A Formal Synthesis of (+)-Lactacystin

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SUPPORTING INFORMATION

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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 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.

2. Materials.

All solvents were reagent grade. 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) and trimethylsilyl chloride (TMSCl) were freshly distilled from calcium hydride under nitrogen. Triethylamine was 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), 1-bromo-3-methyl-2-butene, aluminum trichloride, di-*t*-butyl-dicarbonate (Boc_2O), *m*-chloroperoxybenzoic acid (mCPBA) and, (trimethylsilyl)diazomethane 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 and methyllithium solutions were determined by titration against diphenylacetic acid as an indicator (average of three determinations).[2] 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.

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

1. W. C. Still, M. Kahn and A. Mitra, *J. Org. Chem.* **1978**, *43*, 2923-2925.
2. W. G. Kofron and L. M. Baclawski, *J. Org. Chem.* **1976**, *41*, 1879-1880.

on barium fluoride plates using an ATI Mattson genesis series FTIR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 400 (400 MHz ^{1}H, 100 MHz ^{13}C), a Bruker Avance 500 (500 MHz ^{1}H, 125 MHz ^{13}C), or a Bruker AM-400 (400 MHz ^{1}H, 100 MHz ^{13}C) spectrometer. Chemical shift values (δ) are reported in ppm relative to residual chloroform (δ 7.27 ppm for ^{1}H; δ 77.23 ppm for ^{13}C) and methanol (δ 3.31 ppm for ^{1}H; δ 49.15 ppm for ^{13}C). The ^{1}H 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). 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: $[\alpha]_{\text{wavelength}}^{\text{temperature}}$ (*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.

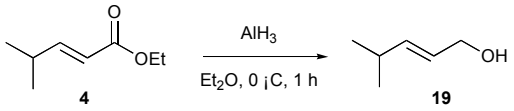
4. Literature Preparations

(*E*)-4-Methyl-pent-2-enoic acid methyl ester (**4**) was prepared according to the method reported by Hale.[3] 1,3-Dibromo-2-methyl-2-propene was prepared from 1-bromo-3-methyl-2-butene following the method of Heck.[4]

3. K. J. Hale,S. Manaviazar, and V. M. Delisser, *Tetrahedron* 1994, **50**, 9181-9188.
4. W. Fischetti, K. T. Mak, F. G. Stakem, J. Kim, A. L. Rheingold and R. F. Heck, *J. Org. Chem.* 1983, **48**, 948-955.

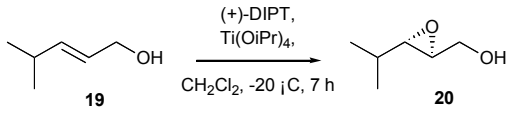
5. Experimental Procedures.

(*E*)-4-Methyl-2-penten-1-ol (19).



A 2-L, three-necked, round-bottomed flask equipped with an efficient mechanical stirrer attached to a Teflon stirring blade, a reflux condenser and a 250 mL pressure-equalizing dropping funnel connected to an nitrogen inlet was charged with anhydrous diethyl ether (600 mL) and lithium aluminum hydride (45.8 g, 322 mmol) then flushed with nitrogen. Upon dissolution of the $LiAlH_4$, the stirred solution was cooled to 0 °C, the addition funnel charged with $AlCl_3$ (26.7 g, 199 mmol) and anhydrous diethyl ether (400 mL) and this solution added then dropwise over 30 min. The resulting mixture was stirred for 30 min at ambient temperature, cooled to 0 °C and a solution of **4** (19.0 g, 148 mmol) in diethyl ether (100 mL) then added via the dropping funnel. After stirring for a further 1 h, the reaction was quenched by the dropwise addition of aqueous sulfuric acid (100 mL, 2 M). The white precipitate that formed was removed by filtration through Celite 521 and the filtrate dried ($MgSO_4$) then concentrated under reduced pressure to provide a colorless oil. Fractional distillation of this material under reduced pressure (60-70 °C/20 mmHg) provided **19**[5] (27.5 g, 85% yield) as a colorless oil: R_f 0.23 (ethyl acetate/hexanes, 1:2); FTIR (film) υ_{max} 3312, 2874, 1664 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.50-5.46 (m, 2 H), 3.94 (d, J = 5.7 Hz, 2 H), 3.32 (s, 1 H), 2.20 (h, J = 6.6 Hz, 1 H), 0.90 (d, J = 6.6 Hz, 6 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 140.1, 125.8, 63.6, 30.6, 22.1.

(2*S*,3*S*)-(-)-2,3-Epoxy-4-methyl-1-pentanol (20).



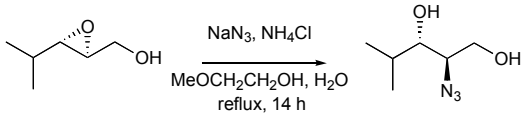
To a stirred suspension of powdered activated 4Å molecular sieves (10 g) in CH_2Cl_2 (500 mL, pre-dried over 4 Å molecular sieves) at –20 °C was added $Ti(OiPr)_4$ (3.94 mL, 13.8 mmol) and (+)-diisopropyl L-tartrate (3.47 mL, 16.5 mmol). *tert*-Butyl hydroperoxide (110 mL, 5.5 M in decane, 550 mmol, pre-dried over 4Å sieves) was then added

5. L. A. Gorthey, M. Vairamani, and C. Djerassi, *J. Org. Chem.* 1984, **49**, 1511-1517.

dropwise via syringe and the mixture stirred for 20 min. A pre-dried (4Å molecular sieves) solution of **19** (27.5 g mL, 275 mmol) in CH_2Cl_2 (100 mL) was added dropwise and the mixture stirred for 7 h at –20 °C. The reaction was then allowed to warm to 0 °C and poured into a cold (5 °C) solution of $FeSO_4 \bullet 7H_2O$ (87.1 g, 330 mmol) and D-tartaric acid (27.5 g, 165 mmol) in H_2O (275 mL). After stirring for 15 min, the aqueous phase was separated and extracted with Et_2O (3 x 100 mL). The combined organic extracts were dried (Na_2SO_4) then concentrated under reduced pressure and the concentrate fractionally distilled under reduced pressure (95-98 °C/20 mmHg) to provide **20** (24.15 g, 76% yield) as a colorless oil: $[\alpha]_D^{25}$ -30.3 (c 0.96, $CHCl_3$) [lit.[6] $[\alpha]_D^{25}$ -32.7 (*c* 1.01, $CHCl_3$)]; R_f 0.16 (ethyl acetate/hexanes, 1:2); FTIR (film) υ_{max} 3412, 1465, 1067, 1018 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.81-3.79 (m, 1 H), 3.51-3.47 (m, 1 H), 3.15 (br s, 1 H), 2.90-2.88 (m, 1 H), 2.67-2.64 (m, 1 H), 1.53-1.44 (m, 1 H), 0.95 (d, J = 4.5 Hz, 3 H), 0.87 (d, J = 4.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 61.9, 61.2, 57.7, 29.9, 18.8, 18.2.

The optical purity of **20** (*ee* 96%) was determined by conversion to the corresponding MTPA ester, following the method of Ward,[7] NMR analysis of the appropriate characteristic protons signals in the unpurified product mixture indicated the presence of two diastereomers in a 98:2 ratio.

(2*R*,3*S*)-(-)-2-Azido-4-methyl-pentane-1,3-diol (6).



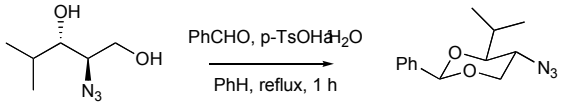
20 **6**

This reaction and subsequent distillations were carried out behind a safety screen. A 1-L, single-necked, round-bottomed flask equipped with reflux condenser attached to a nitrogen inlet was charged with epoxide **20** (6.31 g, 54.4 mmol), NH_4Cl (5.80 g, 108 mmol), NaN_3 (17.7 g, 272 mmol), 2-methoxyethanol (245 mL) and water (30 mL) then flushed with nitrogen. The reaction was heated at reflux for 14 h, cooled to ambient temperature and then concentrated to approximately 10% of its original volume under reduced pressure. The aqueous concentrate was diluted with THF (160 mL) and water (80

6. C. G. Caldwell, and S. S. Bondy, *Synthesis* 1990, 34-36.
7. D. E. Ward and C. K. Rhee, *Tetrahedron Lett.* 1991, **32**, 7165-7166.

mL), $NaIO_4$ (17.4 g, 81.6 mmol) was added and the mixture stirred at ambient temperature for 24 h during which time a white solid precipitated. The reaction mixture was then diluted with water (90 mL), filtered through a Buchner funnel with a glass frit and the filtrate partitioned between CH_2Cl_2 (100 mL) and water (50 mL). The organic phase was separated and the aqueous phase extracted with CH_2Cl_2 (6 x 200 mL). The combined organic extracts were dried ($MgSO_4$), concentrated under reduced pressure and the residue purified by flash chromatography on silica gel (ethyl acetate/hexanes, 1:2) to provide **6** (3.53 g, 47% yield) as a yellow oil: $[\alpha]_D^{25}$ -25.0 (c 1.77, $CHCl_3$); R_f 0.17 (ethyl acetate/hexanes, 1:2); FTIR (film) υ_{max} 3382, 2100, 1267, 1057, 995 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.89-3.85 (m, 2 H), 3.58 (br s, 1 H), 3.45-3.40 (m, 2 H), 3.25 (br s, 1 H), 1.90-1.82 (m, 1 H), 0.94 (d, *J* = 6.8 Hz, 3 H), 0.93 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 76.5, 64.3, 62.6, 30.2, 19.5, 16.5; HRMS-CI *m/z* 177.1552 $[(M+NH_4)^+$; calcd for $C_6H_{13}N_3O_2$ 177.1352].

(2*R*,4*S*,5*R*)-(-)-5-Azido-4-isopropyl-2-phenyl[1,3]dioxane (21).

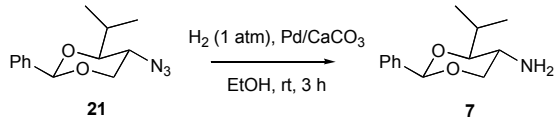


6 **21**

This reaction and subsequent distillations were carried out behind a safety screen. A 3-L, two-necked, round-bottomed flask equipped with a magnetic stirring bar, a septum, a Dean-Stark apparatus and a reflux condenser connected to a nitrogen inlet was charged with **6** (29.3 g, 184 mmol), *p*-toluenesulfonic acid monohydrate (PTSA) (1.79 g, 9.40 mmol) and toluene (2000 mL) then flushed with nitrogen. After heating this mixture to reflux, benzaldehyde (20.5 mL, 202 mmol) was added via syringe and stirring continued for 1 h. The reaction mixture was then allowed to cool to ambient temperature, the reaction mixture filtered through a pad of Celite 521 and the filter cake washed with ethyl acetate. The combined filtrates were concentrated under reduced pressure and the residue purified by flash chromatography on silica gel (ethyl acetate/hexanes, 1:29) to provide **21** (36.4 g, 78% yield) as a yellow oil: $[\alpha]_D^{25}$ -55.8 (c 2.77, $CHCl_3$); R_f 0.37 (ethyl acetate/hexanes, 1:19); FTIR (film) υ_{max} 3068, 3037, 2966, 2875, 2105, 1454, 1280, 1099, 968, 752, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.56-7.55 (m, 2 H), 7.46-7.39 (m, 3 H), 5.50 (s, 1 H), 4.42 (dd, *J* = 11.9, 3.3 Hz, 1 H), 3.72 (t, *J* = 10.5 Hz, 1 H), 3.66-

3.60 (m, 1 H), 3.52 (dd, *J* = 9.6, 2.2 Hz, 1 H), 2.23-2.16 (m, 1 H), 1.18 (d, *J* =6.9 Hz, 3 H), 1.11 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.9, 129.0, 128.3 (2 C), 126.1 (2 C), 101.0, 83.8, 69.1, 54.6, 29.0, 19.5, 15.5; HRMS-CI *m/z* 265.1660 [$(M+NH_4)^+$; calcd for $C_{13}H_{16}N_3O_2$ 265.1664].

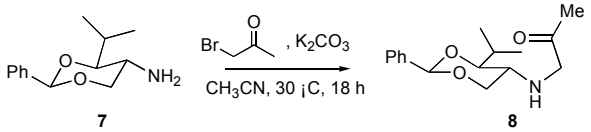
(2*R*,4*S*,5*R*)-(-)-4-Amino-5-isopropyl-2-phenyl[1,3]dioxane (7).



21 **7**

This reaction was carried out behind a safety screen. A mixture of **21** (5.20 g, 20.9 mmol) and 10% $Pd/CaCO_3$ (500 mg, 0.466 mmol) in ethanol (300 mL) was flushed with nitrogen, placed under an atmosphere of H_2 (1 atm) and stirred at ambient temperature for 3 h. The flask was then flushed with nitrogen, the reaction mixture filtered through a pad of Celite 521 and the filter cake washed with ethanol (100 mL). The combined filtrates were concentrated under reduced pressure and the residue purified by flash chromatography on silica gel (ethyl acetate/hexanes, 2:1) to provide **7** (4.55 g, 98% yield) as a colorless oil: $[\alpha]_D^{25}$ -41.3 (c 1.06, CH_2Cl_2); R_f 0.10 (ethyl acetate/hexanes, 2:1); FTIR (film) υ_{max} 3381, 3306, 3035, 2989, 1455, 1374, 1098 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54-7.52 (m, 2 H), 7.41-7.32 (m, 3 H), 5.46 (s, 1 H), 4.19 (dd, *J* = 11.0, 5.0 Hz, 1 H), 3.41 (t, *J* = 10.6 Hz, 1 H), 3.25 (dd, *J* = 9.5, 2.0 Hz, 1 H), 2.98-2.92 (m, 1 H), 2.19-2.12 (m, 1 H), 1.12 (d, *J* = 6.9 Hz, 3 H), 1.02 (d, *J* = 6.9 Hz, 3 H) , 0.85 (br s, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.6, 128.6, 128.1 (2 C), 126.0 (2 C), 100.7, 87.2, 73.0, 45.7, 27.6, 20.0, 15.2; HRMS-CI *m/z* 222.1479 [$(M+H)^+$; calcd for $C_{13}H_{20}NO_2$ 222.1494].

(2*R*,4*S*,5*R*)-(2-Oxopropyl)-(4-isopropyl-2-phenyl-[1,3]dioxan-5-yl)-amine (8).



7 **8**

A mixture of amine **7** (150.0 mg, 0.68 mmol) and powdered anhydrous K_2CO_3 (253 mg, 2.04 mmol) in anhydrous acetonitrile (8 mL) was heated at 30 °C for 30 min then bromoacetone (0.073 mL, 0.88 mmol) was added and the reaction mixture heated at 30 °C for 18 h. After cooling to room temperature the reaction mixture was filtered through a pad of Celite 521 and the filter cake was washed with CH_2Cl_2. The combined filtrates

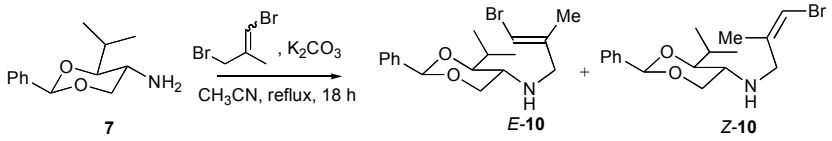
were concentrated under reduced pressure and the resulting residue purified by flash chromatography on silica gel (ethyl acetate/hexanes 1:7) to afford **8** (105 mg, 56% yield) as an unstable colorless solid, which was then utilized immediately in the following C-H insertion reaction: R_f 0.54 (MeOH(NH_3)/CH_2Cl_2, 1:64); FTIR (film) υ_{max} 3332, 3059, 3044, 1720, 1079, 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.49-7.47 (m, 2 H), 7.38-7.33 (m, 3 H), 5.46 (s, 1 H), 4.29 (dd, *J* = 10.2, 4.8 Hz, 1 H), 3.62 (d, *J* = 19.2 Hz, 1 H), 3.58 (d, *J* = 19.2 Hz, 1 H), 3.50 (dd, *J* = 10.2, 10.2 Hz, 1 H), 3.42 (dd, *J* = 10.2, 1.9 Hz, 1 H), 2.74 (ddd, *J* = 10.2, 10.2, 4.8 Hz, 1 H), 2.21-2.15 (m, 1 H), 2.16 (s, 3 H), 1.08 (d, *J* = 6.9 Hz, 3 H), 0.99 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.0, 138.4, 128.7 (2 C), 128.1 (2 C), 100.8, 85.3, 71.0, 57.8, 52.0, 27.8, 20.1, 20.1, 15.3.

(5*R*,6*S*,8*R*)-(-)-6-Isopropyl-3-methyl-8-phenyl-7,9-dioxa-1-azaspiro[4.5]dec-3-ene (9).

To a solution of (trimethylsilyl)diazomethane (108 μL, 2.0 M in hexanes, 217 μmol) in THF (0.5 mL), at –78 °C, was added n-butyllithium (44.6 μL, 2.4 M in hexane, 108 μmol). After stirring for 15 min, a solution of **8** (15.0 mg, 0.054 μmol) in THF (1 mL) was added and the resulting mixture stirred for 1 h min before saturated aqueous NH_4Cl (2 mL) was added to quench the reaction. After warming to room temperature, this mixture was extracted with ethyl acetate (2 x 20 mL), the combined organic extracts dried (Na_2SO_4), filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (ethyl acetate/hexanes, 1:3) to provide **9** (8.4 mg, 36% yield) as yellow oil: $[\alpha]_D^{25}$ -24.5 (c 1.10, CH_2Cl_2); R_f 0.10 (ethyl acetate/hexanes, 1:4); FTIR (film) υ_{max} 3064, 2960, 2361 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.53-7.52 (m, 2 H), 7.40-7.27 (m, 3 H), 5.82 (br s, 1 H), 5.52 (s, 1 H), 3.89 (d, *J* = 10.4 Hz, 1 H), 3.73-3.65 (m, 2 H), 3.64 (d, *J* = 10.4 Hz, 1 H), 3.39 (d, *J* = 4.4 Hz, 1 H), 1.98-1.90 (m, 1 H), 1.77 (s, 3 H), 1.41 (br s, 1 H), 1.05 (d, *J* = 6.9 Hz, 3 H), 0.99 (d, *J* = 6.6 Hz, 3 H), The relative configuration of the C-5 stereocenter was established using a 2D-NOESY experiment; as illustrated above, a correlation was observed between H-1 and H-6/H-10_{ax} and a complementing a correlation was observed between H-8 and H-6/H-10_{ax}; ^{13}C NMR

(100 MHz, $CDCl_3$) δ 139.2, 137.9, 128.8, 128.4 (2 C), 126.3 (2 C), 125.5, 101.5, 89.3, 78.1, 68.9, 58.9, 29.2, 22.1, 18.6, 14.4; HRMS-CI *m/z* 274.1802 $[(M+H)^+$; calcd for $C_{17}H_{24}NO_2$ 274.1807].

(*E*)-(2*R*,4*S*,5*R*)-(-)-(3-Bromo-2-methyl-allyl)-(4-isopropyl-2-phenyl-[1,3]dioxan-5-yl)-amine (10) and (*Z*)-(2*R*,4*S*,5*R*)-(-)-(3-Bromo-2-methyl-allyl)-(4-isopropyl-2-phenyl-[1,3]dioxan-5-yl)-amine (10).



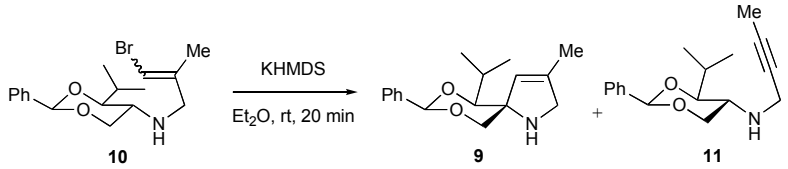
A 2-L, two-necked, round-bottomed flask equipped with a magnetic stirring bar, a septum and a reflux condenser connected to a nitrogen inlet was charged with **7** (13.8 g, 62.4 mmol), powdered anhydrous K_2CO_3 (23.2 g, 187 mmol) and anhydrous acetonitrile (700 mL) then flushed with nitrogen. The mixture was heated at 40 °C for 30 min then 1,3-dibromo-2-methyl-propene (7.82 g, 68.2 mmol, 2:1 mixture of *E* and *Z* isomers, respectively) was added and the reaction mixture heated at reflux for 18 h. After cooling to ambient temperature, the reaction mixture was filtered through a pad of Celite 521 and the filter cake was washed with CH_2Cl_2 (400 mL). The combined filtrates were concentrated under reduced pressure and the residue purified by flash chromatography on silica gel (ethyl acetate/hexanes, 1:7) to provide **10** (16.6 g, 75% yield) as a mixture of vinyl bromide isomers [*E*-**10**/*Z*-**10**, 3:2; isomeric ratio determined by integration of the peaks at δ_H (major) = 6.17 (s) and δ_H (minor) = 6.01 (s) in the ^{1}H NMR]. This mixture was then utilized in the following C-H insertion reaction, or separated by flash chromatography on silica gel (ethyl acetate/hexanes, 1:40).

Analytical Data for *E*-**10**: white crystalline solid; mp 45-46 °C (solidified upon standing); $[\alpha]_D^{25}$ -49.9 (c 3.8, CH_2Cl_2); R_f 0.51 (ethyl acetate/hexanes, 1:4); FTIR (film) υ_{max} 3340, 3066, 3033, 1631, 1392, 1099, 1030, 752 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52-7.49 (m, 2 H), 7.40-7.34 (m, 3 H), 6.17 (br s, 1 H), 5.46 (s, 1 H), 4.37 (dd, *J* = 10.8, 4.8 Hz, 1 H), 3.45-3.43 (m, 1 H) 3.37-3.25 (m, 3 H), 2.83-2.77 (m, 1 H), 2.23-2.15 (m, 1 H), 1.84 (br s, 3 H), 1.10 (d, *J* = 7.0 Hz, 3 H), 1.00 (d, *J* = 6.9 Hz), 3 H), 0.74 (br s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.7, 138.8, 128.8, 128.3 (2 C), 126.2 (2 C), 104.3, 101.0,

85.7, 71.5, 53.8, 51.1, 28.0, 20.2, 18.0, 15.5; HRMS-FAB *m/z* 354.1065 [(M+H)$^+$; calcd for $C_{17}H_{25}BrNO_2$ 354.1063].

Analytical Data for *Z*-**10**: colorless oil; $[\alpha]_D^{25}$ -24.7 (c 1.0, CH_2Cl_2); R_f 0.51 (ethyl acetate/hexanes, 1:4); FTIR (film) υ_{max} 3335, 3060, 3033, 1380, 1040, 712 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52-7.49 (m, 2 H), 7.40-7.34 (m, 3 H), 6.01 (br s, 1 H), 5.47 (s, 1 H), 4.50 (dd, *J* = 10.7, 4.8 Hz, 1 H), 3.51-3.49 (m, 1 H) 3.37-3.25 (m, 3 H), 2.82-2.80 (m, 1 H), 2.23-2.15 (m, 1 H), 1.88 (br s, 3 H), 1.09 (d, *J* = 7.0 Hz, 3 H), 1.02 (d, *J* = 6.9 Hz, 3 H), 0.75 (br s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.2, 138.8, 128.8, 128.3 (2 C), 126.2 (2 C), 103.1, 101.0, 85.6, 71.7, 51.4, 49.8, 28.0, 21.4, 20.2, 15.5; HRMS-FAB *m/z* 354.1065 [(M+H)$^+$; calcd for $C_{17}H_{25}BrNO_2$ 354.1061].

(5*R*,6*S*,8*R*)-(-)-6-Isopropyl-3-methyl-8-phenyl-7,9-dioxa-1-azaspiro[4.5]dec-3-ene (9) and (2*R*,4*S*,5*R*)-(-)-But-2-ynyl-(4-isopropyl-2-phenyl-[1,3]dioxan-5-yl)-amine (11).



10 9 11

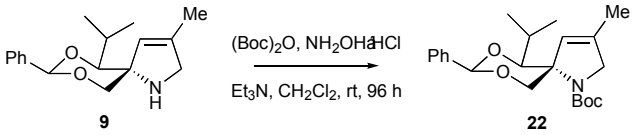
A 3-L, two-necked, round-bottomed flask equipped with a magnetic stirring bar, a nitrogen inlet and a septum was flushed with nitrogen and charged with a solution of vinyl bromide mixture **10** (16.0 g, 45.2 mmol) in anhydrous diethyl ether (1800 mL) via cannula. A freshly prepared solution of KHMDS (13.5 g, 67.8 mmol) in diethyl ether (200 mL) was then added via cannula over 15 min. After addition was complete, the yellow reaction mixture was stirred for 20 min, quenched with saturated aqueous NH_4Cl (200 mL) and partitioned between CH_2Cl_2 (1000 mL) and water (100 mL). The aqueous layer was extracted with CH_2Cl_2 (4 x 200 mL) and the combined organic extracts dried ($NaSO_4$), concentrated under reduced pressure and the residue purified by flash chromatography on silica gel (ethyl acetate/hexanes 1:3) to provide **9** (6.20 g, 50% yield) as a yellow oil and **11** (4.46 g, 36% yield) as a yellow waxy solid.

Analytical Data for **9**: Reported Above.

Analytical Data for **11**: mp 37-40 °C (solidified upon standing); $[\alpha]_D^{25}$ -60.9 (c 2.1, CH_2Cl_2); R_f 0.20 (ethyl acetate/hexanes, 1:4); FTIR (film) υ_{max} 3329, 2197, 1451, 1381, 1098 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54-7.52 (m, 2 H), 7.41-7.34 (m, 3 H), 5.49

(br s, 1 H), 4.46 (dd, *J* = 10.7, 4.9 Hz, 1 H), 3.52 (dd, *J* = 10.5, 10.5 Hz, 1 H), 3.47-3.37 (m, 3 H), 3.06 (ddd, *J* = 9.9, 9.9, 4.8 Hz, 1 H), 2.18-2.12 (m, 1 H), 1.84 (t, *J* = 2.3 Hz, 3 H), 1.11 (d, *J* = 6.9 Hz, 3 H), 1.05 (d, *J* = 6.6 Hz, 3 H), 0.93 (br s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.0, 129.0, 128.5 (2 C), 126.5 (2 C), 101.2, 85.6, 79.9, 77.5, 71.4, 51.1, 37.1, 28.2, 20.4, 15.6, 3.9; HRMS-CI *m/z* 274.1802 [$(M+H)^+$; calcd for $C_{17}H_{24}NO_2$ 274.1799]

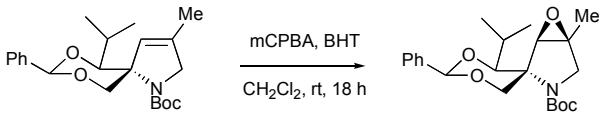
(5*R*,6*S*,8*R*)-(-)-6-Isopropyl-3-methyl-8-phenyl-7,9-dioxa-1-azaspiro[4.5]dec-3-ene-1-carboxylic acid *tert*-butyl ester (22).



9 **22**

A mixture of **9** (540 mg, 1.98 mmol), hydroxylamine hydrochloride (207 mg, 2.97 mmol), triethylamine (1.92 mL, 13.86 mmol) and Boc_2O (1.45 mL, 5.9 mmol) in CH_2Cl_2 (75 mL) was stirred at ambient temperature for 48 h. Additional Boc_2O (0.50 mL, 2.15 mmol) was added and the reaction stirred for a further 48 h. The reaction mixture was then quenched with saturated aqueous NH_4Cl (20 mL) and partitioned between CH_2Cl_2 (20 mL) and water (20 mL). The aqueous layer was extracted with CH_2Cl_2 (4 x 20 mL) and the combined organic extracts dried (Na_2SO_4), concentrated under reduced pressure and the residue purified by flash chromatography on silica gel (ethyl acetate/hexanes 1:9) to provide **22** (690 mg, 93% yield) as white crystals: mp 81-83 °C (CH_2Cl_2); $[\alpha]_D^{25}$ -10.0 (c 1.75, CH_2Cl_2); R_f 0.56 (ethyl acetate/hexanes, 1:4); FTIR (film) υ_{max} 2967, 1699, 1671, 1392, 1167 cm^{-1}; ^{1}H NMR (7:4 mixture of rotamers, 400 MHz, $CDCl_3$) δ 7.52-7.50 (m, 2 H), 7.39-7.33 (m, 3 H), [5.91 (br s), 5.87* (br s), 1 H], [5.66 (s), 5.54* (s), 1 H], [4.75 (d, *J* = 10.3 Hz), 4.52* (d, *J* = 10.2 Hz), 1 H], [4.59 (d, *J* = 7.9 Hz), 4.29* (d, *J* = 7.2 Hz), 1 H], 4.10-4.01 (m, 2 H), 3.78-3.74 (m, 1 H), 1.82-1.75 (m, 4 H), [1.57* (s), 1.48 (s), 9 H], [1.01 (d, *J* = 6.6 Hz), 1.01* (d, *J* = 6.6 Hz), 3 H], 0.93-0.90 (m, 3 H); ^{13}C NMR (7:4 mixture of rotamers, resonances from both rotamers are reported, 100 MHz, $CDCl_3$) δ 153.3, 139.0, 138.6, 134.1, 128.9, 128.8, 128.4, 128.3, 126.2, 126.2, 125.3, 125.3, 101.7, 101.3, 84.9, 83.4, 80.8, 79.9, 73.9, 73.1, 69.3, 68.7, 58.6, 58.6, 30.2, 29.9, 28.9, 28.7, 28.1, 20.2, 19.8, 19.6, 19.4, 14.3; HRMS-CI *m/z* 374.2348 [$(M+H)^+$; calcd for $C_{22}H_{31}NO_4$ 374.2331].

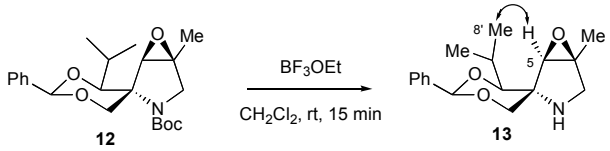
(1*S*,4*R*,5*R*,2′*S*,4′*R*)-(-)-Spiro[1-methyl-6-oxa-3-azabicyclo[3.1.0]hexane-4,1′-3′,5′-dioxa-2′-isopropyl-4′-phenyl-cyclohexane]-3-carboxylic acid *tert*-butyl ester (12).



22 **12**

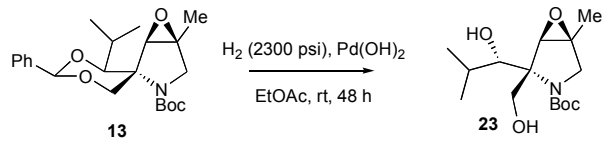
A 100-mL, two-necked, round-bottomed flask equipped with a magnetic stirring bar, a nitrogen inlet and a septum, was charged with **22** (472 mg, 1.27 mmol), *m*-chloroperoxybenzoic acid (657 mg, 3.81 mmol) and 2,6-di-*tert*-butyl-4-methylphenol (BHT) (28 mg, 0.13 mmol) then flushed with nitrogen. Degassed CH_2Cl_2 (30 mL) was then added via syringe and the resulting solution stirred at ambient temperature in the dark for 18 h. Saturated aqueous solutions of Na_2SO_3 (10 mL) and $NaHCO_3$ (10 mL) were then added and the biphasic mixture stirred for 45 min before being partitioned between CH_2Cl_2 (30 mL) and water (10 mL). The aqueous phase was extracted with CH_2Cl_2 (2 x 20 mL) and the combined organic extracts dried (Na_2SO_4), concentrated under reduced pressure and the residue purified by flash chromatography on silica gel (ethyl acetate/hexanes 1:18) to provide **12** (447 mg, 90% yield) as a white solid: mp 97-99 °C (ethyl acetate/hexanes); $[\alpha]_D^{25}$ -4.4 (c 1.01, $CHCl_3$); R_f 0.56 (ethyl acetate/hexanes, 1:4); FTIR (film) υ_{max} 1697, 1456, 1391, 1367, 1338, 1171, 1138; ^{1}H NMR (2:1 mixture of rotamers, 400 MHz, $CDCl_3$) δ 7.53-7.50 (m, 2 H), 7.39-7.35 (m, 3 H), [5.65 (s), 5.54* (s), 1 H], [4.71 (d, *J* = 10.4 Hz), 4.45* (d, *J* = 10.3 Hz), 1 H], [4.52 (d, *J* = 5.8 Hz), 4.26* (d, *J* = 5.1 Hz), 1 H], [4.20* (d, *J* = 10.4 Hz), 4.16 (d, *J* = 10.4 Hz), 1 H], [3.97* (s), 3.96 (s), 1 H], [3.72* (d, *J* = 12.6 Hz), 3.66 (d, *J* = 12.5 Hz), 1 H], [3.37* (d, *J* = 12.6 Hz), 3.33 (d, *J* = 12.5 Hz), 1 H], 1.95-1.83 (m, 1 H), [1.52* (s), 1.52 (s), 3 H], [1.52* (s), 1.43 (s), 9 H], 1.04-1.02 (m, 6 H); ^{13}C NMR (2:1 mixture of rotamers, resonances from both rotamers are reported, 100 MHz, $CDCl_3$) δ 153.8, 153.6, 138.6, 138.3, 129.0, 128.9, 128.4, 126.3, 126.2, 102.2, 101.8, 83.3, 81.7, 81.3, 80.4, 70.2, 69.2, 66.3, 65.6, 63.4, 63.0, 62.5, 62.0, 53.9, 53.8, 29.0, 28.8, 28.7, 28.6, 21.5, 20.9, 18.6, 18.3, 16.3; HRMS-CI *m/z* 390.2253 [$(M+H)^+$; calcd for $C_{22}H_{31}NO_4$ 390.2280].

(1*S*,4*R*,5*R*,2′*S*,4′*R*)-(+)--Spiro[1-methyl-6-oxa-3-azabicyclo[3.1.0]hexane-4,1′-3′,5′-dioxa-2′-isopropyl-4′-phenyl-cyclohexane] (13).



To a stirred mixture of **12** (44.3 mg, 0.114 mmol) and powdered activated 4 Å molecular sieves (400 mg) in CH_2Cl_2 (9 mL) at 0 °C was added BF_3•OEt_2 (35 μL, 0.34 mmol). After 15 min, the reaction mixture was diluted with ethyl acetate (20 mL), filtered through a plug of Celite 521 and the filtrate washed with saturated aqueous $NaHCO_3$ (6 mL). The organic phase was dried (Na_2SO_4), concentrated under reduced pressure and the residue purified by flash chromatography on silica gel (ethyl acetate/hexanes 1:18) to provide the **13** (29.7 mg, 90% yield) as a colorless oil: $[\alpha]_D^{25}$ +4.6 (c 0.43, $CHCl_3$); R_f 0.11 (ethyl acetate/hexanes, 1:2); FTIR (film) υ_{max} 3330, 2962, 1452, 1098, 1019; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54-7.51 (m, 2 H), 7.39-7.37 (m, 3 H), 5.53 (s, 1 H), 4.13 (d, *J* = 10.1 Hz, 1 H), 3.75 (s, 1 H), 3.56-3.54 (m, 2 H), 3.05 (d, *J* = 13.0 Hz, 1 H), 2.85 (d, *J* = 13.0 Hz, 1 H), 2.05-1.97 (m, 1 H), 1.54 (s, 3 H), 1.47 (br s, 1 H), 1.13 (d, *J* = 6.9 Hz, 3 H), 1.01 (d, *J* = 6.8 Hz, 3 H); The relative configuration of the C-5 stereocenter was established using a 2D-NOESY experiment; as illustrated above, a correlation was observed between H-5 and H-8'; ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.8, 128.8, 128.2 (2 C), 126.1 (2 C), 101.8, 88.9, 71.3, 66.4, 64.6, 62.8, 52.9, 28.4, 22.6, 16.6, 15.1; HRMS-FAB *m/z* 290.1763 [$(M+H)^+$; calcd for $C_{17}H_{24}NO_3$ 290.1752].

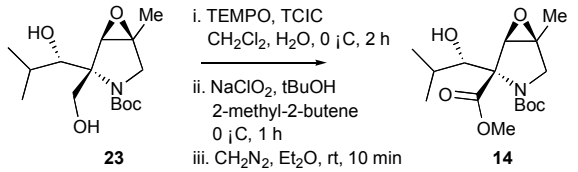
(1*S*,4*R*,5*R*,1′*S*)-(-)-4-Hydroxymethyl-4-(1′-hydroxy-2′-methyl-propyl)-1-methyl-6-oxa-3-aza bicyclo[3.1.0]hexane-3-carboxylic acid *tert*-butyl ester (23).



A stainless steel bomb was charged with benzylidene acetal **12** (132.1 mg, 0.34 mmol), 10% $Pd(OH)_2/C$ (70 mg, 0.50 mmol) and ethyl acetate (15 mL), flushed with nitrogen, placed under an atmosphere of H_2 (2300 psi) and then sealed. After stirring at ambient

temperature for 48 h, the bomb was flushed with nitrogen and the reaction mixture filtered through a plug of Celite 521. After thoroughly washing the filter cake with ethyl acetate, the combined filtrates were concentrated under reduced pressure and the residue purified by flash chromatography on silica gel (ethyl acetate/hexanes, 1:4) to provide **23** (96.8 mg, 94% yield) as a colorless oil: $[\alpha]_D^{25}$ -11.2 (c 0.59, CH_2Cl_2); R_f 0.17 (ethyl acetate/hexanes, 1:4); FTIR (film) υ_{max} 3429, 2968, 1698, 1670, 1670, 1398, 1367, 1172, 1141 cm^{-1}; ^1H NMR (20:1 mixture of rotamers, resonances from major rotamer are reported, 400 MHz, $CDCl_3$) δ 5.12 (dd, *J* = 12.0, 1.6 Hz, 1 H), 4.24 (dd, *J* = 4.7, 3.1 Hz, 1 H), 4.19 (dd, *J* = 12.0, 12.0 Hz, 1 H), 3.89 (dd, *J* = 12.0, 1.6 Hz, 1 H), 3.69 (d, *J* = 12.5 Hz, 1 H), 3.29 (d, *J* = 12.5 Hz, 1 H), 2.95 (d, *J* = 4.7 Hz, 1 H), 1.72-1.60 (m, 1 H), 1.47 (s, 3 H), 1.42 (s, 9 H), 1.02 (d, *J* = 6.9 Hz, 3 H), 0.98 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR (20:1 mixture of rotamers, resonances from major rotamer are reported, 100 MHz, $CDCl_3$) δ 155.8, 81.0, 72.0, 70.6, 66.1, 66.0, 60.4, 53.7, 28.3 (4C), 22.6, 17.0, 15.6; HRMS-FAB *m/z* 302.1988 $[(M+H)^+$; calcd for $C_{15}H_{28}NO_5$ 302.1968].

(1*R*,2*R*,5*S*,1′*S*)-(+)-2-(1′-Hydroxy-2′-methyl-propyl)-5-methyl-6-oxa-3-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-*tert*-butyl ester 2-methyl ester (14).



1. Oxidation of diol 3 to aldehyde: To a stirred solution of **23** (102.9 mg, 0.342 mmol) and TEMPO (0.5 mg, 3 μmol) in CH_2Cl_2 (1.5 mL) at 0 °C was added trichloroisocyanuric acid (87.5 mL, 0.38 mmol). After 1 h, additional TEMPO (0.5 mg, 3 μmol) in CH_2Cl_2 (50 μL) was added and the mixture stirred for a further 1 h. The reaction was then diluted with CH_2Cl_2 (5 mL) and filtered through a plug of Celite 521 to remove the solid dichloroisocyanuric acid that precipitated during the reaction. The filtrate was then washed with saturated aqueous $NaHCO_3$ (5 mL) and the aqueous wash reextracted with CH_2Cl_2 (3 x 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 (ethyl acetate/hexanes 1:9) to provide the desired aldehyde (100.3 mg). Since

this compound proved to be rather unstable, it was immediately submitted to the following oxidation/alkylation procedure.

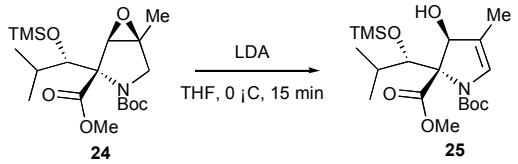
2. Oxidation/alkylation of aldehyde: To a stirred solution of the aldehyde in *tert*-butanol (3 mL) and 2-methyl-2-butene (2 mL) at 0 ºC was added an aqueous solution of $NaClO_2$ (3.0 mL, 1.1 M in water) and NaH_2PO_4 (3 mL, 0.07 M). After stirring for 90 min, the reaction mixture was concentrated under reduced pressure and 2-methyl-2-butene (2 mL) and CH_2Cl_2 (2 mL) were added to the concentrate. The aqueous phase was then acidified to pH 3 with aqueous hydrochloric acid (1 M) and the biphasic mixture extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure and the residue dissolved in diethyl ether (2 mL). An ethereal solution of diazomethane (1.0 mL, 0.5 M, 0.5 mmol) was then added and, after stirring for 10 min at ambient temperature, the mixture concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (ethyl acetate/hexanes 1:7) to provide **14** (107.6 mg, 96% yield) as a colorless oil: $[\alpha]_D^{25}$ +25.6 (c 2.50, $CHCl_3$); R_f 0.69 (ethyl acetate/hexanes, 1:1); FTIR (film) υ_{max} 3527, 2970, 1703, 1393, 1246, 1150; ^{1}H NMR (7:4 mixture of rotamers, 500 MHz, $CDCl_3$) δ [4.43* (dd, *J* = 2.7, 2.7 Hz), 4.27 (dd, *J* = 2.8, 2.8 Hz), 1 H], [3.97 (s), 3.94* (s), 1 H], 3.86-3.79 (m, 2 H), [3.78 (s), 3.76* (s), 3 H], 3.37-3.32 (m, 1 H), 1.90-1.70 (m, 1 H), [1.51 (s), 1.50* (s), 3 H], [1.40* (s), 1.36 (s), 9 H], 1.05-1.02 (m, 3 H), 0.93-0.90 (m, 3 H); ^{13}C NMR (7:4 mixture of rotamers, resonances from both rotamers are reported, 125 MHz, $CDCl_3$) δ 174.2, 173.7, 153.9, 153.1, 81.2, 81.0, 76.2, 75.1, 71.9, 65.3, 64.5, 63.9, 63.1, 53.2, 53.1, 52.4, 52.2, 28.7, 28.6, 28.6, 28.5, 22.7, 22.5, 16.7, 16.3; HRMS-FAB *m/z* 330.1932 $[(M+H)^+$; calcd for $C_{16}H_{28}NO_4$ 330.1917].

(1*R*,2*S*,5*S*,1′*S*)-(+)-5-Methyl-2-(2′-methyl-1′-trimethylsilanyloxy-propyl)-6-oxa-3-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid 3-*tert*-butyl ester 2-methyl ester (24).

To a stirred solution of **14** (620 mg, 1.88 mmol) and imidazole (467 mg, 6.58 mmol) in *N*,*N*-dimethylformamide (10 mL) at 0 °C was added trimethylsilyl chloride (0.660 mL,

5.64 mmol). The reaction mixture was allowed to warm to ambient temperature, stirred for 4 h then concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (ethyl acetate/hexanes 1:9) to provide **24** (708 mg, 94% yield) as a colorless glass: $[\alpha]_D^{25}$ +17.5 (c 2.25, $CHCl_3$); R_f 0.59 (ethyl acetate/hexanes, 1:2); FTIR (film) υ_{max} 2958, 1738, 1707, 1392, 1249, 1148, 1060; ^{1}H NMR (7:3 mixture of rotamers, 500 MHz, $CDCl_3$) δ [4.51* (br s), 4.40 (br s), 1 H], [3.92* (s), 3.86 (s), 1 H], [3.84* (d, *J* = 11.4 Hz), 3.80 (d, *J* = 12.1 Hz), 1 H], [3.73* (s), 3.72 (s), 3 H], 3.36-3.32 (m, 1 H), [1.82-1.79 (m), 1.79-1.73* (m), 1 H], [1.49* (s), 1.48 (s), 3 H], [1.40 (s), 1.36* (s), 9 H], 0.95 (m, 3 H), 0.78 (m, 3 H), 0.17 (s, 9 H); ^{13}C NMR (7:3 mixture of rotamers, resonances from both rotamers are reported, 125 MHz, $CDCl_3$) δ 171.3, 170.7, 154.1, 153.3, 80.9, 80.7, 78.2, 77.9, 72.3, 72.1, 65.8, 65.4, 63.7, 63.1, 52.7, 52.6, 52.2, 29.8, 29.4, 28.6, 22.8, 22.7, 16.4, 16.0, 1.2, 1.0; HRMS-FAB *m/z* 424.2113 $[(M+Na)^+$; calcd for $C_{19}H_{35}NNaO_6Si_1$ 424.2131].

(2*S*,3*S*,1′*S*)-(-)-3-Hydroxy-4-methyl-2-(2′-methyl-1′-trimethylsilanyloxy-propyl)-2,3-dihydro-pyrrole-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester (25).

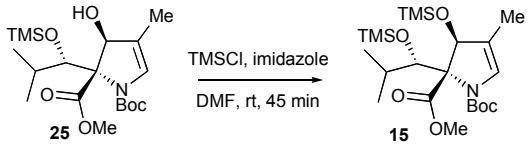


24 **25**

To a stirred solution of **24** (683 mg, 1.70 mmol) in THF (30 mL) at 0 °C was added a solution of LDA (7.56 mL, 0.4 M in THF, 3.06 mmol) via syringe. After 15 min, the reaction mixture was quenched with saturated aqueous NH_4Cl (10 mL) and partitioned between water (5 mL) and CH_2Cl_2 (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 35 mL) and the combined organics dried ($NaSO_4$), concentrated under reduced pressure and the residue purified by flash chromatography on silica gel (ethyl acetate/hexanes 1:9) to provide **25** (636 mg, 93% yield) as a colorless glass: $[\alpha]_D^{25}$ -4.2 (c 1.2, $CHCl_3$); R_f 0.54 (ethyl acetate/hexanes, 1:1); FTIR (film) υ_{max} 3480, 1751, 1709, 1408; ^{1}H NMR (2:1 mixture of rotamers, 400 MHz, $CDCl_3$) δ [6.51* (s), 6.38 (s), 1 H], [5.19* (d, *J* = 8.1 Hz), 5.15 (d, *J* = 8.0 Hz), 1 H], [4.66 (d, *J* = 1.8 Hz), 4.55* (d, *J* = 1.7 Hz), 1 H], 3.70 (s, 3 H), 1.86-1.82 (m, 1 H), 1.74 (s, 3 H), 1.74-1.63 (m, 1 H), [1.45 (s), 1.40* (s), 9 H], [0.93* (d, *J* = 7.0 Hz), 0.92 (d, *J* = 7.0 Hz), 3 H], [0.68 (d, *J* = 6.7 Hz),

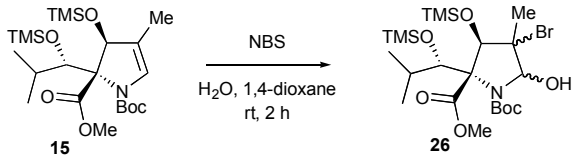
0.67* (d, J = 6.7 Hz), 3 H], [0.21 (s), 0.20* (s), 9 H]; ^{13}C NMR (2:1 mixture of rotamers, resonances from both rotamers are reported, 125 MHz, $CDCl_3$) δ 170.7, 170.6, 151.4, 150.7, 127.3, 127.1, 116.8, 116.7, 81.1, 79.8, 78.7, 76.2, 75.8, 51.8, 30.0, 29.7, 28.2, 28.1, 22.1, 21.9, 15.4, 15.2, 10.8, 0.8, 0.6; HRMS-FAB *m/z* 424.2144 $[(M\cdot)^+$; calcd for $C_{19}H_{35}NNaO_6Si_1$ 424.2131].

(2*R*,3*S*,1′*S*)-(+)-4-Methyl-2-(2′-methyl-1′-trimethylsilanyloxy-propyl)-3-trimethylsilanyloxy-2,3-dihydro-pyrrole-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester (15).



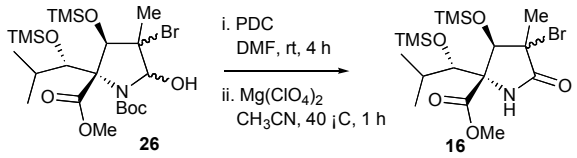
To a stirred solution of **25** (383 mg, 0.956 mmol) and imidazole (101 mg, 1.43 mmol) in *N,N*-dimethylformamide (10 mL) at 0 °C was added trimethylsilyl chloride (0.156 mL, 1.24 mmol). The reaction mixture was allowed to warm to ambient temperature and then stirred for 45 min before being concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (ethyl acetate/hexanes 1:15) to provide **15** (386 mg, 85% yield) as a colorless glass: $[\alpha]_D^{25}$ +33.8 (c 1.4, $CHCl_3$); R_f 0.76 (ethyl acetate/hexanes, 1:2); FTIR (film) υ_{max} 2957, 1749, 1712, 1457, 1413, 1367, 1249, 1168, 1092, 1006; ^{1}H NMR (2:1 mixture of rotamers, 500 MHz, $CDCl_3$) δ [6.55 (d, J = 1.8 Hz), 6.42* (d, J = 1.8 Hz), 1 H], [5.20 (s), 5.09* (s), 1 H], [4.58* (d, J = 1.8 Hz), 4.51 (d, J = 1.8 Hz), 1 H], [3.70 (s), 3.70* (s), 3 H], [1.76 (s), 1.75* (s), 3 H], 1.76-1.65 (m, 1 H), [1.46* (s), 1.43 (s), 9 H], 1.00-0.94 (m, 3 H), 0.76-0.64 (m, 3 H) [0.26 (s), 0.25* (s), 9 H], [0.14 (s), 0.12* (s), 9 H]; ^{13}C NMR (2:1 mixture of rotamers, resonances from both rotamers are reported, 125 MHz, $CDCl_3$) δ 170.9, 170.3, 150.3, 150.1, 127.4, 127.1, 117.8, 117.5, 80.7, 80.5, 80.2, 79.5, 76.3, 51.5, 29.3, 28.9, 28.1, 23.1, 22.8, 16.6, 11.4, 6.9, 5.3; HRMS-FAB *m/z* 496.2560 $[(M+Na)^+$; calcd for $C_{22}H_{43}NNaO_6Si_2$ 496.2526].

(2*R*,3*R*,1′*S*)-(+)-4-Bromo-5-hydroxy-4-methyl-2-(2′-methyl-1′-trimethylsilanyloxy-propyl)-3-trimethylsilanyloxy-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester (26).



To a stirred solution of **15** (361 mg, 0.764 mmol) in 1,4-dioxane (10 mL) and water (10 mL) at 0°C was added *N*-bromosuccinamide (178 mg, 1.0 mmol). After 2 h, the reaction mixture was quenched with saturated aqueous Na_2SO_3 (5 mL), NH_4Cl (10 mL) and $NaHCO_3$ (6 mL) then extracted with CH_2Cl_2 (6 x 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 (ethyl acetate/hexanes 1:9) to provide **26** (413 mg, 95% yield) as a colorless glass: $[\alpha]_D^{25}$ +10.9 (c 1.55, $CHCl_3$); R_f 0.76 (ethyl acetate/hexanes, 1:2); FTIR (film) υ_{max} 3407, 1749, 1714, 1657, 1368; ^{1}H NMR (2:1 mixture of C-4/5 epimers, 500 MHz, $CDCl_3$) δ [5.89* (d, *J* = 9.3 Hz), 5.66 (d, *J* = 10.8 Hz), 1 H], [4.40 (d, *J* = 10.8 Hz), 4.09* (d, *J* = 9.3 Hz), 1 H], [4.18-4.14 (m), 4.06 (s), 2 H], [3.65* (s), 3.63 (s), 3 H], [2.62-2.55 (m), 2.38-2.30* (m), 1 H], [1.79* (s), 1.77 (s), 3 H], [1.43 (s), 1.38* (s), 9 H], 1.02-0.99 (m, 3 H), [0.76* (d, *J* = 6.6 Hz), 0.69 (d, *J* = 6.6 Hz), 3 H], [0.25 (s), 0.24* (s), 9 H], [0.14* (s), 0.13 (s), 9 H]; ^{13}C NMR (2:1 mixture of C-4/5 epimers, resonances from both epimers reported, 125 MHz, $CDCl_3$) δ 169.0, 168.2, 153.2, 152.0, 90.5 (2 C), 82.9, 82.1, 81.9, 81.4, 80.3, 79.7, 78.2, 78.0, 51.8, 51.3, 28.5, 28.4, 27.0, 26.8, 24.1, 17.5, 17.0, 1.7, 1.5, 1.2, 1.1; HRMS(FAB) *m/z* 592.1743 [$(M+Na)^+$; calcd for $C_{22}H_{44}NNaO_7Si_2{}^{79}Br$ 592.1737].

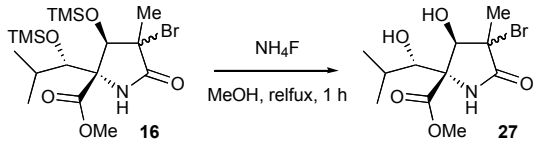
(2*R*,3*R*,1′*S*)-(+)-4-Bromo-4-methyl-2-(1′-trimethylsilanyloxy-2′-methyl-propyl)-5-oxo-3-trimethylsilanyloxy-pyrrolidine-2-carboxylic acid methyl ester (16).



1. Oxidation of 26: A mixture of **26** (106 mg, 0.185 mmol) and pyridinium dichromate (170 mg, 0.45 mmol) in *N,N*-dimethylformamide (4 mL) was stirred at ambient temperature for 4 h then concentrated under reduced pressure. The inorganic salts were triturated with CH_2Cl_2 (10 mL) then removed by filtration through a plug of Celite 521. After repeating this sequence four more times, the combined filtrates were concentrated under reduced pressure to provide the desired amide (105 mg) as a 5:1 mixture of C-5 epimers (by ^{1}H NMR analysis). This material was submitted to the following deprotection without further purification.

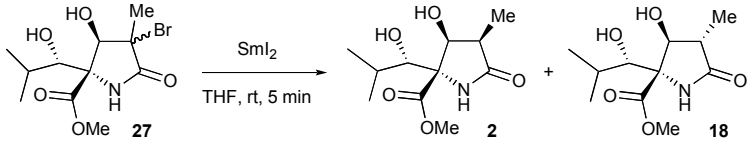
2. Boc Deprotection: A mixture of the crude amide (105 mg) and $Mg(ClO_4)_2$ (8.2 mg, 0.037 mmol) in acetonitrile (3 mL) was heated at 50 °C for 1 h, cooled to ambient temperature, quenched with saturated aqueous NH_4Cl (3 mL) and extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure and the residue purified by flash chromatography on silica gel (ethyl acetate/hexanes 1:4) to provide **16** (58 mg, 67% yield over two steps) as a waxy colorless solid: mp 30-33 °C (solidified upon standing); $[\alpha]_D^{25}$ +15.7 (c 1.2, $CHCl_3$); R_f 0.47 (ethyl acetate/hexanes, 1:2); FTIR (film) υ_{max} 3347, 1740, 1720, 1251, 1071; ^{1}H NMR (5:1 mixture of C-4 epimers, 500 MHz, $CDCl_3$) δ [5.90* (br s), 5.86 (br s), 1 H], [4.90* (s), 4.03 (s), 1 H], [4.09* (d, *J* = 2.6 Hz), 4.07 (d, *J* = 2.1 Hz), 1 H], [3.73 (s), 3.71* (s), 3 H], [1.89-1.83* (m), 1.79-1.74 (m), 1 H], [1.83 (s), 1.73* (s), 3 H], [1.01* (d, *J* = 7.1), 0.98 (d, *J* = 7.0 Hz), 3 H], [0.87* (d, *J* = 6.8 Hz), 0.85 (d, *J* = 6.8 Hz), 3 H], [0.24 (s), 0.23* (s), 9 H], [0.21* (s), 0.19 (s), 9 H]; ^{13}C NMR (5:1 mixture of C-4 epimers, resonances from both epimers reported, 125 MHz, $CDCl_3$) δ 173.4, 169.9, 82.0, 79.9, 78.6, 75.3, 72.8, 62.0, 61.1, 52.5, 31.8, 31.6, 26.7, 24.5, 23.0, 22.6, 17.9, 17.0, 1.6, 1.4, 1.2, 0.9; HRMS-FAB *m/z* 468.1231 [$(M+H)^+$; calcd for $C_{17}H_{35}O_5N^{79}BrSi_2$ 468.1237].

(2*R*,3*R*,1′*S*)-(+)-4-Bromo-3-hydroxy-2-(1′-hydroxy-2′-methyl-propyl)-4-methyl-5-oxo-pyrrolidine-2-carboxylic acid methyl ester (27).



A mixture of **16** (48.0 mg, 0.15 mmol) and ammonium fluoride (48 mg, 1.30 mmol) in anhydrous methanol (4 mL) was stirred at reflux for 1 h, cooled to ambient temperature and concentrated under reduced pressure. The inorganic salts were then triturated with CH_2Cl_2 (10 mL) and removed by filtration through a plug of Celite 521. After repeating this procedure four more times, the combined filtrates were concentrated under reduced pressure and the residue purified by flash chromatography on silica gel (ethyl acetate/hexanes 1:2) to provide **27** (31.1 mg, 95% yield) as a white solid: mp 169-171 °C (CH_2Cl_2); $[\alpha]_D^{25}$ +10.9 (c 1.56, $CHCl_3$); R_f 0.20 (ethyl acetate/hexanes, 1:2); FTIR (film) υ_{max} 3454, 1714, 1250; ^{1}H NMR (5:1 mixture of C-4 epimers, resonances from major isomer are reported, 400 MHz, $CDCl_3$) δ 6.17 (s, 1 H), 4.12 (d, *J* = 11.1 Hz, 1 H), 4.03 (d, *J* = 11.1 Hz, 1 H), 3.90 (dd, *J* = 6.0, 2.9 Hz, 1 H), 3.82 (s, 3 H), 1.90 (m, 1 H), 1.88 (s, 3 H), 1.77-1.71 (m, 1 H), 1.05 (d, *J* = 6.8 Hz, 3 H), 0.92 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (5:1 mixture of C-4 epimers, resonances from major epimer are reported 100 MHz, $CDCl_3$) δ 172.2, 171.9, 78.0, 74.7, 68.5, 67.6, 53.3, 30.5, 24.5, 21.4, 15.3; HRMS-FAB *m/z* 324.0455 [$(M+H)^+$; calcd for $C_{11}H_{19}{}^{79}BrNO_5$ 324.0447].

(2*R*,3*R*,4*R*,1′*S*)-(+)-3-Hydroxy-2-(1-hydroxy-2-methyl-propyl)-4-methyl-5-oxo-pyrrolidine-2-carboxylic acid methyl ester (2) and (2*R*,3*R*,4*S*,1′*S*)-(-)-3-Hydroxy-2-(1-hydroxy-2-methyl-propyl)-4-methyl-5-oxo-pyrrolidine-2-carboxylic acid methyl ester (18).



To a stirred solution of **27** (15.0 mg, 47.0 μmol) in degassed anhydrous THF (1 mL) at ambient temperature was added freshly prepared samarium diiodide (1.0 mL, 0.1 M solution in THF, 100 μmol). The reaction mixture was stirred for 10 min before being

quenched with saturated aqueous NH_4Cl (1 mL) and then extracted with CH_2Cl_2 (6 x 10 mL). The combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure and the residue purified by flash chromatography on silica gel (ethyl acetate/hexanes, 3:1) to provide the title compounds (9.2 mg, 81% yield) as a mixture of C-4 epimers [**2**/**18**, 1:2.5; isomeric ratio determined by integration of the peaks at δ_H (major) = 4.38 (d) and δ_H (minor) = 4.43 (d) in the ^{1}H NMR]. This mixture was then separated by iterative flash chromatography on silica gel ($CHCl_3$/ethanol, 20:1).

Analytical Data for **2**: white solid; mp 190-192 °C (CH_2Cl_2); $[\alpha]_D^{25}$ +60.0 (c 0.20, MeOH) [Lit.[8] $[\alpha]_D^{24}$ +65.0 (c 0.30, MeOH)]; R_f 0.36 ($CHCl_3$/ethanol, 6:1); FTIR (film) υ_{max} 3337, 1735, 1696, 1443, 1038 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52-7.49 (m, 2 H), 7.40-7.34 (m, 3 H), 6.17 (br s, 1 H), 5.46 (s, 1 H), 4.37 (dd, *J* = 10.8, 4.8 Hz, 1 H), 3.45-3.43 (m, 1 H) 3.37-3.25 (m, 3 H), 2.83-2.77 (m, 1 H), 2.23-2.15 (m, 1 H), 1.84 (br s, 3 H), 1.10 (d, *J* = 7.0 Hz, 3 H), 1.00 (d, *J* = 6.9 Hz), 3 H), 0.74 (br s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.7, 138.8, 128.8, 128.3 (2 C), 126.2 (2 C), 104.3, 101.0, 85.7, 71.5, 53.8, 51.1, 28.0, 20.2, 18.0, 15.5; HRMS-FAB *m/z* 354.1065 [$(M+H)^+$; calcd for $C_{17}H_{24}BrNO_2$ 354.1063].

Analytical Data for **18**: white solid; mp 148-151 °C (CH_2Cl_2); $[\alpha]_D^{25}$ -10.0 (c 0.24, MeOH); R_f 0.42 ($CHCl_3$/ethanol, 6:1); FTIR (film) υ_{max} 3339, 1717, 1699, 1453, 1024 cm^{-1}; ^{1}H NMR (500 MHz, MeOD) δ 4.38 (d, *J* = 6.7 Hz, 1 H), 3.86 (d, *J* = 7.2 Hz, 1 H), 3.72 (s, 3 H), 2.35-2.28 (m, 1 H), 1.72-1.65 (m, 1 H), 1.25 (d, *J* = 7.5 Hz, 3 H), 1.01 (d, *J* = 6.7 Hz, 3 H), 0.83 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.9, 171.7, 77.2, 74.8, 73.4, 51.0, 47.0, 43.6, 31.5, 19.1, 18.6, 12.2; HRMS-FAB *m/z* 354.1065 [$(M+H)^+$; calcd for $C_{17}H_{24}BrNO_2$ 354.1064].

[8] T. Nagamitsu, T. Sunazuka, H. Tanaka, S. Omura, P. A. Sprengeler and A. B. Smith, *J. Am. Chem. Soc.,* 1996, **118**, 3584.

6. ^{1}H NMR & ^{13}C NMR Spectra.