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# Synthesis of glycyrrhetinic acid derivatives for the treatment of metabolic diseases

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This publication is dedicated to Professor Peter Stanetty on the occasion of his 65th birthday

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ABSTRACT

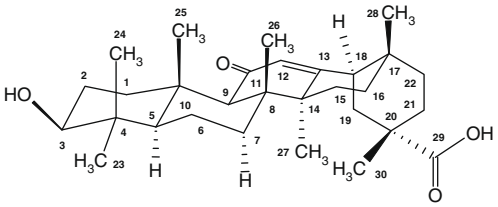
The effect of glycyrrhetinic acid (GA) and GA-derivatives towards 11β-hydroxysteroid dehydrogenase (11β-HSD) was investigated. Novel compounds with modifications at positions C-3, C-11 and C-29 of the GA skeleton were prepared. Single crystal X-ray diffraction data of selected substances are reported and discussed.



## 1. Introduction

Extracts from *glycyrrhiza glabra* have been used as medicines for gastro-intestinal diseases, as expectorants, and for many other indications for more than 4800 years with references from the Chinese medicine, the codex Hammurabi, papyrus Eber, writings by Plinius, Theophrastus Paracelsus and Hildegard von Bingen. Ruzicka first reported the correct molecular formula of glycyrrhetinic acid (**1**) (Scheme 1) as the aglycon of glycyrrhizin in 1937.[1] The biological activities of **1** have been studied extensively and the effects include, among others, antiinflammatory, antiulcer, antiallergic, and antitumor promoter activity, as summarized previously.[2,3]

In the context of the work presented here we were interested in the effect of glycyrrhetinic acid (GA, **1**) and its derivatives towards 11β-hydroxysteroid dehydrogenase (11β-HSD). Glucocorticoids are hormones that regulate a range of pathways involved in regulation of carbohydrate, protein and lipid metabolism, regulation of normal growth and development, influence on cognitive function, and resistance to stress. The principal glucocorticoid hormone in the human body is cortisol (corticosterone in rodents), which is synthesized in the adrenal cortex from cholesterol and secreted in response to the adrenocorticotropic hormone (ACTH) from the



**Scheme 1.** The structure of glycyrrhetinic acid, shown with numbering as used throughout the text.

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*E-mail address:* ujordis@pop.tuwien.ac.at (U. Jordis).

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pituitary gland in a circadian, episodic manner, but the secretion of this hormone can also be stimulated by stress, exercise and infection. In cells, cortisol binds primarily to the glucocorticoid receptor (GR) that then acts as a ligand-inducible transcription factor to induce the expression of glucocorticoid responsive genes. The corticosteroid hormones are found in the body along with their oxidized 11-dehydro counterparts (cortisone and 11-dehydrocorticosterone in human and rodents, respectively), which do not have activity at the glucocorticoid receptor. The local concentration of active hormone can differ significantly from its circulating levels due to the intracellular conversion by 11β-HSD enzymes.[4,5] In mammalians, two distinct isozymes of the 11β-hydroxysteroid dehydrogenases (11β-HSD) control glucocorticoid activity at the tissue level by modification of the oxidation state of the hormones. Both, 11β-HSD1 and 11β-HSD2 are members of the short chain alcohol dehydrogenase (SCAD) superfamily that have been widely conserved throughout evolution.

11β-HSD1, originally isolated from rat liver,[6] acts in vivo predominantly as an oxoreductase using NADPH as a co-factor to transform cortisone into cortisol in a number of tissues including liver, adipose tissue, bone, pancreas, endothelium, ocular tissue, skeletal muscle, vascular smooth muscle and certain parts of the central nervous system.[5,7] Thus, 11β-HSD1 serves as a local regulator of glucocorticoid actions in the tissues and organs where it is expressed. 11β-HSD1 is a reversible enzyme, and in tissue homogenates, upon purification and under certain conditions such as reduced co-factor availability and/or in disease states, dehydrogenase activity prevails.[8–11]

By contrast, the human 11β-HSD2 isozyme is a high-affinity NAD-dependent, unidirectional dehydrogenase that converts the secondary alcohol group at the C-11 position of cortisol to a secondary ketone, thereby producing the inactive metabolite cortisone.[5] 11β-HSD2 is predominantly expressed in mineralocorticoid target tissues such as kidney, sweat glands, salivary glands, colonic mucosa, and placenta, and protects the mineralocorticoid receptor (MR) from illicit occupation by the higher circulating concentrations of cortisol.[12] Its co-localization with the MR plays an important role in the regulation of salt and water balance.[13,14] Thus, 11β-HSD1 allows certain tissues to convert cortisone to cortisol to increase local glucocorticoid activity and potentiate adaptive response, thereby counteracting 11β-HSD2 activity that results in a fall in active glucocorticoids.[15]

Alterations in 11β-HSD activities have been associated with several human diseases, including hypertension, diabetes, obesity and metabolic syndrome. The role of 11β-HSD1 in the metabolic syndrome and type 2 diabetes is supported by several lines of evidence. Cortisol opposes the action of insulin meaning a stimulation of hepatic gluconeogenesis, inhibition of peripheral glucose uptake and increased blood glucose concentration. Inhibition of 11β-HSD1 would decrease the cortisol level and as a result increase glucose uptake and inhibit hepatic gluconeogenesis, giving a reduction in circulatory glucose levels. Pharmacological inhibition of 11β-HSD1 in rat and man with carbenoxolone[16,17] and transgenic knockout in mice[18–21] results in enhanced hepatic insulin sensitivity and reduced gluconeogenesis and glycogenosis, suggesting that the development of a potent 11β-HSD1 inhibitor could therefore have considerable therapeutic potential for the treatment of conditions associated with elevated blood glucose.

The 11β-HSD2 isoform deactivates cortisol to cortisone, thus 11β-HSD2 inhibitors could be used to increase the locally available amount of glucocorticoids in inflammatory diseases—allowing for a decrease of the doses required for anti-inflammatory therapy, resulting in a reduction of the frequency and severity of the side effects of glucocorticoid therapy.

On the other hand, 11β-HSD2 protects the MR in many key regulatory tissues. Aldosterone itself is protected from metabolism by the enzyme by the presence of an aldehyde group at the C-18 position. The importance of protecting the MR from occupation by glucocorticoids is seen in patients with AME (apparent mineralocorticoid excess) where the gene encoding 11β-HSD2 is mutated.[22,23] Defects or inactivity of the type 2 enzyme results in hypertensive syndromes and research has shown that patients with hypertensive syndrome have an increased urinary excretion ratio of cortisol to cortisone.[12,24,25] Inhibition of 11β-HSD2 results in cortisol-dependent mineralocorticoid excess syndrome with hypertension and hypokalemic alkalosis.[26,27] 11β-HSD1 inhibitors used for the therapy of diabetes or metabolic disease should be specific for the type 1 isozyme in order to avoid mineralocorticoid side effects.

As starting point of a program aimed towards determining the activity of GA-derivatives for 11β-HSD1, we have optimized the synthesis of GA-derivatives with emphasis on full characterization of the purity and the identity of these derivatives.

## 2. Results and discussion

18β-Glycyrrhetinic acid **1** was used as the starting material and, with the desire to study the effect of structural changes at the positions of C-3, C-11, C-18 and C-29 of 18β-glycyrrhetinic acid, the following derivatives were prepared.

The C-29 esters were prepared from 18β-GA **1** by treatment with diazomethane or diphenyldiazomethane to give **2a** or **2b** in high yields (Scheme 2). Compounds **2c**–**2e** have previously been prepared (**2c**,[28,29] **2d**, **2e**[30]) using standard methods, for example, with an excess of appropriate alkyl halides in a solution of NaOH in DMSO at room temperature. Substances were purified by column chromatography, and then crystallized to give 40–70% yield. A number of modifications have been examined at the C-3 position; these include the synthesis of ester and ether derivatives. The C-3 esters **3a**, **3d** and **3e** were prepared as previously described by reaction of **1** with corresponding anhydrides.

Ethers **3b**[2] and **3c** were obtained by treatment of 18β-GA 1 with trimethylsilyl chloride or phosphorus oxychloride, respectively, in dry pyridine. Treatment of **3a** with thionyl chloride gave **4a** quantitatively that was used directly without purification. By contrast, **4b** and **4c** were obtained by reaction of the corresponding C-29 esters with acetic anhydride. As shown in Scheme 3, **5a**–**e** were obtained by the condensation of C-29 acid chloride **4a**, and the corresponding amines. Deacetylation of **5d** gave **26d** in high yield. Additionally, the aldehyde **6** was prepared from **5a** and converted into the oxime **7**.

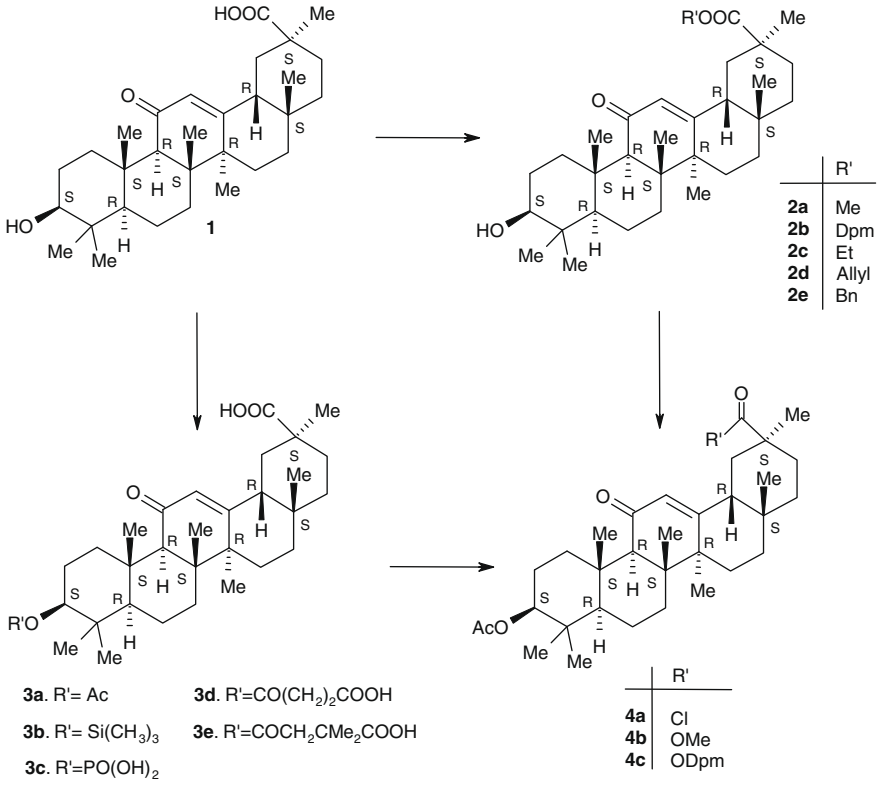
3-Keto compounds **8a**–**b** were obtained in high yield from the corresponding esters **2a**–**b** with PCC in DCM (Scheme 4). These were reacted with hydroxylamine and *O*-methyl-hydroxyamine in pyridine to give oximes **9a**–**d**.

The reduction of the oximes **9a**–**c** with $NaCNBH_3$ in the presence of $Ti^{III}Cl_3$ and $NH_4OAc$ in MeOH afforded corresponding amines **10a**–**d**.

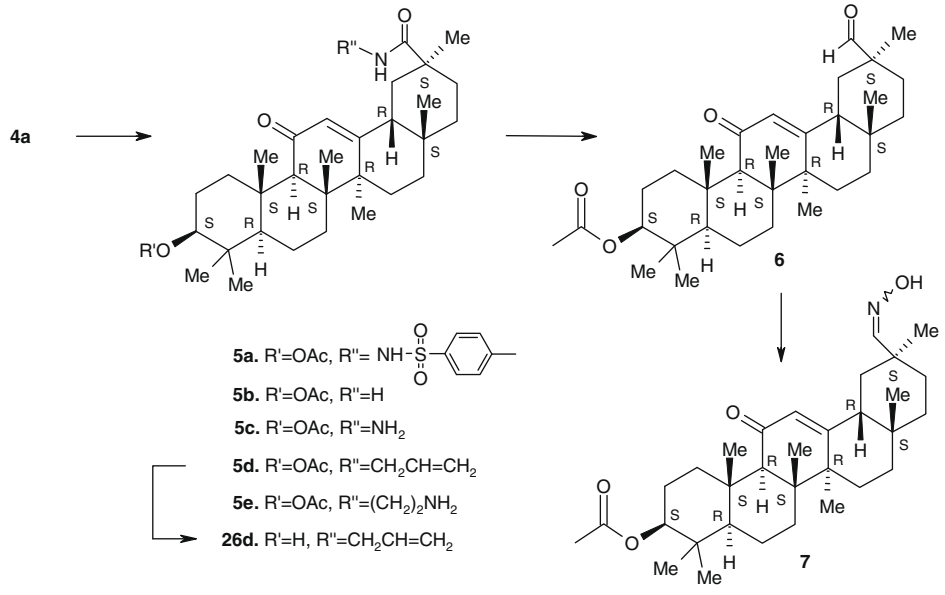
A number of reducing agents for the preparation of 3α-hydroxy-GA **12** from **11** were reported. In our hands, K-Selectride was the most useful among them and allowed for the preparation of **12**[31] in 95% yield (Scheme 5). This was purified by crystallization from MeOH. The other reducing agents were less stereoselective.

To prepare the C-29 protected esters, diazomethane and diphenyldiazomethane were used.

The reduction of **1**–**15** has been reported previously by treatment of **1** in hexamethylphosphoric triamide (HMPT) with an excess of lithium,[32] by catalytic reduction using $PtO_2$[33] or by zinc and concd HCl[34] (Scheme 6). In our hands, the last method worked best—even on larger scales. Methylation of **15** with diazomethane gave **16** in almost quantitative yield. Reduction of **1** with $NaBH_4$ in aq THF containing NaOH gave a mixture of epimers 11β-GA and




**Scheme 2.** Preparations of ethers and esters in position 3 and 29 of GA.

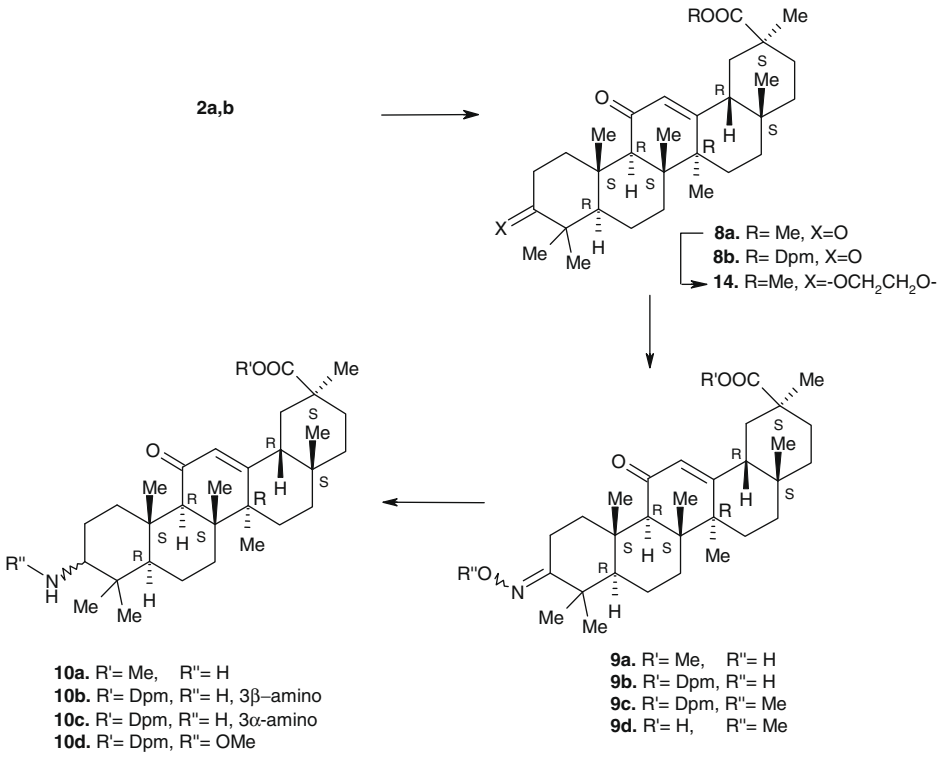



**Scheme 3.** C-29 modification.

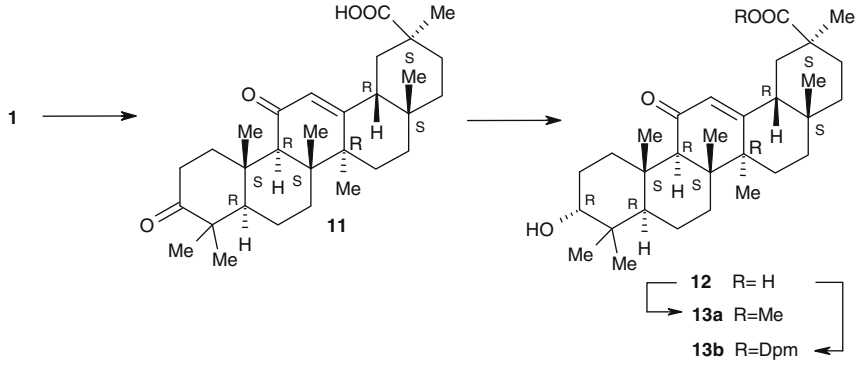
11α-GA **17** that could be separated as their corresponding esters. Pure epimers **18b** and **18c** were obtained in ratio 5:1 by reaction of **17** with diphenyldiazomethane followed by purification via column chromatography. Methylation of **17** with diazomethane with excess reagent gives **19**, methylated at positions C-11 and C-29, whereas treatment with 1 equiv gives the methylester **18a** selectively.

The crude mixture of **17** can be dehydrated to heteroannular diene **22** by refluxing in a mixture of $CH_3COOH$ and HCl or, via **20**, in THF with catalytic amounts of HCl present, followed by methylation with diazomethane to obtain **21**. The synthesis of 18α-GA **23** from 18β-GA **1** has been reported under acid or alkaline[33] conditions. The latter were used by us and the 18α-GA esters were prepared by treatment with diphenyldiazomethane or diazomethane to give **24** or **25**.

A diverse set of amides **26a**–**26j** was synthesized by activation of the carboxylic acid moiety at the 29-position and reaction with a range of amines (Scheme 7). Syntheses were performed classi-




**Scheme 4.** C-3 oximes and amines formation.




**Scheme 5.** Inversion of configuration at C-3.

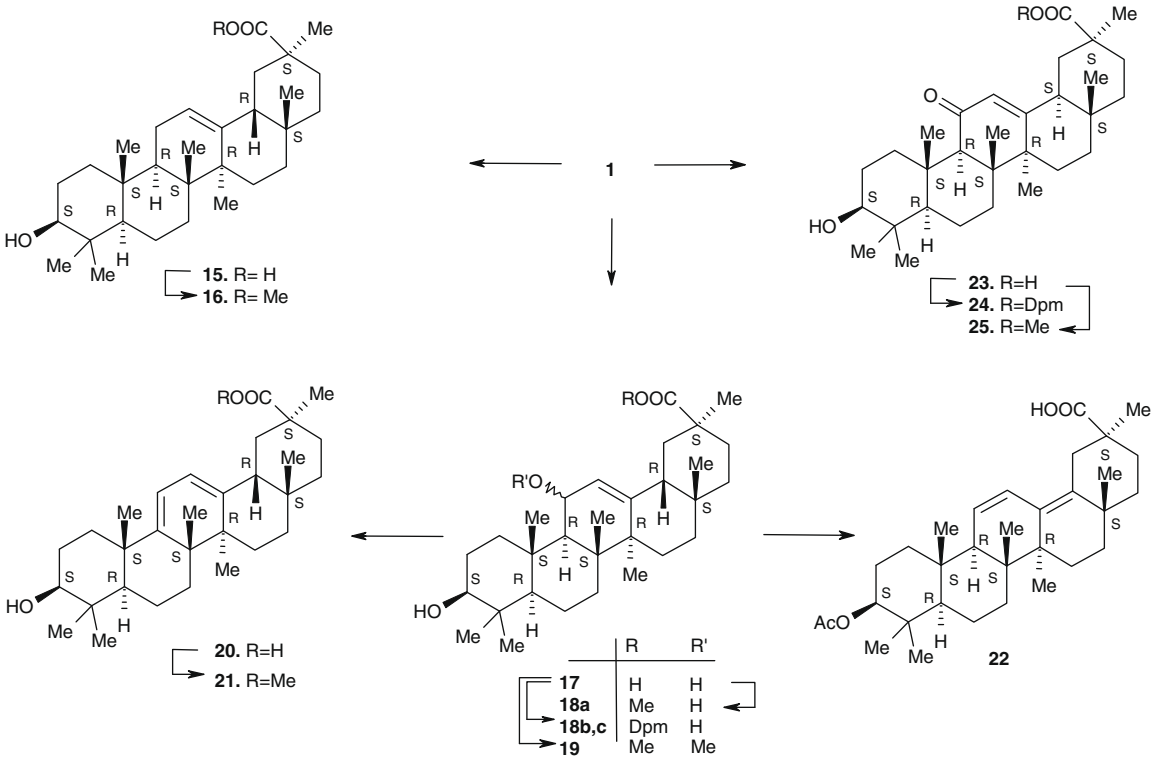
cally with DCC or using the water soluble EDAC as the activating agents.

### 2.1. 11β-HSD activity assays

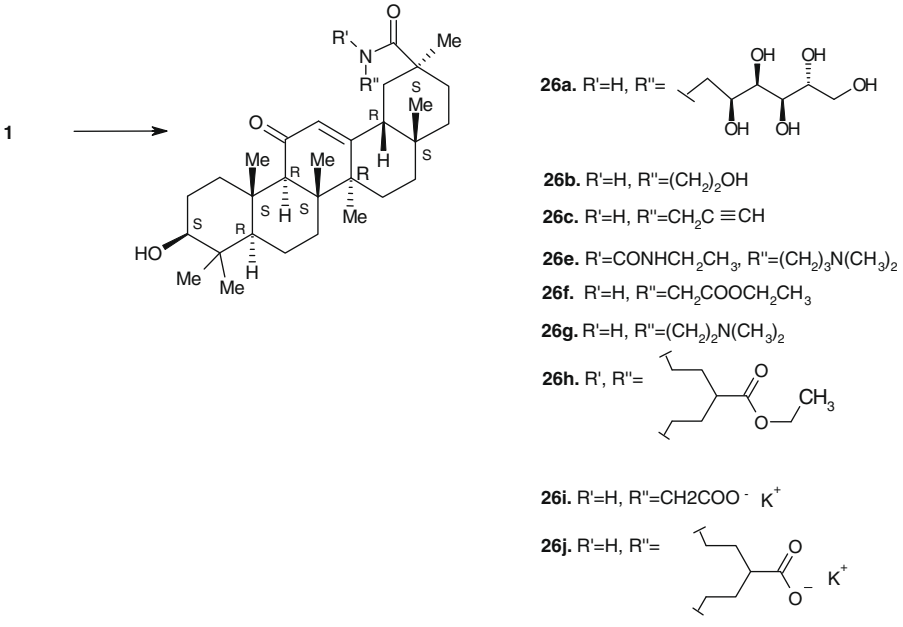
Recombinant human 11β-HSD1 and 11β-HSD2 were expressed in HEK-293 cells that are devoid of endogenous expression of these enzymes.[35] Activities were determined in cell lysates basically as described before.[36] Briefly, 11β-HSD1 dependent reduction of [1,2-3*H*]-labelled cortisone (American Radiolabeled Chemicals, St. Louis, MO) to cortisol was measured for 10 min at 37 °C in a volume of 22 μl containing a final concentration of 200 nM cortisone and 500 μM NADPH. 11β-HSD2 dependent oxidation of cortisol to cortisone was measured similarly using [1,2,6,7-3*H*]-cortisol (Amersham Pharmacia, Piscataway, NJ, USA) at a final concentration of 50 nM and NAD+ (500 μM). 18β-GA and its derivatives at final concentrations between 50 nM and 20 μM were diluted from stock solutions in dimethylsulfoxide and immediately used for activity assays. The solvent concentration did not exceed 0.1% and had no effect on enzyme activities. Reactions were stopped by adding methanol containing 2 mM unlabeled cortisone and cortisol, followed by separation of steroids by TLC and scintillation counting. Enzyme kinetics was analyzed by non-linear regression using four parameter logistic curve fitting (Sigmaplot, Systat Software Inc.). Data (mean ± SD) were obtained from three independent experiments.

### 2.2. Synthesis and biological results

18β-GA **1** has been reported to show potent and non-selective inhibition of both isozymes of 11β-HSD. Shimoyama et al. reported lower $IC_{50}$ value for rat hepatic 11β-HSD1 extract (90 ± 2 nM) compared to rat renal 11β-HSD2 extract (360 ± 2 nM).[37] Potter and coworkers reported 85% inhibition of rat 11β-HSD1 and complete inhibition of rat 11β-HSD2 at an inhibitor concentration of 10 μM of 18β-GA **1**.[30,38,39] We evaluated the inhibitory activity of 18β-




**Scheme 6.** Various reductions of GA.




**Scheme 7.** Amides formation.

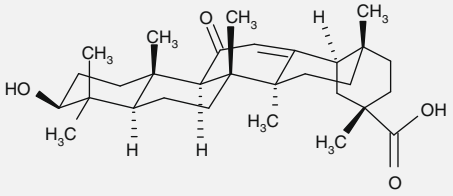
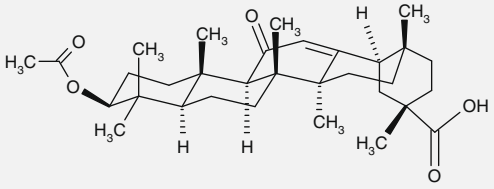
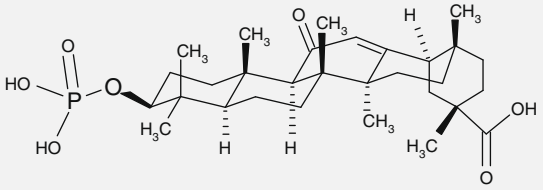
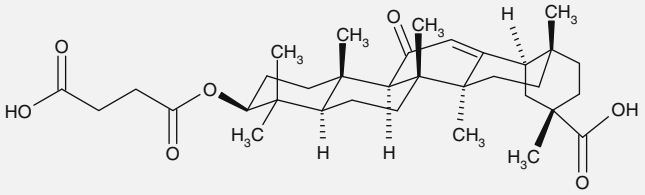
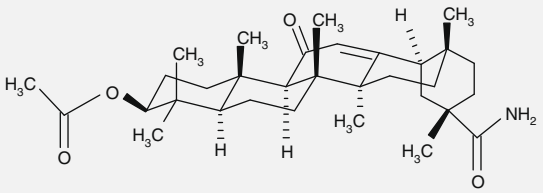
GA **1** and its derivatives against recombinant human 11β-HSD1 and 11β-HSD2. Using a tenfold lower inhibitor concentration (1 μM), we observed an inhibition of 83.9% for human 11β-HSD1 and 93.6% for human 11β-HSD2 for **1**. The licensed drug carbenoxolone **3d** has comparable potency with 87.7% inhibition of 11β-HSD1 and 98.2% inhibition of 11β-HSD2. Although the 18α-derivative has a lower inhibitory potency for 11β-HSD1, it is selective and does not inhibit 11β-HSD2 in concentrations up to 20 μM.[40] By contrast, the natural product glycyrrhizin **GL** has lower inhibitory activity for 11β-HSD1 (63.2%), and especially for 11β-HSD2 (28.1%). Because the lead compounds **1** and **3d** show maximal inhibition of 11β-HSD1 at 1 μM synthesized derivatives were also screened at a concentration of 1 μM against 11β-HSD1 and 11β-HSD2.

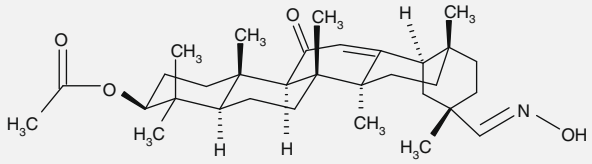
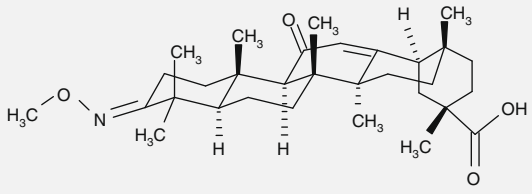
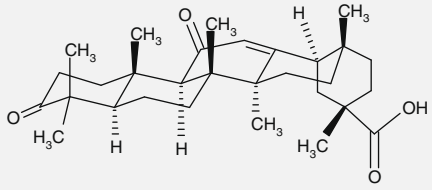
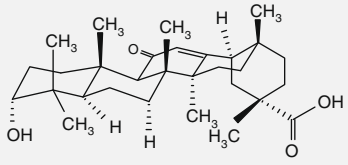
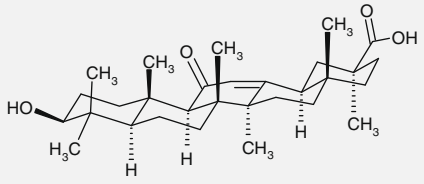
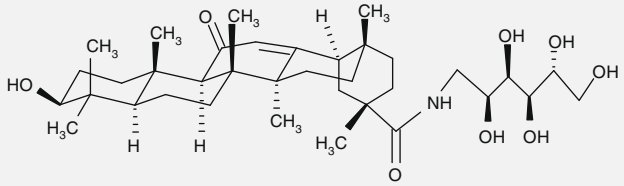
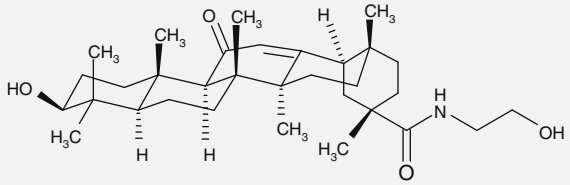
Based on the fact, that activity was conserved when sugar moieties or succinic acid are introduced in position 3, additional deriv-

atives with a modification in that position were synthesized and tested for 11β-HSD1 inhibition. The 3-acetate **3a** has already been suggested as an inhibitor for 11β-HSD isozymes based on a pharmacophore model[41] and was found to be weakly active on 11β-HSD1. The compound does not have the second carboxylic acid function of the carbenoxolone derivative but retains the hydrogen bond acceptor function. The 3-phosphate **3c**, however, is as active as the carbenoxolone derivative, even though the acidic functionality is not attached with a spacer of three carbon atoms. Due to the good activity of **3c**, we also tested its 11β-HSD2 activity of that derivative but could not find a better selectivity compared to carbenoxolone **3d**. On the other hand, **3a** had a weak selectivity for 11β-HSD2.

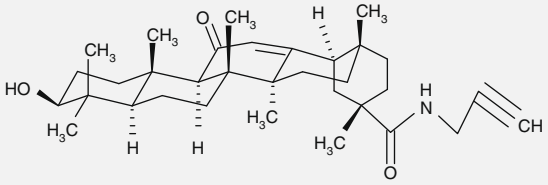
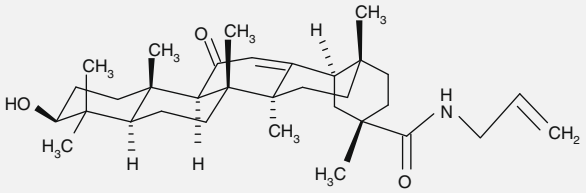
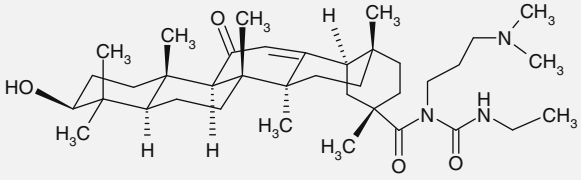
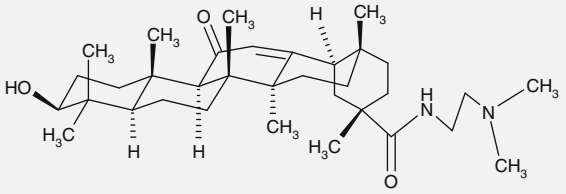
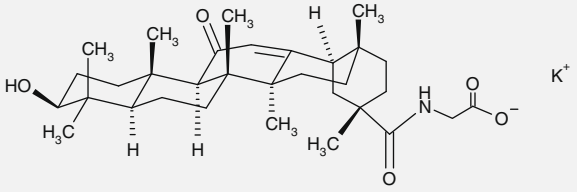
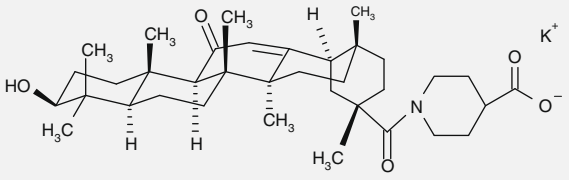
The oxidation of the 3β-hydroxy group to the ketone **11** and the conversion to the *O*-methyloxime **9d** reduced the activity on 11β-HSD1. However, the reduction of ketone **11** to the diastereomeric 3α-hydroxy derivative **12** of the lead compound **1** resulted in excellent inhibition of 11β-HSD1. Therefore, we also tested upon inhibition of the other isozyme and found a comparable inhibition of both enzymes.

Not only the modification in position 3 but also the reduction of position 11 to the deoxo derivate **15** and the inversion of configuration at position 18 to 18α-glycyrrhetinic acid **23** led to a moderate loss in activity. Modification of position 29 to the free amide **5c** let to a compound with comparable activity as **1**, whereas the oxime **7** had significantly reduced activity. Also, secondary amide modifications of the carboxylic acid function in position 29 resulting in compounds **26a–e, 26g, 26i,j** led to a moderate to significant reduction in inhibitory potency against human 11β-HSD1 and also 11β-HSD2.

| Compound | | % Inhibition of human 11β-HSD1 at 1 μM (±SD) | % Inhibition of human 11β-HSD2 at 1 μM (±SD) |
|---|---|---|---|
| **1** |  | 91.2 (±3.1) | 99.9 (±1.2) |
| **3a** |  | 47.1 (±9.2) | 85.7 (±1.3) |
| **3c** |  | 86.0 (±1.7) | 94.6 (±1.0) |
| **3d** |  | 87.7 (±4.4) | 98.2 (±0.9) |
| **5c** |  | 90.9 (±5.3) | 86.9 (±0.7) |

| Compound | | % Inhibition of human 11β-HSD1 at 1 μM (±SD) | % Inhibition of human 11β-HSD2 at 1 μM (±SD) |
|---|---|---|---|
| **7** |  | 43.3 (±17.4) | 59.8 (±7.3) |
| **9d** |  | 63.2 (±16.2) | 97.5 (±0.7) |
| **11** |  | 63.8 (±11.5) | 98.7 (±1.6) |
| **12** |  | 97.4 (±1.9) | 97.0 (±1.6) |
| **23** |  | 49.7 (±15.1) | 49.3 (±1.4) |
| **26a** |  | −12.9 (±17.9) | 3.4 (±9.1) |
| **26b** |  | 2.9 (±4.6) | 40.7 (±19.4) |

(*continued on next page*)

| Compound | | % Inhibition of human 11β-HSD1 at 1 μM (±SD) | % Inhibition of human 11β-HSD2 at 1 μM (±SD) |
|---|---|---|---|
| **26c** |  | 10.1 (±5.6) | −13.1 (±15.6) |
| **26d** |  | 6.2 (±0.8) | −22.5 (±4.7) |
| **26e** |  | 32.5 (±9.8) | 14.8 (±11.8) |
| **26g** |  | 36.0 (±19.0) | 41.1 (±4.8) |
| **26i** |  | 2.7 (±6) | 21.4 (±0.7) |
| **26j** |  | 19.5 (±4.9) | −28.6 (±2.8) |

### 2.3. X-ray crystal structure analyses

Seven crystal structures of compounds of the present study were investigated with X-ray single crystal diffraction, namely glycyrrhetinic acid (**1**) in the form of the solvate **1**·DMSO and two esters of **1** (**2a**·solv where solv is disordered acetone/ethanol; **2b**), the 3-methoxyamino derivative **10d**, and three derivatives (**15**·DMSO, **19**, and **20**) with modifications in the unsaturated ring C (see below). This was done partly to provide support for their chemical structures and partly to learn about the changes introduced by altering the backbone of the parent compound. Technical details of this work are given at the end of the experimental section and in Table 1, selected structural diagrams are shown in Figures 1–4. Glycyrrhetinic acid consists of five six-membered rings with two trans-configured, one cis-configured and one singly unsaturated ring–ring-fusion. Four of the five rings (A, B, D, and E) adopt chair conformations, whereas ring C with one C=C and one C=O double bond adopts a half chair conformation. The molecule is relatively rigid, but shows a limited flexibility that finds expression in some bending along the long axis of the molecule, which is in part

**Table 1**
Details for the crystal structure determinations of **1**·DMSO, **2a**·solv, **2b**, **10d**, **15**·DMSO, **19**, and **20**

| | **1**·DMSO | **2a**·Solv | **2b** | **10d** | **15**·DMSO | **19** | **20** |
|---|---|---|---|---|---|---|---|
| Formula | $C_{32}H_{52}O_5S$ | $C_{32}H_{54}O_4S$[a] | $C_{43}H_{56}O_4$ | $C_{44}H_{59}NO_4$ | $C_{31}H_{48}O_4S$ | $C_{32}H_{52}O_4$ | $C_{30}H_{46}O_3$ |
| fw | 548.80 | 484.69[a] | 636.88 | 665.92 | 534.81 | 500.74 | 454.67 |
| Crystal system | Monoclinic | Hexagonal | Monoclinic | Orthorhombic | Monoclinic | Orthorhombic | Monoclinic |
| Space group | $P2_1$ (no. 4) | $P6_5$ (no. 170) | $P2_1$ (no. 4) | $P2_12_12_1$ (no. 19) | $P2_1$ (no. 4) | $P2_12_12_1$ (no. 19) | $C2$ (no. 5) |
| $a$ (Å) | 13.0687(9) | 26.8604(7) | 13.0784(7) | 7.4426(3) | 12.9717(5) | 7.1475(3) | 36.205(4) |
| $b$ (Å) | 6.4997(4) | 26.8604(7) | 7.1969(4) | 20.4774(9) | 6.5050(3) | 12.4992(5) | 6.7089(7) |
| $c$ (Å) | 18.2299(12) | 7.0894(4) | 20.3287(12) | 24.0381(11) | 18.3846(7) | 31.3422(13) | 25.815(3) |
| $\beta$ (°) | 105.808(1) | 90 | 108.404(1) | 90 | 106.131(1) | 90 | 123.593(2) |
| $V$ (Å$^3$) | 1489.93(17) | 4429.6(3) | 1815.55(18) | 3663.5(3) | 1490.23(11) | 2800.1(2) | 5223.2(9) |
| $T$ (K) | 100 | 100 | 173 | 100 | 100 | 100 | 100 |
| $Z$ | 2 | 6 | 2 | 4 | 2 | 4 | 8 |
| $\rho_{calcd}$ (g cm$^{-3}$) | 1.223 | 1.090[a] | 1.165 | 1.207 | 1.192 | 1.188 | 1.156 |
| $\mu$ (mm$^{-1}$) (Mo K$\alpha$) | 0.147 | 0.070[a] | 0.073 | 0.076 | 0.143 | 0.076 | 0.072 |
| $F$(000) | 600 | 1596[a] | 692 | 1448 | 588 | 1104 | 2000 |
| $\theta$ range (°) | 2.4–30.0 | 2.3–27.0 | 3.0–30.0 | 2.6–30.0 | 2.3–30.0 | 2.5–30.0 | 2.9–30.5 |
| No. of rflns measd | 21,935 | 53,231 | 26,753 | 29,332 | 21,999 | 41,155 | 22,121 |
| $R_{int}$ | 0.014 | 0.043 | 0.025 | 0.024 | 0.013 | 0.025 | 0.033 |
| No. of rflns unique | 8500 | 6380 | 5664 | 10,669 | 8415 | 8128 | 14,314 |
| No. of rflns $I > 2\sigma(I)$ | 8292 | 5584 | 5312 | 9810 | 8279 | 7823 | 11,180 |
| No. of params/constr. | 352/1 | 324/1 | 433/1 | 453/0 | 343/1 | 334/0 | 613/1 |
| $R_1$ ($F^2 > 2\sigma(F^2)$)[b] | 0.0351 | 0.1014 | 0.0449 | 0.0492 | 0.0337 | 0.0446 | 0.0513 |
| $R_1$ (all data) | 0.0358 | 0.1104 | 0.0477 | 0.0537 | 0.0342 | 0.0463 | 0.0748 |
| $wR_2$ ($F^2 > 2\sigma(F^2)$) | 0.0902 | 0.2660 | 0.1113 | 0.1173 | 0.0863 | 0.1111 | 0.1184 |
| $wR_2$ (all data) | 0.0908 | 0.2761 | 0.1139 | 0.1213 | 0.0869 | 0.1123 | 0.1314 |
| Flack abs.str. param. | 0.00(4) | 1(2) | 0.2(9) | −0.2(7) | 0.02(3) | 0.3(7) | −0.1(8) |
| Diff. four peaks min/max (e Å$^{-3}$) | −0.17/0.50 | −0.32/0.70 | −0.16/0.38 | −0.15/0.45 | −0.25/0.45 | −0.17/0.47 | −0.26/0.53 |

[a] Disordered solvate of acetone/ethanol disregarding the unknown solvent content.
[b] $R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$; $wR_2 = \{\Sigma[w(F_o^2 - F_c^2)^2]/\Sigma[w(F_o^2)^2]\}^{1/2}$.

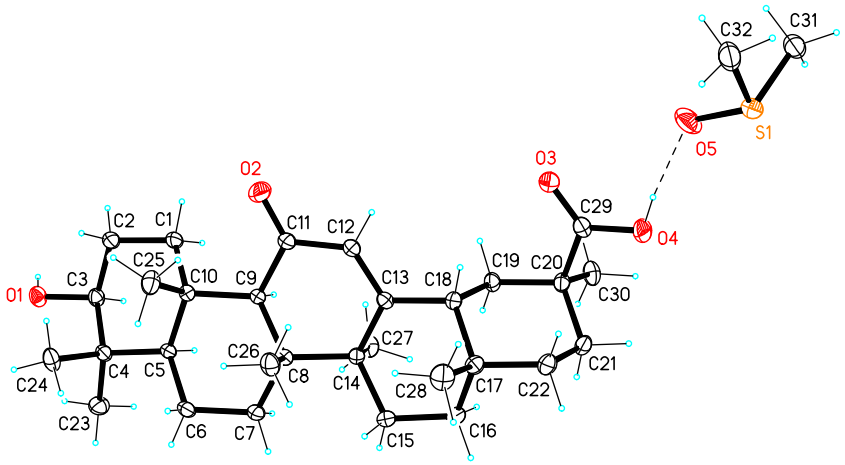



**Figure 1.** Molecular structure of **1**·DMSO in the crystalline state showing the hydrogen bond to the DMSO molecule, O4···O5 = 2.62 Å.

attributable to distance mismatches between the carbon backbone and the three neighbouring methyl groups C24, C25, and C26. These three methyl groups show C24–C25 and C25–C26 contact distances of 3.2 Å, whereas the corresponding C–C distances of their carrier atoms in the ring system, C4–C10 and C10–C8, are distinctly shorter (ca. 2.65 Å). As the result, the molecule shows some kind of bending in the region of the A+B+C rings. A further result of steric congestion between the three methyl groups of C24, C25, and C26 is that the orientation of the methyl group C25H$_3$ relative to the quaternary carbon C10 is not eclipsed but halfway between staggered and eclipsed, showing for instance in **1**·DMSO a C–C–C–H torsion angle of 28°. The molecular structure of glycyrrhetinic acid in the form of its DMSO solvate is shown in Figure 1. Glycyrrhetinic acid is known to crystallize in the form of a variety of solvates of which by now the crystal structures of the solvates with acetone+H$_2$O and MeOH were reported.[42,43] Characteristically, in the solvates of glycyrrhetinic acid both the COOH and the alcoholic OH group are involved in hydrogen bonds, for example, in the DMSO solvate, where the O1–H1 group donates a hydrogen bond to the C=O oxygen O3, the O4–H4 group donates a hydrogen bond to the DMSO oxygen O5, and the keto oxygen O2 is inactive. In order to achieve this, the lipophilic part of glycyrrhetinic forms stacks of molecules with a head to tail arrangement of the OH and the COOH group (Fig. 2). This arrangement is favourable because it separates polar and apolar parts of the molecule and is in a related fashion also found in the acetone–H$_2$O solvate.[42] Remarkably, the crystals of **1**·DMSO and **15**·DMSO are practically isostructural, where **15**·DMSO having in 11-position a CH$_2$ group instead of a C=O group in **1**·DMSO (Table 1). Returning in this context to the conformation of glycyrrhetinic acid derivatives studied in the present work, it is shown in Figure 4 that their cores exhibit only modest variations in shape. This indicates that changed

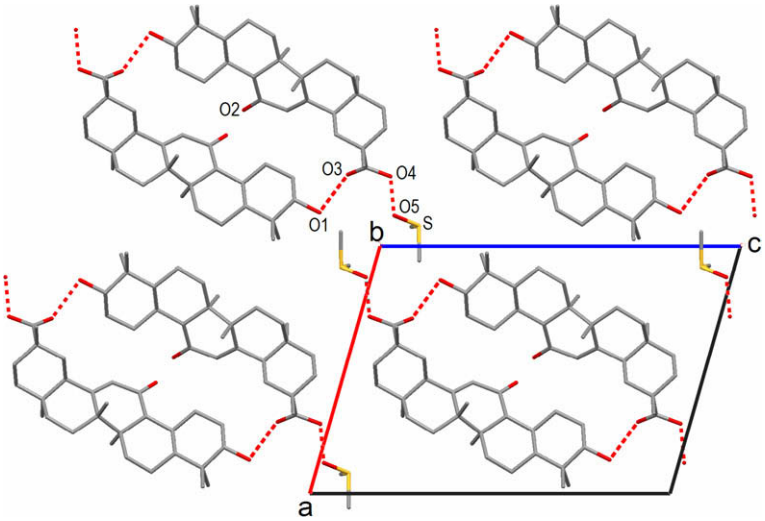



**Figure 2.** Packing diagram of **1**·DMSO viewed along *b*-axis. Broken red lines are the hydrogen bonds O1 → O3 and O4 → O5. **1**·DMSO is in principle isostructural with **15**·DMSO (C11=O2 group replaced by $C11H_2$).

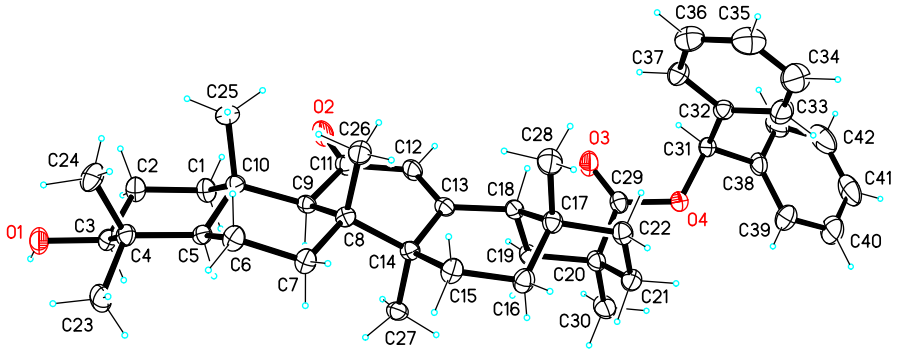



**Figure 3.** Molecular structure of **2b** in the crystalline state.

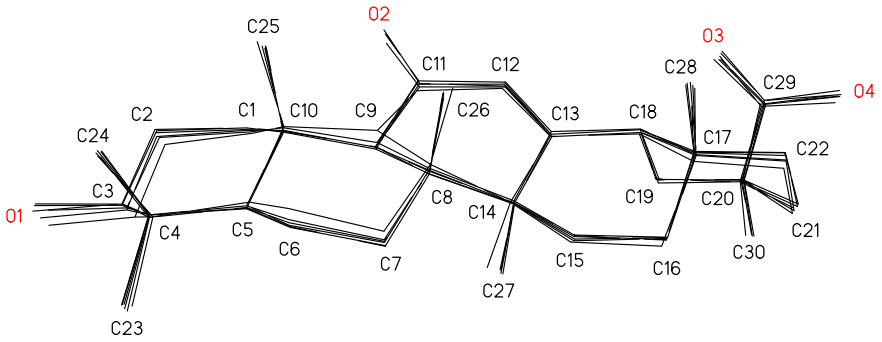



**Figure 4.** Superposition plots of the mutually least-squares fitted glycerrhetinic acid moieties of the crystalline compounds **1**·DMSO, **2a**·solv, **2b**, **10d**, **15**·DMSO, **19**, and **20** (hydrogen atoms and substituting groups omitted for clarity). Note the outlier compound **20**, which mismatches clearly the rest of the compounds for carbon atoms C9, C8, C7, C6, C3, and C2.

hybridization of the C-ring atoms, from $sp^2$ for C11 (**1**, **2a**, **2b**, **10d**) to $sp^3$ (**15**, **19**), has little effects on the molecular conformation of the glycyrrhetinic acid backbone, and that intermolecular forces of crystal packing have comparable effects. The only outlier in this respect is compound **20**, which has a cyclohexadiene structure for the C-ring, which causes by a $sp^3$ to $sp^2$ transition of C10 a more pronounced conformational effect to be seen particularly well at C9, Figure 4.

## 3. Experimental

All solvents were purified and dried by standard procedures. Melting points were measured on a Büchi B-545 melting point apparatus. $^1H$ and $^{13}C$ NMR spectra were recorded on a Bruker AC 200 (200 MHz) and AC 400 (400 MHz) pulse Fourier-transform NMR spectrometer in $CDCl_3$ or DMSO-$d_6$. Chemical shifts are reported relative to the resonance of tetramethylsilane (TMS) or

corresponding solvent peak. Infrared spectra were recorded on a BIORAD ATR-FT-IR spectrometer as solutions in DCM or MeOH. Absorbance peak maxima are given in $\nu$ ($cm^{-1}$). For thin layer chromatography (TLC), Merck TLC aluminum sheets (Silica 60 F254, 0.25 mm) were used. Visualization was by UV light at 254 and 366 nm or spray reagents (molybdophosphoric acid, mixture of molybdophosphoric acid and $Ce^{IV}$ ammonium nitrate or ninhydrine and heating). Compounds were purified by MPLC (medium pressure liquid chromatography) using preparative silica gel (40–63 mm) columns. HPLC was performed using a Waters 2695 instrument with Merck Chromolith RP18 columns and a gradient of 3–60% acetonitrile and water containing HCOOH 0.1% at a flow of 1.0–3.0 mL/min. Preparative LC was performed using a Waters instrument with Merck Geminy RP18 columns and a gradient of 3–60% acetonitrile and water containing HCOOH 0.1% at a flow of 25 mL/min. The HPLC reported purity is the number generated for the peak area as calculated using the Waters Millennium software with the Maxplot option for the UV maximum of the corresponding peak. Mass spectra were measured on a JEOL DX-300. The HRMS positive ionisation mode displayed a $[M+1]^+$ ion corresponding to the elementar formula.

### 3.1. (3β,18β,20β)-3-Hydroxy-11-oxo-olean-12-en-29-oic acid methyl ester (2a)

Compound **1** (20.0 g, 42.5 mmol) was placed into DCM (100 mL) and $Et_2O$ (100 mL) and transferred into a diazomethane apparatus. Diazomethane was added slowly until complete esterification was apparent on TLC. When diazomethane was gone, the solvent was evaporated. The crude product was crystallized from MeOH (500 mL) to give **2a** as colorless crystals (17.1 g, 83%, HPLC >99%). Mp 250–251 °C (Ref. 44: 245–248.5 °C); $[\alpha]_D^{20}$ +161.8 ($c$ 1, $CHCl_3$) (Ref. 44: +161.1°). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 5.65 (s, 1H, 12-H), 3.70 (s, 3H, 31-H), 3.24 (dd, $J$ = 10.7, 5.7 Hz, 1H, 3-H), 2.81 (d, $J$ = 13.7 Hz, 1H, 1-H), 2.35 (s, 1H, 9-H), 2.13–1.78 (m, 5H, 15-H, 16-H, 18-H, 19-H, 21-H), 1.70–1.58 (m, 5H, 2-H, 6-H, 7-H, 19-H), 1.52–1.03 (m, 6H, 6-H, 7-H, 15-H, 16-H, 21-H, 22-H), 1.38 (s, 3H, 27-H), 1.23–1.13 (m, 1H), 1.16 (s, 3H, 30-H), 1.15 (s, 3H, 25-H), 1.14 (s, 3H, 26-H), 1.07–0.99 (m, 2H, 1-H), 1.02 (s, 3H, 23-H), 0.81 (s, 3H, 24-H), 0.80 (s, 3H, 28-H), 0.74–0.69 (m, 1H, H-5); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 200.3 (C-11), 177.0 (C-29), 169.2 (C-13), 128.6 (C-12), 78.7 (C-3), 61.8 (C-9), 54.9 (C-5), 51.8 (C-31), 48.4 (C-18), 45.4 (C-8), 44.1 (C-20), 43.2 (C-14), 41.1 (C-19), 39.1 (C-4), 39.1 (C-1), 37.7 (C-22), 37.0 (C-10), 32.7 (C-7), 31.8 (C-17), 31.1 (C-21), 28.5 (C-28), 28.4 (C-30), 28.1 (C-23), 27.3 (C-2), 26.4 (C-16), 26.4 (C-15), 23.4 (C-27), 18.7 (C-26), 17.5 (C-6), 16.4 (C-25), 15.6 (C-24). IR (DCM) $\nu$: 3350, 2949, 2871, 1725, 1656, 1455, 1389, 1220, 1193, 1158, 1088, 1042, 996. MS-CI, $m/z$ ($I_{rel.}$ (%)): 484.98 [M] (100); 485.99 (36); 135.05 (15); 177.99 (11); 292.98 (11); 188.98 (10); 174.98 (9); 482.97 (8); 316.88 (7); 483.96 (7).

### 3.2. (3β,18β,20β)-3-Hydroxy-11-oxo-olean-12-en-29-oic acid diphenylmethyl ester (2b)

Glycyrrhetinic acid **1** (90.0 g, 192 mmol) in MeOH (500 mL) was heated to 45 °C and a solution of diphenyldiazomethane (113.0 g, 573 mmol) in $Et_2O$ (600 mL) was added slowly until complete esterification was apparent on TLC. The solvent was evaporated at reduced pressure and the crude product was filtered through a short pad of silica, the solvent was evaporated and the crude compound crystallized from a mixture of $Et_2O$ (250 mL)–pentane (800 mL) to yield diphenylmethyl ester **2b** as colorless crystals (108.0 g, 87%, HPLC >99%). Mp 182.5–183.5 °C; $[\alpha]_D^{20}$ +140 ($c$ 0.2, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.41–7.21 (m, 10H, arom), 6.95 (s, 1H, 31-H), 5.54 (s, 1H, 12-H), 3.28–3.18 (m, 1H, 3-H), 2.80 (dd, $J$ = 13.5, 3.5 Hz, 1H, 18-H), 2.33 (s, 1H, 9-H), 2.08–1.88 (m, 3H, 1-H, 16-H, 21-H), 1.87–0.89 (m, 15H, 1-H, 2-H, 6-H, 7-H, 15-H, 16-H, 19-H, 21-H, 22-H), 1.35 (s, 3H, 30-H), 1.17 (s, 3H, 27-H), 1.13 (s, 3H, 25-H), 1.09 (s, 3H, 26-H), 1.00 (s, 3H, 23-H), 0.81–0.65 (m, 1H, 5-H), 0.80 (s, 3H, 24-H), 0.66 (s, 3H, 28-H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 200.1 (C-11), 175.2 (C-29), 168.9 (C-13), 140.1 (C-Ar), 140.1 (C-Ar), 128.6 (C-Ar), 128.6 (C-Ar), 128.5 (C-Ar), 128.5 (C-Ar), 128.1 (C-12), 127.8 (C-Ar), 127.3 (C-Ar), 127.3 (C-Ar), 127.0 (C-Ar), 127.0 (C-Ar), 78.7 (C-3), 76.6 (C-31), 61.8 (C-9), 54.9 (C-5), 48.1 (C-18), 45.3 (C-14), 44.0 (C-8), 43.1 (C-20), 41.1 (C-19), 39.2 (C-1), 39.1 (C-4), 37.5 (C-22), 37.1 (C-10), 32.7 (C-7), 31.7 (C-17), 31.2 (C-21), 28.3 (C-30), 28.3 (C-28), 28.1 (C-23), 27.3 (C-2), 26.4 (C-16), 26.4 (C-15), 23.3 (C-27), 18.7 (C-26), 17.5 (C-6), 16.4 (C-25), 15.6 (C-24). IR (DCM) $\nu$: 3744, 3624, 3057, 2980, 2941, 2871, 1725, 1665, 1459, 1424, 1389, 1312, 1212, 1166, 1158, 1034, 992, 961, 911, 895. MS-CI, $m/z$ ($I_{rel.}$ (%)): 167.04 (100); 637.01 [M+1] (34); 638.05 (16); 168.05 (13); 181.92 (11); 183.86 (7); 427.18 (6); 182.99 (5); 639.06 (4); 425.11 (4).

### 3.3. (3β,18β,20β)-3-Hydroxy-11-oxo-olean-12-en-29-oic acid ethyl ester (2c)

A solution of **1** (1.00 g, 2.1 mmol) in anhydrous DMF (50 mL) containing anhydrous $K_2CO_3$ (2.90 g, 21.2 mmol) was stirred for 24 h at rt, then poured into brine and extracted with EtOAc (3 × 200 mL). The organic phase was washed with water (3 × 100 mL), dried over $MgSO_4$, filtered and evaporated in vacuo to give a white solid. The crude product was subjected to $SiO_2$ chromatography eluting with PE–EtOAc (5–30% gradient elution) to give **2c** as a white solid (0.45 g, 42.5%, HPLC >99%). Mp 104–105 °C (Ref. 51: 93–94 °C); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 5.63 (s, 1H), 4.18–4.10 (m, 2H), 3.22 (dd, $J$ = 10.8, 5.4 Hz, 1H), 2.72 (dd, $J$ = 13.3, 3.5 Hz, 1H), 2.33 (s, 1H), 2.13–1.78 (m, 5H), 1.70–1.58 (m, 6H), 1.52–1.24 (m, 8H), 1.35 (s, 3H), 1.23–1.13 (m, 1H), 1.13 (s, 3H), 1.13 (s, 3H), 1.11 (s, 3H), 1.05–0.98 (m, 2H), 0.99 (s, 3H), 0.81 (s, 3H), 0.79 (s, 3H), 0.74–0.67 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 200.2, 176.4, 169.3, 128.5, 78.7, 61.8, 60.3, 54.9, 48.4, 45.4, 43.8, 43.1, 41.0, 39.1, 37.6, 37.6, 37.1, 32.7, 31.8, 31.1, 28.5, 28.3, 28.1, 27.3, 26.5, 26.4, 23.4, 18.6, 17.5, 16.3, 15.6, 14.3. IR (DCM) $\nu$: 3385, 3053, 2972, 2941, 2871, 1721, 1656, 1621, 1459, 1389, 1362, 1324, 1216, 1173, 1154, 1088, 1042, 996, 949, 922, 899, 880.

### 3.4. (3β,18β,20β)-3-Hydroxy-11-oxo-olean-12-en-29-oic acid allyl ester (2d)

To a solution of **1** (10.0 g, 21.3 mmol) in DMSO (150 mL) at 20 °C was added powdered KOH (2.07 g, 27.6 mmol) and during 10 min allyl bromide (3.6 g, 29.7 mmol). The reaction mixture was stirred for 24 h at rt (monitored by TLC), poured into ice-water (250 mL) and extracted with $CHCl_3$ (3 × 250 mL). The combined organic phases was washed with water (2 × 100 mL), dried ($MgSO_4$), filtered, evaporated and purified by MPLC (solvent system: DCM–MeOH gradient elution 0–3%) to get 8.4 g of product. The thus obtained crude product was finally purified by recrystallization from hot methanol (400 mL) to give **2d** as a white crystalline compound (7.5 g, 69%, HPLC >99%). Mp 208–210 °C. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 6.00–5.80 (m, 1H), 5.62 (s, 1H), 5.37–5.19 (m, 2H), 4.61–4.52 (m, 2H), 3.26–3.14 (m, 1H), 2.77 (dd, $J$ = 13.4, 3.4 Hz, 1H), 2.32 (s, 1H), 2.08–1.86 (m, 4H), 1.73–1.50 (m, 7H), 1.46–1.26 (m, 5H), 1.35 (s, 3H), 1.22–1.08 (m, 1H), 1.15 (s, 3H), 1.11 (s, 3H), 1.10 (s, 3H), 1.06–0.86 (m, 2H), 0.98 (s, 3H), 0.79 (s, 6H), 0.73–0.63 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 200.2, 176.0, 169.2, 132.2, 128.5, 118.4, 78.7, 65.0, 61.8, 54.9, 48.3, 45.3, 44.0, 43.2, 41.0, 39.1, 37.7, 37.0, 32.7, 31.8, 31.1, 28.5, 28.3, 28.1, 27.4, 26.4, 26.4, 23.3, 18.6, 17.4, 16.3, 15.5. IR (DCM) $\nu$: 3740, 3501, 2937, 2871, 1729,

1656, 1621, 1540, 1459, 1389, 1362, 1328, 1316, 1212, 1154, 1085, 1042, 984, 934, 922, 880, 830. MS-CI, *m*/*z* ($I_{rel.}$ (%)): 511.20 [M+1] (100); 512.17 (35); 513.16 (8); 510.25 (4); 135.22 (3); 514.18 (2); 175.13 (2); 189.14 (2); 319.13 (2); 343.09 (2).

### 3.5. (3β,18β,20β)-3-Hydroxy-11-oxo-olean-12-en-29-oic acid benzyl ester (2e)

A solution of glycyrrhetinic acid (10.0 g, 21.0 mmol) in anhydrous DMF (250 mL) containing anhydrous $K_2CO_3$ (29.0 g, 212.0 mmol) was stirred at rt under $N_2$ for 1 h. Benzyl bromide (40.0 g, 234.0 mmol) was added to the reaction mixture followed by tetrabutylammonium iodide (2.0 g, 5.5 mmol). The mixture was stirred for 24 h at room temperature, poured into brine and extracted with EtOAc (3 × 200 mL). The combined organic phases was washed with water (3 × 100 mL), dried over $Na_2SO_4$, filtered and evaporated in vacuo to give a yellow resin. Purification by flash chromatography (PE–EtOAc gradient elution, 5–35%) yielded benzyl ester **2e** as a white solid (5.5 g, 46%, HPLC >99%). Mp 129–130 °C (Ref. 45: 131–133); $[\alpha]_D^{20}$ +141.5 (*c* 0.018, $CHCl_3$) (Ref. 45: 137.5°). $^1$H NMR (400 MHz, $CDCl_3$) δ 7.42–7.33 (m, 5H), 5.56 (s, 1H), 5.22 (d, *J* = 13.3 Hz, 1H), 5.10 (d, *J* = 13.2 Hz, 1H), 3.24 (dd, *J* = 10.7, 5.7 Hz, 1H), 2.80 (dd, *J* = 13.4, 3.2 Hz, 1H), 2.33 (s, 1H), 2.07–1.96 (m, 3H), 1.82 (d, *J* = 4.1 Hz, 1H), 1.69–1.59 (m, 5H), 1.56–1.49 (m, 1H), 1.40–1.29 (m, 3H), 1.36 (s, 3H), 1.20–1.12 (m, 1H), 1.18 (s, 3H), 1.15 (s, 3H), 1.12 (s, 3H), 1.04–0.96 (m, 2H), 1.02 (s, 3H), 0.91–0.84 (m, 1H), 0.82 (s, 3H), 0.75 (s, 3H), 0.73–0.69 (d, *J* = 10.3 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 200.18, 176.22, 169.05, 136.12, 128.62, 128.52, 128.31, 128.25, 78.75, 66.23, 61.78, 54.92, 48.20, 45.35, 43.99, 43.17, 41.07, 39.14, 37.65, 37.06, 32.75, 31.78, 31.17, 28.43, 28.30, 28.11, 27.30, 26.47, 26.39, 23.36, 18.66, 17.49, 16.38, 15.60. IR (DCM) *v*: 3744, 3605, 3057, 2983, 2941, 2871, 1721, 1656, 1459, 1424, 1389, 1212, 1166, 1154, 1085, 1038, 992, 895. MS-CI, *m*/*z* ($I_{rel.}$ (%)): 561.12 [M+1] (100); 562.12 (42); 563.12 (10); 107.93 (9); 560.13 (7); 427.20 (7); 425.20 (2); 106.16 (2); 574.45 (2); 566.73 (2).

### 3.6. (3β,18β,20β)-3-(Acetyloxy)-11-oxo-olean-12-en-29-oic acid (3a)

Glycyrrhetinic acid (10.0 g, 21.3 mmol) was heated under reflux with $Ac_2O$ (160 mL, 1.7 mol) for 1.5 h. AcOH (20 mL) and $H_2O$ (40 mL) were then added to the still hot solution. The product, which crystallized upon cooling was filtered off and washed with cold $H_2O$ (4 × 50 mL) and $Et_2O$ (15 mL) and dried in vacuo to give *O*-acetyl **3a** as a white solid (10.5 g, 96.4%, HPLC >99%). Mp 310–313 °C (Ref. 46: 319–321 °C); $[\alpha]_D^{20}$ +163.3 (*c* 1, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$) δ 5.73 (s, 1H), 4.53 (dd, *J* = 11.5, 5.2 Hz, 1H), 2.80 (d, *J* = 13.9 Hz, 1H, 2.38 (s, 1H), 2.19 (d, *J* = 13.1 Hz, 1H), 2.07 (s, 3H), 2.06–1.55 (m, 12H), 1.48–1.02 (m, 7H), 1.38 (s, 3H), 1.24 (s, 3H), 1.18 (s, 3H), 1.14 (s, 3H), 0.89 (s, 6H), 0.85 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 200.4, 181.8, 171.1, 169.6, 128.4, 80.6, 61.7, 55.0, 48.2, 45.4, 43.8, 43.1, 40.8, 38.7, 38.0, 37.7, 36.9, 32.7, 31.8, 30.8, 28.5, 28.4, 28.0, 26.4, 26.3, 23.5, 23.3, 21.3, 18.6, 17.3, 16.6, 16.3. MS-CI, *m*/*z* ($I_{rel.}$ (%)): 513.12 [M+1] (100); 514.15 (34); 469.22 (7); 515.14 (7); 191.14 (5); 189.08 (4); 135.00 (4); 175.09 (3); 262.04 (3); 303.07 (3).

### 3.7. (3β,18β,20β)-3-[(Trimethylsilyl)oxy]-11-oxo-olean-12-en-29-oic acid (3b)

To a solution of glycyrrhetinic acid (0.65 g, 1.38 mmol) in dry pyridine (25 mL) were added hexamethyldisilazane (1.11 g, 6.91 mmol) and trimethylsilyl chloride (0.75 g, 6.91 mmol). The mixture was allowed to stand for 3 h under nitrogen atmosphere. After the mixture had been cooled, the solid was collected by filtration and dried to give **3b** as a white solid (0.41 g, 54%, HPLC >97%). Mp 260–261 °C (Ref. 2: 244–246 °C). $^1$H NMR (400 MHz, $CDCl_3$) δ 5.73 (s, 1H), 3.22 (dd, *J* = 11.5, 4.5 Hz, 1H), 2.76 (d, *J* = 13.3 Hz, 1H), 2.36 (s, 1H), 2.20 (d, *J* = 10.6 Hz, 1H), 2.07–1.97 (m, 2H), 1.90–1.81 (m, 1H), 1.68–1.59 (m, 3H), 1.49–1.38 (m, 5H), 1.39 (s, 3H), 1.31–1.21 (m, 2H), 1.25 (s, 3H), 1.19–1.13 (m, 1H), 1.16 (s, 3H), 1.14 (s, 3H), 1.08–1.01 (m, 2H), 0.91 (s, 3H), 0.85 (s, 3H), 0.79 (s, 3H), 0.73–0.67 (m, 1H), 0.12 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 200.7, 181.9, 169.5, 128.5, 79.5, 61.9, 55.1, 48.3, 45.5, 43.8, 40.9, 39.5, 39.2, 39.1, 37.7, 37.1, 32.8, 31.9, 30.9, 28.6, 28.5, 28.1, 27.6, 26.5, 26.4, 23.4, 18.7, 17.7, 16.5, 16.1, 0.51. +1, *m*/*z* ($I_{rel.}$ (%)): 543.27 [M] (100); 544.18 (35); 453.41 (12); 545.14 (10); 615.02 (7); 454.45 (5); 90.04 (5); 452.61 (4); 191.19 (4); 471.48 (4).

### 3.8. (3β,18β,20β)-3-[(Phosphono)oxy]-11-oxo-olean-12-en-29-oic acid (3c)

A mixture of glycyrrhetinic acid (2.0 g, 4.3 mmol) in dry pyridine (3.4 mL) and dry THF (20 mL) was added dropwise to a stirred solution of phosphorus oxychloride (1.36 mL, 14.6 mmol) in dry THF (40 mL), during 20 min. at 0 °C. The ice bath was removed and the reaction mixture was stirred additional 1.5 h at rt. The reaction mixture was then concentrated under reduced pressure. The residual oil was slowly poured into acidified cracked ice from 0.5 N HCl (20 mL). The solid part was separated by filtration and washed with cold water (2 × 50 mL). The crude product was dried 2 h under 7 mbar vacuum to yield crude dihydrogen phosphate **3c** as a white solid (2.5 g, 75%, HPLC ~60%). An analytical sample was purified by preparative LC (HPLC >99%). Mp 242–243 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) δ 5.41 (s,1H), 3.75 (m, 1H), 2.61 (d, 1H), 2.36 (s, 1H), 2.08–2.04 (m, 2H), 1.87–1.54 (m, 2H),1.51 (m, 1H), 1.40–1.20 (m, 5H), 1.35 (s, 3H), 1.16–0.84 (m, 3H), 1.09 (s, 3H), 1.04 (s, 3H), 1.03 (s, 3H), 0.94 (s, 3H), 0.83–0.66 (m, 4H), 0.75 (s, 3H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ 199.41, 178.12, 170.27, 127.69, 83.21, 83.15, 61.36, 54.41, 48.49, 45.29, 43.51, 43.36, 41.07, 38.97, 38.91, 38.49, 37.95, 36.85, 32.45, 31.96, 30.80, 28.82, 28.27, 26.51, 26.23, 25.13, 23.42, 22.53, 18.77, 17.55, 16.69, 16.61. IR (MeOH) *v*: 3365, 2950, 2875, 1702, 1656, 1563, 1544, 1463, 1389, 1328, 1212, 1177, 1019, 1000, 880, 841.

### 3.9. (3β,18β,20β)-3-(3-Carboxy-1-oxopropoxy)-11-oxo-olean-12-en-29-oic acid (3d)

A mixture of acid **1** (2.00 g, 4.25 mmol), succinic anhydride (2.13 g, 21.25 mmol) and DMAP (1.04 g, 8.50 mmol) in dry pyridine (50 mL) was refluxed for 24 h. After cooling, the mixture was acidified with 2 N HCl (300 mL) to pH ~3 and extracted with EtOAc (300 mL), the organic phase washed with cold water (150 mL) and dried over $Na_2SO_4$, filtered and the mixture was evaporated in vacuo to give a white powder. The crude product was crystallized from MeOH (20 mL) to give **3d** as a white solid (2.04 g, 83.8%, HPLC >99%). Mp 302–303 °C (Ref. 31: 313–315 °C); $^1$H NMR (400 MHz, DMSO-$d_6$) δ 5.15, 4.23–4.11 (m, 1H), 2.26–2.09 (m, 6H), 1.83–1.75 (m, 1H), 1.61–0.87 (m, 10H), 1.10 (s, 3H), 0.85–0.61 (m, 4H), 0.83 (s, 3H), 0.80 (s, 3H), 0.77 (s, 3H), 0.57–0.41 (m, 6H), 0.56 (s, 3H), 0.55 (s, 3H), 0.49 (s, 3H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ 200.6, 179.3, 175.1, 173.3, 171.5, 128.9, 81.4, 62.5, 55.4, 49.7, 46.5, 44.7, 44.6, 39.6, 39.3, 39.2, 38.2, 33.6, 33.2, 32.0, 30.9, 30.5, 30.1, 29.5, 29.3, 27.8, 27.5, 24.9, 24.7, 24.1, 20.0, 18.6, 18.2, 17.8. IR (DCM) *v*: 3740, 2956, 2871, 1729, 1660, 1497, 1455, 1386, 1362, 1328, 1312, 1208, 1154, 1081, 1030, 980, 965, 888. MS-CI, *m*/*z* ($I_{rel.}$ (%)): 453.00 (100); 167.03 (52); 454.00 (33); 469.73 (14); 135.01 (11); 189.04 (10); 135.96 (8); 234.92 (8); 168.01 (8); 409.07 (7).

### 3.10. (3β,18β,20β)-3-(4-Hydroxy-3,3-dimethyl-1,4-dioxobutoxy)-11-oxo-olean-12-en-29-oic acid (3e)

Compound **1** (1.00 g, 2.13 mmol) was heated with 2,2-dimethylsuccinic anhydride (1.09 g, 8.50 mmol) and DMAP (0.52 g, 4.25 mmol) in pyridine (60 mL) to reflux overnight. After cooling, the mixture was acidified with 2 N HCl (300 mL) to pH ~3 and extracted with EtOAc (300 mL), the organic phase washed with cold water (150 mL) and dried over $Na_2SO_4$, filtered and the mixture was evaporated in vacuo to give a white powder. Purification by flash chromatography (DCM/MeOH, gradient elution 0–5%) gave **3e** as a white solid (0.65 g, 50.9%, HPLC >98%). Mp 301–304 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 5.41 (s, 1H), 4.42 (dd, $J$ = 11.5, 4.5 Hz, 1H), 2.64 (m, 1H), 2.57–2.47 (m, 2H), 2.13–2.04 (m, 2H), 1.83–1.77 (m, 1H), 1.73–1.62 (m, 4H), 1.52–1.43 (m, 2H), 1.41–1.32 (m, 5H), 1.36 (s, 3H), 1.30–1.21 (m, 2H), 1.19–1.13 (m, 1H), 1.18 (s, 3H), 1.17 (s, 3H), 1.10 (s, 3H), 1.08–1.02 (m, 2H), 1.06 (s, 3H), 1.04 (s, 3H), 0.96 (d, $J$ = 10.7 Hz, 1H), 0.91–0.84 (m, 2H), 0.82 (s, 3H), 0.82 (s, 3H), 0.76 (s, 3H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$ 199.3, 178.2, 178.1, 171.0, 170.2, 127.7, 80.3, 61.3, 54.2, 48.5, 45.3, 44.4, 43.5, 43.4, 41.1, 40.6, 40.1, 39.3, 38.4, 38.0, 36.9, 32.4, 32.0, 30.8, 28.8, 28.3, 28.1, 26.5, 26.3, 25.8, 25.7, 23.6, 23.5, 18.8, 17.1, 16.6. IR (DCM) $v$: 3057, 2976, 2941, 2875, 1702, 1656, 1459, 1389, 1324, 1212, 1158, 1139, 992, 946, 895, 880. MS-CI, $m/z$ ($I_{rel.}$ (%)): 453.13 (100); 282.12 (68); 454.09 (33); 298.22 (16); 300.28 (14). 283.12 (12); 471.14 (12); 272.37 (10); 299.05 (10); 244.88 (9).

### 3.11. (3β,18β,20β)-3-(Acetyloxy)-11-oxo-olean-12-en-29-oyl chloride (4a)

Compound **3a** (3.0 g, 5.9 mmol) was added to thionyl chloride (7.0 g, 59 mmol) and the mixture was refluxed for 1 h. After evaporation of excess thionyl chloride, there was added dry toluene (30 mL). The mixture was evaporated in vacuo to give **4a** as a yellow powder (3.1 g, 99%). Mp 289–292 °C (Ref. 47: 297–303 °C). The crude product was used as such.

### 3.12. (3β,18β,20β)-3-(Acetyloxy)-11-oxo-olean-12-en-29-oic acid methyl ester (4b)

Compound **2a** (1.00 g, 2.06 mmol) was heated under reflux with $Ac_2O$ (20 mL, 211.60 mmol) for 1.5 h. The solvent was evaporated in vacuo and the crude product was purified by flash chromatography (PE–EtOAc gradient elution, 5–20%) to yield **4b** as a white solid (0.95 g, 87.4%, HPLC >99%). Mp 282.5–283.5 °C (Ref. 1: 300–301 °C); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 5.63 (s, 1H), 4.48 (dd, $J$ = 10.9, 5.6 Hz, 1H), 3.65 (s, 3H), 2.76 (dd, $J$ = 13.5, 3.4 Hz, 1H), 2.33 (s, 1H), 2.10–1.91 (m, 4H), 2.01 (s, 3H), 1.88–1.83 (m, 1H), 1.72–1.49 (m, 6H), 1.44–1.24 (m, 5H), 1.33 (s, 3H), 1.20–1.13 (m, 1H), 1.12 (s, 3H), 1.11 (s, 3H), 1.09 (s, 3H), 1.04–0.91 (m, 2H), 0.84 (s, 6H), 0.77 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 200.0, 176.9, 170.9, 169.2, 128.4, 80.6, 61.7, 55.0, 51.7, 48.4, 45.4, 44.0, 43.1, 41.0, 38.7, 38.0, 37.7, 36.9, 32.7, 31.8, 31.1, 28.5, 28.3, 28.0, 26.4, 26.4, 23.5, 23.3, 21.3, 18.6, 17.3, 16.7, 16.4. IR (DCM) $v$: 3740, 3057, 2956, 2875, 1729, 1656, 1621, 1459, 1436, 1389, 1366, 1320, 1250, 1216, 1193, 1158, 1088, 1030, 988, 899. MS-CI, $m/z$ ($I_{rel.}$ (%)): 526.98 [M+1] (100); 527.99 [M+1] (30); 467.02 (25); 189.01 (20); 135.01 (17); 191.04 (15); 499.02 (15); 292.94 (11); 135.93 (11); 175.01 (11).

### 3.13. (3β,18β,20β)-3-(Acetyloxy)-11-oxo-olean-12-en-29-oic acid diphenylmethyl ester (4c)

Compound **2b** (1.00 g, 1.57 mmol) was heated under reflux with $Ac_2O$ (25 mL, 264.50 mmol) for 50 min. The solvent was evaporated in vacuo and the crude product was crystallized from MeOH (20 mL) to give *O*-acetyl **4c** as a white solid (1.01 g, 94.7%, HPLC >99%). Mp 130–132 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.40–7.25 (m, 10H), 6.93 (s, 1H), 5.51 (s, 1H), 4.52 (dd, $J$ = 11.5, 5.2 Hz, 1H), 2.80 (dd, $J$ = 13.5, 3.4 Hz, 1H), 2.34 (s, 1H), 2.05 (s, 3H), 2.04–1.94 (m, 4H), 1.75–1.55 (m, 7H), 1.38–1.24 (m, 4H), 1.36 (s, 3H), 1.17 (s, 3H), 1.16 (s, 3H), 1.09 (s, 3H), 1.07–0.94 (m, 3H), 0.88 (s, 3H), 0.88 (s, 3H), 0.80 (d, $J$ = 9.5 Hz, 1H), 0.66 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 199.9, 175.2, 171.0, 168.9, 140.1, 140.0, 128.6, 128.6, 128.5, 128.5, 128.1, 128.1, 127.8, 127.3, 127.3, 127.0, 127.0, 80.6, 76.6, 61.7, 55.0, 48.1, 45.3, 44.0, 43.2, 41.1, 38.8, 38.0, 37.5, 36.9, 32.7, 31.7, 31.2, 28.3, 28.2, 28.0, 26.4, 26.3, 23.6, 23.3, 21.3, 18.7, 17.4, 16.7, 16.4. IR (DCM) $v$: 3740, 3057, 2956, 2871, 1729, 1683, 1656, 1621, 1559, 1540, 1455, 1389, 1366, 1320, 1212, 1150, 1085, 1030, 984, 899, 865. MS-CI, $m/z$ ($I_{rel.}$ (%)): 167.02 (100); 181.96 (38); 168.00 (16); 178.04 (14); 678.79 [M] (12); 513.00 (10); 183.02 (10); 679.83 (6); 183.90 (6); 165.03 (5). Anal. Calcd for $C_{45}H_{58}O_5$: C, 79.61; H, 8.61; O, 11.78. Found: C, 79.57; H, 8.57; O, 11.75.

### 3.14. (3β,18β,20β)-2-[(4-Methylphenyl)sulfonyl]hydrazide-3-(acetyloxy)-11-oxo-olean-12-en-29-oic acid (5a)

To a ice cold solution of tosylhydrazine (160 mg, 0.86 mmol) in dry pyridine (0.25 mL) there was slowly added a solution of **4a** (300 mg, 0.57 mmol) in dry THF (2 mL). The mixture was left standing for 24 h at rt, then poured into 5% HCl (4 mL). The aqueous solution was extracted with DCM (3 × 20 mL) and the organic layers were washed with water (10 mL), dried over $Na_2SO_4$, filtered and concentrated to dryness to obtain the crude product as white solid. Purification by flash chromatography (PE–EtOAc gradient elution, 10–50%) gave **5a** as a white solid (120 mg, 31%, HPLC >97%). Mp 245–246 °C (Ref. 48: 245 °C). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.62 (d, $J$ = 8.2 Hz, 2H), 7.31 (d, $J$ = 8.2 Hz, 2H), 5.62 (s, 1H), 4.52 (dd, $J$ = 11.6, 4.8 Hz, 1H), 2.79 (d, $J$ = 13.5 Hz, 1H), 2.41 (s, 3H), 2.35 (s, 1H), 2.07 (s, 3H), 2.00–1.89 (m, 1H), 1.87–1.55 (m, 9H), 1.49–1.38 (m, 2H), 1.34–1.28 (m, 1H), 1.32 (s, 3H), 1.27–1.18 (m, 2H), 1.18 (s, 3H), 1.14 (s, 3H), 1.15–1.05 (m, 1H), 1.04 (s, 3H), 0.96 (d, $J$ = 14.0 Hz, 2H), 0.89 (s, 3H), 0.89 (s, 3H), 0.81 (d, $J$ = 11.1 Hz, 1H), 0.69 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 200.3, 174.8, 171.1, 169.0, 144.8, 133.6, 129.7, 129.0, 128.6, 80.6, 61.7, 55.0, 47.5, 45.4, 43.1, 42.9, 40.5, 38.8, 38.0, 37.0, 36.9, 32.6, 31.6, 30.7, 29.2, 28.0, 28.0, 26.4, 26.3, 23.5, 23.4, 21.7, 21.3, 18.7, 17.4, 16.7, 16.4. IR (DCM) $v$: 3740, 3616, 3057, 2987, 2879, 1737, 1652, 1459, 1424, 1397, 1343, 1169, 1092, 1030, 984, 895. MS-CI, $m/z$ ($I_{rel.}$ (%)): 537.67 (100); 291.17 (67); 84.06 (46); 59.13 (41); 377.13 (39); 100.94 (20); 840.27 (17); 97.99 (9); 128.04 (9); 416.94 (9).

### 3.15. (3β,18β,20β)-29-Amino-11,29-dioxo-olean-12-en-3-yl acetate (5b)

A cold solution of **4a** (531 mg, 1.0 mmol) in dry DCM (20 mL) was slowly bubbled with gaseous $NH_3$. The mixture was stirred for 15 min and monitored by TLC, till completed. The reaction mixture was stirred additional 30 min. The organic layer was washed with water (20 mL), dried with $Na_2SO_4$ and the solvent was removed in vacuo to obtain **5b** as a white solid (490 mg, 95%, HPLC >96%). Mp 312–314 °C. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 6.12 (br, 2H), 5.68 (s, 1H), 4.52 (dd, $J$ = 11.6, 4.8 Hz, 1H), 2.78 (dd, $J$ = 13.5, 3.4 Hz, 1H), 2.35 (s, 1H), 2.23–2.17 (m, 1H), 2.05 (s, 3H), 2.00–0.99 (m, 17H), 1.36 (s, 3H), 1.19 (s, 3H), 1.15 (s, 3H), 1.12 (s, 3H), 0.91–0.78 (m, 1H), 0.87 (s, 3H), 0.86 (s, 3H), 0.83 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 200.1, 179.3, 171.0, 169.3, 128.5, 80.6, 61.7, 55.0, 48.1, 45.4, 43.2, 41.7, 38.8, 38.0, 37.4, 36.9, 36.9, 32.7, 31.9, 31.3, 29.5, 28.4, 28.0, 26.4, 26.4, 23.5, 23.3, 21.3, 18.7, 17.3,

16.7, 16.4. IR (DCM) *v*: 3362, 3203, 2366, 2335, 1725, 1656, 1617, 1459, 1389, 1366, 1328, 1208, 1142, 1088, 1030, 1000, 984, 903, 884, 865. MS-CI, *m*/*z* ($I_{rel.}$ (%)): 512.18 [M+1] (100); 527.54 (91); 528.54 (69); 526.36 (38); 513.21 (37); 511.22 (32); 523.98 (25); 521.93 (21); 529.21 (17); 510.2 (17).

### 3.16. (3β,18β,20β)-29-Hydrazino-11,29-dioxo-olean-12-en-3-yl acetate (5c)

To a cold solution of $NH_2NH_2{\cdot}H_2O$ (250 mg, 5.0 mmol) in dry THF (20 mL) was dropwise added **4a** (0.531 mg, 1 mmol) in dry THF (5 mL). The reaction mixture was stirred at rt for hour. The organic layer was washed with water (20 mL), dried with $Na_2SO_4$ and the solvent was removed in vacuo to obtain crude product. This was crystallizes from toluene–petrolether mixture to give **5c** as a white solid (250 mg, 47%, HPLC ~94%). Mp >175 °C. $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 5.60 (s, 1H), 4.49 (dd, *J* = 10.8, 5.3 Hz, 1H), 2.76 (d, *J* = 13.4 Hz, 1H), 2.32 (s, 1H), 2.10–0.98 (m, 20H), 2.03 (s, 3H), 1.35 (s, 3H), 1.20 (s, 3H), 1.13 (s, 3H), 1.09 (s, 3H), 0.85 (s, 6H), 0.78 (s, 3H); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 200.0, 178.8, 171.0, 169.1, 128.4, 80.6, 61.7, 55.0, 48.0, 46.7, 45.3, 43.2, 41.9, 41.1, 38.8, 38.0, 36.9, 32.7, 31.8, 29.6, 29.5, 28.4, 28.0, 26.4, 25.5, 23.5, 23.3, 21.3, 18.6, 17.3, 16.6, 16.4. IR (DCM) *v*: 3300, 2366, 2343, 1729, 1656, 1544, 1525, 1509, 1459, 1366, 1324, 1212, 1169, 1142, 1088, 1030, 984, 903, 880, 861. MS-CI, *m*/*z* ($I_{rel.}$ (%)): 567.17 (100); 568.18 (41); 469.15 (36); 527.14 (32); 467.14 (16); 528.14 (16); 113.08 (15); 543.30 (13); 566.20 (12); 58.06 (11).

### 3.17. (3β,18β,20β)-29-(Allylamino)-11,29-dioxo-olean-12-en-3-yl acetate (5d)

To a stirred solution of allylamine (90 mg, 1.6 mmol) and TEA (300 mg, 3 mmol) in DCM (25 mL) were added **4a** (531 mg, 1 mmol) in small portions. After stirring for 12 h at rt, the solution was extracted with 1 N HCl (3 × 10 mL) and water (1 × 10 mL) and sat. $NaHCO_3$ (1 × 10 mL). The organic layer was dried with $Na_2SO_4$ and the solvent was removed in vacuo to obtain crude product. This was crystallizes from EtOH (3 mL)–petrolether (24 mL) mixture to give **5d** as a white solid (230 mg, 42%, HPLC >97%). Mp 230–231 °C. $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 5.90 (br, 1H), 5.80 (m, 1H), 5.62 (s, 1H), 5.13 (m, 1H), 4.5 (m, 1H), 3.87 (m, 1H), 2.7 (m, 1H), 2.03 (m, 1H), 2.38–0.70 (m, 22H), 2.08 (s, 3H), 1.34 (s, 3H), 1.13 (s, 6H), 1.10 (s, 3H), 0.86 (s, 6H), 0.80 (s, 3H); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 199.9, 175.5, 170.9, 169.3, 134.5, 128.4, 116.3, 80.6, 61.7, 54.9, 48.1, 45.3, 43.6, 43.2, 41.9, 41.7, 38.7, 38.0, 37.4, 36.9, 32.6, 31.9, 31.4, 29.6, 28.4, 28.0, 26.4, 26.3, 23.4, 23.3, 21.2, 18.6, 17.3, 16.6, 163. IR (DCM) *v*: 3358, 2362, 2339, 1725, 1656, 1525, 1459, 1432, 1424, 1389, 1366, 1324, 1173, 1169, 1142, 1088, 1030, 984, 919, 880, 865. HRMS, *m*/*z*: 552.4044 [M+1] (calcd for $C_{35}H_{54}O_4N$, 552.4044).

### 3.18. (3β,18β,20β)-29-[(2-Aminoethyl)amino]-11,29-dioxo-olean-12-en-3-yl acetate (5e)

To a cold solution of **4a** (531 mg, 1.0 mmol) in dry DCM (20 mL) was slowly added a solution of ethane-1,2-diamine (600 mg, 10 mmol) in dry DCM (10 mL). The mixture was left for 24 h at rt. The organic layer was washed with water (10 mL), dried with $Na_2SO_4$ and the solvent was removed in vacuo to obtain crude product as white solid. Purification by flash chromatography (DCM–MeOH gradient elution, 1–5%) give **5e** as a white solid (250 mg, 45%, HPLC >98%). Mp >210 °C. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 6.92 (br, 1H), 5.57 (s, 1H), 3.47–3.34 (m, 4H), 3.23–3.18 (m, 1H), 2.64 (dd, *J* = 13.5, 3.4 Hz, 1H), 2.30–2.17 (m, 6H), 2.07–0.93 (m, 18H), 1.33 (s, 3H), 1.19 (s, 3H), 1.17 (s, 3H), 1.10 (s, 3H), 0.98 (s, 3H), 0.90–0.64 (m, 1H), 0.79 (s, 3H), 0.68 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 200.8, 180.2, 177.7, 165.8, 123.9, 78.6, 60.6, 54.9, 50.3, 45.3, 44.8, 44.2, 43.8, 43.5, 43.1, 42.6, 42.3, 40.5, 37.7, 39.0, 37.5, 37.0, 36.8, 35.4, 34.6, 31.9, 29.5, 28.2, 24.8, 23.7, 21.2, 19.2, 16.7, 16.3.

### 3.19. (3β,18β,20β)-3-(Acetyloxy)-11-oxo-olean-12-en-29-al (6)

Compound **5a** (1.00 g, 1.45 mmol) was heated in ethylene glycol (15 mL) to 160 °C. To this solution was quickly added $Na_2CO_3$ (0.47 g, 4.40 mmol). After a minute, the mixture was poured on ice (40 g), extracted with chloroform (3 × 60 mL), the combined organic layers dried over $Na_2SO_4$, filtered and evaporated in vacuo. The crude material was crystallized from MeOH (15 mL) to give **6** as a white solid (0.25 g, 36.4%). Mp 232–235 °C. $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 9.35 (s, 1H), 5.60 (s, 1H), 4.45 (dd, *J* = 11.6, 4.8 Hz, 1H), 2.73 (dd, *J* = 13.4, 3.2 Hz, 1H), 2.29 (s, 1H), 2.06–1.87 (2H), 1.98 (s, 3H), 1.86–1.64 (m, 4H), 1.63–1.45 (m, 5H), 1.40–1.22 (m, 4H), 1.32 (s, 3H), 1.19–1.02 (m, 2H), 1.09 (s, 3H), 1.05 (s, 3H), 1.03–0.94 (m, 1H), 0.91 (s, 3H), 0.81 (s, 3H), 0.81 (s, 3H), 0.79–0.72 (m, 1H), 0.73 (s, 3H); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 205.6, 199.9, 170.9, 168.6, 128.5, 80.6, 61.7, 55.0, 47.6, 46.8, 45.4, 43.2, 38.8, 38.3, 38.0, 37.1, 36.9, 32.6, 31.9, 28.4, 28.3, 28.0, 26.3, 26.1, 24.0, 23.6, 23.5, 21.3, 18.6, 17.3, 16.6, 16.4.

### 3.20. (3β,18β,20β)-3-Hydroxy-11-oxo-olean-12-en-29-al oxime (7)

To a cold solution of **6** (697 mg, 1.0 mmol) in dry pyridine (7 mL) was slowly added a solution of $NH_2OH{\cdot}HCl$ in dry pyridine (3 mL) and stirred for 12 h at rt. The reaction mixture was diluted with DCM (100 mL), washed with 10% HCl (3 × 50 mL) and water (50 mL). The combined organic layers were dried over $Na_2SO_4$, filtered and roto-evaporated to give **7** as a white solid (160 mg, 31%, HPLC ~95%). $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 7.19 (s, 1H), 5.57 (s, 1H), 4.49 (m, 1H), 2.70 (m, 1H), 2.35–0.65 (m, 21H), 1.98 (s, 3H), 1.30 (s, 3H), 1.15 (s, 3H), 1.09 (s, 3H), 0.98 (s, 3H), 0.80 (s, 6H), 0.75 (s, 3H); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 200.0, 171.1, 169.4, 156.7, 128.4, 80.6, 61.6, 55.0, 47.1, 45.4, 43.2, 41.3, 38.8, 38.0, 37.6, 36.9, 36.6, 32.6, 32.1, 31.9, 29.2, 28.4, 28.0, 26.4, 26.3, 23.5, 23.4, 21.3, 18.6, 17.3, 16.7, 16.4. Anal. Calcd for $C_{32}H_{49}NO_4$: C, 75.11; H, 9.65; N, 2.74. Found: C, 74.95; H, 9.82; N, 2.40.

### 3.21. (18β,20β)-3,11-Dioxo-olean-12-en-29-oic acid methyl ester (8a)

To a solution of **2a** (6.0 g, 12.4 mmol) in DCM (0.5 L) was added PCC (4.0 g, 18.6 mmol). The mixture was stirred for 2 h at rt, monitored by TLC. The mixture was diluted with $Et_2O$ (0.5 L) and filtered through a short pad (100 g) of silica. The pad was eluted once with $Et_2O$ (0.5 L), the combined eluates concentrated under vacuum and dried to give **8a** as colorless crystals (4.9 g, 82%). Mp 242–243 °C; (Ref. 49: 242 °C); $[\alpha]_D^{20}$ +182.1 (*c* 0.2, $CHCl_3$) (Ref. 49: 181.5°). $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 5.63 (s, 1H), 3.63 (s, 3H), 2.97–2.82 (m, 1H), 2.66–2.48 (m, 1H), 2.41–2.21 (m, 1H), 2.37 (s, 1H), 2.11–1.14 (m, 16H), 1.30 (s, 3H), 1.20 (s, 3H), 1.10 (s, 3H), 1.08 (s, 3H), 1.03 (s, 3H), 1.00 (s, 3H), 0.95–0.89 (m, 1H), 0.75 (s, 3H); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 217.1, 199.4, 176.9, 169.7, 128.4, 61.0, 55.4, 51.8, 48.4, 47.7, 45.2, 44.0, 43.3, 41.1, 39.7, 37.7, 36.7, 34.2, 32.1, 31.8, 31.1, 28.5, 28.3, 26.5, 26.4, 26.3, 23.3, 21.4, 18.8, 18.5, 15.6. IR (DCM) *v*: 3740, 3682, 3624, 3057, 2976, 2945, 2875, 1721, 1702, 1656, 1459, 1436, 1389, 1366, 1320, 1220, 1208, 1193, 1158, 1112, 1088, 1000, 980, 895. +1, *m*/*z* ($I_{rel.}$ (%)): 483.01 [M] (100); 484.02 (34); 485.04 (21); 499.11 (14). 97.15 (10); 498.16 (9); 135.03 (7); 482.09 (6); 486.05 (6); 189.07 (6).

### 3.22. (18β,20β)-3,11-Dioxo-olean-12-en-29-oic acid diphenylmethyl ester (8b)

To a solution of **2b** (8.0 g, 10 mmol) in DCM (600 mL) was added PCC (4.0 g, 15 mmol). After stirring for 3.5 h at 40–45 °C (conversion was checked by TLC for completeness of turnover), the mixture was filtered through a short pad (100 g) of silica. The pad was eluted once with $Et_2O$ (0.8 L)). The combined eluates were concentrated on a rotavapor to give **8b** as a white solid (7.7 g, 96%, HPLC >97%). Mp 103–104 °C. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.45–7.22 (m, 10H), 6.95 (s, 1H), 5.57 (s, 1H), 3.03–2.95 (m, 1H), 2.71–2.61 (m, 1H), 2.44 (s, 1H), 2.42–2.35 (m, 1H), 2.11–2.01 (m, 3H), 1.88–1.78 (m, 1H), 1.75–1.53 (m, 4H), 1.48–1.26 (m, 7H), 1.39 (s, 3H), 1.29 (s, 3H), 1.25–1.18 (m, 1H), 1.20 (s, 3H), 1.15 (s, 3H), 1.12 (s, 3H), 1.09 (s, 3H), 1.05–0.98 (m, 1H), 0.70 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 217.3, 199.4, 175.2, 169.4, 140.1, 140.0, 128.7, 128.7, 128.5, 128.5, 128.4, 128.2, 127.9, 127.2, 127.2, 127.0, 127.0, 76.7, 61.0, 55.4, 48.1, 47.8, 45.2, 44.0, 43.3, 41.2, 39.8, 37.5, 36.7, 34.3, 32.1, 31.8, 31.2, 28.4, 28.2, 26.5, 26.4, 26.4, 23.3, 21.5, 18.8, 18.5, 15.7. IR (DCM) $\nu$: 3740, 2980, 2945, 2871, 1729, 1702, 1656, 1621, 1494, 1459, 1389, 1362, 1212, 1154, 1112, 1085, 1030, 1000, 980, 915, 749. MS-CI, $m/z$ ($I_{rel.}$ (%)): 167.00 (100); 181.97 (94); 79.98 (84); 177.98 (47); 199.56 (35); 194.52 (20); 182.98 (19); 168.09 (16); 468.99 (13); 183.90 (10); 200.80 (10); 180.03 (8); 105.01 (8); 634.81 [M] (7). Anal. Calcd for $C_{43}H_{54}O_4$: C, 81.35; H, 8.57. Found: C, 81.08; H, 8.25.

### 3.23. (18β,20β)-3-(Hydroxyimino)-11-oxo-olean-12-en-29-oic acid methyl ester (9a)

A solution of **8a** (4.0 g, 8.3 mmol) and $NH_2OH.HCl$ (2.9 g, 41.4 mmol) in dry pyridine (30 mL) were heated for 2.5 h at 50 °C. After cooling to rt, the reaction mixture was diluted with DCM (300 mL) and washed with 10% HCl (3 × 150 mL). The combined organic layers were dried and concentrated on a rotavapor to give **9a** as colorless crystals (3.8 g, 92%, HPLC >99%). Mp 284–285 °C. $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 5.61 (s, 1H), 3.62 (s, 3H), 3.07–2.94 (m, 1H), 2.88–2.75 (m, 1H), 2.31 (s, 1H), 2.30–2.22 (m, 1H), 2.15–1.69 (m, 6H), 1.67–1.31 (m, 8H), 1.27 (s, 3H), 1.24–1.16 (m, 2H), 1.19 (s, 3H), 1.11 (s, 3H), 1.08 (s, 3H), 1.08 (s, 3H), 1.15–0.89 (m, 2H), 1.02 (s, 3H), 0.74 (s, 3H); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 199.8, 176.9, 169.4, 166.9, 128.4, 61.3, 55.6, 51.8, 48.4, 45.3, 44.0, 43.2, 41.1, 40.5, 39.1, 37.7, 37.0, 32.4, 31.8, 31.1, 28.5, 28.3, 27.1, 26.4, 26.4, 23.3, 23.2, 18.6, 18.2, 17.2, 15.7. IR (DCM) $\nu$: 3300, 2362, 1729, 1660, 1459, 1389, 1366, 1316, 1277, 1216, 1189, 1158, 1115, 1088, 1050, 1027, 992, 946, 930, 880, 834, 803. MS-CI, $m/z$ ($I_{rel.}$ (%)): 498.16 [M+1] (100); 499.13 (47); 482.26 (27); 485.18 (16); 83.23 (12). 500.12 (12); 497.07 (8); 486.31 (6); 484.23 (6); 480.26 (6).

### 3.24. (18β,20β)-3-(Hydroxyimino)-11-oxo-olean-12-en-29-oic acid diphenylmethyl ester (9b)

A solution of **8b** (4.0 g, 6.3 mmol) and $NH_2OH.HCl$ (2.2 g, 31.5 mmol) in dry pyridine (30 mL) was heated for 2.5 h at 50 °C. After cooling to rt, the reaction mixture was diluted with DCM (400 mL), washed with 10% HCl (3 × 150 mL) and water (50 mL). The combined organic layers were dried over $Na_2SO_4$, filtered and roto-evaporated to give **9b** as a white solid (4.0 g, 98%, HPLC ~99%). Mp 215–216 °C. $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 7.40–7.27 (m, 10H), 6.94 (s, 1H), 5.54 (s, 1H), 3.08 (dd, $J$ = 15.8, 4.3 Hz, 1H), 2.96–2.86 (m, 1H), 2.37 (s, 1H), 2.34–2.23 (m, 1H), 2.11–1.93 (m, 4H), 1.88–1.72 (m, 2H), 1.68–1.52 (m, 4H), 1.42–1.50 (m, 2H), 1.39–1.24 (m, 3H), 1.35 (s, 3H), 1.26 (s, 3H), 1.20 (s, 3H), 1.18 (s, 3H), 1.14–1.03 (m, 3H), 1.12 (s, 3H), 1.10 (s, 3H), 0.68 (s, 3H); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 199.7, 175.2, 169.2, 167.2, 140.1, 140.0, 128.6, 128.6, 128.5, 128.5, 128.1, 127.8, 127.3, 127.0, 127.0, 126.8, 126.8, 76.6, 61.2, 55.6, 48.1, 45.3, 44.0, 43.2, 41.1, 40.5, 39.0, 37.5, 37.1, 32.4, 31.7, 31.1, 28.3, 28.2, 27.1, 26.4, 26.3, 23.3, 23.2, 18.6, 18.2, 17.4, 15.5. IR (DCM) $\nu$: 3740, 3620, 3061, 2983, 2941, 2875, 1729, 1656, 1459, 1424, 1389, 1316, 1212, 1154, 1085, 1015, 984, 922, 895, 733. MS-CI, $m/z$ ($I_{rel.}$ (%)): 167.04 (100); 650.01 (24). 182.01 (18); 168.04 (14); 651.02 (14); 440.09 (13); 648.83 (11); 183.81 (9); 183.03 (8); 441.05 (7). Anal. Calcd for $C_{43}H_{55}NO_4$: C, 79.47; H, 8.53; N, 2.16. Found: C, 79.28; H, 8.34; N, 1.88.

### 3.25. (18β,20β)-3-(Methoxyimino)-11-oxo-olean-12-en-29-oic acid diphenylmethyl ester (9c)

A solution of **8b** (4.0 g, 6.3 mmol) and O-methylhydroxylamine hydrochloride (2.63 g, 31.5 mmol) in dry pyridine (30 mL) was heated for 2.5 h at 50 °C. After cooling to room temperature the reaction mixture was diluted DCM (400 mL), washed with 10% HCl (3 × 100 mL) and water (50 mL). The combined organic layers were dried over $Na_2SO_4$, filtered and roto-evaporated to give **9c** as a white solid (4.0 g, 95.6%, HPLC >98%). Mp 105–110 °C. $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 7.33–7.15 (m, 10H), 6.86 (s, 1H), 5.44 (s, 1H), 3.73 (s, 3H), 2.93–2.69 (m, 2H), 2.27 (s, 1H), 2.23–2.07 (m, 1H), 2.06–1.85 (m, 4H), 1.66–1.47 (m, 4H), 1.37–1.20 (m, 4H), 1.26 (s, 3H), 1.17–1.02 (m, 2H), 1.15 (s, 3H), 1.09 (s, 3H), 1.09 (s, 3H), 1.04 (s, 3H), 1.01–0.85 (m, 3H), 0.98 (s, 3H), 0.59 (s, 3H); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 199.7, 175.2, 169.0, 165.7, 140.1, 140.0, 128.6, 128.6, 128.5, 128.5, 128.1, 127.8, 127.3, 127.3, 127.0, 127.0, 76.6, 61.3, 61.0, 55.6, 48.1, 45.3, 44.0, 43.2, 41.1, 40.1, 39.1, 37.5, 36.9, 32.4, 31.7, 31.2, 28.3, 28.2, 27.3, 26.4, 26.4, 23.5, 23.3, 18.6, 18.2, 17.7, 15.6. IR (DCM) $\nu$: 3740, 3057, 2980, 2945, 2871, 2821, 1729, 1656, 1621, 1494, 1459, 1389, 1366, 1328, 1312, 1212, 1162, 1150, 1085, 1050, 984, 915, 880, 826. MS-CI, $m/z$ ($I_{rel.}$ (%)): 664.17 [M+1] (100); 167.05 (88); 665.15 (44); 454.18 (29); 182.02 (29); 168.13 (15); 452.21 (13); 183.13 (11); 666.15 (11); 199.53 (9). HRMS, $m/z$: 664.4352 [M+1] calcd for $C_{44}H_{58}O_4N$, 664.4366.

### 3.26. (18β,20β)-3-(Methoxyimino)-11-oxo-olean-12-en-29-oic acid (9d)

Preparation as described for **9c**. Crystallization from MeOH gives product **9d** as a white solid (93.2%, HPLC >98%). $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 5.73 (s, 1H), 3.80 (s, 3H), 3.02–2.70 (m, 2H), 2.38 (s, 1H), 2.30–2.08 (m, 2H), 2.07–1.73 (m, 4H), 1.71–1.28 (m, 8H), 1.35 (s, 3H), 1.25–0.93 (m, 5H), 1.23 (s, 3H), 1.22 (s, 3H), 1.17 (s, 3H), 1.15 (s, 3H), 1.05 (s, 3H), 0.84 (s, 3H); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 200.2, 182.1, 169.8, 165.8, 128.3, 61.3, 61.0, 55.6, 48.2, 45.4, 43.8, 43.2, 40.8, 40.1, 39.0, 37.7, 36.9, 32.4, 31.8, 30.8, 28.5, 28.4, 27.2, 26.4, 26.4, 23.4, 23.3, 18.6, 18.2, 17.7, 15.6. MS-CI, $m/z$ ($I_{rel.}$ (%)): 498.16 [M+1] (100); 499.15 (33); 454.26 (17); 500.21 (7); 452.24 (6); 455.29 (5); 466.23 (3); 453.26 (2); 482.23 (2); 122.01 (2).

### 3.27. (3β,18β,20β)-3-Amino-11-oxo-olean-12-en-29-oic acid methyl ester (10a)

NaOAc (2.64 g, 32.2 mmol) was added portion wise to a $TiCl_3$ solution (10.30 g of 12% in 10% HCl) and allowed to stand for 1 h. The solution was diluted with water (2 mL) and bubbled with argon for 5 min. The solution was added dropwise to a solution of oxime **9a** (1.00 g, 2.0 mmol) and $BH_3{\cdot}t$BuNH$_2$ (0.43 g, 5.0 mmol) in EtOH (20 mL) at 0 °C. The reaction mixture was allowed to come to rt and stirred for 12 h. The reaction was monitored by TLC. The reaction mixture was poured to a brine solution (150 mL) and stirred for 10 min. This mixture was extracted with EtOAc

(3 × 100 mL), washed with $NaHCO_3$, brine, dried with $Na_2SO_4$, filtered and evaporated under vacuum to obtain the white solid. The crude product was subjected to $SiO_2$ chromatography eluting with $CHCl_3$/MeOH+1%AcOH (0–20%) to give **10a** as a white solid (0.85 g, 87.5%, HPLC >95%). $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 5.65 (s, 1H), 3.70 (s, 3H), 3.24 (dd, $J$ = 10.7, 5.7 Hz, 1H), 2.81 (d, $J$ = 13.7 Hz, 1H), 2.35 (s, 1H), 2.13–1.78 (m, 5H), 1.70–1.58 (m, 6H), 1.52–1.03 (m, 5H), 1.38 (s, 3H), 1.23–1.13 (m, 1H), 1.16 (s, 3H), 1.15 (s, 3H), 1.14 (s, 3H), 1.07–0.99 (m, 2H), 1.02 (s, 3H), 0.81 (s, 3H), 0.80 (s, 3H), 0.74–0.69 (m, 1H); $^{13}C$ NMR (200 MHz, $CDCl_3$) $\delta$ 200.3, 177.0, 169.2, 128.6, 78.6, 61.8, 54.9, 51.8, 48.4, 45.4, 44.1, 43.2, 41.1, 39.1, 39.1, 37.7, 37.1, 32.7, 31.8, 31.1, 28.5, 28.4, 28.1, 27.3, 26.5, 26.4, 23.4, 18.7, 17.5, 16.4, 15.6.

### 3.28. (3β,18β,20β)-3-Amino-11-oxo-olean-12-en-29-oic acid diphenylmethyl ester (10b)

$NaBH_3CN$ (8.32 g, 132.0 mmol) was added to a mixture of **9b** (4.0 g, 6,2 mmol) and $NH_4OAc$ (7.73 g, 100.0 mmol) in MeOH (400 ml) under argon atmosphere. The solution was chilled in ice-water and $TiCl_3$ (23 mL, 15% in $H_2O$) was added dropwise over 20 min. The mixture was stirred at room temperature for 12 h and then adjusted with 2 N NaOH to pH 10. The aqueous solution was extracted with DCM (3 × 300 mL) and the combined organic layers were washed with water, dried over $Na_2SO_4$, filtered and concentrated to dryness to obtain the crude product as white solid. The crude product was subjected to $SiO_2$ chromatography eluting with $CHCl_3$/MeOH+1%AcOH (0–20%) to give **10b** as a white solid (2.1 g, 54%, HPLC >99%). Mp 232–235 °C; $[\alpha]_D^{20}$ +129.8 ($c$ 1.0, $CHCl_3$). $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.40–7.28 (m, 10H, Arom.), 6.95 (s, 1H, 31-H), 5.53 (s, 1H, 12-H), 2.78 (dd, $J$ = 13.5, 3.4 Hz, 1H, 1-H), 2.42–2.31 (m, 1H, 3-H), 2.36 (s, 1H, 9-H), 2.10–1.94 (m, 4H, 16-H, 18-H, 19-H, 21-H), 1.87–1.75 (m, 1H, 15-H), 1.74–1.00 (m, 13H, 1-H, 2-H, 6-H, 7-H, 15-H, 16-H, 19-H, 21-H, 22-H), 1.38 (s, 3H, 27-H), 1.19 (s, 3H, 30-H), 1.14 (s, 3H, 25-H), 1.11 (s, 3H, 26-H), 0.98 (s, 3H, 23-H), 0.77 (s, 3H, 24-H), 0.75–0.71 (m, 1H, 5-H), 0.68 (s, 3H, 28-H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 200.2 (C-11), 175.2 (C-29), 168.8 (C-13), 140.1 (C-Ar), 140.1 (C-Ar), 128.6 (C-Ar), 128.6 (C-Ar), 128.5 (C-12), 128.1 (C-Ar), 127.8 (C-Ar), 127.3 (C-Ar), 127.0 (C-Ar), 76.6 (C-31), 61.9 (C-9), 59.6 (C-3), 55.5 (C-5), 48.1 (C-18), 45.3 (C-8), 44.0 (C-20), 43.2 (C-14), 41.1 (C-19), 40.0 (C-1), 38.5 (C-4), 37.5 (C-22), 37.3 (C-10), 32.8 (C-7), 31.7 (C-17), 31.2 (C-21), 28.4 (C-23), 28.3 (C-30), 28.3 (C-28), 28.2 (C-2), 26.4 (C-15), 26.4 (C-16), 23.4 (C-27), 18.7 (C-26), 17.9 (C-6), 16.3 (C-25), 15.7 (C-24). IR (DCM) $v$: 3755, 3686, 2972, 2941, 2871, 1775, 1729, 1656, 1621, 1582, 1563, 1544, 1525, 1494, 1459, 1389, 1366, 1328, 1308, 1212, 1150, 1085, 1050, 1030, 980, 915, 880, 868, 822, 737. MS-CI, $m/z$ ($I_{rel.}$ (%)): 166.97 (100); 635.89 [M] (20); 181.94 (18); 167.99 (17); 425.99 (10). 36.89 (9); 165.01 (8); 424.02 (7); 183.78 (6); 182.95 (5). Anal. Calcd for $C_{43}H_{57}NO_3$: C, 81.22; H, 9.03; N, 2.200. Found: C, 80.87; H, 8.71; N, 1.91.

### 3.29. (3α,18β,20β)-3-Amino-11-oxo-olean-12-en-29-oic acid diphenylmethyl ester (10c)

Another elution gives (3α,18β,20β)-3-Amino-11-oxo-olean-12-en-29-oic acid diphenylmethyl ester (**10c**) as a white solid (0.60 g, 15%, HPLC >96%). $[\alpha]_D^{20}$ +111.6 ($c$ 1.0, $CHCl_3$). $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 7.43–7.22 (m, 10H, arom.), 6.93 (s, 1H, 31-H), 5.52 (s, 1H, 12-H), 2.96–62 (m, 1H, 5-H), 2.56–2.47 (m, 1H, 6-H), 2.46 (s, 1H, 9-H), 2.15–1.93 (m, 4H, 2-H, 18-H, 19-H, 21-H), 1.86–1.76 (m, 1H, 15-H), 1.77–1.53 (m, 3H, 1-H, 16-H, 19-H), 1.52–1.41 (m, 2H, 7-H), 1.41–1.27 (m, 6H, 1-H, 6-H, 16-H, 21-H, 22-H), 1.39 (s, 3H, 27-H), 1.27–1.21 (m, 1H, 3-H), 1.17 (s, 3H, 30-H), 1.16–1.12 (m, 1H, 15-H), 1.15 (s, 3H, 25-H), 1.09 (s, 3H, 26-H), 1.02–0.93 (m, 1H, 2-H), 0.93–0.87 (d, 6H, 23-H, 24-H), 0.67 (s, 3H, 28-H); $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$ 200.3 (C-11), 175.2 (C-29), 168.8 (C-13), 140.1 (C-Ar), 140.1 (C-Ar), 128.6 (C-Ar), 128.6 (C-Ar), 128.6 (C-12), 128.4 (C-Ar), 128.4 (C-Ar), 128.1 (C-Ar), 127.8 (C-Ar), 127.3 (C-Ar), 127.3 (C-Ar), 127.0 (C-Ar), 127.0 (C-Ar), 76.6 (C-31), 61.8 (C-9), 56.2 (C-5), 48.0 (C-3), 48.0 (C-18), 45.5 (C-14), 44.0 (C-8), 43.2 (C-20), 41.1 (C19), 37.5 (C-22), 37.4 (C-10), 36.8 (C-4), 33.6 (C-1), 32.7 (C-6), 31.7 (C-17), 31.2 (C-21), 28.8 (C-23), 28.3 (C-28), 28.3 (C-30), 26.4 (C-2), 26.4 (C-15), 25.6 (C-16), 23.6 (C-27), 23.5 (C-24), 18.7 (C-26), 17.4 (C-7), 16.5 (C-25). Anal. Calcd for $C_{43}H_{57}NO_3$: C, 81.22; H, 9.03; N, 2.20. Found: C, 80.94; H, 8.77; N, 1.88.

### 3.30. (3β,18β,20β)-3-(Methoxyamino)-11-oxo-olean-12-en-29-oic acid diphenylmethyl ester (10d)

Compound **9c** (2.16 g, 3.3 mmol) was suspended in EtOH (7 mL) and dioxane (15 mL), and then cooled to 0 °C. Borane *tert*-butylamine complex (0.93 g, 10.7 mmol) was added, followed by the dropwise addition of 10% HCl (10 mL). The reaction mixture was stirred at 0 °C for 2.5 h. After this time, $Na_2CO_3$ was added until gas evolution ceased, and the mixture was partitioned between saturated $NaHCO_3$ and DCM. The organic layer was dried over $Na_2SO_4$, filtered and concentrated. The crude product was applied on $SiO_2$ column and eluted with PE/EtOAc (2–20%) to give **10d** as a white powder (0.90 g, 42%, HPLC >98%). Mp 198–200 °C. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.44–7.22 (m, 10H), 6.94 (s, 1H), 5.52 (s, 1H), 5.34 (br, 1H), 3.50 (s, 3H), 2.80 (dd, $J$ = 13.5, 3.5 Hz, 1H), 2.59–2.48 (m, 1H), 2.35 (s, 1H), 2.13–1.48 (m, 9H), 1.46–1.25 (m, 6H), 1.37 (s, 3H), 1.23–0.79 (m, 4H), 1.18 (s, 3H), 1.14 (s, 3H), 1.09 (s, 3H), 1.08 (s, 3H), 0.72 (s, 3H), 0.67 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 200.2, 175.2, 168.7, 140.1, 140.1, 128.6, 128.6, 128.5, 128.4, 128.4, 128.1, 127.8, 127.3, 127.2, 126.9, 126.9, 76.6, 67.9, 61.8, 61.6, 56.1, 48.0, 45.3, 44.0, 43.1, 41.1, 39.3, 37.5, 37.1, 36.9, 32.7, 31.7, 31.1, 28.6, 28.3, 28.2, 26.4, 23.5, 23.3, 18.7, 17.3, 16.7, 16.1. Anal. Calcd for $C_{44}H_{459}NO_4$: C, 79.36; H, 8.93; N, 2.10. Found: C, 79.04; H, 8.72; N, 1.82.

### 3.31. (18β,20β)-3,11-Dioxo-olean-12-en-29-oic acid (11)

Jones reagent (20 mL) was added to a solution of **1** (10.0 g, 21 mmol) in acetone (500 mL). The reaction mixture was stirred for 30 min at 0 °C (monitored by TLC), poured into ice-water and extracted with $CHCl_3$ (500 mL). The organic phase was washed with water (3 x 200 mL), dried ($MgSO_4$), filtered and evaporated to give a white solid. The crude product was purified by recrystallization from MeOH (150 mL) to give **11** as white crystals (8.2 g, 82%, HPLC >99%). Mp 311–313 °C; (Ref. 31: 298–302 °C); $[\alpha]_D^{20}$ +184.5 ($c$ 0.4, $CHCl_3$) (Ref. 50: +184°). $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 5.77 (s, 1H), 3.03–2.94 (m, 1H), 2.71–2.60 (m, 1H), 2.47 (s, 1H), 2.43–2.34 (m, 1H), 2.24 (dd, $J$ = 13.5, 3.2 Hz, 1H), 2.10–2.00 (m, 2H), 1.99–1.84 (m, 2H), 1.74–1.67 (m, 1H), 1.66–1.54 (m, 3H), 1.48–1.37 (m, 4H), 1.40 (s, 3H), 1.34–1.22 (m, 1H), 1.30 (s, 3H), 1.27 (s, 3H), 1.25 (s, 3H), 1.19 (s, 3H), 1.13 (s, 3H), 1.09 (s, 3H), 1.07–1.02 (m, 1H), 0.88 (s, 3H). $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 217.3, 199.7, 181.7, 169.9, 128.4, 61.1, 55.5, 48.3, 47.8, 45.3, 43.8, 43.3, 40.9, 39.7, 37.7, 36.7, 34.2, 32.1, 31.9, 30.9, 29.7, 28.6, 28.4, 26.5, 26.4, 23.4, 21.4, 18.8, 18.5, 15.6. IR (DCM) $v$: 3736, 3061, 2937, 2875, 1702, 1656, 1555, 1540, 1459, 1386, 1366, 1324, 1208, 1162, 1112, 1088, 1000, 980, 946, 922, 880, 818. MS-CI, $m/z$ ($I_{rel.}$ (%)): 468.98 [M] (100); 423.03 (98); 425.04 (95); 469.98 (44); 441.82 (38); 424.08 (31); 407.06 (31); 426.07 (27); 440.96 (23); 439.95 (23).

### 3.32. (3α,18β,20β)-3-Hydroxy-11-oxo-olean-12-en-29-oic acid (12)

A solution of **11** (3.0 g, 6.5 mmol) in dry THF (200 mL) under nitrogen atmosphere was cooled in a methanol slush bath

(−74 °C), and a 1.0 M solution of K-selectride in THF (20 mL, 20 mmol) was added dropwise by syringe. After two more hours at this temperature, the reaction mixture was warmed to and left to stand overnight at rt. The reaction was quenched with 1 N HCl to pH 2.0 under ice-cooling and extracted with $CHCl_3$ (750 mL). The extract was washed with brine, dried over anhydrous $MgSO_4$, filtered and evaporated in vacuo. The product was crystallized from MeOH to afford **12** as a white solid (1.2 g, 39.8%, HPLC >99%). Mp 335–338 °C. $^1$H NMR (200 MHz, DMSO-$d_6$) $\delta$ 5.39 (s, 1H), 3.16 (br, 1H), 2.49 (m, 1H), 2.38 (s, 1H), 2.37–2.20 (m, 1H), 2.19–1.95 (m, 2H), 1.92–1.50 (m, 6H), 1.49–1.15 (m, 10H), 1.35 (s, 3H), 1.13–0.94 (m, 1H), 1.09 (s, 3H), 1.02 (s, 6H), 0.92–0.64 (m, 1H), 0.83 (s, 3H), 0.76 (s, 3H), 0.75 (s, 3H); $^{13}$C NMR (50 MHz, DMSO-$d_6$) $\delta$ 199.6, 178.1, 170.0, 127.8, 74.0, 61.6, 48.5, 47.9, 45.5, 43.5, 43.4, 41.1, 38.0, 37.6, 37.2, 33.5, 32.6, 32.0, 30.8, 29.3, 28.8, 28.3, 26.4, 26.3, 25.6, 23.6, 22.7, 18.8, 17.4, 16.6. IR (DCM) $\nu$, 3736, 2956, 2918, 2879, 2852, 1717, 1648, 1617, 1455, 1386, 1362, 1208, 1162, 1088, 1061, 1034, 976, 930, 884. MS-CI, $m/z$ ($I_{rel.}$ (%)): 470.99 [M] (100); 471.99 (30); 178.00 (28); 194.78 (11); 469.01 (10); 427.03 (9); 175.03 (8); 135.02 (8); 303.01 (8); 261.99 (8).

### 3.33. (3α,18β,20β)-3-Hydroxy-11-oxo-olean-12-en-29-oic acid methyl ester (13a)

Preparation as described for **2a**. Purification by flash chromatography (ethylacetate–petrolether) gives methylester **13a** as colorless needles (81%, HPLC >98%). Mp 250–252 °C. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 5.56 (s, 1H, 12-H), 3.68 (s, 3H, 31-H), 3.41 (t, $J$ = 3.2 Hz, 1H, 3-H), 2.53 (dd, $J$ = 13.4, 3.2 Hz, 1H, 1-H), 2.46 (s, 1H, 9-H), 2.09–1.97 (m, 4H, 2-H, 18-H, 19-H, 21-H), 1.94–0.91 (m, 15H, 1-H, 2-H, 5-H, 6-H, 7-H, 15-H, 16-H, 19-H, 21-H, 22-H), 1.37 (s, 3H, 27-H), 1.14 (s, 3H, 25-H), 1.14 (s, 3H, 30-H), 1.12 (s, 3H, 26-H), 0.96 (s, 3H, 24-H), 0.86 (s, 3H, 23-H), 0.80 (s, 3H, 28-H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 200.5 (C-11), 177.0 (C-29), 169.2 (C-13), 128.5 (C-12), 75.7 (C-3), 61.7 (C-9), 51.7 (C-31), 48.4 (C-18), 48.4 (C-5), 45.6 (C-8), 44.0 (C-20), 43.3 (C-14), 41.1 (C-19), 37.8 (C-22), 37.5 (C-4), 37.1 (C-10), 33.4 (C-1), 32.6 (C-7), 31.8 (C-17), 31.1 (C-21), 28.5 (C-28), 28.5 (C-24), 28.3 (C-30), 26.4 (C-15), 26.4 (C-16), 25.4 (C-2), 23.6 (C-27), 22.4 (C-23), 18.7 (C-26), 17.4 (C-6), 16.3 (C-25). IR (DCM) $\nu$: 3736, 3057, 2953, 2871, 2157, 2134, 1729, 1652, 1555, 1540, 1513, 1459, 1389, 1370, 1316, 1220, 1193, 1158, 1088, 1069, 1034, 992, 976, 946, 919, 880, 826. MS-CI, $m/z$ ($I_{rel.}$ (%)): 485.06 [M+1] (100); 486.04 (29); 316.93 (8); 135.03 (7); 292.97 (7); 487.03 (6); 484.07 (5); 175.04 (5); 189.04 (5); 135.94 (4).

### 3.34. (3α,18β,20β)-3-Hydroxy-11-oxo-olean-12-en-29-oic acid diphenylmethyl ester (13b)

Preparation as described for **2b**. Purification by flash chomatography (DCM–MeOH, 0–0.5% gradient elution) gives **13b** as a white solid (85%, HPLC >98%). Mp 131–132 °C. $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 7.44–7.21 (m, 10H), 6.94 (s, 1H, 31-H), 5.52 (s, 1H, 12-H), 3.42 (t, $J$ = 3.1, 1H, 3-H), 2.51 (dd, $J$ = 13.5, 3.1 Hz, 1H, 18-H), 2.45 (s, 1H, 9-H), 2.17–1.85 (m, 5H, 2-H, 16-H, 19-H, 21-H), 1.84–1.01 (m, 13H, 1-H, 2-H, 6-H, 7-H, 15-H, 16-H, 21-H, 22-H), 1.38 (s, 3H, 30-H), 1.18 (s, 3H, 27-H), 1.15 (s, 3H, 25-H), 1.10 (s, 3H, 26-H), 1.00–0.90 (m, 1H, 5-H), 0.97 (s, 3H, 23-H), 0.87 (s, 3H, 24-H), 0.67 (s, 3H, 28-H); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 200.3 (C-11), 175.2 (C-29), 168.9 (C-13), 140.1 (C-Ar), 140.0 (C-Ar), 128.6 (C-Ar), 128.4 (C-12), 127.8 (C-Ar), 127.3 (C-Ar), 127.0 (C-Ar), 76.6 (C-3), 75.8 (C-31), 61.6 (C-9), 48.3 (C-5), 45.5 (C-14), 44.0 (C-8), 43.2 (C-20), 41.1 (C-19), 37.5 (C-4), 37.1 (C-22), 33.5 (C-10), 32.6 (C-7), 31.7 (C-17), 31.1 (C-21), 28.5 (C-30), 28.3 (C-28), 28.2 (C-23), 26.4 (C-2), 25.4 (C-15), 23.5 (C-27), 22.3 (C-26), 18.6 (C-25), 17.4 (C-6), 16.3 (C-24). IR (DCM) $\nu$: 3543, 2937, 2871, 1729, 1656, 1621, 1559, 1540, 1497, 1455, 1386, 1362, 1328, 1312, 1212, 1189, 1162, 1077, 1030, 980, 969, 938, 915, 880. MS-CI, $m/z$ ($I_{rel.}$ (%)): 167.05 (100); 637.02 [M+1] (45); 182.01 (27); 183.10 (20); 298.91 (13); 638.04 (12); 282.09 (12); 272.37 (8); 283.16 (8); 199.84 (7).

### 3.35. (18β,20β)-3,3-Ethane-1,2-diyldioxy-11-oxo-olean-12-en-29-oic acid methyl ester (14)

A suspension of **8a** (1.0 g, 2.1 mmol), toluene (50 mL), ethyleneglycol (0.6 mL) and pyridinium $p$-toluenesulfonate (20.7 mg, 0.09 mmol) was refluxed for 12 h with azeotropic removal of water by a Dean-Stark apparatus filled with molecular sieves in the receiver. The resulting mixture was cooled and washed with water (5 mL) and the aqueous layer was extracted with DCM. The organic layers were combined and concentrated to give crude **14** as a white powder (0.7 g, 64%, HPLC >96%). Mp 188–189 °C. $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 5.59 (s, 1H), 3.89 (m, 4H), 3.62 (s, 3H), 2.63 (dd, $J$ = 13.3, 3.2 Hz, 1H), 2.36 (s, 1H), 2.10–1.61 (m, 5H), 1.50–1.12 (m, 12H), 1.30 (s, 3H), 1.10 (s, 3H), 1.08 (s, 3H), 1.06 (s, 3H), 1.02–0.93 (m, 1H), 0.89 (s, 3H), 0.85–0.75 (m, 1H), 0.79 (s, 3H), 0.73 (s, 3H); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 200.4, 176.9, 169.3, 128.5, 112.3, 64.8, 64.6, 61.7, 52.9, 51.7, 48.3, 45.4, 44.0, 43.2, 42.3, 41.1, 37.7, 37.3, 37.0, 32.6, 31.8, 31.1, 28.5, 28.3, 26.7, 26.4, 26.4, 23.6, 23.0, 20.1, 18.6, 17.6, 16.3. IR (DCM) $\nu$: 2956, 2875, 1729, 1660, 1621, 1459, 1389, 1366, 1320, 1208, 1154, 1127, 1108, 1088, 1058, 1027, 949, 919, 903, 880, 826. MS-CI, $m/z$ ($I_{rel.}$ (%)): 526.99 [M] (100); 528.00 (39); 483.00 (35). 99.03 (19); 427.06 (15); 465.09 (13); 484.02 (12); 543.77 (9); 498.95 (7); 189.09 (7); 529.04 (6); 134.97 (6); 173.06 (5); 135.92 (5); 512.83 (5).

### 3.36. (3β,18β,20β)-3-Hydroxy-olean-12-en-29-oic acid (15)

Zn (6.7 g, 102 mmol) was added to a solution of dioxane (180 mL) and **1** (6.0 g, 14 mmol). The mixture was cooled to 5–10 °C and HCl (35% aq, 27 mL) was added over 30 min. The resulting mixture was stirred for 30 min, the unreacted Zn was removed by decantation and the dioxane was distilled off. The residue was purified by $SiO_2$ column chromatography, eluting with 97:3 DCM/THF to obtain **15** as a white powder (4.0 g, 69%). Mp 324–326 °C; (Ref. 31: 320–325). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 5.17 (t, $J$ = 3.2 Hz, 1H), 3.01 (dd, $J$ = 9.7, 6.1 Hz, 1H), 2.02–1.94 (m, 1H), 1.91–1.81 (m, 3H), 1.79–1.67 (m, 3H), 1.63–1.57 (d, $J$ = 13.2 Hz, 1H), 1.55–1.43 (m, 6H), 1.33–1.23 (m, 5H), 1.12 (s, 3H), 1.06 (s, 3H), 0.99–0.79 (m, 4H), 0.91 (s, 0.91), 0.91 (s, 3H), 0.88 (s, 3H), 0.74 (s, 3H), 0.73–0.62 (m, 1H), 0.69 (s, 3H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$ 178.5, 144.8, 122.3, 77.2, 55.2, 48.3, 47.5, 43.6, 42.9, 41.6, 40.6, 38.6, 38.6, 38.5, 37.0, 32.6, 32.1, 31.1, 28.6, 28.6, 28.6, 27.4, 26.8, 26.2, 26.1, 23.5, 18.5, 17.0, 16.5, 15.7. MS-CI, $m/z$ ($I_{rel.}$ (%)): 439.02 (100); 191.14 (74); 411.09 (42); 203.05 (40); 248.99 (32); 247.99 (29); 189.10 (26); 440.03 (24); 205.08 (24); 265.83 (22); 456.14 [M] (20); 207.09 (19); 393.10 (18); 471.90 (17); 95.12 (17).

### 3.37. (3β,18β,20β)-3-Hydroxy-olean-12-en-29-oic acid methyl ester (16)

Preparation as described for **2a**. Purification by crystallization from MeOH gives **16** as colorless crystals (96.1%). Mp 247–248 °C (Ref. 51: 248–249°); $[\alpha]_D^{20}$ +110 ($c$ 1, $CHCl_3$) (Ref. 47: $[\alpha]_D^{20}$ +122 ($c$ 0.12, $CHCl_3$)). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 5.29 (t, $J$ = 3.5 Hz, 1H, 12-H), 3.69 (s, 3H, 31-H), 3.23 (dd, $J$ = 10.8, 4.7 Hz, 1H, 3-H), 1.99–1.83 (m, 6H, 11-H,16-H, 18-H, 19-H, 21-H), 1.80–0.90 (m, 15H, 1-H, 2-H, 6-H, 7-H, 15-H, 16-H, 19-H, 21-H, 22-H), 1.15 (s, 3H, 27-H), 1.14 (s, 3H, 30-H), 1.01 (s, 3H, 24-H), 0.97 (s, 3H, 26-

H), 0.95 (s, 3H, 25-H), 0.92–0.75 (m, 1H, 5-H), 0.80 (s, 3H, 23-H), 0.79 (s, 3H, 28-H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 177.7 (C-29), 144.4 (C-13), 122.6 (C-12), 79.0 (C-3), 55.2 (C-5), 51.6 (C-31), 48.2 (C-18), 47.6 (C-9), 44.3 (C-20), 42.9 (C-19), 41.5 (C-14), 39.8 (C-8), 38.8 (C-4), 38.6 (C-1), 38.4 (C-22), 36.9 (C-10), 32.7 (C-7), 31.9 (C-17), 31.3 (C-21), 28.6 (C-30), 28.2 (C-28), 28.1 (C-24), 27.2 (C-2), 27.0 (C-16), 26.2 (C-15), 26.0 (C-27), 23.5 (C-11), 18.4 (C-6), 16.8 (C-26), 15.6 (C-23), 15.5 (C-25).

### 3.38. (3β,18β,20β)-3,11-Dihydroxy-olean-12-en-29-oic acid (17)

Compound **1** (5.0 g, 10.6 mmol), $NaBH_4$ (24.0 g, 634.5 mmol) and NaOH (2.5 g, 62.5 mmol) were suspended in a mixture of THF (200 mL) and water (200 mL). The heterogeneous mixture was refluxed for 4 h. The solvent THF was evaporated under reduced pressure and the residue was poured into a 5% aqueous solution of $NaH_2PO_4$ (1 L) and extracted with ethylacetate (2 × 250 mL). The combined organic layers were washed with water (2 × 100 mL), dried ($Na_2SO_4$), filtered and evaporated in vacuo to give **17** as white crystals (4.8 g, 95.6%). Mp 265–270 °C. $^1$H NMR (300 MHz, pyridine-$d_5$) $\delta$ 5.86 (d, $J$ = 3.5 Hz, 1H), 4.67 (d, $J$ = 3.6 Hz, 1H), 3.50 (dd, $J$ = 11.28, 4.16 Hz, 1H), 2.58–2.36 (m, 2H), 2.33–2.11 (m, 4H), 2.00–1.81 (m, 4H), 1.80–1.54 (m, 6H), 1.76 (s, 3H), 1.53–1.21 (m, 4H), 1.49 (s, 3H), 1.35 (s, 3H), 1.27 (s, 3H), 1.27 (s, 3H), 1.18–1.00 (m, 2H), 1.12 (s, 3H), 0.98–0.82 (m, 2H), 0.90 (s, 3H); $^{13}$C NMR (75 MHz, pyridine-$d_5$) $\delta$ (ppm) 179.9, 146.6, 128.9, 78.8, 66.2, 56.9, 53.7, 48.8, 47.5, 44.8, 42.9, 40.4, 39.9, 39.5, 39.3, 39.1, 38.2, 32.6, 32.3, 31.4, 29.6, 29.5, 29.2, 28.2, 26.3, 25.0, 21.3, 19.6, 19.1, 17.2. IR (MeOH) $v$: 3342, 2366, 2347, 1702, 1656, 1640, 1629, 1563, 1536, 1459, 1389, 1366, 1339, 1316, 1277, 1262, 1223, 1177, 1139, 1104, 1027, 976, 949, 922, 892, 857, 814. MS-CI, $m/z$ ($I_{rel.}$ (%)): 314.51 (100); 212.45 (78); 270.50 (68); 57.28 (55); 323.50 (54); 67.36 (53); 311.28 (36); 70.08 (34); 103.22 (33); 463.44 (31).

### 3.39. (3β,11β,18β,20β)-3,11-Dihydroxy-olean-12-en-29-oic acid methyl ester (18a)

Preparation as described for **2a**. Purification by flash chromatography (DCM–MeOH, gradient elution, 0–1%) yields **18a** as a white solid (51%). Mp 206–207 °C. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 5.41 (d, $J$ = 5.4 Hz, 1H), 4.35 (dd, $J$ = 7.9, 2.9 Hz, 1H), 3.71 (s, 3H), 3.26 (dd, $J$ = 10.8, 5.3 Hz, 1H), 2.08 (dd, $J$ = 13.0, 3.4 Hz, 1H), 2.03–1.93 (m, 3H), 1.88–1.72 (m, 5H), 1.64–1.54 (m, 3H), 1.42 (s, 3H), 1.41–1.29 (m, 5H), 1.27–1.19 (m, 2H), 1.25 (s, 3H), 1.15 (s, 3H), 1.12–0.99 (m, 2H), 1.11 (s, 3H), 1.01 (s, 3H), 0.93 (d, $J$ = 13.5 Hz, 1H), 0.84 (s, 3H), 0.83 (s, 3H), 0.72 (dd, $J$ = 10.1, 2.8 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 177.5, 147.7, 126.3, 79.1, 66.7, 55.8, 52.5, 51.7, 47.9, 44.3, 42.8, 42.3, 39.5, 38.8, 38.7, 38.3, 38.2, 33.2, 31.8, 31.3, 28.5, 28.5, 28.3, 27.1, 26.8, 26.5, 25.3, 19.3, 18.7, 18.1, 15.7. IR (DCM) $v$: 3744, 3620, 3057, 2983, 2945, 2871, 2165, 1721, 1459, 1424, 1389, 1223, 1162, 1081, 1038, 1027, 919, 895. MS-CI, $m/z$ ($I_{rel.}$ (%)): 206.93 (100); 189.07 (64); 469.03 (37); 451.12 (29); 470.08 (15); 207.95 (14); 249.00 (12); 452.19 (12); 468.03 (11); 205.01 (10).

### 3.40. (3β,11β,18β,20β)-3,11-Dihydroxy-olean-12-en-29-oic acid diphenylmethyl ester (18b)

Preparation as described for **2b**. Purification by flash chromatography (DCM–MeOH gradient elution, 0–1%) gives 11β isomer **18b** as a white solid (240 mg, 35.5%, HPLC >97%). Mp 101–102 °C. $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 7.42–7.24 (m, 10H), 6.95 (s, 1H), 5.16 (d, $J$ = 3.9 Hz,1H), 4.29 (t, $J$ = 4.1 Hz, 1H), 3.24 (dd, $J$ = 9.6, 6.2 Hz,1H), 2.08–1.84 (m, 5H), 1.77–1.53 (m, 7H), 1.41 (s, 3H), 1.38–1.22 (m, 6H), 1.21 (s, 3H), 1.18 (s, 3H), 1.13–1.05 (m, 1H), 1.10 (s, 3H), 1.04–0.97 (m, 1H), 1.01 (s, 3H), 0.96–0.76 (m, 2H), 0.83 (s, 3H), 0.76–0.66 (m, 1H), 0.71 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 175.7, 147.5, 140.4, 140.2, 128.5, 128.5, 128.4, 128.4, 127.9, 127.8, 127.4, 127.4, 127.0,127.0, 126.3, 79.0, 77.8, 66.6, 55.8, 52.4, 47.6, 44.2, 42.8, 42.2, 39.5, 38.8, 38.7, 38.3, 38.0, 33.2, 31.7, 31.3, 28.5, 28.3, 28.2, 27.0, 26.8, 26.5, 25.3, 19.3, 18.7, 18.1, 15.8. IR (DCM) $v$: 3612, 3057, 2976, 2937, 2871, 1725, 1455, 1420, 1378, 1216, 1153, 1082, 1031, 992, 916, 895, 835. MS-CI, $m/z$ ($I_{rel.}$ (%)): 167.03 (100); 168.05 (14); 183.77 (8); 225.07 (7); 182.98 (5); 181.92 (5); 453.05 (4); 206.90 (2); 180.17 (2); 152.13 (2). Anal. Calcd for $C_{43}H_{58}O_4$: C, 80.83; H, 9.15. Found: C, 81.21; H, 8.81.

### 3.41. (3β,11α,18β,20β)-3,11-Dihydroxy-olean-12-en-29-oic acid diphenylmethyl ester (18c)

Another elution gives (3β,11α,18β,20β)-3,11-dihydroxy-olean-12-en-29-oic acid diphenylmethyl ester (**18c**) as a white solid (60 mg, 9%, HPLC >96%). Mp 115–118 °C. $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 7.34–7.16 (m, 10H), 6.82 (s, 1H), 5.07 (d, $J$ = 3.9 Hz,1H), 4.08 (dd, $J$ = 8.3, 3.6 Hz, 1H), 3.16 (dd, $J$ = 9.9, 6.0 Hz,1H), 2.00–1.80 (m, 5H), 1.75–1.48 (m, 7H), 1.40–1.20 (m, 6H), 1.14 (s, 3H), 1.11–1.05 (m, 1H), 1.09 (s, 3H), 1.04–0.98 (m, 1H), 0.97 (s, 3H), 0.96–0.78 (m, 2H), 0.93 (s, 3H), 0.89 (s, 3H), 0.76–0.68 (m, 1H), 0.73 (s 3H), 0.60 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 175.7, 147.5, 140.4, 140.2, 128.5, 128.5, 128.4, 128.4, 127.9, 127.8, 127.4, 127.4, 127.0,127.0, 126.3, 79.0, 77.8, 66.6, 55.8, 52.4, 47.6, 44.2, 42.8, 42.2, 39.5, 38.8, 38.7, 38.3, 38.0, 33.2, 31.7, 31.3, 28.5, 28.3, 28.2, 27.0, 26.8, 26.5, 25.3, 19.3, 18.7, 18.1, 15.8. IR (DCM) $v$: 3612, 3056, 2980, 2936, 2871, 1724, 1455, 1420, 1378, 1215, 1154, 1081, 1030, 992, 915, 895, 835. MS-CI, $m/z$ ($I_{rel.}$ (%)): 167.32 (100); 167.67 (12); 183.87 (9); 225.07 (7); 183.05 (6); 181.92 (5); 452.74 (5); 207.05 (2); 180.11 (2); 152.69 (2). Anal. Calcd for $C_{43}H_{58}O_4$: C, 80.83; H, 9.15. Found: C, 81.20; H, 8.76.

### 3.42. (3β,11β,18β,20β)-3-Hydroxy-11-methoxyolean-12-en-29-oic acid methyl ester (19)

Compound **17** (1.0 g, 2.1 mmol) was placed into DCM (100 mL) and $Et_2O$ (100 mL) and transferred into a diazomethane apparatus. Diazomethane was added slowly and the mixture was kept at 40 °C for 12 h. When diazomethane was gone, the solvent was evaporated. The crude product was crystallized from MeOH (500 mL) to give **19** as colorless crystals (0.9 g, 85%, HPLC >99%). Mp 185–187 °C.

### 3.43. (3β,18β,20β)-3-Hydroxy-oleana-(9(11),12-dien-29-oic acid (20)

To a solution of **17** (473 mg, 1.0 mmol) in dry THF (20 mL) was added HCl (100 μL) and refluxed for 8 h. The reaction was monitored by TLC. The solvent was evaporated to dryness. The crude product was crystallized from MeOH (10 mL) to give acid **20** as a white solid (395 mg, 87%, HPLC >98%). Mp 301–302 °C. $^1$H NMR (200 MHz, pyridine-$d_5$) $\delta$ 5.85 (d, $J$ = 5.6 Hz, 1H), 5.71 (d, $J$ = 5.6 Hz, 1H), 3.45 (m, 1H), 2.59 (dd, $J$ = 12.6, 3.0 Hz, 1H), 2.28 (d, $J$ = 12.8 Hz, 2H), 2.16–1.59 (m, 6H), 1.57–1.15 (m, 5H), 1.33 (s, 3H), 1.26 (s, 3H), 1.22 (s, 3H), 1.21 (s, 3H), 1.17 (s, 3H), 1.12–0.85 (m, 2H), 1.06 (s, 3H), 0.91 (s, 3H); $^{13}$C NMR (50 MHz, pyridine-$d_5$) $\delta$ 180.0, 155.7, 147.2, 122.2, 116.5, 78.2, 52.2, 47.4, 44.7, 44.0, 43.5, 42.3, 41.3, 40.0, 39.6, 39.6, 39.4, 38.2, 33.0, 32.5, 32.1, 29.4, 29.3, 28.0, 26.5, 26.0, 21.6, 20.8, 19.2, 17.1. IR (MeOH) $v$: 3439, 2366, 2343, 1706, 1656, 1555, 1536, 1525, 1459, 1378, 1366, 1343, 1316, 1277, 1262, 1223, 1177, 1146, 1104, 1077, 1034, 992, 922, 834, 818. MS-CI, $m/z$ ($I_{rel.}$ (%)): 206.94 (100); 437.10

(65); 189.04 (61); 455.09 [M] (46); 454.17 (29); 438.10 (25); 409.14 (18); 207.97 (15); 456.09 (12); 203.10 (12).

### 3.44. (3β,18β,20β)-3-Hydroxy-oleana-(9(11),12-dien-29-oic acid methyl ester (21)

Preparation as described for **2a**. Purification by flash chromatography (DCM–MeOH, gradient elution, 0–1%) yields **21** as a white solid (90%, HPLC >99%). Mp 240–243 °C. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 5.74–5.63 (m, 2H, 11-H, 12-H), 3.78 (s, 3H, 31-H), 3.26–3.18 (m, 1H, 3-H), 2.13–0.92 (m, 19H, 1-H, 2-H, 6-H, 7-H, 15-H, 16-H, 18-H, 19-H, 21-H, 22-H), 1.20 (s, 3H, 25-H), 1.13 (s, 3H, 30-H), 1.13 (s, 3H, 26-H), 1.04 (s, 3H, 23-H), 1.00 (s, 3H, 27-H), 0.87–0.76 (m, 1H, 5-H), 0.85 (s, 3H, 28-H), 0.82 (s, 3H, 24-H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 177.7 (C-29), 154.6 (C-9), 146.0 (C-13), 121.4 (C-12), 115.7 (C-11), 78.7 (C-3), 51.6 (C-31), 51.1 (C-5), 46.4 (C-18), 44.2 (C-20), 42.8 (C-19), 42.7 (C-8), 40.4 (C-14), 38.9 (C-4), 38.7 (C-10), 38.3 (C-22), 37.1 (C-1), 32.1 (C-7), 31.6 (C-17), 31.2 (C-21), 28.4 (C-28), 28.4 (C-30), 28.2 (C-23), 27.9 (C-2), 27.3 (C-16), 25.6 (C-15), 25.3 (C-25), 20.9 (C-26), 20.1 (C-27), 18.3 (C-6), 15.7 (C-24). IR (DCM) $\nu$, 3736, 3350, 3034, 2980, 2949, 2914, 2875, 2157, 1721, 1648, 1555, 1540, 1470, 1455, 1378, 1316, 1277, 1262, 1220, 1189, 1162, 1088, 1065, 1038, 992, 822, 749.

### 3.45. (3β,20β)-3-(Acetyloxy)-oleana-11,13(18)-dien-29-oic acid (22)

The mixture of crude **17** (1.00 g, 2.1 mmol) was added to a mixture of acetic acid (40 mL) and concd hydrochloric acid (10 mL). The mixture was refluxed for 2 h, poured into ice-water (200 mL) and filtered. Purification by flash chromatography (DCM–MeOH gradient elution, 0–5%) gave **22** as a white solid (0.65 g, 62%). Mp 274–275 °C. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 6.30 (d, $J$ = 11.0 Hz, 1H, 12-H), 5.58 (d, $J$ = 11.4 Hz, 1H, 11-H), 4.45 (dd, $J$ = 10.8, 3.8 Hz, 1H, 3-H), 2.7 (d, $J$ = 14.5 Hz, 1H, 19-H), 2.20 (d, $J$ = 14.6 Hz, 1H, 19-H), 2.08–1.04 (m, 18H, 1-H, 2-H, 5-H, 6-H, 7-H, 9-H, 15-H, 16-H, 21-H, 22-H), 1.13 (s, 3H, 30-H), 1.12 (s, 3H, 28-H), 0.98 (s, 3H, 27-H), 0.94 (s, 3H, 25-H), 0.89 (s, 3H, 23-H), 0.87 (s, 3H, 24-H), 0.73 (s, 3H, 26-H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$ 184.5 (C-29), 171.1 (C-31), 135.4 (C-13), 135.0 (C-18), 126.3 (C-11), 125.4 (C-12), 80.9 (C-3), 54.9 (C-5), 54.1 (C-9), 43.8 (C-20), 42.5 (C-14), 40.3 (C-8), 37.8 (C-4), 37.6 (C-1), 37.5 (C-22), 36.6 (C-10), 35.8 (C-16), 34.7 (C-17), 32.2 (C-7), 32.0 (C-19), 29.8 (C-21), 27.8 (C-23), 25.2 (C-28), 24.3 (C-15), 23.4 (C-2), 21.3 (C-32), 20.1 (C-27), 19.5 (C-30), 18.2 (C-6), 18.0 (C-25), 16.5 (C-26), 16.2 (C-24). IR (DCM) $\nu$: 3041, 2941, 2868, 1733, 1698, 1470, 1378, 1370, 1193, 1150, 1115, 1085, 1030, 988, 930, 899, 822, 741. MS-CI, $m/z$ ($I_{rel.}$ (%)): 436.96 (100); 189.06 (86); 248.79 (51); 437.98 (32); 190.04 (13); 203.04 (12); 496.93 [M] (10); 213.02 (10); 496.09 (10); 135.92 (8).

### 3.46. (3β,18α,20β)-3-Hydroxy-11-oxo-olean-12-en-29-oic acid (23)

KOH (16.0 g, 285 mmol) was added to diethylene glycol (100 mL) and heated to 100 °C. Compound **1** (40 g, 85 mmol) was added, and the solution was stirred at 220 °C for 2 h. Afterwards the mixture was cooled rt. Water (500 mL) and concentrated HCl were added to the cooled solution, adjusting it to pH ~5. The solid was filtered, washed with water (200 mL), and then extracted with hot acetone (200 mL). The remaining white solid was filtered and recrystallized from EtOH (2 × 1.5 L) to give **23** as colorless needles (18.0 g, 43.7%, HPLC >99%). Mp 338–340 °C; (Ref. 52: 320–325 °C); $[\alpha]_D^{20}$ +74.4° ($c$ 0.081, EtOH). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 5.32 (s, 1H, 12-H), 3.00 (dd, $J$ = 11.3, 4.3 Hz, 1H, 3-H), 2.46 (d, $J$ = 13.3 Hz, 1H, 1-H), 2.30–2.25 (m, 2H, 9-H, 18-H), 1.89 (dd, $J$ = 13.2, 3.8 Hz, 1H, 15-H), 1.79 (dd, $J$ = 13.8, 3.6 Hz, 1H, 21-H), 1.69–1.18 (m, 17H, 2-H, 6-H, 7-H, 15-H, 16-H, 19-H, 21-H, 22-H, 27-H), 1.17 (s, 3H, 30-H), 1.09 (s, 3H, 25-H), 1.05 (s, 3H, 26-H), 1.05–0.92 (m, 1H, 1-H), 0.90 (s, 3H, 23-H), 0.72–0.67 (m, 1H, 5-H), 0.70 (s, 3H, 24-H), 0.67 (s, 3H, 28-H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$ 199.2 (C-11), 179.9 (C-29), 166.5 (C-13), 123.5 (C-12), 77.0 (C-3), 60.4 (C-9), 54.6 (C-5), 45.1 (C-14), 43.7 (C-8), 42.0 (C-20), 40.6 (C-18), 39.3 (C-4), 38.9 (C-1), 37.1 (C-16), 36.8 (C-10), 35.7 (C-22), 35.5 (C-17), 33.6 (C-7), 31.8 (C-19), 28.8 (C-21), 28.6 (C-23), 27.4 (C-2), 26.7 (C-15), 21.0 (C-30), 20.8 (C-27), 18.7 (C-26), 17.7 (C-6), 16.9 (C-25), 16.5 (C-24), 16.1 (C-28). IR (DCM) $\nu$: 3496, 2969, 2926, 2867, 1704, 1661, 1297, 1200, 1112, 1028, 989, 658. MS-CI, $m/z$ ($I_{rel.}$ (%)): 425.07 (100); 427.08 (68); 471.04 [M+1] (37); 426.07 (32); 428.12 (24); 423.06 (19); 472.08 (17); 191.00 (16); 424.11 (15); 175.02 (15).

### 3.47. (3β,18α,20β)-3-Hydroxy-11-oxo-olean-12-en-29-oic acid diphenylmethyl ester (24)

Preparation as described for **2b**. Purification by crystallization from MeOH gives diphenylmethyl ester **24** as a white powder (84%, HPLC >99%). Mp 128–131 °C; $[\alpha]_D^{20}$ +58 ($c$ 0.061, DCM) (Ref. 47: +57.6°). $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 7.39–7.28 (m, 10H), 6.88 (s, 1H), 5.56 (s, 1H), 3.24 (dd, $J$ = 11.2, 4.9 Hz, 1H), 2.70 (m, 1H), 2.28–2.19 (m, 2H), 2.01–1.84 (m, 2H), 1.83–1.30 (m, 13H), 1.29 (s, 3H), 1.26 (s, 3H), 1.27–1.19 (m, 1H), 1.17 (s, 3H), 1.11 (s, 3H), 0.99 (s, 3H), 0.98–0.86 (m, 1H), 0.79 (s, 3H), 0.69–0.63 (m, 4H); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 199.8, 175.0, 165.5, 140.4, 140.4, 128.6, 128.6, 128.5, 128.5, 128.1, 127.8, 127.3, 127.3, 127.0, 127.0, 78.7, 76.6, 76.5, 60.7, 55.0, 48.7, 45.3, 44.2, 43.1, 41.5, 39.4, 39.1, 37.5, 37.2, 32.7, 31.8, 31.2, 28.3, 28.3, 28.0, 27.3, 26.5, 26.4, 23.3, 18.7, 17.5, 16.1, 15.7. IR (DCM) $\nu$: 3057, 2980, 2945, 2871, 1729, 1656, 1459, 1389, 1227, 1193, 1158, 1104, 1034, 992, 895.

### 3.48. (3β,18α,20β)-3-Hydroxy-11-oxo-olean-12-en-29-oic acid methyl ester (25)

Preparation as described for **2a**. Purification by flash chromatography (DCM–MeOH gradient elution, 0–1%) gives **25** as a white solid (76.3%, HPLC >99%). Mp 264–266 °C. $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 5.55 (s, 1H), 3.67 (s, 3H), 3.21 (dd, $J$ = 11.1, 3.8 Hz), 2.67 (dd, $J$ = 13.3, 3.2 Hz, 1H), 2.25 (s, 1H), 2.22–2.15 (m, 1H), 2.08–1.78 (m, 3H), 1.71–1.43 (m, 12H), 1.41–1.26 (m, 2H), 1.33 (s, 3H), 1.25–1.16 (m, 1H), 1.21 (s, 3H), 1.18 (s, 3H), 1.12 (s, 3H), 0.99 (s, 3H), 0.95–0.90 (m, 1H), 0.79 (s, 3H), 0.70 (s, 3H); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 199.8, 178.8, 165.6, 124.1, 78.7, 60.7, 55.0, 51.9, 44.9, 43.8, 42.5, 40.3, 39.1, 39.0, 37.6, 36.8, 35.9, 35.5, 33.7, 31.8, 28.4, 28.1, 27.2, 26.7, 20.8, 20.8, 18.5, 17.5, 16.5, 16.0, 15.7. IR (DCM) $\nu$: 3732, 3501, 2976, 2945, 2871, 1729, 1663, 1625, 1459, 1389, 1362, 1328, 1277, 1231, 1193, 1158, 1115, 1042, 996, 942, 880, 753, 706. MS-CI, $m/z$ ($I_{rel.}$ (%)): 485.04 [M] (100); 486.05 [M+1] (32); 316.90 (15); 483.04 (14); 191.04 (12); 487.08 (10); 175.05 (9); 135.01 (8); 501.14 (8); 311.85 (8).

### 3.49. 1-Deoxy-1-{[(3β,18α,20β)-3-hydroxy-11,29-dioxo-olean-12-en-29-yl]amino}-D-glucitol (26a)

Compound **1** (470 mg, 1.0 mmol) and D-glucitol (200 mg, 1.1 mmol) were transferred into a cold mixture of DCC (210 mg, 1.0 mmol) in DCM (50 mL) and the solution was stirred rapidly. After 15 h DCM was evaporated in vacuo and the residue was dissolved in EtOAc (50 mL). After 24 h in the fridge the precipitate was filtered, the mother liquor evaporated in vacuo and the residue was purified by flash chromatography (DCM–MeOH gradient elution, 0–20%) to give **26a** as a white powder (200 mg, 31%). Mp 193–

195 °C. $^1$H NMR (200 MHz, DMSO-$d_6$) $\delta$ 7.22 (m, 1H), 5.28 (s, 1H), 4.48 (d, 1H), 4.19 (m, 1H), 4.09 (m, 1H), 3.39–0.20 (m, 33H), 1.08 (s, 3H), 1.02 (s, 3H), 0.76 (s, 6H), 0.64 (s, 3H), 0.46 (s, 3H), 0.42 (s, 3H); $^{13}$C NMR (50 MHz, DMSO-$d_6$) $\delta$ 199.1, 175.5, 169.7, 127.4, 76.5, 72.2, 71.9, 71.4, 69.4, 63.2, 61.1, 54.0, 47.4, 44.7, 42.9, 42.8, 42.1, 40.8, 38.7, 38.7, 37.2, 36.6, 32.1, 31.3, 30.4, 28.6, 28.3, 28.1, 26.9, 25.8 (2C), 22.9, 18.3, 17.1, 16.1, 15.9. IR (DCM) $v$: 3319, 2929, 2868, 1656, 1640, 1532, 1459, 1386, 1366, 1328, 1308, 1208, 1193, 1135, 1077, 1038, 996, 922, 880.

### 3.50. (3β,18α,20β)-3-Hydroxy-*N*-(2-hydroxyethyl)-11-oxo-olean-12-en-29-amide (26b)

DCC (1.30 g, 6.0 mmol) and HOBt (1.00 g, 6 mmol) were dissolved in DCM (150 mL) and stirred for 30 min. Compound **1** (2.40 g, 5.0 mmol) was added to this solution and stirred for 20 min. 2-Aminoethanol (370 mg, 6.0 mmol was added and stirred at rt for 12 h. The solvent was evaporated in vacuo and the residue was dissolved in EtOAc (150 mL). After standing in the fridge for 12 h the solid material was filtered, the solvent evaporated in vacuo and the residue was purified by flash chromatography (DCM–MeOH gradient elution, 0–10%) to give **26b** as a white powder (0.82 g, 32%). Mp 262–265 °C. $^1$H NMR (200 MHz, DMSO-$d_6$) $\delta$ 7.25 (s, 1H), 5.25 (s, 1H), 4.37 (m, 1H), 4.06 (m, 1H), 3.14 (s, 6H), 3.10 (s, 3H), 3.05–0.40 (m, 17H), 1.08 (s, 3H), 1.02 (s, 3H), 0.77 (s, 3H), 0.75 (s, 3H), 0.65 (s, 3H), 0.46 (s, 3H), 0.43 (s, 3H); $^{13}$C NMR (50 MHz, DMSO-$d_6$) $\delta$ 199.0, 175.2, 169.6, 127.4, 76.5, 61.1, 59.8, 54.0, 47.5, 44,7, 42.8, 41.4, 40.8, 38.7, 38.5, 38.5, 37.2, 36.6, 32.1, 31.3, 30.5, 28.5, 28.4, 28.1, 26.9, 26.0, 25.9, 22.9, 18.2, 17.1, 16.2, 15.9. IR (DCM) $v$: 3373, 2937, 2871, 1652, 1544, 1528, 1463, 1389, 1366, 1277, 1208, 1050, 1038, 996.

### 3.51. (3β,18α,20β)-3-Hydroxy-11-*N*-prop-2-yn-1-ylolean-12-en-29-amide (26c)

Compound **1** (705 mg, 1.5 mmol), EDAC (350 mL, 1.8 mmol) and TEA (355 mg, 3.5 mmol) were stirred in DCM (40 mL) at rt. HOBt (275 mg, 1.8 mmol) was added to this mixture and stirred for 30 min, propargylamine (165 mg, 1.8 mmol) was then added and the solution was stirred for 48 h at rt. The solvent was evaporated in vacuo and the residue was purified by flash chromatography (DCM–MeOH gradient elution, 0–15%) to give **26c** as a white powder (600 mg, 78%). Mp >260 °C. $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 6.21 (m, 1H), 5.67 (s, 1H), 4.06 (m, 2H), 3.20 (m, 1H), 2.75 (m, 1H), 2.32 (s, 1H), 2.23 (m, 1H), 2.20–0.70 (m, 19H), 1.35 (s, 3H), 1.12 (s, 3H), 1.10 (s, 6H), 0.98 (s, 3H), 0.79 (s, 3H), 0.78 (s, 3H), 0.67 (d, 1H); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 200.2, 175.6, 169.3, 128.4, 79.9, 78.7, 71.5, 61.8, 54.9, 48.0, 45.4, 43.5, 43.2, 41.6, 39.2, 39.1, 37.3, 37.0, 32.7, 31.8, 31.4, 29.2, 29.1, 28.4, 28.1, 27.2, 26.4, 26.3, 23.3, 18.6, 17.4, 16.3, 15.6. IR (DCM) $v$: 3315, 2933, 2871, 1652, 1525, 1459, 1424, 1389, 1362, 1347, 1332, 1208, 1189, 1135, 1092, 1034, 996, 949, 922, 880. Anal. Calcd for $C_{33}H_{49}NO_3$: C, 78.06; H, 9.73; N, 2.76; O. Found: C, 79.94; H, 9.66; N, 2.39.

### 3.52. (3β,18α,20β)-*N*-Allyl-3-hydroxy-11-oxo-olean-12-en-29-amide (26d)

A solution of **5d** (380 mg, 0.7 mmol) and KOH (100 mg, 1.5 mmol) in MeOH (30 mL) was stirred at rt for 12 h. The solvent was evaporated and the residue diluted with water and 2 N HCl and extracted with DCM (3 × 30 mL). The organic layers were dried and the solvent was evaporated in vacuo. The residue was purified by flash chromatography (DCM–MeOH gradient elution, 5–20%) to give **26d** as a white powder (156 mg, 44%). Mp >260 °C. $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 5.93 (m, 1H), 5.80 (m, 1H), 5.62 (s, 1H), 5.19 (m, 1H), 5.13 (m, 1H), 3.87 (m, 1H), 3.20 (m, 1H), 2.75 (m, 1H), 2.30 (s, 1H), 2.22–0.65 (m, 21H), 1.35 (s, 3H), 1.12 (s, 3H), 1.10 (s, 6H), 0.98 (s, 3H), 0.79 (s, 3H), 0.78 (s, 3H); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 200.1, 175.5, 169.3, 134.5, 128.4, 116.3, 78.7, 61.8, 54.9, 48.1, 45.3, 43.6, 43.2, 41.8, 41.7, 39.1 (2C), 37.4, 37.0, 32.7, 31.9, 31.4, 29.6, 28.4, 28.1, 27.2, 26.4, 26.3, 23.3, 18.6, 17.4, 16.3, 15.6. IR (DCM) $v$: 3362, 2933, 2871, 1648, 1528, 1459, 1424, 1389, 1362, 1328, 1277, 1208, 1189, 1088, 1034, 996, 919.

### 3.53. (3β,18α,20β)-*N*-[3-(Dimethylamino)propyl]-*N*-[(ethylamino)carbonyl]-3-hydroxy-11-oxo-olean-12-en-29-amide (26e)

To a stirred suspension of **1** (470 mg, 1 mmol) in dry DCM (10 ml) was added EDAC (230 mg, 1.2 mmol) and DMAP (150 mg, 1.2 mmol). The reaction mixture was stirred at rt for 30 min. Barbituric acid (160 mg, 1.2 mmol) was added to the clear solution and the stirring was continued at rt for 5 days. The reaction mixture poured into 1 N HCl (40 ml) and extracted with mixture of DCM (32 mL) and MeOH (8 mL). The organic layers were dried and the solvent was evaporated in vacuo to give **26e** as a white powder (53 mg, 8.4%). $^1$H NMR (200 MHz, pyridine-$d_5$) $\delta$ 9.26 (m, 1H), 8.33 (s, 1H), 5.77 (s, 1H), 3.75 (m, 2H), 3.54 (m, 2H), 3.15 (m, 1H), 2.89 (m, 1H), 2.59–0.49 (m, 27H), 2.08 (s, 6H), 1.38 (s, 3H), 1.06 (s, 3H), 1,05 (s, 3H), 0.99 (s, 3H), 0.86 (s, 3H), 0.80 (s, 3H), 0.54 (s, 3H); $^{13}$C NMR (50 MHz, pyridine-$d_5$) $\delta$ 200.2, 178.7, 170.0, 158.5, 129.2, 78.3, 62.6, 55.7, 55.6, 49.5, 48.1, 46.5, 46.0, 44.0, 43.9, 43.9, 43.1, 40.2, 39.2, 38.1, 36.7, 33.9, 33.4, 32.5, 29.2, 29.2, 29.2, 28.6, 27.3, 27.1, 25.2, 25.2, 23.7, 19.3, 18.4, 17.3, 17.0, 15.0. HRMS, $m/z$: 626.4895 [M+1] (calcd for $C_{38}H_{64}O_4N_3$, 626.4887).

### 3.54. Ethyl *N*-[(3β,18α,20β)-3-hydroxy-11,29-dioxo-olean-12-en-29-yl]glycinate (26f)

DCC (2.5 g, 12 mmol) and HOBt (1.8 g, 12 mmol) were dissolved in DCM (150 mL) CH2Cl2 and stirred for 30 min. Glycyrrhetinic acid **1** (4.7 g, 10 mmol) was added to the clear solution and stirred for another 20 min. Glycine ethylester hydrochloride (1.7 g, 12 mmol) and TEA (3.0 g, 30 mmol) were added and stirred at rt for 24 h. The solvent was evaporated and the residue was heated with EtOAc (200 mL) to 50 °C and than put into the fridge. After 24 h the solid material was removed by filtration and solvent was evaporated to give crude material. The residue was purified by flash chromatography (DCM–MeOH gradient elution, 0–5%) to give **26f** as a white powder (5.2 g, 93%). Mp 87–91 °C. $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 6.28 (m, 1H), 4.22 (q, 2H), 4.00 (m, 2H), 3.22 (m, 1H), 2.77 (m, 1H), 2.40–0.72 (m, 22H), 1.37 (s, 3H), 1.28 (t, 3H), 1.15 (s, 3H), 1.11 (s, 6H), 0.99 (s, 3H), 0.81 (s, 3H), 0.79 (s, 3H); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 200.2, 176.2, 170.2, 169.2, 128.5, 78.7, 61.9, 61.5, 55.0, 47.8, 45.3, 43.6, 43.1, 41.7, 41.3, 39.1, 39.0, 37.3, 37.0, 32.7, 31.9, 31.4, 29.5, 28.4, 28.0, 27.2, 26.5, 26.3, 23.4, 18.7, 17.4, 16.4, 15.6, 14.2. IR (DCM) $v$: 3365, 2968, 1744, 1656, 1544, 1528, 1463, 1424, 1389, 1332, 1196, 1100, 1050, 1034, 1019, 996, 884, 868.

### 3.55. (3β18α,20β)-*N*-[2-(Dimethylamino)ethyl]-3-hydroxy-11-oxoolean-12-en-29-amide (26g)

Preparation as described for **26b**. Purification by flash chromatography (DCM–MeOH gradient elution, 0–20%) gives **26g** as a white solid (89%). $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 7.12 (m, 1H), 5.57 (s, 1H), 3.76 (s, 1H), 3.35 (m, 1H), 3.21 (m, 1H), 3.03 (m, 1H), 2.73–0.55 (m, 23H), 2.20 (s, 6H), 1.35 (s, 3H), 1.10 (s, 3H), 1.00 (s, 6H), 0.93 (s, 3H), 0.76 (s, 3H), 0.73 (s, 3H); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 199.6, 176.0, 169.4, 128.0, 78.3, 62.0, 58.2, 55.3, 48.7, 45.5, 44.9 (2C), 43.5, 43.1, 41.4, 40.0, 39.2, 37.4, 37.0, 36.4, 32.8,

31.9, 31.3, 29.4, 28.4, 28.1, 27.0, 26.6, 26.2, 23.3, 18.5, 17.4, 16.4, 15.7. IR (DCM) $\nu$: 3342, 2833, 2787, 1656, 1544, 1528, 1463, 1389, 1362, 1328, 1208, 1193, 1166, 1131, 1092, 1046, 996, 957, 922, 880, 841. HRMS, *m/z*: 541.4374 [M+1] (calcd for $C_{34}H_{57}O_3N_2$, 514.4369).

### 3.56. Ethyl 1-[(3β,18α,20β)-3-hydroxy-11,29-dioxoolean-12-en-29-yl]piperidine-4-carboxylate (26h)

Preparation as described for **26e**. Purification by flash chromatography (DCM–MeOH gradient elution, 0–20%) gives **26h** as a white solid (33%). $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 5.65 (s, 1H), 4.29–4.05 (m, 4H), 3.15 (m, 1H), 3.10–0.63 (m, 29H), 1.34 (s, 3H), 1.24 (s, 3H), 1.20 (s, 6H), 1.11 (s, 3H), 1.09 (s, 3H), 0.98 (s, 3H), 0.78 (s, 3H); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 200.1, 174.2, 173.8, 169.6, 128.5, 78.7, 61.7, 60.6, 54.9, 48.0, 45.2, 45.0, 44.4, 44.0, 43.8, 43.2, 41.0, 39.1, 39.0, 37.8, 37.0, 33.0, 32.8, 31.7, 28.4, 28.3, 28.2, 28.1, 27.2, 27.0, 26.7, 26.4, 23.1, 18.6, 17.5, 16.3, 15.6, 14.2. IR (DCM) $\nu$: 3497, 3481, 2868, 1733, 1656, 1625, 1459, 1420, 1389, 1316, 1277, 1208, 1166, 1096, 1042, 1015, 996. HRMS, *m/z*: 610.4460 [M+1] (calcd for $C_{38}H_{60}O_5N$, 610.4471).

### 3.57. Pottasium *N*-[(3β,18α,20β)-3-hydroxy-11,29-dioxo-olean-12-en-29-yl]glycinate (26i)

A solution of **26f** (220 mg, 0.4 mmol) and KOH (25 mg, 0.44 mmol) in MeOH (15 mL) and water (5 mL) was stirred at rt for 17 h. The solvent was evaporated and the residue was crystallized from EtOH to give **26i** as a yellow powder (214 mg, 96%). Anal. Calcd for $C_{32}H_{48}KNO_5$: C, 67.93; H, 6.91; N, 2.48. Found: C, 68.14; H, 6.90; N, 2.35.

### 3.58. Pottasium 1-[(3β,18α,20β)-3-hydroxy-11,29-dioxo-olean-12-en-29-yl]piperidine-4-carboxylate (26j)

Preparation as described for **26i**. The crude product was crystallized from $Et_2O$ to give **26j** as a white powder (93%). Anal. Calcd for $C_{36}H_{54}NO_5K$: C, 69.75; H, 8.78; N, 2.26. Found: C, 69.52; H, 8.55; N, 2.30.

### 3.59. X-ray crystal structure analyses—experimental

X-ray diffraction data of crystals of **1**·DMSO, **2a**·solv (a disordered solvate from acetone/ethanol), **2b**, **10d**, **15**·DMSO, **19**, and **20** were collected on Bruker Smart APEX CCD diffractometers using graphite-monochromated Mo Kα radiation ($\lambda$ = 0.71073 Å) and 0.3° $\omega$-scan frames covering complete spheres of the reciprocal space with $\theta_{max}$ = 27–30.5°. After data integration with program SAINT+ corrections for absorption, $\lambda$/2 effects, and crystal decay were applied with program SADABS.[53] The structures were solved by direct methods (program SHELXS97) and refined on $F^2$ with program SHELXL97. All non-hydrogen atoms were refined anisotropically. Most H atoms were placed in calculated positions and thereafter treated as riding. A torsional parameter was refined for each methyl group. For compound **2a**·solv the disordered solvent (acetone/ethanol) was squeezed with program PLATON[54] prior to final refinement The crystal structures of **1**·DMSO and **15**·DMSO are practically isostructural with **15**·DMSO having in 11-position a $CH_2$ group instead of in **1**·DMSO a C=O group. Crystal data and experimental are given in Table 1. A complete set of structural drawings is given in the Supplementary data (Figs. S1–S7). For a brief discussion of selected structural aspects see chapter 'X-ray crystal structure analyses' above. CCDC 699828–699834 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.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## Supplementary data

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## References and notes


1. Ruzicka, L.; Furter, M.; Leuenberger, H. *Helv. Chim. Acta* **1937**, *20*, 312.
2. Baran, J. S.; Langford, D. D.; Liang, C.; Pitzele, B. S. *J. Med. Chem.* **1974**, *17*, 184.
3. Asl, M. N.; Hosseinzadeh, H. *Phytother.Res.* **2008**, *22*, 709.
4. Seckl, J. R.; Walker, B. R. *Endocrinology* **2001**, *142*, 1371.
5. Stewart, P. M.; Krozowski, Z. S. *Vitam. Horm.* **1999**, *57*, 249.
6. Lakshmi, V.; Monder, C. *Endocrinology* **1988**, *123*, 2390.
7. Tomlinson, J. W.; Walker, E. A.; Bujalska, I. J.; Draper, N.; Lavery, G. G.; Cooper, M. S.; Hewison, M.; Stewart, P. M. *Endocr. Rev.* **2004**, *25*, 831.
8. Agarwal, A. K.; Tusie-Luna, M. T.; Monder, C.; White, P. C. *Mol. Endocrinol.* **1990**, *4*, 1827.
9. Walker, E. A.; Clark, A. M.; Hewison, M.; Ride, J. P.; Stewart, P. M. *J. Biol. Chem.* **2001**, *276*, 21343.
10. Kotelevtsev, Y. V.; Jamieson, P. M.; Best, R.; Stewart, F.; Edwards, C. R. W.; Seckl, J. R.; Mullins, J. J. *Endocr. Res.* **1996**, *22*, 791.
11. Dzyakanchuk, A. A.; Balazs, Z.; Nashev, L. G.; Amrein, K. E.; Odermatt, A. *Mol. Cell. Endocrinol.* **2009**, *301*, 137.
12. Stewart, P. M.; Corrie, J. E.; Shackleton, C. H.; Edwards, C. R. *J. Clin. Invest.* **1988**, *82*, 340.
13. Albiston, A. L.; Obeyesekere, V. R.; Smith, R. E.; Krozowski, Z. S. *Mol. Cell. Endocrinol.* **1994**, 105.
14. Whorwood, C. B.; Ricketts, M. L.; Stewart, P. M. *Endocrinology* **1994**, *135*, 2533.
15. Seckl, J. R.; Chapman, K. E. *Eur. J. Biochem.* **1997**, *249*, 361.
16. Walker, B. R.; Connacher, A. A.; Lindsay, R. M.; Webb, D. J.; Edwards, C. R. *J. Clin. Endocrinol. Metab.* **1995**, *80*, 3155.
17. Sandeep, T. C.; Yau, J. L.; MacLullich, A. M.; Noble, J.; Deary, I. J.; Walker, B. R.; Seckl, J. R. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 6734.
18. Kotelevtsev, Y.; Holmes, M. C.; Burchell, A.; Houston, P. M.; Schmoll, D.; Jamieson, P.; Best, R.; Brown, R.; Edwards, C. R. W.; Seckl, J. R.; Mullins, J. J. *Proc. Natl. Acad. Sci. U.S.A.* **1997**, *94*, 14924.
19. Morton, N. M.; Seckl, J.; Walker, B. R.; Andrew, R. WO 02/076435, 2002.
20. Masuzaki, H.; Paterson, J.; Shinyama, H.; Morton, N. M.; Mullins, J. J.; Seckl, J. R.; Flier, J. S. *Science* **2001**, *294*, 2166.
21. Paterson, J. M.; Seckl, J. R.; Mullins, J. J. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **2005**, *289*, R642.
22. Stewart, P. M.; Krozowski, Z. S.; Gupta, A.; Milford, D. V.; Howie, A. J.; Sheppard, M. C.; Whorwood, C. B. *Lancet* **1996**, *347*, 88.
23. Mune, T.; Rogerson, F. M.; Nikkila, H.; Agarwal, A. K.; White, P. C. *Nat. Genet.* **1995**, *10*, 394.
24. Nunez, B. S.; Rogerson, F. M.; Mune, T.; Igarashi, Y.; Nakagawa, Y.; Phillipov, G.; Moudgil, A.; Travis, L. B.; Palermo, M.; Shackleton, C.; White, P. C. *Hypertension* **1999**, *34*, 638.
25. Walker, B. R.; Stewart, P. M.; Shackleton, C. H. L.; Padfield, P. L.; Edwards, C. R. W. *Clin.Endocrinol.(Oxf).* **1993**, *39*, 221.
26. Stewart, P. M.; Wallace, A. M.; Atherden, S. M.; Shearing, C. H.; Edwards, C. R. *Clin. Sci. (Lond.)* **1990**, *78*, 49.
27. Stewart, P. M.; Valentino, R.; Wallace, A. M.; Burt, D.; Shackleton, C. H. L.; Edwards, C. R. W. *Lancet* **1987**, *2*, 821.
28. Su, X. D.; Lawrence, H.; Ganeshapillai, D.; Cruttenden, A.; Purohit, A.; Reed, M. J.; Vicker, N.; Potter, B. V. L. *Bioorg. Med. Chem.* **2004**, *12*, 4439.
29. Severini Ricca, G.; Russo, G. *Gazz. Chim. Ital.* **1968**, *98*, 602.
30. Su, X.; Lawrence, H.; Ganeshapillai, D.; Cruttenden, A.; Purohit, A.; Reed, M. J.; Vicker, N.; Potter, B. V. L. *Bioorg. Med. Chem.* **2004**, *12*, 4439.
31. Terasawa, T.; Okada, T.; Hara, T.; Itoh, K. *Eur. J. Med. Chem.* **1992**, *27*, 345.
32. Pellegata, R.; Pinza, M.; Pifferi, G.; Farina, C. *Org. Prep. Proced. Int.* **1999**, *31*, 181.
33. Ullah, N.; Seebacher, W.; Haslinger, E.; Jurenitsch, J.; Rauchensteiner, K.; Weis, R. *Monatsh. Chem.* **2002**, *133*, 139.
34. Mikhailova, L. R.; Baltina, L. A.; Kondratenko, R. M.; Kunert, O.; Spirikhin, L. V.; Galin, F. Z.; Tolstikov, G. A. *Chem. Nat. Compd.* **2006**, *42*, 553.
35. Odermatt, A.; Arnold, P.; Stauffer, A.; Frey, B. M.; Frey, F. J. *J. Biol. Chem.* **1999**, *274*, 28762.
36. Schweizer, R. A.; Atanasov, A. G.; Frey, B. M.; Odermatt, A. *Mol. Cell. Endocrinol.* **2003**, *212*, 41.
37. Shimoyama, Y.; Hirabayashi, K.; Matsumoto, H.; Sato, T.; Shibata, S.; Inoue, H. *J. Pharm. Pharmacol.* **2003**, *55*, 811.
38. Su, X.; Vicker, N.; Lawrence, H.; Smith, A.; Purohit, A.; Reed, M. J.; Potter, B. V. L. *J. Steroid Biochem. Mol. Biol.* **2007**, *104*, 312.

39. Vicker, N.; Su, X.; Lawrence, H.; Cruttenden, A.; Purohit, A.; Reed, M. J.; Potter, B. V. L. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3263.
40. Classen-Houben, D.; Schuster, D.; Da Cunha, T.; Odermatt, A.; Wolber, G.; Jordis, U.; Kueenburg, B. *J. Steroid Biochem. Mol. Biol.* **2009**, *113*, 248.
41. Schuster, D.; Maurer, E. M.; Laggner, C.; Nashev, L. G.; Wilckens, T.; Langer, T.; Odermatt, A. *J. Med. Chem.* **2006**, *49*, 3454.
42. Campsteyn, H.; Dupont, L.; Lamotte, J.; Dideberg, O.; Vermeire, M. *Acta Cryst.* **1977**, *B33*, 3443.
43. Alvarez-Larena, A.; Brianso, J. L.; Capparelli, M. V.; Farran, J.; Piniella, J. F. *Afinidad* **2007**, *64*, 278.
44. Askam, V.; Baines, C. M.; Smith, H. J. *J. Pharm. Pharmacol.* **1966**, *18*, 168.
45. Kanaoka, M.; Kato, J.; Yano, S. *Chem. Pharm. Bull.* **1990**, *38*, 221.
46. Ruzicka, L.; Leuenberger, H. *Helv. Chim. Acta* **1936**, *19*, 1402.
47. Petrenko, N. I.; Petukhova, V. Z.; Shakirov, M. M.; Shults, E. E.; Tolstikov, G. A. *Russ. J. Org. Chem.* **2000**, *36*, 982.
48. Rozen, S.; Shahak, I.; Bergmann, E. D. *Tetrahedron* **1973**, *29*, 2327.
49. Bergmann, F. *Biochem. Ztschr.* **1933**, *267*, 296.
50. Logemann, W.; Lauria, F.; Tosolini, G. *Chem. Ber.* **1957**, *90*, 601.
51. Ruzicka, L.; Leuenberger, H.; Schellenberg, H. *Helv. Chim. Acta* **1937**, *20*, 1271.
52. Brieskorn, C. H.; Wallenstaetter, W. *Arch. Pharm. Ber. Dtsch. Pharm. Ges.* **1967**, *300*, 717.
53. Bruker programs: SMART, version 5.629; SAINT+, version 6.45; SADABS, version 2.10; SHELXTL, version 6.14; Bruker AXS: Madison, WI, 2003.
54. Spek, A. L. *PLATON: A Multipurpose Crystallographic Tool*; University of Utrecht: Utrecht, The Netherlands, 2008.