Supporting Information

Total Synthesis of (-)-Hortonones A-C from Vitamin D2

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Experimental Section

General Information

Distilled water was used in all of the experiments. Organic extracts were dried over Na_2SO_4, filtered, and concentrated using a rotary evaporator at aspirator pressure (20-30 mm Hg). Chromatography refers to flash chromatography and was carried out on SiO_2 (silica gel 60, 230-400 mesh). ^{1}H and ^{13}C NMR spectra were measured in $CDCl_3$ or acetone-d6 at 400 MHz and 100 MHz, respectively, using Me_4Si as internal standard. Chemical shifts are reported in ppm downfield (δ) from Me_4Si. High-resolution mass spectra (HRMS) were recorded on a micrOTOF-Q mass spectrometer using electrospray ionization (ESI). All optical rotations were recorded on a spectropolarimeter at the D-line of the sodium lamp (589 nm) at 25 °C. UV spectra were recorded on a UV-Vis spectrophotometer from 200-400 nm.

Lythgoe-Inhoffen Diol 4

Ozone was bubbled through a solution of vitamin D_2 (1.0 g, 2.52 mmol) in 1:1 mixture of methanol (40 mL) and DCM (40 mL) at -78 °C for 3 hours. The reaction mixture was then flushed with air for 15 minutes to remove the residual ozone and the solution was treated with $NaBH_4$ (0.75 g, 20 mmol). After 20 minutes, the second portion of $NaBH_4$ (0.75 g, 20 mmol) was added, and the mixture was allowed to warm to room temperature. The third portion of $NaBH_4$ (0.75 g, 20 mmol) was then added, and the reaction mixture was stirred for an additional 20 minutes. The reaction was quenched with water (40 mL), and the solution was concentrated under reduced pressure. The residue was extracted with ethyl acetate (3 × 80 mL), and the combined organic phase was washed with 1M aq. HCl, washed with saturated aq. $NaHCO_3$, dried (Na_2SO_4) and *concentrated in vacuo*. Purification of the residue by flash chromatography (1:1 hexanes:ethyl acetate) gave the diol **4** (213 mg, 1 mmol, 40%). The mixture of residual higher R_f and lower R_f compounds eluted from the column was then dissolved in acetone and t-BuOH (1:1, 10 mL) and treated with OsO_4 (100 μL, 4% solution in water) and *N*-methylmorpholine-*N*-oxide (2.5 mL, 50% solution in H_2O) and stirred for 5 hrs at room temperature. EtOAc (10 mL) was added and the layers were separated; the organic extracts were washed with saturated $NaHCO_3$ (25 mL) and brine (25 mL), dried over anhydrous Na_2SO_4, and *concentrated in vacuo*. The diol intermediates were dissolved in acetone and pH 6.5 phosphate buffer (1:3, 60 mL), and KIO_4 (0.20 g, 1.0 mmol) was added. After 3 hours at room temperature water (5 mL) and CH_2Cl_2 (10 mL) were added and the layers were separated; the organic phase was washed with brine (10 mL) and saturated sodium bicarbonate (10 mL) and concentrated *in vacuo*. The crude intermediate was immediately

dissolved in MeOH (20 mL), treated with $NaBH_4$ (189 mg, 5.0 mmol) and stirred for 10 min. Saturated sodium bicarbonate solution (5 mL) and EtOAc (10 mL) were then added and the layers were separated. The organic phase was dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification of the residue by flash chromatography (2:1 hexanes:ethyl acetate) gave additional **4** (187 mg, 0.88 mmol, 35% yield) as white crystals. **4**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.10 (d, *J*=2.6 Hz, 1H); 3.66 (dd, *J*=3.2, 10.5 Hz, 1H); 3.40 (dd, *J*=6.8, 10.5 Hz, 1H); 2.01 (d, *J*=13.4 Hz, 1H); 1.89-1.82 (m, 3H), 1.62-1.50 (m, 2H); 1.49-1.45 (m, 3H); 1.39-1.32 (m, 4H); 1.24-1.16 (m, 2H); 1.05 (d, *J*=3.3 Hz, 3H); 0.98 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 69.2, 67.8, 52.9, 52.3, 41.8, 40.2, 38.2, 33.5, 26.6, 22.5, 17.4, 16.6, 13.5. HRMS (ESI) calculated for $C_{13}H_{24}NaO_2$ 235.1674, found 235.1652 $(M+Na)^+$. $[\alpha]_D$ +32.7° (c 0.001, $CHCl_3$).

*(1R, 3aR, 7aR)-1-isopropyl-7a-methylhexahydro-1H-inden-4(2H)-one (**5**):* To a stirred solution of diol **4** (1 g, 4.7 mmol), DMAP (50 mg, 0.4 mmol), and Et_3N (1.96 mL, 1.42 g, 14.1 mmol) in anhydrous methylene chloride (25 mL), was added *p*-toluenesulfonyl chloride (1.07 g, 5.6 mmol) at 0 °C. The reaction mixture was stirred at rt for 1 hour. Methylene chloride (60 mL) and saturated $NaHCO_3$ solution (20 mL) was added, the phases were separated. The organic extracts were washed with water, dried (anhydrous Na_2SO_4), and concentrated under reduced pressure.

Lithium aluminum hydride (360 mg, 9.5 mmol) was added to a solution of the crude tosylate (1.72 g, 4.7 mmol) in anhydrous THF (25 mL) at 0 °C. The cooling bath was removed, and the reaction mixture was stirred at room temperature for 5 hours. The excess hydride was quenched by addition of water (0.36 mL), 15% NaOH solution (0.36

mL) and water (1.08 mL). After dilution with ethyl acetate (10 mL), the mixture was filtered through celite and concentrated *in* vacuo. The residue was taken up in dry DCM (20 mL) and to it was added Dess-Martin periodinane (2.12 g, 5.0 mmol). The mixture was stirred at rt for 1 hour. Most of the solvent was removed under reduced pressure and ether (10 mL) was added. The precipitated solids were filtered (Celite) and washed with ether (2 x 15 mL) and the organic extracts were combined and *concentrated in vacuo*. Purification of the residue by flash chromatography (10:1 hexanes:ethyl acetate) gave the **5** (775 mg, 4.0 mmol, 85% yield). **5**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.43 (dd, *J*=7.6, 11.6 Hz, 1H); 2.25-2.19 (m, 2H); 2.10 (d, *J*=1.8 Hz, 1H); 2.07-1.96 (m, 1H); 1.91-1.85 (m, 2H); 1.73-1.70 (m, 1H); 1.60-1.47 (m, 3H); 1.34-1.27 (m, 2H); 0.95 (d, *J*=6.5 Hz, 3H); 0.86 (d, *J*=6.5 Hz, 3H); 0.62 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.1, 61.9, 58.7, 49.9, 40.9, 38.9, 30.7, 27.6, 24.1, 22.9, 22.5, 19.1, 12.6. HRMS (ESI) calculated for $C_{13}H_{22}NaO$ 217.1568, found 217.1546 $(M+Na)^+$. $[\alpha]_D$ -26.9° (c 0.002, $CHCl_3$).

*(1R, 3aS, 7aR)-1-isopropyl-7a-methylhexahydro-1H-inden-4(2H)-one (**6**):* Ketone **5** (100 mg, 0.5 mmol) was dissolved in THF (5 mL) at room temperature. Excess NaH solution (30 mg, 60% in mineral oil, 1.5 eq, in 5 mL THF) was added dropwise. The mixture was refluxed for 4 hours. Then the reaction was allowed to cool to room temperature and was quenched with cold water (10 mL). The residue was extracted with ethyl acetate (3 x 15 mL), and the combined organic phase was washed with NH_4Cl, dried (Na_2SO_4) and *concentrated in vacuo*. Purification of the residue by flash chromatography (10:1 hexanes:ethyl acetate) gave **6** (72 mg, 0.37 mmol, 72%). Some trans isomer **5** was recovered (10 mg). **6**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.35-2.25 (m, 3H); 2.24-2.13 (m,

1H); 1.90-1.78 (m, 3H); 1.75-1.70 (m, 2H); 1.66-1,52 (m, 2H); 1.42-1.28 (m, 1H); 1.24-1.19 (m, 1H); 1.03 (s, 3H); 0.96 (d, *J*=6.5 Hz, 3H); 0.88 (d, *J*=6.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.7, 61.3, 51.8, 48.7, 40.1, 36.2, 29.5, 27.7, 23.1, 22.9, 22.5, 21.2, 20.9. HRMS (ESI) calculated for $C_{13}H_{22}NaO$ 217.1568, found 217.1547 $(M+Na)^+$. $[\alpha]_D$ +25.0° (c 0.001, $CHCl_3$)

*(1R, 3aS, 8aR)-1-isopropyl-8a-methyloctahydroazulen-4(5H)-one (**7**):* To a stirring mixture of ketone **6** (41 mg, 0.21 mmol) and $BF_3{\cdot}Et_2O$ (0.12 mL, 0.84 mmol) under argon in DCM (5 mL), $TMSCHN_2$ (0.15 mL, 0.30 mmol, 2M in hexanes) was added dropwise at -40 °C. The mixture was allowed to stir for 2 hours at this temperature. Then, the bath was removed and mixture was allowed to stir at room temperature until desilylation was complete (as monitored by TLC). The reaction was quenched by the addition of cold water (5 mL) and the residue was extracted with DCM (3×15 mL) and the combined organic phases were washed with saturated aq. $NaHCO_3$ (10 mL), dried (Na_2SO_4), and *concentrated in vacuo*. Purification of the residue by flash chromatography (10:1 hexanes:ethyl acetate) gave ketone **7** (32 mg, 0.16 mmol, 74%) as a 10:1 mixture of regioisomers. **7**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.83 (dd, *J*=6.0, 8.5 Hz, 1H); 2.40-2.35 (m, 2H); 2.01-1.89 (m, 1H); 1.84-1.78 (m, 1H); 1.74-1.68 (m, 2H); 1.66-1.61 (m, 1H); 1.60-1.51 (m, 4H); 1.40-1.35 (m, 1H); 1.16-1.07 (m, 2H); 1.04 (s, 3H); 0.91 (d, *J*=9.4 Hz, 3H), 0.87 (d, *J*=9.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.0, 61.7, 55.6, 46.2, 42.6, 37.6, 27.5, 27.3, 24.3, 23.5, 22.7, 22.5, 22.0, 22.0. HRMS (ESI) calculated for $C_{14}H_{24}NaO$ 231.1725, found 231.1715 $(M+Na)^+$. $[\alpha]_D$ +29.7° (c 0.001, $CHCl_3$)

*(1R, 3aS, 8aR,Z)-1-isopropyl-8a-methyl-1,2,3,3a,8,8a-hexahydroazulen-4(7H)-one (**9**):* Ketone **7** (50 mg, 0.24 mmol) was dissolved in DCM (2 mL) and placed in an ice bath under argon. To this mixture was added triethylamine (0.98 mL, 0.7 mmol) and TBSOTf (0.13 mL, 0.55 mmol) with stirring, and the mixture was allowed to stir for 2 hours. The reaction was then diluted with dichoromethane and washed twice with cold saturated aq. $NaHCO_3$ (2 x 10 ml). The organic phase was dried over anhydrous Na_2SO_4 and *concentrated in vacuo* at ice-bath temperatures to provide a crude residue that was used directly for next reaction.

The crude silyl enol ether was dissolved in acetonitrile (2 mL) and stirred at room temperature. To this solution was added $Pd(OAc)_2$ (27 mg, 0.12 mmol, 50 mol%) and the mixture was allowed to stir overnight at rt. The solution was then filtered over celite and the organic phase was *concentrated in vacuo*. Purification of the residue by flash chromatography (10:1 hexanes:ethyl acetate) gave enone **9** (46 mg, 0.23 mmol, 94%). **9**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.61 (ddd, *J*=3.4, 10.3, 11.3 Hz, 1H); 5.97 (dd, *J*= 2.7, 11.6 Hz, 1H); 2.74 (dd, *J*=3.0, 7.6 Hz, 1H); 2.44-2.38 (m, 2H); 2.01-1.93 (m, 3H); 1.59-1.52 (m, 2H); 1.49-1.35 (m, 2H); 1.24-1.19 (m, 1H); 1.02 (s, 3H); 0.89 (d, *J*=6.7 Hz, 3H); 0.87 (d, *J*=7.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.3, 146.2, 132.3, 65.4, 54.6, 48.0, 40.7, 29.2, 29.1, 27.2, 23.1, 22.9, 22.8, 21.1. HRMS (ESI) calculated for $C_{14}H_{22}NaO$ 229.1568, found 229.1575 $(M+Na)^+$. $[\alpha]_D$ -21.0° (c 0.001, $CHCl_3$)

(1R, 3aS, 8aR,Z)-1-isopropyl-8a-methyl-1,2,3,3a,8,8a-oxidohexahydroazulen-4-yl methanesulfonate (**10**) To a stirring solution of enone **9** (50 mg, 0.24 mmol) in dry DCM (3 mL) at -78 °C was added DIBAL (0.36 mL, 0.36 mmol, 1M in toluene) dropwise. The

mixture was allowed to stir at this temperature for 1 hour. The mixture was quenched with the addition of acetic acid (1 mL) and 1M HCl (1 mL). The layers were separated and the aqueous phase was washed with DCM (3 x 5 mL) and the combined organics were washed with brine (2 x 10 mL), dried over anhydrous Na_2SO_4, and *concentrated in vacuo*. The crude residue was used directly in the next step without further purification.

The crude allylic alcohol was dissolved in dry DCM (2 mL) and solid $NaHCO_3$ (42 mg, 0.5 mmol) was added and the mixture was cooled to 0 °C under argon atmosphere for 10 minutes. To this cooled mixture was added 77% mCPBA (258 mg, 1.15 mmol) in 3 portions every 15 minutes. After 1 hour the bath was removed and the mixture was stirred at rt for an additional 2 hours until starting material had been consumed (as monitored by TLC). Once complete, the mixture was diluted with DCM (5 mL) and quenched with aq $Na_2S_2O_3$ (10 mL). The aqueous phase was extracted with DCM (3 x 5mL). The collected organics were washed with aq $NaHCO_3$ (10 mL) and brine (10 mL) and dried over anhydrous $NaSO_4$. The solvent was removed *in vacuo* and the residue was used directly in the next step without further purification.

The crude epoxide was dissolved in DCM (2 mL) and placed in an ice bath under an argon atmosphere. To this mixture was added dry triethylamine (0.07 mL, 0.48 mmol). After 15 min, dry methanesulfonyl chloride (0.04 mL, 0.48mmol) was added. The mixture was then allowed to stir for 1 h at rt. The reaction was quenched by the addition of cold H_2O (5 mL). The aqueous layer was extracted with DCM (3 × 5 mL). The combined organic layer was dried (anhydrous Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (3:1 hexanes:ethyl acetate) to give

mesylate **10** (57 mg, 0.19 mmol, 78% over three steps) as an inseparable 10:1 mixture of stereoisomers. **10** (major isomer): ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.74 (s, 1H); 3.18-3.12 (m, 2H); 3.10 (s, 3H); 2.19-2.16 (m, 1H); 2.03-1.79 (m, 4H); 1.76-1.68 (m, 1H); 1.49-1.37 (m, 3H); 1.33-1.23 (m, 2H); 1.02 (s, 3H); 0.90 (d, *J*=4.2 Hz, 3H); 0.87 (d, *J*=4.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 83.1, 57.8, 53.9, 53.2, 43.6, 38.3, 33.4, 29.7, 28.5, 27.4, 25.4, 24.2, 24.1, 23.5, 21.2. HRMS (ESI) calculated for $C_{15}H_{26}NaO_4S$ 325.1449, found 325.1437 $(M+Na)^+$.

(-)-Hortonone C: A 3 M solution of sodium naphthalenide was prepared from naphthalene (789 mg, 6 mmol), dry THF (2 mL), and Na (138 mg, 6 mmol, small pieces) at RT. After being stirred overnight, a portion (1.9 mmol, 10 eq) of the resulting deep blue solution was added to a solution of **10** (57 mg, 0.19 mmol) in dry THF (2.5 mL) at -10 °C. The mixture was stirred for 30 min and the reaction was quenched by the careful addition of cold H_2O (5 mL). The aqueous layer was extracted with EtOAc (3 × 10 mL) and the combined organics were dried (anhydrous Na_2SO_4), filtered, and *concentrated in vacuo*. The residue was used directly in the next step without further purification.

The crude allylic alcohol was dissolved in dry DCM (2 mL) and Dess-Martin periodinane (127 mg, 0.30 mmol) was added. The mixture was stirred at rt for 1 hour. Most of the solvent was removed under reduced pressure and ether (5 mL) was added. The precipitated solids were filtered through celite and washed with ether (2 x 15 mL). The filtrate was *concentrated in vacuo* and the residue was purified by flash chromatography (5:1 hexanes:ethyl acetate) to give Hortonone C (34.5 mg, 0.167 mmol, 88% yield over two steps). *Hortonone C*: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.38 (dd, *J*= 4.8, 11.8 Hz, 1H);

5.80 (dt, *J*= 1.9, 11.8 Hz, 1H); 2.61-2.66 (m, 1H); 2.50 (ddd, *J*=1.5, 10.9, 17.4 Hz, 2H); 2.45 (m, 1H); 2.05-1.99 (m, 1H); 1.87 (ddd, *J*=1.8, 7.2, 14.4 Hz, 1H); 1.72-1.66 (m, 1H); 1.64-1.52 (m, 2H); 1.46-1.49 (m, 1H); 1.33-1.36 (m, 1H); 1.02 (s, 3H); 0.95 (d, *J*=6.6 Hz, 3H); 0.90 (d, *J*=6.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.7, 152.9, 132.1, 57.8, 52.3, 49.3, 40.8, 36.4, 31.3, 31.2, 23.9, 23.8, 22.1. HRMS (ESI) calculated for $C_{14}H_{22}NaO$ 229.1568, found 229.1582 $(M+Na)^+$. $[\alpha]_D$ -116.0° (c 0.002, $CHCl_3$). UV ($CHCl_3$) λ_{max} (log ε) 246 (3.17) nm.

(-)-Hortonone A: To a solution of Hortonone C (10 mg, 0.05 mmol) in THF (2 mL) was added MeLi (1.00 M in diethyl ether, 0.10 mL, 0.10 mmol) dropwise at −78 °C. The mixture was stirred at −78 °C until completion of the reaction. The reaction was quenched with a saturated aqueous solution of NH_4Cl and the mixture was extracted with ethyl acetate (3 × 5.0 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and filtered. The organic phase was *concentrated in vacuo*. The crude organics were used directly in next step without any further purification.

A round-bottomed flask was charged with 66 mg of oven-dried, powdered 4Å molecular sieves, PCC (33 mg, 0.15 mmol), and dry CH_2Cl_2 (1 mL) under argon. To this was added a solution of the crude residue from the previous step (~0.05 mmol) in 1 mL of CH_2Cl_2, and the resulting brown mixture was stirred for 1.5 hours at room temperature. The mixture was diluted with ether (10 mL), filtered through celite, and *concentrated in vacuo.* Purification via flash chromatography (10:1 hexanes:ethyl acetate) gave hortonone A (7.5 mg, 0.036 mmol, 71% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.84 (s, 1H); 2.72 (dd, *J*= 2.5, 7.4 Hz, 1H); 2.54 (dd, *J*= 10.9, 17.7 Hz, 1H); 2.24 (dd, *J*=7.3, 18.6

Hz, 1H); 1.91-2.05 (m, 2H); 1.90 (s, 3H); 1.51-1.61 (m, 3H); 1.45-1.49 (m, 1H); 1.34-1.42 (m, 1H); 1.18-1.22 (m, 1H); 1.02 (s, 3H); 0.87 (d, *J*= 6.1 Hz, 3H); 0.85 (d, *J*= 6.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.6, 157.9, 129.0, 64.6, 54.7, 47.7, 40.7, 32.4, 29.5, 26.3, 23.0, 22.9, 22.7, 20.9. HRMS (ESI) calculated for $C_{15}H_{24}NaO$ 243.1725, found 243.1762 $(M+Na)^+$. $[\alpha]_D$ -30.7° (c 0.001, $CHCl_3$). UV ($CHCl_3$) λ_{max} (log ε) 244 (3.11) nm.

(-)-Hortonone B: To a solution of hortonone A (8.0 mg, 0.036 mmol) in dry CH_2Cl_2 (2 mL) was added DIPEA (14 mg, 0.11 mmol) and TBSOTf (19 mg, 0.07 mmol) at -78 ^{0}C. The mixture was stirred at this temperature for 1 hour. The reaction was then quenched by the addition of a saturated aqueous $NaHCO_3$ solution (10 mL) and the residue was extracted with cold pentane (3 x 10mL). The organic phase was dried with anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude residue was used in the next step without any further purification.

To a solution of crude dienol silyl ether in DCM (1 mL) was added NaHCO3 (400 mg, 4.8 mmol) and m-CPBA (77%, 10 mg, 0.05 mmol) at -20 °C. The mixture was stirred for 1 h at the same temperature before it was quenched with saturated $Na_2S_2O_3$ solution (5 mL). The aqueous layer was extracted with EtOAc (10 mL) and the organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography (1:1 hexanes: EtOAc) to afford hortonone B (6 mg, 0.025 mmol, 69% for two steps). ^1H NMR (400 MHz, $CDCl_3$) δ 6.10 (s, 1H); 4.17 (d, *J*=4.4 Hz, 2H); 2.76 (dd, *J*= 1.6, 7.3 Hz, 1H); 2.45 (dd, *J*= 11.3, 18.8 Hz, 1H); 2.23 (dd, *J*= 7.2, 18.2 Hz, 1H); 1.99-2.05 (m, 2H); 1.49-1.60 (m, 3H); 1.40-1.44 (m, 3H); 1.19 (dt, *J*= 8.7, 10.9 Hz,

1H); 1.04 (s, 3H); 0.89 (d, *J*= 5.2 Hz, 3H); 0.87 (d, *J*= 6.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.8, 158.9, 126.3, 66.3, 64.8, 54.7, 48.1, 40.5, 29.5, 29.3, 27.4, 23.0, 22.9, 22.5, 20.9. HRMS (ESI) calculated for $C_{15}H_{24}NaO_2$, 259.1674 found 259.1633 $(M+Na)^+$. $[\alpha]_D$ =-37.5° (c 0.0007, $CHCl_3$). UV ($CHCl_3$) λ_{max} (log ε) 246 (3.41) nm.