

## Synthetic Studies of an 18-Membered Antitumor Macrolide, Tedanolide. 6. Synthesis of a Key Intermediate *via* a Highly Efficient Macrolactonization of Computer-Aid Designed Seco-Acid

Tomohiro MATSUSHIMA,<sup>a</sup> Noriyuki NAKAJIMA,<sup>b</sup> Bao-Zhong ZHENG,<sup>c</sup> and Osamu YONEMITSU\*<sup>c</sup>

Faculty of Pharmaceutical Sciences, Hokkaido University,<sup>a</sup> Sapporo 060-0812, Japan, Biotechnology Center, Toyama Prefectural University,<sup>b</sup> Kosugi, Toyama 939-0398, Japan, and Department of Chemistry, Okayama University of Science,<sup>c</sup> Okayama 700-0005, Japan. Received January 20, 2000; accepted February 28, 2000

**A stereoselective synthesis is described of the 18-membered lactone (2) *via* an efficient macrolactonization of the conformation-controlled seco-acid (3); this was designed with the aid of molecular mechanics (MM)-calculation and synthesized by coupling between the C1—C12 (4) and C13—C23 (5) fragments.**

**Key words** macrolide; 18-membered lactone; macrolactonization; seco-acid; aldol reaction; calculation

Tedanolid (1), a potent cytotoxic macrolide, was isolated from the Caribbean “fire sponge” *Tedania ignis* in 1984; its relative and absolute structure was determined by X-ray analysis<sup>1)</sup> and revealed an unusual structural feature: four labile aldol units, an 18-membered lactone formed at a primary hydroxyl instead of the usual secondary hydroxyl,<sup>2)</sup> and an  $\alpha$ -epoxy alcohol. Because of its novel and complex structure as well as strong biological activity,<sup>3)</sup> 1 has recently attracted considerable synthetic attention.<sup>4)</sup>

In 1996, as part of our synthetic studies of 1 we reported in a preliminary communication<sup>4b)</sup> on the synthesis of the 18-membered lactone (2), a key intermediate to 1, *via* modified Yamaguchi macrolactonization<sup>5,6)</sup> of the corresponding seco-acid (3). Quite recently, the synthesis of two fragments, C1—C12 (4)<sup>4d)</sup> and C13—C23 (5)<sup>4f)</sup> as precursors to 3 starting from methyl (*R*)- and (*S*)-3-hydroxy-2-methylpropionates was reported in detail. In this full paper we describe the synthesis of 2 *via* the quite efficient cyclization of 3, which was carried out by coupling between 4 and 5.

In macrolide synthesis the most crucial step to success is usually macrocyclization of a seco-acid to the corresponding lactone, and hence it is extremely important to design a seco-acid derivative suitable for macrolactonization, that is, on the basis of conformational analyses the seco-acid should be designed so that its global conformation is as close as possible to that of the corresponding lactone.<sup>4a,5,7)</sup> Only recent computational chemistry can predict the significantly populated conformers of such complex molecules with considerable accuracy within a reasonable computation time. After careful calculations by virtue of a molecular mechanics (MM) method (CONFLEX-MM2),<sup>8)</sup> we chose 3 and 2 as the most promising seco-acid and its cyclized lactone, respectively. The most dominant conformations of 3a and 2a as calculation models for 3 and 2, respectively, are shown in Fig. 2.<sup>4b)</sup>

**Synthesis of the Seco-Acid (3)** The kinetic enolate of the C1—C12 ketone (4)<sup>9)</sup> was first prepared with a slight excess of lithium hexamethyldisilazide (LHMDS)<sup>10)</sup> at  $-78^\circ\text{C}$ , and then allowed to react with *ca.* one-third equivalent of the

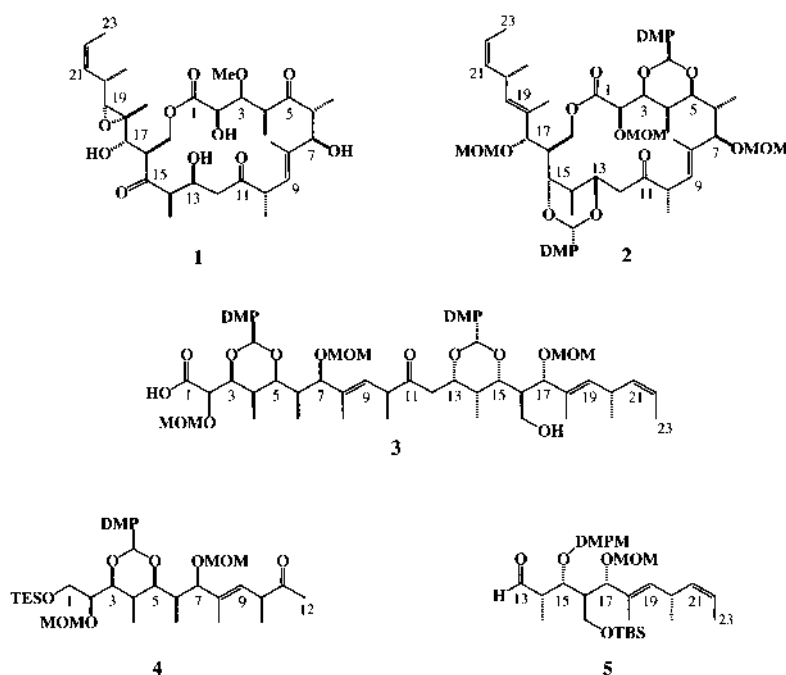


Fig. 1

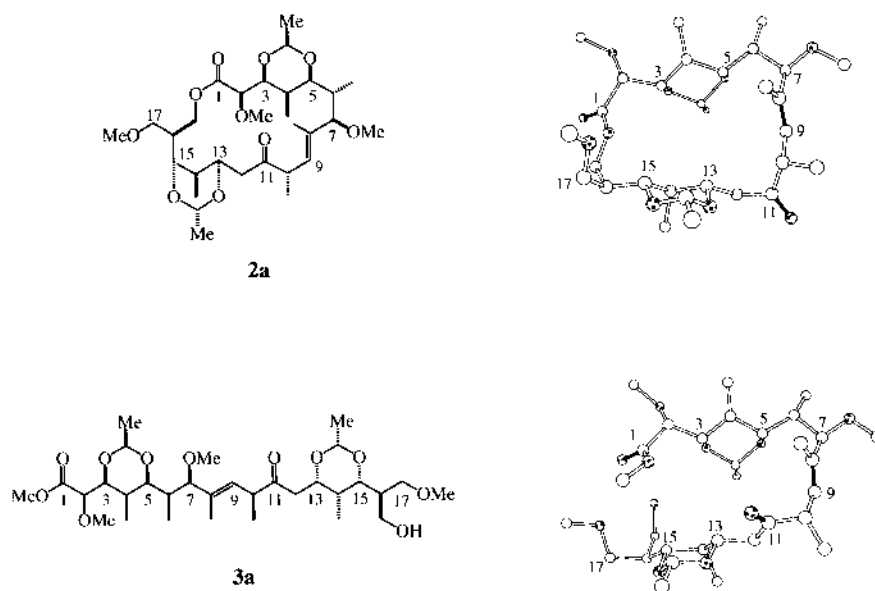
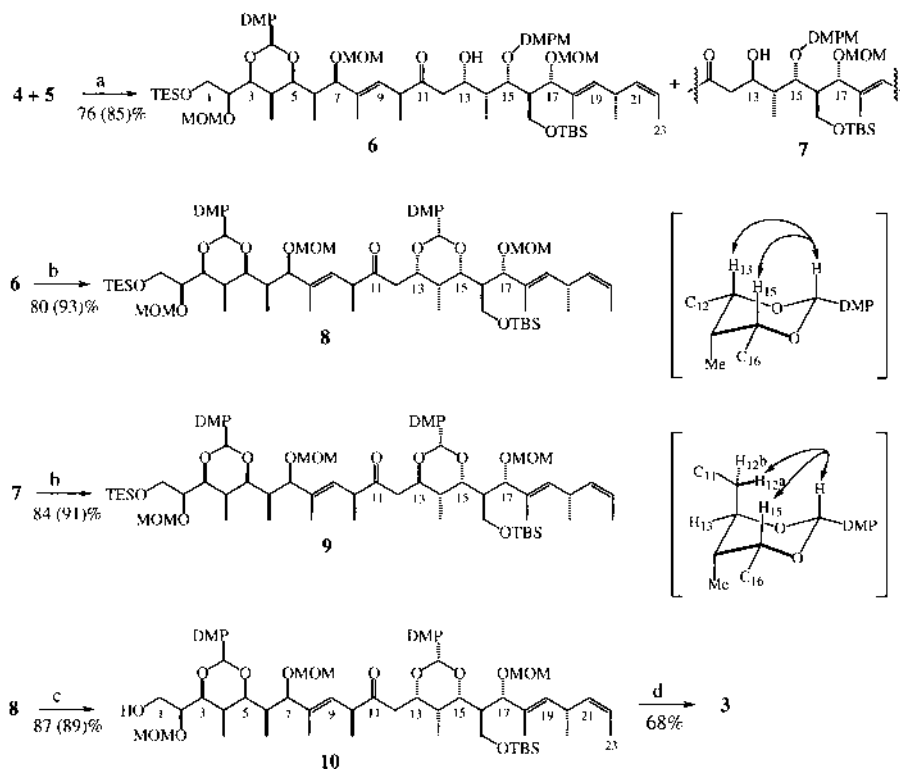


Fig. 2. The Most Stable Conformers of **2a** and **3a** Calculated by CONFLEX-MM2



Values in paren these are yields based on consumed starting materials.

(a)  $\text{LiN}(\text{TMS})_2$ , THF,  $-78^\circ\text{C}$  to  $-40^\circ\text{C}$  (**6** : **7** = 1.0 : 1.9). (b) DDQ,  $\text{CH}_2\text{Cl}_2$ ,  $10^\circ\text{C}$ . (c) TBAF.

AcOH-THF,  $0^\circ\text{C}$ . (d) 1) Dess-Martin reagent, pyridine,  $\text{CH}_2\text{Cl}_2$ , r.t.; 2)  $\text{NaClO}_2$ ,  $\text{NaH}_2\text{PO}_4$ , 2-methyl-butene, *tert*-BuOH- $\text{H}_2\text{O}$ , r.t.; 3) *n*- $\text{Bu}_4\text{NF}$ , AcOH-THF, r.t.

Chart 1

C13—C23 aldehyde (**5**). The aldol condensation between **4** and **5** proceeded rather slowly to give an easily separable mixture of the desired Felkin aldol (**6**)<sup>11</sup> and its C13-epimer (**7**). The ratio of the mixture varied in the range of 1 : 1.2 to 1 : 1.9 with a subtle change in reaction conditions but, unfortunately, **6** was always the minor product.<sup>12</sup> The stereochemistry of **6** and **7** was determined after their conversion to **8**

and **9**, respectively. When **6** was treated with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in anhydrous  $\text{CH}_2\text{Cl}_2$  at  $-10^\circ\text{C}$ , the oxidative acetalization<sup>13</sup> of the C15-*O*-3,4-dimethoxybenzyl (DMPM) group to the C13 hydroxy group proceeded smoothly to give **8**. Similarly, **7** gave **9**. The structures of **8** and **9** were determined by NMR, especially  $^1\text{H}$ - $^1\text{H}$  correlated spectroscopy (COSY) and nuclear Overhauser and

exchange spectroscopy (NOESY). In the latter, correlations of the benzylidene acetal proton with C13 and C15 protons in **8** were clearly observed, whereas these were seen with C12 and C15 protons in **9**.

The triethylsilyl (TES) protecting group was selectively removed with tetra-*n*-butylammonium fluoride (TBAF) in tetrahydrofuran (THF) in the presence of acetic acid (AcOH) at 0 °C to give the primary alcohol (**10**). This selective deprotection proceeded more cleanly with only AcOH in aqueous THF at room temperature. Conversion of **10** to the seco-acid (**3**) was carried out in the usual way. Dess–Martin oxidation<sup>14</sup> of **10** gave a crude aldehyde, which was subjected to the next reaction without purification. Sodium chlorite oxidation in the presence of 2-methyl-2-butene<sup>15</sup> and subsequent deprotection of the *tert*-butyldimethylsilyl (TBS) group with TBAF under acidic conditions easily gave **3**.

**Lactonization of the Seco-Acid (**3**) to the 18-Membered Lactone (**2**)** As pointed out in the synthetic study of erythronolide A,<sup>5,16</sup> among many ways of macrolactonization<sup>17</sup> the Yamaguchi method<sup>6</sup> is extremely effective especially in the presence of a large excess of 4-dimethylaminopyridine (DMAP).<sup>18</sup>

To efficiently synthesize macrolides *via* macrolactonization of the corresponding seco-acids, the high dilution technique is usually essential. However, such a technique should be unnecessary for cyclization of **3** which has favorably controlled conformation. In fact, **3** readily cyclized to the lactone (**2**) under usual acylation conditions *via* a mixed anhydride. When **3** was treated with Yamaguchi's 2,4,6-trichlorobenzoyl chloride<sup>6</sup> in the presence of triethylamine (Et<sub>3</sub>N) in THF at room temperature, acylation proceeded slowly to give the

mixed anhydride, which was dissolved in a 1 : 1 mixture of THF and benzene. To this solution an excess of DMAP was added at once with stirring to give the 18-membered lactone (**2**) quite smoothly in high yield.

The structures of **3** and **2** were confirmed by virtue of their COSY and NOESY, and correlations among many protons in the latter are shown in Fig 3. Finally, the observed vicinal proton coupling constants of the seco-acid methyl ester (**11**), prepared as a model of the mixed anhydride of **3** by treatment of the anhydride itself with methanol, and the lactone (**2**) were compared with the calculated values<sup>19</sup> of **3a** and **2a** as shown in Tables 1 and 2, respectively. There are no practical differences between the observed and calculated values except for the rather flexible C6–C7 bond of **11**. These data clearly substantiate reliability of the computation method as well as of the structural assignment of **2** and **3**.

In summary, we have demonstrated an example of the computational design of key intermediates and their efficient synthesis in the complex natural products synthesis, although in small-scale experiments. Further studies toward completion of a synthesis of **1** and development of an alternative concise and larger-scale synthesis are now in progress.

#### Experimental

(2*S*,3*S*,4*R*,5*S*,6*S*,7*R*,8*E*,10*S*,13*S*,14*R*,15*S*,16*S*,17*S*,18*E*,20*S*,21*Z*)-3,5-[(*S*)-3,4-Dimethoxybenzylidenedioxy]-15-(3,4-dimethoxybenzyloxy)-16-

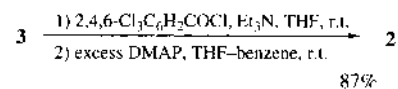


Chart 2

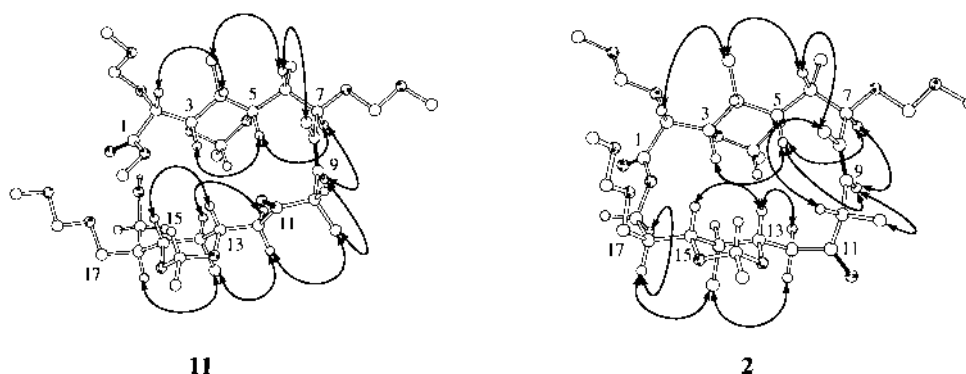


Fig. 3. NOESY Correlations in **11** and **2**

Table 1. Vicinal Proton Coupling Constants (*J*; Hz) of the Seco-Acid Methyl Ester

<i>J</i> <sub>H-H</sub>	Obs ( <b>11</b> )	Calcd ( <b>3a</b> )
2–3	9.0	8.2
3–4	1.5	2.5
4–5	1.5	2.2
5–6	10.0	10.0
6–7	0	5.7
9–10	9.0	—
12–13	8.5; 4.0	9.2; 3.3
13–14	2.0	2.6
14–15	1.5	2.4
15–16	10.0	10.9
16–16'	4.2; 2.0	4.2; 2.3

Table 2. Vicinal Proton Coupling Constants (*J*; Hz) of the Lactone Derivatives

<i>J</i> <sub>H-H</sub>	Obs ( <b>2</b> )	Calcd ( <b>2a</b> )
2–3	8.5	8.2
3–4	1.5	1.8
4–5	1.0	2.7
5–6	0	0
6–7	10.5	12.2
9–10	8.5	—
12–13	8.5; 6.0	9.1; 2.0
13–14	2.0	1.8
14–15	1.5	2.1
15–16	10.5	12.2
16–16'	1.5; 0.5	2.8; 0.5

**[(1,1-dimethylethyl)dimethylsilyloxyethyl]-4,6,8,10,14,18,20-heptamethyl-13-hydroxy-1-triethylsilyloxy-2,7,17-trismethoxymethoxy-8,18,21-tricosatrien-11-one (6)** and **(2S,3S,4R,5S,6S,7R,8E,10S,13R,14R,15S,16S,17S,18E,20S,21Z)-3,5-[(S)-3,4-Dimethoxybenzylidenedioxy]-15-(3,4-dimethoxybenzyloxy)-16-[(1,1-dimethylethyl)dimethylsilyloxy]-4,6,8,10,14,18,20-heptamethyl-13-hydroxy-1-triethylsilyloxy-2,7,17-trismethoxymethoxy-8,18,21-tricosatrien-11-one (7)** A solution of **4** (139 mg, 208  $\mu\text{mol}$ ) in THF (1.5 ml) was added dropwise to a stirred 0.23 M solution of LHMDS in THF (1 ml, 230  $\mu\text{mol}$ ) at  $-78^\circ\text{C}$  under argon. After 1 h, a solution of **5** (39 mg, 68  $\mu\text{mol}$ ) in THF (0.5 ml) was added, and the solution was allowed to warm to  $-40^\circ\text{C}$  over 6.5 h. The reaction was quenched with saturated aqueous  $\text{NH}_4\text{Cl}$ , and the reaction mixture was extracted with  $\text{Et}_2\text{O}$ . The extract was washed with saturated aqueous  $\text{NH}_4\text{Cl}$  and brine, dried over  $\text{Na}_2\text{SO}_4$ , concentrated *in vacuo*, and chromatographed on a silica gel column, eluting with *n*-hexane-EtOAc (5:2—2:1), to give less polar **6** (22 mg, 26%; 29% based on the consumed **5**) and polar **7** (42 mg, 50%; 56% based on the consumed **5**) as colorless oils, and recovered **4** (56 mg, 40%) and **5** (4 mg, 11%). **6**:  $[\alpha]_{\text{D}}^{18} +25^\circ$  ( $c=0.74$ ,  $\text{CHCl}_3$ ). IR (neat)  $\text{cm}^{-1}$ : 3500, 2950, 1710, 1520, 1460, 1265, 1160, 1030, 840.  $^1\text{H-NMR}$  (500 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$ : 0.15 (s, 3H), 0.17 (s, 3H), 0.73 (q, 6H,  $J=8.0$  Hz), 1.05 (d, 3H,  $J=6.5$  Hz, C20Me), 1.06 (s, 9H), 1.11 (t, 9H,  $J=8.0$  Hz), 1.17 (d, 3H,  $J=7.0$  Hz, C10Me), 1.31 (m, 9H, C6Me, C4Me, C14Me), 1.43 (s, 3H, C8Me), 1.62 (dd, 3H,  $J=1.0$ , 6.5 Hz, C23Me), 1.71 (s, 3H, C18Me), 2.11 (m, 1H, H6), 2.32 (m, 1H, H4), 2.36 (dd, 1H,  $J=3.0$ , 16.5 Hz, H12), 2.47 (m, 1H, H14), 2.65 (m, 1H, H16), 2.90 (dd, 1H,  $J=9.5$ , 16.5 Hz, H12), 3.25—3.35 (m, 1H, H10), 3.33 (s, 3H), 3.35—3.50 (m, 1H, H20), 3.39 (s, 3H), 3.42 (s, 3H), 3.43 (s, 3H), 3.45 (s, 3H), 3.54 (s, 3H), 3.60—3.70 (m, 2H, H16'), 3.66 (s, 3H), 3.92 (dd, 1H,  $J=4.5$ , 11.0 Hz, H1), 3.98 (dd, 1H,  $J=3.5$ , 11.0 Hz, H1), 4.06 (dd, 1H,  $J=1.0$ , 9.5 Hz, H5), 4.18 (s, 1H, H7), 4.22 (m, 1H, H2), 4.26 (dd, 1H,  $J=1.0$ , 8.5 Hz, H3), 4.30 (dd, 1H,  $J=1.5$ , 7.0 Hz, H15), 4.46 (d, 1H,  $J=7.0$  Hz), 4.50 (d, 1H,  $J=9.5$  Hz, H17), 4.59 (d, 1H,  $J=6.0$  Hz), 4.74 (d, 1H,  $J=7.0$  Hz), 4.75 (d, 1H,  $J=6.0$  Hz), 4.76 (d, 1H,  $J=11.0$  Hz), 4.78—4.88 (m, 1H, H13), 4.81 (d, 1H,  $J=11.0$  Hz), 4.96 (d, 1H,  $J=6.5$  Hz), 5.12 (d, 1H,  $J=6.5$  Hz), 5.30 (ddq, 1H,  $J=9.5$ , 9.5, 1.5 Hz, H21), 5.34—5.43 (m, 2H, H9, H22), 5.63 (d, 1H,  $J=10.0$  Hz, H19), 5.72 (s, 1H), 6.60—6.70 (m, 2H), 7.00—7.15 (m, 2H), 7.30—7.40 (m, 2H).  $^{13}\text{C-NMR}$  (125 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$ : -5.32, -5.20, 4.80, 7.04, 7.61, 9.83, 10.36, 11.65, 13.06, 14.59, 16.34, 18.48, 21.46, 26.22, 30.69, 30.85, 36.68, 41.60, 44.60, 45.94, 46.68, 55.56, 55.60, 55.64, 56.14, 62.46, 63.19, 68.71, 74.16, 77.37, 78.26, 80.69, 80.98, 83.18, 83.26, 94.02, 95.37, 97.35, 102.60, 111.03, 111.93, 112.24, 112.39, 119.19, 120.30, 121.98, 125.85, 127.92, 128.10, 128.29, 131.33, 132.22, 132.78, 135.14, 135.26, 135.41, 149.77, 149.45, 150.31, 150.46, 210.57. FAB-MS  $m/z$  (%): 1247 ( $\text{M}^+ + 1$ , 1.8), 1246 ( $\text{M}^+$ , 3.9), 1245 ( $\text{M}^+ - 1$ , 4.0), 439 (8.6), 409 (9.1), 349 (20), 281 (19), 253 (18), 227 (40), 211 (84), 166 (100), 115 (94), 73 (91). HR-MS Calcd for  $\text{C}_{67}\text{H}_{115}\text{O}_{17}\text{Si}_2$  ( $\text{M}^+ - 1$ ): 1245.7516. Found: 1245.7450. **7**:  $^1\text{H-NMR}$  (500 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$ : 0.15 (s, 3H), 0.16 (s, 3H), 0.73 (q, 6H,  $J=8.0$  Hz), 1.06 (s, 9H), 1.07 (d, 3H,  $J=6.5$  Hz, C20Me), 1.10 (t, 9H,  $J=8.0$  Hz), 1.17 (d, 3H,  $J=7.0$  Hz, C10Me), 1.21 (d, 3H,  $J=7.0$  Hz, C6Me), 1.28—1.34 (m, 6H, C4Me, C14Me), 1.45 (s, 3H, C8Me), 1.63 (dd, 3H,  $J=1.0$ , 6.5 Hz, C23Me), 1.75 (s, 3H, C18Me), 2.11 (m, 1H, H6), 2.32 (m, 1H, H4), 2.50—2.60 (m, 2H, H14, H16), 2.65 (dd, 1H,  $J=9.0$ , 16.0 Hz, H12), 2.72 (dd, 1H,  $J=2.0$ , 16.0 Hz, H12), 3.33 (s, 3H), 3.35—3.50 (m, 2H, H10, H20), 3.38 (s, 3H), 3.41 (s, 3H), 3.42 (s, 3H), 3.46 (s, 3H), 3.56 (s, 3H), 3.66 (s, 3H), 3.72 (dd, 1H,  $J=5.0$ , 10.0 Hz, H16'), 3.79 (dd, 1H,  $J=7.0$ , 10.0 Hz, H16'), 3.92 (dd, 1H,  $J=4.5$ , 11.0 Hz, H1), 3.97 (dd, 1H,  $J=3.5$ , 11.0 Hz, H1), 4.05 (d, 1H,  $J=9.5$  Hz, H5), 4.18 (s, 1H, H7), 4.21 (m, 1H, H2), 4.26 (d, 1H,  $J=8.5$  Hz, H3), 4.37 (dd, 1H,  $J=3.5$ , 3.5 Hz, H15), 4.40—4.50 (m, 3H, H13, H17, MOM), 4.58 (d, 1H,  $J=6.0$  Hz), 4.70 (d, 1H,  $J=6.8$  Hz), 4.74 (d, 1H,  $J=6.0$  Hz), 4.76 (d, 1H,  $J=11.0$  Hz), 4.83 (d, 1H,  $J=11.0$  Hz), 4.96 (d, 1H,  $J=6.0$  Hz), 5.11 (d, 1H,  $J=6.0$  Hz), 5.33 (ddq, 1H,  $J=10.0$ , 10.0, 1.0 Hz, H21), 5.36—5.46 (m, 2H, H9, H22), 5.63 (d, 1H,  $J=10.0$  Hz, H19), 5.72 (s, 1H), 6.60—6.80 (m, 2H), 7.00—7.15 (m, 2H), 7.30—7.40 (m, 2H).  $^{13}\text{C-NMR}$  (125 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$ : -4.83, -4.73, 5.29, 7.55, 8.11, 10.32, 12.58, 12.95, 13.57, 15.14, 17.05, 18.96, 22.06, 26.73, 31.15, 31.39, 37.19, 42.61, 45.32, 46.72, 47.63, 56.07, 56.15, 56.68, 62.30, 63.66, 71.65, 74.35, 77.79, 78.71, 79.26, 81.28, 83.67, 83.74, 94.63, 95.75, 97.82, 103.13, 111.47, 112.36, 112.72, 112.81, 119.68, 120.70, 122.46, 126.01, 128.41, 128.60, 128.79, 132.50, 132.87, 133.57, 135.64, 135.84, 135.89, 150.23, 150.36, 150.71, 150.96, 212.28.

**(2S,3S,4R,5S,6S,7R,8E,10S,13S,14R,15S,16S,17S,18E,20S,21Z)-3,5-[(S)-3,4-Dimethoxybenzylidenedioxy]-13,15-[(S)-3,4-dimethoxybenzylidenedioxy]-16-[(1,1-dimethylethyl)dimethylsilyloxyethyl]-4,6,8,10,14,18,20-heptamethyl-1-triethylsilyloxy-2,7,17-trismethoxymethoxy-8,18,21-tricosatrien-11-one (8)** DDQ (5.1 mg, 22  $\mu\text{mol}$ ) was added to a stirred

solution of **6** (22 mg, 18  $\mu\text{mol}$ ) in  $\text{CH}_2\text{Cl}_2$  (2 ml) at  $-10^\circ\text{C}$  under argon. After 40 min, saturated aqueous  $\text{NaHCO}_3$  was added to quench the reaction, and the reaction mixture was extracted with  $\text{Et}_2\text{O}$ . The extract was washed with saturated aqueous  $\text{NaHCO}_3$  and brine, dried over  $\text{Na}_2\text{SO}_4$ , concentrated *in vacuo*, and chromatographed on a silica gel column, eluting with *n*-hexane-EtOAc (2:1), to give recovered **6** (3.2 mg, 15%) and **8** as a colorless oil (17.5 mg, 80%; 93% based on the consumed **6**).  $[\alpha]_{\text{D}}^{19} +32^\circ$  ( $c=0.44$ ,  $\text{CHCl}_3$ ). IR (neat)  $\text{cm}^{-1}$ : 2950, 1715, 1520, 1460, 1265, 1165, 1035, 840.  $^1\text{H-NMR}$  (500 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$ : 0.19 (s, 3H), 0.20 (s, 3H), 0.73 (q, 6H,  $J=8.0$  Hz), 1.02 (d, 3H,  $J=7.0$  Hz, C20Me), 1.07 (s, 9H), 1.11 (t, 9H,  $J=8.0$  Hz), 1.15 (d, 3H,  $J=6.5$  Hz, C10Me), 1.27 (d, 3H,  $J=6.5$  Hz, C6Me), 1.29 (d, 3H,  $J=6.5$  Hz, C4Me), 1.37 (s, 3H, C8Me), 1.38 (d, 3H,  $J=6.5$  Hz, C14Me), 1.67 (d, 3H,  $J=5.5$  Hz, C23Me), 1.75 (d, 3H,  $J=0.5$  Hz, C18Me), 2.00—2.15 (m, 2H, H14, H6), 2.30 (m, 1H, H4), 2.32 (dd, 1H,  $J=5.0$ , 16.5 Hz, H12), 2.65 (m, 1H, H16), 2.95 (dd, 1H,  $J=7.5$ , 16.5 Hz, H12), 3.24 (s, 3H), 3.27 (s, 3H), 3.25—3.35 (m, 1H, H10), 3.42 (s, 3H), 3.425 (s, 3H), 3.43 (s, 3H), 3.48 (m, 1H, H20), 3.54 (s, 3H), 3.62 (s, 3H), 3.78 (dd, 1H,  $J=6.0$ , 10.0 Hz, H16'), 3.92 (dd, 1H,  $J=4.0$ , 11.0 Hz, H1), 3.98 (d, 1H,  $J=11.0$  Hz, H1), 4.01 (dd, 1H,  $J=1.0$ , 10.0 Hz, H5), 4.03 (dd, 1H,  $J=1.0$ , 10.0 Hz, H15), 4.13 (s, 1H, H7), 4.18 (dd, 1H,  $J=3.0$ , 10.0 Hz, H16'), 4.18—4.25 (m, 3H, H2, H3, MOM), 4.54 (d, 1H,  $J=6.5$  Hz), 4.60 (d, 1H,  $J=7.0$  Hz), 4.69 (d, 1H,  $J=6.5$  Hz), 4.75 (m, 1H, H13), 4.80 (d, 1H,  $J=5.0$  Hz, H17), 4.97 (d, 1H,  $J=6.5$  Hz), 5.12 (d, 1H,  $J=6.5$  Hz), 5.35—5.45 (m, 2H, H21, H22), 5.57 (dd, 1H,  $J=0.5$ , 8.5 Hz, H19), 5.58 (d, 1H,  $J=10.0$  Hz, H9), 5.69 (s, 1H), 5.71 (s, 1H), 6.60—6.75 (m, 2H), 7.20—7.40 (m, 4H).  $^{13}\text{C-NMR}$  (125 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$ : -5.43, 4.80, 7.03, 7.56, 7.98, 9.72, 13.03, 13.26, 14.58, 16.24, 18.44, 21.50, 26.17, 26.19, 30.55, 30.86, 33.80, 36.49, 43.72, 46.83, 47.64, 55.46, 55.55, 55.60, 56.08, 60.41, 63.19, 77.80, 79.46, 82.00, 83.26, 94.53, 95.28, 97.37, 102.58, 110.95, 111.02, 111.83, 111.91, 119.18, 119.25, 122.34, 127.91, 128.10, 128.29, 132.49, 132.75, 134.89, 135.64, 135.66, 149.96, 150.50, 207.54. FAB-MS  $m/z$  (%): 1245 ( $\text{M}^+ + 1$ , 1.8), 1214 (3.6), 281 (20), 253 (25), 211 (95), 151 (100), 137 (46). HR-MS Calcd for  $\text{C}_{67}\text{H}_{115}\text{O}_{17}\text{Si}_2$  ( $\text{M}^+ + 1$ ): 1245.7516. Found: 1245.7430.

**(2S,3S,4R,5S,6S,7R,8E,10S,13R,14R,15S,16S,17S,18E,20S,21Z)-3,5-[(S)-3,4-Dimethoxybenzylidenedioxy]-13,15-[(S)-3,4-dimethoxybenzylidenedioxy]-16-[(1,1-dimethylethyl)dimethylsilyloxyethyl]-4,6,8,10,14,18,20-heptamethyl-1-triethylsilyloxy-2,7,17-trismethoxymethoxy-8,18,21-tricosatrien-11-one (9)** DDQ (1.7 mg, 7.5  $\mu\text{mol}$ ) was added to a stirred solution of **7** (6.0 mg, 4.8  $\mu\text{mol}$ ) in  $\text{CH}_2\text{Cl}_2$  (0.5 ml) at  $-10^\circ\text{C}$  under argon. After 30 min, work-up as described above gave recovered **7** (0.5 mg, 8.3%) and **9** as a colorless oil (5.0 mg, 84%; 91% based on the consumed **7**).  $^1\text{H-NMR}$  (500 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$ : 0.16 (s, 3H), 0.17 (s, 3H), 0.73 (q, 6H,  $J=8.0$  Hz), 1.04 (s, 9H), 1.07 (d, 3H,  $J=6.9$  Hz, C20Me), 1.11 (t, 9H,  $J=8.0$  Hz), 1.17 (d, 3H,  $J=6.8$  Hz, C10Me), 1.30 (d, 3H,  $J=6.2$  Hz, C6Me), 1.31 (d, 3H,  $J=6.0$  Hz, C4Me), 1.44 (s, 3H, C8Me), 1.65 (d, 3H,  $J=6.6$  Hz, C14Me), 1.74 (dd, 3H,  $J=0.5$ , 6.6 Hz, C23Me), 1.79 (s, 3H, C18Me), 1.98 (m, 1H, H14), 2.10 (m, 1H, H6), 2.30 (m, 1H, H4), 2.59 (m, 1H, H16), 2.82 (dd, 1H,  $J=6.8$ , 15.1 Hz, H12), 3.23 (s, 3H), 3.32 (s, 3H), 3.25—3.37 (m, 1H, H10), 3.41 (s, 3H), 3.42 (s, 3H), 3.43 (s, 3H), 3.38—3.48 (m, 1H, H20), 3.54 (s, 3H), 3.49—3.58 (m, 1H, H12), 3.61 (s, 3H), 3.80 (dd, 1H,  $J=5.7$ , 10.4 Hz, H16'), 3.92 (dd, 1H,  $J=4.6$ , 11.1 Hz, H1), 3.97 (dd, 1H,  $J=3.6$ , 11.1 Hz, H1), 4.04 (d, 1H,  $J=9.7$  Hz, H5), 4.10 (dd, 1H,  $J=3.2$ , 10.4 Hz, H16'), 4.17 (s, 1H, H7), 4.18—4.27 (m, 2H, H2, H3), 4.28 (d, 1H,  $J=10.0$  Hz, H15), 4.38 (d, 1H,  $J=6.9$  Hz), 4.55 (d, 1H,  $J=6.4$  Hz), 4.63—4.71 (m, 3H), 4.80 (d, 1H,  $J=5.2$  Hz, H17), 4.97 (d, 1H,  $J=6.6$  Hz), 5.11 (d, 1H,  $J=6.6$  Hz), 5.52 (ddq, 1H,  $J=9.5$ , 9.5, 0.5 Hz, H21), 5.59 (m, 1H, H22), 5.62 (d, 1H,  $J=9.2$  Hz, H19), 5.71 (s, 1H), 5.72 (d, 1H,  $J=10.0$  Hz, H9), 6.01 (s, 1H), 6.60—6.75 (m, 2H), 7.30—7.50 (m, 4H).

**(2S,3S,4R,5S,6S,7R,8E,10S,13S,14R,15S,16S,17S,18E,20S,21Z)-3,5-[(S)-3,4-Dimethoxybenzylidenedioxy]-13,15-[(S)-3,4-dimethoxybenzylidenedioxy]-16-[(1,1-dimethylethyl)dimethylsilyloxyethyl]-4,6,8,10,14,18,20-heptamethyl-1-hydroxy-2,7,17-trismethoxymethoxy-8,18,21-tricosatrien-11-one (10)** a) AcOH (2.4  $\mu\text{l}$ , 42  $\mu\text{mol}$ ) and a 1.0 M solution of TBAF (21  $\mu\text{l}$ , 21  $\mu\text{mol}$ ) were added to a stirred solution of **8** (17.5 mg, 14  $\mu\text{mol}$ ) in THF (0.5 ml) at  $0^\circ\text{C}$ . After 3 h, the reaction was quenched with saturated aqueous  $\text{NaHCO}_3$ , and the reaction mixture was extracted with  $\text{Et}_2\text{O}$ . The extract was washed with saturated aqueous  $\text{NaHCO}_3$  and brine, dried over  $\text{Na}_2\text{SO}_4$ , concentrated *in vacuo*, and chromatographed on a silica gel column, eluting with *n*-hexane-EtOAc (1:2), to give the recovered starting material (0.4 mg, 2.3%) and **10** as a colorless oil (13.8 mg, 87%; 89% based on the consumed **8**).  $[\alpha]_{\text{D}}^{18} +52^\circ$  ( $c=0.20$ ,  $\text{CHCl}_3$ ). IR (neat)  $\text{cm}^{-1}$ : 3500, 2925, 1710, 1520, 1460, 1260, 1160, 1030.  $^1\text{H-NMR}$  (500 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$ : 0.19 (s, 3H), 0.20 (s, 3H), 1.02 (d, 3H,  $J=6.5$  Hz, C20Me), 1.07 (s, 9H), 1.14 (d, 3H,  $J=7.0$  Hz, C4Me), 1.16 (d, 3H,  $J=7.0$  Hz, C10Me), 1.25 (d,

3H,  $J=6.5$  Hz, C6Me), 1.39 (s, 3H, C8Me), 1.41 (d, 3H,  $J=6.5$  Hz, C14Me), 1.67 (d, 3H,  $J=5.5$  Hz, C23Me), 1.74 (s, 3H, C18Me), 2.00—2.10 (m, 2H, H6, H14), 2.18 (m, 1H, H4), 2.33 (dd, 1H,  $J=5.0$ , 16.5 Hz, H12), 2.43 (br, 1H, OH), 2.76 (m, 1H, H16), 2.97 (dd, 1H,  $J=8.0$ , 16.5 Hz, H12), 3.20 (s, 3H), 3.23 (s, 3H), 3.26 (s, 3H), 3.20—3.35 (m, 1H, H10), 3.42 (s, 3H $\times$ 2), 3.47 (m, 1H, H20), 3.53 (s, 3H), 3.60 (s, 3H), 3.72 (m, 1H, H1), 3.78 (dd, 1H,  $J=6.0$ , 10.0 Hz, H16'), 3.87 (m, 1H, H1), 3.98 (dd, 1H,  $J=2.0$ , 10.0 Hz, H5), 4.03 (m, 1H, H2), 4.05 (dd, 1H,  $J=1.5$ , 10.0 Hz, H15), 4.06 (s, 1H, H7), 4.13—4.20 (m, 3H, H3, H16', MOM), 4.54 (d, 1H,  $J=6.5$  Hz), 4.55 (d, 1H,  $J=6.5$  Hz), 4.69 (d, 1H,  $J=6.5$  Hz), 4.72 (d, 1H,  $J=6.5$  Hz), 4.77 (m, 1H, H13), 4.79 (d, 1H,  $J=5.0$  Hz, H17), 4.92 (d, 1H,  $J=6.5$  Hz), 5.35—5.47 (m, 2H, H21, H22), 5.55 (d, 1H,  $J=9.0$  Hz, H19), 5.57 (d, 1H,  $J=9.0$  Hz, H9), 5.64 (s, 1H), 5.71 (s, 1H), 6.60—6.80 (m, 2H), 7.20—7.40 (m, 4H).  $^{13}\text{C-NMR}$  (125 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$ : -5.42, -5.37, 7.03, 8.01, 9.76, 13.03, 13.25, 14.54, 16.22, 18.43, 21.50, 26.19, 30.07, 30.86, 33.85, 36.30, 43.90, 46.84, 47.64, 53.28, 55.39, 55.47, 55.56, 55.58, 55.63, 56.07, 60.42, 61.46, 77.85, 77.94, 79.48, 79.66, 82.00, 82.32, 94.55, 95.27, 102.51, 102.55, 110.99, 111.85, 111.96, 119.18, 122.34, 125.44, 127.90, 128.19, 130.61, 132.46, 132.69, 134.87, 135.32, 135.67, 149.96, 150.53, 207.55. FAB-MS  $m/z$  (%): 1131 ( $\text{M}^+ + 1$ , 10), 1130 ( $\text{M}^+$ , 7.1), 1114 (5.4), 1068 (4.0), 862 (5.3), 826 (5.5), 811 (7.8), 663 (5.5), 527 (9.2), 459 (8.8), 151 (100). HR-MS Calcd for  $\text{C}_{61}\text{H}_{99}\text{O}_{17}\text{Si}$  ( $\text{M}^+ + 1$ ): 1131.6651. Found: 1131.6590.

b) AcOH (0.1 ml) was added to a stirred solution of **8** (2.8 mg, 2.25  $\mu\text{mol}$ ) in THF-H<sub>2</sub>O (4 : 1, 0.5 ml) at room temperature. After 2 h, the reaction was quenched with saturated aqueous NaHCO<sub>3</sub>, and work-up as described above gave **10** as a colorless oil (2.5 mg, 98%).

**(2R,3S,4R,5S,6S,7R,8E,10S,13S,14R,15S,16S,17S,18E,20S,21Z)-3,5-[(S)-3,4-Dimethoxybenzylidenedioxy]-13,15-[(S)-3,4-dimethoxybenzylidenedioxy]-4,6,8,10,-14,18,20-heptamethyl-16-hydroxymethyl-11-oxo-2,7,17-trimethoxymethoxy-8,18,21-tricosatrienoic Acid (3)** A solution of **10** (13.8 mg, 12  $\mu\text{mol}$ ) in CH<sub>2</sub>Cl<sub>2</sub> (0.5 ml) was added dropwise to a stirred solution of the Dess–Martin reagent (26 mg, 61  $\mu\text{mol}$ ) and pyridine (25  $\mu\text{l}$ , 307  $\mu\text{mol}$ ) in CH<sub>2</sub>Cl<sub>2</sub> (0.5 ml) at room temperature. After 9.5 h, saturated aqueous NaHCO<sub>3</sub> and saturated aqueous Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> were added to quench the reaction, and the reaction mixture was extracted with Et<sub>2</sub>O. The extract was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo*, to leave a crude aldehyde (16.2 mg).

A solution of NaClO<sub>2</sub> (11.0 mg, 122  $\mu\text{mol}$ ) and NaH<sub>2</sub>PO<sub>4</sub> (22.0 mg, 183  $\mu\text{mol}$ ) in H<sub>2</sub>O (2 ml) was added dropwise to a stirred solution of the above aldehyde (16.2 mg) and 2-methyl-2-butene (130  $\mu\text{l}$ ) in 2-methyl-2-propanol (0.8 ml) at room temperature. After 1 h, the reaction mixture was diluted with Et<sub>2</sub>O, washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo* to leave a crude carboxylic acid (20.2 mg), a part of which was purified by silica gel chromatography.  $[\alpha]_{\text{D}}^{21} + 41^\circ$  ( $c=0.21$ , CHCl<sub>3</sub>). IR (neat)  $\text{cm}^{-1}$ : 3500—2400, 2925, 1740, 1715, 1520, 1460, 1260, 1160, 1030, 835, 740.  $^1\text{H-NMR}$  (500 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$ : 0.19 (s, 3H), 0.20 (s, 3H), 1.03 (d, 3H,  $J=6.5$  Hz), 1.09 (s, 9H), 1.17 (d, 3H,  $J=6.5$  Hz), 1.22 (d, 3H,  $J=6.5$  Hz), 1.36 (s, 3H), 1.40—1.45 (m, 6H), 1.67 (d, 3H,  $J=6.5$  Hz), 1.73 (s, 3H), 1.98 (m, 1H), 2.07 (m, 1H), 2.15 (d, 1H,  $J=16.5$  Hz), 2.35 (m, 1H), 2.63 (m, 1H), 2.91 (dd, 1H,  $J=8.5$ , 16.5 Hz), 3.20 (s, 3H), 3.20—3.60 (m, 2H), 3.30 (s, 3H), 3.43 (s, 3H $\times$ 2), 3.49 (s, 3H), 3.53 (s, 3H), 3.62 (s, 3H), 3.75 (dd, 1H,  $J=6.5$ , 10.0 Hz), 3.94 (br, 1H), 3.96 (d, 1H,  $J=10.0$  Hz), 4.00 (d, 1H,  $J=10.5$  Hz), 4.06 (d, 1H,  $J=7.0$  Hz), 4.18 (dd, 1H,  $J=3.0$ , 10.0 Hz), 4.22 (d, 1H,  $J=7.0$  Hz), 4.51 (d, 1H,  $J=6.5$  Hz), 4.65 (d, 1H,  $J=6.5$  Hz), 4.68—4.81 (m, 6H), 5.38—5.48 (m, 3H), 5.53 (d, 1H,  $J=9.0$  Hz), 5.61 (s, 1H), 5.63 (s, 1H), 6.60—6.80 (m, 2H), 7.20—7.40 (m, 4H). FAB-MS  $m/z$  (%): 1146 ( $\text{M}^+ + 2$ , 5.2), 1145 ( $\text{M}^+ + 1$ , 5.6), 1144 ( $\text{M}^+$ , 9.4), 926 (9.6), 803 (9.8), 743 (10), 688 (11), 550 (12), 413 (17), 337 (28), 149 (100).

AcOH (8.4  $\mu\text{l}$ , 150  $\mu\text{mol}$ ) and a 1.0 M solution of TBAF (120  $\mu\text{l}$ , 120  $\mu\text{mol}$ ) were added to a stirred solution of the above crude carboxylic acid (20 mg) in THF (1 ml) at room temperature. After 2 d, the reaction mixture was diluted with Et<sub>2</sub>O, washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated *in vacuo*, and chromatographed on a silica gel column, eluting with CH<sub>2</sub>Cl<sub>2</sub>-MeOH (10 : 1), to give **3** as a colorless solid (8.5 mg, 68%).  $[\alpha]_{\text{D}}^{20} + 81^\circ$  ( $c=0.09$ , CHCl<sub>3</sub>). IR (neat)  $\text{cm}^{-1}$ : 3500—2400, 2925, 1740, 1715, 1520, 1460, 1265, 1160, 1030, 805, 760.  $^1\text{H-NMR}$  (500 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$ : 1.03 (d, 3H,  $J=6.5$  Hz), 1.16 (d, 3H,  $J=6.5$  Hz), 1.23 (d, 6H,  $J=6.5$  Hz), 1.36 (s, 3H), 1.46 (d, 3H,  $J=6.5$  Hz), 1.63 (dd, 3H,  $J=1.5$ , 6.5 Hz), 1.60—1.70 (m, 1H), 1.77 (d, 3H,  $J=1.0$  Hz), 2.00—2.15 (m, 2H), 2.30—2.40 (m, 1H), 2.60—2.70 (m, 1H), 2.85 (dd, 1H,  $J=8.5$ , 16.5 Hz), 3.14 (s, 3H), 3.34 (s, 3H), 3.20—3.35 (m, 1H), 3.44 (s, 6H), 3.35—3.50 (m, 1H), 3.49 (s, 3H), 3.55 (s, 3H), 3.63 (s, 3H), 3.84 (dd, 1H,  $J=4.5$ , 11.5 Hz), 3.91 (dd, 1H,  $J=1.0$ , 10.5 Hz), 3.93 (dd, 1H,  $J=7.5$ , 11.5 Hz), 3.99 (d, 1H,  $J=9.5$  Hz), 4.01 (d, 1H,  $J=9.5$  Hz), 4.11 (d, 1H,  $J=7.0$  Hz), 4.30—4.40 (m, 1H), 4.37 (d, 1H,  $J=$

6.5 Hz), 4.42 (d, 1H,  $J=10.0$  Hz), 4.53 (d, 1H,  $J=10.0$  Hz), 4.60—4.70 (m, 1H), 4.74 (d, 2H,  $J=6.5$  Hz), 4.77—4.85 (m, 2H), 5.30—5.50 (m, 3H), 5.52 (d, 1H,  $J=9.0$  Hz), 5.55 (s, 1H), 5.67 (s, 1H), 6.64 (d, 1H,  $J=8.0$  Hz), 6.70 (d, 1H,  $J=8.0$  Hz), 7.10—7.20 (m, 1H), 7.25—7.40 (m, 3H).  $^{13}\text{C-NMR}$  (125 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$ : 7.22, 7.41, 9.67, 13.21, 13.56, 14.54, 16.35, 21.39, 30.84, 33.49, 36.09, 46.36, 46.69, 53.29, 55.63, 55.76, 56.07, 60.37, 65.27, 77.29, 79.88, 81.20, 82.31, 83.43, 94.58, 96.97, 102.44, 102.76, 110.67, 111.09, 111.59, 111.93, 119.34, 119.37, 122.64, 125.09, 127.91, 128.09, 128.29, 130.57, 132.32, 134.93, 135.34, 149.96, 150.30, 150.60, 178.63, 207.52. FAB-MS  $m/z$  (%): 1032 ( $\text{M}^+ + 2$ , 2.7), 1031 ( $\text{M}^+ + 1$ , 7.7), 1030 ( $\text{M}^+$ , 9.9), 968 (14), 784 (16), 753 (16), 690 (15), 440 (19), 391 (22), 230 (36), 136 (100). HR-MS Calcd for  $\text{C}_{55}\text{H}_{82}\text{O}_{18}$  ( $\text{M}^+$ ): 1030.5501. Found: 1030.5490.

**(2R,3S,4R,5S,6S,7R,8E,10S,13S,14R,15S,16S)-2,7-Bismethoxymethyl-oxo-3,5-[(S)-3,4-dimethoxybenzylidenedioxy]-13,15-[(S)-3,4-dimethoxybenzylidenedioxy]-16-[(1S,2E,4S,5Z)-2,4-dimethyl-1-methoxymethoxy-2,5-heptadienyl]-11-oxo-4,6,8,10,-14-pentamethyl-8-heptadecenoic Acid (2)** Et<sub>3</sub>N (2.0  $\mu\text{l}$ , 15  $\mu\text{mol}$ ) and 2,4,6-trichlorobenzoyl chloride (2.0  $\mu\text{l}$ , 13  $\mu\text{mol}$ ) were added to a stirred solution of **3** (8.0 mg, 7.8  $\mu\text{mol}$ ) in THF (0.5 ml) at room temperature under argon. After 16.5 h, the reaction mixture was diluted with benzene (0.5 ml), then DMAP (2.4 mg, 20  $\mu\text{mol}$ ) was added, and the stirring was continued for 3 h. The reaction was quenched with saturated aqueous NH<sub>4</sub>Cl, and the reaction mixture was extracted with Et<sub>2</sub>O. The extract was washed with saturated aqueous NH<sub>4</sub>Cl and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated *in vacuo*, and chromatographed on a silica gel column, eluting with *n*-hexane-EtOAc (1 : 1), to give **2** as a colorless solid (6.8 mg, 87%).  $[\alpha]_{\text{D}}^{20} + 32^\circ$  ( $c=0.37$ , CHCl<sub>3</sub>). IR (neat)  $\text{cm}^{-1}$ : 2925, 2850, 1740, 1720, 1520, 1460, 1265, 1160, 1030, 810.  $^1\text{H-NMR}$  (500 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$ : 0.94 (d, 3H,  $J=7.0$  Hz, C10Me), 1.00 (d, 3H,  $J=6.5$  Hz, C20Me), 1.40—1.50 (m, 1H, H14), 1.48 (s, 3H, C8Me), 1.58 (d, 3H,  $J=6.5$  Hz, C6Me), 1.60 (d, 3H,  $J=6.5$  Hz, C14Me), 1.65 (d, 3H,  $J=5.5$  Hz, C23Me), 1.67 (s, 3H, C18Me), 1.73 (d, 3H,  $J=6.5$  Hz, C4Me), 1.93 (m, 1H, H4), 1.98 (m, 1H, H6), 2.82 (dd, 1H,  $J=8.5$ , 13.5 Hz, H12), 2.98 (dd, 1H,  $J=6.0$ , 13.5 Hz, H12), 3.03 (m, 1H, H16), 3.08 (s, 3H), 3.23 (s, 3H), 3.31 (s, 3H), 3.28—3.36 (m, 1H, H10), 3.39 (s, 3H), 3.41 (s, 3H), 3.35—3.45 (m, 1H, H20), 3.45 (s, 3H), 3.56 (s, 3H), 3.88 (dd, 1H,  $J=1.0$ , 10.5 Hz, H15), 3.96 (dd, 1H,  $J=0.5$ , 11.5 Hz, H16'), 4.11 (d, 1H,  $J=10.5$  Hz, H7), 4.37 (d, 1H,  $J=6.5$  Hz), 4.35—4.41 (m, 1H, H13), 4.42 (d, 1H,  $J=1.5$  Hz, H5), 4.45 (d, 1H,  $J=6.5$  Hz), 4.53 (d, 1H,  $J=6.5$  Hz), 4.60 (dd, 1H,  $J=1.5$ , 8.5 Hz, H3), 4.63 (d, 1H,  $J=8.5$  Hz, H2), 4.64 (d, 1H,  $J=7.0$  Hz), 4.66 (d, 1H,  $J=7.0$  Hz), 4.68 (d, 1H,  $J=6.5$  Hz), 4.92 (d, 1H,  $J=4.5$  Hz, H17), 5.28 (d, 1H,  $J=8.5$  Hz, H9), 5.31 (dd, 1H,  $J=1.5$ , 11.5 Hz, H16'), 5.40—5.51 (m, 2H, H21, H22), 5.61 (d, 1H,  $J=9.0$  Hz, H19), 5.77 (s, 1H), 6.17 (s, 1H), 6.65 (d, 1H,  $J=8.0$  Hz), 6.66 (d, 1H,  $J=8.0$  Hz), 7.30—7.45 (m, 4H).  $^{13}\text{C-NMR}$  (125 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$ : 7.49, 8.48, 11.10, 12.59, 12.91, 13.33, 14.31, 16.72, 21.24, 23.07, 29.77, 30.08, 30.16, 30.96, 35.23, 37.27, 39.74, 43.68, 44.77, 45.45, 55.35, 55.50, 55.56, 55.60, 55.83, 63.77, 78.25, 80.05, 81.86, 82.92, 85.78, 93.64, 94.44, 97.50, 102.43, 102.80, 110.90, 111.39, 111.95, 111.97, 119.31, 119.51, 122.52, 131.74, 132.41, 132.84, 133.57, 135.90, 136.04, 149.95, 150.20, 150.64, 150.91, 169.80, 207.75. FAB-MS  $m/z$  (%): 1014 ( $\text{M}^+ + 2$ , 8.8), 1013 ( $\text{M}^+ + 1$ , 16), 1012 ( $\text{M}^+$ , 11), 663 (8.2), 211 (31), 154 (73), 136 (56), 45 (100). HR-MS Calcd for  $\text{C}_{55}\text{H}_{84}\text{O}_{17}$  ( $\text{M}^+ + 1$ ): 1013.5473. Found: 1013.5440.

**Methyl (2R,3S,4R,5S,6S,7R,8E,10S,13S,14R,15S,16S,17S,18E,20S,21Z)-3,5-[(S)-3,4-Dimethoxybenzylidenedioxy]-13,15-[(S)-3,4-dimethoxybenzylidenedioxy]-4,6,8,10,14,18,20-heptamethyl-16-hydroxymethyl-11-oxo-2,7,17-trimethoxymethoxy-8,18,21-tricosatrienoate (11)** Et<sub>3</sub>N (1.0  $\mu\text{l}$ , 7.2  $\mu\text{mol}$ ) and 2,4,6-trichlorobenzoyl chloride (1.0  $\mu\text{l}$ , 6.4  $\mu\text{mol}$ ) were added to a stirred solution of **3** (1.0 mg, 1  $\mu\text{mol}$ ) in THF (0.5 ml) at room temperature under argon. After 14 h, the reaction was quenched with MeOH, and the reaction mixture was diluted with Et<sub>2</sub>O, washed with saturated aqueous NH<sub>4</sub>Cl and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated *in vacuo*, and chromatographed on a silica gel column, eluting with *n*-hexane-EtOAc (1 : 2), to give **11** as a colorless solid (0.7 mg, 70%). IR (neat)  $\text{cm}^{-1}$ : 3500, 2950, 2875, 1745, 1720, 1520, 1460, 1265, 1160, 1030, 805.  $^1\text{H-NMR}$  (500 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$ : 1.00 (d, 3H,  $J=6.5$  Hz, C20Me), 1.17 (d, 3H,  $J=7.0$  Hz, C10Me), 1.23 (d, 6H,  $J=6.5$  Hz, C6Me, C14Me), 1.28 (s, 3H, C8Me), 1.41 (d, 3H,  $J=6.5$  Hz, C4Me), 1.62 (dd, 3H,  $J=1.5$ , 6.5 Hz, C23Me), 1.60—1.70 (m, 1H, H14), 1.77 (s, 3H, C18Me), 2.04 (dd, 1H,  $J=4.0$ , 16.5 Hz, H12), 2.00—2.10 (m, 1H, H6), 2.24 (m, 1H, H4), 2.65 (m, 1H, H16), 2.77 (m, 1H, OH), 2.86 (dd, 1H,  $J=8.5$ , 16.5 Hz, H12), 3.15 (s, 3H), 3.21 (m, 1H, H10), 3.28 (s, 3H), 3.30 (s, 3H), 3.42 (s, 3H), 3.43 (s, 3H), 3.40—3.50 (m, 1H, H20), 3.53 (s, 3H), 3.56 (s, 3H), 3.57 (s, 3H), 3.82 (m, 1H, H16'), 3.90 (m, 1H, H16'), 3.95 (dd, 1H,  $J=1.5$ , 10.0 Hz, H15), 3.98 (dd, 1H,  $J=1.0$ , 10.0 Hz, H5), 4.06 (s, 1H, H7), 4.11 (d, 1H,  $J=7.0$  Hz), 4.39 (d, 1H,  $J=6.5$  Hz), 4.43 (dd, 1H,

$J=1.5, 9.0\text{ Hz}$ , H3), 4.52 (d, 1H,  $J=7.0\text{ Hz}$ ), 4.56 (d, 1H,  $J=6.5\text{ Hz}$ ), 4.66 (m, 1H, H13), 4.71 (d, 1H,  $J=9.0\text{ Hz}$ , H2), 4.72 (d, 1H,  $J=7.0\text{ Hz}$ ), 4.77 (d, 1H,  $J=7.0\text{ Hz}$ ), 4.78 (d, 1H,  $J=4.5\text{ Hz}$ , H17), 5.30—5.45 (m, 2H, H21, H22), 5.52 (d, 1H,  $J=9.0\text{ Hz}$ , H9), 5.54 (d, 1H,  $J=8.5\text{ Hz}$ , H19), 5.60 (s, 1H), 5.64 (s, 1H), 6.64 (d, 1H,  $J=8.0\text{ Hz}$ ), 6.70 (d, 1H,  $J=8.0\text{ Hz}$ ), 7.30—7.40 (m, 4H). FAB-MS  $m/z$  (%): 1045 ( $M^+ + 1$ , 12), 1044 ( $M^+$ , 9.3), 1014 (4.3), 979 (9.7), 871 (8.2), 797 (13), 616 (11), 557 (14), 435 (16), 391 (15), 211 (22), 154 (78), 136 (95), 69 (100). HR-MS Calcd for  $C_{56}H_{84}O_{18}$  ( $M^+$ ): 1044.5658. Found: 1044.5710.

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