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Absolute stereochemistries and total synthesis of (+)/(−)-macrosphelides, potent, orally bioavailable inhibitors of cell–cell adhesion

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Abstract—In the current studies, we used the single-crystal X-ray analysis and Kakisawa–Kashman modification of the Mosher NMR method to determine the complete relative and absolute stereochemistries of the (+)-macrosphelides A (+)-**1** and B (+)-**2**. The stereostructure of (+)-**2** was determined by chemical comparison with artificial (+)-**2** from (+)-**1**. We also report the convergent total synthesis of (+)-**1** and (+)-**3**, as well as their antipodes, utilizing an asymmetric dihydroxylation for introduction of chirality and Yamaguchi macrocyclization to form the 16-membered trilactone macrolides.

1. Introduction

Critical early events in inflammation,[1–3] the allergic response,[4–6] and tumor metastasis[7–9] involve interactions between leukocytes and endothelial cells. In particular, tumor metastasis is a multi-step process requiring detachment of malignant cells from primary tumor mass, infiltration and invasion to blood and/or lymph vessels, adhesion to endothelia of distant organs, and finally formation of new tumor colonies.[10] During the early stage of adhesion between endothelial cells and tumor cells, E-selectin is expressed on activated endothelial cells, which recognize sialyl Lewis X on the tumor cells.[11–13] Several groups have demonstrated that sialyl Lewis X and E-selectin molecules perform this important role in tumor cell adhesion to endothelial cells.[14,15]

We previously reported the isolation, determination of planar structures, and preliminary biological evaluation of (+)-macrosphelides A and B ((+)-**1** and (+)-**2**) as cell–cell adhesion inhibitors from *Microsphaeropsis* sp. FO-5050 (Fig. 1).[16] We have now extended this study to

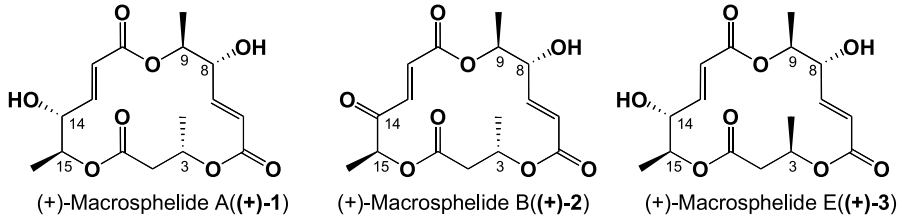

Figure 1. Structures of (+)-macrosphelide A, B and E.

Keywords: Kakisawa–Kashman modification; (+)/(−)-Macrosphelides; Cell–cell adhesion.
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the total synthesis and determination of the absolute stereochemistries of these compounds.[17]

Macrosphelides are the first 16-membered-ring antibiotics embodying three lactone linkages (i.e., macrotriolides). The IC_{50} values of (+)-**1** and (+)-**2** were 3.5 and 36 μM, respectively, for the adhesion of human-leukemia HL-60 cells to human-umbilical-vein endothelial cells (HUVEC).[16] Preliminary studies suggest that (+)-**1** and (+)-**2** prevent cell–cell adhesion by inhibiting the binding of sialyl Lewis X to E-selectin. (+)-**1** also proved to be orally active against lung metastasis of B16/BL6 melanoma in mice (50 mg/kg/day) without body weight loss.[18] On the other hand, Numata and co-workers have found that a strain of *Periconia byssoides* isolated from the seahare *Aplysia kurodai*, produces novel cytotoxic materials containing four new macrolides, macrosphelides E–H.[19] Macrosphelide E ((+)-**3**) is identical to (+)-macrosphelide A ((+)-**1**), differing only in the stereochemistry at C(3). Due to their attractive properties and unique structures, several synthetic approaches to macrosphelides have been reported.[20] In conjunction with our continuing investigations into the structure elucidation and synthesis of important bio-regulatory natural products, we report herein the determination of the complete relative and absolute stereochemistries of (+)-macrosphelides A and B ((+)-**1** and (+)-**2**). We also describe the first total synthesis of these compounds, together with an application of our synthetic route to the preparation of (+)-**3** and some enantiomers of natural macrosphelides.

2. Results and discussion

2.1. Determination of the absolute stereochemistry of (+)-macrosphelides A and B

Initially our attention was directed toward the structure elucidations of (+)-**1** and (+)-**2**. A series of NMR studies revealed the planar structures of (+)-**1** and (+)-**2**, which were also supported by FAB-MS, IR data, chemical characterizations of the derived di- and monoacetates, respectively.[16] The relative structure of (+)-**1** was confirmed by single-crystal X-ray diffraction[21] to be (3*S**,8*R**,9*S**,14*R**,15*S**) (Fig. 2).

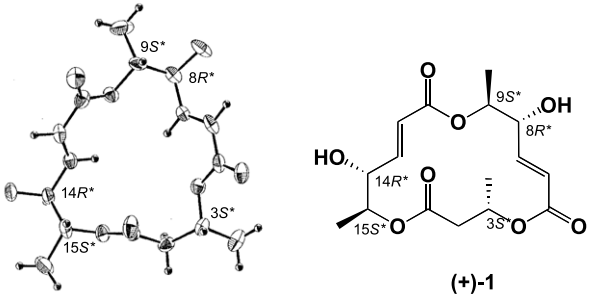


Figure 2. ORTEP plot of (+)-**1**.

The configurations at C(8) and C(14) in (+)-**1** were also elucidated using the Kakisawa–Kashman modification[22] of Mosher's method.[23] Thus, (+)-**1** was treated with (*S*)-(−)- and (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA), dicyclohexylcarbodiimide (DCC), and 4-(dimethylamino)pyridine (DMAP) in THF at room temperature[22] to provide the 8,14-bis-*O*-(*S*)-(−)-MTPA ester (−)-**4** and 8,14-bis-*O*-(*R*)-(+)-MTPA ester (+)-**5**, respectively (Scheme 1).

The ^{1}H NMR spectra of (−)-**4** and (+)-**5** were completely assigned via selective ^{1}H decoupling. The *R* configurations at C(8) and C(14) were confirmed by application of the Kakisawa–Kashman test[22] to determine the ^{1}H $\Delta\delta$ values for (−)-**4** and (+)-**5** (Fig. 3). Thus, the absolute stereochemistry of macrosphelide A is (3*S*,8*R*,9*S*,14*R*,15*S*) as shown in Figure 1. This assignment was also confirmed by total synthesis.

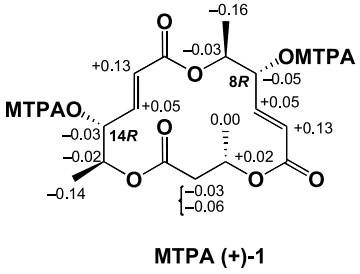
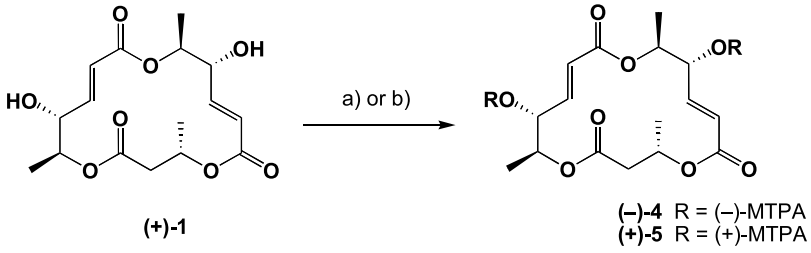
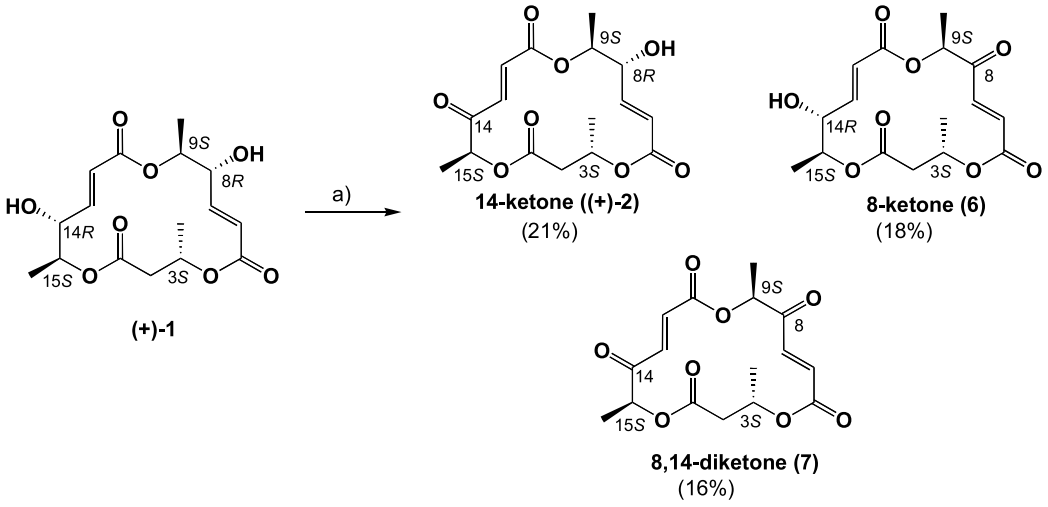


Figure 3. δ Values for the bis-MTPA ester derivatives of (+)-**1** ($\delta = \delta_{(-)} - \delta_{(+)}$).

Our next aim was to determine the absolute structure of (+)-**2**, anticipated to be the a C(14) oxidation product of (+)-**1** (Fig. 1). To prepare (+)-**2**, (+)-**1** was treated with pyridinium dichromate (PDC) in CH_2Cl_2 at room temperature for 3 h (Scheme 2). Initial separation of the reaction mixture gave three major fractions: (i) a mixture of the 14- and 8-monoketones, **2** and **6**, (ii) pure 8, 14-diketone **7** (16% yield), and (iii) recovered starting material (+)-**1** (45%). Further purification of the monoketone mixture (**2** and **6**) by HPLC then provided pure (+)-**2** and **6** in 21 and 18% yields, respectively. Synthetic (+)-**2** derived from (+)-**1** was identical with the natural product sample in all respects.



Scheme 1. Synthesis of bis(+)/(−)-MTPA ester. (a) (−)-MTPA, DCC, DMAP, THF, 100% yield; b) (+)-MTPA, DCC, DMAP, THF, 27% yield.



Scheme 2. PDC oxidation of (+)-**1** to provide (+)-**2**. (a) PDC, CH_2Cl_2.

Thus, the absolute stereochemistry of macrosphelide B ((+)-**2**) is (3*S*,8*R*,9*S*,15*S*) as shown in Scheme 2.

2.2. Synthetic strategy for the preparation of (+)-macrosphelide A

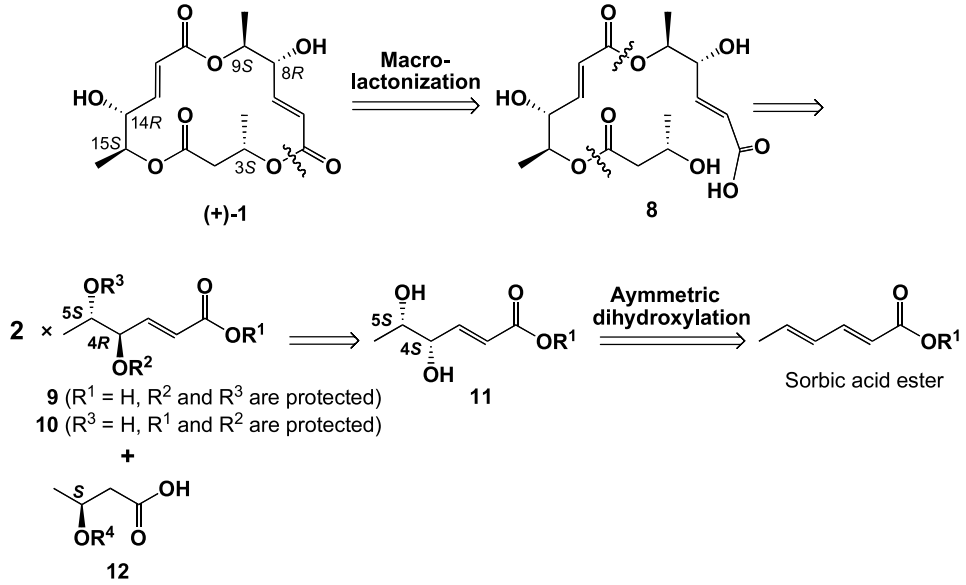
Disconnection of the three esters of (+)-macrosphelide A ((+)-**1**) reveals two trans-(4*R*,5*S*)-4,5-dihydroxyhexenoic acid components and (*S*)-3-hydroxybutanoic acid (commercially available). Thus, the strategy required the enantioselective preparation of *trans*-(4*R*,5*S*)-4,5-dihydroxyhexenoic acid, which was prepared by selective asymmetric dihydroxylation, followed by differential protection for two hydroxy groups and inversion of allyl alcohol (Scheme 3).

2.3. Preparation of building blocks 9 and 10

The starting point of our synthesis required preparation of the two differentially protected building blocks **9** and **10**, from known (*E*,*E*)-hexa-2,4-dienoic acid ester (sorbic acid ester) via the common enantio-active precursor **11** (Scheme 3).

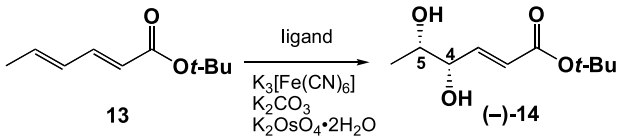
Initially, asymmetric Sharpless dihydroxylation[24] of sorbic *tert*-butyl ester **13**[25] using AD-mix-α, (which uses $(DHQ)_2$-PHAL as a chiral ligand), was employed to afford the corresponding diol (−)-**14** (62%, 85% ee) (Table 1). Three other chiral ligands were examined for the asymmetric dihydroxylation. The best result (71%, 88% ee) was obtained with Corey-AD-ligand-α without MeI salt (**15**)[26] (1,4-bis[(2*S*,8*S*,9*R*)-6′-(4-heptyloxy)-10,11-dihydrocinchonan-9-oxylnaphthopyridazine] (Table 1).

In order to study the biological structure–activity relationships of macrosphelides, preparation of select derivatives of their antipodes was desirable. To this end, the antipode of (−)-**14** was attempted. Four ligands, $(DHQD)_2PHAL$,[24] $(DHQD)_2AQN$,[27] Corey-AD-ligand-β (**18**)[26] and Corey-AD-ligand-β without MeI salt (**17**),[26] were examined for asymmetric dihydroxylation of **13** (Table 2), with **17** giving



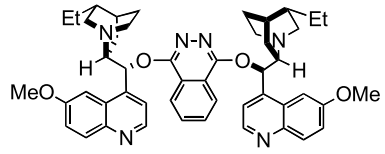
Scheme 3. Synthetic strategy for the preparation of (+)-**1**.

Table 1. Asymmetric dihydroxylation of sorbic acid *tert*-butyl ester using α-ligands

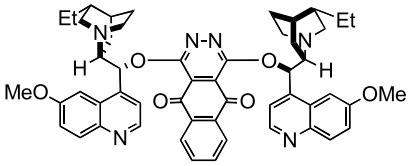


Ligand[a]	Yield of (−)-**14**[b]	%ee of (−)-**14**[c]
$(DHQ)_2PHAL$	62%	85%
$(DHQ)_2AQN$	67%	61%
15	71%	88%
16	66%	75%

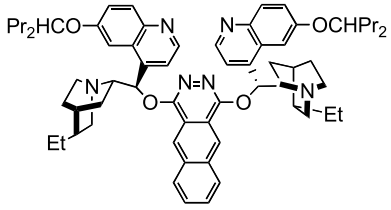
[a] All reactions were carried out with ligands (0.01 equiv), $K_3[Fe(CN)_6]$ (3.0 equiv), K_2CO_3 (3.0 equiv) and $K_2OsO_4 \cdot 2H_2O$ (0.01 equiv) in *t*-BuOH·H_2O (1/1 v/v).
[b] Yields were based on pure materials isolated by chromatography on SiO_2.
[c] The ee of the product was determined by ^1H NMR measurements of the MTPA ester of TBS ether (+)-**19**.



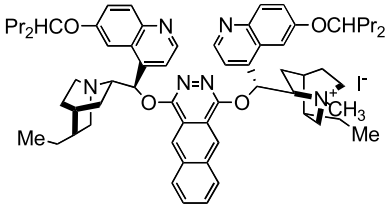
$(DHQ)_2PHAL$



$(DHQ)_2AQN$



Corey-AD-Ligand-α non MeI salt (15)



Corey-AD-Ligand-α (16)

the best result (74%, 98% ee). Interestingly, dihydroxylation with **18** afforded diol (+)-**14** in low yield (5.9%) with large amounts of tetraol products, as diastereomeric mixtures. The enantiomeric purities of (−)- and (+)-**14** were determined by Mosher analysis[23] of the silylated alcohol (**19**).

Selective protection of the C(5)–OH group of (−)-**14**, with TBSCl, Et_3N, and DMAP, provided the desired ether (+)-**19**, together with undesired C(4)–O–TBS ether (+)-**20** and starting material in 56, 11 and 30% yields, respectively, (Scheme 4). Mitsunobu inversion[28] of the C(4)–OH group in (+)-**19** with PPh_3, DEAD, and formic acid, followed by hydrolysis of the formyl ester in diluted NH_4OH/MeOH solution afforded (+)-**21** in 83% yield. Interestingly, the TBS protecting group at the C(5)–OH position was found to migrate to C(4)–OH position, when other carboxylic acids (e.g. AcOH, BzOH) were used for Mitsunobu inversion.

Stereochemistry at the C(4)-position in (+)-**21** was confirmed by the Kakisawa–Kashman[22] modified Mosher's method,[23] after esterification of (+)-**21**. The (−)- and (+)-MTPA esters of (+)-**21** were isolated in 100 and 91% yield, respectively (Scheme 5 and Fig. 4).

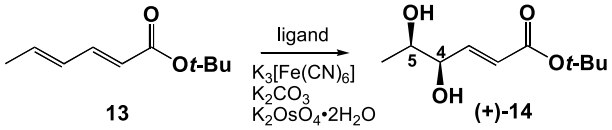
The other secondary hydroxyl group in TBS ether (+)-**21** was protected as β-methoxyethoxymethyl (MEM) ether to provide (−)-**22**. Hydrolysis in aqueous sodium hydroxide solution (0.2 N NaOH MeOH/THF/H_2O) afforded the first building block (−)-**23** (carboxylic acid) in 96% yield (Scheme 6). The second building block, (−)-**24** (secondary alcohol), was prepared by deprotection of TBS group of (−)-**22** with tetra-*n*-butylammonium fluoride (TBAF) in 100% yield (Scheme 6).

2.4. Completion of total synthesis of (+)-macrosphelide A

Condensation of carboxylic acid (−)-**23** and alcohol (−)-**24**, in the presence of DCC, DMAP, and camphorsulfonic acid (CSA) (Keck protocol[29]) furnished diester (−)-**25** in 92% yield. Subsequent desilylation of (−)-**25** was carried out with TFA to give the alcohol (−)-**26** in 99% yield. The requisite third building block (+)-**27**[30] was prepared by silylation of (*S*)-3-hydroxybutylic acid, and coupled by DCC accelerated condensation in the presence of DMAP and CSA (Keck protocol[29]) with the alcohol (−)-**26** to afford the triester (−)-**28** in 96% yield (Scheme 7).

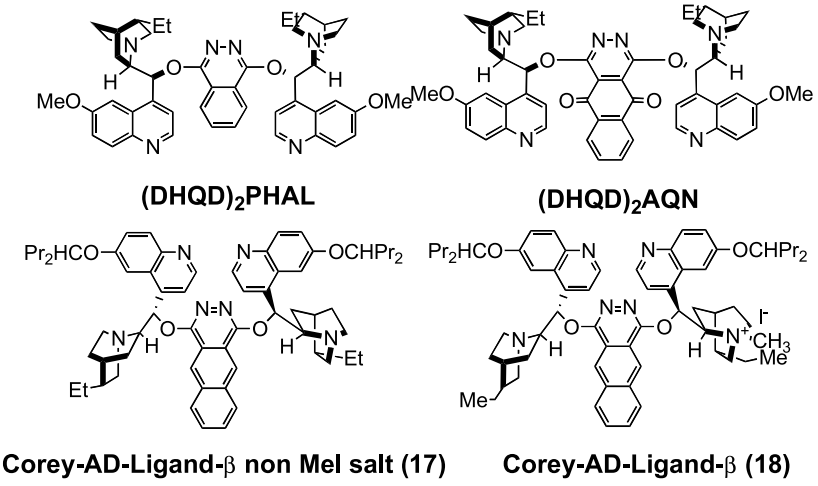
Selective, simultaneous removal of the TBS and *tert*-butyl groups, to convert (−)-**28** to seco acid (−)-**29**, was attempted under a variety of acidic conditions. The best result was obtained by treatment with thioanisole/TFA/CH_2Cl_2 (5:5:1),[31] to give seco acid (−)-**29** in 64% yield, with undesired mono MEM ether **31** in low yield (Table 3).

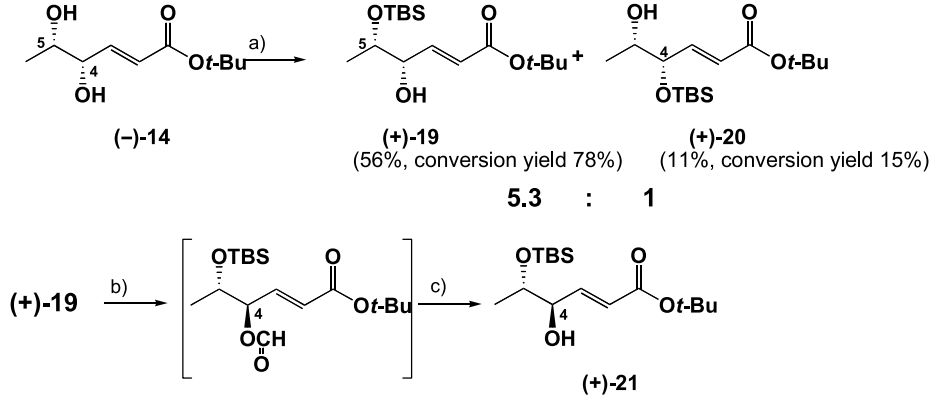
Table 2. Asymmetric dihydroxylation of sorbic acid *tert*-butyl ester using β-ligands



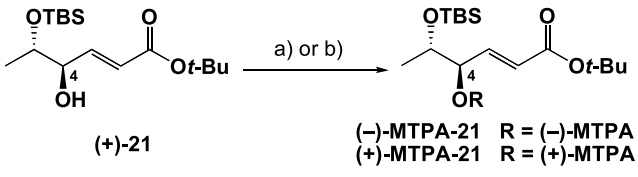
Ligand[a]	Yield of (+)-**14**[b]	%ee of (+)-**14**[c]
$(DHQD)_2PHAL$	68%	95%
$(DHQD)_2AQN$	61%	82%
17	74%	98%
18	5.9%	90%

[a] All reactions were carried out with ligands (0.01 equiv), $K_3[Fe(CN)_6]$ (3.0 equiv), K_2CO_3 (3.0 equiv) and $K_2OsO_4 \cdot 2H_2O$ (0.01 equiv) in *t*-BuOH·H_2O (1/1 v/v).
[b] Yields were based on pure materials isolated by chromatography on SiO_2.
[c] The ee of the product was determined by ^1H NMR measurements of the MTPA ester of TBS ether (−)-**19**.





Scheme 4. Preparation of (+)-**21**. (a) TBSCl, Et_3N, DMAP, CH_2Cl_2; (b) PPh_3, DEAD, HCOOH; (c) dil. NH_4OH, 83% yield for two steps.



Scheme 5. Synthesis of (−)/(+)-MTPA ester. (a) (−)-MTPA, DCC, DMAP, CH_2Cl_2, 100% yield; (b) (+)-MTPA, DCC, DMAP, CH_2Cl_2, 91% yield.

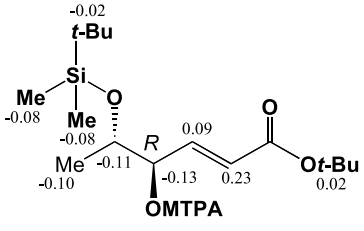
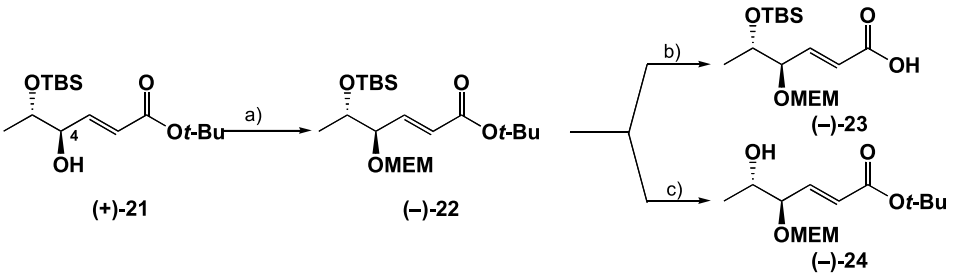
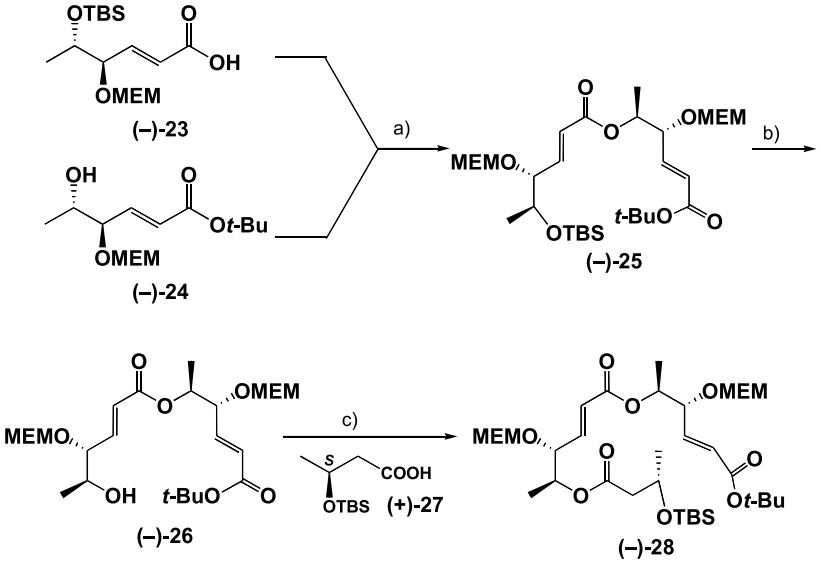


Figure 4. Stereochemistry identification: δ values for the MTPA ester derivatives of (+)-**21**.



Scheme 6. Preparation of acid (−)-**23** and alcohol (−)-**24**. (a) MEMCl, *i*-Pr_2NEt, CH_2Cl_2, 100% yield; (b) 0.2 N NaOH, 96% yield; (c) TBAF, 100% yield.

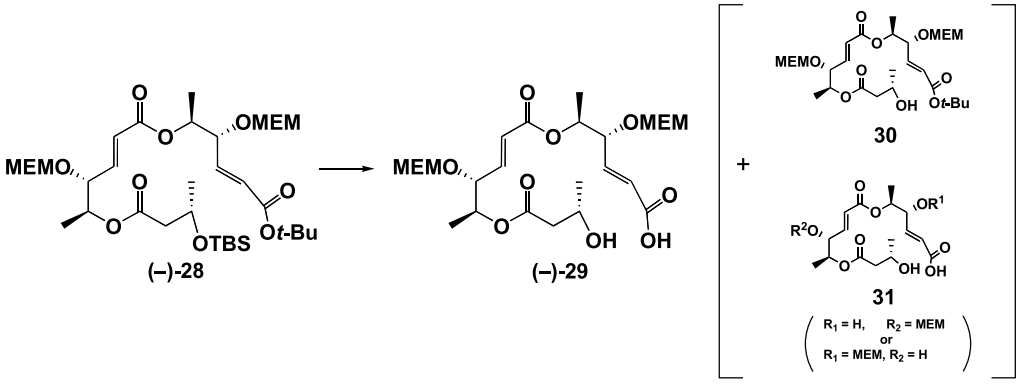


Scheme 7. Synthesis of triester (−)-**28**. (a) DCC, DMAP, CSA, 92% yield; (b) TFA, THF, H_2O, 99% yield; (c) (+)-**27**, DCC, DMAP, CSA, 96% yield.

Yamaguchi macrolactonization[32] of the seco acid (−)-**29** then proceeded in excellent yield (91%) to furnish (−)-**32**. Finally, deprotection of (−)-**32** in TFA/CH_2Cl_2 (1:1) provided totally synthetic (+)-macrosphelide A ((+)-**1**) in 90% yield (Scheme 8). Its spectral properties were identical in all respects (400 MHz ^1H and 100 MHz ^{13}C NMR, IR, HR-FABMS, optical rotation, melting point and mixed melting point, TLC, and HPLC in four solvent systems) to those of the natural product.

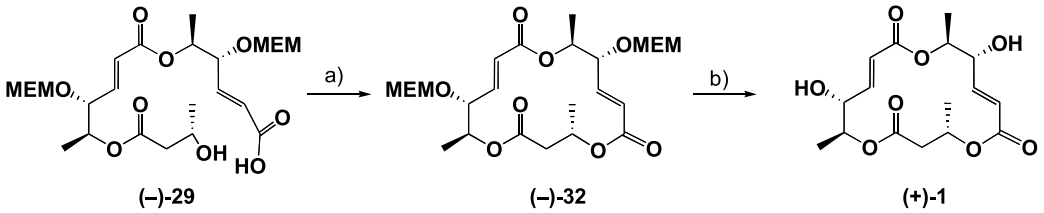
In summary, a highly convergent, stereocontrolled first total synthesis of (+)-macrosphelide A ((+)-**1**) has been

Table 3. Deprotection of TBS and *t*-butyl groups of (−)-**28**

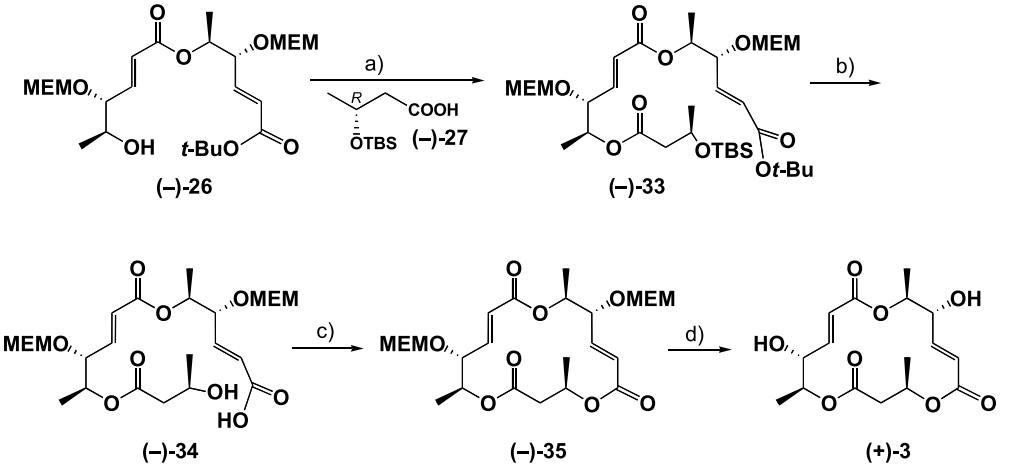


Reaction conditions	Results[a]
TFA·THF·H_2O (1:8:1)	**30** (83%)
HCOOH	(−)-**29** (23%)+**31** (20%)
AcOH·PrOH·H_2O (1:4:4)	(−)-**29** (19%)+**31** (29%)
TFA·thioanisole·CH_2Cl_2 (5:5:1)	(−)-**29** (64%)+**31** (24%)

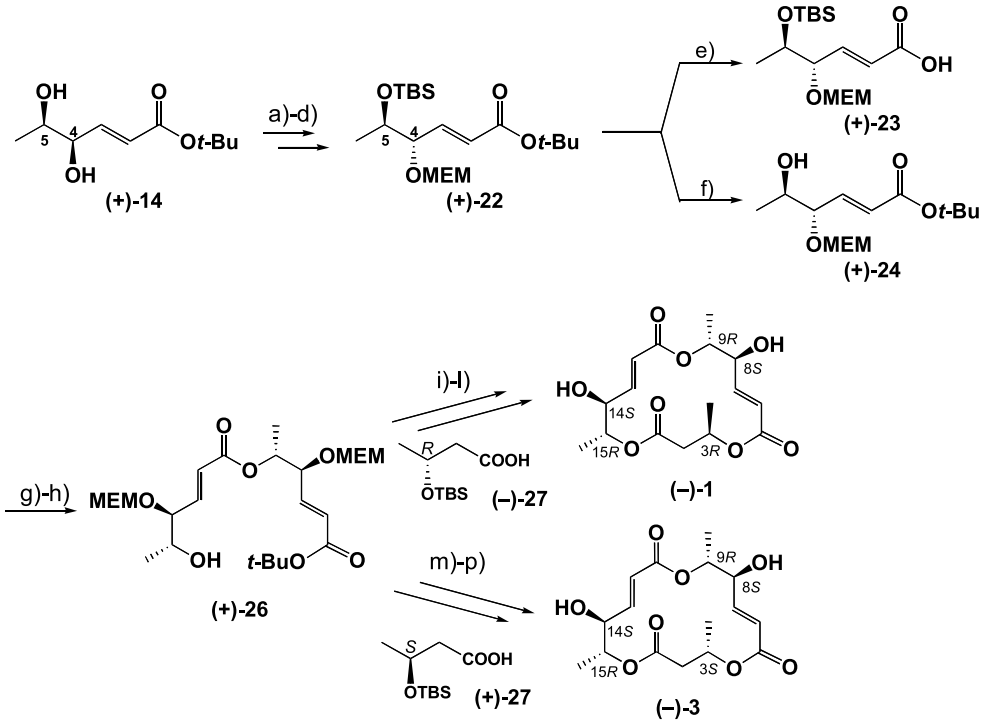
[a] Yields were based on pure materials isolated by chromatography on SiO_2.



Scheme 8. The end game for total synthesis of (+)-macrosphelide A ((+)-**1**). (a) 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, 91% yield; (b) TFA, 90% yield.



Scheme 9. Synthesis of (+)-macrosphelide E ((+)-**3**). (a) (−)-**27**, DCC, DMAP, CSA, CH_2Cl_2, 100% yield; (b) TFA, thioanisole, CH_2Cl_2, 51% yield; (c) 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, 66% yield; (d) TFA, 79% yield.



Scheme 10. Synthesis of (−)-macrosphelides A and E ((−)-**1** and (−)-**3**). (a) TBSCl, Et_3N, CH_2Cl_2, 35% yield; (b) PPh_3, DEAD, HCOOH; (c) dil NH_4OH, 73% yield for two steps; (d) MEMCl, *i*-Pr_2NEt, CH_2Cl_2, 96% yield; (e) 0.2 N NaOH, 85% yield; (f) TBAF, 98% yield; (g) DCC, DMAP, CSA, 62% yield; (h) AcOH, THF, H_2O, 97% yield; (i) (−)-**27**, DCC, DMAP, CSA, 77% yield; (j) TFA, thioanisole, CH_2Cl_2, 38% yield; (k) 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, 86% yield; (l) TFA, 88% yield; (m) (+)-**27**, DCC, DMAP, CSA, 100% yield; (n) TFA, thioanisole, CH_2Cl_2, 41% yield; (o) 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, 85% yield; (p) TFA, 64% yield.

achieved, in 11 steps, from sorbic acid ester, with a 20% overall yield. The synthetic scheme includes the use of a modified Sharpless asymmetric dihydroxylation for the effective introduction of two stereocenters.

2.5. Synthesis of (+)-macroshelode E, and (−)-macrosphelides A and E

We next sought to prepare the (+)-macrosphelide E ((+)-**3**), which was isolated from the gastrointestinal tract of the sea hare *Aplysia kurodai*. Its absolute structure was established via a series of NMR studies in conjunction with HREIMS, UV data, and chemical characterization of the fragmented 3-hydroxybutyric acid and 4,5-dihydroxy-2-*E*-hexenoic acid. Numata and co-workers[19] showed that (+)-macrosphelide E is the C(3) epimer of (+)-macrosphelide A. Synthesis of (+)-**3** was initiated using a Keck protocol[29] of the alcohol precursor (−)-**26** with building block (−)-**27**[30] (prepared by silylation of (*R*)-3-hydroxybutylic acid) to give (−)-**33** in 100% yield. Removal of the silyl and *tert*-butyl moieties from (−)-**33**, (under the same condition as for (−)-**28**[31]) furnished the seco acid (−)-**34**, which was then cyclized by Yamaguchi protocol[32] to give (−)-**35** in 66% yield. Finally, acid treatment of (−)-**35** to remove MEM protecting groups provided synthetic (+)-**3** in 79% yield (Scheme 9), which demonstrated identical, reported spectral data for the naturally occurring compound.[19]

(−)-Macrosphelides A and E, which are the antipodes of the naturally occurring products, were also prepared from (+)-**14** following the same procedure as for the syntheses of (+)-macrosphelides A and E (Scheme 10).

3. Conclusion

As described above, the determination of the absolute structures of (+)-macrosphelides ((+)-**1** and **2**) and the total syntheses of (+)/(−)-macrosphelides A and E were completed. The longest linear synthetic sequence for the synthesis of (+)-macrosphelide A comprised of 11 steps, and proceeded in 20% overall yield (corresponding to an 88% average yield per step). Our synthesis used a modified Sharpless-Asymmetric-Dihydroxylation for the introduction of the two asymmetric carbons. We have also demonstrated that this synthetic route can be applied to the preparation of macrosphelide derivatives, including enantiomers and diastereomers. Studies on the mode of action and the structure–activity relationships of macrosphelides are currently underway.

4. Experimental

4.1. General

Dry THF, toluene, ethyl ether, and CH_2Cl_2 were purchased from Kanto Chemical Co. Precoated silica gel plates with a fluorescent indicator (Merck 60 F254) were used for analytical and preparative thin layer chromatography. Flash column chromatography was carried out with Merk silica gel 60 (Art. 1.09385). ^{1}H and ^{13}C NMR spectra were measured on JEOL JNM-EX270 (270 MHz) or Varian VXR-300 (300 MHz) or Varian XL-400 (400 MHz) or Varian UNITY-400 (400 MHz). All infrared spectra were measured on a Horiba FT-210 spectrometer. Melting points were measured on a Yanagimoto Micro Melting Apparatus. High- and low-resolution mass spectra were measured on JEOL JMS-DX300 and JEOL JMS-AX505 HA spectrometers. Elemental analysis data were measured on a Yanaco CHN CORDER MT-5. Single crystal X-ray spectra were measured on a SMART APEXII diffractometer: AFC-5S. Liquid chromatographic preparation was conducted on a Jasco PU-980 with Senshu Pak-PEGASIL ODS.

4.1.1. (5*R*,6*S*,11*R*,12*S*,16*S*)-(3*E*,9*E*)-5,11-Bis[(*S*)-α-methoxy-α-trifluoromethylphenyl-acetoxy]-6,12,16-trimethyl-1,7,13-trioxacyclohexadeca-3,9-diene-2,8,14-trione (−)-4. At room temperature a solution of (+)-macrosphelide A (10.0 mg, 29.2 μmol) in dry THF (0.6 mL) was treated with *(S)*-(−)-α-methoxy-α-(trifluoromethyl)-phenylacetic acid (41 mg, 175 μmol), dicyclohexylcarbodiimide (18 mg, 88 μmol), and 4-dimethylaminopyridine (3.6 mg, 29 μmol). A white precipitate formed immediately. The resultant mixture was stirred for 2 h, quenched with saturated aqueous $NaHCO_3$ (1 mL), and extracted with dichloromethane (3×1.5 mL). The combined extracts were dried over sodium sulfate, filtered and concentrated. To remove dicyclohexylurea the white solid was taken up in ether (1 mL) and filtered, the cake was washed with ether (1 mL), and the combined ethereal solutions were concentrated. Preparative TLC (250 μm×20×20 cm; 2:1 hexanes/EtOAc) gave (−)-**4** (26.2 mg, 100% yield) as a white powder: $[\alpha]_D^{20}=-20$ (*c* 0.86, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57–7.27 (m, 10H), 6.75 (dd, *J*=15.9, 7.1 Hz, 1H), 6.69 (dd, *J*=15.7, 7.5 Hz, 1H), 5.98 (dd, *J*=15.8, 1.2 Hz, 2H), 5.38 (m, 1H), 5.32 (m, 1H), 5.30 (m, 1H), 5.12 (m, 1H), 5.10 (m, 1H), 3.53 (s, 3H), 3.50 (s, 3H), 2.53 (m, 1H), 2.49 (m, 1H), 1.30 (d, *J*=6.5 Hz, 3H), 1.21 (d, *J*=6.5 Hz, 3H), 1.13 (d, *J*=6.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.1, 17.2, 19.5, 40.6, 55.6 (2 C), 67.7, 69.3, 70.1, 75.3, 77.0, 121.7, 124.6, 125.5 (2 C), 125.6 (2 C), 127.1 (4 C) 128.6 (2 C), 129.9 (2 C), 131.5 (2 C), 140.3 (2 C), 140.4 (2 C) 163.4, 163.6, 165.4, 165.7, 169.1; HRMS (FAB, NaI matrix) *m/z* 797.2053 [$(M+Na)^+$; calcd for $C_{36}H_{36}O_{12}F_6Na$: 797.2009].

4.1.2. (5*R*,6*S*,11*R*,12*S*,16*S*)-(3*E*,9*E*)-5,11-Bis[(*R*)-α-methoxy-α-trifluoromethylphenyl-acetoxy]-6,12,16-trimethyl-1,7,13-trioxacyclohexadeca-3,9-diene-2,8,14-trione (+)-5. Following the procedure described above for the preparation of (−)-**4**, (+)-macrosphelide A (10.0 mg, 29.9 μmol) was acylated with *(R)*-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (41 mg, 175.2 μmol). Work-up and preparative TLC (250 μm×20×20 cm; 2:1 hexanes/EtOAc) afforded (+)-**5** (6.1 mg, 27% yield) as a white powder: $[\alpha]_D^{20}=+36$ (*c* 0.43, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47–7.28 (m, 10H), 6.70 (dd, *J*=15.8, 6.1 Hz, 1H), 6.64 (dd, *J*=15.8, 7.0 Hz, 1H), 5.85 (dd, *J*=15.7, 1.2 Hz, 2H), 5.41 (m, 1H), 5.37 (m, 1H), 5.28 (m, 1H), 5.14 (m, 1H), 5.13 (m, 1H), 3.53 (s, 3H), 3.49 (s, 3H), 2.59 (m, 1H), 2.52 (m, 1H), 1.37 (d, *J*=6.5 Hz, 3H), 1.30 (d, *J*=6.5 Hz, 3H), 1.27 (d, *J*=6.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.4, 17.7, 19.4, 40.6, 55.5, 55.6, 67.7, 69.7, 70.4, 75.2, 76.9, 121.6, 124.5, 124.7 (2 C), 125.2 (2 C), 127.2

(2 C), 127.3 (2 C), 128.6 (2 C), 129.9 (2 C), 131.3, 131.4, 140.1 (4 C), 163.2, 163.5, 165.7 (2 C), 169.1; HRMS (FAB, NaI matrix) *m/z* 797.2000 [(M+Na)$^+$; calcd for $C_{36}H_{36}O_{12}F_6Na$: 797.2009].

4.1.3. (5*R*,6*S*,12*S*,16*S*)-(3*E*,9*E*)-5-Hydroxy-6,12,16-trimethyl-1,7,13-trioxacyclohexa-deca-3,9-diene-2,8,11,14-tetraone [macrosphelide B (+)-2]. A mixture of (+)-**1** (10.9 mg, 32 μmol), pyridinium dichromate (72 mg, 192 μmol) in CH_2Cl_2 (3 mL) was stirred at room temperature for 3 h, diluted with ether (3 mL), filtered and concentrated in vacuo. Preparative TLC (250 μm×20×20 cm; 9:1 chloroform/methanol) gave a mixture of monoketones (+)-**2** and 5-ketone (**6**) (5.1 mg) as a colorless oil, diketone (**7**) (1.7 mg, 16% yield) as a colorless oil, and recovered **1** (4.9 mg, 45% yield) as a white solid. Further purification by HPLC (Senshu Pak, PEGASIL ODS, 20×25 cm; 35% CH_3CN in H_2O, 0.8 mL/min) afforded pure (+)-**2** (2.3 mg, 21% yield) and **6** (1.9 mg, 18% yield) as colorless oils. (+)-**2**: $[\alpha]_D^{24}=+10.0$ (*c* 0.39, MeOH) [lit. +4.1 (*c* 0.99, MeOH); IR (KBr) 3437 (s), 1736 (s), 1267 (m), 1190 (m), 1130 (m), 1055 (m) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (d, *J*=15.8 Hz, 1H), 6.92 (dd, *J*=15.8, 3.7 Hz, 1H), 6.74 (d, *J*=15.8 Hz, 1H), 6.08 (dd, *J*=15.8, 2.1 Hz, 1H), 5.46 (m, 1H), 5.07 (m, 1H), 5.05 (m, 1H), 4.32 (br s, 1H), 2.82 (dd, *J*=16.3, 11.0 Hz, 1H), 2.62 (dd, *J*=16.3, 2.3 Hz, 1H), 1.50 (d, *J*=6.9 Hz, 3H), 1.43 (d, *J*=6.9 Hz, 3H), 1.36 (d, *J*=6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.1, 17.9, 19.8, 40.6, 67.7, 74.8, 75.8, 76.8, 122.6, 132.1, 132.5, 144.2, 164.1, 165.4, 170.3, 196.2; HRMS (FAB, m-NBA matrix) *m/z* 341.1212 [(M+H)$^+$; calcd for $C_{16}H_{21}O_8$: 341.1236].

Compound **6**. ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.25 (d, *J*=15.8 Hz, 1H), 7.02 (dd, *J*=15.8, 5.3 Hz, 1H), 6.65 (d, *J*=15.8 Hz, 1H), 6.19 (dd, *J*=15.8, 1.3 Hz, 1H), 5.35 (m, 1H), 5.20 (q, *J*=6.9 Hz, 1H), 4.90 (m, 1H), 4.19 (m, 1H), 2.71 (dd, *J*=16.2, 10.6 Hz, 1H), 2.57 (dd, *J*=16.2, 2.6 Hz, 1H), 1.51 (d, *J*=7.3 Hz, 3H), 1.39 (d, *J*=6.3 Hz, 3H), 1.36 (d, *J*=6.3, 3H); HRMS (FAB, m-NBA matrix) *m/z* 341.1231 [(M+H)$^+$; calcd for $C_{16}H_{21}O_8$: 341.1236].

Compound **7** ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.29 (d, *J*=16.2 Hz, 1H), 6.78 (d, *J*=15.8 Hz, 1H), 7.09 (d, *J*=15.8 Hz, 1H), 6.56 (d, *J*=16.2 Hz, 1H), 5.20 (q, *J*=7.3 Hz, 1H), 5.12 (q, *J*=6.9 Hz, 1H), 5.31 (m, 1H), 2.84 (dd, *J*=16.5, 11.3 Hz, 1H), 2.61 (dd, *J*=16.5, 2.1 Hz, 1H), 1.51 (d, *J*=7.3 Hz, 3H), 1.39 (d, *J*=6.9 Hz, 3H), 1.34 (d, *J*=6.3 Hz, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 15.9, 17.0, 19.5, 40.6, 69.2, 75.5, 76.3, 132.0, 132.2, 132.3, 134.3, 163.1, 163.5, 170.1, 195.6, 197.4; HRMS (FAB, m-NBA matrix) *m/z* 339.1075 [(M+H)$^+$; calcd for $C_{16}H_{19}O_8$: 339.1080].

4.1.6. 3.1.4. (4*S*, 5*S*)-(*E*)-4,5-Dihydroxyl-2-hexenoic acid *t*-butyl ester (−)-14. *Reaction of asymmetric dihydroxylation with AD-mix-α*. To a well-stirred solution of AD-mix-α (488 mg) in 3.2 mL of *t*-BuOH/H_2O (1/1 v/v) was added 30.4 mg (0.32 mmol) of methansulfonamide at ambient temperature. The clear yellow solution was cooled to 0 °C and added 53.8 mg (0.32 mmol) of unsaturated ester **13**. The solution was stirred vigorously at 0 °C. After stirring for 27 h, the reaction was quenched with 500 mg of solid Na_2SO_3, warmed to ambient temperature and stirred for 50 min. The mixture was extracted with 3×8 mL of CH_2Cl_2, dried over Na_2SO_4, filtered and concentrated. Flash chromatography (50% EtOAc/hexane) provided 39.9 mg of diol (−)-**14** (0.20 mmol, 62%) as a colorless oil.

Reaction of asymmetric dihydroxylation with Corey AD-ligand-α non MeI salt (**15**). To a well-stirred solution of 588 mg (1.8 mmol) of potassium hexacyanoferrate, 247 mg (1.8 mmol) of potassium carbonate, 2.2 mg (6.0 μmol) of potassium osmate(VI) dihydrate and 5.9 mg (6.0 μmol) of Corey AD-ligand-α non MeI salt **15** in 3.2 mL of *t*-BuOH/H_2O (1/1 v/v) was added 57 mg (0.6 mmol) of methansulfonamide at ambient temperature. The clear yellow solution was cooled to 0 °C and added 100 mg (0.6 mmol) of unsaturated ester **13**. The solution was stirred vigorously at 0 °C. After stirring for 18.5 h, the reaction was quenched with 1.0 g of solid Na_2SO_3, warmed to ambient temperature and stirred for 50 min. The mixture was extracted with 3×20 mL of $CHCl_3$, dried over Na_2SO_4, filtered and concentrated. Flash chromatography (50% EtOAc/hexane) provided 86 mg of diol (−)-**14** (0.42 mmol, 71%) as a colorless oil: R_f 0.18 (1:1 hexane/EtOAc); $[\alpha]_D^{20}=-10.3$ (*c* 1.04, $CHCl_3$); IR (KBr) 3435 (s), 1716 (s), 1369 (m), 1157 (s) cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 6.81 (dd, *J*=15.8, 5.3 Hz, 1H), 6.06 (dd, *J*=15.8, 1.7 Hz, 1H), 4.04 (m, 1H), 3.73 (m, 1H), 2.34 (d, *J*=4.6 Hz, 1H), 2.11 (d, *J*=4.0 Hz, 1H), 1.49 (s, 9H), 1.25 (d, *J*=6.3 Hz, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 19.1, 28.1, 70.2, 75.7, 80.8, 124.3, 145.2, 165.7; HRMS (FAB, NBA matrix) *m/z* 203.1273 [(M+H)$^+$; calcd for $C_{10}H_{19}O_4$: 203.1283]. Anal. Calcd for $C_{10}H_{19}O_4$: C, 59.39; H, 8.97. Found: C, 59.12; H, 8.88.

4.1.7. (4*R*,5*R*)-(*E*)-4,5-Dihydroxyl-2-hexenoic acid *t*-butyl ester (+)-14. Following the procedure described above for the preparation of (−)-**14**, dihydroxylation of 100 mg (0.60 mmol) of **13** with Corey AD-ligand-β non MeI salt (**17**) afforded 89.3 mg of (+)-**14** (74%): $[\alpha]_D^{29}=+12.4$ (*c* 1.56, $CHCl_3$); HRMS (FAB, NBA matrix) *m/z* 203.1310 [(M+H)$^+$; calcd for $C_{10}H_{19}O_4$: 203.1283].

4.1.8. (4*S*,5*S*)-(*E*)-5-(*t*-Butyldimethylsiloxy)-4-hydroxyl-2-hexenoic acid *t*-butyl ester (+)-19. To a solution of 1.12 g (5.53 mmol) of diol (−)-**14**, 34 mg (0.28 mmol) of 4-dimethylaminopyridine and 1.84 g (12.2 mmol) of *tert*-butyldimethylsilyl chloride in 11.0 mL of CH_2Cl_2 at 0 °C was added 1.85 mL (13.3 mmol) of triethylamine. The reaction mixture was gradually warmed to ambient temperature for 5 h. After 7 h 15 min, the solution was quenched with 5 mL of H_2O. This mixture was extracted with 3×30 mL of $CHCl_3$, washed with 20 mL of saturated NaCl aqueous solution, dried over Na_2SO_4, filtered, and concentrated. Chromatography (1.6% EtOAc/hexane) provided 986 mg of (+)-**19** (3.12 mmol, 78% based on recovered (−)-**14**, 186 mg of 4-silyl ether (+)-**20** (0.59 mmol, 11%) and 316 mg of starting material (1.56 mmol, 30%). (+)-**19**: R_f 0.58 (3:1 hexane/EtOAc); $[\alpha]_D^{24}=+6.0$ (*c* 1.81, $CHCl_3$); IR (KBr) 3435 (s), 2978 (m), 2931 (m), 2858 (m), 1716 (s), 1369 (m), 1257 (m), 1157 (s), 1097 (m) cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 6.79 (dd, *J*=15.8, 4.6 Hz, 1H), 6.02 (dd, *J*=15.8, 1.7 Hz, 1H), 3.99 (m, 1H), 3.76 (m, 1H), 2.56 (d, *J*=5.9 Hz, 1H), 1.48 (s, 9H), 1.21 (d, *J*=6.3 Hz, 3H), 0.89 (s, 9H), 0.08 (s, 3H), 0.06 (s,

3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ −4.9, −4.4, 18.0, 20.1, 25.7, 28.1, 71.1, 75.2, 80.3, 123.8, 146.0, 165.6; HRMS (FAB, NaI matrix) *m/z* 339.1978 [$(M+Na)^+$; calcd for $C_{16}H_{32}O_4SiNa$: 339.1968]. Anal. Calcd for $C_{10}H_{32}O_4Si$: C, 60.72; H, 10.19. Found: C, 60.88; H, 10.06.

4.1.9. (4*R*,5*R*)-(*E*)-5-(*t*-Butyldimethylsiloxy)-4-hydroxyl-2-hexenoic acid *t*-butyl ester (−)-19. Following the procedure described above for the preparation of (+)-**19**, silylation of 78 mg (0.39 mmol) of (+)-**14** afforded 89.3 mg of (−)-**19** (33%, 69% based on recovered (+)-**14**): $[\alpha]_D^{27}=-8.2$ (*c* 0.85, $CHCl_3$); HRMS (FAB, NaI matrix) *m/z* 339.1968 [$(M+Na)^+$; calcd for $C_{16}H_{32}O_4SiNa$: 339.1968]. Anal. Calcd for $C_{10}H_{32}O_4Si$: C, 60.72; H, 10.19. Found: C, 60.38; H, 10.11.

4.1.10. (4*R*,5*S*)-(*E*)-5-(*t*-Butyldimethylsiloxy)-4-hydroxyl-2-hexenoic acid *t*-butyl ester (+)-19. At room temperature, to a solution of 836 mg (2.65 mmol) of (+)-**21** and 1.39 g (5.29 mmol) of triphenylphosphine in 5.0 mL of benzene was added a solution of 0.83 mL (5.29 mmol) of diethyl azodicarboxylate and 0.21 mL (5.56 mmol) of formic acid in 8.3 mL of benzene over 45 min. The reaction mixture was stirred for 3.5 h then quenched with 10 mL of H_2O. This mixture was extracted with 3×20 mL of $CHCl_3$, washed with 5.0 mL of saturated $NaHCO_3$ aqueous solution, dried over Na_2SO_4, filtered, and concentrated. This crude product was used directly in the subsequent reaction. To this product was added 13.0 mL of diluted NH_4OH solution (pH 10.0–10.2) in $MeOH\cdot H_2O$ (3:1), the solution was stirred for 1.5 h at ambient temperature, and then quenched with 40 mL of saturated NH_4Cl aqueous solution. This mixture was extracted with 3×50 mL of $CHCl_3$, dried over Na_2SO_4, filtered, and concentrated. Chromatography (5% EtOAc/hexane) provided 697 mg of (+)-**21** (2.21 mmol, 83%) as a colorless oil: R_f 0.42 (4:1 hexane/EtOAc); $[\alpha]_D^{25}=+17.9$ (*c* 2.58, $CHCl_3$); IR (KBr) 3435 (s), 2931 (m), 2858 (m), 1716 (s), 1369 (m), 1257 (m), 1157 (s), 1097 (m) cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 6.77 (dd, *J*=15.8, 5.3 Hz, 1H), 6.00 (dd, *J*=15.8, 1.7 Hz, 1H), 4.16 (m, 1H), 3.90 (m, 1H), 2.36 (d, *J*=3.6 Hz, 1H), 1.48 (s, 9H), 1.09 (d, *J*=6.3 Hz, 3H), 0.89 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ −5.0, −4.5, 17.8, 18.0, 25.7, 28.1, 70.8, 74.9, 80.4, 123.6, 144.4, 165.6; HRMS (FAB, NaI matrix) *m/z* 339.1968 [$(M+Na)^+$; calcd for $C_{16}H_{32}O_4SiNa$: 339.1968]. Anal. Calcd for $C_{16}H_{32}O_4Si$: C, 60.72; H, 10.19. Found: C, 60.88; H, 10.23.

4.1.11. (4*S*,5*R*)-(*E*)-5-(*t*-Butyldimethylsiloxy)-4-hydroxyl-2-hexenoic acid *t*-butyl ester (−)-21. Following the procedure described above for the preparation of (+)-**21**, inversion of 777 mg of (−)-**19** afforded 89.3 mg of (−)-**21** (73%): $[\alpha]_D^{28}=-20.0$ (*c* 0.70, $CHCl_3$); HRMS (FAB, NaI matrix) *m/z* 339.1970 [$(M+Na)^+$; calcd for $C_{16}H_{32}O_4SiNa$: 339.1968]. Anal. Calcd for $C_{16}H_{32}O_4Si$: C, 60.72; H, 10.19. Found: C, 60.40; H, 10.22.

4.1.12. (4*R*,5*S*)-(*E*)-5-(*t*-Butyldimethylsiloxy)-4-[(*S*)-α-methoxy-α-trifluoromethylphenyl-acetoxy]-2-hexenoic acid *t*-butyl ester (−)-MTPA-21. At room temperature a solution of (+)-**21** (6.9 mg, 0.02 mmol) in dry THF (0.4 mL) was treated with *(S)*-(−)-α-methoxy-α-(trifluoromethyl)-phenylacetic acid (31 mg, 0.13 mmol), dicyclohexylcarbodiimide (14 mg, 0.07 mmol), and 4-dimethylaminopyridine (2.7 mg, 0.02 mmol). A white precipitate formed immediately. The resultant mixture was stirred for 15 min, quenched with H_2O (1 mL), and extracted with $CHCl_3$ (3×4.0 mL). The combined extracts were dried over sodium sulfate, filtered and concentrated. To remove dicyclohexylurea the white solid was taken up in ether (1 mL) and filtered, the cake was washed with ether (1 mL), and the combined ethereal solutions were concentrated. Preparative TLC (250 μm×20×20 cm; 6:1 hexanes/EtOAc) gave (−)-MTPA-**21** (11.3 mg, 100% yield) as a colorless oil: $[\alpha]_D^{27}=-20.5$ (*c* 1.00, $CHCl_3$); IR (KBr) 2858 (m), 1755 (s), 1720 (s), 1662 (w), 1254 (s), 779 (m), 719 (m) cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.46 (m, 5H), 6.74 (dd, *J*=15.8, 6.3 Hz, 1H), 5.91 (dd, *J*=15.8, 1.3 Hz, 1H), 5.47 (m, 1H), 3.88 (m, 1H), 3.57 (s, 3H), 1.48 (s, 9H), 1.04 (d, *J*=6.3 Hz, 3H), 0.84 (s, 9H), −0.01, −0.04 (s, each 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ −5.2, −4.7, 17.9, 19.2, 25.6, 28.1, 55.6, 69.5, 78.7, 78.7, 80.4, 126.6, 127.5, 128.4, 129.6, 132.1, 139.9, 164.8, 165.7; HRMS (FAB, m-NBA+NaI matrix) *m/z* 555.2367 [$(M+Na)^+$; calcd for $C_{26}H_{39}O_6F_3SiNa$: 555.2366].

4.1.13. (4*R*,5*S*)-(*E*)-5-(*t*-Butyldimethylsiloxy)-4-(*R*)-α-methoxy-α-trifluoromethylphenyl-acetoxy-2-hexenoic acid *t*-butyl ester (+)-MTPA-21. At room temperature a solution of (+)-**21** (8.9 mg, 0.03 mmol) in dry THF (0.6 mL) was treated with *(R)*-(+)-α-methoxy-α-(trifluoromethyl)-phenylacetic acid (40 mg, 0.17 mmol), dicyclohexylcarbodiimide (17 mg, 0.08 mmol), and 4-dimethylaminopyridine (3.4 mg, 0.03 mmol). A white precipitate formed immediately. The resultant mixture was stirred for 20 min, quenched with H_2O (1 mL), and extracted with $CHCl_3$ (3×4.0 mL). The combined extracts were dried over sodium sulfate, filtered and concentrated. To remove dicyclohexylurea the white solid was taken up in ether (1 mL) and filtered, the cake was washed with ether (1 mL), and the combined ethereal solutions were concentrated. Preparative TLC (250 μm×20×20 cm; 6:1 hexanes/EtOAc) gave (+)-MTPA-**21** (13.1 mg, 91% yield) as a colorless oil: $[\alpha]_D^{27}=+21.7$ (*c* 1.00, $CHCl_3$); IR (KBr) 2858 (m), 1755 (s), 1718 (s), 1662 (w), 1255 (s), 779 (m), 719 (m) cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.51 (m, 5H), 6.65 (dd, *J*=15.8, 5.6 Hz, 1H), 5.68 (dd, *J*=15.8, 1.7 Hz, 1H), 5.60 (m, 1H), 3.99 (m, 1H), 3.61 (s, 3H), 1.46 (s, 9H), 1.14 (d, *J*=6.3 Hz, 3H), 0.86 (s, 9H), 0.07, 0.04 (s, each 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ −5.2, −4.7, 18.0, 18.5, 25.6, 28.0, 55.7, 69.5, 78.4, 78.7, 80.8, 125.5, 127.4, 128.4, 129.6, 132.2, 139.7, 164.8, 165.7; HRMS (FAB, m-NBA+NaI matrix) *m/z* 555.2370 [$(M+Na)^+$; calcd for $C_{26}H_{39}O_6F_3SiNa$: 555.2366].

4.1.14. (4*R*,5*S*)-(*E*)-5-(*t*-Butyldimethylsiloxy)-4-methoxyethoxymethoxy-2-hexenoic acid *t*-butyl ester (−)-22. At room temperature, to a solution of 368 mg (1.16 mmol) of (+)-**21** and 2.63 mL (15.08 mmol) of *N*-ethyldiisopropylamine in 6.0 mL of CH_2Cl_2 was added 1.32 mL (11.60 mmol) of β-methoxyethoxymethyl chloride, the reaction mixture was stirred for 66 h, and then quenched with 5.0 mL of water. This mixture was extracted with 3× 20 mL of CH_2Cl_2, washed with 10 mL of saturated NaCl solution, dried over Na_2SO_4, filtered, and concentrated. Chromatography (3.3% EtOAc/hexane) provided 410.4 mg

of (−)-**22** (1.02 mmol, 87%) as a colorless oil: R_f 0.58 (30:1 $CHCl_3$/MeOH); $[\alpha]_D^{26} = -28.4$ (*c* 0.62, $CHCl_3$); IR (KBr) 3435 (s), 2956 (m), 2931 (m), 2889 (m), 2858 (m), 1716 (s), 1369 (m), 1254 (m), 1155 (s), 1105 (s) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 6.72 (dd, $J=15.8$, 6.6 Hz, 1H), 5.90 (dd, $J=15.8$, 1.0 Hz, 1H), 4.72 (s, 2H), 4.02 (dd, $J=11.2$, 6.9 Hz, 1H), 3.80 (m, 1H), 3.77 (m, 1H), 3.63 (m, 1H), 3.54 (m, 2H), 3.38 (s, 3H), 1.47 (s, 9H), 1.17 (d, $J=5.9$ Hz, 3H), 0.86 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ −4.8, −4.6, 18.0, 20.0, 25.8, 27.9, 59.0, 67.1, 70.6, 71.6, 79.9, 80.3, 93.8, 125.4, 144.3, 165.3; HRMS (FAB, NBA matrix) *m/z* 405.2658 $[(M+H)^+$; calcd for $C_{20}H_{41}O_6Si$: 405.2672]. Anal. Calcd for $C_{20}H_{41}O_6Si$: C, 59.37; H, 9.96. Found: C, 59.34; H, 10.00.

4.1.15. (4*S*,5*R*)-(*E*)-5-(*t*-Butyldimethylsiloxy)-4-methoxyethoxymethoxy-2-hexenoic acid *t*-butyl ester (+)-22. Following the procedure described above for the preparation of (−)-**22**, MEM protection of 719 mg (2.3 mmol) of (−)-**21** afforded 884 mg of (+)-**22** (96%): $[\alpha]_D^{28} = +29.3$ (*c* 0.15, $CHCl_3$); HRMS (FAB, NaI matrix) *m/z* 427.2488 $[(M+Na)^+$; calcd for $C_{20}H_{40}O_6Si$ Na: 427.2492]. Anal. Calcd for $C_{20}H_{40}O_6Si$: C, 59.37; H, 9.96. Found: C, 59.60; H, 9.86.

4.1.16. (4*R*,5*S*)-(*E*)-5-(*t*-Butyldimethylsililoxy)-4-methoxyethoxymethoxy-2-hexenoic acid (−)-23. At room temperature, 192 mg (0.48 mmol) of (−)-**22** was dissolved in 4.8 mL of 0.2 N NaOH in MeOH·THF·H_2O (3:1:1) solution, the mixture was stirred for 6 days, and then quenched with 5.0 mL of 0.2 N HCl aqueous solutin became neutral solution. This mixture was extracted with 4×15 mL of $CHCl_3$, dried over Na_2SO_4, and concentrated. Chromatography (5–9% MeOH/$CHCl_3$) provided 154 mg of (−)-**23** (0.44 mmol, 94%) as a colorless oil: R_f 0.35 (10:1 $CHCl_3$/MeOH); $[\alpha]_D^{22} = -30.0$ (*c* 0.62, $CHCl_3$); IR (KBr) 3435 (s), 2954 (m), 2931 (m), 2891 (m), 2858 (m), 1722 (m), 1703 (s), 1255 (m), 1111 (s), 1043 (s) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 6.98 (dd, $J=15.8$, 6.3 Hz, 1H), 6.02 (dd, $J=15.8$, 1.0 Hz, 1H), 4.74 (dd, $J=10.9$, 6.9, 2H), 4.10 (m, 1H), 3.84 (m, 1H), 3.76 (m, 1H), 3.66 (m, 1H), 3.54 (m, 2H), 3.38 (s, 3H), 1.17 (d, $J=6.3$ Hz, 3H), 0.86 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ −4.8, −4.6, 18.0, 19.9, 25.7, 59.0, 67.3, 70.5, 71.6, 79.9, 94.2, 122.4, 148.5, 170.8; HRMS (FAB, NaI matrix) *m/z* 371.1861 $[(M+Na)^+$; calcd for $C_{16}H_{32}O_6SiNa$: 371.1866]. Anal. Calcd for $C_{16}H_{32}O_6Si$: C, 55.14; H, 9.25. Found: C, 54.86; H, 9.18.

4.1.17. (4*S*,5*R*)-(*E*)-5-(*t*-Butyldimethylsililoxy)-4-methoxyethoxymethoxy-2-hexenoic acid (+)-23. Following the procedure described above for the preparation of (−)-**23**, hydrolysis of 27.1 mg (0.07 mmol) of (+)-**22** afforded 19.3 mg of (+)-**23** (85%): $[\alpha]_D^{28} = +33.2$ (*c* 0.62, $CHCl_3$); HRMS (FAB, NBA matrix) *m/z* 347.1888 $[(M-H)^-$; calcd for $C_{16}H_{31}O_6Si$: 347.1888]. Anal. Calcd for $C_{16}H_{31}O_6Si$: C, 55.14; H, 9.25. Found: C, 54.76; H, 9.31.

4.1.18. (4*R*,5*S*)-(*E*)-5-Hydroxy-4-methoxyethoxymethoxy-2-hexenoic acid *t*-butyl ester (−)-24. At room temperature, to a solution of 186 mg (0.46 mmol) of silyl ether (−)-**22** in 0.9 mL THF was added 1.4 mL of 1.0 M tetra-*n*-butylammonium fluorid in THF, the solution was stirred for 1 h, and then quenched with 2 mL of H_2O. This mixture was extracted with 3×20 mL of $CHCl_3$, dried over Na_2SO_4, filtered, and concentrated. Chromatography (50% EtOAc/hexane) provided 133 mg of (−)-**24** (0.46 mmol, 100%) as a colorless oil: R_f 0.20 (1:1 hexane/EtOAc); $[\alpha]_D^{27} = -51.3$ (*c* 1.01, $CHCl_3$); IR (KBr) 3435 (s), 2978 (m), 2933 (m), 2891 (m), 1716 (s), 1367 (m), 1308 (m), 1254 (m), 1155 (s), 1039 (m) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 6.73 (dd, $J=15.8$, 6.3 Hz, 1H), 5.96 (dd, $J=15.8$, 1.3 Hz, 1H), 4.75 (dd, $J=15.5$, 6.9 Hz, 2H), 4.21 (m, 1H), 3.93 (m, 1H), 3.86 (m, 1H), 3.67 (m, 1H), 3.55 (m, 2H), 3.39 (s, 3H), 1.48 (s, 9H), 1.14 (d, $J=6.3$ Hz, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 17.5, 28.1, 59.0, 67.5, 69.0, 71.6, 80.7, 80.8, 94.4, 125.8, 142.3, 165.2; HRMS (FAB, NaI matrix) *m/z* 313.1623 $[(M+Na)^+$; calcd for $C_{14}H_{26}O_6Na$: 313.1627]. Anal. Calcd for $C_{14}H_{26}O_6$: C, 57.91; H, 9.03. Found: C, 57.59; H, 8.93.

4.1.19. (4*S*,5*R*)-(*E*)-5-hydroxy-4-methoxyethoxymethoxy-2-hexenoic acid *t*-butyl ester (+)-24. Following the procedure described above for the preparation of (−)-**24**, desilylation of 437 mg (1.1 mmol) of (+)-**22** afforded 306 mg of (+)-**24** (98%): $[\alpha]_D^{31} = +63.9$ (*c* 0.51, $CHCl_3$); HRMS (FAB, NaI matrix) *m/z* 313.1630 $[(M+Na)^+$; calcd for $C_{14}H_{26}O_6Na$: 313.1627]. Anal. Calcd for $C_{14}H_{26}O_6$: C, 57.91; H, 9.03. Found: C, 57.65; H, 9.06.

4.1.20. (4*S*,5*S*,10*R*,11*S*)-(2*E*,8*E*)-11-(*tert*-Butyldimethylsiloxy)-4,10-bis(2-methoxy-ethoxymethoxy)-5-methyl-6-oxa-1,7-dioxo-2,8-dodecadienoic acid *tert*-butyl ester (−)-25. At room temperature, to a solution of 300 mg (0.86 mmol) of (−)-**23**, 277 mg (0.78 mmol) of (−)-**24**, 23 mg (0.19 mmol) of 4-dimethylaminopyridine and 22 mg (0.093 mmol) of camphorsulfonic acid in 10.0 mL of CH_2Cl_2 was added 243 mg (1.18 mmol) of dicyclohexylcarbodiimide, the solution was stirred for 18 h 30 min, and then quenched with 10.0 mL of H_2O. This mixture was extracted with 3×10 mL of $CHCl_3$, washed with 10.0 mL of H_2O, dried over Na_2SO_4, filtered, and concentrated. Chromatography (17–25% EtOAc/hexane) provided 447 mg of (−)-**25** (0.71 mmol, 92%) as a colorless oil: R_f 0.44 (1:1 hexane/EtOAc); $[\alpha]_D^{23} = -40.4$ (*c* 0.50, $CHCl_3$); IR (KBr) 3435 (s), 2954 (w), 2931 (w), 2889 (w), 1718 (m), 1637 (w), 1255 (w), 1157 (m), 1038 (m) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 6.82 (dd, $J=15.8$, 6.6 Hz, 1H), 6.71 (dd, $J=15.8$, 6.3 Hz, 1H), 5.98 (dd, $J=15.8$, 1.0 Hz, 1H), 5.97 (dd, $J=15.8$, 1.3 Hz, 1H), 5.09 (m, 1H), 4.72 (dd, $J=11.2$, 6.9 Hz, 2H), 4.71 (dd, $J=11.2$, 6.9 Hz, 2H), 4.34 (m, 1H), 4.05 (m, 1H), 3.74 (m, 1H), 3.65 (m, 2H), 3.60 (m, 2H), 3.52 (m, 4H), 3.37 (s, 3H), 3.36 (s, 3H), 1.47 (s, 9H), 1.22 (d, $J=6.3$ Hz, 3H), 1.15 (d, $J=6.4$ Hz, 3H), 0.85 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ −4.8, −4.7, 15.0, 18.0, 19.8, 25.7, 28.0, 59.0, 59.0, 67.1, 67.1, 70.4, 70.5, 71.4, 71.6, 71.6, 79.8, 80.7, 93.7, 93.9, 123.3, 126.2, 141.7, 146.1, 165.0, 165.2; HRMS (FAB, NaI matrix) *m/z* 643.3488 $[(M+Na)^+$; calcd for $C_{30}H_{56}O_{11}SiNa$: 643.3490]. Anal. Calcd for $C_{30}H_{56}O_{11}Si$: C, 58.04; H, 9.09. Found: C, 57.99; H, 9.12.

4.1.21. (4*R*,5*R*,10*S*,11*R*)-(2*E*,8*E*)-11-(*tert*-Butyldimethylsiloxy)-4,10-bis(2-methoxy-ethoxymethoxy)-5-methyl-6-oxa-1,7-dioxo-2,8-dodecadienoic acid *tert*-butyl ester (+)-25. Following the procedure described above for the preparation of (−)-**25**, condensation of 169 mg (0.5 mmol)

of (+)-**23** and 169 mg (0.6 mmol) of (+)-**24** afforded 186 mg of (+)-**25** (62%): $[\alpha]_D^{28}=+48.5$ (*c* 0.85, $CHCl_3$); HRMS (FAB, NaI matrix) *m/z* 643.3515 $[(M+Na)^+$; calcd for $C_{30}H_{56}O_{11}SiNa$: 643.3490]. Anal. Calcd for $C_{30}H_{56}O_{11}Si$: C, 58.04; H, 9.09. Found: C, 57.94; H, 8.96.

4.1.22. (4*S*,5*S*,10*R*,11*S*)-(2*E*,8*E*)-11-Hydroxy-4,10-bis(2-methoxyethoxymethoxy)-5-methyl-6-oxa-1,7-dioxo-2,8-dodecadienoic acid *tert*-butyl ester (−)-26. 392 mg (0.63 mmol) of (−)-**25** was dissolved in 6.3 mL of TFA·THF·H_2O (2:8:1) and the solution was stirred for 22 h at ambient temperature, and then quenched with 15.0 mL of saturated $NaHCO_3$ aqueous solution. This solution was then extracted with 3×40 mL of $CHCl_3$, washed with 50 mL of saturated NaCl aqueous solution, dried over Na_2SO_4, filtered, and concentrated. Chromatography (6% MeOH/$CHCl_3$) provided 105 mg of (−)-**26** (0.21 mmol, 83%) as a colorless oil: R_f 0.54 (15:1 $CHCl_3$/MeOH); $[\alpha]_D^{27}=-58.5$ (*c* 0.66, $CHCl_3$); IR (KBr) 3440 (s), 2980 (w), 2933 (w), 2893 (w), 1716 (s), 1659 (w), 1369 (m), 1296 (m), 1255 (m), 1157 (s), 1039 (s) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 6.86 (dd, *J*=15.8, 5.9 Hz, 1H), 6.71 (dd, *J*=15.8, 6.3 Hz, 1H), 6.04 (dd, *J*=15.8, 1.3 Hz, 1H), 5.97 (dd, *J*=15.8, 1.3 Hz, 1H), 5.09 (m, 1H), 4.75 (dd, *J*=20.1, 7.3 Hz, 2H), 4.72 (s, 2H), 4.36 (m, 1H), 4.22 (m, 1H), 3.93 (m, 1H), 3.82 (m, 2H), 3.65 (m, 2H), 3.53 (m, 4H), 3.38 (s, 3H), 3.37 (s, 3H), 2.93 (d, *J*=5.9 Hz, 1H), 1.48 (s, 9H), 1.24 (d, *J*=6.6 Hz, 3H), 1.14 (d, *J*=6.6 Hz, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 15.0, 17.7, 28.1, 59.0, 59.0, 67.2, 67.2, 67.5, 67.5, 69.0, 71.6, 71.6, 80.8, 80.9, 93.7, 94.5, 123.6, 126.2, 141.7, 144.3, 165.0, 165.0; HRMS (FAB, NaI matrix) *m/z* 529.2632 $[(M+Na)^+$; calcd for $C_{24}H_{42}O_{11}Na$: 529.2625]. Anal. Calcd for $C_{24}H_{42}O_{11}$: C, 56.90; H, 8.36. Found: C, 56.53; H, 8.39.

4.1.23. (4*R*,5*R*,10*S*,11*R*)-(2*E*,8*E*)-11-Hydroxy-4,10-bis(2-methoxyethoxymethoxy)-5-methyl-6-oxa-1,7-dioxo-2,8-dodecadienoic acid *tert*-butyl ester (+)-26. Following the procedure described above for the preparation of (−)-**26**, desilylation of 178 mg (0.3 mmol) of (+)-**25** afforded 142 mg of (+)-**26** (97%): $[\alpha]_D^{28}=+76.8$ (*c* 0.87, $CHCl_3$); HRMS (FAB, NaI matrix) *m/z* 529.2616 $[(M+Na)^+$; calcd for $C_{24}H_{42}O_{11}Na$: 529.2625]. Anal. Calcd for $C_{24}H_{42}O_{11}$: C, 56.90; H, 8.36. Found: C, 56.76; H, 8.44.

4.1.24. (4*R*,5*S*,10*R*,11*S*,15*S*)-(2*E*,8*E*)-15-(*tert*-Butyldimethylsiloxy)-4,10-bis(2-methoxyethoxy-methoxy)-5,11-dimethyl-6,12-dioxa-1,7,13-trioxo-2,8-hexadeca-dienoic acid *tert*-butyl ester (−)-28. At room temperature, to a solution of 89.7 mg (0.177 mmol) of (−)-**26**, 50.2 mg (0.230 mmol) of (*S*)-3-*tert*-butyldimethylsiloxybutylic acid (+)-**27**, 5.2 mg (0.043 mmol) of 4-dimethylaminopyridine and 4.9 mg (0.021 mmol) of camphorsulfonic acid in 2.0 mL of CH_2Cl_2 was added 54.9 mg (0.266 mmol) of dicyclohexylcarbodiimide, the solution was stirred for 14 h, and then quenched with 1.5 mL of H_2O. This mixture was extracted with 3×10 mL of $CHCl_3$, washed with 8 mL of saturated NaCl solution, dried over Na_2SO_4, filtered, and concentrated. Chromatography (50% EtOAc–hexane) provided 119.6 mg of (−)-**28** (0.169 mmol, 96%) as a colorless oil: R_f 0.47 (1:1 hexane/EtOAc); $[\alpha]_D^{28}=-28.3$ (*c* 0.48, $CHCl_3$); IR (KBr) 3435 (s), 2931 (w), 2895 (w), 1718 (s), 1654 (w), 1369 (w), 1304 (m), 1255 (m), 1155 (s), 1088 (m), 1065 (m), 1039 (s) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 6.82 (dd, *J*=15.8, 6.3 Hz, 1H), 6.71 (dd, *J*=15.8, 6.6 Hz, 1H), 6.05 (dd, *J*=15.8, 1.3 Hz, 1H), 5.99 (dd, *J*=15.8, 1.3 Hz, 1H), 5.10 (m, 1H), 5.04 (m, 1H), 4.74 (s, 2H), 4.72 (dd, *J*=17.5, 6.9 Hz, 2H), 4.36 (m, 2H), 4.24 (m, 1H), 3.77 (m, 2H), 3.63 (m, 2H), 3.53 (m, 4H), 3.37 (s, 6H), 2.48 (dd, *J*=14.5, 6.6 Hz, 1H), 2.36 (dd, *J*=14.5, 6.3 Hz, 1H), 1.48 (s, 9H), 1.24 (d, *J*=6.6 Hz, 3H), 1.20 (d, *J*=6.6 Hz, 3H), 1.18 (d, *J*=5.9 Hz, 3H), 0.85 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ −4.9, −4.5, 14.9, 15.0, 18.0, 23.7, 25.8, 28.1, 44.9, 59.0, 59.0, 65.6, 65.6, 67.2, 67.2, 71.1, 71.6, 71.6, 71.7, 80.8, 80.8, 93.7, 93.8, 124.0, 126.3, 141.7, 143.8, 165.0, 165.0, 170.7; HRMS (FAB, NaI matrix) *m/z* 729.3853 $[(M+Na)^+$; calcd for $C_{34}H_{62}O_{13}SiNa$: 729.3857]. Anal. Calcd for $C_{34}H_{62}O_{13}Si$: C, 57.77; H, 8.84. Found: C, 57.62; H, 8.80.

4.1.25. (4*S*,5*R*,10*S*,11*R*,15*R*)-(2*E*,8*E*)-15-(*tert*-Butyldimethylsiloxy)-4,10-bis(2-methoxyethoxy-methoxy)-5,11-dimethyl-6,12-dioxa-1,7,13-trioxo-2,8-hexadeca-dienoic acid *tert*-butyl ester (+)-28. Following the procedure described above for the preparation of (−)-**28**, condensation of 57.3 mg (0.1 mmol) of (+)-**26** and 29.6 mg (0.1 mmol) of (−)-**27** afforded 61.7 mg of (+)-**28** (77%): $[\alpha]_D^{28}=+42.9$ (*c* 0.55, $CHCl_3$); HRMS (FAB, NaI matrix) *m/z* 729.3856 $[(M+Na)^+$; calcd for $C_{34}H_{62}O_{13}SiNa$: 729.3857]. Anal. Calcd for $C_{34}H_{62}O_{13}Si$: C, 57.77; H, 8.84. Found: C, 57.58; H, 8.97.

4.1.26. (4*R*,5*S*,10*R*,11*S*,15*S*)-(2*E*,8*E*)-15-Hydroxy-4,10-bis(2-methoxyethoxymethoxy)-5,11-dimethyl-6,12-dioxa-1,7,13-trioxo-2,8-hexadecadienoic acid (−)-29. At 0 °C, to a solution of 12.7 mg (0.018 mmol) of (−)-**28** in 0.82 mL of thioanisole and 0.16 mL of CH_2Cl_2 was added 0.82 mL of trifluoroacetic acid with stirring. After stirring for 35 min, the reaction mixture was warmed to room temperature, and the solvent was removed in vacuo. Chromatography (9% MeOH/$CHCl_3$) provided 6.2 mg of (−)-**29** (0.012 mmol, 64%) as a colorless oil: R_f 0.18 (10:1 $CHCl_3$/MeOH); $[\alpha]_D^{24}=-49.8$ (*c* 0.35, $CHCl_3$); IR (KBr) 3437 (s), 1718 (s), 1655 (w), 1304 (m), 1180 (m), 1065 (m), 1039 (s) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 6.92 (dd, *J*=15.8, 6.3 Hz, 1H), 6.82 (dd, *J*=15.8, 6.3 Hz, 1H), 6.09 (dd, *J*=15.8, 1.3 Hz, 1H), 6.05 (dd, *J*=15.8, 1.3 Hz, 1H), 5.11 (m, 2H), 4.75 (dd, *J*=15.5, 6.9 Hz, 2H), 4.73 (dd, *J*=15.5, 6.9 Hz, 2H), 4.38 (m, 1H), 4.32 (m, 1H), 4.20 (m, 1H), 3.79 (m, 2H), 3.66 (m, 2H), 3.53 (m, 4H), 3.39 (s, 3H), 3.38 (s, 3H), 2.46 (d, *J*=5.6 Hz, 2H), 1.28 (d, *J*=6.3 Hz, 3H), 1.24 (d, *J*=6.3 Hz, 6H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 15.2, 15.3, 22.5, 43.2, 59.0, 59.0, 64.4, 64.4, 67.3, 67.3, 71.4, 71.4, 71.5, 71.5, 71.5, 93.7, 93.9, 123.7, 124.2, 143.6, 145.3, 164.8, 169.7, 172.0; HRMS (FAB, NaI matrix) *m/z* 559.2346 $[(M+Na)^+$; calcd for $C_{24}H_{40}O_{13}Na$: 559.2367]. Anal. Calcd for $C_{24}H_{40}O_{13}$: C, 53.72; H, 7.51. Found: C, 53.80; H, 7.86.

4.1.27. (4*S*,5*R*,10*S*,11*R*,15*R*)-(2*E*,8*E*)-15-Hydroxy-4,10-bis(2-methoxyethoxymethoxy)-5,11-dimethyl-6,12-dioxa-1,7,13-trioxo-2,8-hexadecadienoic acid (+)-29. Following the procedure described above for the preparation of (−)-**29**, deprotection of 31.3 mg (0.04 mmol) of (+)-**28** afforded 8.9 mg of (+)-**29** (38%): $[\alpha]_D^{29}=+57.8$ (*c*

0.18, $CHCl_3$); HRMS (FAB, NaI matrix) *m/z* 559.2333 [$(M+Na)^+$; calcd for $C_{24}H_{40}O_{13}Na$: 559.2367].

4.1.28. (5*R*,6*S*,11*R*,12*S*,16*S*)-(3*E*,9*E*)-5,11-Bis(2-methoxyethoxymethoxy)-6,12,16-trimethyl-1,7,13-trioxacyclohexadeca-3,9-diene-2,8,14-trione (−)-32. To a solution of 25.4 mg (0.047 mmol) of (−)-**29** was added 570 μl (0.284 mmol) of 0.5 M triethylamine in toluene and 470 μl (0.237 mmol) of 0.5 M 2,4,6-trichlorobenzoyl chloride in toluene at room temperature, and the solution was stirred for 1 h. This solution was diluted with 12.3 mL of toluene and added to a solution of 145 mg (1.18 mmol) of 4-dimethylaminopyridine in 4.7 mL of toluene at 80 °C over 2 h. The anhydride flask was washed with 6.2 mL of toluene and the washing added to the mixture over 30 mim. The reaction was then heated at 80 °C for a total of 3.5 h. After cooling, the white suspension was diluted with 16 mL of saturated $NaHCO_3$ aqueous solution became clear. The two layers were separated and aqueous layer was extracted with 3×25 mL of EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Chromatography (9% MeOH/$CHCl_3$) provided 22.3 mg of (−)-**32** (0.043 mmol, 91%) as a colorless oil: R_f 0.61 (10:1 $CHCl_3$/MeOH); $[\alpha]_D^{27}=-86.5$ (*c* 0.68, $CHCl_3$); IR (KBr) 1724 (s), 1252 (m), 1188 (s), 1138 (m), 1109 (m), 1055 (s) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 6.71 (dd, $J=15.8$, 7.3 Hz, 1H), 6.69 (dd, $J=15.8$, 6.9 Hz, 1H), 5.96 (dd, $J=15.8$, 1.0 Hz, 1H), 5.89 (dd, $J=15.8$, 1.0 Hz, 1H), 5.29 (m, 1H), 5.02 (m, 1H), 4.92 (m, 1H), 4.70 (dd, $J=8.6$, 4.6 Hz, 2H), 4.67 (s, 2H), 4.08 (m, 2H), 3.76 (m, 2H), 3.62 (m, 2H), 3.53 (m, 4H), 3.37 (s, 6H), 2.58 (dd, $J=14.8$, 3.0 Hz, 1H), 2.47 (dd, $J=14.8$, 8.3 Hz, 1H), 1.39 (d, $J=6.3$ Hz, 3H), 1.30 (d, $J=6.3$ Hz, 3H), 1.28 (d, $J=6.3$ Hz, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 18.1, 18.3, 20.0, 41.3, 59.5, 59.5, 67.7, 67.7, 67.9, 71.0, 72.0, 72.0, 72.1, 79.1, 79.1, 93.7, 94.3, 124.9, 125.0, 144.4, 145.5, 164.7, 164.8, 170.0; HRMS (FAB, NaI matrix) *m/z* 541.2272 [$(M+Na)^+$; calcd for $C_{24}H_{38}O_{12}Na$: 541.2261]. Anal. Calcd for $C_{24}H_{38}O_{12}$: C, 55.59; H, 7.39. Found: C, 55.83; H, 7.49.

4.1.29. (5*S*,6*R*,11*S*,12*R*,16*R*)-(3*E*,9*E*)-5,11-Bis(2-methoxyethoxymethoxy)-6,12,16-trimethyl-1,7,13-trioxacyclohexadeca-3,9-diene-2,8,14-trione (+)-32. Following the procedure described above for the preparation of (−)-**32**, lactonization of 11.6 mg (0.02 mmol) of (+)-**29** afforded 9.8 mg of (+)-**32** (86%): $[\alpha]_D^{29}=+94.5$ (*c* 0.22, $CHCl_3$); HRMS (FAB, NaI matrix) *m/z* 541.2247 [$(M+Na)^+$; calcd for $C_{24}H_{38}O_{12}Na$: 541.2261].

4.1.30. (+)-Macrosphelide A (+)-1. To a solution of 2.7 mg (5.2 mmol) of (−)-**32** in 0.29 mL of CH_2Cl_2 was added 0.29 mL of trifluoroacetic acid. After stirring for 7.5 h at ambiemt temperature, the reaction mixture was concentrated in vacuo, and chromatographed (10% MeOH/$CHCl_3$) to provide 1.6 mg (4.7 mmol, 90%) of (+)-**1** as colorless solid: R_f 0.43 (10:1 $CHCl_3$/MeOH); mp 146–147 °C (MeOH) (lit. 141–142 °C); $[\alpha]_D^{27}=+82.0$ (*c* 0.10, MeOH) [lit. +84.1 (*c* 0.59, MeOH)]; IR (KBr) 3437 (s), 1713 (s), 1284 (m), 1190 (m), 1051 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.87 (dd, $J=15.8$, 5.8 Hz, 1H), 6.86 (dd, $J=15.8$, 5.8 Hz, 1H), 6.05 (dd, $J=15.8$, 1.7 Hz, 1H), 6.03 (dd, $J=15.8$, 1.7 Hz, 1H), 5.38 (m, 1H), 4.95 (m, 1H), 4.86 (m, 1H), 4.22 (m, 1H), 4.14 (m, 1H), 2.62 (dd, $J=15.5$, 8.5 Hz, 1H), 2.56 (dd, $J=15.5$, 3.5 Hz, 1H), 1.45 (d, $J=6.6$ Hz, 3H), 1.37 (d, $J=6.6$ Hz, 3H), 1.33 (d, $J=6.6$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.8, 18.0, 19.7, 41.0, 67.7, 73.2, 74.1, 74.8, 75.0, 122.3, 122.8, 145.0, 146.0, 164.5, 165.7, 170.1; HRMS (FAB, NaI matrix) *m/z* 365.1219 [$(M+Na)^+$; calcd for $C_{16}H_{22}O_8Na$: 365.1212].

4.1.31. (−)-Macrosphelide A (−)-1. Following the procedure described above for the preparation of (+)-**1**, deprotection of 4.3 mg (0.008 mmol) of (+)-**32** afforded 2.5 mg of (−)-**1** (88%): $[\alpha]_D^{25}=-80.0$ (*c* 0.07, MeOH); HRMS (FAB, NaI matrix) *m/z* 365.1219 [$(M+Na)^+$; calcd for $C_{16}H_{22}O_8Na$: 365.1212].

4.1.32. (4*R*,5*S*,10*R*,11*S*,15*R*)-(2*E*,8*E*)-15-(*tert*-Butyldimethylsiloxy)-4,10-bis(2-methoxyethoxy-methoxy)-5,11-dimethyl-6,12-dioxa-1,7,13-trioxo-2,8-hexadeca-dienoic acid *tert*-butyl eter (−)-33. To a solution of 123 mg (0.24 mmol) of (−)-**26**, 63 mg (0.29 mmol) of (−)-**27**, 7 mg (0.06 mmol) of 4-dimethylaminopyridine and 7 mg (0.03 mmol) of camphorsulfonic acid in 2.0 mL of CH_2Cl_2 was added 75 mg (0.36 mmol) of dicyclohexylcarbodiimide at room temperature. The reaction mixture was stirred for 22 h, and then quenched with 2.0 mL of H_2O. The mixture was extracted with 3×20 mL of $CHCl_3$, the combined organic layers were washed with 15 mL of saturated NaCl solution, dried over Na_2SO_4, filtered, and concentrated. Chromatography (50% EtOAc/hexane) provided 171 mg of (−)-**33** (0.24 mmol, 100%) as a colorless oil: R_f 0.47 (1:1 hexane/EtOAc); $[\alpha]_D^{28}=-54.0$ (*c* 0.49, $CHCl_3$); IR (KBr) 3431 (s), 2931 (w), 2895 (w), 1720 (s), 1659 (w), 1369 (w), 1298 (m), 1255 (m), 1153 (s), 1038 (s) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 6.78 (dd, $J=15.8$, 6.3 Hz, 1H), 6.68 (dd, $J=15.8$, 6.3 Hz, 1H), 6.02 (dd, $J=15.8$, 1.3 Hz, 1H), 5.95 (dd, $J=15.8$, 1.3 Hz, 1H), 5.06 (m, 1H), 5.00 (m, 1H), 4.71 (s, 2H), 4.69 (dd, $J=17.8$, 6.9 Hz, 2H), 4.31 (m, 2H), 4.22 (m, 1H), 3.74 (m, 2H), 3.61 (m, 2H), 3.49 (m, 4H), 3.34 (s, 6H), 2.45 (dd, $J=14.9$, 7.3 Hz, 1H), 2.31 (dd, $J=14.9$, 5.6 Hz, 1H), 1.45 (s, 9H), 1.21 (d, $J=6.6$ Hz, 3H), 1.17 (d, $J=6.6$ Hz, 3H), 1.09 (d, $J=6.6$ Hz, 3H), 0.82 (s, 9H), 0.02 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ −4.9, −4.6, 14.9(2C), 17.8, 23.7, 25.7(3C), 28.0(3C), 44.7, 58.9(2C), 65.6, 67.2(2C), 71.1, 71.6(2C), 71.8, 76.5, 80.7(2C), 93.6, 93.7, 124.0, 126.2, 141.6, 143.8, 164.9(2C), 170.8; HRMS (FAB, NaI matrix) *m/z* 729.3855 [$(M+Na)^+$; calcd for $C_{34}H_{62}O_{13}SiNa$: 729.3857].

4.1.33. (4*S*,5*R*,10*S*,11*R*,15*S*)-(2*E*,8*E*)-15-(*tert*-Butyldimethylsiloxy)-4,10-bis(2-methoxyethoxy-methoxy)-5,11-dimethyl-6,12-dioxa-1,7,13-trioxo-2,8-hexadeca-dienoic acid *tert*-butyl ester (+)-33. Following the procedure described above for the preparation of (−)-**33**, condensation of 53.8 mg (0.1 mmol) of (+)-**26** and 30.1 mg (0.1 mmol) of (+)-**27** afforded 81.6 mg of (+)-**33** (100%): $[\alpha]_D^{27}=+70.2$ (*c* 0.45, $CHCl_3$); HRMS (FAB, NaI matrix) *m/z* 729.3881 [$(M+Na)^+$; calcd for $C_{34}H_{62}O_{13}SiNa$: 729.3857].

4.1.34. (4*R*,5*S*,10*R*,11*S*,15*R*)-(2*E*,8*E*)-15-Hydroxy-4,10-bis(2-methoxyethoxymethoxy)-5,11-dimethyl-6,12-dioxa-1,7,13-trioxo-2,8-hexadecadienoic acid (−)-34. To a solution of 29 mg (0.042 mmol) of (−)-**33** in 2.0 mL of thioanisole and 0.4 mL of CH_2Cl_2 was added 2.0 mL of

trifluoroacetic acid dropwise at 0 °C. After stirring for 30 min, the reaction was concentrated in vacuo. Chromatography (9% MeOH/$CHCl_3$) provided 12 mg of (−)-**34** (0.021 mmol, 51%) as a colorless oil: R_f 0.18 (10:1 $CHCl_3$/MeOH); $[\alpha]_D^{28} = -68.8$ (*c* 0.25, $CHCl_3$); IR (KBr) 3437 (s), 1720 (s), 1660 (w), 1300 (m), 1180 (m), 1039 (s) cm^{-1}; $_1H$ NMR (270 MHz, $CDCl_3$) δ 6.92 (dd, $J=15.8$, 6.3 Hz, 1H), 6.82 (dd, $J=15.8$, 6.3 Hz, 1H), 6.07 (dd, $J=15.8$, 1.3 Hz, 1H), 6.05 (dd, $J=15.8$, 1.3 Hz, 1H), 5.12 (m, 2H), 4.76 (dd, $J=15.5$, 6.8 Hz, 2H), 4.72 (dd, $J=15.5$, 6.8 Hz, 2H), 4.38 (m, 1H), 4.34 (m, 1H), 4.21 (m, 1H), 3.78 (m, 2H), 3.65 (m, 2H), 3.53 (m, 4H), 3.38 (s, 6H), 2.51 (dd, $J=15.8$, 8.6 Hz, 1H), 2.43 (dd, $J=15.8$, 4.0 Hz, 1H), 1.27 (d, $J=6.6$ Hz, 3H), 1.22 (d, $J=6.6$ Hz, 6H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 15.3, 15.4, 22.4, 43.3, 59.0(2C), 64.3(2C), 67.3(2C), 71.6(3C), 76.5(2C), 93.8, 93.9, 124.3(2C), 143.5, 145.4, 164.9(2C), 171.8; HRMS (FAB, NaI matrix) *m/z* 559.2352 $[(M+Na)^+$; calcd for $C_{24}H_{40}O_{13}Na$: 559.2367].

4.1.35. (4*S*,5*R*,10*S*,11*R*,15*S*)-(2*E*,8*E*)-15-Hydroxy-4,10-bis(2-methoxyethoxymethoxy)-5,11-dimethyl-6,12-dioxa-1,7,13-trioxo-2,8-hexadecadienoic acid (+)-34. Following the procedure described above for the preparation of (−)-**34**, deprotection of 29.6 mg (0.04 mmol) of (+)-**33** afforded 9.2 mg of (+)-**34** (41%): $[\alpha]_D^{25} = +70.0$ (*c* 0.12, $CHCl_3$); HRMS (FAB, NaI matrix) *m/z* 559.2363 $[(M+Na)^+$; calcd for $C_{24}H_{40}O_{13}Na$: 559.2367].

4.1.36. (5*R*,6*S*,11*R*,12*S*,16*R*)-(3*E*,9*E*)-5,11-Bis(2-methoxyethoxymethoxy)-6,12,16-trimethyl-1,7,13-trioxacyclohexadeca-3,9-diene-2,8,14-trione (−)-35. To a solution of 32.0 mg (0.060 mmol) of (−)-**34** was added 720 µl (0.36 mmol) of 0.5 M triethylamine in toluene and 600 µl (0.30 mmol) of 0.5 M 2,4,6-trichlorobenzoyl chloride in toluene at room temperature, and stirred for 1 h. The solution was then diluted with 15.0 mL of toluene and added to a solution of 180 mg (1.48 mmol) of 4-dimethylaminopyridine in 5.9 mL of toluene at 80 °C over 2 h. The anhydride flask was washed with 8.0 mL of toluene and the washing added to the mixture over 30 mim. The reaction was then heated at 80 °C for a total of 3.5 h. After cooling, the white suspension was diluted with 20 mL of saturated $NaHCO_3$ aqueous solution became clear. The two layers were separated and aqueous layer was extracted with 3× 25 mL of EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Chromatography (9% MeOH/$CHCl_3$) provided 20.0 mg of (−)-**35** (0.039 mmol, 66%) as a colorless oil: R_f 0.61 (10:1 $CHCl_3$/MeOH); $[\alpha]_D^{28} = -30.0$ (*c* 0.52, $CHCl_3$); IR (KBr) 1722 (s), 1191 (m), 1134 (m), 1111 (m), 1035 (m) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 6.81 (dd, $J=15.8$, 5.9 Hz, 1H), 6.78 (dd, $J=15.8$, 6.9 Hz, 1H), 6.12 (dd, $J=15.8$, 1.0 Hz, 1H), 5.94 (dd, $J=15.8$, 1.0 Hz, 1H), 5.22 (m, 1H), 5.10 (m, 2H), 4.72 (dd, $J=15.5$, 6.9 Hz, 2H), 4.72 (s, 2H), 4.31 (m, 1H), 4.12 (m, 1H), 3.75 (m, 2H), 3.62 (m, 2H), 3.53 (m, 4H), 3.37 (s, 6H), 2.75 (dd, $J=14.9$, 3.0 Hz, 1H), 2.53 (dd, $J=14.9$, 6.6 Hz, 1H), 1.39 (d, $J=6.6$ Hz, 3H), 1.35 (d, $J=6.6$ Hz, 3H), 1.18 (d, $J=6.6$ Hz, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 17.1, 17.5, 19.2, 40.6, 59.0(2C), 67.2, 67.3(2C), 71.2, 71.8(2C), 72.0, 77.2, 77.5, 93.4(2C), 124.6, 124.8, 142.9, 143.1, 164.4, 165.0, 169.4; HRMS (FAB, NaI matrix) *m/z* 541.2258 $[(M+Na)^+$; calcd for $C_{24}H_{38}O_{12}Na$: 541.2261].

4.1.37. (5*S*,6*R*,11*S*,12*R*,16*S*)-(3*E*,9*E*)-5,11-Bis(2-methoxyethoxymethoxy)-6,12,16-trimethyl-1,7,13-trioxacyclohexadeca-3,9-diene-2,8,14-trione (+)-35. Following the procedure described above for the preparation of (−)-**35**, lactonization of 11.8 mg (0.02 mmol) of (+)-**34** afforded 9.7 mg of (+)-**35** (85%): $[\alpha]_D^{25} = +37.3$ (*c* 0.22, $CHCl_3$); HRMS (FAB, NaI matrix) *m/z* 541.2261 $[(M+Na)^+$; calcd for $C_{24}H_{38}O_{12}Na$: 541.2261].

4.1.38. (+)-Macrosphelide E (+)-3. To a solution of 11 mg (0.02 mmol) of (−)-**35** in 0.15 mL of CH_2Cl_2 was added 0.45 mL of trifluoroacetic acid. After being stirred at ambiemt temperature for 2 h, the reaction mixture was concentrated in vacuo, and chromatographed (10% MeOH/$CHCl_3$) to provide 5.8 mg (0.017 mmol, 79%) of (+)-**3** as colorless solid: R_f 0.43 (10:1 $CHCl_3$/MeOH); $[\alpha]_D^{28} = +21.5$ (*c* 0.31, MeOH); IR (KBr) 3433 (s), 1716 (s), 1665 (w), 1645 (w), 1280 (m), 1192 (m), 1053 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.02 (dd, $J=16.0$, 4.0 Hz, 1H), 6.80 (dd, $J=16.0$, 5.0 Hz, 1H), 6.13 (dd, $J=16.0$, 1.8 Hz, 1H), 6.06 (dd, $J=16.0$, 1.8 Hz, 1H), 5.32 (m, 1H), 5.12 (m, 1H), 4.97 (m, 1H), 4.37 (br s, 1H), 4.18 (br s, 1H), 2.73 (dd, $J=16.0$, 3.0 Hz, 1H), 2.60 (dd, $J=16.0$, 7.3 Hz, 1H), 1.42 (d, $J=6.7$ Hz, 3H), 1.39 (d, $J=6.7$ Hz, 3H), 1.31 (d, $J=6.7$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.3, 17.8, 19.6, 40.5, 66.6, 73.8, 75.2, 75.4, 76.0, 122.3, 123.0, 145.0, 145.3, 165.3, 166.7, 170.8; HRMS (FAB, NBA matrix) *m/z* 343.1381 $[(M+H)^+$; calcd for $C_{16}H_{23}O_8$: 343.1393].

4.1.39. (−)-Macrosphelide E (−)-3. Following the procedure described above for the preparation of (+)-**3**, deprotection of 5.9 mg (0.01 mmol) of (+)-**35** afforded 2.4 mg of (−)-**3** (64%): $[\alpha]_D^{28} = -25.0$ (*c* 0.20, MeOH); HRMS (FAB, NBA matrix) *m/z* 343.1394 $[(M+H)^+$; calcd for $C_{16}H_{23}O_8$: 343.1393].

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21. Compound (+)-**1**, $C_{16}H_{22}O_8$, crystallizes in the monoclinic space group $P2_1$ with $a=10.3502(4)$, $b=5.6291(3)$, and $c=16.0611(6)$ Å, $\beta=106.365(2)°$, $V=897.85(7)$ Å^3, $Z=2$, and $d_{calcd}=1.266$ g/cm^3. X-ray intensity data were collected on a SMART APEXII diffractometer employing Cu Kα radiation ($\lambda=1.54178$ Å) and the $\omega-2\theta$ scan technique. The structure was solved by direct methods. For refinement, 2747 unique reflections with $F^2>2\sigma(F^2)$ were used. Full-matrix least-squares refinement based on F, minimizing the quantity $\Sigma w(|F_o|-|F_c|)^2$ with $w=4F_o^2/\sigma^2(Fo^2)$, converged $R=0.055$ and $Rw=0.146$. Crystallographic data of (+)-**1** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 258197. Copies of the data can be obtained, free of charge, on application to CDCC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].
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