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Oxidative transformations of betulinol

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ABSTRACT

Starting from commercially available betulinol by a combination of several selective oxidation procedures betutinal, betulinic acid, betulonal as well as betulonic acid were obtained in high yields on a multi-gram scale.

1. Introduction

Quite recently, several derivatives of triterpene derived compounds have gained significant interest in medicinal chemistry[1–5] due to their pharmaceutical activities. Of special interest are derivatives of betulinol (**1**) with a special focus on betulinic acid (**2**) since several of these compounds have shown quite promising results in the therapy of a variety of malignous cell lines in vivo; triterpenoic aldehyde or ketone derived compounds were reported to possess antimelanoma as well as anti-HIV activity.[6–10]

2. Results and discussion

Whereas **1** is easily accessible by extraction from natural sources[11] in a very economic way, the isolation of **2** from plant material is rather laborious and yields material of lower purity needing[12–14] either further tedious chromatographic purification or exhaustive re-crystallization at low temperatures. Usual literature known procedures accessing **2** starting from **1** use protection–oxidation–deprotection schemes or sequences using exhaustive oxidation followed by partial reduction.[15–21] The number of direct syntheses[16,22] of **2** from **1** is rather limited. Recently, we[23] could demonstrate that a TEMPO/$NaClO_2$/NaOCl[24] mediated oxidation of **1** either leads to **2** or to betulinal (**3**). These methods work quite well and result in high yields on a laboratory scale but we observed incomplete reactions during the synthesis of **2** upon scaling up. Thus, we became interested in the development of robust but selective oxidation procedures allowing the conversion of **1** into **2** and/or into **3**. As far as the oxidation of **1** to **3** is concerned, the scaling up of our 4-acetamido-TEMPO/$NaOCl_2$/NaOCl[25] procedure proceeded smoothly and allowed the synthesis of **3** in isolated yields >80%. In addition, **3** can be obtained from **1** by oxidation using DMSO/oxalyl chloride in 94% yield; up-scaling of this reaction into >100 g scale was easily performed.

As an alternative, a two-step synthesis[26,27] can be performed consisting of a trimethylsilyl-protection of **1** yielding the bis-trimethylsilyloxy compound[28] **4** in quantitative yield followed by a *Swern*-oxidation using a work-up under acidic conditions to afford **3** in excellent yields.

Either **1** or betulinal **3** is ideal starting material for the synthesis of **2**; since yields for the direct conversion of **1** into **2** dropped slightly upon scaling up our 4-acetamido-TEMPO/$NaOCl_2$/NaOCl procedure, a different approach starting from **3** was investigated in more detail. Whereas the oxidation of **3** to **2** with activated MnO_2 afforded only 18% of **2**, the oxidation[29,30] of **3** with $NaMnO_4$[31] proceeded very smoothly and gave **2** in 85% isolated yield. Similar high yields were obtained for the $AgNO_3$-mediated oxidation of **3** to **2** as well as for the $MnSO_4$/$AgNO_3$/ammonium peroxodisulfate route (Scheme 1).

The oxidation of **1** to betulonic acid (**5**) using the well established *Jones*-oxidation[32,33] utilizing CrO_3/H_2SO_4 invariably gave lower yields as reported in several[15,34,35] patents. Many affords in optimizing this reaction were undertaken and finally we could success in obtaining reasonably high yields. However, higher yields of **5** were obtained when starting from betulonal (**6**) using a two-step sequence. Betulonal (**6**) was obtained in >90% yield from **1** either by

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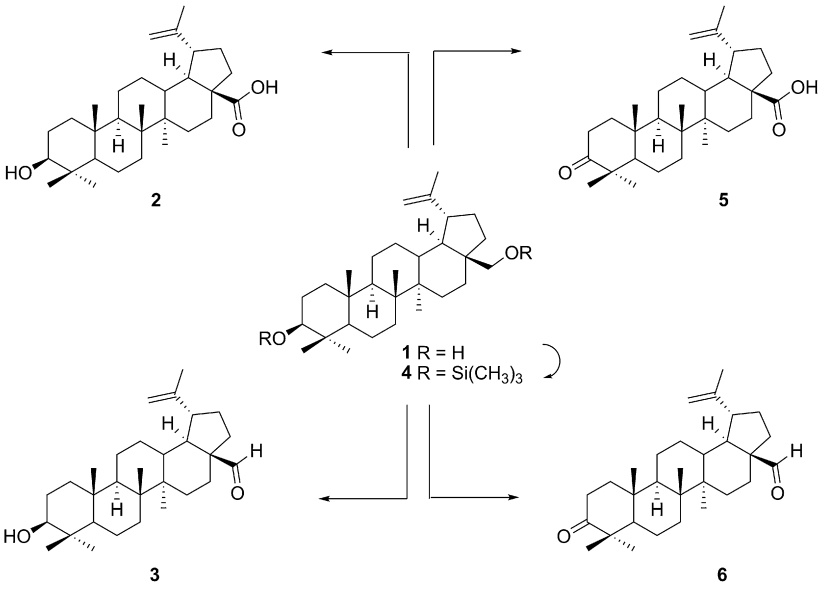

Scheme 1. Synthesis of betulinal, betulinic acid, betulonal, and betulonic acid from betulinol.

a *Swern*-type oxidation or with slightly diminished yields from a *Jones*-oxidation of **1** (thus yielding **6** in about 75% yield on a multi-gram scale). Oxidation of **1** using the IBX/HYP protocol[36] gave only 5% of **5** whereas the oxidation of **6** using 2-methyl-2-butene/*tert*-BuOH/sodium chlorite (procedure A)[37] gave reasonably high yields of **5**; similar high yields of **5** were obtained for the permanganate oxidation (procedure B) of **6**; for both procedures yields between 70 and 75% were obtained also for scaling up into the 100 g scale.

In summary, by a combination of several selective oxidation procedures starting from betulinol, betulinic or betulonic acid as well as betulinal or betulonal can be accessed very easily even on a multi-gram scale.

3. Experimental

3.1. General

Melting points are uncorrected (*Leica* hot stage microscope), optical rotations were obtained using a Perkin–Elmer 341 polarimeter (1 cm microcell), NMR spectra were recorded using the Varian spectrometers Gemini 200, Gemini 2000 or Unity 500 (δ given in ppm, J in Hz, internal Me_4Si), IR spectra (film or KBr pellet) on a Perkin–Elmer FT-IR spectrometer Spectrum 1000, and MS spectra were taken on an Intectra GmbH AMD 402 (electron impact, 70 eV) or on a Finnigan MAT TSQ 7000 (electrospray, voltage 4.5 kV, sheath gas nitrogen) instrument. TLC was performed on silica gel (Merck 5554, detection by UV absorption). The solvents were dried according to usual procedures.

3.2. Synthesis of betulinic acid (2)

*3.2.1. From betulinol (**1**) by 4-acetamido-TEMPO mediated oxidation*

To a 50 °C warm mixture of butylacetate (1000 ml) and aq phosphate buffer (0.67 M, pH 7.6, 450 ml) containing **1** (50.0 g, 0.11 mol), 4-acetamido-TEMPO (1.0 g, 8 mmol), $Bu_4NBr\cdot H_2O$ (1.8 g, 5.5 mmol) and aq solutions of $NaOCl_2$ (25%, 67.6 ml, 0.22 mol) and NaOCl (12%, 0.1 ml, 2.5 mmol) were slowly added within 120 min. Stirring at this temperature was continued and some additional NaOCl (12%, 100 ml, 0.19 mol) was slowly added until TLC showed the reaction to be complete. After cooling to room temperature, water (500 ml) was added and the pH adjusted to 8 by addition of aq NaOH (2 N). After extraction with butylacetate (7×100 ml) the phases were separated, the organic phase was washed (water, brine) and dried (Na_2SO_4), the solvents were evaporated, and crude **2** was re-crystallized from ethanol to afford pure **2** (37.1 g, 72%, purity >98% by HPLC).

*3.2.2. From betulinal (**3**) by $NaMnO_4$ oxidation*

To a solution of **3** (40 g, 0.09 mol) in *tert*-BuOH (800 ml), dichloromethane (200 ml), and aq NaH_2PO_4 (1000 ml, 1.25 M) at 25 °C, an aq solution of $NaMnO_4$ (400 ml, 1 M) was added and the reaction mixture was stirred for 3 h. Extractive work-up with ethyl acetate (5×200 ml) followed by evaporation of the solvent furnished crude material that was either purified by crystallization from ethanol or by chromatography (silica gel, hexanes/ethyl acetate 4:1) to afford pure **2** (34 g, 85%, purity >98% by HPLC).

*3.2.3. From betulinal (**3**) by $MnSO_4/AgNO_3$ oxidation*

To a solution of $MnSO_4$ (0.7 g, 10 mol%) and $AgNO_3$ (0.3 g) in water (1000 ml), ammonium peroxodisulfate (140 g, 0.6 mol) was added; after stirring for several minutes the reaction mixture turned to magenta and a solution of **3** (20 g, 45 mmol) in *tert*-BuOH (300 ml) and dichloromethane (100 ml) was added. Stirring at 25 °C was continued for another 24 h followed by extractive work-up with ethyl acetate (5×200 ml) and chromatography (silica gel, toluene/ethyl acetate 4:1) to yield **2** (17 g, 85%, purity >98% by HPLC) as a white solid.

*3.2.4. From betulinal (**3**) by MnO_2 oxidation*

A mixture of **3** (1.0 g, 2.4 mmol) and activated MnO_2 (2.0 g, 24 mmol) in xylene (200 ml) was heated under reflux for 24 h. The filtrate was evaporated and the residue subjected to chromatography (silica gel, toluene/ethyl acetate 4:1) to afford **2** (0.2 g, 18%, purity >98% by HPLC) as a colorless solid.

An analytical sample of **2** showed: mp 313–315 °C (lit.: 316–318,[38–40] $[\alpha]_D^{25}$ +9.5 (*c* 0.4, $CHCl_3$)) [lit.: $[\alpha]_D$ +9 (*c* 0.36, $CHCl_3$),[23] $[\alpha]_D$: +5 ($CHCl_3$)[27]].

3.3. Synthesis of betulinal (3)

*3.3.1. From betulinol (**1**) by TEMPO mediated oxidation*

To a 30 °C warm stirred mixture of dichloromethane (1000 ml) and phosphate buffer (0.67 M, pH 6.8, 450 ml) containing betulinol

(**1**) (50 g, 113 mmol), TEMPO (1.25 g, 8 mmol) and $Bu_4NBr \cdot H_2O$ (1.8 g, 5.5 mmol), aq solutions of $NaClO_2$ (25%, 68 ml, 226 mmol) and NaOCl (12%, 01 ml, 2.5 mmol) were added dropwise within 180 min and then additional aq NaOCl (180 ml, 34.7 mmol) was slowly added. After completion of the reaction (as monitored by TLC) and cooling to room temperature, water (500 ml) was added and the pH adjusted to 8 by the addition of aq NaOH (2 N). The reaction mixture was poured into ice cold water (1000 ml), the aq phase was extracted (methyl-t.butyl-ether, 5×100 ml), and the combined organic phases were washed (water, brine), dried (Na_2SO_4), evaporated in vacuo to furnish crude **3** that was recrystallized from methanol to afford pure **3** (43.3 g, 87%) as white crystals; mp 182–186 °C.

*3.3.2. From betulinol (**1**) via **4***

To a solution of **1** (45.6 g, 0.1 mol) and imidazole (34.0 g, 0.5 mol) in dry dichloromethane (300 ml) at 0 °C, chlorotrimethylsilane (45.0 g, 0.4 mol) was slowly added and after completion of the addition stirring at 25 °C was continued for another 180 min. After extraction with aq ammonium hydroxide (5%, 100 ml) and water (100 ml), the organic layers were dried (Na_2SO_4), the solvents evaporated, and crude **4** (58 g, quant.) was obtained as a colorless solid (that was directly used in the following step). An analytical sample of **4** showed: mp 130 °C (lit.:[28] 127–129 °C); $[\alpha]_D^{25}$ 16.5 (*c* 4.5, $CHCl_3$); IR (KBr): ν=2954 s, 2869 m, 1637 w, 1456 m, 1390 m, 1359 w, 1252 s, 1109 m, 1088 s, 1069 s; ^{1}H NMR (400 MHz, $CDCl_3$): δ=4.65 (d, 1H, *J*=2.1 Hz, CH_a (30)), 4.55 (dd, 1H, *J*=2.1, 1.2 Hz, CH_b (30)), 3.64 (d, 1H, *J*=9.5 Hz, CH_a (28)), 3.20 (d, 1H, *J*=9.5 Hz, CH_b (28)), 3.16 (dd, 1H, *J*=11.6, 4.6 Hz, C*H* (3)), 2.37 (ddd, 1H, *J*=11.5, 11.0, 6.8 Hz, C*H* (19)), 1.97–1.83 (m, 3H, *J*=12.2, 12.2, 3.8 Hz, CH_a (16)+CH_a (21)+CH_a (22)), 1.68–1.52 (m, 4H, C*H* (13)+CH_a (15)+CH_a (12)+CH_a (1)), 1.66 (s, 3H, CH_3 (29)), 1.52–1.31 (m, 9H, C*H* (18)+CH_2 (6)+CH_2 (2)+CH_a (11)+CH_2 (7)+CH_b (21)), 1.27–1.06 (m, 9H, C*H* (9)+CH_b (11)+CH_b (16)), 1.06–0.86 (m, 3H, CH_b (15)+CH_b (22)+CH_b (12)), 1.00 (s, 3H, CH_3 (25)), 0.95 (s, 3H, CH_3 (27)), 0.85 (s, 3H, CH_3 (23)), 0.81 (s, 3H, CH_3 (26)), 0.84–0.79 (m, 1H, CH_b (1)), 0.71 (s, 3H, CH_3 (24)), 0.65 (d, 1H, *J*=9.5 Hz, C*H* (5)), 0.09 (s, 9H, Si(CH_3)$_3$), 0.08 (s, 9H, Si(CH_3)$_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ=150.9 (C20, *C*=CH$_2$), 109.4 (C30, *C*H$_2$=C), 79.6 (C3, *C*H), 60.0 (C28, *C*H$_2$), 55.4 (C5, *C*H), 50.4 (C9, *C*H), 48.5 (C18, *C*H), 48.0 (C19, *C*H), 47.8 (C17, $C_{quart.}$), 42.6 (C14, $C_{quart.}$), 40.9 (C8, $C_{quart.}$), 39.2 (C4, $C_{quart.}$), 38.8 (C1, *C*H$_2$), 37.3 (C13, *C*H), 37.1 (C10, $C_{quart.}$), 34.3 (C7, *C*H$_2$), 34.2 (C22, *C*H$_2$), 29.9 (C21, *C*H$_2$), 29.4 (C16, *C*H$_2$), 28.4 (C23, *C*H$_3$), 27.8 (C2, *C*H$_2$), 27.1 (C15, *C*H$_2$), 25.3 (C12, *C*H$_2$), 20.8 (C11, *C*H$_2$), 19.1 (C29, *C*H), 18.5 (C6, *C*H$_2$), 16.1 (C25, *C*H$_3$), 15.9 (C26, *C*H$_3$), 15.8 (C24, *C*H$_3$), 14.7 (C27, *C*H$_3$), 0.5 (Si(*C*H$_3$)$_3$), −0.5 (Si(*C*H$_3$)$_3$); ^{29}Si (99 MHz, $CDCl_3$): δ=16.5 ($SiMe_3$), 14.2 ($SiMe_3$); UV–vis (methanol): λ_{max} (log ε)=222 nm (4.20); MS (EI, 70 eV): *m*/*z*=586 (14), 496 (100), 483 (81), 393 (41), 279 (18), 203 (61), 189 (56), 147 (44). Anal. Calcd for $C_{36}H_{66}O_2$ (587.08): C, 73.65; H, 11.33. Found: C, 73.52; H, 11.57.

To a solution of oxalyl chloride (6.0 g, 47.1 mmol) in dry dichloromethane (100 ml) at −78 °C a solution of dry DMSO (7.8 ml) in dry dichloromethane (100 ml) was slowly added and stirring at −78 °C was continued for another 30 min. Maintaining this temperature a solution of **4** (25.0 g, 42.6 mmol) in dry dichloromethane (50 ml) was slowly added and stirring at this temperature was continued for another 180 min. Then dry triethylamine (14 ml) was added, stirring at −78 °C continued for another hour and then the reaction mixture was allowed to warm to room temperature. Diluted aq HCl (10%, 100 ml) was added under vigorous stirring, the phases were separated, the organic layer was washed with aq Na_2SO_4 (2×50 ml), water (2×50 ml), and brine (2×50 ml), the solvents were removed, and the residue was subjected to chromatography (silica gel, toluene/ethyl acetate 4:1) to afford **3** (14.1 g, 75%); mp 193 °C; (lit.: 189–191;[23] 183–187;[41] 192–193[42]); $[\alpha]_D^{25}$ 17.3 (*c* 4.9, $CHCl_3$) (lit.: $[\alpha]_D$ 18.4 (*c* 0.4, $CHCl_3$),[23] $[\alpha]_D$ +19 ($CHCl_3$)[43]); R_f=0.48 (silica gel, hexanes/ethyl acetate, 8:2); IR (KBr): ν=2942 s, 2868 m, 1726 m, 1642 w, 1604 w, 1451 m, 1388 m, 1376 m, 1300 w, 1188 w, 1106 w, 1083 w, 1044 m, 1012 m; UV–vis (methanol): λ_{max} (log ε)=214 nm (4.13); ^{1}H NMR (500 MHz, $CDCl_3$): δ=9.65 (d, 1H, *J*=1.7 Hz, C*H*O (28)), 4.74 (d, 1H, *J*=2.1 Hz, CH_a (30)), 4.61–4.60 (m, 1H, CH_b (30)), 3.16 (dd, 1H, *J*=11.2, 5.0 Hz, C*H*OH (3)), 2.84 (ddd, 1H, *J*=11.2, 11.2, 5.8 Hz, C*H* (19)), 2.06 (dd, 1H, *J*=9.1, 2.9 Hz, CH_a (16)), 2.00 (ddd, 1H, *J*=12.5, 12.5, 3.7 Hz, C*H* (13)), 1.90–1.82 (m, 1H, CH_a (21)), 1.77–1.70 (m, 3H, C*H* (18)+CH_a (22)+CH_a (12)), 1.68 (s, 3H, CH_3 (29)), 1.67–1.54 (m, 2H, CH_a (1)+CH_2 (2)), 1.53–1.29 (m, 9H, CH_2 (6)+CH_b (21)+CH_a (15)+CH_b (16)+CH_a (11)+CH_2 (7)+CH_b (22)), 1.27–1.13 (m, 3H, C*H* (9)+CH_b (15)+CH_b (11)), 1.06–0.98 (m, 1H, CH_b (12)), 0.96 (s, 3H, CH_3 (27)), 0.95 (s, 3H, CH_3 (23)), 0.90 (s, 3H, CH_3 (25)), 0.97–0.89 (m, 1H, CH_b (1)), 0.80 (s, 3H, CH_3 (26)), 0.74 (s, 3H, CH_3 (24)), 0.65 (d, 1H, *J*=10.0 Hz, C*H* (5)); ^{13}C NMR (125 MHz, $CDCl_3$): δ=206.8 (C28, *C*=O), 149.6 (C20, *C*=CH$_2$), 110.1 (C30, *C*H$_2$=C), 79.0 (C3, *C*HOH), 59.4 (C17, $C_{quart.}$), 55.5 (C5, *C*H), 50.6 (C9, *C*H), 48.3 (C18, *C*H), 47.6 (C19, *C*H), 42.7 (C14, $C_{quart.}$), 41.0 (C8, $C_{quart.}$), 38.9 (C4, $C_{quart.}$), 39.0 (C1, *C*H$_2$), 38.8 (C13, *C*H), 37.4 (C10, $C_{quart.}$), 34.5 (C7, *C*H$_2$), 33.4 (C22, *C*H$_2$), 30.1 (C16, *C*H$_2$), 29.4 (C21, *C*H$_2$), 29.0 (C15, *C*H$_2$), 28.1 (C23, *C*H$_3$), 27.6 (C2, *C*H$_2$), 25.7 (C12, *C*H$_2$), 21.0 (C11, *C*H$_2$), 19.2 (C29$_3$, *C*H), 18.5 (C6, *C*H$_2$), 16.3 (C26, *C*H$_3$), 16.1 (C25, *C*H$_3$), 15.5 (C24, *C*H$_3$), 14.5 (C27, *C*H$_3$); MS (EI, 70 eV): *m*/*z*=440 (32), 412 (27), 207 (75), 189 (100), 175 (43), 135 (60), 121 (53).

3.4. Betulonic acid (5)

*3.4.1. From **1** by Jones-oxidation*

To a mixture of betulinol (**1**) (15 g, 33 mmol) in acetone (400 ml) at 10 °C *Jones* reagent [freshly prepared from CrO_3 (37.5 g), sulfuric acid (98%, 25 ml), and water (120 ml)] was added dropwise within 60 min. The mixture was stirred for 1 h at 25 °C, then quenched by the addition of methanol (300 ml) keeping the temperature <30 °C. The acetone was distilled off and the aq residue extracted with ethyl acetate (4×250 ml). The combined organic phases were washed (water, brine), dried (Na_2SO_4), the solvents were removed, and the residue was subjected to chromatography (silica gel, hexanes/ethyl acetate 8:1) to afford **5** (8.4 g, 52%) as a white solid. The content of trace amounts of chromium was below 5 ppm as determined by ICP-MS.

*3.4.2. From **6**; procedure A*

To a solution of **6** (20 g, 46 mmol) in *tert*-BuOH (200 ml) containing 2-methyl-2-butene (10 ml, 94 mmol) a mixture of sodium chlorite (5.0 g, 60 mmol), NaH_2PO_4 (7.0 g, 54 mmol) in water (200 ml) was added and stirring at room temperature was continued for 24 h. An aq solution of NaOH (1 M, 320 ml) was added, organic solvents were removed in vacuo, and the remaining aq reaction mixture was extracted with dichloromethane (10×50 ml). After drying (Na_2SO_4) and removal of the solvents, the residue was subjected to chromatographic work-up (silica gel, hexanes/ethyl acetate 4:1) and **5** (16 g, 76%) was obtained as a white solid.

*3.4.3. From **6**; procedure B*

To an ice cold solution of **6** (17 g, 39 mmol) in 1,4-dioxane (300 ml) and water (100 ml) an aq solution of $KMnO_4$ (0.1 M, 390 ml) was added dropwise keeping the temperature <5 °C. After stirring for 2 h, the organic solvents were removed under diminished pressure and the aq phase was extracted with ethyl acetate (10×50 ml). The solvent was removed and the residue subjected to chromatography (silica gel, hexane/ethyl acetate 4:1) to afford **5** (12 g, 70%) as a white solid; mp 245–247 °C (lit.: 249–250 °C,[44] 258 °C;[45] $[\alpha]_D^{25}$ +45 (*c* 0.51, $CHCl_3$)) [lit.: $[\alpha]_D^{25}$ +40.1 (*c* 0.86, $CHCl_3$)];[46] R_f=0.58 (silica gel, hexanes/ethyl acetate 8:2); IR (KBr): ν=2948 s, 2870 m, 1689 s, 1642 w, 1459 m, 1377 m, 1319 w,

1239 m, 1141 m, 1115 w; UV–vis (methanol): λ_{max} (log ε)=218 (3.90); ^{1}H NMR (500 MHz, $CDCl_3$): δ=4.73 (d, 1H, J=1.8 Hz, CH_a (30)), 4.60 (br s, 1H, CH_b (30)), 3.00 (ddd, 1H, J=10.7, 10.7, 4.9 Hz, CH (19)), 2.51–2.36 (m, 2H, CH_2 (2)), 2.27 (ddd, 1H, J=13.1, 3.4, 3.1 Hz, CH_a (16)), 2.21 (ddd, 1H, J=12.5, 11.9, 3.4 Hz, CH (13)), 2.04–1.95 (m, 2H, CH_a (22)+CH_a (21)), 1.89 (ddd, 1H, J=12.5, 7.6, 4.6 Hz, CH_a (1)), 1.74–1.67 (m, 1H, CH_a (12)), 1.68 (s, 3H, CH_3 (29)), 1.63 (dd, 1H, J=11.3 Hz, CH (18)), 1.57–1.24 (m, 13H, CH_a (15)+CH_b (22)+CH_2 (6)+CH_2 (11)+CH_2 (7)+CH_b (16)+CH_b (21)+CH_b (1)+CH (9)+CH (5)), 1.21 (ddd, 1H, J=13.8, 3.1 Hz, CH_b (15)), 1.10–1.02 (m, 1H, CH_b (12)), 1.06 (s, 3H, CH_3 (23)), 1.00 (s, 3H, CH_3 (24)), 0.98 (s, 3H, CH_3 (27)), 0.96 (s, 3H, CH_3 (25)), 0.91 (s, 3H, CH_3 (26)); ^{13}C NMR (125 MHz, $CDCl_3$): δ=218.2 (C3, *C*O), 182.4 (C28, *C*OOH), 150.3 (C20, *C*=CH$_2$), 109.7 (C30, C=*C*H$_2$), 56.4 (C17, $C_{quart.}$), 54.9 (C5, *C*H), 49.8 (C9, *C*H), 49.2 (C18, *C*H), 47.3 (C4, $C_{quart.}$), 46.9 (C19, *C*H), 42.5 (C14, $C_{quart.}$), 40.6 (C8, $C_{quart.}$), 39.6 (C1, *C*H$_2$), 38.5 (C13, *C*H), 37.0 (C22, *C*H$_2$), 36.9 (C10, $C_{quart.}$), 34.1 (C2, *C*H$_2$), 33.6 (C7, *C*H$_2$), 32.1 (C16, *C*H$_2$), 30.5 (C21, *C*H$_2$), 29.7 (C15, *C*H$_2$), 26.6 (23, *C*H$_3$), 25.5 (C12, *C*H$_2$), 21.4 (C11, *C*H$_2$), 21.0 (C24, *C*H$_3$), 19.6 (C6, *C*H$_2$), 19.3 (C29, *C*H$_3$), 15.9 (C26, *C*H$_3$), 15.8 (C25, *C*H$_3$), 14.6 (C27, *C*H$_3$); MS (ESI, MeOH): m/z=453.5 (100% [M−H]$^-$). Anal. Calcd for $C_{30}H_{46}O_3$ (454.68): C, 79.25; H, 10.20. Found: C, 79.02; H, 10.36.

3.5. Betulonal (6)

3.5.1. From **1** by Swern-oxidation

To a solution of oxalyl chloride (4.0 ml, 47 mmol) in dry dichloromethane (25 ml), a solution of DMSO (6.8 ml, 96 mmol) in dichloromethane (10 ml) was simultaneously added with a solution of **1** (2.21 g, 10 mmol) in DMSO (15 ml)/dichloromethane (25 ml) at −15 °C. Dry triethylamine (28 ml) was added, stirring continued for another 10 min, and the reaction mixture was then allowed to warm to room temperature. After quenching the reaction by addition of water (50 ml) and extraction with dichloromethane (50 ml), the combined organic phases were washed with brine (100 ml) and dried ($MgSO_4$), the solvents removed, and the residue was purified by chromatography (silica gel, chloroform/methanol 10:1) to afford **6** (2.07 g, 93%) as an off-white solid.

3.5.2. From **1** by Jones-oxidation

To a solution of **1** (22.1 g, 50 mmol) in 1,4-dioxane (250 ml) at 5 °C freshly prepared *Jones*-oxidant [prepared from CrO_3 (50.0 g, 0.5 mol), water (300 ml), and sulfuric acid (98%, 41 ml, 0.78 mol)] was added in several portions and stirring was continued for another 2 h. After quenching the reaction by addition of brine (200 ml), the reaction mixture was extracted with ethyl acetate (3×200 ml), the solvents were removed, and the residue was subjected to chromatography (silica gel, hexanes/ethyl acetate 4:1) to afford **6** (16.5 g, 75%) as an off-white solid; mp 163–166 °C (lit.: 165–166 °C;[44] 162–164 °C[47]), $[\alpha]_D^{25}$ 47.7 (*c* 4.1, $CHCl_3$) (lit.: $[\alpha]_D$ 33.8 (*c* 0.45, $CHCl_3$),[48] $[\alpha]_D$ 52.4 ($CHCl_3$)[44]); R_f=0.83 (silica gel, hexanes/ethyl acetate 8:2); IR (KBr): ν=3432 m, 3072 w, 2942 s, 2864 m, 1706 s, 1644 w, 1453 m, 1377 w, 1140 w, 1082 w, 985 w; UV–vis (methanol): λ_{max} (log ε)=218 nm (4.06); ^{1}H NMR (500 MHz, $CDCl_3$): δ=9.64 (d, 1H, J=1.3 Hz, C*H*O (28)), 4.73 (br d, 1H, CH_a (30)), 4.60 (br t, 1H, CH_b (30)), 2.84 (ddd, 1H, J=11.5, 11.1, 6.1 Hz, CH (19)), 2.51–2.41 (m, 1H, CH_a (2)), 2.40–2.33 (m, 1H, CH_b (2)), 2.08–1.99 (m, 2H, CH_a (21)+CH (13)), 1.91–1.80 (m, 2H, CH_a (1)+CH_a (15)), 1.77–1.68 (m, 3H, CH_a (12)+CH_a (16)+CH (18)), 1.67 (s, 3H, CH_3 (29)), 1.51–1.14 (m, 14H, CH_b (15)+CH_b (21)+CH_2 (6)+CH_2 (11)+CH_2(7)+CH_b (1)+CH (9)+CH_b (16)+CH (5)+CH_2 (22)), 1.08–1.01 (m, 1H, CH_b (12)), 1.04 (s, 3H, CH_3 (23)), 0.99 (s, 3H, CH_3 (24)), 0.96 (s, 3H, CH_3 (27)), 0.93 (s, 3H, CH_3 (25)), 0.90 (s, 3H, CH_3 (26)); ^{13}C NMR (125 MHz, $CDCl_3$): δ=218.0 (C3, *C*O), 206.5 (C28, *C*HO), 149.6 (C20, *C*=CH$_2$), 110.2 (C30, C=*C*H$_2$), 59.3 (C17, $C_{quart.}$), 54.9 (C5, *C*H), 49.8 (C9, *C*H), 48.0 (C18, *C*H), 47.5 (C19, *C*H), 47.3 (C4, $C_{quart.}$), 42.6 (C14, $C_{quart.}$), 40.8 (C8, $C_{quart.}$), 39.6 (C1, *C*H$_2$), 38.7 (C13, *C*H), 36.9 (C10, $C_{quart.}$), 34.1 (C2, *C*H$_2$), 33.6 (C7, *C*H$_2$), 33.1 (C16, *C*H$_2$), 29.8 (C15, *C*H$_2$), 29.1 (C21, *C*H$_2$), 28.8 (C22, *C*H$_2$), 26.6 (23, *C*H$_3$), 25.5 (C12, *C*H$_2$), 21.3 (C11, *C*H$_2$), 21.0 (C24, *C*H$_3$), 19.6 (C6, *C*H$_2$), 19.0 (C29, *C*H$_3$), 15.9 (C26, *C*H$_3$), 15.7 (C25, *C*H$_3$), 14.2 (C27, *C*H$_3$); MS (EI, 70 eV): m/z=438 (49), 410 (87), 232 (46), 219 (65), 205 (100), 189 (93), 175 (67), 161 (48), 147 (51), 135 (57), 121 (66), 107 (63), 95 (58). Anal. Calcd for $C_{30}H_{46}O_2$ (438.69): C, 82.14; H, 10.57. Found: C, 81.92; H, 10.63.

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