

**Methyl (3*R*)-3-(*tert*-butyldiphenylsilyloxy)-butyrate (5a).** A solution of methyl (*R*)-3-hydroxy-butyrate (**5**, 1.9 g, 16.0 mmol) in 20 mL of anhydrous CH<sub>2</sub>Cl<sub>2</sub> at 0 °C was treated with imidazole (2.2 g, 32.0 mmol) in one portion. After 10 min, *tert*-butyldiphenyl-chlorosilane was added dropwise and the resulting exothermic reaction was allowed to warm to 25 °C for 4 h. The reaction mixture was diluted with Et<sub>2</sub>O (200 mL), and washed successively with 5% aqueous NH<sub>4</sub>Cl (100 mL) and saturated aqueous NaCl (100 mL). The organic layer was dried (MgSO<sub>4</sub>), concentrated under reduced pressure, and purified by flash chromatography (SiO<sub>2</sub>, 6 x 12 cm, 0–5% EtOAc/hexanes gradient) to provide **5a** (5.6 g, 97%) as a colorless oil: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 7.69 (m, 4H), 7.41 (m, 6H), 4.31 (m, 1H), 3.60 (s, 3H), 2.57 (dd, *J* = 7.1, 14.6 Hz, 1H), 2.40 (dd, *J* = 5.7, 14.6 Hz, 1H), 1.12 (d, *J* = 6.1 Hz, 3H), 1.03 (s, 9H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 400 MHz) δ 171.8, 135.8, 135.8, 134.2, 133.8, 129.6, 129.5, 127.5, 127.5, 66.8, 51.4, 44.4, 26.8, 23.6, 19.1; IR (film) ν<sub>max</sub> 2953, 2858, 1742, 1428, 1378, 1303 1194, 1111 cm<sup>-1</sup>; ESIMS *m/z* 379 (M + Na<sup>+</sup>, C<sub>21</sub>H<sub>28</sub>O<sub>3</sub>Si requires 379). (–)-(3*R*)-**5a**: [α]<sub>D</sub><sup>25</sup> –5.1 (*c* 0.67, CH<sub>2</sub>Cl<sub>2</sub>).

**(3*R*)-3-(*tert*-Butyldiphenylsilyloxy)-butan-1-al (6).** A solution of **5a** (5.6 g, 15.7 mmol) in 100 mL of anhydrous toluene at –78 °C was treated dropwise with DIBAL-H (17.3 mL, 17.3 mmol). After 10 min, the reaction was treated successively with MeOH

(1.0 mL) and saturated aqueous  $\text{NH}_4\text{Cl}$  (10.0 mL). The resulting mixture was stirred 1 h at 25 °C followed by addition of  $\text{Et}_2\text{O}$  (200 mL) and after 1 h further stirring addition of  $\text{MgSO}_4$  (3 g). The resulting suspension was filtered through celite and concentrated under reduced pressure to provide **6** (5.0 g, 92%) which was carried on crude as a colorless oil:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  9.77 (t, 1H), 7.69 (m, 4H), 7.44 (m, 6H), 4.34 (m, 1H), 2.50 (m, 2H), 1.18 (d,  $J$  = 6.2 Hz, 3H), 1.04 (s, 9H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  202.0, 135.8, 135.8, 134.0, 133.5, 129.8, 129.7, 127.7, 127.5, 65.6, 52.7, 26.8, 23.8, 19.1; IR (film)  $\nu_{\text{max}}$  2962, 2858, 1728, 1427, 1111, 1024  $\text{cm}^{-1}$ ; ESIMS  $m/z$  349 ( $\text{M} + \text{Na}^+$ ,  $\text{C}_{20}\text{H}_{26}\text{O}_2\text{Si}$  requires 349).

**Ethyl (5*R*)-5-(*tert*-butyldiphenylsilyloxy)-hex-2-enoate (7).** To a stirred suspension of LiCl (0.78 g, 18.4 mmol), triethylphosphonoacetate (3.65 mL, 18.4 mmol) and diisopropylethylamine (2.67 mL, 15.3 mmol) in 80 mL of anhydrous  $\text{CH}_3\text{CN}$  at 25 °C was added a solution of **6** (5.0 g, 15.3 mmol) in anhydrous  $\text{CH}_3\text{CN}$ . After 12 h, the reaction mixture was diluted with  $\text{Et}_2\text{O}$  (200 mL), and washed successively with  $\text{H}_2\text{O}$  (200 mL) and saturated aqueous NaCl (200 mL). The organic layer was dried ( $\text{MgSO}_4$ ), and concentrated under reduced pressure. Flash chromatography ( $\text{SiO}_2$ , 6 x 12 cm, 4% EtOAc/hexanes) provided **7** (5.8 g, 95%) as a colorless oil:  $\delta$  7.70 (m, 4H), 7.43 (m, 6H), 6.94 (dt,  $J$  = 15.3, 7.5 Hz, 1H), 5.78 (d,  $J$  = 15.3 Hz, 1H), 4.19 (q,  $J$  = 7.0 Hz, 2H), 3.98

(m, 1H), 2.33 (m, 2H), 1.30 (t,  $J = 7.0$  Hz, 3H), 1.11 (d,  $J = 7.5$  Hz, 3H), 1.06 (s, 9H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  166.4, 145.5, 135.8, 135.8, 134.3, 133.9, 129.6, 129.6, 127.6, 127.5, 123.4, 68.5, 60.1, 42.1, 26.9, 23.2, 19.2, 14.2; IR (film)  $\nu_{\text{max}}$  2964, 1722, 1654, 1427, 1265, 1176, 1111  $\text{cm}^{-1}$ ; ESIMS  $m/z$  419 ( $\text{M} + \text{Na}^+$ ,  $\text{C}_{24}\text{H}_{32}\text{O}_3\text{Si}$  requires 419). (+)-**(5R)-7**:  $[\alpha]_{\text{D}}^{25} +31$  ( $c$  0.71,  $\text{CH}_2\text{Cl}_2$ ).

**(5R)-5-(tert-Butyldiphenylsilyloxy)-hex-2-en-1-ol (8)**. A solution of **7** (5.6 g, 14.1 mmol) in 100 mL of anhydrous  $\text{CH}_2\text{Cl}_2$  at  $-20$  °C was treated dropwise with DIBAL-H (30.0 mL, 30.0 mmol). After 2 h, the reaction was warmed to  $0$  °C for 1 h and then for 2 h at  $25$  °C. The reaction was then treated with saturated aqueous  $\text{NH}_4\text{Cl}$  (10.0 mL) and stirred 1 h at  $25$  °C. The resulting mixture was then diluted with  $\text{Et}_2\text{O}$  (200 mL) and stirred 1 h at  $25$  °C followed by addition of  $\text{MgSO}_4$  (3 g). The resulting suspension was filtered through celite and concentrated under reduced pressure. Flash chromatography ( $\text{SiO}_2$ , 6 x 12 cm, 0–30%  $\text{EtOAc}$ /hexanes) provided **8** (4.8 g, 96%) as a colorless oil:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  7.69 (m, 4H), 7.42 (m, 6H), 5.57 (m, 2H), 4.01 (d,  $J = 4.1$  Hz, 2H), 3.90 (m, 1H), 2.18 (m, 2H), 1.09 (d,  $J = 6.0$  Hz, 3H), 1.06 (s, 9H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  135.8, 135.8, 134.7, 134.6, 131.3, 129.4, 129.3, 127.5, 127.4, 69.2, 63.6, 42.2, 26.9, 23.2, 19.2; IR (film)  $\nu$  3333, 2857, 1428, 1111, 997

cm<sup>-1</sup>; ESIMS  $m/z$  377 (M + Na<sup>+</sup>, C<sub>22</sub>H<sub>30</sub>O<sub>2</sub>Si requires 377). (+)-(5*R*)-**8**: [α]<sub>D</sub><sup>25</sup> +20 (*c* 0.71, CH<sub>2</sub>Cl<sub>2</sub>).

**(2*R*, 3*R*, 5*R*)-5-(*tert*-Butyldiphenylsilyl)-2,3-(oxiranyl)-hexan-1-ol (9).** To a suspension of flame dried 5Å molecular sieves in 20 mL of anhydrous CH<sub>2</sub>Cl<sub>2</sub> at –30 °C was added in sequential fashion: (D)-(-)-diethyl tartrate (116 µL, 0.67 mmol), Ti(O*i*Pr)<sub>4</sub> (168 µL, 0.56 mmol) and *tert*-butylhydroperoxide (2.5 mL, 3.4 M solution, 8.5 mmol). The reaction mixture was stirred at –30 °C for 30 min before the addition of **8** (2.0 g, 5.6 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (3.0 mL). The reaction was then stored in a –30 °C freezer for 12 h without the need for stirring. The reaction was then warmed to –20 °C and quenched by the addition of 10% NaOH/saturated aqueous NaCl (2.0 mL). Upon further warming to –10 °C, the reaction was diluted with Et<sub>2</sub>O (50 mL), treated with MgSO<sub>4</sub> (2.0 g) and celite (500 mg) and stirred an addition 15 min. The reaction was allowed to stand and settle for 1 h before filtration through celite using Et<sub>2</sub>O. Concentration of the solvents under reduced pressure, followed by flash chromatography (SiO<sub>2</sub>, 6 x 8 cm, 30% EtOAc/hexanes) afforded **9** (1.9 g, 90%) as a colorless oil: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 7.71 (m, 4H), 7.43 (m, 6H), 4.07 (m, 1H), 3.85 (ddd, *J* = 12.6, 5.7, 2.6 Hz, 1H), 3.55 (ddd, *J* = 12.6, 7.2, 4.5 Hz, 1H), 3.08 (dt, *J* = 5.9, 2.3 Hz, 1H), 2.84 (m, 1H), 1.81 (m, 2H), 1.74 (dt, *J* = 13.9, 5.8 Hz, 1H), 1.17 (d, *J* = 6.2 Hz, 3H), 1.07 (s, 9H); <sup>13</sup>C NMR

(CDCl<sub>3</sub>, 400 MHz)  $\delta$  135.8, 135.8, 134.3, 134.0, 129.6, 129.6, 127.6, 127.5, 67.4, 61.6, 58.1, 52.9, 41.1, 26.9, 23.2, 19.1; IR (film) 3446, 2931, 2857, 1472, 1427, 1111 cm<sup>-1</sup>; ESIMS  $m/z$  393 (M + Na<sup>+</sup>, C<sub>22</sub>H<sub>30</sub>O<sub>3</sub>Si requires 393). (+)-(2*R*, 3*R*, 5*R*)-**9**: [ $\alpha$ ]<sub>D</sub><sup>25</sup> +23 (*c* 0.8, CH<sub>2</sub>Cl<sub>2</sub>).

**(2*R*, 3*R*, 5*R*)-5-(*tert*-Butyldiphenylsilyl)-2,3-(oxiranyl)-hexan-1-al (9a).** A solution of **9** (1.8 g, 4.9 mmol) and Et<sub>3</sub>N (3.4 mL, 24 mmol) in 50 mL of 4:1 CH<sub>2</sub>Cl<sub>2</sub>/DMSO at 0 °C was treated with SO<sub>3</sub>•pyridine (2.9 g, 17 mmol) and stirred 30 min at 25 °C. The reaction was diluted with EtOAc (200 mL), washed sequentially with H<sub>2</sub>O (3 x 50 mL), saturated aqueous NaHCO<sub>3</sub> (50 mL), and saturated aqueous NaCl (50 mL) and dried (MgSO<sub>4</sub>). Evaporation of the solvents under reduced pressure directly provided pure **9a** (1.6 g, 90%) as a colorless oil: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$  8.96 (d, *J* = 6.3 Hz, 1H), 7.68 (m, 4H), 7.45 (m, 6H), 4.09 (m, 1H), 3.39 (dt, *J* = 6.6, 1.9 Hz, 1H), 3.06 (dd, *J* = 6.3, 1.9 Hz, 1H), 1.75 (m, 2H), 1.19 (d, *J* = 6.2 Hz, 3H), 1.08 (s, 9H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$  198.2, 135.8, 135.7, 134.0, 133.7, 129.8, 129.7, 127.7, 127.6, 67.2, 58.6, 53.9, 40.6, 26.9, 23.2, 19.1; IR (film) 2931, 1733, 1472, 1111 cm<sup>-1</sup>; ESIMS  $m/z$  391 (M + Na<sup>+</sup>, C<sub>22</sub>H<sub>28</sub>O<sub>3</sub>Si requires 391). (-)-(2*R*, 3*R*, 5*R*)-**9a**: [ $\alpha$ ]<sub>D</sub><sup>25</sup> -15 (*c* 0.54, CH<sub>2</sub>Cl<sub>2</sub>).

**(3*R* , 4*R* , 6*R* )-6-(*tert*-Butyldiphenylsilyl)-3,4-(oxiranyl)-hept-1-ene (10).**

Methyltriphenylphosphonium bromide (1.93 g, 5.42 mmol) and a stir bar were added to a flask and thoroughly flame dried. Anhydrous THF (30 mL) was added via cannula under Ar and the resulting suspension was cooled to 0 °C prior to the addition of NaHMDS (5.13 mL, 5.13 mmol, 1.0 M in THF) in dropwise fashion. The resulting gold suspension was warmed to 25 °C for 30 min and then recooled to –10 °C prior to the addition of **9a** (1.05 g, 2.85 mmol) in anhydrous THF (5.0 mL). The reaction was complete within 10 min, and was quenched by the addition of saturated aqueous NH<sub>4</sub>Cl (50 mL). The mixture was then extracted with Et<sub>2</sub>O (100 mL), washed sequentially with H<sub>2</sub>O (50 mL) and saturated aqueous NaCl (50 mL) and dried (MgSO<sub>4</sub>). Removal of the solvents under reduced pressure followed by flash chromatography (SiO<sub>2</sub>, 6 x 6 cm, 5% EtOAc/hexanes) provided **10** (0.85 g, 82%) as a colorless oil: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 7.69 (m, 4H), 7.45 (m, 6H), 5.58 (ddd, *J* = 17.3, 9.9, 7.4 Hz, 1H), 5.45 (dd, *J* = 17.3, 1.6 Hz, 1H), 5.28 (dd, *J* = 9.9, 1.6 Hz, 1H), 4.09 (m, 1H), 3.06 (dd, *J* = 7.4, 2.1 Hz, 1H), 3.00 (dt, *J* = 5.8, 2.1 Hz, 1H), 1.82 (dt, *J* = 13.9, 5.8 Hz, 1H), 1.66 (dt, 3.9, 5.8 Hz, 1H), 1.18 (d, *J* = 6.2 Hz, 3H), 1.08 (s, 9H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 400 MHz) δ 135.8, 135.8, 134.4, 134.0, 129.6, 129.5, 127.6, 127.5, 119.1, 67.5, 58.5, 57.3, 41.5, 26.9, 23.2, 19.2; IR (film) 2963, 2857, 1472, 1379, 1111 cm<sup>-1</sup>; ESIMS *m/z* 389 (M + Na<sup>+</sup>, C<sub>23</sub>H<sub>30</sub>O<sub>2</sub>Si requires 389). (+)-(3*R*, 4*R*, 6*R*)-**10**: [α]<sub>D</sub><sup>25</sup> +15 (*c* 0.67, CH<sub>2</sub>Cl<sub>2</sub>).

**(3*R*, 4*R*, 6*R*)-6-(Hydroxy)-3,4-(oxiranyl)-hept-1-ene (3).** To a solution of **10** (0.78 g, 2.13 mmol) in 20 mL of anhydrous THF at 25 °C was treated with *n*Bu<sub>4</sub>NF (2.55 mL, 1.0 M solution in THF, 2.55 mmol) and stirred 4 h. The reaction was concentrated under reduced pressure, and directly loaded onto the column. Flash chromatography (SiO<sub>2</sub>, 3 x 8 cm, 0–50% EtOAc/hexanes gradient) provided **3** (0.243 g, 89%) as a colorless and volatile oil: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 5.36 (ddd, *J* = 17.0, 7.2, 3.0 Hz, 1H), 5.26 (dd, *J* = 17.0, 1.8 Hz, 1H), 5.07 (dd, *J* = 9.8, 1.8 Hz), 3.87 (m, 1H), 2.92 (dd, *J* = 7.2, 2.2 Hz, 1H), 2.77 (m, 1H), 2.0 (br s, 1H), 1.64 (dt, *J* = 14.2, 4.4 Hz, 1H), 1.39 (dt, *J* = 14.2, 7.6 Hz, 1H), 1.08 (d, *J* = 6.2 Hz, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 400 MHz) δ 135.2, 119.6, 66.4, 58.3, 58.2, 40.8, 23.4; IR (film) 3403, 2966, 1428, 1113 cm<sup>-1</sup>; ESIMS *m/z* 151 (M + Na<sup>+</sup>, C<sub>7</sub>H<sub>12</sub>O<sub>2</sub> requires 151). (+)-(3*R*, 4*R*, 6*R*)-**3**: [α]<sub>D</sub><sup>25</sup> +18 (*c* 0.38, CH<sub>2</sub>Cl<sub>2</sub>).

**(*E,E*)-2-(1,3-Pentadien-1-yl)-1,3-dithiane (4).** To a stirred solution of 1,3 propanedithiol (**11**, 5.0 mL, 50.0 mmol), MgClO<sub>4</sub> (0.6 g, 2.5 mmol) and H<sub>2</sub>SO<sub>4</sub> (20 μL) in anhydrous CHCl<sub>3</sub> (80 mL) at –10 °C was added hexadienal (5.5 mL, 50.0 mmol) in anhydrous CHCl<sub>3</sub> (20 mL) in dropwise fashion via cannula. The reaction stirred at 25 °C for 2 h before being poured into cold 10% KOH (100 mL) followed by stirring for 15 min. The organic layer was separated, washed sequentially with 10% KOH (50 mL), H<sub>2</sub>O

(50 mL), dried (MgSO<sub>4</sub>) and filtered through celite. Concentration under reduced pressure was followed by flash chromatography (SiO<sub>2</sub>, 6 x 12 cm, 4% EtOAc/hexanes) to provide **4** (6.4 g, 67%) as a slightly yellow oil (9:1 *E:Z*): <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 6.33 (dd, *J* = 15.1, 10.4 Hz, 1H), 6.01 (ddd, *J* = 15.1, 10.4, 1.3 Hz, 1H), 5.74 (dq, *J* = 15.1, 6.6 Hz, 1H), 5.59 (dd, *J* = 15.1, 7.8 Hz, 1H), 4.64 (d, *J* = 7.8 Hz, 1H), 2.85 (m, 4H), 2.07 (m, 1H), 1.83 (m, 1H), 1.74 (d, *J* = 6.6 Hz, 3H), 1.06 (s, 9H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 400 MHz) δ 134.2, 131.9, 130.7, 126.9, 47.9, 30.7, 25.6, 18.6; IR (film) ν<sub>max</sub> 3018, 2899, 1421, 1274, 986 cm<sup>-1</sup>; ESIMS *m/z* 209 (M + Na<sup>+</sup>, C<sub>9</sub>H<sub>14</sub>S<sub>2</sub> requires 209). *Z* isomer: <sup>1</sup>H NMR δ 6.67 (dd, *J* = 15.1, 11.0 Hz, 1H), 4.70 (d, 7.8 Hz, 1H).

**2-(Chloromethyl)-4,6-dimethoxy-benzaldehyde (13).** POCl<sub>3</sub> (11.1 mL, 119.0 mmol) was dropped slowly via cannula into anhydrous DMF (17.0 mL) at 0 °C, and the resulting solution was stirred at 25 °C for 20 min. A solution of 3,5-dimethoxybenzylalcohol (**12**, 5.0 g, 29.0 mmol) in anhydrous DMF (3.0 mL) was added slowly and the reaction was warmed to 75 °C for 2 h. The reaction was allowed to cool to 25 °C and poured into ice water (250 mL). The mixture was neutralized with 2N NaOH to pH = 7 and stirred 1.5 h at 25 °C. The resulting precipitate was filtered, washed thoroughly with H<sub>2</sub>O (5 x 50 mL) and dried under vacuum to give pure **13** (6.0 g, 93%): <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 10.46 (s, 1H), 6.75 (d, *J* = 2.1 Hz, 1H), 6.44 (d, *J* = 2.1 Hz, 1H), 5.10 (s,



2H), 3.91 (s, 3H), 3.91 (s, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  189.9, 165.2, 165.0, 142.3, 115.9, 107.5, 97.6, 56.0, 55.6, 44.8; IR (film)  $\nu_{\text{max}}$  2980, 2884, 1670, 1597, 1327, 1204, 1150  $\text{cm}^{-1}$ ; ESIMS  $m/z$  237 ( $\text{M} + \text{Na}^+$ ,  $\text{C}_{10}\text{H}_{11}\text{O}_3\text{Cl}$  requires 237).

**2-(Chloromethyl)-4,6-dimethoxy-benzoic acid (2).** Aldehyde **13** (0.75 g, 3.4 mmol) and sulfamic acid (1.13 g, 11.7 mmol) in 21 mL  $\text{H}_2\text{O}$ :THF:DMSO (20:10:1) at 0  $^\circ\text{C}$  was treated with  $\text{NaClO}_2$  (1.25 g, 11.0 mmol) in 3 mL  $\text{H}_2\text{O}$ . The reaction was stirred 20 min at 0  $^\circ\text{C}$ . The reaction was diluted with EtOAc (100 mL), washed with saturated aqueous  $\text{NH}_4\text{Cl}$  (2 x 50 mL) and saturated aqueous NaCl, and dried ( $\text{Na}_2\text{SO}_4$ ). Evaporation of the solvents gave a 7:1 mixture of **2**:chloro-**2**. This material was carried onto the next step crude as only the desired acid **2** proceeded to esterify. For **2**:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  6.84 (d,  $J = 2.2$  Hz, 1H), 6.52 (d,  $J = 2.2$  Hz, 1H), 5.02 (s, 2H), 3.99 (s, 3H), 3.90 (s, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  167.1, 163.0, 159.8, 142.9, 110.8, 108.4, 98.7, 56.8, 55.7, 45.2; IR (film)  $\nu_{\text{max}}$  3000 (br), 2896, 1691, 1333, 1288  $\text{cm}^{-1}$ ; ESIMS  $m/z$  253 ( $\text{M} + \text{Na}^+$ ,  $\text{C}_{10}\text{H}_{11}\text{O}_4\text{Cl}$  requires 253).

**Benzoic ester (14).** To a suspension of **2** (0.53 g, 2.3 mmol) in 10 mL of anhydrous  $\text{CH}_2\text{Cl}_2$  and catalytic DMF (10  $\mu\text{L}$ ) at 0  $^\circ\text{C}$  was added oxalyl chloride (1.13 mL, 2.0 M solution in  $\text{CH}_2\text{Cl}_2$ , 2.3 mmol). The suspension became a gold solution over 1

h stirring at 25 °C. The reaction was then recooled to 0 °C, and treated sequentially with Et<sub>3</sub>N (0.73 mL, 5.2 mmol) and **3** (0.225 g, 1.75 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (3 mL), and DMAP (catalytic). The reaction was allowed to stir 12 h at 25 °C. The reaction was then diluted with CH<sub>2</sub>Cl<sub>2</sub> (50 mL), washed saturated aqueous NH<sub>4</sub>Cl (50 mL) and dried (MgSO<sub>4</sub>). Evaporation of the solvents under reduced pressure followed by flash chromatography (SiO<sub>2</sub>, 3 x 6 cm, 0–30% EtOAc/hexanes gradient) yielded **14** (0.47 g, 80%) as a colorless oil: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 6.53 (d, *J* = 2.2 Hz, 1H), 6.43 (d, *J* = 2.2 Hz, 1H), 5.56 (ddd, *J* = 17.3, 10.2, 6.2 Hz, 1H), 5.46 (dd, *J* = 17.3, 1.6 Hz, 1H), 5.36 (m, 1H), 5.26 (dd, *J* = 10.2, 1.6 Hz, 1H), 4.63 (d, *J* = 11.6 Hz, 1H), 4.58 (d, *J* = 11.6 Hz, 1H), 3.82 (s, 3H), 3.79 (s, 3H), 3.15 (dd, *J* = 7.3, 2.0 Hz, 1H), 3.04 (dt, *J* = 5.7, 2.0 Hz, 1H), 2.01 (dt, *J* = 14.4, 6.3 Hz, 1H), 1.89 (dt, *J* = 14.4, 6.3 Hz, 1H), 1.42 (d, *J* = 6.4 Hz, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 400 MHz) δ 166.9, 162.1, 159.0, 138.1, 135.8, 119.7, 116.5, 106.7, 99.3, 70.1, 58.5, 57.4, 56.4, 56.0, 44.0, 38.5, 20.3; IR (film) ν<sub>max</sub> 2978, 1717, 1615, 1456, 1338, 1270, 1164, 1100, 1046 cm<sup>-1</sup>; ESIMS *m/z* 363 (M + Na<sup>+</sup>, C<sub>17</sub>H<sub>21</sub>O<sub>5</sub>Cl requires 363). (–)-(R, R, R)-**14**: [α]<sub>D</sub><sup>25</sup> –7.6 (*c* 0.45, CH<sub>2</sub>Cl<sub>2</sub>).

**Dithiane adduct (16).** The dithiane **4** (0.100 g, 0.54 mmol) was charged to a flame dried flask equipped with a stir bar under Ar pressure. Anhydrous THF (4.0 mL) was added via cannula and the resulting solution was cooled to –30 °C. *n*BuLi (0.22 mL,

2.5 M solution in hexanes, 0.54 mmol) was added dropwise and the resulting dark green reaction was stirred at  $-30\text{ }^{\circ}\text{C}$  for 1 h. The solution was cooled to  $-78\text{ }^{\circ}\text{C}$  and was cannulated *into* a solution of **14** (0.092 mg, 0.27 mmol) in anhydrous THF (4.0 mL) at  $-78\text{ }^{\circ}\text{C}$ . The resulting purple reaction was stirred 90 min at  $-78\text{ }^{\circ}\text{C}$  before it was stored overnight in a  $-78\text{ }^{\circ}\text{C}$  freezer. The reaction was then quenched by the addition of 1 N HCl (5 mL). The mixture was extracted with  $\text{CH}_2\text{Cl}_2$  (15 mL) and dried ( $\text{Na}_2\text{SO}_4$ ). Evaporation of the solvents under reduced pressure followed by flash chromatography ( $\text{SiO}_2$ , 3 x 6 cm, 20% EtOAc/hexanes) afforded a 4:1 mixture of  $\alpha$  (**15**): $\gamma$  (**15a**) alkylation products. This mixture was easily separated by HPLC (Dynamax 60 Å,  $\text{SiO}_2$ , 25 x 100 mm, 20 mL/min, 12% EtOAc/hexanes, 50 mg injections) to afford pure **15** (80 mg, 60%) as a colorless oil:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  6.54 (d,  $J = 2.2\text{ Hz}$ , 1H), 6.36 (d,  $J = 2.2\text{ Hz}$ , 1H), 6.31 (dd,  $J = 14.5, 4.0\text{ Hz}$ , 1H), 6.14 (ddd,  $J = 15.0, 10.7, 1.4\text{ Hz}$ , 1H), 5.71 (dq,  $J = 13.6, 6.7\text{ Hz}$ , 1H), 5.59 (ddd,  $J = 17.4, 10.2, 7.3\text{ Hz}$ , 1H), 5.52 (d,  $J = 5.5\text{ Hz}$ , 1H), 5.46 (dd,  $J = 17.4, 1.4\text{ Hz}$ , 1H), 5.31 (m, 1H), 5.26 (dd,  $J = 10.1, 1.5\text{ Hz}$ , 1H), 3.77 (s, 3H), 3.76 (s, 3H), 3.27 (s, 2H), 3.15 (dd,  $J = 7.3, 2.0\text{ Hz}$ , 1H), 3.07 (dt,  $J = 5.7, 2.0\text{ Hz}$ , 1H), 2.88 (m, 2H), 2.64 (m, 2H), 2.03 (dt,  $J = 14.4, 6.3\text{ Hz}$ , 1H), 1.98 (m, 1H), 1.87 (dt,  $J = 14.4, 6.3\text{ Hz}$ , 1H), 1.85 (m, 1H) 1.77 (d,  $J = 6.7\text{ Hz}$ , 3H), 1.44 (d,  $J = 6.3\text{ Hz}$ , 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  167.0, 160.3, 158.0, 135.5, 135.3, 134.3, 132.9, 130.6, 130.2, 119.2, 118.0, 108.1, 97.8, 69.3, 58.2, 57.0, 55.7, 55.3, 55.1, 45.0, 38.0, 27.3, 25.0, 19.8,

18.2; IR (film)  $\nu_{\max}$  2936, 1716, 1605, 1455, 1276, 1161, 1095  $\text{cm}^{-1}$ ; ESIMS  $m/z$  513 ( $\text{M} + \text{Na}^+$ ,  $\text{C}_{26}\text{H}_{34}\text{O}_5\text{S}_2$  requires 513). (–)-(R, R, R)-**15**:  $[\alpha]_{\text{D}}^{25} -5.5$  ( $c$  1.0,  $\text{CH}_2\text{Cl}_2$ ).

**$\gamma$ -adduct (15a):**  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  6.33 (s, 2H), 5.51 (ddd,  $J = 17.3$ , 10.2, 6.2 Hz, 1H), 5.81 (dd,  $J = 9.5$ , 3.1 Hz, 1H), 5.58 (ddd,  $J = 17.2$ , 9.5, 7.1 Hz, 1H), 5.47 (d,  $J = 17.0$ , 1H), 5.35 (m, 4H), 3.81 (s, 3H), 3.76 (s, 3H), 3.61 (m, 1H), 3.15 (dd,  $J = 7.2$ , 2.0 Hz, 1H), 3.05 (m, 1H), 2.82–2.61 (m, 6H), 2.08 (m, 2H), 2.04 (m, 1H), 1.89 (m, 1H), 1.62 (d,  $J = 5.6$  Hz, 3H), 1.44 (dd,  $J = 6.3$ , 3.6 Hz, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$ ; ESIMS  $m/z$  513 ( $\text{M} + \text{Na}^+$ ,  $\text{C}_{26}\text{H}_{34}\text{O}_5\text{S}_2$  requires 513).

**14-membered macrolide (17).** A solution of **15** (30 mg, 61  $\mu\text{mol}$ ) in 30 mL anhydrous  $\text{CH}_2\text{Cl}_2$  under Ar was treated with Ru-catalyst **16** (5 mg, 6.1  $\mu\text{mol}$ ) and heated to 45  $^\circ\text{C}$  for 5 h. The reaction was concentrated and loaded directly onto a column and flash chromatography ( $\text{SiO}_2$ , 2 x 5 cm, 0–40% EtOAc/hexanes gradient) provided pure macrocycle **17** (15.0 mg, 55%) as a colorless oil:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  7.17 (d,  $J = 2.0$  Hz, 1H), 6.70 (dd,  $J = 15.7$ , 8.8 Hz, 1H), 6.34 (d,  $J = 2.0$  Hz, 1H), 6.02 (dd,  $J = 9.9$ , 9.8 Hz, 1H), 5.94 (d,  $J = 15.6$  Hz, 1H), 5.39 (m, 2H), 3.77 (s, 3H), 3.73 (s, 3H), 3.75 (d,  $J = 15.6$ , 1H), 3.46 (m, 1H), 3.45 (d,  $J = 15.6$  Hz, 1H), 3.05 (m, 3H), 2.88 (m, 2H), 2.34 (dt,  $J = 14.5$ , 3.3 Hz, 1H), 2.06 (m, 1H), 1.97 (m, 1H), 1.70 (m, 1H), 1.55 (d,  $J = 6.6$  Hz,

3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  167.6, 160.8, 157.6, 136.7, 135.6, 130.5, 129.3, 128.5, 118.3, 106.3, 97.1, 69.3, 56.5, 55.8, 55.7, 55.4, 53.0, 40.5, 37.1, 27.9, 27.2, 24.3, 18.8; IR (film)  $\nu_{\text{max}}$  2937, 1717, 1603, 1456, 1277, 1161  $\text{cm}^{-1}$ ; ESIMS  $m/z$  471 ( $\text{M} + \text{Na}^+$ ,  $\text{C}_{23}\text{H}_{28}\text{O}_5\text{S}_2$  requires 471). (–)-(R, R, R)-**17**:  $[\alpha]_{\text{D}}^{25} -74$  ( $c$  0.65,  $\text{CH}_2\text{Cl}_2$ ).

**Macrolide ketone (18).** A solution of **17** (12.5 mg, 27.9  $\mu\text{mol}$ ) in 5.0 mL of anhydrous  $\text{CH}_2\text{Cl}_2$  was treated with *m*CPBA (6.5 mg, 28.0  $\mu\text{mol}$ , 75%) in one portion and stirred 5 min. The reaction was diluted with  $\text{CH}_2\text{Cl}_2$  (20 mL), washed with 5% aqueous  $\text{NaHCO}_3$  (2 x 15 mL) and dried ( $\text{MgSO}_4$ ). The solvents were removed under reduced pressure and the crude monosulfoxide was dissolved in 5.4 mL of  $\text{THF}:\text{H}_2\text{O}:\text{Ac}_2\text{O}:\text{Et}_3\text{N}$  (10:1:3:4) and heated to 60  $^\circ\text{C}$  for 12 h. The reaction was concentrated under reduced pressure and flash chromatography ( $\text{SiO}_2$ , 2 x 5 cm, 0–50%  $\text{EtOAc}$ /hexanes) provided the desired ketone **18** (7.0 mg, 70%) as a colorless oil:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  7.70 (dd,  $J = 15.8, 11.4$  Hz, 1H), 6.36 (s, 1H), 6.36 (s, 1H), 6.24 (dd,  $J = 11.2, 11.1$  Hz, 1H), 6.02 (d,  $J = 16.0$  Hz, 1H), 5.82 (dd,  $J = 10.5, 4.4$  Hz, 1H), 5.36 (m, 1H), 3.96 (d,  $J = 13.8$  Hz, 1H), 3.86 (d,  $J = 13.8$  Hz, 1H), 3.80 (s, 3H), 3.77 (s, 3H), 3.57 (m, 1H), 3.10 (m, 1H), 2.45 (dt,  $J = 15.1, 4.0$  Hz, 1H), 1.73 (ddd,  $J = 15.1, 7.4, 3.0$  Hz, 1H), 1.55 (d,  $J = 6.2$  Hz, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  198.3, 167.1, 161.8, 158.8, 140.4, 136.9, 134.7, 131.7, 130.2, 116.1, 103.7, 98.0, 69.7, 55.9, 55.8, 55.5, 54.9, 42.5, 37.0, 18.9; IR (film)

$\nu_{\max}$  2938, 1661, 1604, 1203, 1162  $\text{cm}^{-1}$ ; ESIMS  $m/z$  381 ( $\text{M} + \text{Na}^+$ ,  $\text{C}_{20}\text{H}_{22}\text{O}_6$  requires 381). (–)-(R, R, R)-**18**:  $[\alpha]_{\text{D}}^{25} -130$  ( $c$  0.20,  $\text{CH}_2\text{Cl}_2$ ).

**Chlorinated macrolide (19).** A solution of **18** (2.1 mg, 5.9  $\mu\text{mol}$ ) in 1 mL of acetone was added to a solution of  $\text{Ca}(\text{OCl})_2$  (1.5 mg, 7.1  $\mu\text{mol}$ ) in 10:1  $\text{H}_2\text{O}$ :acetic acid (1.1 mL) at 0 °C and stirred 30 min. The reaction was diluted with  $\text{CH}_2\text{Cl}_2$  (10 mL), washed with 5% aqueous  $\text{NaHCO}_3$  (10 mL), and dried ( $\text{MgSO}_4$ ). The solvents were removed under reduced pressure, and the crude was purified via flash chromatography ( $\text{SiO}_2$ , 1 x 4 cm, 50% EtOAc/hexanes) to provide **19** as a colorless oil:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  7.52 (dd,  $J = 16.0, 10.1$  Hz, 1H), 6.55 (s, 1H), 6.15 (t,  $J = 10.2$  Hz, 1H), 6.10 (d,  $J = 16.1$  Hz, 1H), 5.73 (dd,  $J = 11.0, 4.5$  Hz, 1H), 5.39 (m, 1H), 3.98 (d,  $J = 16.1$  Hz, 1H), 3.93 (s, 3H), 3.86 (s, 3H), 3.78 (d,  $J = 16.0$  Hz, 1H), 3.44 (m, 1H), 3.05 (m, 1H), 2.44 (dt,  $J = 14.6, 3.5$  Hz, 1H), 1.64 (m, 1H), 1.55 (d,  $J = 6.5$  Hz, 3H); ESIMS  $m/z$  381 ( $\text{M} + \text{H}^+$ ,  $\text{C}_{20}\text{H}_{21}\text{ClO}_6$  requires 393). (+)-(R, R, R)-**19**:  $[\alpha]_{\text{D}}^{25} -55$  ( $c$  0.1,  $\text{CHCl}_3$ ).