Diastereoselective Nitrenium Ion-Mediated Cyclofunctionalization Total Synthesis of (+)-Castanospermine

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Supporting Information, Part 1

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1.1 General Procedures

All non-aqueous reactions were carried out in oven- or flame-dried glassware under an atmosphere of dry argon or nitrogen, unless otherwise noted. Except as otherwise indicated, all reactions were magnetically stirred and monitored by analytical thin-layer chromatography using Merck pre-coated silica gel plates with F_{254} indicator. Visualization was accomplished by UV light, phosphomolybdic acid, and/or potassium permanganate solution. Flash column chromatography was performed according to the method of Still[1] using silica gel 60 (mesh 230-400) supplied by E. Merck. Yields refer to chromatographically and spectrographically pure compounds, unless otherwise noted.

1.2 Materials

All solvents were reagent grade. Methanol (MeOH) was dried from magnesium methoxide, prepared from magnesium turnings and iodine. Diethyl ether (Et_2O), 1,4-dioxane, and tetrahydrofuran (THF) were freshly distilled from sodium/benzophenone under argon. Acetonitrile (CH_3CN), dichloromethane (CH_2Cl_2), dimethylsulfoxide (DMSO), hexanes, pyridine and trimethylsilyl chloride (TMSCl) were freshly distilled from calcium hydride under nitrogen. Anhydrous chloroform ($CHCl_3$) was prepared from bench-grade, stabilized $CHCl_3$ by washing with H_2O, drying over anhydrous $CaCl_2$, and distillation from anhydrous, solid $CaCl_2$ immediately prior to use. Triethylamine and *N*-methylmorpholine were distilled from calcium hydride, under nitrogen and stored over potassium hydroxide. *N,N*-dimethylformamide (DMF) was purchased from Aldrich and dried with freshly activated 4 Å molecular sieves prior to use. Trichloroisocyanuric acid, 2,2,6,6-tetramethyl-1-piperidinyloxy, free radical (TEMPO), and 1-bromo-3-methyl-2-butene were purchased from Aldrich and used without further purification. Potassium hexamethyldisilylazide (KHMDS), purchased from Aldrich, was stored and dispensed in a glove box. The molarities of *n*-butyllithium (*n*-BuLi) solutions were determined by titration against diphenylacetic acid as an indicator (average of three determinations).[2] Saturated solutions of ammonia in methanol (NH_3-MeOH) were prepared by bubbling anhydrous $NH_3(g)$ through cold (0 °C), anhydrous MeOH for 20 min. The molarity of this solution was titrated against a standardized aqueous solution of HCl using bromocresol blue as an indicator (average of three determinations). Phenyliodine(III) bis(trifluoroacetate) (PIFA) was prepared from phenyliodine(III) bis(acetate) using the method of Vargolis.[3] Brine refers to a saturated aqueous solution of NaCl. All other reagents and starting materials, unless otherwise noted, were purchased from commercial vendors and used without further purification.

1.3 Instrumentation

All melting points were determined in Pyrex capillaries with a Thomas Hoover Unimelt melting point apparatus and are uncorrected. Infrared spectra were recorded as thin films on barium fluoride plates using an ATI Mattson genesis series FTIR spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance 400 (400 MHz ^1H, 100 MHz ^{13}C), a Bruker Avance 500 (500 MHz ^1H, 125 MHz ^{13}C), or a Bruker AM-400 (400 MHz ^1H, 100 MHz ^{13}C) spectrometer. Chemical shift values (δ) are reported in ppm relative to residual chloroform (δ 7.27 ppm for ^1H; δ 77.23 ppm for ^{13}C) and methanol (δ 3.31 ppm for ^1H; δ 49.15 ppm for ^{13}C). The ^1H NMR spectra are reported as follows: δ

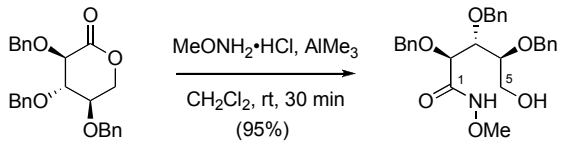
(multiplicity, coupling constant, integration). Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), h (heptet), m (multiplet) and br (broad). The identification of ^{1}H and ^{13}C signals was achieved using a combination of ^{1}H, ^{13}C, DEPT, COSY, HMBC, HMQC and NOESY experiments. In those situations where products are a mixture of rotamers or diastereomers, ^{1}H resonances arising from the *same* proton in *different* rotamers (or diastereomers) are reported as follows: [δ downfield resonance, (multiplicity, coupling constant), δ upfield resonance (multiplicity, coupling constant), total integration for *both* resonances]; the signals arising from the minor rotamers/diastereomers are designated by asterisks (*). Optical rotations were measured with a Perkin-Elmer model 241 polarimeter and reported as follows: $[\alpha]^{\text{temperature}}_{\text{wavelength}}$ (*c*, solvent); $[\alpha]_D$ is reported in 10^{-1} deg $cm^{-2}g^{-1}$; concentration (*c*) is reported g in per 100 mL. High-resolution electron impact (HRMS-EI) mass spectra were obtained on a Kratos Concept 1H spectrometer at the Mass Spectrometry Service Laboratory, University of Minnesota with a typical ionization voltage of 70 eV. High-resolution chemical ionization (HRMS-CI) mass spectra were obtained on a FINNIGAN MAT 95 and high-resolution fast atom bombardment (HRMS-FAB) spectra were obtained on a VG 7070-HF at the Mass Spectrometry Service Laboratory, University of Minnesota. High-resolution electron impact (EI) mass spectra were obtained on a Kratos Concept 1H spectrometer at the University of Illinois Research Resources Center with a typical ionization voltage of 70 eV. High-resolution chemical ionization (CI) mass spectra were obtained on a FINNIGAN MAT 95 and high-resolution fast atom bombardment (FAB) spectra were obtained on a VG 7070-HF at the Mass Spectrometry Service Laboratory, University of Minnesota. High-resolution electrospray ionization (HRMS-ESI) mass spectra were obtained on a Micro Mass QTOF II instrument at the University of Illinois Research Resources Center.

1.4 Literature Preparations

(3-Bromopropyl)triisopropylsilane was prepared according to the method of Baldwin.[4] (3-*tert*-Butyldimethylsilyloxy)propyltriphenylphosphonium bromide was prepared according to the method of Tamm.[5] Pivalate ester **15** was prepared from D-xylose in two steps, according to the method of Rosenberg.[6]

1.5 Total Synthesis of (+)-Castanospermine

(2*R*,3*S*,4*R*)-2,3,4-Tris(benzyloxy)-5-hydroxy-*N*-methoxypentanamide (8).

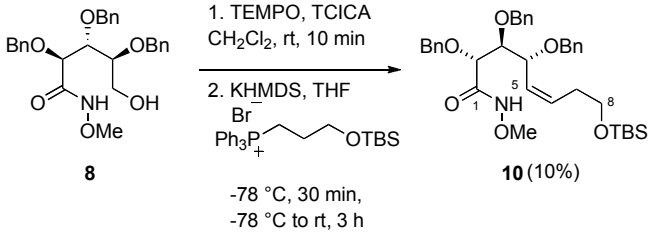


7 **8**

At ambient temperature, **7** (268 mg, 0.64 mmol) and methoxylamine hydrochloride (208.8 mg, 2.50 mmol) were suspended in CH_2Cl_2 (10 mL) and stirred for 30 min. Trimethylaluminum (1.25 mL, 2.5 mmol, 2.0 M in hexanes) was then added dropwise via syringe and the mixture stirred for 30 min. The reaction was then quenched with pH 7.0 phosphate buffer solution (0.5 M, 20 mL) and extracted with EtOAc (3 × 25 mL). The

combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure and the residue purified by flash chromatography on silica gel (EtOAc/hexanes, 1:1→1:0) to afford **8** (281.4 mg, 95%): white crystalline solid; mp 116-117 °C (CH_2Cl_2/hexanes); R_f 0.10 (EtOAc/hexanes, 1:1); $[\alpha]_D^{24}$ -5.9 (*c* 1.08, $CHCl_3$); IR (film/ZnSe) υ_{max} 3029, 2920, 2866, 1749, 1494, 1461, 1452, 1411, 1392, 1351, 1309, 1255, 1178, 1139, 1105, 1074, 1020, 873, 738, 696 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.00 (s, 1 H, NH), 7.40-7.22 (m, 15 H, Ph), 4.70 (d, *J* = 11.4 Hz, 1 H, OC*H*HPh), 4.68 (d, *J* = 11.3 Hz, 1 H, OCH*H*Ph), 4.65-4.54 (m, 3 H, OCH*H*Ph, OCH_2Ph), 4.52 (d, *J* = 11.3 Hz, 1 H, OCH*H*Ph), 4.19 (d, *J* = 2.7 Hz, 1 H, HC-2), 4.06 (dd, *J* = 2.7, 6.9 Hz, 1 H, HC-3), 3.75 (ddd, *J* = 4.3, 5.3, 6.8 Hz, 1 H, HC-4), 3.68 (s, 3 H, OCH_3), 3.66 (dd, *J* = 6.8, 12.0 Hz, 1 H, *H*HC-5), 3.47 (dd, *J* = 5.3, 12.0 Hz, 1 H, H*H*C-5), 2.20-1.63 (bs, 1 H, OH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.9 (s, C-1), 138.4 (s), 137.9 (s), 136.6 (s), 129.2 (d), 129.0 (d), 128.9 (d), 128.9 (d), 128.5 (d), 128.4 (d) 79.9 (d), 79.7 (d), 79.5 (d), 75.8 (t), 74.3 (t), 73.7 (t), 64.9 (q, OCH_3), 62.0 (t, C-5); HRMS-ESI calcd for $C_{27}H_{31}NO_6SiNa$ $[M+Na]^+$: 488.2049, found: 488.2053.

(*Z*,2*R*,3*S*,4*R*)-2,3,4-Tris(benzyloxy)-8-*t*-butylsilanyloxy-*N*-methoxyoct-5-enamide (10).

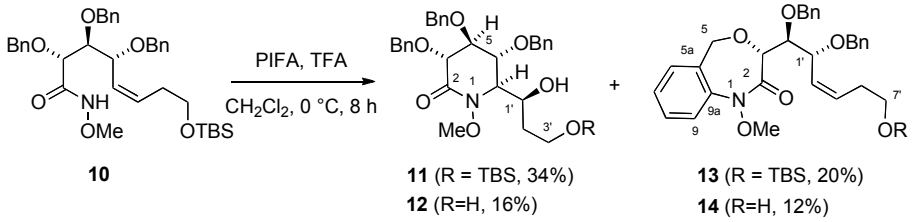


Oxidation: At ambient temperature, a 100 mL round-bottom flask was charged with a solution of TEMPO (0.6 mg, 0.0038 mmol) and **8** (178.8 mg, 0.385 mmol) in CH_2Cl_2 (10 mL). Trichloroisocyanuric acid (89.5 mg, 0.385 mmol) was added and the reaction stirred for 10 min, before filtering the resulting suspension through Celite 521 and washing the filter cake with CH_2Cl_2 (20 mL). The filtrates were partitioned with saturated aqueous $NaHCO_3$ (20 mL), extracted with CH_2Cl_2 (2 × 10 mL) and the combined organic layers dried with Na_2SO_4, and concentrated under reduced pressure. Without further purification, unstable aldehyde **9** was immediately used in the next step.

Wittig Reaction: To a stirred, cooled (0 °C, ice bath) suspension of *tert*-butyldimethylsiloxypropyltriphenylphosphonium bromide[7] (391.4 mg, 0.760 mmol) in THF (5 mL) was added a solution of KHMDS (151.2 mg, 0.760 mmol) in THF (5 mL) via cannula, and the reaction stirred for 30 min before being cooled to -78 °C (acetone/$CO_{2(s)}$). A solution of aldehyde **9** in THF (5 mL) was then added to the ylide solution via cannula. After stirring for 30 min at -78 °C, the reaction was warmed to ambient temperature over 30 min and stirred for a further 3 h. The reaction was then quenched with water (5 mL) and saturated aqueous ammonium chloride (5 mL), then extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4), concentrated under reduced pressure, and the residue purified by flash chromatography on silica gel (EtOAc/hexanes, 1:1) to afford **10** (15.5 mg, 10%): colorless waxy solid; R_f 0.61 (EtOAc/hexanes, 1:1); $[\alpha]_D^{24}$ +0.8 (*c* 0.48,

$CHCl_3$); IR (film/ZnSe) υ_{max} 3388, 3242, 2952, 2929, 2856, 1689, 1496, 1454, 1388, 1357, 1254, 1211, 1092, 930, 835, 777, 735, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.93 (s, 1 H, NH), 7.35-7.25 (m, 15 H, Ph), 5.84 (ddd, *J* = 6.0, 8.3, 11.2 Hz, 1 H, HC-6), 5.54 (dd, *J* = 10.6, 10.6 Hz, 1 H, HC-5), 4.88 (d, *J* = 10.7 Hz, 1 H), 4.63 (d, *J* = 11.7 Hz, 1 H), 4.61-4.55 (m, 2 H), 4.53 (d, *J* = 11.3 Hz, 1 H), 4.47 (d, *J* = 11.5 Hz, 1 H), 4.43 (d, *J* = 11.6 Hz, 1 H), 4.16 (d, *J* = 2.4 Hz, 1 H, HC-2), 3.99 (dd, *J* = 2.6, 7.6 Hz, 1 H, HC-3), 3.61 (t, *J* = 6.6 Hz, 2 H, H_2C-8), 3.59 (s, 3 H, OCH_3), 2.48-2.35 (m, 1 H, *H*HC-7), 2.27-2.15 (m, 1 H, H*H*C-7), 0.89 (s, 9 H, $SiC(CH_3)_3$), 0.03 (s, 3 H, $SiCH_3$), 0.03 (s, 3 H, $SiCH_3$);^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6 (s, C-1), 138.5 (s), 138.0 (s), 136.7 (s), 133.0 (d, C-6), 128.6 (d), 128.5 (d), 128.3 (d), 128.3 (d), 128.1 (d), 127.8 (d), 127.6 (d), 127.6 (d, C-5), 82.2 (d), 80.7 (d), 76.1 (t), 75.9 (d), 74.1 (t), 70.5 (t), 64.3 (q, OCH_3), 62.5 (t, C-8), 31.5 (t, C-7), 25.9 (q, 3 C, $SiC(CH_3)_3$), 18.3 (s, $SiC(CH_3)_3$), -5.3 (q, 2 C, $Si(CH_3)_2$); HRMS-ESI calcd for $C_{36}H_{50}NO_6Si$ $[M+H]^+$: 620.3407, found: 620.3409.

(3*R*,4*S*,5*R*,6*R*)-3,4,5-Tris(benzyloxy)-6-(3'-(*tert*-butyldimethylsilanyloxy)-(*S*)-1'-hydroxypropyl)-1-methoxypiperidin-2-one (11); (1'*R*,2'*S*,3*R*)-3-((*Z*))-1,2-Bis-benzyloxy-7-(*tert*-butyldimethylsilanyloxy)-hept-3-enyl)-1-methoxy-1,5-dihydro-benzo[*e*][1,4]oxazepin-2-one (12) (3*R*,4*S*,5*R*,6*R*)-3,4,5-Tris(benzyloxy)-6-((*S*)-1',3'-dihydroxypropyl)-1-methoxypiperidin-2-one (13); (1'*R*,2'*S*,3*R*)-3-((*Z*))-1',2'-Bis-benzyloxy-7'-hydroxy-hept-3'-enyl)-1-methoxy-1,5-dihydro-benzo[*e*][1,4]oxazepin-2-one (14).



A stirred solution of **10** (85.6 mg, 0.138 mmol) in CH_2Cl_2 (1 mL) was cooled to 0 °C (ice bath), and a solution of PIFA (71.4 mg, 0.166 mmol) and trifluoroacetic acid (12.2 μL, 0.128 mmol) in CH_2Cl_2 (2 mL) was added. After 8 h, the reaction was quenched with anhydrous methanolic ammonia (2 mL, 0.07 M NH_3 in MeOH), stirred for 10 min, filtered through Celite 521, and the filter cake washed with EtOAc (70 mL). The combined filtrates were concentrated under reduced pressure and the residue purified by flash chromatography on silica gel (EtOAc/hexanes, 1:8→1:4→1:2→1:1→1:0, 100 mL each) to afford **11** (29.8 mg, 34%), **12** (11.6 mg, 16%), **13** (17.6 mg, 20%) and **14** (8.7 mg, 12%).

Compound **11**: colorless oil; R_f 0.88 (EtOAc/hexanes, 1:1); $[\alpha]_D^{24}$ -31.9 (*c* 0.47, $CHCl_3$); IR (film/ZnSe) υ_{max} 3086, 3061, 2951, 2927, 2856, 1690, 1665, 1603, 1461, 1343, 1254, 1094, 836, 777, 734, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.48 (dd, *J* = 1.5, 8.0 Hz, 1 H), 7.46 (ddd, *J* = 1.5, 8.3, 8.3 Hz, 1H), 7.40-7.21 (m, 11 H), 7.18-7.15 (m, 1 H), 5.78-5.72 (m, 1 H), 5.64-5.59 (m, 1 H), 4.81 (d, *J* = 11.0 Hz, 1 H), 4.75 (d, *J* = 12.8 Hz, 1 H), 4.73 (d, *J* = 11.0 Hz, 1 H), 4.59 (d, *J* = 12.8 Hz, 1 H), 4.55-4.50 (m, 2 H), 4.48 (d, *J* = 4.4 Hz, 1 H), 4.30 (d, *J* = 11.4 Hz, 1 H), 4.10 (dd, *J* = 4.4, 6.2 Hz, 1 H), 3.78 (s, 3 H), 3.66-3.60 (m, 2 H), 2.42-2.36 (m, 1 H), 2.31-2.23 (m, 1 H), 0.90 (s, 9 H), 0.06 (s, 3 H), 0.06 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.9 (s, C-1), 138.8 (s, 2 C), 132.3 (d), 129.6 (d),

129.1 (d), 128.3 (s), 128.3 (d), 128.2 (d), 128.1 (d), 128.0 (d), 127.8 (d), 127.4 (d), 127.3 (s), 126.2 (d), 119.6 (d), 82.3 (d), 78.8 (d), 76.0 (t), 75.9 (d), 70.5 (t), 69.4 (t), 62.7 (t), 62.0 (q, OCH_3), 31.5 (t, C-7), 26.0 (q, 3 C, $SiC(CH_3)_3$), 18.4 (s, $SiC(CH_3)_3$), -5.2 (q, 2 C, $Si(CH_3)_2$); HRMS-ESI calcd for $C_{36}H_{47}NO_6SiNa$ $[M+Na]^+$: 640.3071, found: 640.3065.

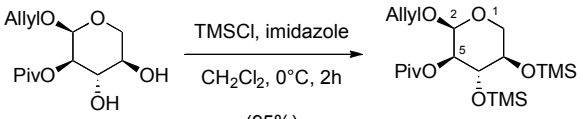
Compound **12**: colorless oil; R_f 0.19 (EtOAc/hexanes, 1:1); $[\alpha]_D^{24}$ -44.7 (*c* 0.95, $CHCl_3$); IR (film/ZnSe) υ_{max} 3473, 3086, 3061, 3030, 2927, 2861, 1683, 1667, 1603, 1455, 1347, 1285, 1205, 1089, 1066, 1027, 950, 736, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.49 (dd, *J* = 1.5, 8.0 Hz, 1 H), 7.46 (ddd, *J* = 1.5, 8.8, 8.8 Hz, 1H), 7.40-7.21 (m, 11 H), 7.18-7.15 (m, 1 H), 5.70 (ddd, *J* = 7.7, 7.7, 11.4 Hz, 1 H, HC-6), 5.63-5.59 (m, 1 H, HC-5), 4.78 (s, 2 H, OC*H*$_2$Ph), 4.78 (d, *J* = 12.8 Hz, 1 H, OC*H*HPh), 4.64 (d, *J* = 12.8 Hz, 1 H, OCH*H*Ph), 4.53 (d, *J* = 11.8 Hz, 1 H, OC*H*HPh), 4.47 (d, *J* = 5.3 Hz, 1 H, HC-2), 4.47 (dd, *J* = 5.3, 9.2 Hz, 1 H, HC-4), 4.28 (d, *J* = 11.8 Hz, 1 H, OCH*H*Ph), 4.13 (dd, *J* = 5.3, 5.3 Hz, 1 H, HC-5), 3.77 (s, 3 H, OMe), 3.69-3.58 (m, 2 H, H_2C-7), 2.35-2.30 (m, 2 H, H_2C-8); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.6 (s, C-1), 138.7 (s, Ph), 138.3 (s, Ph), 131.5 (d), 129.8 (d), 129.7 (d), 129.3 (s), 128.4 (d), 128.3 (s), 128.2 (d), 127.7 (d), 127.5 (d), 127.3 (s), 126.5 (d), 119.8 (d), 82.0 (d), 77.8 (d), 76.0 (t), 74.9 (d), 70.3 (t), 69.1 (t), 62.1 (q, OCH_3), 62.0 (t), 31.6 (t, C-7); HRMS-ESI calcd for $C_{30}H_{33}NO_6SiNa$ $[M+Na]^+$: 526.2206, found: 526.2211.

Compound **13**: colorless oil; R_f 0.75 (EtOAc/hexanes, 1:1); $[\alpha]_D^{24}$ +63.7 (*c* 0.14, $CHCl_3$); IR (film/ZnSe) υ_{max} 3436, 3064, 3031, 2953, 2928, 2855, 1689, 1453, 1360, 1252, 1211, 1092, 937, 836, 778, 736, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.45-7.42 (m, 2 H, Ph), 7.34-7.27 (m, 13 H, Ph), 5.17 (d, *J* = 11.1 Hz, 1 H, OC*H*HPh), 4.88 (d, *J* = 11.2 Hz, 1 H, OC*H*HPh), 4.75 (d, *J* = 11.5 Hz, 1 H, OC*H*HPh), 4.74 (d, *J* = 11.1 Hz, 1 H, OCH*H*Ph), 4.67 (d, *J* = 11.2 Hz, 1 H, OCH*H*Ph), 4.63 (d, *J* = 11.5 Hz, 1 H, OCH*H*Ph), 4.30 (d, *J* = 9.0 Hz, 1 H, HC-3), 3.92 (dd, *J* = 3.2, 6.3 Hz, 1 H, HC-5), 3.91-3.87 (m, 1 H, *H*HC-3'), 3.87-3.78 (m, 2 H, HC-4, HC-1'), 3.76 (s, 3 H, OMe), 3.71-3.69 (m, 1 H, H*H*C-3'), 3.65 (dd, *J* = 2.8, 2.8 Hz, 1 H, HC-6), 1.92 (dddd, *J* = 4.3, 9.9, 9.9, 14.3 Hz, 1 H, *H*HC-2'), 1.65-1.53 (m, 1 H, H*H*C-2'), 0.88 (s, 9 H), 0.07 (s, 3 H), 0.06 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.0 (s, C-1), 138.0 (s), 138.0 (s), 138.0 (s), 128.5 (d), 128.4 (d), 128.3 (d), 128.0 (d), 127.9 (d), 127.7 (d), 81.6 (d), 78.1 (d), 77.5 (d), 74.8 (t), 74.4 (t), 73.1 (d), 73.0 (t), 67.1 (d), 62.8 (t), 61.1 (q, OCH_3), 36.0 (t, C-2'), 25.8 (q, 3 C, $SiC(CH_3)_3$), 18.1 (s, $SiC(CH_3)_3$), -5.6 (q, 2 C, $Si(CH_3)_2$); HRMS-ESI calcd for $C_{36}H_{50}NO_7Si$ $[M+H]^+$: 636.3357, found: 636.3383.

Compound **14**: colorless oil; R_f 0.05 (EtOAc/hexanes, 1:1); $[\alpha]_D^{24}$ +54.3 (*c* 0.32, $CHCl_3$); IR (film/ZnSe) υ_{max} 3425, 3064, 3029, 2933, 2873, 1679, 1496, 1454, 1357, 1092, 1070, 740, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.45-7.41 (m, 2 H, Ph), 7.34-7.27 (m, 13 H, Ph), 5.17 (d, *J* = 11.4 Hz, 1 H, OC*H*HPh), 4.79 (d, *J* = 11.0 Hz, 1 H, OC*H*HPh), 4.73 (d, *J* = 11.4 Hz, 1 H, OCH*H*Ph), 4.71 (d, *J* = 11.8 Hz, 1 H, OC*H*HPh), 4.60 (d, *J* = 11.0 Hz, 1 H, OCH*H*Ph), 4.58 (d, *J* = 11.8 Hz, 1 H, OCH*H*Ph), 4.29 (d, *J* = 7.3 Hz, 1 H, HC-3), 3.96 (ddd, *J* = 2.6, 2.6, 10.2 Hz, 1 H, HC-1'), 3.86-3.80 (m, 2 H, HC-4, *H*HC-3'), 3.77 (s, 3 H, OMe), 3.75-3.71 (m, 1 H. H*H*C-3'), 3.69 (dd, *J* = 2.2, 2.2 Hz, 1 H, HC-6), 1.95

(dddd, J = 4.0, 8.4, 10.3, 14.3 Hz, 1 H, *H*HC-2'), 1.65-1.53 (dddd, J = 3.3, 3.3, 3.3, 14.3 Hz, 1 H, H*H*C-2'); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.0 (s, C-1), 138.0 (s), 138.0 (s), 138.0 (s), 128.5 (d), 128.4 (d), 128.3 (d), 128.0 (d), 127.9 (d), 127.7 (d), 81.4 (d), 77.9 (d), 77.1 (d), 74.7 (t), 74.0 (t), 72.7 (d), 72.1 (t), 67.3 (d), 61.5 (t), 60.9 (q, OCH_3), 36.2 (t, C-2'); HRMS-ESI calcd for $C_{30}H_{36}NO_7$ $[M+H]^+$: 522.2492, found: 522.2491.

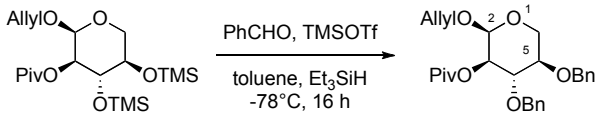
(2*S*,3*R*,4*S*,5*R*)-2-(Allyloxy)-tetrahydro-4,5-bis(trimethylsilanyloxy)-2*H*-pyran-3-yl pivalate (25).



15 **25**

To a stirred, cooled (0 °C, ice bath) solution of diol **15** (6.02 g, 21.97 mmol) and imidazole (3.59 g, 52.73 mmol) in CH_2Cl_2 (150 mL) was added TMSCl (6.13 mL, 48.34 mmol) via syringe. After 2 h, the reaction was quenched with saturated aqueous $NaHCO_3$ (50 mL) and extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were washed with brine (50 mL), dried (Na_2SO_4), concentrated under reduced pressure, and the residue purified by flash chromatography on silica gel (EtOAc/hexanes, 1:20) to afford **25** (8.62 g, 95%): colorless oil; R_f 0.77 (EtOAc/hexanes, 1:4); $[\alpha]_D^{24}$ +127.9 (*c* 1.04, $CHCl_3$); IR (film/ZnSe) υ_{max} 3082, 2960, 2906, 1731, 1481, 1461, 1396, 1367, 1332, 1305, 1280, 1251, 1168, 1128, 1087, 1047, 937, 889, 867, 842, 750, 449 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.90-5.77 (m, 1 H, $OCH_2C\textit{H}=CH_2$), 5.27 (dd, J = 1.4, 17.3 Hz, 1 H, $OCH_2CH=CH\textit{H}$), 5.16 (dd, J = 1.4, 10.4 Hz, 1 H, $OCH_2CH=C\textit{H}H$), 4.96 (d, J = 3.7 Hz, 1 H, HC-2), 4.56 (dd, J = 3.6, 9.8 Hz, 1 H, HC-3), 4.14 (tdd, J = 1.4, 5.1, 13.1 Hz, 1 H, $OC\textit{H}HCH=CH_2$), 3.95 (dd, J = 8.3, 9.5 Hz, 1 H, HC-4), 3.87 (tdd, J = 1.4, 6.0, 13.1 Hz, 1 H, $OCH\textit{H}CH=CH_2$), 3.61 (ddd, J = 6.1, 8.1, 9.9 Hz, 1 H, HC-5), 3.54-3.48 (m, 2 H, H_2C-6), 1.22 (s, 9 H, $C(CH_3)_3$), 0.14 (s, 9 H, $Si(CH_3)_3$), 0.14 (s, 9 H, $Si(CH_3)_3$; ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.3 (s), 133.8 (d, $C\textit{H}=CH_2$), 117.1 (t, $CH=C\textit{H}_2$), 95.2 (d, C-2), 74.0 (d), 72.6 (d), 71.9 (d), 68.3 (t), 62.1 (t), 33.8 (s, $\textit{C}(CH_3)_3$), 27.3 (q, 3 C, $C(\textit{C}H_3)_3$), 0.9 (q, $Si(CH_3)_3$), 0.4 (q, $Si(CH_3)_3$); HRMS-ESI calcd for $C_{19}H_{38}O_6Si_2Na$ $[M+Na]^+$: 441.2105, found: 441.2101.

(2*S*,3*R*,4*S*,5*R*)-2-(Allyloxy)-4,5-bis(benzyloxy)-tetrahydro-2*H*-pyran-3-yl pivalate (16).

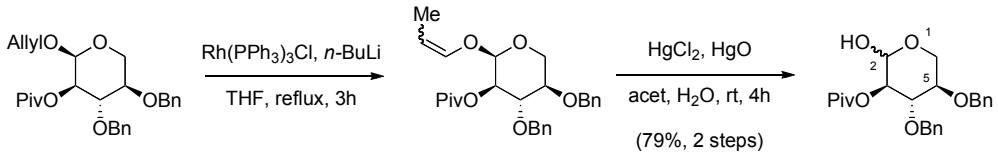


25 **16**

To a stirred, cooled (–78 °C, acetone/$CO_{2(s)}$) solution of **25** (414.6 mg, 0.992 mmol) and benzaldehyde (253 μL, 2.38 mmol) in CH_2Cl_2 (10 mL) was added TMSOTf (89.7 μL, 0.496 mmol). After 1 h, triethylsilane (383 μL, 2.38 mmol) was added, and the reaction warmed to room temperature and stirred for 16 h. Et_2O (25 mL) was then added, the reaction quenched with saturated aqueous $NaHCO_3$ (50 mL), and the two-phase mixture

partitioned. The organic phase was washed with brine, dried ($MgSO_4$), concentrated under reduced pressure and the residue purified by flash chromatography on silica gel (EtOAc/hexanes, 1:19→1:9) to afford **16** (246.4 mg, 55%): colorless oil; R_f 0.61 (EtOAc/hexanes, 1:4); $[\alpha]_D^{24}$ +93.6 (*c* 1.75, $CHCl_3$); IR (film/ZnSe) υ_{max} 3087, 3064, 3029, 2973, 2933, 2908, 2873, 1732, 1496, 1479, 1456, 1396, 1363, 1330, 1290, 1162, 1133, 1049, 941, 736, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.4-7.21 (m, 10 H, Ph), 5.88 (dddd, *J* = 5.3, 5.9, 10.6, 17.3 Hz, 1 H, $OCH_2CH{=}CH_2$), 5.31 (qd, *J* = 1.6, 17.2 Hz, 1 H, $OCH_2CH{=}CHH$), 5.21 (qd, *J* = 1.3, 10.4 Hz, 1 H, $OCH_2CH{=}CHH$), 5.03 (d, *J* = 3.7 Hz, 1 H, HC-2), 4.88 (d, *J* = 11.0 Hz, 1 H, OC*H*HPh), 4.81 (d, *J* = 11.0 Hz, 1 H, OCH*H*Ph), 4.76 (dd, *J* = 3.7, 10.0 Hz, 2 H, HC-3), 4.74 (d, *J* = 11.5 Hz, 1 H, OC*H*HPh), 4.65 (d, *J* = 11.6 Hz, 1 H, OCH*H*Ph), 4.18 (tdd, *J* = 1.4, 5.2, 13.0 Hz, 1 H, OC*H*HCH=CH_2), 4.01 (m, 1 H, HC-4), 3.94 (tdd, *J* = 1.3, 6.0, 13.0 Hz, 1 H, OCH*H*CH=CH_2), 3.72-3.58 (m, 3 H, HC-5, H_2C-6), 1.24 (s, 9 H, $C(CH_3)_3$)); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.9 (s), 138.6 (s), 138.2 (s), 133.7 (d, *C*H=CH_2), 128.5 (d, 2 C), 128.3 (d, 2 C), 127.8 (d), 127.8 (d, 2 C), 127.6 (d, 3 C), 117.5 (t, CH=*C*H_2), 95.1 (d, C-2), 79.2 (d), 78.0 (d), 75.4 (t), 73.5 (t), 73.4 (d), 68.4 (t), 60.0 (t, C-6), 38.7 (s, *C*$(CH_3)_3$), 27.2 (q, 3 C, C(*C*$H_3)_3$); HRMS-ESI calcd for $C_{27}H_{35}O_6$ $[M+H]^+$: 455.2434, found: 455.2407.

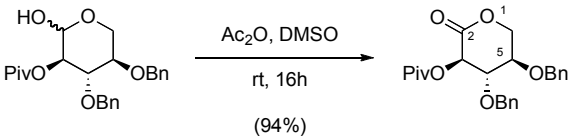
(2*S*,3*R*,4*S*,5*R*)-4,5-Bis(benzyloxy)-tetrahydro-2-hydroxy-2*H*-pyran-3-yl pivalate (27).



At ambient temperature, *n*-BuLi (270 μL, 0.68 mmol, 2.5 M in hexanes) was added to a solution of $Rh(PPh_3)_3Cl$ (500 mg, 0.45 mmol) in THF (5 mL). After 10 min, a solution of **16** (2.05 g, 4.52 mmol) in THF (45 mL) was added via cannula, and the reaction was heated at reflux for 2 days. After cooling to ambient temperature, the reaction was concentrated on a rotary evaporator, and the residue was dissolved in acetone (20 mL) and water (20 mL), and both HgO (2.60 g, 12.0 mmol) and $HgCl_2$ (3.25 g, 12.0 mmol) were added. After stirring 2 h, additional HgO (1.08 g, 5.0 mmol) and $HgCl_2$ (1.49 g, 5.5 mmol) were added. After stirring for a further 2 h, the reaction was diluted with Et_2O (50 mL), filtered through Celite 521 and the filter cake washed with Et_2O (20 mL). The combined organics were washed with 50% saturated aqueous KI (6 × 25 mL), washed with brine (20 mL), dried ($MgSO_4$), concentrated under reduced pressure and the residue purified by flash chromatography on silica gel (EtOAc/hexanes, 1:8→1:4→1:2) to afford **27** (1.48 g, 79%) as a 7:3 mixture of anomers: white solid; mp 123-126 °C (CH_2Cl_2/hexanes); R_f 0.45 (EtOAc/hexanes, 1:2); $[\alpha]_D^{24}$ +45.0 (*c* 1.02, $CHCl_3$); IR (film/ZnSe) υ_{max} 3434, 3087, 3062, 3029, 2971, 2935, 2904, 2873, 1730, 1602, 1496, 1479, 1454, 1396, 1365, 1282, 1166, 1135, 1097, 1051, 943, 736, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, major β-anomer) δ 7.41-7.21 (m, 10 H, Ph), 5.34 (d, *J* = 3.4 Hz, 1 H, HC-2), 4.90 (d, *J* = 11.1 Hz, 1 H, OC*H*HPh), 4.87-4.60 (m, 4 H, HC-3, OCH*H*Ph, OCH_2Ph), 4.00 (dd, *J* = 8.8, 8.8 Hz, 1 H, HC-4), 3.84 (dd, *J* = 10.7, 10.7 Hz, 1 H, *H*HC-

6), 3.72-3.68 (m, 1 H, H*H*C-6), 3.66 (ddd, *J* = 5.3, 8.4, 10.2 Hz, 1 H, HC-5), 2.87 (br s, 1 H, OH), 1.22 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$, major β-anomer) δ major beta 178.0 (s, C-1'), 138.4 (s, Ph), 138.1 (s, Ph), 128.4 (d, 2 C, Ph), 128.3 (d, 2 C, Ph), 127.8 (d, Ph), 127.8 (d, 2 C, Ph), 127.6 (d, 3 C, Ph), 90.5 (d, C-2), 78.4 (d), 77.6 (d), 75.2 (t), 73.3 (t), 73.3 (d), 63.6 (t), 60.2 (t), 38.8 (s, $C(CH_3)_3$), 27.1 (q, $C(CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$, minor α-anomer) δ 179.3 (s, C-1'), 138.0 (s, Ph), 137.8 (s, Ph), 128.5 (d, 2 C, Ph), 128.4 (d, 2 C, Ph), 128.0 (d, Ph), 127.8 (d, 2 C, Ph), 127.8 (d, Ph), 127.6 (d, 2 C, Ph), 96.4 (d, C-2), 80.6 (d), 77.3 (d), 75.0 (t), 74.8 (d), 73.2 (t), 60.2 (t), 38.9 (s, $C(CH_3)_3$), 27.0 (q, $C(CH_3)_3$); HRMS-ESI calcd for $C_{24}H_{30}O_6Na$ $[M+Na]^+$: 437.1940, found: 437.1950.

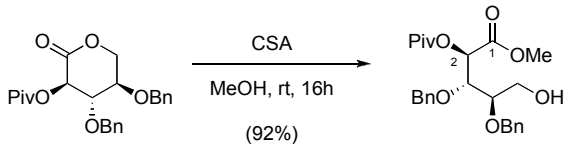
(3*R*,4*S*,5*R*)-4,5-Bis(benzyloxy)-tetrahydro-2-oxo-2*H*-pyran-3-yl pivalate (17).



27 **17**

At ambient temperature, acetic anhydride (5.1 mL, 54 mmol) was added to a solution of **27** (1.48 g, 3.57 mmol) in DMSO (10.1 mL, 143 mmol). After stirring for 16 h, the volatiles were removed under reduced pressure and the residue was purified by flash chromatography on silica gel (EtOAc/hexanes, 1:8→1:3) to afford **17** (1.38 g, 94%): colorless oil; R_f 0.48 (EtOAc/hexanes, 1:2); $[\alpha]_D^{24}$ -30.1 (*c* 1.86, $CHCl_3$); IR (film/ZnSe) υ_{max} 3064, 3031, 2974, 2931, 2908, 2871, 1774, 1739, 1496, 1479, 1456, 1398, 1361, 1280, 1255, 1207, 1139, 1072, 1027, 995, 885, 740, 698 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42-7.26 (m, 10 H, Ph), 5.44 (d, *J* = 7.6 Hz, 1 H, C-3), 4.63 (d, *J* = 11.9 Hz, 1 H, OC*H*HPh), 4.60 (s, 2 H, OC*H*$_2$Ph), 4.53 (d, *J* = 11.9 Hz, 1 H, OCH*H*Ph), 4.48 (ddd, *J* = 1.5, 2.9, 12.6 Hz, 1 H, *H*HC-6), 4.42 (dd, *J* = 1.9, 12.6 Hz, 1 H, H*H*C-6), 3.96 (ddd, *J* = 1.6, 2.1, 7.6 Hz, 1 H, HC-4), 3.87 (td, *J* = 2.1, 2.8 Hz, 1 H, HC-5), 1.29 (s, 9 H, $C(CH_3)_3$);^{13}C NMR (125 MHz, $CDCl_3$) δ 177.2 (s, C-1'), 166.7 (s, C-2), 137.0 (s, Ph), 136.8 (s, Ph), 128.6 (d, 2 C, Ph), 128.6 (d, 2 C, Ph), 128.2 (d, 2 C, Ph), 127.8 (d, 4 C, Ph), 79.5 (d), 75.2 (d), 72.4 (t), 71.7 (d), 70.6 (t), 65.6 (t), 38.8 (s, *C*$(CH_3)_3$), 27.1 (q, 3 C, C(*C*$H_3)_3$) ; HRMS-ESI calcd for $C_{24}H_{28}O_6Na$ $[M+Na]^+$: 435.1784, found: 435.1775.

(2*R*,3*S*,4*R*)-Methyl 3,4-bis(benzyloxy)-5-hydroxy-2-(pivaloyloxy)pentanoate (28).

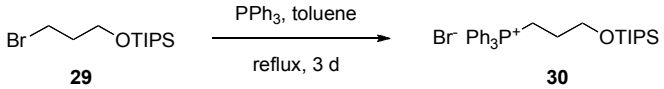


17 **28**

At ambient temperature, a solution of **17** (1.34 g, 3.25 mmol) and camphorsulfonic acid (175.6 mg, 0.813 mmol) in MeOH (40 mL) was stirred for 16 h. The reaction was then quenched with pH 7.0 phosphate buffer solution (0.5 M, 20 mL) and partitioned with CH_2Cl_2 (50 mL). The organic layer was washed with brine (20 mL), dried (Na_2SO_4), concentrated under reduced pressure and the residue purified by flash chromatography on

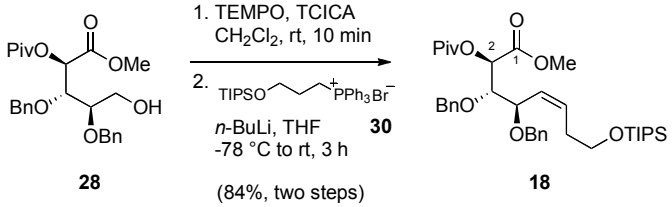
silica gel (EtOAc/hexanes, 1:8→1:2) to afford **28** (1.33 g, 92%): colorless oil; R_f 0.39 (EtOAc/hexanes, 1:2); $[\alpha]_D^{24}$ -0.7 (*c* 1.06, $CHCl_3$); IR (film/ZnSe) υ_{max} 3531, 3087, 3062, 3029, 2973, 2954, 2904, 2871, 1765, 1735, 1558, 1479, 1456, 1436, 1396, 1363, 1274, 1211, 1147, 1070, 740, 698, 667 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.42-7.10 (m, 10 H, Ph), 5.30 (d, *J* = 3.4 Hz, 1 H, HC-2), 4.71 (d, *J* = 11.6 Hz, 1 H, OC*H*HPh), 4.67 (d, *J* = 11.4 Hz, 1 H, OC*H*HPh), 4.65 (d, *J* = 11.6 Hz, 1 H, OCH*H*Ph), 4.58 (d, *J* = 11.4 Hz, 1 H, OCH*H*Ph), 4.22 (dd, *J* = 3.5, 6.2 Hz, 1 H, HC-3), 3.79 (dd, *J* = 4.0, 11.7 Hz, 1 H, *H*HC-5), 3.73 (ddd, *J* = 4.0, 5.3, 6.2 Hz, 1 H, HC-4), 3.62 (s, 3 H, OCH_3), 3.57 (dd, *J* = 5.3, 11.7 Hz, 1 H, H*H*C-5), 1.98 (s, 1 H, OH), 1.29 (s, 9 H, $C(CH_3)_3$);^{13}C NMR (125 MHz, $CDCl_3$) δ 177.6 (s), 168.9 (s, C-1), 137.8 (d), 137.7 (d), 128.5 (d, 2 C), 128.4 (d, 2 C), 128.0 (d), 128.0 (d), 127.9 (d, 4 C), 79.3 (d), 77.7 (d), 74.2 (t), 73.3 (t), 71.4 (d), 61.5 (t, C-5), 52.3 (q, OCH_3), 38.8 (s, $C(CH_3)_3$), 27.0 (q, 3 C, $C(CH_3)_3$); HRMS-ESI calcd for $C_{25}H_{33}O_7$ $[M+H]^+$: 467.2046, found: 467.2039.

1.5.1 3-Triisopropylsilanyloxypropyltriphenylphosphonium bromide (30).



A stirred solution of triphenylphosphine (1.87 g, 7.12 mmol) and alkyl bromide **29**[8] (2.00 g, 6.78 mmol) in toluene (25 mL) was heated at reflux for 3 days then cooled to room temperature and the reaction mixture triturated with hexanes (25 mL). The resulting suspension was then filtered, the solid washed with hexane (50 mL) and residual solvent removed under vacuum to afford phosphonium salt **30** (3.01 g, 78%): white powder; mp 183-185 °C (toluene/hexanes); IR (film/ZnSe) υ_{max} 2962, 2926, 2864, 1585, 1485, 1438, 1332, 1186, 1109, 995, 931, 881, 755, 722, 689, 533 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.71-7.64 (m, 9 H, Ph), 7.61-7.54 (m, 6 H, Ph), 3.79 (t, *J* = 5.0 Hz, 2 H), 3.68-3.59 (m, 2 H), 1.83-1.77 (m, 2 H, H_2C-2), 1.10-0.85 (m, 21); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.1 (d, 3 C), 133.4 (d, $J_{C\text{-}P}$ = 10.0 Hz, 6 C), 130.5 (d, $J_{C\text{-}P}$ = 12.5 Hz, 6 C), 118.0 (d, $J_{C\text{-}P}$ = 86.2 Hz, 3 C), 61.8 (t, $J_{C\text{-}P}$ = 16.7 Hz), 26.0 (t), 19.0 (t, $J_{C\text{-}P}$ = 53.2 Hz), 17.9 (q, 6 C, $Si(CH(CH_3)_2)_3$), 11.7 (d, 3 C, $Si(CH(CH_3)_2)_3$); HRMS-ESI calcd for $C_{30}H_{42}OSiP$ $[M-Br]^+$: 477.2743, found: 477.2742.

(*Z*,2*R*,3*S*,4*R*)-Methyl 3,4-bis(benzyloxy)-2-(pivaloyloxy)-8-triisopropylsilanyloxy-oct-5-enoate (18).

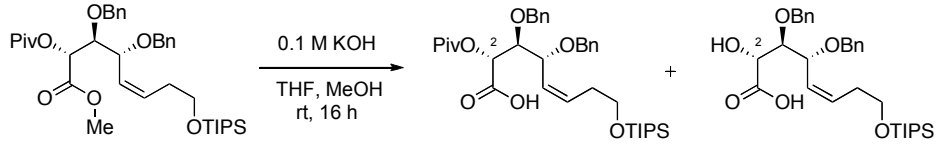


Oxidation: At ambient temperature, trichloroisocyanuric acid (744 mg, 3.20 mmol) was added to a solution of alcohol **28** (1.29 g, 2.905 mmol) and TEMPO (4.5 mg, 0.029 mmol) in CH_2Cl_2 (30 mL). After stirring the mixture for 10 min, the reaction was quenched with saturated aqueous $NaHCO_3$ (20 mL) and the layers partitioned. The aqueous layer was then extracted with CH_2Cl_2 (2 × 20 mL), the combined organic

extracts dried with Na_2SO_4 and then concentrated under reduced pressure. Without further purification, the aldehyde product (**9**) was immediately used in the subsequent Wittig reaction.

Wittig Reaction: To a stirred, cooled (–78 °C, acetone/$CO_{2(s)}$) suspension of phosphonium salt **30** (1.94 g, 3.49 mmol) in THF (40 mL) was added *n*-BuLi (1.45 mL, 3.63 mmol, 2.1 M in hexanes) via syringe and the mixture stirred for 30 min. A solution of the aldehyde (**9**) in THF (10 mL) was then added via cannula and the mixture stirred for 20 min at -78 °C. The reaction was allowed to warm to ambient temperature over 40 min and then quenched with water (5 mL) and saturated aqueous ammonium chloride (5 mL). The two-phase mixture was then extracted with EtOAc (3 × 25 mL) and the organic extracts washed with brine (20 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel (EtOAc/hexanes, 1:20→1:9→1:4) to afford **18** (1.57 g, 84%) as a single *Z*-isomer: colorless oil; R_f 0.79 (EtOAc/hexanes, 1:2); $[\alpha]_D^{24}$ -8.1 (*c* 10.4, $CHCl_3$); IR (film/ZnSe) υ_{max} 3087, 3062, 3029, 2942, 2890, 2865, 1766, 1737, 1479, 1454, 1394, 1365, 1290, 1270, 1211, 1143, 1097, 1070, 1027, 1014, 925, 883, 734, 696, 659 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38-7.23 (m, 10 H), 5.82 (ddd, *J* = 5.8, 8.8, 11.1 Hz, 1 H, HC-6), 5.50-5.41 (m, 1 H, HC-5), 5.18 (d, *J* = 2.8 Hz, 1 H, HC-2), 4.90 (d, *J* = 11.7 Hz, 1 H, OC*H*HPh), 4.67 (d, *J* = 11.7 Hz, 1 H, OCH*H*Ph), 4.62 (d, *J* = 11.6 Hz, 1 H, OC*H*HPh), 4.45 (dd, *J* = 8.1, 9.6 Hz, 1 H, HC-4), 4.42 (d, *J* = 11.6 Hz, 1 H, OCH*H*Ph), 4.08 (dd, *J* = 2.8, 7.7 Hz, 1 H, HC-3), 3.73-3.62 (m, 2 H, H_2C-8), 3.57 (s, 3 H, OCH_3), 2.41-2.29 (m, 1 H, *H*HC-7), 2.17-2.08 (m, 1 H, H*H*C-7), 1.27 (s, 9 H, $C(CH_3)_3$), 1.15-0.96 (m, 21 H, $Si(CH(CH_3)_2)_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.7 (s, C-1'), 168.8 (s, C-1), 138.4 (s, Ph), 138.3 (s, Ph), 133.2 (d, C=C), 128.2 (d, 2 C), 128.2 (d, 2 C), 127.8 (d, 3 C), 127.8 (d), 127.5 (d), 127.2 (d, 2 C), 80.5 (d), 75.2 (d), 74.7 (t), 72.2 (d), 70.6 (t), 62.7 (t), 52.2 (q, OCH_3), 38.9 (s, $C(CH_3)_3$), 31.9 (t, C-7), 27.1 (q, 3 C, $C(CH_3)_3$), 18.0 (q, 6 C, $Si(CH(CH_3)_2)_3$), 11.9 (d, 3 C, $Si(CH(CH_3)_2)_3$); HRMS-ESI calcd for $C_{37}H_{56}O_7SiNa$ $[M+Na]^+$: 663.3694, found: 663.3693.

(*Z*,1*R*,2*S*,3*R*)-1-(Methoxycarbamoyl)-2,3-bis(benzyloxy)-7-triisopropylsilyloxyhept-4-enyl pivalate (31).



18 **31** (66%; 74% brsm) **32** (7%; 8% brsm)

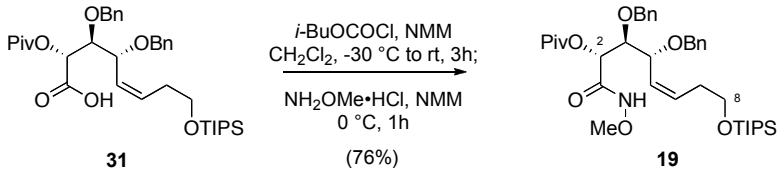
At ambient temperature, a solution of **18** (760 mg, 1.19 mmol) in THF (40 mL) and MeOH (5 mL) was treated with aqueous KOH (0.1 M, 36 mL, 3.6 mmol). After stirring for 16 h, the reaction was quenched with saturated aqueous NH_4Cl (10 mL) then partitioned between CH_2Cl_2 (15 mL) and aqueous HCl (1 M, 10 mL). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure and the residue purified by flash chromatography on silica gel (EtOAc/hexanes/EtOH,

1:4:0→1:1:0→1:0:0→4:0:1) to afford carboxylic acid **31** (448.3 mg, 66%), α-hydroxy carboxylic acid **32** (47.9 mg, 7%), and recovered starting material **18** (81.8 mg, 8%).

Carboxylic Acid **31**: colorless oil; R_f 0.25 (EtOAc); $[\alpha]_D^{24}$ -16.2 (*c* 3.7, $CHCl_3$); IR (film/ZnSe) υ_{max} 3199, 3087, 3064, 3029, 2942, 2866, 2725, 1739, 1456, 1396, 1367, 1284, 1209, 1143, 1103, 1070, 1014, 924, 883, 734, 696 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37-7.21 (m, 10 H, Ph), 5.81 (ddd, *J* = 6.0, 8.6, 11.2 Hz, 1 H, HC-6), 5.50-5.42 (m, 1 H, HC-5), 5.22 (d, *J* = 3.0 Hz, 1 H, HC-2), 4.86 (d, *J* = 11.5 Hz, 1 H, OC*H*HPh), 4.67 (d, *J* = 11.5 Hz, 1 H, OCH*H*Ph), 4.60 (d, *J* = 11.6 Hz, 1 H, OC*H*HPh), 4.44 (dd, *J* = 7.2, 9.5 Hz, 1 H, HC-4), 4.40 (d, *J* = 11.6 Hz, 1 H, OCH*H*Ph), 4.04 (dd, *J* = 3.0, 7.2 Hz, 1 H, HC-3), 3.73-3.59 (m, 2 H, H_2C-8), 2.37-2.26 (m, 1 H, *H*HC-7), 2.16-2.04 (m, 1 H, H OC*H*HPh C-7), 1.24 (s, 9 H, $C(CH_3)_3$), 1.13-0.99 (m, 21 H, $Si(CH(CH_3)_2)_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.4 (s, C-1'), 172.7 (s, C-1), 138.0 (s, Ph), 137.7 (s, Ph), 133.3 (d, *C*=C), 128.3 (d, 2 C), 128.0 (d, 4 C), 127.9 (d, 2 C, Ph), 127.8 (d, Ph), 127.5 (d, Ph), 127.1 (d, C=*C*), 80.1 (d), 74.8 (t), 74.6 (d), 70.8 (d), 70.5 (t), 62.7 (t, C-8), 38.8 (s, *C*$(CH_3)_3$), 31.9 (t, C-7), 27.1 (q, 3 C, C(*C*$H_3)_3$), 18.0 (q, 6 C, $Si(CH(CH_3)_2)_3$), 11.9 (d, 3 C, $Si(CH(CH_3)_2)_3$); HRMS-ESI calcd for $C_{36}H_{55}O_7Si$ $[M+H]^+$: 627.3717, found: 627.3734.

α-Hydroxy Carboxylic Acid **32**: colorless oil; R_f 0.08 (EtOAc); $[\alpha]_D^{24}$ -40.0 (*c* 1.3, $CHCl_3$); IR (film/ZnSe) υ_{max} 3382, 3085, 3064, 3029, 2942, 2865, 1608, 1454, 1419, 1384, 1211, 1103, 1070, 1014, 925, 883, 732, 696 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.33-7.13 (m, 10 H, Ph), 5.75 (ddd, *J* = 7.2, 7.2, 11.1 Hz, 1 H, HC-6), 5.40 (dd, *J* = 10.4, 10.4 Hz, 1 H, HC-5), 4.74 (d, *J* = 11.1 Hz, 1 H, OC*H*HPh), 4.55 (d, *J* = 11.1 Hz, 1 H, OCH*H*Ph), 4.74 (d, *J* = 12.2 Hz, 1 H, OC*H*HPh), 4.42-4.36 (dd, *J* = 9.1, 9.1 Hz, 1 H, HC-4), 4.34 (d, *J* = 12.2 Hz, 1 H, OCH*H*Ph), 3.86 (d, *J* = 8.6 Hz, 1 H, HC-3), 3.75 (s, 1 H, HC-2), 3.73-3.58 (m, 2 H, H_2C-8), 3.60 (br s, 1 H, OH), 2.43-2.20 (m, 2 H, H_2C-7), 1.23-0.83 (m, 21 H, $Si(CH(CH_3)_2)_3$); ^{13}C NMR (100 MHz, DMSO-d_6) δ 175.6 (s, C-1), 139.9 (s, Ph), 139.4 (s, Ph), 132.1 (d, *C*=C), 128.9 (d, Ph), 128.5 (d, 2 C, Ph), 128.3 (d, 2 C, Ph), 128.0 (d, 2 C, Ph), 127.7 (d, 2 C, Ph), 127.6 (d, Ph), 127.4 (d, C=*C*), 83.1 (d), 77.1 (d), 74.5 (t), 71.5 (d), 70.0 (t), 63.0 (t, C-8), 31.8 (t, C-7), 18.3 (q, 6 C, $Si(CH(CH_3)_2)_3$), 11.8 (d, 3 C, $Si(CH(CH_3)_2)_3$); HRMS-ESI calcd for $C_{31}H_{47}O_6Si$ $[M+H]^+$: 543.3142, found: 543.3163.

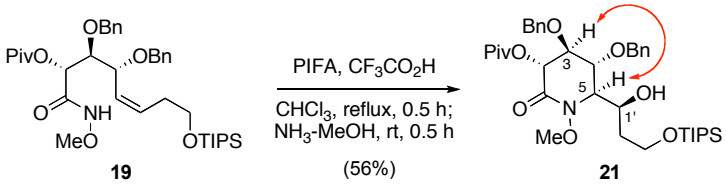
(*Z*,1*R*,2*S*,3*R*)-1-(Methoxycarbamoyl)-2,3-bis(benzyloxy)-7-triisopropylsilyloxyhept-4-enyl pivalate (19).



To a stirred, cooled (–30°C, acetone/$CO_{2(s)}$) solution of **31** (183.4 mg, 0.287 mmol) and Et_3N (43.5 μL, 0.315 mmol) in CH_2Cl_2 (4 mL) was added isobutylchloroformate (40.9 μL, 0.287 mmol). After stirring for 30 min, a solution of methoxylamine hydrochloride

(29.5 mg, 0.373 mmol) and Et_3N (91.3 μL, 0.66 mmol) was added. The cold bath was then removed, and the reaction stirred for 3 h at -30 °C, before being allowed to warm to room temperature. The reaction was then quenched with 1 M HCl (10 mL), extracted with CH_2Cl_2 (3 × 30 mL), and the combined organic extracts dried (Na_2SO_4) and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel (EtOAc/hexanes, 1:4) to afford **19** (144.5 mg, 77%): colorless oil; R_f 0.45 (EtOAc/hexanes, 1:2); $[\alpha]_D^{24}$ -26.6 (*c* 2.88, $CHCl_3$); IR (film/ZnSe) υ_{max} 3153, 3089, 3064, 3027, 2958, 2943, 2899, 2866, 1735, 1691, 1673, 1537, 1497, 1461, 1394, 1367, 1301, 1276, 1211, 1151, 1099, 1054, 912, 883, 736, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.55 (s, 1 H, NH), 7.41-7.20 (m, 10 H, Ph), 5.80 (ddd, *J* = 6.7, 7.6, 11.2 Hz, 1 H, HC-6), 5.59-5.49 (m, 1 H, HC-5), 5.23 (d, *J* = 4.8 Hz, 1 H, HC-2), 4.82 (d, *J* = 11.1 Hz, 1 H, OC*H*HPh), 4.70 (d, *J* = 11.1 Hz, 1 H, OCH*H*Ph), 4.62 (d, *J* = 11.8 Hz, 1 H, OC*H*HPh), 4.36 (dd, *J* = 5.8, 9.0 Hz, 1 H, HC-4), 4.34 (d, *J* = 11.7 Hz, 1 H, OCH*H*Ph), 3.94 (dd, *J* = 5.1, 5.1 Hz, 1 H, HC-3), 3.73-3.65 (m, 2 H, H_2C-8), 3.62 (s, 3 H, OMe), 2.36-2.23 (m, 1 H, *H*HC-7), 2.20-2.08 (m, 1 H, H*H*C-7), 1.23 (s, 9 H, $C(CH_3)_3$), 1.16-1.02 (m, 21 H, $Si(CH(CH_3)_2)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.2 (s, C-1'), 167.0 (s, C-1), 138.0 (s, Ph), 137.8 (s, Ph), 132.8 (C-6), 128.4 (d, 2 C, Ph), 128.4 (d, 2 C, Ph), 128.1 (d, 4 C, Ph), 127.9 (d, Ph), 127.7 (d, Ph), 127.4 (d, C-5), 80.6 (d, C-3), 75.6 (t, OCH_2Ph), 73.9 (d, C-4), 71.7 (d, C-2), 70.3 (t, OCH_2Ph), 64.2 (q, OCH_3), 62.7 (t, C-8), 38.8 (s, *C*$(CH_3)_3$), 31.8 (t, C-7), 27.1 (q, 3 C, C(*C*$H_3)_3$), 17.9 (q, 6 C, Si(CH(*C*$H_3)_2)_3$), 11.8 (d, 3 C, Si(*C*H$(CH_3)_2)_3$); HRMS-ESI calcd for $C_{37}H_{58}NO_7Si$ $[M+H]^+$: 656.3983, found: 656.4012.

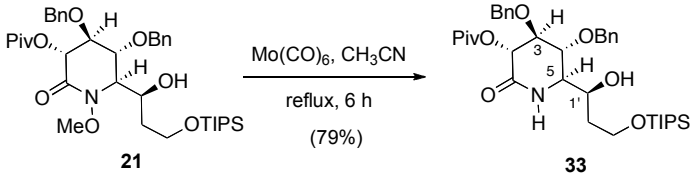
(3*R*,4*S*,5*R*,6*R*)-4,5-Bis(benzyloxy)-6-(3'-triisopropylsilanyloxy-(*S*)-1'-hydroxypropyl)-1-methoxy-2-oxopiperidin-3-yl pivalate (21).



To a stirred solution of PIFA (103 mg, 0.240 mmol) and trifluoroacetic acid (24 μL, 0.240 mmol) in anhydrous $CHCl_3$ (3 mL) heated at reflux was added a solution of **19** (144.5 mg, 0.218 mmol) in anhydrous $CHCl_3$ (2 mL) via cannula. After stirring for 30 min, the reaction was cooled to 0 °C (ice bath), quenched with a saturated solution of anhydrous methanolic ammonia (5 mL, 0.15 M NH_3 in MeOH) and stirred for a further 30 min. The reaction mixture was then concentrated under reduced pressure and the residue purified by flash chromatography on silica gel (EtOAc/hexanes, 1:9→1:4) to afford **21** (81.7 mg, 56%) as a single diastereomer: colorless oil; R_f 0.23 (EtOAc/hexanes, 1:4); $[\alpha]_D^{24}$ +40.8 (*c* 0.13, $CHCl_3$); IR (film/ZnSe) υ_{max} 3446, 2937, 2865, 1734, 1701, 1558, 1456, 1361, 1139, 1101, 883, 738, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38-7.26 (m, 10 H, Ph), 5.60 (d, *J* = 9.5 Hz, 1 H, HC-3), 4.76 (d, *J* = 11.3 Hz, 1 H, Ph*H*HCOC-3), 4.76 (d, *J* = 11.4 Hz, 1 H, Ph*H*HCOC-4), 4.69 (d, *J* = 11.4 Hz, 1 H, PhH*H*COC-4), 4.69 (d, *J* = 11.3 Hz, 1 H, PhH*H*COC-3), 4.07 (ddd, *J* = 2.3, 2.3, 10.3 Hz, 1 H, HC-1'), 4.03 (dd, *J* = 3.7, 6.6 Hz, 1 H, HC-5), 3.96 (td, *J* = 4.2, 9.9 Hz, 1 H, *H*HC-

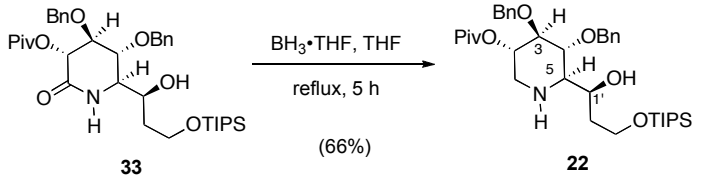
3'), 3.93 (dd, *J* = 6.6, 9.5 Hz, 1 H, HC-4), 3.85 (s, 1 H, OH), 3.81 (dt, *J* = 3.0, 9.9 Hz, 1 H, H*H*C-3'), 3.77 (s, 3 H, OCH_3), 3.72 (dd, *J* = 1.6, 3.3 Hz, 1 H, HC-5), 1.95 (dtd, *J* = 4.3, 10.1, 18.7 Hz, 1 H, *H*HC-2'), 1.65-1.57 (m, 1 H, H*H*C-2'), 1.27 (s, 9 H, $C(CH_3)_3$), 1.15-1.01 (m, 21 H, $Si(CH(CH_3)_2)_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.4 (s, C-1''), 167.8 (s, C-2), 137.6 (s, Ph), 137.6 (s, Ph), 128.5 (d, Ph), 128.4 (d, 2 C, Ph), 128.0 (d, 4 C, Ph), 127.8 (d, Ph), 128.6 (d, 2 C, Ph), 80.0 (d, C-3), 77.6 (d, C-4), 74.0 (t, PhH_2COC-3), 73.1 (t, PhH_2COC-4), 72.2 (d, C-1'), 70.6 (d, C-2), 67.2 (d, C-5), 63.3 (t, C-3'), 61.4 (q, OCH_3), 38.8 (s, $C(CH_3)_3$), 35.8 (t, C-2'), 27.2 (q, 3 C, $C(CH_3)_3$), 17.9 (q, 6 C, $Si(CH(CH_3)_2)_3$), 11.7 (d, 3 C, $Si(CH(CH_3)_2)_3$); HRMS-ESI calcd for $C_{37}H_{58}NO_8Si$ $[M+H]^+$: 672.3932, found: 672.3905.

(3*R*,4*S*,5*R*,6*R*)-4,5-Bis(benzyloxy)-6-(3'-triisopropylsilanyloxy-(*S*)-1'-hydroxypropyl)-2-oxopiperidin-3-yl pivalate (33).



To a stirred solution of **21** (40.0 mg, 0.0596 mmol) in CH_3CN (2 mL) and water (0.3 mL) was added molybdenum hexacarbonyl (31 mg, 0.119 mmol) and the resulting solution heated to reflux. After 6 h, the reaction was cooled to ambient temperature, air admitted to the vessel and the mixture stirred for 2 h. The reaction was then concentrated under reduced pressure and the residue purified by column chromatography on silica gel (EtOAc/hexanes, 1:5→1:3) to afford **33** (30.0 mg, 79%): colorless oil; R_f 0.38 (EtOAc/hexanes, 1:2); $[\alpha]_D^{24}$ +50.0 (*c* 0.10, $CHCl_3$); IR (film/ZnSe) υ_{max} 3434, 3064, 3029, 2941, 2866, 1741, 1688, 1462, 1366, 1279, 1142, 1102, 1070, 1028, 940, 883, 735, 695 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38-7.26 (m, 10 H, Ph), 6.22 (s, NH), 5.30 (d, *J* = 9.0 Hz, 1 H, HC-3), 4.89 (d, *J* = 11.1 Hz, 1 H, OC*H*HPh), 4.78 (d, *J* = 11.1 Hz, 1 H, OC*H*HPh), 4.75 (d, *J* = 11.1 Hz, 1 H, OCH*H*Ph), 4.65 (d, *J* = 11.1 Hz, 1 H, OCH*H*Ph), 4.07 (dd, *J* = 8.9, 8.9 Hz, 1 H, HC-4), 4.03 (dddd, *J* = 4.0, 4.0, 4.0, 9.5 Hz, 1 H 1 H, HC-1'), 3.96 (ddd, *J* = 3.8, 5.7, 10.4 Hz, 1 H, *H*HC-3'), 3.93 (dd, *J* = 8.5, 8.5 Hz, 1 H, HC-5), 3.86 (ddd, *J* = 3.3, 9.0, 10.4 Hz, 1 H, H*H*C-3'), 3.72 (dd, *J* = 1.6, 3.3 Hz, 1 H, HC-6), 3.61 (d, *J* = 3.8 Hz, 1H, OH), 3.33 (dd, *J* = 3.3, 8.4 Hz, 1 H, HC-6), 1.80 (dtd, *J* = 4.0, 9.0, 14.0 Hz, 1 H, *H*HC-2'), 1.68 (tdd, *J* = 3.3, 5.7, 14.0 Hz, 1 H, H*H*C-2'), 1.27 (s, 9 H, $C(CH_3)_3$), 1.15-1.01 (m, 21 H, $Si(CH(CH_3)_2)_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.5 (s, C-1''), 167.8 (s, C-2), 137.8 (s, Ph), 137.8 (s, Ph), 128.4 (d, Ph), 128.4 (d, 2 C, Ph), 127.9 (d, 4 C, Ph), 127.9 (d, Ph), 128.7 (d, 2 C, Ph), 80.6 (d), 77.3 (d), 74.7 (t), 74.5 (t), 72.4 (d), 70.1 (d), 62.5 (t, C-3'), 58.8 (d, C-6), 38.8 (s, $C(CH_3)_3$), 35.4 (t, C-2'), 27.1 (q, 3 C, $C(CH_3)_3$), 17.9 (q, 6 C, $Si(CH(CH_3)_2)_3$), 11.7 (d, 3 C, $Si(CH(CH_3)_2)_3$); HRMS-ESI calcd for $C_{36}H_{56}NO_7Si$ $[M+H]^+$: 642.3826, found: 642.3855.

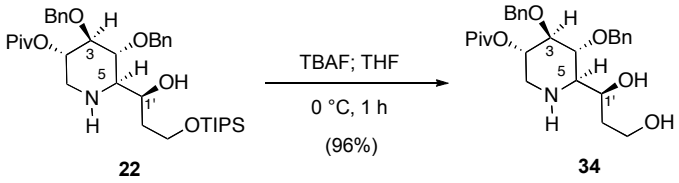
(3*S*,4*R*,5*R*,6*R*)-4,5-Bis(benzyloxy)-6-(3'-triisopropylsilanyloxy-(*S*)-1'-hydroxypropyl)-piperidin-3-yl pivalate (22).



33 22

To a stirred, cooled (0 °C, ice bath) solution of **33** (29.9 mg, 0.0452 mmol) in THF (4 mL) was added borane dimethylsulfide complex (2.0 M in THF, 0.182 mL, 0.364 mmol). After 30 min, the cold bath was removed, the reaction allowed warm to room temperature and then stirred for 5 h. The reaction was then quenched with saturated aqueous Na_2SO_4 (1 mL), stirred for 30 min and then extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure and the residue purified by column chromatography on silica gel (EtOAc/hexanes, 1:4→1:3) to afford **22** (18.8 mg, 66%): colorless oil; R_f 0.56 (EtOAc/hexanes, 1:2); $[\alpha]_D^{24}$ +31.9 (*c* 0.63, $CHCl_3$); IR (film/ZnSe) υ_{max} 3502, 3343, 3062, 3030, 2956, 2941, 2866, 1730, 1461, 1359, 1282, 1166, 1103, 1033, 883, 736, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.26 (m, 10 H, Ph), 4.89 (d, *J* = 10.9 Hz, 1 H, OC*H*HPh), 4.84 (d, *J* = 11.0 Hz, 1 H, OC*H*HPh), 4.80 (d, *J* = 11.0 Hz, 1 H, OCH*H*Ph), 4.76 (dt, *J* = 5.5, 10.3 Hz, 1 H, HC-3), 4.72 (d, *J* = 10.9 Hz, 1 H, OCH*H*Ph), 4.24 (app td, *J* = 1.9, 10.1 Hz, 1 H, HC-1'), 4.02 (td, *J* = 4.1, 10.0 Hz, 1 H, *H*HC-3'), 3.91 (dt, *J* = 2.9, 10.3 Hz, H*H*C-3'), 3.65 (br s, 1 H, OH), 3.64-3.59 (m, 2 H, HC-4, HC-5), 3.27 (dd, *J* = 5.1, 13.2 Hz, 1 H, *H*HC-2), 2.43-2.40 (m, 1 H, HC-6), 2.40 (dd, *J* = 10.3, 13.2 Hz, 1 H, H*H*C-2), 2.10 (dtd, *J* = 4.0, 10.2, 14.3 Hz, 1 H, *H*HC-2'), 1.65 (br s, 1 H, NH), 1.53 (app d, *J* = 14.3 Hz, 1 H, H*H*C-2'), 1.19 (s, 9 H, $C(CH_3)_3$), 1.15-1.01 (m, 21 H, $Si(CH(CH_3)_2)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.8 (s, C-1''), 137.7 (s, Ph), 137.6 (s, Ph), 128.3 (d, 2 C, Ph), 128.3 (d, 2 C, Ph), 128.0 (d, 2 C, Ph), 127.6 (d, Ph), 127.4 (d, Ph), 127.3 (d, 2 C, Ph), 85.0 (d, C-4), 80.0 (d, C-5), 75.4 (t, O*C*H_2Ph), 75.1 (t, O*C*H_2Ph), 74.3 (d, C-3), 69.5 (d, C-1'), 63.8 (t, C-3'), 63.7 (d, C-6), 46.8 (t, C-2), 38.8 (s, *C*$(CH_3)_3$), 35.9 (t, C-2'), 27.2 (q, 3 C, C(*C*$H_3)_3$), 17.9 (q, 6 C, $Si(CH(CH_3)_2)_3$), 11.7 (d, 3 C, $Si(CH(CH_3)_2)_3$); HRMS-ESI calcd for $C_{36}H_{58}NO_6Si$ $[M+H]^+$: 628.4033, found: 628.4049.

(3*S*,4*R*,5*R*,6*R*)-4,5-Bis(benzyloxy)-6-(3'-hydroxy-(*S*)-1'-hydroxypropyl)-piperidin-3-yl pivalate (34).

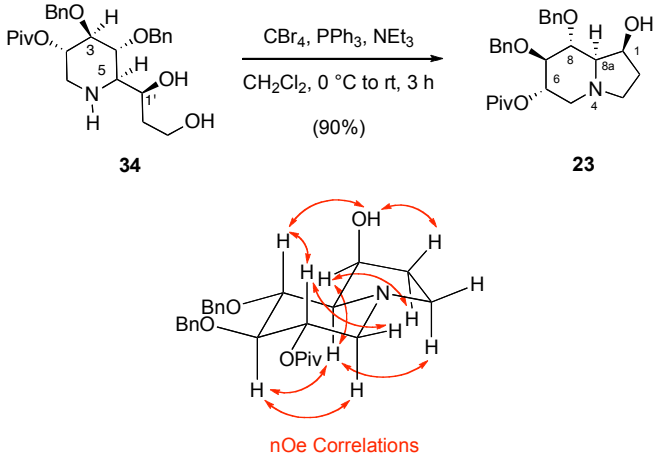


22 34

To a stirred, cooled (0 °C, ice bath) solution of **22** (17.8 mg, 0.028 mmol) in THF (2 mL) was added TBAF (1 M in THF, 84 μL, 0.084 mmol). After stirring for 2 h, silica gel (100 mg, 35-60 μm particle size) was added to the reaction mixture, which was then concentrated under reduced pressure. The residue was then purified via column chromatography on silica gel (NH_3-MeOH/$CHCl_3$, 1:100→1:20) to afford alcohol **34**

(13.0 mg, 96%): colorless oil; R_f 0.28 (NH_3-MeOH:$CHCl_3$, 1:13); mp 127-128 °C (solidified from CH_2Cl_2); $[\alpha]_D^{24}$ +66.7 (*c* 0.43, $CHCl_3$); IR (film/ZnSe) υ_{max} 3309, 3251, 3064, 3031, 2942, 2912, 2869, 1731, 1456, 1359, 1282, 1159, 1118, 1076, 1035, 989, 946, 734, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.26 (m, 10 H, Ph), 4.88 (d, *J* = 11.2 Hz, 1 H, OC*H*HPh), 4.82 (s, 2 H, OCH_2Ph), 4.76 (dt, *J* = 5.2, 10.1 Hz, 1 H, HC-3), 4.68 (d, *J* = 11.2 Hz, 1 H, OCH*H*Ph), 4.17-4.09 (m, 1 H, HC-1'), 3.83-3.80 (m, *H*HC-3'), 3.70-3.64 (m, 1 H, H*H*C-3'), 3.67 (dd, *J* = 8.9, 8.9 Hz, 1 H, HC-4), 3.51 (dd, *J* = 9.3, 9.3 Hz, 1 H, HC-5), 3.25 (dd, *J* = 5.2, 13.1 Hz, 1H, *H*HC-2), 2.45 (dd, *J* = 1.1, 9.6 Hz, 1 H, HC-6), 2.43 (dd, *J* = 10.7, 13.2 Hz, 1 H, H*H*C-2), 2.00-1.92 (br s, 1 H, HOC-1'), 1.86 (dddd, *J* = 3.5, 6.4, 9.7, 14.6 Hz, 1 H, *H*HC-2'), 1.71 (dddd, *J* = 2.6, 4.6, 4.6, 14.6 Hz, 1 H, H*H*C-2'), 1.61 (bs s, 1 H, OH), 1.42 (br s, 1 H, NH), 1.18 (s, 9 H, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.8 (s, C-1''), 138.4 (s, Ph), 138.1 (s, Ph), 128.5 (d, 2 C, Ph), 128.4 (d, 2 C, Ph), 128.3 (d, 2 C, Ph), 128.0 (d, Ph), 127.6 (d, Ph), 127.4 (d, 2 C, Ph), 84.7 (d, C-4), 78.8 (d, C-5), 75.2 (t), 75.0 (t), 73.8 (d, C-3), 67.7 (d, C-1'), 62.5 (d, C-6), 59.0 (t, C-3'), 46.2 (t, C-2), 38.8 (s, *C*$(CH_3)_3$), 37.3 (t, C-2'), 27.2 (q, 3 C, C(*C*$H_3)_3$); HRMS-ESI calcd for $C_{27}H_{38}NO_6$ $[M+H]^+$: 472.2699, found: 472.2688.

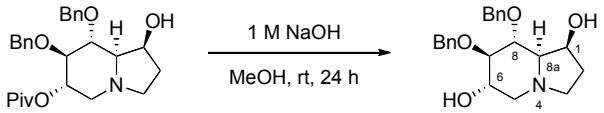
(1*S*,6*S*,7*R*,8*R*,8a*R*)-6,7-Bis(benzyloxy)-octahydro-1-hydroxyindolizin-8-yl pivalate (23).



To a stirred, cooled (0 °C, ice bath) solution of **34** (12.5 mg, 0.027 mmol) and CBr_4 (20.6 mg, 0.062 mmol) in CH_2Cl_2 (2 mL) was added dropwise, via syringe pump over 3 h (0.5 mL/h), a solution of triphenylphosphine (0.086 M, 0.129 mmol) and triethylamine (0.135 M, 0.20 mmol) in CH_2Cl_2. After consumption of the starting material, as noted by TLC, the reaction was quenched with anhydrous methanolic ammonia (2 mL) and the mixture concentrated under reduced pressure. The resulting residue was then purified by column chromatography on silica gel (NH_3-MeOH/$CHCl_3$, 1:100→1:20) to provide **23** contaminated with triphenylphosphine oxide. Further purification by column chromatography using silica gel (EtOAc/hexanes, 1:1) then afforded **23** (11.2 mg, 90%): colorless oil; R_f 0.75 (EtOAc); $[\alpha]_D^{24}$ +52.5 (*c* 0.37, $CHCl_3$); IR (film/ZnSe) υ_{max} 3450, 3089, 3062, 3029, 2967, 2931, 2872, 2807, 1730, 1479, 1454, 1396, 1359, 1280, 1160, 1134, 1097, 1027, 737, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.22 (m, 10 H, Ph), 5.01 (dt, *J* = 5.2, 9.9 Hz, 1 H, HC-6), 4.85 (d, *J* = 11.0 Hz, 1 H, OC*H*HPh), 4.81 (s, 2 H,

OC*H*$_2$Ph), 4.80 (d, *J* = 11.1 Hz, 1 H, OCH*H*Ph), 4.31-4.22 (m, 1 H, HC-1), 3.77 (dd, *J* = 9.1, 9.1 Hz, HC-8), 3.64 (dd, *J* = 9.2, 9.2 Hz, 1 H, HC-7), 3.29 (dd, *J* = 5.2, 10.2 Hz, 1 H, *H*HC-5β), 3.13 (ddd, *J* = 2.4, 8.7, 8.7 Hz, 1 H, *H*HC-3β), 2.21 (dddd, *J* = 2.9, 6.4, 9.9, 16.3 Hz, 1H, *H*HC-2α), 2.13 (ddd, *J* = 9.3, 9.3, 16.2 Hz, 1 H, H*H*C-3α), 1.99 (dd, *J* = 3.5, 9.4 Hz, 1 H, HC-8a), 1.94 (dd, *J* = 10.2, 10.2 Hz, 1 H, H*H*C-5α), 1.79 (ddd, *J* = 7.9, 7.9, 16.3 Hz, 1 H, H*H*C-2β), 1.66 (br d, 1 H, OH), 1.18 (s, 9 H, C(CH$_3$)$_3$); ^{13}C NMR (100 MHz, CDCl$_3$) δ 177.7 (s, C-1'), 138.7 (s, Ph), 138.5 (s, Ph), 128.5 (d, 2 C, Ph), 128.3 (d, 2 C, Ph), 128.1 (d, 2 C, Ph), 127.8 (d, Ph), 127.5 (d, Ph), 127.5 (d, 2 C, Ph), 85.1 (d), 77.0 (d), 75.2 (t), 75.4 (t), 72.7 (d), 71.8 (d), 70.9 (d), 53.2 (t), 51.4 (t), 38.8 (s, *C*(CH$_3$)$_3$), 33.7 (t, C-2), 27.2 (q, 3 C, C(*C*H$_3$)$_3$); NOESY correlations (CDCl$_3$) H-1/HO-1, H-1/H-2β, H-3β/HO-1, H-6/H-5β, H-6/H-8, H-7/H-5α, H-8/HO-1, H-8a/H-1, H-8a/H-3α, H-8a/H-7; HRMS-ESI calcd for $C_{27}H_{36}NO_5$ $[M+H]^+$: 454.2593, found: 454.2577.

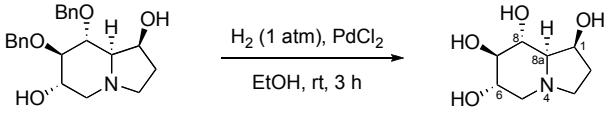
(1*S*,6*S*,7*R*,8*R*,8a*R*)-7,8-Bis(benzyloxy)-octahydro-1-hydroxyindolizin-6-yl pivalate (35).



23 **35**

To a stirred solution of **23** (11.0 mg, 0.024 mmol) in THF (2 mL) and MeOH (2 mL) at ambient temperature was added NaOH (1 M, 300 μL, 0.300 mmol). After stirring for 12 h, a second portion of NaOH (1 M, 300 μL, 0.300 mmol) was added, and the reaction stirred for a further 12 h. The reaction was then partitioned between brine (1 mL) and CH_2Cl_2 (5 mL) and the aqueous phase extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure to afford **35** (7.2 mg, 81%), which required no additional purification: white solid; R_f 0.48 (EtOAc/EtOH, 4:1); mp 159-160 °C (solidified from CH_2Cl_2); $[\alpha]_D^{24}$ +10.7 (*c* 0.24, $CHCl_3$); IR (film/ZnSe) υ_{max} 3407, 3058, 3023, 2927, 2833, 1456, 1357, 1324, 1276, 1257, 1130, 1093, 1054, 748, 729, 698 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 7.41-7.32 (m, 2 H, Ph), 7.32-7.18 (m, 8 H, Ph), 4.94 (d, *J* = 11.1 Hz, 1 H, OC*H*HPh), 4.85-4.80 (m, 2 H), 4.78 (d, *J* = 10.9 Hz, 1 H, OCH*H*Ph), 4.34 (t, *J* = 4.8, 4.8 Hz, 1 H, HC-1), 3.80-3.74 (m, 1 H, HC-6), 3.76 (dd, *J* = 9.3, 9.3 Hz, HC-8), 3.34 (dd, *J* = 9.0, 9.0 Hz, 1 H, HC-7), 3.18-3.05 (m, 2 H, *H*HC-3, *H*HC-5), 2.26 (dddd, *J* = 2.6, 6.9, 9.5, 13.2 Hz, 1 H, *H*HC-2), 2.16 (ddd, *J* = 9.0, 9.0, 9.0 Hz, 1H, H*H*C-3), 2.02-1.90 (m, 2 H, HC-8a, H*H*C-5), 1.79 (ddd, *J* = 7.9, 7.9, 14.2 Hz, 1 H, H*H*C-2); ^{13}C NMR (100 MHz, CD_3OD) δ 138.7 (s, Ph), 138.7 (s, Ph), 127.8 (d, 2 C, Ph), 127.8 (d, 2 C, Ph), 127.8 (d, 2 C, Ph), 127.5 (d, 2 C, Ph), 127.1 (d, Ph), 127.0 (d, Ph), 88.0 (d), 77.4 (d), 74.9 (t), 74.0 (t), 72.0 (d), 70.8 (d), 69.8 (d), 56.6 (t), 51.5 (t), 33.7 (t, C-2); HRMS-ESI calcd for $C_{22}H_{28}NO_4$ $[M+H]^+$: 370.2018, found: 370.2003.

(1*S*,6*S*,7*R*,8*R*,8a*R*)-1,6,7,8-Tetrahydroxyindolizidine [(+)-Castanospermine (1)].



To a solution of **35** (6.4 mg, 0.017 mmol) in EtOH (1 mL) was added palladium dichloride (4.0 mg, 0.0225 mmol) and the reaction vessel flushed with H_2 (1 atm). After stirring for 3 h, the reaction was flushed with N_2, filtered through a cotton plug and concentrated under reduced pressure. The residue was then dissolved in water (0.5 mL) and stirred with Dowex 1X8-50 resin ($^-$OH form) for 30 min. This solution was then purified by ion-exchange chromatography on Dowex 1X8-50 resin ($^-$OH form) eluting with H_2O to afford (+)-castanospermine (**1**) (2.9 mg, 88%): white crystals; mp 211-212 °C dec (EtOH) [*lit.* 212-215 °C dec (EtOH),[9] 213.5-215 °C dec (EtOH),[10]]; R_f 0.43 (CH_2Cl_2/MeOH/conc.NH_3OH, 1:1:0.3); $[\alpha]_D^{24}$ +74.5 (*c* 0.1, H_2O) [*lit.* $[\alpha]_D^{25}$ +79.7 (*c* 0.93, H_2O),[11] +74.1 (*c* 0.3, H_2O),[12] $[\alpha]_D^{24}$ +77.8 (*c* 0.16, H_2O)[13], $[\alpha]_D^{24}$ +71 (*c* 0.27, H_2O)[14]]; IR (film/ZnSe) υ_{max} 3347, 2968, 2943, 2916, 2817, 1444, 1365, 1326, 1131, 1089, 1007, 957 cm^{-1}; ^1H NMR (500 MHz, D_2O) δ 4.39 (ddd, *J* = 1.8, 4.4, 6.6 Hz, 1 H, HC-1), 3.61 (ddd, *J* = 5.1, 10.5, 10.5 Hz, 1 H, HC-6), 3.59 (dd, *J* = 9.5, 9.5 Hz, HC-8), 3.32 (dd, *J* = 9.1, 9.1 Hz, 1 H, HC-7), 3.17 (dd, *J* = 5.1, 10.8 Hz, 1 H, *H*HC-5), 3.08 (ddd, *J* = 2.2, 9.1, 9.1 Hz, 1 H, *H*HC-3), 2.32 (dddd, *J* = 2.2, 7.4, 9.4, 14.2 Hz, 1 H, *H*HC-2), 2.21 (ddd, *J* = 9.2, 9.2, 9.2 Hz, 1H, H*H*C-3), 2.05 (dd, *J* = 10.8, 10.8 Hz, 1 H, H*H*C-5), 2.02 (dd, *J* = 4.5, 10.0 Hz, 1 H, HC-8a), 1.71 (dddd, *J* = 1.7, 8.8, 8.8, 14.1 Hz, 1 H, H*H*C-2); ^{13}C NMR (125 MHz, D_2O) δ 78.0 (d), 70.4 (d), 69.1 (d), 68.6 (d), 68.0 (d), 54.4 (t), 50.6 (t), 31.7 (t, C-2); HRMS-ESI calcd for $C_8H_{16}NO_4$ $[M+H]^+$: 190.1079, found: 190.1071.

1.6 ^{1}H and ^{13}C NMR Chemical Shifts for Natural and Synthetic (+)-Castanospermine.

	Natural (+)-Castanospermine (**2**)[15]		Synthetic (+)-Castanospermine [Chamberlin][16]		Synthetic (+)-Castanospermine [Bowen]	
Position	^{1}H NMR[a]	^{13}C NMR[b]	^{1}H NMR[c]	^{13}C NMR[d]	^{1}H NMR[e]	^{13}C NMR[f]
1	4.41 (ddd, *J* = 2, 4.4, 7 Hz)	69.4 (d)	4.41 (ddd, *J* = 1.5, 4.6, 6.8 Hz)	71.7 (d)	4.39 (ddd, *J* = 1.8, 4.4, 6.6 Hz)	68.0 (d)
2α	2.33 (dddd, *J* = 0, 2, 7, 14 Hz)	33.1 (t)	2.33 (dddd, *J* = 2.2, 7.3, 8.1, 14.8 Hz)	35.5 (t)	2.32 (dddd, *J* = 2.2, 7.4, 9.4, 14.2 Hz)	31.7 (t)
2β	1.70 (dddd, *J* = 2, 10, 10, 14 Hz)		1.71 (dddd, *J* = 1.8, 8.7, 8.7, 14.2 Hz)		1.71 (dddd, *J* = 1.7, 8.8, 8.8, 14.1 Hz)	
3α	2.20 (app q, *J* = 10 Hz)	51.6 (t)	2.21 (app q, *J* = 10.7 Hz)	54.3 (t)	2.21 (ddd, *J* = 9.2, 9.2, 9.2 Hz)	50.6 (t)
3β	3.08 (app dt, *J* = 2, 10 Hz)		3.08 (dt, *J* = 2.1, 9.1 Hz)		3.08 (ddd, *J* = 2.2, 9.1, 9.1 Hz)	
5α	2.06 (dd, *J* = 10, 10.7 Hz)	55.4 (t)	2.06 (app t, *J* = 10.7 Hz)	58.1 (t)	2.05 (dd, *J* = 10.8, 10.8 Hz)	54.4 (t)
5β	3.16 (dd, *J* = 5, 10.7 Hz)		3.18 (dd, *J* = 5.1, 10.8 Hz)		3.17 (dd, *J* = 5.1, 10.8 Hz)	
6	3.60 (ddd, *J* = 5, 8.5, 10 Hz)	68.8 (d)	3.61 (m, 1 H)	72.3 (d)	3.61 (ddd, *J* = 5.1, 10.5, 10.5 Hz)	68.6 (d)
7	3.30 (app t, *J* = 8.5 Hz)	78.7 (d)	3.32 (app t, *J* = 9.1 Hz)	81.8 (d)	3.32 (dd, *J* = 9.1, 9.1 Hz)	78.0 (d)
8	3.58 (dd, *J* = 8.5, 10 Hz)	69.9 (d)	3.60 (app t, *J* = 9.6 Hz)	72.8 (d)	3.59 (dd, *J* = 9.5, 9.5 Hz)	69.1 (d)
8a	2.01 (dd, *J* = 4.4, 10 Hz)	71.2 (d)	2.02 (dd, *J* = 4.4, 9.8 Hz)	74.2 (d)	2.02 (dd, *J* = 4.5, 10.0 Hz)	70.4 (d)

[a](360 MHz, D_2O). [b](90 MHz, D_2O). [c](500 MHz, D_2O). [d](125 MHz, D_2O). [e](500 MHz, D_2O). [f](125 MHz, D_2O).

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