A Cycloaddition Cascade Approach to the Total Synthesis of (–)FR182877

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Supporting Information

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Experimental Procedures. All reactions were carried out under an atmosphere of argon in flame-dried glassware. The reaction solvents: THF, Et₂O, CH₂Cl₂ were purified by passage over activated alumina. Reagents were used as received from the manufacturer unless otherwise stated. Flash chromatography was carried out using EM reagent silica gel 60 (230-400 mesh). Analytical thin layer chromatography was performed on EM Reagent 0.25 mm silica gel 60-F plates. All TLC plates were visualized by UV fluorescence quenching and were stained with either p-anisaldehyde or ceric ammonium molybdate (CAM). Optical rotations were measured on a Jasco DIP-0181 digital polarimeter with a sodium lamp and are reported as follows: $[\alpha]_{\lambda}^{T\text{ }^{\circ}\text{C}}$ (c=g/100 mL solvent). Infrared spectra were recorded on a Perkin-Elmer 1600 series FT-IR spectrometer. ¹H-NMR spectra were recorded on a Varian Inova-500 (500 MHz) spectrometer and are reported in ppm using solvent as an internal standard (CDCl₃=7.26 ppm). Data are reported as: [δ shift]([s= singlet, d=doublet, t=triplet, q=quartet, m=multiplet, b=broad], [integration], and [J=coupling constant in Hz]). Proton decoupled ¹³C-NMR spectra were recorded on a Varian Mercury 400 (100 MHz) spectrometer and are reported in ppm using solvent as internal standard (CDCl₃=77.0 ppm). Low and high resolution mass spectra were obtained at the Harvard University Mass Spectrometry Laboratory.

(4E)-4-methyl-7-(1,1,2,2-tetramethyl-1-silapropoxy)hept-4-enal (8).

To a solution of TBSCl (24.0 g, 159 mmol) in 100 mL of DMF at 0 °C under argon was added imidazole (17.3 g, 254 mmol) followed by 3-butenol (10.3 g, 143 mmol). The reaction was warmed to rt and stirred for 24 h during which time the product, 1-*tert*-butyldimethylsilyloxy-3-butene (6), formed an immiscible layer on top of the reaction. The top layer was collected and the DMF layer was poured onto 300 mL of water and extracted with 3x100 mL of pentane. The combined organic layers were washed with 1x50 mL 10% aq CuSO₄, 3x100 mL of water, 1x100 mL of brine then dried over Na₂SO₄. Concentration *in vacuo* yielded 24.0 g (90%) of 1-*tert*-butyldimethylsilyloxy-3-butene (7) as a colorless oil that was used without purification.

Into a solution of 1-*tert*-butyldimethylsilyloxy-3-butene (7) (24.0 g, 129 mmol) in 200 mL of CH₂Cl₂ and 50 mL of MeOH at –78 °C was passed a dilute stream of O₃ in O₂ until the reaction achieved a persistent blue color. Triphenylphosphine (33.8 g, 129 mmol) was then added and the reaction was warmed to rt under argon and stirred for 6 h. The mixture was then concentrated *in vacuo* to give a slurry of white precipitate and oil which was resuspended in 300 mL of hexanes and filtered. The filter cake was washed with 3x50 mL of hexanes and the combined filtrates were concentrated *in vacuo*. The resulting oil was distilled (23 torr, 90-95 °C) to give 19.9 g (83%) of pure 3-*tert*-butyldimethylsilyloxy-propanal.

To a solution of isopropenylmagnesium bromide (80 mL, 1.0 M, 80 mmol) at 0 °C under argon was added 3-*tert*-butyldimethylsilyloxy-propanal (8.28 g, 43.9 mmol) dropwise. The reaction was immediately poured onto 100 mL of sat aq NH₄Cl and extracted with 3x100 mL of Et₂O.

The combined organic layers were washed with 1x100 mL of brine then dried over Na₂SO₄. Solvent removal *in vacuo* gave a quantitative return of unpurified (+/-)-5-*tert*-butyldimethylsilyloxy-2-methyl-1-penten-3-ol as a colorless oil. This oil was dissolved in 50 mL of freshly distilled triethylorthoacetate and propionic acid (0.02 mL) was added. The solution was heated at reflux for 1 h then the solvent was directly distilled off the reaction under vacuum (50 torr). The residue was purified by silica gel chromatography (20:1 hexanes / EtOAc) to give 9.86 g (75% 2 steps) of ethyl 7-*tert*-butyldimethylsilyloxy-4-methyl-*trans*-4-heptenoate as a colorless oil. To a solution of ethyl 7-*tert*-butyldimethylsilyloxy-4-methyl-*trans*-4-heptenoate (8.88 g, 29.5 mmol) in 50 mL of CH₂Cl₂ at -78 °C under argon was added DIBAL (29.5 mL, 1.0 M in CH₂Cl₂, 29.5 mmol) dropwise while maintaining the internal temperature at below -65 °C. The reaction was quenched by the addition of 0.1 mL of EtOAc then 50 mL of sat aq Na/K tartrate was added and the slurry was stirred vigorously at rt for 12 h. The resulting clear biphasic was extracted with 3x100 mL of CH₂Cl₂ and the combined organic layers were washed with 1x100 mL of brine then dried over Na₂SO₄. Concentration *in vacuo* yielded a colorless oil that was purified by silica gel chromatography (20:1 pentane / Et₂O) to give 7.37 g (97%) of aldehyde **8** as a colorless pungent oil. **R_f**: 0.25 (9:1 hexanes / Et₂O) **¹H-NMR** (500 MHz, CDCl₃) δ 9.76 (s, 1H), 5.18 (t, 1H, *J*=7.6 Hz), 3.57 (t, 2H, *J*=7.3 Hz), 2.52 (t, 2H, *J*=7.3 Hz), 2.33 (t, 2H, *J*=7.3 Hz), 2.22 (q, 2H, *J*=6.8 Hz), 1.64 (s, 3H), 0.89 (s, 9H), 0.05 (s, 6H) **¹³C-NMR** (100 MHz, CDCl₃) δ 202.38, 134.79, 121.53, 62.75, 42.01, 31.74, 31.66, 25.86, 18.25, 16.15, -5.35 **FTIR** ν 2929, 2858, 1727, 1472, 1255, 1096, 938, 835, 775 **HRMS** (FAB) Calc'd for C₁₄H₂₈O₂Si [M + Na]: 274.2202; found 274.2197

(6E)-1-[(4R)-2-oxo-4-benzyl (1,3-oxazolidin-3-yl)] (3S, 2R)-3-hydroxy-2, 6-dimethyl-9-(1,1,2,2-tetra-methyl-1-silaproxy) non-6-en-1-one (13). To a solution of (*R*)-4-benzyl-N-propionyl-2-oxazolidinone (**12**) (5.74 g, 24.6 mmol) in 60 mL of CH₂Cl₂ at 0 °C under Ar was added Bu₂BOTf (8.00 mL,

31.7 mmol) followed by TEA (6.0 mL, 43.0 mmol). The reaction was cooled to -78 °C and aldehyde **8** (7.35 g, 28.6 mmol) was added in one portion. The reaction was stirred for 30 minutes, warmed to 0 °C, and stirred for 2 h. The reaction was quenched by the addition of 40 mL of pH=7 phosphate buffer followed by addition of 60 mL of MeOH. To the resulting slurry was then added slowly 60 mL of a 2:1 v/v mixture of MeOH / 30% aq H₂O₂ and the mixture was stirred vigorously for 1 h. The reaction was then extracted with 3x100 mL of Et₂O and the combined organic layers were washed with 1x100 mL of water, 1x50 mL of sat aq NaHCO₃, 1x100 mL of brine, and dried over MgSO₄. Evaporation *in vacuo* yielded an oil that was purified by silica gel chromatography (gradient 4:1–2:1 hexanes/EtOAc) to give 10.52 g (88%) of **13** as a colorless oil. **R_f**: 0.5 (2:1 hexanes / EtOAc) [α]_D²⁵ = -45.8° (c=0.60, CH₂Cl₂) **¹H-NMR** (500 MHz, CDCl₃) δ 7.4-7.3 (m, 3H), 7.20 (d, 2H, *J*=7.3 Hz), 5.17 (t, 1H, *J*=7.3 Hz), 4.71 (m, 1H), 4.22 (m, 2H), 3.93 (m, 1H), 3.76 (qd, 1H, *J*=6.8, 2.9 Hz), 3.57 (t, 2H, *J*=7.4 Hz), 3.24 (dd, 1H, *J*=13.7, 3.3 Hz), 2.86 (bm, 1H), 2.76 (dd, 1H, *J*=13.7, 9.3 Hz), 2.25-2.15 (m, 3H), 2.05 (m, 1H), 1.63 (m, 1H), 1.62 (s, 3H), 1.53 (m, 1H), 1.26 (d, 3H, *J*=6.8 Hz), 0.89 (s, 9H), 0.05 (s, 6H) **¹³C-NMR** (100 MHz, CDCl₃) δ 177.38, 152.97, 136.55, 134.97, 129.39, 128.94, 127.40, 120.83, 71.14, 66.11, 62.99, 55.06, 42.15, 37.73, 36.04, 31.96, 31.79, 25.93, 18.34, 16.10, 10.53, -5.27 **FTIR** (film) ν 3500, 2930, 1782, 1698, 1455, 1385, 1211, 1098, 836, 764, 702 **HRMS** (ES) Calc'd for C₂₇H₄₃NO₅Si [M+H]: 490.2989; found 490.2982

(6E) (3S,2R)-9-hydroxy-N-methoxy-2,6-dimethyl-N-methyl-3-(1,1,2,2-tetramethyl-1-silapropoxy) non-6-enamide (15). To a suspension of MeNHOMe hydrochloride (2.19 g, 22.5 mmol) in 25 mL of THF at 0 °C under Ar was added neat Me₃Al (2.20 mL, 22.9 mmol) dropwise. Gas evolution was noted. The solution was cooled to -78 °C and a solution of **13** (3.60 g, 7.35 mmol) in 15 mL of THF was added *via* cannula. The reaction was then warmed to 0 °C, stirred for 1 h, then poured onto sat aq 200 mL NH₄Cl, acidified with 200 mL 1N HCl and extracted with 3 x 100 mL Et₂O. The combined organic layers were washed with 1 x 100 mL 1N HCl, 1x50 mL of sat aq NaHCO₃, 1x100 mL of brine then dried over Na₂SO₄. Solvent removal *in vacuo* gave a colorless oil that was triturated by slow addition of 20 mL of 10:1 hexanes/Et₂O and gentle agitation until the formation of copious white solid appeared to cease. The slurry was then filtered and the filter cake was washed with 3x100 mL of hexanes. The combined filtrates were evaporated *in vacuo* to yield 2.66 g pure Weinreb amide (96%) as a colorless oil. Instead of trituration smaller runs were purified by silica gel chromatography (gradient 5:2–3:2 hexanes/EtOAc). To a solution of Weinreb amide (2.66 g, 7.11 mmol), and imidazole (2.91 g, 42.7 mmol) in 10 mL of DMF was added TBSCl (2.42 g, 16.1 mmol) and the reaction was stirred under Ar for 24 h. The reaction was then poured onto 500 mL of water and extracted with 3x100 mL of Et₂O. The combined organic extracts were washed with 1x50 mL of 10% of aq CuSO₄, 3x100 mL of water, 1x100 mL of brine then dried over Na₂SO₄. Evaporation *in vacuo* gave 3.33 g (96%) of the silylated product as a colorless oil. To a solution of the bis(silylated) product (1.50g, 3.07 mmol) in 30 mL of MeOH at 0 °C under argon was added tetrabutylammonium hydrogensulfate (0.117 g, 0.345 mmol) followed by *p*-toluenesulfonic acid (0.025g, 0.13 mmol). The reaction was stirred for 1 h then 10 mL of sat aq NaHCO₃ was added and the mixture was poured onto 100 mL of water. The aqueous mixture was extracted with 3x50 mL of Et₂O and the combined organic layers were washed with 1x50 mL of water, 1x50 mL of brine and dried over MgSO₄. Evaporation *in vacuo* gave a colorless oil that was purified by silica gel chromatography (gradient 1:1 – 0:1 hexanes / Et₂O) to give 1.025 g (89%) of alcohol **15** as a colorless oil. **R_f**: 0.33 (1:1 hexanes / EtOAc) [α]_D²⁵ = +2.5° (c=1.34, CH₂Cl₂) **¹H-NMR** (500 MHz, CDCl₃) δ 5.12 (t, 1H, *J*=7.4 Hz), 3.93 (ddd, 1H, *J*= 7.8, 4.9, 4.9), 3.69 (s, 3H), 3.61 (m, 2H), 3.17 (s, 3H), 3.00 (bm, 1H), 2.26 (q, 2H, *J*=6.7 Hz), 2.06 (t, 2H, *J*=8.3 Hz), 1.61 (s, 3H), 1.6-1.5 (m, 2H), 1.15 (d, 3H, *J*=6.8 Hz), 0.91 (s, 9H), 0.07 (s, 6H) **¹³C-NMR** (100 MHz, CDCl₃) δ 138.99, 119.67, 73.31, 62.44, 61.47, 40.53, 34.37, 34.32, 31.51, 25.94, 18.14, 16.30, 14.86, -4.10, -4.39 **FTIR** (film) ν 3448, 2933, 2857, 1661, 1462, 1382, 1255, 1046, 995, 835, 774, 668 **HRMS** (ES) Calc'd for C₁₉H₃₉NO₄Si [M+H]⁺: 374.2726; found 374.2719

(3S,2R) (9Z,6E)-10,10-dibromo-N-methoxy-2,6-dimethyl-N-methyl-3-(1,1,2,2-tetramethyl-1-silapropoxy) deca-6,9-dienamide (17) To a solution of alcohol **15** (1.49 g, 3.98 mmol) in 30 mL of CH₂Cl₂ at 0 °C under argon was added NaHCO₃ (0.503 g) followed by Dess-Martin periodinane (2.32g, 5.47 mmol). The reaction was stirred vigorously for 3 h then poured onto water and extracted with 3x50 mL of Et₂O. The combined organic layers were washed with 2x50 mL of sat aq NaHCO₃ then dried over Na₂SO₄. Evaporation *in vacuo* yielded 1.39 g of the unstable aldehyde product as a colorless resin. To a solution of CBr₄ (2.94 g, 8.86 mmol) in 20 mL of CH₂Cl₂ at 0 °C under argon was added PPh₃ (4.65 g, 17.7 mmol) portionwise over 10 min. The resulting orange/red solution was stirred for 30 min, cooled to -78 °C, and the aldehyde (1.15 g, 3.09 mmol) was added *via* cannula as a solution in 7 mL of CH₂Cl₂. The reaction was warmed to

0 °C and stirred for 30 min, then it was poured directly onto a silica gel column. Chromatography (gradient 6:1–4:1 hexanes / EtOAc) gave 1.20 g (74%) of the desired dibromide

17. **R_f:** 0.74 (1:1 hexanes / EtOAc) $[\alpha]_D^{25} = +5.3^\circ$ ($c=1.4$, CH₂Cl₂) **¹H-NMR** (500 MHz, CDCl₃) δ 6.33 (t, 1H, $J=6.8$ Hz), 5.09 (t, 1H, $J=7.3$ Hz), 3.93 (dt, 1H, $J=7.8, 4.8$ Hz), 3.69 (s, 3H), 3.18 (s, 3H), 3.00 (bm, 1H), 2.76 (t, 2H, $J=7.3$ Hz), 2.04 (t, 2H, $J=8.3$ Hz), 1.60 (s, 3H), 1.6–1.5 (m, 2H), 1.15 (d, 3H, $J=6.9$ Hz), 0.91 (s, 9H), 0.07 (s, 6H) **¹³C-NMR** (100 MHz, CDCl₃) δ 138.37, 137.36, 118.30, 88.52, 73.37, 61.48, 40.43, 34.15, 34.06, 32.09, 25.94, 18.14, 16.33, 14.85, -4.12, -4.43 **FTIR** (film) 2932, 2856, 1660, 1461, 1383, 1253, 1174, 1105, 1059, 997, 835, 774 **HRMS** (ES) Calc'd for C₂₀H₃₇Br₂NO₃Si [M+H]: 526.0987; found 526.0988

(2E)-4-(2,2-dimethyl-1,1-diphenyl-1-silaprop-oxy)but-2-enal (11). To a solution of *cis*-2-butene-1,4-diol (**9**) (9.48g, 107 mmol) in 300 mL of THF at 0 °C under argon was added *n*-BuLi (41.0 mL, 2.60 M, 107 mmol)

dropwise. The resulting thick milky suspension was stirred vigorously while TBDPSCl (26.2 mL, 101 mmol) was added dropwise. After 1.5 h, the reaction was quenched with pH-7 buffer and extracted with 3x300 mL of Et₂O. The combined organic layers were washed with 1x200 mL of brine then dried over Na₂SO₄. Evaporation *in vacuo* yielded 33.1 g (94%) of 1-*tert*-butyldiphenylsilyloxy-*cis*-2-butene-4-ol (**10**) as a colorless oil that was used without purification.

To a solution of 1-*tert*-butyldiphenylsilyloxy-*cis*-2-butene-4-ol (**10**) (10.2 g, 31.2 mmol), Et₃N (18.0 mL, 129 mmol), and DMSO (20 mL) in 200 mL of CH₂Cl₂ at 0 °C was added SO₃-pyridine complex (9.75 g, 61.3 mmol). The reaction was warmed to rt, stirred for 2 h then poured onto 200 mL of water and extracted with 3x200 mL of Et₂O. The combined organic layers were washed with 1 x 100 mL of sat aq NH₄Cl, 1x50 mL of 10% aq CuSO₄, 3x100 mL of water, 1x100 mL of brine then dried over Na₂SO₄. Concentration *in vacuo* gave an orange oil. **¹H-NMR** analysis of the unpurified mixture showed a 2:1 mixture of the isomeric *cis* and *trans* aldehydes. The orange oil was allowed to stand at RT under HIVAC (<1 torr) for 24 h whereupon complete isomerization to the *trans* aldehyde was observed by TLC. The oil was then subjected to silica gel chromatography (20:1 hexanes / EtOAc) to give 6.35 g (63%) of aldehyde **18** as a colorless solid. **R_f:** 0.35 (4:1 hexanes/ EtOAc) **¹H-NMR** (500 MHz, CDCl₃) δ 9.61 (d, 1H, $J=8.3$ Hz), 7.66 (d, 2H, $J=5.8$ Hz), 7.4 (m, 3H), 6.84 (dt, 1H, $J=15.1, 1.0$ Hz), 6.57 (dd, 1H, $J=15.1, 8.3$ Hz), 4.45 (d, 2H, $J=1.0$ Hz), 1.08 (s, 9H) **¹³C-NMR** (100 MHz, CDCl₃) δ 193.38, 155.94, 135.37, 132.66, 130.52, 129.94, 127.83, 62.91, 26.67, 19.18 **FTIR** (film) ν 3071, 2931, 2857, 1688, 1472, 1427, 1362, 1113, 965, 823, 741, 702 **HRMS** (FAB) Calc'd for C₂₀H₂₄O₂Si [M + Na]: 342.1890; found 342.1890

(4E)-1-[(4R)-2-oxo-4-benzyl (1,3-oxazolidin-3-yl)] (3S, 2R)-6-(2,2-dimethyl-1,1-diphenyl-1-silapropoxy)-3-hydroxy-2-methylhex-4-en-1-one (18). To a solution of (*R*)-4-benzyl-N-propionyl-2-oxazolidinone (**12**) (3.81 g, 16.3 mmol) in 70 mL of CH₂Cl₂ at 0 °C under Ar was added Bu₂BOTf (5.00 mL, 19.8

mmol) followed by TEA (3.50 mL, 25.1 mmol). The reaction was cooled to -78 °C and *trans*-4-*tert*-butyldiphenylsilyloxy-2-butenal (**11**) (6.00 g, 18.5 mmol) was added in one portion. The reaction was stirred for 30 min then warmed to 0 °C and stirred for 2 h. The reaction was quenched by the addition of 40 mL of pH-7 phosphate buffer followed by addition of 60 mL of MeOH. To the resulting slurry was then added slowly 60 mL of a 2:1 v/v mixture of MeOH / 30% aq H₂O₂ and the mixture was stirred vigorously for 1 h. The reaction was then extracted with 3x100 mL of Et₂O and the combined organic layers were washed with 1x100 mL of water,

1x sat aq NaHCO₃, 1x100 mL of brine, and dried over MgSO₄. Evaporation *in vacuo* yielded an oil that was purified by silica gel chromatography (gradient 4:1 – 2:1 hexanes/EtOAc) to give 8.14 g (89%) of **18** as a colorless oil. **R_f**: 0.62 (1:1 hexanes / EtOAc). $[\alpha]_D^{25} = -45.9^\circ$ (c=1.0, CH₂Cl₂) **¹H-NMR** (500 MHz, CDCl₃) δ 7.68 (d, 2H, *J*= Hz), 7.44-7.28 (m, 6H), 7.22 (d, 2H, *J*= 7 Hz), 5.87 (m, 1H), 5.79 (dd, 1H, *J*= 15, 4.8 Hz), 4.68 (m, 1H), 4.53 (bs, 1H), 4.23 (bs, 2H), 4.17 (d, 2H, *J*=4.8 Hz), 3.85 (m, 1H), 3.24 (d, 1H, *J*= 13.5 Hz), 2.79 (dd, 2H, *J*= 13.5, 9.2 Hz), 1.25 (d, 3H, *J*=7.0 Hz), 1.06 (s, 9H) **¹³C-NMR** (100 MHz, CDCl₃) δ 176.66, 153.04, 135.49, 135.00, 133.59, 133.55, 131.18, 129.65, 129.41, 128.96, 128.69, 127.66, 127.42, 71.99, 66.16, 63.70, 55.15, 42.77, 37.76, 26.79, 19.21, 11.07 **FTIR** (film) ν 3500, 2931, 1781, 1698, 1428, 1388, 1210, 1112, 822, 702 **HRMS** (CI) Calc'd for C₃₃H₃₉NO₅Si [M +NH₄]: 575.2941; found 575.2932

(6E) (3S, 5S, 4R)-8-(2, 2-dimethyl-1, 1-diphenyl-1-silapropoxy)-4-methyloct-6-en-1-yne-3, 5-diol (21). To a suspension of MeNHOMe hydrochloride (1.55 g, 15.9 mmol) in 20 mL of THF at 0 °C under argon was added neat Me₃Al (1.50 mL, 15.6

mmol) dropwise. Gas evolution was noted. The solution was cooled to -78 °C and a solution of **18** (3.01 g, 5.39 mmol) in 10 mL of THF was added *via* cannula. The reaction was then warmed to 0 °C, stirred for 1 h, then poured onto 200 mL of sat aq NH₄Cl, acidified with 200 mL of 1N HCl and extracted with 3x100 mL of Et₂O. The combined organic layers were washed with 1 x 100 mL of 1N HCl, 1x50 mL of sat aq NaHCO₃, 1x100 mL of brine then dried over MgSO₄. Solvent removal *in vacuo* gave a colorless oil that was triturated by slow addition of 20 mL of 10:1 hexanes/Et₂O and gentle agitation until the formation of copious white solid appeared to cease. The slurry was then filtered and the filter cake was washed with 3x100 mL of hexanes. The combined filtrates were evaporated *in vacuo* to yield 2.28 g of pure Weinreb amide (97%) as a colorless oil. Instead of trituration smaller runs were purified by silica gel chromatography (gradient 5:2 – 3:2 hexanes/EtOAc). To a solution of Weinreb amide (1.42 g, 3.21 mmol) in 5 mL of THF at 0 °C under argon was added ethynylmagnesium bromide (25 mL, 0.5 M, 12.5 mmol). The reaction was stirred 3 h then poured onto 50 mL of sat aq NH₄Cl and extracted with 3x50 mL of Et₂O. The combined organic layers were washed with 1x50 mL of brine and dried over Na₂SO₄. Evaporation *in vacuo* yielded a yellow oil that was purified by silica gel chromatography (4:1 hexanes / EtOAc) to give 1.00 g (77%) of the desired ynone as a slightly yellow oil. To a solution of ynone (0.893 g, 2.20 mmol) in 15 mL of THF at -78 °C under argon was added DIBAL (4.40 mL, 1 M in CH₂Cl₂, 4.40 mmol) dropwise. After 30 min the reaction was quenched by the addition of 0.1 mL of EtOAc and 15 mL of sat aq Na/K tartrate and the slurry was warmed to rt with vigorous stirring for 12 h. The resulting clear biphasic was extracted with 3x30 mL of Et₂O and the combined organic layers were washed with 1x30 mL of brine then dried over Na₂SO₄. Evaporation *in vacuo* gave a pale yellow oil that was purified by silica gel chromatography (2:1 hexanes / EtOAc) to give 0.880 g (98%) of diol **21**. **R_f**: 0.4 (2:1 hexanes / EtOAc) $[\alpha]_D^{25} = -5.2^\circ$ (c=1.5, CH₂Cl₂) **¹H-NMR** (500 MHz, CDCl₃) δ 7.69 (d, 2H, *J*=7.0 Hz), 7.5-7.35 (m, 3H), 5.89-5.79 (m, 2H), 4.62 (s, 1H), 4.49 (s, 1H), 4.25 (m, 2H), 2.60 (bs, 1H), 2.53 (s, 1H), 2.15 (bs, 1H), 1.88 (m, 1H), 1.10 (d, 3H, *J*=6.5 Hz), 1.08 (s, 9H) **¹³C-NMR** (100 MHz, CDCl₃) δ 135.49, 133.56, 130.48, 130.44, 129.68, 127.66, 83.70, 74.67, 73.79, 65.98, 63.66, 60.41, 43.68, 26.78, 21.04, 19.20, 14.16, 7.46 **FTIR** (film) ν 3288, 2933, 2856, 1466, 1427, 1379, 1256, 1112, 968, 823, 742, 702 **HRMS** (FAB) Calc'd for C₂₅H₃₂O₃Si [M+Na]: 431.2019; found 431.2010

(3*S*, 15*S*, 2*R*, 13*R*, 14*R*) (9*Z*, 6*E*, 11*E*, 16*E*)-18-(2,2-dimethyl-1, 1-diphenyl-1-silapropoxy)-10-bromo-*N*-methoxy-2, 6, 14-trimethyl-*N*-methyl-3, 13, 15-tris (1,1,2,2-tetramethyl-1-silapropoxy)octadeca-6,9,11,16-tetraenamide (**26**). To a solution of diol **21** (0.810 g, 1.98 mmol) and imidazole (0.572 g, 8.40 mmol) in 6 mL of DMF at rt under argon was added TBSCl (0.719 g, 4.77 mmol). The reaction was stirred 36 h then poured onto 50 mL of water and extracted with 3x50 mL of pentane. The combined organic layers were dried over Na₂SO₄ then concentrated *in vacuo* to afford a colorless oil. Chromatography on silica gel (20:1 hexanes / EtOAc) gave 1.19 g (94%) of the desired bis(silylated) product **22**. To a solution of **22** (0.914 g, 1.43 mmol) in 3 mL of THF at rt under argon was added freshly distilled catecholborane (0.20 mL, 1.9 mmol) followed by freshly prepared dicyclohexylborane (0.70 mL, 0.20 M in THF, 0.14 mmol). After 2 h the reaction was poured into 100 mL of Et₂O and washed with 10x20 mL of 1 *N* NaOH (until aqueous layers were no longer colored), 1x50 mL of brine then dried over MgSO₄. The yellow solution gradually decolorized as the remaining colored contaminants in the organic phase were adsorbed onto the MgSO₄ surface. The solution was filtered and solvent removal *in vacuo* gave 0.952 g (97% unpurified) of the desired boronic acid **23** as a colorless resin that was used immediately.

To a degassed (4x freeze/pump/thaw under N₂) solution of dibromide **17** (1.00 g, 1.89 mmol) and boronic acid **23** (1.67 g, 2.44 mmol) in 30 mL of THF and 10 mL of water was added Pd(PPh₃)₄ (0.187 g, 0.162 mmol) followed by Ti₂CO₃ (1.73 g, 3.70 mmol). A yellow precipitate rapidly formed. After 5 h the reaction was poured onto 100 mL of Et₂O and washed with 1x100 mL of 1 M NaHSO₄ (gas evolution!). The resulting precipitate was removed by filtration through Celite and the aqueous layer was discarded. The remaining organic layer was then washed with 2x50 mL of water, 1x50 mL of brine then dried over Na₂SO₄. Evaporation *in vacuo* gave an orange oil. Chromatography on silica gel (gradient 10:1–6:1 hexanes / EtOAc) gave 1.73 g (84%) of the desired coupled product **26** as a slightly yellow oil. *R*_f: 0.34 (9:1 hexanes / EtOAc)

[α]_D²⁵ = +0.66° (c=0.90, CH₂Cl₂) ¹H-NMR (500 MHz, CDCl₃) δ 7.67 (d, 2H, *J*=7.8 Hz), 7.42–7.35 (m, 3H), 6.15–6.00 (m, 2H), 5.80 (t, 1H, *J*=6.7 Hz), 5.75 (dd, 1H, *J*=15.7, 7.4 Hz), 5.68 (dt, 1H, *J*=15.7, 4.8 Hz), 5.15 (t, 1H, 6.8 Hz), 4.22 (t, 1H, *J*=5.4 Hz), 4.18 (d, 2H, *J*=4.4 Hz), 4.12 (t, 1H, *J*=6.3), 3.93 (dt, 1H, *J*=8.8, 4.4 Hz), 3.68 (s, 3H), 3.17 (s, 3H), 2.97 (bm, 1H + t, 2H, *J*=6.8 Hz), 2.05 (t, 2H, *J*=7.3 Hz), 1.60–1.45 (m, 2H + s, 3H), 1.16 (d, 3H, *J*=6.9 Hz), 1.05 (s, 9H), 0.95 (d, 3H, *J*=6.9 Hz), 0.90 (s, 9H), 0.89 (s, 18H), 0.066 (s, 6H), 0.034 (s, 3H), 0.010 (s, 6H), -0.016 (s, 3H) ¹³C-NMR (100 MHz, CDCl₃) δ 137.43, 136.61, 135.48, 133.69, 132.74, 132.19, 129.74, 129.60, 129.07, 127.64, 124.50, 119.88, 73.85, 73.37, 73.34, 63.87, 61.44, 47.51, 40.40, 34.21, 34.10, 31.57, 30.77, 26.77, 25.93, 25.63, 22.64, 19.21, 18.21, 18.19, 18.13, 16.33, 14.78, 14.13, 9.72, -3.65, -3.73, -4.13, -4.45, -4.75 FTIR (film) ν 2930, 2857, 1712, 1633, 1471, 1254, 1112, 836, 776, 702

Ethyl (5*S*,17*S*,4*R*,15*R*,16*R*) (11*Z*,8*E*,13*E*,18*E*)-12-bromo-20-hydroxy-4, 8, 16-trimethyl-3-oxo-5, 15, 17-tris (1, 1, 2, 2-tetramethyl-1-silapropoxy) icosanoate (**29**). To a solution of amide **26** (1.14 g, 1.05 mmol) in 10 mL of THF at -78 °C under argon was added DIBAL (0.22 mL, 1.23 mmol) dropwise. The reaction was stirred for 3 h then quenched by the addition of 0.5 mL of EtOAc followed by 10 mL of sat aq Na/K

tartrate. The resulting slurry was warmed to rt, stirred vigorously for 12 h, then extracted with 3x50 mL of Et₂O. The combined organic layers were washed with 1x50 mL of brine and dried over Na₂SO₄. Evaporation *in vacuo* yielded a colorless oil that was immediately redissolved in 8 mL of CH₂Cl₂ at rt under argon. In a separate flask, SnCl₂ (0.230 g, 0.880 mmol) was suspended in 2 mL of CH₂Cl₂ at rt and EDA (1.25 g, 8.00 mmol) was added (gas evolution!). To this opaque yellow mixture was then added the aldehyde solution and the reaction was stirred vigorously for 2 h. The reaction was then poured onto 50 mL of brine and extracted with 3x50 mL of Et₂O. The combined organic layers were dried over Na₂SO₄ and solvent removal *in vacuo* gave a yellow oil. The oil was placed under HIVAC (<1 torr) for 24 h to remove the bulk of residual EDA then chromatographed on silica gel (gradient 50:1–20:1 hexanes / EtOAc) to afford 0.818 g (70%) of β -keto ester **28** as a colorless oil.

To a stirring solution of TBAF trihydrate (0.0569 g, 0.181 mmol) and AcOH (0.0109 g, 0.182 mmol) in 1 mL of DMF in a plastic vial was added the β -keto-ester **28** (0.145 g, 0.130 mmol) as a solution in 1 mL of DMF. After 3 h the reaction was poured onto 20 mL of water and extracted with 3 x 20 mL of Et₂O. The combined organic layers were washed with 1 x 30 mL of water, 1 x 30 mL of sat aq NaHCO₃, 1 x 30 mL of brine then dried over Na₂SO₄. Evaporation *in vacuo* yielded a yellow oil that was purified by silica gel chromatography (6:1 hexanes / EtOAc) to give 0.105g (92%) of the desired alcohol **29** as a colorless oil. **R_f**: 0.39 (4:1 hexanes / EtOAc)

$[\alpha]_D^{25} = -15.8^\circ$ (c=1.1, CH₂Cl₂) **¹H-NMR** (500 MHz, CDCl₃, 1:1 keto/enol) δ 12.14 (s, 0.5H, enol-OH), 6.09 (d, 1H, *J*=14.6 Hz), 6.03 (dd, 1H, *J*=14.6, 6.3 Hz), 5.83 (t, 1H, *J*=6.9 Hz), 5.72 (m, 2H), 5.16 (bm, 1H), 5.01 (s, 0.5H, enol), 4.23 (t, 1H, *J*=5.4 Hz), 4.18 (q, 2H, *J*=7.3 Hz), 4.16-4.10 (m, 3H), 3.92 (q, 0.5H, *J*=5.8 Hz, keto), 3.84 (dt, 0.5H, *J*=6.8, 4.9 Hz, enol), 3.60 (d, 0.5H, *J*=15.6 Hz, keto), 3.53 (d, 0.5H, *J*=15.6 Hz, keto), 3.00 (t, 2H, *J*=6.8 Hz), 2.84 (m, 0.5H, enol), 2.36 (m, 0.5H, keto), 2.1-2.0 (m, 1.5H, keto + enol), 1.91 (m, 0.5H, enol), 1.64 (s, 3H), 1.6-1.5 (m, 2.5H, keto + enol), 1.41 (m, 0.5H, enol), 1.28 (m, 3H), 1.09 (d, 1.5H, *J*=6.8 Hz, keto), 1.06 (d, 1.5H, *J*=6.9 Hz, enol), 0.94 (d, 3H, *J*=6.8 Hz), 0.89 (s, 18H), 0.87 (s, 9H), 0.077 (s, 3H), 0.073 (s, 3H), 0.030 (s, 3H), 0.021 (s, 3H), -0.006 (s, 3H), -0.011 (s, 3H) **¹³C-NMR** (100 MHz, CDCl₃) δ 205.26, 180.66, 172.80, 167.48, 137.00, 136.54, 136.48, 136.35, 134.76, 134.35, 132.27, 132.03, 129.69, 129.67, 129.59, 129.25, 129.17, 127.67, 124.57, 124.42, 120.42, 120.18, 89.64, 73.78, 73.57, 73.25, 73.21, 72.74, 63.21, 61.16, 59.92, 51.68, 49.45, 47.36, 43.88, 35.69, 34.74, 33.58, 32.32, 30.76, 30.73, 26.53, 25.91, 25.89, 25.84, 18.98, 18.16, 18.08, 18.02, 16.33, 16.31, 14.27, 14.08, 12.20, 11.66, 9.84, -3.61, -3.73, -4.28, -4.41, -4.77 **FTIR** (film) ν 3445, 2954, 2939, 2886, 1747, 1715, 1651, 1472, 1361, 1255, 1225, 1094, 1030, 957, 835, 774, 672 **HRMS** (FAB) Calc'd for C₄₃H₈₁BrO₇Si₃ [M+Na]: 895.4371; found 895.4379

Ethyl (5S, 17S, 6R, 7R, 18R)-10-bromo-6, 14, 18-trimethyl-19-oxo-5, 7, 17-tris (1, 1, 2, 2-tetramethyl-1-silapropoxy) cyclononadeca-3, 8, 10, 13-tetraene carboxylate (31). To a solution of alcohol **29** (0.020 g, 0.0230 mmol) in 1 mL of CH₂Cl₂ at 0 °C under argon was added a pre-mixed solution of PPh₃ (0.0125 g, 0.0477 mmol), imidazole (0.0110 g, 0.162 mmol), and iodine (0.0159 g, 0.0626 mmol) in 1 mL of CH₂Cl₂. After 5 min the reaction was diluted to 10 mL of with hexane (precipitate formed)

and the orange heterogeneous mixture was passed through a short plug of silica. The silica plug was washed with 3x2 mL of 10:1 hexanes / EtOAc and the combined filtrates were concentrated *in vacuo* to give a quantitative yield of allylic iodide **30** as a colorless resin. The iodide was immediately redissolved in 5 mL of THF and Cs₂CO₃ (0.0110 g, 0.034 mmol) was added. After 5 h of vigorous stirring the reaction was quenched with 1 mL of 1 N HCl (gas evolution!),

diluted with 20 mL of EtOAc and washed with 2x20 mL of water, 1x20 mL of sat aq NaHCO₃, 1x20 mL of brine then dried over Na₂SO₄. Solvent removal *in vacuo* afforded a colorless film that was purified by silica gel chromatography (50:1 hexane / EtOAc) to give 0.0151 g (77%) of the desired macrocycle **31** as a 1:1 mixture of diastereomers. A portion of the more polar isomer eluted free of its epimer and was characterized. In practice, the mixture was used in the subsequent step without being separated. **R_f**: 0.65 (20:1 hexanes / EtOAc) $[\alpha]_D^{25} = -120.5^\circ$ (c=0.66, CH₂Cl₂) **¹H-NMR** (500 MHz, CDCl₃) δ 5.92 (m, 2H), 5.80 (t, 1H, *J*=7.4 Hz), 5.53 (dd, 1H, *J*=15.1, 6.8 Hz), 5.24 (t, 1H, *J*=7.4 Hz), 5.09 (dt, 1H, *J*=15.1, 7.3 Hz), 4.17 (q, 2H, *J*=6.8 Hz), 3.91 (dd, 1H, *J*=8.3, 6.3 Hz), 3.85 (m, 1H), 3.76 (m, 1H), 3.71 (t, 1H, *J*=7.2 Hz), 2.94 (t, 2H, *J*=7.8 Hz), 2.92 (m, 1H), 2.50 (t, 2H, *J*=6.9 Hz), 2.09 (m, 1H), 1.94 (m, 1H), 1.67 (s, 3H), 1.64 (m, 2H), 1.25 (m, 3H), 1.03 (d, 3H, *J*=7.3 Hz), 1.01 (d, 3H, *J*=7.3 Hz), 0.89 (s, 9H), 0.88 (s, 9H), 0.87 (s, 9H), 0.04 (s, 3H), 0.016 (s, 3H), 0.014 (s, 3H), 0.003 (s, 6H), -0.007 (s, 3H) **¹³C-NMR** (100 MHz, CDCl₃) δ 205.62, 169.14, 136.45, 135.36, 132.85, 130.87, 130.12, 127.86, 123.80, 120.94, 75.92, 75.20, 72.73, 70.01, 61.35, 58.36, 50.69, 47.31, 36.04, 33.58, 29.99, 25.91, 25.87, 25.84, 18.23, 18.20, 18.05, 15.92, 14.13, 13.57, 11.95, -3.83, -4.01, -4.27, -4.72, -5.01 **FTIR** (film) ν 2929, 2856, 1738, 1715, 1471, 1364, 1255, 1112, 1057, 835, 774 **HRMS** (FAB) Calc'd for C₄₃H₇₉BrO₆Si₃ [M+Na]: 877.4266; found 877.4273

Ethyl (1S, 10S, 17S, 8R, 9R, 16R)-5-bromo-1, 9, 16-trimethyl-20-oxa-8, 10, 17-tris (1, 1, 2, 2-tetramethyl-1-silapropoxy) pentacyclo-[13.4.1.0<2,13>.0<4,12>.0<7,11>]icosa-5,14-diene-14-carboxylate (34**).**

To a suspension of Ph₂Se₂O₃ (0.0492 g, 0.137 mmol) and SO₃-pyridine complex (0.0229 g, 0.144 mmol) in 1 mL of THF at rt under argon was added Et₃N (0.050 mL, 0.36 mmol) and the mixture was stirred vigorously for 15 min to form an “oxidant solution.” To a solution of macrocycle **31** (0.0580 g, 0.0677 mmol) in 1 mL of THF at rt under argon was added Et₃N (0.050 mL, 0.36 mmol) followed by the oxidant solution and the reaction was stirred for 2 h. Hexane (10 mL) was then added (a precipitate formed). The resulting opaque mixture was filtered through a short plug of silica and the bright yellow filtrate was heated to 50 °C for 6 h. Concentration *in vacuo* gave a yellow oil that was purified by silica gel chromatography (4:1 hexane / benzene) to give 0.036 g (63%) of the desired Diels-Alder adduct

34 as a colorless film. **R_f**: 0.69 (20:1 hexanes/ EtOAc) $[\alpha]_D^{25} = -44.4^\circ$ (c=0.15, CH₂Cl₂) **¹H-NMR** (500 MHz, CDCl₃) δ 5.89 (s, 1H), 4.23 (m, 1H), 4.02 (m, 1H), 3.70 (m, 1H), 3.67 (q, 1H, *J*=6.8 Hz), 3.63 (d, 1H, *J*=3.4 Hz), 3.59 (bs, 1H), 2.78 (q, 1H, *J*=5.9 Hz), 2.46 (m, 1H), 2.38 (m, 1H), 2.22 (td, 1H, *J*=12.2, 7.8 Hz), 2.1-2.0 (m, 3H), 1.85 (m, 1H), 1.73 (m, 2H), 1.54 (s, 3H), 1.46 (m, 1H), 1.28 (t, 3H, *J*=7.3 Hz), 1.24 (s, 3H), 1.07 (d, 3H, *J*=7.3 Hz), 1.01 (d, 3H, *J*=7.8 Hz), 0.88 (s, 9H), 0.86 (s, 9H), 0.84 (s, 9H), 0.14 (s, 3H), 0.10 (s, 3H), 0.04 (s, 6H), -0.005 (s, 6H) **¹³C-NMR** (100 MHz, CDCl₃) δ 168.21, 165.79, 128.40, 127.72, 117.95, 82.55, 79.47, 78.60, 73.78, 59.49, 53.06, 50.71, 48.65, 47.86, 46.21, 46.08, 42.73, 42.65, 34.06, 27.92, 27.82, 25.98, 25.88, 25.80, 25.69, 23.99, 19.01, 18.11, 17.93, 17.69, 14.55, 13.17, -3.44, -4.35, -4.43, -4.86, -4.95, -5.18 **FTIR** (film) ν 2928, 2854, 1698, 1627, 1465, 1359, 1258, 1055, 836, 767 **HRMS** (FAB) Calc'd for C₄₃H₇₇BrO₆Si₃ [M+H]: 853.4289; found 853.4296.

IMDA cycloadducts (36a + 37a) A solution of α,β -unsaturated aldehyde **44a** (0.01 g) in 0.75 mL of CDCl_3 in a standard NMR tube was heated at 60 °C until complete conversion of **35a** to two new species was observed by $^1\text{H-NMR}$ (3h). The ratio of the two new species was determined to be **37a**:**36a** = 37:63 by integration of the C10 methine signals in the $^1\text{H-NMR}$ spectrum of the mixture. Purification by silica gel chromatography (8:1 hexanes/EtOAc) gave 0.003g (30%) of **36a** and 0.005g (50%) of **37a**. **36a**: $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ 9.66 (d, 1H, $J=5.4$ Hz),

6.03 (s, 1H), 5.02 (t, 1H, $J=6.3$ Hz), 3.93 (m, 1H), 3.68 (s, 3H), 3.67 (m, 1H), 3.37 (dd, 1H, $J=8.8, 3.9$ Hz), 3.18 (s, 3H), 2.98 (bm, 1H), 2.88 (td, 1H, $J=9.9, 8.8$ Hz), 2.76 (m, 1H), 2.55 (m, 2H), 2.00 (m, 2H), 1.82 (m, 1H), 1.61 (s, 3H), 1.5-1.6 (m, 2H), 1.14 (d, 3H, $J=6.8$ Hz), 1.03 (d, 3H, $J=7.4$ Hz), 0.90 (s, 18H), 0.85 (s, 9H), 0.068 (s, 3H), 0.062 (s, 3H), 0.058 (s, 3H), 0.045 (s, 3H), 0.036 (s, 3H), -0.031 (s, 3H). **37a**: $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ 9.63 (s, 1H), 6.22 (s, 1H), 4.97 (t, 1H, $J=7.4$ Hz), 4.04 (d, 1H, 3.4 Hz), 3.92 (m, 1H), 3.69 (s, 3H), 3.24 (dd, 1H, $J=9.8, 4.9$ Hz), 3.18 (s, 3H), 3.02 (m, 3H), 2.64 (dd, 1H, $J=12.2, 10.3$ Hz), 2.4 (bd, 1H, $J=11.9$ Hz), 2.13 (m, 1H), 1.98 (t, 2H, $J=8.8$ Hz), 1.7-1.8 (m, 2H), 1.5 (s, 3H), 1.14 (d, 3H, $J=6.8$ Hz), 1.07 (d, 3H, $J=7.4$ Hz), 0.90 (s, 9H), 0.88 (s, 9H), 0.81 (s, 9H), 0.068 (s, 3H), 0.063 (s, 6H), 0.053 (s, 3H), 0.018 (s, 3H), -0.084 (s, 3H) **Stereochemistry**: The relative stereochemical assignments of IMDA products **36a** and **37a** were determined using NOESY analysis and the diagnostic NOE's are shown in Figure 1 below.

Figure 1. Diagnostic NOE cross peaks observed in NOESY analyses of **36a** and **37a**.

Ethyl (1 S, 9 S, 10 S, 17 S, 8 R, 16 R)-8, 10, 17-trihydroxy-1, 5, 9, 16-tetramethyl-20-oxapentacyclo [13.4.1.0 <2,13>.0 <4,12>.0 <7,11>] icos-5, 14-diene-14-carboxylate (39) Diels-Alder adduct **34** (0.036 g, 0.042 mmol) was dissolved in $\text{HF-CH}_3\text{CN}$ (95:5:1 CH_3CN /48% aq HF /water, 10 mL) in a plastic vial at rt under argon. After 4 h the reaction was poured onto 50 mL of sat aq NaHCO_3 (gas evolution!) and extracted with 3x20 mL of EtOAc. The combined organic layers were washed with 1x20 mL of brine and dried over Na_2SO_4 . Evaporation *in vacuo* yielded a colorless oil that was purified by silica gel chromatography (100% EtOAc)

to give the desire product as an oil. Azeotropic removal of residual EtOAc with hexane (3 x 10 mL) gave 0.0186 g (89%) of **38** as a colorless amorphous solid. R_f : 0.29 (100% EtOAc) $[\alpha]_D^{25} = -0.66^\circ$ ($c=0.75$, CH_2Cl_2) To a portion of the desilylated product **38** (0.010 g, 0.019 mmol) in 1.0 mL of DMF was added $\text{Pd(dppf)Cl}_2 - \text{CH}_2\text{Cl}_2$ (0.0021g, 0.0026 mmol) followed by a premixed solution of Cs_2CO_3 (0.573 g, 1.75 mmol) and trimethylboroxine (0.048 g, 0.38 mmol) in 0.75 mL

of water. The reaction was heated at 80 °C under argon, stirred vigorously for 2 h, then was then cooled to rt, poured onto 10 mL of water, and extracted with 3x5 mL of Et₂O. The combined ethereal extracts were dried over Na₂SO₄. Evaporation *in vacuo* gave a yellow film that was purified by silica gel chromatography (100% EtOAc) to give 0.0064 g (71%) of the desired methyl adduct **39**. A small amount (~5%) of the saponified Suzuki product (FR182877 seco-acid) could be recovered from the combined aqueous layers after acidification (1 N HCl) and extraction with CH₂Cl₂. **R_f**: 0.34 (100% EtOAc) $[\alpha]_D^{25} = -18.3$ (c=0.13, CH₂Cl₂) **¹H-NMR** (500 MHz, C₆D₆) δ 5.31 (s, 1H), 4.48 (bd, 1H, *J*=4.4 Hz), 4.03 (m, 1H), 3.91-3.83 (m, 3H), 3.52 (s, 2H), 3.48 (d, 1H, *J*=4.8 Hz), 2.55 (m, 1H), 2.21 (m, 1H), 2.15 (dd, 1H, *J*=13.2, 6.9 Hz), 2.06 (ddd, 1H, *J*=12.2, 12.2, 9.3 Hz), 1.91 (m, 3H), 1.78 (m, 1H), 1.61 (s, 3H), 1.55 (dd, 1H, *J*=13.7, 13.7), 1.42 (m, 2H), 1.12 (d, 3H, *J*= 7.3 Hz), 1.01 (m, 6H), 0.95 (t, 3H, *J*=7.3 Hz) **¹³C-NMR** (100 MHz, C₆D₆) δ 169.94, 166.64, 139.45, 121.55, 120.71, 84.02, 81.39, 77.33, 72.99, 70.10, 61.03, 53.48, 52.49, 47.11, 46.99, 46.80, 46.09, 44.52, 40.64, 34.55, 30.32, 27.22, 22.66, 18.75, 14.18, 13.69 **FTIR** (film) ν 3394, 2924, 1669, 1558, 1457, 1375, 1328, 1284, 1162, 1085, 1046 **HRMS**(ES) Calc'd for C₂₆H₃₈O₆ [M+H]: 447.2746; found 447.2742

FR182877 (1) To a solution of ethyl ester **39** (0.0030 g, 0.0067 mmol) in 1 mL of THF at rt was added TMSOK (0.0048 g, 0.037 mmol) and the resulting solution was stirred for 12 h. The reaction was then diluted to 5 mL with 0.1 M NaHCO₃ and extracted with 2x2 mL of Et₂O and the organic layers were discarded. The aqueous layer was then acidified by the addition of 5 mL of 1 N HCl and extracted with 3x3 mL of CH₂Cl₂. The combined organic layers were then dried over Na₂SO₄. Evaporation *in vacuo* yielded a quantitative return of the FR182877 seco acid as a colorless amorphous solid. To a suspension of the FR182877 seco acid (0.0010 g, 0.0025 mmol) in 2 mL of CH₂Cl₂ was added powdered NaHCO₃ (0.0491 g) and the mixture was degassed by 3 cycles of “freeze-pump-thaw.” To the reaction was added Mukaiyama’s reagent (0.010g, 0.039 mmol) and the yellow heterogeneous mixture was vigorously stirred for 24 h then transferred directly to a silica gel column and purified by chromatography (100:1 EtOAc/MeOH) to give 0.00061 g (62%) of FR182877 as a white solid.

R_f: 0.26 (100:1 EtOAc/MeOH) $[\alpha]_D^{25} = -5^\circ$ (c=0.15, MeOH) **¹H-NMR** (500 MHz, D₃COD) δ 5.41 (s, 1H), 4.43 (s, 1H), 3.61 d, 1H, *J*=3.9 Hz), 3.46 (m, 2H), 2.77 (m, 1H), 2.65 (t, 1H, *J*=8.3 Hz), 2.44 (m, 1H), 2.28 (dd, 1H, *J*=13.2, 8.3 Hz), 2.04 (dd, 1H, *J*=11.7, 6.9 Hz), 1.85 (bd, 1H, *J*=9.8 Hz), 1.83-1.73 (m, 4H), 1.71 (s, 3H), 1.66 (d, 1H, *J*=3.9 Hz), 1.62-1.55 (m, 2H), 1.40 (s, 3H), 1.12 (d, 3H, *J*=7.4 Hz), 1.10 (d, 3H, *J*=6.9 Hz) **¹³C-NMR** (100 MHz, D₃COD) δ 172.9, 168.7, 140.5, 121.2, 115.9, 88.6, 84.5, 79.3, 78.4, 54.6, 53.1, 52.4, 47.4, 46.9, 46.1, 43.4, 42.5, 36.2, 33.7, 25.2, 24.1, 22.9, 18.6, 9.4 **FTIR** (film) ν 3420, 2925, 1704, 1624, 1457, 1366, 1269, 1212, 1018 **HRMS**(FAB) Calc'd for C₂₄H₃₂O₅ [M + H]: 401.2328; found 401.2329

Figure 2. ^1H -NMR comparison of natural FR182877 (top, 400 MHz; D_3COD) and synthetic FR182877 (bottom, 500 MHz; D_3COD). Additional singlets at 3.3 and 2.0 ppm in the spectrum of natural **1** are not recorded as part of the natural product structure by the authors of the original report.

Table 1. Tabular comparison of ^{13}C -NMR data for natural and synthetic FR182877.

Carbon Number	δ Natural (125 MHz; D_3COD)	δ Synth. (100 MHz; D_3COD)
1	172.9	172.9
2	115.9	115.9
3	43.4	43.4
4	53.2	53.1
5	46.2	46.1
6	84.6	84.5
7	54.6	54.6
7-Me	18.6	18.6
8	78.4	79.3
9	46.9	47.4
10	121.2	121.2
11	140.5	140.5
11-Me	22.7	22.9
12	46.5	46.9
13	33.3	33.7
14	52.5	52.4
15	87.7	88.6
15-Me	23.9	24.1
17	167.7	168.7
18	41.5	42.5
18-Me	9.3	9.4
19	77.8	78.4
20	24.4	25.2
21	36.0	36.2

Molecular Modeling. Tables 2 and 3 tabulate all computational data used for the “Transition State Approach Analysis.” All calculations were performed at the PM3 level of theory using Spartan running on a SGI Indigo². Geometry optimizations were performed under the following dihedral angle constraints: O (ester carbonyl)=C1-C2=C3: 180°; C2=C3-C4=C5: 180°; C9=C10-C11=C12: 0 °C. “d- $\pi/\text{\AA}$ ” indicates the constrained interatomic distances between C5-C9 and C4-C12 during individual geometry optimizations. “Endo-I” indicates the structures were optimized for a *local minimum* corresponding to the π -face alignment leading to the stereochemistry of the ABC ring fusion of **1**. “Endo-II” indicates the structures were optimized for a *local minimum* corresponding to the π -face alignment leading to the opposite *endo* product (Figure 7). Notation of substitution and stereochemistry are as follows: “[18, 19][R, S, N]” where 18 or 19 refer to the substituted carbon number and R or S refer to the absolute configuration of the substitution and N indicates no substitution is present on that carbon. “IMDA” indicates data obtained for the acyclic intramolecular Diels-Alder control substrate (**64**). All data points are in kcal/mol.

Table 2

Endo-I	53	56	57	54	55	60	59	58	61	64
d- $\pi/\text{\AA}$	18N,19N	18R,19N	18S,19N	18N,19R	18N,19S	18R,19R	18R,19S	18S,19R	18S,19S	IMDA
2.1	-101.19	-130.5	-136.55	-103.5	-98.65	-129.76	-124.33	-131.49	-132.83	-41.66
2.3	-106.35	-135.41	-140.85	-108.1	-101.84	-134.94	-129.33	-136.45	-136.38	-46.21
2.5	-117.83	-147.55	-152.23	-119.79	-113.75	-147.38	-141.59	-148.88	-148.77	-55.99
2.7	-125.9	-156.61	-159.89	-128.23	-120.54	-156.8	-150.93	-158.05	-156.2	-63.06
2.9	-130.88	-161.88	-164.09	-133.09	-127.43	-162.29	-154.87	-163.54	-160.27	-67.18

Table 3

Endo-II	53	56	57	54	55	60	59	58	61	64
d- $\pi/\text{\AA}$	18N,19N	18R,19N	18S,19N	18N,19R	18N,19S	18R,19R	18R,19S	18S,19R	18S,19S	IMDA
2.1	-102.33	-136.97	-131.02	-98.82	-104.1	-132.85	-133.46	-124.56	-129.28	-41.83
2.3	-106.52	-141.04	-135.66	-101.79	-108.4	-136.27	-136.8	-131.56	-134.25	-46.51
2.5	-118.22	-152.58	-147.81	-113.82	-120.24	-148.28	-150.13	-139.52	-146.74	-56.22
2.7	-126.59	-160.8	-156.57	-120.02	-128.65	-155.47	-159.07	-150.17	-155.41	-61.99
2.9	-131.38	-165.21	-161.72	-125.47	-133.57	-160.2	-164.25	-157.83	-159.79	-66.72