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Total syntheses of (+)-spiculoic acid A and (+)-zyggomphic acid, new marine natural products of polyketide origin

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ABSTRACT

The total syntheses of both natural (+)-spiculoic acid A and (+)-zyggomphic acid, new cytotoxic marine natural products of polyketide origin, have been accomplished for the first time. These syntheses were achieved by the highly stereoselective and high-yielding intramolecular Diels–Alder reaction of a functionalized (*E*,*E*,*E*)-2,7,9-dodecanal derivative to construct the core tetrahydroindan-2-one skeleton. A stereocongener of (+)-spiculoic acid A, i.e., the (2*R*,5*S*,6*R*)-isomer, was also synthesized. The details of these total syntheses are described.

1. Introduction

Marine organisms produce a number of structurally unique and synthetically formidable natural products.[1] Many marine natural products exhibit a useful level of biological activities, including antibacterial, antifungal, and cytotoxic activities against tumor cells. In 2004, Andersen et al. reported the isolation, structural determination, and biological assay of two polyketides, (+)-spiculoic acid A (**1**) and (−)-spiculoic acid B (**2**) (Fig. 1), as secondary metabolites produced by the Caribbean marine sponge *Plakortis angulospiculatus* (Carter).[2] The relative stereochemistries of **1** and **2** were determined by the Andersen group based on NMR spectroscopic analysis. Although the natural product **1** showed in vitro cytotoxicity against human breast cancer MCF-7 cells, compound **2** showed no cytotoxicity against the same cancer cells. To date, a number of closely related spiculane-type natural products have been isolated from the *Plakortis* species.[3] The Amade group has been involved in the isolation of new spiculoic acid congeners from the *Plakortis* species. In 2005, their group reported three spiculoic acid congeners: (+)-isospiculoic acid A (**3**), (+)-nor-spiculoic acid A (**4**), and (+)-dinor-spiculoic acid A (**5**) isolated from *Plakortis zyggompha*.[4] Later, the Amade group reported the isolation and characterization of additional spiculoic acid congeners from the same sponge.[5] One of these marine natural products was (+)-zyggomphic acid (**6**), a polyketide possessing an (*E*,*E*)-conjugated diene unit in the side chain. All of these natural products **3**–**6** showed marginal cytotoxicity against several tumor cells. The structures of **1**–**6** are characterized by their multiply substituted *trans*-fused tetrahydroindan-2-one core structure carrying six stereogenic carbons, including two contiguous all-carbon quaternary centers, a trisubstituted *Z*-olefin, and a styryl side chain. The Andersen group has proposed that the bicyclic structure of **1** might be constructed in its biosynthetic pathway through an enzyme-catalyzed intramolecular Diels–Alder (IMDA) reaction of a linear (*E*,*E*,*E*)-2,7,9-triene carboxylic acid, which is equipped with all of the alkyl and styryl groups.[2] Since their isolation, synthetic studies on these spiculane-polyketides have been conducted by several groups.[6–9] In 2006, Baldwin et al. reported the first total synthesis of (−)-spiculoic acid A, thereby establishing the absolute stereochemistry of the natural product **1** as depicted in Fig. 1.[7a,10] The Baldwin/Lee group has achieved the total synthesis of (−)-spiculoic acid A by using the IMDA reaction of a linear conjugated diene (4π) installing a terminal unsaturated ester (2π) for the stereoselective construction of the bicyclic core structure. In 2009, we reported the first total synthesis of natural (+)-spiculoic acid A (**1**).[11] Furthermore, we have recently completed the total synthesis of natural (+)-zyggomphic acid (**6**) using a modified synthetic approach to**1**. In this paper, we describe the details of our total syntheses of **1** and **6** and the establishment of the undetermined absolute stereochemistry of **6**.

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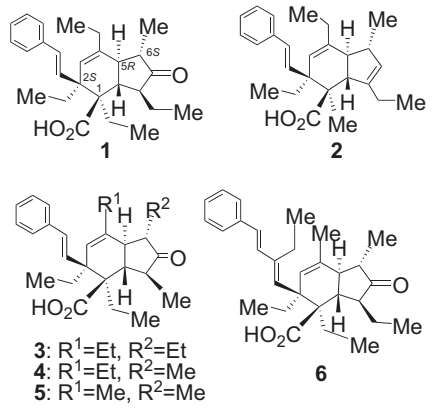
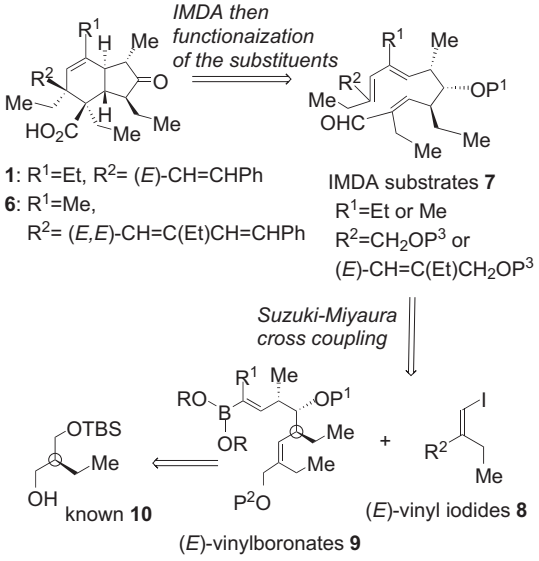


Fig. 1. (+)-Spiculoic acid A and related natural products.

2. Results and discussion

2.1. Unified retrosynthetic analyses of (+)-spiculoic acid A (1) and (+)-zyggomphic acid (6)

In Scheme 1, our common synthetic approach to **1** and **6** is summarized. The central feature of the total syntheses of **1** and **6** is the construction of the core tetrahydroindan-2-one structure using the stereoselective (*endo*/*exo* and π-facial) IMDA reaction[12] of a common triene, such as two types of (*E*,*E*,*E*)-2,7,9-decatrienal derivatives**7**. The substituents (OP^1 and R^2) in the resulting cycloadducts would be further functionalized for completion of the total syntheses of **1** and **6**. We considered that the attempted IMDA reactions would be accelerated in the presence of the terminal unsaturated aldehyde moiety as a dienophile in place of the corresponding unsaturated ester used in Baldwin and Lee's total synthesis. Moreover, the presence of a bulky silyl ether, such as (*tert*-butyldimethylsilyloxy)methyl ($TBSOCH_2$) as R^2 would be beneficial for the outcome of stereoselectivity in the IMDA reactions. The Baldwin/Lee group incorporated a styryl group as R^2 for their IMDA reaction, which may have deactivated to some extent in the diene part.

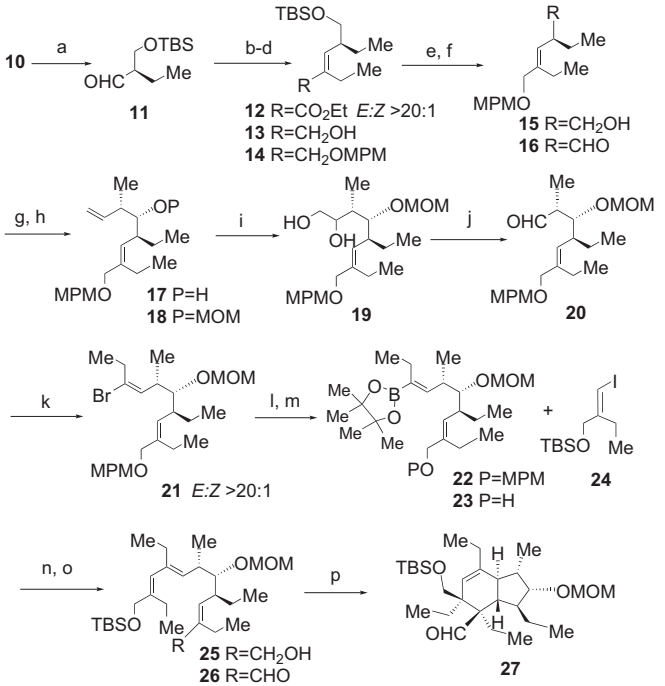


Scheme 1. Retrosynthetic analysis.

The IMDA substrates **7** would be obtained via stereoselective Suzuki–Miyaura coupling between (*E*)-vinyl iodides **8** (two types of R^2) and highly functionalized (*E*)-vinylboronates **9** (R^1 is ethyl for **1**or methyl for **6**). These two vinylboronates **9** in turn would be synthesized straightforwardly from known enantiomerically homogeneous branched five-carbon diol **10**. The conventional synthesis of the differentially protected chiral diol **10**, i.e., (2*S*)-2-[(*tert*-butyldimethylsilyloxy)methyl]butan-1-ol, was developed by Fukumoto et al. using Evans' asymmetric aldol strategy with (*S*)-phenylalanine-derived chiral oxazolin-2-one.[13]

2.2. Total synthesis of (+)-spiculoic acid A (1)

The synthesis and IMDA reaction of substrate **26** for the total synthesis of **1** is depicted in Scheme 2. Swern oxidation of the starting chiral pool **10** provided aldehyde **11**, which was subjected to Wittig olefination with $Ph_3P{=}C(Et)CO_2Et$ in refluxing toluene to provide the (*E*)-unsaturated ester **12** stereoselectively (*E*/*Z* >20:1 based on ^1H NMR analysis). Hydride reduction of **12** followed by protection of the resulting allylic alcohol **13** as (4-methoxyphenyl) methyl (MPM) ether provided **14**. Deprotection of the TBS ether with aqueous acetic acid produced **15**. Swern oxidation of **15** produced aldehyde **16**, which was subjected to *anti*-selective methylhomoallylic alcohol formation. We eventually found that crotylboration using Brown chiral borane,[14] produced in situ by treating *trans*-2-butene with a mixed base (*t*-BuOK and *n*-BuLi) and then adding (−)-methoxydiisopinocampheylborane in the presence of $BF_3{\cdot}Et_2O$, was the best choice of reagent in terms of stereoselectivity. After oxidative treatment of the reaction mixture with alkaline aqueous H_2O_2, *anti*-β-methylhomoallylic alcohol **17** was obtained as the major product of an inseparable diastereomeric



Scheme 2. Synthesis of the IMDA substrate **26** and the IMDA reaction. Reagents and conditions: (a) DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C then Et_3N, rt; (b) $Ph_3P{=}C(Et)CO_2Et$, toluene, reflux, 85% over two steps; (c) DIBAL-H, CH_2Cl_2, −78 °C, 95%; (d) MPMCl, NaH, Bu_4NI, DMF, rt, 94%; (e) AcOH/THF/H_2O=3:2:1, rt, 87%; (f) DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C then Et_3N, rt, 95%; (g) *t*-BuOK, *n*-BuLi, THF, *trans*-2-butene, −100 °C to −50 °C then (−)-B-methoxydiisopinocampheylborane, $BF_3{\cdot}Et_2O$, **16**, −78 °C then 3 M aq NaOH, 35% H_2O_2, reflux; (h) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, reflux, 65% over two steps: (i) OsO_4 in *t*-BuOH, NMO, acetone/H_2O=6:1, rt, 92%; (j) $NaIO_4$, acetone/H_2O=4:1, rt; (k) 1,1-(dibromopropyl)triphenylphosphonium bromide, *n*-BuLi, Et_2O, −78 °C, 77% over two steps; (l) bis(pinacolato)diboron, $PdCl_2(PPh_3)_2$, PPh_3, PhOK, toluene, 50 °C, 78%; (m) DDQ, CH_2Cl_2, aq phosphate buffer, rt, 79%; (n) $PdCl_2$(dppf) (cat.), 3 M aq NaOH, degassed THF, rt, 71%; (o) MnO_2, CH_2Cl_2, rt, 97%; (p) degassed toluene, BHT (cat.), 70 °C, 5 days, 97%.

mixture. The diastereomeric ratio of the crotylboration was approximately 3 to 1 based on ^{1}H NMR analysis, and the minor isomer was cleanly separated by chromatography on silica gel after subsequent protection of the allylic alcohol. Protection of the mixture as the methoxymethyl (MOM) ethers provided the *anti*-isomer **18** in 65% yield over the two steps. The structure of the desired **18** was confirmed by examination of the ^{1}H NMR analysis of some advanced intermediates. Oxidative two-step carbon–carbon bond cleavage via diol **19** produced aldehyde **20**, which was subjected to Wittig olefination using the ylide produced by the treatment of 1,1-(dibromopropyl)triphenylphosphonium bromide with *n*-BuLi at −78 °C,[15] which in turn provided (*E*)-trisubstituted vinyl bromide **21** (*E*/*Z* >20:1 based on ^{1}H NMR analysis). Treatment of **21** with bis(pinacolate)diboron in the presence of $PdCl_2(PPh_3)_2$, PPh_3, and PhOK in toluene at 50 °C[16] provided vinylboronate **22** (**9**: R^1=Et, P^1=MOM, P^2=MPM) in a good yield of 78%. Deprotection of the MPM group in **22** with DDQ in aqueous phosphate buffer provided allylic alcohol **23**. Suzuki–Miyaura coupling between (*E*)-vinylboronate **23** and (*E*)-vinyl iodide **24** (**8**: R^2=CH_2OTBS) was performed under the Pd-catalyzed standard conditions to construct the (*E*,*E*)-diene moiety, producing **25** efficiently in 71% yield. The vinyl iodide **24** was conventionally synthesized from diethyl ethylmalonate by the procedure analogous to Baker's precedent, which was adapted to diethyl methylmalonate.[17] Oxidation of the allylic alcohol moiety in **25** with MnO_2 provided the IMDA substrate **26** (**7**: R^1=Et, R^2=CH_2OTBS, P^1=MOM). To our satisfaction, prolonged (5 days) heating **26** in toluene at 70 °C produced the desired *endo*-adduct **27** as a sole product in an excellent yield of 97%.The IMDA reaction of **26** proceeded rather slowly but cleanly at 70 °C. After heating was performed at 70 °C for 1 or 2 days, a substantial amount of the substrate **26** remained intact.

As depicted in Fig. 2, the observed exclusive *endo*- and π-facial selectivity in the IMDA reaction of **26** was reasonably explained using two transition states, *endo* ***TS*** leading to **27** and *exo* ***TS*** leading to undesired *cis*-fused *exo*-adduct **28** (not obtained). It is obvious that the C-8 substituent (an ethyl group) cooperated in realizing the high stereoselectivity. In the transition states depicted in Fig. 2, both π-facial selectivities were the same. On the other hand, the opposite π-facial attack in *endo* ***TS*** was significantly unfavorable owing to a severe allylic interaction ($A^{1,3}$ strain) generated between the ethyl group at C-8 and the ethyl group in the dienophile part. Regarding the two transition states depicted in Fig. 2, *exo* ***TS*** was significantly disfavored as a result of a severe $A^{(1,3)}$ strain occurring between the ethyl substituent at C-4 and the methyl group at C-6. In the case of *endo* ***TS***, this interaction could be avoided; thus the IMDA reaction proceeded via *endo* ***TS*** exclusively to produce **27** as the sole product.

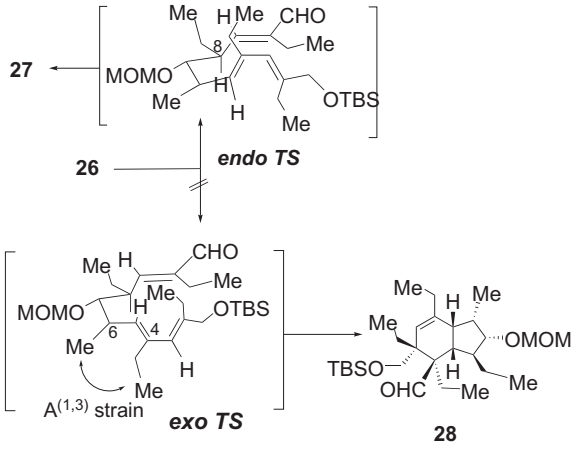
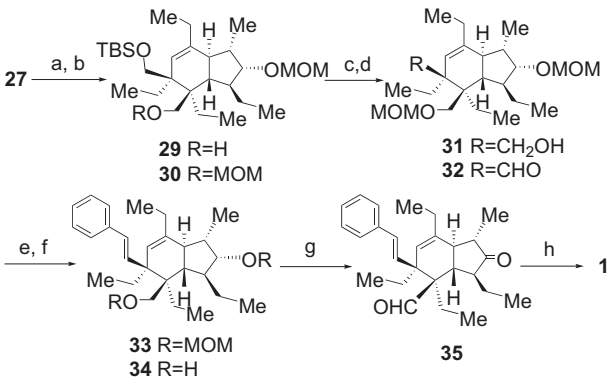


Fig. 2. The *endo*- and *exo*-transition states for the IMDA reaction of **26**.

The completion of the total synthesis of **1** from the IMDA adduct **27** is shown in Scheme 3. $NaBH_4$ reduction of **27** produced **29**. On the other hand, we observed a one-step formation of the IMDA substrate **26** in the Suzuki–Miyaura coupling between **23** and **24** when the cross-coupling was executed with an excess amount of the Pd-catalyst in DMF in the presence of Cs_2CO_3 at 70 °C for a prolonged reaction time (more than 3 days). Under these conditions, the formation of **26**[18] and a spontaneous IMDA reaction occurred. $NaBH_4$ reduction of the crude mixture and purification on silica gel provided **29** in a less effective yield of 33% from **23**. Protection of the resulting primary alcohol **29** as the MOM ether produced **30**. Deprotection of the TBS group in **30** and successive Swern oxidation of the resulting **31** provided aldehyde **32**. Horner–Wadsworth–Emmons (HWE) olefination of **32** with the anion generated from diethyl benzylphosphonate using *n*-BuLi as base introduced a styryl moiety to produce **33** in a good yield of 88%. Deprotection of both MOM groups in **33** and Dess–Martin oxidation[19] of the resulting diol **34** provided aldehyde–keto intermediate **35**. Kraus–Pinnick oxidation[20] of **35** eventually provided (+)-spiculoic acid A (**1**). The spectral data of the synthetic **1** were identical to those reported for the natural product. Furthermore, $[\alpha]_D$ of the synthetic **1** [$[\alpha]_D^{25}$ +102 (*c* 0.38, CH_2Cl_2)] established the absolute stereochemistry of the natural product [$[\alpha]_D$ +110 (*c* 0.1, CH_2Cl_2) for natural **1**[2]] as depicted.



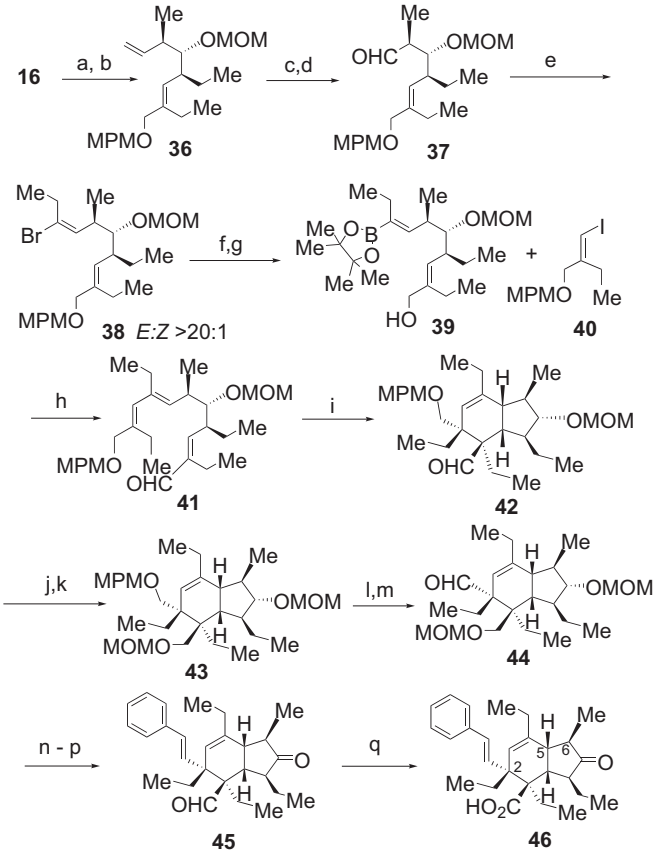
Scheme 3. Completion of the total synthesis of (+)-spiculoic acid A (**1**). Reagent and conditions: (a) $NaBH_4$, MeOH/THF=1:1, rt, 91%; (b) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, reflux; (c) *n*-Bu_4NF, THF, 50 °C, 99% over two steps; (d) DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C then Et_3N, rt, 90%; (e) diethyl benzylphoshonate, *n*-BuLi, THF, −78 °C then **32**, 0 °C, 88%; (f) CSA, MeOH, 40 °C, 6 days; (g) Dess–Martin periodinane, CH_2Cl_2, rt, 85% over two steps; (h) $NaClO_2$, 2-methyl-2-butene, phosphate buffer, *t*-BuOH/H_2O=5:1, rt, 82%.

In another approach, we obtained the following unsuccessful results.$NaClO_2$oxidation of the aldehyde functionality in an *endo*-adduct similar to **27**, which possessed a (4-methoxyphenyl)methyl (MPM) group in place of TBS group in **27**, provided the corresponding carboxylic acid. After methyl esterification and the removal of the MPM group of the resulting ester, the γ-lactonization product was obtained as a sole product. It was thus obvious that the facile γ-lactone formation occurred spontaneously owing to the vicinal *cis*-relationship of the carboxylic acid and the primary hydroxy group. We could not find efficient conditions to open this γ-lactone for further functionalization. We concluded that the synthetic route involving direct oxidation of the aldehyde **27** to the corresponding carboxylic acid could not evade the above-mentioned synthetic dead end.

2.3. Synthesis of (2*R*,5*S*,6*R*)-isomer of (+)-spiculoic acid A (46)

To obtain greater insight into the stereoselectivity of the IMDA reaction to construct the core bicyclic structure and to synthesize the stereoisomers of (+)-spiculoic acid A (**1**), we next investigated

the synthesis of another diastereomeric substrate for the IMDA reaction. The synthesis of the substrate **41**, its IMDA reaction, and transformation of the IMDA adduct into the (2*R*,5*S*,6*R*)-isomer (**46**)[21] of (+)-spiculoic acid A are summarized in Scheme 4.



Scheme 4. Synthesis of the (2*R*,5*S*,6*R*)-isomer (**46**) of spiculoic acid A. Reagents and conditions: (a) *t*-BuOK, *n*-BuLi, THF, *cis*-2-butene, −78 °C to −50 °C then (2′*Z*,4*S*,5*S*)-2-(but-2-enyl)-4,5-di(isopropyloxycarbonyl)-1,3,2-dioxaborolane, toluene, **16**, MS 4 Å, −78 °C then 3 M aq NaOH, rt, 83%; (b) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, reflux, 94%; (c) OsO_4 in *t*-BuOH, NMO, acetone/H_2O=6:1, rt, 96%; (d) $NaIO_4$, acetone/H_2O=4:1, rt; (e) 1,1-(dibromopropyl)triphenylphosphonium bromide, *n*-BuLi, Et_2O, −78 °C, 50% over two steps; (f) bis(pinacolato)diboron, $PdCl_2(PPh_3)_2$, PPh_3, PhOK, toluene, 50 °C, 74%; (g) DDQ, CH_2Cl_2, aq phosphate buffer, rt, 88%; (h) $Pd(PPh_3)_4$ (excess), Cs_2CO_3, degassed DMF, 70 °C, 74%; (i) toluene, BHT (cat.), Wako Gel C-300, 80 °C, 2 days, 82% (>11:1 mixture); (j) $NaBH_4$, MeOH, rt, 77%; (k) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, reflux, 88%; (l) DDQ, CH_2Cl_2, aq phosphate buffer, rt, 99%; (m) Dess–Martin periodinane, CH_2Cl_2, rt, 82%; (n) diethyl benzylphoshonate, *n*-BuLi, THF, −78 °C then **44**, 0 °C, 96%; (o) 6 M aq HCl/THF=1:1, rt, 84%; (p) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, rt, 81%; (q) $NaClO_2$, 2-methyl-2-butene, phosphate buffer, *t*-BuOH/H_2O=5:1, rt, 91%.

The aforementioned aldehyde **16** was subjected to the crotylboration conditions developed by Roush et al. using (*S*,*S*)-diisopropyl tartrate-modified chiral crotylboronate prepared from *cis*-2-butene.[22] As a result, *syn*-β-methyl-homoallylic alcohol, with a configuration at the methyl-bearing carbon opposite to that in **17**, was obtained as the sole product in a high yield of 83%. Thus obtained *syn*-β-methyl-homoallylic alcohol was protected as the MOM ether to provide **36**. The reaction sequence from **36** to **46** was mostly analogous to that used for the synthesis of **1**. OsO_4-mediated diol formation of **36**, with oxidative cleavage of the resulting diol provided **37**, which was subjected to Wittig olefination to produce the expected (*E*)-bromoolefin **38** almost exclusively (*E*/*Z* >20:1). The Miyaura vinylboronation of **38** and deprotection provided **39** without event. The Suzuki–Miyaura coupling between **39** and vinyl iodide **40**, which was prepared analogously as TBS ether **24**, efficiently provided the desired (*E*,*E*)-diene **41**. By using an excess amount of the palladium catalyst, the coupling reaction furnished the unsaturated aldehyde **41** directly. The IMDA reaction of **41** started at 110 °C (toluene, reflux) slowly. After 16 h, 76% of **41** was recovered. Although the IMDA reaction completed by heating **41** at 160 °C (toluene in a sealed tube) for 16 h, a significant amount of an inseparable unidentified product was produced along with the desired IMDA adduct **42** (approximately 1:1 ratio). The thermal IMDA reaction of **41** accelerated in the presence of silica gel (Wako gel C-300) at 80 °C. After 2 days of heating, an IMDA adduct **42** was obtained as a predominant product in a high yield of 82%. Although we have no rational explanation for the role of the silica gel, some examples of the silica-gel-promoted IMDA reaction are known.[23] The adduct **42** contained a small amount of another product as an inseparable byproduct in a ratio of >11:1 (based on ^1H NMR analysis). Although this minor product was removed in the next step, we could not determine its precise structure. The structure and stereochemistry of the predominant IMDA adduct **42** were determined to be a *cis*-fused hexahydroindane derivative by NOE experiments on **42** and the final product **46** (Fig. 3). $NaBH_4$ reduction of the aldehyde group in **42** and protection of the resulting primary hydroxyl group as the MOM ether provided **43**. By deprotection of the MPM group with DDQ, followed by Dess–Martin oxidation, the fully protected bicyclic compound **43** was converted into aldehyde **44**. By using the analogous four steps employed for the conversion of **32** into **1** (Scheme 3), the (2*R*,5*S*,6*R*)-isomer **46** of (+)-spiculoic acid A was efficiently obtained from **44** via **45**. The structure of **46** was determined precisely by examination of its NOE experiment as depicted in Fig. 3. The formation of the *exo*-adduct **42** is rationalized by the transition state argument using an *exo*-mode transition state (*exo* **TS**) as depicted in Fig. 4. In this TS, the π-facial selectivity is the same as that in the case of the *exo* **TS** in Fig. 2. Consequently, the configuration of carbon bearing the methyl substituent(C-6) is a sole stereocontrolling factor for the IMDA reaction of substrate **26** or **41**. In the case of **41**, a severe $A^{(1,3)}$ strain interaction was most likely in the case of the *endo*-transition state. As a result, the IMDA reaction proceeded favorably through the *exo* **TS**.

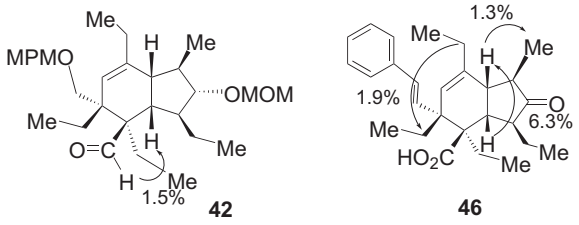


Fig. 3. NOE experiments for **42** and **46**.

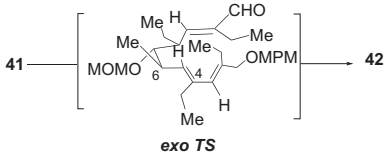
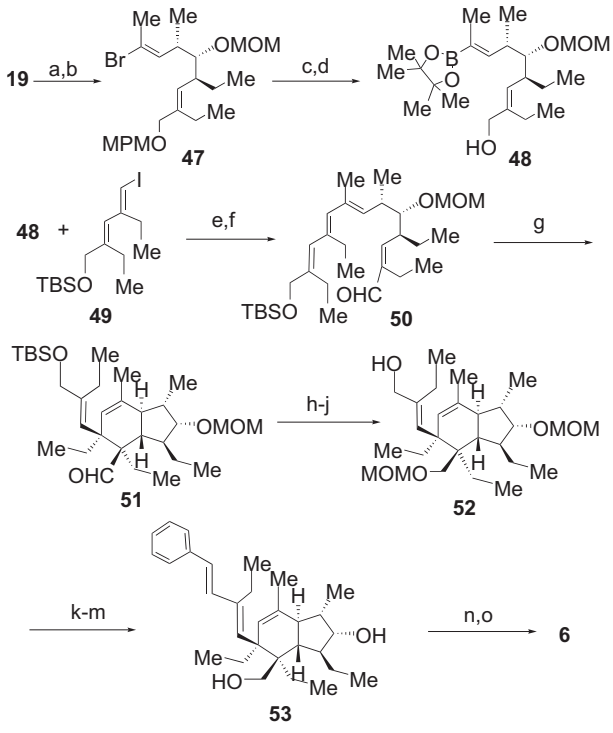


Fig. 4. *exo*-Transition state for the IMDA reaction of **41**.

2.4. Total synthesis of (+)-zyggomphic acid (6)

The proposed planar structure of (+)-zyggomphic acid (**6**) differs from that of (+)-spiculoic acid A (**1**) in the C-4 substituent of the trisubstituted olefin moiety (an ethyl for **1** and a methyl for **6**) and in one of the C-2 substituents [an (*E*)-styryl for **1** and an (*E*,*E*)-2-ethyl-4-phenyl-1,3-butadienyl for **6**]. As the relative stereochemistries of **1** and **6** for all stereogenic carbons are same, the total synthesis of **6** would be expected to be realized using the

synthetic approach analogous to that employed for **1**. The total synthesis of **6** was started from diol **19**, which was subjected to oxidative cleavage to produce aldehyde **20** (Scheme 5). The Wittig olefination of **20** with 1,1-(dibromoethyl)triphenylphosphonium bromide[15] using *n*-BuLi as a base provided (*E*)-vinyl bromide **47** stereoselectively. The vinylboronate formation by the Pd-catalyzed coupling between **47**and bis(pinacolate)diboron and deprotection of the MPM group in the resulting boronate produced (*E*)-vinyl boronate **48** in moderate overall yield. The Suzuki–Miyaura coupling between **48** and (*E*,*E*)-4-iodo-1,3-diethyl-1-(*tert*-butyldimethylsilyloxy)methyl-1,3-butadiene (**49**) proceeded smoothly under the same conditions used for the coupling of **23** and **24**. The vinyl iodide **49** was synthesized from diethyl ethylmalonate.[24] Dess–Martin oxidation of the resulting coupling product provided unsaturated aldehyde **50**. The IMDA reaction of the conjugate triene enal-type substrate **50** proceeded regio- and stereoselectively at 70 °C in the presence of Wako gel C-300 to produce the desired *endo*-adduct **51** in 74% yield and a separable minor product. Although this minor product could not be fully characterized, it may be a hetero-Diels–Alder adduct. The IMDA adduct **51** was transformed to (+)-zyggomphic acid (**6**) in eight further conventional steps without event. Thus, reduction of the aldehyde group in **51**, protection as the MOM ether, and deprotection of the TBS group provided allylic alcohol **52**. Dess–Martin oxidation of **52**, the HWE olefination of the resulting unsaturated aldehyde with diethyl benzylphosphonate, followed by deprotection of the MOM groups by acid hydrolysis produced **53**. The final two-step oxidation of **53** eventually provided (+)-zyggomphic acid (**6**). The spectral comparison (^{1}H and ^{13}C NMR) of the synthetic **6** with the reported data for the natural product revealed that they are identical. Furthermore, specific rotation of the synthetic **6** [$[\alpha]_D^{21.5}$ +82.0 (*c* 0.140, CH_2Cl_2)] well matched with that of natural sample [$[\alpha]_D^{24}$ +85.9 (*c* 0.05, $CHCl_3$)].[5] Thus we established the relative and absolute stereo-chemistries of natural (+)-zyggomphic acid as shown.



Scheme 5. Total synthesis of (+)-zyggomphic acid (**6**). Reagents and conditions: (a) $NaIO_4$, acetone/H_2O=4:1, rt; (b) 1,1-(dibromoethyl)triphenylphosphonium bromide, *n*-BuLi, THF, −78 °C, 41% over two steps; (c) bis(pinacolato)diboron, $PdCl_2(PPh_3)_2$, PPh_3, PhOK, toluene, 50 °C, 50%; (d) DDQ, CH_2Cl_2, aq phosphate buffer, rt, 60%; (e) $PdCl_2$(dppf) (cat), 3 M aq NaOH, degassed THF, rt, 72%; (f) Dess–Martin periodinane, CH_2Cl_2, rt, 88%; (g) degassed toluene, BHT (cat.), Wako Gel C-300, rt, 21 h, 74%; (h) $NaBH_4$, MeOH/THF=1:1, rt, 81%; (i) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, reflux, 89%; (j) *n*-Bu_4NF, THF, rt, 93%; (k) Dess–Martin periodinane, CH_2Cl_2, rt; (l) diethyl benzylphoshonate, *n*-BuLi, THF, −78 °C then aldehyde, 0 °C, 78% over two steps; (m) CSA, MeOH, 40 °C, 5 days; (n) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, rt, 86% over two steps; (o) $NaClO_2$, 2-methyl-2-butene, phosphate buffer, *t*-BuOH/H_2O=5:1, rt, 68%.

3. Conclusion

We have achieved the total synthesis of (+)-spiculoic acid A (**1**) for the first time. The total synthesis featured the highly *endo*- and π-facial selective IMDA reaction of a multisubstituted trienal derivative **26** for an expeditious construction of the core bicyclic skeleton with correct stereochemistry. The synthesis of the IMDA substrate should be specified by the Suzuki–Miyaura coupling between the (*E*)-vinylboronate **23** and the (*E*)-vinyl iodide **24** for the construction of the 1,1,3,4-tetra-substituted (*E*,*E*)-1,3-butadiene moiety. The highly stereoselective outcome of the IMDA reaction can be rationalized by the configuration at the C-6 methyl group in **26**, which directs the *endo*-transition states. Relying on this transition state argument, we also synthesized the (2*R*,5*S*,6*R*)-isomer **46** of (+)-spiculoic acid A through the *exo*-selective IMDA reaction using a C-6 diastereomeric trienal **41**. Finally, we have completed the first total synthesis of natural (+)-zyggomphic acid (**6**), which relied on the *endo*- and π-facial selective IMDA reaction of a more functionalized tetraenal **50**. Our approaches to the syntheses of **1** and **6** are promisingly applicable for the syntheses of other spiculane-type natural products of polyketide origin.

4. Experimental section

4.1. General

Specific rotations were measured in a 10 mm cell. ^{1}H NMR spectra were recorded at 300 MHz with tetramethylsilane as an internal standard with a Varian 300 or a JEOL JNM LA-300 spectrometer. ^{13}C NMR spectra were recorded at 68 MHz or at 75 MHz with the same spectrometer. High-resolution mass spectra (HRMS) were measured with a JEOL GC-Mate mass spectrometer by the EI method (70 eV). Thin-layer chromatography (TLC) was performed on Merck Kieselgel 60 F_{254} plates. The crude reaction mixtures and extractive materials were purified by chromatography on Silica gel 60 (Merck) or Wako gel C-300 (Wako). Combined organic extracts were dried over anhydrous Na_2SO_4. Solvents were removed from the reaction mixture or combined organic extracts by concentration under reduced pressure using an evaporator with bath at 35–45 °C.

4.2. Total synthesis of (+)-spiculoic acid A (1)

*4.2.1. Ethyl (2E,4S)-4-(tert-butyldimethylsilyloxy)methyl-2-ethyl-hex-2-enoate (**12**).* The following reaction was carried out under argon. To a cooled (−78 °C), stirred solution of oxalyl chloride (1.9 mL, 22 mmol) in CH_2Cl_2 (50 mL) was added dropwise DMSO (3.1 mL, 43 mmol). The mixture was stirred at −78 °C for 30 min and then a solution of **10** (3.05 g, 14.0 mmol) in CH_2Cl_2 (3.4 mL) was added. The mixture was stirred at −78 °C for 1 h and then Et_3N (12 mL, 86 mmol) was added. The mixture was warmed gradually to room temperature and then stirred for 1 h. The mixture was diluted with H_2O (120 mL) at 0 °C and extracted with CH_2Cl_2 (60 mL×2). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (40 mL) and H_2O (40 mL×2), dried, and concentrated under reduced pressure to give crude **11**, which was used in the next step without further purification.

The following reaction was carried out under argon. To a stirred solution of the crude **11** obtained above in toluene (30 mL) was added 1-[(ethoxycarbonyl)propylidene]triphenylphosphorane (13.5 g, 35.8 mmol). The mixture was refluxed for 40 h. After being

cooled to room temperature, the mixture was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:200) to provide 3.74 g (85% for two steps) of **12** (E/Z=>20:1, ^{1}H NMR) as a pale yellow oil: TLC R_f 0.46 (EtOAc/hexane, 1:5); $[\alpha]_D^{26}$ +16.4 (*c* 1.53, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.02 (s, 3H), 0.03 (s, 3H), 0.87 (t, *J*=7.5 Hz, 3H), 0.88 (s, 9H), 1.02 (t, *J*=7.5 Hz, 3H), 1.30 (t, *J*=7.2 Hz, 3H), 1.57–1.69 (m, 2H), 2.27–2.40 (m, 2H), 2.43–2.57 (m, 1H), 3.48–3.59 (m, 2H), 4.12–4.27 (m, 2H), 6.47 (d, *J*=10.8 Hz, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ −5.5, −5.4, 11.8 (2C), 14.3 (2C), 20.4, 24.0, 25.9 (3C), 43.3, 60.2, 65.9, 135.2, 143.5, 167.8; IR (neat) 2980, 2935, 2860, 1715, 1650, 1460 cm^{-1}; HRMS calcd for $C_{13}H_{25}O_3Si$ [M−*t*-Bu]$^+$ 257.1573, found 257.1573.

*4.2.2. (2E,4S)-4-(tert-Butyldimethylsilyloxy)methyl-2-ethylhex-2-en-1-ol (**13**).* The following reaction was carried out under argon. To a cooled (−78 °C), stirred solution of **12** (3.74 g, 11.9 mmol) in CH_2Cl_2 (75 mL) was added DIBAL-H (36 mL of 0.99 M solution in toluene, 36 mmol). The mixture was stirred at −78 °C for 40 min and quenched with H_2O (5 mL) at −78 °C. This was diluted with aqueous solution (150 mL) of potassium sodium (+)-tartrate tetrahydrate (50.4 g) and warmed to room temperature. The mixture was stirred vigorously for 3.5 h, diluted with H_2O (75 mL), and extracted with CH_2Cl_2 (60 mL×2). The combined organic layers were dried and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:40 to 1:5) to provide 3.08 g (95%) of **13** as a colorless oil: TLC R_f 0.72 (EtOAc/hexane, 1:5); $[\alpha]_D^{25}$ +28.4 (*c* 1.89, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.03 (s, 6H), 0.85 (t, *J*=7.4 Hz, 3H), 0.88 (s, 9H), 1.01 (t, *J*=7.6 Hz, 3H), 1.09–1.18 (m, 1H), 1.29 (br s,1H), 1.58–1.66 (m, 1H), 2.13 (dq, *J*=2.4, 7.6 Hz, 2H), 2.34–2.44 (m, 1H), 3.46 (d, *J*=6.6 Hz, 2H), 4.07 (s, 2H), 5.10 (d, *J*=10.0 Hz, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ −5.4 (2C), 11.7 (2C), 13.6, 21.4, 24.4, 25.9 (3C), 42.0, 66.7 (2C), 127.7, 142.3; IR (neat) 3340, 2880, 2860, 1460 cm^{-1}; HRMS calcd for $C_{11}H_{23}O_2Si$ [M−*t*-Bu]$^+$ 257.1467, found 257.1468.

*4.2.3. (3E,5S)-5-(tert-Butyldimethylsilyloxy)methyl-3-(4-methoxybenzyloxy)methylhept-3-ene (**14**).* To a cooled (0 °C), stirred solution of **13** (3.08 g, 11.3 mmol) in DMF (62 mL) was added NaH (60% in oil, 839 mg, 20.8 mmol). The mixture was stirred at 0 °C for 10 min and MPMCl (3.8 mL, 28 mmol) and *n*-Bu_4NI (10.5 g, 28.3 mmol) were added at 0 °C. The mixture was stirred at room temperature for 21 h, diluted with saturated aqueous $NaHCO_3$ (120 mL), and extracted with Et_2O (120 mL×3). The combined organic layers were washed with H_2O (60 mL×3), dried, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:150) to provide 4.16 g (94%) of **14** as a colorless oil: TLC R_f 0.58 (EtOAc/hexane, 1:6); $[\alpha]_D^{23.5}$ +19.2 (*c* 1.44, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.03 (s, 6H), 0.87 (t, *J*=7.5 Hz, 3H), 0.88 (s, 9H), 1.00 (t, *J*=7.5 Hz, 3H), 1.05–1.17 (m, 1H), 1.57–1.70 (m, 1H), 2.14 (q, *J*=7.5 Hz, 2H), 2.35–2.48 (m, 1H), 3.44 (dd, *J*=6.4, 9.8 Hz, 1H), 3.49 (dd, *J*=6.4, 9.8 Hz, 1H), 3.80 (s, 3H), 3.96 (s, 2H), 4.38 (s, 2H), 5.10 (d, *J*=10.0 Hz, 1H), 6.85–6.90 (m, 2H), 7.24–7.29 (m, 2H); ^{13}C NMR (68 MHz, $CDCl_3$) δ −5.3 (2C), 11.8 (2C), 13.3, 21.4, 24.5, 25.9 (3C), 42.2, 55.2, 66.7, 70.8, 73.7, 113.7 (2C), 129.3 (3C), 130.0, 139.2, 159.0; IR (neat) 2940, 2860, 1615, 1515, 1460 cm^{-1}; HRMS calcd for $C_{19}H_{31}O_3Si$ [M−*t*-Bu]$^+$ 335.2043, found 335.2042.

*4.2.4. (2S,3E)-2-Ethyl-4-(4-methoxybenzyloxy)methylhex-3-en-1-ol (**15**).* A solution of **14** (4.16 g, 10.6 mmol) in AcOH/THF/H_2O (3:2:1, 84 mL) was stirred at room temperature for 21.5 h and concentrated under reduced pressure with the aid of EtOH and toluene. The residue was chromatographed on silica gel (EtOAc/hexane, 1:40 to 1:8) to provide 2.55 g (87%) of **15** as a colorless oil: TLC R_f 0.25 (EtOAc/hexane, 1:3); $[\alpha]_D^{22}$ +9.8 (*c* 1.62, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, *J*=7.5 Hz, 3H), 1.01 (t, *J*=7.5 Hz, 3H), 1.12–1.27 (m, 1H), 1.39–1.56 (m, 1H), 1.67 (br s, 1H), 2.07–2.25 (m, 2H), 2.43–2.55 (m, 1H), 3.38 (dd, *J*=8.3, 10.4 Hz, 1H), 3.56 (dd, *J*=5.6, 10.4 Hz, 1H), 3.81 (s, 3H), 3.96 (s, 2H), 4.41 (s, 2H), 5.11 (d, *J*=10.2 Hz, 1H), 6.86–6.91 (m, 2H), 7.24–7.29 (m, 2H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 11.7, 13.3, 21.5, 24.4, 42.3, 55.2, 66.3, 71.3, 73.4, 113.7 (2C), 128.9, 129.3 (2C), 130.4, 141.5, 159.1; IR (neat) 3270, 2960, 2890, 1615, 1515, 1455 cm^{-1}; HRMS calcd for $C_{17}H_{26}O_3$ [M]$^+$ 278.1882, found 278.1870.

*4.2.5. (2S,3E)-2-Ethyl-4-(4-methoxybenzyloxy)methylhex-3-enal (**16**).* The following reaction was carried out under argon. To a cooled (−78 °C), stirred solution of oxalyl chloride (0.72 mL, 8.4 mmol) in CH_2Cl_2 (20 mL) was added dropwise DMSO (1.2 mL, 17 mmol). The mixture was stirred at −78 °C for 40 min and a solution of **15** (1.33 g, 4.78 mmol) in CH_2Cl_2 (2.8 mL) was added. The mixture was stirred at −78 °C for 1 h and Et_3N (4.7 mL, 34 mmol) was added. The mixture was warmed gradually to room temperature and stirred for 1 h. The mixture was diluted with H_2O (30 mL) at 0 °C and extracted with CH_2Cl_2 (15 mL×3). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL), dried, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:35) to provide 1.26 g (95%) of **16** as a colorless oil: TLC R_f 0.50 (EtOAc/hexane, 1:3); $[\alpha]_D^{24.5}$ +43.9 (*c* 1.18, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.93 (t, *J*=7.5 Hz, 3H), 1.01 (t, *J*=7.5 Hz, 3H), 1.45–1.59 (m, 1H), 1.75–1.89 (m, 1H), 2.15 (q, *J*=7.5 Hz, 2H), 3.12–3.21 (m, 1H), 3.81 (s, 3H), 3.98 (s, 2H), 4.41 (s, 2H), 5.25 (d, *J*=9.9 Hz, 1H), 6.86–6.91 (m, 2H), 7.24–7.28 (m, 2H), 9.50 (d, *J*=2.7 Hz, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 11.5, 13.1, 21.8, 22.6, 53.3, 55.3, 71.5, 72.8, 113.8 (2C), 121.4, 129.3 (2C), 130.3, 143.8, 159.2, 201.3; IR (neat) 2960, 2940, 2880, 1725, 1615, 1515, 1460 cm^{-1}; HRMS calcd for $C_{17}H_{24}O_3$ [M]$^+$ 276.1726, found 276.1722.

*4.2.6. (3S,4S,5S,6E)-5-Ethyl-7-(4-methoxybenzyloxy)methyl-4-methoxymethoxy-3-methylnona-1,6-diene (**18**).* The following reaction was carried out under argon. To a cooled (−100 °C), stirred suspension of *t*-BuOK (2.04 g, 18.2 mmol) and *trans*-2-butene (excess) in THF (15 mL) was added dropwise *n*-BuLi (5.7 mL of 2.73 M solution in hexane, 15 mmol). The mixture was stirred at −50 °C for 15 min. The resulting solution was cooled to −100 °C, and a solution of (−)-B-methoxydiisopinocampheylborane (4.89 g, 15.5 mmol) in THF (15 mL) was added. The mixture was stirred at −78 °C for 30 min, and $BF_3\cdot OEt_2$ (2.7 mL, 21 mmol) was added dropwise. Then a solution of **16** (1.26g, 4.55 mmol) in THF (3.5 mL) was added dropwise. After being stirred at −78 °C for 20 h, to the mixture were added 3 M aqueous NaOH (50 mL) and 35% H_2O_2 (25 mL), and the resulting mixture was refluxed for 1 h. After being cooled to room temperature, the mixture was extracted with EtOAc (30 mL×3). The combined organic layers were washed with H_2O (20 mL) and brine (20 mL), dried, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (acetone/hexane, 1:30) to provide 5.45 g of an inseparable mixture of **17**, one diastereomer (dr=ca. 3:1), and IpcOH. By further column chromatographic purification, 5.17 g of an inseparable mixture of **17** and (−)-IpcOH was obtained as a colorless oil, which was used in the next step.

To a stirred solution of the mixture obtained above in CH_2Cl_2 (100 mL) were added *i*-Pr_2NEt (27 mL, 0.16 mol) and MOMCl (5.9 mL, 78 mmol). The mixture was refluxed for 14 h, diluted with saturated aqueous NH_4Cl (200 mL), and extracted with CH_2Cl_2 (100 mL×3). The combined organic layers were dried and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:50 to 1:20) to provide 1.11 g (65% for two steps) of **18** as a colorless oil: TLC R_f 0.50 (EtOAc/hexane, 1:4); $[\alpha]_D^{23}$ +7.5 (*c* 2.23, $CHCl_3$); ^{1}H NMR(300 MHz, $CDCl_3$) δ 0.83 (t, *J*=7.4 Hz, 3H), 0.99 (t, *J*=7.5 Hz, 3H), 1.07 (d, *J*=7.2 Hz, 3H), 1.12–1.28 (m, 1H), 1.69–1.81 (m, 1H),

2.03–2.23 (m, 2H), 2.41–2.51 (m, 2H), 3.22 (dd, *J*=3.3, 7 5 Hz, 1H), 3.41 (s, 3H), 3.81 (s, 3H), 3.96 (s, 2H), 4.38 (s, 2H), 4.65 (d, *J*=6.9 Hz 1H), 4.68 (d, *J*=6.9 Hz, 1H), 4.96–5.04 (m, 2H), 5.12 (d, *J*=10.5 Hz, 1H), 5.88 (ddd, *J*=7.2, 9.9, 17.7 Hz, 1H), 6.88 (d, *J*=8.4 Hz, 2H), 7.26 (d, *J*=8.4 Hz, 2H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 11.9, 12.6, 18.2, 21.6, 23.6, 40.8, 42.8, 55.2, 56.1, 71.0, 73.4, 87.0, 98.5, 113.7 (2C), 114.8, 129.2 (2C), 129.4, 130.7, 138.9, 140.4, 159.1; IR (neat) 2960, 2930, 1615,1515 cm^{-1}; HRMS calcd for $C_{23}H_{36}O_4$ $[M]^+$ 376.2614, found 376.2617.

*4.2.7. (2RS,3S,4R,5S,6E)-5-Ethyl-7-(4-methoxybenzyloxy)methyl-4-methoxymethoxy-3-methylnon-6-ene-1,2-diol (**19** as a ca. 3:1 diastereomeric mixture).* To a stirred solution of **18** (1.11 g, 2.95 mmol) in acetone/H_2O (6:1, 35 mL) were added OsO_4 (3.0 mL of 0.05 M solution in *t*-BuOH, 0.15 mmol) and NMO (995 mg, 8.49 mmol). The mixture was stirred at room temperature for 6 h and additional OsO_4 (1.5 mL of 0.05 M solution in *t*-BuOH, 75 mmol) was added. The mixture was stirred at room temperature for 2 h and additional NMO (350 mg, 2.99 mmol) was added. The mixture was stirred at room temperature for additional 1.5 h, quenched with 1 M aqueous $NaHSO_3$ (55 mL) at 0 °C, filtered through cotton, and washed with EtOAc. The combined filtrate and washings were extracted with EtOAc (30 mL×3), dried, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 2:1 to 1:2) to provide 1.11 g (92%) of **19** as a pale yellow oil: TLC R_f 0.35 (EtOAc/hexane, 2:1); $[\alpha]_D^{21}$ −14.7 (*c* 0.98, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) for major isomer δ 0.85 (t, *J*=7.5 Hz, 3H), 0.92 (d, *J*=6.9 Hz, 3H), 1.00 (t, *J*=7.5 Hz, 3H), 1.11–1.28 (m, 1H), 1.64–1.84 (m, 1H), 1.89–2.02 (m, 1H), 2.09–2.22 (m, 2H), 2.51–2.61 (m, 1H), 3.31–3.53 (m, 2H), 3.42 (s, 3H), 3.64–3.73 (m, 2H), 3.81 (s, 3H), 3.96 (s, 2H), 4.39 (s, 2H), 4.69 (s, 2H), 5.19 (d, *J*=10.2 Hz, 1H), 6.88 (d, *J*=8.4 Hz, 2H), 7.26 (d, *J*=8.4 Hz, 2H); ^{13}C NMR (68 MHz, $CDCl_3$) for major isomer δ 12.1, 12.7, 14.7, 21.6, 23.2, 38.4, 43.2, 55.3, 56.4, 64.8, 71.2, 73.3, 74.3, 87.2, 98.4, 113.7 (2C), 129.3 (3C), 130.5, 139.5, 159.1; IR (neat) 3500, 2960, 1615, 1515 cm^{-1}; HRMS calcd for $C_{23}H_{37}O_6$ $[M-H]^+$ 409.2590, found 409.2579.

*4.2.8. (3E,5S,6S,7S,8E)-3-Bromo-7-ethyl-9-(4-methoxybenzyl-oxy) methyl-6-methoxymethoxy-5-methylundeca-3,8-diene (**21**).* To a cooled (0 °C), stirred solution of the 3:1 diastereomeric mixture **19** (1.11 g, 2.70 mmol) in acetone/H_2O (4:1, 35 mL) was added $NaIO_4$ (1.56 g, 7.29 mmol). The mixture was stirred at room temperature for 30 min and additional $NaIO_4$ (288 mg, 1.35 mmol) was added at 0 °C. The mixture was stirred at room temperature for 20 min, quenched with 1 M aqueous $NaHSO_3$ (55 mL), and extracted with EtOAc (30 mL×3). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (30 mL) and brine (30 mL), dried, and concentrated under reduced pressure to provide 977 mg of crude (2*R*,3*R*,4*S*,5*E*)-4-ethyl-6-(4-methoxybenzyloxy)methyl-3-methoxymethoxy-2-methyloct-5-enal (**20**), which was used in the next step without further purification.

The following reaction was carried out under argon. To a cooled (−40 °C), stirred suspension of (1,1-dibromopropyl)triphenylphosphonium bromide (6.31 g, 11.6 mmol) in Et_2O (30 mL) was added *n*-BuLi (4.0 mL of 2.73 M solution in hexane, 11 mmol). The mixture was stirred at −40 °C for 40 min and cooled to −78 °C. Then a solution of the crude **20** obtained above (977 mg) in Et_2O (3.0 mL) was added dropwise. The mixture was stirred at −78 °C for 1.5 h, quenched with H_2O (5 mL), diluted with saturated aqueous $NaHCO_3$ (40 mL) and H_2O (200 mL), and extracted with EtOAc (80 mL×3).The combined organic layers were washed with saturated aqueous $NaHCO_3$ (40 mL), dried, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:100 to 1:50) to provide 1.01 g (77% for two steps) of **21** as a colorless oil: TLC R_f 0.47 (EtOAc/hexane, 1:5); $[\alpha]_D^{21}$ +5.4 (*c* 1.33, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84 (t, *J*=7.5 Hz, 3H), 0.99 (t, *J*=7.5 Hz, 3H), 1.03 (d, *J*=7.2 Hz, 3H), 1.07 (t, *J*=7.5 Hz, 3H), 1.19–1.34 (m, 1H), 1.62–1.79 (m, 1H), 1.98–2.32 (m, 3H), 2.35–2.55 (m,2H), 2.57–2.70 (m, 1H), 3.22 (dd, *J*=3.9, 6.9 Hz, 1H), 3.40 (s, 3H), 3.81 (s, 3H), 3.95 (s,2H), 4.40 (s, 2H), 4.64 (d, *J*=7.1 Hz, 1H), 4.67 (d, *J*=7.1 Hz, 1H), 5.13 (d, *J*=10.2 Hz, 1H), 5.89 (d, *J*=9.6 Hz, 1H), 6.86–6.89 (m, 2H), 7.24–7.27 (m, 2H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 11.9, 12.7, 13.4, 18.6, 21.5, 23.6, 29.3, 37.5, 42.6, 55.3, 56.2, 71.2, 73.5, 86.2, 98.3, 113.7 (2C), 127.9, 128.7 (2C), 129.2 (2C), 133.6, 139.2, 159.1; IR (neat) 2960, 1615, 1515 cm^{-1}; HRMS calcd for $C_{25}H_{39}O_4Br$ $[M]^+$ 482.2032, found 482.2020.

*4.2.9. 2-[(3Z,5S,6S,7S,8E)-7-Ethyl-9-(4-methoxybenzyloxy)-methyl-6-methoxymethoxy-5-methylundeca-3,8-dien-3-yl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**22**).* The following reaction was carried out under argon. To a stirred solution of **21** (1.01 g, 2.09 mmol) in toluene (40 mL) were added bis(pinacolato)diboron (1.19 g, 4.69 mmol), $PdCl_2(PPh_3)_2$ (117 mg, 0.170 mmol), PPh_3 (91.4 mg, 0.348 mmol), and KOPh (670 mg, 5.07 mmol). The mixture was stirred at 50 °C for 5 h and additional bis(pinacolato) diboron (265 mg, 1.05 mmol) and KOPh (60 mg, 0.45 mmol) were added. The mixture was stirred at 50 °C for 2 h and then additional bis(pinacolato)diboron (159 mg, 0.626 mmol) and KOPh (80 mg, 0.61 mmol) were added. The mixture was stirred at 50 °C for 1 h. After being cooled to room temperature, the mixture was diluted with H_2O (50 mL) and extracted with EtOAc (50 mL). The organic layer was washed with 2 M aqueous NaOH (30 mL×2) and brine (30 mL), dried, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:50 to 1:20) to provide 862 mg (78%) of **22** as a colorless oil: TLC R_f 0.35 (EtOAc/hexane, 1:5); $[\alpha]_D^{18.5}$ +20.9 (*c* 1.55, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84 (t, *J*=7.5 Hz, 3H), 0.94 (t, *J*=7.5 Hz, 3H), 0.98 (t, *J*=7.5 Hz, 3H), 1.01 (d, *J*=6.9 Hz, 3H), 1.19–1.32 (m, 1H), 1.23 (s, 6H), 1.24 (s, 6H), 1.66–1.76 (m, 1H), 1.99–2.21(m, 4H), 2.39–2.49 (m, 1H), 2.78–2.90 (m, 1H), 3.23 (t, *J*=5.7 Hz, 1H), 3.38 (s, 3H), 3.80(s, 3H), 3.91 (d, *J*=12.0 Hz, 1H), 3.99 (d, *J*=12.0 Hz, 1H), 4.35 (d, *J*=11.4 Hz, 1H), 4.40(d, *J*=11.4 Hz, 1H), 4.65 (s, 2H), 5.18 (d, *J*=10.2 Hz, 1H), 6.28 (d, *J*=9.3 Hz, 1H),6.86–6.90 (m, 2H), 7.24–7.27 (m, 2H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 12.0, 12.7, 14.9, 18.1, 21.5, 22.1, 23.3, 24.5 (2C), 24.9 (2C), 35.8, 42.2, 55.2, 56.1, 70.8, 73.7, 82.8, 86.4 (2C), 98.0, 113.7 (2C), 129.2 (2C), 129.3, 129.8, 130.8, 138.4, 147.1, 159.0; IR (neat) 2960, 1615, 1515 cm^{-1}; HRMS calcd for $C_{31}H_{51}BO_6$ $[M]^+$ 530.3779, found 530.3770.

*4.2.10. 2-[(3Z,5S,6S,7S,8E)-7-Ethyl-9-hydroxymethyl-6-methoxymethoxy-5-methylundeca-3,8-dien-3-yl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**23**).* To a cooled (0 °C), stirred solution of **22** (862 mg, 1.62 mmol) in CH_2Cl_2 (18 mL) were added aqueous phosphate buffer (0.5 M aqueous Na_2HPO_4/0.5 M aqueous NaH_2PO_4, 2:1, 2.0 mL) and DDQ (1.10 g, 4.86 mmol). The mixture was stirred at room temperature for 1 h, diluted with saturated aqueous $NaHCO_3$ (35 mL), and extracted with CH_2Cl_2 (20 mL×3). The combined organic layers were dried and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:30 to 1:10) to provide 525 mg (79%) of **23** as a colorless oil: TLC R_f 0.30 (EtOAc/hexane, 1:4); $[\alpha]_D^{19.5}$ +81.6 (*c* 1.05, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.80 (t, *J*=7.5 Hz, 3H), 0.98 (t, *J*=7.5 Hz, 3H), 1.01 (d, *J*=7.2 Hz, 3H), 1.02 (t, *J*=7.5 Hz, 3H), 1.06–1.19 (m, 1H), 1.26 (s, 6H), 1.27 (s, 6H), 1.69–1.82 (m, 1H), 2.05–2.29(m, 4H), 2.40–2.51 (m, 1H), 2.92–3.03 (m, 1H), 3.34 (dd, *J*=3.3, 8.1 Hz, 1H), 3.42 (s, 3H),3.96 (d, *J*=13.5 Hz, 1H), 4.10 (d, *J*=13.5 Hz, 1H), 4.68 (d, *J*=6.9 Hz, 1H), 4.74 (d, *J*=6.9 Hz, 1H), 4.96 (d, *J*=10.8 Hz, 1H), 6.08 (d, *J*=8.7 Hz, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 11.5, 12.6, 14.9, 15.1, 21.3, 22.0, 24.3 (2C), 24.6, 24.7 (2C), 35.9, 41.1, 55.9, 66.0,83.3, 85.5 (2C), 97.0, 127.0 (2C), 140.6, 148.7; IR (neat) 3500, 2970, 1630 cm^{-1}; HRMS calcdfor$C_{23}H_{43}BO_5$ $[M]^+$ 410.3204, found 410.3215.

*4.2.11. (2E,4S,5S,6S,7E,9E)-10-(tert-Butyldimethylsilyloxy)-methyl-2,4,8-triethyl-5-methoxymethoxy-6-methyldodeca-2,7,9-trien-1-ol (**25**).* The following reaction was carried out under argon. To a stirred solution of **23** (16.6 mg, 40.4 μmol) and **24** (34.6 mg, 0.106 mmol) in degassed THF (4.2 mL) were added 3 M aqueous NaOH (80 μL, 0.24 mmol) and $PdCl_2$(dppf) (3.3 mg, 4.0 mmol). The mixture was stirred at room temperature for 53.5 h, diluted with saturated aqueous NH_4Cl (10 mL), and extracted with EtOAc (5 mL×3). The combined organic layers were dried and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:150 to 1:15) to provide 13.8 mg (71% from **23**) of **25** as a colorless oil: TLC R_f 0.17 (EtOAc/hexane, 1:5); $[\alpha]_D^{25}$ +57.6 (*c* 1.18, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.07 (s, 6H), 0.82 (t, *J*=7.5 Hz, 3H), 0.92 (s, 9H), 0.93 (t, *J*=7.5 Hz, 3H), 0.98 (t, *J*=7.8 Hz, 3H), 1.01 (t, *J*=7.5 Hz, 3H), 1.04 (d, *J*=6.6 Hz, 3H), 1.12–1.28 (m, 1H), 1.66–1.79 (m, 1H), 1.85–1.96 (m, 1H), 1.97–2.08 (m, 1H), 2.09–2.23 (m, 4H), 2.35–2.45 (m,1H), 2.65–2.76 (m, 1H), 3.22 (dd, *J*=4.2, 6.6 Hz, 1H), 3.39 (s, 3H), 4.06 (s, 2H), 4.12 (d, *J*=1.5 Hz, 2H), 4.64 (d, *J*=6.6 Hz, 1H), 4.66 (d, *J*=6.6 Hz, 1H), 5.14 (d, *J*=9.9 Hz, 1H), 5.28 (d, *J*=9.6 Hz, 1H), 5.80 (br s, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ −5.3 (2C), 11.9, 12.8, 13.3, 13.6, 18.4, 19.1, 21.4, 21.6, 23.4, 24.2, 25.9 (3C), 35.6, 42.4, 55.9, 66.3, 66.6, 87.5, 98.3, 126.2, 128.0, 129.8, 137.7, 141.1, 141.2; IR (neat) 3430, 2960, 2930, 1460 cm^{-1}; HRMS calcd for $C_{28}H_{54}O_4Si$ $[M]^+$ 482.3791, found 482.3792.

*4.2.12. (2E,4S,5S,6S,7E,9E)-10-(tert-Butyldimethylsilyloxy)-methyl-2,4,8-triethyl-5-methoxymethoxy-6-methyldodeca-2,7,9-trienal (**26**).* To a stirred solution of **25** (13.3 mg, 27.5 μmol) in CH_2Cl_2 (1.0 mL) was added MnO_2 (66.5 mg). The mixture was stirred at room temperature for 30 min, filtered through a pad of Celite, and washed well with CH_2Cl_2. The combined filtrate and washings were concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:40) to provide 12.8 mg (97%) of **26** as a colorless oil: TLC R_f 0.45(EtOAc/hexane, 1:5); $[\alpha]_D^{26}$ +52.6(*c* 0.59, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.07 (s, 6H), 0.85 (t, *J*=7.5 Hz, 3H), 0.92 (s, 9H), 0.92 (t, *J*=7.5 Hz, 3H), 0.97 (t, *J*=7.5 Hz, 3H), 1.00 (t, *J*=7.5 Hz, 3H), 1.06 (d, *J*=6.9 Hz, 3H), 1.34–1.49 (m, 1H), 1.78–1.95 (m, 2H), 2.06–2.29 (m, 5H), 2.61–2.78 (m, 2H), 3.36 (dd, *J*=2.1, 4.2 Hz, 1H), 3.40 (s, 3H), 4.12 (d, *J*=1.5 Hz, 2H), 4.65 (d, *J*=6.9 Hz, 1H), 4.68 (d, *J*=6.9 Hz, 1H), 5.27 (d, *J*=9.6 Hz, 1H), 5.79 (br s, 1H), 6.26 (d, *J*=10.5 Hz, 1H), 9.37 (s, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ −5.3 (2C), 12.0, 13.1, 13.3, 13.6, 17.9 (2C), 19.3, 21.7, 23.3, 24.3, 25.9 (3C), 35.9, 44.2, 56.1, 66.2, 86.0, 98.2, 125.8, 128.7, 138.5, 141.4, 145.6, 155.9, 195.3; IR (neat) 2960, 2930, 1695, 1460 cm^{-1}; HRMS calcd for$C_{28}H_{52}O_4Si$ $[M]^+$ 480.3635, found 480.3656.

*4.2.13. (1R,2Z,4S,5R,6R,7S,8S,9S)-4-(tert-Butyldimethylsilyloxy) methyl-2,4,5,7-tetraethyl-5-formyl-8-methoxymethoxy-9-methylbicyclo[4.3.0]non-2-ene (**27**).* The following reaction was carried out under argon. To a stirred solution of **26** (59.9 mg, 0.124 mmol) in degassed toluene (12.4 mL) was added a crystal of BHT. The mixture was stirred at 70 °C for 5.5 days. After being cooled to room temperature, the mixture was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane, to EtOAc/hexane, 1:60) to provide 58.0 mg (97%) of **27**as a colorless oil: TLC R_f 0.61 (EtOAc/hexane, 1:5); $[\alpha]_D^{25.5}$ +13.0 (*c* 1.02, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.03 (s, 3H), 0.04 (s, 3H), 0.86 (t, *J*=7.2 Hz, 3H), 0.88 (s, 9H), 0.93 (t, *J*=7.5 Hz, 3H), 1.00 (t, *J*=7.5 Hz, 3H), 1.02 (t, *J*=7.5 Hz, 3H), 1.06–1.19 (m, 1H), 1.24–1.35 (m, 3H), 1.25 (d, *J*=6.6 Hz, 3H), 1.54–1.83 (m, 3H), 1.91–2.21 (m, 4H), 2.36 (t, *J*=11.4 Hz, 1H), 3.36 (s, 3H), 3.36 (d, *J*=10.8 Hz, 1H), 3.69 (d, *J*=5.1 Hz, 1H), 3.83 (d, *J*=10.8 Hz, 1H), 4.53 (d, *J*=6.8 Hz, 1H), 4.65 (d, *J*=6.8 Hz, 1H), 4.97 (br s, 1H), 9.71 (s, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ −6.0, −5.8, 8.3, 10.0, 12.2, 13.0, 15.0, 18.0, 20.9, 24.3, 25.6 (3C), 28.2, 28.3, 40.0, 45.5 (2C), 50.0, 51.3, 55.5, 56.3, 63.0, 85.4, 94.2, 122.2, 144.7, 204.5; IR (neat) 2960, 2920, 1715, 1470 cm^{-1}; HRMS calcd for $C_{28}H_{52}O_4Si$ $[M]^+$ 480.3635, found 480.3650.

*4.2.14. (1R,2Z,4S,5R,6R,7S,8S,9S)-4-(tert-Butyldimethylsilyloxy) methyl-2,4,5,7-tetraethyl-5-hydroxymethyl-8-methoxymethoxy-9-methylbicyclo[4.3.0]non-2-ene (**29**).* To a cooled (0 °C), stirred solution of **27** (55.6 mg, 0.116 mmol) in MeOH/THF (1:1, 2.0 mL) was added $NaBH_4$ (15.0 mg, 0.397 mmol). The mixture was stirred at room temperature for 2.5 h and additional $NaBH_4$ (13.2 mg, 0.348 mmol) was added at 0 °C. The mixture was stirred at room temperature for 1 h and additional $NaBH_4$ (13.2 mg, 0.348 mmol) was added at 0 °C. The mixture was stirred at room temperature for 1 h and additional $NaBH_4$ (13.2 mg, 0.348 mmol) was added at 0 °C. The mixture was stirred at room temperature for additional 1.5 h, quenched with saturated aqueous NH_4Cl (10 mL) at 0 °C, and extracted with EtOAc (5 mL×3). The combined organic layers were dried and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:60 to 1:50) to provide 51.0 mg (91%) of **29** as a colorless oil: TLC R_f 0.50 (EtOAc/hexane, 1:5); $[\alpha]_D^{22}$ −25.1 (c 1.51, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.13 (s, 3H), 0.14 (s, 3H), 0.92 (t, *J*=7.5 Hz, 3H), 0.94 (s, 9H), 0.95 (t, *J*=7.5 Hz, 3H), 1.01 (t, *J*=7.5 Hz, 3H), 1.02 (t, *J*=7.5 Hz, 3H), 1.24 (d, *J*=6.9 Hz, 3H), 1.30–1.38 (m, 2H), 1.41–1.53 (m, 2H), 1.56–1.69 (m, 2H), 1.80–1.91 (m, 2H), 1.96–2.21 (m, 3H), 2.33 (t, *J*=11.4 Hz, 1H), 3.34 (d, *J*=10.8 Hz, 1H), 3.37 (s, 3H), 3.54 (dd, *J*=5.3, 9.2 Hz, 1H), 3.62 (d, *J*=4.5 Hz, 1H), 3.64–3.73 (m, 2H), 3.79 (d, *J*=10.8 Hz, 1H), 4.53 (d, *J*=6.9 Hz, 1H), 4.69 (d, *J*=6.9 Hz, 1H), 4.94 (br s, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ −5.9, −5.8, 8.8, 9.5, 12.7, 13.2, 14.7, 18.2, 21.9, 25.9 (4C), 28.4, 29.2, 40.7, 44.1, 44.6, 44.9, 49.4, 52.8, 55.4, 64.4, 65.2, 86.3, 93.8, 123.9, 144.8; IR (neat) 3520, 2960, 2880, 1470 cm^{-1}; HRMS calcd for $C_{28}H_{54}O_4Si$ $[M]^+$ 482.3791, found 482.3777.

*4.2.15. (1R,2Z,4S,5R,6R,7S,8S,9S)-4-(tert-Butyldimethylsilyloxy) methyl-2,4,5,7-tetraethyl-8-methoxymethoxy-5-(methoxymethoxy) methyl-9-methylbicyclo[4.3.0]non-2-ene (**30**).* To a stirred solution of **29** (48.7 mg, 0.10 mmol) in CH_2Cl_2 (2.0 mL) were added *i*-Pr_2NEt (40 μL, 0.50 mmol) and MOMCl (0.18 mL, 1.0 mmol). The mixture was refluxed for 13 h, diluted with saturated aqueous NH_4Cl (15 mL), and extracted with CH_2Cl_2 (5 mL×3). The combined organic layers were dried and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:100) to provide 52.7 mg (quantitative) of **30** as a colorless oil: TLC R_f 0.60 (EtOAc/hexane, 1:6); $[\alpha]_D^{22.5}$ +10.4 (*c* 1.40, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.01 (s, 3H), 0.02 (s, 3H), 0.89 (s, 9H), 0.90 (t, *J*=7.5 Hz, 3H), 0.92–0.99 (m, 6H), 1.01 (t, *J*=7.5 Hz, 3H), 1.23–1.33 (m, 1H), 1.24 (d, *J*=6.9 Hz, 3H), 1.35–1.47 (m, 3H), 1.53–1.65 (m, 2H), 1.69–1.75 (m, 1H), 1.79–1.95 (m, 2H), 2.00–2.18 (m, 2H), 2.28 (t, *J*=11.6 Hz, 1H), 3.38 (s, 6H), 3.41 (d, *J*=10.7 Hz, 1H), 3.53 (d, *J*=9.8 Hz, 1H), 3.57 (d, *J*=9.8 Hz, 1H), 3.60 (d, *J*=4.5 Hz, 1H), 3.83 (d, *J*=10.7 Hz, 1H), 4.54 (d, *J*=6.8 Hz, 1H), 4.55 (d, *J*=6.5 Hz, 1H), 4.61 (d, *J*=6.5 Hz, 1H), 4.73 (d, *J*=6.8 Hz, 1H), 4.99 (br s, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ −5.7, −5.6, 9.2, 10.3, 13.1, 13.2, 14.7, 18.2, 22.5, 25.4, 25.9 (3C), 28.3, 29.1, 40.5, 43.4, 44.2, 45.4, 48.8, 54.3, 55.3, 55.6, 65.6, 70.9, 86.0, 93.6, 97.3, 124.8, 143.1; IR (neat)2960, 2880, 1470 cm^{-1}; HRMS calcd for$C_{30}H_{58}O_5Si$ $[M]^+$526.4054, found 526.4043.

*4.2.16. (1R,2Z,4S,5R,6R,7S,8S,9S)-2,4,5,7-Tetraethyl-4-hydroxymethyl-8-methoxymethoxy-5-(methoxymethoxy)methyl-9-methylbicyclo[4.3.0]non-2-ene (**31**).* To a cooled (0 °C), stirred solution of **30** (51.8 mg, 98.3 μmol) in THF (1.0 mL) was added *n*-Bu_4NF (0.30 mL of 1.0 M solution in THF, 0.30 mmol). The mixture was stirred at 50 °C for 19.5 h, diluted with saturated aqueous NH_4Cl (12 mL) at 0 °C, and extracted with EtOAc (5 mL×3). The combined organic layers were dried and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:30 to 1:10) to provide 40.3 mg (99%) of **31** as a colorless oil: TLC R_f 0.19 (EtOAc/hexane, 1:6); $[\alpha]_D^{27}$ −53.3 (*c* 0.94, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.98 (t, *J*=7.5 Hz, 3H), 0.99 (t, *J*=7.5 Hz, 3H), 1.00 (t, *J*=7.5 Hz, 3H), 1.01 (t, *J*=7.5 Hz, 3H), 1.24 (d,

J=6.6 Hz, 3H), 1.31–1.55 (m, 4H), 1.59–1.80 (m, 3H), 1.81–1.87 (m, 1H), 1.92–2.21 (m, 3H), 2.35 (t, J=11.4 Hz, 1H), 3.32 (br s, 1H), 3.37 (s, 3H), 3.42 (s, 3H), 3.63 (dd, J=4.2, 9.3 Hz, 1H), 3.70 (d, J=10.2 Hz, 1H), 3.79 (d, J=10.2 Hz, 1H), 3.83 (d, J=10.2 Hz, 1H), 3.83 (d, J=10.2 Hz, 1H), 4.53 (d, J=6.9 Hz, 1H), 4.63 (d, J=6.6 Hz, 1H), 4.67 (d, J=6.6 Hz, 1H), 4.69 (d, J=6.9 Hz, 1H), 5.02 (br s, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 9.0, 9.3, 12.6, 13.2, 14.7, 22.2, 25.5, 28.3, 29.1, 40.7, 43.2, 44.5, 45.0, 49.8, 52.6, 55.4, 56.1, 64.6, 70.6, 86.2, 93.8, 97.0, 124.5, 143.8; IR (neat) 3500, 2960, 2880, 1470 cm^{-1}; HRMS calcd for $C_{24}H_{44}O_5$ [M]$^+$ 412.3189, found 412.3189.

*4.2.17. (1R,2Z,4S,5R,6R,7S,8S,9S)-2,4,5,7-Tetraethyl-4-formyl-8-methoxymethoxy-5-(methoxymethoxy)methyl-9-methylbicyclo-[4.3.0] non-2-ene (**32**).* The following reaction was carried out under argon. To a cooled (−78 °C), stirred solution of oxalyl chloride (40 μL, 0.41 mmol) in CH_2Cl_2 (1.0 mL) was added dropwise DMSO (60 μL, 0.81 mmol). The mixture was stirred at −78 °C for 40 min and then a solution of **31** (16.7 mg, 40.5 μmol) in CH_2Cl_2 (0.8 mL) was added. The mixture was stirred at −78 °C for 1 h and then Et_3N (0.23 mL, 1.6 mmol) was added. The mixture was warmed gradually to room temperature and stirred for 40 min. The mixture was diluted with H_2O (10 mL) at 0 °C and extracted with CH_2Cl_2 (5 mL×3). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (5 mL) and brine (5 mL), dried, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:30) to provide 15.0 mg (90%) of **32** as a colorless oil: TLC R_f 0.57 (EtOAc/hexane, 1:6); $[\alpha]_D^{23.5}$ +75.5 (*c* 0.90, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (t, J=7.5 Hz, 6H), 0.99 (t, J=7.5 Hz, 3H), 1.04 (t, J=7.5 Hz, 3H), 1.27 (d, J=6.6 Hz, 3H), 1.37–1.50 (m, 2H), 1.51–1.61 (m, 1H), 1.64–1.84 (m, 5H), 2.17–2.34 (m, 3H), 2.41 (t, J=12.3 Hz, 1H), 3.37 (s, 3H), 3.38 (s, 3H), 3.54 (d, J=10.2 Hz, 1H), 3.62 (d, J=4.5 Hz, 1H), 3.70 (d, J=10.2 Hz, 1H), 4.54 (d, J=6.6 Hz, 1H), 4.57 (d, J=6.6 Hz, 1H), 4.60 (d, J=6.6 Hz, 1H), 4.69 (d, J=6.6 Hz, 1H), 4.91 (br s, 1H), 9.68 (s, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 9.2, 9.5, 12.5, 13.0, 14.7, 22.8, 23.9, 28.2, 28.4, 40.9, 44.5, 44.6, 45.2, 51.9, 55.4, 56.0, 61.0, 69.7, 86.0, 93.9, 97.1, 119.5, 146.8, 205.0; IR (neat) 2960, 2880, 1715, 1470 cm^{-1}; HRMS calcd for $C_{24}H_{42}O_5$ [M]$^+$ 410.3032, found 410.3050.

*4.2.18. (1R,2Z,4S,5R,6R,7S,8S,9S)-2,4,5,7-Tetraethyl-8-methoxymethoxy-5-(methoxymethoxy)methyl-9-methyl-4-(1E)-styrylbicyclo[4.3.0]non-2-ene (**33**).* The following reaction was carried out under argon. To a cooled (−78 °C), stirred solution of diethyl benzylphosphonate (0.10 mL, 0.46 mmol) in THF (1.0 mL) was added *n*-BuLi (0.15 mL of 2.63 M solution in hexane, 0.39 mmol). The mixture was stirred at −78 °C for 30 min and a solution of **32** (31.7 mg, 77.2 μmol) in THF (1.0 mL) was added dropwise at −78 °C. The mixture was warmed to 0 °C over 3 h, quenched with saturated aqueous NH_4Cl (10 mL), and extracted with EtOAc (5 mL×3). The combined organic layers were dried and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:100 to 1:60) to provide 32.9 mg (88%) of **33** as a colorless oil: TLC R_f 0.57 (EtOAc/hexane, 1:4); $[\alpha]_D^{24}$ −2.6 (*c* 0.83, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.81 (t, J=7.5 Hz, 6H), 1.03 (t, J=7.5 Hz, 3H), 1.09 (t, J=7.5 Hz, 3H), 1.28 (d, J=6.6 Hz, 3H), 1.38–1.73 (m, 6H), 1.80–1.97 (m, 2H), 2.13–2.27 (m, 3H), 2.40 (t, J=11.1 Hz, 1H), 3.37 (s, 3H), 3.46 (s, 3H), 3.56 (d, J=10.5 Hz, 1H), 3.58 (d, J=4.2 Hz, 1H), 3.59 (d, J=10.5 Hz, 1H), 4.53 (d, J=7.2 Hz, 1H), 4.64 (d, J=7.2 Hz, 1H), 4.68 (d, J=7.2 Hz, 1H), 4.68 (d, J=7.2 Hz, 1H), 5.13 (br s, 1H), 6.21 (d, J=16.1 Hz, 1H), 6.27 (d, J=16.1 Hz, 1H), 7.19 (tt, J=1.5, 7.1 Hz, 1H), 7.27–7.32 (m, 2H), 7.35 (dd, J=1.5, 8.4 Hz, 2H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 9.5, 9.6, 12.3, 13.6, 14.7, 21.7, 28.1, 28.3, 28.9, 41.0, 44.5, 44.7, 44.9, 51.1, 52.6, 55.4, 55.7, 70.6, 86.3, 93.8, 97.1, 124.3, 126.1 (2C), 126.6, 128.4 (2C), 131.8, 137.9, 138.3, 142.7; IR (neat) 2960, 2880, 1470 cm^{-1}; HRMS calcd for $C_{31}H_{48}O_4$ [M]$^+$ 484.3553, found 484.3550.

*4.2.19. (1R,2Z,4S,5R,6R,7S,8S,9S)-2,4,5,7-Tetraethyl-8-hydroxy-5-hydroxymethyl-9-methyl-4-(1E)-styrylbicyclo-[4.3.0]non-2-ene (**34**).* To a stirred solution of **33** (32.9 mg, 67.9 μmol) in MeOH (1.0 mL) was added CSA (79.0 mg, 0.340 mmol). The mixture was stirred at 40 °C for 60 h and additional CSA (8.0 mg, 34 μmol) was added. The mixture was stirred at 40 °C for 25 h and additional CSA (8.0 mg, 34 μmol) was added. The mixture was stirred at 40 °C for 48 h, diluted with saturated aqueous $NaHCO_3$ (10 mL), and extracted with EtOAc (5 mL×3). The combined organic layers were dried and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:10 to 1:8) to provide 26.9 mg (quantitative) of **34** as a colorless oil: TLC R_f 0.09 (EtOAc/hexane, 1:4); $[\alpha]_D^{26}$ +3.9 (*c* 0.67, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83 (t, J=7.2 Hz, 3H), 0.86 (t, J=7.2 Hz, 3H), 1.09 (t, J=7.1 Hz, 3H), 1.11 (t, J=7.1 Hz, 3H), 1.27 (d, J=7.2 Hz, 3H), 1.44–1.64 (m, 6H), 1.70–1.90 (m, 2H), 2.10–2.25 (m, 3H), 2.34 (t, J=11.0 Hz, 1H), 3.69 (dd, J=6.0, 10.2 Hz, 1H), 3.74 (d, J=11.3 Hz, 1H), 3.81 (d, J=11.3 Hz, 1H), 5.13 (br s, 1H), 6.21 (d, J=16.1 Hz, 1H), 6.31 (d, J=16.1 Hz, 1H), 7.19 (t, J=7.5 Hz, 1H), 7.30 (t, J=7.5 Hz, 2H), 7.37 (d, J=7.5 Hz, 2H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 9.6, 10.3, 12.4, 13.5, 14.2, 21.3, 28.2, 28.5, 29.7, 41.2, 44.1, 45.3, 48.4, 50.6, 52.5, 65.3, 82.9, 124.3, 126.2 (2C), 126.7, 128.4 (2C), 131.9, 137.6, 138.0, 142.6; IR (neat) 3360, 2960, 2880, 1470 cm^{-1}; HRMS calcd for $C_{27}H_{40}O_2$ [M]$^+$ 396.3028, found 396.3027.

*4.2.20. (1R,2Z,4S,5R,6R,7S,9S)-2,4,5,7-Tetraethyl-5-formyl-9-methyl-4-(1E)-styrylbicyclo[4.3.0]non-2-en-8-one (**35**).* To a cooled (0 °C), stirred solution of **34** (27.5 mg, 69.3 μmol) in CH_2Cl_2 (1.0 mL) was added Dess–Martin periodinane (76.5 mg, 0.180 mmol). The mixture was stirred at room temperature for 1.5 h, quenched saturated aqueous $NaHCO_3$ (5 mL) and 20% aqueous $Na_2S_2O_3$ (5 mL), and extracted with CH_2Cl_2 (5 mL×3). The combined organic layers were dried and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:80) to provide 22.7 mg (85%) of**35** as a colorless oil: TLC R_f 0.63 (EtOAc/hexane, 1:4); $[\alpha]_D^{25}$ +83.9 (*c* 0.47, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.67 (t, J=7.4 Hz, 3H), 0.85 (t, J=7.5 Hz, 3H), 0.96 (t, J=7.4 Hz, 3H), 1.15 (t, J=7.4 Hz, 3H), 1.21–1.40 (m, 1H), 1.38 (d, J=6.9 Hz, 3H), 1.43–1.58 (m, 3H), 1.80–1.98 (m, 2H), 2.17–2.33 (m, 4H), 2.44 (ddd, J=3.6, 5.1, 12.5 Hz, 1H), 2.87 (t, J=12.5 Hz, 1H), 5.20 (d, J=1.2 Hz, 1H), 6.05 (d, J=15.8 Hz, 1H), 6.42 (d, J=15.8 Hz, 1H), 7.20–7.28 (m, 1H), 7.30–7.32 (m, 4H), 9.68 (d, J=0.9 Hz, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 9.0, 9.4, 11.4, 12.9, 16.0, 20.2, 20.7, 27.4, 28.2, 41.0, 44.5, 48.4, 51.6, 52.3, 57.8, 122.6, 126.2 (2C), 127.6, 128.6 (2C), 134.2, 134.4, 136.8, 141.8, 206.6, 219.5; IR (neat) 2960, 2880, 1730, 1715, 1455 cm^{-1}; HRMS calcd for $C_{27}H_{36}O_2$ [M]$^+$ 392.2715, found 392.2715.

*4.2.21. (+)-Spiculoic acid A (**1**).* To a cooled (0 °C), stirred solution of **35** (22.7 mg, 57.8 μmol) in *t*-BuOH/H_2O (5:1, 1.0 mL) were added 2-methyl-2-butene (40 μL, 0.35 mmol), NaH_2PO_4 (20.8 mg, 0.173 mmol), and $NaClO_2$ (20.1 mg, 0.173 mmol). The mixture was stirred at room temperature for 1.5 h and additional 2-methyl-2-butene (0.20 mL, 1.7 mmol), NaH_2PO_4 (104 mg, 0.865 mmol), and $NaClO_2$ (101 mg, 0.865 mmol) were added at 0 °C. The mixture was stirred at room temperature for 1.5 h and additional 2-methyl-2-butene (0.14 mL, 1.2 mmol), NaH_2PO_4 (69.3 mg, 0.577 mmol), and $NaClO_2$ (67.0 mg, 0.577 mmol) were added at 0 °C. The mixture was stirred at room temperature for 3 h, quenched saturated aqueous NH_4Cl (10 mL) at 0 °C, and extracted with CH_2Cl_2 (5 mL×3). The combined organic layers were dried and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:60 to 1:15) to provide 19.4 mg (82%) of **1** as a colorless oil: TLC R_f 0.22 (Et_2O/petroleum ether, 3:7); $[\alpha]_D^{25}$ +102 (*c* 0.38, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.65 (t, J=7.4 Hz, 3H), 0.88 (t, J=7.4 Hz, 3H), 1.08 (t, J=7.4 Hz, 3H), 1.15 (t, J=7.4 Hz, 3H), 1.36 (d, J=6.9 Hz, 3H), 1.52–1.63 (m, 1H), 1.64–1.73

(m, 2H), 1.77–1.86 (m, 2H), 1.86–1.95 (m, 1H), 2.16 (t, J=11.7 Hz, 1H), 2.24–2.32 (m, 3H), 2.46 (ddd, J=3.5, 5.3, 11.7 Hz, 1H), 2.66 (t, J=11.7 Hz, 1H), 5.26 (br s, 1H), 6.06 (d, J=15.8 Hz, 1H), 6.27 (d, J=15.8 Hz, 1H), 7.17 (dd, J=1.7, 7.1 Hz, 1H), 7.25 (t, J=7.1 Hz, 2H), 7.31 (dd, J=1.7, 7.1 Hz, 2H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 9.1, 9.6, 12.3, 13.0, 15.5, 22.1, 22.8, 27.2, 28.2, 42.1, 46.0, 47.7, 51.1, 52.3, 54.0, 123.1, 126.2 (2C), 127.1, 128.5 (2C), 132.2, 136.5, 137.7, 140.9, 179.0, 220.3; IR (neat) 3060, 2980, 2860, 1730, 1715, 1470 cm^{-1}; HRMS calcd for $C_{27}H_{36}O_3$ [M]$^+$ 408.2665, found 408.2662.

4.3. Synthesis of (2*R*,5*S*,6*R*)-isomer (46) of (+)-spiculoic acid A

*4.3.1. (3R,4S,5S,6E)-5-Ethyl-7-(4-methoxybenzyloxy)methyl-4-methoxymethoxy-3-methylnona-1,6-diene (**36**).* The following reaction was carried out under argon. To a stirred suspension of MS 4 Å powder (380 mg) in toluene (19 mL) was added (2′*Z*,4*S*,5*S*)-2-(but-2-enyl)-4,5-di(isopropyloxycarbonyl)-1,3,2-dioxaborolane (0.73 M solution in toluene, 14 mL, 10 mmol), prepared from *cis*-2-butene.The mixture was cooled to −78 °C and a solution of **16** (1.89 g, 6.84 mmol) in toluene (9.5 mL) was added. After being stirred at −78 °C for 1 h, the mixture was treated with 3 M aqueous NaOH (20 mL), stirred at room temperature for 18 h, and extracted with EtOAc (10 mL×3). The combined organic layers were dried and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (Et_2O/toluene, 1:50) to provide 1.88 g (83%) of the crotylation product as a colorless oil: TLC R_f 0.34 (EtOAc/hexane, 1:5); $[\alpha]_D^{22}$ −0.5 (*c* 1.48, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ0.86 (t, J=7.5 Hz, 3H), 0.98 (d, J=6.9 Hz, 3H), 1.01 (t, J=7.5 Hz, 3H), 1.17–1.27 (m, 1H), 1.54 (br s, 1H), 1.78–1.88 (m, 1H), 2.17 (q, J=7.5 Hz, 2H), 2.34–2.48 (m, 2H), 3.39 (dd, J=6.6, 3.6 Hz, 1H), 3.80 (s, 3H), 3.97 (s, 2H), 4.38 (s, 2H), 5.05–5.11 (m, 2H), 5.15 (d, J=10.5 Hz, 1H), 5.79–5.90 (m, 1H), 6.87–6.90 (m, 2H), 7.24–7.27 (m, 2H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 11.7, 12.2, 12.7, 21.5, 23.5, 40.3, 42.4, 55.3, 71.0, 73.3, 77.3, 113.7 (2C), 114.7, 128.9 (2C), 129.3, 130.6, 139.2, 142.1, 159.1; IR (neat) 3460, 2960, 2930,1615, 1515 cm^{-1}; HRMS calcd for $C_{21}H_{32}O_3$ [M]$^+$332.2352, found 332.2360.

To a stirred solution of the product obtained above (1.50 g, 4.51 mmol) in CH_2Cl_2 (30 mL) were added *i*-Pr_2NEt (7.9 mL, 45 mmol) and MOMCl (1.7 mL, 23 mmol). The mixture was refluxed for 13 h, diluted with saturated aqueous NH_4Cl (130 mL), and extracted with CH_2Cl_2 (30 mL×3). The combined organic layers were dried and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:30) to provide 1.60 g (94%) of **36** as a colorless oil: TLC R_f 0.66 (EtOAc/hexane, 1:3); $[\alpha]_D^{23}$ +9.3 (*c*1.25, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84 (t, J=7.5 Hz, 3H), 1.00 (t, J=7.5 Hz, 3H), 1.03 (d, J=6.9 Hz, 3H), 1.14–1.25 (m, 1H), 1.70–1.84 (m, 1H), 2.14 (q, J=7.5 Hz, 2H), 2.38–2.55 (m, 2H), 3.29 (dd, J=6.6, 4.5 Hz, 1H), 3.39 (s, 3H), 3.81 (s, 3H), 3.96 (s, 2H), 4.38 (s, 2H), 4.61–4.68 (m, 2H), 4.98–5.05 (m, 2H), 5.16 (d, J=10.5 Hz, 1H), 5.80–5.92 (m, 1H), 6.86–6.90 (m, 2H), 7.23–7.28 (m, 2H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 12.0, 12.7, 14.1, 21.4, 23.4, 40.5, 42.4, 55.3, 56.1, 70.9, 73.4, 85.9, 98.1, 113.7 (2C), 113.8, 129.2 (2C), 129.8, 130.6, 139.0, 142.7, 159.1; IR (neat) 2960, 2930, 1615, 1515 cm^{-1}; HRMS calcd for $C_{23}H_{36}O_4$ [M]$^+$ 376.2614, found 376.2612.

*4.3.2. (3E,5R,6S,7S,8E)-3-Bromo-7-ethyl-9-(4-methoxybenzyloxy) methyl-6-methoxymethoxy-5-methylundeca-3,8-diene (**38**).* To a stirred solution of **36** (1.60 g, 4.25 mmol) in acetone/H_2O (6:1, 35 mL) were added OsO_4 (0.05 M solution in *t*-BuOH, 4.3 mL, 0.22 mmol) and NMO (1.24 g, 10.6 mmol). The mixture was stirred at room temperature for 4.5 h and additional NMO (150 mg, 1.28 mmol) was added. The mixture was stirred at room temperature for 2.5 h, quenched with 1 M aqueous $NaHSO_3$ (80 mL) at 0 °C, and extracted with EtOAc (40 mL×3). The combined organic layers were dried and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:2.5 to 1:2) to provide 1.69 g (96%) of diol (ca. 2:1 diastereomeric mixture based on ^{1}H NMR)as a colorless oil: TLC R_f 0.29 (EtOAc/hexane, 2:1); $[\alpha]_D^{22}$ −5.2 (*c*1.52, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) for major isomer δ 0.84 (t, J=6.9 Hz, 3H), 0.87 (d, J=7.5 Hz, 3H), 1.00 (t, J=7.5 Hz, 3H), 1.06–1.15 (m, 1H), 1.62–1.78 (m, 2H), 2.16 (q, J=7.5 Hz, 2H), 2.33 (br s, 1H), 2.46–2.58 (m, 1H), 3.35–3.46 (m, 1H), 3.45 (s, 3H), 3.49–3.54 (m, 1H), 3.69–3.76 (m, 2H), 3.80 (s, 3H), 3.94 (s, 2H), 4.05 (br s, 1H) 4.35 (s, 2H), 4.71 (d, J=6.9 Hz, 1H), 4.76 (d, J=6.9 Hz, 1H), 4.98 (d, J=10.8 Hz, 1H) 6.85–6.90 (m, 2H), 7.22–7.27 (m, 2H); ^{13}C NMR (68 MHz, $CDCl_3$) for major isomer δ 10.2, 11.8, 12.4, 21.5, 24.6, 38.0, 42.8, 55.2, 56.3, 65.1, 70.9, 73.1, 73.6, 83.2, 99.3, 113.8 (2C), 128.3, 129.3 (2C), 130.5, 139.4, 159.1; IR (neat) 3460, 2960, 2930, 1615,1515 cm^{-1}; HRMS calcd for $C_{23}H_{37}O_6$ [M−H]$^+$ 409.2590, found 409.2571.

To a cooled (0 °C), stirred solution of diol obtained above (1.56 g, 3.80 mmol) in acetone/H_2O (4:1, 50 mL) was added $NaIO_4$ (2.19 g, 10.3 mmol). The mixture was stirred at room temperature for 30 min, quenched with 1 M aqueous $NaHSO_3$ (50 mL) at 0 °C, and extracted with EtOAc (25 mL×3). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL), dried, and concentrated under reduced pressure to provide crude (2*S*,3*R*,4*S*,5*E*)-4-ethyl-6-(4-methoxybenzyloxy)methyl-3-methoxymethoxy-2-methyloct-5-enal (**37**), which was used in the next step without further purification.

The following reaction was carried out under argon. To a cooled (−40 °C), stirred suspension of 1,1-dibromopropytriphenylphosphonium bromide (8.83 g, 16.3 mmol) in Et_2O (45 mL) was added *n*-BuLi (2.77 M solution in hexane, 5.5 mL, 15 mmol). The mixture was stirred at −40 °C for 30 min and cooled to −78 °C. Then a solution of the crude **37** obtained above in Et_2O (4.5 mL) was added dropwise. The mixture was stirred at −78 °C for 1 h, quenched with H_2O (5 mL), diluted with saturated aqueous $NaHCO_3$ (45 mL) and H_2O (50 mL), and extracted with EtOAc (25 mL×3). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (40 mL), dried, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:60 to 1:30) to provide 915 mg (50% for two steps) of **38** as a colorless oil: TLC R_f 0.46 (EtOAc/hexane, 1:5); $[\alpha]_D^{24.5}$ +9.9 (*c*1.43, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$)δ 0.84 (t, J=7.5 Hz, 3H), 1.01 (d, J=6.6 Hz, 3H), 1.01 (t, J=7.5 Hz, 3H), 1.08 (t, J=7.5 Hz, 3H), 1.14–1.25 (m, 1H), 1.63–1.80 (m, 1H), 2.14 (q, J=7.5 Hz, 2H), 2.33–2.49 (m, 1H), 2.39 (q, J=7.5 Hz, 2H), 2.56–2.68 (m, 1H), 3.18 (t, J=5.7 Hz, 1H), 3.41 (s, 3H), 3.81 (s, 3H), 3.96 (s, 2H), 4.38 (s, 2H), 4.65 (s, 2H), 5.16 (d, J=10.5 Hz, 1H), 5.78 (d, J=10.2 Hz, 1H), 6.86–6.89 (m, 2H), 7.24–7.26 (m, 2H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 12.1, 12.7, 13.3, 15.5, 21.5, 23.3, 29.3, 37.3, 42.5, 55.3, 56.2, 71.1, 73.4, 86.1, 98.3, 113.7 (2C), 127.5, 129.2 (2C), 129.3, 130.6. 135.3, 139.5, 159.1; IR (neat) 2980, 2930, 1615, 1515 cm^{-1}; HRMS calcd for $C_{25}H_{39}BrO_4$ [M]$^+$ 482.2032, found 482.2033.

*4.3.3. 2-[(3Z,5R,6S,7S,8E)-7-Ethyl-9-hydroxymethyl-6-methoxymethoxy-5-methylundeca-3,8-dien-3-yl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**39**).* The following reaction was carried out under argon. To a stirred solution of **38** (1.05 g, 2.17 mmol) in toluene (40 mL) were added bis(pinacolato)diboron (993 mg, 3.91 mmol), $PdCl_2(PPh_3)_2$ (122 mg, 0.173 mmol), PPh_3 (91.1 mg, 0.347 mmol), and KOPh (517 mg, 3.91 mmol). The mixture was stirred at 50 °C for 4 h and additional bis(pinacolato)diboron (276 mg, 1.08 mmol) and KOPh (72.0 mg, 0.544 mmol) were added. The mixture was stirred at 50 °C for 2 h, diluted with H_2O (50 mL), and extracted with EtOAc (50 mL). The organic layer was washed with 2 M aqueous NaOH (20 mL×2) and brine (20 mL), dried, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:30) to provide 855 mg (74%) of boronate as a colorless oil: TLC R_f 0.37 (EtOAc/hexane, 1:5); $[\alpha]_D^{23}$

+8.4 (*c* 1.33, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.82 (t, *J*=7.5 Hz, 3H), 0.94 (t, *J*=7.5 Hz, 3H), 0.99 (t, *J*=7.5 Hz, 3H), 1.01 (d, *J*=6.6 Hz, 3H), 1.16–1.29 (m, 1H), 1.24 (s, 6H), 1.26 (s, 6H), 1.67–1.76 (m, 1H), 2.12 (q, *J*=7.5 Hz, 2H), 2.39–2.48 (m, 1H), 2.78–2.90 (m, 1H), 3.23 (t, *J*=5.7 Hz, 1H), 3.41 (s, 3H), 3.81 (s, 3H), 3.97 (s, 2H), 4.37 (s, 2H), 4.64 (d, *J*=6.6 Hz, 1H), 4.67 (d, *J*=6.6 Hz, 1H), 5.23 (d, *J*=10.5 Hz, 1H), 6.18 (d, *J*=9.9 Hz, 1H), 6.85–6.90 (m, 2H), 7.23–7.27 (m, 2H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 12.2, 12.8, 14.9, 15.8, 21.3, 22.1, 22.9, 24.4 (2C), 25.0 (2C), 35.6, 42.4, 55.2, 56.2, 70.8, 73.7, 83.0, 86.5 (2C), 98.3, 113.7 (2C), 129.2 (3C), 130.4, 130.7, 138.9, 148.2, 159.0; IR (neat)2960, 2930, 1615, 1515 cm^{-1}; HRMS calcd for $C_{31}H_{51}BO_6$ $[M]^+$ 530.3779, found 530.3782.

To a cooled (0 °C), stirred solution of boronate obtained above (855 mg, 1.61 mmol) in CH_2Cl_2 (16 mL) were added aqueous phosphate buffer (0.5 M aqueous Na_2HPO_4/0.5 M aqueous NaH_2PO_4, 2:1, 2.0 mL) and DDQ (1.06 g, 4.67 mmol). The mixture was stirred at room temperature for 30 min, diluted with saturated aqueous $NaHCO_3$ (30 mL), and extracted with CH_2Cl_2 (30 mL×3). The combined organic layers were dried and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:25 to 1:8) to provide 579 mg (88%) of **39** as a colorless oil: TLC R_f 0.10 (EtOAc/hexane, 1:4); $[\alpha]_D^{22.5}$ +13.2 (*c*1.88, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.80 (t, *J*=7.5 Hz, 3H), 0.96 (t, *J*=7.5 Hz, 3H), 0.99 (t, *J*=7.5 Hz, 3H), 1.00 (d, *J*=7.5 Hz, 3H), 1.11–1.35 (m, 1H), 1.24 (s, 6H), 1.26 (s, 6H), 1.60–1.75 (m, 1H), 2.10 (q, *J*=7.5 Hz, 2H), 2.10 (q, *J*=7.5 Hz, 2H), 2.31–2.43 (m, 1H), 2.76–2.89 (m, 1H), 3.20 (dd, *J*=6.8, 4.8 Hz, 1H), 3.42 (s, 3H), 4.06 (s, 2H), 4.63 (d, *J*=6.6 Hz, 1H), 4.68 (d, *J*=6.6 Hz, 1H), 5.24 (d, *J*=10.2 Hz, 1H), 6.14 (d, *J*=9.9 Hz, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 12.2, 13.0, 14.9, 16.4, 21.3, 22.0, 22.7, 24.4 (2C), 24.9 (2C), 35.9, 42.3, 56.1, 66.6, 83.0, 87.1 (2C), 98.4, 128.6 (2C), 141.6, 148.0; IR (neat) 3280, 2960, 2930, 1630 cm^{-1}; HRMS calcd for $C_{23}H_{43}BO_5$ $[M]^+$ 410.3204, found 410.3192.

*4.3.4. (2E,4S,5S,6R,7E,9E)-2,4,8-Triethyl-10-(4-methoxybenzyloxy) methyl-5-methoxymethoxy-6-methyldodeca-2,7,9-trienal (**41**).* The following reaction was carried out under argon. To a stirred solution of **39** (148 mg, 0.361 mmol) and **40**(314 mg, 0.945 mmol) in degassed DMF (38 mL) were added Cs_2CO_3 (724 mg, 2.22 mmol) and $Pd(PPh_3)_4$ (42.0 mg, 36.3 μmol). The mixture was stirred at 70 °C for 20 h, diluted with saturated aqueous NH_4Cl (80 mL), and extracted with Et_2O (40 mL×3). The combined organic layers were dried and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:40) to provide 129 mg (74%) of **41** as a colorless oil: TLC R_f 0.33 (EtOAc/hexane, 1:4); $[\alpha]_D^{21}$ +5.1 (*c*1.70, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.82 (t, *J*=7.5 Hz, 3H), 0.94–1.06 (m, 12H), 1.38–1.51 (m, 1H), 1.77–1.85 (m, 1H), 2.03–2.17 (m, 2H), 2.21–2.33 (m, 4H),2.66–2.80 (m, 2H), 3.26 (dd, *J*=7.3, 3.9 Hz, 1H), 3.42 (s, 3H), 3.81 (s, 3H), 3.98 (s, 2H), 4.41 (s, 2H), 4.64 (d, *J*=6.6 Hz, 1H), 4.67 (d, *J*=6.6 Hz, 1H), 5.11 (d, *J*=10.0 Hz, 1H), 5.83 (s, 1H), 6.36 (d, *J*=10.5 Hz, 1H), 6.87–6.91 (m, 2H), 7.26–7.28 (m, 2H), 9.41 (s, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 12.3, 13.2, 13.3 (2C), 17.5, 17.9, 21.9, 22.0, 24.3, 36.2, 43.9, 55.3, 56.2, 71.3, 73.3, 86.6, 98.6, 113.7 (2C), 129.2 (2C), 129.3, 130.2, 130.5, 138.0, 139.3, 145.7, 156.7, 159.1, 195.2; IR (neat) 2960, 2930, 1715, 1615, 1515 cm^{-1}; HRMS calcd for $C_{30}H_{46}O_5$ $[M]^+$ 486.3345, found 486.3348.

*4.3.5. (1S,2Z,4R,5R,6R,7S,8S,9R)-2,4,5,7-Tetraethyl-5-formyl-4-(4-methoxybenzyloxy)methyl-8-methoxymethoxy-9-methylbicyclo [4.3.0]non-2-ene (**42**).* The following reaction was carried out under argon. To a stirred solution of **41** (129 mg, 0.265 mmol) in toluene (27 mL) were added a crystal of BHT and Wako Gel C-300 (1.29 g). The mixture was stirred at 80 °C for 47 h and cooled to room temperature. The silica gel was removed by filtration through cotton wool and washed with CH_2Cl_2. The combined filtrate and washings were concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:35) to provide 106 mg (82%) of an inseparable mixture of **42** and a small amount of a byproduct (>11:1 based on ^1H NMR analysis) as a colorless oil: TLC R_f 0.31 (EtOAc/hexane, 1:6); $[\alpha]_D^{22}$ +4.1 (*c*1.07, $CHCl_3$); ^1H NMR for **42**(300 MHz, $CDCl_3$) δ 0.70 (t, *J*=7.5 Hz, 3H), 0.88 (t, *J*=7.5 Hz, 3H), 0.97 (t, *J*=7.5 Hz, 3H), 1.00 (t, *J*=7.5 Hz, 3H), 1.24 (d, *J*=6.3 Hz, 3H), 1.21–1.45 (m, 2H), 1.60–1.81 (m, 4H), 1.84–1.94 (m, 2H), 2.01–2.11 (m, 2H), 2.17 (dd, *J*=9.6, 7.8 Hz, 1H), 2.67 (dd, *J*=9.6, 6.6 Hz, 1H), 3.36 (dd, *J*=10.5, 4.8 Hz, 1H), 3.37 (d, *J*=9.6 Hz, 1H), 3.38 (s, 3H), 3.44 (d, *J*=9.6 Hz, 1H), 3.80 (s, 3H), 4.37 (d, *J*=11.7 Hz, 1H), 4.48 (d, *J*=11.7 Hz, 1H), 4.64 (d, *J*=6.9 Hz, 1H), 4.68 (d, *J*=6.9 Hz, 1H), 4.87 (br s, 1H), 6.85–6.90 (m, 2H), 7.21–7.26 (m, 2H), 9.79 (s, 1H); ^{13}C NMR for **42** (68 MHz, $CDCl_3$) δ 8.5, 9.7, 12.1, 12.7, 20.6, 23.1, 25.2, 25.3, 27.1, 27.6, 41.2, 44.9, 45.1, 46.6, 46.8, 55.2, 55.5, 71.0, 72.7, 89.8, 96.3, 113.7 (2C), 122.6, 129.0 (2C), 130.3, 141.2, 159.1, 208.1; IR (neat) 2960, 2930, 1715, 1615, 1515 cm^{-1}; HRMS calcd for $C_{30}H_{46}O_5$ $[M]^+$ 486.3345, found 486.3341.

*4.3.6. (1S,2Z,4R,5R,6R,7S,8S,9R)-2,4,5,7-Tetraethyl-4-(4-methoxybenzyloxy)methyl-8-methoxymethoxy-5-[(methoxymethoxy) methyl]-9-methylbicyclo[4.3.0]non-2-ene (**43**).* To a cooled (0 °C), stirred solution of **42** containing a small amount of byproduct (ca. 11:1, 106 mg, 0.219 mmol) in MeOH (4.0 mL) was added $NaBH_4$ (25.0 mg, 0.661 mmol). The mixture was stirred at room temperature for 40 min and $NaBH_4$ (13.0 mg, 0.343 mmol) was added. The mixture was stirred at room temperature for 30 min and $NaBH_4$ (17.0 mg, 0.449 mmol) was added. The mixture was stirred at room temperature for 30 min and then additional $NaBH_4$ (15.0 mg, 0.397 mmol) was added. The mixture was stirred at room temperature for additional 30 min, quenched with saturated aqueous NH_4Cl (10 mL) at 0 °C, and extracted with EtOAc (5 mL×3). The combined organic layers were dried and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:25 to 1:10) to provide 80.4 mg (77%) of alcohol as a colorless oil: TLC R_f 0.31 (EtOAc/hexane, 1:4); $[\alpha]_D^{26}$ +4.8 (*c* 0.515, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.75 (t, *J*=7.5 Hz, 3H), 0.91 (t, *J*=7.5 Hz, 3H), 0.99 (t, *J*=7.5 Hz, 3H), 1.08 (t, *J*=7.5 Hz, 3H), 1.20 (d, *J*=5.4 Hz, 3H), 1.36–1.68 (m, 5H), 1.80–2.12 (m, 7H), 3.21 (dd, *J*=5.4, 7.2 Hz, 1H), 3.27 (d, *J*=10.2 Hz, 1H), 3.38 (s, 3H), 3.44 (d, *J*=10.2 Hz, 1H), 3.49 (d, *J*=12.0 Hz, 1H), 3.61 (d, *J*=12.0 Hz, 1H), 3.80 (s, 3H), 4.42 (d, *J*=11.4 Hz, 1H),4.56 (d, *J*=11.4 Hz, 1H), 4.65 (d, *J*=6.9 Hz, 1H), 4.72 (d, *J*=6.9 Hz, 1H), 4.80 (br s, 1H), 6.87–6.90 (m, 2H), 7.25–7.28 (m, 2H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 8.3, 11.3, 11.4, 13.1, 19.8, 23.3, 25.0, 28.7, 29.2, 44.5, 45.4, 45.9 (2C), 46.0 (2C), 55.2, 55.4, 64.3, 71.4, 73.1, 92.9, 96.6, 113.9 (2C), 124.8, 128.8, 129.8 (2C), 140.5, 159.5; IR (neat) 3420, 2960, 2920 cm^{-1}; HRMS calcd for $C_{30}H_{48}O_5$ $[M]^+$ 488.3502, found 488.3493.

To a stirred solution of alcohol (77.0 mg, 0.158 mmol) in CH_2Cl_2 (1.5 mL) were added *i*-Pr_2NEt (60 μL, 0.79 mmol) and MOMCl (280 μL, 1.61 mmol). The mixture was refluxed for 16 h, diluted with saturated aqueous NH_4Cl (10 mL), and extracted with CH_2Cl_2 (5 mL×3). The combined organic layers were dried and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:35 to 1:25) to provide 73.8 mg (88%) of **43** as a colorless oil: TLC R_f 0.58 (EtOAc/hexane, 1:4); $[\alpha]_D^{23.5}$ +2.7 (*c* 1.15, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.80 (t, *J*=6.6 Hz, 3H), 0.93 (t, *J*=7.2 Hz, 3H), 0.94 (t, *J*=7.2 Hz, 3H), 0.99 (t, *J*=7.5 Hz, 3H), 1.17 (d, *J*=4.8 Hz, 3H), 1.25–1.48 (m, 2H), 1.50–1.78 (m, 3H), 1.80–2.12 (m, 1H),1.89 (q, *J*=6.6 Hz, 2H), 2.08 (q, *J*=7.5 Hz, 2H), 2.16–2.20 (m, 1H), 2.33 (dd, *J*=5.7, 6.9 Hz, 1H), 3.28–3.40 (m, 3H), 3.11 (s, 3H), 3.37 (s, 3H), 3.55 (br, 1H), 3.66 (br, 1H), 3.80 (s, 3H), 4.33 (d, *J*=11.7 Hz, 1H),4.40 (d, *J*=11.7 Hz, 1H), 4.53 (d, *J*=6.6 Hz, 1H), 4.56 (d, *J*=6.6 Hz, 1H), 4.65 (br, 1H), 4.94 (br, 1H), 6.85–6.89 (m, 2H), 7.25–7.27 (m, 2H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 8.6, 10.0, 11.5, 13.0, 21.1, 24.6, 26.3, 28.7 (2C), 43.2 (2C), 46.7 (2C), 46.8 (2C), 55.2, 55.3, 55.5, 71.9 (2C), 72.7, 95.7, 97.3 (2C), 113.5 (2C),

128.9 (3C), 131.0, 140.2, 158.9; IR (neat) 2960, 2920 cm^{-1}; HRMS calcd for $C_{32}H_{52}O_6$ $[M]^+$ 532.3764, found 532.3755.

*4.3.7. (1S,2Z,4R,5R,6R,7S,8S,9R)-2,4,5,7-Tetraethyl-4-formyl-8-methoxymethoxy-5-(methoxymethoxy)methyl-9-methylbicyclo[4.3.0] non-2-ene (**44**).* To a cooled (0 °C), stirred solution of **43** (73.0 mg, 0.137 mmol) in CH_2Cl_2 (1.5 mL) were added aqueous phosphate buffer (0.5 M aqueous Na_2HPO_4/0.5 M aqueous NaH_2PO_4, 2:1, 0.15 mL) and DDQ (93.0 mg, 0.41 mmol). The mixture was stirred at room temperature for 40 min, diluted with saturated aqueous $NaHCO_3$ (10 mL), and extracted with CH_2Cl_2 (5 mL×3). The combined organic layers were dried and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:30 to 1:10) to provide 55.7 mg (99%) of de-MPM derivative as a colorless oil: TLC R_f 0.25 (EtOAc/hexane, 1:4); $[\alpha]_D^{23}$ +24.0 (*c* 0.635, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, *J*=7.5 Hz, 3H), 0.94 (t, *J*=7.5 Hz, 3H), 1.02 (t, *J*=7.5 Hz, 3H), 1.06 (t, *J*=7.8 Hz, 3H), 1.21 (d, *J*=6.0 Hz, 3H), 1.25–1.54 (m, 3H), 1.62–1.85 (m, 3H), 1.88–2.18 (m, 6H), 3.29 (dd, *J*=5.4, 6.6 Hz, 1H), 3.39 (s, 3H), 3.42 (s, 3H), 3.39–3.47 (m, 2H), 3.61–3.65 (m, 2H), 4.66 (d, *J*=6.6 Hz, 1H),4.67 (s, 2H), 4.72 (d, *J*=6.6 Hz, 1H), 4.87 (br s, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 8.4, 11.4, 11.6, 13.1, 20.0, 23.9, 24.4, 24.5, 28.9, 29.1, 44.3, 46.4, 46.5, 46.9, 47.1, 55.4, 56.4, 64.3, 71.3, 92.5, 96.4, 97.0, 126.0, 140.0; IR (neat) 3440, 2960, 2920 cm^{-1}; HRMS calcd for $C_{24}H_{44}O_5$ $[M]^+$ 412.3189, found 412.3190.

To a cooled (0 °C), stirred solution of the de-MPM derivative (45.6 mg, 0.111 mmol) in CH_2Cl_2 (1.0 mL) was added Dess–Martin periodinane (84.5 mg, 0.199 mmol). The mixture was stirred at room temperature for 50 min and Dess–Martin periodinane (26.1 mg, 61.5 μmol) was added at 0 °C. The mixture was stirred at room temperature for 50 min and additional Dess–Martin periodinane (25.3 mg, 59.7 μmol) was added. The mixture was stirred at room temperature for 30 min, quenched with saturated aqueous $NaHCO_3$ (5 mL) and 20% aqueous $Na_2S_2O_3$ (5 mL), and extracted with CH_2Cl_2 (5 mL×3). The combined organic layers were dried and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:40 to 1:15) to provide 37.4 mg (82%) of **44** as a colorless oil: TLC R_f 0.50 (EtOAc/hexane, 1:4); $[\alpha]_{D25}$ +6.9 (*c* 0.605, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.77 (t, *J*=7.5 Hz, 3H), 0.93 (t, *J*=7.5 Hz, 3H), 0.95 (t, *J*=7.5 Hz, 3H), 1.06 (t, *J*=7.5 Hz, 3H), 1.18 (d, *J*=6.0 Hz, 3H), 1.34–1.71 (m, 4H), 1.67 (q, *J*=7.5 Hz, 2H), 1.87 (br, 1H), 1.99–2.30 (m, 5H), 3.34–3.39 (m, 1H), 3.36 (s, 3H), 3.39 (s, 3H), 3.54 (d, *J*=9.9 Hz, 1H),3.62 (d, *J*=9.9 Hz, 1H),4.62 (s, 2H), 4.63 (s, 2H), 5.54 (br s, 1H), 9.91 (s, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 8.9, 10.3, 11.7, 12.9, 20.2, 24.6, 24.7, 28.8, 28.9, 43.8, 44.7, 46.2, 46.3, 46.9 (2C), 55.3, 56.0, 71.2, 91.2, 95.8, 97.2, 120.2, 141.3, 207.8; IR (neat) 2960, 2930, 1715 cm^{-1}; HRMS calcd for $C_{24}H_{42}O_5$ $[M]^+$ 410.3032, found 410.3029.

*4.3.8. (1S,2Z,4R,5R,6R,7S,9R)-2,4,5,7-Tetraethyl-5-formyl-9-methyl-4-(1E)-styrylbicyclo[4.3.0]non-2-en-8-one (**45**).* The following reaction was carried out under argon. To a cooled (−78 °C), stirred solution of diethyl benzylphosphonate (0.72 mL, 3.5 mmol) in THF (4.0 mL) was added *n*-BuLi (2.63 M solution in hexane, 1.0 mL, 2.6 mmol). The mixture was stirred at −78 °C for 30 min and a solution of **44** (35.0 mg, 85.2 μmol) in THF (2.2 mL) was added dropwise at −78 °C. The mixture was warmed to 0 °C over 2 h, quenched with saturated aqueous NH_4Cl (10 mL), and extracted with EtOAc (5 mL×3). The combined organic layers were dried and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:100) to provide 39.6 mg (96%) of the styryl derivative as a colorless oil: TLC R_f 0.69 (EtOAc/hexane, 1:4); $[\alpha]_D^{23}$ +15.8 (*c* 0.80, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.76 (t, *J*=7.5 Hz, 3H), 0.79 (t, *J*=7.8 Hz, 3H), 1.01 (t, *J*=7.2 Hz, 3H), 1.06 (t, *J*=7.5 Hz, 3H),1.03–1.07 (m, 3H), 1.26–1.42 (m, 1H), 1.52–1.87 (m, 5H), 2.16–2.30 (m, 5H), 2.46 (m, 1H), 3.23 (s, 3H), 3.38 (s, 3H), 3.30–3.44 (m, 2H), 3.57 (d, *J*=9.6 Hz, 1H),4.41 (br, 1H), 4.49 (d, *J*=6.6 Hz, 1H), 4.58 (d, *J*=6.9 Hz, 1H), 4.61 (d, *J*=6.9 Hz, 1H), 5.40 (br s, 1H), 6.22 (d, *J*=16.2 Hz, 1H), 6.34 (d, *J*=16.2 Hz, 1H), 7.16 (t, *J*=7.2 Hz, 1H), 7.24–7.34 (m, 4H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 8.5, 10.0, 12.6, 12.9, 20.1, 24.7 (2C), 28.3, 28.4, 29.1, 43.5, 46.2, 46.3, 46.4 (2C), 55.0, 55.7, 72.5, 94.4, 97.3 (2C), 123.0, 126.0 (2C), 126.4, 128.3 (2C), 130.6, 136.0, 138.6, 140.0; IR (neat) 2960, 2930 cm^{-1}; HRMS calcd for $C_{31}H_{48}O_4$ $[M]^+$ 484.3553, found 484.3552.

A solution of the styryl derivative (16.0 mg, 33.0 μmol) in 6 M aqueous HCl/THF (1:1, 1.0 mL) was stirred at room temperature for 8 h. The mixture was quenched with saturated aqueous $NaHCO_3$ (10 mL) and extracted with EtOAc (5 mL×3). The combined organic layers were dried and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:30 to 15:1) to provide 10.9 mg (84%) of de-MOM derivative as a colorless oil: TLC R_f 0.27 (EtOAc/hexane, 1:4); $[\alpha]_D^{25}$ +7.6 (*c* 0.55, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.79 (t, *J*=7.2 Hz, 3H), 0.82 (t, *J*=7.2 Hz, 3H), 1.03 (t, *J*=7.2 Hz, 3H), 1.09 (t, *J*=7.5 Hz, 3H),1.01–1.87 (m, 9H), 2.17–2.30 (m, 6H), 3.39 (br s, 1H), 3.61 (br, 1H), 3.77 (d, *J*=11.1 Hz, 1H),5.54 (br s, 1H), 6.24 (d, *J*=16.2 Hz, 1H), 6.31 (d, *J*=16.2 Hz, 1H), 7.17–7.22 (m, 1H), 7.27–7.35 (m, 4H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 8.5, 10.0, 12.7, 12.9, 19.5, 24.2 (2C), 28.0, 28.4, 29.0, 44.2, 45.9 (2C), 46.0 (2C), 67.1, 85.9, 126.0 (2C), 126.8, 128.5 (2C), 130.0 (2C), 138.0 (3C); IR (neat) 3440, 2960, 2930 cm^{-1}; HRMS calcd for $C_{27}H_{40}O_2$ $[M]^+$ 396.3028, found 396.3037.

To a cooled (0 °C), stirred solution of the de-MOM derivative (15.0 mg, 37.8 μmol) in CH_2Cl_2 (1.0 mL) were added Dess–Martin periodinane (55.0 mg, 0.130 mmol) and $NaHCO_3$ (23.0 mg, 0.273 mmol). The mixture was stirred at room temperature for 2 h, quenched with saturated aqueous $NaHCO_3$ (5 mL) and 20% aqueous $Na_2S_2O_3$ (5 mL) at 0 °C, and extracted with CH_2Cl_2 (5 mL×3). The combined organic layers were dried and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:100) to provide 12.0 mg (81%) of **45** as a colorless oil: TLC R_f 0.63 (EtOAc/hexane, 1:4); $[\alpha]_D^{25.5}$ +14.3 (*c* 0.60, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.83 (t, *J*=7.2 Hz, 3H), 0.84 (t, *J*=7.5 Hz, 3H), 1.00 (t, *J*=7.2 Hz, 3H), 1.13 (t, *J*=7.2 Hz, 3H), 1.30 (d, *J*=7.2 Hz, 3H), 1.38–1.87 (m, 6H), 1.99–2.37 (m, 4H), 2.69 (t, *J*=8.4 Hz, 1H), 2.96 (dd, *J*=3.3, 8.4 Hz, 1H), 5.55 (d, *J*=1.2 Hz, 1H), 6.23 (d, *J*=16.2 Hz, 1H), 6.40 (d, *J*=16.2 Hz, 1H), 7.22–7.28 (m, 1H), 7.31–7.40 (m, 4H), 9.83 (s, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 8.9, 11.0, 11.7, 12.7, 18.7, 23.6, 26.1, 28.8, 30.8, 39.7, 43.9, 47.8, 48.3, 53.1, 56.5, 123.5, 126.2 (2C), 127.5, 128.7 (2C), 131.5, 134.0, 137.1, 141.0, 207.2, 223.7; IR (neat) 2960, 2930, 1730, 1715 cm^{-1}; HRMS calcd for $C_{27}H_{36}O_2$ $[M]^+$ 392.2715, found 392.2717.

*4.3.9. (1S,2Z,4R,5R,6R,7S,9R)-5-Carboxy-2,4,5,7-tetraethyl-9-methyl-4-(1E)-styrylbicyclo[4.3.0]non-2-en-8-one (**46**).* To a cooled (0 °C), stirred solution of **45** (12.0 mg, 30.6 μmol) in *t*-BuOH/H_2O (5:1, 1.0 mL) were added 2-methyl-2-butene (30 μL, 0.28 mmol), NaH_2PO_4 (18.5 mg, 0.15 mmol), and $NaClO_2$ (18.0 mg, 0.16 mmol). The mixture was stirred at room temperature for 40 min and 2-methyl-2-butene (100 μL, 0.94 mmol), NaH_2PO_4 (54.9 mg, 0.46 mmol), and $NaClO_2$ (53.1 mg, 0.46 mmol) were added at 0 °C. The mixture was stirred at room temperature for 30 min and additional 2-methyl-2-butene (60 μL, 0.57 mmol), NaH_2PO_4 (36.6 mg, 0.305 mmol), and $NaClO_2$ (35.4 mg, 0.305 mmol) were added. The mixture was stirred at room temperature for 50 min, quenched with saturated aqueous NH_4Cl (10 mL) at 0 °C, and extracted with CH_2Cl_2 (5 mL×3). The combined organic layers were dried and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:100 to 1:10) to provide 11.4 mg (91%) of **46** as a colorless oil: TLC R_f 0.31 (EtOAc/hexane, 1:4); $[\alpha]_D^{26}$ +13.4 (*c* 0.60, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.78 (t, *J*=7.5 Hz, 3H), 0.85 (t, *J*=7.5 Hz, 3H), 1.04 (t, *J*=7.5 Hz, 3H), 1.16 (t, *J*=7.5 Hz, 3H), 1.34 (d, *J*=7.2 Hz, 3H),1.35–1.56 (m, 1H),

1.61–1.96 (m, 4H), 2.00–2.39 (m, 4H), 2.46 (t, *J*=7.2 Hz, 1H), 2.67 (dd, *J*=8.1, 9.6 Hz, 1H), 3.10 (d, *J*=8.1 Hz, 1H), 5.63 (br s, 1H), 6.36 (br s, 2H), 7.23 (t, *J*=7.5 Hz, 1H), 7.32 (t, *J*=7.5 Hz, 2H), 7.42 (d, *J*=7.5 Hz, 2H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 9.3, 11.9 (2C), 12.8, 18.7, 25.6, 27.3, 29.1, 32.3, 42.6, 44.7, 47.6, 48.8, 54.7, 55.6, 123.4, 126.2 (2C), 127.2, 128.6 (2C), 131.1, 135.5, 137.7, 139.4, 179.6, 224.4; IR (neat) 3450–3100, 2960, 2930, 1730, 1715 cm^{-1}; HRMS calcd for $C_{27}H_{36}O_3$ $[M]^+$ 408.2665, found 408.2669.

4.4. Total synthesis of (+)-zyggomphic acid (6)

*4.4.1. (2E,4S,5S,6S,7E)-2-Bromo-6-ethyl-8-(4-methoxybenzyloxy) methyl-5-methoxymethoxy-4-methyldeca-2,7-diene (2:1 geometric mixture) (**47**).* To a cooled (0 °C), stirred solution of **19** (133 mg, 0.324 mmol) in acetone/H_2O (4:1, 4.0 mL) was added $NaIO_4$ (187 mg, 0.875 mmol). The mixture was stirred at room temperature for 30 min, quenched with 1 M aqueous $NaHSO_3$ (7 mL) at 0 °C, and extracted with EtOAc (5 mL×3). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (5 mL) and brine (5 mL), dried, and concentrated under reduced pressure to provide 119 mg of crude aldehyde, which was used in the next step without further purification.

The following reaction was carried out under argon. To a cooled (−40 °C), stirred suspension of 1,1-(dibromoethyl)triphenylphosphonium bromide (741 mg, 1.40 mmol) in THF (4.0 mL) was added *n*-BuLi (0.48 mL of 2.69 M solution in hexane, 1.2 mmol). The mixture was stirred at −40 °C for 30 min and cooled to −78 °C. Then a solution of the crude aldehyde obtained above (119 mg) in THF (1.3 mL) was added dropwise. The mixture was stirred at −78 °C for 20 min, quenched with H_2O (5 mL) at −78 °C, diluted with saturated aqueous $NaHCO_3$ (10 mL) and H_2O (5 mL), and extracted with EtOAc (5 mL×3). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (10 mL), dried, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:50) to provide 62.9 mg (41% for two steps) of **47** (*E*/*Z*=2:1) as a colorless oil: TLC R_f 0.45 (EtOAc/hexane, 1:4); $[\alpha]_D^{24}$ +26.4 (*c* 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) for major isomer **47** δ 0.84 (t, *J*=7.5 Hz, 3H), 0.99 (t, *J*=7.5 Hz, 3H), 1.02 (d, *J*=7.2 Hz, 3H), 1.11–1.26 (m, 1H), 1.56–1.79 (m, 1H), 2.01–2.15 (m, 2H), 2.15 (d, *J*=1.2 Hz, 3H), 2.31–2.44 (m, 1H), 2.53–2.65 (m, 1H), 3.22 (dd, *J*=3.6, 7.2 Hz, 1H), 3.41 (s, 3H), 3.81 (s, 3H), 3.95 (s, 2H), 4.40 (s, 2H), 4.66 (s, 2H), 5.10 (d, *J*=10.5 Hz, 1H), 5.92 (dd, *J*=1.2, 9.8 Hz, 1H), 6.86–6.89 (m, 2H), 7.24–7.27 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) for major isomer **47** δ 11.9, 12.7, 17.4, 21.6, 23.8, 28.9, 37.8, 43.1, 55.3, 56.2, 71.4, 73.6, 86.3, 98.5, 113.8 (2C), 128.5 (2C), 129.3 (2C), 130.9, 134.2, 139.4, 159.2; IR (neat) 2960, 1615, 1515 cm^{-1}; HRMS calcd for $C_{24}H_{37}O_4Br$ $[M]^+$ 468.1899, found 468.1875.

*4.4.2. 2-[(2Z,4S,5S,6S,7E)-6-Ethyl-8-hydroxymethyl-5-methoxymethoxy-4-methyldeca-2,7-dien-2-yl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**48**).* The following reaction was carried out under argon. To a stirred solution of **47** (69.1 mg, 0.147 mmol, *E*/*Z*=2:1) in toluene (2.8 mL) were added bis(pinacolato)diboron (101 mg, 0.397 mmol), $PdCl_2(PPh_3)_2$ (10.3 mg, 14.7 μmol), PPh_3 (7.7 mg, 29 μmol), and KOPh (52.5 mg, 0.397 mmol). The mixture was stirred at 50 °C for 4 h. After being cooled to room temperature, the mixture was diluted with H_2O (20 mL) and extracted with EtOAc (20 mL). The organic layer was washed with 2 M aqueous NaOH (10 mL×2) and brine (10 mL), dried, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:40 to 1:20) to provide 38.1 mg (50%) of (*E*)-boronate as a colorless oil: TLC R_f 0.35 (EtOAc/hexane, 1:5); $[\alpha]_D^{24}$ +37.5 (*c*0.56, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84 (t, *J*=7.5 Hz, 3H), 0.96 (t, *J*=7.2 Hz, 3H), 1.00 (d, *J*=6.9 Hz, 3H), 1.24 (s, 12H), 1.68–1.79 (m, 1H), 1.97–2.18 (m, 3H), 2.38–2.48 (m, 1H), 2.78–2.90 (m, 1H), 3.31 (dd, *J*=4.2, 6.3 Hz, 1H), 3.39 (s, 3H), 3.81 (s, 3H), 3.91 (d, *J*=12.2 Hz, 1H), 3.99 (d, *J*=12.2 Hz, 1H), 4.35 (d, *J*=11.6 Hz, 1H), 4.40 (d, *J*=11.6 Hz, 1H), 4.66 (d, *J*=6.0 Hz, 1H), 4.68 (d, *J*=6.0 Hz, 1H), 5.14 (d, *J*=10.5 Hz, 1H), 6.37 (dd, *J*=1.5, 9.3 Hz, 1H), 6.86–6.89 (m, 2H), 7.24–7.26 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.9, 12.6, 13.9, 17.2, 21.4, 23.6, 24.7 (2C), 24.8 (2C), 36.1, 42.5, 55.2, 56.1, 70.9, 73.7, 83.0, 86.4 (2C), 98.1, 113.7 (2C), 129.1 (2C), 129.5 (2C), 130.8, 138.6, 148.2, 159.1; IR (neat) 2960, 1615, 1515 cm^{-1}; HMRS calcd for $C_{30}H_{49}O_6B$ $[M]^+$ 516.3643, found 516.3622.

To a cooled (0 °C), stirred solution of the (*E*)-boronate obtained above (38.1 mg, 73.7 μmol) in CH_2Cl_2 (1.0 mL) were added aqueous phosphate buffer (0.5 M aqueous Na_2HPO_4/0.5 M aqueous NaH_2PO_4, 2:1, 0.1 mL) and DDQ (50.2 mg, 0.22 mmol). The mixture was stirred at room temperature for 40 min, diluted with saturated aqueous $NaHCO_3$ (10 mL) at 0 °C, and extracted with CH_2Cl_2 (5 mL×3). The combined organic layers were dried and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:25 to 1:15) to provide 17.6 mg (60%) of **48** as a colorless oil: TLC R_f 0.31 (EtOAc/hexane, 1:3); $[\alpha]_D^{24.5}$ +112 (*c* 0.62, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.80 (t, *J*=7.4 Hz, 3H), 1.00 (d, *J*=6.9 Hz, 3H), 1.02 (t, *J*=7.2 Hz, 3H), 1.07–1.15 (m, 1H), 1.26 (s, 6H), 1.27 (s, 6H), 1.66–1.83 (m, 1H), 1.70 (d, *J*=1.5 Hz, 3H), 2.05–2.29 (m, 2H), 2.40–2.50 (m, 1H), 2.84 (br s, 1H), 2.90–3.01 (m, 1H), 3.35 (dd, *J*=3.2, 8.6 Hz, 1H), 3.42 (s, 3H), 3.95 (d, *J*=13.2 Hz, 1H), 4.10 (d, *J*=13.2 Hz, 1H), 4.68 (d, *J*=6.8 Hz, 1H), 4.75 (d, *J*=6.8 Hz, 1H), 4.92 (d, *J*=10.8 Hz, 1H), 6.13 (dd, *J*=1.5, 8.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.6, 12.7, 13.8, 14.9 (2C), 21.4, 24.5, 24.6, 24.8 (2C), 36.3, 41.4, 56.0, 66.2, 83.5, 84.9 (2C), 97.1, 127.2 (2C), 140.7, 150.0; IR (neat) 3500, 2970, 1630 cm^{-1}; HRMS calcd for $C_{22}H_{41}O_5B$ $[M]^+$ 396.3052, found 396.3047.

*4.4.3. (2E,4S,5S,6S,7E,9E,11E)-12-(tert-Butyldimethylsilyloxy)-methyl-2,4,10-triethyl-5-methoxymethoxy-6,8-dimethyltetradeca-2,7,9,11-tetraenal (**50**).* The following reaction was carried out under argon. To a stirred solution of **48** (17.6 mg, 44.4 μmol) and **49** (43.9 mg, 115 μmol) in degassed THF (4.4 mL) were added 3 M aqueous NaOH (88 μL, 0.27 mmol), $PdCl_2(dppf)\cdot CH_2Cl_2$ (3.6 mg, 4.4 μmol), and a crystal of BHT. The mixture was stirred at room temperature for 20 h, diluted with saturated aqueous NH_4Cl (10 mL), and extracted with EtOAc (5 mL×3). The combined organic layers were dried and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:15) to provide 16.8 mg (72%) of tetraene as a colorless oil: TLC R_f 0.21 (EtOAc/hexane, 1:4); $[\alpha]_D^{21.5}$ +82.0 (*c* 0.14, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$)δ 0.08 (s, 6H), 0.82 (t, *J*=7.5 Hz, 3H), 0.92 (s, 9H), 0.97 (t, *J*=7.5 Hz, 3H), 0.98 (t, *J*=7.5 Hz, 3H), 1.02 (t, *J*=7.5 Hz, 3H), 1.03 (d, *J*=7.5 Hz, 3H), 1.13–1.23 (m, 1H), 1.66–1.81 (m, 1H), 1.71 (d, *J*=0.6 Hz, 3H), 2.02 (dq, *J*=7.5, 14.3Hz, 1H), 2.10–2.33 (m, 5H), 2.34–2.45 (m, 1H), 2.63–2.74 (m, 1H), 3.25 (dd, *J*=3.9, 7.2 Hz, 1H), 3.41 (s, 3H), 4.07 (s, 2H), 4.14 (d, *J*=1.2 Hz, 2H), 4.66 (d, *J*=6.9 Hz, 1H), 4.68 (d, *J*=6.9 Hz, 1H), 5.13 (d, *J*=10.2 Hz, 1H), 5.39 (d, *J*=9.3 Hz, 1H), 5.70 (s, 1H), 5.86 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.3 (2C), 11.9, 12.8, 13.6, 13.9, 17.1, 18.4, 21.4, 21.7, 23.7, 25.2, 26.0 (3C), 36.0, 42.6, 56.0, 66.3, 66.6, 87.4, 98.4, 126.8, 127.8, 131.1, 131.6, 132.3, 138.2, 141.4, 141.6; IR (neat) 3420, 2960, 2880, 2860, 1460 m^{-1}; HRMS calcd for $C_{31}H_{58}O_4Si$ $[M]^+$ 522.4103, found 522.4104.

To a cooled (0 °C), stirred solution of the tetraene obtained above (16.8 mg, 32.1 μmol) in CH_2Cl_2 (1.0 mL) were added Dess–Martin periodinane (21.8 mg, 51.4 μmol), $NaHCO_3$ (8.7 mg, 0.10 mmol), and a crystal of BHT. The mixture was stirred at room temperature for 15 min, quenched with saturated aqueous $NaHCO_3$ (5 mL) and 20% aqueous $Na_2S_2O_3$ (5 mL) at 0 °C, and extracted with CH_2Cl_2 (5 mL×3). The combined organic layers were dried and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:80 to 1:60) to provide 14.7 mg (88%) of **50**as a colorless oil: TLC R_f 0.58 (EtOAc/hexane, 1:4); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.08 (s, 6H), 0.85 (t,

J=7.5 Hz, 3H), 0.88–0.96 (m, 3H), 0.94 (s, 9H), 0.97 (t, *J*=7.5 Hz, 3H), 1.02 (t, *J*=7.5 Hz, 3H), 1.06 (d, *J*=7.2 Hz, 3H), 1.33–1.48 (m, 1H), 1.68 (s, 3H), 1.82–1.93 (m, 1H), 2.16–2.28 (m, 6H), 2.59–2.79 (m, 2H), 3.36–3.42 (m, 1H), 3.42 (s, 3H), 4.14 (d, *J*=1.2 Hz, 2H), 4.68 (d, *J*=6.6 Hz, 1H), 4.71 (d, *J*=6.6 Hz, 1H), 5.36 (d, *J*=9.3 Hz, 1H), 5.67 (s, 1H), 5.85 (s, 1H), 6.23 (d, *J*=10.8 Hz, 1H), 9.38 (s, 1H).

*4.4.4. (1R,2Z,4R,5R,6R,7S,8S,9S)-4-[[(1E)-2-(tert-Butyldimethylsilyloxy)methyl]but-1-en-1-yl]]-4,5,7-triethyl-5-formyl-8-methoxymethoxy-2,9-dimethylbicyclo[4.3.0]non-2-ene (**51**).* The following reaction was carried out under argon. To a stirred solution of **50** (14.7 mg, 28.2 μmol) in degassed toluene (2.8 mL) were added Wako Gel C-300 (147 mg) and a crystal of BHT. The mixture was stirred at room temperature for 21 h, filtered through cotton, and washed with EtOAc. The combined filtrate and washings were concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane to EtOAc/hexane, 1:200) to provide 10.8 mg (74%) of **51** and 3.3 mg of a byproduct. Compound **51** was obtained as a colorless oil: TLC R_f 0.60 (EtOAc/hexane, 1:6); $[\alpha]_D^{24}$ +26.4 (*c* 0.50, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.03 (s, 6H), 0.79 (t, *J*=7.4 Hz, 3H), 0.88 (s, 9H), 0.89 (t, *J*=7.2 Hz, 3H), 0.90 (t, *J*=7.2 Hz, 3H), 0.94 (t, *J*=7.4 Hz, 3H), 1.00–1.16 (m, 1H), 1.25 (d, *J*=6.6 Hz, 3H), 1.30–1.38 (m, 2H), 1.50–1.60 (m, 2H), 1.77–1.88 (m, 1H), 1.82 (s, 3H), 1.90–2.12 (m, 3H), 2.30 (t, *J*=11.4 Hz, 1H), 2.38–2.53 (m, 2H), 3.36 (s, 3H), 3.69 (dd, *J*=1.5, 5.4 Hz, 1H), 3.94 (d, *J*=13.1 Hz, 1H), 4.01 (d, *J*=13.1 Hz, 1H), 4.54 (d, *J*=6.8 Hz, 1H), 4.65 (d, *J*=6.8 Hz, 1H), 5.04 (s, 1H), 5.32 (br s, 1H), 9.76 (s, 1H); ^{13}C NMR (75 Hz, $CDCl_3$) δ −5.5, −5.4, 9.1, 10.2, 11.5, 13.5, 15.0, 18.2, 20.1, 20.6, 22.5, 25.8 (3C), 27.6, 29.1, 39.6, 46.1, 46.7, 48.7, 53.8, 55.5, 59.0, 67.3, 85.2, 94.6, 126.5, 127.5, 135.5, 143.5, 208.0; IR (neat) 2960, 2930, 2880, 2860, 1715, 1460 cm^{-1}; HRMS calcd for $C_{31}H_{56}O_4Si$ $[M]^+$ 520.3961, found 520.3948.

*4.4.5. (1R,2Z,4R,5R,6R,7S,8S,9S)-4,5,7-Triethyl-4-[(1E)-2-hydroxymethylbut-1-en-1-yl]-8-methoxymethoxy-5-(methoxymethoxy) methyl-2,9-dimethylbicyclo[4.3.0]non-2-ene (**52**).* To a cooled (0 °C), stirred solution of **51** (10.8 mg, 20.7 μmol) in MeOH/THF (1:1, 1.0 mL) was added $NaBH_4$ (2.4 mg, 62 μmol). The mixture was stirred at room temperature for 30 min, quenched with saturated aqueous NH_4Cl (10 mL) at 0 °C, and extracted with EtOAc (5 mL×3). The combined organic layers were dried and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:100 to 1:30) to provide 8.7 mg (81%) of primary alcohol as a colorless oil: TLC R_f 0.29 (EtOAc/hexane, 1:6); $[\alpha]_D^{24.5}$ −45.7 (*c* 0.16, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.05 (s, 6H), 0.81 (t, *J*=7.4 Hz, 3H), 0.88–0.93 (m, 3H), 0.90 (s, 9H), 0.90 (t, *J*=7.2 Hz, 3H), 1.01 (t, *J*=7.5 Hz, 3H), 1.23 (d, *J*=6.6 Hz, 3H), 1.25–1.44 (m, 4H), 1.57–1.72 (m, 3H), 1.75–1.92 (m, 2H), 1.79 (s, 3H), 2.01 (dq, *J*=7.5, 13.4 Hz, 1H), 2.30 (t, *J*=11.4 Hz, 1H), 2.44 (dq, *J*=7.5, 13.4 Hz, 1H), 3.37 (s, 3H), 3.61 (d, *J*=4.8 Hz, 1H), 3.76 (d, *J*=11.4 Hz, 1H), 3.81 (d, *J*=11.4 Hz, 1H), 3.98 (d, *J*=12.5 Hz, 1H), 4.05 (d, *J*=12.5 Hz, 1H), 4.54 (d, *J*=6.9 Hz, 1H), 4.70 (d, *J*=6.9 Hz, 1H), 5.26 (s, 1H), 5.35 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.4 (2C), 9.5, 9.7, 12.4, 13.6, 14.7, 18.3, 19.9, 21.1, 22.7, 25.9 (3C), 28.5, 29.8, 40.5, 45.5, 46.1, 46.2, 51.7, 52.8, 55.4, 64.7, 67.8, 86.3, 94.1, 127.8, 129.3, 134.5, 142.0; IR (neat) 3490, 2930, 2880, 2955, 1460 cm^{-1}; HRMS calcd for $C_{31}H_{58}O_4Si$ $[M]^+$ 522.4122, found 522.4104.

To a stirred solution of the primary alcohol obtained above (8.7 mg, 17 μmol) in CH_2Cl_2 (2.0 mL) were added *i*-Pr_2NEt (60 μL, 0.34 mmol) and MOMCl (13 μL, 0.17 mmol). The mixture was refluxed for 10.5 h, diluted with saturated aqueous NH_4Cl (10 mL), and extracted with CH_2Cl_2 (5 mL×3). The combined organic layers were dried and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:100 to 1:60) to provide 8.4 mg (89%) of di-*O*-MOM derivative as a colorless oil: TLC R_f 0.60 (EtOAc/hexane, 1:5); $[\alpha]_D^{21}$ −12.7 (*c* 0.55, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.04 (s, 6H), 0.79 (t, *J*=7.4 Hz, 3H), 0.88–0.93 (m, 3H), 0.89 (s, 9H), 0.90 (t, *J*=7.2 Hz, 3H), 1.00 (t, *J*=7.5 Hz, 3H), 1.23 (d, *J*=6.9 Hz, 3H), 1.26–1.43 (m, 4H), 1.55–1.72 (m, 3H), 1.75–1.85 (m, 1H), 1.79 (s, 3H), 1.92–2.06 (m, 2H), 2.31 (t, *J*=11.9 Hz, 1H), 2.44 (dq, *J*=7.5, 13.4 Hz, 1H), 3.37 (s, 3H), 3.40 (s, 3H), 3.58 (d, *J*=9.8 Hz, 1H), 3.60 (d, *J*=3.3 Hz, 1H), 3.61 (d, *J*=9.8 Hz, 1H), 3.96 (d, *J*=12.3 Hz, 1H), 4.05 (d, *J*=12.3 Hz, 1H), 4.53 (d, *J*=6.8 Hz, 1H), 4.58 (d, *J*=6.5 Hz, 1H), 4.62 (d, *J*=6.5 Hz, 1H),4.69 (d, *J*=6.8 Hz, 1H), 5.21 (s, 1H), 5.36 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.3 (2C), 9.4, 9.6, 12.3, 13.6, 14.6, 18.3, 19.8, 21.3, 22.6, 25.9 (2C), 28.8, 29.3, 40.5, 45.4, 45.6, 46.0, 51.9, 53.0, 55.4, 55.5, 68.2, 70.2, 86.2, 94.0, 97.0, 128.0, 129.5, 134.3141.7; IR (neat) 2960, 2930, 2880, 2860, 1460 cm^{-1}; HRMS calcd for $C_{33}H_{62}O_5Si$ $[M]^+$ 566.4385, found 566.4367.

To a cooled (0 °C), stirred solution of the di-*O*-MOM derivative obtained above (8.4 mg, 15 μmol) in THF (1.0 mL) was added *n*-Bu_4NF (50 μL of 1.0 M solution in THF, 50 μmol). The mixture was stirred at room temperature for 2 h, diluted with saturated aqueous NH_4Cl (12 mL) at 0 °C, and extracted with EtOAc (5 mL×3). The combined organic layers were dried and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:8) to provide 6.2 mg (93%) of **52** as a colorless oil: TLC R_f 0.33 (EtOAc/hexane, 1:2); $[\alpha]_D^{25}$ +42.7 (*c* 0.30, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.80 (t, *J*=7.4 Hz, 3H), 0.93 (t, *J*=7.5 Hz, 6H), 0.99 (t, *J*=7.5 Hz, 3H), 1.24 (d, *J*=6.9 Hz, 3H), 1.29–1.43 (m, 3H), 1.50–1.72 (m, 3H), 1.75–1.87 (m, 2H), 1.80 (s, 3H), 2.01 (dq, *J*=7.5, 13.4 Hz, 1H), 2.11 (dq, *J*=7.5, 13.6 Hz, 1H), 2.33 (t, *J*=11.7 Hz, 1H), 2.47 (dq, *J*=7.5, 13.6 Hz, 1H), 3.37 (s, 3H), 3.41 (s, 3H), 3.56 (d, *J*=9.9 Hz, 1H), 3.61 (d, *J*=3.0 Hz, 1H), 3.62 (d, *J*=9.9 Hz, 1H), 4.03 (s, 2H), 4.53 (d, *J*=6.8 Hz, 1H), 4.59 (d, *J*=6.5 Hz, 1H), 4.64 (d, *J*=6.5 Hz, 1H), 4.69 (d, *J*=6.8 Hz, 1H), 5.28 (s, 1H), 5.36 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.4, 9.7, 12.3, 13.6, 14.7, 20.0, 21.3, 22.6, 28.9, 29.3, 40.6, 45.4, 45.5, 46.0, 52.0, 53.0, 55.4, 55.7, 68.8, 70.5, 86.1, 94.0, 97.2, 127.7, 131.5, 134.7, 142.3; IR (neat) 3440, 2960, 2930, 2880, 1460 cm^{-1}; HRMS calcd for $C_{27}H_{48}O_5$ $[M]^+$ 452.3498, found 452.3502.

*4.4.6. (1R,2Z,4R,5R,6R,7S,8S,9S)-4,5,7-Triethyl-4-[(1E,3E)-2-ethyl-4-phenylbuta-1,3-dien-1-yl]-8-hydroxy-5-hydroxymethyl-2,9-dimethylbicyclo[4.3.0]non-2-ene (**53**).* To a cooled (0 °C), stirred solution of **52** (6.2 mg, 13 μmol) in CH_2Cl_2 (1.0 mL) was added Dess–Martin periodinane (9.3 mg, 22 μmol). The mixture was stirred at room temperature for 30 min, quenched with saturated aqueous $NaHCO_3$ (5 mL) and 20% aqueous $Na_2S_2O_3$ (5 mL) at 0 °C, and extracted with CH_2Cl_2 (5 mL×3). The combined organic layers were dried and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:25) to provide 6.2 mg of unsaturated aldehyde as a colorless oil: TLC R_f 0.60 (EtOAc/hexane, 1:2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.81 (t, *J*=7.5 Hz, 3H), 0.86–0.88 (m, 3H), 0.91 (t, *J*=7.5 Hz, 3H), 1.02 (t, *J*=7.5 Hz, 3H), 1.25 (d, *J*=6.3 Hz, 3H), 1.35–1.50 (m, 4H), 1.57–1.72 (m, 2H), 1.83–1.95 (m, 2H), 1.83 (s, 3H), 2.22 (dq, *J*=7.5, 13.5 Hz, 1H), 2.31–2.40 (m, 2H), 2.49 (dq, *J*=7.5, 12.8 Hz, 1H), 3.37 (s, 3H), 3.43 (s, 3H), 3.55 (d, *J*=10.4 Hz, 1H), 3.60 (d, *J*=4.8 Hz, 1H), 3.65 (d, *J*=10.4 Hz, 1H), 4.53 (d, *J*=6.9 Hz, 1H), 4.62 (d, *J*=6.5 Hz, 1H), 4.66 (d, *J*=6.5 Hz, 1H), 4.67 (d, *J*=6.9 Hz, 1H), 5.41 (br s, 1H), 6.40 (s, 1H), 9.36 (s, 1H).

The following reaction was carried out under argon. To a cooled (−78 °C), stirred solution of diethyl benzylphosphonate (40 μL, 0.19 mmol) in THF (1.0 mL) was added *n*-BuLi (50 μL of 2.69 M solution in hexane, 0.13 mmol). The mixture was stirred at −78 °C for 30 min and then a solution of aldehyde obtained above (6.2 mg, 14 μmol) in THF (0.7 mL) was added dropwise at −78 °C. The mixture was warmed to 0 °C over 3 h, quenched with saturated aqueous NH_4Cl (10 mL) at 0 °C, and extracted with EtOAc (5 mL×3). The combined organic layers were dried and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:70 to 1:50) to provide

5.6 mg (78%) of styryl derivative as a colorless oil: TLC R_f 0.58 (EtOAc/hexane, 1:4); $[\alpha]_D^{25.5}$ −21.0 (*c* 0.21, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$)δ0.82 (t, *J*=7.5 Hz, 3H), 0.85–0.92 (m, 3H), 1.01 (t, *J*=7.4 Hz, 3H), 1.02 (t, *J*=7.4 Hz, 3H), 1.26 (d, *J*=6.0 Hz, 3H), 1.30–1.43 (m, 4H), 1.53–1.59 (m, 2H), 1.62–1.72 (m,1H), 1.78–1.88 (m, 1H), 1.83 (s, 3H), 2.06 (dq, *J*=7.4, 13.4 Hz, 1H), 2.31–2.41 (m, 1H), 2.35 (t, *J*=10.8 Hz, 1H), 2.75 (dq, *J*=7.4, 13.7 Hz, 1H), 3.37 (s, 3H), 3.46 (s, 3H), 3.59 (d, *J*=9.6 Hz, 1H), 3.60 (d, *J*=3.6 Hz, 1H), 3.65 (d, *J*=9.6 Hz, 1H), 4.53 (d, *J*=6.8 Hz, 1H), 4.63 (d, *J*=6.6 Hz, 1H), 4.67 (d, *J*=6.6 Hz, 1H), 4.69 (d, *J*=6.8 Hz, 1H), 5.43 (br s, 1H), 5.46 (s, 1H), 6.45 (d, *J*=16.2 Hz, 1H), 6.68 (d, *J*=16.2 Hz, 1H), 7.18 (t, *J*=7.6 Hz, 1H), 7.30 (t, *J*=7.6 Hz, 2H), 7.41 (d, *J*=7.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.5, 9.8, 12.4, 14.4, 14.7, 18.9, 21.5, 22.8, 29.0, 29.9, 40.7, 45.6 (2C), 46.2, 52.3, 54.4, 55.5, 55.8, 70.5, 86.2, 94.1, 97.2, 124.6, 126.2 (2C), 126.8, 127.5, 128.7 (2C), 135.0, 135.4 (2C), 139.8, 141.6; IR (neat) 2960, 2930, 2860, 1460 cm^{-1}; HRMS calcd for $C_{34}H_{52}O_4$ $[M]^+$ 524.3864, found 524.3866.

To a stirred solution of the styryl derivative obtained above (5.6 mg, 11 μmol) in MeOH (1.0 mL) was added CSA (12.4 mg, 53.4 μmol). The mixture was stirred at 40 °C for 5 days, diluted with saturated aqueous $NaHCO_3$ (10 mL), and extracted with EtOAc (5 mL×3). The combined organic layers were dried and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:10) to provide 4.7 mg of **53** (quantitatively) as a colorless oil: TLC R_f 0.36 (EtOAc/hexane, 1:2); $[\alpha]_D^{25}$ −32.3 (*c* 0.13, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.85 (t, *J*=7.5 Hz, 3H), 0.85–0.89 (m, 3H), 1.02 (t, *J*=7.5 Hz, 3H), 1.09 (t, *J*=7.5 Hz, 3H), 1.24 (d, *J*=6.9 Hz, 3H), 1.35–1.50 (m, 4H), 1.51–1.68 (m, 2H), 1.73–1.80 (m, 1H), 1.83 (s, 3H), 2.00–2.10 (m, 1H), 2.26–2.41 (m, 2H), 2.30 (t, *J*=11.4 Hz, 1H), 2.76 (dq, *J*=7.5, 13.7 Hz, 1H), 3.70 (d, *J*=4.8 Hz, 1H), 3.80 (d, *J*=11.9 Hz, 1H), 3.84 (d, *J*=11.9 Hz, 1H), 5.44 (br s, 1H), 5.52 (s, 1H), 6.45 (d, *J*=16.4 Hz, 1H), 6.74 (d, *J*=16.4 Hz, 1H), 7.18 (t, *J*=7.5 Hz, 1H), 7.30 (t, *J*=7.5 Hz, 2H), 7.42 (d, *J*=7.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.4, 9.9, 12.2, 14.0, 14.1, 18.5, 20.7, 22.4, 28.3, 29.5, 40.5, 45.5, 46.8, 48.7, 51.6, 53.9, 64.9, 82.4, 122.4, 125.9 (2C), 126.5, 127.2 (2C), 128.3 (2C), 135.0, 137.9, 139.3, 141.5; IR (neat) 3460, 2980, 2930, 2880, 2855, 1455 cm^{-1}; HRMS calcd for $C_{30}H_{44}O_2$ $[M]^+$ 436.3343, found 436.3341.

*4.4.7. (+)-Zyggomphic acid (**6**).* To a cooled (0 °C), stirred solution of **53** (4.7 mg, 11 μmol) in CH_2Cl_2 (1.0 mL) was added Dess–Martin periodinane (11.9 mg, 28.1 μmol). The mixture was stirred at room temperature for 30 min, quenched with saturated aqueous $NaHCO_3$ (5 mL) and 20% aqueous $Na_2S_2O_3$ (5 mL) at 0 °C, and extracted with CH_2Cl_2 (5 mL×3). The combined organic layers were dried and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:100) to provide 4.0 mg (86%) of keto aldehyde as a colorless oil: TLC R_f 0.60 (EtOAc/hexane, 1:4); ^1H NMR (300 MHz, $CDCl_3$) δ 0.74 (t, *J*=7.5 Hz, 3H), 0.86 (t, *J*=7.2 Hz, 3H), 0.92 (t, *J*=7.5 Hz, 3H), 1.05 (t, *J*=7.4 Hz, 3H), 1.26–1.49 (m, 2H), 1.37 (d, *J*=6.6 Hz, 3H), 1.56–1.77 (m, 2H), 1.91 (s, 3H), 1.93–2.05 (m, 2H), 2.12–2.25 (m, 1H), 2.21 (t, *J*=12.3 Hz, 1H), 2.30–2.42 (m, 1H), 2.46 (ddd, *J*=3.8, 5.0, 12.3 Hz, 1H), 2.85 (dq, *J*=7.4, 13.4 Hz, 1H), 2.91 (t, *J*=12.3 Hz, 1H), 5.17 (s, 1H), 5.53 (br s, 1H), 6.50 (d, *J*=16.2 Hz, 1H), 6.62 (d, *J*=16.2 Hz, 1H), 7.21 (t, *J*=7.5 Hz, 1H), 7.31 (t, *J*=7.5 Hz, 2H), 7.40 (d, *J*=7.5 Hz, 2H), 9.75 (d, *J*=1.2 Hz, 1H).

To a cooled (0 °C), stirred solution of the keto aldehyde obtained above (4.0 mg, 9.3 μmol) in *t*-BuOH/H_2O (5:1, 1.0 mL) were added 2-methyl-2-butene (20 μL, 0.19 mmol), NaH_2PO_4 (11.1 mg, 92.5 μmol), and $NaClO_2$ (10.8 mg, 92.5 μmol). The mixture was stirred at room temperature for 1.5 h and then additional 2-methyl-2-butene (20 μL, 0.19 mmol), NaH_2PO_4 (11.1 mg, 92.5 μmol), and $NaClO_2$ (10.8 mg, 92.5 μmol) were added at 0 °C. The mixture was stirred at room temperature for 1.5 h then additional 2-methyl-2-butene (20 μL, 0.19 mmol), NaH_2PO_4 (11.1 mg, 92.5 μmol), and $NaClO_2$ (10.8 mg, 92.5 μmol) were added at 0 °C. The mixture was stirred at room temperature for 2 h then additional 2-methyl-2-butene (20 μL, 0.19 mmol), NaH_2PO_4 (11.1 mg, 92.5 μmol), and $NaClO_2$ (10.8 mg, 92.5 μmol) were added at 0 °C. The mixture was stirred at room temperature for 1 h, quenched with saturated aqueous NH_4Cl (10 mL) at 0 °C, and extracted with CH_2Cl_2 (5 mL×3). The combined organic layers were dried and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:30 to 1:20) to provide 2.8 mg (68%) of **6** as a colorless oil: TLC R_f 0.24 (EtOAc/hexane, 1:4); $[\alpha]_D^{21.5}$ +82.0 (*c* 0.140, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 0.72 (t, *J*=7.4 Hz, 3H), 0.88 (t, *J*=7.4 Hz, 3H), 0.99 (t, *J*=7.4 Hz, 3H), 1.03 (t, *J*=7.5 Hz, 3H), 1.33 (d, *J*=6.3 Hz, 3H), 1.49 (dq, *J*=7.4, 13.4 Hz, 1H), 1.60–1.72 (m, 2H), 1.84 (dq, *J*=7.4, 13.4 Hz, 1H), 1.89 (s, 3H), 1.93–2.03 (m, 2H), 2.08 (t, *J*=11.4 Hz, 1H), 2.18–2.29 (m, 1H), 2.38 (dq, *J*=7.5, 14.0 Hz, 1H), 2.43 (ddd, *J*=3.1, 5.8, 11.4 Hz, 1H), 2.63 (t, *J*=11.4 Hz, 1H), 2.73 (dq, *J*=7.5, 14.0 Hz, 1H), 5.21 (s, 1H), 5.59 (br s, 1H), 6.48 (d, *J*=16.2 Hz, 1H), 6.62 (d, *J*=16.2 Hz, 1H), 7.18 (t, *J*=7.2 Hz, 1H), 7.29 (t, *J*=7.2 Hz, 2H), 7.39 (d, *J*=7.2 Hz, 2H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 9.3, 9.9, 12.1, 14.2, 15.2, 19.1, 22.6, 22.9, 23.2, 28.7, 43.3, 47.0, 47.2, 52.6, 52.7, 56.4, 125.8, 126.2 (2C), 126.3, 127.0, 128.5 (2C), 133.5, 134.6, 137.2, 137.8, 141.9, 176.8, 220.3; IR (neat) 3300, 2960, 2930, 1730, 1700, 1460 cm^{-1}; HRMS calcd for $C_{30}H_{40}O_3$ $[M]^+$ 448.2961, found 448.2978.

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