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Synthesis and crystal structures of ring A modified glycyrrhetinic acid derivatives derived from 2,3-oxirane and 2,3-thiirane intermediates

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ABSTRACT

A general method for the introduction of thiol groups at positions 1, 2, and 3 of glycyrrhetinic acid has been developed starting from a protected 2α,3α-oxido-derivative. Conversion into the corresponding 2β,3β-epithio-derivative was followed by ring-opening leading to either 2- or 3-substituted thio derivatives. Conversely, 3α-configured allylic alcohol intermediates derived from the 2,3-epoxide provided efficient access to both diastereoisomeric 3-thio derivatives as well as 1α-thio derivatives. The stereochemistry of the newly formed stereogenic centers was rigorously proven using X-ray crystallography.

1. Introduction

The major bioactive compounds extracted from licorice roots (Glycyrrhizae glabra) are glycyrrhizin and its natural metabolite glycyrrhetinic acid (GA), which have been used for a long time in traditional medicines for the treatment of allergic, pulmonary, and hepatic ailments.[1–4] The broad spectrum of activities comprises antiinflammatory, cytotoxic, antiulcer, antiproliferative, antioxidative, and endocrine activities.[5–9] GA as well as the hemisuccinate ester carbenoxolone are potent inhibitors of 11β-hydroxysteroid dehydrogenase 1 and 2.[10–13] Numerous modifications in the ring skeleton of the oleanolic acid backbone have been performed.[14] With respect to ring A modification, most approaches have focussed on the modification of position 3 of GA by oxidation, followed by reductive amination, as well on utilization of the 2,3-dehydro derivative.[15–17] These studies succeeded in introducing O-, N-, and C-linked appendices into ring A as well as affording halide-substituted derivatives.[5,6,18] Furthermore, sulfone and phosphonate moieties have been installed in ring A of GA.[19] Within the framework of ongoing studies aimed at the development of selective inhibitors of 11β-hydroxysteroid dehydrogenase 1 and 2 we have set out to synthesize thio derivatives of glycyrrhetinic acid modified at positions 1, 2, and 3 of ring A, to be used as versatile educts for further modification by alkylation, acylation as well as glycosylation protocols. The major approaches described herein utilize the known 2,3-oxido derivative of GA as the central intermediate as well as the novel 2β,3β-epithio compounds followed by allylic rearrangement reactions and full deprotection.

2. Results and discussion

The previously described[20] diphenylmethyl ester derivative **1** was converted into the crystalline 3-*O*-*p*-toluenesulfonyl derivative **2** in 99% yield by reaction with *p*-toluenesulfonyl chloride in pyridine. Subsequent elimination was effected by treatment of **2** with tetrabutyl ammonium iodide in DMF at 100 °C, which afforded the 2,3-diene derivative **3** as crystalline material in 91% yield. In addition, a small amount of the fully deprotected diene **4,** formed during the reaction, was isolated by silica gel chromatography. The NMR spectral characteristics of **4** are consistent with previously published data of the 2,3-dehydro methyl ester of glycyrrhetinic acid and also agree with the data of the free acid derivative.[17,21] Reaction of the diene derivative **3** with *m*-chloroperbenzoic acid was performed in a multigram scale and furnished the crystalline 2α,3α-oxido derivative **5** (Scheme 1). The crystal structure of the epoxide **5** (Fig. 1) unambiguously established the stereochemistry

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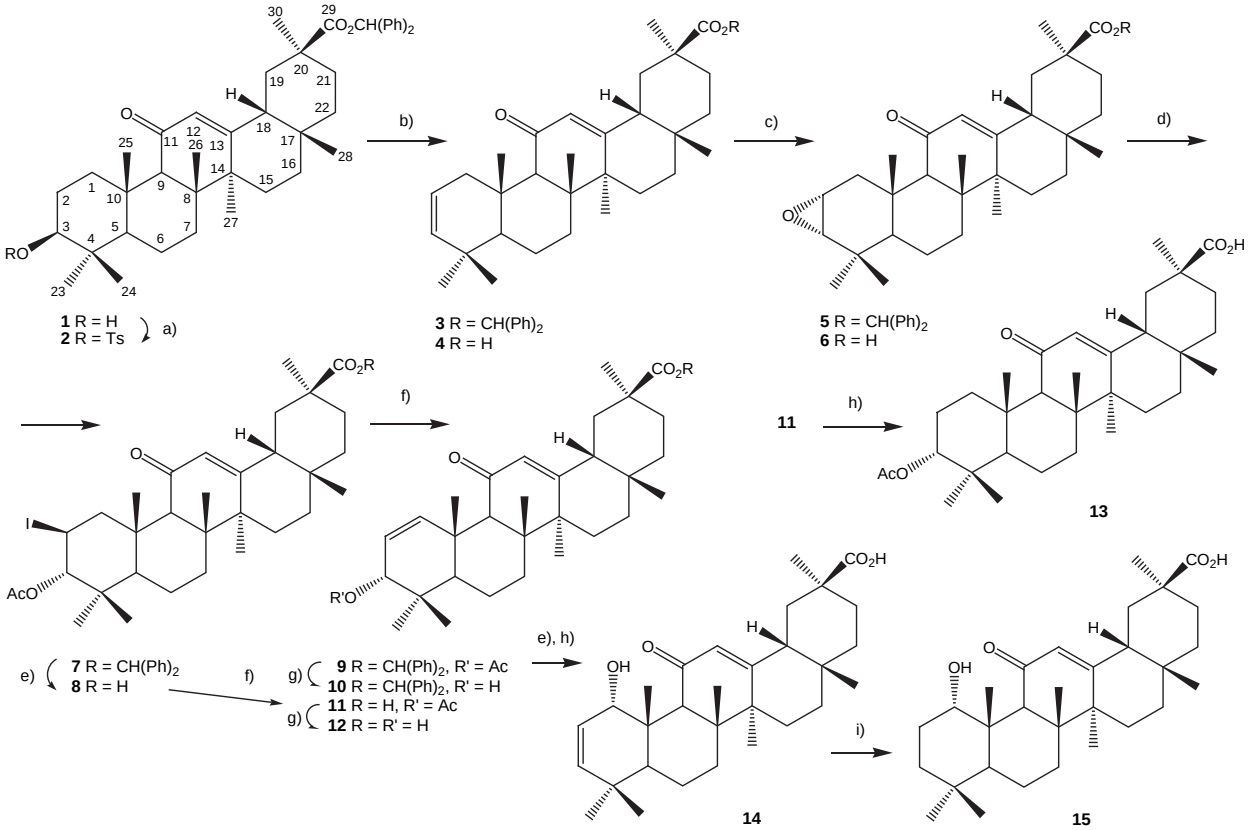


Scheme 1. Synthesis of **5** and **6** and 1α- and 3α-hydroxy derivatives. Reagents and conditions: (a) TsCl, Pyr., 0 °C→rt, 15 h, 99%; (b) Bu_4NI, NaI, DMF, 100 °C, 15 h, 91% for **3**, 4.8% for **4**; (c) *m*CPBA, CH_2Cl_2, 4 °C→8 °C, 15 h, 73% for **5**, 53.5% for **6**; (d) Ph_3P, I_2, CH_2Cl_2, −30 °C, 0.5 h, Ac_2O, pyr., DMAP, rt, 15 h, 85% for **7**; (e) anisole, TFA, CH_2Cl_2, 8 °C, 15 h, 72.5% for **8**; (f) DBU, toluene, 100 °C, 15 h, 83% for **9**; DBU, MeCN, 80 °C, 15 h, 72% for **11**; (g) 1 M KOH, EtOH, rt, 15 h, 90% for **10**, 87% for **12**; (h) 0.1 M NaOMe, 4 h, rt, 82% for **14**; (i) 10% Pd–C, H_2, MeOH, rt, 15 h, 80% for **13**, 85% for **15**.

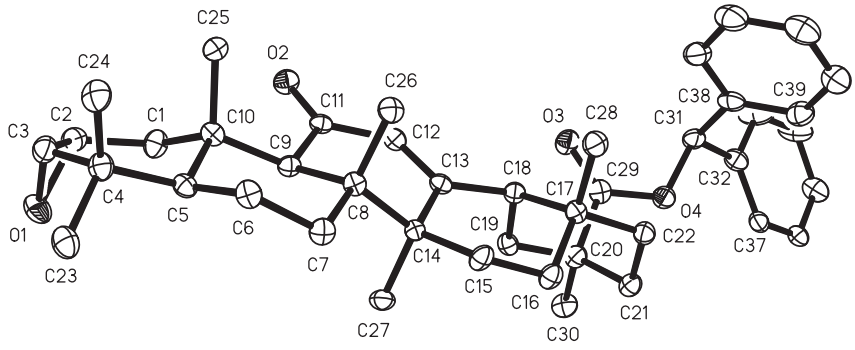


Figure 1. Crystal structure of epoxide **5**. H-atoms omitted for clarity. C2–O1=1.451(3) Å, C3–O1=1.437(3) Å, C2–C3=1.471(4) Å.

at C-2 and C-3, thereby confirming the previously reported assignment of an epoxide generated from the methyl ester of glycyrrhetinic acid.[17] The NMR data of **5** also confirm the previous assignments of 2α,3α- and 2β,3β-oxido triterpenoid derivatives, which had been based on B3LYP/631G*//MM^+ and DFT calculations.[22] Since the ^1H NMR chemical shift values as well as the homonuclear coupling constants are similar for both configurations, ^{13}C NMR chemical shift arguments had been employed to assign the epoxide configuration. Indeed, the ^{13}C NMR chemical shift values for C-1 (δ 41.02), C-2 (δ 52.51, Table 1) and C-5 (δ 46.51) of the 2α,3α-epoxide **5** were in very close agreement with the published values for a related 2α,3α-epoxide triterpene derivative.[22] Using the free acid derivative **4** in a similar reaction gave the epoxide derivative **6** in 53.5% isolated yield. The epoxide **5** provided a versatile starting material for numerous chemical modifications of ring A of glycyrrhetinic acid. Thus, the diphenylmethyl ester derivative **5** was reacted with triphenylphosphine and iodine in dichloromethane followed by acetylation with acetic anhydride/pyridine/DMAP.[22] The resulting acetylated iodohydrin **7** was isolated in 85% yield and its crystal and molecular structure was determined. The structure of **7** (Fig. 2) revealed the presence of a twist boat conformation for ring A, which was also reflected in a large value of the coupling constant of $J_{2,3}$ (12.6 Hz). Removal of the diphenylmethyl ester group from **7** was accomplished using trifluoroacetic acid to generate the benzylium cation, which was trapped by anisole to afford the acid derivative **8**, isolated by silica gel chromatography in 72.5% yield. The elimination reaction of **7** in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) afforded the 1,2-dehydro derivative **9** in 83% yield. Removal of the 3-*O*-acetyl group under alkaline conditions furnished the allylic alcohol **10** in 90% yield.

Table 1
^{13}C NMR data (ppm) of compounds **4**–**16**[a]

Carbon atom	4	5	6	7	8	9	10	11	12	13	14	15	16
1	41.47	40.58	40.62	54.63	56.43	143.61	142.29	143.64	141.35	34.09	70.50	70.89	49.46
2	121.95	52.51	52.69	29.23	30.26	119.39	123.27	119.48	123.70	22.72	124.62	24.67	68.98
3	136.99	61.25	61.40	77.28	79.03	74.72	73.40	74.81	73.03	78.03	141.25	34.07	77.79
4	34.36	31.64[b]	31.85	39.16[b]	40.25	35.71	37.39	35.78	36.80	36.66	35.60	31.92	37.83[b]
5	51.79	46.51	46.63	49.94	50.54	48.09[b]	47.63	48.33[b]	47.86	49.68	45.47	47.22	50.36
6	18.67	17.78[c]	17.88	19.11	20.15	16.65	16.87	16.70	16.93	17.27	19.57	17.22	19.11
7	31.86[b]	31.75[b]	31.85	31.51[c]	32.45	31.09	32.98	32.90	33.02	32.58	32.57	32.83	31.74[c]
8	45.38	44.99	45.22	45.17	46.55	45.51	45.44	45.69	45.86	45.64	46.10	45.10	45.29
9	60.47	60.27	60.41	62.63	63.77	57.85	58.17	57.94	58.31	61.61	53.09	53.32	63.10
10	36.16	35.82	35.95	39.67[b]	40.99	37.42	38.39	38.36	38.52	37.03	41.80	41.39	37.71[b]
11	200.46	199.52	200.00	198.29	201.16	199.68	199.77	200.06	201.63	200.59	203.10	202.56	199.47
12	128.54	128.37	128.48	128.22	128.66	128.10	128.08	128.17	127.76	128.44	129.11	127.89	128.33
13	169.72	169.28	169.88	169.77	173.88	169.42	169.42	169.88	172.14	169.42	172.89	171.16	170.27
14	43.81[c]	43.87	43.75	43.97	44.79[b]	43.94	43.91	43.77[c]	43.80[b]	43.78[b]	44.89[b]	43.48[b]	43.35[d]
15	26.44[d]	26.28[d]	26.41[b]	26.39[d]	27.57[c]	26.42[c]	26.44[b]	26.51[d]	26.55[c]	26.63[c]	27.64[c]	26.24[c]	26.44[e]
16	26.42[d]	26.23[d]	26.38[b]	26.29[d]	27.32[c]	26.29[c]	26.35[b]	26.37[d]	26.37[c]	26.46[c]	27.45[c]	26.16[c]	26.38[e]
17	30.86	32.49	32.59	31.68	32.90	32.83	31.06	31.85	31.91	31.86	32.96	31.56	31.83[c]
18	48.21	47.94	48.20	47.98	49.90	48.38[b]	48.15	48.48[b]	47.86	48.27	49.87	48.23	48.23
19	40.92	41.02	40.88	41.19	42.52	41.05	41.08	40.86	41.23	40.95	42.52	41.01	41.04
20	43.35[c]	43.13	43.28	43.32	44.87[b]	43.30	43.26	43.40[c]	43.68[b]	43.26[b]	45.06[b]	43.48[b]	43.74[d]
21	31.91[b]	31.03	30.88	31.14[c]	31.95	32.83	31.16	30.89	31.03	30.91	32.00	30.77	30.93
22	37.72	37.37	37.70	37.46	38.99	38.25	36.74	37.68	37.84	37.71	39.05	37.52	36.97
23	32.01	28.13[e]	28.22	23.98	23.81[d]	26.07[c]	26.49[b]	26.09[d]	26.21[c]	28.44[d]	31.63	32.87	23.47[f]
24	23.05[e]	21.98	22.06	23.27[e]	23.75[d]	23.37[d]	23.59[c]	23.39[e]	23.50[d]	21.95	23.31	21.19	23.21[f]
25	18.26	18.18	18.27	21.92	22.56	19.21	18.64	18.74	18.30	16.22	17.10	17.29	21.92
26	16.10	17.84[c]	17.88	18.11	18.66	18.73	19.24	19.28	19.10	18.71	19.16	18.67	18.20
27	23.29[e]	23.09	23.24	23.37[e]	24.11	23.53[d]	23.63[c]	23.61[e]	23.25[d]	23.54	23.77	23.07	23.73[f]
28	28.46[f]	28.13[e]	28.41	28.23[f]	29.22	28.24[e]	28.31[d]	28.50[f]	28.16[e]	28.53[d]	29.28	28.28[d]	28.57[g]
29	182.19	175.08	181.48	175.17	180.23	175.15	175.12	181.51	179.38	181.42	180.37	179.18	180.75
30	28.57[f]	28.24[e]	28.56	28.33[f]	28.70	28.18[e]	28.24[d]	28.40[f]	28.40[e]	27.98	28.77	28.10[d]	28.42[g]

[a] Assignments were based on cosy, hsqc and hmbc measurements.
[b–g] Assignments within a column may have to be reversed

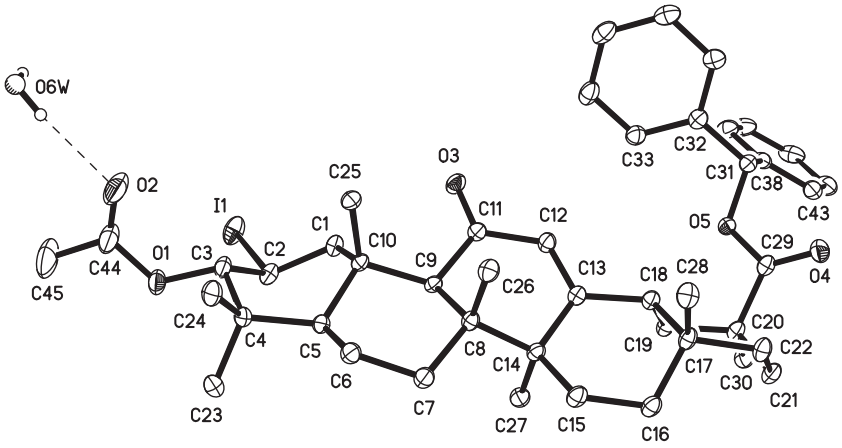
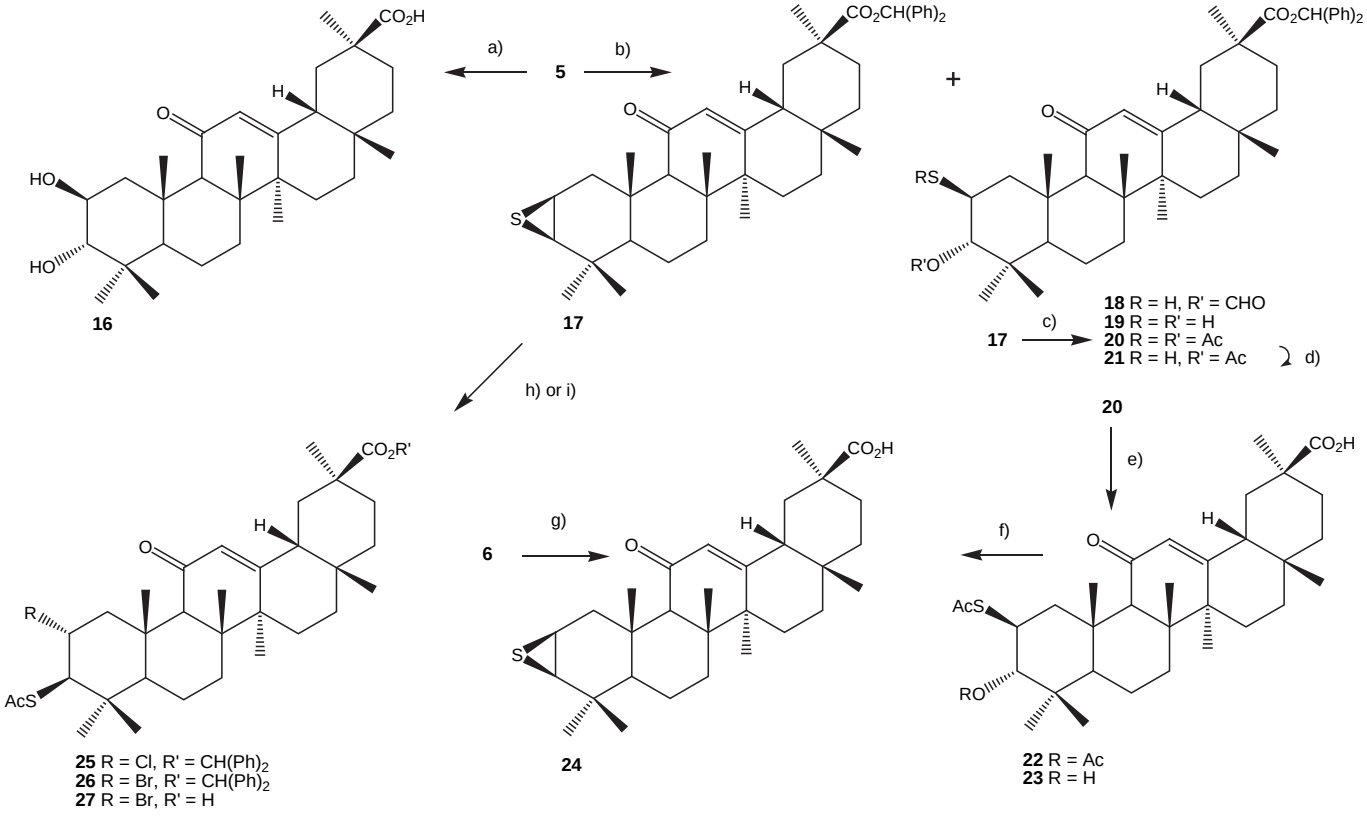


Figure 2. Crystal structure of iodohydrin **7** as $7\cdot H_2O$. H-atoms omitted for clarity except for the hydrogen bonded water molecule on upper left. C2–I1=2.166(2) Å, C3–O1=1.454 (2) Å, I1–C2–C3–O1 46.1(2)°.

For the synthesis of the corresponding C-29 acid derivative **12**, the 2-iodo derivative **8** was subjected to the elimination step to provide the 3-*O*-acetyl derivative **11** (72% yield), which was subsequently deacetylated under alkaline conditions to give the acid derivative **12** in 87% yield. Hydrogenation of the allylic 3-*O*-acetyl derivative **9** in the presence of Pd–C afforded the 3α-acetyl derivative **13** of 18β-glycyrrhetinic acid. The low-field shifted signal of H-3 of **13** showed small homonuclear coupling constants to the neighboring H-2 protons being diagnostic for the equatorial position of H-3 thereby verifying the configurational assignment for compounds **9**–**12**. The allylic system present in ring A of this series provides also a versatile entry into the corresponding 1α-series via an allylic rearrangement reaction. Thus, deprotection of the diphenylmethyl ester group of compound **9** using trifluoroacetic acid/anisole followed by transesterification with methanolic NaOMe afforded compound **14** in 82% yield. The α-configuration of C-1 was substantiated following hydrogenation of the double bond in ring A, which furnished the 1α-hydroxy isomer of glycyrrhetinic acid **15** in 85% yield. The ^{1}H NMR signal of H-1 of **15** appeared as a broadened triplet with coupling constants of 2.8 Hz, again proving its equatorial arrangement. The migration of the hydroxy group to position 1 was further inferred from the observed HMBC-correlations of the low-field shifted C-1 ^{13}C NMR signal to the signals of the methyl group at position 25 and H-9, respectively. The introduction of the 1α-hydroxy group also led to a substantial low-field shift of H-9 seen in the ^{1}H NMR spectrum as well as a β-shift of the ^{13}C NMR signal of C-9 in compound **14** (δ 53.09) and **15** (δ 53.32, Table 1), respectively. The 1α-hydroxylation of 4,4-dimethyl-2-ene

triterpene derivatives has previously been accomplished via SeO_2 oxidation of the corresponding 2-ene derivatives.[23]

Acid-catalyzed ring-opening of the 2,3-oxide derivative **5** with concomitant removal of the diphenylmethyl ester group gave the known diol derivative **16** in 70% yield (Scheme 2).[24,25] The 2,3-epoxide **5** was used as starting material for the introduction of thiol groups at positions 1, 2 and 3 of ring A, respectively (Scheme 2). Reaction of **5** with *N*,*N*-dimethylthioformamide in toluene at 45 °C in the presence of TFA produced the crystalline 2,3-epithio derivative **17** in 80% yield.[26] The crystal and molecular structure of the epithio compound **17** could be solved and revealed the inverted configuration at C-2 and C-3 in contrast to the epoxide **5** (Fig. 3). The use of higher temperatures (80 °C) gave an increased amount of the ring-opened derivatives **18** and **19** (30% and 35%, respectively) in addition to the thiirane **17** (20%). Acetolysis of the thiirane derivative **17** using a 1:1 mixture of acetic acid-acetic anhydride produced the diacetate **20** in 70% yield, whereas treatment of **17** with acetic anhydride in pyridine afforded compound **20** in 92% yield. The stereochemical features of the resulting 2β-*S*-acetyl-3α-*O*-acetyl product were unambiguously proven by the crystal structure of **20** (Fig. 4). Similar to the crystal structure of the 2-iodo-3-*O*-acetyl derivative **7**, ring A was present in a twist boat



Scheme 2. Synthesis of 2,3-epithio derivatives **17** and **24** and 2- and 3-thio-substituted derivatives. Reagents and conditions: (a) TFA, toluene, 40 °C, 2 h, then 0.1 M NaOMe, MeOH, rt, 2 h, then 10% Pd–C, MeOH, rt 15 h, 70% for **16**; (b) *A*: TFA, DMTF, toluene, 45 °C, 4 h, 80% for **17**; *B*: TFA, DMTF, toluene, 80 °C, 2 h, 20% for **17**, 35% for **18**, 30% for **19**; (c) *p*TsOH, 1:1 Ac_2O/AcOH, rt, 2 h, 70%, or Ac_2O/pyr, rt, 15 h, 92% for **20**; (d) $H_2NNH_2 \cdot H_2O$, THF–cyclohexene–EtOH, rt, 0.5 h, 94% for **21**; (e) TFA, anisole, CH_2Cl_2, 8 °C, 15 h, 93% for **22**; (f) 0.2 M NaOH, rt, 12 h, 80% for **24**, (g) TFA, DMTF, toluene, 40 °C, 15 h, 40% for **24**; (h) AcCl, $CoCl_2$, CH_2Cl_2, 0 °C→rt, 83% for **25**; (i) AcBr, $CoCl_2$, CH_2Cl_2, 0 °C, 0.5 h, 33% for **26**, 43% for **27**.

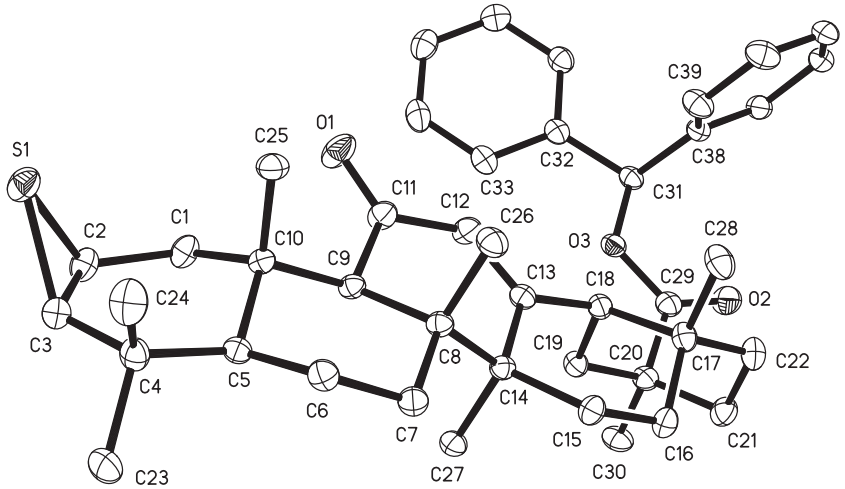


Figure 3. Crystal structure of epithioderivative **17**. H-atoms omitted for clarity. C2–*S*1=1.832(2) Å, C3–S1=1.838(2) Å, C2–C3=1.482(2) Å.

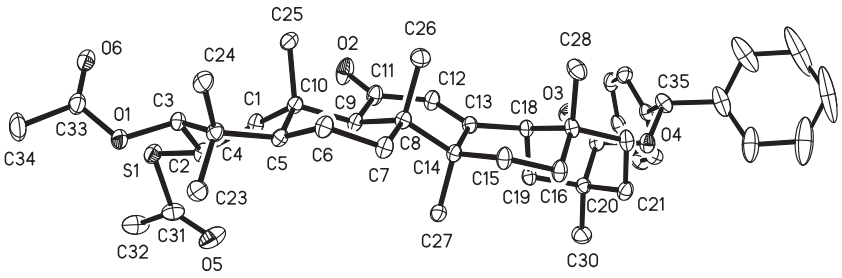
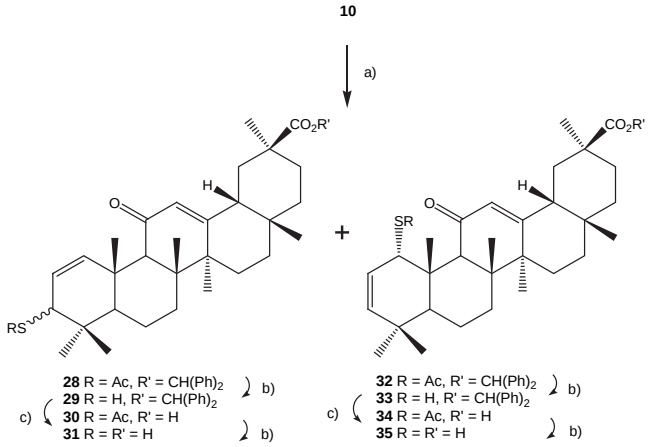


Figure 4. Crystal structure of **20**. *H*-atoms omitted for clarity. C2–S1=1.820(1) Å, S1–C31=1.767(1) Å, C31–S1–C2=101.1(1)°.

conformation, thereby leading to a deceptive, large homonuclear coupling constant for H-2 and H-3 ($J_{2,3}$ 11.7 Hz). Selective deacetylation of the 2-*S*-acetyl group of **20** was effected by reaction with hydrazine hydrate to give the 2β-thiol derivative **21** in 94% yield.

Deprotection of the diphenylmethyl ester group using TFA–anisole furnished the acid derivative **22** in 93% yield. Attempted de-*O*-acetylation of **22** under alkaline conditions, however, was unsuccessful and resulted in reformation of the thiirane ring giving **24** in 80% yield. The epithio compound **24** was also prepared—although in lower yield (40%)—by direct conversion of the 2,3-epoxide derivative **6** by treatment with DMTF/TFA.

Finally, the epithio compound **17** also served as the educt for producing a series of 3-thio substituted derivatives with inverted configuration at C-2. Reaction of **17** with $CoCl_2$/acetyl chloride or $CoCl_2$/acetyl bromide gave the corresponding 2α-halo-3β-thioacetyl derivatives **25** and **26** in 43% and 33% yield, respectively.[27] In the former reaction, a small portion of the elimination product **3** was isolated (10%), whereas in the latter reaction the major product isolated had resulted from cleavage of the diphenylmethyl ester group under the acidic conditions giving the 2-bromo acid **27**. Again, the configurational assignments were corroborated from the solved crystal structure of compound **27** (Fig. 5), which revealed the presence of the chair conformation of ring A in accordance with the observed ^{1}H NMR spectral characteristics of *trans*-oriented vicinal protons ($J_{2,3}$=12.0 Hz). The allylic alcohol **10** was used as educt for



Scheme 3. Synthesis of 1- and 3-thio-substituted compounds **31** and **35**. Reagents and conditions: (a) CH_3COSH, DMF–dineopentylacetal, CH_2Cl_2, 40 °C, 40 min, 30% for **28**; 40.6% for **32**; (b) $H_2NNH_2 \cdot H_2O$, cyclohexene/THF/EtOH, rt, 0.5 h, 92.5% for **29**; 70% for **31**; 95% for **33**; 90.5% for **35**; (c) TFA, anisole, CH_2Cl_2, 8 °C, 15 h, 86% for **30**; 85% for **34**.

the presence of the 3β substitution product as the major isomer (ratio ~7:3). The configuration at C-3 of the minor isomer was inferred from the value of the homonuclear coupling constant $J_{2,3}$, which was in a similar range (5.4 Hz) as observed for the 3α-derivatives **9**–**12**

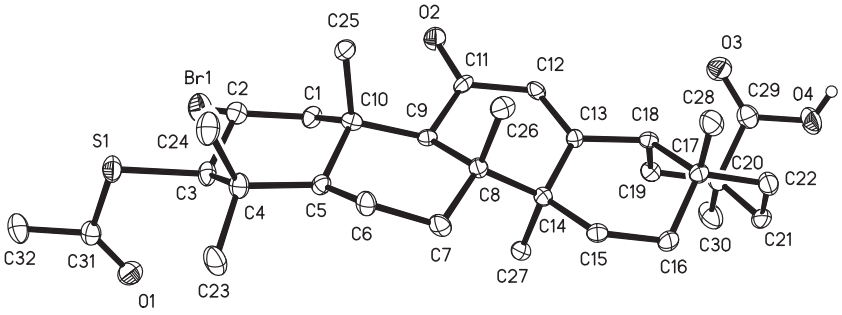


Figure 5. Crystal structure of **27**. C2–Br1=1.969(4) Å, C3–S1=1.829(5) Å, S1–C31=1.758(6), Br1–C2–C3–S1=–57.4(4)°.

the installment of thiol groups at positions 1 and 3, respectively (Scheme 3). Reaction of **10** with DMF–dineopentylacetal and thioacetic acid[28] in dichloromethane at elevated temperature afforded the 3-epimeric *S*-acetyl derivative **28** and the 1α-*S*-acetyl derivative **32** in yields of 35% and 50%, respectively, after chromatographic separation.

The structural assignments of the regioisomers **28** and **32** was based upon the identification of the thio-substituted carbons at δ 54.00 and δ 50.91 (Table 2), respectively, followed by their HMBC-correlation to either the methyl groups at position 23 and 24 or the C-25 methyl group, respectively. Formation of the 1α-thioisomer is presumed to occur via a similar pathway as observed for the 1α-allylic alcohol **14**. The epimeric mixture of the 3-thio compounds, however, could not be resolved by chromatography. The ^{1}H NMR data indicated (4.8–6.2 Hz), whereas the corresponding values were smaller for the β-isomeric forms (~2 Hz), being indicative of a pseudoaxial orientation of H-3 in a half-chair conformation in the latter case (Fig. 6).

Treatment of **32** with hydrazine hydrate afforded the 1α-thiol compound **33** in 95% yield. Similarly, the 3-*S*-acetyl derivative **28** was converted into the 3α,3β-thiol derivative **29** in 90% yield. Finally, the diphenylmethyl ester groups were cleaved without affecting the *S*-acetyl groups using TFA–anisole to give the free acid derivatives **30** and **34** in 90% and 85% yield, respectively. Eventually, the fully deprotected compounds **31** and **35** were generated from **30** and **34** by hydrazinolysis in yields of 70% and 90%, respectively. The ^{13}C NMR data (Tables 1 and 2) closely match previous assignments made for glycyrrhizin.[29] Major chemical shift deviations are observed for ring A carbons and the neighboring Me-groups at

Table 2
^{13}C NMR data (ppm) of compounds **17**–**35**[a]

Carbon atom	**17**	**18**	**19**	**20**	**21**	**22**	**24**	**25**	**26**
1	39.20	51.81	52.99	47.37	52.14	46.88	39.00	51.53	52.67
2	38.08	36.40	41.09[c]	40.54	36.99	40.15	38.03	59.43	53.53
3	48.41	80.01	77.57	76.11	79.21	76.15	48.09	61.89	62.03
4	32.45	38.31[c]	38.32	38.28	38.37	37.90[c]	32.29	41.11	41.11
5	52.67	50.65	51.77	50.23	50.65	49.85	52.51	55.65	55.59
6	19.00	19.22	18.66	19.04	19.23	18.59	18.80	18.70	18.76
7	32.01	31.72[d]	31.72[d]	31.73[c]	31.73[c]	31.47[d]	31.84[c]	32.50	32.48
8	45.23	45.22	45.35	45.25	45.23	45.11	45.29	45.27	45.28
9	62.94	62.83	63.01	62.77	62.86	62.50	62.85	61.10	61.06
10	36.96	37.51	37.73[e]	37.24	37.53	36.94	36.85	38.65	39.54
11	199.34	198.46	198.85	198.66	198.53	199.62	200.40	199.12	199.10
12	128.48	128.27	128.27	128.28	128.31	127.49	127.95	128.29	128.30
13	169.06	169.76	169.84	169.69	169.66	171.09	170.84	169.23	169.25
14	43.19	43.36[e]	43.35[f]	43.39	43.35	43.23[e]	43.21[d]	43.26[c]	43.27
15	26.29[c]	26.35[f]	26.41[g]	26.44[d]	26.45[d]	26.12[f]	26.14	26.38[d]	26.38[c]
16	26.26[c]	26.44[f]	26.34[g]	26.37[d]	26.37[d]	25.99[f]	26.14	26.33[d]	26.33[c]
17	31.62	31.62[d]	31.67[d]	31.67[c]	31.65[c]	31.26[d]	31.58[c]	31.74	31.75
18	47.88	48.03	48.06	48.05	48.03	48.10	48.44	48.10	48.10
19	41.14	41.28	41.24[c]	41.26	41.28	40.95	41.01	40.44	40.89
20	43.91	43.99[e]	43.99[f]	44.00	44.00	43.37[e]	43.47[d]	43.99[c]	44.00
21	31.09	31.18[d]	31.16	31.19	31.19	30.65	30.78	31.16	31.16
22	37.42	37.45[c]	37.62[e]	37.52	37.53	37.39[c]	37.49	37.45	37.45
23	34.40	24.18	23.28[h]	24.31	24.08	23.84	34.16	29.77	30.02
24	26.38	22.96	22.84	22.89	23.07	23.02	26.14	19.38	19.22
25	17.61	21.87	22.18	21.40	21.89	20.91	17.39	16.81	16.59
26	18.53	18.14	18.15	18.17	18.16	17.75	18.35	18.61	18.59
27	23.28	23.28	23.38[h]	23.48	23.40	22.40	23.08	23.30	23.29
28	28.26[d]	28.35[g]	28.35[i]	28.36[e]	28.35[e]	28.17[g]	28.28[e]	28.29[e]	28.29[d]
29	175.10	175.16	175.18	175.19	175.18	178.93	179.07	175.15	175.16
30	28.17[d]	28.23[g]	28.22[i]	28.24[e]	28.24[e]	27.94[g]	28.14[e]	28.22[e]	28.23[d]

Carbon atom	**27**	**28** (3β)	**28** (3α)	**30**[b]	**31**[b]	**32**	**33**	**34**	**35**
1	53.37	139.88	139.71	139.60	138.56	50.91	46.89	50.75	46.85
2	54.77	123.73	121.57	123.70	126.55	124.09	125.64	124.02	125.66
3	62.66	54.00	52.33	53.88	50.45	136.74	136.21	136.65	136.24
4	41.52	35.88	35.88	35.71	36.58	34.55	34.38	34.49	34.39
5	55.97	54.39	50.66	54.28	54.78	48.79	44.19	48.76	44.04
6	19.51	17.48	16.68	17.28	17.86	18.93	18.68	18.89	18.69
7	31.72	33.04	33.04	32.86	33.14	31.22[c]	31.15	31.19	31.17
8	45.83	45.53	45.57	45.56	45.73	45.00	44.71	45.12	44.85
9	61.53	58.40	58.46	58.31	58.58	54.84	55.36	54.86	55.38
10	40.43	38.09	38.26	37.97	38.31	39.27	39.86	39.21	39.90
11	198.32	199.74	199.74	200.65	200.11	198.63	200.39	199.28	200.96
12	128.86	128.55	128.55	127.66	128.25	128.55	128.44	128.37	128.37
13	169.37	169.25	169.34	171.01	169.272	169.04	170.10	169.73	170.87
14	43.99[c]	43.33	43.27	43.51[c]	43.78	43.85	43.99	43.77[c]	43.85
15	27.22[d]	26.33[c]	26.42[c]	26.22[d]	26.48[c]	26.45	26.48[c]	26.49[d]	26.54[c]
16	27.10[d]	26.29[c]	26.42[c]	26.13[d]	26.43[c]	26.45	26.40[c]	26.36[d]	26.42[c]
17	32.46	30.78	30.78	31.65	31.87	31.13[d]	31.66	31.78	31.82
18	48.95	48.10	48.10	48.30	48.30	47.75	47.88	48.16	48.16
19	41.97	40.98	40.98	40.86	40.80	41.26	41.32	40.97	41.10
20	44.09[c]	43.98	43.98	43.32[c]	43.38	44.00	43.99	43.84[c]	44.04
21	33.00	31.72	31.72	30.80	30.89	31.65[c]	31.15	30.78	30.88
22	38.68	37.44	37.44	37.49	37.69	37.57	37.54	37.65	37.76
23	30.44	28.22[d]	24.85	28.18[e]	28.71[d]	31.32[d]	31.53	31.32	31.55
24	19.29	20.72	20.72	20.50	19.48[e]	23.35	23.07	23.32	23.09
25	16.59	19.23	19.40	19.01	19.28[e]	16.85	17.05	16.84	17.06
26	18.85	19.23	18.76	19.15	19.42	18.34	18.18	18.26	18.20
27	23.59	23.48	23.40	23.25	23.53	23.73	23.86	23.68	23.89
28	28.88[e]	28.44[d]	28.26[d]	28.27[e]	28.52[d]	28.35[e]	28.38[d]	28.53[e]	28.64[d]
29	177.62	175.21	175.21	179.13	181.71	175.22	175.22	182.10	182.22
30	28.42[e]	28.26[d]	27.90[d]	28.18[e]	28.44[d]	28.26[e]	28.19[d]	28.42[e]	28.45[d]

[a] Assignments were based on cosy, hsqc and hmbc measurements.
[b] Data are listed for the major isomer.
[c–i] Assignments within a column may be reversed.

positions 23, 24, and 25, respectively. Biological data obtained with the compounds will be reported elsewhere.

3. Conclusion

Introduction of thiol groups into ring A of glycyrrhetinic acid has been achieved in gram-scale utilizing the ester protected as well the acidic 2,3-oxido derivative as educts. Conversion into the corresponding 2,3-epithio derivatives with inverted configuration was followed by ring-opening to provide either 2β-thio- as well as 3β-thio- equipped derivatives. Finally, an allylic 3α-hydroxy intermediate—again conveniently accessible from the 2,3-oxido intermediate—may be transformed into 1α-configured as well as 3α,3β-thio analogs.

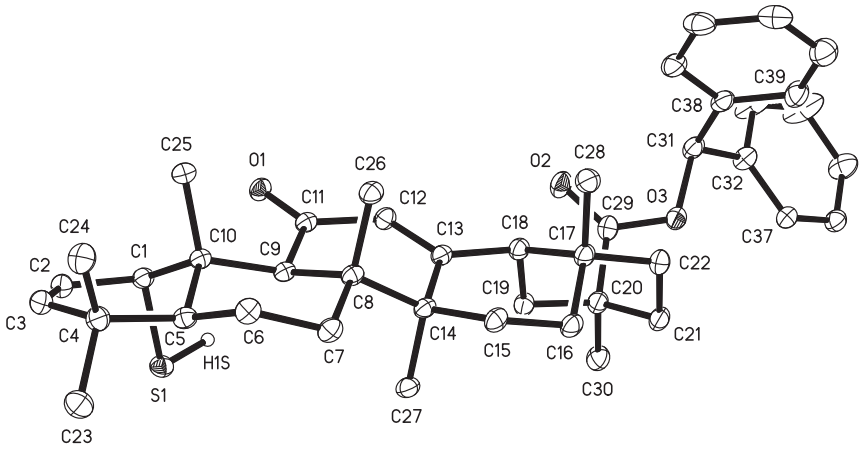


Figure 6. Crystal structure of **33**. C1–S1=1.853(1) Å, C2–C3=1.330(2) Å.

4. Experimental section

4.1. General methods

Glycyrrhetinic acid ester derivative **1** was prepared according to published procedures.[20] Concentration of solutions was performed at reduced pressure at temperatures<40 °C. Dichloromethane was dried by stirring with CaH_2 (5 g per L) for 16 h, then distilled and stored under Ar over molecular sieves 0.4 nm. Column chromatography was performed on silica gel 60 (230–400 mesh, Merck). Analytical TLC was performed using silica gel 60 F_{254} HPTLC plates with 2.5 cm concentration zone (Merck). Spots were detected by treatment with anisaldehyde–H_2SO_4. Ion exchange treatment was performed on Dowex 50 WX8 resin, H^+ form, 50–100 mesh. Melting points were determined on a Kofler hot stage microscope and are uncorrected. Optical rotations were measured with a Perkin–Elmer 243 B polarimeter. NMR spectra were recorded at 297 K in CD_3OD and $CDCl_3$ with a Bruker DPX 300 or Avance 400 spectrometer (^1H at 300.13 MHz, ^{13}C at 75.47 MHz or ^1H at 400.13 MHz, ^{13}C at 100.62 MHz, respectively) using standard Bruker NMR software. ^1H NMR and ^{13}C NMR spectra were referenced to internal tetramethylsilane (δ=0). ^{13}C NMR signals of the glycyrrhetinic acid scaffold are compiled in Tables 1 and 2. For MS analyses, samples were dissolved in MeCN (~1 nmol/μL). An aliquot of the sample was diluted in 50% aq MeCN containing 0.1% formic acid to give a final concentration of ~10 pmol/μL. This solution was subjected to offline ESI Q-TOF MS on a Waters Micromass Q-TOF Ultima Global. Capillary voltage was adjusted to obtain approx. 200 counts/s. The MS had been previously tuned with [Glu1]-fibrinopeptide B to give the highest sensitivity and a resolution of ca. 10.000 (FWHM). Mass tuning of the TOF analyzer was done in the tandem MS mode using again [Glu1]-fibrinopeptide B.

*4.1.1. Diphenylmethyl 3β-p-toluonesulfonyloxy-11-oxo-18β-olean-12-en-29-oate (**2**).* A cooled solution of *p*-toluenesulfonyl chloride (31.4 g, 0.165 mol) in dry pyridine (65 mL) was added dropwise at 0 °C to a solution of **1** (30 g, 47.1 mmol) in dry pyridine (150 mL). The reaction mixture was stirred at rt overnight. The solution was poured onto ice-water, stirred for 30 min and diluted with dichloromethane (200 mL). The organic layer was washed with 0.1 M HCl, water, and satd aq $NaHCO_3$ and brine. The organic phase was dried (Na_2SO_4) and concentrated. Purification of the residue by MPLC (5:1 toluene/EtOAc) afforded **2** as a colorless solid. Yield: 37 g (99%). Crystallization from 10:1 EtOH/EtOAc gave colorless crystals. Mp 173 °C. $[\alpha]_D^{20}$ +102 (*c* 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.79 (d, 2H, arom. H), 7.40–7.25 (m, 12H, arom. H), 6.93 (s, 1H, C*H*$(Ph)_2$), 5.49 (s, 1H, 12-H), 4.28 (dd, $J_{3,2a}$ 4.7, $J_{3,2b}$ 12.0 Hz, 1H, 3-H), 2.76 (dt, $J_{1a,2a}=J_{1a,2b}$ 3.5, $J_{1a,1b}$ 12.2 Hz, 1H, 1a-H), 2.43 (s, 3H, CH_3), 2.27 (s, 1H, 9-H), 2.06–0.94 (m, 17H, 18-H, 15a-H, 16a-H, 19a-H, 21a-H, 6a-H, 7a-H, 19b-H, 6b-H, 7b-H, 21b-H, 22a-H, 22b-H, 5-H, 16b-H, 1b-H, 15b-H), 1.34 (s, 3H, 27-CH_3), 1.17 (s, 3H), 1.10 (s, 3H), 1.06 (s, 3H), 0.89 (s, 3H), and 0.83 (s, 3H, 25-CH_3, 30-C*H*$_3$, 26-C*H*$_3$, 23-C*H*$_3$, 24-C*H*$_3$ and 28-C*H*$_3$). ESI-TOFMS: *m*/*z*=791.4345 $[M+H]^+$; calcd for $C_{50}H_{62}O_6S$: 791.4926.

*4.1.2. Diphenylmethyl 11-oxo-18β-olean-2,12-dien-29-oate (**3**) and 11-oxo-18β-olean-2,12-dien-29-oic acid (**4**).* Tetra-*n*-butylammonium iodide (910 mg, 2.47 mmol) was added to a solution of **2** (4.0 g, 5.06 mmol) and sodium iodide (3.26 g, 21.74 mmol) in DMF (40 mL) and the reaction mixture was stirred overnight at 100 °C. After cooling to rt, the reaction mixture was diluted with dichloromethane (100 mL) and washed with 5% aq $Na_2S_2O_3$, $NaHCO_3$, and brine. The aqueous layer was washed once more with EtOAc, the organic phases were combined, dried (Na_2SO_4) and concentrated. The residue was coevaporated three times with toluene and purified by flash chromatography (6:1 *n*-hexane/EtOAc) to afford **3** (2.85 g, 91%) as a colorless solid. Mp 235 °C. $[\alpha]_D^{20}$ +19 (*c* 0.7, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ=7.41–7.26 (m, 10H, arom. H), 6.93 (s, 1H, C*H*$(Ph)_2$), 5.55 (s, 1H, 12-H), 5.44 (ddd, $J_{3,2}$ 10.0, $J_{2,1a}$ 6.0, $J_{2,1b}$ 1.6 Hz, 1H, 2-H), 2.40 (s, 1H, 9-H), 2.07–1.98 (m, 4H, 21a-H, 16a-H, 19a-H, 18-H), 1.80 (dt, $J_{15a,15b}$ 13.6, $J_{15a,16}$ 4.4 Hz, 1H, 15a-H), 1.73–1.63 (m, 2H, 7a-H, 19b-H), 1.63–1.50 (m, 2H, 6a-H, 6b-H), 1.48–1.18 (m, 5H, 7b-H, 21b-H, 22a-H, 22b-H, 15b-H), 1.11 (dd, 1H, 5-H), 0.98 (m, 1H, 16b-H), 1.36 (s, 3H, 27-CH_3), 1.19 (s, 3H, 30-C*H*$_3$), 1.17 (s, 3H), 1.12 (s, 3H), 0.97 (s, 3H), and 0.91 (s, 3H, 25-CH_3, 26-C*H*$_3$, 23-C*H*$_3$, 24-C*H*$_3$) and 0.68 (s, 3H, 28-C*H*$_3$). ESI-TOFMS: *m*/*z*=619.3989 $[M+H]^+$; calcd for $C_{43}H_{54}O_3$: 619.4151. Further elution of the column with (1:1 *n*-hexane/EtOAc) afforded **4** (110 mg, 4.8%) as a colorless solid, which was crystallized from dichloromethane/*n*-hexane. Mp 253–258 °C. $[\alpha]_D^{20}$ +210 (*c* 0.6, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ 5.75 (s, 1H, 12-H), 5.43 (ddd, J_{AB} 10.8, J_{BX} 6.0, J_{AX} 1.5 Hz, 1H, 2-H), 5.36 (dd, *J* 2.2, *J* 10.8 Hz, 1H, 3-H), 3.04 (ddd, $J_{1a,1b}$ 17.0 Hz, 1H, 1a-H), 2.40 (s, 1H, 9-H), 2.20 (dd, *J* 13.4, *J* 4.4 Hz, 1H, 18-H), 2.07–1.90 (m, 3H, 16a-H, 21a-H, 19a-H), 1.85 (dt, $J_{15a,15b}$ 12.5 Hz, 1H, 15a-H), 1.75–1.20 (m, 10H, 7a-H, 1b-H, 19b-H, 6a-H, 6b-H, 7b-H, 22a-H, 22b-H, 21b-H, 15b-H), 1.11 (dd, 1H, 5-H), 1.03 (dddd, 1H, 16b-H), 1.37 (s, 3H, 27-CH_3), 1.25 (s, 3H, 30-CH_3), 1.16 (2 s, 6H, 25-C*H*$_3$, 26-C*H*$_3$), 0.96 (s, 3H, 23-C*H*$_3$), 0.91 (s, 3H, 24-C*H*$_3$), and 0.86 (s, 3H, 28-C*H*$_3$). ESI-TOFMS: *m*/*z*=453.3367 $[M+H]^+$; calcd for $C_{30}H_{44}O_3$: 453.336.

*4.1.3. Diphenylmethyl 2α,3α-oxido-11-oxo-18β-olean-12-en-29-oate (**5**).* $NaHCO_3$ (8.8 g, 105 mmol) and *m*-chloroperbenzoic acid (22 g, 89.25 mmol) was added portionwise to a stirred solution of **3** (36.2 g, 58.49 mmol) in dry dichloromethane (0.5 L) at 4 °C under

Ar. The suspension was stirred at 8 °C overnight, diluted with Et_2O (300 mL) and filtered over Celite. The filtrate was washed with water and brine. The organic layer was dried (Na_2SO_4) and concentrated. The crude product was purified by flash chromatography (1:5→1:3 Et_2O/*n*-hexane) to afford **5** (27 g, 73%). Crystallization was achieved by dissolving the material in dry EtOH at 50 °C and gradual cooling to +4 °C. Mp 178 °C. $[\alpha]_D^{20}$ +126 (*c* 0.9, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.41–7.26 (m, 10H, arom. H), 6.93 (s, 1H, C*H*$(Ph)_2$), 5.54 (s, 1H, 12-H), 3.22 (ddd, $J_{2,3}$ 3.7, $J_{2,1a}$ 6.4 Hz, 1H, 2-H), 3.16 (dd, $J_{1a,1b}$ 14.9 Hz, 1H, 1a-H), 2.82 (d, 1H, 3-H), 2.30 (s, 1H, 9-H), 2.08–1.96 (m, 4H, 16a-H, 21a-H, 18-H, 19a-H), 1.76 (dt, $J_{15a,15b}$ 13.6 Hz, 1H, 15a-H), 1.73–1.20 (m, 10H, 19b-H, 7a-H, 6a-H, 6b-H, 7b-H, 1b-H, 22a-H, 22b-H, 21b-H, 15b-H), 1.11–0.90 (m, 2H, 16b-H, 5-H), 1.315 (s, 3H, 27-CH_3), 1.17 (s, 3H, 30-CH_3), 1.15 (s, 3H, 25-C*H*$_3$), 1.11 (s, 3H, 23-C*H*$_3$), 1.06 (s, 3H, 26-C*H*$_3$), 1.04 (s, 3H, 24-C*H*$_3$), and 0.66 (s, 3H, 28-C*H*$_3$). ^{13}C NMR ($CDCl_3$, 75.47 MHz): δ 140.03, 139.45, 128.53, 128.02, 127.74, 127.15, 126.85 (arom. C), 76.50 (*C*HPh_2). ESI-TOFMS: *m*/*z*=635.3943 $[M+H]^+$; calcd for $C_{43}H_{54}O_4$: 635.4000.

*4.1.4. 2α,3α-Oxido-11-oxo-18β-olean-12-en-29-oic acid (**6**).* $NaHCO_3$ (1.5 g, 18.67 mmol) and *m*-chloroperbenzoic acid (3.72 g, 0.268 mmol) were added portionwise to a stirred solution of **4** (6.5 g, 14.36 mmol) in dry dichloromethane (100 mL) at 4 °C under Ar. The suspension was stirred at 8 °C overnight, diluted with EtOAc (300 mL) and filtered over Celite. The filtrate was washed with water and brine. The organic layer was dried (Na_2SO_4) and concentrated. The crude product was purified by flash chromatography (50:1→20:1 CH_2Cl_2/EtOH) and was finally purified by crystallization from DMSO. Crystals were washed with *n*-hexane and dried to give 3.6 g (53.5%) of **6** as crystals. Mp 260 °C. $[\alpha]_D^{20}$ +144 (*c* 0.9, 5:1 $CHCl_3$/MeOH). ^1H NMR ($CD_3OD/CDCl_3$, 400 MHz): δ 5.73 (s, 1H, 12-H), 3.23 (dd, $J_{2,1a}$ 6.0, $J_{2,3}$ 3.6 Hz, 1H, 2-H), 3.16 (ddd, $J_{1a,1b}$ 14.8 Hz, 1H, 1a-H), 2.83 (d, 1H, 3-H), 2.33 (s, 1H, 9-H), 2.20 (dd, *J* 13.2, *J* 3.0 Hz, 1H, 18-H), 2.07–1.90 (m, 3H, 16a-H, 21a-H, 19a-H), 1.81 (dt, $J_{15a,15b}$ 12.5, $J_{15a,16a}$ 3.6 Hz, 1H, 15a-H), 1.69–1.01 (m, 11H, 7a-H, 1b-H, 19b-H, 6a-H, 6b H, 7b-H, 22a-H, 22b-H, 21b-H, 16b-H, 15b-H), 0.96 (dd, 1H, 5-H), 1.33 (s, 3H, 27-CH_3), 1.23 (s,3H, 30-CH_3), 1.16 (s, 3H, 25-C*H*$_3$), 1.11 (s, 3H, 23-C*H*$_3$), 1.10 (s, 3H, 26-C*H*$_3$), 1.04 (s, 3H, 24-C*H*$_3$), and 0.84 (s, 3H, 28-C*H*$_3$). ESI-TOFMS: *m*/*z*=469.3318 $[M+H]^+$; calcd for $C_{30}H_{44}O_4$: 469.308.

*4.1.5. Diphenylmethyl 3α-acetyloxy-2β-iodo-11-oxo-18β-olean-12-en-29-oate (**7**).* A solution of **5** (10.2 g, 16.19 mmol) in dry CH_2Cl_2 (30 mL) was added at −25 °C to a solution of triphenylphosphine (6.58 g, 25.1 mmol) and I_2 (6.16 g, 24.3 mmol) in dry CH_2Cl_2 (100 mL) under Ar and the mixture was stirred at −30 °C for 30 min. The reaction mixture was diluted with dichloromethane (200 mL) and washed with aq 5% $Na_2S_2O_3$, satd aq $NaHCO_3$, and brine. The organic phase was dried (Na_2SO_4) and concentrated. The residue and a catalytic amount of 4-*N*,*N*-dimethylaminopyridine were dissolved in pyridine (40 mL) at rt. The solution was cooled to 0 °C and acetic anhydride (20 mL) was added dropwise. The reaction mixture was stirred overnight at rt. MeOH (5 mL) was added and the solution was coevaporated four times with the addition of toluene and concentrated in vacuo. The residue was submitted to flash column chromatography (10:1→8:1 *n*-hexane/EtOAc) to give **7** as colorless crystals. Mp 168 °C (*n*-hexane/EtOAc). Yield: 11.0 g, (85%). $[\alpha]_D^{20}$ +129 (*c* 0.8, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.42–7.27 (m, 10H, arom. H), 6.935 (s, 1H, C*H*$(Ph)_2$), 5.55 (s, 1H, 12-H), 5.38 (d, $J_{2,3}$ 12.6 Hz, 1H, 3-H), 4.39 (ddd, $J_{1a,2}$ 11.5, $J_{1b,2}$ 7.5 Hz, 1H, 2-H), 3.135 (dd, $J_{1a,1b}$ 15.2 Hz, 1H, H-1a), 2.48 (s, 1H, 9-H), 2.29 (dd, 1H, 1b-H), 2.14 (s, 3H, CH_3CO), 2.07–1.96 (m, 4H, 16a-H, 21a-H, 18-H, 19a-H), 1.78 (dt, $J_{15a,15b}$ 13.4 Hz, 1H, 15a-H), 1.69–1.23 (m, 9H, 19b-H, 7a-H, 6a-H, 6b-H, 7b-H, 22a-H, 22b-H, 21b-H, 15b-H), 1.15–0.98 (m, 2H, 16b-H, 5-H), 1.375 (s, 3H, 25-CH_3), 1.35 (s, 3H, 27-CH_3), 1.18 (s, 3H, 30-CH_3), 1.05 (s, 3H, 26-CH_3), 0.96 and 0.93 (2 s, 6H, 23-C*H*$_3$, 24-C*H*$_3$), and 0.66 (s, 3H, 28-C*H*$_3$). ^{13}C NMR ($CDCl_3$, 75.47 MHz): δ 140.09, 139.98, 128.24, 128.18, 127.85, 127.28, 126.93 (arom. C), 76.65 (*C*HPh_2). ESI-TOFMS: *m*/*z*=805.3813 $[M+H]^+$; calcd for $C_{45}H_{57}IO_5$: 805.3320.

*4.1.6. 3β-Acetyloxy-2α-iodo-11-oxo-18β-olean-12-en-29-oic acid (**8**).* Anisole (0.4 mL) was added to a solution of **7** (200 mg, 0.249 mmol) in dry dichloromethane (5 mL) followed by addition of trifluoroacetic acid (0.4 mL) at +8 °C. The solution was stirred overnight at +8 °C. The solution was diluted with toluene (50 mL) and evaporated. The residue was purified by silica gel chromatography using first 2:1 *n*-hexane/EtOAc to remove anisole followed by 50:1 CH_2Cl_2/EtOH to afford **8** as colorless solid. Yield: 115 mg, (72.5%). $[\alpha]_D^{20}$ +136 (*c* 0.7, 5:1 $CHCl_3$/MeOH). ^1H NMR ($CDCl_3$, 400 MHz): δ 5.64 (s, 1H, 12-H), 5.35 (d, $J_{2,3}$ 12.8 Hz, 1H, 3-H), 4.57 (ddd, $J_{1a,2}$ 11.2, $J_{1b,2}$ 8.0 Hz, 1H, 2-H), 3.00 (dd, $J_{1a,1b}$ 14.8 Hz, 1H, 1a-H), 2.70 (s, 1H, 9-H), 2.34 (dd, 1H, 1b-H), 2.225 (br dd, $J_{18,19b}$ 13.2, $J_{18,19a}$ 4.5 Hz, 1H, 18-H), 2.15 (ddd, $J_{16a,16b}$=$J_{16a,15b}$ 13.2, $J_{16a,15a}$ 4.4 Hz, 1H, 16a-H), 2.11 (s, 3H, CH_3CO), 1.97–1.83 (m, 3H, 21a-H, 19a-H, 15a-H), 1.72 (ddd, 1H, 7a-H), 1.67(t, $J_{19b,19a}$ 13.2 Hz, 1H, 19b-H), 1.56–1.52 (m, 2H, 6a-H, 6b-H), 1.46–1.14 (m, 6H, 7b-H, 22a-H, 22b-H, 21b-H, 15b-H, 5-H), 1.06 (ddd, 1H, 16b-H), 1.43 (s, 3H, 27-CH_3), 1.36 (s, 3H, 25-CH_3), 1.17 (s, 3H, 30-CH_3), 1.11 (s, 3H, 26-CH_3), 1.06 (ddd, 1H, 16b-H), 0.97 and 0.96 (2 s, 6H, 23-CH_3, 24-CH_3), 0.84 (s, 3H, 28-CH_3). ^{13}C NMR ($CDCl_3/CD_3OD$, 75.47 MHz): δ=172.22 (CH_3CO) and 21.36 (CH_3CO). ESI-TOFMS: *m*/*z*=639.2054 $[M+H]+$; calcd for $C_{32}H_{47}IO_5$: 639.2546.

*4.1.7. Diphenylmethyl 3α-acetyloxy-11-oxo-18β-olean-1,12-dien-29-oate (**9**).* DBU (1.0 mL, 7.213 mmol) was added to a solution of **7** (1.0 g, 1.242 mmol) in dry toluene (20 mL) and the solution was stirred at 100 °C overnight. After cooling to rt, the solution was diluted with dichloromethane (100 mL) and washed with aq NH_4Cl, satd aq $NaHCO_3$, and brine. The organic layer was dried (Na_2SO_4) and concentrated. The residue was submitted to chromatography on silica gel (10:1→1:3 *n*-hexane/EtOAc) to afford **9** as a colorless solid (700 mg, 83.2%). $[\alpha]_D^{20}$ +54 (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.32–7.18 (m, 10H, arom. H), 6.86 (s, 1H, C*H*$(Ph)_2$), 6.82 (d, $J_{1,2}$ 10.0 Hz, 1H, 1-H), 5.47 (s, 1H, 12-H), 5.39 (dd, $J_{2,3}$ 4.8 Hz, 1H, 2-H), 4.79 (d, 1H, 3-H), 3.135 (dd, $J_{1a,1b}$ 15.2 Hz, 1H, 1a-H), 2.52 (s, 1H, 9-H), 1.98 (s, 3H, CH_3CO), 2.01–1.89 (m, 4H, 16a-H, 21a-H, 18-H, 19a-H), 1.74 (dt, $J_{15a,15b}$ 13.5 Hz, $J_{15a,16a}$ 4.5 Hz, 1H, 15a-H), 1.65 (ddd, 1H, 7a-H), 1.59 (t, $J_{19a,19b}$=$J_{19b,18}$ 14.4 Hz, 1H, 19b-H), 1.43–1.08 (m, 8H, 6a-H, 6b-H, 21b-H, 5-H, 7b-H, 22a-H, 22b-H, 15b-H), 0.92 (ddd, 1H, 16b-H), 1.32 (s, 3H, 27-CH_3), 1.19 (s, 3H, 25-CH_3), 1.10 (s, 3H, 30-CH_3), 1.04 (s, 3H, 26-CH_3), 0.85 and 0.84 (2 s, 6H, 23-C*H*$_3$, 24-C*H*$_3$), and 0.60 (s, 3H, 28-C*H*$_3$). ^{13}C NMR ($CDCl_3$, 75.47 MHz): δ 170.71 (CH_3CO), 140.06, 140.02, 128.59, 128.10, 127.81, 127.19, 126.93 (arom. C), 76.59 (*C*HPh_2), and 21.25 (*C*H$_3$CO). ESI-TOFMS: *m*/*z*=677.4206 $[M+H]^+$; calcd for $C_{45}H_{56}O_5$: 677.4708.

*4.1.8. Diphenylmethyl 3α-hydroxy-11-oxo-18β-olean-1,12-dien-29-oate (**10**).* A 1.0 M KOH solution (2 mL) was added to a solution of **9** (650 mg, 0.96 mmol) in EtOH (10 mL). The reaction mixture was stirred at rt overnight. The solution was made neutral by addition of Dowex $50H^+$ cation exchange resin and filtered. The filtrate was concentrated and the residue was purified on a column of silica gel (4:1→2:1 *n*-hexane/EtOAc) to give **10** as colorless solid (550 mg, 90.2%). $[\alpha]_D^{20}$ +111 (*c* 0.9, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.34–7.19 (m, 10H, arom. H), 6.86 (s, 1H, C*H*$(Ph)_2$), 6.72 (d, $J_{1,2}$ 10.0 Hz, 1H, 1-H), 5.51 (dd, $J_{2,3}$ 4.8 Hz, 1H, 2-H), 5.47 (s, 1H, 12-H), 3.48 (br d, 1H, 3-H), 2.49 (s, 1H, 9-H), 2.01–1.91 (m, 4H, 16a-H, 21a-H, 18-H, 19a-H), 1.74 (dt, $J_{15a,15b}$ 14.0 Hz, $J_{15a,16a}$ 4.8 Hz, 1H, 15a-H), 1.63 (ddd, 1H, 7a-H), 1.59 (t, $J_{19a,19b}$=$J_{19b,18}$ 14.4 Hz, 1H, 19b-H), 1.43–1.08 (m, 9H, 6a-H, 6b-H, 21b-H, 5-H, 7b-H, 22a-H, 22b-H, 16b-H, 15b-H), 1.29 (s, 3H, 27-CH_3), 1.18 (s, 3H, 25-CH_3), 1.11 (s, 3H, 30-CH_3), 1.03 (s, 3H, 26-CH_3), 0.92 (s, 3H, 23-C*H*$_3$), 0.79 (s, 3H, 24-C*H*$_3$), and 0.60 (s, 3H,

28-C*H*$_3$). ^{13}C NMR ($CDCl_3$, 100.62 MHz): δ 140.03, 139.98, 128.55, 128.38, 128.06, 127.76, 127.17, 126.90 (arom. C), and 76.54 (*C*HPh$_2$). ESI-TOFMS: m/z=635.4459 $[M+H]^+$; calcd for $C_{43}H_{54}O_4$: 635.4100.

*4.1.9. 3α-Acetyloxy-11-oxo-18β-olean-1,12-dien-29-oic acid (**11**).* A solution of **8** (500 mg, 0.294 mmol) in dry MeCN (15 mL) was stirred with DBU (0.375 mL, 2.463 mmol) at 80 °C overnight. The solution was concentrated and the residue was purified by silica gel chromatography (50:1 CH_2Cl_2/EtOH) to furnish **11** as colorless solid. Yield: 287.5 mg (72%). $[\alpha]_D^{20}$ +34 (*c* 0.9, $CHCl_3$). ^{1}H NMR ($CD_3OD/CDCl_3$, 400 MHz): δ 6.90 (d, $J_{1,2}$ 10.2 Hz, 1H, 1-H), 5.75 (s, 1H, 12-H), 5.47 (dd, $J_{2,3}$ 4.8 Hz, 1H, 2-H), 4.87 (d, 1H, 3-H), 2.63 (s, 1H, 9-H), 2.21 (br dd, $J_{18,19b}$ 13.6, $J_{18,19a}$ 4.0 Hz, 1H, 18-H), 2.06 (s, 3H, CH_3CO), 2.12–1.84 (m, 4H, 16a-H, 21a-H, 19a-H, 15a-H), 1.77 (ddd, 1H, 7a-H), 1.64 (t, $J_{19a,19b}$ 13.6 Hz, 1H, 19b-H), 1.67–1.19 (m, 8H, 6a-H, 6b-H, 7b-H, 22a-H, 22b-H, 21b-H, 5-H, 15b-H), 1.05 (ddd, 1H, 16b-H), 1.41 (s, 3H, 27-CH_3), 1.28 (s, 3H, 25-CH_3), 1.23 (s, 3H, 30-CH_3), 1.16 (s, 3H, 26-CH_3), 0.93 and 0.92 (2 s, 6H, 23-C*H*$_3$, 24-C*H*$_3$), and 0.86 (s, 3H, 28-C*H*$_3$). ^{13}C NMR ($CDCl_3$, 75.47 MHz): δ=170.80 (CH_3CO) and 21.25 (*C*H$_3$CO). ESI-TOFMS: m/z=511.3285 $[M+H]^+$; calcd for $C_{32}H_{46}O_5$: 511.3423.

*4.1.10. 3α-Hydroxy-11-oxo-18β-olean-1,12-dien-29-oic acid (**12**).* A solution of **11** (250 mg, 0.489 mmol) in EtOH (8 mL) was stirred with 1 M KOH (2 mL) overnight at rt. The solution was concentrated and the residue was purified by silica gel chromatography (50:1 → 25:1 CH_2Cl_2/EtOH) to furnish **12** as colorless solid. Yield: 200 mg, (87%). $[\alpha]_D^{20}$ +144 (*c* 0.9, 5:1 $CHCl_3$/MeOH). ^{1}H NMR ($CD_3OD/CDCl_3$, 300 MHz): δ 6.67 (d, $J_{1,2}$ 13.7 Hz, 1H, 1-H), 5.68 (s, 1H, 12-H), 5.53 (dd, $J_{2,3}$ 6.2 Hz, 1H, 2-H), 3.52 (d, 1H, 3-H), 2.71 (s, 1H, 9-H), 2.23 (br dd, $J_{18,19b}$ 13.6, $J_{18,19a}$ 4.2 Hz, 1H, 18-H), 2.16–1.61 (m, 7H, 16a-H, 21a-H, 19a-H, 15a-H, 7a-H, 6a-H, 19b-H), 1.55–1.19 (m, 7H, 6b-H, 7b-H, 22a-H, 22b-H, 21b-H, 5-H, 15b-H), 1.06 (ddd, 1H, 16b-H), 1.42 (s, 3H, 27-CH_3), 1.24 (s, 3H, 25-CH_3), 1.19 (s, 3H, 30-CH_3), 1.16 (s, 3H, 26-CH_3), 0.98, and 0.87 (2 s, 6H, 23-C*H*$_3$, 24-C*H*$_3$) and 0.85 (s, 3H, 28-C*H*$_3$). ESI-TOFMS: m/z=469.2889 $[M+H]^+$; calcd for $C_{30}H_{44}O_4$: 469.3318.

*4.1.11. Hydrogenation of **9**.* A solution of **9** (30 mg, 0.044 mmol) in dry methanol (4 mL) was hydrogenated in the presence of 10% Pd–C (30 mg) at rt and atmospheric pressure for 15 h. The catalyst was filtered over a layer of Celite and the filtrate was concentrated. Purification of the residue on silica gel (50:1 CH_2Cl_2/EtOH) gave **13** as amorphous solid. Yield: 18 mg (80%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.72 (s, 1H, 12-H), 4.64 (dd, $J_{3,2a}$=$J_{3,2b}$ 3.2 Hz, 1H, 3-H), 2.56 (ddd, $J_{1a,b}$ 13.2, $J_{1a,2}$ 3.6 Hz, 1H, 1a-H), 2.47 (s, 1H, 9-H), 2.19 (br dd, $J_{18,19b}$ 13.6, $J_{18,19a}$ 3.2 Hz, 1H, 18-H), 2.07–1.81 (m, 5H, 16a-H, 21a-H, 2a-H, 19a-H, 15a-H), 1.72 (ddd, 1H, 7a-H), 1.645 (t, $J_{19a,19b}$ 13.6 Hz, 1H, 19b-H), 1.56 (dddd, 1H, 2b-H), 1.50–1.16 (m, 9H, 6a-H, 6b-H, 7b-H, 22a-H, 22b-H, 21b-H, 1b-H, 5-H, 15b-H), 1.04 (ddd, 1H, 16b-H), 1.43 (s, 3H, 27-CH_3), 1.23 (s, 3H, 30-CH_3), 1.17 (s, 3H, 25-CH_3), 1.14 (s, 3H, 26-CH_3), 0.92 (s, 3H, 23-C*H*$_3$), 0.86 (s, 3H, 24-C*H*$_3$), and 0.84 (s, 3H, 28-C*H*$_3$). ^{13}C NMR ($CDCl_3/CD_3OD$, 100.62 MHz): δ=170.74 (CH_3CO) and 21.36 (*C*H$_3$CO).

*4.1.12. 1α-Hydroxy-11-oxo-18β-olean-2,12-dien-29-oic acid (**14**).* A solution of **9** (100 mg, 0.158 mmol) in dichloromethane (5 mL) was stirred with trifluoroacetic acid (0.2 mL) and anisole (0.1 mL) at rt for 12 h. The solution was concentrated and the residue was purified by silica gel chromatography (1:1 *n*-hexane/EtOAc). Product-containing fractions were pooled and concentrated. The residue was dissolved in dry MeOH (5 mL) and treated with 0.1 M methanolic NaOMe (0.1 mL) for 4 h at rt. The solution was made neutral by addition of Dowex 50H$^+$ cation exchange resin and filtered. The filtrate was concentrated and purified by silica gel chromatography (1:1 *n*-hexane/EtOAc) to afford **14** as colorless amorphous solid. Yield: 60 mg (82%). $[\alpha]_D^{20}$ +197 (*c* 0.75, MeOH). ^{1}H NMR (CD_3OD, 400 MHz): δ 5.63 (s, 1H, 12-H), 5.62 (dd, $J_{3,2}$ 10.4, $J_{1,2}$ 6.0 Hz, 1H, 2-H), 5.51 (d, 1H, 3-H), 4.55 (dd, 1H, 1-H), 3.47 (s, 1H, 9-H), 2.225 (br dd, $J_{18,19b}$ 13.0, $J_{18,19a}$ 4.5 Hz, 1H, 18-H), 2.155 (dt, $J_{16a,16b}$ 13.6, $J_{16a,15a}$ 13.6, $J_{16a,15b}$ 4.8 Hz, 1H, 16a-H), 1.97–1.86 (m, 2H, 21a-H, 15a-H), 1.865 (ddd, $J_{19a,19b}$ 13.5, $J_{18,19a}$ 4.5 Hz, 1H, 19a-H), 1.76 (ddd, $J_{7a,7b}$=$J_{7a,6a}$ 13.0, $J_{7a,6b}$ 4.5 Hz, 1H, 7a-H), 1.72 (t, 1H, 19b-H), 1.65–1.38 (m, 7H, 6a-H, 6b-H, 7b-H, 22a-H, 22b-H, 5-H, 21b-H), 1.28 (ddd, 1H, 15b-H), 1.05 (ddd, 1H, 16b-H), 1.45 (s, 3H, 27-CH_3), 1.20 (s, 3H, 26-CH_3), 1.16 (s, 3H, 30-CH_3), 1.115 (s, 3H, 25-CH_3), 1.01(s, 3H, 23-C*H*$_3$), 0.91 (s, 3H, 24-C*H*$_3$), and 0.85 (s, 3H, 28-C*H*$_3$). ESI-TOFMS: m/z=469.3313 $[M+H]^+$; calcd for $C_{30}H_{44}O_4$: 469.3318.

*4.1.13. 1α-Hydroxy-11-oxo-18β-olean-12-en-29-oic acid (**15**).* A solution of **14** (100 mg, 0.213 mmol) in dry MeOH (10 mL) was stirred with 10% Pd/C (100 mg) under hydrogen overnight at rt. The catalyst was filtered off on Celite and the filtrate was concentrated. Chromatography of the residue on silica gel (20:1 CH_2Cl_2/EtOH) afforded **15** as a colorless solid (85 mg, 85%). $[\alpha]_D^{20}$ +144 (*c* 0.5, 5:1 $CHCl_3$/MeOH). ^{1}H NMR (5:1 $CDCl_3/CD_3OD$, 400 MHz): δ 5.66 (s, 1H, 12-H), 4.55 (dd, $J_{1,2a}$=$J_{1,2b}$ 2.8 Hz, 1H, 1-H), 3.33 (s, 1H, 9-H), 2.20 (br dd, $J_{18,19b}$ 12.5, $J_{18,19a}$ 4.5 Hz, 1H, 18-H), 2.11–1.94 (m, 3H, 2a-H, 16a-H, 21a-H), 1.88 (ddd, $J_{19a,19b}$ 13.6 Hz, 1H, 19a-H), 1.84 (dt, $J_{15a,15b}$ 13.6, $J_{15a,16a}$ 4.0 Hz, 1H, 15a-H), 1.71–1.58 (m, 4H, 6a-H, 7a-H, 19b-H, 3a-H), 1.47 (ddd, $J_{2b,2a}$ 14.4 Hz, 1H, 2b-H), 1.43–1.29 (m, 5H, 6b-H, 22a-H, 22b-H, 21b-H, 7b-H), 1.24–1.14 (m, 3H, 15b-H, 5-H, 3b-H), 1.04 (ddd, 1H, 16b-H), 1.415 (s, 3H, 27-CH_3), 1.18 (s, 3H, 30-CH_3), 1.15 (s, 3H, 26-CH_3), 1.14 (s, 3H, 25-CH_3), 0.91(s, 3H 23-C*H*$_3$), 0.86 (s, 3H, 24-C*H*$_3$), and 0.83 (s, 3H, 28-C*H*$_3$). ESI-TOFMS: m/z=471.2991 $[M+H]^+$; calcd for $C_{30}H_{46}O_4$: 471.3747.

*4.1.14. 2β,3α-Dihydroxy-11-oxo-18β-olean-12-en-29-oic acid (**16**).* Compound **5** (150 mg, 0.236 mmol) was dissolved in toluene (5 mL) and a solution of TFA (200 μL, 2.481 mmol) in toluene (2 mL) was added dropwise at rt. The mixture was stirred at 40 °C for 2 h. The reaction mixture was coevaporated with toluene three times and the residue was dissolved in dry MeOH (5 mL). 0.1 M Methanolic NaOMe (0.1 mL) was added and the reaction mixture was stirred at rt for 2 h. Dowex 50H$^+$ cation exchange resin was added until neutral pH, the resin was filtered off and the filtrate was concentrated. A solution of the residue in MeOH (5 mL) was stirred at rt with 10% Pd–C (50 mg) under hydrogen at atmospheric pressure. The catalyst was filtered over Celite and the filtrate was concentrated. Chromatography (10:1 CH_2Cl_2/MeOH) of the residue on a column of silica gel afforded **16** as a colorless crystalline solid. Yield: 80 mg (70%). Mp 182–184 °C. $[\alpha]_D^{20}$ +147 (*c* 0.6, MeOH). ^{1}H NMR (5:1 $CD_3OD/CDCl_3$, 400 MHz): δ 5.74 (s, 1H, 12-H), 3.75–3.65 (m, 2H, 2-H, 3-H), 2.54 (s, 1H, 9-H), 2.21 and 2.19 (m, 2H, 18-H, 1a-H), 2.08–1.10 (m, 16H, 15a-H, 16a-H, 19a-H, 21a-H, 6a-H, 7a-H, 19b-H, 6b-H, 7b-H, 15b-H, 21b-H, 22a-H, 22b-H, 5-H, 16b-H, 1b-H), 1.37 (s, 3H, 27-CH_3), 1.31 (s, 3H, 25-CH_3), 1.23 (s, 3H, 30-C*H*$_3$), 1.10 (s, 3H, 26-C*H*$_3$), 1.05 (s, 3H, 23-C*H*$_3$), 0.94 (s, 3H, 24-C*H*$_3$), and 0.84 (s, 3H, 28-C*H*$_3$). ESI-TOFMS: m/z=487.3375 $[M+H]^+$; calcd for $C_{30}H_{46}O_5$: 487.3318.

*4.1.15. Diphenylmethyl 2β,3β-epithio-11-oxo-18β-olean-12-en-29-oate (**17**), diphenylmethyl 3α-formyloxy-2β-mercapto-11-oxo-18β-olean-12-en-29-oate (**18**), and diphenylmethyl 3α-hydroxy-2β-mercapto-11-oxo-18β-olean-12-en-29-oate (**19**). Method A.* A solution of trifluoroacetic acid (0.135 mL, 1.18 mmol) in dry toluene (10 mL) was added dropwise to an ice-cooled solution of **5** (5.0 g, 7.88 mmol) and dimethylthioformamide (1.4 mL, 16.5 mmol) in dry toluene (150 mL) under Ar. The reaction mixture was stirred at 45 °C for 4 h, then coevaporated with toluene three times and concentrated. The residue was submitted to silica gel chromatography (15:1 → 10:1 CH_2Cl_2/EtOH) to afford **17** as the major product (4.1 g, 80%) as colorless crystals. Mp 169 °C. $[\alpha]_D^{20}$ +163 (*c* 0.9, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.41–7.26 (m, 10H, arom. H), 6.93 (s, 1H, C*H*(Ph)$_2$), 5.54 (s, 1H, 12-H), 3.54 (dd, $J_{1a,2}$ 1.2, $J_{1a,1b}$

16.0 Hz, 1H, 1a-H), 3.36 (ddd, $J_{2,1b}$ 4.0 Hz, 1H, 2-H), 3.15 (d, $J_{2,3}$ 7.2 Hz, 1H, 3-H), 2.21 (s, 1H, 9-H), 2.07–1.96 (m, 4H, 21a-H, 16a-H 18-H, 19a-H), 1.77 (dt, $J_{15a,15b}$ 13.6, $J_{15a,16a}$ 4.8 Hz, 1H, 15a-H), 1.68–1.42 (m, 5H, 1b-H, 19b-H, 7a-H, 6a-H, 6b-H), 1.39–1.12 (m, 5H, 7b-H, 22a-H, 22b-H, 21b-H, 15b-H), 0.98 (ddd, 1H, 16b-H), 0.81 (br dd, $J_{5,6a}$ 2.4, $J_{5,6b}$ 11.6 Hz, 1H, 5-H), 1.36 (s, 3H, 25-CH_3), 1.33 (s, 3H, 27-CH_3), 1.28 (s, 3H, 23-CH_3), 1.17 (s, 3H, 30-CH_3), 1.10 (s, 3H, 24-CH_3), 1.07 (s, 3H, 26-CH_3), and 0.66 (s, 3H, 28-CH_3). ^{13}C NMR ($CDCl_3$, 100.62 MHz): δ 140.05, 139.99, 128.96, 128.59, 128.40, 128.08, 127.78, 127.42, 127.19, 126.91 (arom. C), and 76.56 (CHPh$_2$). ESI-TOFMS: m/z=651.3872 $[M+H]^+$; calcd for $C_{43}H_{54}O_3S$: 651.3746.

Method B. Trifluoroacetic acid (0.45 mL, 5.88 mmol) was added dropwise to an ice-cooled solution of **6** (5.0 g, 7.88 mmol) and dimethylthioformamide (1.4 mL, 16.5 mmol) in dry toluene (150 mL) under Ar. The reaction mixture was stirred at 80 °C for 2 h. Workup and chromatography of the material as described for method A afforded **17** as the higher running product (1.0 g, 20%). Elution of the column using 10:1→3:1 *n*-hexane/EtOAc as eluant furnished compound **18** as a colorless solid. Yield: 1.9 g (35%). $[\alpha]_D^{20}$ +144 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.25 (s, 1H, CHO), 7.41–7.25 (m, 10H, arom. H), 6.93 (s, 1H, CH(Ph)$_2$), 5.56 (s, 1H, 12-H), 5.14 (d, $J_{2,3}$ 11.9 Hz, 1H, 3-H), 3.13 (dddd, $J_{2,1a}$ 11.5, $J_{2,1b}$ 7.2 Hz, 1H, 2-H), 2.50 (s, 1H, 9-H), 2.32 (dd, $J_{1a,1b}$ 15.1 Hz, 1H, 1a-H), 2.10 (dd, 1H, 1b-H), 2.09–1.96 (m, 4H, 21a-H, 16a-H, 18-H, 19a-H), 1.79 (dt, $J_{15a,15b}$ 13.4, $J_{15a,16a}$ 4.3 Hz, 1H, 15a-H), 1.65 (t, $J_{19a,19b}$=$J_{18,19b}$ 14.3 Hz, 1H, 19b-H), 1.62–0.96 (m, 11H, 7a-H, 6a-H, 6b-H, SH, 7b-H, 22a-H, 22b-H, 21b-H, 15b-H, 5-H, 16b-H), 1.35 (s, 3H, 27-CH_3), 1.33 (s, 3H, 25-CH_3), 1.16 (s, 3H, 30-CH_3), 1.06 (s, 3H, 26-CH_3), 0.97 and 0.94 (2 s, 6H, 24-CH_3, 23-CH_3), and 0.65 (s, 3H, 28-CH_3). ^{13}C NMR ($CDCl_3$, 100.62 MHz): δ 161.03 (CHO), 140.13, 140.03, 128.64, 128.27, 128.16, 127.85, 127.28, 126.97 (arom. C), 76.68 (CHPh$_2$). ESI-TOFMS: m/z=697.4388 $[M+H]^+$; calcd for $C_{44}H_{56}O_5S$: 697.3926. Further elution of the column finally gave compound **19** as a colorless crystalline solid. Yield: 1.6 g (30%). Mp 124–125 °C. $[\alpha]_D^{20}$ +164 (*c* 0.9, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.38–7.24 (m, 10H, arom. H), 6.93 (s, 1H, CH(Ph)$_2$), 5.56 (s, 1H, 12-H), 3.52 (d, $J_{2,3}$ 11.2 Hz, 1H, 3-H), 2.92 (dddd, $J_{2,1a}$ 11.4, $J_{2,1b}$ 8.1 Hz, 1H, 2-H), 2.51 (s, 1H, 9-H), 2.20 (dd, $J_{1a,1b}$ 15.1 Hz, 1H, 1a-H), 2.12 (dd, 1H, 1b-H), 2.10–1.98 (m, 4H, 21a-H, 16a-H, 18-H, 19a-H), 1.80 (dt, $J_{15a,15b}$ 13.7, $J_{15a,16a}$ 4.4 Hz, 1H, 15a-H), 1.66 (t, $J_{19a,19b}$=$J_{18,19b}$ 14.2 Hz, 1H, 19b-H), 1.65–1.45 (m, 3H, 7a-H, 6a-H, 6b-H), 1.40–0.95 (m, 8H, 7b-H, 22a-H, 22b-H, SH, 21b-H, 15b-H, 5-H, 16b-H), 1.35 (s, 3H, 27-CH_3), 1.26 (s, 3H, 25-CH_3), 1.21 (s, 3H, 30-CH_3), 1.08 (s, 3H, 23-CH_3), 1.07 (s, 3H, 26-CH_3), 0.90 (s, 3H, 24-CH_3), and 0.67 (s, 3H, 28-CH_3). ^{13}C NMR ($CDCl_3$, 100.62 MHz): δ 140.12, 140.04, 128.64, 128.51, 128.27, 128.14, 127.84, 127.26, 126.96 (arom. C), and 76.65 (CHPh$_2$). ESI-TOFMS: m/z=669.3704 $[M+H]^+$; calcd for $C_{43}H_{56}O_4S$: 669.3977.

*4.1.16. 2β-S-acetylthio-3α-acetyloxy-11-oxo-18β-olean-12-en-29-oate (**20**). Method A*. A solution of episulfide **17** (100 mg, 0.15 mmol) and *p*-toluenesulfonic acid (10 mg, 0.05 mmol) in 1:1 AcOH/Ac_2O (3 mL) was stirred for 2 h at rt. The solution was diluted with diethyl ether (50 mL) and extracted with ice-water. The organic layer was dried (Na_2SO_4) and concentrated. Purification of the residue by silica gel chromatography (5:1 *n*-hexane/EtOAc) afforded unreacted **17** (20 mg, 18%) followed by **20** (90 mg, 70%) as colorless solid. Mp 214 °C. $[\alpha]_D^{20}$ +124 (*c* 0.8, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.41–7.24 (m, 10H, arom. H), 6.93 (s, 1H, CH(Ph)$_2$), 5.54 (s, 1H, 12-H), 5.13 (d, $J_{2,3}$ 11.7 Hz, 1H, 3-H), 3.90 (dt, $J_{2,1a}$ 11.2, $J_{2,1b}$ 7.8 Hz, 1H, 2-H), 2.51 (s, 1H, 9-H), 2.45 (dd, $J_{1a,1b}$ 14.9 Hz, 1H, 1a-H), 2.29 (s, 3H, CH_3C(O)S), 2.04 (s, 3H, CH_3CO), 2.08–1.96 (m, 4H, 21a-H, 16a-H, 18-H, 19a-H), 1.95 (dd, 1H, 1b-H), 1.85–0.98 (m, 12H, 15a-H, 19b-H, 7a-H, 6a-H, 6b-H, 7b-H, 22a-H, 22b-H, 21b-H, 15b-H, 5-H, 16b-H), 1.38 (s, 3H, 27-CH_3), 1.31 (s, 3H, 25-CH_3), 1.18 (s, 3H, 30-CH_3), 1.06 (s, 3H, 26-CH_3), 1.01 (s, 3H, 24-CH_3), 0.94 (s, 3H, 23-CH_3), and 0.67 (s, 3H, 28-CH_3). ^{13}C NMR ($CDCl_3$, 75.47 MHz): δ 195.35 (SC=O), 170.65 (OC=O), 140.15, 140.06, 128.64, 128.48, 128.28, 128.15, 127.84, 127.28, 126.96 (arom. C), 76.67 (CHPh$_2$), 30.59 [SC(O)CH_3], 20.90 (OCCH_3). ESI-TOFMS: m/z=753.4758 $[M+H]^+$; calcd for $C_{47}H_{60}O_6S$: 753.4189.

Method B. A solution of **17** (300 mg, 0.45 mol) in dry pyridine (4 mL) was cooled to 0 °C. Acetic anhydride (2 mL) was added and the solution was stirred at rt for 15 h. The solution was diluted with dichloromethane (50 mL) and washed with ice-cold 10% HCl, water, satd aq $NaHCO_3$ and brine. Processing as described for method A afforded **20** (310 mg, 92%).

*4.1.17. Diphenylmethyl 2β-mercapto-3α-acetyloxy-11-oxo-18β-olean-12-en-29-oate (**21**)*. A solution of **20** (900 mg, 1.195 mmol) and hydrazine hydrate (120 mg, 2.39 mmol) in 5:1:1 THF/cyclohexene/EtOH was stirred for 30 min at rt. The solution was diluted with EtOAc (100 mL) and washed with ice-cold 0.1 M HCl, satd aq $NaHCO_3$ and brine. The organic phase was dried (Na_2SO_4) and concentrated. Purification of the residue by silica gel chromatography (6:1 *n*-hexane/EtOAc) afforded **21** as a colorless solid. Yield: 800 mg (94%). Mp 121–123 °C. $[\alpha]_D^{20}$ +135 (*c* 0.8, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.37–7.27 (m, 10H, arom. H), 6.94 (s, 1H, CH(Ph)$_2$), 5.56 (s, 1H, 12-H), 5.12 (d, $J_{2,3}$ 12.0 Hz, 1H, 3-H), 3.08 (ddd, $J_{2,1a}$ 12.6, $J_{2,1b}$ 7.9 Hz, 1H, 2-H), 2.50 (s, 1H, 9-H), 2.32 (dd, $J_{1a,1b}$ 13.6 Hz, 1H, 1a-H), 2.13 (s, 3H, CH_3CO), 2.12–1.98 (m, 5H, 21a-H, 16a-H, 18-H, 19a-H, 1b-H), 1.85–0.98 (m, 13H, 15a-H, 19b-H, 7a-H, 6a-H, 6b-H, 7b-H, 22a-H, 22b-H, SH, 21b-H, 15b-H, 5-H, 16b-H), 1.36 (s, 3H, 27 CH_3), 1.33 (s, 3H, 25-CH_3), 1.18 (s, 3H, 30-CH_3), 1.06 (s, 3H, 26 CH_3), 0.94 and 0.92 (2 s, 6H, 23-CH_3, 24-CH_3), and 0.67 (s, 3H, 28-CH_3). ^{13}C NMR ($CDCl_3$, 75.47 MHz): δ 170.89 (OC=O), 140.13, 140.05, 128.65, 128.31, 128.17, 127.845, 127.29, 126.98 (arom. C), 76.69 (CHPh$_2$), and 21.03 (OCCH_3). ESI-TOFMS: m/z=711.4276 $[M+H]^+$; calcd for $C_{45}H_{58}O_5S$: 711.0830.

*4.1.18. 2β-S-Acetylthio-3α-acetyloxy-11-oxo-18β-olean-12-en-29-oic acid (**22**)*. Compound **20** (900 mg, 1.2 mmol) was dissolved in dry CH_2Cl_2 (10 mL). Anisole (0.9 mL) was added followed by dropwise addition of trifluoroacetic acid (0.9 mL). The solution was stirred overnight at 8 °C, diluted with toluene (50 mL) and concentrated. Purification of the residue by silica gel chromatography (50:1 CH_2Cl_2→CH_2Cl_2/EtOH) afforded **22** as a colorless solid. Yield: 650 mg (93%). $[\alpha]_D^{20}$ +129 (*c* 0.7, 5:1 $CHCl_3$/MeOH). ^{1}H NMR (3:1 $CDCl_3/CD_3OD$, 400 MHz): δ 5.69 (s, 1H, 12-H), 5.11 (d, $J_{2,3}$11.6 Hz, 1H, 3-H), 3.90 (ddd, $J_{2,1a}$ 11.2, $J_{2,1b}$ 7.6 Hz, 1H, 2-H), 2.59 (s, 1H, 9-H), 2.41 (dd, $J_{1a,1b}$ 14.8 Hz, 1H, 1a-H), 2.30 (s, 3H, CH_3COS), 2.23 (br dd, $J_{18,19b}$ 13.2, $J_{18,19a}$ 4.8 Hz, 1H, 18-H), 2.11–1.83 (m, 5H, 16a-H, 21a-H, 1b-H, 19a-H, 15a-H), 2.06 (s, 3H, CH_3COO), 1.71 (dt, $J_{7a,7b}$ 11.8, $J_{7a,6a}$ 5.0 Hz, 1H, 7a-H), 1.63 (t, $J_{19a,19b}$ 13.5 Hz, 1H, 19b-H), 1.57–1.08 (m, 9H, 6a-H, 6b-H, 7b-H, 22a-H, 22b-H, 21b-H, 5-H, 15b-H, 16b-H), 1.42 (s, 3H, 27-CH_3), 1.32 (s, 3H, 25-CH_3), 1.23 (s, 3H, 30-CH_3), 1.12 (s, 3H, 26-CH_3), 1.03 (s, 3H, 23-CH_3), 0.95 (s, 3H, 24-CH_3), and 0.84 (s, 3H, 28-CH_3). ^{13}C NMR ($CDCl_3/CD_3OD$, 100.62 MHz): δ 195.91 (O=CS), 171.06 (O=CO), 30.01 [SC(O)CH_3], 20.34 (OCCH_3). ESI-TOFMS: m/z=587.2231 $[M+H]^+$; calcd for $C_{34}H_{50}O_6S$: 587.3406.

*4.1.19. 2β,3β-Epithio-11-oxo-18β-olean-12-en-29-oic acid (**24**). Method A*. A solution of **22** (190 mg, 0.324 mmol) and 0.2 M aq NaOH (2 mL) in methanol (6 mL) was stirred for 12 h at rt. The solution was diluted with EtOAc (100 mL) and washed twice with ice-cold 0.1 M HCl and water. The organic phase was dried (Na_2SO_4) and concentrated. Purification of the residue by silica gel chromatography (50:1→25:1 CH_2Cl_2/EtOH) furnished **24** as a colorless solid. Yield: 130 mg, (80%). $[\alpha]_D^{20}$ +169 (*c* 0.7, 5:1 $CHCl_3$/MeOH). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.68 (s, 1H, 12-H), 3.50 (dd, $J_{1a,1b}$ 16.0, $J_{2,1a}$ 0.8 Hz, 1H, 1a-H), 3.37 (ddd, 1H, 2-H), 3.17 (d, $J_{2,3}$ 7.2 Hz, 1H, 3-H), 2.27 (s, 1H, 9-H), 2.20 (br dd, $J_{18,19b}$ 13.2, $J_{18,19a}$ 4.0 Hz, 1H, 18-H), 2.05 (dd, $J_{16a,16b}$=$J_{16a,15a}$ 13.2, $J_{16a,15b}$ 4.2 Hz, 1H, 16a-H), 1.97 (ddd, $J_{21a,21b}$ 13.0, *J* 3.2, *J* 6.0 Hz, 1H, 21a-H), 1.90 (ddd, 1H, 19a-H), 1.83 (ddd, $J_{15a,15b}$ 13.6, $J_{15a,16b}$ 4.8 Hz, 1H, 15a-H), 1.64 (m, 2H, 1b-H, 7a-H), 1.60 (t, $J_{19a,19b}$ 13.2 Hz, 1H, 19b-H), 1.52–1.16 (m, 8H, 6a-H, 6b-H, 7b-H, 22a-H, 22b-

H, 21b-H, 5-H, 15b-H), 1.04 (ddd, 1H, 16b-H), 1.36 (s, 3H, 27-CH_3), 1.36 (s, 3H, 25-CH_3), 1.30 (s, 3H, 23-CH_3), 1.18 (s, 3H, 30-CH_3), 1.11 (s, 3H, 26-CH_3), 1.11 (s, 3H, 24-CH_3), and 0.82 (s, 3H, 28-CH_3). ESI-TOFMS: m/z=485.2656 $[M+H]^+$; calcd for $C_{30}H_{44}O_3S$: 485.3089.

Method B. Trifluoroacetic acid (0.050 mL) was added to a solution of **6** (1.0 g, 2.134 mmol) and dimethylthioformamide (0.28 mL, 4.267 mmol) in dichloromethane (10 mL) and the solution was stirred overnight at 40 °C. Toluene (50 mL) was added and the solution was concentrated. The residue was purified by silica gel chromatography (50:1 →20:1 CH_2Cl_2/EtOH) to furnish **24** as a colorless solid. Yield: 420 mg, (40%).

*4.1.20. Diphenylmethyl 3β-S-acetylthio-2α-chloro-11-oxo-18β-olean-12-en-29-oate (**25**).* A solution of **17** (300 mg, 0.461 mmol) and $CoCl_2$ (6 mg, 0.046 mmol) in CH_2Cl_2 (5 mL) was cooled to 0 °C. Acetyl chloride (72 μL, 0.922 mmol) was added and the suspension was stirred for 15 h at rt. The reaction mixture was diluted with CH_2Cl_2 (100 mL) and then washed twice with satd aq $NaHCO_3$, water, and brine and dried (Na_2SO_4). The organic layer was concentrated and the residue was purified by flash chromatography on silica gel (6:1 *n*-hexane/EtOAc) to afford **3** (29 mg, 10%) followed by **25** (278 mg, 83%) as colorless solid. $[\alpha]_D^{20}$ +106 (*c* 0.8, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.41–7.24 (m, 10H, arom. H), 6.93 (s, 1H, C*H*$(Ph)_2$), 5.51 (s, 1H, 12-H), 4.15 (ddd, $J_{2,1a}$ 4.1 Hz, 1H, 2-H), 3.59 (d, $J_{3,2}$ 11.8 Hz, 1H, 3-H), 3.55 (dd, $J_{1a,1b}$ 13.3 Hz, 1H, 1a-H), 2.42 (s, 1H, 9-H), 2.39 (s, 3H, CH_3C═OS), 2.07–1.96 (m, 4H, 21a-H, 16a-H, 18-H, 19a-H), 1.84–1.59 (m, 4H, 15a-H, 7a-H, 19b-H, 6a-H), 1.52–0.88 (m, 9H, 1b-H, 6b-H, 7b-H, 22a-H, 22b-H, 21b-H, 5-H, 15b-H, 16b-H), 1.38 (s, 3H, 27-CH_3), 1.18 (s, 3H, 25-CH_3), 1.18 (s, 3H, 30-CH_3), 1.08 (s, 3H, 26-CH_3), 1.04 (s, 3H, 23-CH_3), 0.87 (s, 3H, 24-CH_3), and 0.66 (s, 3H, 28-CH_3). ^{13}C NMR ($CDCl_3$, 75.47 MHz): δ 194.73 (SC═O), 140.14, 140.06, 128.65, 128.47, 128.15, 127.83, 127.28, 126.95 (arom. C), 76.59 (*C*HPh_2), and 30.58 [SC(O)CH_3]. ESI-TOFMS: m/z=729.4123 $[M+H]^+$; calcd for $C_{45}H_{57}ClO_4S$: 729.4497.

*4.1.21. Diphenylmethyl 3β-S-acetylthio-2α-bromo-11-oxo-18β-olean-12-en-29-oate (**26**) and 3β-S-acetylthio-2α-bromo-11-oxo-18β-olean-12-en-29-oic acid (**27**).* A solution of **17** (300 mg, 0.461 mmol) and $CoCl_2$ (6 mg, 0.046 mmol) in CH_2Cl_2 (5 mL) was cooled to 0 °C. Acetyl bromide (72 μL, 0.922 mmol) was added and the suspension was stirred for 30 min at 0 °C. The reaction mixture was diluted with CH_2Cl_2 (100 mL) and then washed twice with satd aq $NaHCO_3$, water, and brine and dried (Na_2SO_4). The organic layer was concentrated and the residue was purified by flash chromatography on silica gel (6:1 *n*-hexane/EtOAc) to afford **26** (118 mg, 33%) as colorless solid. $[\alpha]_D^{20}$ +124 (*c* 0.8, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.41–7.23 (m, 10H, arom. H), 6.93 (s, 1H, C*H*$(Ph)_2$), 5.51 (s, 1H, 12-H), 4.15 (ddd, $J_{2,1a}$ 4.4 Hz, 1H, 2-H), 3.69 (d, $J_{3,2}$ 12.0 Hz, 1H, 3-H), 3.69 (dd, $J_{1a,1b}$ 13.3 Hz, 1H, 1a-H), 2.42 (s, 1H, 9-H), 2.39 (s, 3H, CH_3C═OS), 2.08–1.96 (m, 4H, 21a-H, 16a-H, 18-H, 19a-H), 1.78 (ddd, $J_{15a,15b}$ 13.2, $J_{15a,16b}$ 4.4 Hz, 1H, 15a-H), 1.73–1.57 (m, 4H, 1b-H, 7a-H, 19b-H, 6a-H), 1.48–0.88 (m, 8H, 6b-H, 7b-H, 22a-H, 22b-H, 21b-H, 5-H, 15b-H, 16b-H), 1.38 (s, 3H, 27-CH_3), 1.18 (s, 3H, 25-CH_3), 1.18 (s, 3H, 30-CH_3), 1.07 (s, 3H, 26 CH_3), 1.04 (s, 3H, 23-CH_3), 0.87 (s, 3H, 24-CH_3), and 0.66 (s, 3H, 28-CH_3). ^{13}C NMR ($CDCl_3$, 100.62 MHz): δ 194.56 (SC═O), 140.14, 140.05, 128.65, 128.47, 128.15, 127.96, 127.29, 126.95 (arom. C), 76.64 (*C*HPh_2), and 30.52 [SC(O)CH_3]. ESI-TOFMS: m/z=773.3782 $[M+H]^+$; calcd for $C_{45}H_{57}BrO_4S$: 773.239. Elution of the column using 50:1 CH_2Cl_2/EtOH gave **27** (120 mg, 43%) as colorless crystals. Mp 228 °C. $[\alpha]_D^{20}$ +106 (*c* 0.9, 5:1 $CHCl_3$/MeOH). ^{1}H NMR (CD_3OD, 400 MHz): δ 5.57 (s, 1H, 12-H), 4.49 (ddd, $J_{2,1a}$ 4.0 Hz, 1H, 2-H), 3.68 (d, $J_{3,2}$ 12.0 Hz, 1H, 3-H), 3.65 (dd, $J_{1a,1b}$ 13.2 Hz, 1H, 1a-H), 2.53 (s, 1H, 9-H), 2.31 (s, 3H, CH_3C═OS), 2.25 (br dd, $J_{18,19b}$ 12.4, $J_{18,19a}$ 3.6 Hz, 1H, 18-H), 2.14 (dd, $J_{16a,16b}$=$J_{16a,15a}$ 13.6, $J_{16a,15b}$ 4.0 Hz, 1H, 16a-H), 1.97–1.60 (m, 7H, 21a-H, 15a-H, 19a-H, 7a-H, 1b-H, 19b-H, 6a-H), 1.54–0.92 (m, 8H, 6b-H, 7b-H, 22a-H, 22b-H, 21b-H, 5-H, 15b-H, 16b-H), 1.45 (s, 3H, 27-CH_3), 1.19 (s, 3H, 25-CH_3), 1.15 (s, 3H, 30-CH_3), 1.13 (s, 3H, 26-CH_3), 1.03 (s, 3H, 23-CH_3), 0.89 (s, 3H, 24-CH_3), and 0.83 (s, 3H, 28-CH_3). ^{13}C NMR (CD_3OD/$CDCl_3$, 100.62 MHz): δ 193.15 (SC═O) and 30.17 [SC(O)CH_3]. ESI-TOFMS: m/z=607.2012 $[M+H]^+$; calcd for $C_{32}H_{47}BrO_4S$: 607.2456.

*4.1.22. Diphenylmethyl 3α,3β-S-acetylthio-11-oxo-18β-olean-1,12-dien-29-oate (**28**) and diphenylmethyl 1α-S-acetylthio-11-oxo-18β-olean-2,12-dien-29-oate (**32**).* Thioacetic acid (4.2 mL, 55.1 mmol) was added dropwise during 30 min to a solution of **10** (7.0 g, 11.0 mmol) and DMF·dineopentylacetal (3.82 mL, 16.51 mmol) in dry CH_2Cl_2 (100 mL) at rt. The reaction mixture was stirred at 40 °C for 2 h and concentrated The residue was purified by flash chromatography on silica gel (15:1 →10:1 *n*-hexane/EtOAc) to afford first **28** as a colorless solid (2.3 g, 30%). ^{1}H NMR ($CDCl_3$, 300 MHz) of major 3β-isomer (70%): δ 7.42–7.26 (m, 10H, arom. H), 6.93 (s, 1H, C*H*$(Ph)_2$), 6.65 (dd, $J_{2,1}$ 10.4, $J_{3,1}$ 2.8 Hz, 1H, 1-H), 5.53 (s, 1H, 12-H), 5.19 (dd, $J_{3,2}$ 2.0 Hz, 1H, 2-H), 4.13 (t, 1H, 3-H), 2.57 (s, 1H, 9-H), 2.36 (s, 3H, CH_3C═OS), 2.07–1.96 (m, 4H, 21a-H, 16a-H, 18-H, 19a-H), 1.79 (ddd, $J_{15a,15b}$ 13.6, $J_{15a,16b}$ 3.9 Hz, 1H, 15a-H), 1.72–0.95 (m, 11H, 7a-H, 19b-H, 6a-H, 6b-H, 7b-H, 22a-H, 22b-H, 21b-H, 5-H, 15b-H, 16b-H), 1.37 (s, 3H, 27-CH_3), 1.30 (s, 3H, 25-CH_3), 1.18 (s, 3H, 30-CH_3), 1.10 (s, 3H, 26-CH_3), 0.98 (s, 3H, 23-CH_3), 0.89 (s, 3H, 24-CH_3), and 0.66 (s, 3H, 28-CH_3). Selected data for minor 3α-isomer (30%): δ 6.69 (dd, $J_{2,1}$ 10.2, $J_{3,1}$<1.0 Hz, 1H, 1-H), 5.53 (s, 1H, 12-H), 5.43 (dd, $J_{3,2}$ 5.4 Hz, 1H, 2-H), 3.93 (dd, 1H, 3-H). ESI-TOFMS: m/z=693.4413 $[M+H]^+$; calcd for $C_{45}H_{56}O_4S$: 693.977. Further elution gave **32** (3.1 g, 40.6%) as a colorless solid. Mp 100–101 °C. $[\alpha]_D^{20}$ +271 (*c* 0.9, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.40–7.26 (m, 10H, arom. H), 6.94 (s, 1H, C*H*$(Ph)_2$), 5.75 (dd, 1H, $J_{2,1}$ 6.0 Hz, 2-H), 5.59 (s, 1H, 12-H), 5.36 (d, $J_{3,2}$ 9.6 Hz, 1H, 3-H), 5.01 (d, 1H, 1-H), 3.21 (s, 1H, 9-H), 2.29 (s, 3H, CH_3C═OS), 2.08–1.98 (m, 4H, 21a-H, 16a-H, 18-H, 19a-H), 1.80 (ddd, $J_{15a,15b}$ 13.6, $J_{15a,16b}$ 4.4 Hz, 1H, 15a-H), 1.68–1.46 (m, 4H, 7a-H, 19b-H, 6a-H, 6b-H), 1.42–1.14 (m, 6H, 7b-H, 22a-H, 22b-H, 21b-H, 5-H, 15b-H), 0.99 (ddd, 1H, 16b-H), 1.39 (s, 3H, 27-CH_3), 1.33 (s, 3H, 25-CH_3), 1.18 (s, 3H, 30-CH_3), 1.14 (s, 3H, 26-CH_3), 0.98 (s, 3H, 23-CH_3), 0.92 (s, 3H, 24-CH_3), and 0.67 (s, 3H, 28-CH_3). ^{13}C NMR ($CDCl_3$, 75.47 MHz): δ 193.27 (SC═O), 140.05, 128.59, 128.46, 128.09, 127.87, 127.28, 127.15 (arom. C), 76.65 (*C*HPh_2), and 31.13 [SC(O)CH_3]. ESI-TOFMS: m/z=693.3875 $[M+H]^+$; calcd for $C_{45}H_{56}O_4S$: 693.977.

*4.1.23. Diphenylmethyl 3α,3β-mercapto-11-oxo-18β-olean-1,12-dien-29-oate (**29**).* Hydrazine monohydrate (190 mg, 3.82 mmol) was added to a solution of **28** (530 mg, 0.765 mmol) in 5:1:1 THF/cyclohexene/EtOH (14 mL). The reaction mixture was stirred at rt for 30 min and diluted with CH_2Cl_2 (100 mL). The organic phase was washed with water, dried over cotton and concentrated. The residue was purified by column chromatography (10:1 *n*-hexane/EtOAc) to give **29** as amorphous solid (460 mg 92.5%). ^{1}H NMR ($CDCl_3$, 400 MHz) of major isomer: δ 7.39–7.26 (m, 10H, arom. H), 6.93 (s, 1H, C*H*$(Ph)_2$), 6.59 (br d, $J_{2,1}$ 10.3 Hz, 1H, 1-H), 5.53 (s, 1H, 12-H), 5.38 (dd, $J_{2,3}$ 2.0 Hz, 1H, 2-H), 3.30 (dt, $J_{3,SH}$ 10.2 Hz, 1H, 3-H), 2.53 (s, 1H, 9-H), 2.06–1.96 (m, 4H, 21a-H, 16a-H, 18-H, 19a-H), 1.85–1.10 (m, 13H, 15a-H, 7a-H, 19b-H, 6a-H, 6b-H, 7b-H, 22a-H, 22b-H, 21b-H, SH, 5-H, 15b-H, 16b-H), 1.36 (s, 3H, 27-CH_3), 1.29 (s, 3H, 25-CH_3), 1.17 (s, 3H, 30-CH_3), 1.10 (s, 3H, 26-CH_3), 1.03 (s, 3H, 23-CH_3), 0.90 (s, 3H, 24-CH_3), and 0.66 (s, 3H, 28-CH_3). ESI-TOFMS: m/z=651.3746 $[M+H]^+$; calcd for $C_{43}H_{54}O_3S$: 651.872.

*4.1.24. 3α,3β-S-Acetylthio-11-oxo-18β-olean-1,12-dien-29-oic acid (**30**).* Anisole (0.2 mL) and trifluoroacetic acid (0.2 mL) were added to an ice-cold solution of **28** (160 mg, 0.231 mmol) in dry CH_2Cl_2 (8 mL) and the reaction mixture was stirred at 8 °C overnight. The solution was coevaporated with toluene (50 mL) and concentrated. The crude product was purified by column chromatography (3:1 *n*-hexane/EtOAc) to remove the excess of anisole and was followed by

50:1 CH_2Cl_2/EtOH to afford **30** as colorless solid (105 mg, 86.3%). $[\alpha]_D^{20}$ +114 (*c* 0.6, 5:1 $CHCl_3$/MeOH). ^1H NMR ($CDCl_3$, 400 MHz) of major 3β-isomer (70%): δ 6.64 (dd, $J_{2,1}$ 10.4, $J_{3,1}$ 2.8 Hz, 1H, 1-H), 5.68 (s, 1H, 12-H), 5.19 (dd, $J_{3,2}$ 2.0 Hz, 1H, 2-H), 4.12 (t, 1H, 3-H), 2.61 (s, 1H, 9-H), 2.37 (s, 3H, CH_3C═OS), 2.19 (br dd, $J_{18,19b}$ 12.4, $J_{18,19a}$ 4.4 Hz, 1H, 18-H), 2.05 (dd, $J_{16a,16b}$=$J_{16a,15a}$ 13.2, $J_{16a,15b}$ 4.4 Hz, 1H, 16a-H), 1.98 (ddd, $J_{21a,21b}$ 12.4, *J* 2.8, 1H, 21a-H), 1.90 (ddd, 1H, 19a-H), 1.84 (ddd, 1H, 15a-H), 1.72–0.95 (m, 10H, 7a-H, 19b-H, 6a-H, 6b-H, 7b-H, 22a-H, 22b-H, 21b-H, 5-H, 15b-H), 1.02 (ddd, 1H, 16b-H), 1.40 (s, 3H, 27-CH_3), 1.31 (s, 3H, 25-CH_3), 1.19 (s, 3H, 30-CH_3), 1.14 (s, 3H, 26-CH_3), 0.98 (s, 3H, 23-CH_3), 0.88 (s, 3H, 24-*CH*$_3$), and 0.82 (s, 3H, 28-*CH*$_3$). ^{13}C NMR (CD_3OD/$CDCl_3$, 100.62 MHz): δ 196.13 (SC═O) and 30.47 [SC(O)*CH*$_3$]. Selected ^1H NMR data for minor 3α-isomer (30%): δ 6.68 (dd, $J_{2,1}$ 10.4, $J_{3,1}$ 1.2 Hz, 1H, 1-H), 5.69 (s, 1H, 12-H), 5.43 (dd, $J_{3,2}$ 5.6 Hz, 1H, 2-H), 3.92 (dd, 1H, 3-H). ESI-TOFMS: *m*/*z*=527.3195 $[M+H]^+$; calcd for $C_{32}H_{46}O_4S$: 527.2593.

*4.1.25. 3α,3β-Mercapto-11-oxo-18β-olean-1,12-dien-29-oic acid (**31**).* A solution of **30** (150 mg, 0.285 mmol) and $NH_2NH_2\cdot H_2O$ (143 mg, 0.284 mmol) in 5:1:1 THF/cyclohexene/EtOH (7.0 mL) was stirred for 30 min at rt. The reaction mixture was diluted with EtOAc (100 mL) and washed with ice-cold 0.1 M HCl and water. The organic layer was dried over cotton and concentrated. The crude product was purified by column chromatography (50:1 CH_2Cl_2/EtOH) to afford **31** (97 mg, 70%) as a syrup. ^1H NMR (CD_3OD/$CDCl_3$, 400 MHz, major isomer): δ 6.55 (dd, $J_{1,2}$ 10.4, $J_{1,3}$<1.0 Hz, 1H, 1-H), 5.68 (s, 1H, 12-H), 5.36 (dd, $J_{3,2}$ 2.0 Hz, 1H, 2-H), 3.31 (d, 1H, 3-H), 2.59 (s, 1H, 9-H), 2.21 (br dd, $J_{18,19b}$ 13.6 Hz, 1H, 18-H), 2.11–2.05 (m, 16H, 16a-H, 21a-H, 19a-H, 15a-H, 6a-H, 7a-H, 19b-H, 6b-H, 7b-H, 22a-H, 22b-H, SH, 21b-H, 15b-H, 5-H, 16b-H), 1.39 (s, 3H, 27-CH_3), 1.30 (s, 3H, 25-CH_3), 1.18 (s, 3H, 30-CH_3), 1.15 (s, 3H, 26-CH_3), 1.04 (s, 3H, 23-*CH*$_3$), 0.91 (s, 3H, 24-*CH*$_3$), and 0.83 (s, 3H, 28-*CH*$_3$). ESI-TOFMS: *m*/*z*=485.2659 $[M+H]^+$; calcd for $C_{30}H_{44}O_3S$: 485.3089.

*4.1.26. Diphenylmethyl 1α-mercapto-11-oxo-18β-olean-2,12-dien-29-oate (**33**).* A solution of **32** (1.0 g, 1.44 mmol), hydrazine hydrate (217 mg, 4.33 mmol) in 5:1:1 THF/cyclohexene/EtOH (14 mL) was stirred for 30 min at rt. The solution was diluted with EtOAc (100 mL) and washed with ice-cold 0.1 M HCl and water. The organic layer was dried (Na_2SO_4) and concentrated. Purification of the crude product on silica gel (10:1 *n*-hexane/EtOAc) afforded **33** (900 mg, 95%) as colorless crystals. Mp 197 °C (EtOAc/*n*-hexane). $[\alpha]_D^{20}$ +235 (*c* 0.9, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.40–7.27 (m, 10H, arom. H), 6.95 (s, 1H, *CH*(Ph)$_2$), 5.76 (dd, $J_{2,1}$ 6.0 Hz, 1H, 2-H), 5.58 (s, 1H, 12-H), 5.305 (d, $J_{3,2}$ 10.0 Hz, 1H, 3-H), 4.455 (dd, 1H, 1-H), 3.70 (s, 1H, 9-H), 2.11–2.01 (m, 4H, 21a-H, 16a-H, 18-H, 19a-H), 1.82 (ddd, $J_{15a,15b}$ 13.6, $J_{15a,16b}$ 4.4 Hz, 1H, H15a-H), 1.77–1.46 (m, 4H, 7a-H, 19b-H, 6a-H, 6b-H), 1.44–1.14 (m, 7H, 7b-H, 22a-H, 22b-H, 21b-H, SH, 5-H, 15b-H), 1.01 (ddd, 1H, 16b-H), 1.45 (s, 3H, 27-CH_3), 1.25 (s, 3H, 25-CH_3), 1.19 (s, 3H, 30-CH_3), 1.16 (s, 3H, 26-CH_3), 0.99 (s, 3H, 23-CH_3), 0.91 (s, 3H, 24-*CH*$_3$), and 0.70 (s, 3H, 28-*CH*$_3$). ^{13}C NMR ($CDCl_3$, 100.62 MHz): δ 194.56 (SC═O), 140.13, 140.05, 128.64, 128.45, 128.35, 127.92, 127.72, 126.84 (arom. C), 76.61 (*CH*Ph_2). ESI-TOFMS: *m*/*z*=651.3642 $[M+H]^+$; calcd for $C_{43}H_{54}O_3S$: 651.3872.

*4.1.27. 1α-S-Acetylthio-11-oxo-18β-olean-2,12-dien-29-oic acid (**34**).* Trifluoroacetic acid (0.5 m) was added dropwise to an ice-cold solution of **32** (500 mg, 0.722 mmol) and anisole (0.5 mL) in dry CH_2Cl_2 (20 mL) and the solution was stirred at 8 °C for 15 h. The solution was coevaporated with toluene (50 mL) and concentrated. The crude product was purified by column chromatography using first 3:1 *n*-hexane/EtOAc to remove the excess of anisole followed by elution with 50:1 CH_2Cl_2/EtOH to afford **34** (194 mg, 85%). The purified product was dissolved in EtOAc (100 mL) and washed with ice-cold 0.1 M HCl and water. The organic layer was dried with cotton and concentrated. Lyophilization of the residue from dioxane gave **34** as a colorless solid. $[\alpha]_D^{20}$ +324 (*c* 0.4, 5:1 $CHCl_3$/MeOH). ^1H NMR ($CDCl_3$, 300 MHz): δ 5.74 (s, 1H, 12-H), 5.73 (dd, $J_{2,1}$ 6.2 Hz, 1H, 2-H), 5.36 (d, $J_{3,2}$ 9.8 Hz, 1H, 3-H), 5.06 (d, 1H, 1-H), 3.25 (s, 1H, 9-H), 2.28 (s, 3H, CH_3C═OS), 2.20 (br dd, $J_{18,19b}$ 13.7, $J_{18,19a}$ 3.7 Hz, 1H, 18-H), 2.10–1.94 (m, 3H, 16a-H, 21a-H, 19a-H), 1.85 (ddd, $J_{15a,15b}$ 13.8, $J_{15a,16b}$ 4.1 Hz, 1H, 15a-H), 1.75–1.14 (m, 10H, 7a-H, 19b-H, 6a-H, 6b-H, 22a-H, 22b-H, 7b-H, 21b-H, 15b-H, 5-H), 1.04 (ddd, $J_{16a,16b}$ 13.9 Hz, 1H, 16b-H), 1.41 (s, 3H, 27-CH_3), 1.34 (s, 3H, 25-CH_3), 1.23 (s, 3H, 30-CH_3), 1.18 (s, 3H, 26-CH_3), 0.97 (s, 3H, 23-CH_3), 0.93 (s, 3H, 24-*CH*$_3$), and 0.85 (s, 3H, 28-*CH*$_3$). ^{13}C NMR ($CDCl_3$, 75.47 MHz): δ 193.24 (SC═O) and 31.07 [SC(O)*CH*$_3$]. ESI-TOFMS: *m*/*z*=527.2200 $[M+H]^+$; calcd for $C_{32}H_{46}O_4S$: 527.3195.

*4.1.28. 1α-Mercapto-11-oxo-18β-olean-2,12-dien-29-oic acid (**35**).* A solution of **34** (1.8 g, 3.42 mmol) and $NH_2NH_2\cdot H_2O$ (855 mg, 17.1 mmol) in 5:1:1 THF/cyclohexene/EtOH (12 mL) was stirred for 30 min at rt. The solution was diluted with EtOAc (100 mL) and washed with ice-cold 0.1 M HCl, and water. The organic layer was dried over cotton and was concentrated. The crude product was purified by column chromatography (50:1 CH_2Cl_2/EtOH) to give **35** as colorless solid (510 mg, 90.5%). Mp 230–232 °C. $[\alpha]_D^{20}$ +242 (*c* 0.6, 5:1 $CHCl_3$/MeOH). ^1H NMR ($CDCl_3$, 400 MHz): δ 5.75 (s, 1H, 12-H), 5.74 (dd, $J_{3,2}$ 9.8, $J_{1,2}$ 6.4 Hz, 1H, 2-H), 5.29 (d, 1H, 3-H), 4.44 (dd, 1H, 1-H), 3.73 (s, 1H, 9-H), 2.24 (br dd, $J_{18,19b}$ 13.4 Hz, 1H, 18-H), 2.06 (dt, $J_{16a,16b}$ 13.6, $J_{16a,15a}$ 13.6, $J_{16a,15b}$ 4.5 Hz, 1H, 16a-H), 2.00–1.95 (m, 2H, 21a-H, 19a-H), 1.86 (ddd, $J_{15a,15b}$ 13.6, $J_{15a,16b}$ 4.0 Hz, 1H, 15a-H), 1.73 (ddd, $J_{7a,7b}$=$J_{7a,6a}$ 12.8, $J_{7a,6b}$ 3.7 Hz, 1H, 7a-H), 1.64 (t, 1H, 19b-H), 1.63–1.15 (m, 9H, 6a-H, 5-H, 6b-H, 22a-H, 22b-H, SH, 7b-H, 21b-H, 15b-H), 1.06 (ddd, 1H, 16b-H), 1.45 (s, 3H, 27-CH_3), 1.25 (s, 3H, 25-CH_3), 1.23 (s, 3H, 30-CH_3), 1.19 (s, 3H, 26-CH_3), 0.98 (s, 3H, 23-*CH*$_3$), 0.90 (s, 3H, 24-*CH*$_3$), and 0.88 (s, 3H, 28-*CH*$_3$). ESI-TOFMS: *m*/*z*=485.2653 $[M+H]^+$; calcd for $C_{30}H_{44}O_3S$: 485.3089.

*4.1.29. X-ray structure determination of compounds **5**, **7**·H_2O, **17**, **20**, **27**, and **33**.* X-ray data were collected on a Bruker Smart APEX CCD area detector diffractometer using graphite-monochromated Mo Kα radiation (λ=0.71073 Å) and 0.3° ω-scan frames. Corrections for absorption (multi-scan method) and λ/2 effects were applied.[30] After structure solution with program SHELXS97 and direct methods, refinement on F^2 was carried out with the program SHELXL97.[31] Non-hydrogen atoms were refined anisotropically. All H-atoms were placed in calculated positions and thereafter treated as riding. Except for **5**, the absolute structures could be unambiguously determined by anomalous dispersion effects and the Flack absolute structure parameter (*FASP*). Important crystallographic data are given below, crystallographic data for structures **5**, 7·H_2O, 17, 20, 27, and 33 have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications CCDC 759592–759597.

Compound **5**: $C_{43}H_{54}O_4$, M_r=634.86, colorless block from EtOAc/hexane, 0.50×0.45×0.40 mm, monoclinic, space group $P2_1$ (no. 4), *a*=7.6234(8) Å, *b*=33.691(4) Å, *c*=13.9033(15) Å, β=90.309(2)°, *V*=3570.8(7) Å^3, *Z*=4, μ=0.074 mm^{-1}, d_x=1.181 g cm^{-3}, *T*=100 K. 36,626 reflections collected (θ_{max}=30.0°) and merged to 20,209 independent data (R_{int}=0.028); final *R* indices (all data): R_1=0.0570, wR_2=0.1110, 862 parameters, *FASP*=0.5(9). The structure contains two independent molecules and is pseudosymmetric.

Compound 7·H_2O: $C_{45}H_{57}IO_5\cdot H_2O$, M_r=822.82, colorless prism from wet EtOAc/hexane, 0.60×0.19×0.08 mm, orthorhombic, space group $P2_12_12_1$ (no. 19), *a*=9.6240(4) Å, *b*=13.4522(6) Å, *c*=30.5377(14) Å, *V*=3953.5(3) Å^3, *Z*=4, μ=0.858 mm^{-1}, d_x=1.382 g cm^{-3}, *T*=100 K. 43,594 reflections collected (θ_{max}=30.0°) and merged to 11,452 independent data (R_{int}=0.021); final *R* indices (all data): R_1=0.0235, wR_2=0.0534, 480 parameters, *FASP*=−0.019(7). The compound contains a water molecule, which is hydrogen bonded to the carbonyl oxygen atoms of the two COOR groups (O···O=2.89 and 2.97 Å).

Compound **17**: $C_{43}H_{54}O_3S$, M_r=714.45, colorless prism from ethanol, 0.59×0.44×0.42 mm, orthorhombic, space group $P2_12_12_1$ (no. 19), a=10.6918(6) Å, b=17.5747(9) Å, c=18.7998(10) Å, V=3532.6 (3) Å^3, Z=4, μ=0.131 mm^{-1}, d_x=1.224 g cm^{-3}, T=100 K. 52,033 reflections collected (θ_{max}=30.0°) and merged to 10,266 independent data (R_{int}=0.032); final R indices (all data): R_1=0.0448, wR_2=0.1018, 431 parameters, *FASP*=−0.07(4).

Compound **20**: $C_{47}H_{60}O_6S$, M_r=753.01, colorless block from CH_2Cl_2/hexane, 0.48×0.37×0.25 mm, monoclinic, space group $P2_1$ (no. 4), a=11.9330(5) Å, b=16.2826(6) Å, c=11.9601(5) Å, β=116.530 (1)°, V=2079.15(14) Å^3, Z=2, μ=0.126 mm^{-1}, d_x=1.203 g cm^{-3}, T=100 K. 27,869 reflections collected (θ_{max}=30.0°) and merged to 11,412 independent data (R_{int}=0.019); final R indices (all data): R_1=0.0346, wR_2=0.0875, 496 parameters, *FASP*=−0.01(3).

Compound **27**: $C_{32}H_{47}BrO_4S$, M_r=607.67, colorless blade from EtOAc/hexane, 0.58×0.34×0.02 mm, monoclinic, space group $P2_1$ (no. 4), a=7.9488(13) Å, b=11.3585(19) Å, c=16.754(3) Å, β=90.216 (3)°, V=1512.7(4) Å^3, Z=2, μ=1.462 mm^{-1}, d_x=1.334 g cm^{-3}, T=297 K. 6109 reflections collected (θ_{max}=28.3°) and merged to 4109 independent data (R_{int}=0.052); final R indices (all data): R_1=0.0695, wR_2=0.0865, 354 parameters, *FASP*=0.001(10).

Compound **33**: $C_{43}H_{54}O_3S$, *Mr*=650.92, colorless prism from EtOAc/hexane, 0.58×0.20×0.20 mm, monoclinic, space group $P2_1$ (no. 4), a=7.6070(4) Å, b=14.2467(7) Å, c=16.6541(8) Å, β=90.275 (1)°, V=1804.86(16) Å^3, Z=2, μ=0.128 mm^{-1}, d_x=1.198 g cm^{-3}, T=100 K. 18,728 reflections collected (θ_{max}=30.0°) and merged to 10,296 independent data (R_{int}=0.014); final R indices (all data): R_1=0.0317, wR_2=0.0812, 435 parameters, *FASP*=0.03(3).

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Supplementary data

Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.03.098. These data include MOL files and InChIKeys of the most important compounds described in this article.

References and notes

1. Kitagawa, I. *Pure Appl. Chem.* **2002**, *74*, 1189–1198.
2. Yu, B.; Hui, Y. In *Glycochemistry: Principles, Synthesis, and Application*; Wang, P., Bertozzi, C. R., Eds.; Marcel Dekker: New York, NY, Basel, 2001; pp 163–176.
3. Baran, J. S.; Langford, D. D.; Liang, C.; Pitzele, B. S. *J. Med. Chem.* **1974**, *17*, 184–191.
4. Asl, M. N.; Hosseinzadeh, H. *Phytother. Res.* **2008**, *22*, 709–724.
5. Rao, S. G. S. R.; Kondaiah, P.; Singh, S. K.; Ravanan, P.; Sporn, M. B. *Tetrahedron* **2008**, *64*, 11541–11548.
6. Maitraie, D.; Hung, C.-F.; Tu, H.-Y.; Liou, Y.-T.; Wie, B.-L.; Yang, S.-C.; Wang, J.-P.; Lin, C.-N. *Bioorg. Med. Chem.* **2009**, *17*, 2785–2792.
7. Chintharlapalli, S.; Papineni, S.; Jutooru, I.; McAlees, A.; Safe, S. *Mol. Cancer Ther.* **2007**, *6*, 1588–1598.
8. Papineni, S.; Chintharlapalli, S.; Safe, S. *Mol. Pharmacol.* **2008**, *73*, 553–565.
9. Liu, D.; Song, D.; Guo, G.; Wang, R.; Lv, J.; Jing, Y.; Zhao, L. *Bioorg. Med. Chem.* **2007**, *15*, 5432–5439.
10. Vicker, N.; Su, X.; Lawrence, H.; Cruttenden, A.; Purohit, A.; Reed, M. J.; Potter, B. V. L. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3263–3267.
11. Classen-Houben, D.; Schuster, D.; Da Cunha, T.; Odermatt, A.; Wolber, G.; Jordis, U.; Kueenburg, B. *J. Steroid Biochem. Mol. Biol.* **2009**, *113*, 248–252.
12. Walker, B. R.; Connacher, A. A.; Lindsay, R. M.; Webb, D. J.; Edwards, C. R. *J. Clin. Endocrinol. Metab.* **1995**, *80*, 3155–3159.
13. Sandeep, T. C.; Yau, J. L.; MacLullich, A. M.; Noble, J.; Deary, I. J.; Walker, B. R.; Seckl, J. R. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 6734–6739.
14. Pellissier, H. *Tetrahedron* **2004**, *60*, 5123–5162.
15. Baltina, L. A. *Curr. Med. Chem.* **2003**, *10*, 155–171.
16. Aranda, G.; Lallemand, J.-Y.; Azerad, R.; Maurs, M.; Cortes, M.; Ramirez, H.; Vernal, G. *Synth. Commun.* **1994**, *24*, 2525–2535.
17. Teresawa, T.; Okada, T.; Hara, T.; Itoh, K. *Eur. J. Med. Chem.* **1992**, *27*, 345–351.
18. Honda, T.; Rounds, B. V.; Bore, L.; Finlay, H. J.; Favaloro, F. G., Jr.; Suh, N.; Wang, Y.; Sporn, M. B.; Gribble, G. W. *J. Med. Chem.* **2000**, *43*, 4233–4246.
19. Chadalapaka, G.; Jutooru, I.; McAlees, A.; Stefanac, T.; Safe, S. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2633–2639.
20. Beseda, I.; Czollner, L.; Shah, P. S.; Khunt, R.; Gaware, R.; Kosma, P.; Stanetty, C.; del Ruiz Ruiz, M. C.; Amer, H.; Mereiter, K.; Da Cunha, T.; Odermatt, A.; Claßen-Houben, D.; Jordis, U. *Bioorg. Med. Chem.* **2010**, *18*, 433–454.
21. Elgamal, M. H. A.; Fayez, M. B. E. *Tetrahedron* **1967**, *23*, 1633–1640.
22. García-Granados, A.; López, P. E.; Melguizo, E.; Moliz, J. N.; Parra, A.; Simeó, Y. *J. Org. Chem.* **2003**, *68*, 4833–4844.
23. Aranda, G.; Bertranne-Delahaye, M.; Azerad, R.; Maurs, M.; Cortes, M.; Ramirez, H.; Vernal, G.; Prangé, T. *Synth. Commun.* **1997**, *27*, 45–60.
24. Pitzele, B. S. *J. Med. Chem.* **1973**, *17*, 191–194.
25. Amr, A.; E-, G. E.; Ali, K. A.; Abdalla, M. M. *Eur. J. Med. Chem.* **2009**, *44*, 901–907.
26. Candela, K.; Fellous, R.; Joulain, D.; Faure, R. *Flavour Fragrance J.* **2003**, *18*, 52–56.
27. Iranpoor, N.; Firouzabadi, H.; Jafari, A. A. *Synth. Commun.* **2003**, *33*, 2321–2327.
28. Fuji, L.; Koreyuki, M.; Krematsu, K. *Chem. Pharm. Bull.* **1988**, *36*, 1750–1757.
29. Baltina, L. A.; Kunert, O.; Fatykhov, A. A.; Kondratenko, R. M.; Spirikhin, L. V.; Baltina, L. A., Jr.; Galin, F. Z.; Tolstikov, G. A.; Haslinger, E. *Chem. Nat. Compd.* **2005**, *41*, 432–435.
30. *Bruker programs: SMART, version 5.629; SAINT+, version 6.45; SADABS, version 2.10; SHELXTL, version 6.14*; Bruker AXS: Madison, WI, 2003.
31. Sheldrick, G. M. *Acta Crystallogr.* **2008**, *A64*, 112–122.