Design and Synthesis of 23,24-Dinoroleanolic Acid Derivatives, Novel Triterpenoid−Steroid Hybrid Molecules

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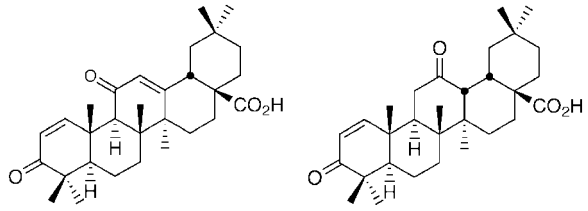
In a previous paper, we reported that oleanolic acid derivatives with a 1-en-3-one functionality in ring A, e.g., **1** and **2**, show significant inhibitory activity against interferon-γ-induced nitric oxide (NO) production in mouse macrophages.[1] Mechanism studies reveal that enones **1** and **2** suppress transcription or translation of inducible nitric oxide synthase (iNOS) and inducible cyclooxygenase (COX-2) genes.[2] Glucocorticoids, e.g., hydrocortisone and dexamethasone, are also well known to have similar activities.[3] For the structure of glucocorticoids, a 4-en-3-one or 1,4-dien-3-one functionality in ring A is characteristic.[4] Thus, the design and synthesis of triterpenoid−steroid hybrid molecules, i.e., 23,24-dinoroleanolic acid derivatives **3**−**6**, is deemed to be very interesting from the perspective of structure−activity relationships. We herein describe the synthesis of compounds **3**−**6** derived from oleanolic acid (**7**).



The removal of the two methyl groups at C-4 from tetracyclic and pentacyclic triterpenoids has been the subject of a considerable number of reports.[5] On the basis of these studies, we envisioned two strategies for the removal of the two methyl groups at C-4 from oleanolic acid (**7**). In our first strategy, it was ambiguous whether phosphorus pentachloride (PCl_5) would give the desired ring contraction product **9a** in the first step according to classical procedures.[5a−d,g] In our second strategy, there were two potential problems as follows. A Beckmann or Schmidt rearrangement on the C-3 ketone was known to give lactam **10b** in addition to the desired compound **10a**.[6] In addition, it was unclear whether olefin **11** would be obtained from **10a** in the second step of this sequence. Initially, we examined the first sequence involving ring contraction of methyl oleanolate (**8**)[7] to **9a** since this plan seemed to have fewer complications than the alternative strategy.

Results and Discussion

In the event, dehydration of methyl oleanolate (**8**), derived from oleanolic acid (**7**) with ethereal diazomethane, with PCl_5 in benzene and toluene gave the desired ring contraction product **9a** and an unknown byproduct **9b** [**9a**:**9b** = 7:1].[8] Although both compounds have the same R_f value on TLC, pure **9a** was obtained as colorless needles in 63% yield by recrystallization from acetone. This successful ring contraction led us to pursue the first synthetic strategy as shown in Scheme 1.

For the transformation of olefin **9a** into ketone **12a**, the obvious ozonolysis cannot be used because ozone also reacts with the C-12 olefin of oleanane triterpenoids to give the 12α,13α-epoxide, 12-ketone,[9] and 12α-hydroxy lactone.[11] Therefore, various other oxidation conditions were examined. Oxidation of **9a** with a catalytic amount of osmium tetraoxide and 4-methylmorpholine *N*-oxide in aqueous acetone[12] gave a complex mixture. A catalytic amount of ruthenium tetraoxide (RuO_4) and sodium metaperiodate in aqueous CH_3CN and CCl_4[13] also gave a complex mixture. Under the conditions of a catalytic amount of RuO_4 and sodium hypochlorite in CCl_4,[14] **9a** was recovered. However, a stoichiometric amount of

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(7) Frazier, D.; Noller, C. R. *J. Am. Chem. Soc.* **1944**, *66*, 1267.

(8) This ratio was determined from the integration ratio of the olefin proton at C-12 of each compound [**9a**: δ 5.32 (1H, t, J = 3.4 Hz), **9b**: δ 5.37 (1H, t)] in the ^{1}H NMR spectrum.

(9) Unpublished results: Methyl 3β-acetoxyolean-12-en-28-oate was converted into methyl 3β-acetoxy-12α,13α-epoxyolean-28-oate by ozonolysis in CH_2Cl_2 (−78 °C) followed by triethylamine,[10] and this compound was also converted into methyl 3β-acetoxy-12-oxoolean-28-oate by ozonolysis, followed by triphenylphosphine.[10]

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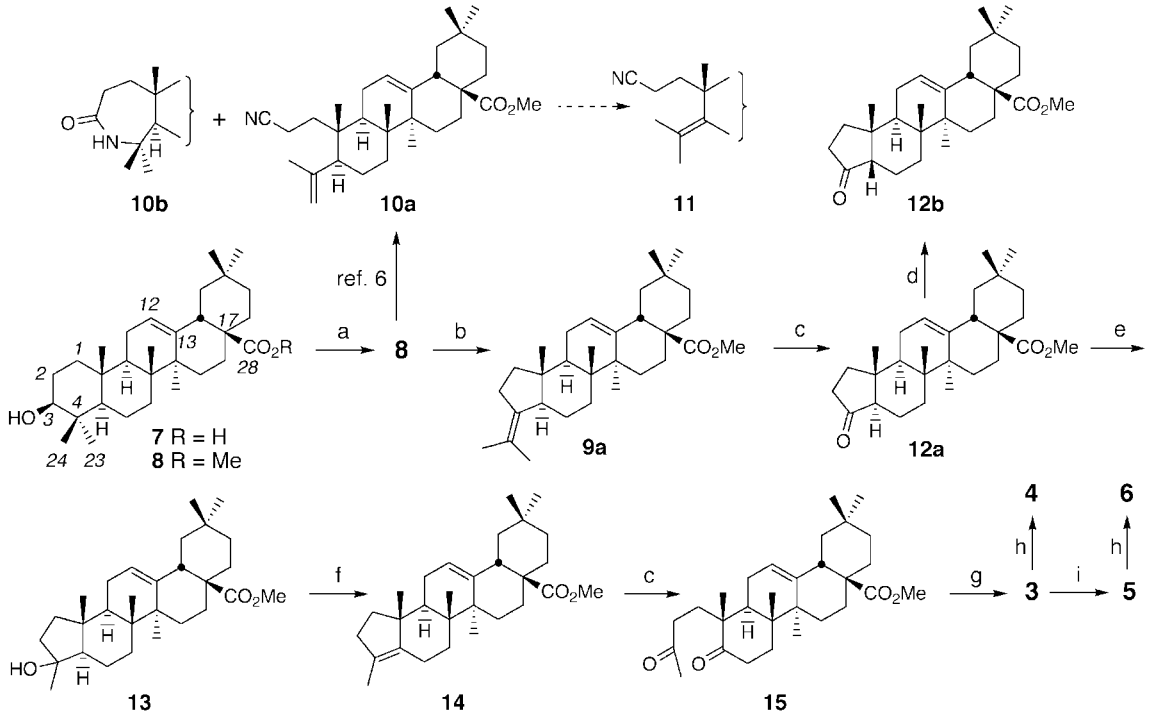
Scheme 1[a]



[a] Key: (a) $CH_2N_2/Et_2O/THF$; (b) PCl_5/PhH/toluene; (c) RuO_4/CCl_4; (d) $AcOH/CH_2Cl_2$; (e) $MeMgBr/Et_2O$; (f) $POCl_3$/pyr; (g) $NaOH/H_2O$/MeOH; (h) Li/DMF; (i) PhSeCl/EtOAc, $30\%H_2O_2$/THF.

RuO_4 in CCl_4[15] was found to afford the desired ketone **12a** in 86% yield.[16] Because of partial isomerization of **12a** to **12b** on silica gel column chromatography and, also, because treatment of **12a** with acetic acid in CH_2Cl_2 gave **12b** in 54% yield, **12a** and **12b** were assigned to have the 5α and 5β configurations, respectively,[5g] although this assignment was not proven.

We initially examined the introduction of the methyl group into the C-3 carbonyl group using the pure cis ketone **12b**. However, with both methylmagnesium bromide (MeMgBr) and methyllithium (MeLi), only the starting material **12b** was recovered in quantitative yield.[17] On the other hand, methylation of crude **12a** with MeLi in Et_2O (−78 °C) gave **13**[18] (42% yield) and some byproducts whose structures are unknown. Moreover, MeMgBr in Et_2O at room temperature gave **13** in 69% yield as a sole product. This difference in reactivity between **12a** and **12b** is not at all obvious.

Dehydration of **13** with phosphoryl chloride in pyridine[19] at room temperature for 1 day gave olefin **14** in 95% yield. Oxidation of **14** with a stoichiometric amount of RuO_4 in CCl_4 gave 1,5-diketone **15**. Without further purification, **15** was cyclized via an aldol condensation with sodium hydroxide[5g] in methanol to afford the desired enone **3**, a new triterpenoid−steroid hybrid molecule (75% yield from **14**). Three other new triterpenoid−steroid hybrid molecules were synthesized from **3** as follows. Enone acid **4** was prepared in 81% yield by halogenolysis of **3** with lithium iodide (LiI) in DMF.[20] Insertion of a double bond into the C-1 position of **3** was accomplished by phenylselenenyl chloride in ethyl acetate, followed by oxidation with hydrogen peroxide[21] to provide dienone **5** in 62% yield. In the ^{13}C NMR spectrum of **5**, the chemical shift of the C-3 ketone was observed at 186 ppm. This value is characteristic for a 1,4-dien-3-one functionality.[22,23] Halogenolysis of **5** with LiI in DMF gave dienone acid **6** in 78% yield.

Studies on the biological properties of compounds **3**−**6** are in progress.[24]

Experimental Section

General Methods. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Elemental microanalysis was performed by Atlantic Microlab, Inc. TLC was fulfilled with Merck precoated TLC plates (silica gel 60 F_{254}). Flash column chromatography was done with Select Scientific silica gel (230−400 mesh). The standard workup method was as follows: an organic extract was washed with saturated aqueous $NaHCO_3$ solution (three times) and then saturated aqueous NaCl solution (three times), dried over anhydrous $MgSO_4$, and filtered.

Methyl 3-Isopropylidene-*A*-norolean-12-en-28-oate (9a). To a cold (ice bath) solution of methyl oleanolate (**8**) (2.60 g, 5.52 mmol) in benzene (350 mL) and toluene (125 mL) was added PCl_5 (3.00 g, 14.4 mmol, in 50 mL of CH_2Cl_2). After the mixture was stirred in an ice bath for 30 min, saturated aqueous Na_2CO_3

(15) Nakata, H. *Tetrahedron* **1963**, *19*, 1959.
(16) Pure **12a** could not be obtained because of partial isomerization of **12a** into **12b** upon silica gel column chromatography.
(17) Similarily, Ruzicka[5a] and Ourisson[5c] reported that they used drastic conditions for the introduction of a methyl group into a lanostane triterpenoid with the same A ring moiety as **12b**.
(18) Although the ^1H and ^{13}C NMR spectra showed that **13** was a single compound, the configuration at C-3 was not determined.
(19) Paquette, L. A.; Roberts, R. A.; Drtina, G. J. *J. Am. Chem. Soc.* **1984**, *106*, 6690.
(20) Dean, P. D. G. *J. Chem. Soc.* **1965**, 6655.
(21) Sharpless, K. B.; Lauer, R. F.; Teranishi, A. Y. *J. Am. Chem. Soc.* **1973**, *95*, 6137.
(22) Pouchert, C. J.; Behnke, J. In *The Aldrich Library of 13C and 1H FT NMR Spectra*, 1st ed.; Aldrich Chemical Co., Inc.: Milwaukee, 1993; Vol. 3, pp 563−617.
(23) In a 1-en-3-one and 1,3-dien-5-one functionality, the carbonyl carbon was observed at 199−200 ppm.[22]
(24) Preliminary evaluation of these compounds on an iNOS assay revealed that compound **6** showed moderate inhibitory activity at the 1 μM level.

solution (50 mL) and water (100 mL) were added, and stirring was continued at room temperature for another 30 min. After the upper organic phase was separated, the aqueous phase was twice extracted with a mixture of CH_2Cl_2 and Et_2O (1:2). The extract was combined with the original organic phase and worked up according to the standard method. The filtrate was evaporated in vacuo to give a solid (2.47 g). The solid was recrystallized from acetone to afford the title compound as colorless crystals (1.40 g, 56%). The mother liquid was evaporated in vacuo to give a residue (1.02 g). The residue was subjected to flash column chromatography [hexanes−EtOAc (10:1)] to give an amorphous solid (670 mg). This was recrystallized from acetone to give the title compound as colorless crystals (178 mg, 7%): mp 144−145 °C; TLC [hexane/EtOAc (10/1)] R_f 0.5; IR (KBr) 2945, 2860, 1732 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.32 (1H, t, J = 3.4 Hz), 3.64 (3H, s), 2.87 (1H, dd, J = 3.8, 13.6 Hz) 1.75, 1.59, 1.16, 0.94, 0.91, 0.78, 0.69 (each 3H, s); ^{13}C NMR ($CDCl_3$) δ 178.6, 144.5, 135.6, 122.8, 121.1, 56.1, 53.7, 51.8, 47.1, 46.1, 45.5, 44.3, 42.0, 39.5, 39.3, 34.2, 33.4, 32.9, 32.7, 31.0, 28.9, 28.2, 26.4, 25.7, 23.9, 23.4, 23.3, 23.1, 19.8, 17.3, 14.8; EIMS (70 eV) m/z 452 $[M]^+$ (63), 437 (16), 393 (9), 203 (100); HREIMS calcd for $C_{31}H_{48}O_2$ 452.3654, found 452.3640. Anal. Calcd for $C_{31}H_{48}O_2$: C, 82.25; H, 10.69. Found: C, 82.12; H, 10.74.

Methyl 3-Oxo-*A*-norolean-12-en-28-oate (12a). To a stirred suspension of ruthenium dioxide dihydrate (240 mg, 1.42 mmol) in CCl_4 (25 mL) was added a solution of sodium metaperiodate (2.40 g, 11.2 mmol) in water (25 mL) in an ice bath. After the mixture was stirred for 1 h in an ice bath, the lower yellow solution containing RuO_4 (ca. 0.7−0.8 mmol) was separated. To a solution of olefin **9a** (300 mg, 0.663 mmol) in CCl_4 (15 mL), which was covered with water (9 mL), was added the yellow solution of RuO_4, which was prepared as described above. The mixture was stirred at room temperature for 2 h. After the water layer was separated, 2-propanol (1 mL) was added to the mixture. An insoluble matter was removed by filtration through Celite. The filtrate was dried over $MgSO_4$ and filtered. The filtrate was evaporated in vacuo to afford the crude title compound as an amorphous solid (244 mg, 86%): TLC [hexane/EtOAc (5/1)] R_f 0.43; ^1H NMR ($CDCl_3$) δ 5.33 (1H, t, J = 3.3 Hz), 3.62 (3H, s), 2.88 (1H, dd, J = 4.4, 14.2 Hz), 1.17, 0.93, 0.90, 0.81, 0.78 (each 3H, s); ^{13}C NMR ($CDCl_3$) δ 217.0, 178.4, 144.9, 122.1, 62.0, 51.8, 47.0, 46.4, 46.0, 42.2, 41.9, 41.5, 40.6, 36.7, 34.8, 34.1, 33.4, 32.6, 31.7, 31.0, 28.2, 26.4, 24.8, 23.9, 23.3, 17.3, 17.0, 14.8; EIMS (70 eV) m/z 426 $[M]^+$ (57), 367 (55), 203 (100); HREIMS calcd for $C_{28}H_{42}O_3$ 426.3134, found 426.3133. This material was used for the next reaction without further purification.

Methyl 3-oxo-*A*-nor-5-*β*-olean-12-en-28-oate (12b). To a solution of crude olefin **12a** (635 mg, 1.49 mmol) in CH_2Cl_2 (63 mL) was added AcOH (14 mL). The mixture was stirred at room temperature overnight. After it was washed with water (three times), it was worked up according to the standard method. The filtrate was evaporated in vacuo to give a solid (612 mg). The solid was subjected to flash column chromatography [hexanes−EtOAc (5:1)] to give the title compound as a crystalline solid (341 mg, 54%). An analytically pure sample was obtained by recrystallization from MeOH as colorless needles: mp 189−190 °C; TLC [hexane/EtOAc (5/1)] R_f 0.53; IR (KBr) 2962, 2856, 1724 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.35 (1H, t, J = 3.5 Hz), 3.62 (3H, s), 2.86 (1H, dd, J = 4.0, 14.0 Hz) 1.24, 1.02, 0.91, 0.88, 0.81 (each 3H, s); ^{13}C NMR ($CDCl_3$) δ 221.6, 178.4, 144.1, 122.4, 58.1, 51.8, 47.2, 45.9, 42.3, 42.2, 41.4, 38.9, 36.2, 35.6, 34.1, 33.4, 32.5, 31.0, 27.8, 27.0, 25.5, 25.2, 24.9, 23.8, 23.4, 17.4, 16.4; EIMS (70 eV) m/z 426 $[M]^+$ (58), 367 (25), 366 (22), 203 (100); HREIMS calcd for $C_{28}H_{42}O_3$ 426.3134, found 426.3122. Anal. Calcd for $C_{28}H_{42}O_3$: C, 78.83; H, 9.92. Found: C, 78.79; H, 9.91.

Methyl 3-Hydroxy-3-methyl-*A*-norolean-12-en-28-oate (13). (**a**) To a solution of crude olefin **12a** (264 mg, 0.62 mmol) in anhydrous Et_2O (9.6 mL) was added dropwise a solution of MeLi in Et_2O (1.4 M, 0.70 mL, 0.98 mmol) in a dry ice−acetone bath. The mixture was stirred in a dry ice−acetone bath for 1 h. To the mixture was added saturated aqueous NH_4Cl solution (6 mL). After the upper organic layer, separated, the aqueous layer was extracted with a mixture of CH_2Cl_2 and Et_2O (1:2) three times. The extract was combined with the original organic layer and washed with water (twice) and brine (twice), dried over $MgSO_4$, and filtered. The filtrate was evaporated in vacuo to give an amorphous solid (246 mg). The solid was subjected to flash column chromatography [hexanes−EtOAc (4:1)] to give the title compound as colorless crystals (116 mg, 42%).

(**b**) To a solution of crude olefin **12a** (316 mg, 0.74 mmol) in anhydrous Et_2O (12.5 mL) was added dropwise a solution of MeMgBr in Et_2O (3 M, 0.75 mL, 2.3 mmol) in an ice bath. The mixture was stirred at room temperature for 30 min. To the mixture were added saturated aqueous NH_4Cl solution and water. The aqueous mixture was extracted with a mixture of CH_2Cl_2 and Et_2O (1:2) three times. The extract was washed with water (twice) and brine (twice), dried over $MgSO_4$, and filtered. The filtrate was evaporated in vacuo to give an amorphous solid (313 mg). The solid was subjected to flash column chromatography [hexanes−EtOAc (3:1)] to give the title compound as colorless crystals (225 mg, 69%). An analytically pure sample was obtained by recrystallization from MeOH as colorless needles: mp 157−158 °C; TLC [hexane/EtOAc (3/1)] R_f 0.45; IR (KBr) 3565, 2944, 2865, 1718 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.31 (1H, t, J = 3.4 Hz), 3.63 (3H, s), 2.87 (1H, dd, J = 3.9, 13.9 Hz), 1.30, 1.16, 1.00, 0.93, 0.90, 0.77 (each 3H, s); ^{13}C NMR ($CDCl_3$) δ 178.6, 144.5, 122.7, 79.1, 61.2, 51.8, 47.1, 46.8, 46.1, 44.6, 42.1, 41.9, 40.9, 40.3, 34.1, 33.4, 33.0, 32.6, 31.0, 30.1, 28.3, 26.5, 25.3, 23.9, 23.4, 17.7, 17.4, 15.6; CIMS (NH_3) m/z 460 $[M + NH_4]^+$ (6), 443 $[M + H]^+$ (35), 425 (100); HRCIMS (NH_3) calcd for $C_{29}H_{46}O_3$ + H 443.3525, found 443.3519. Anal. Calcd for $C_{29}H_{46}O_3$: C, 78.68; H, 10.47. Found: C, 78.57; H, 10.53.

Methyl 3-Methyl-*A*-norolean-3,12-dien-28-oate (14). To a solution of alcohol **13** (221 mg, 0.50 mmol) in dry pyridine (4.5 mL) was added dropwise $POCl_3$ (1.1 mL) in an ice bath. The mixture was stirred at room temperature overnight. It was poured into ice−water and acidified with 6 M aqueous HCl. The mixture was extracted with a mixture of CH_2Cl_2 and Et_2O (1:2) three times and worked up according to the standard method. The filtrate was evaporated in vacuo to give the title compound as a crystalline solid (201 mg, 95%). An analytically pure sample was obtained by recrystallization from MeOH as colorless needles: mp 170−171 °C; TLC [hexane/EtOAc (10/1)] R_f 0.51; IR (KBr) 2940, 2830, 1729 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.36 (1H, t, J = 3.4 Hz), 3.64 (3H, s), 2.88 (1H, dd, J = 3.9, 13.7 Hz) 1.60, 1.11, 0.94, 0.93, 0.90, 0.85 (each 3H, s); ^{13}C NMR ($CDCl_3$) δ 178.6, 143.9, 142.2, 125.9, 123.2, 51.8, 49.8, 47.2, 46.4, 46.1, 42.2, 42.1, 42.0, 39.9, 35.6, 34.2, 33.4, 32.6, 32.0, 31.0, 28.2, 26.0, 25.4, 23.9, 23.5, 20.0, 19.7, 16.0, 13.9; EIMS (70 eV) m/z 424 $[M]^+$ (87), 409 (48), 365 (19), 162 (100); HREIMS calcd for $C_{29}H_{44}O_2$ 424.3341, found: 424.3343. Anal. Calcd for $C_{29}H_{44}O_2$: C, 82.02; H, 10.44. Found: C, 81.94; H, 10.52.

Methyl 23,24-Dinor-3-oxoolean-4,12-dien-28-oate (3). To a solution of olefin **14** (85 mg, 0.20 mmol) in CCl_4 (5 mL), which was covered with water (3 mL), was added a yellow solution of RuO_4 in CCl_4 (8 mL), which was prepared from ruthenium dioxide dihydrate (66 mg, 0.39 mmol) and sodium metaperiodide (528 mg, 2.5 mmol) according to the same method as for **12a**. The mixture was stirred at room temperature for 1 h. After the water layer was separated, 2-propanol (0.2 mL) was added to the mixture. An insoluble matter was removed by filtration through Celite. The filtrate was dried over $MgSO_4$ and filtered. The filtrate was evaporated in vacuo to afford the crude methyl 3-methyl-3,5-dioxo-3,5-seco-*A*-norolean-12-en-28-oate (**15**) as an amorphous solid (78 mg): TLC [hexane/EtOAc (3/1)] R_f 0.31; ^1H NMR ($CDCl_3$) δ 5.40 (1H, t, J = 3.5 Hz), 3.64 (3H, s), 2.91 (1H, dd, J = 3.9, 13.7 Hz), 2.14, 1.17, 1.10, 0.94, 0.93, 0.91 (each 3H, s); ^{13}C NMR ($CDCl_3$) δ 216.9, 209.0, 178.4, 143.6, 123.1, 51.9, 50.0, 47.4, 45.7, 43.0, 42.2, 40.6, 39.6, 38.9, 35.7, 34.2, 33.4, 32.4, 32.3, 31.0, 30.32, 30.27, 28.0, 25.4, 24.9, 23.8, 23.4, 21.5, 17.4. This material was used for the next reaction without further purification. To a solution of diketone **15** (100 mg) in MeOH (10 mL) was added 10% aqueous NaOH solution. The mixture was heated under reflux for 1 h. After removal of MeOH, water was added to the mixture. The aqueous mixture was extracted with a mixture of CH_2Cl_2 and Et_2O (1:2) three times. The extract was washed with saturated aqueous NH_4Cl solution (three times) and then saturated aqueous NaCl solution (three times), dried over anhydrous $MgSO_4$, and filtered. The filtrate was evaporated in vacuo to give the crude title compound as a crystalline solid (84 mg, 75% from **14**). An analytically pure sample was obtained by recrystallization from MeOH as colorless needles: mp 195−196 °C; $[\alpha]^{23}_D$ +157 ° (*c* 0.31, $CHCl_3$); TLC

[hexane/EtOAc (3/1)] R_f 0.38; UV (EtOH) λ_{max} (log ϵ) 240.2 (4.19) nm; IR (KBr) 2946, 2856, 1729, 1667, 1612 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.73 (1H, s), 5.36 (1H, t, J = 3.5 Hz), 3.63 (3H, s), 2.89 (1H, dd, J = 4.0, 13.6 Hz) 1.22, 1.10, 0.94, 0.91, 0.88 (each 3H, s); ^{13}C NMR ($CDCl_3$) δ 199.7, 178.4, 172.4, 143.9, 123.9, 122.2, 51.8, 47.1, 46.0, 45.9, 42.5, 41.8, 39.6, 38.8, 37.7, 34.1, 33.7, 33.3, 32.5, 32.2, 30.9, 30.0, 27.9, 25.6, 23.9, 23.8, 23.3, 18.6, 16.5; EIMS (70 eV) m/z 438 $[M]^+$ (58), 379 (62), 203 (100); HREIMS calcd for $C_{29}H_{42}O_3$ 438.3134, found 438.3136. Anal. Calcd for $C_{29}H_{42}O_3$: C, 79.41; H, 9.65. Found: C, 79.31; H, 9.68.

23,24-Dinor-3-oxoolean-4,12-dien-28-oic Acid (**4**). A mixture of enone **3** (58 mg, 0.13 mmol) and LiI (300 mg, 2.2 mmol) in dry DMF (1.0 mL) was heated under reflux for 5 h. The mixture was acidified with 5% aqueous HCl and then extracted with a mixture of CH_2Cl_2 and Et_2O (1:2) three times. The extract was worked up according to the standard method. The filtrate was evaporated in vacuo to give a solid (61 mg). The solid was subjected to flash column chromatography [hexanes−EtOAc (1.5:1)] to give the title compound as an amorphous solid (46 mg, 81%): $[\alpha]^{23}_D$ +150 ° (c 0.28, $CHCl_3$); TLC [hexane/EtOAc (1/1)] R_f 0.42; UV (EtOH) λ_{max} (log ϵ) 240.7 (4.11) nm; IR (KBr) 3100 (br), 2942, 2851, 1722, 1694, 1673, 1650, 1617 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.76 (1H, s), 5.37 (1H, t, J = 3.4 Hz), 2.88 (1H, dd, J = 3.9, 13.7 Hz) 1.24, 1.12, 0.99, 0.94, 0.91 (each 3H, s); ^{13}C NMR ($CDCl_3$) δ 199.8, 184.2, 172.4, 143.8, 124.0, 122.5, 47.0, 46.0, 42.6, 41.5, 39.7, 38.9, 37.7, 34.1, 33.7, 33.3, 32.6, 32.2, 31.0, 30.0, 27.9, 25.7, 23.9, 23.8, 23.2, 18.7, 16.6, 14.5; EIMS (70 eV) m/z 424 $[M]^+$ (52), 409 (13), 378 (88), 363 (38), 203 (100); HREIMS calcd for $C_{28}H_{40}O_3$ 424.2977, found 424.2982. Anal. Calcd for $C_{28}H_{40}O_3 \cdot 1/2H_2O$ C, 77.56; H, 9.53. Found: C, 77.64; H, 9.50.

Methyl 23,24-Dinor-3-oxoolean-1,4,12-trien-28-oate (**5**). To a solution of enone **3** (44 mg, 0.10 mmol) in EtOAc (2.5 mL) was added phenylselenenyl chloride (29 mg, 0.15 mmol). The mixture was stirred at room temperature for 5 h. The mixture was washed with water (0.55 mL). After removal of water, THF (0.95 mL) and 30% aqueous H_2O_2 solution (0.09 mL) were added to the mixture. Then, the mixture was stirred for 1 h. After the mixture was diluted with EtOAc (10 mL), it was worked up according to the standard method. The filtrate was evaporated in vacuo to give a crystalline solid (46 mg). The solid was subjected to flash column chromatography [hexanes−EtOAc (2.5:1)] to give the title compound as a crystalline solid (27 mg, 62%). An analytically pure sample was obtained by recrystallization from MeOH as colorless needles: mp 184−185 °C dec; $[\alpha]^{23}_D$ +107° (c 0.28, $CHCl_3$); TLC [hexane/EtOAc (2/1)] R_f 0.42; UV (EtOH) λ_{max} (log ϵ) 242.9 (4.19) nm; IR (KBr) 2947, 2854, 1728, 1658, 1622, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.97 (1H, d, J = 9.8 Hz), 6.11 (1H, dd, J = 2.0, 9.8 Hz), 6.10 (1H, s), 5.35 (1H, t, J = 3.5 Hz), 3.63 (3H, s), 2.89 (1H, dd, J = 4.2, 13.7 Hz) 2.55 (1H, m), 1.26, 1.02, 1.01, 0.91, 0.87 (each 3H, s); ^{13}C NMR ($CDCl_3$) δ 186.6, 178.3, 170.5, 156.5, 144.5, 126.0, 124.1, 121.8, 51.9, 47.1, 45.7, 43.9, 43.0, 42.7, 41.8, 39.9, 34.9, 34.0, 33.3, 32.4, 30.9, 30.1, 28.1, 25.6, 25.2, 23.8, 23.2, 20.2, 17.1; EIMS (70 eV) m/z 436 $[M]^+$ (100), 421 (11), 377 (53); HREIMS calcd for $C_{29}H_{40}O_3$ 436.2977, found 436.2973. Anal. Calcd for $C_{29}H_{40}O_3 \cdot 1/4H_2O$: C, 78.96; H, 9.25. Found: C, 79.09; H, 9.37.

23,24-Dinor-3-oxoolean-1,4,12-trien-28-oic Acid (**6**). A mixture of dienone **5** (58 mg, 0.13 mmol) and LiI (300 mg, 2.2 mmol) in dry DMF (1.0 mL) was heated under reflux for 5 h. The mixture was acidified with 5% aqueous HCl and then extracted with a mixture of CH_2Cl_2 and Et_2O (1:2) three times. The extract was worked up according to the standard method. The filtrate was evaporated in vacuo to give a solid (60 mg). The solid was subjected to flash column chromatography [hexanes−EtOAc (1:1)] to give the title compound as a crystalline solid (43 mg, 78%). An analytically pure sample was obtained by recrystallization from MeOH as colorless needles: mp >290 °C dec; $[\alpha]^{23}_D$ +106 ° (c 0.32, $CHCl_3$); TLC [hexane/EtOAc (1/1)] R_f 0.27; UV (EtOH) λ_{max} (log ϵ) 243.7 (4.11) nm; IR (KBr) 3130 (br), 2940, 2865, 1724, 1654, 1611 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.99 (1H, d, J = 10.0 Hz), 6.16 (1H, dd, J = 2.0, 10.0 Hz), 6.13 (1H, s), 5.37 (1H, t, J = 3.5 Hz), 2.87 (1H, dd, J = 4.3, 13.6 Hz) 2.54 (1H, m), 1.28, 1.06, 1.05, 0.93, 0.90 (each 3H, s); ^{13}C NMR ($CDCl_3$) δ 186.8, 184.0, 170.5, 156.7, 144.3, 126.1, 124.2, 122.0, 46.9, 45.8, 44.0, 43.0, 42.8, 41.5, 40.0, 35.0, 34.0, 33.3, 32.5, 30.9, 30.1, 28.1, 25.6, 25.2, 23.8, 23.1, 20.2, 17.1; EIMS (70 eV) m/z 422 $[M]^+$ (67), 376 (55), 361 (15), 161 (100); HREIMS calcd for $C_{28}H_{38}O_3$ 422.2821, found: 422.2821. Anal. Calcd for $C_{28}H_{38}O_3 \cdot 1/3H_2O$ C, 78.46; H, 9.09. Found: C, 78.72; H, 9.07.

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