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Synthesis of topsentolides A_2 and C_2, and non-enzymatic conversion of the former to the latter

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ABSTRACT

The first total synthesis of the marine-derived cytotoxin topsentolide A_2, which eventually culminated in its stereochemical determination, was accomplished in 17 steps from a known chiral alcohol. An improved synthesis of its congener, topsentolide C_2, from a synthetic intermediate of topsentolide A_2 was also performed by utilizing the Yamaguchi lactonization to construct its nine-membered lactone ring. Treatment of epoxide ring-containing topsentolide A_2 with HCl/MeOH brought about its quantitative conversion into topsentolide C_2.

1. Introduction

In the search for cytotoxic substances from the marine sponge *Topsentia* sp., Jung and co-workers isolated seven oxylipins containing a nine-membered lactone ring and named them topsentolides A_1, A_2, B_1–B_3, C_1, and C_2.[1,2] The marine natural products were all shown to exhibit significant cytotoxicity against five human solid tumor cell lines with ED_{50} values of 2.4–17.5 μg/mL. The planar structures of the topsentolides were determined based on extensive spectroscopic analyses, while their stereochemistry was not assigned conclusively except for the relative configuration between the C11 and C12 stereogenic centers of topsentolides A_1, A_2, and B_1–B_3 as well as the absolute configuration at the hydroxy-bearing C12 position of topsentolide C_2, which was determined to be *S* by the modified Mosher method (see compound **2** in Fig. 1).[1] The naturally rare nine-membered lactone unit embedded in common in the topsentolides and their medicinally important biological activity attracted considerable attention from organic chemists, and thereby six synthetic studies on topsentolides have been reported so far.[3–7] Among them, the one reported by Watanabe and co-workers led to the determination of the absolute stereochemistry of topsentolide A_1 as 8*R*, 11*R*, and 12*S* (structure **1**, Fig. 1) by comparison of the ^{1}H NMR spectra and specific rotations of two synthetic stereoisomers of topsentolide A_1 with those of natural topsentolide A_1.[3] We also conducted a stereodivergent synthesis of all of the four diastereomers of topsentolide C_2 bearing a methoxy group at the C11 position and established its stereochemistry as 8*R*, 11*S*, and 12*S* (structure **2**).[7]

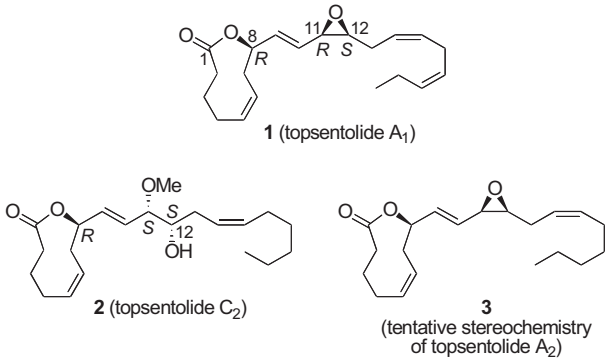

Fig. 1. Absolute configuration of topsentolides A_1 (**1**) and C_2 (**2**), and assumed stereochemistry of topsentolide A_2 (**3**).

As part of our ongoing efforts toward the total synthesis of bioactive oxylipins,[7,8] we set about the first synthesis and stereochemical determination of topsentolide A_2 (17,18-dihydro derivative of **1**). Although the stereochemistry of topsentolide A_2 was not established by Jung et al. except for the relative configuration of the epoxide ring moiety as cis, we tentatively assumed its

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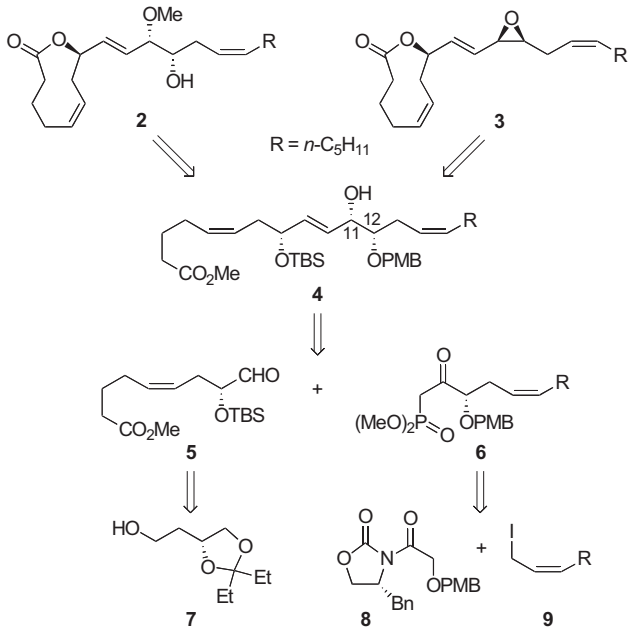
stereochemistry to be 8*R*, 11*R*, and 12*S* as depicted in **3** based on their speculation that topsentolide C_2 (**2**) might be an artifact derived non-enzymatically from topsentolide A_2 during the extraction of the latter with MeOH from the marine sponge as well as by analogy to the absolute configuration of topsentolide A_1 (**1**).[3] We describe herein the total synthesis of the tentative structure of topsentolide A_2 (**3**), determination of the stereochemistry of topsentolide A_2, improved synthesis of topsentolide C_2 (**2**), and non-enzymatic conversion of **3** into **2**.

2. Results and discussion

2.1. Retrosynthetic analysis of 2 and 3

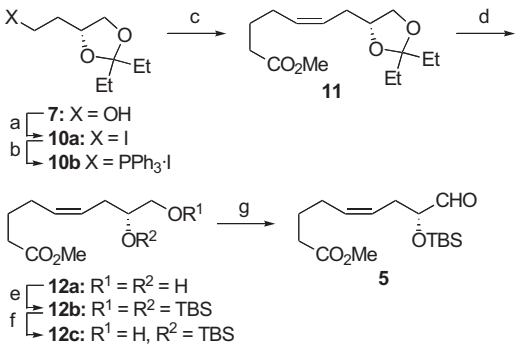
Scheme 1 delineates our retrosynthetic analysis of topsentolides C_2 (**2**) and A_2 (**3**) that features the use of appropriately protected seco acid **4** as a common precursor. The nine-membered lactone ring contained in **2** and **3** would be installable by the Yamaguchi lactonization of a seco acid intermediate generated by deprotection of the methyl ester and TBS ether functionalities of **4**, while the epoxide ring in **3** would be constructed by properly manipulating the oxygen-containing functional groups at the C11 and C12 positions. With a view to establishing the *E*-geometry at the C9–C10 double bond of **4** by the Horner–Wadsworth–Emmons olefination, the pivotal intermediate **4** was traced back to two building blocks **5** and **6**. The aldehyde **5** would readily be accessible from known alcohol **7**, and the phosphonate **6** via the Evans asymmetric alkylation of oxazolidinone derivative **8** with allylic iodide **9**.



Scheme 1. Retrosynthetic analysis of **2** and **3**.

2.2. Preparation of aldehyde 5

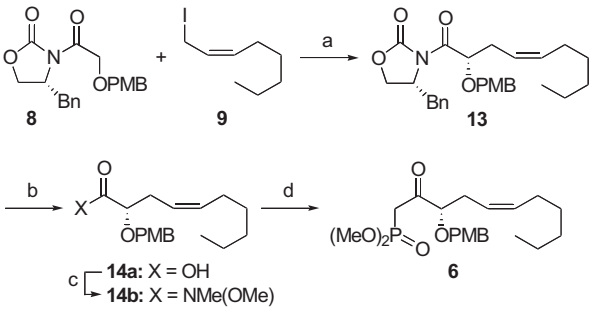
The preparation of the aldehyde segment **5** is depicted in Scheme 2.[9] The starting alcohol **7**, which was prepared from D-malic acid in two steps according to the literature procedure,[10] was converted into phosphonium salt **10b** via iodide **10a** in 83% yield for the two steps. The Wittig olefination of **10b** with methyl 5-oxopentanoate proceeded in a highly *Z*-selective manner, affording **11** in 73% yield. Acidic hydrolysis of its acetal protecting group with Amberlite IR-120 Plus[11] followed by bis-TBS etherification of the resulting diol **12a** afforded **12b** almost quantitatively from **11**. Treatment of **12b** with HF·Py effected selective unmasking of the primary hydroxy group,[12] furnishing **12c** (70% yield), which, on exposure to the Swern oxidation conditions, afforded the aldehyde **5** quantitatively.



Scheme 2. Preparation of aldehyde **5**. Reagents and conditions: (a) I_2, Ph_3P, imidazole, CH_2Cl_2; (b) Ph_3P, MeCN, 83% from **7**; (c) NaHMDS, methyl 5-oxopentanoate, THF, 73%; (d) Amberlite IR-120 Plus, MeOH/H_2O; (e) TBSCl, imidazole, DMF, 99% from **11**; (f) HF·Py, THF/Py, 70%; (g) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, quant.

2.3. Preparation of phosphonate 6

The preparation of the phosphonate segment **6** commenced with the Evans asymmetric alkylation of **8**[8b,13] with iodide **9**[8b,14] to give **13** in 73% yield after chromatographic purification (Scheme 3).[15] The *N*-acyl oxazolidinone **13** was hydrolyzed with aq LiOH and the resulting carboxylic acid **14a** was converted into the corresponding Weinreb's amide **14b** in 80% yield over the two steps. Finally, treatment of **14b** with dimethyl lithiomethylphosphonate gave **6** in 94% yield.

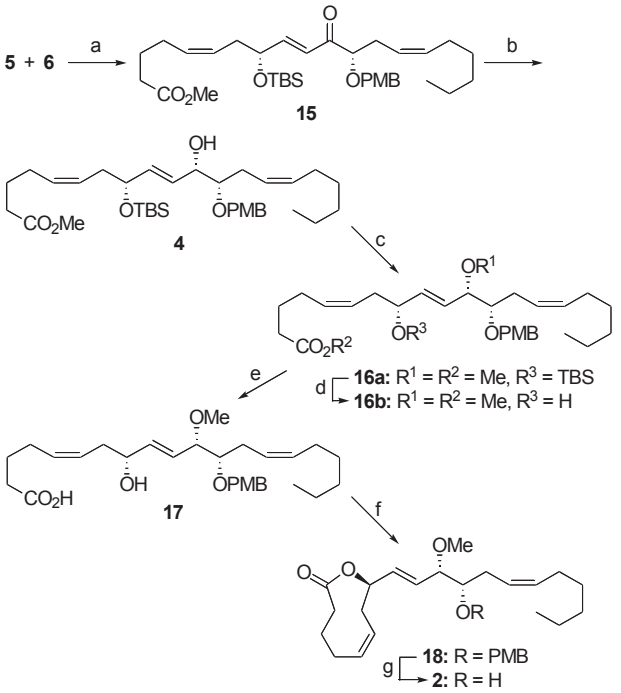


Scheme 3. Preparation of phosphonate **6**. Reagents and conditions: (a) NaHMDS, THF, 73%; (b) LiOH·H_2O, H_2O_2, THF/H_2O; (c) MeNH(OMe)·HCl, DCC, DMAP, CH_2Cl_2, 80% from **13**; (d) $MePO(OMe)_2$, *n*-BuLi, THF, 94%.

2.4. Synthesis of topsentolide C_2

With the two building blocks, **5** and **6**, in hand, we proceeded to their connection followed by transformation of the resulting product into topsentolide C_2 (**2**) (Scheme 4). The *E*-selective Horner–Wadsworth–Emmons reaction between **5** and **6** under the Roush–Masamune conditions gave an 85% yield of enone **15**,[16] which was then subjected to Luche's reduction conditions, delivering Felkin–Ahn product **4** as a single diastereomer in 98% yield.[8b] O-Methylation of **4** was efficiently performed by its treatment with NaHMDS and MeI in HMPA/THF and exposure of the resulting product **16a** to TBAF in THF furnished alcohol **16b** in 80% yield for the two steps. Saponification of the methyl ester **16b** with aq LiOH gave seco acid **17** almost quantitatively, which set the stage for the Yamaguchi lactonization to install the nine-membered

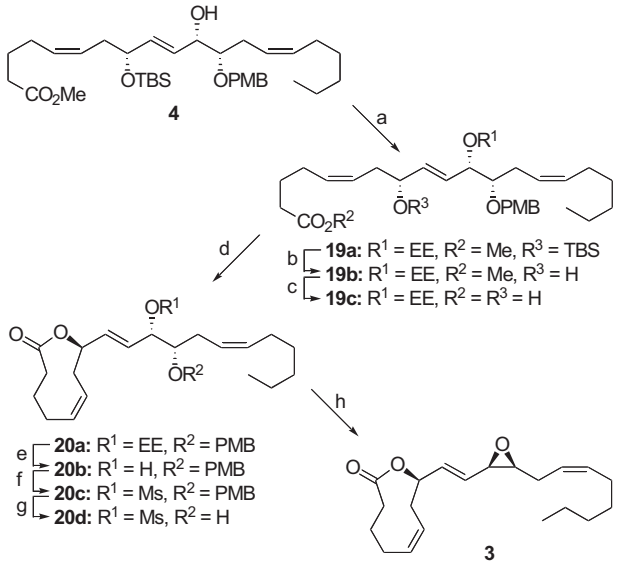
lactone ring.[17] The ring forming reaction of **17** was effected in an excellent yield of 95%, and subsequent removal of the PMB protecting group of the cyclization product **18** gave topsentolide C_2 (**2**) quantitatively. The ^1H and ^{13}C NMR spectra of **2** were identical with those of natural topsentolide C_2 and, of course, with those of our synthetic sample of **2** previously obtained in a lower overall yield due to poor efficiency (56% yield) in the Mitsunobu lactonization employed for the formation of the lactone ring.[7] The specific rotation value of **2** {$[\alpha]_D^{21}$ +77.2 (*c* 0.820, MeOH)} showed good agreement with our previous data {$[\alpha]_D^{29}$ +86.8 (*c* 1.33, MeOH)}.[7]



Scheme 4. Synthesis of **2**. Reagents and conditions: (a) Et_3N, LiBr, THF, 80%; (b) $NaBH_4$, $CeCl_3\cdot 7H_2O$, MeOH, 98%; (c) NaHMDS, MeI, HMPA, THF, 82%; (d) TBAF, THF, 98%; (e) $LiOH\cdot H_2O$, THF/H_2O, 99%; (f) $Cl_3C_6H_2COCl$, DIPEA, THF, then DMAP, toluene, 95%; (g) DDQ, CH_2Cl_2/H_2O, 99%.

2.5. Synthesis of topsentolide A_2

Scheme 5 outlines the transformation of the intermediate **4** into the tentative structure of topsentolide A_2 (**3**). Protection of the alcohol **4** as its 1-ethoxyethyl ether followed by deprotection of the TBS group of the resulting product **19a** afforded hydroxy ester **19b**, which was then subjected to basic hydrolysis conditions, providing seco acid **19c** (94% yield from **4**) as a mixture of diastereomers due to the newly formed stereocenter in the EE group. Lactonization of **19c** under the Yamaguchi conditions furnished nine-membered lactone derivative **20a** in 88% yield. Removal of the EE group of **20a** with PPTS in EtOH and subsequent mesylation of alcohol intermediate **20b** gave **20c**. Treatment of the PMB ether **20c** with DDQ in CH_2Cl_2/phosphate buffer (pH 7) afforded a very unstable hydroxy mesylate **20d**, which was, after quick purification by silica gel column chromatography to remove *p*-methoxybenzaldehyde generated as a by-product, exposed to K_2CO_3 in MeOH, providing epoxy lactone **3**, albeit in a modest overall yield of 16% for the four steps (mainly due to the instability of **20d**). The ^1H and ^{13}C NMR spectral data of **3** were identical with those reported for natural topsentolide A_2,[1] and the specific rotation of **3** {$[\alpha]_D^{21}$ +73 (*c* 0.22, MeOH)} was in good accord with that of natural topsentolide A_2 {$[\alpha]_D^{24}$ +84.6 (*c* 0.27, MeOH)}.[1] Based on these results as well as by analogy to the stereochemistry of topsentolide A_1 (**1**), we



Scheme 5. Synthesis of **3**. Reagents and conditions: (a) EtOCH=CH_2, PPTS, CH_2Cl_2; (b) TBAF, THF; (c) $LiOH\cdot H_2O$, THF/H_2O, 94% from **4**; (d) $Cl_3C_6H_2COCl$, DIPEA, THF, then DMAP, toluene, 88%; (e) PPTS, EtOH; (f) Ms_2O, DIPEA, DMAP, CH_2Cl_2; (g) DDQ, CH_2Cl_2/phosphate buffer (pH 7); (h) K_2CO_3, MeOH, 16% from **20a**.

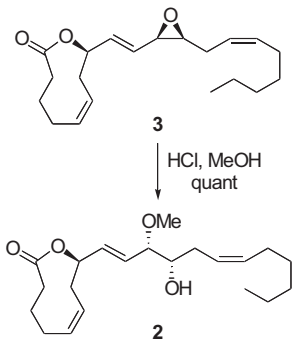
concluded that the absolute configuration of topsentolide A_2 should be represented by structure **3**.

2.6. Methanolytic epoxide ring-opening of 3 into 2 under acidic conditions

To demonstrate the speculation by Jung and co-workers that topsentolide C_2 (**2**) might be an artifact derived non-enzymatically from topsentolide A_2 (**3**) during the extraction of **3** from *Topsentia* sp. with MeOH,[1] we tried exposing **3** to a mixture of MeOH and CH_2Cl_2 at room temperature; both the solvents were employed in their extraction process. Under these neutral conditions, compound **3** was quite stable and did not change at all after 3 h of stirring. On the other hand, refluxing the solution of **3** in MeOH/CH_2Cl_2 brought about gradual decomposition of **3** and finally led to its disappearance and the formation of a mixture of unidentified products after overnight stirring, none of which was found to be identical with topsentolide C_2 (**2**) by TLC analysis. Quite interestingly, however, treatment of **3** with hydrogen chloride in MeOH at room temperature for a few hours effected complete consumption of **3** and generated topsentolide C_2 (**2**) almost quantitatively with inversion of configuration at the allylic C11 position (see Supplementary data for the NMR spectra of the crude reaction product) (Scheme 6).[18] These results would support the above-mentioned speculation by Jung et al. that topsentolide C_2 (**2**) might be an artifact formed from topsentolide A_2 (**3**), although, at present, we have no way of knowing whether their sponge extract was acidic or not.

3. Conclusion

In conclusion, the first total synthesis of topsentolide A_2 (**3**) was accomplished in 4.4% overall yield from the known alcohol **7** by a 17-step sequence (or 5.7% yield from the allylic iodide **9** through 14 steps) involving the Evans asymmetric alkylation as a source of chirality and the highly diastereoselective reduction of the α-alkoxy ketone **15** to install the C12 stereogenic center. We also achieved an improved synthesis of topsentolide C_2 (**2**) by exploiting the Yamaguchi lactonization for the formation of the nine-membered lactone ring instead of the Mitsunobu lactonization previously employed in our first synthesis of **2**. Treatment of **3** with



Scheme 6. Methanolytic epoxide ring-opening of **3** into **2**.

methanolic HCl brought about methanolytic opening of the epoxide ring at the C11 allylic position with inversion of configuration and afforded **2** quantitatively, which supported the speculation by Jung et al. that topsentolide C_2 (**2**) might be an artifact derived from topsentolide A_2 (**3**).

4. Experimental section

4.1. General

IR spectra were recorded by a Jasco FT/IR-4100 spectrometer using an ATR (ZnSe) attachment. ^{1}H NMR spectra were recorded with TMS as an internal standard in $CDCl_3$ by a Varian MR-400 spectrometer (400 MHz) unless otherwise stated. ^{13}C NMR were recorded in $CDCl_3$ by the same spectrometer (100 MHz) and chemical shifts were reported with reference to the solvent peak ($CDCl_3$, 77.16 ppm) unless otherwise stated. Optical rotation values were measured with a Horiba Septa-300 polarimeter, and the mass spectra were obtained with Jeol JMS-700 spectrometer operated in the EI or FAB mode. Merck silica gel 60 (70–230 mesh) was used for column chromatography. Solvents for reactions were distilled prior to use: THF from Na and benzophenone; CH_2Cl_2, MeCN, DMF, and HMPA from CaH_2; MeOH from $Mg(OMe)_2$; toluene from $LiAlH_4$; EtOH from Na and diethyl phthalate. All air- or moisture-sensitive reactions were conducted under a nitrogen atmosphere.

4.2. Methyl (*Z*)-7-[(*R*)-2,2-diethyl-1,3-dioxolan-4-yl]-5-heptenoate (11)

To a stirred solution of **7** (5.78 g, 33.2 mmol) in CH_2Cl_2 (150 mL) were successively added imidazole (6.82 g, 100.0 mmol), Ph_3P (11.5 g, 43.8 mmol), and I_2 (10.8 g, 42.6 mmol) at 0 °C. The resulting mixture was gradually warmed to room temperature and stirred overnight. The mixture was quenched with saturated aq $Na_2S_2O_3$ and extracted with hexane. The extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo to give crude **10a** (8.40 g), which was taken up in MeCN (100 mL). To the solution was added Ph_3P (9.34 g, 35.6 mmol) while stirring at room temperature, and the mixture was then heated under reflux for 17 h. The mixture was cooled to room temperature and concentrated in vacuo to give a solid, which was suspended in Et_2O and filtered to give **10b** (15.0 g, 83% from **7**). To a stirred suspension of **10b** (2.44 g, 4.46 mmol) in THF (10 mL) was added dropwise a solution of NaHMDS (1.0 M in THF, 6.70 mL, 6.70 mmol) at 0 °C, and the resulting solution was stirred at the same temperature for 1 h. To the solution was added dropwise a solution of methyl 5-oxopentanoate (700 mg, 5.35 mmol) in THF (5 mL) at −78 °C. After 3 h, the mixture was gradually warmed to room temperature, stirred overnight, and then quenched with saturated aq NH_4Cl. The mixture was concentrated in vacuo and filtered. The filtrate was extracted with hexane/EtOAc (4:1), and the extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc=10:1) to give **11** (880 mg, 73%) as a pale yellow oil. $[\alpha]_{27}D$ −23.0 (*c* 1.06, $CHCl_3$); IR: ν_{max} 3015 (w), 1738 (s), 1160 (m), 1077 (m); ^{1}H NMR: δ 0.89 (3H, t, *J*=7.4 Hz), 0.91 (3H, t, *J*=7.4 Hz), 1.58–1.75 (6H, m), 2.10 (2H, q, *J*=7.2 Hz), 2.22–2.29 (1H, m), 2.32 (2H, t, *J*=7.6 Hz), 2.38–2.47 (1H, m), 3.50 (1H, dd, *J*=7.6, 6.5 Hz), 3.67 (3H, s), 4.04 (1H, dd, *J*=7.6, 6.5 Hz), 4.10 (1H, quint, *J*=6.5 Hz), 5.37–5.53 (2H, m); ^{13}C NMR: δ 8.14, 8.40, 24.8, 26.9, 29.8, 30.0, 31.5, 33.6, 51.7, 69.8, 75.9, 113.0, 125.3, 131.5, 174.2; HRMS (FAB): *m*/*z* calcd for $C_{15}H_{27}O_4$ ($[M+H]^+$) 271.1909, found 271.1910.

4.3. Methyl (5*Z*,8*R*)-8,9-bis[(*tert*-butyldimethylsilyl)oxy]-5-nonenoate (12b)

To a stirred solution of **11** (650 mg, 2.40 mmol) in MeOH/H_2O (20:1, 8.4 mL) was added Amberlite IR-120 Plus (500 mg) at room temperature. After 15 h, the mixture was filtered and the filtrate was concentrated in vacuo. The residue was diluted with Et_2O, dried (Na_2SO_4), and concentrated in vacuo to give crude **12a** (480 mg), which was taken up in DMF (5 mL). To the solution were successively added imidazole (975 mg, 14.3 mmol) and TBSCl (1.09 g, 7.23 mmol) at 0 °C. After 12 h, the mixture was quenched with H_2O at 0 °C and extracted with EtOAc. The extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc=50:1) to give **12b** (1.02 g, 99% from **11**) as a pale yellow oil. $[\alpha]_D^{23}$ +1.73 (*c* 1.42, $CHCl_3$); IR: ν_{max} 3014 (w), 1742 (s), 1252 (m), 1098 (m), 832 (s); ^{1}H NMR: δ 0.04 (6H, s), 0.05 (6H, s), 0.88 (9H, s), 0.89 (9H, s), 1.69 (2H, quint, *J*=7.5 Hz), 2.08 (2H, q, *J*=7.5 Hz), 2.11–2.19 (1H, m), 2.26–2.34 (1H, m), 2.31 (2H, t, *J*=7.7 Hz), 3.41 (1H, dd, *J*=10.0, 6.3 Hz), 3.49 (1H, dd, *J*=10.0, 5.5 Hz), 3.64–3.71 (4H, m), 5.37–5.52 (2H, m); ^{13}C NMR: δ −5.22, −5.16, −4.5, −4.2, 18.3, 18.5, 25.0, 26.0 (3C), 26.1 (3C), 26.9, 32.3, 33.7, 51.6, 67.1, 73.3, 127.1, 130.3, 174.3; HRMS (FAB): *m*/*z* calcd for $C_{22}H_{46}O_4Si_2Na$ ($[M+Na]^+$) 453.2833, found 453.2837.

4.4. Methyl (5*Z*,8*R*)-8-[(*tert*-butyldimethylsilyl)oxy]-9-hydroxy-5-nonenoate (12c)

To a solution of **12b** (418 mg, 0.970 mmol) in THF (5 mL) was added dropwise a solution of HF·Py (40% HF·Py/Py/THF=1:2:5, 4.0 mL) at −10 °C. After 24 h, the mixture was quenched with saturated aq $NaHCO_3$ and extracted with Et_2O. The extract was successively washed with saturated aq $CuSO_4$ and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc=50:1–4:1) to give **12c** (215 mg, 70%) as a yellow oil. $[\alpha]_D^{24}$ −17.5 (*c* 1.06, $CHCl_3$); IR: ν_{max} 3477 (m), 1739 (s), 834 (s), 775 (s). ^{1}H NMR: δ 0.09 (6H, s), 0.90 (9H, s), 1.69 (2H, quint, *J*=7.4 Hz), 1.90 (1H, t, *J*=6.3 Hz), 2.08 (2H, q, *J*=7.4 Hz), 2.19–2.29 (2H, m), 2.32 (2H, t, *J*=7.4 Hz), 3.40–3.47 (1H, m), 3.51–3.58 (1H, m), 3.67 (3H, s), 3.72–3.79 (1H, m), 5.36–5.49 (2H, m); ^{13}C NMR: δ −4.5, −4.3, 18.2, 24.9, 26.0 (3C), 26.8, 32.1, 33.6, 51.7, 66.0, 72.8, 126.0, 131.1, 174.2; HRMS (FAB): *m*/*z* calcd for $C_{16}H_{33}O_4Si$ ($[M+H]^+$) 317.2148, found 317.2152.

4.5. Methyl (5*Z*,8*R*)-8-[(*tert*-butyldimethylsilyl)oxy]-9-oxo-5-nonenoate (5)

To a stirred solution of $(COCl)_2$ (0.130 mL, 1.58 mmol) in CH_2Cl_2 (2.6 mL) was added dropwise a solution of DMSO (0.220 mL, 3.15 mmol) in CH_2Cl_2 (4 mL) at −78 °C. After 5 min, a solution of **12c** (400 mg, 1.26 mmol) in CH_2Cl_2 (2.5 mL) was added and the resulting mixture was stirred at −78 °C for 30 min. To the mixture

was added dropwise Et_3N (0.880 mL, 6.30 mmol) and the mixture was gradually warmed to −30 °C. The mixture was quenched with saturated aq $NaHCO_3$, gradually warmed to room temperature, and extracted with CH_2Cl_2. The extract was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc=10:1) to give **5** (400 mg, quant) as a pale yellow oil. $[\alpha]_D^{22}$ +13.4 (*c* 1.04, $CHCl_3$); IR: ν_{max} 3020 (w), 1738 (s), 1252 (m), 836 (m), 777 (m); ^1H NMR: δ 0.07 (3H, s), 0.09 (3H, s), 0.92 (9H, s), 1.69 (2H, quint, *J*=7.5 Hz), 2.03–2.13 (2H, m), 2.31 (2H, t, *J*=7.5 Hz), 2.39 (2H, t, *J*=6.4 Hz), 3.67 (3H, s), 4.00 (1H, dt, *J*=1.3, 6.4 Hz), 5.40–5.53 (2H, m), 9.60 (1H, d, *J*=1.3 Hz); ^{13}C NMR: δ −4.7, −4.6, 18.3, 24.8, 25.9 (3C), 26.8, 31.0, 33.6, 51.7, 77.6, 124.6, 131.9, 174.1, 204.0; HRMS (FAB): *m*/*z* calcd for $C_{16}H_{31}O_4Si$ ($[M+H]^+$) 315.1992, found 315.1994.

4.6. (*R*)-4-Benzyl-3-[(2*S*,4*Z*)-2-(4-methoxyphenyl)methoxy-4-decenoyl]-2-oxazolidinone (13)

To a stirred solution of NaHMDS (1.0 M in THF, 7.60 mL, 7.60 mmol) in THF (10 mL) was added dropwise a solution of **8** (1.80 g, 5.06 mmol) in THF (15 mL) at −78 °C. After 30 min, a solution of **9** (2.86 g, 12.0 mmol) in THF (10 mL) was added and the resulting mixture was stirred at −78 °C for 30 min. The mixture was gradually warmed to −40 °C and stirred overnight. The mixture was quenched with saturated aq NH_4Cl and extracted with Et_2O. The extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc=4:1) to give **13** (1.72 g, 73%) as a colorless oil. $[\alpha]_D^{24}$ −71.2 (*c* 0.960, $CHCl_3$); IR: ν_{max} 1778 (s), 1708 (m), 1612 (w), 1513 (m), 1248 (s); ^1H NMR: δ 0.87 (3H, t, *J*=7.1 Hz), 1.22–1.38 (6H, m), 2.05 (2H, q, *J*=6.8 Hz), 2.48–2.65 (2H, m), 2.70 (1H, dd, *J*=13.3, 9.6 Hz), 3.23 (1H, dd, *J*=13.3, 3.2 Hz), 3.79 (3H, s), 4.12–4.18 (2H, m), 4.48 (1H, d, *J*=11.2 Hz), 4.53 (1H, d, *J*=11.2 Hz), 4.55–4.63 (1H, m), 5.12 (1H, dd, *J*=7.0, 5.2 Hz), 5.44–5.57 (2H, m), 6.86 (2H, d, *J*=8.6 Hz), 7.19 (2H, d, *J*=6.8 Hz), 7.24–7.35 (5H, m); ^{13}C NMR: δ 14.2, 22.7, 27.5, 29.4, 31.1, 31.6, 38.0, 55.1, 55.4, 66.8, 72.5, 76.6, 113.8 (2C), 123.5, 127.5, 129.1 (2C), 129.6 (2C), 129.8, 130.1 (2C), 133.5, 135.2, 153.1, 159.5, 172.8; HRMS (FAB): *m*/*z* calcd for $C_{28}H_{35}NO_5Na$ ($[M+Na]^+$) 488.2413, found 488.2413.

4.7. (2*S*,4*Z*)-*N*-Methoxy-2-(4-methoxyphenyl)methoxy-*N*-methyl-4-decenamide (14b)

To a stirred solution of **13** (0.320 g, 0.687 mmol) in THF/H_2O (3:1, 12 mL) were successively added 30% aq H_2O_2 (0.270 g, 2.35 mmol) and $LiOH\cdot H_2O$ (60.4 mg, 1.44 mmol) at 0 °C. After 3 h, the mixture was quenched with 1.5 M aq Na_2SO_3 and gradually warmed to room temperature over 2 h. The mixture was concentrated in vacuo, and the residue was diluted with saturated aq $NaHCO_3$ and extracted with Et_2O. The aqueous layer was acidified with 2 M aq HCl and extracted with CH_2Cl_2. The extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo to give crude **14a** (197 mg), which was taken up in CH_2Cl_2 (4 mL). To the solution were successively added $MeNH(OMe)\cdot HCl$ (94.2 mg, 96.6 mmol), DMAP (118 mg, 96.7 mmol), and DCC (199 mg, 96.7 mmol) while stirring at 0 °C. The mixture was gradually warmed to room temperature over 3 h and filtered through a pad of Celite. The filtrate was successively washed with saturated aq NH_4Cl, saturated $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc=5:1) to give **14b** (192 mg, 80% from **13**) as a yellow oil. $[\alpha]_D^{24}$ −53.4 (*c* 1.00, $CHCl_3$); IR: ν_{max} 1672 (s), 1613 (m), 1513 (s), 1247 (s); ^1H NMR: δ 0.87 (3H, t, *J*=7.0 Hz), 1.20–1.36 (6H, m), 2.01 (2H, q, *J*=6.9 Hz), 2.46–2.52 (2H, m), 3.21 (3H, s), 3.57 (3H, s), 3.80 (3H, s), 4.28 (1H, br t *J*=5.5 Hz), 4.35 (1H, d, *J*=11.7 Hz), 4.62 (1H, d, *J*=11.7 Hz), 5.39–5.53 (2H, m), 6.86 (2H, d, *J*=8.6 Hz), 7.28 (2H, d, *J*=8.6 Hz); ^{13}C NMR: δ 13.9, 22.4, 27.1, 29.1, 30.2, 31.3, 32.1, 55.0, 61.1, 70.9, 74.8, 113.5 (2C), 124.0, 129.4 (2C), 129.7, 132.5, 159.1, 172.7; HRMS (FAB): *m*/*z* calcd for $C_{20}H_{32}NO_4$ ($[M+H]^+$) 350.2331, found 350.2329.

4.8. Dimethyl [(3*S*,5*Z*)-3-(4-methoxyphenyl)methoxy-2-oxo-5-undecenyl]phosphonate (6)

To a stirred solution of $MePO(OMe)_2$ (2.0 mL, 18.7 mmol) in THF (110 mL) was added dropwise a solution of *n*-BuLi (1.59 M in hexane, 11.0 mL, 17.5 mmol) at −78 °C. After 1 h, a solution of **14b** (1.27 g, 3.63 mmol) in THF (30 mL) was added, and the resulting mixture was stirred at −78 °C for 6 h. The mixture was quenched with saturated aq NH_4Cl, gradually warmed to room temperature, and extracted with EtOAc. The extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc=1:1) to give **6** (1.41 g, 94%). $[\alpha]_D^{23}$ −19.7 (*c* 1.00, $CHCl_3$); IR: ν_{max} 1720 (w), 1612 (w), 1514 (m), 1248 (s), 1027 (s); ^1H NMR: δ 0.88 (3H, t, *J*=6.8 Hz), 1.21–1.37 (6H, m), 2.00 (2H, q, *J*=7.2 Hz), 2.38–2.53 (2H, m), 3.16 (1H, dd, *J*=21.8, 14.7 Hz), 3.32 (1H, dd, *J*=21.8, 14.7 Hz), 3.76 (3H, d, *J*=5.9 Hz), 3.79 (3H, d, *J*=5.9 Hz), 3.81 (3H, s), 3.96 (1H, t, *J*=6.0 Hz), 4.46 (1H, d, *J*=11.1 Hz), 4.57 (1H, d, *J*=11.1 Hz), 5.35 (1H, dt, *J*=10.8, 7.2 Hz), 5.51 (1H, dt, *J*=10.8, 7.2 Hz), 6.88 (2H, d, *J*=8.6 Hz), 7.28 (2H, d, *J*=8.6 Hz); ^{13}C NMR: δ 14.2, 22.7, 27.5, 29.3, 29.6, 31.6, 36.3 (d, *J*=132.4 Hz), 53.1 (2C), 55.4, 72.4, 84.2, 114.0 (2C), 123.3, 129.6, 129.8 (2C), 133.6, 159.6, 204.1 (d, *J*=7.5 Hz); HRMS (FAB): *m*/*z* calcd for $C_{21}H_{34}O_6P$ ($[M+H]^+$) 413.2093, found 413.2093.

4.9. Methyl (5*Z*,8*R*,9*E*,12*S*,14*Z*)-8-(*tert*-butyldimethylsilyl)oxy-12-(4-methoxyphenyl)methoxy-11-oxo-5,9,14-icosatrienoate (15)

A mixture of **6** (576 mg, 1.40 mmol) and LiBr (243 mg, 2.80 mmol) in THF (14 mL) was stirred at room temperature for 30 min. To the mixture was added Et_3N (0.260 mL, 1.90 mmol) and the mixture was stirred for 1 h. Then a solution of **5** (400 mg, 1.27 mmol) in THF (12 mL) was added, and the resulting mixture was stirred overnight at room temperature. The mixture was quenched with saturated aq NH_4Cl and extracted with Et_2O. The extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc=10:1 to 1:1) to give **15** (668 mg, 80%) as a pale yellow oil. $[\alpha]_D^{22}$ −37.0 (*c* 1.10, $CHCl_3$); IR: ν_{max} 1739 (s), 1696 (w), 1630 (w), 1514 (m), 1249 (s); ^1H NMR: δ 0.03 (3H, s), 0.06 (3H, s), 0.87 (3H, t, *J*=7.0 Hz), 0.90 (9H, s), 1.20–1.35 (6H, m), 1.68 (2H, quint, *J*=7.4 Hz), 1.98 (2H, q, *J*=7.4 Hz), 2.05 (2H, q, *J*=6.9 Hz), 2.23–2.36 (4H, m), 2.36–2.50 (2H, m), 3.66 (3H, s), 3.80 (3H, s), 3.92 (1H, t, *J*=6.6 Hz), 4.32 (1H, d, *J*=11.5 Hz), 4.32–4.37 (1H, m), 4.53 (1H, d, *J*=11.5 Hz), 5.31–5.52 (4H, m), 6.69 (1H, dd, *J*=15.6, 1.3 Hz), 6.86 (2H, d, *J*=8.6 Hz), 6.99 (1H, dd, *J*=15.6, 4.4 Hz), 7.24 (2H, d, *J*=8.6 Hz); ^{13}C NMR: δ −4.7, −4.5, 14.2, 18.3, 22.7, 24.8, 25.9 (3C), 26.9, 27.5, 29.3, 30.5, 31.6, 33.6, 35.5, 51.6, 55.4, 71.8, 72.0, 83.8, 113.9 (2C), 123.2, 123.5, 125.5, 129.5 (2C), 129.8, 131.4, 133.2, 150.1, 159.4, 174.1, 201.0; HRMS (FAB): *m*/*z* calcd for $C_{35}H_{56}O_6SiNa$ ($[M+Na]^+$) 623.3743, found 623.3741.

4.10. Methyl (5*Z*,8*R*,9*E*,11*S*,12*S*,14*Z*)-8-(*tert*-butyldimethylsilyl)oxy-11-hydroxy-12-(4-methoxyphenyl)methoxy-5,9,14-icosatrienoate (4)

A mixture of **15** (145 mg, 0.241 mmol) and $CeCl_3\cdot 7H_2O$ (98.2 mg, 0.264 mmol) in MeOH (4 mL) was stirred at room temperature for 5 min. To the mixture was added dropwise a solution of $NaBH_4$ (9.03 mg, 0.239 mmol) in MeOH (0.8 mL) at −78 °C and the resulting mixture was stirred for 1 h. The mixture was quenched with saturated aq NH_4Cl, gradually warmed to room temperature,

and extracted with Et_2O. The extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc=10:1–4:1) to give **4** (142 mg, 98%) as a pale yellow oil. $[\alpha]_D^{23}$ +3.45 (*c* 1.00, $CHCl_3$); IR: ν_{max} 3529 (w), 3006 (w), 1739 (m), 1613 (w), 1513 (m), 1248 (s); ^{1}H NMR: δ 0.03 (3H, s), 0.05 (3H, s), 0.86–0.91 (12H, m), 1.22–1.39 (6H, m), 1.68 (2H, quint, *J*=7.5 Hz), 1.97–2.10 (4H, m), 2.17–2.34 (5H, m), 2.36–2.44 (1H, m), 2.56 (1H, br s, OH), 3.33 (1H, q, *J*=5.6 Hz), 3.66 (3H, s), 3.80 (3H, s), 4.04 (1H, br s), 4.11–4.19 (1H, m), 4.45 (1H, d, *J*=11.0 Hz), 4.62 (1H, d, *J*=11.0 Hz), 5.37–5.53 (4H, m), 5.64 (1H, dd, *J*=15.3, 6.2 Hz), 5.76 (1H, dd, *J*=15.3, 5.3 Hz), 6.87 (2H, d, *J*=8.2 Hz), 7.25 (2H, d, *J*=8.2 Hz); ^{13}C NMR: δ −4.6, −4.2, 14.2, 18.4, 22.7, 24.9, 26.0 (3C), 26.9, 27.6, 28.5, 29.4, 31.7, 33.6, 36.4, 51.6, 55.4, 72.3, 72.6, 73.5, 82.2, 114.0 (2C), 124.7, 126.7, 128.8, 129.6 (2C), 130.5 (2C), 132.6, 135.9, 159.4, 174.2; HRMS (FAB): *m*/*z* calcd for $C_{35}H_{58}O_6SiNa$ ($[M+Na]^+$) 625.3901, found 625.3896.

4.11. Methyl (5*Z*,8*R*,9*E*,11*S*,12*S*,14*Z*)-8-(*tert*-Butyldimethylsilyl) oxy-11-methoxy-12-(4-methoxyphenyl)methoxy-5,9,14-icosatrienoate (16a)

To a stirred solution of **4** (142 mg, 0.236 mmol) and HMPA (0.140 mL, 0.826 mmol) in THF (2.4 mL) was added dropwise a solution of NaHMDS (1.0 M in THF, 0.230 mL, 0.230 mmol) at −78 °C. After 1 h, MeI (0.23 mL, 0.230 mmol) was added, and the resulting mixture was stirred at −78 °C for 5 h. The mixture was gradually warmed to room temperature and stirred overnight. The mixture was quenched with saturated aq NH_4Cl and extracted with Et_2O. The extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc=10:1 to 4:1) to give **16a** (119 mg, 82%) as a colorless oil. $[\alpha]_D^{20}$ −7.72 (*c* 0.950, $CHCl_3$); IR: ν_{max} 3008 (w), 1740 (s), 1613 (w), 1514 (m), 1248 (s), 1081 (s); ^{1}H NMR: δ 0.04 (3H, s), 0.06 (3H, s), 0.88 (3H, t, *J*=7.3 Hz), 0.89 (9H, s), 1.20–1.37 (6H, m), 1.67 (2H, quint, *J*=7.4 Hz), 1.96–2.09 (4H, m), 2.13–2.24 (2H, m), 2.24–2.39 (4H, m), 3.28 (3H, s), 3.33–3.39 (1H, m), 3.60 (1H, dd, *J*=7.6, 5.1 Hz), 3.66 (3H, s), 3.79 (3H, s), 4.16 (1H, q, *J*=5.8 Hz), 4.52 (1H, d, *J*=11.4 Hz), 4.59 (1H, d, *J*=11.4 Hz), 5.34–5.49 (4H, m), 5.55 (1H, dd, *J*=15.7, 7.6 Hz), 5.66 (1H, dd, *J*=15.7, 5.8 Hz), 6.85 (2H, d, *J*=8.3 Hz), 7.26 (2H, d, *J*=8.3 Hz); ^{13}C NMR: δ −4.6, −4.3, 14.2, 18.3, 22.7, 24.9, 26.0 (3C), 26.9, 27.5, 28.9, 29.4, 31.7, 33.6, 36.4, 51.6, 55.4, 56.8, 72.7, 72.9, 81.4, 83.9, 113.7 (2C), 125.7, 126.6, 127.2, 129.5 (2C), 130.4, 131.2, 132.1, 137.7, 159.1, 174.1; HRMS (FAB): *m*/*z* calcd for $C_{36}H_{60}O_6SiNa$ ($[M+Na]^+$) 639.4057, found 639.4053.

4.12. (5*Z*,8*R*,9*E*,11*S*,12*S*,14*Z*)-8-Hydroxy-11-methoxy-12-(4-methoxyphenyl)methoxy-5,9,14-icosatrienoate (16b)

TBS ether **16a** (97.4 mg, 0.158 mmol) and a solution of TBAF (1.0M in THF, 0.470 mL, 0.470 mmol) was mixed at 0 °C, and the mixture was stirred at the same temperature for 30 min. The mixture was warmed to room temperature and stirred for an additional 3 h. The mixture was quenched with saturated aq NH_4Cl and extracted with Et_2O. The extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc=2:1) to give **16b** (78.0 mg, 98%) as a colorless oil. $[\alpha]_D^{20}$ +4.17 (*c* 1.27, $CHCl_3$); IR: ν_{max} 3459 (m), 3006 (w), 1737 (s), 1613 (m), 1514 (s), 1247 (s); ^{1}H NMR: δ 0.88 (3H, t, *J*=6.6 Hz), 1.21–1.38 (6H, m), 1.70 (2H, quint, *J*=7.4 Hz), 1.77 (1H, d, *J*=3.9 Hz, OH), 2.01 (2H, q, *J*=6.8 Hz), 2.09 (2H, q, *J*=7.2 Hz), 2.16–2.26 (1H, m), 2.26–2.42 (5H, m), 3.29 (3H, s), 3.34–3.41 (1H, m), 3.63 (1H, dd, *J*=7.2, 4.9 Hz), 3.66 (3H, s), 3.79 (3H, s), 4.14–4.22 (1H, m), 4.55 (2H, s), 5.35–5.56 (4H, m), 5.64 (1H, dd, *J*=15.5, 7.2 Hz), 5.73 (1H, dd, *J*=15.5, 5.5 Hz), 6.85 (2H, d, *J*=8.4 Hz), 7.26 (2H, d, *J*=8.4 Hz); ^{13}C NMR: δ 14.2, 22.7, 24.8, 26.8, 27.5, 28.7, 29.4, 31.7, 33.5, 35.4, 51.7, 55.4, 57.0, 71.7, 72.6, 81.0, 83.3, 113.7 (2C), 125.6, 125.8, 128.2, 129.7 (2C), 131.0, 132.1, 132.2, 136.4, 159.2, 174.2; HRMS (FAB): *m*/*z* calcd for $C_{30}H_{46}O_6Na$ ($[M+Na]^+$) 525.3192, found 525.3191.

4.13. (5*Z*,8*R*,9*E*,11*S*,12*S*,14*Z*)-8-Hydroxy-11-methoxy-12-(4-methoxyphenyl)methoxy-5,9,14-icosatrienoic acid (17)

To a stirred mixture of **16b** (78.0 mg, 0.155 mmol) in THF/H_2O (3:1, 2 mL) was added $LiOH\cdot H_2O$ (64.5 mg, 1.54 mmol) at room temperature and the resulting mixture was stirred at 40 °C for 16 h. The mixture was cooled to room temperature, quenched with 1 M oxalic acid, and extracted with CH_2Cl_2. The extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc=1:1) to give **17** (75.2 mg, 99%) as a colorless oil. $[\alpha]_D^{19}$ +5.50 (*c* 1.07, $CHCl_3$); IR: ν_{max} 3397 (m), 3005 (m), 1709 (s), 1614 (w), 1514 (s), 1248 (s); ^{1}H NMR: δ 0.88 (3H, t, *J*=6.7 Hz), 1.20–1.38 (6H, m), 1.70 (2H, quint, *J*=7.1 Hz), 2.01 (2H, q, *J*=6.7 Hz), 2.11 (2H, q, *J*=7.1 Hz), 2.17–2.26 (1H, m), 2.26–2.42 (5H, m), 3.29 (3H, s), 3.39 (1H, q, *J*=5.7 Hz), 3.63 (1H, dd, *J*=6.6, 4.9 Hz), 3.79 (3H, s), 4.18 (1H, q, *J*=5.7 Hz), 4.53 (1H, d, *J*=11.7 Hz), 4.56 (1H, d, *J*=11.7 Hz), 5.34–5.56 (4H, m), 5.64 (1H, dd, *J*=15.6, 7.2 Hz), 5.73 (1H, dd, *J*=15.6, 5.4 Hz), 6.85 (2H, d, *J*=8.3 Hz), 7.26 (2H, d, *J*=8.3 Hz); ^{13}C NMR: δ 14.2, 22.7, 24.6, 26.7, 27.5, 28.7, 29.4, 31.7, 33.4, 35.3, 55.4, 57.0, 71.8, 72.5, 81.0, 83.2, 113.7 (2C), 125.6, 125.9, 128.1, 129.7 (2C), 130.9, 131.9, 132.2, 136.4, 159.2, 178.8; HRMS (FAB): *m*/*z* calcd for $C_{29}H_{44}O_6Na$ ($[M+Na]^+$) 511.3036, found 511.3038.

4.14. (6*Z*,9*R*)-4,5,8,9-Tetrahydro-9-[(1*E*,3*S*,4*S*,6*Z*)-3-methoxy-4-(4-methoxyphenyl)methoxy-1,6-dodecadienyl]-2(3*H*)-oxononinone (18)

To a stirred solution of **17** (57.5 mg, 0.118 mmol) and DIPEA (145 μL, 0.833 mmol) in THF (2.4 mL) was added 2,4,6-trichlorobenzoyl chloride (92.0 μL, 0.589 mmol) at 0 °C. After 30 min, the mixture was warmed to room temperature and stirred for 1.5 h. The mixture was filtered and the filtrate was concentrated in vacuo. The residue was diluted with toluene (8 mL) and added dropwise to a solution of DMAP (360 mg, 2.95 mmol) in toluene (100 mL) at 90 °C over 8 h. After being stirred at 90 °C for an additional 1 h, the mixture was cooled to room temperature and diluted with EtOAc. The resulting solution was successively washed with 0.5 M aq HCl, saturated aq $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc=10:1) to give **18** (52.7 mg, 95%) as a colorless oil. $[\alpha]_D^{19}$ +57.0 (*c* 1.40, $CHCl_3$); IR: ν_{max} 3009 (w), 1740 (s), 1612 (w), 1513 (m), 1247 (m), 1079 (s); ^{1}H NMR: δ 0.88 (3H, t, *J*=6.7 Hz), 1.20–1.38 (6H, m), 1.75–1.86 (1H, m), 1.97–2.13 (5H, m), 2.18–2.55 (6H, m), 3.30 (3H, s), 3.37 (1H, q, *J*=5.7 Hz), 3.60–3.65 (1H, m), 3.79 (3H, s), 4.53 (1H, d, *J*=11.6 Hz), 4.58 (1H, d, *J*=11.6 Hz), 5.29 (1H, br d, *J*=10.8 Hz), 5.35–5.56 (4H, m), 5.69–5.79 (2H, m), 6.85 (2H, d, *J*=8.4 Hz), 7.26 (2H, d, *J*=8.4 Hz); ^{13}C NMR: δ 14.2, 22.7, 25.4, 26.6, 27.5, 28.6, 29.4, 31.7, 33.6, 34.6, 55.4, 57.1, 72.36, 72.42, 80.7, 83.0, 113.7 (2C), 124.5, 125.4, 129.5, 129.7 (2C), 130.9, 131.7, 132.3, 135.2, 159.2, 173.9; HRMS (FAB): *m*/*z* calcd for $C_{29}H_{42}O_5Na$ ($[M+Na]^+$) 493.2929, found 493.2928.

4.15. (6*Z*,9*R*)-4,5,8,9-Tetrahydro-9-[(1*E*,3*S*,4*S*,6*Z*)-4-hydroxy-3-methoxy-1,6-dodecadienyl]-2(3*H*)-oxoninone (2)

To a stirred mixture of **18** (50.0 mg, 0.106 mmol) in CH_2Cl_2/H_2O (10:1, 1.1 mL) was added DDQ (72.3 mg, 0.319 mmol) at 0 °C. After 2 h, the mixture was quenched with saturated aq $NaHCO_3$ and extracted with CH_2Cl_2. The extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc=4:1) to give **2**

(36.7 mg, 99%) as a colorless oil. $[\alpha]_D^{21}$ +77.2 (*c* 0.820, MeOH); IR: ν_{max} 3476 (m), 3012 (m), 1742 (s), 1138 (m), 1080 (m); ^{1}H NMR (CD_3OD): δ 0.90 (3H, t, *J*=6.6 Hz), 1.24–1.40 (7H, m), 1.70–1.83 (1H, m), 1.99–2.25 (7H, m), 2.29–2.58 (4H, m), 3.29 (3H, s), 3.47–3.53 (2H, m), 5.24–5.30 (1H, m), 5.41–5.53 (4H, m), 5.69 (1H, dd, *J*=15.6, 7.4 Hz), 5.86 (1H, dd, *J*=15.6, 5.4 Hz); ^{13}C NMR (CD_3OD, δ 49.00 ppm): δ 14.4, 23.6, 26.3, 27.6, 28.4, 30.4, 31.8, 32.7, 34.4, 35.5, 57.0, 73.9, 74.8, 85.7, 125.6, 126.6, 130.1, 132.7, 134.0, 136.2, 175.6; HRMS (FAB): *m*/*z* calcd for $C_{21}H_{34}O_4Na$ ($[M+Na]^+$) 373.2355, found 373.2354.

4.16. (5*Z*,8*R*,9*E*,11*S*,12*S*,14*Z*)-11-[(*R*/*S*)-1-Ethoxyethoxy]-8-hydroxy-12-(4-methoxyphenyl)methoxy-5,9,14-icosatrienoic aicd (19c)

To a stirred mixture of **4** (134 mg, 0.222 mmol) and ethyl vinyl ether (32.0 μL, 0.334 mmol) in CH_2Cl_2 (2 mL) was added PPTS (7.4 mg, 0.029 mmol) at room temperature. After being stirred overnight, the solution was poured into saturated aq $NaHCO_3$ and extracted with CH_2Cl_2. The extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo to give crude **19a**, which was dissolved in THF (0.7 mL). To the solution was added a solution of TBAF (1 M in THF, 0.70 mL, 0.70 mmol) at 0 °C, and the mixture was stirred for 1 h. The mixture was warmed to room temperature, stirred for an additional 3 h, and quenched with saturated aq NH_4Cl. The mixture was extracted with Et_2O, and the extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo to give crude **19b**, which was then taken up in a THF/H_2O (3:1, 4.4 mL). To the solution was added $LiOH\cdot H_2O$ (37.6 mg, 0.896 mmol) at room temperature and the mixture was stirred overnight at 40 °C. The mixture was quenched with saturated aq NH_4Cl and extracted with CH_2Cl_2. The extract was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc=1:1) to give **19c** (as a ca. 3:2 diastereomeric mixture, 115 mg, 94% from **4**) as a colorless oil. $[\alpha]_D^{19}$ +11.2 (*c* 1.57, $CHCl_3$); IR: ν_{max} 1709 (m), 1514 (m), 1246 (s), 1037 (s); ^{1}H NMR: δ 0.878 (0.6×3H, t, *J*=6.8 Hz), 0.884 (0.4×3H, t, *J*=6.8 Hz), 1.15 (0.6×3H, t, *J*=7.0 Hz), 1.16 (0.4×3H, t, *J*=7.0 Hz), 1.22–1.37 (9H, m), 1.71 (2H, quint, *J*=7.2 Hz), 2.00 (2H, q, *J*=6.4 Hz), 2.12 (2H, q, *J*=7.2 Hz), 2.16–2.23 (1H, m), 2.25–2.37 (5H, m), 3.37–3.68 (3H, m), 3.80 (3H, s), 4.05–4.21 (2H, m), 4.52–4.61 (2H, m), 4.73 (0.6×1H, q, *J*=5.3 Hz), 4.75 (0.4×1H, q, *J*=5.3 Hz), 5.40–5.56 (4H, m), 5.61–5.76 (2H, m), 6.85 (0.6×2H, d, *J*=8.7 Hz), 6.86 (0.4×2H, d, *J*=8.7 Hz), 7.26 (2H, d, *J*=8.7 Hz); ^{13}C NMR: δ 14.2, 15.3/15.4, 20.4/20.6, 22.7, 24.5, 26.7, 27.50/27.53, 28.5/28.6, 29.4, 31.0/33.3, 31.7, 35.2/35.3, 55.3, 59.2/61.0, 71.7/71.8, 72.6, 77.4/77.7, 81.2/81.4, 97.4/100.0, 113.69/113.74 (2C), 125.8/125.9, 126.0, 128.0/128.8, 129.6/129.7 (2C), 130.8/130.9, 131.75/131.78, 131.84/131.9, 134.9/136.2, 159.19/159.21, 178.5/178.6; HRMS (FAB): *m*/*z* calcd for $C_{32}H_{50}O_7Na$ ($[M+Na]^+$) 569.3454, found 569.3453.

4.17. (6*Z*,9*R*)-9-{(1*E*,3*S*,4*S*,6*Z*)-3-[(*R*/*S*)-1-Ethoxyethoy]-4-(4-methoxyphenyl)methoxy-1,6-dodecadienyl}-4,5,8,9-tetrahydro-2(3*H*)-oxoninone (20a)

To a stirred solution of **19c** (115 mg, 0.209 mmol) and DIPEA (260 μL, 1.49 mmol) in THF (4 mL) was added 2,4,6-trichlorobenzoyl chloride (163 μL, 1.04 mmol) at 0 °C. After 30 min, the mixture was warmed to room temperature and stirred for 1.5 h. The mixture was filtered and the filtrate was concentrated in vacuo. The residue was diluted with toluene (6 mL) and added dropwise to a solution of DMAP (638 mg, 5.23 mmol) in toluene (205 mL) at 90 °C over 8 h. After being stirred at 90 °C for an additional 1 h, the mixture was cooled to room temperature and diluted with EtOAc. The resulting solution was successively washed with saturated aq $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc=10:1) to give **20a** (97.4 mg, 88%) as a pale yellow oil. $[\alpha]_D^{19}$ +62.0 (*c* 0.900, $CHCl_3$); IR: ν_{max} 1741 (m), 1613 (w), 1513 (m), 1247 (m), 1079 (s); ^{1}H NMR: δ 0.88 (3H, t, *J*=6.7 Hz), 1.15 (3H, t, *J*=7.0 Hz), 1.20–1.37 (9H, m), 1.74–1.86 (1H, m), 1.96–2.13 (5H, m), 2.13–2.54 (6H, m), 3.36–3.53 (2H, m), 3.53–3.66 (1H, m), 3.80 (3H, s), 4.08 (0.4×1H, t, *J*=5.8 Hz), 4.16–4.20 (0.6×1H, m), 4.49–4.62 (2H, m), 4.70 (0.6×1H, q, *J*=5.4 Hz), 4.75 (0.4×1H, q, *J*=5.4 Hz), 5.24–5.31 (1H, m), 5.39–5.56 (4H, m), 5.70–5.88 (2H, m), 6.85 (0.6×2H, d, *J*=8.4 Hz), 6.86 (0.4×2H, d, *J*=8.4 Hz), 7.26 (2H, d, *J*=8.4 Hz); ^{13}C NMR: δ 14.2, 15.3/15.5, 20.4/20.6, 22.7, 25.4, 26.6, 27.5/27.6, 28.4/28.6, 29.4, 31.7, 33.6, 34.55/34.61, 55.3/55.4, 59.4/60.7, 72.5, 77.8, 81.0, 81.1 97.8/100.2, 113.69/113.74 (2C), 124.5, 125.6/125.8, 129.55/129.64 (2C), 130.2/130.3, 130.8/130.9, 131.5, 131.9/132.0, 135.1, 159.21/159.23, 173.8/173.9; HRMS (FAB): *m*/*z* calcd for $C_{32}H_{48}O_6Na$ ($[M+Na]^+$) 551.3349, found 551.3347.

4.18. (6*Z*,9*R*)-9-[(1*E*,3*R*,4*S*,6*Z*)-3,4-Epoxy-1,6-dodecadienyl]-4,5,8,9-tetrahydro-2(3*H*)-oxoninone (3)

To a stirred solution of **20a** (66.0 mg, 0.125 mmol) in EtOH (1.2 mL) was added PPTS (94.1 mg, 0.375 mmol) at room temperature. After being stirred overnight, the solution was quenched with saturated aq $NaHCO_3$ and extracted with CH_2Cl_2. The extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo to give crude **20b**, which was dissolved in CH_2Cl_2 (1.2 mL). To the solution were successively added DIPEA (0.110 mL, 0.632 mmol), DMAP (76.3 mg, 0.625 mmol), and Ms_2O (76.2 mg, 0.437 mmol) while stirring at 0 °C. After 5 h, the solution was quenched with saturated aq NH_4Cl and extracted with CH_2Cl_2. The extract was washed with brine, dried (Na_2SO_4), and concentrated in vacuo to give crude **20c**, which was taken up in CH_2Cl_2/pH 7 phosphate buffer (10:1, 2.2 mL). To the solution was added DDQ (90.4 mg, 0.396 mmol) while stirring at 0 °C, and the mixture was stirred overnight at the same temperature. The mixture was quenched with saturated aq $NaHCO_3$ and extracted with CH_2Cl_2. The extract was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was roughly purified by silica gel column chromatography to remove *p*-methoxybenzaldehyde (hexane/EtOAc=4:1) to give crude **20d**. The hydroxy mesylate **20d** just obtained was dissolved in MeOH (1 mL) and mixed with K_2CO_3 (17.3 mg, 0.125 mmol) while stirring at −15 °C. After 1 h, the mixture was filtered into a stirred solution of Et_2O/saturated aq NH_4Cl at 0 °C and extracted with ether. The extract was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc=8:1) to give **3** (6.4 mg, 16% from **20a**) as a colorless oil. $[\alpha]_D^{21}$ +73 (*c* 0.22, MeOH); IR: ν_{max} 3011 (w), 1741 (s), 1257 (m), 1218 (m), 1136 (m); ^{1}H NMR (CD_3OD): δ 0.90 (3H, t, *J*=6.6 Hz), 1.26–1.41 (6H, m), 1.69–1.82 (1H, m), 1.98–2.27 (7H, m), 2.32–2.58 (4H, m), 3.11 (1H, dt, *J*=4.3, 6.4 Hz), 3.47 (1H, dd, *J*=6.9, 4.3 Hz), 5.29 (1H, dd, *J*=10.9, 5.6 Hz), 5.40 (1H, dt, *J*=10.8, 7.3 Hz), 5.45–5.56 (3H, m), 5.75 (1H, dd, *J*=15.5, 6.9 Hz), 6.03 (1H, dd, *J*=15.5, 5.7 Hz); ^{13}C NMR (CD_3OD, δ 49.00 ppm): δ 14.4, 23.7, 26.3, 27.0, 27.6, 28.4, 30.4, 32.7, 34.4, 35.4, 57.3, 59.5, 73.8, 124.7, 125.5, 127.3, 133.8, 135.2, 136.2, 175.6; HRMS (FAB): *m*/*z* calcd for $C_{20}H_{30}O_3Na$ ($[M+Na]^+$) 341.2093, found 341.2092.

4.19. Conversion of topsentolide A_2 (3) into topsentolide C_2 (2)

To a stirred solution of **3** (1.5 mg, 4.7 μmol) in MeOH (1 mL) was added a solution of HCl in MeOH (0.125 M, 5.0 μL, 0.63 μmol) at 0 °C. The mixture was stirred at 0 °C for 1 h and then at room temperature for an additional 1 h. To the mixture was added again the methanolic HCl solution (10 μL, 1.3 μmol) at room temperature and the resulting solution was stirred for 1.5 h. The mixture was

quenched with saturated aq $NaHCO_3$ and extracted with ether. The extract was washed with brine, dried (Na_2SO_4), and concentrated in vacuo to give **2** (1.7 mg, quant) as a virtually pure compound, as judged by its ^1H and ^{13}C NMR spectra.

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Supplementary data

^1H and ^{13}C NMR spectra of **2**, **3**, key synthetic intermediates, and the crude ring-opening product of **3**. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2014.04.040. These data include MOL file and InChiKeys of the most important compounds described in this article.

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