AN AVENUE TO THE SORDARIN CORE ADAPTABLE TO ANALOG SYNTHESIS

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Experimental protocols. Unless otherwise indicated, $^1$H (300 MHz) and $^{13}$C (75 MHz) NMR spectra were recorded at room temperature from CDCl$_3$ solutions. Chemical shifts are reported as ppm on the $\delta$ scale and coupling constants, $J$, are in Hz. Multiplicities are described as s (singlet), d / dd / ddd (doublet / doublet of doublets / doublet of doublet of doublets), t (triplet), q (quartet), sept (septuplet), m (multiplet), and further qualified as app (apparent), b (broad), c (complex). All 2D NMR spectra were recorded at 400 MHz ($^1$H) / 100 MHz ($^{13}$C). Low- and high resolution mass spectra were obtained in the EI (70 eV), CI (isobutane) or ESI modes, as indicated. Infrared spectra (cm$^{-1}$) were recorded as neat films. Chromatographic separations were effected over Fluka 60 silica gel. Analytical and preparative TLC utilized Analtech 250 and 1000 µ silica gel plates, respectively, with fluorescent indicator. Melting points are uncorrected. All reagents and solvents were commercial products and used without further purification except THF (freshly distilled from Na/benzophenone under Ar) and CH$_2$Cl$_2$ (freshly distilled from CaH$_2$ under Ar). Anhydrous DMF and LHMDS solution were purchased from Aldrich and used as received. Commercial n-BuLi was titrated against N-benzylbenzamide in THF at $-78\,^\circ\text{C}$ until persistence of a light blue color. Flash chromatography was performed on Silicycle 230 – 400 mesh silica gel. All reactions were performed under dry Ar in flame or over dried flasks equipped with Teflon$^\text{TM}$ stirbars. All flasks were fitted with rubber septa for the introduction of substrates, reagents, and solvents via syringe.

Ketoester 11. A solution of 3-methoxy-cyclopent-2-ene-1-one (500 mg, 4.5 mmol) in THF (1.5 mL) was added dropwise to a cold ($-50\,^\circ\text{C}$) solution of LHMDS (commercial 1M soln. in THF, 5.8 mL, 5.8 mmol,) in THF (7.5 mL), and the resulting mixture was stirred for 30 min at $-50\,^\circ\text{C}$. Neat MeOOCCN (0.4 mL, 4.9 mmol; CAUTION: source of highly toxic HCN) was injected. The solution was stirred for 2.5 h, during which time it was allowed to warm to RT, then it was cooled to 0 °C, neutralized with aq. 1N HCl (10 mL; CAUTION: formation of highly toxic HCN), and extracted with EtOAc (3 x 15 mL).

The combined extracts were washed with sat’d aq. NaCl (10 mL), dried (Na$_2$SO$_4$) and evaporated. Chromatography of the residue (50:50 EtOAc/hexane) furnished 394 mg (2.32 mmol, 52 %) of the known [(a) Irie, H.; Katakawa, J.; Tomita, M.; Mizuno, Y. Chem. Lett. 1981, 637. (b) Boschelli, D.; Smith, A. B., III; Stringer, O. D.; Jenkins, R. H., Jr.; Davis, F. A. Tetrahedron Lett. 1981, 22, 4385] $\beta$-ketoester 11. $^1$H: 5.28 (s, 1H); 3.87 (s, 3H); 3.76 (s, 3H); 3.53 (dd, $J = 7.5, 3.0, 1\text{H}$); 3.04 (dd, $J = 17.7, 3.0, 1\text{H}$); 2.77 (dd, $J = 17.7, 7.5, 1\text{H}$). $^{13}$C: 198.3; 191.1; 169.9; 103.2; 59.6; 53.1; 51.7; 32.5. HRCIMS: Calc. for C$_8$H$_{11}$O$_4$ [M + H]$^+$ 171.0657; found 171.0654.

Enone 10. Neat Me$_2$SO$_4$ (4.5 g, 36.0 mmol; CAUTION: toxic, corrosive, cancer suspect agent) was added at RT to a vigorously stirred suspension of 8 (5.0 g, 36.0 mmol) and K$_2$CO$_3$ (4.5 g, 36.0 mmol) in acetone (60 mL). The mixture was then heated to 60 °C for 8 h with continued stirring, then it was cooled and concentrated. The residue was partitioned between EtOAc (10 mL) and aq. 1M NaOH (15 mL), the layers were separated, and the aqueous phase was further extracted with EtOAc (3 x 30 mL). The combined extracts were washed with brine (30 mL), dried (MgSO$_4$) and concentrated. Chromatography of the residue (25 % EtOAc / hexanes) gave 5.5 g (35.0 mmol, 99%) of 10 as an oil. $^1$H: 3.91 (s, 3H); 2.73 (sept, $J = 7.0, 1\text{H}$); 2.62 (m, 2H); 2.39 (m, 2H); 1.11 (d, $J = 7.0, 6\text{H}$). $^{13}$C: 204.8; 184.6; 125.8; 56.5; 33.8; 24.4; 23.1; 20.4. IR: 1682, 1621. HRCIMS: Calc. for C$_9$H$_{10}$O$_2$ [M + H]$^+$ 155.1072; found: 155.1078.
**Ketoester 12.** A solution of 10 (306 mg, 2 mmol) in THF (2 mL) was added dropwise to a cold (−78 °C) solution of LHMDS (2.1 mL of commercial 1M THF solution, 2.1 mmol, diluted an additional 2 mL of THF), and the mixture was stirred at −78 °C for 2 h. Neat MeOOCN (160 µL, 2 mmol; CAUTION: source of highly toxic HCN) was injected and the solution was stirred −78 °C for 30 min. The reaction was quenched at −78 °C by addition of aq. 1N HCl (4 mL; CAUTION: formation of HCN), allowed to warm to RT, and extracted with EtOAc (3 x 15 mL). The combined extracts were washed with brine (10 mL), dried (Na2SO4) and concentrated. Chromatography of the residue (50:50 EtOAc/hexanes) gave 340 mg (81 %) of 12 as an oil. 1H: 3.90 (s, 3H); 3.83 (dd, J = 7.6, 2.3, 1H); 3.78 (s, 3H); 2.79 (sept, J = 6.7, 1H); 2.72 (d, J = 7.4, 1H); 2.47 (dd, J = 17.8, 2.3, 1H); 1.14 (d, J = 6.8, 6H). 13C: 202.2; 179.5; 172.1; 128.1; 57.4; 53.2; 42.7; 39.3; 23.4; 20.2. IR: 1736, 1702, 1620. HRCIMS: Calc. for C9H17O4 [M + H]+ 213.1127; found 213.1131.

**Aldehyde 13.** Neat DBU (4 µL, 24 µmol) was added to a cold (0 °C) MeCN (2.4 mL) solution of 11 (204 mg, 1.20 mmol) and acrolein (90 µL, 1.3 mmol; CAUTION: toxic, cancer suspect agent). The solution was then warmed to RT, stirred for 3 h, and finally diluted with EtOAc (10 mL). The mixture was sequentially washed with aq. sat’d NH4Cl (5 mL) and aq. sat’d NaCl (5 mL), dried (Na2SO4) and evaporated to afford 271 mg of 13 (1.2 mmol, 100%). 1H: 9.74 (s, 1H); 5.27 (s, 1H); 3.88 (s, 3H); 3.71 (s, 3H); 3.16 (d, J = 18.0, 1H); 2.55 (m, 2H); 2.44 (d, J = 18.0, 1H); 2.28 (m, 1H); 2.15 (m, 1H). 13C: 201.3; 200.9; 190.2; 171.4; 102.6; 59.6; 58.3; 53.3; 39.8; 38.9; 26.8. IR: 1731, 1698. HRCIMS: Calc. for C11H15O5 [M + H]+ 227.0919; found 227.0920.

**Nitrile 14.** A mixture of 13 (70 mg, 301 µmol), acrylonitrile (0.6 mL; CAUTION: toxic, cancer suspect agent) and DABCO (7 mg, 62 µmol) was stirred at RT for 2 days, then it was concentrated. Chromatography of the residue (50:50 EtOAc/ hexanes) provided 49 mg of 14 (176 µmol, 57 %). 1H: 6.02 (dd, J = 17.0, 2.0, 2H); 5.28 (s, 1H); 4.27 (m, 1H); 3.90 (s, 3H); 3.72 (s, 3H); 3.19 (d, J = 18.0, 1H); 2.53 (d, J = 18.0, 1H); 2.30-2.10 (m, 2H); 1.95-1.60 (m, 3H). 13C: 201.5; 190.9; 171.6; 130.8; 126.6; 117.4; 102.6; 71.9; 59.6; 59.0; 53.3; 38.3; 30.9; 29.6. HRCIMS: Calc. for C14H18NO5 280.1185[M + H]+; found 280.1183.

**Aldehyde 15.** Neat DBU (13 µL, 87 µmol) was added to a cold (0 °C) solution of 12 (920 mg, 4.3 mmol) and acrolein (308 µL, 4.6 mmol; CAUTION: toxic, cancer suspect agent) in MeCN (9 mL). The mixture was stirred at 0 °C for 30 min, then at RT for 4h, and finally it was concentrated. The residue was treated with aq. sat’d. NH4Cl (20 mL) and extracted with EtOAc (4 x 10 mL). The combined extracts were washed with brine (15 mL), dried (MgSO4) and concentrated to afford crude 15 (1.1 g, 95%), which was used without further purification. 1H: 9.76 (s, 1H); 3.99 (s, 3H); 3.74 (s, 3H); 2.99 (sept, J = 6.8, 1H); 2.69 (d, J = 17.8, 1H); 2.48 (m, 1H); 2.32-2.28 (m, 3H); 2.23 (d, J = 17.7, 1H); 1.23 (dd, J = 7.1, 4.3, 6H). 13C: 202.8; 200.9; 180.2; 173.6; 126.6; 59.7; 53.1; 52.2; 45.3; 39.0; 26.1; 24.5; 20.7; 20.4. IR: 1730, 1692, 1611. HRCIMS: Calc. for C14H17O5 [M + H]+ 269.1389; found 269.1390.
**Nitrile 16. Method A.** A solution of 15 (4.1 g, 15.2 mmol) and DABCO (341 mg, 3.0 mmol) in acrylonitrile (30 mL; **CAUTION:** toxic, cancer suspect agent) was stirred at RT for 2 days, then additional DABCO (341 mg, 3.0 mmol) was added and the mixture was stirred at RT for another 2 days. The mixture was concentrated and the residue was chromatographed (50:50 EtOAc/hexanes) to give a nearly 1:1 mixture of diastereomers of 16 (3.3 g, 68 %) as an oil. **Method B.** A solution of 15 (65 mg, 242 μmol), DABCO (27 mg, 242 μmol), triethanolamine (16 μL, 121 μmol) and La(OTf)₃ (7 mg, 12 μmol) in acrylonitrile (0.5 mL; **CAUTION:** see above) was stirred at RT for 11 h, then it was concentrated. The residue was taken up with aq. sat’d. NaHCO₃ (20 mL) and extracted with EtOAc (3 x 10 mL). The combined extracts were washed with brine (15 mL), dried (MgSO₄) and concentrated. Chromatography of the residue (50:50 EtOAc/hexanes) gave a nearly 65:35 mixture of diastereomers of 16 (39 mg, 50%) as an oil.

**Compound 18.** Neat TIPS-OTf (2.7 mL, 11.2 mmol) was added to a cold (0 °C) solution of 14 (1.3 g, 4.5 mmol) and Hüning base (2 mL, 11.2 mmol) in CH₂Cl₂ (18 mL), then the mixture was allowed to warm to RT and stirred for 12 h. The solution was diluted with a 3:1 mixture of pentane-CH₂Cl₂ (100 mL), resulting in the appearance of a white precipitate that was filtered off. The organic filtrate was washed with aq. sat’d. NaHCO₃, dried (Na₂SO₄) and evaporated. Chromatography of the residue (5:95 EtOAc/hexanes) provided 18 (1.90 g, 3.2 mmol, 72 %) as a nearly 1:1 mixture of diastereomers. **¹H:** 4.85-4.80 (m, 2H); 4.13 (t, J = 4.1, 2H); 3.32 (s, 3H); 3.25 (s, 3H); 3.16 (s, 3H); 3.13 (s, 3H); 2.71 (d, J = 4.1, 2H); 2.38 (d, J = 4.5, 2H); 2.27 (dd, J = 13.6, 4.1, 2H); 2.17 (m, 2H); 2.00-1.80 (m, 6H); 1.50-0.90 (m, 84H). **¹³C:** 174.0; 173.4; 170.9; 169.5; 128.7; 123.6; 123.0; 96.6; 97.3; 91.6; 91.2; 76.0; 70.2; 66.5; 65.9; 56.9; 54.7; 53.2; 51.8; 51.7; 47.2; 42.6; 33.3; 28.1; 27.9; 25.1; 19.5; 19.3; 18.8; 18.3; 14.6; 13.5; 13.1. **HRCIMS:** Calc. for C₁₇H₂₄NO₃ [M + H]⁺ 322.1654; found: 322.1654.

**Compound 19.** Neat TES-OTf (190 μL, 830 μmol) was added to a cold (0 °C) CH₂Cl₂ (1.5 mL) solution of 16 (121 mg, 380 μmol, 1:1 mixture of diastereomers) and Hüning base (160 μL, 940 μmol). The solution was warmed to RT and stirred for 12 h, then it was diluted with a 3:1 mixture of pentane / CH₂Cl₂ (10 mL), resulting in precipitation of a white solid which was filtered off. The filtrate was washed with aq. sat’d. NaHCO₃ (3 mL), dried (Na₂SO₄) and concentrated. Chromatography of the residue (5:95 EtOAc/hexanes) gave 108 mg (52 %) of a nearly 1:1 mixture of diastereomers of 19 as an oil. **¹H:** 4.39 (m, 1H); 4.25 (t, J = 7.6, 1H); 3.88 (s, 3H); 3.75 (s, 3H); 3.65 (s, 3H); 3.61 (s, 3H); 2.71-2.67 (m, 2H); 2.51 (m, 2H); 2.41 (m, 2H); 2.17-1.87 (m, 8H); 1.70-1.40 (m, 2H); 1.30 (dd, J = 6.7, 1.5, 6H); 1.14 (dd, J = 6.9, 5.7, 6H); 1.02-0.90 (m, 36H); 0.75-0.62 (m, 24H). **¹³C:** 173.7; 173.6; 157.3; 154.9; 123.8; 123.5; 123.4; 122.0; 94.5; 93.4; 74.8; 68.9; 66.5; 65.9; 58.6; 56.4; 56.1; 51.9; 48.8; 48.4; 47.9; 41.4; 32.8; 27.3; 27.2;
25.6; 25.4; 22.4; 22.3; 20.6; 20.2; 6.8; 6.7; 6.6; 6.4; 5.5; 5.0; 4.8. HRCIMS: Calc. for C_{20}H_{32}NO_3Si_2 [M + H]^+ 550.3384; found 550.3383.

**Compound 20.** Neat TBS-O Tf (147 µL, 550 µmol) was added to a cold (0° C) THF (1.3 mL) solution of 16 (30 mg, 93 µmol) and Hünig base (140 µL, 810 µmol). The solution was warmed to RT and then heated up to 60 °C for 12 h. It was diluted with EtOAc (15 mL) and neutralized with aq. sat’d. NaHCO_3 (5 mL). The organic phase was separated and washed with brine (5 mL), dried (Na_2SO_4) and concentrated. Chromatography of the residue (30:70 methylene chloride / hexanes) gave 23 mg (45%) of a mixture of diastereomers of 20 as a colorless oil. \(^1^H\) (single diastereoisomer): 4.39 (m, 1H); 3.74 (s, 3H); 3.62 (s, 3H); 2.71 (d, J= 4.3, 1H); 2.51 (sept, J= 6.9, 1H); 2.46 (dd, J= 13.1, 4.4, 1H); 2.04-1.87 (m, 2H); 1.73-1.54 (m, 2H); 1.48 (d, J=13.1, 1H); 1.32 (d, J=6.8, 3H); 1.15 (d, J=6.8, 3H); 0.96 (s, 9H); 0.91 (s, 9H); 0.22 (s, 3H); 0.21 (s, 3H); 0.19 (s, 3H); 0.11 (s, 3H). \(^1^3^C\) (single diastereoisomer): 174.7; 158.7; 124.6; 122.9; 95.6; 70.1; 67.4; 57.4; 52.8; 52.6; 49.1; 33.7; 28.1; 26.7; 26.5; 25.7; 25.5; 23.5; 21.4; 19.0; 18.9; -2.2; -2.7; -3.2; -3.6. IR: 2315, 1730. HRMS: calc. for C_{20}H_{35}NO_5Si_2 [M + Na]^+ 572.3306; found 572.3305.

**Compound 21.** Neat TIPS-O Tf (190 µL, 710 µmol) was added to a cold (0° C) CH_2Cl_2 (1.3 mL) solution of 16 (104 mg, 320 µmol; 1:1 mixture of diastereomers) and Hünig base (140 µL, 810 µmol). The solution was warmed to RT and stirred for 12 h, then it was diluted with a 3:1 mixture of pentane / CH_2Cl_2 (10 mL), resulting in precipitation of a white solid which was filtered off. The filtrate was washed with aq. sat’d. NaHCO_3 (3 mL), dried (Na_2SO_4) and concentrated. Chromatography of the residue (5:95 EtOAc/hexanes) gave 123 mg (61%) of a nearly 1:1 mixture of diastereomers of 21 as a colorless oil. \(^1^H\): 4.57 (dd, J= 8.6, 6.1, 1H); 4.41 (t, J= 8.3, 1H); 3.91 (s, 3H); 3.77 (s, 3H); 3.64 (s, 3H); 3.59 (s, 3H); 2.75-2.65 (m, 2H); 2.58 (m, 2H); 2.49-2.42 (m, 2H); 2.16 (d, J= 12.9, 2H); 2.05-1.80 (m, 6H); 1.75-1.40 (m, 2H); 1.34 (d, J= 6.7, 12H); 1.23-1.00 (m, 84H). \(^1^3^C\): 173.8; 156.6; 154.4; 124.2; 123.9; 123.8; 122.9; 94.8; 94.2; 75.9; 69.8; 66.6; 66.1; 56.8; 56.5; 52.1; 51.9; 49.9; 49.2; 48.8; 42.5; 33.4; 27.8; 27.7; 26.5; 25.5; 25.1; 22.7; 21.3; 20.6; 18.3; 13.5; 12.9. IR: 2324, 1745, 1645. HRCIMS: Calc. for C_{35}H_{64}NO_5Si_2 [M + H]^+ 634.4323; found 634.4322.

**Ketoalcohol 22.** Pyridine-HF complex (70% HF, 2 mL) was added to a cold (0 °C) solution of 19 (206 mg, 380 µmol) in MeCN (2 mL). The mixture was stirred for 1 h, during which time it was allowed to warm to RT, then it was diluted with EtOAc (20 mL) and neutralized with aq. sat’d. NaHCO_3 (5 mL). The organic phase was separated and washed with brine (5 mL), dried (Na_2SO_4) and concentrated to afford 120 mg (100%) of a mixture of diastereomers of 22 as an oil. \(^1^H\): 4.48 (app dd, J = 10.5, 6.2, 1H); 4.00 (m, 1H); 3.71 (s, 3H); 3.68 (s, 3H); 3.58 (s, 3H); 3.47 (s, 3H); 2.82 (d, J = 6.0, 1H); 2.76 (d, J = 6.2, 1H); 2.70 (d, J = 10.0, 1H); 2.68-2.38 (m, 4.5H); 2.18-1.80 (m, 8H); 1.60 (d, J = 15.0, 2H); 1.31 (d, J = 6.4, 6H); 1.24 (app dd, J = 6.8, 4.5, 6H). \(^1^3^C\): 206.9, 205.7; 173.6, 173.2; 121.1; 91.4; 90.5; 75.0; 67.7; 57.3; 57.0; 54.3; 54.1; 53.6; 53.3; 53.0; 52.8; 49.2; 44.7; 29.8; 27.4; 27.3; 25.9; 25.6; 24.4; 24.4; 23.5; 22.5; 22.4; 21.6. IR: 3455, 2246, 1728. HRCIMS: Calc. for C_{17}H_{24}NO_5 [M + H]^+ 322.1654; found 322.1652.
**Diketone 23.** Neat DMSO (70 µL, 900 µmol) was added to a cold (−78 °C) solution of (COCl)₂ (40 µL, 430 µmol; CAUTION: vigorous reaction, formation of highly toxic CO). The mixture was stirred at −78 °C for 15 min, then a solution of 22 (60 mg, 190 µmol) in CH₂Cl₂ (600 µL) was added dropwise and the mixture was stirred at −78 °C for 30 min. Neat Et₃N (210 µL, 1500 µmol) was then slowly injected and the mixture was stirred at −78 °C for another 30 min, then it was warmed to RT. The mixture was diluted with half-saturated aq. NH₄Cl solution (2 mL) and more CH₂Cl₂ (10 mL). The organic phase was separated, dried (Na₂SO₄) and concentrated. The residue was chromatographed (2:70 EtOAc/hexanes) to furnish 40 mg (67 %) of a nearly 1:1 mixture of diastereomers of 23. ^1H: 3.76 (s, 3H); 3.50 (s, 3H); 2.92 (d, J = 6.0, 1H); 2.83-2.73 (m, 4H); 2.65-2.53 (m, 1H); 2.50 (dd, J = 15.2, 5.8, 1H); 2.25-2.10 (m, 2H); 1.31 (d, J = 6.6, 3H); 1.21 (d, J = 6.7, 3H). ^13C: 206.8; 199.1; 172.8; 117.0; 94.4; 56.9; 56.0; 55.8; 55.3; 54.3; 31.9; 30.3; 27.0; 23.5; 23.1; 22.8. IR: 2954, 2872, 2238, 1750, 1716, 1621, 1435. HRCIMS: Calc. for C₁₇H₂₂NO₅ [M + H]⁺ 320.1498; found 320.1499.

**Ketone 24.** A solution of 16 (800 mg, 2.5 mmol), imidazole (253 mg, 3.7 mmol), DMAP (30 mg, 245 µmol) and TBSCI (747 mg, 5 mmol) in dry DMF (2 mL) was stirred at 60 °C for 11 h, then it was cooled to RT, diluted with sat'd. aq. NH₄Cl (20 mL) and extracted with EtOAc (3 x 10 mL). The combined extracts were washed with brine (15 mL), dried (MgSO₄) and concentrated. Chromatography of the residue (gradient 0 → 25 % EtOAc / heptanes) gave 758 mg (70 %) of a nearly 60:40 mixture of diastereomers of 24 as a light yellow oil. ^1H: 5.98-5.89 (m, 2H); 4.30-4.20 (m, 1H); 3.98-3.93 (m, 3H); 3.72 (s, 3H); 3.01-2.91 (m, 1H); 2.66 (dd, J = 17.5, 4.2, 1H); 2.26 (dd, J = 17.5, 6.6, 1H); 1.95-1.82 (m, 2H); 1.56-1.43 (m, 2H); 1.22 (dd, J = 6.9, 4.3, 6H); 0.90 (s, 9H); 0.06-0.04 (m, 6H). ^13C: 202.5; 179.8; 179.7; 173.5; 129.6; 126.6; 126.5; 126.4; 116.8; 99.5; 72.0; 71.8; 59.2; 59.1; 52.6; 52.0; 45.0; 44.9; 30.5; 30.3; 28.0; 27.6; 25.5; 24.1; 24.0; 20.3; 19.97; 19.95; 17.95; -4.96; -4.96; -5.16; -5.18. IR: 2223, 1736, 1619. HRESIMS: Calc. for C₂₃H₃₈NO₅Si [M + H]⁺ 436.2516; found 436.2519.

**Cyanoenone 25.** Commercial Et₂AlCN solution (1.0 M in toluene, 3.3 mL, 3.3 mmol) was added at RT to a stirred solution of 24 (729 mg, 1.7 mmol, 60:40 mixture of diastereomers) in dry benzene (15 mL). The mixture was stirred at RT for 1.5 h, then it was quenched with 1M NaOH (4 mL) and concentrated. The residue was taken up with aq. sat'd NaHCO₃ (20 mL) and with EtOAc (20 mL). The organic phase was recovered and the aqueous phase was further extracted with EtOAc (3 x 10 mL). The combined extracts were washed with brine (15 mL), dried (MgSO₄), and concentrated. The residue was chromatographed (25:75 EtOAc/hexanes) to give 508 mg (70 %) of a nearly 60:40 mixture of diastereomers of 25 as a light yellow oil. ^1H: 6.05-5.95 (m, 2H); 4.35-4.25 (m, 1H); 3.85-3.77 (m, 3H); 3.07 (dd, J = 19.0, 3.0, 1H); 3.01-2.95 (m, 1H); 2.37 (dd, J = 19.0, 3.0, 1H); 2.25-2.15 (m, 1H); 1.85-1.45 (m, 3H); 1.30-1.23 (m, 6H); 0.95-0.85 (m, 9H); 0.12-0.05 (m, 6H). ^13C: 203.1; 171.6; 171.5; 161.8; 161.7; 136.0; 135.9; 130.5; 126.3; 126.1; 117.0; 116.9; 113.8; 113.7; 71.9; 71.7; 53.7; 53.6; 43.8; 43.6; 31.5; 31.3; 31.0; 30.6; 26.7; 25.9; 25.8; 20.2; 20.1; -4.60; -4.8. IR: 2225, 1726. HRESIMS: Calc. for C₂₃H₃₄N₂O₄Si [M + Na]⁺ 453.2183; found. 453.2186.
Cyanoalcohol 26. Solid NaBH₄ (4 mg) was added to a cold (0 °C) solution of 25 (40 mg, 90 µmol) and CeCl₃·7H₂O (22 mg, 59 µmol) in MeOH (1 mL), and the mixture was stirred for 15 min. The reaction was quenched with aq. sat'd NH₄Cl (5mL) and the mixture was concentrated. The residue was partitioned between EtOAc (10 mL) and aq. sat'd. NH₄Cl (10 mL). The organic phase was washed with aq. sat'd. NH₄Cl (10 mL) and further extracted with EtOAc (3 x 10 mL). The combined extracts were washed with brine (15 mL), dried (MgSO₄) and concentrated. Chromatography of the residue (25:75 EtOAc/hexanes) gave 20 mg (51 %) of 26, a mixture of diastereomers, as a light yellow oil. ¹H: 6.02-5.91 (m, 2H); 5.08-4.95 (m, 1H); 4.33-4.20 (m, 1H); 3.84-3.68 (m, 3H); 3.01-2.84 (m, 2.2H); 2.59-2.48 (m, 0.4H); 2.29-1.76 (m, 3H); 1.76-1.47 (m, 1.4H); 1.40-1.13 (m, 6H); 0.97-0.77 (m, 9H); 0.23-0.01 (m, 6H). IR: 3473, 2221, 1734. HRESIMS: calc. for C₂₃H₃₆N₂O₄Si [M + Na]⁺ 455.2343; found 455.2342.

Diene 27. A solution of 26 (19 mg, 44 µmol) and Burgess reagent (21mg, 88 µmol) in dry benzene (0.5 mL) was stirred at 60 °C for 15 h, then it was cooled (RT) and concentrated. The residue was partitioned between EtOAc (10 mL) and aq. sat'd NaHCO₃ (10 mL), the organic phase was recovered and the aqueous phase was further extracted with EtOAc (3 x 10 mL). The combined extracts were washed with brine (15 mL), dried (MgSO₄) and concentrated. Chromatography of the residue (25:75 EtOAc/hexanes) gave 10 mg (54 %) of a nearly 70:30 mixture of diastereomers of 27 as a light yellow oil. ¹H: 6.60-6.44 (m, 1H); 6.03-5.91 (m, 3H); 4.33-4.16 (m,1H);3.83-3.62 (m, 3H); 3.13-3.00 (m, 1H); 3.00-2.85 (m, 1H); 2.37-1.87 (m, 3H); 1.37-1.10 (m, 6H); 0.97-0.77 (m, 9H); 0.14-0.01 (m, 6H). IR: 2222, 1739. HRESIMS: calc. for C₂₃H₃₄N₂O₄Si [M + Na]⁺ 437.2233; found 437.2236.

Compound 29. A cold (–78 °C) solution of 25 (1.00 g, 2.32 mmol) in dry THF (15 mL), containing 95% NaH (84 mg, 3.5 mmol) was stirred for 1.3 h, then it was carefully quenched with aq. sat'd. NH₄Cl (5 mL); CAUTION: evolution of flammable H₂ gas) and concentrated. The residue was partitioned between EtOAc (30 mL) and aq. sat'd NH₄Cl (30 mL). The organic phase was recovered and the aqueous phase was further extracted with EtOAc (3 x 20 mL). The combined extracts were washed with brine (15 mL), dried (MgSO₄) and concentrated. Chromatography of the residue (10:90 EtOAc/hexanes) gave 298mg (29 %) of a mixture of diastereomers of 29 as a light yellow oil. ¹H: 4.47-4.42 (m, 0.3H); 4.42-4.34 (m, 0.2H); 4.32-4.21 (m, 0.5H); 3.88-3.81 (s, 1.3H); 3.81-3.74(m, 1.7H); 3.37-3.29 (m, 0.45H); 3.05-2.90 (m, 1H); 2.85-2.65 (m, 1H); 2.64-2.29 (m, 1.85H); 2.29-1.90 (m, 2.95H); 1.85-1.44 (m, 1.75H); 1.42-1.34 (d, J=6.3, 0.6H); 1.34-1.22 (m, 4.2H); 1.13-1.03 (d, J=6.8, 1.2H); 0.99-0.82 (m, 9H); 0.25-0.08 (m, 6H). ¹³C: 205.3 205.2; 204.4; 172.0; 171.2; 171.0; 160.4; 136.3; 121.0; 119.1; 116.2; 115.0; 114.1; 70.3; 69.5; 62.0; 59.8; 59.0; 58.2; 57.9; 53.9; 53.7; 53.5; 52.6; 51.9; 50.8; 47.9; 37.3; 32.2; 29.8; 29.3; 27.9; 27.8; 27.6; 27.4; 26.9; 26.4; 26.1; 26.0; 25.9; 25.8; 25.0; 24.3; 24.1; 22.5; 20.4; 20.3; 20.0; 18.3; 18.2; -3.93; -3.99; -4.29; -4.52; -4.63. IR: 2260, 1767, 1735. HRESIMS: calc. for C₂₃H₃₄N₂O₄Si [M + Na]⁺ 453.2185; found 453.2186.

Silyl enol ether 30. Commercial LHMDS solution (1.0 M in THF, 0.3 mL, 0.3 mmol) was slowly added to a cold (–78 °C), stirred solution of 25 (133 mg, 0.3 mmol), LiCl (347 mg, 8.7 mmol) and TBSCl (924 mg, 6.2 mmol) in dry THF (2 mL) and HMPA (0.7 mL); CAUTION: cancer suspect agent). The mixture was stirred at –78 °C for 30 min, then it was heated to 50
Cycloadduct 31. A solution of 30 (80 mg, 147 μmol) in dry toluene (1 mL) was stirred at 140 °C in a 20 mL glass pressure vessel for 12 h, then it was cooled to RT and applied to a silica gel column (10 g). Elution (gradient 0 → 15% EtOAc / hexanes) gave 62 mg (77.5 %) of a nearly 50:50 mixture of diastereomers of 31 as a light yellow oil. \(^{1}H\): 4.43-4.32 (m, 1H); 3.76-3.66 (m, 3H); 2.85 (d, J = 4.1, 0.5H); 2.78 (d, J = 4.1, 0.5H); 2.65-2.49 (m, 2H); 2.26-1.89 (m, 3H); 1.81 (dd, J =12.0, 4.0, 1H); 1.62 (d, J = 12.0, 1H); 1.24 (d, J = 8, 3H) 1.15 (d, J = 8, 3H); 0.98-0.86 (m, 18 H); 0.21-0.09 (m, 12H). \(^{13}C\): 172.1; 171.7; 158.1; 157.9; 120.7; 120.9; 119.8; 120.5; 116.4; 116.7; 72.9; 70.1; 67.1; 66.8; 52.1; 52.0; 51.3; 50.4; 50.0; 38.2; 32.9; 29.5; 26.7; 26.4; 25.6; 25.3; 22.0; 22.5; 20.4; 20.3; 17.7; 17.8; -3.7; -3.6; -4.2; -4.5; -4.96; -4.94. IR: 2210, 1739. HRESIMS: calc. for C\(_{29}H_{48}N_{2}O_{3}Si\) [M + Na]\(^+\) 567.3054; found 567.3050.

Tricyclic ketone 33. Commercial HF - pyridine complex (70% HF, 0.9 mL) was added to a cold (0 °C), stirred solution of 31 (91 mg, 167 μmol) in MeCN (3 mL). The mixture was stirred for 6 h, during which time it was allowed to warm to RT, and then quenched with aq. sat'd NaHCO\(_3\) (2 mL) and concentrated. The residue was partitioned between EtOAc (15mL) and more aq. sat'd NaHCO\(_3\) (20 mL). The organic phase was recovered and the aqueous phase was extracted with EtOAc (3 x 10 mL). The combined extracts were washed with brine (15 mL), dried (MgSO\(_4\)) and concentrated. The crude was deprotected alcohol (crude 74 mg, 172 μmol) and Dess-Martin periodinane (219 mg, 516 μmol) in CH\(_2\)Cl\(_2\) was stirred at RT for 3h, then it was concentrated. Chromatography of the residue (gradient 5% → 10% EtOAc / hexanes) gave 33 (58 mg, 79 % over two steps) as a colorless oil. \(^{1}H\): 3.78 (s, 3H); 3.05 (d, J =3.9, 1H); 2.90-2.68 (m, 2H); 2.62 (sept, J =7.0, 1H); 2.47 (dd, J =13.5, 3.9, 1H, 2.29-2.18 (m, 1H), 2.10 (d, J = 3.5, 1H); 2.04-1.90 (m, 1H); 1.30 (d, J =6.8, 3H); 1.17 (d, J =6.8, 3H); 0.96 (s, 9H); 0.26 (s, 3H); 0.23 (s, 3H). \(^{13}C\): 198.8; 170.9; 156.7; 120.7; 116.3; 115.8; 66.5; 59.6; 57.1; 52.9; 52.7; 36.6; 31.2; 27.2; 25.6; 23.6; 22.1; 20.8; -3.3; -3.9. IR: 2359, 1734, 1646. HRESIMS: calc. for C\(_{23}H_{33}N_{2}O_{3}Si\) [M + H]\(^+\) 429.2206; found 429.2210.
Compound 11
Compound 10
Compound 12
Compound 13
Compound 14
Compound 15
Compound 16
Compound 18
Compound 19
Compound 20
Compound 21
Compound 22
Compound 24
Compound 25
Compound 29
Compound 30
Sample No: 9874 Steven JH-3-81 / ZD
stevan9874 2 1 13C / CDC13

Compound 33