Enantioselective Syntheses of Ring-C Precursors of Vitamin B_{12}. Substrate control. A Novel Si-Assisted Elimination of Vinyl Bromides.

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SUPPORTING INFORMATION

Experimental procedures and spectral data for all new compounds reported. This material is available free of charge via the Internet at http://pubs.acs.org.

Experimental Section

All reactions were carried out in oven-dried glassware under an inert atmosphere of nitrogen or argon. Air- and moisture-sensitive compounds were introduced *via* syringe or cannula and weighed in a dry-box. Commercial reagents were used without purification unless otherwise noted. Tetrahydrofuran, diethyl ether and dichloromethane were obtained from a dry system (Alumina) and used without further drying. Removal of solvents was accomplished on a rotary evaporator at reduced pressure. Melting points are uncorrected and were measured on a Fisher-Jones melting point apparatus. ^{1}H NMR spectra were recorded at either 300 or 500 MHz and are reported in parts per million using residual non-deuterated solvent as internal reference. IR spectra were taken as thin films, neat or tetrachloroethylene (TCE) mull on a Perkin Elmer 1600 FT-IR Spectrometer. Enantiomeric ratios were determined by HPLC (Hewlett Packard 1100 Series) using a Diacel OJ-H chiral column. Optical rotations were recorded on a Jasco DIP-370 digital polarimeter using a 1 dm cell at the reported temperatures and concentrations (g/100mL). Elemental analyses were performed by Atlantic Microlab Inc. and high resolution mass spectrometry was performed at the University of Illinois Urbana-Champain mass spectrometry laboratory.

2-But-2-ynyloxy-tetrahydro-pyran (14).[1] A solution of 5.0 g (71 mmol) of 2-butynol, 0.17 g (0.71 mmol) of aluminum chloride hexahydrate, and 6.1 g (73 mmol) of dihydropyran (DHP) was stirred at rt under Ar for a period of 6-8 h in a 50 mL round-bottom flask. After reaction was complete (TLC analysis) the resulting solution was directly chromatographed on silica gel to afford 9.6 g (87%) of **14** as a colorless oil, R_f 0.67 (1:4 EtOAc/Hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.44-1.62 (m, 4H), 1.65-1.72 (m, 1H), 1.74-1.82 (m, 1H), 1.81 (dt, J = 0.98, 2.4 Hz, 3H), 3.45-3.52 (m, 1H), 3.79 (m, 1H), 4.09-4.15 (m, 1H), 4.19-4.25 (m, 1H), 4.75 (t, J = 3.4 Hz, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 3.7, 19.2, 25.5, 30.3, 54.7, 62.0, 75.0, 82.2, 96.8.

2-Bromo-3-methyl-1-trimethylsilanyl-but-2-en-1-one (17).[2] A solution of 4.00 g (25.9 mmol) of alkyne **14** in 42 mL of dry THF was cooled to -45 ^{o}C under Ar, and treated dropwise with vigorous stirring with 32.3 mL (26.5 mmol) of 0.82 M *n*-BuLi in hexanes. After stirring an additional 15 min at -45 ^{o}C the reaction was treated dropwise with 1.68 mL (27.0 mmol) of MeI, and after 10 min cooled to -78 ^{o}C (a precipitate formed on cooling). The reaction was then treated with an additional 32.3 mL (26.5 mmol) of 0.82 M *n*-BuLi in hexanes, followed 10 min later by 3.42 mL (27.0 mmol) of TMSCl. After 10 min the cold bath was removed, a few drops Et_3N were added and the mixture was stored in a -15 ^{o}C freezer overnight (~10.5 hr). The cold mixture was then partitioned in a separatory funnel containing sat'd $NaHCO_3$ and 1:1 ether /pentane, and the organic layer was washed with H_2O and brine, dried over Na_2SO_4, followed by K_2CO_3, and concentrated under reduced pressure. The residue was dissolved in 67 mL of CH_2Cl_2, cooled to -78 ^{o}C, and treated dropwise with vigorous stirring with 12.5 mL of a 2.0 M bromine solution in CH_2Cl_2. After stirring an additional 10 min the reaction was partitioned in a separatory funnel containing 20% aqueous $Na_2S_2O_3$ and 1:1 ether /pentane. The organic layer was washed with H_2O and brine, dried over Na_2SO_4 and concentrated under reduced pressure. The bright yellow residue was purified by flash chromatography (silica gel, 1:9 ether/hexanes) to afford 3.57 g (59%) of enone **17** as a bright yellow oil, R_f 0.47 (1:19 ether/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.30 (s, 9H), 1.90 (s, 3H), 1.96 (s, 3H).

(±)-2-Bromo-3-methyl-1-trimethylsilanyl-but-2-en-1-ol (18). A solution of 1.31 g (5.57 mmol) of enone **17** in 30 mL of EtOH was treated at rt with vigorous stirring with 0.113 g (3.00 mmol) of $NaBH_4$. After stirring an additional 3 h at rt the reaction was diluted with 20 mL H_2O and extracted with CH_2Cl_2.

The aqueous phase was then acidified with 1.0 M HCl and re-extracted. The combined organic extracts were washed with H_2O and brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, 1:4 EtOAc/hexanes) to afford 0.998 g (76%) of allyl alcohol **18** as a colorless oil, R_f 0.48 (1:4 EtOAc/hexanes). IR cm^{-1} (neat): 3417 (broad), 2956, 1636; ^1H NMR (300 MHz, $CDCl_3$) δ 0.12 (s, 9H), 1.81 (s, 3H), 1.92 (s, 3H), 4.50 (s, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ -2.6, 21.5, 25.8, 68.1, 125.8, 130.0; HRMS (EI) Calcd for $C_8H_{16}BrOSi$: 235.0154; found: 235.0153.

***S*-(+)-2-Bromo-3-methyl-1-trimethylsilanyl-but-2-en-1-ol (*S*-(+)-18).** Alcohols (±)-**18** were esterified with (*S*)-(-)-MTPA following the procedure of Ireland and Varney,[3] and the resulting diastereomers were separated by flash chromatography using 5% diethyl ether/pet ether. A total of 0.388 g (0.856 mol) of the less polar (*S*,*S*)-diastereomer, $[\alpha]_D^{23}$ = -31.7° (*c* = 1.0, $CHCl_3$), was dissolved in 5 mL of THF, cooled to 0° C under Ar and treated with 0.90 mL (0.90 mmol) of 1.0 M LAH in THF. After stirring 30 min the cold bath was removed and the reaction was allowed to warm to rt over a period 1 h. The reaction was then quenched with saturated aqueous NH_4Cl, acidified to pH < 2 with 1.0 M HCl, and extracted with ether. The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, 1:4 EtOAc/hexanes) to afford 0.182 g (90%) of allyl alcohol *S*-(+)-**18** as a colorless oil, $[\alpha]_D^{23}$ = + 6.9° (*c* = 2.0, $CHCl_3$), having identical NMR spectral properties to (±)-**18**. The enantiomeric excess was determined to be 99.9 % using a chiral Diacel OJ-H column eluting at 0.5 mL/sec using 99.9 hexanes/0.1 isopropanol as eluent.

(±)-**Propionic acid 2-bromo-3-methyl-1-trimethylsilanyl-but-2-enyl ester (20).** An ice-cold solution of 0.10 mL (1.2 mmol) of propionyl chloride and 0.26 g (1.1 mmol) of alcohol **18** in 20 mL CH_2Cl_2 was treated with 12 mg (0.11 mmol) of DMAP and 0.10 mL (1.2 mmol) of pyridine, and the reaction was stirred for 3 h without recharging the cold bath. The resulting mixture was then poured into a separatory funnel, washed with 1.0 M HCl, sat'd $NaHCO_3$, and brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, 1:4 EtOAc/hexanes) to afford 0.27 g (84%) of allyl ester **20** as a colorless oil, R_f 0.68 (1:4 EtOAc/hexanes). IR cm^{-1} (neat): 2956, 1738, 1638; ^1H NMR (500 MHz, $CDCl_3$) δ 0.13 (s, 9H), 1.17 (t, *J* = 7.6 Hz, 3H), 1.90 (s, 6H), 2.39 (q, *J* = 7.6 Hz, 2H), 5.62 (s, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ -2.4, 9.5, 21.5, 25.7, 27.9, 69.3, 119.8, 132.4, 174.6; HRMS (EI) Calcd for $C_{11}H_{21}BrO_2Si$: 292.0494; found: 292.0491.

(±)-4-Bromo-2,3,3-trimethyl-5-trimethylsilanyl-pent-4-enoic acid (22). A solution of 0.232 g (0.791 mmol) of ester **20** in 5.60 mL THF was cooled to -78° under Ar and treated with 0.55 mL (3.16 mmol) of HMPA. The reaction was then treated dropwise with vigorous stirring with 0.87 mL (0.87 mmol) of 1.0 M TBDMSCl in THF. After stirring an additional 10 min the reaction was treated in one portion with 0.87 mL (0.87 mmol) of 1.0 M LHMDS in THF, stirred a further 10 min at -78°, and then allowed to warm to rt over a period of 1 h. The resulting solution was treated with 3.5 mL of 1.0 M HCl, stirred for 60 min, and extracted with ether. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, 1:1 EtOAc:hexanes, 1% AcOH) to afford 0.171 g (74%) of alkene acid **22** as a colorless solid, R_f 0.75 (1:1 EtOAc/hexanes, 1% AcOH) (decomposes on heating). IR cm^{-1} (TCE): 3050 (broad), 2978, 1702, 1591; ^1H NMR (500 MHz, $CDCl_3$) δ 0.20 (s, 9H), 1.07 (d, *J* = 7.1 Hz, 3H), 1.23 (s, 3H), 1.30 (s, 3H), 3.00 (q, *J* = 7.1 Hz, 1H), 6.13 (s, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ -0.59, 12.7, 22.6, 26.7, 46.3, 47.0, 128.9, 152.3, 181.0; Anal. Calcd for $C_{11}H_{21}BrO_2Si$: C, 45.05%; H, 7.22%; found: C, 46.02%; H, 7.26%.

(±)-2,3,3-Trimethyl-5-trimethylsilanyl-pent-4-ynoic acid (23). A solution of 0.120g (0.409 mmol) of alkene acid **22** in 4.0 mL of THF was treated with 0.18 mL (1.2 mmol) of DBU, and within 5 min a precipitate had formed. After stirring a total of 20 min the reaction was treated with 3 mL of 1.0 M HCl and the mixture was extracted with ether. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The solid residue was purified by flash chromatography (silica gel, 1:1 EtOAc/hexanes, 1% AcOH) to afford 0.084 g (97%) of alkyne acid **19** as a colorless solid, mp 55-57°. R_f 0.76 (1:1 EtOAc/hexanes, 1% AcOH); IR cm^{-1} (TCE): 3050 (broad), 2975, 2158, 1708; ^1H NMR (500 MHz, $CDCl_3$) δ 0.14 (s, 9H), 1.29 (s, 3H), 1.30 (d, *J* = 7.1 Hz, 3H), 1.31 (s, 3H), 2.53 (q, *J* = 7.1 Hz, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 0.32, 13.6, 25.9, 27.8, 34.3, 49.2, 85.5, 112.2, 180.4; Anal. Calcd for $C_{11}H_{20}O_2Si$: C, 62.21%; H, 9.49%; found: C, 62.23%; H, 9.48%.

(±)-4-Bromo-2,3,3-trimethyl-hex-4-enoic acid (24). An ice-cold solution of 0.523 g (2.92 mmol) of 3-bromo-4-methyl-pent-3-en-2-ol[4] and 0.28 mL (3.2 mmol) of propionyl chloride in 20 mL of CH_2Cl_2 was treated with 36 mg (0.29 mmol) of DMAP and 0.26 mL (3.2 mmol) of pyridine, and the reaction was stirred overnight without recharging the cold bath. The resulting mixture was then acidified with 1.0 M HCl, and the organic phase was separated, washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, 1:9 EtOAc/hexanes) to afford 0.59 g (86%) of propionic acid 2-bromo-1,3-dimethyl-but-2-enyl ester as a colorless oil, R_f 0.47 (1:9 EtOAc/hexanes). IR cm^{-1} (neat): 2982, 1738, 1646; ^1H NMR (500 MHz, $CDCl_3$) δ 1.13 (t, *J* = 7.6 Hz, 3H), 1.36 (d, *J* = 6.4 Hz, 3H) 1.89 (s, 3H), 1.93 (s, 3H), 2.34 (q, *J* = 7.6 Hz, 2H), 5.77 (q, *J* = 6.4 Hz, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 9.2, 20.0, 21.1, 25.8, 27.8, 68.8, 122.2, 134.8, 173.8; HRMS (EI) Calcd for $C_9H_{14}BrO_2$: 233.0177; found: 233.0176.

A solution of 0.423g (1.80 mmol) of the above ester in 12.8 mL of THF and 1.25 mL (7.20 mmol) of HMPA was cooled to -78° under Ar. The reaction was then treated dropwise with vigorous stirring with 1.98 mL (1.98 mmol) of 1.0 M TBDMSCl in THF. After stirring an additional 10 min the reaction was treated in one portion with 1.98 mL (1.98 mmol) of 1.0 M LHMDS in THF, stirred a further 10 min at -78°, and then allowed to warm to rt over a period of 1 h. The resulting solution was treated with 4.5 mL of 1.0 M HCl, stirred for 20 min and extracted with ether. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, 1:1 EtOAc:hexanes , 1% AcOH) to afford 0.305 g (72%) of alkene acid **24** as a colorless solid, mp 93-95°. R_f 0.77 (1:1 EtOAc/hexanes, 1% AcOH); IR cm^{-1} (TCE): 3050 (broad), 2979, 1703, 1647; ^1H NMR (500 MHz, $CDCl_3$) δ 1.06 (d, *J* = 7.3 Hz, 3H), 1.26 (s, 3H), 1.31 (s, 3H), 1.78 (d, *J* = 6.3 Hz, 3H), 3.00 (q, J = 7.3 Hz, 1H), 5.87 (q, J = 6.3 Hz, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 12.7, 17.8, 22.7, 26.8, 44.6, 46.2, 123.1, 139.1, 180.7; Anal. Calcd for $C_9H_{15}BrO_2$: C, 45.98%; H, 6.43%, Br, 33.98%; found: C, 46.22%; H, 6.39%, Br, 33.70%.

(±)-2,3,3-Trimethyl-hex-4-ynoic acid (25). A solution of 0.296 g (1.26 mmol) of alkene acid **24** in 20 mL of DME was treated with 0.520 g (13.0 mmol) of NaH 60% dispersion in mineral oil, and the resulting mixture was heated at reflux under Ar for 8 hr. After cooling to rt, the reaction was quenched with H_2O, acidified with 1.0 M HCl, and extracted with ether. The organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, 1:1EtOAc/hexanes) to afford 0.120 g of a 3:1 mixture of alkyne acid **25** (47%) and alkene acid **24** as a colorless oil. Alkyne acid **25** had R_f 0.62 (1:1 EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 1.27 (s, 3H), 1.28 (s, 3H), 1.29 (d, *J* = 7.1 Hz, 3H), 1.82 (s, 3H), 2.49 (q, *J* = 7.1 Hz, 1H); ^{13}C NMR (500

MHz, $CDCl_3$) δ 3.7, 13.7, 26.6, 28.3, 33.6, 49.4, 77.2, 84.4, 180.6; HRMS (EI) Calcd for $C_9H_{15}O_2$: 155.1072; found: 155.1072.

General procedure for preparing allylic esters 32a-c: A solution of 1.0 mmol of alcohol **18** in 15 mL of CH_2Cl_2 is treated with 1.2 mmol of the appropriate carboxylic acid **31**, 1.2 mmol of DCC, and 0.1-0.2 mmol of DMAP. After stirring overnight the reaction mixture is filtered to remove dicyclohexylurea, which is washed with additional CH_2Cl_2. The filtrate is washed with 1.0 M HCl and brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue is chromatographed on silica gel.

(±)-Pentanedioic acid 2-bromo-3-methyl-1-trimethylsilanyl-but-2-enyl ester methyl ester (32a). This material was prepared following the general procedure outlined above using 0.436 g (1.84 mmol) of allyl alcohol **18** and 0.322 g (2.20 mmol) of carboxylic acid **31a**. The crude oil was purified by flash chromatography (silica gel, 1:4 EtOAc/hexanes) to afford 0.524 g (78%) of allyl ester **32a** as a colorless oil, R_f 0.53 (1:4 EtOAc/hexanes). IR cm^{-1} (neat): 2953, 1738, 1638; ^1H NMR (500 MHz, $CDCl_3$) δ 0.12 (s, 9H), 1.90 (s, 6H), 1.95-2.02 (m, 2H), 2.39-2.46 (m, 4H), 3.68 (s, 3H), 5.62 (s, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ -2.4, 20.4, 21.6, 25.7, 33.3, 33.6, 51.8, 69.5, 119.6, 132.5, 173.0, 173.7; HRMS (EI) Calcd for $C_{14}H_{25}BrO_4Si$: 364.0705; found: 364.0704.

***S*-(+)-Pentanedioic acid 2-bromo-3-methyl-1-trimethylsilanyl-but-2-enyl ester methyl ester (S-(+)-32a).** This material was prepared following the general procedure outlined above using 0.182 g (0.767 mmol) of allyl alcohol *S*-(+)-**18** and 0.135 g (0.921 mmol) of carboxylic acid **31a**. The crude oil was purified by flash chromatography (silica gel, 1:1 ether/pet ether) to afford 0.234 g (84%) of allyl ester *S*-(+)-**32a** as a colorless oil, R_f 0.81 (1:1 ether/pet ether), $[\alpha]_D^{23}$ = +8.5° (*c* = 1.0, $CHCl_3$); identical NMR spectral data as (±)-**32a** above.

(±)-4-Cyano-butyric acid 2-bromo-3-methyl-1-trimethylsilanyl-but-2-enyl ester (32b). This material was prepared following the general procedure outlined above using 0.553 g (2.33 mmol) of allyl alcohol **18** and 0.578 g (2.80 mmol) of carboxylic acid **31b**. The crude oil was purified by flash chromatography (silica gel, 1:4 EtOAc/hexanes) to afford 0.589 g (76%) of allyl ester **32b** as a colorless oil, R_f 0.37 (1:4 EtOAc/hexanes). IR cm^{-1} (neat): 2956, 2247, 1733, 1638; ^1H NMR (300 MHz, $CDCl_3$) δ 0.13 (s, 9H), 1.90 (s, 6H), 1.97-2.06 (m, 2H), 2.46-2.59 (m, 4H), 5.61 (s, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ -2.4, 16.9, 21.2, 21.6, 25.8, 32.8, 70.0, 119.2, 119.3, 132.9, 172.1; HRMS (EI) Calcd for $C_{13}H_{22}BrNO_2Si$: 331.0603; found: 331.0603.

(±)-4-Carbamoyl-butyric acid 2-bromo-3-methyl-1-trimethylsilanyl-but-2-enyl ester (32c). This material was prepared following the general procedure outlined above using 0.268 g (1.13 mmol) of allyl alcohol **18** and 0.163 g (1.24 mmol) of carboxylic acid **31c**. The crude oil was purified by flash chromatography (silica gel, EtOAc) to afford 0.320 g (81%) of allyl ester **32c** as a colorless oil, R_f 0.34 (EtOAc). IR cm^{-1} (neat): 3333, 3194, 2956, 1733, 1672, 1621; ^1H NMR (500 MHz, $CDCl_3$) δ 0.13 (s, 9H), 1.91 (s, 6H), 1.96-2.05 (m, 2H), 2.29-2.35 (m, 2H), 2.44-2.50 (m, 2H), 5.47 (br, 1H), 5.57 (br, 1H), 5.62 (s, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ -2.4, 21.1, 21.6, 25.7, 33.5, 34.9, 69.6, 119.6, 132.7, 173.3, 174.7; HRMS (EI) Calcd for $C_{13}H_{25}BrNO_3Si$: 350.0787; found: 350.0792.

(±)-2-(2-Bromo-1,1-dimethyl-3-trimethylsilanyl-allyl)-pentanedioic acid 5-methyl ester (33a). A solution of 0.410 g (1.12 mmol) of ester **32a** in 5.30 mL of THF and 1.17 mL (6.73 mmol) of HMPA was cooled to -78° under Ar. The reaction was then treated dropwise with vigorous stirring with 2.36 mL (2.36

mmol) of 1.0 M TBDMSCl in THF. After stirring an additional 20 min the reaction was treated in one portion with 2.36 mL (2.36 mmol) of 1.0 M LHMDS in THF, stirred a further 15 min at -78°, and then allowed to warm to rt over a period of 1 h. The resulting solution was treated with 7.5 mL of 1.0 M HCl, stirred for 20 min and extracted with ether. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, 1:1 EtOAc:hexanes , 1% AcOH) to afford 0.339 g (83%) of alkene acid **33a** as a colorless oil, along with 0.033 g (8%) of the diacid corresponding to ester hydrolysis (R_f 0.48). Alkene acid **33a** had R_f 0.59 (1:1 EtOAc/hexanes, 1% AcOH); IR cm^{-1} (neat): 3100 (broad), 2656, 1740, 1703, 1590; ^1H NMR (300 MHz, $CDCl_3$) δ 0.19 (s, 9H), 1.26 (s, 3H), 1.27 (s, 3H), 1.67-1.75 (m, 1H), 1.84-1.94 (m, 1H), 2.24-2.43 (m, 2H), 2.88 (dd, *J* = 12.0, 2.7 Hz, 1H), 3.67 (s, 3H), 6.16 (s, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ -0.63, 23.0, 23.2, 27.0, 32.9, 47.2, 51.9, 52.2, 129.5, 151.8, 173.4, 180.0; HRMS (EI) Calcd for $C_{14}H_{26}O_4BrSi$: 365.0784; found: 365.0771.

***S*-(+)-2-(2-Bromo-1,1-dimethyl-3-trimethylsilanyl-allyl)-pentanedioic acid 5-methyl ester (*S*-(+)-33a).** This material was prepared as described above for (±)-**33a**, affording *S*-(+)-**33a** as a colorless oil, $[\alpha]_D^{23}$ = +1.5° (*c* = 1.0, $CHCl_3$), having identical NMR spectral data as (±)-**33a** above.

(±)-4-Bromo-2-(2-cyano-ethyl)-3,3-dimethyl-5-trimethylsilanyl-pent-4-enoic acid (33b). A solution of 0.265 g (0.797 mmol) of ester **32b** in 5.66 mL of THF and 0.55 mL (3.19 mmol) of HMPA was cooled to -78° under Ar. The reaction was then treated dropwise with vigorous stirring with 0.88 mL (0.88 mmol) of 1.0 M TBDMSCl in THF. After stirring an additional 10 min the reaction was treated in one portion with 0.88 mL (0.88 mmol) of 1.0 M LHMDS in THF, stirred a further 10 min at -78°, and then allowed to warm to rt over a period of 1 h. The resulting solution was treated with 3.5 mL of 1.0 M HCl, stirred for 20 min and extracted with ether. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, 1:1 EtOAc:hexanes , 1% AcOH) to afford 0.250 g (94%) of alkene acid **33b** as colorless solid, R_f 0.37 (1:1 EtOAc/hexanes, 1% AcOH) (decomposes on heating). IR cm^{-1} (neat): 3000 (broad), 2969, 2247, 1713, 1589; ^1H NMR (300 MHz, $CDCl_3$) δ 0.22 (s, 9H), 1.25 (s, 3H), 1.31 (s, 3H), 1.64-1.77 (m, 1H), 1.91-2.06 (m, 1H), 2.25-2.48 (m, 2H), 3.02 (dd, *J* = 11.8, 2.7 Hz, 1H), 6.19 (s, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ -0.62, 16.4, 22.6, 24.1, 27.5, 47.3, 52.0, 118.9, 130.1, 151.0, 178.4; HRMS (EI) Calcd for $C_{13}H_{23}BrNO_2Si$: 332.0681; found: 332.0680.

(±)-4-Bromo-2-(2-carbamoyl-ethyl)-3,3-dimethyl-5-trimethylsilanyl-pent-4-enoic acid (33c). A solution of 0.320 g (0.913 mmol) of ester **32c** in 9.50 mL of THF and 1.27 mL (7.30 mmol) of HMPA was cooled to -78° under Ar. The reaction was then treated dropwise with vigorous stirring with 3.75 mL (3.75 mmol) of 1.0 M TBDMSCl in THF. After stirring an additional 10 min the reaction was treated in one portion with 3.75 mL (3.75 mmol) of 1.0 M LHMDS in THF, stirred a further 10 min at -78°, and then allowed to warm to rt over a period of 1 h. The resulting solution was treated with 12 mL of 1.0 M HCl, stirred for 30 min and extracted with ether. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, 1:1 EtOAc:hexanes , 1% AcOH) to afford 0.182 g (57%) of alkene acid **33c** as colorless solid, R_f 0.1 (1:1 EtOAc/hexanes, 1% AcOH) (decomposes on heating), along with 0.018g (~6%) of **33b** (see above). Compound **33c** had IR cm^{-1} (TCE): 3403, 3228, 2990 (broad), 2953, 1711, 1660, 1601; ^1H NMR (500 MHz, $DMSO_{d6}$) δ 0.18 (s, 9H), 1.15 (s, 3H), 1.18 (s, 3H), 1.44-1.52 (m, 1H), 1.56-1.66 (m, 1H), 1.84-1.95 (m, 1H), 1.96-2.04 (m, 1H), 2.60 (dd, *J* = 12.0, 2.7 Hz, 1H), 6.20 (s, 1H), 6.72 (s, 1H), 7.25 (s, 1H), 12.30 (s, 1H); ^{13}C NMR (500 MHz, $DMSO_{d6}$) δ -0.71, 23.3, 23.9, 27.4, 34.3, 47.2, 52.5, 128.8,

153.5, 174.0, 175.3; Anal. Calcd for $C_{13}H_{24}BrNO_3Si$: C, 44.57%; H, 6.91%; N, 4.00%; found: C, 44.29%; H, 6.79%; N, 3.81%.

General Procedure for preparing alkyne acids 34a-c (HBr Elimination): A solution of 1.0 mmol of alkene acid **33** in 13 mL of THF is treated with 4.0 mmol of DBU at rt with vigorous stirring. The reaction is stirred for 1 h after the initial formation of a precipitate and then acidified with 5.0 mmol of 1.0 M HCl. The resulting mixture is extracted with ether, and the extracts are washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue is chromatographed on silica gel.

(±)-2-(1,1-Dimethyl-3-trimethylsilanyl-prop-2-ynyl)-pentanedioic acid 5-methyl ester (34a). This material was prepared following the general procedure outlined above for HBr elimination. The crude oil was purified by flash chromatography (silica gel, 1:1 EtOAc:hexanes) to afford 91% of alkyne acid **34a** as a colorless oil. IR cm^{-1} (neat): 3100 (broad), 2956, 2167, 1743, 1711; ^1H NMR (500 MHz, $CDCl_3$) δ 0.14 (s, 9H), 1.29 (s, 3H), 1.33 (s, 3H), 1.99-2.16 (m, 2H), 2.30-2.47 (m, 3H), 3.69 (s, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 0.28, 23.9, 26.2, 28.0, 32.6, 34.3, 52.0, 54.8, 85.8, 111.8, 173.4, 179.3; HRMS (EI) Calcd for $C_{14}H_{25}O_4Si$: 285.1522; found: 285.1523.

(±)-2-(2-Cyano-ethyl)-3,3-dimethyl-5-trimethylsilanyl-pent-4-ynoic acid (34b). This material was prepared following the general procedure outlined above for HBr elimination. The crude material was purified by recrystallization from hexanes to afford 90% of alkyne acid **34b** as a colorless solid, mp 106-107 °C. IR cm^{-1} (TCE): 3050 (broad), 2960, 2247, 2171, 1707; ^1H NMR (500 MHz, $CDCl_3$) δ 0.16 (s, 9H), 1.29 (s, 3H), 1.35 (s, 3H), 2.13-2.19 (m, 2H), 2.32-2.41 (m, 1H), 2.47-2.59 (m, 2H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 0.25, 16.3, 24.9, 25.8, 28.5, 34.4, 54.2, 86.5, 110.9, 118.9, 177.9; Anal. Calcd for $C_{13}H_{21}NO_2Si$: C, 62.11%; H, 8.42%; N, 5.57%; found: C, 61.84%; H, 8.39%; N, 5.41%; HRMS (EI) Calcd for $C_{13}H_{22}NO_2Si$: 252.1420; found: 252.1420.

(±)-2-(2-Carbamoyl-ethyl)-3,3-dimethyl-5-trimethylsilanyl-pent-4-ynoic acid (34c). This material was prepared following the general procedure outlined above for HBr elimination. The crude oil was purified by flash chromatography (silica gel, 1:1 EtOAc:hexanes) to afford 91% of alkyne acid **34c** as a colorless solid, mp 153-154 °C. R_f 0.1 (1:1 EtOAc/hexanes); IR cm^{-1} (TCE): 3436, 3236, 2974, 2161, 1701, 1636; ^1H NMR (500 MHz, $DMSO_{d6}$) δ 0.10 (s, 9H), 1.18 (s, 3H), 1.21 (s, 3H), 1.70-1.79 (m, 1H), 1.83-1.90 (m, 1H), 1.92-2.09 (m, 2H), 2.20 (dd, J = 11.7, 2.7 Hz, 1H), 6.74 (s, 1H), 7.27 (s, 1H), 12.23 (s, 1H); ^{13}C NMR (500 MHz, $DMSO_{d6}$) δ 0.19, 24.0, 25.9, 27.7, 33.3, 33.5, 54.2, 84.1, 113.1, 173.4, 174.3; Anal. Calcd for $C_{13}H_{23}NO_3Si$: C, 57.96%; H, 8.60%; N, 5.20%; found: C, 57.92%; H, 8.74%; N, 5.15%.

(±)-2-(1,1-Dimethyl-prop-2-ynyl)-pentanedioic acid 5-methyl ester (3a). *Method A.* A solution of 0.160 g (0.563 mmol) of alkyne acid **34a** in 10 mL of MeOH was treated with 0.233 g (1.69 mmol) of K_2CO_3 and the resulting mixture was stirred at rt overnight. The reaction was then acidified to pH~2 by dropwise addition of 1.0 M HCl and extracted with ether. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The semi-solid residue was further dried under high vacuum and then recrystallized from hexanes to afford 0.090 g (76%) of alkyne acid **3a** as a colorless solid, mp 59-60 °C. IR cm^{-1} (TCE): 3291, 3100 (broad), 2977, 2110, 1737, 1710; ^1H NMR (300 MHz, $CDCl_3$) δ 1.33 (s, 3H), 1.37 (s, 3H), 2.04-2.19 (m, 2H), 2.21 (s, 1H), 2.28-2.50 (m, 3H), 3.69 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 24.0, 26.3, 28.4, 32.5, 33.5, 51.9, 54.5, 69.9, 89.2, 173.4, 178.7; Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25%; H, 7.60%; found: C, 62.53%; H, 7.64%.

(±)-2-(2-Cyano-ethyl)-3,3-dimethyl-pent-4-ynoic acid (3b). *Method A.* This material was prepared following an identical procedure as described above for **3a**. The crude product was purified by flash chromatography (silica gel, 1:1 EtOAc/hexanes) to afford 94% of alkyne acid **3b** as a colorless solid, mp 51-52 °C. IR cm^{-1} (TCE): 3273, 3100 (broad), 2976, 2246, 2108, 1708; ^1H NMR (500 MHz, $CDCl_3$) δ 1.33 (s, 3H), 1.39 (s, 3H), 2.15-2.21 (m, 2H), 2.24 (s, 1H), 2.35-2.42 (m, 1H), 2.47-2.56 (m, 2H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 16.2, 24.9, 25.9, 28.7, 33.6, 54.0, 70.5, 88.5, 118.9, 177.9; Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.02%; H, 7.31%; N, 7.82%; found: C, 66.73%; H, 7.28; N, 7.64%; HRMS (EI) Calcd for $C_{10}H_{14}NO_2$: 180.1025; found: 180.1023.

***S*-(-)-2-(1,1-Dimethyl-prop-2-ynyl)-pentanedioic acid 5-methyl ester (*S*-(-)-3a).** *Method B.* A solution of 0.153 g (0.419 mmol) alkene acid *S*-(+)-**33a** in 1.0 mL of THF was treated with 4.2 mL of a 1.0 M solution of TBAF in THF, and the reaction was stirred at rt for 22 h. At the end of this period 4.5 mL of 1.0 M HCl was added and stirring was continued for an additional 30 min. The resulting mixture was then extracted with ether and the combined extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 1:1 ether/pet-ether) to afford 0.084 g (95%) of alkyne acid *S-(-)*-**3a** as a colorless oil, $[\alpha]_D^{23}$ = -19.0° (*c* = 2.0, $CHCl_3$), having identical NMR spectral data as (±)-**3a**.

(±)-3-(4,4-Dimethyl-5-methylene-2-oxo-tetrahydro-furan-3-yl)-propionic acid methyl ester (35). A solution of 40 mg (0.19 mmol) of alkyne acid **3a** in 2.5 mL of THF was treated with 5 mg (0.019 mmol) of $PdCl_2(CH_3CN)_2$ and 8 μL (0.057 mmol) of Et_3N under Ar. The resulting mixture was then heated at 65 °C for 3 h. After cooling to rt, the solvent was removed under reduced pressure and the residue was purified by flash chromatography (silica gel, 1:4 EtOAc/hexanes) to afford 0.025 g (63%) of enelactone **35** as a colorless oil, R_f 0.38 (1:4 EtOAc/hexanes). IR cm^{-1} (neat): 2967, 1800, 1736, 1671; ^1H NMR (500 MHz, $CDCl_3$) δ 1.16 (s, 3H), 1.33 (s, 3H), 1.82-1.87 (m, 2H), 2.42-2.48 (m, 1H), 2.57-2.64 (m, 1H), 2.74-2.80 (m, 1H), 3.70 (s, 3H), 4.33 (d, J = 2.7 Hz, 1H), 4.67 (d, J = 2.7 Hz, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 20.4, 23.5, 25.4, 31.4, 42.8, 49.5, 51.9, 86.7, 164.6, 173.6, 175.5; HRMS (EI) Calcd for $C_{11}H_{16}O_4$: 212.1049; found: 212.1044.

***S*-(-)-3-(4,4-Dimethyl-5-methylene-2-oxo-tetrahydro-furan-3-yl)-propionic acid methyl ester (*S*-(-)-35).** This material was prepared as described above for (±)-**35.** Enelactone *S-(-)*-**35** was isolated as a colorless oil, $[\alpha]_D^{23}$ = -92.7° (*c* = 0.67, $CHCl_3$), having identical NMR spectral data as (±)-**35**.

2-Bromo-1-(tert-butyl-dimethyl-silanyl)-3-methyl-but-2-en-1-one (40).[2] A solution of 5.14 g (33.3 mmol) of alkyne **14** in 42 mL of dry THF was cooled to -45 °C under Ar, and treated dropwise with vigorous stirring with 26.3 mL (35.0 mmol) of 1.33 M *n*-BuLi in hexanes. After stirring an additional 10 min at -45 °C the reaction was treated dropwise with 2.28 mL (36.7 mmol) of MeI, and after a further 10 min the reaction was allowed to warm to rt. The resulting mixture was then partitioned between sat'd $NaHCO_3$ and 1:1 ether/pentane, and the organic layer was washed with H_2O and brine, dried over Na_2SO_4 followed by K_2CO_3, and concentrated under reduced pressure to give 5.51 g (32.8 mmol) of crude methylated product. This material was dissolved in 50 mL of THF, cooled to -78 °C under Ar, and treated dropwise with efficient stirring with 25.2 mL (33.5 mmol) of 0.1.33 M *n*-BuLi in hexanes, followed 5 min later by 34.5 mL (34.5 mmol) of 1.0 M TBDMSCl in THF and 5.87 g (32.8 mmol) of HMPA in 6.0 mL THF. The resulting mixture was stirred for 5 min at -78 °C and then stored in a -15 °C freezer overnight. The cold mixture was then partitioned in a separatory funnel containing sat'd $NaHCO_3$ and 1:1 ether/pentane, and the organic layer was washed with H_2O and brine, dried over Na_2SO_4, followed by

K_2CO_3, and concentrated under reduced pressure. The residue was dissolved in 100 mL of CH_2Cl_2, cooled to -78 °C, and treated dropwise with vigorous stirring with 8.0 mL of a 4.0 M bromine solution in CH_2Cl_2. After stirring an additional 10 min the reaction was partitioned in a separatory funnel containing 20% aqueous $Na_2S_2O_3$ and 1:1 ether/pentane. The organic layer was washed with H_2O and brine, dried over Na_2SO_4 and concentrated under reduced pressure. The bright yellow residue was purified by flash chromatography (silica gel, 1:9 ether/hexanes) to afford 3.20 g (35%) of enone **40** as a bright yellow oil, R_f 0.7 (1:19 ether/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.29 (s, 6H), 0.99 (s, 9H), 1.85 (s, 3H), 1.95 (s, 3H).

***S*-(+)-2-Bromo-1-(*tert*-butyl-dimethyl-silanyl)-3-methyl-but-2-en-1-ol (*S*-(+)-41).** A solution of 3.15 g (9.82 mmol) of (+)-DIP-Cl and 1.94 g (7.00 mmol) of silyl ketone **40** in 16 mL THF was stirred under Ar for 12 h at rt. At the end of this period the reaction was concentrated to dryness, first on a rotary evaporator and then under high vacuum for 4 h. The viscous oil obtained was dissolved in 10 mL of THF, cooled to 0° and treated with vigorous stirring with 15 mL 3.0 M NaOH and 15 mL 30% H_2O_2. After stirring 2.5 h the mixture was extracted with ether and the combined extracts were washed with H_2O and brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, 1:4 EtOAc/hexanes) to afford 0.852 g (45%) of allyl alcohol *S-(+)*-**41** as a colorless oil, $[\alpha]_D^{23}$ = +18.5° (*c* = 1.0, $CHCl_3$), R_f 0.61 (1:9 ether/hexanes). IR cm^{-1} (neat): 3453 (broad), 2928, 1632; ^{1}H NMR (500 MHz, $CDCl_3$) δ -0.04 (s, 3H), 0.19 (s, 3H), 0.97 (s, 9H), 1.81 (s, 3H), 1.91 (s, 3H), 4.69 (s, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ -7.2, -7.0, 17.0, 21.4, 25.7, 26.9, 65.2, 127.0, 129.5; HRMS (EI) Calcd for $C_{11}H_{22}BrOSi$: 277.0623; found: 277.0630.

***S*-(+)-Pentanedioic acid 2-bromo-1-(tert-butyl-dimethyl-silanyl)-3-methyl-but-2-enyl ester methyl ester (*S*-(+)-42).** This material was prepared following the general esterification procedure outlined above for **32a-c**, employing 0.70 g (2.5 mmol) of allyl alcohol *S*-(+)-**41** and 0.44 g (3.0 mmol) of carboxylic acid **31a**. The crude product was purified by flash chromatography (silica gel, 1:9 ether/hexanes) to afford 0.871 g (85%) of allyl ester *S*-(+)-**42** as a colorless oil, $[\alpha]_D^{23}$ = +25.1° (*c* = 1.0, $CHCl_3$), R_f 0.32 (1:9 ether/hexanes). IR cm^{-1} (neat): 2953, 2930, 2857, 1739, 1638, 1367; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.0 (s, 3H), 0.22 (s, 3H), 0.90 (s, 9H), 1.88 (s, 3H), 1.92 (s, 3H), 1.93-2.00 (m, 2H), 2.34-2.46 (m, 4H), 3.67 (s, 3H), 5.80 (s, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ -7.1, -6.6, 17.0, 20.3, 21.5, 25.6, 26.7, 33.3, 33.6, 51.8, 66.5, 120.6, 132.4, 172.9, 173.6; HRMS (EI) Calcd for $C_{17}H_{31}BrO_4Si$: 406.1175; found: 406.1170.

***S*-(+)-2-[2-Bromo-3-(tert-butyl-dimethyl-silanyl)-1,1-dimethyl-allyl]-pentanedioic acid 5-methyl ester (*S*-(+)-43).** This material was prepared following the identical procedure as described above for alkene acid **33a**. The crude product was purified by flash chromatography (silica gel, 1:1 ether/hexanes) to afford 68% of alkene acid *S*-(+)-**43** as a colorless oil, $[\alpha]_D^{23}$ = +4.5° (*c* = 1.0, $CHCl_3$), R_f 0.37 (1:1 ether/ether) , plus 10% of the diacid corresponding to ester hydrolysis (R_f 0.1). Compound *S*-(+)-**43**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.19 (s, 3H), 0.21 (s, 3H), 0.92 (s, 9H), 1.28 (s, 3H), 1.30 (s, 3H), 1.71-1.79 (m, 1H), 1.86-1.95 (m, 1H), 2.25-2.33 (m, 1H), 2.36-2.43, (m, 1H) 2.91 (dd, J = 11.7, 2.4 Hz, 1H), 3.68 (s, 3H), 6.19 (s, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ -4.9, -4.8, 17.4, 23.2, 23.4, 26.7, 26.9, 33.0, 47.6, 51.9, 52.2, 126.8, 152.3, 173.4, 180.1; HRMS (EI) Calcd for $C_{17}H_{32}BrO_4Si$: 407.1253; found: 407.1253.

***S*-(-)-2-[3-(tert-Butyl-dimethyl-silanyl)-1,1-dimethyl-prop-2-ynyl]-pentanedioic acid 5-methyl ester (*S*-(-)-44)**. A solution of 0.340 g (0.835 mmol) of alkene acid *S*-(+)-**43** in 8 mL of THF was treated

with 0.31 mL (2.09 mmol) of DBU at rt with vigorous stirring. After a total of 2.5 h the reaction mixture was acidified with 3.0 mL of 1.0 M HCl and stirring was continued for an additional 5 min. The resulting mixture was then extracted with ether and the combined extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. Chromatography afforded 0.268 g (97%)of alkyne acid *S*-(-)-**44** as a colorless oil, $[\alpha]_D^{23}$ = -10.7° (*c* = 2.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.08 (s, 6H), 0.92 (s, 9H), 1.30 (s, 3H), 1.34 (s, 3H), 2.02-2.18 (m, 2H), 2.29-2.37 (m, 1H), 2.40-2.48 (m, 2H), 3.69 (s, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ -4.4, 16.7, 24.1, 26.2, 26.4, 28.2, 32.7, 34.4, 51.9, 54.8, 83.9, 112.2, 173.4, 179.0.

***S*-(-)-2-(1,1-Dimethyl-prop-2-ynyl)-pentanedioic acid 5-methyl ester (*S*-(-)-3a).** *Derived from chiral reduction.* A solution of 0.220g (0.674 mmol) of alkyne acid *S*-(-)-**44** in 1.0 mL of THF was treated with 10.1 mL (10.1 mmol) of 1.0 M TBAF in THF. After stirring 36 hr at rt, the reaction mixture was acidified with 13 mL of 1.0 M HCl and extracted with ether. The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 1:1 ether/pet ether) to afford 0.101 g (71%) of alkyne acid *S*-(-)-**3a** as a colorless oil, $[\alpha]_D^{23}$ = -18.2° (*c* = 2.0, $CHCl_3$), having identical spectral data as authentic *S*-(-)-**3a** prepared above by resolution (enantiomeric excess >95% based on optical rotation from compound *S*-(-)-**3a** derived by resolution).

***S*-(-)-3-(4,4-Dimethyl-5-methylene-2-oxo-tetrahydro-furan-3-yl)-propionic acid methyl ester (*S*-(-)-35).** *Derived from chiral reduction.* This material was synthesized as described for (±)-**35** from alkyne acid *S*-(-)-**3a** above. Enelactone *S-(-)*-**35** thus prepared was isolated as a colorless oil, $[\alpha]_D^{23}$ = -88.7° (*c* = 1.0, $CHCl_3$), having identical NMR spectral data as (±)-35 (enantiomeric excess >95% based on optical rotation from compound *S*-(-)-**35** derived by resolution).

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