Supporting Information

A Scalable Route to Trisubstituted (*E*)-Vinyl Bromides

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Materials and Methods. Reactions were carried out in oven or flame-dried glassware under an argon atmosphere, unless otherwise noted. All solvents were reagent grade. Diethyl ether (Et₂O) and tetrahydrofuran (THF) were freshly distilled from sodium/benzophenone under argon. *n*-Butyllithium and *t*-butyllithium were purchased from Aldrich. Reactions were magnetically stirred and monitored by thin layer chromatography (TLC) with 0.25 mm E. Merck pre-coated silica gel plates. Flash chromatography was performed with silica gel 60 (particle size 0.040 – 0.062 mm) supplied by Silicycle and Sorbent Technologies. Yields refer to chromatographically and spectroscopically pure compounds, unless otherwise stated. All melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Infrared spectra were recorded on a Jasco Model FT/IR-480 Plus spectrometer. Proton and carbon-13 NMR spectra were recorded on a Bruker AMX-500 spectrometer. Chemical shifts are reported relative to chloroform (δ 7.26) for ¹H NMR and chloroform (δ 77.0) for ¹³C NMR. Optical rotations were measured on a Perkin-Elmer model 241 polarimeter. High resolution mass spectra were measured at the University of Pennsylvania Mass Spectrometry Service Center.

Experimental Procedures

3,4-Dibromo-3,5-dimethyl-tetrahydro-pyran-2-one [(-)-23a and (+)-23b]. To a solution of (+)-**22** (3.7 g, 29.3 mmol) in 20 mL of CH₂Cl₂ was added Br₂ (4.6 mL, 3 equiv) slowly over 10 min at -10 °C (wet ice/acetone bath). After 2 h at -10 °C, the reaction mixture was slowly poured into a beaker containing 30 mL of sat. sodium bisulfite and 30 g of ice with aid of EtOAc with vigorous stirring (the quenching is quite exothermic). The organic layer was separated, washed with brine, concentrated and chromatographed (9:1 hexanes:EtOAc) to afford (-)-**23a** and (+)-**23b** in the ratio of 3.7 to 1, both as clear oils that slowly

solidified upon standing to yield crystalline needles (total 5.9 g, 71% yield, well separated on column, but need not be collected separately).

Dibromide (-)-23a: mp 65 – 66 °C; $[\alpha]_D^{23}$ -11.6 ($c = 3.4$, CHCl_3); IR (NaCl) 2977.6, 2935.1, 1739.5, 1461.8, 1380.8, 1338.4, 1261.2 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 4.51 (d, $J = 1.9$ Hz, 1H), 4.37 – 4.32 (m, 2H), 3.31 – 3.24 (m, 1H), 2.20 (s, 3H), 1.07 (d, $J = 6.4$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 166.9, 72.0, 63.5, 55.9, 30.5, 30.1, 15.1; high resolution mass spectrum (Cl^+) m/z 284.9131, $[(\text{M}+\text{H})]^+$, calcd for $\text{C}_7\text{H}_{11}\text{Br}_2\text{O}_2$: 284.9126].

ORTEP representation of the X-ray structure of (-)-23a.

Dibromide (+)-23b: mp 85 – 87 °C; $[\alpha]_D^{23} +11.3$ (c = 2.6, CHCl₃); IR (NaCl) 2973.1, 2931.3, 1747.2, 1457.9, 1384.6, 1311.3 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 4.51 (d, J = 8.3 Hz, 1H), 4.40 – 4.38 (m, 2H), 2.71 – 2.62 (m, 1H), 2.15 (s, 3H), 1.23 (d, J = 6.8 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 167.0, 71.7, 62.0, 56.4, 37.9, 30.5, 16.8; high resolution mass spectrum (CI⁺) m/z 284.9125, [(M+H)⁺, calcd for C₇H₁₁Br₂O₂: 284.9126].

ORTEP representation of the X-ray structure of (+)-23b.

4-Bromo-2-methyl-pent-3-en-1-ol [(-)-24]. To a flask charged with (-)-**23a** and (+)-**23b** (12.6 g, 44.0 mmol) were added 100 mL of DMF/H₂O (4:1) and LiOH monohydrate (5.3 g, 3 equiv) at rt. After 16 h, the reaction mixture was directly chromatographed (9:1 → 7:3 pentane/Et₂O) to furnish (-)-**24** (5.8 g, 73% yield) as an essentially colorless liquid: $[\alpha]_D^{23}$ -25.3 (*c* = 2.6, CHCl₃); IR (NaCl) 3351.7, 2962.1, 2927.4, 2873.4, 1704.8, 1650.8, 1454.1, 1380.8 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 5.66 (dd, *J* = 9.9, 1.1 Hz, 1H), 3.50 (dd, *J* = 10.6, 5.8 Hz, 1H), 3.41 (dd, *J* = 10.6, 7.7 Hz, 1H), 2.64 – 2.55 (m, 1H), 2.27 (d, *J* = 1.1 Hz, 3H), 0.98 (d, *J* = 6.9 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 134.6, 121.2, 67.2, 37.7, 23.8, 16.5; high resolution mass spectrum: decomposition.

(S)-3-Hydroxypentanenitrile [(+)-S-2]. To a solution of (S)-1,2-epoxybutane [(-)-**S-1**, 6.0 mL, 69.6 mmol] in 50 mL anhydrous CH₃CN were added KCN (9.0 g, 138 mmol) and LiClO₄ (14.8 g, 139 mmol) at rt. The reaction mixture was sealed and heated to 70 °C. After overnight at 70 °C, the reaction mixture was diluted with EtOAc and washed with saturated NaHCO₃, water, and brine, dried over MgSO₄, filtered and concentrated. Purification by flash chromatography (2:1 hexanes/EtOAc) afforded 6.0 g (87% yield) of (S)-(-)-3-hydroxypentanenitrile [(+)-**S-2**] as a liquid, with spectral data matching that previously reported.¹

3-(Tetrahydro-2H-pyran-2-yloxy)pentanal (34). To a solution of (+)-**S-2** (5.7 g, 57.5 mmol) in 100 mL of CH₂Cl₂ was added 3,4-dihydro-2H-pyran (DHP, 9.8 g, 116 mmol), and pyridinium p-toluenesulfonate (PPTS, 2.9 g, 11.6 mmol) at rt. After 2 h at rt, the reaction mixture was diluted with Et₂O (150 mL) and

washed with half-saturated brine (50 mL) to remove the catalyst. The organic layer was separated and washed with saturated NaHCO_3 , water, and brine, dried over Na_2SO_4 , concentrated and distilled (105-106 °C at 0.1 mmHg) to give 10.4 g (99% yield) of **S-3** (1:1 mixture of diastereomers) as a colorless liquid: IR (NaCl) 2942.8, 2877.3, 2248.6, 1457.9, 1349.9 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 4.77 (dd, J = 4.0, 3.5 Hz, 1H), 4.68 (dd, J = 4.1, 3.6 Hz, 1H), 3.97 – 3.93 (m, 1H), 3.91 – 3.86 (m, 2H), 3.80 – 3.75 (m, 1H), 3.55 – 3.50 (m, 2H), 2.67 (s, 1H), 2.66 (s, 1H), 2.55 (dd, J = 16.7, 5.2 Hz, 1H), 2.48 (dd, J = 16.7, 5.6 Hz, 1H), 1.90 – 1.50 (m, 16H), 0.99 (t, J = 7.4 Hz, 3H), 0.95 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 117.5, 117.2, 99.2, 97.4, 74.5, 72.6, 62.7, 62.6, 30.7, 30.6, 28.0, 26.7, 25.2, 23.9, 22.1, 19.4, 19.3, 9.5, 9.2; high resolution mass spectrum (Cl^+) m/z 184.1334, $[(\text{M}+\text{H})^+]$, calcd for $\text{C}_{10}\text{H}_{18}\text{NO}_2$ 184.1337]. To a solution of **S-3** (6.9 g, 37.6 mmol) in 200 mL of CH_2Cl_2 at -78 °C was added DIBAL in hexanes (1.0 M, 75.0 mL, 75.0 mmol) via syringe over 30 min. After being stirred for 3 h, the reaction was quenched by slowly adding MeOH at -78 °C followed by saturated Rochelle salts solution (Na^+/K^+ tartrate) and allowing the mixture to warm to rt. After vigorous stirring for 1 h, the CH_2Cl_2 layer was collected, and the aqueous phase was washed with brine, dried over MgSO_4 , and concentrated. The crude was purified by flash chromatography (10:1 hexanes/EtOAc) to give 5.8 g (83% yield) of **34** (1:1 mixture of diastereomers) as a liquid: IR (NaCl) 2942.8, 2873.4, 2730.7, 1724.1, 1457.9, 1384.6 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 9.81 – 9.79 (m, 2H), 4.69 (dd, J = 4.1, 3.9 Hz, 1H), 4.65 (dd, J = 4.8, 3.0 Hz, 1H), 4.12 – 4.06 (m, 1H), 3.91 – 3.79 (m, 2H), 3.51 – 3.43 (m, 2H), 2.69 – 2.49 (m, 3H), 1.80 – 1.51 (m, 18H), 0.96 (t, J = 7.4 Hz, 3H), 0.91 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 202.1, 201.6, 98.5, 98.0, 73.7, 73.6, 63.0, 62.8, 48.8, 47.7, 31.0, 28.6, 27.2, 25.4, 25.3, 19.9, 19.7, 9.8, 9.3; high resolution mass spectrum (Cl^+) m/z 187.1337, $[(\text{M}+\text{H})^+]$, calcd for $\text{C}_{10}\text{H}_{19}\text{O}_3$ 187.1334].

6-Ethyl-5,6-dihydro-3-methylpyran-2-one [(-)-35]. To a solution of diisopropylamine (DIPA, 10.5 mL, 74.7 mmol) in 50 mL of THF at $-15\text{ }^{\circ}\text{C}$ was added dropwise *n*-BuLi in hexanes (2.5 M, 29.9 mL, 74.7 mmol) via syringe over 20 min. After the addition, the reaction mixture was stirred for 15 min and then cooled to $-78\text{ }^{\circ}\text{C}$. To this solution was slowly added ethyl propionate (7.2 mL, 62.3 mmol) via syringe over 10 min. The resulting solution was stirred for 1 h at $-78\text{ }^{\circ}\text{C}$. Then, aldehyde **34** (5.8 g, 31.1 mmol) was added dropwise to the vigorously stirring solution at $-78\text{ }^{\circ}\text{C}$ over 15 min. After the solution was stirred for 30 min, saturated NH_4Cl was added, and the mixture was allowed to warm to rt. The phases were separated, and the aqueous layer was extracted with CH_2Cl_2 . The combined organic layers were washed with H_2O and brine, dried over MgSO_4 , and concentrated. The crude aldol adduct (1.0 equiv) and *p*-toluenesulfonic acid (1.1 equiv) in benzene (150 mL) was heated to reflux for 12 h. The water generated was trapped by means of a Dean-Stark apparatus. The reaction mixture was allowed to cool to rt, washed with 10% NaHCO_3 , water, brine, dried over Na_2SO_4 , concentrated and distilled ($90 - 93\text{ }^{\circ}\text{C}$ at 0.1 mmHg) to give 2.5 g (57% yield for 2 steps) of (-)-**35** as a liquid: $[\alpha]_{\text{D}}^{23} -0.8$ ($c = 1.4$, CHCl_3); IR (NaCl) 2969.8, 2931.3, 1716.3, 1454.7, 1376.9 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 6.55 (bs, 1H), 4.31 – 4.25 (m, 1H), 2.27 – 2.25 (m, 2H), 1.88 (s, 3H), 1.81 – 1.72 (m, 1H), 1.70 – 1.61 (m, 1H), 0.98 (t, $J = 7.4\text{ Hz}$, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 166.1, 138.8, 128.3, 79.2, 29.2, 27.8, 16.9, 9.2; high resolution mass spectrum (Cl^+) m/z 141.0919, $[(\text{M}+\text{H})^+]$, calcd for $\text{C}_8\text{H}_{13}\text{O}_2$ 141.0915].

Hex-5-en-3-yl methacrylate [(-)-32]. To a stirred solution of (-)-**31** (1.5 g, 14.9 mmol) in 20 mL of anhydrous CH_2Cl_2 at 0 °C was slowly added Et_3N (6.3 mL, 44.9 mmol), and a catalytic amount of DMAP (0.3 g, 2.25 mmol). Methacryloyl chloride (3.1 mL, 32.2 mmol) was then added dropwise. After removal of the cooling bath, the mixture was stirred overnight at rt, and then quenched by the addition of saturated aqueous NH_4Cl (20 mL) solution. The aqueous layer was extracted with CH_2Cl_2 . The organic layers were combined, washed with a saturated brine, dried over MgSO_4 , filtered, concentrated and purified by flash chromatography (100:1 hexanes: Et_2O) to provide (-)-**32** (1.4 g, 55% yield) as a liquid: $[\alpha]_{\text{D}}^{23}$ -25.3 ($c = 0.6$, CHCl_3); IR (NaCl) 2969.3, 2935.8, 1717.6, 1638.2, 1453.8, 1380.4, 1319.0, 1296.3, 1171.2 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 6.08 (bs, 1H), 5.79 – 5.73 (m, 1H), 5.51 (bs, 1H), 5.09 – 5.03 (m, 2H), 4.94 – 4.89 (m, 1H), 2.35 (t, $J = 7.1$ Hz, 2H), 1.93 (s, 3H), 1.66 – 1.59 (m, 2H), 0.90 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 167.1, 136.8, 133.8, 124.9, 117.5, 74.8, 38.1, 26.5, 18.3, 9.5; high resolution mass spectrum (Cl^+) m/z 169.1171, $[(\text{M}+\text{H})]^+$, calcd for $\text{C}_{10}\text{H}_{17}\text{O}_2$ 169.1229].

6-Ethyl-5,6-dihydro-3-methylpyran-2-one [(-)-35]. To a solution of (-)-**32** (107 mg, 0.64 mmol) in CH_2Cl_2 (0.05 M) was added the ruthenium complex **33** (27 mg, 0.03 mmol) at rt. The reaction mixture was heated at reflux for 14 h. The reaction mixture was then concentrated and purified directly on a silica gel column, eluting with 10:1 (hexanes/ EtOAc) to give 51 mg (57% yield) of (-)-**35**.

Dibromides (+)-S-4-A and S-4-B. To a solution of (-)-**35** (2.4 g, 17.1 mmol) in 30 mL of CH_2Cl_2 was added Br_2 (2.6 mL, 51.4 mmol) slowly over 10 min at -10 °C (wet ice/acetone bath). After 3 h at -10 °C, the reaction mixture was slowly poured into a beaker containing 30 mL of saturated sodium bisulfite and 30 g of ice with aid of EtOAc with vigorous stirring. The organic layer was separated, washed with brine,

concentrated and chromatographed (15:1 hexanes:Et₂O) to afford **S-4-A** and **S-4-B** (in the ratio of 4 to 1, total 3.2 g, 62% yield): (+)-**S-4-A**. $[\alpha]_{\text{D}}^{23} + 22.0$ (c 0.7, CHCl₃); IR (NaCl) 2973.7, 2935.1, 1739.5, 1442.5, 1380.8, 1284.4 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 4.94 – 4.88 (m, 1H), 4.71 (dd, $J = 2.9, 2.7$ Hz, 1H), 2.99 (ddd, $J = 14.1, 11.5, 2.7$ Hz, 1H), 2.20 (dd, $J = 3.7, 3.7$ Hz, 1H), 2.17 (s, 3H), 1.89-1.73 (m, 2H), 1.05 (t, $J = 7.8$ Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 167.3, 79.8, 54.9, 54.2, 34.4, 29.6, 28.2, 9.0; high resolution mass spectrum (Cl⁺) m/z 298.9280, [(M+H)⁺, calcd for C₈H₁₃O₂Br₂ 298.9282]. **S-4-B** (unstable): ¹H NMR (500 MHz, CDCl₃) δ 4.81-4.76 (m, 1H), 4.69 (dd, $J = 6.3, 4.0$ Hz, 1H), 2.93-2.87 (m, 1H), 2.36 (ddd, $J = 12.5, 8.5, 3.9$ Hz, 1H), 2.15 (s, 3H), 1.89-1.71 (m, 2H), 1.05 (t, $J = 7.4$ Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 166.7, 78.4, 54.9, 51.9, 36.4, 29.7, 29.4, 9.0; high resolution mass spectrum (Cl⁺) m/z 298.9273, [(M+H)⁺, calcd for C₈H₁₃O₂Br₂ 298.9282].

6-Bromo-hept-5-en-3-ol [(-)-36]. To a solution To a flask charged with (+)-**S-4-A** and **S-4-B** (3.0 g, 10.0 mmol) were added 25 mL of DMF/H₂O (4:1) and LiOH monohydrate (1.3 g, 30.0 mmol) at rt. After 16 h, the reaction mixture was directly chromatographed (9:1 → 7:3 pentane/Et₂O) to furnish (-)-**36** (1.3 g, 68% yield) as a liquid: $[\alpha]_{\text{D}}^{23} -1.8$ (c = 1.6, CHCl₃); IR (NaCl) 3371.3, 2963.4, 2926.8, 1649.8, 1597.9, 1458.7, 1428.5, 1380.0 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 5.90 (t, $J = 8.8$ Hz, 1H), 3.58 (bs, 1H), 2.23 (s, 3H), 2.22-2.12 (m, 2H), 1.65 (d, $J = 3.0$ Hz, 1H), 1.56-1.41 (m, 2H), 0.95 (t, $J = 7.4$ Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 128.3, 121.5, 72.3, 37.0, 29.6, 23.4, 9.9; high resolution mass spectrum (Cl⁺) m/z 175.0115, [(M-OH)⁺, calcd for C₇H₁₂Br 175.0122].

3,4-Dibromo-3-methyl-dihydro-furan-2-one (40). Under the conditions similar to those used for (+)-**22**, the bromination of **37** (2.5 g, 25.48 mmol) gave **40** (6.1 g, 93% yield) as a white solid: IR (NaCl) 3023.8,

1785.8, 1446.4, 1376.9, 1180.2 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 4.98 (dd, $J = 11.7, 3.7$ Hz, 1H), 4.84 (d, $J = 3.7$ Hz, 1H), 4.53 (d, $J = 11.1$ Hz, 1H), 2.06 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 171.9, 73.8, 54.3, 52.8, 25.3; high resolution mass spectrum (Cl^+) m/z 256.8817, $[(\text{M}+\text{H})^+]$, calcd for $\text{C}_5\text{H}_7\text{Br}_2\text{O}_2$ 256.8813].

(E)-5-Bromo-but-2-en-1-ol (43). Under the conditions similar to those used for (-)-**23a**, decarboxylative debromination of **40** (5.5 g, 21.3 mmol) gave **43** (1.9 g, 59% yield) as a tan oil, upon direct chromatography (9:1 $\rightarrow$ 7:3 pentane/ Et_2O), with spectral data matching that previously reported.²

3,4-Dibromo-3-methyl-tetrahydro-pyran-2-one (41). Under conditions similar to those used for (+)-**22**, the bromination of **38** (1.0 g, 8.9 mmol) gave **41** (1.58 g, 65% yield) as white solids. IR (NaCl) 2985.1, 1737.4, 1275.9, 1164.2 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 4.88 (ddd, $J = 16.2, 11.9, 4.4$ Hz, 1H), 4.74 (dd, $J = 3.4, 0.9$ Hz, 1H), 4.62 (qt, $J = 6.6, 1.3$ Hz, 1H), 3.32 – 3.25 (m, 1H), 2.17 (s, 3H), 2.17 – 2.13 (m, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 166.9, 67.1, 55.2, 54.4, 29.7, 29.3; high resolution mass spectrum (Cl^+) m/z 270.8965, $[(\text{M}+\text{H})^+]$, calcd for $\text{C}_6\text{H}_9\text{Br}_2\text{O}_2$ 270.8969].

(E)-5-Bromo-but-2-en-1-ol (44). Under the conditions similar to those used for (-)-**23a**, decarboxylative debromination of **41** (1.00 g, 3.49 mmol) gave **44** (0.46 g, 80% yield) as a tan oil, upon direct chromatography (9:1 $\rightarrow$ 7:3 pentane/ Et_2O): IR (NaCl) 3243.7, 2950.3, 1651.9, 1429.1, 1379.3, 1054.4 cm^{-1}

^1H NMR (500 MHz, CDCl_3) δ 5.86 (td, $J = 7.7, 1.1$ Hz, 1H), 3.64 (t, $J = 6.4$ Hz, 2H), 2.28 (td, $J = 7.7, 6.5$ Hz, 2H), 2.24 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 128.2, 121.8, 61.5, 33.0, 23.4; high resolution mass spectrum: decomposition.

3,4-Dibromo-3-methyl-oxepan-2-one (42). Under conditions similar to those used for (+)-**22**, bromination of **39** (0.8 g, 6.34 mmol) gave **42** (1.0 g, 55% yield): IR (NaCl) 2968.4, 2938.5, 1723.0, 1468.8, 1434.9, 1288.2, 1226.5, 1172.8 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 4.97 (t, $J = 12.4$ Hz, 1H), 4.45 (t, $J = 3.4$ Hz, 1H), 4.41 – 4.37 (m, 1H), 2.88 – 2.81 (m, 1H), 2.47 – 2.39 (m, 1H), 2.32 – 2.27 (m, 1H), 2.23 (s, 3H) 1.91 – 1.86 (m, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 167.4, 69.9, 61.0, 56.2, 35.1, 33.8, 24.4; high resolution mass spectrum (Cl^+) m/z 284.9113, $[(\text{M}+\text{H})^+]$, calcd for $\text{C}_7\text{H}_{11}\text{Br}_2\text{O}_2$ 284.9126].

(E)-5-Bromo-hex-4-en-1-ol (45). Under the conditions similar to those used for (+)-**23a**, the hydrolytic fragmentation of **42** (1.00 g, 3.5 mmol) gave **45** (0.39 g, 62% yield) as a tan oil, upon direct chromatography (9:1 $\rightarrow$ 7:3 pentane/ Et_2O), with spectral data matching that previously reported.³

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