## **SUPPORTING INFORMATION**

# Furan Approach to Vitamin D Analogues. Synthesis of the A-Ring of Calcitriol and 1α-Hydroxy-3-deoxyvitamin D<sub>3</sub>.

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**Materials and Methods.** All reactions were carried out under Ar. All glassware was dried in the oven (110 °C) before use. For reactions employing acid-sensitive 3-methylene-2,3-dihydrofuran, the glassware was first washed with aqueous NaOH before drying. IR spectra were obtained on a FT-IR spectrometer. The <sup>1</sup>H and <sup>13</sup>C NMR were recorded at 400 MHz and 100 MHz, respectively. All chemicals shifts in the <sup>1</sup>H NMR are reported in ppm relative to TMS ( $\delta$ =0.00 ppm) or CHCl<sub>3</sub> ( $\delta$ =7.26 ppm) and in the <sup>13</sup>C NMR are reported in ppm relative to CDCl<sub>3</sub> ( $\delta$ =77.16 ppm). Flash chromatography was performed on 60 Å silica gel (40-75 µm). Diethyl ether and THF were purified on alumina using a Sol-Tech solvent purification system or distilled from sodium and benzophenone. Methylene chloride was distilled from CaH<sub>2</sub>. Powdered 4 Å molecular sieves were stored in an oven at 110 °C or dried as described in the text. (*R*)- and (*S*)-BINOL were purchased from commercial sources.

**4-(3-Furyl)butanal (7).**<sup>1,2</sup>



3-Methylene-2,3-dihydrofuran<sup>2,3</sup> (12.2 g of a 3.5:1 mixture of **6**:3-methylfuran, approximately 113 mmol) was dissolved in methylene chloride (100 mL) and freshly distilled acrolein (10.0 mL, 8.36 g, 150 mmol) was added. After refluxing for 44 h, the methylene chloride and excess acrolein were removed at reduced pressure and then the crude product was distilled under vacuum (0.1 mm, 65-70 °C) to give **7** (12.73 g, 82% yield) as an oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  9.75 (t, *J* = 1.4 Hz, 1H), 7.34 (br s, 1H), 7.21 (br s, 1H), 6.25 (br s, 1H), 2.43-2.47 (m, 4H), 1.88 (p, *J* = 7.3 Hz, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  202.3, 143.1, 139.2, 124.0, 110.9, 43.2, 24.1, 22.4.

Ethyl 4-(3-furyl)butanoate (8).<sup>2</sup>



3-Methylene-2,3-dihydrofuran<sup>2,3</sup> (13.3 g of a 3.5:1 mixture of **6** and 3-methylfuran, approximately 123 mmol) and ethyl acrylate (25.0 mL, 23.1 g, 231 mmol) in methylene chloride (25 mL) were refluxed for 44 h. The methylene chloride and excess ethyl acrylate were removed at reduced pressure and then the crude product was distilled under vacuum (0.1 mm, 81-86 °C) to give **8** (16.24 g, 72% yield) as an oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.33 (br s, 1H), 7.21 (br s, 1H), 6.26 (br s, 1H), 4.11 (q, *J* = 7.2 Hz, 2H), 2.45 (t, *J* = 7.5 Hz, 2H), 2.31 (t, *J* = 7.3 Hz, 2H), 1.87 (p, *J* = 7.5 Hz, 2H), 1.24 (t, *J* = 7.1 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  173.5, 142.9, 139.1, 124.1, 110.9, 60.3, 33.6, 25.3, 24.1, 14.2.

3-(*tert*-Butyldimethylsiloxy)propanal (9).<sup>4</sup>



To a solution of 3-(*tert*-butyldimethylsiloxy)propan-1-ol<sup>4</sup> (19.95 g, 105 mmol) dissolved in CH<sub>2</sub>Cl<sub>2</sub> (200 mL) was added 0.04 M TEMPO in CH<sub>2</sub>Cl<sub>2</sub> (4.0 mL, 0.16 mmol, 0.16 mol%) and 0.4 M KBr in water (4.0 mL, 1.6 mol, 1.6 mol%).<sup>4</sup> The reaction mixture was cooled in an ice-water bath and a solution of NaHCO<sub>3</sub> (7.0 g) in bleach (140 mL) was added dropwise over fifteen to twenty min, maintaining the reaction temperature between 10-15 °C. After stirring for 20 min, the reaction mixture was transferred to a separatory funnel, the organic phase separated, and the aqueous was extracted with additional CH<sub>2</sub>Cl<sub>2</sub> (200 mL). The combined cloudy organic phases were washed with brine (200 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and the volatiles were removed on the rotary evaporator. The bath temperature for the rotary evaporator was kept below 35 °C. The crude product was redissolved in petroleum ether (300 mL) and washed with 10% NaHCO<sub>3</sub>/brine (100 mL) and brine (200 mL). After drying over Na<sub>2</sub>SO<sub>4</sub>, the volatiles were removed on the rotary evaporator. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  9.80 (t, *J* = 2.0 Hz, 1H), 3.98 (t, *J* = 6.0 Hz, 2H), 2.59 (dt, *J* = 2.1, 6.0 Hz, 2H), 0.87 (s, 9H), 0.06 (s, 6H).



Ester **8** (12.4 g, 68.0 mmol) was added to KOH (2.0 M in 95% ethanol, 100 mL) and the reaction mixture was heated to reflux for 1.5 hours, allowed to cool, and water (100 mL) was added. The volatiles were removed on the rotary evaporator and more water was added to the reaction mixture to give a total volume of ~200 mL. The aqueous solution was washed with ethyl acetate (200 mL) and then acidified with 1 M hydrochloric acid (200 mL). The aqueous layer was extracted with ethyl acetate (3 x 200 mL). The combined organic extracts were dried over Na<sub>2</sub>SO<sub>4</sub> and the volatiles were removed on the rotary evaporator. The crude product was further purified by flash chromatography (50 g of silica gel; 50% ethyl acetate in hexanes) to give 4-(3-furyl)butanoic acid<sup>5</sup> (9.75 g, 93% yield) as a clear oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  11.76 (br s, 1H), 7.34 (d, *J* = 1.4 Hz, 1H), 7.23 (s, 1H), 6.27 (br s, 1H), 2.48 (t, *J* = 7.5 Hz, 2H), 2.38 (t, *J* = 7.5 Hz, 2H), 1.89 (p, *J* = 7.5 Hz, 2H); <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  180.4, 142.9, 139.1, 123.9, 110.8, 33.4, 24.8, 23.8.

To a solution of 4-(3-furyl)butanoic acid (7.00 g, 45.4 mmol) and DMF (0.5 mL) in methylene chloride (100 mL) was added oxalyl chloride (5.0 mL, 57 mmol) dropwise over 15 min. After stirring for 2 hours at ambient temperature (<sup>1</sup>H NMR analysis of an aliquot at this time indicated a significant amount of the ketone product **14** as well as acid chloride), the reaction mixture was cooled to 0°C and SnCl<sub>4</sub> (5.3 mL, 45 mmol) was added over a 15 min period. The reaction mixture was stirred for an additional 30 min at 0 °C, quenched with water (250 mL), and the aqueous layer was extracted with methylene chloride (250 mL). The organic layer was washed with 5% sodium hydroxide (250 mL), brine (250 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and the volatiles were removed on the rotary evaporator. The crude product was purified by flash chromatography (50 g silica gel; 50% ethyl acetate in hexanes) to give **14** (4.478 g, 72% yield) as a white solid: mp 55-58 °C (lit.<sup>5</sup> 49 °C). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.55 (d,

J = 1.4 Hz, 1H), 6.40 (d, J = 1.5 Hz, 1H), 2.76 (t, J = 6.1 Hz, 2H), 2.56 (t, J = 6.4 Hz, 2H), 2.14 (p, J = 6.3 Hz, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  186.4, 147.8, 147.5, 140.0, 111.6, 38.4, 24.6, 23.0. (7*S*)-4,5,6,7-Tetrahvdro-1-benzofuran-7-ol (13).<sup>5</sup>



Ketone **14** (2.724 g, 20.0 mmol) and RuCl[1*S*,2*S*)-p-TsNCH(C<sub>6</sub>H<sub>5</sub>)CH-(C<sub>6</sub>H<sub>5</sub>)NH<sub>2</sub>]( $\eta^6$ -*p*-cymene)<sup>6</sup> (0.123 g, 0.09 mmol) were dissolved in a 5:2 formic acid:triethylamine azeotropic mixture (17 mL) and stirred for 6 days at 22 °C. Water (170 mL) was added and extracted with ethyl acetate (3 x 170 mL). The organic layer was washed with saturated sodium bicarbonate (50 mL), brine (50 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and the solvent was removed on the rotary evaporator. The crude product was purified by flash chromatography (100 g of silica gel; 25% ethyl acetate in hexanes) to give **13** (2.515 g, 91% yield, 96% ee) as an oil. [ $\alpha$ ]<sup>22</sup><sub>D</sub> -39.0 (*c* 1.0, CH<sub>2</sub>Cl<sub>2</sub>); IR (neat) 3368 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.31 (d, *J* = 1.8 Hz, 1H), 6.20 (d, *J* = 1.9 Hz, 1H), 4.78 (br d, *J* = 3.6 Hz, 1H), 2.50 (dt, *J* = 16.5, 4.8 Hz, 1H), 2.36 (m, 1H), 2.08 (s, 1H), 1.95 (m, 1H), 1.86 (m, 1H), 1.74 (m, 1H), 1.65 (br s, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  151.1, 142.0, 120.2, 110.3, 62.3, 32.5, 22.3, 19.2.

The enantiomeric excess was determined by the use of the chiral shift reagent europium tris[3-heptafluoropropylhydroxymethylene)-(+)-camphorate]. The proton off of C-7 resonates at  $\delta$  8.70 for *ent*-13 and  $\delta$  8.42 for 13 as a broad singlet (0.1 M of 13 with 25 mol% Eu(hfc)<sub>3</sub> in CDCl<sub>3</sub>).

(7*S*)-4,5,6,7-Tetrahydro-1-benzofuran-7-ol (13) by cyclization of 7 (Table 1 in paper, entry 7). (*R*)-6,6'-Dibromo-1,1'-bi-2-naphthol (0.321 g, 0.724 mmol) and Ti(OCH(CH<sub>3</sub>)<sub>2</sub>)<sub>4</sub> (0.103 mL, 0.100 g, 0.362 mmol) were added to 4 Å molecular sieves (0.50 g; dried under vacuum (0.05 mm) at 200 °C for 16 h) in dry ether (100 mL). After refluxing for 1 h, the catalyst solution was cooled in an ice-water bath and aldehyde **7** (0.50 mL, 0.50 g, 3.6 mmol) was added in one portion. After stirring at 0 °C for 0.5 h, the reaction mixture was allowed to warm up to 22 °C over 0.5 h. Saturated NaHCO<sub>3</sub> (1 mL) was added and the reaction mixture was stirred for 1 h. The reaction mixture was filtered through a Celite bed, washing with additional ether. The organic phase was washed with 0.25 M NaOH (50 mL), dried with Na<sub>2</sub>SO<sub>4</sub>, and concentrated on the rotary evaporator. The crude product was purified by flash chromatography (25 g of silica gel; 5% ethyl acetate in hexanes) to give **13** (0.243 g, 49% yield; 61% ee) as an oil.

(7S)-(*tert*-Butyldimethylsiloxy)-4,5,6,7-tetrahydro-1-benzofuran (5c).<sup>5</sup>



Alcohol **13** (2.494 g, 18.1 mmol; 96% ee), *tert*-butyldimethylsilyl chloride (3.54 g, 23.5 mmol), and imidazole (3.074 g, 45.2 mmol) were added to DMF (14 mL) and stirred under an argon atmosphere overnight at 22 °C. Water (100 mL) was added and the aqueous layer was extracted with ethyl ether (3 x 100 mL). The combined organic extracts were washed with brine (100 mL), dried over sodium sulfate, and the solvent was removed on the rotary evaporator. The crude product was purified by flash chromatography (100 g of silica gel; hexane $\rightarrow$ 3% ethyl acetate in hexanes) to give **5c** (3.706 g, 81% yield) as an oil. [ $\alpha$ ]<sup>22</sup><sub>D</sub> -35.5 (*c* 1.2, CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.28 (d, *J* = 1.8 Hz, 1H), 6.17 (d, *J* = 1.8 Hz, 1H), 4.74 (t, *J* = 4.4 Hz, 1H), 2.48 (dt, *J* = 16.1, 4.9 Hz, 1H), 2.33 (m, 1H), 1.80 – 1.97 (m, 3H), 1.69 (m, 1H), 0.91 (s, 9H), 0.14 (s, 3H), 0.09 (s, 3H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  151.6, 141.5, 119.7, 110.3, 63.2, 33.8, 26.0, 22.5, 19.5, 18.5, -4.56, -4.64.

*rac*-7-(*tert*-Butyldimethylsiloxy)-4,5,6,7-tetrahydrobenzo[2,1-b]furan (*rac*-5c)<sup>5</sup> from 7.



Aldehyde **7** (7.50 g, 54.3 mmol) was dissolved in methylene chloride (125 mL), the solution was cooled to 0 °C, and 2,6-lutidine (7.5 mL, 9.9 g. 64 mmol) was added. TBSOTf (13.8 mL, 15.9 g, 60

mmol) was added dropwise over ten min. After stirring for one h at 0 °C, the reaction was quenched with 0.1 M HCl (200 mL). The reaction mixture was transferred to a separatory funnel and the organic phase was separated, washed with 0.1 M NaOH (50 mL), dried over MgSO<sub>4</sub>, and the volatiles were removed on the rotary evaporator. The crude product was purified by flash chromatography (150 g of silica gel, hexanes) to give *rac-5c* (9.74 g, 71% yield) as an oil.

### (7S)-7-(tert-Butyldimethylsiloxy)-7a-hydroxy-5,6,7,7a-tetrahydro-1-benzofuran-2(4H)-one (19c).



To a solution of furan **5c** (2.470, 9.79 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (50 mL) was added NaOAc (2.19 g, 23.2 mmol) followed by 32% peracetic acid (4.50 mL, 21.4 mmol) at 22 °C. The reaction mixture was stirred vigorously for 6.5 h at 22 °C. Water (50 mL) was added to the reaction mixture, the organic phase was separated, and the aqueous was extracted with CH<sub>2</sub>Cl<sub>2</sub> (50 mL). The combined organic extracts were washed with brine (100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and the volatiles were removed on the rotary evaporator. The resulting oil was dissolved in hexane (150mL) and the organic layer was washed with water (50 mL) and brine (50 mL). After removing the solvent on the rotary evaporator, the crude product was purified by flash chromatography (75 g of silica gel; 10% ethyl acetate in hexanes) to give  $\gamma$ -hydroxybutenolide **19c** (2.425 g, 87% yield) as a white solid: mp 77-80 °C. [ $\alpha$ ]<sup>22</sup><sub>D</sub> -22.0 (*c* 1.0, CH<sub>2</sub>Cl<sub>2</sub>); IR (CH<sub>2</sub>Cl<sub>2</sub>) 3499, 1760, 1661 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  5.78 (d, *J* = 1.5 Hz, 1H), 4.50 (br s, 1H), 3.65 (dd, *J* = 5.1, 11.0 Hz, 1H), 2.68 (br d, *J* = 13.5 Hz, 1H), 2.32 (dt, *J* = 4.0, 13.4 Hz, 1H), 1.54–1.99 (m, 3H), 1.27 (m, 1H), 0.92 (s, 9H), 0.17 (s, 3H), 0.12 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  170.6, 166.7, 116.4, 104.4, 76.3, 31.7, 25.8, 25.7, 23.3, 18.2, -4.6, -4.8. Anal. Calcd for C<sub>14</sub>H<sub>24</sub>O<sub>4</sub>Si: C, 59.12; H, 8.50. Found: C, 59.29; H, 8.51.

# (7S,7aR) - 7 - (tert-Butyl dimethyls iloxy) - 7a - [(trimethyls ilyl)methane] - 5,6,7,7a - tetrahydro-1000 - 100

benzofuran-2(4H)-one (21c).



CeCl<sub>3</sub>•7H<sub>2</sub>O (3.96 g, 10.6 mmol) was dried under vacuum (0.1 mm) at 140 °C for two hours. THF (30 mL) was added and the slurry was stirred for 2 h at ambient temperature. After cooling to -78 °C, LiCH<sub>2</sub>Si(CH<sub>3</sub>)<sub>3</sub> (9.0 mL, 9.0 mmol, 1.0 M in pentane) was added dropwise over five minutes and the reaction mixture was stirred at -78 °C for 0.5 h. y-Hydroxybutenolide **19c** (1.00 g, 3.52 mmol) was added in one portion and the reaction mixture was stirred at -78 °C for one h and then at -42 °C for one h. TMEDA (1.15 mL, 0.87 g, 7.6 mmol) was added and the reaction mixture was stirred for 0.25 h. The reaction mixture was poured into saturated ammonium chloride (40 mL) and 2.5 M HCl (20 mL), and the mixture was extracted with  $CH_2Cl_2$  (3 x 50 mL). The combined organic extracts were washed with brine (100 mL), dried over sodium sulfate, and volatiles were removed on the rotary evaporator. The crude product was purified by flash chromatography (50 g of silica gel; 5% ethyl acetate in hexanes) to give the lactone **21c** (0.950 g, 76% yield) as a white solid: mp 49-51 °C.  $[\alpha]^{22}_{D}$  +42.1 (*c* 1.0, CH<sub>2</sub>Cl<sub>2</sub>); IR (CH<sub>2</sub>Cl<sub>2</sub>) 1748, 1650 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  5.67 (d, J = 1.1 Hz, 1H), 4.06 (br s, 1H), 2.67 (m, 1H), 2.22 (m, 1H), 1.66-1.88 (m, 4H), 1.18 (d, J = 15.0 Hz, 1H), 1.08 (d, J = 15.0 Hz, 1H), 0.81 (s, 9H), 0.05 (s, 3H), 0.04 (s, 9H), 0.02 (s, 3H); <sup>13</sup>C (100 MHz, CDCl<sub>3</sub>) δ 173.3, 172.8, 114.2, 89.7, 75.3, 30.0, 26.9, 25.8, 23.6, 21.5, 18.1, 0.1, -4.9, -5.1. Anal. Calcd for C<sub>18</sub>H<sub>34</sub>O<sub>3</sub>Si<sub>2</sub>: C, 60.96; H, 9.66. Found: C, 61.28; H, 9.54.

#### (1R,2S,6Z)-2-(tert-butyldimethylsiloxy)-6-(2-hydroxyethylidene)-1-

[(trimethylsilyl)methane]cyclohexanol (22c).



Lactone 21c (0.757g, 2.13 mmol) was dissolved in toluene (10 mL) and cooled to -78 °C. DIBAL (3.1 mL, 1.5 M in toluene, 4.7 mmol) was added dropwise. The reaction mixture was stirred for 1 h at -78 °C and then allowed to slowly warm to -30 °C. Methanol (0.25 mL) and then 30% sodium potassium tartrate (20 mL) were added to quench the reaction mixture. The reaction mixture was transferred to an Erlenmeyer flask and stirred vigorously with ether (40 mL) for 1 h. The organic phase was separated and the aqueous phase was extracted with ether (2 x 40 mL). The combined extracts were washed with brine (100 mL), dried over sodium sulfate, and concentrated on the rotary evaporator. The crude lactol was dissolved in ethanol (8 mL) and NaBH<sub>4</sub> (0.50 g, 13 mmol) was added. After stirring the reaction mixture at 22 °C for 18 h, water was added (10 mL) and the reaction mixture was heated to reflux for 5 min. The reaction mixture was extracted with ether (3 x 40 mL), the combined organic extracts were washed with brine (50 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated on the rotary evaporator. The crude product was purified by flash chromatography (50 g of silica gel;  $2\% \rightarrow 10\%$  ethyl acetate in hexanes) to give the diol **22c** (0.681 g, 89% yield) as a colorless oil.  $[\alpha]^{22}_{D}$  -2.5 (*c* 1.0, CH<sub>2</sub>Cl<sub>2</sub>); IR (neat) 3548, 3391, 1648 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  5.47 (br t, J = 5.5 Hz, 1H), 4.30 (br dd, J = 5.7, 13.0 Hz, 1H), 4.23 (m, 1H), 3.69 (m, 1H), 3.52 (s, 1H), 2.73 (m, 1H), 2.10 (m, 2H), 1.45-1.80 (m, 4H), 1.17 (d, J = 14.7 Hz, 1H), 1.03 (br d, J = 15.0 Hz, 1H), 0.88 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H), 0.05 (s, 9H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 146.8, 124.4, 79.2, 78.3, 59.5, 36.3, 32.2, 30.2, 26.8, 25.9, 21.5, 18.2, 0.6, -4.2, -4.8. Anal. Calcd for C<sub>18</sub>H<sub>38</sub>O<sub>3</sub>Si<sub>2</sub>: C, 60.25; H, 10.68. Found: C, 60.71; H, 10.62. Diol **22c** is thermally unstable (slow conversion to 4c and other unidentified products) and was stored in the freezer.



To a solution of diol **22c** (0.555 g, 1.55 mmol) in acetonitrile (3 mL) was added a solution of HF in CH<sub>3</sub>CN (prepared by adding 48% HF (0.18 g, 4.3 mmol) to acetonitrile (12 mL)) at 22 °C. After 12 min, the reaction mixture was poured into 5% NaHCO<sub>3</sub> (50 mL). The reaction mixture was transferred to a separatory funnel and extracted with ether (3 x 25 mL). The combined organic extracts were washed with brine (25 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and the volatiles were removed on the rotary evaporator. The crude product was purified by flash chromatography (50 g of silica gel; 2% $\rightarrow$ 10% ethyl acetate in hexanes) to give the dienol **4c** (0.284 g, 68% yield) as a colorless oil. [ $\alpha$ ]<sup>22</sup><sub>D</sub> -44.9 (*c* 1.0, CH<sub>2</sub>Cl<sub>2</sub>); IR (neat) 3326, 1655, 1638cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  5.49 (br t, *J* = 6.6 Hz, 1H), 5.21 (t, *J* = 2.0 Hz, 1H), 4.71 (t, *J* = 1.8 Hz, 1H), 4.20 (m, 2H), 4.05 (m, 1H), 2.18 (m, 2H), 1.89 (m, 2H), 1.53 (m, 2H), 0.90 (s, 9H), 0.06 (s, 6H); <sup>13</sup>C NMR (100 MHz)  $\delta$  148.9, 143.2, 124.3, 109.7, 73.9, 59.8, 37.0, 25.9, 23.8, 18.5, -4.7, -4.8. The enantiomeric excess (>95% ee) was determined by the use of the chiral shift reagent Eu(hfc)<sub>3</sub>. The methylene protons adjacent to the hydroxyl group resonate at  $\delta$  8.15 for **4c** and at  $\delta$  7.96 for (*R*)-**4c** (0.07 M of *rac*-**4c** with 30 mol% Eu(hfc)<sub>3</sub> in CDCl<sub>3</sub>). The diastereotopic methyl groups of the TBS group also were well resolved at higher concentrations of Eu(hfc)<sub>3</sub>.

#### (5S)-5-(tert-butyldimethylsiloxy)-7a-hydroxy-5,6,7,7a-tetrahydro-1-benzofuran-(4H)-one (19b).



To a solution of furan **5b** (3.854 g, 15.3 mmol) in  $CH_2Cl_2$  (100 mL) was added NaOAc (5.17 g, 63.0 mmol) and  $CH_3CO_3H$  (32%; 7.0 mL, 33 mmol) at 22 °C. After the initial exotherm, the reaction mixture was stirred at ambient temperature for 6 h. The reaction mixture was transferred to a separatory funnel

with water (100 mL), separated, and the aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 x 100 mL). The combined CH<sub>2</sub>Cl<sub>2</sub> extracts were washed with brine (100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and the volatiles were removed on the rotary evaporator. The crude product was purified by flash chromatography (100 g of silica gel; 10% $\rightarrow$ 20% ethyl acetate in hexanes) to give the γ-hydroxybutenolide **19b** (3.748 g, 86% yield; 2:1 mixture of diastereomers) as a white solid: mp 104-106 °C. [ $\alpha$ ]<sup>22</sup><sub>D</sub> -51.8 (*c* 1.0, CH<sub>2</sub>Cl<sub>2</sub>); IR (CH<sub>2</sub>Cl<sub>2</sub>) 3559, 1759, 1662 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.77 (br d, *J* = 1.8 Hz, 0.67 H), 5.76 (br d, *J* = 1.8 Hz, 0.33 H), 4.30 (m, 0.67 H), 3.69 (m, 0.33 H), 3.11 (br s, 0.33 H), 3.02 (br s, 0.67 H), 2.90 (ddd, *J* = 1.8, 4.8, 12.2 Hz, 0.33 H), 2.70 (dt, *J* = 13.6, 2.4 Hz, 0.67 H), 2.62 (br dt, *J* = 13.6, 2.6 Hz, 0.67 H), 2.53 (ddd, *J* = 2.1, 10.5, 12.7 Hz, 0.33 H), 2.36 (dt, *J* = 13.9, 3.4 Hz, 0.33 H), 2.21 (br dt, *J* = 13.2, 3.1 Hz, 0.67 H), 2.07 (dt, *J* = 13.2, 4.3 Hz, 0.67 H), 1.5-1.95 (m, 2.33 H), 0.89 (s, 3H), 0.83 (s, 6 H), 0.079 (s, 1H), 0.075 (s, 1H), 0.05 (s, 2 H), 0.03 (s, 2 H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 171.9, 168.1 167.7, 116.1, 115.1, 105.0, 104.5, 71.8, 67.8, 36.8, 35.6, 34.0, 32.7, 31.5, 30.0, 25.8, 25.7, 18.1, 18.0, -4.61, -4.64, -4.8. Anal. Calcd for C<sub>14</sub>H<sub>24</sub>O<sub>4</sub>Si: C, 59.12; H, 8.50. Found: C, 59.17; H, 8.63.

(5*S*)-5-(*tert*-butyldimethylsiloxy)-7a-[(trimethylsilyl)methyl]-5,6,7,7a-tetrahydro-1-benzofuran-(4H)-one (21b).



CeCl<sub>3</sub>•7H<sub>2</sub>O (6.59 g, 17.7 mmol) was dried under vacuum (0.1 mm) at 140 °C for two hours. THF (50 mL) was added, the slurry was stirred for 2 h at 22 °C, and then cooled to -78 °C. LiCH<sub>2</sub>Si(CH<sub>3</sub>)<sub>3</sub> (12.5 mL, 13.8 mmol, 1.1 M in pentane) was added dropwise over five minutes and the reaction mixture was stirred at -78 °C for 0.5 h.  $\gamma$ -Hydroxybutenolide **19b** (1.190 g, 4.18 mmol) was added in one portion and the reaction mixture was stirred at -78 °C for an hour and then at -42 °C for another hour. TMEDA (1.90 mL, 12.7 mmol) was added and the reaction mixture was stirred for 0.25 h at -42 °C. The reaction mixture was poured into saturated ammonium chloride (60 mL) and 2.5 M HCl (30 mL), and the

mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 100 mL). The combined organic extracts were washed with brine (100 mL), dried over sodium sulfate, and volatiles were removed on the rotary evaporator. The crude product was purified by flash chromatography (75 g of silica gel; 5% ethyl acetate in hexanes) to give the lactone **21b** (1.450 g, 98% yield; 2:1 mixture of diastereomers) as a solid: mp 58-65 °C.  $[\alpha]^{22}_{D}$  -5.6 (*c* 1.1, CH<sub>2</sub>Cl<sub>2</sub>); IR (CH<sub>2</sub>Cl<sub>2</sub>) 1745, 1650 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  5.67 (br d, *J* = 1.8 Hz, 0.67 H), 5.65 (br d, *J* = 1.4 Hz, 0.33 H), 4.25 (m, 0.67 H), 3.63 (m, 0.33 H), 2.91 (ddd, *J* = 1.8, 5.1, 12.6 Hz, 0.33 H), 2.71 (dt, *J* = 13.6, 2.5 Hz, 0.67 H), 2.43 (ddd, *J* = 1.8, 3.3, 13.6 Hz, 0.67 H), 2.35 (ddd, *J* = 1.8, 10.5, 12.3 Hz, 0.33 H), 2.21 (dt, *J* = 12.8, 3.4 Hz, 0.33 H), 2.05 (br dt, *J* = 12.4, 3.3 Hz, 0.67 H), 1.50-1.90 (m, 2.67 H), 1.38 (dt, *J* = 3.6, 13.6 Hz, 0.33 H), 1.31 (d, *J* = 15.0 Hz, 0.33 H), 1.25 (d, *J* = 15.0 Hz, 0.67 H), 1.11 (d, *J* = 15.0 Hz, 0.33 H), 1.03 (d, *J* = 15.0 Hz, 0.67 H), 0.89 (s, 3H), 0.82 (s, 6 H), 0.073 (s, 1H), 0.067 (s, 1H), 0.05 (s, 9H), 0.05 (s, 2 H), 0.03 (s, 2 H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  174.0, 173.9, 172.8, 172.6, 114.6, 113.4, 88.7, 88.4, 72.3, 67.8, 37.2, 37.1, 36.0, 35.9, 32.2, 30.7, 25.9, 25.7, 24.0, 23.5, 18.2, 18.0, 0.0, -4.63, -4.65, -4.8. Anal. Calcd for C<sub>18</sub>H<sub>34</sub>O<sub>3</sub>Si<sub>2</sub>: C, 60.96; H, 9.66. Found: C, 60.78; H, 9.78.

(2Z)-2-[(5S)-5-(tert-butyldimethylsiloxy)-2-methylenecyclohexylidene]ethanol (4b).<sup>9</sup>



To a solution of lactone **21b** (0.193 g, 0.544 mmol) in Et<sub>2</sub>O (10 mL) was added LiAlH<sub>4</sub> (0.060 g, 1.6 mmol). The reaction mixture was stirred for 18 h at 22 °C. After cooling in an ice-water bath, the reaction mixture was quenched with water (1 mL). Potassium sodium tartrate (30%, 10 mL) was added and the reaction mixture was stirred vigorously for 1 h at 0°C. The reaction mixture was extracted with Et<sub>2</sub>O (3 x 25 mL), the combined organic phase was washed with brine (50 mL), dried with Na<sub>2</sub>SO<sub>4</sub>, and the volatiles were removed on the rotary evaporator to give crude diol **22b** (0.18 g). Crude diol **22b**, which was unstable on silica gel and decomposed at room temperature, was dissolved in CH<sub>3</sub>CN (5 mL)

and a solution of HF in CH<sub>3</sub>CN (0.35 M; 1.0 mL, 0.35 mmol; a stock solution was prepared by the addition of 48% HF to CH<sub>3</sub>CN) was added. Additional HF in CH<sub>3</sub>CN (0.35 M; 2x1.0 mL, 0.70 mmol) was added after 10 min and 20 min. After stirring for a total of 30 min, hexane (10 mL) and water (3 mL) was added and stirred for 2 min. The hexane layer was decanted and the aqueous acetonitrile layer was extracted with additional hexane (3 x 20 mL). The combined hexane solutions were washed with brine (50 mL), dried with  $Na_2SO_4$ , and the volatiles were removed on the rotary evaporator. The crude product (0.082 g) was purified by flash chromatography (20 g of silica gel; hexanes $\rightarrow$ 5% ethyl acetate in hexanes) to give impure **4b** (0.030 g). Further purification by chromatography on alumina (hexanes $\rightarrow$ 10% ethyl acetate in hexanes) gave **4b** as a colorless oil (0.008 g, 5% yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  5.44 (br t, J = 6.6 Hz, 1 H), 4.96 (br s, 1 H), 4.62 (br s, 1 H), 4.26 (dd, J = 6.2, 12.5 Hz, 1 H), 4.20 (br dd, J = 7.3, 12.5 Hz, 1 H), 3.84 (m, 1 H), 2.40 (m, 2 H), 2.20 (m, 1 H), 2.06 (m, 1 H), 1.86 (m, 1 H), 1.59 (m, 1H), 1.38 (m, 1H), 0.88 (s, 9 H), 0.05 (s, 3 H), 0.04 (s, 3 H); <sup>13</sup>C NMR (100 MHz) § 145.1, 140.7, 125.1, 112.0, 70.1, 60.0, 46.2, 36.2, 32.5, 26.0, 18.3, -4.50, -4.54. Although this procedure was successful in obtaining **4b** in low yields in our initial runs, we were not able to reproduce these substandard yields using the above procedure at a later date, despite numerous attempts and for reasons the investigators could not determine.

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