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## SYNTHESIS OF 1-DEOXYELDECALCITOL, A BIOLOGICALLY INTERESTING ANALOG OF $1\alpha,25$ -DIHYDROXY- $2\beta$ -(3-HYDROXY-PROPOXY)VITAMIN D<sub>3</sub> (ELDECALCITOL)\*<sup>1</sup>

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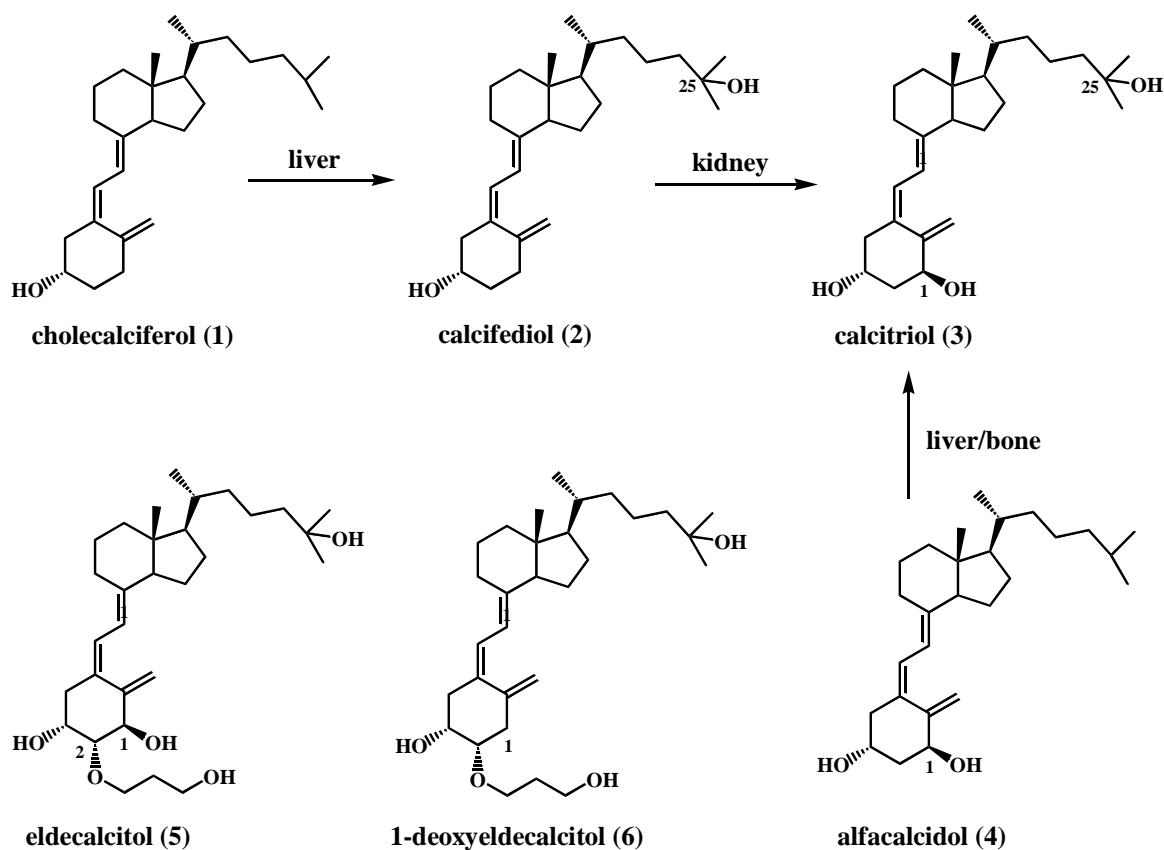
**Abstract** – A synthesis of biologically interesting 1-deoxyeldecalcitol, a dehydroxylated analog at the  $1\alpha$ -position of  $1\alpha,25$ -dihydroxy- $2\beta$ -(3-hydroxy-propoxy)vitamin D<sub>3</sub> (eldecalcitol), using Trost's coupling methodology is described.

It is well-established that vitamin D<sub>3</sub> (cholecalciferol **1**) ingested into foods or synthesized in the skin is metabolized to 25-hydroxyvitamin D<sub>3</sub> (calcifediol **2**) in the liver, which is further hydroxylated at the  $1\alpha$ -position in the kidney to produce the active form,  $1\alpha,25$ -dihydroxyvitamin D<sub>3</sub> (calcitriol **3**).<sup>2</sup> Calcitriol (**3**) is well recognized as a potent regulator of calcium and phosphorous metabolism while also possessing regulatory effects on cell proliferation and differentiation processes.<sup>3</sup> In Japan, calcitriol (**3**) and its synthetic prodrug,  $1\alpha$ -hydroxyvitamin D<sub>3</sub> (alfacalcidol **4**), which is also activated to **3** in the body (liver and bone), have been widely used for the treatment of osteoporosis for more than a quarter-century.<sup>4</sup> Calcitriol (**3**) and alfacalcidol (**4**) have been recognized as very safe medicines that show mild or moderate increase in bone mineral density (BMD) in osteoporotic patients. There exists intense interest in obtaining active vitamin D<sub>3</sub> analogs more potent than **3** and **4** in increasing BMD and preventing bone fracture with less calcemic activity for treating osteoporosis.  $1\alpha,25$ -Dihydroxy- $2\beta$ -(3-hydroxypropoxy)vitamin D<sub>3</sub> (eldecalcitol **5**, developing code; ED-71), which possesses a hydroxypropoxy substituent at the  $2\beta$ -position of the A-ring of **3**, is such an analog that shows potent

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\*This paper is dedicated to the memory of the late Dr. Etsuro Ogata, Professor Emeritus, Tokyo University/Director Emeritus, Cancer Institute Hospital Japan, who passed away on November 1, 2009.

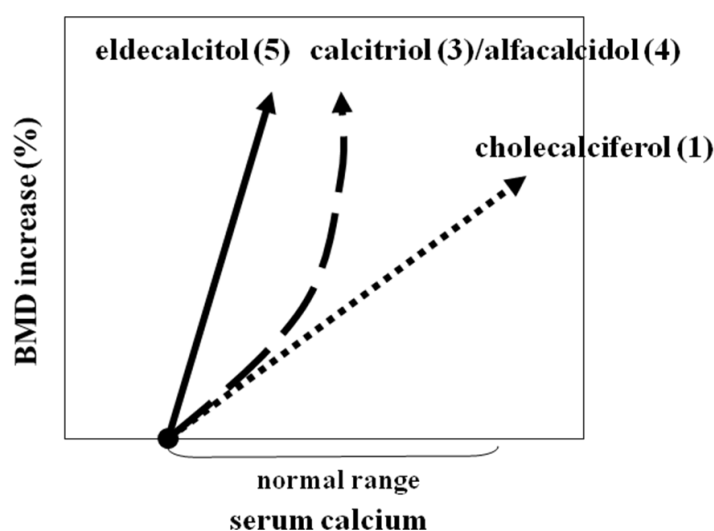
effects on bone therapy.<sup>5-7</sup> Recent completion of a phase III clinical trial of **5** for bone fracture prevention and increase in BMD in comparison with alfacalcidol (**4**) produced excellent results.<sup>8,9</sup> Eldecalcitol (**5**) is now ready for marketing as an excellent medicine for the treatment of osteoporosis in Japan (Scheme 1).



**Scheme 1.** Activation of cholecalciferol (**1**) and alfacalcidol (**4**) to calcitriol (**3**) and structures of eldecalcitol (**5**) and 1-deoxyeldecalcitol (**6**)

Figure 1 illustrates the basic relationship between serum calcium level (calcemic activity) and the targeted effect on bone (BMD increase) with cholecalciferol (**1**), calcitriol (**3**)/alfacalcidol (**4**), and eldecalcitol (**5**).<sup>10</sup> The potent effect on bone is highest with **5** followed by **3** and **4** and then **1**, at doses that induce approximately the same level of serum calcium (Figure 1). The question is what the different mode-of-action between calcitriol (**3**)/alfacalcidol (**4**) and eldecalcitol (**5**) is. Although specific physiological properties and mechanism of action of **5** are constantly being investigated, the long duration of **5** in the blood stream arises from its strong affinity for vitamin D binding protein (DBP) and might explain, in part, the enhanced activity of **5** over **3** and **4** toward bone.<sup>11,12</sup> Interestingly, an idea was presented recently that calcitriol (**3**) is responsible for calcemic activity whereas the strong

binding of calcifediol (**2**) to DBP and the long existence of **2** in blood are responsible for an anabolic effect on bone such as BMD increase.<sup>13</sup> Since the structural relationship between **3** and **2** corresponds to that between eldecalcitol (**5**) and 25-hydroxy-2 $\beta$ -(3-hydroxypropoxy)vitamin D<sub>3</sub> (1-deoxyeldecalcitol **6**), we have been very interested in the biological actions of **6**, e.g. possible hydroxylation of **6** to **5** in the kidney, affinity for DBP, duration in blood stream, and anabolic effect on bone (Scheme 1). Therefore, in this paper we describe the synthesis of 1-deoxyeldecalcitol (**6**) to explore structure-biological activity relationships between medicinally important eldecalcitol (**5**) and related analogs including **6**.<sup>11,14-18</sup>

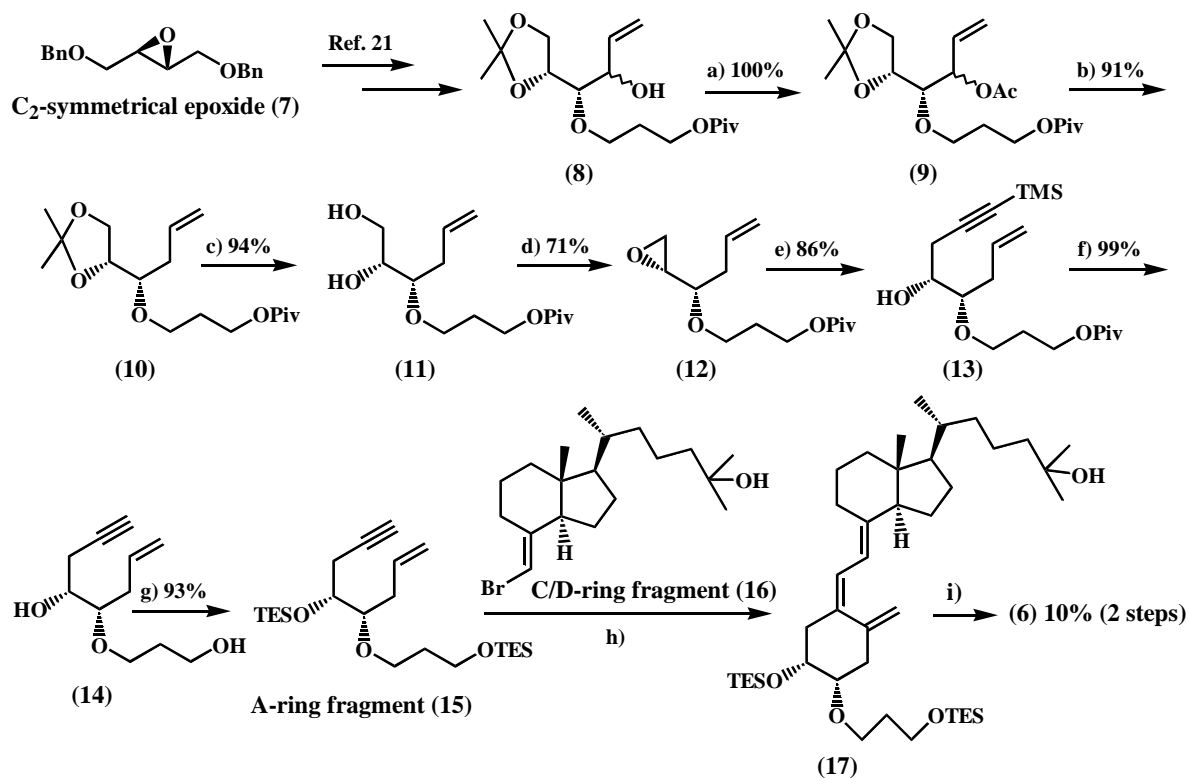


**Figure 1.** Basic relationship between calcemic activity (serum calcium) and effect on bone (BMD increase) with cholecalciferol (**1**), calcitriol (**3**)/alfacalcidol (**4**), and eldecalcitol (**5**)

The synthesis of 1-deoxyeldecalcitol (**6**) was envisioned using Trost's methodology involving palladium-catalyzed coupling between A-ring fragment **15** and C/D-ring fragment **16** (Scheme 2).<sup>19,20</sup> The synthesis of A-ring fragment **15** started from epimeric alcohol **8**<sup>21</sup> which was developed in our previous synthesis of eldecalcitol analogs from C<sub>2</sub>-symmetrical epoxide **7**.<sup>22</sup> Thus, alcohol **8** was acetylated to acetate **9**, which was treated with tetrakis(triphenylphosphine)palladium (0) [(PPh<sub>3</sub>)<sub>4</sub>Pd] and ammonium formate (HCO<sub>2</sub>NH<sub>4</sub>) to give deacetoxy product **10** in 91% yield from **8**.<sup>23</sup> Diol **11** was obtained in 94% yield after deprotection of the acetonide moiety in **10** using 60% acetic acid. Mitsunobu reaction<sup>24</sup> of **11** with diethyl azodicarboxylate (DEAD) and triphenylphosphine (PPh<sub>3</sub>) in 1,4-dioxane afforded epoxide **12** in 71% yield as a sole product. Reaction of **12** with lithium trimethylsilylacetylide in the presence of boron trifluoride diethyl etherate (BF<sub>3</sub>-OEt<sub>2</sub>) at -78 °C gave the

enyne **13** in 86% yield, which was then converted to A-ring fragment **15** by saponification with 3 M sodium hydroxide (NaOH) and subsequent protection of the hydroxyl groups as their triethylsilyl (TES) ether in 93% overall yield.

With A-ring fragment **15** in hands, we next coupled it to C/D-ring fragment **16** using Trost's methodology.<sup>19,20</sup> Thus, A-ring fragment **15** was coupled with C/D-ring fragment **16**, which was readily secured by our method<sup>25</sup> from commercially available calcifediol (**2**), in the presence of  $(\text{PPh}_3)_4\text{Pd}$  and triethylamine ( $\text{Et}_3\text{N}$ ) in boiling toluene to produce the desired coupling product **17**, although the coupling reaction conditions were not optimized. Desilylation of **17** with 47% hydrofluoric acid (HF) in acetonitrile (MeCN) at room temperature gave rise to 1-deoxyeldecaltol (**6**) in 10% yield from **15** (Scheme 2).



**Scheme 2. Synthesis of 1-deoxyeldecaltol (6).** Reagents and conditions: a)  $\text{Ac}_2\text{O}$ /pyridine/DMAP/ $\text{CH}_2\text{Cl}_2$ , rt. b)  $(\text{PPh}_3)_4\text{Pd}/\text{HCO}_2\text{NH}_4/\text{Et}_3\text{N}/\text{THF}$ , reflux. c) 60% aqueous AcOH, rt. d)  $\text{PPh}_3/\text{DEAD}/1,4\text{-dioxane}$ , reflux. e)  $\text{HC}\equiv\text{CTMS}/n\text{-BuLi}/\text{BF}_3\text{-OEt}_2/\text{THF}$ ,  $-78\text{ }^\circ\text{C}$  to rt. f) 3 M NaOH/MeOH, rt. g) TESOTf/2,6-lutidine/ $\text{CH}_2\text{Cl}_2$ ,  $-40\text{ }^\circ\text{C}$ . h)  $(\text{PPh}_3)_4\text{Pd}/\text{Et}_3\text{N}/\text{toluene}$ , reflux. i) 47% aqueous HF/MeCN,  $0\text{ }^\circ\text{C}$ .

Based on the Trost's coupling methodology involving A-ring fragment **15** and C/D-ring fragment **16**, we completed the synthesis of 1-deoxyeldecaltol (**6**). The detailed biological actions of **6** in comparison

with eldecalcitol (**5**) and related analogs will be investigated and reported in due course.

## EXPERIMENTAL

Anhydrous THF was purchased from Kanto Chemical Co., Inc. MeOH and EtOH were distilled from sodium, toluene was distilled from phosphorus pentoxide, and CH<sub>2</sub>Cl<sub>2</sub>, Et<sub>3</sub>N, DMF, and pyridine were distilled from calcium hydride. All other purchased solvents and reagents were used without further purification. All reactions were carried out under an atmosphere of argon unless otherwise noted. Celite 545 was purchased from Nacalai Tesque Inc. All extracts were dried over magnesium sulfate and evaporated under reduced pressure with a rotary evaporator. Chromatographic purification was carried out with Silica Gel 60N Cat. No. 37560-84 purchased from Kanto Chemical Co., Inc., and flash column chromatography with Silica Gel 60N Cat. No. 37563-84 from Kanto Chemical Co., Inc. Optical rotations were measured with JASCO DIP-370 polarimeter. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on VARIAN Gemini-300 and Gemini-400 spectrometers using CDCl<sub>3</sub> as a solvent. Chemical shifts are reported in parts per million (ppm) calibrated from CHCl<sub>3</sub> (7.26 ppm) or tetramethylsilane (0.00 ppm) for <sup>1</sup>H NMR and CDCl<sub>3</sub> (77.1 ppm) for <sup>13</sup>C NMR. Infrared (FTIR) spectra were obtained using JASCO FT/IR-5300, JEOL JIR-6000, and Hitachi 270-30 spectrophotometers. Mass spectra (MS) were measured with JEOL JMS-DX303 instrument. High resolution mass spectra (HRMS) were recorded on JEOL JMS-AX-500 and VG Auto Spec Q instruments.

**3-((S)-1-((R)-2,2-Dimethyl-1,3-dioxolan-4-yl)but-3-enyloxy)propyl Pivalate (10):** To a stirred solution of **8** (450 mg, 1.36 mmol), pyridine (0.26 mL, 3.26 mmol), and DMAP (1.6 mg, 0.013 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (4 mL) at rt, was added Ac<sub>2</sub>O (0.19 mL, 1.96 mmol). The resulting mixture was stirred at rt, diluted with Et<sub>2</sub>O, washed with 1 M HCl, saturated NaHCO<sub>3</sub>, and saturated NaCl, evaporated, and chromatographed on silica gel short column. Elution with *n*-hexane-AcOEt (12:1) gave **9** (510 mg, 100%), which was used for the next reaction without further purification. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.20 (9H, s), 1.33 (3H, s), 1.42 (3H, s), 1.88 (2H, quint, *J* = 6.1 Hz), 2.09 (1.5H, s), 2.11 (1.5H, s), 3.52-4.16 (8H, m), 5.24-5.34 (2.5H, m), 5.54 (0.5H, d, *J* = 5.6 Hz), 5.80-5.89 (1H, m). To a stirred and degassed solution of **9** (0.3 g, 0.81 mmol) and Et<sub>3</sub>N (0.6 mL, 4.3 mmol) in THF (8 mL), were added HCO<sub>2</sub>NH<sub>4</sub> (0.5 g, 7.93 mmol) and (PPh<sub>3</sub>)<sub>4</sub>Pd (2.7 mg, 0.023 mmol). The resulting mixture was refluxed for 2 h. To the mixture, was added additional (PPh<sub>3</sub>)<sub>4</sub>Pd (2.7 mg, 0.023 mmol). The resulting mixture was refluxed for 40 min, diluted with AcOEt, washed with saturated NaCl, evaporated, and chromatographed on silica gel. Elution with *n*-hexane-AcOEt (9:1) gave **10** (227 mg, 91%) as a colorless oil. [α]<sub>D</sub><sup>27</sup>

+20.8° (*c* 1.00, CHCl<sub>3</sub>). FTIR (neat):  $\nu$  1729, 1472, 1374, 1281, 1216, 1158, 1071 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  1.25 (9H, s), 1.41 (3H, s), 1.43 (3H, s), 1.87 (2H, quint, *J* = 6.4 Hz), 2.25-2.37 (2H, m), 3.38-3.40 (1H, m), 3.57-3.68 (2H, m), 3.87 (1H, m), 4.03 (2H, q, *J* = 4.6 Hz), 4.15 (2H, t, *J* = 6.4 Hz), 5.06-5.14 (2H, m), 5.84 (1H, dt, *J* = 7.1, 10.0 Hz). <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  25.3, 26.6, 27.1, 29.3, 35.5, 38.7, 61.2, 66.2, 66.8, 76.7, 79.6, 109.0, 117.4, 134.1, 178.4. EIMS *m/z* 314 (M<sup>+</sup>), 143 (100%). HRMS (EI) calcd for C<sub>17</sub>H<sub>36</sub>O<sub>5</sub> (M<sup>+</sup>) 314.2093, found 314.2080.

**3-((2*R*,3*S*)-1,2-Dihydroxyhex-5-en-3-yloxy)propyl Pivalate (11):** A solution of **10** (380 mg, 1.21 mmol) in 60% AcOH (15 mL) was stirred at rt for 8 h, basified with saturated NaHCO<sub>3</sub>, extracted with CH<sub>2</sub>Cl<sub>2</sub>, washed with saturated NaCl, evaporated, and chromatographed on silica gel. Elution with *n*-hexane-AcOEt (3:2 then 1:1) gave **11** (311 mg, 94%) as a colorless oil.  $[\alpha]_D^{28} +19.1^\circ$  (*c* 1.00, CHCl<sub>3</sub>). FTIR (neat):  $\nu$  3437, 1725, 1287, 1166, 1107 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  1.20 (9H, s), 1.88 (2H, quint, *J* = 6.1 Hz), 2.30-2.40 (3H, m), 2.79 (1H, m), 3.46-3.50 (2H, m), 3.66-3.78 (4H, m), 4.10 (1H, quint, *J* = 6.1 Hz), 4.27 (1H, quint, *J* = 6.1 Hz), 5.08-5.16 (2H, m), 5.78-5.88 (1H, m). <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  27.1, 29.3, 34.7, 61.1, 63.2, 66.4, 72.3, 80.5, 117.4, 134.2, 178.7. EIMS *m/z* 274 (M<sup>+</sup>), 143 (100%). HRMS (EI) calcd for C<sub>14</sub>H<sub>26</sub>O<sub>5</sub> (M<sup>+</sup>) 274.1780, found 274.1762.

**3-((*S*)-1-((*R*)-Oxiran-2-yl)but-3-enyloxy)propyl Pivalate (12):** To a stirred solution of **11** (311 mg, 1.13 mmol) in 1,4-dioxane (11 mL) at rt, were added PPh<sub>3</sub> (0.86 g, 3.4 mmol) and DEAD (40% in toluene, 1.56 mL, 5.16 mmol). The resulting mixture was refluxed for 24 h, cooled to rt, evaporated, and chromatographed on silica gel. Elution with *n*-hexane-AcOEt (10:1) gave **12** (206 mg, 71%) as a colorless oil.  $[\alpha]_D^{26} +7.61^\circ$  (*c* 1.00, CHCl<sub>3</sub>). IR (neat):  $\nu$  1724, 1476, 1284, 1161 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  1.20 (9H, s), 1.86 (2H, quint, *J* = 6.3 Hz), 2.30-2.44 (2H, m), 2.73-2.80 (2H, m), 2.94-2.96 (1H, m), 3.18-3.23 (1H, m), 3.46-3.52 (1H, m), 3.64-3.68 (1H, m), 4.14 (2H, t, *J* = 6.3 Hz), 5.07-5.16 (2H, m), 5.82-5.92 (1H, dt, *J* = 7.1, 10.3 Hz). <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  27.1, 29.3, 37.0, 38.7, 45.3, 53.0, 61.2, 66.6, 78.4, 117.3, 133.9, 178.4. EIMS *m/z* 256 (M<sup>+</sup>), 143 (100%). HRMS (EI) calcd for C<sub>14</sub>H<sub>24</sub>O<sub>4</sub> (M<sup>+</sup>) 256.1675, found 256.1672.

**3-((4*S*,5*R*)-5-Hydroxy-8-(trimethylsilyl)oct-1-en-7-yn-4-yloxy)propyl Pivalate (13):** To a stirred solution of trimethylsilylacetylene (423  $\mu$ L, 2.99 mmol) in THF (8 mL) at -78 °C, was added *n*-BuLi (2.66 M solution in *n*-hexane, 1.0 mL, 2.66 mmol) and stirring was continued at -78 °C for 4 h. To the stirred mixture at -78 °C, were added **12** (150 mg, 0.586 mmol) in THF (8 mL) and BF<sub>3</sub>-OEt<sub>2</sub> (384  $\mu$ L,

0.434 mmol). The resulting mixture was allowed to warm to rt, stirred at rt for 14 h, quenched with saturated NaHCO<sub>3</sub> (1.0 mL), extracted with CH<sub>2</sub>Cl<sub>2</sub>, washed with saturated NaCl, evaporated, and chromatographed on silica gel. Elution with *n*-hexane-AcOEt (20:1) gave **13** (178 mg, 86%) as a colorless oil.  $[\alpha]_{\text{D}}^{28} +17.0^{\circ}$  (*c* 1.00, CHCl<sub>3</sub>). FTIR (neat):  $\nu$  3500, 1728, 1477, 1402, 1286, 1252, 1162, 1106 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  0.15 (9H, s), 1.19 (9H, s), 1.87 (2H, quint, *J* = 6.1 Hz), 2.32-2.35 (2H, m), 2.51 (2H, d, *J* = 6.1 Hz), 3.37 (1H, q, *J* = 5.6 Hz), 3.52-3.63 (2H, m), 3.76 (1H, q, *J* = 5.6 Hz), 4.09-4.20 (2H, m), 5.05-5.14 (2H, m), 5.80-5.89 (1H, m). <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  0.00, 24.3, 27.2, 29.3, 34.1, 38.7, 61.2, 66.4, 70.4, 80.9, 87.5, 103.0, 117.2, 134.6, 178.5. EIMS *m/z* 354 (M<sup>+</sup>), 57 (100%). HRMS (EI) calcd for C<sub>19</sub>H<sub>34</sub>O<sub>4</sub>Si (M<sup>+</sup>) 354.2227, found 354.2224.

**(4R,5S)-5-(3-Hydroxypropoxy)oct-7-en-1-yn-4-ol (14)**: To a stirred solution of **13** (77.5 mg, 0.219 mmol) in MeOH (2 mL) at 0 °C, was added 3 M NaOH (1 mL). The resulting mixture was stirred at rt for 8 h, neutralized with 1 M HCl (0.5 mL), evaporated, and chromatographed on silica gel. Elution with *n*-hexane-AcOEt (20:1) gave **14** (43.1 mg, 99%) as a colorless oil.  $[\alpha]_{\text{D}}^{28} +23.5^{\circ}$  (*c* 1.00, CHCl<sub>3</sub>). FTIR (neat):  $\nu$  3296, 1641, 1423, 1004 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  1.81 (2H, quint, *J* = 2.7 Hz), 2.06 (1H, s), 2.34-2.38 (2H, m), 2.51 (3H, m), 3.43-3.46 (1H, m), 3.73-3.80 (5H, m), 5.10-5.17 (2H, m), 5.83-5.90 (1H, m). <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  22.9, 32.5, 34.6, 61.1, 69.1, 70.7, 70.9, 81.2, 81.4, 117.7, 134.7. EIMS *m/z* 198 (M<sup>+</sup>), 59 (100%). HRMS (EI) calcd for C<sub>11</sub>H<sub>18</sub>O<sub>3</sub> (M<sup>+</sup>) 198.1256, found 198.1242.

**(4S,5R)-4-(3-(Trimethylsilyloxy)propoxy)-5-(trimethylsilyloxy)oct-1-en-7-yne (15)**: To a stirred mixture of **14** (50 mg, 0.252 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) at -40 °C, were added 2,6-lutidine (283  $\mu$ L, 1.26 mmol) and TESOTf (240  $\mu$ L, 1.26 mmol). The resulting mixture was stirred at the same temperature for 9 h, quenched with saturated NaHCO<sub>3</sub> (2 mL), extracted with CH<sub>2</sub>Cl<sub>2</sub>, washed with saturated NaHCO<sub>3</sub> and saturated NaCl, evaporated, and chromatographed on silica gel. Elution with *n*-hexane-CH<sub>2</sub>Cl<sub>2</sub> (6:1) containing 2% Et<sub>3</sub>N gave **15** (100 mg, 93%) as a colorless oil.  $[\alpha]_{\text{D}}^{24} -3.7^{\circ}$  (*c* 1.06, CHCl<sub>3</sub>). FTIR (neat):  $\nu$  1463, 1416, 1238, 1100, 1010 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  0.60 (12H, q, *J* = 8.1 Hz), 0.93 (18H, t, *J* = 8.1 Hz), 1.77 (2H, quint, *J* = 6.4 Hz), 1.97 (1H, s), 2.27-2.47 (4H, m), 3.38 (1H, q, *J* = 5.1 Hz), 3.61 (2H, q, *J* = 6.3 Hz), 3.68 (2H, t, *J* = 6.3 Hz), 3.78 (1H, q, *J* = 5.1 Hz), 5.03-5.12 (2H, m), 5.82-5.93 (1H, m). <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  4.4, 5.0, 6.7, 6.8, 23.8, 33.4, 34.8, 59.9, 67.4, 70.0, 72.2, 81.3, 81.6, 116.6, 135.3. EIMS *m/z* 426 (M<sup>+</sup>), 115 (100%). HRMS (EI) calcd for C<sub>23</sub>H<sub>46</sub>O<sub>3</sub>Si<sub>2</sub> (M<sup>+</sup>) 426.2986, found 426.2997.

**(1R,2S,5Z)-2-(3-Hydroxypropoxy)-5-((E)-2-((1R,3aS,7aR)-hexahydro-1-((R)-6-hydroxy-6-methylheptan-2-yl)-7a-methyl-1H-inden-4(7aH)-ylidene)ethylidene-4-methylenecyclohexanol (6):** To a stirred and degassed solution of **15** (90 mg, 0.211 mmol), **16** (90 mg, 0.253 mmol), and Et<sub>3</sub>N (4.7 mL) in toluene (3.2 mL) at rt, was added (PPh<sub>3</sub>)<sub>4</sub>Pd (20 mg, 0.017 mmol). The resulting mixture was refluxed for 22 h, diluted with Et<sub>2</sub>O, and filtrated with Celite. The filtrate was diluted with AcOEt, washed with H<sub>2</sub>O and saturated NaCl, evaporated, and chromatographed on silica gel. Elution with *n*-hexane-AcOEt (20:1) containing 2% Et<sub>3</sub>N gave crude **17** (64 mg), which was used for the next reaction without further purification. To a stirred mixture of crude **17** (64 mg) in MeCN (16 mL) at 0 °C, was added 47% HF (100 μL). The resulting mixture was stirred at the same temperature for 10 min, neutralized with NaHCO<sub>3</sub> (3 g), extracted with Et<sub>2</sub>O, washed with saturated NaCl, evaporated, and chromatographed on silica gel. Elution with AcOEt gave **6** (10.2 mg, 10%) as a white solid.  $[\alpha]_D^{20} +19.9^\circ$  (*c* 0.32, CHCl<sub>3</sub>). FTIR (neat):  $\nu$  3387, 2942, 1710, 1374, 1081 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  0.54 (3H, s), 0.93 (3H, d, *J* = 6.6 Hz), 1.03-1.06 (1H, m), 1.25 (3H, s), 1.27-1.35 (4H, m), 1.41-1.54 (10H, m), 1.65-1.67 (2H, m), 1.83-1.87 (2H, m), 1.95-2.05 (2H, m), 2.26 (1H, br s), 2.37 (2H, m), 2.49-2.57 (2H, m), 2.81 (1H, m), 3.58 (1H, quint, *J* = 4.2 Hz), 3.68-3.79 (5H, m), 4.01 (1H, br s), 4.92 (1H, s), 5.11 (1H, s), 6.02 (1H, d, *J* = 11.5 Hz), 6.26 (1H, d, *J* = 11.5 Hz). <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  12.0, 18.8, 20.8, 22.3, 23.6, 27.7, 29.0, 29.2, 29.3, 32.2, 36.1, 36.4, 40.5, 41.0, 44.4, 45.8, 56.3, 56.5, 61.6, 67.2, 68.9, 71.1, 79.2, 114.7, 117.5, 122.9, 133.6, 141.6, 142.6. EIMS *m/z* 474 (M<sup>+</sup>), 134 (100%). HRMS (EI) calcd for C<sub>30</sub>H<sub>50</sub>O<sub>4</sub> (M<sup>+</sup>) 474.3709, found 474.3710.

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