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Simple structural modifications confer cytotoxicity to allobetulin

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ABSTRACT

A variety of allobetulin derivatives was synthesized from allobetulin or allobetulone. These compounds were screened for their cytotoxic activity using a photometric SRB assay employing six different human tumor cell lines. In summary, opening of ring A of allobetulin in general lowers the cytotoxicity, but the 2,3-*seco* diethyl ester was highly cytotoxic and remarkable selective for A549 lung carcinoma cells while being significantly less cytotoxic for non-malignant mouse fibroblasts. The introduction of an amino group at position C-3 in the allobetulin skeleton enhances cytotoxicity and furnishes highly cytotoxic compounds. Their selectivity to distinguish between cancer cell and non-malignant cell depends on the configuration at position C-3.

1. Introduction

Plant derived secondary metabolites have been exploited by humankind for thousands of years to combat diseases. Over the last decade, these natural products were subject to many biological studies, and—in order to improve their biological activities—miscellaneous chemical transformations have been performed, and numerous new derivatives were obtained and screened for their activity.[1]

Natural triterpenoids[2] have been used in traditional medicine for their anticancer, antiviral/virostatic, anti-inflammatory and hepatoprotective activity.[3–11] These triterpenes are important for the survival of the plant, and they form a wide family of compounds. They are biosynthesized by numerous higher plants and some higher fungi from 2,3-epoxy-squalene by a cyclization reaction; by this way, most abundant betulin (Fig. 1) is formed. A re-arrangement reaction, however, transforms betulin to allobetulin (**1**).

While betulin was first accessed as early as 1788[12] from the sublimation of birch bark, and its oxidized product betulinic acid (Fig. 1) was first described[13] in 1902—albeit of uncertain structure—the structure of a 're-arranged' betulin remained unclear until 1922 when Schulze and Pieroh[14] treated betulin with formic acid, and allobetulin (**1**), a (3β,18α,19β) 19,28-epoxy-18-olean-3-ol was formed. The correct molecular formula was determined by Dischendorfer,[15] but it took almost another century to obtain a single crystal X-ray structure.[16]

The cytotoxic activity of betulin and betulinic acid has been investigated,[17] and numerous derivatives have been prepared and screened. Interestingly enough, only a few reports have been published concerning the biological activity of **1** and derivatives thereof.[18] Thus, allobetulin as well as some acetylated and phosphorylated analogs and some oxime-derived compounds have been shown to exhibit moderate antiviral activity.[18–20] In addition, for several derivatives a moderate antiulcer activity[21,22] was determined, and the cytotoxicity of some quinoxaline, pyrazine, azoles or 2-hydroxymethylene derivatives of **1** was significantly lower than those of the corresponding betulin derived analogs.[23–25] Quite recently, a moderate activity was reported for an allobetulin derived ozonide.[26]

The diminished cytotoxicity of allobetulin derivatives as compared to their parent betulin analog is not unexpected at all. The presence of a carbonyl or carboxyl group at C-28 of the betulin skeleton seems mandatory for obtaining good cytotoxicity, although there some exceptions to this rule of thumb.[27] As previously shown for several pentacyclic triterpenoids, the presence of an amino group at position C-3 seems favorable and enhances cytotoxicity.[28–30] Hence, we decided to investigate allobetulin and derivatives thereof in more detail.

2. Results and discussion

2.1. Chemistry

Allobetulin (**1**) can be obtained (Scheme 1) from betulin by a Wagner–Meerwein re-arrangement, and many different conditions have been applied including formic acid, sulfuric acid, hydrochloric acid, or solid supported reagents as well as ferric chloride hydrate, trifluoroacetic acid, orthophosphoric acid, bismuth triflate or *p*-toluenesulfonic acid.[18] In our hands, the reaction of betulin with

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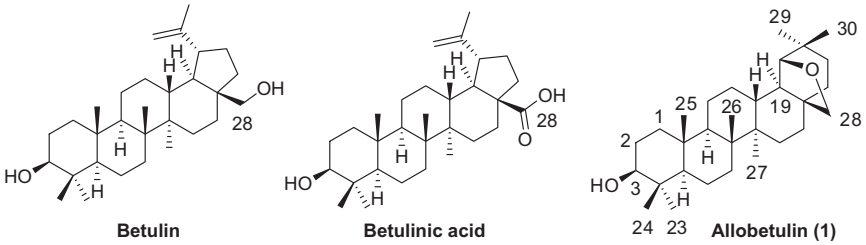
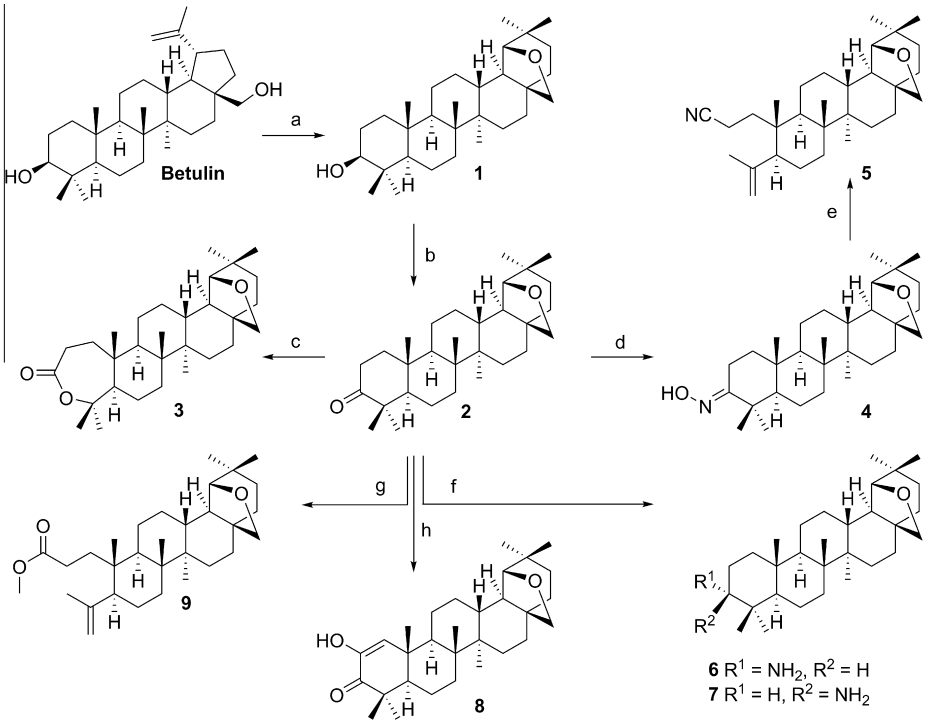


Figure 1. Structure of betulin, betulinic acid and allobetulin (**1**).

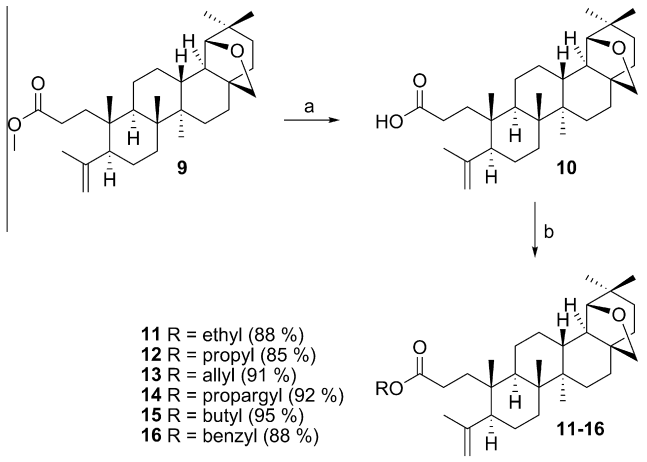


Scheme 1. Synthesis of allobetulin (**1**) and allobetulone (**2**) derived compounds **3**–**8**: (a) Montmorillonit K10, DCM, 3 h reflux, 5 days 25 °C, 79%; (b) CrO_3, H_2SO_4, acetone, 81%; (c) *m*-CPBA, $NaHCO_3$, DCM, 25 °C, 3 h, 85%; (d) $HONH_2{\cdot}HCl$, pyridine, 60 °C, 3 h, 91.5%; (e) $POCl_3$, pyridine, 25 °C, overnight, 46%; (f) $NH_4^+CH_3CO_2^-$, MeOH, $NaBH_3CN$, 25 °C, 24 h, 16% (of **6**) and 46% (of **7**); (g) Oxone®, MeOH, H_2SO_4, 25 °C, 7 days, 65%; (h) KO^{t}Bu, ^{t}BuOH, air, 40 °C, 1 h, 80%.

Montmorillonit K[31] worked quite nicely, and **1** was obtained in 79% yield. Jones oxidation of **1** gave 81% of allobetulone (**2**).[32] This compound is characterized in its IR spectrum by the presence of a signal at $\nu = 1702\ cm^{-1}$ being assigned to the C=O moiety. For this carbonyl group in the ^{13}C NMR spectrum a signal at $\delta = 218.2$ ppm was detected. Reaction of **2** with *m*-CPBA[33] in DCM in the presence of $NaHCO_3$ resulted in a Bayer–Villiger reaction, and lactone **3**[34–37] was obtained in 85% isolated yield.

From the reaction of **2** with hydroxylammonium chloride[38] in pyridine for 3 h at 60 °C oxime **4**[37,39,40] was obtained, whose treatment with $POCl_3$ gave *seco*-**5**. Reductive amination of **2** with ammonium acetate and sodium cyanoborohydride[41] gave a mixture of amines (3α)-**6** and (3β)-**7** that were easily separated by chromatography and their absolute configuration with respect to C-3 was established from their ^1H NMR spectra. From the reaction of **2** with potassium *tert*-butanolate in the presence of air compound **8** was obtained by the process of an abnormal Beckmann rearrangement.[42] A ring opening formation of an alkene occurred (as a consequence of a Bayer–Villiger rearrangement followed by an elimination reaction of the transient tertiary alcohol) also upon treatment of **2** with oxone®, and a yield of 65% of *seco*-**9** was obtained.

Treatment of **9** with potassium hydroxide in methanol (Scheme 2) furnished acid **10**. Esterification of **10** in DMF with



Scheme 2. Synthesis of *seco*-**10** and esters **9**, **11**–**16**: (a) MeOH, KOH, 25 °C, 7 d, 87%; (b) K_2CO_3, DMF, RX, 25 °C, 12 h.

different alkyl halides in the presence of potassium carbonate yielded esters **11**–**16**. Reaction of **1** with acetic acid and nitric acid (Scheme 3) as previously reported by Tolstikov et al.[43] gave 70% of

2-nitro-substituted **17** and 8% of 2,2-dinitro-substituted **18**. The reaction of **17** with hydrogen peroxide in the presence of potassium carbonate for 5 days resulted in the formation of diacid **19** in 78% yield whose esterification as described above gave diesters **20**–**26**.

2.2. Biology

Many natural occurring triterpenes are cytotoxic, and usually EC_{50} values between 10–80 μM have been reported. Performing photometric SRB assays[44] allowed exploring the cytotoxic activities of our compounds. The EC_{50} values from these tests employing several different human cancer cell lines are compiled in Table 1.

As compared to betulin, allobetulin (**1**) lost all of its cytotoxicity while some of the cytotoxicity is restored upon oxidation at position C-3. No activity was found for the lactone **3** and the nitrile **5**. Not unexpected but nevertheless disappointing was the performance of esters **11**–**15** and most of the diesters **20**–**26**. For most of these compounds EC_{50} values >30 μM (cut-off of the assay) were determined. A somewhat higher cytotoxicity was observed for the di-propargyl ester **24**. Surprisingly enough, the di-ethyl ester **21** showed an excellent cytotoxicity for the A549 lung carcinoma cell line, and an EC_{50} = 5.9 μM was observed.

Good cytotoxicity, however, was established for the (3α) 3-amino-derivative **6**, and an even better result was obtained for (3β) 3-amino **7** showing EC_{50} values ranging between 5.5 and 10.4 μM. This parallels previous findings for other triterpenoids, for example, glycyrrhetinic acid,[28] boswellic acid,[45,46] oleanolic[47–49] or usolic acid,[41] where the introduction of an amino group at position C-3 led to highly increased cytotoxicity. High cytotoxicity for tumor cells, however, is not sufficient to make a compound ready for broader biological screening; a low cytotoxicity for non-malignant cells is mandatory. Hence, compounds **6**, **7** and **21** were screened in SRB assays employing non-malignant mouse fibroblasts NIH 3T3. For (3α)-configurated **6** EC_{50} = 15.9 ± 0.1 μM was found; (3β)-configurated **7** showed increased cytotoxicity for the fibroblasts, and an EC_{50} = 7.3 ± 0.4 μM was determined. Improved selectivity was found for **21**, since NIH 3T3 cells gave an EC_{50} = 25.0 ± 1.0 μM.

3. Conclusions

Several different *seco*-compounds derived from allobetulin or allobetulone were synthesized in short sequences. Ring opening of ring A led to products more or less not cytotoxic at all. Reductive amination of allobetulone, however, yielded two epimeric amines **6** and **7** that showed rather low EC_{50} values in photometric SRB assays. Loss of a carboxyl at C-28 (as present in betulinic acid) lowers cytotoxicity, but the introduction of an amino moiety at C-3 compensates and increases the cytotoxicity of the compounds towards human tumor cell lines. The configuration at C-3 is important to obtain compounds of sufficient non-malignant/malignant selectivity. Screening of compounds using a broad panel of tumor cell lines seems appropriate to find selective compounds as exemplified for the *seco*-diester 21.

4. Experimental

4.1. General—chemistry

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, internal Me4Si; typical experiments: H–H-COSY, HMBC, HMQC, NOESY and DQF-COSY), MS spectra were taken on a Finnigan MAT LCQ 7000 (electrospray, voltage 4.1 kV, sheath gas nitrogen) instrument, IR and spectra were taken as KBR pills on a Perkin-Elmer Spectrum 1000 instrument. The optical rotation was 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 were determined by HPLC and found to be >98%. Betulinic acid was obtained from different commercial suppliers in bulk quantities.

4.2. General—biological screening

The SRB assay was performed as previously described.[44,50–52]

4.3. Syntheses

4.3.1. Allobetulin (1)

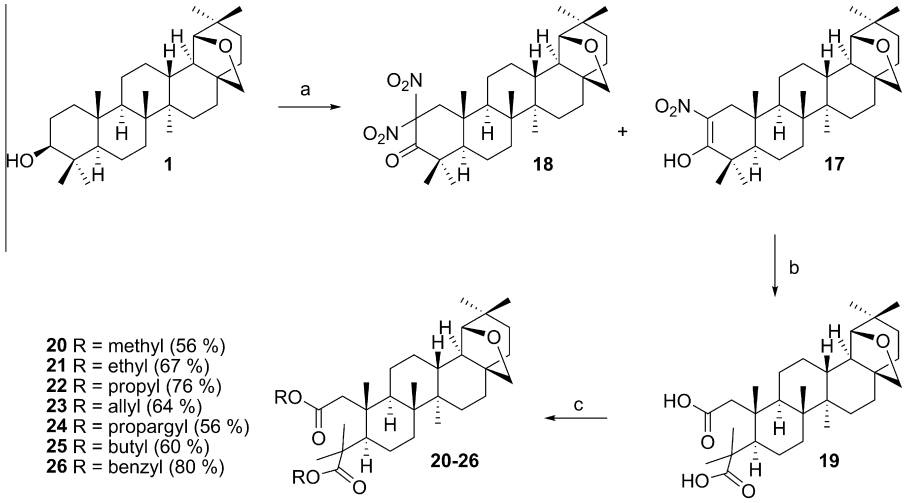
Following the procedure of Li et al.[31] from betulin (3.0 g, 6.79 mmol) and Montmorillonit K10 (3.0 g) followed by chromatography (SiO_2, hexane/ethyl acetate, 95:5) **1** (2.36 g, 79%) was obtained as a colorless solid; R_f = 0.47 (hexane/ethyl acetate, 8:2); mp 268–273 °C (lit.: 266–268 °C[31]); $[\alpha]_D$ = +48.2° (c = 0.11, $CHCl_3$) (lit.: $[\alpha]_D$ = +48° (c = 0.2, $CHCl_3$)[53]); MS (ESI, MeOH): m/z = 443.1 (60%, $[M+H]^+$), 885.4 (100%, $[2M+H]^+$), 907.4 (11%, $[2M+Na]^+$).

4.3.2. Allobetulone (2)

Jones oxidation of **1** (1.76 g, 3.98 mmol) in acetone (700 mL) with a fresh prepared mixture of CrO_3 (1.58 g, 15.8 mmol), water (15.2 mL) and sulfuric acid (98%, 3.6 mL) followed by chromatographic purification (SiO_2, hexane/ethyl acetate, 95:5) gave **2** (1.42 g, 81%) as a colorless solid; R_f = 0.70 (hexane/ethyl acetate, 8:2); mp 235–238 °C (lit.: 235–238 °C[32]); $[\alpha]_D$ = +82.2° (c = 0.11, $CHCl_3$) (lit.: $[\alpha]_D$ = +86° (c = 1.0, $CHCl_3$)[53]); MS (ESI, MeOH): m/z = 441.1 (100%, $[M+H]^+$), 463.3 (6%, $[M+Na]^+$), 472.7 (11%, $[M+H+MeOH]^+$), 494.7 (14%, $[M+Na+MeOH]^+$), 881.5 (98%, $[2M+H]^+$), 903.3 (19%, $[2M+Na]^+$).

4.3.3. (18α,19β) 19,28-Epoxy-A-homo-4-oxa-18-oleanan-3-one (3)

To a solution of **2** (350 mg, 0.8 mmol) in DCM (20 mL), *m*-CPBA (420 mg, 2.43 mmol) and $NaHCO_3$ (420 mg, 5 mmol) were added, and the mixture was stirred at 25 °C for 3 h. The mixture was washed in succession with an aq solution of KI (10%, 20 mL), aq $NaHCO_3$ (satd, 20 mL), aq Na_2S (1%, 20 mL), water (3 × 200 mL), and dried. The solvent was removed, and the residue subjected to chromatography (SiO_2, hexane/ethyl acetate, 7:3) to yield **3** (310 mg, 85%) as a colorless solid; R_f = 0.29 (hexane/ethyl acetate, 8:2); mp 227–230 °C (lit.: 246–248 °C[35]); $[\alpha]_D$ = +90.8° (c 0.7, $CHCl_3$); IR (KBr): ν = 3416m, 2934s, 1720s, 1462s, 1373s, 1355s, 1328m, 1285s, 1264m, 1248s, 1215m, 1192s, 1152s, 1138s, 1113s, 1056m, 1031s, 1005s cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 3.76 (d, J = 7.8 Hz, 1H, CH_a (28)), 3.52 (s, 1H, CH (19)), 3.44 (d, J = 7.8 Hz, 1H, CH_b (28)), 2.63 (ddd, J = 14.1, 12.9, 4.6 Hz, 1H, CH_a (2)), 2.48 (ddd, J = 14.3, 5.9, 3.5 Hz, 1H, CH_b (2)), 1.81 (ddd, J = 14.3, 13.0, 3.4 Hz, 1H, CH_a (1)), 1.74 (dd, J = 12.2, 2.8 Hz, 1H, CH (9)), 1.70–1.59 (m, 2H, CH_a (12) + CH_a (11)), 1.58–1.45 (m, 6H, CH_b (1) + CH_a (22) + CH (13) + CH_a (6) + CH_a (21) + CH (18)), 1.47 (s, 3H, CH_3 (24)), 1.44–1.32 (m, 4H, CH_a (7) + CH (5) + CH_a (16) + CH_b (11)), 1.38 (s, 3H, CH_3 (23)), 1.32–1.26 (m, 5H, CH_b (7) + CH_b (6) + CH_a (15) + CH_b (22) + CH_b (16)), 1.22 (dd, J = 13.4, 5.1 Hz, 1H, CH_b (21)), 1.11 (ddd, J = 12.7, 4.0, 2.4 Hz, 1H, CH_b (15)), 1.07 (s, 3H, CH_3 (25)), 1.01 (s, 3H, CH_3 (26)), 0.95–0.88 (m, 1H, CH_b (12)) 0.92 (s, 3H, CH_3 (30)), 0.89 (s, 3H, CH_3 (27)), 0.79 (s, 3H, CH_3 (29)) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.1 (C=O, C3), 88.0 (CH, C19), 86.1 (C_{quart}, C4), 71.4 (CH_2, C28), 53.1



Scheme 3. Synthesis of nitro-compounds **17** and **18**, *seco*-diacid **19** and diesters **20**–**26**: (a) HOAc, HNO_3, 25 °C, 1 h, 70% (of **20**) and 8% (of **21**); (b) MeOH, H_2O_2, K_2CO_3, 25 °C, 5 days, 78%; (c) K_2CO_3, DMF, RX, 25 °C, 12 h.

Table 1
Cytotoxicity of selected compounds (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%; cut-off 30 μM)

EC_{50}	518A2	HT29	MCF7	A549	8505C	A2780
Betulin	28.8 ± 1.9	>30	24.4 ± 0.8	20.6 ± 1.1	>30	29.3 ± 0.9
1	>30	>30	>30	>30	>30	>30
2	22.5 ± 2.6	26.8 ± 2.5	>30	20.8 ± 2.7	>30	18.5 ± 1.7
3	>30	>30	>30	>30	>30	>30
4	n.s.					
5	25.7 ± 0.4	>30	>30	21.5 ± 2.2	>30	>30
6	10.2 ± 0.19	6.8 ± 0.2	15.2 ± 0.1	12.6 ± 0.6	15.5 ± 1.8	12.9 ± 1.4
7	5.4 ± 0.7	6.2 ± 0.6	10.4 ± 0.3	7.3 ± 0.1	7.8 ± 0.2	6.6 ± 0.1
8	>30	>30	>30	23.3 ± 3.8	>30	>30
9	>30	>30	>30	>30	>30	>30
10	n.s.					
11–15	>30	>30	>30	>30	>30	>30
16	n.s.					
19	n.s.					
20	29.4 ± 2.8	17.5 ± 1.7	29.4 ± 4.5	>30	27.1 ± 4.0	18.1 ± 3.0
21	26.1 ± 1.4	17.6 ± 1.7	26.1 ± 1.6	5.9 ± 0.6	24.6 ± 2.5	18.9 ± 2.0
22	>30	27.0 ± 2.9	>30	>30	>30	22.4 ± 3.0
23	>30	29.2 ± 4.0	>30	>30	>30	22.7 ± 1.0
24	17.4 ± 1.8	15.7 ± 0.6	27.2 ± 1.0	21.1 ± 2.0	18.7 ± 2.4	12.5 ± 1.7
25	>30	>30	>30	>30	>30	>30
26	n.s.					

Human cancer cell lines: 518A2 (melanoma), HT29 (colorectal adenocarcinoma), MCF7 (breast adenocarcinoma), A2780 (ovarian adenocarcinoma); A549 (alveolar basal epithelial adenocarcinoma) and 8505C (thyroid carcinoma); n.s. stands for not soluble.

(*C*H, C9), 51.8 (*C*H, C5), 46.8 (*C*H, C18), 41.6 (C_{quart}, C20), 40.9 (C_{quart}, C14), 40.6 (C_{quart}, C8), 40.4 (CH_2, C1), 39.6 (C_{quart}, C10), 36.8 (CH_2, C16), 36.4 (C_{quart}, C17), 34.6 (*C*H, C13), 32.9 (CH_2, C7), 32.8 (CH_{21}, C21), 32.5 (CH_2, C2), 31.1 (CH_3, C24), 28.9 (CH_3, C30), 26.9 (CH_3, C23), 26.7 (CH_2, C12), 26.5 (CH_2, C15), 26.3 (CH_2, C22), 24.7 (CH_3, C29), 23.7 (CH_2, C11), 22.4 (CH_2, C6), 18.8 (CH_3, C25), 15.5 (CH_3, C26), 13.4 (CH_3, C27) ppm; MS (ESI, MeOH): m/z = 457.2 (100%, $[M+H]^+$), 479.3 (22%, $[M+Na]^+$), 489.1 (54%, $[M+H+MeOH]^+$), 510.8 (14%, $[M+Na+MeOH]^+$).

4.3.4. (18α,19β) 19,28-Epoxy-18-oleanan-3-one oxime (4)

To a solution of **2** (1.56 g, 3.55 mmol) in pyridine (40 mL), hydroxylammonium chloride (460 mg, 6.62 mmol) was added, and the mixture was stirred at 60 °C for 3 h. The reaction was quenched by adding hydrochloric acid (concd, aq, 5 mL). Aq $NaHCO_3$ (concd) was added until pH = 7.0, the mixture was diluted with water (150 mL) and extracted with chloroform (3 × 100 mL). The organic phases were dried (Na_2SO_4) and concentrated. Compound **4** (1.48 g, 91.5%) was obtained as an extremely insoluble off-white solid; R_f = 0.65 (hexane/ethyl acetate, 8:2); mp 285–287 °C; IR (KBr): ν = 3268s, 2925s, 2879s, 1452m, 1388m, 1376m, 1263w, 1171w, 1140w, 1020w, 1005w, 924m cm^{-1}; MS (ESI, MeOH): m/z = 456.4 (100%, $[M+H]^+$); analysis calcd for $C_{30}H_{49}NO_2$ (455.72): C 79.09, H 10.84, N 3.07; found: C 78.81, H 11.12, N 2.92.

4.3.5. (18α,19β) 19,28-Epoxy-3,4-*seco*-18-olean-4(23)-ene-3-nitrile (5)

To a solution of **4** (50 mg, 0.11 mmol) in dry pyridine (10 mL), $POCl_3$ (0.03 mL, 0.2 mmol) was added, and the mixture was stirred overnight. Aqueous work-up (1% aq hydrochloric acid, 300 mL) followed by extraction with chloroform (2 × 50 mL), evaporation of the solvent and chromatography (SiO_2, hexane/ethyl acetate, 95:5) yielded **5** (20 mg, 46%) as a colorless solid; R_f = 0.80 (hexane/ethyl acetate, 8:2); mp 267–269 °C (lit.: 266–267 °C[38]); $[\alpha]_D$ = +43.5° (c = 0.78, $CHCl_3$) (lit.: $[\alpha]_D$ = +61° (c = 2.6, $CHCl_3$)[54]);

IR (KBr): ν = 3448br, 3079w, 3065m, 2930s, 2861s, 2245m, 1811w, 1735w, 1636m, 1454s, 1387w, 1384s, 1297w, 1274m, 1255m, 1228w, 1203w, 1184w, 1165w, 1105w, 1085w, 1063 w, 1038s, 1006s cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.87 (s, 1H, CH_a (24)), 4.63 (s, 1H, CH_b, (24)), 3.76 (d, J = 7.8 Hz, 1H, CH_a (28)), 3.52 (s, 1H, CH (19)), 3.44 (d, J = 7.8 Hz, 1H, CH_b (28)), 2.33 (ddd, J = 15.6, 7.6, 3.0 Hz, 1H, CH_a (2)), 2.20 (ddd, J = 16.9, 9.7, 7.4 Hz, 1H, CH_b (2)), 1.91 (dd, J = 12.5, 2.3 Hz, 1H, CH (9)), 1.79–1.62 (m, 4H, CH_a (1) + CH_2 (7) + CH_a (22)), 1.71 (s, 3H, CH_3 (23)), 1.61–1.50 (m, 2H, CH_a (12) + CH_a (21)), 1.50–1.35 (m, 8H, CH (13) + CH_a (15) + CH (18) + CH (5) + CH_a (11) + CH_a (16) + CH_b (1) + CH_a (6)), 1.34–1.19 (m, 5H, CH_b (11) + CH_b (15) + CH_b (6) + CH_b (16) + CH_b (21)), 1.15–1.10 (m, 1H, CH_b (12)), 1.02 (s, 3H, CH_3 (26)), 0.95–0.91 (m, 1H, CH_b (22)), 0.93 (s, 3H, CH_3 (30)), 0.92 (s, 3H, CH_3 (27)), 0.85 (s, 3H, CH_3 (25)), 0.79 (s, 3H, CH_3 (29)) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 147.1 (C_{quart}, C4), 120.3 (C≡N, C3), 114.1 (CH_2, C24), 88.0 (CH, C19), 71.4 (CH_2, C28), 50.8 (CH, C9), 46.9 (CH, C18), 41.6 (C_{quart}, C20), 41.2 (C_{quart}, C14), 41.6 (CH, C5), 40.5 (C_{quart}, C8), 39.8 (C_{quart}, C10), 36.8 (CH_2, C16), 36.4 (C_{quart}, C17), 34.6 (CH_2, C7), 34.3 (CH, C13), 32.8 (CH_2, C2), 32.4 (CH_2, C6), 28.9 (CH_3, C30), 26.5 (CH_2, C12), 26.3 (CH_2, C15), 26.1 (CH_2, C22), 24.7 (CH_3, C29), 24.3 (CH_2, C1), 22.9 (CH_3, C23), 21.9 (CH_2, C11), 20.3 (CH_3, C25), 15.9 (CH_3, C26), 13.6 (CH_3, C27), 11.5 (CH_2, C2) ppm; MS (ESI, CH_2Cl_2/MeOH): m/z = 438.2 (100%, [M+H]$^+$), 460.3 (13%, [M+Na]$^+$), 491.9 (6 %, [M+Na+MeOH]$^+$).

4.3.6. (3α,18α,19β) 3-Amino-19,28-epoxy-18-oleanan (6) and (3β,18α,19β) 3-amino-19,28-epoxy-18α-oleanan (7)

A suspension of **2** (900 mg, 2.05 mmol) and ammonium acetate (2.0 g) in methanol (400 ml) was stirred for 15 min at 25 °C. Sodium cyanoborohydride (0.18 g) was added, and the mixture was stirred at 25 °C for 24 h. Most of the solvents were removed under diminished pressure, conc. aq. hydrochloric acid (30 mL) was added, and the crude product was filtered off, washed with water (3 × 100 mL) and purified by chromatography (SiO_2, $CHCl_3$/MeOH 9:1) to afford **6** (140 mg, 16%) and **7** (420 mg, 46%).

Data for **6**: off-white solid; R_f = 0.79 ($CHCl_3$/MeOH 9:1); mp 216–220 °C; $[\alpha]_D$ = +37.4° (c = 0.7, $CHCl_3$); IR (KBr): ν = 3442br, 2927s, 2867s, 1627w, 1532w, 1384s, 1039w, 1206w cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.77 (d, J = 7.8 Hz, 1H, CH_a (28)), 3.53 (s, 1H, CH (19)), 3.44 (d, J = 7.8 Hz, 1H, CH_b (28)), 3.17 (dd, J = 2.6, 2.6 Hz, 1H, CH (3)), 2.12–2.03 (m, 1H, CH_a (2)), 1.94–1.88 (m, 1H, CH_b (2)), 1.71–1.62 (m, 2H, CH (5) + CH_a (15)), 1.62–1.50 (m, 3H, CH_a (7) + CH_a (21) + CH_a (12)), 1.50–1.39 (m, 8H, CH (9) + CH (18) + CH (13) + CH_b (7) + CH_a (1) + CH_a (11) + CH_a (6) + CH_a (22)), 1.39–1.27 (m, 4H, CH_a (16) + CH_b (6) + CH_b (22) + CH_b (1)), 1.27–1.19 (m, 3H, CH_b (16) + CH_b (11) + CH_b (21)), 1.16–1.09 (m, 1H, CH_b (12)), 1.11 (s, 3H, (23)), 0.97 (s, 9H, CH_3 (24) + CH_3 (26) + CH_3 (27)), 0.93 (s, 3H, CH_3 (30)), 0.88 (s, 3H, CH_3 (25)), 0.91–0.84 (m, 1H, CH_b (15)), 0.78 (s, 3H, CH_3 (29)) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 88.0 (CH, C19), 71.5 (CH_2, C28), 58.6 (CH, C3), 50.0 (CH, C5), 48.6 (CH, C9), 47.6 (CH, C18), 41.6 (C_{quart}, C20), (41.0 C_{quart}, C14), 40.8 (C_{quart}, C8), 37.3 (C_{quart}, C10), 36.9 (CH_2, C16), 36.4 (C_{quart}, C17), 35.7 (C_{quart}, C4), 34.3 (CH, C13), 34.1 (CH_2, C7), 32.9 (CH_2, C21), 32.7 (CH_2, C1), 28.9 (CH_3, C30), 27.5 (CH_3, C23), 26.8 (CH_2, C12), 26.7 (CH_2, C15), 26.4 (CH_2, C22), 24.5 (CH_3, C29), 22.7 (CH_3, 24), 22.2 (CH_2, C2), 21.0 (CH_2, C11), 18.3 (CH_2, C6), 16.6 (CH_3, C25), 15.9 (CH_3, C26), 13.8 (CH_3, C27) ppm; MS (ESI, MeOH): m/z = 442.3 (100%, [M+H]$^+$); analysis calcd for $C_{30}H_{51}NO$ (441.73): C 81.57, H 11.64, N 3.17; found: C 81.42, H 11.76, N 3.02.

Data for **7**: off-white solid; R_f = 0.88 ($CHCl_3$/MeOH 9:1); mp 234–238 °C; $[\alpha]_D$ = +29.6° (c = 0.78, DMSO); IR (KBr): ν = 3442br, 2947s, 2863s, 2344w, 1625w, 1528w, 1449m, 1384s, 1140w, 1036m, 1009w cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD): δ = 3.77 (d, J = 7.6 Hz, 1H, CH_a (28)), 3.53 (s, 1H, CH (19)), 3.46 (d, J = 7.8 Hz, 1H, CH_b (28)), 2.83 (dd, J = 11.6, 5.3 Hz, 1H, CH (3)), 1.82 (ddd, J = 13.2, 3.5 Hz, 1H, CH_a (1)), 1.75–1.69 (m, 1H, CH_a (2)), 1.69–1.60 (m, 1H, CH_a (15)), 1.60–1.55 (m, 2H, CH_a (12) + CH_a (6)), 1.54–1.47 (m, 2H, CH_a (11) + CH (18)), 1.47–1.37 (m, 7H, CH_a (7) + CH_a (16) + CH (13) + CH_a (21) + CH_a (22) + CH_b (6) + CH (9)), 1.36–1.22 (m, 5H, CH_b (7) + CH_b (16) + CH_b (22) + CH_b (11) + CH_b (21)), 1.15–1.10 (m, 1H, CH_b (12)), 1.03 (s, 3H, CH_3 (23)), 1.00 (s, 3H, CH_3 (24)), 1.02–0.96 (m, 1H, CH_b (1)), 0.93 (s, 3H, CH_3 (27)), 0.90 (s, 3H, CH_3 (30)), 0.88 (s, 3H, CH_3 (25)), 0.85 (s, 3H, CH_3 (26)), 0.86–0.79 (m, 3H, CH_b (15) + CH (5) + CH_b (2)), 0.80 (s, 3H, CH_3 (29)) ppm; ^{13}C NMR (125 MHz, CD_3OD): δ = 89.1 (CH, C19), 71.8 (CH_2, C28), 61.0 (CH, C3), 56.5 (CH, C5), 51.7 (CH, C9), 47.5 (CH, C18), 42.2 (C_{quart}, C20), 41.4 (C_{quart}, C14), 41.2 (C_{quart}, C8), 39.1 (CH_2, C1), 37.8 (C_{quart}, C10), 37.2 (CH_2, C16), 37.2 (C_{quart}, C17), 36.8 (C_{quart}, C4), 34.9 (CH, C13), 34.4 (CH_2, C7), 33.3 (CH_2, C21), 29.1 (CH_3, C30), 28.0 (CH_3, C23), 27.0 (CH_2, C12), 27.0 (CH_2, C15), 26.7 (CH_2, C22), 24.8 (CH_3, C29), 23.9 (CH_2, C2), 21.7 (CH_2, C11), 18.8 (CH_2, C6), 16.6 (CH_3, C25), 16.1 (CH_3, C26), 15.9 (CH_3, C24), 13.9 (CH_3, C27) ppm; MS (ESI, MeOH): m/z = 442.3 (100%, [M+H]$^+$); analysis calcd for $C_{30}H_{51}NO$ (441.73): C 81.57, H 11.64, N 3.17; found: C 81.37, H 11.81, N 3.11.

4.3.7. (18α,19β) 19,28-Epoxy-2-hydroxy-18-olean-1-en-3-one (8)

Air was bubbled at 40 °C through a mixture of **2** (100 mg, 0.22 mmol) and potassium *tert* butanolate (0.95 g, 8.47 mmol) in *tert*. butanol (10 mL) for one hour. The crude product was precipitated by the addition of dil. aq. hydrochloric acid (1%, 200 mL), filtered off, washed with water (3 × 50 mL) and purified by chromatography (SiO_2, hexane/ethyl acetate, 4:1) to yield **8** (80 mg, 80%) as a colorless solid; R_f = 0.63 (hexane/ethyl acetate, 8:2); mp 122–125 °C; $[\alpha]_D$ = +65.4° (c = 0.74, $CHCl_3$); IR (KBr): ν = 3434m, 2928s, 2866s, 1724w, 1669m, 1455m, 1385m, 1234w, 1163w, 1140w, 1058m, 1036m cm^{-1}; UV–vis ($CHCl_3$): λ_{max} (log ε) = 271 (3.64) nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.48 (s, 1H, CH (1)), 5.91 (s, 1H, OH), 3.77 (d, J = 7.7 Hz, 1H, CH_a (28)), 3.54 (s, 1H, CH (19)), 3.45 (d, J = 7.8 Hz, 1H, CH_b (28)), 1.77–1.56 (m, 5H, CH_a (15) + CH_a (11) + CH (9) + CH (5) + CH_a (12)), 1.56–1.37 (m, 11H, CH_a (21) + CH_2 (7) + CH (13) + CH_2 (6) + CH (18) + CH_a (28) + CH_a (16) + CH_a (22) + CH_b (11)), 1.37–1.19 (m, 3H, CH_b (22) + CH_b (16) + CH_b (21)), 1.21 (s, 3H, CH_3 (23)), 1.15 (s, 3H, CH_3 (25)), 1.17–1.07 (m, 1H, CH_b (12)), 1.11 (s, 3H, CH_3 (24)), 1.04 (s, 3H, CH_3 (26)), 1.02–0.90 (m, 1H, CH_b (15)), 0.94 (s, 3H, CH_3 (30)), 0.91 (s, 3H, CH_3 (27)), 0.81 (s, 3H, CH_3 (29)) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 201.3 (C=O, C3), 144.1 (C_{quart}, C2), 129.1 (CH, C1), 88.0 (CH, C19), 71.4 (CH, C28), 54.4 (CH, C5), 46.9 (CH, C18), 46.4 (CH, C9), 44.2 (C_{quart}, C4), 41.6 (C_{quart}, C20), 41.6 (C_{quart}, C14), 41.2 (C_{quart}, C8), 38.9 (C_{quart}, C10), 36.9 (CH_2, C16), 36.4 (C_{quart}, C17), 34.4 (CH, C13), 33.7 (CH_2, C7), 32.8 (CH_2, C21), 29.0 (CH_3, C30), 27.3 (CH_3, C23), 26.5 (CH_2, C12), 26.4 (CH_2, C15), 26.4 (CH_2, C22), 24.7 (CH_4, C29), 21.7 (CH_3, C24), 21.4 (CH_2, C11), 20.7 (CH_3, C25), 18.9 (CH_2, C6), 16.4 (CH_3, C26), 13.5 (CH_3, C27) ppm; MS (ESI, MeOH): m/z = 455.2 (100%, [M+H]$^+$), 477.3 (30%, [M+Na]$^+$), 486.7 (14%, [M+H+MeOH]$^+$), 493.0 (6%, [M+K]$^+$), 508.7 (3%, [M+Na+MeOH]$^+$), 909.3 (47%, [2 M+H]$^+$), 928.9 (23%, [4 M+K+H]$^{2+}$); analysis calcd for $C_{30}H_{46}O_3$ (454.68): C 79.25, H 10.20; found: C 79.01, H 10.42.

4.3.8. Methyl (18α,19β) 19,28-epoxy-3,4-*seco*-18-olean-4(23)-ene-3-carboxylate (9)

To a solution of **2** (3.27 g 7.42 mmol) in methanol (155 mL) oxone® (460 mg, 21.47 mmol) and methanolic H_2SO_4 (98 mL, 0.05 mmol H_2SO_4) were added; the mixture was stirred at 25 °C for a week and filtered. The solvents were removed under diminished pressure, and the residue subjected to chromatography to afford **9** (2.26 g, 65 %) as a colorless solid; R_f = 0.57 (hexane/ethyl acetate, 8:2); mp 146–150 °C (lit.: 146–147 °C[54]); $[\alpha]_D$ = +61.2°

(c = 0.79, $CHCl_3$) (lit.: $[\alpha]_D$ = +59.5° (c = 2.0, $CHCl_3$)[54]); IR (KBr): ν = 3442br, 2948s, 2865s, 1740s, 1634w, 1455m, 1433m, 1382m, 1358w, 1290w, 1254m, 1174m, 1139w, 1114w, 1032m, 1008w cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 4.84 (s, 1H, CH_a (24)), 4.64 (s, 1H, CH_b (24)), 3.76 (d, J = 7.8 Hz, 1H, CH_a (28)), 3.65 (s, 3H, CH_3 (31)), 3.52 (s, 1H, CH (19)), 3.44 (d, J = 7.8 Hz, 1H, CH_b (28)), 2.34 (ddd, J = 15.9, 11.0, 5.3 Hz, 1H, CH_a (2)), 2.17 (ddd, J = 14.9, 11.2, 6.5 Hz, 1H, CH_b (2)), 1.95 (dd, J = 12.7, 2.3 Hz, 1H, CH (9)), 1.80–1.73 (m, 1H, CH_a (1)), 1.72 (s, 3H, CH_3 (23)), 1.69–1.56 (m, 3H, CH_a (22) + CH (13) + CH_a (7)), 1.56–1.49 (m, 3H, CH_b (22) + CH (5) + CH_a (6)), 1.49–1.45 (m, 2H, CH_b (7) + CH (18)), 1.44–1.35 (m, 5H, CH_a (11) + CH_b (6) + CH_a (21) + CH_a (12) + CH_a (16)), 1.35–1.26 (m, 3H, CH_b (1) + CH_b (16) + CH_a (15)), 1.26–1.19 (m, 2H, CH_b (21) + CH_b (11)), 1.12 (ddd, J = 13.1, 3.8, 2.3 Hz, 1H, CH_b (12)), 1.01 (s, 3H, CH_3 (26)), 0.92 (s, 3H, CH_3 (30)), 0.92 (s, 3H, CH_3 (27)), 0.91–0.84 (m, 1H, CH_b (15)), 0.84 (s, 3H, CH_3 (25)), 0.78 (s, 3H, CH_3 (29)) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.7 (C=O, C3), 147.5 (C_{quart}, C4), 113.6 (CH_2, C24), 88.0 (CH, C19), 71.4 (CH_2, (28)), 51.7 (CH_3, C31), 50.6 (CH, C9), 46.9 (CH, C18), 41.6 (CH_2, C20), 41.4 (CH, C5), 41.2 (C_{quart}, C20), 40.4 (C_{quart}, C8), 39.5 (C_{quart}, C10), 36.9 (CH_2, C16), 36.4 (C_{quart}, C17), 34.4 (CH, C13), 34.4 (CH_2, C7), 32.9 (CH_2, C21), 32.6 (CH_2, C6), 28.9 (CH_3, C30), 28.6 (CH_2, C2), 26.6 (CH_2, C12), 26.5 (CH_2, 15), 26.4 (CH_2, C22), 24.7 (CH_2, C1), 24.7 (CH_3, C29), 23.4 (CH_3, C23), 21.7 (CH_2, C11), 20.6 (CH_3, C25), 15.9 (CH_3, C26), 13.6 (CH_3, C27) ppm; MS (ESI, MeOH): m/z = 471.1 (73%, $[M+H]^+$), 493.3 (14%, $[M+Na]^+$), 503.1 (46%, $[M+H+MeOH]^+$), 726.3 (11%, $[3\,M+K+H]^{2+}$), 941.3 (100%, $[2\,M+H]^+$), 963.3 (35%, $[2\,M+Na]^+$).

4.3.9. (18α,19β) 19,28-Epoxy-3,4-*seco*-18-olean-4(23)-ene-3-carboxylic acid (10)

Compound **9** (2.26 g, 4.81 mmol) was dissolved methanol (100 mL) containing finely powdered potassium hydroxide (3.77 g, 67.19 mmol), and the mixture was stirred at 25 °C for a week. After pouring onto diluted aq. HCl (500 mL, 4%), the precipitate was filtered off, washed with water (3 × 100 mL) and purified by chromatography (SiO_2, hexane/ethyl acetate, 7:3) to yield **10** (1.90 g, 87 %) as a colorless solid; R_f = 0.44 (hexane/ethyl acetate, 8:2); mp 237–241 °C (lit.: 238–240 °C[55]); $[\alpha]_D$ = +63.2° (c = 1.03, $CHCl_3$) (lit.: $[\alpha]_D$ = +60° (c 1.2, $CHCl_3$)[55]); IR (KBr): ν = 2924s, 1718s, 1638w, 1490w, 1455m, 1374m, 1246s, 1182m, 1142w, 1129w, 1021m, 1004m, 1008w cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 4.85 (s, 1H, CH_a (24)), 4.66 (s, 1H, CH_b (24)), 3.78 (d, J = 7.7 Hz, 1H, CH_a (28)), 3.55 (s, 1H, CH (19)), 3.45 (d, J = 7.8 Hz, 1H, CH_b (28)), 2.43–2.32 (m, 1H, CH_a (2)), 2.25–2.14 (m, 1H, CH_b (2)), 2.00–1.92 (m, 1H, CH (9)), 1.82–1.70 (m, 1H, CH_a (1)), 1.73 (s, 3H, CH_3 (23)), 1.70–1.58 (m, 3H, CH_a (15) + CH_2 (7)), 1.58–1.43 (m, 5H, CH_a (12) + CH_a (21) + CH (5) + CH (18) + CH (13)), 1.42–1.20 (m, 10H, CH_2 (11) + CH_2 (22) + CH_2 (6) + CH_b (21) + CH_b (1) + CH_2 (16)), 1.17–1.10 (m, 1H, CH_b (12)), 1.02 (s, 3H, CH_3 (26)), 0.97–0.90 (m, 1H, CH_b (15)), 0.93 (s, 3H, CH_3 (30)), 0.93 (s, 3H, CH_3 (27)), 0.85 (s, 3H, CH_3 (25)), 0.80 (s, 3H, CH_3 (29)) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 179.9 (C=O, C3), 147.6 (C_{quart}, C4), 113.7 (CH_2, C24), 88.1 (CH, C19), 71.4 (CH_2, C28), 50.6 (CH, C9), 46.9 (CH, C18), 41.6 (C_{quart}, C20), 41.4 (CH, C5), 41.2 (C_{quart}, C14), 40.4 (C_{quart}, C8), 39.5 (C_{quart}, C10), 36.9 (CH_2, C16), 36.4 (CH, C17), 34.4 (CH, C13), 34.2 (CH_2, C7), 32.9 (CH_2, C21), 32.6 (CH_2, C6), 28.9 (CH_3, C30), 28.5 (CH_2, C2), 26.6 (CH_2, C12), 26.5 (CH_2, C15), 26.4 (CH_2, C22), 24.7 (CH_3, C29), 24.7 (CH_2, C1), 23.3 (CH_3 C23), 21.7 (CH_2, C11), 20.6 (CH_3, C25), 15.9 (CH_3, C26), 13.6 (CH_3, C27) ppm; MS (ESI, MeOH): m/z = 455.6 (23%, $[M-H]^-$), 911.5 (100%, $[2M-H]^-$).

4.3.10. Ethyl (18α,19β) 19,28-epoxy-3,4-*seco*-18-olean-4(23)-ene-3-carboxylate (11)

A suspension of **10** (150 mg, 0.33 mmol), freshly grounded potassium carbonate (80 mg, 0.58 mmol) in dry DMF (15 mL) was stirred for 1 h at 25 °C; ethyl bromide (0.03 mL, 0.39 mmol) was added, and stirring at 25 °C was continued for another 12 h. Usual aqueous workup followed by chromatography (SiO_2, hexane/ethyl acetate, 9:1) yielded **11** (140 mg, 88%) as a colorless solid; R_f = 0.83 (hexane/ethyl acetate, 8:2); mp 168–171 °C (lit.: 146–148 °C)[35]; $[\alpha]_D$ = +60.8° (c = 0.81, $CHCl_3$); IR (KBr): ν = 3449w, 3067w, 2952s, 2865s, 1734s, 1636w, 1490m, 1451s, 1383s, 1338w, 1294m, 1253m, 1231w, 1175s, 1112m, 1094m, 1033s, 1007m cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 4.84 (s, 1H, CH_a (24)), 4.66 (s, 1H, CH_b (24)), 4.10 (q, J = 7.2 Hz, 2H, CH_2 (31)), 3.77 (d, J = 7.7 Hz, 1H, CH_a (28)), 3.52 (s, 1H, CH (19)), 3.44 (d, J = 7.8 Hz, 1H, CH_b (28)), 2.37–2.28 (m, 1H, CH_a (2)), 2.15 (ddd, J = 14.8, 11.2, 6.8 Hz, 1H, CH_b (2)), 1.96 (dd, J = 12.7, 2.6 Hz, 1H, (CH (9)), 1.81–1.73 (m, 1H, CH_a (1)), 1.72 (s, 3H, CH_3 (23)), 1.67–1.57 (m, 3H, CH_a (15) + CH_2 (7)), 1.56–1.45 (m, 5H, CH_a (21) + CH_a (12) + CH (5) + CH (18) + CH (13)), 1.45–1.34 (m, 6H, CH_a (22) + CH_a (11) + CH_a (16) + CH_2 (6) + CH_b (1)), 1.34–1.19 (m, 4H, CH_b (22) + CH_b (16) + CH_b (11) + CH_b (21)), 1.24 (t, J = 7.1 Hz, 3H, CH_3 (32)), 1.13 (ddd, J = 13.0, 4.2, 2.3 Hz, 1H, CH_b (12)), 1.01 (s, 3H, CH_3 (26)), 0.93 (s, 3H, CH_3 (30)), 0.92 (s, 3H, CH_3 (27)), 0.96–0.89 (m, 1H, CH_b (15)), 0.84 (s, 3H, CH_3 (25)), 0.79 (s, 3H, CH_3 (29)) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.3 (C=O, C3), 147.7 (C_{quart}, C4), 113.6 (CH_2, C24), 88.0 (CH, C19), 71.4 (CH_2, C28), 60.4 (CH_2, C31), 50.5 (CH, C9), 46.9 (CH, C18), 41.6 (C_{quart}, C20), 41.4 (CH, C5), 41.2 (C_{quart}, C14), 40.4 (C_{quart}, C8), 39.6 (C_{quart}, C10), 36.9 (CH_2, C16), 36.4 (C_{quart}, C17), 34.4 (CH, C13), 34.4 (CH_2, C7), 32.9 (CH_2, C21), 32.6 (CH_2, C6), 29.0 (CH_3, C30), 28.9 (CH_2, C2), 26.6 (CH_2, C12), 26.5 (CH_2, C15), 26.4 (CH_2, C22), 24.7 (CH_3, C29), 24.7 (CH_2, C1), 23.4 (CH_3, C23), 21.7 (CH_2, C11), 20.6 (CH_3, C25), 15.9 (CH_3, C26), 14.4 (CH_3, C32), 13.6 (CH_3, C27) ppm; MS (ESI, MeOH): m/z = 485.3 (100%, $[M+H]^+$), 507.3 (8%, $[M+Na]^+$), 517.1 (42%, $[M+H+MeOH]^+$).

4.3.11. Propyl (18α,19β) 19,28-epoxy-3,4-*seco*-18-olean-4(23)-ene-3-carboxylate (12)

Following the procedure given for the synthesis of **11**, from **10** (150 mg, 0.33 mmol), potassium carbonate, DMF (25 mL) and propyl bromide (0.04 mL, 0.39 mmol) followed by chromatography (SiO_2, hexane/ethyl acetate, 9:1) **12** (140 mg, 85%) was obtained as a colorless solid; R_f = 0.83 (hexane/ethyl acetate, 8:2); mp 168–171 °C; $[\alpha]_D$ = +59.3° (c = 0.76, $CHCl_3$); IR (KBr): ν = 3468w, 3082w, 2951s, 2862s, 1734s, 1636m, 1460s, 1420w, 1384s, 1338m, 1294s, 1253w, 1157s, 1070m, 1039s cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 4.85 (s, 1H CH_a (24)), 4.66 (s, 1H, CH_b (24)), 4.05–3.97 (m, 2H, CH_2 (31)), 3.77 (d, J = 7.7 Hz, 1H, CH_a (28)), 3.53 (s, 1H, CH (19)), 3.44 (d, J = 7.8 Hz, 1H, CH_b (28)), 2.38–2.30 (m, 1H, CH_a (2)), 2.15 (ddd, J = 14.8, 11.2, 6.7 Hz, 1H, CH_b (2)), 1.96 (dd, J = 12.7, 2.5 Hz, 1H, CH (9)), 1.81–1.74 (m, 1H, CH_a (1)), 1.73 (s, 3H, CH_3 (23)), 1.68–1.59 (m, 5H, CH_a (15) + CH_2 (32) + CH_2 (7)), 1.59–1.47 (m, 5H, CH_a (12) + CH (5) + CH_a (21) + CH (18) + CH (13)), 1.47–1.34 (m, 6H, CH_a (11) + CH_a (22) + CH_a (16) + CH_2 (6) + CH_b (1)), 1.34–1.25 (m, 3H, CH_b (22) + CH_b (16) + CH_b (11)), 1.26–1.19 (m, 1H, CH_b (21)), 1.13 (ddd, J = 13.1, 4.2, 2.3 Hz, 1H, CH_b (12)), 1.01 (s, 3H, CH_3 (26)), 0.97–0.87 (m, 4H, CH_b (15) + CH_3 (33)), 0.93 (s, 3H, CH_3 (30)), 0.92 (s, 3H, CH_3 (27), 0.84 (s, 3H, CH_3 (25)), 0.79 (s, 3H, CH_3 (29)) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.4 (C=O, C3), 147.7 (C_{quart}, C4), 113.6 (CH_2, C24), 88.0 (CH, C19), 71.4 (CH_2, C28), 66.1 (CH_2, C31), 50.5 (CH, C9), 46.9 (CH, C18), 41.6 (C_{quart}, C20), 41.4 (CH, C5), 41.2 (C_{quart}, C14), 40.4 (C_{quart}, C8), 39.6 (C_{quart}, C10), 36.9 (CH_2, C16), 36.4 (C_{quart}, C17), 34.5 (CH_2, C7), 34.4 (CH, C13), 32.9 (CH_2, C21), 32.6 (CH_2, C6), 28.9 (CH_3, C30), 28.9 (CH_2, C2), 26.6 (CH_2, C12), 26.5 (CH_2, C15), 26.4 (CH_2, C22), 24.7 (CH_3, C29), 24.7 (CH_2, C1), 23.4 (CH_3, C23), 22.1 (CH_2, C32), 21.7 (CH_2, C11), 20.6 (CH_3, C25), 15.9 (CH_3, C26), 13.6 (CH_3, C27), 10.6 (CH_3, C33) ppm; MS (ESI, MeOH): m/z = 499.3 (100%, $[M+H]^+$), 521.4 (8%,

[M+Na]$^+$), 531.1 (41%, [M+H+MeOH]$^+$), analysis calcd for $C_{33}H_{54}O_3$ (498.78): C 79.46, H 10.91; found: C 79.34, H 11.02.

4.3.12. Allyl (18α,19β) 19,28-epoxy-3,4-*seco*-18-olean-4(23)-ene-3-carboxylate (13)

Following the procedure given for the synthesis of **11**, from **10** (150 mg, 0.33 mmol), potassium carbonate (0.08 g, 0.58 mmol), DMF (15 mL) and allyl iodide (0.04 mL, 0.39 mmol) followed by chromatography (SiO_2, hexane/ethyl acetate, 8:2) **13** (150 mg, 91 %) was obtained as a colorless solid; R_f = 0.68 (hexane/ethyl acetate, 8:2); mp 152–154 °C; $[\alpha]_D$ = +58.3° (c = 0.74, $CHCl_3$); IR (KBr): ν = 3473w, 3082w, 2949s, 2862s, 1745s, 1636w, 1460m, 1419w, 1386s, 1360m, 1296m, 1253w, 1184m, 1154s, 1068w, 1039m, 1005m cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.91 (ddt, J = 16.6, 11.2, 5.7 Hz, 2H, CH_2 (32)), 5.30 (d, J = 17.2 Hz, 1H, CH^Z (33)), 5.22 (d, J = 10.5 Hz, 1H, CH^E (33)), 4.84 (s, 1H, CH_a (24)), 4.65 (s, 1H, CH_b (24)), 4.56 (d, J = 5.6 Hz, 2H, CH_2 (31)), 3.77 (d, J = 7.8 Hz, 1H, CH_a (28)), 3.52 (s, 1H, CH (19)), 3.44 (d, J = 7.8 Hz, 1H, CH_b (28)), 2.41–2.33 (m, 1H, CH_a (2)), 2.24–2.15 (m, 1H, CH_b (2)), 1.98–1.93 (m, 1H, CH (9)), 1.82–1.74 (m, 1H, CH_a (1)), 1.72 (s, 3H, CH_3 (23)), 1.68–1.60 (m, 3H, CH_a (15) + CH_2 (7)), 1.60–1.45 (m, 5H, CH_a (12) + CH (5) + CH (18) + CH_a (21) + CH (13)), 1.45–1.34 (m, 6H, CH_a (22) + CH_a (11) + CH_a (16) + CH_2 (6) + CH_b (1)), 1.34–1.25 (m, 3H, CH_b (22) + CH_b (16) + CH_b (11)), 1.25–1.19 (m, 1H, CH_b (21)), 1.16–1.09 (m, 1H, CH_b (12)), 1.01 (s, 3H, CH_3 (26)), 0.97–0.87 (m, 1H, CH_b (15)), 0.93 (s, 3H, CH_3 (30)), 0.92 (s, 3H, CH_3 (27)), 0.84 (s, 3H, CH_3 (25)), 0.79 (s, 3H, CH_3 (29)) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.9 (C═O, C3), 147.6 (C_{quart}, C4), 132.4 (CH, C32), 118.3 (CH_2, C33), 113.6 (CH_2, C24), 88.0 (CH, C19), 71.4 (CH_2, C28), 65.2 (CH_2, C31), 50.6 (CH, C9), 46.9 (CH, C18), 41.6 (C_{quart}, C20), 41.4 (CH, C5), 41.3 (C_{quart}, C14), 40.4 (C_{quart}, C8), 39.6 (C_{quart}, C10), 36.9 (CH_2, C16), 36.4 (C_{quart}, C17), 34.4 (CH, C13), 34.4 (CH_2, C7), 32.9 (CH_2, C21), 32.6 (CH_2, C6), 28.9 (CH_3, C30), 28.8 (CH_2, C2), 26.6 (CH_2, C12), 26.5 (CH_2, C15), 26.4 (CH_2, C22), 24.7 (CH_3, C29), 24.7 (CH_2, C1), 23.4 (CH_3, C23), 21.7 (CH_2, C11), 20.6 (CH_3, C25), 15.9 (CH_3, C26), 13.6 (CH_3, C27) ppm; MS (ESI, MeOH): m/z = 497.3 (100%, [M+H]$^+$), 519.3 (14%, [M+Na]$^+$), 545.1 (48%, [M+H+MeOH]$^+$); analysis calcd for $C_{33}H_{52}O_3$ (496.76): C 79.79, H 10.55; found: C 79.61, H 10.73.

4.3.13. Propargyl (18α,19β) 19,28-epoxy-3,4-*seco*-18-olean-4(23)-ene-3-carboxylate (14)

Following the procedure given for the synthesis of **11**, from **10** (150 mg, 0.33 mmol), potassium carbonate (0.08 g, 0.58 mmol), DMF (15 mL) and propargyl bromide (80% in toluene, 0.04 mL, 0.39 mmol) followed by chromatography (SiO_2, hexane/ethyl acetate, 8:2) **14** (150 mg, 92%) was obtained as a colorless solid; R_f = 0.74 (hexane/ethyl acetate, 8:2); mp 122–124 °C; $[\alpha]_D$ = +58.7° (c = 0.59, $CHCl_3$); IR (KBr): ν = 3498w, 3289s, 3080w, 2949s, 2860s, 2130w, 1758s, 1636w, 1459m, 1418w, 1387s, 1296m, 1253w, 1228w, 1184w, 1139s, 1070w, 1039m, 1005m cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.84 (s, 1H, CH_a (24)), 4.69–4.62 (m, 3H, CH_b (24) + CH_2 (31), 3.77 (d, J = 7.7 Hz, 1H, CH_a (28)), 3.52 (s, 1H, CH (19)), 3.44 (d, J = 7.8 Hz, 1H, CH_b (28)), 2.46 (t, J = 2.3 Hz, 1H, CH (33)), 2.44–2.34 (m, 1H, CH_a (2)), 2.27–2.17 (m, 1H, CH_b (2)), 1.94 (dd, J = 12.5, 1.9 Hz, 1H, CH (9)), 1.84–1.73 (m, 1H, CH_a (1)), 1.72 (s, 3H, CH_3 (23)), 1.68–1.57 (m, 3H, CH_a (15) + CH_2 (7)), 1.56–1.45 (m, 5H, CH_a (12) + CH_a (21) + CH (5) + CH (18) + CH (13)), 1.44–1.19 (m, 10H, CH_2 (22) + CH_2 (6) + CH_2 (16) + CH_2 (11) + CH_b (1) + CH_b (21)), 1.16–1.09 (m, 1H, CH_b (12)), 1.01 (s, 3H, CH_3 (26)), 0.95–0.89 (m, 1H, CH_b (15)), 0.93 (s, 3H, CH_3 (30)), 0.92 (s, 3H, CH_3 (27)), 0.85 (s, 3H, CH_3 (25)), 0.79 (s, 3H, CH_3 (29)) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.3 (C═O, C3), 147.6 (C_{quart}, C4), 113.7 (C_{quart}, C24), 88.0 (CH, C19), 77.9 (C_{quart}, C32), 74.9 (CH, C33), 71.4 (CH, C28), 52.0 (CH_2, C31), 50.6 (CH, C9), 46.9 (CH, C18), 41.6 (C_{quart}, C20), 41.4 (CH, C5), 41.2 (C_{quart}, C14), 40.4 (C_{quart}, C8), 39.6 (C_{quart}, C10), 36.9 (CH_2, C16), 36.4 (C_{quart}, C17), 34.4 (CH, C13), 34.1 (CH_2, C7), 32.9 (CH_2, C21), 32.5 (CH_2, C6), 28.9 (CH_3, C30), 28.5 (CH_2, C2), 26.6 (CH_2, C12), 26.5 (CH_2, C15), 26.4 (CH_2, C21), 24.7 (CH_3, C29), 24.6 (CH_2, C1), 23.3 (CH_3, C23), 21.7 (CH_2, C11), 20.6 (CH_3, C25), 15.9 (CH_3, C26), 13.6 (CH_3, C27) ppm; MS (ESI, MeOH): m/z = 495.3 (100%, [M+H]$^+$), 512.1 (6%, [M+NH$_4$]$^+$), 527.1 (39%, [M+H+MeOH]$^+$); analysis calcd for $C_{33}H_{50}O_3$ (494.75): C 80.11, H 10.19; found: C 79.89, H 10.31.

4.3.14. Butyl (18α,19β) 19,28-epoxy-3,4-*seco*-18-olean-4(23)-ene-carboxylate (15)

Following the procedure given for the synthesis of **11**, from **10** (150 mg, 0.33 mmol), potassium carbonate (0.80 g, 0.58 mmol), DMF (15 mL) and *n*-butylbromide (0.04 mL, 0.39 mmol) followed by chromatography (SiO_2, hexane/ethyl acetate, 8:2) **15** (160 mg, 95%) was obtained as a colorless solid; R_f = 0.84 (hexane/ethyl acetate, 8:2); mp 145–148 °C; $[\alpha]_D$ = +58.2° (c = 0.71, $CHCl_3$); IR (KBr): ν = 3462w, 3083w, 2950s, 2863s, 1734s, 1638w, 1459m, 1420w, 1386m, 1358m, 1296m, 1253w, 1231w, 1157s, 1072w, 1037m, 1037m, 1003w cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.84 (s, 1H, CH_a (24)), 4.65 (s, 1H, CH_b (24)), 4.05 (t, J = 6.6 Hz, 2H, CH_2 (31)), 3.77 (d, J = 7.6 Hz, 1H, CH_a (28)), 3.50 (d, J = 16.0 Hz, 1H, CH (19)), 3.44 (d, J = 7.7 Hz, 1H, CH_b (28)), 2.42–2.27 (m, 1H, CH_a (2)), 2.15 (ddd, J = 14.8, 11.0, 6.8 Hz, 1H, CH_b (2)), 1.96 (dd, J = 12.6, 2.0 Hz, 1H, CH (9)), 1.84–1.75 (m, 1H, CH_a (1)), 1.72 (s, 3H, CH_3 (23)), 1.69–1.56 (m, 5H, CH_a (15) + CH_2 (7) + CH_2 (32)), 1.56–1.44 (m, 5H, CH_a (12) + CH_a (21) + CH (18) + CH (5) + CH (13)), 1.44–1.26 (m, 11H, CH_a (22) + CH_2 (11) + CH_2 (33) + CH_2 (16) + CH_2 (6) + CH_b (1) + CH_b (21)), 1.25–1.18 (m, 1H, CH_b (22)), 1.16–1.09 (m, 1H, CH_b (12), 1.01 (s, 3H, CH_3 (26)), 0.97–0.89 (m, 3H, CH_b (15) + CH_2 (34)), 0.93 (s, 3H, CH_3 (30)), 0.92 (s, 3H, CH_3 (27)), 0.84 (s, 3H, CH_3 (25)), 0.79 (s, 3H, CH_3 (29)) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.4 (C═O, C3), 147.7 (C_{quart}, C4), 113.6 (CH_2, C24), 88.0 (CH, C19), 71.4 (CH_2, C28), 64.4 (CH_2, C31), 50.5 (CH, C9), 46.9 (CH, C18), 41.6 (C_{quart}, C20), 41.4 (CH, C5), 41.2 (C_{quart}, C14), 40.4 (C_{quart}, C8), 39.6 (C_{quart}, C10), 36.9 (CH_2, C16), 36.4 (C_{quart}, C17), 34.4 (CH_2, C7), 34.4 (CH, C13), 32.9 (CH_2, C21), 32.6 (CH_2, C6), 30.8 (CH_2, C32), 28.9 (CH_3, C30), 28.9 (CH_2, C2), 26.6 (CH_2, C12), 26.5 (CH_2, C15), 26.4 (CH_2, C22), 24.7 (CH_3, C29), 24.7 (CH_2, C1), 23.4 (CH_3, C23), 21.7 (CH_2, C11), 20.6(CH_3, C25), 19.3 (CH_2, C33), 15.9 (CH_3, C26), 13.9 (CH_3, C27), 13.6 (CH_3, C34) ppm; MS (ESI, MeOH): m/z = 513.3 (100%, [M+H]$^+$), 535.3 (5%, [M+Na]$^+$), 545.1 (34%, [M+H+MeOH]$^+$); analysis calcd for $C_{34}H_{56}O_3$ (512.81): C 79.63, H 11.01; found: C 79.57, H 11.18.

4.3.15. Benzyl (18α,19β) 19,28-epoxy-3,4-*seco*-18-olean-4(23)-ene-3-carboxylate (16)

Following the procedure given for the synthesis of **11**, from **10** (150 mg, 0.33 mmol), potassium carbonate (0.08 g, 0.58 mmol), DMF (15 mL) and benzylbromide (0.05 mL, 0.39 mmol) followed by chromatography (SiO_2, hexane/ethyl acetate, 8:2) **18** (160 mg, 88%) was obtained as a colorless solid; R_f = 0.73 (hexane/ethyl acetate, 8:2); mp 146–149 °C; $[\alpha]_D$ = +56.1° (c = 0.87, $CHCl_3$); IR (KBr): ν = 3439w, 3086w, 3070w, 3035m, 2951s, 2869s, 2364w, 1960w, 1896w, 1803w, 1728s, 1687w, 1634m, 1454s, 1387s, 1387s, 1359m, 1336m, 1295s, 1256m, 1217s, 1196s, 1170s, 1156s, 1126s, 1112s, 1084w, 1062m, 1035s, 1004m cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.39–7.30 (m, 5H, CH_{aromat}), 5.11 (d, J = 12.7 Hz, 1H, CH_a (31)), 5.09 (d, J = 12.7 Hz, 1H, CH_b (31)), 4.84 (s, 1H, CH_a (24)), 4.65 (s, 1H, CH_b (24)), 3.77 (d, J = 7.8, 1H, CH_a (28)), 3.52 (s, 1H, CH (19)), 3.44 (d, J = 7.8 Hz, 1H, CH_b (28)), 2.40 (ddd, J = 15.9, 10.3, 5.9 Hz, 1H, CH_a (2)), 2.22 (ddd, J = 15.0, 10.7, 7.2 Hz, 1H, CH_b (2)), 1.96 (dd, J = 12.6, 2.6 Hz, 1H, CH (9)), 1.81–1.73 (m, 1H, CH_a (1)), 1.72 (s, 3H, CH_3 (23)), 1.69–1.60 (m, 3H, CH_a (15) + CH_2 (7)), 1.58–1.45 (m, 5H, CH_a (12) + CH (5) + CH_a (21) + CH (18) + CH (13)), 1.45–1.32 (m, 6H, CH_a (22) + CH_a

(11) + CH_a (16) + CH_2 (6) + CH_b (1)), 1.32–1.25 (m, 3H, CH_b (22) + CH_b (16) + CH_b (11)), 1.22 (dd, J = 13.5, 4.8 Hz, 1H, CH_b (21)), 1.12 (ddd, J = 12.9, 4.0, 2.2 Hz, 1H, CH_b (12)), 1.01 (s, 3H, CH_3 (26)), 0.95–0.90 (m, 1H, CH_b (15)), 0.93 (s, 3H, CH_3 (30)), 0.91 (s, 3H, CH_3 (27)), 0.85 (s, 3H, CH_3 (CH_3 (25)), 0.79 (s, 3H, CH_3 (29)) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.1 (C=O, C3), 147.6 (C_{quart}, C4), 136.2 (C_{aromat}, C32), 128.7 (CH_{aromat}, C34), 128.3 (CH_{aromat}, C35), 128.3 (CH_{aromat}, C33), 113.6 (CH_2, C24), 88.0 (CH, C19), 71.4 (CH_2, C28), 66.4 (CH_2, C31), 50.5 (CH, C9), 46.9 (CH, C18), 41.6 (C_{quart}, C20), 41.4 (CH, C5), 41.2 (C_{quart}, C14), 40.4 (C_{quart}, C8), 39.6 (C_{quart}, C10), 36.9 (CH_2, C16), 36.4 (C_{quart}, C17), 34.4 (CH, C13), 34.3 (CH_2, C7), 32.9 (CH_2, C21), 32.6 (CH_2, C6), 29.0 (CH_3, C30), 28.8 (CH_2, C2), 26.6 (CH_2, C12), 26.5 (CH_2, C15), 26.4 (CH_2, C22), 24.7 (CH_3, C29), 24.6 (CH_2, C1), 23.3 (CH_3, C23), 21.7 (CH_2, C11), 20.6 (CH_3, C25), 15.9 (CH_3, C26), 13.6 (CH_3, C27) ppm; MS (ESI, MeOH): m/z = 547.3 (100%, $[M+H]^+$), 569.5 (6%, $[M+Na]^+$), 614.9 (11%, $[M+H+MeOH]^+$); analysis calcd for $C_{37}H_{54}O_3$ (546.82): C 81.27, H 9.95; found: C 80.99, H 10.13.

4.3.16. (18α,19β) 19,28-Epoxy-2-nitro-olan-2-en-3-ol (17) and (18α,19β) 19,28-epoxy-2,2-dinitro-oleanan-3-one (18)

Acetic acid (2 mL) was warmed to 70 °C and **1** (100 mg, 0.23 mmol) was added. After cooling in an ice-bath, conc. nitric acid (1 mL) was added, and stirring at 25 °C was continued for another 5 h. The mixture was diluted with water (50 mL), and the crude product was filtered off. Chromatographic purification (SiO_2, hexane/ethyl acetate, 9:1) gave **17** (80 mg, 70%) and **18** (10 mg, 8%).

Data for **17**: colorless solid; R_f = 0.62 (hexane/ethyl acetate, 8:2); mp 238–240 °C (lit.: 235.8 °C)[43]; $[\alpha]_D$ = +141.1° (c = 0.71, $CHCl_3$); IR (KBr): ν = 3422br, 2929s, 2866s, 1736w, 1709w, 1602s, 1513s, 1456s, 1403s, 1376s, 1326m, 1295s, 1263m, 1232s, 1202s, 1160m, 1138m, 1103m, 1086m, 1060m, 1034s, 1008m cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.76 (d, J = 7.8 Hz, 1H, CH_a (28)), 3.53 (s, J = 9.8 Hz, 1H, CH (19)) 3.44 (d, J = 7.8 Hz, 1H, CH_b (28)), 2.83 (d, J = 15.7 Hz, 1H, CH_a (1)), 1.98 (d, J = 15.7 Hz, 1H, CH_b (1)), 1.73–1.65 (m, 1H, CH_a (15)), 1.63–1.53 (m, 2H, CH_a (11) + CH_a (12)), 1.53–1.45 (m, 4H, CH_2 (6) + CH (13) + CH_a (7)), 1.45–1.27 (m, 5H, CH_2 (16) + CH_2 (21) + CH_a (22)), 1.26 (s, 3H, CH_3 (23)), 1.25–1.20 (m, 3H, CH_b (22) + CH_b (7) + CH_b (11)), 1.18 (s, 3H, CH_3 (24)), 1.18–1.09 (m, 1H, CH_b (12)), 1.00 (s, 3H, CH_3 (26)), 0.98–0.90 (m, 1H, CH_b (15)), 0.93 (s, 3H, CH_3 (30)), 0.91 (s, 3H, CH_3 (27)), 0.87 (s, 3H, CH_3 (25)), 0.80 (s, 3H, CH_a (29)) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 178.6 (C_{quart}, C3), 123.0 (C_{quart}, C2), 88.0 (CH, C19), 71.4 (CH_2, C28), 52.2 (CH, C5), 49.5 (CH, C9), 46.9 (CH, C18), 41.6 (C_{quart}, C20), 40.9 (C_{quart}, C14), 40.6 (C_{quart}, C8), 40.4 (C_{quart}, C4), 40.3 (CH_2, C1), 36.9 (CH_2, C16), 36.6 (C_{quart}, C10), 36.4 (C_{quart}, C17), 34.4 (CH, C13), 32.8 (CH_2, C7), 32.7 (CH_2, C21), 28.9 (CH_3, C30), 28.8 (CH_3, C23), 26.5 (CH_2, C12), 26.4 (CH_2, C15), 26.3 (CH_2, C22), 24.7 (CH_3, C29), 21.7 (CH_2, C11), 20.6 (CH_3 (C24), 19.6 (CH_2, C6), 16.6 (CH_3, C25), 15.5 (CH_3, C26), 13.6 (CH_3, C27) ppm; MS (ESI, MeOH): m/z = 486.2 (100%, $[M+H]^+$), 503.1 (38%, $[M+NH_4]^+$), 508.3 (46%, $[M+Na]^+$), 540.1 (16%, $[M+Na+MeOH]^+$).

Data for **18**: colorless solid; R_f = 0.48 (hexane/ethyl acetate, 8:2); mp 217–220 °C (lit.: 202.4 °C[43]); $[\alpha]_D$ = +64.0° (c = 0.92, $CHCl_3$); IR (KBr): ν = 3434m, 2953s, 2870s, 1728m, 1574s, 1470w, 1387w, 1314w, 1254w, 1210w, 1140w, 1060w, 1028w cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.76 (d, J = 7.8 Hz, 1H, CH_a (28)), 3.53 (s, 1H, CH (19)), 3.46 (d, J = 7.8 Hz, 1H, CH_b (28)), 3.10 (d, J = 16.2 Hz, 1H, CH_a (1)), 2.95 (d, J = 16.2 Hz, 1H, CH_b (1)), 1.77–1.67 (m, 1H, CH_a (15)), 1.61–1.44 (m, 12H, CH (9) + CH_a (7) + CH (5) + CH (18) + CH_a (6) + CH_2 (21) + CH_a (16) + CH_a (12) + CH_a (22) + CH_2 (11)), 1.44–1.39 (m, 1H, CH (13)), 1.39–1.35 (m, 1H, CH_b (22)), 1.34–1.31 (m, 1H, CH_b (16)), 1.30–1.19 (m, 2H, CH_b (7) + CH_b (6)), 1.24 (s, 3H, CH_3 (23)), 1.24 (s, 3H, CH_3 (24)), 1.16–1.06 (m, 1H, CH_b (12)), 1.01 (s, 6H, CH_3 (26) + CH_3 (25)), 1.05–0.90 (m, 1H, CH_b (15)), 0.94 (s, 6H, CH_3 (27) + CH_3 (30)), 0.81 (s, 3H, CH_3 (29)) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.4 (C=O, C3), 119.4 (C_{quart}, C2), 88.0 (CH, C19), 71.3 (CH_2, C28), 52.5 (CH, C5), 50.2 (CH, C9), 48.9 (CH_2, C1), 47.6 (C_{quart}, C4), 46.8 (CH, C18), 41.6 (C_{quart}, C20), 41.1 (C_{quart}, C14), 40.6 (C_{quart}, C8), 37.0 (CH_2, C16), 36.8 (C_{quart}, C10), 36.4 (CH_2, C17), 34.4 (CH, C13), 32.8 (CH_2, C7), 32.3 (CH_2, C21), 30.6 (CH_3, C23), 28.9 (CH_3, C30), 26.5 (CH_3, C12), 26.3 (CH_2, C15), 26.3 (CH_2, C22), 24.7 (CH_3, C29), 23.3 (CH_3, C24), 22.1 (CH_2, C11), 19.8 (CH_2, C6), 17.9 (CH_3, C25), 15.3 (CH_3, C26), 13.6 (CH_3, C27) ppm; MS (ESI, MeOH): m/z = 531.1 (44%, $[M+H]^+$), 548.2 (11%, $[M+NH_4]^+$), 553.2 (100%, $[M+Na]^+$), 563.0 (17%, $[M+H+MeOH]^+$), 571.3 (22%, $[M+Na+H_2O]^+$), 584.8 (8%, $[M+Na+MeOH]^+$).

4.3.17. (18α,19β) 19,28-Epoxy-2,3-*seco*-18-oleanan-2,3-dicarboxylic acid (19)

To a suspension of **17** (100 mg, 0.21 mmol) in methanol (2 mL) hydrogen peroxide (30%, 0.4 mL) and potassium carbonate (0.16 g, 1.16 mmol) were added. The mixture was diluted with methanol (2 mL), and stirred for 5 days at 25 °C, neutralized by the careful addition of diluted aq hydrochloric acid (10:1), diluted with water (10 mL) and an aq. solution of sodium pyrosulfite (satd, 5 mL). The precipitate was filtered off and purified by chromatography (SiO_2, $CHCl_3$/MeOH 9:1) to afford **19** (80 mg, 78%) as a colorless solid; R_f = 0.27 (hexane/ethyl acetate, 2:3); mp 301–304 °C (lit.: 305–306 °C)[32]; IR (KBr): ν = 2952s, 2362w, 1700s, 1457m, 1393m, 1239m, 1179m, 1037m, 1004w cm^{-1}; MS (ESI, MeOH): m/z = 487.4 (100%, $[M-H]^-$), 975.2 (86%, $[2M-H]^-$), 997.5 (79%, $[2M-2H+Na]^-$).

4.3.18. Dimethyl (18α,19β) 19,28-epoxy-2,3-*seco*-18-oleanan-2,3-dicarboxylate (20)

Following the procedure given for the synthesis of **11**, from **19** (200 mg, 0.41 mmol), potassium carbonate (0.22 g, 1.59 mmol), DMF (25 mL) and methyl iodide (0.06 mL, 0.99 mmol) followed by chromatography (SiO_2, hexane/ethyl acetate, 8:2) **20** (120 mg, 56%) was obtained as a colorless solid; R_f = 0.63 (hexane/ethyl acetate, 8:2); mp 143–146 °C (lit.: 238–240 °C[32]); $[\alpha]_D$ = +40.8° (c = 0.80, $CHCl_3$) (lit.: $[\alpha]_D$ = +30° (c = 1.10, $CHCl_3$)[32]; IR (KBr): ν = 3436w, 2947s, 2948s, 2290s, 1740s, 1438s, 1394m, 1374m, 1355m, 1283w, 1253m, 1234m, 1206m, 1154s, 1128s, 1058w, 1032m, 1015w cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.75 (d, J = 7.7 Hz, 1H, CH_a (28)), 3.64 (s, 3H, CH_3 (31)), 3.60 (s, 3H, CH_3 (32)), 3.51 (s, 1H, CH (19)), 3.42 (d, J = 7.7 Hz, 1H, CH_b (28)), 2.46 (d, J = 17.8 Hz, 1H, CH_a (1)), 2.41–2.33 (m, 2H, CH (5) + CH (9)), 2.30 (d, J = 17.9 Hz, 1H, CH_b (1)), 1.71–1.58 (m, 2H, CH_a (15) + CH_a (12)), 1.57–1.34 (m, 9H, CH_a (11) + CH (18) + CH_a (22) + CH_a (6) + CH_a (16) + CH_a (17) + CH (13) + CH_a (7) + CH_a (21)), 1.33–1.15 (m, 5H, CH_b (22) + CH_b (16) + CH_b (17) + CH_b (7) + CH_b (21)), 1.23 (s, 6H, CH_3 (23) + CH_3 (24)), 1.15–1.06 (m, 3H, CH_b (11) + CH_b (12) + CH_b (6)), 0.96 (s, 3H, CH_3 (26)), 0.92 (s, 3H, CH_3 (27)), 0.91 (s, 6H, CH_3 (25) + CH_3 (30)), 0.89–0.79 (m, 1H, CH_b (15)), 0.77 (s, 3H, CH_3 (29)) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 180.1 (C=O, C3), 172.2 (C=O, C2), 88.0 (CH, C19), 71.4 (CH_2, C28), 51.8 (CH_3, C32), 51.0 (CH_3, C31), 48.6 (CH, C5), 46.8 (CH, C18), 46.6 (C_{quart}, C4), 42.9 (CH, C9), 42.3 (C_{quart}, C8), 42.1 (C_{quart}, C10), 41.6 (CH_2, C1), 41.2 (C_{quart}, C20), 40.6 (C_{quart}, C14), 36.8 (CH_2, C16), 36.4 (CH_2, C17), 34.5 (CH, C13), 33.0 (CH_2, C7), 32.9 (CH_2, C21), 28.9 (CH_3, C30), 27.7 (CH_3, C23), 26.7 (CH_2, C12), 26.6 (CH_2, C15), 26.4 (CH_2, C22), 24.7 (CH_3, C29), 24.1 (CH_3, C24), 22.1 (CH_2, C11), 20.9 (CH_2, C6), 20.2 (CH_3, C25), 15.9 (CH_3, C26), 13.6 (CH_3, C27) ppm; MS (ESI, MeOH): m/z = 517.3 (100%, $[M+H]^+$), 534.3 (22%, $[M+NH_4]^+$), 539.5 (6%, $[M+Na]^+$), 795 (5%, $[3M+K+H]^{2+}$), 1055.5 (100%, $[2M+Na]^+$).

4.3.19. Diethyl (18α,19β) 19,28-epoxy-2,3-*seco*-18-oleanan-2,3-dicarboxylate (21)

Following the procedure given for the synthesis of **11**, from **19** (200 mg, 0.41 mmol), potassium carbonate (0.22 g, 1.59 mmol),

DMF (20 mL) and ethyl iodide (0.08 mL, 0.99 mmol)) followed by chromatography (SiO_2, hexane/ethyl acetate, 9:1) **21** (150 mg, 67%) was obtained as a colorless solid; R_f = 0.58 (hexane/ethyl acetate, 8:2); mp 103–107 °C; $[\alpha]_D$ = +41.3° (*c* = 0.84, $CHCl_3$); IR (KBr): *v* = 3421w, 2930s, 2867s, 1737s, 1452s, 1391s, 1373s, 1340m, 1283m, 1255s, 1236s, 1208s, 1148s, 1037s, 1008m cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 4.21–4.11 (m, 1H, C*H*$_a$ (33)), 4.12 (q, *J* = 7.2 Hz, 2H, C*H*$_2$ (31)), 3.98 (dq, *J* = 10.8, 7.1 Hz, 1H, C*H*$_b$ (33)), 3.76 (d, *J* = 7.6 Hz, 1H, C*H*$_a$ (28)), 3.51 (s, 1H, C*H* (19)), 3.43 (d, *J* = 7.7 Hz, 1H, C*H*$_b$ (28)), 2.48–2.41 (m, 2H, C*H*$_2$ (1)), 2.40–2.37 (m, 1H, C*H* (5)), 2.24 (dd, *J* = 12.3, 2.0 Hz, 1H, C*H* (9)), 1.71–1.59 (m, 1H, C*H*$_a$ (15)), 1.58–1.44 (m, 7H, C*H*$_a$ (6) + C*H*$_a$ (11) + C*H*$_a$ (7) + C*H* (18) + C*H* (13) + C*H*$_a$ (12) + C*H*$_a$ (22)), 1.43–1.34 (m, 4H, C*H*$_a$ (16) + C*H*$_b$ (7) + C*H*$_a$ (21) + C*H*$_b$ (6)), 1.33–1.15 (m, 10H, C*H*$_b$ (22) + C*H*$_b$ (16) + C*H*$_b$ (21) + C*H*$_b$ (11) + C*H*$_3$ (32) + C*H*$_3$ (34)), 1.25 (s, 3H, C*H*$_3$ (23)), 1.23 (s, 3H, C*H*$_3$ (24)), 1.15–1.07 (m, 1H, C*H*$_b$ (12)), 0.96 (s, 3H, C*H*$_3$ (26)), 0.93 (s, 3H, C*H*$_3$ (25)), 0.91 (s, 3H, C*H*$_3$ (27)), 0.91 (s, 1H, C*H*$_3$ (30)), 0.92–0.83 (m, 1H, C*H*$_b$ (15)), 0.78 (s, 3H, C*H*$_3$ (29)) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 179.4 (*C*=O, C3), 171.9 (*C*=O, C2), 88.0 (*C*H, C19), 71.4 (*C*H$_2$, C28), 60.4 (*C*H$_2$, C33), 59.8 (*C*H$_2$, C31), 48.4 (*C*H, C5), 47.0 (*C*$_{quart}$, C4), 46.8 (*C*H, C18), 43.3 (*C*H, C9), 42.9 (*C*H$_2$, C1), 42.6 (*C*$_{quart}$, C8), 41.6 (*C*$_{quart}$, C10), 41.2 (*C*$_{quart}$, C20), 40.6 (*C*$_{quart}$, C14), 36.8 (*C*H$_2$, C16), 36.4 (*C*$_{quart}$, C17), 34.5 (*C*H, C13), 33.0(*C*H$_2$, C7), 32.9 (*C*H$_2$, C21), 29.0 (*C*H$_3$, C30), 26.8 (*C*H$_3$, C23), 26.6 (*C*H$_2$, C12), 26.6 (*C*H$_2$, C15), 26.4 (*C*H$_2$, C22), 24.9 (*C*H$_3$, C29), 24.7 (*C*H$_3$, C24), 22.1 (*C*H$_2$, C11), 21.4 (*C*H$_2$, C6), 20.3 (*C*H$_3$, C25), 15.9 (*C*H$_3$, C26), 14.5 (*C*H$_3$, C34), 14.2 (*C*H$_3$, C32), 13.6 (*C*H$_3$, C27) ppm; MS (ESI, MeOH): *m*/*z* = 545.2 (80%, $[M+H]^+$), 562.0 (6%, $[M+NH_4]^+$), 1111.4 (100%, $[2M+Na]^+$); analysis calcd for $C_{34}H_{56}O_5$ (544.81): C 74.96, H 10.36; found: C 74.73, H 10.41.

4.3.20. Dipropyl (18α,19β) 19,28-epoxy-2,3-*seco*-18-oleanan-2,3-dicarboxylate (22)

Following the procedure given for the synthesis of **11**, from **19** (200 mg, 0.41 mmol), potassium carbonate (0.22 g, 1.59 mmol), DMF (20 mL) and propyl bromide (0.09 mL, 0.98 mmol) followed by chromatography (SiO_2, hexane/ethyl acetate, 9:1) **22** (180 mg, 76%) was obtained as a colorless solid; R_f = 0.87 (hexane/ethyl acetate, 8:2); mp 92–96 °C; $[\alpha]_D$ = +41.8° (*c* = 0.55, $CHCl_3$); IR (KBr): *v* = 3420w, 2967s, 2867s, 1739*s*,1717s, 1457m, 1387m, 1375m, 1338w,1305w, 1284m, 1255s, 1236m, 1208m, 1148s, 1134*s*,1059w, 1037s, 1008m cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 4.09–4.02 (m, 1H, C*H*$_a$ (34)), 4.02 (*t*, *J* = 6.7 Hz, 2H, C*H*$_2$ (31)), 3.88 (dt, *J* = 10.8, 6.5 Hz, 1H, C*H*$_b$ (34)), 3.76 (d, *J* = 7.6 Hz, 1H, C*H*$_a$ (28)), 3.52 (s, 1H, C*H* (19)), 3.43 (d, *J* = 7.7 Hz, 1H, C*H*$_b$ (28)), 2.51–2.43 (m, 2H, C*H*$_2$ (1)), 2.43–2.40 (m, 1H, C*H* (5)), 2.27–2.20 (m, 1H, C*H* (9)), 1.72–1.58 (m, 5H, C*H*$_2$ (32) + C*H*$_2$ (35) + C*H*$_a$ (15)), 1.59–1.44 (m, 7H, C*H*$_a$ (11) + C*H*$_a$ (6) + C*H*$_a$ (7) + C*H* (18) + C*H*$_a$ (12) + C*H*$_a$ (22) + C*H* (13)), 1.43–1.33 (m, 4H, C*H*$_a$ (21) + C*H*$_b$ (7) + C*H*$_b$ (6) + C*H*$_a$ (16)), 1.34–1.17 (m, 4H, C*H*$_b$ (22) + C*H*$_b$ (16) + C*H*$_b$ (7) + C*H*$_b$ (11)), 1.27 (s, 3H, C*H*$_3$ (24)), 1.26 (s, 3H, C*H*$_3$ (23)), 1.15–1.06 (m, 1H, C*H*$_b$ (12)), 1.00–0.84 (m, 7H, C*H*$_b$ (15) + C*H*$_3$ (33) + C*H*$_3$ (36)), 0.96 (s, 3H, C*H*$_3$ (26)), 0.94 (s, 3H, C*H*$_3$ (25)), 0.92 (s, 3H, C*H*$_3$ (30)), 0.91 (s, 3H, C*H*$_3$ (27)), 0.78 (s, 3H, C*H*$_3$ (29)) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 179.4 (*C*$_{quart}$, C3), 172.1 (*C*$_{quart}$, C2), 88.0 (*C*H, C19), 71.4 (*C*H$_2$, C28), 66.2 (*C*H$_2$, C34), 65.7 (*C*H$_2$, C31), 48.4 (*C*H, C5), 47.2 (*C*$_{quart}$, C4), 46.8 (*C*H, C18), 43.4 (*C*H, C9), 43.0 (*C*H$_2$, C1), 42.5 (*C*$_{quart}$, C8), 41.6 (*C*$_{quart}$, C10), 41.2 (*C*$_{quart}$, C20), 40.6 (*C*$_{quart}$, C14), 36.9 (*C*H$_2$, C16), 36.4 (*C*$_{quart}$, C17), 34.5 (*C*H, C13), 33.0 (*C*H$_2$, C7), 32.9 (*C*H$_2$, C21), 29.0 (*C*H$_3$, C30), 26.7 (*C*H$_3$, C23), 26.6 (*C*H$_2$, C12), 26.6 (*C*H$_2$, C15), 26.4 (*C*H$_2$, C22), 25.1 (*C*H$_3$, C29), 24.7 (*C*H$_3$, C24), 22.2 (*C*H$_2$, C32), 22.1 (*C*H$_2$, C35), 22.0 (*C*H$_2$, C11), 21.5 (*C*H$_2$, C6), 20.3 (*C*H$_3$, C25), 15.9 (*C*H$_3$, C26), 13.6 (*C*H$_3$, C27), 10.7 (*C*H$_3$, C36), 10.7 (*C*H$_3$, C33) ppm; MS (ESI, MeOH): *m*/*z* = 573.9 (28%, $[M+H]^+$), 595.9 (3%, $[M+NH_4]^+$), 1167.9 (100%, $[2\ M+Na]^+$); analysis calcd for $C_{36}H_{60}O_5$ (572.86): C 75.48, H 10.56; found: C 75.39, H 10.71.

4.3.21. Diallyl (18α,19β) 19,28-epoxy-2,3-*seco*-18-oleanan-2,3-dicarboxylate (23)

Following the procedure given for the synthesis of **11**, from **19** (200 mg, 0.41 mmol) potassium carbonate (0.22 g, 1.59 mmol), DMF (15 mL) and allyl iodide (0.09 mL, 0.95 mmol) followed by chromatography (SiO_2, hexane/ethyl acetate, 9:1) **23** (150 mg, 64%) was obtained as a colorless solid; R_f = 0.64 (hexane/ethyl acetate, 8:2); mp 115–120 °C; $[\alpha]_D$ = +38.9° (*c* = 0.67, $CHCl_3$); IR (KBr): *v* = 3096m, 2927s, 2862s, 1720s, 1648m, 1451s, 1374s, 1338m, 1284s, 1256s, 1235s, 1208s, 1133s, 1059m, 1038s, 1008s cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 5.98–5.85 (m, 4H, C*H*$_2$ (32) + C*H*$_2$ (35)), 5.34 (q, *J* = 1.5 Hz, 1H, C*H*$_a$ (33)), 5.30 (q, *J* = 1.5 Hz, 1H, C*H*$_b$ (33)), 5.22 (ddd, *J* = 5.6, 2.6, 1.2 Hz, 1H, C*H*$_a$ (36)), 5.21–5.19 (m, 1H, C*H*$_b$ (36)), 4.63–4.58 (m, 2H, C*H*$_a$ (34)), 4.56 (ddt, *J* = 7.2, 6.0, 1.4 Hz, 2H, C*H*$_2$ (31)), 4.43 (ddt, *J* = 13.4, 5.5, 1.4 Hz, 1H, C*H*$_b$ (34)), 3.76 (d, *J* = 7.7 Hz, 1H, C*H*$_a$ (28)), 3.52 (s, 1H, C*H* (19)), 3.43 (d, *J* = 7.8 Hz, 1H, C*H*$_b$ (28)), 2.53–2.41 (m, 3H, C*H*$_2$ (1) + C*H* (5)), 2.26 (dd, *J* = 12.5, 2.5 Hz, 1H, C*H* (9)), 1.66–1.60 (m, 1H, C*H*$_a$ (15)), 1.56–1.35 (m, 10H, C*H*$_a$ (11) + C*H*$_a$ (7) + C*H* (18) + C*H* (13) + C*H*$_a$ (12) + C*H*$_2$ (6) + C*H*$_2$ (21) + C*H*$_a$ (16)), 1.33–1.25 (m, 3H, C*H*$_b$ (16) + C*H*$_2$ (22)), 1.29 (s, 3H, C*H*$_3$ (24)), 1.27 (s, 3H, C*H*$_3$ (23)), 1.25–1.18 (m, 2H, C*H*$_b$ (7) + C*H*$_b$ (11)), 1.15–1.10 (m, 1H, C*H*$_b$ (12)), 0.96 (s, 3H, C*H*$_3$ (26)), 0.94 (s, 3H, C*H*$_3$ (25)), 0.92 (s, 3H, C*H*$_3$ (30)), 0.91 (s, 3H, C*H*$_3$ (25)), 0.89–0.83 (m, 1H, C*H*$_b$ (15)), 0.78 (s, 3H, C*H*$_3$ (29)) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 179.0 (*C*=O, C3), 171.5 (*C*=O, C2), 132.6 (*C*H, C35), 132.5 (*C*H, C32), 118.3 (*C*H$_2$, C36), 117.9 (*C*H$_2$, C33), 88.0 (*C*H, C19), 71.5 (*C*H$_2$, C28), 65.2 (*C*H$_2$, C34), 64.8 (*C*H$_2$, C31), 48.5 (*C*H, C5), 47.1 (*C*$_{quart}$, C4), 46.8 (*C*H, C18), 43.3 (*C*H, C9), 42.7 (*C*$_{quart}$, C8), 42.6 (*C*H$_2$, C1), 41.6 (*C*$_{quart}$, C10), 41.2 (*C*$_{quart}$, C20), 40.6 (*C*$_{quart}$, C14), 36.8 (*C*H$_2$, C16), 36.4 (*C*$_{quart}$, C17), 34.5 (*C*H, C13), 32.9 (*C*H$_2$, C7), 32.9 (*C*H$_2$, C21), 29.0 (*C*H$_3$, C23), 27.0 (*C*H$_3$, C23), 26.6 (*C*H$_2$, C12), 26.6 (*C*H$_2$, C15), 26.4 (*C*H$_2$, C22), 24.8 (*C*H$_3$, C29), 24.7 (*C*H$_3$, C24), 22.1 (*C*H$_2$, C11), 21.4 (*C*H$_2$, C6), 20.2 (*C*H$_3$, C25), 15.9 (*C*H$_2$, C26), 13.6 (*C*H$_2$, C27) ppm; MS (ESI, MeOH): *m*/*z* = 569.3 (100%, $[M+H]^+$), 595.9 (8%, $[M+NH_4]^+$), 1167.9 (9%, $[M+Na]^+$); analysis calcd for $C_{36}H_{56}O_5$ (568.83): C 76.01, H 9.92; found: C 75.79, H 10.05.

4.3.22. Dipropargyl (18α,19β) 19,28-epoxy-2,3-*seco*-18-oleanan-2,3-dicarboxylate (24)

Following the procedure given for the synthesis of **11**, from **19** (200 mg, 0.41 mmol), potassium carbonate (0.20 g, 1.45 mmol), DMF (10 mL) and propargyl bromide (80% in toluene, 0.11 mL, 0.98 mmol) followed by chromatography (SiO_2, hexane/ethyl acetate, 9:1) **24** (130 mg, 56%) was obtained as a colorless solid; R_f = 0.59 (hexane/ethyl acetate, 8:2); mp 102–108 °C; $[\alpha]_D$ = +38.7° (*c* = 0.55, $CHCl_3$); IR (KBr): *v* = 3287s, 2927s, 2868s, 2130w, 1744s, 1720s, 1451s, 1374s, 1338m, 1252s, 1214m, 1170s, 1119s, 1059w, 1038*s*, 1026*s* cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 4.71 (dd, *J* = 15.6, 2.2 Hz, 1H, C*H*$_a$ (34)), 4.69 (d, *J* = 2.2 Hz, 2H, C*H*$_2$ (31)), 4.59 (dd, *J* = 15.6, 2.3 Hz, 1H, C*H*$_b$ (34)), 3.76 (d, *J* = 7.6 Hz, 1H, C*H*$_a$ (28)), 3.52 (s, 1H, C*H* (19)), 3.43 (d, *J* = 7.8 Hz, 1H, C*H*$_b$ (28)), 2.57–2.49 (m, 1H, C*H*$_a$ (1)), 2.47–2.36 (m, 4H, C*H*$_b$ (1) + C*H* (5) + C*H* (33) + C*H* (36)), 2.27–2.20 (m, 1H, C*H* (9)), 1.68–1.60 (m, 1H, C*H*$_a$ (15)), 1.57–1.43 (m, 8H, C*H*$_2$ (11) + C*H*$_2$ (6) + C*H* (18) + C*H*$_a$ (12) + C*H* (13) + C*H*$_a$ (21)), 1.42–1.34 (m, 3H, C*H*$_2$ (7) + C*H*$_a$ (16)), 1.33–1.25 (m, 3H, C*H*$_2$ (22) + C*H*$_b$ (16)), 1.29 (s, 3H, C*H*$_3$ (24)), 1.28 (s, 3H, C*H*$_3$ (23)), 1.25–1.16 (m, 1H, C*H*$_b$ (21)), 1.15–1.06 (m, 1H, C*H*$_b$ (12)), 0.99–0.87 (m, 1H, C*H*$_b$ (15)), 0.96 (s, 3H, C*H*$_3$ (26), 0.95 (s, 3H, C*H*$_3$ (25)), 0.92 (s, 6H, C*H*$_3$ (27) + C*H*$_3$ (30)), 0.78 (s, 3H, C*H*$_3$ (27)) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.5 (*C*=O, C3), 170.9 (*C*=O, C2), 88.0 (*C*H, C19), 78.1 (*C*H, C36), 77.9 (*C*H, C33), 74.8

(C_{quart}, C35), 74.7 (C_{quart}, C32), 71.4 (CH_2, C28), 52.2 (CH_2, C34), 51.5 (CH_2, C31), 48.5 (*C*H, C5), 47.0 (C_{quart}, C4), 46.8 (*C*H, C18), 43.3 (*C*H, C9), 42.7 (C_{quart}, C8), 42.6 (CH_2, C1), 41.6 (C_{quart}, C10), 41.2 (C_{quart}, C20), 40.6 (C_{quart}, C14), 36.8 (CH_2, C16), 36.4 (C_{quart}, C17), 34.5 (*C*H, C13), 32.9 (CH_2, C7), 32.9 (CH_2, C21), 28.9 (CH_3, C30), 27.1 (CH_3, C23), 26.6 (CH_2, C12), 26.5 (CH_2, C15), 26.4 (CH_2, C22), 24.7 (CH_3, C29), 24.6 (CH_3, C24), 22.1 (CH_2, C11), 21.2 (CH_2, C6), 20.2 (CH_3, C25), 15.9 (CH_3, C26), 13.7 (CH_3, C27) ppm; MS (ESI, MeOH): m/z = 565.2 (100%, $[M+H]^+$), 582.3 (58%, $[M+NH_4]^+$), 587.5 (16%, $[M+Na]^+$); analysis calcd for $C_{36}H_{52}O_5$ (564.80): C 76.56, H 9.28; found: C 76.44, H 9.37.

4.3.23. Dibutyl (18α,19β) 19,28-epoxy-2,3-*seco*-18-oleanan-2,3-dicarboxylate (25)

Following the procedure given for the synthesis of **11**, from **19** (200 mg, 0.41 mmol), potassium carbonate (0.20 g, 1.45 mmol), DMF (25 mL) and butyl bromide (0.11 mL, 0.98 mmol)) followed by chromatography (SiO_2, hexane/ethyl acetate, 9:1) **25** (150 mg, 60 %) was obtained as an off-white solid; R_f = 0.72 (hexane/ethyl acetate, 8:2); mp 54–57 °C; $[\alpha]_D$ = +37.5° (c = 0.56, $CHCl_3$); IR (KBr): ν = 3447br, 2959s, 2868s, 1739s, 1716s, 1457m, 1385m, 1284w, 1255m, 1236w, 1208w, 1148s, 1134s, 1060w, 1036m, 1008m cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 4.16–4.07 (m, 1H, CH_a (35)), 4.07–4.00 (m, 2H, CH_2 (31)), 3.91 (*dt*, J = 11.0, 6.5 Hz, 1H, CH_b (35)), 3.76 (d, J = 7.6 Hz, 1H, CH_a (28)), 3.52 (s, 1H, C*H* (19)), 3.43 (d, J = 7.7 Hz, 1H, CH_b (28)), 2.49–2.39 (m, 3H, CH_2 (1) + C*H* (5)), 2.26–2.19 (m, 1H, C*H* (9)), 1.70–1.56 (m, 5H, CH_a (15) + CH_2 (36) + CH_2 (32)), 1.56–1.44 (m, 5H, CH_a (11) + CH_a (12) + CH_a (21) + C*H* (18) + C*H* (13)), 1.43–1.34 (m, 10H, CH_a (22) + CH_2 (6) + CH_2 (37) + CH_2 (33) + CH_a (16) + CH_2 (7)), 1.33–1.21 (m, 2H, CH_b (22) + CH_b (16)), 1.27 (s, 3H, CH_3 (24)), 1.26 (s, 3H, CH_3 (23)), 1.22–1.17 (m, 2H, CH_b (11) + CH_b (21)), 1.15–1.09 (m, 1H, CH_b (12)), 0.99–0.89 (m, 6H, CH_3 (38) + CH_3 (34)), 0.96 (s, 3H, CH_3 (26)), 0.93 (s, 3H, CH_3 (25)), 0.91 (s, 3H, CH_3 (30)), 0.89–0.84 (m, 1H, CH_b (15)), 0.78 (s, 3H, CH_3 (29)) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 179.4 (*C*=O, C3), 172.1 (*C*=O, C2), 88.0 (*C*H, C19), 71.5 (CH_2, C28), 64.4 (CH_2, C35), 63.9 (CH_2, C31), 48.4 (*C*H, C5), 47.2 (C_{quart}, C4), 46.9 (*C*H, C18), 43.4 (*C*H, C9), 43.0 (C_{quart}, C8), 42.6 (CH_2, C1), 41.6 (C_{quart}, C10), 41.2 (C_{quart}, C20), 40.6 (C_{quart}, C14), 36.9 (CH_2, C16), 36.4 (C_{quart}, C17), 34.5 (*C*H, C13), 33.0 (CH_2, C7), 32.9 (CH_2, C21), 31.0 (CH_2, C36), 30.7 (CH_2, C32), 29.0 (CH_3, C30), 26.7 (CH_3, C23), 26.6 (CH_2, C12), 26.6 (CH_2, C15), 26.4 (CH_2, C22), 25.1 (CH_3, C29), 24.7 (CH_3, C24), 22.1 (CH_2, C11), 21.5 (CH_2, C6), 20.2 (CH_3, C25), 19.4 (CH_2, C37), 19.4 (CH_2, C33), 15.9 (CH_3, C26), 13.9 (CH_3, C27), 13.9 (CH_3, C38), 13.6 (CH_3, C34) ppm; MS (ESI, MeOH): m/z = 601.4 (100%, $[M+H]^+$), 618.4 (3%, $[M+NH_4]^+$), 623.6 (8%, $[M+Na]^+$), 921.1 (11%, $[3M+K+H]^{2+}$), 1223.6 (94%, $[2M+Na]^+$); analysis calcd for $C_{38}H_{64}O_5$ (600.91): C 75.95, H 10.74; found: C 75.81, H 10.90.

4.3.24. Dibenzyl (18α,19β) 19,28-epoxy-2,3-*seco*-18-oleanan-2,3-dicarboxylate (26)

Following the procedure given for the synthesis of **11**, from **19** (200 mg, 0.41 mmol), potassium carbonate (0.20 g, 1.45 mmol), DMF (10 mL) and benzyl bromide (0.12 mL, 0.98 mmol)) followed by chromatography (SiO_2, hexane/ethyl acetate, 9:1) **26** (220 mg, 80 %) was obtained as a colorless solid; R_f = 0.70 (hexane/ethyl acetate, 8:2); mp 122–124 °C; $[\alpha]_D$ = +24.3° (c = 0.88, $CHCl_3$); IR (KBr): ν = 3430w, 2950s, 2868s, 1739*s*,1723s, 1496w, 1456m, 1394m, 1374m, 1340w,1300w, 1252w, 1235m, 1211m, 1146s, 1104m, 1032m, 1004m cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.27 (m, 10H, CH_{aromat}), 5.14 (d, J = 13. Hz, 1H, CH_a (36)), 5.11 (d, J = 12.7 Hz, 1H, CH_a (31)), 4.93 (d, J = 12.2 Hz, 1H, CH_b (31)),4.92 (d, J = 12.2 Hz, 1H, CH_b (36)), 3.74 (d, J = 7.6 Hz, 1H, CH_a (28)), 3.49 (s, 1H, C*H* (19)), 3.42 (d, J = 7.7 Hz, 1H, CH_b (28)), 2.54–2.47 (m, 3H, C*H* (5) + CH_2 (1)), 2.13 (dd, J = 12.2, 1.7 Hz, 1H, C*H* (9)), 1.56–1.45 (m, 3H, CH_a (15) + CH_a (11) + CH_a (7)), 1.45–1.32 (m, 7H, CH_a (12) + CH_a (22) + C*H* (13) + C*H* (18) + CH_a (16) + CH_2 (6)), 1.32–1.26 (m, 3H, CH_b (22) + CH_b (16) + CH_b (22)), 1.30 (s, 3H, CH_3 (24)), 1.28 (s, 3H, CH_3 (23)), 1.26–1.18 (m, 1H, CH_b (7)), 1.17–1.11 (m, 1H, CH_b (11)), 1.11–1.06 (m, 1H, CH_b (12)), 0.93 (s, 9H, CH_3 (30) + CH_3 (25) + CH_3 (26)), 0.80 (s, 3H, CH_3 (29)), 0.78 (s, 3H, CH_3 (27)), 0.74–0.62 (m, 1H, CH_b (15)) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 179.1 (*C*=O, C3), 171.6 (*C*=O, C2), 136.4 (C_{aromat}, C37), 136.3 (C_{aromat}, C32), 128.8 (CH_{aromat}, C39), 128.6 (CH_{aromat}, C34), 128.5 (CH_{aromat}, C40), 128.2 (CH_{aromat}, C35), 128.0 (CH_{aromat}, C38), 127.9 (CH_{aromat}, C33), 87.9 (*C*H, C19), 71.4 (CH_2, C28), 66.2 (CH_2, C36), 65.9 (CH_2, C31), 48.4 (*C*H, C5), 47.1 (C_{quart}, C4), 46.8 (*C*H, C18), 43.4 (*C*H, C9), 42.9 (C_{quart}, C8), 42.7 (CH_2, C1), 41.6 (C_{quart}, C10), 41.1 (C_{quart}, C20), 40.5 (C_{quart}, C14), 36.8 (CH_2, C16), 36.4 (C_{quart}, C17), 34.4 (*C*H, C13), 32.8 (CH_2, C7), 32.8 (CH_2, C21), 28.9 (CH_3, C30), 26.7 (CH_3, C23), 26.6 (CH_2, C12), 26.4 (CH_2, C15), 26.3 (CH_2, C22), 24.9 (CH_3, C29), 24.7 (CH_3, C24), 22.0(CH_2, C11), 21.4(CH_2, C6), 20.2(CH_3, C25), 15.8 (CH_3, C26), 13.5 (CH_3, C27) ppm; MS (ESI, MeOH): m/z = 669.3 (100%, $[M+H]^+$), 686.2 (8%, $[M+NH_4]^+$), 691.7 (6%, $[M+Na]^+$); analysis calcd for $C_{44}H_{60}O_5$ (668.94): C 79.00, H 9.04; found: C 78.81, H 9.25.

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