

–Supporting Information for–

Fluorous mixture synthesis of four stereoisomers of the C21–C40 fragment of tetrafibricin

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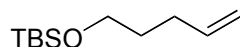
Experimental Procedures and Compound Characterization

General: All reactions were performed under an atmosphere of argon unless otherwise noted. Reaction solvents were freshly dried either by distillation or by passing through an activated alumina column. THF and toluene were freshly distilled from Na/benzophenone. Methylene chloride and Et₂O were dried by activated alumina. All other reagents were purchased commercially and used without further purification unless stated otherwise. Mixtures were magnetically stirred and progress was monitored by TLC with 0.25 mm E. Merck precoated silica gel plates. Flash chromatography was performed with silica gel 60 (particle size 0.040-0.063 mm) supplied by Sorbent Technologies.

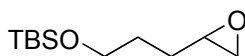
Products were analyzed by ¹H NMR, ¹³C NMR, COSY, ¹⁹F NMR, FT-IR, high and low resolution mass spectroscopy, and HPLC. NMR spectra were taken on a Bruker Avance™ 300 or a Bruker Avance™ 500 or a Bruker Avance™ 600 NMR or a Bruker Avance™ 700 spectrometer. Spectra were recorded at room temperature in the indicated deuteriated solvents and chemical shifts are reported in parts per million (ppm) downfield relative to TMS using the residual solvent proton resonance of CDCl₃ (7.26 ppm), MeOD (4.87 ppm) or central CDCl₃ carbon peak (77.0 ppm), central carbon peak MeOD (47.0 ppm) as the internal standard. In reporting spectral data, the following abbreviations were used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet doublet, dt = doublet triplet, td = triplet double, ddt = doublet double triplet, dtd = doublet triplet doublet. Infrared spectra were taken on a Mattson Genesis Series FTIR using thin film on NaCl plate. Peaks are reported in wavenumbers (cm⁻¹).

High resolution mass spectra were obtained on a V/G 70/70 double focusing machine and are reported in units of m/e . HPLC analysis was performed on a Waters 600 E system with a UV detector.

Synthesis of quasiracemate M-3a,b, Scheme 1

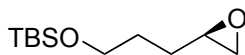


***tert*-Butyldimethyl(pent-4-enyloxy)silane** : To a solution of pent-4-en-1-ol (6.00 g, 69.8 mmol) in dichloromethane (400 ml) at 0 °C were added *tert*-butyldimethylsilyl chloride (11.6 g, 76.7 mmol) and imidazole (5.70 g, 83.7 mmol). The reaction mixture was stirred at 0 °C for 20 min, then warmed to room temperature and stirred for 1.5 h. Then the reaction was quenched with water. The layers were separated and the aqueous layer was extracted with dichloromethane. The combined organic extracts were dried over MgSO₄ and concentrated to give the alkene (14.0 g) as an oil. The crude product was taken to the next step without further purification: ¹H NMR (300 MHz, CDCl₃) δ 5.83 (ddt, $J = 17.0, 10.4, 6.6$ Hz, 1 H), 4.93-5.07 (m, 2 H), 2.07-2.16 (m, 2 H), 1.56-1.68 (m, 2 H), 0.09 (s, 9 H), 0.06 (s, 6 H); ¹³C NMR (75 MHz, CDCl₃) δ 138.6, 114.6, 62.6, 32.1, 30.1, 26.0, 18.4, -5.2.

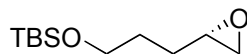


(*rac*)-*tert*-Butyldimethyl(3-(oxiran-2-yl)propoxy)silane : *m*-Chloroperbenzoic acid (75% w/w in H₂O, 16.0 g) was added to a solution of the above alkene (14.0 g, 69.8 mmol) in

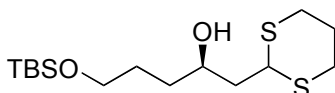
dichloromethane at 0 °C. The reaction mixture was stirred at 0 °C for 20 min, then warmed to room temperature and stirred for 1 h followed by adding saturated aqueous NaHCO₃ solution. The layers were separated and aqueous layer was further extracted with dichloromethane. The combined organic layers were dried over MgSO₄ and concentrated. Bulb-to-bulb (kugelrohr) distillation of the crude product under reduced pressure (0.1 mbar, 90-105 °C) gave the epoxide (13.0 g, 88%) as an oil: ¹H NMR (300 MHz, CDCl₃) δ 3.59-3.72 (m, 2 H), 2.91-2.99 (m, 1 H), 2.74-2.79 (m, 1 H), 2.49 (dd, *J* = 4.9, 2.7 Hz, 1 H), 1.53-1.76 (m, 4 H), 0.90 (s, 9 H), 0.06 (s, 6 H); ¹³C NMR (75 MHz, CDCl₃) δ 62.6, 52.1, 47.0, 29.1, 29.0, 25.9, 18.3, -5.3; IR (neat) cm⁻¹ 2954, 2857, 1472, 1256; EIMS (*M* - *t*Bu)⁺ :159; HRMS for C₇H₁₅O₂Si (*M* - *t*Bu)⁺ : Calcd 159.0841; found 159.0828.



(*R*)-*tert*-Butyldimethyl(3-(oxiran-2-yl)propoxy)silane ((*R*)-6): The (*R,R*)-Jacobsen catalyst (92 mg, 0.15 mmol) was dissolved in the above epoxide (3.22 g, 14.9 mmol), AcOH (35 μL) and THF (0.17 mL). The solution was cooled to 0 °C, treated with water (0.15 mL, 8.2 mmol), and stirred for 16 h at room temperature followed by concentration. Bulb-to-bulb (kugelrohr) distillation of crude product under reduced pressure (0.08 mm Hg, 90-105 °C) gave diastereomerically pure epoxide (*R*)-**6** (1.42 g, 6.8 mmol, 45%) as colorless oil: ¹H NMR (300 MHz, CDCl₃) δ 3.62-3.69 (m, 2 H), 2.92-2.98 (m, 1 H), 2.75 (t, *J* = 4.5 Hz, 1 H), 2.47 (dd, *J* = 4.8, 2.7 Hz, 1 H), 1.57-1.69 (m, 4 H), 0.90 (s, 9 H), 0.06 (s, 6 H); ¹³C NMR (75 MHz, CDCl₃) δ 62.6, 52.2, 47.1, 29.1, 29.0, 25.9, 18.3, -5.3; IR (neat) cm⁻¹ 2954, 2857, 1472, 1256.

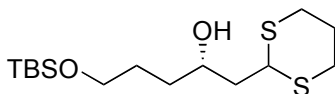


(S)-tert-Butyldimethyl(3-(oxiran-2-yl)propoxy)silane ((S)-6): Following the same procedure as above, epoxide (S)-6 (1.75 g, 8.1 mmol, 47%) was obtained as colorless oil: ^1H NMR (300 MHz, CDCl_3) δ 3.62-3.69 (m, 2 H), 2.92-2.98 (m, 1 H), 2.75 (t, $J = 4.5$ Hz, 1 H), 2.47 (dd, $J = 4.8, 2.7$ Hz, 1 H), 1.57-1.70 (m, 4 H), 0.90 (s, 9 H), 0.06 (s, 6 H); ^{13}C NMR (75 MHz, CDCl_3) δ 62.6, 52.2, 47.1, 29.1, 29.0, 25.9, 18.3, -5.3; IR (neat) cm^{-1} 2954, 2857, 1472, 1256.

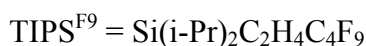
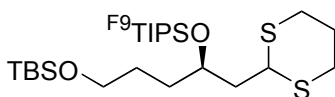


(R)-5-(tert-Butyldimethylsilyloxy)-1-(1,3-dithian-2-yl)pentan-2-ol ((R)-7): $t\text{-BuLi}$ (1.7 M in pentane, 5.8 mL, 9.9 mmol) was added to a solution of 1,3-dithiane (1.19 g, 9.9 mmol) in THF/HMPA (6.8 mL/3.4 mL) at -78 $^\circ\text{C}$ and the mixture was stirred for 30 min. Epoxide (R)-6 (1.44 g, 6.7 mmol) in THF (3.4 mL) and HMPA (1.7 mL) was added to the reaction mixture. The mixture was stirred for 1 h at -78 $^\circ\text{C}$ and then allowed to warm to 0 $^\circ\text{C}$ and stirred for 2 h. The reaction was quenched by adding saturated aqueous NH_4Cl solution. The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over MgSO_4 and concentrated. The crude product was purified by flash column chromatography (SiO_2 , 25% ethyl acetate in hexanes) to yield (R)-7 (1.59 g, 70%) as an oil: $[\alpha]_{\text{D}} -6.7$ (c 1.1 CHCl_3); ^1H NMR (300 MHz, CDCl_3) δ 4.28 (dd, $J = 9, 5.4$ Hz, 1 H), 3.88-3.98 (m, 1 H), 3.66 (t, $J = 5.4$ Hz, 2 H), 2.78-2.98 (m, 4 H), 2.07-2.18 (m, 1 H), 1.76-1.96 (m, 3 H), 1.42-1.71 (m, 4 H), 0.90 (s, 9 H), 0.07 (s, 6 H); ^{13}C NMR (126 MHz, CDCl_3) δ 67.9, 63.2, 44.1, 42.8, 34.6, 30.2,

30.0, 28.8, 25.9, 25.8, 18.2, -5.5; HRMS for $C_{15}H_{32}O_2S_2Si$ (M^+): Calcd 336.161303; found 336.162389.

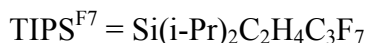
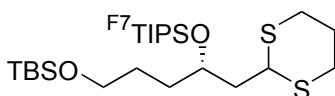


(S)-5-(tert-Butyldimethylsilyloxy)-1-(1,3-dithian-2-yl)pentan-2-ol ((S)-7): Following the same procedure as above, (S)-7 (1.54 g, 60%) was obtained as an oil: $[\alpha]_D +7.4$ (c 1.1 $CHCl_3$); 1H NMR (300 MHz, $CDCl_3$) δ 4.25 (dd, $J = 9, 5.4$ Hz, 1 H), 3.87-3.96 (m, 1 H), 3.64 (t, $J = 5.4$ Hz, 2 H), 2.77-2.99 (m, 4 H), 2.03-2.15 (m, 1 H), 1.74-1.93 (m, 3 H), 1.40-1.70 (m, 4 H), 0.90 (s, 9 H), 0.07 (s, 6 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 68.0, 63.3, 44.3, 42.8, 34.7, 30.2, 30.0, 28.9, 26.0, 25.9, 18.3, -5.4; HRMS for $C_{15}H_{32}O_2S_2Si$ (M^+): Calcd 336.161303; found 336.162292.



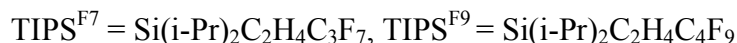
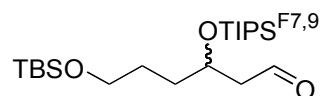
(R)-8-((1,3-dithian-2-yl)methyl)-13,13,14,14,15,15,16,16,16-nonafluoro-10,10-diisopropyl-2,2,3,3-tetramethyl-4,9-dioxa-3,10-disilaheptadecane ((R)-9a): Diisopropyl(3,3,4,4,5,5,6,6,6-nonafluorohexyl)silane **8a** (1.83 g, 3.9 mmol) was added to a 10 mL flask followed by adding CF_3SO_3H (0.351 mL, 3.9 mmol) dropwise under Ar at 0 °C. The reaction mixture was stirred for 15 min at 0 °C, then warmed to room temperature and stirred for 15 h. Then the homogeneous solution was cooled to 0 °C. A solution of 2,6-lutidine (0.61 mL), alcohol (R)-7 (437 mg, 1.3 mmol) in CH_2Cl_2 (5 mL) was added slowly and the reaction mixture was stirred for

4 h. The reaction was quenched by adding saturated NH_4Cl (10 mL) solution at 0 °C. The layers were separated and the aqueous layer was extracted with ethyl ether. The combined organic layers were dried over MgSO_4 and concentrated. Purification of the crude product by flash column chromatography (5% ethyl acetate in hexanes) provided (*R*)-**9a** (748 mg, 88%) as oil: $[\alpha]_D -12.0$ (*c* 1.0 CHCl_3); $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 4.10 (t, $J = 7.2$ Hz, 2 H), 3.53-3.66 (m, 2 H), 2.74-2.93 (m, 4 H), 2.04-2.24 (m, 3 H), 1.80-1.94 (m, 3 H), 1.47-1.65 (m, 4 H), 1.06 (m, 14 H), 0.88 (s, 11 H), 0.04 (s, 6 H); $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 69.3, 63.0, 44.0, 42.3, 33.7, 30.6, 30.2, 28.0, 26.0, 25.9, 18.3, 17.7, 17.7, 17.7, 17.6, 13.0, 0.8, -5.4; $^{19}\text{F NMR}$ (CDCl_3) -126.0 (2 F), -124.2 (2 F), -116.6 (2 F), -81.0 (3 F); HRMS for $\text{C}_{27}\text{H}_{49}\text{F}_9\text{O}_2\text{Si}_2\text{S}_2\text{K}$ ($\text{M} + \text{K}$) $^+$: Calcd 735.2206; found 735.2278.



(S)-8-((1,3-dithian-2-yl)methyl)-13,13,14,14,15,15,15-heptafluoro-10,10-diisopropyl-2,2,3,3-tetramethyl-4,9-dioxa-3,10-disilapentadecane ((S)-9b): Diisopropyl(3,3,4,4,5,5,5-heptafluoropentyl)silane **8b** (1.71 g, 5.5 mmol) was added to a 10 mL flask followed by adding $\text{CF}_3\text{SO}_3\text{H}$ (0.379 mL, 4.2 mmol) dropwise under Ar at 0 °C. The reaction mixture was stirred for 15 min at 0 °C, then warmed to room temperature and stirred for 15 h. Then the homogeneous solution was cooled to 0 °C. A solution of 2,6-lutidine (0.66 mL), alcohol (*S*)-**7** (470 mg, 1.4 mmol) in CH_2Cl_2 (5 mL) was added slowly and the reaction mixture was stirred for 4 h. The

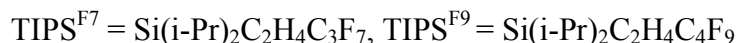
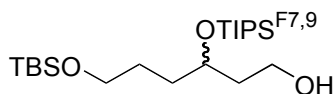
reaction was quenched by adding saturated NH_4Cl (10 mL) solution at 0 °C. The layers were separated and the aqueous layer was extracted with ethyl ether. The combined organic layers were dried over MgSO_4 and concentrated. Purification of the crude product by flash column chromatography (5% ethyl acetate in hexanes) provided (*S*)-**9b** (878 mg, 90%) as oil: $[\alpha]_{\text{D}} +11.3$ (*c* 1.0 CHCl_3); ^1H NMR (300 MHz, CDCl_3) δ 4.10 (t, $J = 7.2$ Hz, 2 H), 3.52-3.66 (m, 2 H), 2.73-2.93 (m, 4 H), 2.05-2.24 (m, 3 H), 1.78-1.94 (m, 3 H), 1.47-1.66 (m, 4 H), 1.05 (m, 14 H), 0.88 (s, 11 H), 0.04 (s, 6 H); ^{13}C NMR (75 MHz, CDCl_3) δ 69.2, 62.9, 44.0, 42.3, 33.6, 30.6, 30.2, 27.9, 26.0, 25.9, 18.3, 17.8, 17.7, 17.7, 17.6, 12.9, 0.7, -5.4; ^{19}F NMR (CDCl_3) -126.0 (2 F), -124.2 (2 F), -116.6 (2 F), -81.0 (3 F); HRMS for $\text{C}_{26}\text{H}_{49}\text{F}_7\text{O}_2\text{Si}_2\text{S}_2\text{K}$ ($\text{M} + \text{K}$) $^+$: Calcd 685.2238; found 685.2222.



(*Qrac*)-6-(*tert*-Butyldimethylsilyloxy)-3-(perfluoroalkyldiisopropylsilyloxy)hexanal

(M-10a,b): A solution of alcohol **M-9a,b** (1.34 g, 2.0 mmol) in THF/ H_2O (4:1, 28 mL) was cooled to 0 °C followed by addition of 2,6-lutidine (1.9 mL, 16 mmol) at once and $\text{Hg}(\text{ClO}_4)_3 \cdot \text{H}_2\text{O}$ (2.86 g) in portions. The reaction mixture was stirred at 0 °C for 3 h then filtered through a pad of celite and followed by a rinse with ethyl acetate. The filtrate was diluted with ethyl acetate and saturated aqueous NH_4Cl . The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over MgSO_4 and

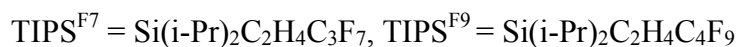
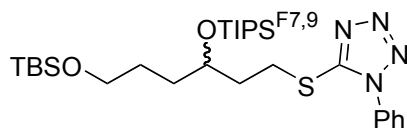
concentrated. The crude product was purified by flash column chromatography (SiO₂, 5% ethyl acetate in hexanes) to yield aldehyde M-**10a,b** (831 mg, 72%) as light yellow oil: ¹H NMR (300 MHz, CDCl₃) δ 9.83 (s, 1 H), 4.33-4.37 (m, 1 H), 4.33-4.37 (m, 1 H), 2.57 (m, 2 H), 2.01-2.17 (m, 2 H), 1.47-1.72 (m, 4 H), 1.04 (s, 14 H), 0.88 (s, 11 H), 0.04 (s, 6 H); ¹³C NMR (126 MHz, CDCl₃) δ 201.4, 68.5, 62.8, 50.5, 34.3, 28.3, 25.9, 25.3, 18.3, 17.6, 17.6, 17.5, 12.8, 12.7, 0.6, -5.4; ¹⁹F NMR (CDCl₃) -127.6 (2 F), -126.0 (2 F), -124.3 (2 F), -117.4 (2 F), -116.7 (2 F), -81.0 (3 F), -80.6 (3 F).



(Qrac)-6-(tert-Butyldimethylsilyloxy)-3-(diisopropylperfluoroalkylsilyloxy)hexan-1-ol :

DIBAL-H (1.0 M in hexane, 2.2 mL, 2.2 mmol) was added to a solution of aldehyde M-**10a,b** (811 mg, 1.39 mmol) in THF (20 mL) at -78 °C and the mixture was stirred for 1 h. The reaction mixture was warmed to 0 °C. Then the reaction was quenched with ethanol (1 mL) and saturated sodium-potassium tartrate solution (15 mL) followed by stirring it for 1 h. The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over MgSO₄ and concentrated. Purification of the crude product by flash column chromatography (25% ethyl acetate in hexanes) provided the alcohol (594 mg, 73%) as a clear oil: ¹H NMR (500 MHz, CDCl₃) δ 4.00-4.07 (m, 1 H), 3.78-3.85 (m, 1 H), 3.69-3.76 (m, 1 H), 3.55-3.65 (m, 2 H), 2.01-2.19 (m, 3 H), 1.79-1.88 (m, 1 H), 1.66-1.74 (m, 1 H), 1.57-1.65 (m, 2

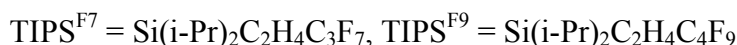
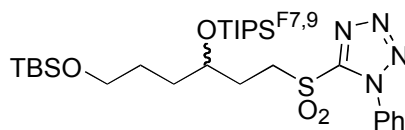
H), 1.46-1.55 (m, 2 H), 1.05 (s, 14 H), 0.88 (s, 11 H), 0.04 (s, 6 H); ^{13}C NMR (126 MHz, CDCl_3) δ 71.8, 63.0, 59.8, 37.8, 33.0, 28.5, 25.9, 25.2, 18.3, 17.6, 17.6, 17.6, 12.8, 0.6, -5.4; ^{19}F NMR (CDCl_3) -127.6 (2 F), -126.0 (2 F), -124.2 (2 F), -117.4 (2 F), -116.7 (2 F), -81.0 (3 F), -80.6 (3 F).



(*Qrac*)-5-(6-(*tert*-Butyldimethylsilyloxy)-3-(perfluoroalkyldiisopropylsilyloxy)hexylthio)-1-p

henyl-1*H*-tetrazole : Diisopropylazodicarboxylate (0.35 mL) was added to a solution of the above alcohol (574 mg, 0.98 mmol), 1-phenyl-1*H*-tetrazole-5-thiol (486 mg, 1.73 mmol) and triphenylphosphine (460 mg, 1.74 mmol) in THF (15 mL) at 0 °C. The reaction mixture was stirred at room temperature for 2.5 h. Then the reaction was quenched by adding saturated NaCl (20 mL) solution. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over MgSO_4 and concentrated. Purification of the crude product by flash column chromatography (5% ethyl acetate in hexanes) provided the sulfide (670 mg, 92%) as oil: ^1H NMR (500 MHz, CDCl_3) δ 7.52-7.57 (m, 5 H), 3.97 (tt, $J = 6, 5$ Hz, 1 H), 3.56-3.64 (m, 2 H), 3.38-3.50 (m, 2 H), 1.96-2.16 (m, 4 H), 1.45-1.67 (m, 4 H), 1.03 (s, 14 H), 0.088 (s, 11 H), 0.031 (s, 6 H); ^{13}C NMR (126 MHz, CDCl_3) δ 154.2, 133.7, 130.0, 129.8, 123.8, 71.4, 62.9, 35.6, 33.3, 29.1, 28.2, 25.9, 25.3, 18.3, 17.7, 17.7, 17.7, 12.6, 0.6, -5.3; ^{19}F NMR (CDCl_3) -127.5 (2 F), -126.0 (2 F), -124.2 (2 F), -117.3 (2 F), -116.7

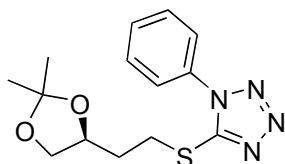
(2 F), -81.0 (3 F), -80.7 (3 F); HRMS for $C_{30}H_{50}N_4O_2F_7SSi_2$ (M^+): Calcd 719.3081; found 719.3055; HRMS for $C_{31}H_{50}N_4O_2F_9SSi_2$ (M^+): Calcd 769.3096; found 769.3049.



(*Qrac*)-5-(6-(*tert*-Butyldimethylsilyloxy)-3-(perfluoroalkyldiisopropylsilyloxy)hexylsulfonyl)

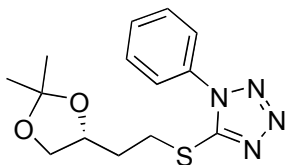
-1-phenyl-1*H*-tetrazole (M-3a,b): *m*-Chloroperbenzoic acid (590 mg, 3.41 mmol) was added to a solution of the above sulfide (636 mg, 0.85 mmol) in dichloromethane (10 mL) at 0 °C. The mixture was stirred for 2 h followed by warming to room temperature and stirring overnight. The reaction was quenched by adding saturated $NaHCO_3$ solution (10 mL). The organic layer was separated and the aqueous layer was extracted with dichloromethane and concentrated. Purification of the crude product by flash column chromatography (SiO_2 , 10% ethyl acetate in hexanes) to provide sulfone M-3a,b (562 mg, 85%) as oil: 1H NMR (500 MHz, $CDCl_3$) δ 7.57-7.70 (m, 5 H), 4.03-4.09 (m, 1 H), 3.75-3.89 (m, 2 H), 3.56-3.67 (m, 2 H), 2.03-2.24 (m, 4 H), 1.47-1.70 (m, 4 H), 1.05 (s, 14 H), 0.88 (s, 11 H), 0.039 (s, 6 H); ^{13}C NMR (126 MHz, $CHCl_3$) δ 153.4, 133.0, 131.4, 129.7, 125.0, 70.4, 62.6, 52.0, 33.0, 28.3, 25.8, 25.3, 18.2, 17.6, 17.5, 17.5, 12.7, 0.6, -5.5; ^{19}F NMR ($CDCl_3$) -127.5 (2 F), -126.0 (2 F), -124.2 (2 F), -117.3 (2 F), -116.7 (2 F), -81.0(3 F), -80.7 (3 F); IR (neat) cm^{-1} 2953, 2867, 1499, 1472, 1463, 1347, 1231, 1098, 838, 776; HRMS for $C_{30}H_{50}N_4O_4F_7SSi_2$ ($M + H$) $^+$: Calcd 751.2980; found 751.3050; HRMS for $C_{31}H_{50}N_4O_4F_9SSi_2$ ($M + H$) $^+$: Calcd 801.2948; found 801.3012.

Synthesis of quasiracemate M-4a,c, Scheme 2

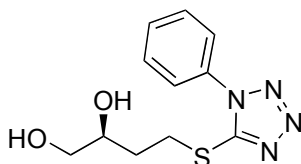


(S)-5-(2-(2,2-Dimethyl-1,3-dioxolan-4-yl)ethylthio)-1-phenyl-1H-tetrazole :

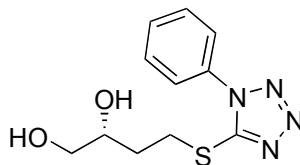
Diisopropylazodicarboxylate (2.8 g, 14 mmol) was added to a solution of alcohol (*S*)-**11** (1.2 g, 8.2 mmol), 1-phenyl-1*H*-tetrazole-5-thiol (2.60 g, 14.8 mmol) and triphenylphosphine (3.00 g, 11.5 mmol) in THF (20 mL) at 0 °C. The reaction mixture was stirred at room temperature for 3 h. Then the reaction was quenched with water. The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over MgSO₄ and concentrated. The crude product was purified by flash column chromatography (25% ethyl acetate in hexanes) to provide the (*S*)-sulfide (1.97 g, 6.45 mmol, 79%) as colorless crystal: $[\alpha]_D -1.0$ (*c* 1.0 CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 7.53 (br s, 6 H), 4.18-4.27 (m, 1 H), 4.06 (dd, *J* = 8.1, 6.1 Hz, 1 H), 3.59 (dd, *J* = 8.1, 6.6 Hz, 1 H), 3.36-3.55 (m, 2 H), 1.99-2.20 (m, 2 H), 1.39 (s, 3 H), 1.31 (s, 3 H); ¹³C NMR (75 MHz, CDCl₃) δ 154.1, 133.6, 130.1, 129.8, 123.7, 109.2, 74.2, 68.9, 33.4, 29.6, 26.9, 25.5; IR (neat) cm⁻¹ 3070, 2985, 2933, 2868, 1570, 1500, 1066; EIMS (*M* - CH₃)⁺ 291; HRMS for C₁₃H₁₅N₄O₂S (*M* - CH₃): Calcd 291.0916; found 291.0919.



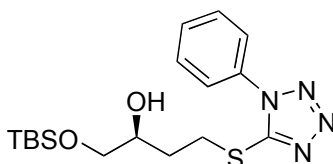
(R)-5-(2-(2,2-Dimethyl-1,3-dioxolan-4-yl)ethylthio)-1-phenyl-1H-tetrazole : Following the same procedure as above, the (*R*)-sulfide (2.15 g, 7.03 mmol, 86%) was obtained as colorless crystal: ^1H NMR (300 MHz, CDCl_3) δ 7.53 (br s, 6 H), 4.18-4.27 (m, 1 H), 4.06 (dd, $J = 8.1, 6.1$ Hz, 1 H), 3.59 (dd, $J = 8.1, 6.6$ Hz, 1 H), 3.36-3.55 (m, 2 H), 1.99-2.20 (m, 2 H), 1.39 (s, 3 H), 1.31 (s, 3 H).



(S)-4-(1-Phenyl-1H-tetrazol-5-ylthio)butane-1,2-diol : To a solution of the above (*S*)-sulfide (810 mg, 2.64 mmol) in methanol (10 mL) was treated with a drop of acetyl chloride (21 mg). Then the reaction mixture was stirred for 30 min. Concentration of the reaction mixture followed by purification of the crude product with flash column chromatography (SiO_2 , 80% ethyl acetate in hexanes) provided the (*S*)-diol (650 mg, 2.45 mmol, 93%) as viscous oil: $[\alpha]_{\text{D}} -7.5$ (c 1.82 CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 7.58 (br s, 5 H), 3.85-4.13 (m, 2 H), 3.68-3.81 (m, 1 H), 3.56-3.68 (m, 2 H), 3.42-3.55 (m, 1 H), 2.55 (br s, 1 H), 1.90-2.09 (m, 2 H); ^{13}C NMR (126 MHz, CDCl_3) δ 155.1, 133.5, 130.4, 129.9, 124.0, 69.5, 66.4, 29.8; IR (neat) cm^{-1} 3384, 2936, 1644, 1596, 1499, 1462, 1388, 1318, 1280; EIMS ($\text{M} + \text{H}$) $^+$ 267; HRMS for $\text{C}_{10}\text{H}_{11}\text{N}_4\text{O}_1\text{S}(\text{M} - \text{CH}_3\text{O})$: Calcd 235.065358; found 235.065690.

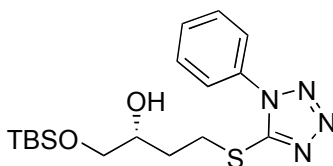


(R)-4-(1-Phenyl-1H-tetrazol-5-ylthio)butane-1,2-diol : Following the same procedure as above, the (*R*)-diol (650 mg, 2.45 mmol, 93%) was obtained as viscous oil: ^1H NMR (500 MHz, CDCl_3) δ 7.58 (br s, 5 H), 3.85-4.13 (m, 2 H), 3.68-3.81 (m, 1 H), 3.56-3.68 (m, 2 H), 3.42-3.55 (m, 1 H), 2.55 (br s, 1 H), 1.90-2.09 (m, 2 H).

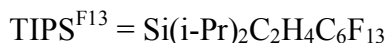
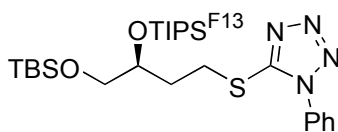


(S)-1-(tert-butyldimethylsilyloxy)-4-(1-phenyl-1H-tetrazol-5-ylthio)butan-2-ol ((S)-12): To a solution of the above (*S*)-diol (5.40 g, 20.3 mmol) in dichloromethane (200 ml) at 0 °C was added imidazole (1.52 g, 22.3 mmol). *Tert*-butyldimethylsilyl chloride (3.67 g, 24.4 mmol) was added in one portion. The resulting suspension was stirred at room temperature for 14 h. The reaction was quenched with water. The layers were separated and the aqueous phase was extracted with dichloromethane. The combined organic extracts were dried over MgSO_4 and concentrated. The residue was purified by flash column chromatography (25% ethyl acetate in hexanes) to provide compound (*S*)-**12** (6.96 g, 91%) as a colorless oil: $[\alpha]_D -3.0$ (*c* 1.0 CHCl_3) ^1H NMR (300 MHz, CDCl_3) δ 7.56 (s, 2 H), 3.77-3.87 (m, 1 H), 3.63-3.67 (dd, $J = 10.2, 6.3$ Hz, 1 H), 3.46-3.58 (m, 3 H), 2.81-2.82 (d, $J = 4.5$ Hz, 1 H), 1.83-2.12 (m, 2 H), 0.90 (s, 9 H), 0.07 (s, 6 H); ^{13}C NMR (126 MHz, CHCl_3) δ 154.5, 133.7, 130.1, 129.8, 123.8, 70.0, 66.8, 32.7, 31.0, 29.8, 25.9, 18.3, -5.4; HRMS for $\text{C}_{13}\text{H}_{19}\text{N}_4\text{O}_2\text{SSi}$ ($\text{M} - \text{C}_4\text{H}_9$) $^+$: Calcd 323.099801; found

323.098886.

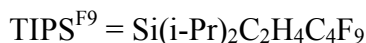
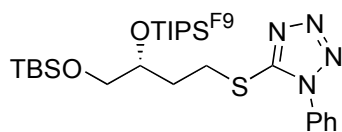
**(R)-1-(tert-butyldimethylsilyloxy)-4-(1-phenyl-1H-tetrazol-5-ylthio)butan-2-ol ((R)-12):**

Following the same procedure as above, compound (R)-12 (5.98 g, 90%) was obtained as a colorless oil: $[\alpha]_D +3.1$ (*c* 1.0 CHCl₃) ¹H NMR (300 MHz, CDCl₃) δ 7.53 (s, 2 H), 3.73-3.83 (m, 1 H), 3.59-3.64 (dd, *J* = 9.9, 6.0 Hz, 1 H), 3.43-3.55 (m, 3 H), 2.80-2.81 (d, *J* = 4.2 Hz, 1 H), 1.78-2.08 (m, 2 H), 0.87 (s, 9 H), 0.05 (s, 6 H); HRMS for C₁₃H₁₉N₄O₂SSi (M - C₄H₉)⁺: Calcd 323.099801; found 323.099465.

**(S)-5-(4-(tert-Butyldimethylsilyloxy)-3-(diisopropyl(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)silyloxy)butylthio)-1-phenyl-1H-tetrazole ((S)-13c):**

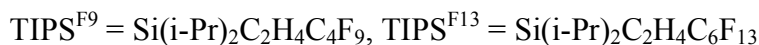
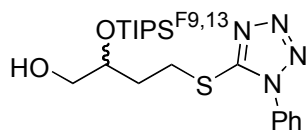
Diisopropyl(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluoro-octyl)silane **8c** (540 mg, 1.17 mmol) was added to a 5 mL flask followed by adding CF₃SO₃H (0.081 mL, 0.90 mmol) dropwise under Ar at 0 °C. The reaction mixture was stirred for 15 min at 0 °C, then warmed to room temperature and stirred for 15 h. Then the homogeneous solution was cooled to 0 °C. A solution of 2,6-lutidine (0.144 mL), compound (S)-12 (114 mg, 0.30mmol) in CH₂Cl₂ (5 mL) was added slowly and the reaction mixture was stirred for 4 h. The reaction was quenched by adding saturated NH₄Cl (10 mL) solution at 0 °C.

The organic layer was separated and the aqueous layer was extracted with ethyl ether. The combined organic layers were dried over MgSO₄ and concentrated. Purification of the crude product by flash column chromatography (5% ethyl acetate in hexanes) provided (*S*)-**13c** (230 mg, 90%) as oil: [α]_D -8.7 (*c* 1.1 CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 0.042 (s, 6 H), 0.84 (s, 9 H), 1.04 (s, 16 H) 1.96-2.18 (m, 4 H), 3.41-3.72 (m, 4 H), 3.94-3.98 (m, 1 H), 7.56 (s, 5 H); ¹³C NMR (75 MHz, CDCl₃) δ 154.2, 133.8, 130.0, 129.7, 123.8, 72.3, 66.7, 33.7, 29.0, 25.5, 18.3, 17.6, 17.6, 17.2, 12.8, 12.2, 0.7, -5.3; ¹⁹F NMR (CDCl₃) -126.2 (2 F), -123.3 (2 F), -122.9 (2 F), -122.0 (2 F), -116.6 (2 F), -80.9 (3 F); HRMS for C₃₁H₄₆F₁₃N₄O₂Si₂S (M + H)⁺: Calcd 841.2672; found 841.2695.



(*R*)-5-(4-(*tert*-Butyldimethylsilyloxy)-3-(diisopropyl(3,3,4,4,5,5,6,6,6-nonafluoro-hexyl)silyloxy)butylthio)-1-phenyl-1*H*-tetrazole ((*R*)-13a**):** Diisopropyl(3,3,4,4,5,5,6,6,6-nonafluoro-hexyl)silane **8a** (416 mg, 0.90 mmol) was added to a 5 mL flask followed by adding CF₃SO₃H (0.062 mL, 0.69 mmol) dropwise under Ar at 0 °C. The reaction mixture was stirred for 15 min at 0 °C, then warmed to room temperature and stirred for 15 h. Then the homogeneous solution was cooled to 0 °C. A solution of 2,6-lutidine (0.108 mL), compound (*R*)-**12** (86 mg, 0.23mmol) in CH₂Cl₂ (5 mL) was added slowly and the reaction mixture was stirred for 4 h. The reaction was quenched by adding saturated NH₄Cl (10 mL) solution at 0 °C. The organic layer was

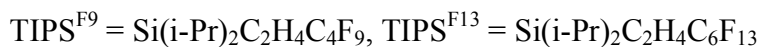
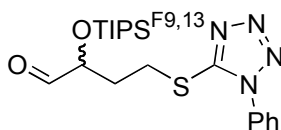
separated and the aqueous layer was extracted with ethyl ether. The combined organic layers were dried over MgSO_4 and concentrated. Purification of the crude product by flash column chromatography (5% ethyl acetate in hexanes) provided (*R*)-**13a** (153 mg, 90%) as oil: $[\alpha]_D +6.6$ (*c* 1.1 CHCl_3); ^1H NMR (300 MHz, CDCl_3) δ 0.042 (s, 6 H), 0.84 (s, 9 H), 1.03 (s, 16 H) 2.03-2.17 (m, 4 H), 3.41-3.73 (m, 4 H), 3.90-3.98 (m, 1 H), 7.53-7.60 (s, 5 H); ^{13}C NMR (75 MHz, CDCl_3) δ 154.2, 133.7, 130.0, 129.7, 123.7, 72.2, 66.7, 33.7, 29.0, 25.8, 18.3, 17.6, 17.6, 17.5, 12.8, 12.2, 0.7, -5.3; ^{19}F NMR (CDCl_3) -126.6 (2 F), -124.8 (2 F), -117.2 (2 F), -81.6 (3 F); HRMS for $\text{C}_{29}\text{H}_{46}\text{F}_9\text{N}_4\text{O}_2\text{Si}_2\text{S}$ ($\text{M} + \text{H}$) $^+$: Calcd 741.2736; found 741.2677.



(*Qrac*)-2-(diisopropylperfluoroalkylsilyloxy)-4-(1-phenyl-1*H*-tetrazol-5-ylthio)butan-1-ol :

A solution of sulfide M-**13a,c** (948 mg, 1.2 mmol) in methanol (28 mL) was treated with acetyl chloride (0.28 mL) at -20 °C. The reaction mixture was stirred at -20 °C for 3 h. Then the reaction was quenched by adding saturated NaHCO_3 (20 mL) solution. The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over MgSO_4 and concentrated. Purification of the crude product by flash column chromatography (50% ethyl acetate in hexanes) provided the primary alcohol (488 mg, 60%) as oil: ^1H NMR (500 MHz, CDCl_3) δ 7.53-7.57 (m, 5 H), 4.03 (q, $J = 5.0$ Hz, 1 H), 3.44-3.70 (m, 3 H), 3.34-3.38 (m, 1 H), 2.63 (br, 1H), 2.04-2.16 (m, 4 H), 1.037 (s, 14 H), 0.849-0.894 (m, 2 H);

^{13}C NMR (126 MHz, CDCl_3) δ 154.2, 133.5, 130.1, 129.8, 123.7, 71.7, 65.3, 33.4, 28.4, 17.5, 17.5, 17.5, 12.6, 12.2, 0.5; ^{19}F NMR (CDCl_3) -126.6 (4 F), -124.8 (2 F), -123.8 (2 F), -123.4 (2 F), -122.5 (2 F), -117.2 (2 F), -117.0 (2 F), -81.6 (3 F), -81.3 (3 F); IR (neat) cm^{-1} 3427, 2943, 2868, 2361, 2342, 1598, 1501, 1388, 1239; HRMS for $\text{C}_{23}\text{H}_{32}\text{N}_4\text{O}_2\text{F}_9\text{SSi}$ ($\text{M} + \text{H}^+$): Calcd 627.1872; found 627.1858; HRMS for $\text{C}_{25}\text{H}_{32}\text{N}_4\text{O}_2\text{F}_{13}\text{SSi}$ ($\text{M} + \text{H}^+$): Calcd 727.1808; found 727.1820.

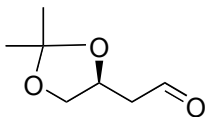


(*Qrac*)-2-(diisopropylperfluoroalkylsilyloxy)-4-(1-phenyl-1*H*-tetrazol-5-ylthio)butanal

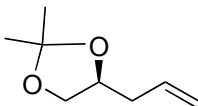
(M-4a,c): To a solution of the above alcohol (20 mg, 0.026 mmol) in dichloromethane (0.5 mL) was added sodium bicarbonate (solid, 13 mg) followed by Dess-Martin reagent (13 mg, 0.03 mmol). The reaction mixture was stirred for 1.5 h. Then the reaction was quenched by adding saturated aqueous NaHCO_3 solution (2 mL), extracted with dichloromethane, dried over MgSO_4 and concentrated. The crude product was purified by flash column chromatography (SiO_2 , 15% ethyl acetate in hexanes) to provide aldehyde **M-4a,c** (16 mg, 0.021 mmol, 81%) as oil: ^1H NMR (500 MHz, CDCl_3) δ 9.66 (s, 1 H), 7.53-7.59 (m, 5 H), 4.32 (dd, $J = 6.0, 5.7$ Hz, 1 H), 3.61 (t, $J = 6.5$ Hz, 1 H), 3.20 (t, $J = 6.5$ Hz, 1 H), 2.30-2.37 (m, 2 H), 2.06-2.23 (m, 2 H), 1.00-1.02 (m, 14 H), 0.85-0.94 (m, 2 H); ^{13}C NMR (126 MHz, CDCl_3) δ 0.6, 1.0, 12.6, 12.6, 17.4, 17.5, 28.2, 32.2, 77.2, 123.8, 129.8, 130.2, 133.6, 153.5, 201.6; ^{19}F NMR (CDCl_3) -126.6 (4 F), -124.8 (2

F), -123.8 (2 F), -123.4 (2 F), -122.5 (2 F), -117.3 (2 F), -117.0 (2 F), -81.6 (3 F), -81.3 (3 F).

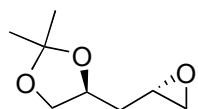
Synthesis of single isomer fragment 5, Scheme 3



(S)-2-(2,2-Dimethyl-1,3-dioxolan-4-yl)acetaldehyde : To a solution of alcohol (S)-11 (5.00 g, 34.1 mmol) in dichloromethane (200 mL) at 0 °C was added diisopropylethylamine (26.3 mL, 153.9 mmol). After 5 min, DMSO (24.3 mL, 341 mmol) was added and the mixture was stirred for another 10 min. Then SO₃•Py (13.6 g, 85.5 mmol) was added and the resulting mixture was stirred for 45 min. Saturated aqueous NaHCO₃ was added and the mixture was allowed to warm to room temperature. The layers were separated and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with brine, dried over MgSO₄ and concentrated. The residue was purified by flash column chromatography (35% ethyl acetate in hexanes) to yield the aldehyde (4.30 g, 29.4 mmol, 86%) as oil: [α]_D +8.1 (c 3.8 CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 9.8 (t, *J* = 1.4 Hz, 1 H), 4.54 (p, *J* = 6.3 Hz, 1 H), 4.19 (dd, *J* = 8.5, 6.0 Hz, 1 H), 3.60 (dd, *J* = 8.5, 6.9 Hz, 1 H), 2.85 (ddd, *J* = 17.3, 6.6, 1.9 Hz, 1 H), 2.65 (ddd, *J* = 17.3, 6.0, 1.1 Hz, 1 H), 1.42 (s, 3 H), 1.37 (s, 3 H); ¹³C NMR (76 MHz, CDCl₃) δ 199.9, 109.3, 70.7, 69.2, 47.9, 26.9, 25.5; IR (neat) cm⁻¹ 2987, 2936, 2735, 1725, 1372, 1217; HRMS for C₆H₉O₃ (M - CH₃)⁺: Calcd 129.0552; found 129.0550.



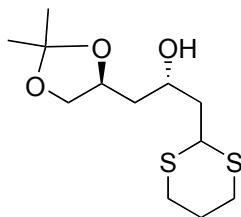
(S)-4-Allyl-2,2-dimethyl-1,3-dioxolane : To a solution of $\text{CH}_3\text{PPh}_3\text{Br}$ (15.8 g, 44.2 mmol) in THF (500 mL) at 0 °C was added *n*-BuLi (1.6 M in hexane, 27.6 mL, 44.2 mmol). The reaction mixture was stirred at that temperature for 20 min and then cooled to -78 °C. A solution of the above aldehyde (4.9 g, 34 mmol) in THF (5 mL) was added slowly to the reaction mixture. The mixture was stirred for 30 min at -78 °C and then warmed to room temperature and stirred overnight. The reaction mixture was poured into saturated aqueous NH_4Cl . The layers were separated and the aqueous layer was extracted with Et_2O . The combined organic layers were dried over MgSO_4 and concentrated. Purification of the crude product by flash column chromatography (SiO_2 , 20% ethyl acetate in hexanes) afforded the alkene (4.0 g, 83%) as a volatile oil: ^1H NMR (300 MHz, CDCl_3) δ 5.81 (ddt, $J = 17.0, 10.4, 7.1$ Hz, 1 H), 4.13-4.21 (m, 1 H), 5.07-5.17 (m, 2 H), 4.03 (dd, $J = 8.2, 6.0$ Hz, 1 H), 3.59 (dd, $J = 8.2, 7.1$ Hz, 1 H), 2.37-2.48 (m, 1 H), 2.25-2.34 (m, 1 H), 1.43 (s, 3 H), 1.37 (s, 3 H); ^{13}C NMR (75 MHz, CDCl_3) δ 133.7, 117.7, 109.0, 75.2, 69.0, 38.1, 26.9, 25.7.



(S)-2,2-dimethyl-4-((S)-oxiran-2-ylmethyl)-1,3-dioxolane ((S,S)-14):¹ The above alkene was dissolved in dichloromethane and *m*-CPBA was added at room temperature. The mixture was stirred for overnight. Then the reaction was quenched by adding saturated NaHCO_3 solution. The

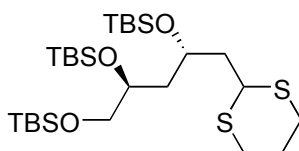
¹ CAS # 101977-98-4

layers were separated and the aqueous layer was extracted with dichloromethane and the combined organic extracts were dried over MgSO_4 and concentrated. Purification by flash column chromatography (SiO_2 , 25% ethyl acetate in hexanes) gave the epoxide as a mixture of two diastereomers. The (*S,S*)-Jacobsen catalyst (165 mg, 0.27 mmol) was dissolved in the above epoxide (4.2 g, 26.5 mmol), AcOH (65 mg) and THF (0.26 mL). The solution was cooled to 0 °C, treated with water (0.27 mL, 15.0 mmol), and stirred for 16 h at room temperature followed by concentration. Bulb-to-bulb (kugelrohr) distillation of crude product under reduced pressure (0.08 mm Hg, 90-105 °C) gave diastereomerically pure epoxide (*S,S*)-**14** (1.89 g, 11.9 mmol, 45%) as colorless oil ^1H NMR (500 MHz, CDCl_3) δ 4.22 -4.27 (m, 1 H), 4.05 (dd, $J = 7.8, 5.6$ Hz, 1 H), 3.53 (t, $J = 7.3$ Hz, 1 H), 2.97-3.00 (m, 1 H), 2.75 (t, $J = 4.6$ Hz, 1 H), 2.45 (dd, $J = 4.6, 2.3$ Hz, 1 H), 1.91 (ddd, $J = 14.2, 7.8, 4.1$ Hz, 1 H), 1.49 (ddd, $J = 13.8, 7.3, 5.5$ Hz, 1 H), 1.36 (s, 3 H), 1.31 (s, 3 H); ^{13}C NMR (126 MHz, CDCl_3) δ 108.9, 73.6, 69.3, 49.3, 47.1, 37.1, 26.9, 25.6; IR (neat) cm^{-1} 2987, 2942, 2872, 1454, 1371, 1060; HRMS for $\text{C}_7\text{H}_{11}\text{O}_3$ ($\text{M} - \text{CH}_3$) $^+$: Calcd 143.0708; found 143.0706.



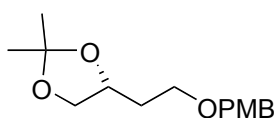
(S)-1-((S)-2,2-Dimethyl-1,3-dioxolan-4-yl)-3-(1,3-dithian-2-yl)propan-2-ol : *t*-BuLi (1.7 M in pentane, 5.3 mL, 9.0 mmol) was added to a solution of 1,3-dithiane (1.10 g, 9.04 mmol) in THF/HMPA (5 mL/0.3 mL) at -78 °C. After 30 min, epoxide (*S,S*)-**14** (1.3 g, 8.2 mmol) in THF

(3 mL) and HMPA (1 mL) was added to the above reaction mixture. After 1 h, the reaction mixture was allowed to warm to 0 °C, treated with saturated aqueous NH₄Cl solution. The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over MgSO₄ and concentrated. The residue was purified by flash column chromatography (SiO₂, 25% ethyl acetate in hexanes) to yield the product (1.9 g, 83%) as an oil: $[\alpha]_D +6.75$ (*c* 0.80 CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 4.31-4.36 (m, 1 H), 4.27 (dd, *J* = 8.9, 5.3 Hz, 1 H), 4.14-4.20 (m, 1 H), 4.09 (dd, *J* = 8.2, 6.0 Hz, 1 H), 3.59 (t, *J* = 7.8 Hz, 1 H), 2.82-2.95 (m, 4 H), 2.67 (d, *J* = 5.0 Hz, 1 H), 2.10-2.16 (m, 1 H), 1.84-1.99 (m, 3 H), 1.69-1.79 (m, 2 H), 1.42 (s, 3 H), 1.36 (s, 3 H); ¹³C NMR (126 MHz, CDCl₃) δ 108.9, 73.4, 69.4, 66.1, 44.2, 42.8, 39.8, 30.3, 30.1, 26.9, 25.9, 25.6; IR (neat) cm⁻¹ 3435, 2983, 2935, 2899, 1456, 1423, 1370; EIMS (*M*⁺) 278; HRMS for C₁₂H₂₂O₃S₂ (*M*⁺): Calcd 278.1010; found 278.1006.



2-((2*S*,4*S*)-2,4,5-tris(*tert*-butyldimethylsilyloxy)pentyl)-1,3-dithiane (15): To a solution of the above compound (1.9 g, 6.8 mmol) in methanol (16 mL) was added acetyl chloride (200 μL). After 1 h, the mixture was concentrated to dryness. Then the residue (triol) in dichloromethane (30 mL) were added 2,6-lutidine (2.4 g, 22.4 mmol) and TBSOTf (5.90 g, 22.4 mmol) at 0 °C. After 1 h, the reaction was quenched with water. The layers were separated and the aqueous layer was extracted with dichloromethane. The combined organic extracts were dried over MgSO₄ and concentrated. The crude product was purified by flash column chromatography (5%

ethyl acetate in hexanes) to provide compound **15** (3.25 g, 88%) as an oil: ^1H NMR (300 MHz, CDCl_3) δ 4.02-4.14 (m, 2 H), 3.69-3.79 (m, 1 H), 3.54 (dd, $J = 10.2, 5.2$ Hz, 1 H), 3.42 (dd, $J = 10.2, 5.8$ Hz, 1 H), 2.75-2.94 (m, 4 H), 2.06-2.19 (m, 1 H), 1.76-1.96 (m, 4 H), 1.47-1.56 (m, 1 H), 0.90 (s, 18 H), 0.89 (s, 9 H), 0.12 (s, 3 H), 0.10 (s, 6 H), 0.08 (s, 3 H), 0.06 (s, 6 H); ^{13}C NMR (75 MHz, CDCl_3) δ 71.2, 67.8, 67.0, 44.2, 44.0, 43.4, 30.8, 30.4, 26.1, 18.5, 18.2, -3.8, -3.9, -4.1, -4.3, -5.2; IR (neat) cm^{-1} 2954, 2929, 2897, 2857, 1472, 1463, 1255.

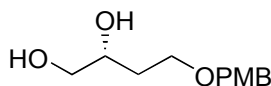


(R)-4-(2-(4-Methoxybenzyloxy)ethyl)-2,2-dimethyl-1,3-dioxolane : ²

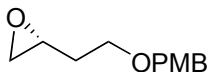
(R)-2-(2,2-dimethyl-1,3-dioxolan-4-yl)ethanol (1.30 g, 8.07 mmol) was added slowly over 10 min to a suspension of NaH (60%, 271 mg, 11.3 mmol) in DMF (15 mL) at 0 °C. The mixture was stirred for 30 min followed by the addition of *p*-methoxybenzylchloride (1.33 g, 8.48 mmol). The above reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched by adding methanol (1 mL) and then the mixture was poured into water (100 mL). The layers were separated and the aqueous layer was extracted with ether and the combined organic extracts were dried over MgSO_4 and concentrated. Purification by flash column chromatography (SiO_2 , 25% ethyl acetate in hexanes) gave the product (1.53 g, 84%) as colorless oil: $[\alpha]_D +0.87$ (c 1.2 CHCl_3); ^1H NMR (500 MHz, CHCl_3) δ 7.25 (d, $J = 8.2$ Hz, 2 H), 6.88 (d, $J = 8.2$ Hz, 2 H), 4.44 (s, 2 H), 4.17-4.25 (m, 1 H), 4.06 (dd, $J = 8.2, 6.0$ Hz, 1 H), 3.81 (s, 3 H), 3.50-3.60 (m, 3 H), 1.89-1.97 (m, 1 H), 1.79-1.89 (m, 1 H), 1.41 (s, 3 H), 1.36 (s, 3 H);

² CAS # 213978-60-0

^{13}C NMR (126 MHz, CDCl_3) δ 159.3, 130.5, 129.3, 113.9, 108.6, 74.0, 72.8, 69.7, 66.8, 55.3, 33.9, 27.0, 25.9; IR (neat) cm^{-1} 2985, 2936, 2865, 1613, 1514, 1248; HRMS for $\text{C}_{12}\text{H}_{18}\text{O}_4$ (M^+): Calcd 226.1205; found 226.1199.

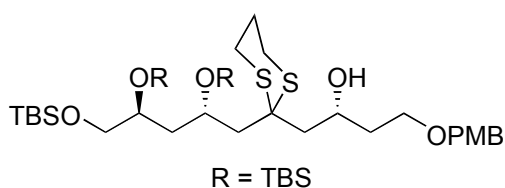


(R)-4-(4-Methoxybenzyloxy)butane-1,2-diol : To a solution of the above compound (1.70 g, 6.04 mmol) in methanol (25 mL) was added acetyl chloride (~100 mg). The reaction mixture was stirred at room temperature for 2 h, followed by concentration of the reaction mixture. The crude product was purified by flash column chromatography (SiO_2 , 80% ethyl acetate in hexanes) to yield the diol (1.40 g, 87%) as clear colorless oil: $[\alpha]_{\text{D}} -2.6$ (c 1.4 CHCl_3); ^1H NMR (300 MHz, CHCl_3) δ 7.24 (d, $J = 8.2$ Hz, 2 H), 6.88 (d, $J = 8.2$ Hz, 2 H), 4.46 (s, 2 H), 3.81 (s, 3 H), 3.86-3.94 (m, 1 H), 3.58-3.70 (m, 3 H), 3.45-3.54 (m, 1 H), 1.60-1.90 (m, 2 H); ^{13}C NMR (126 MHz, CDCl_3) δ 158.9, 129.6, 129.0, 113.5, 72.5, 67.1, 54.9, 32.8; IR (neat) cm^{-1} 3384, 2934, 1613, 1514, 1249; HRMS for $\text{C}_{15}\text{H}_{22}\text{O}_4$ (M^+): Calcd 266.1518; found 266.1514.



(R)-2-(2-(4-Methoxybenzyloxy)ethyl)oxirane ((R)-16): To a solution of the above diol (800 mg, 3.98 mmol) in toluene (15 mL) were added PPh_3 (1.30 g, 4.97 mmol) and DIAD (1.00 g, 4.97 mmol). The mixture was refluxed overnight and concentrated. The crude product was purified by flash column chromatography (SiO_2 , 25% ethyl acetate in hexanes) to yield epoxide **(R)-16** (779 mg, 94%) as oil: $[\alpha]_{\text{D}} +12.0$ (c 1.0 CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 7.27 (d, $J = 8.7$ Hz, 2

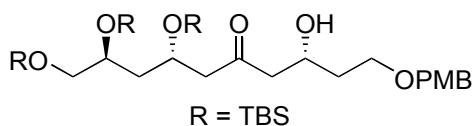
H), 6.89 (d, $J = 8.7$ Hz, 2 H), 4.47 (s, 2 H), 3.81 (s, 3 H), 3.55-3.64 (m, 2 H), 3.03-3.10 (m, 1 H), 2.79 (t, $J = 4.6$ Hz, 1 H), 2.53 (dd, $J = 5.0, 2.7$ Hz, 1 H), 1.85-1.95 (m, 1 H), 1.72-1.82 (m, 1 H); ^{13}C NMR (126 MHz, CDCl_3) δ 159.3, 130.4, 129.3, 113.9, 72.8, 66.8, 55.3, 50.1, 47.2, 33.0; IR (neat) cm^{-1} 2997, 2924, 2860, 1613, 1513; HRMS for $\text{C}_{12}\text{H}_{16}\text{O}_3$ (M^+): Calcd 208.1099; found 208.1094.



(*R*)-1-(2-((2*S*,4*S*)-2,4,5-*tris*(*tert*-Butyldimethylsilyloxy)pentyl)-1,3-dithian-2-yl)-4-(4-methoxybenzyloxy)butan-2-ol (17**):**

t-BuLi (1.7 M in pentane, 1 mL, 1.7 mmol) was added to a solution of dithiane **15** (0.9 g, 1.55 mmol) in THF (2.4 mL)-HMPA (0.6 mL) at -78 °C. After stirring at -78 °C for 10 min, epoxide (*R*)-**16** (0.36 g, 1.7 mmol) in THF (1 mL) was added. The reaction mixture was stirred at -78 °C for 15 min, then warmed to 0 °C and stirred for 1 h. The reaction was quenched with saturated aqueous NH_4Cl solution. The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over MgSO_4 and concentrated. The residue was purified by flash column chromatography (SiO_2 , 20% ethyl acetate in hexanes) to provide compound **17** (1.1 g, 90%) as an oil: $[\alpha]_{\text{D}} -5.0$ (c 0.9 CHCl_3); ^1H NMR (300 MHz, CDCl_3) δ 7.28 (d, $J = 8.5$ Hz, 2 H), 6.89 (d, $J = 8.8$ Hz, 2 H), 4.47 (s, 2 H), 4.18-4.33 (m, 2 H), 3.81 (s, 3 H), 3.46-3.74 (m, 5 H), 2.84-3.04 (m, 2 H), 2.68-2.83 (m, 2 H), 1.66-2.47 (m, 11 H), 0.94 (s, 9 H), 0.93 (s, 9 H), 0.91 (s, 9 H), 0.09-0.16 (m, 18 H); ^{13}C NMR

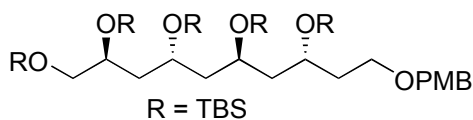
(76 MHz, CDCl₃) δ 159.1, 130.4, 129.2, 113.7, 72.7, 71.3, 67.9, 67.5, 67.4, 66.9, 60.3, 55.1, 51.4, 48.3, 46.5, 45.0, 37.6, 26.3, 26.0, 24.6, 18.4, 18.2, 18.0, 14.2, -3.1, -3.6, -3.8, -4.4, -5.3; IR (neat) cm⁻¹ 2953, 2928, 2855, 1614, 1514, 1463, 1250; HRMS for C₃₉H₇₆O₆S₂Si₃Na: Calcd 811.4289; found 811.4284.



(3*R*,7*S*,9*S*)-1-(4-Methoxybenzyloxy)-7,9,10-tris(*tert*-butyldimethylsilyloxy)-3-hydroxy-

decan-5-one : A solution of **17** (610 mg, 0.77 mmol) in THF/H₂O (4:1, 10 mL) was cooled to 0 °C, followed by addition of 2,6-lutidine (662 mg, 6.18 mmol) and Hg(ClO₄)₃•H₂O (1.05 g, 2.32 mmol) in portions. The reaction mixture was stirred at 0 °C for 45 min and then filtered through a pad of celite and followed by a rinse with ethyl acetate. The filtrate was diluted with ethyl acetate and saturated aqueous NH₄Cl. The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over MgSO₄ and concentrated. Purification by flash column chromatography (20% ethyl acetate in hexanes) provided the ketone (454 mg, 84%) as oil: $[\alpha]_D -6.53$ (*c* 1.73 CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 7.25 (d, *J* = 8.6 Hz, 2 H), 6.87 (d, *J* = 8.6 Hz, 2 H), 4.44 (s, 2 H), 4.15-4.35 (m, 2 H), 3.80 (s, 3 H), 3.64-3.76 (m, 1 H), 3.50-3.63 (m, 3 H), 3.36-3.43 (m, 2 H), 2.54-2.70 (m, 4 H), 1.70-1.83 (m, 3 H), 1.48-1.60 (m, 1 H), 0.93 (s, 9 H), 0.92 (s, 9 H), 0.89 (s, 9 H), 0.13 (s, 6 H), 0.12 (s, 3 H), 0.09 (s, 6 H), 0.08 (s, 3 H); ¹³C NMR (75 MHz, CHCl₃) δ 209.9, 159.3, 130.4, 129.3, 113.9, 72.9, 71.2, 67.8, 67.6, 67.0, 66.3, 55.3, 52.1, 50.9, 43.4, 36.2, 26.0, 26.0, 25.9, 18.4,

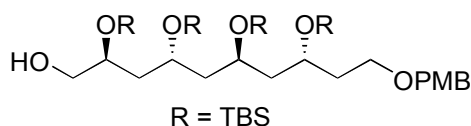
18.2, 18.0, -3.9, -4.2, -4.3, -4.5, -5.3; IR (neat) cm^{-1} 3509, 2954, 2929, 2857, 1709, 1614, 1514, 1472, 1251; HRMS for $\text{C}_{36}\text{H}_{70}\text{O}_7\text{Si}_3\text{Na}$ ($\text{M} + \text{Na}$)⁺: Calcd 721.4327; found 721.4329.



1-(((3*R*,5*S*,7*R*,9*S*)-3,5,7,9,10-pentakis(*tert*-Butyldimethylsilyloxy)decyloxy)methyl)-

4-methoxybenzene (18): To a solution of the above ketone (445 mg, 0.64 mmol) in acetonitrile (2 mL) at $-25\text{ }^{\circ}\text{C}$ was added $(\text{CH}_3)_4\text{NBH}(\text{OAc})_3$ (253 mg, 0.96 mmol) as a solution in acetic acid (0.4 mL). The reaction mixture was stirred at that temperature for 48 h, quenched with 3 mL aqueous 1.0 M sodium potassium tartrate, diluted with ethyl acetate and neutralized with sodium bicarbonate. The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over MgSO_4 and concentrated. To the crude compound (412 mg) in dichloromethane at $0\text{ }^{\circ}\text{C}$ were added 2,6-lutidine (189 mg, 1.77 mmol) and TBSOTf (327 mg, 1.24 mmol). The resulting mixture was stirred at that temperature for 1 h and then quenched with water. The layers were separated and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried over MgSO_4 and concentrated. The crude product was purified by flash column chromatography (SiO_2 , 10% ethyl acetate in hexanes) to yield compound **18** (434 mg, 73%) as oil: ^1H NMR (600 MHz, CDCl_3) δ 7.26 (d, $J = 9.6$ Hz, 2 H), 6.87 (d, $J = 8.8$ Hz, 2 H), 4.42 (s, 2 H), 3.87-3.92 (m, 2 H), 3.83-3.87 (m, 1 H), 3.81 (s, 3 H), 3.76-3.80 (m, 1 H), 3.49-3.54 (m, 3 H), 3.41 (dd, $J = 10.2, 5.5$ Hz, 1 H), 1.79-1.84 (m, 1 H), 1.67-1.75 (m, 2 H), 1.59-1.67 (m, 3 H), 1.52-1.58 (m, 1 H), 1.45-1.50 (m, 1 H), 0.90 (s, 9 H),

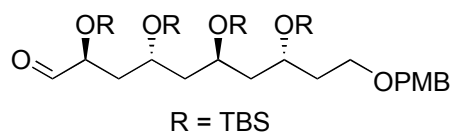
0.888 (s, 9 H), 0.883 (s, 9 H), 0.88 (s, 9 H), 0.877 (s, 9 H), 0.084 (s, 3 H), 0.082 (s, 3 H), 0.08 (s, 3 H), 0.076 (s, 6 H), 0.07 (s, 3 H), 0.063 (s, 3 H), 0.06 (s, 3 H), 0.055 (s, 3 H), 0.04 (s, 3 H); ^{13}C NMR (151 MHz, CDCl_3) δ 159.1, 130.9, 129.2, 113.8, 72.6, 70.8, 67.6, 67.5, 67.4, 67.2, 66.8, 55.3, 46.8, 46.0, 42.6, 37.7, 26.1, 26.1, 26.1, 26.1, 18.5, 18.3, 18.2, 18.1, -3.4, -3.5, -3.7, -3.8, -4.2, -4.4, -5.2; HRMS for $\text{C}_{48}\text{H}_{100}\text{O}_7\text{Si}_5\text{Na}$ ($\text{M} + \text{Na}$) $^+$: Calcd 951.6213; found 951.6311.



(2*S*,4*R*,6*S*,8*R*)-10-(4-Methoxybenzyloxy)-2,4,6,8-tetrakis(*tert*-butyldimethylsilyloxy)

decan-1-ol : To a solution of **18** (70 mg, 0.075 mmol) in THF (0.5 mL) was added HF•Py in pyridine (1 mL). The reaction mixture was stirred at room temperature for 6 h followed by quenching the reaction with saturated aqueous sodium bicarbonate solution (5 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were dried over MgSO_4 and concentrated. Purification by flash column chromatography (SiO_2 , 10% ethyl acetate in hexanes) provided the primary alcohol (30 mg, 49%) as colorless oil along with recovered starting material (29 mg, 0.031 mmol): $[\alpha]_{\text{D}} +16.5$ (c 0.2 CHCl_3); ^1H NMR (600 MHz, CDCl_3) δ 7.76 (d, $J = 8.5$ Hz, 2 H), 6.88 (d, $J = 8.5$ Hz, 2 H), 4.41 (ddd, $J = 19.8, 11.5, 5.0$ Hz, 1 H) 3.85-3.89 (m, 1 H), 3.80-3.85 (m, 6 H), 3.61 (ddd, $J = 11.0, 5.5, 3.6$ Hz, 1 H), 3.50 (t, $J = 7.1$ Hz, 2 H), 3.44 (ddd, $J = 11.8, 7.1, 5.2$ Hz, 1 H), 1.91 (t, $J = 6.0$ Hz, 1 H), 1.80-1.85 (m, 1 H), 1.55-1.73 (m, 7 H), 0.91 (s, 9 H), 0.883 (s, 9 H), 0.88 (s, 18 H), 0.104 (s, 3 H), 0.10 (s, 3 H), 0.08 (s, 6 H), 0.072 (s, 6 H), 0.07 (s, 3 H), 0.05 (s, 3 H); ^{13}C NMR (151 MHz,

CDCl₃) δ 159.1, 130.8, 129.2, 113.7, 72.6, 70.4, 67.4, 67.2, 67.1, 66.7, 66.6, 55.3, 46.5, 46.3, 42.4, 37.5, 26.0, 18.2, 18.1, -3.5, -3.6, -3.6, -3.7, -4.2, -4.3, -4.3; IR (neat) cm⁻¹ 3420, 2950, 2925, 2929, 2852, 1614, 1511, 1462, 1251, 1102; HRMS for C₄₂H₈₆O₇Si₄Na (M + Na)⁺: Calcd 837.5348; found 837.5363.

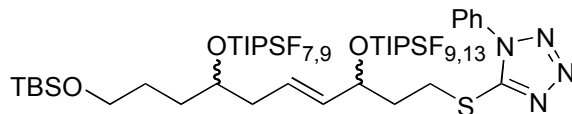


(2*S*,4*R*,6*S*,8*R*)-10-(4-Methoxybenzyloxy)-2,4,6,8-tetrakis(*tert*-butyldimethylsilyloxy) decanal

(5): To a solution of the above primary alcohol (28 mg, 0.034 mmol) in DCM (2 mL) were added solid NaHCO₃ (15 mg) and Dess-Martin reagent (17 mg, 0.041 mmol). The reaction mixture was stirred at room temperature for 1 h. Then the reaction was quenched with saturated NaHCO₃ solution. The layers were separated and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried over MgSO₄ and concentrated. The crude product was purified by flash column chromatography (10% ethyl acetate in hexanes) to yield aldehyde **5** (26 mg, 93%) as an oil used immediately for the next reaction: ¹H NMR (600 MHz, CD₂Cl₂) δ 8.58 (d, *J* = 1.7 Hz, 1 H), 7.24 (d, *J* = 8.5 Hz, 2 H), 6.85 (d, *J* = 8.8 Hz, 2 H), 4.38 (s, 2 H), 4.15-4.18 (m, 1 H), 3.95-4.00 (m, 1 H), 3.91-3.95 (m, 1 H), 3.82-3.86 (m, 1 H), 3.79 (s, 3 H), 3.47-3.52 (m, 2 H), 1.66-1.81 (m, 6 H), 1.53-1.60 (m, 2 H), 0.97 (s, 9 H), 0.93 (s, 9 H), 0.89 (s, 9 H), 0.88 (s, 9 H), 0.10 (s, 3 H), 0.09 (s, 6 H), 0.08 (s, 9 H), 0.06 (s, 3 H), 0.05 (s, 3 H); ¹³C NMR (151 MHz, CD₂Cl₂) δ 203.8, 159.7, 131.6, 129.7, 114.1, 76.1, 73.1, 68.0, 67.6, 67.6, 67.2, 55.8, 47.1, 46.3, 41.2, 38.4, 26.4, 26.3, 18.7, 18.5, -3.0, -3.1, -3.4, -3.5, -3.8, -3.9,

−4.3; IR (neat) cm^{-1} ; 2954, 2929, 2894, 2857, 1736, 1653, 1635, 1558, 1251; HRMS for $\text{C}_{42}\text{H}_{84}\text{O}_7\text{Si}_4\text{Na}$ ($\text{M} + \text{Na}$)⁺: Calcd 835.5192; found 835.5197.

Fragment coupling, demixing and detagging, Scheme 4



(*Qrac*)-5-((*E*)-10-(*tert*-butyldimethylsilyloxy)-3-(perfluoroalkyldiisopropylsilyloxy)-7-(perfluoroalkyldiisopropylsilyloxy)dec-4-enylthio)-1-phenyl-1*H*-tetrazole (M-19a,b/a,c): KHMDs

(0.5 M in DME, 0.45 ml, 0.225 mmol) was added to a solution of sulfone M-3a,b (0.13 g, 0.19

mmol) in DME (5 mL) at -78 °C. After 30 min, aldehyde M-4a,c (92.3 mg, 0.244 mmol) in

DME (2 mL) was added. The mixture was stirred at -78 °C for 1.5 h, then overnight stirring at

room temperature. The reaction was quenched with water. The layers were separated and the

aqueous layer was extracted with ethyl acetate. The combined organic extracts were dried over

MgSO₄ and concentrated. Purification of the crude product by flash column chromatography

provided *E/Z* mixture alkene M-19a,b/a,c (*E/Z* > 9:1) of product (95 mg, 80%) as oil. The

(*E*)-isomer was then separated by preparative chiral HPLC ((*S,S*) Whelk-O column, 25 cm ×

2.1 mm, hexanes: isopropanol = 95:5) to give the pure compound M-19a,b/a,c as colorless oil:

¹H NMR (500 MHz, CDCl₃) δ 7.55 (s, 5 H), 5.63 (dt, *J* = 16.0, 8.5 Hz, 1 H), 5.44 (dd, *J* = 15.5,

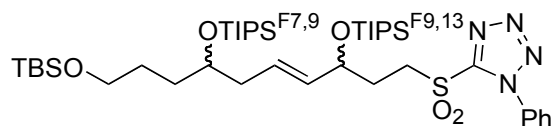
7.0 Hz, 1 H), 4.32 (q, *J* = 6.0 Hz, 1 H), 3.81-3.83 (m, 1 H), 3.52-3.62 (m, 2 H), 3.34-3.47 (m, 2

H), 2.17-2.29 (m, 2 H), 1.98-2.16 (m, 6 H), 1.45-1.55 (m, 4 H), 1.02 (s, 28 H), 0.87 (s, 13 H),

0.02 (s, 6 H); ¹³C NMR (126 MHz, CDCl₃) δ 154.5, 134.5, 134.4, 133.7, 130.1, 129.8, 128.0,

123.8, 86.0, 72.8, 72.7, 72.1, 63.1, 39.4, 37.5, 34.7, 34.4, 32.8, 32.7, 31.6, 29.1, 29.0, 28.3, 28.2,

25.9, 25.3, 22.7, 20.7, 18.3, 17.5, 17.5, 14.1, 12.8, 12.7, 12.7; ^{19}F NMR (CDCl_3) -128.2 (2 F), -126.6 (6 F), -124.8 (4 F), -123.8 (2 F), -123.4 (2 F), -122.5 (2 F), -118.0 (2 F), -117.2 (6 F), -81.6 (3 F), -81.4 (3 F), -81.2 (3 F); IR (neat) cm^{-1} 2955, 2928, 2856, 1740, 1698, 1501, 1367, 1124; HRMS ($\text{M} + \text{Na}$) $^+$ for $\text{C}_{46}\text{H}_{72}\text{N}_4\text{O}_3\text{F}_{16}\text{Si}_3\text{SNa}$: Calcd 1171.4275; found 1171.4237. HRMS ($\text{M} + \text{Na}$) $^+$ for $\text{C}_{47}\text{H}_{72}\text{N}_4\text{O}_3\text{F}_{18}\text{Si}_3\text{SNa}$: Calcd 1221.4243; found 1221.4243. HRMS ($\text{M} + \text{Na}$) $^+$ for $\text{C}_{48}\text{H}_{72}\text{N}_4\text{O}_3\text{F}_{20}\text{Si}_3\text{SNa}$: Calcd 1271.4211; found 1271.4146. HRMS ($\text{M} + \text{Na}$) $^+$ for $\text{C}_{49}\text{H}_{73}\text{N}_4\text{O}_3\text{F}_{22}\text{Si}_3\text{SNa}$: Calcd 1321.4179; found 1321.4214.

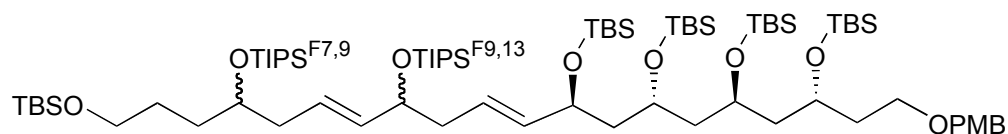


$\text{TIPS}^{\text{F}7} = \text{Si}(\text{i-Pr})_2\text{C}_2\text{H}_4\text{C}_3\text{F}_7$, $\text{TIPS}^{\text{F}9} = \text{Si}(\text{i-Pr})_2\text{C}_2\text{H}_4\text{C}_4\text{F}_9$, $\text{TIPS}^{\text{F}13} = \text{Si}(\text{i-Pr})_2\text{C}_2\text{H}_4\text{C}_6\text{F}_{13}$

(*Qrac*)-5-((*E*)-10-(*tert*-butyldimethylsilyloxy)-3-(perfluoroalkyldiisopropylsilyloxy)-7-(perfluoroalkyldiisopropylsilyloxy)dec-4-enylsulfonyl)-1-phenyl-1*H*-tetrazole (M-20a,b/a,c): To a solution of sulfide M-19a,b/a,c (62 mg, 0.078 mmol) in ethanol (1.5 mL) was added oxidant (0.3 mL, prepared from 0.6 g of $\text{Mo}_7\text{O}_{24}(\text{NH}_4)_6 \cdot 4\text{H}_2\text{O}$ in 2.5 mL of 30% w/v aq H_2O_2). The reaction mixture was stirred at room temperature for 18 h. Then the reaction was quenched with water. The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were dried over MgSO_4 and concentrated. Purification of the crude product by flash column chromatography provided (SiO_2 , 10% ethyl acetate in hexanes) to yield sulfone M-20a,b/a,c (60 mg, 88%) as an oil: ^1H NMR (300 MHz, CDCl_3) δ 7.59-7.70 (m, 5 H), 5.66-5.77 (m, 1 H), 5.46 (dd, $J = 15.5, 6.6$ Hz, 1 H), 4.43 (m, 1 H), 3.75-3.92 (m, 3 H), 3.50-3.65

(s, 2 H), 1.98-2.30 (m, 8 H), 1.45-1.55 (m, 4 H), 1.02 (s, 28 H), 0.87 (s, 13 H), 0.02 (s, 6 H); ^{13}C NMR (126 MHz, CDCl_3) δ 153.4, 133.4, 133.3, 133.0, 131.4, 129.7, 125.0, 72.0, 71.9, 71.8, 71.5, 71.4, 71.3, 63.0, 52.0, 39.3, 32.8, 32.7, 30.7, 30.5, 30.3, 29.7, 28.3, 26.1, 25.9, 25.8, 25.6, 18.3, 17.6, 17.4, 12.7, 0.5, -5.2; ^{19}F NMR (CDCl_3) -128.1 (2 F), -126.6 (6 F), -124.8 (4 F), -123.8 (2 F), -123.4 (2 F), -122.5 (2 F), -118.0 (2 F), -117.2 (6 F), -81.6(3 F), -81.4 (3 F), -81.2 (3 F); IR (neat) cm^{-1} 2954, 2930, 2857, 1743, 1696, 1367, 1343, 1124; HRMS ($\text{M} + \text{Na}$) $^+$ for $\text{C}_{46}\text{H}_{72}\text{N}_4\text{O}_5\text{F}_{16}\text{Si}_3\text{SNa}$: Calcd 1203.4147; found 1203.4174. HRMS ($\text{M} + \text{Na}$) $^+$ for $\text{C}_{47}\text{H}_{72}\text{N}_4\text{O}_5\text{F}_{18}\text{Si}_3\text{SNa}$: Calcd 1253.4103; found 1253.4142. HRMS ($\text{M} + \text{Na}$) $^+$ for $\text{C}_{48}\text{H}_{72}\text{N}_4\text{O}_5\text{F}_{20}\text{Si}_3\text{SNa}$: Calcd 1303.4099; found 1303.4110. HRMS ($\text{M} + \text{Na}$) $^+$ for $\text{C}_{49}\text{H}_{73}\text{N}_4\text{O}_5\text{F}_{22}\text{Si}_3\text{SNa}$: Calcd 1353.4044; found 1353.4078.

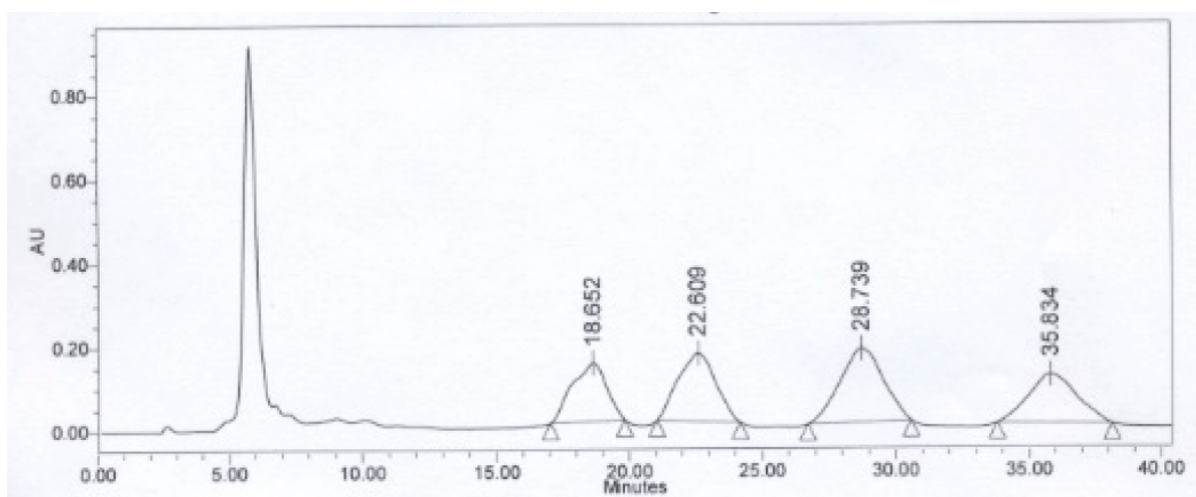
M-21a,b/a,c:



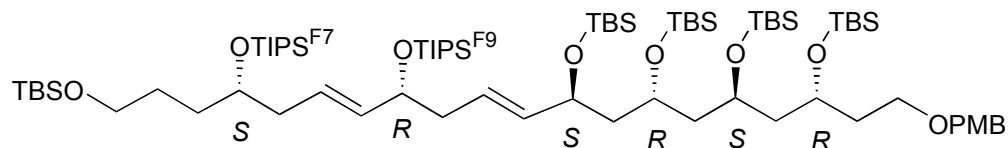
KHMDS (0.5 M in DME, 55 μL , 0.225 mmol) was added to a solution of sulfone M-20a,b/a,c (20 mg, 0.023 mmol) in 1 mL DME at -78°C . The reaction mixture was stirred for 30 min followed by addition of aldehyde **5** (24 mg, 0.029 mmol) in DME (1 mL). The reaction mixture was stirred at -78°C for 1.5 h followed by overnight stirring at room temperature. The reaction mixture was quenched with water. The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were dried over MgSO_4 and

concentrated. The residue was purified by flash column chromatography (10% ethyl acetate in hexanes) to yield compound M-**21a,b/a,c** (25 mg, 77%) as a colorless oil. The (*E, E*)-isomer was then separated by preparative chiral HPLC ((*S,S*) Whelk-O column, 25 cm × 2.1 mm, hexanes: isopropanol = 95:5). Compound M-**21a,b/a,c** was then demixed by preparative fluoros HPLC (FluoroFlash HPLC Column, 250 mm × 20 mm, 100% MeOH) to afford four single quasidiastereomers (*33R, 37S*)-**21a,b**, (*33R, 37R*)-**21a,a**, (*33S, 37S*)-**21b,c**, (*33S, 37R*)-**21a,c**.

Figure S1. Preparative HPLC result of quasidiastereomers M-21a,b/a,c^(a)

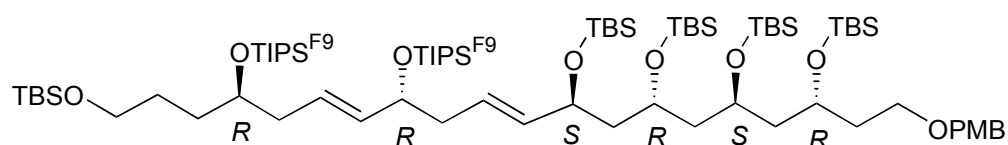


(a) FluoroFlash Column, 100% MeOH, 10 mL/min, 20 mg M-**21a,b/a,c** in 1 mL MeOH/injection

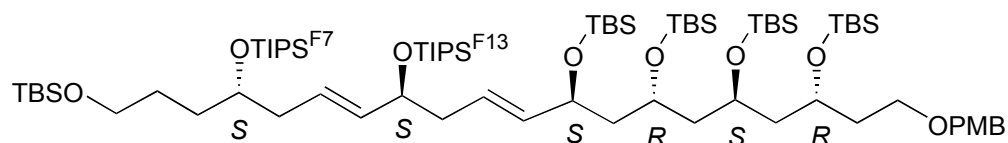


(*33R, 37S*)-**21a,b**: $[\alpha]_D -1.8$ (*c* 0.5 CHCl₃); ¹H NMR (600 MHz, CDCl₃) δ 7.25 (d, *J* = 7.8 Hz, 2 H), 6.86 (d, *J* = 7.8 Hz, 2 H), 5.39-5.60 (m, 4 H), 4.41 (s, 2 H), 4.13-4.23 (m, 2 H), 3.78-3.92 (m,

7 H), 3.54-3.59 (m, 2 H), 3.45-3.51 (m, 2 H), 2.16-2.27 (m, 4 H), 2.03-2.15 (m, 4 H), 1.37-1.82 (m, 12 H), 1.00-1.06 (m, 28 H), 0.85-0.89 (s, 45 H), -0.02-0.01 (m, 30 H); ^{13}C NMR (150 MHz, CDCl_3) δ 159.0, 136.8, 135.2, 130.8, 129.1, 126.6, 125.8, 113.7, 73.9, 72.6, 72.2, 70.9, 67.4, 67.0, 66.9, 66.7, 63.1, 46.7, 46.5, 45.6, 41.7, 39.6, 37.8, 26.0, 26.0, 25.9, 25.9, 18.2, 18.1, 18.0, 17.6, 17.6, 17.5, 12.8, 12.8, 12.7, 12.7, -3.5, -3.5, -3.6, -3.9, -4.2, -4.3, -4.7, -5.4; ^{19}F NMR (CDCl_3) -128.2 (2 F), -126.7 (2 F), -124.8 (2 F), -118.0 (2 F), -117.3 (2 F), -81.6 (3 F), -81.2 (3 F).

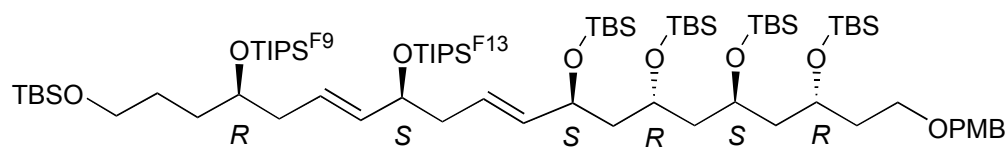


(33*R*, 37*R*)-**21a,a**: $[\alpha]_{\text{D}}$ -4.4 (*c* 1.1 CHCl_3); ^1H NMR (600 MHz, CDCl_3) δ 7.25 (d, $J = 7.8$ Hz, 2 H), 6.86 (d, $J = 7.8$ Hz, 2 H), 5.39-5.60 (m, 4 H), 4.41 (s, 2 H), 4.13-4.23 (m, 2 H), 3.78-3.92 (m, 7 H), 3.54-3.59 (m, 2 H), 3.45-3.51 (m, 2 H), 2.16-2.27 (m, 4 H), 2.03-2.15 (m, 4 H), 1.37-1.82 (m, 12 H), 1.00-1.06 (m, 28 H), 0.85-0.89 (s, 45 H), -0.02-0.01 (m, 30 H); ^{13}C NMR (150 MHz, CDCl_3) δ 159.0, 136.6, 135.4, 130.9, 129.1, 126.5, 125.7, 113.7, 73.7, 72.6, 72.3, 70.8, 67.3, 67.0, 67.0, 66.7, 63.2, 46.7, 46.6, 45.7, 42.0, 39.6, 37.8, 26.0, 26.0, 25.9, 25.6, 18.3, 18.1, 18.0, 17.6, 17.6, 17.5, 13.0, 12.8, 12.7, -3.5, -3.9, -4.2, -4.3, -4.7, -5.4; ^{19}F NMR (CDCl_3) -126.7 (4 F), -124.8 (4 F), -117.3 (4 F), -81.6 (6 F).

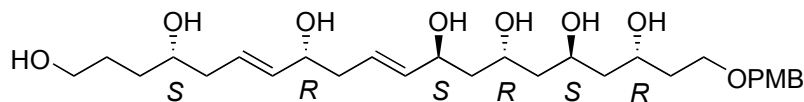


(33*S*, 37*S*)-**21b,c**: $[\alpha]_{\text{D}}$ -7.7 (*c* 0.7 CHCl_3); ^1H NMR (600 MHz, CDCl_3) δ 7.25 (d, $J = 7.8$ Hz, 2 H), 6.86 (d, $J = 7.8$ Hz, 2 H), 5.39-5.60 (m, 4 H), 4.41 (s, 2 H), 4.13-4.23 (m, 2 H), 3.78-3.92 (m, 7 H), 3.54-3.59 (m, 2 H), 3.45-3.51 (m, 2 H), 2.16-2.27 (m, 4 H), 2.03-2.15 (m, 4 H), 1.37-1.82

(m, 12 H), 1.00-1.06 (m, 28 H), 0.85-0.89 (s, 45 H), -0.02-0.01 (m, 30 H); ^{13}C NMR (150 MHz, CDCl_3) δ 159.0, 136.8, 135.2, 130.8, 129.1, 126.6, 125.8, 113.7, 73.9, 72.6, 72.2, 70.9, 67.4, 67.0, 66.9, 66.7, 63.1, 46.7, 46.5, 45.6, 41.7, 39.6, 37.8, 26.0, 26.0, 25.9, 25.9, 18.2, 18.1, 18.0, 17.6, 17.6, 17.5, 12.8, 12.8, 12.7, 12.7, -3.5, -3.5, -3.6, -3.9, -4.2, -4.3, -4.7, -5.4; ^{19}F NMR (CDCl_3) -128.1 (2 F), -126.7 (2 F), -123.8 (2 F), -123.4 (2 F), -122.5 (2 F), -117.9 (2 F), -117.1 (2 F), -81.3 (3 F), -81.2 (3 F).

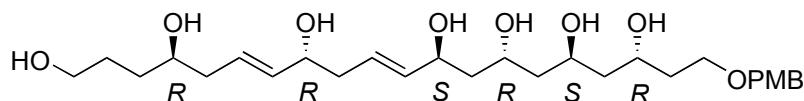


(33*S*, 37*R*)-**21a,c**: $[\alpha]_{\text{D}} -1.6$ (*c* 0.8 CHCl_3); ^1H NMR (600 MHz, CDCl_3) δ 7.25 (d, $J = 7.8$ Hz, 2 H), 6.86 (d, $J = 7.8$ Hz, 2 H), 5.39-5.60 (m, 4 H), 4.41 (s, 2 H), 4.13-4.23 (m, 2 H), 3.78-3.92 (m, 7 H), 3.54-3.59 (m, 2 H), 3.45-3.51 (m, 2 H), 2.16-2.27 (m, 4 H), 2.03-2.15 (m, 4 H), 1.37-1.82 (m, 12 H), 1.00-1.06 (m, 28 H), 0.85-0.89 (s, 45 H), -0.02-0.01 (m, 30 H); ^{13}C NMR (150 MHz, CDCl_3) δ 159.0, 136.8, 135.4, 130.8, 129.1, 126.6, 125.7, 113.7, 74.0, 72.6, 72.3, 70.9, 67.3, 67.0, 66.9, 66.7, 63.2, 46.7, 46.6, 45.6, 41.6, 39.5, 37.8, 26.0, 26.0, 25.9, 25.9, 18.2, 18.1, 18.0, 17.6, 17.6, 17.5, 12.8, 12.8, 12.7, 12.7, -3.5, -3.5, -3.6, -3.9, -4.2, -4.3, -4.7, -5.4; ^{19}F NMR (CDCl_3) -126.6 (4 F), -124.8 (2 F), -123.8 (2 F), -123.4 (2 F), -122.5 (2 F), -117.3 (2 F), -117.0 (2 F), -81.6 (3 F), -81.3 (3 F).



(4*S*,6*E*,8*R*,10*E*,12*S*,14*R*,16*S*,18*R*)-20-(4-methoxybenzyloxy)icosa-6,10-diene-1,4,8,12,14,16,18-heptaol ((33*R*, 37*S*)-2) :

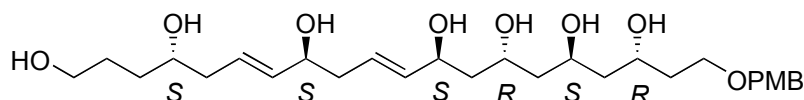
TASF (15 mg) in DMF (0.2 mL) was added to a solution of (33*R*, 37*S*)-**21a,b** (5.0 mg) in DMF (1 mL) at 0 °C. The solution was stirred for overnight after warming to room temperature. DMF was removed by speed-vacuum. The crude product was purified by flash column chromatography (20% MeOH in CH₂Cl₂) to afford compound (33*R*, 37*S*)-**2** (1.1 mg, 75%) as oil: $[\alpha]_D +1.0$ (*c* 1.1 CHCl₃); ¹H NMR (700 MHz, MeOD) δ 7.26 (d, *J* = 8.4 Hz, 2 H), 6.89 (d, *J* = 8.4 Hz, 2 H), 5.63-5.71 (m, 2 H), 5.51-5.59 (m, 2 H), 4.43 (s, 2 H), 4.33 (m, 1 H), 4.01-4.11 (m, 3 H), 3.96-4.01 (m, 1 H), 3.78 (s, 3 H), 3.53-3.66 (m, 5 H), 2.15-2.31 (m, 4 H), 1.64-1.79 (m, 4 H), 1.47-1.63 (m, 6 H), 1.38-1.45 (m, 2 H); ¹³C NMR (175 MHz, MeOD) δ 160.82, 137.25, 136.18, 131.70, 130.54, 128.96, 127.61, 114.72, 73.73, 73.34, 72.16, 70.32, 68.27, 66.90, 66.25, 66.20, 63.03, 55.66, 46.64, 46.35, 46.22, 41.44, 41.41, 38.86, 34.17, 29.86; EIMS (*M* + Na)⁺ 549.



(4*R*,6*E*,8*R*,10*E*,12*S*,14*R*,16*S*,18*R*)-20-(4-methoxybenzyloxy)icosa-6,10-diene-1,4,8,12,14,16,18-heptaol ((33*R*, 37*R*)-2):

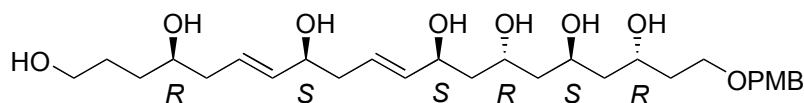
Following the same procedure as above, compound (33*R*, 37*R*)-**2** was obtained as oil: $[\alpha]_D +3.2$ (*c* 1.0 CHCl₃); ¹H NMR (700 MHz, MeOD) δ 7.26 (d, *J* = 8.4 Hz, 2 H), 6.89 (d, *J* = 8.4 Hz, 2 H), 5.63-5.71 (m, 2 H), 5.51-5.59 (m, 2 H), 4.43 (s, 2 H), 4.33 (m, 1 H), 4.01-4.11 (m, 3 H),

3.96-4.01 (m, 1 H), 3.78 (s, 3 H), 3.53-3.66 (m, 5 H), 2.15-2.31 (m, 4 H), 1.64-1.79 (m, 4 H), 1.47-1.63 (m, 6 H), 1.38-1.45 (m, 2 H); ^{13}C NMR (175 MHz, MeOD) δ 160.81, 137.23, 136.19, 131.69, 130.54, 128.80, 127.64, 114.71, 73.73, 73.32, 72.10, 70.33, 68.27, 66.89, 66.24, 66.20, 63.03, 55.65, 46.64, 46.35, 46.21, 41.43, 41.36, 38.86, 34.13, 29.89; EIMS ($M + \text{Na}$) $^+$ 549.



(4*S*,6*E*,8*S*,10*E*,12*S*,14*R*,16*S*,18*R*)-20-(4-methoxybenzyloxy)icosa-6,10-diene-1,4,8,12,14,16,18-heptaol ((33*S*, 37*S*)-2):

Following the same procedure as above, compound (33*S*, 37*S*)-2 was obtained as oil: $[\alpha]_{\text{D}}$ +4.4 (*c* 1.0 CHCl_3); ^1H NMR (700 MHz, MeOD) δ 7.26 (d, $J = 8.4$ Hz, 2 H), 6.89 (d, $J = 8.4$ Hz, 2 H), 5.63-5.71 (m, 2 H), 5.51-5.59 (m, 2 H), 4.43 (s, 2 H), 4.33 (m, 1 H), 4.01-4.11 (m, 3 H), 3.96-4.01 (m, 1 H), 3.78 (s, 3 H), 3.53-3.66 (m, 5 H), 2.15-2.31 (m, 4 H), 1.64-1.79 (m, 4 H), 1.47-1.63 (m, 6 H), 1.38-1.45 (m, 2 H); ^{13}C NMR (175 MHz, MeOD) δ 160.82, 137.20, 136.19, 131.70, 130.54, 128.84, 127.69, 114.73, 73.73, 73.36, 72.12, 70.34, 68.28, 66.93, 66.26, 66.22, 63.03, 55.67, 46.62, 46.35, 46.16, 41.45, 41.36, 38.86, 34.12, 29.90; EIMS ($M + \text{Na}$) $^+$ 549.



(4*R*,6*E*,8*S*,10*E*,12*S*,14*R*,16*S*,18*R*)-20-(4-methoxybenzyloxy)icosa-6,10-diene-1,4,8,12,14,16,18-heptaol ((33*S*, 37*R*)-2):

Following the same procedure as above, compound (33*S*, 37*R*)-2 was obtained as oil: $[\alpha]_{\text{D}}$ +0.8

(*c* 0.8 CHCl₃); ¹H NMR (700 MHz, MeOD) δ 7.26 (d, *J* = 8.4 Hz, 2 H), 6.89 (d, *J* = 8.4 Hz, 2 H), 5.63-5.71 (m, 2 H), 5.51-5.59 (m, 2 H), 4.43 (s, 2 H), 4.33 (m, 1 H), 4.01-4.11 (m, 3 H), 3.96-4.01 (m, 1 H), 3.78 (s, 3 H), 3.53-3.66 (m, 5 H), 2.15-2.31 (m, 4 H), 1.64-1.79 (m, 4 H), 1.47-1.63 (m, 6 H), 1.38-1.45 (m, 2 H); ¹³C NMR (175 MHz, MeOD) δ 160.81, 137.22, 136.16, 131.69, 130.54, 129.03, 127.66, 114.72, 73.73, 73.37, 72.15, 70.33, 68.27, 66.90, 66.24, 66.19, 63.03, 55.66, 46.64, 46.36, 46.18, 41.44, 41.41, 38.86, 34.18, 29.86; EIMS (M + Na)⁺ 549.

Table S1, ¹³C NMR chemical shifts of isomers 2 with subtraction comparisons

C#	(33R,37S)-2	(33R,37R)-2	(33S,37S)-2	(33S,37R)-2	RR - RS	SS - RS	SR - RS	SS - RR	SR - RR	SR - SS
PMB	160.82	160.81	160.82	160.81	-0.01	0	-0.01	0.01	0	-0.01
C30	137.25	137.23	137.2	137.22	-0.02	-0.05	-0.03	-0.03	-0.01	0.02
C34	136.18	136.19	136.19	136.16	0.01	0.01	-0.02	0	-0.03	-0.03
PMB	131.70	131.69	131.70	131.69	-0.01	0	-0.01	0.01	0	-0.01
PMB	130.54	130.54	130.54	130.54	0.00	0.00	0.00	0.00	0.00	0.00
C35	128.96	128.80	128.84	129.03	-0.16	-0.12	0.07	0.04	0.23	0.19
C31	127.61	127.64	127.69	127.66	0.03	0.08	0.05	0.05	0.02	-0.03
PMB	114.72	114.71	114.73	114.72	-0.01	0.01	0	0.02	0.01	-0.01
PMB	73.73	73.73	73.73	73.73	0.00	0.00	0.00	0.00	0.00	0.00
C33	73.34	73.32	73.36	73.37	-0.02	0.02	0.03	0.04	0.05	0.01
C37	72.16	72.10	72.12	72.15	-0.06	-0.04	-0.01	0.02	0.05	0.03
C29	70.32	70.33	70.34	70.33	0.01	0.02	0.01	0.01	0.00	-0.01
C21	68.27	68.27	68.28	68.27	0.00	0.01	0.00	0.01	0.00	-0.01
C23	66.90	66.89	66.93	66.90	-0.01	0.03	0	0.04	0.01	-0.03
C27	66.25	66.24	66.26	66.24	-0.01	0.01	-0.01	0.02	0.00	-0.02
C25	66.20	66.20	66.22	66.19	0.00	0.02	-0.01	0.02	-0.01	-0.03
C40	63.03	63.03	63.03	63.03	0.00	0.00	0.00	0.00	0.00	0.00
PMB	55.66	55.65	55.67	55.66	-0.01	0.01	0.00	0.02	0.01	-0.01
C26*	46.64	46.64	46.62	46.64	0.00	-0.02	0.00	-0.02	0.00	0.02
C24*	46.35	46.35	46.35	46.36	0.00	0.00	0.01	0.00	0.01	0.01
C28*	46.22	46.21	46.16	46.18	-0.01	-0.06	-0.04	-0.05	-0.03	0.02
C32	41.44	41.43	41.45	41.44	-0.01	0.01	0.00	0.02	0.01	-0.01
C36	41.41	41.36	41.36	41.41	-0.05	-0.05	0.00	0.00	0.05	0.05
C22	38.86	38.86	38.86	38.86	0.00	0.00	0.00	0.00	0.00	0.00
C38	34.17	34.13	34.12	34.18	-0.04	-0.05	0.01	-0.01	0.05	0.06
C39	29.86	29.89	29.9	29.86	0.03	0.04	0.00	0.01	-0.03	-0.04

*tentative assignments, may be interchanged

