Total Synthesis of the Immunosuppressant FR901483 via an Amidoacrolein Cycloaddition.

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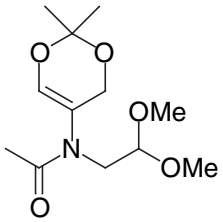
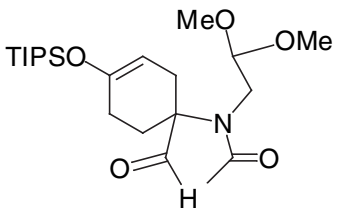
Supporting Information

Characterization data, detailed experimental procedures and copies of ^{1}H and ^{13}C NMR spectra for all new compounds (**1-18**) and X-ray crystallographic data for **15**.

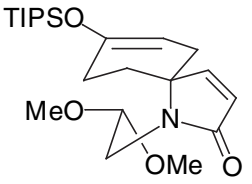


Dioxin 9. To a solution of 2,2-dimethyl-1,3-dioxan-5-one (3.6 g, 27.7 mmol) in benzene (20 mL) were added molecular sieves (4 Å, 5.4 g) and aminoacetaldehyde dimethyl acetal (3.2 g, 30.5 mmol). The mixture was stirred for 1.5 days at rt and cooled to 0 °C. Triethylamine (4.3 mL, 30.5 mmol) followed by acetic anhydride (2.6 mL, 27.7 mmol) were added at 0 °C. The resulting reaction mixture was allowed to warm to rt overnight. The mixture was diluted with Et_2O, washed with brine, dried ($MgSO_4$), and concentrated. The crude material was purified by silica-gel column chromatography (ethyl ether-hexane, 2:1) to give a colorless oil (5.96 g, 83%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.49 (s, 6 H), 2.10 (s, 3 H), 3.37 (s, 6 H), 3.51 (d, J = 5.5 Hz, 2 H), 4.16 (d, J = 1.5 Hz, 2 H), 4.57 (t, J = 5.5 Hz, 1 H), 6.57 (t, J = 1.5 Hz, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.2, 24.0, 49.7, 53.8, 59.5, 98.9, 101.5, 116.6, 142.0, 171.3; IR (neat) 1672 cm^{-1}; HRMS (M^+) calcd for $C_{12}H_{21}O_5N$ 259.1413, found 259.1408.



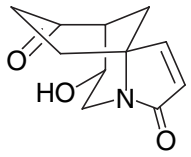
Cycloadduct 5. To a solution of dioxin **9** (10.0 g, 38.6 mmol), 8 crystals of BHT and propylene oxide (5.4 mL, 77.1 mmol) in benzonitrile (16.5 mL) was added 2-(triisopropylsilyloxy)butadiene (**7**, 17.5 g, 77.1 mmol). The resulting solution was heated at 120° C for 16 h. The reaction mixture was cooled to rt, concentrated and purified by silica gel column chromatography (ethyl acetate-hexane, 1:1) to give a colorless oil (10.6 g, 64%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90-1.19 (m, 21 H), 1.99-2.24 (m, 8 H), 2.62 (br dd, *J* = 4.3, 16.5 Hz, 1 H), 3.39 (s, 3 H), 3.40 (s, 3 H), 3.46 (br d, *J* = 5.3 Hz, 2 H), 4.41 (t, *J* = 5.3 Hz, 1 H), 4.80 (t, *J* = 3.5 Hz, 1H), 9.51 (s, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.4, 17.8, 22.3, 26.8, 27.0, 28.6, 48.0, 55.2, 55.4, 63.9, 99.7, 104.8, 150.9, 172.2, 198.2; IR (neat) 1636, 1723 cm^{-1}; HRMS (M^+) calcd for $C_{22}H_{41}NO_5Si$ 427.2742, found 427.2744.

A 2-vinyl-2-silyloxy-5-acylamino-3,4-dihydropyran **i** hetero Diels-Alder adduct was also isolated as a colorless oil (1.97 g, 12%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.91-1.10 (m, 21H), 1.72-1.82 (m, 1H), 1.95-2.05 (m, 2H), 2.00 (s, 3H), 2.20-2.40 (m, 1H), 3.30 (s, 3H), 3.31 (s, 3H), 3.46 (br s, 2H), 4.55 (t, *J* = 5.6 Hz, 1H), 5.17 (dd, *J* = 1.3, 10.7 Hz, 1H), 5.38 (dd, *J* = 1.3, 17.2 Hz), 5.92 (dd, *J* = 10.7, 17.2 Hz, 1H), 6.46 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$), δ 13.0, 18.0, 21.5, 21.6, 33.1, 48.3, 53.4, 53.5, 96.4, 101.4, 115.4, 118.9, 138.7, 142.6, 171.6; IR (neat) 1673 cm^{-1}; HRMS (MH+) calcd for $C_{22}H_{42}NO_5Si$ 428.2832, found 428.2812.

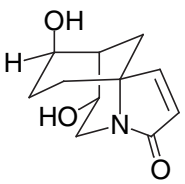


First aldol adduct. To a solution of **5** (12.3 g, 28.8 mmol) in THF (230 mL) and ethyl acetate (28.0 mL, 288 mmol) was added potassium t-butoxide (6.46 g, 57.6 mmol) at 0 °C. The

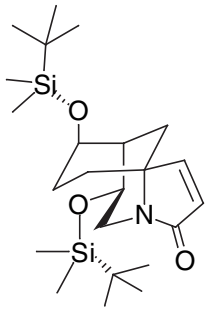
mixture was stirred for 40 min at 0 °C and then quenched with saturated aqueous NH_4Cl, extracted with Et_2O, dried ($MgSO_4$) and concentrated. The colorless oil was of sufficient purity for the next step. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.81-1.18 (m, 21 H), 1.59 (br dd, *J* = 5.0, 17.8 Hz, 1 H), 2.01-2.13 (m, 4 H), 2.55 (br d, *J* = 17.8 Hz, 1 H), 3.18 (d, *J* = 5.3 Hz, 2 H), 3.28 (s, 6 H) 4.62 (t, *J* = 5.3 Hz, 1 H), 4.72 (br d, *J* = 5.0 Hz, 1 H), 6.00 (d, *J* = 6.1 Hz, 1H), 7.22 (d, *J* = 6.1 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.3, 17.8, 28.9, 30.2, 30.4, 42.6, 55.3, 55.5, 66.0, 100.1, 102.5, 125.4, 149.1, 151.7, 170.9; IR (neat) 1696 cm^{-1}; HRMS (M^+) calcd for $C_{22}H_{39}NO_4Si$ 409.2637, found 409.2640.



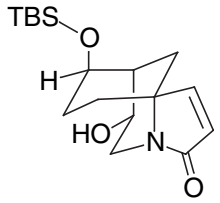
Second aldol adduct 3. To a mixture of trifluoroacetic acid and H_2O (1:1, 124 mL) was added the crude aldol adduct from the previous step (11.8 g, 28.8 mmol) at 0 °C. The reaction mixture was slowly warmed to rt over 4 h. The solvent was distilled off, benzene was added and evaporated. The crude material was purified by column chromatography (methanol-ethyl acetate, 1:9) to give a white solid (4.72g, 79% for two steps): mp 195-197 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.59 (dt, *J* = 2.7, 13.5 Hz, 1 H), 1.79-1.98 (m, 1H), 2.12-2.41 (m, 2 H), 2.58-2.71 (m, 2 H), 2.88 (br s, 1H), 2.94 (dd, *J* = 9.6, 13.4 Hz, 1H), 3.95 (ddd, *J* = 5.0, 7.3, 9.6 Hz, 1 H), 4.58 (dd, *J* = 7.3, 13.4 Hz, 1 H), 6.17 (d, *J* = 7.0 Hz, 1 H), 7.02 (d, *J* = 7.0 Hz, 1 H); ^{13}C NMR (50 MHz, d_6-DMSO) δ 32.0, 34.4, 37.6, 43.1, 51.5, 61.3, 66.7, 125.2, 153.3, 168.2, 208.3; IR (neat) 1659, 1710, 3372 cm^{-1}; HR-MS (M^+) calcd for $C_{11}H_{13}NO_3$ 207.0891, found 207.0901.



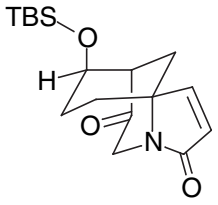
Diol 10. Sodium borohydride (2.0 g, 52.6 mmol) was added to acetic acid (80 mL) at 0 ^{o}C in four portions. The solution was stirred at rt for 5 min. To this solution was added aldol adduct **3** (4.54 g, 21. 9 mmol) in acetic acid (70 mL) at rt. The resulting solution was stirred for 0.5 h and then quenched with H_2O (5 mL). The solvent was distilled off under high vacuum and the crude product was purified by silica gel column chromatography (methanol–ethyl acetate, 1:6.6) to give a white solid (4.21 g, 92%): mp 208-211 ^{o}C; ^{1}H NMR (200 MHz, CD_3OD) δ 0.98 (dt, *J* = 2.3, 12.8 Hz, 1H), 1.31-1.34 (m, 1H), 1.73-1.77 (m, 1H), 1.96-2.07 (m, 2H), 2.22 (br s, 1H), 2.37 (dd, *J* = 4.0, 12.8 Hz,1H), 3.04 (dd, *J* =10.4, 13.3 Hz, 1H), 3.79 (ddd, *J* = 5.3, 7.9, 10.4 Hz, 1H), 4.18 (dd, *J* = 7.9, 13.3 Hz, 2H), 4.20 (br s, 1H), 5.93 (d, *J* = 5.9 Hz, 1H), 7.09 (d, *J* = 5.9 Hz, 1H); ^{13}C NMR (50 MHz, CD_3OD) δ 28.6, 29.7, 31.0, 42.4, 45.3, 64.0, 65.1, 67.9, 125.1, 156.8, 171.8; IR (neat) 1660, 3378 cm^{-1}; HRMS (MNa^+) calcd for $C_{11}H_{15}NO_3Na$ 210.1130, found 210.1129.



Bis(*t*-butyldimethylsilyl) ether derivative of 10. To a solution of **10** (6.53 g, 31.2 mmol) in DMF (240 mL) was added imidazole (8.50 g, 124.8 mmol) followed by *tert*-butyldimethylsilyl chloride (14.1 g, 93.6 mmol). After stirring overnight at rt, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with EtOAc (2x) and $CHCl_3$ (1x). The combined organic layer was washed with H_2O (3x), dried ($MgSO_4$) and concentrated. The crude product (13.6 g, 100%) was used for the next step without purification.

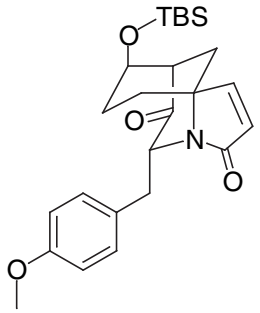


Mono *t*-butyldimethylsilyl ether derivative of 10. To a solution of the bis(t-butyldimethylsilyl) ether (13.6 g 31.1 mmol) in THF (230 mL) was added TBAF (1.0 M in THF, 31.1 mL, 31.1 mmol) at rt. After stirring 1h at rt, the reaction mixture was quenched with saturated aqueous $NaHCO_3$, extracted with Et_2O, dried ($MgSO_4$) and concentrated. Purification by silica gel flash chromatography (ethyl acetate-hexane, 2.5:1 ∅ 100 % ethyl acetate) gave a white solid (9.44 g, 93%): mp 99-102 ^oC; ^1H NMR (200 MHz, $CDCl_3$) δ 0.10 (s, 6H), 0.93 (s, 9H), 1.02 (dt, *J* = 2.3, 12.6 Hz, 1H), 1.43 (br d, *J* = 8.9 Hz, 1H), 1.78 (br d, *J* = 9.2 Hz, 1H), 2.00-2.32 (m, 4H), 2.47 (dd, *J* = 3.9, 12.6 Hz, 1H), 3.18 (dd, *J* = 10.2, 13.4 Hz, 1H), 4.00 (ddd, *J* = 5.4, 8.1, 10.2 Hz, 1H), 4.35 (br s, 1H), 4.42 (dd, *J* = 8.1, 13.4 Hz, 1H); 6.05 (d, *J* = 5.9 Hz, 1H), 6.98 (d, *J* = 5.9 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ -5.1,-5.0, 17.8, 25.7, 28.4, 28.8, 30.2, 41.7, 4.45, 63.3, 63.9, 66.6, 124.7, 154.1, 169.7; IR (neat) 1681, 3358 cm^{-1}; HRMS (MH^+) calcd for $C_{17}H_{29}N0_3Si$ 324.1995, found 324.1966.

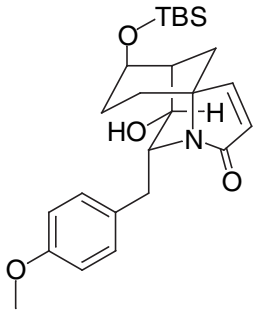


Ketone 2. To a solution of oxalyl chloride (1.57 mL, 18.2 mmol) in CH_2Cl_2 (85 mL) was added DMSO (2.71 mL, 37.9 mmol) at –78 ^oC. After the mixture was stirred 5 min, the alcohol from the previous step (5.34 g, 16.5 mmol) in CH_2Cl_2 (40 mL) was added at –78 ^oC and then stirred another 30 min. Et_3N (7.92 mL, 56.1 mmol) was added dropwise and the resulting mixture was stirred at –78 ^oC. The reaction mixture was quenched with H_2O, extracted with Et_2O, dried ($MgSO_4$) and concentrated. Purification by silica gel flash chromatography (ethyl acetate-hexane, 1.5:1) gave a pale pink solid (5.23 g, 98%): mp 108-110 ^oC; ^1H NMR (200 MHz, $CDCl_3$) δ 0.03 (s, 6H), 0.83

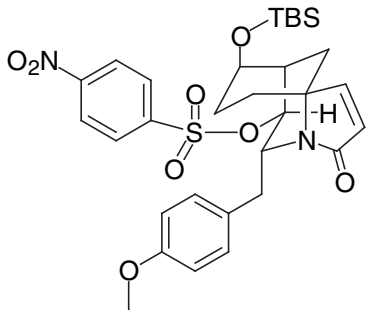
(s, 9H), 1.49 (m, 2H), 1.64-1.77 (m, 2H), 2.21 (dt, *J* = 6.4, 13.0 Hz, 1H), 2.61 (dd, *J* = 2.3, 13.0 Hz, 1H), 2.65 (br s, 1H), 3.95 (d, *J* = 21.3 Hz, 1H), 4.00 (br s, 1H), 4.42 (d, *J* = 21.3 Hz, 1H), 6.06 (d, *J* = 5.9 Hz, 1H), 7.04 (d, *J* = 5.9 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ -5.2, 17.8, 25.5, 27.4, 28.3, 28.9, 50.7, 51.9, 63.2, 66.8, 125.3, 153.7, 170.8, 205.6; IR (neat) 1694 cm^{-1}; HRMS (MH^+) calcd for $C_{17}H_{28}NO_3S$ 322.1838, found 322.1863.



***p*-Methoxybenzylation product.** To a solution of ketone **2** (8.20 g, 25.5 mmol) in THF (80 mL) was added potassium *t*-butoxide (1.0 M in THF, 25.5 mL, 25.5 mmol) at –40 °C. The mixture was stirred for 20 min at 0 °C and then was cooled to –40 °C. This solution was cannulated into a solution of *p*-methoxybenzyl bromide (13.7 mL, 76.5 mmol) in DMF (80 mL) at 0 °C. The resulting mixture was stirred 20 min at 0 °C and then quenched with saturated aqueous NH_4Cl and extracted with Et_2O (3x). The combined organic layer was washed with H_2O (2x), dried ($MgSO_4$) and concentrated. Purification by silica gel flash chromatography (ether–hexane, 2:1) gave a colorless oil (11.0 g, 97%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.03 (s, 6H), 0.23 (dt, *J* = 2.8, 12.9 Hz, 1H), 0.84 (s, 9H), 1.10-1.25 (m, 1H), 1.39-1.62 (m, 2H), 1.95-2.10 (m, 2H), 2.25 (br s, 1H), 3.05 (dd, *J* = 3.0, 13.7 Hz, 1H), 3.72 (s, 3H), 4.00 (br s, 1H), 4.20 (dd, *J* = 5.1, 13.7 Hz, 1H), 4.65 (br t, *J* = 4.0 Hz, 1H), 6.10 (d, *J* = 5.9 Hz, 1H), 6.68 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 6.90 (d, *J* = 5.9 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ -5.1, -5.1, 17.9, 22.6, 25.6, 29.0, 31.9, 34.2, 50.2, 55.1, 64.1, 65.4, 67.9, 113.7, 126.5, 128.3, 131.0, 153.9, 158.6, 171.2, 210.0; IR (neat) 1688, 1709 cm^{-1}; HRMS (MNa^+) calcd for $C_{25}H_{35}NO4SiNa$ 464.2233 found 464.2278.

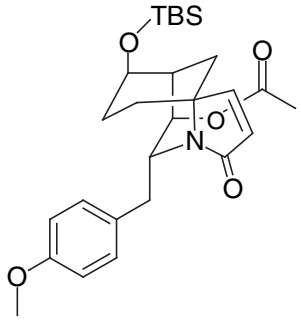


Alcohol 11. To a solution of the ketone from the previous step (3.40 g, 7.70 mmol) in THF (120 mL) was added sodium bis(2-methoxyethoxy)aluminum hydride (65% in toluene, 4.64 mL, 15.4 mmol) at –30 °C. After stirring 1h at –30 to –10 °C, the reaction mixture was poured into a saturated Rochelle salt solution in Et_2O, extracted with Et_2O, dried ($MgSO_4$) and concentrated. Purification by silica gel flash chromatography (ethyl acetate–hexane, 1:2) gave a white solid (2.45 g, 72%): mp 50-52 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.00 (s, 3H), 0.02 (s, 3H), 0.87 (s, 9H), 1.15 (br d, *J* = 12.6, Hz, 1H), 1.33 (br d, *J* = 8.2 Hz, 1H) 1.61-1.72 (m, 1H), 2.00-2.28 (m, 3H), 2.40 (dd, *J* = 3.5, 12.7 Hz, 1H), 3.01 (dd, *J* = 6.6, 14.2 Hz, 1H), 3.76 (s, 3H), 3.81 (dd, *J* = 6.2, 8.6 Hz, 1H), 4.05 (br m, 1H), 4.26 (br s, 1H), 4.59 (dd, *J* = 5.0, 14.2 Hz, 1H), 5.96 (d, *J* = 5.9 Hz, 1H), 6.84 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 5.9 Hz, 1H); 7.24 (d, *J* = 8.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ –5.1, -5.0, 17.9, 25.7, 28.0, 28.3, 30.5, 36.9, 40.6, 55.2, 61.2, 64.2, 65.0, 73.6, 114.4, 126.6, 130.4, 130.7, 153.0, 158.3, 170.3; IR (neat) 1666, 3349 cm^{-1}; HRMS (MH^+) calcd for $C_{25}H_{38}NO_4Si$ 444.2570, found 444.2561.



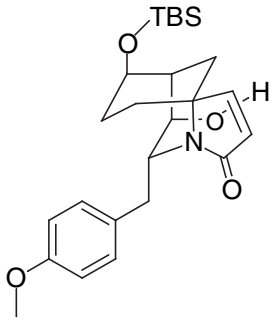
Nosylate derivative of alcohol 11. To a solution of alcohol **11** (1.30 g, 2.93 mmol) in CH_2Cl_2 (150 mL) were added Et_3N (2.10 mL, 14.7 mmol), p-nitrobenzenesulfonyl chloride (2.60 g, 11.7

mmol) and 4-(dimethylamino)pyridine (0.72 g, 5.86 mmol). The mixture was stirred for 3d at rt and then was quenched with saturated aqueous $NaHCO_3$, extracted with Et_2O (2x) and EtOAc (2x), dried ($MgSO_4$) and concentrated. Purification by silica gel flash chromatography (ethyl acetate-hexane, 2:3) gave a yellow solid (1.54 g, 84%): mp 59-64 ^oC ^1H NMR (200 MHz, $CDCl_3$) δ 0.07 (s, 3H), 0.09 (s 3H), 0.90 (s, 9H), 1.12-1.27 (m, 1H), 1.34-1.46 (m, 1H), 1.70-1.85 (m, 1H), 1.95-2.19 (m, 2H), 2.50 (dd, *J* = 3.8, 13.1 Hz, 1H), 2.65-2.75 (m, 1H), 3.44 (br s, 2H), 3.75 (s, 3H), 4.23 (m, 1H), 4.30 (br s, 1H), 4.90 (dd, *J* = 6.4, 9.3 Hz, 1H), 5.91 (d, *J* = 5.9 Hz, 1H), 6.62 (d, *J* = 8.1 Hz, 2H), 6.90 (d, *J* = 5.9 Hz, 1H), 6.98 (d, *J* = 8.1 Hz, 2H), 8.06 (d, *J* = 6.9 Hz, 2H), 8.38 (d, *J* = 8.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.1 (2C), 17.8, 25.6, 28.2, 28.3, 30.1, 32.1, 39.7, 55.0, 57.7, 63.7, 64.1, 82.3, 113.5, 124.5, 126.8, 128.9, 129.9, 130.1, 141.7, 150.7, 152.8, 157.8, 169.8; IR (neat) 1688 cm^{-1}; HRMS (MH^+) calcd for $C_{31}H_{41}N_2O_8SiS$ 629.2353, found 629.2376.



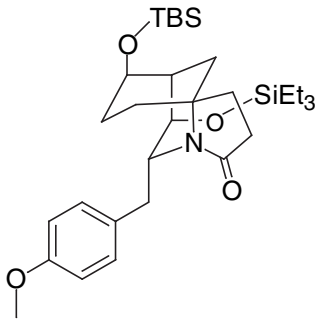
Acetate 12. Rubidium acetate (1.72 g, 11.9 mmol) was placed in a 100 mL round bottom flask and frame-dried under Ar. 18-Crown-6 (3.15 g, 11.9 mmol) in toluene (45 mL) was added followed by the nosylate (1.50 g, 2.38 mmol) in toluene (10 mL). The mixture was stirred at 95 ^oC for 1d and the reaction mixture was quenched with saturated aqueous $NaHCO_3$, extracted with EtOAc, dried ($MgSO_4$) and concentrated. Purification by silica gel flash chromatography (ethyl acetate-hexane, 4:6 ∅ 1:1) gave **12** (r_f = 0.3, ethyl acetate-hexane, 2:3; 740 mg, 64%) and recovered nosylate (r_f = 0.4, ethyl acetate-hexane, 2:3; 236 mg, 16%): ^1H NMR (200 MHz, $CDCl_3$) δ 0.02 (s, 3H), 0.04 (s, 3H), 0.88 (s, 9H), 1.38-1.59 (m, 2H), 1.68-1.86 (m, 1H), 2.15 (s, 3H), 1.98-2.28 (m, 4H), 3.20 (dd,

J = 12.6, 15.7 Hz, 1H), 3.79 (s, 3H), 3.90 (br s, 1H), 4.28-4.43 (m, 3H), 6.02 (d, *J* = 5.9 Hz, 1H), 6.82 (d, *J* = 8.6 Hz, 2H), 6.90 (d, *J* = 5.9 Hz, 1H), 7.04 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ -5.1, 17.7, 21.1, 25.6, 26.3, 28.5, 28.7, 32.7, 40.5, 54.9, 58.2, 64.5, 65.4, 69.1, 113.9, 126.9, 129.5, 130.3, 152.3, 158.0, 169.6, 170.2: IR (neat) 1686, 1740 cm^{-1}; HRMS (MH^+) calcd for $C_{27}H_{40}NO_5Si$ 486.2676, found 486.2670. An elimination product **13** was also isolated (r_f = 0.6, ethyl acetate-hexane, 2:3, 148 mg, 15%): ^{1}H NMR (400 MHz, $CDCl_3$) δ -0.06 (s, 3H), -0.05 (s, 3H), 0.85 (s, 9H), 0.96 (br d, *J* = 11.9 Hz, 1H), 1.17-1.35 (m, 2H), 1.85 (br t, *J* = 13.5 Hz, 1H), 1.99 (dt, *J* = 5.0, 13.5 Hz, 1H), 2.29 (br d, *J* = 3.1 Hz, 1H), 2.48 (dd, *J* = 2.5, 11.9 Hz, 1H), 3.29 (br d, *J* = 5.0 Hz, 2H), 3.58 (br d, *J* = 3.1Hz, 1H), 3.77 (s, 3H), 6.05 (d, *J* = 5.9 Hz, 1H), 6.79 (d, *J* = 8.7 Hz, 2H), 6.98 (s, 1H), 7.00 (d, *J* = 5.9 Hz, 1H), 7.08 (br d, *J* = 8.7 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ -5.2, -5.1, 17.9, 25.7, 26.1, 27.8, 30.8, 39.6, 40.5, 55.1, 63.7, 67.1, 113.8, 121.3, 121.7, 125.0, 129.6, 131.2, 153.7, 158.2, 169.7; IR (neat) 1511, 1694 cm^{-1}; HRMS (M^+) calcd for $C_{25}H_{36}NO_3Si$ 426.2464, found 426.2474.



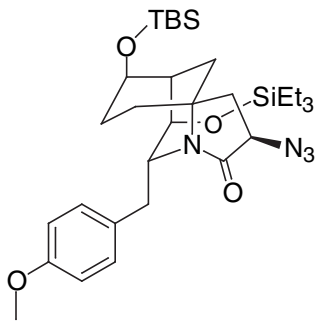
Alcohol 14. To a solution of acetate **12** (1.53 g, 3.15 mmol) in MeOH (28 mL) was added KOH (1M, 28 mL) at 0 °C. The mixture was stirred for 12h at rt and then quenched with saturated aqueous NH_4Cl, extracted with Et_2O (2x) and EtOAc (2x), dried ($MgSO_4$) and concentrated. Purification by silica gel flash chromatography (ethyl acetate–hexane, 2:1) gave a white solid (1.04 g, 74%) and the recovered starting material (259 mg, 17%): mp 154-156 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ -0.03 (s, 3H), -0.01 (s, 3H), 0.88 (s, 9H), 1.42-1.78 (m, 3H), 1.92-2.18 (m, 3H), 2.24 (dd, *J* = 2.8, 15.2 Hz, 1H), 2.97 (br s, 1H), 3.29-3.44 (m, 2H), 3.78 (br s, 4H), 4.08-4.19 (m, 1H), 4.22 (dd, *J* = 4.4, 13.4 Hz, 1H), 6.00 (d, *J* = 5.9 Hz, 1H), 6.83 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 5.9 Hz, 1H), 7.24 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ –5.0, 17.8, 25.6, 26.0, 28.5, 28.6,

32.9, 43.9, 55.1, 59.9, 64.9, 66.2, 66.3, 113.8, 126.9, 130.2, 131.2, 152.5, 157.9, 170.8; IR (neat) 1669, 3362 cm^{-1}; HRMS (MH^+) calcd for $C_{25}N_{38}NO_4Si$ 444.2570, found 444.2580.



Triethylsilyl ether derivative of 14. To a solution of **14** (1.0 g, 2.25 mmol) in CH_2Cl_2 (36 mL) were added N,N-diisopropylethylamine (1.17 mL, 6.75 mmol) followed by triethylsilyl-trifluoromethanesulfonate (1.03 mL, 4.5 mmol) at 0 ^oC. The mixture was stirred for 1h at 0 ^oC and then quenched with saturated aqueous $NaHCO_3$, extracted with Et_2O, dried ($MgSO_4$) and concentrated. The crude product was used for the next step without purification.

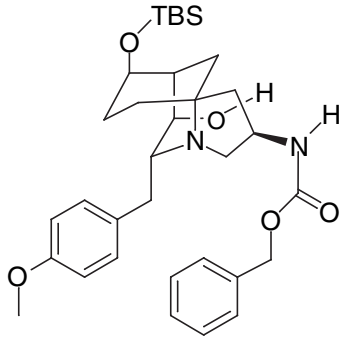
To the crude material (1.26 g, 2.26 mmol) in EtOH (50 mL) was added platinum (IV) oxide (200 mg). The mixture was stirred at rt under H_2 (1 atm) for 12h and then the reaction mixture was filtered through celite and concentrated. Purification by silica gel flash chromatography (ethyl acetate-hexane, 1:1) gave a colorless oil (1.20 g, 95%) : ^1H NMR (200 MHz, $CDCl_3$) δ 0.01 (s, 3H), 0.02 (s, 3H), 0.51 (q,*J* = 8.1Hz, 6H), 0.86 (s, 9H), 0.90 (t, *J* = 8.1 Hz, 9H), 1.51-1.95 (m, 8H), 2.00 (br s, 1H), 2.25-2.50 (m, 2H), 3.03 (dd, *J* = 8.8, 14.0 Hz, 1H), 3.61 (dd, *J* = 2.7, 4.1 Hz, 1H), 3.77 (br s, 4H), 3.90 (dd, *J* =3.8, 14.0 Hz, 1H), 4.12 (q**,** *J* = 4.2 Hz, 1H), 6.79 (d, *J* = 8.6 Hz, 2H), 7.20 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR (50 MHZ, CDO_3) δ –5.1, -4.9, 5.0, 6.9, 17.9, 25.6, 27.9, 29.3, 30.9, 32.0, 33.9, 34.2, 45.5, 55.1, 58.5, 60.5, 67.4, 68.8, 113.4, 130.2, 132.5, 157.7, 176.2: IR (neat) 1690 cm^{-1}; HRMS (M Na^+) calcd for $C_{31}H_{53}NO_4Si_2Na$ 582.3411, found 582.3440.



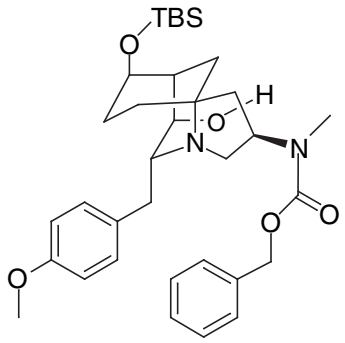
Azide 15. To a solution of disopropylamine (960 μL, 6.85 mmol) in THF (20 mL) was added n-BuLi (2.5 M, 2.6 mL, 6.42 mmol). The reaction mixture was stirred 0.5 h at –78° C. The lactam from the previous step (1.20 g, 2.14 mmol) in THF (16 mL) was added into the LDA at –78° C. The mixture was stirred 0.5 h at 0° C and then cooled to –78° C. Trisyl azide (1.99 g, 6.42 mmol) in THF (16 mL) was cannulated into the solution at –78° C. The resulting mixture was stirred for 5 min at –78° C and then acetic acid (1.4 mL, 24.6 mmol) was added and the dry ice bath was removed. The mixture was stirred for 1h and then quenched with dilute aqueous NaCl and extracted with EtOAc. The combined organic layer was washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$) and concentrated. Purification by silica gel flash chromatography (ether-hexane, 1:3 ∅ 1:1) gave a white solid (755 mg, 59%): mp 111-113 °C; r_f = 0.7 (ether-hexane, 1:2); ^{1}H NMR (200 MHz, $CDCl_3$) δ –0.01 (s, 3H), 0.01 (s, 3H), 0.58 (q, *J* = 8.2 Hz, 6H), 0.85 (s, 9H), 0.93 (t, *J* = 8.2 Hz, 9H), 1.53 (dd, *J* = 6.9, 13.3 Hz, 1H), 1.59-2.12 (m, 8H), 3.10 (dd, *J* = 8.3, 13.3 Hz, 1H), 3.55 (br t, *J* = 2.6 Hz, 1H), 3.74 (br s, 1H), 3.79 (s, 3H), 3.95-4.18 (m, 2H), 4.30 (dd, *J* = 6.9, 9.0 Hz, 1H), 6.83 (d, *J* = 8.7 Hz, 2H), 7.18 (d, *J* = 8.7 Hz, 2H); ^{13}C NMR (50 MHz, CDO_3) δ –5.0, -4.9, 5.2, 7.0, 17.9, 25.7, 27.7, 30.2, 32.7, 33.2, 39.4, 45.5, 55.2, 58.9, 59.3, 59.8, 66.8, 68.5, 113.7, 129.9, 131.8, 157.9, 171.5; IR (neat) 1702, 2104 cm^{-1}; HRMS (MH^+) calcd for $C_{31}H_{53}N_4O_4Si_2$ 601.3605, found 601.3635.

The epimeric azide was also isolated as a waxy solid (307 mg, 24%): r_f = 0.4 (ether-hexane, 1:2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.01 (s, 3H), 0.02 (s, 3H), 0.53 (q, *J* = 8.1 Hz, 6H), 0.87 (s, 9H), 0.92 (t, *J* = 8.1 Hz, 9H), 1.51-2.12 (m, 9H), 3.07 (dd, *J* = 8.8, 14.1 Hz, 1H), 3.64 (br t, *J* = 3.7 Hz, 1H), 3.78 (br s, 4H), 3.96 (dd, *J* = 3.7, 14.1 Hz, 1H), 4.10-4.20 (m, 1H), 4.18 (t, *J* = 8.5 Hz, 1H), 6.82 (d, *J* = 8.7 Hz, 2H), 7.21 (d, *J* = 8.7 Hzz, 2H); 13C NMR (50MHz, $CDCl_3$) δ -5.0, -4.9, 5.1,

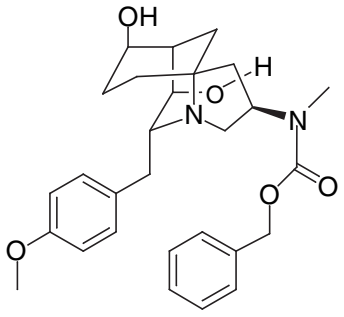
6.9, 17.9, 25.6, 28.3, 29.4, 32.9, 33.6, 41.0, 45.4, 55.3, 58.5, 59.2, 59.5, 67.0, 68.6, 113.6, 130.3, 131.9, 157.9, 172.0; IR (neat) 1698, 2104 cm^{-1}; HRMS (MNa^+) calcd for $C_{31}H_{53}N_4O_4Si_2Na$ 623.3425, found 623.3468.



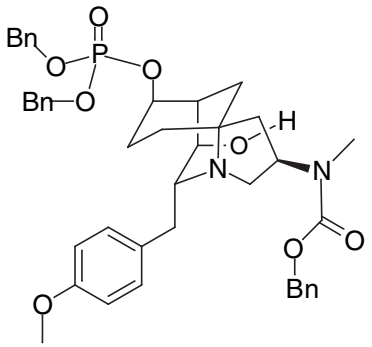
Carbamate 16. To a solution of azide **15** (720 mg, 1.20 mmol) in THF (75 mL) was added lithium aluminum hydride (228 mg, 6.0 mmol) at 0° C. The mixture was warmed to 45° C and stirred for 12 h. The reaction mixture was cooled to 0° C and KOH (10% solution, 6.3 mL) was added and the resulting solution was stirred 0.5 h at 0° C. The reaction mixture was extracted with CH_2Cl_2, dried (Na_2SO_4) and concentrated. The crude product was used directly in the next step without purification. To the crude diamino alcohol (536 mg, 1.20 mmol) in MeOH (36 mL) were added sodium carbonate (763 mg, 7.2 mmol) followed by benzyl chloroformate (909 μL, 6.0 mmol) at 0° C. The mixture was stirred for 1.5 h at rt and then concentrated, diluted (CH_2Cl_2), washed with saturated aqueous $NaHCO_3$, dried (Na_2SO_4) and concentrated. Purification by silica gel flash chromatography (ethyl acetate) gave a white solid (493 mg, 71%): mp 112-114 ^oC ^1H NMR (200 MHz, $CDCl_3$) δ –0.02 (s, 3H), 0.00 (s, 3H), 0.82 (s, 9H), 1.30-1.72 (m, 5H), 1.78-2.18 (m, 5H), 2.52-2.67 (v br s, 1H), 2.70-2.88 (m, 2H), 3.26 (br s, 1H), 3.31-3.44 (m, 1H), 3.68 (br s, 1H), 3.78 (s, 3H), 4.10-4.29 (m, 1H), 5.09 (s, 2H), 6.82 (d, J = 8.5 Hz, 2H), 7.20 (d, J = 8.5 Hz, 2H), 7.38 (s, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) –5.0, -4.9, 17.9, 25.7, 26.7, 28.2, 29.6, 30.9, 35.8, 45.5, 47.7, 55.1, 55.6, 58.9, 60.2, 66.6, 66.9, 67.1, 113.7, 128.1 (2C), 128.5, 130.3, 130.7, 136.5, 155.8, 157.9; IR (neat) 1700, 3330 cm^{-1}; HRMS (MH^+) calcd for $C_{33}H_{49}N_2O_5Si$ 581.3411, found 581.3392.



Methylation of carbamate 16. To a solution of carbamate **16** (468 mg, .806 mmol) in DMF (40 mL) were added methyl iodide (514 μL, 8.06 mmol) followed by sodium hydride (60%, 161 mg, 4.03 mmol) at 0° C. After the reaction mixture was stirred 10 minutes at 0° C, EtOAc was added followed by the dropwise addition of H_2O. The resulting mixture was poured into saturated aqueous $NaHCO_3$ and EtOAc, extracted with CH_2Cl_2, dried (Na_2SO_4) and concentrated. Purification by silica gel flash chromatography (ethyl acetate-hexane-ammonium hydroxide, 1:1:0.01) gave a white solid (308 mg, 64%): mp 49-51 °C; ^{1}H NMR (200 MHz, CD_3CN) δ 0.00 (s, 6H), 0.85 (s, 9H), 1.40-2.10 (m, 10H), 2.65 (s, 3H), 2.75-3.00 (m, 3H), 3.31 (br s, 1H), 3.47-3.65 (m, 3H), 3.70 (s, 3H), 3.78 (br s, 1H), 4.72 (v br s, 1H), 5.05 (s, 2H), 6.81 (d, J = 8.4 Hz, 2H), 7.21 (d, J = 8.2 Hz, 2H), 7.35 (s, 5H); ^{13}C NMR (50 MHz, CD_3CN), -4.6, 18.6, 23.4, 26.2, 29.2, 31.6, 31.9, 36.4, 44.6, 47.1, 51.3, 52.8, 55.8, 58.4, 59.4, 67.3, 68.8, 69.4, 114.4, 128.5, 128.7, 129.4, 131.0, 133.0, 138.5, 156.8, 158.8; IR (neat) 1693, 3422 cm^{-1}; HRMS (MH^+) calcd for $C_{34}H_{51}N_2O_5Si$ 595.3567, found 595.3526.

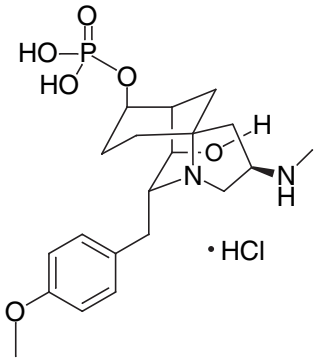


Alcohol 17. HF (5% in CH_3CN, 10 mL) was added to the methylated carbamate (253 mg, .425 mmol) at 0° C and the resulting solution was stirred 5 h. The reaction mixture was diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (2x) and CH_2Cl_3 (2x), and the combined organic layers were dried (Na_2SO_4) and concentrated. Purification by silica gel flash chromatography (ethyl acetate–ammonium hydroxide, 98:2) gave a white solid (188 mg, 92%): mp 50-53 °C ^{1}H NMR (200 MHz, CD_3CN) δ 1.30-2.20 (m, 9H), 2.55-2.59 (m, 8H), 3.30 (br s, 1H), 3.49 (v br s, 2H), 3.67 (br s, 1H), 3.73 (s, 3H), 4.68 (br s, 1H), 5.04 (s, 2H), 6.81 (d, J = 8.7 Hz, 2H), 7.25 (d, J = 8.6 Hz, 2H), 7.35 (s, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 24.5, 29.0, 29.6, 30.0, 35.7, 43.1, 45.3, 49.9, 51.9, 55.2, 58.3, 58.7, 66.9, 67.1, 67.9, 113.7, 127.8, 127.9, 128.4, 130.1, 130.9, 136.5, 156.4, 157.9; IR (neat) 1675, 3408 cm^{-1}; HRMS (MH^+) calcd for $C_{28}H_{37}N_2O_5$ 481.2702, found 481.2690.



Dibenzyl phosphate 18. To a solution of alcohol **17** (168 mg, 0.35 mmol) in $CHCl_2$ (25 mL) were added 1-*H*-tetrazole (74 mg, 1.05 mmol) and dibenzyl diisopropylphosphoramidite (156 μL, .455 mmol) at 0° C. The mixture was stirred for 2 h at 0° C and cooled to –78° C. Et_3N (194 μL, 1.40 mmol) was added to the reaction mixture followed by a solution of *m*-chloroperbenzoic acid (72 mg, 0.42 mmol) in CH_2Cl_2 (5 mL). The resulting solution was stirred for 30 min at –78° C, diluted with a cold CH_2Cl_2 and poured into saturated aqueous $NaSO_3$ in CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4) and concentrated. Purification by silica gel flash chromatography (ethyl acetate–MeOH, 95:5) gave a colorless oil (188 mg, 73%) : ^{1}H NMR (400 MHz, CD_3OD) δ 1.34 (d, J = 11.4 Hz, 1H), 1.44 (dd, J = 6.9, 13.0 Hz, 1H), 1.66 (br s, 2H), 1.74-

1.88 (m, 2H), 1.97 (br d, J = 12.3 Hz, 1H), 2.03-2.17 (m, 1H), 2.25 (s, 1H), 2.69 (s, 3H), 2.74-2.93 (m, 3H), 3.25 (br s, 1H), 3.36 (br t, J = 6.0 Hz, 1H), 3.58 (br s, 1H), 3.75 (s, 3H), 4.31 (br s, 1H), 4.73 (br s, 1H), 4.96-5.05 (m, 4H), 5.08 (s, 2H), 6.83 (d, J = 8.5 Hz, 2H), 7.19 (d, J =8.5 Hz, 2H), 7.33 (s, 10H), 7.34 (s, 5H); ^{13}C NMR (100 MHz, CD_3OD) δ 23.2, 29.5, 29.7, 31.5, 36.5, 44.3, 45.0, 51.7, 53.4, 55.8, 59.5, 60.0, 68.3, 68.4, 71.0, 77.4, 114.9, 129.0, 129.2, 129.3, 129.7, 129.8, 129.9, 131.3, 132.7, 137.4, 138.3, 158.1, 159.7; IR (neat) 1694, 3419 cm^{-1}; HRMS (MH^+) calcd for $C_{42}H_{50}N_2O_8P$ 741.3305, found 741.3258.



FR901483 (1). To a solution of dibenzyl phosphate **18** (50.0 mg, 0.067 mmol) in 95% EtOH (12 mL) was added palladium on activated carbon (10%, 50.0 mg). The reaction mixture was stirred 3.5 h under H_2 (100 psi) and then filtered and concentrated. The crude product was dissolved in 97.5% aqueous CH_3CN and 0.1 N HCl (590 μL) was added dropwise at 0° C. The mixture was concentrated and then rinsed with cold CH_3CN to give a white solid (27.0 mg, 93%): dec 213-216 °C; ^{1}H NMR 400 MHz, CD_3OD) δ 1.88 (br d, J = 14.5 Hz, 1H), 2.02-2.18 (m, 4H), 2.25 (br d,J = 11.6 Hz, 2H), 2.44 (br s, 1H), 2.58 (br dd, J = 8.8, 13.6 Hz, 1H), 2.72 (s, 3H), 3.04 (br d, J = 10.4 Hz, 1H), 3.30 (br t, J = 11.5 Hz, 1H), 3.59 (br s, 1H), 3.77 (s, 3H), 3.85 (br d, J = 11.3 Hz, 2H), 4.16-4.27 (m, 2H), 4.46 (dd, J = 9.8, 13.2 Hz, 1H), 6.88 (d, J = 8.4 Hz, 2H), 7.31 (d, J = 8.4 Hz, 2H); ^{13}C NMR (125 MHz, CD_3OD) δ 22.6, 28.2, 28.5, 32.4, 34.1, 42.0, 43.1 (d, J = 3.7 Hz), 51.9, 55.0, 55.9, 61.7, 64.3, 68.3, 71.0 (d, J = 5.3 Hz), 115.4, 128.9, 131.8, 160.6; IR (neat) 1248, 1444, 1513, 1612, 3338 cm^{-1}; HRMS (MH^+) calcd for $C_{20}H_{33}N_2O_6PCl$ 427.1998, found 427.1989.