Enantio- and Diastereoselective Synthesis of (*E*)-1,5-*syn*-Diols: Application to the C(23)-C(40) Fragment of Tetrafibricin

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SUPPORTING INFORMATION – Experimental Procedures

General Methods: Tetrahydrofuran, dichloromethane, diethyl ether and toluene were purified by passing through a column of activated alumina (A-1). Hexanes, acetonitrile and trimethylsilyl chloride were purified by distillation from calcium hydride. Anhydrous pentane and methanol were purchased from Aldrich Chemical Company. Commercially available reagents were used without purification, except for the commercially available aldehydes that were purified by vacuum distillation before use. Unless otherwise indicated, all reactions were conducted under an atmosphere of argon using flamed-dried or oven-dried (140°C) glassware. Standard handling techniques for air-sensitive compounds were employed for all the operations. Celite 545® was dried at 140°C for at least 12 h prior to use. Removal of solvents was accomplished on a rotary evaporator at reduced pressure. Reaction mixtures were maintained at low temperature by using a Thermo NESLAB CB-60 cold bath. Enantiomeric excess and absolute configurations were determined using the Mosher method.[1]

Physical Properties and Spectroscopic Measurements: ^{1}H NMR spectra were recorded on a commercial NMR spectrometer at 400 MHz. ^{13}C NMR spectra were recorded on a commercial NMR spectrometer at 100 MHz. The proton signal for non-deuterated solvent (δ 7.24 ppm for $CHCl_3$) was used as an internal reference for ^{1}H NMR spectra. For ^{13}C NMR spectra, chemical shifts are reported relative to the δ 77.24 ppm resonance of $CDCl_3$. Infrared (IR) spectra were recorded as thin films using CH_2Cl_2 as the solvent on a FTIR instrument. Optical rotations were measured on a polarimeter using a quartz cell with 1 mL capacity and a 1 dm path length. Melting points were determined on a hot stage melting point apparatus and are uncorrected. High-resolution mass spectra were obtained at the University of Florida Mass Spectrometry Laboratory.

Analytical thin layer chromatography (TLC) was performed on Kieselgel 60 F254 glass plates precoated with a 0.25 mm thickness of silica gel. TLC plates were visualized with UV light and/or by staining with cerium molybdate (5g $Ce(SO_4)_2$, 25g $(NH_4)Mo_7O_{24}.4H_2O$, 450 mL H_2O, 50 mL H_2SO_4). Preparative thin layer chromatography (TLC) was performed on Kieselgel 60 F254 glass plates precoated with a 0.5 mm thickness of silica gel. Column chromatography was generally performed according to the method of Still[2] using Kieselgel 60 (230-400 mesh) silica gel.

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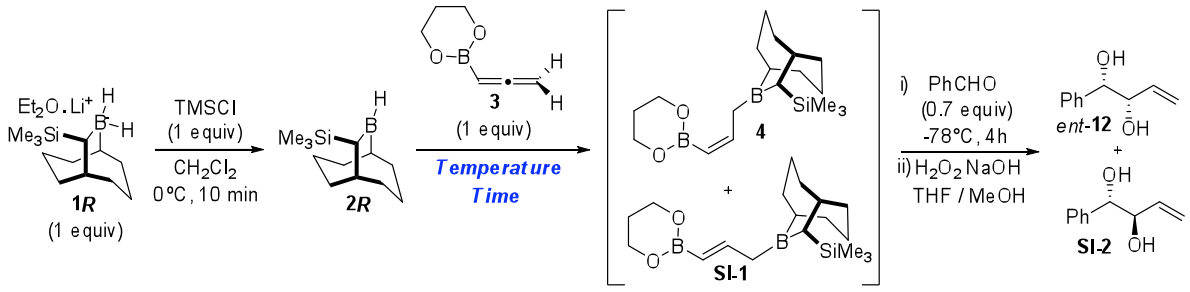
1. Preliminary Studies on the Synthesis of (*E*)-1,5-*syn*-diol 6 Using Allene 3.

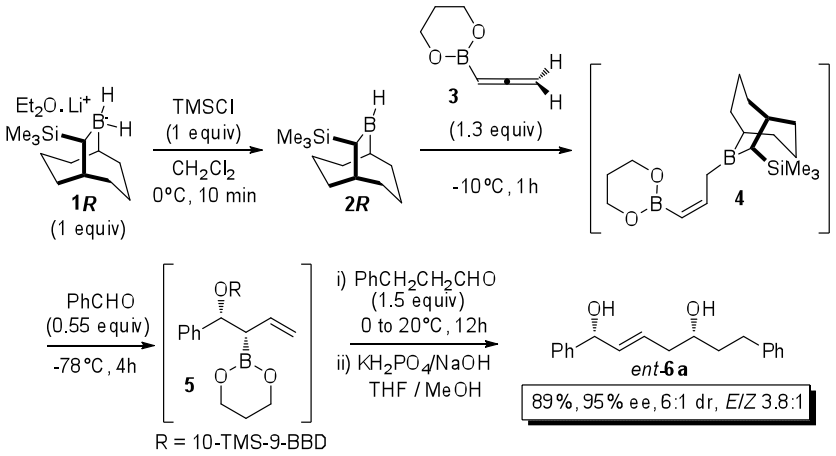
(a) Allene Hydroboration / First Allylboration Reaction:



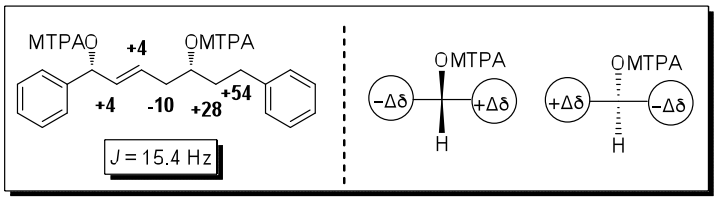
entry	*Temperature*	*Time*	*Results*
1	-10°C	1 h	73%, *syn*/*anti* (10:1)
2	-10°C	5 h	*syn*/*anti* (1.5:1)

The hydroboration reaction of **3** using in situ generated borane **2R** was performed under previously defined conditions.[3] When the hydroboration was performed at –10 °C for 1 h, followed by addition of PhCHO at -78 °C (entry 1 above), a 10 : 1 mixture of *ent*-**12** and the anti diastereomer **SI-2** was obtained following oxidative workup. Increasing the hydroboration reaction time to 5 h resulted in an erosion of the reaction diastereoselectivity (entry 2 above). This result indicates that the [1,3]-boratropic rearrangement that converts the kinetically formed (*Z*)-γ-boryl allylborane **4** to the thermodynamically favored (*E*)-γ-boryl allylborane **SI-1** is competitive under these conditions.

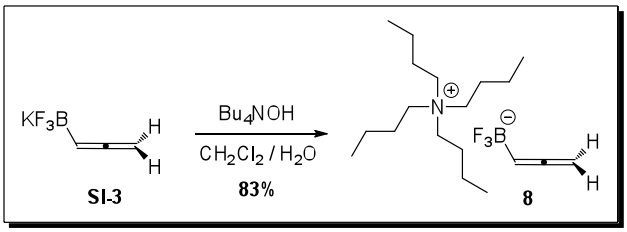
(b) Double Allylboration Reaction. Studies of double allylboration reactions of reagent **4** indicated that the second allylboration step of intermediate allylboronate **5** is not highly selective, in that a ca. 4-5 : 1 mixture of *ent*-**6a** together with the 1,5-anti diastereomer possessing an intervening (Z)-olefin is also obtained.



The relative and absolute stereochemistry of *ent*-**6a** from the preceding experiment was assigned by using the Mosher method; key data are summarized below.

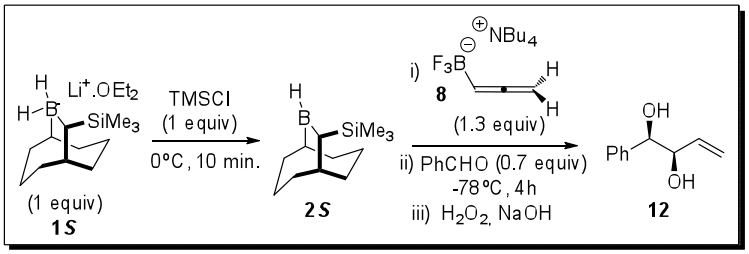


2. Synthesis of Allene 8



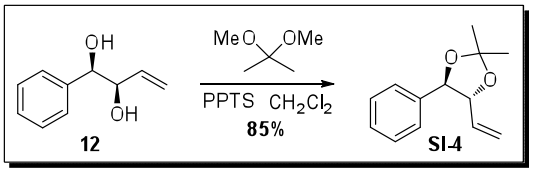
***N,N,N*-tributylbutan-1-aminium trifluoro(propa-1,2-dien-1-yl)borate (8)**. An established procedure[4] for synthesis of allylic trifluoroborate tetrabutylammonium salts was modified for preparation of allene **8**. A 1 M aqueous solution of tetrabutylammonium hydroxide (20.0 mL, 20.0 mmol, 1 equiv) was added to a suspension of the known potassium allenyl trifluoroborate[5] **SI-3** (2.92 g, 20.0 mmol, 1 equiv) in CH_2Cl_2 (30 mL). The reaction was stirred at room temperature for 30 min. The reaction mixture was then diluted with CH_2Cl_2 (20 mL), the organic layer was separated, dried over Mg_2SO_4, filtered, and concentrated in vacuo to afford tetrabutylammonium allenyl trifluoroborate **8** (5.81g, 83%) as a hygroscopic colorless solid which was stored in the glove box: ^{1}H (400 MHz, $CDCl_3$) 4.76 (bs, 1H), 4.09-4.06 (m, 2H), 3.18-3.14 (m, 8H), 1.61-1.53 (m, 8H), 1.38 (sextuplet, J = 7.3 Hz, 8H), 0.95 (t, J = 7.3 Hz, 12H); ^{13}C (100 MHz, $CDCl_3$) 210.6 (q, J = 4.3 Hz), 86.8 (bs), 65.6, 58.6, 24.0, 19.8, 13.8; ^{19}F (376 MHz, $CDCl_3$) -137.1 (d, J = 48 Hz); IR (neat) 2963, 2936, 2876, 1930, 1473, 1382, 1248, 1071, 996, 968, 882, 795, 739, 600 cm^{-1}; LRMS (ESI) calcd for $C_3H_3BF_3$ $[M\text{-}NBu_4]^-$ 107.0, found 107.2.

3. Optimization of Allene Hydroboration of 8 and the First Allylboration Reaction



(1*R*,2*R*)-1-phenylbut-3-ene-1,2-diol (12). To a 0 °C solution of borohydride **1*S*** (81.0 mg, 0.250 mmol, 1 equiv, considering a 90% yield for the conversion of borohydride **1*S*** to borane **2*S*** based on the borane **2*S*** titration[3]) in toluene (0.5 mL) was added TMSCl (32.0 μL, 0.250 mmol, 1 equiv). The reaction mixture was stirred for 10 min, then was cooled to -78 °C and a solution of allene **8** (0.114 g, 0.325 mmol,

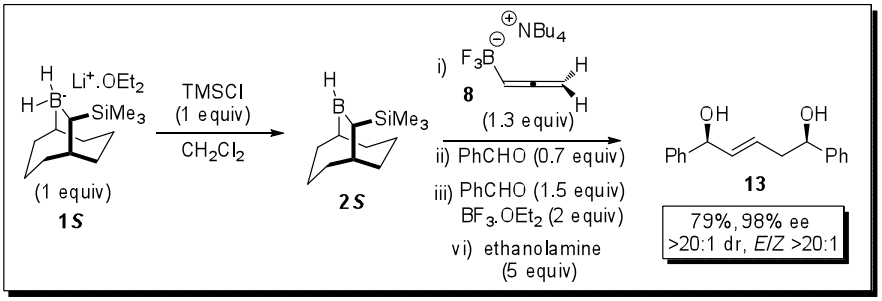
1.3 equiv) in toluene/CH_2Cl_2 (1.0 mL/0.1 mL) was added dropwise. The viscous mixture was stirred at -30 ^oC for 1 h. The resulting clear reaction mixture was then cooled to -78 ^oC and a solution of benzaldehyde (18.0 μL, 0.175 mmol, 0.7 equiv) in CH_2Cl_2 (0.3 mL) was added. After 4 h, aqueous 3 N NaOH (0.25 mL) and aqueous 50% H_2O_2 (0.1 mL) solutions were added follow by THF (1 mL) and MeOH (0.5 mL). The resulting mixture was stirred at 20 ^oC for 12 h. The biphasic mixture was poured into saturated aqueous NH_4Cl, and the crude product was extracted with ethyl acetate (3×). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, hexanes / ethyl acetate, gradient elution: 9:1 to 8:2 to 7:3) to afford *syn*-1,2-diol **12** (25.1 mg, 87%) as a colorless oil: $[\alpha]_D^{25}$ = -4.2 (*c* 0.66, $CHCl_3$); ee 97%; ^1H (400 MHz, $CDCl_3$) 7.34-7.25 (m, 5H), 5.68 (ddd, *J* = 17.4, 10.6, 5.6 Hz, 1H), 5.20 (dt, *J* = 17.2, 1.5 Hz, 1H), 5.10 (dt, *J* = 10.6, 1.5 Hz, 1H), 4.44 (d, *J* = 7.1 Hz, 1H), 4.19-4.15 (m, 1H), 2.98 (bs, 2H); ^{13}C (100 MHz, $CDCl_3$) 140.3, 136.5, 128.5, 128.3, 127.2, 117.2, 77.8, 77.1; IR (neat) 3390, 3086, 3064, 3031, 2892, 1494, 1454, 1424, 1334, 1257, 1197, 1126, 1053, 1017, 996, 928, 843, 763, 700, 666, 636 cm^{-1}; HRMS (ESI) calcd for $C_{10}H_{12}O_2Na$ $[M+Na]^+$ 187.0735, found 187.0738.



Absolute and relative stereochemistry assignment of 12: **(4*R*,5*R*)-2,2-dimethyl-4-phenyl-5-vinyl-1,3-dioxolane (SI-4)**.[6] To a solution of *syn*-1,2-diol **12** (0.100 g, 0.609 mmol, 1 equiv) in CH_2Cl_2 (0.25 mL) was added 2,2-dimethoxypropane (0.25 mL) and PPTS (15 mg, 0.061 mmol, 0.1 equiv). The reaction mixture was stirred at 20 ^oC for 12 h, and then poured into a saturated aqueous $NaHCO_3$ solution. The crude product was extracted with ethyl acetate (3×). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, hexanes / ethyl acetate, 9:1) to afford acetonide **SI-4** (0.105 g, 85%) as a colorless oil: $[\alpha]_D^{25}$ = -31.6 (*c* 0.74, $CHCl_3$); ^1H (400 MHz, $CDCl_3$) 7.33-7.24 (m, 5H), 5.83 (ddd, *J* = 17.4, 10.1, 7.1 Hz. 1H), 5.22-5.17 (m, 2H), 4.61 (d, *J* = 8.3 Hz, 1H), 4.15-4.11 (m, 1H), 1.54 (s, 3H), 1.49 (s, 3H); ^{13}C (100 MHz, $CDCl_3$) 137.4, 134.1, 128.6, 128.4, 126.6, 119.5, 109.5, 84.9, 83.2, 27.32, 27.26; IR (neat) 3086, 3066, 3032, 2986, 2934, 2877, 1454, 1379, 1371, 1238, 1172, 1124, 1084, 1055, 1030, 988, 930, 887, 812, 755, 699, 510 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{16}O_2Na$ $[M+Na]^+$ 227.1048, found 227.1049.

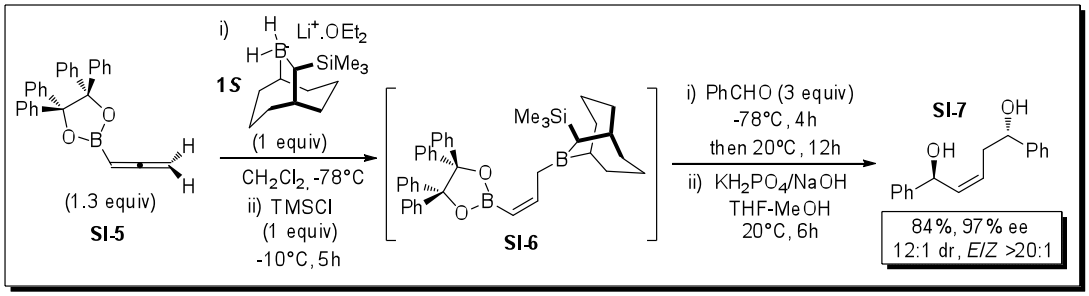
4. Double Allylboration Reactions of 9.

(a) Synthesis of (*E*)-1,5-*syn*-diol (13) as reference.



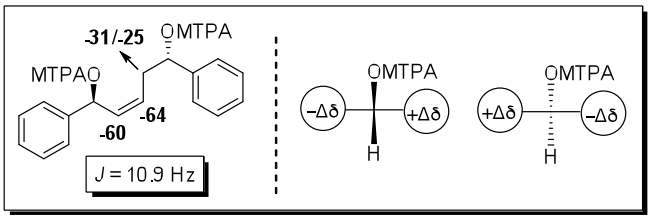
(1*S*,2*E*,5*R*)-1,5-diphenylpent-2-ene-1,5-diol (13). To a 0 °C solution of borohydride **1*S*** (81.0 mg, 0.250 mmol, 1 equiv, considering a 90% yield for the conversion of borohydride **1*S*** to borane **2*S*** based on titration[3]) in CH_2Cl_2 was added TMSCl (32.0 μL, 0.250 mmol, 1 equiv). The mixture was stirred for 10 min, then was cooled to -78 °C and a solution of allene **8** (0.114 g, 0.325 mmol, 1.3 equiv) in CH_2Cl_2 (1.0 mL) was added dropwise. The mixture was stirred at -30 °C for 1 h. The resulting clear reaction mixture was then cooled to -78 °C and benzaldehyde (18.0 μL, 0.175 mmol, 0.7 equiv) was added. Additional benzaldehyde (38.0 μL, 0.375 mmol, 1.5 equiv) was added 4 h later, followed by $BF_3.OEt_2$ (63.0 μL, 0.500 mmol, 2 equiv). The reaction mixture was stirred for an additional 4 h. Ethanolamine (75 μL, 1.25 mmol, 5 equiv) was then added and the reaction was allowed to warm to 20 °C and stirred for 2 h. The mixture was poured into a saturated aqueous NH_4Cl solution, and the crude product was extracted with ethyl acetate (3×). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The product was purified by flash column chromatography (SiO_2, hexanes / ethyl acetate, gradient elution: 8:2 to 7:3 to 6:4) to afford (*E*)-1,5-*syn*-diol **13** (35.0 mg, 79%) as a colorless oil: $[\alpha]_D^{25}$ = +49.6 (*c* 0.23, $CHCl_3$); ee 98%; ^{1}H (400 MHz, $CDCl_3$) 7.27-7.17 (m, 10H), 5.69-5.66 (m, 2H), 5.08-5.06 (m, 1H), 4.63 (t, *J* = 6.6 Hz, 1H), 2.56 (bs, 2H), 2.42-2.39 (m, 2H); ^{13}C (100 MHz, $CDCl_3$) 144.1, 143.1, 136.3, 128.7, 128.1, 127.8, 127.7, 126.4, 126.0, 75.1, 73.8, 42.3; IR (neat) 3360, 3085, 3061, 3029, 2921, 1667, 1602, 1493, 1452, 1318, 1197, 1028, 1007, 969, 913, 758, 699 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{18}O_2Na$ $[M+Na]^+$ 277.1204, found 227.1205.

(b) Synthesis of (*Z*)-1,5-*anti*-diol (SI-7) as reference.

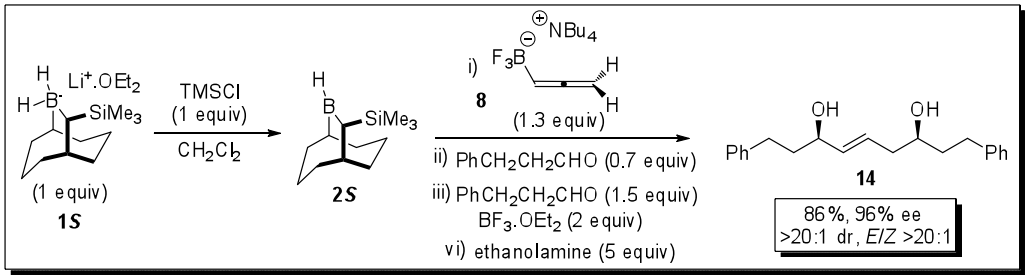


(1*S*,2*Z*,5*S*)-1,5-diphenylpent-2-ene-1,5-diol (SI-7). To a -78 °C suspension of borohydride **1*S*** (81.0 mg, 0.250 mmol, 1 equiv considering a 90% yield for the conversion of borohydride **1*S*** to borane **2*S*** based on titration[3]) in CH_2Cl_2 (0.5 mL) was added a solution of allenyl boronate[5] **SI-5** (0.135 g, 0.325 mmol, 1.3 equiv) in CH_2Cl_2 (1.0 mL). TMSCl (32.0 μL, 0.250 mmol, 1 equiv) was then added. The reaction mixture was stirred at -10°C for 5 h. Benzaldehyde (76.0 μL, 075 mmol, 3 equiv) was added at -78°C and the reaction was stirred for 4 h then allowed to warm to 20 °C and stirred for an additional 12 h. An aqueous KH_2SO_4/NaOH buffer solution (pH 7) (1 mL), THF (1.0 mL) and MeOH (0.5 mL) were added, and after 6 h the biphasic mixture was poured into a saturated aqueous NH_4Cl solution, and the crude product was extracted with ethyl acetate (3×). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, hexanes / ethyl acetate, gradient elution: 9:1 to 8:2 to 7:3) to afford (*Z*)-1,5-*anti*-diols **SI-7** (53.1 mg, 84%): $[\alpha]_D^{25}$ = +58.2 (*c* 0.81, $CHCl_3$); ee 97%; ^{1}H (400 MHz, $CDCl_3$) 7.32-7.16 (m, 10H), 5.76 (ddt, *J* = 10.9, 8.6, 1.3 Hz, 1H), 5.65-5.58 (m, 1H), 5.41 (d, *J* = 8.3 Hz, 1H), 4.65 (dd, *J* = 8.8, 3.5 Hz, 1H), 2.87 (bs, 2H), 2.80-2.72 (m, 1H), 2.43-2.37 (m, 1H); ^{13}C (100 MHz, $CDCl_3$) 144.3, 143.4, 136.1, 128.8, 128.7, 128.4, 128.0, 127.6, 126.1, 126.0, 73.4, 69.1, 38.0; IR (neat) 3346, 3061, 3028, 2920, 1602, 1493, 1452, 1303, 1197, 1028, 913, 879, 846, 742, 698 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{18}O_2Na$ $[M+Na]^+$ 277.1204, found 277.1209.

The relative and absolute stereochemical assignment for **SI-7** is consistent with the Mosher ester data summarized below.



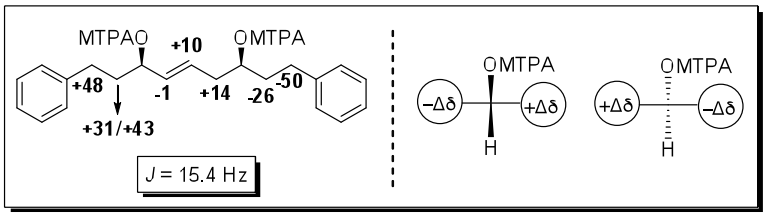
(c) Synthesis of (*E*)-1,5-*syn*-diol (14) as a reference.



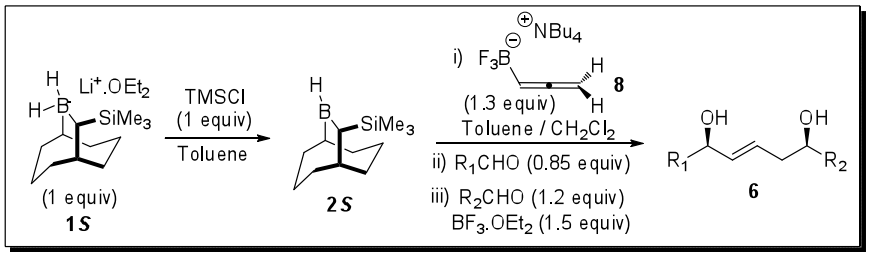
(3*R*,4*E*,7*S*)-1,9-diphenylnon-4-ene-3,7-diol (14). 1,5-Diol **14** was synthesized by using the procedure described above for the synthesis of **13**. The crude product was purified by flash column chromatography (SiO_2, hexanes / ethyl acetate, gradient elution: 7:3 to 6:4 to 1:1) to afford (*E*)-1,5-*syn*-diol **14** (86% yield) as a white solid: $[\alpha]_D^{25}$ = -6.4 (*c* 0.64, $CHCl_3$); ee 96%; ^{1}H (400 MHz, $CDCl_3$) 7.21-

7.08 (m, 10H), 5.61-5.49 (m, 2H), 4.01 (q, J = 6.8 Hz, 1H), 3.60-3.54 (m, 1H), 2.75-2.67 (m, 1H), 2.64-2.54 (m, 3H), 2.24-2.18 (m, 1H), 2.11-2.04 (m, 1H), 1.84-1.67 (m, 4H); ^{13}C (100 MHz, $CDCl_3$) 142.0, 141.9, 136.5, 128.44, 128.40, 127.8, 125.88, 125.85, 72.1, 70.3, 40.5, 38.7, 38.6, 32.0, 31.8; IR (neat) 3347, 3084, 3061, 3025, 2924, 2857, 1668, 1602, 1495, 1454, 1312, 1051, 1030, 971, 923, 746, 698 cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{26}O_2Na$ $[M+Na]^+$ 333.1831, found 333.1822.

The relative and absolute stereochemical assignment for **14** is consistent with the Mosher ester data summarized below.

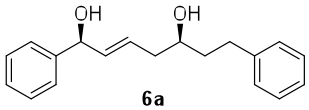


(d) General Procedure for the Synthesis of (E)-1,5-*syn*-Diols 6 from Two Different Aldehydes.



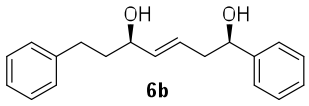
To a 0 °C solution of borohydride **1*S*** (81.0 mg, 0.250 mmol, 1 equiv, considering a 90% yield for the conversion of borohydride **1*S*** to borane **2*S*** based on titration[3]) in toluene (0.5 mL) was added TMSCl (32.0 μL, 0.250 mmol, 1 equiv). The reaction mixture was stirred for 10 min, then was cooled to -78 °C and a solution of allene **8** (0.114 g, 0.325 mmol, 1.3 equiv) in toluene (1 mL) and CH_2Cl_2 (0.1 mL) was added dropwise. The viscous mixture was stirred at -30 °C for 1 h. The resulting clear reaction mixture was then cooled to -78 °C and a solution of R_1CHO (0.213 mmol, 0.85 equiv) in CH_2Cl_2 (0.25 mL) was added. After 4 h, a solution of R_2CHO (0.300 mmol, 1.2 equiv) in CH_2Cl_2 (0.25 mL) followed by $BF_3.OEt_2$ (47.0 μL, 0.375 mmol, 1.5 equiv) were added and the reaction mixture was stirred for an additional 4 h. A pH 7 buffer solution (KH_2SO_4/NaOH) (1 mL) followed by THF (1.5 mL) and MeOH (0.5 mL) were then added and stirred at 20°C for 12-24 h. The biphasic mixture was poured into a saturated aqueous NH_4Cl solution, and the crude product was extracted with ethyl acetate (3×). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure (*Note*: if the O-BR_2 cleavage is not completed at this stage, the crude reaction mixture is dissolved in a mixture of THF (1.5 mL) and MeOH (0.5 mL) mixture and treated with pH 7 buffer solution (KH_2SO_4/NaOH) (1 mL) for 12 h before repeating the work-up procedure). The residue was

purified by flash column chromatography (SiO_2, hexanes / ethyl acetate, gradient elution: 7:3 to 6:4 to 1:1) to afford (*E*)-1,5-*syn*-diol **6** (72-98%).



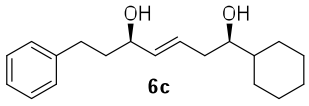
6a

(1*S*,2*E*,5*S*)-1,7-diphenylhept-2-ene-1,5-diol (6a). Colorless oil; Yield 73%; $[\alpha]_D^{25}$ = +2.7 (*c* 1.28, $CHCl_3$); ee 97%; ^1H (400 MHz, $CDCl_3$) 7.33-7.28 (m, 4H), 7.25-7.21 (m, 3H), 7.15-7.12 (m, 3H), 5.74-5.70 (m, 2H), 5.13 (d, *J*= 4.8 Hz, 1H), 3.66-3.60 (m, 1H), 2.77-2.70 (m, 1H), 2.66-2.58 (m, 1H), 2.28-2.22 (m, 1H), 2.17-2.09 (m, 1H), 1.75-1.70 (m, 2H); ^{13}C (100 MHz, $CDCl_3$) 143.2, 142.2, 136.1, 128.8, 128.63, 128.61, 128.1, 127.9, 126.4, 126.0, 75.2, 70.5, 40.6, 38.8, 32.2; IR (neat) 3360, 3084, 3061, 3026, 2923, 2854, 1602, 1494, 1453, 1319, 1069, 1048, 1030, 969, 748, 698 cm^{-1}; $[\alpha]_D^{25}$ = +2.7 (*c* 1.28, $CHCl_3$).



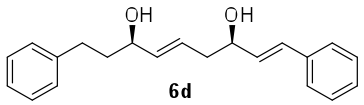
6b

(1*R*,3*E*,5*R*)-1,7-diphenylhept-3-ene-1,5-diol (6b). White solid; Yield 92%; $[\alpha]_D^{25}$ = +31.2 (*c* 0.47, $CHCl_3$); ee 97%; ^1H (400 MHz, $CDCl_3$) 7.32-7.27 (m, 4H), 7.25-7.20 (m, 3H), 7.15-7.12 (m, 3H), 5.64-5.52 (m, 2H), 4.65 (t, *J* = 6.6 Hz, 1H), 4.02 (q, *J* = 6.3 Hz, 1H), 2.66-2.52 (m, 2H), 2.43 (t, *J* = 6.3 Hz, 2H), 2.15 (bs, 2H), 1.86-1.68 (m, 2H); ^{13}C (100 MHz, $CDCl_3$) 144.1, 142.1, 136.8, 128.67, 128.65, 128.5, 127.92, 127.86, 126.01, 125.99, 73.9, 72.4, 42.3, 38.8, 31.9; IR (neat) 3356, 3061, 3027, 2925, 2858, 1602, 1494, 1453, 1308, 1051, 1029, 970, 748, 699, 546 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{22}O_2Na$ $[M+Na]^+$ 305.1517, found 305.1524.



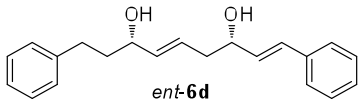
6c

(1*R*,3*E*,5*R*)-1-cyclohexyl-7-phenylhept-3-ene-1,5-diol (6c). White solid; Yield 96%;$[\alpha]_D^{25}$ = +7.5 (*c* 0.59, $CHCl_3$); ee 96%; ^1H (400 MHz, $CDCl_3$) 7.28-7.23 (m, 2H), 7.18-7.13 (m, 3H), 5.65 (ddd, *J* = 15.4, 7.3, 6.1 Hz, 1H), 5.58 (dd, *J* = 15.4, 6.6 Hz, 1H), 4.08 (q, *J* = 6.3 Hz, 1H), 3.38-3.33 (m, 1H), 2.74-2.60 (m, 2H), 2.30-2.24 (m, 1H), 2.13-2.05 (m, 1H), 1.93 (bs, 1H), 1.91-1.72 (m, 5H), 1.66-1.63 (m, 2H), 1.37-1.28 (m 1H), 1.27-094 (m, 5H); ^{13}C (100 MHz, $CDCl_3$) 142.1, 136.3, 128.8, 128.65, 128.57, 126.0, 75.4, 72.4, 43.4, 38.9, 37.4, 32.0, 29.3, 28.3, 26.7, 26.5, 26.3; IR (neat) 3352, 3085, 3062, 3026, 2924, 2852, 1495, 1450, 1311, 1057, 1030, 969, 892, 746, 698 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{28}O_2Na$ $[M+Na]^+$ 311.1987, found 311.1990.



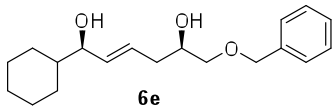
6d

(1*E*,3*R*,5*E*,7*R*)-1,9-diphenylnona-1,5-diene-3,7-diol (6d). White solid; Yield 98%;$[\alpha]_D^{25}$ = +12.6 (*c* 0.45, $CHCl_3$); ee 95%; ^1H (400 MHz, $CDCl_3$) 7.34-7.32 (m, 2H), 7.29-7.18 (m, 5H), 7.16-7.12 (m, 3H), 6.55 (d, *J* = 15.7 Hz, 1H), 6.19 (dd, *J* = 15.9, 6.6 Hz, 1H), 5.67 (dt, *J* = 15.4, 6.6 Hz, 1H), 5.60 (dd, *J* = 15.7, 6.1 Hz, 1H), 4.32-4.27 (m, 1H), 4.07 (q, *J* = 6.6 Hz, 1H), 2.70-2.58 (m, 2H), 2.41-2.28 (m, 2H), 2.10 (bs, 2H), 1.90-1.73 (m, 2H); ^{13}C (100 MHz, $CDCl_3$) 142.1, 136.9, 136.7, 131.8, 130.7, 128.8, 128.63, 128.55, 127.9, 127.5, 126.7, 126.0, 72.4, 72.2, 40.6, 38.8, 31.9; IR (neat) 3350, 3060, 3026, 2923, 2857, 1494, 1452, 1316, 1100, 1030, 967, 747, 694 cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{24}O_2Na$ $[M+Na]^+$ 331.1674, found 331.1679.



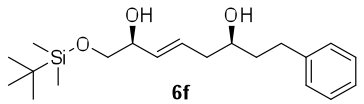
ent-**6d**

(1*E*,3*S*,5*E*,7*S*)-1,9-diphenylnona-1,5-diene-3,7-diol (*ent*-6d). White solid; Yield 91%; $[\alpha]_D^{25}$ = -14.0 (*c* 0.59, $CHCl_3$); ee 95%; ^1H NMR, ^{13}C NMR and IR and HRMS data were identical to **6d**.



6e

(1*R*,2*E*,5*R*)-6-(benzyloxy)-1-cyclohexylhex-2-ene-1,5-diol (6e). White solid; Yield 72%; $[\alpha]_D^{25}$ = -14.0 (*c* 0.59, $CHCl_3$); ee 96%; ^1H (400 MHz, $CDCl_3$) 7.33-7.23 (m, 5H), 5.56 (dt, *J* = 15.4, 6.6 Hz, 1H), 5.49 (dd, *J* = 15.4, 6.3 Hz, 1H), 4.50 (s, 2H), 3.84-3.78 (m, 1H), 3.72 (t, *J* = 6.6 Hz, 1H), 3.43 (dd, *J* = 9.3, 3.3 Hz, 1H), 3.31 (dd, *J* = 9.3, 7.3 Hz, 1H), 2.41 (bs, 1H), 2.20-2.14 (m, 2H), 1.82-1.78 (m, 1H), 1.72-1.58 (m, 4H), 1.36-1.27 (m, 1H), 1.24-1.05 (m, 3H), 0.96-0.83 (m, 2H); ^{13}C (100 MHz, $CDCl_3$) 138.1, 135.2, 128.6, 128.1, 128.0, 127.9, 77.6, 74.2, 73.6, 70.1, 43.7, 36.6, 29.0, 28.9, 26.7, 26.32, 26.25; IR (neat) 3399, 2923, 2852, 1451, 1097, 1027, 1001, 971, 735, 697 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{28}O_3Na$ $[M+Na]^+$ 327.1936, found 327.1942.

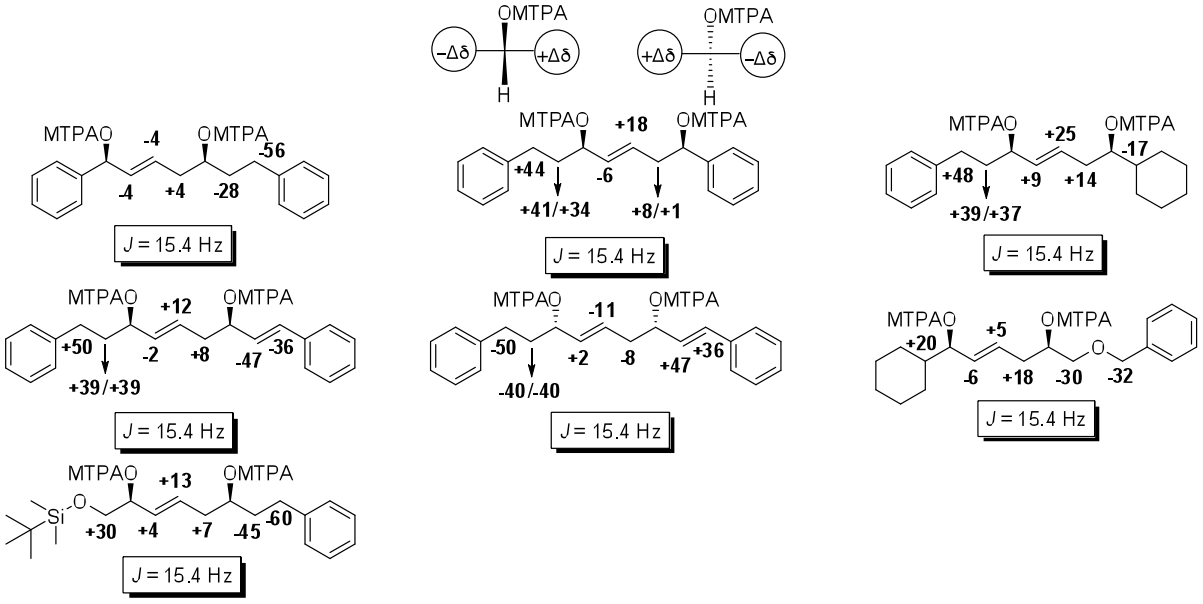


6f

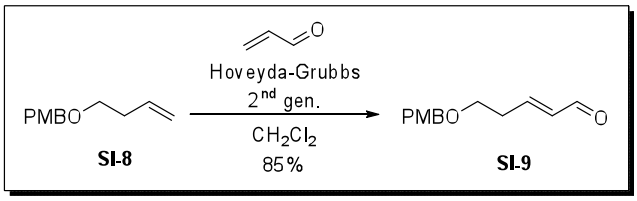
(2*S*,3*E*,6*S*)-1-{[*tert*-butyl(dimethyl)silyl]oxy}-8-phenyloct-3-ene-2,6-diol (6f). Colorless oil; Yield 82%; $[\alpha]_D^{25}$ = -14.0 (*c* 0.59, $CHCl_3$); ee 96%; ^1H (400 MHz, $CDCl_3$) 7.26-7.22 (m, 2H), 7.17-7.12 (m, 3H), 5.77-5.69 (m, 1H), 5.50 (ddd, *J* = 15.4, 6.1, 1.3 Hz, 1H), 4.13-4.09 (m, 1H), 3.65-3.60 (m, 1H),

3.59 (dd, J = 10.1, 3.8 Hz, 1H), 3.41 (dd, J = 10.1, 7.8 Hz, 1H), 2.77 (dt, J = 13.9, 7.6 Hz, 1H), 2.64 (dt, J = 13.9, 8.1 Hz, 1H), 2.28-2.22 (m, 1H), 2.14 (dt, J = 14.1, 7.8 Hz, 1H), 1.77-1.72 (m, 2H), 0.87 (s, 9H), 0.04 (s, 6H); ^{13}C (100 MHz, $CDCl_3$) 142.3, 132.3, 129.3, 128.64, 128.57, 126.0, 72.8, 70.2, 67.3, 40.9, 38.7, 32.2, 26.1, 18.5, -5.13, -5.16; IR (neat) 3383, 3027, 2951, 2928, 2857, 1471, 1462, 1455, 1361, 1254, 1111, 1052, 1006, 971, 837, 778, 747, 699 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{34}O_3NaSi$ $[M+Na]^+$ 373.2175, found 373.2184.

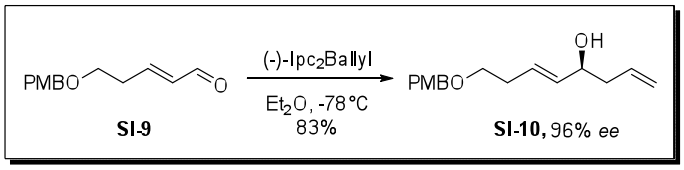
Absolute stereochemistry assignments for 1,5-diols 6 or *ent*-6:



5. Synthesis of Aldehydes 17 and 18:



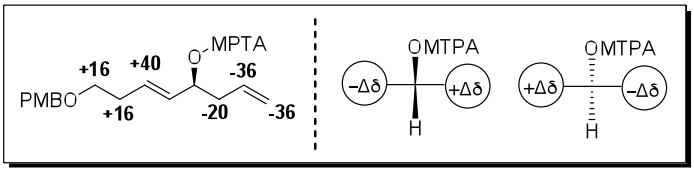
(*E*)-5-(4-Methoxy-benzyloxy)-pent-2-en-1-al (**SI-9**):[7] We followed a procedure described in the literature.[8] To a solution of alkene **SI-8** (3.12 g, 16.22 mmol) in CH_2Cl_2 (70 mL) under argon, were successively added acrolein (freshly distilled, 3.25 mL, 48.7 mmol) and Hoveyda-Grubbs 2nd generation catalyst (weighed in a glove box, 254 mg, 0.40 mmol) in solution in CH_2Cl_2 (3 mL). The reaction was stirred overnight at room temperature, then directly concentrated in *vacuo*. The product was purified by flash chromatography (8/2 : hexanes/EtOAc) afforded **SI-9** (3.04 g, 85%) as a brown oil; ^{1}H NMR (400 MHz, $CDCl_3$) 9.51 (d, *J* = 7.8 Hz, 1H), 7.26 (d, *J* = 8.7 Hz, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 6.87 (dt, *J* = 16.1, 6.0 Hz, 1H), 6.17 (ddt, *J* = 15.7, 7.8, 1.4 Hz, 1H), 4.46 (s, 2H), 3.81 (s, 3H), 3.61 (t, *J* = 6.2 Hz, 2H), 2.62 (tdd, *J* = 6.4, 6.4, 1.5 Hz, 2H); ^{13}C (100 MHz, $CDCl_3$) 194.1, 159.5, 155.4, 134.3, 130.2, 129.5, 114.1, 73.0, 67.8, 55.5, 33.3; IR (neat) 2999, 2934, 2907, 2855, 1614, 1586, 1514, 1464, 1442, 1361, 1302, 1247, 1209, 1173, 1097, 1036, 972, 821 cm^{-1}. HRMS (ESI) calcd for $C_{13}H_{16}O_3$ $[M+Na]^+$ 243.0997, found 243.0995.

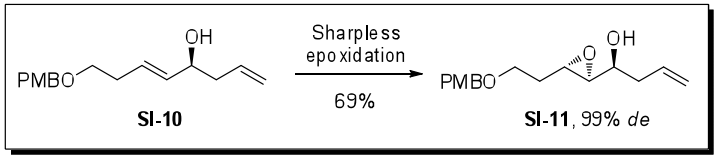


(*S*, *E*)-8-(4-Methoxy-benzyloxy)-octa-1,5-dien-4-ol (**SI-10**). (-)-Ipc_2BOMe (5.68 g, 17.94 mmol) was weighed in a glove box. Et_2O (72 mL) was added and the solution cooled to 0°C. Allylmagnesium bromide (1 M in Et_2O, 16.6 mL, 16.6 mmol) was added dropwise.[9] The mixture was stirred for 1 h, then was cooled to –78 °C and a solution of aldehyde **SI-9** (3.04 g, 13.80 mmol) in Et_2O (17.5 mL) was added *via* cannula. The mixture was stirred for 3 h, then MeOH (1.8 mL) followed by NaOH (3 N, 17.4 mL, 52.3 mmol) and H_2O_2 (30% in H_2O, 17.3 mL, 169.3 mmol) were added. The solution was warmed to 23°C and stirred overnight. The mixture was cooled at 0°C and neutralized by HCl (3N) and the aqueous phase extracted with Et_2O. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the crude by flash chromatography (gradient elution 85/15 to 70/30 : hexanes/ethyl acetate) provided **SI-10** (2.99 g, 83%) as a colorless oil: ee 96%; $[\alpha]_D^{22}$ = -10.5 (c = 0.89, $CHCl_3$); ^{1}H (400 MHz, $CDCl_3$) 7.24-7.28 (m, 2H), 6.86-6.90 (m, 2H), 5.80 (ddt, *J* = 17.3, 9.9, 7.1 Hz, 1H), 5.70 (dt, *J* = 15.5, 6.6 Hz, 1H), 5.57 (dd, *J* = 15.5, 6.5 Hz), 5.14-5.16 (m, 1H), 5.11 (br. s, 1H), 4.44 (s, 2H), 4.13 (m_c, 1H), 3.81 (s, 3H), 3.48 (t, *J* = 6.8 Hz, 2H), 2.35 (dt, *J* = 6.8, 6.7 Hz, 2H), 2.23-2.31 (m, 2H), 1.70 (m, OH); ^{13}C (100 MHz, $CDCl_3$) 159.4, 134.50, 134.1, 130.7, 129.5, 128.5, 118.3, 113.9, 72.7, 71.8, 69.6, 55.5, 42.1, 32.8; IR (neat) 3419 (br.),

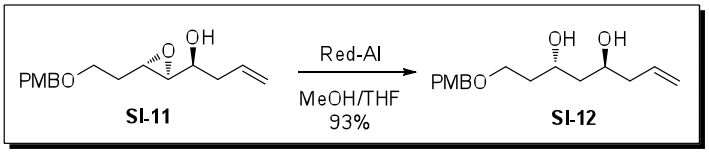
2933, 2907, 2858, 1613, 1514, 1464, 1448, 1361, 1302, 1248, 1174, 1094, 1035, 972, 916, 821 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{22}O_3$ $[M+Na]^+$ 285.1467, found 285.1468.

The absolute stereochemistry assignment for **SI-10** is based on the following Mosher ester data.



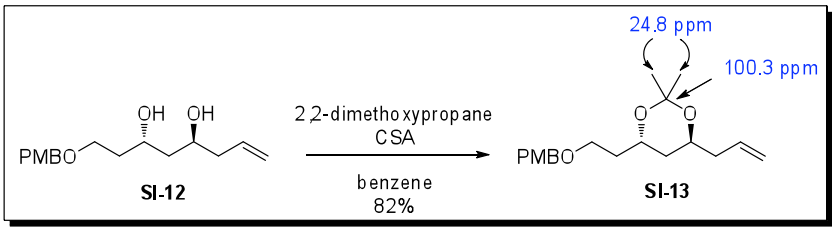


(*S*)-1-((2*S*,3*S*)-3-(2-(4-Methoxy-benzyloxy)-ethyl)oxiran-2-yl)-but-3-en-1-ol (**SI-11**). To a solution *L*-(+)-DET (freshly distilled, 1.19 mL, 6.86 mmol, dried over MS 4Å for 1.5 h) in CH_2Cl_2 (11.2 mL) was added $Ti(OiPr)_4$ (freshly distilled, 1.75 mL, 5.72 mmol) at –40 °C, resulting in a slightly yellow solution.[10] This mixture was stirred for 40 min, then a solution of alcohol **SI-10** (3.0 g, 11.44 mmol, dried over MS 4Å for 2 h) in CH_2Cl_2 (9 ml) was added *via* cannula. The mixture was stirred for 45 min at –20 °C, then a cold solution of TBHP (5.5 M in decane, 2.08 mL, 11.4 mmol, dried over MS 4Å for 2 h) in CH_2Cl_2 (9 mL) was added *via* cannula. The solution was stirred at –20 °C for 7 h, then stored in a -20 °C freezer for 20 h. The mixture was allowed to warm to 0 °C, then NaOH (1 M, sat with NaCl, 17.6 mL) and H_2O (11 mL) were added. This mixture solution was stirred at room temperature for 2 h. It was then filtered through a plug of Celite, which was rinsed with CH_2Cl_2 and the combined filtrate was washed with brine. The aqueous phase was extracted with CH_2Cl_2, the combined organic extracts dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the crude product by flash chromatography (gradient elution 85/15 to 70/30 : hexanes/ethyl acetate) afforded **SI-11** (2.20 g, 69%) as a clear oil: 99% de; $[\alpha]_D^{22}$ = -5.5 (c = 1.02, $CHCl_3$); ^1H (400 MHz, $CDCl_3$) 7.25-7.27 (m, 2H), 6.86-6.90 (m, 2H), 5.86 (ddt, *J* = 17.1, 10.1, 7.1 Hz, 1H), 5.14-5.17 (m, 1H), 5.11-5.13 (m, 1H), 4.45 (m, 2H), 3.81 (br. s, 4H), 3.58 (t, *J* = 6.3 Hz, 2H), 3.14 (td, *J* = 9.1, 2.2 Hz, 1H), 2.84 (dd, *J* = 3.0, 3.0 Hz, 1H), 2.25-2.42 (m, 2H), 2.08 (bs, 1H), 1.76-1.91 (m, 2H); ^{13}C (100 MHz, $CDCl_3$) 159.4, 133.9, 130.4, 129.5, 118.3, 114.0, 73.0, 68.4, 66.8, 60.5, 55.5, 53.4, 38.3, 32.3; IR (neat) 3437 (br.), 2933, 2912, 2862, 1745, 1642, 1613, 1586, 1514, 1465, 1442, 1363, 1302, 1249, 1175, 1096, 1035, 917, 821 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{22}O_4$ $[M+Na]^+$ 301.1416, found 301.1415.

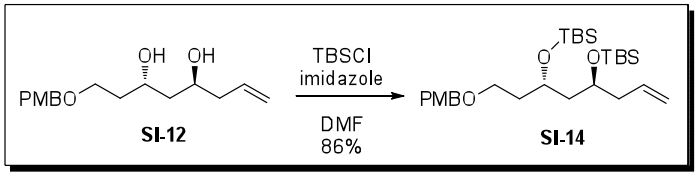


(3*S*,5*S*)-1-(4-Methoxy-benzyloxy)-oct-7-ene-3,5-diol (**SI-12**). To a solution of epoxide **SI-11** (2.2 g, 7.90 mmol) in THF (39.5 mL) was added MeOH (0.16 mL) and Red-Al® (3.3 M in toluene, 6.0 mL, 19.75 mmol) at 0°C (gas evolution!) over a period of 10 min.[11] The solution was allowed to warm to 23 °C over 2 h, then was stirred for 16 h. The mixture was cooled to 0 °C, then NaOH (3 N, 23.7 mL) was added followed by water. The aqueous phase was extracted with Et_2O and the combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the crude product by flash chromatography (1:2 hexanes/ethyl acetate) afforded **SI-12** (2.06 g, 93%) as colorless oil: $[\alpha]_D^{24}$ = +16.8 (c = 1.06, $CHCl_3$); ^{1}H (400 MHz, $CDCl_3$) 7.23-7.25 (m, 2H), 6.86-6.90 (m, 2H), 5.83 (ddt, *J* = 17.1, 10.2, 7.1 Hz, 1H), 5.11-5.15 (m, 1H), 5.09-5.11 (m, 1H), 4.46 (s, 2H), 4.13-4.19 (m, 1H), 3.95-4.02 (m, 1H), 3.81 (s, 3H), AB-Signal (δ_A = 3.65, δ_B = 3.71, J_{AB} = 9.3 Hz, A-signal further split by dd with *J* = 9.2, 3.9 Hz, B-signal further split by dd with *J* = 4.8, 4.8 Hz), 3.51 (d, *J* = 2.6 Hz, OH), 2.84 (d, *J* = 3.9 Hz, OH), 2.26 (ddt, *J* = 6.7, 6.7, 1.2 Hz, 2H), 1.86-1.94 (m, 1H), 1.61-1.71 (m, 3H); ^{13}C (100 MHz, $CDCl_3$) 159.5, 135.1, 130.0, 129.6, 117.9, 114.1, 73.3, 69.8, 69.4, 68.3, 55.5, 42.3, 42.3, 36.4; IR (neat) 3402, 2937, 1613, 1514, 1303, 1249, 1175, 1090, 1035, 821 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{24}O_4$ $[M+Na]^+$ 303.1572, found 303.1566.

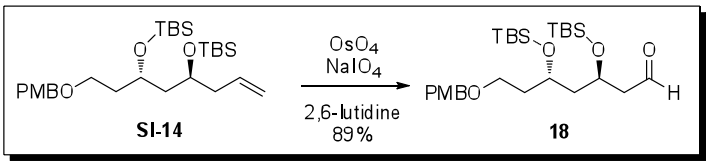
The relative stereochemistry of **SI-12** was assigned by using Rychnovsky's acetonide analysis.[12]



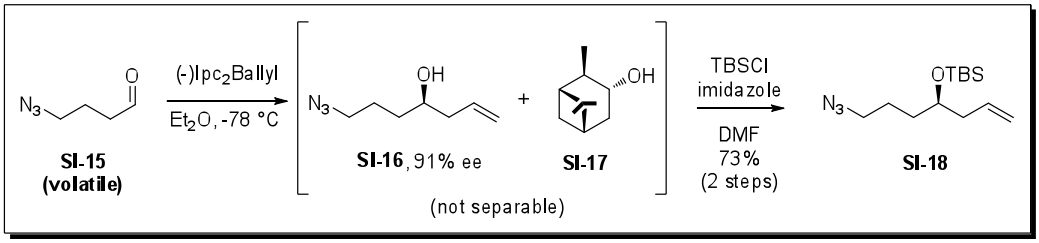
(4*S*,6*S*)-4-Allyl-6-(2-(4-methoxy-benzyloxy)ethyl)-2,2-dimethyl-1,3-dioxane (**SI-13**): To a solution of diol **SI-12** (34 mg, 0.120 mmol) in benzene (2 mL) was added CSA (5 crystals) and 2,2-dimethoxypropane (0.04 mL, 0.33 mmol). The mixture was stirred at 23 °C for 3.5 h, then was directly purified by column chromatography (5/1 : hexanes/ethyl acetate) which provided **SI-13** (32 mg, 82%) as colorless oil: $[\alpha]_D^{24}$ = +16.5 (c = 1.47, $CHCl_3$); ^{1}H (400 MHz, $CDCl_3$) 7.24-7.27 (m, 2H), 6.86-6.89 (m, 2H), 5.79 (ddt, *J* = 17.1, 10.3, 6.8 Hz, 2H), 5.03-5.12 (m, 2H), 4.42 (m, 2H), 3.98 (m, 1H), 3.82-3.87 (m, 1H), 3.80 (s, 3H), 3.47-3.56 (m, 2H), 2.15-2.40 (m, 2H), 1.71-1.80 (m, 2H), 1.54-1.65 (m, 2H), 1.34 (s, 3H), 1.33 (s, 3H); ^{13}C (100 MHz, $CDCl_3$) 159.3, 134.7, 130.8, 129.5, 117.0, 113.9, 100.5, 72.9, 66.5, 66.4, 63.9, 55.5, 40.4, 38.2, 36.2, 25.0; IR (neat) 3075, 2986, 2937, 2857, 1642, 1613, 1586, 1513, 1464, 1443, 1378, 1302, 1247, 1224, 1172, 1121, 1096, 1037, 995, 915, 821 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{28}O_4$ $[M+Na]^+$ 343.1885, found 343.1883.



(3*S*,5*S*)-3,5-Bis-(*tert*-butyldimethylsilanyloxy)-1-(4-methoxy-benzyloxy)-oct-7-ene (**SI-14**): To a solution of diol **SI-12** (2.06 g, 7.35 mmol) in DMF (14.7 mL) was added imidazole (2.02 g, 29.4 mmol) and TBSCl (4.31 g, 27.2 mmol). The mixture was stirred overnight and then poured into water (100 mL) and diluted with Et_2O. The aqueous phase was extracted with Et_2O and the combined organic phases were washed several times with water, then with brine. The extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the crude product by flash chromatography (95/5 : hexanes/ethyl acetate) afforded the **SI-14** (3.2 g, 86%) as pale yellow oil: $[\alpha]_D^{24}$ = +3.4 (c = 1.23, $CHCl_3$); ^{1}H (400 MHz, $CDCl_3$) 7.24-7.27 (m, 2H), 6.85-6.89 (m, 2H), 5.81 (m_c, 1H), 5.02-5.06 (m, 2H), AB signal (δ_A = 4.40, δ_B = 4.42, J_{AB} = 11.5 Hz), 3.87 (m_c, 1H), 3.76-3.82 (m, 4H), 3.50 (t, J = 6.8 Hz, 2H), 2.14-2.28 (m, 2H), 1.53-1.83 (m, 4H), 0.87 (s, 9H), 0.86 (s, 9H), 0.05 (s, 9H), 0.03 (s, 3H); ^{13}C (100 MHz, $CDCl_3$) 159.3, 135.2, 130.9, 129.4, 117.1, 113.9, 72.9, 69.8, 67.7, 67.0, 55.5, 45.6, 42.4, 37.9, 26.1, 18.32, 18.28, -3.86, -3.91, -4.0, -4.1; IR (neat) = 2945, 2929, 2895, 2857, 1614, 1514, 1472, 1463, 1361, 1250, 1099, 1041, 1004, 836, 807, 884 cm^{-1}; HRMS (ESI) calcd for $C_{28}H_{52}O_4Si_2$ $[M+Na]^+$ 531.3302, found 531.3305.

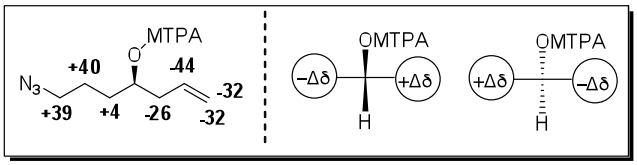


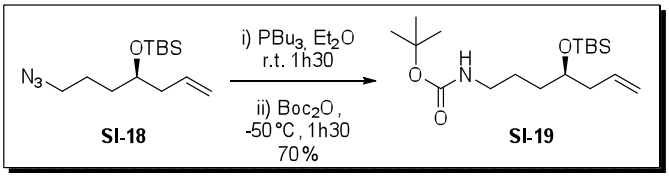
(3*S*,5*S*)-3,5-Bis-(*tert*-butyldimethylsilanyloxy)-7-(4-methoxy-benzyloxy)-heptane-1-al (**18**). To a solution of alkene **SI-14** (1.75 g, 3.439 mmol) in dioxane (26 mL) and water (8.6 mL) was added 2,6-lutidine (freshly distilled, 0.865 mL, 7.43 mmol), OsO_4 (2.5 wt% in 2-methyl-2-propanol, 0.862 mL, 0.07 mmol) and $NaIO_4$ (2.95 g, 13.65 mmol).[13] The mixture was stirred for 5 h, then the brown suspension was diluted with water and CH_2Cl_2. The aqueous phase was extracted with CH_2Cl_2, the combined organic phases washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification of the crude product by flash chromatography (95/5 : hexanes/ethyl acetate) afforded **18** (1.57 g, 89%) as yellow oil: $[\alpha]_D^{24}$ = -4.9 (c = 1.23, $CHCl_3$); ^{1}H (400 MHz, $CDCl_3$) 9.78 (t, J = 2.5 Hz, 1H), 7.23-7.26 (m, 2H), 6.85-6.89 (m, 2H), AB signal (δ_A = 4.39, δ_B = 4.42, J_{AB} = 11.5 Hz), 4.24 (dddd, app. tt, J = 6.0 Hz, 1H), 3.87 (dddd, app. tt, J = 6.1 Hz, 1H), 3.81 (s, 3H), 3.49 (t, J = 6.6 Hz, 2H), AB signal (δ_A = 2.49, δ_B = 2.57, J_{AB} = 15.6 Hz, A signal further split as dd with J = 6.5, 3.1 Hz, B signal further split as dd with J = 4.7, 2.0 Hz), 1.64-1.84 (m, 4H), 0.87 (s, 9H), 0.86 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H), 0.054 (s, 3H), 0.047 (s, 3H); ^{13}C (100 MHz, $CDCl_3$) 202.3, 159.3, 130.7, 129.5, 113.9, 72.9, 67.5, 66.6, 66.5, 55.5, 51.5, 46.3, 38.0, 26.1, 25.9, 18.2, 18.1, -4.0, -4.1, -4.2; IR (neat) 2954, 2930, 2857, 1727, 1514, 1472, 1464, 1250, 1102, 1040, 1005, 837, 809, 776 cm^{-1}; HRMS (ESI) calcd for $C_{27}H_{50}O_5Si_2$ $[M+Na]^+$ 533.3095, found 533.3099.



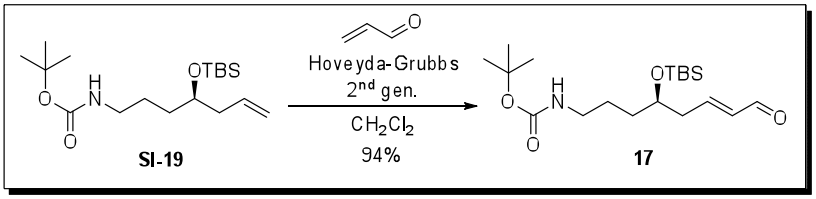
(*R*)-7-Azido-4-[(*tert*-butyldimethylsilanyloxy]-1-hepten (SI-18): (-)-Ipc_2BOMe (6.64 g, 21.00 mmol) was weighed in a glove box. Et_2O (84 mL) was added and the solution cooled to 0°C. Allylmagnesium bromide (1 M in Et_2O, 19.25 mL, 19.25 mmol) was added dropwise.[9] The mixture was stirred for 1 h, then was cooled to –78 °C and a solution of known aldehyde **SI-15**[14] (3.04 g, 13.8 mmol) in Et_2O (22.0 mL) was added *via* cannula. The mixture was stirred for 3 h, then MeOH (2.1 mL) followed by NaOH (3 N, 22.0 mL, 66.32 mmol) and H_2O_2 (30% in H_2O, 22.0 mL, 215.0 mmol) were added. The solution was warmed to 23°C and stirred overnight. The mixture was cooled at 0°C and neutralized with HCl (3N) and the aqueous phase extracted with Et_2O. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and carefully concentrated under reduced pressure (removal of solvent at 250 torr/0°C). The azidoalcohol **SI-16** was obtained as an approximate 1:2 mixture with pinane-3-ol (**SI-17**) as a viscous oil. To the crude mixture of **SI-16** and pinane-3-ol (**SI-17**) in DMF (10 ml) were added TBSCl (11.3 g, 71.4 mmol) and imidazole (5.27 g, 77.35 mmol). The mixture was stirred overnight, then was poured into water (100 ml) and diluted with Et_2O. The aqueous phase was extracted with Et_2O and the combined organic phases were washed several times with water, then with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the crude product by flash chromatography (95/5 : hexanes/ethyl acetate) afforded **SI-18** (3.4 g, 73% over two steps) as a clear oil: ee 91%; $[\alpha]_D^{26}$ = +13,1 (c = 1.09, $CHCl_3$); ^1H (400 MHz, $CDCl_3$) 5.74-5.84 (m, 1H), 5.06-5.08 (m, 1H), 5.03 (br. s, 1H), 3.73 (dddd, app. tt, *J* = 5.7 Hz, 1H), 3.27 (t, *J* = 6.9 Hz, 2H), 2.22 (dd, app. t, *J* = 6.0 Hz, 2H), 1.43-1.74 (m, 4H), 0.89 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C (100 MHz, $CDCl_3$) 134.84, 117.05, 71.34, 51.66, 41.90, 33.60, 25.85, 24.74, 18.08, -4.36, -4.60; IR (neat) 2955, 2931, 2858, 2093, 1472, 1464, 1361, 1256, 1092, 1041, 1005, 939, 914, 837, 809, 775 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{27}N_3OSi$ $[M+Na]^+$ 292.1821, found 292.1830.

Absolute stereochemistry of **SI-18** was assigned by using the modified Mosher ester method:



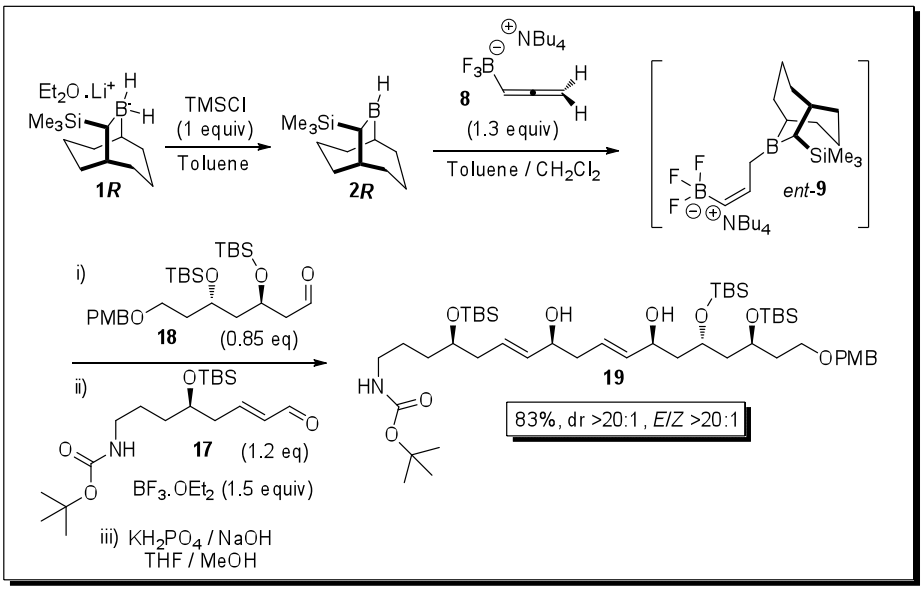


***tert*-butyl ((4*R*)-4-{[*tert*-butyl(dimethyl)silyl]oxy}hept-6-en-1-yl)carbamate (SI-19).** To a solution of alkene **SI-18** (1 g, 3.49 mmol) in Et_2O (9 mL) at room temperature was added tributylphosphine (1.07 mL, 4.19 mmol).[15] The mixture was stirred 1.5 h at 23 °C and then cooled at -50°C. Di-*tert*-butyl dicarbonate (923 mg, 4.19 mmol) in solution in Et_2O (2.6 mL) was slowly added and the solution was stirred for 2 h. The reaction mixture was quenched with a solution of saturated $NaHCO_3$ (11.6 mL), then was allowed to warm to room temperature and stirred overnight. The aqueous phase was extracted with Et_2O and the combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the crude product by flash chromatography (gradient elution 98/2 to 80/20 : hexanes/ethyl acetate) afforded the **SI-19** (845 mg, 70%) as clear oil: $[\alpha]_D^{27}$ = +10.6 (c = 0.5, $CHCl_3$); ^1H (400 MHz, $CDCl_3$) 5.71-5.84 (m, 1H), 5.02-5.06 (m, 1H), 5.01 (bs, 1H), 4.54 (bs, 1H), 3.71 (app quint, *J* = 5.7 Hz, 1H), 3.02-3.17 (m, 2H), 2.18-2.23 (m, 2H), 1.43 (s, 9H), 1.39-1.60 (m, 4H), 0.88 (s, 9H), 0.044 (s, 3H), 0.037 (s, 3H); ^{13}C (100 MHz, $CDCl_3$) 156.2, 135.3, 117.1, 79.2, 71.7, 42.1, 40.9, 34.0, 28.6, 27.6, 26.1, 18.3, -4.2, -4.3; IR (neat) 3349, 2929, 2857, 1693 (broad), 1513, 1365, 1251, 1172, 1117, 1002, 912, 835, 773 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{37}NO_3Si$ $[M+Na]^+$ 366.2440, found 366.2449.



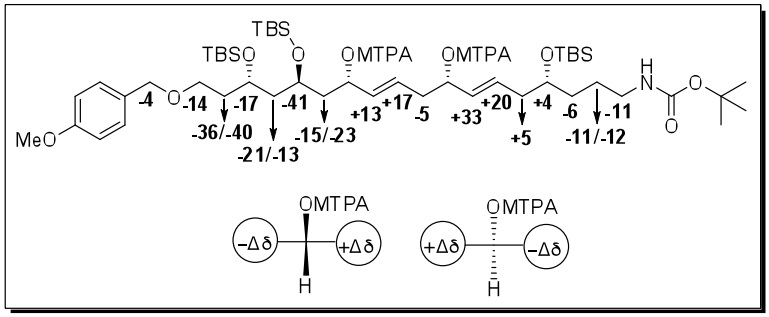
***tert*-butyl ((4*R*,6*E*)-4-{[*tert*-butyl(dimethyl)silyl]oxy}-8-oxooct-6-en-1-yl)carbamate (17).** To a solution of alkene **SI-19** (273 mg, 0.79 mmol) in CH_2Cl_2 (2.4 mL) under argon, were successively added acrolein (freshly distilled, 0.159 mL, 2.38 mmol) and Hoveyda-Grubbs 2nd generation catalyst (weighed in a glove box, 12 mg, 0.020 mmol) in solution in CH_2Cl_2 (1 mL).[8] The reaction was stirred overnight at room temperature, then directly concentrated in *vacuo* and purified by flash chromatography (8/2 : hexanes/EtOAc) afforded **17** (276 mg, 94%) as a clear oil which solidified when stored in the freezer: $[\alpha]_D^{27}$ = +10.0 (c = 0.69, $CHCl_3$); ^1H (400 MHz, $CDCl_3$) 9.51 (d, *J* = 8.0 Hz, 1H), 6.86 (dt, *J* = 15.6, 7.4 Hz, 1H), 6.13 (ddt, *J* = 15.6, 7.9, 1.3 Hz, 1H), 4.52 (bs, 1H), 3.87 (app quint, *J* = 5.6 Hz, 1H), 3.03-3.19 (m, 2H), 2.41-2.56 (m, 2H), 1.46-4.56 (m, 4H), 1.44 (s, 9H), 0.88 (s, 9H), 0.06 (s, 3H), 0.035 (s, 3H); ^{13}C (100 MHz, $CDCl_3$) 194.0, 156.2, 155.1, 135.1, 79.4, 70.8, 40.6, 34.5, 28.6, 26.0, 25.9, 18.3, -4.25, -4.27; IR (neat) 3360, 2930, 2858, 1693 (broad), 1520, 1365, 1252, 1172, 836, 775 cm^{-1}. HRMS (ESI) calcd for $C_{19}H_{37}NO_4Si$ $[M+Na]^+$ 394.2390, found 394.2391.

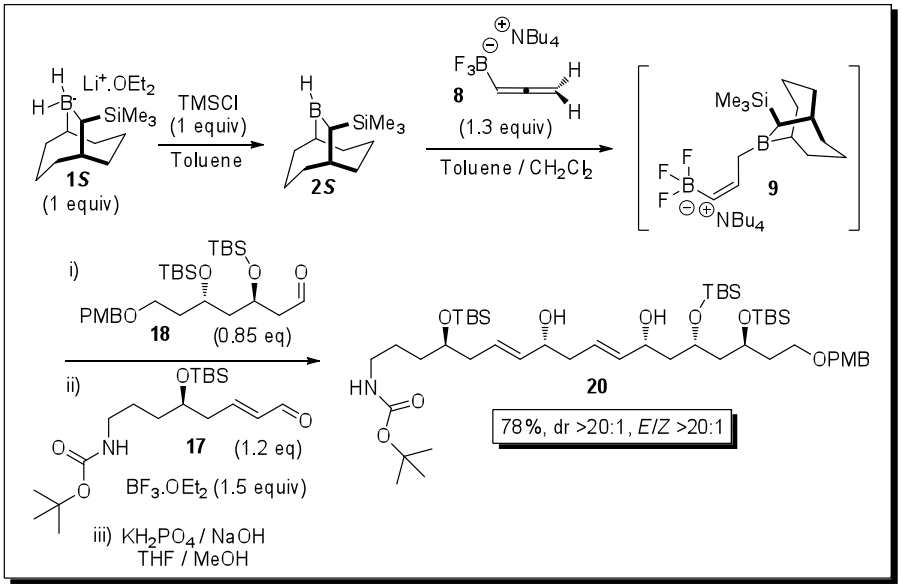
6. Synthesis of C(23)-C(40) Tetrafibricin Fragment 19 and its Diastereomer 20



tert*-butyl {(4*R*,6*E*,8*S*,10*E*,12*S*,14*S*,16*S*)-4,14,16-tris{[*tert*-butyl(dimethyl)silyl]oxy}-8,12-dihydroxy-18-[(4-methoxybenzyl)oxy]octadeca-6,10-dien-1-yl}carbamate (19).** To a 0 °C solution of borohydride **1*R (81.0 mg, 0.250 mmol, 1 equiv, considering a 90% yield for the conversion of borohydride **1*R*** to borane **2*R*** based on titration[3]) in toluene (0.5 mL) was added TMSCl (32.0 μL, 0.250 mmol, 1 equiv). The reaction mixture was stirred for 10 min, then was cooled to -78 °C and a solution of allene **8** (0.114 g, 0.325 mmol, 1.3 equiv) in toluene (1 mL) / CH_2Cl_2 (0.1 mL) was added dropwise. The viscous mixture was stirred at -30 °C for 1 h. The resulting clear reaction mixture was then cooled to -78 °C and a solution of **18** (0.213 mmol, 0.85 equiv) in CH_2Cl_2 (0.25 mL) was added. Four hours later, a solution of **17** (0.300 mmol, 1.2 equiv) in CH_2Cl_2 (0.25 mL) followed by $BF_3.OEt_2$ (47.0 μL, 0.375 mmol, 1.5 equiv) were added and the reaction mixture was stirred for an additional 4 h. A pH 7 buffer solution (KH_2SO_4/NaOH) (1 mL) followed by THF (1.5 mL) and MeOH (0.5 mL) were then added and the mixture was stirred at 20 °C for 24 h. The biphasic mixture was poured into a saturated aqueous NH_4Cl solution, and the crude product was extracted with ethyl acetate (3×). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, hexanes / ethyl acetate, gradient elution: 7:3 to 6:4 to 1:1) to afford **19** (163 mg, 83%) as a colorless oil: $[\alpha]_D^{25}$ = -4.7 (*c* 0.64, $CHCl_3$); ^{1}H (400 MHz, $CDCl_3$) 7.24 (d, J = 8.6 Hz, 2H), 6.87 (d, J = 8.6 Hz, 2H), 5.47-5.70 (m, 4H), 4.63 (bs, 1H), 4.41 (m, overlap, 1H), 4.40 (dd, *J* = 12.0, 11.6 Hz, 2H), 4.10 (app q, *J* = 6.2 Hz, 1H), 3.99-4.06 (m, 1H), 3.82 (m, 1H), 3.79 (s, 3H), 3.66-3.74 (m, 1H), 3.50 (t, J = 6.8 Hz, 2H), 3.02-3.15 (m, 2H), 2.13-2.34 (m, 4H), 1.63-1.89 (m, 6H), 1.43 (s, 9H), 1.35-1.62 (m, 7H), 0.88 (s, 18H), 0.86 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H), 0.06 (s, 3H), 0.041 (s, 3H), 0.035 (s, 6H); ^{13}C (100 MHz, $CDCl_3$) 159.3, 156.2, 136.8, 134.9, 130.8, 129.5, 128.1, 126.2, 114.0, 79.23, 72.9, 72.1, 71.8, 69.4, 69.3, 67.7, 66.8, 55.5, 45.0, 42.8, 40.8, 40.6, 40.4, 37.5, 33.9, 28.7, 26.3, 26.1, 26.0, 18.3, 18.2, 18.1, -3.9, -4.1, -4.1, -4.3, -4.4; IR (neat) 3375, 2953, 2929, 2896, 2856, 1694, 1514, 1472, 1463, 1389, 1365, 1250, 1172, 1098, 1041, 1005, 971, 836, 809, 774 cm^{-1}. HRMS (ESI) calcd for $C_{49}H_{93}NO_9NaSi_3$ $[M+Na]^+$ 946.6056, found 946.6063.

The stereochemical assignments for the two new hydroxyl groups of **19** are based on the Mosher ester data summarized below.

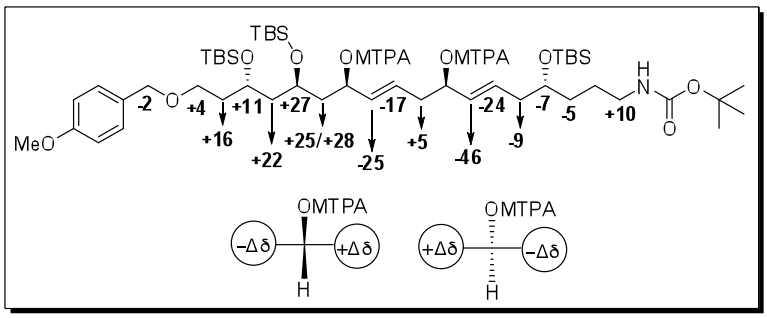




tert*-butyl {(4*R*,6*E*,8*R*,10*E*,12*R*,14*S*,16*S*)-4,14,16-tris{[*tert*-butyl(dimethyl)silyl]oxy}-8,12-dihydroxy-18-[(4-methoxybenzyl)oxy]octadeca-6,10-dien-1-yl}carbamate (20).** To a 0 °C solution of borohydride **1*S (81.0 mg, 0.250 mmol, 1 equiv, considering a 90% yield for the conversion of borohydride **1*S*** to borane **2*S*** based on titration[3]) in toluene (0.5 mL) was added TMSCl (32.0 μL, 0.250 mmol, 1 equiv). The reaction mixture was stirred for 10 min, then was cooled to -78 °C and a solution of allene **8** (0.114 g, 0.325 mmol, 1.3 equiv) in toluene (1 mL) / CH_2Cl_2 (0.1 mL) was added dropwise. The viscous mixture was stirred at -30 °C for 1 h. The resulting clear reaction mixture was then cooled to -78 °C and a solution of **18** (0.213 mmol, 0.85 equiv) in CH_2Cl_2 (0.25 mL) was added. Four hours later, a solution of **17** (0.300 mmol, 1.2 equiv) in CH_2Cl_2 (0.25 mL) followed by $BF_3.OEt_2$ (47.0 μL, 0.375 mmol, 1.5 equiv) were added. The reaction mixture was stirred for an additional 4 h at this temperature. A pH 7 buffer solution (KH_2SO_4/NaOH) (1 mL) followed by THF (1.5 mL) and MeOH (0.5 mL) were then added and the mixture was stirred at 20 °C for 24 h. The biphasic mixture was poured into saturated aqueous NH_4Cl solution, and the crude product was extracted with ethyl acetate (3×). The combined organic layers

were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, hexanes / ethyl acetate, gradient elution: 7:3 to 6:4 to 1:1) to afford **20** (153 mg, 78%) as a colorless oil: $[\alpha]_D^{25}$ = -7.8 (*c* 0.50, $CHCl_3$); ^1H (400 MHz, $CDCl_3$) (d, J = 8.6 Hz, 2H), 6.86 (d, J = 8.6 Hz, 2H), 5.47-5.70 (m, 4H), 4.67 (bs, 1H), 4.40 (dd, *J* = 12.0, 11.6 Hz, 2H), 4.17-4.26 (m, 1H), 4.08 (app q, *J* = 6.3 Hz, 1H), 3.85-3.92 (m, 1H), 3.78-3.85 (m, 1H), 3.79 (s, 3H), 3.66-3.74 (m, 1H), 3.48 (t, J = 6.8 Hz, 2H), 3.02-3.15 (m, 2H), 2.14-2.31 (m, 4H), 1.90-2.10 (bs, 1H), 1.57-1.83 (m, 6H), 1.43 (s, 9H), 1.36-1.57 (m, 6H), 0.88 (s, 9H), 0.87 (s, 9H), 0.85 (s, 9H), 0.084 (s, 3H), 0.079 (s, 3H), 0.044 (s, 3H), 0.035 (s, 3H), 0.030 (s, 6H); ^{13}C (100 MHz, $CDCl_3$) 159.3, 156.2, 136.3, 134.9, 130.7, 129.5, 127.9, 126.6, 113.9, 79.2, 72.9, 71.8, 71.7, 71.3, 70.7, 67.5, 66.8, 55.4, 47.0, 44.6, 40.8, 40.6, 40.4, 37.6, 33.9, 28.6, 26.08, 26.06, 26.04, 25.9, 18.3, 18.2, 18.1, -3.6, -4.0, -4.2, -4.3, -4.4; IR (neat) 3374, 2953, 2929, 2895, 2856, 1695, 1514, 1472, 1462, 1365, 1250, 1172, 1098, 1040, 1005, 971, 835, 808, 774 cm^{-1}; HRMS (ESI) calcd for $C_{49}H_{93}NO_9NaSi_3$ $[M+Na]^+$ 946.6056, found 946.6060.

The stereochemical assignments for the two new hydroxyl groups of **20** are based on the Mosher ester data summarized below.



References

[1] (a) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc*. **1973**, *95*, 512. (b) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc*. **1991**, *113*, 4092.

[2] Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem*. **1978**, *43*, 2923.

[3] Kister, J.; DeBaillie, A, C.; Lira, R.; Roush, W. R. *J. Am. Chem. Soc.* **2009**, *131*, 14174.

[4] (a) Batey, R. A.; Quach, T. D. *Tetrahedron Lett.* **2001**, *42*, 9099. (b) Thadani, A. N.; Batey, R. A. *Org. Lett.* **2002**, *4*, 3827.

[5] Bagutski, V.; Ros, A.; Aggarwal, V. K. *Tetrahedron* **2009**, *65*, 9956.

[6] Lombardo, M.; Licciulli, S.; Trombini, C. *Tetrahedron: Asymmetry* **2004**, *15*, 289.

[7] Six, Y. *Eur. J. Org. Chem.* **2003**, 1157.

[8] BouzBouz, S.; Cossy, J. *Org. Lett.* **2001**, *3*, 1451-1454.

[9] a) Jadhav, P. K.; Bhat, K.S.; Perumal, P. T.; Brown, H. C. *J. Org. Chem.* **1986**, *51*, 432-439. b) Brown, H. C.; Bhat, K. S.; Randad, R. S. *J. Org. Chem.* **1989**, *54*, 1570-1576. c) Racherla, U. S.; Brown, H. C. *J. Org. Chem.* **1991**, *56*, 401-404.

[10] Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc*. **1987**, *109*, 5765-5780.

[11] Bulman Page, P. C; Rayner, C. M; Sutherland, I. O. *J. Chem. Soc. Perkin Trans. 1*, **1990**, 2403-2408.

[12] Rychnovsky, S. D; Rogers, B.; Yang, G. *J. Org. Chem*. **1993**, *58*, 3511-3515.

[13] Yu, W.; Mei, Y.; Kang, Y.; Hua, Z.; Jin, Z. *Org. Lett.* **2004**, *6*, 3217-3219.

[14] Hudlicky, T.; Frazier, J. O.; Seoane, G.; Tiedje, M.; Seoane, A.; Kwart, L. D.; Beal, C. *J. Am. Chem. Soc*., **1986**, *108*, 3755–3762.

[15] Afonso, C. A. M. *Tetrahedron Lett.* **1995**, *36*, 8857-8858.