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Total Synthesis of Macrosphelide M from Diacetone Glucose

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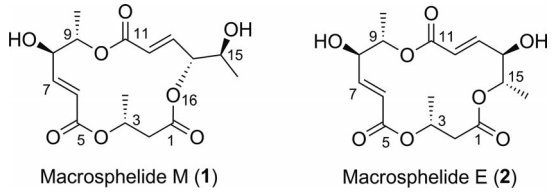
Dedicated to Dr. Christian Bruneau on the occasion of his 60th birthday[‡]

Keywords: Carbohydrates / Esterification / Metathesis / Macrocycles

The total synthesis of macrosphelide M is described. The key steps include the preparation of the acid and alcohol fragments from diacetone glucose and (*S*)-malic acid, respectively, followed by Yamaguchi esterification and macrocyclization of the tris-olefin by ring-closing metathesis. Finally, one-pot deprotection of the PMB and TBS groups with $TiCl_4$ results in the target. The C-3/C-4 stereocenters of diacetone glucose are used for the introduction of four stereocenters, whereas the fifth stereocenter is realized from (*S*)-malic acid.

Introduction

Macrosphelides A–L[1] are a 16-membered macrotriolide class of antibiotics having a trilactone backbone in their structures, whereas macrosphelide M[2] (**1**) is a 15-membered macrotriolide that is a positional isomer of macrosphelide E[3] (**2**, Scheme 1). compound **1** was isolated[2] from a strain of *Periconia byssoides*, originally isolated from *Aplysia kurodai*. The absolute stereochemistry of **1** was reported by Yamada et al.[2] on the basis of its spectroscopic analysis and some chemical transformations. Tris-lactone **1** has five stereocenters, whose absolute configuration was defined as (3*R*,8*R*,9*S*,14*R*,15*S*) and whose skeleton contained two *trans* double bonds. It was found to inhibit the adhesion of human leukemia HL-60 cells to human umbilical vein endothelial cells (HUVEC). Herein, we report a carbohydrate-based[3b,4] total synthesis of macrosphelide M (**1**) from diacetone glucose (**9**) by using ring-closing metathesis (RCM) to construct the macrocycle.[3d,5]



Scheme 1. Structures of macrosphelides M and E.

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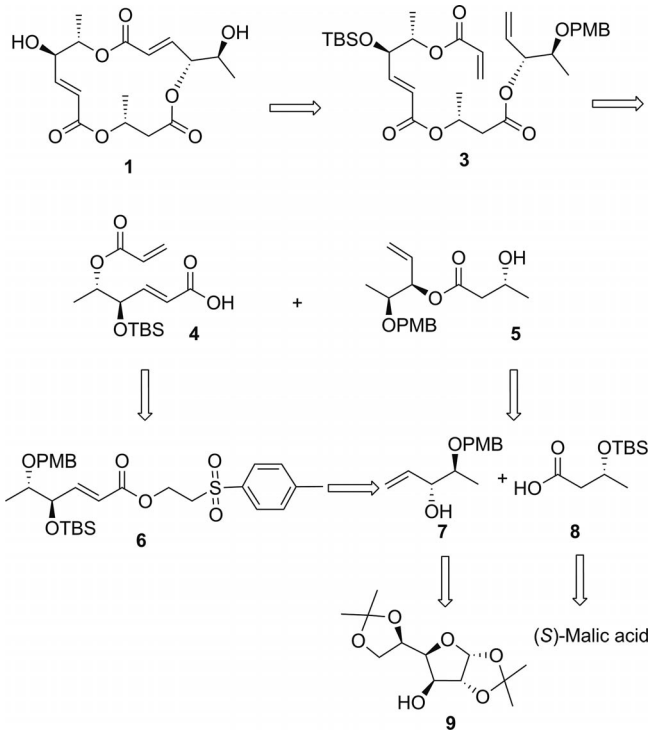
Results and Discussion

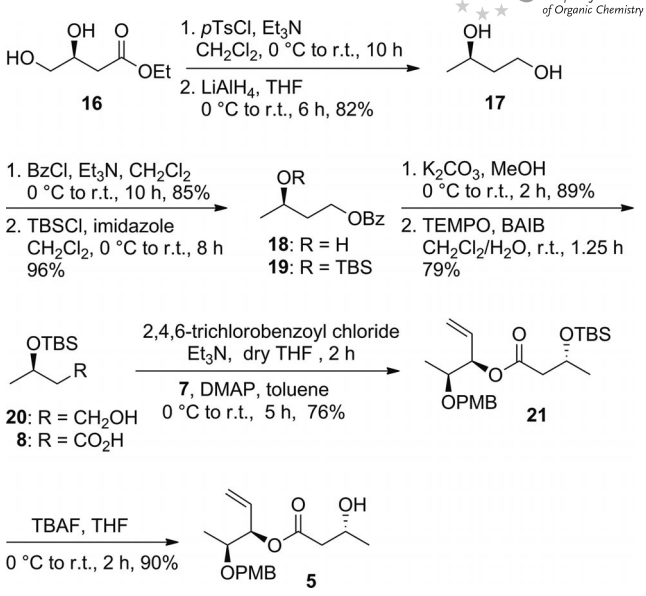
Retrosynthetic analysis of **1** is shown in Scheme 2. The formation of **1** was envisaged to occur through macrocyclization of **3**, which could be obtained by Yamaguchi esterification of fragments **4** and **5**. Both fragments **4** and **5** could be obtained from common intermediate **7**, realized from diacetone glucose (**9**), whereas acid **8** could be made from (*S*)-malic acid.

Accordingly, known PMB-ether **10**[6] (Scheme 3), prepared from **9**, upon selective hydrolysis with 60% aq. CH_3COOH gave diol **11**[6] (88%), which upon treatment with Ph_3P, imidazole, and I_2[7a] was converted into olefin **12**[7b] in 65% yield. Hydrolysis of olefin **12** with 60% aq. CH_3COOH and a catalytic amount of concentrated HCl afforded diol **13**[7b] (68%). Oxidative cleavage of diol **13** with $NaIO_4$ in acetone/water and subsequent reduction of unstable aldehyde **14** with $LiAlH_4$ gave **15** in 81% yield by concomitant reduction of the formyl group and formate ester. Diol **15** was treated with *p*TsCl and Et_3N in CH_2Cl_2 to give the primary tosylate, which upon subsequent reduction with $LiAlH_4$ furnished alcohol **7** in 89% yield. Alcohol **7** is a common fragment for **4** and **5**.

The synthesis of fragment **5** (Scheme 4) was initiated from commercially available diol **17**, which was prepared from known ester **16**[8a] in two steps. Accordingly, selective tosylation (*p*TsCl, Et_3N, CH_2Cl_2) of **16** and subsequent reduction of the resulting tosylate with $LiAlH_4$ afforded 1,3-diol **17**[8b,8c] in 82% yield. Reaction of **17** with benzoyl chloride and Et_3N gave benzoate **18** (85%), which upon silylation with TBSCl and imidazole furnished **19** in 96% yield. Base hydrolysis of ester **19** with K_2CO_3 and MeOH gave **20** (89%), which upon oxidation with TEMPO and BAIB[9] afforded carboxylic acid **8** in 79% yield. Yamaguchi esterification[10] of alcohol **7** with acid **8**, through the mixed



Scheme 2. Retrosynthesis of macrosphelide M.

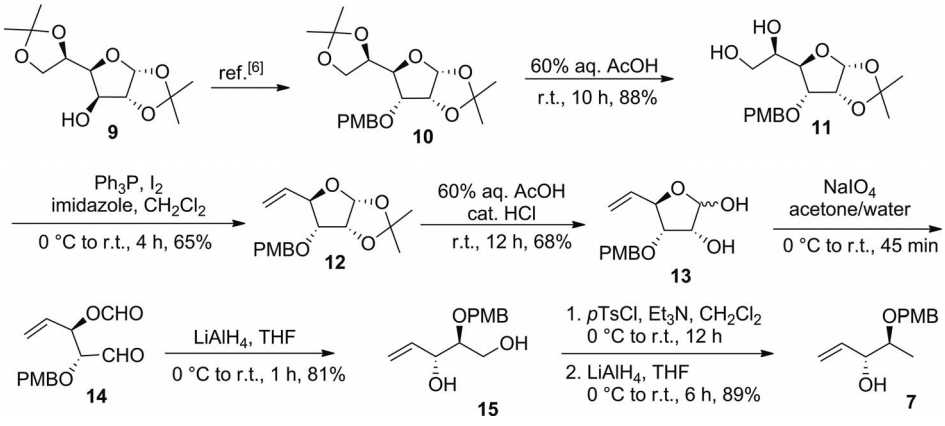


Scheme 4. Synthesis of segment **5**.

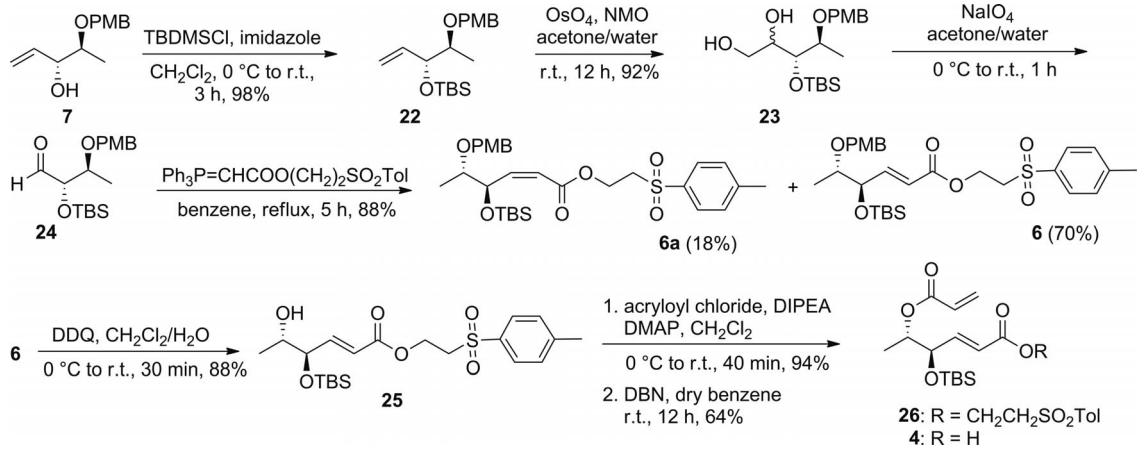
anhydride prepared upon reaction of **8** with 2,4,6-trichlorobenzoyl chloride (Et_3N, THF) in the presence of DMAP in toluene, afforded ester **21** in 76% yield. Finally, desilylation of **21** with TBAF in THF afforded alcohol fragment **5** in 90% yield {$[\alpha]_D^{27}$ = –90.7 (c = 0.15, $CHCl_3$)}.

For the synthesis of fragment **4** (Scheme 5), allylic alcohol **7** was treated with TBSCl and imidazole in CH_2Cl_2 to afford **22** in 98% yield. Dihydroxylation[11] of olefin **22** with OsO_4 and NMO in acetone/water gave diol **23** (92%), which upon oxidative cleavage with $NaIO_4$ in acetone/water and subsequent olefination of aldehyde **24** with (*p*-toluenesulfonylethoxycarbonylmethylene)triphenylphosphorane[12] gave ester **6** in 70% yield [*cis* (**6a**)/*trans* (**6**) = 1:4, isomers were separated by column chromatography]. Deprotection of PMB-ether in **6** with DDQ in CH_2Cl_2/H_2O gave alcohol **25** (88%), which upon treatment with acryloyl chloride, DIPEA, and DMAP in CH_2Cl_2 afforded **26** in 94% yield. Selective removal of the *p*-toluenesulfonylethyl ester group in **26** was effected with DBN[12] in benzene at room temperature to furnish carboxylic acid **4** in 64% yield {$[\alpha]_D^{27}$ = –33.1 (c = 0.20, $CHCl_3$)}.

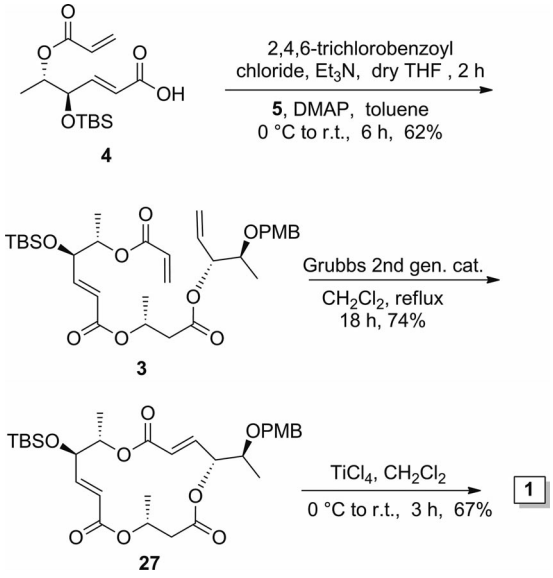
Yamaguchi esterification[10] of alcohol **5** with carboxylic acid **4** (Scheme 6) by using 2,4,6-trichlorobenzoyl chloride and Et_3N in THF in the presence of DMAP in toluene afforded ester **3** in 62% yield {$[\alpha]_D^{27}$ = +11.9 (c = 0.15, $CHCl_3$)}. Macrocyclization by RCM of **3** with Grubbs second generation catalyst[5,13] (5 mol-%) gave **27** in 74% yield {based on 20% recovery of the starting material, $[\alpha]_D^{27}$ = +1.0 (c = 0.10, $CHCl_3$)}. Finally, treatment of **27** with $TiCl_4$ in CH_2Cl_2 afforded **1** in 67% yield {$[\alpha]_D^{22}$ = +8.9 (c = 0.15, EtOH); ref.[2] $[\alpha]_D^{22}$ = +5.5 (c = 0.30, EtOH)}.



Scheme 3. Synthesis of segment **7**.



Scheme 5. Synthesis of **4**.



Scheme 6. Synthesis of **1**.

Conclusions

In summary, the synthesis of macrosphelide M was achieved from **9** and (*S*)-malic acid, wherein four stereocenters (8*R*,9*S*,14*R*,15*S*) were obtained from **4** and the (3*R*) stereocenter was obtained from (*S*)-malic acid. The ^{1}H NMR and ^{13}C NMR[14] spectral data of synthetic **1** matches the data reported for the natural product well,[2] though deviation is observed in the optical rotation value.

Experimental Section

General Methods: Reactions were carried out as described in the procedures; organic layers were dried with Na_2SO_4, and the crude products were purified by column chromatography using 60–120 mesh silica gel. ^{1}H NMR spectra were recorded at 300, 400, and 500 MHz, whereas ^{13}C NMR spectra were recorded at 50 and 75 MHz. NMR spectra (^{1}H and ^{13}C) were recorded in $CDCl_3$ except for compound **1** ([D_6]acetone) with respect to internal TMS (tetramethylsilane) reference. FTIR spectra were measured with a Thermo Nicolet Nexus 670 spectrometer. Optical rotations were measured with a JASCO DIP 300 digital polarimeter. Mass spectra were recorded with a Fannigan Mat 1210 double-focusing mass spectrometer operating with a direct inlet system.

(*R*)-1-[(3a*R*,5*R*,6*R*,6a*R*)-6-(4-Methoxybenzyloxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl]ethane-1,2-diol (11): A solution of **10** (14.25 g, 37.50 mmol) in 60% aq. CH_3COOH (71 mL) was stirred at room temperature for 10 h. The reaction mixture was neutralized with solid $NaHCO_3$ (143 g), and the crude residue was extracted with EtOAc (3 × 200 mL) and dried (Na_2SO_4). The solvent was evaporated under reduced pressure, and the residue was purified by column chromatography [60–120 mesh silica gel, 50% EtOAc in petroleum ether (PE)] to afford diol **11** (8.67 g, 88%) as a colorless syrup. $[a]_D^{22}$ = +99.2 (*c* = 0.30, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 295 K): δ = 7.25 (d, *J* = 8.3 Hz, 2 H, Ar-H), 6.84 (d, *J* = 8.3 Hz, 2 H, Ar-H), 5.71 (d, *J* = 3.8 Hz, 1 H, C1 H), 4.71 (d, *J* = 11.0 Hz, 1 H, OCHPMP), 4.55 (m, 1 H, C2 H), 4.43 (d, *J* = 11.0 Hz, 1 H, OCH′PMP), 4.01 (dd, *J* = 3.4, 8.7 Hz, 1 H, OCH), 3.94–3.86 (m, 1 H, OCH), 3.83 (dd, *J* = 4.5, 9.1 Hz, 1 H, OCH), 3.80 (s, 3 H, OCH_3), 3.68–3.53 (m, 2 H, OCH, CHOPMB), 2.71–2.25 (m, 2 H, 2 OH), 1.57 (s, 3 H, CH_3), 1.35 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 295 K): δ = 159.7, 130.0 (2 C), 128.6, 114.0 (2 C), 113.1, 104.1, 79.1, 77.2, 76.3, 71.8, 70.7, 63.0, 55.2, 26.7, 26.5 ppm. IR (neat): $\tilde{\nu}$ = 3434, 2935, 1613, 1514, 1377, 1248, 1170, 1126, 1025, 876, 824, 758 cm^{-1}. HRMS (ESI): calcd. for $C_{17}H_{24}O_7$ [M + Na]$^+$ 363.1419; found 363.1413.

(3a*R*,5*R*,6*R*,6a*R*)-6-(4-Methoxybenzyloxy)-2,2-dimethyl-5-vinyltetrahydrofuro[2,3-*d*][1,3]dioxole (12): To a mixture of **11** (8.67 g, 25.49 mmol), Ph_3P (26.72 g, 102.0 mmol), and imidazole (6.94 g, 102.0 mmol) in CH_2Cl_2 was added I_2 (19.28 g, 76.50 mmol) at 0 °C, and the mixture was stirred at room temperature for 4 h. A saturated aqueous solution of NaOH was added to the reaction mixture, which was then extracted with $CHCl_3$ (100 mL). The organic layers were washed with sat. aq. sodium thiosulphate (40 mL) and brine (40 mL) and then dried (Na_2SO_4). The solvent was evaporated under reduced pressure, and the residue was purified by column chromatography (60–120 mesh silica gel, 5% EtOAc in PE) to give olefin **12** (5.07 g, 65%) as a colorless syrup. $[a]_D^{22}$ = +52.0 (*c* = 0.60, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 295 K): δ = 7.22 (d, *J* = 8.7 Hz, 2 H, Ar-H), 6.84 (d, *J* = 8.7 Hz, 2 H, Ar-H), 5.77 (ddd, *J* = 6.4, 10.6, 17.0 Hz, 1 H, CH=CH_2), 5.67 (d, *J* = 3.8 Hz, 1 H,

C1 H), 5.37 (d, J = 17.0 Hz, 1 H, =CH_2), 5.20 (d, J = 10.6 Hz, 1 H, =CH_2), 4.54–4.46 (m, 2 H, OCH_2PMP), 4.42–4.35 (m, 1 H, OCH-allyl), 3.79 (s, 3 H, OCH_3), 3.39 (dd, J = 4.3, 9.1 Hz, 1 H, OCH_2), 1.59 (s, 3 H, CH_3), 1.34 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 295 K): δ = 159.4, 134.8, 129.5 (3 C), 118.5, 113.7 (2 C), 112.7, 103.6, 81.3, 78.9, 77.5, 71.8, 55.2, 26.6, 26.4 ppm. IR (neat): $\tilde{\nu}$ = 2987, 2934, 1613, 1513, 1375, 1248, 1026, 823, 768 cm^{-1}. HRMS (ESI): calcd. for $C_{17}H_{22}O_5$ [M + Na]$^+$ 329.1364; found 329.1375.

(3*R*,4*R*)-4-(4-Methoxybenzyloxy)-5-oxopent-1-en-3-yl Formate (14): To a solution of **12** (5.07 g, 16.58 mmol) in 60% aq. CH_3COOH (25 mL) was added a catalytic amount of conc. HCl at room temperature, and the mixture was stirred for 12 h. The reaction mixture was neutralized with solid $NaHCO_3$ (50 g), and the crude residue was extracted with EtOAc (3 × 50 mL) and dried (Na_2SO_4). The solvent was evaporated under reduced pressure, and the residue was purified by column chromatography (60–120 mesh silica gel, 45% EtOAc in PE) to furnish **13** (3.0 g, 68%) as a colorless syrup. To a solution of diol **13** (3.0 g, 11.28 mmol) in acetone/water (5:1, 15 mL) at 0 °C was added $NaIO_4$ (2.90 g, 13.53 mmol), and the mixture was stirred at room temperature for 45 min. The solvent was evaporated under reduced pressure, and the residue was extracted with $CHCl_3$ (30 mL), dried (Na_2SO_4), and concentrated to give aldehyde **14**, which was directly used in the next step without any further purification. ^{1}H NMR (300 MHz, $CDCl_3$, 295 K): δ = 9.52 (d, J = 1.5 Hz, 1 H, CHO), 8.02 (s, 1 H, OCHO), 7.21 (d, J = 8.3 Hz, 2 H, Ar-H), 6.82 (d, J = 8.3 Hz, 2 H, Ar-H), 5.86 (ddd, J = 6.8, 10.6, 17.4 Hz, 1 H, CH=CH_2), 5.70–5.67 (m, 1 H, OCH-allyl), 5.33 (d, J = 17.4 Hz, 1 H, =CH_2), 5.30 (d, J = 10.6 Hz, 1 H, =CH_2), 4.64 (d, J = 12.1 Hz, 1 H, OCHPMP), 4.56 (d, J = 12.1 Hz, 1 H, OCH′PMP), 3.88–3.83 (m, 1 H, CHOPMB), 3.79 (s, 3 H, OCH_3) ppm.

(2*S*,3*R*)-2-(4-Methoxybenzyloxy)pent-4-ene-1,3-diol (15): To a stirred suspension of $LiAlH_4$ (0.43 g, 11.28 mmol) in THF (7 mL) at 0 °C was dropwise added a solution of aldehyde **14** (2.98 g, 11.28 mmol) in THF (8 mL) under nitrogen atmosphere, and the mixture was stirred at room temperature for 1 h. The reaction mixture was cooled to 0 °C, treated with saturated aq. Na_2SO_4 solution (10 mL), and filtered. The mixture was washed with EtOAc (50 mL), and the filtrate was dried (Na_2SO_4). The solvent was evaporated under reduced pressure, and the residue was purified by column chromatography (60–120 mesh silica gel, 35% EtOAc in PE) to furnish **15** (2.18 g, 81%) as a colorless oil. $[\alpha]_D^{27}$ = +8.3 (c = 0.25, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 295 K): δ = 7.21 (d, J = 8.5 Hz, 2 H, Ar-H), 6.83 (d, J = 8.5 Hz, 2 H, Ar-H), 5.87 (ddd, J = 5.3, 10.6, 17.2 Hz, 1 H, CH=CH_2), 5.35 (d, J = 17.2 Hz, 1 H, =CH_2), 5.22 (d, J = 10.6 Hz, 1 H, =CH_2), 4.64–4.52 (m, 2 H, OCH_2PMP), 4.33 (m, 1 H, OCH-allyl), 3.79 (s, 3 H, OCH_3), 3.71 (d, J = 4.3 Hz, 2 H, OCH_2), 3.40 (q, J = 4.5 Hz, 1 H, CHOPMB) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 295 K): δ = 159.1, 137.0, 129.8, 129.4 (2 C), 116.0, 113.7 (2 C), 80.8, 72.5, 71.6, 61.1, 55.1 ppm. IR (neat): $\tilde{\nu}$ = 3396, 2880, 1612, 1513, 1459, 1301, 1247, 1176, 1096, 1035, 929, 822 cm^{-1}. HRMS (ESI): calcd. for $C_{13}H_{18}O_4$ [M + Na]$^+$ 261.1102; found 261.1113.

(3*R*,4*S*)-4-(4-Methoxybenzyloxy)pent-1-en-3-ol (7): To a stirred solution of **15** (2.0 g, 8.40 mmol) in CH_2Cl_2 (30 mL) was sequentially added Et_3N (3.51 mL, 25.21 mmol) and pTsCl (1.60 g, 8.40 mmol) at 0 °C, and the mixture was stirred at room temperature for 12 h. The reaction mixture was treated with water (20 mL) and extracted with CH_2Cl_2 (40 mL). The organic layer was washed with brine (20 mL), dried (Na_2SO_4), and evaporated under reduced pressure, and the crude tosylate was directly used in the next step without any further purification. To a stirred suspension of $LiAlH_4$ (0.32 g, 8.40 mmol) in THF (7.5 mL) was dropwise added a solution of tosylate in THF (9 mL) at 0 °C under a nitrogen atmosphere, and the mixture was stirred at room temperature for 6 h. The reaction mixture was worked up as described for **15**, and the crude residue was purified by column chromatography (60–120 mesh silica gel, 12% EtOAc in PE) to afford **7** (1.87 g, 89%) as a colorless oil. $[\alpha]_D^{27}$ = +58.4 (c = 0.35, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 295 K): δ = 7.22 (d, J = 8.7 Hz, 2 H, Ar-H), 6.84 (d, J = 8.7 Hz, 2 H, Ar-H), 5.79 (ddd, J = 5.7, 10.2, 17.4 Hz, 1 H, CH=CH_2), 5.25 (dd, J = 1.5, 17.4 Hz, 1 H, =CH_2), 5.16 (dd, J = 1.5, 10.2 Hz, 1 H, =CH_2), 4.56 (d, J = 11.3 Hz, 1 H, OCHPMP), 4.41 (d, J = 11.7 Hz, 1 H, OCH′PMP), 4.17 (m, 1 H, OCH-allyl), 3.79 (s, 3 H, OCH_3), 3.57–3.49 (m, 1 H, CHOPMB), 1.09 (d, J = 6.4 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 295 K): δ = 159.1, 136.5, 130.3, 129.2 (2 C), 116.3, 113.7 (2 C), 77.0, 74.4, 70.4, 55.2, 13.9 ppm. IR (neat): $\tilde{\nu}$ = 3445, 2874, 2102, 1612, 1513, 1456, 1379, 1301, 1247, 1173, 1085, 1034, 990, 927, 822 cm^{-1}. HRMS (ESI): calcd. for $C_{13}H_{18}O_3$ [M + Na]$^+$ 245.1153; found 245.1158.

(*R*)-Butane-1,3-diol (17): To a stirred solution of **16** (1.0 g, 6.76 mmol) in CH_2Cl_2 (20 mL) was added Et_3N (2.82 mL, 20.27 mmol) at 0 °C followed by pTsCl (1.29 g, 6.76 mmol) after 15 min, and the mixture was stirred at room temperature for 10 h. The reaction mixture was treated with water (20 mL) and extracted with CH_2Cl_2 (40 mL). The combined extracts were washed with brine (20 mL) and dried (Na_2SO_4). The solvent was evaporated under reduced pressure and the tosylate was directly used in the next step without any further purification. To a stirred suspension of $LiAlH_4$ (0.51 g, 13.51 mmol) in THF (10 mL) at 0 °C was dropwise added a solution of tosylate in THF (10 mL) under a nitrogen atmosphere, and the mixture was stirred at room temperature for 8 h. The reaction mixture was worked up as described for **15**, and the residue was purified by column chromatography (60–120 mesh silica gel, 50% EtOAc in PE) to give **17** (0.50 g, 82%) as a colorless oil. $[\alpha]_D^{22}$ = –28.8 (c = 0.50, EtOH). ^{1}H NMR (300 MHz, $CDCl_3$, 295 K): δ = 4.11–4.0 (m, 1 H, OCH), 3.91–3.75 (m, 2 H, OCH_2), 2.58–2.41 (br. s, 2 H, 2 OH), 1.70–1.64 (m, 2 H, CH_2), 1.24 (d, J = 6.2 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 295 K): δ = 67.2, 60.7, 40.0, 23.4 ppm. IR (neat): $\tilde{\nu}$ = 3358, 2934, 1419, 1376, 1054 cm^{-1}. MF: $C_4H_{10}O_2$. MS (EI): m/z (%) = 91 (38) [M + 1]$^+$, 90 (4) [M]$^+$, 72 (21), 57 (47), 43 (100), 41 (77).

(*R*)-3-Hydroxybutyl Benzoate (18): To a solution of **17** (0.50 g, 5.56 mmol) in CH_2Cl_2 (10 mL) was added Et_3N (2.32 mL, 16.67 mmol) followed by BzCl (0.65 mL, 5.56 mmol) at 0 °C, and the mixture was stirred at room temperature for 10 h. The reaction mixture was treated with water (15 mL) and extracted with CH_2Cl_2 (20 mL). The organic layer was washed with brine (10 mL) and dried (Na_2SO_4). The solvent was evaporated under reduced pressure, and residue was purified by column chromatography (60–120 mesh silica gel, 15% EtOAc in PE) to furnish **18** (0.91 g, 85%) as a colorless oil. $[\alpha]_D^{22}$ = –24.8 (c = 0.30, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 295 K): δ = 8.02 (d, J = 7.2 Hz, 2 H, Ar-H), 7.53 (dd, J = 7.2, 7.6 Hz, 1 H, Ar-H), 7.41 (dd, J = 7.9, 7.2 Hz, 2 H, Ar-H), 4.64–4.55 (m, 1 H, CHOBz), 4.39–4.31 (m, 1 H, CHOBz), 3.98–3.88 (m, 1 H, OCH), 2.44–2.32 (br. s, 1 H, OH), 1.97–1.72 (m, 2 H, CH_2), 1.24 (d, J = 6.0 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 295 K): δ = 166.9, 132.9, 130.0, 129.5 (2 C), 128.3 (2 C), 64.6, 62.1, 38.0, 23.4 ppm. IR (neat): $\tilde{\nu}$ = 3428, 3067, 2969, 2926, 1721, 1597, 1453, 1279, 1113, 1026 cm^{-1}. HRMS (ESI): calcd. for $C_{11}H_{14}O_3$ [M + Na]$^+$ 217.0840; found 217.0849.

(*R*)-3-(*tert*-Butyldimethylsilyloxy)butyl Benzoate (19): To a solution of **18** (0.91 g, 4.69 mmol) in CH_2Cl_2 (9.1 mL) was added imidazole

(0.64 g, 9.38 mmol) at 0 °C followed by TBSCl (0.85 g, 5.63 mmol) after 15 min, and the mixture was stirred at room temperature for 8 h. The reaction mixture was treated with water (10 mL) and extracted with CH_2Cl_2 (20 mL). The organic layer was washed with brine (10 mL) and dried (Na_2SO_4). The solvent was evaporated under reduced pressure, and the residue was purified by column chromatography (60–120 mesh silica gel, 5% EtOAc in PE) to afford **19** (1.38 g, 96%) as a colorless oil. $[\alpha]_D^{22}$ = –35.8 (*c* = 0.40, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 295 K): δ = 7.99 (d, *J* = 7.2 Hz, 2 H, Ar-H), 7.52 (dd, *J* = 7.2, 7.6 Hz, 2 H, Ar-H), 7.41 (t, *J* = 7.6 Hz, 2 H, Ar-H), 4.46–4.29 (m, 2 H, CH_2OBz), 4.08–3.98 (m, 1 H, OCH), 1.96–1.76 (m, 2 H, CH_2), 1.22 (d, *J* = 6.0 Hz, 3 H, CH_3), 0.89 [s, 9 H, $C(CH_3)_3$], 0.05 (s, 3 H, CH_3), 0.04 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 295 K): δ = 166.5, 132.8, 130.4, 129.5 (2 C), 128.3 (2 C), 65.3, 62.1, 38.4, 25.8 (3 C), 24.1, 18.0, –4.4, –5.0 ppm. IR (neat): $\tilde{\nu}$ = 2957, 2930, 2855, 1725, 1601, 1454, 1379, 1277, 1109, 1015, 835 cm^{-1}. HRMS (ESI): calcd. for $C_{17}H_{28}O_3Si$ $[M + Na]^+$ 331.1705; found 331.1695.

(*R*)-3-(*tert*-Butyldimethylsilyloxy)butan-1-ol (20): To a solution of **19** (1.38 g, 4.48 mmol) in methanol (5.5 mL) was added K_2CO_3 (1.85 g, 13.44 mmol), and the mixture was stirred at room temperature for 2 h. Methanol was evaporated, water (20 mL) was added, and the mixture was extracted with EtOAc (2 × 20 mL). The organic layer was washed with brine (10 mL) and dried (Na_2SO_4). The solvent was evaporated under reduced pressure, and the residue was purified by column chromatography (60–120 mesh silica gel, 15% EtOAc in PE) to give **20** (0.81 g, 89%) as a colorless oil. $[\alpha]_D^{22}$ = –27.7 (*c* = 0.40, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 295 K): δ = 4.14–4.02 (m, 1 H, CHOTBS), 3.86–3.61 (m, 2 H, OCH_2), 2.28 (br. s, 1 H, OH), 1.80–1.50 (m, 2 H, CH_2), 1.19 (d, *J* = 6.4 Hz, 3 H, CH_3), 0.89 [s, 9 H, $C(CH_3)_3$], 0.09 (s, 3 H, CH_3), 0.08 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 295 K): δ = 68.3, 60.4, 40.4, 25.8 (3 C), 23.4, 17.9, –4.4, –5.0 ppm. IR (neat): $\tilde{\nu}$ = 3401, 2917, 2849, 1723, 1588, 1429, 1109, 1019 cm^{-1}. HRMS (ESI): calcd. for $C_{10}H_{24}O_2Si$ $[M + Na]^+$ 227.1443; found 227.1449.

(*R*)-3-(*tert*-Butyldimethylsilyloxy)butanoic Acid (8): To a solution of **20** (0.81 g, 3.97 mmol) in CH_2Cl_2/H_2O (1:1, 8.1 mL) was added TEMPO (0.19 g, 1.19 mmol) and BAIB (3.84 g, 11.91 mmol) at 0 °C, and the mixture was stirred at room temperature for 1.25 h. The reaction mixture was diluted with $CHCl_3$ (2 × 15 mL), washed with sat. aq. sodium thiosulphate (15 mL) and brine (10 mL), and dried (Na_2SO_4). The solvent was evaporated under reduced pressure, and the residue was purified by flash column chromatography (60–120 mesh silica gel, 10% EtOAc in PE) to furnish **8** (0.69 g, 79%) as a light yellow syrup. $[\alpha]_D^{22}$ = –10.8 (*c* = 0.25, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 295 K): δ = 4.33–4.23 (m, 1 H, CHOTBS), 2.56–2.36 (m, 2 H, CH_2), 1.23 (d, *J* = 6.1 Hz, 3 H, CH_3), 0.86 [s, 9 H, $C(CH_3)_3$], 0.06 (s, 3 H, CH_3), 0.05 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 295 K): δ = 176.9, 65.7, 44.4, 25.7 (3 C), 23.7, 17.9, –4.6, –5.1 ppm. IR (neat): $\tilde{\nu}$ = 3380, 2930, 2859, 1713, 1640, 1414, 1132, 1090, 1015, 835 cm^{-1}. HRMS (ESI): calcd. for $C_{10}H_{22}O_3Si$ $[M + Na]^+$ 241.1235; found 241.1241.

(*R*)-[(3*R*,4*S*)-4-(4-Methoxybenzyloxy)pent-1-en-3-yl] 3-(*tert*-Butyldimethylsilyloxy)butanoate (21): To a stirred solution of **8** (0.20 g, 0.88 mmol) in THF (2 mL) was added Et_3N (0.37 mL, 2.63 mmol) followed by 2,4,6-trichlorobenzoyl chloride (0.27 mL, 1.75 mmol) after 10 min at 0 °C under a N_2 atmosphere, and the mixture was stirred at room temperature for 2 h. The reaction mixture was filtered and evaporated, and the resulting product was dissolved in toluene (1 mL). To this mixture was added DMAP (0.27 g, 2.19 mmol) and alcohol **7** (0.21 g, 0.96 mmol) in toluene (1 mL) at 0 °C under a N_2 atmosphere, and the mixture was stirred at room temperature for 5 h. The reaction mixture was filtered through Celite, the filtrate was evaporated, and the residue was purified by column chromatography (60–120 mesh silica gel, 7% EtOAc in PE) to afford **21** (0.29 g, 76%) as a colorless syrup. $[\alpha]_D^{27}$ = –23.7 (*c* = 0.30, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 295 K): δ = 7.18 (d, *J* = 8.7 Hz, 2 H, Ar-H), 6.82 (d, *J* = 8.7 Hz, 2 H, Ar-H), 5.83 (ddd, *J* = 6.8, 10.6, 17.0 Hz, 1 H, CH=CH_2), 5.36–5.22 (m, 3 H, =CH_2, CHOCO), 4.49 (d, *J* = 11.3 Hz, 1 H, OCHPMP), 4.46 (d, *J* = 11.3 Hz, 1 H, OCH′PMP), 4.32–4.20 (m, 1 H, CHOTBS), 3.78 (s, 3 H, OCH_3), 3.62–3.54 (m, 1 H, CHOPMB), 2.53 (dd, *J* = 6.4, 14.7 Hz, 1 H, CH), 2.38 (dd, *J* = 6.0, 14.7 Hz, 1 H, CH′), 1.18 (d, *J* = 6.0 Hz, 3 H, CH_3), 1.14 (d, *J* = 6.4 Hz, 3 H, CH_3), 0.86 [s, 9 H, $C(CH_3)_3$], 0.06 (s, 3 H, CH_3), 0.04 (s, 3 H, CH_3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 295 K): δ = 170.4, 159.0, 132.9, 130.3, 129.1 (2 C), 118.4, 113.7 (2 C), 76.4, 75.5, 70.9, 65.6, 55.2, 45.0, 25.8 (3 C), 23.8, 18.0, 15.9, –4.6, –4.9 ppm. IR (neat): $\tilde{\nu}$ = 2938, 2859, 1739, 1613, 1513, 1461, 1376, 1251, 1177, 1093, 997, 829 cm^{-1}. HRMS (ESI): calcd. for $C_{23}H_{38}O_5Si$ $[M + Na]^+$ 445.2386; found 445.2407.

(*R*)-[(3*R*,4*S*)-4-(4-Methoxybenzyloxy)pent-1-en-3-yl] 3-Hydroxybutanoate (5): To a solution of **21** (0.29 g, 0.67 mmol) in THF (1 mL) was added TBAF (1.0 M in THF, 0.81 mL) at 0 °C, and the mixture was stirred at room temperature for 2 h. The reaction mixture was concentrated, and the residue was purified by column chromatography (60–120 mesh silica gel, 15% EtOAc in PE) to give **5** (0.19 g, 90%) as a yellow syrup. $[\alpha]_D^{27}$ = –90.7 (*c* = 0.15, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 295 K): δ = 7.22 (d, *J* = 8.3 Hz, 2 H, Ar-H), 6.84 (d, *J* = 8.3 Hz, 2 H, Ar-H), 5.81 (ddd, *J* = 6.4, 10.3, 16.7 Hz, 1 H, CH=CH_2), 5.45 (m, 1 H, OCHO), 5.29 (d, *J* = 16.7 Hz, 1 H, =CH_2), 5.25 (d, *J* = 10.3 Hz, 1 H, =CH_2), 4.51 (d, *J* = 11.8 Hz, 1 H, OCHPMP), 4.45 (d, *J* = 11.8 Hz, 1 H, OCH′PMP), 4.17–4.11 (m, 1 H, OCH), 3.79 (s, 3 H, OCH_3), 3.61–3.59 (m, 1 H, CHOPMB), 2.94 (br. s, 1 H, OH), 2.50–2.39 (m, 2 H, CH_2), 1.21 (d, *J* = 5.9 Hz, 3 H, CH_3), 1.14 (d, *J* = 6.4 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 295 K): δ = 172.0, 159.1, 132.6, 130.1, 129.3 (2 C), 118.4, 113.7 (2 C), 76.1, 75.2, 70.7, 64.5, 55.2, 43.3, 22.4, 15.2 ppm. IR (neat): $\tilde{\nu}$ = 3446, 2974, 2932, 1733, 1613, 1514, 1249, 1175, 1092, 1035, 988, 939, 823 cm^{-1}. HRMS (ESI): calcd. for $C_{17}H_{24}O_5$ $[M + Na]^+$ 331.1521; found 331.1534.

***tert*-Butyl[(3*R*,4*S*)-4-(4-methoxybenzyloxy)pent-1-en-3-yloxy]dimethylsilane (22):** To a solution of **7** (1.0 g, 4.50 mmol) in CH_2Cl_2 (10 mL) was added imidazole (0.61 g, 9.01 mmol) at 0 °C. After 15 min TBSCl (0.81 g, 5.41 mmol) was added portionwise at 0 °C, and the mixture was stirred at room temperature for 3 h. The reaction mixture was worked up as described for **19**, and the residue was purified by column chromatography (60–120 mesh silica gel, 3% EtOAc in PE) to afford **22** (1.48 g, 98%) as a colorless oil. $[\alpha]_D^{27}$ = +0.8 (*c* = 0.25, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$, 295 K): δ = 7.18 (d, *J* = 8.3 Hz, 2 H, Ar-H), 6.79 (d, *J* = 8.3 Hz, 2 H, Ar-H), 5.84 (ddd, *J* = 5.9, 10.2, 17.1 Hz, 1 H, CH=CH_2), 5.22 (d, *J* = 17.1 Hz, 1 H, =CH_2), 5.12 (d, *J* = 10.2 Hz, 1 H, =CH_2), 4.46 (s, 2 H, OCH_2PMP), 4.08 (m, 1 H, CHOTBS), 3.78 (s, 3 H, OCH_3), 3.42–3.36 (m, 1 H, CHOPMB), 1.09 (d, *J* = 5.9 Hz, 3 H, CH_3), 0.90 [s, 9 H, $C(CH_3)_3$], 0.05 (s, 3 H, CH_3), 0.02 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 295 K): δ = 158.9, 138.8, 131.0, 129.1 (2 C), 115.3, 113.6 (2 C), 78.3, 76.7, 70.9, 55.1, 25.9 (3 C), 18.2, 15.6, –4.5, –4.8 ppm. IR (neat): $\tilde{\nu}$ = 2934, 2858, 1614, 1513, 1464, 1375, 1301, 1249, 1173, 1092, 1037, 925, 835 cm^{-1}. HRMS (ESI): calcd. for $C_{19}H_{32}O_3Si$ $[M + Na]^+$ 359.2018; found 359.2024.

(4*R*,5*S*,*E*)-2-Tosylethyl 4-(*tert*-Butyldimethylsilyloxy)-5-(4-methoxybenzyloxy)hex-2-enoate (6): To a mixture of alkene **22** (1.48 g, 4.40 mmol), 50% aq. NMO (2.06 mL, 8.81 mmol) in acetone/water (4:1, 6 mL) was added a catalytic amount of OsO_4 (0.02 M in tolu-

ene, 0.19 mL) at 0 °C, and the mixture was stirred at room temperature for 12 h. The reaction mixture was treated with aq. Na_2SO_3 (5 mL), acetone was removed under reduced pressure and extracted with EtOAc (2 × 30 mL). The organic phase was dried (Na_2SO_4), concentrated, and purified by column chromatography (60–120 mesh silica gel, 25% EtOAc in PE) to afford **23** (1.50 g, 92%) as a colorless oil. To a stirred solution of diol **23** (1.50 g, 4.05 mmol) in acetone/water (5:1, 7.5 mL) at 0 °C was added $NaIO_4$ (1.04 g, 4.86 mmol), and the mixture was stirred to room temperature for 1 h. Acetone was removed under reduced pressure, and the residue was extracted with $CHCl_3$ (15 mL), dried (Na_2SO_4), and evaporated to give aldehyde **24** as a colorless oil. To a solution of (*p*-toulenesulfonylethoxycarbonylmethylene)triphenylphosphorane (4.07 g, 8.11 mmol) in benzene (10 mL) at reflux was added aldehyde **24** in benzene (5 mL), and the mixture was stirred for 5 h. Benzene was evaporated under reduced pressure, and the residue was purified by column chromatography (*cis*/*trans* isomers **6a**/**6** in 1:4). First eluted (60–120 mesh silica gel, 9% EtOAc in PE) was **6a** (0.41 g, 18%) as a colorless oil. Second eluted (60–120 mesh silica gel, 10% EtOAc in PE) was **6** (1.60 g, 70%) as a colorless oil. Data for **6a**: $[\alpha]_D^{27}$ = +5.8 (*c* = 0.28, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 295 K): δ = 7.72 (d, *J* = 8.3 Hz, 2 H, Ar-H), 7.29 (d, *J* = 8.3 Hz, 2 H, Ar-H), 7.20 (d, *J* = 8.7 Hz, 2 H, Ar-H), 6.80 (d, *J* = 8.7 Hz, 2 H, Ar-H), 6.10 (dd, *J* = 8.3, 11.1 Hz, 1 H, CH=CH), 5.41 (dd, *J* = 1.1, 11.1 Hz, 1 H, CH=CH), 5.39 (m, 1 H, CHOTBS), 4.54 (d, *J* = 11.7 Hz, 1 H, OCHPMP), 4.47 (d, *J* = 11.7 Hz, 1 H OCH′PMP), 4.46–4.31 (m, 2 H, CH_2OCO), 3.80 (s, 3 H, OCH_3), 3.41–3.32 (m, 3 H, CHOPMB, CH_2SO_2), 2.45 (s, 3 H, CH_3), 1.03 (d, *J* = 6.4 Hz, 3 H, CH_3), 0.88 [s, 9 H, $C(CH_3)_3$], 0.06 (s, 3 H, CH_3), 0.01 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 295 K): δ = 164.7, 158.9, 152.2, 144.9, 136.4, 131.0, 129.9 (2 C), 129.3 (2 C), 128.0 (2 C), 117.9, 113.5 (2 C), 77.6, 70.6, 70.5, 57.4, 55.2, 55.0, 25.7 (3 C), 21.6, 18.1, 15.7, –4.8 (2 C) ppm. IR (neat): $\tilde{\nu}$ = 2925, 1750, 1604, 1510, 1309, 1248, 1145, 1088, 815 cm^{-1}. HRMS (ESI): calcd. for $C_{29}H_{42}O_7SSi$ [M + Na]$^+$ 585.2318; found 585.2320. Data for **6**: $[\alpha]_D^{27}$ = –4.3 (*c* = 0.45, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 295 K): δ = 7.77 (d, *J* = 8.3 Hz, 2 H, Ar-H), 7.33 (d, *J* = 8.3 Hz, 2 H, Ar-H), 7.21 (d, *J* = 8.7 Hz, 2 H, Ar-H), 6.85 (dd, *J* = 4.5, 15.9 Hz, 1 H, CH=CH), 6.83 (d, *J* = 8.7 Hz, 2 H, Ar-H), 5.80 (dd, *J* = 1.5, 15.9 Hz, 1 H, CH=CH), 4.55–4.36 (m, 4 H, CH_2OCO, OCH_2PMP), 4.28–4.22 (m, 1 H, CHOTBS), 3.81 (s, 3 H, OCH_3), 3.52–3.36 (m, 3 H, CHOPMB, CH_2SO_2), 2.46 (s, 3 H, CH_3), 1.11 (d, *J* = 6.4 Hz, 3 H, CH_3), 0.93 [s, 9 H, $C(CH_3)_3$], 0.07 (s, 3 H, CH_3), 0.02 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 295 K): δ = 165.6, 159.1, 150.1, 144.9, 136.3, 130.4, 129.9 (2 C), 129.2 (2 C), 128.1 (2 C), 119.8, 113.7 (2 C), 77.5, 74.6, 70.9, 57.7, 55.2, 55.1, 25.8 (3 C), 21.6, 18.1, 15.4, –4.7, –4.8 ppm. IR (neat): $\tilde{\nu}$ = 2934, 2857, 1722, 1647, 1513, 1462, 1383, 1250, 1144, 1089, 1032, 829 cm^{-1}. HRMS (ESI): calcd. for $C_{29}H_{42}O_7SSi$ [M + Na]$^+$ 585.2318; found 585.2319.

(4*R*,5*S*,*E*)-2-Tosylethyl 4-(*tert*-Butyldimethylsilyloxy)-5-hydroxyhex-2-enoate (25): To a stirred solution of **6** (1.60 g, 2.85 mmol) in CH_2Cl_2/H_2O (19:1, 8 mL) at 0 °C was added DDQ (0.71 g, 3.13 mmol), and the mixture was stirred to room temperature for 30 min. The reaction mixture was treated with satd. aq. $NaHCO_3$ (1 mL), dried (Na_2SO_4), and filtered through Celite by using $CHCl_3$. The solvent was evaporated, and the residue was purified by column chromatography (60–120 mesh silica gel, 25% EtOAc in PE) to give **25** (1.11 g, 88%) as a colorless oil. $[\alpha]_D^{27}$ = –22.0 (*c* = 0.20, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 295 K): δ = 7.80 (d, *J* = 8.3 Hz, 2 H, Ar-H), 7.36 (d, *J* = 8.3 Hz, 2 H, Ar-H), 6.78 (dd, *J* = 4.9, 15.9 Hz, 1 H, CH=CH), 5.76 (d, *J* = 1.5, 15.9 Hz, 1 H, CH=CH), 4.54–4.36 (m, 2 H, CH_2OCO), 4.18–4.11 (m, 1 H, CHOTBS), 3.83–3.68 (m, 1 H, OCH), 3.46–3.40 (m, 2 H, CH_2SO_2), 2.46 (s, 3 H, CH_3), 1.90 (br. s, 1 H, OH), 1.10 (d, *J* = 6.4 Hz, 3 H, CH_3), 0.92 [s, 9 H, $C(CH_3)_3$], 0.08 (s, 3 H, CH_3), 0.04 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 295 K): δ = 165.2, 148.0, 145.0, 136.3, 129.9 (2 C), 128.1 (2 C), 121.0, 75.6, 70.1, 57.7, 55.0, 25.7 (3 C), 21.6, 18.1, 17.2, –4.6, –5.0 ppm. IR (neat): $\tilde{\nu}$ = 3515, 2933, 2892, 2858, 1721, 1654, 1599, 1462, 1390, 1257, 1143, 1082, 1021, 981, 835 cm^{-1}. HRMS (ESI): calcd. for $C_{21}H_{34}O_6SSi$ [M + Na]$^+$ 465.1743; found 465.1760.

(4*R*,5*S*,*E*)-2-Tosylethyl 5-(Acryloyloxy)-4-(*tert*-butyldimethyl silyloxy)hex-2-enoate (26): To a stirred solution of **25** (1.11 g, 2.51 mmol) in CH_2Cl_2 (11 mL) was added DIPEA (1.74 mL, 10.05 mmol) followed by acrolyl chloride (0.24 mL, 3.01 mmol) at 0 °C. A catalytic amount of DMAP was added to the reaction mixture, which was then stirred at room temperature for 40 min. Water (10 mL) was added, and the organics were extracted with CH_2Cl_2 (20 mL). The solution was washed with brine (8 mL) and dried (Na_2SO_4). The solvent was evaporated under reduced pressure, and the residue was purified by column chromatography (60–120 mesh silica gel, 12% EtOAc in PE) to afford **26** (1.18 g, 94%) as a light yellow oil. $[\alpha]_D^{27}$ = –13.2 (*c* = 0.35, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 295 K): δ = 7.81 (d, *J* = 8.3 Hz, 2 H, Ar-H), 7.37 (d, *J* = 8.3 Hz, 2 H, Ar-H), 6.70 (dd, *J* = 4.2, 15.5 Hz, 1 H, CH=CH), 6.39 (dd, *J* = 1.1, 17.0 Hz, 1 H, =CH_2), 6.08 (dd, *J* = 10.6, 17.4 Hz, 1 H, CH=CH_2), 5.87–5.80 (m, 2 H, CH=CH, =CH_2), 4.90 (qd, *J* = 2.6, 6.4 Hz, 1 H, CHOCO), 4.52–4.35 (m, 3 H, CH_2OCO, CHOTBS), 3.47–3.37 (m, 2 H, CH_2SO_2), 2.47 (s, 3 H, CH_3), 1.15 (d, *J* = 6.4 Hz, 3 H, CH_3), 0.92 [s, 9 H, $C(CH_3)_3$], 0.04 (s, 3 H, CH_3), 0.00 (s, 3 H, CH_3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 295 K): δ = 165.4, 165.2, 147.9, 144.9, 136.4, 131.0, 129.9 (2 C), 128.4, 128.1 (2 C), 120.8, 73.1, 72.5, 57.8, 55.1, 25.7 (3 C), 21.6, 18.2, 13.5, –4.7, –5.0 ppm. IR (neat): $\tilde{\nu}$ = 2935, 2858, 1723, 1653, 1403, 1321, 1262, 1194, 1145, 1066, 1030, 979, 834 cm^{-1}. HRMS (ESI): calcd. for $C_{24}H_{36}O_7SSi$ [M + Na]$^+$ 519.1848; found 519.1838.

(4*R*,5*S*,*E*)-5-(Acryloyloxy)-4-(*tert*-butyldimethylsilyloxy)hex-2-enoic Acid (4): To a solution of **26** (1.18 g, 2.38 mmol) in benzene (4 mL) was added DBN (0.29 g, 2.38 mmol) in benzene (2 mL) at room temperature, and the mixture was stirred for 12 h. Then ether/water (1:1, 4 mL) was added to the reaction mixture. The water layer was acidified with aq. 1 N HCl and extracted with EtOAc (2 × 20 mL). The organic layer was dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by column chromatography (60–120 mesh silica gel, 30% EtOAc in PE) to afford **4** (0.48 g, 64%) as a colorless oil. $[\alpha]_D^{27}$ = –33.1 (*c* = 0.20, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 295 K): δ = 7.02 (dd, *J* = 4.2, 15.5 Hz, 1 H, CH=CH), 6.42 (dd, *J* = 1.1, 17.4 Hz, 1 H, =CH_2), 6.15–6.03 (m, 2 H, CH=CH_2, CH=CH), 5.85 (dd, *J* = 1.1, 10.6 Hz, 1 H, =CH_2), 4.99 (qd, *J* = 3.0, 6.4 Hz, 1 H, CHOCO), 4.53 (m, 1 H, CHOTBS), 1.20 (d, *J* = 6.4 Hz, 3 H, CH_3), 0.94 [s, 9 H, $C(CH_3)_3$], 0.06 (s, 3 H, CH_3), 0.04 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 295 K): δ = 170.8, 165.5, 149.2, 131.1, 128.5, 121.4, 73.3, 72.6, 25.7 (3 C), 18.2, 13.7, –4.7, –5.0 ppm. IR (neat): $\tilde{\nu}$ = 3436, 2932, 2858, 1725, 1702, 1657, 1465, 1409, 1295, 1262, 1194, 1160, 1065, 1035, 982, 837 cm^{-1}. HRMS (ESI): calcd. for $C_{15}H_{26}O_5Si$ [M + Na]$^+$ 337.1447; found 337.1450.

(4*R*,5*S*,*E*)-{(*R*)-4-[(3*R*,4*S*)-4-(4-Methoxybenzyloxy)pent-1-en-3-yloxy]-4-oxobutan-2-yl} 5-(Acryloyloxy)-4-(tert-butyldimethyl silyloxy)hex-2-enoate (3): To a stirred solution of **4** (0.05 g, 0.16 mmol) in THF (1 mL) was added Et_3N (0.07 mL, 0.48 mmol) followed by 2,4,6-trichlorobenzoyl chloride (0.05 mL, 0.32 mmol) at 0 °C under a N_2 atmosphere, and the mixture was stirred at room temperature for 2 h. The reaction mixture was filtered, and the fil-

trate was evaporated. The resulting anhydride was dissolved in toluene (1 mL). To this mixture was added DMAP (0.05 g, 0.40 mmol) followed by a solution of alcohol **5** (0.06 g, 0.18 mL) in toluene (1 mL) at 0 °C under a N_2 atmosphere, and the mixture was stirred at room temperature for 6 h. The reaction mixture was filtered through Celite, and the filtrate was evaporated. The crude residue was purified by column chromatography (60–120 mesh silica gel, 7% ethyl acetate in PE) to give **3** (0.06 g, 62%) as a colorless syrup. $[\alpha]_D^{27}$ = +11.9 (*c* = 0.15, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 295 K): δ = 7.18 (d, *J* = 8.5 Hz, 2 H, Ar-H), 6.83 (dd, *J* = 4.3, 16.0 Hz, 1 H, CH=CH), 6.81 (d, *J* = 8.5 Hz, 2 H, Ar-H), 6.40 (dd, *J* = 1.5, 17.2 Hz, 1 H, =CH_2), 6.08 (dd, *J* = 10.4, 17.4 Hz, 1 H, CH=CH_2), 5.97 (dd, *J* = 1.7, 15.5 Hz, 1 H, =CH_2), 5.87–5.71 (m, 2 H, CH=CH_2, CH=CH), 5.41–5.19 (m, 4 H, =CH_2, 2 CHOCO), 5.0–4.89 (m, 1 H, CHOCO), 4.53–4.39 (m, 3 H, OCH_2PMP, CHOTBS), 3.78 (s, 3 H, OCH_3), 3.61–3.52 (m, 1 H, CHOPMB), 2.73 (dd, *J* = 7.0, 15.5 Hz, 1 H, CH), 2.55 (qd, *J* = 6.4, 15.5 Hz, 1 H, CH′), 1.37 (d, *J* = 6.2 Hz, 3 H, CH_3), 1.16 (d, *J* = 6.4 Hz, 3 H, CH_3), 1.12 (d, *J* = 6.4 Hz, 3 H, CH_3), 0.92 [s, 9 H, $C(CH_3)_3$], 0.04 (s, 3 H, CH_3), 0.01 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 295 K): δ = 169.2, 165.5, 165.2, 159.1, 146.8, 132.8, 131.0, 130.4, 129.2 (2 C), 128.5, 122.1, 118.3, 113.7 (2 C), 76.4, 75.4, 73.3, 72.7, 70.8, 67.6, 55.2, 41.1, 25.7 (3 C), 19.8, 18.2, 15.5, 13.5, –4.7, –5.0 ppm. IR (neat): $\tilde{\nu}$ = 2927, 2857, 1728, 1617, 1513, 1460, 1376, 1254, 1188, 1063, 982, 835 cm^{-1}. HRMS (ESI): calcd. for $C_{32}H_{48}O_9Si$ $[M + Na]^+$ 627.2965; found 627.2975.

(2*R*,6*R*,7*E*,11*S*,12*R*,13*E*)-12-(*tert*-Butyldimethylsilyloxy)-6-[(*S*)-1-(4-methoxybenzyloxy)ethyl]-2,11-dimethyl-1,5,10-trioxacyclopentadeca-7,13-diene-4,9,15-trione (27): To a solution of **3** (0.05 g, 0.08 mmol) in dry CH_2Cl_2 (50 mL) was added Grubbs second generation catalyst (5 mol-%), and the mixture was stirred at reflux for 18 h under a N_2 atmosphere. Most of the solvent was then distilled off, and the concentrated solution was left to stir at room temperature for 2 h under a flow of air to decompose the catalyst. The reaction mixture was evaporated to dryness to give a brown residue, which was purified by column chromatography (60–120 mesh silica gel, 9% EtOAc in PE) to afford compound **27** (0.028 g, 74% of yield; based on 20% starting material [eluted first at 7% EtOAc in PE] recovery) as a yellow solid. M.p. 67–69 °C. $[\alpha]_D^{27}$ = +1.0 (*c* = 0.10, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 295 K): δ = 7.23 (d, *J* = 8.7 Hz, 2 H, Ar-H), 7.03 (dd, *J* = 3.8, 15.5 Hz, 1 H, CH=CH), 6.86 (d, *J* = 8.7 Hz, 2 H, Ar-H), 6.40 (dd, *J* = 8.3, 15.7 Hz, 1 H, CH=CH), 6.07 (dd, *J* = 1.5, 15.5 Hz, 1 H, CH=CH), 5.86 (d, *J* = 15.7 Hz, 1 H, CH=CH), 5.40 (dd, *J* = 4.2, 8.7 Hz, 1 H, CHOCO), 5.35–5.23 (m, 1 H, CHOCO), 5.14–5.06 (m, 1 H, CHOCO), 4.53 (d, *J* = 12.1 Hz, 1 H, OCHPMP), 4.49 (d, *J* = 12.1 Hz, 1 H, OCH′PMP), 4.34–4.30 (m, 1 H, CHOTBS), 3.81 (s, 3 H, OCH_3), 3.67–3.55 (m, 1 H, CHOPMB), 2.77 (dd, *J* = 3.8, 15.1 Hz, 1 H, CH), 2.58 (dd, *J* = 10.2, 15.1 Hz, 1 H, CH′), 1.39 (d, *J* = 6.4 Hz, 3 H, CH_3), 1.36 (d, *J* = 7.2 Hz, 3 H, CH_3), 1.15 (d, *J* = 6.4 Hz, 3 H, CH_3), 0.88 [s, 9 H, $C(CH_3)_3$], 0.09 (s, 3 H, CH_3), 0.05 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 295 K): δ = 168.4, 166.0, 163.6, 159.3, 146.0, 142.6, 130.0, 129.4 (2 C), 125.4, 122.9, 113.8 (2 C), 75.6, 75.5, 74.9, 74.3, 71.1, 68.1, 55.3, 41.6, 25.7 (3 C), 20.0, 18.2, 17.6, 16.0, –4.9, –5.1 ppm. IR (KBr): $\tilde{\nu}$ = 2928, 2856, 1734, 1657, 1615, 1517, 1466, 1382, 1254, 1093, 1036, 983, 837 cm^{-1}. HRMS (ESI): calcd. for $C_{30}H_{44}O_9Si$ $[M + Na]^+$ 599.2652; found 599.2663.

(2*R*,6*R*,7*E*,11*S*,12*R*,13*E*)-12-Hydroxy-6-[(*S*)-1-hydroxyethyl]-2,11-dimethyl-1,5,10-trioxacyclopentadeca-7,13-diene-4,9,15-trione (1): To a solution of **27** (0.01 g, 0.02 mmol) in CH_2Cl_2 (1 mL) was added $TiCl_4$ (0.006 g, 0.03 mmol) in CH_2Cl_2 (1 mL) at 0 °C under a N_2 atmosphere, and the mixture was stirred at room temperature for 3 h. Sat. aq. $NaHCO_3$ solution (5 mL) was added and extracted with $CHCl_3$ (2 × 15 mL). The combined organic layers were washed with water (5 mL) and brine (5 mL) and dried (Na_2SO_4). The solvent was evaporated under reduced pressure, and the residue was purified by column chromatography (60–120 mesh silica gel, 1.3% MeOH in $CHCl_3$) to afford **1** (0.004 g, 67%) as a pale yellow oil. $[\alpha]_D^{22}$ = +8.9 (*c* = 0.15, EtOH) {ref.[2] $[\alpha]_D^{22}$ = +5.5 (*c* = 0.30, EtOH)}. ^{1}H NMR (500 MHz, [D$_6$]acetone, 295 K): δ = 7.04 (dd, *J* = 3.5, 15.5 Hz, 1 H, CH=CH), 6.47 (dd, *J* = 8.5, 16.2 Hz, 1 H, CH=CH), 6.08 (dd, *J* = 1.4, 15.5 Hz, 1 H, CH=CH), 5.89 (dd, *J* = 0.4, 16.2 Hz, 1 H, CH=CH), 5.28 (dqd, *J* = 4.2, 6.3, 10.6 Hz, 1 H, CHOCO), 5.18 (ddd, *J* = 3.5, 4.9, 8.5 Hz, 1 H, CHOCO), 5.12 (d, *J* = 2.8, 6.3 Hz, 1 H, CHOCO), 4.56 (d, *J* = 4.2 Hz, 1 H, OH), 4.47 (br. s, 1 H, CHOH), 4.15 (d, *J* = 4.9 Hz, 1 H, OH), 3.90 (qdd, *J* = 4.9, 5.6, 6.3 Hz, 1 H, CHOH), 2.89 (dd, *J* = 3.5, 14.8 Hz, 1 H, CH), 2.51 (dd, *J* = 10.6, 14.8 Hz, 1 H, CH′), 1.39 (d, *J* = 6.3 Hz, 3 H, CH_3), 1.36 (d, *J* = 6.3 Hz, 3 H, CH_3), 1.14 (d, *J* = 6.3 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, [D$_6$]acetone, 295 K): δ = 169.08, 166.20, 164.72, 147.23, 144.40, 126.15, 122.92, 78.19, 75.24, 75.11, 68.98, 68.49, 42.10, 20.07, 19.11, 17.94 ppm. IR (neat): $\tilde{\nu}$ = 3450, 2926, 1716, 1650, 1644, 1272 cm^{-1}. HRMS (ESI): calcd. for $C_{16}H_{22}O_8$ $[M + Na]^+$ 365.1212; found 365.1209.

Supporting Information (see footnote on the first page of this article): Copies of the ^{1}H NMR and ^{13}C NMR spectra for all compounds.

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[1] a) M. Hayashi, Y.-P. Kim, H. Hiraoka, M. Natori, S. Takamatsu, T. Kawakubo, R. Masuma, K. Komiyama, S. Omura, *J. Antibiot.* **1995**, *48*, 1435–1439; b) S. Takamatsu, Y.-P. Kim, M. Hayashi, H. Hiraoka, M. Natori, K. Komiyama, S. Omura, *J. Antibiot.* **1996**, *49*, 95–98; c) S. Takamatsu, H. Hiraoka, Y.-P. Kim, M. Hayashi, M. Natori, K. Komiyama, S. Omura, *J. Antibiot.* **1997**, *50*, 878–880; d) A. Numata, M. Iritani, T. Yamada, K. Minoura, E. Matsumura, T. Yamori, T. Tsuruo, *Tetrahedron Lett.* **1997**, *38*, 8215–8218; e) A. Fukami, Y. Taniguchi, T. Nakamura, M.-C. Rho, K. Kawaguchi, M. Hayashi, K. Komiyama, S. Omura, *J. Antibiot.* **1999**, *52*, 501–504; f) T. Yamada, M. Iritani, M. Doi, K. Minoura, T. Ito, A. Numata, *J. Chem. Soc. Perkin Trans. 1* **2001**, 3046–3053; g) T. Yamada, M. Iritani, K. Minoura, A. Numata, Y. Kobayashi, Y.-G. Wang, *J. Antibiot.* **2002**, *55*, 147–154; h) Y. Matsuya, H. Nemoto, *Heterocycles* **2005**, *65*, 1741–1749; i) Y. Matsuya, H. Nemoto, *Heterocycles* **2010**, *81*, 57–66.

[2] T. Yamada, K. Minoura, R. Tanaka, A. Numata, *J. Antibiot.* **2007**, *60*, 370–375.

[3] Synthesis of macrosphelide E: a) M. Ono, H. Nakamura, F. Konno, H. Akita, *Tetrahedron: Asymmetry* **2000**, *11*, 2753–2764; b) G. V. M. Sharma, Ch. Chandramouli, *Tetrahedron Lett.* **2002**, *43*, 9159–9161; c) H. Akita, H. Nakamura, M. Ono, *Chirality* **2003**, *15*, 352–359; d) T. Kawaguchi, N. Funamori, Y. Matsuya, H. Nemoto, *J. Org. Chem.* **2004**, *69*, 505–509; e) K. R. Prasad, P. Gutala, *Tetrahedron* **2011**, *67*, 4514–4520.

[4] G. V. M. Sharma, Ch. Chandramouli, *Tetrahedron Lett.* **2003**, *44*, 8161–8163.

[5] Synthesis of macrosphelides by using a RCM protocol: a) Y. Matsuya, T. Kawaguchi, H. Nemoto, *Org. Lett.* **2003**, *5*, 2939–

2941; b) G. V. M. Sharma, K. V. Babu, *Tetrahedron: Asymmetry* **2007**, *18*, 2175–2184.
[6] W. W. Wood, G. M. Watson, *J. Chem. Soc. Perkin Trans. 1* **1987**, 2681–2688.
[7] a) P. J. Garegg, B. Samuclson, *Synthesis* **1979**, 813–815; b) K. Krohn, U. Florke, J. Keine, I. Terstiege, *J. Carbohydr. Chem.* **1998**, *17*, 171–195.
[8] a) S. Saito, T. Ishikawa, A. Kuroda, K. Koga, T. Moriwake, *Tetrahedron* **1992**, *48*, 4067–4086; b) For (±)-**17** to (±)-**20**: E. Hungerbuhler, D. Seebach, D. Wasmuth, *Helv. Chim. Acta* **1981**, *64*, 1467–1486; c) For (+)-**17** to (+)-**20**: J. Lu, J. Ma, X. Xie, B. Chen, X. She, X. Phan, *Tetrahedron: Asymmetry* **2006**, *17*, 1066–1073.
[9] H. Miyaoka, M. Yamanishi, A. Hoshino, A. Kinbara, *Tetrahedron* **2006**, *62*, 4103–4109.
[10] J. Inanaga, K. Hirata, H. Saeki, Y. Katsuki, M. Yamaguchi, *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989–1993.
[11] a) H. C. Kolb, M. S. V. Nieuwenhze, K. B. Sharpless, *Chem. Rev.* **1994**, *94*, 2483–2547; b) S. Chandrasekhar, A. Sudhakar, *Org. Lett.* **2010**, *12*, 236–238.
[12] E. W. Colvin, T. A. Purcell, R. A. Raphael, *J. Chem. Soc. Perkin Trans. 1* **1976**, 1718–1722.
[13] a) R. H. Grubbs, S. Chang, *Tetrahedron* **1998**, *54*, 4413–4450; b) M. Scholl, S. Ding, C. W. Lee, R. H. Grubbs, *Org. Lett.* **1999**, *1*, 953–956; c) H. M. A. Hassan, *Chem. Commun.* **2010**, *46*, 9100–9106.
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