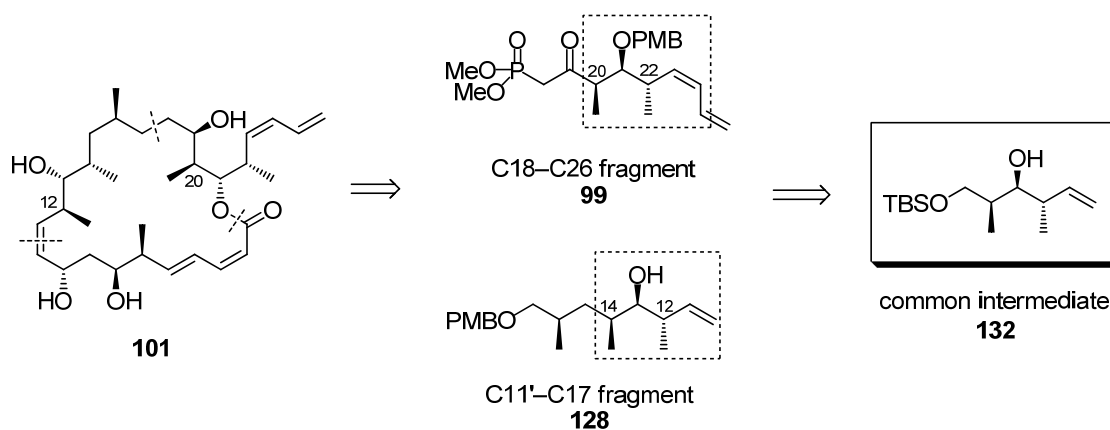


Figure 42. Structural analysis of the C11–C14 and C20–23 regions

As summarized in Figure 43, the starting point for synthesis of the common intermediate **132** was the protection of 75 g of the (*S*)-Roche ester **23** as a TBS ether.^{24c} Formation of the corresponding Weinreb amide was achieved in a single step by addition of magnesium *N,O*-dimethylhydroxamate to the methyl ester.^{24c} Reduction of the Weinreb amide with DIBAL-H provided the aldehyde,^{24c} which was subjected without purification to the Roush *anti*-crotylation reaction.⁴⁵ The crude product⁶⁵ was purified by silica gel chromatography to provide the alcohol **132**. Overall, 136 g of the common intermediate **132** was synthesized in four steps and 58% overall yield starting from 75 g of the ester **23**, with one silica-gel chromatographic purification.

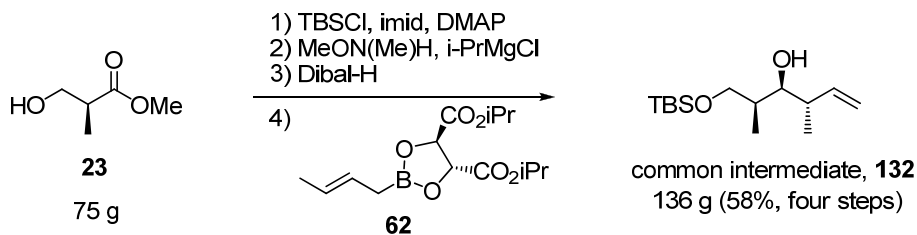


Figure 43. Synthesis of the common intermediate **132**

3.5 SYNTHESIS OF THE C18–C26 FRAGMENT **99**

The synthesis of the C18–C26 fragment **99** is outlined in Figure 44. The common intermediate **132** was treated with NaH and PMBBr to provide the PMB ether **133** in 84% yield after silica gel chromatography.^{9a,b} The ether **133** was submitted to ozonolysis to give the crude aldehyde **134**.^{9a,b}

Construction of the C23–C26 diene was accomplished by a Matteson protocol⁶⁶ as shown in Figure 44. The crude aldehyde **134** was reacted with 1-trimethylsilyl-1-propene boronate **135** at room temperature to provide the β -hydroxysilane (not shown). The crude silane was treated with sodium hydride to produce the *Z*-diene **136**^{24c} as a single isomer after silica gel chromatography in 72% yield over three steps. This Matteson protocol seems to be more practical for construction of the C23–C26 diene than the Nozaki–Hiyama or Wittig reactions used by the Curran group, because it allows for mild reaction conditions and no use of chromium salt.

The resulting TBS ether **136** was deprotected with CSA as a catalyst to give a primary alcohol. The installation of the phosphonate group on the C19 of the alcohol was based on procedures previously established by the Curran group.^{24c} The crude alcohol was subjected to Parikh–Doering oxidation conditions (SO₃•pyr, DMSO and DIPEA) to give the aldehyde. Subsequent treatment of the crude aldehyde with lithium phosphonate provided a secondary alcohol, which was used for the next step without purification. Swern oxidation⁶⁷ of the crude alcohol produced the ketophosphonate **99**^{24c} via silica gel chromatography in four steps and 61% yield.

Overall, 8 g of the C18–C26 fragment **99** was synthesized in eight steps and in 37% overall yield starting from the common intermediate **132**, via three chromatographic purification steps.

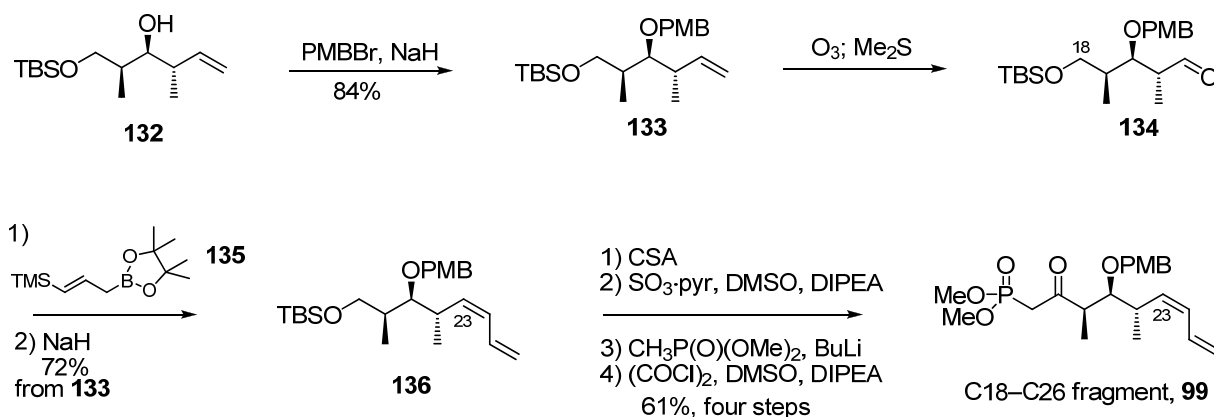


Figure 44. Synthesis of the C18–C26 fragment **99**

3.6 SYNTHESIS OF THE C11'–C17 FRAGMENT **128**

The C11'–C17 fragment **128** was synthesized on the basis of the methods used in the Curran group for the synthesis of dictyostatin **5**,^{22b} as shown in Figure 45. This began with the TBS protection of the secondary hydroxy group of the common intermediate **132** by using TBSOTf and 2,6-lutidine. The crude TBS ether was treated with a catalytic amount of CSA to provide the primary alcohol **137** in 67% yield over two steps. Next, the alcohol **137** was converted to a primary iodide by using PPh_3 , iodine and imidazole.⁶⁸ The crude iodide was submitted to Myers alkylation conditions⁶⁹ by using the chiral amide **138** to give an alkylated product, which was used for the next reaction without purification. The alkylated product was

reduced with $\text{BH}_3 \cdot \text{NH}_3$ and LDA to provide a primary alcohol **139** after silica gel chromatography in 78% yield over three steps.

The alcohol **139** was protected as a PMB ether by using trichloroimidate **24**²⁰ in 70% yield, and the C13 TBS group was subsequently removed with TBAF to provide the secondary alcohol **128**⁷⁰ in 63% yield. Overall, 13 g of the C11'–C17 fragment **128** was synthesized in eight steps and 23% overall yield, starting from the common intermediate **132**, via four silica gel chromatographic purification.

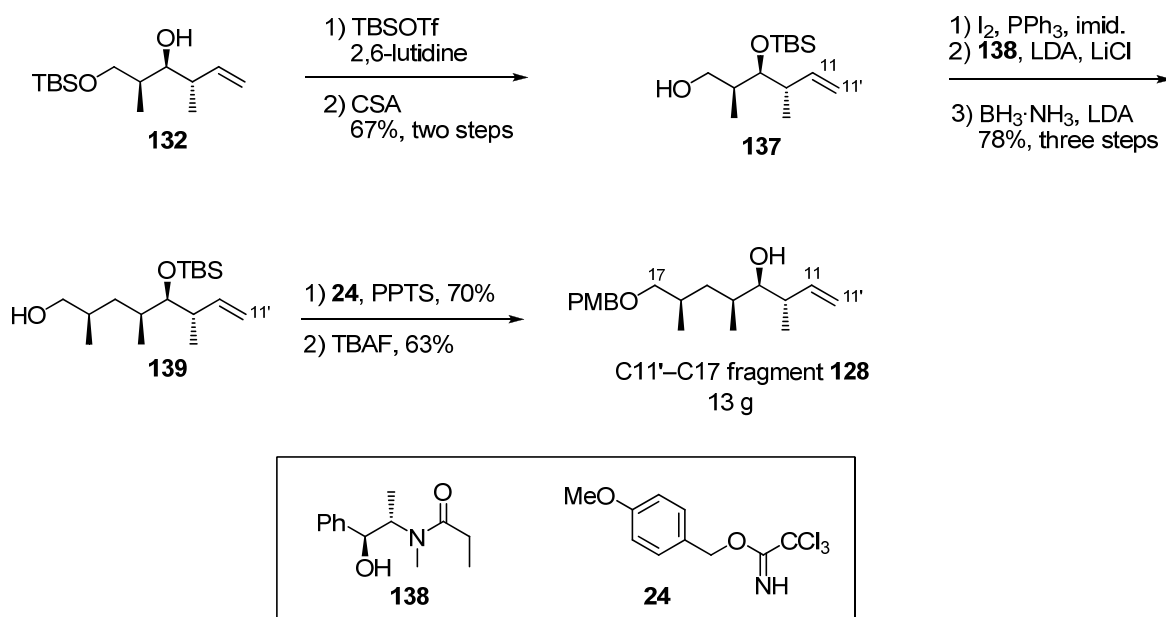


Figure 45. Synthesis of the C11'–C17 fragment **128**

3.7 SYNTHESIS OF THE C1–C10' FRAGMENT **127**

The C1–C10' fragment **127** was synthesized by Dr. G. Moura-Letts⁷¹ (Figure 46). The Brown *syn*-crotylboration³⁸ of the aldehyde **41** gave an alcohol, which was protected to give the

TBS ether **140**. The cross metathesis between the alkene **140** and the diene **141** was mediated by a fluororous Hoveyda–Grubbs II catalyst **142**⁷² to produce the C1–C9 dienoate **143**. Removal of the TBS group of **143** with HF•pyr and then the Dess–Martin oxidation of the resulting primary alcohol provided the aldehyde **112**, which was then submitted to Wipf reaction conditions (1-hexyne, Cp₂Zr(H)Cl, Me₂Zn, **133**)⁷³ to provide an inseparable mixture of two C9-epimers **127** and **145** in a 7:1 ratio favoring the desired alcohol **127** in 80% yield.

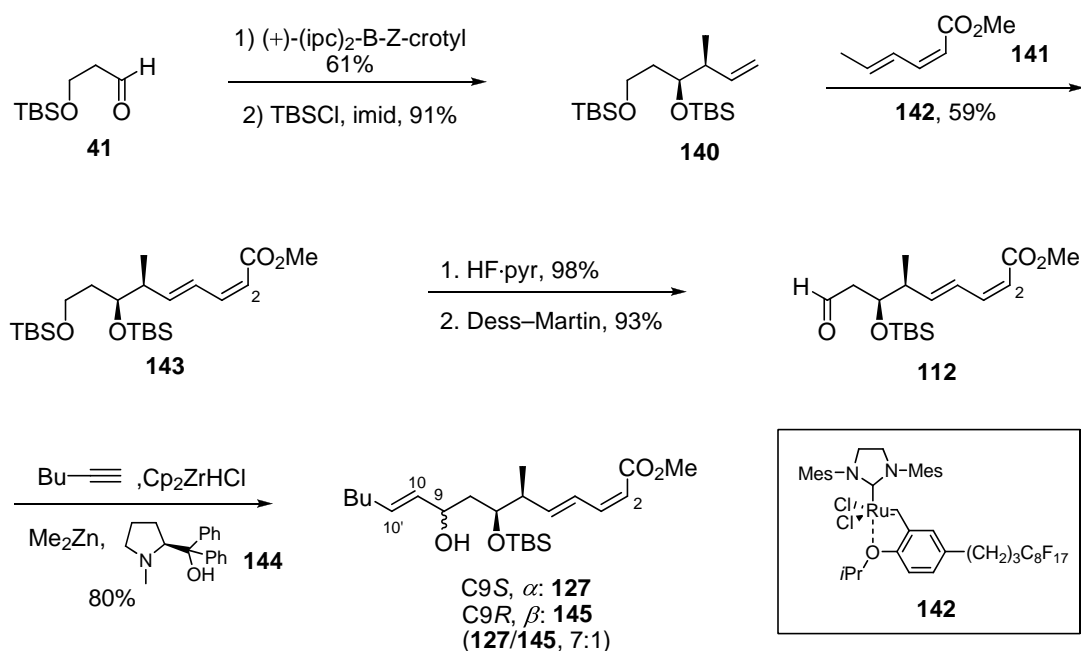


Figure 46. Synthesis of the C1–C10' fragment **127**

3.8 FRAGMENT COUPLINGS

3.8.1 Coupling of the C1–C10' and C11'–C17 fragments

The silylketals (a mixture of **126** and **147**) were synthesized by Dr. G. Moura-Letts.⁵³ As shown in Figure 47, the C11'–C17 alcohol **128** was treated with BuLi then 8 equiv of dimethyldichlorosilane to produce the intermediate **146**. The reaction mixture was concentrated and dried under vacuum to remove solvents and excess dimethyldichlorosilane. The dissolution of the residue in THF was followed by addition of imidazole and the C1–C10' alcohols (a mixture of the C9-epimers **127** and **145**) to provide an inseparable mixture of the silylketals (**126** and **147**) in 73% yield.

At this point, the validation of this RCM strategy for the large-scale synthesis was required prior to the scale-up of the synthesis of 6-*epi*-dictyostatin. Henceforth, research on a ten-milligram scale synthesis of 6-*epi*-dictyostatin was performed to validate the scalability of the new synthetic approach.

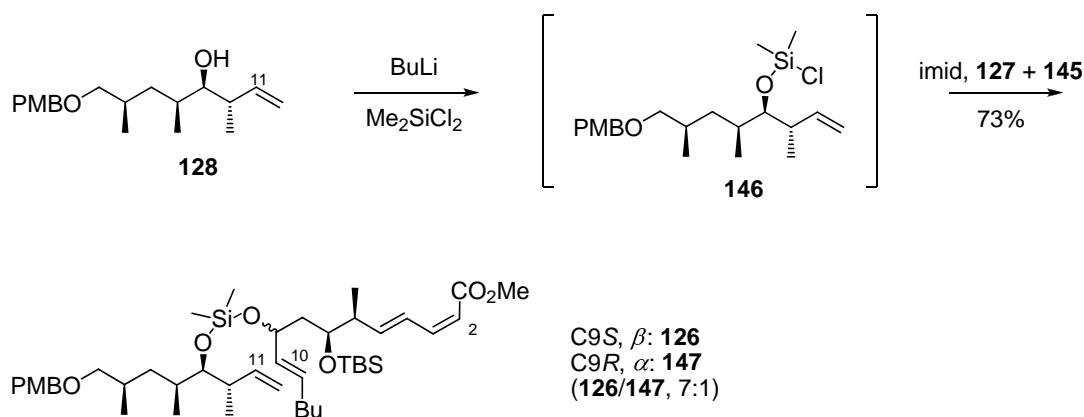


Figure 47. Synthesis of the silylketals **126** and **147**

3.8.2 RCM reactions of the silylketals

The silylketals (a mixture of **126** and **147**, from Dr. G. Moura-Letts) were submitted to the RCM reaction conditions (at a 0.01 M concentration in toluene at 110 °C with 0.1 equiv of a Hoveyda-Grubbs II (H-G II) catalyst, Figure 48).⁷⁴ These conditions gave an inseparable mixture of the RCM products **148** and **149** contaminated with impurities in 53% yield. In addition to the 8-membered disiloxanes (**148** and **149**), a mixture of a 11-membered disiloxane **150** and the recovered silylketals (29%) was isolated after silica gel chromatography. The ¹H NMR spectrum of the pure fraction of the 11-membered disiloxane **150** showed the resonances from the C10' butyl group and two alkenes, but no resonances from the characteristic H2–H4 and methyl group of the C1 ester. The geometry of the C5 alkene was not clear because the resonances of two C5 and C10 alkenes were overlapped in the spectrum. It was postulated that the 11-membered disiloxane **150** might originate from the metathesis reaction between the C11–C11' and the C4–C5 alkenes (pathway (b) in Figure 48).

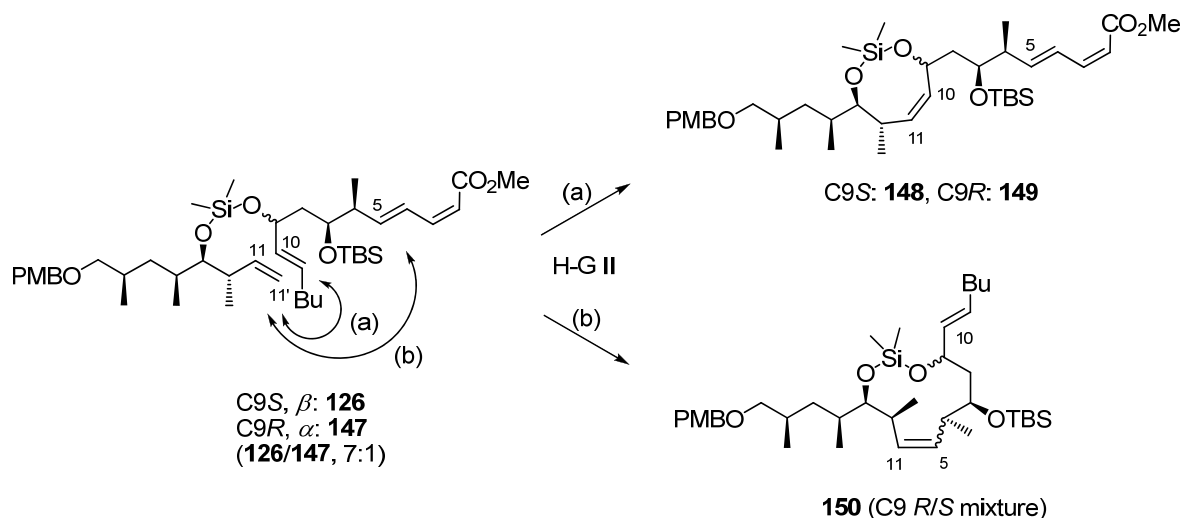


Figure 48. Two reaction pathways in the RCM reaction of the silylketals **126** and **147**

Next, the C1–C10' alcohol **151** possessing the terminal alkene at the C10 was selected to increase the preference for the metathesis of the C10–C10' alkene over the C4–C5 because, in general, terminal olefins are more reactive than internal olefins toward the metathesis reaction mediated by Grubbs catalysts.⁷⁵

The synthesis of the new C1–C10' fragment **151** is summarized in Figure 49. The reaction of the aldehyde **112** with vinylmagnesium bromide and subsequent oxidation of the resulting alcohol gave a ketone. Next, a Corey–Bakshi–Shibata (CBS) reduction⁷⁶ of the ketone provided an inseparable mixture of two C9-epimers **151** and **152** in a 5:1 ratio favoring the desired alcohol **151**. The ratio of two epimers was determined by ¹H NMR spectroscopic analysis. To this end, the ketone (not shown) was reduced with (*R*)-CBS or (*S*)-CBS independently to give two C9 epimers. The resonances of ¹H NMR from the C9 proton were shown at δ 4.33 ppm for the epimer treated with (*R*)-CBS, and at δ 4.26 ppm for (*S*)-CBS. The ¹H NMR spectrum of a mixture of two epimers (**151** and **152**) showed a major peak at δ 4.33 ppm and a minor one at δ 4.26 in a 5:1 ratio by integration. The assignment of the C9 configuration was based on Rychnovsky acetonide analysis.⁷⁷ For this, the C7 TBS group of a mixture of two epimers (**151** and **152**) was removed with HCl to give diols, which was treated with 2,2-dimethoxypropane to provide a mixture of the acetonides **153** and **154** (Figure 50). The ¹³C NMR spectrum of the acetonide mixture showed two signals from two methyl groups of a major acetonide at δ 24.66 and 25.45 ppm (Figure 51). This indicated the *anti*-relationship of the C7 and C9 hydroxy groups of the major acetonide. In addition, the resonances from two methyl groups of a minor acetonide were at δ 19.95 and 30.38 ppm, which indicated the *syn*-relationship of the C7 and C9 hydroxy groups of the minor acetonide. In conclusion, the C9 configuration of

the major component of a mixture of the C9-epimers (**151** and **152**) was assigned as "*S*" (α or *anti*-diol).

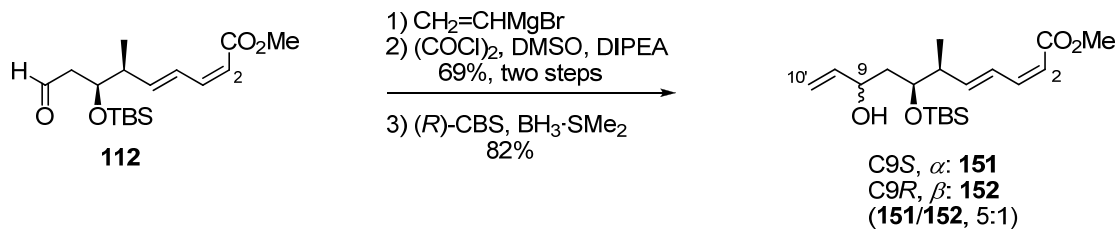


Figure 49. Synthesis of the new C1–C10' fragment (**151** and **152**)

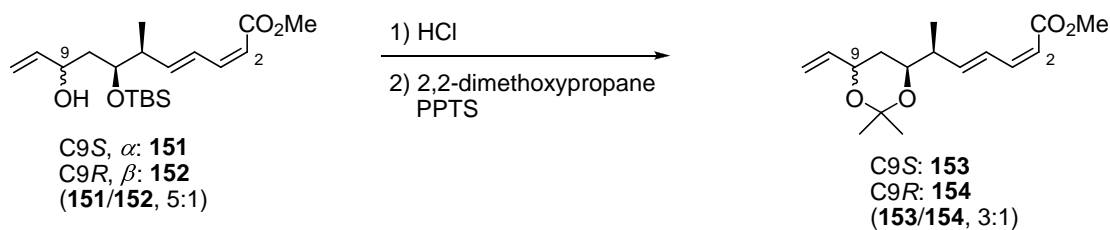


Figure 50. Synthesis of a mixture of the acetonides **153** and **154**

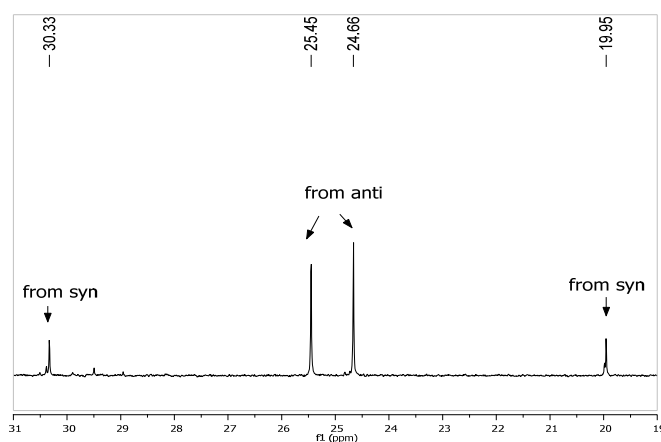


Figure 51. Selected resonances of the acetonide mixture (**153** and **154**) on the ¹³C NMR spectrum

Next, the C1–C10' fragment (**151** and **152**) and the C11'–C17 fragment **128** were coupled to provide an inseparable mixture of the silylketals (**155** and **156**) in 85% yield by following the procedures used for the silylketal **126**, as shown in Figure 52. The silylketal mixture (**155** and **156**) possessing terminal alkenes at both the C10 and C11 positions was treated with a Hoveyda-Grubbs II (H-G II) catalyst to provide the 8-membered disiloxanes (an inseparable mixture of **148** and **149**). The RCM reaction of 0.28 g of the silylketal mixture (**155** and **156**) produced 0.17 g (69% yield) of the RCM products (**148** and **149**). In addition, with 2.23 g of the silylketal mixture, 1.23 g (57% yield) of the RCM products was obtained along with a mixture of the 11-membered disiloxane **150** and the recovered silylketals (0.21 g, 10% yield). The ratio of an inseparable mixture of the disiloxanes (**148** and **149**) could not be determined because the resonances from two epimers were overlapped in the ^1H NMR spectrum.

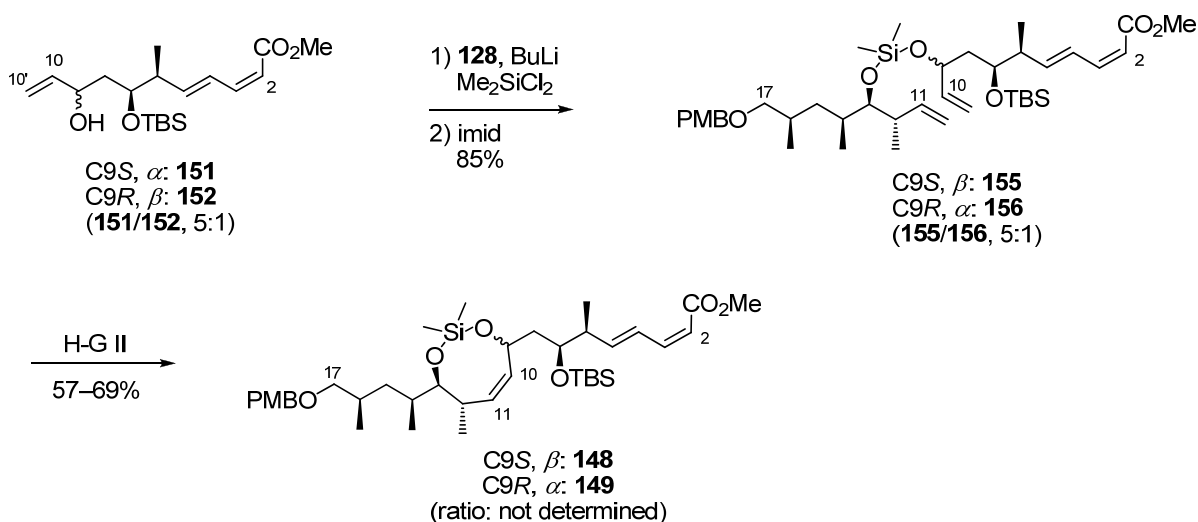


Figure 52. Synthesis of the 8-membered disiloxanes **148** and **149**

3.8.3 Coupling of the C1–C17 and C18–C26 fragments

As summarized in Figure 53, a mixture of the disiloxanes (**148** and **149**) was treated with dichloroacetic acid to provide the desired diol **157** (more polar, C9S only) in 65% yield after careful silica gel chromatography. In addition, the C9R-isomer **158** originating from the CBS reduction was isolated in 10% yield. The diol **157** was protected with TBSOTf to give the TBS ether **159** (0.73 g, 85% yield). The TBS ether **159** was treated with DDQ to produce the alcohol **160** (70 % yield), which was oxidized to the aldehyde **125** (Figure 40) by using the Dess–Martin periodinane. The crude aldehyde **125** (0.42 g) was coupled with the phosphonate **99** (0.35 g) by using $\text{Ba}(\text{OH})_2^{22b}$ to provide the enone **161** possessing the full C1–C26 carbon skeleton of 6-*epi*-dictyostatin (0.51 g, 89% yield over two steps).

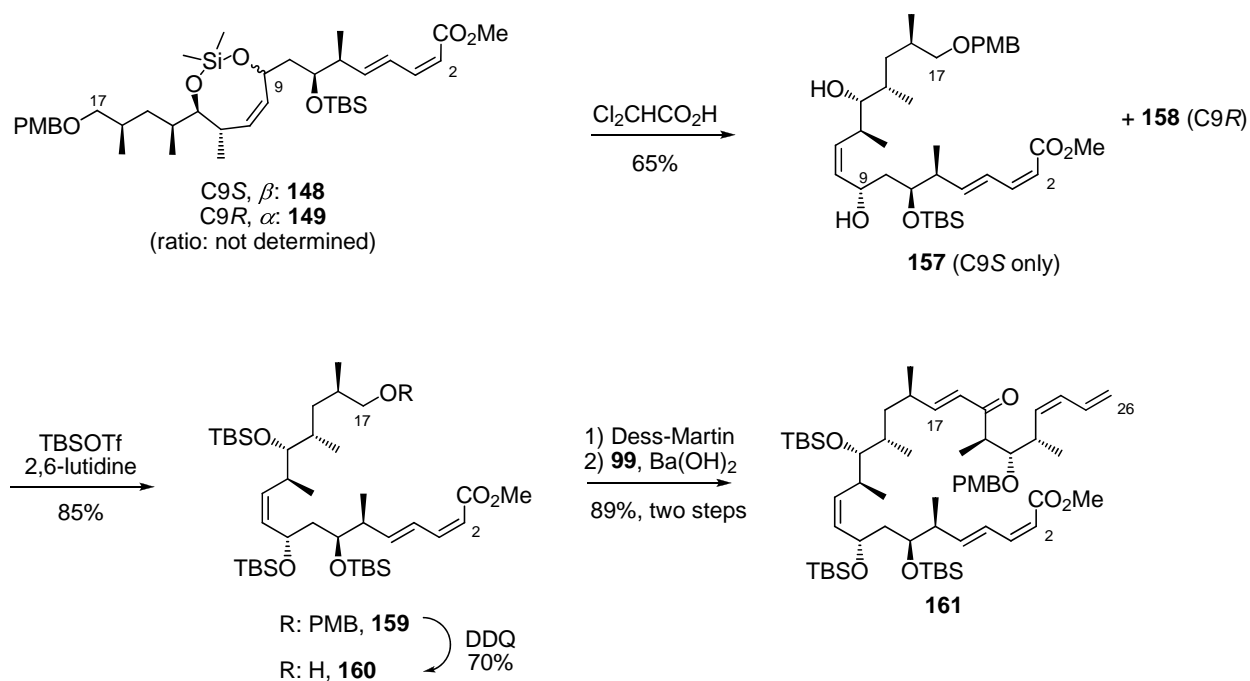


Figure 53. Construction of the full C1–C26 carbon skeleton

3.9 COMPLETION OF THE SYNTHESIS

3.9.1 Selective reduction reactions of the C17–C19 region

Prior to the reduction of the C17–C18 alkene of the enone **161**, a model study on regioselective reduction of an enone in the presence of a dienoate was performed (Figure 54). A mixture of the dienoate **58** and the enone **162** was treated with a Stryker reagent ($[\text{Ph}_3\text{PCuH}]_6$),⁶² which selectively reduced the enone **162** to the ketone **163** without reduction of the dienoate **58**. Then, as summarized in Figure 55, the C17–C18 olefin of the enone **161** was selectively reduced under Stryker reduction conditions to provide the ketone **164** (0.39 g, 78% yield).

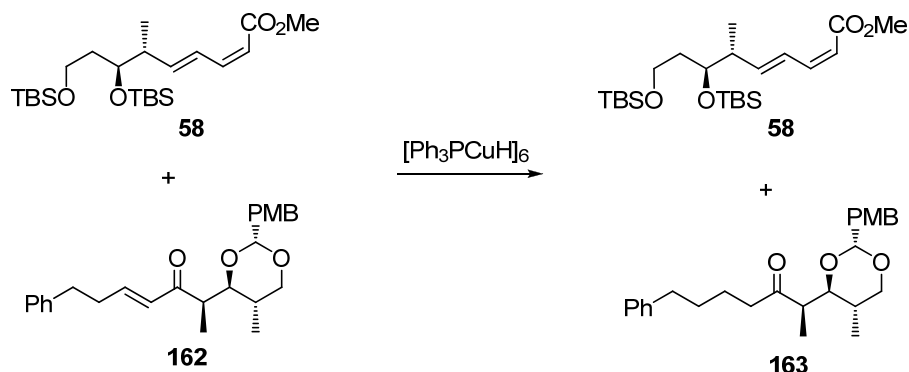


Figure 54. Model study on the selective reduction of the enone

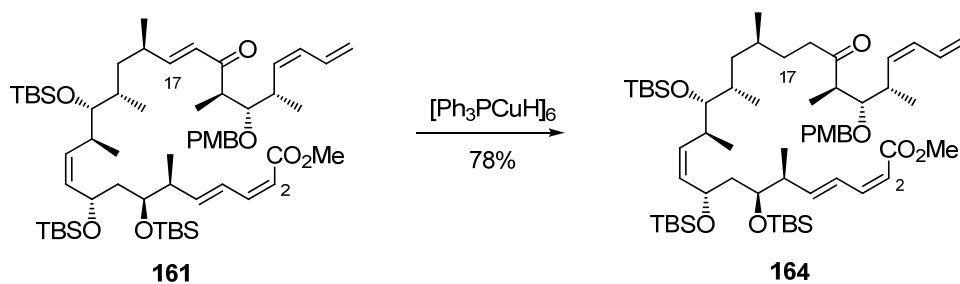


Figure 55. Regioselective reduction of the C17–C18 olefin of the enone **164**

Next, a model study on the reduction of the C19 ketone was performed (Figure 56). A mixture of the dienoate **58** and the ketone **163** was treated with $\text{LiAlH}(\text{O}t\text{-Bu})_3$ to give a mixture of the C2–C3 saturated ester **165** and the alcohol **166**. This suggests that treatment of the ketone **164** possessing the C1–C5 dienoate with $\text{LiAlH}(\text{O}t\text{-Bu})_3$ may reduce the C2 alkene.

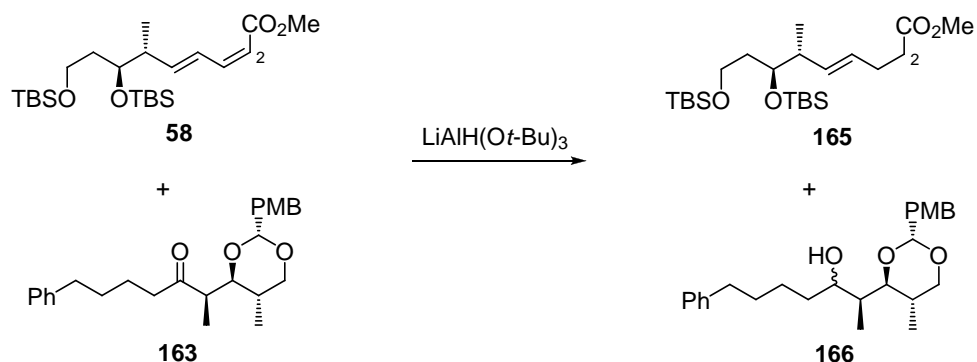


Figure 56. Model study on the selective reduction of the ketone

At this time, we attempted the Shapiro reduction conditions (NaBH_4 and Et_2BOMe)³¹ used for the reduction of the C19 ketone of 16-normethyl-15,16-dehydrodictyostatin **9**.^{24d} To this end, the C21 PMB group of the ketone **164** was removed with DDQ to provide the β -hydroxyketone (not shown, 0.23g, 87% yield, Figure 57). The β -hydroxyketone was then treated with NaBH_4 and Et_2BOMe to produce the diol **167** (0.20 g, 87% yield) without reduction of the C1–C5 dienoate region. The selectivity of the C19 reduction was measured by comparison of ^1H NMR spectrum of a C19 mixture (not shown), which was synthesized from reduction of the β -hydroxyketone with NaBH_4 . The resonances from the C21 protons of the C19 mixture were shown at δ 3.68 (minor) and 3.47 (major) ppm in a 1:2 ratio by integration. The signal from the C21 proton of the diol **167** was shown at δ 3.47 ppm without observable signal at δ 3.68 ppm.

The C19 configuration of the diol **167** was assigned by analog to 16-normethyl-15,16-dehydrodictyostatin **9**.^{24d}

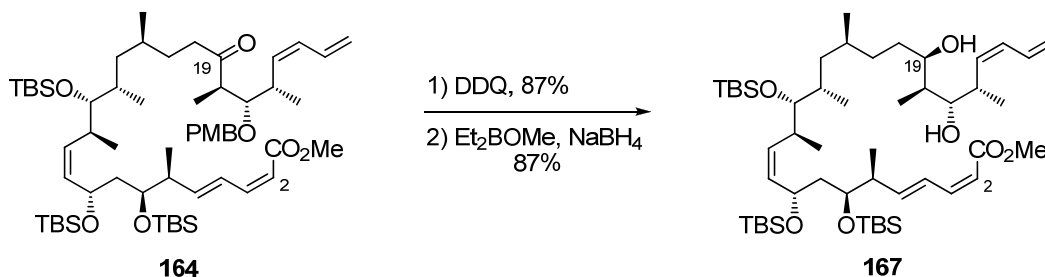


Figure 57. Diastereoselective reduction of the C19 ketone **164**

3.9.2 Completion of the synthesis of 6-*epi*-dictyostatin **101**

As shown in Figure 58, the C19 hydroxy group of the diol **167** was selectively protected with TBSOTf and 2,6-lutidine in the presence of the C21 hydroxy group to provide the alcohol **168** (0.19g, 85% yield).⁷⁸ In turn, the C1 methyl ester of **168** was hydrolyzed by using KOH to produce a *seco*-acid **169**, which was used for the next reaction without further purification.

Next, the crude *seco*-acid **169** was submitted to the macrolactonization conditions by using a Yamaguchi reagent (2,4,6-trichlorobenzoyl chloride), Et₃N and DMAP.⁵⁴ This gave a mixture of the C2 *E/Z*-isomers of the macrolactone, as shown in Table 6. In toluene, the use of 5 equiv of DMAP at room temperature gave a 1:1.5 ratio (C2 *E/Z*), and 0.1 equiv of DMAP at 80 °C gave a 1:5 ratio (C2 *E/Z*). Next, solvents were screened. THF gave a 1:1 ratio (C2 *E/Z*), and dichloromethane gave a >10:1 ratio (C2 *E/Z*). The ratios were determined by integration of resonances from H3's on the ¹H NMR spectra (Figure 59). Their C2 geometries were confirmed

by the coupling constants of the H2–H3 ($J = 12.0$ Hz for *Z*-isomer and 15.6 Hz for *E*-isomer) in the ^1H NMR spectra.

Next, we used a Shiina reagent (2,6-methylnitrobenzoyl anhydride)⁷⁹ for macrolactonization. The reaction of the *seco*-acid **169** with the Shiina reagent, Et_3N and DMAP in CH_2Cl_2 gave a >10:1 ratio (C2 *E/Z*). In contrast, use of toluene preferentially produced the C2 *Z*-isomer of the macrolactone (1:13, *E/Z*). The ^1H NMR spectra of the TBS-protected macrolactones produced by using Yamaguchi or Shiina reagents, are compared as shown in Figure 60. This macrolactone was contaminated with impurities after silica gel chromatography and used for the next reaction without further purification.

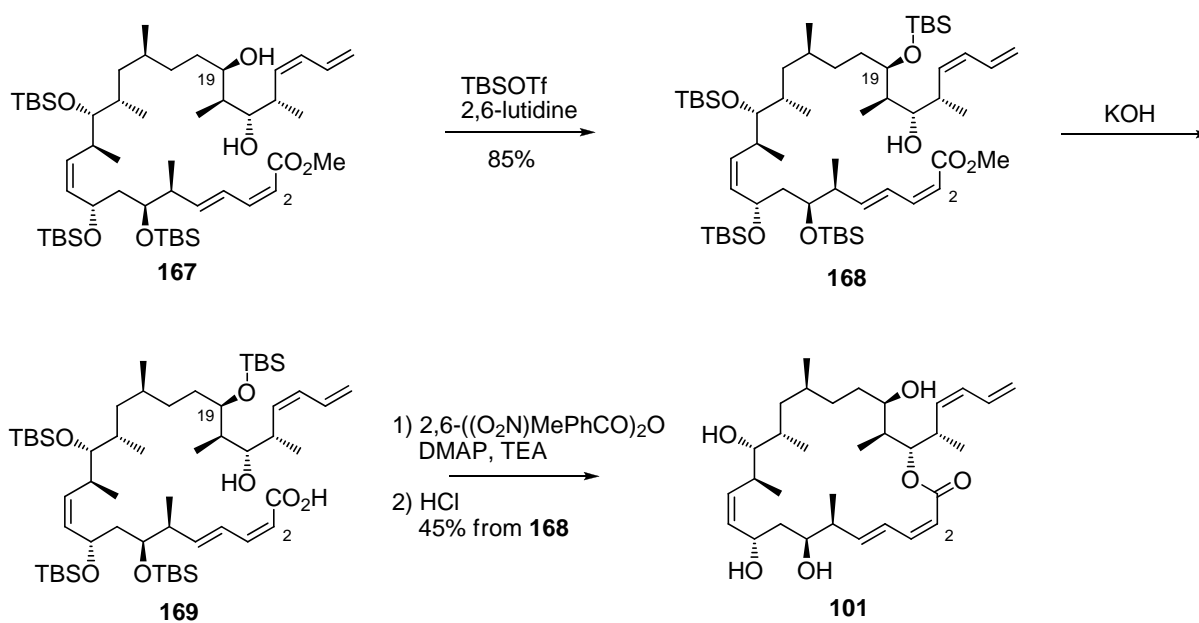
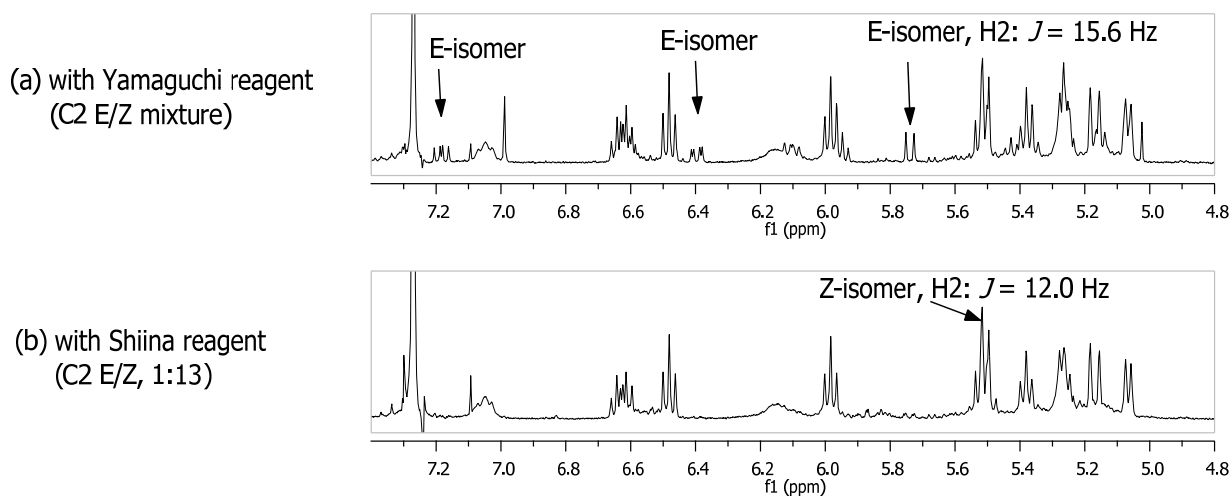


Figure 58. Completion of the synthesis of 6-*epi*-dictyostatin **101**

Table 6. Macrolactonization of the *seco*-acid **169**

reagent	DMAP (equiv)	solvent	<i>E/Z</i> ratio
Yamaguchi	5	toluene	1:1.5
Yamaguchi	0.1	toluene	1:5
Yamaguchi	5	THF	1:1
Yamaguchi	5	CH ₂ Cl ₂	> 10:1
Shiina	1	CH ₂ Cl ₂	> 10:1
Shiina	1	toluene	1:13

**Figure 59.** Comparison of ¹H NMR spectra of the TBS-protected macrolactones

The four TBS groups of the macrolactone was removed by using about 30 equiv of HCl to produce 33 mg of 6-*epi*-dictyostatin **101** as a white powder and in 45% yield, starting from 0.14 g of the ester **168**. This newly synthesized 6-*epi*-dictyostatin was identical in all respects with ¹H and ¹³C NMR spectroscopic data provided for the previously synthesized one.^{24c}

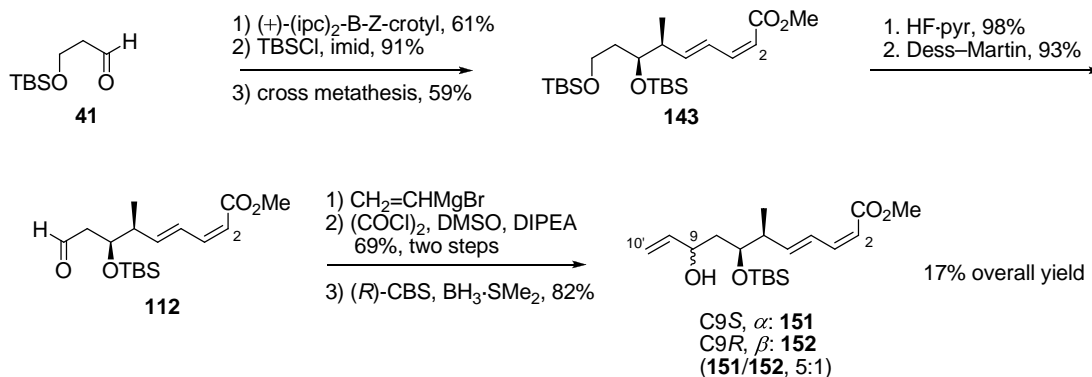
3.10 SUMMARY AND CONCLUSIONS

A convergent total synthesis of 6-*epi*-dictyostatin was achieved to produce 33 mg of the material for a biological evaluation. A common intermediate **132** was used to efficiently construct the C11'–C17 and C18–C26 fragments. However, more selective methods for installing the C9 stereocenter is still needed.

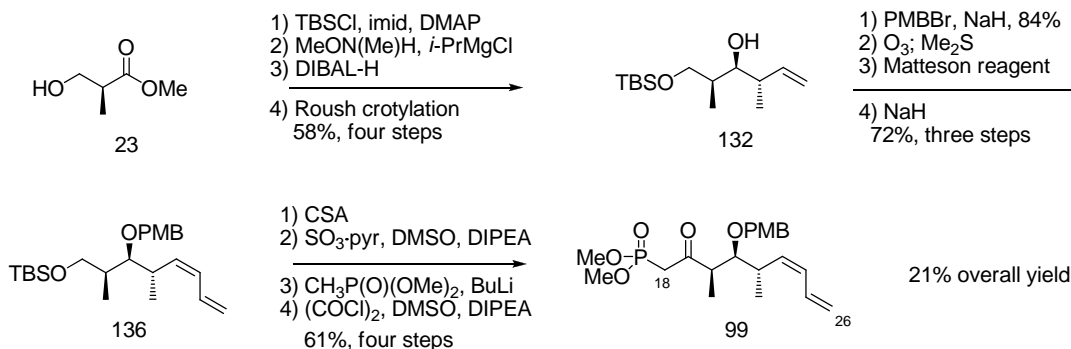
Three advanced fragments for 6-*epi*-dictyostatin, each of which possesses a full carbon skeleton, were coupled via a silicon-tethered RCM reaction and a HWE reaction. The optimization of the RCM reaction is still needed. Improved and reproducible methods for diastereoselective reduction of the C19 ketone, macrolactonization, and global deprotection were developed. This synthesis proceeded in totally 43 steps (longest linear sequence, 26 steps, Scheme 2), which is more efficient than that of dictyostatin by the Curran group (the number of the total steps is 52 and the longest linear sequence is 34). The overall yield is 0.04% starting from the (*S*)-Roche ester and 5% from the fragment coupling.

Scheme 2. Summary of the synthesis of 6-*epi*-dictyostatin **101**

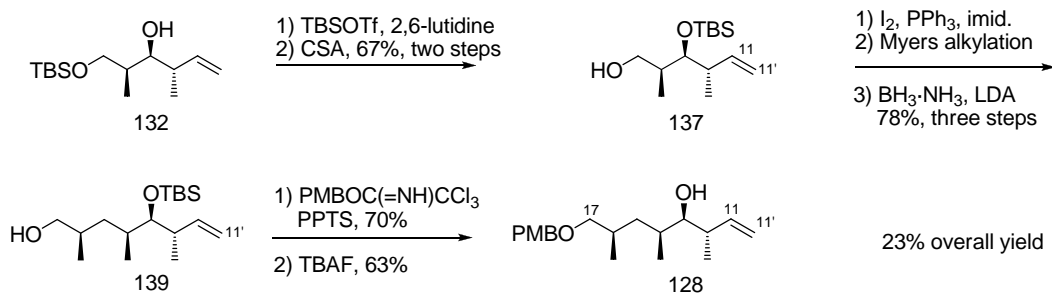
Synthesis of the C1–C10' fragment



Synthesis of the C18–C26 fragment

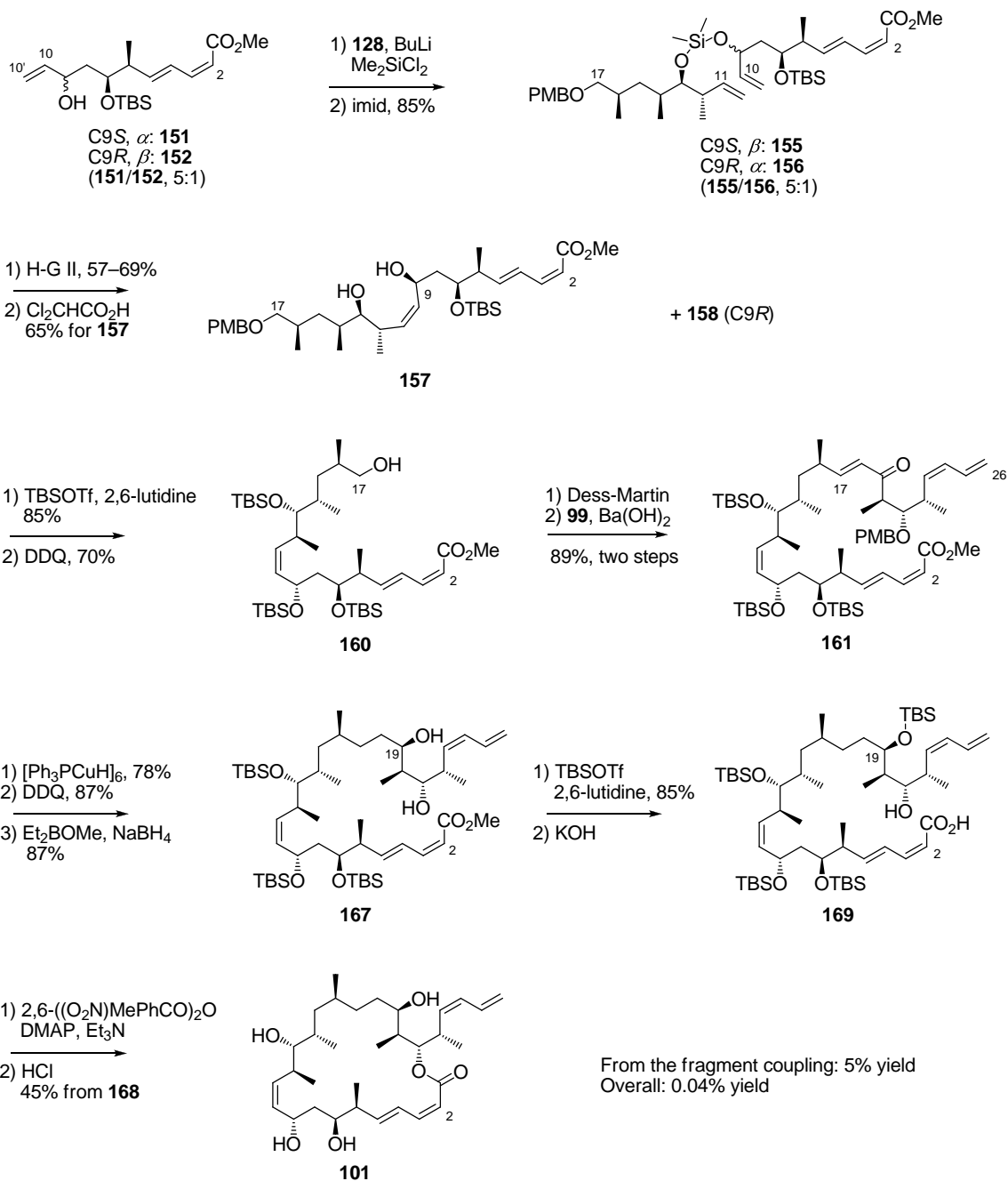


Synthesis of the C11'–C17 fragment



Scheme 2. Summary of the synthesis of 6-*epi*-dictyostatin **101** (*continued*)

Fragment couplings and completion of the synthesis



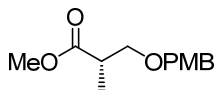
4.0 EXPERIMENTAL

4.1 GENERAL INFORMATION

All reactions were run under argon unless otherwise noted. Toluene, THF, dichloromethane, and diethyl ether were purified by filtration through an activated alumina under a nitrogen atmosphere. Other reagents were used as they were received from Aldrich. 4 Å Molecular sieves were flame-dried for at least 30 min before use. All new compounds were fully characterized by ^1H NMR, ^{13}C NMR, IR, optical rotation, and mass spectrometry. ^1H and ^{13}C NMR spectra were recorded on Bruker Avance DPX 300 (300 MHz), Avance DRX 500 (500 MHz) and Avance 600 (600 MHz) spectrometers. Chemical shifts were reported in ppm. CDCl_3 was used as the NMR solvent unless otherwise noted. In reporting spectral data, the following abbreviations were used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Coupling constants were measured in Hertz (Hz). Infrared spectra were taken on a Mattson Genesis Series FTIR using thin film deposition on NaCl plates unless otherwise noted. Peaks are reported in wavenumbers (cm^{-1}). Low and high resolution mass spectra were obtained on Waters LC/Q-Tof and reported in m/z units. High resolution mass spectra were obtained on a VG Autospec double focusing instrument and are reported in units of m/z . Optical rotations are measured on a Perkin-Elmer 241 polarimeter at the Na D-line ($\lambda = 589 \text{ nm}$) using a 1 dm cell at 20 °C. HPLC analyses

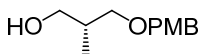
were conducted by using Waters 600 controller and Waters 2487 dual λ absorbance detector or polymer laboratory PL-ELS 1000 detector controlled with the Millennium™ program. Thin layer chromatography (TLC) was performed on silica gel 60 F₂₅₄ glass backed plates with a layer thickness of 0.25 mm manufactured by E.Merck. TLC visualization was performed by illumination with a 254 nm UV lamp or by staining with phosphomolybdic acid in ethanol (50 mg/mL) and subsequent heating. Silica gel chromatography was performed on silica gel (230–400 mesh ASTM) purchased from Sorbtech or Bodman.

4.2 PROCEDURES AND DATA



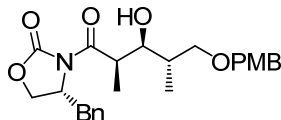
(S)-Methyl 3-(4-methoxybenzyloxy)-2-methylpropanoate (25):

Following the procedure for the same compound in reference 10c, (*S*)-Roche ester **23** (12.9 g, 0.11 mol) was protected with trichloroimidate (37.1 g, 0.13 mol) to give the title PMB-ether (22.8 g, 87% yield).



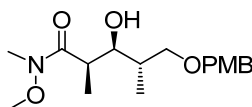
(R)-3-(4-Methoxybenzyloxy)-2-methylpropan-1-ol (61):

Following the procedure for the same compound in reference 17, the PMB ether **25** (22.8 g, 0.10 mol) was reduced with LiBH₄ (2.0 M in THF, 138 mL, 0.27 mol) to give the title alcohol (20.12 g, 100% yield).



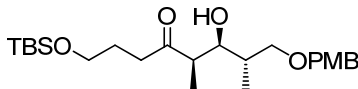
(R)-4-Benzyl-3-((2R,3S,4S)-3-hydroxy-5-(4-methoxybenzyloxy)-2,4-dimethylpentanoyl)oxazolidin-2-one (27):

Following the procedure for the same compound in reference 10c, the alcohol **61** (6.3 g, 30.0 mmol) was oxidized with $(\text{COCl})_2$ (4.1 mL, 48.0 mmol), DMSO (6.8 mL, 96.0 mmol) and Et_3N (27.2 mL, 195.0 mmol) to give the corresponding aldehyde (6.54 g). Next, the aldehyde was reacted with the oxazolidinone **26** (6.54 g, 58.5 mmol), Bu_2BOTf (1.0 M in CH_2Cl_2 , 28.5 mL, 28.5 mmol) and Et_3N (7.1 mL, 51.0 mmol) to give the title compound (11.75 g, 89% yield for two steps).



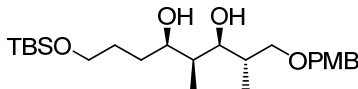
(2R,3S,4S)-3-Hydroxy-N-methoxy-5-(4-methoxybenzyloxy)-N,2,4-trimethylpentanamide (28):

Following the procedure for the same compound in reference 10c, the aldol product **27** (5.45 g, 12.34 mmol) was reacted with AlMe_3 (2.0 M in hexane, 18.5 mL, 37.03 mmol) and *N,O*-dimethylhydroxylamine hydrochloride (3.61 g, 37.03 mmol) to give the title amide (3.84 g, 96% yield).



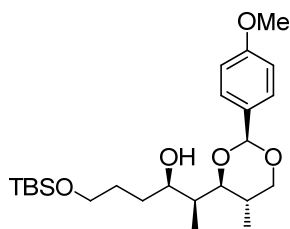
(5*R*,6*S*,7*S*)-8-(4-Methoxybenzyloxy)-1-(*tert*-butyldimethylsilyloxy)-6-hydroxy-5,7-dimethyloctan-4-one (30):

A 1.7 M solution of *tert*-BuLi in pentane (35.6 mL, 60.54 mmol) was added to a solution of *tert*-butyl(3-iodopropoxy)dimethylsilane **29** (8.53 g, 28.38 mmol) in diethyl ether (240 mL) at $-78\text{ }^{\circ}\text{C}$ dropwise over 30 min. After 15 min, a solution of the Weinreb amide **28** (3.08 g, 9.46 mmol) in diethyl ether (20 mL) was added to the above solution dropwise over 15 min. The mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 1 h and at $-40\text{ }^{\circ}\text{C}$ for 2.5 h. After quenching at $-40\text{ }^{\circ}\text{C}$ by addition of a sat. aq. NH_4Cl (50 mL), the mixture was extracted with diethyl ether ($3 \times 50\text{ mL}$) and the combined organic layers were washed with brine, dried (MgSO_4) and concentrated. Purification by column chromatography (2:1 hexanes/diethyl ether) provided the title compound (3.48 g, 84%) as a colorless oil: IR (NaCl) 3480, 2955, 2930, 2856, 1705, 1613, 1249, 1094, 835 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.26 (d, $J = 8.5\text{ Hz}$, 2H), 6.88 (d, $J = 8.5\text{ Hz}$, 2H), 4.43 (s, 2H), 3.89 (dd, $J = 8.4, 3.3\text{ Hz}$, 1H), 3.79 (s, 3H), 3.60 (t, $J = 6.1\text{ Hz}$, 3H), 3.55 (m, 2H), 2.64 (m, 1H), 2.60 (t, $J = 7.2\text{ Hz}$, 2H), 1.91 (m, 1H), 1.82 (qn, $J = 6.8\text{ Hz}$, 2H), 1.13 (d, $J = 7.0\text{ Hz}$, 3H), 0.90 (d, $J = 4.5\text{ Hz}$, 3H), 0.88 (s, 9H), 0.03 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 214.6, 159.5, 130.3, 129.6, 114.1, 75.3, 74.5, 73.4, 62.4, 55.5, 49.0, 37.5, 36.2, 27.0, 26.2, 18.5, 14.2, 9.4, -5.0 ; LRMS (ESI) 461 $[\text{M} + \text{Na}]^+$; HRMS (ESI) calcd. for $\text{C}_{24}\text{H}_{42}\text{O}_5\text{SiNa}$ 461.2699, found 461.2671; $[\alpha]_{\text{D}}^{20} +22.5$ (c 0.08, CHCl_3).



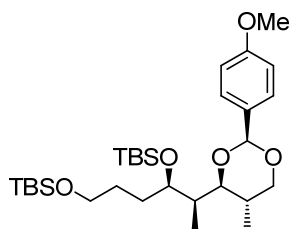
(2*S*,3*S*,4*S*,5*R*)-1-(4-Methoxybenzyloxy)-8-(*tert*-butyldimethylsilyloxy)-2,4-dimethyloctane-3,5-diol (31):

A solution of the ketone **30** (3.48 g, 7.93 mmol) in THF (79 mL) and MeOH (20 mL) at –78 °C was treated with a 1.0 M solution of Et₂BOMe in THF (12.7 mL, 12.69 mmol) dropwise over 10 min. After 30 min, NaBH₄ (0.36 g, 9.52 mmol) was added in three portions over 10 min. The mixture was stirred at –78 °C for 7 h, and quenched by the dropwise addition of acetic acid (7 mL). Water (80 mL) was added and the mixture was extracted with CH₂Cl₂ (3 × 50 mL) and the combined organic layers were washed with NaOH (1.0 M, 100 mL), dried (MgSO₄) and concentrated. The residue was taken up in a 1.0 M solution of NaOAc in MeOH (360 mL) and H₂O (40 mL), then 30% H₂O₂ (30 mL) was added. After stirring at ambient temperature for 1 h, the mixture was concentrated, then diluted with H₂O (50 mL) and extracted with CH₂Cl₂ (4 × 50 mL), dried (MgSO₄) and concentrated. Purification by column chromatography (1:1 hexanes/diethyl ether) provided the title compound (2.95 g, 85%) as a colorless oil: IR (NaCl) 3440, 2953, 2930, 2856, 1513, 1463, 1249, 1096, 835 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.25 (d, *J* = 8.5 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 4.46 (s, 2H), 4.41 (s, 1H), 4.06 (s, 1H), 3.84 (m, 1H), 3.80 (s, 3H), 3.71–3.64 (m, 3H), 3.57 (dd, *J* = 4.6, 9.1 Hz, 1H), 3.48 (t, *J* = 8.6 Hz, 1H), 1.99 (m, 1H), 1.65–1.53 (m, 5H), 0.91 (d, *J* = 7.0 Hz, 3H), 0.89 (s, 9H), 0.77 (d, *J* = 6.9 Hz, 3H), 0.05 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 159.6, 130.1, 129.5, 114.1, 81.9, 76.8, 76.0, 73.4, 63.6, 55.4, 38.5, 36.3, 32.1, 29.9, 26.2, 18.5, 13.5, 4.6, –5.0; LRMS (ESI) 463 [M + Na]⁺; HRMS (ESI) calcd. for C₂₄H₄₄O₅SiNa 463.2856, found 463.2851; [α]_D²⁰ +17.7 (*c* 0.18, CHCl₃).



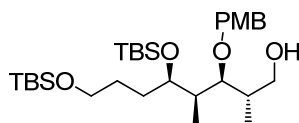
(2*S*,3*R*)-6-(*tert*-Butyldimethylsilyloxy)-2-((2*S*,4*S*,5*S*)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)hexan-3-ol (33):

A solution of the diol **31** (3.48 g, 7.93 mmol) in CH₂Cl₂ (136 mL) was treated with 4 Å molecular sieves (3.00 g) at room temperature. After stirring for 20 min, the mixture was cooled to 0 °C and DDQ (3.09 g, 13.62 mmol) was added in three portions over 3 min. The reaction mixture was stirred for 1.5 h and warmed to ambient temperature over 30 min, then filtered through Celite. Sat. aq. NaHCO₃ (100 mL) was added and the mixture was extracted with CH₂Cl₂ (2 × 100 mL) and the combined organic layers were washed with sat. aq. NaHCO₃ (2 × 100 mL), dried (MgSO₄) and concentrated. Purification by column chromatography (5:1 hexanes/EtOAc) provided the title compound (3.47 g, 60%) as a colorless oil: IR (NaCl) 3535, 2954, 2929, 2855, 1518, 1251, 1100, 834 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.37 (d, *J* = 8.7 Hz, 2H), 6.98 (d, *J* = 8.7 Hz, 2H), 5.50 (s, 1H), 4.12 (dd, *J* = 4.7, 11.2 Hz, 1H), 3.87 (m, 1H), 3.79 (s, 3H), 3.69 (dd, *J* = 2.1, 9.9, 2H), 3.65 (m, 1H), 3.52 (t, *J* = 11.1 Hz, 1H), 3.24 (s, 1H), 2.12 (m, 1H), 1.80 (tq, *J* = 1.8, 7.1 Hz, 1H), 1.67–1.49 (m, 4H), 1.04 (d, *J* = 7.1 Hz, 3H), 0.90 (s, 9H), 0.77 (d, *J* = 6.7 Hz, 3H), 0.06 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 160.0, 131.1, 127.5, 113.9, 101.4, 88.7, 76.2, 73.4, 63.5, 55.5, 37.8, 31.6, 30.7, 29.7, 26.2, 18.6, 12.2, 6.3, -4.9; LRMS (ESI) 461 [M + Na]⁺; HRMS (ESI) calcd. for C₂₄H₄₂O₅SiNa 461.2699, found 461.2673; [α]_D²⁰ +38.6 (*c* 0.15, CHCl₃).



(2*S*,4*S*,5*S*)-4-((2*R*,3*R*)-3,6-Bis(*tert*-butyldimethylsilyloxy)hexan-2-yl)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxane (34):

A solution of the alcohol **33** (3.47 g, 7.91 mmol) and 2,6-lutidine (2.80 mL, 23.73 mmol) in CH₂Cl₂ (79 mL) at -78 °C was treated with TBSOTf (2.40 mL, 10.28 mmol). The reaction mixture was stirred for 1 h and warmed to 0 °C over 30 min. After quenching by addition of sat. aq. NaHCO₃ (50 mL), the mixture was extracted with CH₂Cl₂ (3 × 50 mL) and the combined organic layers were washed with brine, dried (MgSO₄) and concentrated. Purification by column chromatography (9:1 hexanes/EtOAc) provided the title compound (4.32 g, 99%) as a colorless oil: IR (NaCl) 2954, 2929, 2856, 1518, 1462, 1251, 1038, 835, 774 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.40 (d, *J* = 8.7 Hz, 2H), 6.90 (d, *J* = 8.7 Hz, 2H), 5.43 (s, 1H), 4.11 (dd, *J* = 4.6, 11.1 Hz, 1H), 3.81 (s, 3H), 3.74 (m, 1H), 3.69 (dd, *J* = 1.4, 10.1, 2H), 3.60 (m, 1H), 3.51 (t, *J* = 11.1 Hz, 1H), 3.24 (s, 1H), 2.05 (m, 1H), 1.80 (dq, *J* = 1.2, 7.0 Hz, 1H), 1.60 (m, 4H), 1.03 (d, *J* = 7.0 Hz, 3H), 0.92 (s, 9H), 0.90 (s, 9H), 0.76 (d, *J* = 6.7 Hz, 3H), 0.06 (d, *J* = 2.7 Hz, 6H), 0.04 (d, *J* = 1.6 Hz, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 159.8, 131.7, 127.3, 113.5, 100.7, 81.9, 74.4, 73.4, 63.6, 55.3, 38.8, 30.8, 29.8, 28.3, 26.1, 18.4, 18.2, 12.4, 10.7, -4.1 -4.2, -5.1 -5.2; LRMS (ESI) 575 [M + Na]⁺; HRMS (ESI) calcd. for C₃₀H₅₆O₅Si₂Na 575.3564, found 575.3616; [α]_D²⁰ +26.2 (*c* 0.16, CHCl₃).

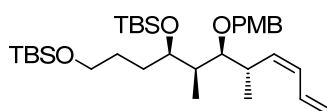


(2*S*,3*S*,4*R*,5*R*)-3-(4-Methoxybenzyloxy)-5,8-bis(*tert*-butyldimethylsilyloxy)-2,4-dimethyloctan-1-ol (35):

A solution of the PMB acetal **34** (3.70 g, 6.69 mmol) in CH₂Cl₂ (33 mL) at –78 °C was treated with a 1.0 M solution of diisobutylaluminum hydride in hexane (66.9 mL, 66.9 mmol) dropwise over 30 min, and the reaction mixture was stirred at –45 °C for 12 h. After quenching by addition of sat. aq. potassium sodium tartrate (130 mL), the mixture was stirred at ambient temperature for 1 h, extracted with CH₂Cl₂ (3 × 50 mL). The combined organic layers were washed with brine, dried (MgSO₄) and concentrated. Purification by column chromatography (4:1 hexanes/EtOAc) provided the title compound (1.49 g, 41%) as a colorless oil and the more polar diol **36** (1.57 g, 55%) as a colorless oil: IR (NaCl) 3434, 2954, 2929, 2856, 1514, 1250, 1036, 835, 773 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.28 (d, *J* = 8.7 Hz, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 4.52 (s, 2H), 3.82 (dd, *J* = 3.4, 11.0 Hz, 1H), 3.80 (s, 3H), 3.68 (m, 1H), 3.61–3.56 (m, 3H), 3.47 (dd, *J* = 4.7, 6.3 Hz, 1H), 2.65 (s, 1H), 1.95 (m, 1H), 1.88 (m, 1H), 1.59 (m, 2H), 1.48 (m, 2H), 1.11 (d, *J* = 7.0 Hz, 3H), 1.02 (d, *J* = 6.9 Hz, 3H), 0.91 (s, 9H), 0.90 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H), 0.05 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 159.5, 130.8, 129.5, 114.1, 86.0, 75.4, 73.6, 65.6, 63.4, 55.5, 40.9, 37.4, 31.1, 28.9, 26.2, 18.5, 18.4, 15.9, 10.4, –3.5, –4.1, –5.0; LRMS (ESI) 577 [M + Na]⁺; HRMS (ESI) calcd. for C₃₀H₅₈O₅Si₂Na 557.3721, found 557.3687; [α]_D²⁰ +3.5 (*c* 0.17, CHCl₃).

Conversion of the diol 36 to the title compound 35. A solution of the diol **36** (1.57 g, 3.68 mmol) and imidazole (0.38, 5.52 mmol) in CH₂Cl₂ (37 mL) was treated with a solution of

TBSCl (0.57 g, 0.57 mmol) in CH₂Cl₂ (18 mL) at -78 °C. The reaction mixture was warmed to 0 °C over 3 h, then additional imidazole (0.38, 5.52 mmol) and TBSCl (0.57 g, 0.57 mmol) were added. The mixture was stirred at -25 °C for 2 h and at ambient temperature for 1.5 h. After concentration in vacuum, purification by column chromatography (4:1 hexanes/EtOAc) provided the TBS ether (1.09 g, 55%). The ¹H NMR spectrum of this product was consistent with the title compound **35**.



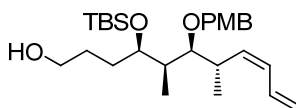
1-(((5S,6S,7R,8R,Z)-8,11-bis(*tert*-Butyldimethylsilyloxy)-5,7-dimethylundeca-1,3-dien-6-yloxy)methyl)-4-methoxybenzene (37):

A solution of the alcohol **35** (2.10 g, 3.78 mmol) and triethylamine (1.60 mL, 11.34 mmol) in CH₂Cl₂ (8 mL) and DMSO (6 mL) at 0 °C was treated with a solution of SO₃•pyr (1.50 g, 9.45 mmol) in DMSO (9.5 mL) dropwise over 10 min. The reaction mixture was stirred for 1 h. After quenching by addition of H₂O (80 mL), the mixture was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine, dried (MgSO₄) and concentrated. The aldehyde as a colorless oil was used immediately in the next step without further purification.

A suspension of CrCl₂ (5.11 g, 41.58 mmol) in THF (42 mL) at ambient temperature was treated with a solution of the aldehyde and 1-bromoallyltrimethylsilane **13** (4.38 g, 22.68 mmol) in THF (19 mL) via cannula, and the mixture was stirred for 17 h. After quenching by addition of pH 7 phosphate buffer (250 mL), the mixture was extracted with diethyl ether (3 × 150 mL). The

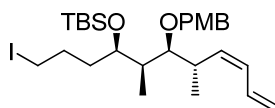
combined organic layers were washed with brine, dried (MgSO₄) and concentrated. The alcohol as a pale blue oil was used immediately in the next step without further purification.

A solution of the alcohol in THF (95 mL) at 0 °C was treated with NaH (95 wt. %, 1.91 g, 75.60 mmol) in three portions over 3 min. The mixture was stirred at 0 °C for 15 min and at ambient temperature for 1 h. After quenching by addition of water (100 mL), the mixture was extracted with diethyl ether (3 × 100 mL). The combined organic layers were washed with brine, dried (MgSO₄) and concentrated. Purification by column chromatography (95:5 hexanes/EtOAc) provided the title compound (1.85 g, 85% for three steps) as a colorless oil: IR (NaCl) 2955, 2929, 2856, 1514, 1249, 1085, 835, 773 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.29 (d, *J* = 8.8 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 6.61 (dt, *J* = 10.6, 16.6 Hz, 1H), 6.01 (t, *J* = 11.0 Hz, 1H), 5.58 (t, *J* = 10.7 Hz, 1H), 5.21 (d, *J* = 16.9 Hz, 1H), 5.12 (d, *J* = 10.1 Hz, 1H), 4.57 (d, *J* = 10.5 Hz, 1H), 4.50 (d, *J* = 10.5 Hz, 1H), 3.80 (s, 3H), 3.65 (m, 1H), 3.53 (dt, *J* = 1.7, 6.2 Hz, 2H), 3.34 (dd, *J* = 3.4, 7.6 Hz, 1H), 2.98 (m, 1H), 1.67 (m, 1H), 1.52 (m, 2H), 1.36 (m, 2H), 1.11 (d, *J* = 6.8 Hz, 3H), 0.97 (d, *J* = 6.8 Hz, 3H), 0.92 (s, 9H), 0.88 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H), 0.05 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 159.3, 134.9, 132.6, 131.7, 129.4, 129.2, 117.5, 113.9, 84.5, 75.2, 72.8, 63.4, 55.5, 40.8, 35.6, 31.5, 28.9, 26.3, 26.2, 19.0, 18.5, 18.4, 9.5, -3.4, -4.2, -4.9; LRMS (ESI) 599 [M + Na]⁺; HRMS (ESI) calcd. for C₃₃H₆₀O₄Si₂Na 599.3928, found 599.3958; [α]_D²⁰ +2.2 (*c* 0.10, CHCl₃).



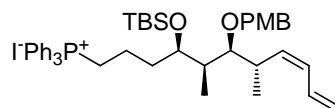
(4*R*,5*R*,6*S*,7*S*,*Z*)-6-(4-Methoxybenzyloxy)-4-(*tert*-butyldimethylsilyloxy)-5,7-dimethylundeca-8,10-dien-1-ol (38):

A solution of the TBS ether **37** (3.70 g, 6.69 mmol) in THF (34 mL) at 0 °C was treated with a solution of HF•pyr in pyr/THF (78 mL, prepared by slow addition of HF•pyr (6 mL) to a solution of pyridine (24 mL) and THF (48 mL)) dropwise, and the reaction mixture was stirred at 0 °C for 1 h and at ambient temperature for 5 h. After quenching by addition of sat. aq. NaHCO₃ (150 mL), the mixture was extracted with EtOAc (4 × 80 mL). The combined organic layers were washed with sat. aq. CuSO₄ (3 × 50 mL), brine, dried (MgSO₄) and concentrated. Purification by column chromatography (4:1 hexanes/EtOAc) provided the title compound (1.20 g, 75%) as a colorless oil: IR (NaCl) 3366, 2954, 2929, 1514, 1249, 1038, 835 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.27 (d, *J* = 8.5 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 6.60 (dt, *J* = 10.3, 16.8 Hz, 1H), 6.01 (t, *J* = 11.0 Hz, 1H), 5.56 (t, *J* = 10.5 Hz, 1H), 5.21 (d, *J* = 16.8 Hz, 1H), 5.11 (d, *J* = 10.1 Hz, 1H), 4.57 (d, *J* = 10.6 Hz, 1H), 4.46 (d, *J* = 10.6 Hz, 1H), 3.78 (s, 3H), 3.66 (m, 1H), 3.55 (t, *J* = 6.4 Hz, 2H), 3.33 (dd, *J* = 3.9, 7.0 Hz, 1H), 2.99 (m, 1H), 1.71 (m, 1H), 1.50 (m, 2H), 1.41 (m, 2H), 1.09 (d, *J* = 6.8 Hz, 3H), 0.96 (d, *J* = 6.8 Hz, 3H), 0.91 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 159.3, 135.1, 132.7, 131.6, 129.4, 129.2, 117.6, 113.9, 84.2, 75.1, 72.7, 63.2, 55.5, 40.7, 35.6, 31.4, 28.8, 26.2, 19.0, 18.4, 9.8, -3.4, -4.1; LRMS (ESI) 485 [M + Na]⁺; HRMS (ESI) calcd. for C₂₇H₄₆O₄SiNa 485.3063, found 485.3071; [α]_D²⁰ +38.6 (*c* 0.07, CHCl₃).



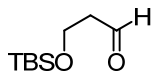
((4*R*,5*R*,6*S*,7*S*,*Z*)-6-(4-Methoxybenzyloxy)-1-iodo-5,7-dimethylundeca-8,10-dien-4-yloxy)(*tert*-butyl)dimethylsilane (39**):**

A solution of the alcohol **38** (1.10 g, 2.38 mmol) in benzene (15 mL) and diethyl ether (30 mL) at ambient temperature was treated with triphenylphosphine (0.93 g, 3.56 mmol) and imidazole (0.24 g, 3.56 mmol). Then, iodine (0.90 g, 3.56 mmol) was added to the vigorously stirred mixture portionwise over 10 min. After 30 min, the mixture was diluted with EtOAc (50 mL), quenched with sat. aq. Na₂S₂O₃ (50 mL), and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with sat. aq. Na₂S₂O₃, brine, dried (MgSO₄) and concentrated. Purification by column chromatography (19:1 hexanes/EtOAc) provided the title compound (1.26 g, 93%) as a colorless oil: IR (NaCl) 2955, 2928, 1514, 1249, 835 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.30 (d, *J* = 8.4 Hz, 2H), 6.89 (d, *J* = 8.5 Hz, 2H), 6.60 (dt, *J* = 10.4, 16.9 Hz, 1H), 6.04 (t, *J* = 11.0 Hz, 1H), 5.58 (t, *J* = 10.5 Hz, 1H), 5.25 (d, *J* = 16.8 Hz, 1H), 5.16 (d, *J* = 10.0 Hz, 1H), 4.60 (d, *J* = 10.5 Hz, 1H), 4.51 (d, *J* = 10.5 Hz, 1H), 3.81 (s, 3H), 3.67 (m, 1H), 3.36 (dd, *J* = 3.6, 7.2 Hz, 1H), 3.11 (t, *J* = 6.3 Hz, 2H), 2.99 (m, 1H), 1.66 (m, 3H), 1.58 (m, 2H), 1.12 (d, *J* = 6.8 Hz, 3H), 0.99 (d, *J* = 6.8 Hz, 3H), 0.94 (s, 9H), 0.01 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 159.3, 134.9, 132.5, 131.5, 129.4, 129.3, 117.9, 114.0, 84.1, 75.1, 71.9, 55.5, 40.9, 35.8, 35.6, 29.6, 26.2, 19.0, 18.4, 9.8, 7.4, -3.4, -4.1; LRMS (EI) 515 [M - *tert*-Bu]⁺; HRMS (EI) calcd. for C₂₃H₃₆IO₃Si 515.147851, found 515.14812; [α]_D²⁰ +24.6 (*c* 0.15, CHCl₃).



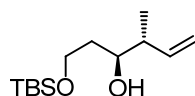
((4*R*,5*R*,6*S*,7*S*,*Z*)-6-(4-Methoxybenzyloxy)-4-(*tert*-butyldimethylsilyloxy)-5,7-dimethylundeca-8,10-dienyl)triphenylphosphonium iodide (20):

A solution of the iodide **39** (1.26 g, 2.20 mmol) in benzene (8 mL) at ambient temperature was treated with triphenylphosphine (2.97 g, 11.0 mmol). The mixture was heated at 80 °C for 16 h in the dark. After concentration under vacuum, purification by column chromatography (19:1 CH₂Cl₂/MeOH) provided the title compound (1.42 g, 78%) as a white solid: IR (NaCl) 2955, 2928, 2855, 1513, 1438, 1248, 1112 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.86–7.73 (m, 15H), 7.29 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.3 Hz, 2H), 6.59 (dt, *J* = 10.6, 16.8 Hz, 1H), 5.91 (t, *J* = 10.9 Hz, 1H), 5.60 (t, *J* = 10.4 Hz, 1H), 5.06 (d, *J* = 15.8 Hz, 1H), 5.01 (d, *J* = 9.4 Hz, 1H), 4.64 (d, *J* = 11.0 Hz, 1H), 4.47 (d, *J* = 11.0 Hz, 1H), 3.78 (s, 3H), 3.68 (dd, *J* = 7.2, 12.2 Hz, 1H), 3.59 (q, *J* = 5.0 Hz, 1H), 3.47 (t, *J* = 5.0 Hz, 1H), 3.39 (dd, *J* = 7.2, 12.5 Hz, 1H), 2.95 (m, 1H), 1.96 (m, 1H), 1.77 (m, 1H), 1.58 (m, 3H), 1.03 (d, *J* = 6.7 Hz, 3H), 0.93 (d, *J* = 6.6 Hz, 3H), 0.83 (s, 9H), 0.04 (s, 3H), –0.04 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 159.1, 135.8, 135.5, 135.4, 133.9, 133.8, 132.6, 131.8, 130.9, 130.7, 129.4, 128.9, 128.5, 118.8, 117.7, 117.5, 113.9, 83.4, 74.6, 72.6, 55.6, 40.5, 36.0, 35.6, 35.4, 26.2, 23.9, 23.3, 18.7, 18.5, 18.3, 10.2, –3.5, –4.1; LRMS (ESI) 707 [M]⁺; HRMS (ESI) calcd. for C₄₅H₆₀O₃PSi 707.4049, found 707.4058; [α]_D²⁰ +23.3 (*c* 2.7, CHCl₃).



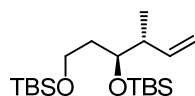
3-(*tert*-Butyldimethylsilyloxy)propanal (41):

Following the procedure for the same compound in reference 51, propandiol (4.5 mL, 61.0 mmol) was protected with TBSCl (9.5 g, 61.0 mmol), NaH (95 wt. %, 1.7 g, 67.1 mol) to give the crude alcohol (11.9 g). The alcohol was oxidized with TEMPO (95 mg, 0.61 mmol), KBr (15.0 g, 41.2 mmol), KHCO₃ (67.0 g) and bleach (6.15% in H₂O, 99.0 g) to give the title aldehyde (8.68 g, 76% yield, two steps).



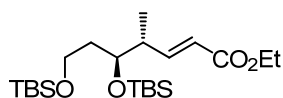
(3*S*,4*R*)-1-(*tert*-Butyldimethylsilyloxy)-4-methylhex-5-en-3-ol (42):

Following the procedure for the same compound in reference 22b, the aldehyde **41** (5.13 g, 27.1 mmol) was reacted with K(*Ot*-Bu) (4.20 g, 37.4 mmol), *trans*-2-butene (6.7 mL, 74.2 mmol), (+)-(ipc)₂-B-OMe (12.0 g, 37.9 mmol), BF₃•OEt (5.1 mL, 40.0 mmol), BuLi (1.6 M in hexane, 25.0 mL, 40.0 mL) to give the title alcohol (4.6 g, 69% yield).



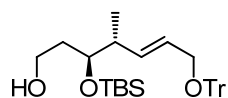
(*S*)-5-((*R*)-But-3-en-2-yl)-2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecane (43):

Following the procedure for the same compound in reference 22b, the alcohol **42** (9.0 g, 36.8 mmol) was protected with TBSCl (7.5 g, 47.9 mmol), imidazole (5.1 g, 73.6 mmol), DMAP (0.5 g, 3.7 mmol) to give the title TBS ether (12.5 g, 95% yield).



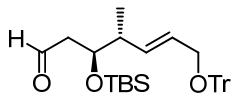
(4*R*,5*S*,*E*)-Ethyl 5,7-bis(*tert*-butyldimethylsilyloxy)-4-methylhept-2-enoate (44):

Following the procedure for the same compound in references 22b, the alkene **43** (24.5 g, 68.4 mmol) was oxidatively cleaved with OsO₄ (2.5 wt. % in *t*-BuOH, 27.8 mL, 2.7 mmol), NMO (17.6 g, 150.5 mmol) and NaIO₄ (17.5 g, 82.1 mmol) to give the crude aldehyde (22.8 g). The aldehyde (22.8 g) was reacted with ethyl 2-(diethoxyphosphoryl)acetate (72.1 g, 355.9 mmol), and NaH (95 wt. %, 7.19 g, 284.8 mmol) to give the ester (23.8 g, 78% yield).



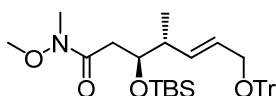
(3*S*,4*R*,*E*)-3-(*tert*-Butyldimethylsilyloxy)-4-methyl-7-(trityloxy)hept-5-en-1-ol (46):

Following the procedure for the same compound in reference 22b, the ester **44** (15.8 g, 36.7 mmol) was reduced with DIBAL-H (1.0 M in hexane, 80.7 mL, 80.7 mmol) to give the crude alcohol (14.5 g). Next, the alcohol was protected with TrCl (11.5 g, 40.4 mmol) and DMAP (3.7 mmol, 0.5 g) to give the crude ether **45** (23.0 g). Next, the crude ether **45** was deprotected with HF•pyr in pyridine/THF(630 mL, made with HF•pyr (60%, 42 mL), pyridine (168 mL) and THF (420 mL)) to give the title alcohol (8.1 g, 45% yield, three steps from the ester **44**).



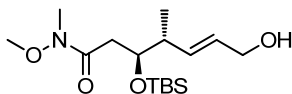
(3*S*,4*R*,*E*)-3-(*tert*-Butyldimethylsilyloxy)-4-methyl-7-(trityloxy)hept-5-enal (47):

Following the procedure for the same compound in reference 22b, the alcohol **46** (7.5 g, 14.5 mmol) was oxidized with SO₃•pyr (9.4 g, 58.0 mmol), DMSO (20.6 mL, 290.0 mmol), Et₃N (14.2 mL, 101.5 mmol) to give the title aldehyde (6.5 g, 87% yield).



(3*S*,4*R*,*E*)-3-(*tert*-Butyldimethylsilyloxy)-*N*-methoxy-*N*,4-dimethyl-7-(trityloxy)hept-5-enamide (18):

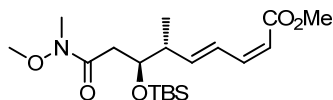
Following the procedure for the same compound in reference 22b, the aldehyde **47** (6.5 g, 13.3 mmol) was oxidized with NaClO₂ (4.5 g, 39.9 mmol), NaH₂PO₄•H₂O (5.5 g, 39.9 mmol), 2-methyl-2-butene (2 M in THF, 66.6 mL, 133.0 mmol) to give the crude carboxylic acid (7.5 g). The carboxylic acid was coupled with *N,O*-dimethylhydroxylamine hydrochloride (1.6 g, 15.9 mmol) by using DCC (3.3 g, 15.9 mmol), DMAP (0.2 g, 1.3 mmol) and Et₃N (2.8 mL, 19.9 mmol) to give the Weinreb amide (5.5 g, 75% yield).



(3*S*,4*R*,*E*)-3-(*tert*-Butyldimethylsilyloxy)-7-hydroxy-*N*-methoxy-*N*,4-dimethylhept-5-enamide (56):

A solution of the trityl ether **18** (5.00 g, 8.71 mmol) in CH₂Cl₂ (87 mL) at -5 °C was treated with a solution of ZnBr₂ (9.80 g, 43.51 mmol) in MeOH (12 mL) and CH₂Cl₂ (65 mL)

dropwise over 30 min. The reaction mixture was stirred at 0 °C for 1 h and at ambient temperature for 1 h. The mixture was cooled to -10 °C, and solid ZnBr₂ (14.70 g, 65.28 mmol) was added portionwise over 5 min. The mixture was warmed to ambient temperature and stirred for 1 h. After quenching by addition of sat. aq. NaHCO₃ (50 mL), the mixture was extracted with CH₂Cl₂ (3 × 50 mL) and the combined organic layers were washed with brine, dried (MgSO₄) and concentrated. Purification by column chromatography (1:2 hexanes/EtOAc) provided the title compound (2.63 g, 91%) as a colorless oil: IR (NaCl) 3422, 2956, 2929, 2894, 1638, 1077, 836 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 5.67–5.62 (m, 2H), 4.22 (ddd, *J* = 3.3, 5.2, 7.5 Hz, 1H), 4.10–4.06 (m, 2H), 3.66 (s, 3H), 3.14 (s, 3H), 2.59 (m, 1H), 2.43–2.28 (m, 3H), 1.04 (d, *J* = 6.9 Hz, 3H), 0.85 (s, 9H), 0.06 (s, 3H), 0.00 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 172.9, 134.0, 130.3, 72.7, 63.8, 61.5, 42.4, 36.2, 32.3, 26.1, 18.3, 15.3, -4.3, -4.6; LRMS (ESI) 354 [M + Na]⁺; HRMS (ESI) calcd. for C₁₆H₃₃NO₄SiNa 354.2077, found 354.2069; [α]_D²⁰ +20.0 (*c* 0.18, CHCl₃).

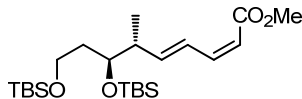


(2Z,4E,6R,7S)-Methyl 7-(*tert*-butyldimethylsilyloxy)-9-(methoxy(methyl)amino)-6-methyl-9-oxonona-2,4-dienoate (22):

A solution of the alcohol **56** (3.85 g, 11.60 mmol) and diisopropylethylamine (5.75 mL, 34.80 mmol) in CH₂Cl₂ (116 mL) and DMSO (23 mL) at 0 °C was treated with a solution of SO₃•pyr (5.54 g, 34.80 mmol) in DMSO (35 mL) dropwise over 15 min, and the reaction mixture was stirred for 1 h. After quenching by addition of brine at 0 °C, the mixture was extracted with diethyl ether (2 × 100 mL). The combined organic layers were washed with sat. aq. CuSO₄ (2 × 100 mL) and brine, dried (MgSO₄) and concentrated. The aldehyde as a pale

yellow oil was used immediately in the next step without further purification: ^1H NMR (300 MHz, CDCl_3) δ 9.55 (d, $J = 7.9$ Hz, 1H), 6.90 (dd, $J = 7.9, 15.8$ Hz, 1H), 6.11 (ddd, $J = 1.0, 7.8, 15.7$ Hz, 1H), 4.33 (dt, $J = 3.0, 6.4$ Hz, 1H), 3.65 (s, 3H), 3.16 (s, 3H), 2.75–2.58 (m 2H), 2.38 (dd, $J = 6.3, 15.6$ Hz, 1H), 1.18 (d, $J = 6.8$ Hz, 3H), 0.90 (s, 9H), 0.13 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 193.8, 171.8, 159.4, 133.5, 72.0, 61.4, 60.3, 42.9, 37.5, 32.1, 26.0, 18.2, 15.8, –4.3, –4.7.

A mixture of bis(2,2,2-trifluoroethyl) (methoxycarbonylmethyl)phosphate **14** (2.75 mL, 12.32 mmol) and 18-crown-6 (14.80 g, 60.00 mol) in THF (112 mL) at -78 °C was treated with a 1.0 M solution of sodium bis(trimethylsilyl)amide in THF (13.40 mL, 13.40 mmol) dropwise over 13 min. The mixture was stirred at 0 °C for 45 min, cooled to -78 °C. A solution of the crude aldehyde in THF (24 mL) was added dropwise over 20 min and the mixture was stirred at -78 °C for 3 h and at -40 °C for 10 h. After quenching by addition of sat. aq. NH_4Cl , the mixture was extracted with EtOAc (3×100 mL) and the combined organic layers were washed with brine, dried (MgSO_4) and concentrated. Purification by column chromatography (4:1 hexanes/EtOAc) provided the title compound (3.01 g, 70% over two steps) as a colorless oil: IR (NaCl) 2955, 2895, 2856, 1721, 1666, 1439, 1196, 836 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.38 (dd, $J = 11.2, 15.4$ Hz, 1H), 6.57 (t, $J = 11.3$ Hz, 1H), 6.09 (dd, $J = 8.0, 15.4$ Hz, 1H), 5.60 (d, $J = 11.3$ Hz, 1H), 4.29 (ddd, $J = 3.2, 5.1, 7.4$ Hz, 1H), 3.72 (s, 3H), 3.65 (s, 3H), 3.17 (s, 3H), 2.68–2.48 (m, 2H), 2.33 (dd, $J = 5.2, 15.4$ Hz, 1H), 1.13 (d, $J = 6.8$ Hz, 3H), 0.88 (s, 9H), 0.09 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 172.6, 167.1, 146.7, 145.6, 127.6, 115.9, 72.6, 61.5, 51.3, 43.4, 37.1, 26.1, 18.3, 15.8, –4.2, –4.6; LRMS (ESI) 408 $[\text{M} + \text{Na}]^+$; HRMS (ESI) calcd. for $\text{C}_{19}\text{H}_{35}\text{NO}_5\text{SiNa}$ 408.2182, found 408.2177; $[\alpha]_{\text{D}}^{20}$ –53.6 (c 0.33, CHCl_3).

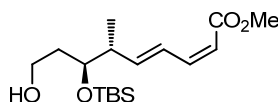


(2Z,4E,6R,7S)-Methyl 7,9-bis(*tert*-butyldimethylsilyloxy)-6-methylnona-2,4-dienoate (58):

Cross metathesis reaction. A mixture of the alkene **43** (180 mg, 0.491 mmol) and crotonaldehyde (80 μ L, 0.982 mmol) in degassed CH_2Cl_2 (5 mL, argon sparged) was refluxed for 15 min, then cooled to ambient temperature. Grubbs second generation catalyst **49** (12.5 mg, 0.015 mmol) was added and the mixture was refluxed at 50 $^\circ\text{C}$. Two portions of Grubbs second generation catalyst (4.2 mg, 0.005 mmol) were added every 12 h. After 36 h, the mixture was concentrated under vacuum. Purification by column chromatography (4:1 hexanes/diethyl ether) provided the aldehyde **57** (150 mg, 77%) as a colorless oil, which was used immediately in the next step: ^1H NMR (300 MHz, CDCl_3) δ 9.58 (d, $J = 7.9$ Hz, 1H), 6.93 (dd, $J = 7.6, 15.8$ Hz, 1H), 6.18 (dd, $J = 7.9, 15.8$ Hz, 1H), 3.96 (m, 1H), 3.72 (t, $J = 5.9$ Hz, 1H), 2.72 (m, 1H), 1.82–1.55 (m, 2H), 1.21 (d, $J = 6.8$ Hz, 3H), 0.98 (s, 9H), 0.96 (s, 9H), 0.15 (s, 3H), 0.14 (s, 3H), 0.11 (s, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ 194.0, 160.5, 133.2, 72.4, 59.6, 42.6, 37.7, 26.1, 18.4, 18.3, 15.5, –4.2, –4.3, –5.4.

Formation of the dienoate. A mixture of bis(2,2,2-trifluoroethyl) (methoxycarbonylmethyl)phosphonate **14** (0.97 mL, 4.56 mmol) and 18-crown-6 (5.02 g, 19.00 mol) in THF (19 mL) at -78 $^\circ\text{C}$ was treated with a 0.5 M solution of potassium bis(trimethylsilyl)amide in toluene (11.40 mL, 5.70 mmol) dropwise over 12 min. The mixture was stirred at -45 $^\circ\text{C}$ for 1 h, cooled to -78 $^\circ\text{C}$. A solution of the aldehyde **57** (1.47 g, 3.80 mmol) in THF (4 mL) was added. The mixture was stirred to -78 $^\circ\text{C}$ for 5.5 h and warmed to ambient temperature over 30 min. After quenching by addition of sat. aq. NH_4Cl (50 mL), the mixture was extracted with EtOAc (3×50 mL) and the combined organic layers were washed with brine, dried (MgSO_4) and concentrated.

Purification by column chromatography (95:5 hexanes/EtOAc) provided the title compound (1.68 g, 100%) as a colorless oil: IR (NaCl) 2954, 2857, 1721, 1175, 1097, 835, 775 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.23 (ddd, $J = 0.9, 11.3, 15.4$ Hz, 1H), 6.44 (t, $J = 11.2$ Hz, 1H), 5.93 (dd, $J = 7.9, 15.3$ Hz, 1H), 5.46 (d, $J = 11.3$ Hz, 1H), 3.69 (m, 1H), 3.60 (s, 1H), 3.52 (dt, $J = 2.0, 6.5$ Hz, 1H), 2.37 (m, 1H), 1.56–1.39 (m, 3H), 0.96 (d, $J = 6.8$ Hz, 3H), 0.80–0.74 (m, 18H), –0.06 (s, 6H), –0.08 (s, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ 167.1, 147.6, 145.8, 127.1, 115.6, 72.6, 60.0, 51.2, 42.9, 37.4, 26.1, 18.5, 18.3, 15.7, –4.1, –5.0; $[\alpha]_{\text{D}}^{20}$ –6.6 (c 0.36, CHCl_3).



(2Z,4E,6R,7S)-Methyl 7-(*tert*-butyldimethylsilyloxy)-9-hydroxy-6-methylnona-2,4-dienoate (59):

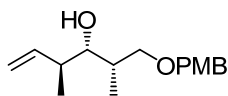
A solution of the TBS ether **58** (0.80 g, 1.75 mmol) in THF (9 mL) at 0 °C was treated with a solution of HF•pyr in pyr/THF (39 mL, prepared by slow addition of HF•pyr (3 mL) to a solution of pyridine (12mL) and THF (24 mL)) dropwise. The reaction mixture was warmed to ambient temperature and stirred for 8 h. After quenching by addition of sat. aq. NaHCO_3 , the mixture was extracted with EtOAc (4 × 40 mL). The combined organic layers were washed with sat. aq. CuSO_4 (3 × 30 mL), brine, dried (MgSO_4) and concentrated. Purification by column chromatography (2:1 hexanes/EtOAc) provided the title compound (0.54 g, 92%) as a colorless oil: IR (NaCl) 3428, 2953, 2857, 1719, 1412, 1196, 1176, 837 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.33 (dd, $J = 11.3, 15.4$ Hz, 1H), 6.53 (t, $J = 11.3$ Hz, 1H), 5.97 (dd, $J = 7.8, 15.4$ Hz, 1H), 5.59 (d, $J = 11.3$ Hz, 1H), 3.83 (dt, $J = 4.5, 7.0$ Hz, 1H), 3.73–3.65 (m, 5H), 2.53 (m, 1H), 2.16 (s, 1H), 1.73–1.57 (m, 2H), 1.06 (d, $J = 6.8$ Hz, 3H), 0.87 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H); ^{13}C

NMR (75 MHz, CDCl₃) δ 166.8, 147.2, 145.5, 126.8, 115.5, 73.2, 59.4, 51.0, 42.7, 36.0, 25.8, 18.0, 15.0, -4.4, -4.5; $[\alpha]_D^{20}$ -14.3 (*c* 0.21, CHCl₃).

Synthesis of the Weinreb amide 22 from the alcohol 59. A solution of the alcohol **59** (0.52 g, 1.58 mmol) and triethylamine (0.66 mL, 4.74 mmol) in CH₂Cl₂ (4 mL) and DMSO (2 mL) at 0 °C was treated with a solution of SO₃•pyr (0.63 g, 3.96 mmol) in DMSO (5 mL) dropwise over 2 min, and the reaction mixture was stirred for 1 h. After quenching by addition of water (50 mL), the mixture was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with sat. aq. CuSO₄ (2 × 30 mL) and brine, dried (MgSO₄) and concentrated. Purification by column chromatography (9:1 hexanes/EtOAc) provided the aldehyde **60** (0.47 g, 91%) as a pale yellow oil, which was used immediately in the next step: ¹H NMR (300 MHz, CDCl₃) δ 9.78 (dd, *J* = 1.7, 2.5 Hz, 1H), 7.39 (ddd, *J* = 1.1, 11.2, 15.4 Hz, 1H), 6.56 (dt, *J* = 0.7, 11.3 Hz, 1H), 6.02 (dd, *J* = 7.6, 15.6 Hz, 1H), 5.65 (d, *J* = 11.3 Hz, 1H), 4.22 (ddd, *J* = 4.0, 4.9, 6.8 Hz, 1H), 3.75 (s, 3H), 2.63–2.42 (m, 3H), 1.11 (d, *J* = 6.8 Hz, 3H), 0.88 (s, 9H), 0.09 (s, 3H), 0.05 (s, 3H).

A mixture of the aldehyde **60** (0.43 g, 1.32 mmol) and NaH₂PO₄•H₂O (1.09 g, 7.92 mmol) in *t*-BuOH (97 mL) and H₂O (32 mL) at 0 °C was treated with a 2.0 M solution of 2-methyl-2-butene in THF (33.0 mL, 66.00 mmol), then NaClO₄ (0.35 g, 3.96 mmol) was added. The reaction mixture was stirred at 0 °C for 15 min and at ambient temperature for 2 h. After quenching by addition of a mixture of sat. aq. NH₄Cl (20 mL) and brine (20 mL), the mixture was extracted with diethyl ether (4 × 80 mL). The combined organic layers were washed with brine, dried (MgSO₄) and concentrated. The carboxylic acid as a pale yellow oil was used immediately in the next step without further purification.

A solution of the carboxylic acid (0.43 g, 1.32 mmol) in CH₂Cl₂ (8.4 mL) at 0 °C was treated with triethylamine (0.35 mL, 2.50 mmol), *N,O*-dimethylhydroxylamine hydrochloride (0.16 g, 1.67 mmol), and DCC (0.34 g, 1.67 mmol). The reaction mixture was warmed to ambient temperature and stirred for 12 h. The reaction mixture was concentrated under vacuum. Purification by column chromatography (2:1 hexanes/EtOAc) provided the title compound as a colorless oil (0.36 g, 70% for two steps). The ¹H NMR spectrum of the product was consistent with that of the Weinreb amide **16**.

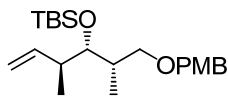


(2*S*,3*S*,4*S*)-1-(4-Methoxybenzyloxy)-2,4-dimethylhex-5-en-3-ol (63).

A solution of the alcohol **61** (4.20 g, 20.0 mmol) and diisopropylethylamine (9.90 mL, 60.0 mmol) in CH₂Cl₂ (200 mL) and DMSO (40 mL) at 0 °C was treated with a solution of SO₃•pyr (9.74 g, 60.0 mmol) in DMSO (60 mL) dropwise over 20 min. The reaction mixture was stirred for 1 h. After quenching by addition of H₂O (200 mL), the mixture was extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with sat. aq. CuSO₄ (2 × 50 mL) and brine, dried (MgSO₄). The concentration under vacuum provided the aldehyde as a colorless oil, which was used immediately in the next step without further purification.

A 1.0 M solution of (*R,R*)-diisopropyl tartrate (*E*)-crotylboronate **62** in toluene (28.16 mL, 28.16 mmol) was added to a slurry of powdered 4 Å molecular sieves (0.8 g) in toluene (17 mL) at ambient temperature. After 20 min, the mixture was cooled to -78 °C, then a solution of the aldehyde (4.20 g, 20.0 mmol) in toluene (17 mL) was added via cannula over 50 min. After 8 h, the reaction mixture was quenched by 1 M NaOH (60 mL), stirred vigorously for 30 min and

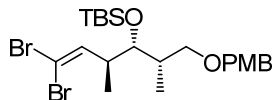
extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with brine, dried (MgSO₄) and concentrated. Purification by column chromatography (4:1 hexanes/EtOAc) provided the title compound (3.54 g, 67% for two steps) as a colorless oil: IR (NaCl) 3479, 2966, 2932, 1613, 1513, 1248, 1036 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.25 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 5.80 (ddd, *J* = 8.4, 10.2, 17.1 Hz, 1H), 5.17–5.06 (m, 2H), 4.45 (s, 2H), 3.80 (s, 3H), 3.58–3.43 (m, 3H), 2.28 (m, 1H), 1.97 (m, 1H), 0.98 (d, *J* = 6.8 Hz, 3H), 0.94 (d, *J* = 6.9 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 159.5, 142.1, 130.7, 129.4, 115.8, 114.1, 75.9, 74.7, 73.2, 55.5, 42.1, 35.4, 16.9, 10.2; [α]_D²⁰ -2.4 (*c* 1.08, CHCl₃).



((2*S*,3*S*,4*S*)-1-(4-Methoxybenzyloxy)-2,4-dimethylhex-5-en-3-yloxy)(*tert*-butyl)dimethylsilane (64):

Following the procedure for the TBS ether **34**, the alcohol **63** (3.50 g, 13.2 mmol) in CH₂Cl₂ (130 mL) was protected with 2,6-lutidine (4.0 mL, 17.2 mmol) and TBSOTf (4.6 mL, 39.6 mmol) for 1 h. Purification by column chromatography (95:5 hexanes/EtOAc) provided the title compound (4.07 g, 82%) as a colorless oil: IR (NaCl) 2957, 2929, 2856, 1513, 1249, 1039, 836 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.27 (d, *J* = 7.6 Hz, 2H), 6.89 (d, *J* = 8.5 Hz, 2H), 5.86 (ddd, *J* = 7.7, 10.2, 17.8 Hz, 1H), 5.01–4.94 (m, 2H), 4.43 (d, *J* = 11.5 Hz, 1H), 4.38 (d, *J* = 11.5 Hz, 1H), 3.81 (s, 3H), 3.65 (dd, *J* = 3.4, 4.6 Hz, 1H), 3.37 (dd, *J* = 6.6, 9.0 Hz, 1H), 3.22 (dd, *J* = 6.8, 8.8 Hz, 1H), 2.35 (m, 1H), 1.94 (m, 1H), 1.01 (d, *J* = 6.9 Hz, 3H), 0.91–0.89 (m, 12H), 0.04 (s, 3H), 0.02 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 159.1, 142.0, 130.9, 129.2, 114.1, 113.8,

76.0, 73.4, 72.5, 55.3, 42.9, 37.2, 26.2, 18.5, 17.4, 12.4, -3.5, -3.9; LRMS (ESI) 401 [M + Na]⁺; HRMS (ESI) calcd. for C₂₂H₃₈O₃Si Na 401.2488, found 401.2481; [α]_D²⁰ -5.0 (c 0.20, CHCl₃).

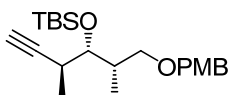


((2S,3S,4S)-1-(4-Methoxybenzyloxy)-6,6-dibromo-2,4-dimethylhex-5-en-3-yloxy)(tert-butyl)dimethylsilane (65):

Oxidative cleavage of the alkene 64. A solution of the alkene **64** (4.00 g, 10.56 mmol) in dioxane (75 mL) and H₂O (25 mL) at ambient temperature was treated with 2,6-lutidine (2.5 mL, 21.12 mmol), OsO₄ (2.5% in 2-methyl-2-propanol, 2.2 mL, 0.02 mmol), and NaIO₄ (9.00 g, 42.24 mmol). After 5 h, additional OsO₄ (2.5% in 2-methyl-2-propanol, 1.1 mL, 0.01 mmol) was added and the mixture was stirred for 1 h. After quenching by addition of sat. aq. Na₂S₂O₃ (50 mL), the mixture was extracted with CH₂Cl₂ (3 × 50 mL) and the combined organic layers were washed with brine, dried (MgSO₄) and concentrated. The aldehyde as a pale yellow oil was used immediately in the next step without further purification.

Formation of the vinyl dibromide. A solution of PPh₃ (11.08 g, 42.24 mmol) in CH₂Cl₂ (35 mL) at 0 °C was treated with CBr₄ (7.00 g, 21.12 mmol) portionwise over 7 min. After 10 min, 2,6-lutidine (6.1 mL, 52.80 mmol) was added and the mixture was stirred for 10 min. A solution of the aldehyde in CH₂Cl₂ (20 mL) was added and the mixture was stirred for 1 h. After quenching by addition of sat. aq. NH₄Cl (50 mL), the mixture was extracted with CH₂Cl₂ (2 × 50 mL) and the combined organic layers were washed with brine, dried (MgSO₄) and concentrated. Purification by column chromatography (95:5 hexanes/EtOAc) provided the title compound (4.20 g, 74% for two steps) as a colorless oil: IR (NaCl) 2955, 2930, 2856, 1513, 1249, 1038,

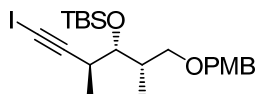
838 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.27 (d, $J = 8.5$ Hz, 2H), 6.90 (d, $J = 8.6$ Hz, 2H), 6.4 (d, $J = 9.5$ Hz, 1H), 4.44 (d, $J = 11.6$ Hz, 1H), 4.39 (d, $J = 11.6$ Hz, 1H), 3.81 (s, 3H), 3.69 (t, $J = 3.9$ Hz, 1H), 3.38 (dd, $J = 6.1, 8.9$ Hz, 1H), 3.21 (dd, $J = 7.0, 8.9$ Hz, 1H), 2.62 (m, 1H), 1.89 (m, 1H), 1.00 (d, $J = 7.0$ Hz, 3H), 0.93–0.90 (m, 12H), 0.07 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 159.2, 141.7, 130.7, 129.4, 113.8, 88.0, 75.8, 72.7, 72.4, 55.4, 42.6, 38.5, 26.2, 26.1, 18.4, 17.2, 12.5, -3.7 , -3.8 ; LRMS (ESI) 559 $[\text{M} + \text{Na}]^+$; HRMS (ESI) calcd. for $\text{Br}_2\text{C}_{22}\text{H}_{36}\text{O}_3\text{SiNa}$ 557.0698, found 557.0715; $[\alpha]_{\text{D}}^{20} +3.7$ (c 0.27, CHCl_3).



((2S,3S,4S)-1-(4-Methoxybenzyloxy)-2,4-dimethylhex-5-yn-3-yloxy)(tert-butyl)dimethylsilane (21):

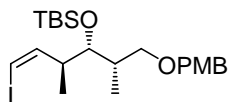
A solution of the vinyl dibromide **65** (6.43 g, 12.00 mmol) in THF (60 mL) at -78 $^{\circ}\text{C}$ was treated with a 1.6 M solution of BuLi in hexane (18.75 mL, 30.00 mmol) dropwise over 10 min. After 30 min, an additional solution of BuLi (9.3 mL, 14.88 mmol) was added and the mixture was stirred for 2.5 h. After quenching by addition of sat. aq. NH_4Cl (50 mL) at -78 $^{\circ}\text{C}$, the mixture was extracted with EtOAc (3×50 mL) and the combined organic layers were washed with brine, dried (MgSO_4) and concentrated. Purification by column chromatography (95:5 hexanes/EtOAc) provided the title compound (4.36 g, 96%) as a colorless oil: IR (NaCl) 3309, 2955, 2930, 2856, 1513, 1249, 1055, 836 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.28 (d, $J = 8.7$ Hz, 2H), 6.89 (d, $J = 8.7$ Hz, 2H), 4.42 (s, 2H), 3.81 (s, 3H), 3.79 (dd, $J = 3.3, 5.1$ Hz, 1H), 3.45 (dd, $J = 6.8, 9.2$ Hz, 1H), 3.29 (dd, $J = 6.6, 9.2$ Hz, 1H), 2.62 (m, 1H), 2.21 (m, 1H), 2.04 (d, $J = 2.5$ Hz, 1H), 1.20 (d, $J = 7.1$ Hz, 3H), 0.98–0.89 (m, 12H), 0.09 (s, 3H), 0.05 (s, 3H); ^{13}C NMR

(75 MHz, CDCl₃) δ 159.2, 130.9, 129.3, 113.8, 87.4, 74.5, 73.2, 72.5, 70.1, 55.3, 37.0, 31.7, 26.2, 18.5, 17.5, 12.2, -3.7, -4.0; LRMS (ESI) 399 [M + Na]⁺; HRMS (ESI) calcd. for C₂₂H₃₆O₃SiNa 399.2331, found 399.2336; [α]_D²⁰ +2.2 (*c* 0.23, CHCl₃).



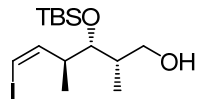
((2*S*,3*S*,4*S*)-1-(4-Methoxybenzyloxy)-6-iodo-2,4-dimethylhex-5-yn-3-yloxy)(*tert*-butyl)dimethylsilane (81**):**

A solution of the alkyne **21** (3.50 g, 9.29 mmol) in THF (46 mL) at -50 °C was treated with a 1.6 M solution of BuLi in hexane (7.00 mL, 11.15 mmol) dropwise over 7 min. After 1 h, a solution of I₂ (4.00 g, 15.79 mmol) in THF (4 mL) was added. The mixture was stirred for 20 min, warmed to ambient temperature over 30 min. After quenching by addition of a mixture of sat. aq. Na₂S₂O₃ (25 mL) and brine (25 mL), the mixture was extracted with EtOAc (3 × 50 mL) and the combined organic layers were washed with brine, dried (MgSO₄) and concentrated. Purification by column chromatography (95:5 hexanes/EtOAc) provided the title compound (4.60 g, 99%) as a colorless oil: IR (NaCl) 2930, 2881, 2855, 1612, 1513, 1462, 1248, 1062, 837 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.28 (d, *J* = 8.4 Hz, 2H), 6.90 (d, *J* = 8.5 Hz, 2H), 4.42 (s, 2H), 3.81 (s, 3H), 3.75 (dd, *J* = 3.0, 5.5 Hz, 1H), 3.43 (dd, *J* = 7.0, 9.0 Hz, 1H), 3.26 (dd, *J* = 6.6, 9.0 Hz, 1H), 2.76 (m, 1H), 2.04 (m, 1H), 1.18 (d, *J* = 7.1 Hz, 3H), 0.93–0.85 (m, 12H), 0.09 (s, 3H), 0.04 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 159.2, 130.8, 129.3, 113.8, 97.8, 74.8, 73.0, 72.5, 55.3, 36.9, 34.0, 26.2, 18.5, 17.7, 11.7, -3.7, -4.0, -4.4; LRMS (EI) 445 [M - *tert*-Bu]⁺; HRMS (EI) calcd. for C₁₈H₂₆O₃SiI 445.0696, found 445.0672; [α]_D²⁰ -3.3 (*c* 0.42, CHCl₃).



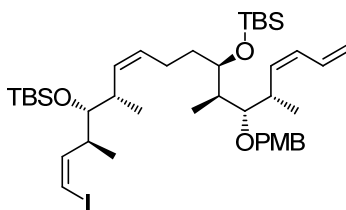
((2*S*,3*S*,4*S*,*Z*)-1-(4-Methoxy)benzyloxy)-6-iodo-2,4-dimethylhex-5-en-3-yloxy)(*tert*-butyl)dimethylsilane (82**):**

A solution of the iodoalkyne **81** (3.50 g, 9.29 mmol) in THF (20 mL) and *i*-PrOH (20 mL) at ambient temperature was treated with triethylamine (1.70 mL, 12.21 mmol) and *o*-nitrobenzenesulfonylhydrazide (2.30 g, 10.58 mmol). After 12 h, additional triethylamine (0.79 mL, 5.69 mmol) and *o*-nitrobenzenesulfonylhydrazide (1.06 g, 4.88 mmol) were added and the mixture was stirred for 12 h. After quenching by addition of H₂O (50 mL), the mixture was extracted with EtOAc (3 × 50 mL) and the combined organic layers were washed with brine, dried (MgSO₄) and concentrated. Purification by column chromatography (95:5 hexanes/EtOAc) provided the title compound (3.90 g, 95%) as a colorless oil: IR (NaCl) 2955, 2929, 2855, 1513, 1249, 1039, 837, 773 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.27 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 6.24 (dd, *J* = 7.3, 8.8 Hz, 1H), 6.13 (d, *J* = 7.3 Hz, 1H), 4.61 (s, 2H), 3.81 (s, 3H), 3.74 (t, *J* = 3.8 Hz, 1H), 3.40 (dd, *J* = 5.8, 9.0 Hz, 1H), 3.21 (dd, *J* = 7.1, 9.0 Hz, 1H), 2.69 (m, 1H), 1.90 (m, 1H), 1.00 (d, *J* = 7.0 Hz, 3H), 0.94 (d, *J* = 6.9 Hz, 3H), 0.90 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 159.2, 144.0, 130.9, 129.3, 113.8, 81.8, 76.0, 72.7, 55.3, 43.8, 38.9, 26.3, 18.5, 17.7, 13.4, -3.5, -3.7; LRMS (EI) 447 [M - *tert*-Bu]⁺; HRMS (EI) calcd. for C₁₈H₂₈IO₃Si 447.0853, found 447.0851; [α]_D²⁰ +32.4 (*c* 0.61, CHCl₃).



(2*S*,3*S*,4*S*,*Z*)-3-(*tert*-Butyldimethylsilyloxy)-6-iodo-2,4-dimethylhex-5-en-1-ol (83):

A mixture of the PMB ether **82** (1.5 g, 2.97 mmol) in CH₂Cl₂ (60 mL) and H₂O (4 mL) at 0 °C was treated with DDQ (0.81 g, 3.56 mmol). After 25 min, additional DDQ (0.24 g, 1.48 mmol) was added and the mixture was stirred for 15 min. After quenching by addition of sat. aq. NaHCO₃ (50 mL), the mixture was extracted with EtOAc (3 × 50 mL) and the combined organic layers were washed with sat. aq. NaHCO₃ and brine, dried (MgSO₄) and concentrated. The residue was diluted with CH₂Cl₂ (15 mL) and MeOH (1.5 mL). The mixture was cooled to 0 °C and NaBH₄ (0.11 g, 2.97 mmol) was added. After 30 min, sat. aq. NH₄Cl (50 mL) was added and the mixture was extracted with EtOAc (3 × 50 mL) and the combined organic layers were washed with brine, dried (MgSO₄) and concentrated. Purification by column chromatography (4:1 hexanes/EtOAc) provided the title compound (1.13 g, 98%) as a colorless oil: IR (NaCl) 3353, 2956, 2929, 2856, 1471, 1461, 1256, 1024, 837, 773 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 6.37 (dd, *J* = 7.4, 9.0 Hz, 1H), 6.18 (d, *J* = 7.3 Hz, 1H), 3.76 (t, *J* = 3.4 Hz, 1H), 3.68 (m, 1H), 3.46 (m, 1H), 2.75 (m, 1H), 2.05–1.88 (m, 2H), 1.05 (d, *J* = 7.0 Hz, 3H), 0.96–0.87 (m, 12H), 0.12 (s, 3H), 0.10 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 143.5, 81.9, 77.5, 65.4, 42.6, 40.9, 26.1, 18.3, 18.2, 13.1, -3.8, -3.9; LRMS (EI) 327 [M - *tert*-Bu]⁺; HRMS (EI) calcd. for C₁₀H₂₀IO₂Si 327.0277, found 327.0286; [α]_D²⁰ +2.3 (*c* 0.57, CHCl₃).

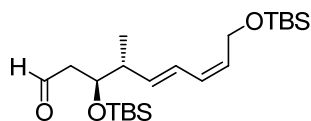


1-(((3Z,5S,6S,7R,8R,11Z,13S,14R,15S,16Z)-8,14-bis(*tert*-Butyldimethylsilyloxy)-17-iodo-5,7,13,15-tetramethylheptadeca-1,3,11,16-tetraen-6-yloxy)methyl)-4-methoxybenzene (76**):**

A solution of the alcohol **83** (0.38 g, 1.00 mmol) in CH₂Cl₂ (10 mL) at 0 °C was treated with Dess-Martin periodinane (0.57 g, 1.30 mmol). The mixture was warmed to ambient temperature and stirred for 1 h. After quenching by addition of a mixture of sat. aq. Na₂S₂O₃ (10 mL) and sat. aq. NaHCO₃ (10 mL), the mixture was extracted with EtOAc (3 × 20 mL) and the combined organic layers were washed with sat. aq. NaHCO₃ (2 × 20 mL) and brine, dried (MgSO₄). The concentration under vacuum provided the aldehyde **77** as a colorless oil, which was used immediately in the next step without further purification: ¹H NMR (300 MHz, CDCl₃) δ 9.77 (s, 1H), 6.27–6.18 (m, 2H), 4.06 (dd, *J* = 3.2, 4.8 Hz, 1H), 2.75 (m, 1H), 2.50 (m, 1H), 1.14 (d, *J* = 6.9 Hz, 3H), 1.06 (d, *J* = 6.9 Hz, 3H), 0.92 (s, 9H), 0.13 (s, 3H), 0.07 (s, 3H).

A solution of the phosphonium salt **20** (0.64 g, 0.77 mmol, dried azeotropically with benzene and at 40 °C for 1 h under vacuum) in THF (2 mL) at 0 °C was treated with a 1.0 M solution of sodium bis(trimethylsilyl)amide in THF (0.71 mL, 0.71 mmol) dropwise over 5 min. The mixture was warmed to ambient temperature and stirred for 45 min. The mixture was cooled to –78 °C and a solution of the aldehyde **77** (0.38 g, 1.00 mmol) in THF (2 mL) was added via cannula over 5 min. The mixture was warmed to ambient temperature and stirred for 4 h. After quenching by addition of sat. aq. NH₄Cl (30 mL), the mixture was extracted with EtOAc (3 × 30 mL) and the combined organic layers were washed with brine, dried (MgSO₄) and concentrated.

Purification by column chromatography (95:5 hexanes/EtOAc) provided the title compound (0.47 g, 82%) as a colorless oil: IR (NaCl) 2956, 2929, 2856, 1514, 1461, 1250, 1078, 1038, 836, 773 cm^{-1} ; ^1H NMR (500 MHz, C_6D_6) δ 7.31 (d, $J = 8.5$ Hz, 2H), 6.82 (d, $J = 8.6$ Hz, 2H), 6.75 (dt, $J = 10.4, 16.7$ Hz, 1H), 6.30 (t, $J = 7.7$ Hz, 1H), 6.08 (t, $J = 11.0$ Hz, 1H), 6.00 (d, $J = 7.3$ Hz, 1H), 5.76 (t, $J = 10.7$ Hz, 1H), 5.41 (dt, $J = 7.0, 10.7$ Hz, 1H), 5.20 (t, $J = 10.3$ Hz, 1H), 5.18 (d, $J = 18.0$ Hz, 1H), 5.11 (d, $J = 10.1$ Hz, 1H), 4.57 (q, $J = 10.6$ Hz, 2H), 3.84 (m, 1H), 3.49 (dd, $J = 3.6, 7.0$ Hz, 1H), 3.38 (dd, $J = 2.5, 7.8$ Hz, 1H), 3.30 (s, 3H), 3.15 (m, 1H), 2.84 (m, 1H), 2.62 (m, 1H), 2.13 (m, 1H), 2.06 (m, 1H), 1.93 (m, 1H), 1.81 (m, 1H), 1.66 (m, 1H), 1.24–1.17 (m, 7 H), 1.07 (d, $J = 6.9$ Hz, 3H), 1.05 (s, 9H), 1.03 (d, $J = 7.1$ Hz, 3H), 0.99 (s, 9H), 0.15 (s, 3H) 0.14 (s, 3H), 0.08 (s, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ 159.3, 143.6, 134.9, 133.3, 132.7, 131.6, 129.5, 129.3, 129.1, 117.6, 114.0, 84.4, 82.2, 79.9, 75.3, 73.0, 55.5, 44.5, 41.0, 37.4, 35.7, 35.6, 26.6, 26.3, 24.1, 19.1, 18.7, 18.6, 18.5, 17.2, 9.8, $-3.0, -3.1, -3.3, -3.9$; LRMS (ESI) 833 $[\text{M} + \text{Na}]^+$; HRMS (ESI) calcd. for $\text{C}_{41}\text{H}_{71}\text{IO}_4\text{Si}_2\text{Na}$ 833.3833, found 833.3850; $[\alpha]_D^{20} +117.8$ (c 0.09, CHCl_3).

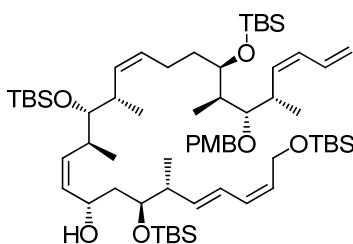


(3*S*,4*R*,5*E*,7*Z*)-3,9-bis(*tert*-Butyldimethylsilyloxy)-4-methylnona-5,7-dienal (70):

A solution of the Weinreb amide **22** (0.37 g, 0.96 mmol) in THF (5 mL) at -78 °C was treated with a 1.0 M solution of diisobutylaluminum hydride in hexane (3.16 mL, 3.16 mmol) dropwise over 3 min, and the reaction mixture was warmed to ambient temperature over 1 h. After quenching by addition of sat. aq. potassium sodium tartrate (7 mL), the mixture was stirred for 1 h at ambient temperature, extracted with CH_2Cl_2 (3×10 mL). The combined organic layers

were washed with brine, dried (MgSO₄) and concentrated. The alcohol as a pale yellow oil was used immediately in the next step without further purification.

A solution of the alcohol and 2,6-lutidine (0.34 mL, 2.88 mmol) in CH₂Cl₂ (10 mL) at –78 °C was treated with TBSOTf (0.28 mL, 1.25 mmol). The reaction mixture was stirred for 1 h. After quenching by addition of sat. aq. NaHCO₃ (10 mL) at –78 °C, the mixture was extracted with CH₂Cl₂ (3 × 10 mL). The combined organic layers were washed with brine, dried (MgSO₄) and concentrated. Purification by column chromatography (4:1 hexanes/EtOAc) provided the title compound (0.38 g, 95% for two steps) as a colorless oil which was used immediately in the next step: ¹H NMR (300 MHz, CDCl₃) δ 9.77 (dd, *J* = 1.8, 2.6 Hz, 1H), 6.28 (dd, *J* = 11.0, 15.1 Hz, 1H), 5.97 (t, *J* = 11.0 Hz, 1H), 5.59 (dd, *J* = 7.9, 15.2 Hz, 1H), 5.54 (dt, *J* = 6.3, 10.9 Hz, 1H), 4.32 (dd, *J* = 1.5, 6.4 Hz, 1H), 4.17 (ddd, *J* = 4.3, 5.0, 6.7 Hz, 1H), 2.58–2.38 (m, 3H), 1.05 (d, *J* = 6.9 Hz, 3H), 0.91–0.86 (m, 18H), 0.09–0.04 (m, 12H).

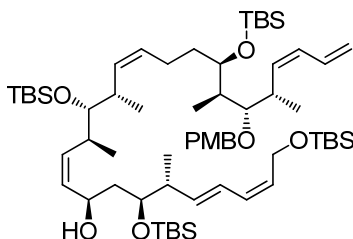


(2Z,4E,6R,7S,9S,10Z,12S,13R,14S,15Z,19R,20R,21S,22S,23Z)-21-(4-Methoxybenzyloxy)-1,7,13,19-tetrakis(*tert*-butyldimethylsilyloxy)-6,12,14,20,22-pentamethylhexacos-2,4,10,15,23,25-hexaen-9-ol (84 α):

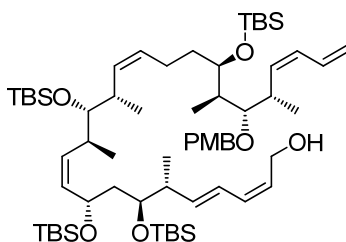
A solution of the vinyl iodide **76** (0.76 g, 0.94 mmol) in diethyl ether (47 mL) at –78 °C was treated with a 1.7 M solution of *tert*-BuLi in pentane (1.26 mL, 2.13 mmol) dropwise over 5 min. After 15 min, a solution of the aldehyde **70** (0.37 g, 0.88 mmol) in diethyl ether (12 mL)

was added via cannula over 10 min. The mixture was warmed to $-10\text{ }^{\circ}\text{C}$ over 1 h. After quenching at $-10\text{ }^{\circ}\text{C}$ by addition of a sat. aq. NH_4Cl (30 mL), the mixture was extracted with diethyl ether ($3 \times 30\text{ mL}$) and the combined organic layers were washed with brine, dried (MgSO_4) and concentrated. The residue was diluted with CH_2Cl_2 (10 mL) and MeOH (1 mL). The mixture was cooled to $0\text{ }^{\circ}\text{C}$ and NaBH_4 (0.10 g, 2.64 mmol) was added. After 30 min, sat. aq. NH_4Cl (30 mL), was added and the mixture was extracted with diethyl ether ($3 \times 30\text{ mL}$) and the combined organic layers were washed with brine, dried (MgSO_4) and concentrated. Purification by column chromatography (15:1 hexanes/ EtOAc) provided the title compound (0.26 g, 27%) as a colorless oil and the less polar C9 β -epimer **84 β** (0.42 g, 43%) as a colorless oil: IR (NaCl) 3493, 2956, 2929, 2856, 1514, 1471, 1462, 1251, 903, 807, 774 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.28 (m, 2H), 6.86 (d, $J = 8.5\text{ Hz}$, 2H), 6.60 (dt, $J = 11.1, 16.7\text{ Hz}$, 1H), 6.27 (dd, $J = 11.0, 15.0\text{ Hz}$, 1H), 6.02 (t, $J = 11.2\text{ Hz}$, 1H), 5.98 (t, $J = 11.1\text{ Hz}$, 1H), 5.64–5.48 (m, 3H), 5.44 (dt, $J = 6.4, 10.9\text{ Hz}$, 1H), 5.34 (dd, $J = 8.4, 11.0\text{ Hz}$, 1H), 5.24–5.15 (m, 3H), 5.10 (d, $J = 10.2\text{ Hz}$, 1H), 4.59 (m, 1H), 4.55 (d, $J = 10.5\text{ Hz}$, 1H), 4.48 (d, $J = 10.5\text{ Hz}$, 1H), 4.34 (d, $J = 6.3\text{ Hz}$, 1H), 3.89–3.75 (m, 4H), 3.65 (m, 1H), 3.37–3.26 (m, 2H), 2.99 (m, 1H), 2.68 (m, 1H), 2.58–2.40 (m, 3H), 1.95–1.62 (m, 4H), 1.53 (m, 1H), 1.45 (m, 1H), 1.11 (d, $J = 6.8\text{ Hz}$, 3H), 1.00 (d, $J = 6.9\text{ Hz}$, 3H), 0.98 (d, $J = 8.0\text{ Hz}$, 3H), 0.95 (d, $J = 7.0\text{ Hz}$, 3H), 0.94–0.85 (m, 39H), 0.13–0.03 (m, 24H); ^{13}C NMR (75 MHz, CDCl_3) δ 159.3, 138.6, 134.8, 134.5, 134.1, 132.6, 132.5, 131.6, 129.6, 129.4, 129.3, 128.5, 125.6, 117.6, 113.9, 84.4, 80.5, 75.3, 73.6, 72.8, 65.0, 60.0, 55.5, 42.8, 40.8, 39.8, 37.0, 36.3, 35.6, 35.5, 26.5, 26.3, 26.2, 23.8, 19.8, 19.0, 18.7, 18.4, 18.3, 17.2, 15.1, 9.6, -2.9 , -3.2 , -3.4 , -4.1 , -4.2 , -4.8 ; LRMS (ESI) 1119 $[\text{M} + \text{Na}]^+$;

HRMS (ESI) calcd. for C₆₃H₁₁₆O₇Si₄Na 1119.7696, found 1119.7727; $[\alpha]_D^{20}$ +42.0 (*c* 0.94, CHCl₃).



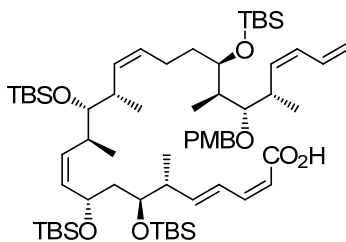
The C9 β -epimer 84 β : IR (NaCl) 3385, 2956, 2929, 2856, 1514, 1462, 1251, 1082, 836, 774 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.27 (m, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 6.58 (dt, *J* = 10.5, 16.8 Hz, 1H), 6.27 (dd, *J* = 11.2, 14.9 Hz, 1H), 6.01 (t, *J* = 11.3 Hz, 1H), 5.97 (t, *J* = 11.1 Hz, 1H), 5.64 (dd, *J* = 7.8, 15.1 Hz, 1H), 5.57 (t, *J* = 10.5 Hz, 1H), 5.50–5.32 (m, 3H), 5.28–5.16 (m, 3H), 5.11 (d, *J* = 10.0 Hz, 1H), 4.55 (d, *J* = 10.5 Hz, 1H), 4.47 (d, *J* = 10.5 Hz, 1H), 4.43–4.25 (m, 3H), 3.87–3.72 (m, 4H), 3.66 (m, 1H), 3.37–3.25 (m, 2H), 2.99 (m, 1H), 2.62 (m, 1H), 2.56–2.38 (m, 2H), 2.01 (m, 1H), 1.98–1.73 (m, 2H), 1.72–1.60 (m, 2H), 1.48–1.37 (m, 2H), 1.10 (d, *J* = 6.7 Hz, 3H), 1.04 (d, *J* = 6.7 Hz, 3H), 0.96 (d, *J* = 6.8 Hz, 3H), 0.96–0.83 (m, 42H), 0.11–0.00 (m, 24H); ¹³C NMR (75 MHz, CDCl₃) δ 159.3, 137.9, 134.9, 134.2, 134.1, 133.3, 132.6, 131.6, 129.6, 129.5, 129.4, 129.3, 128.7, 125.8, 117.6, 114.0, 84.4, 80.5, 75.2, 74.5, 72.9, 66.1, 60.0, 55.5, 42.3, 41.3, 40.8, 37.4, 36.6, 35.7, 35.5, 35.0, 34.1, 26.6, 26.3, 26.2, 25.9, 23.9, 19.1, 19.0, 18.7, 18.5, 18.3, 17.8, 15.8, 9.7, -2.7, -3.3, -3.4, -4.0, -4.1, -4.7; LRMS (ESI) 1119 [M + Na]⁺; HRMS (ESI) calcd. for C₆₃H₁₁₆O₇Si₄Na 1119.7696, found 1119.7708; $[\alpha]_D^{20}$ +38.4 (*c* 0.19, CHCl₃).



(2Z,4E,6R,7S,9S,10Z,12S,13R,14S,15Z,19R,20R,21S,22S,23Z)-21-(4-Methoxybenzyloxy)-7,9,13,19-tetrakis(*tert*-butyldimethylsilyloxy)-6,12,14,20,22-pentamethylhexacos-2,4,10,15,23,25-hexaen-1-ol (89 α):

Following the procedure for the TBS ether **34**, the alcohol **84 α** (0.26 g, 0.24 mmol) in CH₂Cl₂ (4.7 mL) was protected with 2,6-lutidine (0.083 mL, 0.71 mmol) and TBSOTf (0.082 mL, 0.36 mmol) to provide the TBS ether (0.29 g, 100%) as a colorless oil, which was used in the next step without further purification: IR (NaCl) 2956, 2929, 2857, 1471, 1462, 1252, 1171, 836, 774 cm⁻¹; ¹H NMR (300 MHz, C₆D₆) δ 7.32 (d, *J* = 8.4 Hz, 2H), 6.96–6.70 (m, 3H), 6.50 (dd, *J* = 11.0, 15.4 Hz, 1H), 6.12 (t, *J* = 11.0 Hz, 1H), 6.05 (t, *J* = 11.2 Hz, 1H), 5.83–5.69 (m, 2H), 5.67–5.42 (m, 6H), 5.23 (d, *J* = 16.9 Hz, 1H), 5.13 (d, *J* = 10.4 Hz, 1H), 4.77 (t, *J* = 7.6 Hz, 1H), 4.59 (d, *J* = 10.6 Hz, 1H), 4.54 (d, *J* = 10.6 Hz, 1H), 4.40 (d, *J* = 6.3 Hz, 1H), 4.16 (m, 1H), 3.87 (m, 1H), 3.54–3.42 (m, 2H), 3.32 (s, 3H), 3.15 (m, 1H), 2.92–2.74 (m, 2H), 2.60 (m, 1H), 2.29–1.87 (m, 3H), 1.86–1.53 (m, 4H), 1.27–1.14 (m, 12H), 1.12–0.97 (m, 48H), 0.29–0.06 (m, 30H); ¹³C NMR (75 MHz, CDCl₃) δ 159.3, 138.5, 134.8, 134.2, 133.9, 132.6, 132.1, 131.6, 129.6, 129.5, 129.3, 129.1, 128.5, 125.4, 117.6, 113.9, 84.5, 80.7, 75.3, 72.7, 72.6, 66.9, 60.0, 55.5, 43.4, 42.2, 40.8, 36.7, 36.1, 35.6, 35.5, 26.6, 26.3, 26.2, 26.0, 23.8, 19.1, 18.9, 18.7, 18.6, 18.5, 18.4, 17.1, 14.4, 9.6, -2.6, -2.7, -2.8, -3.3, -3.4, -3.7, -3.9, -4.0, -4.1, -4.7, -4.9; LRMS (ESI) 1233 [M + Na]⁺; HRMS (ESI) calcd. for C₆₉H₁₃₀O₇Si₅Na 1233.8561, found 1233.8673; [α]_D²⁰+17.0 (*c* 0.20, CHCl₃).

Following the procedure for the alcohol **59**, the TBS ether (0.29 g, 0.24 mmol) at 0 °C was treated with a solution of HF•pyr in pyr/THF (8 mL) for 15 h. Purification by column chromatography (95:1 hexanes/EtOAc) provided the title compound (0.22 g, 85%) as a colorless oil: IR (NaCl) 3422, 2955, 1613, 1514, 1462, 1250, 1039, 835, 773, 735 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.29 (d, $J = 8.5$ Hz, 2H), 6.88 (d, $J = 8.6$ Hz, 2H), 6.60 (dt, $J = 10.6, 16.8$ Hz, 1H), 6.30 (dd, $J = 11.1, 14.9$ Hz, 1H), 6.06 (t, $J = 11.3$ Hz, 1H), 6.02 (t, $J = 11.2$ Hz, 1H), 5.67 (dd, $J = 7.0, 15.1$ Hz, 1H), 5.58 (t, $J = 10.9$ Hz, 1H), 5.50 (dt, $J = 7.0, 10.7$ Hz, 1H), 5.39 (t, $J = 11.0$ Hz, 1H), 5.34–5.16 (m, 4H), 5.12 (d, $J = 10.1$ Hz, 1H), 4.58–4.44 (m, 3H), 4.28 (dd, $J = 2.4, 6.7$ Hz, 2H), 3.91 (m, 1H), 3.81 (s, 3H), 3.67 (m, 1H), 3.42–3.26 (m, 2H), 3.01 (m, 1H), 2.68–2.36 (m, 3H), 1.95–1.64 (m, 3H), 1.60–1.31 (m, 4H), 1.12 (d, $J = 6.7$ Hz, 3H), 1.04–0.82 (m, 48H), 0.15–0.02 (m, 24H); ^{13}C NMR (75 MHz, CDCl_3) δ 158.9, 139.1, 134.3, 133.7, 133.5, 132.1, 131.4, 131.2, 131.1, 129.1, 128.9, 128.1, 127.4, 124.5, 117.3, 113.6, 84.1, 80.3, 75.0, 72.2, 72.1, 66.4, 58.7, 55.1, 42.9, 41.8, 40.3, 36.1, 35.8, 35.1, 26.1, 25.8, 23.4, 18.6, 18.4, 18.0, 17.0, 13.4, 9.1, -3.0, -3.2, -3.7, -4.1, -4.3, -4.4, -4.5; LRMS (ESI) 1119 $[\text{M} + \text{Na}]^+$; HRMS (ESI) calcd. for $\text{C}_{63}\text{H}_{116}\text{O}_7\text{Si}_4\text{Na}$ 1119.7696, found 1119.7795; $[\alpha]_{\text{D}}^{20} +16.9$ (c 0.61, CHCl_3).

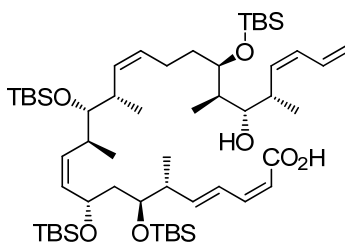


(2Z,4E,6R,7S,9S,10Z,12S,13R,14S,15Z,19R,20R,21S,22S,23Z)-21-(4-Methoxybenzyloxy)-7,9,13,19-tetrakis(*tert*-butyldimethylsilyloxy)-6,12,14,20,22-pentamethylhexacos-2,4,10,15,23,25-hexaenoic acid:

A solution of the alcohol **89 α** (0.22 g, 0.20 mmol) in CH₂Cl₂ (20 mL) at 0 °C was treated with Dess–Martin periodinane (0.17 g, 0.40 mmol). The mixture was warmed to ambient temperature and stirred for 2 h. After quenching by addition of a mixture of sat. aq. Na₂S₂O₃ (10 mL) and sat. aq. NaHCO₃ (10 mL), the mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with sat. aq. NaHCO₃ (20 mL) and brine, dried (MgSO₄). The concentration under vacuum provided the aldehyde as a colorless oil, which was used in the next step without further purification: ¹H NMR (300 MHz, CDCl₃) δ 10.18 (d, *J* = 8.1 Hz, 1H), 7.29 (d, *J* = 8.4 Hz, 2H), 7.02 (dd, *J* = 11.9, 14.3 Hz, 1H), 6.91 (t, *J* = 10.5 Hz, 1H), 6.86 (d, *J* = 8.6 Hz, 2H), 6.58 (dt, *J* = 10.6, 16.8 Hz, 1H), 6.10 (dd, *J* = 7.2, 14.3 Hz, 1H), 6.01 (t, *J* = 11.0 Hz, 1H), 5.80 (dd, *J* = 8.2, 10.3 Hz, 1H), 5.57 (t, *J* = 10.7 Hz, 1H), 5.37 (t, *J* = 11.1 Hz, 1H), 5.32–5.14 (m, 4H), 5.10 (d, *J* = 10.2 Hz, 1H), 4.59–4.43 (m, 3H), 3.93 (m, 1H), 3.80 (s, 3H), 3.66 (m, 1H), 3.38–3.27 (m, 2H), 3.00 (m, 1H), 2.64–2.46 (m, 3H), 1.91–1.62 (m, 3H), 1.54 (m, 1H), 1.49–1.36 (m, 3H), 1.11 (d, *J* = 6.8 Hz, 3H), 1.05 (d, *J* = 6.7 Hz, 3H), 1.02–0.81 (m, 45H), 0.16–0.01 (m, 24H).

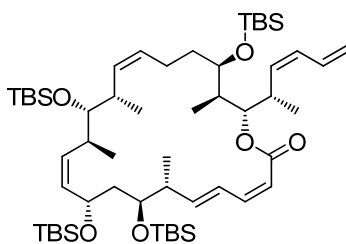
Following the procedure for the aldehyde **60**, the aldehyde in *t*-BuOH (15 mL) and H₂O (5 mL) was oxidized with NaH₂PO₄•H₂O (0.165 g, 1.20 mmol), a 2.0 M solution of 2-methyl-2-

butene in THF (5.00 mL, 10.00 mmol), and NaClO₄ (0.068 g, 0.60 mmol) to provide the title compound as a pale yellow oil, which was used in the next step without further purification: IR (NaCl) 2956, 2856, 1693, 1471, 1462, 1250, 1039, 835, 773 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.32 (dd, *J* = 11.5, 15.2 Hz, 1H), 7.28 (d, *J* = 8.5 Hz, 2H), 6.85 (d, *J* = 8.5 Hz, 2H), 6.62 (t, *J* = 11.4 Hz, 1H), 6.58 (dt, *J* = 10.6, 16.9 Hz, 1H), 6.03 (dd, *J* = 7.2, 15.9 Hz, 1H), 5.99 (t, *J* = 11.0 Hz, 1H), 6.02 (t, *J* = 11.2 Hz, 1H), 5.58 (d, *J* = 11.1 Hz, 1H), 5.55 (t, *J* = 10.6 Hz, 1H), 5.43–5.31 (m, 2H), 5.29–5.15 (m, 3H), 5.10 (d, *J* = 10.3 Hz, 1H), 4.56 (d, *J* = 10.6 Hz, 1H), 4.52–4.43 (m, 2H), 3.91(m, 1H), 3.79 (s, 3H), 3.65 (m, 1H), 3.35 (dd, *J* = 3.2, 7.9 Hz, 1H), 3.28 (t, *J* = 4.6 Hz, 1H), 2.98 (m, 1H), 2.61–2.42 (m, 3H), 1.85 (m, 1H), 1.79–1.63 (m, 2H), 1.60–1.36 (m 4H), 1.08 (d, *J* = 6.8 Hz, 3H), 1.02 (t, *J* = 6.7 Hz, 6H), 0.99–0.77 (m, 42H), 0.12–0.00 (m, 24H); ¹³C NMR (125 MHz, CDCl₃) δ 170.9, 159.0, 148.1, 147.1, 134.2, 133.7, 133.4, 132.1, 131.5, 130.9, 129.3, 128.9, 128.1, 126.9, 117.3, 115.1, 113.6, 84.2, 80.3, 74.9, 72.2, 71.9, 66.4, 55.1, 43.3, 42.2, 40.2, 36.3, 35.8, 35.1, 29.6, 26.1, 25.8, 23.4, 18.6, 18.3, 18.0, 17.0, 13.4, 9.1, -3.2, -3.7, -4.2, -4.5, -4.6; LRMS (ESI) 1133 [M + Na]⁺; HRMS (ESI) calcd. for C₆₃H₁₁₄O₈Si₄Na 1133.7489, found 1133.7568; [α]_D²⁰ +15.9 (*c* 0.27, CHCl₃).



(2Z,4E,6R,7S,9S,10Z,12S,13R,14S,15Z,19R,20R,21S,22S,23Z)-7,9,13,19-tetrakis(*tert*-Butyldimethylsilyloxy)-21-hydroxy-6,12,14,20,22-pentamethylhexacos-2,4,10,15,23,25-hexaenoic acid (85 α):

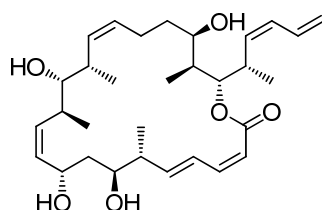
Following the procedure for the alcohol **83**, the above-obtained carboxylic acid in CH₂Cl₂ (20 mL) and H₂O (2 mL) was treated with DDQ (0.136 g, 0.60 mmol). Two chromatographic purification steps (95:1 MeOH/ CH₂Cl₂, then 4:1 hexanes/EtOAc) provided the title compound (0.062 g, 31% for three steps), which was used immediately in the next step: ¹H NMR (300 MHz, CDCl₃) δ 7.35 (dd, J = 11.3, 15.2 Hz, 1H), 6.72–6.53 (m, 2H), 6.10 (t, J = 11.0 Hz, 1H), 6.03 (dd, J = 6.9, 15.5 Hz, 1H), 5.60 (d, J = 11.4 Hz, 1H), 5.47–5.36 (m, 2H), 5.34–5.17 (m, 4H), 5.13 (d, J = 10.1 Hz, 1H), 4.56 (d, J = 10.6 Hz, 1H), 4.48 (m, 1H), 3.93 (m, 1H), 3.77 (m, 1H), 3.49 (dd, J = 3.5, 7.0 Hz, 1H), 3.32 (dd, J = 4.1, 5.5 Hz, 1H), 2.83 (m, 1H), 2.65–2.45 (m, 3H), 2.08–1.80 (m, 2H), 1.78–1.35 (m, 5H), 1.08–0.82 (m, 51H), 0.12–0.02 (m, 24H).



(3Z,5E,7R,8S,10S,11Z,13S,14R,15S,16Z,20R,21S,22S)-8,10,14,20-tetrakis(*tert*-Butyldimethylsilyloxy)-7,13,15,21-tetramethyl-22-((1S,2Z)-1-methyl-penta-2,4-dienyl)-oxa-cyclodocosa-3,5,11,16-tetraen-2-one (90α):

A solution of the *seco*-acid **85α** (62 mg, 0.063 mmol) in THF (6.3 mL) at 0 °C was treated with triethylamine (61 μL, 0.434 mmol), 2,4,6-trichlorobenzoyl chloride (49 μL, 0.313 mmol). The reaction mixture was stirred at 0 °C for 30 min and at ambient temperature for 1 h. A solution of DMAP (76 mg, 0.625 mmol) in toluene (63 mL) was added at ambient temperature. The reaction mixture was stirred for 17 h. After quenching by addition of sat. aq. NaHCO₃ (30 mL), the mixture was extracted with diethyl ether (3 × 30 mL) and the combined organic layers were washed with a 0.2 M solution of HCl (3 × 50 mL), a sat. aq. NaHCO₃ (50 mL), brine, then dried (MgSO₄) and concentrated. Purification by column chromatography (98:2 hexanes/EtOAc) provided the title compound (43 mg, 71%) as a colorless oil: IR (NaCl) 3359, 2956, 2926, 2855, 1713, 1463, 1256, 1086, 835, 773 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 7.10 (dd, *J* = 11.5, 14.7 Hz, 1H), 6.61 (dt, *J* = 10.7, 16.7 Hz, 1H), 6.55 (t, *J* = 11.2 Hz, 1H), 6.07 (dd, *J* = 7.6, 15.4 Hz, 1H), 6.00 (t, *J* = 11.0 Hz, 1H), 5.63 (t, *J* = 8.2 Hz, 1H), 5.57 (d, *J* = 11.5 Hz, 1H), 5.40 (t, *J* = 10.3 Hz, 1H), 5.32 (dd, *J* = 8.1, 11.1 Hz, 1H), 5.20 (d, *J* = 16.8 Hz, 1H), 5.17–5.10 (m, 4H), 4.46 (q, *J* = 7.1 Hz, 1H), 3.88 (m, 1H), 3.54 (m, 1H), 3.37 (d, *J* = 4.0 Hz, 1H), 3.04 (m, 1H), 2.55–2.29 (m, 3H), 1.96 (m, 1H), 1.85 (m, 1H), 1.77 (m, 1H), 1.65–1.51 (m, 2H), 1.48–1.28 (m, 2H),

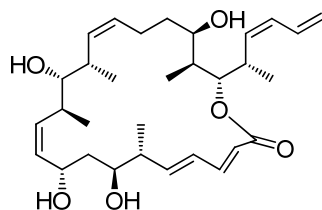
1.04 (dd, $J = 7.1, 9.7$ Hz, 6H), 1.00 (t, $J = 6.6$ Hz, 6H), 0.97–0.84 (m, 39H), 0.12–0.01 (m, 24H); ^{13}C NMR (125 MHz, CDCl_3) δ 166.3, 144.7, 142.8, 134.0, 133.6, 133.4, 132.1, 131.2, 129.7, 128.1, 127.7, 117.7, 117.5, 79.9, 77.3, 73.4, 71.6, 66.8, 66.1, 43.5, 39.5, 37.6, 37.3, 34.5, 34.4, 29.7, 26.1, 25.9, 25.8, 25.4, 19.6, 18.5, 18.0, 17.9, 17.5, 15.4, 10.5, -2.8, -3.1, -3.6, -4.0, -4.3; LRMS (ESI) 995 $[\text{M} + \text{Na}]^+$; HRMS (ESI) calcd. for $\text{C}_{55}\text{H}_{104}\text{O}_6\text{Si}_4\text{Na}$ 995.6808, found 995.6902; $[\alpha]_D^{20} +5.6$ (c 0.20, CHCl_3).



(3Z,5E,7R,8S,10S,11Z,13S,14R,15S,16Z,20R,21S,22S)-8,10,14,20-Tetrahydroxy-7,13,15,21-tetramethyl-22-((1S,2Z)-1-methyl-penta-2,4-dienyl)-oxa-cyclodocosa-3,5,11,16-tetraen-2-one (9):

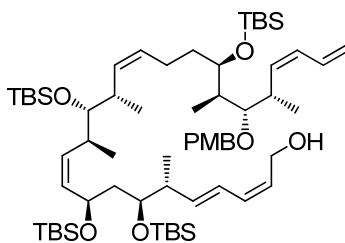
A solution of the TBS-protected macrolactone **90 α** (43.0 mg, 0.044 mmol) in THF (2.4 mL) at 0 °C was treated with a 6 M solution of HCl in $\text{H}_2\text{O}/\text{MeOH}$ (2.4 mL, prepared by slow addition of conc. HCl (1.2 mL) to MeOH (1.2 mL)). The reaction mixture was warmed to ambient temperature and stirred. Three portions of a 6 M solution of HCl (2.4 mL) and THF (2.4 mL) were added every 45 min. After 4 h, the solid NaHCO_3 was added to the reaction mixture until no gas evolved. The mixture was extracted with diethyl ether (3×30 mL) and the combined organic layers were washed with brine, dried (MgSO_4) and concentrated. Purification by column chromatography (15:85 hexanes/EtOAc) provided the title compound (**9**) (9.6 mg, 42%) as a colorless powder and the more polar C2 *E*-isomer **91** (0.7 mg, 3%) as a colorless powder: IR

(NaCl) 3390, 2965, 2927, 1704, 1639, 1455, 1275, 1179, 1002, 959 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 7.20 (dd, $J = 11.2, 15.5$ Hz, 1H), 6.60 (dt, $J = 11.0, 16.8$ Hz, 1H), 6.53 (t, $J = 11.3$ Hz, 1H), 6.01 (dd, $J = 8.5, 15.5$ Hz, 1H), 6.00 (t, $J = 10.8$ Hz, 1H), 5.62 (t, $J = 10.8$ Hz, 1H), 5.54 (d, $J = 11.5$ Hz, 1H), 5.52 (dd, $J = 8.9, 10.7$ Hz, 1H), 5.32 (t, $J = 10.5$ Hz, 1H), 5.22 (dt, $J = 6.9, 10.9$ Hz, 1H), 5.19 (t, $J = 11.0$ Hz, 1H), 5.18 (d, $J = 16.7$ Hz, 1H), 5.10 (dd, $J = 2.9, 8.6$ Hz, 1H), 5.08 (d, $J = 11.0$ Hz, 1H), 4.66 (dt, $J = 3.8, 8.4$ Hz, 1H), 4.01 (dt, $J = 2.6, 10.7$ Hz, 1H), 3.38 (ddd, $J = 2.8, 6.8, 12.7$ Hz, 1H), 3.29 (dd, $J = 3.6, 8.0$ Hz, 1H), 3.05 (m, 1H), 2.66 (m, 1H), 2.51 (m, 1H), 2.38 (m, 1H), 2.14 (m, 1H), 1.97 (m, 1H), 1.90 (dt, $J = 3.0, 6.9$ Hz, 1H), 1.66 (m, 1H), 1.59 (ddd, $J = 3.9, 10.5, 14.3$ Hz, 1H), 1.44 (ddd, $J = 2.4, 8.3, 14.2$ Hz, 1H), 1.22 (dt, $J = 4.1, 9.6$ Hz, 1H), 1.17 (d, $J = 6.8$ Hz, 3H), 1.10 (d, $J = 6.9$ Hz, 3H), 1.08 (d, $J = 6.9$ Hz, 3H), 1.02 (d, $J = 6.8$ Hz, 3H), 1.00 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (151 MHz, CDCl_3) δ 166.6, 134.0, 132.5, 132.3, 132.0, 131.8, 129.9, 129.5, 127.9, 79.0, 76.4, 73.0, 71.1, 65.4, 43.3, 40.2, 40.1, 36.9, 35.4, 34.4, 33.9, 24.8, 19.3, 18.0, 17.4, 15.8, 10.1; LRMS (ESI) 539 $[\text{M} + \text{Na}]^+$; HRMS (ESI) calcd. for $\text{C}_{31}\text{H}_{48}\text{O}_6\text{Na}$ 539.3349, found 539.3352; $[\alpha]_{\text{D}}^{20} -74.0$ (c 0.17, CHCl_3).



The C2 *E*-isomer 92: IR (NaCl) 3408, 2962, 2926, 1698, 1640, 1455, 1300, 1261, 1003 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 7.15 (dd, $J = 10.9, 15.3$ Hz, 1H), 6.59 (dt, $J = 10.3, 17.3$ Hz, 1H), 6.16 (dt, $J = 10.8, 15.2$ Hz, 1H), 6.04 (dd, $J = 7.9, 15.3$ Hz, 1H), 5.97 (t, $J = 10.9$ Hz, 1H), 5.73 (d, $J = 15.3$ Hz, 1H), 5.50 (dd, $J = 8.8, 11.0$ Hz, 1H), 5.42 (t, $J = 10.1$ Hz, 1H), 5.38–5.32 (m, 2H), 5.20 (t, $J = 10.8$ Hz, 1H), 5.17 (d, $J = 17.7$ Hz, 1H), 5.09 (d, $J = 10.1$ Hz, 1H), 4.96 (dd,

$J = 1.7, 8.7$ Hz, 1H), 4.79 (dt, $J = 2.7, 7.3$ Hz, 1H), 4.03 (d, $J = 10.5$ Hz, 1H), 3.48–3.35 (m, 2H), 3.01 (m, 1H), 2.73 (m, 1H), 2.61 (m, 1H), 2.42 (m, 1H), 2.20 (m, 1H), 2.10 (m, 1H), 1.83 (m, 1H), 1.69 (ddd, $J = 2.5, 10.6, 13.9$ Hz, 1H), 1.58 (m, 1H), 1.54 (m, 1H), 1.34–1.28 (m, 2H), 1.16 (d, $J = 6.8$ Hz, 3H), 1.10 (d, $J = 6.9$ Hz, 3H), 1.02 (d, $J = 6.8$ Hz, 3H), 1.00 (d, $J = 6.7$ Hz, 3H), 0.93 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (151 MHz, CDCl_3) δ 166.7, 145.5, 145.1, 134.3, 133.2, 131.9, 131.5, 131.3, 130.7, 129.7, 129.0, 119.7, 117.8, 78.3, 76.1, 71.7, 71.2, 65.8, 42.4, 40.5, 40.2, 35.9, 34.2, 34.1, 31.8, 23.7, 19.3, 17.3, 15.7, 14.6, 9.8; LRMS (ESI) 539 $[\text{M} + \text{Na}]^+$; HRMS (ESI) calcd. for $\text{C}_{31}\text{H}_{48}\text{O}_6\text{Na}$ 539.3349, found 539.3362; $[\alpha]_{\text{D}}^{20} +21.9$ (c 0.16, CHCl_3).

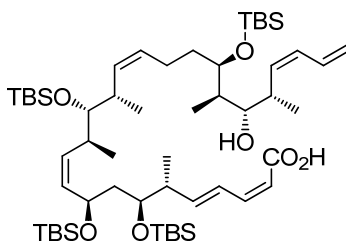


(2Z,4E,6R,7S,9R,10Z,12S,13R,14S,15Z,19R,20R,21S,22S,23Z)-21-(4-Methoxybenzyloxy)-7,9,13,19-tetrakis(*tert*-butyldimethylsilyloxy)-6,12,14,20,22-pentamethylhexacosan-2,4,10,15,23,25-hexaen-1-ol (89β):

Following the procedure for the TBS ether **89α**, the alcohol **84β** (0.20 g, 0.20 mmol) in CH_2Cl_2 (4.0 mL) was protected with 2,6-lutidine (0.069 mL, 0.59 mmol) and TBSOTf (0.068 mL, 0.30 mmol) to provide the TBS ether as a colorless oil, which was used in the next step without further purification.

The TBS ether at 0 °C was treated with a solution of $\text{HF}\cdot\text{pyr}$ in pyr/THF (6.7 mL) for 14 h. Purification by column chromatography (9:1 hexanes/EtOAc) provided the title compound (0.12 g, 60%) as a colorless oil: IR (NaCl) 3400, 2956, 2928, 2856, 1250, 1084, 1037, 835, 773

cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.30 (d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 8.5 Hz, 2H), 6.61 (dt, *J* = 10.5, 16.8 Hz, 1H), 6.30 (dd, *J* = 11.1, 15.2 Hz, 1H), 6.15–5.95 (m, 2H), 5.85 (dd, *J* = 8.6, 15.2 Hz, 1H), 5.59 (t, *J* = 10.5 Hz, 1H), 5.50–5.05 (m, 7H), 4.58 (d, *J* = 10.5 Hz, 1H), 4.51 (d, *J* = 10.5 Hz, 1H), 4.40 (m, 1H), 4.30 (dd, *J* = 7.4, 12.8 Hz, 1H), 4.23 (dd, *J* = 6.9, 12.8 Hz, 1H), 3.87 (m, 1H), 3.80 (s, 3H), 3.68 (m, 1H), 3.40 (t, *J* = 4.2 Hz, 1H), 3.35 (dd, *J* = 3.2, 7.7 Hz, 1H), 3.00 (m, 1H), 2.67–2.49 (m, 2H), 2.43 (m, 1H), 1.92–1.80 (m, 2H), 1.69 (m, 1H), 1.62–1.40 (m, 4H), 1.12 (d, *J* = 6.8 Hz, 3H), 1.08 (d, *J* = 6.9 Hz, 3H), 1.00–0.84 (m, 45H), 0.12–0.02 (m, 24H); ¹³C NMR (75 MHz, CDCl₃) δ 159.3, 152.4, 138.8, 134.8, 134.5, 133.6, 132.6, 131.6, 129.4, 129.3, 128.2, 127.5, 125.5, 118.8, 117.5, 114.0, 84.5, 79.8, 75.3, 72.7, 66.7, 59.1, 55.5, 44.8, 41.0, 40.7, 37.7, 35.9, 35.6, 35.4, 29.9, 26.5, 26.2, 26.1, 23.7, 19.0, 18.9, 18.7, 18.4, 18.3, 17.0, 9.68, -3.2, -3.3, -3.7, -4.1, -4.3, -4.4; LRMS (ESI) 1119 [M + Na]⁺; HRMS (ESI) calcd. for C₆₃H₁₁₆O₇Si₄Na 1119.7696, found 1119.7700; [α]_D²⁰ +50.0 (*c* 0.18, CHCl₃).



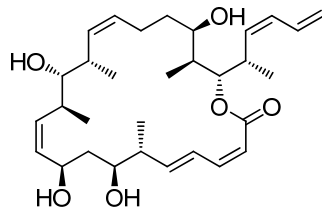
(2Z,4E,6R,7S,9R,10Z,12S,13R,14S,15Z,19R,20R,21S,22S,23Z)-7,9,13,19-tetrakis(*tert*-Butyldimethylsilyloxy)-21-hydroxy-6,12,14,20,22-pentamethylhexacos-2,4,10,15,23,25-hexaenoic acid (85β):

A solution of the alcohol **89β** (0.11 g, 0.10 mmol) in CH₂Cl₂ (10 mL) at 0 °C was treated with Dess–Martin periodinane (0.085 g, 0.20 mmol). The mixture was warmed to ambient temperature and stirred for 1 h. After quenching by addition of a mixture of sat. aq. Na₂S₂O₃ (5 mL) and sat. aq. NaHCO₃ (5 mL), the mixture was extracted with EtOAc (3 × 10 mL). The

combined organic layers were washed with sat. aq. NaHCO₃ (10 mL) and brine, dried (MgSO₄). The concentration under vacuum provided the aldehyde as a pale yellow oil, which was used in the next step without further purification.

The aldehyde in *t*-BuOH (6 mL) and H₂O (2 mL) was oxidized with NaH₂PO₄•H₂O (0.083 g, 0.60 mmol), a 2.0 M solution of 2-methyl-2-butene in THF (2.50 mL, 5.00 mmol), and NaClO₄ (0.034 g, 0.30 mmol) to provide the carboxylic acid as a pale yellow oil, which was used in the next step without further purification.

The carboxylic acid in CH₂Cl₂ (10 mL) and H₂O (1 mL) was treated with DDQ (0.068 g, 0.30 mmol). Purification by chromatography (15:1 hexanes/EtOAc) provided the title compound (0.047 g, 47% for three steps) as a colorless oil, which was used immediately in the next step: ¹H NMR (300 MHz, CDCl₃) δ 7.38 (dd, *J* = 11.4, 17.3 Hz, 1H), 6.75–6.52 (m, 2H), 6.24 (dd, *J* = 8.7, 15.3 Hz, 1H), 6.11 (t, *J* = 10.9 Hz, 1H), 5.58 (d, *J* = 11.3 Hz, 1H), 5.52–5.33 (m, 3H), 5.32–5.17 (m, 3H), 5.13 (d, *J* = 10.2 Hz, 1H), 4.41 (t, *J* = 8.0 Hz, 1H), 3.92 (d, *J* = 9.4 Hz, 1H), 3.80 (m, 1H), 3.52 (dd, *J* = 2.6, 7.5 Hz, 1H), 3.41 (t, *J* = 3.8 Hz, 1H), 2.81 (m, 1H), 2.64–2.44 (m, 2H), 2.10–1.82 (m, 2H), 1.78 (m, 1H), 1.72–1.31 (m, 5H), 1.11 (d, *J* = 6.7 Hz, 1H), 1.02–0.80 (m, 48H), 0.18–0.02 (m, 24H).

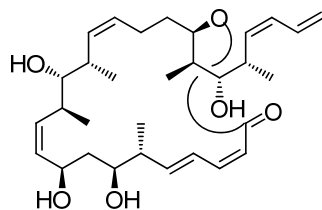


(3Z,5E,7R,8S,10R,11Z,13S,14R,15S,16Z,20R,21S,22S)-8,10,14,20-Tetrahydroxy-7,13,15,21-tetramethyl-22-((1S,2Z)-1-methyl-penta-2,4-dienyl)-oxa-cyclodocosa-3,5,11,16-tetraen-2-one (94):

A solution of the *seco*-acid **85β** (0.037g, 0.037 mmol) in THF (3.7 mL) at 0 °C was treated with triethylamine (0.036 mL, 0.259 mmol), 2,4,6-trichlorobenzoyl chloride (0.029 mL, 0.186 mmol). The reaction mixture was stirred at 0 °C for 30 min and at ambient temperature for 1 h. A solution of DMAP (0.045 g, 0.370 mmol) in toluene (37 mL) was added at ambient temperature. The reaction mixture was stirred for 15 h. After quenching by addition of sat. aq. NaHCO₃ (15 mL), the mixture was extracted with diethyl ether (3 × 15 mL) and the combined organic layers were washed with a 0.2 M solution of HCl (3 × 25 mL), a sat. aq. NaHCO₃ (25 mL), brine, then dried (MgSO₄) and concentrated. Purification by column chromatography (98:2 hexanes/EtOAc) provided a mixture (0.035 g) of **90β** and the C2 *E*-isomer **93** as a pale yellow oil. The same reaction with 0.034 g of the *seco*-acid **85β** gave the mixture of macrolactone (0.027 g).

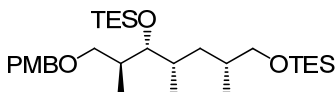
A solution of a mixture of the TBS-protected macrolactones (0.062 g, 0.064 mmol) in THF (3.2 mL) at 0 °C was treated with a 6 M solution of HCl in H₂O/MeOH (3.2 mL, prepared by slow addition of conc. HCl (1.6 mL) to MeOH (1.6 mL)). The reaction mixture was warmed to ambient temperature and stirred. Three portions of a 6 M solution of HCl (1.6 mL) and THF (1.6 mL) were added every 45 min. After 8 h, the solid NaHCO₃ was added to the reaction

mixture until no gas evolved. The mixture was extracted with diethyl ether (3 × 50 mL) and the combined organic layers were washed with brine, dried (MgSO₄) and concentrated. Purification by column chromatography (15:85 hexanes/EtOAc) provided the title compound (0.004 g, 14%, two steps) as a colorless powder and the more polar C19-lactone **95** (0.005 g, 16%, two steps) as a colorless powder: IR (NaCl) 3384, 2964, 1698, 1635, 1456, 1271, 1001 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 7.28 (dd, *J* = 10.9, 15.8 Hz, 1H), 6.61 (dt, *J* = 10.7, 16.8 Hz, 1H), 6.55 (t, *J* = 11.4 Hz, 1H), 6.05 (t, *J* = 11.0 Hz, 1H), 6.02 (dd, *J* = 5.9, 16.0 Hz, 1H), 5.59 (dd, *J* = 8.4, 10.9 Hz, 1H), 5.58 (d, *J* = 11.2 Hz, 1H), 5.38–5.32 (m, 2H), 5.28 (dt, *J* = 4.9, 10.2 Hz, 1H), 5.22 (d, *J* = 16.8 Hz, 1H), 5.12 (d, *J* = 10.0 Hz, 1H), 4.87 (dd, *J* = 3.3, 6.7 Hz, 1H), 4.67 (dt, *J* = 3.6, 9.0 Hz, 1H), 4.14 (m, 1H), 3.58 (dt, *J* = 4.4, 6.4 Hz, 1H), 3.15 (t, *J* = 7.3 Hz, 1H), 3.00 (m, 1H), 2.74 (m, 2H), 2.61 (m, 1H), 2.40 (m, 1H), 2.05 (m, 1H), 1.80 (m, 1H), 1.66 (m, 1H), 1.55 (m, 1H), 1.31 (m, 1H), 1.10 (d, *J* = 6.6 Hz, 3H), 1.08 (d, *J* = 7.1 Hz, 3H), 1.06 (d, *J* = 6.8 Hz, 3H), 1.00 (d, *J* = 6.7 Hz, 3H), 0.97 (d, *J* = 7.0 Hz, 3H); ¹³C NMR (151 MHz, CDCl₃) δ 167.3, 146.3, 144.6, 134.5, 133.9, 133.8, 133.2, 130.0, 128.6, 126.5, 118.0, 116.7, 79.2, 78.7, 73.2, 72.3, 67.8, 41.0, 38.9, 38.3, 38.2, 35.6, 34.1, 29.7, 23.6, 19.1, 18.9, 17.5, 14.7, 8.3 ; LRMS (ESI) 539 [M + Na]⁺; HRMS (ESI) calcd. for C₃₁H₄₈O₆Na 539.3349, found 539.3339; [α]_D²⁰ -58.0 (*c* 0.20, CHCl₃).



The C19-lactone 95: IR (NaCl) 3390, 2963, 2929, 1698, 1635, 1456, 1267, 1180, 1003 736 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 7.27 (m, 1H), 6.66 (dt, *J* = 10.2, 16.8 Hz, 1H), 6.58 (t, *J*

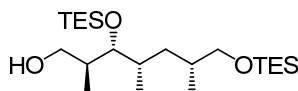
= 11.2 Hz, 1H), 6.17 (t, $J = 10.9$ Hz, 1H), 6.14 (dd, $J = 6.4, 15.7$ Hz, 1H), 5.63 (d, $J = 11.3$ Hz, 1H), 5.50 (dd, $J = 8.8, 11.0$ Hz, 1H), 5.41–5.29 (m, 3H), 5.27 (d, $J = 16.7$ Hz, 1H), 5.18 (d, $J = 10.1$ Hz, 1H), 5.07 (dd, $J = 5.0, 6.4$ Hz, 1H), 4.57 (m, 1H), 3.40 (dd, $J = 3.2, 7.9$ Hz, 1H), 3.17 (dd, $J = 6.0, 7.7$ Hz, 1H), 2.86 (m, 1H), 2.67 (m, 1H), 2.58 (m, 1H), 2.48 (q, $J = 7.5$ Hz, 1H), 2.13 (m, 1H), 2.00 (dt, $J = 3.3, 6.7$ Hz, 1H), 1.81 (m, 2H), 1.70 (ddd, $J = 7.3, 10.1, 14.1$ Hz, 1H), 1.60 (ddd, $J = 3.5, 5.2, 14.1$ Hz, 1H), 1.14 (d, $J = 7.0$ Hz, 3H), 1.05 (d, $J = 6.7$ Hz, 3H), 1.02 (d, $J = 6.9$ Hz, 3H), 1.01 (d, $J = 6.7$ Hz, 3H), 0.98 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (151 MHz, CDCl_3) δ 166.3, 146.1, 143.8, 134.1, 134.0, 133.8, 133.7, 132.0, 131.4, 128.1, 126.7, 118.7, 117.3, 78.8, 76.2, 75.0, 72.7, 67.3, 41.3, 39.8, 38.4, 38.1, 37.6, 36.1, 31.4, 22.9, 19.5, 18.0, 17.1, 14.1, 8.8; LRMS (ESI) 539 $[\text{M} + \text{Na}]^+$; HRMS (ESI) calcd. for $\text{C}_{31}\text{H}_{48}\text{O}_6\text{Na}$ 539.3349, found 539.3356; $[\alpha]_{\text{D}}^{20} -10.5$ (c 0.19, CHCl_3).



(5R,6S,8R)-3,3,11,11-Tetraethyl-5-((S)-1-(4-methoxybenzyloxy)propan-2-yl)-6,8-dimethyl-4,10-dioxo-3,11-disilatridecane (115):

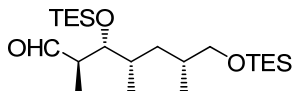
Following the procedure for the alcohol **9**, the TBS **114** (12.70 g, 29.90 mmol) in MeOH (60 mL) was deprotected with a 3 M solution of HCl in MeOH (60 mL, 180.00 mmol). After workup, the crude diol (10.32 g) was protected with TESOTf (15.00 mL, 56.69 mmol) and 2,6-lutidine (7.50 mL, 64.43 mmol). Purification by chromatography (15:1 hexanes/EtOAc) provided the title compound (13.65 g, 86% over two steps) as a colorless oil: ^1H NMR (500 MHz, CDCl_3) δ 7.28 (d, $J = 8.5$ Hz, 2H), 6.89 (d, $J = 8.5$ Hz, 2H), 4.47 (d, $J = 12.0$ Hz, 1H), 4.41 (d, $J = 11.5$ Hz, 1H), 3.81 (s, 3H), 3.55 (dd, $J = 4.0, 8.5$ Hz, 1H), 3.50 (dd, $J = 5.0, 9.5$ Hz, 1H), 3.46 (dd, $J =$

2.5, 7.5 Hz, 1H), 3.35–3.25 (m, 2H), 1.91 (m, 1H), 1.80–1.62 (m, 2H), 1.41 (m, 1H), 1.03–0.96 (m, 22H), 0.92 (d, $J = 7.0$ Hz, 3H), 0.87 (d, $J = 7.0$ Hz, 3H), 0.68–0.57 (m, 12H); ^{13}C NMR (125 MHz, CDCl_3) δ 158.9, 130.8, 129.0, 113.5, 109.4, 72.8, 72.6, 67.9, 55.0, 38.6, 37.9, 33.3, 32.9, 17.8, 14.9, 14.2, 7.0, 6.7, 5.4, 4.3; LRMS (ESI) 561 $[\text{M} + \text{Na}]^+$; HRMS (ESI) calcd. for $\text{C}_{30}\text{H}_{58}\text{O}_4\text{Si}_2\text{Na}$ 561.3874, found 561.3885.



(2*S*,3*R*,4*S*,6*R*)-2,4,6-Trimethyl-3,7-bis(triethylsilyloxy)heptan-1-ol (116):

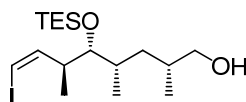
Following the procedure for the alcohol **83**, the PMB ether **115** (32.00 g, 59.37 mmol) in CH_2Cl_2 (900 mL) and pH 7 phosphate buffer (100 mL) was deprotected with DDQ (26.96 g, 118.75 mmol). Purification by chromatography (4:1 hexanes/EtOAc) provided the title compound (22.45 g, 90%) as a colorless oil: ^1H NMR (300 MHz, CDCl_3) δ 3.59 (d, $J = 5.1$ Hz, 2H), 3.52–3.42 (m, 2H), 3.30 (dd, $J = 6.9, 9.9$ Hz, 1H), 1.81 (m, 1H), 1.76–1.58 (m, 2H), 1.44 (m, 1H), 1.02–0.86 (m, 27H), 0.70–0.51 (m, 12H); ^{13}C NMR (75 MHz, CDCl_3) δ 81.3, 67.7, 66.3, 38.2, 37.8, 34.9, 33.5, 18.1, 15.8, 15.3, 7.0, 6.8, 5.4, 4.4; LRMS (ESI) 441 $[\text{M} + \text{Na}]^+$; HRMS (ESI) calcd. for $\text{C}_{22}\text{H}_{50}\text{O}_3\text{Si}_2\text{Na}$ 441.3196, found 441.3184.



(2*R*,3*R*,4*S*,6*R*)-2,4,6-Trimethyl-3,7-bis(triethylsilyloxy)heptanal (117):

Following the procedure for the aldehyde **60**, the alcohol **116** (21.53 g, 51.4 mmol) in CH_2Cl_2 (186 mL) and DMSO (93 mL) was oxidized with $\text{SO}_3 \cdot \text{pyr}$ (26.68 g, 167.62 mmol) in DMSO (93 mL) and Et_3N (31.15 mL, 223.48 mmol). Purification by chromatography (95:5 to

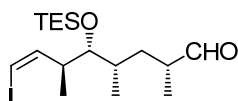
9:1 hexanes/EtOAc) provided the title compound (17.18 g, 80%) as a colorless oil: ^1H NMR (300 MHz, CDCl_3) δ 9.77 (d, $J = 2.7$ Hz, 1H), 3.77 (dd, $J = 3.6, 5.7$ Hz, 1H), 3.49 (dd, $J = 5.1, 9.9$ Hz, 1H), 3.34 (dd, $J = 6.6, 9.6$ Hz, 1H), 2.56 (m, 1H), 1.82–1.62 (m, 2H), 1.44 (m, 1H), 1.06 (d, $J = 7.2$ Hz, 3H), 1.02–0.88 (m, 24H), 0.67–0.54 (m, 12H); ^{13}C NMR (75 MHz, CDCl_3) δ 205.2, 78.0, 67.6, 50.2, 37.5, 34.7, 33.4, 18.1, 14.9, 11.9, 7.0, 6.8, 5.4, 4.4.



(2R,4S,5R,6S,Z)-8-Iodo-2,4,6-trimethyl-5-(triethylsilyloxy)oct-7-en-1-ol (118):

A suspension of methyltriphenylphosphonium iodide (28.00 g, 69.26 mmol) in THF (140 mL) at 0 °C was treated with a 1.6 M solution of BuLi in hexane (43.29 mL, 69.26 mmol) dropwise over 20 min. The resulting red solution was transferred via cannula to a solution of I_2 (17.58 g, 69.26 mmol) in THF (210 mL) vigorously stirring at -78 °C. The resulting brown suspension was stirred for 0.5 h at -78 °C, and then a 1.0 M solution of sodium bis(trimethylsilyl)amide in THF (62.91 mL, 62.91 mmol) was added dropwise over 15 min. The red suspension was stirred at -78 °C for 30 min, and then at -20 °C for 15 min. The red solution was cooled to -78 °C, and then the aldehyde **117** (13.26 g, 31.81 mmol) in THF (33 mL) was added dropwise over 45 min. The mixture was stirred at -78 °C for 30 min, and then at -20 °C for 60 min. After quenching the reaction by addition of sat. aq. NH_4Cl (5 mL), the mixture was filtered through a pad of Celite. The filtrate was concentrated under vacuum, then treated with hexane. The mixture was filtered through a pad of Celite. The filtrate was concentrated. The filtration followed by concentration was repeated two more times to give the crude vinyl iodide (16.52 g), which was used for the next reaction without further purification.

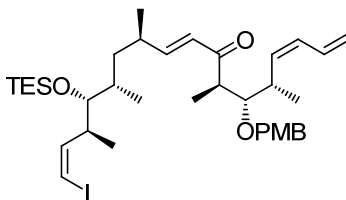
The vinyl iodide was dissolved in CH₂Cl₂ (400 mL) and MeOH (300 mL). The mixture was cooled to -10 °C, and then a solution of dichloroacetic acid (26.17 mL, 318.10 mmol) in MeOH (100 mL) was added dropwise over 30 min. The mixture was stirred -10 °C for 4 h. After quenching the reaction by addition of sat. aq. NaHCO₃ (300 mL), the mixture was concentrated under vacuum. The residue was extracted with diethyl ether (3 × 150 mL), and the combined organic layers were washed with brine, dried (MgSO₄) and concentrated. Purification by column chromatography (4:1 hexanes/EtOAc) provided the title compound (6.43 g, 48% over two steps) as a colorless oil: ¹H NMR (300 MHz, CDCl₃) δ 6.28 (dd, *J* = 7.3, 8.7 Hz, 1H), 6.14 (d, *J* = 7.5 Hz, 1H), 3.53 (dd, *J* = 4.5, 10.8 Hz, 1H), 3.46 (dd, *J* = 3.6, 4.8 Hz, 1H), 3.33 (dd, *J* = 6.9, 10.5 Hz, 1H), 2.68 (m, 1H), 1.75–1.55 (m, 3H), 1.39 (m, 1H), 1.02–0.92 (m, 15H), 0.90 (d, *J* = 6.6 Hz, 3H), 0.65–0.56 (m, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 144.0, 81.4, 79.7, 67.7, 43.1, 37.1, 35.8, 33.4, 18.2, 17.9, 16.2, 7.2, 5.6; LRMS (ESI) 449 [M + Na]⁺; HRMS (ESI) calcd. for C₁₇H₃₅IO₂SiNa 449.1349, found 449.1338.



(2R,4S,5R,6S,Z)-8-Iodo-2,4,6-trimethyl-5-(triethylsilyloxy)oct-7-enal (113):

Following the procedure for the aldehyde **60**, the alcohol **118** (6.43 g, 15.08 mmol) in CH₂Cl₂ (50 mL) and DMSO (10 mL) was oxidized with SO₃•pyr (7.20 g, 45.23 mmol), DMSO (25 mL) and Et₃N (8.41 mL, 60.32 mmol). Purification by chromatography (9:1 hexanes/EtOAc) provided the title compound (6.01 g, 70%) as a colorless oil: ¹H NMR (300 MHz, CDCl₃) δ 9.51 (d, *J* = 3.0 Hz, 1H), 6.29 (dd, *J* = 7.2, 8.7 Hz, 1H), 6.14 (d, *J* = 7.2 Hz, 1H), 3.50 (dd, *J* = 3.3, 4.5 Hz, 1H), 2.69 (m, 1H), 2.34 (m, 1H), 1.86 (m, 1H), 1.56 (m, 1H), 1.08 (d, *J* = 6.9 Hz, 3H), 0.99–

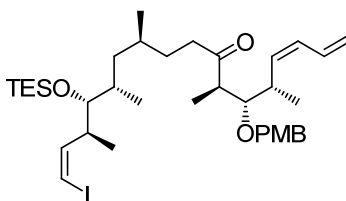
0.88 (m, 15H), 0.68–0.55 (m, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ 205.3, 143.8, 81.5, 79.6, 44.4, 42.6, 36.4, 34.3, 18.0, 15.8, 14.7, 7.2, 5.5.



(3Z,5S,6S,7R,9E,11R,13S,14R,15S,16Z)-17-Iodo-6-(4-methoxybenzyloxy)-5,7,11,13,15-pentamethyl-14-(triethylsilyloxy)heptadeca-1,3,9,16-tetraen-8-one (119):

A solution of the phosphonate **99** (5.94 g, 14.48 mmol) in THF (70 mL) was treated with $\text{Ba}(\text{OH})_2$ (1.65 g, 9.65 mmol) at room temperature. The suspension was stirred for 0.5 h. The aldehyde **113** (5.12 g, 12.06 mmol) in THF (70 mL) and H_2O (1.8 mL) was added to the above suspension. The mixture was stirred for 6 h, then $\text{Ba}(\text{OH})_2$ (0.84 g) was added. After additional 6 h, the phosphonate **99** (0.99 g) was added. After additional 6h, H_2O (200 mL) and diethyl ether (60 mL) were added. After separation of the organic layer, the aqueous layer was extracted with diethyl ether (100 mL \times 3). The combined organic layers were washed with brine, dried (MgSO_4) and concentrated. Purification by column chromatography (9:1 hexanes/ EtOAc) provided the title compound (11.86 g, 88%) as a colorless oil: ^1H NMR (300 MHz, CDCl_3) δ 7.29 (d, $J = 8.7$ Hz, 2H), 6.89 (d, $J = 8.4$ Hz, 2H), 6.68 (d, $J = 8.3, 15.7$ Hz, 1H), 6.40 (dt, $J = 10.5, 16.8$ Hz, 1H), 6.28 (dd, $J = 7.4, 8.7$ Hz, 1H), 6.14 (d, $J = 7.3$ Hz, 1H), 6.06 (d, $J = 15.7$ Hz, 2H), 6.01 (t, $J = 11.4$ Hz, 1H), 5.53 (t, $J = 10.8$ Hz, 1H), 5.18 (dd, $J = 1.8, 16.8$ Hz, 1H), 5.00 (d, $J = 10.2$ Hz, 1H), 4.58 (d, $J = 10.8$ Hz, 1H), 4.53 (d, $J = 11.1$ Hz, 1H), 3.80 (s, 3H), 3.69 (dd, $J = 3.0, 8.4$ Hz, 1H), 3.45 (dd, $J = 3.3, 4.8$ Hz, 1H), 2.94 (m, 1H), 2.78 (m, 1H), 2.69 (m, 1H), 2.35 (m, 2H), 1.60–1.40 (m, 3H), 1.21 (d, $J = 6.9$ Hz, 3H), 1.10 (d, $J = 6.9$ Hz, 3H), 1.04 (d, $J = 6.9$

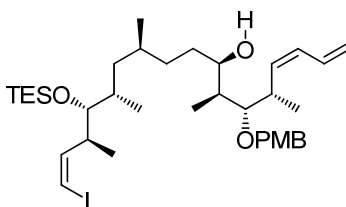
Hz, 3H), 0.99–0.92 (m, 12H), 0.87 (d, $J = 6.6$ Hz, 3H), 0.68–0.56 (m, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ 203.2, 159.2, 152.8, 143.8, 134.0, 132.4, 130.9, 129.7, 129.4, 128.2, 117.5, 113.8, 84.3, 81.5, 80.0, 75.5, 55.3, 48.6, 42.7, 39.5, 36.5, 36.3, 34.6, 20.8, 19.0, 18.0, 15.6, 14.6, 7.2, 5.6; LRMS (ESI) 731 $[\text{M} + \text{Na}]^+$; HRMS (ESI) calcd. for $\text{C}_{36}\text{H}_{57}\text{IO}_4\text{SiNa}$ 731.2968, found 731.2975.



(3Z,5S,6S,7R,11S,13S,14R,15S,16Z)-17-Iodo-6-(4-methoxybenzyloxy)-5,7,11,13,15-pentamethyl-14-(triethylsilyloxy)heptadeca-1,3,16-trien-8-one (120):

A solution of the enone **119** (11.34 g, 16.00 mmol) in benzene (argon-sparged, 400 mL) at 0 °C was treated with $[\text{Ph}_3\text{PCuH}]_6$ (red powder, 20.00 g, 10.20 mmol). The red mixture was warmed to room temperature and stirred for 1 h. After quenching the reaction by addition of H_2O (5.50 mL), the mixture was stirred under air for 1 h, then filtered through a pad of silica gel (2 cm). The filtrate was concentrated, and then hexane (100 mL) was added to the residue. The mixture was filtered through a pad of silica gel. The filtrate was concentrated. Purification by chromatography (15:1 to 4:1 hexanes/EtOAc) provided the title compound (9.07 g, 77%) as a colorless oil: ^1H NMR (300 MHz, CDCl_3) δ 7.28 (d, $J = 8.7$ Hz, 2H), 6.89 (d, $J = 8.7$ Hz, 2H), 6.44 (dt, $J = 10.5, 17.1$ Hz, 1H), 6.31 (dd, $J = 7.5, 9.0$ Hz, 1H), 6.14 (d, $J = 7.2$ Hz, 1H), 6.03 (t, $J = 10.8$ Hz, 1H), 5.57 (t, $J = 10.8$ Hz, 1H), 5.22 (dd, $J = 1.8, 16.8$ Hz, 1H), 5.10 (d, $J = 10.2$ Hz, 1H), 4.59 (d, $J = 10.8$ Hz, 1H), 4.52 (d, $J = 10.5$ Hz, 1H), 3.81 (s, 3H), 3.66 (dd, $J = 3.3, 8.4$ Hz, 1H), 3.46 (dd, $J = 3.6, 4.8$ Hz, 1H), 2.83–2.62 (m, 3H), 2.45–2.35 (m, 2H), 1.78–1.57 (m, 3H), 1.46 (m, 1H), 1.25 (m, 1H), 1.19 (d, $J = 7.2$ Hz, 3H), 1.10 (d, $J = 6.6$ Hz, 3H), 1.03–0.92 (m,

12H), 0.88 (d, $J = 6.9$ Hz, 3H), 0.83 (d, $J = 6.6$ Hz, 3H), 0.68–0.57 (m, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ 214.5, 159.2, 144.0, 134.0, 132.2, 130.8, 129.7, 129.4, 117.9, 113.8, 83.9, 81.4, 80.0, 75.4, 55.3, 50.5, 43.1, 41.0, 40.1, 36.3, 35.5, 29.8, 29.1, 20.5, 18.9, 17.7, 15.9, 14.2, 7.2, 5.6; LRMS (ESI) 733 $[\text{M} + \text{Na}]^+$; HRMS (ESI) calcd. for $\text{C}_{36}\text{H}_{59}\text{IO}_4\text{SiNa}$ 733.3125, found 733.3132.

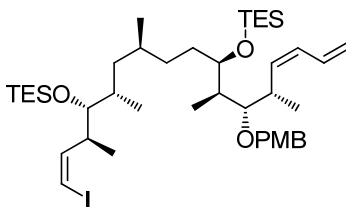


(3Z,5S,6S,7S,8R,11S,13S,14R,15S,16Z)-17-Iodo-6-(4-methoxybenzyloxy)-5,7,11,13,15-pentamethyl-14-(triethylsilyloxy)heptadeca-1,3,16-trien-8-ol (121):

The ketone **120** (8.24 g, 11.59 mmol) in THF (58 mL) at 0°C was treated with a 1.0 M solution of $\text{LiAlH}(\text{O}t\text{-Bu})_3$ in THF (57.96 mL, 57.96 mmol). After 24 h, the reaction was quenched with sat. aq. NH_4Cl (100 mL) and diluted with diethyl ether (100 mL). The mixture was extracted with diethyl ether (3 \times 100 mL) and the combined organic layers were washed with brine, dried (MgSO_4) and concentrated. Purification by chromatography (9:1 hexanes/ EtOAc) provided the title compound (6.01 g, 70%) as a colorless oil and the less polar C19 α -epimer contaminated with impurities: ^1H NMR (300 MHz, CDCl_3) δ 7.27 (d, $J = 8.7$ Hz, 2H), 6.86 (d, $J = 8.7$ Hz, 2H), 6.74 (dt, $J = 10.8, 16.8$ Hz, 1H), 6.33 (dd, $J = 7.2, 8.4$ Hz, 1H), 6.13 (d, $J = 7.5$ Hz, 1H), 6.07 (t, $J = 11.1$ Hz, 1H), 5.54 (t, $J = 10.5$ Hz, 1H), 5.27 (dd, $J = 1.2, 16.8$ Hz, 1H), 5.16 (d, $J = 10.2$ Hz, 1H), 4.72 (d, $J = 10.5$ Hz, 1H), 4.42 (d, $J = 10.2$ Hz, 1H), 3.79 (s, 3H), 3.69 (m, 1H), 3.52–3.36 (m, 2H), 3.06 (m, 1H), 2.81 (d, $J = 1.8$ Hz, 1H), 2.69 (m, 1H), 1.72 (m, 1H), 1.65–1.20 (m, 9H), 1.04 (d, $J = 6.9$ Hz, 3H), 1.02–0.92 (m, 15H), 0.89 (d, $J = 6.3$ Hz, 3H), 0.85 (d, $J = 6.6$ Hz, 3H), 0.67–0.59 (m, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ 159.3,

144.0, 135.4, 132.5, 130.3, 129.8, 129.5, 117.9, 113.8, 87.8, 81.4, 80.1, 75.4, 74.2, 55.3, 43.1, 41.2, 38.9, 35.6, 35.5, 32.4, 32.1, 30.4, 20.8, 18.2, 17.8, 15.9, 7.3, 6.7, 5.7; LRMS (ESI) 735 [M + Na]⁺; HRMS (ESI) calcd. for C₃₆H₆₁IO₄SiNa 735.3281, found 735.3287.

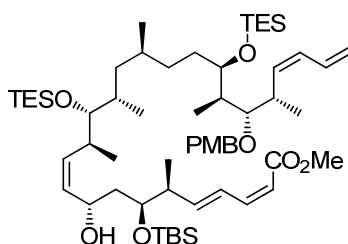
The C19 α -epimer of 121: ¹H NMR (300 MHz, CDCl₃) δ 7.25 (d, J = 6.9 Hz, 2H), 6.86 (d, J = 8.7 Hz, 2H), 6.67 (dt, J = 10.8, 17.1 Hz, 1H), 6.30 (t, J = 8.7 Hz, 1H), 6.13 (d, J = 7.5 Hz, 1H), 6.00 (t, J = 10.8 Hz, 1H), 5.58 (t, J = 10.5 Hz, 1H), 5.25 (dd, J = 1.5, 16.5 Hz, 1H), 5.10 (d, J = 9.9 Hz, 1H), 4.58 (d, J = 10.8 Hz, 1H), 4.52 (d, J = 10.5 Hz, 1H), 3.80 (s, 3H), 3.60–3.51 (m, 2H), 3.46 (m, 2H), 3.01 (m, 1H), 2.69 (m, 1H), 2.58 (d, J = 4.8 Hz, 1H), 1.79 (m, 1H), 1.55–1.23 (m, 8H), 1.12–0.85 (m, 24H), 0.68–0.58 (m, 6H).



(5R,6S,8S,11R)-3,3,13,13-Tetraethyl-5-((S,Z)-4-iodobut-3-en-2-yl)-11-(((2R,3S,4S,Z)-3-(4-methoxybenzyloxy)-4-methylocta-5,7-dien-2-yl)-6,8-dimethyl-4,12-dioxo-3,13-disilapentadecane (111):

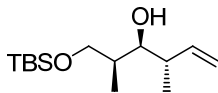
Following the procedure for the TBS ether **34**, the alcohol **121** (6.00 g, 8.42 mmol) in CH₂Cl₂ (84 mL) was protected with TESOTf (2.28 mL, 10.10 mmol) and 2,6-lutidine (1.37 mL, 11.79 mmol). Purification by chromatography (9:1 hexanes/EtOAc) provided the title compound (6.89 g, 99%) as a colorless oil: ¹H NMR (300 MHz, CDCl₃) δ 7.32 (d, J = 8.7 Hz, 2H), 6.90 (d, J = 8.7 Hz, 2H), 6.64 (dt, J = 10.5, 16.8 Hz, 1H), 6.30 (dd, J = 7.5, 8.7 Hz, 1H), 6.16 (d, J = 7.5 Hz, 1H), 6.07 (t, J = 11.1 Hz, 1H), 5.63 (t, J = 10.5 Hz, 1H), 5.23 (d, J = 16.8 Hz, 1H), 5.13 (d, J = 10.2 Hz, 1H), 4.59 (d, J = 10.5 Hz, 1H), 4.53 (d, J = 10.8 Hz, 1H), 3.82 (s, 3H), 3.67 (m, 1H),

3.48 (t, $J = 4.2$ Hz, 1H), 3.36 (dd, $J = 3.3, 7.5$ Hz, 1H), 3.02 (m, 1H), 2.70 (m, 1H), 1.75–1.50 (m, 3H), 1.47–1.20 (m, 8H), 1.14 (d, $J = 6.9$ Hz, 3H), 1.07–0.95 (m, 24H), 0.87 (d, $J = 6.6$ Hz, 3H), 0.85 (d, $J = 6.3$ Hz, 3H), 0.68–0.60 (m, 12H); ^{13}C NMR (75 MHz, CDCl_3) δ 159.1, 144.1, 134.8, 132.4, 131.4, 129.2, 129.0, 117.3, 113.7, 84.5, 81.4, 80.0, 75.1, 73.1, 43.4, 41.5, 40.7, 35.4, 35.2, 32.6, 31.2, 30.6, 20.6, 18.9, 17.6, 15.6, 9.3, 7.3, 5.7; LRMS (ESI) 849 $[\text{M} + \text{Na}]^+$; HRMS (ESI) calcd. for $\text{C}_{42}\text{H}_{75}\text{IO}_4\text{Si}_2\text{Na}$ 849.4146, found 849.4153.



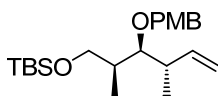
(2Z,4E,6S,7S,9S,10Z,12S,13R,14S,16S,19R,20R,21S,22S,23Z)-Methyl 7-(*tert*-butyldimethylsilyloxy)-9-hydroxy-21-(4-methoxybenzyloxy)-6,12,14,16,20,22-hexamethyl-13,19-bis(triethylsilyloxy)hexacosanoate (122 α):

Following the procedure for the alcohol **84 α** , the vinyl iodide **111** (1.00 g, 1.21 mmol) in diethyl ether (24 mL) was treated with a 1.7 M solution of *tert*-BuLi in pentane (1.78 mL, 3.02 mmol), (–)-sparteine (0.36 mL, 1.57 mmol) and the aldehyde **112** (0.47 g, 1.45 mmol). Purification by chromatography (9:1 hexanes/EtOAc) provided the title compound (0.32 g, 26%) as a colorless oil and the less polar C9 β -epimer **122 β** (0.32 g, 26%): ^1H NMR (300 MHz, CDCl_3) δ 7.42 (dd, $J = 11.3, 15.3$ Hz, 1H), 7.29 (d, $J = 7.8$ Hz, 2H), 6.88 (d, $J = 8.7$ Hz, 2H), 6.91–6.85 (m, 2H), 6.21 (dd, $J = 6.3, 15.0$ Hz, 1H), 6.00 (t, $J = 11.1$ Hz, 1H), 5.61–5.55 (m, 2H), 5.44–5.32 (m, 2H), 5.20 (d, $J = 16.5$ Hz, 1H), 5.10 (d, $J = 10.5$ Hz, 1H), 4.58–4.39 (m, 3H), 3.93 (m, 1H), 3.80 (s, 3H), 3.72 (s, 3H), 3.33–3.28 (m, 2H), 2.99 (m, 1H), 2.72–2.59 (m, 2H), 2.34 (s,



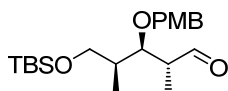
(2*S*,3*S*,4*S*)-1-(*tert*-Butyldimethylsilyloxy)-2,4-dimethylhex-5-en-3-ol (132):

Following the procedure for the crotylated product **63**, the title alcohol (136.05 g, 0.53 mol) was synthesized from the crude aldehyde (128.46 g, 0.63 mol) and the Roush reagent **62** (2 M in toluene, 425 mL, 0.85 mol) in four steps and 58% overall yield, starting from the (*S*)-Roche ester. This is a known compound (reference 45).



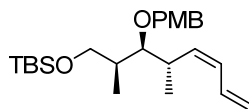
***tert*-Butyl((2*S*,3*S*,4*S*)-3-(4-methoxybenzyloxy)-2,4-dimethylhex-5-enyloxy)dimethylsilane (133):**

Following the procedure for the same compound in reference 9b, the title PMB ether (72.35 g, 0.19 mol) was synthesized from the alcohol **132** (58.95 g, 0.23 mol), PMBBr (100.00 g, 0.50 mol) and NaH (60 wt. %, 12.0 g, 0.60 mol) in 84% yield.



(2*R*,3*R*,4*S*)-5-(*tert*-Butyldimethylsilyloxy)-3-(4-methoxybenzyloxy)-2,4-dimethylpentanal (134):

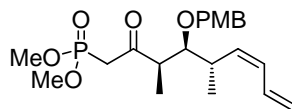
Following the procedure for the same compound in reference 9b, the alkene **133** (24.70 g, 65.30 mmol) was ozonized to give the crude aldehyde (24.84 g). The aldehyde was used for the next reaction without further purification.



***tert*-Butyl((2*S*,3*S*,4*S*,*Z*)-3-(4-methoxybenzyloxy)-2,4-dimethylocta-5,7-dienyloxy)dimethylsilane (136):**

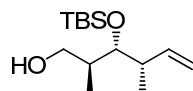
A Matteson reagent **135**⁶⁶ (20.88 g, 86.93 mmol) was added to a mixture of 4 Å molecular sieves (3.0 g, powdered) and the above-obtained aldehyde (24.84 g) in diethylether (65 mL) at room temperature. After 2 days, the mixture was diluted with H₂O (100 mL), and extracted with diethyl ether (3 × 100 mL). The combined organic layers were washed with brine, dried (MgSO₄) and concentrated to give the crude β -hydroxysilane (35.2 g).

A solution of the β -hydroxysilane in THF (650 mL) at 0 °C was treated with NaH (95 wt. %, 33.00 g, 1.31 mol) portionwise over 30 min. The mixture was warmed to room temperature and stirred for 2 h. Then the mixture was carefully poured into a mixture of ice and NH₄Cl. The mixture was extracted with diethyl ether (3 × 100 mL). The combined organic layers were washed with brine, dried (MgSO₄) and concentrated. Purification by column chromatography (95:5 hexanes/EtOAc) provided the title compound (19.10 g, 72% yield for three steps). This is a known compound (reference 24(c)).



Dimethyl (3*R*,4*S*,5*S*,*Z*)-4-(4-methoxybenzyloxy)-3,5-dimethyl-2-oxonona-6,8-dienylphosphonate (99):

Following the procedures for the same compound in reference 24(c), the title phosphonate (7.80 g) was synthesized from the TBS ether **136** (19.00 g, 46.73 mol) in 61% yield for four steps.

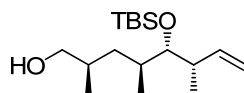


(2*S*,3*R*,4*S*)-3-(*tert*-Butyldimethylsilyloxy)-2,4-dimethylhex-5-en-1-ol (137):

Following the procedure for the TBS ether **34**, the alcohol **132** (58.0 g, 224.4 mmol) was protected with TBSOTf (56.7 mL, 246.8 mmol) and 2,6-lutidine (39.2 mL, 336.2 mmol) in CH₂Cl₂ (224 mL). After workup, the crude TBS ether (92.35 g) was used for the next reaction without further purification.

A solution of the TBS ether in CH₂Cl₂ (750 mL) and MeOH (700 mL) at -50 °C was treated with a solution of camphor-10-sulfonic acid (10.4 g, 44.9 mmol) in MeOH (50 mL) dropwise over 30 min. The mixture was warmed to -10 °C and stirred. After 2 h, additional camphor-10-sulfonic acid (10.4 g) was added. The mixture was stirred for 1.5 h. After quenching the reaction at -10 °C by addition of NaHCO₃ (15 g) and H₂O (150 mL), the mixture was concentrated under vacuum. The residue was extracted with ether (2 × 300 mL) and the combined organic layers were washed with brine, dried (MgSO₄) and concentrated. Purification by column chromatography (9:1 hexanes/EtOAc) provided the title compound (38.6 g, 67% over

two steps) as a colorless oil: IR (NaCl) 3346, 2958, 2931, 2886, 2858, 1462, 1254, 1041 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 5.89 (ddd, $J = 8.0, 10.5, 17.0$ Hz, 1H), 5.05–4.95 (m, 2H), 3.66 (t, $J = 3.5$ Hz, 1H), 3.61 (dd, $J = 7.5, 11.0$ Hz, 1H), 2.46 (s, 1H), 2.40 (m, 1H), 1.88 (m, 1H), 1.02 (d, $J = 7.0$ Hz, 3H), 0.90 (s, 9H), 0.87 (d, $J = 7.0$ Hz, 3H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 141.6, 114.3, 77.0, 65.6, 41.9, 39.6, 26.0, 18.2, 17.9, 12.3, $-3.9, -4.1$; LRMS (ESI) 281 $[\text{M} + \text{Na}]^+$; HRMS (ESI) calcd. for $\text{C}_{14}\text{H}_{30}\text{O}_2\text{SiNa}$ 281.1913, found 281.1918; $[\alpha]_{\text{D}}^{20} -2.0$ (c 0.70, CHCl_3).



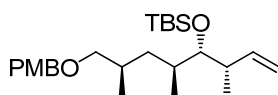
(2R,4S,5S,6S)-5-(*tert*-Butyldimethylsilyloxy)-2,4,6-trimethyloct-7-en-1-ol (139):

Iodination. PPh_3 (94.0 g, 358 mmol), imidazole (24.4 g, 358 mmol) and DIPEA (62.4 mL, 358 mmol) were added to a mixture of benzene (440 mL), diethyl ether (900 mL) and acetonitrile (150 mL). Then, I_2 (90.9 g, 358 mmol) was added to the above solution portionwise over 1 h, maintaining the internal temperature at 15–25 $^\circ\text{C}$. The mixture was stirred at room temperature for 1.5 h. The alcohol **137** (62.0 g, 239 mmol) in diethyl ether (30 mL) was added. After 3 h, the reaction mixture was quenched with ice. H_2O (300 mL) was added to the mixture. The organic layer was separated, and washed with 0.5 N NaHSO_4 (300 mL \times 2) then sat. aq. NaHCO_3 (300 mL). Then, the organic layer was dried (MgSO_4) and concentrated. Pentane (500 mL) was added to the residue, and the mixture was filtered through a pad of Celite. The filtrate was concentrated. The crude iodide (92.05 g, 105% yield) was used for the next reaction without further purification.

Myers alkylation. A suspension of LiCl (128.6 g, 3035 mmol) and diisopropylamine (144.0 mL, 1028 mmol) in THF (500 mL) at $-78\text{ }^{\circ}\text{C}$ was treated with a solution of BuLi in hexane (1.6 M, 597.5 mL, 956 mmol) dropwise over 1 h, maintaining the internal temperature below $-65\text{ }^{\circ}\text{C}$. The mixture was warmed to $0\text{ }^{\circ}\text{C}$, stirred for 15 min, and then cooled to $-78\text{ }^{\circ}\text{C}$. The Myers amide **138** (111.1 g, 502 mmol) in THF (500 mL) was added to the above mixture dropwise over 1 h, maintaining the internal temperature below $-65\text{ }^{\circ}\text{C}$. The mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 2.5 h, and warmed to room temperature over 1 h, and stirred for 15 min, and then cooled to $-50\text{ }^{\circ}\text{C}$. The crude iodide was added dropwise over 1 h. The mixture was stirred at $0\text{ }^{\circ}\text{C}$ for 3 h and then at room temperature for 48 h. After quenching the reaction at $0\text{ }^{\circ}\text{C}$ by addition of sat. aq. NH_4Cl (100 mL) and H_2O (200 mL), the mixture was extracted with diethyl ether ($3 \times 300\text{ mL}$). The combined organic layers were washed with brine, dried (MgSO_4) and concentrated. A mixture of hexane (400 mL) and diethyl ether (100 mL) was added to the residue. The mixture was filtered through a pad of Celite. The filtrate was concentrated. The alkylated compound (115.3 g, 104%) was used for the next reaction without further purification.

Reductive removal of the auxiliary. A solution of diisopropylamine (107.0 mL, 765 mmol) in THF (765 mL) at $-78\text{ }^{\circ}\text{C}$ was treated with a solution of BuLi in hexane (1.6 M, 448.0 mL, 717 mmol) dropwise over 1 h, maintaining the internal temperature below $-65\text{ }^{\circ}\text{C}$. The mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 10 min, and then at $0\text{ }^{\circ}\text{C}$ for 10 min. $\text{BH}_3 \cdot \text{NH}_3$ (tech. 90%, 25.7 g, 748 mmol) was added to the mixture portionwise over 30 min, maintaining the internal temperature below $5\text{ }^{\circ}\text{C}$. The mixture was stirred at $0\text{ }^{\circ}\text{C}$ for 30 min, and at room temperature for 30 min, and then cooled to $0\text{ }^{\circ}\text{C}$. The above-obtained alkylated compound in THF (240 mL) was added to the reaction mixture dropwise over 25 min. The mixture was warmed to room

temperature and stirred for 6 h. After quenching the reaction at 0 °C by slow addition of 2 M NaOH (230 mL), the mixture was stirred at room temperature for 1.5 h, and then extracted with diethyl ether (2 × 300 mL). The combined organic layers were washed with brine, dried (MgSO₄) and concentrated. Hexane (400 mL) was added to the residue. The mixture was filtered through a pad of Celite. The filtrate was concentrated. Purification by column chromatography (4:1 hexanes/EtOAc) provided the title compound (56.0 g, 78% over three steps) as a colorless oil: IR (NaCl) 3347, 2957, 2929, 2857, 1460, 1253, 1038 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 5.84 (ddd, *J* = 8.0, 10.5, 18.0 Hz, 1H), 4.98–4.93 (m, 2H), 3.52 (dd, *J* = 4.5, 10.5 Hz, 1H), 3.37 (dd, *J* = 4.0, 4.5 Hz, 1H), 3.26 (dd, *J* = 7.0, 10.5 Hz, 1H), 2.51 (s, 1H), 2.35 (m, 1H), 1.68–1.63 (m, 2H), 1.38 (m, 1H), 0.99 (d, *J* = 7.0 Hz, 3H), 0.92–0.86 (m, 16H), 0.03 (s, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 142.1, 113.8, 79.0, 67.5, 42.7, 38.2, 33.9, 33.2, 26.1, 18.3, 17.8, 17.6, 15.7, –3.6, –3.7; LRMS (ESI) 323 [M + Na]⁺; HRMS (ESI) calcd. for C₁₇H₃₆O₂SiNa 323.2382, found 323.2375; [α]_D²⁰ –9.2 (*c* 0.13, CHCl₃).

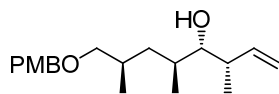


***tert*-Butyl((3*S*,4*S*,5*S*,7*R*)-8-(4-methoxybenzyloxy)-3,5,7-trimethyloct-1-en-4-yloxy)dimethylsilane:**

Preparation of trichloroimidate 24. A suspension of sodium hydride (0.79 g, 30 mol) in diethyl ether (300 mL) at –10 °C was treated with *p*-methoxybenzyl alcohol (47.7 g, 330 mmol) dropwise over 1 h. The mixture was warmed to room temperature, stirred for 30 min, and then cooled to –10 °C. A solution of trichloroacetonitrile (47.65 g, 330 mmol) in diethyl ether (100 mL) was added dropwise over 1 h. The mixture was warmed to 0 °C then stirred for 30 min. The

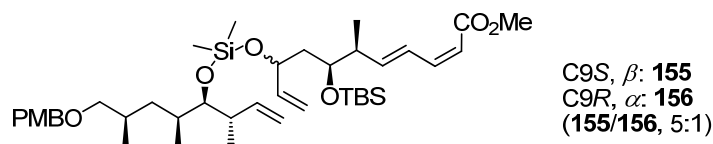
mixture was concentrated under vacuum, then pentane (400 mL) was added. The mixture was filtered through a pad of Celite. The filtrate was concentrated. The crude trichloroimidate (93.24 g) was used for the next reaction without further purification.

Formation of the PMB ether. A solution of the alcohol **139** (29.9 g, 99.7 mmol) in CH₂Cl₂ (100 mL) and cyclohexane (200 mL) at 0 °C was treated with trichloroimidate **24** (42.2 g) dropwise over 10 min. Then, BF₃•OEt₂ in CH₂Cl₂ (50 mL) was added over 8 h via syringe pump. After quenching the reaction at 0 °C by addition of ice and sat. aq. NaHCO₃ (200 mL), the mixture was warmed to room temperature and extracted with diethyl ether (3 × 200 mL). The combined organic layers were washed with brine, dried (MgSO₄) and concentrated. Purification by column chromatography (95:5 hexanes/EtOAc) provided the title compound (27.9 g, 70%) as a colorless oil: IR (NaCl) 2956, 2930, 2856, 1513, 1462, 1249, 1091 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.30 (d, *J* = 8.5 Hz, 2H), 6.92 (d, *J* = 9.0 Hz, 2H), 5.87 (ddd, *J* = 8.0, 10.5, 18.0 Hz, 1H), 5.03–4.98 (m, 2H), 4.49 (d, *J* = 11.5 Hz, 1H), 4.43 (d, *J* = 11.5 Hz, 1H), 3.84 (s, 3H), 3.43 (dd, *J* = 3.5, 4.5 Hz, 1H), 3.36 (dd, *J* = 4.5, 9.0 Hz, 1H), 3.18 (dd, *J* = 7.0, 9.0 Hz, 1H), 2.39 (m, 1H), 1.83 (m, 1H), 1.73 (m, 1H), 1.48 (m, 1H), 1.04 (d, *J* = 7.0 Hz, 3H), 0.99 (d, *J* = 6.5 Hz, 3H), 0.96–0.94 (m, 10H), 0.92 (d, *J* = 7.0 Hz, 3H), 0.09 (s, 3H), 0.07 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 159.0, 142.2, 130.9, 129.0, 127.5, 113.8, 113.7, 113.6, 79.1, 75.4, 72.6, 55.2, 42.8, 39.0, 34.0, 31.2, 26.2, 26.0, 18.4, 17.6, 15.7, -3.6, -3.7; LRMS (ESI) 443 [M + Na]⁺; HRMS (ESI) calcd. for C₂₅H₄₄O₃SiNa 443.2957, found 443.2968; [α]_D²⁰ -14.4 (*c* 0.25, CHCl₃).



(3*S*,4*S*,5*S*,7*R*)-8-(4-Methoxybenzyloxy)-3,5,7-trimethyloct-1-en-4-ol (128):

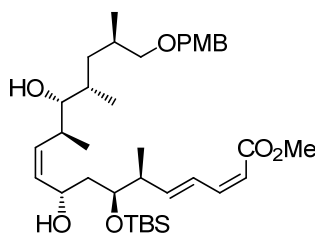
A solution of TBAF in THF (1.0 M, 164.5 mL, 164.5 mmol) was added to the above-obtained PMB ether (27.70 g, 65.84 mmol) at room temperature. The mixture was warmed to 50 °C, then stirred for 24 h. An additional solution of TBAF (65 mL) was added, and the mixture was stirred for 8 h. After quenching the reaction at room temperature by addition of brine (250 mL), the mixture was extracted with EtOAc (4 × 200 mL). The combined organic layers were washed with brine, dried (MgSO₄) and concentrated. Purification by column chromatography (4:1 hexanes/EtOAc) provided the title compound (12.8 g, 63%) as a colorless oil: IR (NaCl) 3465, 2961, 2931, 2870, 1513, 1247, 1091 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.27 (d, *J* = 8.7 Hz, 2H), 6.89 (d, *J* = 8.4 Hz, 2H), 5.74 (m, 1H), 5.15–5.10 (m, 2H), 4.43 (s, 3H), 3.81 (s, 3H), 3.35 (dd, *J* = 5.4, 9.0 Hz, 1H), 3.23–3.11 (m, 2H), 2.27 (m, 1H), 1.86 (m, 1H), 1.76 (m, 1H), 1.60–1.50 (m, 2H), 0.98 (d, *J* = 6.6 Hz, 3H), 0.94 (d, *J* = 6.6 Hz, 3H), 0.89 (d, *J* = 6.9 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 159.7, 142.4, 131.4, 129.6, 116.3, 114.3, 76.7, 76.2, 73.2, 55.7, 42.4, 38.9, 32.4, 31.3, 18.7, 17.2, 14.0; LRMS (ESI) 329 [M + Na]⁺; HRMS (ESI) calcd. for C₁₉H₃₀O₃SiNa 329.2093, found 329.2088; [α]_D²⁰ -3.9 (*c* 0.58, CHCl₃).



Mixture of the silylketals **155** and **156**:

A solution of the C11'–C17 alcohol **128** (1.12 g, 3.67 mmol) in THF (30 mL) at $-78\text{ }^{\circ}\text{C}$ was treated with a 1.6 M solution of BuLi in hexane (2.50 mL, 4.04 mmol) dropwise over 3 min. The mixture was stirred for 15 min and warmed to room temperature over 15 min, and then cooled to $-78\text{ }^{\circ}\text{C}$. Dichlorodimethylsilane (3.54 mL, 29.36 mmol) was added to the mixture, which was warmed to room temperature over 15 min and stirred for 1.5 h. The mixture was concentrated under vacuum for 4 h. CH_2Cl_2 (3 mL) was added to the residue and the mixture was cooled to $0\text{ }^{\circ}\text{C}$. A mixture of the C9 *S/R* alcohols **151** and **152** (1.30 g, 3.67 mmol) and imidazole (0.97 g, 14.68 mmol) in CH_2Cl_2 (3.7 mL) was added to the reaction mixture. This was warmed to room temperature and stirred for 36 h. After quenching the reaction by addition of sat. aq. NaHCO_3 (10 mL), the mixture was extracted with EtOAc ($3 \times 15\text{ mL}$) and the combined organic layers were washed with brine, dried (MgSO_4) and concentrated. Purification by column chromatography (95:5 to 9:1 hexanes/EtOAc) provided the title compound (2.23 g, 85%) as a colorless oil: IR (NaCl) 2959, 2931, 2857, 1720, 1254, 1089 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.38 (dd, $J = 11.4, 15.6\text{ Hz}$, 1H), 7.27 (d, $J = 8.1\text{ Hz}$, 2H), 6.89 (d, $J = 8.7\text{ Hz}$, 2H), 6.60 (t, $J = 11.4\text{ Hz}$, 1H), 6.19 (dd, $J = 6.9, 15.6\text{ Hz}$, 1H), 5.93–5.75 (m, 2H), 5.60 (d, $J = 11.4\text{ Hz}$, 1H), 5.20–4.92 (m, 4H), 4.46 (q, $J = 12.0\text{ Hz}$, 2H), 4.29 (m, 1H), 3.81 (m, 4H), 3.77 (s, 3H), 3.41–3.32 (m, 2H), 3.16 (dd, $J = 7.5, 9.0\text{ Hz}$, 1H), 2.53 (m, 1H), 2.34 (q, $J = 6.6\text{ Hz}$, 1H), 1.87 (m, 1H), 1.80–1.60 (m, 2H), 1.50–1.30 (m, 2H), 1.05 (d, $J = 5.1\text{ Hz}$, 3H), 0.98–0.92 (m, 7H), 0.89–0.84 (m,

12H), 0.10–0.04 (m, 12H); ^{13}C NMR (75 MHz, CDCl_3) δ 166.7, 159.0, 147.9, 145.6, 142.0, 141.6, 130.8, 128.9, 126.3, 115.3, 114.4, 114.1, 113.6, 80.1, 75.2, 72.6, 71.6, 55.0, 50.8, 42.6, 42.2, 41.8, 38.6, 33.4, 31.0, 25.9, 18.5, 18.0, 17.5, 14.8, 13.8, 1.0, -0.6, -1.0, -4.1, -4.2; LRMS (ESI) 739 $[\text{M} + \text{Na}]^+$; HRMS (ESI) calcd. for $\text{C}_{40}\text{H}_{68}\text{O}_7\text{Si}_2\text{Na}$ 739.4401, found 739.4431; $[\alpha]_D^{20}$ -34.4 (*c* 1.10, CHCl_3).



(2Z,4E,6S,7S,9S,10Z,12S,13R,14S,16R)-Methyl 7-(*tert*-butyldimethylsilyloxy)-9,13-dihydroxy-17-(4-methoxybenzyloxy)-6,12,14,16-tetramethylheptadeca-2,4,10-trienoate (157):

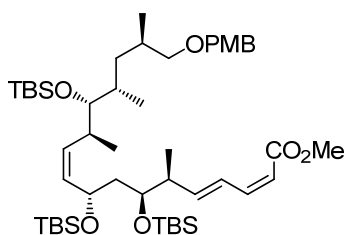
Ring-closing metathesis. A solution of the silylketal mixture **155** and **156** (2.23 g, 3.11 mmol) in degassed benzene (310 mL, argon-sparged) was treated with a Hoveyda-Grubbs II catalyst (0.1 g, 0.16 mmol). The mixture was warmed to 90 °C and stirred for 1 h. An additional catalyst (0.1 g, 0.16 mmol) in benzene (16 mL) was added to the mixture over 2 h via a syringe pump. After 3 h, an additional catalyst (0.1 g, 0.16 mmol) was added. After 1h, the mixture was cooled to room temperature and concentrated under vacuum. Purification of the residue by column chromatography (9:1 hexanes/EtOAc) provided the disiloxane mixture **148** and **149** (1.23 g, 57%) contaminated with impurity, and a mixture of the 11-membered disiloxane **150** and the recovered silylketals (0.21 g, 10% yield).

Deprotection. A solution of the disiloxane mixture **148** and **149** (1.23 g, 1.78 mmol) in CH₂Cl₂ (35 mL) and MeOH (25 mL) at 0 °C was treated with a solution of dichloroacetic acid (0.74 mL, 8.93 mmol) in MeOH (10 mL) dropwise over 1 min. The mixture was stirred at 0 °C for 3 h, and then an additional solution of dichloroacetic acid (0.37 mL, 4.47 mmol) in MeOH (5 mL) was added. The mixture was stirred for 1 h. After quenching the reaction at 0 °C by addition of sat. aq. NaHCO₃ (50 mL), the mixture was concentrated under vacuum. The residue was extracted with EtOAc (3 × 50 mL) and the combined organic layers were washed with brine, dried (MgSO₄) and concentrated. Purification by column chromatography (4:1 hexanes/EtOAc with 2% MeOH) provided the title compound (more polar, 0.73 g, 65%) and the impure C₉R diol (0.12 g, 10% yield): IR (NaCl) 3415, 2957, 2930, 2857, 1718, 1250, 1069 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 7.41 (dd, *J* = 11.1, 15.4 Hz, 1H), 7.25 (d, *J* = 8.3 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 6.58 (t, *J* = 11.3 Hz, 1H), 6.17 (dd, *J* = 6.9, 15.5 Hz, 1H), 5.59 (d, *J* = 11.3 Hz, 1H), 5.51 (dd, *J* = 8.0, 11.0 Hz, 1H), 5.30 (t, *J* = 10.6 Hz, 1H), 4.65 (t, *J* = 7.6 Hz, 1H), 4.43 (q, *J* = 11.8 Hz, 2H), 3.90 (m, 1H), 3.80 (s, 3H), 3.73 (s, 3H), 3.29 (dd, *J* = 5.7, 8.9 Hz, 1H), 3.21 (m, 1H), 3.17 (m, 1H), 2.72 (m, 1H), 2.65 (m, 1H), 1.86 (m, 1H), 1.75 (m, 1H), 1.65–1.49 (m, 3H), 1.10 (d, *J* = 6.8 Hz, 3H), 1.06 (m, 1H), 0.96–0.90 (m, 15H), 0.86 (d, *J* = 6.7 Hz, 3H), 0.15–0.10 (m, 6H); ¹³C NMR (151 MHz, CDCl₃) δ 166.9, 159.1, 147.1, 145.6, 134.7, 133.9, 130.7, 129.2, 129.1, 126.7, 115.5, 113.8, 113.7, 76.2, 75.8, 73.6, 72.6, 65.2, 55.2, 51.1, 42.2, 40.3, 38.4, 36.1, 31.4, 30.6, 26.0, 25.9, 18.0, 17.9, 17.4, 17.3, 15.5, 13.0, -4.4, -4.5; LRMS (ESI) 655 [M + Na]⁺; HRMS (ESI) calcd. for C₃₆H₆₀O₇SiNa 655.4006, found 655.4026; [α]_D²⁰ -27.8 (*c* 0.50, CHCl₃).

The 11-membered disiloxane 150: ¹H NMR (300 MHz, CDCl₃) δ 7.27 (d, *J* = 9.0 Hz, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 5.64 (m, 1H), 5.52 (m, 1H), 5.40–5.35 (m, 2H), 4.50–4.35 (m,

3H), 3.81 (s, 3H), 3.69 (m, 1H), 3.40–3.33 (m, 2H), 3.15 (t, $J = 7.5$ Hz, 1H), 2.33 (m, 1H), 2.12–1.95 (m, 3H), 1.93–1.77 (m, 2H), 1.75–1.62 (m, 2H), 1.50–1.25 (m, 6H), 1.06 (d, $J = 7.2$ Hz, 3H), 1.00–0.80 (m, 24H), 0.15–0.03 (m, 12H).

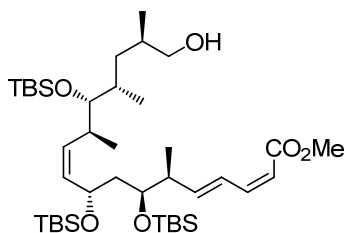
The C9R diol 158: ^1H NMR (300 MHz, CDCl_3) δ 7.37 (dd, $J = 11.1, 15.6$ Hz, 1H), 7.25 (d, $J = 8.7$ Hz, 2H), 6.89 (d, $J = 8.7$ Hz, 2H), 6.59 (t, $J = 11.1$ Hz, 1H), 6.23 (dd, $J = 6.3, 15.3$ Hz, 1H), 5.52 (d, $J = 11.1$ Hz, 1H), 5.51 (dd, $J = 7.8, 10.8$ Hz, 1H), 5.35 (t, $J = 10.2$ Hz, 1H), 4.49–4.47 (m, 1H), 4.42 (s, 2H), 3.81 (s, 3H), 3.77 (m, 1H), 3.73 (s, 3H), 3.25 (d, $J = 6.0$ Hz, 2H), 3.17 (dd, $J = 1.5, 8.1$ Hz, 1H), 2.70 (m, 1H), 2.59 (m, 1H), 1.86–1.50 (m, 6H), 1.05 (d, $J = 7.2$ Hz, 3H), 0.95–0.80 (m, 18H), 0.07 (s, 6H).



(2Z,4E,6S,7S,9S,10Z,12S,13R,14S,16R)-Methyl 7,9,13-tris(*tert*-butyldimethylsilyloxy)-17-(4-methoxybenzyloxy)-6,12,14,16-tetramethylheptadeca-2,4,10-trienoate (159):

A solution of the alcohol **157** (0.20 g, 0.32 mmol) and 2,6-lutidine (0.15 mL, 1.26 mmol) in CH_2Cl_2 (6 mL) at -78 °C was treated with TBSOTf (0.22 mL, 0.95 mmol). The reaction mixture was warmed to 0 °C and stirred for 1.5 h. After quenching the reaction by addition of H_2O , the mixture was extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine, dried (MgSO_4) and concentrated. Purification by column chromatography (9:1 hexanes/EtOAc) provided the title compound (0.23 g, 85%) as a colorless oil: IR (NaCl) 2957, 2931, 2858, 1721, 1252, 1090 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 7.35 (dd, $J = 11.3, 15.5$

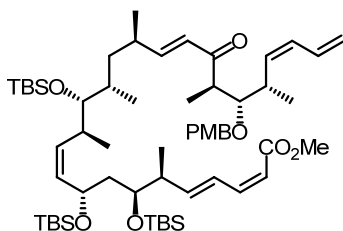
Hz, 1H), 7.25 (d, $J = 8.4$ Hz, 2H), 6.88 (d, $J = 8.4$ Hz, 2H), 6.54 (t, $J = 11.3$ Hz, 1H), 6.22 (dd, $J = 5.9, 15.6$ Hz, 1H), 5.55 (d, $J = 11.3$ Hz, 1H), 5.38 (t, $J = 10.5$ Hz, 1H), 5.25 (dd, $J = 8.4, 10.8$ Hz, 1H), 4.54 (t, $J = 9.2$ Hz, 1H), 4.41 (q, $J = 11.7$ Hz, 2H), 3.93 (dd, $J = 3.4, 9.0$ Hz, 1H), 3.81 (s, 3H), 3.72 (s, 3H), 3.35 (m, 1H), 3.32 (dd, $J = 4.7, 9.0$ Hz, 1H), 3.08 (t, $J = 8.3$ Hz, 1H), 2.55 (m, 2H), 1.75 (m, 1H), 1.62 (m, 1H), 1.51–1.30 (m, 3H), 1.04 (d, $J = 6.9$ Hz, 3H), 0.95 (d, $J = 6.8$ Hz, 3H), 0.92–0.87 (m, 31H), 0.85 (d, $J = 6.8$ Hz, 3H), 0.10–0.00 (m, 18H); ^{13}C NMR (151 MHz, CDCl_3) δ 166.7, 159.1, 146.8, 145.7, 132.7, 132.4, 130.8, 129.0, 126.6, 115.1, 113.6, 79.8, 75.4, 72.8, 72.6, 66.4, 55.0, 50.8, 42.9, 42.2, 37.8, 35.6, 35.4, 31.6, 31.2, 26.3, 26.2, 26.0, 25.9, 19.5, 18.8, 18.4, 18.1, 15.5, 14.6, -2.8, -3.5, -3.8, -4.2; LRMS (ESI) 883 $[\text{M} + \text{Na}]^+$; HRMS (ESI) calcd. for $\text{C}_{48}\text{H}_{88}\text{O}_7\text{Si}_3\text{Na}$ 883.5736, found 883.5770; $[\alpha]_D^{20} -72.2$ (c 0.68, CHCl_3).



(2Z,4E,6S,7S,9S,10Z,12S,13R,14S,16R)-Methyl 7,9,13-tris(*tert*-butyldimethylsilyloxy)-17-hydroxy-,12,14,16-tetramethylheptadeca-2,4,10-trienoate (160):

A mixture of the PMB ether **159** (0.73 g, 0.85 mmol), CH_2Cl_2 (17 mL) and pH 7 buffer (0.85 mL) at 0 °C was treated with DDQ (0.23 g, 1.02 mmol). The mixture was stirred for 1.5 h. After quenching the reaction at 0 °C by addition of sat. aq. NaHCO_3 (20 mL), the mixture was warmed to room temperature and extracted with diethyl ether (3 \times 20 mL). The combined organic layers were washed with sat. aq. NaHCO_3 and brine, dried (MgSO_4) and concentrated. Purification by column chromatography (9:1 hexanes/EtOAc) provided the title compound (0.44

g, 73%) as a colorless oil: IR (NaCl) 3376, 2957, 2931, 2858, 1723, 1463, 1254, 1070 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.35 (dd, $J = 11.3, 15.5$ Hz, 1H), 6.56 (t, $J = 11.3$ Hz, 1H), 6.22 (dd, $J = 6.0, 15.6$ Hz, 1H), 5.58 (d, $J = 11.1$ Hz, 1H), 5.44 (t, $J = 10.2$ Hz, 1H), 5.28 (dd, $J = 8.4, 11.2$ Hz, 1H), 4.56 (t, $J = 9.0$ Hz, 1H), 3.95 (dd, $J = 2.9, 8.1$ Hz, 1H), 3.74 (s, 3H), 3.52 (m, 1H), 3.38–3.30 (m, 2H), 2.57 (m, 2H), 1.64–1.58 (m, 2H), 1.50–1.23 (m, 3H), 1.05 (d, $J = 6.9$ Hz, 3H), 0.98 (d, $J = 7.0$ Hz, 3H), 0.92–0.86 (m, 31H), 0.11–0.03 (m, 18H); ^{13}C NMR (75 MHz, CDCl_3) δ 167.4, 147.5, 146.2, 133.3, 132.8, 127.1, 115.7, 80.4, 73.4, 68.1, 66.9, 51.5, 43.4, 42.7, 37.8, 36.1, 36.0, 33.8, 26.8, 26.5, 20.1, 18.9, 18.6, 16.1, 15.2, -2.2, -3.0, -3.1; LRMS (ESI) 763 $[\text{M} + \text{Na}]^+$; HRMS (ESI) calcd. for $\text{C}_{40}\text{H}_{80}\text{O}_6\text{Si}_3\text{Na}$ 763.5160, found 763.5157; $[\alpha]_D^{20}$ -96.1 (c 0.34, CHCl_3).



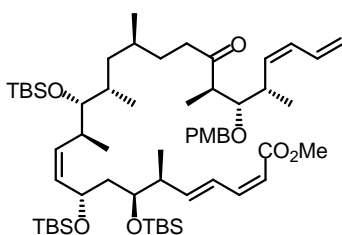
(2Z,4E,6S,7S,9S,10Z,12S,13R,14S,16R,17E,20R,21S,22S,23Z)-Methyl 7,9,13-tris(*tert*-butyldimethylsilyloxy)-21-(4-methoxybenzyloxy)-6,12,14,16,20,22-hexamethyl-19-oxohexacos-2,4,10,17,23,25-hexaenoate (161):

A solution of the alcohol **160** (0.42 g, 0.57 mmol) in CH_2Cl_2 (5.7 mL) at 0 °C was treated with Dess–Martin periodinane (0.29 g, 0.68 mmol). The mixture was warmed to room temperature and stirred for 2 h. After quenching the reaction by addition of a mixture of sat. aq. $\text{Na}_2\text{S}_2\text{O}_3$ (3 mL) and sat. aq. NaHCO_3 (3 mL), the mixture was extracted with EtOAc (3 \times 10 mL). The combined organic layers were washed with sat. aq. NaHCO_3 (10 mL) and brine, then

dried over MgSO₄. Concentration under vacuum provided the crude aldehyde **125** (0.51 g), which was used in the next step without further purification: ¹H NMR (300 MHz, CDCl₃) δ 9.48 (d, *J* = 2.7 Hz, 1H), 7.35 (dd, *J* = 10.9, 15.2 Hz, 1H), 6.55 (t, *J* = 11.2 Hz, 1H), 6.24 (dd, *J* = 5.6, 15.4 Hz, 1H), 5.59 (d, *J* = 11.1 Hz, 1H), 5.45 (t, *J* = 10.0 Hz, 1H), 5.28 (dd, *J* = 8.7, 10.8 Hz, 1H), 4.55 (t, *J* = 9.2 Hz, 1H), 3.95 (dd, *J* = 2.0, 6.0 Hz, 1H), 3.72 (s, 3H), 3.39 (m, 1H), 2.65–2.50 (m, 3H), 2.34 (m, 1H), 1.84 (m, 1H), 1.65–1.42 (m, 3H), 1.27 (m, 1H), 1.08–1.01 (m, 6H), 0.98 (d, *J* = 6.9 Hz, 3H), 0.93–0.85 (m, 31H), 0.11–0.02 (m, 18H).

A solution of the phosphonate **99** (0.35 g, 0.85 mmol) in THF (2.8 mL) at room temperature was treated with Ba(OH)₂ (0.10 g, 0.57 mmol). The mixture was stirred for 0.5 h, and then the aldehyde **125** in THF (5.6 mL) and water (0.14 mL) was added. The mixture was stirred for 12 h. After quenching the reaction by addition of water (10 mL), the mixture was extracted with diethyl ether (3 × 10 mL). The combined organic layers were washed with brine, dried (MgSO₄) and concentrated. Purification by column chromatography (15:1 hexanes/EtOAc) provided the title compound (0.51 g, 89% over two steps) as a colorless oil: IR (NaCl) 3351, 2958, 2931, 2857, 1722, 1630, 1462, 1251, 1072 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.36 (dd, *J* = 11.5, 15.5 Hz, 1H), 7.28 (d, *J* = 9.0 Hz, 2H), 6.88 (d, *J* = 8.5 Hz, 2H), 6.65 (dd, *J* = 8.0, 15.5 Hz, 1H), 6.53 (t, *J* = 11.0 Hz, 1H), 6.39 (dt, *J* = 10.5, 16.5 Hz, 1H), 6.22 (dd, *J* = 6.0, 15.5 Hz, 1H), 6.04 (dd, *J* = 11.5, 15.0 Hz, 1H), 6.01 (t, *J* = 10.5 Hz, 1H), 5.57 (d, *J* = 11.0 Hz, 1H), 5.53 (t, *J* = 10.5 Hz, 1H), 5.41 (t, *J* = 8.5 Hz, 1H), 5.26 (dd, *J* = 8.5, 11.0 Hz, 1H), 5.15 (d, *J* = 16.5 Hz, 1H), 5.02 (d, *J* = 10.0 Hz, 1H), 4.57–4.50 (m, 3H), 3.95 (dd, *J* = 3.5, 8.0 Hz, 1H), 3.87 (s, 3H), 3.72 (s, 3H), 3.69 (dd, *J* = 3.5, 8.5 Hz, 1H), 3.35 (t, *J* = 3.5 Hz, 1H), 2.93 (m, 1H), 2.79 (m, 1H), 2.60–2.50 (m, 2H), 2.20 (m, 1H), 1.53–1.42 (m, 2H), 1.35–1.25 (m, 2H), 1.19 (d, *J* = 7.0

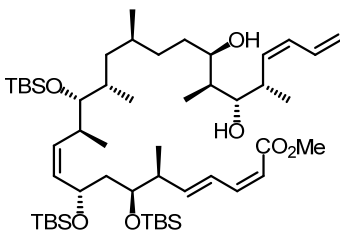
Hz, 3H), 1.09 (d, $J = 7.0$ Hz, 3H), 1.05 (d, $J = 7.0$ Hz, 3H), 1.02 (m, 1H), 0.98–0.94 (m, 6H), 0.91–0.87 (m, 27H), 0.83 (d, $J = 7.0$ Hz, 3H), 0.11–0.00 (m, 18H); ^{13}C NMR (125 MHz, CDCl_3) δ 166.7, 159.1, 152.6, 146.7, 145.5, 133.9, 132.6, 132.4, 132.1, 130.7, 129.6, 129.3, 127.9, 126.5, 125.4, 117.3, 115.2, 113.6, 84.1, 80.0, 75.3, 72.8, 66.3, 55.1, 50.9, 48.7, 42.9, 42.1, 38.9, 36.4, 36.0, 34.5, 34.4, 30.3, 26.2, 25.9, 20.7, 19.8, 18.9, 18.3, 18.1, 15.2, 14.6, 14.3, -2.7, -3.7, -4.1, -4.2; LRMS (ESI) 1045 $[\text{M} + \text{Na}]^+$; HRMS (ESI) calcd. for $\text{C}_{59}\text{H}_{102}\text{O}_8\text{Si}_3\text{Na}$ 1045.6780, found 1045.6769; $[\alpha]_{\text{D}}^{20}$ -51.0 (c 0.30, CHCl_3).



(2Z,4E,6S,7S,9S,10Z,12S,13R,14S,16S,20R,21S,22S,23Z)-Methyl 7,9,13-tris(*tert*-butyldimethylsilyloxy)-21-(4-methoxybenzyloxy)-6,12,14,16,20,22-hexamethyl-19-oxohexacos-2,4,10,23,25-pentaenoate (164):

A mixture of $[\text{Ph}_3\text{PCuH}]_6$ (red powder, 0.78 g, 0.40 mmol) in benzene (12.5 mL, argon-sparged) at 0 °C was treated with a solution of the enone **161** (0.51g, 0.50 mmol) in benzene (2 mL). The mixture was warmed to room temperature and stirred for 1.5 h. After quenching the reaction by addition of pH 7 phosphate buffer (0.2 mL), the mixture was stirred under air for 1 h. The mixture was filtered through Celite-pad, and then concentrated. Purification by column chromatography (95:5 to 9:1 hexanes/EtOAc) provided the title compound (0.39 g, 78%) as a colorless oil: IR (NaCl) 3350, 2957, 2930, 2857, 1718, 1641, 1462, 1251, 1072 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.35 (dd, $J = 10.5, 15.0$ Hz, 1H), 7.28 (d, $J = 8.5$ Hz, 2H), 6.88 (d, $J = 9.0$

Hz, 2H), 6.55 (t, $J = 11.0$ Hz, 1H), 6.44 (dt, $J = 10.5, 17.0$ Hz, 1H), 6.22 (dd, $J = 5.5, 15.5$ Hz, 1H), 6.01 (t, $J = 11.0$ Hz, 1H), 5.58–5.50 (m, 2H), 5.42 (t, $J = 11.0$ Hz, 1H), 5.28 (dd, $J = 8.5, 11.0$ Hz, 1H), 5.21 (d, $J = 17.0$ Hz, 1H), 5.08 (d, $J = 10.5$ Hz, 1H), 4.58–4.49 (m, 3H), 3.95 (dd, $J = 2.5, 8.0$ Hz, 1H), 3.81 (s, 3H), 3.72 (s, 3H), 3.65 (dd, $J = 3.5, 8.5$ Hz, 1H), 3.36 (t, $J = 4.0$ Hz, 1H), 2.80–2.71 (m, 2H), 2.60–2.50 (m, 2H), 2.43–2.33 (m, 2H), 1.70–1.60 (m, 2H), 1.52 (dd, $J = 10.5, 13.0$ Hz, 1H), 1.40–1.20 (m, 3H), 1.18 (d, $J = 8.0$ Hz, 3H), 1.10 (d, $J = 6.5$ Hz, 3H), 1.04 (d, $J = 8.0$ Hz, 3H), 0.97 (m, 4H), 0.90–0.87 (m, 27H), 0.83 (d, $J = 8.0$ Hz, 3H), 0.78 (d, $J = 6.5$ Hz, 3H), 0.11–0.00 (m, 18H); ^{13}C NMR (125 MHz, CDCl_3) δ 166.7, 159.2, 147.0, 145.7, 133.9, 132.6, 132.4, 132.1, 130.7, 129.6, 129.3, 126.4, 117.7, 115.1, 113.7, 83.8, 80.0, 75.3, 72.8, 66.4, 55.1, 50.9, 50.4, 42.9, 42.2, 40.9, 40.2, 36.1, 35.3, 35.2, 29.7, 29.3, 26.2, 25.9, 20.4, 19.6, 18.8, 18.4, 18.1, 15.3, 14.6, 14.0, -2.7, -3.5, -3.6, -4.1, -4.2; LRMS (ESI) 1047 $[\text{M} + \text{Na}]^+$; HRMS (ESI) calcd. for $\text{C}_{59}\text{H}_{104}\text{O}_8\text{Si}_3\text{Na}$ 1047.6937, found 1047.6963; $[\alpha]_{\text{D}}^{20}$ -50.6 (c 0.34, CHCl_3).



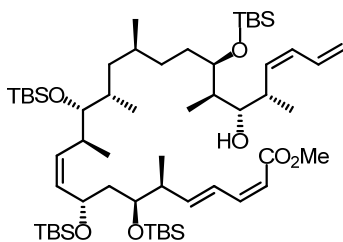
(2Z,4E,6S,7S,9S,10Z,12S,13R,14S,16S,19R,20S,21S,22S,23Z)-Methyl 7,9,13-tris(*tert*-butyldimethylsilyloxy)-19,21-dihydroxy-6,12,14,16,20,22-hexamethylhexacos-2,4,10,23,25-pentaenoate (167):

PMB-deprotection. A mixture of the PMB ether **164** (0.30 g, 0.29 mmol), CH_2Cl_2 (10 mL) and pH 7 buffer (0.50 mL) at 0 °C was treated with DDQ (0.10 g, 0.44 mmol). The mixture was stirred for 1.5 h. After quenching the reaction by addition of sat. aq. NaHCO_3 (10 mL), the

mixture was warmed to room temperature and stirred for 1.5 h, and then extracted with diethyl ether (3×10 mL). The combined organic layers were washed with sat. aq. NaHCO_3 and brine, dried (MgSO_4) and concentrated. Purification by column chromatography (9:1 hexanes/EtOAc) provided a ketone (0.23g, 87%), which was contaminated with unknown impurities: ^1H NMR of the pure fraction (300 MHz, CDCl_3) δ 7.38 (dd, $J = 11.1, 15.3$ Hz, 1H), 6.63–6.49 (m, 2H), 6.25 (dd, $J = 6.0, 15.6$ Hz, 1H), 6.12 (t, $J = 11.10$ Hz, 1H), 5.57 (d, $J = 11.4$ Hz, 1H), 5.45–5.37 (m, 2H), 5.29–5.20 (m, 2H), 5.15 (d, $J = 10.2$ Hz, 1H), 4.58 (t, $J = 9.0$ Hz, 1H), 3.95 (dd, $J = 2.4, 7.5$ Hz, 1H), 3.75–3.70 (m, 4H), 3.37 (m, 1H), 2.80 (m, 1H), 2.69 (m, 1H), 2.63–2.43 (m, 4H), 2.36 (d, $J = 3.3$ Hz, 1H), 1.70–1.61 (m, 2H), 1.57–1.20 (m, 6H), 1.18 (d, $J = 7.2$ Hz, 3H), 1.05–0.80 (m, 42H), 0.11–0.03 (m, 18H).

Reduction. A solution of the ketone (0.23 g, 0.25 mmol) in THF (2.5 mL) and MeOH (0.5 mL) at -78 °C was treated with a 1.0 M solution of Et_2BOMe in THF (0.76 mL, 0.76 mmol) dropwise over 2 min. After 1 h, NaBH_4 (19 mg, 0.51 mmol) was added. The mixture was stirred at -78 °C for 6 h, and quenched by the dropwise addition of acetic acid (1 mL). H_2O (10 mL) was added and the mixture was extracted with diethyl ether (4×10 mL). The combined organic layers were washed with brine, dried (MgSO_4) and concentrated. The residue was taken up in a 1.0 M solution of NaOAc in MeOH (18 mL) and H_2O (2 mL), to which 30% H_2O_2 (1.5 mL) was added. After stirring at room temperature for 2 h, the mixture was diluted with H_2O (10 mL) and extracted with diethyl ether (4×10 mL), dried (MgSO_4) and concentrated. Purification by column chromatography (4:1 hexanes/EtOAc) provided the title compound (0.20 g, 87%) as a colorless oil: IR (NaCl) 3382, 2957, 2930, 2857, 1721, 1462, 1254, 1073 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 7.35 (dd, $J = 11.4, 15.6$ Hz, 1H), 6.65 (dt, $J = 10.8, 16.8$ Hz, 1H), 6.56 (t, $J =$

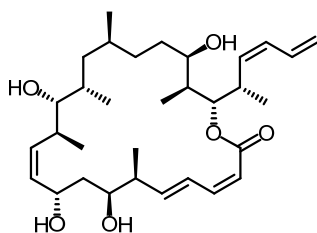
11.4 Hz, 1H), 6.24 (dd, $J = 6.0, 15.6$ Hz, 1H), 6.20 (t, $J = 10.8$ Hz, 1H), 5.58 (d, $J = 11.4$ Hz, 1H), 5.42 (t, $J = 10.8$ Hz, 1H), 5.30–5.20 (m, 3H), 5.18 (d, $J = 10.2$ Hz, 1H), 4.57 (t, $J = 9.6$ Hz, 1H), 3.94 (dd, $J = 3.6, 9.0$ Hz, 1H), 3.77 (m, 1H), 3.72 (s, 3H), 3.47 (d, $J = 9.0$ Hz, 1H), 3.36 (t, $J = 3.6$ Hz, 1H), 3.29 (s, 1H), 2.80 (m, 1H), 2.60–2.53 (m, 2H), 2.30 (s, 1H), 1.75–1.63 (m, 2H), 1.50–1.40 (m, 5H), 1.30–1.25 (m, 3H), 1.05 (d, $J = 7.2$ Hz, 3H), 1.10–0.94 (m, 10H), 0.92–0.88 (m, 27H), 0.85 (d, $J = 6.6$ Hz, 3H), 0.83 (d, $J = 7.2$ Hz, 3H), 0.11–0.03 (m, 18H); ^{13}C NMR (75 MHz, CDCl_3) δ 167.5, 147.7, 146.3, 135.0, 133.2, 133.0, 132.5, 132.3, 127.0, 119.4, 115.6, 81.2, 80.7, 77.8, 73.3, 67.0, 51.5, 43.5, 42.8, 41.5, 37.6, 36.9, 35.9, 32.9, 32.8, 30.9, 26.8, 26.5, 21.2, 20.2, 19.0, 18.6, 17.3, 16.0, 15.1, 4.8, -2.2, -2.9, -3.0, -3.5, -3.6; LRMS (ESI) 929 $[\text{M} + \text{Na}]^+$; HRMS (ESI) calcd. for $\text{C}_{51}\text{H}_{98}\text{O}_7\text{Si}_3\text{Na}$ 929.6518, found 929.6531; $[\alpha]_{\text{D}}^{20} -55.4$ (c 0.26, CHCl_3).



(2Z,4E,6S,7S,9S,10Z,12S,13R,14S,16S,19R,20R,21S,22S,23Z)-Methyl 7,9,13,19-tetrakis(*tert*-butyldimethylsilyloxy)-21-hydroxy-6,12,14,16,20,22-hexamethylhexacos-2,4,10,23,25-pentaenoate (168):

A solution of the diol **167** (0.20 g, 0.22 mmol) and 2,6-lutidine (77 μL , 0.66 mmol) in CH_2Cl_2 (4.4 mL) at -78 $^\circ\text{C}$ was treated with TBSOTf (50 μL , 0.22 mmol). The reaction mixture was stirred at -78 $^\circ\text{C}$ for 0.5 h and at 0 $^\circ\text{C}$ for 1 h. After quenching the reaction by addition of sat. aq. NaHCO_3 (5 mL), the mixture was extracted with diethyl ether (3×5 mL). The combined organic layers were washed with brine, dried (MgSO_4) and concentrated. Purification by column

chromatography (95:5 hexanes/EtOAc) provided the title compound (0.19 g, 85%) as a colorless oil: IR (NaCl) 2956, 2930, 2857, 1722, 1462, 1254, 1089 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.39 (dd, $J = 11.7, 14.7$ Hz, 1H), 6.65–6.52 (m, 2H), 6.21 (dd, $J = 5.7, 15.6$ Hz, 1H), 6.11 (t, $J = 10.8$ Hz, 1H), 5.56 (d, $J = 11.1$ Hz, 1H), 5.45–5.32 (m, 2H), 5.30–5.15 (m, 2H), 5.10 (d, $J = 9.9$ Hz, 1H), 4.54 (t, $J = 8.4$ Hz, 1H), 3.94 (d, $J = 5.4$ Hz, 1H), 3.56–3.52 (m, 4H), 3.47 (d, $J = 4.5$ Hz, 1H), 3.35 (m, 1H), 2.80 (m, 1H), 2.60–2.50 (m, 2H), 2.33 (s, 1H), 1.60–1.52 (m, 3H), 1.50–1.21 (m, 7H), 1.10–0.75 (m, 55H), 0.15–0.00 (m, 24H); ^{13}C NMR (75 MHz, CDCl_3) δ 166.8, 147.1, 145.7, 135.2, 132.6, 132.5, 132.2, 129.9, 126.4, 117.7, 115.0, 79.9, 76.5, 72.7, 66.4, 50.9, 42.9, 42.1, 41.1, 37.7, 36.0, 35.3, 35.0, 32.0, 31.3, 30.5, 26.2, 25.9, 20.4, 19.4, 18.4, 18.1, 18.0, 17.6, 15.3, 14.5, 6.9, -2.8, -3.4, -3.7, -4.1, -4.4; LRMS (ESI) 1043 $[\text{M} + \text{Na}]^+$; HRMS (ESI) calcd. for $\text{C}_{57}\text{H}_{112}\text{O}_7\text{Si}_4\text{Na}$ 1043.7383, found 1043.7358; $[\alpha]_{\text{D}}^{20}$ -62.2 (c 0.37, CHCl_3).



(3Z,5E,7S,8S,10S,11Z,13S,14R,15S,17S,20R,21S,22S)-22-((S,Z)-Hexa-3,5-dien-2-yl)-8,10,14,20-tetrahydroxy-7,13,15,17,21-pentamethyloxacyclodocosa-3,5,11-trien-2-one (101):

The *seco*-acid 169. A solution of the ester **168** (0.14 g, 0.14 mmol) in ethanol (15 mL) and THF (3 mL) at room temperature was treated with a 1.0 M solution of KOH (aqueous, 1.47 mL, 1.47 mmol). The mixture was warmed to 80 °C and stirred for 5 h. After concentration under vacuum, the residue was acidified with 0.1 M HCl to pH 4. The mixture was extracted with EtOAc (4 × 5 mL). The combined organic layers were washed with brine, dried (MgSO_4)

and concentrated after addition of triethylamine (1 mL). The residue was dissolved in toluene (3 mL), and the solution was evaporated under vacuum. This process was repeated two more times to give a Et₃N salt of the *seco*-acid **169** (0.16 g). This was used for the next reaction without further purification; ¹H NMR (600 MHz, CDCl₃) δ 7.33 (dd, *J* = 11.4, 15.6 Hz, 1H), 6.68–6.58 (m, 2H), 6.25 (dd, *J* = 6.0, 15.6 Hz, 1H), 6.10 (t, *J* = 10.8 Hz, 1H), 5.58 (d, *J* = 11.4 Hz, 1H), 5.45–5.37 (m, 2H), 5.26 (dd, *J* = 8.4, 10.8 Hz, 1H), 5.20 (d, *J* = 16.8 Hz, 1H), 5.12 (d, *J* = 10.2 Hz, 1H), 4.57 (t, *J* = 9.6 Hz, 1H), 3.94 (dd, *J* = 3.0, 8.4 Hz, 1H), 3.75 (m, 1H), 3.49 (dd, *J* = 2.4, 7.8 Hz, 1H), 3.36 (t, *J* = 3.6 Hz, 1H), 3.31 (q, *J* = 7.2 Hz, 5H), 2.80 (m, 1H), 2.60–2.51 (m, 2H), 1.75–1.50 (m, 6H), 1.42 (t, *J* = 7.2 Hz, 7.5 H), 1.40–1.20 (m, 4H), 1.04 (d, *J* = 7.2 Hz, 3H), 0.96 (d, *J* = 6.6 Hz, 6H), 0.94–0.87 (m, 40H), 0.83 (d, *J* = 6.6 Hz, 3H), 0.81 (d, *J* = 6.0 Hz, 3H), 0.13–0.00 (m, 24H).

Macrolactonization. The *seco*-acid **169** (0.14 g) was divided into four fractions. Each fraction (0.034 mmol, assumed) was dissolved in toluene (17 mL), to which triethylamine (0.18 mL, 0.34 mmol), (2,6-Me(NO₂)PhCO)₂O (35 mg, 0.10 mmol), and DMAP (4.2 mg, 0.034 mmol) were added at room temperature. The mixture was stirred for 48 h. After quenching the reaction by addition of a sat. aq. NaHCO₃ (2 mL), the mixture was stirred for 1 h. The separated organic layer was washed with 0.1 M HCl (2 × 5 mL) and brine, dried (MgSO₄) and concentrated. Four fractions were combined and purified by column chromatography (95:5 hexanes/EtOAc) provided the TBS-protected macrolactone (0.12 g) contaminated with impurities. This was used for the next reaction without further purification; ¹H NMR (600 MHz, CDCl₃) δ 7.07 (m, 1H), 6.68 (dt, *J* = 10.5, 17.0 Hz, 1H), 6.51 (t, *J* = 11.5 Hz, 1H), 6.15 (m, 1H), 6.01 (t, *J* = 11.0 Hz, 1H), 5.58–5.50 (m, 2H), 5.41 (t, *J* = 10.5 Hz, 1H), 5.32–5.26 (m, 2H), 5.19 (d, *J* = 16.5 Hz, 1H),

5.08 (d, $J = 10.5$ Hz, 1H), 4.57 (t, $J = 8.5$ Hz, 1H), 3.92 (m, 1H), 3.43 (m, 1H), 3.37 (m, 1H), 3.04 (m, 1H), 2.60–2.51 (m, 2H), 1.96 (m, 1H), 1.80–1.20 (m, 9H), 1.06–1.00 (m, 9H), 0.94–0.87 (m, 40H), 0.82 (d, $J = 7.0$ Hz, 3H), 0.73 (d, $J = 6.5$ Hz, 3H), 0.14–0.04 (m, 24H).

The C2 *E*-isomer of the TBS-protected macrolactone. This was obtained from the reaction of the crude *seco*-acid **169** (1.5 mg, 1.49 μ mol) with triethylamine (2.1 μ L, 14.88 μ mol), 2,4,6-trichlorobenzoyl chloride (1 M solution in CH₂Cl₂, 4.5 μ L, 4.46 mol) and DMAP (1 M solution in CH₂Cl₂, 7.5 μ L, 7.44 μ mol) in CH₂Cl₂ (0.7 mL). After preparative thin layer chromatography (95:5 hexanes/EtOAc), the C2 *E*-isomer of the TBS-protected macrolactone (1.0 g, 67% from the ester **168**) was obtained as a colorless oil: ¹H NMR (600 MHz, CDCl₃) δ 7.20 (dd, $J = 10.8, 15.0$ Hz, 1H), 6.61 (dt, $J = 10.2, 16.8$ Hz, 1H), 6.40 (dd, $J = 4.2, 15.6$ Hz, 1H), 6.10 (dd, $J = 11.4, 15.6$ Hz, 1H), 5.94 (t, $J = 10.8$ Hz, 1H), 5.73 (d, $J = 15.6$ Hz, 1H), 5.42 (t, $J = 10.8$ Hz, 1H), 5.36 (t, $J = 10.8$ Hz, 1H), 5.27–5.23 (m, 2H), 5.16 (d, $J = 16.8$ Hz, 1H), 5.07 (d, $J = 10.2$ Hz, 1H), 4.60 (t, $J = 9.0$ Hz, 1H), 3.97 (dd, $J = 4.8, 10.2$ Hz, 1H), 3.45–3.40 (m, 2H), 2.94 (m, 1H), 2.62 (m, 1H), 2.53 (m, 1H), 1.94 (m, 1H), 1.76 (m, 1H), 1.58–1.49 (m, 2H), 1.40–1.35 (m, 2H), 1.15–1.11 (m, 2H), 1.05 (m, 1H), 1.02–0.95 (m, 12H), 0.94–0.87 (m, 36H), 0.77 (d, $J = 6.6$ Hz, 3H), 0.67 (d, $J = 6.0$ Hz, 3H), 0.40 (m, 1H), 0.11–0.00 (m, 24H).

Global deprotection. The TBS-protected macrolactone (0.12 g) was divided into three fractions. The first fraction (0.046 mmol, assumed) was dissolved in THF (1 mL) and MeOH (1 mL). The mixture was cooled to 0 °C, and then a 3 M solution of HCl in H₂O/MeOH (0.43 mL, 1.29 mmol, prepared by slow addition of conc. HCl to MeOH) was added. The mixture was warmed to room temperature and stirred for 16 h. Solid NaHCO₃ was added to the reaction mixture until no gas evolved. After concentration under vacuum, the residue was diluted with

H₂O (10 mL) and extracted with EtOAc (4 × 10 mL). The combined organic layers were washed with brine, dried (MgSO₄) and concentrated. Purification by column chromatography (3:7 hexanes/EtOAc) provided the title compound (12 mg, 49% over three steps) as a white powder. The second and third fractions were combined (0.092 mmol, assumed), and submitted to the reaction conditions (0.86 mL of 3M HCl). This provided 21 mg of the title compound. The combined amount was 33 mg and an overall yield was 45%, starting from the ester **168** (0.14 g, 0.14 mmol): IR (NaCl) 3365, 2958, 2924, 1706, 1181, 965 cm⁻¹; ¹H NMR (500 MHz, CD₃OD) δ 7.26 (dd, *J* = 11.5, 15.0 Hz, 1H), 6.71 (dt, *J* = 11.0, 16.5 Hz, 1H), 6.59 (t, *J* = 11.0 Hz, 1H), 6.03 (t, *J* = 11.0 Hz, 1H), 5.82 (dd, *J* = 10.0, 11.0 Hz, 1H), 5.54 (d, *J* = 11.0 Hz, 1H), 5.49 (t, *J* = 10.0 Hz, 1H), 5.35 (dd, *J* = 8.5, 10.5 Hz, 1H), 5.26 (t, *J* = 10.5 Hz, 1H), 5.22 (t, *J* = 18.5 Hz, 1H), 5.13 (d, *J* = 10.5 Hz, 1H), 5.07 (dd, *J* = 3.0, 9.5 Hz, 1H), 4.69 (t, *J* = 9.0 Hz, 1H), 3.60 (dt, *J* = 2.0, 11.0 Hz, 1H), 3.11–3.02 (m, 2H), 2.98 (t, *J* = 8.5 Hz, 1H), 2.71 (m, 1H), 2.23–2.14 (m, 2H), 1.89 (t, *J* = 13.0 Hz, 1H), 1.74 (m, 1H), 1.65–1.53 (m, 2H), 1.49 (m, 1H), 1.36 (m, 1H), 1.24 (m, 1H), 1.19 (d, *J* = 6.5 Hz, 3H), 1.11 (d, *J* = 7.0 Hz, 3H), 1.09 (d, *J* = 7.0 Hz, 3H), 1.01 (d, *J* = 6.5 Hz, 6H), 0.97 (d, *J* = 6.5 Hz, 3H), 0.95–0.86 (m, 2H), 0.41 (m, 1H); ¹³C NMR (125 MHz, CD₃OD) δ 165.8, 145.9, 143.5, 133.9, 133.5, 132.2, 129.8, 128.6, 127.0, 116.8, 116.3, 79.1, 75.8, 73.5, 70.1, 63.7, 46.7, 43.2, 40.4, 40.3, 34.3, 33.9, 33.8, 32.2, 31.2, 30.1, 20.8, 17.8, 16.8, 15.9, 14.8, 8.6; LRMS (ESI) 555 [M + Na]⁺; HRMS (ESI) calcd. for C₃₂H₅₂O₆Na 555.3662, found 555.3662; $[\alpha]_D^{20}$ -54.0 (*c* 0.10, MeOH).

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APPENDIX

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

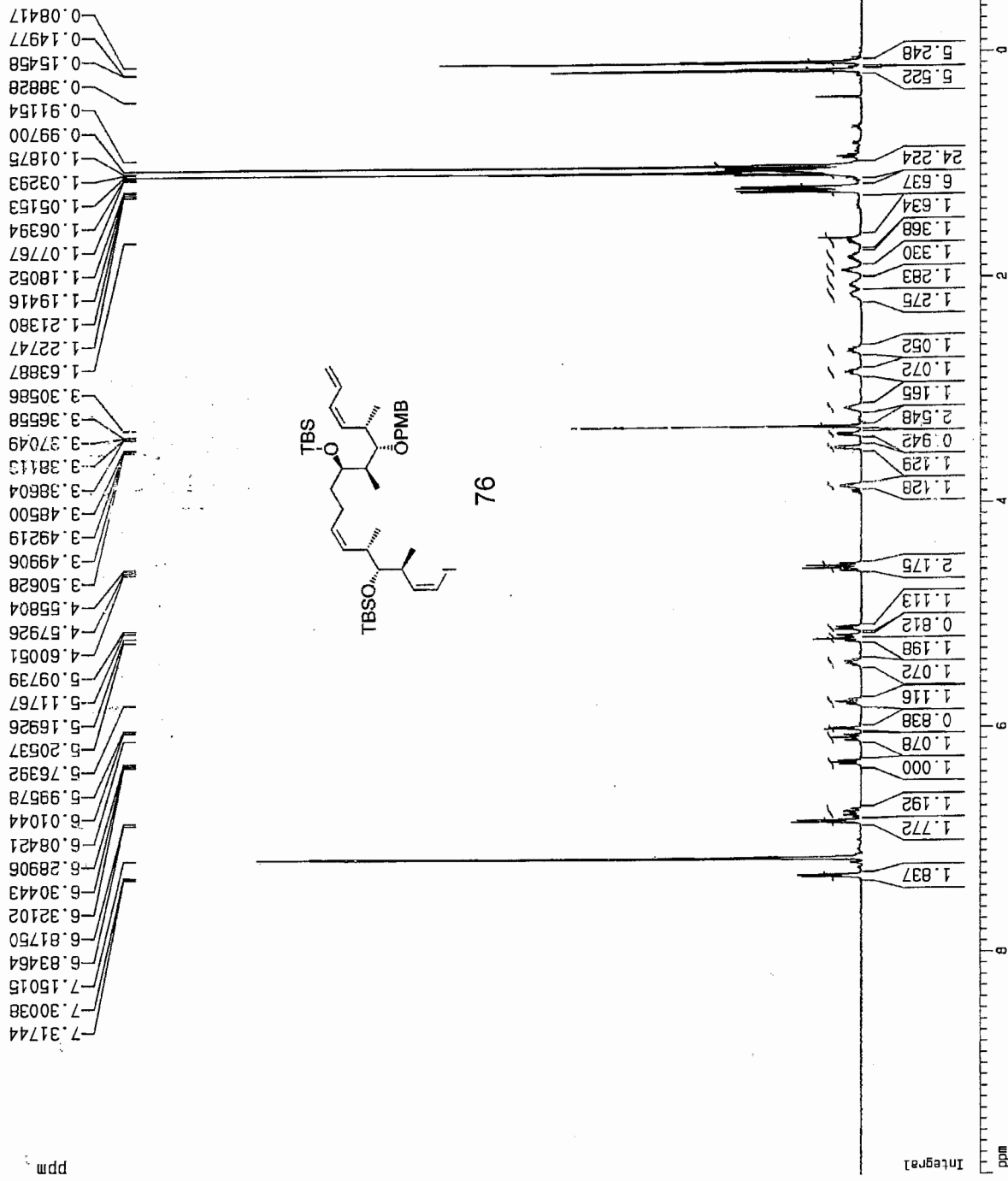
whj 272

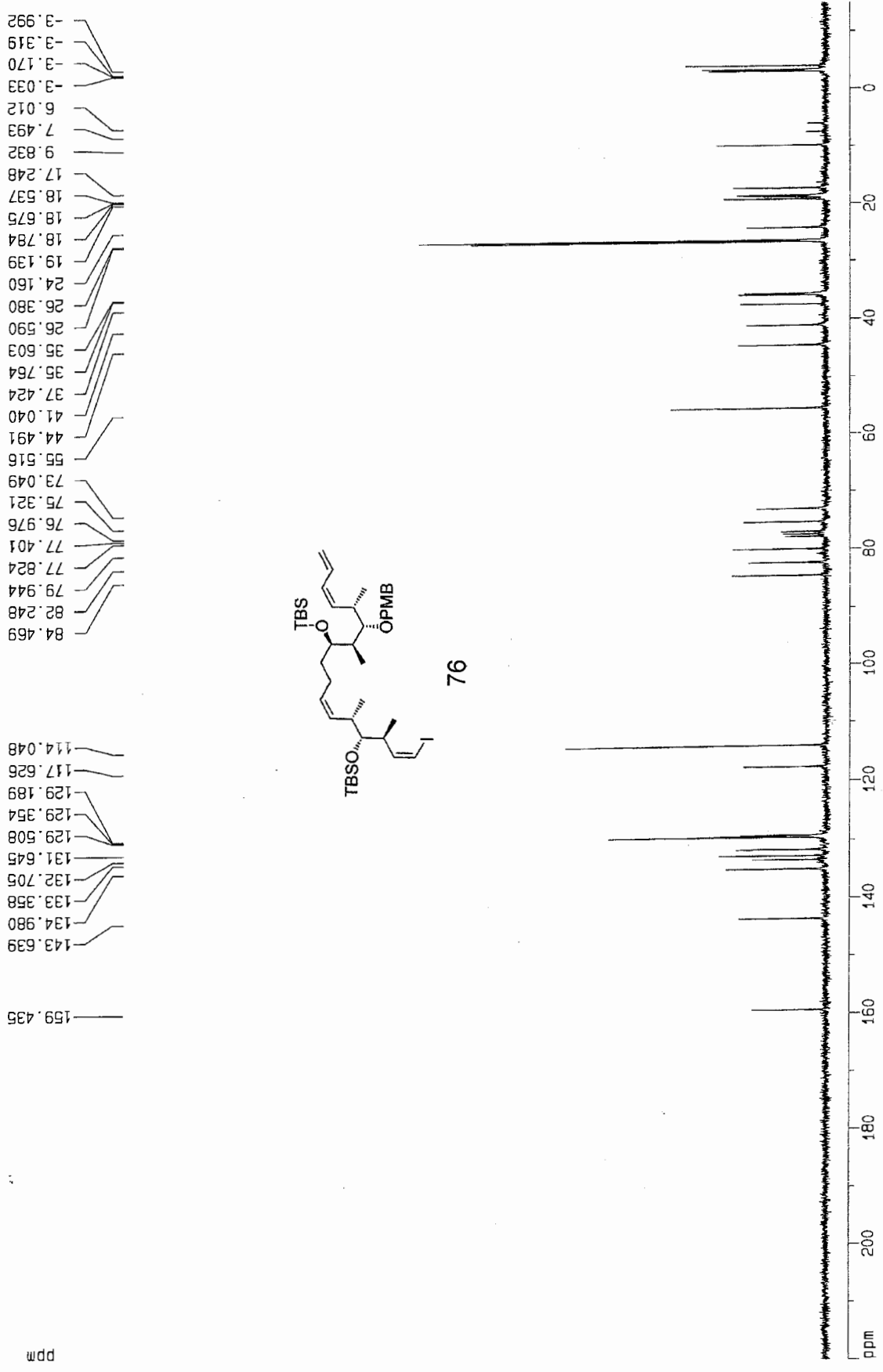
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PROCNO 1

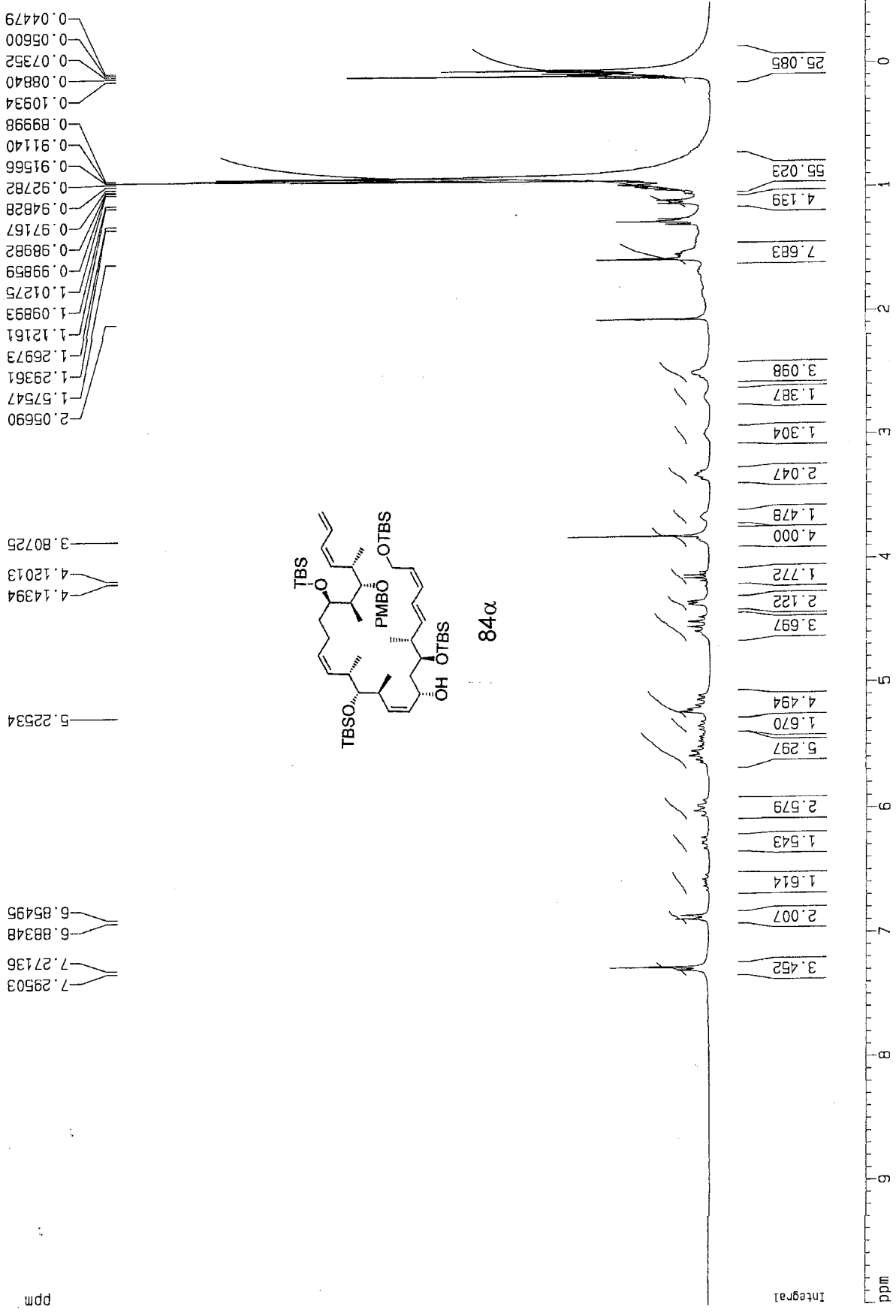
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Time 17.24
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PULPROG zg
TD 32768
SOLVENT C6D6
NS 16
DS 0
SWH 7507.507 Hz
FIDRES 0.229111 Hz
AQ 2.1823988 sec
RG 2
DW 66.600 usec
DE 6.00 usec
TE 290.0 K
D1 1.0000000 sec
P1 10.60 usec
OE 6.00 usec
SF01 500.1330008 MHz
NUC1 1H
PL1 0.00 dB

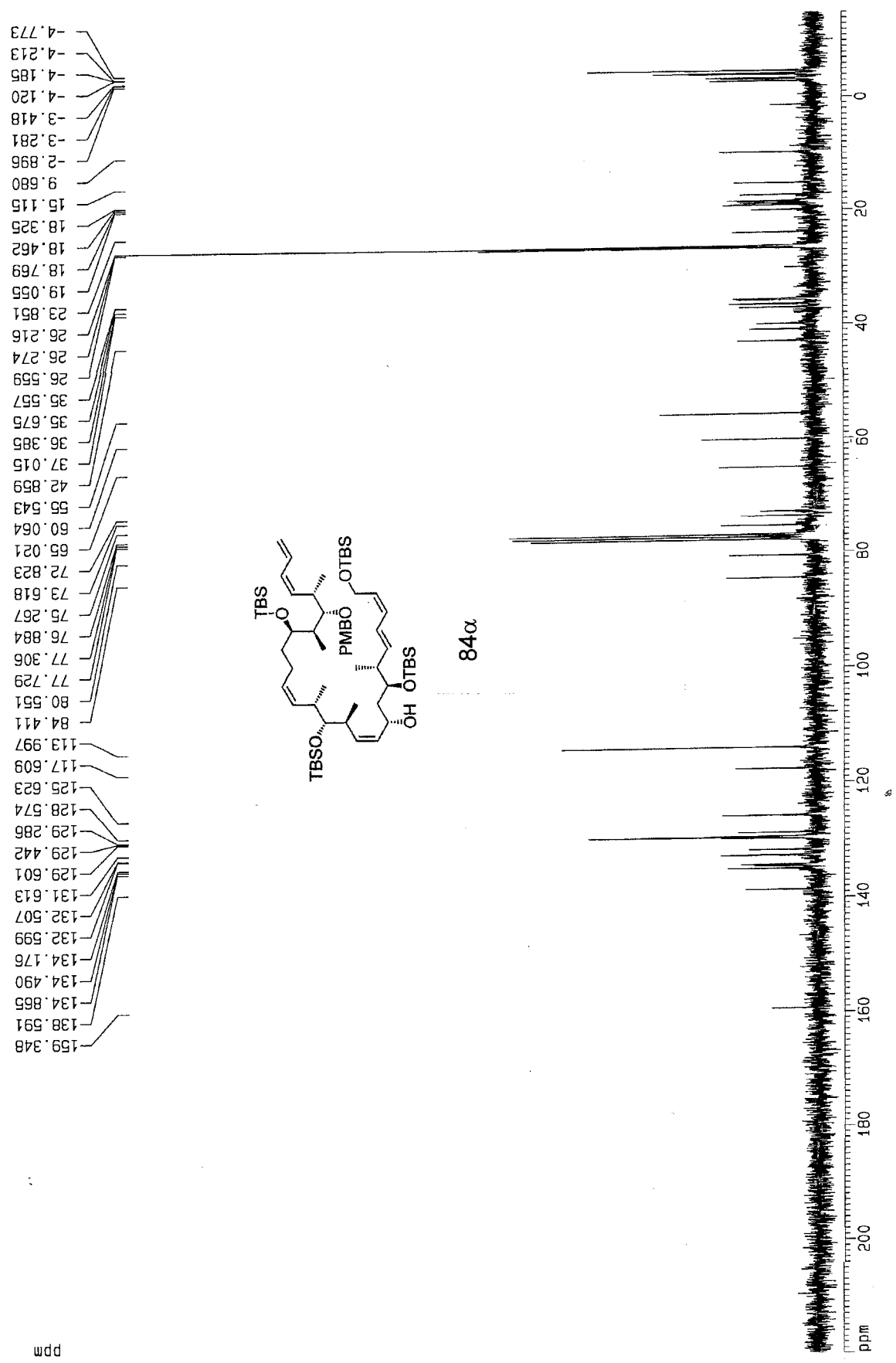
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GB 0
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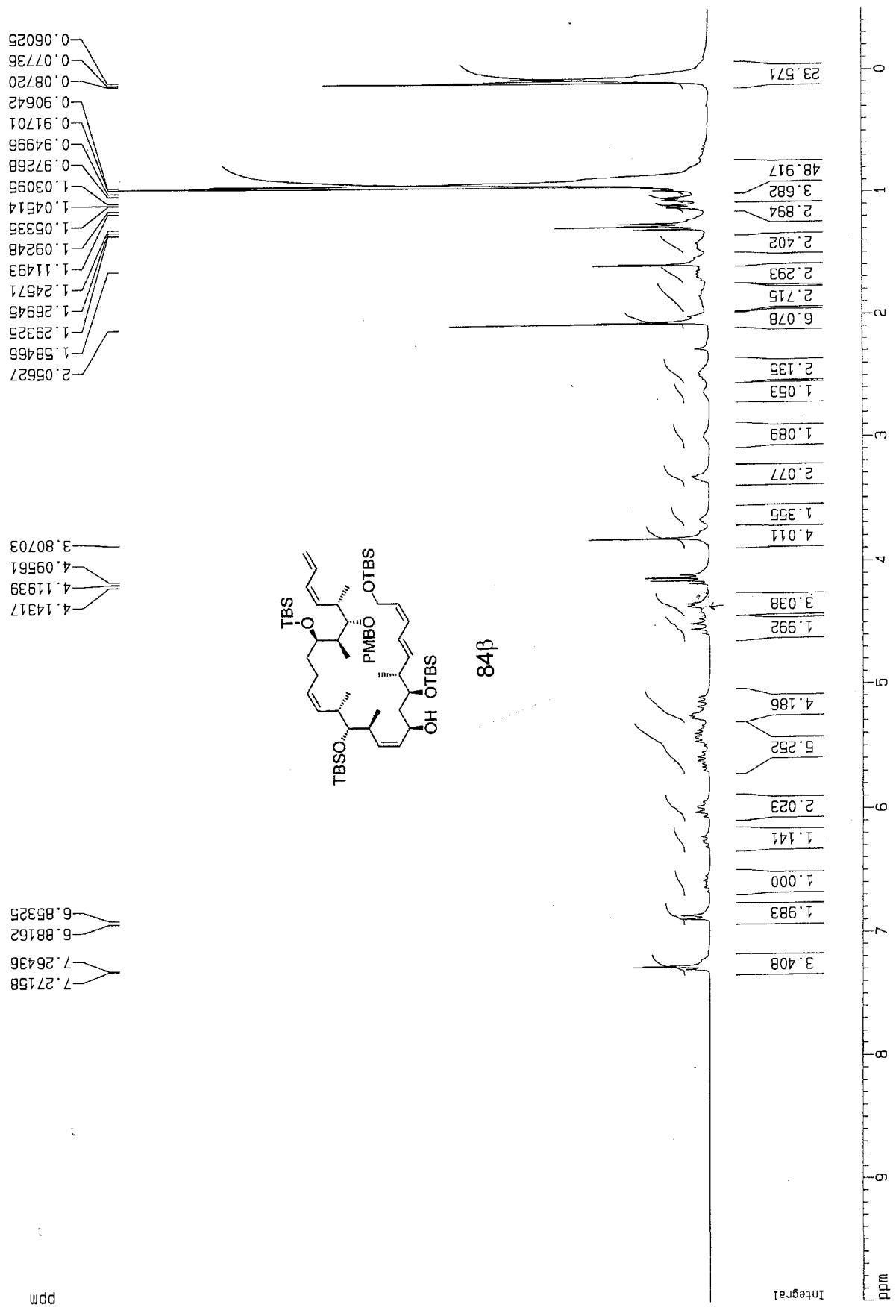
1D NMR plot parameters
CX 20.00 cm
F1P 10.000 ppm
F1 5001.30 Hz
F2P -0.500 ppm
F2 -250.07 Hz
PPMCM 0.52500 ppm/cm
HZCM 262.56924 Hz/cm

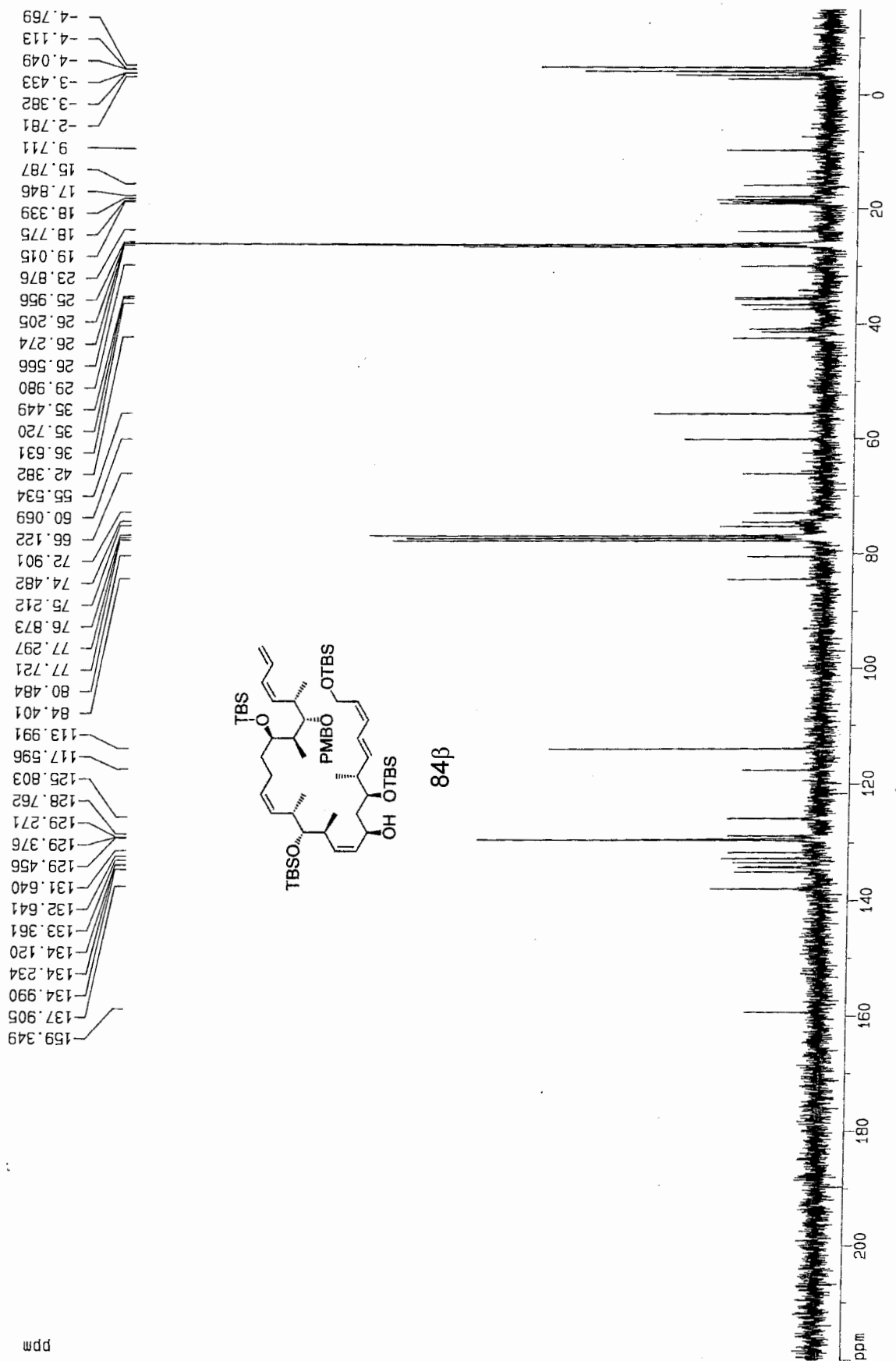


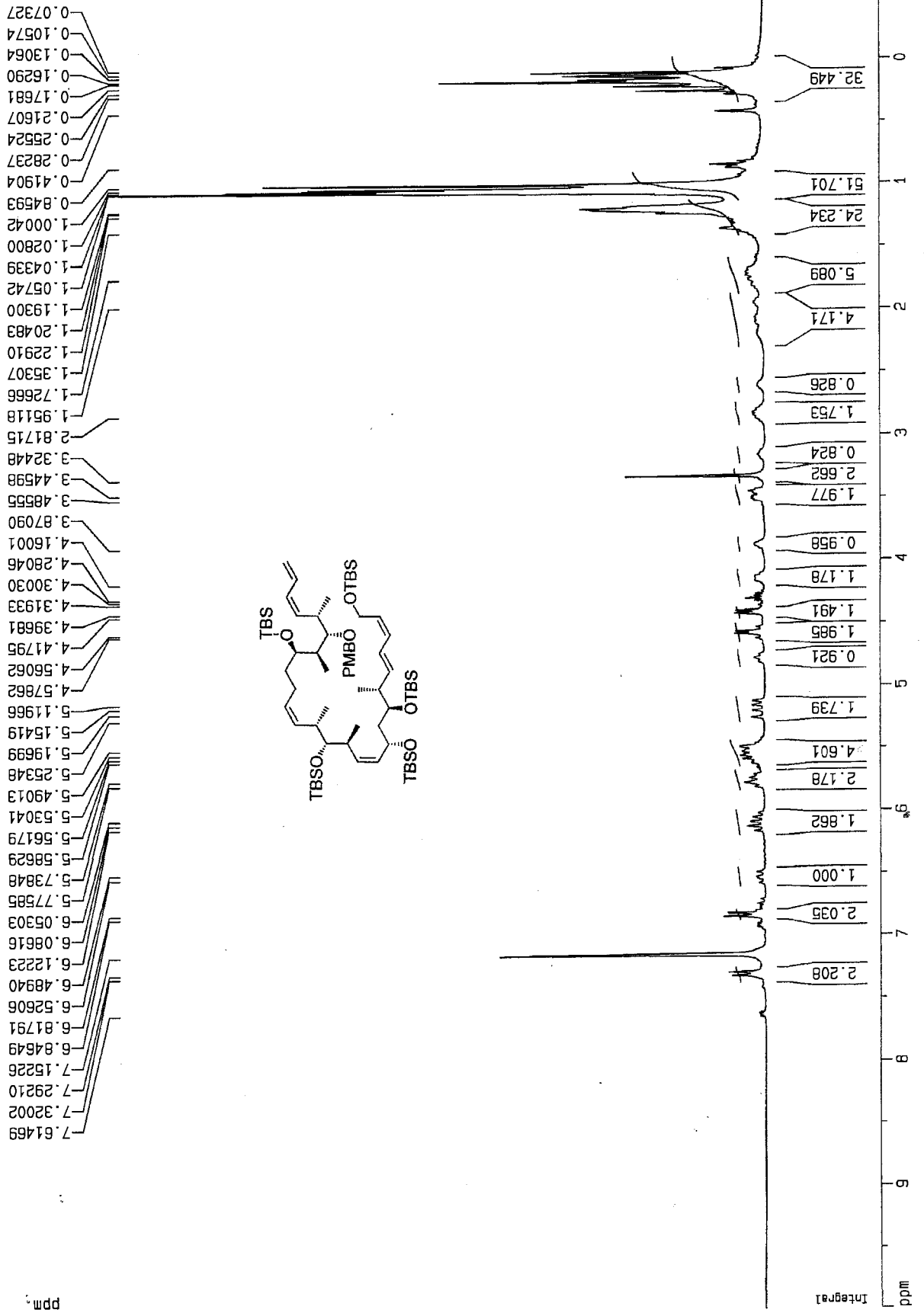


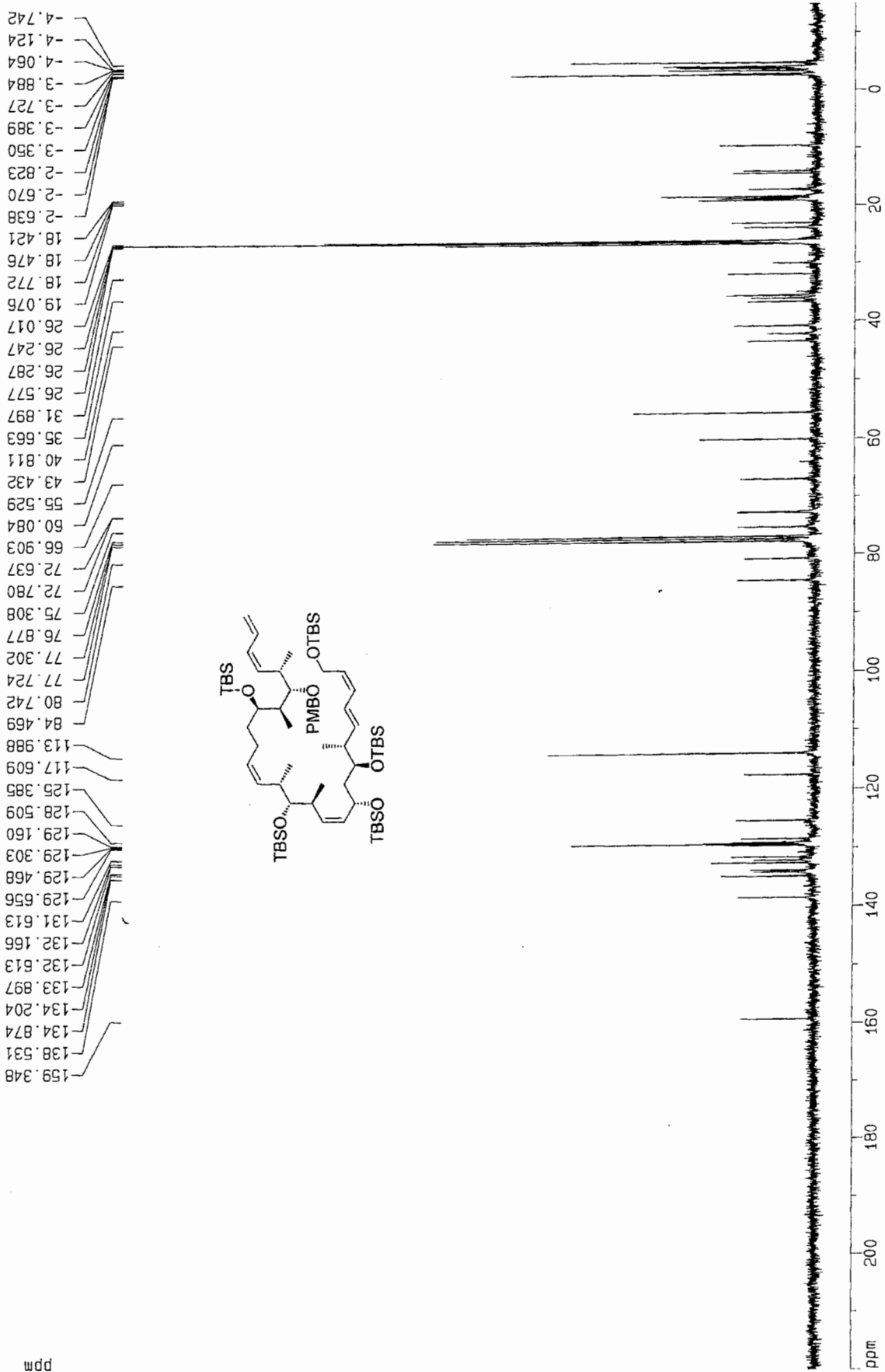


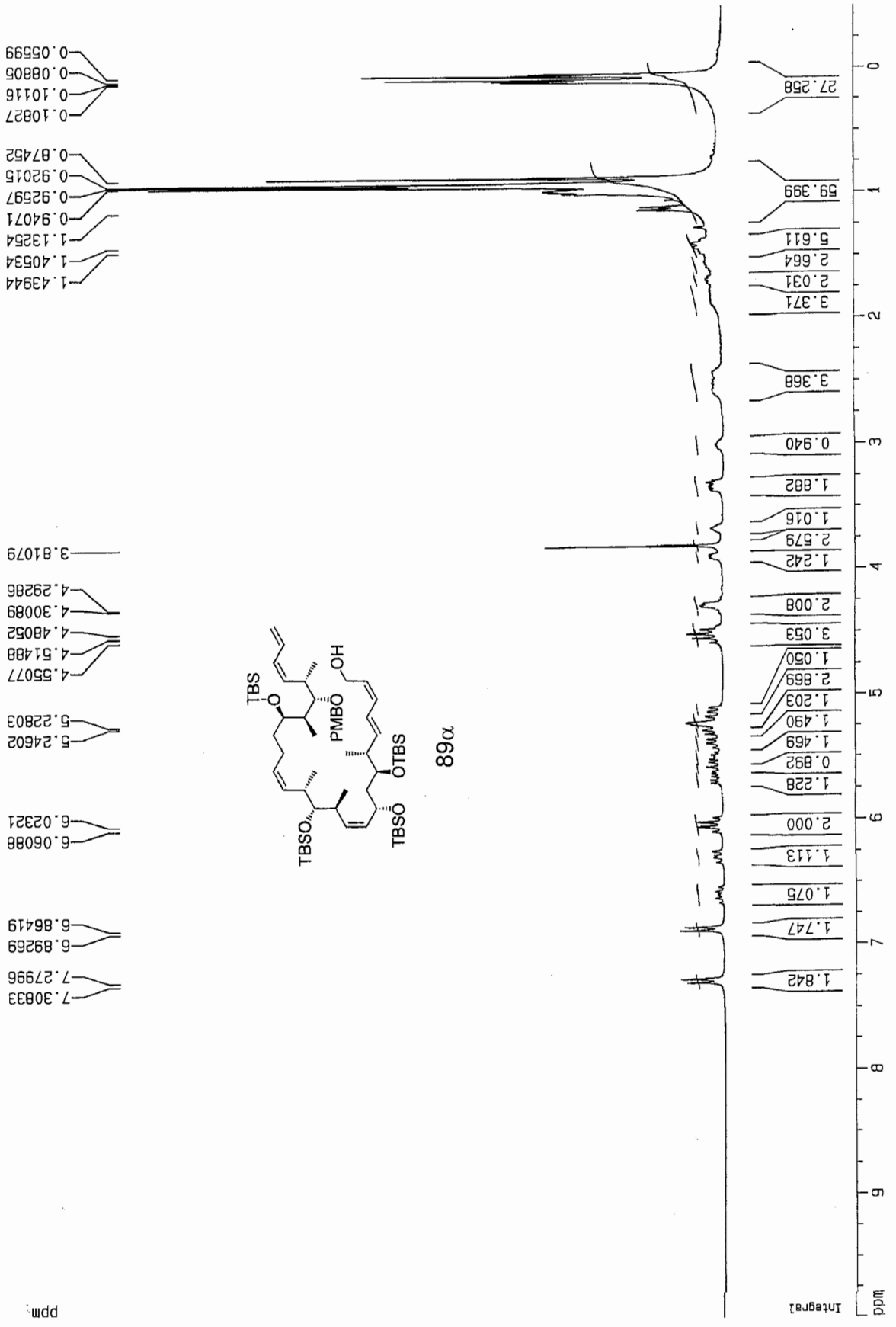












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 PROCNO 1

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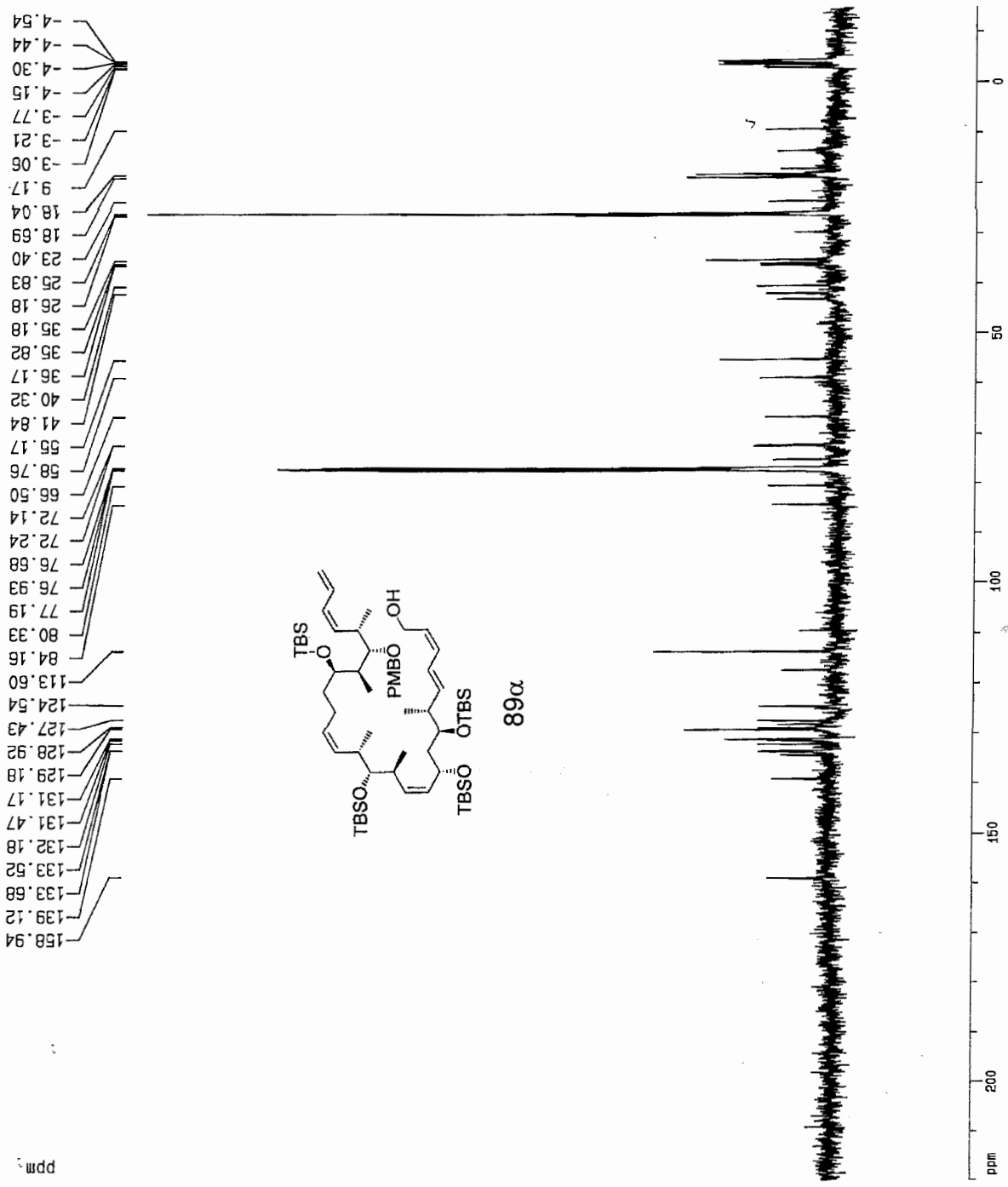
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 SOLVENT CDC13
 NS 709
 DS 0
 SWH 32679.738 Hz
 FIDRES 0.997306 Hz
 AQ 0.5014004 sec
 RG 32768
 DW 15.300 usec
 DE 6.00 usec
 TE 290.0 K
 D3 0.00100000 sec
 PL12 6.00 dB
 D1 8.00000000 sec
 CPDPRG2 waltz16
 PCPO2 100.00 usec
 SF02 500.1330008 MHz
 NUC2 1H
 PL2 120.00 dB
 P1 21.60 usec
 DE 6.00 usec
 SF01 125.7715724 MHz
 NUC1 13C
 PL1 0.00 dB

F2 - Processing parameters

SI 8192
 SF 125.7578047 MHz
 WDW EM
 SSB 0
 LB 4.00 Hz
 GB 0
 PC 1.00

1D NMR plot parameters

CX 20.00 cm
 F1P 220.000 ppm
 F1 27666.72 Hz
 F2P -15.000 ppm
 F2 -1666.37 Hz
 PPMCM 11.75000 ppm/cm
 HZCM 1477.65417 Hz/cm



WHJ323-2

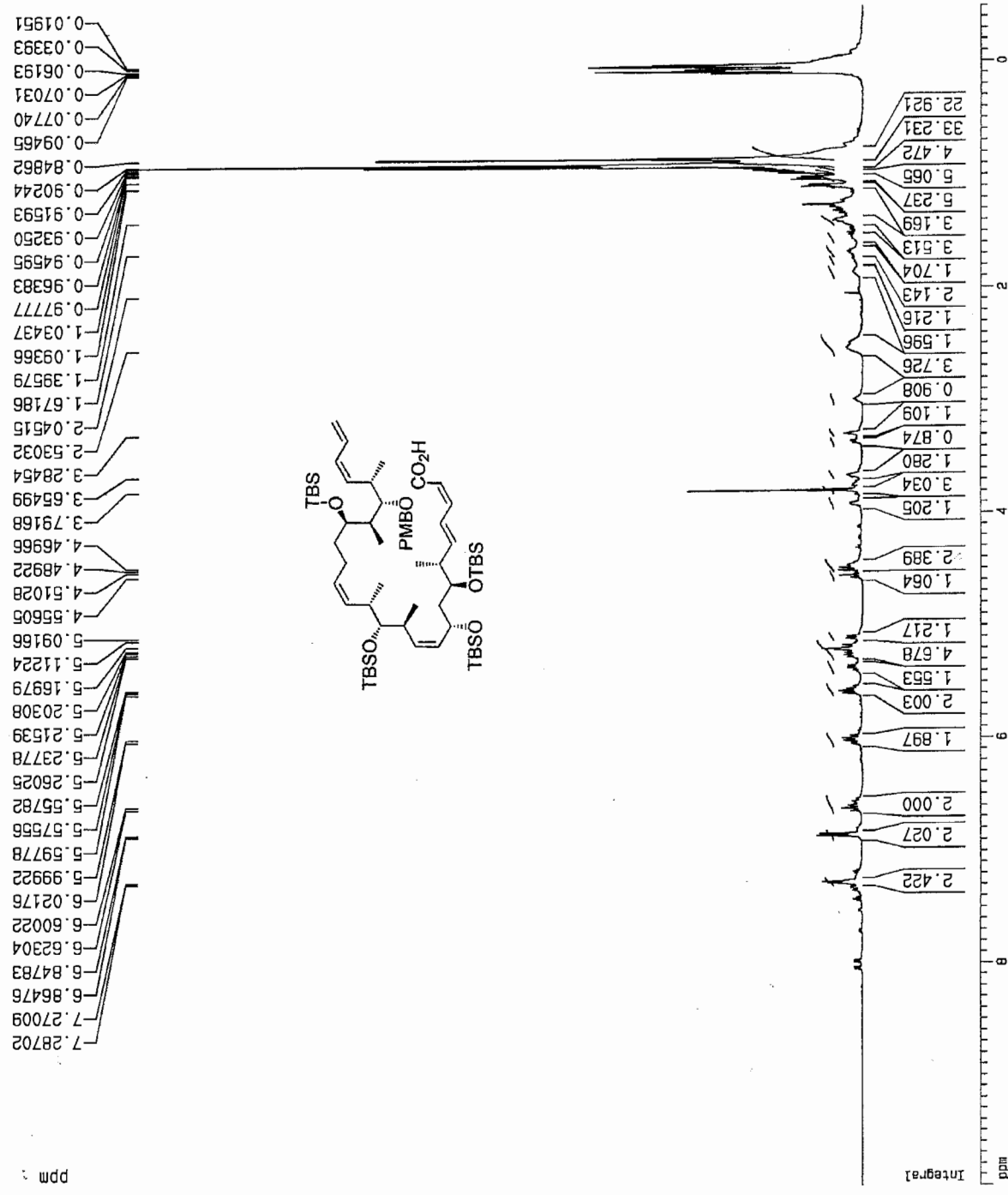
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 PULPROG zg
 TD 32768
 SOLVENT D2O
 NS 107
 DS 0

SWH 7507.507 Hz
 FIDRES 0.229111 Hz
 AQ 2.1823988 sec
 RG 12.7
 DW 66.600 usec
 DE 6.00 usec
 TE 290.0 K
 D1 12.0000000 sec
 P1 10.60 usec
 DE 6.00 usec
 SFO1 500.1330008 MHz
 NUC1 1H
 PL1 0.00 dB

F2 - Processing parameters
 SI 32768
 SF 500.1300306 MHz
 WDW EM
 SSB 0
 LB 0.40 Hz
 GB 0
 PC 1.00

1D NMR plot parameters
 CX 20.00 cm
 F1P 10.000 ppm
 F1 5001.30 Hz
 F2P -0.500 ppm
 F2 -250.07 Hz
 PPMCM 0.52500 ppm/cm
 HZCM 262.56827 Hz/cm



WHJ323_2

Current Data Parameters
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 PROCNO 1

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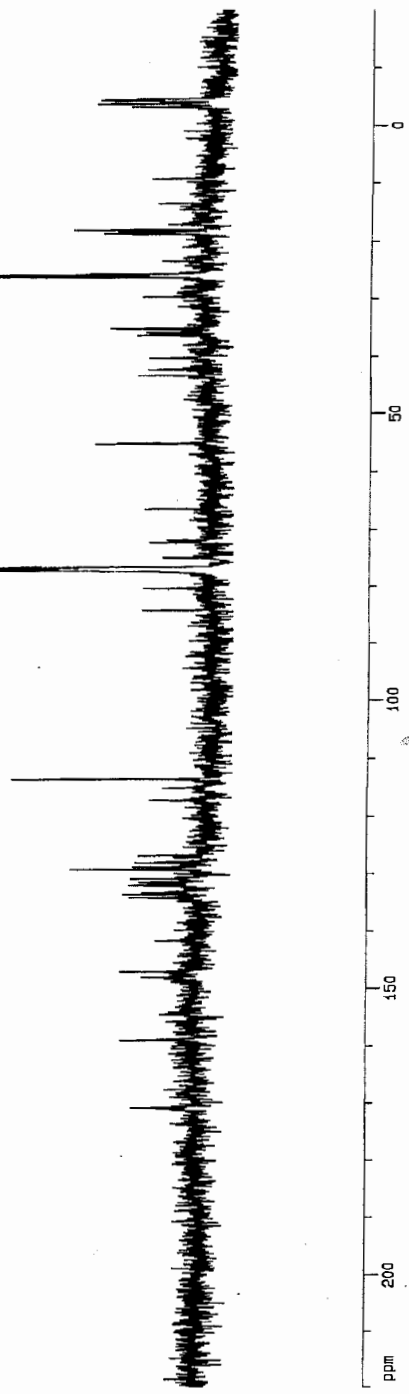
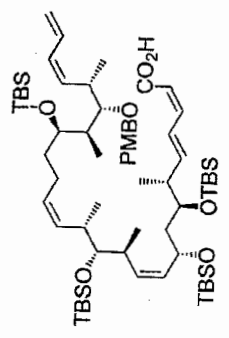
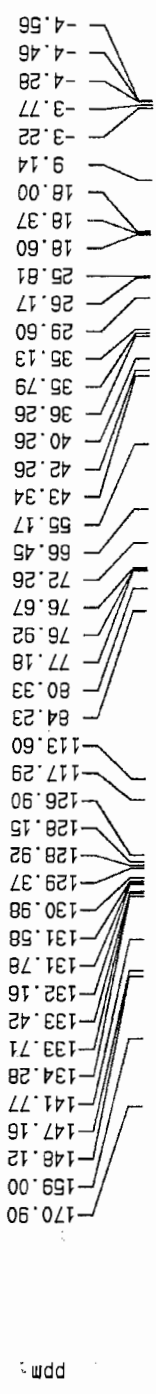
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 SOLVENT CDCl3
 NS 973
 DS 0
 SWH 32679.738 Hz
 FIDRES 0.997306 Hz
 AQ 0.5014004 sec
 RG 32768
 DW 15.300 usec
 DE 6.00 usec
 TE 290.0 K
 D3 0.00100000 sec
 PL12 6.00 dB
 D1 8.00000000 sec
 CPDPRG2 waltz16
 PCPD2 100.00 usec
 SF02 500.1330008 MHz
 NUC2 1H
 PL2 120.00 dB
 P1 21.60 usec
 DE 6.00 usec
 SF01 125.7715724 MHz
 NUC1 13C
 PL1 0.00 dB

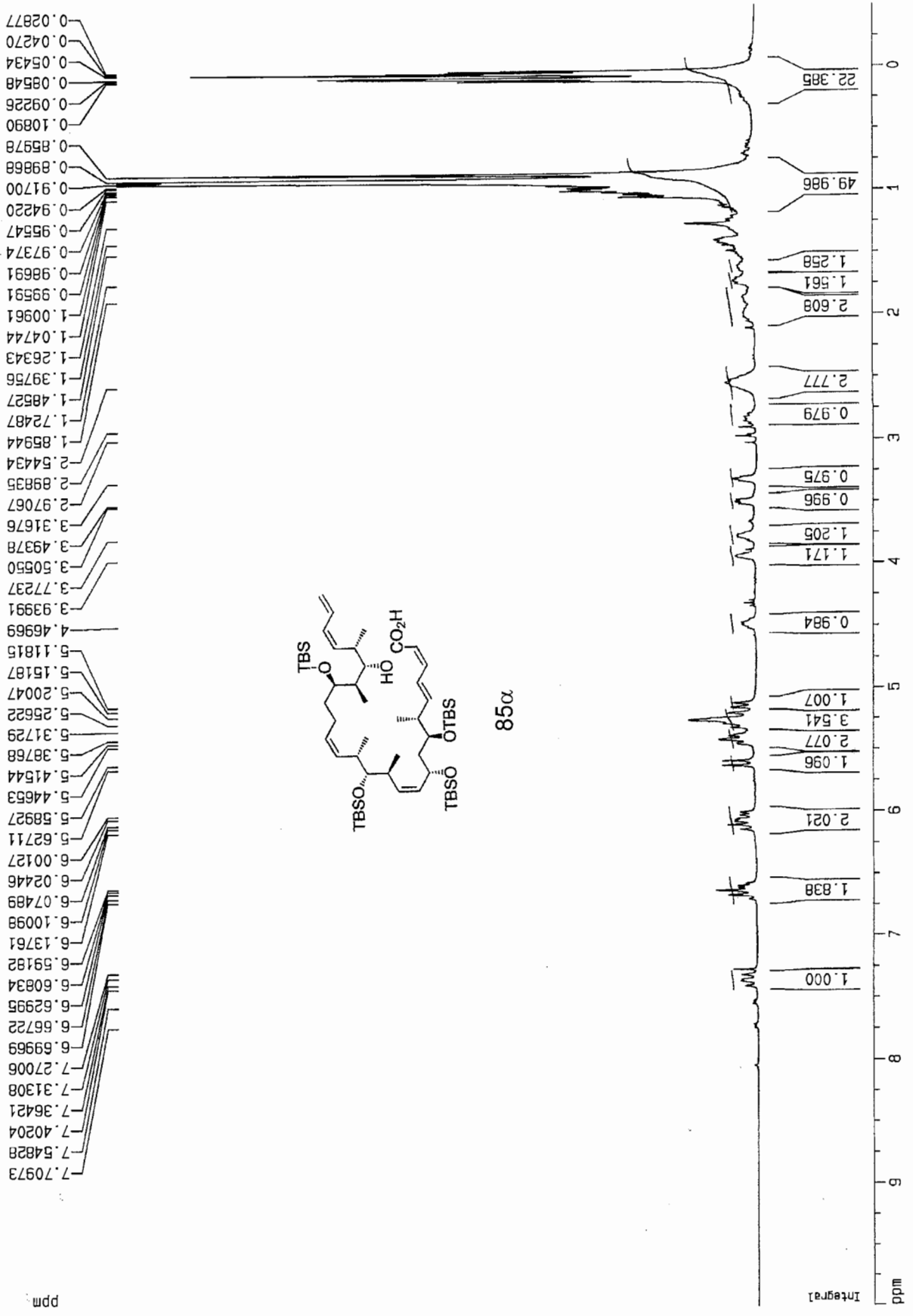
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 LB 4.00 Hz
 GB 0
 PC 1.00

1D NMR plot parameters

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 F1P 220.000 ppm
 F1 27666.72 Hz
 F2P -20.000 ppm
 F2 -2515.16 Hz
 PPMCM 12.00000 ppm/cm
 HZCM 1509.09363 Hz/cm





WHJ348

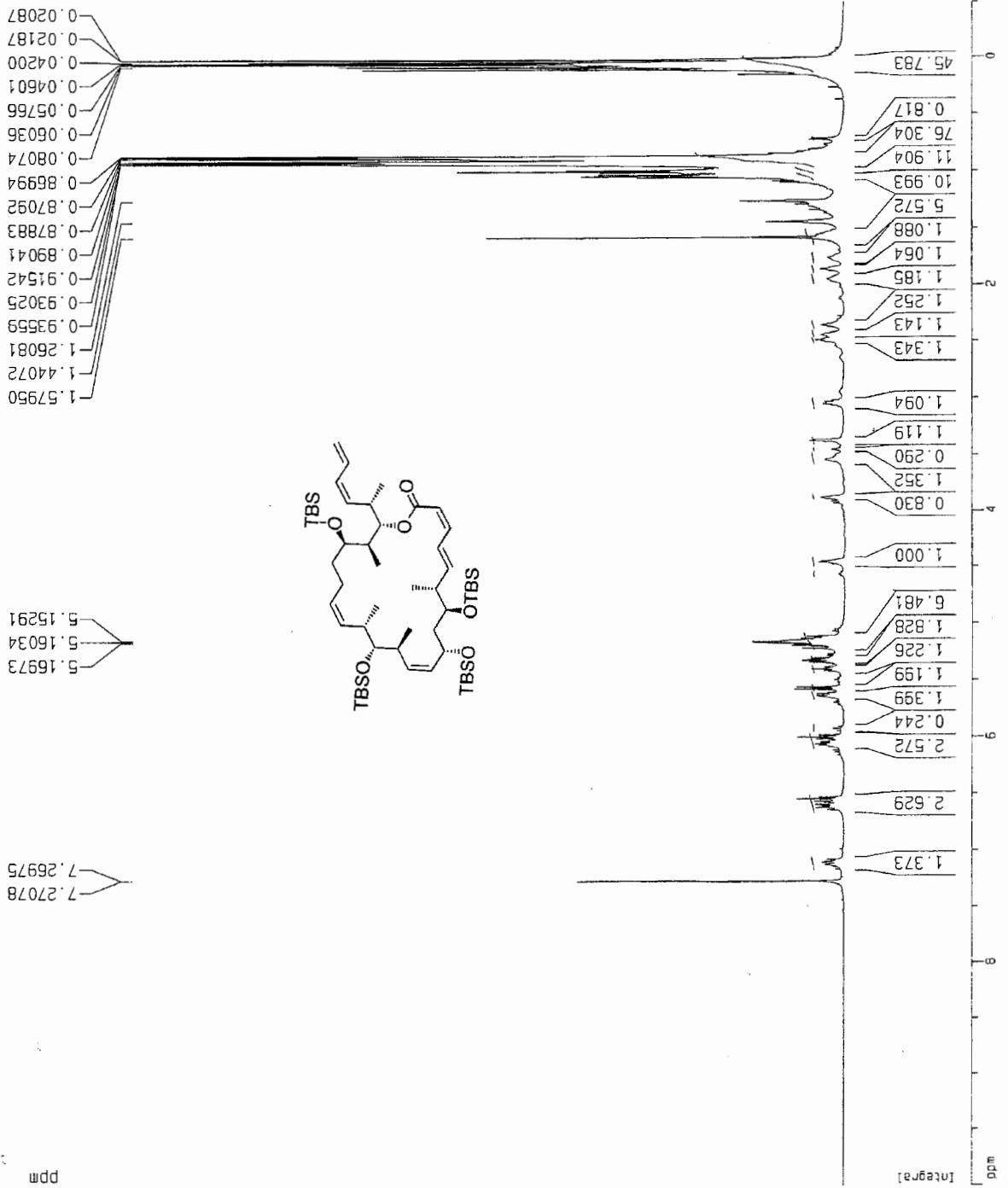
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PROCNO 1

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PULPROG zg
TD 65536
SOLVENT CDCl3
NS 16
DS 0
SWH 8992.806 Hz
FIDRES 0.137219 Hz
AQ 3.6438515 sec
RG 35.9
DM 55.600 usec
DE 6.00 usec
TE 290.0 K
D1 5.0000000 sec

==== CHANNEL f1 ===
NUC1 1H
P1 9.00 usec
PL1 0.00 dB
SF01 600.8336050 MHz

F2 - Processing parameters
SI 65536
SF 600.8300266 MHz
WDW EM
SSB 0
LB 0.10 Hz
GB 0
PC 1.00

1D NMR plot parameters
CX 20.00 cm
F1P 10.000 ppr
F1 6006.30 Hz
F2P -0.500 ppr
F2 -300.42 Hz
PPMCM 0.52500 ppr
HZCM 315.43576 Hz



WHJ350

Current Data Parameters
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EXPNO 1
PROCNO 1

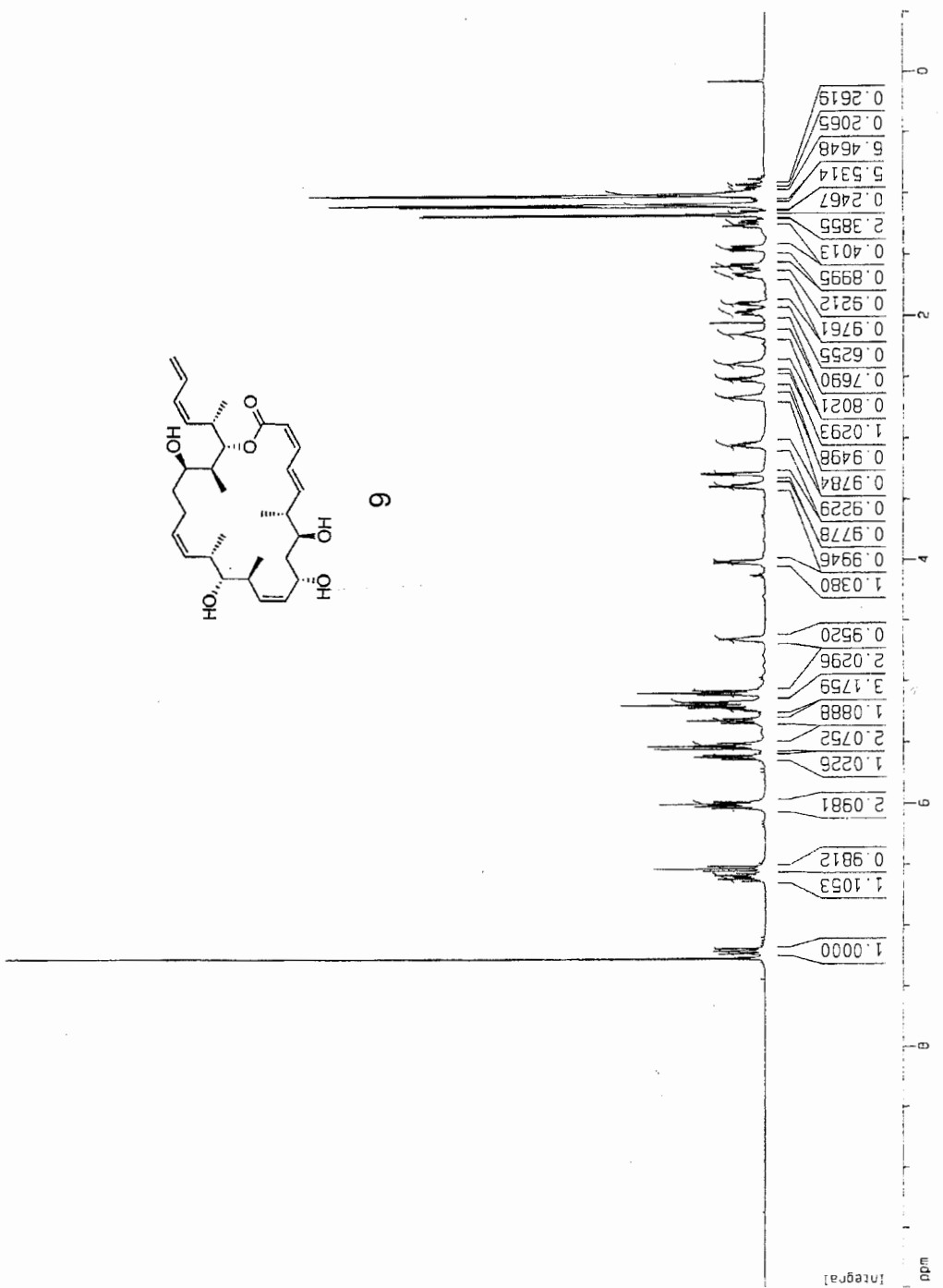
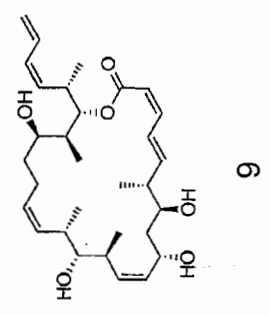
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PULPROG zg
TD 65536
SOLVENT CDC13
NS 16
DS 0
SWH 8992.806 Hz
FIDRES 0.137219 Hz
AQ 3.6438515 sec
RG 64
DM 55.600 usec
DE 6.00 usec
TE 290.0 K
D1 12.0000000 sec

==== CHANNEL f1 ===
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P1 9.00 usec
PL1 0.00 dB
SFO1 600.8336050 MHz

F2 - Processing parameters
SI 65536
SF 600.8300268 MHz
WDW EM
SSB 0
LB 0.10 Hz
GB 0
PC 1.00

10 NMR plot parameters
CX 20.00 cm
F1P 10.000 ppr
F1 6008.30 Hz
F2P -0.500 ppr
F2 -300.42 Hz
PPMCM 0.52500 ppr
HZCM 315.43576 Hz

7.2705
6.53239
6.02278
6.00238
5.62032
5.55264
5.53886
5.53354
5.52396
5.32238
5.21714
5.19825
5.18242
5.17221
5.17039
5.16920
5.14676
5.11190
5.10242
5.09744
5.07901
3.28975
1.18254
1.17111
1.10559
1.0912
1.09398
1.08758
1.02548
1.02102
1.01422
1.00980
1.00512



1.0000
1.1053
0.9812
2.0981
1.0226
2.0752
1.0888
3.1759
2.0296
0.9520
1.0380
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0.8995
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2.3855
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Current Data Parameters
 NAME WHJ350
 EXPNO 5
 PROCNO 1

WHJ350

F2 - Acquisition Parameters
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 Time 14.23
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 PULPROG zgpg30
 TD 65536
 SOLVENT CDCl3
 NS 7644
 DS 0
 SWH 37878.769 Hz
 FIDRES 0.577984 Hz
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 D3 0.00100000 sec

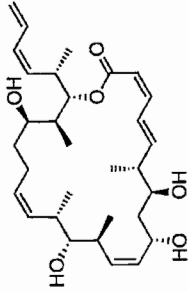
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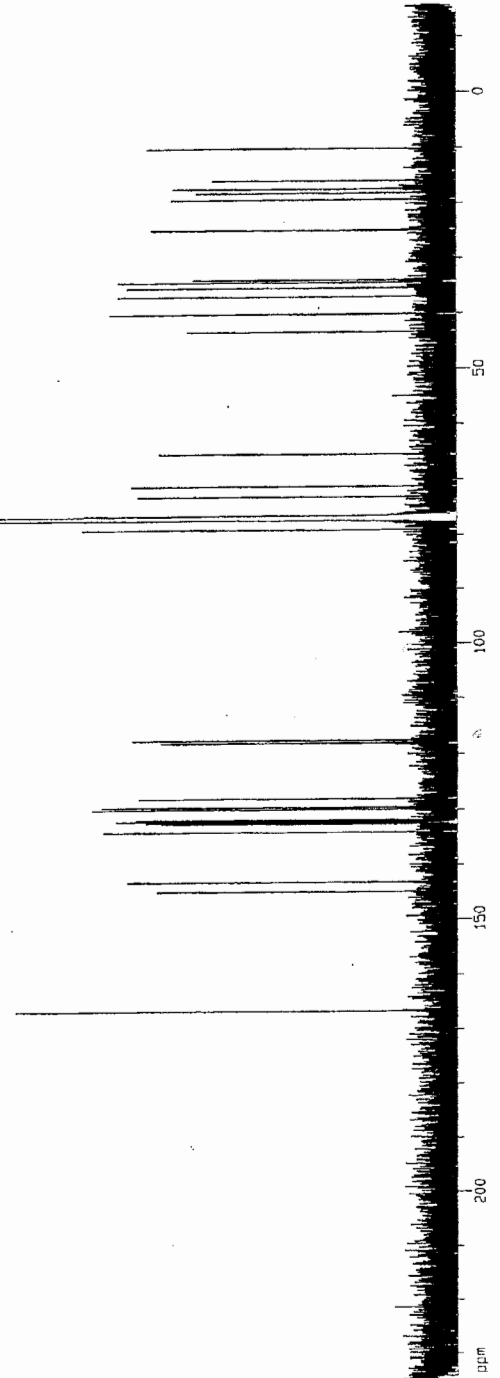
F2 - Processing parameters
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 SF 151.0788344 MHz
 WDW EM
 SSB 0
 LB 1.00 Hz
 GB 0
 PC 1.00

1D NMR plot parameters
 CX 20.00 cm
 F1P 234.895 ppm
 F1 35487.63 Hz
 F2P -15.627 ppm
 F2 -2391.15 Hz
 PPMCM 12.53610 ppm/cm
 HZCM 1893.93933 Hz/cm

166.60
144.82
143.16
134.07
132.55
132.34
132.01
131.80
129.93
129.55
127.97
117.93
117.48
79.06
77.21
77.00
76.78
76.42
73.07
71.16
65.39
43.30
40.18
40.12
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34.45
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24.82
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18.09
17.40
15.87
10.11



9



WHJ330

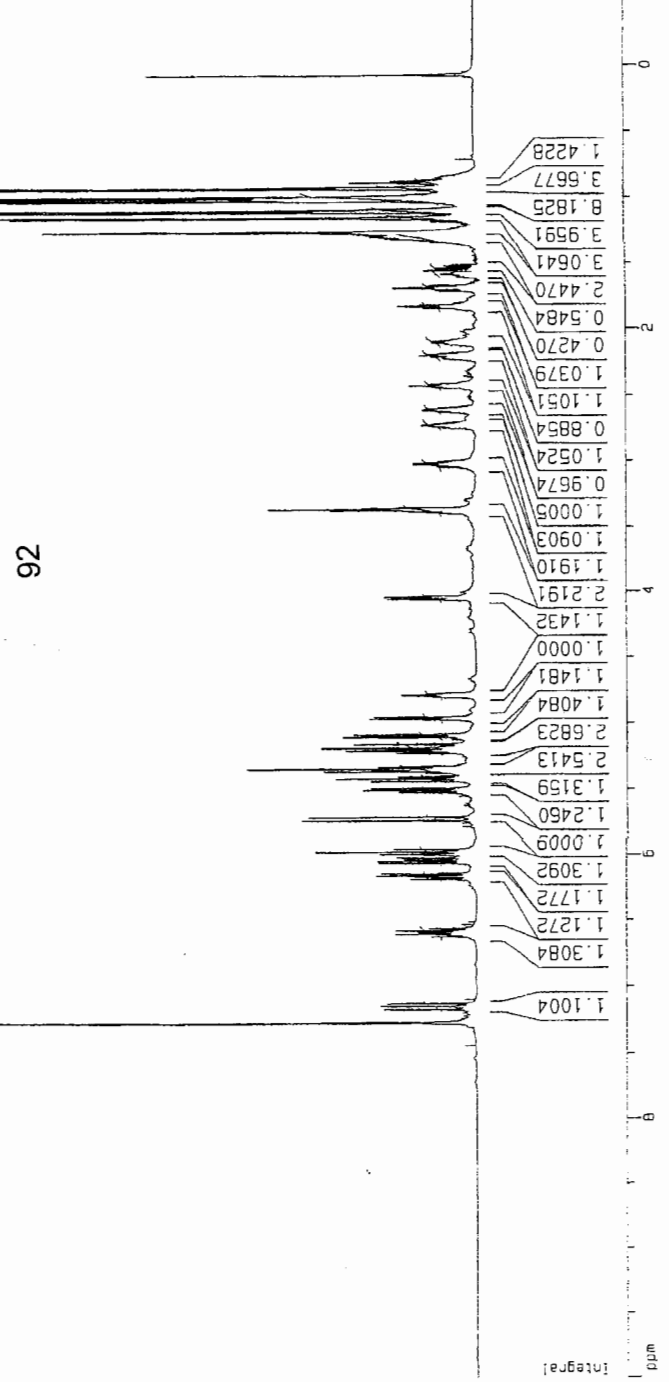
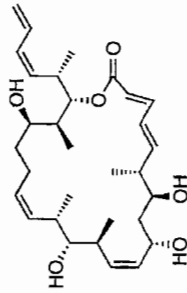
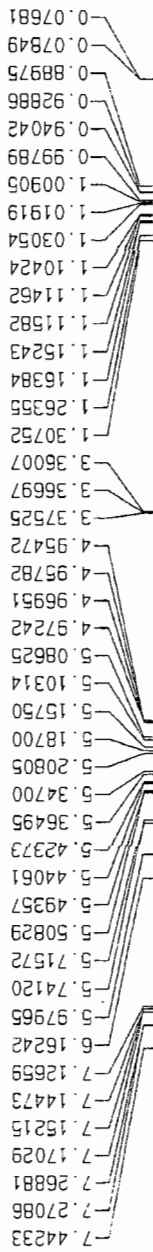
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 PULPROG zg
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 SOLVENT CDC13
 NS 128
 DS 0
 SWH 8992.806 Hz
 FIDRES 0.137219 Hz
 AQ 3.6438515 sec
 RG 181
 DW 55.600 usec
 DE 6.00 usec
 TE 290.0 K
 D1 4.0000000 sec

===== CHANNEL f1 =====
 NUC1 1H
 P1 8.56 usec
 PL1 0.00 dB
 SFO1 600.8336050 MHz

F2 - Processing parameters
 SI 65536
 SF 600.8330272 MHz
 WDW EM
 SSB 0
 LB 0.10 Hz
 GB 0
 PC 1.00

1D NMR plot parameters
 CX 20.00 cm
 F1P 10.000 ppr
 F1 6008.30 Hz
 F2P -0.500 ppr
 F2 -300.42 Hz
 PPMCM 0.52500 ppr
 HZCM 315.43576 Hz



WHJ330

Current Data Parameters
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EXPNO 2
PROCNO 1

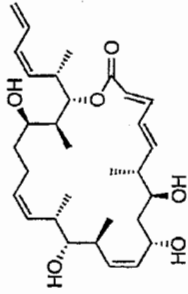
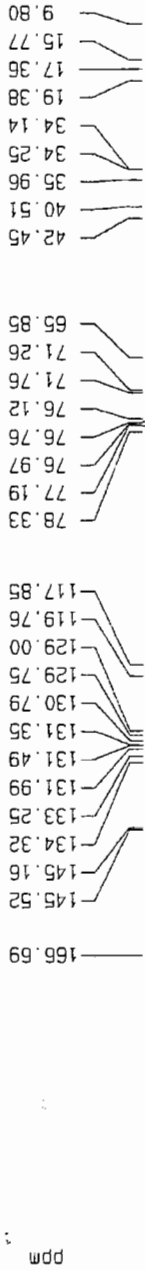
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TD 65536
SOLVENT CDC13
NS 17704
DS 0
SWH 37878.789 Hz
FIDRES 0.577984 Hz
AQ 0.8651252 sec
RG 32768
DM 13.200 usec
DE 6.00 usec
TE 290.0 K
D1 8.0000000 sec
D3 0.00100000 sec

==== CHANNEL f1 =====
NUC1 13C
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SFO1 151.0953827 MHz

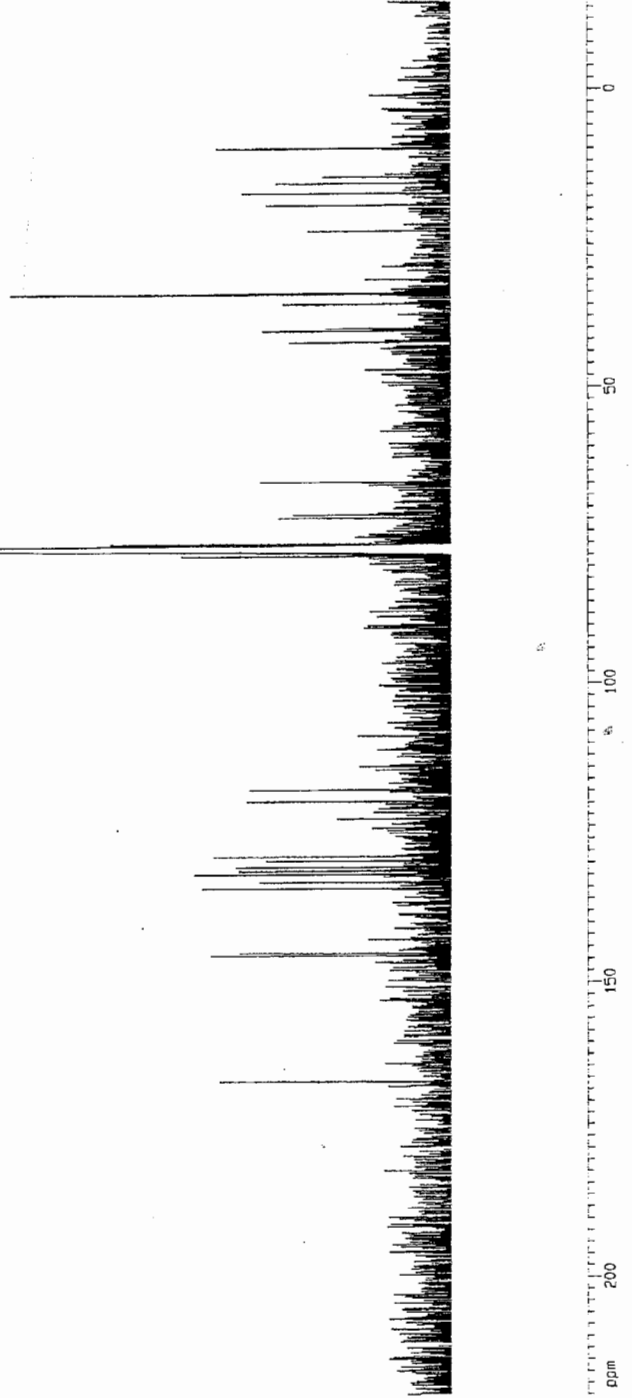
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PL12 12.00 dB
SFO2 600.8336050 MHz

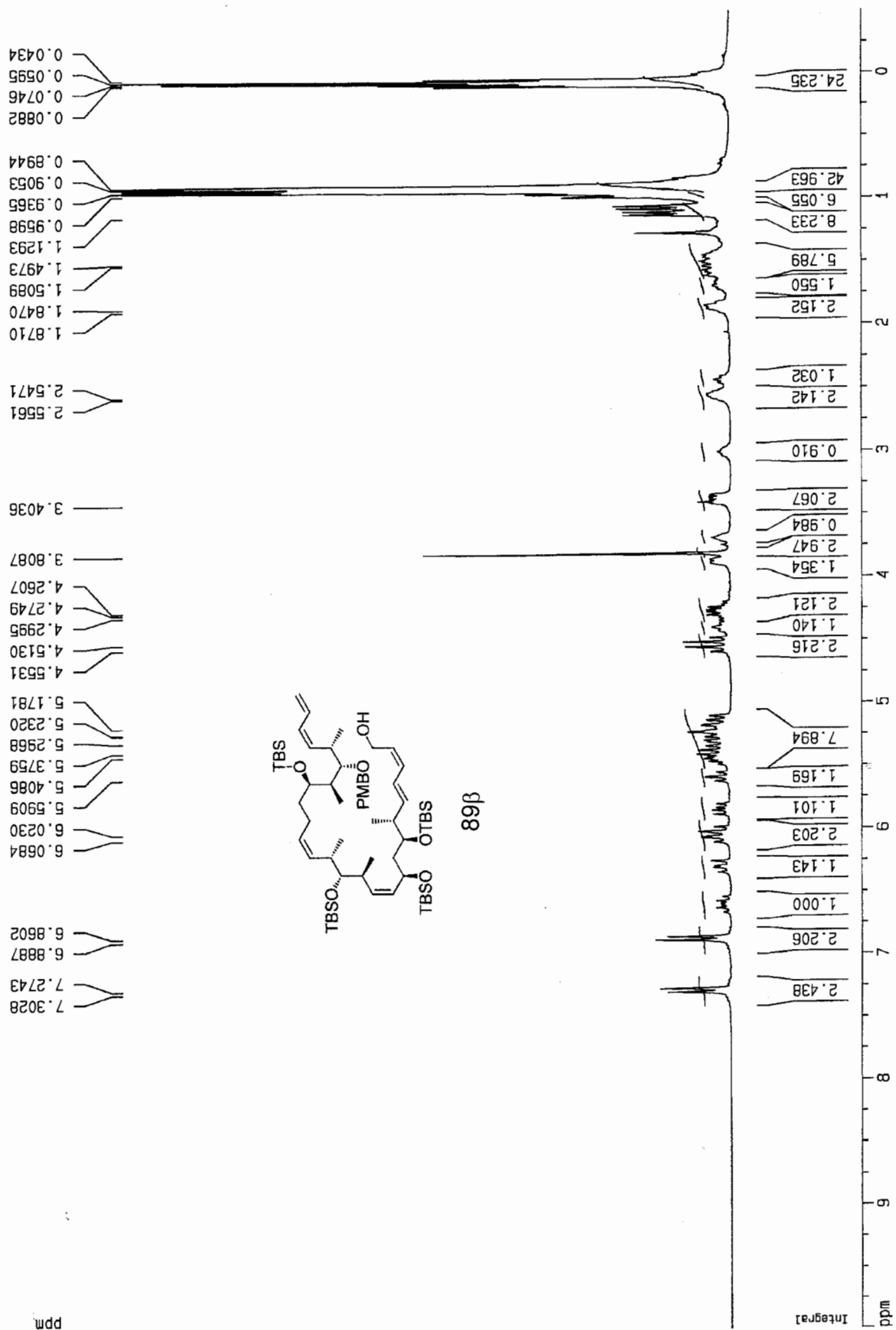
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LB 1.00 Hz
GB 0
PC 1.00

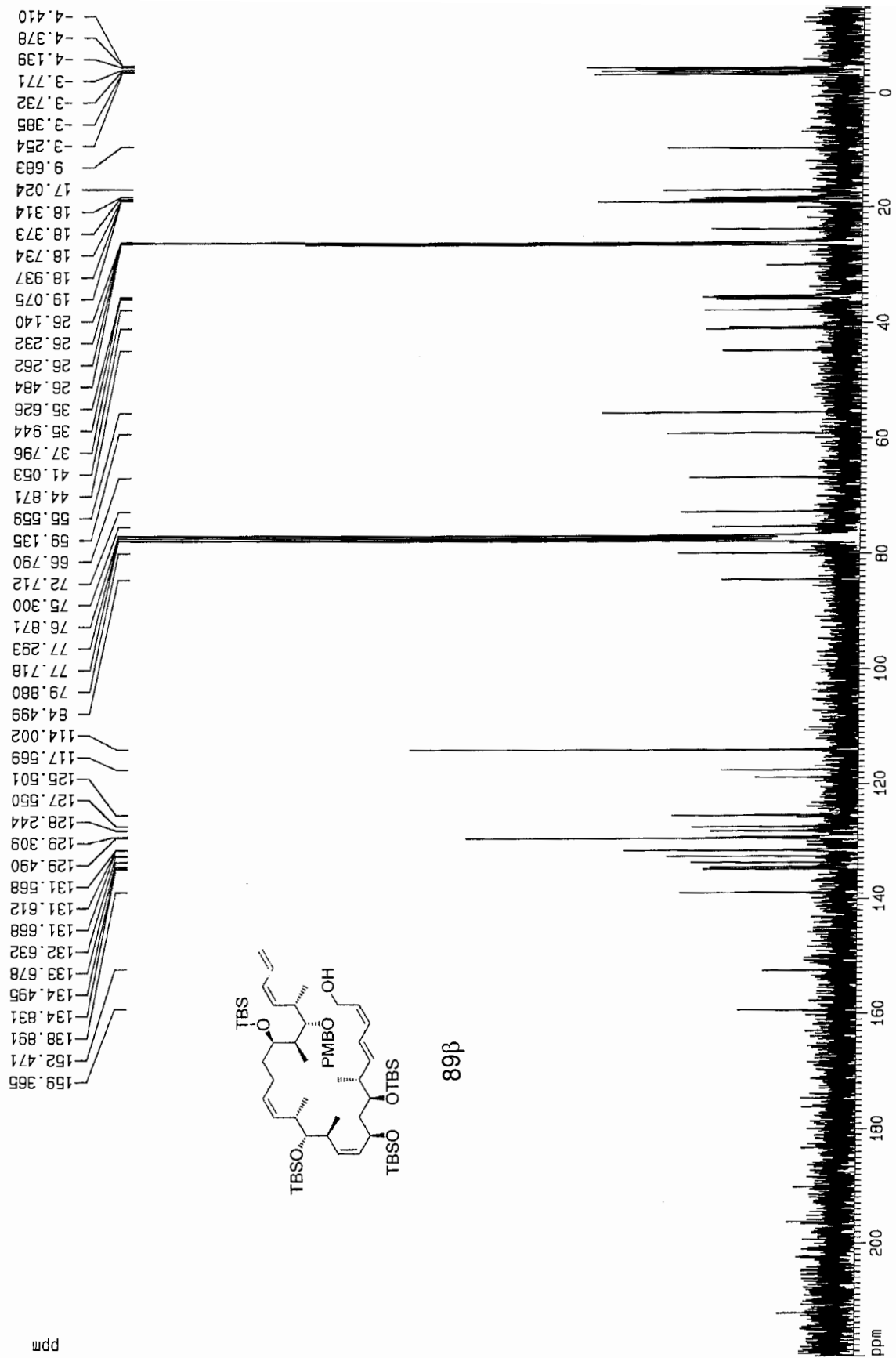
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F1 33237.34 Hz
F2P -15.000 ppm
F2 -2266.18 Hz
PPMCM 11.75000 ppm/cm
HZCM 1775.17627 Hz/cm

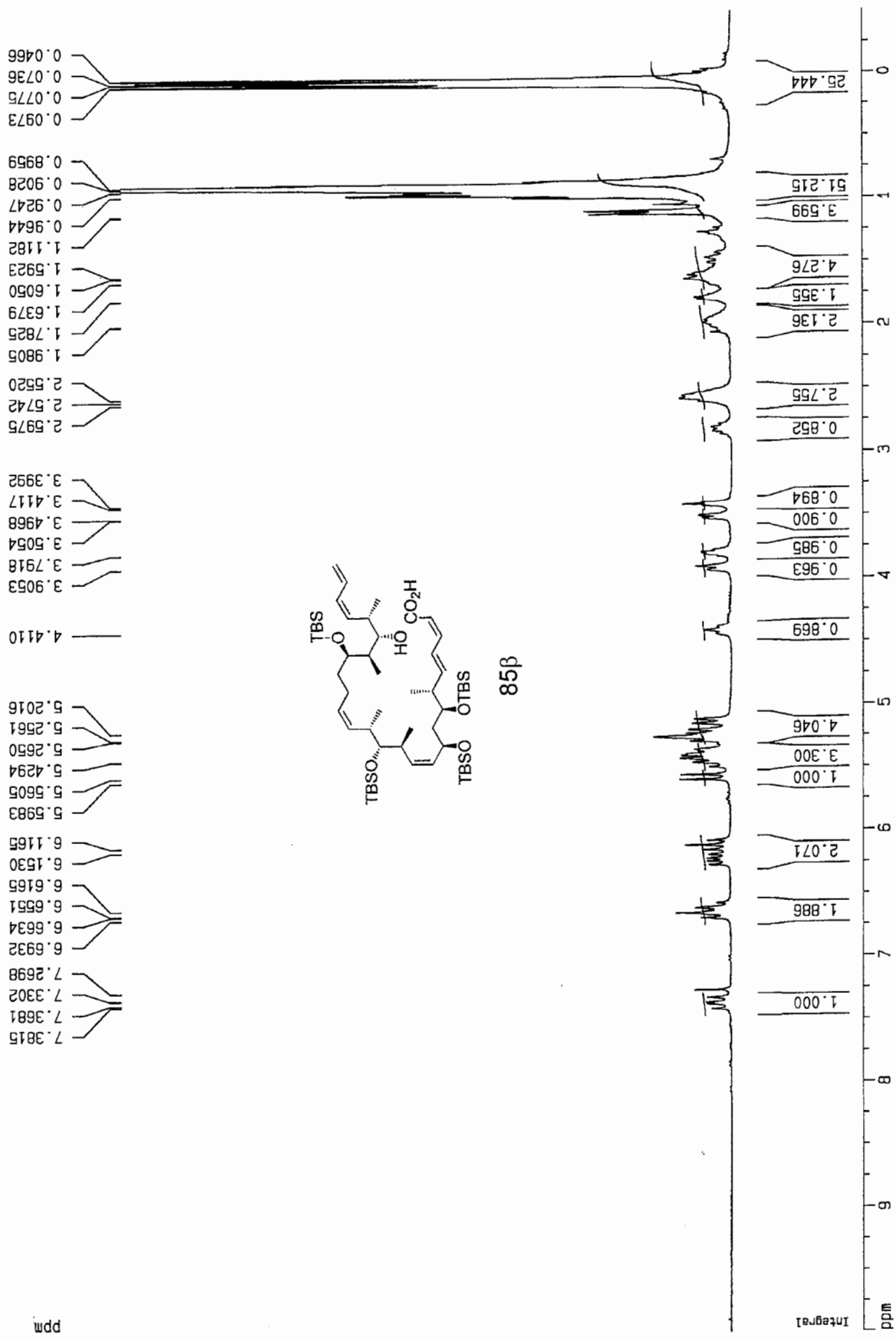


92









WHJ360

Current Data Parameters
NAME WHJ360up_pure
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters:

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Time 9.36

INSTRUM spect
PROBHD 5 mm TXI 13C
PULPROG zg
TD 32768
SOLVENT CDCl3
NS 32
DS 0

SWH 7507.507 Hz

FIDRES 0.229111 Hz

RG 322.5

DW 66.600 usec

DE 6.00 usec

TE 290.0 K

D1 4.00000000 sec

P1 10.60 usec

DE 6.00 usec

SF01 500.1330008 MHz

NUC1 1H

PL1 0.00 dB

F2 - Processing parameters

SI 32768

SF 500.1300231 MHz

WDW EM

SSB 0

LB 0.40 Hz

GB 0

PC 1.00

1D NMR plot parameters

CX 20.00 cm

F1P 10,000 ppr

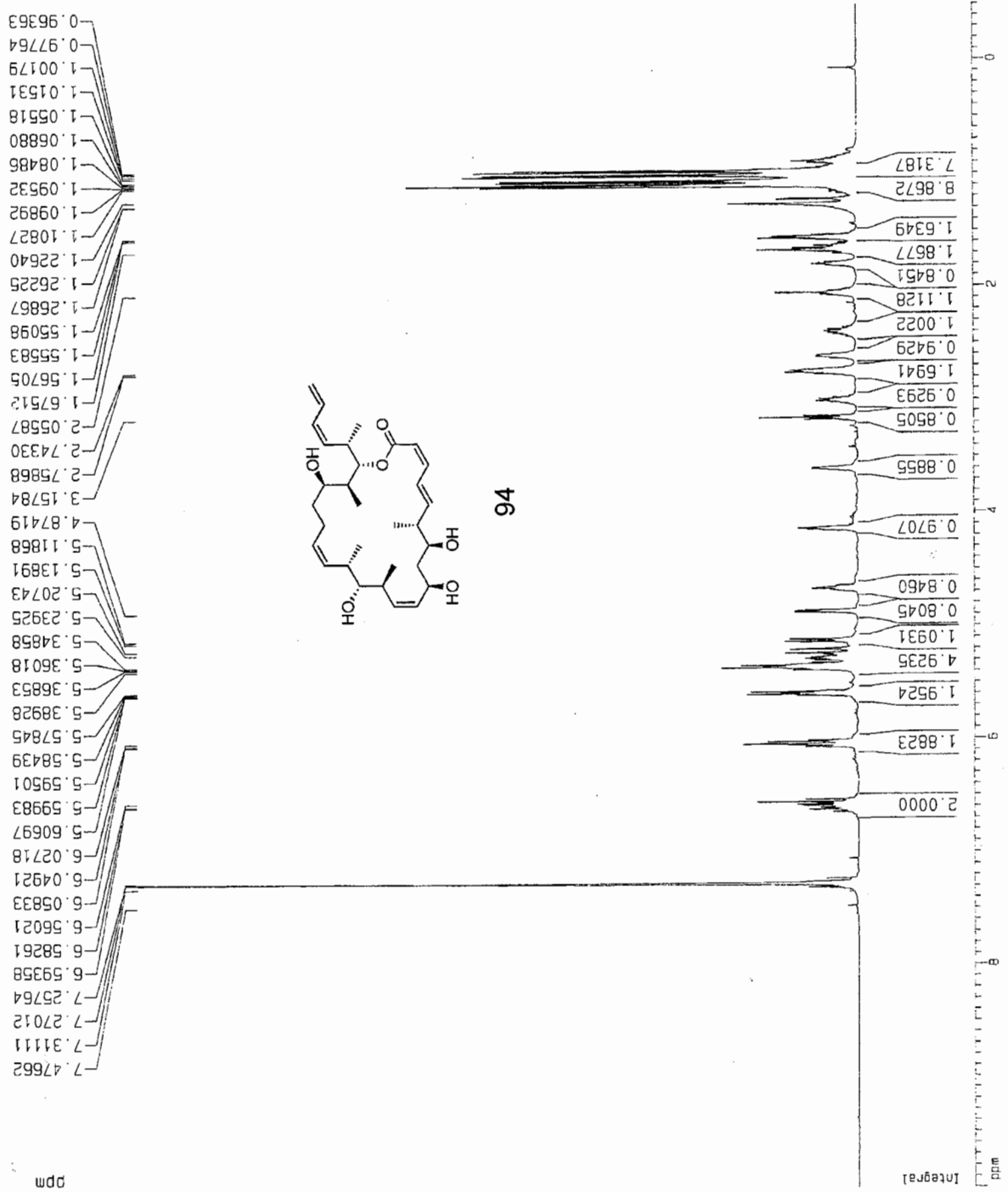
F1 5001.30 Hz

F2P -0.500 ppr

F2 -250.07 Hz

PPMCM 0.52500 ppr

HZCM 262.56827 Hz



Current Data Parameters
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 EXPNO 14
 PROCNO 1

F2 - Acquisition Parameters
 Date_ 20060124
 Time 21.00
 INSTRUM spect
 PROBHD 5 mm TBI 1H/
 PULPROG c13wznoe
 TD 65536
 SOLVENT CDCl3
 NS 18196
 DS 0
 SWH 37870.789 Hz
 FIDRES 0.577984 Hz
 AQ 0.8651252 sec
 RG 32768
 DW 13.200 usec
 DE 6.00 usec
 TE 290.0 K
 O1 4.00000000 sec
 O3 0.00100000 sec

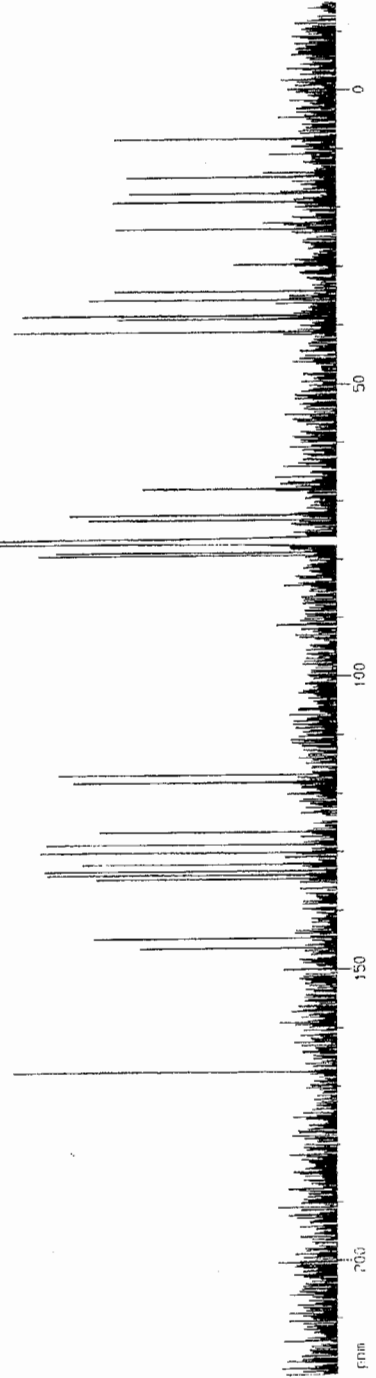
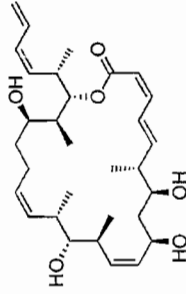
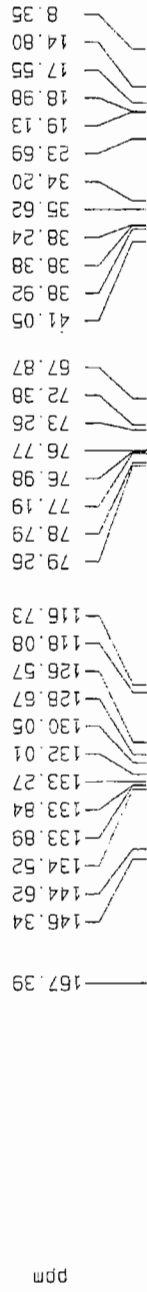
***** CHANNEL f1 *****
 NUC1 13C
 P1 13.50 usec
 PL1 0.00 dB
 SF01 151.0953627 MHz

***** CHANNEL f2 *****
 CPDPRG2 waltz16
 NUC2 1H
 PCPD2 100.00 usec
 PL2 0.00 dB
 PL12 12.00 dB
 SF02 600.8336050 MHz

F2 - Processing parameters
 SI 65536
 SF 151.0786344 MHz
 WDW EM
 SSB 0
 LB 1.00 Hz
 GB 0
 PC 1.00

1D NMR plot parameters
 CX 20.00 cm
 F1P 220.000 ppm
 F1 33237.34 Hz
 F2P -15.000 ppm
 F2 -2266.18 Hz
 FREQ 11.75000 ppm/cm
 HZCM 1775.17627 Hz/cm

WHJ360



WHJ362

Current Data Parameters
NAME WHJ360midpure
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters:

Date_ 500000
Time 13.44
INSTRUM spect
PROBHD 5 mm TXI 13C
PULPROG zg

TD 32768

SOLVENT CDCl3

NS 64

DS 0

SWH 7507.507 Hz

FIDRES 0.229111 Hz

AQ 2.1823988 sec

RG 181

OW 66.600 usec

DE 6.00 usec

TE 290.0 K

D1 8.00000000 sec

P1 10.50 usec

DE 6.00 usec

SFO1 500.1330008 MHz

NUC1 1H

PL1 0.00 dB

F2 - Processing parameters

SI 32768

SF 500.1300233 MHz

WDW EM

SSB 0

LB 0.40 Hz

GB 0

PC 1.00

1D NMR plot parameters

CX 20.00 cm

F1P 10.000 ppr

F1 5001.30 Hz

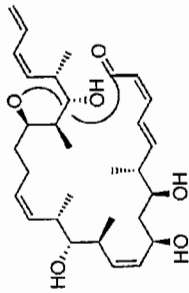
F2P -0.500 ppr

F2 -250.07 Hz

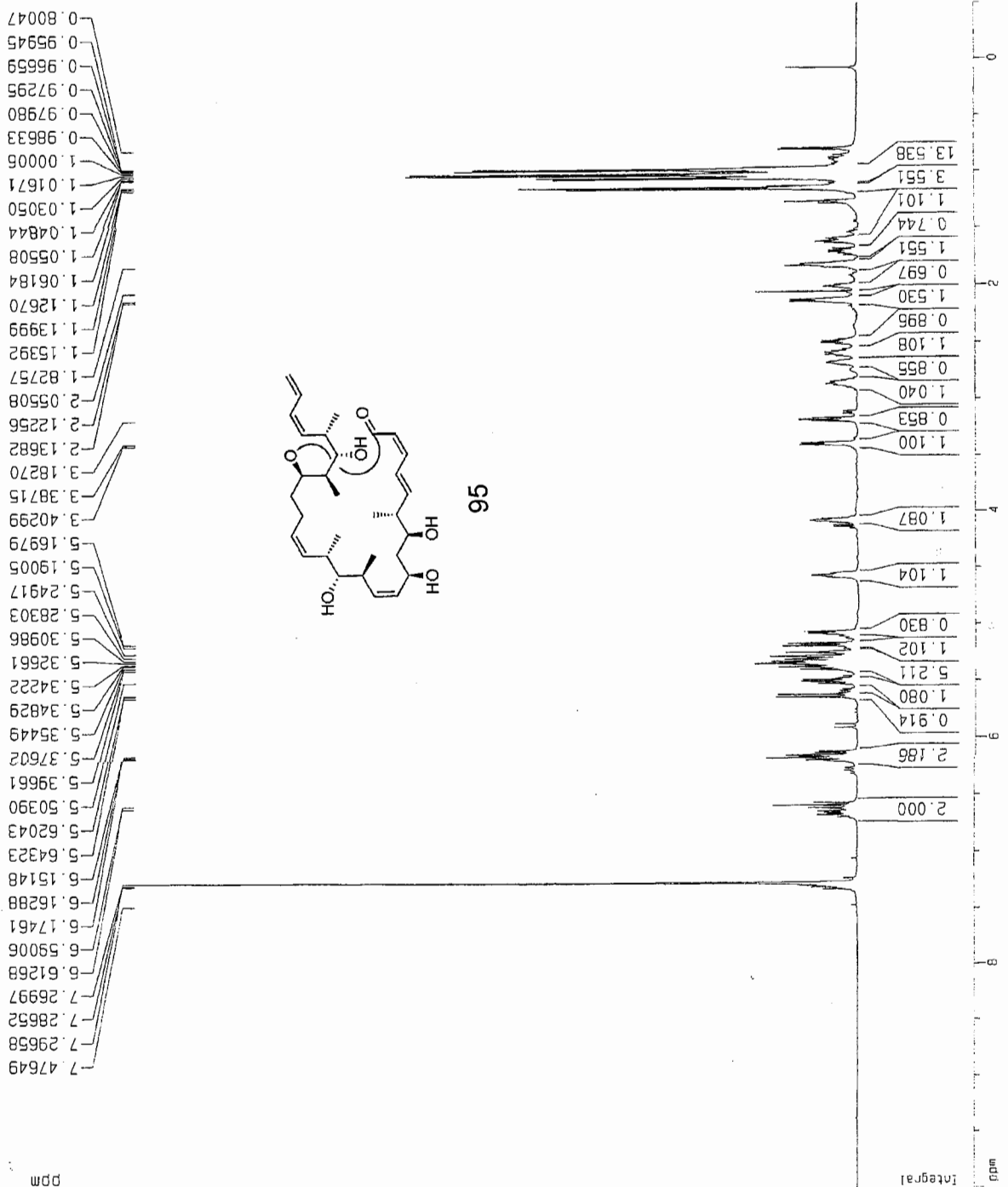
PPMCM 0.52500 ppr

HZCM 262.56827 Hz

7.47649
7.29658
7.28652
7.26997
6.61268
6.59006
6.17461
6.16288
6.15148
5.64323
5.62043
5.50390
5.39661
5.37602
5.35449
5.34829
5.34222
5.32661
5.30986
5.28303
5.24917
5.19005
5.16979
3.40299
3.38715
3.18270
2.13682
2.12256
2.05508
1.82757
1.15392
1.13999
1.12670
1.06184
1.05508
1.04844
1.03050
1.01671
1.00006
0.98633
0.97980
0.97295
0.96659
0.95945
0.80047



95



Current Data Parameters
 NAME WHJ360
 EXPNO 13
 PROCNO 1

WHJ362

F2 - Acquisition Parameters

Date_ 20060105
 Time 10.15
 INSTRUM spect
 PROBHD 5 mm TBI 1H/
 PULPROG zgpg30
 TD 65536
 SOLVENT CDCl3
 NS 9539
 DS 0
 SWH 37078.789 Hz
 FIDRES 0.577984 Hz
 AQ 0.8651252 sec
 RG 32768
 DW 13.200 usec
 DE 6.00 usec
 TE 290.0 K
 D1 8.00000000 sec
 D3 0.00100000 sec

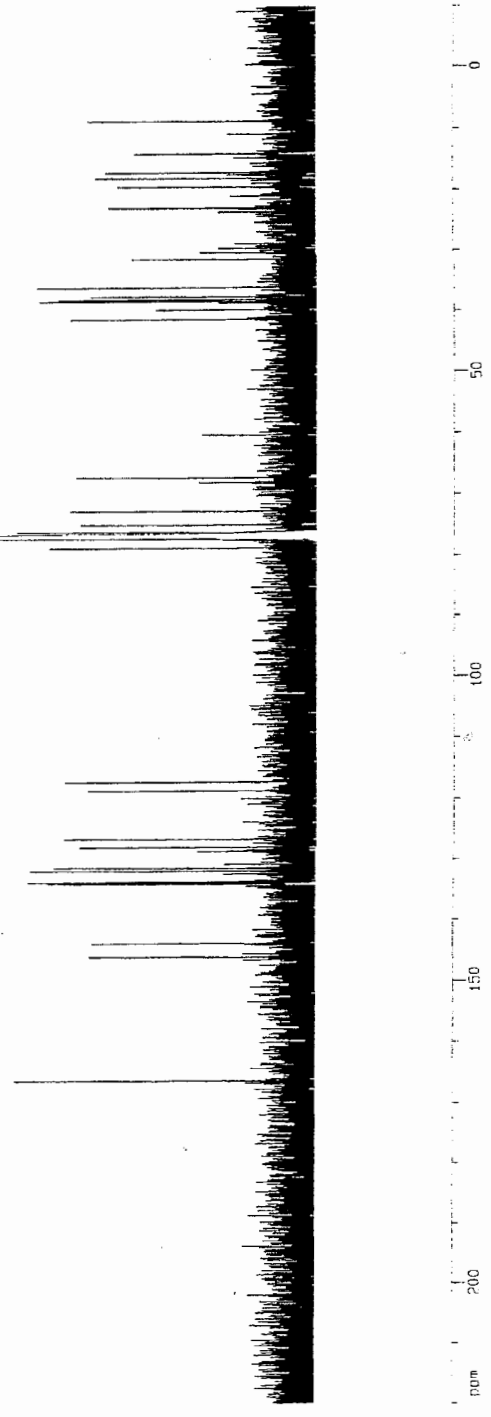
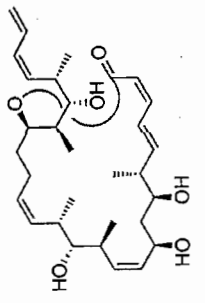
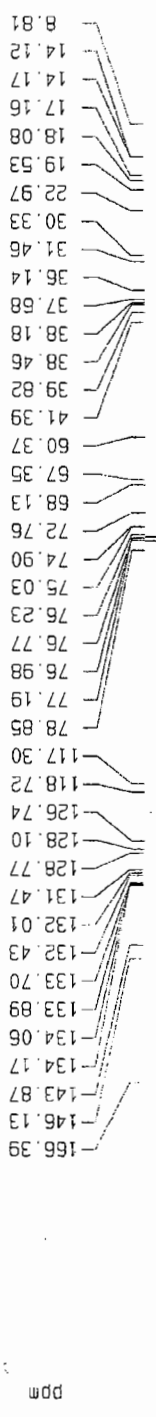
===== CHANNEL f1 =====
 NUC1 13C
 P1 13.50 usec
 PL1 0.00 dB
 SF01 151.0953827 MHz

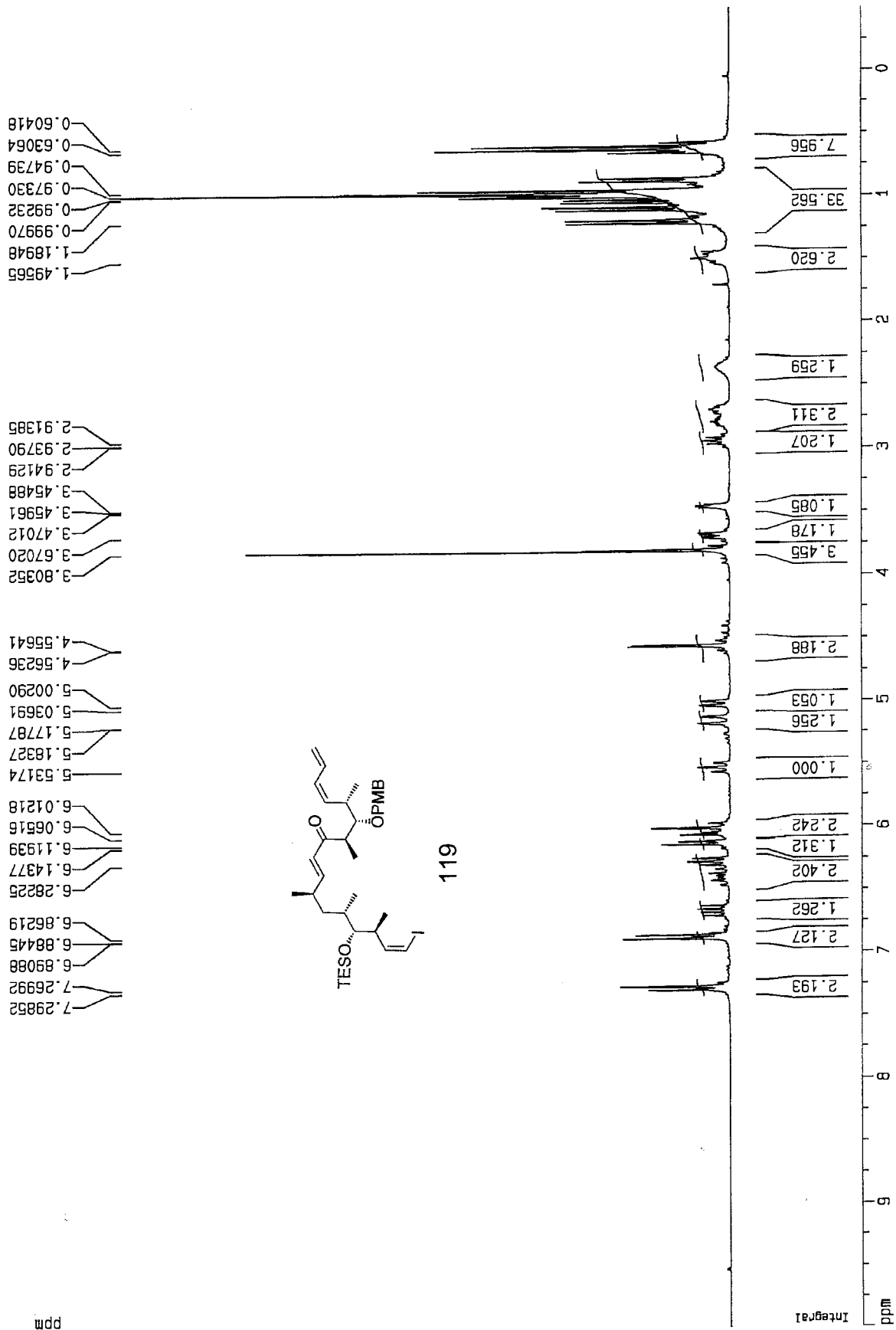
===== CHANNEL f2 =====
 CPDPRG2 waltz16
 NUC2 1H
 PCPD2 100.00 usec
 PL2 0.00 dB
 PL12 12.00 dB
 SF02 600.8336050 MHz

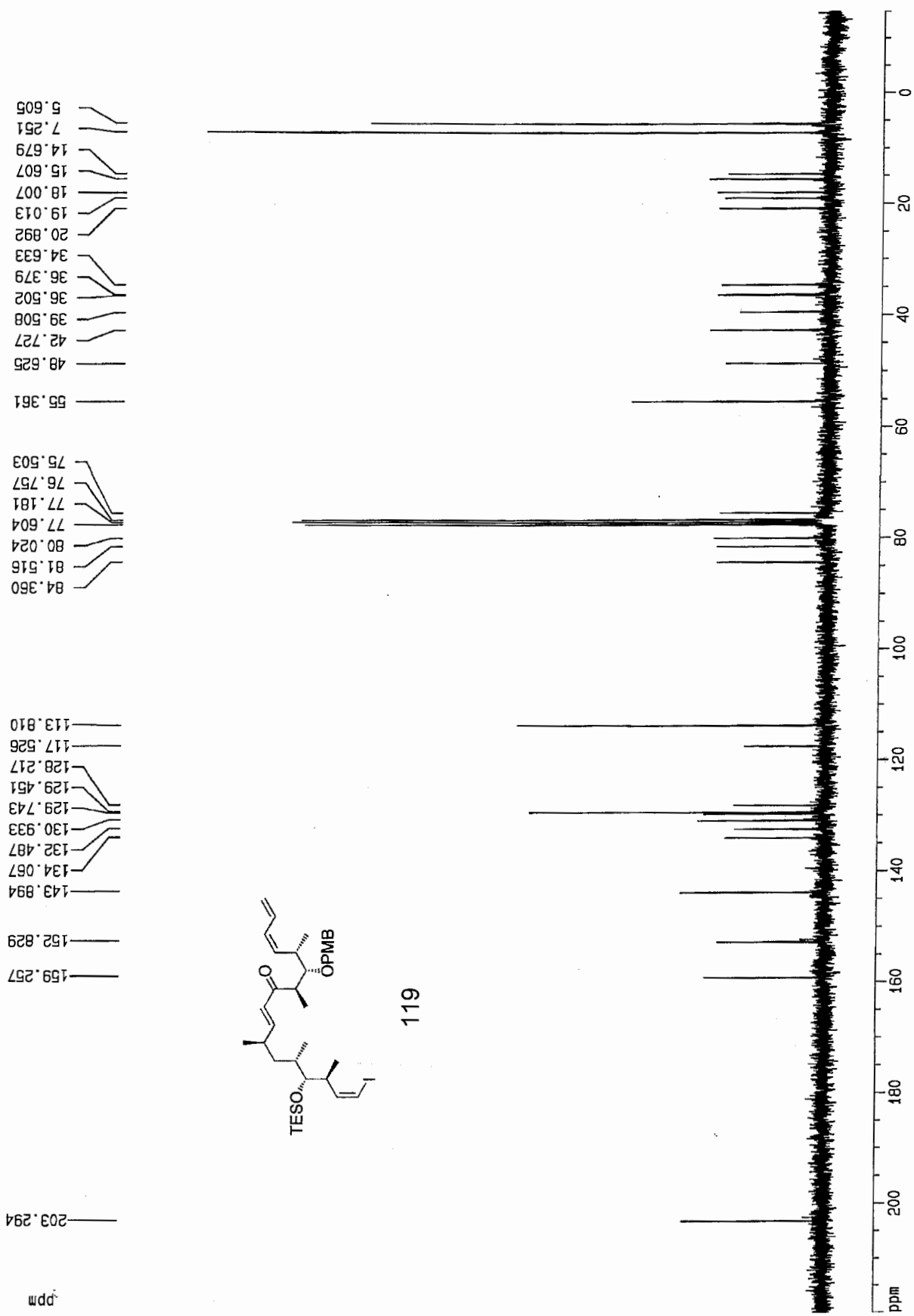
F2 - Processing parameters

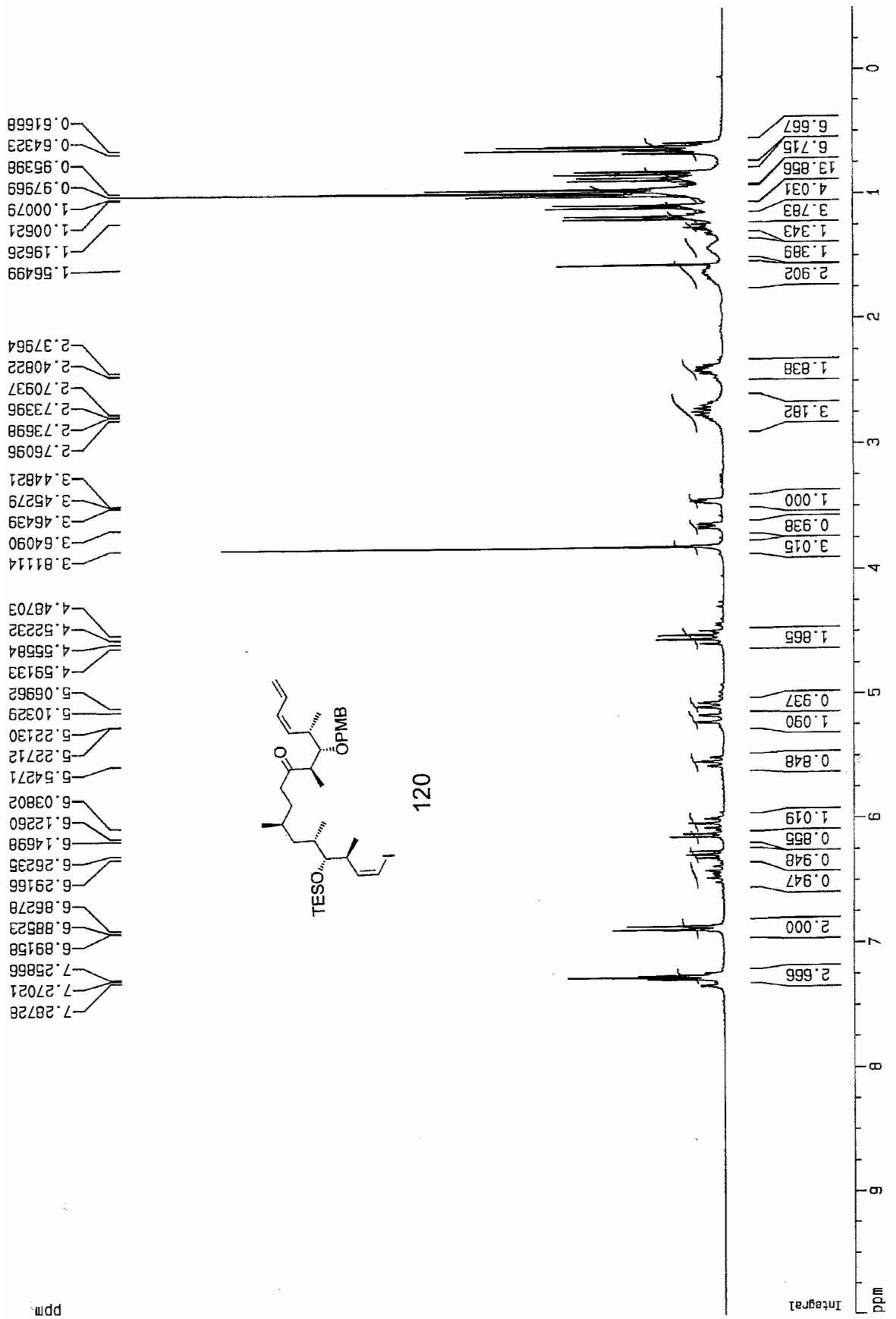
SI 65536
 SF 151.0788344 MHz
 WDW EM
 SSB 0
 LB 1.00 Hz
 GB 0
 PC

===== ID NMR plot parameters =====
 CX 20.00 cm
 F1P 220.000 ppm
 F1 33237.34 Hz
 F2P -10.000 ppm
 F2 -1510.79 Hz
 PPMCM 11.50000 ppm/cm
 HZCM 1737.40649 Hz/cm









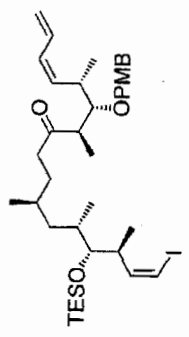
5.693
7.290
14.270
15.904
17.792
18.953
20.571
29.126
29.869
35.557
36.308
40.186
41.011
43.145
50.558
55.371

75.431
76.740
77.164
77.588
80.091
81.488
83.930

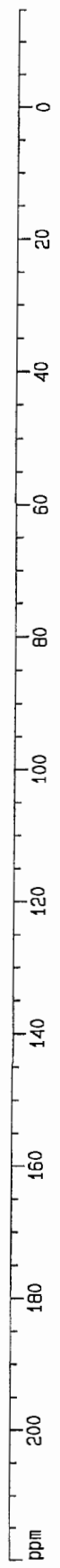
113.830
113.871
117.915
128.546
129.454
129.714
130.858
132.217
133.711
134.079
144.091

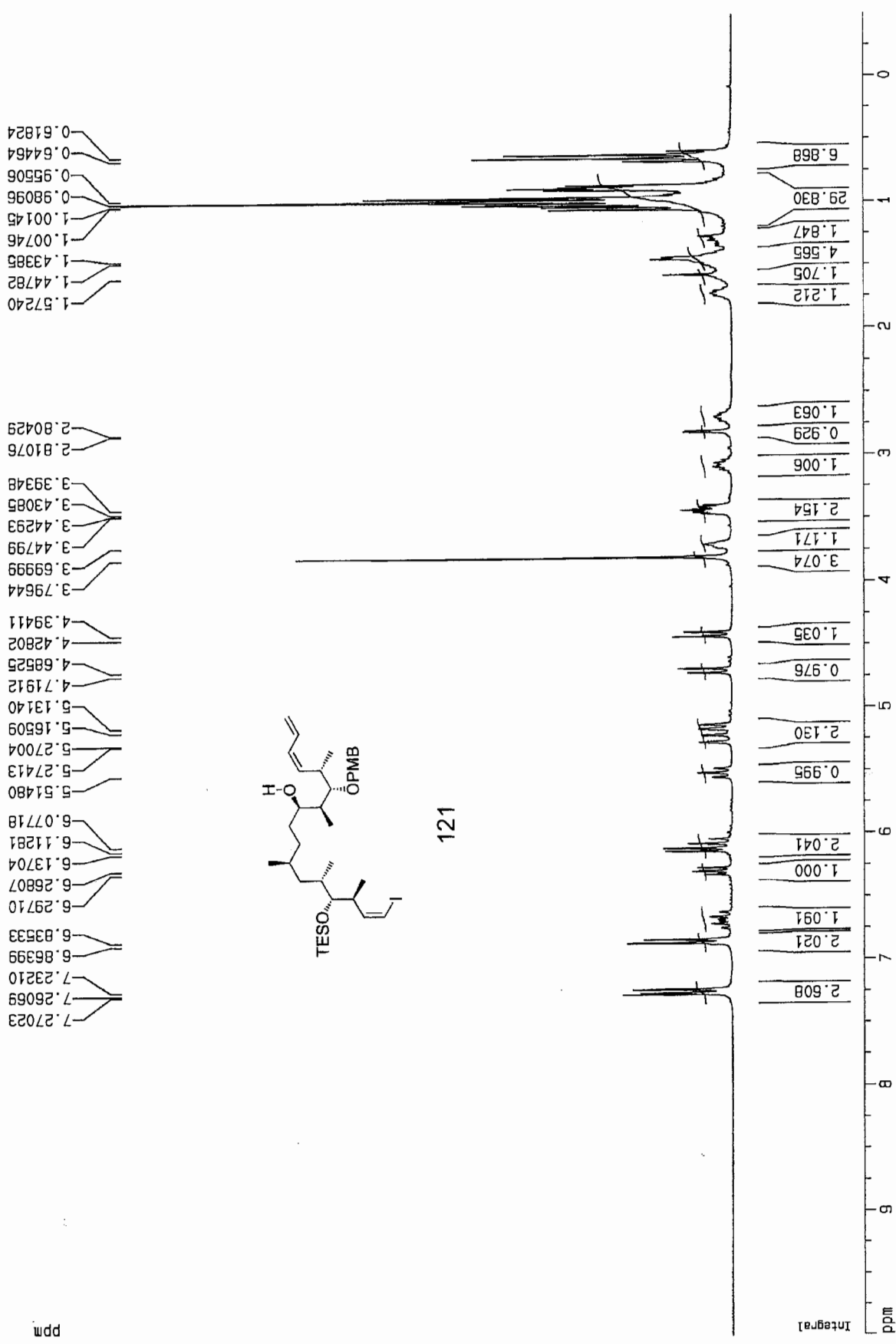
159.276

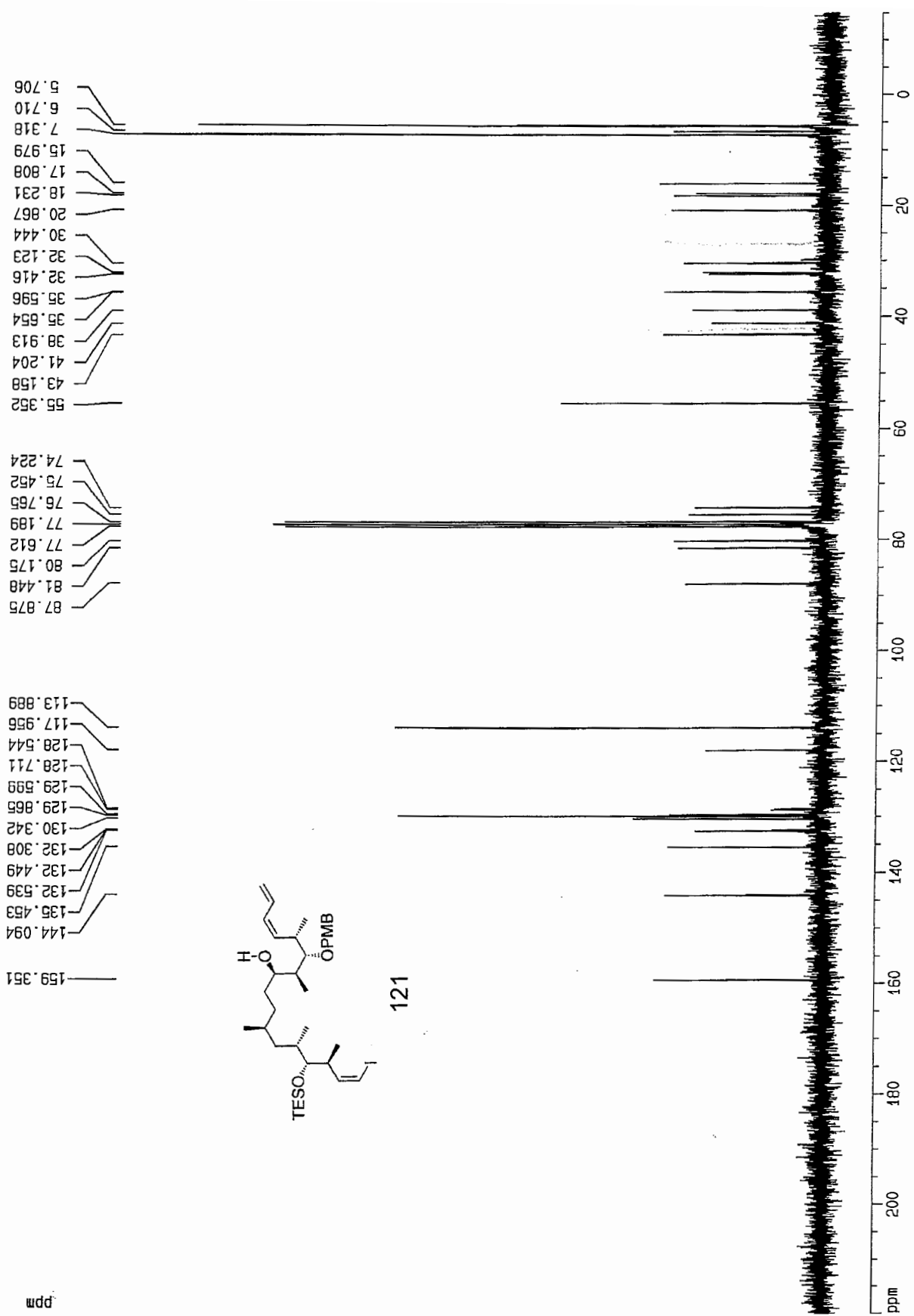
214.559
-ppm

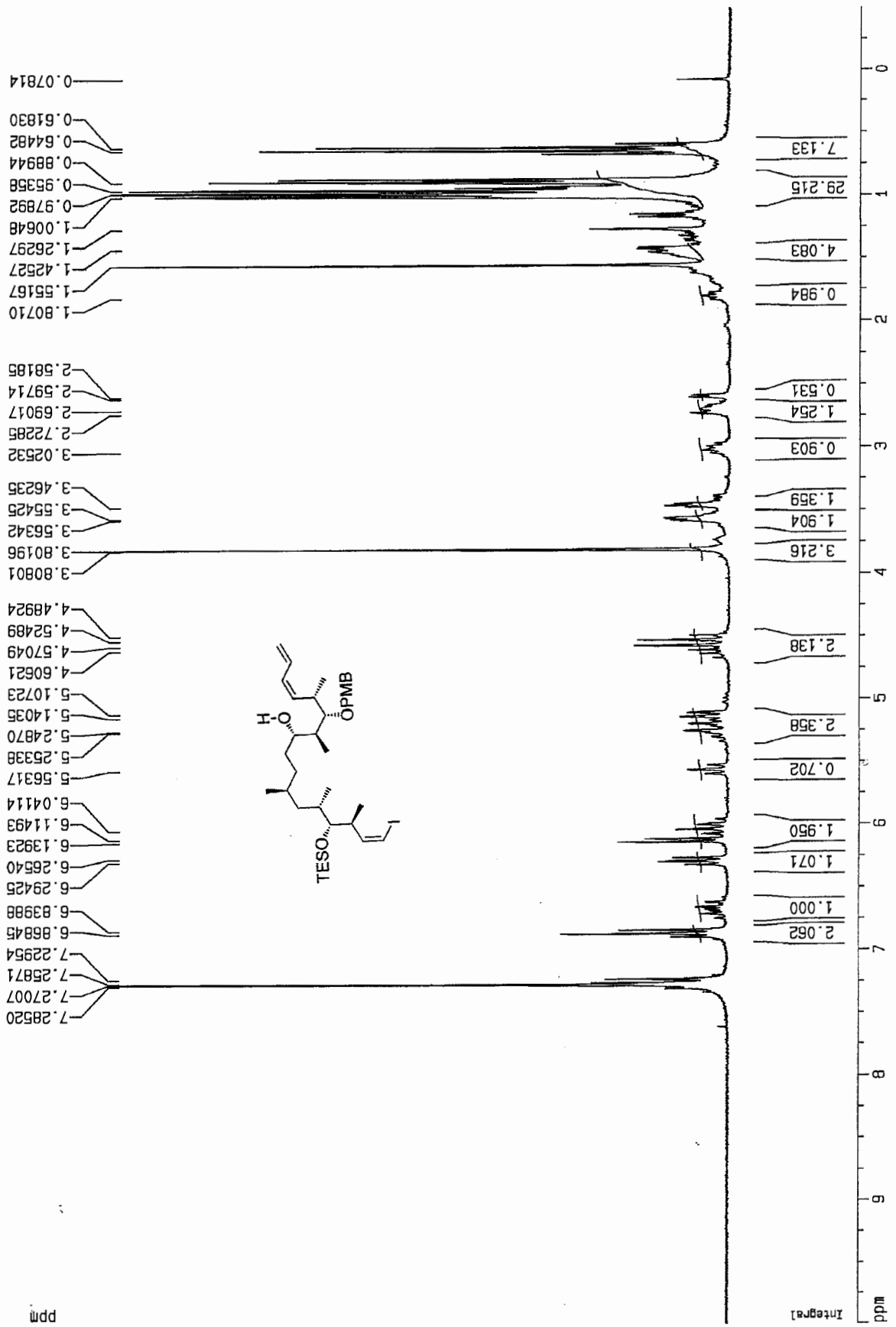


120









WHJ453

