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Synthesis of novel 3-amino and 29-hydroxamic acid derivatives of glycyrrhetinic acid as selective 11β-hydroxysteroid dehydrogenase 2 inhibitors

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Chronic inflammatory disease
Cancer

ABSTRACT

Glycyrrhetinic acid, the metabolite of the natural product glycyrrhizin, is a well known nonselective inhibitor of 11β-hydroxysteroid dehydrogenase (11β-HSD) type 1 and type 2. Whereas inhibition of 11β-HSD1 is currently under consideration for treatment of metabolic diseases, such as obesity and diabetes, 11β-HSD2 inhibitors may find therapeutic applications in chronic inflammatory diseases and certain forms of cancer. So far, no selective 11β-HSD2 inhibitor has been developed and neither animal studies nor clinical trials have been reported based on 11β-HSD2 inhibition. Starting from the lead compound glycyrrhetinic acid, novel triterpene type derivatives were synthesized and analyzed for their biological activity against overexpressed human 11β-HSD1 and 11β-HSD2 in cell lysates. Several hydroxamic acid derivatives showed high selectivity for 11β-HSD2. The most potent and selective compound is active against human 11β-HSD2 in the low nanomolar range with a 350-fold selectivity over human 11β-HSD1.

1. Introduction

11β-Hydroxysteroid dehydrogenases (11β-HSDs) are microsomal enzymes belonging to the short-chain dehydrogenase/reductase (SDR) family. In humans and rodents, two isozymes, 11β-HSD1 and 11β-HSD2 have been identified which catalyze the interconversion of active 11β-hydroxyglucocorticoids and their inactive 11-keto counterparts (Fig. 1).[1,2] 11β-HSD1 NADPH-dependently activates the 11-ketosteroids cortisone (human) and 11-dehydrocorticosterone (rodents) to cortisol and corticosterone, respectively. 11β-HSD1 is highly expressed in many glucocorticoid target tissues, including liver, adipose tissue, skeletal muscle and macrophages. 11β-HSD2 is a NAD^+-dependent dehydrogenase and inactivates 11β-hydroxyglucocorticoids by oxidation in kidney, colon, placenta and inflamed tissue. In classical aldosterone target tissues, such as renal cortical collecting ducts and distal colon, 11β-HSD2 protects the mineralocorticoid receptor from activation by glucocorticoids.[3,4]

Active glucocorticoids play a vital role in the regulation of carbohydrate, protein, lipid, and bone metabolism, the maturation and differentiation of cells, and the modulation of inflammatory responses and stress. These cortisol effects are mediated by the activation of glucocorticoid receptors. The local concentration of active cortisol in specific tissues is tuned by the pre-receptor metabolism performed by 11β-HSDs. Cortisone in plasma provides a pool of inactive precursor that can be converted to active glucocorticoids at sites where 11β-HSD1 reductase activity is predominant. Local excess or deficiency of glucocorticoids due to impaired function of 11β-HSDs has been associated with specific diseases, pointing to potential therapeutic indications for selective inhibitors of both, 11β-HSD1 and 11β-HSD2.

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Elevated 11β-HSD1-dependent glucocorticoid activation is associated with multiple features of the metabolic syndrome like insulin and leptin resistance, visceral obesity, dyslipidemia, and type 2 diabetes.[5–7] Over-expression of 11β-HSD1 within adipose tissue in transgenic mice results in insulin resistance, hyperlipidemia and visceral obesity, whereas 11β-HSD1 knockout mice show decreased triglyceride and cholesterol levels and resistance to stress-induced hyperglycemia.[8,9]

Glycyrrhetinic acid (GA), the metabolite of the natural product glycyrrhizin, inhibits both, 11β-HSD1 and 11β-HSD2.[10–12] In homogenates of rat liver and kidney, a 20- to 40-fold selectivity for 11β-HSD1 over 11β-HSD2 was reported for 11-deoxo-glycyrrhetinic acid, glycyrrhetinic acid 3-hemiphthalate and glycyrrhetol, based on IC_{50} values.[13] Other compounds that are not triterpenes have been identified in high throughput screening campaigns and lead optimization programs as selective 11β-HSD1 inhibitors by different pharmaceutical companies and are currently being developed for the treatment of metabolic diseases.[14–21]

Whereas beneficial effects have been reported for the inhibition of 11β-HSD1 in metabolic diseases such as obesity and diabetes, the target 11β-HSD2 has been associated with (chronic) inflammatory diseases and cancer. Several studies found an over-expression of 11β-HSD2 in inflamed tissues and in many cancer cell lines. It has been demonstrated that in rheumatoid arthritis synovial cells have a reduced capacity of local reactivation of cortisone which has been associated with increased activity of 11β-HSD2.[22–26] Thus, the impaired immunomodulatory effect of glucocorticoids may be improved upon pharmacological inhibition of 11β-HSD2. However, no selective 11β-HSD2 inhibitor has been developed so far and neither animal studies nor clinical trials have been executed based on the selective inhibition of 11β-HSD2. To our knowledge, the only compound reported to exhibit noteworthy selectivity for 11β-HSD2 is a hydroxyethylamide derivative of glycyrrhetinic acid reported by Vicker et al.[27] with only 36% inhibition of rodent 11β-HSD1 but 92% inhibition of rodent 11β-HSD2 at 10 μM. The reported IC_{50} value of 0.004 nM for 11β-HSD2 is very low. However, using human 11β-HSD2, an IC_{50} value in the lower micromolar range was obtained (own observations).[28]

In previous work, the selectivity of several GA derivatives has been studied using 11β-HSD1 and 11β-HSD2 isolated from rat liver and kidney, respectively.[13,27,29,30] Some of the published compounds were selective for rat 11β-HSD1 over 11β-HSD2 and also showed inhibitory activity against human 11β-HSD1. Other studies demonstrated significant species-specific differences in the activities of inhibitors and the conversion of substrates by 11β-HSD1, implicating that the primary biological assay should be performed with the human enzymes.[31–33]

GA, as a nonselective inhibitor of both isozymes is a valuable starting point for the development of selective 11β-HSD2 inhibitors. Here, we describe the synthesis of novel hydroxamic acid derivatives of GA, as well as their inhibitory activity against human recombinant 11β-HSD1 and 11β-HSD2.

2. Results and discussion

2.1. Chemistry

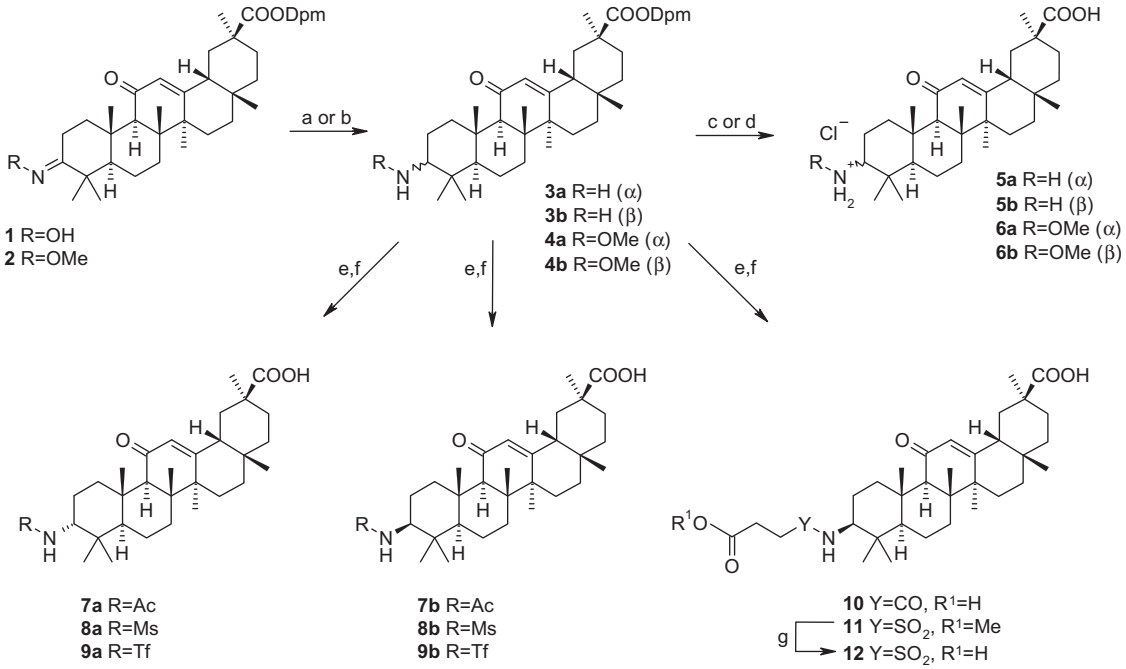
Within the framework of ongoing studies various modifications of the GA A-ring, including the introduction of sulfur, halides, double bonds and additional hydroxy groups, the installation of an episulfide and ring expansions have already been reported.[28,34] Furthermore, the synthesis and inhibitory potential of a variety of C29 amides[28] and a large number of Ugi-type-products have been published.[35] In the current report we discuss the synthesis of a variety of 3-amino-GA derivatives, the installation of C-29 hydroxamic acid motifs on the GA scaffold and finally the combination of both modifications for selected compounds.

2.2. Synthetic modification at the 3-amino moiety

Within this part of GA-based structures a set of related 3-amino-GA derivatives has been synthesized varying the relative stereochemistry at the 3-position and the NH-acidity (nucleophilicity), respectively, and attaching additional carboxylic acid moieties. In order to facilitate workup and purification of the intermediates, a synthetic strategy with C29-protection was envisaged accepting the additional deprotection step of the ester protecting group. The syntheses of the relevant starting materials, 3-oximo- and 3-methoximo GA diphenylmethyl esters (**1** and **2**) have been described previously.[28] The oximes **1** and **2** were reduced to the corresponding amines and methoxyamines (**3a**/**3b** and **4a**/**4b**)[28] with tBuNH$_2$·BH$_3$/TiCl$_3$ and tBuNH$_2$·BH$_3$/HCl, respectively (Scheme 1). Both pairs of diastereomers were successfully separated by chromatography on a multigram scale. The single diastereomeric esters were deprotected to the corresponding free acids with TFA/anisole or by catalytic hydrogenation and isolated as hydrochlorides (**5a**/**5b**[36] and **6a**/**6b**). Starting from the 3-amino-esters **3a** and **3b** a variety of 3-(sulfon)amido GA derivatives was prepared via standard acylation or sulfonylation protocols and subsequent hydrogenolysis (**7a**–**9b** and **10**–**12**). In total, a subset of thirteen 3-amino GA derivatives was prepared varying in the stereochemistry of the 3-position and the acidity of the NH group (Scheme 1). Furthermore, compounds **10**–**12** carry an additional carboxylic acid moiety and thus mimic the hemisuccinate of GA, carbenoxolone (Fig. 1).

2.3. Synthetic modifications of the C29 hydroxamic acid motif

In addition to the ring-A modifications, the C29 carboxylic acid moiety has been widely varied in previous publications, wherein the C29 hydroxamic acid motif was considered as one of the most relevant C29-modification for inhibition of 11β-HSD2.[30] Hence, a systematic variation of the substitution pattern of the hydroxamic acid motif of GA and its 3-*O*-acetylated derivative **13** was performed to allow a first insight into structure–activity relationships. To come up with a reliable protocol for the conversion of GA-type carboxylic acids to hydroxamic acids, several methods have been evaluated with varying success. A literature protocol based on PPAA-coupling-reagent (1-propanephosphonic acid cyclic anhydride)[37] describing the conversion of GA to the corresponding hydroxamic acid **20** gave significantly lower yields in our hands (also in the analogous attempt to prepare **20**). The attempted conversion of a readily formed mixed anhydride (ethyl carbonate)[38] to the corresponding hydroxamic acid lead only to recovery of starting acid **13**. It turned out that the installation of the hydroxamic acid motif at the C29 position of GA is best accomplished via formation of the corresponding acid chloride and treatment with relevant hydroxylamine (as hydrochloride salt). By applying these conditions a large set of 3-*O*-GA based hydroxamic acids has been prepared (Scheme 2). While *O*-substituted and *N*-substituted hydroxamic acids could be directly synthesized from or via the acid chloride **13a** in good yields, the unsubstituted hydroxamic acid motif (e.g., **20**) was most reliably installed in two steps via the corresponding *O*-benzyl hydroxamic acid and subsequent hydrogenolysis. Attempts to analogously react acid chloride **13a** directly with NH_2OH·HCl lead to irreproducible low yields and difficult purification. It is noteworthy that the conversion of **13a** into **20** with NH_2OH·HCl was successfully implemented under TEA/TMSCl conditions.[39] However, this latter method could not be applied to the following cases of 3-*N*-derivatives of GA, which were therefore again synthesized in two steps (vide infra).



Scheme 1. Towards 3-(sulfon)amido-GA derivatives. Reagents and conditions: (a) **1**, $TiCl_3$, $tBuNH_2{\cdot}BH_3$ (58% **3b**, 17% **3a**); (b) $tBuNH_2{\cdot}BH_3$, HCl (66% **4b**, 14% **4a**); (c) H_2, Pd/C 65–83% for **5a**, **5b**, **6a**; (d) TFA, anisole 85% for **6b**; (e) Ac_2O, MsCl, Tf_2O, succinic anhydride or $MeOOC(CH_2)_2SO_2Cl$ in DCM/TEA 0 °C to rt (42–95%); (f) H_2, Pd/C (50–99%); (g) NaOH in $MeOH/H_2O$, 97% for **12**.

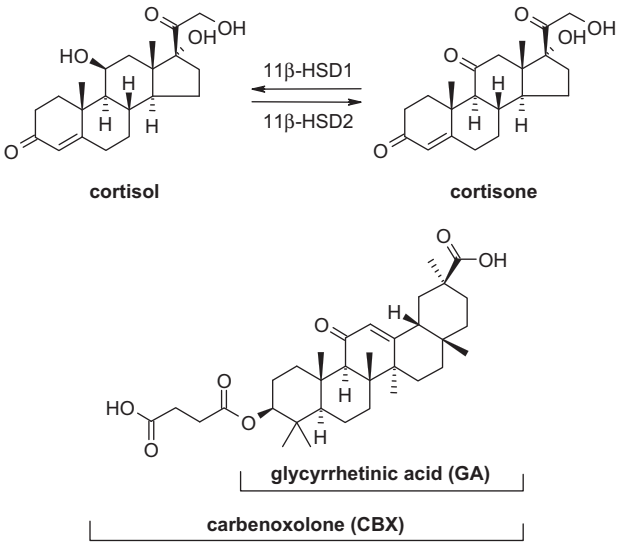


Figure 1. 11β-HSD enzymes catalyze the interconversion of cortisone and cortisol. Glycyrrhetinic acid and carbenoxolone represent nonselective 11β-HSD inhibitors that serve as lead molecules in the present study.

2.4. Synthesis of selected 3-amino-GA based C29 hydroxamic acid derivatives

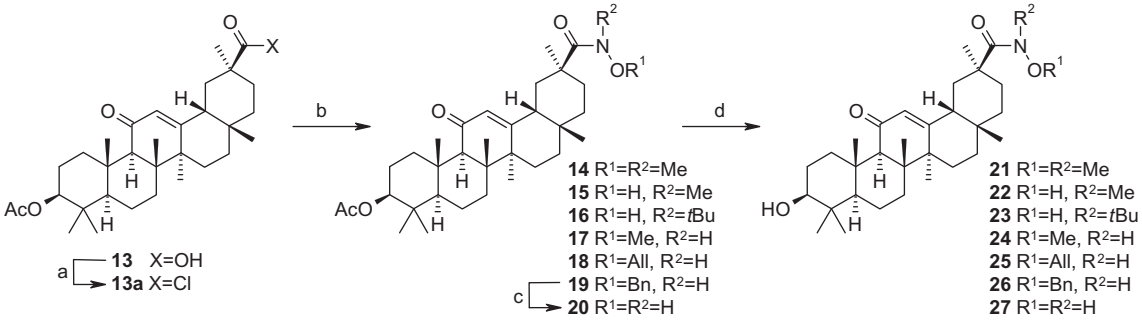
Based on preliminary results from the 11β-HSD screening, some structural elements (TfNH–, AcNH– and MeONH– for C3 and –CONHOH and –CON(Me)OH) for C29) were selected to be formally combined as new compounds. Two different strategies have been applied (Scheme 3).

For the (sulfon)amide type compounds the optimized procedure from the 3-AcO-GA series was thus used to install the hydroxamic acid moieties as the final reaction step. The corresponding carboxylic acids (**7a**/**7b** and **9a**/**9b**) were therefore converted to the hydroxamic acid derivatives via the corresponding acid chlorides (in situ). As explained in the 3-OAc series, the *N*-methyl hydroxamic acids (**28a**–**29b**) were prepared directly and the unsubstituted hydroxamic acids (**32a**–**33b**) were prepared via the corresponding *O*-benzyl-hydroxamic acids (**30a**–**31b**). For the modification of the 3-methoxyamino-GA **4a**/**4b** with the hydroxamic acid motif another strategy was envisaged via initial conversion of 3-keto GA **34** to the corresponding hydroxamic acid derivatives (**36** via **35** and **37**) and subsequent transformation to the 3-methoxyamino compounds. This way the 3-keto- and 3-oximo GA hydroxamic acid derivatives (**35–41**) could be included in this investigation.

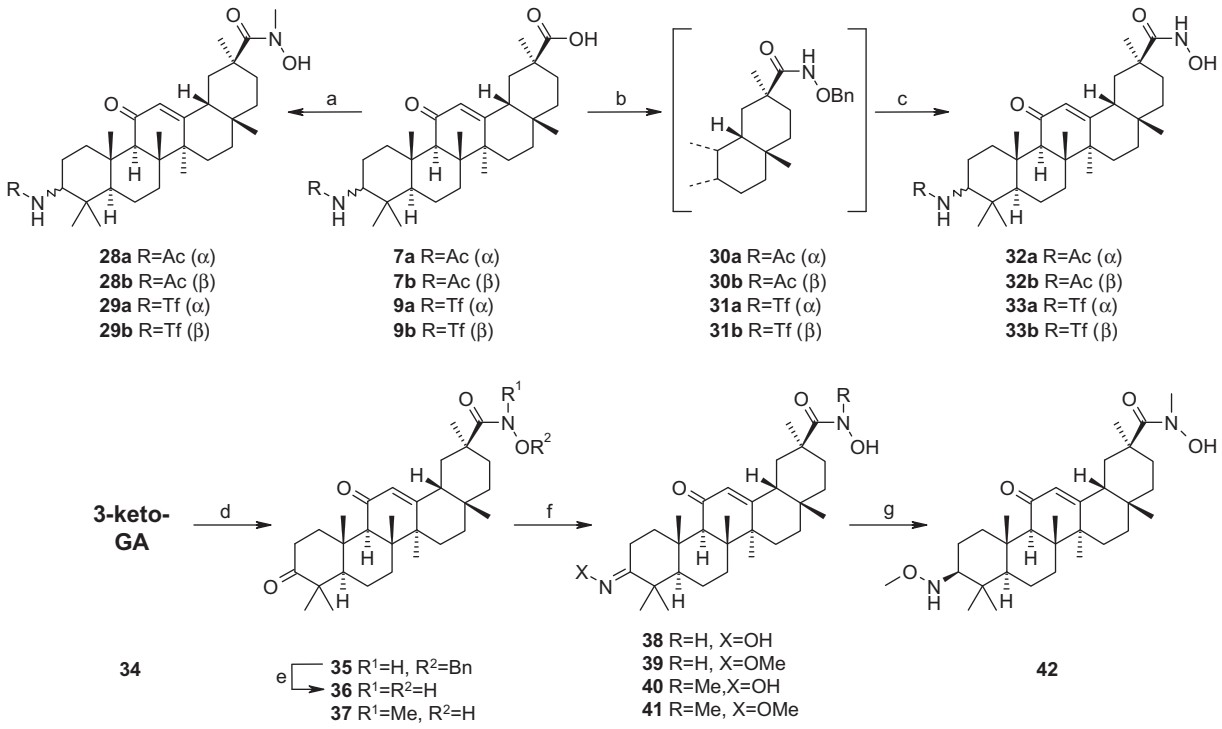
It is noteworthy that in the purification of crude 3-keto hydroxamic acid species **35** and **37** small amounts of remaining 3-keto-GA **34** turned out to be very difficult to separate by standard normal-phase chromatography or aqueous extraction. Gratifyingly, by passing contaminated **35** and **37** over a short bed of amino-phase the contaminating amounts of **34** could be separated. With pure **35** and **36** in hands the corresponding oximes were then prepared by standard procedures. The preparation of targeted 3β-methoxyamino GA-*N*-methyl-hydroxamic acid **42** could eventually be accomplished by $tBuNH_2{\cdot}BH_3$-reduction of oxime ether **41** and purification of diastereomers by column chromatography and repprecipitation. The analogous reduction of oxime ether **39** (unsubstituted hydroxamic acid) failed, however, due to the hydrolytic lability of the free hydroxamic acid.

2.5. Biology

Glycyrrhetinic acid (GA) is a potent and nonselective inhibitor of both 11β-HSD isozymes. Shimoyama et al. reported a lower IC_{50} value using rat hepatic 11β-HSD1 homogenate (90 ± 2 nM) compared to rat renal 11β-HSD2 homogenate (360 ± 2 nM).[13] Potter et al. reported 85% inhibition of rat 11β-HSD1 and complete inhibition of rat 11β-HSD2 at a concentration of 10 μM of GA.[27,29,30,40] We evaluated the inhibitory activity of GA and its derivatives against recombinant human 11β-HSD1 and 11β-HSD2. Using a tenfold lower inhibitor concentration (1 μM) we



Scheme 2. Towards 3-hydroxy-GA hydroxamic acid derivatives. Reagents and conditions: (a) $SOCl_2$, reflux, 99%; (b) relevant hydroxylamines as hydrochloride salts, DCM, TEA, 40–90%; (c) H_2, Pd/C, THF, 94%; (d) KOH, MeOH, 30–99%.



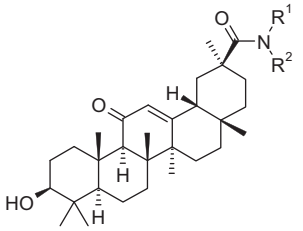
Scheme 3. Synthesis of 3-amino-GA based hydroxamic acid derivatives. Reagents and conditions: (a) $SOCl_2$, reflux, NH(Me)OH·HCl DCM, TEA (61–81%); (b) $SOCl_2$, reflux, $BnONH_2$, DCM, TEA (81–93%); (c) H_2, Pd/C in MeOH or MeOH/EtOAc with 1% AcOH (40–64%); (d) $SOCl_2$, reflux; $BnONH_2$ or HN(Me)OH·HCl, DCM, TEA; (e) H_2, Pd/C in MeOH 56%); (f) NH_2OH·HCl in pyridine or NH(Me)OH·Cl, NaOAc in $CHCl_3$/MeOH; (g) $tBuNH_2{\cdot}BH_3$, dioxane/EtOH, 3 M HCl.

found an inhibition of 83.9% of human 11β-HSD1 and 93.6% of human 11β-HSD2 for GA. The licensed drug carbenoxolone (CBX) had comparable potency with 87.7% inhibition of 11β-HSD1 and 98.2% inhibition of 11β-HSD2. As the lead compounds GA and CBX showed significant inhibition of 11β-HSD1 and 11β-HSD2 at 1 μM, novel derivatives were first screened at a concentration of 1 μM. As soon as first highly active compounds were found further derivatives were screened at 0.2 μM. The activity of the compounds is summarized in Tables 1–3, showing the residual convertive activity of both isoenzymes. IC_{50} values were determined for selected 11β-HSD2 selective compounds that comprised a low residual acitivty for 11β-HSD2 and a high residual activity for 11β-HSD1.

The crystal structure of 11β-HSD1 in complex with carbenoxolone (CBX) and $NADP^+$ was analyzed for necessary and potential interactions between inhibitor and protein (PDB ID: 2BEL).[41,42] Besides multiple hydrophobic interactions of the triterpene core with surrounding amino acids (Thr124, Leu126, Leu171, Ala172, Tyr177, Val180, Tyr183, Leu217, Ala223, Ala226, and Val227), specific interactions are formed with the carboxylic acid oxygen atom, the 11-keto function and the carbonyl oxygen of the ester between GA and succinic acid. The carboxylic acid of GA interacts with the hydrogen bond donor functions of Tyr183 and the 2′-hydroxy-group of the ribose of the nicotinamide nucleotide of $NADP^+$. The 11-keto function acts as a hydrogen bond acceptor for the hydroxy group of Ser170 and the backbone amide of Ala172. Finally the carbonyl oxygen atom of the ester between GA and succinic acid forms a hydrogen bond from the amide nitrogen of Leu217 as well as from a conserved water molecule. The free acid function of the succinate is not well resolved in the crystal structure which might be due to high conformational flexibility and lack of specific interactions. Based on this structural information a series of different modifications of the carboxylic acid in position 29 was synthesized and biologically evaluated (Table 1).

The dipeptide derivatives **43** and **44** synthesized using Ugi-type multiple component reaction,[35] as well as the glycine amide deriv-

Table 1
Amide type derivatives (C29) of GA and their inhibition of 11β-HSD1 and 11β-HSD2



Compound	R^1	R^2	Concd (nM)	% Residual conversion (mean ± SD)	
				11β-HSD2	11β-HSD1
GA			1000	6 ± 2	16 ± 2
CBX			1000	2 ± 1	12 ± 4
43	$CH_2CONHCH_2COOH$	CH_2CH_2OH	1000	109 ± 9	109 ± 15
44	$CH_2CONHCH_2COOH$	CH_2COOH	1000	89 ± 3	79 ± 4
45	CH_2COOH	H	1000	79 ± 1	97 ± 6
46	$CH_2CH_2N(CH_3)_2$	H	1000	59 ± 5	64 ± 19
47	CH_2CH_2OH	H	1000	59 ± 19	97 ± 5
48[a]	H	H	1000	13 ± 1	9 ± 5
27	OH	H	1000	2 ± 2	53 ± 14

[a] Tested as 3-acetate.

ative **45** were not active, neither against 11β-HSD1 nor against 11β-HSD2. Weak activity on both enzymes was observed for the dimethylaminoethyl amide derivative **46**. The hydroxyethyl amide derivative **47** showed a complete loss of activity against 11β-HSD1 whereas the activity against 11β-HSD2 was significantly reduced, compared to GA. The free amide **48** had activity in a similar range compared to GA, but with a slightly preferential inhibition of 11β-HSD1 over 11β-HSD2. The most potent compound for 11β-HSD2 was the hydroxamic acid derivative **27**, which in addition showed reasonable selectivity over 11β-HSD1 (Table 1). Determination of IC_{50} values (Table 4) confirmed the high activity and demonstrated an approximately 10-fold selectivity for 11β-HSD1 over 11β-HSD2.

In summary, many modifications of position 29 lead to a partial or even complete loss of activity against both enzymes at concentrations of 1 μM. Exceptions are the free amide **48**, where the activity is retained for both enzymes, and the hydroxamic acid derivative **27**, which is the most potent and selective compound in this series with IC_{50} values of 122 nM and 1157 nM for 11β-HSD2 and 11β-HSD1, respectively, resulting in an approximately 10-fold selectivity (Table 4).

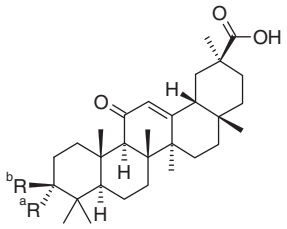
The 3-acetate **13** has already been suggested as an inhibitor of 11β-HSD isozymes based on a pharmacophore model.[43] The compound does not have the second carboxylic acid function present in CBX; however, observations from the crystal structure of 11β-HSD1 with CBX suggested that this group is not involved in essential interactions. Compound **13** and further modifications (*O*-based and *N*-based) of the 3-position were obtained and subjected to biological testing (Table 2). Compound **13** retains the potential hydrogen bond acceptor function seen in the crystal structure of 11β-HSD1 with CBX and is weakly active on both enzymes, with a preference for 11β-HSD2. Based on the fact that the ester oxygen atom does not participate in the interaction network with the protein, the corresponding 3β-acetamide **7b** was synthesized. Both **7b** but also the 3α-acetamide **7a** were active on 11β-HSD1 and 11β-HSD2. Whereas the 3α-derivative showed similar activity on both enzymes, the 3β-derivative preferentially inhibited 11β-HSD2. The free 3β-amine derivative **5b**, which does not have the hydrogen bond acceptor function, was only a weak inhibitor. The 3-keto-GA **34**, the 3-methoxyimine derivative **49**, and the 3α- and 3β-methoxyamine derivatives **6a** and **6b** inhibited both enzymes with a preference for 11β-HSD2. The amino-carbenoxolone derivatives **10**–**12** did not enhance enzyme inhibition or selectivity compared to the parent CBX.

In summary, activity against 11β-HSD2 can be retained with small modifications of position 3. The hydrogen bond acceptor seen in the crystal structure of 11β-HSD1 complexed with CBX and $NADP^+$ has proven to be favorable for activity. The 3β-acetate derivative **13** was the most selective compound within this series. The findings above with the modifications of position 3 and 29 and the published influence of a modification of position 11[30] were combined and led to the synthesis of a series of hydroxamic acids, which retain the native keto function in position 11 (Table 3).

Position 3 was modified with the residues found to be active within the above series of compounds and the hydroxamic acid was substituted on the nitrogen or oxygen atom. The 3-acetate of the hydroxamic acid **20** was twice as active as the position 3 unsubstituted hydroxamic acid **27** (Table 4). Methylation of the hydroxamic acid oxygen atom led to compound **24** and a significant loss in 11β-HSD2 activity. In contrast, methylation of the hydroxamic acid nitrogen atom resulting in compounds **15** (3-acetate) and **22** had no influence on 11β-HSD1 activity but increased the 11β-HSD2 activity significantly. Interestingly, methylation of both nitrogen and oxygen (compound **14**) as well as the substitution of the hydroxamic acid oxygen with an allyl function (**18**) led to a significant decrease of inhibitory activity (Table 4). Whereas the *N*-methyl-hydroxamic acid **15** was the most active and selective compound, more spacious substituents like an *N*-*tert*-butyl group in compound **16** were not accepted in this position. Replacement of the 3β-*O*-acetyl function of compound **15** with a 3β-*N*-acetyl group resulted in the comparably active compound **28b**.

In summary, modification of position 3 of the hydroxamic acid derivatives had only a minor impact on the selectivity and activity of the compounds. The substitution of the 3-hydroxy group of the hydroxamic acid derivatives led in all cases to a significant loss of activity. Introduction of a methyl substituent at the hydroxamic acid nitrogen atom resulted in compounds **15** and **22** with significantly increased activity and selectivity toward 11β-HSD2.

Table 2
Derivatives of the 3 hydroxy group of GA and their inhibition of 11β-HSD1 and 11β-HSD2



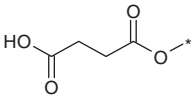
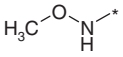
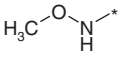
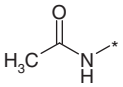
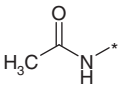
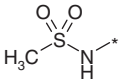
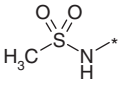
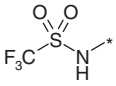
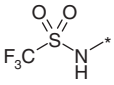
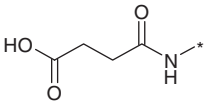
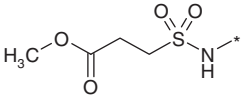
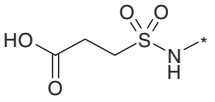
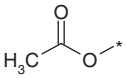
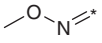
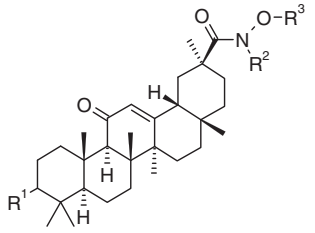
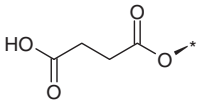
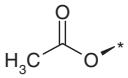
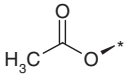
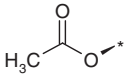
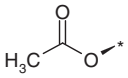
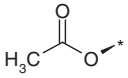
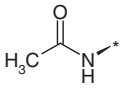
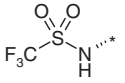
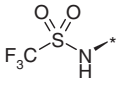
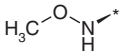
Compound	[a]R	[b]R	Concd (nM)	% Residual conversion (mean ± SD)	
				11β-HSD2	11β-HSD1
GA	H		1000	6 ± 2	16 ± 2
CBX	H		1000	2 ± 1	12 ± 4
3b	H		1000	42 ± 2	15 ± 2
6a		H	200	5 ± 2	43 ± 3
6b	H		200	2 ± 1	33 ± 9
7a		H	1000	4 ± 1	4 ± 2
7b	H		1000	0.2 ± 0.4	36 ± 15
8a		H	200	4 ± 5	32 ± 29
8b	H		200	4 ± 7	58 ± 45
9a		H	200	50 ± 1	99 ± 19
9b	H		200	22 ± 1	87 ± 21
10	H		1000	13 ± 4	6 ± 2
11	H		1000	3 ± 1	1 ± 2
12	H		1000	40 ± 8	5 ± 4
13	H		1000	14 ± 1	53 ± 9
34			1000	1 ± 2	36 ± 11
49			1000	3 ± 1	37 ± 16

Table 3
Hydroxamic acid derivatives of GA and their inhibition of 11β-HSD1 and 11β-HSD2



Compound	R^1	R^2	R^3	Concd (nM)	% residual conversion (mean ± SD)	
					11β-HSD2	11β-HSD1
GA				1000	6 ± 1.5	16 ± 2
CBX				1000	2 ± 1	12 ± 4
14		CH_3	CH_3	200	72 ± 1	95 ± 22
15		CH_3	H	1000	3 ± 1	51 ± 11
16		$C(CH_3)_3$	H	200	85 ± 14	86 ± 3
17		H	CH_3	1000	36 ± 40	38 ± 9
18		H	$CH_2CH{=}CH_2$	200	84 ± 2	99 ± 12
20		H	H	1000	1 ± 2	48 ± 8
22		CH_3	H	200	7 ± 2	71 ± 13
27		H	H	1000	2 ± 1.5	53 ± 14
28b		CH_3	H	200	4 ± 3	72 ± 12
29a		CH_3	H	200	82 ± 3	88 ± 8
29b		CH_3	H	200	44 ± 40	71 ± 27
42		CH_3	H	200	30 ± 18	93 ± 9

3. Conclusions

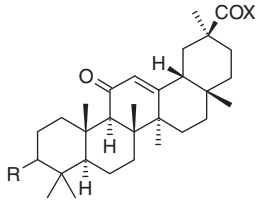
Using glycyrrhetinic acid as a lead compound and starting point, novel highly potent and selective inhibitors of human 11β-HSD2 have been identified. The data generated lead to a significant extension of the knowledge about structure–activity relationship of glycyrrhetinic acid derivatives as inhibitors of human 11β-hydroxysteroid dehydrogenases. The selectivity of synthesized compounds for 11β-HSD2 over 11β-HSD1 ranges from 0.4 to 350, spanning nearly three orders of magnitude. The compounds and information will be used for the further optimization and improvement of potency of the compound class. Compound **15** is the most potent (IC_{50} value of 2.9 nM) and selective (350-fold) inhibitor of human 11β-HSD2 reported to date. As synovial cells have a reduced capacity of local reactivation of cortisone in rheumatoid arthritis, which is expected to result from an increased 11β-HSD2 activity the reported compounds should prove useful as mechanistic tools for further anti-inflammatory in vitro and in vivo studies.

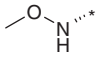
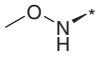
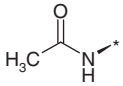
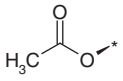
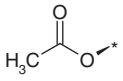
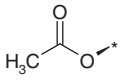
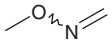
4. Experimental

4.1. General

Compounds **1**, **2**, **13**, **13a**, and **34** have been prepared as reported before.[28] Compound **27** was prepared according to a literature protocol.[37] Whenever reasonable, solvents were purified and

Table 4
IC_{50} values and selectivities of GA and novel selective 11β-HSD2 inhibitors



Compound	R	COX	11β-HSD2		11β-HSD1		Selectivity HSD2/HSD1
			IC_{50} (nM)	95% CI	IC_{50} (nM)	95% CI	
GA			257	186–354	778	631–960	3
6a			4.9	2.8–8.6	61.9	49–78	13
6b			14.5	9.0–23.4	42.7	12.7–144	3
7b			458	385–546	825	634–1076	2
13			750	416–1350	7138	2240–22750	10
15			2.9	0.65–13.1	1012	747–1372	350
20			61.1	48–79	626	465–846	10
24			2130	1740–2600	929	787–1097	0.4
27			122	93–160	1157	932–1440	10
34			329	219–492	619	522–735	1
49			268	193–371	1508	1120–2030	6

dried by standard procedures. Melting points were measured on a Büchi B-545 melting point apparatus or a Kofler-type Reichert Thermovar micro hot stage microscope and are uncorrected. Regarding NMR-assignment and nomenclature the carboxylic acid of GA was assigned as C29 and the adjacent methyl group as C30. NMR spectra were recorded at 297 K in the solvent indicated with a Bruker AC 200-, a Bruker DPX 300-, a Bruker AC 400-, and a Bruker DPX 400 spectrometer using standard Bruker NMR software. Spectra were referenced to tetramethylsilane via calibration with the residual solvent peaks.[44] Reactions were monitored by TLC on Silica Gel 60 F_{254} plates; spots were detected by UV light examination or visualized by spraying with anisaldehyde-sulfuric acid, molybdophosphoric acid, mixture of molybdophosphoric acid and Ce^{IV} ammonium nitrate or ninhydrine and heating. Normal phase column chromatography was performed on Silica Gel 60 (230–400 mesh, Merck). HPLC-HRMS analysis was carried out from CH_3CN solutions (concentration: 1–10 mg/L) using an HTC PAL system autosampler (CTC Analytics AG, Zwingen, Switzerland), an Agilent 1100/1200 HPLC with binary pumps, degasser and column thermostat (Agilent Technologies, Waldbronn, Germany) and Agilent 6210 ESI-TOF mass spectrometer (Agilent Technologies, Palo Alto, United States).

4.2. (3α,18β,20β)-3-Amino-11-oxo-olean-12-en-29-oic acid, diphenylmethyl ester (3a) and (3β,18β,20β)-3-amino-11-oxo-olean-12-en-29-oic acid, diphenylmethyl ester (3b)

Solid NaOAc (12.35 g, 150.5 mmol, 16.3 equiv) was added portionwise to a $TiCl_3$ solution (12% in 5–10% HCl, 47.6 g, 36.9 mmol, ~4 equiv) and the solution was stripped with argon. This solution was added dropwise (30 min) to an Ar-stripped solution of oxime **1** (6.00 g, 9.23 mmol, 1.00 equiv) and tBuNH$_2$·BH$_3$ (2.00 g, 23.1 mmol, 2.5 equiv) in dry EtOH at −9 °C. The dark blue solution was stirred for around 2 h before satd NH_4Cl (600 mL) and DCM (600 mL) were added and the phases were separated. The aqueous layer was extracted with DCM (3×), the combined organic layers were washed with satd NH_4Cl, satd $NaHCO_3$ and brine, dried over Na_2SO_4 and evaporated. Column chromatography (SiO_2: 680 g, $CHCl_3$/MeOH 8:1 + 0.1% AcOH→$CHCl_3$/MeOH 4:1 + 0.1% AcOH) gave (after treatment with satd $NaHCO_3$, brine and drying over Na_2SO_4) pure 3α-amine **3a** (980 mg, 16.7%) and pure 3β-amine (3.40 g, 57.9%) as white solid foams. Analytical data for **3a**: R_f = 0.33 ($CHCl_3$/MeOH 9:1 + 0.1% AcOH), $[\alpha]_D^{20}$ +111.6 (*c* 1.0, $CHCl_3$), ^{1}H NMR ($CDCl_3$): δ 0.67 (s, 3H, H28), 0.87–0.93 (m, 6H, H23, H24), 0.93-1.02 (m, 1H, H2b), 1.09 (s, 3H, H26), 1.15 (s, 3H, H25), 1.12-

1.16 (m, 1H, H15b), 1.17 (s, 3H, H30), 1.21–1.27 (m, 1H, H3), 1.39 (s, 3H, H27), 1.27-1.41 (m, 6H, H1b, H6b, H16b, H21b, H22b, H22a), 1.41-1.52 (m, 2H, H7b, H7a), 1.53–1.77 (m, 3H, H1a, H16a, H19b), 1.76-1.86 (m, 1H, H15a), 1.93–2.15 (m, 4H, H2a, H18, H19a, H21a), 2.46 (s, 1H, H9), 2.47–2.56 (m, 1H, H6a), 2.62–2.96 (m, 1H, H5), 5.52 (s, 1H, H12), 6.93 (s, 1H, $OCHPh_2$), 7.22-7.43 (m, 10H, 10 × PhCH); ^{13}C NMR ($CDCl_3$): δ 16.5 (q, C25), 17.4 (t, C7), 18.7 (q, C26), 23.5 (q, C23/24), 23.6 (q, C27), 25.6 (t, C16), 26.4 (2 × t, C2, C15), 28.3 (2 × q, C28, C30), 28.8 (q, C23/24), 31.2 (t, C21), 31.7 (s, C17), 32.7 (t, C6), 33.6 (t, C1), 36.8 (s, C4), 37.4 (s, C10), 37.5 (t, C22), 41.1 (t, C19), 43.2 (s, C20), 44.0 (s, C8), 45.5 (s, C14), 48.0 (2 × d, C3, C18), 56.2 (d, C5), 61.8 (d, C9), 76.6 (d, $OCHPh_2$), 127.0 (d, PhCH), 127.3 (d, PhCH), 127.8 (d, PhCH), 128.1 (d, PhCH), 128.4 (d, PhCH), 128.58 (d, C12), 128.63 (d, PhCH), 140.10 (s, PhC), 140.13 (s, PhC), 168.8 (s, C13), 175.2 (s, C29), 200.3 (s, C11). Analytical data for **3b**: R_f = 0.23 ($CHCl_3$/MeOH 9:1 + 0.1% AcOH), $[\alpha]_D^{20}$ +129.8 (*c* 1.0, $CHCl_3$) HRMS: calcd $[M+H]^+$: 636.4411 found $[M+H]^+$: 636.4423; ^1H NMR ($CDCl_3$): δ 0.66 (s, 3H, H28), 0.69–0.77 (m, 2H, H5, H16b), 0.84 (s, 3H, H23/24), 0.91-1.07 (m, 3H, H1b, H7b, H16a), 1.04 (s, 3H, H23/24), 1.09 (s, 3H, H26), 1.13 (s, 3H, H25), 1.17 (s, 3H, H30), 1.22-1.53 (m, 4H, H6b, H21b, H22b, H22a), 1.36 (s, 3H, H27), 1.55-1.73 (m, 5H, H2b, H2a, H6a, H7a, C19b), 1.73-1.87 (m, 1H, H15b), 1.92-2.10 (m, 4H, H15a, H18, H19a, H21a), 2.33 (s, 1H, H9), 2.50-2.59 (m, 1H, H3), 2.75–2.86 (m, 1H, H1a), 5.51 (s, 1H, H12), 6.93 (s, 1H, $OCHPh_2$), 7.22–7.42 (m, 10H, 10 × PhCH); ^{13}C NMR ($CDCl_3$): δ 16.05 (q, C25), 16.13 (q, C23/24), 17.7 (t, C7), 18.7 (q, C26), 23.3 (q, C27), 26.4 (3 × t, C2, C15, C16), 28.2 (2 × q, C28, C30), 28.5 (q, C23/C24), 31.2 (t, C21), 31.7 (s, C17), 32.7 (t, C6), 37.2 (s, C10), 37.5 (t, C22), 38.0 (s, C4), 39.6 (t, C1), 41.1 (t, C19), 43.2 (s, C20), 44.0 (s, C8), 45.2 (s, C14), 48.0 (d, C18), 55.4 (d, C5), 60.0 (d, C3), 61.7 (d, C9), 76.6 (d, $OCHPh_2$), 127.0 (d, PhCH), 127.3 (d, PhCH), 127.8 (d, PhCH), 128.1 (d, PhCH), 128.4 (d, PhCH), 128.5 (d, C12), 128.6 (d, PhCH), 140.07 (s, PhC), 140.11 (s, PhC), 168.7 (s, C13), 175.2 (s, C29), 199.9 (s, C11).

4.3. (3α,18β,20β)-3-Methoxyamino-11-oxo-olean-12-en-29-oic acid, diphenylmethyl ester (4a) and (3β,18β,20β)-3-methoxyamino-11-oxo-olean-12-en-29-oic acid, diphenylmethyl ester (4b)

t$BuNH_2 \cdot BH_3$ (196 mg, 2.26 mmol, 3.0 equiv) was added to a solution of the methoxime **2** (664 mg, 0.753 mmol, 1.00 equiv) in EtOH/dioxane (1:2, 5.5 mL). The reaction mixture was cooled to 0 °C and 10% HCl (2.6 mL) was added dropwise keeping the temperature below 5 °C. The reaction mixture was stirred at 0 °C for 2.5 h. Upon complete conversion (TLC, Hex/EtOAc 9:1), solid Na_2CO_3 (~1 g) was added portionwise and the mixture was distributed between satd $NaHCO_3$ and DCM. The organic layer was dried over Na_2SO_4, filtered and evaporated. Column chromatography of the residue (Hex/EtOAc 20:1→Hex/EtOAc 5:1) gave pure 3α-methoxyamine **4a** (70 mg, 14%) and pure 3β-methoxyamine **4b** (330 mg, 65.8%) as white solid foams. Analytical data for **4a**: R_f = 0.11 (Hex/EtOAc 5:1) Due to the instability of the material, it was deprotected and characterized as free acid only. Analytical data of **4b**: R_f = 0.17 (Hex/EtOAc 5:1); $[\alpha]_D^{20}$ +143.0 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 0.66 (s, 3H, H28), 0.72 (s, 3H, H23/24), 0.69–0.77 (m, 1H, H5), 0.89–1.01 (m, 2H, H1b, H16b), 1.07 (s, 3H, H23/24), 1.09 (s, 3H, H26), 1.12–1.19 (m, 1H, H15b), 1.13 (s, 3H, H25), 1.17 (s, 3H, H30), 1.20–1.43 (m, 6H, H2b, H6b, H7b, H21b, H22a, H22b), 1.36 (s, 3H, H27), 1.55–1.71 (m, 3H, H6a, H7a, H19b), 1.79 (td, *J* = 13.5 Hz, *J* = 3.8 Hz, 1H, H15a), 1.86–1.94 (m, 1H, H2a), 1.94–2.08 (m, 4H, H16a, H18, H19a, H21a), 2.34 (s, 1H, H9), 2.51 (dd, *J* = 11.8 Hz, *J* = 4.0 Hz, 1H, H3), 2.75–2.83 (m, 1H, H1a), 3.50 (s, 3H, OCH_3), 5.34 (br s, 1H, NH), 5.51 (s, 1H, H12), 6.93 (s, 1H, $OCHPh_2$), 7.26–7.40 (m, 10H, 10 × PhCH); ^{13}C NMR ($CDCl_3$): δ 16.1 (q, C25), 16.7 (q, C23/24), 17.3 (t, C6), 18.7 (q, C26), 23.3 (q, C27), 23.5 (t, C2), 26.37, 26.40 (2 × t, C15, C16), 28.23, 28.27, 28.6 (3 × q, C23/24, C28, C30), 31.1 (t, C21), 31.7 (s, C17), 32.8 (t, C7), 36.9 (s, C4), 37.1 (s, C10), 37.5 (t, C22), 39.3 (t, C1), 41.1 (t, C19), 43.1 (s, C14), 44.0 (s, C20), 45.3 (s, C8), 48.0 (d, C18), 56.2 (d, C5), 61.6 (d, C9), 61.8 (q, OMe), 67.9 (d, C3), 76.6 (d, $OCHPh_2$), 127.0 (d, PhCH), 127.3 (d, PhCH), 127.8 (d, PhCH), 128.1 (d, PhCH), 128.4 (d, PhCH), 128.5 (d, C12), 128.6 (d, PhCH), 140.06 (s, PhC), 140.10 (s, PhC), 168.7 (s, C13), 175.2 (s, C29), 200.1 (s, C11).

4.4. (3α,18β,20β)-3-Amino-11-oxo-olean-12-en-29-oic acid hydrochloride (5a)

Diphenylmethyl ester **3a** (200 mg, 0.314 mmol, 1.00 equiv) was dissolved in MeOH/AcOH 100:1, 5 mL). The atmosphere was exchanged to argon by evaporation and purging with argon (3 cycles), Pd/C (10%, 300 mg) was added and the atmosphere was exchanged to H_2 (3 cycles). The reaction mixture was stirred under an atmosphere of hydrogen and monitored by TLC. Upon complete conversion of starting material the reaction mixture was filtered over a bed of Celite®. Purification of the crude material was done by dropwise addition of HCl in Et_2O (1 M, 0.6 mmol) to a concentrated solution in MeOH and completion of precipitation by addition of Et_2O (10 mL). The suspension was stirred for several hours before the target compound was collected by filtration and washed excessively with Et_2O to provide compound **5a** (115 mg, 72.2%) as white solid. R_f = 0.12 ($CHCl_3$/MeOH 9:1 + 0.5% AcOH) mp: >350 °C (MeOH/Et_2O); $[\alpha]_D^{20}$ +152.4 (*c* 1.0, MeOH); HRMS: calcd $[M+H]^+$: 470.3629, found $[M+H]^+$: 470.3625; ^1H NMR (DMSO): δ 0.78 (s, 3H, H28), 0.89 (s, 3H, H23/24), 0.91 (s, 3H, H23/24), 0.93–1.03 (m, 1H, H15b), 1.03 (s, 3H, H26), 1.05 (s, 3H, H25), 1.08 (s, 3H, H30), 1.15–1.50 (m, 9H, H1b, H5, H6a, H6b, H7b, H16b, H21b, H22a, H22b), 1.4 (s, 3H, H27), 1.55–1.85 (m, 6H, H2b, H7a, H16a, H19a, H19b, H21a), 1.95–2.15 (m, 3H, H2a, H15a, H18), 2.41–2.53 (m, 1H, H1a), 2.61 (s, 1H, H9), 2.94 (br s, 1H, H3), 5.45 (s, 1H, H12); ^{13}C NMR (DMSO): δ 16.5 (q, C25), 17.3 (t, C6), 18.7 (q, C26), 21.6 (t, C2), 22.8 (q, C23/24), 23.9 (q, C27), 26.2, 26.5 (2 × t, C15, C16), 28.20, 28.28 (2 × q, C23/24, C30), 28.8 (q, C28), 30.8 (t, C21), 31.9 (s, C17), 32.1 (t, C7), 32.5 (t, C1), 35.4 (s, C8), 36.9 (s, C10), 37.9 (t, C22), 41.1 (t, C19), 43.5 (s, C20), 43.6 (s, C8), 45.4 (s, C14), 46.7 (d, C5), 48.5 (d, C18). 56.9 (d, C3), 60.6 (d, C9), 127.5 (d, C12), 170.5 (s, C13), 178.0 (s, C29), 199.6 (s, C11).

4.5. (3β,18β,20β)-3-Amino-11-oxo-olean-12-en-29-oic acid hydrochloride (5b)

Ester **3b** (467 mg, 0.734 mmol, 1.00 equiv) was deprotected by hydrogenolysis analogous to **5a** in MeOH/AcOH 100:1 (8 mL) with Pd/C (100 mg). Upon complete conversion but prior to filtration, 2 M HCl (2 equiv) was added and the reaction mixture was stirred for 30 min. The crude material was purified by column chromatography (SiO_2, $CHCl_3$/MeOH 10:1 + 0.1% AcOH). Precipitation from a concentrated eluent solution was achieved with 1 M HCl in Et_2O (1.4 mmol) and additional Et_2O. The suspension was stirred for several hours, filtered and the crystals were washed with Et_2O to give pure **5b** (307 mg, 82.6%) as white solid. R_f = 0.07 ($CHCl_3$/MeOH 9:1 + 0.1% AcOH); mp: 287–290 °C (toluene, MeOH) (Lit.[36]: >300 °C *dec*., MeOH); $[\alpha]_D^{20}$ +125.9 (*c* 1.0, MeOH/$CHCl_3$ 1:1); HRMS: calcd $[M+H]^+$: 470.3629, found $[M+H]^+$: 470.3625; ^1H NMR (MeOD): δ 0.84 (s, 3H, H28), 0.91 (s, 3H, H23/24), 0.90–0.99 (m, 1H, H5), 1.00–1.20 (m, 3H, H1b, H15b, H16b), 1.09 (s, 3H, H23/24), 1.12–1.18 (br s, 9H, H25, H26, H30), 1.30–1.60 (m, 5H, H6b, H7b, H21b, H22a, H22b), 1.60–2.02 (m, 8H, H2a, H2b, H6a, H7a, H15a, H19a, H19b, H21a), 2.08–2.30 (m, 2H, H16a, H18), 2.52 (s, 1H, H9), 2.76–2.89 (m, 1H, H1a), 2.90–3.00 (m, 1H, H3), 5.59 (s, 1H,

H12); ^{13}C NMR (MeOD): δ 17.33, 17.43 (2 × q, C23/24, C25), 19.3 (t, C6), 20.1 (q, C26), 24.7 (q, C27), 25.0 (t, C2), 28.19, 28.42 (2 × t, C15, C16), 29.2, 29.6, 30.1 (3 × q, C23/24, C28, C30), 32.8 (t, C21), 33.8 (s, C17), 34.4 (t, C7), 38.6 (s, C4), 39.0 (s, C10), 39.9 (t, C22), 40.3 (t, C1), 43.2 (t, C19), 45.5, 45.8, 47.5 (3 × s, C8, C14, C20), 50.8 (d, C18), 56.7 (d, C5), 62.1 (d, C3), 63.5 (d, C9), 129.7 (d, C12), 174.0 (s, C13), 181.2 (s, C29), 203.0 (s, C11).

4.6. (3α,18β,20β)-3-Methoxyamino-11-oxo-olean-12-en-29-oic acid hydrochloride (6a)

Ester **4a** (200 mg, 0.3 mmol, 1.0 equiv) was deprotected by hydrogenolysis analogous to **5a** in MeOH/EtOAc 1:1 + 1% AcOH (30 mL). The crude material was purified by precipitation as hydrochloride by dissolution in THF and addition of 1 M HCl in Et_2O (2 equiv). Filtration and washing with Et_2O and collection of solids by centrifugation gave pure **6a** (104 mg, 64.6%) as white solid. R_f = 0.29 (Hex/EtOAc 1:1 + 0.1% AcOH); $[\alpha]_D^{20}$ +115.0 (*c* 0.3, MeOH) HRMS: calcd $[M+H]^+$: 500.3734, found $[M+H]^+$: 500.3734; ^{1}H NMR ($CDCl_3$/MeOD 1:5): δ 0.85 (s, 3H, H28), 0.98–1.08 (m, 1H, H16b), 1.09 (s, 3H, H23/24), 1.12 (s, 3H, H23/24), 1.15–1.25 (m, 1H, H15b), 1.16 (s, 3H, H26), 1.18 (s, 3H, H30), 1.22 (s, 3H, H25), 1.17–1.27 (m, 1H, H1b), 1.35–1.50 (m, 5H, H5, H7b, H21b, H22a, H22b), 1.45–1.65 (m, 2H, H6a, H6b), 1.49 (s, 3H, H27), 1.65–1.75 (m, 1H, H19b), 1.75–2.05 (m, 5H, H2b, H7a, H15a, H19a, H21a), 2.05–2.30 (m, 1H, H2a, H16a, H18), 2.61–2.70 (m, 1H, H1a), 2.69 (s, 1H, H9), 3.36–3.40 (m, 1H, H3), 4.01 (s, 3H, OCH_3), 5.64 (s, 1H, H12); ^{13}C NMR ($CDCl_3$/MeOD 1:5): δ 17.4 (q, C25), 18.5 (t, C6), 18.9 (t, C2), 19.2 (q, C26), 23.7 (q, C23/24), 24.1 (q, 27), 27.2 (t, C16/15), 27.2 (q, C23/24), 27.4 (t, C15/16), 28.8 (q, C30), 29.1 (q, C28), 31.9 (t, C21), 32.8 (s, C17), 33.1 (t, C7), 34.9 (t, C1), 36.7 (s, C4), 37.9 (s, C10), 38.8 (t, C22), 42.3 (t, C19), 44.66, 44.69 (2 × s, C14, C20), 46.6 (s, C8), 49.6 (d, C18), 50.0 (d, C5), 62.0 (q, OCH_3), 62.1 (d, C9), 67.8 (d, C3), 128.7 (d, C12), 173.1 (s, C13), 180.2 (s, C29), 202.0 (s, C11).

4.7. (3β,18β,20β)-3-Methoxyamino-11-oxo-olean-12-en-29-oic acid hydrochloride (6b)

To a solution of ester **4b** in dry DCM (13 mL), first anisole (1.60 g, 15.02 mol, 50 equiv) and then TFA (4.5 mL) was added dropwise at −10 °C and the reaction mixture was stirred at 0 °C until all starting material was consumed (TLC, Hex/EtOAc 5:2). After 1 h the reaction mixture was diluted with DCM and treated with satd $NaHCO_3$ (55 mL) until the pH was slightly basic. The solution was buffered by addition of AcOH, the phases were separated and the aqueous layer was extracted with DCM (3×). The combined organic layers were washed with brine, dried over Na_2SO_4 and evaporated to give a crude material, which was submitted to column chromatography (SiO_2: 25 g, stepwise gradient from toluene/EtOAc 4:1→1:1 with 0.1% AcOH) to give pure **6b** (137 mg, 85.1%) as white solid. Part of the material was converted to the hydrochloride by dissolving in MeOH and precipitation with 2 M HCl in Et_2O (2–3 equiv) and Et_2O. Filtration and washing with Et_2O gave **6b** as hydrochloride as white solid. R_f = 0.29 ($CHCl_3$/MeOH 30:1); mp: 249–251 °C (Et_2O); $[\alpha]_D^{20}$ +160.3 (*c* 0.8, MeOH); HRMS: calcd $[M+H]^+$: 500.3735, found $[M+H]^+$: 500.3734; ^{1}H NMR ($CDCl_3$/MeOD 2:5) δ 0.78–0.86 (m, 1H, H5), 0.83 (s, 3H, H28), 0.96–1.09 (m, 2H, H1b, H16b), 1.00 (s, 3H, H23/24), 1.15 (s, 3H, H26), 1.17 (s, 3H, H25), 1.19–1.26 (m, 1H, H15a), 1.19 (s, 3H, H30), 1.27 (s, 3H, H23/24), 1.29–1.45 (m, 3H, H21b, H22a, H22b), 1.39 (s, 3H, H27), 1.41–1.52 (m, 1H, H6b, H7b), 1.56–1.66 (m, 3H, H6a, H7a, H19b), 1.80–2.11 (m, 6H, H2a, H2b, H15b, H16a, H19a, H21a), 2.18–2.25 (m, 1H, H18), 2.39 (s, 1H, H9), 2.89–2.99 (m, 1H, H1a), 3.03–3.11 (m, 1H, H3), 4.06 (s, 3H, OCH_3), 5.67 (s, 1H, H12); ^{13}C NMR ($CDCl_3$/MeOD 2:5): δ 15.5 (q, 25), 16.5 (q, C23/24), 16.9 (t, C6), 18.4 (q, C26), 19.4 (t, C2), 23.0 (q, C27), 26.1, 26.2 (2 × t, C15, C16), 28.1, 28.16, 28.22 (3 × q, C23/24, C28, C30), 30.7 (t, C21), 31.6 (s, C17), 32.2 (t, C7), 36.3, 36.6 (2 × s, C4, C10), 37.4 (t, C22), 38.0 (t, C1), 40.9 (t, C19), 43.1 (s, C14), 43.5 (s, C20), 45.2 (s, C8), 48.2 (d, C18), 55.5 (d, C5), 61.1 (d, C9), 61.6 (q, OCH_3), 70.0 (d, C3), 127.8 (d, C12), 171.0 (s, C13), 179.0 (s, C29), 200.2 (s, C11).

4.8. (3α,18β,20β)-3-(Acetylamino)-11-oxo-olean-12-en-29-oic acid (7a)

Amino ester **3a** (500 mg, 0.79 mmol, 1.00 equiv) was dissolved in dry DCM (10 mL) before TEA was added and the reaction mixture was cooled to 0 °C. Acetic anhydride (370 μL, 3.93 mmol, 5.00 equiv) was added slowly under temperature control and the reaction mixture was allowed to warm to rt and was stirred until complete conversion of starting material. The reaction mixture was diluted with EtOAc or DCM, washed with diluted HCl, with satd $NaHCO_3$ and brine, dried over Na_2SO_4 and evaporated (aqueous workup). The crude material was submitted to chromatography (SiO_2, Hex/EtOAc 1:3) to give pure ester intermediate (509 mg, 95.5%) as white solid. Analytical data for intermediate ester: R_f = 0.20 (Hex/EtOAc 1:2) $[\alpha]_D^{20}$ +99.0 (*c* 1.0, $CHCl_3$); HRMS: calcd $[M+H]^+$: 678.4517, found $[M+H]^+$: 678.4523. An aliquot of the intermediate ester (170 mg, 0.251 mmol, 1.00 equiv) was deprotected by hydrogenolysis analogous to **5a** in MeOH/EtOAc 50:50 + 1% AcOH (6 mL) with Pd/C (17 mg, 10%). Trituration of the crude material with hot EtOAc gave pure **7a** (105 mg, 81.8%) as white solid. R_f = 0.27 (DCM/MeOH 8:1); $[\alpha]_D^{20}$ +95.0 (*c* 1.0, $CHCl_3$/MeOH); HRMS: calcd $[M+H]^+$: 512.3734, found $[M+H]^+$: 512.3737; ^{1}H NMR ($CDCl_3$): δ 0.84 (s, 3H, H28), 0.86 (s, 3H, H23/24), 0.93–1.29 (m, 4H, H1b, H5, H15b, H16b), 0.98 (s, 3H, H23/24), 1.15 (s, 3H, H26), 1.16 (s, 3H, H25), 1.19 (s, 3H, H30), 1.28–1.59 (m, 8H, H2a, H2b, H6b, H7a, H7b, H21b, H22a, H22b), 1.46 (s, 3H, H27), 1.58–1.76 (m, 2H, H6a, H19b), 1.84–2.15 (m, 4H, H10a, H15a, H19a, H21a), 2.02 (s, 3H, NHAc), 2.15–2.27 (m, 1H, H18), 2.56 (s, 1H, H9), 2.62 (br s, 1H, H1a), 3.79 (s, 1H, H9), 5.66 (s, 1H, H12); ^{13}C NMR ($CDCl_3$): δ 16.1 (q, C25), 17.0 (t, C7), 18.3 (q, C26), 22.2 (q, $NHCOCH_3$), 22.8 (q, C27), 22.9 (t, C2), 23.0 (q, C23/24), 26.0 (t, C15), 26.1 (t, C16), 27.8 (q, C23/24), 28.1 (q, C30), 28.2 (q, C28), 30.7 (t, C21), 31.5 (s, C17), 32.1 (t, C6), 33.9 (t, C1), 36.0 (s, C4), 36.9 (s, C10), 37.4 (t, C22), 40.9 (t, C19), 43.1 (s, C20), 43.4 (s, C8), 45.4 (s, C14), 48.1 (d, C18), 49.6 (d, C5), 53.6 (d, C3), 61.2 (d, C9), 127.7 (d, C12), 170.6 (s, $NHCOCH_3$), 171.0 (s, C13), 179.2 (s, C29), 201.2 (s, C11).

4.9. (3β,18β,20β)-3-(Acetylamino)-11-oxo-olean-12-en-29-oic acid (7b)

Amino ester **3b** (440 mg, 0.692 mmol, 1.00 equiv) was acylated analogous to **7a** in dry DCM (10 mL) with TEA (0.490 g, 4.8 mmol, 7.00 equiv) and Ac_2O (350 mg, 3.46 mmol, 5.00 equiv). Aqueous workup and recrystallization from DCM/EtOAc gave intermediate ester (395 mg, 84.2%) as white crystals. Analytical data of intermediate ester: R_f = 0.22 (Hex/EtOAc 1:2); mp: 162–165 °C (EtOAc/DCM); $[\alpha]_D^{20}$ +101.2 (*c* 1.0, $CHCl_3$); HRMS: calcd $[M+H]^+$: 678.4517, found $[M+H]^+$: 678.4522. An aliquot of the intermediate ester (200 mg, 0.295 mmol, 1.00 equiv) was deprotected by hydrogenolysis analogous to **5a** in MeOH/EtOAc 50:50 + 1% AcOH (10 mL) with Pd/C (20 mg, 10%). The crude material was purified by separation between 0.5 M NaOH and Et_2O, reacidification and subsequent trituration with hot EtOAc to give pure **7b** (104 mg, 68.9%) as white solid. R_f = 0.48 (Hex/EtOAc 1:5) $[\alpha]_D^{20}$ +113.0 (*c* 1.0, $CHCl_3$/MeOH 3:1); HRMS: calcd $[M+H]^+$: 512.3734, found $[M+H]^+$: 512.3739; ^{1}H NMR ($CDCl_3$): δ 0.82 (s, 3H, H25), 0.83 (s, 3H, H28), 0.85–0.94 (m, 1H, H5), 0.89 (s, 3H, H23/24), 0.99–1.17 (m, 2H, H1b, H16b), 1.14

(2 × s, 6H, H23/24, H26), 1.17–1.28 (m, 1H, H15b), 1.20 (s, 3H, H30), 1.30–1.54 (m, 6H, H2b, H6b, H7b, H21b, H22a, H22b), 1.41 (s, 3H, H27), 1.55–1.74 (m, 4H, H2a, H6a, H7a, H19b), 1.79–2.15 (m, 4H, H15a, H16a, H19a, H21a); 1.99 (s, 3H, NHAc), 2.15–2.26 (m, 1H, H18), 2.44 (s, 1H, H9), 2.69–2.80 (m, 1H, H1a), 3.58–3.70 (m, 1H, H3), 5.65 (s, 1H, H12); ^{13}C NMR ($CDCl_3$): δ 15.8 (q, C23/24), 16.0 (q, C25), 17.3 (t, C7), 18.2 (q, C26), 22.3 (q, $NHCOCH_3$), 22.8 (q, C27), 24.6 (t, C2), 26.0 (2 × t, C15, C16), 27.9–28.1 (3 × q, C23/24, C28, C30), 30.6 (t, C21), 31.5 (s, C17), 32.2 (t, C6), 36.6 (s, C10), 37.3 (t, C22), 37.9 (s, C4), 39.4 (t, C1), 40.7 (t, C19), 43.0 (s, C20), 43.3 (s, C8), 45.1 (s, C14), 48.6 (d, C18), 55.0 (d, C5), 56.3 (d, C3), 61.4 (d, C9), 127.6 (d, C12), 170.8 (2 × s, $NHCOCH_3$, C13), 179.0 (s, C29), 201.0 (s, C11).

4.10. (3α,18β,20β)-3-Methylsulfonylamino-11-oxo-olean-12-en-29-oic acid (8a)

Amino ester **3a** (250 mg, 0.393 mmol, 1.00 equiv) was sulfonylated analogous to **7a** in dry DCM (8 mL) with TEA (0.164 mL, 1.18 mmol, 3.0 equiv) and mesyl chloride (520 μL, 0.67 mmol, 1.7 equiv in 2 mL DCM) at −10 °C. The reaction mixture was directly evaporated onto SiO_2 (700 mg) and purified by column chromatography (SiO_2: 30 g, Hex/EtOAc 2:1) to give pure diphenylmethyl ester (208 mg, 74.0%) as white solid which was submitted to the hydrogenolysis step. Intermediate ester (187 mg, 0.262 mmol, 1.00 equiv) was deprotected by hydrogenolysis analogous to **5a** in MeOH/EtOAc 2:1 + 1% AcOH. Crude material was evaporated onto SiO_2 (650 mg) and submitted to column chromatography (SiO_2: 10 g, Hex/EtOAc 1:1 + 0.1% AcOH) to give pure compound **8a**. R_f = 0.42 (Hex/EtOAc 3:4 + 0.5% AcOH); $[\alpha]_D^{20}$ +96.3 (*c* 1.0, MeOH/$CHCl_3$ 5:1); HRMS: calcd $[M+H]^+$: 548.3404, found $[M+H]^+$: 548.3415; ^{1}H NMR ($CDCl_3$): δ 0.77–0.83 (m, 1H, H5), 0.80 (s, 3H, H28), 0.97 (s, 3H, H23/24), 0.97–1.05 (m, 1H, H16b), 1.01 (s, 3H, H23/24), 1.10 (s, 3H, H26), 1.10–1.20 (m, 1H, H15b), 1.19, 1.20 (2 × s, 2 × 3H, H25, H30), 1.24–1.45 (m, 6H, H1b, H6b, H7b, H21b, H22a, H22b), 1.40 (s, 3H, H27), 1.41–1.51 (m, 4H, H2b, H6a, H7a, H19b), 1.76–1.86 (m, 2H, H15a, H19a), 1.94–2.06 (m, 4H, H2a, H18, H21a, H16a), 2.50 (s, 1H, H9), 2.72–2.81 (m, 1H, H1a), 2.96 (s, 3H, SO_2CH_3), 3.16–3.23 (m, 1H, H3), 5.45 (s, 1H, H12), 6.21 (d, 10.0 Hz, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 16.4 (q, C25), 17.2 (t, C6), 18.5 (q, C26), 23.1 (q, C23/24), 23.9 (t, C2), 24.4 (q, C27), 26.25, 26.38 (2 × t, C15, C16), 28.4 (q, C30), 28.6 (q, C28), 29.4 (q, C23/24), 31.0 (t, C21), 31.9 (s, C17), 32.6 (t, C7), 33.2 (t, C1), 36.8, 37.1 (2 × s, C4, C10), 38.1 (t, C22), 41.1 (t, C19), 41.9 (q, SO_2CH_3), 43.3 (s, C20), 43.8 (s, C14), 45.6 (s, C8), 48.1 (d, C18), 49.9 (d, C5), 59.6 (d, C3), 61.2 (d, C9), 128.1 (d, C12), 168.0 (s, C13), 180.4 (s, C29), 198.7 (s, C11).

4.11. (3β,18β,20β)-3-Methylsulfonylamino-11-oxo-olean-12-en-29-oic acid (8b)

Amino ester **3b** (252 mg, 0.396 mmol, 1.00 equiv) was sulfonylated analogous to **7a** in dry DCM (8 mL) with TEA (0.165 mL, 1.19 mmol, 3.00 equiv) and mesyl chloride (670 μL, 0.859 mmol, 2.17 equiv in 2 mL DCM) at −10 °C (EtOH/ice bath). The reaction mixture was diluted with DCM (50 mL), evaporated onto SiO_2 (600 mg) and purified by column chromatography (SiO_2: 30 g, Hex/EtOAc 2:1→Hex/EtOAc 3:2) to give pure diphenylmethyl ester (224 mg, 79.2%) as white solid which was submitted to the hydrogenolysis step. Intermediate ester (196 mg, 0.274 mmol, 1.00 equiv) was deprotected by hydrogenolysis analogous to **5a** in MeOH/EtOAc 2:1 + 1% AcOH (55 mL). The reaction mixture was evaporated onto SiO_2 (600 mg) and submitted to column chromatography (SiO_2: 23 g, Hex/EtOAc 3:4 + 0.1% AcOH) to give pure **8b** (148 mg, 98.6%) as white solid. R_f = 0.35 (Hex/EtOAc 3:4 + 0.5% AcOH); $[\alpha]_D^{20}$ +122.6 (*c* 1.0, MeOH/$CHCl_3$ 5:1); HRMS: calcd $[M+H]^+$: 548.3404, found $[M+H]^+$: 548.3405; ^{1}H NMR ($CDCl_3$/MeOD 5:1): δ 0.80 (s, 3H, H23/24), 0.80–0.87 (m, 1H, H5), 0.83 (s, 3H, H28), 1.00–1.12 (m, 2H, H1b, H16b), 1.04 (s, 3H, H23/24), 1.14 (br s, 6H, H25, H26), 1.19–1.24 (m, 1H, H15b), 1.19 (s, 3H, H30), 1.30–1.54 (m, 5H, H6b, H7b, H21b, H22a, H22b), 1.40 (s, 3H, H27), 1.57–1.82 (m, 5H, H2a, H2b, H6a, H7a, H19b), 1.83–2.03 (m, 3H, H15a, H19a, H21a), 2.00–2.13 (m, 1H, H16a), 2.20 (dd, *J* = 13.4 Hz, *J* = 3.3 Hz, 1H, H18), 2.40 (s, 1H, H9), 2.79 (dt, *J* = 13.0 Hz, *J* = 4.0 Hz, 1H, H1a), 2.94–3.02 (m, 1H, H3), 2.97 (s, 3H, SO_2CH_3), 5.66 (s, 1H, H12); ^{13}C NMR ($CDCl_3$/MeOD 5:1): δ 15.8 (q, C25), 15.9 (q, C23/24), 17.7 (t, C6), 18.3 (q, C26), 22.9 (q, C27), 26.04 (t, C15/16), 26.15 (t, C2 + C15/16), 28.02, 28.09, 28.15 (3 × q, C23/24, C28, C30), 30.7 (t, C21), 31.6 (s, C17), 32.4 (t, C7), 36.6 (s, C10), 37.4 (t, C22), 38.3 (s, C4), 39.6 (t, C1), 40.8 (t, C19), 41.1 (q, SO_2CH_3), 43.1 (s, C14), 43.4 (s, C20), 45.2 (s, C8), 48.1 (d, C18), 55.6 (d, C5), 61.5 (d, C9), 61.9 (d, C3), 127.7 (d, C12), 170.8 (s, C13), 179.0 (s, C29), 200.8 (s, C11).

4.12. (3α,18β,20β)-11-Oxo-3-trifluoromethylsulfonylamino-olean-12-en-29-oic acid (9a)

Amino ester **3a** (250 mg, 0.393 mmol, 1.00 equiv) was sulfonylated analogous to **7a** in dry DCM (25 mL) with TEA (119 mg, 1.18 mmol, 3.00 equiv) and Tf_2O (133 mg, 0.427 mmol, 1.20 equiv, precooled in 1 mL dry DCM) at −10 °C and stirred at −10 °C for 1 h. The reaction mixture was directly evaporated onto SiO_2 and purified by column chromatography (SiO_2: 40 g, Hex/EtOAc 10:1) to give pure diphenylmethyl ester (243 mg, 80.5%) as white solid which was submitted to hydrogenolysis. Analytical data of ester: R_f = 0.51 (Hex/EtOAc 2:1); $[\alpha]_D^{20}$ +86.8 (*c* 1.0, $CHCl_3$/MeOH 3:1); HRMS: calcd $[M+H]^+$: 768.3904, found $[M+H]^+$: 768.3904. Intermediate ester (140 mg, 1.82 mmol, 1.00 equiv) was deprotected by hydrogenolysis analogous to **5a** in MeOH/AcOH 100:1 (12 mL) with Pd/C (14 mg, 10%). The crude material was purified by column chromatography (SiO_2: 30 g, Hex/EtOAc 3:1→Hex/EtOAc 2:1 + 0.1% AcOH) to give pure **9a** (101 mg, 92.1%) as white solid. R_f = 0.41 ($CHCl_3$/MeOH 9:1 + 0.5% AcOH); $[\alpha]_D^{20}$ +82.0 (*c* 1.0, $CHCl_3$/MeOH 3:1); HRMS: calcd $[M+H]^+$: 602.3122, found $[M+H]^+$: 602.3121; ^{1}H NMR ($CDCl_3$/MeOD 5:1): δ 0.83 (s, 3H, H28), 0.98 (s, 3H, H23/24), 0.99 (s, 3H, H23/24), 0.95–1.10 (m, 2H, H16b, H5), 1.14 (s, 3H, H26), 1.16 (s, 3H, H25), 1.19 (s, 3H, H30), 1.10–1.28 (m, 2H, H1b, H15b), 1.42 (s, 3H, H27), 1.28–1.47 (m, 5H, H6b, H7b, H21b, H22a, H22b), 1.50–1.75 (m, 4H, H2b, H6a, H7a, H19b), 1.75–1.94 (m, 2H, H15a, H19a), 1.94–2.16 (m, 3H, H2a, H16a, H21a), 2.20 (dd, 1H, *J* = 13.6 Hz, *J* = 3.6 Hz, H18), 2.58 (s, 1H, H9), 2.62 (dt, 1H, *J* = 14.2 Hz, *J* = 3.7 Hz, H1a), 3.29–3.36 (m, 1H, H3), 5.66 (s, 1H, 12); ^{13}C NMR ($CDCl_3$/MeOD 5:1): δ 16.3 (q, C25), 17.0 (t, C6), 18.4 (q, C26), 22.7 (q, C23/24), 22.9 (q, C27), 23.9 (t, C2), 26.1 (t, C15), 26.2 (t, C16), 28.1 (q, C30), 28.2 (q, C28), 28.5 (q, C23/24), 30.8 (t, C21), 31.6 (s, C17), 32.2 (t, C7), 33.3 (t, C1), 36.67 (s, C10), 36.74 (s, C4), 37.5 (t, C22), 41.0 (t, C19), 43.2 (s, C20), 43.5 (s, C8), 45.4 (s, C14), 48.2 (d, C18), 48.9 (d, C5), 61.0 (d, C9), 61.4 (d, C3), 127.8 (d, C12), 170.8 (s, C13), 179.1 (s, C29), 201.1 (s, C11).

4.13. (3β,18β,20β)-11-Oxo-3-trifluoromethylsulfonyl-amino-olean-12-en-29-oic acid (9b)

Amino ester **3b** (250 mg, 0.393 mmol, 1.00 equiv) was sulfonylated analogous to **7a** in dry DCM (7 mL) with TEA (119 mg, 1.18 mmol, 3.00 equiv) and Tf_2O (122 mg, 0.432 mmol, 1.10 equiv; precooled in 1 mL DCM) at -10 °C. The reaction mixture was directly evaporated onto SiO_2 (1 g) and purified by column chromatography (Hex/EtOAc 7:1) to give pure diphenylmethyl ester (250 mg, 82.8%) as white solid foam which was submitted to hydrogenolysis. Analytical data of ester: R_f = 0.46 (Hex/EtOAc

2:1); $[\alpha]_D^{20}$ +82.8 (*c* 1.0, $CHCl_3$/MeOH 3:1); HRMS: calcd $[M+H]^+$: 768.3904, found $[M+H]^+$: 768.3907. Diphenylmethyl ester (140 mg, 0.182 mmol, 1.00 equiv) was deprotected by hydrogenolysis analogous to **5a** in MeOH/AcOH 100:1 with Pd/C (12 mg, 10%). The crude material was purified by column chromatography (SiO_2: 23 g, Hex/EtOAc 2:1→1:1 + 0.1% AcOH) and subsequent trituration with Et_2O to give pure **9b** (100 mg, 91.2%) as white solid. R = 0.40 ($CHCl_3$/MeOH 9:1 + 0.5% AcOH); $[\alpha]_D^{20}$ +96.4 (*c* 1.0, $CHCl_3$/MeOH 3:1); HRMS: calcd $[M+H]^+$: 602.3122, found $[M+H]^+$: 602.3130; ^{1}H NMR ($CDCl_3$/MeOD 5:1): δ 0.83 (s, 6H, H23/24, H28), 0.76–0.87 (m, 1H, H5), 1.03 (s, 3H, H23/24), 0.97–1.11 (m, 2H, H1b, H16b), 1.14 (s, 6H, H25, H26), 1.19 (s, 3H, H30), 1.22–1.30 (m, 1H, H15b), 1.39 (s, 3H, H27), 1.30–1.56 (m, 5H, H6b, H7b, H21b, H22a, H22b), 1.56–1.73 (m, 5H, H2a, H2b, H6a, H7a, H19b), 1.74–2.14 (m, 4H, H15a, H16a, H19a, H21a), 2.21 (dd, 1H, *J* = 13.5 Hz, *J* = 3.8 Hz, H18), 2.41 (s, 1H, H9), 2.79 (dt, 1H, *J* = 13.4 Hz, *J* = 3.3 Hz, H1a), 3.13 (dd, 1H, *J* = 12.5 Hz, *J* = 4.2 Hz, H3), 5.66 (s, 1H, H12); ^{13}C NMR ($CDCl_3$/MeOD 5:1): δ 15.8 (q, C25), 15.9 (q, C23/24), 17.7 (t, C6), 18.2 (q, C26), 22.9 (q, C27), 25.3 (t, C2), 26.0 (t, C15), 26.1 (t, C16), 28.0 (q, C30), 27.9 (q, C28), 28.1 (q, C23/24), 30.7 (t, C21), 31.5 (s, C17), 32.3 (t, C7), 36.5 (s, C10), 37.4 (t, C22), 38.4 (s, C4), 39.6 (t, C1), 40.8 (t, C19), 43.1 (s, C20), 43.4 (s, C8), 45.1 (s, C14), 48.1 (d, C18), 55.3 (d, C5), 61.4 (d, C9), 63.8 (d, C3), 127.7 (d, C12), 171.0 (s, C13), 179.0 (s, C29), 200.8 (s, C11).

4.14. (3β,18β,20β)-11-Oxo-3-succinylamino-olean-12-en-29-oic acid (10)

Amino ester **3b** (400 mg, 0.629 mmol, 1.00 equiv) was acylated analogous to **7a** in dry DCM (9.5 mL) with TEA (610 μL, 4.40 mmol, 7.00 equiv) and succinic anhydride (315 mg, 3.15 mmol, 5.00 equiv) at 0 °C to rt for **3d**. Aqueous workup and purification by column chromatography (SiO_2: 20 g, Hex/EtOAc 1:1 + 0.1% AcOH to Hex/EtOAc 1:3 + 0.1% AcOH) and (SiO_2: 7 g, DCM/MeOH 70:1 + 0.1% AcOH) gave pure diphenylmethyl ester (192 mg, 41.5%) as white solid foam which was submitted to hydrogenolysis. Analytical data for ester: R_f = 0.15 (Hex/EtOAc 3:1 + 0.5% AcOH); $[\alpha]_D^{20}$ +97.6 (*c* 0.3, $CHCl_3$); HRMS: calcd $[M+H]^+$: 736.4572, found $[M+H]^+$: 736.4568. Intermediate ester (260 mg, 0.253 mmol, 1.00 equiv) was deprotected by hydrogenolysis analogous to **5a** on Pd/C in MeOH with 1% AcOH. The crude material was distributed between Et_2O and 0.3 M NaOH. The aqueous layer was acidified with 2 M HCl and extracted with DCM. The combined organic layers were washed twice with water, once with brine, dried over Na_2SO_4 and evaporated. Trituration with hot EtOAc and washing with EtOAc and Et_2O gave pure **10** (100 mg, 49.7%) as white solid. R_f = 0.32 ($CHCl_3$/MeOH 9:1 + 0.5% AcOH); $[\alpha]_D^{20}$ +106.6 (*c* 1.0, $CHCl_3$/MeOH 5:1); HRMS: calcd $[M+H]^+$: 570.3789, found $[M+H]^+$: 570.3799; ^{1}H NMR ($CDCl_3$/MeOD 5:1): δ 0.73 (s, 3H, H23/24), 0.74 (s, 3H, H28), 0.76–0.83 (m, 1H, H5), 0.79 (s, 3H, H23/24), 0.90–1.05 (m, 2H, H1b, H16b), 1.05 (s, 6H, H25, H26), 1.11 (s, 3H, H30), 1.09–1.43 (m, 7H, H2b, H6b, H7b, H15b, H21b, H22a, H22b), 1.32 (s, 3H, H27), 1.48–1.58 (m, 4H, H2a, H6a, H7a, H19b), 1.70–1.90 (m, 3H, H15a, H19a, H21a), 1.91–2.05 (m, 1H, H16a), 2.07–2.17 (m, 1H, H18), 2.35 (s, 1H, H9), 2.36–2.46 (m, 2H, CH_2), 2.51–2.61 (m, 2H, CH_2), 2.60–2.71 (m, 1H, H1a), 3.50–3.58 (m, 1H, H3), 5.57 (s, 1H, H12), 6.78 (d, *J* = 9.8 Hz, 1H, NH); ^{13}C NMR ($CDCl_3$/MeOD 5:1): δ 15.8 (q, C25), 16.0 (q, C23/24), 17.3 (t, C6), 18.2 (q, C26), 22.9 (q, C27), 24.6 (t, C2), 25.97, 26.07 (2 × t, C15, C16), 27.97, 28.01 (2 × q, C23/24, C30), 28.11 (q, C28), 29.5 (t, CH_2), 30.62, 30.70 (2 × t, CH_2, C21), 31.5 (s, C17), 32.3 (t, C7), 36.6 (s, C10), 37.4 (t, C22), 37.9 (s, C4), 39.4 (t, C1), 40.8 (t, C19), 43.0 (s, C20), 43.4 (s, C14), 45.2 (s, C8), 48.1 (s, C18), 55.1 (s, C5), 56.3 (s, C3), 61.4 (s, C9), 127.7 (s, C12), 170.9 (s, C13), 172.1 (s, NHCO), 175.0 (s, COOH), 179.0 (s, C29), 201.1 (s, C11).

4.15. (3β,18β,20β)-3-(2-Methoxycarbonyl-ethylsulfonylamino)-11-oxo-olean-12-en-29-oic acid (11)

Amino ester **3b** (400 mg, 0.629 mmol, 1.00 equiv) was sulfonylated analogously to **7a** in dry DCM (14 mL) with TEA (0.26 mL, 1.89 mmol, 3.0 equiv) and 3-chlorosulfonyl propionic acid methylester (141 mg, 0.755 mmol, 1.2 equiv; in <2 mL dry DCM). The temperature was kept below 0 °C during addition and the reaction mixture was stirred for 1 h at rt. The reaction mixture was diluted with DCM, evaporated onto SiO_2 (1.5 g) and purified by column chromatography (SiO_2: 40 g, Hex/EtOAc 2:1) to give pure diphenylmethyl ester (381 mg, 77.1%) as white solid which was submitted to hydrogenolysis. Analytical data for ester: R_f = 0.31 (Hex/EtOAc 2:1) $[\alpha]_D^{20}$ +100.9 (*c* 0.8, $CHCl_3$); HRMS: calcd $[M+H]^+$: 786.4398, found $[M+H]^+$: 786.4403. Intermediate ester (350 mg, 0.445 mmol, 1.00 equiv) was deprotected by hydrogenolysis analogous to **5a** in MeOH/AcOH 100:1 (22 mL) with Pd/C at rt for 3 h. The crude material was evaporated onto SiO_2 (1 g) and submitted to column chromatography (SiO_2: 25 g, Hex/EtOAc 2:1 + 0.1% AcOH to Hex/EtOAc 1:1 + 0.1% AcOH). The product fractions were dissolved in EtOAc and washed twice with water, once with brine, dried over Na_2SO_4, evaporated and co-evaporated from DCM to afford pure **11** (270 mg, 97.8%) as solid white foam. R_f = 0.25 (Hex/EtOAc 1:1 + 0.5% AcOH); $[\alpha]_D^{20}$ +100.4 (*c* 1.0, MeOH/$CHCl_3$ 5:1); HRMS: calcd $[M+H]^+$: 620.3616, found $[M+H]^+$: 620.3626; ^{1}H NMR ($CDCl_3$): δ 0.79–0.87 (m, 1H, H5), 0.79 (s, 3H, H23/24), 0.84 (s, 3H, H28), 0.98–1.11 (m, 2H, H1b, H16b), 1.04 (s, 3H, H23/24), 1.13 (br s, 6H, H25, H26), 1.15–1.23 (m, 1H, H15b), 1.23 (s, 3H, H30), 1.37 (s, 3H, H27), 1.38–1.53 (m, 5H, H6b, H7b, H21b, H22a, H22b), 1.56–1.77 (m, 5H, H2a, H2b, H6a, H7a, H19b), 1.81 (td, *J* = 13.7 Hz, *J* = 3.8 Hz, 1H, H15a), 1.88–2.09 (m, 3H, H16a, H19a, H21a), 2.19 (dd, *J* = 13.2 Hz, *J* = 3.4 Hz, 1H, H18), 2.36 (s, 1H, H9), 2.78–2.87 (m, 1H, H1a), 2.85 (app. t, *J* = 7.6 Hz, 2H, $COCH_2$), 2.99–3.09 (m, 1H, H3), 3.29–3.40 (m, 2H, SO_2CH_2), 3.73 (s, 3H, OCH_3), 4.31 (d, *J* = 9.9 Hz, 1H, NH), 5.71 (s, 1H, H12); ^{13}C NMR ($CDCl_3$): δ 16.2 (q, C25), 16.4 (q, C23/24), 18.0 (t, C6), 18.6 (q, C26), 23.3 (q, C27), 26.37, 26.43 (2 × t, C15, C16), 27.2 (t, C2), 28.42 (3 × q, C23/24, C28, C30), 28.8 (t, $COCH_2$), 30.9 (t, C21), 31.9 (s, C17), 32.7 (t, C7), 36.8 (s, C10), 37.7 (t, C22), 38.5 (s, C4), 39.8 (t, C1), 40.8 (t, C19), 43.2 (s, C14), 43.8 (s, C20), 45.4 (s, C8), 48.2 (d, C18), 49.3 (t, SO_2CH_2), 52.3 (q, OCH_3), 55.9 (d, C5), 61.6 (d, C9), 62.4 (d, C3), 128.4 (d, C12), 169.5 (s, C13), 171.0 (s, $COOCH_3$), 181.5 (s, C29), 200.2 (s, C11).

4.16. (3β,18β,20β)-3-(2-Carboxy-ethylsulfonylamino)-11-oxo-olean-12-en-29-oic acid (12)

Ester **11** (210 mg, 0.339 mmol, 1.00 equiv) was dissolved in MeOH (5 mL), 0.2 M NaOH in MeOH (5 mL, 3 equiv) was added at 0 °C and the reaction mixture was stirred at rt overnight. Another 5 mL of 0.2 M NaOH in MeOH, then water (1 mL) and finally 2 M NaOH (0.5 mL) were added and the reaction mixture was stirred at 6 °C for another night to complete conversion. The reaction mixture was diluted with DCM, acidified with diluted AcOH (10%) and extracted with EtOAc. The combined organic layers were washed once with diluted AcOH, with water, with brine, dried over Na_2SO_4 and evaporated. The crude material was evaporated onto SiO_2 (1 g) and submitted to flash column chromatography (SiO_2: 10 g, DCM/MeOH 30:1 + 0.1% AcOH to DCM/MeOH 15:1 + 0.1% AcOH) to give pure acid **12** (199 mg, 97%) as white solid. R_f = 0.18 (Hex/EtOAc 1:3 + 0.5% AcOH); $[\alpha]_D^{20}$ +95.9 (*c* 1.0, MeOH/$CHCl_3$ 5:1); HRMS: calcd $[M+H]^+$: 606.3459, found $[M+H]^+$: 606.3467; ^{1}H NMR ($CDCl_3$ + 3dr MeOD): δ 0.79 (s, 3H, H23/24), 0.80–0.87 (m, 1H, H5), 0.82 (s, 3H, H28), 0.98–1.09 (m, 2H, H1b, H16b), 1.03 (s, 3H, H23/24), 1.12 (br s, 6H, H25, H26), 1.19 (s, 3H, H30), 1.19–1.22 (m, 1H, H15b), 1.25–1.51 (m, 5H, H6b, H7b, H21b, H22a, H22b), 1.37 (s, 3H, H27), 1.56–

1.77 (m, 5H, H2a, H2b, H6a, H7a, H19b), 1.83 (td, J = 13.9 Hz, J = 4.2 Hz, 1H, H15a), 1.88–2.08 (m, 3H, H19a, H21a, H16a), 2.19 (dd, J = 13.3 Hz, J = 3.9 Hz, 1H, H18), 2.37 (s, 1H, H9), 2.75–2.83 (m, 1H, H1a), 2.82 (app. t, J = 7.6 Hz, 2H, $HOOCCH_2$), 3.00 (dd, J = 12.0 Hz, J = 4.6 Hz, 1H, H3), 3.27–3.39 (m, 2H, SO_2CH_2), 5.20 (d, J = 9.8 Hz, 1H, NH), 5.66 (s, 1H, H12); ^{13}C NMR ($CDCl_3$ + 3dr MeOD): δ 16.1 (q, C25), 16.2 (q, C23/24), 17.9 (t, C6), 18.5 (q, C26), 23.1 (q, C27), 26.23, 26.31 (2 × t, C15, C16) 26.7 (t, C2), 28.28, 28.32, 28.36 (3 × q, C23/24, C28, C30), 28.6 (t, $HOOCCH_2$), 30.9 (t, C21), 31.7 (s, C17), 32.5 (t, C7), 36.7 (s, C10), 37.6 (t, C22), 38.4 (s, C4), 39.7 (t, C1), 40.9 (t, C19), 43.2 (s, C14), 43.6 (s, C20), 45.3 (s, C8), 48.2 (d, C18), 49.1 (t, SO_2CH_2), 55.7 (d, C5), 61.5 (d, C9), 62.0 (d, C3), 128.0 (d, C12), 170.5 (s, C13), 172.9 (s, COOH), 179.4 (s, C29), 200.7 (s, C11).

4.17. (3β,18β,20β)-3-Acetoxy-*N*-methyl-*N*-methoxy-11-oxo-olean-12-en-29-amide (14)

To a solution of acid chloride **13a** (531 mg, 1.00 mmol, 1.00 equiv) and TEA (1.011 g, 10.0 mmol, 10.0 equiv) in dry DCM (5% solution), *N*,*O*-dimethylhydroxylamine hydrochloride (945 mg, 10.0 mmol, 10.0 equiv) was added portionwise. The reaction mixture was stirred at rt under TLC-monitoring. Upon complete conversion of starting material the reaction mixture was washed with 2 M HCl, water and brine, dried with $MgSO_4$ and evaporated. The crude material was purified by column chromatography (DCM/MeOH gradients) to give pure **14** (300 mg, 54%) as yellowish solid. R_f = 0.38 ($CHCl_3$/MeOH = 96:4); HRMS: calcd $[M+H]^+$: 556.3997, found $[M+H]^+$: 556.4045; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.75 (s, 3H), 0.81 (s, 6H), 1.06 (s, 3H), 1.1 (s, 3H), 1.12 (s, 3H), 1.30 (s, 3H), 0.66–2.32 (m, 20H), 1.98 (s, 3H), 2.72 (dt, 1H), 3.11 (s, 3H), 3.6 (s, 3H), 4.44 (dd, 1H), 5.63 (s, 1H); ^{13}C NMR (200 MHz, $CDCl_3$): δ 16.4., 16.6, 17.3, 18.6, 21.3, 23.1, 23.5, 26.2, 26.5, 26.7, 28.0, 28.4, 31.9, 31.9, 32.7, 33.8, 36.9, 37.9, 38.0, 38.8, 42.3, 43.2, 44.7, 45.3, 48.3, 55.0, 60.5, 61.6, 80.6, 128.4, 169.7, 170.9, 176.8, 200.0.

4.18. (3β,18β,20β)-3-Acetoxy-*N*-methyl-*N*-hydroxy-11-oxo-olean-12-en-29-amide (15)

Carboxylic acid **13** (500 mg, 0.98 mmol, 1.00 equiv) was stirred in $SOCl_2$/toluene 1:1 (14 mL each) for 2 h. Upon complete conversion according to TLC (SiO_2, DCM/MeOH) the excess $SOCl_2$ was evaporated and the residue was coevaporated from toluene twice. The residue was dissolved in DCM (20 mL) and first TEA (540 μL, 3.90 mmol, 4.00 equiv) and then *N*-methyl-hydroxylamine hydrochloride (122 mg, 1.46 mmol, 1.50 equiv) were added at rt. The reaction mixture was stirred at rt monitored by TLC (SiO_2: DCM/Et_2O 1:1) for given periods of time. Upon complete conversion, solvents were evaporated, the residue was taken up in DCM and washed with water, $NaHCO_3$ and brine, dried over Na_2SO_4 and evaporated (aqueous workup). The crude material was purified by flash column chromatography (SiO_2: 20 g, DCM/MeOH 94:6) to give pure **15** (486 mg, 92%) as white solid. R_f = 0.20 (DCM/MeOH 94:6); $[\alpha]_D^{20}$ +121.7 (c 1.0, $CHCl_3$/MeOH 3:1); HRMS: calcd $[M+H]^+$: 540.3689, found $[M+H]^+$: 540.3635; ^{1}H NMR ($CDCl_3$/MeOD 5:1): δ 0.78–0.87 (m, 1H, H5), 0.82 (s, 3H, H28), 0.90 (s, 6H, H23/24), 0.99–1.12 (m, 2H, H1b, H16b), 1.14 (s, 3H, H26), 1.17 (s, 3H, H25), 1.21 (s, 3H, H30), 1.26–1.36 (m, 1H, H21b), 1.36–1.55 (m, 4H, H6b, H7b, H22a, H22b), 1.39 (s, 3H, H27), 1.55–1.77 (m, 5H, H2a, H7a, H2b, H6a, H19b), 1.77–1.92 (dt, 1H, J = 13.9 Hz, J = 4.7 Hz, H15a), 2.042.18 (m, 1H, H16a), 2.06 (s, 3H, OAc), 2.18–2.33 (m, 3H, H19a, H21a, H18), 2.42 (s, 1H, H9), 1.18–1.26 (m, 1H, H15b), 2.72–2.82 (td, 1H, J = 13.6 Hz, J = 3.4 Hz, H1a), 3.25 (s, 3H, $NHCH_3$), 4.13 (s, 1H, NH/OH), 4.46–4.55 (dd, 1H, J = 11.5 Hz, J = 4.9 Hz, H3), 5.71 (s, 1H, H12); ^{13}C NMR ($CDCl_3$/MeOD 5:1): δ 16.0 (q, C25), 16.3 (q, C23/24), 17.0 (t, C6), 18.3 (q, C26), 20.8 (q, $COCH_3$), 22.7 (q, C27), 23.2 (t, C2), 25.5 (q, C30), 26.2 (t, C15), 26.4 (t, C16), 27.6 (q, C23/24), 28.2 (q, C28), 31.5 (t, C21), 31.7 (s, C17), 32.4 (t, C7), 36.7 (s, C10), 37.59 (t, C22), 37.61 (q, N-Me), 37.7 (s, C4), 38.5 (t, C1), 42.0 (t, C19), 43.2 (s, C20), 44.0 (s, C8), 45.2 (s, C14), 48.4 (d, C18), 54.7 (d, C5), 61.4 (d, C9), 80.7 (d, C3), 127.6 (d, C12), 171.4 (s, $COCH_3$), 171.6 (s, C13), 175.6 (s, C29), 201.1 (s, C11).

4.19. (3β,18β,20β)-3-Acetoxy-*N*-*tert*butyl-*N*-hydroxy-11-oxo-olean-12-en-29-amide (16)

Acid chloride **13a** (2.0 g, 3.7 mmol, 1.00 equiv) was reacted analogously to **14** with TEA (1 mL, 10.0 mmol, 2.7 equiv) and *N*-*tert*-butyl-hydroxylamine hydrochloride (500 mg, 4.0 mmol, 1.08 equiv) to give compound **16** (1.95 g, 88%) as solid foam. R_f = 0.3 (DCM/MeOH 98:2); HRMS: calcd $[M+H]^+$: 584.4310, found $[M+H]^+$: 584.4300; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.77 (s, 3H), 0.84 (s, 6H), 1.09 (s, 3H), 1.12 (s, 3H), 1.14 (s, 9H), 1.18 (s, 3H), 1.33 (s, 3H), 2.37–0.72 (m, 19H), 2.01 (s, 3H), 2.91 (m, 1H), 4.32 (m, 1H), 5.20 (s, 1H), 5.92 (s, 1H), 6.95 (br, 1H); ^{13}C NMR (200 MHz, $CDCl_3$): δ 26.7 (3C), 26.3 (2C), 4.7, 8.5, 16.4, 16.6, 17.3, 18.6, 21.3, 23.3, 23.5, 28.0, 28.4, 28.7, 31.1, 31.8, 32.6, 36.9, 37.6, 38.7, 39.0, 43.1, 44.0, 48.1, 54.3, 54.9, 55.7, 61.7, 128.6, 168.8, 170.9, 176.1, 199.9.

4.20. (3β,18β,20β)-3-Acetoxy-*N*-methoxy-11-oxo-olean-12-en-29-amide (17)

Acid chloride **13a** (531 mg, 1.00 mmol, 1.00 equiv) was reacted analogously to **14** with TEA (1.011 g, 10.0 mmol, 10.0 equiv) and *O*-methyl-hydroxylamine hydrochloride (835 mg, 10.0 mmol, 10.0 equiv) to give compound **17** (250 mg, 46%) as solid foam. R_f = 0.38 (DCM/MeOH 96:4); HRMS: calcd $[M+H]^+$: 542.3840, found $[M+H]^+$: 542.3826; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.40–2.70 (m, 19H), 0. 79 (s, 3H), 0.85 (s, 6H), 1.09 (s, 3H), 1.12 (s, 6H), 1.32 (s, 3H), 2.02 (s, 3H), 2.75 (m, 1H), 3.72 (s, 3H), 4.47 (dd, 1H), 5.67 (s, 1H), 9.80 (br, 1H); ^{13}C NMR (200 MHz, $CDCl_3$): δ 16.3, 16.6, 17.3, 18.6, 21.3, 23.3, 23.5, 26.3, 26.4, 28.0, 28.4, 29.2, 31.1, 31.8, 32.6, 36.9, 37.3, 38.0, 38.8, 41.0, 42.6, 43.2, 45.4, 48.0, 55.0, 61.7, 63.9, 80.6, 128.4, 169.6, 171.1, 173.6, 200.3.

4.21. (3β,18β,20β)-3-Acetoxy-*N*-allyloxy-11-oxo-olean-12-en-29-amide (18)

Acid chloride **13a** (531 mg, 1.00 mmol, 1.00 equiv) was reacted analogous to **14** with TEA (1.011 g, 10.0 mmol, 10.0 equiv) and *O*-allyl-hydroxylamine hydrochloride (1.096 g, 10.0 mmol, 10.0 equiv) to give compound **18** (250 mg, 44%) as solid foam. R_f = 0.4 (DCM/MeOH 97:3); HRMS: calcd $[M+H]^+$: 568.3997, found $[M+H]^+$: 568.3993; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.76 (s, 3H), 0.82 (s, 6H), 1.07 (s, 3H), 1.1 (s, 6H), 1.30 (s, 3H), 0.65–2.40 (m, 20H), 2.00 (s, 3H), 2.70 (m, 1H), 4.34 (m, 2H), 4.43 (m, 1H), 5.26 (m, 2H), 5.65 (m, 1H), 5.93 (m, 1H), 9.48 (s, 1H); ^{13}C NMR (200 MHz, $CDCl_3$): δ 16.3, 16.6, 17.3, 18.6, 21.2, 23.2, 23.4, 26.4, 28.0, 28.4, 29.2, 31.2, 31.7, 32.6, 36.8, 37.3, 38.0, 38.8, 40.9, 42.8, 43.2, 45.4, 48.0, 53.4, 54.9, 61.7, 77.1, 80.6, 120.3, 128.3, 132.9, 169.8, 171.0, 173.5, 200.3.

4.22. (3β,18β,20β)-3-Acetoxy-*N*-benzyloxy-11-oxo-olean-12-en-29-amide (19)

Carboxylic acid **13** (500 mg, 0.98 mmol, 1.00 equiv) was - analogous to **15** - first converted to the acid chloride in $SOCl_2$/toluene (14 mL each) within 2 h which was then reacted with a solution of NH_2OBn (144 mg 1.17 mmol, 1.20 equiv) and TEA (540 μL,

3.90 mmol, 4.00 equiv) in DCM (30 mL). Aqueous workup gave crude material which was purified by flash column chromatography (SiO_2: 25 g, DCM/Et_2O 5:1→DCM/Et_2O 1:1) to give pure **19** (554 mg, 90.3%) as orange solid. R_f = 0.46 (DCM/MeOH 20:1); HRMS: calcd $[M+H]^+$: 618.4153, found $[M+H]^+$: 618.4145; ^1H NMR ($CDCl_3$): δ 0.78–0.80 (m, 1H, H5), 0.80 (s, 3H, H28), 0.88 (s, 6H, H23/24, H25), 0.96–1.09 (m, 2H, H1b, H16b), 1.11 (s, 6H, H26, H30), 1.16 (s, 3H, H23/24), 1.32 (s, 3H, H27), 1.24–1.50 (m, 5H, H6b, H7b, H22a, H22b, H21b), 2.05 (s, 3H, OAc), 2.32 (s, 1H, H9), 1.13–1.20 (m, 1H, H15b), 1.54–1.72 (m, 6H, H2a, H19a, H19b, H7a, H2b, H6a), 1.73–1.85 (m, 1H, H15a), 1.89–2.11 (m, 3H, H18, H16a, H21a), 2.74–2.83 (td, 1H, J = 13.4 Hz, J = 3.3 Hz, H1a), 4.46–4.55 (dd, 1H, J = 11.6 Hz, J = 4.8 Hz, H3), 4.94 (s, 2H, Bn), 5.44 (s, 1H, H12), 7.29–7.45 (m, 5H, Bn), 8.42 (s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 16.4 (q, C23/24), 16.6 (q, C25), 17.3 (t, C6), 18.6 (q, C26), 21.3 (q, $COCH_3$), 23.3 (q, C27), 23.5 (t, C2), 26.3 (t, C15), 26.4 (t, C16), 28.0 (q, C23/24), 28.3 (q, C28), 29.5 (q, C30), 31.2 (t, C21), 31.8 (s, C17), 32.6 (t, C7), 36.9 (s, C10), 37.3 (t, C22), 38.0 (s, C4), 38.8 (t, C1), 41.1 (t, C19), 43.0 (s, C20), 43.1 (s, C8), 45.3 (s, C14), 47.9 (d, C18), 55.0 (d, C5), 61.7 (d, C9), 77.9 (2 × d, Bn), 80.6 (d, C3), 128.5 (d, C12), 128.7 (2 × d, Bn), 128.9 (d, Bn), 129.2 (2 × d, Bn), 135.3 (s, Bn), 168.8 (s, C13), 171.0 (s, $COCH_3$), 173.5 (s, C29), 200.0 (s, C11).

4.23. (3β,18β,20β)-3-Acetoxy-*N*-hydroxy-11-oxo-olean-12-en-29-amide (20)

O-Benzyl-hydroxamic acid **19** (544 mg, 0.88 mmol, 1.00 equiv) was dissolved in THF (11 mL). The atmosphere was exchanged to argon by evaporation and purging with argon (3 cycles), Pd/C (110 mg, 20%) was added and the atmosphere was exchanged to H_2 (3 cycles). The reaction mixture was stirred under an atmosphere of hydrogen under TLC-monitoring. Upon complete conversion of starting material the reaction mixture was filtered over a bed of Celite®. The reaction mixture was evaporated onto SiO_2 (600 mg) and submitted to column chromatography (SiO_2: 25 g, DCM/Et_2O 1:1→DCM/MeOH 5:1) to give pure **20** (465 mg, 94.7%) as white solid. R_f = 0.19 (DCM/Et_2O), HRMS: calcd $[M+H]^+$: 528.3689, found $[M+H]^+$: 528.3867; ^1H NMR ($CDCl_3$): δ 0.77–0.83 (m, 1H, H5), 0.81 (s, 3H, H28), 0.88 (s, 6H, H23/24), 0.98–1.06 (m, 2H, H1b, H16b), 1.12 (s, 3H, H26), 1.15 (s, 3H, H25), 1.18 (s, 3H, H30), 1.21–1.16 (m, 1H, H15b), 1.33–1.48 (m, 5H, H6b, H22a, H22b, H7b, H21b), 1.36 (s, 3H, H27), 1.54–1.75 (m, 5H, H19b, H2a, H7a, H2b H6a), 1.77–1.93 (m, 2H, H19a, H15a), 1.97–2.07 (m, 2H, H21a, H16a), 2.05 (s, 3H, OAc), 2.36 (s, 1H, H9), 2.20–2.27 (m, 1H, H18), 2.73–2.80 (td, 1H, J = 13.3 Hz, J = 3.4 Hz, H1a), 4.47–4.54 (dd, 1H, J = 11.6 Hz, J = 4.8 Hz, H3), 5.79 (s, 1H, H12), 7.66 (br s, NH/OH); ^{13}C NMR ($CDCl_3$): δ 16.4 (q, C25), 16.6 (q, C23/24), 17.3 (t, C6), 18.6 (q, C26), 21.3 (q, $COCH_3$), 23.3 (q, C27), 23.5 (t, C2), 26.4 (2 × t, C15, C16), 28.0 (q, C23/24), 28.4 (q, C28), 29.3 (q, C30), 31.0 (t, C21), 31.8 (s, C17), 32.6 (t, C7), 36.9 (s, C10), 37.2 (t, C22), 38.0 (s, C4), 38.8 (t, C1), 40.7 (t, C19), 42.3 (s, C20), 43.2 (s, C8), 45.4 (s, C14), 47.7 (d, C18), 55.0 (d, C5), 61.7 (d, C9), 80.6 (d, C3), 128.5 (d, C12), 169.5 (s, C13), 171.0 (s, $COCH_3$), 173.9 (s, C29), 200.6 (s, C11).

4.24. (3β,18β,20β)-3-Hydroxy-*N*-methyl-*N*-methoxy-11-oxo-olean-12-en-29-amide (21)

To a stirred solution of the ester (180 mg, 0.324 mmol, 1.00 equiv) in methanol (~1% solution) KOH pellets (85%; 211 mg, 3.20 mmol, 10.0 equiv) were added and the reaction mixture was stirred at rt under TLC-monitoring. After 48 h the solvent was evaporated and the residue was separated between water and DCM. The combined organic layers were washed with 2 M HCl and water, dried over Na_2SO_4 and evaporated. The crude material was purified by column chromatography (SiO_2, gradient of 0–5% methanol in DCM) to give pure compound **21** (50 mg, 30%) as white solid. R_f = 0.30 (DCM/MeOH 96:4); HRMS: calcd $[M+H]^+$: 514.3891, found $[M+H]^+$: 514.3900; ^1H NMR (200 MHz, $CDCl_3$): δ 0.58–2.31 (m, 26H), 0.74 (s, 3H), 0.94 (s, 3H), 1.05 (s, 3H), 1.06 (s, 3H), 1.12 (s, 3H), 1.30 (s, 3H), 2.70 (m, 1H), 3.12 (s, 3H), 3.35 (m, 1H), 3.61 (s, 3H), 5.64 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 15.6, 16.4, 17.5, 18.7, 23.1, 26.2, 26.5, 26.7, 27.2, 28.1, 28.4, 32.8, 33.9, 37.0, 37.9, 31.9 (2C), 39.1 (2C), 42.4, 43.3, 44.8, 45.3, 48.3, 54.9, 60.6, 61.7, 78.8, 128.4, 169.9, 176.9, 200.4.

4.25. (3β,18β,20β)-3,*N*-Dihydroxy-*N*-methyl-11-oxo-olean-12-en-29-amide (22)

Ester **15** (300 mg, 0.55 mmol, 1.00 equiv) was reacted analogous to **21** with KOH (310 mg, 5.5 mmol, 10.0 equiv) in MeOH to give compound **22** (141 mg, 51%) as white solid. R_f = 0.45 (DCM/MeOH 96:4) HRMS: calcd $[M+H]^+$: 500.3734, found $[M+H]^+$: 500.3729; ^1H NMR (200 MHz, pyridine-d_5): δ 0.70–3.56 (m, 23H), 0.79 (s, 3H), 1.05 (s, 3H), 1.11 (s, 3H), 1.24 (s, 3H), 1.31 (s, 3H), 1.38 (s, 3H), 1.45 (s, 3H), 3.46 (s, 3H), 5.67–5.77 (m, 1H), 6.05 (s, 1H); ^{13}C NMR (200 MHz, pyridine-d_5) δ 17.06, 17.30, 18.41, 19.32, 23.71, 26.75, 27.25, 27.43, 28.60, 29.22, 32.28, 32.59, 33.51, 38.09, 39.03, 39.07, 40.25, 40.26, 43.78, 44.03, 45.08, 45.95, 49.12, 50.12, 55.80, 62.62, 78.37, 129.14, 170.61, 176.46, 200.17.

4.26. (3β,18β,20β)-3,*N*-Dihydroxy-*N*-*tert*butyl-11-oxo-olean-12-en-29-amide (23)

Ester **16** (1.60 g, 2.70 mmol, 1.00 equiv) was reacted analogous to **21** with KOH (0.70 g, 10.6 mmol, 3.9 equiv) in MeOH/DCM (50 mL + 10 mL) to give compound **23** (990 mg, 67.7%) as white solid. R_f = 0.35 (DCM/MeOH 95:5); HRMS: calcd $[M+H]^+$: 542.4204, found $[M+H]^+$: 542.4202; ^1H NMR (200 MHz, $CDCl_3$): δ 0.75–2.40 (m, 19H), 0.79 (s, 3H), 0.80 (s, 3H), 0.99 (s, 3H), 1.11 (s, 6H), 1.16 (s, 9H), 1.20 (s, 3H), 1.36 (s, 3H), 2.76 (m, 1H), 3.20 (m, 1H), 5.65 (s, 1H), 7.00 (br, 1H); ^{13}C NMR (200 MHz, $CDCl_3$): δ 15.58, 16.33, 17.47, 176.15, 18.65, 23.43, 26.35, 26.39, 26.40, 26.67 (3C), 27.28, 28.09, 28.42, 28.78, 31.08, 31.80, 32.73, 37.06, 37.67, 39.11, 40.76, 43.18, 44.01, 45.36, 48.11, 54.90, 55.77, 61.80, 78.67, 128.67, 168.78, 200.09.

4.27. (3β,18β,20β)-3-Hydroxy-*N*-methoxy-11-oxo-olean-12-en-29-amide (24)

Ester **17** (148 g, 0.27 mmol, 1.00 equiv) was reacted analogous to **21** with KOH (179 mg, 2.7 mmol, 10 equiv) in MeOH (13 mL) to give compound **24** (135 mg, 99%) as white solid. R_f = 0.25 (DCM/MeOH 96:4); HRMS: calcd $[M+H]^+$: 500.3734, found $[M+H]^+$: 500.3725; ^1H NMR (200 MHz, $CDCl_3$): δ 0.60–2.40 (m, 21H), 0.78 (s, 3H), 0.80 (s, 3H), 0.98 (s, 3H), 1.10 (s, 6H), 1.14 (s, 3H), 1.34 (s, 3H), 2.74 (d, 1H), 3.20 (m, 1H), 3.73 (s, 3H), 5.67 (s, 1H), 9.33 (br, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 15.6, 16.3, 169.6, 17.4, 18.6, 23.3, 26.4 (2C), 27.2, 28.1, 28.5, 29.2, 31.1, 31.8, 32.7, 37.1, 37.3, 39.1, 39.2, 41.1, 42.5, 43.2, 45.4, 48.1, 55.0, 61.8, 64.0, 78.8, 128.4, 173.6, 200.4.

4.28. (3β,18β,20β)-*N*-Allyloxy-3-hydroxy-11-oxo-olean-12-en-29-amide (25)

Ester **18** (243 mg, 0.43 mmol, 1.00 equiv) was reacted analogous to **21** with KOH (283 mg, 4.3 mmol, 10 equiv) in MeOH (20 mL) to give compound **25** (90 mg, 40%) as yellow solid. R_f = 0.25 (DCM/MeOH 96:4); HRMS: calcd $[M+H]^+$: 526.3891, found $[M+H]^+$: 526.3882; ^1H NMR (200 MHz, $CDCl_3$): δ 0.65–2.33 (m,

20H), 0.79 (s, 3H), 0.80 (s, 3H), 0.98 (s, 3H), 1.11 (s, 6H), 1.14 (s, 3H), 1.34 (s, 3H), 2.72 (m, 1H), 2.75 (m, 1H), 3.21 (m, 1H), 4.38 (d, 2H), 5.28 (s, 1H), 5.34 (d, 1H), 5.67 (s, 1H), 6.00 (m, 1H), 9.05 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 15.6, 16.3, 17.5, 18.7, 23.3, 26.3, 26.4, 27.2, 28.1, 28.4, 29.4, 31.2, 31.4, 32.7, 37.1, 37.3, 39.2 (2C), 41.1, 42.9, 43.2, 45.4, 47.9, 55.0, 61.8, 64.5, 78.8, 120.6, 128.5, 132.7, 169.4, 173.8, 200.4.

4.29. (3β,18β,20β)-*N*-Benzyloxy-3-hydroxy-11-oxo-olean-12-en-29-amide (26)

Ester **19** (483 mg, 0.78 mmol, 1.00 equiv) was reacted analogous to **21** with KOH (514 mg, 7.8 mmol, 10 equiv) in MeOH (35 mL) to give compound **26** (180 mg, 40%) as yellow solid. R_f = 0.27 (DCM/MeOH=96:4); HRMS: calcd $[M+H]^+$: 576.4047, found $[M+H]^+$: 576.4050; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.59–2.30 (m, 21H), 0.76 (s, 3H), 0.78 (s, 3H), 0.96 (s, 3H), 1.11 (s, 9H), 1.31 (s, 3H), 2.72 (m, 1H), 3.15 (m, 1H), 4.92 (s, 2H), 5.44 (s, 1H), 7.37 (m, 5H), 8.98 (m, 1H); ^{13}C NMR (200 MHz, $CDCl_3$): δ 15.5, 16.3, 17.4, 18.6, 23.3, 26.3, 26.4, 27.1, 28.1, 28.3, 29.4, 31.1, 31.8, 32.7, 37.0, 37.3, 39.1, 39.4, 40.9, 42.8, 43.1, 45.4, 47.9, 55.0, 61.8, 77.7, 78.8, 128.6, 128.8 (5C), 135.6, 169.1, 175.2, 200.1.

4.30. (3α,18β,20β)-3-Acetylamino-*N*-hydroxy-*N*-methyl-11-oxo-olean-12-en-29-amide (28a)

Carboxylic acid **7a** (50 mg, 0.098 mmol, 1.00 equiv) was—analogous to **15**—first converted to the acid chloride in $SOCl_2$/toluene (1.4 mL each) within 2 h and was then reacted with MeNHOH·HCl (12.0 mg, 0.15 mmol, 1.50 equiv) and TEA (54 μL, 0.39 mmol, 4.00 equiv) in DCM (10 mL). Aqueous workup gave crude material which was purified by flash column chromatography (SiO_2: 5 g, DCM/MeOH 30:1→DCM/MeOH 10:1) to give pure **28a** (38 mg, 71.2%) as orange solid. R_f = 0.74 (DCM/MeOH 5:1); $[\alpha]_D^{20}$ +96.4 (*c* 1.0, $CHCl_3$/MeOH 3:1); HRMS: calcd $[M-H]^-$: 539.3849, found $[M-H]^-$: 539.3737; ^{1}H NMR ($CDCl_3$): δ 0.75–0.84 (m, 1H, H5), 0.82 (s, 3H, H28), 0.87 (s, 3H, H23/24), 0.94–1.09 (m, 2H, H16b, H1b), 0.98 (s, 3H, H23/24), 1.13 (s, 3H, H26), 1.16 (s, 3H, H25), 1.21 (s, 3H, H30), 1.25–1.76 (m, 11H, H7a, H19b, H6a, H22a, H7b, H6b, H22b, H21b, H15b, H2a, H2b), 1.41 (s, 3H, H27), 1.77–1.92 (m, 1H, H15a), 1.96–2.27 (m, 4H, H18, H21a, H19a, H16a), 2.04 (s, 3H, NHAc), 2.41 (s, 1H, H9), 2.62–2.73 (d, 1H, *J* = 13.1 Hz, H1a), 3.36 (s, 3H, N-Me), 3.79–3.88 (d, 1H, *J* = 7.6 Hz, H3), 5.68 (s, 1H, H12), 6.02 (br s, NH), 8.59 (br s, OH); ^{13}C NMR ($CDCl_3$): δ 16.5 (q, C25), 17.3 (t, C6), 18.7 (q, C26), 23.2 (q, C23/24), 23.4 (q, C27), 23.6 (q, $COCH_3$), 26.3 (q, C30), 26.4 (2 × t, C2, C15), 26.7 (t, C16), 28.4 (q, C23/24), 28.5 (q, C28), 31.8 (t, C21), 32.5 (s, C17), 32.6 (t, C7), 34.9 (t, C1), 36.5 (s, C10), 37.3 (s, C4), 37.7 (t, C22), 38.3 (q, N-Me), 42.6 (t, C19), 43.4 (s, C20), 43.5 (s, C8), 45.5 (s, C14), 48.4 (d, C18), 51.1 (d, C5), 53.8 (d, C3), 61.8 (d, C9), 128.3 (d, C12), 169.6 (s, C13), 170.5 (s, $COCH_3$), 173.8 (s, C29), 200.4 (s, C11).

4.31. (3β,18β,20β)-3-Acetylamino-*N*-hydroxy-N-methyl-11-oxo-olean-12-en-29-amide (28b)

Carboxylic acid **7b** (300 mg, 0.59 mmol, 1.00 equiv) was—analogous to **15**–first converted to the acid chloride in $SOCl_2$/toluene (8.5 mL each) within 3 h and was then reacted with MeNHOH·HCl (73.0 mg, 0.88 mmol, 1.50 equiv) and TEA (325 μL, 2.35 mmol, 4.00 equiv) in DCM (10 mL). Aqueous workup gave crude material which was purified by flash column chromatography (SiO_2: 85 g, DCM/MeOH 20:1) to give pure **28b** (255 mg, 80.4%) as white solid. R_f = 0.49 ($CHCl_3$/MeOH 9:1 + AcOH); $[\alpha]_D^{20}$ +115.2 (*c* 1.0, $CHCl_3$/MeOH 3:1); HRMS: calcd $[M-H]^-$: 539.3849, found $[M-H]^-$: 539.3854; ^{1}H NMR ($CDCl_3$/MeOD 5:1): δ 0.80 (s, 3H, H25), 0.81 (s, 3H, H28), 0.90 (s, 3H, H23/24), 0.83–0.93 (m, 1H, H5), 0.96–1.07 (m, 1H, H16b), 1.11 (s, 3H, H26), 1.13 (s, 3H, H23/24), 1.21 (s, 3H, H30), 1.36 (s, 3H, H27), 1.23–1.45 (m, 5H, H7b, H6b, H22b, H21b, H15b), 1.45–1.75 (m, 7H, H7a, H19b, H2a, H6a, H22a, H1b, H2b), 1.81 (dt, 1H, *J* = 13.6 Hz, *J* = 4.0 Hz, H15a), 2.03 (s, 3H, OAc), 2.05–2.26 (m, 4H, H21a, H19a, H18, H16a), 2.39 (s, 1H, H9), 2.80–2.70 (m, 1H, H1a), 3.35 (s, 3H, N-Me), 3.62–3.74 (m, 1H, H3), 5.68 (s, 1H, H12), 8.34 (br s, NH/OH); ^{13}C NMR ($CDCl_3$/MeOD 5:1): δ 16.3 (q, C23/24), 16.6 (q, C25), 17.7 (t, C6), 18.6 (q, C26), 23.0 (q, C27), 23.6 (q, $COCH_3$), 25.3 (t, C2), 26.3 (q, C30), 26.4 (t, C15), 26.7 (t, C16), 28.5 (q(2C), C23/24, C28), 31.8 (t, C21), 32.5 (s, C17), 32.7 (t, C7), 36.9 (s, C10), 37.7 (t, C22), 38.0 (s, C4), 38.3 (q, N-Me), 39.7 (t, C1), 42.3 (t, C19), 43.3 (s, C20), 43.6 (s, C8), 45.3 (s, C14), 48.5 (d, C18), 55.5 (d, C5), 56.7 (d, C3), 61.7 (d, C9), 128.2 (d, C12), 170.0 (s, $COCH_3$), 170.5 (s, C13), 174.0 (s, C29), 200.6 (s, C11).

4.32. (3α,18β,20β)-*N*-Hydroxy-*N*-methyl-11-oxo-3-[(trifluoromethylsulfonyl)amino]-olean-12-en-29-amide (29a)

Carboxylic acid **9a** (150 mg, 0.25 mmol, 1.00 equiv) was—analogous to **15**—first converted to the acid chloride in $SOCl_2$/toluene (3.6 mL each) within 2 h and then reacted with MeNHOH·HCl (31.0 mg, 0.37 mmol, 1.50 equiv) and TEA (138 μL, 1.00 mmol, 4.00 equiv) in DCM (10 mL). Aqueous workup gave crude material which was purified by flash column chromatography (SiO_2: 20 g, DCM/MeOH 50:1→DCM/MeOH 30:1) to give pure **29a** (96 mg, 61.0%) as orange solid. R_f = 0.61 ($CHCl_3$/MeOH 9:1 + AcOH); $[\alpha]_D^{20}$ +81.9 (*c* 1.0, $CHCl_3$/MeOH 3:1); HRMS: calcd $[M-H]^-$: 629.3236, found $[M-H]^-$: 629.2848; ^{1}H NMR ($CDCl_3$/MeOD 5:1): δ 0.82 (s, 3H, H28), 0.98 (s, 3H, H23/24), 0.99 (s, 3H, H23/24), 0.96–1.08 (m, 2H, H16b, H5), 1.13 (s, 3H, H26), 1.16 (s, 3H, H25), 1.21 (s, 3H, H30), 1.08–1.25 (m, 2H, H15b, H1b), 1.25–1.37 (m, 1H, H21b), 1.41 (s, 3H, H27), 1.37–1.50 (m, 4H, H22a, H7b, H6b, H22b), 1.61–1.91 (m, 3H, H15a, H7a, H19b), 1.61 1.50 (m, 2H, H6a, H2b), 2.03–2.31 (m, 5H, H19a, H21a, H18, H2a, H16a), 2.58 (s, 1H, H9), 2.57–2.67 (m, 1H, H1a), 3.25 (s, N-Me), 3.28–3.38 (m, 1H, H3), 3.67 (br s, NH/OH), 5.70 (s, 1H, H12); ^{13}C NMR ($CDCl_3$/MeOD 5:1): δ 16.3 (q, C25), 17.1 (t, C6), 18.5 (q, C26), 22.7 (q, C23/24), 22.8 (q, C27), 23.9 (t, C2), 25.7 (q, C30), 26.3 (t, C15), 26.5 (t, C16), 28.3 (q, C28), 28.5 (q, C23/24), 31.6 (t, C21), 31.9 (s, C17), 32.3 (t, C7), 33.3 (t, C1), 36.7 (s, C10), 36.8 (s, C4), 37.7 (t, C22), 37.8 (q, N-Me), 42.1 (t, C19), 43.4 (s, C20), 44.1 (s, C8), 45.4 (s, C14), 48.5 (d, C18), 48.9 (d, C5), 61.0 (d, C9), 61.4 (d, C3), 127.6 (d, C12), 171.9 (s, C13), 175.6 (s, C29), 201.6 (s, C11).

4.33. (3β,18β,20β)-*N*-Hydroxy-*N*-methyl-11-oxo-3-[(trifluoromethylsulfonyl)amino]-olean-12-en-29-amide (29b)

Carboxylic acid **9b** (300 mg, 0.50 mmol, 1.00 equiv) was—analogous to **15**—first converted to the acid chloride in $SOCl_2$/toluene (7.2 mL each) within 2 h and then reacted with MeNHOH·HCl (62.0 mg, 0.75 mmol, 1.50 equiv) and TEA (276 μL, 2.00 mmol, 4.00 equiv) in DCM (25 mL). Aqueous workup gave crude material which was purified by flash column chromatography (SiO_2: 30 g, DCM/MeOH 40:1→DCM/MeOH 30:1) to give pure **29b** (257 mg, 81.4%) as white solid. R_f = 0.30 ($CHCl_3$/MeOH 9:1 + AcOH); $[\alpha]_D^{20}$ +97.1 (*c* 1.0, $CHCl_3$/MeOH 3:1); HRMS: calcd $[M-H]^-$: 629.3236, found $[M-H]^-$: 629.2745; ^{1}H NMR ($CDCl_3$): δ 0.75 (s, 3H, H23/24), 0.82 (s, 3H, H28), 0.80–0.87 (m, 1H, H5), 1.04 (s, 3H, H23/24), 1.08 (s, 3H, H26), 1.10 (s, 3H, H25), 0.99–1.13 (m, 2H, H1b, H16b), 1.21 (s, 3H, H30), 1.16–1.29 (m, 2H, H21b, H15b), 1.37 (s, 3H, H27), 1.34–1.48 (m, 3H, H7b, H6b, H22b), 1.57–1.87 (m, 6H, H2b, H15a, H19b, H7a, H6a, H22a), 1.88–1.98 (m, 1H, H2a), 2.04–2.17 (m, 3H, H21a, H18, H16a), 2.22–2.30 (d, 1H, *J* = 13.6 Hz, H19a), 2.40 (s, 1H, H9), 2.80–2.88 (m, 1H, H1a), 3.14–3.24 (m,

1H, H3), 3.33 (s, 3H, N-Me), 3.70 (br s, 1H, NH/OH), 5.81 (s, 1H, H12), 7.21 (br s, NH/OH); ^{13}C NMR ($CDCl_3$): δ 16.0 (q, C25), 16.5 (q, C23/24), 18.0 (t, C6), 18.5 (q, C26), 23.0 (q, C27), 25.7 (t, C2), 25.9 (q, C30), 26.5 (t, C15), 26.7 (t, C16), 28.48 (q, C28), 28.52 (q, C23/24), 31.8 (s, C17), 32.6 (t, C21), 33.3 (t, C7), 36.9 (s, C10), 37.5 (t, C22), 38.3 (q, N-Me), 38.8 (s, C4), 39.7 (t, C1), 42.0 (t, C19), 43.4 (s, C20), 43.8 (s, C8), 45.5 (s, C14), 49.1 (d, C18), 55.5 (d, C5), 61.5 (d, C9), 64.4 (d, C3), 127.4 (d, C12), 172.8 (s, C13), 174.6 (s, C29), 201.7 (s, C11).

4.34. (3α,18β,20β)-3-(Acetylamino)-*N*-benzyloxy-11-oxo-olean-12-en-29-amide (30a)

Carboxylic acid **7a** (100 mg, 0.20 mmol, 1.00 equiv) was—analogous to **15**—first converted to the acid chloride in $SOCl_2$/toluene (2.8 mL each) overnight, and was then reacted with a pre-stirred solution of NH_2OBn (29 mg 0.23 mmol, 1.20 equiv) and TEA (54 μL, 0.40 mmol, 2.00 equiv) in acetonitrile (4 mL). Aqueous workup gave crude material which was purified by flash column chromatography (SiO_2: 10 g, DCM/Et_2O 5:1→DCM/MeOH 10:1) to give pure **30a** (102 mg, 84.6%) as orange solid. R_f = 0.41 (DCM/MeOH 5:1); $[\alpha]_D^{20}$ +89.6 (*c* 1.0, $CHCl_3$/MeOH 3:1); HRMS: calcd $[M-H]^-$: 615.4162, found $[M-H]^-$: 615.4016; ^{1}H NMR ($CDCl_3$): δ 0.68–0.77 (m, 1H, H5), 0.72 (s, 3H, H28), 0.80 (s, 3H, H23/24), 0.86–1.00 (m, H, H2b, H16b), 0.90 (s, 3H, H25), 1.00–1.16 (m, 1H, H15b), 1.06 (s, 6H, H26, H30), 1.09 (s, 3H, H23/24), 1.16–1.50 (m, 7H, H2a, H2b, H6b, H7a, H7b, H22a, H22b), 1.31 (s, 3H, H27), 1.50–1.82 (m, 5H, H6a, H16a, H19a, H19b, H21b), 1.82–2.08 (m, 3H, H15a, H18, H21a), 1.97 (s, 3H, NHAc), 2.32 (s, 1H, H9), 2.54–2.65 (td, 1H, H2a), 3.72–3.81 (m, 1H, H3), 4.88 (s, 2H, CH_2-Ph), 5.43 (s, 1H, H12), 7.22 7.38 (m, 5H, Aromat), 8.71 (s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 16.5 (q, C25), 17.2 (t, C7), 18.6 (q, C26), 23.1 (q, C23/24), 23.6 (t, 2 × q, C2, $COCH_3$, C27), 26.3 (2 × t, C15, C16), 28.4 (2 × q, C23/24, C28), 29.4 (q, C30), 31.2 (t, C21), 31.7 (s, C17), 32.4 (t, C6), 34.8 (t, C1), 36.5 (s, C4), 37.2 (s, C10), 37.3 (t, C22), 41.1 (t, C19), 42.9 (s, C20), 43.2 (s, C8), 45.5 (s, C14), 47.8 (d, C18), 51.0 (d, C5), 53.8 (d, C3), 61.7 (d, C9), 77.9 (t, OCH_2Ph), 128.4 (d, C12), 128.6 (2 × d, PhC3, PhC5), 128.8 (d, PhC4), 129.2 (2 × d, PhC2, PhC6), 135.3 (s, PhC1), 169.2 (s, $COCH_3$), 169.5 (s, C13), 173.5 (s, C29), 200.0 (s, C11).

4.35. (3β,18β,20β)-3-(Acetylamino)-*N*-benzyloxy-11-oxo-olean-12-en-29-amide (30b)

Carboxylic acid **7b** (200 mg, 0.39 mmol, 1.00 equiv) was—analogous to **15**—first converted to the acid chloride in $SOCl_2$/toluene (5.7 mL each) overnight and was then reacted with a pre-stirred solution of NH_2OBn (58 mg, 0.47 mmol, 1.20 equiv) and TEA (108 μL, 0.78 mmol, 2.00 equiv) in acetonitrile (3 mL). Aqueous workup gave crude material which was purified by flash column chromatography (SiO_2: 25 g, DCM/Et_2O 5:1→DCM/MeOH 20:1) to give pure **30b** (224 mg, 92.9%) as orange solid. R_f = 0.45 (DCM/MeOH 5:1); $[\alpha]_D^{20}$ +108.9 (*c* 1.0, $CHCl_3$/MeOH 3:1); HRMS: calcd $[M-H]^-$: 615.4162, found $[M-H]^-$: 615.4016; ^{1}H NMR ($CDCl_3$): δ 0.70 (s, 3H, H28), 0.72 (s, 3H, C23/24), 0.73–0.79 (m, 1H, H5), 0.81 (s, 3H, H23/24), 0.86–0.99 (m, 2H, H16b, H1b), 1.04 (s, 6H, H26, H30), 1.05 (s, 3H, H25), 1.07–1.14 (m, 1H, H15b), 1.14–1.39 (m, 6H, H6b, H7b, H16a, H21b, H22a, H22b), 1.26 (s, 3H, H27), 1.39–1.60 (m, 5H, H2a, H2b, H6a, H7a, H19b), 1.63–1.79 (m, 2H, H15a, H19a), 1.83–1.93 (m, 1H, H21a), 1.94 (s, 3H, NHAc), 1.97–2.06 (m, 1H, H18), 2.26 (s, 1H, H9), 2.63–2.73 (m, 1H, H1a), 2.64–2.74 (m, 1H, H3), 4.89 (s, 2H, CH_2Ph), 5.43 (s, 1H, H12), 7.24–7.38 (m, 5H, Aromat), 8.83 (s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 16.2 (q, C25), 16.6 (q, C23/24), 17.6 (t, C7), 18.6 (q, C26), 23.3 (q, C27), 23.4 (q, $COCH_3$), 25.3 (t, C2), 26.3 (2 × t, C15, C16), 28.3 (q, C28), 28.6 (q, C23/24), 29.4 (q, C30), 31.2 (t, C21), 31.7 (s, C17), 32.6 (t, C6), 36.9 (s, C10), 37.3 (t, C22), 38.1 (s, C4), 39.8 (t, C1), 40.8 (t, C19), 42.8 (s, C20), 43.1 (s, C8), 45.3 (s, C14), 47.7 (d, C18), 55.5 (d, C5), 56.7 (d, C3), 61.7 (d, C9), 77.7 (t, OCH_2Ph), 128.5 (d, C12), 128.6 (2 × d, PhC3, PhC5), 128.8 (d, PhC4), 129.2 (d, PhC2, PhC6), 135.4 (s, PhC1), 169.0 (s, C13), 170.0 (s, $COCH_3$), 173.5 (s, C29), 200.0 (s, C11).

4.36. (3α,18β,20β)-*N*-Benzyloxy-11-oxo-3-[(trifluoromethyl-sulfonyl)amino]-olean-12-en-29-amide (31a)

Carboxylic acid **9a** (150 mg, 0.25 mmol, 1.00 equiv) was—analogous to **15**—first converted to the acid chloride in $SOCl_2$/toluene (4 mL each) within 2 h and was then reacted with NH_2OBn (37.0 mg, 0.30 mmol, 1.20 equiv) and TEA (69.0 μL, 0.50 mmol, 2.00 equiv) in DCM (20 mL). Aqueous workup gave crude material which was purified by flash column chromatography (SiO_2: 20 g, Hex/EtOAc 3:1→Hex/EtOAc 1:1 + 0.1% AcOH) to give pure **31a** (157 mg, 89.2%) as orange solid. R_f = 0.68 ($CHCl_3$/MeOH 9:1 + AcOH); $[\alpha]_D^{20}$ +94.2 (*c* 1.0, $CHCl_3$/MeOH 3:1) HRMS: calcd $[M-H]^-$: 705.3549, found $[M-H]^-$: 705.4057; ^{1}H NMR ($CDCl_3$/MeOD 5:1): δ 0.77 (s, 3H, H28), 0.98 (s, 3H, H23/24), 0.99 (s, 3H, H23/24), 1.01–1.10 (m, 2H, H5, H16b), 1.11 (s, 3H, H30), 1.12 (s, 3H, H26), 1.16 (s, 3H, H25), 1.15–1.25 (m, 2H, H15b, H1b), 1.27–1.34 (m, 3H, H22a, H22b, H21b), 1.39 (s, 3H, H27), 1.38–1.42 (m, 2H, H6b, H7b), 1.49–1.69 (m, 3H, H19b, H2b, H6a), 1.69–1.88 (m, 3H, H15a, H19a, H7a), 1.88–1.96 (m, 1H, H21a), 1.96–2.08 (m, 2H, H18, H16a), 2.08–2.16 (m, 1H, H2a), 2.59 (s, 1H, H9), 2.57–2.66 (m, 1H, H1a), 3.31–3.36 (m, 1H, H3), 4.17 (br s, NH/OH), 4.91 (s, 2H, Bn), 5.48 (s, 1H, H12), 7.32–7.46 (m, 5H, Bn); ^{13}C NMR ($CDCl_3$/MeOD 5:1): δ 16.2 (q, C25), 16.9 (t, C6), 18.3 (q, C26), 22.6 (q, C23/24), 22.8 (q, C27), 23.8 (t, C2), 25.98 (t, C15), 26.02 (t, C16), 28.0 (q, C28), 28.3 (q, C23/24), 28.7 (q, C30), 30.5 (t, C21), 31.3 (s, C17), 32.0 (t, C7), 33.1 (t, C1), 36.5 (s, C10), 36.7 (s, C4), 37.0 (t, C22), 40.5 (t, C19), 42.4 (s, C20), 43.1 (s, C8), 45.2 (s, C14), 47.5 (d, C18), 48.5 (d, C5), 60.9 (d, C9), 61.3 (d, C3), 77.3 (t, OCH_2Ph), 127.7 (d, C12), 128.2 (2 × d, PhCH), 128.4 (d, PhCH), 128.9 (2 × d, 2 × PhCH), 135.3 (s, PhC), 170.8 (s, C13), 173.7 (s, C29), 201.4 (s, C11).

4.37. (3β,18β,20β)-*N*-Benzyloxy-11-oxo-3-[(trifluoromethyl-sulfonyl)amino]-olean-12-en-29-amide (31b)

Carboxylic acid **9b** (500 mg, 0.83 mmol, 1.00 equiv) was—analogous to **15**—first converted to the acid chloride in $SOCl_2$/toluene (12 mL each) (within 2 h) and was then reacted with a pre-stirred solution of NH_2OBn (123 mg, 1.00 mmol, 1.20 equiv) and TEA (230 μL, 1.66 mmol, 2.00 equiv) in DCM (20 mL). Aqueous workup gave crude material which was purified by flash column chromatography (SiO_2: 30 g, Hex/EtOAc 3:1 + 0.1% AcOH to Hex/EtOAc 1:1 + 0.1% AcOH to $CHCl_3$/MeOH 9:1 + 0.1% AcOH) to give pure **31b** (476 mg, 81.0%) as white solid. R_f = 0.67 ($CHCl_3$/MeOH 9:1 + AcOH); $[\alpha]_D^{20}$ +106.4 (*c* 1.0, $CHCl_3$/MeOH 3:1); HRMS: calcd $[M-H]^-$: 705.3549, found $[M-H]^-$: 705.4055; ^{1}H NMR ($CDCl_3$/MeOD 5:1): δ 0.76 (s, 3H, H28), 0.83 (s, 3H, H23/24), 0.73–0.87 (m, 1H, H5), 1.02 (s, 3H, H23/24), 0.96–1.06 (m, 2H, H1b, H16b), 1.11 (s, 3H, H30), 1.12 (s, 3H, H26), 1.14 (s, 3H, H25), 1.06–1.25 (m, 1H, H15b), 1.35 (s, 3H, H27), 1.25–1.38 (m, 3H, H22a, H22b, H21b), 1.38–1.55 (m, 2H, H6b, H7b), 1.55–1.71 (m, 5H, H7a, H6a, H2a, H2b, H19b), 1.71–1.93 (m, 2H, H15a, H19a), 1.93–2.09 (m, 3H, H18, H16a, H21a), 2.38 (s, 1H, H9), 2.75–2.86 (m, 1H, H1a), 3.08–3.17 (m, 1H, H3), 4.09 (s, 1H, NH), 4.91 (s, 2H, OCH_2Ph), 5.49 (s, 1H, H12), 7.29–7.48 (m, 5H, Bn); ^{13}C NMR ($CDCl_3$/MeOD 5:1): δ 15.9 (q, C25), 16.0 (q, C23/24), 17.7 (t, C6), 18.3 (q, C26), 23.0 (q, C27), 25.3 (t, C2), 26.1 (2 × t, C15, C16), 28.0 (q, C28), 28.1 (q, C30), 28.7 (q, C23/24), 30.6 (t, C21), 31.3 (s, C17), 32.3 (t, C7), 36.6 (s, C10), 37.0 (t, C22), 38.4 (s, C4), 39.7 (t, C1), 40.5 (t, C19), 42.4 (s, C20), 43.0 (s, C8), 45.1 (s, C14), 47.5 (d, C18), 55.3

(d, C5), 61.4 (d, C9), 63.8 (d, C3), 77.4 (t, OCH_2Ph), 127.8 (d, C12), 128.2 (2 × d, 2 × PhCH), 128.4 (d, PhCH), 128.9 (2 × d, PhCH), 135.3 (s, PhC), 170.7 (s, C13), 173.7 (s, C29), 200.9 (s, C11).

4.38. (3α,18β,20β)-3-(Acetylamino)-*N*-hydroxy-11-oxo-olean-12-en-29-amide (32a)

O-Bn-hydroxamic acid **30a** (90 mg, 0.15 mmol, 1.00 equiv) was debenzylated by hydrogenolysis analogous to **20** in THF (2 mL) with Pd/C (18 mg, 22%). The crude material was purified by flash column chromatography (SiO_2: 6 g, DCM/Et_2O 1:1 + 0.1% AcOH to DCM/MeOH 20:1 and DCM/MeOH 5:1). Target compound containing fractions were pooled and washed with $NaHCO_3$ and brine, dried over Na_2SO_4 and evaporated to give pure **32a** (31 mg, 40.0%) as orange solid. R_f = 0.29 (DCM/MeOH 5:1); $[\alpha]_D^{20}$ +87.8 (*c* 1.0, $CHCl_3$/MeOH 3:1); HRMS: calcd $[M-H]^-$: 525.3693, found $[M-H]^-$: 525.3559; ^1H NMR ($CDCl_3$): δ 0.71–0.93 (m, 2H, H5, H16b), 0.82 (s, 3H, H28), 0.87 (s, 3H, H23/24), 0.93–1.09 (m, 2H, H1b, H15b), 0.97 (s, 3H, H23/24), 1.09–1.30 (m, 2H, H16a, H21b), 1.13 (s, 3H, H26), 1.15 (s, 3H, H25), 1.19 (s, 3H, H30), 1.30–1.58 (m, 7H, H2a, H2b, H6b, H7a, H7b, H22a, H22b), 1.41 (s, 3H, H27), 1.58–1.76 (m, 2H, H6a, H19b), 1.77–1.95 (m, 2H, H15a, H19a), 1.94–2.13 (m, 1H, H21a), 2.03 (s, 3H, NHAc), 2.15–2.32 (m, 1H, H18), 2.41 (s, 1H, H9), 2.57–2.71 (m, 1H, H1a), 3.78–3.89 (m, 1H, H3), 5.78 (s, 1H, H12); ^{13}C NMR ($CDCl_3$): δ 16.5 (q, C25), 17.2 (t, C7), 18.6 (q, C26), 23.1 (q, C23/24), 23.6 (2 × q, $COCH_3$, C27), 26.4 (3 × t, C2, C15, C16), 28.4 (2 × q, C23/24, C28), 29.5 (q, C30), 30.9 (t, C21), 31.8 (s, C17), 32.4 (t, C6), 34.8 (t, C1), 36.5 (s, C4), 37.2 (s, C10, t, C22), 40.8 (t, C19), 42.3 (s, C20), 43.3 (s, C8), 45.6 (s, C14), 47.7 (d, C18), 51.0 (d, C5), 53.7 (d, C3), 61.7 (d, C9), 128.5 (d, C12), 169.7 (s, $COCH_3$), 169.9 (s, C13), 173.7 (s, C29), 200.7 (s, C11).

4.39. (3β,18β,20β)-3-(Acetylamino)-*N*-hydroxy-11-oxo-olean-12-en-29-amide (32b)

O-Bn-hydroxamic acid **30b** (90 mg, 0.15 mmol, 1.00 equiv) was debenzylated by hydrogenolysis analogous to **20** in THF (2 mL) with Pd/C (18 mg, 22%). The crude material was purified by column chromatography (SiO_2: 6 g, DCM/MeOH 20:1, DCM/MeOH 10:1). Target compound containing fractions were pooled and washed with $NaHCO_3$ and brine, dried over Na_2SO_4 and evaporated to give pure **30b** (37 mg, 47.5%) as orange solid. R_f = 0.37 (DCM/MeOH 5:1); $[\alpha]_D^{20}$ +112.1 (*c* 1.0, $CHCl_3$/MeOH 3:1); HRMS: calcd $[M-H]^-$: 525.3693, found $[M-H]^-$: 525.3465; ^1H NMR ($CDCl_3$): δ 0.67–0.77 (m, 1H, H5), 0.72 (s, 3H, H23/24), 0.75 (s, 3H, H23/24), 0.81 (s, 3H, H23/24), 0.82–0.92 (m, 1H, H1b), 0.92–0.99 (m, 1H, H16b), 1.03 (s, 3H, H26), 1.04 (s, 3H, H25), 1.05–1.17 (m, 1H, H15b), 1.08 (s, 3H, H30), 1.16–1.41 (m, 5H, H6b, H7b, H21b, H22a, H22b), 1.31 (s, 3H, H27), 1.41–1.68 (m, 5H, H2a, H2b, H6a, H7a, H19b), 1.68–1.81 (m, 1H, H15a), 1.86–2.10 (m, 3H, H16a, H19a, H21a), 2.00 (s, 3H, NHAc), 2.12–2.23 (m, 1H, H18), 2.28 (s, 1H, H9), 2.64–2.74 (m, 1H, H1a), 3.50–3.61 (m, 1H, H3), 5.76 (s, 1H, H12), 10.37 (s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 16.2 (q, C25), 16.6 (q, C23/24), 17.7 (t, C7), 18.6 (q, C26), 23.5 (2 × q, C27, $COCH_3$), 25.3 (t, C2), 26.4 (2 × t, C15, C16), 28.4 (q, C28), 28.7 (q, C23/24), 29.4 (q, C30), 31.1 (t, C21), 31.7 (s, C17), 32.7 (t, C6), 37.0 (s, C10), 37.4 (t, C22), 38.2 (s, C4), 40.2 (2 × t, C1, C19), 42.3 (s, C20), 43.2 (s, C8), 45.4 (s, C14), 47.6 (d, C18), 55.8 (d, C5), 56.8 (d, C3), 61.8 (d, C9), 129.1 (d, C12), 168.9, 169.8 (2 × s, C13, $COCH_3$), 173.2 (s, C29), 200.1 (s, C11).

4.40. (3α,18β,20β)-*N*-Hydroxy-11-oxo-3-[(trifluoromethylsulfonyl)amino]-olean-12-en-29-amide (33a)

O-Bn-hydroxamic acid **31a** (142 mg, 0.20 mmol, 1.00 equiv) was debenzylated by hydrogenolysis analogous to **20** in THF (2.8 mL) with Pd/C (28 mg, 20%). The crude material was purified by flash column chromatography (SiO_2: 20 g, Hex/EtOAc 3:1, 240 mL to DCM/MeOH 20:1→DCM/MeOH 5:1) to give pure **33a** (57 mg, 64%) as orange solid. R_f = 0.43 ($CHCl_3$/MeOH 9:1 + AcOH); $[\alpha]_D^{20}$ +89.9 (*c* 1.0, $CHCl_3$/MeOH 3:1); HRMS: calcd $[M-H]^-$: 615.3080, found $[M-H]^-$: 615.2673; ^1H NMR ($CDCl_3$/MeOD 5:1): δ 0.83 (s, 3H, H28), 0.98 (s, 3H, H23/24), 0.99 (s, 3H, H23/24), 1.13 (s, 3H, H26), 1.15 (s, 6H, H25, H30), 1.01–1.27 (m, 5H, H15b, H1b, H21b, H16b, H5), 1.42 (s, 3H, H27), 1.37–1.47 (m, 4H, H7b, H6b, H22a, H22b), 1.50–1.61 (m, 2H, H2b, H6a), 1.62–1.75 (m, 2H, H7a, H19b), 1.78–1.99 (m, 3H, H21a, H15a, H19a), 2.00–2.34 (m, 3H, H18, H2a, H16a), 2.61 (s, 1H, H9), 2.56–2.67 (m, 1H, H1a), 3.30–3.35 (m, 1H, H3), 4.02 (br s, NH/OH), 5.68 (s, 1H, H12); ^{13}C NMR ($CDCl_3$/MeOD 5:1): δ 16.2 (q, C25), 17.0 (t, C6), 18.4 (q, C26), 22.6 (q, C23/24), 22.8 (q, C27), 23.9 (t, C2), 26.1 (2 × t, C15, C16), 28.1 (q, C28), 28.4 (q, C23/24), 28.9 (q, C30), 30.5 (t, C21), 31.4 (s, C17), 32.2 (t, C7), 33.2 (t, C1), 36.6 (s, C10), 36.7 (s, C4), 37.0 (t, C22), 40.7 (t, C19), 42.1 (s, C20), 43.2 (s, C8), 45.3 (s, C14), 47.8 (d, C18), 48.7 (d, C5), 60.9 (d, C9), 61.4 (d, C3), 127.7 (d, C12), 170.8 (s, C13), 173.5 (s, C29), 201.4 (s, C11).

4.41. (3β,18β,20β)-*N*-Hydroxy-11-oxo-3-[(trifluoro-methylsulfonyl)amino]-olean-12-en-29-amide (33b)

O-Bn-hydroxamic acid **31b** (375 mg, 0.53 mmol, 1.00 equiv) was debenzylated by hydrogenolysis analogous to **20** in THF (7.5 mL) with Pd/C (75 mg, 20%). The crude material was purified by flash column chromatography (SiO_2: 85 g, DCM/MeOH 9:1 + 0.1% AcOH to DCM/MeOH 5:1 + 0.1% AcOH) to give pure **33b** (149 mg, 45.4%) as orange solid. R_f = 0.43 ($CHCl_3$/MeOH 9:1 + AcOH); $[\alpha]_D^{20}$ +96.2 (*c* 1.0, $CHCl_3$/MeOH 3:1); HRMS: calcd $[M-H]^-$: 615.3080, found $[M-H]^-$: 615.2993; ^1H NMR ($CDCl_3$/MeOD 5:1): δ 0.74 (s, 3H, H28), 0.75 (s, 3H, H23/24), 0.69–0.78 (m, 1H, H5), 0.94 (s, 3H, H23/24), 1.05 (s, 6H, H25, H26), 1.07 (s, 3H, H30), 0.89–1.10 (m, 2H, H16b, H1b), 1.10–1.17 (m, 1H, H15b), 1.30 (s, 3H, H27), 1.17–1.42 (m, 5H, H6b, H7b, H22a, H22b, H21b), 1.50–1.65 (m, 4H, H19b, H7a, H6a, H15a), 1.69–2.16 (m, 6H, H18, H16a, H21a, H19a, H2a, H2b), 2.31 (s, 1H, H9), 2.66–2.77 (m, 1H, H1a), 3.09–3.00 (m, 1H, H3), 3.93 (br s, NH/OH), 5.60 (s, 1H, H12); ^{13}C NMR ($CDCl_3$/MeOD 5:1): δ 16.1 (q, C25), 16.2 (q, C23/24), 17.9 (t, C6), 18.5 (q, C26), 23.2 (q, C27), 25.0 (t, C2), 25.5 (t, C15), 26.3 (t, C16), 28.2 (q, C23/24), 28.3 (q, C28), 29.1 (q, C30), 30.7 (t, C21), 31.6 (s, C17), 32.5 (t, C7), 36.8 (s, C10), 37.2 (t, C22), 38.6 (s, C4), 39.9 (t, C1), 40.8 (t, C19), 42.3 (s, C20), 43.3 (s, C8), 45.4 (s, C14), 47.9 (d, C18), 55.5 (d, C5), 61.7 (d, C9), 64.0 (d, C3), 128.0 (d, C12), 171.0 (s, C13), 173.5 (s, C29), 201.2 (s, C11).

4.42. (18β,20β)-*N*-Benzyloxy-3,11-dioxo-olean-12-en-29-amide (35)

Carboxylic acid **34** (1.00 g, 2.13 mmol, 1.00 equiv) was suspended in dry DCM (20 mL, 5 drops DMF added as catalyst) and oxalyl chloride (240 μL, 2.55 mmol, 1.2 equiv) was added at 0 °C. The reaction mixture was allowed to reach rt and was stirred under TLC-monitoring (sample from MeOH solution, SiO_2: Hex/EtOAc 2:1) until complete conversion was obtained. The reaction mixture was evaporated at rt, co-evaporated from DCM once and re-dissolved in DCM. The clear solution was cooled to 0 °C and first TEA (648 mg, 6.40 mmol, 3.0 equiv) and then a concentrated solution of $BnONH_2$ (289 mg, 2.35 mmol, 1.1 equiv) in DCM was added at 0 °C. The formation of hydroxamic acid was followed via TLC (SiO_2: Hex/EtOAc 2:1 and amino-phase: DCM/MeOH 20:1). Upon complete conversion, the reaction mixture was diluted with DCM and washed with 1 M HCl, satd $NaHCO_3$ and brine, dried over Na_2SO_4 and evaporated to give crude material which was purified

by column chromatography (SiO_2: 60 g DCM/MeOH 50:1) and passing over a short bed of amino-phase gel (7 g) to give pure **35** (1.05 g, 85.8%) as white solid foam. R_f = 0.29 (Hex/EtOAc 1:1); R_f = 0.45 (DCM/MeOH 30:1 + TEA); $[\alpha]_D^{20}$ +138.8 (*c* 1.0, $CHCl_3$); HRMS: calcd $[M+H]^+$: 574.3891, found $[M+H]^+$: 574.3886; ^1H NMR ($CDCl_3$): δ 0.81 (s, 3H, H28), 0.97–1.05 (m, 1H, H16b), 1.07 (s, 3H, H23/24), 1.1 (s, 3H, H23/24), 1.12 (s, 3H, H30), 1.16 (s, 3H, H26), 1.15–1.23 (m, 1H, H15b), 1.27 (s, 3H, H25), 1.25–1.32 (m, 1H, H5), 1.31 (s, 3H, H27), 1.32–1.42 (m, 4H, H1b, H21b, H22a, H22b), 1.4–1.48 (m, 1H, H6b), 1.49–1.60 (m, 2H, H7a, H7b), 1.60–1.69 (m, 3H, H6a, H19a, H19b), 1.78–1.87 (m, 1H, H15a), 1.84–1.92 (m, 1H, H21a), 2.00 (dt, *J* = 13.6 Hz, *J* = 4.3 Hz, 1H, H16a), 2.05–2.13 (m, 1H, H18), 2.3–2.40 (m, 1H, H2b), 2.39 (s, 1H, H9), 2.57–2.68 (m, 1H, H2a), 2.90–3.00 (m, 1H, H1a), 4.94 (br s, 2H, OCH_2Ph), 5.50 (s, 1H, H12), 7.35–7.45 (m, 5H, 5 × Ph-H), 8.31 (s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 15.6 (q, C25), 18.5 (q, C26), 18.7 (t, C7), 21.4 (q, C23/24), 23.3 (q, C27), 26.31 (t, C15/16), 26.35 (q, C23/24), 26.4 (t, C15/16), 28.4 (q, C28), 29.5 (q, C30), 31.2 (t, C21), 31.8 (s, C17), 32.1 (t, C6), 34.2 (t, C2), 36.7 (s, C10), 37.3 (t, C22), 39.8 (t, C1), 41.3 (t, C19), 43.0 (s, C20), 43.2 (s, C14), 45.1 (s, C8), 47.78 (s, C4), 47.84 (d, C18), 55.4 (d, C5), 61.0 (d, C9), 78.0 (t, OCH_2Ph), 128.4 (d, PhCH), 128.7 (d, PhCH), 128.9 (d, C12), 129.3 (d, PhCH), 135.3 (s, PhC), 169.2 (s, C13), 173.6 (s, C29), 199.3 (s, C11), 217.2 (s, C3).

4.43. (18β,20β)-*N*-Hydroxy-3,11-dioxo-olean-12-en-29-amide (36)

O-Benzyl-hydroxamic acid **35** (500 mg, 0.871 mmol, 1.00 equiv) was debenzylated by hydrogenolysis analogous to **20** in MeOH (50 mL) with Pd/C (50 mg, 10%). The crude material was purified by column chromatography (SiO_2: 40 g, DCM/MeOH 50:1 + 0.1% TEA to DCM/MeOH 30:1 + 0.1% TEA) pure **35** (236 mg, 56%) as white lyophilisate after lyophilization from dioxane/water solution. R_f = 0.09 (DCM/MeOH 30:1 + TEA); $[\alpha]_D^{20}$ +168.9 (*c* 1.1, $CHCl_3$); HRMS: calcd $[M+H]^+$: 484.3421, found $[M+H]^+$: 484.3423; ^1H NMR ($CDCl_3$): δ 0.83 (s, 3H, H28), 1.00–1.05 (m, 1H, H16b), 1.07 (s, 3H, H23/24), 1.10 (s, 3H, H23/24), 1.15–1.24 (m, 1H, H15b), 1.16 (s, 3H, H26), 1.17 (s, 3H, H30), 1.25–1.34 (m, 1H, H5), 1.26 (s, 3H, H25), 1.34–1.49 (m, 5H, H1b, H7b, H21b, H22a, H22b), 1.37 (s, 3H, H27), 1.47–1.61 (m, 2H, H6a, H6b), 1.61–1.73 (m, 2H, H7a, H19b), 1.77–2.00 (m, 3H, H15a, H19a, H21a), 1.97–2.08 (m, 1H, H16a), 2.16–2.27 (m, 1H, H18), 2.30–2.40 (m, 1H, H2b), 2.43 (s, 1H, H9), 2.55–2.66 (m, 1H, H2a), 2.88–2.98 (m, 1H, H1a), 5.78 (s, 1H, H12); ^{13}C NMR ($CDCl_3$): δ 15.7 (q, C25), 18.5 (q, C26), 18.8 (t, C6), 21.4 (q, C23/24), 23.3 (q, C27), 26.4 (q, C23/24), 26.4 (t, C15/16), 26.5 (t, C15/16), 28.4 (q, C28), 29.5 (q, C30), 31.0 (t, C21), 31.8 (s, C17), 32.1 (t, C7), 34.2 (t, C2), 36.7 (s, C10), 37.3 (t, C22), 39.8 (t, C1), 40.9 (t, C19), 42.3 (s, C20), 43.3 (s, C14), 45.2 (s, C8), 47.77 (s, C4), 47.82 (d, C18), 55.4 (d, C5), 61.1 (d, C9), 128.5 (d, C12), 169.9 (s, C13), 173.8 (s, C29), 199.8 (s, C11), 217.3 (s, C3).

4.44. (18β,20β)-*N*-Hydroxy-*N*-methyl-3,11-dioxo-olean-12-en-29-amide (37)

Carboxylic acid **34** (2.00 g, 4.27 mmol, 1.00 equiv) was converted to the hydroxamic acid derivative analogous to **35** by first converting to the acid chloride in dry DCM (40 mL + 20 drops of DMF) with oxalyl chloride (490 μL, 5.12 mmol, 1.2 equiv) and subsequent treatment with TEA (2.38 mL, 17.1 mmol, 4.0 equiv) and *N*-methyl-hydroxylamine hydrochloride (392 mg, 4.69 mmol, 1.1 equiv) which was added in one portion. Aqueous workup and column chromatography (SiO_2: 115 g, DCM/MeOH 45:1→35:1) and column chromatography on amino-phase (15 g, DCM to DCM/MeOH 50:1) gave pure **37** (1.48 g, 69.7%) as white solid. R_f = 0.14 (Hex/EtOAc 1:1 + 0.1% AcOH); $[\alpha]_D^{20}$ +164.4 (*c* 0.55, $CHCl_3$); HRMS: calcd $[M+H]^+$: 498.3578, found $[M+H]^+$: 498.3572; ^1H NMR ($CDCl_3$): δ 0.83 (s, 3H, H28), 1.00–1.08 (m, 1H, H16b), 1.07 (s, 3H, H23/24), 1.10 (s, 3H, H23/24), 1.16 (s, 3H, H26), 1.2 (s, 3H, H30), 1.21–1.36 (m, 3H, H5, H15b, H21b), 1.26 (s, 3H, H25), 1.33–1.46 (m, 2H, H1b, H22b), 1.37 (s, 3H, H27), 1.41–1.64 (m, 6H, H6a, H6b, H7a, H7b, H19b, H22a), 1.86 (td, *J* = 13.6 Hz, *J* = 4.3 Hz, 1H, H15a), 2.09 (td, *J* = 13.6 Hz, *J* = 4.3 Hz, 1H, H16a), 2.18–2.25 (m, 3H, H18, H19a, H21a), 2.37 (ddd, *J* = 15.8 Hz, *J* = 6.5 Hz, *J* = 4.1 Hz, 1H, H2b), 2.45 (s, 1H, H9), 2.62 (ddd, *J* = 15.8 Hz, *J* = 11.1 Hz, *J* = 7.1 Hz, 1H, H2a), 2.93 (ddd, *J* = 13.5 Hz, *J* = 7.1 Hz, *J* = 4.1 Hz, 1H, H1a), 3.36 (s, 3H, NCH_3), 5.69 (s, 1H, H12); ^{13}C NMR ($CDCl_3$): δ 15.7 (q, C25), 18.5 (q, C26), 18.7 (t, C7), 21.4 (q, C23/24), 23.1 (q, C27), 26.3 (q, C30), 26.4 (q, C23/24), 26.5 (t, C15), 26.7 (t, C16), 28.6 (q, C28), 31.9 (s, C17), 32.1 (t, C6), 32.5 (t, C21), 34.2 (t, C2), 36.7 (s, C10), 37.7 (t, C22), 38.3 (q, NCH_3), 39.7 (t, C1), 42.5 (t, C19), 43.5 (s, C8/20), 43.6 (s, C8/20), 45.3 (s, C14), 47.8 (s, C4), 48.5 (d, C18), 55.4 (d, 5), 61.1 (d, C9), 128.1 (d, C12), 171.4 (s, C13), 174.0 (s, C29), 200.2 (s, C11), 217.4 (s, C3).

4.45. (18β,20β)-*N*-Hydroxy-3-hydroxyimino-11-oxo-olean-12-en-29-amide (38)

Ketone **36** (50 mg, 0.103 mmol, 1.00 equiv), NaOAc (30 mg, 0.36 mmol, 3.5 equiv) and $NH_2OH{\cdot}HCl$ (25 mg, 0.36 mmol, 3.5 equiv) were dissolved in $CHCl_3$/MeOH 2:1 (2.5 mL). In a closed reaction tube (15 mL-volume) the reaction mixture was stirred at 60 °C in a sand-bath under HPLC monitoring for 90 min and for 2 h at rt. The reaction mixture was diluted with $CHCl_3$, washed three times with half satd NaCl. The aqueous layers were extracted with $CHCl_3$ (some MeOH added), the combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated (a drop of TEA was added for stability). The residue was taken up in distilled dioxane (5 mL) and lyophilized to give pure **38** (45 mg, 87%) as white lyophilisate, only contaminated with small amounts of TEA and dioxane according to ^1H NMR and ^{13}C NMR. R_f = 0.15 (DCM/MeOH 20:1 + 0.5% TEA); $[\alpha]_D^{20}$ +93.9 (*c* 0.5, $CHCl_3$); HRMS: calcd $[M+H]^+$: 499.3530, found $[M+H]^+$: 499.3531; ^1H NMR ($CDCl_3$): δ 0.83 (s, 3H, H28), 0.98–1.10 (m, 3H, H1b, H5, H16b), 1.07 (s, 3H, H23/24), 1.15 (s, 3H, H26), 1.16 (s, 3H, H23/24), 1.17–1.25 (m, 1H, H15b), 1.18 (s, 3H, H30), 1.23 (s, 3H, H25), 1.34 (s, 3H, H27), 1.36–1.52 (m, 5H, H6b, H7b, H21b, H22a, H22b), 1.57–1.75 (m, 3H, H6a, H7a, H19b), 1.78–1.90 (m, 2H, H15a, H19a), 1.92–2.04 (m, 2H, H16a, H21a), 2.15–2.29 (m, 2H, H2b, H18), 2.37 (s, 1H, H9), 2.83 (app. dt, *J* = 13.4 Hz, *J* = 4.6 Hz, 1H, H1a), 3.04 (app. dt, *J* = 15.5 Hz, *J* = 4.3 Hz, 1H, H2a), 5.74 (s, 1H, H12); ^{13}C NMR ($CDCl_3$): δ 15.7 (q, C25), 17.2 (t, C2), 18.2 (t, C6), 18.7 (q, C26), 23.2 (q, C23/24), 23.3 (q, C27), 26.38, 26.42 (2 × t, C15, C16), 27.1 (q, C23/24), 28.4 (q, C28), 29.5 (q, C30), 31.0 (t, C21), 31.8 (s, C17), 32.4 (t, C7), 37.0 (s, C10), 37.3 (t, C22), 39.1 (t, C1), 40.4 (s, C4), 40.9 (t, C19), 42.3 (s, C17), 43.3, 45.4 (2 × s, C8, C20), 47.9 (d, C18), 55.6 (d, C5), 61.4 (d, C9), 128.5 (d, C12), 167.0 (s, C3), 169.5 (s, C13), 173.8 (s, C29), 200.1 (s, C11).

4.46. (18β,20β)-*N*-Hydroxy-3-methoxyimino-11-oxo-olean-12-en-29-amide (39)

Ketone **36** (96 mg, 0.198 mmol, 1.00 equiv), NaOAc (65 mg, 0.79 mmol, 4.0 equiv) and $NH_2OMe{\cdot}HCl$ (50 mg, 0.60 mmol, 3.0 equiv) were dissolved in $CHCl_3$/MeOH 2:1 (4.5 mL) and stirred at 60 °C in a sand-bath under an atmosphere of argon for 7 h and at rt overnight. The reaction mixture was diluted with DCM, washed twice with half saturated NaCl, diluted AcOH, satd $NaHCO_3$ and brine (always with subsequent back-extraction with DCM/MeOH 10:1). The organic layer was dried over Na_2SO_4, one drop of TEA was added and evaporated, taken up in distilled dioxane (5 mL) and lyophilized to give pure **39** (97 mg, 95.3%) as white lyophili-

sate. R_f = 0.19 (DCM/MeOH 20:1 + 0.5% TEA); $[\alpha]_D^{20}$ +102.0 (*c* 0.5, $CHCl_3$); HRMS: calcd $[M+H]^+$: 513.3687, found $[M+H]^+$: 513.3688; ^1H NMR ($CDCl_3$): δ 0.82 (s, 3H, H28), 0.99–1.10 (m, 3H, H1b, H5, H16b), 1.06 (s, 3H, H23/24), 1.14 (s, 3H, H26), 1.17 (br s, 6H, H23/24, H30), 1.15–1.30 (m, 2H, H15b, H21b), 1.22 (s, 3H, H25), 1.34 (s, 3H, H27), 1.34–1.55 (m, 4H, H6b, H7b, H22a, H22b), 1.56–1.76 (m, 3H, H6a, H7a, H19a), 1.76–1.90 (m, 2H, H15a, H19b), 1.90–2.10 (m, 2H, H16a, H21a), 2.12–2.26 (m, 2H, H2b, H18), 2.37 (s, 1H, H9), 2.75–2.85 (m, 1H, H1a), 2.85–2.98 (m, 1H, H2a), 3.81 (s, 3H, OCH_3), 5.75 (br s, 1H, H12); ^{13}C NMR ($CDCl_3$): δ 15.6 (q, C25), 17.7 (t, C2), 18.2 (t, C6), 18.6 (q, C26), 23.28, 23.43 (2 × q, C23/24, C27), 26.4 (t, C16), 26.4 (t, C15), 27.2 (q, C23/24), 28.4 (q, C28), 29.5 (q, C30), 31.0 (t, C21), 31.8 (s, C17), 32.4 (t, C7), 37.0 (s, C10), 37.3 (t, C22), 39.1 (t, C1), 40.1 (s, C4), 40.8 (t, C19), 42.3, 43.3, 45.4 (s, C8, C14, C20), 47.8 (d, C18), 55.6 (d, C5), 61.0 (q, OCH_3), 61.4 (d, C9), 128.6 (d, C12), 165.6 (s, C3), 169.4 (s, C13), 173.8 (s, C29), 200.2 (s, C11).

4.47. (18β,20β)-*N*-Hydroxy-3-hydroxyimino-*N*-methyl-11-oxo-olean-12-en-29-amide (40)

A solution of ketone **37** (320 mg, 0.643 mmol, 1.00 equiv) and hydroxylamine hydrochloride (223 mg, 3.22 mmol, 5.00 equiv) in dry pyridine (4 mL) was stirred at rt under TLC-monitoring (DCM/MeOH 40:1). Upon complete conversion (3 h), the reaction mixture was diluted with DCM and washed with cooled 10% HCl, satd $NaHCO_3$, and brine, dried over Na_2SO_4 and evaporated. The residual white solid was dissolved in MeOH and evaporated to give a fine white solid, which was triturated with DCM to give pure **40** (320 mg, 97%) as white solid. R_f = 0.14 (Hex/EtOAc 1:1 + 0.1% AcOH); $[\alpha]_D^{20}$ +110.8 (*c* 1.0, $CHCl_3$); HRMS: calcd $[M+H]^+$: 513.3687, found $[M+H]^+$: 513.3681; ^1H NMR ($CDCl_3$): δ 0.82 (s, 3H, H28), 0.97–1.16 (m, 3H, H1b, H5, H16b), 1.07 (s, 3H, H23/24), 1.15–1.27 (m, 2H, H15b, H21b), 1.15 (s, 3H, H26), 1.17 (s, 3H, H23/24), 1.2 (s, 3H, H30), 1.23 (s, 3H, H25), 1.31–1.40 (m, 2H, H6b, H22b), 1.35 (s, 3H, H27), 1.44–1.73 (m, 5H, H6a, H7a, H7b, H19b, H22a), 1.85 (td, *J* = 13.6 Hz, *J* = 4.4 Hz, 1H, H15a), 2.02–2.15 (m, 1H, H16a), 2.13–2.33 (m, 1H, H2b, H18, H19a, H21a), 2.41 (s, 1H, H9), 2.75–2.85 (m, 1H, H1a), 3 (dt, *J* = 15.6 Hz, *J* = 4.6 Hz, 1H, H2a), 3.26 (s, 3H, NCH_3), 5.70 (s, 1H, H12); ^{13}C NMR ($CDCl_3$): δ 15.6 (q, C25), 17.1 (t, C2), 18.1 (t, C7), 18.5 (q, C26), 22.9 (q, C27), 23.2 (q, C23/24), 25.9 (q, C30), 26.4 (t, C16), 26.6 (t, C15), 27.2 (q, C23/24), 28.5 (q, C28), 31.8 (s + t, C17, C21), 32.3 (t, C6), 37 (s, C10), 37.7 (t, C22), 38 (q, NCH_3), 38.9 (t, C1), 40.2 (s, C4), 42.1 (t, C19), 43.5 (s, C20), 44.1, 45.3 (2 × s, C8, C14), 48.7 (d, C18), 55.4 (d, C5), 61.3 (d, C9), 127.7 (d, C12), 166.8 (s, C3), 171.9 (s, C13), 175.5 (s, C29), 201.1 (s, C11).

4.48. (18β,20β)-*N*-Hydroxy-*N*-methyl-3-methoxyimino-11-oxo-olean-12-en-29-amide (41)

A solution of ketone **37** (500 mg, 1.01 mmol, 1.00 equiv) and methoxylamine hydrochloride (252 mg, 3.01 mmol, 3.00 equiv) in dry pyridine (5 mL) was stirred at rt under TLC-monitoring (DCM/MeOH 40:1). Upon complete conversion (3 h), the reaction mixture was diluted with DCM and washed with chilled 10% HCl, satd $NaHCO_3$, and brine, dried over Na_2SO_4 and evaporated. The crude material was purified by column chromatography (SiO_2: 25 g DCM/MeOH 60:1→DCM/MeOH 50:1) to give pure **41** (536 mg, quantitative) as white solid foam. R_f = 0.23 (Hex/EtOAc 1:1 + 0.1% AcOH); $[\alpha]_D^{20}$ +96.7 (*c* 0.5. $CHCl_3$); HRMS: calcd $[M+H]^+$: 527.3843, found $[M+H]^+$: 527.3833; ^1H NMR ($CDCl_3$): δ 0.82 (s, 3H, H28), 0.96–1.05 (m, 3H, H1b, H5, H16b), 1.07 (s, 3H, H23/24), 1.12–1.24 (m, 1H, H15b), 1.14 (s, 3H, H26), 1.18 (s, 3H, H23/24), 1.19 (s, 3H, H30), 1.22 (s, 3H, H25), 1.23–1.40 (m, 2H, H21b, H22b), 1.34 (s, 3H, H27), 1.38–1.68 (m, 6H, H6a, H6b, H7a, H7b, H19b, H22a), 1.83 (td, *J* = 13.5 Hz, *J* = 4.1 Hz, 1H, H15a), 1.99–2.14 (m, 1H, H16a), 2.11–2.24 (m, 4H, H2b, H18, H19a, H21a), 2.38 (s, 1H, H9), 2.72–2.82 (m, 1H, H1a), 2.86–2.96 (m, 1H, H2a), 3.36 (s, 3H, NCH_3), 3.82 (s, 3H, OCH_3), 5.66 (s, 1H, H12); ^{13}C NMR ($CDCl_3$): δ 15.7 (q, C25), 17.7 (t, C2), 18.2 (t, C7), 18.6 (q, C26), 23.1 (q, C27), 23.4 (q, C23/24), 26.3 (q, C30), 26.5 (t, C15), 26.7 (t, C16), 27.3 (q, C23/24), 28.5 (q, C28), 31.9 (s, C17), 32.5, 32.7 (2 × t, C6, C21), 37.0 (s, C10), 37.7 (t, 22), 38.3 (q, NCH_3), 39.1 (t, C1), 40.1 (s, C4), 42.4 (t, C19), 43.4, 43.5 (2 × s, C8, C20), 45.4 (s, C14), 48.5 (d, C18), 55.6 (d, C5), 61 (q, OCH_3), 61.4 (d, C9), 128.2 (d, C12), 165.6 (s, C3), 170.9 (s, C13), 173.7 (s, C29), 200.5 (s, C11).

4.49. (3β,18β,20β)-*N*-Hydroxy-*N*-methyl-3-methoxyamino-11-oxo-olean-12-en-29-amide (42)

Oxime **41** (275 mg, 0.522 mmol, 1.0 equiv) was dissolved in dioxane/EtOH 2:1 (12 mL). This solution was cooled to 0 °C before $tBuNH_2{\cdot}BH_3$ (91 mg, 1.04 mmol, 2.00 equiv) was added at 0 °C and 5 min later 3 M HCl (1.2 mL) was added dropwise via a syringe. The reaction mixture was stirred at 0 °C for several hours. After some time the reaction mixture became milky turbid but well stirrable. According to TLC almost all starting material was converted to the target compound. Addition of another equivalent of $tBuNH_2{\cdot}BH_3$ and HCl did not lead to further conversion. The reaction mixture was worked up by pouring onto satd $NaHCO_3$ and extraction with EtOAc, washing of the organic layers with brine, drying over Na_2SO_4 and evaporation to give crude material which was purified by column chromatography (SiO_2: 30 g, DCM/Et_2O 2:1) and subsequent precipitation from DCM/MeOH to give pure target compound **42** (50 mg, 18.1%) as white solid. For better solubility part of the material was transformed to the corresponding hydrochloride by taking up in THF, precipitating with HCl in Et_2O (1 M, 2 equiv equiv) and washing with Et_2O. R_f = 0.31 (toluene/EtOAc 2:1 + 0.1% AcOH); $[\alpha]_D^{20}$ +152.6 (*c* 0.7, $CHCl_3$/MeOH 5:1); HRMS: calcd $[M+H]^+$: 529.4000, found $[M+H]^+$: 529.3993; ^1H NMR ($CDCl_3$/MeOD 5:1): δ 0.73 (s, 3H, H23/24), 0.73–0.79 (m, 1H, H5), 0.82 (s, 3H, H28), 0.90–0.99 (m, 1H, H1b), 0.98–1.05 (m, 1H, H16b), 1.07 (s, 3H, H23/24), 1.13 (s, 3H, H26), 1.14 (s, 3H, H25), 1.16–1.32 (m, 2H, H15b, H21b), 1.21 (s, 3H, H30), 1.32–1.52 (m, 5H, H2b, H6b, H7b, H22a, H22b), 1.39 (s, 3H, H27), 1.54–1.74 (m, 3H, H6a, H7a, H19b) 1.79–1.92 (m, 2H, H2a, H15a), 2.05 (td, *J* = 13.6 Hz, *J* = 4.4 Hz, 1H, H16a), 2.16–2.32 (m, 1H, H18, H19a, H21a), 2.40 (s, 1H, H9), 2.52 (dd, *J* = 11.8 Hz, *J* = 4.1 Hz, 1H, H3), 2.72 (dt, *J* = 13.4 Hz, *J* = 3.4 Hz, 1H, H1a), 3.25 (s, 3H, NCH_3), 3.52 (s, 3H, OMe), 5.69 (s, 1H, H12); ^{13}C NMR ($CDCl_3$/MeOD 5:1): δ 15.8 (q, C25), 16.4 (q, C23/24), 17.0 (t, C6), 18.4 (q, C26), 22.8 (q, C27), 23.0 (t, C2), 25.6 (q, C30), 26.2 (t, C15), 26.4 (t, C16), 28.2, 28.3 (2 × q, C28, C23/24), 31.6 (s, C17), 31.9 (t, C21), 32.5 (t, C7), 36.6 (s, C4), 37.0 (s, C10), 37.6 (t, C22), 37.7 (q, NCH_3), 38.9 (t, C1), 41.9 (t, C19), 43.2 (s, C20), 44.1 (s, C14), 45.2 (s, C8), 48.5 (d, C18), 55.9 (d, C5), 61.2 (q, OCH_3), 61.6 (d, C9), 67.5 (d, C3), 127.6 (d, C12), 171.6 (s, C13), 175.6 (s, C29), 201.5 (s, C11).

4.50. Biology

The activity of 11β-HSD1 and 11β-HSD2 was measured as described previously.[45] Briefly, HEK-293 cells were transfected with pcDNA3 plasmids containing either human 11β-HSD1 or 11β-HSD2 with a C-terminal FLAG epitope. 11β-HSD1 dependent reduction of [1,2-^{3}H]-labeled cortisone (American Radiolabeled Chemicals, St. Louis, MO) to cortisol was measured in cell lysates 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). In a

first step, inhibitors were tested at final concentrations of 1 μM or 200 nM. Potent inhibitors were diluted from stock solutions in dimethylsulfoxide and immediately used for activity assays. Selected active compounds were measured also at multiple final concentrations between 1 nM and 40 μM in order to calculate IC_{50} values. 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 and 95% confidence intervals (CI)) were obtained from three independent experiments.

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