Supporting Information

"Formal Synthesis of Uvaricin via Palladium-Mediated Double Cyclization "

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General Procedures

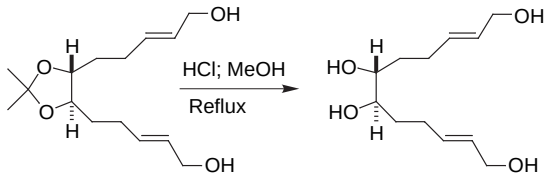
Optical rotations were measured on a Perkin-Elmer 241 digital polarimeter. Concentrations (c) are reported in g/100 mL. Infrared spectra (IR) were obtained on a Matteson Polaris FT-IR equipped with a DTGS detector. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker AC-300 (300 MHz). Proton NMR splitting patterns are designated as singlet (s), doublet (d), triplet (t), quartet (q), quintet (quin), sextet (sex), septet (sept), AB quartet (ABq), multiplet (m), and broad (br). Spectra were interpreted assuming first-order behavior, and coupling constants were rounded to the nearest 0.5 hertz (Hz). All expansions were calibrated to 20 Hz/cm. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Bruker AC-300 (75 MHz). Carbon resonances were assigned using Distortionless Enhancement by Polarization Transfer (DEPT) spectra obtained with a phase angle of 135°: (C) not observed; (CH) positive; (CH_2) negative; (CH_3) positive. High resolution fast atom bombardment (FAB) mass spectra were obtained on VG Analytical ZAB-2F (Ion Tech FAB gun, 8 kV, Xe carrier gas).

All moisture-sensitive reactions were performed in flame-dried and/or oven dried glassware under a positive pressure of nitrogen unless otherwise noted. "Concentrated" refers to the removal of volatile solvents via distillation using a Buchi rotary evaporator at

water aspirator pressure, followed by residual solvent removal at high vacuum when necessary. "Dried" refers to pouring onto, or passing through, anhydrous sodium sulfate or magnesium sulfate followed by filtration.

Analytical thin layer chromatography (TLC) was carried out on E. Merck (Darmstadt) TLC plates precoated with silia gel 60 F_{254} (0.25 mm layer thickness). Visualization was accomplished using UV light and/or a *p*-anisaldehyde (PAA) charring solution. Flash column chromatography (FCC) was performed on EM Science silica gel 60 (230-400 mesh). Solvent mixtures for TLC and FCC are reported in either v_1:v_2 ratios or V_1/V_{total} x 100%. For columns using MeOH-containing eluents, the column was slurry packed in MeOH, washed with 2 column volumes (c.v.) of the same, then 2 c.v. of the first eluent.

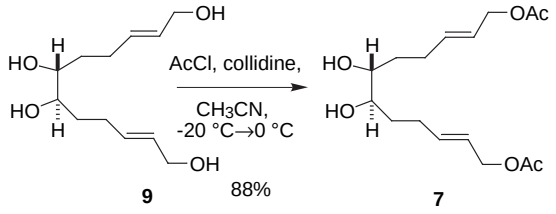
Immediately prior to use, toluene ($PhCH_3$) was distilled from sodium naphthalide; benzene (PhH), diethyl ether (Et_2O) and tetrahydrofuran (THF) were distilled from sodium benzophenone ketyl; methanol (MeOH) was distilled from magnesium methoxide; and dichloromethane (CH_2Cl_2), hexanes, acetonitrile(CH_3CN) and triethylamine (Et_3N) were distilled from calcium hydride. All other reagents were used as supplied, assuming reagent purity designated by supplier.



8 **9**

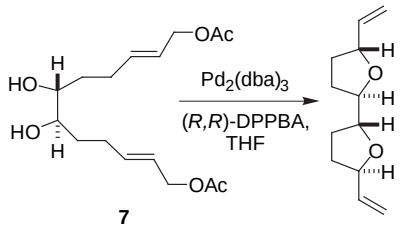
Preparation of Compound 9. Diol **8** (2.80 g, 10.3 mmol) was dissolved in 90% methanol (100 mL) and 5% aq. HCl (40 mL) was added. The reaction mixture was brought to reflux for 1 h, then it was cooled to room temperature, and quenched with $NaHCO_3$. The resulting mixture was concentrated, and FCC (10% MeOH/EtOAc) gave tetraol **9** (2.17 g, 92%) as pale yellow solid. ^{1}H NMR (Acetone-d_6) δ 5.63 (m, 4H), 3.98 (d, J = 4.5 Hz, 4H), 3.55 (t, J

= 5.5 Hz, 1H), 3.48 (d, J = 5.0 Hz, 1H), 3.38 (m, 2H), 2.84 (s, 2H), 2.06-2.29 (m, 4H), 1.35-1.65 (m, 4H); ^{13}C NMR (Acetone-d_6) δ 131.7 (CH), 131.4 (CH), 74.2 (CH), 63.4 (CH_2), 34.0 (CH_2), 33.9 (CH_2); IR (thin film) 3403, 3291, 2988, 2895, 2847, 1436, 993, 946 cm^{-1}; $[\alpha]^{24}_D$ = +22° (c = 0.45, MeOH); HRMS (FAB) calcd. for $C_{12}H_{22}O_4Na$ ($M+Na^+$) 253.1416, found 253.1408.



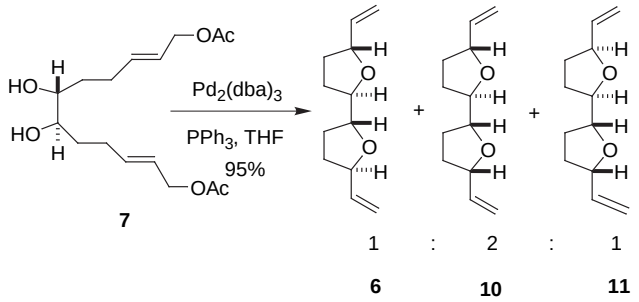
9 **7**

Preparation of Compound 7. To a solution of tetraol **9** (0.89 g 3.87 mmol) in dry CH_3CN (150 mL), collidine (2.34 g, 19.3 mmol) was added. The mixture was cooled to –20 °C, followed by the addition of a solution of acetyl chloride (0.607 g, 7.74 mmol) in CH_3CN (20 mL) via syringe pump over a period of 1 h. After stirring at this temperature for 2 h, the reaction mixture was allowed to warm to 0 °C, 5% HCl and EtOAc was added to quench the reaction, and the layers were separated. The aqueous phase was extracted with EtOAc three times, the combined organic layers were dried, concentrated, and FCC (2/1=EtOAc/hexanes) gave pure diacetate **7** (1.07 g, 88%) as a white solid, mp 46-47 °C, which was recrystallized from Et_2O/hexanes. ^{1}H NMR ($CDCl_3$) δ 5.74 (dtt, J = 15.5, 6.5, 1 Hz, 2H), 5.57 (dtt, J = 15.5, 6.5, 1 Hz, 2H), 4.47 (dd, J = 6.5, 1 Hz, 4H), 3.37 (m, 2H), 2.38 (s, 2H), 2.05-2.30 (m, 4H), 2.01 (s, 6H), 1.41-1.62 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 170.7 (C), 135.4 (CH), 124.3 (CH), 73.5 (CH), 64.9 (CH_2), 32.5 (CH_2), 28.2 (CH_2), 20.8 (CH_3); IR (KBr pellet) 3441, 3359, 3019, 2945, 2892, 1735, 1716, 1674, 1249, 1030, 962 cm^{-1}; $[\alpha]^{24}_D$ = +15.4° (c = 1.1, $CHCl_3$); HRMS (FAB) calcd. for $C_{16}H_{26}O_6Na$ ($M+Na^+$) 337.1627, found 337.1643.

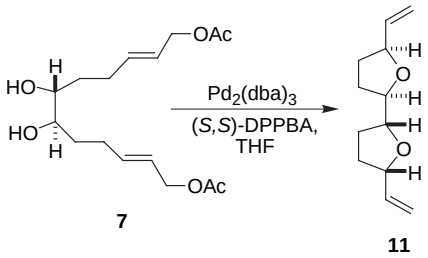


7 **6**

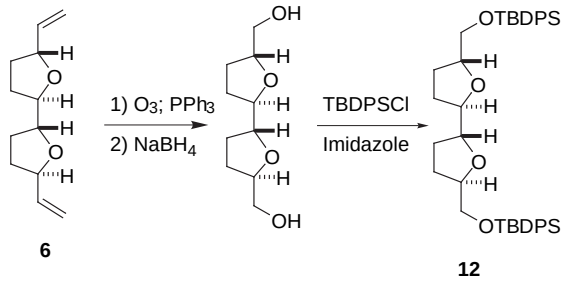
Preparation of Diene 6. To a dry round bottom flask under N_2 charged with $Pd_2(dba)_3$•$CHCl_3$ (100 mg, 0.1 mmol) and chiral ligand (*R,R*)-DPPBA (276 mg, 0.4 mmol), was added freshly distilled THF (200 mL). The resulting purple solution was brought to reflux until it turned orange, then the mixture was cooled to 0 °C. A solution of diacetate **7** (810 mg, 2.57 mmol) in THF (50 mL) was added via cannula, the ice bath was removed, and the reaction was allowed to stir at room temperature until TLC showed the reaction to be complete. The mixture was filtered through a pad of silica gel, concentrated, and FCC (10% Et_2O/pentane) gave pure **6** (481 mg, 97%) as a clear oil. ^{1}H NMR ($CDCl_3$) δ 5.78 (ddd, J = 17.0, 10.5, 6.5 Hz, 2H), 5.16 (ddd, J = 17.0, 2, 1.5 Hz, 2H), 5.00 (ddd, J = 10.5, 1.5, 1 Hz, 2H), 4.37 (qd, J = 6.5, 1 Hz, 2H), 3.93 (m, 2H), 1.87-2.10 (m, 4H), 1.52-1.76 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 139.2 (CH), 114.9 (CH_2), 81.4 (CH), 80.4 (CH), 32.5 (CH_2), 28.3 (CH_2); IR (thin film) 3081, 3007, 2974, 2870, 1643, 1425, 1108, 1052, 920 cm^{-1}; $[\alpha]^{24}_D$ = –18.1° (c = 0.85, $CHCl_3$); HRMS (FAB) calcd. for $C_{12}H_{18}O_2Na$ ($M+Na^+$) 217.1204, found 217.1205.



Preparation of Dienes 6, 10, and 11. To a dry round bottom flask under N_2 charged with $Pd_2(dba)_3$•$CHCl_3$ (32 mg, 0.03 mmol) and PPh_3 (32 mg, 0.12 mmol) was added freshly distilled THF (30 mL). The resulting purple solution turned orange readily. A solution of diacetate **7** (120 mg, 0.38 mmol) in THF (10 mL) was added via cannula. The mixture was allowed to stir for 24 h. The solvent was removed *in vacuo*, and FCC (10% Et_2O/pentane) gave pure **6** (18mg) and a mixture of **10** and **11** (54mg) along with a small amount of the dba ligand. For diene **10** ^{13}C NMR ($CDCl_3$) δ 139.3 (CH), 139.2 (CH), 115.2 (CH_2), 115.0 (CH_2), 82.0 (CH), 81.4 (CH), 80.7 (CH), 80.5 (CH), 32.5 (CH_2), 31.8 (CH_2), 28.4 (CH_2), 27.8 (CH_2).

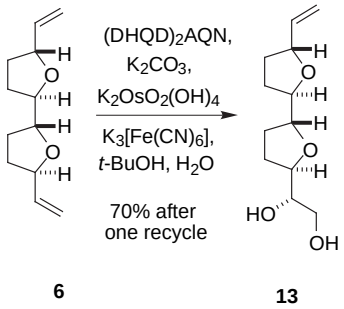


Preparation of Diene 11. Diene **11** was prepared analogously to diene **6** except that (*S,S*)-DPPBA ligand was used. ^{1}H NMR ($CDCl_3$) δ 5.85 (ddd, J = 17.0, 10.5, 6.5 Hz, 1H), 5.22 (ddd, J = 17.0, 2, 1 Hz, 1H), 5.05 (ddd, J = 10.5, 2, 1 Hz, 1H), 4.32 (qt, J = 6.5, 1 Hz, 1H), 3.85-3.94 (m, 1H), 1.83-2.06 (m, 2H), 1.61-1.75 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 139.4 (CH), 115.3 (CH_2), 82.0 (CH), 80.8 (CH), 31.9 (CH_2), 27.9 (CH_2); $[\alpha]^{24}_D$ = –9.7° (c = 0.48, $CHCl_3$).



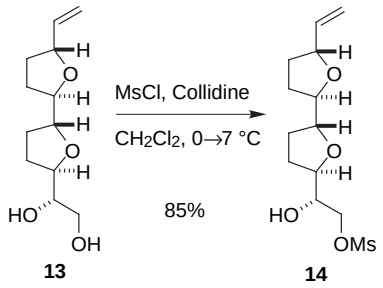
6 **12**

Preparation of Bis(silyl ether) 12. A solution of diene **6** (60 mg, 0.31 mmol) in $MeOH/CH_2Cl_2$ (1:1) (3 mL) was ozonized at –78 °C for 5 minutes, at which time the mixture turned blue. To this solution was added $NaBH_4$ (24 mg, 0.65 mmol). The resulting slurry was stirred at rt for 4 h, when it was quenched with acidic resin Dowex 50W-X8. Filtration, followed by concentration afforded crude diol (49 mg). This diol was redissolved in DMF (3 mL), and both TBDPSCl (256 mg, 0.93 mmol) and imidazole (104 mg, 1.53 mmol) were added. The reaction mixture was stirred at room temperature overnight, then it was quenched with H_2O, extracted with diethyl ether, and the combined organics were dried and concentrated. FCC (15% Et_2O/hexanes) afforded bis(silyl ether) **12** (149 mg, 71%) as an oil. ^1H NMR ($CDCl_3$) δ 7.6-7.73 (m, 8H), 7.38-7.48 (m, 12H), 4.10-4.20 (m, 2H), 3.92 (quin, J = 6.0 Hz, 2H), 3.79 (ABX, J = 10.5, 4.5 Hz, 2H), 3.59 (ABX, J = 10.5, 6.0 Hz, 2H), 1.63-2.15 (m, 8H), 1.07 (s, 18H); ^{13}C NMR ($CDCl_3$) δ 135.6 (CH), 133.7 (C), 129.5 (CH), 127.6 (CH), 81.9 (CH), 79.6 (CH), 66.6 (CH_2), 28.5 (CH_2), 28.4 (CH_2), 26.8 (CH_3), 19.2 (C); IR (thin film) 3070, 2929, 2857, 1471, 1427, 1113 cm^{-1}; $[\alpha]^{24}_D$ = +1.6° (c = 3.0, $CHCl_3$). HRMS (FAB) calcd. for $C_{42}H_{54}O_4Si_2Na$ ($M+Na^+$) 701.3458, found 701.3453. The experimental ^1H NMR and ^{13}C NMR data for **12** matched with literature data for its enantiomer.[11] The experimental optical rotation data for **12** had the opposite sign as the literature data for its enantiomer.



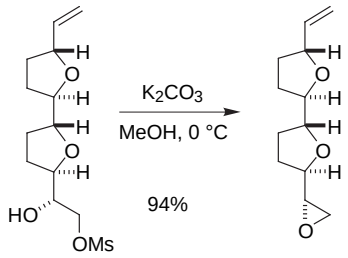
6 **13**

Preparation of Compound 13. $(DHQD)_2AQN$ (120 mg, 0.176 mmol), K_2CO_3 (1.26 g, 10.5 mmol), $K_3Fe(CN)_6$ (3.46 g, 10.5 mmol), and $K_2OsO_2(OH)_4$ (4.5 mg, 0.014 mmol), were dissolved in 1:1 *t*-BuOH/H_2O (35 mL) at room temperature. The solution was stirred for 30 min before it was cooled to 0 °C and the olefin **6** (650 mg, 3.5 mmol) was added. The reaction was quenched with Na_2SO_3 after 4 h, followed by the addition of EtOAc. The aqueous layer was extracted with EtOAc three times, the combined organics were dried ($MgSO_4$), and concentrated. Purification by FCC (80% EtOAc/pentane) gave pure **13** (383 mg, 48%) as a clear oil along with unreacted diene **6** (310 mg, 1.6 mmol), which was resubjected to the same reaction conditions to afford compound **13** (557 mg combined, 70% overall). ^{1}H NMR ($CDCl_3$) δ 5.80 (ddd, J = 17.0, 10.5, 6.5 Hz, 1H), 5.18 (dt, J = 17, 1 Hz, 1H), 5.04 (dt, J = 10.5, 1 Hz, 1H), 4.38 (q, J = 7Hz, 1H), 3.81-3.97 (m, 3H), 3.73-3.80 (m, 1H), 3.64 (ABX, J=11.5, 3.5 Hz, 1H), 3.55 (ABX, J=11.5, 6.5 Hz,1H), 2.94 (b, 2H), 1.50-2.15 (m, 8H); ^{13}C ($CDCl_3$) δ 139.0 (CH), 115.4 (CH_2), 82.2 (CH), 81.8 (CH), 80.6 (CH), 80.3 (CH), 73.1 (CH), 63.9 (CH_2), 32.5 (CH_2), 28.5 ($2CH_2$), 27.0 (CH_2); IR (thin film) 3412, 3080, 2930, 2872, 1643, 1463, 1425, 1316, 1055, 924 cm^{-1}; $[\alpha]^{24}_D$ = –14.5° (c = 0.4, $CHCl_3$); HRMS (FAB) calcd. for $C_{12}H_{20}O_4Na$ ($M+Na^+$) 251.1259, found 251.1262.

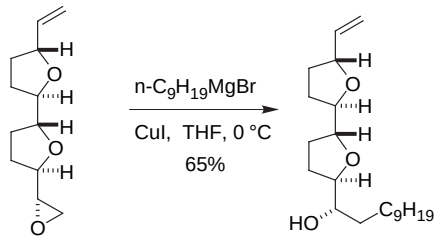


13 14

Preparation of Compound 14. To a solution of diol **13** (285 mg, 1.27 mmol) in CH_2Cl_2 (15 mL) was added collidine (1.36 g, 12.7 mmol) at room temperature. The solution was cooled to 0 °C and a solution MsCl (145 mg, 1.27 mmol) in CH_2Cl_2 (2 mL)was added slowly. Stirring was continued for 2 h at 0 °C after which the flask was placed in the refrigerator (7 °C) for 12 h without stirring. The reaction was quenched with H_2O. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3x50 mL), the combined organics were washed with 5% HCl (aq.) (50 mL), dried, and concentrated. FCC (70% Et_2O/hexanes) gave mesylate **14** (312 mg, 85%) as an oil. ^{1}H NMR ($CDCl_3$) δ 5.80 (ddd, J = 17, 10.5, 6.5 Hz, 1H), 5.19 (dt, J = 17, 1.5 Hz, 1H), 5.05 (dt, J = 10, 1.5 Hz, 1H), 4.38 (q, J = 7Hz, 1H), 4.32 (ABX, J = 11, 3 Hz, 1H), 4.18 (ABX, J=11, 6.5 Hz, 1H), 3.85-4.00 (m, 4H), 3.05 (s, 3H), 2.52-2.65 (br, 1H), 1,55-2.12 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 139.0 (CH), 115.3 (CH_2), 82.5 (CH), 81.6 (CH), 80.6 (CH), 79.0 (CH), 71.2 (CH_2), 70.9 (CH), 37.5 (CH_3), 32.4 (CH_2), 28.5 (CH_2), 28.4 (CH_2), 27.1 (CH_2); IR (thin film) 3429, 3080, 2969, 2878, 1772, 1734, 1645, 1353, 1174, 1052 cm^{-1}; $[\alpha]^{24}_D$ = –11.0° (c = 1.4, $CHCl_3$); HRMS (FAB) calcd. for $C_{13}H_{22}O_6SNa$ ($M+Na^+$) 329.1035, found 329.1035.

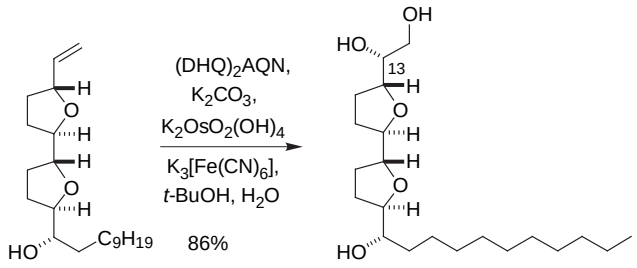


Preparation of Compound 5. To a solution of mesylate **14** (200 mg, 0.65 mmol) in MeOH (7 mL) at 0 °C was added K_2CO_3 (304 mg, 2.2 mmol). The resulting slurry was allowed to stir for 45 min. The reaction was quenched with brine and extracted with 1:1 hexanes/ether three times. The combined organics were dried ($MgSO_4$) and concentrated. Purification by FCC (40% Et_2O/hexanes) gave epoxide **5** (129 mg, 94%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 5.81 (ddd, J = 17.5, 10.5, 6.5 Hz, 1H), 5.18 (dt, J = 17.5, 1.5 Hz, 1H), 5.04 (dt, J = 10.5, 2.5 Hz, 1H), 4.40 (q, J = 6.5 Hz, 1H), 3.83-4.00 (m, 3H), 2.90-3.01 (m, 1H), 2.86 (ABX, J= 5, 4 Hz, 1H), 2.45 (ABX, J= 5, 3 Hz, 1H), 1.9-2.1 (m, 4H), 1.55-1.85 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 139.1 (CH), 115.1 (CH_2), 82.2 (CH), 81.5 (CH), 80.5 (CH), 79.5 (CH), 53.3 (CH), 45.7 (CH_2), 32.5 (CH_2), 28.4 (CH_2), 28.2 (CH_2), 28.0 (CH_2); IR (thin film) 3077, 3053, 2974, 2873, 1645, 1464, 1303, 1054 cm^{-1}; $[\alpha]^{24}_D$ = –8.4° (c = 1.25, $CHCl_3$); HRMS (FAB) calcd. for $C_{12}H_{18}O_3Na$ ($M+Na^+$) 233.1154, found 233.1152.



5 **15**

Preparation of Compound 15. To a suspension of CuI (17 mg, 0.89 mmol) in THF (1 mL) was added a solution of epoxide **5** (37 mg, 0.177 mmol) in THF (2 mL) and the mixture was cooled to 0 °C. A solution of 0.4 M nonyl magnisium bromide (0.5 ml) was added to the mixture, the resulting solution was stirred for 3 h, and was quenched with NH_4Cl/NH_4OH (9:1) (5 mL). The aquous phase was extracted with ether three times, the combined organics were dried and concentrated. Purification by FCC (33% EtOAc/hexane) gave **15** (39 mg, 65%). ^{1}H NMR ($CDCl_3$) δ 5.82 (ddd, J = 17, 10.5, 6.5 Hz, 1H), 5.20 (dt, J = 17.5, 1.5 Hz, 1H), 5.05 (dt, J = 10.5, 1.5 Hz, 1H), 4.42 (q, J = 6.5 Hz, 1H), 3.70-3.95 (m, 4H), 1.5-2.1 (m, 10H), 1.15-1.35 (m, 16H), 0.85 (t, J = 6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 139.2 (CH), 115.2 (CH_2), 82.6 (CH), 82.5 (CH), 82.1 (CH), 80.6 (CH), 71.2 (CH), 32.5 ($2CH_2$), 31.9 (CH_2), 29.7 ($3CH_2$), 29.6 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 28.8 (CH_2), 28.5 (CH_2), 26.1 (CH_2), 24.6 (CH_2), 22.7 (CH_2), 14.1 (CH_3); IR (thin film) 3448, 3086, 2953, 2921, 2852, 1649, 1454, 1051 cm^{-1}; $[\alpha]^{24}_D$ = -0.71° (c = 3.5, $CDCl_3$); HRMS (FAB) calcd. for $C_{21}H_{38}O_3Na$ ($M+Na^+$) 361.2719, found 361.2704.



Preparation of Compound 16. $(DHQ)_2AQN$ (30.5 mg, 0.035 mmol), K_2CO_3(370 mg, 2.64 mmol), $K_3Fe(CN)_6$ (871 mg, 2.64 mmol) and $K_2OsO_2(OH)_4$ (1.3 mg, 0.0035 mmol) were dissolved in 1:1 *t*-BuOH/H_2O (10 mL) at room temperature. The solution was stirred for 30 min before it was cooled to 0 °C and the olefin **15** (300 mg, 0.88 mmol) was added. The reaction was quenched with Na_2SO_3 after 4 h, followed by the addition of EtOAc. The aqueous layer was extracted with EtOAc three times. The combined organics were dried ($MgSO_4$), and concentrated. Purification by FCC (80% EtOAc/Hexanes) gave pure **16** (281 mg, 86%). ^{1}H NMR ($CDCl_3$) δ 4.00 (q, J = 6.5 Hz, 1H), 3.78-3.95 (m, 4H), 3.45-3.70 (m, 3H), 2.86 (br, 3H), 1.65-2.05 (m, 6H), 1.15-1.65 (m, 20H), 0.86 (t, J = 7 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 82.8 (CH), 82.6 (CH), 82.5 (CH), 80.6 (CH), 73.7 (CH), 71.3 (CH), 64.2 (CH_2), 32.4 (CH_2), 31.9 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 28.9 (CH_2), 28.7 (CH_2), 28.1 (CH_2), 26.0 (CH_2), 24.4 (CH_2), 22.7 (CH_2), 14.1 (CH_3); IR (thin film) 3428, 2924, 2853, 1457, 1059 cm^{-1}; $[\alpha]^{24}_D$ = +0.4° (c = 0.28, $CHCl_3$); HRMS (FAB) calcd. for $C_{21}H_{40}O_5Na$ ($M+Na^+$) 395.2773, found 395.2767. The experimental ^{1}H NMR, ^{13}C NMR and MS data for **16** matched with literature data.[14]