Synthesis of β-Boswellic Acid Analogues with a Carboxyl Group at C-17 Isolated from the Bark of *Schefflera octophylla*

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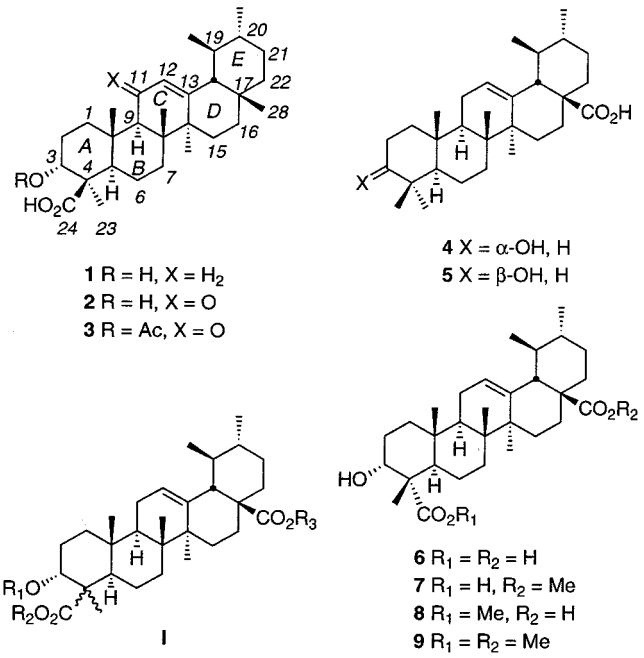
β-Boswellic acid (**1**) and its analogues, **2** and **3**, having a β-carboxyl group at C-4 and an α-hydroxyl group at C-3 in ring A as structural features, are reported to have interesting biological, pharmacological, and medicinal activities, such as antiinflammatory activity, anti-brain tumor activity, inhibition of human leukocyte elastase, anti-complementary activity, and 5-lipoxygenase inhibitory activity.[1] In connection with our triterpenoid project involving the design and synthesis of various oleanane and ursane triterpenoids to discover new structures with high potency against inflammation and/or carcinogenesis,[2] we found that 3-epi-ursolic acid (**4**) inhibits production of nitric oxide (NO) induced by interferon-γ in mouse macrophages[2g] and suppresses the inducible cyclooxygenase (COX-2) gene,[2b] although ursolic acid (**5**) does not show such activity in either assay. Therefore, to further discern structure−activity relationships, we designed β-boswellic acid analogues with a carboxyl group at C-17 having the general structural formula **I** based on structures of both β-boswellic acid (**1**) and 3-epi-ursolic acid (**4**). Our literature survey of these structures disclosed 3α-hydroxyurs-12-ene-23,28-dioic acid (**6**), a naturally occurring triterpene isolated from the bark of *Schefflera octophylla*, and its derivatives **7**−**9**.[3] We herein describe the first synthesis of the 28-methyl ester **7** and the 23,-28-dimethyl ester **9** of this naturally occurring triterpene **6** from commercially available ursolic acid (**5**). Our work also confirms the structures proposed for these compounds.



Results and Discussion

Functionalization of the hindered C-4 equatorial methyl group of ursolic acid (**5**) was achieved by Baldwin's method, which involves cyclopalladation of the methyl group at C-4 from a 3-one oxime functionality.[4] Dimeric organopalladium complex **11** was prepared in 98% yield from methyl ursonate oxime (**10**),[5] which was prepared in three steps from **5** according to a known method, with Na_2PdCl_4 and NaOAc in AcOH. Acetylation of **11** with Ac_2O in the presence of Et_3N and DMAP in CH_2Cl_2 gave an unstable acetate, **12**, which was immediately oxidized with $Pb(OAc)_4$ and pyridinium acetate in THF, followed by reductive workup with $NaBH_4$ to afford diacetate **13** (81% yield from **11**). Deacetylation of **13** with Na_2CO_3 in MeOH gave oxime **14** (98% yield), which was hydrolyzed with $TiCl_3$ in aqueous THF to give ketol **15**[6] in 88% yield.

Transformation of **15** into the target compounds **7** and **9** has the following three problems. First, because **15** has an α-hydroxymethyl-ketone functionality in ring A, the hydroxymethyl group is readily cleaved via a retro-aldol reaction under basic conditions. Second, if an intermediate that is derived from **15** has a β-keto-carboxylic acid functionality in ring A, decarboxylation readily occurs under both basic and acidic conditions. Third, conversion of a carbonyl group at C-3 into an α-hydroxyl group by

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(6) Triterpene acid corresponding to this methyl ester **15** is a naturally occurring triterpene isolated from twigs and leaves of *Cussonia natalensis*: Fourie, T. G.; Matthee, E.; Snyckers, F. O. *Phytochemistry* **1989**, *28*, 2851. This conversion of ursolic acid (**5**) into **15** is also the first synthesis of this natural product.

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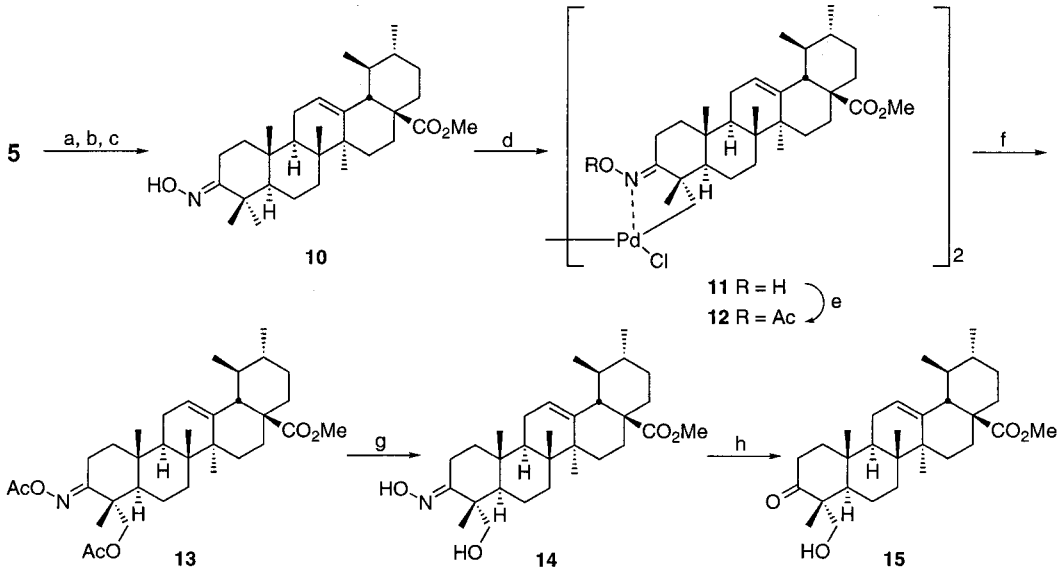
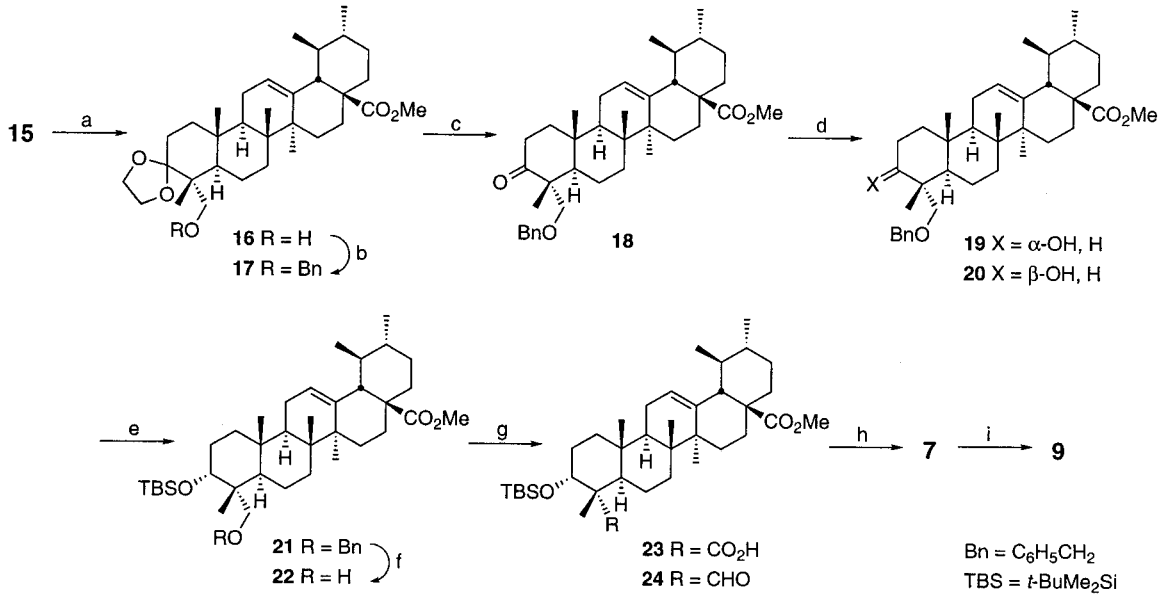
Scheme 1[a]



[a] Key: (a) CH_2N_2, Et_2O, THF; (b) Jones, acetone; (c) $NH_2OH{\cdot}HCl$, NaOAc, MeOH, CH_2Cl_2; (d) Na_2PdCl_4, NaOAc, AcOH; (e) Ac_2O, Et_3N, DMAP, CH_2Cl_2; (f) $Pb(OAc)_4$, pyr., AcOH, THF; $NaBH_4$, NaOH (aq); (g) Na_2CO_3, MeOH; (h) $TiCl_3$, NH_4OAc, H_2O, THF.

Scheme 2[a]



[a] Key: (a) ethylene glycol, PPTS, benzene; (b) BnBr, KH, *n*-Bu_4NI, THF; (c) *p*-TsOH, PPTS, acetone; (d) $Al(i\text{-}PrO)_3$, *i*-PrOH; (e) TBSCl, KH, 18-crown-6, THF; (f) H_2, 10% Pd/C, THF; (g) $RuO_2{\cdot}xH_2O$, $NaIO_4$, H_2O, CH_3CN, CCl_4; (h) 48% aq HF, CH_3CN; (i) CH_2N_2, Et_2O, THF.

reducing agents was initially considered to be difficult because the β-face of the C-3 carbonyl group of **15** is sterically hindered. However, our literature survey revealed that Meerwein−Ponndorf reduction of 3-oxours-12-en-28-oic acid (ursonic acid)[7] gives 3-epi-ursolic acid (**4**) predominantly.[8,9] Therefore, in considering these problems, we adopted the synthetic route shown in Scheme 2. Because direct benzylation of **15** did not give benzyl ether **18** due to a retro-aldol reaction as expected, we attempted to synthesize **18** via ethylene ketal **16**. Ketalization of **15** with ethylene glycol in the presence of PPTS in benzene gave **16** in 99% yield. Benzylation of **16** with benzyl bromide in the presence of KH and *n*-Bu_4NI in THF afforded benzyl ether **17** in 94% yield. Ketone **18** was obtained in 91% yield by deketalization of **17** with *p*-TsOH and PPTS in acetone. Pleasingly, as we initially expected, Meerwein−Ponndorf reduction of **18** gave the desired α-alcohol **19** as the major product and β-alcohol **20** as the minor product (72% and 28% yield, respectively). Structures of both alcohols were assigned by ^1H NMR. Each proton at C-3 of **19** and **20** is observed at δ 3.70 ppm (1H, t, J = 2.3 Hz) and δ 3.64 ppm (1H, dd, J = 4.5, 10.5 Hz), respectively. Protection of the C-3 hydroxyl group of **19** with *tert*-butylchlorodimethylsilane

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(9) Because our preliminary work disclosed that a Mitsunobu reaction[10] does not give methyl 3α-hydroxyurs-12-en-28-oate (methyl 3-epi-ursolate) from methyl 3β-hydroxyurs-12-en-28-oate (methyl ursolate) due to steric hindrance of the C-3 β-hydroxyl group (Honda, T. Unpublished data), we excluded this reaction from our synthetic route.

in the presence of KH and 18-crown-6 in THF[11] yielded silyl ether **21** quantitatively. Debenzylation of **21** was achieved by hydrogenolysis in the presence of 10% Pd/C at atmospheric pressure to give alcohol **22** quantitatively. After several attempts using various oxidizing agents, we found that oxidation of **22** with RuO_4 (catalytic amount) in CH_3CN, CCl_4 and water[12] gives acid **23** and aldehyde **24** in 65% and 9% yield, respectively. Deprotection of **23** with 48% aqueous HF solution in CH_3CN[13] afforded the target compound **7** in 99% yield, which was converted to the second target compound, dimethyl ester **9**, with ethereal CH_2N_2 in 91% yield. The structures of both compounds **7** and **9** are fully characterized by ^1H and ^{13}C NMR, low- and high-resolution mass spectra, IR spectra, and elemental analyses.[14] Studies on the biological properties of both compounds are in progress.

Experimental Section

General Procedures. 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). All experiments were performed under N_2 atmosphere unless otherwise stated.

Methyl 3-Acetoxyimino-23-acetoxyurs-12-en-28-oate (13). To a solution of methyl 3-hydroxyiminours-12-en-28-oate (**10**)[5] (2.00 g, 4.1 mmol) in AcOH (220 mL) were added NaOAc (0.37 g, 4.5 mmol) and Na_2PdCl_4 (1.34 g, 4.6 mmol). The solution was stirred for 72 h, and then ice water (300 mL) was added to give a yellow precipitate. The precipitate was filtered and dried in vacuo at 60 °C for 24 h to give palladium complex **11** (2.53 g, 98%), which was used for the next reaction without further purification. To a solution of **11** in dry CH_2Cl_2 (180 mL) were added DMAP (10 mg), Et_3N (0.82 mL), and Ac_2O (0.6 mL). The mixture was stirred at room temperature for 45 min. It was washed with water (twice), dried over $MgSO_4$, filtered, and evaporated in vacuo to afford **12** as an oil. A solution of **12** and pyridine (0.3 mL) in THF (150 mL) was stirred at room temperature for 15 min. To the solution was added a solution of $Pb(OAc)_4$ (1.85 g, 4.2 mmol) in AcOH (62 mL) in a dry ice−acetone bath. The solution was stirred at room temperature for 16 h. To remove remaining Pd salts, a solution of $NaBH_4$ (164 mg) in 1 N aqueous NaOH solution (60 mL) was added to the reaction mixture. The mixture was stirred for 10 min. After the mixture was filtered, the filtrate was diluted with CH_2Cl_2 (300 mL), which was washed with saturated aqueous $NaHCO_3$ solution (until the AcOH was completely removed), dried over $MgSO_4$, filtered, and evaporated in vacuo to give a solid. The solid was purified by flash column chromatography [hexanes−EtOAc (2:1)] to give **13** as an amorphous solid (1.92 g, 81% from **11**): TLC [hexanes/EtOAc (2:1)] R_f 0.68; IR (KBr) 2976, 2932, 1769, 1736 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.27 (1H, t, J = 3.5 Hz), 4.19 (1H, d, J = 10.6 Hz), 4.13 (1H, d, J = 10.6 Hz), 3.60 (3H, s), 2.75 (1H, m), 2.53 (1H, m), 2.24 (1H, d, J = 11.0 Hz), 2.17, 2.05, 1.17, 1.07, 0.98 (each 3H, s), 0.94 (3H, d, J = 6.0 Hz), 0.85 (3H, d, J = 6.5 Hz), 0.78 (3H, s); ^{13}C NMR ($CDCl_3$) δ 178.2, 171.1, 170.7, 169.9, 138.5, 125.5, 68.5, 53.2, 51.7, 48.6, 48.3, 46.8, 44.0, 42.3, 39.6, 39.2, 39.0, 37.3, 37.1, 36.8, 36.6, 32.4, 30.8, 28.1, 24.4, 23.7, 23.6, 21.3, 21.1, 20.5, 20.2, 19.5, 17.2, 17.1, 15.6; CIMS m/z 584 $[M + H]^+$; HRCIMS calcd for $C_{35}H_{53}NO_6$+H 584.3951, found 584.3949. Anal. Calcd for $C_{35}H_{53}NO_6$: C, 72.01; H, 9.15; N, 2.40. Found: C, 71.75; H, 9.27; N, 2.22.

Methyl 23-Hydroxy-3-hydroxyiminours-12-en-28-oate (14). A solution of **13** (1.92 g, 3.3 mmol) and Na_2CO_3 (1.23 g, 14.8 mmol) in MeOH (185 mL) was stirred at room temperature for 16 h. After removal of MeOH in vacuo, the resultant colorless solid was dissolved in Et_2O (50 mL) and 1 N aqueous HCl solution (50 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ solution (three times), dried over $MgSO_4$, filtered, and evaporated in vacuo to give a solid. The solid was purified by flash column chromatography [hexanes−EtOAc (2:1)] to give **14** as an amorphous solid (1.61 g, 98%): TLC [hexanes/EtOAc (2:1)] R_f 0.34; IR (KBr) 3392, 2971, 2907, 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.26 (1H, t, J = 3.5 Hz), 3.63 (1H, d, J = 11.5 Hz), 3.62 (3H, s), 3.52 (1H, d, J = 11.5 Hz), 3.13 (1H, m), 2.24 (1H, d, J = 11.0 Hz), 1.08 (6H, s), 1.05 (3H, s), 0.94, 0.86 (each 3H, d, J = 6.5 Hz), 0.79 (3H, s); ^{13}C NMR ($CDCl_3$) δ 178.3, 167.0, 138.5, 125.5, 67.8, 53.1, 51.7, 50.0, 48.3, 47.1, 45.0, 42.3, 39.7, 39.2, 39.1, 38.2, 37.0, 36.8, 32.7, 30.8, 28.2, 24.4, 23.8, 23.6, 21.4, 19.1, 18.8, 17.7, 17.3, 15.5; CIMS m/z 500 $[M + H]^+$; HRCIMS calcd for $C_{31}H_{49}NO_4$+H 500.3740, found 500.3740. Anal. Calcd for $C_{31}H_{49}NO_4$: C, 74.51; H, 9.88; N, 2.80. Found: C, 74.23; H, 9.79; N, 2.85.

Methyl 23-Hydroxy-3-oxours-12-en-28-oate (15). To a buffered solution of $TiCl_3$ (1.31 mL of 20% aqueous HCl solution containing 19% $TiCl_3$) and NH_4OAc (750 mg, 9.7 mmol) in water (28 mL) was added a solution of **14** (180 mg, 0.36 mmol) in THF (26.5 mL). The mixture was stirred at room temperature for 4 h. It was extracted with Et_2O (three times). The extract was washed with saturated aqueous $NaHCO_3$ solution (three times), dried over $MgSO_4$, filtered, and evaporated in vacuo to give a solid. The solid was purified by flash column chromatography [hexanes−EtOAc (2:1)] to give **15** as an amorphous solid (154 mg, 88%): TLC [hexanes/EtOAc (2:1)] R_f 0.43; $[\alpha]^{24}_D$ +67° (c 0.39, $CHCl_3$); IR (KBr) 3478, 2950, 2917, 1725, 1676 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.27 (1H, t, J = 3.8 Hz), 3.65 (1H, d, J = 11.5 Hz), 3.62 (3H, s), 3.43 (1H, d, J = 11.5 Hz), 2.63 (1H, m), 2.28 (1H, m), 2.25 (1H, d, J = 12.5 Hz), 1.15, 1.10, 1.03 (each 3H, s), 0.95 (3H, d, J = 6.0 Hz), 0.87 (3H, d, J = 7.0 Hz), 0.82 (3H, s); ^{13}C NMR ($CDCl_3$) δ 219.4, 178.3, 138.7, 125.4, 67.2, 53.1, 52.6, 51.7, 49.4, 48.3, 46.9, 42.4, 39.7, 39.3, 39.2, 39.1, 36.8, 36.7, 35.5, 32.6, 30.9, 28.3, 24.4, 23.8, 23.7, 21.4, 19.4, 17.29, 17.25, 17.1, 15.6; CIMS m/z 485 $[M + H]^+$; HRCIMS calcd for $C_{31}H_{48}O_4$+H 485.3631, found 485.3629. Anal. Calcd for $C_{31}H_{48}O_4 \cdot H_2O$: C, 74.06; H, 10.02. Found: C, 73.69; H, 9.69.

Methyl 3,3-Ethylenedioxy-23-hydroxyurs-12-en-28-oate (16). A mixture of **15** (130 mg, 0.27 mmol), ethylene glycol (1.3 mL, 23 mmol), and PPTS (24 mg, 0.095 mmol) in benzene (13 mL) was heated under reflux with a Dean−Stark apparatus filled with molecular sieves for 20 h. It was diluted with a mixture of Et_2O and CH_2Cl_2 (2:1) (20 mL). It was washed with water (four times), dried over $MgSO_4$, filtered, and evaporated in vacuo to give a solid. The solid was purified by flash column chromatography [hexanes−EtOAc (5:1)] to give **16** as an amorphous solid (140 mg, 99%): TLC [hexanes/EtOAc (5:1)] R_f 0.26; IR (KBr) 3511, 2960, 2906, 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.22 (1H, t, J = 3.3 Hz), 4.00 (2H, m), 3.93 (2H, m), 3.63 (1H, d, J = 11.5 Hz), 3.57 (3H, s), 3.15 (1H, d, J = 11.5 Hz), 2.20 (1H, d, J = 11.0 Hz), 1.08, 0.97 (each 3H, s), 0.92 (3H, d, J = 6.0 Hz), 0.83 (3H, d, J = 6.5 Hz), 0.73 (6H, s); ^{13}C NMR ($CDCl_3$) δ 178.0, 138.3, 125.4, 115.4, 65.7, 64.6, 63.9, 53.1, 51.6, 48.3, 47.7, 46.2, 44.5, 42.3, 39.7, 39.2, 39.1, 37.0, 36.8, 36.6, 32.7, 30.9, 28.2, 26.5, 24.4, 23.9, 23.5, 21.4, 18.4, 17.2, 17.1, 16.9, 15.8; CIMS m/z 529 $[M + H]^+$; HRCIMS calcd for $C_{33}H_{52}O_5$+H 529.3893, found 529.3894. Anal. Calcd for $C_{33}H_{52}O_5$: C, 74.96; H, 9.91. Found: C, 74.91; H, 10.27.

Methyl 23-Benzyloxy-3,3-ethylenedioxyurs-12-en-28-oate (17). A mixture of **16** (140 mg, 0.27 mmol), benzyl bromide (0.2 mL, 1.6 mmol), KH (35% in mineral oil) (0.2 mL), and n-Bu_4NI (10 mg, 0.027 mmol) in THF (3 mL) was heated under reflux for 28 h. After it was cooled in an ice bath, i-PrOH (1 mL) was carefully added to decompose unreacted KH. The mixture was diluted with a mixture of Et_2O and CH_2Cl_2 (2:1) (20 mL). It was washed with water (three times), dried over $MgSO_4$, filtered, and evaporated in vacuo to give a solid. The solid was purified by flash column chromatography [hexanes−EtOAc (5:1)] to give **17** as an amorphous solid (155 mg, 94%): TLC [hexanes/EtOAc (5:1)] R_f 0.61; IR (KBr) 2955, 2860, 1719 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.35 (5H, m), 5.26 (1H, t, J = 3.5 Hz), 4.51 (1H, d, J = 12.5 Hz),

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(14) Unfortunately, because we were unable to obtain authentic samples and spectral data from the authors,[3] we could not compare our synthetic analogues with the natural products directly.

4.47 (1H, d, J = 12.5 Hz), 3.92 (4H, m), 3.62 (3H, s), 3.37 (1H, d, J = 9.5 Hz), 3.13 (1H, d, J = 9.5 Hz), 2.24 (1H, d, J = 11.0 Hz), 1.15, 1.01 (each 3H, s), 0.98 (3H, d, J = 6.0 Hz), 0.92 (3H, s), 0.90 (3H, d, J = 6.5 Hz), 0.78 (3H, s); ^{13}C NMR ($CDCl_3$) δ 178.3, 139.1, 138.4, 128.3, 127.8, 127.4, 125.6, 113.3, 74.1, 73.6, 64.8, 64.6, 53.1, 51.6, 49.7, 48.2, 47.4, 45.6, 42.3, 39.7, 39.2, 39.0, 36.9, 36.8, 32.7, 30.9, 28.2, 27.4, 24.4, 24.1, 23.5, 21.4, 19.0, 17.2, 17.1, 17.0, 15.8; CIMS m/z 619 $[M + H]^+$; HRCIMS calcd for $C_{40}H_{58}O_5$+H 619.4363, found 619.4354. Anal. Calcd for $C_{40}H_{58}O_5$: C, 77.63; H, 9.45. Found: C, 77.57; H, 9.33.

Methyl 23-Benzyloxy-3-oxours-12-en-28-oate (18). A mixture of **17** (1.17 g, 18.9 mmol), *p*-TsOH (50 mg, 0.26 mmol), and PPTS (50 mg, 0.20 mmol) in acetone (350 mL) was stirred at room temperature for 48 h. After removal of acetone, the resultant residue was dissolved in CH_2Cl_2 (25 mL). The solution was washed with water (three times), dried over $MgSO_4$, filtered, and evaporated in vacuo to give a solid. The solid was purified by flash column chromatography [hexanes−EtOAc (5:1)] to give **18** as an amorphous solid (986 mg, 91%): TLC [hexanes/EtOAc (5:1)] R_f 0.54; IR (KBr) 2960, 2863, 1720, 1698 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.31 (5H, m), 5.30 (1H, t, J = 3.0 Hz), 4.55 (1H, d, J = 12.5 Hz), 4.38 (1H, d, J = 12.5 Hz), 3.62 (3H, s), 3.53 (1H, d, J = 8.5 Hz), 3.23 (1H, d, J = 8.5 Hz), 2.47 (2H, dd, J = 5.5, 9.0 Hz), 2.27 (1H, d, J = 11.0 Hz), 1.14, 1.00 (each 3H, s), 0.97 (3H, d, J = 6.0 Hz), 0.93 (3H,s), 0.89 (3H, d, J = 6.0 Hz), 0.82 (3H, s); ^{13}C NMR ($CDCl_3$) δ 217.4, 178.8, 139.3, 139.0, 129.0, 128.2, 128.1, 126.3, 75.9, 73.8, 53.8, 52.2, 51.9, 48.9, 47.9, 46.8, 43.0, 40.2, 39.8, 39.6, 38.2, 37.4, 36.9, 36.4, 32.9, 31.4, 28.8, 25.0, 24.3, 24.2, 21.9, 20.3, 18.7, 17.8, 17.7, 16.0; CIMS m/z 575 $[M + H]^+$; HRCIMS calcd for $C_{38}H_{54}O_4$+H 575.4100, found 575.4101. Anal. Calcd for $C_{38}H_{54}O_4$: C, 79.40; H, 9.47. Found: C, 79.17; H, 9.36.

Methyl 23-Benzyloxy-3α-hydroxyurs-12-en-28-oate (19) and Methyl 23-Benzyloxy-3*β*-hydroxyurs-12-en-28-oate (20). A mixture of **18** (193 mg, 0.34 mmol) and Al(*i*-PrO)$_3$ (206 mg, 1.0 mmol) in *i*-PrOH (4 mL) was heated under reflux for 10 h. After the mixture was diluted with a mixture of Et_2O and CH_2Cl_2 (2:1) (20 mL), it was washed with 5% aqueous HCl solution (twice) and saturated aqueous $NaHCO_3$ solution (twice), dried over $MgSO_4$, filtered, and evaporated in vacuo to give a solid. The solid was purified by flash column chromatography [hexanes−EtOAc (5:1)] to give **19** as an amorphous solid (139 mg, 72%) and **20** as an amorphous solid (53 mg, 28%). **19**: TLC [hexanes/EtOAc (5:1)] R_f 0.49; IR (KBr) 3450, 2917, 2863, 1720 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.37 (5H, m), 5.30 (1H, t, J = 3.5 Hz), 4.61 (1H, d, J = 11.8 Hz), 4.48 (1H, d, J = 11.8 Hz), 3.70 (1H, t, J = 2.3 Hz), 3.65 (3H, s), 3.50 (1H, d, J = 9.5 Hz), 3.29 (1H, d, J = 9.5 Hz), 2.28 (1H, d, J = 11.0 Hz), 1.16 (3H, s), 0.99 (3H, d, J = 8.0 Hz), 0.98 (3H,s), 0.90 (3H, d, J = 7.0 Hz), 0.79 (6H, s); ^{13}C NMR ($CDCl_3$) δ 178.2, 138.2, 137.9, 128.6, 128.0, 127.7, 125.8, 78.5, 75.3, 73.6, 53.1, 51.6, 48.3, 47.5, 43.4, 42.2, 40.8, 39.7, 39.2, 39.0, 37.0, 36.8, 33.1, 32.7, 30.9, 28.2, 25.0, 24.4, 23.8, 23.3, 21.4, 18.4, 18.1, 17.2, 17.1, 15.9; CIMS m/z 577 $[M + H]^+$; HRCIMS calcd for $C_{38}H_{56}O_4$+H 577.4257, found 577.4259. Anal. Calcd for $C_{38}H_{56}O_4$·3/4H_2O: C, 77.31; H, 9.82. Found: C, 77.10; H, 9.56. **20**: TLC [hexanes/EtOAc (5:1)] R_f 0.32; IR (KBr) 3522, 2928, 2863, 1725 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.35 (5H, m), 5.26 (1H, t, J = 3.5 Hz), 4.56 (1H, d, J = 12.0 Hz), 4.50 (1H, d, J = 12.0 Hz), 3.64 (1H, dd, J = 4.5, 10.5 Hz), 3.62 (3H, s), 3.57 (1H, d, J = 8.5 Hz), 3.26 (1H, d, J = 8.5 Hz), 2.25 (1H, d, J = 11.5 Hz), 1.09, 0.97 (each 3H, s), 0.96 (3H, d, J = 6.0 Hz), 0.94 (3H, s), 0.87 (3H, d, J = 6.5 Hz), 0.75 (3H, s); ^{13}C NMR ($CDCl_3$) δ 178.3, 138.3, 128.7, 127.9, 127.7, 125.8, 81.0, 76.8, 73.8, 53.1, 51.7, 50.6, 48.3, 47.8, 42.2, 42.0, 39.7, 39.3, 39.1, 38.4, 37.0, 36.8, 32.9, 32.1, 30.9, 28.2, 26.2, 24.4, 23.8, 23.5, 21.4, 18.9, 17.2, 17.1, 15.9, 14.3, 12.4; CIMS m/z 575 $[M - H]^+$; HRCIMS calcd for $C_{38}H_{56}O_4$−H 575.4100, found 575.4101. Anal. Calcd for $C_{38}H_{56}O_4$·1/2H_2O: C, 77.90; H, 9.81. Found: C, 78.13; H, 9.93.

Methyl 23-Benzyloxy-3α-(*tert*-butyldimethyl)silyloxyurs-12-en-28-oate (21). A mixture of **19** (559 mg, 0.97 mmol), *tert*-butylchlorodimethylsilane (603 mg, 4.0 mmol), KH (35% in mineral oil, 3 mL), whose oil was removed by washing with hexanes, and 18-crown-6 (10 mg, 0.038 mmol) in THF (30 mL) was heated under reflux for 3 h. To the mixture was added *i*-PrOH (2 mL) carefully to decompose unreacted KH in an ice bath. After the mixture was diluted with a mixture of Et_2O and CH_2Cl_2 (2:1) (50 mL), it was washed with 5% aqueous HCl solution (twice) and saturated aqueous $NaHCO_3$ solution (twice), dried over $MgSO_4$, filtered, and evaporated in vacuo to give a solid. The solid was purified by flash column chromatography [hexanes−EtOAc (10:1)] to give **21** as an amorphous solid (669 mg, 100%): TLC [hexanes/EtOAc (10:1)] R_f 0.57; IR (KBr) 2954, 2921, 1730 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.30 (5H, m), 5.28 (1H, t, J = 3.3 Hz), 4.54 (1H, d, J = 12.3 Hz), 4.36 (1H, d, J = 12.3 Hz), 3.77 (1H, s), 3.62 (3H, s), 3.38 (1H, d, J = 8.0 Hz), 3.21 (1H, d, J = 8.0 Hz), 2.25 (1H, d, J = 11.5 Hz), 1.10 (3H, s), 0.97 (3H, d, J = 4.5 Hz), 0.96 (3H, s), 0.92 (9H, s), 0.90 (3H, d, J = 4.5 Hz), 0.89, 0.75, 0.04, −0.01 (each 3H, s); ^{13}C NMR ($CDCl_3$) δ 178.3, 139.4, 138.3, 128.3, 127.5, 127.3, 126.0, 77.9, 73.2, 71.9, 53.1, 51.7, 48.3, 47.7, 46.5, 42.1, 42.0, 39.6, 39.3, 39.1, 37.1, 36.9, 33.3, 33.1, 30.9, 28.2, 26.3, 25.2, 24.5, 23.6, 23.5, 21.4, 18.6, 18.5, 17.44, 17.38, 17.1, 16.1, −3.9, −4.9; CIMS m/z 691 $[M + H]^+$; HRCIMS calcd for $C_{44}H_{70}O_4Si$+H 691.5122, found 691.5121. Anal. Calcd for $C_{44}H_{70}O_4Si$·1/3H_2O: C, 75.81; H, 10.22. Found: C, 75.89; H, 10.38.

Methyl 3α-(*tert*-Butyldimethyl)silyloxy-23-hydroxyurs-12-en-28-oate (22). A mixture of **21** (669 mg, 0.97 mmol) and 10% Pd/C (a catalytic amount) in THF (20 mL) was stirred at room temperature under H_2 at atmospheric pressure for 3 h. After insoluble matter was removed through Celite, the filtrate was evaporated in vacuo to give a solid. The solid was purified by flash column chromatography [hexanes−EtOAc (5:1)] to give **22** as an amorphous solid (581 mg, 100%): TLC [hexanes/EtOAc (5:1)] R_f 0.60; IR (KBr) 3545, 2951, 2855, 1718 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.26 (1H, t, J = 3.5 Hz), 3.62 (1H, t, J = 3.0 Hz), 3.61 (3H, s), 3.42 (1H, d, J = 11.8 Hz), 3.27 (1H, d, J = 11.8 Hz), 2.24 (1H, d, J = 11.0 Hz), 1.11, 0.95 (each 3H, s), 0.94 (3H, d, J = 6.3 Hz), 0.93 (9H, s), 0.89 (3H, d, J = 6.5 Hz), 0.76, 0.67, 0.14, 0.13 (each 3H, s); ^{13}C NMR ($CDCl_3$) δ 178.3, 138.5, 125.8, 78.9, 71.4, 53.1, 51.6, 48.3, 47.7, 42.9, 42.2, 41.0, 39.8, 39.2, 39.1, 36.9, 36.7, 33.4, 32.7, 31.8, 30.9, 28.2, 26.2, 26.0, 24.5, 23.8, 23.5, 22.9, 21.4, 18.5, 18.2, 17.4, 17.2, 15.9, 14.3, −3.9, −4.7; CIMS m/z 601 $[M + H]^+$; HRCIMS calcd for $C_{37}H_{64}O_4Si$+H 601.4652, found 601.4654. Anal. Calcd for $C_{37}H_{64}O_4Si$: C, 73.95; H, 10.73. Found: C, 73.83; H, 10.74.

3α-(*tert*-Butyldimethyl)silyloxyurs-12-ene-23,28-dioic Acid 28-Methyl Ester (23) and Methyl 3α-(*tert*-Butyldimethyl)-silyloxy-23-oxours-12-en-28-oate (24). A mixture of **22** (45 mg, 0.074 mmol), RuO_2·xH_2O (25 mg), and $NaIO_4$ (62 mg, 0.29 mmol) in CCl_4 (0.5 mL), CH_3CN (0.5 mL), and water (0.75 mL) was stirred at room temperature for 5.5 h. To the mixture was added CH_2Cl_2 (8 mL). The aqueous layer was extracted with CH_2Cl_2 (10 mL) (three times). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated in vacuo to give a solid. The solid was purified by flash column chromatography [hexanes−EtOAc (5:1)] to give **23** as an amorphous solid (30 mg, 65%) and **24** as an amorphous solid (4 mg, 9%). **23**: TLC [hexanes/EtOAc (5:1)] R_f 0.38; IR (KBr) 3314, 2943, 2856, 1725, 1698 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.27 (1H, t, J = 3.5 Hz), 3.88 (1H, s), 3.62 (3H, s), 2.25 (1H, d, J = 11.5 Hz), 1.17, 0.97 (each 3H, s), 0.96, 0.91 (each 3H, d, J = 6.5 Hz), 0.90 (3H, s), 0.88 (9H, s), 0.77, 0.06, 0.01 (each 3H, s); ^{13}C NMR ($CDCl_3$) δ 182.1, 178.3, 138.7, 125.6, 74.5, 53.1, 52.2, 51.7, 48.3, 47.8, 43.9, 42.3, 40.2, 39.2, 39.1, 36.9, 36.8, 32.8, 32.5, 31.8, 30.8, 28.2, 26.0, 25.2, 24.5, 23.9, 23.5, 22.9, 21.4, 21.2, 18.2, 17.42, 17.38, 16.1, 14.4, −3.9, −5.3; CIMS m/z 613 $[M - H]^+$; HRCIMS calcd for $C_{37}H_{62}O_5Si$−H 613.4288, found 613.4288. Anal. Calcd for $C_{37}H_{62}O_5Si$: C, 72.26; H, 10.16. Found: C, 71.98; H, 10.27. **24**: TLC [hexanes/EtOAc (5:1)] R_f 0.59; IR (KBr) 2954, 2856, 1723 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.49 (1H, s), 5.27 (1H, t, J = 3.5 Hz), 3.72 (1H, s), 3.60 (3H, s), 2.24 (1H, d, J = 11.5 Hz), 1.14 (3H, s), 0.95 (6H, s), 0.94 (3H, d, J = 6.0 Hz), 0.89 (3H, d, J = 6.5 Hz), 0.87 (9H, s), 0.76, 0.02, −0.05 (each 3H, s); ^{13}C NMR ($CDCl_3$) δ 210.1, 178.2, 138.5, 125.6, 74.5, 53.1, 52.3, 51.6, 48.3, 47.5, 43.8, 42.2, 40.3, 39.2, 39.0, 36.8, 36.3, 32.9, 32.8, 30.8, 28.1, 26.0, 25.8, 24.4, 23.7, 23.4, 21.4, 20.7, 18.2, 17.3, 17.2, 15.8, 14.5, −4.1, −5.2; CIMS m/z 599 $[M + H]^+$; HRCIMS calcd for $C_{37}H_{62}O_4Si$+H 599.4496, found 599.4497.

3α-Hydroxyurs-12-ene-23,28-dioic Acid 28-Methyl Ester (7). A solution of **23** (56 mg, 0.091 mmol) in a mixture of 48% aqueous HF solution and CH_3CN (1:9) (3 mL) was stirred at room temperature for 16 h. After the mixture was diluted with a mixture of Et_2O and CH_2Cl_2 (2:1) (10 mL), it was washed with water (four times) and saturated aqueous $NaHCO_3$ solution (twice), dried over $MgSO_4$, filtered, and evaporated in vacuo to give **7** as an amorphous solid (45 mg, 99%): TLC [hexanes/EtOAc

(2:1)] R_f 0.09; $[\alpha]^{24}_D$ +35° (*c* 0.27, acetone); IR (KBr) 3448, 2931, 2861, 1719 cm^{-1}; ^1H NMR (acetone-d_6) δ 5.20 (1H, t, J = 3.5 Hz), 3.78 (1H, t, J = 2.5 Hz), 3.54 (3H, s), 2.21 (1H, d, J = 11.0 Hz), 1.15, 1.12, 0.97 (each 3H, s), 0.92 (3H, d, J = 5.5 Hz), 0.86 (3H, d, J = 6.5 Hz), 0.75 (3H, s); ^{13}C NMR (acetone-d_6) δ 178.6, 178.3, 139.8, 126.8, 73.5, 54.4, 52.14, 52.06, 49.2, 48.9, 45.4, 43.4, 41.3, 40.4, 40.2, 37.94, 37.91, 34.0, 33.4, 31.8, 29.2, 26.3, 25.5, 24.7, 24.4, 22.2, 22.0, 18.4, 18.2, 18.1, 16.6; CIMS *m*/*z* 501 $[M + H]^+$; HRCIMS calcd for $C_{31}H_{48}O_5$+H 501.3580, found 501.3582. Anal. Calcd for $C_{31}H_{48}O_5 \cdot 1/3H_2O$: C, 73.48; H, 9.68. Found: C, 73.50; H, 9.75.

Dimethyl 3α-Hydroxyurs-12-ene-23,28-dioate (9). To a solution of **7** (42 mg, 0.084 mmol) in THF (5 mL) was added ethereal CH_2N_2 (10 mL). The solution was stirred at room temperature for 1 h and then evaporated in vacuo to give a solid. The solid was purified by flash column chromatography [hexanes−EtOAc (2:1)] to give **9** as an amorphous solid (39 mg, 91%): TLC [hexanes/EtOAc (2:1)] R_f 0.52; $[\alpha]^{24}_D$ +41° (*c* 0.38, $CHCl_3$); IR (KBr) 3519, 2979, 2948, 2924, 2871, 1726 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.25 (1H, t, J = 3.5 Hz), 3.78 (1H, t, J = 2.5 Hz), 3.70 (3H, s), 3.60 (3H, s), 2.23 (1H, d, J = 11.5 Hz), 1.19, 1.13, 0.97 (each 3H, s), 0.94 (3H, d, J = 6.0 Hz), 0.86 (3H, d, J = 6.5 Hz), 0.75 (3H, s); ^{13}C NMR ($CDCl_3$) δ 178.34, 178.30, 138.4, 125.4, 72.7, 53.1, 52.2, 51.7, 51.6, 48.3, 47.8, 45.1, 42.3, 40.1, 39.2, 39.1, 36.9, 36.8, 32.8, 32.3, 30.8, 28.1, 24.9, 24.4, 24.0, 23.3, 21.5, 21.4, 17.24, 17.21, 17.19, 16.0; CIMS *m*/*z* 515 $[M + H]^+$; HRCIMS calcd for $C_{32}H_{50}O_5$+H 515.3737, found 515.3735. Anal. Calcd for $C_{32}H_{50}O_5$: C, 74.67; H, 9.79. Found: C, 74.81; H, 9.87.

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