



Supporting Information

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**Stereoselective Synthesis of 2,4,6-Trisubstituted Tetrahydropyrans  
by Use of Cyclopropanols as Homo-enols**

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**Representative Procedure for Preparing All-*cis*-2,4,6-trisubstituted Tetrahydropyrans:  
(2*S*\*,4*R*\*,6*S*\*)-1-(2-Heptyl-6-isopropyl-tetrahydropyran-4-yl)ethanone (**4b**).**

To a stirred solution of bis(TMS) ether **2** (65mg, 0.24 mmol) and *n*-octanal (**3b**) (57.5 mg, 0.26 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (0.5 mL) was added dropwise at –78 °C TMSOTf (4 μL, 0.024 mmol). After stirring for 10 min at –78 °C, the reaction mixture was allowed to warm slowly to rt over 2 h and then stirred for an additional 2 h. The reaction mixture was quenched with saturated aqueous NaHCO<sub>3</sub> (1 mL). The resulting mixture was diluted with ethyl ether. The organic layer was separated and washed sequentially with saturated aqueous NaHCO<sub>3</sub> and brine, and dried over MgSO<sub>4</sub>. The filtrate was concentrated under reduced pressure and the residue was purified by chromatography on silica gel (2 g, 5% EtOAc–hexanes) to afford **4b** (45 mg, 77%) as a colorless liquid: IR (thin film) 1713 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 3.24 (m, 1H), 2.95 (ddd, *J* = 11.4, 7.3 Hz, 1.6 Hz, 1H), 2.53 (tt, *J* = 12.1, 3.2 Hz, 1H), 2.15 (s, 3H), 1.86–1.74 (m,

2H), 1.65 (hep,  $J = 6.5$  Hz, 1H), 1.57–1.48 (m, 1H), 1.46–1.24 (m, 11H), 1.24–1.14 (m, 2H), 0.95 (d,  $J = 6.5$  Hz, 3H), 0.89 (d,  $J = 6.5$  Hz, 3H), 0.87 (t,  $J = 7.3$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  210.6, 81.9, 76.7, 49.3, 36.3, 33.4, 33.3, 31.8, 30.1, 29.5, 29.3, 27.6, 25.6, 22.6, 18.8, 18.6, 14.1; HRMS calcd for  $\text{C}_{17}\text{H}_{32}\text{O}_2$  ( $\text{M}^+$ ) 268.2402, found 268.2412.

**All-*cis*-1-(2,6-diisopropyl-tetrahydropyran-4-yl)ethanone (4a).**

IR (thin film)  $1712\text{ cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  2.94 (ddd,  $J = 9.7, 7.3, 1.7$  Hz, 2H), 2.51 (tt,  $J = 12.2, 3.2$  Hz, 1H), 2.17 (s, 3H), 1.80 (ddd,  $J = 12.2, 3.2, 1.7$  Hz, 2H), 1.67 (hep,  $J = 6.7$  Hz, 2H), 1.18 (apparent q,  $J = 12.2$  Hz, 2H), 0.94 (d,  $J = 6.7$  Hz, 6H), 0.89 (d,  $J = 6.7$  Hz, 6H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  210.8, 81.7, 49.3, 33.3, 30.2, 27.7, 18.62, 18.58.

**(2*R*\*,4*R*\*,6*S*\*)-1-(6-Isopropyl-2-*E*-propenyl-tetrahydropyran-4-yl)ethanone (4c).**

IR (thin film)  $1712\text{ cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  5.71 (dq,  $J = 15.2, 6.6$  Hz, 1H), 5.51 (dd,  $J = 15.2, 6.1$  Hz, 1H), 3.80 (dd,  $J = 10.6, 6.1$  Hz, 1H), 3.08 (dd,  $J = 11.1, 6.1$  Hz, 1H), 2.56 (tt,  $J = 12.4, 3.8$  Hz, 1H), 2.16 (s, 3H), 1.86–1.70 (m, 3H), 1.69 (d,  $J = 6.6$  Hz, 3H), 1.31 (apparent q,  $J = 12.4$  Hz, 1H), 1.22 (apparent q,  $J = 12.4$  Hz, 1H), 0.95 (d,  $J = 6.9, 3\text{H}$ ), 0.90 (d,  $J = 6.9$  Hz, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  210.3, 131.9, 126.8, 81.6, 77.1, 49.0, 33.6, 33.0, 29.1, 27.7, 18.8, 18.1, 17.8; HRMS calcd for  $\text{C}_{13}\text{H}_{22}\text{O}_2$  ( $\text{M}^+$ ) 210.1620, found 210.1621.

**(2*S*\*,4*S*\*,6*R*\*)-1-(2-Isopropyl-6-phenyl-tetrahydropyran-4-yl)ethanone (4d).**

IR (thin film)  $1710\text{ cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.39–7.31 (m, 4H), 7.29–7.24 (m, 1H), 4.40 (dd,  $J = 11.4, 2.4$  Hz, 1H), 3.27 (ddd,  $J = 11.4, 5.7, 2.4$  Hz, 1H), 2.74 (tt,  $J = 12.2, 3.2$  Hz, 1H), 2.18 (s, 3H), 2.12–2.05 (m, 1H), 1.91–1.79 (m, 2H), 1.49 (apparent q,  $J = 12.2$  Hz, 1H), 1.38 (apparent q,  $J = 12.2$  Hz, 1H), 1.00 (d,  $J = 7.3$  Hz, 3H), 0.98 (d,  $J = 7.3$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  210.0, 142.8, 128.2, 127.3, 125.6, 81.9, 78.4, 49.4, 35.6, 33.1, 29.2, 27.8, 18.5, 18.4; MS (GC/MS)  $m/z$  246 ( $\text{M}^+$ ), 203 (100%), 176, 167, 143, 131, 104, 91.

**(2*R*\*,4*S*\*,6*S*\*)-1-(2-Hept-1'-ynyl)-6-isopropyl-tetrahydropyran-4-yl)ethanone (4e).**

IR (thin film)  $2240, 1713\text{ cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  4.10 (dd,  $J = 11.4, 1.6$  Hz, 1H), 3.02 (ddd,  $J = 11.4, 6.5, 1.6$  Hz, 1H), 2.53 (tt,  $J = 12.2, 4.1$  Hz, 1H), 2.19 (td,  $J = 7.3, 1.6$  Hz, 2H), 2.14 (s, 3H), 2.06–1.98 (m, 1H), 1.83–1.71 (m, 2H), 1.60 (apparent q,  $J = 12.2$  Hz, 1H),

1.54–1.45 (m, 2H), 1.37–1.22 (m, 5H), 0.95 (d,  $J = 6.5$  Hz, 3H), 0.89 (d,  $J = 6.5$  Hz, 3H), 0.89–0.85 (m, 6H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  209.2, 85.5, 82.2, 78.9, 67.6, 48.8, 34.6, 33.0, 31.1, 29.0, 28.3, 27.7, 22.2, 19.0, 18.8, 18.2, 14.0; MS (GC/MS)  $m/z$  264 ( $\text{M}^+$ ), 221 (100%), 203, 177, 161, 151, 135, 126, 107.

**(2*S*\*,4*S*\*,6*R*\*)-1-[2,6-Bis(2-benzyloxyethyl)-tetrahydropyran-4-yl]ethanone (9).**

IR (thin film)  $1709\text{ cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.36–7.25 (m, 10H), 4.49 (s, 4H), 3.65–3.50 (m, 6H), 2.60 (tt,  $J = 12.2, 4.0$  Hz, 1H), 2.14 (s, 3H), 1.87–1.72 (m, 6H), 1.25 (apparent q,  $J = 12.2$  Hz, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  210.0, 138.4, 128.3, 127.6, 127.5, 73.5, 73.0, 66.6, 48.8, 36.4, 33.2, 27.7; HRMS calcd for  $\text{C}_{25}\text{H}_{32}\text{O}_4$  ( $\text{M}^+$ ) 396.2301, found 396.2283.

**(2*S*\*,4*S*\*,6*R*\*)-1-[2-(2-Benzyloxyethyl)-6-vinyl-tetrahydropyran-4-yl]ethanone (10).**

IR (thin film)  $1710\text{ cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.40–7.20 (m, 5H), 5.86 (ddd,  $J = 17.0, 10.5, 5.5$  Hz, 4H), 5.26 (dt,  $J = 17.0, 1.6$  Hz, 6H), 5.13 (dt,  $J = 10.5, 1.6$  Hz, 1H), 4.50 (AB q, 2H), 3.86 (m, 1H), 3.70–3.55 (m, 3H), 2.63 (tt,  $J = 12.2, 4.1$  Hz, 1H), 2.18 (s, 3H), 1.94–1.75 (m, 4H), 1.40–1.22 (m, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  209.7, 138.5, 128.3, 127.6, 127.5, 115.2, 77.0, 73.6, 72.9, 66.5, 48.7, 36.3, 33.0, 32.9, 27.7; HRMS calcd for  $\text{C}_{18}\text{H}_{24}\text{O}_3$  ( $\text{M}^+$ ) 288.1725, found 288.1737.

**(2*S*,4*S*,6*R*)-1-[2-(2-Benzyloxyethyl)-6-(2'*S*-benzyloxy-pent-4'-enyl)tetrahydropyran-4-yl]ethanone (13).**

$[\alpha]_{\text{D}} = +28.3$  ( $c$  0.29,  $\text{CHCl}_3$ ); IR (thin film)  $1710\text{ cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.38–7.22 (m, 10H), 5.85 (ddt,  $J = 17.0, 10.5$  Hz, 7.3 Hz, 1H), 5.10 (d,  $J = 17.0$  Hz, 1H), 5.08 (d,  $J = 10.5$  Hz, 1H), 4.58 (d,  $J = 11.4$  Hz, 1H), 4.48 (s, 2H), 4.45 (d,  $J = 11.4$  Hz, 1H), 3.60–3.40 (m, 5H), 2.51 (tt,  $J = 12.2, 4.1$  Hz, 1H), 2.43–2.30 (m, 2H), 2.16 (s, 3H), 1.96–1.86 (m, 1H), 1.84–1.72 (m, 3H), 1.68–1.56 (m, 2H), 1.32–1.12 (m, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  210.0, 138.7, 138.4, 134.6, 128.4, 128.3, 128.0, 127.9, 127.6, 127.5, 117.3, 74.9, 73.6, 73.5, 73.0, 70.6, 66.6, 48.8, 40.1, 38.1, 36.4, 33.2, 32.9, 27.7; HRMS calcd for  $\text{C}_{28}\text{H}_{36}\text{O}_4$  ( $\text{M}^+$ ) 436.2614, found 436.2619.

**(2*S*,4*S*,6*R*)(2'*R*,4'*S*,6'*S*)-(15).**

$[\alpha]_D = +6.2$  (*c* 0.5, CHCl<sub>3</sub>); IR (thin film) 1709 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.22–7.38 (m, 15H), 4.58–4.40 (m, 6H), 3.91 (m, 1H), 3.68–3.42 (m, 8H), 2.64–2.50 (m, 2H), 2.13 (s, 3H), 2.10 (s, 3H), 1.98–1.58 (m, 12H), 1.32–1.16 (m, 4H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 209.9 (2 C's), 138.7, 138.5, 138.3, 129.5, 128.4, 128.3, 127.9, 127.6, 127.5, 73.5, 73.45, 73.4, 73.3, 73.2, 73.0, 72.9, 71.7, 66.7, 66.6, 48.9, 41.8, 40.9, 36.4, 36.3, 33.6, 33.5, 33.2, 27.7, 27.6 (There are a considerable number of overlapped C's.); MS (ESI) *m/z* 677 (M<sup>+</sup> + Li); 693 (M<sup>+</sup> + Na); 709 (M<sup>+</sup> + K).

**(2*S*,4*S*,6*R*)(2'*R*,4'*S*,6'*S*)-16.**

IR (neat) 1740 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.20–7.38 (m, 15H), 4.94–4.80 (m, 2H), 4.58–4.36 (m, 6H), 3.90–3.80 (m, 1H), 3.64–3.44 (m, 8H), 2.04 (s, 3H), 2.03 (s, 3H), 2.00–1.50 (m, 12H), 1.80–0.92 (m, 4H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 170.4, 170.4, 138.6, 138.5, 138.3, 128.4, 128.4, 128.3, 127.9, 127.6, 127.6, 127.5, 73.0, 72.6, 72.3, 72.3, 72.2, 72.0, 71.8, 71.6, 70.4, 70.4, 66.7, 66.7, 41.6, 40.7, 37.7, 37.6, 37.4, 37.3, 36.2, 29.7, 21.3, 21.3 (There are a considerable number of overlapped C's.).

**(2*S*\*,4*S*\*,6*R*\*)-1-[2,6-Bis(2-hydroxyethyl)-tetrahydropyran-4-yl]ethanone (17).**

IR (neat) 1704 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 3.77 (m, 4H), 3.63 (m, 2H), 2.77 (bs, 2H), 2.63 (tt, *J* = 12.2, 3.7 Hz, 1H), 2.18 (s, 3H), 1.85–1.72 (m, 6H), 1.34 (apparent q, *J* = 12.2 Hz, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 210.0, 75.8, 60.3, 48.5, 38.1, 33.0, 27.7.

**(2*S*,4*S*,6*R*)(2'*R*,4'*S*,6'*S*)(2''*R*,4''*R*,6''*S*)-1-[2-[4-Acetyl-6-(4-acetyl-6-benzyloxymethyl)-tetrahydropyran-2-ylmethyl)-tetrahydropyran-2-ylmethyl]-6-(2-benzyloxyethyl)-tetrahydropyran-4-yl]ethanone (18).**

$[\alpha]_D = +5.2$  (*c* 0.5, CH<sub>2</sub>Cl<sub>2</sub>); IR (neat) 1709 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.22–7.38 (m, 10H), 4.51 (d, *J* = 12.2 Hz, 1H), 4.48 (s, 2H), 4.46 (d, *J* = 12.2 Hz, 1H), 3.62–3.45 (m, 10H), 2.66–2.45 (m, 3H), 2.13 (s, 3H), 2.12 (s, 3H), 2.10 (s, 3H), 1.94–1.72 (m, 10H), 1.62–1.50 (m, 4H), 1.29–1.12 (m, 6H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 210.0, 209.9, 209.8, 138.43, 138.41, 128.4, 127.7, 127.6, 127.5, 73.8, 73.7, 73.6, 73.22, 73.17, 73.1, 73.0, 72.8, 66.8, 66.6, 48.9, 48.8,

43.0, 43.0, 42.31, 42.28, 36.34, 36.28, 33.8, 33.6, 33.3, 33.0, 32.9, 32.5, 27.8, 27.7 (There are a considerable number of overlapped C's.).

**(2*S*\*,4*R*\*,6*R*\*)-1-(2-Heptyl-6-isopropyltetrahydropyran-4-yl)ethanone (21).**

To a stirred solution of **20** (16.6 mg, 0.05 mmol) and octanal (6.5 mg, 0.05 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (0.25 mL) was added TMSOTf (1.0 μL, 0.006 mmol) in one portion at -78 °C. After stirring for 10 min at -78 °C, the reaction mixture was allowed to warm up to 0 °C slowly (over 30 min) and then stirred for an additional 2 h. The reaction mixture was quenched with saturated aqueous NaHCO<sub>3</sub> (1 mL) and diluted with ether. The organic layer was separated and washed sequentially with saturated aqueous NaHCO<sub>3</sub> and brine, and dried over Na<sub>2</sub>SO<sub>4</sub>. After filtration, the filtrate was passed through a short pad of alumina and concentrated under reduced pressure to afford the crude acetal (13.7 mg, 93%) as a colorless liquid. To a cooled (-78 °C) solution of the crude acetal (8.0 mg, 0.03 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (0.05 mL) was added dropwise a TiCl<sub>4</sub> (11.4 mg, 0.06 mmol) solution in CH<sub>2</sub>Cl<sub>2</sub> (0.06 mL). The resulting mixture was stirred for 10 min at -78 °C, allowed to warm up to 0 °C slowly (over 1 h), quenched with saturated brine, and then extracted by ether. The organic layer was passed through a short pad of Na<sub>2</sub>SO<sub>4</sub> and alumina. The filtrate was concentrated under reduced pressure to afford a 10:1 mixture (7.0 mg, 88%) of **21** and **22**. Preparatory TLC gave pure **21**: IR (thin film) 1710 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 3.52–3.38 (m, 2H), 2.64 (tt, *J* = 12.1 Hz, 3.3 Hz, 1H), 2.15 (s, 3H), 2.08 (m, 1H), 1.96–1.89 (m, 1H), 1.78 (br d, *J* = 13.0 Hz, 1H), 1.65 (td, *J* = 13.0, 5.7 Hz, 1H), 1.53–1.20 (m, 13H), 0.97 (d, *J* = 6.5 Hz, 3H), 0.90–0.86 (m, 3H), 0.86 (d, *J* = 6.5 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 210.5, 78.4, 68.7, 44.2, 36.8, 33.4, 31.9, 29.8, 29.4, 27.9, 27.6, 26.5, 25.8, 22.7, 19.8, 19.3, 14.2; MS (GC/MS) *m/z* 268 (M<sup>+</sup>), 225 (100%), 207, 189, 163, 142, 107, 75, 81, 71.