Synthesis of Amino Acid Conjugates and Further Derivatives of 3α-Hydroxylup-20(29)ene-23,28-dioic acid

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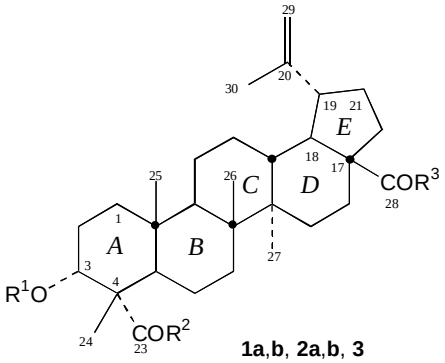
Abstract. Triterpenes of betulinic acid type exhibit many interesting biological activities. Therefore a series of new 3α-hydroxy-lup-20(29)-ene-23,28-dioic acid derivatives **2a**–**22** with putative pharmacological activities were synthesized. As starting compounds 3α-hydroxy-lup-20(29)-ene-23,28-dioic acid (**1a**), isolated from *Schefflera octophylla*, or its 3-*O*-acetyl derivative **1b** were used. Mono- and diesters (**2a**–**b** from **1a**, and **4d** from **4c**) were prepared with CH_2N_2. Oxidation of the isopropenyl side chain with OsO_4 yielded the 20,29-diols (**4a**–**b** from **1b**, and **19** from **17**), which were in the case of **4b** further transformed to the 29-norketones **8a**–**b**. Oxidation of the isopropenyl side chain with *m*-chloroperbenzoic acid afforded the 20,29-epoxide **12** (from **1b**) and the 29-aldehydes and α-hydroxy aldehydes (**13a**–**c** from **2a**, **14a**–**c** from **2b**, and **16a**–**c** from **15a**). Ring A was modified by a tosylation–elimination sequence using *p*-TsCl/NaOAc, which afforded diolefin **15a** (from **2a**) with $\Delta^{2,20(29)}$ double bonds or 23-nor-$\Delta^{3,20(29)}$diolefin **17** (from **1a**). Compounds **4b**, **4c**, and **8a** were coupled with L-methionin, L-phenylalanin, L-alanin, L-serin, and L-glutaminic acid *via* amide bonds at positions **23** and **28** to afford the amino acid conjugates **5a**–**7b** and **9a**–**11**.

Triterpenes of the betulinic acid type are getting more and more importance because of their interesting pharmacological activities. Especially they display anti-inflammatory [1], antitumor [2], leishmanicidal [3], and antimalarial [4] activities. Most interesting is the fact that betulinic acid, dihydrobetulinic acid, and platanic acid also exhibit anti-HIV activity [5]. Further investigations showed that some amides of betulinic acid are potent HIV inhibitors. The presence of an amide function within the side chain was found to be important for optimal activity. Minor modifications in the lupane backbone strongly affected activity [6, 7].

3α-Hydroxy-lup-20(29)-ene-23,28-dioic acid (**1a**) is a rare natural product isolated in surprisingly high yield (7%) from leaves of the Vietnamese plant *Schefflera octophylla* (Araliaceae) [8]. It is structurally closely related to betulinic acid. Therefore, we have recently synthesized a series of amino acid conjugates of **1a** with retainment of the isopropenyl side chain and of the backbone [9]. In continuation of these studies, we now report the synthesis of further derivatives of **1a** by oxidation of the isopropenyl side chain, preparation of various mono- and diesters as well as modifications at ring A. Selected derivatives were transformed to amino acid conjugates.



1a,**b**, **2a**,**b**, **3**

Comp.	R^1	R^2	R^3	Formula	m.w.
1a	H	OH	OH	$C_{30}H_{46}O_5$	486.7
1b	Ac	OH	OH	$C_{32}H_{48}O_6$	528.7
2a	H	OMe	OH	$C_{31}H_{48}O_5$	500.7
2b	H	OMe	OMe	$C_{32}H_{50}O_5$	514.7
3	H	–NH–cyclohexyl	OH	$C_{36}H_{57}NO_4$	567.9

Oxidation of the Isopropenyl Side Chain

A 20,29-dihydroxy functionality was generated by reaction of the 3α-acetyl derivative **1b** [8] with OsO_4 leading to the two diastereomeric diols **4a** and **4b**. Subsequent oxidation with KIO_4 yielded the 29-norketone

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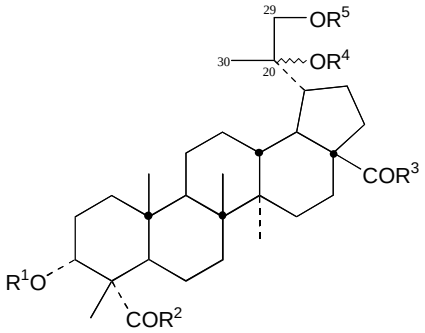
8a. Alkaline hydrolysis of **4b** and **8a** gave the corresponding 3α-hydroxy compounds **4c** and **8b**, respectively. Oxidation of the isopropenyl side chain of the 3α-acetoxy compound **1b** with *m*-chloroperbenzoic acid furnished the 20,29-epoxide **12** as pure diastereomer (configuration at C-20 not determined). On the other hand the 3α-hydroxy compounds **2a**, **2b**, and **15a** (synthesis see below) afforded as main products their corresponding 29-aldehydes as mixtures of the C-20 epimers **13a**/**b**, **14a**/**b**, and **16a**/**16b**, respectively, separated by chromatography in the case of the pair **16a**/**16b**. As minor products the corresponding α-hydroxy aldehydes **13c**, **14c**, and **16c**, respectively, were obtained as only one isomer.

Mono- and Diesters

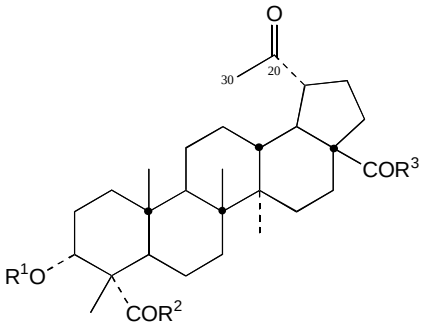
The monomethyl ester **2a** and dimethylester **2b** [8] of **1a** were prepared by reaction with equimolar or excess amounts of CH_2N_2. The location of the ester group in **2a** was determined by comparison of the carbon signals of **2a** and **1a** in CD_3OD, which showed identical signals ($\Delta\delta < 0.1$ ppm) for all carbons except for C-3 ($\Delta\delta$ +0.4), C-4 ($\Delta\delta$+0.7), C-5 ($\Delta\delta$+0.2) and C-6 ($\Delta\delta$+0.2), thus proving **2a** to be the 23-monomethyl ester of **1a**. From the 20,29-dihydroxy derivative **4c**, too, the diester **4d** was prepared, which was further oxidized with KIO_4 to give 29-norketone **8c**.



4a–**d**, **5a**,**b**, **6a**,**b**, **7a**,**b**

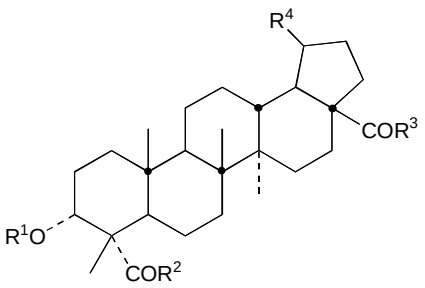
Comp.	R^1	R^2	R^3	R^4	R^5	Formula	m.w.
4a [a]	Ac	OH	OH	H	H	$C_{32}H_{50}O_8$	562.7
4b [a]	Ac	OH	OH	H	H	$C_{32}H_{50}O_8$	562.7
4c	H	OH	OH	H	H	$C_{30}H_{48}O_7$	520.7
4d	H	OMe	OMe	H	H	$C_{32}H_{52}O_7$	548.8
5a	Ac	L-Met–OMe	L-Met–OMe	R^4–R^5 = –CO–		$C_{45}H_{70}N_2O_{11}S_2$	879.2
5b	H	L-Met–OH	L-Met–OH	H	H	$C_{40}H_{66}N_2O_9S_2$	783.1
6a	Ac	L-Phe–OEt	L-Phe–OEt	R^4–R^5 = –CO–		$C_{55}H_{74}N_2O_{11}$	939.2
6b	H	L-Phe–OH	L-Phe–OH	H	H	$C_{48}H_{66}N_2O_9$	815.1
7a	CO–CO-L-Ala–OMe	L-Ala–OMe	L-Ala–OMe	R^4–R^5 = –CO–		$C_{45}H_{67}N_3O_{14}$	874.0
7b	H	L-Ala–OH	L-Ala–OH	H	H	$C_{36}H_{58}N_2O_9$	662.9

[a]) Configuration at C-20 not assigned



8a–**c**, **9a**,**b**, **10**, **11**

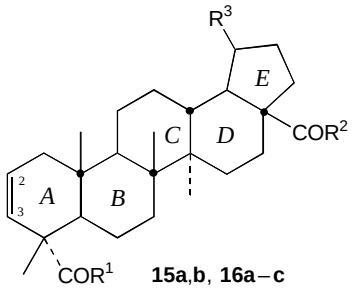
Comp	R^1	R^2	R^3	Formula	m.w.
8a	Ac	OH	OH	$C_{31}H_{46}O_7$	530.7
8b	H	OH	OH	$C_{29}H_{44}O_6$	488.7
8c	H	OMe	OMe	$C_{31}H_{48}O_6$	516.7
9a	Ac	L-Ala–OMe	L-Ala–OMe	$C_{39}H_{60}N_2O_9$	700.9
9b	H	L-Ala–OH	L-Ala–OH	$C_{35}H_{54}N_2O_8$	630.8
10	Ac	L-Ser–OMe	L-Ser–OMe	$C_{39}H_{60}N_2O_{11}$	732.9
11	Ac	L-Glu(OMe)$_2$	L-Glu(OMe)$_2$	$C_{45}H_{68}N_2O_{13}$	845.0



12, **13a**–**c**, **14a**–**c**

Comp.	R^1	R^2	R^3	R^4	Formula	m.w.
12 [a]	Ac	OH	OH	1,2-epoxyisopropyl	$C_{32}H_{48}O_7$	544.7
13a/b [b]	H	OMe	OH	–C(H,CH_3)–CHO	$C_{31}H_{48}O_6$	516.7
13c [a]	H	OMe	OH	–C(OH,CH_3)–CHO	$C_{31}H_{48}O_7$	532.7
14a/b [b]	H	OMe	OMe	–C(H,CH_3)–CHO	$C_{32}H_{50}O_6$	530.7
14c [a]	H	OMe	OMe	–C(OH,CH_3)–CHO	$C_{32}H_{50}O_7$	546.7

[a]) Configuration at C-20 not determined [b]) Mixture of C-20 epimers



15a,**b**, **16a**–**c**

Comp.	R^1	R^2	R^3	Formula	m.w.
15a	OMe	OH	isopropenyl	$C_{31}H_{46}O_4$	482.7
15b	OH	OH	isopropenyl	$C_{30}H_{44}O_4$	468.7
16a [a])	OMe	OH	–C(H,CH_3)–CHO	$C_{31}H_{46}O_5$	498.7
16b [a])	OMe	OH	–C(H,CH_3)–CHO	$C_{31}H_{46}O_5$	498.7
16c [a])	OMe	OH	–C(OH,CH_3)–CHO	$C_{31}H_{46}O_6$	514.7

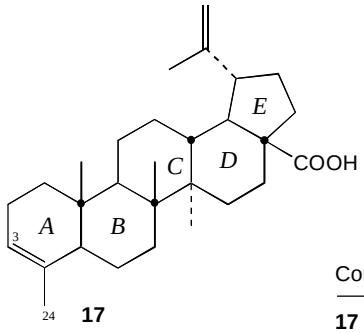
[a]) Configuration at C-20 not assigned

Modifications of Ring A

Starting from 23-methylester **2a**, a double bond was introduced at ring A *via* a tosylation–elimination sequence using *p*-TsCl and NaOAc. The obtained $\Delta^{2,20(29)}$ diolefin **15a** was hydrolyzed to give the free acid **15b**. The presence of the newly introduced Δ^2 double bond was revealed by the carbon spectra, which show two new olefinic methin carbons at δ 125.7 and 130.4 and a significant downfield shift of C-1 (δ 40.7).

Starting from the free diacid **1a**, the tosylation–elimination sequence interestingly yielded the 23-nor-$\Delta^{3,20(29)}$ diolefin **17** with decarboxylation of the 23-carboxy group. OsO_4-Hydroxylation of **17** afforded a mixture of 3α,4α-diol **18** and 3α,4α,20ξ,29-tetrol **19**, the latter one isolated as pure diastereomer. Oxidative diol cleavage of **18** with KIO_4 yielded the 3,4-*seco* compound **20**.

The 23-nor-3-ketone **21** was prepared by oxidation of **1a** with Jones reagent.

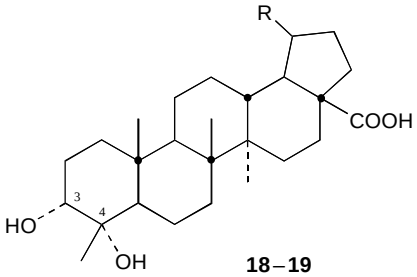


17

Comp.	Formula	m.w.
17	$C_{29}H_{44}O_2$	424.7

Synthesis of Amino Acid Conjugates and Further Nitrogen Containing Compounds

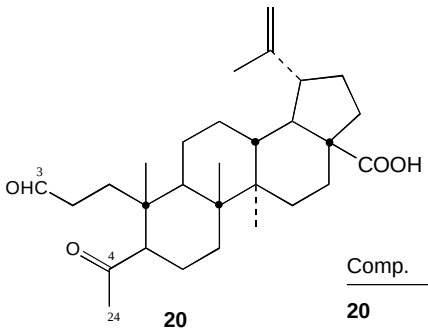
The diacids **4b**, **4c**, and **8a** were transformed to the diamino acid esters **5a** and **6a** (from **4b**), **7a** (from **4c**) and **9a**, **10**, and **11** (from **8a**) by activation of the carboxyl group with oxalyl chloride followed by reaction with amino acid ester hydrochlorides in the presence of triethylamine [9]. Hereby, the 20,29-dihydroxy functions in **4b** and **4c** were transformed to oxo-1,3-dioxolan side chains (compounds **5a**, **6a**, and **7a**) at C-19.



18–**19**

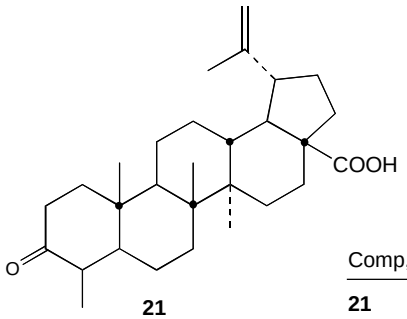
Comp.	R	Formula	m.w.
18	isopropenyl	$C_{29}H_{46}O_4$	458.7
19 [a])	1,2-dihydroxyisopropyl	$C_{29}H_{48}O_6$	492.7

[a]) Configuration at C-20 not assigned



20

Comp.	Formula	m.w.
20	$C_{29}H_{44}O_4$	456.7



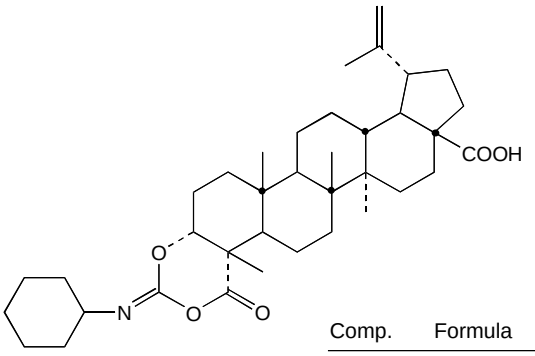
21

Comp,	Formula	m.w.
21	$C_{29}H_{44}O_3$	440.7

Because of the unprotected 3α-hydroxy group **4c** gave the 3-*O*-oxamoyl compound **7a** with three conjugated amino acids. Subsequent alkaline hydrolysis of the esters yielded the corresponding diamino acids **5b**, **6b**, **7b**, and **9b** with simultaneous regeneration of the 3α-hydroxy and the 20,29-dihydroxy functionalities. In the

case of the methyl esters of the diserin and diglutaminic acid conjugates **10** and **11**, their corresponding free acid conjugates could not be obtained pure, probably due to further intra- and intermolecular reactions.

Upon reaction of diacid **1a** with dicyclohexylcarbodiimide, the 28-carboxylic function remained untouched, leading to a mixture of cyclohexyl amide **3** and imino-oxo-1,3-dioxane **22**.



22

Comp.	Formula	m.w.
22	$C_{37}H_{55}NO_5$	593.8

The structures of all new compounds were confirmed by MS and NMR spectroscopy (^1H, ^{13}C, APT). The compounds are subjected to an extensive biological screening.

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Experimental

m.p. were measured with a Zeiss heating stage microscope (Boëtius) and are uncorrected. EI MS were recorded at 70 eV on a AMD 402 spectrometer. ESI MS were measured with a Finnigan TSQ 700 spectrometer. ^1H and ^{13}C NMR spectra were taken on a Varian Gemini 300 spectrometer (300/75 MHz). Chemical shifts are given in ppm (δ-scale), coupling constants (J) in Hz. ^1H-chemical shifts were referenced to TMS, ^{13}C-chemical shifts were referenced to $CDCl_3$ (77.0), CD_3OD (49.0) or C_5D_5N (123.5). IR-spectra were taken on a Bruker IFS28 spectrometer. Optical rotations were measured on a Jasco DIP 1000 Polarimeter, cell length 100 mm. Flash-chromatography was carried out on siliga gel 60, 40–63 µm (Merck) using a glass column equipment for normal pressure and 0.5 bar N_2.

OsO_4-Dihydroxylation of 1b and 17 (General Procedures)

A solution of 529 mg (1 mmol) 3α-acetoxy-20(29)-ene-23,28-dioic acid (**1b**), 176 mg (1.5 mmol) *N*-methylmorpholine-*N*-oxide and 20 mg (0.08 mmol) of OsO_4 in 20 ml acetone/H_2O (8:2) was stirred at *r.t.* for 48 h [10]. 10 mg (0.1 mmol) $NaHSO_3$ and 15 ml H_2O were added, the solution filtered and the filtrate neutralized with 1N H_2SO_4. After evaporation of the organic solvent under reduced pressure, the aqueous layer was extracted with EtOAc, dried with Na_2SO_4, and concentrated to dryness. The residue was chromatographed on silica gel with $CHCl_3$/EtOAc (95:5) and yielded the diastereomeric compounds **4a** (27%) and **4b** (48%). Analogously, **18** (30%) and **19** (15%) were prepared from **17**.

Oxidation of 4b, 4d, and 18 with KIO_4

A solution of **4b**, **4d** or **18** (1 mmol) and 690 mg (3 mmol) KIO_4 in 20 ml MeOH/H_2O (8:2) was stirred at *r.t.* for 20 h. The mixture was concentrated under reduced pressure and purified by flash chromatography (silica gel, $CHCl_3$/MeOH 95:5) to afford **8a** (96%), **8c** (94%) or **20** (90%), respectively.

Oxidation of 1b, 2a, 2b, and 15a with *m*-Chloroperbenzoic Acid

A solution of 529 mg (1 mmol, dissolved in Et_2O) **1b** and 432 mg (2.5 mmol) *m*-chloroperbenzoic acid in 10 ml CH_2Cl_2 was stirred at 25 °C for 24 h. The resulting reaction mixture was washed twice with H_2O, dried with Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (silica gel, *n*-hexane/EtOAc 75:25) afforded **12** (82%). Analogously, **13a**/**b** (50%) and **13c** (20%) were prepared from **2a**. **14a**/**b** (60%), and **14c** (20%) were obtained from **2b**. **15a** afforded **16a** (35%), **16b** (25%), and **16c** (15%).

Alkaline Hydrolysis of Compounds 4b, 8a, and 15a

Compound **4b**, **8a** or **15a** (1 mmol) was hydrolyzed with 5% KOH in MeOH (10 ml) by stirring at *r.t.* for 20 h. H_2O (30 ml) was added, the mixture acidified to pH 4 with HCl (5%) and extracted with EtOAc. The organic layer was washed with H_2O, dried with Na_2SO_4 and the solvent was evaporated under reduced pressure to afford **4c** (92%), **8b** (95%) or **15b** (90%).

Preparation of Methyl Esters 2a, 2b, and 4d

487 mg (1 mmol) of compound **1a** in MeOH (20 ml) were stirred for 1 h at 25 ºC with CH_2N_2 (1 mmol, dissolved in Et_2O). The solvent was removed under reduced pressure and the residue purified by flash chromatography (*n*-hexane/EtOAc 8:2) to yield **2a** (72%). Analogously, **2b** (98%) and **4d** (92%) were prepared from **1a** and **4c**, respectively, but using 4 mmol CH_2N_2.

Two-Step Tosylation/Elimination of 1a and 2a

To a solution of **1a** or **2a** (1 mmol) in pyridine (5 ml) 477 mg (2.5 mmol) *p*-toluenesulfonylchloride were added and the solution stirred for 24 h at *r.t.* After addition of H_2O (15 ml) a white solid precipitated, which was filtered off and used in the next step without purification. It was dissolved in DMF (30 ml), NaOAc was added and the mixture heated at 120 °C for 6 h. After evaporation of the solvent, the residue was treated with H_2O (20 ml) and extracted with EtOAc. The organic layer was dried with Na_2SO_4, filtered and concentrated under

reduced pressure. The product was chromatographed on silica gel (*n*-hexane/EtOAc 8:2) to give **17** (92%) or **15a** (82%).

Jones Oxidation of 1a

487 mg (1 mmol) of **1a** in acetone (20 ml) were stirred with 1 ml Jones reagent (2.8 g $K_2Cr_2O_7$ in 2.3 ml conc. H_2SO_4 and 10 ml H_2O) in an ice bath for 1 minute and then for 30 minutes at *r.t.* After addition of ice, the mixture was extracted with $CHCl_3$. The organic layer was washed with H_2O and dilute $NaHCO_3$ solution, dried with $NaSO_4$ and concentrated. The residue was purified by flash chromatography (*n*-hexane/EtOAc 7:3) to afford 21 (76%).

Preparation of the Amino Acid Conjugates 5a, 5b, 6a, 6b, 7a, 7b, 9a, 9b, 10, and 11

A solution of 563 mg (1 mmol) of **4b** and 1.02 g oxalyl chloride (8 mmol) in benzene (20 ml) was stirred at *r.t.* for 24 h and concentrated under reduced pressure. A solution of the residue, amino acid methyl or ethylester hydrochloride (5 mmol) and 1.01 g (10 mmol) triethylamine in CH_2Cl_2 (30 ml) was stirred at *r.t.* for 20 h. The resulting reaction mixture was washed twice with H_2O, dried with Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (silica gel, *n*-hexane/EtOAc) furnished the ester derivatives **5a** (86%) and **6a** (90%). The esters were hydrolyzed (same procedure as described for hydrolysis of **4b**) to give **5b** (88%) and **6b** (90%).

Analogously, **7a** (68%) and **7b** (86%) were prepared from **4c**. **9a** (96%), **9b** (94%), **10** (98%), and **11** (87%) were prepared from **8a**.

Reaction of 1a with Dicyclohexylcarbodiimide

A solution of 487 mg (1 mmol) of **1a** in tetrahydrofuran (50 ml) was cooled to –5 °C. Then a concentrated solution of 206 mg (1 mmol) dicyclohexylcarbodiimide was added. After 10 h at –5 °C and 15 h at *r.t.*, CH_2Cl_2 (20 ml) was added and the solution washed with 5% HCl, 5% $NaHCO_3$ and H_2O and dried with Na_2SO_4. The solvent was evaporated under reduced pressure and the residue chromatographed on silica gel with $CHCl_3$/EtOAc to afford **3** (18%) and **22** (30%).

Physical Data of the Compounds Prepared [11, 12]

3α-Hydroxy-lup-20(29)-ene-23,28-dioic acid 23-methyl ester (**2a**)

m.p. 125–126 °C (Me_2CO/*n*-hexane). – $[\alpha]_D^{24}$ –1.6 ($CHCl_3$, c = 1.0). – ^{1}H NMR ($CDCl_3$): δ/ppm = 3.75 (br s, H-3), 3.70 (s, OMe), 1.16 (s, H_3-24). – ^{13}C NMR (CD_3OD): δ/ppm = 180.1 (C-28), 178.7 (C-23), 74.2 (C-3), 57.5 (C-17), 52.0 (OMe), 48.5 (C-19), 45.2 (C-5), 22.5 (C-6). – EIMS: *m/z* (%) = 500 $[M]^+$ (22), 482 (8), 468 (8), 454 (14), 248 (37), 233 (79), 201 (55), 187 (80), 173 (99), 119 (100), 107 (81), 95 (77).

3α-Hydroxy-lup-20(29)-ene-23,28-dioic acid dimethyl ester (**2b**)

m.p. 83–84 °C (Me_2CO/*n*-hexane). – $[\alpha]_D^{24}$ –4.0 ($CHCl_3$, c = 1.0). – ^{1}H NMR ($CDCl_3$): δ/ppm = 4.70 (m, *J* = 2.2 Hz, H-29^B), 4.60 (q, *J* = 1.3 Hz, H-29^A), 3.73 (br s, H-3), 3.70, 3.66 (each s, OMe), 3.00 (m, H-19), 1.16 (s, H_3-24). – ^{13}C NMR ($CDCl_3$): δ/ppm = 178.1 (C-23), 176.6 (C-28), 72.4 (C-3), 56.6 (C-17), 51.8, 51.1 (OMe) 24.9 (C-2). – EIMS: *m/z* (%) = 514 $[M]^+$ (56), 496 (10), 482 (11), 454 (26), 264 (75), 249 (77), 233 (59), 203 (57), 189 (100), 175 (66), 107 (53), 93 (51), 81 (49).

3α-Hydroxy-lup-20(29)-ene-23,28-dioic acid 23-cyclohexylamide (**3**)

m.p. 186–187 °C (Me_2CO/*n*-hexane). – $[\alpha]_D^{24}$ +16.6 ($CHCl_3$, c = 1.0). – ^{1}H NMR ($CDCl_3$): δ/ppm = 3.79 (m, CHN), 3.64 (br s, H-3), 4.74 (d, *J* = 1.7 Hz, H-29^B), 4.61 (br s, H-29^A), 3.01 (td, *J* = 10.4 and 4.1 Hz, H-19), 1.69 (s, H_3-30), 1.13 (s, H_3-24). – ^{13}C NMR ($CDCl_3$): δ/ppm = 181.7 (C-28), 177.8 (C-23), 71.8 (C-3), 56.3 (C-17), 46.9 (C-19), 48.5, 32.5, 32.1, 24.9, 24.7 (cyclohexyl), 19.2 (C-30). – EIMS: *m/z* (%) = 567 $[M]^+$ (38), 549 (31), 534 (15), 424 (25), 259 (16), 194 (100), 155 (52).

3α-Acetoxy-20ξ,29-dihydroxylupane-23,28-dioic acid (**4a**)

m.p. 206–208 °C (MeOH/$CHCl_3$). – $[\alpha]_D^{24}$ –36.5 (MeOH, c = 2.0). – IR: *v*/cm^{-1} (KBr) = 3 446 (m, br), 2 947 (s), 2 872 (w), 1 718 (s), 1 457 (m), 1 378 (m), 1 260 (s), 1 025 (m) 988 (w). – ^{1}H NMR (CD_3OD): δ/ppm = 4.92 (br s, H-3), 3.45 (d, *J* = 11.0 Hz, H-29^B), 3.36 (d, *J* = 11.0 Hz, H-29^A), 1.04 (s, H_3-30). – ^{13}C NMR (CD_3OD): δ/ppm = 180.4 (C-28), 179.0 (C-23), 77.0 (C-3), 76.1 (C-20), 71.1 (C-29), 59.5 (C-17), 45.6 (C-19), 23.3 (C-2), 19.5 (C-30). – Negative ESI MS: *m/z* (%) = 561.6 (100) $[M–H]^-$.

C-20 Epimer **4b**

m.p. 197–198 °C (MeOH/$CHCl_3$). – $[\alpha]_D^{24}$ –7.1 (MeOH, c = 2.0). – IR: *v*/cm^{-1} (KBr) = 3 446 (m, br), 2 947 (s), 2 878 (w), 1 718 (s), 1 457 (m), 1 378 (m), 1 259 (s), 1 027 (m), 989 (w). – ^{1}H NMR (CD_3OD): δ/ppm = 3.41 (s, H_2-29), 1.15 (s, H_3-30). (H-3 hidden under HDO at δ 4.92). – ^{13}C NMR (CD_3OD): δ/ppm = 180.6 (C-28), 179.0 (C-23), 76.1 (C-20), 69.5 (C-29), 60.1 (C-17), 46.6 (C-19), 24.8 (C-30), 23.3 (C-2). – Negative ESI MS: *m/z* (%) = 561.5 (100) $[M–H]^-$.

3α, 20ξ,29-Trihydroxylupane-23,28-dioic acid (**4c**)

m.p. 234–235 °C (MeOH). – $[\alpha]_D^{24}$ +6.5 (MeOH, c = 1.0). – ^{1}H NMR (CD_3OD): δ/ppm = 3.72 (br s, H-3), 3.41 (s, H_2-29), 1.15 (s, H_3-24, H_3-30). – Negative ESI-MS: *m/z* (%) = 519.4 $[M–H]^-$ (100).

3α,20ξ,29-Trihydroxylupane-23,28-dioic acid 23,28-dimethyl ester (**4d**)

m.p. 130–131 °C (Me_2CO/*n*-hexane). – $[\alpha]_D^{24}$ +174.6 (MeOH, c = 0.5). – IR: *v*/cm^{-1} ($CHCl_3$) = 3 689 (m), 2 951 (m), 2 871 (w), 1 717 (s), 1 602 (m), 1 457 (m), 1 434 (m), 1 379 (w), 1 351 (w), 1 269 (m), 1 142 (w), 1 126 (w), 1 105 (w), 994 (w). – ^{1}H NMR ($CDCl_3$): δ/ppm = 3.75 (br s, H-3), 3.70 (s, OMe), 3.66 (s, OMe), 3.61 (d, *J* = 10.9 Hz, H-29^B), 3.40 (d, *J* = 10.9 Hz, H-29^A), 1.19, 1.17, 1.01, 0.89, 0.87 (each s, CH_3). – ^{13}C NMR ($CDCl_3$): δ/ppm = 178.2 (C-28), 176.9 (C-23), 75.0 (C-20), 72.5 (C-3), 67.7 (C-29), 59.1 (C-17), 51.9, 51.3 (both OMe), 24.9 (C-2), 24.5 (C-30). – Positive ESI MS:*m/z* (%) = 571.5 $[M+Na]^+$ (11), 531.4 $[M+H–H_2O]^+$ (53), 513.4 (73), 471.4 (56), 453.4 (100).

Dioxolan derivative **5a**

m.p. 120–121 °C (Me_2CO/*n*-hexane). – $[\alpha]_D^{24}$ –18.9 (MeOH, c = 2.0). – IR: *v*/cm^{-1} ($CHCl_3$) = 3 693 (w), 3 438 (w), 2 954

(s), 2 870 (w), 1 795 (s), 1 734 (s), 1 661 (s), 1 500 (s), 1 438 (m), 1 374 (m), 1 301 (w), 1 109 (w), 1 070 (m), 1 023 (w), 994 (w). – ^{1}H NMR ($CDCl_3$): δ/ppm = 4.86 (br s, H-3), 4.30 (d, J = 8.8 Hz, H-29^B), 4.12 (d, J = 8.5 Hz, H-29^A), 2.77 (td, H-19), 2.08 (s, CO–C$\underline{H}_3$), 1.52 (s, H_3-30). – ^{13}C NMR ($CDCl_3$): δ/ppm = 175.6, 174.6 (C-23, C-28), 154.5 (O–$\underline{C}$O–O), 85.9 (C-20), 75.0 (C-3), 72.1 (C-29), 57.6 (C-17), 45.8 (C-19), 26.7 (C-30). – EIMS: *m/z* (%) = 878 $[M]^+$ (7), 818 (16), 744 (24), 628 (69).

3α,20ξ,29-Trihydroxylupane-23,28-dioic acid 23,28-dimethionin amide (**5b**)

m.p. 165–166 °C (EtOAc). – $[\alpha]_D^{24}$ –54.1 (MeOH, c = 1.0). – IR: ν/cm^{-1} (KBr) = 3 420 (m, br), 2 941 (s), 2 870 (w), 1 734 (s), 1 636 (s), 1 507 (s), 1 448 (m), 1 387 (w), 1 203 (m, br), 1 042 (w), 960 (w). – ^{1}H NMR (CD_3OD): δ/ppm = 3.74 (br s, H-3), 3.40 (s, H_2-29), 1.154, 1.145 (each s, H_3-24, H_3-30). – ^{13}C NMR (CD_3OD): δ/ppm = 175.9, 175.8 (C-23, C-28), 76.1 (C-20), 73.6 (C-3), 69.6 (C-29), 59.6 (C-17), 46.4 (C-19), 28.7 (C-15), 24.7 (C-30). – Positive ESI MS: *m/z* (%) = 783 $[M+H]^+$ (100), 381 (14).

Dioxolan Derivative **6a**

m.p. 110–112 °C (Me_2CO/*n*-hexane). – $[\alpha]_D^{24}$ +76.9 (MeOH, c = 2.0). – IR: ν/cm^{-1} ($CHCl_3$) = 3 447 (m), 2 951 (m), 2 868 (w), 1 795 (s), 1 733 (s), 1 662 (s), 1 497 (s), 1 374 (m), 1 246 (m), 1 109 (m), 1 069 (m), 1 024 (w). – ^{1}H NMR ($CDCl_3$): δ/ppm = 4.79 (br s, H-3), 4.26 (*d*, J = 8.6 Hz, H-29^B), 4.10 (d, J = 8.8 Hz, H-29^A), 2.72 (t, J = 8.8 Hz, H-19), 1.88 (s, CO–C$\underline{H}_3$), 1.50 (s, H_3-30), 1.13, 0.94, 0.86, 0.69 (each s, 3H, CH_3). – ^{13}C NMR ($CDCl_3$): δ/ppm = 175.3, 174.5 (C-23, C-28), 154.6 (O–$\underline{C}$O–O), 86.0 (C-20), 75.3 (C-3), 72.1 (C-29), 57.5 (C-17), 46.0 (C-19), 29.0, 27.9 (C-21, C-15), 26.8 (C-30). – Positive ESI MS: *m/z* (%) = 961.8 $[M+Na]^+$ (70), 941.0 (55), 880.6 (100).

3α,20ξ,29-Trihydroxylupane-23,28-dioic acid 23,28-di(phenylalanin)amide (**6b**)

m.p. 168–169 °C (EtOAc/*n*-hexane). – $[\alpha]_D^{24}$ +169.5 (MeOH, c 1.0). – IR: ν/cm^{-1} (KBr) = 3 434 (s), 2 938 (s), 2 870 (w), 1 734 (s), 1 636 (s), 1 507 (s), 1 456 (m), 1 387 (m), 1 207 (m, br), 1 032 (m), 919 (w), 737 (w), 701 (m). – ^{1}H NMR (CD_3OD): δ/ppm = 3.65 (br s, H-3), 3.35 (s, H_2-29), 2.38 (t, H-19), 1.10, 1.05, 0.91, 0.81, 0.41 (each s, CH_3). – ^{13}C NMR (CD_3OD): δ/ppm = 175.5, 175.2 (C-23, C-28), 76.1 (C-20), 73.5 (C-3), 69.5 (C-29), 59.4 (C-17), 46.3 (C-19), 24.6 (C-30). – Positive ESI MS: *m/z* (%) = 854 $[M+K]^+$ (20), 815 $[M+H]^+$ (100).

3-O-Oxamoyl Derivative **7a**

m.p. 128–130 °C (Me_2CO/*n*-hexane). – $[\alpha]_D^{24}$ –46.4 (MeOH, c = 0.5). – IR: ν/cm^{-1} ($CHCl_3$) = 3 674 (w), 3 437 (m), 3 408 (w), 2 954 (s), 2 872 (m), 1 795 (s), 1 742 (s), 1 706 (s), 1 654 (s), 1 506 (s), 1 452 (s), 1 378 (m), 1 342 (m), 1 279 (m), 1 069 (m), 984 (m). – ^{1}H NMR ($CDCl_3$): δ/ppm = 4.87 (br s, H-3), 4.28 (d, J = 8.8 Hz, H-29^B), 4.11 (d, J = 8.3 Hz, H-29^A), 2.77 (tm, J = 8.9 Hz, H-19), 1.50 (s, H_3-30). – ^{13}C NMR ($CDCl_3$): δ/ppm = 175.1, 174.1 (C-23, C-28), 158.3, 156.2 (O–$\underline{C}$O–$\underline{C}$O) 154.5 (O–$\underline{C}$O–O), 86.1 (C-20), 78.0 (C-3), 72.5 (C-29), 57.4 (C-17), 46.5 (C-19), 26.4 (C-30). – Positive ESI MS: *m/z* (%) = 897.5 $[M+Na+H]^+$ (32), 874.6 $[M+H]^+$ (100), 699.5 (61).

3α,20ξ,29-Trihydroxylupane-23,28-dioic acid 23,28-dialanin amide (**7b**)

m.p. 195–196 °C (EtOAc/*n*-hexane). – $[\alpha]_D^{24}$ –45.9 (MeOH, c = 0.5). – ^{1}H NMR (CD_3OD): δ/ppm = 3.76 (br s, H-3), 3.40 (*s*, H_2-29), 2.58 (*t*, J = 11.7 Hz, H-19), 1.15 (*s*, H_3-30). – ^{13}C NMR (CD_3OD): δ/ppm = 176.9, 176.5 (C-23, C-28), 76.1 (C-20), 73.8 (C-3), 69.6 (C-29), 59.4 (C-17), 46.4 (C-19), 24.7 (C-30). – Positive ESI MS: *m/z* (%) = 663.6 $[M+H]^+$ (100), 645.5 (33), 554.7 (64).

3α-Acetoxy-20-oxo-29-norlupane-23,28-dioic acid (**8a**)

m.p. 155–157 °C (EtOAc). – $[\alpha]_D^{24}$ +61.8 (MeOH, c = 1.0). – IR: ν/cm^{-1} ($CHCl_3$) = 3 674 (w), 3 511 (w), 2 950 (s), 2 869 (m), 1 733 (s), 1 700 (s), 1 602 (w), 1 452 (m), 1 375 (m), 1 357 (m), 1 248 (s), 1 172 (m), 1 130 (w), 1 027 (m), 990 (w). – ^{1}H NMR ($CDCl_3$): δ/ppm = 4.95 (br s, H-3), 3.23 (td, J = 10.7 and 4.4 Hz, H-19), 2.19 (s, H_3-30). – ^{13}C NMR ($CDCl_3$): δ/ppm = 212.2 (C-20), 182.7 (C-28), 181.7 (C-23), 75.3 (C-3), 56.3 (C-17), 30.0 (C-30). – EIMS: *m/z* (%) = 530 $[M]^+$ (35), 512 (16), 484 (20), 470 (46), 452 (84), 426 (100), 383 (54), 261 (53), 219 (88), 189 (69), 175 (74).

3α-Hydroxy-20-oxo-29-norlupane-23,28-dioic acid (**8b**)

m.p. 231–232 °C (EtOAc). – $[\alpha]_D^{24}$ –38.6 (MeOH, c = 1.0). – ^{1}H NMR (CD_3OD): δ/ppm = 3.71 (br s, H-3), 3.27 (dt, H-19), 2.18 (s, H_3-30). – ^{13}C NMR (CD_3OD): δ/ppm = 215.5 (C-20), 180.5 (C-23), 179.6 (C-28), 73.8 (C-3), 57.3 (C-17), 50.6 (C-19), 29.8 (C-30). – EIMS: *m/z* (%) = 488 $[M]^+$ (14), 470 (21), 452 (18), 442 (44), 426 (78), 424 (45), 383 (31), 261 (70), 219 (51), 175 (100), 147 (58).

3α-Hydroxylupane-20-oxo-29-norlupane-23,28-dioic acid 23,28-dimethyl ester (**8c**)

m.p. 133–134 °C (Me_2CO/*n*-hexane). – $[\alpha]_D^{24}$ +97.2 (MeOH, c = 0.5). – ^{1}H NMR ($CDCl_3$): δ/ppm = 3.74 (br s, H-3), 3.70 (s, OMe), 3.67 (s, OMe), 3.25 (td, J = 11.2 and 4.1 Hz, H-19), 2.25 (m, 1H), 2.18 (s, H_3-30), 1.16 (s, H_3-24). – ^{13}C NMR ($CDCl_3$): δ/ppm = 212.3 (C-20), 178.1 (C-23), 176.5 (C-28), 72.5 (C-3), 56.4 (C-17), 51.4, 51.3 (both OMe), 49.4 (C-19), 30.0 (C-30). – EIMS: *m/z* (%) = 516 $[M]^+$ (100), 498 (36), 484 (33), 466 (63), 456 (32), 438 (34), 275 (29), 233 (73), 189 (42), 147 (36), 57 (41).

3α-Acetoxy-20-oxo-29-norlupane-23,28-dioic acid 23,28-di(alanin methyl ester)amide (**9a**)

m.p. 139–141 °C (Me_2CO/*n*-hexane). – $[\alpha]_D^{24}$ –55.0 ($CHCl_3$, c = 2.0). – IR: ν/cm^{-1} ($CHCl_3$) = 3 691 (w), 3 446 (m), 2 953 (s), 2 868 (m), 1 735 (s), 1 706 (w), 1 656 (m), 1 602 (w), 1 502 (m), 1 450 (m), 1 374 (w), 1 250–1 233 (m), 1 172 (w), 985 (w). – ^{1}H NMR ($CDCl_3$): δ/ppm = 4.84 (br s, H-3), 3.41 (td, J = 11.1 and 4.0 Hz, H-19), 2.17 (s, H_3-30). – ^{13}C NMR ($CDCl_3$): δ/ppm = 212.7 (C-20), 175.7, 174.1 (C-23, C-28), 75.0 (C-3), 55.4 (C-17), 49.8 (C-19), 30.2 (C-30). – Positive ESI MS: *m/z* (%) = 723.6 $[M+Na]^+$ (33), 641.6 $[M+H-CH_3COOH]^+$ (100), 510.4 (44).

3α-Hydroxy-20-oxo-29-norlupane 23,28-dioic acid 23,28-dialanin amide (**9b**)

m.p. 210–212 °C (EtOAc/*n*-hexane). – $[\alpha]_D^{24}$ +21.8 (MeOH, c = 2.0). – IR: ν/cm^{-1} (KBr) = 3 420 (m, br), 2 944 (s), 2 869 (w), 1 734 (s), 1 636 (s), 1 521 (s), 1 457 (m), 1 379 (w), 1 201 (m), 1066 (w). – ^{1}H NMR (CD_3OD): δ/ppm = 3.75 (br s, H-

3), 2.16 (s, H_3-30). – ^{13}C NMR (CD_3OD): δ/ppm = 215.9 (C-20), 179.6, 178.8 (C-23, C-28), 73.7 (C-3), 56.7 (C-17), 49.2 (C-19), 29.8 (C-30). – Positive ESI MS: *m/z* (%) = 653 $[M+Na]^+$ (12), 631 $[M+H]^+$ (100).

3α-Acetoxy-20-oxo-29-norlupane-23,28-dioic acid 23,28-di (serin methyl ester)amide (**10**)

m.p. 138–139 °C (Me_2CO/*n*-hexane). – $[\alpha]_D^{24}$ –77.4 (MeOH, c = 2.0). – IR: *ν*/cm^{-1} ($CHCl_3$) = 3 691 (w), 3 442 (w), 2 955 (m), 2 870 (w), 1 735 (s), 1 706 (w), 1 659 (m), 1 602 (w), 1 501 (m), 1 438 (m), 1 375 (m), 1 356 (m), 1 240 (s). – ^{1}H NMR ($CDCl_3$): δ/ppm = 4.86 (br s, H-3), 3.37 (td, *J* = 11.0 and 3.9 Hz, H-19), 2.17 (s, H_3-30), 2.08 (s, CO–C$\underline{H}_3$). – ^{13}C NMR ($CDCl_3$): δ/ppm = 213.0 (C-20), 176.6, 175.3 (C-23, C-28), 74.8 (C-3), 55.6 (C-17), 49.7 (C-19), 30.1 (C-30). – EIMS: *m/z* (%) = 732 $[M]^+$ (7), 714 (10), 672 (61), 654 (20), 526 (40), 201 (39), 120 (32), 57 (100).

3α-Acetoxy-20-oxo-29-norlupane-23,28-dioic acid 23,28-di (glutaminic acid dimethyl ester) amide (**11**)

m.p. 124–125 °C (Me_2CO/*n*-hexane). – $[\alpha]_D^{24}$ –42.4 ($CHCl_3$, c = 1.0). – IR: *ν*/cm^{-1} ($CHCl_3$) = 3 687 (w), 3 436 (w), 2 953 (m), 2 868 (w), 1 743 (s), 1 661 (m), 1 602 (w), 1 502 (m), 1 438 (m), 1 373 (w), 1 356 (m), 1 245 (m), 1 173 (m), 1 023 (w), 990 (w). – ^{1}H NMR ($CDCl_3$): δ/ppm = 4.84 (br s, H-3), 3.38 (td, *J* = 10.9 and 3.6 Hz, H-19), 2.16 (s, H_3-30), 2.03 (s, CO–C$\underline{H}_3$). – ^{13}C NMR ($CDCl_3$): δ/ppm = 212.7 (C-20), 176.4, 174.9 (C-23, C-28), 75.2 (C-3), 55.6 (C-17), 49.6 (C-19), 30.2 (C-30). – Positive ESI MS: *m/z* (%) = 867 $[M+Na]^+$ (26), 845 $[M+H]^+$ (100), 785 (52).

3α-Acetoxy-20ξ,29-epoxylupane-23,28-dioic acid (**12**)

m.p. 180–182 °C ($CHCl_3$). – $[\alpha]_D^{24}$ –29.2 ($CHCl_3$, c = 1.0). – IR: *ν*/cm^{-1} ($CHCl_3$) = 2 693 (w), 3 510 (m), 2 951 (s), 2 871 (m), 1 733 (s), 1 700 (s), 1 602 (w), 1 453 (m), 1 376 (m), 1 249 (s), 1 129 (w), 1 105 (w), 1 023 (w), 986 (w), 941 (w). – ^{1}H NMR ($CDCl_3$): δ/ppm = 4.95 (br s, H-3), 2.65 (br s, H_2-29), 1.24, 1.25 (each s, H_3-24, H_3-30). – ^{13}C NMR ($CDCl_3$): δ/ppm =182.4 (C-28), 181.6 (C-23), 77.2 (C-20), 75.4 (C-3), 60.2 (C-29), 56.6 (C-17), 45.3 (C-19), 26.9 (C-21), 18.2 (C-30). – Positive ESI MS: *m/z* (%) = 583 $[M+K]^+$ (31), 567 $[M+Na]^+$ (49), 562 $[M+NH_4]^+$ (100), 545 $[M+H]^+$ (18), 526 (12), 439 (18).

3α-Hydroxy-29-oxolupane-23,28-dioic acid 23-methyl ester (C-20 epimers **13a**/**b***)*

Solid. – $[\alpha]_D^{24}$ –13.4 ($CHCl_3$, c = 0.65). – ^{1}H NMR ($CDCl_3$): δ/ppm = 9.85 (d, *J* = 1.7 Hz, H-29)/9.64 (s, H-29), 3.76 (brs, H-3), 3.71 (s, OMe), 1.12 (d, *J* = 6.9 Hz, H_3-30)/1.02 (d, *J* = 6.9 Hz, H_3-30). – ^{13}C NMR ($CDCl_3$): δ/ppm = 206.7/204.7 (C-29), 181.6/181.5 (C-28), 178.2 (C-23), 72.5 (C-3), 24.9 (C-2), 56.6/56.3 (C-17), 52.0 (OMe), 49.2/48.1 (C-19), 42.6/42.7 (C-14), 42.4/36.9 (C-20), 27.3/24.3 (C-21), 14.4/6.8 (C-30). – EIMS: *m/z* (%) = 516 $[M]^+$ (11), 498 (6), 486 (14), 459 (14), 436 (16), 414 (27), 233 (100), 173 (88), 147 (64), 133 (64), 121 (84), 107 (81), 81 (82).

3α,20ξ-Dihydroxy-29-oxolupane-23,28-dioic acid 23-methyl ester (**13c**)

m.p. 230–232 °C (Me_2CO/*n*-hexane). – $[\alpha]_D^{24}$ –3.8 ($CHCl_3$, c = 1.0). – ^{1}H NMR ($CDCl_3$): δ/ppm = 9.53 (s, H-29), 3.75 (br s, H-3), 3.71 (s, OMe), 2.45 (t, *J* = 9.2 Hz, H-19), 1.27 (s, H_3-30). 1.16 (s, H_3-24). – ^{13}C NMR ($CDCl_3$): δ/ppm =204.3 (C-29), 182.0 (C-28), 178.1 (C-23), 80.0 (C-20), 72.5 (C-3), 58.8 (C-17), 45.0 (C-19), 24.9 (C-2), 22.5 (C-30). – EIMS: *m/z* (%) = 532 $[M]^+$ (17), 514 (6), 503 (18), 487 (100), 460 (16), 409 (16), 381 (19), 233 (63), 173 (55), 147 (75), 121 (68), 95 (64), 81 (68). – HRMS: 532.3382 $[M]^+$ ($C_{31}H_{48}O_7$ requires 532.3400).

3α-Hydroxy-29-oxolupane-23,28-dioic acid dimethyl ester (C-20 epimers **14a**/**b***)*

Solid. – $[\alpha]_D^{24}$ –10.7 ($CHCl_3$, c = 0.85). – ^{1}H NMR ($CDCl_3$): δ/ppm = 9.85 (d, *J* = 1.7 Hz, H-29)/9.64 (s, H-29), 3.75 (br s, H-3), 3.704/3.665 (each s, OMe), 3.689/3.669 (each s, OMe), 2.98 (m, H-19), 1.00/1.11 (each d, *J* = 6.8 Hz, H_3-30). 1.17 (*s*, H_3-24). – ^{13}C NMR ($CDCl_3$): δ/ppm = 206.8/204.7 (C-29), 178.12/178.08 (C-23), 176.47/176.42 (C-28), 72.4 (C-3), 56.75/56.53 (C-17), 51.9 (OMe), 51.32/51.27 (OMe), 42.46/36.87 (C-20), 49.96/49.89 (C-18), 49.2/48.2 (C-19), 24.9 (C-2), 14.4/6.7 (C-30). – EIMS: *m/z* (%) = 530 $[M]^+$ (8), 500 (37), 473 (16), 440 (14), 264 (42), 251 (32), 233 (100), 189 (52), 175 (61), 161 (68), 119 (79), 105 (61), 81 (63).

3α,20ξ-Dihydroxy-29-oxolupane-23,28-dioic acid dimethyl ester (**14c**)

m.p. 116–117 °C (Me_2CO/*n*-hexane). – $[\alpha]_D^{24}$ +62.6 ($CHCl_3$, c = 0.3). – ^{1}H NMR ($CDCl_3$): δ/ppm = 9.53 (*s*, H-29), 3.75 (t, *J* = 2.8 Hz, H-3), 3.70, 3.66 (each s, OMe), 2.47 (t, *J* = 8.5 Hz, H-19), 1.27 (s, H_3-30). 1.17 (s, H_3-24). – ^{13}C NMR ($CDCl_3$): δ/ppm = 204.4 (C-29), 178.1 (C-23), 176.7 (C-28), 80.0 (C-20), 72.5 (C-3), 51.9, 51.4 (both OMe), 24.9 (C-2), 22.4 (C-30). – EIMS: *m/z* (%) = 546 $[M]^+$ (9), 528 (6), 517 (24), 501 (91), 473 (34), 423 (16), 329 (15), 233 (40), 175 (32), 161 (48), 147 (56), 119 (38), 83 (100).

Lup-2,20(29)-diene-23,28-dioic acid 23-methyl ester (**15a**)

m.p. 238–240 °C (MeOH). – $[\alpha]_D^{24}$ +28.6 ($CHCl_3$, c = 1.0). – IR: *ν*/cm^{-1} ($CHCl_3$) = 2 950 (s), 2 871 (w), 1 717 (s), 1 697 (m), 1 646 (w), 1 602 (w), 1 457 (m), 1 435 (m), 1 377 (m), 1 146 (w), 1 103 (m), 1 084 (m), 891 (m). – ^{1}H NMR ($CDCl_3$): δ/ppm = 5.64 (ddd, *J* = 9.9, 6.1 and 1.6 Hz, H-2), 5.49 (dd, *J* = 9.9 and 2.2 Hz, H-3), 1.20 (s, H_3-24). – ^{13}C NMR ($CDCl_3$): δ/ppm = 182.7 (C-28), 177.6 (C-23), 130.4 (C-3), 125.7 (C-2), 56.4 (C-17), 40.7 (C-1), 18.1 (C-24). – EIMS: *m/z* (%) = 482 $[M]^+$ (34), 467 (8), 456 (11), 436 (16), 423 (34), 377 (20), 248 (40), 246 (39), 233 (39), 203 (27), 189 (86), 119 (100), 105 (54). – HRMS: 482.3400 $[M]^+$ ($C_{31}H_{46}O_4$ requires 482.3396).

Lup-2,20(29)-diene-23,28-dioic acid (**15b**)

m.p. 290–292 °C (EtOAc). – $[\alpha]_D^{24}$ –22.9 (MeOH, c = 1.0). – ^{1}H NMR (pyridine-d_5): δ/ppm = 5.92 (dd, *J* = 10.0 and 2.1 Hz, H-3), 5.75 (ddd, *J* = 10.4 and 4.5 Hz, H-2), 3.54 (td, *J* = 10.7 and 4.2 Hz, H-19), 2.76 (td, 1H, *J* = 11.8 and 3.0 Hz), 2.59 (dm, 1H, *J* = 12.9 Hz), 2.49 (dm, 1H, *J* = 8.3 Hz), 1.78 (*s*, H_3-30), 1.48 (*s*, H_3-24). – ^{13}C NMR (pyridine-d_5): δ/ppm = 179.4, 178.9 (C-28, C-23), 132.3 (C-3), 125.3 (C-2), 56.6 (C-17), 48.5 (C-4), 41.3 (C-1), 18.2 (C-24). – EIMS: *m/z* (%) = 468 $[M]^+$ (6), 440 (11), 422 (14), 248 (24), 235 (30), 203 (33), 189 (68), 173 (42), 105 (44), 97 (53), 81 (56) 69 (65), 57 (100).

[20ξ]-29-Oxo-lup-2-ene-23,28-dioic acid 23-methyl ester (**16a**)

m.p. 194–196 °C ($CHCl_3$/*n*-hexane). – $[\alpha]_D^{24}$ –43.5 ($CHCl_3$, c = 1.0). – IR: *v*/cm^{-1} ($CHCl_3$) = 2 950 (s), 2 872 (m), 1 716 (s), 1 700 (m), 1 602 (w), 1 456 (m), 1 435 (m), 1 378 (m), 1 146 (m), 1 102 (m), 1 083 (m), 997 (w). – ^{1}H NMR ($CDCl_3$): δ/ppm = 9.84 (d, *J* = 1.9 Hz, H-29), 5.65 (ddd, *J* = 9.9, 4.3 and 1.4 Hz, H-2), 5.51 (dd, *J* = 10.2 and 2.2 Hz, H-3), 3.67 (s, OMe), 2.57 (qm, *J* = 7.1 and 2.3 Hz, H-20), 2.45 (m, H-19), 1.20 (*s*, H_3-24), 1.13 (d, *J* = 7.2 Hz, H_3-30). – ^{13}C NMR ($CDCl_3$): δ/ppm = 206.8 (C-29), 182.1 (C-28), 177.5 (C-23), 130.5 (C-3), 125.5 (C-2), 56.6 (C-17), 52.2 (OMe), 48.8 (C-19), 48.2 (C-4), 42.4 (C-20), 40.7 (C-1), 27.4 (C-21), 18.1 (C-24), 14.4 (C-30). – EIMS: *m/z* (%) = 498 $[M]^+$ (4), 485 (9), 469 (23), 442 (17), 233 (24), 219 (37), 189 (42), 173 (84), 161 (52), 147 (74), 133 (71), 119 (100), 105 (89), 93 (87), 67 (73), 55 (96).

C-20 Epimer **16b**

m.p. 197–198 °C ($CHCl_3$/*n*-hexane). – $[\alpha]_D^{24}$ +39.1 ($CHCl_3$, c = 1.0). – IR: *v*/cm^{-1} ($CHCl_3$) = 2 950 (s), 2 870 (m), 1 717 (s), 1 700 (m), 1 602 (w), 1 453 (m), 1 434 (w), 1 378 (m), 1 146 (w), 1 103 (w), 1 083 (w), 997 (w). – ^{1}H NMR ($CDCl_3$): δ/ppm = 9.65 (s, H-29), 5.65 (ddd, *J* = 10.5, 4.8 and 1.4 Hz, H-2), 5.51 (dd, *J* = 10.2 and 2.2 Hz, H-3), 3.67 (s, OMe), 2.99 (tm, *J* = 10.7 Hz, H-19), 2.65 (qd, *J* = 6.8 and 2.9 Hz, H-20), 1.21 (s, H_3-24), 1.02 (d, *J* = 6.9 Hz, H_3-30). – ^{13}C NMR ($CDCl_3$): δ/ppm = 204.7 (C-29), 182.1 (C-28), 177.6 (C-23), 130.5 (C-3), 125.5 (C-2), 56.4 (C-17), 52.2 (OMe), 48.3 (C-4), 36.9 (C-20), 40.7 (C-1), 24.3 (C-21), 18.1 (C-24), 6.8 (C-30). – EIMS: *m/z* (%) = 498 $[M]^+$ (11), 439 (14), 396 (24), 233 (38), 187 (36), 173 (99), 148 (54), 133 (42), 119 (100), 105 (51), 95 (56).

20ξ-Hydroxy-29-oxo-lup-2-ene-23,28-dioic acid 23-methyl ester (**16c**)

m.p. 218–219 °C ($CHCl_3$/*n*-hexane). – $[\alpha]_D^{24}$ –14.6 ($CHCl_3$, c = 0.25). – IR: *v*/cm^{-1} ($CHCl_3$) = 3 691 (w), 3 510 (m), 2 951 (s), 2 872 (m), 1 718 (s), 1 602 (w), 1 454 (m), 1 435 (w), 1 378 (w), 1 146 (w), 1 104 (w), 1 083 (w), 831 (w). – ^{1}H NMR ($CDCl_3$): δ/ppm = 9.54 (s, H-29), 5.65 (dd, *J* = 9.9 and 4.7 Hz, H-2), 5.50 (dd, *J* = 10.2 and 2.2 Hz, H-3), 3.67 (s, OMe) 2.47 (t, *J* = 9.1 Hz, H-19), 1.19 (s, H_3-24), 1.28 (s, H_3-30). – ^{13}C NMR ($CDCl_3$): δ/ppm = 204.3 (C-29), 182.3 (C-28), 177.5 (C-23), 130.5 (C-3), 125.6 (C-2), 80.0 (C-20), 58.9 (C-17), 52.2 (OMe), 48.2 (C-4), 43.9 (C-19), 40.8 (C-1), 29.9 (C-21), 22.5 (C-30), 18.1 (C-24). – EIMS: *m/z* (%) = 514 $[M]^+$ (4), 485 (38), 469 (36), 395 (21), 231 (22), 173 (63), 147 (48), 119 (100), 105 (64), 95 (60), 81 (48).

23-Nor-lup-3,20(29)-dien-28-oic acid (**17**)

m.p. 208–210 °C (EtOAc). – $[\alpha]_D^{24}$ +37.7 (MeOH, c = 0.5). – ^{1}H NMR (pyridine-d_5): δ/ppm = 5.29 (*br s*, H-3), 3.54 (*td*, H-19), 1.80 (*s*, H_3-24), 1.65 (s, H_3-30), 1.09, 1.05, 0.73 (each *s*, Me). – ^{13}C NMR (pyridine-d_5): δ/ppm = 178.9 (C-28), 135.1 (C-4), 120.6 (C-3), 56.6 (C-17), 47.7 (C-19), 21.6 (C-24). – EIMS: *m/z* (%) = 424 $[M]^+$ (100), 409 (32), 369 (12), 259 (47), 248 (23), 201 (16), 189 (28), 175 (56). – HRMS: 424.3318 $[M]^+$ ($C_{29}H_{44}O_2$ requires 424.3341).

3α,4α-Dihydroxy-23-norlup-20(29)-en-28-oic acid (**18**)

m.p. 258–259 °C (EtOAc/*n*-hexane). – $[\alpha]_D^{24}$ +35.9 (MeOH, c = 1.0). – IR: *v*/cm^{-1} ($CHCl_3$) = 3 679 (w), 3 517 (w), 2 948 (s), 2 871 (m), 1 793 (w), 1 737 (w), 1 697 (s), 1 641 (w), 1 602 (w), 1 452 (m), 1 376 (m), 1 129 (m), 1 104 (m), 1 067 (w), 890 (m). – ^{1}H NMR ($CDCl_3$): δ/ppm = 3.56 (br s, H-3), 3.01 (m, H-19), 1.69 (s, H_3-30), 1.11 (s, H_3-24), 1.00, 0.94, 0.80 (each s, Me). – ^{13}C NMR ($CDCl_3$): δ/ppm = 182.1 (C-28), 73.9 (C-3), 73.6 (C-4), 56.4 (C-17), 49.2 (C-19), 29.6 (C-12), 25.4 (C-2), 21.7 (C-24), 19.3 (C-30), 17.2 (C-6). – EIMS: *m/z* (%) = 458 $[M]^+$ (14), 440 (28), 422 (15), 248 (51), 234 (33), 203 (32), 191 (56), 187 (50), 173 (65), 81 (54), 43 (100).

3α,4α,20ξ,29-Tetrahydroxy-23-norlupan-28-oic acid (**19**)

m.p. 234–236 °C (MeOH). – $[\alpha]_D^{24}$ +14.7 (MeOH, c = 0.5). – ^{1}H NMR (pyridine-d_5): δ/ppm = 4.04 (d, *J* = 10.5 Hz, H-29^B), 3.95 (d, *J* = 10.5 Hz, H-29^A), 3.85 (br s, H-3), 1.62, 1.26, 1.12, 0.99, 0.82 (each s, Me). – ^{13}C NMR (pyridine-d_5): δ/ppm = 179.4 (C-28), 75.0 (C-20), 74.1 (C-3), 72.7 (C-4), 69.2 (C-29), 59.3 (C-17), 48.6 (C-19), 28.4 (C-12), 26.5 (C-2), 25.8 (C-30), 22.1 (C-24), 17.7 (C-6). – EIMS: *m/z* (%) = 592 $[M]^+$ (1), 474 (13), 461 (59), 456 (38), 438 (28), 219 (29), 205 (33), 191 (96), 175 (64), 173 (100), 81 (45), 55 (51).

3,4-Dioxo-23-nor-3,4-seco-lup-20(29)-en-28-oic acid (**20**)

m.p. 94–96 °C (MeOH/*n*-hexane). – $[\alpha]_D^{24}$ +35.4 (MeOH, c = 1.0). – ^{1}H NMR ($CDCl_3$): δ/ppm = 9.76 (t, *J* = 1.6 Hz, H-3), 3.01 (td, *J* = 10.9 and 4.4 Hz, H-19), 2.57 (td, 1H, *J* = 12.1 and 3.3 Hz), 2.11 (s, H_3-24), 1.70 (s, H_3-30), 1.01, 0.99, 0.97 (each s, Me). – ^{13}C NMR ($CDCl_3$): δ/ppm = 212.3 (C-4), 202.3 (C-3), 181.9 (C-28), 56.7 (C-17), 56.3 (C-9), 46.8 (C-19), 40.8 (C-5), 31.0 (C-24), 30.4, 29.6, 25.2 (C-15, C-12, C-2), 19.8, 19.3 (C-30, C-25). – EIMS: *m/z* (%) = 456 $[M]^+$ (24), 438 (31), 412 (59), 395 (24), 369 (91), 259 (66), 189 (67), 175 (58), 107 (63), 93 (73), 81 (87), 55 (100). – HRMS: 456.3246 $[M]^+$ ($C_{29}H_{44}O_4$ requires 456.3240).

3-Oxo-23-nor-lup-20(29)-en-28-oic acid (**21**)

m.p. 202–204 °C (EtOAc). – $[\alpha]_D^{24}$ +44.5(MeOH, c = 0.5). – IR: *v*/cm^{-1} ($CHCl_3$) = 2 950 (s), 2 875 (m), 1 698 (s), 1 646 (w), 1 456 (m), 1 377 (m), 1 179 (m), 1 134 (m), 890 (m). – ^{1}H NMR ($CDCl_3$): δ/ppm = 3.02 (td, *J* = 10.7 and 4.3 Hz, H-19), 2.44 (ddd, 1H, *J* = 15.1, 13.2 and 6.9 Hz), 1.70 (s, H_3-30), 0.978 (d, *J* = 6.6 Hz, H_3-24), 1.02, 1.00, 0.976, (each s, Me). – ^{13}C NMR ($CDCl_3$): δ/ppm = 214.0 (C-3), 182.6 (C-28), 56.3 (C-17), 53.3 (C-4), 46.9 (C-19), 40.3 (C-2), 19.3 (C-30), 15.8, 14.5, 13.5, 11.6 (C-24, C-25, C-26, C-27). – EIMS: *m/z* (%) = 440 $[M]^+$ (31), 425 (13), 394 (24), 248 (56), 235 (41), 219 (35), 203 (54), 189 (100), 177 (36), 107 (39), 95 (37), 81 (44).

2-Imino-1,3-dioxane derivative (**22**)

m.p. 187–188 °C (Me_2CO/*n*-hexane). – $[\alpha]_D^{24}$ +82.3 ($CHCl_3$, c = 1.0). – ^{1}H NMR (CD_3OD): δ/ppm = 4.71 (br s, H-29^B), 4.59 (br s, H-29^A), 4.41 (m, C<u>H</u>–N), 4.40 (br s, H-3), 3.01 (td, *J* = 10.7 and 4.1Hz, H-19), 1.69 (s, H_3-30), 1.16 (s, H_3-24), 0.98, 0.97, 0.95 (each s, Me). – ^{13}C NMR (CD_3OD): δ/ppm = 180.0 (C-28), 175.2 (C-23), 151.9 (-C=N-), 79.5 (C-3), 57.4 (C-17), 46.2 (C-4), 48.5 (C-19), 56.2, 29.6, 27.5, 27.4, 26.6 (cyclohexyl), 19.5 (C-30). – EIMS: *m/z* (%) = 593 $[M]^+$

(56), 575 (19), 547 (100), 512 (29), 372 (22), 359 (86), 248 (35), 190 (69). – HRMS: 593.4086 $[M]^+$ ($C_{37}H_{55}NO_5$ requires 593.4080).

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