JOC*Note*

Structural Revision of Terpenoids with a (3*Z*)-2-Methyl-3-penten-2-ol Moiety by the Synthesis of (23*E*)- and (23*Z*)-Cycloart-23-ene-3β,25-diols

Shunya Takahashi,*[,†] Hiroko Satoh,[‡] Yayoi Hongo,[†] and Hiroyuki Koshino*[,†]

RIKEN (The Institute of Physical and Chemical Research), Wako, Saitama 351-0198, Japan, and National Institute of Informatics, 2-1-2 Hitotsubashi, Chiyoda-ku, Tokyo 101-8430, Japan

shunyat@riken.jp; koshino@riken.jp

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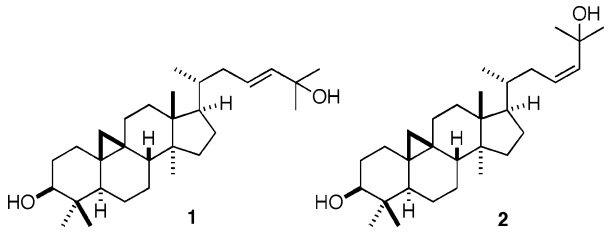

Synthesis of (23*E*)-cycloart-23-ene-3β,25-diol (**1**) and its 23*Z*-isomer **2** was achieved by using cycloartenol as a starting material, thus revising the proposed structure of natural **2** to **1** unequivocally. These synthetic studies revealed that the structural revision (*Z*-form → *E*-form) should also be applied to terpenoids such as (23*Z*)-3β-acetoxyeupha-7,23-diene-25-ol, (23*Z*)-tirucalla-7,23-diene-3β,25-diol, quadrangularol A, quadrangularic acid K, and daurichromene C.

Cycloart-23-ene-3β,25-diol was first discovered from Spanish moss (*Tillandsia usneoides*) by Djerassi and McCrindle in 1962.[1] Greca et al.[2] isolated the diol from *Juncus effusus*, and determined its structure to be (23*Z*)-cycloart-23-ene-3β,25-diol (**2**);[3−5] the double bond stereochemistry was assigned by the small vicinal coupling constant values, which were extracted from overlapping olefinic signals with a half-bandwidth of 8 Hz. On the contrary Weber et al.[6] identified (23*E*)-cycloart-23-ene-3β,25-diol (**1**)[7,8] from *Aglaria rubiginosa*, and suggested that NMR data of **1** in $CDCl_3$ were identical with those of the compound previously reported as the corresponding *Z*-isomer **2**.[2] In spite of that report, isolation and identification of **2** and its 3-acyl derivatives[9] from the plant kingdom have been disclosed since by several groups.[10,11] These confusing results suggest that reexaminations were necessary to confirm the stereochemistry for not only many other (23*Z*)-cycloart-23-en-25-ol derivatives with oxygenated functional groups[12,13] but also other triterpenoids with the same side chain portion such as (23*Z*)-3β-acetoxyeupha-7,23-diene-25-ol[9] and (23*Z*)-tirucalla-7,23-diene-3β,25-diol.[14]

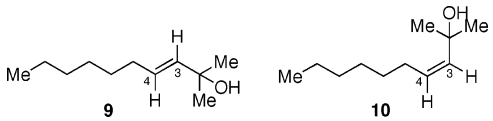

FIGURE 1. Structures of olefins (**9** and **10**).

To distinguish the stereochemistry of a 1,2-disubstituted double bond, the vicinal coupling constant value is generally used, but in the case of the above-mentioned compounds, olefinic proton signals are overlapped in $CDCl_3$ solution. A ^{13}C NMR chemical shift comparison is also a very useful and promising method for the determination of the double bond stereochemistry. In previous papers, some of us (H.K. and H.S.) developed a new stereochemical coding method, CAST (CAnonical-representation of STereochemistry)[15−17] and successfully applied it to a database-oriented ^{13}C NMR chemical shift prediction system, called CAST/CNMR.[18−20] In the course of studies applying CAST/CNMR to cycloart-23-en-25-ol derivatives, we could not find reliable ^{13}C NMR data of compounds with the 2-methyl-3-penten-2-ol moiety that possesses *Z*

* Address correspondence to this author. Phone: +81-48-467-9223. Fax: +81-48-462-4627.
† RIKEN.
‡ National Institute of Informatics.

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SCHEME 1. Synthesis of (23*E*)-Cycloart-23-ene-3*β*,25-diol (1) and Its 23*Z*-Isomer (2)

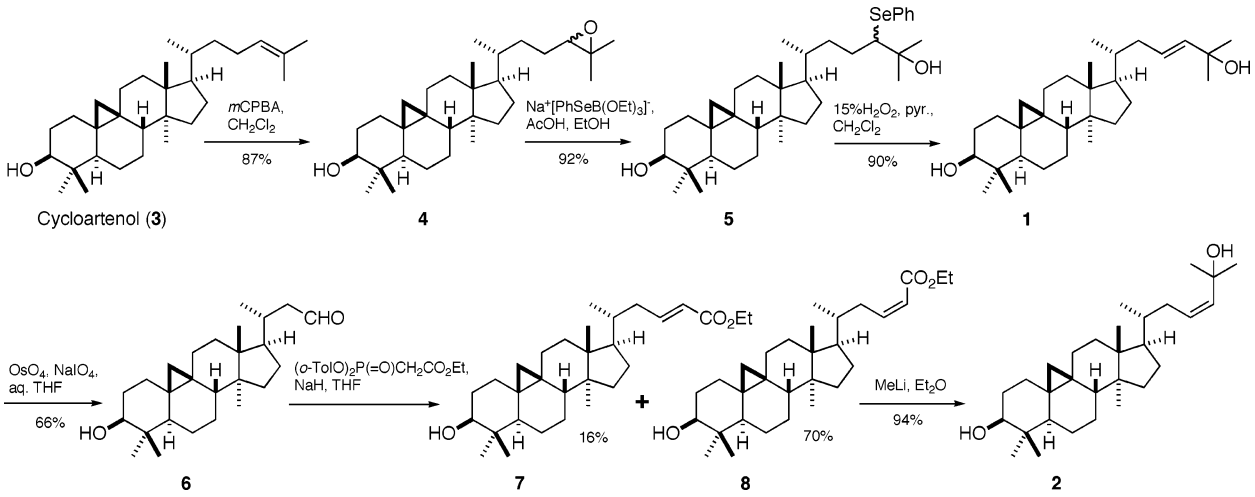

TABLE 1. ^{1}H NMR Data (*δ*) for (23*E*)-Cycloart-23-ene-3*β*,25-diol (1) and Its (23*Z*)-Isomer 2

position	**1**	**2**	**2**[a]	**2**[b]	**2**[c]
H-22a	1.74 m	2.13 dddd (14.8, 9.9, 8.8, 1.7)			
H-22b	2.17 ddd (14.0, 3.3, 3.3)	2.38 dddd (14.8, 6.1, 3.8, 1.7)			
H-23	5.60 m	5.31 ddd (12.1, 8.8, 6.1)	5.59 m[d]	5.60 dd (4.1, 3.1)	5.59 m
H-24	5.60 m	5.53 ddd (12.1, 1.7, 1.7)	5.59 m[d]	5.60 dd (4.1, 3.1)	5.59 br d (8.0)
H-26	1.31 s	1.36 s	1.33 s	1.32 s	1.32 s
H-27	1.32 s	1.37 s	1.33 s	1.32 s	1.32 s

[a] Reference 2. [b] Reference 3. [c] Reference 9. [d] Half-bandwidth of 8 Hz.

stereochemistry.[21−25] Total synthesis of **1** and **2** also has not been reported. Therefore, we planned to prepare authentic samples to add into the database of CAST/CNMR. Described herein are the stereoselective synthesis of (23*E*)-cycloart-23-ene-25-ol (**1**) and its *Z*-isomer **2**, and a detailed comparison of their NMR data with those from the literature.[2,3,9,11−14]

Prior to the synthesis of **1** and **2**, simple model compounds, (3*E*)- and (3*Z*)-2-methyl-3-decen-2-ol (**9** and **10**),[22] were prepared (Figure 1).[26] The ^{1}H NMR spectrum of **9** revealed the olefinic protons H-3 and H-4 at *δ* 5.60−5.61 as complicated multiplets whereas those of **10** were observed at *δ* 5.48 (dt, $J_{3,4}$ = 11.6 Hz, $J_{3,5}$ = 1.8 Hz) and *δ* 5.31 (dt, $J_{3,4}$ = 11.6 Hz, $J_{4,5}$ = 7.1 Hz). In the ^{13}C NMR spectra, compounds **9** and **10** each showed two olefinic carbons C-3 and C-4 at 137.8 and 127.4 ppm, and 136.7 and 131.4 ppm, respectively. It should be mentioned that the misassignment with regard to *E*/*Z* stereochemistry was made in ref 22. In the case of a compound showing overlapping olefinic signals in the ^{1}H NMR spectrum such as **9**, ^{1}H NMR measurement in a solvent other than $CDCl_3$ should be examined to determine the geometry of the double bond clearly (vide infra). Compared with the reported data,[2,3,5] it seemed that the relationship between H-23 and H-24 of all reported natural cycloart-23-ene-3*β*,25-diol should be *E*. To confirm this precisely, we synthesized both isomers of cycloart-23-ene-3*β*,25-diol as follows. Cycloartenol (**3**), prepared from *γ*-oryzanol,[27−29] was epoxidized with *m*CPBA to give a mixture of epoxides **4** in 87% yield (Scheme 1). Nucleophilic opening of **4** with a selenide anion prepared from diphenyldiselenide-sodium borohydride in ethanol[30,31] afforded a mixture of selenide alcohols **5** in 92% yield. Oxidation of the compound with hydrogen peroxide in the presence of pyridine gave the *E*-olefin **1** exclusively in 90% yield. In the ^{1}H NMR spectrum of **1** in $CDCl_3$, two olefinic protons were observed at *δ* 5.60 as a multiplet (Table 1), but the large coupling constant value of *J* = 15.5 Hz for the *E* double bond was observed from ^{13}C satellite signals by ^{13}C selectively decoupled ^{1}H NMR experiments irradiating the C-23 or C-24 resonance.[32] Additionally, the ^{1}H NMR spectrum of **1** in C_6D_6 supported the *E* geometry based on a large vicinal coupling constant value (*J* = 15.8 Hz) between H-23 and H-24 whose signals were observed at *δ* 5.68 (ddd, *J* = 15.8, 8.3, 6.7 Hz) and 5.68 (d, *J* = 15.8 Hz), respectively.[6] In the ^{13}C NMR spectra ($CDCl_3$), two olefin carbons and quaternary C-25 were observed at 125.6, 139.4, and 70.7 ppm, respectively (Table 2). The ^{1}H and ^{13}C NMR spectral data of **1**

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TABLE 2. ^{13}C NMR Data (δ) for Synthetic and Natural Compounds 1, 2, and 11−15

	$CDCl_3$							pyridine-d_5			
position[a]	**1**	**2**	**2**[b]	**2**[c]	**11**[c]	**12**[d]	**15**[e]	**1**	**2**	**13**[f]	**14**[g]
C-22 (5′)	39.0	34.6	39.0	39.0	38.0	38.9	42.3	39.5	35.0	39.5	39.3
C-23 (6′)	125.6	130.2	139.3[h]	125.6	126.0	125.6	125.3	124.5	129.1	124.6	124.4
C-24 (7′)	139.4	137.4	125.6[h]	139.3	139.1	139.4	139.2	141.7	139.5	141.6	141.3
C-25 (8′)	70.7	71.6	70.8	70.8	70.7	70.7	70.8	69.7	70.7	69.7	69.6
C-26 (9′)	30.0	31.3	29.9	29.9	29.9	29.9	29.9	30.9	31.9	30.5	30.0
C-27 (10′)	29.9	31.1	29.9	29.9	29.9	29.9	29.9	30.9	31.8	30.5	30.6

[a] In the case of compound **15**, the numbering system in parentheses is used. [b] Reference 2. [c] Reference 9. [d] Reference 14. [e] Reference 25. [f] Reference 13. [g] Reference 12. [h] These assignments should be interchanged.

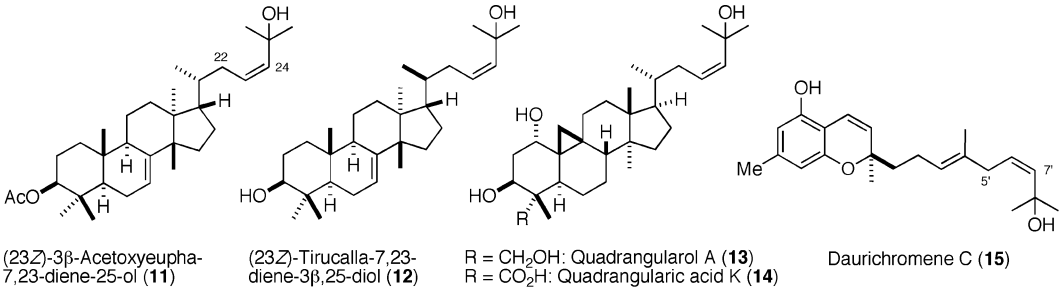

FIGURE 2. Originally proposed structures of terpenoids (**11**−**15**).

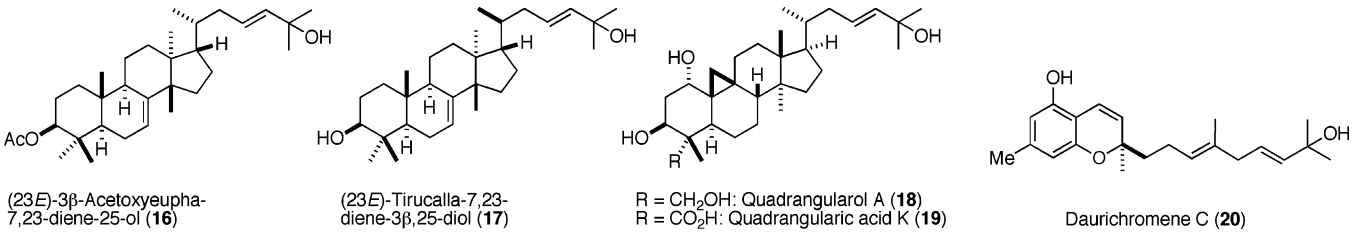

FIGURE 3. Revised structures of terpenoids (**11**−**15**).

in $CDCl_3$ were consistent with those of the reported *Z*-isomer.[3,4,6] Synthesis of the corresponding *Z*-isomer (**2**) started from **1**. The double bond in the latter was oxidized under Lemieux−Johnson oxidation to afford aldehyde **6** in 66% yield. The Wittig reaction of **6** with Ando's protocol[33] gave a desired *Z*-ester **8** in 70% yield along with the corresponding *E*-isomer **7** (15%). After separation by chromatography on silica gel, the *Z*-ester **8** was treated with a small excess of methyllithium in ether at −78 °C, giving *tert*-alcohol **2** in 88% yield. The spectrum of **2** in $CDCl_3$ showed the olefinic protons H-23 at δ 5.31 (ddd, J= 12.1, 8.8, 6.1 Hz) and H-24 at δ 5.53 (ddd, J = 12.1, 1.7, 1.7 Hz), which were clearly different from the reported data for **2**.[2,3,5] On the basis of these results, we concluded that the structure of the previously reported *Z*-isomer **2** and its 3-acyl derivatives[2−5,9−11] should be revised to that of the corresponding *E*-isomers.

The (3*Z*)-2-methyl-3-penten-2-ol moiety is recognized as a common substructure included in many natural products such as (23*Z*)-3β-acetoxyeupha-7,23-diene-25-ol (**11**),[9] (23*Z*)-tirucalla-7,23-diene-3β,25-diol (**12**),[11] quadrangularol A (**13**),[13] quadrangularic acid K (**14**),[12] and daurichromene C (**15**)[25] (Figure 2). However, spectral data of the olefin part in such natural products were well matched with those of synthetic **1** as shown in Table 2. Therefore, the geometry of the terminal olefin should be revised to the *E* stereochemistry as shown in Figure 3.

In summary, we synthesized both geometrical isomers of cycloart-23-ene-3β,25-diol (**1** and **2**). The detailed NMR studies including complete ^{1}H and ^{13}C NMR assignments in $CDCl_3$, pyridine-d_5, C_6D_6, and methanol-d_4 (see the Supporting Information) of **1** and **2** together with model compounds **9** and **10**, which were confirmed by analyses of 2D DQFCOSY, HSQC, and HMBC spectra, revealed that most terpenoids with a (3*Z*)-2-methyl-3-penten-2-ol moiety such as (23*Z*)-cycloart-23-ene-3β,25-diol (**2**), (23*Z*)-3β-acetoxyeupha-7,23-diene-25-ol (**11**), (23*Z*)-tirucalla-7,23-diene-3β,25-diol (**12**), quadrangularol A (**13**), quadrangularic acid K (**14**), and daurichromene C (**15**), should be revised to the corresponding *E*-isomers (**1**, and **16**−**20**), respectively. Further work on these studies is in progress.

Experimental Section

Epoxides (4). To a stirred solution of **3** (1.05 g, 2.5 mmol) in dichloromethane (20 mL) was added *m*-chloroperoxybenzoic acid (70−75% assay, 0.73 g, ca. 3.0 mmol) at 0 °C. The mixture was stirred at 0 °C to rt for 5 h, and then poured into aqueous saturated $NaHCO_3/Na_2S_2O_3$ (1:1) with stirring. The resulting mixture was extracted with dichloromethane. The extracts were washed with water and brine, dried, and concentrated. Chromatography on silica gel with *n*-hexane−ethyl acetate (10:1) as the eluent yielded **4** (0.95

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g, 87%) as an amorphous solid. IR (neat) 3320, 3039, 2927, 2860, 1445, 1378, 1099, 1046 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.27 (1H, m), 2.68 (1H, t, $J = 6.3$ Hz), 2.02−0.73 (25H, m), 1.30 (3H, br s), 1.26 (3H, br s), 0.96 (6H, s), 0.89 (3H, s), 0.88 (3H, d, $J = 6.1$ Hz), 0.80 (3H, s), 0.55 (1H, br d, $J = 3.9$ Hz), 0.32 (1H, br d, $J = 3.9$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 78.8, 64.9, 64.8, 58.4, 58.1, 52.2, 52.1, 48.8, 47.9, 47.1, 45.2, 40.4, 35.9, 35.8, 35.5, 32.9, 32.8, 32.7, 32.6, 31.9, 30.3, 29.9, 29.7, 28.1, 28.0, 26.4, 26.0, 25.9, 25.6, 25.4, 24.9, 21.1, 19.9, 19.3, 18.7, 18.6, 18.2, 18.1, 18.0, 14.0; HRMS (EI) calcd for $C_{30}H_{50}O_2$ (M^+) 442.3811, found 442.3811.

Selenoalcohols (5). At 0 °C, acetic acid (25 μL, 0.44 mmol) was added to an ethanolic solution of $Na^+[PhSeB(OEt)_3]^-$, prepared by the reduction of diphenyl diselenide (423 mg, 1.36 mmol) with sodium borohydride (103 mg, 2.72 mmol) in ethanol (8 mL), and the mixture was stirred at the same temperature for 10 min. To the solution was added dropwise a solution of **4** (400 mg, 0.90 mmol) in ethanol (3 mL). The resulting mixture was stirred at 80 °C for 5 h, cooled, diluted with ether, and then washed with water and brine, dried, and concentrated. Chromatography on silica gel with *n*-hexane−ethyl acetate (1:0 → 10:1 → 4:1) as the eluent yielded **5** (501 mg, 92%) as an amorphous solid. IR (neat) 3304, 3052, 2932, 2864, 1578, 1470, 1437, 1377, 1047, 1022 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.61−7.55 (2H, m), 7.26−7.22 (3H, m), 3.28 (1H, m), 3.09 (0.6H, dd, $J = 8.7$, 2.0 Hz), 3.01 (0.4H, dd, $J = 11.7$, 2.0 Hz), 2.02−0.71 (47H, m), 0.55 (0.4H, d, $J = 3.9$ Hz), 0.54 (0.6H, d, $J = 3.9$ Hz), 0.33 (0.4H, d, $J = 3.9$ Hz), 0.32 (0.6H, d, $J = 3.9$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.7, 133.4, 131.4, 129.1, 127.2, 127.1, 78.8, 72.9, 72.8, 66.8, 65.7, 52.3, 52.2, 48.7, 48.0, 47.1, 40.5, 36.4, 35.9, 35.5, 35.4, 35.2, 35.1, 32.9, 31.9, 30.4, 29.9, 29.5, 28.1, 27.9, 26.9, 26.8, 26.4, 26.2, 25.4, 21.1, 19.9, 18.6, 18.0, 17.9, 13.9; HRMS (EI) calcd for $C_{36}H_{56}O_2Se$ (M^+) 600.3445, found 600.3420.

(23*E*)-Cycloart-23-ene-3β,25-ol (1). Aqueous hydrogen peroxide (15%, 2 mL, ca. 8.9 mmol) was added to a solution of **5** (333 mg, 0.56 mmol) and pyridine (0.16 mL) in dichloromethane (4 mL) at 0 °C. The mixture was stirred at 0 °C to rt for 13 h, and then diluted with ether. The solution was washed with 10% aqueous copper sulfate, water, and brine, and then dried and concentrated. Chromatography on silica gel with *n*-hexane−ethyl acetate (1:0 → 10:1 → 4:1) as the eluent gave **1** (221 mg, 90%) as a crystalline solid. Mp 199−200 °C (ethyl acetate); $[\alpha]^{25}_D$ +36.2 (*c* 0.13, $CHCl_3$); IR (neat) 3281, 3049, 2928, 2865, 1457, 1441, 1375, 1143, 1049, 970 cm^{-1}; HRMS (EI) calcd for $C_{30}H_{50}O_2$ (M^+) 442.3811, found 442.3812.

Aldehyde (6). To a stirred solution of **1** (136 mg, 0.31 mmol) in tetrahydrofuran (3 mL) and water (1 mL) was added dropwise a solution of OsO_4 (ca. 0.008 mmol) in 2-methyl-2-propanol (0.1 mL) at rt. After the solution was stirred for few minutes, $NaIO_4$ (263 mg, 1.23 mmol) was added in portions. After being stirred for an additional 12 h, the mixture was filtered through a pad of Celite, and the filtrate was extracted with ethyl acetate. The extracts were washed successively with aqueous $Na_2S_2O_3$, water, saturated aqueous $NaHCO_3$, water, and brine, dried, and concentrated. Chromatography on silica gel with *n*-hexane-ethyl acetate (1:0 → 10:1 → 4:1) as the eluent yielded **6** (78 mg, 66%) as an amorphous solid. $[\alpha]^{24}_D$ +25.6 (*c* 0.31, $CHCl_3$); IR (neat) 3440, 3040, 2930, 2702, 1716, 1447, 1438, 1374, 1362, 1335, 1022 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.75 (1H, dd, $J = 3.4$, 1.5 Hz), 3.27 (1H, ddd, $J = 11.2$, 4.4, 3.9 Hz), 2.46 (1H, dd, $J = 15.6$, 1.9 Hz), 2.16 (1H, ddd, $J = 15.6$, 9.3, 3.4 Hz), 2.09−0.72 (21H, m), 1.01 (3H, s), 0.96 (3H, d, $J = 6.3$ Hz), 0.95 (3H, s), 0.89 (3H, s), 0.80 (3H, s), 0.55 (1H, d, $J = 3.9$ Hz), 0.33 (1H, d, $J = 0.39$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.5, 78.7, 52.2, 51.1, 48.9, 47.9, 47.0, 45.4, 40.4, 35.4, 32.7, 31.9, 30.3, 29.8, 28.3, 26.3, 26.1, 25.9, 25.4, 21.0, 19.8, 19.6, 19.3, 18.0, 14.0; HRMS (EI) calcd for $C_{26}H_{42}O_2$ (M^+) 386.3185, found 386.3179.

$\alpha\beta$-Unsaturated esters (7 and 8). To a stirred suspension of NaH (60% oil dispersion, 14.5 mg, 0.36 mmol) in THF (1.0 mL) was added dropwise ethyl di-*O*-tolylphosphonoacetate (106 μL, 0.36 mmol) at 0 °C, and the mixture was stirred at 0 °C for 30 min. To this solution was added a solution of **6** (31 mg, 0.08 mmol) in THF (0.2 mL) at −78 °C and the mixture was stirred at −78 °C for 1 h and then −78 to 0 °C for 1 h. After addition of water, the mixture was extracted with ether. The extracts were washed successively with water and brine, dried, and concentrated. The residue was purified by preparative TLC (*n*-hexane−ethyl acetate (4:1), 8 developments) to give **7** (5.8 mg, 16%) and **8** (25.6 mg, 70%).

7: $[\alpha]^{25}_D$ +39.1 (*c* 0.12, $CHCl_3$); IR (neat) 3426, 3031, 2931, 2864, 1702, 1648, 1442, 1366, 1305, 1267, 1162, 1044, 1023, 981 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.95 (1H, ddd, $J = 15.7$, 8.8, 6.3 Hz), 5.80 (1H, d, $J = 15.7$ Hz), 4.18 (2H, q, $J = 7.3$ Hz), 3.26 (1H, m), 2.32 (1H, dd, $J = 14.1$, 6.3 Hz), 2.02−0.75 (22H, m), 1.28 (3H, t, $J = 7.3$ Hz), 0.97 (3H, s), 0.96 (3H, s), 0.89 (3H, d, $J = 6.3$ Hz), 0.88 (3H, s), 0.80 (3H, s), 0.55 (1H, d, $J = 3.9$ Hz), 0.32 (1H, d, $J = 3.9$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 148.4, 122.4, 78.8, 60.1, 52.0, 48.8, 48.0, 47.1, 45.4, 40.5, 39.3, 36.0, 35.5, 32.7, 31.9, 30.4, 29.9, 28.1, 26.4, 26.1, 26.0, 25.4, 21.1, 19.9, 19.3, 18.6, 18.0, 14.3, 14.0; HRMS (EI) calcd for $C_{30}H_{48}O_3$ (M^+) 456.3603, found 456.3621.

8: $[\alpha]^{24}_D$ +22.6 (*c* 0.31, $CHCl_3$); IR (neat) 3300, 3030, 2925, 2860, 1718, 1638, 1445, 1373, 1170, 1037, 1020 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.25 (1H, ddd, $J = 11.2$, 8.3, 6.8 Hz), 5.80 (1H, dt, $J = 11.2$, 1.9 Hz), 4.16 (2H, q, $J = 7.4$ Hz), 3.28 (1H, m), 2.64−2.58 (2H, m), 2.03−0.75 (21H, m), 1.28 (3H, t, $J = 7.4$ Hz), 0.98 (3H, s), 0.96 (3H, s), 0.90 (3H, d, $J = 6.6$ Hz), 0.89 (3H, s), 0.81 (3H, s), 0.55 (1H, $J = 3.9$ Hz), 0.33 (1H, d, $J = 3.9$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 149.8, 120.4, 78.8, 59.7, 52.4, 48.8, 48.0, 47.1, 45.4, 40.5, 36.7, 35.7, 35.6, 32.8, 32.0, 30.4, 29.9, 28.1, 26.4, 26.1, 26.0, 25.5, 21.1, 20.0, 19.3, 18.5, 18.1, 14.3, 14.0; HRMS (EI) calcd for $C_{30}H_{48}O_3$ (M^+) 456.3603, found 456.3587.

(23*Z*)-Cycloart-23-ene-3β,25-ol (2). To a stirred solution of **8** (17.0 mg, 0.04 mmol) in ether (0.6 mL) was added a 0.98 M ether solution of methyllithium (0.4 mL, 0.39 mmol) at −78 °C, and the mixture was stirred at −78 °C for 2 h, and then 0 °C for 30 min. After being quenched with saturated aqueous NH_4Cl, the mixture was extracted with ether. The extracts were washed successively with water and brine, dried, and concentrated. Chromatography on silica gel with *n*-hexane−ethyl acetate (10:0 → 4:1) as the eluent gave **2** (15.5 mg, 94%) as a white solid. Mp 145−147 °C (*n*-hexane−ether); $[\alpha]^{24}_D$ +31.2 (*c* 0.16, $CHCl_3$); IR (neat) 3336, 3047, 3010, 2948, 2933, 2861, 1636, 1449, 1373, 1359, 1335, 1146, 1053, 1025, 951 cm^{-1}; HRMS (EI) calcd for $C_{30}H_{50}O_2$ (M^+) 442.3811, found 442.3811.

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Supporting Information Available: ^1H and ^{13}C NMR data of **1**, **2**, **9**, and **10**, and NMR spectra of **1**, **2**, and **4**−**8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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