Supporting Information to Accompany "Total Synthesis of the Immunosuppressant (-)-Pironetin (PA48153C)"

(G. E. Keck*, C. E. Knutson, and Sarah A. Wiles)

Submitted Electronically For Publication in ***Organic Letters*** January 8, 2001

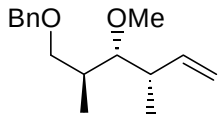
Includes Experimental Details, Spectral and Characterization Data

email: keck@chemistry.chem.utah.edu

Experimental

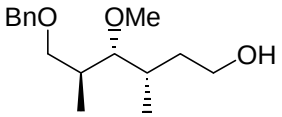
Solvents were purified according to the guidelines in Purification of Common Laboratory Chemicals (Perrin, Armarego, and Perrin, Pergamon: Oxford, 1966). Reagent grade dimethoxypropane, methanol, and acetone were purchased and used without further purification. Samarium metal was purchased from Strem Chemical Company; all other reagents were purchased from Aldrich and used without further purification. Yields were calculated for material judged homogeneous by thin layer chromatography and NMR. Thin layer chromatography was performed on Merck Kieselgel 60 F_{254} plates eluting with the solvents indicated, visualized by a 254 nm UV lamp, and stained with either an ethanolic solution of 12-molybdophosphoric acid, p-anisaldehyde, or a solution of ammonium molybdate/ceric ammonium sulfate. Flash column chromatography was performed with Davisil 62 silica gel. Preparative chromatography was also carried out using a Chromatotron using glass plates coated with silica gel (P. F. 254 60) of 2 and 4 mm thickness (RPLC). Nuclear magnetic resonance spectra were acquired at 500 MHz for ^{1}H and 125 MHz for ^{13}C. Chemical shifts for carbon nuclear magnetic resonance (^{13}C NMR) spectra are reported in parts per million downfield relative to the center line of the $CDCl_3$ triplet at 77.0 ppm. The abbreviations s, d, t, q, br s, br t, sep and ABq stand for the resonance multiplicities singlet, doublet, triplet, quartet, broad singlet, broad triplet, septet, and AB quartet, respectively. Optical rotations were obtained (Na D line) using a micro cell with a 1 dm path length. Concentrations are reported in g/100 mL. Melting points were obtained on an Electro thermal melting point apparatus and are uncorrected. Analytical C & H combustion analyses were performed by Atlantic Microlab, Inc., Norcross, Georgia. Glassware for all reactions was oven dried at 125 °C, evacuated and

placed under N_2 prior to use. All samarium reduction reactions were carried out with pretreated flasks and stir bars Liquid reagents and solvents were introduced by oven dried syringes through septa sealed flasks under an argon atmosphere.



9 **1-[(1S)-1-methyl-2-(phenylmethoxy)ethyl](2S,1R)-1-methoxy-2-methylbut-3-ene**: Potassium hydride (0.80 g, 7.0 mmol, 35% mineral oil dispersion) was weighed into a round bottom flask and washed with hexanes (3 × 10 mL) dry THF (40 mL) was added, and the suspension solution was cooled to –5 °C. A solution of **8** (810 mg, 3.50 mmol) in THF (2 mL) was added slowly *via* cannula,the solution was stirred for 30 min and then methyl iodide (1.50 g, 10.4 mmol) was added. The reaction mixture was allowed to return to rt and then stirred 2.5 h at which time the excess potassium hydride was quenched by addition of several chunks of ice. The mixture was diluted with CH_2Cl_2 (20 mL) followed by addition of saturated aqueous NaHCO3 solution (30 mL). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3 × 20 mL). The combined organics were washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated by rotary evaporation. The residue was purified by RPLC (4 mm plate), eluting with ethyl acetate/ hexanes mixtures (100 mL each: hexanes, 2%, 4% and 8%). The product containing fractions were combined and concentrated providing the product **9** (0.79 g, 92%) as a clear colorless liquid: R_f = 0.70 (20% EtOAc/ hexanes); $[\alpha]_D^{26}$ – 16.97 (*c* 1.09, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40-7.36 (m, 4H), 7.33 (t, *J* = 4.7 Hz, 1H), 5.90 (ddd, *J* = 17.8, 10.0, 8.6 Hz, 1H), 5.08 (dd, *J* = 17.3, 1.2 Hz, 1H), 5.02 (dd,

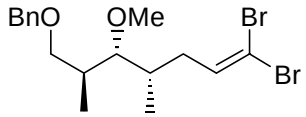
J = 10.5, 1.2 Hz, 1H), 4.55 (s, 2H), 3.62 (dd, *J* = 9.0, 3.9 Hz, 1H), 3.48 (dd, *J* = 8.8, 8.0 Hz, 1H), 3.44 (s, 3H), 3.05 (t, *J* = 6.1 Hz, 1H), 2.49-2.42 (m, 1H), 2.05-2.00 (m, 1H), 1.07 (d, *J* = 7.1 Hz, 3H), 1.06 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.5, 138.8, 128.3, 127.5, 127.4, 113.8, 87.1, 73.0, 72.2, 61.0, 40.2, 36.7, 15.2, 14.2; IR (neat) 1640 cm^{-1}; Anal. Calcd for $C_{16}H_{24}O_2$: C, 77.38; H, 9.74. Found: C, 77.12; H, 9.69.



10

(3S,5S,4R)-4-methoxy-3,5-dimethyl-6-(phenylmethoxy)hexan-1-ol: To a solution of **9** (1.8 g, 7.3 mmol) in THF (70 mL) was added 9-BBN (21.0 mL, 10.8 mmol, 1.00 M in THF). Sonication of the reaction mixture was conducted for 6 h at which time the reaction was treated sequentially with pH 7 buffer (8 mL), methanol (16 mL) and 2:1 methanol:H_2O_2 (16 mL) and stirred overnight. The mixture was concentrated to half its original volume by rotary evaporation, diluted with H_2O (20 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organics were dried over Na_2SO_4 and concentrated. The yellow liquid was purified by RPLC (2 mm plate), eluting with ethyl acetate/ hexanes mixtures (200 mL each: hexanes, 10%, 20%, 30%, and 35%); collecting 8 mL fractions. Concentration of the product containing fractions (56–104) gave the product **10** (1.7 g, 88%) as a clear colorless oil: R_f = 0.24 (20% EtOAc/ hexanes); $[\alpha]_D^{26}$ -13.81 (*c* 0.98, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41–7.38 (m, 3H), 7.32 (d, *J* = 5.6 Hz, 2H), 3.79-3.74 (m, 1H), 3.70-3.66 (m, 1H), 3.57 (dd, *J* = 8.8, 3.9 Hz, 1H), 4.51 (s, 2H), 3.53 (dd, *J* = 8.8, 5.9 Hz, 1H), 3.44 (s, 3H), 3.04 (dd, *J* = 8.3, 3.2 Hz, 1H), 2.02-1.96 (m, 1H), 1.93-1.87 (m, 1H), 1.79-1.72 (m, 2H), 1.62-1.55 (m, 1H),

1.01 (d, J = 7.1 Hz, 3H) 0.92 (d, J = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.7, 128.3, 127.6, 127.4, 86.5, 73.1, 72.6, 61.1, 60.9, 37.4, 36.7, 31.8, 15.1, 13.5; IR (neat) 3458 cm^{-1}; Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.11; H, 9.84. Found: C, 71.89; H, 9.67.

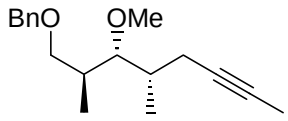


12

(4E)-1-[(1S)-1-methyl-2-(phenylmethoxy)ethyl](2S,1R)-5,5-dibromo-1-methoxy-2-methylpent-4-ene: To a solution of alcohol **10** (1.5 g, 5.6 mmol) in CH_2Cl_2 (113 mL) were added 4 Å molecular sieves (1.5 g) and NMO (0.99 g, 8.5 mmol). The heterogeneous mixture was stirred at 0 °C for 1 h and then TPAP (59 mg, 0.17 mmol) was added. The reaction was monitored by TLC and judged complete after 30 min at 0 °C. The black heterogeneous mixture was filtered through a plug of silica gel and Celite, the plug was rinsed with 40% ethyl acetate/ hexanes (150 mL). The filtrate was concentrated by rotary evaporation giving the crude aldehyde **11** as a colorless oil. This material was used without further purification in the subsequent reaction: R_f = 0.55 (35% EtOAc/ hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.79 (dd, J = 2.8, 1.7 Hz, 1H), 7.35 (d, J = 2.4 Hz, 2H), 7.35 (s, 2H), 7.32 (d, J = 2.2 Hz, 1H), 4.52 (s, 2H), 3.57-3.52 (m, 2H), 3.39 (s, 3H), 2.55 (ddd, J = 16.2, 5.6, 1.7, 1H), 2.43 (ddd, J = 16.2, 7.6, 2.8 Hz, 1H), 2.42-2.35 (m, 2H), 1.97-1.90 (m, 1H), 1.02 (d, J = 6.6 Hz, 3H), 0.97 (d, J = 6.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.4, 138.6, 128.3, 127.6, 127.5, 85.6, 73.1, 72.4, 60.9, 48.9, 36.9, 30.3, 14.9, 13.4.

To a 0 °C solution of CBr_4 (3.9 g, 12 mmol) in CH_2Cl_2 (40 mL) was added PPh_3 (6.2 g, 24 mmol) in one portion. The bright yellow solution was stirred for 10 min, then cooled to –78 °C and the crude aldehyde **11** (1.5 g, 5.6 mmol, theoretical) in CH_2Cl_2 (9 mL + 9

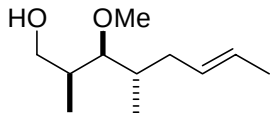
mL wash) was added by cannula. The reaction mixture was stirred for 30 min, at which time TLC analysis showed the reaction to be complete. After addition of saturated aqueous NaHCO3 solution (20 mL) the mixture was shaken in a separatory funnel and the organic layer removed. The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated by rotary evaporation. The residue was purified by flash chromatography over silica gel eluting with ethyl acetate/ hexanes (5%, 400 mL). The product containing fractions were combined and concentrated to provide **12** as a colorless oil (1.6 g, 68% yield from **10**): R_f = 0.66 (35% EtOAc/ hexanes); $[\alpha]_D^{26}$ –8.43 (*c* 0.83, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.17 (m, 5H), 6.35 (t, *J* = 7.2 Hz, 1H), 4.44 (s, 2H), 3.52 (app. s, 1H), 3.41 (app. d, *J* = 1.1 Hz, 1H), 3.39 (s, 3H), 2.91 (dd, *J* = 8.4, 3.2 Hz, 1H), 2.12 (ddd, *J* = 14.8, 6.9, 6.1 Hz, 1H), 2.04 (ddd, *J* = 15.0, 8.0, 7.3 Hz, 1H), 1.94-1.81 (m, 1H), 1.80-1.70 (m, 1H), 0.89 (d, *J* = 7.0 Hz, 3H), 0.81 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.8, 138.0, 128.5, 127.8, 127.7, 89.4, 85.8, 73.3, 72.6, 61.3, 38.3, 37.1, 34.8, 15.1, 13.3; IR (neat) 1605 cm^{-1}.



13

1-[(1S)-1-methyl-2-(phenylmethoxy)ethyl](2S,1R)-1-methoxy-2-methylhex-4-yne: To a –78 °C solution of dibromide **12** (570 mg, 1.35 mmol) in THF (14 mL) was added *n*-BuLi (1.20 mL, 2.97 mmol, 2.50 M in hexanes). After 1 h at –78 °C, TLC analysis showed that the starting material was consumed; DMPU (245 µl, 2.03 mmol) was then added by syringe and the solution was stirred for 15 min; CH_3I (420 µL,

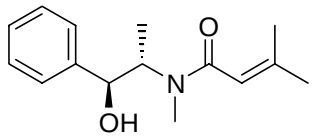
6.75 mmol) was then added. The mixture was stirred for 30 min at –78 °C, then the bath was removed, and the solution stirred an additional 30 min. The reaction was quenched by addition of water (10 mL). The reaction mixture was partitioned between CH_2Cl_2 (15 mL) and water (15 mL). The organic layer was removed and the aqueous layer extracted with CH_2Cl_2 (3 × 15 mL) The combined organic phases were dried over Na_2SO_4 and concentrated by rotary evaporation. The residue was purified by flash chromatography eluting with 5% ethyl acetate/ hexanes (300 mL). The product containing fractions were combined and concentrated to give **13** as a colorless oil (370 mg, 99% yield); R_f = 0.65 (35% EtOAc/ hexanes); $[\alpha]_D^{26}$ +3.8 (*c* 1.05, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.27 (m, 5H), 4.51 (s, 2H), 3.55 (dd, *J* = 8.8, 3.7 Hz, 1H), 3.48 (dd, *J* = 8.8, 6.0 Hz, 1H), 3.42 (s, 3H), 3.18 (dd, *J* = 8.6, 3.2 Hz, 1H), 2.22 (ddq, *J* = 16.6, 7.5, 2.8 Hz, 1H), 2.13 (ddq, *J* = 16.3, 6.9, 2.3 Hz, 1H), 1.97-1.75 (m, 2H), 1.79 (app t, *J* = 2.6 Hz, 3H), 0.97 (d, *J* = 6.9 Hz, 3H), 0.90 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz $CDCl_3$) δ 139.0, 128.5, 127.7, 127.6, 84.7, 78.4, 76.6, 73.2, 72.8, 61.5, 37.2, 35.6, 24.3, 15.1, 13.4, 3.7; IR (neat) 2966 cm^{-1}; Anal. Calcd for $C_{18}H_{26}O_2$: C, 78.79; H, 9.55. Found: C, 78.84; H, 9.62.



14

(6E)(2S,4S,3R)-3-methoxy-2,4-dimethyloct-6-en-1-ol: To a vigorously stirred –78 °C solution of ammonia (8 mL) in THF (8 mL) were added substrate **13** (400 mg, 1.46 mmol) and several small pieces of lithium wire. After 20 min the reaction mixture was warmed to –40 °C and monitored by TLC analysis. When the reaction was judged complete (3 h) the ammonia was allowed to evaporate and solid

NH_4Cl was added in several small portions until the reaction mixture became colorless. The solution was transferred to a separatory funnel and shaken with saturated aqueous NH_4Cl. The organic phase was removed and the aqueous layer extracted with CH_2Cl_2 (3 × 15 mL). The combined organics were washed with brine (30 mL), dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography eluting with 20% acetone/ hexanes. The product containing fractions were combined and concentrated to provide the desired alcohol **14** as a colorless oil (228 mg, 84 % yield); R_f = 0.39 (35% EtOAc/ hexanes); $[\alpha]_D^{26}$ –7.58 (*c* 0.80, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.52-5.33 (m, 2H), 3.66-3.63 (m, 2H), 3.48 (s, 3H), 3.00 (dd, *J* = 7.6, 3.5 Hz, 1H), 2.86 (br. s, 1H), 2.18-2.09 (m,1H), 2.00-1.82 (m, 2H), 1.76-1.69 (m, 1H), 1.66 (d, *J* = 4.7 Hz, 3H), 0.91 (d, *J* = 7.0 Hz, 3H), 0.89 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 129.9, 126.8, 90.2, 66.9, 61.4, 37.8, 37.8, 36.5, 18.2, 15.3, 13.9; IR (neat) 3417 cm^{-1}; Anal. Calcd for $C_{11}H_{22}O_2$: C, 70.92; H, 11.90. Found: C, 70.80; H, 11.95.

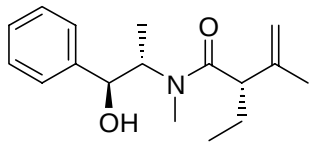


15

N-((1S,2S)-2-hydroxy-1-methyl-2-phenylethyl)(2Z)-3-methyl-N-methylbut-2-enamide: 3,3-Dimethyl acryloyl chloride (7.75 mL, 69.6 mmol) was added *via* syringe over 5 min to a 0 °C solution of (+)-(1S, 2S)-psuedoephedrine (10.0 g, 60 mmol) and NEt_3 (11.0 mL, 78.4 mmol) in THF (150 mL). The suspension was stirred for 20 min at which time the reaction was judged complete by TLC analysis. Excess acid chloride was quenched by the careful addition of water (20 mL). The reaction mixture was partitioned between ethyl acetate (200 mL) and brine (100 mL). The

organic layer was separated, washed with brine (2 × 100 mL), dried over Na_2SO_4, filtered and concentrated to give a yellow solid. The residue was recrystallized from hot toluene (200 mL) providing the product **15** (11.2 g, 79% yield) as a colorless solid; mp 121–123 °C; R_f 0.22 (50% EtOAc/ hexanes); $[\alpha]_D^{27}$ +141.2 (*c* 1.05, $CHCl_3$) (3.3:1 ratio of amide rotamers by ^{1}H NMR), ^{1}H NMR (major rotamer, 500 MHz, $CDCl_3$) δ 7.39-7.26 (m, 5H), 5.84 (s, 1H), 4.80 (br. s, 1H), 4.63 (dd, *J* = 7.3, 7.3 Hz, 1H), 4.42 (dq, *J* = 7.3, 7.3 Hz, 1H), 2.83 (s, 3H), 1.85 (s, 6H), 1.14 (d, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 142.6, 128.3, 127.6, 126.4, 118.5, 76.6, 59.0, 33.7, 26.3, 20.2, 14.5; IR (neat) 1672 cm^{-1}; Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56, N, 5.66. Found: C, 72.58; H, 8.50, N, 5.70.

^{1}H NMR (minor rotamer, 500 MHz, $CDCl_3$) δ 7.39-7.26 (m, 5H), 5.76 (s,1H), 4.56 (d, *J* = 8.3 Hz, 1H), 4.16 (dq, *J* = 6.84, 6.84 Hz, 1H), 2.95 (s, 3H), 2.25 (br.s, 1H), 1.90 (s, 6H), 1.00 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (minor rotamer, 125 MHz, $CDCl_3$) δ 170.8, 147.5, 128.7, 127.6, 126.9, 119.1, 75.6, 58.7, 33.7, 25.9, 20.3, 15.3.

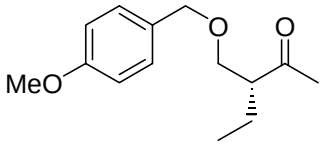


16 **(2S)-N-((1S,2S)-2-hydroxy-1-methyl-2-phenylethyl)-2-ethyl-3-methyl-N-methylbut-3-enamide:** A three-necked 100 mL flask equipped with a mechanical stirrer was charged with LiCl (5.0 g, 120 mmol), diisopropylamine (6.3 mL, 45 mmol) and THF (25 mL). The suspension was cooled to –78 °C and *n*-BuLi (17 mL, 42 mmol, 2.5 M in hexanes) was added *via* syringe. The cold bath was removed and the suspension was stirred for 10 min and then re-cooled to –78 °C. A 0 °C solution of the

amide **15** (5.0 g, 20 mmol) in a minimal amount of THF (35 mL) was added to the reaction flask *via* cannula. The reaction mixture was stirred at –78 °C for 1 h, at 0 °C for 15 min and at rt for 15 min. The reaction mixture was then re-cooled to 0 °C and ethyl iodide (3.2 mL, 40 mmol) was added. The alkylation reaction was allowed to stir at 0 °C for 30 min at which time the reaction was judged complete by TLC analysis. The reaction was quenched by the addition of saturated aqueous NH_4Cl solution (10 mL) and then diluted with ethyl acetate and transferred to a separatory funnel. The organic layer was removed and the aqueous layer extracted with ethyl acetate (3×20 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated to give a yellow oil. The oil was purified by gravity chromatography over silica gel (5×25 cm) eluting with ethyl acetate/ hexanes mixtures (300 mL 25%, 800 mL 40 %). The product containing fractions were combined to provide the amide **16** as a colorless oil (5.6 g, 93%): R_f 0.46 (50 % EtOAc/ hexanes); $[\alpha]_D^{27}$ +148.1 (*c* 1.05, $CHCl_3$); (3.3:1 ratio of amide rotamers by NMR), ^{1}H NMR (major rotamer, 500 MHz, $CDCl_3$) δ 7.41-7.25 (m, 5H); 4.92 (s, 1H), 4.82 (s, 1H), 4.62 (dd, *J* = 6.3, 6.3 Hz, 1H), 4.39 (br. s, 1H), 4.20 (dq, *J* = 6.8, 6.8 Hz, 1H), 2.98 (dd, *J* = 6.8, 6.8 Hz, 1H), 1.71 (s, 3H), 1.64-1.56 (m, 1H), 1.15 (d, *J* = 6.4 Hz, 3H), 0.9 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.1, 142.9, 142.6, 128.3, 127.5, 126.3, 113.7, 76.7, 57.6, 53.2, 27.2, 24.0, 19.9, 14.3, 12.3; IR (neat) 1645 cm^{-1}; Anal. Calcd for $C_{17}H_{25}NO_2$: C, 74.14; H, 9.15; N, 5.09. Found: C, 73.94; H, 9.23; N, 4.96.

^{1}H NMR (minor rotamer, 500 MHz, $CDCl_3$) δ 7.41-7.25 (m, 5H), 4.86 (s, 1H), 4.79 (s, 1H), 4.56 (d, *J* = 8.3 Hz, 1H), 3.31 (dd, *J* = 6.8, 6.8 Hz, 1H), 2.92 (s, 3H), 2.18 (br. s, 1H), 1.68 (s, 3H), 0.93 (d, *J* = 6.4 Hz, 3H), 0.85 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (minor

rotamer, 125 MHz, $CDCl_3$) δ 175.1, 143.7, 141.2, 128.8, 128.4, 126.8, 113.4, 76.7, 75.6, 57.6, 52.9, 27.2, 23.9, 19.6, 14.3.



18 **(3R)-3-{[(4-methoxyphenyl)methoxy]methyl}pentan-2-one**:

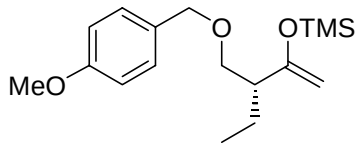
A single portion of H_3N •BH_3 (1.15 g, 37.3 mmol) was added to a 0 °C solution of LDA (36.5 mmol) in THF (20 mL). The suspension was stirred for 20 min at 0 °C and then warmed to rt for 15 min and then the reaction mixture was re-cooled to 0 °C. The amide **16** (2.00 g, 7.26 mmol) was dissolved in THF (5 mL + 2 mL wash) cooled to 0 °C and then added to the borane solution dropwise *via* cannula over 5 min; the reaction mixture was stirred an additional 10 min at 0 °C and the bath removed. The reaction mixture was stirred for 3 h at which time TLC analysis indicated that the amide was consumed. The solution was recooled to 0 °C and the excess borane was carefully quenched by dropwise addition of 3N HCl (80 mL) by addition funnel. This bi-phasic mixture was stirred for 30 min at 0 °C, 15 min at rt, then transferred to an addition funnel and the aqueous layer was extracted with 30% diethyl ether/pentane (3 × 30 mL). The combined organic extracts were washed sequentially with 3N HCL, 3N NaOH and brine, dried over $NaSO_4$, filtered and concentrated by rotary evaporation to approximately 10 mL of solution. Due to the volatility of the primary alcohol product this solution was reserved and used directly in the next reaction: R_f 0.34 (25 % EtOAc/ hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.95 (dq, *J* = 3.4, 1.5 Hz, 1H), 4.83 (br. s, 1H), 3.55 (dd, *J* = 10.3, 5.4 Hz, 1H), 3.49 (dd, *J* =

10.8, 8.8 Hz, 1H), 2.19 (m, 1H), 1.68 (s, 3H), 1.45-1.30 (m, 2H), 0.88 (t, 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.0, 113.8, 63.8, 51.8, 22.1, 18.6, 11.7.

To a suspension of potassium hydride (1.70 g, 14.5 mmol, 35% suspension in mineral in mineral oil) in THF (15 mL) at –15 °C, the crude ether/pentane solution the alcohol product reserved from the previous reaction was added *via* cannula. The heterogeneous reaction mixture was stirred for 15 min and then *p*-methoxybenzyl bromide (2.20 g, 10.9 mmol) was added by syringe. The reaction was stirred for 5 h at rt at which time the reaction was judged complete by TLC analysis, and the excess potassium hydride was quenched by addition of several pieces of ice. The reaction mixture was partitioned between CH_2Cl_2 and saturated aqueous NH_4Cl solution. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic extracts were washed with brine, then dried over Na_2SO_4 and concentrated to provide a **17** as a yellow liquid. The crude material was used directly in the next reaction: R_f 0.42 (35 % EtOAc/ hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (d, *J* = 7.3 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 4.84 (d, *J* = 1.5 Hz, 1H), 4.43 (d, *J* = 1.5 Hz, 1H), 3.81 (s, 3H), 3.41 (dd, *J* = 9.3, 7.3 Hz, 1H), 3.35 (dd, *J* = 9.3, 6.4 Hz, 1H), 2.30 (m, 1H), 1.52 (m ,1H), 1.30 (m,1H), 1.65 (s, 3H), 0.84 (t, *J* = 7.3 Hz, 3H);^{13}C NMR (125 MHz, $CDCl_3$) δ 159.0, 145.6, 130.7, 129.2, 113.7, 112.1, 72.5, 72.4, 55.2, 48.8, 22.6, 19.3, 11.6.

The crude PMB ether **17** (0.90 g, 7.3 mmol, theoretical) prepared above was transferred to a round bottom flask and taken up in THF/*t*-butanol/water (50 mL, 5:5:1). The solution was cooled to 0 ºC, and NMO (0.46 g, 4.1 mmol) was added, followed by an OsO_4 solution (2.8 ml, 0.38 mmol, 4% w/v in THF). The reaction mixture was stirred 5 h at rt and then sodium meta-bisulphite (solid, 10 g) was added to the yellow solution,

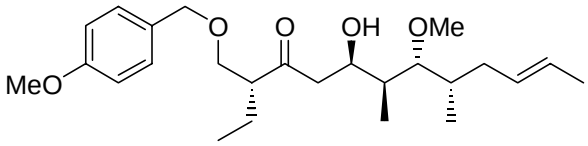
stirring was continued until the solution became colorless (3 h). The suspension was filtered and the solid residue washed with ethyl acetate (50 ml). The solution was concentrated by rotary evaporation, the residue was taken up in THF/water (4:1, 50 mL), and $NaIO_4$ (2.0 g, 9.5 mmol) was added in one portion, The suspension was stirred for 2.5 h at which time it was filtered and the solid residue washed with ethyl acetate. The organic phase was washed with water and brine, dried over Na_2SO_4 and concentrated to provide a colorless oil. The crude material was purified by RPLC (4mm plate), eluting with 15% ethyl acetate/ hexanes. The product containing fractions were concentrated to give the product **18** as a colorless oil (0.85 g, 52% from **16**): R_f 0.44 (35% EtOAc/ hexanes); $[\alpha]_D^{27}$ +9.7 (*c* 1.15, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (d, *J* = 8.8 Hz, 2H), 6.87 (d, *J* = 8.3 Hz, 2H), 4.41 (s, 2H), 3.81 (s, 3H), 3.59 (dd, *J* = 8.8, 8.3 Hz, 1H), 3.51 (dd, *J* = 9.3, 4.9 Hz, 1H), 2.77-2.71 (m, 1H), 2.17 (s, 3H), 1.67-1.59 (m, 1H), 1.51-1.43 (m, 1H), 0.88 (t, 7.3). ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.4, 159.2,130.1, 129.2, 113.8, 72.9, 70.4, 55.2, 54.5, 30.0, 21.5, 11.6; IR (neat) 1714 cm^{-1}; Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 70.90; H, 8.56.



5

1-[1-((1R)-1-{[(4-methoxyphenyl)methoxy]methyl}propyl)vinyloxy]-1,1-dimethyl-1-silaethane: A solution of ketone **18** (0.270 g, 1.32 mmol) in THF (1 mL + 0.5 mL wash) was added to a –78 °C solution of lithium hexamethyldisilazide (3.25 mL, 3.25 mmol, 1.0 M solution in hexane) in THF (20 mL). The reaction mixture was stirred for 15 min at –78 °C. TMSCl

(2 mL) and NEt_3 (2 mL) were combined in a centrifuge tube fitted with a septum and then centrifuged for 15 min and the supernatant fluid was added (420 μl) to the enolate solution by syringe. After 15 min the bath was removed and the reaction mixture was diluted with diethyl ether (5 mL) and then concentrated to 1 mL by rotary evaporation. The resultant heterogeneous mixture was diluted with 4:1 hexanes/ether and concentrated; this process was performed two times. The residue was taken up in 4:1 hexanes/ether and filtered through paper wetted with NEt_3. The solvent was evaporated to give the product **5** as a clear colorless oil. This material was used without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16 (d, *J* = 8.5 Hz, 2H), 6.77 (d, *J* = 8.3 Hz, 2H), 4.35 (s, 2H), 3.98 (d, *J* = 7.3 Hz, 2H), 3.71 (s, 3H), 3.38 (dd, *J* = 9.3, 7.8 Hz, 1H), 3.21 (dd, *J* = 9.3, 6.8 Hz, 2H), 2.13-2.05 (m, 1H), 1.39-1.29 (m, 1H), 1.31-1.21 (m, 1H), 0.77 (t, *J* = 7.3 Hz, 3H), 0.11 (s, 9H).



19

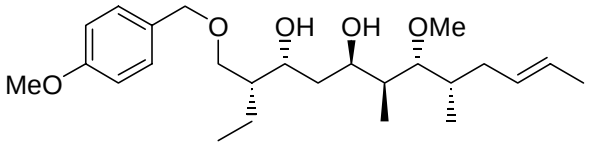
(11E)(3S,6S,8S,7R,9R)-6-hydroxy-8-methoxy-3-{[(4-methoxyphenyl)methoxy]methyl}-7,9-dimethyltridec-11-en-4-one:

To a solution of the crude alcohol **14** (200 mg, 1.1 mmol) in CH_2Cl_2 (10 mL) were added 4 Å molecular sieves (300 mg) and NMO (150 mg, 1.3 mmol). The heterogeneous mixture was stirred at 0 °C for 15 min and then TPAP (19 mg, 0.06 mmol) was added. The reaction was monitored by TLC and judged complete after 30 min at 0 °C. The black heterogeneous mixture was filtered through a plug of silica gel and Celite, the plug was washed with 40% ethyl acetate/ hexanes (50 mL). The filtrate was concentrated by

rotary evaporation giving the crude aldehyde **6** as a colorless oil. This material was used without further purification in the subsequent reaction: R_f = 0.62 (35% EtOAc/ hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.80 (d, *J* = 2.5 Hz, 1H), 5.53-5.32 (m, 2H), 3.41 (s, 3H), 3.26 (dd, *J* = 7.2, 3.9 Hz, 1H), 2.64 (ddd, *J* = 7.1, 2.7 1.9 Hz, 1H), 2.19-2.10 (m, 1H), 1.98-1.88 (m, 1H), 1.76-1.69 (m, 2H), 1.67 (dd, *J* = 5.8, 1.0 Hz, 3H), 1.05 (d, *J* = 7.1 Hz, 3H), 0.92 (d, *J* = 6.8 Hz, 3H).

The crude aldehyde **6** (198 mg, 1.10 mmol, theoretical) and the crude silyl enolether **5** (271 mg, 1.32 mmol, theoretical) were combined, diluted with CH_2Cl_2 (10 mL) and cooled to –90 °C. BF_3•OEt_2 (1.0 M in CH_2Cl_2, 1.4 mL) was added *via* syringe and the reaction mixture was stirred at –90 °C for 1 h and then quenched by addition of 2 mL of saturated aqueous NaHCO3 solution. The mixture was warmed to rt, transferred to a separatory funnel and the organic layer removed; the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL) and ethyl acetate (1 × 20 mL). The combined organics were dried over Na_2SO_4 and concentrated by rotary evaporation. The residue was purified by gravity chromatography on silica gel (5 × 25 cm) eluting with ethyl acetate/hexane mixtures (100 mL each of 15%, 20%, and 25%). The product containing fractions were combined and concentrated to give **19** as a colorless oil (398 mg, 86% yield): R_f 0.44 (35 % EtOAc/hexanes); $[\alpha]_D^{27}$ +10.7 (*c* 1.65, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (d, *J* = 8.3 Hz, 2H), 6.87 (d, *J* = 8.8 Hz, 2H), 5.50-5.38 (m, 2H), 4.44 (br d, *J* = 6.3 Hz, 1H), 4.41 (s, 2H), 3.80 (s, 3H), 3.59 (dd, *J* = 8.8, 8.8 Hz, 1H), 3.49 (dd, *J* = 9.7, 4.9 Hz, 1H), 3.48 (s, 3H), 3.39 (d, *J* = 2.0 Hz, 1H), 3.12 (dd, *J* = 7.8, 3.1 Hz, 1H), 2.83-2.77 (m, 1H), 2.76 (dd, *J* = 17.1, 9.3 Hz, 1H), 2.48 (dd, *J* =17.1, 3.4 Hz, 1H), 2.19-1.55 (m, 2H), 2.00-1.94 (m 1H), 1.67 (d, *J* = 5.9 Hz, 3H), 1.65-1.55 (m, 2H), 1.49-1.41 (m, 1H), 0.88 (t,

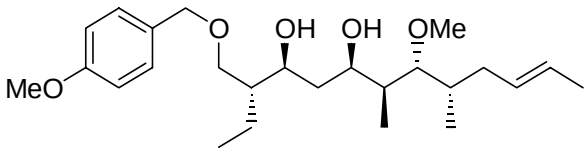
J = 7.8 Hz, 3H), 0.85 (d, J = 7.3 Hz, 6H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.2, 159.2, 129.9, 129.9, 129.3, 126.4, 113.8, 86.9, 72.9., 70.5, 66.5, 61.6, 55.2, 54.3, 48.2, 39.8, 37.6, 35.8, 21.6, 18.0, 13.2, 11.7, 10.4; IR (neat) 1709 cm^{-1}; Anal. Calcd for $C_{25}H_{40}O_5$: C, 71.39; H, 9.59. Found: C, 71.60; H, 9.62.



***anti*-20**

(11E)(7S,9S,3R,4R,6R,8R)-8-methoxy-3-{[(4-methoxyphenyl)methoxy]methyl}-7,9-dimethyltridec-11-ene-4,6-diol: To a suspension of samarium chips (660 mg, 4.34 mmol) in THF (18 mL) under an argon atmosphere was added diiodomethane (161 μl, 2.0 mmol) *via* syringe. The suspension was stirred vigorously under argon and became blue/ purple over a 30 min period. Stirring was continued for 3 h and the reaction mixture was cooled to –15 °C. The β-hydroxy ketone **19** (100 mg, 0.237 mmol) was weighed into a separate flask, diluted with THF (1 mL) and then MeOH (540 μl, 13.3 mmol) was added by cannula. The THF solution of substrate and MeOH was added to the SmI_2 solution *via* cannula, the reaction vessel sealed with parafilm and placed in the freezer at –16 °C. TLC analysis was performed after 14 h and indicated that the starting material had been consumed. The reaction mixture was transferred to a separatory funnel diluted with ethyl acetate, and washed with 1% aqueous HCl solution. The organic layer was removed and the aqueous solution was extracted with ethyl acetate (4 × 20 mL). The combined organic materials were washed with sodium thiosulfate (2 × 20 mL). The sodium thiosulfate washes were combined and extracted with ethyl acetate (1 × 20 mL). The combined organic material

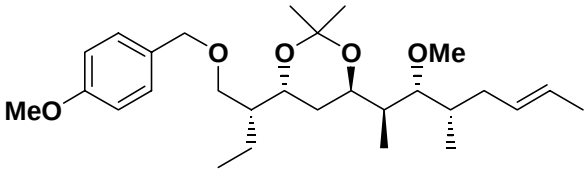
was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by chromatography on a column of gravity silica gel (2.5 × 20 cm) eluting with 25% ethyl acetate/hexanes. Collection of the product containing fractions provided **20** as a colorless solid (76 mg), **20'** as a colorless oil (16 mg) (91% yield of diols). Analytical data for the major diastereomer: mp 70-71 °C; R_f 0.42 (35 % EtOAc/ hexanes); $[\alpha]_D^{27}$ +4.6 (*c* 1.09, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.3 Hz, 2H), 6.87 (d, *J* = 8.3 Hz, 2H), 5.44 (dq, *J* = 15.8, 5.9 Hz, 1H), 5.41-5.35 (m, 1H), 4.44 (ABq, ΔAB = 29.3 Hz, *J* = 11.7 Hz, 2H), 4.20 (br d, *J* = 9.3 Hz, 1H), 4.01 (br d, *J* = 4.4 Hz, 1H), 3.8 (s, 3H), 3.57 (dd, *J* = 10.7, 9.3 Hz, 1H), 3.54 (dd, *J* = 9.3, 3.9 Hz, 1H), 3.47 (s, 3H), 3.28 (br. s, 1H), 3.16 (br. d, *J* = 5.4 Hz, 1H), 3.01 (dd, *J* = 5.4, 5.4 Hz, 1H), 2.15-2.09 (m, 1H), 1.91-1.80 (m, 2H), 1.79-1.70 (m, 2H), 1.66 (d, *J* = 6.8 Hz, 3H), 1.56 (ddd, *J* = 12.2, 9.3, 2.4 Hz, 1H), 1.45-1.35 (m, 2H), 0.96 (d, *J* = 7.3 Hz, 3H), 0.94 (d, *J* = 7.3 Hz, 3H), 0.92 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.3, 130.1, 129.3, 129.9, 129.2, 126.7, 113.8, 90.5, 73.1, 71.7, 71.5, 68.5, 61.5, 55.3, 45.4, 39.3, 38.1, 37.3, 36.1, 19.1, 17.9, 14.8, 12.2, 12.0; IR (neat) 3396 cm^{-1}.



20'

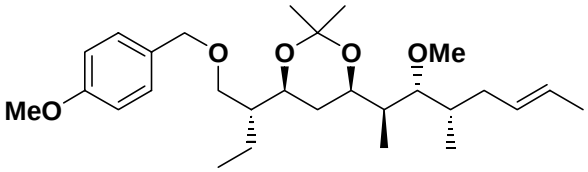
(11E)(4S,7S,9S,3R,6R,8R)-8-methoxy-3-{[(4-methoxyphenyl)methoxy]methyl}-7,9-dimethyltridec-11-ene-4,6-diol: R_f 0.47 (35 % EtOAc/ hexanes); ^{1}H NMR (500 MHz**,** $CDCl_3$) δ 7.26 (d, *J* = 8.3 Hz, 2H), 6.89 (d, *J* = 8.3 Hz, 2H), 5.49-5.38 (m, 2H), 4.45 (s, 2H), 4.19 (d, *J* = 9.8 Hz, 1H), 4.01 (br. s, 1H) 3.95 (br. d, *J* = 10.7 Hz, 1H), 3.81 (s, 3H), 3.67 (dd, *J* = 9.3, 3.4 Hz, 1H), 3.55 (dd, *J* =

9.3, 4.9 Hz, 1H), 3.52 (s, 3H), 3.13 (dd, *J* = 6.8, 3.9 Hz, 1H), 2.17-2.11 (m, 1H), 1.92-1.80 (m,1H), 1.76-1.69 (m, 1H), 1.67 (d, *J* = 5.9 Hz, 3H), 1.61-1.49 (m, 2H), 1.45-1.38 (m, 2H), 0.92 (t, *J* = 6.8 Hz, 3H), 0.89 (d, *J* = 6.8, 3H), 0.86 (d, *J* = 6.8, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 130.1, 129.8, 129.3, 126.4, 113.9, 87.4, 75.3, 73.1, 71.9, 70.8, 61.5, 55.3, 45.6, 40.7, 39.2, 37.7, 35.8, 21.4, 18.0, 13.4, 11.8, 10.9.



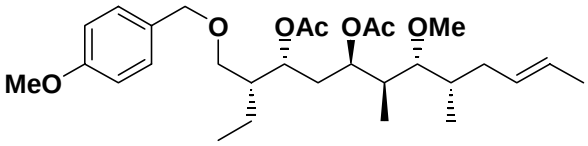
(4E)-1-{(1R)-1-[6-((1R)-1-{[(4-methoxyphenyl)methoxy]methyl}propyl)(4R,6R)-2,2-dimethyl(1,3-dioxan-4-yl)]ethyl}(2S,1R)-1-methoxy-2-methylhex-4-ene: The diol **20** was taken up in dimethoxypropane (1 mL) and a catalytic amount of *p*-toluenesulphonic acid was added. The reaction mixture was stirred for 6 h, diluted with CH_2Cl_2 (2 mL) and then quenched by addition of saturated aqueous $NaHCO_3$ solution (2 ml). The organic layer was removed, dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography over silica gel, eluting with 5% ethyl acetate/ hexanes. The product containing fractions were combined to give the desired acetonide product: R_f 0.80 (25 % EtOAc/ hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (d, *J* = 9.8 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 5.50-5.39 (m, 2H), 4.43 (d, J_{AB} = 11.7 Hz, 1H), 4.40 (d, J_{AB} = 11.7 Hz, 1H), 4.09 (ddd, *J* = 9.3, 7.3, 2.0 Hz, 1H), 3.81 (s, 3H), 3.80-3.77 (m, 1H), 3.47 (s, 3H), 3.45 (dd, *J* = 9.3, 5.4 Hz, 1H), 3.40 (dd, *J* = 9.3, 4.4 Hz, 1H), 3.08 (dd, *J* = 9.3, 2.0 Hz, 1H), 2.16 (ddd, *J* = 12.2, 5.4, 5.4 Hz, 1H), 2.03-1.97 (m, 1H), 1.68 (d, *J* = 5.4 Hz, 3H), 1.66-1.58 (m, 2H), 1.54-1.44 (m, 1H), 1.43-1.36 (m, 1H), 1.35 (s, 3H), 1.30 (s, 3H), 0.91 (t, *J*

= 7.8 Hz, 3H), 0.82 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 130.7, 130.5, 129.3, 126.2, 113.7, 100.0, 85.2, 72.8, 68.5, 67.3, 65.4, 61.1, 55.3, 45.0, 41.1, 38.7, 35.9, 34.0, 31.6, 29.7, 25.0, 24.9, 20.0, 18.0, 12.3, 11.7, 10.1; DEPT (125 MHz, $CDCl_3$) δ CH_3: 61.1, 55.3, 25.0, 24.9, 18.0, 15.1, 13.2, 10.1. CH_2: 72.8, 68.5, 38.7, 34.0, 29.7, 20.2. CH: 130.7, 129.3, 126.2, 113.7, 85.2, 67.3, 65.4, 45.0, 41.1, 35.9.



(4E)-1-{(1R)-1-[6-((1R)-1-{[(4-methoxyphenyl)methoxy]methyl}propyl)(6S,4R)-2,2-dimethyl(1,3-dioxan-4-yl)]ethyl}(2S,1R)-1-methoxy-2-methylhex-4-ene: The diol **20'** was taken up in dimethoxypropane (1 mL) and a catalytic amount of *p*-toluenesulphonic acid was added. The reaction mixture was stirred for 6 h, diluted with CH_2Cl_2 (2 mL) and then quenched by addition of saturated aqueous $NaHCO_3$ solution (2 ml). The organic layer was removed, dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography over silica gel, eluting with 5% ethyl acetate/ hexanes. The product containing fractions were combined to give the desired acetonide product: R_f 0.80 (25 % EtOAc/ hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (d, *J* = 9.8 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 5.50-5.40 (m, 2H), 4.43 (d, J_{AB} = 11.7 Hz, 1H), 4.41 (d, J_{AB} = 11.7 Hz, 1H), 4.19 (ddd, *J* = 9.8, 2.0, 2.0, Hz 1H), 3.96 (ddd, *J* = 11.7, 9.8, 6.4 Hz, 1H), 3.81 (s, 1H), 3.49 (app. d, *J* = 4.9 Hz, 2H), 3.46 (s, 3H), 3.10 (dd, *J* = 9.8, 1.5 Hz, 1H), 2.16 (ddd, *J* = 12.7, 5.4, 5.4 Hz, 1H), 2.04-1.99 (m, 1H), 1.68 (d, *J* = 4.9 Hz, 3H), 1.66-1.63 (m, 1H), 1.58-1.53 (m, 2H), 1.51-1.44 (m, 1H), 1.43 (s, 3H), 1.35 (s, 3H), 1.22 (ddd, *J* = 12.7, 2.4,

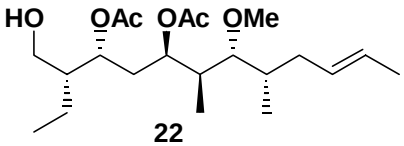
2.4 Hz, 1H), 0.90 (t, *J* = 7.3 Hz, 3H), 0.80 (d, *J* = 6.8 Hz, 3H), 0.79 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 130.5, 129.1, 126.1, 113.7, 98.2, 84.8, 72.7, 69.2, 68.3, 67.5, 61.3, 55.3, 45.3, 41.1, 38.5, 35.8, 31.7, 30.2, 20.1, 19.6, 18.0, 11.9, 11.5, 10.0; DEPT (125 MHz, $CDCl_3$) δ CH_3: 61.3, 55.3, 30.2, 20.1, 18.0, 11.9, 11.5, 10.0. CH_2: 72.7, 68.3, 38.5, 31.7, 19.6. CH: 130.5, 129.1, 113.7, 84.8, 69.2, 67.5, 45.3, 41.1, 35.8.



21

(8E)-1-((1R)-1-{[(4-methoxyphenyl)methoxy]methyl}propyl)(3S,6S,1R,4R,5R)-3-acetyloxy-5-methoxy-4,6-dimethyldec-8-enyl acetate: To a solution of **20** (61 mg, 0.14 mmol) in CH_2Cl_2 (1 mL) were added sequentially NEt_3 (0.25 ml, 2.5 mmol), Ac_2O (0.25 ml, 2.5 mmol) and DMAP (1 mg). The reaction mixture was stirred at rt for 14 h, then diluted with 5 mL CH_2Cl_2, poured into saturated aqueous $NaHCO_3$ solution (10 mL) and stirred at rt for 2 h. The bi-phasic mixture was transferred to a separatory funnel, the organic layer was removed, and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organics were washed with brine, dried over Na_2SO_4, and concentrated by rotary evaporation. Purification by gravity chromatography, eluting with 10% ethyl acetate/ hexanes, provided the product **21** as a colorless oil (71 mg, 97% yield): R_f 0.82 (35 % EtOAc/ hexanes); $[\alpha]_D^{27}$ +5.8 (*c* 1.74, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (d, *J* = 7.3 Hz, 2H), 6.87 (d, *J* = 8.3 Hz, 2H), 5.45 (dq, *J* = 15.1, 5.9 Hz, 1H), 5.42-5.36 (m, 1H), 5.25 (ddd, *J* = 9.3, 4.4, 2.0 Hz, 1H), 5.03 (ddd, *J* = 10.3, 3.9, 3.9 Hz), 4.40 (s, 2H), 3.81 (s, 3H), 3.45 (s, 3H), 3.41 (dd, *J* = 9.8, 5.2 Hz, 1H), 3.38 (dd, *J* = 9.8, 6.1 Hz, 1H), 2.87

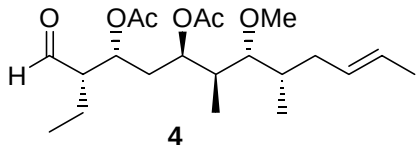
(dd, *J* = 9.3, 2.0 Hz, 1H), 2.15 (ddd, *J* = 13.1, 5.9, 5.9 Hz, 1H), 2.04 (s, 3H), 2.03-1.96 (m,1H), 2.00 (s, 3H), 1.90 (ddd, *J* = 14.4, 9.8, 3.9 Hz, 1H), 1.87 (d, *J* = 6.4 Hz, 3H), 1.77 (ddd, *J* = 14.4, 10.3, 4.4 Hz, 1H), 1.65-1.61 (m, 1H), 1.42 (ddd, *J* = 14.4, 7.8, 7.8 Hz, 1H), 0.95 (t, *J* = 7.6 Hz, 3H), 0.83 (d, *J* = 7.6 Hz, 3H), 0.80 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7, 170.6, 159.0, 130.7, 130.1, 129.1, 126.4, 113.7, 85.4, 72.7, 71.2, 70.2, 69.2, 61.1, 55.2, 43.7, 40.4, 38.4, 35.8, 34.4, 21.1, 21.1, 20.2, 17.9, 12.3, 12.0, 10.6; DEPT (125 MHz, $CDCl_3$) δ CH_3: 61.2, 55.2, 21.0, 21.0, 17.9, 12.3, 12.0, 10.6. CH_2: 72.7, 69.2, 38.4, 34.4, 20.2. CH: 130.7, 130.1, 129.1, 113.7, 85.4, 71.2, 70.2, 43.7, 46.4, 35.8; IR (neat) 1739 cm^{-1}. Anal. Calcd for $C_{29}H_{40}O_7$: C, 68.74; H, 9.15. Found: C, 68.89; H, 9.16.



22

1-((7E)(5S,2R,3R,4R)-2-acetyloxy-4-methoxy-3,5-dimethylnon-7-enyl)(1S,2R)-2-ethyl-3-hydroxypropyl acetate: To a solution of **21** (97 mg, 0.19 mmol) in CH_2Cl_2/H_2O (1.0 mL: 0.09 mL) was added DDQ (108 mg, 0.48 mmol). Upon addition the solution turned green and over 15 min became red-orange in color. TLC analysis at this point showed that the starting material had been consumed. The reaction was diluted with CH_2Cl_2 and quenched by addition of saturated aqueous NaHCO3 solution (3 mL). The reaction mixture was transferred to a separatory funnel and the organic layer removed; the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and ethyl acetate (10 mL). The combined organics were washed with brine, dried over Na_2SO_4 and concentrated by rotary evaporation. The residue was purified by chromatography on gravity silica gel eluting with ethyl acetate mixtures (100 mL each,

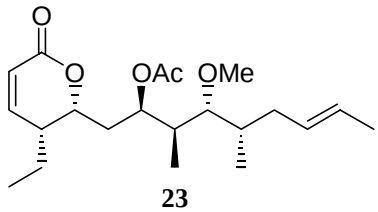
18%, 20% 25% and 30%). The product containing fractions were combined and the solvent removed to provide the primary alcohol **22** as a colorless oil (60 mg, 82% yield): R_f 0.44 (35 % EtOAc/ hexanes); $[\alpha]_D^{27}$ +4.3 (*c* 3.02, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.45 (dq, *J*= 15.1, 5.9 Hz, 1H), 5.41-5.35 (m, 1H), 5.32 (ddd, *J* = 9.8, 3.4, 1.9 Hz, 1H), 5.07 (ddd, *J* = 11.2, 2.4, 2.4 Hz, 1H), 3.64 (ddd, *J* = 11.7, 9.3, 4.9, 1H), 3.4 (s, 3H), 3.25 (ddd, *J* = 11.7, 9.8, 4.4 Hz, 1H), 2.96 (dd, *J* = 9.3, 4.9 Hz, 1H), 2.84 (dd, *J* = 9.3, 2.0 Hz, 1H), 2.16-2.07 (m, 2H), 2.08 (s, 3H), 2.05 (s, 3H), 2.02-1.98 (m, 1H), 1.93 (ddd, *J* = 14.6, 11.2, 3.9 Hz, 1H), , 1.76 (ddd, *J* = 14.2, 10.3, 2.4 Hz, 1H), 1.66 (d, *J* = 7.33, 3H), 1.64-1.58 (m, 2H), 1.49 (ddd, *J* = 15.1, 7.3, 3.9 Hz, 1H), 1.14 (m, 1H) 0.94 (t, *J* = 7.3 Hz, 3H), 0.84 (d, *J* = 6.8 Hz, 3H), 0.82 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.5, 170.7, 130.0, 126.5, 85.3, 76.1, 70.1, 69.8, 61.8, 61.2, 46.2, 40.6, 38.3, 35.8, 35.5, 21.0, 21.0, 18.5, 17.9, 12.3, 12.3, 10.6; DEPT (125 MHz, $CDCl_3$) δ CH_3: 61.2, 21.0, 21.0, 17.9, 12.3, 12.3, 10.6. CH_2: 61.8, 38.3, 35.5, 18.5. CH: 130.0, 126.5, 76.7, 70.1, 69.8, 46.2, 40.6, 35.7; IR (neat) 3370, 1737 cm^{-1}.



4

1-((7E)(5S,2R,3R,4R)-2-acetyloxy-4-methoxy-3,5-dimethylnon-7-enyl)(1S,2S)-2-ethyl-3-oxopropyl acetate: To a 0 °C solution of the primary alcohol **22** (200 mg, 0.52 mmol) in dichloromethane (10 mL) were added sequentially 4Å molecular sieves (250 mg), NMO (91.0 mg, 0.78 mmol), and TPAP (9.0 mg, 0.03 mmol). After 5 min the bath was removed and dark green heterogenous solution stirred an additional 20 min at which time the starting material had been

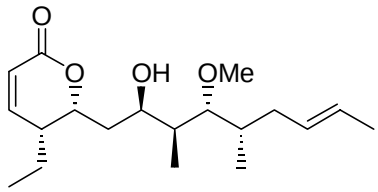
consumed. The reaction mixture was diluted with 35% ethyl acetate/ hexanes (10 mL) and filtered through a pad of Celite (1 cm) and Florisil (3 cm). The pad was washed with 35% ethyl acetate/ hexanes (60 mL) and the filtrate concentrated by rotary evaporation. The crude aldehyde **4** was used immediately without purification in the subsequent reaction: R_f 0.62 (35 % EtOAc/ hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.72 (d, *J* = 1.9 Hz, 1H), 5.52-5.35 (m, 2H), 5.29 (ddd, *J* = 8.8, 4.3, 1.9 Hz, 1H), 5.13 (ddd, *J* = 10.5, 4.3, 4.3 Hz, 1H), 3.44 (s, 3H), 2.84 (dd, *J* = 9.5, 2.4 Hz, 1H), 2.50 (ddd, *J* = 9.0, 4.8, 2.4 Hz, 1H), 2.15-1.98 (m, 2H), 2,07 (s, 3H), 2.06 (s, 3H), 1.97-1.71 (m, 3H), 1.66 (d, *J* = 4.8 Hz, 3H), 1.64-1.58 (m, 2H), 1.54-1.42 (m, 1H), 0.96 (t, *J* = 7.6 Hz, 3H), 0.83 (d, *J* = 8.1 Hz, 3H), 0.81 (d, *J* = 7.1 Hz, 3H).



23

(6E)-1-[((2R,3R)-3-ethyl-6-oxo(3-hydro-2H-pyran-2-yl))methyl](4S,1R,2R,3R)-3-methoxy-2,4-dimethyloct-6-enyl acetate: To a 0 °C solution of diisopropylamine (88 μL, 0.57 mmol) in THF (6 mL), was added *n*-BuLi (208 μL ,0.52 mmol). After 20 min at 0 °C the solution was cooled to –78 °C and methyl acetate (45 μL, 0.57 mmol) was added by syringe and stirring continued for 15 min. The aldehyde **4** (198 mg, 0.52 mmol; theoretical from TPAP oxidation) was taken up in THF (2 mL), cooled to –78 °C and transferred to the enolate solution *via* cannula. Stirring was continued for 15 min at which time TLC analysis indicated the starting material was consumed. The reaction mixture was warmed to 0 °C, stirred an additional 30 min and finally warmed to rt for 15 min. The solution was transferred via cannula into an

Erlenmeyer flask containing pH=7 buffer (25 mL) and CH_2Cl_2 (25 mL). The resulting solution was extracted with CH_2Cl_2 (2 × 10 mL) and ethyl acetate (1 × 10 mL). The combined organics were dried over Na_2SO_4, filtered through a pad of Celite, and concentrated by rotary evaporation. The residue was purified by flash chromatography over silica gel eluting with 10% acetone/ hexanes. The product containing fractions were concentrated to provide the product **23** (130 mg, 73% yield) as a colorless solid: mp 73-75 °C; R_f 0.44 (35 % EtOAc/ hexanes); $[\alpha]_D^{27}$ −122 (*c* 0.65, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.01 (dd, *J* = 10.5, 6.4 Hz, 1H), 6.02 (dd, *J* = 9.8, 1Hz, 1H), 5.47 (dq, *J* = 15.1, 6.4 Hz, 1H), 5.43-5.37 (m, 1H), 5.27 (ddd, *J* = 8.3, 6.4, 1.6 Hz, 1H), 4.47 (ddd, *J* = 7.8, 5.9, 3.4 Hz, 1H), 3.40 (s, 3H), 2.89 (dd, *J* = 9.3, 2.4 Hz, 1H) 2.27 (ddd, *J* = 9.8, 9.8, 3.9 Hz, 1H), 2.16-2.10 (m, 1H) 2.08-2.02 (m, 1H), 2.07 (s, 3H), 2.03-1.97 (m, 1H), 1.98-1.92 (m, 1H) 1.82-1.73 (m, 2H), 1.69-1.62 (m, 1H), 1.67 (dd, *J* = 3.9, 1 hz, 3H), 1.57-1.50 (m,1H), 0.98 (t, *J* = 5.9 Hz, 3H), 0.95 (d, *J* = 6.8 Hz, 3H), 0.81 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7, 164.1, 150.4, 130.1, 126.5, 120.8, 85.2, 77.6, 71.0, 61.3, 39.2, 38.3, 38.2, 35.8, 34.1, 21.2, 20.5, 17.9, 12.4, 10.9, 10.3; DEPT (125 MHz, $CDCl_3$) δ CH_3: 61.3, 21.1, 17.9, 12.4, 10.9, 10.3. CH_2: 38.3, 34.1, 20.5. CH: 150.4, 130.0, 126.5, 120.8, 85.2, 77.6, 71.0, 39.2, 38.2, 35.8; IR (neat) 1731 cm^{-1}; HR/FAB spectrum in 3NBA and EtOAc. Mass at m/z 367 matched against 307 & 460 of 3NBA. Calculated Mass (theoretical) = 367.24638. $C_{35}H_{47}NO_7$ Measured Mass (mass spectrometry) = 367.24845 Difference = 0.00207 amu (Approx. 2.1 mmu.).



1 (-)-pironetin

6-((7E)(3S,5S,2R,4R)-2-hydroxy-4-methoxy-3,5-dimethylnon-7-enyl)(5R,6R)-5-ethyl-5,6-dihydro-2H-pyran-2-one: To a solution of **23** (48 mg, 0.19 mmol) in MeOH (1 mL) at was added 3M HCl (200 μL). The reaction mixture was placed in a 60 °C oil bath for 12 h, at which time it was removed and the reaction quenched by addition of saturated aqueous $NaHCO_3$ solution (3 mL). The reaction mixture was extracted with $CHCl_3$ (3 × 3 mL) and ethyl acetate (1 × 3 mL). The combined organics were dried over Na_2SO_4, filtered and concentrated by rotary evaporation. The residue was purified on a column of flash silica gel eluting with acetone/ hexanes mixtures 20 mL each: 20%, 30%, and 40%. The product containing fractions were concentrated to provide the natural product **1** (36 mg, 86% yield) as a colorless solid: mp 75-77 °C; R_f 0.25 (45 % EtOAc/ hexanes); $[\alpha]_D^{27}$ −139.0 (*c* 0.35, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.02 (dd, *J* = 9.8, 5.9 Hz, 1H), 6.03 (d, *J* = 9.8 Hz, 1H), 5.45 (dq, *J* = 15.2, 5.9 Hz, 1H), 5.38 (dt, *J* = 15.4, 5.9 Hz, 1H), 4.75 (ddd, *J* = 8.8, 4.3, 4.3 Hz, 1H), 4.21, (br d, *J* = 8.5Hz, 1H), 3.84, (s, 3H), 2.99, (dd, *J* = 6.3, 4.4 Hz, 1H), 2.32-2.27, (m, 1H), 2.14-2.07 (m, 1H), 1.91-1.84 (m, 2H), 1.82-1.76 (m, 1H), 1.74-1.65 (m, 3H), 1.67 (d, *J* = 6.4 Hz, 3H), 1.56-1.48 (m, 1H), 1.01 (d, *J* = 7.3 Hz, 3H), 0.98 (t, *J* = 7.8 Hz, 3H), 0.97 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.7, 150.7, 128.7, 126.9, 120.8, 91.2, 77.8, 67.4, 61.6, 39.1, 38.9, 37.3, 36.7, 36.1, 20.8, 17.9, 15.3, 12.2, 11.0; IR (neat) 1726 cm^{-1}; HR/FAB spectrum in 3NBA and EtOAc. Mass at m/z 325 matched against 307 & 460 of 3NBA. Calculated Mass (theoretical) = 325.23788.

$C_{35}H_{47}NO_7$ Measured Mass (mass spectrometry) = 325.23727 Difference = 0.00061 amu (Approx. 0.6 mmu.).