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Supporting Information

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Polycyclic Molecules from Linear Precursors. The Stereoselective Synthesis of Clavolonine and Related Complex Structures

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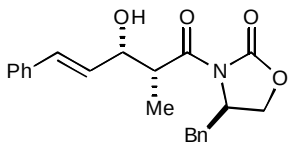
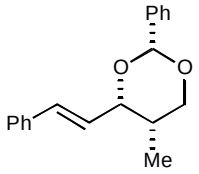
General Information. Purification of reaction products was carried out by flash chromatography using EM Reagent silica gel 60 (230-400 mesh). Analytical thin layer chromatography was performed on EM Reagent 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light and ceric ammonium nitrate stain, followed by heating. Optical rotations were measured on a Jasco DIP-0181 digital polarimeter with a sodium lamp and are reported as follows: $[\alpha]_{\lambda}^{T\ °C}$ (c = g/100 mL, solvent). Infrared spectra were recorded on a Perkin Elmer 1600 series FT-IR spectrometer. ^{1}H NMR spectra were recorded on a Varian Inova-500 (500 MHz) spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 7.26 ppm). Data are reported as (a = apparent, obs = obscured, s = singlet, d = doublet, t = triplet, m = multiplet; coupling constant(s) in Hz; integration. Proton-decoupled ^{13}C NMR spectra were recorded on a Varian Mercury 400 (100 MHz) spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 77.0 ppm). Low and high-resolution mass spectra were obtained on Jeol AX-505 or SX-102 spectrometers in the Harvard University Mass Spectrometry Laboratory. Yields refer to isolated yields of compounds estimated to be >95% pure as determined by ^{1}H-NMR.



(*R*)-4-benzyl-3-((2*R*,3*S*,*E*)-3-hydroxy-2-methyl-5-phenylpent-4-enoyl)oxazolidin-2-one (4). The following procedure is adapted from earlier work in this laboratory on the total synthesis of the polyether antibiotic X-206 (D. A. Evans, S. L. Bender, J. Morris, *J. Am. Chem. Soc.*, **1988**, *110*, 2506-2526.).

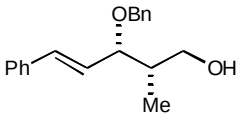
To a solution of propionyl-4-benzyloxazolidinone (15.0 g, 64.4 mmol) in 190 mL CH_2Cl_2 at 0 °C was added Bu_2BOTf (20.3 g, 18.7 mL, 74.0 mmol) followed immediately by NEt_3 (13.5 mL, 97.0 mmol). The solution was allowed to stir for 5 min before cooling to –78 °C (15 min). *trans*-Cinnamaldehyde (9.8 g, 9.4 mL, 74.0 mmol) was added dropwise over 10 min. The reaction mixture was allowed to stir at –78 °C for 60 min then warmed to 0 °C over 10 min and stirred at 0 °C for 30 min. 220 mL of 1M NaOAc in 90:10 MeOH/H_2O was added over 10 min followed by the addition of 30 ml of 30% H_2O_2 over 20 min. The reaction mixture was partitioned between 600 mL of hexane and 1L of H_2O. The aqueous layer was separated and extracted with 400 mL of hexane. Organic solutions were combined and washed with sat. $NaHCO_3$. Hexanes (500 mL) were added to the organic solution to facilitate precipitation of the desired product. The solid was collected by filtration and washed with cold hexane affording 21.7 g (92%) of fine white crystals. The filtrate was washed with brine, dried over Na_2SO_4, and concentrated to give 2.0 g of a light yellow solid which could be purified by chromatography.

Spectral data agrees with previously published material.



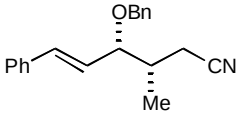
(2*R*,4*S*,5*S*,*E*)-5-methyl-2-phenyl-4-styryl-1,3-dioxane. To the imide **4** (17.56 g, 48.1 mmol) in 500 mL of reagent grade ether was added $LiBH_4$ (2.0 M in THF, 24.0 mL, 48.1 mmol) at –10 °C. The reaction was stirred for 1h and quenched with 100 mL of 1M NaOH. The reaction mixture was diluted with water (250 mL) and extracted with ether (4 x 150 mL). The organic solutions were combined and washed with brine, dried (Na_2SO_4), and concentrated. The white solid was dissolved in CH_2Cl_2 and filtered through a short silica pad (2", elution with CH_2Cl_2). Concentration afforded a white powder containing a mixture of diol and chiral auxiliary. To the mixture dissolved in PhH (200 mL) was added $PhCH(OMe)_2$ (9.5 g, 9.3 mL, 62.5 mmol) and $TsOH•H_2O$ (100 mg, 0.53 mmol). The reaction was allowed to stir overnight at RT and was queched by addition of sat. $NaHCO_3$ (250 mL). The reaction mixture was extracted with CH_2Cl_2 (1 x 300 mL, 2 x 100 mL). The combined organic solutions were washed with brine, dried (Na_2SO_4), and concentrated. The white solid was purified by chromatography (5→10% EtOAc in hexanes) to afford 12.5 g (93%, 2 steps) of the benzylidene acetal as fine white crystals.

$[\alpha]_D$: +40.0 (CH_2Cl_2) *c* = 2.0; IR (neat) 2966, 2851, 1496, 1450, 1397, 1359, 1241, 1212, 1159, 1107, 1003, 973, 745, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, *J* = 6.3, 2H, Ar**H**), 7.42–7.36 (m, 5H, Ar**H**), 7.34–7.32 (m, 2H, Ar**H**), 7.25–7.22 (m, 1H, Ar**H**), 6.66 (dd, J_1 = 1.5, J_2 = 16.1 Hz, 1H, PhC**H**=CH-), 6.23 (dd, J_1 = 5.37, J_2 = 16.1 Hz, 1H, PhCH=C**H**-), 5.63 (s, 1H, $(RO)_2$C**H**Ph), 4.71 (m, *J* = 4.4 Hz, 1H, =CHC**H**(OR)R), 4.20 (dd, J_1 = 2.4, J_2 = 11.2 Hz, 1H, OC**H₂**CH(Me)R), 4.09 (dd, J_1 = 1.0, J_2 = 11.2 Hz, 1H, OC**H₂**CH(Me)R), 1.78 (m, 1H, R_2C**H**Me), 1.25 (d, *J* = 6.8 Hz, 3H, **Me**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7, 136.8, 130.4, 128.9, 128.5, 128.3, 128.1, 127.6, 126.4, 126.2, 101.9, 80.1, 73.4, 33.3, 11.7; HRMS (CI) calc. for $C_{19}H_{20}O_2NH_4$ $[M+NH_4]^+$: 298.1807. Found: 298.1808. mp: 125.6–127.5 °C.



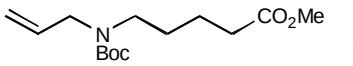
(2*S*,3*S*,*E*)-3-(benzyloxy)-2-methyl-5-phenylpent-4-en-1-ol. To a solution of benzylidene acetal (11.25 g, 40.18 mmol) in CH_2Cl_2 (0.25M, 160 mL) was added dibal-H (17.14 g, 21 mL, 120 mmol) at –78 °C. Following addition of dibal-H, the reaction was transferred to a –35 °C bath and stirred until TLC showed consumption of starting material (36 h). MeOH (10 mL) was added dropwise (*careful*: gas evolution!), the reaction mixture was warmed to 0 °C and 1M HCl (250 mL) was added slowly. After the aluminum salts dissolved, the reaction mixture was extracted with CH_2Cl_2 (3 x 100 mL). The combined organics solutions were washed with sat. $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated. The white solid was purified by flash column chromatography (20→40% EtOAc in hexane) affording 8.6 g (76%) of the primary alcohol product as a fine white needles; 575 mg (5%) of the regioisomeric allylic alcohol product was also isolated.

$[\alpha]_D$: +81.1 (CH_2Cl_2) *c* = 1.0; IR (neat) 3385, 2875, 1494, 1452, 1028, 970 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.45–7.41 (m, *J* = 7.3, 2H, Ar**H**), 7.38–7.26 (m, 8H, Ar**H**), 6.60 (d, *J* = 16.1 Hz, 1H, PhC**H**=CH-), 6.25 (dd, J_1 = 8.3, J_2 = 16.1 Hz, 1H, PhCH=C**H**-), 4.67 (d, *J* = 12.2 Hz, 1H, PhC**H₂**O-), 4.40 (d, *J* = 12.2 Hz, 1H, PhC**H₂**O-), 4.09 (dd, J_1 = 4.4, J_2 = 8.3 Hz, 1H, BnOC**H**R_2), 3.72 (m, 1H, -C**H₂**OH), 3.59 (m, 1H, -C**H₂**OH), 2.48 (dd, J_1 = 4.9, J_2 = 6.8 Hz, 1H, **H**OR), 2.18 (m, 1H, R_2C**H**Me), 0.95 (d, *J* = 6.8 Hz, 3H, **Me**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.1, 136.2, 133.6, 128.5, 128.31, 128.27, 127.7, 127.54, 127.47, 127.0, 126.8, 126.4, 125.8, 82.9, 70.3, 65.7, 39.9, 12.1; HRMS (CI) calc. for $C_{19}H_{22}O_2NH_4$ $[M+NH_4]^+$: 300.1964. Found: 300.1970. mp: 86.9–87.4 °C.

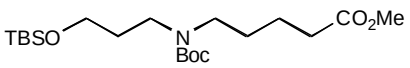


(3*S*,4*R*,*E*)-4-(benzyloxy)-3-methyl-6-phenylhex-5-enenitrile (5). The alcohol (4.38 g, 15.5 mmol), NEt_3 (2.7 mL, 19.4 mmol), TsCl (3.26 g, 17 mmol), and DMAP (180 mg, 1.5 mmol) were dissolved in CH_2Cl_2 (20 mL) at RT. After 4 h, 50 mL of 1M HCl was added. Following extraction (3 x 25 mL of CH_2Cl_2), the organic phases were washed with sat. $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated. The yellow oil was taken up in 15 mL of DMSO and KCN (2.0 g, 30 mmol) was added in one lot, turning the mixture orange. The reaction mixture was stirred with heating (50 °C) for 24 h. 1M NaOH (50 mL) was added and the mixture was extracted with ether (3 x 75 mL).

Combined organics were washed with brine, dried (Na_2SO_4), and concentrated. Purification by chromatography (10→20% EtOAc in hexane) afforded 4.23 g (94%, 2 steps) of the nitrile as a clear oil.
$[\alpha]_D$: +43.6 (CH_2Cl_2) *c* = 1.5; IR (neat) 2863, 2245, 1494, 1451, 1062, 970 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.44–7.40 (m, 2H, Ar**H**), 7.38–7.26 (m, 8H, Ar**H**), 6.64 (d, *J* = 15.6 Hz, 1H, PhC**H**=CH-), 6.10 (dd, J_1 = 7.8, J_2 = 15.6 Hz, 1H, PhCH=C**H**-), 4.65 (d, *J* = 11.7 Hz, 1H, PhC**H$_2$**O-), 4.39 (d, *J* = 11.7 Hz, 1H, PhC**H$_2$**O-), 3.92 (dd, J_1 = 5.4, J_2 = 7.8 Hz, 1H, BnOC**H**R_2), 2.53 (dd, J_1 = 5.9, J_2 = 16.6 Hz, 1H, -C**H$_2$**CN), 2.31 (dd, J_1 = 7.8, J_2 = 16.6 Hz, 1H, -C**H$_2$**CN), 2.18 (m, 1H, R_2C**H**Me), 1.18 (d, *J* = 6.8 Hz, 3H, **Me**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.1, 135.9, 134.4, 128.6, 128.3, 128.1, 127.59, 127.56, 126.5, 118.9, 81.7, 70.4, 35.7, 20.8, 15.0; HRMS (CI) calc. for $C_{20}H_{21}ON+NH_4$ $[M+NH_4]^+$: 309.1967. Found: 309.1970.

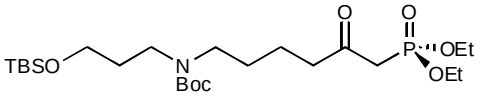


methyl 5-(allyl(*tert*-butoxycarbonyl)amino)pentanoate. NaH dispersion was washed free of oil with pentane (5 x 5 mL) and dried *in vacuo* to give 1.64 g (68.3 mmol) which was taken up in DMF (20 mL). Allyl bromide (20 mL, 227 mmol) that had been dried over 4Å mol sieves and K_2CO_3 was added to the mixture at –20 °C. The carbamate protected δ-amino valeric acid methyl ester (15 g, 65 mmol) was added dropwise via cannula as a solution in DMF (20 mL) at –20 °C. The reaction was allowed to warm slowly to 10 °C over 9 h. The reaction was quenched by addition of sat. NH_4Cl (50 mL), diluted with water (100 mL) and extracted with ether (3 x 50 mL). The combined organics were washed with brine, dried ($MgSO_4$), and concentrated. The resulting oil was purified by flash chromatography (9") with a gradient eluent (5→10% EtOAc in hexane) providing 9.68 g of the desired allylation product (55% yeild, 90% based on recovered starting material) as a light yellow oil; 5.38 g (35%) of unreacted starting material was recovered.
IR (neat) 2976, 1740, 1695, 1457, 1410, 1366, 1248, 1163 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.82–5.72 (m, 1H, -C**H**=CH_2), 5.14–5.06 (m, 2H, -CH=C**H$_2$**), 3.86–3.72 (m, 2H, =CHC**H$_2$**N-), 3.67 (s, 3H, CO_2**Me**), 3.24–3.12 (m, 2H, -NC**H$_2$**CH_2-), 2.33 (t, *J* = 7.3 Hz, 2H, -C**H$_2$**CO_2Me), 1.61–1.54 (m, 4H, -C**H$_2$**-), 1.45 (s, 9H, **Boc**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 155.2, 134.1, 134.0, 116.1, 115.6, 79.1, 51.1, 51.0, 49.5, 49.0, 45.8, 33.4, 33.3, 31.3, 28.1, 28.0, 27.4, 22.4, 21.9, 21.8; HRMS (CI) calc. for $C_{14}H_{25}NO_4$+H $[M+H]^+$: 272.1862. Found: 272.1867.



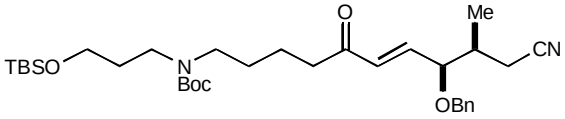
methyl 5-(*tert*-butoxycarbonyl(3-(*tert*-butyldimethylsilyloxy) amino)pentanoate. To the allylic carbamate (11.15 g, 41.1 mmol) in THF (100 mL) at 0 °C was added dropwise 9-BBN (0.5 M in THF, 110 mL) using an addition funnel. After 15 min, addition was complete and the reaction was held at 0 °C for 15 min. The ice bath was removed and the reaction mixture was stirred for 1.5 h at RT. After cooling to –10 °C, 1.0M NaOH (25 mL) was added dropwise followed by 30% H_2O_2 (25 mL) over 15 min ensuring the internal temperature remained below 15 °C. After stirring an additional 30 min under ice cooling, the mixture was diluted with 1.0M NaOH (100 mL), and extracted with ether (3 x 100 mL). The combined organic portions were washed with brine, diluted with an equal volume of hexanes, dried (Na_2SO_4), and concentrated. The resulting cloudy oil was taken up in DMF (50 mL) and cooled to 0 °C. Imidazole (8.4 g, 123 mmol) and TBSCl (8.65 g, 57.5 mmol) were added to the reaction vessel. Following dissolution, the ice bath was removed and the reaction was stirred for 3 h at RT. Sat. NH_4Cl (100 mL) was added and the mixture was extracted with ether (1 x 100 mL, 2 x 50 mL). The combined organic portions were washed with brine, diluted with an equal volume of hexanes, dried (Na_2SO_4), and concentrated. Purification by chromatography (8", 10→20% EtOAc in hexane) afforded 13.8 g (83%) of desired material as a clear oil.

IR (neat) 2858, 1742, 1697, 1472, 1416, 1365, 1253, 1175, 1102, 837, 776 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.66 (s, 3H, CO_2**Me**), 3.61 (t, *J* = 5.8 Hz, 2H, TBSOC**H**$_2$-), 3.26–3.16 (broad m, 4H, BocN(C**H**$_2$-)$_2$), 2.33 (t, *J* = 7.3 Hz, 2H, -C**H**$_2$CO$_2$Me), 1.76–1.68 (broad m, 2H, -C**H**$_2$-), 1.64–1.50 (m, 4H, -C**H**$_2$-), 1.44 (s, 9H, **Boc**), 0.89 (s, 9H, **tBu**Me$_2$SiO), 0.04 (s, 6H, tBu**Me**$_2$SiO); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 155.0, 78.5, 60.1, 50.9, 46.3, 43.7, 33.1, 31.5, 30.9, 27.9, 27.2, 25.3, 21.6, 17.66, –10.0); HRMS (ES) calc. for $C_{20}H_{41}NO_5$+Na $[M+Na]^+$: 426.2646. Found: 426.2658.



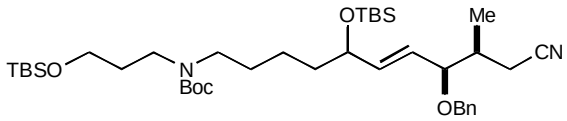
***tert*-butyl 3-(*tert*-butyldimethylsilyloxy)propyl(6-(diethoxyphosphoryl)-5-oxohexyl)carbamate (7).** To a solution of diethyl-methylphosphonate (10.0 mL, 67 mmol) in THF (120 mL) was added freshly titrated *n*-BuLi (2.70M, 25.4 mL, 68 mmol) at –78 °C. After 40 min, a solution of methyl ester (13.5 g, 33.5 mmol in 50 mL THF) was added over 20 min via cannula. The flask and cannula were rinsed with an additional 10 mL of THF. The reaction mixture was allowed to slowly warm to 10 °C overnight (10 h) and quenched by the addition of 200 mL of sat. NH_4Cl. The mixture was diluted with water and extracted with ether (1 x 200 mL, 2 x 150 mL). Following a brine wash, the organic layers were diluted with an equal portion of hexanes, dried over Na_2SO_4, and concentrated. The bulk of excess diethyl-methylphosphonate was removed under vacuum for several hours. Purification by flash chromatography (25→75% EtOAc in hexane) afforded 17.3 g (98%) of the keto-phosphonate as a clear oil.

IR (neat) 3454, 2931, 2858, 1691, 1477, 1415, 1365, 1252, 1171, 1025 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.14 (m, 4H, POC**H**$_2$CH$_3$), 3.61 (t, *J* = 6.4 Hz, 2H, TBSOC**H**$_2$-), 3.26–3.12 (broad m, 4H, BocN(C**H**$_2$-)$_2$), 3.06 (d, *J* = 22.5 Hz, 2H, C(O)C**H**$_2$P), 2.65 (t, *J* = 6.8 Hz, 2H, -C**H**$_2$C(O)CH$_2$P), 1.76–1.68 (broad m, 2H, -C**H**$_2$-), 1.58–1.48 (m, 4H, -C**H**$_2$-), 1.44 (s, 9H, **Boc**), 1.34 (t, *J* = 7.3 Hz, 6H, POCH$_2$C**H**$_3$), 0.89 (s, 9H, **tBu**Me$_2$SiO), 0.04 (s, 6H, tBu**Me**$_2$SiO); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.6, 155.4, 79.0, 62.4, 62.3, 60.6, 47.0, 46.6, 44.1, 43.5, 42.9, 41.6, 31.9, 31.3, 28.3, 27.9, 27.3, 25.8, 20.5, 18.1, 16.2, –5.7; HRMS (CI) calc. for $C_{24}H_{50}NO_7$+NH_4 $[M+NH_4]^+$: 541.3438. Found: 541.3438.



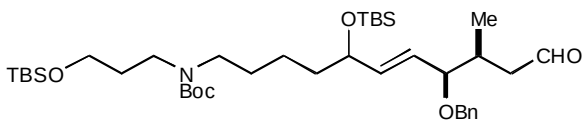
***tert*-butyl (8*R*,9*S*,*E*)-8-(benzyloxy)-10-cyano-9-methyl-5-oxodec-6-enyl(3-(*tert*-butyldimethylsilyloxy)propyl)carbamate (8).** The nitrile **5** (1.687 g, 5.79 mmol) was dissolved in 6 mL of MeOH and 6 mL of CH_2Cl_2. Ozone was bubbled through the solution at –78 °C until the excess ozone was observed (light blue color). After degassing with N_2, 10 equiv of DMS (4 mL) was added and the mixture was allowed to stir at RT for 3 h. Following filtration and concentration, the aldehyde was subjected to sequential azeotropic distillations of benzene and placed under high-vacuum with stirring for 60 min. Concomitantly, the keto-phosphonate (3.03 g, 5.79 mmol) in 18 mL of THF was added to a slurry of 95% NaH (146 mg, 6.08 mmol) in 12 mL of THF at –78 °C. After enolzation for 25 min., the aldehyde was added (via cannula) as a solution in (12 mL) THF over 20 min. The reaction mixture was stirred at –78 °C for 1 h and warmed to –20 °C for 1 h. Following addition of 50 mL of sat. NH_4Cl, the mixture was extracted with ether (3 x 50 mL). The organic portions were washed with brine, diluted with hexanes, dried over Na_2SO_4, and concentrated. Purification by flash chromatography afforded 3.04 g (90%) of desired enone as a clear oil.

$[\alpha]_D$: +19.5 (CH_2Cl_2) *c* = 1.3; IR (neat) 2936, 2858, 2246, 1690, 1634, 1472, 1416, 1365, 1253, 1175, 1100, 986, 837, 776 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36–7.29 (m, 5H Ar**H**), 6.67 (dd, J_1 = 6.4, J_2 = 16.1 Hz, 1H, C=C**H**-CH(OBn)R), 6.33 (d, J = 16.1 Hz, 1H, C**H**=CH-CH(OBn)R), 4.60 (d, J = 11.7 Hz, 1H, PhC**H$_2$**O-), 4.37 (d, J = 11.7 Hz, 1H, PhC**H$_2$**O-), 4.02 (m, 1H, R_2C**H**(OBn)), 3.62 (t, J = 5.9 Hz, 2H, TBSOC**H$_2$**-), 3.21 (broad s, 4H, BocN(C**H$_2$**)$_2$), 2.61 (broad s, 2H, -C**H$_2$**C(O)R), 2.48 (dd, J_1 = 6.4, J_2 = 16.6 Hz, 1H, RC**H$_2$**CN), 2.26 (dd, J_1 = 7.3, J_2 = 16.6 Hz, 1H, RC**H$_2$**CN), 2.16 (m, 1H, R_2C**H**Me), 1.76–1.68 (broad s, 2H, -C**H$_2$**-), 1.64–1.52 (m, 4H, -C**H$_2$**-), 1.44 (s, 9H, **Boc**), 1.09 (d, *J* = 7.3 Hz, 3H, **Me**-), 0.88 (s, 9H, **tBu**Me_2Si-), 0.04 (s, 6H, tBu**Me$_2$**Si-); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.1, 155.4, 142.0, 137.3, 131.7, 128.3, 128.2, 127.8, 127.6, 118.4, 79.5, 78.9, 71.4, 60.5, 46.4, 44.0, 40.2, 35.0, 31.8 28.3, 27.4, 25.7, 20.9, 20.8, 20.6, 18.0, 14.3, –5.5; HRMS (ES) calc. for $C_{33}H_{54}N_2O_5Si$ + H[M+H]$^+$: 587.3875. Found: 587.3864.



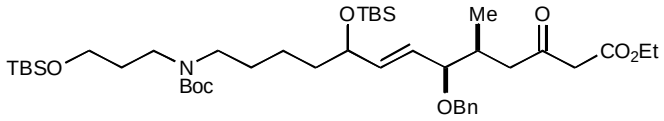
***tert*-butyl (8*R*,9*S*,*E*)-8-(benzyloxy)-5-(*tert*-butyldimethylsilyloxy)-10-cyano-9-methyldec-6-enyl(3-(*tert*-butyldimethylsilyloxy)propyl)carbamate.** A 100 mL flask was charged with enone (9.50 g, 16.18 mmol) and THF (50 mL). A solution of 1.0 M L-selectride in THF (20.0 mL, 20 mmol) was added by syringe at –78 °C. After 1.5 h, sat. NH_4Cl (50 mL) was added and the mixture was extracted with ether (3 x 50 mL). Combined organic portions were washed with brine, diluted with hexanes, dried over Na_2SO_4, and concentrated. The resulting oil was purified on a short pad of silica (4", elution 20% EtOAc in hexanes). Following concentration, the resulting clear oil (8.8 g) was diluted with 20 mL DMF. Imidazole (2.7 g, 38.8 mmol) and TBSCl (2.8 g, 18.7 mmol) were added and the reaction mixture was allowed to stir for 18 h. Sat. NH_4Cl (30 mL) was added and the mixture was extracted with ether (3 x 30 mL). Combined organic portions were washed with brine, diluted with hexanes, dried over Na_2SO_4, and concentrated. Purification by flash chromatography (eluent: 15→20% EtOAc in hexane) afforded 9.22 g (81%, 2 steps) of the desired product as a clear oil.

$[\alpha]_D$: +12.7 (CH_2Cl_2) *c* = 1.0; IR (neat) 2930, 2857, 2359, 1696, 1467, 1418, 1364, 1253, 1172, 1097, 836, 775 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36–7.26 (m, 5H, Ar**H**), 5.77–5.71 (m, 1H, -CH=C**H**-CH(OBn)-), 5.53–5.45 (m, 1H, -(TESO)CH-C**H**=CH-), 4.61–4.54 (m, 1H, ROC**H$_2$**Ph), 4.32–4.26 (m, 1H, ROC**H$_2$**Ph), 4.20–4.12 (m, 1H, R_2C**H**(OR)), 3.74 (m, 1H, R_2C**H**(OR)), 3.61 (t, *J* = 6.2 Hz, 2H, TBSOC**H$_2$**-), 3.26–3.11 (broad m, 4H, BocN(C**H$_2$**-)$_2$), 2.52–2.46 (m, 1H, RC**H$_2$**CN), 2.25–2.17 (m, 1H, RC**H$_2$**CN), 2.25–2.17 (m, 1H, R_2C**H**Me), 1.77–1.67 (m, 2H, -C**H$_2$**-), 1.56–1.46 (m, 4H, -C**H$_2$**-), 1.44 (s, 9H, **Boc**), 1.37-1.23 (m, 2H, -C**H$_2$**-), 1.10 (m, 3H, **Me**), 0.92–0.86 (m, 18H, 2 x **tBu**Me_2Si-), 0.08–0.02 (m, 12H, 2 x tBu**Me$_2$**Si-); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.5, 139.5, 139.2, 138.1, 128.4, 127.70, 127.65, 126.2, 126.0, 119.1, 81.1, 81.0, 79.0, 72.5, 72.3, 70.4, 60.7, 47.2, 44.3, 38.2, 35.7, 33.6, 32.1, 31.5, 28.5, 28.3, 25.9, 25.8, 25.6, 22.6, 20.9, 18.24, 18.19, 14.93, 14.86, –3.8, –4.2, –4.9, –5.4; HRMS (FAB) calc. for $C_{39}H_{70}N_2O_5Si_2$ [M]$^+$: 703.4899. Found: 703.4901.



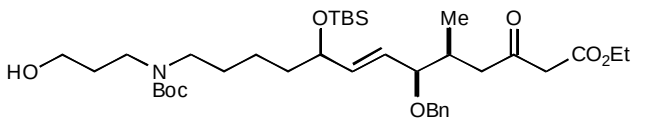
***tert*-butyl (8*R*,9*S*,*E*)-8-(benzyloxy)-5-(*tert*-butyldimethylsilyloxy)-9-methyl-11-oxoundec-6-enyl(3-(*tert*-butyldimethylsilyloxy)propyl)carbamate.** To the nitrile (4.38 g, 6.23 mmol) in CH_2Cl_2 (15 mL) was added Dibal-H (1600 ? L, 9.35 mmol) at –78 °C. After 15 min., the reaction mixture was warmed to –50 °C for 6 h. MeOH (1 mL) was added (*gas evolution*!) followed by CH_2Cl_2 (10 mL) and of sat. aq. Rochelle's salt (25 mL). The biphasic mixture was stirred vigorously for 4 h at RT. After extraction (2 x CH_2Cl_2), the organic phases were combined, washed with brine, dried over Na_2SO_4, and concentrated. Purification by flash chromatography (3", 10% EtOAc in hexanes) afforded 3800 mg (87%) of aldehyde as a clear oil.

$[\alpha]_D$: +16.9 (CH_2Cl_2) *c* = 1.4; IR (neat) 2930, 2858, 2710, 1727, 1696, 1472, 1415, 1365, 1253, 1171, 1096, 978, 775 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.72 (m, 1H, RC**H**O), 7.35–7.25 (m, 5H, Ar**H**), 5.69–5.64 (m, 1H, -CH=C**H**-CH(OBn)-), 5.64–5.54 (m, 1H, -(TESO)CH-C**H**=CH-), 4.59–4.56 (m, 1H, ROC**H₂**Ph), 4.31–4.26 (m, 1H, ROC**H₂**Ph), 4.18–4.11 (m, 1H, R_2C**H**(OBn)), 3.70–3.64 (m, 1H, TBSOC**H**R_2), 3.61 (t, *J* = 5.9 Hz, 2H, TBSOC**H₂**-), 3.26–3.10 (broad m, 4H, BocN(C**H₂**-)$_2$), 2.63–2.56 (m, 1H, RC**H₂**CHO), 2.40–2.32 (m, 1H, RC**H₂**CHO), 2.24–2.16 (m, 1H, R_2C**H**Me), 1.76–1.68 (m, 2H), 1.58–1.46 (m, 3H), 1.44 (s, 9H, **Boc**), 1.40-1.24 (m, 4H), 0.98–0.92 (m, 3H, **Me**-), 0.94–0.86 (m, 18H, 2 x **tBu**Me_2Si-), 0.09–0.02 (m, 12H, 2 x tBu**Me₂**Si-); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.3, 155.5, 139.2, 138.8, 128.3, 127.61, 127.57, 127.4, 126.8, 126.5, 82.1, 79.0, 72.7, 70.1, 60.7, 46.99, 46.94, 44.3, 38.3, 33.2, 32.1, 31.8, 28.5, 25.9, 25.8, 22.6, 18.3, 18.2, 15.9, 15.8, –5.0, –5.5; HRMS (ES) calc. for $C_{39}H_{71}NO_6Si_2$+H $[M+H]^+$: 706.4893. Found: 706.4897



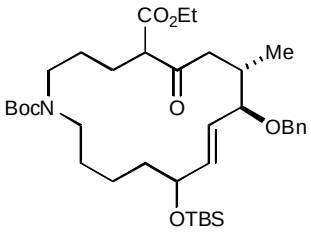
(5*S*,6*R*,*E*)-ethyl 6-(benzyloxy)-13-(*tert*-butoxycarbonyl(3-(*tert*-butyldimethylsilyloxy) propyl)amino)-9-(*tert*-butyldimethylsilyloxy)-5-methyl-3-oxotridec-7-enoate. A dry flask was charged with $SnCl_2$ and melted under flame heating. After cooling to RT, ethyl diazoacetate was added (*gas evolution*), stirred for 5 min, and diluted with CH_2Cl_2 (5 mL). The aldehyde (4.07 g, 5.80 mmol) was added via cannula as a solution in CH_2Cl_2 (10 mL). After 10 min, gas evolution ceased and a small aliquot was removed and checked for consumption of starting material by ^1H NMR. After 20 min (total), sat. aq. $NaHCO_3$ (50 mL) was added with rapid stirring. The mixture was extracted with CH_2Cl_2 (3 x 50 mL), washed with brine, dried (Na_2SO_4), and concentrated. The bulk of excess ethyl diazoacetate was removed on exposure to high vacuum for several hours. Purification by flash chromatography (10% EtOAc in hexanes) afforded 3750 mg (82%) of the keto-ester as a clear oil.

$[\alpha]_D$: +6.8 (CH_2Cl_2) *c* = 1.0; IR (neat), 2944, 2858, 1747, 1696, 1468, 1416, 1365, 1253, 1172, 1096, 976, 836, 776 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 12.09 (s, <1H, enol), 7.35–7.26 (m, 5H, Ar**H**), 5.68–5.62 (m, 1H, -CH=C**H**-CH(OBn)-), 5.56–5.47 (m, 1H, -(TESO)CH-C**H**=CH-), 4.92 (s, <1H, enol), 4.60–4.53 (m, 1H, ROC**H₂**Ph), 4.32–4.26 (m, 1H, ROC**H₂**Ph), 4.20–4.12 (m, 1H, TBSOC**H**R_2), 4.17 (q, *J* = 6.8 Hz, 2H, CO_2C**H₂**CH_3), 3.70–3.64 (m, 1H, R_2C**H**(OBn)), 3.61 (t, *J* = 6.3 Hz, 2H, TBSOC**H₂**-), 3.37 (s, ~2H, C(O)C**H₂**CO_2R), 3.27–3.11 (broad m, 4H, BocN(C**H₂**-)$_2$), 2.71 (m, 1H), 2.45 (m, 1H), 2.36–2.30 (m, 2H), 2.15–2.06 (m, 1H), 1.96–1.86 (m, 1H), 1.72 (broad s, 2H), 1.58–1.46 (m, 4H), 1.44 (s, 9H, **Boc**), 1.40–1.23 (m, 6H, **Me** and CO_2CH_2C**H₃**), 0.97–0.86 (m, 18H, **Me** and **tBu**Me_2Si-), 0.08–0.02 (m, 12H, tBu**Me₂**Si-); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.3, 167.1, 155.4, 138.6, 138.1, 128.24, 128.19, 127.6, 127.5, 127.3, 126.9, 126.7, 81.9, 81.7, 78.9, 72.5, 70.0, 61.1, 60.6, 49.6, 47.2, 45.8, 44.2, 38.2, 33.8, 33.7, 32.0, 28.7, 28.4, 25.84, 25.78, 22.6, 18.6,2, 18.1, 15.4, 15.3, 14.2, 14.0, –4.4, –4.8, –5.4. HRMS (ES) calc. for $C_{43}H_{77}NO_8Si_2$+H $[M+H]^+$: 792.5260. Found: 792.5258.



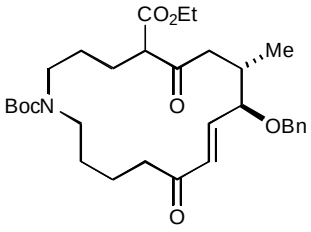
(5*S*,6*R*,*E*)-ethyl 6-(benzyloxy)-13-(*tert*-butoxycarbonyl(3-hydroxypropyl)amino)-9-(*tert*-butyldimethylsilyloxy)-5-methyl-3-oxotridec-7-enoate (9). In a plastic vial, the ketoester (4.24 g, 5.36 mmol) was dissolved in THF (5.5 mL) and cooled to 0 °C. In a separate vial, a stock solution of HF-pyridine was prepared (0.8 mL HF-pyr, 1.6 mL pyr, and 6 mL THF). 5.5 mL of the stock solution was added to the reaction vial and stirred for 7 h at 0 °C. Sat. aq. $NaHCO_3$ (10 mL) was added (*gas evolution*) and the mixture was extracted with ether (3 x 10 mL), washed with brine, diluted with an equal volume of hexanes, dried (Na_2SO_4), and concentrated. Purification by flash chromatography (10→20% EtOAc in hexanes) provided 2630 mg (72%, 93% based on recovered starting material) of the alcohol as a clear oil and 875 mg of starting material.

$[\alpha]_D$: +16.6 (CH_2Cl_2) *c* = 1.65; IR (neat) 3452, 2931, 2876, 2710, 1744, 1715, 1692, 1667, 1472, 1419, 1366, 1304, 1254, 1169, 1065 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 12.09 (s, <1H, enol), 7.36–7.25 (m, 5H, Ar**H**), 5.69–5.62 (m, 1H, -CH=C**H**-CH(OBn)-), 5.55–5.48 (m, 1H, -(TESO)CH-C**H**=CH-), 4.92 (s, <1H, enol), 4.57–4.52 (m, 1H, ROC**H**$_2$Ph), 4.30–4.26 (m, 1H, ROC**H**$_2$Ph), 4.20–4.13 (m, 2H, $CO_2C\mathbf{H}_2CH_3$), 3.82 (m, 1H, RC**H**(OTBS)-), 3.70–3.50 (m, 3H), 3.40–3.30 (m, 3-4H, C(O)C**H**$_2CO_2R$), 3.10 (m broad, 2H, RNBocC**H**$_2$-), 2.74–2.67 (m, 1H), 2.36–2.30 (m, 2H), 1,57–1.48 (m, 4H), 1.46 (s, 9H, **Boc**), 1.39–1.28 (m, 5H), 1.26 (t, *J* = 6.8 Hz, 3H, $CO_2CH_2C\mathbf{H}_3$), 0.94–0.87 (m, 12H, **Me** and **tBu**Me_2Si-), 0.08–0.04 (m, 6H, tBu**Me**$_2$Si-); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.4, 167.2, 157.1, 138.6, 138.0, 128.3, 127.8, 127.60, 127.56, 127.47, 127.46, 127.2, 126.9, 79.9, 72.5, 70.1, 61.2, 58.2, 49.6, 47.1, 45.9, 42.5, 38.2, 33.8, 33.7, 30.6, 28.6, 28.4, 25.8, 22.5, 18.2, 16.6, 15.3, 14.1, –4.4, –4.9; HRMS (ES) calc. for $C_{37}H_{63}NO_8Si$+H $[M+H]^+$: 678.4401. Found: 678.4401.

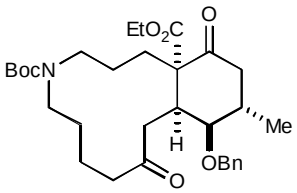


(8*S*,9*R*,*E*)-1-*tert*-butyl 5-ethyl 9-(benzyloxy)-12-(*tert*-butyldimethylsilyloxy)-8-methyl-6-oxoazacyclohexadec-10-ene-1,5-dicarboxylate (10). To a mixture of imidazole (144 mg, 2.11 mmol) and PPh_3 (485 mg, 1.85 mmol) in CH_2Cl_2 (4 mL) at –5 °C was added I_2 (470 mg, 1.85 mmol). After 5 min, the alcohol (900 mg, 1.32 mmol) was added as a solution in CH_2Cl_2 (4 mL) over 5 min. The reaction was allowed to stir at –5 °C for 2.5 h. The yellow mixture was loaded directly onto a short column of silica (3–4", 30 mm diameter) and flushed rapidly with 50% pentane in ether and then 100% ether. Fractions containing alkyl iodide were combined in a 1000 mL flask, diluted with benzene, and swiftly concentrated under reduced pressure (bath temp. 20–25 °C). (NB: if combined fractions were yellow, a wash with sodium thiosulfate and subsequent drying over $MgSO_4$ proved advantageous before proceeding to macrocyclization). The flask was briefly placed under high vacuum with a stir bar (5 min) and diluted with dry THF (200 mL, approx 0.007M). Dry Cs_2CO_3 (900 mg, 2.77 mmol) was added in one lot and the heterogeneous mixture was heated with stirring at 37 °C for 40 h. The reaction mixture was diluted with water (500 mL) and extracted with ether (4 x 100 mL), washed with brine, diluted with hexanes, dried (Na_2SO_4), and concentrated. Purification by flash chromatography (10→20% EtOAc in hexanes) afforded 566 mg (65%, 2 steps) of macrocycle as a light yellow oil.

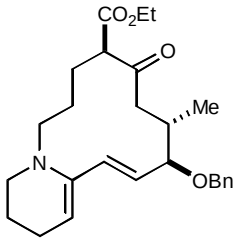
$[\alpha]_D$: +18.2 (CH_2Cl_2) *c* = 0.6; IR (neat) 2930, 2857, 1747, 1715, 1654, 1464, 1416, 1366, 1253, 1169, 1094, 1068, 980, 836, 776 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35–7.26 (m, 5H, Ar**H**), 5.72–5.53 (m, 1.5H, -C**H**=C**H**-), 5.43–5.32 (m, 0.5H, -C**H**=C**H**-), 4.62–4.52 (m, 1H, ROC**H**$_2$Ph), 4.38–4.27 (m, 1H, ROC**H**$_2$Ph), 4.22–4.08 (m, 2H, $CO_2C\mathbf{H}_2CH_3$), 3.70–2.88 (m, 6H), 2.71–2.52 (m, 1H), 2.42–2.23 (m, 2H), 1.95–1.76 (m, 2H), 1.63–1.40 (m, 9H), 1.45 (s, 9H, **Boc**), 1.23 (t, *J* = 6.8 Hz, 3H, $CO_2CH_2C\mathbf{H}_3$), 1.03–0.96 (m 3H, **Me**-), 0.91 (m, 9H, **tBu**Me_2Si-), 0.08 (m, 6H, tBu**Me**$_2$Si-); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.9, 204.7, 169.4, 169.4, 169.3, 169.24, 169.16, 155.9, 139.2, 138.9, 138.6, 138.44, 138.41, 137.6, 129.5, 129.2, 128.28, 128.25, 127.74, 127.68, 127.6, 127.45, 83.1, 82.83, 82.78, 82.4, 79.33, 79.25, 79.1, 79.0, 73.6, 71.2, 71.1, 70.2, 70.1, 70.0, 61.2, 61.1, 58.6, 58.3, 48.7, 48.35, 48.25, 48.0, 47.8, 47.2, 46.6, 45.0, 38.5, 38.2, 37.6, 34.0, 33.6, 33.2, 32.8, 29.6, 28.4, 25.82, 25.77, 22.6, 21.7, 21.5, 18.3, 18.2, 16.9, 16.7, 16.3, 16.1, 14.2, 14.0, –4.7, –4.9; HRMS (ES) calc. for $C_{37}H_{61}NO_7Si$+H $[M+H]^+$: 660.4299. Found 660.4295.



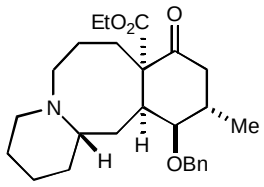
(8*S*,9*R*,*E*)-1-*tert*-butyl 5-ethyl 9-(benzyloxy)-8-methyl-6,12-dioxoazacyclohexadec-10-ene-1,5-dicarboxylate (11). To a solution of macrocycle (300 mg, 0.45 mmol) in THF (4.0 mL) in a plastic vial was added pyridine (0.75 mL) and HF-pyridine (0.50 mL). The reaction was stirred for 12 h at RT. Sat. aq. $NaHCO_3$ (10 mL) was added (*gas evolution*) and the mixture was extracted with ether (3 x 5 mL), washed with brine, diluted with an equal volume of hexanes, dried (Na_2SO_4), and concentrated. The yellow oil was dissolved in CH_2Cl_2 (4 mL) and solid $NaHCO_3$ (450 mg) was added followed by Dess-Martin Periodinane (470 mg, 1.125 mmol) in approx. 100 mg batches over 1.5 h. Sat. aq. $NaHCO_3$, sat. sodium thiosulfate, and CH_2Cl_2 (5 mL of each) was added with vigorous stirring. After 5 min, the reaction mixture turned clear and was diluted with additional $NaHCO_3$ solution and was extracted (2 x CH_2Cl_2), dried (Na_2SO_4), and concentrated. Purification by flash chromatography (20→30% EtOAc in hexanes) afforded 180 mg (74%, 2 steps) of bis-keto macrocycle as a clear oil that crystallized on refrigeration.
$[\alpha]_D$: +18.5 (CH_2Cl_2) *c* = 0.625; IR (neat) 2922, 1743, 1726, 1689, 1456, 1417, 1366, 1248, 1164 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36–7.26 (m, 5H, Ar**H**), 6.96–6.61 (m, 1H, =C**H**-CH(OBn)-), 6.35–6.21 (m, 1H, C(O)C**H**=), 4.54 (d, *J* = 11.7 Hz, 1H, OC**H**$_2$Ph), 4.39–4.35 (m, 1H, ROC**H**$_2$Ph), 4.20–4.10 (m, 2H, $CO_2C\mathbf{H}_2CH_3$), 3.85 and 3.66 (m, 1H, C(O)C**H**RCO_2R), 3.38–2.99 (m, XH), 2.80–2.73 (m, 1H), 2.68–2.24 (m), 1.95–1.57 (m), 1.53–1.39 (m), 1.43 (s, 9H, **Boc**), 1.27–1.21 (m, 3H, $CO_2CH_2C\mathbf{H}_3$), 1.09–1.03 (m, 3H, **Me**); ^{13}C NMR (100 MHz, $CDCl_3$) d 204.2, 203.9, 169.3, 169.2, 155.5, 145.4, 144.8, 137.8, 132.8, 128.42, 128.41, 127.8, 127.7, 81.8, 79.5, 71.12, 71.05, 61.40, 61.35, 68.8, 47.7, 39.1, 38.6, 33.5, 28.43, 28.41, 25.7, 17.42, 16.6, 14.1, 14.0; HRMS (ES) calc. for $C_{31}H_{45}NO_7$+H $[M+H]^+$: 544.3274. Found: 544.3276. mp: 127 °C. *X-ray.*



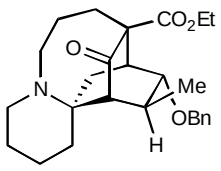
(10a*S*,11*R*,12*S*,14a*S*)-4-*tert*-butyl 14a-ethyl 11-(benzyloxy)-12-methyl-9,14-dioxo-tetradecahydrobenzo[*e*][1]azacyclododecine-4,14a(1*H*)-dicarboxylate (21). A solution of macrocycle (46 mg, 0.085 mmol) in EtOH (1.5 mL, dried over 4Å sieves) was cooled to −78 °C. In a separate flask dry Cs_2CO_3 (27 mg, 0.085 mmol) was dissolved in EtOH (0.5 mL) with gentle warming. The Cs_2CO_3 solution was added dropwise via syringe over 10 min to the solution of macrocycle. The reaction was held at −78 °C for 6 h, then warmed to 0 °C over 1 h. The reaction mixture was diluted with 10 mL of 0.1 N HCl and extracted with ether (4 x 10 mL). The combined organic portions were washed with sat. aq. $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated. Purification by flash chromatography (20→30% EtOAc in hexane) afforded 38 mg (83%) of desired Michael adduct as a white solid. *dr*: 94:06 (by unpurified ^1H NMR) $[\alpha]_D$: +32.5 (CH_2Cl_2) *c* = 0.65; IR (neat) 1713, 1693, 1414, 1366, 1252, 1163, 1094, 737, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) d 7.38–7.26 (m, 5H, ArH), 4.91 (d, *J* = 11.2 Hz, 1H, OC**H**$_2$Ph), 4.46 (d, *J* = 11.2 Hz, 1H, OC**H**$_2$Ph), 4.21 (q, *J* = 7.3, Hz, 2H, $CO_2C\mathbf{H}_2CH_3$), 4.00 (broad m, 1H), 3.81–3.72 (m, 2H), 3.52 (dd, J_1 = 4.4, J_2 = 11.2 Hz, 1H, $R_2C\mathbf{H}$(OBn)), 2.77–2.70 (m, 1H), 2.68–2.59 (m, 1H), 2.42–2.25 (m, 3H), 2.20 (dt, J_1 = 3.4, J_2 = 12.2 Hz, 1H), 1.88–1.66 (m, 3H), 1.60–1.40 (m, 8H), 1.54 (s, 9H, **Boc**), 1.25 (t, *J* = 7.3 Hz, 3H, $CO_2CH_2C\mathbf{H}_3$), 1.01 (d, *J* = 6.3 Hz, 3H, **Me**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.1, 205.0, 171.4, 138.1, 128.4, 128.35, 128.30, 127.7, 80.2, 71.0, 62.1, 61.4, 49.0, 48.7, 46.1, 43.1, 35.7, 35.6, 30.5, 28.4, 28.3, 26.9, 21.9, 19.0, 14.1; HRMS (FAB) calc. for $C_{31}H_{45}NO_7$+Na $[M+Na]^+$: 566.3094. Found: 566.3094. mp: 136 °C. *X-Ray.*



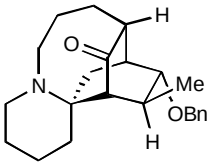
(9*R*,12*S*,13*R*,*E*)-ethyl 13-(benzyloxy)-12-methyl-10-oxo-3,4,6,7,8,9,10,11,12,13-decahydro-2*H*-pyrido[1,2-*a*][1]azacyclododecine-9-carboxylate (13). To a solution of macrocycle (180 mg, 0.33 mmol) in CH_2Cl_2 (2.5 mL) was added dimethylsulfide (0.250) mL) and TFA (0.50 mL) at 0 °C. The reaction mixture was allowed to warm to RT overnight (20 h). After concentration under a stream of nitrogen, the reaction mixture was diluted with 10 mL of 1.0 M NaOH and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic portions were washed with brine, dried (Na_2SO_4), and concentrated to afford 136 mg (97%) of the enamine as a beige solid that darkens over time and was used without purification. $[\alpha]_D$: +54.0 (CH_2Cl_2) *c* = 0.04; IR (neat) 2929, 2870, 2741, 1712, 1630, 1452, 1362, 1181, 1115, 1067, 1028, 977, 802, 738 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35–7.26 (m, 5H, Ar**H**), 6.02 (d, *J* = 15.6 Hz, 1H, -**H**C=CH-CH(OBn)R), 5.51 (dd, J_1 = 9.8, J_2 = 15.6 Hz, 1H, -HC=C**H**-CH(OBn)R), 4.71 (m, 1H, RC**H**=C(NR_2)R), 4.56 (d, *J* = 12.2 Hz, 1H, OC**H_2**Ph), 4.27 (d, *J* = 12.2 Hz, 1H, OC**H_2**Ph), 4.13 (q, *J* = 6.8, Hz, 2H, CO_2C**H_2**CH_3), 3.59 (dd, J_1 = 4.9, J_2 = 9.8 Hz, 1H, R_2CH(OBn)), 3.19 (t, *J* = 9.3 Hz, 1H), 3.10 (m, 1H), 3.02 (m, 2H), 2.66–2.57 (m, 2H), 2.56–2.40 (m, 2H), 2.14–2.06 (m, 1H), 2.03 (m, 2H), 1.80–1.64 (m, 2H), 1.62–1.46 (m, 3H), 1.24 (t, *J* = 7.3 Hz, 3H, CO_2CH_2C**H_3**), 1.10 (d, *J* = 6.3 Hz, **Me**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.8, 169.3, 143.7, 138.5, 133.8, 131.9, 128.3, 127.9, 127.6, 127.4, 102.3, 94.3, 85.5, 69.8, 61.5, 56.6, 50.1, 49.1, 48.6, 33.9, 25.6, 22.9, 22.3, 22.2, 18.9, 14.0; HRMS (FAB) calc. for $C_{26}H_{35}NO_4$+H $[M+H]^+$: 426.2647. Found 426.4244.



ethyl (1*S*,3*S*,5*S*,8*S*,4*R*)-12-aza-5-methyl-4-(phenylmethoxy)tricyclo[10.4.0.0<3,8>]hexadecane-8-carboxylate (19): To a solution of tricyclic enamine (10 mg, 0.023 mmol) in MeOH (1.0 mL) was added $NaBH_3CN$ (8 mg) and 1 drop of AcOH. After stirring 5 h at RT, sat. aq. $NaHCO_3$ (10 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated. Purification by pipet column chromatography on silica (5% MeOH in EtOAc + 1% NEt_3) afforded one major product (6 mg). The product was dissolved in ether and the solution was saturated with HCl(g). The white precipitate was filtered washed with hexanes and dried under vacuum. A single crystal was grown by slow diffusion of ether into a solution of the amine-HCl salt in MeOH and analyzed by X-ray diffraction. LRMS (ES) calc. for $C_{26}H_{37}NO_4$+H $[M+H]^+$: 428.3. Found 427.9. mp: 225 °C. *X-ray.*

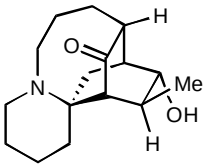


ethyl (1*S*,5*S*,4*R*,6*R*)-12-aza-5-methyl-7-oxo-4-(phenylmethoxy)tetracyclo[10.4.0.0<1,6>.0<3,8>]hexadecane-8-carboxylate (17). A sealed tube was charged with α,β-unsaturated enamine (37 mg, 0.089 mmol), EtOH (5 mL, dried over 4Å sieves), and piperidinium acetate (0.098 mmol, 0.49 mL of a freshly prepared 0.2 M solution). The light yellow solution was degassed with nitrogen for 5 min, sealed, and heated to 80 °C (bath temp). After 48 h, the solution was cooled to RT, concentrated under a stream of nitrogen, diluted with 1.0 M NaOH (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated. Purification by flash chromatography on silica (0→5% MeOH in EtOAc + 1% NEt_3) afforded 30 mg (81%) of a yellow oil.
$[\alpha]_D$: +8.3 (CH_2Cl_2) *c* = 0.4; IR (neat) 2959, 1713, 1732, 1460, 1260, 1207 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38–7.22 (m, 5H, Ar**H**), 4.59 (d, *J* = 12.2 Hz, 1H, OC**H_2**Ph), 4.37 (d, *J* = 12.2 Hz, 1H, OC**H_2**Ph), 4.08 (dq, J_1 = 6.8, J_2 = 22.9 Hz, 2H, CO_2C**H_2**CH_3), 3.23 (dt, J_1 = 4.9, J_2 = 14.6 Hz, 1H), 3.11 (m, *J* = 5.4 Hz, 1H), 2.95 (m, 1H), 2.78 (s, 1H), 2.69 (d, *J* = 5.4 Hz, 1H), 2.57 (m, 1H), 2.41 (d, *J* = 14.6 Hz, 1H), 2.24 (dd, J_1 = 4.4, J_2 = 15.1 Hz, 1H), 2.13 (m, 2H), 1.99 (d, *J* = 15.6, 1H), 1.62-1.20 (m, 8H); ^{13}C NMR (100 MHz, CDCl3) δ 204.7, 179.5, 138.3, 128.4, 127.7, 82.3, 70.6, 61.2, 58.5, 55.8, 50.3, 49.3, 38.9, 34.3, 34.2, 32.0, 28.1, 26.3, 23.7, 21.1, 19.2, 14.0; HRMS (ES) calc. for $C_{26}H_{35}NO_4$+H $[M+H]^+$: 426.2639. Found: 426.2644.



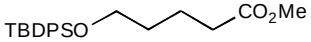
(1*S*,4*S*,5*S*,6*R*)-12-aza-5-methyl-4-(phenylmethoxy)tetracyclo [10.4.0.0<1,6>.0<3,8>]hexadecan-7-one. A vial was charged with keto ester (17 mg, 0.04 mmol), DMSO (1 mL) and wet *t*BuOK (11.2 mg, 0.10 mmol) and stirred overnight (18 h) at RT. HCl (1.0 M, 1.0 mL) was added and the mixture was concentrated under high vacuum overnight under gentle heating at 40–45 °C. The white solid was partitioned between 1.0M NaOH and EtOAc and extracted with EtOAc (3 x 5 mL). Organic phases were combined washed with brine brine, dried (Na_2SO_4), and concentrated. Purification by flash chromatography on silica (0→5% MeOH in EtOAc + 1% NEt_3) afforded 12 mg (85%) of a clear oil.

$[\alpha]_D$: +10.4 (CH_2Cl_2) *c* = 0.25; IR (neat) 2924, 2870, 1706 1456, 1362, 1092, 1071 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38–7.28 (m, 5H, ArH), 4.59 (d, *J* = 11.7 Hz, 1H, OC**H**$_2$Ph), 4.42 (d, *J* = 11.7 Hz, 1H, OC**H**$_2$Ph), 3.26 (broad d, *J* = 14.6 Hz, 1H), 3.02 (d, *J* = 5.4 Hz, 1H), 2.91 (m, 1H), 2.63 (s, 1H), 2.53 (m, 1H, *J* = 7.3 Hz), 2.44 (d, *J* = 14.2 Hz, 1H), 2.28 (m, 1H), 2.12 (dd, J_1 = 5.4, J_2 = 15.6 Hz, 1H), 2.00–1.80 (m, 4H), 1.71–1.32 (m, 8H), 0.99 (d, *J* = 7.3 Hz, 3H, **Me**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.5, 138.5, 128.4, 127.64, 127.59, 86.8, 71.0, 58.2, 55.9, 50.0, 49.9, 47.3, 35.0, 34.1, 30.6, 28.7, 27.3, 25.2, 23.2, 21.2, 19.6; HRMS calc. for $C_{23}H_{31}NO_2$+H $[M+H]^+$: 354.2428. Found 354.2425.



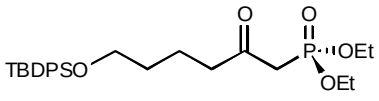
(1*S*,4*S*,5*S*,6*R*)-12-aza-4-hydroxy-5-methyltetracyclo[10.4.0.0<1,6>.0<3,8>]hexadecan-7-one (18). To a solution of benzyl ether (19 mg, 0.054 mmol) in EtOH (2.2 mL) was added $Pd(OH)_2$ on carbon (wet, 20% Pd by weight, 20 mg) under a balloon of H_2. The mixture was rapidly stirred for 23 h, filtered through celite, washed with CH_2Cl_2 (25 mL), and concentrated to give 10 mg (70%) of a yellow oil that crystallized on standing. Re-crystallization by slow diffusion of hexane into a solution of EtOAc provided crystals of sufficient purity for X-ray analysis.

$[\alpha]_D$: +9 (CH_2Cl_2) *c* = 0.5; IR (neat) 3400, 2925, 2871, 1699, 1460, 1108, 1040 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.36 (m, 1H), 3.28 (broad d, *J* = 12.2 Hz, 1H), 2.92 (m, 1H), 2.63 (s, 1H), 2.51 (m 1H), 2.44 (broad d, *J* = 14.2 Hz, 1H), 2.14 (broad d, *J* = 15.2 Hz, 1H), 2.02 (m, 2H), 1.96–1.78 (m, 4H), 1.70–1.50 (m, 5H), 1.50–1.42 (m, 2H), 1.40–1.30 (m, 2H), 1.04 (d, *J* = 7.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.1, 79.8, 58.2, 50.0, 49.6, 47.5, 40.3, 35.8, 30.3, 29.7, 28.4, 27.1, 25.3, 23.0, 21.2, 19.3, 14.1; HRMS calc. for $C_{16}H_{25}NO_2$+H $[M+H]^+$: 264.1958. Found 264.1954. mp: 194 °C. *X-ray.*



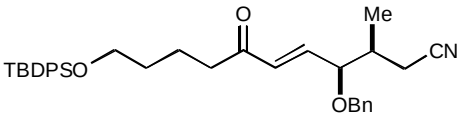
methyl 5-(*tert*-butyldiphenylsilyloxy)pentanoate. δ-Valerolactone (4.2 g, 42 mmol), NEt_3 (2 mL) and MeOH (40 mL) were combined and stirred at RT for 16 h. Benzene (20-30 mL) was added and the reaction mixture was concentrated under reduced pressure. The resulting clear oil was dissolved in DMF (40 mL). TBDPSCl (10 mL) and imidazole (6.5 g) were added and the reaction mixture was stirred for 14 h at RT. Saturated NH_4Cl (150 mL) was added, followed by extraction with ether (3 x 100 mL). After a brine wash, the organic portions were diluted with an equal volume of hexanes, dried over Na_2SO_4, and concentrated. Purification by flash column chromatography (10% EtOAc in hexanes) afforded 11.8 g (76%) of desired product as a clear oil.

IR (neat) 1741, 1590, 1428, 1111 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, *J* = 6.3 Hz, 4H, Ar**H**), 7.43 (m, 6H, Ar**H**), 3.72 (t, *J* = 6.1 Hz, 2H, -C**H**$_2$OR), 3.69 (s, 3H, CO_2C**H**$_3$), 2.31 (t, *J* = 7.8 Hz, -C**H**$_2$$CO_2$Me), 1.73 (m, 2H, -C**H**$_2$-), 1.58 (m, 2H, -C**H**$_2$-), 1.11 (s, 9H, **tBu**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 135.5, 133.8, 129.5, 127.6, 63.3, 51.3, 33.7, 31.8, 26.8, 19.1; HRMS (ES) calc. for $C_{22}H_{31}O_3Si$ $[M+H]^+$: 371.2042. Found: 371.2043.



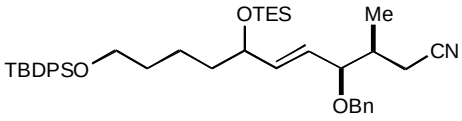
diethyl 6-(*tert*-butyldiphenylsilyloxy)-2-oxohexylphosphonate. Diethyl-methylphosphonate (9.0 mL, 62 mmol) was dissolved in 50 mL of THF. Freshly titrated *n*-BuLi (2.55M, 24.3 mL, 62 mmol) was added at –78 °C. After 30 min, a solution of methyl ester (11.5 g, 31 mmol in 25 mL THF) was added over 15 min via cannula. The flask and cannula were rinsed with an additional 5 mL of THF. The reaction mixture was stirred at –78 °C for 1 h, warmed to 0 °C over 30 min, and quenched by the addition of 100 mL of sat. NH_4Cl. The mixture was diluted with water and extracted (3 x 100 mL ether). Following a brine wash, the organic layers were diluted with an equal portion of hexanes, dried over Na_2SO_4, and concentrated under reduced pressure. The bulk of excess diethyl-methylphosphonate was removed under vacuum overnight. Purification of the yellow oil by flash chromatography (50→100% EtOAc in hexane) afforded 15.05 g (99%) of the keto-phosphonate as a clear oil.

IR (neat) 3071, 1715,1589, 1428, 1257, 1110, 1024, 967, 704 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, J = 6.3 Hz, 4H, Ar**H**), 7.62–7.47 (m, 6H, Ar**H**), 4.13 (m, 4H, POC**H**$_2$Me), 3.65 (t, J = 6.3 Hz, 2H, -C**H**$_2$OR), 3.05 (d, J = 23 Hz, -C(O)C**H**$_2$P), 2.61 (t, 7.3 Hz, 2H, -C**H**$_2$C(O)-), 1.67 (m, 2H, -C**H**$_2$-), 1.55 (m, 2H, -C**H**$_2$-), 1.33 (t, J = 6.8 Hz, 6H, POCH$_2$C**H**$_3$), 1.04 (s, 9H, **tBu**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.9, 201.8, 135.5, 133.8, 129.5, 127.5, 63.4, 62.44, 62.37, 43.6, 42.9, 41.6, 31.7, 26.8, 19.8, 16.3, 16.2; HRMS (ES) calc. for $C_{26}H_{40}O_3PSi$ $[M+H]^+$: 491.2377. Found: 491.2375.



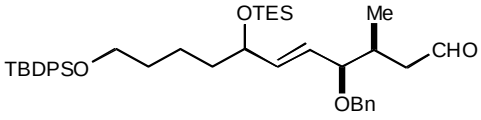
(3*S*,4*R*,*E*)-4-(benzyloxy)-11-(*tert*-butyldiphenylsilyloxy)-3-methyl-7-oxoundec-5-enenitrile (23). The nitrile (5.12 g, 17.6 mmol) was dissolved in 18 mL of MeOH and 18 mL of CH_2Cl_2. Ozone was bubbled through the solution at –78 °C until the excess ozone was observed (light blue color). After degassing with N_2, 10 equiv of DMS (12 mL) was added and the mixture was allowed to stir at RT for 3h. Following filtration and concentration, the aldehyde was sub*J*ected to sequential azeotropic distillations of benzene and placed under high-vacuum with stirring for 40–60 min. Concomitantly, the keto-phosphonate (8.62 g, 17.6 mmol) in 18 mL of THF was added to a slurry of 95% NaH (430 mg, 17.9 mmol) in 8 mL of THF at –78 °C. After enolzation for 25 min., the aldehyde was added (via cannula) as a solution in (18 mL) THF over 20 min. The reaction mixture was stirred at –78 °C for 1h and warmed to –20 °C for 1h. 50 mL of sat. NH_4Cl was added and the mixture was extracted with ether (3 x 50 mL). The organic portions were washed with brine, diluted with hexanes, dried over Na_2SO_4, and concentrated. Purification by flash chromatography afforded 7.1 g (73%) of desired enone as a clear oil.

$[\alpha]_D$: +11.1 (CH_2Cl_2) c = 1.0; IR (neat) 2246, 1688, 1674, 1634, 1428, 1361, 1111, 986, 703 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, J = 6.8, 4H, Ar**H**), 7.44–7.28 (m, 11H, Ar**H**), 6.64 (dd, J_1 = 6.3, J_2 = 16.1 Hz, -CH=C**H**-CH(OBn)-), 6.32 (dd, J_1 = 1.0, J_2 = 15.6 Hz, -C(O)C**H**=CH-), 4.59 (d, J = 11.7 Hz, ROC**H**$_2$Ph), 4.36 (d, J = 11.7 Hz, ROC**H**$_2$Ph), 4.01 (m, 1H, R$_2$C**H**OBn), 3.68 (t, J = 6.3 Hz, 2H, R$_3$SiOC**H**$_2$-), 2.57 (t, J = 6.3 Hz, 2H, -C**H**$_2$C(O)-), 2.47 (dd, J_1 = 7.8, J_2 = 16.6 Hz, 1H, -C**H**$_2$CN), 2.24 (dd, J_1 = 6.3, J_2 = 16.1 Hz, 1H, -C**H**$_2$CN), 2.14 (m, 1H, -C**H**(Me)-), 1.73 (m, 2H, -C**H**$_2$-), 1.61 (m, 2H, -C**H**$_2$-), 1.08 (d, J = 6.8 Hz, 3H, **Me**-), 1.04 (s, 9H, **tBu**Ph$_2$SiO-); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.4, 141.9, 137.4, 135.5, 133.8, 131.8, 129.5, 128.5, 128.2, 127.9, 127.7, 127.6, 118.6, 79.6, 71.5, 63.4, 40.5, 35.2, 31.8, 26.8, 20.7, 20.3, 19.1, 14.5; HRMS (ES) calc. for $C_{35}H_{44}NO_3Si$ $[M+H]^+$: 554.3090. Found: 554.3083.



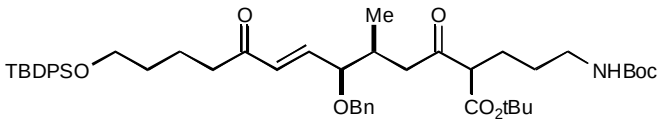
(3*S*,4*R*,*E*)-4-(benzyloxy)-11-(*tert*-butyldiphenylsilyloxy)-3-methyl-7-(triethylsilyloxy)undec-5-enenitrile. A 100 mL flask was charged with 6.00 g (10.8 mmol) of enone and 30 mL of THF. 12.5 mL of 1.0 M L-selectride in THF was added by syringe at –78 °C. After 1.5 h, sat. NH_4Cl (30 mL) was added and the mixture was extracted with ether (3 x 30 mL). Combined organic portions were washed with brine, diluted with hexanes, dried over Na_2SO_4, and concentrated. The resulting oil was filtered through a short pad of silica (3-4", elution 20% EtOAc in hexanes). Following concentration, the clear oil was diluted with 15 mL DMF. Imidazole (2.00 g) and TESCl (2.3 mL, 13.5 mmol) were added and the reaction mixture was allowed to stir for 30 h at RT. Sat. NH_4Cl (30 mL) was added and the mixture was extracted with ether (3 x 30 mL). Combined organic portions were washed with brine, diluted with hexanes, dried over Na_2SO_4, and concentrated. Purification by flash chromatography afforded 5.25 g (73%, 2 steps) of the desired product as a clear oil.

$[\alpha]_D$ (CH_2Cl_2) c = 1.0: +8.3; IR (neat) 2246, 1589, 1462, 1428, 1383, 1239, 1111, 1007, 978, 823, 739, 701 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, *J* = 6.8 Hz, 4H, Ar**H**), 7.44–7.26 (m, 11H, Ar**H**), 5.78–5.72 (m, 1H, -CH=C**H**-CH(OBn)-), 5.52–5.46 (m, 1H, -(TESO)CH-C**H**=CH-), 4.60–4.54 (m, 1H, ROC**H**$_2$Ph), 4.32–4.29 (m, 1H, ROC**H**$_2$Ph), 4.20–4.14 (m, 1H), 3.77–3.72 (m, 1H), 3.66 (t, *J* = 6.3 Hz, 2H, TBDPSOC**H**$_2$-), 2.51–2.45 (m, 1H), 2.24–2.16 (m, 1H), 2.10–2.02 (m, 1H), 1.62–1.36 (m, 6H), 1.10–1.07 (m, 3H, **Me**), 1.04 (s, 9H, **tBu**Ph$_2$SiO-), 0.96 (m, 9H, -OSiCH$_2$C**H**$_3$), 0.64–0.58 (m, 6H, -OSiC**H**$_2$CH$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.5, 139.3, 138.15, 138.12, 135.5, 134.0, 129.5, 128.33, 128.26, 127.64, 127.58, 127.54, 126.2, 125.9, 119.0, 81.1, 80.9, 72.5, 72.3, 70.34, 70.31, 63.7, 38.2, 35.7, 35.6, 32.5, 26.8, 21.7, 20.82, 20.78, 19.14, 14.8, 14.7, 6.9, 4.90, 4.88; HRMS (CI) calc. for $C_{41}H_{59}NO_3Si_2$ $[M+NH_4]^+$: 687.4377. Found: 687.4380.

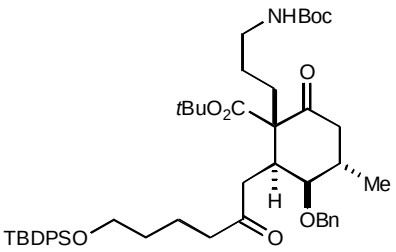


(3*S*,4*R*,*E*)-4-(benzyloxy)-11-(*tert*-butyldiphenylsilyloxy)-3-methyl-7-(triethylsilyloxy)undec-5-enal (24). To the nitrile (1.10 g, 1.64 mmol) in CH_2Cl_2 (3.7 mL) was added Dibal-H (350 ? L, 1.97 mmol) at –78 °C. After 15 min., the reaction mixture was warmed to –50 °C for 1.25 h. MeOH (1 mL) was added (*gas evolution*!) followed by 5 mL CH_2Cl_2 and 10 mL of sat. aqueous Rochelle's salt. The biphasic mixture was stirred vigorously for 3 h at RT. After extraction (2 x CH_2Cl_2), the organic phases were combined, dried over Na_2SO_4, and concentrated. Purification by flash chromatography afforded 916 mg (83%) of aldehyde as a clear oil.

$[\alpha]_D$: +20.3 (CH_2Cl_2) *c* = 1.25; IR (neat) 2715, 1726, 1589, 1458, 1420, 1379, 1238, 1111, 1007, 977, 823, 741, 702 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.72 (m, 1H, RC**H**O), 7.67 (d, *J* = 6.3 Hz, 4H, Ar**H**), 7.43–7.26 (m, 11H, Ar**H**), 5.70–5.64 (m, 1H, -CH=C**H**-CH(OBn)-), 5.53–5.46 (m, 1H, -(TESO)CH-C**H**=CH-), 4.60–4.52 (m, 1H, ROC**H**$_2$Ph), 4.31–4.25 (m, 1H, ROC**H**$_2$Ph), 4.18–4.11 (m, 1H,), 3.69–3.63 (m, 3H), 3.62–3.56 (m, 1H), 2.38–2.32 (m, 1H), 2.23–2.16 (m, 1H), 1.61–1.36 (m, 7H), 1.04 (s, 9H, **tBu**Ph$_2$SiO-), 0.98–0.92 (m, 12H, **Me** and OSiCH$_2$C**H**$_3$), 0.64–0.56 (m, 6H, -OSiC**H**$_2$CH$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.4, 202.3, 139.8, 138.8, 138.6, 138.5, 135.5, 134.0, 129.5, 128.3, 127.60, 127.56, 127.5, 127.4, 126.8, 126.5, 82.4, 82.1, 72.8, 72.6, 70.15, 70.09, 63.8, 47.0, 38.4, 33.3, 33.2, 32.6, 26.8, 21.8, 19.2, 15.9, 15.8, 6.9, 5.0, 4.9; HRMS (CI) calc. for $C_{41}H_{60}O_4Si_2$+NH_4 $[M+NH_4]^+$: 690.4374. Found: 690.4389.

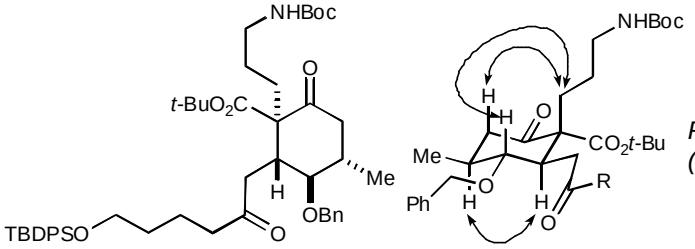


(12*R*,13*S*,*E*)-*tert*-butyl 12-(benzyloxy)-2,2,13,23,23-pentamethyl-9,15,21-trioxo-3,3-diphenyl-4,22-dioxa-20-aza-3-silatetracos-10-ene-16-carboxylate (26). A dry flask was charged with *t*-butyl ester **25** (201 mg, 0.74 mmol) and THF (0.35 mL). In a separate flask, a 1.0 M solution of LDA in THF and hexane was prepared by standard methods. LDA (1.47 mL, 1.47 mmol, 2.0 equiv) was added to the reaction vessel in one lot at –78 °C and stirred for 25 min. Aldehyde (283 mg, 0.42 mmol) was added via cannula as a solution in THF (0.50 mL) at –78 °C. The reaction mixture was held at –78 °C for 1 h and warmed to 0 °C slowly over 1h. Saturated aqueous NH_4Cl (20 mL) was added and the mixture was extracted with Et_2O (3 x 15 mL). Organic portions were combined and washed with brine, diluted with hexanes, dried over Na_2SO_4 and concentrated. The clear oil was passed through a short pad of silica (4", elution with 20% EtOAc in hexane) to remove unreacted aldehyde (<3%) and excess *t*-butyl ester. HRMS (ES) calc. for $C_{55}H_{87}NO_8Si_2$+H $[M+H]^+$: 946.6048. Found: 946.6048. The resulting oil (387 mg) was taken up in 2.0 mL of EtOH and PPTS (100 mg, 0.41 mmol) was added at RT with stirring. After 2.5 h, the reaction was concentrated to an oil under nitrogen. Following addtion of sat. aqueous NH_4Cl (15 mL), the mixture was extracted with Et_2O (3 x 15 mL). The organic portions were combined and washed with brine, diluted with hexanes, dried over Na_2SO_4 and concentrated. The resulting oil was dissolved in CH_2Cl_2 (4.0 mL). Solid $NaHCO_3$ (500 mg) was added followed by Dess-Martin periodinane (500 mg 1.22 mmol) in portions of 50-100 mg over 1 h at RT until the starting material appeared consumed by TLC. Sat. aqueous sodium thiosulfate (3 mL), sat. $NaHCO_3$ (5 mL), and CH_2Cl_2 were added with vigourous stirring. After 5 min, the reaction mixture turned clear and the organic layer was removed. Following extraction of the aqueous layer (20 mL of CH_2Cl_2), organics were combined, washed with brine, dried (Na_2SO_4) and concentrated. Purification by flash chromatography (25% EtOAc in hexanes) afforded 301 mg (87%, 3 steps) of desired keto-ester as an approx. 1:1 mixture of diastereomers.
$[\alpha]_D$: +5.4 (CH_2Cl_2) c = 0.75; IR (neat) 3395, 2933, 2860, 2366, 1708, 1508, 1458, 1367, 1250, 1157, 1111 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.80–7.64 (m, 4H, Ar**H**), 7.44–7.26 (m, 11H, Ar**H**), 6.71–6.64 (m, 1H, -C=C**H**-CH(OBn)-), 6.30–6.23 (m, 1H, -**H**C=CH-CH(OBn)-), 4.57–4.51 (m, 2H, -OC**H**$_2$Ph, RBocN**H**), 4.36–4.29 (m, 1H, -OC**H**$_2$Ph), 3.92 (m, 1H, R_2C**H**OBn), 3.67 (t, *J* = 6.2 Hz, 2H, R_3SiOC**H**$_2$-), 3.33–3.22 (m, 1H, C(O)C**H**RCO_2R), 3.12–3.02 (broad m, 2H, RHNC**H**$_2$-), 2.77–2.52 (m, 3H), 2.46–2.30 (m, 2H), 1.80–1.66 (m, 4H), 1.66–1.55 (m, 2H), 1.47–1.36 (m, 18H, CO_2**tBu** and **Boc**NHR), 1.05 (s, 9H, **tBu**Ph_2SiO-), 0.93–0.88 (m, 3H, **Me**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.5, 204.2, 199.8, 168.7, 168.6, 155.9, 143.6, 138.0, 137. 9, 135.5, 133.9, 131.2, 131.1, 129.5, 128.39, 128.36, 127.74, 127.68, 127.58, 127.55, 81.99, 81.95, 80.9, 80.64, 79.1, 71.3, 71.2, 63.5, 59.8, 59.7, 44.8, 44.6, 40.4, 40.3, 40.0, 33.0, 32.8, 32.0, 28.4, 27.9, 27.6, 26.8, 25.1, 24.9, 20.4, 19.2, 15.08, 15.07; HRMS (FAB) calc. for $C_{49}H_{69}NO_8Si$+Na $[M+Na]^+$: 850.4690. Found: 850.4680.



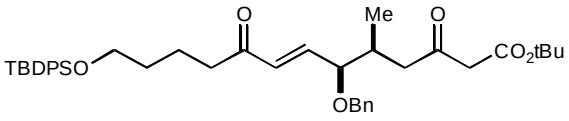
(1*S*,2*S*,3*R*,4*S*)-*tert*-butyl 3-(benzyloxy)-1-(3-(*tert*-butoxycarbonylamino)propyl)-2-(6-(*tert*-butyldiphenylsilyloxy)-2-oxohexyl)-4-methyl-6-oxocyclohexanecarboxylate (30A). To the ketoester (40 mg, 0.048 mmol) in EtOH (1 mL) at –78 °C was added Cs_2CO_3 (33 mg, 0.1 mol) as a solution in EtOH. After 6 h, the reaction was warmed to 0 °C, diluted with 0.1N HCl and extracted with ether (3 x 15 mL). The combined organic portions were washed with sat. $NaHCO_3$ (25 mL) and brine, diluted with hexanes, dried (Na_2SO_4), and concentrated. The unpurified material indicated a ratio of diastereomeric products (5:2). Purification by flash chromatography (20→30% EtOAc in hexanes) afforded 23 mg (57% yield) of the major, illustrated diastereomer **30A** and 8 mg (20%) of the minor diasteromer **30B** (epimeric at C7).

30A: $[\alpha]_D$: +26.4 (CH_2Cl_2) c = 0.5; IR (neat) 3401, 2831, 2860, 1715, 1508, 1456, 1428, 1391, 1367, 1250, 1167, 1112 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.63 (m, 4H, Ar**H**), 7.44–7.34 (m, 6H, ArH), 7.31–7.20 (m, 5H, Ar**H**), 4.57 (d, *J* = 11.0 Hz, 1H, -OC**H**$_2$Ph), 4.54 (m, 1H, BocN**H**-), 4.37 (d, *J* = 11.0 Hz, 1H, -OC**H**$_2$Ph), 3.70 (m, 1H), 3.58 (t, *J* = 5.9 Hz, 2H, TBDPSOC**H**$_2$-), 3.52 (dd, J_1 = 6.3, J_2 = 13.2 Hz, 1H), 3.14–2.96 (m, 2H, RHNC**H**$_2$-), 2.47 (dd, J_1 = 5.9, J_2 = 17.6 Hz, 1H), 2.40–2.26 (m, 4H), 2.00–1.90 (m, 2H), 1.64–1.24 (m, 29H), 1.03 (s, 9H, **tBu**Ph$_2$SiO), 1.00 (d, *J* = 6.2 Hz, 3H, **Me**), 0.88 (dt, J_1 = 1.1, J_2 = 7.3 Hz, 1H);); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.5, 206.1, 170.3, 155.8, 137.9, 135.5, 133.9, 129.5, 128.3, 128.2, 127.7, 127.6, 82.7, 80.3, 71.2, 63.4, 62.8, 45.5, 43.0, 40.5, 38.9, 36.9, 34.7, 31.9, 28.7, 28.4, 27.9, 26.8, 24.2, 20.0, 19.2, 19.1; HRMS (ES) calc. for $C_{49}H_{69}NO_8Si$+H $[M+H]^+$: 828.4870. Found: 828.4874.



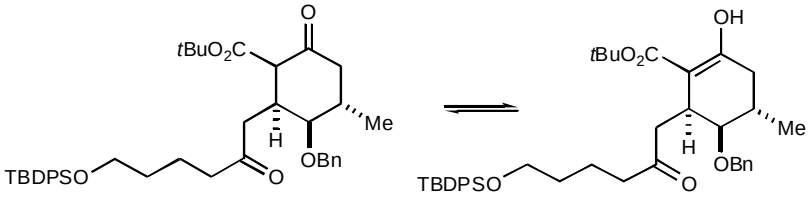
Relevant NOE (MeOH-d_4)

(1*R*,2*R*,3*R*,4*S*)-*tert*-butyl 3-(benzyloxy)-1-(3-(*tert*-butoxycarbonylamino)propyl)-2-(6-(*tert*-butyldiphenylsilyloxy)-2-oxohexyl)-4-methyl-6-oxocyclohexanecarboxylate (30C). $[\alpha]_D$: +13.0 (CH_2Cl_2) c = 0.95; IR (neat) 3396, 2931, 2860, 1713, 1057, 1454, 1366, 1250, 1168, 1112, 702 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.63 (d, *J* = 6.3 Hz, 4H, Ar**H**), 7.43–7.36 (m, 6H, Ar**H**), 7.27–7.19 (m, 5H, Ar**H**), 4.62 (m, 1H, BocN**H**-), 4.57 (d, *J* = 11.0 Hz, 1H, -OC**H**$_2$Ph), 4.52 (d, *J* = 11.0 Hz, 1H, -OC**H**$_2$Ph), 3.52 (t, *J* = 5.9 Hz, 2H, TBDPSOC**H**$_2$-), 3.35–3.28 (m, 2H), 3.19–3.05 (m, 2H, RHNC**H**$_2$-), 2.53–2.28 (m, 3H), 2.23–2.10 (m, 3H), 2.03 (d, *J* = 10.3 Hz, 1H), 1.76 (m, 1H), 1.64–1.55 (m, 2H), 1.45 (s, 9H, CO_2**tBu**), 1.43 (s, 9H, **Boc**), 1.46–1.32 (m, 4H), 1.21 (m, 1H), 1.14 (d, *J* = 6.3 Hz, 3H, **Me**), 1.02 (s, 9H, **tBu**Ph$_2$SiO-); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.2, 206.3, 170.2, 156.1, 137.8, 155.5, 133.9, 129.5, 128.3, 127.61, 127.58, 127.5, 83.7, 82.1, 79.1, 73.1, 64.4, 63.5, 45.5, 43.8, 42.9, 41.7, 40.6, 37.5, 31.9, 30.4, 28.4, 27.8, 26.9, 26.8, 25.1, 19.8, 19.2, 19.1; HRMS (ES) calc. for $C_{49}H_{69}NO_8Si$+H $[M+H]^+$: 828.4870. Found: 828.4864.



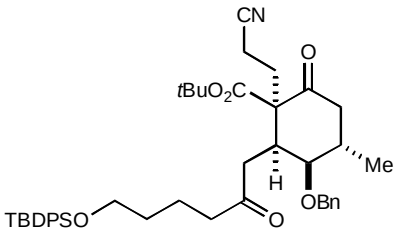
(5*S*,6*R*,*E*)-*tert*-butyl 6-(benzyloxy)-13-(*tert*-butyl diphenylsilyloxy)-5-methyl-3,9-dioxotridec-7-enoate (27). A dry flask was charged with *t*-butyl acetate (217 mg, 0.25 mL, 1.87 mmol) and THF (1.0 mL). In a separate flask, a 1.0 M solution of LDA in THF and hexane was prepared by standard methods. LDA (1.87 mL, 1.87 mmol) was added to the reaction vessel in one lot at –78 °C and stirred for 25 min. The aldehyde (630 mg, 0.94 mmol) was added via cannula as a solution in THF (1.0 mL) at –78 °C. The reaction mixture was held at –78 °C for 1 h and warmed to 0 °C over 10 min. Sat. aqueous NH_4Cl (20 mL) was added and the mixture was extracted with Et_2O (3 x 15 mL). Organic portions were combined and washed with brine, diluted with hexanes, dried over Na_2SO_4 and concentrated. The clear oil was dissolved in 5.0 mL of EtOH and PPTS (230 mg, 0.94 mmol) was added at RT with stirring. After 1.25 h, the reaction was concentrated to a yellow oil under nitrogen. Following addition of sat. aqueous NH_4Cl (15 mL), the mixture was extracted with Et_2O (3 x 15 mL). Organic portions were combined and washed with brine, diluted with hexanes, dried over Na_2SO_4 and concentrated. The light yellow oil was passed through a short plug of silica (3", elution with 20–40% EtOAc in hexane). The resulting clear oil (560 mg) was dissolved in CH_2Cl_2 (5.0 mL). Solid $NaHCO_3$ (500 mg) was added followed by Dess-Martin periodinane (1000 mg, 2.5 mmol) in portions of 100-50 mg over 1.5 h at RT until the starting material appeared consumed by TLC. Sat. aqueous sodium thiosulfate, sat. $NaHCO_3$, and CH_2Cl_2 (5 mL of each) were added with vigorous stirring. After 5 min., reaction mixture turned clear and organic layer was removed. The reaction mixture was diluted with 25 mL of sat. $NaHCO_3$ and extracted with Et_2O (1 x 50 mL, 2 x 20 mL).

Organic portions were combined, washed with sat. $NaHCO_3$ and brine, diluted with hexanes, dried (Na_2SO_4) and concentrated. The resulting material (535 mg, 84%, >90% purity by H-NMR) was used swiftly without purification. *NB*: attempted purification on silica effected an intramolecular Michael reaction in moderate selectivity. Indicative signals ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.23 (s, <1H, enol), 7.66 (d, *J* = 6.3, 4H, Ar**H**), 7.43–7.26 (m, 11H, Ar**H**), 6.67 (dd, J_1 = 6.3, J_2 = 16.1 Hz, 1H, C(O)CH=C**H**R), 6.27 (dd, J_1 = 1.5, J_2 = 16.1 Hz, 1H, C(O)C**H**=CHR), 4.80 (s, <1H, enol), 4.55 (d, *J* = 11.7 Hz, 1H, -OC**H$_2$**Ph), 4.32 (d, *J* = 11.7 Hz, 1H, -OC**H$_2$**Ph), 3.67 (t, *J* = 6.3 Hz, 2H, TBDPSOC**H$_2$**-), 3.24 (d, *J* = 6.3 Hz, 2H, C(O)C**H$_2$**CO_2R), 2.68 (dd, J_1 = 4.9, J_2 = 17.1 Hz, 1H), 2.56 (t, *J* = 7.3 Hz, 1H, -C**H$_2$**C(O)CH_2-), 2.45–2.32 (m, 2H, RMeCHC**H$_2$**C(O)-), 1.72 (m, 1H, -C**H$_2$**-), 1.59 (m, 1H, -C**H$_2$**-), 1.44 (s, 9H, CO_2**tBu**), 1.04 (s, 9H, **tBu**Ph_2SiO), 0.92 (d, *J* = 6.8 Hz, 3H, **Me**-).



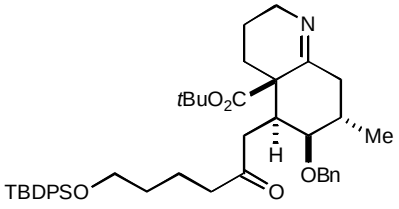
(2*S*,3*R*,4*S*)-*tert*-butyl 3-(benzyloxy)-2-(6-(*tert*-butyldiphenylsilyloxy)-2-oxohexyl)-4-methyl-6-oxocyclohexanecarboxylate (28). To the enone in EtOH (4 mL) was added a solution of Cs_2CO_3 (270 mg, 0.83 mmol) in EtOH (4 mL) at –78 °C. After stirring at –78 °C for 5 h, the reaction mixture was warmed to 0 °C and partitioned between water and Et_2O (30 mL of each). The organic layer was removed and the aqueous portion extracted twice with Et_2O (30 mL). Combined organics were washed with brine, diluted with hexanes, dried (Na_2SO_4) and concentrated to afford 535 mg (96%) of a pale yellow viscous oil. H-NMR analysis indicates that the product exists as an approx. 1:2 mixture of keto and enol tautomers. Because of this complication, purification and characterization were delayed; the Michael adduct was carried on without purification.
Indicative ^{1}H NMR signals (500 MHz, $CDCl_3$) δ 12.47 (s, <1H, =C(O**H**)R, enol), 4.61 (d, *J* = 11.2 Hz, <1H, OC**H$_2$**Ph), 4.55 (d, *J* = 10.7 Hz, <1H, OC**H$_2$**Ph), 4.39 (d, *J* = 11.2 Hz, <1H, OC**H$_2$**Ph), 4.28 (d, *J* = 10.7 Hz, 0.66H, OC**H$_2$**Ph), 3.62 (t, *J* = 6.3 Hz, <2H, TBDPSOC**H$_2$**-), 3.55 (t, *J* = 6.3 Hz, <2H, TBDPSOC**H$_2$**-), 3.34 (d, *J* = 10.3 Hz, <1H) 3.18 (dd, J_1 = 5.4, J_2 = 10.3 Hz, <1H), 2.65 (dd, J_1 = 8.3, J_2 = 16.6 Hz, <1H); ; HRMS (ES) calc. for $C_{41}H_{54}O_6Si$+H $[M+H]^+$: 671.3768. Found: 671.3762.

A small amount of the above material was decarboxylated under Krapcho conditions (DMSO, H_2O, NaCl, 140 °C, 2 h). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (m, 4H, Ar**H**), 7.42–7.26 (m, 11H, Ar**H**), 4.62 (d, *J* = 1.7 Hz, 1H, OC**H$_2$**Ph), 4.30 (d, *J* = 11.7, 1H, OC**H$_2$**Ph), 3.63 (t, *J* = 6.3 Hz, 2H, TBDPSOC**H$_2$**-), 3.46 (m, 1H, R_2C**H**(OBn)), 2.80 (m, 1H, R_2C**H**-CH(OBn)R), 2.70–2.64 (m, 2H), 2.46 (m, 1H, R_2C**H**(Me)), 2.40–2.20 (m, 6H), 2.06 (dd, J_1 = 5.4, J_2 = 14.2 Hz, 1H, C(O)C**H**$_2$CH(Me)R), 1.64–1.46 (m, 4H, -C**H$_2$**-), 1.04 (s, 9H, **tBu**), 1.02 (d, *J* = 7.3 Hz, 3H, **Me**); ; HRMS (ES) calc. for $C_{36}H_{46}O_4Si$+H $[M+H]^+$: 571.3243. Found: 571.3239.
The stereochemistry and selectivity of the Michael reaction was proven by NOE on the derived material. Unpurified (^{1}H NMR) >10:1 isomeric purity.



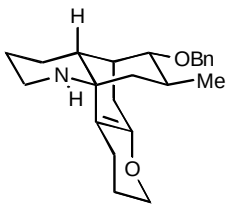
(1*R*,2*S*,3*R*,4*S*)-*tert*-butyl 3-(benzyloxy)-2-(6-(*tert*-butyldiphenylsilyloxy)-2-oxohexyl)-1-(2-cyanoethyl)-4-methyl-6-oxocyclohexanecarboxylate (29). To the keto-ester (210 mg, 0.31 mmol) in MeCN (1.6 mL) was added acrylonitrile (62 μL, 0.94 mmol) followed by $Bu_4NOH•30H_2O$ (25 mg, 0.03 mmol) at 0 °C. The ice bath was removed and the reaction mixture was stirred at RT for 2 h, when an additional 20 mg of $Bu_4NOH•30H_2O$ was added. An additional 3 h of stirring was required to effect consumption of the starting material. The reaction mixture was diluted with water (20 mL) and extracted with ether (3 x 20 mL). Combined organics were washed with brine, diluted with hexanes, dried (Na_2SO_4) and concentrated. Purification by flash chromatography on silica (elution with 20% EtOAc in hexane) afforded 160 mg (71%) of the desired product as a clear oil. H-NMR indicates as single diastereomer.

$[\alpha]_D$: –59.3 (CH_2Cl_2) c = 1.0; IR (neat) 2249, 1714, 1589, 1455, 1428, 1369, 1247, 1156, 1111 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, *J* = 6.3 Hz, 4H, Ar**H**), 7.45–7.37 (m, 6H, Ar**H**), 7.33–7.22 (m, 5H, Ar**H**), 4.63 (d, *J* = 12.2 Hz, 1H, OC**H**$_2$Ph), 4.30 (d, *J* = 12.2, 1H, OC**H**$_2$Ph), 3.63 (t, *J* = 6.3 Hz, 2H, TBDPSOC**H**$_2$-), 3.42 (dd, J_1 = 6.3, J_2 = 13.2 Hz, 1H), 3.25 (s, 1H), 2.98 (dd, J_1 = 9.8, J_2 = 19.0 Hz, 1H), 2.73 (d, *J* = 19.0 Hz, 1H), 2.63–2.50 (m, 3H), 2.28–2.22 (m, 1H), 2.15 (d, *J* = 15.1, 1H), 2.12 (dd, J_1 = 4.4, J_2 = 11.7 Hz, 1H), 2.06–1.88 (m, 3H), 1.56–1.46 (m, 4H), 1.37 (s, 9H, CO_2**tBu**), 1.06 (s, 9H, **tBu**Ph_2SiO-), 0.96 (d, *J* = 7.3, 1H, **Me**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.4, 207.1, 169.6, 137.5, 135.5, 133.9, 129.6 128.7, 128.5, 128.1, 127.6, 119.5, 82.9, 78.6, 71.1, 63.5, 59.8, 42.6, 42.5, 39.7, 38.1, 32.5, 31.9, 29.5, 27.8, 26.8, 19.9, 19.2, 17.0, 13.0; HRMS (ES) calc. for $C_{44}H_{57}NO_6Si$ $[M+H]^+$: 724.4033. Found: 724.4041.



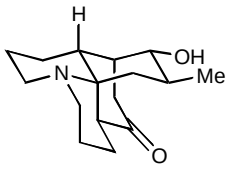
(4a*R*,5*S*,6*R*,7*S*)-*tert*-butyl 6-(benzyloxy)-5-(6-(*tert*-butyldiphenylsilyloxy)-2-oxohexyl)-7-methyl-2,3,4,4a,5,6,7,8-octahydroquinoline-4a-carboxylate (32). To the nitrile (48 mg, 0.066 mmol) in EtOH (1 mL) was added 1 mL of a slurry of Raney nickel. The reaction mixture was rapidly stirred at RT under a balloon of H_2 for 38 h, filtered through a pad of celite that was rinsed with CH_2Cl_2 and EtOAc, and concentrated to a light green oil. Purification by flash chromatography on silica (elution with EtOAc) afforded 35 mg (74%) of a clear oil.
$[\alpha]_D$: –70.1 (CH_2Cl_2) c = 1.0; IR (neat) 1715, 1651, 1455, 1428, 1366, 1235, 1156, 1111, 702 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.64 (d, *J* = 6.8 Hz, 4H, Ar**H**), 7.43–7.35 (m, 6H, Ar**H**), 7.29–7.18 (m, 5H, Ar**H**), 4.59 (d, *J* = 11.7 Hz, 1H, OC**H**$_2$Ph), 4.30 (d, *J* = 11.7, 1H, OC**H**$_2$Ph), 3.72 (broad d, *J* = 15.1, 1H, =NC**H**$_2$-), 3.60 (t, *J* = 5.9 Hz, 2H, TBDPSOC**H**$_2$-), 3.45–3.36 (m, 1H, =NC**H**$_2$-), 3.27–3.23 (m, 1H, R_2C**H**OBn), 3.14 (s, 1H), 2.91 (dd, J_1 = 9.8, J_2 = 18.6 Hz, 1H, N=CRC**H**$_2$-), 2.71 (dd, J_1 = 2.0, J_2 = 19.0 Hz, 1H, N=CRC**H**$_2$-), 2.41–2.34 (m, 2H), 2.26–2.20 (m, 1H), 2.16 (d, *J* = 12.7 Hz, 1H), 2.04 (d, *J* = 13.7 Hz, 1H), 1.95–1.92 (m, 1H), 1.60–1.37 (m, 6H), 1.34 (s, 9H, CO_2**tBu**), 1.31–1.24 (m, 1H), 1.03 (s, 9H, **tBu**Ph_2SiO-), 0.98 (d, *J* = 7.3, 1H, **Me**-); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.6, 172.5, 167.3, 138.4, 135.5, 133.9, 129.5, 128.5, 128.3, 127.7, 127.6, 81.2, 79.6, 70.8, 63.6, 49.6, 49.1, 42.9, 40.4, 39.7, 39.2, 32.9, 32.0, 31.1, 27.9, 26.8, 20.0, 19.3, 19.2, 16.9; HRMS (ES) calc. for $C_{44}H_{59}NO_5Si$ $[M+H]^+$: 710.4241. Found: 710.4252.

ALTERNATIVE PROCEDURE:
To the nitrile (130 mg, 0.18 mmol) in EtOH (2 mL) was added a 2 mL of a slurry of Raney nickel. The reaction mixture was rapidly stirred at RT under a balloon of H_2 for 36 h, filtered through a pad of celite which was rinsed with CH_2Cl_2 and EtOAc, and concentrated to a light green oil. Purification by flash chromatography on silica (elution with EtOAc) afforded 67 mg (52%, 96% based on recovered starting material (57 mg, 44%)) of the desired imine as a clear oil.



(16*S*,1*R*,9*R*,10*R*,17*R*)-14-aza-16-methyl-6-oxa-17-(phenylmethoxy)tetracyclo[7.5.3.0<1,10>.0<2,7>]heptadec-2(7)-ene (31). To the imine (21 mg, 0.030 mmol) in a vial was added 1.0 mL of a sat. solution of $HCl_{(g)}$ in anhydrous MeOH (~3 M). The vial was sealed and the reaction temperature was elevated to 70 °C and stirred for 42 h. The reaction mixture was concentrated under a stream of N_2, partitioned between 5 mL of 2M HCl and a 1:1 mixture of ether and hexanes (5 mL). The aqueous portion was removed and the organic layer was twice extracted with additional 2M HCl. The combined acidic aqueous portions were made basic (pH 9) by addition of solid K_2CO_3, extracted with EtOAc (3 x 5 mL), washed with brine, dried (Na_2SO_4) and concentrated. Purification by flash chromatography (short column, 3", elution with 2.5, 5, and 10% MeOH in $CHCl_3$) gave 10.0 mg (96%) of the desired product.

$[\alpha]_D$: +53.2 (CH_2Cl_2) c = 0.27; IR (neat) 3306, 1678, 1584, 1454, 1368, 1261, 1095, 736 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36–7.30 (m, 3H, Ar**H**), 7.30–7.24 (m, 2H, Ar**H**), 4.58 (d, *J* = 11.2 Hz, 1H, OC**H**$_2$Ph), 4.34 (d, *J* = 11.2, 1H, OC**H**$_2$Ph), 4.06 (d, *J* = 10.7, 1H, =CROC**H**$_2$-), 3.78 (t, *J* = 10.7 Hz, 1H, =CROC**H**$_2$-), 3.09 (dd, J_1 = 4.4, J_2 = 10.6 Hz, 1H, R_2C**H**OBn), 2.94 (broad m, 1H, RHNC**H**$_2$-), 2.62 (broad t, *J* = 9.8 Hz, 1H, RHNC**H**$_2$-), 2.28 (d, *J* = 17.6 Hz, 1H, R_2CH-C**H**$_2$C=C), 2.17 (m, 1H, R_2C**H**-CHOBn-), 2.00 (dd, J_1 = 6.8, J_2 = 18.1 Hz, 1H, R_2CH-C**H**$_2$C=C), 1.96–1.84 (m, 3H), 1.82–1.42 (m, 9H), 0.99 (d, *J* = 6.3 Hz, 3H, **Me**-); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.3, 138.7, 128.3, 128.1, 127.6, 127.4, 102.6, 85.9, 70.8, 65.5, 57.1, 44.5, 41.9, 41.6, 34.8, 32.1, 25.3, 23.7, 3.0, 18.4; HRMS (ES) calc. for $C_{23}H_{32}NO_2$ $[M+H]^+$: 354.2433. Found: 354.2429.



(10*S*,15*S*,1*R*,2*R*,13*R*,14*R*)-6-aza-15-methyl-14-(phenylmethoxy)tetracyclo[8.6.0.0<1,6>.0<2,13>]hexadecan-11-one (2). A dry 5 mL vial was charged with the benzyl ether (10.0 mg, 0.028 mmol) and 100 µL of CH_2Cl_2. Following addition of 500 µL of 30% HBr in HOAc the vial was capped and stirred for 21 h at RT. The reaction mixture then was concentrated under N_2 (1h). The brown oil was washed several times with 1:1 ether/hexanes (to remove benzyl bromide). The brown oil was dissolved in MeOH (0.7 mL) and aq. NaOH (300 mg in 0.7 mL of H_2O) and stirred for 18 h at RT. After dilution with water (5 mL), the reaction mixture was extracted with CH_2Cl_2 (5 x 5 mL), dried (Na_2SO_4), filtered and concentrated to afford 7 mg (95%) of clavolonine as a white solid. *X-ray.*

$[\alpha]_D$: +21.3 (EtOH) c = 0.5; IR (neat) 3447, 2930, 2865, 1699, 1458, 1419, 1356 1314, 1131, 1063, 908, 730 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.41 (dd, J_1 = 3.9, J_2 = 10.3 Hz, 1H, R_2C**H**OH), 3.30 (dt, J_1 = 3.9, J_2 = 14.2 Hz, 1H,), 3.13 (dt, J_1 = 2.4, J_2 = 12.2 Hz, 1H,), 2.91 (dd, J_1 = 3.4, J_2 = 11.7 Hz, 1H,), 2.65–2.58 (m, 3H,), 2.52 (dd, J_1 = 4.9, J_2 = 14.2 Hz, 1H,), 2.32 (dd, J_1 = 6.3, J_2 = 16.6 Hz, 1H,), 2.14 (m, 1H,), 2.06 (d, *J* = 12.7 Hz, 1H,), 1.89–1.71 (m, 4H,), 1.65–1.53 (m, 4H), 1.38–1.24 (m, 2H), 0.98 (d, *J* = 5.9 Hz, 3H, **Me**-); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.5, 78.7, 60.0, 47.1, 47.0, 43.6, 43.0, 42.7, 41.4, 36.4, 32.9, 25.8, 24.7, 19.11, 19.07, 18.5; HRMS (CI) calc. for $C_{16}H_{25}NO_2$+H $[M+H]^+$: 264.1964. Found: 264.1960.