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# Hydroxylated boswellic and glycyrrhetinic acid derivatives: synthesis and cytotoxicity

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**Abstract**: Oxidation of 2,3-dehydro-11-keto-β-boswellic acid gave derivatives holding extra hydroxyl groups at positions C-1, C-2 or C-1 and C-9, respectively. The synthesis of 2,3-dehydro-1,9-dihydroxy-11-keto-β-boswellic acid represents the first partial-synthetic access to this class of compounds. The synthetic strategy can be expanded easily, and a corresponding analogue derived from glycyrrhetinic acid was accessed by the same synthetic scheme in good overall yield. Boswellic and glycyrrhetinic acid 1,9-endoperoxides are intermediates for the synthesis of the 1,9-dihydroxylated compounds. These 1,9-endo-peroxides were highly cytotoxic for several human tumor cell lines but only diminished cytotoxicity was observed in SRB assays for the 1,9-dihydroxylated compounds.

**Keywords**: β-Boswellic acid; cytotoxicity; triterpenoids; oxidation

## Introduction

Frankincense and its extracts have been in use for many centuries[1–5]. The first indications of the use of incense can be found in 3500 years old texts from the Nile Valley[6]. Thereby, the Egyptians used incense for the good smell of the air, for ointments but also for wound treatment. Frankincense was a valuable commodity, and as a result of its trade routes soon developed. Thus, three thousand years ago there were already fixed trade routes, the incense routes, which brought the precious resin from its homeland South Arabia (above all Oman) and the island of Sokotra at the horn of Africa to Egypt and Mesopotamia. Incense is the air-dried gum resin obtained from the incense tree. The resin is mainly obtained from trees of the genus *Boswellia sacra*, *Boswellia papyrifera*, *Boswellia serrata*, *Boswellia frereana*, each of which produces a slightly different type of resin. Through cuts in the trunk and branches, a sticky-milky liquid emerges, which causes the incense resin to form by drying in the air. Frankincense was and is not only used as a cult incense but also as a phytotherapeutic[7–10]. In modern medicine; preparations from frankincense with standardized active substance content are investigated in the therapy of chronic inflammatory diseases such as Crohn's disease [11,12], ulcerative colitis or poly-arthritis [7,11]. First clinical study results suggest the effectiveness of frankincense preparations in Crohn's disease [1] and ulcerative colitis[13–16].

Frankincense consists of a mixture of different compounds whereby β-boswellic acids are considered to be the most important ingredients. In particular, 3-*O*-acetyl-11-keto-β-boswellic acid (AKBA, **1**, Figure 1) and 11-keto-β-boswellic acid (KBA, **2**) hold anti-inflammatory effects by inhibiting the enzyme 5-lipoxygenase and thus reducing the biosynthesis of leukotrienes [17–19].

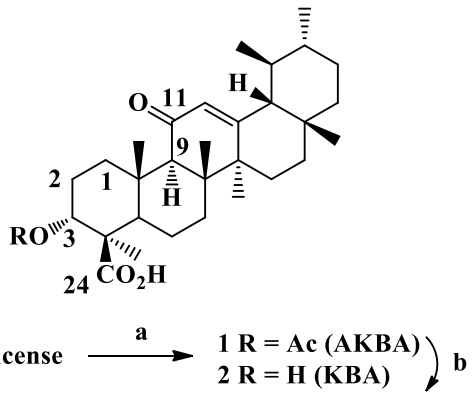


**Figure 1.** Structure of AKBA (**1**) and KBA (**2**); a) isolation from frankincense according to Jauch et al. [36]; b) NaOMe, MeOH, 12 h, 25 °C, 98%.

Boswellic acids and their derivatives [20–32] show cytotoxic effects and have been investigated for the

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treatment of tumors [9,10]. Frankincense holds many terpenoids, and several hydroxylated boswellic acids have also been found in incense as minor components [33,34]. However, they have rarely been isolated in pure form, and therefore hardly any research has been carried out on their physicochemical and biological properties [35]. Therefore, we studied the synthesis of some β-boswellic acids with additional hydroxyl groups at positions C-1, C-2 and C-9, and screened them for cytotoxic effects.

**Results and discussion**

AKBA (**1**, Figure 1) can easily be obtained from the resin by extraction, oxidation and acetylation following Jauch's procedure [36,37]. Deacetylation of **1** with NaOMe in MeOH gave **2**. Mitsunobu elimination [38] of **2** (Scheme 1) with triphenyl-phosphane (TPP), diethyl azodicarboxylate (DEAD) and 3,3-dimethyl-glutarimide (DMGI) yielded **3** [39-41] in excellent yield. Compound **3** is a well-suited starting material for the synthesis of hydroxylated AKBA derivatives.

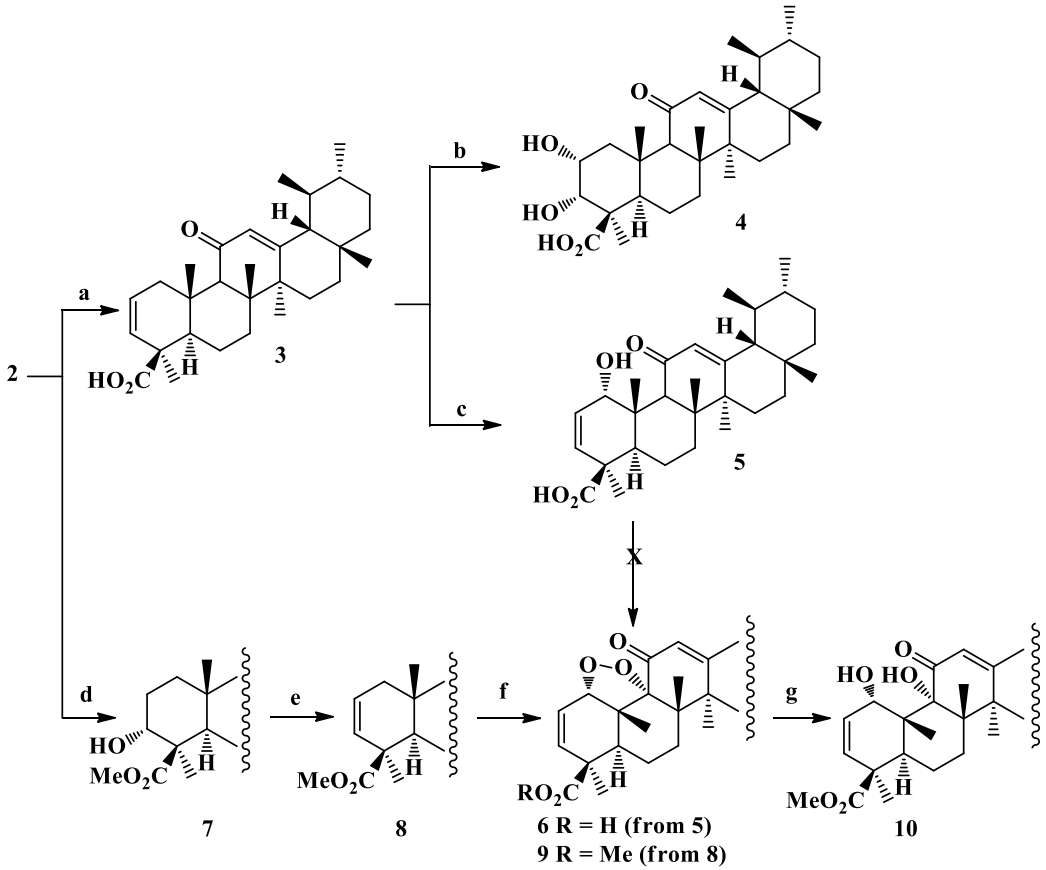
While the reaction of **3** with catalytic amounts of $OsO_4$ in the presence of a five-fold molar excess of *N*-methylmorpholine *N*-oxide in THF/water (5/1) resulted in a very low yield of di-hydroxylated **4**, the reaction of **3** with equimolar amounts of $OsO_4$ proceeded smoothly at 5 °C and 76% of **4** could be isolated. The configuration at position C-2 and C-3 was deduced from the coupling constants $^3J_{H\text{-}2,H\text{-}3}$ and 2D-$^1$H-$^1$H-NOESY-NMR experiments.

Riley-oxidation of **3** with $SeO_2$ in 1,4-dioxane at 70 °C for one day gave a 56% yield of **5** holding an additional hydroxyl group at position C-1. The absolute configuration of the newly created stereogenic center C-1 in compound **5** [42] was again deduced from 2D-$^1$H-$^1$H-NOESY spectra. Oxidation of **3** with *N*-hydroxy-phthalimide (NHPI) and sodium dichromate in the presence of oxygen[21,43], however, proceeded very sluggish, and only traces of a peroxo-compound **6** were detected by TLC-MS. Therefore, compound **2** was esterified ($Cs_2CO_3$/MeI) and ester **7** was obtained. An elimination reaction as described above gave **8**. The oxidation of **8** with oxygen, $Na_2Cr_2O_7$. 2 $H_2O$ in the presence of NHPI gave 76% of peroxo compound **9**. Reduction of **9** with thiourea at 40 °C for one day furnished 68% of **10** holding hydroxyl moieties at positions C-1 and C-9. This strategy for the synthesis of triterpenes with additional hydroxyl groups at positions C-1 and C-9 seems to be generally feasible. For comparison, glycyrrhetinic acid (**11**, Scheme 2) was transformed into its methyl ester **12** [44,45] followed by an elimination reaction to afford **13**. Oxidation of **13** as described above gave endo-peroxide **14** [44] whose reduction with thiourea [46,47] finally yielded 1,9-dihydroxylated **15**. There are only a few reports describing the isolation of 1,3,9-trihydroxylated triterpenoic acids [48–51]; there is none, however, dealing with their (partial) synthesis.

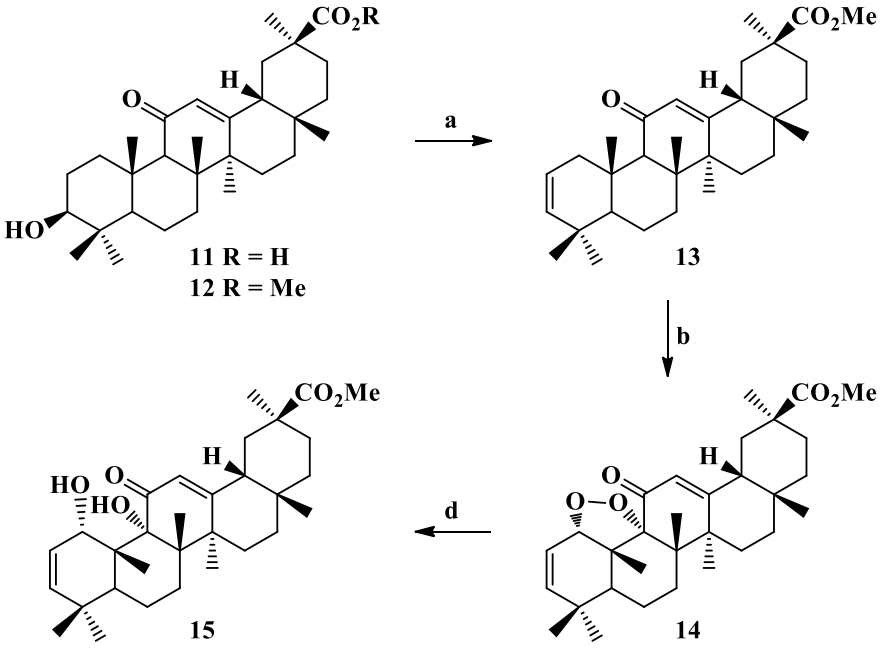
Compounds **1**-**5** and **7**-**15** were screened for their cytotoxic activity in SRB assays [20,22,52]. Most of the compounds showed only weak to medium activity. Interestingly, while endo-peroxides **9** and **14** are highly cytotoxic for several human tumor cell lines, only diminished cytotoxicity was observed for **10** and **15** in SRB assays (Table 1); the cytotoxicity of compounds **10** and **15** is – by and large - in the same magnitude as of parent AKBA (**1**) and glycyrrhetinic acid (**12**), respectively. The highest cytotoxicity was observed for **9** albeit its selectivity malignant cells vs. non-malignant mouse fibroblast was low. Higher selectivity was observed, however, for **11**. Thus, this compound was most cytotoxic for A375 melanoma cells ($EC_{50}$ = 6.3 μM) while being significantly less cytotoxic for non-malignant mouse fibroblasts NIH 3T3 ($EC_{50}$ = 22.8 μM).

**Table 1.** Cytotoxicity of compounds **1**-**15** and betulinic acid (**BA**, positive standard; $EC_{50}$ values in μM from SRB assays after 96 h of treatment, the values are averaged from three independent experiments performed each in triplicate, confidence interval CI = 95%; mean ± standard mean error). Human cancer cell lines: A375 (epithelial melanoma), A2780 (ovarian carcinoma), HT29 (colorectal adenocarcinoma), MCF7 (breast adenocarcinoma), 518A2 (melanoma); non-malignant: NIH3T3 (mouse fibroblasts).

| Compound | A375 | A2780 | HT29 | MCF7 | 518A2 | NIH3T3 |
|---|---|---|---|---|---|---|
| **1** | 24.1 ± 3.7 | 21.1 ± 1.9 | 19.4 ± 1.1 | 17.4 ± 1.7 | 20.5 ± 1.1 | > 50 |
| **2** | 47.9 ± 2.4 | 37.9 ± 3.6 | 71.3 ± 2.8 | 35.8 ± 3.2 | 48.5 ± 1.3 | > 50 |
| **3** | 41.3 ± 1.7 | 39.5 ± 2.6 | 38.1 ± 1.9 | 41.3 ± 1.7 | 40.1 ± 2.3 | 42.3 ± 2.4 |
| **4** | 39.2 ± 1.4 | 40.2 ± 2.0 | 39.4 ± 1.7 | 37.4 ± 3.5 | 39.1 ± 1.9 | 40.0 ± 2.3 |
| **5** | 38.7 ± 3.0 | 37.4 ± 2.3 | 40.3 ± 2.4 | 41.0 ± 2.6 | 39.2 ± 1.4 | 39.5 ± 2.5 |
| **7** | 51.4 ± 2.8 | 37.9 ± 3.6 | 71.3 ± 2.8 | 35.8 ± 3.2 | 48.5 ± 1.3 | 41.9 ± 6.3 |
| **8** | 40.9 ± 2.8 | 40.1 ± 2.5 | 30.2 ± 3.2 | 30.9 ± 1.7 | 35.2 ± 1.9 | 29.4 ± 3.0 |
| **9** | 0.9 ± 0.2 | 0.7 ± 0.1 | 1.3 ± 0.6 | 1.8 ± 0.9 | 0.8 ± 0.2 | 1.4 ± 0.4 |
| **10** | 25.9 ± 2.5 | 17.1 ± 0.8 | 26.7 ± 1.9 | 12.5 ± 0.7 | 26.3 ± 4.7 | 29.9 ± 2.4 |
| **11** | 6.3 ± 1.4 | 25.5 ± 1.3 | 27.5 ± 1.4 | 22.1 ± 1.2 | 27.5 ± 1.4 | 22.8 ± 1.1 |
| **12** | 83.2 ± 2.9 | 74.6 ± 3.7 | 80.1 ± 4.0 | 84.7 ± 4.2 | 75.1 ± 3.2 | 18.5 ± 0.9 |
| **13** | 45.3 ± 2.0 | 47.3 ± 1.9 | 40.2 ± 2.3 | 41.4 ± 1.7 | 39.6 ± 2.9 | 40.8 ± 3.0 |
| **14** | 1.5 ± 0.5 | 1.01 ± 0.3 | 1.7 ± 0.4 | 2.9 ± 0.4 | 1.2 ± 0.4 | 1.9 ± 0.3 |
| **15** | 27.0 ± 2.2 | 23.8 ± 0.7 | 26.5 ± 1.3 | 14.3 ± 0.6 | 25.6 ± 3.7 | 30.9 ± 1.3 |
| **BA** | 17.1 ± 1.7 | 11.0 ± 1.9 | 14.4 ± 2.3 | 14.8 ± 1.9 | 16.3 ± 2.5 | 13.1 ± 1.1 |




**Scheme 1**. Synthesis of boswellic acid derivatives **3**-**10**: a) TPP, DMGI, DEAD, THF, 24 h, 40 °C, 81%; b) $OsO_4$, pyridine, 3 days, 5 °C, 76%; c) $SeO_2$, dioxane, 1 day, 70 °C, 56%; d) $Cs_2CO_3$, THF, MeI, 12 h, 25 °C, 95%; e) TPP, DMGI, DEAD, THF, 24 h, 40 °C, 85%; f) NHPI, $Na_2Cr_2O_7{\cdot}2\ H_2O$, $O_2$, 12 h, 40 °C, 76%; g) $H_2N$-(C=S)-$NH_2$, MeOH, 1 day, 40 °C, 68%.




**Scheme 2.** a) TPP, DMGI, DEAD, THF, 1 day, 40 °C, 82%; b) NHPI, $Na_2Cr_2O_7.2H_2O$, $O_2$, 12 h, 40 °C, 76%; c) $H_2N$-(C=S)-$NH_2$, MeOH, 1 day, 40 °C, 70%.

## Conclusion

Starting from 11-keto-β-boswellic acid several derivatives were prepared holding extra hydroxyl groups at positions C-1, C-2 or C-1 and C-9, respectively. For the latter compound, this represents the first partial-synthetic access to this class of compounds. The synthetic strategy seems to be universal, and a corresponding analogue derived from glycyrrhetinic acid was accessed by the same synthetic scheme in good overall yield. Central intermediates for these 1,9-dihydroxylated-2,3-eno compounds are 1,9-endoperoxides. While these 1,9-endo-peroxides were highly cytotoxic for several human tumor cell lines, only diminished cytotoxicity was observed for the 1,9-dihydroxylated compounds in SRB assays.

## Experimental

Melting points are uncorrected (*Leica* hot stage microscope), NMR spectra were recorded using the Varian spectrometers Gemini 2000 or Unity 500 (δ given in ppm, *J* in Hz), MS spectra were taken on a Finnigan MAT LCQ 7000 (electrospray, voltage 4.5 kV, sheath gas nitrogen) instrument. The optical rotations were measured on a Perkin-Elmer polarimeter at 20 °C; TLC was performed on silica gel (Merck 5554); elemental analyses were performed on a Vario EL (CHNS). The solvents were dried according to usual procedures. The purity of the compounds was determined by HPLC and found to be > 97%. Frankincense was bought from different commercial suppliers in bulk quantities. The SRB assays were performed as previously reported.

### 3-O-Acetyl-11-keto-β-boswellic acid [AKBA (1)]

**AKBA** was isolated following a modified Jauch's procedure [36] and obtained as a white solid; m.p. 268-270 °C (lit.: [36] 271-276 °C), $[\alpha]_D$ = +81.1° (*c* = 1.0, $CHCl_3$) (lit.: [36] $[\alpha]_D$ = +82° (*c* = 1.25, $CHCl_3$)).

### 11-Keto-β-boswellic acid (2, KBA)

Deacetylation of **AKBA** (**1**, 10.0 g, 19.5 mmol) in methanol (200 mL) with an aq. solution of sodium hydroxide (4 M, 100 mL) at 25 °C for 12 h followed by usual work-up and chromatography (silica gel, *n*-hexane/ethyl acetate, 98:2) gave **2** (9.3 g, 98%) as a white solid; m.p. 192-195 °C (lit.: [36] 194-195 °C); $[\alpha]_D$ = +118.2° (*c* = 3.72, $CHCl_3$), lit.: [36]) $[\alpha]_D$ = +121° (*c* = 1.11, $CHCl_3$)).

### 2,3-Dehydro-11-keto-β-boswellic acid (3)

To a solution of **2** (3.42 g, 7.26 mmol) in dry THF (80 mL), $PPh_3$ (9.54 g, 36.3 mmol) and 3,3-dimethylglutarimide (5.13 g, 36.4 mmol) were added, and stirring at 25 °C was continued for 10 min. A solution of DEAD in toluene (14.2 mL, 36.3 mmol, 40%) was slowly added. Stirring at 40 °C was continued for one day. The solvent was removed under diminished pressure, and the residue subjected to chromatography (*n*-hexane/ethyl acetate, 15:1) to yield **8** (2.66 g, 81%) as a white solid; m.p. 279-282 °C; $[\alpha]_D$ = +238.1° (*c* = 0.9, $CHCl_3$);
$^1$H NMR (500 MHz, $CDCl_3$): δ = 5.65 (*m*, 2H, 2-H, 3-H), 5.60 (*bs*, 1H, 12-H), 3.13 (*dd*, *J* = 18.3, 5.1 Hz, 1H, 1-$H_a$), 2.42 (*s*, 1H, 9-H), 2.08 (*m*, 1H, 16-$H_a$), 1.90 (*m*, 2H, 6-$H_a$, 15-$H_a$), 1.85-1.62 (*m*, 3H, 1-Hb, 6-Hb, 7-Ha), 1.55 (*m*, 1H, 18-H), 1.50-1.40 (*m*, 4H, 7-$H_a$, 19-$H_a$, 21-$H_a$, 22-$H_a$), 1.37 (*bs*, 4H, 21-$H_b$, 23-H), 1.32 (*m*, 1H, 22-$H_b$), 1.31 (*bs*, 4H, 5-H, 27-H), 1.22 (*m*, 1H, 15-$H_b$), 1.20 (*s*, 3H, 26-H), 1.14 (*s*, 3H, 25H), 1.03 (*m*, 1H, 16-$H_b$), 0.93 (*bs*, 4H, 20-H, 30-H), 0.81 (*s*, 3H, 28-H), 0.82 (*d*, *J* = 6.4 Hz, 3H, 29-H) ppm;
$^{13}$C NMR (125 MHz, $CDCl_3$): δ = 199.5 (C-11), 182.0 (C-24), 165.0 (C-13), 130.4 (C-12), 129.8 (C-3), 125.4 (C-2), 60.2 (C-9), 58.9 (C-18), 52.8 (C-5), 45.0 (C-8), 44.1 (C-4), 43.3 (C-14), 42.0 (C-1), 41.2 (C-22), 39.2 (C-19), 39.1 (C-20), 36.0 (C-10), 34.3 (C-17), 32.4 (C-7), 31.3 (C-21), 28.6 (C-28), 27.9 (C-23), 27.4 (C-16), 27.0 (C-15), 21.0 (C-30), 20.4 (C-27), 19.6 (C-6), 17.5 (C-26), 17.4 (C-29), 14.9 (C-25) ppm;
MS (ESI, MeOH): m/z (%): 453.2 (72, [M+H]+);
Analysis calcd for $C_{30}H_{44}O_3$ (452.67): C 79.60, H 9.80; found: C 79.42, H 10.01.

### 2α-Hydroxy-11-keto-β-boswellic acid (4)

A solution of $OsO_4$ (300 mg, 1.18 mmol) in THF (30 ml) was added to a solution of **3** (450 mg, 1.0 mmol) in THF containing pyridine (0.5 mL), and the mixture was stirred at 5 °C for three days. The supernatant was decanted, the residue dissolved in DCM (150 mL) and treated with an aq. solution of $NaHSO_3$ (100 mL). The organic phase was dried ($Na_2SO_4$), the solvent evaporated, and the residue subjected to chromatography (silica gel, *n*-hexane/ether/acetic acid, 1:5/1%) to yield **4** (370 mg, 76%) as a white solid; m.p. 220-223 °C; $[\alpha]_D$ = +114.3° (*c* = 1.1, acetone);
$^1$H NMR (500 MHz, acetone): δ = 5.51 (*s*, 1H, 12-H), 4.21 (*ddd*, *J* = 12.0, 4.8, 2.9 Hz, 1H, 2-H), 3.94 (*d*, *J* = 2.5 Hz, 1H, 3-H), 2.67 (*dd*, *J* = 12.4, 4.5 Hz, 1H, 1-$H_a$), 2.50 (*s*, 1H, 9-H), 2.20 (*dt*, *J* = 13.6, 5.0 Hz, 1H, 16-$H_a$), 1.98-1.84 (*m*, 2H, 6-$H_a$, 15-$H_a$), 1.81-1.68 (*m*, 2H, 6-$H_b$, 7-$H_a$), 1.61 (*dd*, *J* = 11.2, 1.5 Hz, 1H, 18-H), 1.56-1.41 (*m*, 5H, 5-H, 7-$H_b$, 19-H, 21-$H_a$, 22-$H_a$), 1.40 (*s*, 3H, 27-H), 1.37 (*m*, 2H, 21-$H_b$, 22-$H_b$), 1.37 (*s*, 3H, 23-H), 1.30-1.22 (*m*, 2H, 1-H, 15-H), 1.18 (*s*, 3H, 26-H), 1.17 (*s*, 3H, 25-H), 1.04 (*m*, 1H, 16-$H_b$), 0.97 (bs, 4H, 20-H, 30-H), 0.84 (*s*, 3H, 28-H), 0.82 (*d*, *J* = 6.3 Hz, 3H, 29-H) ppm;
$^{13}$C NMR (125 MHz, acetone): δ = 200.3 (C-11), 179.0 (C-24), 165.6 (C-13), 132.1 (C-12), 75.6 (C-3), 66.5 (C-2), 62.1 (C-9), 61.2 (C-18), 49.2 (C-4), 49.1 (C-5), 46.5 (C-8), 45.5 (C-14), 44.6 (C-1), 42.6 (C-22), 40.8 (C-19), 40.7 (C-20), 39.7 (C-10), 35.4 (C-17), 34.5 (C-7), 32.3 (C-21), 30.0 (C-28), 29.1 (C-16), 29.0 (C-15), 25.5 (C-23), 22.3 (C-30), 22.0 (C-27), 20.6 (C-6), 20.1 (C-26), 18.6 (C-29), 16.0 (C-25) ppm;
MS (ESI, MeOH): m/z (%): 487.3 (100, $[M+H]^+$);
Analysis calcd for $C_{30}H_{46}O_5$ (486.68): C 74.04, H 9.53; found: C 73.83, H 9.71.

**1α-Hydroxy-2,3-dehydro-11-keto-β-boswellic acid (5)**

To a solution of **3** (0.9 g, 1.99 mmol) in dry 1,4-dioxane (25 mL) $SeO_2$ (510 mg, 4.6 mmol) was added and the mixture was heated at 70 °C for one day. The mixture was filtered, and the filtrate was evaporated under reduced pressure. The residue was dissolved in ether (100 mL), followed by usual aqueous work up and chromatography (silica gel, *n*-hexane/ether/acetic acid, 2:1/0.1%) gave **5** (0.52g, 56%) as an off-white solid; m.p. 283-286 °C; $[\alpha]_D$ = +276.1° (*c* = 1.3, $CHCl_3$);

$^1$H NMR (500 MHz, $CDCl_3$): δ = 5.87 (*dd*, *J* = 10.1, 5.2 Hz, 1H, 2-H), 5.79 (*d*, *J* = 10.1 Hz, 1H, 3-H), 5.64 (*s*, 1H, 12-H), 4.65 (*d*, *J* = 5.2 Hz, 1H, 1-H), 3.35 (*s*, 1H, 9-H), 2.14 (*dt*, *J* = 13.5, 4.6 Hz, 1H, 16-$H_a$), 1.95-1.81 (*m*, 2H, 6-$H_a$, 15-$H_a$), 1.87-1.70 (*m*, 1H, 6-$H_a$), 1.71-1.51 (*m*, 4H, 5-H, 7-$H_a$, 18-H, 22-$H_a$), 1.50-1.35 (*m*, 3H, 7-$H_a$, 19-H, 21-$H_a$), 1.34 (*s*, 3H, 23-H), 1.32 (*m*, 1H, 21-$H_b$), 1.30 (*bs*, 4H, 22-$H_b$, 27-H), 1.26 (*m*, 1H, 15-$H_b$), 1.20 (*s*, 3H, 26-H), 1.08 (*s*, 3H, 25-H), 1.04 (*m*, 1H, 16-$H_b$), 0.93 (*bs*, 4H, 20-H, 30-H), 0.82 (*s*, 3H, 28-H), 0.81 (*d*, *J* = 6.4 Hz, 3H, 29-H) ppm;

$^{13}$C NMR (125 MHz, $CDCl_3$): δ = 201.5 (C-11), 180.9 (C-24), 166.0 (C-13), 133.6 (C-3), 130.0 (C-12), 126.4 (C-2), 69.2 (C-1), 59.4 (C-18), 51.4 (C-9), 46.7 (C-5), 44.8 (C-8), 43.8 (C-4), 44.0 (C-14), 41.1 (C-22), 40.7 (C-10), 39.1 (C-19), 38.9 (C-20), 34.2 (C-17), 31.1 (C-7), 31.0 (C-21), 28.4 (C-28), 27.7 (C-23), 27.5 (C-16), 27.4 (C-15), 21.4 (C-30), 20.1 (C-27), 19.2 (C-6), 18.0 (C-26), 17.3 (C-29), 15.3 (C-25) ppm;

MS (ESI, MeOH): m/z (%): 469.5 (100, $[M+H]^+$);

Analysis calcd for $C_{30}H_{44}O_4$ (468.67): C 76.88, H 9.46; found: C 76.57, H 9.61.

**11-Keto-β-boswellic acid methyl ester (7)**

A suspension of **2** (4.73 g, 10.0 mmol) and $Cs_2CO_3$ (9.8 g, 30 mmol) in THF (50 mL) was stirred at 0 °C for 30 min, then MeI (6.23 mL, 100 mmol) was added, and stirring was continued for 12 h. Usual work-up gave **7** (4.60 g, 95%) as an off-white solid that was used for the next reaction without any purification; an analytical sample showed m.p. 223-225 °C (lit.: 220-225 °C [21]; $[\alpha]_D$ = +109.8° (*c* = 1.3, $CHCl_3$) (lit.: $[\alpha]_D$ = +111.2° (*c* = 4.34, $CHCl_3$) [21].

**2,3-Dehydro-11-keto-β-boswellic acid methyl ester (8)**

To a solution of **7** (3.52 g, 7.26 mmol) in dry THF (80 mL), $PPh_3$ (9.54 g, 36.3 mmol) and 3,3-dimethylglutarimide (5.13 g, 36.4 mmol) were added, and stirring at 25 °C was continued for 10 min. A solution of DEAD in toluene (14.2 mL, 36.3 mmol, 40%) was slowly added. Stirring at 40 °C was continued for 1 day. The solvent was removed under diminished pressure, and the residue subjected to chromatography (*n*-hexane/ethyl acetate, 15:1) to yield **8** (2.9 g, 85%) as a white solid; m.p. 187-190 °C (lit.: 185-188 °C [21]); $[\alpha]_D$ = +194.4° (*c* = 0.31, $CHCl_3$) (lit.: $[\alpha]_D$ = +187.4° (*c* = 5.32, $CHCl_3$) [21].

**Methyl 2,3-dihydro-1α,9α-peroxo-11-oxo-urs-12-en-24-oate (9)**

To a solution of **8** (2.94 g, 6.3 mmol in acetone (150 mL), NHPI (5.13 g, 10.5 mmol) and $Na_2Cr_2O_7.2H_2O$ (0.39 g, 1.26 mmol) were added, and the suspension was stirred over night at 40 °C. Usual work-up followed by chromatography (silica gel, *n*-hexane/ethyl acetate, 10:1) gave **9** (2.23 g, 76%) as a white solid; m.p. 148-151 °C (lit.: [21] amorphous solid); $[\alpha]_D$ = 68.3° (*c* = 4.1, $CHCl_3$) (lit.: $[\alpha]_D$ = 65.6° (*c* = 4.98, $CHCl_3$)[21]; MS (ESI, MeOH): m/z (%) = 1015.1 (100, $[2M+ Na]^+$), 764.3 (25, $[3M+Ca]^{2+}$), 519.3 (54, $[M+Na]^+$), 497.2 (14, $[M+H]^+$).

**Methyl 2,3-dihydro-1α,9α-dihydroxy-11-oxo-urs-12-en-24-oate (10)**

To a solution of **9** (1.68 g, 3.4 mmol) in MeOH (150 mL) thiourea (0.5 g, 6.8 mmol) was added, and the mixture was stirred at 40 °C for 1 day. Usual work-up followed by chromatography (silica gel, *n*-hexane/chloroform/ethyl acetate/acetic acid, 8:5:2:0.2%) gave **10** (1.15 g, 68%) as a white solid; m.p. 228-231 °C; $[\alpha]_D$ = +158.5° (*c* = 0.32, $CHCl_3$);

$^1$H NMR (400 MHz, $CDCl_3$): δ = 5.74-5.72 (*m*, 2H, 3-H, 2-H), 5.64 (*s*, 1H, 12-H), 4.96 (*m*, 1H, 1-H), 3.63 (*s*, 3H, OMe), 2.30 (*dd*, *J* = 12.6, 3.1 Hz, 1H, 5-H), 2.22 (*ddd*, *J* = 13.3, 13.3, 3.8 Hz, 1H, 7-$H_a$), 2.16 (*ddd*, *J* = 13.5, 13.5, 4.8 Hz, 1H, 16-$H_a$) 2.01-1.89 (m, 2H, 6-$H_a$, 15-$H_a$), 1.68 (*ddd*, *J* = 13.5, 13.5, 3.6 Hz, 1H, 6-$H_b$), 1.56 (*dd*, *J* = 11.5, 1.3 Hz, 1H, 18-H), 1.52-1.41 (*m*, 3H, 22-$H_a$, 19-H, 21-$H_a$), 1.47 (*s*, 3H, 27-H), 1.37 (*s*, 3H, 23-H), 1.36-1.19 (*m*, 4H, 22-$H_b$, 21-$H_b$, 15-$H_b$, 7-$H_b$), 1.18 (*s*, 3H, 26-H), 1.04 (*s*, 3H, 25-H), 0.97 (*m*, 1H, 16-$H_b$), 0.94-0.90 (*m*, 1H, 20-H), 0.93 (*s*, 3 H, 30-H), 0.84 (*s*, 3H, 28-H), 0.82 (*d*, *J* = 6.4 Hz, 3H, 29-H) ppm;

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 201.0 (C-11), 175.6 (C-24), 168.1 (C-13), 133.5 (C-3), 128.0 (C-12), 126.1 (C-2), 83.5 (C-9), 74.0 (C-l), 60.4 (C-18), 51.7 (OMe), 47.6 (C-4), 46.0 (C-14), 44.9 (C-8), 43.8 (C-10), 42.1 (C-5), 41.0 (C-22), 39.5 (C-19), 39.3 (C-20), 34.6 (C-17), 31.0 (C-21), 29.4 (C-15), 29.3 (C-28), 27.7 (C-23), 27.5 (C-16), 27.3 (C-7), 25.3 (C-27), 21.0 (C-30), 20.6 (C-6), 20.5 (C-25), 19.1 (C-26), 17.5 (C-29) ppm;

MS (ESI, MeOH): m/z (%) = 1019.3 (100, $[2M+Na]^+$, 521.4 (16, $[M+Na]^+$), 481.2 (8, $[M+H-H_2O]^+$);

Analysis calcd for $C_{31}H_{46}O_5$ (498.70): C 74.66, H9.30; found: 74.42, H 9.47.

**Glycyrrhetinic acid (11)**

This material was commercially obtained in bulk from Orgentis GmbH (Neugatersleben, Germany) and used as received.

**Glycyrrhetinic acid methyl ester (12)**

This compound was prepared as previously described from **12** (30.0 g, 65.9 mmol), iodomethane (4.94 mL, 79.0 mmol) and potassium carbonate (15.34 g, 111.0 mmol) in dry DMF (150 mL), and obtained as a white solid (29.1 g, 91%); m.p. 255-258 °C (lit.: 254-258 °C

[45]); $[\alpha]_D$ = +140.9° (*c* = 2.5, $CHCl_3$) (lit.: $[\alpha]_D$ = + 141.2 (*c* = 4.8, $CHCl_3$)) [45].

**2,3-Dehydro-glycyrrhetinic acid methyl ester (13)**
To a solution **12** (1.52 g, 3.14 mmol) in THF (80 mL), TPP (4.11 g, 15.7 mmol) and DMGI (2.21 g, 15.7 mmol) were added, and the mixture was stirred for 10 min. A solution of DEAD (14.2 mL, 36.3 mmol, 40% in toluene) was slowly added, and the mixture has stirred at 40 °C for one day. Usual work-up followed by chromatography (silica gel, *n*-hexane/ethyl acetate, 15:1) gave **13** (1.2 g, 82%) as a white solid; m.p. 225-228 °C (lit.: 182-186 °C) [44]; $[\alpha]_D$ = +211.4° (*c* = 0.30, $CHCl_3$) (lit.: $[\alpha]_D$ = +204.6° (*c* = 3.42, $CHCl_3$))[44]; MS (ESI, MeOH): m/z (%) = 955.4 (30, $[2M+Na]^+$), 933.3 (100, $[2M+H]^+$), 467.3 (79, $[M+H]^+$).

**Methyl 2,3-dihydro-1α,9α-peroxo-11-oxo-olean-12-en-30-oate (14)**
Following the procedure given for the synthesis of **9**, from **13** (2.0 g, 4.4 mmol), NHPI (3.72 g, 21.6 mmol) and $Na_2Cr_2O_7 \cdot 2\ H_2O$ (300 mg, 0.86 mmol) followed by chromatography (silica gel, *n*-hexane/ethyl acetate, 10:1) **14** (1.44 g, 76%) was obtained as a white solid; m.p. 152-155 °C (lit.: 151-155 °C) [44]; $[\alpha]_D$ = +56.9° (*c* = 0.31, $CHCl_3$) (lit.: $[\alpha]_D$ = +48.1° (*c* = 3.08, $CHCl_3$) [44]; MS (ESI, MeOH): m/z (%) = 529.0 (24, $[M+H+MeOH]^+$), 497.2 (100, $[M+H]^+$).

**Methyl 2,3-dihydro-1α,9α-dihydroxy-11-oxo-olean-12-en-30-oate (15)**
Following the procedure given for the synthesis of **10**, from **14** (1.25 g, 3.24 mmol) and thiourea (0.52 g, 6.48 mmol) followed by chromatography (silica gel, *n*-hexane/chloroform/ethyl acetate/acetic acid, 8:5:2:0.2%) gave **15** (1.17 g, 70%) as a white solid; m.p. 210-213 °C; $[\alpha]_D$ = +185.4° (*c* = 0.34, $CHCl_3$);
$^1$H NMR (500 MHz, $CDCl_3$): δ = 5.16 (*s*, 1H, 12-H), 5.60 (*dd*, *J* = 10.0, 5.0 Hz, 1H, 2-H), 5.55 (*d*, *J* = 10.0 Hz, 1H, 3-H), 5.02 (*d*, *J* = 5.0 Hz, 1H, 1-H), 3.68 (*s*, 3H, OMe), 2.26-2.17 (*m*, 2H, 5-H, 7-$H_a$), 2.11 (*m*, 1H, 16-$H_a$), 2.09 (*dd*, *J* = 13.2, 4.4 Hz, 1H, 18-H), 2.03-1.95 (*m*, 2H, 19-$H_a$, 21-$H_a$), 1.88 (*ddd*, *J* = 13.3, 13.3, 4.7 Hz, 1H, 15-$H_a$), 1.74-1.54 (*m*, 3H, 19-$H_b$, 6-H), 1.53 (*s*, 3H, 27-H), 1.41-1.29 (*m*, 3H, 22-H, 21-$H_b$), 1.26-1.20 (*m*, 2H, 15-$H_b$, 7-$H_b$), 1.19 (*s*, 3H, 26-H), 1.14 (*s*, 3H, 29-H), 1.10 (*s*, 3H, 25-H), 1.04 (*s*, 3H, 23-H), 0.97 (*m*, 1H, 16-$H_b$), 0.91 (*s*, 3H, 24-H), 0.83 (*s*, 3H, 28-H) ppm;
$^{13}$C NMR (125 MHz, $CDCl_3$): δ = 200.9 (C-11), 177.1 (C-30), 171.2 (C-13), 140.8 (C-3), 126.5 (C-12), 123.3 (C-2), 83.9 (C-9), 73.9 (C-1), 51.7 (OMe), 49.6 (C-18), 47.9 (C-8), 45.5 (C-14), 44.0 (C-20), 43.9 (C-10), 41.0 (C-19), 39.2 (C-5), 37.9 (C-22), 34.6 (C-4), 32.4 (C-l7), 31.7 (C-23), 31.3 (C-21), 28.9 (C-28), 28.8 (C-15), 28.4 (C-27), 28.3 (C-29), 26.9 (C-7), 26.5 (C-l6), 23.0 (C-24), 21.4 (C-25), 19.8 (C-6), 19.7 (C-26) ppm;
MS (ESI, MeOH): m/z (%) = 1019.5 (13, $[2M+Na]^+$), 997.1 (100, $[2M+H]^+$, 499.1 (30, $[M+H]^+$);
Analysis calcd for $C_{31}H_{46}O_5$ (498.70): C 74.66, H 9.30; found: 76.41, H 9.51.

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