JOC The Journal of Organic Chemistry

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J. Org. Chem., **Just Accepted Manuscript** • Publication Date (Web): 20 Feb 2017

ACS Publications

The Journal of Organic Chemistry is published by the American Chemical Society.
1155 Sixteenth Street N.W., Washington, DC 20036

Total Synthesis of (−)-Marinisporolide C

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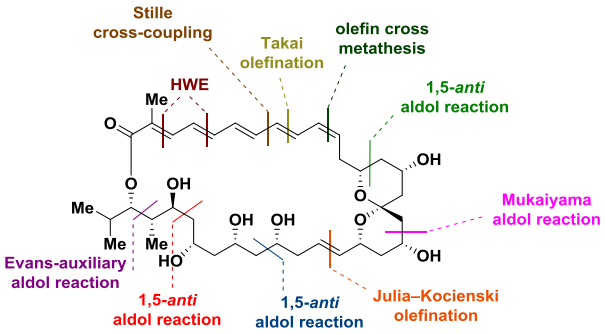


ABSTRACT

The first total synthesis of (−)-marinisporolide C is described, which establishes unequivocally the relative and absolute configuration of this oxopolyene macrolide. Key features of this synthesis include of a series of highly stereoselective aldol reactions followed by directed reductions to build the polyol domain, a Stille cross-coupling reaction to assemble the polyene, and an intramolecular Horner−Wadsworth−Emmons olefination to forge the macrocyclic ring. Despite the initial approach to marinisporolide A using a Yamaguchi macrolactonization reaction that was unsuccessful due to steric hindrance of the oxygen at the C33 position, we were able to prepare a known derivative of marinisporolide A and consequently confirm its stereochemical assignment.

INTRODUCTION

The polyene macrolides are a class of natural products characterized by having a macrolactone containing a conjugated polyene system and a polyol moiety.[1] In general, polyene unit has four to seven conjugated double bonds. The polyol portion contains 1,2-, 1,3- and/or 1,4-diol sequences, with 1,3-diol as the most common unit.

Although many of these compounds are known for their remarkable antifungal activity, only three of them, amphotericin B, nystatin A1 and natamycin (pimaricin) are used by the pharmaceutical industry.

Due to its complex molecular architecture, combined with low natural occurrence, and biological potential, polyene macrolides have been selected as a synthetic target by numerous research groups. In addition to amphotericin B,[2] mycoticin A,[3] roxaticin,[4] roflamycoin,[5] filipin III,[6] dermostatin A,[7] and RK-397[8] had their total synthesis completed.

In 2009, Fenical and co-workers isolated the polyene macrolides marinisporolide A (**1**, 16 mg from 40 cultures of 1 L) and B (**2**, 42 mg from 40 cultures of 1 L) (Figure 1) from the saline culture of the marine actinomycete *Marinispora*, strain CNQ-140.[9]

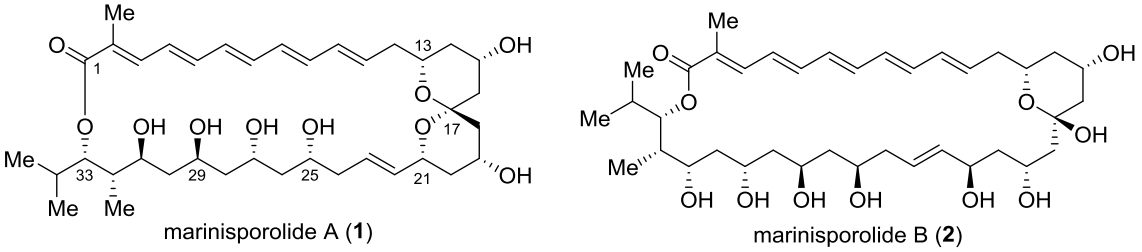


Figure 1: Marinisporolides A and B.

The marinisporolide A (**1**) is a 34-membered macrolactone, containing 11 stereogenic centers, an internal spiroketal with one anomeric effect, and a conjugate pentaene, while marinisporolide B (**2**) is the corresponding hemiketal.

A configuration analysis of marinisporolide A suggests that the spiroketal exists in its thermodynamically favored configuration on the basis of anomeric stabilization and steric effects.[10] Although marinisporolide A spiroketal presents only one anomeric effect, the substituents in C13, C15, C19, and C21 are in equatorial positions (Figure 2).

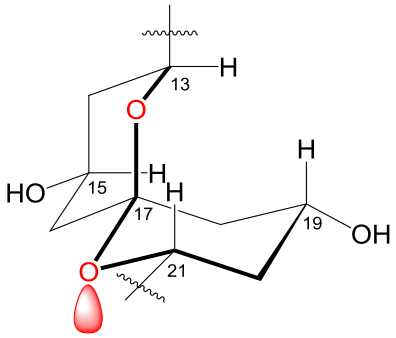


Figure 2: Conformation of marinisporolide A [6,6]spiroketal.

Since marinisporolides A and B are photosensitive, the authors also isolated three olefin geometric isomers: marinisporolides C−E (**3**−**5**) (Figure 3).

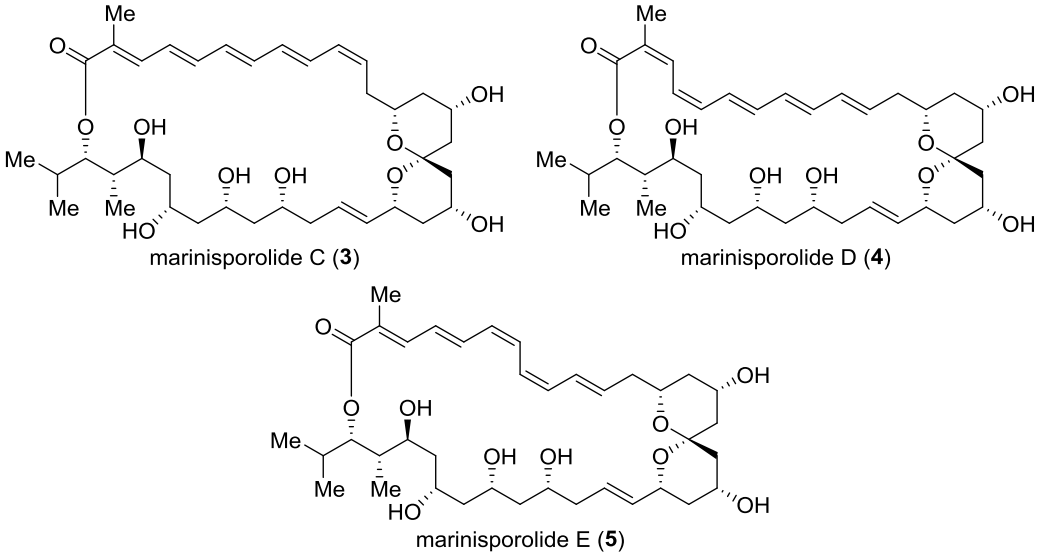
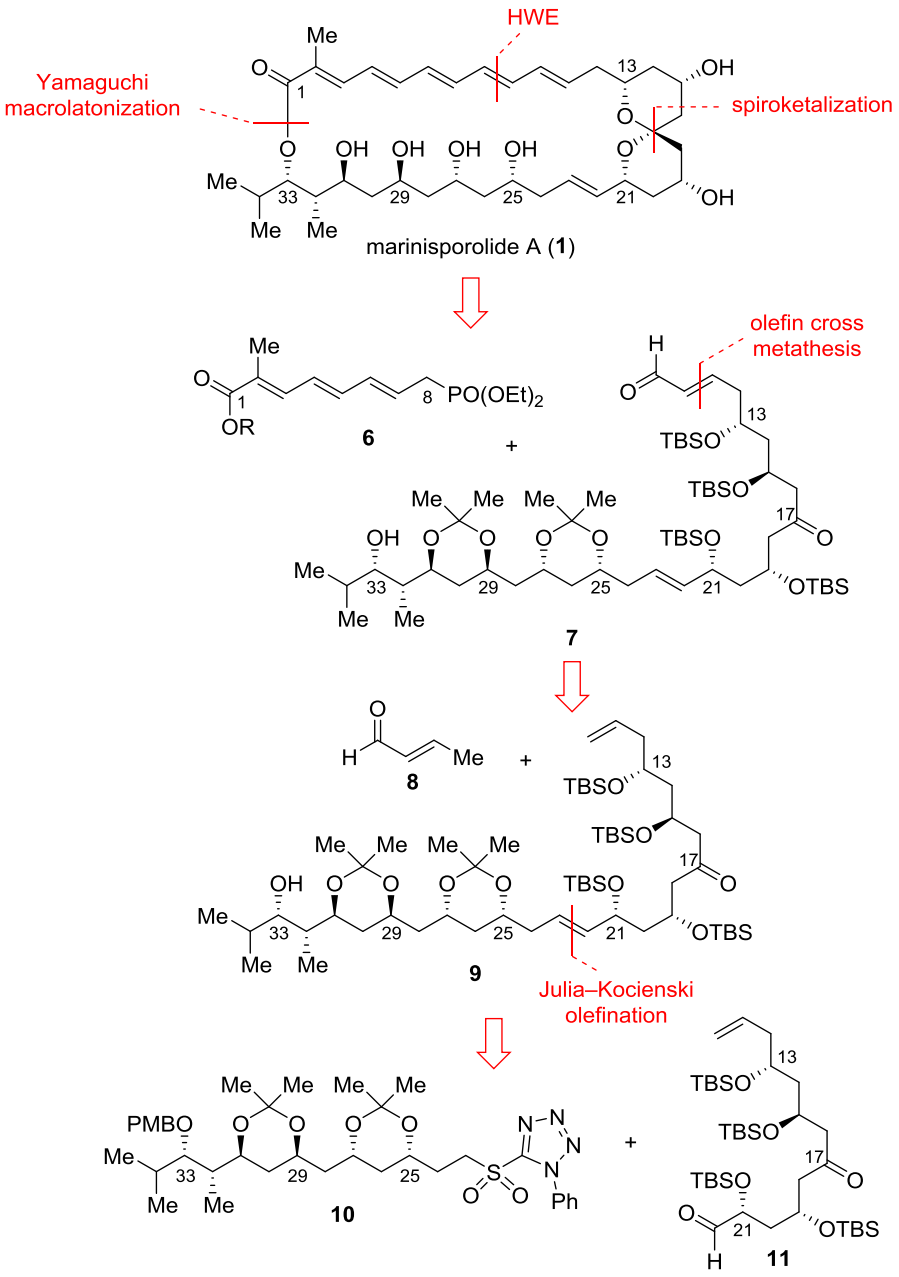


Figure 3: Olefin geometric isomers: marinisporolides C−E.

Recently, we concluded the first total synthesis of marinisporolide C (**3**).[11] Herein, we provide full details of our efforts that culminated in the total synthesis of marinisporolide C and the preparation of a known derivative of marinisporolide A. We also established unambiguously the relative and absolute configuration of marinisporolide C.

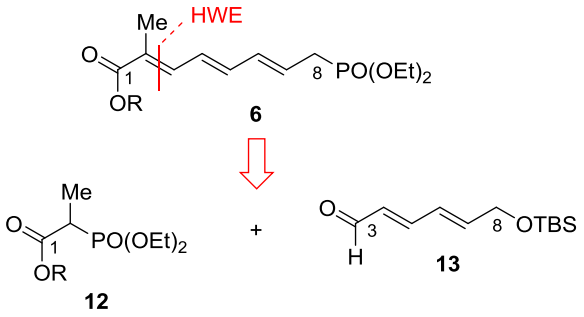
RETROSYNTHETIC ANALYSIS

Our retrosynthetic analysis[12] is outlined in schemes 1−4. Marinisporolide A could be obtained from the phosphonate **6** and the aldehyde **7** through a Horner−Wadsworth−Emmons reaction and a Yamaguchi macrolactonization (Scheme 1). The controlled ketalization event would be incorporated into the synthesis plan under the assumption that the desired configuration would be achieved under equilibration conditions. An olefin cross-metathesis between crotonaldehyde (**8**) and olefin **9** would be envisioned to build up the fragment **7**. The compound **9** could be prepared from a Julia−Kocieński olefination between sulfone **10** and aldehyde **11**.



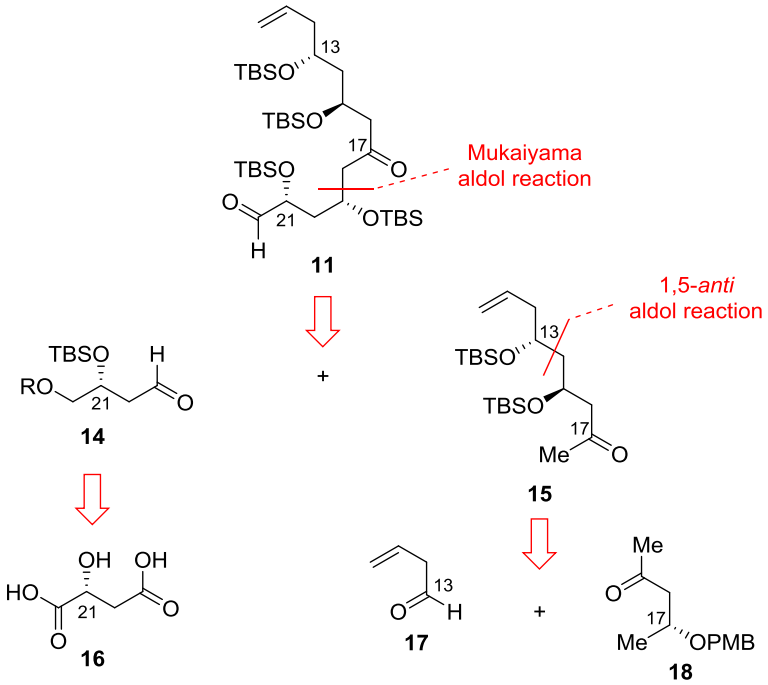
Scheme 1: Retrosynthetic analysis of marinisporolide A (**1**).

The phosphonate **6**, which corresponds to C1−C8 fragment of marinisporolide A, could be generated by a Horner−Wadsworth−Emmons olefination between phosphonate **12** and aldehyde **13** (Scheme 2).



Scheme 2: Retrosynthetic analysis of phosphonate **6**.

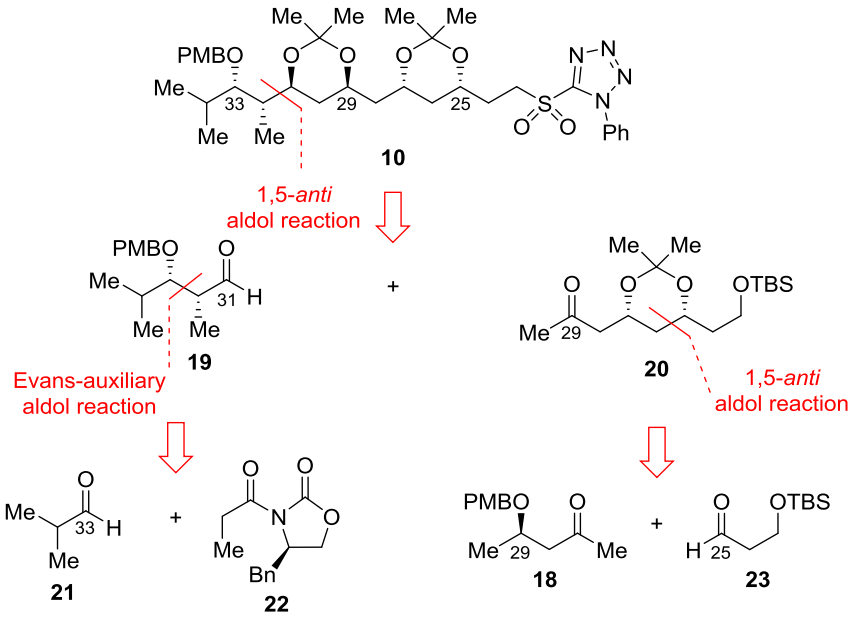
The aldehyde **11**, which corresponds to C10−C22 fragment of marinisporolide A, would be prepared by a Mukaiyama aldol reaction between aldehyde **14** and enolsilane of methylketone **15** (Scheme 3). The aldehyde **14** could be obtained from (*R*)-malic acid (**16**). Compound **15** would be generated by an aldol reaction between aldehyde **17** and the boron enolate of methylketone **18**.



Scheme 3: Retrosynthetic analysis of aldehyde **11**.

The sulfone **10**, which corresponds to the C23−C35 fragment of marinisporolide A, was thought to be synthesized by an aldol reaction between aldehyde **19** and the boron enolate of

methylketone **20** (Scheme 4). The aldehyde **19** could be prepared by an aldol reaction between isobutyraldehyde (**21**) and the boron enolate of oxazolidinone **22**. Finally, the methylketone **20** would be originated from an aldol reaction between boron enolate of methylketone **18** and aldehyde **23**.



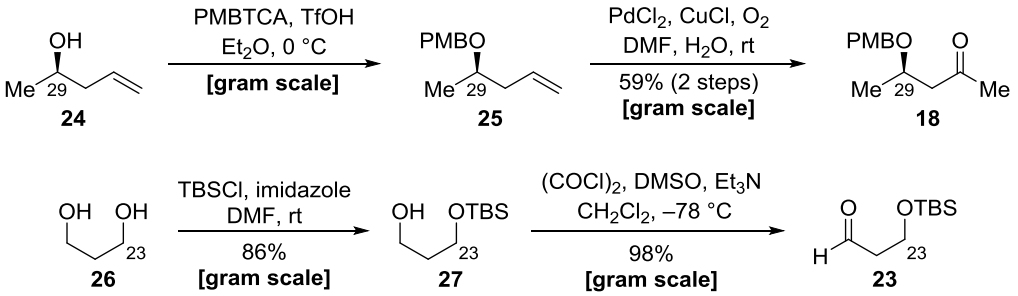
Scheme 4: Retrosynthetic analysis of sulfone **10**.

RESULTS AND DISCUSSION

Synthesis of C23−C30 Fragment of Marinisporolides

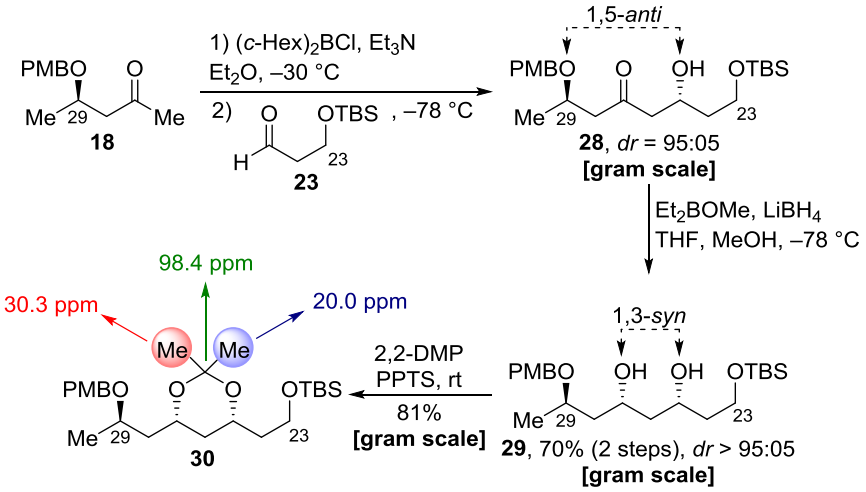
The synthesis of the C23−C30 fragment of marinisporolides began with the preparation of the methylketone **18** and the aldehyde **23** (Scheme 5). The acid-catalyzed protection of the commercially available homoallylic alcohol **24** using *p*-methoxybenzyl-2,2,2-trichloroacetimidate (PMBTCA)[13] was followed by a Wacker oxidation to provide the methylketone **18** in 59% yield over 2 steps.[14]

Monoprotection of commercially available 1,3-propanediol (**26**) (TBSCl, imidazole, DMF, 86%)[15] afforded silicon ether **27** which underwent a Swern oxidation to furnish the desired aldehyde **23** in 98% yield.[16]



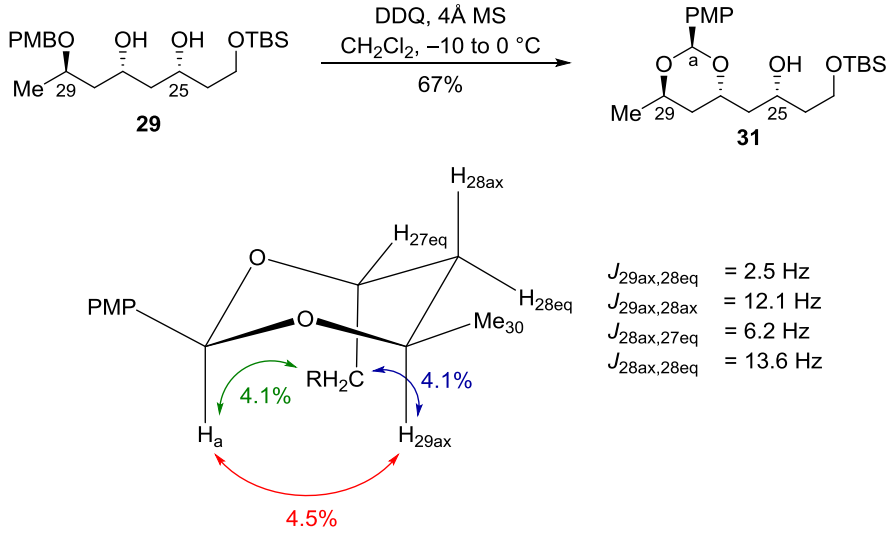
Scheme 5: Preparation of methylketone **18** and aldehyde **23**.

The aldol reaction between boron enolate of methylketone **18** and aldehyde **23** gave the 1,5-*anti* aldol adduct **28** (*dr* = 95:05) (Scheme 6).[17] The Narasaka stereoselective reduction of compound **28** provided the 1,3-*syn* diol **29** (70% yield, *dr* > 95:05).[18] Protection of the diol **29** using 2,2-dimethoxypropane (2,2-DMP) and PPTS delivered the acetonide **30** in 81% yield. The spectral fingerprints of the acetonide **30** confirmed the 1,3-*syn* configuration between C25 and C27.[19]



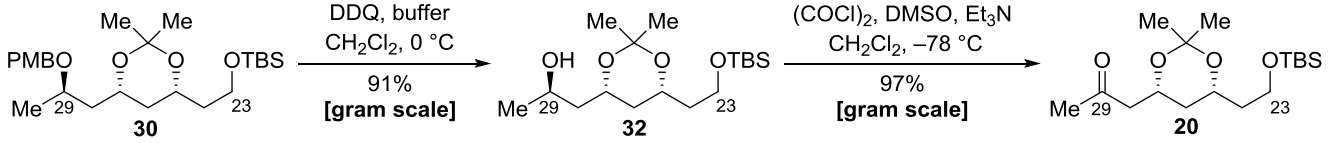
Scheme 6: Preparation of acetonide **30**.

After conversion of the diol **29** into benzilidene acetal **31** (DDQ, 4Å MS, CH_2Cl_2, 67%), the 1,3-*anti* relationship between hydroxyls at C27 and C29 was determined on the basis of ^{1}H NMR spectrum and 1D selective NOE analyses (Scheme 7).[20]



Scheme 7: Stereochemistry proof of compound **29**.

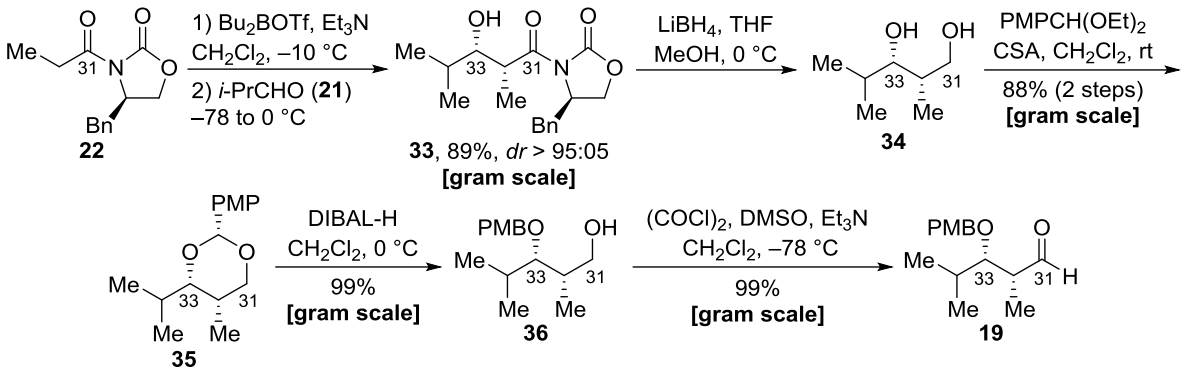
Removal of PMB ether of compound **30** (DDQ, pH = 7 buffer solution, CH_2Cl_2, 91%)[21] provided alcohol **32** which underwent a Swern oxidation to give the methylketone **20**, which corresponds to the C23−C30 fragment of marinisporolides, in 97% yield (Scheme 8).[16]



Scheme 8: Preparation of methylketone **20**.

Synthesis of C31−C35 Fragment of Marinisporolides

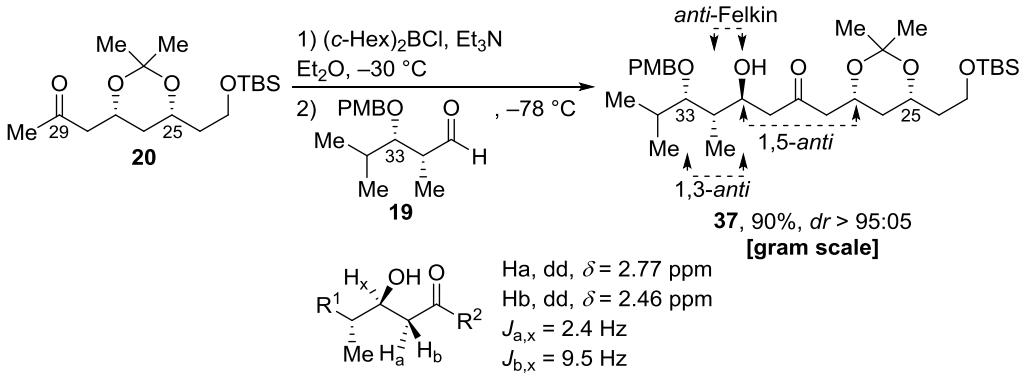
The aldol reaction between *Z* boron enolate of oxazolidinone **22** and isobutyraldehyde (**21**) lead to the formation of the known Evans-1,2-*syn* aldol adduct **33** (89% yield, *dr* > 95:05) (Scheme 9).[22] Reductive removal of chiral auxiliary ($LiBH_4$, MeOH, THF) delivered the diol **34** which, after an acid-catalyzed reaction with *p*-anisaldehyde diethylacetal, gave the compound **35** in 88% yield over 2 steps. The regioselective cleavage of the PMP acetal **35** (DIBAL-H, CH_2Cl_2, 99%) yielded the primary alcohol **36**. Oxidation of compound **36** using the Swern conditions provided aldehyde **19**, which corresponds to the C31−C35 fragment of marinisporolides, in 99% yield.[16]



Scheme 9: Preparation of aldehyde **19**.

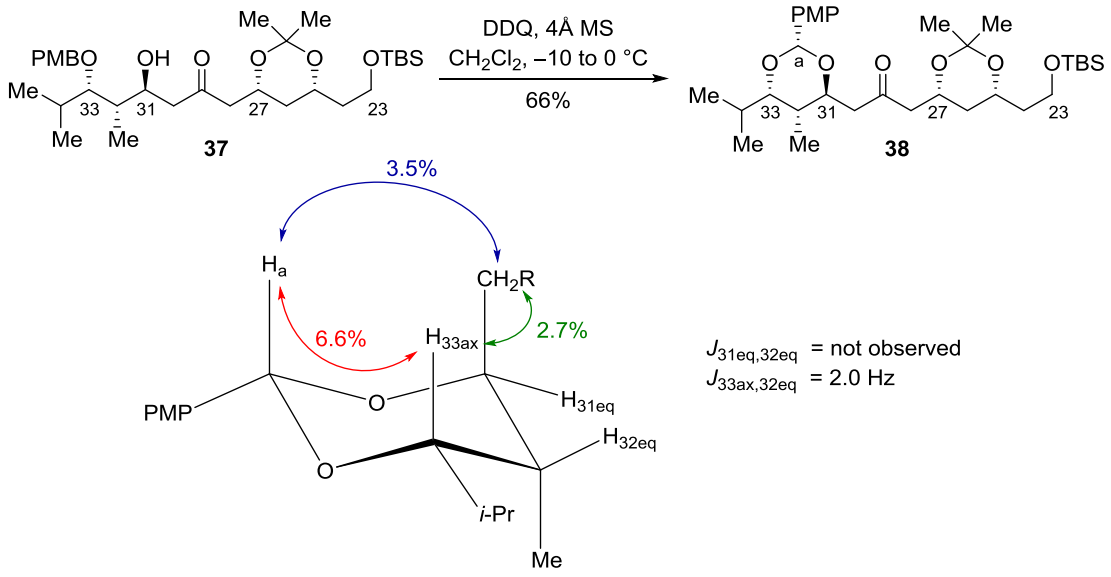
Synthesis of C23−C35 Fragment of Marinisporolides

The aldol reaction between boron enolate of methylketone **20** and aldehyde **19** gave the 1,5-*anti*/*anti*-Felkin/1,3-*anti* aldol adduct **37** (90% yield, *dr* > 95:05) (Scheme 10).[17,23] The *anti*-Felkin relative configuration between C31 and C32 was determined on the basis of Roush's method.[24]



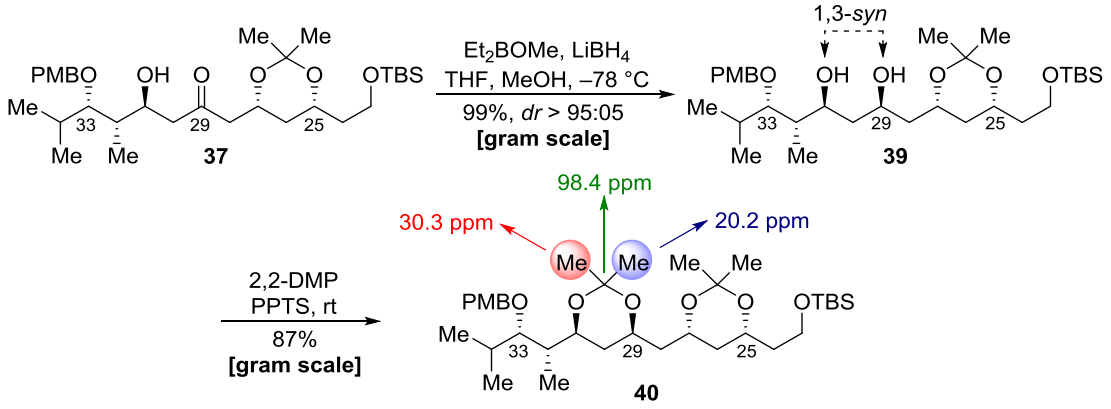
Scheme 10: Preparation of aldol adduct **37**.

After conversion of the aldol adduct **37** into the PMP acetal **38** (DDQ, 4Å MS, CH_2Cl_2, 66%), the 1,3-*anti* relationship between hydroxyls at C31 and C33 was determined on the basis of ^{1}H NMR spectrum and 1D selective NOE analyses (Scheme 11).[20]



Scheme 11: Stereochemistry proof of compound **37**.

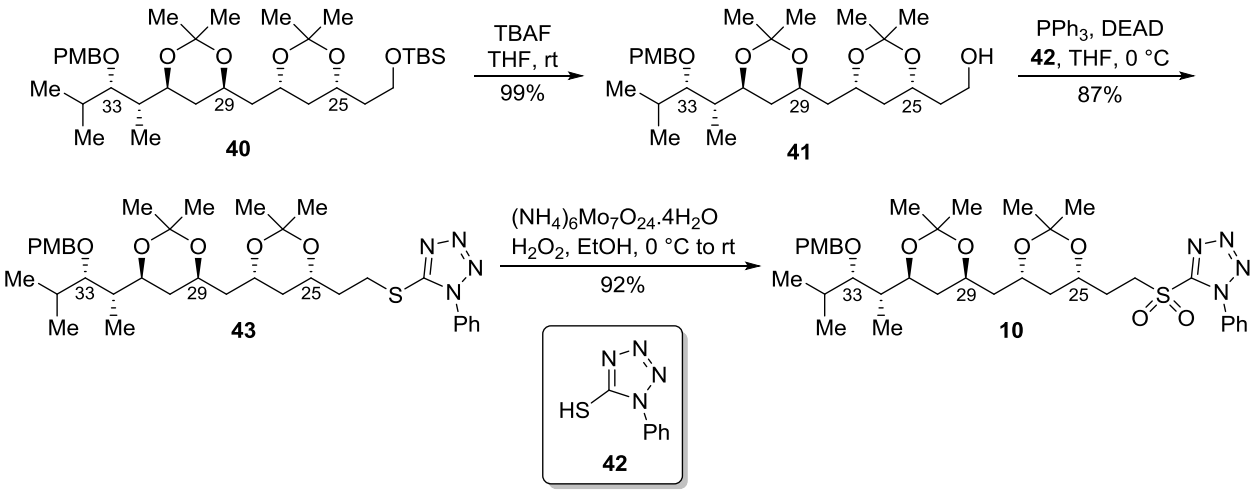
Reduction of aldol adduct **37** under Narasaka conditions provided 1,3-*syn* diol **39** (99%, *dr* > 95:05) (Scheme 12).[18] Protection of compound **39** using 2,2-DMP and PPTS delivered the acetonide **40** in 87% yield. The ^{13}C NMR spectrum of the compound **40** shows chemical shifts in agreement with a *cis* configuration between C29 and C31, according to the Rychnovsky's method.[19]



Scheme 12: Preparation of acetonide **40**.

Incorporation of the phenyltetrazole sulfone moiety at C23 terminus of the compound **40** was executed by a three-step procedure (Scheme 13). Removal of TBS ether of compound **40** (TBAF, THF, 99%)[25] provided the primary alcohol **41** which was subjected to a Mitsunobu

reaction to deliver sulfide **43** in 87% yield.[26] Finally, oxidation of compound **43** (H_2O_2, $(NH_4)_6Mo_7O_{24}.4H_2O$, EtOH, 92%) gave the sulfone **10**, which corresponds to the C23−C35 fragment of marinisporolides.[26]

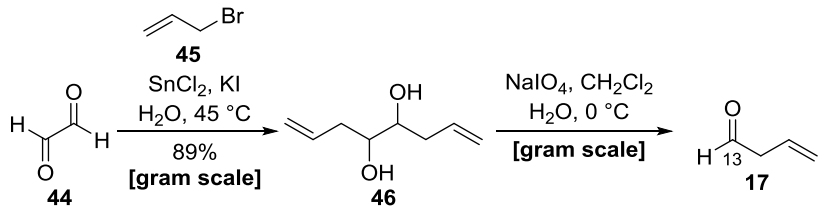


Scheme 13: Preparation of sulfone **10**.

The synthesis of the C23−C35 fragment of marinisporolides required a longest linear sequence of 13 steps (from alcohol **24**) and proceeded with an overall yield of 18%, which corresponds to an average yield of 88% per step. Due to the convergence, generally excellent yields and high stereocontrol of our synthetic strategy, we were able to prepare 1.5 grams of sulfone **10**.

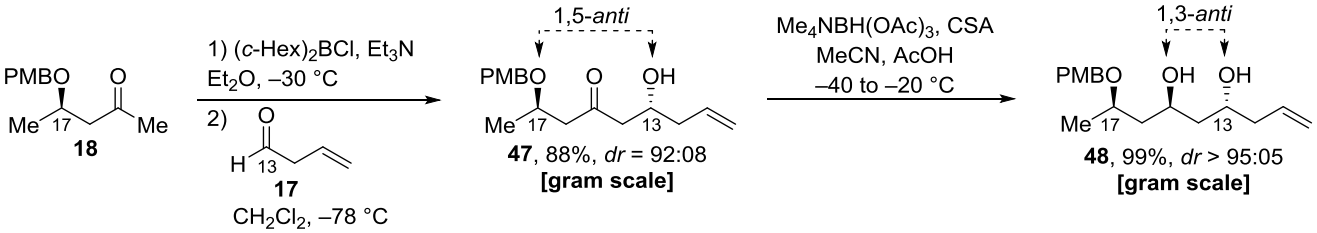
Synthesis of C10−C18 Fragment of Marinisporolides

The synthesis of the C10−C18 fragment of marinisporolides began with the preparation of aldehyde **17** (Scheme 14). The tin-mediated Barbier reaction between glyoxal (**44**) and allyl bromide (**45**) gave the diol **46** in 89% yield which underwent a $NaIO_4$-mediated oxidative cleavage to yield the β,γ-unsaturated aldehyde **17**.[27] Compound **17** is too labile and must be used immediately in the aldol reaction with methylketone **18**.



Scheme 14: Preparation of β,γ-unsaturated aldehyde **17**.

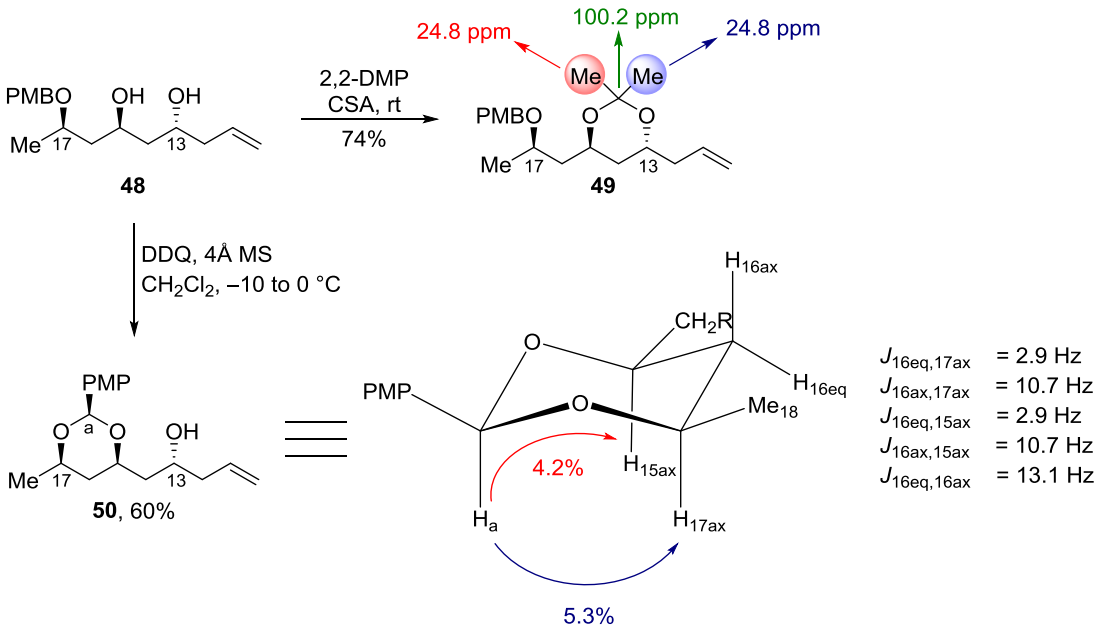
The aldol reaction between boron enolate of methylketone **18** and aldehyde **17** gave the 1,5-*anti* aldol adduct **47** (88% yield, *dr* = 92:08) (Scheme 15).[17] Reduction of compound **47** under Saksena−Evans conditions provided 1,3-*anti* diol **48** in 99% yield (*dr* > 95:05).[28]



Scheme 15: Preparation of diol **48**.

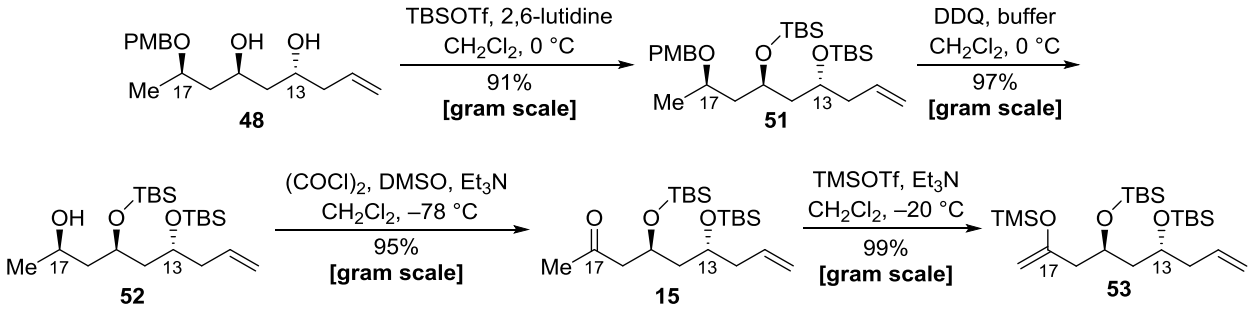
At this point, we decided to determine the relative configuration between C13, C15, and C17 in compound **48** (Scheme 16). Protection of diol **48** delivered the acetonide **49** (2,2-DMP, CSA 74%). The ^{13}C NMR spectrum of compound **49** shows chemical shifts in agreement with a *trans* configuration between C13 and C15, according to the method of Rychnovsky.[19]

After conversion of diol **48** into the PMP acetal **50** (DDQ, 4Å MS, CH_2Cl_2, 60%), the 1,3-*syn* relationship between hydroxyls at C15 and C17 was determined on the basis of ^1H NMR spectrum and 1D selective NOE analyses.[20]



Scheme 16: Stereochemistry proof of compound **48**.

Protection of diol **48** (TBSOTf, 2,6-lutidine, CH_2Cl_2, 91%) delivered compound **51** (Scheme 17).[29] Removal of PMB ether of compound **51** (DDQ, pH = 7 buffer solution, CH_2Cl_2, 97%) gave alcohol **52** which underwent a Swern oxidation to provide the methylketone **15** in 95% yield.[16] Finally, treatment of compound **15** with TMSOTf and Et_3N delivered enolsilane **53**, which corresponds to the C23−C30 fragment of marinisporolides, in 99% yield.[30]



Scheme 17: Preparation of enolsilane **53**.

Synthesis of C19−C22 Fragment of Marinisporolides

With the enolsilane **53** in hands, the next step would be the synthesis of the prospective aldehyde partners for the Mukaiyama aldol reaction. The Evans research group has showed good levels of 1,3-*anti* asymmetric induction in Mukaiyama aldol reactions using benzylic (i.e. PMB or Bn) protecting groups at the β-position of the aldehyde.[31] However, the incorporation of a PMB protecting group at C21, would be problematic considering the forthcoming removal of PMB ether at C33. Similarly, the using of a benzyl as protecting group would also be problematic for the deprotection step. Considering that, we decided to prepare the aldehydes **14a** and **14b** (Figure 4).

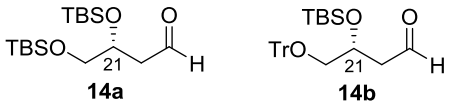
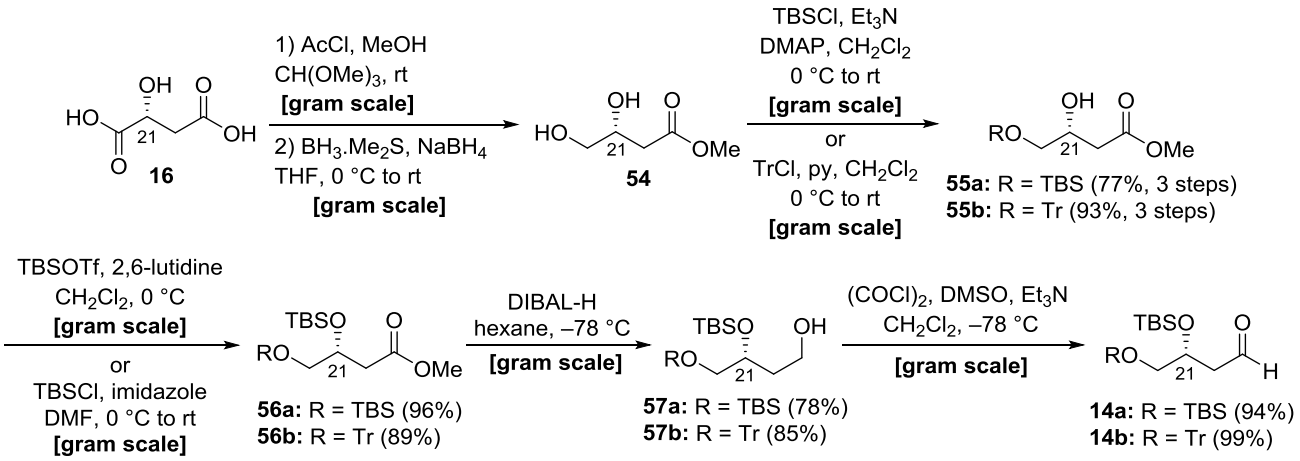


Figure 4: Aldehydes **14a** and **14b**.

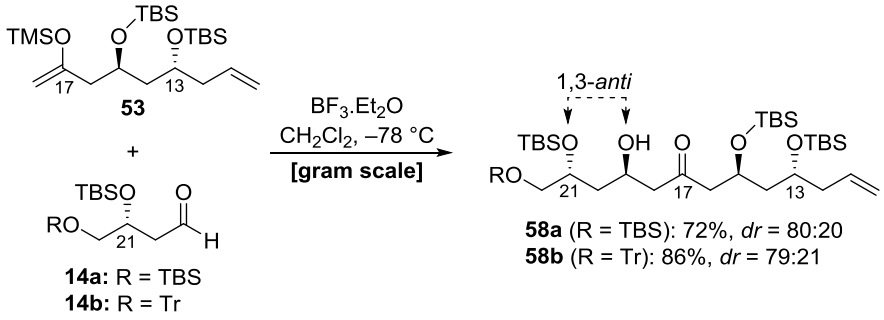
The esterification[32] of the (*R*)-malic acid (**16**) (AcCl, MeOH, $CH(OMe)_3$) followed by a chemoselective reduction ($BH_3.Me_2S$, $NaBH_4$, THF) gave the diol **54** (Scheme 18).[33] Protection of primary alcohol (TBSCl, Et_3N, DMAP, CH_2Cl_2, 77%[34] or TrCl, pyridine, CH_2Cl_2, 93%[35]) yielded compounds **55a** and **55b**. Conversion of the remaining hydroxyl into a TBS ether afforded compounds **56a** and **56b** in good yields.[36] Reduction of esters **56a** and **56b** (DIBAL-H, hexanes)[37] delivered alcohols **57a** and **57b** which underwent a Swern oxidation to give the aldehydes **14a** and **14b**.[16]



Scheme 18: Preparation of aldehydes **14a** and **14b**.

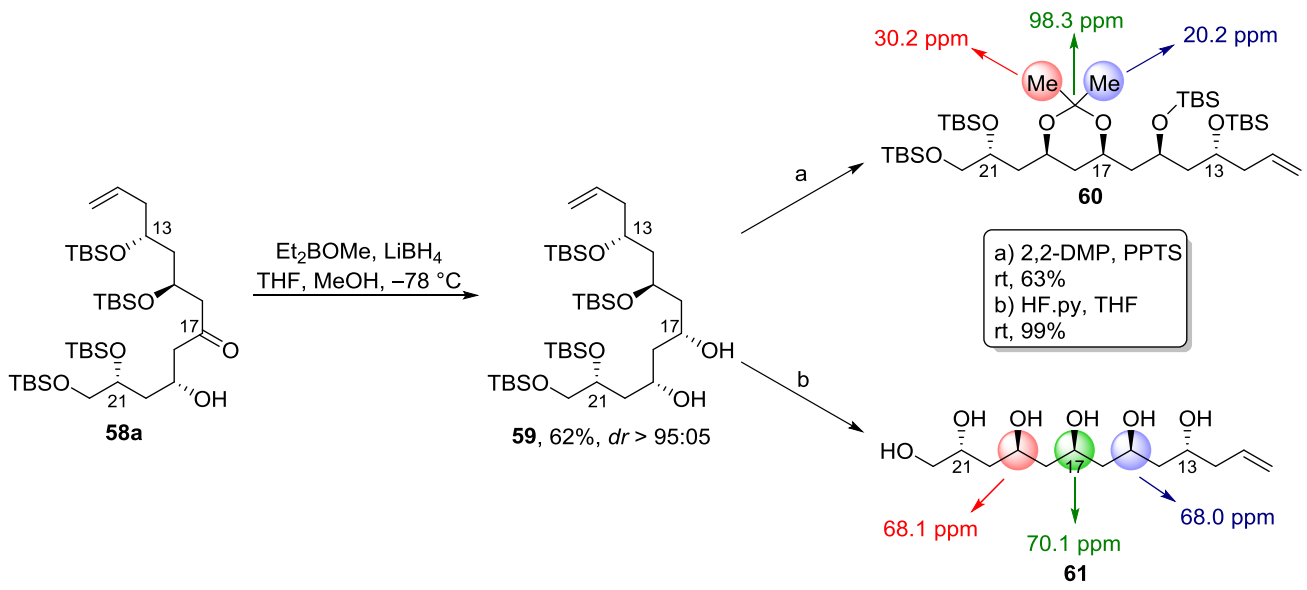
Synthesis of C10−C22 Fragment of Marinisporolides

The $BF_3.Et_2O$-catalyzed Mukaiyama aldol reaction between enolsilane **53** and aldehydes **14a** and **14b** gave 1,3-*anti* aldol adducts **58a** and **58b** in good yields and diastereoselectivities (Scheme 19).[38]



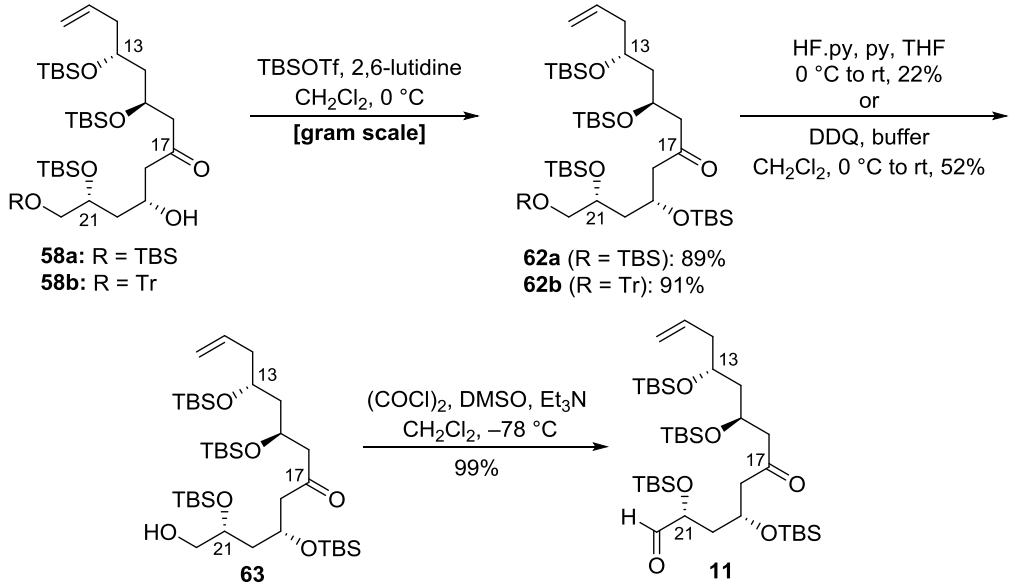
Scheme 19: Mukaiyama aldol reaction between enolsilane **53** and aldehydes **14a** and **14b**.

After conversion of aldol adduct **58a** into hexaol **61** (i. Et_2BOMe, $LiBH_4$, THF, MeOH, 62%, *dr* > 95:05; ii. HF.py, THF, 99%), the 1,3-*anti* relationship between hydroxyls at C19 and C21 was determined on the basis of Kishi's method (Scheme 20).[39] Furthermore, the spectral fingerprints of the acetonide **60** confirmed the 1,3-*syn* configuration between C17 and C19.[19]



Scheme 20: Stereochemistry proof of compound **58a**.

Protection of aldol adducts **58a** and **58b** (TBSOTf, 2,6-lutidine, CH_2Cl_2) provided compounds **62a** and **62b** in excellent yields (Scheme 21).[29] Removal of primary silyl ether of compound **62a** (HF.py, pyridine, THF) delivered alcohol **63** in only 22% yield.[40] On the other hand, removal of trityl ether of compound **62b** gave alcohol **63** (DDQ, pH = 7 buffer solution, CH_2Cl_2) in 52%,[41] which underwent to a Swern oxidation to provide aldehyde **11** in 99% yield.[16]

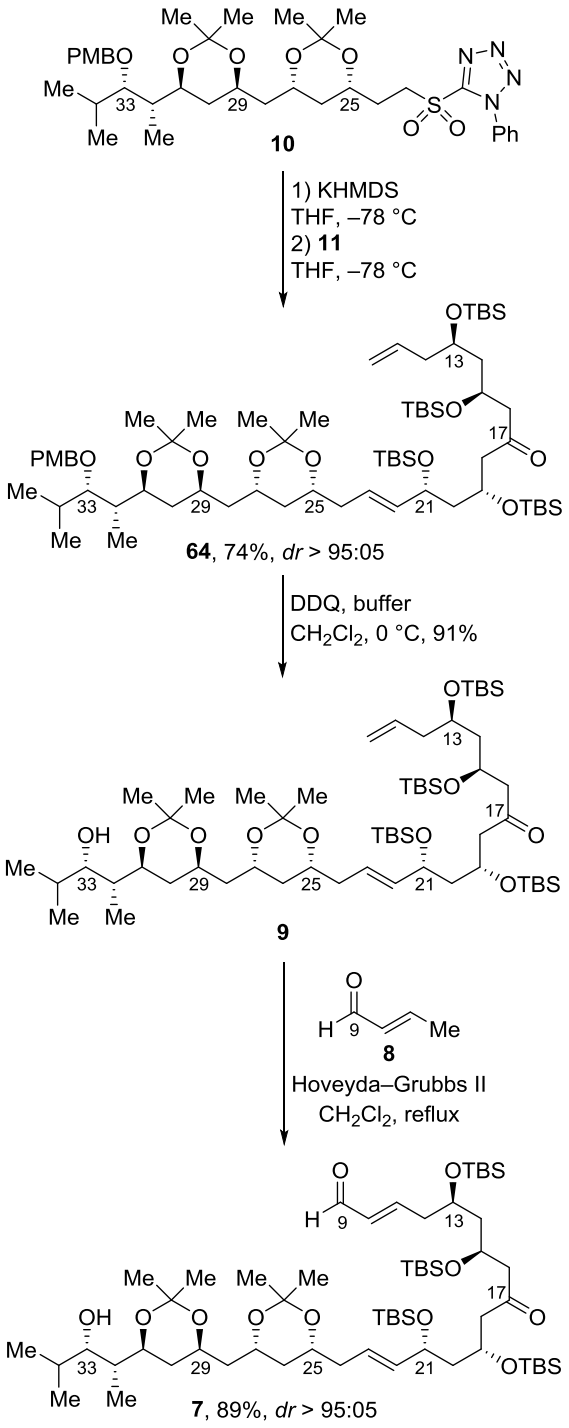


Scheme 21: Preparation of aldehyde **11**.

The synthesis of the C10−C22 fragment of marinisporolides required a longest linear sequence of 12 steps (from alcohol **24**) and proceeded with an overall yield of 17%, which corresponds to an average yield of 86% per step. Due to the convergence, generally excellent yields and high stereocontrol of our synthetic strategy, we were able to prepare more than 1 gram of aldehyde **11**.

Synthesis of C9−C35 Fragment of Marinisporolides

The Julia−Kocieński reaction between sulfone **10** and aldehyde **11** gave the *E* olefin **64** (74% yield, *dr* > 95:05) (Scheme 22).[42] Removal of PMB ether of compound **64** delivered compound **9** (DDQ, pH = 7 buffer solution, CH_2Cl_2, 91%),[21] which underwent to an olefin cross-metathesis with crotonaldehyde (**8**) to provide the C9−C35 fragment **7** (Hoveyda−Grubbs II, CH_2Cl_2, 89%, *dr* > 95:05).[43]

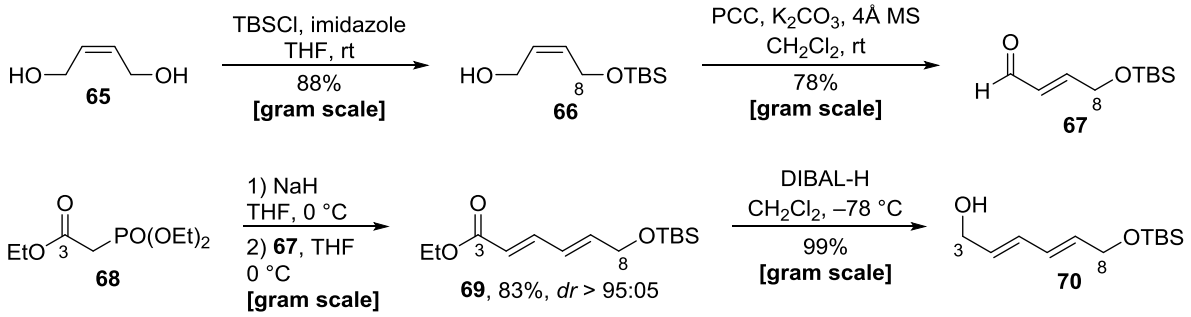


Scheme 22: Preparation of aldehyde **7**.

Synthesis of C1−C8 Fragment of Marinisporolides

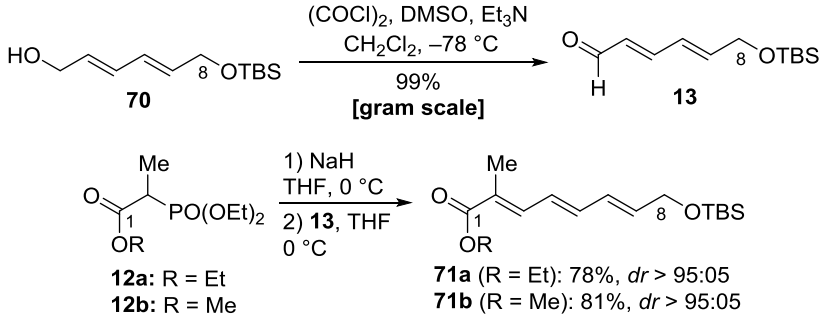
With the aldehyde **7** in hands, the synthesis of the prospective phosphonate partners **6a** and **6b** was addressed (Schemes 23−25).

Monoprotection of diol **65** (TBSCl, imidazole, THF, 88%) furnished the compound **66** (Scheme 23).[44] Oxidation of alcohol **66** (PCC, K_2CO_3, 4Å MS, CH_2Cl_2, 78%) gave the aldehyde **67**, which underwent to a Horner−Wadsworth−Emmons olefination to deliver the *E*,*E*-ester **69** in 83% yield (*dr* > 95:05). Finally, reduction of compound **69** with DIBAL-H provided the alcohol **70** in 99% yield.



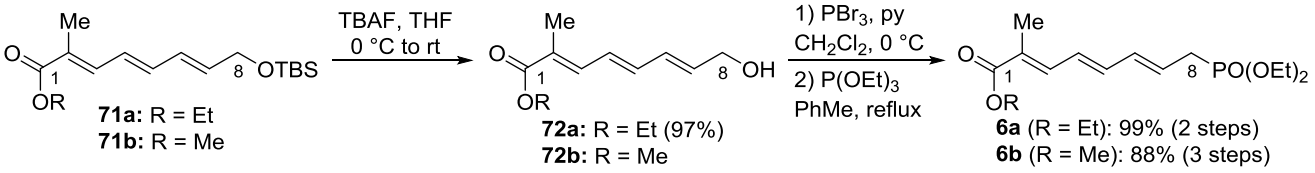
Scheme 23: Preparation of alcohol **70**.

A Swern oxidation of alcohol **70** provided compound **13** in 99% yield (Scheme 24).[16] A Horner−Wadsworth−Emmons olefination between aldehyde **13** and phosphonates **12a** or **12b** furnished *E*,*E*,*E*-trieneesters **71a** and **71b** in good yields and excellent levels of diastereoselectivity.



Scheme 24: Preparation of esters **71a** and **71b**.

The synthesis of C1−C8 fragment proceeded uneventfully and phosphonates **6a** and **6b** were obtained in good yields from removal of silicon ether of compounds **71a** and **71b**,[25] followed by treatment with PBr_3 and pyridine, and finally a Michaelis−Arbuzov reaction (Scheme 25).

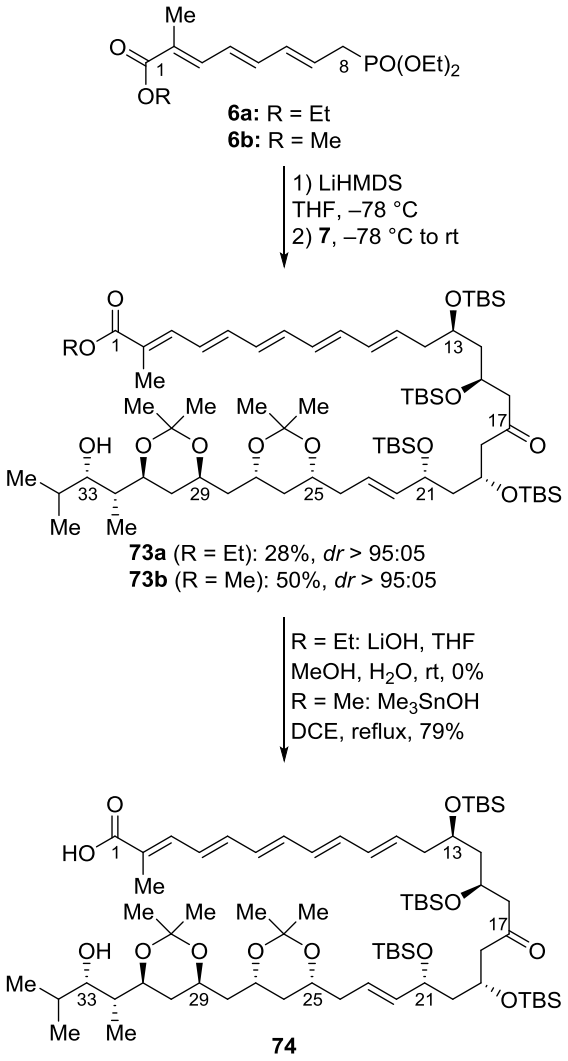


Scheme 25: Preparation of phosphonates **6a** and **6b**.

Synthesis of C1−C35 Fragment of Marinisporolide A and Attempts to Macrolactonization

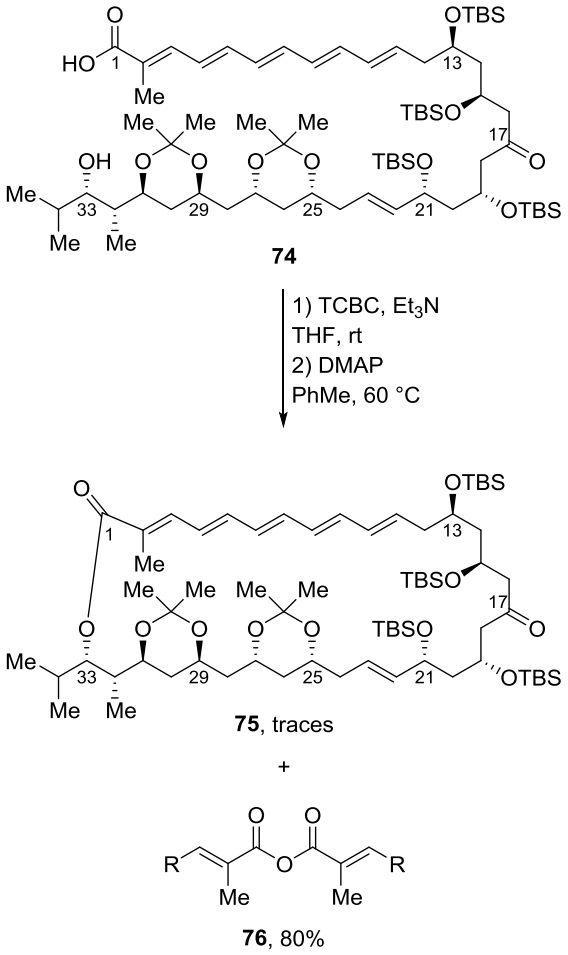
At this point, we turned our attention to the installation of polyene fragment (Scheme 26). The Horner−Wadsworth−Emmons olefination between aldehyde **7** and phosphonate **6a** (R = Et) furnished pentaene **73a** in 28% yield and excellent levels of diastereoselectivity (*dr* > 95:05). At this point, we suspected our system was unstable under basic conditions. For this reason, we lowered the reaction time of the olefination with phosphonate **6b** (R = Me) and pentaene **73b** was obtained in 50% yield (*dr* > 95:05).

As expected, hydrolysis of ethyl ester **73a** under basic conditions completely destroyed the starting material, while removal of methyl ester of compound **73b** using Me_3SnOH gave seco acid **74** in 79% yield.[45]



Scheme 26: Synthesis of seco acid **74**.

The macrolactonization[46] of seco acid **74** posed a problem as the standard Yamaguchi procedure[47] provided only trace yields of macrolactone **75** accompanied by the symmetric anhydride **76** as the predominant product (Scheme 27). In addition, investigation of various lactonization conditions reported by Yonemitsu,[48] Shiina,[49] and Keck[50] did not result in any improvement in the yield of **75**.



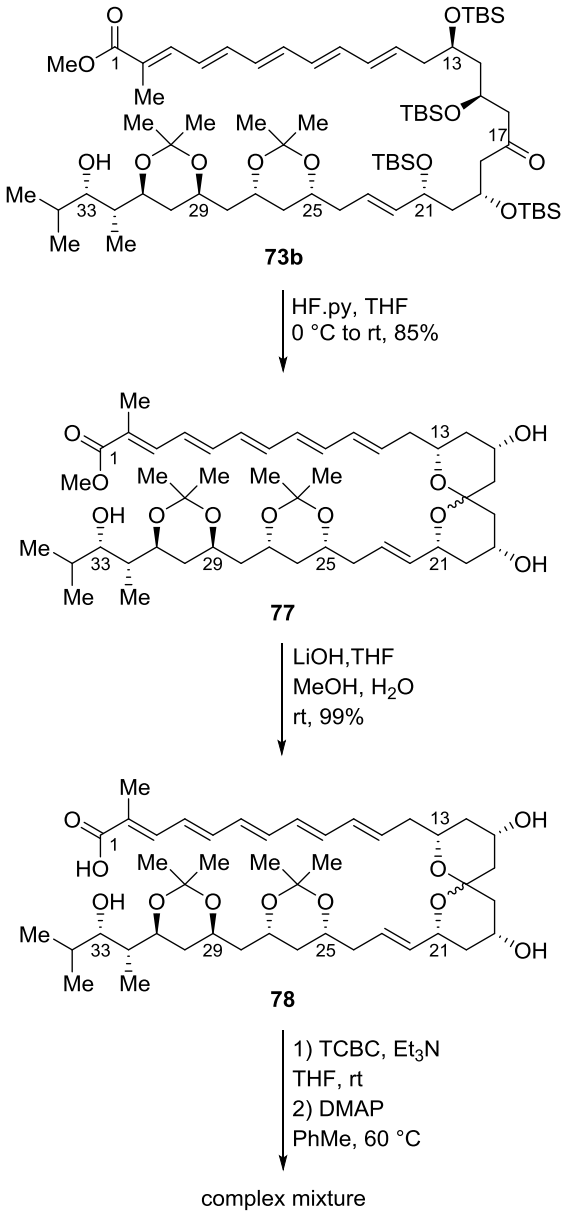
Scheme 27: Attempts of macrolactonization of seco acid **74**.

As shown by the research groups of Yonemitsu,[51] Roush,[52] and Evans,[53] the presence of a α substituent in a α,β-unsaturated seco acid creates a bulky environment, which decreases the efficiency of the macrolactonization step. With the aim to increase this efficiency, we decided to incorporate a preorganization element[54] through the prior formation of the spiroketal before the macrolactonization step (Scheme 28). So the deprotection of silyl ethers of the compound **73b** with HF.py provided the spiroketal **77** in 85% yield as a mixture of C17 epimers.[55]

The ^{1}H NMR of our synthetic spiroketal **77** was identical to the compound prepared by the Fenical's research group.[9a] Thus the unambiguous nature of our synthesis with regard to setting stereocenters confirms Fenical's assignment of stereochemistry of marinisporolide A (**1**).

At this point we were not concerned about the epimer mixture, because in the final stage of the synthesis we were expecting to reequilibrate this mixture under acidic conditions to remove the acetonide groups.

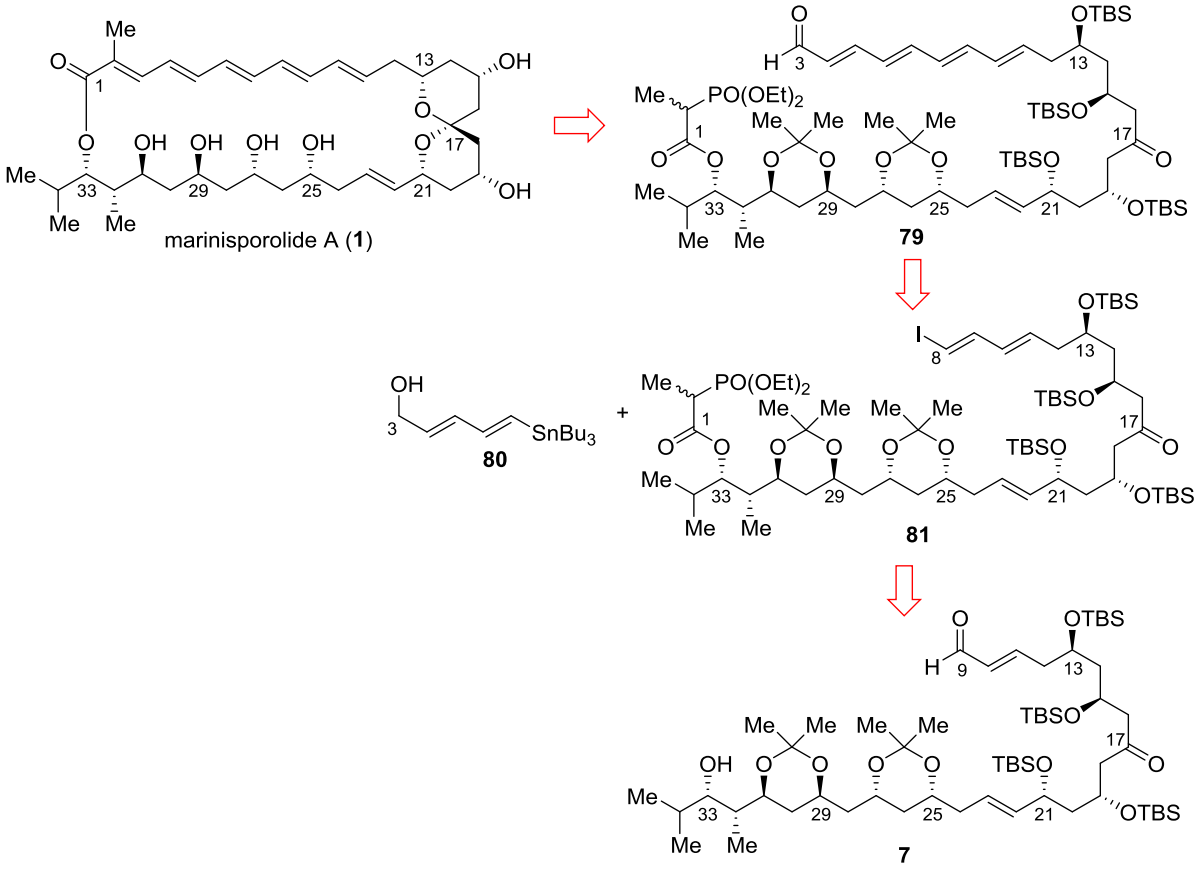
Hydrolysis of the methyl ester **77** (LiOH, THF, MeOH, H_2O, 99%) gave seco acid **78**. Unfortunately, the use of the Yamaguchi's protocol with compound **78** provided a complex mixture.



Scheme 28: Attempts of macrolactonization of seco acid **78**.

New Retrosynthetic Analysis of Marinisporolide A

At this point, we decided to redesign our synthetic strategy using the C9−C35 aldehyde **7** (Scheme 29). Marinisporolide A could be obtained from the phosphonate-aldehyde **79** through an intramolecular Horner−Wadsworth−Emmons reaction. A Stille cross-coupling between stannane **80** and vinyl iodide **81** would be envisioned to build up the compound **79**. The compound **81** could be prepared from a Takai−Utimoto olefination using aldehyde **7**.

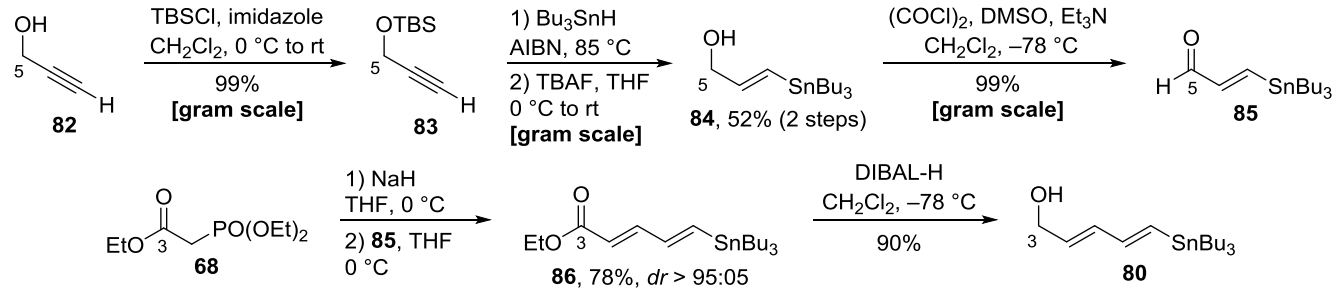


Scheme 29: New retrosynthetic analysis of marinisporolide A (**1**).

Synthesis of C3−C7 Fragment of Marinisporolides

Protection of propargyl alcohol (**82**) (TBSCl, imidazole, CH_2Cl_2, 99%) gave compound **83**,[56] which underwent to a hydrostannation reaction (Bu_3SnH, AIBN), followed by a deprotection

(TBAF, THF) to provide compound **84** in 52% yield (2 steps) (Scheme 30).[57] The Swern oxidation of alcohol **84** furnished the aldehyde **85** in 99% yield.[16]



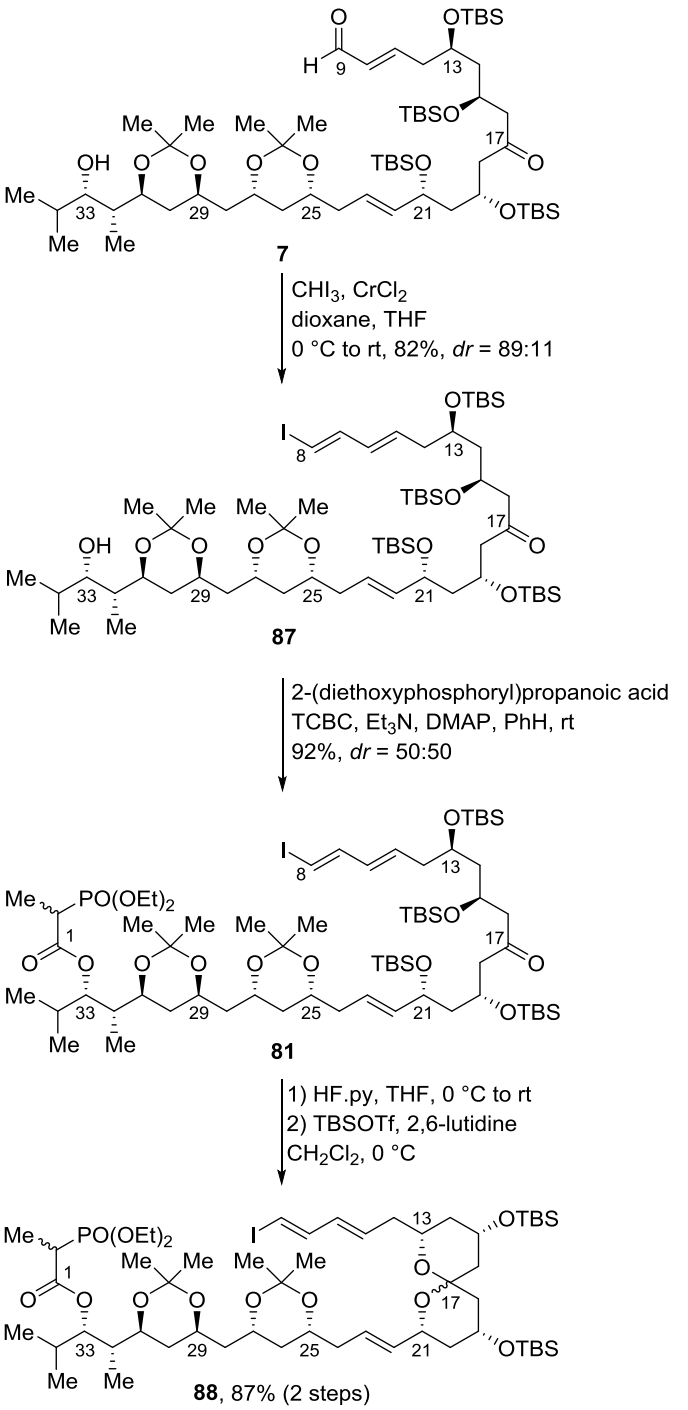
Scheme 30: Preparation of stannane **80**.

A Horner−Wadsworth−Emmons olefination between phosphonate **68** and aldehyde **85** delivered the *E*,*E*-ester **86** in 78% yield (*dr* > 95:05). Finally, reduction of compound **86** with DIBAL-H provided the alcohol **80** in 90% yield.

Synthesis of C8−C35 Fragment of Marinisporolide A

The Takai−Utimoto olefination between aldehyde **7** and iodoform gave the *E* vinylic iodide **87** (82% yield, *dr* = 89:11),[58] which underwent to a Yamaguchi esterification to afford compound **81** (92%, *dr* = 50:50) (Scheme 31).[47]

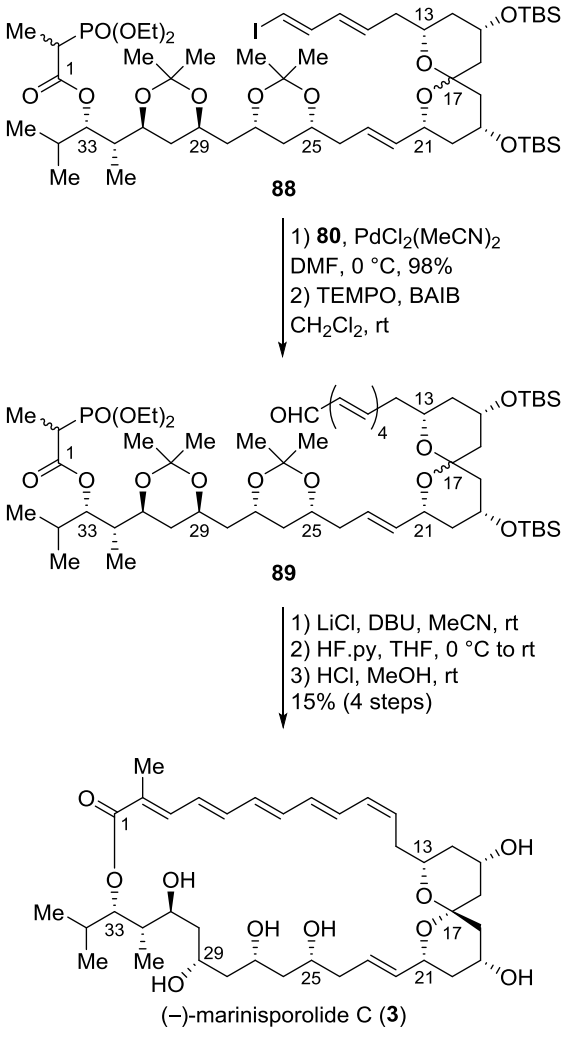
As an earlier version of this strategy with the free ketone did not furnish the desired macrolactone during the macrocyclization step, we decided to prepare the spiroketal at this point. Removal of TBS ethers (HF.py, THF), followed by protection of remaining hydroxyls (TBSOTf, 2,6-lutidine, CH_2Cl_2) delivered the spiroketal **88** in 87% yield (2 steps) as a mixture of epimers.



Scheme 31: Preparation of compound **88**.

Total Synthesis of (−)-Marinisporolide C

The Stille cross-coupling between vinyl iodide **88** and stannane **80** ($PdCl_2(MeCN)_2$, DMF, 98%),[59] followed by an oxidation (TEMPO, BAIB, CH_2Cl_2) provided aldehyde **89** (Scheme 32).[60] Compound **89** was submitted to a Horner−Wadsworth−Emmons macrocyclization under Masamune−Roush conditions to give the desired macrolactone.[61] To our complete surprise,[62] after full deprotection, first with HF.py and then with HCl, (−)-marinisporolide C (**3**), which was identical in all aspects (^1H and ^{13}C NMR, HRMS, UV/Vis, and circular dichroism) to the natural sample, was obtained in 15% yield (over 4 steps).



Scheme 32: Endgame: total synthesis of marinisporolide C (**3**).

CONCLUSIONS

We concluded the first total synthesis of (−)-marinisporolide C in 25 steps (longest linear sequence) and an overall yield of 1.15%, which corresponds to an average yield of 83% yield per step, starting from alcohol **24**. Since the configuration of all the stereogenic centers created in this synthetic endeavor were unambiguously determined, this work ultimately established the relative and absolute configuration of marinisporolide C.

Key features of this synthesis include of a series of highly stereoselective aldol reactions followed by directed reductions to build the polyol domain, a Stille cross-coupling reaction to assemble the polyene, and an intramolecular Horner−Wadsworth−Emmons olefination to forge the macrocyclic ring.

Despite the initial approach to marinisporolide A using a Yamaguchi macrolactonization that was unsuccessful due to steric hindrance of the oxygen at the C33 position, we were able to prepare a known derivative of marinisporolide A and consequently confirm its stereochemical assignment.

EXPERIMENTAL SECTION

General Information

All reactions were carried out under an atmosphere of argon with dry solvents under anhydrous conditions unless otherwise stated. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous material, unless otherwise stated.

Tetrahydrofuran (THF), diethyl ether (Et_2O), and dioxane were distilled from sodium/benzophenone prior to use. Triethylamine (Et_3N), pyridine (py), 2,6-lutidine, dichloromethane (CH_2Cl_2), benzene (PhH), toluene (PhMe), hexane, and 1,2-dichloroethane (DCE) were distilled from CaH_2 prior to use. Oxalyl chloride ($(COCl)_2$), acetonitrile (MeCN), isobutyraldehyde (*i*-PrCHO), and crotonaldehyde were distilled prior to use. Acetic acid (AcOH) was fractionally distilled from acetic anhydride and chromium (VI) oxide prior to use. Methanol (MeOH) was distilled from $Mg(OMe)_2$ and stored over molecular sieves. *N*,*N*-dimethylformamide (DMF) and dimethyl sulfoxide (DMSO) were distilled under reduced pressure from CaH_2 and

stored over molecular sieves. Camphorsulfonic acid (CSA) was recrystallized from ethyl acetate. The other reagents were used without further purification, unless otherwise stated.

The purification of reaction products was performed by flash column chromatography using silica gel (230−400 mesh). Reactions were monitored by thin layer chromatography carried out on silica-gel 60 and GF (5−40 μm thickness) plates, and visualization was accomplished using UV light and phosphomolybdic acid staining followed by heating.

Optical rotations were measured on a polarimeter with a sodium lamp using a 1.0 cm cell and are reported as follows: $[\alpha]_D^{T\,(°C)}$ (*c* (g/100 mL), solvent). Melting points are uncorrected.

^{1}H and proton-decoupled ^{13}C NMR spectra were at 250 MHz (^{1}H) and 62.5 MHz (^{13}C), at 400 MHz (^{1}H) and 100 MHz (^{13}C), at 500 MHz (^{1}H) and 125 MHz (^{13}C), or at 600 MHz (^{1}H) and 150 MHz (^{13}C). Chemical shifts (δ) are reported in ppm using residual undeuterated solvent as an internal standard ($CHCl_3$ at 7.25 ppm, C_6H_6 at 7.16 ppm, MeOH at 3.30 ppm, DMSO at 2.49 ppm, and TMS at 0.00 ppm for ^{1}H NMR spectra and $CDCl_3$ at 77.0 ppm, C_6D_6 at 128.0 ppm, CD_3OD at 49.0 ppm and DMSO-d_6 at 39.5 ppm for ^{13}C NMR spectra). Multiplicity data are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sext = sextet, br s = broad singlet, dd = doublet of doublets, dt = doublet of triplets, ddd = doublet of doublet of doublets, ddt = doublet of doublet of triplets, dtd = doublet of triplet of doublets, dqd = doublet of quartet of doublets, and m = multiplet. The multiplicity is followed by the coupling constant(s) in Hz and integration.

Infrared spectra were recorded and the wavelengths of maximum absorbance (max) are quoted in wavenumbers (cm^{-1}).

High-resolution mass spectrometry (HRMS) were measured using electrospray ionization (ESI) or using electron ionization (EI).

(−)-(*R*)-4-((4-methoxybenzyl)oxy)pentan-2-one (18): NOTE: Compound 25 is volatile and its permanence for more than 5 minutes on a high vacuum pump (approximately 0.5 mmHg) drastically reduces the reaction yield. To a solution of homoallylic alcohol **24** (2.0 g, 23.2 mmol, 100 mol%) and *p*-methoxybenzyl-2,2,2-trichloroacetimidate (9.83 g, 34.8 mmol, 150 mol%) in Et_2O (110 mL, 0.20 M) at 0 °C was carefully added a solution of TfOH (1.05 mL, 0.12 mmol, 0.11 M in Et_2O, 0.5 mol%). The reaction mixture was stirred under the same conditions for 30 min before being quenched by the addition of saturated aqueous solution of $NaHCO_3$ (25

mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 25 mL). The combined organic layers were washed with H_2O (50 mL), brine (50 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Compound **25** was partially purified by flash column chromatography using a solution of hexane/ethyl acetate (80:20) as the eluent.

A mixture of $PdCl_2$ (411 mg, 2.32 mmol, 10 mol%) and CuCl (2.30 g, 23.2 mmol, 100 mol%) in DMF:H_2O (7:1) (440 mL, 0.05 M) was purged with O_2 with vigorous stirring to activate the reaction medium. The reaction mixture was stirred for 30 min, yielding a deep-green mixture. After this period, a solution of olefin **25** (theor. 23.2 mmol, 100 mol%) in DMF (24 mL, 0.97 M) was added, and the reaction medium was stirred vigorously for 16 h under an O_2 atmosphere. The reaction was diluted with Et_2O (300 mL) and quenched by the addition of H_2O (90 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with H_2O (3 × 100 mL), brine (100 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography using a solution of hexane/ethyl acetate (80:20) as the eluent to provide methylketone **18** (3.06 g, 13.8 mmol, 59% over 2 steps) as a pale yellow oil. **TLC:** R_f = 0.31 (80:20 hexane:EtOAc) **Optical rotation:** $[\alpha]_D^{20}$ −30 (*c* 1.0, $CHCl_3$) **^{1}H NMR (250 MHz, C_6D_6)** δ 1.04 (d, *J* = 6.2 Hz, 3H), 1.74 (s, 3H), 2.04 (dd, *J* = 15.8 and 5.4 Hz, 1H), 2.44 (dd, *J* = 15.8 and 7.3 Hz, 1H), 3.34 (s, 3H), 3.82−3.95 (m, 1H), 4.23 (d, *J* = 11.4 Hz, 1H), 4.35 (d, *J* = 11.4 Hz, 1H), 6.75−6.81 (m, 2H), 7.17−7.21 (m, 2H). **^{13}C NMR (62.5 MHz, C_6D_6)** δ 19.8, 30.5, 50.6, 54.8, 70.5, 71.4, 114.0, 129.3, 131.4, 159.6, 205.4. **IR (film)** ν_{max}/cm^{-1} 2970, 2934, 2905, 2870, 2837, 1715, 1614, 1587, 1514, 1466, 1373, 1302, 1248, 1175, 1136, 1090, 1036, 822.

(−)-(2*R*,6*R*)-8-((*tert*-butyldimethylsilyl)oxy)-6-hydroxy-2-((4-methoxybenzyl)oxy)octan-4-one (28): To a solution of methylketone **18** (1.12 g, 5.02 mmol, 100 mol%) in Et_2O (50 mL, 0.10 M) at −30 ºC was added (*c*-Hex)$_2$BCl (2.17 mL, 10.0 mmol, 200 mol%) dropwise, followed by the addition of Et_3N (1.47 mL, 10.5 mmol, 210 mol%) dropwise, which resulted in the formation of a white cloud. The mixture was stirred under the same conditions for 30 min. The reaction medium was then cooled to −78 ºC, and a solution of aldehyde **23**[63] (1.23 g, 6.53 mmol, 130 mol%) in Et_2O (8.0 mL, 0.80 M) was added over 30 min using a syringe pump. The resulting mixture was stirred for 3 h at −78 ºC, followed by quenching via the dropwise addition of MeOH (20 mL). The volatiles were removed under reduced pressure, and the residue was partially purified by flash

column chromatography using a solution of hexane/CH_2Cl_2/ethyl acetate (55:35:10) as the eluent to provide the aldol adduct **28** (*dr* = 95:05, 1,5-*anti*:1,5-*syn*) and cyclohexanol as impurity as a colorless oil. Diastereoisomeric ratio was determined by ^{13}C NMR analysis of the diastereoisomeric mixture of aldol adducts. **TLC:** R_f = 0.59 (55:35:10 hexane:CH_2Cl_2:EtOAc) **Optical rotation:** $[\alpha]_D^{20}$ −24 (*c* 1.5, CH_2Cl_2) **^{1}H NMR (500 MHz, C_6D_6)** δ 0.03 (s, 3H), 0.04 (s, 3H), 0.94 (s, 9H), 1.02 (d, *J* = 6.1 Hz, 3H), 1.49−1.54 (m, 1H), 1.59−1.64 (m, 1H), 2.08 (dd, *J* = 15.7 and 4.9 Hz, 1H), 2.25 (dd, *J* = 16.8 and 3.8 Hz, 1H), 2.38 (dd, *J* = 16.8 and 8.5 Hz, 1H), 2.52 (dd, *J* = 15.7 and 7.7 Hz, 1H), 3.31 (s, 3H), 3.46 (d, *J* = 2.5 Hz, 1H), 3.66 (ddd, *J* = 10.2, 6.4 and 5.4 Hz, 1H), 3.72 (ddd, *J* = 10.2, 6.8 and 5.2 Hz, 1H), 3.91−3.98 (m, 1H), 4.23 (d, *J* = 11.2 Hz, 1H), 4.29−4.34 (m, 1H), 4.35 (d, *J* = 11.2 Hz, 1H), 6.79−6.82 (m, 2H), 7.20−7.22 (m, 2H). **^{13}C NMR (125 MHz, C_6D_6)** δ −5.4 (2 × CH_3), 18.4, 19.8, 26.0, 39.2, 50.7, 51.1, 54.7, 61.1, 66.3, 70.6, 71.4, 114.0, 129.5, 131.2, 159.7, 209.0. **IR (film)** ν_{max}/cm^{-1} 3460, 2955, 2930, 2856, 1711, 1614, 1514, 1472, 1375, 1250, 1094, 1036, 837, 777, 737. **HRMS (ESI TOF-MS)** *m*/*z* calcd for $C_{22}H_{38}O_5SiK$ $[M + K]^+$: 449.2126, found: 449.2157.

(−)-(3*R*,5*R*,7*R*)-1-((*tert*-butyldimethylsilyl)oxy)-7-((4-methoxybenzyl)oxy)octane-3,5-diol (29): To a solution of aldol adduct **28** (theor. 5.02 mmol, 100 mol%) in THF:MeOH (4:1) (24 mL, 0.21 M) at −78 ºC was added Et_2BOMe (0.84 mL, 6.02 mmol, 120 mol%). The solution was stirred for 15 min under these conditions, and $LiBH_4$ (3.0 mL, 6.00 mmol, 2.0 M in THF, 120 mol%) was added over 1 h using a syringe pump. The reaction was stirred for 1 h and then warmed to −40 ºC. The reaction was quenched by the addition of pH 7 phosphate buffer (58 mL) and MeOH (110 mL). The reaction was warmed to 0 ºC, and 30% H_2O_2 (44 mL) was added dropwise. The mixture was stirred for 1 h, and the volatiles were removed under reduced pressure. The aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with saturated aqueous solution of $NaHCO_3$ (2 × 100 mL), brine (100 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was dissolved in MeOH (50 mL), and the solvent was removed under reduced pressure in a 60 ºC bath to remove chelated boron species. This procedure was repeated 6 times to provide the diol **29** (1.45 g, 3.51 mmol, 70% over 2 steps, *dr* > 95:05, 1,3-*syn*:1,3-*anti*), which was used in the next step without further purification, as a yellow oil. **TLC:** R_f = 0.59 (60:40 hexane:EtOAc)

Optical rotation: $[\alpha]_D^{20}$ −32 (*c* 2.2, CH_2Cl_2) **^{1}H NMR (600 MHz, $CDCl_3$)** *δ* 0.09 (s, 6H), 0.91 (s, 9H), 1.24 (d, *J* = 6.0 Hz, 3H), 1.50 (dt, *J* = 14.1 and 2.6 Hz, 1H), 1.58−1.76 (m, 5H), 3.79−3.83 (m, 1H), 3.81 (s, 3H), 3.84−3.89 (m, 2H), 3.94 (br s, 1H), 4.06−4.10 (m, 1H), 4.15−4.18 (m, 2H), 4.41 (d, *J* = 11.2 Hz, 1H), 4.56 (d, *J* = 11.2 Hz, 1H), 6.88−6.89 (m, 2H), 7.27−7.29 (m, 2H). **^{13}C NMR (150 MHz, $CDCl_3$)** *δ* −5.5, −5.5, 18.1, 19.6, 25.8, 39.0, 43.6, 44.0, 55.2, 61.9, 69.2, 70.4, 72.1 (2 × CH), 113.8, 129.4, 130.6, 159.2. **IR (film)** ν_{max}/cm^{-1} 3454, 2955, 2932, 2858, 1641, 1614, 1514, 1265, 1250, 1086, 1036, 837, 739. **HRMS (ESI TOF-MS)** *m*/*z* calcd for $C_{22}H_{41}O_5Si$ $[M + H]^+$: 413.2723, found: 413.2719.

(−)-*tert*-butyl(2-((4*R*,6*S*)-6-((*R*)-2-((4-methoxybenzyl)oxy)propyl)-2,2-dimethyl-1,3-dioxan-4-yl)ethoxy)dimethylsilane (30): To a solution of diol **29** (1.36 g, 3.29 mmol, 100 mol%) in 2,2-DMP (37 mL, 0.09 M) at room temperature was added PPTS (416 mg, 1.65 mmol, 50 mol%). The reaction medium was stirred for 20 h. The mixture was filtered through silica and Celite, and the residue was washed with CH_2Cl_2 (5 × 50 mL) and concentrated under reduced pressure. The residue was purified by flash column chromatography using a solution of hexane/ethyl acetate (90:10) as the eluent to provide acetonide **30** (1.21 g, 2.68 mmol, 81%) as a colorless oil. **TLC:** R_f = 0.46 (90:10 hexane:EtOAc) **Optical rotation:** $[\alpha]_D^{20}$ −27 (*c* 0.9, CH_2Cl_2) **^{1}H NMR (250 MHz, $CDCl_3$)** *δ* 0.04 (s, 6H), 0.89 (s, 9H), 1.18 (d, *J* = 6.0 Hz, 3H), 1.36 (s, 3H), 1.40 (s, 3H), 1.42−1.69 (m, 6H), 3.60−3.77 (m, 3H), 3.80 (s, 3H), 3.97−4.15 (m, 2H), 4.35 (d, *J* = 11.2 Hz, 1H), 4.52 (d, *J* = 11.2 Hz, 1H), 6.84−6.90 (m, 2H), 7.24−7.28 (m, 2H). **^{13}C NMR (62.5 MHz, $CDCl_3$)** *δ* −5.4 (2 × CH_3), 18.3, 20.0, 20.1, 25.9, 30.3, 37.7, 39.5, 44.5, 55.2, 58.9, 65.5, 65.7, 70.5, 70.7, 98.4, 113.8, 129.3, 131.1, 159.1. **IR (film)** ν_{max}/cm^{-1} 2993, 2951, 2935, 2856, 1614, 1514, 1472, 1464, 1379, 1250, 1200, 1171, 1101, 1038, 960, 835, 775, 739. **HRMS (ESI TOF-MS)** *m*/*z* calcd for $C_{25}H_{45}O_5Si$ $[M + H]^+$: 453.3036, found: 453.3026.

(+)-(*R*)-4-((*tert*-butyldimethylsilyl)oxy)-1-((2*R*,4*R*,6*R*)-2-(4-methoxyphenyl)-6-methyl-1,3-dioxan-4-yl)butan-2-ol (31): To a solution of diol **29** (50 mg, 0.12 mmol, 100 mol%) in CH_2Cl_2 (2.5 mL, 0.05 M) at room temperature was added activated 4 Å molecular sieves (37 mg). After 15 min, the mixture was cooled to −10 ºC, and DDQ (34 mg, 0.15 mmol, 125 mol%) was added. The reaction medium was stirred for 5 min at −10 ºC and warmed to 0 ºC. After 2 h, the reaction mixture was loaded directly onto a flash column chromatography using a solution of hexane/ethyl

acetate (80:20) as the eluent to provide the PMP acetal **31** (33 mg, 80 μmol, 67%) as a pale yellow solid. **TLC:** R_f = 0.39 (70:30 hexane:EtOAc) **mp** 39−41 °C **Optical rotation:** $[\alpha]_D^{20}$ +10 (*c* 1.5, CH_2Cl_2) **^{1}H NMR (600 MHz, $CDCl_3$)** *δ* 0.06 (s, 6H), 0.88 (s, 9H), 1.26 (d, *J* = 6.0 Hz, 3H), 1.46−1.49 (m, 1H), 1.61 (dt, *J* = 14.3 and 4.9 Hz, 1H), 1.69−1.74 (m, 2H), 1.98 (ddd, *J* = 13.6, 11.8 and 6.2 Hz, 1H), 2.42 (ddd, *J* = 14.4, 10.2 and 7.6 Hz, 1H), 3,60 (br s, 1H), 3.77 (s, 3H), 3.77−3.83 (m, 1H), 3.84−3.89 (m, 1H), 4.05 (quint, *J* = 6.0 Hz, 1H), 4.13 (dqd, *J* = 12.1, 6.2 and 2.5 Hz, 1H), 4.42 (quint, *J* = 5.3 Hz, 1H), 5.81 (s, 1H), 6.85−6.87 (m, 2H), 7.38−7.41 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)** *δ* −5.5, −5.5, 18.1, 21.9, 25.8, 35.9, 37.6, 38.4, 55.2, 61.8, 68.6, 69.8, 71.4, 94.4, 113.6, 127.4, 131.3, 159.9. **IR (film)** ν_{max}/cm^{-1} 3468, 2953, 2932, 2856, 1616, 1518, 1464, 1377, 1304, 1250, 1173, 1122, 1094, 1036, 837, 777, 737. **HRMS (ESI TOF-MS)** *m*/*z* calcd for $C_{22}H_{38}O_5SiNa$ $[M + Na]^+$: 433.2386, found: 433.2373.

(−)-(*R*)-1-((4*S*,6*R*)-6-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)propan-2-ol (32): To a solution of PMB ether **30** (2.03 g, 4.48 mmol, 100 mol%) in CH_2Cl_2:phosphate buffer pH 7 (9:1) (75 mL, 0,06 M) at 0 ºC was added DDQ (1.21 g, 5.33 mmol, 120 mol%). The mixture was stirred for 45 min under the same conditions, followed by quenching via the addition of a solution of H_2O:saturated aqueous solution of $NaHCO_3$ (1:1) (16 mL). The resulting mixture was filtered over Celite, washed with CH_2Cl_2 (5 × 50 mL) and concentrated under reduced pressure. The residue was purified by flash column chromatography using hexane/ethyl acetate (80:20) as the eluent to provide alcohol **32** (1.36 g, 4.09 mmol, 91%) as a pale yellow oil. **TLC:** R_f = 0.33 (80:20 hexane:EtOAc) **Optical rotation:** $[\alpha]_D^{20}$ −1.6 (*c* 3.7, $CHCl_3$) **^{1}H NMR (250 MHz, C_6D_6)** *δ* 0.07 (s, 3H), 0.07 (s, 3H), 0.99 (s, 9H), 1.05−1.12 (m, 1H), 1.10 (d, *J* = 6.3 Hz, 3H), 1.17−1.31 (m, 1H), 1.34 (s, 3H), 1.39−1.77 (m, 4H), 1.43 (s, 3H), 2.17 (br s, 1H), 3.59−3.67 (m, 1H), 3.72−3.82 (m, 1H), 3.93−4.05 (m, 3H). **^{13}C NMR (62.5 MHz, C_6D_6)** *δ* −5.3, −5.2, 18.5, 19.8, 24.0, 26.1, 30.5, 37.3, 40.0, 44.8, 59.1, 64.3, 65.8, 67.0, 98.6. **IR (film)** ν_{max}/cm^{-1} 3443, 2993, 2955, 2930, 2883, 2858, 1637, 1472, 1381, 1265, 1257, 1200, 1167, 1101, 1020, 1005, 959, 837, 777, 739. **HRMS (ESI TOF-MS)** *m*/*z* calcd for $C_{17}H_{37}O_4Si$ $[M + H]^+$: 333.2461, found: 333.2472.

(+)-1-((4*R*,6*R*)-6-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)propan-2-one (20): To a solution of oxalyl chloride (0.43 mL, 4.81 mmol, 120 mol%) in CH_2Cl_2

(23 mL, 0.21 M) at −78 ºC was added DMSO (0.66 mL, 9.35 mmol, 240 mol%) dropwise. The reaction medium was stirred for 30 min, followed by the dropwise addition of a solution of alcohol **32** (1.30 g, 3.91 mmol, 100 mol%) in CH_2Cl_2 (9.5 mL, 0.41 M). After 30 min, Et_3N (2.8 mL, 20.0 mmol, 510 mol%) was added dropwise, and the resulting slurry was warmed to 0 ºC and stirred for 1 h. The reaction was then diluted with Et_2O (20 mL) and saturated aqueous solution of NH_4Cl (20 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with H_2O (3 × 50 mL), brine (50 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography using hexane/ethyl acetate (80:20) as the eluent to provide methylketone **20** (1.25 g, 3.78 mmol, 97%) as a pale yellow oil. **TLC:** R_f = 0.61 (80:20 hexane:EtOAc) **Optical rotation:** $[\alpha]_D^{20}$ +18 (*c* 1.4, CH_2Cl_2) **^{1}H NMR (250 MHz, C_6D_6)** δ 0.06 (s, 6H), 0.98 (s, 9H), 1.04 (q, *J* = 12.6 Hz, 1H), 1.22 (dt, *J* = 12.6 and 2.6 Hz, 1H), 1.35 (s, 3H), 1.45 (s, 3H), 1.52−1.70 (m, 2H), 1.73 (s, 3H), 1.97 (dd, *J* = 15.9 and 4.9 Hz, 1H), 2.38 (dd, *J* = 15.9 and 7.4 Hz, 1H), 3.58−3.67 (m, 1H), 3.70−3.80 (m, 1H), 3.91−4.01 (m, 1H), 4.16−4.27 (m, 1H). **^{13}C NMR (62.5 MHz, C_6D_6)** δ −5.3, −5.2, 18.4, 19.8, 26.1, 30.4, 30.5, 37.3, 40.0, 50.0, 59.1, 65.6, 65.9, 98.7, 204.5. **IR (film)** ν_{max}/cm^{-1} 2995, 2955, 2930, 2858, 1717, 1472, 1381, 1362, 1265, 1257, 1200, 1171, 1097, 957, 837, 777, 739. **HRMS (ESI TOF-MS)** *m*/*z* calcd for $C_{17}H_{34}O_4SiK$ $[M + K]^+$: 369.1863, found: 369.1852.

(+)-(4*S*,5*S*,6*S*)-1-((4*R*,6*R*)-6-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)-4-hydroxy-6-((4-methoxybenzyl)oxy)-5,7-dimethyloctan-2-one (37): To a solution of methylketone **20** (1.20 g, 3.63 mmol, 100 mol%) in Et_2O (50 mL, 0.07 M) at −30 ºC was added (*c*-Hex)$_2$BCl (1.7 mL, 7.26 mmol, 200 mol%) dropwise, followed by the addition of Et_3N (2.3 mL, 9.20 mmol, 250 mol%) dropwise, which resulted in the formation of a white cloud. The mixture was stirred under the same conditions for 30 min. The reaction medium was then cooled to −78 ºC, and a solution of aldehyde **19** (1.18 g, 4.72 mmol, 130 mol%) in Et_2O (5.0 mL, 0.94 M) was added over 30 min using a syringe pump. The resulting mixture was stirred for 3 h at −78 ºC, followed by quenching via the dropwise addition of MeOH (20 mL). The volatiles were removed under reduced pressure, and the residue was purified by flash column chromatography using a solution of hexane/ethyl acetate (80:20) as the eluent to provide the aldol adduct **37** (1.90 g, 3.26 mmol, 90%, *dr* > 95:05, 1,5-*anti*:1,5-*syn*) as a pale yellow oil. **TLC:** R_f = 0.36 (80:20

hexane:EtOAc) **Optical rotation:** $[\alpha]_D^{20}$ +2 (*c* 2.3, $CHCl_3$) **^{1}H NMR (600 MHz, $CDCl_3$)** δ 0.03 (s, 6H), 0.84 (d, *J* = 7.0 Hz, 3H), 0.86 (d, *J* = 6.8 Hz, 3H), 0.88 (s, 9H), 1.04 (d, *J* = 6.6 Hz, 3H), 1.18 (q, *J* = 12.7 Hz, 1H), 1.33 (s, 3H), 1.42 (s, 3H), 1.54 (dt, *J* = 12.7 and 2.4 Hz, 1H), 1.58−1.65 (m, 2H), 1.71−1.76 (m, 1H), 1.81−1.89 (m, 1H), 2.37 (dd, *J* = 15.6 and 4.4 Hz, 1H), 2.46 (dd, *J* = 16.8 and 9.5 Hz, 1H), 2.69 (dd, *J* = 15.6 and 8.1 Hz, 1H), 2.77 (dd, *J* = 16.8 and 2.4 Hz, 1H), 3.42 (d, *J* = 3.6 Hz, 1H), 3.47 (dd, *J* = 8.7 and 2.1 Hz, 1H), 3.63 (dt, *J* = 10.4 and 5.5 Hz, 1H), 3.70 (ddd, *J* = 10.2, 8.1 and 5.3 Hz, 1H), 3.78 (s, 3H), 3.99−4.07 (m, 2H), 4.32−4.37 (m, 1H), 4.56 (d, *J* = 10.9 Hz, 1H), 4.58 (d, *J* = 10.9 Hz, 1H), 6.85−6.87 (m, 2H), 7.27−7.28 (m, 2H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ −5.4, −5.4, 10.0, 18.3, 19.6, 19.7, 20.0, 25.9, 30.0, 31.1, 36.9, 39.3, 40.3, 49.1, 49.5, 55.2, 58.7, 65.4, 66.1, 69.4, 74.2, 83.8, 98.8, 113.7, 129.2, 131.4, 159.0, 210.6. **IR (film)** ν_{max}/cm^{-1} 3441, 2957, 2930, 2856, 1705, 1645, 1614, 1514, 1464, 1381, 1265, 1250, 1094, 1036, 837, 739. **HRMS (ESI TOF-MS)** *m*/*z* calcd for $C_{32}H_{56}O_7SiNa$ $[M + Na]^+$: 603.3693, found: 603.3720.

(−)-1-((4*R*,6*R*)-6-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)-3-((2*R*,4*S*,5*S*,6*S*)-6-isopropyl-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)propan-2-one (38): To a solution of aldol adduct **37** (50 mg, 86 μmol, 100 mol%) in CH_2Cl_2 (1.8 mL, 0.05 M) at room temperature was added activated 4 Å molecular sieves (27 mg). After 15 min, the mixture was cooled to −10 ºC, and DDQ (25 mg, 0.11 mmol, 130 mol%) was added. The reaction medium was stirred for 5 min at −10 ºC and warmed to 0 ºC. After 1.5 h, the reaction mixture was loaded directly onto a flash column chromatography using a solution of hexane/ethyl acetate (80:20) as the eluent to provide the PMP acetal **38** (33 mg, 57 μmol, 66%) as a pale yellow oil. **TLC:** R_f = 0.76 (70:30 hexane:EtOAc) **Optical rotation:** $[\alpha]_D^{20}$ −21 (*c* 3.3, $CHCl_3$) **^{1}H NMR (500 MHz, $CDCl_3$)** δ 0.03 (s, 6H), 0.80 (d, *J* = 6.8 Hz, 3H), 0.88 (s, 9H), 1.00 (d, *J* = 6.4 Hz, 3H), 1.14 (q, *J* = 11.9 Hz, 1H), 1.20 (d, *J* = 6.9 Hz, 3H), 1.34 (s, 3H), 1.42 (s, 3H), 1.52−1.62 (m, 4H), 1.75−1.82 (m, 1H), 2.47 (dd, *J* = 15.6 and 5.1 Hz, 1H), 2.70 (dd, *J* = 15.6 and 7.2 and Hz, 1H), 2.92 (dd, *J* = 16.0 and 7.2 Hz, 1H), 3.17 (dd, *J* = 16.0 and 7.1 Hz, 1H), 3.44 (dd, *J* = 9.7 and 2.0 Hz, 1H), 3.62 (dt, *J* = 10.2 and 5.2 Hz, 1H), 3.70 (ddd, *J* = 10.2, 8.0 and 5.4 Hz, 1H), 3.78 (s, 3H), 4.01−4.06 (m, 1H), 4.30−4.35 (m, 1H), 4.42 (t, *J* = 7.1 Hz, 1H), 5.66 (s, 1H), 6.85−6.87 (m, 2H), 7.37−7.39 (m, 2H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ −5.4, −5.4, 12.9, 17.4, 18.2, 19.8 (2 × CH_3), 25.9, 29.2, 30.1, 32.3, 36.9, 39.3, 45.5, 49.8, 55.3, 58.7, 65.4, 65.9, 75.8, 80.8, 95.4, 98.7,

113.5, 127.3, 131.5, 159.8, 206.7. **IR (film)** ν_{max}/cm^{-1} 2957, 2930, 2856, 1715, 1616, 1518, 1472, 1464, 1381, 1250, 1171, 1101, 1038, 960, 835, 777, 739. **HRMS (ESI TOF-MS)** *m*/*z* calcd for $C_{32}H_{55}O_7Si$ [M + H]$^+$: 579.3717, found: 579.3720.

(+)-(2*R*,4*S*,5*S*,6*S*)-1-((4*S*,6*R*)-6-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)-6-((4-methoxybenzyl)oxy)-5,7-dimethyloctane-2,4-diol (39): To a solution of aldol adduct **37** (1.20 g, 2.06 mmol, 100 mol%) in THF:MeOH (4:1) (10 mL, 0.21 M) at −78 ºC was added Et_2BOMe (0.35 mL, 2.50 mmol, 120 mol%). The solution was stirred for 15 min under these conditions, and $LiBH_4$ (1.26 mL, 2.52 mmol, 2.0 M in THF, 120 mol%) was added over 1 h using a syringe pump. The reaction was stirred for 1 h and then warmed to −40 ºC. The reaction was quenched by the addition of pH 7 phosphate buffer (28 mL) and MeOH (52 mL). The reaction was warmed to 0 ºC, and 30% H_2O_2 (21 mL) was added dropwise. The mixture was stirred for 1 h, and the volatiles were removed under reduced pressure. The aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with saturated aqueous solution of $NaHCO_3$ (2 × 50 mL), brine (100 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was dissolved in MeOH (50 mL), and the solvent was removed under reduced pressure in a 60 ºC bath to remove chelated boron species. This procedure was repeated 6 times to provide the diol **39** (1.20 g, 2.06 mmol, 99%, *dr* > 95:05, 1,3-*syn*:1,3-*anti*), which was used in the next step without further purification, as a white gum. **TLC:** R_f = 0.30 (80:20 hexane:EtOAc) **Optical rotation:** $[\alpha]_D^{20}$ +7 (*c* 2.0, $CHCl_3$) **^{1}H NMR (500 MHz, $CDCl_3$)** δ 0.03 (s, 6H), 0.86−0.88 (m, 6H), 0.88 (s, 9H), 1.02 (d, *J* = 6.4 Hz, 3H), 1.30−1.50 (m, 3H), 1.37 (s, 3H), 1.45 (s, 3H), 1.58−1.67 (m, 5H), 1.70−1.76 (m, 1H), 1.88 (oct, *J* = 6.9 Hz, 1H), 3.44 (dd, *J* = 7.9 and 1.9 Hz, 1H), 3.64 (dt, *J* = 10.3 and 5.3 Hz, 1H), 3.69−3.74 (m, 1H), 3.78 (s, 3H), 3.78−3.83 (m, 1H), 3.91−4.22 (m, 5H), 4.54 (d, *J* = 10.8 Hz, 1H), 4.62 (d, *J* = 10.8 Hz, 1H), 6.85−6.86 (m, 2H), 7.26−7.28 (m, 2H). **^{13}C NMR (62.5 MHz, $CDCl_3$)** δ −5.4 (2 × CH_3), 10.8, 18.3, 19.8 (2 × CH_3), 19.9, 25.9, 30.2, 30.8, 36.8, 39.4, 41.0, 41.1, 43.0, 55.3, 58.7, 65.6, 67.0, 70.2, 73.7, 75.0, 84.4, 98.7, 113.7, 129.2, 131.3, 159.0. **IR (film)** ν_{max}/cm^{-1} 3441, 3055, 2986, 2957, 2930, 2856, 1659, 1645, 1614, 1514, 1421, 1265, 1095, 897, 837, 739, 706. **HRMS (ESI TOF-MS)** *m*/*z* calcd for $C_{32}H_{59}O_7Si$ [M + H]$^+$: 583.4030, found: 583.4047.

(+)-*tert*-butyl(2-((4*R*,6*R*)-6-(((4*S*,6*S*)-6-((2*S*,3*S*)-3-((4-methoxybenzyl)oxy)-4-methylpentan-2-yl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)ethoxy)dimethylsilane (40): To a solution of diol **39** (1.20 g, 2.06 mmol, 100 mol%) in 2,2-DMP (25 mL, 0.08 M) at room temperature was added PPTS (260 mg, 1.03 mmol, 50 mol%). The reaction medium was stirred for 24 h. The mixture was filtered through silica and Celite, and the residue was washed with CH_2Cl_2 (5 × 50 mL) and concentrated under reduced pressure. The residue was purified by flash column chromatography using a solution of hexane/ethyl acetate (80:20) as the eluent to provide acetonide **40** (1.12 g, 1.80 mmol, 87%) as a pale yellow oil. **TLC:** R_f = 0.74 (80:20 hexane:EtOAc) **Optical rotation:** $[\alpha]_D^{20}$ +10 (*c* 1.6, $CHCl_3$) **^{1}H NMR (600 MHz, $CDCl_3$)** δ 0.03 (s, 6H), 0.82 (d, *J* = 7.2 Hz, 3H), 0.84 (d, *J* = 6.8 Hz, 3H), 0.88 (s, 9H), 1.02 (d, *J* = 6.6 Hz, 3H), 1.06 (q, *J* = 12.2 Hz, 1H), 1.15 (q, *J* = 12.2 Hz, 1H), 1.36 (s, 3H), 1.37 (s, 3H), 1.39 (s, 3H), 1.40 (s, 3H), 1.45 (dt, *J* = 12.8 and 2.3 Hz, 1H), 1.50 (dd, *J* = 6.4 and 5.8 Hz, 2H), 1.57−1.68 (m, 4H), 1.79−1.85 (m, 1H), 3.41 (dd, *J* = 9.0 and 1.7 Hz, 1H), 3.64 (dt, *J* = 10.3 and 5.3 Hz, 1H), 3.71 (ddd, *J* = 10.3, 8.3 and 5.3 Hz, 1H), 3.79 (s, 3H), 3.79−3.83 (m, 1H), 4.00−4.09 (m, 3H), 4.50 (d, *J* = 11.8 Hz, 1H), 4.52 (d, *J* = 11.8 Hz, 1H), 6.85−6.87 (m, 2H), 7.25−7.26 (m, 2H). **^{13}C NMR (150 MHz, $CDCl_3$)** δ −5.4 (2 × CH_3), 8.8, 18.3, 19.4, 19.9, 20.1, 20.2, 25.9, 30.3, 30.4, 31.2, 35.9, 37.7, 39.5, 41.3, 43.4, 55.2, 58.9, 64.9, 64.9, 65.8, 70.1, 74.0, 82.7, 98.4, 98.4, 113.7, 128.7, 131.8, 158.9. **IR (film)** ν_{max}/cm^{-1} 2991, 2953, 2937, 2858, 1614, 1514, 1472, 1464, 1379, 1248, 1202, 1171, 1107, 1092, 959, 835, 775, 739. **HRMS (ESI TOF-MS)** *m*/*z* calcd for $C_{35}H_{63}O_7Si$ $[M + H]^+$: 623.4343, found: 623.4360.

(+)-2-((4*R*,6*R*)-6-(((4*S*,6*S*)-6-((2*S*,3*S*)-3-((4-methoxybenzyl)oxy)-4-methylpentan-2-yl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)ethanol (41): To a solution of compound **40** (300 mg, 0.48 mmol, 100 mol%) in THF (3.2 mL, 0.15 M) at room temperature was added TBAF (0.96 mL, 0.96 mmol, 1 M in THF, 200 mol%). After 2.5 h, the volatiles were removed under reduced pressure, and the residue was purified by flash column chromatography using a solution of hexane/ethyl acetate (50:50) as the eluent to provide alcohol **41** (244 mg, 0.48 mmol, 99%) as a colorless oil. **TLC:** R_f = 0.50 (50:50 hexane:EtOAc) **Optical rotation:** $[\alpha]_D^{20}$ +5 (*c* 1.4, $CHCl_3$) **^{1}H NMR (500 MHz, $CDCl_3$)** δ 0.83 (d, *J* = 6.8 Hz, 3H), 0.84 (d, *J* = 6.6 Hz, 3H), 1.02 (d, *J* = 6.6 Hz, 3H), 1.07 (q, *J* = 12.5 Hz, 1H), 1.25−1.32 (m, 2H), 1.37 (s, 3H), 1.38 (s, 3H), 1.39 (s, 3H), 1.42−1.45 (m, 1H), 1.44 (s, 3H), 1.50−1.53 (m, 2H), 1.60 (dt, *J* = 12.5 and

2.3 Hz, 1H), 1.63−1.77 (m, 2H), 1.80−1.87 (m, 1H), 2.60 (br s, 1H), 3.42 (dd, *J* = 9.0 and 1.9 Hz, 1H), 3.73−3.84 (m, 3H), 3.80 (s, 3H), 4.03−4.14 (m, 3H), 4.52−4.54 (m, 2H), 6.86−6.88 (m, 2H), 7.26−7.27 (m, 2H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 8.7, 19.4, 19.9, 20.1, 20.2, 30.3, 30.4, 31.2, 35.9, 37.1, 38.0, 41.3, 43.2, 55.3, 61.0, 64.8 (2 × CH), 69.8, 70.1, 74.0, 82.7, 98.4, 98.7, 113.7, 128.7, 131.7, 158.9. **IR (film)** ν_{max}/cm^{-1} 3463, 2991, 2944, 2916, 2874, 1614, 1515, 1465, 1380, 1248, 1203, 1170, 1105, 1037, 956, 917, 874, 831, 738. **HRMS (ESI TOF-MS)** *m*/*z* calcd for $C_{29}H_{48}O_7Na$ $[M + Na]^+$: 531.3298, found: 531.3328.

(+)-5-((2-((4*S*,6*S*)-6-(((4*S*,6*S*)-6-((2*S*,3*S*)-3-((4-methoxybenzyl)oxy)-4-methylpentan-2-yl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)ethyl)thio)-1-phenyl-1*H*-tetrazole (43): To a solution of compound **41** (115 mg, 0.23 mmol, 100 mol%) in THF (2.0 mL, 0.11 M) at 0 °C were added PPh_3 (89 mg, 0.34 mmol, 150 mol%) and 1-phenyl-1*H*-tetrazole-5-thiol (**42**) (81 mg, 0.45 mmol, 200 mol%), followed by the addition of DEAD (64 µL, 0.41 mmol, 180 mol%) dropwise. After 30 min at 0 °C, the reaction was diluted with Et_2O (5 mL) and quenched by the addition of saturated aqueous solution of $NaHCO_3$ (5 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography using a solution of hexane/ethyl acetate (80:20) as the eluent to provide sulfide **43** (131 mg, 0.196 mmol, 87%) as a viscous colorless oil. **TLC:** R_f = 0.33 (80:20 hexane:EtOAc) **Optical rotation:** $[\alpha]_D^{20}$ +20 (*c* 1.2, $CHCl_3$) **^{1}H NMR (500 MHz, $CDCl_3$)** δ 0.82 (d, *J* = 6.8 Hz, 3H), 0.84 (d, *J* = 6.0 Hz, 3H), 1.02 (d, *J* = 6.6 Hz, 3H), 1.06 (q, *J* = 12.5 Hz, 1H), 1.20 (q, *J* = 12.5 Hz, 1H), 1.37 (s, 3H), 1.37 (s, 3H), 1.38 (s, 3H), 1.40 (s, 3H), 1.46 (dt, *J* = 12.5 and 2.2 Hz, 1H), 1.49−1.52 (m, 2H), 1.60 (dt, *J* = 12.5 and 2.2 Hz, 1H), 1.64−1.68 (m, 1H), 1.80−1.87 (m, 1H), 1.88−1.96 (m, 1H), 1.99−2.07 (m, 1H), 3.41−3.54 (m, 3H), 3.79−3.84 (m, 1H), 3.80 (s, 3H), 3.97−4.11 (m, 3H), 4.52−4.54 (m, 2H), 6.86−6.88 (m, 2H), 7.25−7.27 (m, 2H), 7.52−7.59 (m, 5H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 8.7, 19.4, 19.8, 20.1, 20.2, 29.2, 30.2, 30.4, 31.2, 35.5, 35.8, 37.1, 41.3, 43.2, 55.2, 64.8, 64.8, 67.5, 70.1, 74.0, 82.7, 98.3, 98.7, 113.7, 123.8, 128.7, 129.8, 130.1, 131.7, 133.7, 154.4, 158.8. **IR (film)** ν_{max}/cm^{-1} 2991, 2953, 2943, 2915, 2873, 1613, 1598, 1514, 1501, 1464, 1381, 1248, 1203, 1170, 1036, 979, 943, 873, 829, 761, 738, 695. **HRMS (ESI TOF-MS)** *m*/*z* calcd for $C_{36}H_{53}O_6N_4S$ $[M + H]^+$: 669.3686, found: 669.3727.

(+)-5-((2-((4*S*,6*S*)-6-(((4*S*,6*S*)-6-((2*S*,3*S*)-3-((4-methoxybenzyl)oxy)-4-methylpentan-2-yl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)ethyl)sulfonyl)-1-phenyl-1*H*-tetrazole (10): To a solution of sulfide **43** (107 mg, 0.16 mmol, 100 mol%) in EtOH (1.2 mL, 0.13 M) at 0 °C was added a solution of $(NH_4)_6Mo_7O_{24}.4H_2O$ (20 mg, 16 μmol, 10 mol%) in H_2O_2 (0.3 mL, 0.05 M) dropwise. The reaction was slowly warmed to room temperature. After 15 h, the reaction was diluted with Et_2O (10 mL) and quenched by the addition of brine (10 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography using a solution of hexane/ethyl acetate (80:20) as the eluent to provide sulfone **10** (104 mg, 0.15 mmol, 92%) as a white solid. **TLC:** R_f = 0.43 (80:20 hexane:EtOAc) **mp** 46−48 °C **Optical rotation:** $[\alpha]_D^{20}$ +11 (*c* 2.3, $CHCl_3$) **^{1}H NMR (600 MHz, $CDCl_3$)** δ 0.82 (d, *J* = 7.0 Hz, 3H), 0.84 (d, *J* = 6.6 Hz, 3H), 1.02 (d, *J* = 6.6 Hz, 3H), 1.07 (q, *J* = 12.0 Hz, 1H), 1.19 (q, *J* = 12.0 Hz, 1H), 1.36 (s, 3H), 1.37 (s, 3H), 1.39 (s, 3H), 1.39 (s, 3H), 1.47−1.52 (m, 3H), 1.59−1.61 (m, 1H), 1.64−1.69 (m, 1H), 1.79−1.87 (m, 1H), 1.99−2.06 (m, 1H), 2.12−2.18 (m, 1H), 3.42 (dd, *J* = 9.0 and 1.5 Hz, 1H), 3.78−3.83 (m, 2H), 3.80 (s, 3H), 3.92 (ddd, *J* = 14.8, 10.1 and 5.1 Hz, 1H), 4.01−4.11 (m, 3H), 4.52 (s, 2H), 6.86−6.88 (m, 2H), 7.26−7.27 (m, 2H), 7.59−7.64 (m, 3H), 7.68−7.69 (m, 2H). **^{13}C NMR (150 MHz, $CDCl_3$)** δ 8.8, 19.4, 19.8, 20.1, 20.2, 28.6, 30.1, 30.4, 31.2, 35.8, 37.0, 41.3, 43.1, 52.4, 55.3, 64.6, 64.8, 66.9, 70.1, 74.0, 82.7, 98.4, 98.9, 113.7, 125.1, 128.6, 129.7, 131.5, 131.7, 133.0, 153.4, 158.9. **IR (film)** ν_{max}/cm^{-1} 2992, 2955, 2943, 2916, 2873, 1614, 1514, 1499, 1464, 1381, 1346, 1248, 1204, 1171, 1153, 1104, 1077, 1036, 981, 941, 873, 830, 763, 738, 689. **HRMS (ESI TOF-MS)** *m*/*z* calcd for $C_{36}H_{53}O_8N_4S$ $[M + H]^+$: 701.3584, found: 701.3583.

(−)-(2*R*,6*R*)-6-hydroxy-2-((4-methoxybenzyl)oxy)non-8-en-4-one (47): To a solution of methylketone **18** (2.53 g, 11.4 mmol, 100 mol%) in Et_2O (110 mL, 0.10 M) at −30 ºC was added $(c\text{-Hex})_2BCl$ (4.9 mL, 22.7 mmol, 200 mol%) dropwise, followed by the addition of Et_3N (3.4 mL, 24.4 mmol, 210 mol%) dropwise, which resulted in the formation of a white cloud. The mixture was stirred under the same conditions for 30 min. The reaction medium was then cooled to −78 ºC, and a solution of aldehyde **17**[27] (theor. 34.0 mmol, 300 mol%) in CH_2Cl_2 (6.0 mL, 5.7 M) was added over 30 min using a syringe pump. The resulting mixture was stirred for 1 h at −78 ºC,

followed by quenching via the addition of pH 7 phosphate buffer (22 mL). The mixture was warmed to 0 ºC, and MeOH (67 mL) and a solution of 30% H_2O_2 (22 mL) in MeOH (45 mL) were added dropwise. The reaction medium was stirred for 1 h under the same conditions. The volatiles were removed under reduced pressure, and the aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with saturated aqueous solution of $NaHCO_3$ (2 × 50 mL), brine (100 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography using a solution of hexane/ethyl acetate (70:30) as the eluent to provide the aldol adduct **47** (2.93 g, 10.0 mmol, 88%, *dr* = 92:08, 1,5-*anti*:1,5-*syn*) as a pale yellow oil. Diastereoisomeric ratio was determined by ^{13}C NMR analysis of the diastereoisomeric mixture of aldol adducts. **TLC:** R_f = 0.46 (60:40 hexane:EtOAc) **Optical rotation:** $[\alpha]_D^{20}$ −49 (*c* 2.5, $CHCl_3$) **^{1}H NMR (500 MHz, C_6D_6)** δ 1.01 (d, *J* = 6.1 Hz, 3H), 1.98−2.08 (m, 2H), 2.11−2.27 (m, 3H), 2.46 (ddd, *J* = 15.5, 7.7 and 4.1 Hz, 1H), 2.97−3.04 (m, 1H), 3.30 (s, 3H), 3.88−3.94 (m, 1H), 4.00−4.09 (m, 1H), 4.21 (d, *J* = 11.2 Hz, 1H), 4.35 (d, *J* = 11.2 Hz, 1H), 4.98−5.01 (m, 2H), 5.77 (ddt, *J* = 16.7, 9.6 and 7.1 Hz, 1H), 6.79−6.81 (m, 2H), 7.19−7.21 (m, 2H). **^{13}C NMR (125 MHz, C_6D_6)** δ 19.7, 41.4, 50.0, 50.6, 54.7, 67.2, 70.6, 71.4, 114.0, 117.3, 129.5, 131.1, 135.1, 159.7, 209.4. **IR (film)** ν_{max}/cm^{-1} 3448, 3076, 2972, 2932, 2907, 2837, 1709, 1641, 1614, 1587, 1514, 1466, 1375, 1302, 1248, 1175, 1080, 1034, 918, 824, 754. **HRMS (ESI TOF-MS)** *m*/*z* calcd for $C_{17}H_{24}O_4K$ $[M + K]^+$: 331.1312, found: 331.1299.

(−)-(4*R*,6*S*,8*R*)-8-((4-methoxybenzyl)oxy)non-1-ene-4,6-diol (48): To a slurry of $Me_4NBH(OAc)_3$ (16.7 g, 63.6 mmol, 400 mol%) in MeCN (45 mL, 1.4 M) was added AcOH (45 mL). The mixture was stirred at room temperature for 30 min and then cooled to −40 ºC. A solution of aldol adduct **47** (4.66 g, 15.9 mmol, 100 mol%) in MeCN (45 mL, 0.35 M) was added dropwise, followed by the addition of a solution of CSA (1.85 g, 8.0 mmol, 50 mol%) in MeCN:AcOH (1:1) (90 mL, 0.09 M). The reaction medium was warmed to −20 ºC and stirred for 20 h. The mixture was poured into an Erlenmeyer flask containing saturated aqueous solution of $NaHCO_3$ (1400 mL). After gas liberation ceased, saturated aqueous solution of sodium potassium tartrate (800 mL) and Et_2O (800 mL) were added. The mixture was stirred vigorously for 8 h. The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 500 mL). The combined organic layers were washed with brine (500 mL), dried over $MgSO_4$, filtered,

and concentrated under reduced pressure to provide diol **48** (4.68 g, 15.9 mmol, 99%, *dr* > 95:05, 1,3-*anti*:1,3-*syn*), which was used in the next step without further purification, as a yellow oil. **TLC:** R_f = 0.47 (50:50 hexane:EtOAc) **Optical rotation:** $[\alpha]_D^{20}$ −49 (*c* 2.5, $CHCl_3$) **^{1}H NMR (500 MHz, $CDCl_3$)** *δ* 1.24 (d, *J* = 6.1 Hz, 3H), 1.51−1.58 (m, 3H), 1.80 (dt, *J* = 14.6 and 10.1 Hz, 1H), 2.19−2.29 (m, 2H), 3.17 (br s, 1H), 3.79 (s, 3H), 3.79−3.85 (m, 1H), 3.96 (quint, *J* = 6.2 Hz, 1H), 4.11−4.15 (m, 1H), 4.18 (br s, 1H), 4.34 (d, *J* = 11.0 Hz, 1H), 4.60 (d, *J* = 11.0 Hz, 1H), 5.07−5.11 (m, 2H), 5.82 (ddt, *J* = 17.3, 10.2 and 7.1 Hz, 1H), 6.87−6.88 (m, 2H), 7.24−7.25 (m, 2H). **^{13}C NMR (62.5 MHz, $CDCl_3$)** *δ* 19.6, 42.0, 42.3, 43.5, 55.2, 67.9, 69.7, 70.0, 75.9, 113.9, 117.4, 129.4, 129.9, 135.0, 159.3. **IR (film)** ν_{max}/cm^{-1} 3437, 3053, 2972, 2937, 2914, 2872, 2839, 1641, 1614, 1587, 1514, 1466, 1441, 1377, 1302, 1265, 1250, 1175, 1090, 1034, 918, 824, 739, 704. **HRMS (ESI TOF-MS)** *m*/*z* calcd for $C_{17}H_{26}O_4Na$ $[M + Na]^+$: 317.1729, found: 317.1718.

(−)-(4*R*,6*R*)-4-allyl-6-((*R*)-2-((4-methoxybenzyl)oxy)propyl)-2,2-dimethyl-1,3-dioxane (49): To a solution of diol **48** (1.07 g, 3.64 mmol, 100 mol%) in 2,2-DMP (43 mL, 0.08 M) at room temperature was added CSA (85 mg, 0.36 mmol, 10 mol%). After 17 h, the reaction was quenched by the addition of $NaHCO_3$ (100 mg), filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography using a solution of hexane/ethyl acetate (90:10) as the eluent to provide acetonide **49** (895 mg, 2.68 mmol, 74%) as a colorless oil. **TLC:** R_f = 0.77 (80:20 hexane:EtOAc) **Optical rotation:** $[\alpha]_D^{20}$ −43 (*c* 2.4, $CHCl_3$) **^{1}H NMR (500 MHz, $CDCl_3$)** *δ* 1.20 (d, *J* = 6.1 Hz, 3H), 1.33 (s, 6H), 1.48 (dt, *J* = 13.9 and 6.2 Hz, 1H), 1.51−1.58 (m, 2H), 1.94 (dt, *J* = 14.0 and 6.9 Hz, 1H), 2.16 (dt, *J* = 14.0 and 6.8 Hz, 1H), 2.28 (dt, *J* = 14.0 and 6.9 Hz, 1H), 3.62 (sext, *J* = 6.3 Hz, 1H), 3.80 (s, 3H), 3.81−3.87 (m, 1H), 3.90−3.96 (m, 1H), 4.36 (d, *J* = 11.3 Hz, 1H), 4.49 (d, *J* = 11.3 Hz, 1H), 5.03−5.10 (m, 2H), 5.78 (ddt, *J* = 17.1, 10.2 and 6.8 Hz, 1H), 6.86−6.89 (m, 2H), 7.25−7.26 (m, 2H). **^{13}C NMR (125 MHz, $CDCl_3$)** *δ* 19.5, 24.8, 24.8, 38.0, 40.1, 42.8, 55.2, 63.7, 66.1, 69.9, 71.1, 100.2, 113.7, 116.8, 129.3, 131.0, 134.4, 159.1. **IR (film)** ν_{max}/cm^{-1} 3074, 2984, 2937, 2837, 1643, 1614, 1587, 1514, 1464, 1443, 1379, 1302, 1248, 1225, 1173, 1117, 1036, 995, 947, 912, 822, 754. **HRMS (ESI TOF-MS)** *m*/*z* calcd for $C_{20}H_{30}O_4Na$ $[M + Na]^+$: 357.2042, found: 357.2037.

(−)-(*R*)-1-((2*R*,4*S*,6*R*)-2-(4-methoxyphenyl)-6-methyl-1,3-dioxan-4-yl)pent-4-en-2-ol (50): To a solution of diol **48** (52 mg, 0.18 mmol, 100 mol%) in CH_2Cl_2 (3.8 mL, 0.05 M) at room

temperature was added activated 4 Å molecular sieves (56 mg). After 15 min, the mixture was cooled to −10 ºC, and DDQ (51 mg, 0.22 mmol, 120 mol%) was added. The reaction medium was stirred for 5 min at −10 ºC and warmed to 0 ºC. After 1.5 h, the reaction mixture was loaded directly onto a flash column chromatography using a solution of hexane/ethyl acetate (60:40) as the eluent to provide the PMP acetal **50** (32 mg, 0.11 mmol, 60%) as a pale yellow oil. **TLC:** R_f = 0.57 (60:40 hexane:EtOAc) **Optical rotation:** $[\alpha]_D^{20}$ −35 (*c* 3.2, $CHCl_3$) **^{1}H NMR (500 MHz, $CDCl_3$)** δ 1.30 (d, *J* = 6.1 Hz, 3H), 1.50 (dt, *J* = 13.1 and 10.7 Hz, 1H), 1.56 (dt, *J* = 13.1 and 2.7 Hz, 1H), 1.66 (ddd, *J* = 14.5, 9.3 and 3.4 Hz, 1H), 1.76 (ddd, *J* = 14.5, 8.2 and 2.6 Hz, 1H), 2.19−2.30 (m, 2H), 2.39 (br s, 1H), 3.78 (s, 3H), 3.92−3.97 (m, 1H), 3.99−4.03 (m, 1H), 4.10−4.15 (m, 1H), 5.10−5.14 (m, 2H), 5.49 (s, 1H), 5.82 (ddt, *J* = 17.2, 10.3 and 7.2 Hz, 1H), 6.86−6.88 (m, 2H), 7.40−7.42 (m, 2H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 21.6, 38.4, 42.0, 42.2, 55.2, 67.0, 72.9, 74.0, 100.7, 113.6, 117.9, 127.4, 131.2, 134.7, 159.8. **IR (film)** ν_{max}/cm^{-1} 3439, 3076, 2974, 2935, 2914, 2851, 1641, 1616, 1589, 1518, 1340, 1304, 1250, 1155, 1111, 1061, 1034, 1011, 912, 825, 775, 737. **HRMS (ESI FTMS)** *m*/*z* calcd for $C_{17}H_{25}O_4$ $[M + H]^+$: 293.1747, found: 293.1746.

(−)-(5*R*,7*R*)-5-allyl-7-((*S*)-2-((4-methoxybenzyl)oxy)propyl)-2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecane (51): To a solution of diol **48** (1.19 g, 4.04 mmol, 100 mol%) in CH_2Cl_2 (58 mL, 0.07 M) at 0 °C were added 2,6-lutidine (2.82 mL, 24.2 mmol, 600 mol%) and TBSOTf (2.8 mL, 12.1 mmol, 300 mol%) dropwise. After 1.5 h, the reaction was quenched by the addition of saturated aqueous solution of $NaHCO_3$ (30 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography using a solution of hexane/ethyl acetate (90:10) as the eluent to provide compound **51** (1.93 g, 3.69 mmol, 91%) as a colorless oil. **TLC:** R_f = 0.81 (90:10 hexane:EtOAc) **Optical rotation:** $[\alpha]_D^{20}$ −12 (*c* 2.4, $CHCl_3$) **^{1}H NMR (250 MHz, $CDCl_3$)** δ 0.02 (s, 3H), 0.05 (s, 9H), 0.85 (s, 9H), 0.87 (s, 9H), 1.18 (d, *J* = 6.0 Hz, 3H), 1.48 (dt, *J* = 13.8 and 6.1 Hz, 1H), 1.60−1.65 (m, 2H), 1.86 (dt, *J* = 13.8 and 6.4 Hz, 1H), 2.12−2.31 (m, 2H), 3.63 (sext, *J* = 6.2 Hz, 1H), 3.79 (s, 3H), 3.79−3.93 (m, 2H), 4.38 (d, *J* = 11.3 Hz, 1H), 4.47 (d, *J* = 11.3 Hz, 1H), 5.00−5.06 (m, 2H), 5.81 (ddt, *J* = 17.8, 9.5 and 7.0 Hz, 1H), 6.83−6.87 (m, 2H), 7.24−7.27 (m, 2H). **^{13}C NMR (62.5 MHz, $CDCl_3$)** δ −4.3,

−4.1, −4.0, −3.9, 18.0, 18.1, 19.8, 25.9 (2 × $(CH_3)_3$), 42.3, 45.2, 45.5, 55.2, 67.5, 69.5, 69.9, 71.7, 113.7, 116.9, 129.1, 131.1, 135.0, 159.0. **IR (film)** ν_{max}/cm^{-1} 3076, 2955, 2930, 2888, 2857, 1614, 1514, 1472, 1463, 1374, 1249, 1061, 913, 836, 774. **HRMS (ESI TOF-MS)** *m*/*z* calcd for $C_{29}H_{54}O_4Si_2Na$ $[M + Na]^+$: 545.3458, found: 545.3439.

(+)-(2*R*,4*R*,6*R*)-4,6-bis((*tert*-butyldimethylsilyl)oxy)non-8-en-2-ol (52): To a solution of PMB ether **51** (7.40 g, 14.1 mmol, 100 mol%) in CH_2Cl_2:phosphate buffer pH 7 (9:1) (235 mL, 0.06 M) at 0 ºC was added DDQ (3.84 g, 16.9 mmol, 120 mol%). The mixture was stirred for 1 h under the same conditions, followed by quenching via the addition of a solution of H_2O:saturated aqueous solution of $NaHCO_3$ (1:1) (60 mL). The resulting mixture was filtered over Celite, washed with CH_2Cl_2 (5 × 100 mL) and concentrated under reduced pressure. The residue was purified by flash column chromatography using hexane/ethyl acetate (90:10) as the eluent to provide alcohol **52** (5.50 g, 13.7 mmol, 97%) as a pale yellow oil. **TLC:** R_f = 0.59 (90:10 hexane:EtOAc) **Optical rotation:** $[\alpha]_D^{20}$ +11 (*c* 2.3, $CHCl_3$) **^{1}H NMR (500 MHz, $CDCl_3$)** δ 0.05 (s, 3H), 0.05 (s, 3H), 0.08 (s, 3H), 0.09 (s, 3H), 0.87 (s, 9H), 0.88 (s, 9H), 1.16 (d, *J* = 6.3 Hz, 3H), 1.52 (dt, *J* = 14.2 and 8.9 Hz, 1H), 1.58−1.74 (m, 3H), 2.12−2.24 (m, 2H), 3.11 (br s, 1H), 3.74 (quint, *J* = 6.1 Hz, 1H), 3.87−3.95 (m, 2H), 5.02−5.06 (m, 2H), 5.75−5.83 (m, 1H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ −4.5, −4.4, −4.2, −3.8, 17.9, 18.0, 23.5, 25.8, 25.8, 42.0, 45.9 (2 × CH_2), 67.0, 69.7, 71.4, 117.3, 134.6. **IR (film)** ν_{max}/cm^{-1} 3445, 3078, 2957, 2931, 2896, 2858, 1642, 1473, 1463, 1362, 1256, 1070, 1005, 913, 836, 807, 774. **HRMS (ESI TOF-MS)** *m*/*z* calcd for $C_{21}H_{47}O_3Si_2$ $[M + H]^+$: 403.3064, found: 403.3055.

(+)-(4*S*,6*R*)-4,6-bis((*tert*-butyldimethylsilyl)oxy)non-8-en-2-one (15): To a solution of oxalyl chloride (1.42 mL, 16.5 mmol, 120 mol%) in CH_2Cl_2 (80 mL, 0.21 M) at −78 ºC was added DMSO (2.34 mL, 33.0 mmol, 240 mol%) dropwise. The reaction medium was stirred for 30 min, followed by the dropwise addition of a solution of alcohol **52** (5.50 g, 13.7 mmol, 100 mol%) in CH_2Cl_2 (33 mL, 0.42 M). After 30 min, Et_3N (11.5 mL, 82.5 mmol, 600 mol%) was added dropwise, and the resulting slurry was warmed to 0 ºC and stirred for 1 h. The reaction was then diluted with Et_2O (100 mL) and saturated aqueous solution of NH_4Cl (100 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with H_2O (3 × 100 mL), brine (100 mL), dried over $MgSO_4$, filtered, and concentrated

under reduced pressure. The residue was purified by flash column chromatography using hexane/ethyl acetate (90:10) as the eluent to provide methylketone **15** (5.23 g, 13.1 mmol, 95%) as a colorless oil. **TLC:** R_f = 0.68 (90:10 hexane:EtOAc) **Optical rotation:** $[\alpha]_D^{20}$ +1 (*c* 2.7, $CHCl_3$) **^{1}H NMR (500 MHz, $CDCl_3$)** δ 0.01 (s, 3H), 0.05 (s, 3H), 0.06 (s, 6H), 0.84 (s, 9H), 0.87 (s, 9H), 1.54 (dt, *J* = 13.7 and 6.8 Hz, 1H), 1.66 (dt, *J* = 13.7 and 5.8 Hz, 1H), 2.13 (s, 3H), 2.16−2.26 (m, 2H), 2.51 (dd, *J* = 15.0 and 5.0 Hz, 1H), 2.59 (dd, *J* = 15.0 and 7.1 Hz, 1H), 3.76 (quint, *J* = 6.0 Hz, 1H), 4.21 (quint, *J* = 6.2 Hz, 1H), 5.02−5.05 (m, 2H), 5.78 (ddt, *J* = 17.7, 9.5 and 7.1 Hz, 1H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ −4.4 (2 × CH_3), −4.3, −4.1, 18.0, 18.0, 25.8, 25.9, 31.5, 42.2, 45.3, 51.9, 67.2, 69.6, 117.2, 134.6, 207.5. **IR (film)** ν_{max}/cm^{-1} 3079, 2956, 2930, 2896, 2858, 1721, 1642, 1473, 1464, 1361, 1256, 1092, 1005, 914, 836, 775. **HRMS (ESI TOF-MS)** *m*/*z* calcd for $C_{21}H_{45}O_3Si_2$ $[M + H]^+$: 401.2907, found: 401.2891.

(6*S*,8*R*)-8-allyl-6-((*tert*-butyldimethylsilyl)oxy)-2,2,10,10,11,11-hexamethyl-4-methylene-3,9-dioxa-2,10-disiladodecane (53): To a solution of methylketone **15** (1.0 g, 2.50 mmol, 100 mol%) in CH_2Cl_2 (20 mL, 0.12 M) at room temperature was added Et_3N (1.0 mL, 7.50 mmol, 300 mol%). After 5 min, the reaction medium was cooled to −20 ºC and TMSOTf (1.0 mL, 5.00 mmol, 200 mol%) was added dropwise. After 30 min, the reaction was diluted with Et_2O (20 mL), transferred to a separatory funnel, washed with saturated aqueous solution of $NaHCO_3$ (10 mL), brine (10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to provide the enolsilane **53** (1.18 g, 2.50 mmol, 99%), which was used in the next step without further purification, as a yellow oil. **TLC:** R_f = 0.81 (95:05 hexane:EtOAc) **^{1}H NMR (250 MHz, C_6D_6)** δ 0.13 (s, 3H), 0.17 (s, 6H), 0.19 (s, 3H), 0.21 (s, 9H), 1.02 (s, 18H), 1.77 (ddd, *J* = 14.1, 8.1 and 4.4 Hz, 1H), 1.93 (ddd, *J* = 14.1, 7.4 and 4.1 Hz, 1H), 2.22 (dd, *J* = 13.5 and 7.6 Hz, 1H), 2.33−2.38 (m, 2H), 2.44 (dd, *J* = 13.5 and 5.4 Hz, 1H), 4.03−4.12 (m, 1H), 4.14−4.15 (m, 2H), 4.23−4.33 (m, 1H), 5.06−5.14 (m, 2H), 5.94 (ddt, *J* = 17.2, 10.1 and 7.0 Hz, 1H).

(+)-(*R*)-methyl 3,4-bis((*tert*-butyldimethylsilyl)oxy)butanoate (56a): To a solution of compound **55a**[34] (500 mg, 2.01 mmol, 100 mol%) in CH_2Cl_2 (27 mL, 0.07 M) at 0 °C were added 2,6-lutidine (0.70 mL, 6.00 mmol, 300 mol%) and TBSOTf (0.69 mL, 3.00 mmol, 150 mol%) dropwise. After 1 h, the reaction was quenched by the addition of saturated aqueous solution of $NaHCO_3$ (20 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2

(3 × 20 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography using a solution of hexane/ethyl acetate (90:10) as the eluent to provide known compound **56a**[64] (701 mg, 1.93 mmol, 96%) as a pale yellow oil. **TLC:** R_f = 0.73 (90:10 hexane:EtOAc) **Optical rotation:** $[\alpha]_D^{20}$ +30 (*c* 0.9, $CHCl_3$) **^{1}H NMR (500 MHz, $CDCl_3$)** δ 0.03 (s, 3H), 0.03 (s, 6H), 0.05 (s, 3H), 0.84 (s, 9H), 0.87 (s, 9H), 2.36 (dd, *J* = 14.6 and 8.3 Hz, 1H), 2.63 (dd, *J* = 14.6 and 4.3 Hz, 1H), 3.38 (dd, *J* = 9.8 and 7.3 Hz, 1H), 3.58 (dd, *J* = 9.8 and 5.2 Hz, 1H), 3.65 (s, 3H), 4.10−4.15 (m, 1H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ −5.4, −5.4, −5.1, −4.5, 18.0, 18.3, 25.7, 25.9, 40.0, 51.4, 66.9, 70.3, 172.4. **IR (film)** ν_{max}/cm^{-1} 2955, 2930, 2896, 2858, 1744, 1473, 1437, 1362, 1257, 1172, 1121, 1085, 1006, 837, 778.

(+)-(*R*)-3,4-bis((*tert*-butyldimethylsilyl)oxy)butan-1-ol (57a): To a solution of ester **56a** (671 mg, 1.85 mmol, 100 mol%) in hexane (4.0 mL, 0.46 M) at −78 ºC was added DIBAL-H (4.7 mL, 4.7 mmol, 1 M in hexane, 250 mol%) over 40 min using a syringe pump. After 30 min, the reaction was quenched by the addition of saturated aqueous solution of potassium sodium tartrate (17 mL), warmed to room temperature and stirred for 3 h. After this period, the layers were separated, and the aqueous layer was extracted with Et_2O (3 × 25 mL). The combined organic layers were washed with brine (25 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography using hexane/ethyl acetate (90:10) as the eluent to provide alcohol **57a**[37] (484 mg, 1.45 mmol, 78%) as a colorless oil. **TLC:** R_f = 0.50 (90:10 hexane:EtOAc) **Optical rotation:** $[\alpha]_D^{20}$ +20 (*c* 0.9, $CHCl_3$) **^{1}H NMR (500 MHz, $CDCl_3$)** δ 0.05 (s, 3H), 0.05 (s, 3H), 0.06 (s, 3H), 0.08 (s, 3H), 0.87 (s, 9H), 0.88 (s, 9H), 1.70−1.76 (m, 1H), 1.87 (ddt, *J* = 14.4, 8.0 and 4.9 Hz, 1H), 2.72 (br s, 1H), 3.49 (dd, *J* = 10.1 and 7.2 Hz, 1H), 3.60 (dd, *J* = 10.1 and 4.9 Hz, 1H), 3.72−3.78 (m, 2H), 3.84−3.89 (m, 1H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ −5.5, −5.4, −5.0, −4.5, 18.0, 18.3, 25.8, 25.9, 36.7, 59.7, 66.8, 72.2. **IR (film)** ν_{max}/cm^{-1} 3414, 2955, 2930, 2886, 2858, 1638, 1472, 1464, 1256, 1094, 1026, 1006, 836, 777.

(+)-(*R*)-3,4-bis((*tert*-butyldimethylsilyl)oxy)butanal (14a): To a solution of oxalyl chloride (0.17 mL, 2.00 mmol, 150 mol%) in CH_2Cl_2 (8.0 mL, 0.25 M) at −78 ºC was added DMSO (0.28 mL, 4.00 mmol, 300 mol%) dropwise. The reaction medium was stirred for 30 min, followed by

the dropwise addition of a solution of alcohol **57a** (454 mg, 1.36 mmol, 100 mol%) in CH_2Cl_2 (3.5 mL, 0.39 M). After 30 min, Et_3N (1.4 mL, 10.0 mmol, 730 mol%) was added dropwise, and the resulting slurry was warmed to 0 ºC and stirred for 1 h. The reaction was then diluted with Et_2O (25 mL) and saturated aqueous solution of NH_4Cl (25 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 25 mL). The combined organic layers were washed with H_2O (3 × 25 mL), brine (50 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to provide the aldehyde **14a** (426 mg, 1.28 mmol, 94%), which was used in the next step without further purification, as a pale yellow oil. **TLC:** R_f = 0.76 (90:10 hexane:EtOAc) **Optical rotation:** $[\alpha]_D^{20}$ +14 (*c* 2.4, $CHCl_3$) **^{1}H NMR (500 MHz, $CDCl_3$)** δ 0.04 (s, 3H), 0.04 (s, 3H), 0.06 (s, 3H), 0.07 (s, 3H), 0.85 (s, 9H), 0.87 (s, 9H), 2.50 (ddd, *J* = 15.8, 6.5 and 2.4 Hz, 1H), 2.62 (ddd, *J* = 15.8, 5.1 and 2.4 Hz, 1H), 3.44 (dd, *J* = 9.9 and 7.0 Hz, 1H), 3.62 (dd, *J* = 9.9 and 4.9 Hz, 1H), 4.16−4.21 (m, 1H), 9.80 (t, *J* = 2.4 Hz, 1H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ −5.5, −5.5, −5.0, −4.4, 18.0, 18.3, 25.7, 25.8, 48.8, 67.0, 69.0, 201.8. **IR (film)** ν_{max}/cm^{-1} 2956, 2930, 2887, 2859, 2714, 1730, 1634, 1473, 1389, 1362, 1257, 1101, 1006, 836, 778, 669. **HRMS (ESI TOF-MS)** *m*/*z* calcd for $C_{16}H_{36}O_3Si_2Na$ $[M + Na]^+$: 355.2101, found: 355.2099.

(+)-(*R*)-3-((*tert*-butyldimethylsilyl)oxy)-4-(trityloxy)butanal (14b): To a solution of oxalyl chloride (0.50 mL, 5.80 mmol, 150 mol%) in CH_2Cl_2 (23 mL, 0.25 M) at −78 ºC was added DMSO (0.82 mL, 11.6 mmol, 300 mol%) dropwise. The reaction medium was stirred for 30 min, followed by the dropwise addition of a solution of alcohol **57b**[36] (1.80 g, 3.89 mmol, 100 mol%) in CH_2Cl_2 (10 mL, 0.39 M). After 30 min, Et_3N (4.0 mL, 29.0 mmol, 750 mol%) was added dropwise, and the resulting slurry was warmed to 0 ºC and stirred for 1 h. The reaction was then diluted with Et_2O (50 mL) and saturated aqueous solution of NH_4Cl (25 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with H_2O (3 × 50 mL), brine (50 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to provide the aldehyde **14b** (1.77 g, 3.85 mmol, 99%), which was used in the next step without further purification, as a white solid. **TLC:** R_f = 0.33 (95:05 hexane:EtOAc) **mp** 70−72 °C **Optical rotation:** $[\alpha]_D^{20}$ +10 (*c* 1.3, $CHCl_3$) **^{1}H NMR (500 MHz, C_6D_6)** δ −0.05 (s, 3H), −0.01 (s, 3H), 0.88 (s, 9H), 2.38 (ddd, *J* = 16.0, 6.6 and 2.0 Hz, 1H), 2.44 (ddd, *J* = 16.0, 4.8 and 2.0 Hz, 1H), 3.15 (dd, *J* = 9.3 and 6.6 Hz, 1H), 3.22 (dd, *J* = 9.3 and 4.8 Hz, 1H), 4.17 (tt, *J* = 6.6 and 4.8 Hz, 1H), 7.03 (t, *J* = 7.3 Hz, 3H), 7.12 (t, *J* = 7.3 Hz, 6H), 7.50−7.52 (m, 6H), 9.53 (t, *J* =

2.0 Hz, 1H). **^{13}C NMR (125 MHz, C_6D_6)** δ −4.9, −4.4, 18.1, 25.9, 49.3, 67.8, 67.8, 87.3, 127.3, 128.1, 129.1, 144.4, 199.7. **IR (film)** ν_{max}/cm^{-1} 3087, 3060, 3033, 3024, 2955, 2929, 2885, 2857, 2724, 1727, 1648, 1634, 1491, 1472, 1449, 1254, 1088, 1077, 1016, 836, 776, 762, 746, 706, 632. **HRMS (ESI FT-ICR-MS)** *m*/*z* calcd for $C_{30}H_{40}O_4SiNa$ [M + Na + MeOH]$^+$: 515.2594, found: 515.2584.

(+)-(5*R*,7*S*,11*R*,13*R*)-5-allyl-7,13-bis((*tert*-butyldimethylsilyl)oxy)-11-hydroxy-2,2,3,3,16,16,17,17-octamethyl-4,15-dioxa-3,16-disilaoctadecan-9-one (58a): To a solution of enolsilane **53** (118 mg, 0.25 mmol, 100 mol%) and aldehyde **14a** (125 mg, 0.38 mmol, 150 mol%) in CH_2Cl_2 (3.2 mL, 0.08 M) at −78 °C was added $BF_3.Et_2O$ (0.05 mL, 0.38 mmol, 150 mol%) dropwise. After 1 h, the reaction was quenched by the addition of saturated aqueous solution of $NaHCO_3$ (5 mL) and warmed to room temperature. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography using hexane/ethyl acetate (95:05) as the eluent to provide aldol adduct **58a** (132 mg, 0.18 mmol, 72%, *dr* = 80:20, 1,3-*anti*:1,3-*syn*) as a colorless oil. Diastereoisomeric ratio was determined by ^{1}H NMR analysis of the diastereoisomeric mixture of compounds. **TLC:** R_f = 0.48 (95:05 hexane:EtOAc)
Optical rotation: $[\alpha]_D^{20}$ +4 (*c* 1.5, $CHCl_3$) **^{1}H NMR (600 MHz, $CDCl_3$)** δ 0.02 (s, 3H), 0.04 (s, 3H), 0.05 (s, 3H), 0.05 (s, 3H), 0.05 (s, 6H), 0.07 (s, 3H), 0.09 (s, 3H), 0.84 (s, 9H), 0.87 (s, 18H), 0.88 (s, 9H), 1.49−1.56 (m, 2H), 1.64−1.69 (m, 2H), 2.16−2.26 (m, 2H), 2.53−2.56 (m, 3H), 2.60 (dd, *J* = 15.2 and 7.2 Hz, 1H), 3.48 (dd, *J* = 10.1 and 6.8 Hz, 1H), 3.55 (d, *J* = 2.4 Hz, 1H), 3.58 (dd, *J* = 10.1 and 5.3 Hz, 1H), 3.76 (quint, *J* = 5.8 Hz, 1H), 3.92−3.96 (m, 1H), 4.19−4.23 (m, 1H), 4.24−4.28 (m, 1H), 5.03−5.05 (m, 2H), 5.78 (ddt, *J* = 17.7, 9.7 and 7.0 Hz, 1H). **^{13}C NMR (150 MHz, $CDCl_3$)** δ −5.4, −5.4, −4.9, −4.4, −4.4 (2 × CH_3), −4.3, −4.1, 17.9, 18.0 (2 × C_0), 18.3, 25.8, 25.9, 25.9, 25.9, 40.7, 42.2, 45.2, 51.6, 51.7, 64.3, 66.9, 67.2, 69.6, 70.9, 117.2, 134.6, 209.6. **IR (film)** ν_{max}/cm^{-1} 3467, 3078, 2955, 2930, 2895, 2858, 1709, 1642, 1473, 1388, 1369, 1256, 1096, 939, 914, 836, 776, 667. **HRMS (ESI TOF-MS)** *m*/*z* calcd for $C_{37}H_{81}O_6Si_4$ [M + H]$^+$: 733.5110, found: 733.5134.

(+)-(5*R*,7*S*,11*R*,13*R*)-5-allyl-7-((*tert*-butyldimethylsilyl)oxy)-11-hydroxy-2,2,3,3,15,15,16,16-octamethyl-13-((trityloxy)methyl)-4,14-dioxa-3,15-disilaheptadecan-9-one (58b): To a solution of enolsilane **53** (946 mg, 2.00 mmol, 100 mol%) and aldehyde **14b** (1.13 g, 2.46 mmol, 125 mol%) in CH_2Cl_2 (25 mL, 0.08 M) at −78 °C was added $BF_3.Et_2O$ (0.30 mL, 2.40 mmol, 120 mol%) dropwise. After 1 h, the reaction was quenched by the addition of phosphate buffer pH 7 (10 mL) and warmed to room temperature. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography using hexane/ethyl acetate (90:10) as the eluent to provide aldol adduct **58b** (1.48 g, 1.72 mmol, 86%, *dr* = 79:21, 1,3-*anti*:1,3-*syn*) as a colorless oil. Diastereoisomeric ratio was determined by ^{13}C NMR analysis of the diastereoisomeric mixture of compounds. **TLC:** R_f = 0.49 (90:10 hexane:EtOAc) **Optical rotation:** $[\alpha]_D^{20}$ +6 (*c* 1.0, $CHCl_3$) **^{1}H NMR (500 MHz, $CDCl_3$)** δ −0.08 (s, 3H), 0.02 (s, 3H), 0.03 (s, 3H), 0.06 (s, 9H), 0.81 (s, 9H), 0.84 (s, 9H), 0.87 (s, 9H), 1.51−1.61 (m, 2H), 1.65−1.70 (m, 1H), 1.77 (ddd, *J* = 13.6, 10.4 and 3.0 Hz, 1H), 2.16−2.27 (m, 2H), 2.49−2.63 (m, 4H), 3.04 (dd, *J* = 9.2 and 6.8 Hz, 1H), 3.12 (dd, *J* = 9.2 and 4.7 Hz, 1H), 3.38−3.40 (m, 1H), 3.77 (quint, *J* = 5.8 Hz, 1H), 4.05−4.10 (m, 1H), 4.20−4.25 (m, 2H), 5.03−5.06 (m, 2H), 5.75−5.83 (m, 1H), 7.22 (t, *J* = 7.5 Hz, 3H), 7.28 (t, *J* = 7.5 Hz, 6H), 7.44 (d, *J* = 7.5 Hz, 6H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ −5.0, −4.6, −4.4 (2 × CH_3), −4.3, −4.1, 17.9, 18.0, 18.0, 25.8, 25.8, 25.9, 40.9, 42.2, 45.2, 51.5, 51.6, 64.1, 66.9, 67.2, 69.1, 69.6, 86.6, 117.2, 126.9, 127.7, 128.7, 134.6, 144.0, 209.8. **IR (film)** ν_{max}/cm^{-1} 3449, 3087, 3062, 3034, 2954, 2929, 2888, 2857, 1706, 1641, 1472, 1256, 1076, 836, 775, 706, 633. **HRMS (ESI FT-ICR-MS)** *m*/*z* calcd for $C_{50}H_{80}O_6Si_3Na$ $[M + Na]^+$: 883.5160, found: 883.5152.

(+)-(6*R*,8*S*,10*R*,12*R*,14*R*)-14-allyl-6,12-bis((*tert*-butyldimethylsilyl)oxy)-2,2,3,3,16,16,17,17-octamethyl-4,15-dioxa-3,16-disilaoctadecane-8,10-diol (59): To a solution of aldol adduct **58b** (100 mg, 0.14 mmol, 100 mol%) in THF:MeOH (4:1) (0.68 mL, 0.21 M) at −78 ºC was added Et_2BOMe (0.02 mL, 0.16 mmol, 114 mol%). The solution was stirred for 15 min under these conditions, and $LiBH_4$ (0.08 mL, 0.16 mmol, 2.0 M in THF, 114 mol%) was added. The reaction was stirred for 1 h and then warmed to −40 ºC. The reaction was quenched by the addition of pH 7 phosphate buffer (1.7 mL) and MeOH (3.3 mL). The reaction was warmed to 0 ºC, and

30% H_2O_2 (1.3 mL) was added dropwise. After 1 h, the volatiles were removed under reduced pressure and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with saturated aqueous solution of $NaHCO_3$ (10 mL), brine (10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography using hexane/ethyl acetate (95:05) as the eluent to provide diol **59** (61 mg, 84 μmol, 62%, *dr* > 95:05, 1,3-*syn*:1,3-*anti*) as a colorless oil. **TLC:** R_f = 0.38 (95:05 hexane:EtOAc) **Optical rotation:** $[\alpha]_D^{20}$ +8 (*c* 0.6, $CHCl_3$) **^{1}H NMR (500 MHz, $CDCl_3$)** δ 0.05 (s, 12H), 0.06 (s, 3H), 0.07 (s, 3H), 0.07 (s, 3H), 0.09 (s, 3H), 0.87 (s, 9H), 0.87 (s, 9H), 0.88 (s, 9H), 0.88 (s, 9H), 1.46−1.77 (m, 8H), 2.13−2.19 (m, 1H), 2.21−2.26 (m, 1H), 3.52 (dd, *J* = 10.1 and 7.3 Hz, 1H), 3.60 (dd, *J* = 10.1 and 5.3 Hz, 1H), 3.78 (quint, *J* = 5.9 Hz, 1H), 3.87−4.12 (m, 6H), 5.02−5.05 (m, 2H), 5.80 (ddt, *J* = 17.8, 9.4 and 7.1 Hz, 1H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ −5.4, −5.4, −5.0, −4.5, −4.3, −4.2, −4.2, −3.9, 18.0, 18.0, 18.1, 18.3, 25.8, 25.9 (2 × $(CH_3)_3$), 25.9, 41.4, 42.1, 44.3, 45.0, 45.6, 66.6, 69.0, 69.5, 69.7, 70.2, 71.8, 117.0, 134.9. **IR (film)** ν_{max}/cm^{-1} 3468, 3078, 2955, 2930, 2897, 2858, 1642, 1472, 1463, 1256, 1101, 836, 775. **HRMS (ESI TOF-MS)** *m*/*z* calcd for $C_{37}H_{83}O_6Si_4$ $[M + H]^+$: 735.5267, found: 735.5273.

(+)-(5*R*,7*R*)-5-allyl-7-(((4*R*,6*S*)-6-((*R*)-2,3-bis((*tert*-butyldimethylsilyl)oxy)propyl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecane (60): To a solution of diol **59** (10 mg, 13.6 μmol, 100 mol%) in 2,2-DMP (0.2 mL, 0.07 M) at room temperature was added of PPTS (1 crystal). After 24 h, the reaction mixture was loaded directly onto a flash column chromatography using a solution of hexane/ethyl acetate (90:10) as the eluent to provide the acetonide **60** (7 mg, 8.51 μmol, 63%) as a colorless oil. **TLC:** R_f = 0.80 (90:10 hexane:EtOAc) **Optical rotation:** $[\alpha]_D^{20}$ +8 (*c* 0.7, $CHCl_3$) **^{1}H NMR (600 MHz, $CDCl_3$)** δ 0.03 (s, 6H), 0.04 (s, 3H), 0.04 (s, 3H), 0.05 (s, 3H), 0.05 (s, 6H), 0.06 (s, 3H), 0.86 (s, 9H), 0.87 (s, 9H), 0.87 (s, 9H), 0.88 (s, 9H), 1.12 (q, *J* = 12.0 Hz, 1H), 1.33 (s, 3H), 1.38−1.46 (m, 3H), 1.40 (s, 3H), 1.50−1.72 (m, 4H), 2.15−2.20 (m, 1H), 2.24 (dt, *J* = 13.8 and 6.4 Hz, 1H), 3.42 (dd, *J* = 10.2 and 5.8 Hz, 1H), 3.52 (dd, *J* = 10.2 and 5.2 Hz, 1H), 3.75−4.05 (m, 5H), 5.02−5.04 (m, 2H), 5.80 (ddt, *J* = 17.6, 9.5 and 7.0 Hz, 1H). **^{13}C NMR (150 MHz, $CDCl_3$)** δ −5.3 (2 × CH_3), −4.7, −4.3, −4.0, −4.0, −3.9 (2 × CH_3), 18.0, 18.1, 18.1, 18.4, 20.2, 25.9 (2 × $(CH_3)_3$), 25.9, 26.0, 30.2, 38.0, 42.2, 42.4, 44.6, 45.2, 65.2, 65.9, 66.6, 68.0, 69.3, 69.5, 98.3, 116.9, 135.0. **IR (film)** ν_{max}/cm^{-1} 3078, 2992, 2955, 2929, 2858, 1746, 1642, 1473, 1463, 1379, 1256,

1200, 1102, 835, 775. **HRMS (ESI FT-ICR-MS)** *m*/*z* calcd for $C_{40}H_{86}O_6Si_4Na$ $[M + Na]^+$: 797.5399, found: 797.5393.

(+)-(2*R*,4*S*,6*S*,8*S*,10*R*)-tridec-12-ene-1,2,4,6,8,10-hexaol (61): To a solution of diol **59** (40 mg, 54.4 µmol, 100 mol%) in THF (1.0 mL, 0.05 M) at 0 °C, was added HF.pyridine (4 drops). The reaction medium was stirred for 5 min at 0 ºC and warmed to room temperature. After 24 h, the reaction medium was cooled to 0 °C and quenched by the addition of TMSOMe (0.20 mL). The reaction medium was stirred for 5 min at 0 ºC and 15 min at room temperature. After this period, the volatiles were removed under reduced pressure to provide the hexaol **61** (15 mg, 53.9 µmol, 99%) as a white solid. **TLC:** R_f = 0.38 (80:20 $CHCl_3$:MeOH) **Optical rotation:** $[\alpha]_D^{20}$ +3 (*c* 0.76, MeOH) **^{1}H NMR (500 MHz, MeOD-*d*$_4$)** δ 1.51−1.54 (m, 8H), 2.19−2.25 (m, 2H), 3.42−3.49 (m, 2H), 3.82−3.90 (m, 2H), 3.95−4.08 (m, 3H), 5.02−5.08 (m, 2H), 5.85 (ddt, *J* = 17.2, 10.1 and 7.2 Hz, 1H). **^{13}C NMR (125 MHz, MeOD-*d*$_4$)** δ 41.9, 43.8, 45.0, 45.9, 46.0, 67.9, 68.0, 68.1, 68.7, 70.1, 70.1, 117.3, 136.4. **IR (film)** ν_{max}/cm^{-1} 3435, 2921, 2852, 1640, 1435, 1337, 1092, 749. **HRMS (ESI TOF-MS)** *m*/*z* calcd for $C_{13}H_{27}O_6$ $[M + H]^+$: 279.1808, found: 279.1828.

(+)-(5*R*,7*S*,11*R*,13*R*)-5-allyl-7,11,13-tris((*tert*-butyldimethylsilyl)oxy)-2,2,3,3,16,16,17,17-octamethyl-4,15-dioxa-3,16-disilaoctadecan-9-one (62a): To a solution of aldol adduct **58a** (132 mg, 0.18 mmol, 100 mol%) in CH_2Cl_2 (2.4 mL, 0.08 M) at 0 °C were added 2,6-lutidine (0.06 mL, 0.54 mmol, 300 mol%) and TBSOTf (0.06 mL, 0.27 mmol, 150 mol%) dropwise. After 1 h, the reaction was quenched by the addition of saturated aqueous solution of $NaHCO_3$ (5 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography using a solution of hexane/ethyl acetate (95:05) as the eluent to provide compound **62a** (140 mg, 0.16 mmol, 89%) as a colorless oil. **TLC:** R_f = 0.68 (95:05 hexane:EtOAc) **Optical rotation:** $[\alpha]_D^{20}$ +2 (*c* 2.2, $CHCl_3$) **^{1}H NMR (500 MHz, $CDCl_3$)** δ 0.01 (s, 3H), 0.03 (s, 3H), 0.03 (s, 3H), 0.03 (s, 3H), 0.05 (s, 3H), 0.06 (s, 6H), 0.06 (s, 3H), 0.07 (s, 6H), 0.84 (s, 9H), 0.84 (s, 9H), 0.87 (s, 27H), 1.48 (ddd, *J* = 13.6, 7.1 and 6.1 Hz, 1H), 1.54−1.58 (m, 1H), 1.63 (dt, *J* = 13.6 and 6.1 Hz, 1H), 1.74 (ddd, *J* = 13.8, 6.4 and 4.7 Hz, 1H), 2.15−2.26 (m, 2H), 2.50 (dd, *J* = 15.6 and 5.5 Hz, 1H), 2.55−2.61 (m, 3H), 3.38 (dd, *J* = 10.1 and 6.0 Hz, 1H),

3.52 (dd, *J* = 10.1 and 5.3 Hz, 1H), 3.71−3.78 (m, 2H), 4.21 (quint, *J* = 6.2 Hz, 1H), 4.29 (quint, *J* = 6.1 Hz, 1H), 5.02−5.05 (m, 2H), 5.74−5.82 (m, 1H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ −5.4, −5.3, −4.5, −4.3, −4.3 (2 × CH_3), −4.2 (2 × CH_3), −4.1, −3.9, 18.0, 18.0, 18.1, 18.1, 18.4, 25.9 (2 × $(CH_3)_3$), 25.9, 26.0, 26.0, 42.2, 43.3, 45.4, 52.2, 52.6, 66.8, 66.8, 67.8, 69.5, 71.1, 117.1, 134.8, 207.2. **IR (film)** ν_{max}/cm^{-1} 3079, 2956, 2930, 2889, 2858, 1717, 1641, 1473, 1463, 1256, 1101, 836, 775. **HRMS (ESI FT-ICR-MS)** *m*/*z* calcd for $C_{43}H_{94}O_6Si_5Na$ [M + Na]$^+$: 869.5794, found: 869.5786.

(+)-(5*R*,7*S*,11*R*,13*R*)-5-allyl-7,11-bis((*tert*-butyldimethylsilyl)oxy)-2,2,3,3,15,15,16,16-octamethyl-13-((trityloxy)methyl)-4,14-dioxa-3,15-disilaheptadecan-9-one (62b): To a solution of aldol adduct **58b** (1.26 g, 1.46 mmol, 100 mol%) in CH_2Cl_2 (19 mL, 0.08 M) at 0 °C were added 2,6-lutidine (0.51 mL, 4.38 mmol, 300 mol%) and TBSOTf (0.50 mL, 2.19 mmol, 150 mol%) dropwise. After 1 h, the reaction was quenched by the addition of saturated aqueous solution of $NaHCO_3$ (10 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were washed with brine (25 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography using a solution of hexane/ethyl acetate (95:05) as the eluent to provide compound **62b** (1.30 g, 1.33 mmol, 91%) as a colorless oil. **TLC:** R_f = 0.74 (95:05 hexane:EtOAc) **Optical rotation:** $[\alpha]_D^{20}$ +5 (*c* 1.0, $CHCl_3$) **^{1}H NMR (500 MHz, $CDCl_3$)** δ −0.08 (s, 3H), 0.00 (s, 3H), 0.01 (s, 3H), 0.03 (s, 3H), 0.06 (s, 9H), 0.07 (s, 3H), 0.84 (s, 9H), 0.84 (s, 9H), 0.86 (s, 9H), 0.88 (s, 9H), 1.50−1.57 (m, 2H), 1.63 (dt, *J* = 13.4 and 5.8 Hz, 1H), 1.94 (dt, *J* = 13.7 and 5.8 Hz, 1H), 2.16−2.27 (m, 2H), 2.41−2.63 (m, 4H), 2.90 (dd, *J* = 9.0 and 6.4 Hz, 1H), 3.03 (dd, *J* = 9.0 and 4.7 Hz, 1H), 3.76 (quint, *J* = 5.8 Hz, 1H), 3.92 (quint, *J* = 5.8 Hz, 1H), 4.21 (quint, *J* = 5.8 Hz, 1H), 5.02−5.05 (m, 2H), 5.75−5.83 (m, 1H), 7.22 (t, *J* = 7.4 Hz, 3H), 7.28 (t, *J* = 7.4 Hz, 6H), 7.44 (d, *J* = 7.4 Hz, 6H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ −4.6, −4.3, −4.3, −4.2, −4.2, −4.2, −4.2, −4.1, 18.0, 18.0, 18.0, 18.1, 25.9 (3 × $(CH_3)_3$), 25.9, 42.2, 43.9, 45.4, 52.2, 52.4, 66.7, 66.7, 67.9, 69.5 (2 × CH), 86.5, 117.1, 126.9, 127.7, 128.7, 134.8, 144.1, 207.0. **IR (film)** ν_{max}/cm^{-1} 3086, 3062, 3034, 2955, 2929, 2891, 2857, 1717, 1641, 1491, 1472, 1463, 1449, 1387, 1361, 1256, 1099, 1076, 1005, 836, 808, 775, 745, 705, 633. **HRMS (ESI FT-ICR-MS)** *m*/*z* calcd for $C_{56}H_{94}O_6Si_4Na$ [M + Na]$^+$: 997.6025, found: 997.6029.

(−)-(5*R*,7*S*,11*R*,13*R*)-5-allyl-7,11-bis((*tert*-butyldimethylsilyl)oxy)-13-(hydroxymethyl)-2,2,3,3,15,15,16,16-octamethyl-4,14-dioxa-3,15-disilaheptadecan-9-one (63): To a solution of compound **62a** (140 mg, 0.16 mmol, 100 mol%) in THF (2.1 mL, 0.08 M) at 0 °C, was added a solution of HF.pyridine:pyridine:THF (1:4:5) (0.42 mL). The reaction medium was stirred for 30 min at 0 ºC and warmed to room temperature. After 20 h, the reaction medium was cooled to 0 °C and quenched by the addition of TMSOMe (0.53 mL). The reaction medium was stirred for 5 min at 0 ºC and 15 min at room temperature. After this period, the volatiles were removed under reduced pressure, and the residue was purified by flash column chromatography using a solution of hexane/ethyl acetate (85:15) as the eluent to provide the alcohol **63** (25 mg, 35.2 µmol, 22%) as a colorless oil. **TLC:** R_f = 0.43 (90:10 hexane:EtOAc) **Optical rotation:** $[\alpha]_D^{20}$ −5 (*c* 1.7, $CHCl_3$) **^{1}H NMR (500 MHz, $CDCl_3$)** δ 0.01 (s, 3H), 0.03 (s, 3H), 0.05 (s, 3H), 0.05 (s, 6H), 0.07 (s, 3H), 0.08 (s, 3H), 0.09 (s, 3H), 0.84 (s, 9H), 0.85 (s, 9H), 0.87 (s, 9H), 0.89 (s, 9H), 1.54 (dt, *J* = 13.9 and 6.5 Hz, 1H), 1.61−1.73 (m, 3H), 2.10 (br s, 1H), 2.15−2.26 (m, 2H), 2.50 (dd, *J* = 15.6 and 5.2 Hz, 1H), 2.55−2.59 (m, 2H), 2.62 (dd, *J* = 16.2 and 6.3 Hz, 1H), 3.44−3.46 (m, 1H), 3.57−3.59 (m, 1H), 3.76 (quint, *J* = 6.0 Hz, 1H), 3.80 (quint, *J* = 5.2 Hz, 1H), 4.22 (m, 2H), 5.02−5.05 (m, 1H), 5.78 (ddt, *J* = 17.7, 9.5 and 7.1 Hz, 1H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ −4.5, −4.4 (3 × CH_3), −4.3, −4.3, −4.3, −4.1, 17.9, 18.0, 18.1 (2 × C_0), 25.8, 25.8 (2 × $(CH_3)_3$), 25.9, 42.0, 42.2, 45.3, 52.1, 52.3, 66.6, 66.6, 66.8, 69.5, 70.9, 117.2, 134.7, 207.3. **IR (film)** ν_{max}/cm^{-1} 3445, 2955, 2930, 2888, 2858, 1715, 1641, 1473, 1463, 1256, 1101, 836, 808, 775. **HRMS (ESI FT-ICR-MS)** *m*/*z* calcd for $C_{37}H_{80}O_6Si_4Na$ $[M + Na]^+$: 755.4930, found: 755.4917.

(−)-(5*R*,7*S*,11*R*,13*R*)-5-allyl-7,11-bis((*tert*-butyldimethylsilyl)oxy)-13-(hydroxymethyl)-2,2,3,3,15,15,16,16-octamethyl-4,14-dioxa-3,15-disilaheptadecan-9-one (63): To a solution of trityl ether **62b** (800 mg, 0.82 mmol, 100 mol%) in CH_2Cl_2:phosphate buffer pH 7 (9:1) (76 mL, 0.01 M) at 0 ºC was added DDQ (617 mg, 2.72 mmol, 330 mol%). After 5 min, the reaction was warmed to room temperature. After 24 h, the reaction was quenched via the addition of a solution of H_2O:saturated aqueous solution of $NaHCO_3$ (1:1) (11 mL). The resulting mixture was filtered over Celite, washed with CH_2Cl_2 (5 × 50 mL) and concentrated under reduced pressure. The residue was purified by flash column chromatography using hexane/ethyl acetate (90:10) as the eluent to provide alcohol **63** (309 mg, 0.42 mmol, 52%).

(+)-(2*R*,4*R*,8*S*,10*R*)-2,4,8,10-tetrakis((*tert*-butyldimethylsilyl)oxy)-6-oxotridec-12-enal (11): To a solution of oxalyl chloride (0.12 mL, 1.38 mmol, 300 mol%) in CH_2Cl_2 (6.6 mL, 0.21 M) at −78 ºC was added DMSO (0.20 mL, 2.88 mmol, 610 mol%) dropwise. The reaction medium was stirred for 30 min, followed by the dropwise addition of a solution of alcohol **63** (343 mg, 0.47 mmol, 100 mol%) in CH_2Cl_2 (2.9 mL, 0.16 M). After 30 min, Et_3N (0.98 mL, 7.04 mmol, 1500 mol%) was added dropwise, and the resulting slurry was warmed to 0 ºC and stirred for 1 h. The reaction was then diluted with Et_2O (25 mL) and saturated aqueous solution of NH_4Cl (25 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with H_2O (3 × 50 mL), brine (50 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to provide the aldehyde **11** (344 mg, 0.47 mmol, 99%), which was used in the next step without further purification, as a yellow oil. **TLC:** R_f = 0.60 (90:10 hexane:EtOAc) **Optical rotation:** $[\alpha]_D^{20}$ +7 (*c* 2.2, $CHCl_3$) **^{1}H NMR (500 MHz, $CDCl_3$)** δ 0.00 (s, 3H), 0.02 (s, 3H), 0.04 (s, 3H), 0.05 (s, 3H), 0.05 (s, 6H), 0.06 (s, 3H), 0.09 (s, 3H), 0.83 (s, 9H), 0.84 (s, 9H), 0.87 (s, 9H), 0.91 (s, 9H), 1.53 (dt, *J* = 13.7 and 6.6 Hz, 1H), 1.64 (dt, *J* = 13.7 and 6.1 Hz, 1H), 1.86 (dt, *J* = 14.2 and 6.0 Hz, 1H), 1.92 (dt, *J* = 14.2 and 5.3 Hz, 1H), 2.15−2.26 (m, 2H), 2.46 (dd, *J* = 15.6 and 4.9 Hz, 1H), 2.56 (dd, *J* = 15.6 and 7.2 Hz, 1H), 2.59 (dd, *J* = 16.7 and 5.5 Hz, 1H), 2.78 (dd, *J* = 16.7 and 7.2 Hz, 1H), 3.74 (quint, *J* = 5.9 Hz, 1H), 4.13−4.15 (m, 1H), 4.21 (quint, *J* = 5.3 Hz, 1H), 4.31−4.36 (m, 1H), 5.02−5.05 (m, 2H), 5.74−5.82 (m, 1H), 9.58 (d, *J* = 1,4 Hz, 1H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ −4.8, −4.5, −4.4, −4.4 (3 × CH_3), −4.3, −4.1, 18.0 (2 × C_0), 18.1, 18.2, 25.8 (2 × $(CH_3)_3$), 25.8, 25.9, 40.2, 42.1, 45.4, 51.9 (2 × CH_2), 65.8, 66.6, 69.5, 75.9, 117.2, 134.7, 202.8, 207.0. **IR (film)** ν_{max}/cm^{-1} 2955, 2930, 2896, 2858, 2710, 1737, 1717, 1472, 1463, 1362, 1256, 1103, 1005, 836, 808, 776. **HRMS (ESI FT-ICR-MS)** *m*/*z* calcd for $C_{37}H_{78}O_6Si_4Na$ $[M + Na]^+$: 753.4773, found: 753.4768.

(+)-(5*R*,7*S*,11*R*,13*R*)-5-allyl-7,11-bis((*tert*-butyldimethylsilyl)oxy)-13-((*E*)-3-((4*R*,6*R*)-6-(((4*S*,6*S*)-6-((2*S*,3*S*)-3-((4-methoxybenzyl)oxy)-4-methylpentan-2-yl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)prop-1-en-1-yl)-2,2,3,3,15,15,16,16-octamethyl-4,14-dioxa-3,15-disilaheptadecan-9-one (64): To a solution of sulfone **10** (296 mg, 0.42 mmol, 100 mol%) in THF (5.0 mL, 0.08 M) at −78 ºC was added KHMDS (0.46 mL, 0.46 mmol, 1 M in THF, 110 mol%) dropwise. The reaction medium was stirred for 5 min, followed by the dropwise addition of a solution of aldehyde **11** (344 mg, 0.47 mmol, 110 mol%)

in THF (2.6 mL, 0.18 M). After 20 min, the reaction was diluted with Et_2O (10 mL) and quenched by the addition of brine (10 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 25 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography using hexane/ethyl acetate (90:10) as the eluent to provide compound **64** (370 mg, 0.31 mmol, 74%, *dr* > 95:05, *E*:*Z*) as a colorless oil. **TLC:** R_f = 0.48 (90:10 hexane:EtOAc) **Optical rotation:** $[\alpha]_D^{20}$ +2 (*c* 0.7, $CHCl_3$) **^{1}H NMR (500 MHz, $CDCl_3$)** δ 0.01 (s, 9H), 0.03 (s, 3H), 0.05 (s, 3H), 0.06 (s, 9H), 0.82 (d, *J* = 6.6 Hz, 3H), 0.83 (d, *J* = 7.0 Hz, 3H), 0.84 (s, 9H), 0.85 (s, 9H), 0.87 (s, 9H), 0.87 (s, 9H), 1.00 (d, *J* = 6.6 Hz, 3H), 1.06 (q, *J* = 12.2 Hz, 1H), 1.06 (q, *J* = 12.2 Hz, 1H), 1.35 (s, 3H), 1.36 (s, 3H), 1.38 (s, 3H), 1.39 (s, 3H), 1.42 (dt, *J* = 12.2 and 2.0 Hz, 1H), 1.48−1.70 (m, 8H), 1.78−1.85 (m, 1H), 2.09 (dt, *J* = 13.8 and 6.4 Hz, 1H), 2.15−2.26 (m, 3H), 2.48−2.59 (m, 4H), 3.41 (dd, *J* = 8.9 and 1.7 Hz, 1H), 3.76 (quint, *J* = 5.8 Hz, 1H), 3.79 (s, 3H), 3.79−3.87 (m, 2H), 4.03−4.09 (m, 2H), 4.10 (q, *J* = 7.2 Hz, 1H), 4.18−4.23 (m, 2H), 4.50 (d, *J* = 11.6 Hz, 1H), 4.52 (d, *J* = 11.6 Hz, 1H), 5.02−5.05 (m, 2H), 5.43 (dd, *J* = 15.4 and 7.2 Hz, 1H), 5.52 (dt, *J* = 15.4 and 6.9 Hz, 1H), 5.74−5.82 (m, 1H), 6.84−6.87 (m, 2H), 7.24−7.26 (m, 2H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ −4.6, −4.3 (3 × CH_3), −4.2 (2 × CH_3), −4.1, −3.6, 8.8, 18.0 (2 × C_0), 18.1, 18.2, 19.5, 19.8, 20.1, 20.2, 25.9 (2 × $(CH_3)_3$), 25.9, 26.0, 30.2, 30.4, 31.2, 35.9, 37.1, 39.3, 41.3, 42.2, 43.3, 45.4, 46.8, 52.1, 52.3, 55.3, 64.7, 64.8, 66.4, 66.8, 69.0, 69.5, 70.2, 71.2, 74.0, 82.7, 98.4, 98.5, 113.7, 117.1, 126.5, 128.7, 131.8, 134.8, 135.9, 158.9, 207.3. **IR (film)** ν_{max}/cm^{-1} 2991, 2954, 2930, 2857, 1717, 1641, 1615, 1515, 1472, 1463, 1379, 1250, 1203, 1169, 1088, 1040, 836, 775. **HRMS (ESI FT-ICR-MS)** *m*/*z* calcd for $C_{66}H_{124}O_{11}Si_4Na$ $[M + Na]^+$: 1227.8118, found: 1227.8110.

(−)-(5*R*,7*S*,11*R*,13*R*)-5-allyl-7,11-bis((*tert*-butyldimethylsilyl)oxy)-13-((*E*)-3-((4*R*,6*R*)-6-(((4*S*,6*S*)-6-((2*R*,3*S*)-3-hydroxy-4-methylpentan-2-yl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)prop-1-en-1-yl)-2,2,3,3,15,15,16,16-octamethyl-4,14-dioxa-3,15-disilaheptadecan-9-one (9): To a solution of PMB ether **64** (370 mg, 0.31 mmol, 100 mol%) in CH_2Cl_2:phosphate buffer pH 7 (9:1) (5.0 mL, 0.06 M) at 0 ºC was added DDQ (104 mg, 0.46 mmol, 150 mol%). The mixture was stirred for 1 h under the same conditions, followed by quenching via the addition of a solution of H_2O:saturated aqueous solution of $NaHCO_3$ (1:1) (5 mL). The resulting mixture was filtered over Celite, washed with CH_2Cl_2 (5 × 25 mL) and

concentrated under reduced pressure. The residue was purified by flash column chromatography using hexane/ethyl acetate (80:20) as the eluent to provide alcohol **9** (305 mg, 0.28 mmol, 91%) as a pale yellow oil. **TLC:** R_f = 0.72 (80:20 hexane:EtOAc) **Optical rotation:** $[\alpha]_D^{20}$ −5 (*c* 1.0, $CHCl_3$) **^{1}H NMR (500 MHz, $CDCl_3$)** δ 0.01 (s, 9H), 0.03 (s, 3H), 0.05 (s, 3H), 0.05 (s, 9H), 0.78 (d, *J* = 6.8 Hz, 3H), 0.84 (s, 9H), 0.85 (s, 9H), 0.87 (s, 9H), 0.87 (s, 9H), 0.92 (d, *J* = 7.1 Hz, 3H), 1.01 (d, *J* = 6.4 Hz, 3H), 1.13 (q, *J* = 12.0 Hz, 1H), 1.32−1.44 (m, 3H), 1.34 (s, 3H), 1.35 (s, 3H), 1.39 (s, 6H), 1.47−1.70 (m, 8H), 2.09 (dt, *J* = 14.0 and 6.4 Hz, 1H), 2.15−2.26 (m, 3H), 2.48−2.58 (m, 4H), 2.99 (br s, 1H), 3.51 (d, *J* = 9.3 Hz, 1H), 3.76 (quint, *J* = 5.7 Hz, 1H), 3.82−3.87 (m, 1H), 3.90−3.93 (m, 1H), 4.02−4.12 (m, 3H), 4.19−4.23 (m, 2H), 5.02−5.05 (m, 2H), 5.43 (dd, *J* = 15.4 and 7.1 Hz, 1H), 5.52 (dt, *J* = 15.4 and 6.7 Hz, 1H), 5.74−5.82 (m, 1H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ −4.6, −4.3 (3 × CH_3), −4.2 (2 × CH_3), −4.1, −3.6, 10.0, 18.0 (2 × C_0), 18.1, 18.2, 19.0, 19.5, 19.8, 19.9, 25.9 (2 × $(CH_3)_3$), 25.9, 26.0, 30.2 (2 × CH_3), 30.9, 35.1, 37.1, 38.7, 39.2, 42.2, 43.0, 45.4, 46.8, 52.1, 52.3, 64.6, 65.0, 66.4, 66.8, 69.0, 69.5, 71.2, 74.0, 76.1, 98.5, 98.9, 117.1, 126.5, 134.8, 136.0, 207.3. **IR (film)** ν_{max}/cm^{-1} 3526, 2991, 2954, 2930, 2858, 1717, 1473, 1468, 1380, 1256, 1203, 1168, 1095, 836, 775. **HRMS (ESI FT-ICR-MS)** *m*/*z* calcd for $C_{58}H_{116}O_{10}Si_4Na$ $[M + Na]^+$: 1107.7543, found: 1107.7534.

(−)-(2*E*,5*R*,7*S*,11*R*,13*R*,14*E*)-5,7,11,13-tetrakis((*tert*-butyldimethylsilyl)oxy)-16-((4*R*,6*R*)-6-(((4*S*,6*S*)-6-((2*R*,3*S*)-3-hydroxy-4-methylpentan-2-yl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)-9-oxohexadeca-2,14-dienal (7): A solution of olefin **9** (200 mg, 0.184 mmol, 100 mol%) and crotonaldehyde (**8**) (0.05 mL, 0.550 mmol, 300 mol%) in CH_2Cl_2 (1.8 mL, 0.10 M) at room temperature was purged with argon for 10 min. After this period, Hoveyda−Grubbs 2nd generation catalyst (11 mg, 18.4 μmol, 10 mol%) was added, and the reaction medium was warmed to 50 °C. After 24 h, the volatiles were removed under reduced pressure, and the residue was purified by flash column chromatography using a solution of hexane/ethyl acetate (80:20) as the eluent to provide the aldehyde **7** (181 mg, 0.163 mmol, 89%, *dr* > 95:05, *E*:*Z*) as a colorless oil. **TLC:** R_f = 0.66 (80:20 hexane:EtOAc) **Optical rotation:** $[\alpha]_D^{20}$ −8 (*c* 1.0, $CHCl_3$) **^{1}H NMR (500 MHz, $CDCl_3$)** δ 0.01 (s, 6H), 0.01 (s, 3H), 0.03 (s, 3H), 0.04 (s, 3H), 0.05 (s, 6H), 0.07 (s, 3H), 0.78 (d, *J* = 6.7 Hz, 3H), 0.84 (s, 18H), 0.86 (s, 9H), 0.87 (s, 9H), 0.92 (d, *J* = 6.7 Hz, 3H), 1.00 (d, *J* = 6.7 Hz, 3H), 1.12 (q, *J* = 12.2 Hz, 1H), 1.34 (s, 3H), 1.36 (s,

3H), 1.38 (s, 6H), 1.38−1.68 (m, 11H), 2.08 (dt, *J* = 14.0 and 6.7 Hz, 1H), 2.20 (dt, *J* = 14.0 and 6.7 Hz, 1H), 2.41−2.62 (m, 6H), 2.99 (br s, 1H), 3.50 (d, *J* = 9.2 Hz, 1H), 3.82−3.86 (m, 1H), 3.88−3.92 (m, 2H), 4.03−4.12 (m, 3H), 4.19 (quint, *J* = 6.1 Hz, 2H), 5.42 (dd, *J* = 15.3 and 7.0 Hz, 1H), 5.52 (dt, *J* = 15.3 and 6.7 Hz, 1H), 6.13 (dd, *J* = 15.9 and 7.9 Hz, 1H), 6.84 (dt, *J* = 15.9 and 7.9 Hz, 1H), 9.48 (d, *J* = 7.9 Hz, 1H). **^{13}C NMR (125 MHz, $CDCl_3$)** *δ* −4.6, −4.3, −4.3, −4.3 (2 × CH_3), −4.3, −4.2, −3.6, 10.0, 17.9, 18.0, 18.0, 18.2, 19.0, 19.5, 19.8, 19.9, 25.8 (2 × $(CH_3)_3$), 25.9, 26.0, 30.2 (2 × CH_3), 30.9, 35.1, 37.0, 38.7, 39.2, 41.0, 43.0, 45.7, 46.7, 52.1, 52.3, 64.6, 65.0, 66.5 (2 × CH), 68.8, 68.9, 71.2, 74.0, 76.1, 98.5, 98.9, 126.5, 135.0, 135.9, 154.8, 193.8, 207.1. **IR (film)** ν_{max}/cm^{-1} 3452, 2954, 2929, 2857, 1691, 1650, 1633, 1472, 1463, 1379, 1256, 1202, 1167, 1095, 836, 776. **HRMS (ESI FT-ICR-MS)** *m*/*z* calcd for $C_{59}H_{116}O_{11}Si_4Na$ $[M + Na]^+$: 1135.7492, found: 1135.7488.

(2*E*,4*E*)-ethyl 6-((*tert*-butyldimethylsilyl)oxy)hexa-2,4-dienoate (69): To a suspension of NaH (868 mg, 21.7 mmol, 60% in mineral oil, 140 mol%) in THF (47 mL, 0.46 M) at 0 ºC was added phosphonate **68** (3.9 mL, 19.7 mmol, 130 mol%) dropwise. After 1 h, a solution of aldehyde **67** (3.03 g, 15.1 mmol, 100 mol%) in THF (12 mL, 1.3 M) was added dropwise. After 15 min, the reaction was quenched by the addition of H_2O (15 mL) and the volatiles were removed under reduced pressure. The aqueous layer was extracted with Et_2O (3 × 25 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography using hexane/ethyl acetate (90:10) as the eluent to provide compound **69**[65] (3.41 g, 12.6 mmol, 83%, *dr* > 95:05, *E*:*Z*) as a pale yellow oil. **TLC:** R_f = 0.50 (90:10 hexane:EtOAc) **^{1}H NMR (500 MHz, $CDCl_3$)** *δ* 0.07 (s, 6H), 0.91 (s, 9H), 1.28 (t, *J* = 7.1 Hz, 3H), 4.19 (q, *J* = 7.1 Hz, 2H), 4.28−4.29 (m, 2H), 5.86 (d, *J* = 15.4 Hz, 1H), 6.16 (dt, *J* = 15.1 and 4.3 Hz, 1H), 6.36−6.41 (m, 1H), 7.28 (dd, *J* = 15.4 and 11.2 Hz, 1H). **^{13}C NMR (125 MHz, $CDCl_3$)** *δ* −5.3, 14.3, 18.4, 25.9, 60.2, 62.9, 120.8, 126.8, 141.8, 144.0, 167.1. **IR (film)** ν_{max}/cm^{-1} 2956, 2932, 2887, 2859, 1721, 1650, 1621, 1472, 1368, 1304, 1259, 1229, 1181, 1129, 1000, 838, 780.

(2*E*,4*E*)-6-((*tert*-butyldimethylsilyl)oxy)hexa-2,4-dien-1-ol (70): To a solution of ester **69** (3.41 g, 12.6 mmol, 100 mol%) in CH_2Cl_2 (26 mL, 0.48 M) at −78 ºC was added DIBAL-H (31.5 mL,

31.5 mmol, 1 M in hexanes, 250 mol%) over 40 min using a syringe pump. After 30 min, the reaction was quenched by the addition of saturated aqueous solution of potassium sodium tartrate (50 mL), warmed to room temperature and stirred for 3 h. After this period, the layers were separated, and the aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to provide alcohol **70**[4f] (2.94 g, 12.6 mmol, 99%), which was used in the next step without further purification, as a yellow oil. **TLC:** R_f = 0.37 (80:20 hexane:EtOAc) **^{1}H NMR (500 MHz, $CDCl_3$)** δ 0.06 (s, 6H), 0.90 (s, 9H), 1.38 (br s, 1H), 4.18 (d, J = 3.8 Hz, 2H), 4.22 (d, J = 4.9 Hz, 2H), 5.74−5.83 (m, 2H), 6.20−6.28 (m, 2H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ −5.2, 18.4, 25.9, 63.4, 63.4, 128.9, 131.0, 131.4, 133.3. **IR (film)** ν_{max}/cm^{-1} 3390, 3029, 2955, 2930, 2857, 1662, 1630, 1472, 1463, 1256, 1083, 989, 836, 777.

(2*E*,4*E*)-6-((*tert*-butyldimethylsilyl)oxy)hexa-2,4-dienal (13): To a solution of oxalyl chloride (1.6 mL, 18.9 mmol, 150 mol%) in CH_2Cl_2 (75 mL, 0.25 M) at −78 ºC was added DMSO (2.7 mL, 37.8 mmol, 300 mol%) dropwise. The reaction medium was stirred for 30 min, followed by the dropwise addition of a solution of alcohol **70** (2.94 g, 12.6 mmol, 100 mol%) in CH_2Cl_2 (33 mL, 0.38 M). After 30 min, Et_3N (13 mL, 94.6 mmol, 750 mol%) was added dropwise, and the resulting slurry was warmed to 0 ºC and stirred for 1 h. The reaction was then diluted with Et_2O (50 mL) and saturated aqueous solution of NH_4Cl (50 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with H_2O (3 × 50 mL), brine (100 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to provide the aldehyde **13**[4f] (2.85 g, 12.6 mmol, 99%), which was used in the next step without further purification, as a yellow oil. **TLC:** R_f = 0.63 (80:20 hexane:EtOAc) **^{1}H NMR (500 MHz, $CDCl_3$)** δ 0.08 (s, 6H), 0.91 (s, 9H), 4.32−4.33 (m, 2H), 6.13 (dd, J = 15.3 and 8.0 Hz, 1H), 6.30 (dt, J = 15.1 and 4.1 Hz, 1H), 6.51−6.57 (m, 1H), 7.12 (dd, J = 15.3 and 11.0 Hz, 1H), 9.55 (d, J = 8.0 Hz, 1H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ −5.4, 18.4, 25.8, 62.8, 126.8, 131.2, 144.3, 151.6, 193.8. **IR (film)** ν_{max}/cm^{-1} 2956, 2930, 2886, 2857, 2729, 1686, 1646, 1603, 1472, 1254, 1162, 1108, 1012, 987, 961, 838, 778.

(2*E*,4*E*,6*E*)-ethyl 8-((*tert*-butyldimethylsilyl)oxy)-2-methylocta-2,4,6-trienoate (71a): To a suspension of NaH (48 mg, 1.21 mmol, 60% in mineral oil, 140 mol%) in THF (4.0 mL, 0.30 M)

at 0 ºC was added phosphonate **12a** (0.24 mL, 1.10 mmol, 125 mol%) dropwise. After 1 h, a solution of aldehyde **13** (199 mg, 0.88 mmol, 100 mol%) in THF (1.0 mL, 0.88 M) was added dropwise. After 15 min, the reaction was quenched by the addition of H_2O (1 mL) and the volatiles were removed under reduced pressure. The aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography using hexane/ethyl acetate (95:05) as the eluent to provide compound **71a** (212 mg, 0.68 mmol, 78%, *dr* > 95:05, *E*:*Z*) as a pale yellow oil. **TLC:** R_f = 0.54 (90:10 hexane:EtOAc) **^{1}H NMR (500 MHz, $CDCl_3$)** δ 0.07 (s, 6H), 0.91 (s, 9H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.94 (s, 3H), 4.19 (q, *J* = 7.1 Hz, 2H), 4.26 (d, *J* = 4.9 Hz, 2H), 5.92 (dt, *J* = 15.0 and 4.9 Hz, 1H), 6.36 (ddt, *J* = 15.0, 10.7 and 1.8 Hz, 1H), 6.44 (dd, *J* = 14.8 and 11.2 Hz, 1H), 6.52 (dd, *J* = 14.8 and 10.7 Hz, 1H), 7.20 (dt, *J* = 11.2 and 0.9 Hz, 1H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ −5.3, 12.7, 14.3, 18.4, 25.9, 60.5, 63.2, 126.9, 127.2, 129.2, 136.6, 138.1, 138.8, 168.4. **IR (film)** ν_{max}/cm^{-1} 3034, 2956, 2930, 2897, 2886, 2857, 1704, 1616, 1472, 1463, 1367, 1309, 1240, 1211, 1099, 991, 837, 777, 748. **HRMS (ESI FTMS)** *m*/*z* calcd for $C_{17}H_{30}O_3SiNa$ $[M + Na]^+$: 333.1856, found: 333.1856.

(2*E*,4*E*,6*E*)-methyl 8-((*tert*-butyldimethylsilyl)oxy)-2-methylocta-2,4,6-trienoate (71b): To a suspension of NaH (120 mg, 3.01 mmol, 60% in mineral oil, 140 mol%) in THF (8.7 mL, 0.35 M) at 0 ºC was added a solution of phosphonate **12b** (614 mg, 2.74 mmol, 125 mol%) in THF (2.2 mL, 1.2 M) dropwise. After 1 h, a solution of aldehyde **13** (496 mg, 2.19 mmol, 100 mol%) in THF (2.1 mL, 1.0 M) was added dropwise. After 15 min, the reaction was quenched by the addition of H_2O (5 mL) and the volatiles were removed under reduced pressure. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography using hexane/ethyl acetate (90:10) as the eluent to provide compound **71b**[66] (527 mg, 1.78 mmol, 81%, *dr* > 95:05, *E*:*Z*) as a white solid. **TLC:** R_f = 0.53 (90:10 hexane:EtOAc) **mp** 43−45 °C **^{1}H NMR (500 MHz, $CDCl_3$)** δ 0.07 (s, 6H), 0.91 (s, 9H), 1.95 (s, 3H), 3.74 (s, 3H), 4.26 (d, *J* = 4.6 Hz, 2H), 5.94 (dt, *J* = 15.0 and 4.6 Hz, 1H), 6.36 (ddt, *J* = 15.0, 10.6 and 1.5 Hz, 1H), 6.44 (dd, *J* = 14.7 and 11.2 Hz, 1H), 6.52 (dd, *J* = 14.7 and 10.6 Hz, 1H), 7.20 (dq, *J* = 11.2 and 1.0 Hz, 1H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ −5.3, 12.7, 18.4,

25.9, 51.8, 63.2, 126.6, 127.1, 129.1, 136.8, 138.4, 139.0, 168.9. **IR (film)** ν_{max}/cm^{-1} 2952, 2929, 2886, 2856, 1711, 1610, 1462, 1434, 1382, 1302, 1245, 1099, 1004, 957, 836, 776, 748.

(2*E*,4*E*,6*E*)-ethyl 8-hydroxy-2-methylocta-2,4,6-trienoate (72a): To a solution of compound **71a** (190 mg, 0.61 mmol, 100 mol%) in THF (2.9 mL, 0.21 M) at room temperature was added TBAF (0.92 mL, 0.92 mmol, 1 M in THF, 150 mol%). After 1 h, the volatiles were removed under reduced pressure, and the residue was purified by flash column chromatography using a solution of hexane/ethyl acetate (50:50) as the eluent to provide alcohol **72a**[67] (115 mg, 0.59 mmol, 97%) as a yellow oil. **TLC:** R_f = 0.62 (50:50 hexane:EtOAc) **^{1}H NMR (500 MHz, $CDCl_3$)** δ 1.29 (t, J = 7.2 Hz, 3H), 1.68 (br s, 1H), 1.94 (s, 3H), 4.20 (q, J = 7.2 Hz, 2H), 4.24 (d, J = 5.6 Hz, 2H), 5.99 (dt, J = 15.2 and 5.6 Hz, 1H), 6.38 (ddt, J = 15.2, 10.0 and 1.5 Hz, 1H), 6.48 (dd, J = 14.6 and 10.8 Hz, 1H), 6.52 (dd, J = 14.6 and 10.0 Hz, 1H), 7.19 (dt, J = 10.8 and 1.2 Hz, 1H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 12.7, 14.3, 60.6, 63.1, 127.5, 127.9, 130.6, 135.7, 137.8, 138.3, 168.4. **IR (film)** ν_{max}/cm^{-1} 3436, 3032, 2984, 2932, 2870, 1696, 1683, 1614, 1368, 1254, 1105, 1082, 990, 749.

(2*E*,4*E*,6*E*)-ethyl 8-(diethoxyphosphoryl)-2-methylocta-2,4,6-trienoate (6a): To a solution of alcohol **72a** (446 mg, 2.28 mmol, 100 mol%) in CH_2Cl_2 (8.0 mL, 0.28 M) at 0 °C were added pyridine (0.02 mL, 0.27 mmol, 12 mol%) and a solution of PBr_3 (3.4 mL, 3.40 mmol, 1 M in CH_2Cl_2, 150 mol%) dropwise. After 15 min, the reaction was quenched by the addition of H_2O (5 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with H_2O (5 mL), saturated aqueous solution of $NaHCO_3$ (10 mL), brine (10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to provide a bromide, which was used immediately in the next step without further purification.

To a solution of the bromide (theor. 2.28 mmol, 100 mol%) in toluene (15 mL, 0.15 M) at room temperature was added $P(OEt)_3$ (1.2 mL, 6.84 mmol, 300 mol%) and the reaction was warmed to reflux. After 15 h, the reaction was diluted with Et_2O (20 mL), transferred to a separatory funnel, washed with H_2O (10 mL), brine (10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography using ethyl acetate as the eluent to provide phosphonate **6a**[67] (721 mg, 2.28 mmol, 99% over 2 steps) as a

pale yellow oil. **TLC:** R_f = 0.64 (EtOAc) **^{1}H NMR (500 MHz, $CDCl_3$)** δ 1.29 (t, *J* = 7.0 Hz, 6H), 1.30 (t, *J* = 7.0 Hz, 3H), 1.93 (s, 3H), 2.68 (dd, *J* = 23.0 and 7.7 Hz, 2H), 4.05−4.13 (m, 4H), 4.19 (q, *J* = 7.2 Hz, 2H), 5.76−5.84 (m, 1H), 6.29 (ddd, *J* = 15.1, 10.1 and 5.0 Hz, 1H), 6.42 (ddq, *J* = 14.8, 10.9 and 2.1 Hz, 1H), 6.50 (dd, *J* = 14.9 and 10.0 Hz, 1H), 7.17 (d, *J* = 10.8 Hz, 1H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 12.7, 14.3, 16.4 (d, *J* = 6.4 Hz), 31.1 (d, *J* = 139.9 Hz), 60.6, 62.1 (d, *J* = 6.4 Hz), 126.0 (d, *J* = 13.6 Hz), 127.5 (d, *J* = 4.5 Hz), 127.5 (d, *J* = 1.8 Hz), 134.8 (d, *J* = 15.4 Hz), 137.7 (d, *J* = 2.7 Hz), 138.2 (d, *J* = 5.4 Hz), 168.3.

(2*E*,4*E*,6*E*)-methyl 8-(diethoxyphosphoryl)-2-methylocta-2,4,6-trienoate (6b): To a solution of compound **71b** (945 mg, 3.19 mmol, 100 mol%) in THF (15 mL, 0.21 M) at room temperature was added TBAF (4.8 mL, 4.80 mmol, 1 M in THF, 150 mol%). After 1 h, the volatiles were removed under reduced pressure, and the residue was purified by flash column chromatography using a solution of hexane/ethyl acetate (50:50) as the eluent to provide alcohol **72b**, which was used immediately in the next step.

To a solution of alcohol **72b** (theor. 3.19 mmol, 100 mol%) in CH_2Cl_2 (11 mL, 0.29 M) at 0 °C were added pyridine (0.03 mL, 0.32 mmol, 10 mol%) and a solution of PBr_3 (4.8 mL, 4.80 mmol, 1 M in CH_2Cl_2, 150 mol%) dropwise. After 15 min, the reaction was quenched by the addition of H_2O (5 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with H_2O (5 mL), saturated aqueous solution of $NaHCO_3$ (10 mL), brine (10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to provide a bromide, which was used immediately in the next step without further purification.

To a solution of the bromide (theor. 3.19 mmol, 100 mol%) in toluene (21 mL, 0.15 M) at room temperature was added $P(OEt)_3$ (1.6 mL, 9.57 mmol, 300 mol%) and the reaction was warmed to reflux. After 24 h, the reaction was diluted with Et_2O (20 mL), transferred to a separatory funnel, washed with H_2O (25 mL), brine (25 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography using ethyl acetate as the eluent to provide phosphonate **6b** (852 mg, 2.82 mmol, 88% over 3 steps) as a pale yellow oil. **TLC:** R_f = 0.60 (EtOAc) **^{1}H NMR (500 MHz, $CDCl_3$)** δ 1.28 (t, *J* = 7.0 Hz, 6H), 1.92 (s, 3H), 2.67 (dd, *J* = 23.0 and 7.7 Hz, 2H), 3.73 (s, 3H), 4.04−4.12 (m, 4H), 5.80 (dq, *J* = 15.4 and 7.7 Hz, 1H), 6.28 (ddd, *J* = 15.4, 10.0 and 4.9, 1H), 6.41 (ddd, *J* = 14.8, 11.0 and 2.1

Hz, 1H), 6.48 (dd, *J* = 14.8 and 10.0 Hz, 1H), 7.16 (d, *J* = 11.0 Hz, 1H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 12.7, 16.4 (d, *J* = 5.4 Hz), 31.1 (d, *J* = 139.9 Hz), 51.8, 62.0 (d, *J* = 7.3 Hz), 126.1 (d, *J* = 13.6 Hz), 127.1, 127.4 (d, *J* = 5.4 Hz), 134.7 (d, *J* = 14.5 Hz), 138.0 (d, *J* = 2.7 Hz), 138.3 (d, *J* = 5.4 Hz), 168.7. **IR (film)** ν_{max}/cm^{-1} 3030, 2986, 2952, 2908, 1712, 1699, 1615, 1436, 1392, 1367, 1326, 1268, 1230, 1100, 1024, 994, 964, 852, 788, 751. **HRMS (ESI FT-ICR-MS)** *m*/*z* calcd for $C_{14}H_{23}O_5PNa$ $[M + Na]^+$: 325.1181, found: 325.1174.

(2*E*,4*E*,6*E*,8*E*,10*E*,13*R*,15*S*,19*R*,21*R*,22*E*)-ethyl 13,15,19,21-tetrakis((*tert*-butyldimethylsilyl)oxy)-24-((4*R*,6*R*)-6-(((4*S*,6*S*)-6-((2*R*,3*S*)-3-hydroxy-4-methylpentan-2-yl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)-2-methyl-17-oxotetracosa-2,4,6,8,10,22-hexaenoate (73a): NOTE: This entire experimental procedure was performed in the dark. To a solution of phosphonate **6a** (76 mg, 0.24 mmol, 300 mol%) in THF (2.0 mL, 0.12 M) at −78 °C was added LiHMDS (0.24 mL, 0.24 mmol, 1 M in THF, 300 mol%) dropwise. After 30 min, a solution of aldehyde **7** (89 mg, 80 µmol, 100 mol%) in THF (1.2 mL, 0.07 M) was added dropwise. After 30 min, the reaction was warmed to room temperature over 3 h. After 12 h, the reaction was quenched by the addition of saturated aqueous solution of NH_4Cl (2 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography using a solution of hexane/ethyl acetate (80:20) as the eluent to provide compound **73a** (29 mg, 22.4 µmol, 28%, *dr* > 95:05, *E*:*Z*) as a yellow oil. **TLC:** R_f = 0.57 (80:20 hexane:EtOAc) **^{1}H NMR (500 MHz, $CDCl_3$)** δ 0.00 (s, 3H), 0.01 (s, 6H), 0.03 (s, 3H), 0.04 (s, 3H), 0.04 (s, 3H), 0.05 (s, 3H), 0.05 (s, 3H), 0.78 (d, *J* = 6.8 Hz, 3H), 0.83 (s, 9H), 0.84 (s, 9H), 0.87 (s, 9H), 0.87 (s, 9H), 0.92 (d, *J* = 7.1 Hz, 3H), 1.01 (d, *J* = 6.6 Hz, 3H), 1.12 (q, *J* = 12.1 Hz, 1H), 1.28−1.72 (m, 11H), 1.35 (s, 3H), 1.36 (s, 3H), 1.38 (s, 6H), 1.95 (s, 3H), 2.08 (dt, *J* = 14.3 and 5.8 Hz, 1H), 2.18−2.25 (m, 2H), 2.28−2.32 (m, 1H), 2.44−2.61 (m, 4H), 2.99 (br s, 1H), 3.50 (d, *J* = 9.3 Hz, 1H), 3.76 (quint, *J* = 5.8 Hz, 1H), 3.82−3.86 (m, 1H), 3.92 (dt, *J* = 12.6 and 3.7 Hz, 1H), 4.03−4.13 (m, 3H), 4.17−4.22 (m, 4H), 5.43 (dd, *J* = 15.4 and 7.2 Hz, 1 H), 5.51 (dt, *J* = 15.4 and 6.7 Hz, 1H), 5.74 (dt, *J* = 15.1 and 7.2 Hz, 1H), 6.01−6.58 (m, 7H), 7.22 (d, *J* = 11.3 Hz, 1H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ −4.6, −4.3, −4.3 (2 × CH_3), −4.3 (2 × CH_3), −4.1, −3.6, 10.0, 12.7, 14.3, 18.0, 18.0, 18.1, 18.2, 19.0, 19.5, 19.8, 19.9, 25.9 (3 × $(CH_3)_3$), 26.0, 30.2 (2 ×

CH_3), 30.9, 35.1, 37.0, 38.7, 39.2, 41.3, 43.0, 45.6, 46.7, 52.1, 52.2, 60.5, 64.6, 65.0, 66.5, 66.7, 69.0, 69.7, 71.2, 74.0, 76.1, 98.5, 98.9, 126.5, 126.7, 127.5, 130.9, 131.9, 132.6, 132.9, 135.1, 136.0, 136.5, 138.2, 139.5, 168.4, 207.3.

(−)-(2*E*,4*E*,6*E*,8*E*,10*E*,13*R*,15*S*,19*R*,21*R*,22*E*)-methyl 13,15,19,21-tetrakis((*tert*-butyldimethylsilyl)oxy)-24-((4*R*,6*R*)-6-(((4*S*,6*S*)-6-((2*R*,3*S*)-3-hydroxy-4-methylpentan-2-yl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)-2-methyl-17-oxotetracosa-2,4,6,8,10,22-hexaenoate (73b): NOTE: This entire experimental procedure was performed in the dark. To a solution of phosphonate **6b** (172 mg, 0.57 mmol, 300 mol%) in THF (4.8 mL, 0.12 M) at −78 °C was added LiHMDS (0.57 mL, 0.57 mmol, 1 M in THF, 300 mol%) dropwise. After 30 min, a solution of aldehyde **7** (213 mg, 0.19 mmol, 100 mol%) in THF (2.9 mL, 0.07 M) was added dropwise. After 30 min, the reaction was warmed to room temperature over 3 h. After 9 h, the reaction was quenched by the addition of saturated aqueous solution of NH_4Cl (5 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography using a solution of hexane/ethyl acetate (80:20) as the eluent to provide compound **73b** (120 mg, 95 µmol, 50%, *dr* > 95:05, *E*:*Z*) as a yellow oil. **TLC:** R_f = 0.48 (80:20 hexane:EtOAc) **Optical rotation:** $[\alpha]_D^{20}$ −9 (*c* 1.0, $CHCl_3$) **^{1}H NMR (500 MHz, $CDCl_3$)** δ 0.00 (s, 3H), 0.01 (s, 6H), 0.03 (s, 3H), 0.03 (s, 3H), 0.04 (s, 3H), 0.05 (s, 3H), 0.05 (s, 3H), 0.78 (d, *J* = 6.7 Hz, 3H), 0.83 (s, 9H), 0.84 (s, 9H), 0.86 (s, 9H), 0.87 (s, 9H), 0.92 (d, *J* = 7.0 Hz, 3H), 1.01 (d, *J* = 6.6 Hz, 3H), 1.12 (q, *J* = 12.0 Hz, 1H), 1.33−1.70 (m, 11H), 1.35 (s, 3H), 1.36 (s, 3H), 1.38 (s, 6H), 1.95 (s, 3H), 2.09 (dt, *J* = 14.1 and 6.1 Hz, 1H), 2.18−2.25 (m, 2H), 2.30 (dt, *J* = 14.1 and 6.1 Hz), 2.47−2.59 (m, 4H), 3.03 (br s, 1H), 3.50 (d, *J* = 9.3 Hz, 1H), 3.74 (s, 3H), 3.74−3.78 (m, 1H), 3.82−3.86 (m, 1H), 3.92 (dt, *J* = 11.6 and 3.0 Hz, 1H), 4.03−4.12 (m, 3H), 4.18−4.21 (m, 2H), 5.42 (dd, *J* = 15.4 and 7.2 Hz, 1H), 5.51 (dt, *J* = 15.4 and 6.7 Hz, 1H), 5.74 (dt, *J* = 15.1 and 7.3 Hz, 1H), 6.12 (dd, *J* = 15.0 and 10.7 Hz, 1H), 6.18 (dd, *J* = 14.7 and 10.4 Hz, 1H), 6.28 (dd, *J* = 15.9 and 10.5 Hz, 1H), 6.32 (dd, *J* = 15.2 and 10.4 Hz, 1H), 6.38 (dd, *J* = 14.8 and 10.3 Hz, 1H), 6.46 (dd, *J* = 14.5 and 11.6 Hz, 1H), 6.56 (dd, *J* = 14.5 and 10.4 Hz, 1H), 7.22 (d, *J* = 10.4 Hz, 1H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ −4.6, −4.4, −4.3 (2 × CH_3), −4.3, −4.3, −4.1, −3.6, 10.0, 12.8, 18.0 (2 × C_0), 18.1, 18.2, 19.0, 19.5, 19.8, 19.9, 25.9 (3 × $(CH_3)_3$), 26.0,

30.2 (2 × CH_3), 30.9, 35.1, 37.0, 38.7, 39.2, 41.2, 43.0, 45.6, 46.7, 51.8, 52.1, 52.2, 64.6, 64.9, 66.4, 66.7, 68.9, 69.7, 71.1, 74.1, 76.1, 98.5, 98.9, 126.3, 126.5, 127.4, 130.8, 131.8, 132.6, 132.9, 135.2, 135.9, 136.6, 138.5, 139.7, 168.9, 207.4. **IR (film)** ν_{max}/cm^{-1} 3460, 2991, 2953, 2930, 2857, 1708, 1638, 1472, 1380, 1256, 1100, 1004, 836, 776. **HRMS (ESI FT-ICR-MS)** *m*/*z* calcd for $C_{69}H_{128}O_{12}Si_4Na$ $[M + Na]^+$: 1283.8381, found: 1283.8376.

(−)-(2*E*,4*E*,6*E*,8*E*,10*E*,13*R*,15*S*,19*R*,21*R*,22*E*)-13,15,19,21-tetrakis((*tert*-butyldimethylsilyl)oxy)-24-((4*R*,6*R*)-6-(((4*S*,6*S*)-6-((2*R*,3*S*)-3-hydroxy-4-methylpentan-2-yl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)-2-methyl-17-oxotetracosa-2,4,6,8,10,22-hexaenoic acid (74): NOTE: This entire experimental procedure was performed in the dark. To a solution of ester **73b** (20 mg, 15.8 μmol, 100 mol%) in DCE (2.0 mL, 8 mM) at room temperature was added Me_3SnOH (30 mg, 0.17 mmol, 1000 mol%) and the reaction was warmed to reflux. After 3 days, the reaction medium was cooled to room temperature and the volatiles were removed under reduced pressure. The residue was purified by flash column chromatography using a solution of hexane/ethyl acetate (60:40) as the eluent to provide acid **74** (16 mg, 12.4 μmol, 79%) as a yellow oil. **TLC:** R_f = 0.50 (60:40 hexane:EtOAc) **Optical rotation:** $[\alpha]_D^{20}$ −11 (*c* 1.0, $CHCl_3$) **^{1}H NMR (500 MHz, $CDCl_3$)** δ 0.00 (s, 3H), 0.01 (s, 6H), 0.03 (s, 3H), 0.04 (s, 3H), 0.04 (s, 3H), 0.05 (s, 3H), 0.05 (s, 3H), 0.78 (d, *J* = 6.7 Hz, 3H), 0.83 (s, 9H), 0.84 (s, 9H), 0.87 (s, 9H), 0.87 (s, 9H), 0.92 (d, *J* = 7.2 Hz, 3H), 1.01 (d, *J* = 6.4 Hz, 3H), 1.12 (q, *J* = 12.0 Hz, 1H), 1.33−1.70 (m, 11H), 1.35 (s, 3H), 1.36 (s, 3H), 1.38 (s, 6H), 1.95 (s, 3H), 2.09 (dt, *J* = 14.0 and 6.2 Hz, 1H), 2.18−2.26 (m, 2H), 2.28−2.35 (m, 1H), 2.47−2.59 (m, 4H), 3.51 (d, *J* = 9.3 Hz, 1H), 3.76 (quint, *J* = 5.5 Hz, 1H), 3.82−3.86 (m, 1H), 3.92 (dt, *J* = 11.6 and 2.8 Hz, 1H), 4.03−4.12 (m, 3H), 4.19−4.20 (m, 2H), 5.42 (dd, *J* = 15.4 and 7.3 Hz, 1H), 5.51 (dt, *J* = 15.4 and 6.8 Hz, 1H), 5.76 (dt, *J* = 15.0 and 7.5 Hz, 1H), 6.12 (dd, *J* = 15.0 and 10.7 Hz, 1H), 6.20 (dd, *J* = 14.6 and 10.7 Hz, 1H), 6.30 (dd, *J* = 15.0 and 10.7 Hz, 1H), 6.33 (dd, *J* = 14.8 and 10.8 Hz, 1H), 6.42 (dd, *J* = 14.6 and 10.7 Hz, 1H), 6.48 (dd, *J* = 14.5 and 11.5 Hz, 1H), 6.60 (dd, *J* = 14.5 and 10.7 Hz, 1H), 7.32 (d, *J* = 11.5 Hz, 1H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ −4.6, −4.4, −4.3 (3 × CH_3), −4.3, −4.1, −3.6, 10.0, 12.4, 18.0 (2 × C_0), 18.1, 18.2, 19.0, 19.5, 19.8, 19.9, 25.9 (3 × $(CH_3)_3$), 26.0, 30.2 (2 × CH_3), 30.9, 35.1, 37.0, 38.6, 39.2, 41.2, 43.0, 45.6, 46.7, 52.1, 52.2, 64.6, 64.9, 66.4, 66.7, 68.9, 69.6, 71.2, 74.1, 76.1, 98.5, 98.9, 125.4, 126.5, 127.3, 130.8, 131.7, 132.9 (2 × CH), 135.6, 135.9, 137.2, 140.4, 140.6, 172.7, 207.4. **IR**

(film) ν_{max}/cm^{-1} 3442, 2992, 2954, 2929, 2857, 1707, 1674, 1575, 1472, 1463, 1417, 1381, 1257, 1203, 1167, 1095, 1004, 977, 939, 836, 775. **HRMS (ESI FTMS)** *m*/*z* calcd for $C_{68}H_{126}O_{12}Si_4Na$ [M + Na]$^+$: 1269.8219, found: 1269.8223.

(2*E*,4*E*,6*E*,8*E*,10*E*)-methyl 12-((2*R*,4*S*,8*R*,10*R*)-4,10-dihydroxy-8-((*E*)-3-((4*R*,6*R*)-6-(((4*S*,6*S*)-6-((2*R*,3*S*)-3-hydroxy-4-methylpentan-2-yl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)prop-1-en-1-yl)-1,7-dioxaspiro[5.5]undecan-2-yl)-2-methyldodeca-2,4,6,8,10-pentaenoate (77): NOTE: This entire experimental procedure was performed in the dark. To a solution of compound **73b** (79 mg, 62.6 μmol, 100 mol%) in THF (3.4 mL, 0.02 M) at 0 °C, was added HF.pyridine (90 μL, 3.47 mmol, 5540 mol%). The reaction medium was stirred for 5 min at 0 ºC and warmed to room temperature. After 48 h, the reaction medium was cooled to 0 °C and quenched by the addition of TMSOMe (0.45 mL). The reaction medium was stirred for 5 min at 0 ºC and 15 min at room temperature. After this period, the volatiles were removed under reduced pressure, and the residue was purified by flash column chromatography using a solution of $CHCl_3$/MeOH (95:05) as the eluent to provide a mixture of spiroketals **77a−d** (42 mg, 53.2 μmol, 85%) as a yellow oil. **Spiroketals 77a and 77b: TLC:** R_f = 0.53 (95:05 $CHCl_3$:MeOH) **^{1}H NMR (400 MHz, MeCN-*d*$_3$)** δ 0.77−0.82 (m, 6H), 0.94 (d, *J* = 6.5 Hz, 3H), 0.87−1.47 (m, 14H), 1.28 (s, 6H), 1.38 (s, 6H), 1.54−1.63 (m, 2H), 1.86−2.38 (m, 4H), 1.93 (s, 3H), 2.66 (br s, 1H), 2.67 (br s, 1H), 2.80 (br s, 1H), 3.38 (d, *J* = 8.8 Hz, 1H), 3.70 (s, 3H), 3.71−4.39 (m, 8H), 5.44−5.64 (m, 2H), 5.77−5.96 (m, 2H), 6.06−6.69 (m, 6H), 7.20 (d, *J* = 10.9 Hz, 1H). **^{13}C NMR (125 MHz, MeCN-*d*$_3$)** δ 9.2, 9.2, 13.0, 19.4, 20.0, 20.2, 20.2, 29.8, 30.1, 30.2, 30.4, 30.6, 30.6, 30.7, 31.8, 36.1, 36.1, 37.7, 37.9, 39.4, 39.9, 40.2, 40.4, 40.4, 40.5, 41.1, 41.6, 42.1, 43.5, 44.1, 44.1, 44.2, 52.3, 64.5, 65.8, 65.8, 65.9, 66.0, 66.1, 69.5, 69.6, 69.8, 71.0, 71.5, 72.2, 72.8, 72.9, 75.9, 76.0, 97.2, 97.9, 99.2, 99.3, 126.6, 127.2, 127.5, 127.5, 127.9, 128.0, 128.2, 128.5, 128.5, 131.2, 131.2, 131.9, 132.0, 133.0, 133.2, 133.4, 133.6, 133.7, 134.0, 134.1, 134.2, 134.3, 136.2, 136.4, 137.6, 137.7, 139.0, 139.0, 140.8, 140.8, 169.3. **HRMS (ESI FTMS)** *m*/*z* calcd for $C_{45}H_{68}O_{10}Na$ [M + Na − H_2O]$^+$: 791.4694, found: 791.4703. **Spiroketals 77c and 77d: TLC:** R_f = 0.38 (95:05 $CHCl_3$:MeOH) **^{1}H NMR (500 MHz, MeCN-*d*$_3$)** δ 0.78 (d, *J* = 6.8 Hz, 3H), 0.81 (d, *J* = 7.1 Hz, 3H), 0.94 (d, *J* = 6.6 Hz), 0.99−1.49 (m, 14H), 1.28 (s, 6H), 1.39 (s, 6H), 1.55−1.65 (m, 2H), 1.85−1.94 (m, 2H), 1.93 (s, 3H), 2.04−2.11 (m, 1H), 2.25−2.38 (m, 1H), 2.69 (d, *J* = 3.8 Hz, 1H), 2.81 (br s, 1H), 2.90 (br s, 1H), 3.38 (d, *J* = 8.5 Hz, 1H), 3.47−4.39

(m, 8H), 3.70 (s, 3H), 5.46 (dd, *J* = 15.6 and 6.6 Hz, 1H), 5.56−5.67 (m, 1H), 5.78−5.91 (m, 1H), 6.18−6.50 (m, 5H), 6.58 (dd, *J* = 14.6 and 11.2 Hz, 1H), 6.66 (dd, *J* = 14.6 and 10.1 Hz, 1H), 7.20 (d, *J* = 11.2 Hz, 1H). **^{13}C NMR (125 MHz, MeCN-*d*$_3$)** *δ* 9.2, 13.0, 19.4, 20.0, 20.2, 20.2, 30.6, 30.7, 31.8, 36.1, 37.8, 39.3, 39.9, 40.0, 40.2, 40.2, 40.3, 40.4, 41.4, 41.5, 41.6, 42.1, 44.1, 45.7, 46.1, 52.3, 64.0, 64.1, 65.2, 65.4, 65.8, 65.9, 66.1, 66.1, 69.5, 70.0, 71.0, 71.1, 71.9, 72.8, 76.0, 99.2, 99.3, 100.4, 100.5, 127.5, 127.8, 128.0, 128.5, 132.0, 132.1, 133.0, 133.1, 133.5, 133.6, 133.7, 133.9, 134.0, 134.1, 136.1, 136.2, 137.6, 139.0, 140.8, 169.3.

(2*E*,4*E*,6*E*,8*E*,10*E*)-12-((2*R*,4*S*,8*R*,10*R*)-4,10-dihydroxy-8-((*E*)-3-((4*R*,6*R*)-6-(((4*S*,6*S*)-6-((2*R*,3*S*)-3-hydroxy-4-methylpentan-2-yl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)prop-1-en-1-yl)-1,7-dioxaspiro[5.5]undecan-2-yl)-2-methyldodeca-2,4,6,8,10-pentaenoic acid (78): NOTE: This entire experimental procedure was performed in the dark. To a solution of the mixture of spiroketals **77** (20.5 mg, 26.0 μmol, 100 mol%) in THF:MeOH:H_2O (4:1:1) (1.3 mL, 0.02 M) at room temperature was added a solution of LiOH (0.26 mL, 0.26 mmol, 1 M in H_2O, 1000 mol%) dropwise. After 24 h, the reaction was diluted with Et_2O (5 mL) and quenched by the addition of 1 M aqueous solution of HCl (1 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to provide the mixture of acids **78** (20 mg, 26.0 μmol, 99%) as a yellow oil. **TLC:** R_f = 0.36 (95:05 $CHCl_3$:MeOH) **^{1}H NMR (600 MHz, MeCN-*d*$_3$)** *δ* 0.78 (d, *J* = 6.6 Hz, 3H), 0.81 (d, *J* = 7.0 Hz, 3H), 0.94 (d, *J* = 6.4 Hz, 3H), 0.99−1.31 (m, 13H), 1.27 (s, 3H), 1.28 (s, 3H), 1.39 (s, 6H), 1.42−1.48 (m, 3H), 1.56−1.65 (m, 2H), 1.80−1.91 (m, 2H), 1.91 (s, 3H), 2.05−2.34 (m, 2H), 2.68 (br s, 1H), 2.77 (br s, 1H), 2.88 (br s, 1H), 3.38 (d, *J* = 8.8 Hz, 1H), 3.47−4.39 (m, 8H), 5.46 (dd, *J* = 15.5 and 6.8 Hz, 1H), 5.57−5.68 (m, 1H), 5.79−5.90 (m, 1H), 6.16−6.51 (m, 5H), 6.59 (dd, *J* = 14.5 and 11.5 Hz, 1H), 6.66 (dd, *J* = 14.5 and 10.4 Hz. 1H), 7.21 (d, *J* = 11.5 Hz, 1H). **^{13}C NMR (150 MHz, MeCN-*d*$_3$)** *δ* 9.2, 12.9, 19.4, 20.0, 20.2, 20.2, 30.6, 30.7, 31.8, 36.1, 37.8, 37.8, 39.3, 39.9, 40.0, 40.2, 40.2, 40.3, 40.5, 41.4, 41.5, 41.6, 42.1, 44.1, 45.7, 46.1, 64.0, 64.1, 65.2, 65.4, 65.9, 65.9, 66.1, 66.1, 69.5, 70.0, 71.0, 71.1, 71.9, 72.9, 76.0, 99.2, 99.4, 100.4, 100.5, 127.2, 127.8, 128.0, 128.6, 132.0, 132.1, 133.0, 133.1, 133.5, 133.6, 133.8, 133.9, 134.0, 134.1, 136.1, 136.3, 137.6, 139.5, 140.8, 169.6. **HRMS (ESI FTMS)** *m*/*z* calcd for $C_{44}H_{66}O_{10}Na$ $[M + Na - H_2O]^+$: 777.4537, found: 777.4540.

(2*E*,4*E*)-5-(tributylstannyl)penta-2,4-dien-1-ol (80): To a solution of ester **86** (463 mg, 1.12 mmol, 100 mol%) in CH_2Cl_2 (2.4 mL, 0.47 M) at −78 °C was added DIBAL-H (2.8 mL, 2.8 mmol, 1 M in hexanes, 250 mol%) over 40 min using a syringe pump. After 30 min, the reaction was quenched by the addition of saturated aqueous solution of sodium potassium tartrate (10 mL) and warmed to room temperature. After 3 h, the layers were separated and the aqueous layer was extracted with Et_2O (3 × 25 mL). The combined organic layers were washed with brine (25 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography using a solution of hexane/ethyl acetate (80:20) as the eluent to provide alcohol **80**[68] (376 mg, 1.01 mmol, 90%) as a colorless oil. **TLC:** R_f = 0.53 (80:20 hexane:EtOAc) **^{1}H NMR (500 MHz, $CDCl_3$)** δ 0.88 (t, J = 7.3 Hz, 9H), 0.89 (t, J = 7.5 Hz, 6H), 1.26−1.35 (m, 6H), 1.46−1.52 (m, 6H), 4.19 (t, J = 5.8 Hz, 2H), 5.78 (dt, J = 15.1 and 5.8 Hz, 1H), 6.22 (dd, J = 15.1 and 10.0 Hz, 1H), 6.25 (d, J = 18.8 Hz, 1H), 6.52 (dd, J = 18.8 and 10.0 Hz, 1H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 9.5, 13.7, 27.2, 29.1, 63.4, 130.7, 134.6, 135.1, 145.9. **IR (film)** ν_{max}/cm^{-1} 3347, 2956, 2924, 2852, 1566, 1464, 1418, 1376, 1083, 999, 659.

(−)-(5*R*,7*R*,11*S*,13*R*)-7,11-bis((*tert*-butyldimethylsilyl)oxy)-5-((*E*)-3-((4*R*,6*R*)-6-(((4*S*,6*S*)-6-((2*R*,3*S*)-3-hydroxy-4-methylpentan-2-yl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)prop-1-en-1-yl)-13-((2*E*,4*E*)-5-iodopenta-2,4-dien-1-yl)-2,2,3,3,15,15,16,16-octamethyl-4,14-dioxa-3,15-disilaheptadecan-9-one (87): To a suspension of $CrCl_2$ (141 mg, 1.15 mmol, 3000 mol%.) in dioxane:THF (6:1) (1.8 mL, 0.64 M) at 0 °C was added a solution of the aldehyde **7** (42 mg, 38.3 μmol, 100 mol%) and CHI_3 (122 mg, 0.31 mmol, 800 mol%) in dioxane:THF (6:1) (1.2 mL, 0.03 M). The reaction medium was stirred for 30 min at 0 ºC and 1.5 h at 0 ºC. After this period, the reaction was diluted with EtOAc (5 mL) and quenched by the addition of saturated aqueous solution of NH_4Cl (5 mL) and saturated aqueous solution of $Na_2S_2O_3$ (5 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography using a solution of hexane/ethyl acetate (90:10) as the eluent to provide vinyl iodide **87** (39 mg, 31.5 μmol, 82%, dr = 89:11, E:Z) as a pale yellow oil.

Diastereoisomeric ratio was determined by ^{1}H NMR analysis of the diastereoisomeric mixture of compounds. **TLC:** R_f = 0.30 (90:10 hexane:EtOAc)

Optical rotation: $[\alpha]_D^{20}$ −6 (*c* 0.5, $CHCl_3$) **^{1}H NMR (500 MHz, $CDCl_3$)** δ 0.01 (s, 3H), 0.01 (s, 3H), 0.01 (s, 3H), 0.03 (s, 6H), 0.04 (s, 3H), 0.05 (s, 3H), 0.06 (s, 3H), 0.78 (d, *J* = 6.7 Hz, 3H), 0.84 (s, 9H), 0.85 (s, 9H), 0.87 (s, 18H), 0.92 (d, *J* = 7.2 Hz, 3H), 1.02 (d, *J* = 6.4 Hz, 3H), 1.13 (q, *J* = 12.0 Hz, 1H), 1.34−1.46 (m, 3H), 1.35 (s, 3H), 1.36 (s, 3H), 1.39 (s, 6H), 1.47−1.70 (m, 8H), 2.07−2.27 (m, 4H), 2.24−2.64 (m, 4H), 2.99 (s, 1H), 3.51 (d, *J* = 9.3 Hz, 1H), 3.73−3.79 (m, 1H), 3.82−3.87 (m, 1H), 3.90−3.94 (m, 1H), 4.02−4.13 (m, 3H), 4.16−4.22 (m, 2H), 5.43 (dd, *J* = 15.4 and 7.2 Hz, 1H), 5.52 (dt, *J* = 15.4 and 6.9 Hz, 1H), 5.69 (dt, *J* = 15.2 and 7.2 Hz, 1H), 5.98 (dd, *J* = 15.2 and 10.5 Hz, 1H), 6.18 (d, *J* = 14.3 Hz, 1H), 6.98 (dd, *J* = 14.3 and 10.5 Hz, 1H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ −4.6, −4.3, −4.3 (2 × CH_3), −4.3, −4.2, −4.1, −3.6, 10.0, 18.0, 18.0, 18.0, 18.2, 19.0, 19.5, 19.8, 19.9, 25.9 (3 × $(CH_3)_3$), 26.0, 30.2 (2 × CH_3), 30.9, 35.1, 37.0, 38.7, 39.2, 40.7, 43.0, 45.5, 46.7, 52.2, 52.2, 64.6, 65.0, 66.5, 66.7, 69.0, 69.3, 71.2, 74.1, 76.1, 77.0, 98.5, 98.9, 126.5, 131.8, 132.6, 136.0, 145.3, 207.3. **IR (film)** ν_{max}/cm^{-1} 3508, 2991, 2954, 2930, 2897, 2857, 1716, 1642, 1472, 1463, 1380, 1256, 1202, 1168, 1094, 979, 939, 836, 808, 776, 740. **HRMS (ESI FTMS)** *m*/*z* calcd for $C_{60}H_{117}O_{10}Si_4INa$ $[M + Na]^+$: 1259.6666, found: 1259.6663.

2-(2*S*,3*S*)-2-((4*S*,6*S*)-6-(((4*R*,6*R*)-2,2-dimethyl-6-((2*E*,4*R*,6*R*,10*S*,12*R*,14*E*,16*E*)-4,6,10,12-tetrakis((*tert*-butyldimethylsilyl)oxy)-17-iodo-8-oxoheptadeca-2,14,16-trien-1-yl)-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)-4-methylpentan-3-yl 2-(diethoxyphosphoryl)propanoate (81): To a solution of alcohol **87** (62 mg, 50.1 μmol, 100 mol%) and 2-(diethoxyphosphoryl)propanoic acid (111 mg, 0.53 mmol, 1060 mol%) in benzene (2.8 mL, 0.02 M) at room temperature were added Et_3N (0.24 mL, 1.71 mmol, 3400 mol%), TCBC (0.13 mL, 0.80 mmol, 1600 mol%), and DMAP (131 mg, 1.07 mmol, 2100 mol%). After 1 h, the reaction was quenched by the addition of saturated aqueous solution of $NaHCO_3$ (5 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography using a solution of hexane/ethyl acetate (60:40) as the eluent to provide compound **81** (66 mg, 46.2 μmol, 92%, *dr* = 1:1, C2*R*:C2*S*) as a pale yellow oil.

Diastereoisomeric ratio was determined by ^{1}H NMR analysis of the diastereoisomeric mixture of compounds. **TLC for compound less polar:** R_f = 0.60 (60:40 hexane:EtOAc) **TLC for compound more polar:** R_f = 0.48 (60:40 hexane:EtOAc) **Optical rotation:** $[\alpha]_D^{20}$ +2 (*c* 0,5, $CHCl_3$) **^{1}H NMR (500 MHz, $CDCl_3$)** δ 0.00 (s, 3H), 0.01 (s, 6H), 0.03 (s, 6H), 0.04 (s, 3H), 0.05 (s, 3H), 0.05 (s, 3H), 0.81−0.89 (m, 42H), 0.92 (d, *J* = 6.6 Hz, 3H), 1.04 (q, *J* = 12.0 Hz, 1H), 1.12 (q, *J* = 12.0 Hz, 1H), 1.30−1.48 (m, 27H), 1.50−1.69 (m, 6H), 1.71−1.78 (m, 1H), 1.83−1.90 (m, 1H), 2.06−2.26 (m, 4H), 2.46−2.62 (m, 4H), 3.00 (dq, *J* = 23.3 and 7.3 Hz, 1H), 3.48−3.59 (m, 1H), 3.70−3.86 (m, 2H), 3.99−4.06 (m, 2H), 4.08−4.22 (m, 7H), 5.10 (dd, *J* = 8.9 and 2.1 Hz, 1H), 5.42 (dd, *J* = 15.4 and 7.2 Hz, 1H), 5.51 (dt, *J* = 15.4 and 6.8 Hz, 1H), 5.69 (dt, *J* = 15.3 and 7.3 Hz, 1H), 5.98 (dd, *J* = 15.2 and 10.6 Hz, 1H), 6.18 (d, *J* = 14.3 Hz, 1H), 6.98 (dd, *J* = 14.3 and 10.6 Hz, 1H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ −4.6, −4.3, −4.3 (2 × CH_3), −4.3, −4.2, −4.1, −3.6, 8.5, 12.2 (d, *J* = 6.4 Hz), 16.4 (d, *J* = 5.4 Hz, 2 × CH_3), 18.0, 18.0, 18.1, 18.2, 19.0, 19.5, 19.8, 19.9, 25.9 (3 × $(CH_3)_3$), 26.0, 30.2, 30.2, 30.9, 35.3, 37.1, 39.3, 39.7 (d, *J* = 134.4 Hz), 39.9, 40.7, 43.3, 45.6, 46.7, 52.2, 52.2, 62.4 (d, *J* = 7.3 Hz), 62.5 (d, *J* = 6.4 Hz), 64.8, 64.8, 66.5, 66.7, 68.9, 69.3, 71.2, 77.0, 78.4, 98.5, 98.6, 126.5, 131.8, 132.6, 135.9, 145.3, 168.9 (d, *J* = 4.5 Hz), 207.3. **IR (film)** ν_{max}/cm^{-1} 2990, 2954, 2930, 2907, 2857, 1732, 1644, 1634, 1472, 1463, 1380, 1256, 1204, 1168, 1098, 1053, 1027, 977, 836, 776. **HRMS (ESI FTMS)** *m*/*z* calcd for $C_{67}H_{130}O_{14}Si_4IPNa$ $[M + Na]^+$: 1451.7212, found: 1451.7208.

(2*S*,3*S*)-2-((4*S*,6*S*)-6-(((4*R*,6*R*)-6-((*E*)-3-((2*R*,4*R*,8*R*,10*S*)-4,10-bis((*tert*-butyldimethylsilyl)oxy)-8-((2*E*,4*E*)-5-iodopenta-2,4-dien-1-yl)-1,7-dioxaspiro[5.5]undecan-2-yl)allyl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)-4-methylpentan-3-yl 2-(diethoxyphosphoryl)propanoate (88): To a solution of compound **81** (50 mg, 35.0 µmol, 100 mol%) in THF (1.9 mL, 0.02 M) at 0 °C, was added HF.pyridine (50.3 µL, 1.94 mmol, 5540 mol%). The reaction medium was stirred for 5 min at 0 ºC and warmed to room temperature. After 24 h, the reaction medium was cooled to 0 °C and HF.pyridine (50.3 µL, 1.94 mmol, 5540 mol%) was added The reaction medium was stirred for 5 min at 0 ºC and warmed to room temperature. After 24 h, the reaction medium was cooled to 0 °C and quenched by the addition of TMSOMe (0.50 mL). The reaction medium was stirred for 5 min at 0 ºC and 15 min at room temperature. After this period, the volatiles were removed under reduced pressure, and the residue was used in the next step without further purification.

To a solution of resulting residue (theor. 35.0 μmol, 100 mol%) in CH_2Cl_2 (0.58 mL, 0.06 M) at 0 °C were added 2,6-lutidine (0.04 mL, 0.43 mmol, 1200 mol%) and TBSOTf (0.05 mL, 0.22 mmol, 630 mol%) dropwise. After 1 h, the reaction mixture was loaded directly onto a flash column chromatography using a solution of hexane/CH_2Cl_2/ethyl acetate (30:30:40) as the eluent to provide the compound **88** (36 mg, 30.4 μmol, 87% over 2 steps) as a pale yellow oil. **TLC:** R_f = 0.67 (50:50 hexane:EtOAc)

(2*S*,3*S*)-2-((4*S*,6*S*)-6-(((4*R*,6*R*)-6-((*E*)-3-((2*R*,4*R*,8*R*,10*S*)-4,10-bis((*tert*-butyldimethylsilyl)oxy)-8-((2*E*,4*E*,6*E*,8*E*)-10-hydroxydeca-2,4,6,8-tetraen-1-yl)-1,7-dioxaspiro[5.5]undecan-2-yl)allyl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)-4-methylpentan-3-yl 2-(diethoxyphosphoryl)propanoate (S1): NOTE: This entire experimental procedure was performed in the dark. To a solution of compound **88** (36 mg, 30.4 μmol, 100 mol%) and stannane **80** (34 mg, 91.2 μmol, 300 mol%) in DMF (3.4 mL, 8.9 mM) at 0 °C was added a solution of $PdCl_2(MeCN)_2$ (2.4 mg, 9.12 μmol, 30 mol%) in DMF (1.0 mL, 9 mM) dropwise. After 30 min, the reaction was diluted with Et_2O (10 mL) and quenched by the addition of pH 7 phosphate buffer (5 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography using a solution of hexane/ethyl acetate/Et_3N (50:48:02) as the eluent to provide compound **S1** (34 mg, 29.8 μmol, 98%) as a pale yellow oil. **TLC:** R_f = 0.37 (50:50 hexane:EtOAc) **^{1}H NMR (400 MHz, C_6D_6)** δ 0.01−0.15 (m, 12H), 0.81−2.50 (m, 68H), 2.92−3.04 (m, 1H), 3.41−4.45 (m, 14H), 5.48−6.77 (m, 11H).

(2*S*,3*S*)-2-((4*S*,6*S*)-6-(((4*R*,6*R*)-6-((*E*)-3-((2*R*,4*R*,8*R*,10*S*)-4,10-bis((*tert*-butyldimethylsilyl)oxy)-8-((2*E*,4*E*,6*E*,8*E*)-10-oxodeca-2,4,6,8-tetraen-1-yl)-1,7-dioxaspiro[5.5]undecan-2-yl)allyl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)-4-methylpentan-3-yl 2-(diethoxyphosphoryl)propanoate (89): NOTE: This entire experimental procedure was performed in the dark. This compound was used immediately after purification. To a solution of compound **S1** (34 mg, 29.8 μmol, 100 mol%) in CH_2Cl_2 (0.3 mL, 0.10 M) at room temperature were added TEMPO (0.9 mg, 5.96 μmol, 20 mol%) and BAIB (29 mg, 89.4 μmol, 300 mol%). After 1.5 h, volatiles were removed in a gentle

stream of argon gas. The residue was purified by flash column chromatography using a solution of hexane/ethyl acetate/Et_3N (50:48:02) as the eluent to provide aldehyde **89**, which was immediately used in the next step without further purification, as a pale yellow oil. **TLC:** R_f = 0.46 (50:50 hexane:EtOAc)

(−)-Marinisporolide C (3): NOTE: This entire experimental procedure was performed in the dark. A separate dry flask had been charged with LiCl (26 mg, 0.626 mmol, 2100 mol%) and heated at 140 °C overnight under high vacuum. After allowing the flask to cool to room temperature, a solution of aldehyde **89** (theor. 29.8 μmol, 100 mol%) in MeCN (24.5 mL, 1.2 mM) was added using a cannula. The mixture was stirred for 30 min under these conditions, and DBU (71 μL, 0.477 mmol, 1600 mol%) was added dropwise. After 48 h, the reaction was diluted with Et_2O (50 mL) and quenched by the addition of pH 7 phosphate buffer (50 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure, and the residue was used in the next step without further purification. **TLC:** R_f = 0.69 (80:20 hexane:EtOAc)

To a solution of resulting residue (theor. 29.8 μmol, 100 mol%) in THF (2.2 mL, 0.01 M) at 0 °C, was added HF.pyridine (43.0 μL, 1.65 mmol, 5540 mol%). The reaction medium was stirred for 5 min at 0 ºC and warmed to room temperature. After 24 h, the reaction medium was cooled to 0 °C and quenched by the addition of TMSOMe (0.43 mL). The reaction medium was stirred for 5 min at 0 ºC and 15 min at room temperature. After this period, the volatiles were removed under reduced pressure, and the residue was purified by flash column chromatography using a solution of $CHCl_3$/MeOH (95:05) as the eluent. **TLC for compound less polar:** R_f = 0.48 (95:05 $CHCl_3$:MeOH) **TLC for compound more polar:** R_f = 0.31 (95:05 $CHCl_3$:MeOH)

To a solution of resulting residue (theor. 29.8 μmol, 100 mol%) in MeOH (30 mL, 1 mM) at room temperature was added 12 M aqueous solution of HCl (210 μL, 2.52 mmol, 8400 mol%). After 21 h, Et_3N (0.42 mL, 3.0 mmol, 10000 mol%) was added and the volatiles were removed under reduced pressure. The residue was purified by flash column chromatography using a solution of $CHCl_3$/MeOH (85:15) as the eluent to provide the (−)-marinisporolide C (**3**) (3.0 mg, 4.45 μmol, 15% over 4 steps) as a yellow solid. **TLC:** R_f = 0.33 (85:15 $CHCl_3$:MeOH). **Optical rotation:** $[\alpha]_D^{20}$ −7 (*c* 0.03, MeOH) **^{1}H NMR (600 MHz, DMSO-d_6)** δ 0.80 (d, J = 6.8 Hz, 3H), 0.88 (d, J =

6.8 Hz, 3H), 0.90 (d, *J* = 7.0 Hz, 3H), 0.91 (m, 1H), 1.00 (q, *J* = 11.5 Hz, 1H), 1.06 (q, *J* = 11.5 Hz, 1H), 1.17 (m, 1H), 1.18 (m, 1H), 1.36 (m, 1H), 1.38 (m, 1H), 1.44 (m, 1H), 1.54 (m, 1H), 1.59 (m, 1H), 1.73 (quint, *J* = 7.3 Hz, 1H), 1.80 (m, 1H), 1.81 (m, 1H), 1.82 (m, 1H), 1.89 (s, 3H), 1.89 (m, 1H), 1.92 (m, 1H), 2.09 (dd, *J* = 12.4 and 6.4 Hz, 1H), 2.22 (dd, *J* = 13.0 and 3.0 Hz, 1H), 2.49 (m, 1H), 3.15 (m, 1H), 3.30 (m, 1H), 3.50 (m, 1H), 3.52 (m, 1H), 3.73 (m, 1H), 3.81 (m, 1H), 3.84 (m, 1H), 4.17 (ddd, *J* = 11.3, 7.5 and 1.7 Hz, 1H), 4.40 (d, *J* = 4.3 Hz, OH-25), 4.44 (d, *J* = 5.1 Hz, OH-31), 4.49 (br s, OH-19), 4.54 (br s, OH-27), 4.57 (br s, OH-29), 4.74 (br s, OH-15), 4.93 (d, *J* = 10.0 Hz, 1H), 5.26 (dd, *J* = 15.4 and 7.3 Hz, 1H), 5.34 (ddd, *J* = 15.4, 7.5 and 6.0 Hz, 1H), 5.57 (td, *J* = 10.4 and 6.4 Hz, 1H), 6.21 (t, *J* = 11.4 Hz, 1H), 6.34 (dd, *J* = 14.6 and 11.2 Hz, 1H), 6.45 (dd, *J* = 14.6 and 10.2 Hz, 1H), 6.62 (dd, *J* = 14.6 and 11.2 Hz, 1H), 6.63 (dd, *J* = 14.7 and 9.6 Hz, 1H), 6.66 (dd, *J* = 14.7 and 10.2 Hz, 1H), 6.72 (dd, *J* = 14.6 and 11.4 Hz, 1H), 7.05 (d, *J* = 9.6 Hz, 1H). **^{13}C NMR (150 MHz, DMSO-d_6)** δ 8.9, 13.0, 18.9, 19.9, 29.5, 34.0, 38.2, 40.5, 40.6, 41.0, 41.3, 41.7, 42.2, 45.0, 45.5, 61.8, 63.8, 65.6, 66.7, 68.1, 69.3, 69.8, 70.7, 78.3, 98.8, 126.3, 127.2, 128.4, 130.3, 131.0, 131.7, 131.8, 132.1, 132.8, 137.4, 137.6, 140.1, 167.4. **IR (film)** ν_{max}/cm^{-1} 3417, 2958, 2925, 2854, 1679, 1644, 1579, 1448, 1233, 1099, 1025, 987. **HRMS (ESI FTMS)** *m*/*z* calcd for $C_{38}H_{58}O_{10}Na$ $[M + Na]^+$: 697.3922, found: 697.3923. **UV−Vis (MeOH) λ_{max}/nm:** 261, 360, 373.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. Spectral data for all new compounds (^{1}H and ^{13}C NMR, IR, and HRMS) are provided (PDF).

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We are grateful to FAPESP (2012/02230-0 and 2013/07600-3) for financial support and a fellowship to E.C.L.Jr. (2011/06721-6). We also thank CNPq, CAPES, INCT-INOFAR (CNPq–Proc. 573.564/2008-6), and FAEPEX-UNICAMP (Conv. 519.292). The authors thank Prof. Marcos N. Eberlin (Thomson Laboratory) for HRMS analyses.

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