PREPARATION AND CONFORMATIONAL ANALYSIS OF 1,2-SECO DERIVATIVES OF 19β,28-EPOXY-18α-OLEANANE+

Jan SEJBAL[1,*], Martina HOMOLOVÁ, Iva TIŠLEROVÁ[2] and Václav KŘEČEK[3]

Department of Organic Chemistry, Charles University, 128 40 Prague 2, Czech Republic; e-mail: [1] sejbal@prfdec.natur.cuni.cz, [2] ivatis@prfdec.natur.cuni.cz, [3] krecek@prfdec.natur.cuni.cz

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Oxidation of 19β,28-epoxy-18α-oleanan-3-one (**1**) with chromium(VI) oxide in acetic acid leads to the formation of the 1β,3β;19β,28-diepoxy-3-hydroxy-1,2-seco-18α-oleanano-2,1α-lactone (**2**). Its structure follows from spectral data, molecular modelling. Lactone **2** was converted to its acetate **3**, methyl 19β,28-epoxy-1,3-dioxo-1,2-seco-18α-oleanan-2-oate (**4**) and to the stereoisomers at C(3) of methyl 1,3;19β,28-diepoxy-1-oxo-1,2-seco-18α-oleanan-2-oate (**6** and **7**) and dimethyl 19β,28-epoxy-3-hydroxy-1,2-seco-18α-oleanan-1,2-dioate (**8** and **9**). Lactone **2** reacts slowly with diazomethane which is indicative for its equilibrium with a small amount of free acid. Alkaline hydrolysis of compound **2** leads to compounds **8** and **9**; the reaction involves hydride transfer of a Cannizzaro reaction type. A high rotational barriers were found in compounds **8** and **9**. A combination of NMR methods and molecular modelling revealed that most sterically hindered bond in both compounds is the C(1)–C(10) single bond.

Key words: Triterpenoids; Triterpenes; 1,2-Seco derivatives; Oxidations; Oxidative cleavage; Chromium(VI) oxide; NMR spectroscopy; Molecular modelling.

Many of the papers published in the series Triterpenes deal with the preparation of triterpenoids with an open ring A (seco derivatives) because such seco derivatives have interesting chemical properties and moreover they may exhibit some antibacterial activity. The preparation of triterpenoid seco derivatives (especially 3,4-seco derivatives) is reviewed in ref.[2] 1,10-Seco triterpenoids may be prepared by the Beckmann rearrangement of 1-oximes[3]. Baeyer–Villiger oxidation of 1-oxo derivatives[4] leads to unstable lactones which readily decompose to unsaturated 1,10-seco acids. 2,3-Seco derivatives are formed together with other products when 3-oxo derivatives are oxidised with nitric acid in acetic acid[5]. Another possible

+ Part CX in the series Triterpenes; Part CIX see ref.[1]

method involves oxidation of 3-ketones to 2,3-diketones by air oxygen in the presence of base[6–11]. The diketones formed are then opened, for example, with hydrogen peroxide in methanolic sodium hydroxide[6,11,12]. α-Hydroxymethylene ketones obtained by Claisen condensation of 3-oxo derivatives with suitable esters undergo oxidative ring opening when treated with hydrogen peroxide, chromium(VI) oxide or potassium permanganate[13–15]. Triterpene 2,3-seco derivatives may also be prepared directly from 3-ketones with selenium dioxide in the presence of hydrogen peroxide[16–18]. Another possibility is oxidative cleavage of α-hydroxy ketones[19] with lead tetraacetate[11]. The Beckmann rearrangement of 3-oximes[20] leads to unsaturated 3,4-seco nitriles which can be converted to 3,4-seco-3-acids. Another useful method is Baeyer–Villiger oxidation of 3-oxo derivatives[4,21–23] when 3,4-lactone is formed in the reaction with organic peroxy acids. In comparison with a number of papers dealing with 1,10-, 2,3- and 3,4-seco derivatives, no attention was paid to 1,2-seco derivatives.

As a continuation of our efforts in the preparation of triterpenoids with the open ring A, we studied the possibility of oxidative cleavage of 3-oxo derivatives. Oxidation of 3-oxo derivative allobetulone (**1**) with chromium(VI) oxide led to compound **2**, which precipitated from the reaction mixture and is nearly insoluble in most common organic solvents. The IR spectrum of compound **2** shows bands at 1 802 cm^{-1} representative of a strained five-membered lactone and at 3 272 cm^{-1} typical for a bonded hydroxyl. Seven singlet methyl signals are present in the ^1H NMR spectrum together with signals characteristic for protons in positions 19α (3.51 s) and 28 (3.45 d and 3.76 dd) in derivatives of 19β,28-epoxy-18α-oleanane. Similarly, an ion characteristic for the fragmentation of ring E of 19β,28-epoxy-18α-oleanane derivatives ($M^+ - 71$) is present in the mass spectrum of compound **2**. Another observed ions are caused by losses of carbon monoxide, carbon dioxide and ring A (see Fig. 1). From these spectral data it is clear

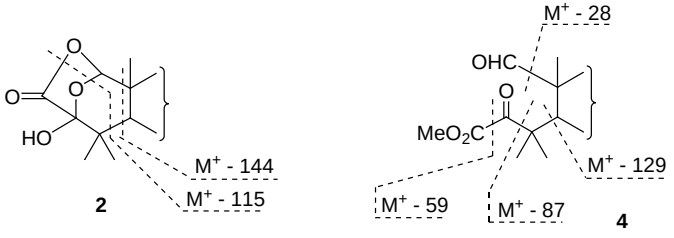
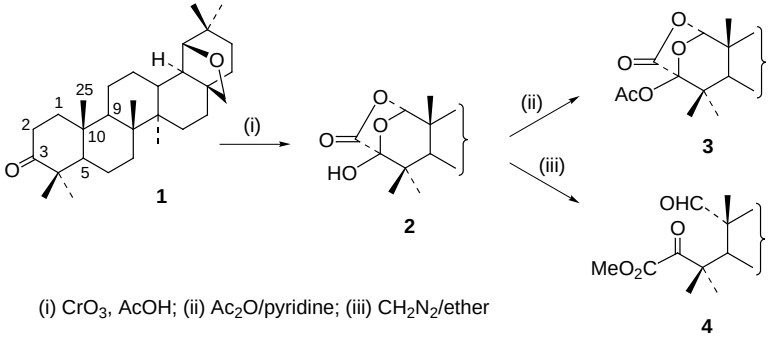


FIG. 1
MS fragmentation of compounds **2** and **4**

that the ether moiety in the ring E remains unchanged and so five-membered lactone is located in ring A. This is rather surprising because this cyclic ether is well known to be readily oxidised to a lactone[24].

The hydroxy group in compound **2** undergoes acetylation forming much more soluble acetate **3** (Scheme 1). NMR correlation spectra (HSQC, HMBC) of this acetate clearly show that fragment $–CH(OR)_2$ is situated on C-10 and that C-5 bears the fragment $–C(CH_3)_2–C(OR)_2–R$. Compound **2** also reacts with diazomethane giving methyl ester **4**. Spectral data of this compound show the presence of three carbonyls: carbaldehyde on C-10 and 3-oxo group, with C-2 as only possible position for ester carbonyl. The mass spectrum of this compound contains besides fragmentation of ring E ($M^+ – 31$, $M^+ – 71$) successive losses of chains at C-5 and C-10 (see Fig. 1). Structures **2**, **3** (except of configuration at C-1 and C-3) and **4** follow from the data discussed above.

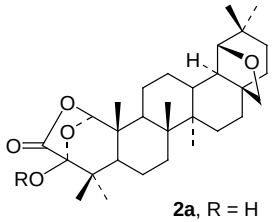


(i) CrO_3, AcOH; (ii) Ac_2O/pyridine; (iii) CH_2N_2/ether

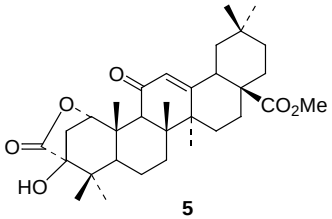
SCHEME 1

Attempts to elucidate the stereochemistry of compounds **2** and **3** using NMR data failed, in the NOESY spectra there were no spatial contacts solving this problem and there is no grouping in the molecule allowing measurement of three-bond couplings H–H or C–H. So we used molecular modelling for prediction of stability of compounds **2** and **3** (Table I). Energies of three rotamers of the –OH or –OAc group were calculated for each structure. The energy differences in pairs of stereoisomers (about 30 kJ mol^{-1}) is high above the possible errors of this method and shows that configurations with lactone ring situated below the plane of ring A are much more stable than reverse configurations in structures **2a** and **3a**. Keeping in mind the reaction of compound **2** with diazomethane, we may conclude that this compound is in equilibrium with very small amount of free keto acid (acetate **3** does not react with diazomethane). The modelling represents possible

thermodynamical equilibrium between lactones **2** and **2a** containing lactone **2** almost exclusively. These results are in good agreement with X-ray analysis[25] of similar compound **5** obtained, among many products from the oxidation[26] of methyl oleanonate and similar compounds with chromium(VI) oxide.



2a, R = H
3a, R = Ac



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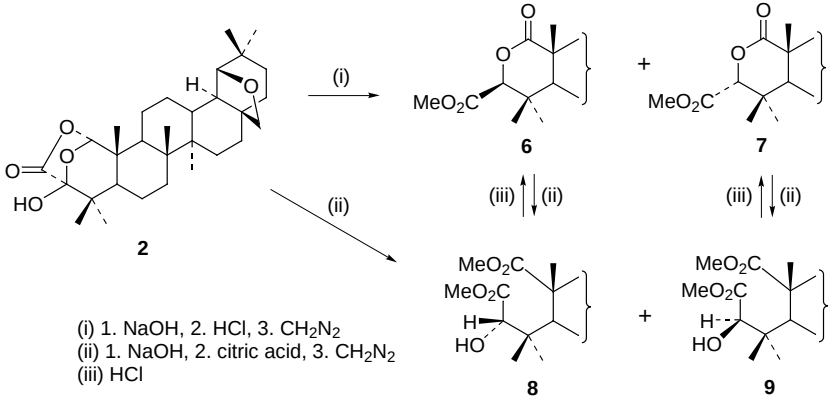
Alkaline hydrolysis of compound **2** gave two pairs of different products in dependence on the work-up of reaction mixture (Scheme 2). When 20% hydrochloric acid was used, the chromatographically separable mixture of lactones **6** and **7** was obtained after methylation of the crude product. Spectral data show for both compounds unchanged rings B–E and the presence of one methyl ester and a six-membered lactone. The fragmentation of both lactones **6** and **7** in the mass spectra is almost the same and started with loss of formaldehyde ($M^+ - 30$) and ring E ($M^+ - 71$). The spatial contact was found in the NOESY spectrum of lactone **6** between H-3 (singlet at δ 4.65) and H-5α indicating the α configuration of H-3. This cross peak is not present in the NOESY spectrum of isomeric lactone **7**.



2

SCHEME 2

When the reaction mixture after hydrolysis of compound **2** was acidified with citric acid, an unseparable mixture of two unstable acids was obtained. Treatment of this mixture with diazomethane led to a chromatographically unseparable mixture of diastereomeric dimethyl esters **8** and **9** (according to the NMR spectrum). On the other hand, both compounds **8** and **9** may be obtained separately in good yields when each of lactones **6** and **7** is hydrolysed and mild acid conditions are used for conversion to free diacids before methylation. IR and NMR spectra of compounds **8** and **9** confirm the presence of one hydroxyl and two methyl ester groupings. The configuration at C-3 in compounds **8** and **9** was derived from the known configurations in compounds **6** and **7**. Both dimethyl esters **8** and **9** undergo two fragmentation pathways in the mass spectra: (i) methanol is eliminated first and the same ions being observed as for lactones **6** and **7** are present in spectra or (ii) splitting of the side chain in position 5 between atoms C-3 and C-4 (ion *m/z* 443) or between atoms C-4 and C-5 (ion *m/z* 401).

In addition, alkaline hydrolysis was performed with acetate **3** and methyl ester **4**. In both cases similar reaction mixtures as with compound **2** were obtained. All three compounds **2**–**4** are derived from a 1,2-seco compound with an aldehyde group in position 1, oxo group in position 3 and a carboxy group in position 2. Compounds **6**–**9** are derived from a compound with two carboxyls in positions 1 and 2 and hydroxy group in position 3. So, hydrolysis of compounds **2**–**4** is accompanied with redox reaction, probably intramolecular hydride transfer similar to Cannizzaro reaction.

^{1}H NMR and ^{13}C NMR spectra of both dimethyl ester **8** and **9** exhibit at ambient temperature broadening or splitting of some signals, especially

TABLE I
Energy minima (kJ mol^{-1}) calculated for compounds **2** and **3** and their stereoisomers **2a** and **3a** (lowest-energy conformers in each structure are bold-faced)

Compound	Configuration		Torsion (C-4)–(C-3)–O–X, X = H, Ac		
	C-1	C-3	*– gauche*	*+ gauche*	*anti*
2	*R*	*R*	**368.4**	372.0	–
2a	*S*	*S*	402.5	**398.8**	400.6
3	*R*	*S*	**375.1**	382.8	399.1
3a	*S*	*R*	**406.4**	420.2	411.7

those of atoms on opened ring A and in neighbourhood, typical for hindered rotation of one single bond. NOESY spectra measured at –25 °C did not shed light on the problem of which bond has high rotational barrier. The same sets of cross peaks were found for both conformers. Full assignment of the ^{13}C NMR spectra allowed us to identify the carbon signals with the largest separation at low temperature. The difference of chemical shifts in individual conformers is largest for carbons C-5, C-9 and C-25. These three carbon atoms are in the γ position with respect to oxygen atoms of C-1 ester and hence they are most affected by changes in spatial positions of these oxygens. This indicates that bond C(1)–C(10) as the bond which is responsible for the slow interconversion.

This assumption is strongly supported by a molecular modelling study. Figure 2 shows the calculated dependence of energy on torsion angle for four most suspect bonds in side chains resulting from the opening of ring A. The rotation barriers calculated for the C(1)–C(10) bond are about 45 kJ mol^{-1}; for other three bonds, they are less than 30 kJ mol^{-1}. The values for rotation of the C(1)–C(10) bond were recalculated for some other low energy confor-

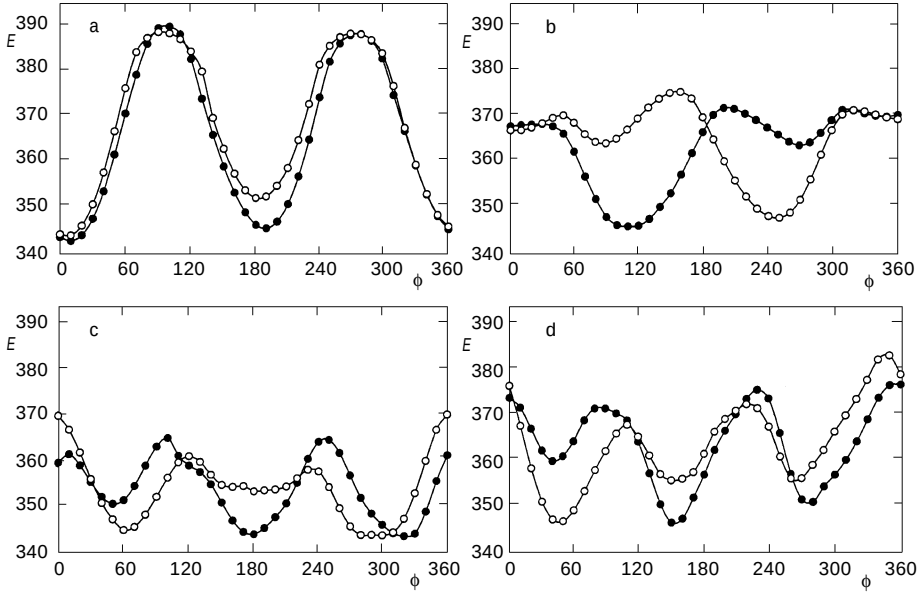


FIG. 2

The dependence of internal energy E (kJ mol^{-1}) on torsion angles (°) in compounds **8** and **9** as calculated using the MM2+ force field. Compound: ● **8**, ❍ **9**. Torsion angle: a O=C(1)–C(10)–C(25), b O=C(2)–C(3)–C(4), c C(2)–C(3)–C(4)–C(5), d C(3)–C(4)–C(5)–C(10)

mations of the side chain at C-5 to ensure that the geometry selected for the above modelling is optimum (Fig. 3). The dependencies have two minima with torsion angles O=C(1)–C(10)–C(25) near 0 and 180°. In the case of diester **8**, the structures corresponding to these minima have the same conformation of the C-5 side chain. However, with diester **9**, the sequential changes of torsion angle C(1)–C(10) starting from lowest-energy conformer (global minimum) do not reach the second minimum at 180° (found by simulated annealing). Changes in the conformation of the C-5 side chain are required. The part of the dependence of energy on torsion starting from the second rotamer is denoted by filled squares in Fig. 3b.

The experimental values of the population of both slowly interconverting conformers were obtained as an arithmetic mean of intensities of all well-resolved signals of methoxy groups in ^{1}H NMR spectra (measured in $CDCl_3$ or $CDCl_2$–$CDCl_2$ at temperatures ranging from –25 to 20 °C): 59 : 41 for compound **8** and 52 : 48 for compound **9**. This is in good agreement with nearly the same internal energies calculated for these structures by molecular modelling.

The temperature dependences of signals in ^{1}H NMR spectra ($CDCl_2$–$CDCl_2$, from –10 to 60 °C) of diesters **8** and **9** were measured for comparison of experimental activation energies with the barriers computed by molecular modelling. The attempted use of EXSY cross peaks for obtaining dynamic parameters completely failed because of small separation of

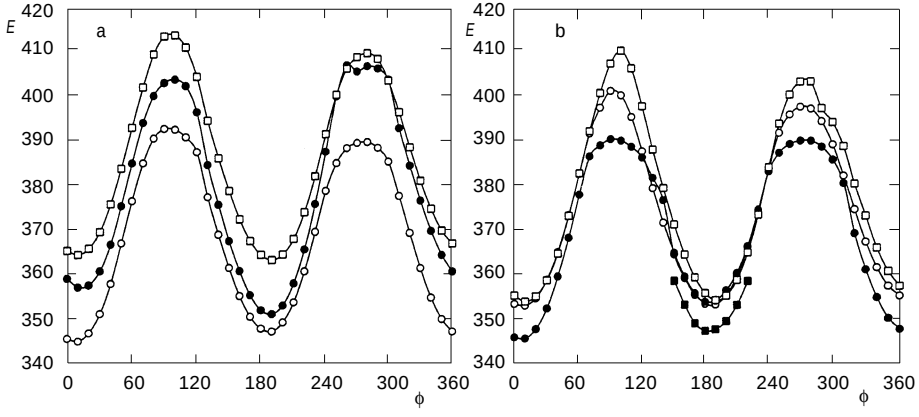


FIG. 3

The dependence of internal energy E (kJ mol^{-1}) on torsion angle (°) O=C(1)–C(10)–C(25) in compounds a **8** and b **9** as calculated using the MM2+ force field. Torsion angle C(3)–C(4)–C(5)–C(10): ● *+gauche*, ❍ *–gauche*, ❑ *anti*, ■ for the dependence near the second lowest-energy conformer

signals in individual rotamers. Therefore, signals of methoxy groups assumed to be sharp singlets in the absence of exchange were chosen for evaluation of broadening. Two sets of data were obtained: from linewidths (for the full temperature range, see Table II) and from comparison of the observed signal shapes with those calculated for given dynamic parameters (available only at temperatures near coalescence). We divided the rate constants obtained from broadening and lineshapes by number two before calculation of thermodynamical parameters.

The values of activation Gibbs energy $\Delta G^{\ddagger}$ calculated for esters **8** and **9** at temperatures between –10 and 60 °C from linewidths (excess broadening) and lineshapes (peak-to-valley ratios) are summarised in Table II. Each compound has two signals of methoxy groups which coalesce at different temperatures. Each value of $\Delta G^{\ddagger}$ is the arithmetic mean of values for each methoxyl obtained by one or both (if applicable for given temperature) methods mentioned above.

Among various parameters used for evaluation of activation energy, values of $\Delta H^{\ddagger}$ are assumed to be the best comparison with internal energies E_i calculated by molecular modelling[27]. Taking into account all data collected from lineshapes and linewidths we obtained values of $\Delta H^{\ddagger}$ with estimated

TABLE II
Linewidths (Hz) of OMe signals corrected for linewidth of TMS[a] and calculated activation Gibbs energies $\Delta G^{\ddagger}$ (kJ mol^{-1}) for compounds **8** and **9**

Temperature °C	**8**			**9**		
	C(1)–OMe	C(2)–OMe	$\Delta G^{\ddagger}$	C(1)–OMe	C(2)–OMe	$\Delta G^{\ddagger}$
–10	1.0, 1.1	0.9, 1.0	61.7	0.9	2.1, 2.2	63.5
0	1.3, 1.3	×, ×	63.6	0.8	×, ×	65.4
10	2.1, 2.0	×, ×	64.8	0.8	×, ×	67.4
20	3.2, 3.0	×	66.3	0.8	7.8	68.4
30	7.0, ≈4.2	1.5	67.3	0.6	3.8	69.5
40	×, ×	0.7	68.0	0.5	1.9	69.8
50	9.5	0.5	68.9	0.5	1.1	71.3
60	4.5	0.4	70.1	0.3	0.6	73.1

[a] × Linewidth not available; two numbers or two × denote signals at temperature below coalescence.

errors 32 ± 4 kJ mol^{-1} for diester **8** and $\Delta H^{\ddagger}$ 31 ± 4 kJ mol^{-1} for diester **9**. For both compounds surprisingly big negative value of $\Delta S^{\ddagger}$ about –120 J mol^{-1} K^{-1} was found. When only data obtained from the lineshape analysis were used, more probable values of $\Delta H^{\ddagger}$ 47 ± 7 kJ mol^{-1} for diester **8** and 44 ± 9 kJ mol^{-1} for diester **9** were obtained. Assuming the computer assisted lineshape analysis more safe than other methods containing systematic errors, we consider the last-mentioned values as correct despite the higher value of estimated error. These values are also in good agreement with barriers energies E_i computed by molecular modelling.

Concluding the experimental data and MM calculations, diesters **8** and **9** exist as equilibria of two similarly populated, slowly interconverting rotamers of the C(1)–C(10) bond.

EXPERIMENTAL

Thin-layer chromatography (TLC) was performed on silica gel plates G (Merck), visualisation by spraying with 10% sulfuric acid and heating. Kieselgel 60 G (Merck) was used for preparative TLC (spraying with 0.3% methanolic solution of morin), column chromatography was carried out on silica gel Silpearl (Kavalier, Votice). Mixtures of light petroleum and ether ranging from 2 : 1 to 6 : 1 were used as eluants. The usual work-up means dilution of reaction mixture with water, extraction of products with ether and successive washing of ethereal layer with dilute (1 : 4) hydrochloric acid (if necessary), water, saturated sodium hydrogencarbonate solution, water, drying over anhydrous sodium sulfate and evaporation of solvents under reduced pressure. Samples for elemental analysis were dried over phosphorus pentoxide under reduced pressure. Starting allobetulone (**1**) was prepared according to ref.[28].

Melting points were determined on a Kofler block and are uncorrected. Optical rotations were carried out in chloroform (if not specified in experiment), *c* 0.3–0.5, at ambient temperature on an automatic polarimeter ETL-NPL (Bendix–Ericsson) with an accuracy ±2 and are given in 10^{-1} deg cm^2 g^{-1}. Infrared spectra were recorded in chloroform solution on a PE 684 (Perkin–Elmer) spectrometer, wavenumbers are given in cm^{-1}. Hydroxyl bands, obtained by recording spectra of $1.05 \cdot 10^{-3}$ M solutions in tetrachloromethane, are denoted as IR(OH). Bands were separated using the spectrometer software and are given in cm^{-1} in the format: wavenumber (ε, $\Delta\nu_{1/2}$). Mass spectra were recorded on Finnigan MAT-Incos 50 instrument, ionizing electron energy 70 eV and direct inlet temperatures 150–180 °C. Data are presented in the format *m/z* (%), intensities are scaled to most intensive ion above *m/z* 80.

NMR spectra were recorded on a Varian^{UNITY} INOVA 400 instrument (proton frequency 400 MHz) in deuteriochloroform (if not specified otherwise). For ^{1}H NMR spectra, tetramethylsilane (TMS) was used as internal standard, chemical shifts (δ scale, ppm) and coupling constants (*J*, Hz) were obtained by first-order analysis. ^{13}C NMR chemical shifts obtained from the spectra measured in deuteriochloroform were referenced to solvent signal (δ($CDCl_3$) 77.00); with $CDCl_2$–$CDCl_2$ as solvent, TMS was used as internal standard (δ 0). COSY experiments were recorded in absolute value mode using standard two pulse sequence. NOESY experiments were performed in the phase-sensitive mode with standard three pulse sequence (mixing time 0.3 s). HETCOR and COLOC were performed in the absolute value

mode, HSQC and HMBC were performed as gradient experiments. All 2D experiments were recorded with spectral windows 5 000 Hz for proton and 25 000 Hz for carbon. Excess broadening was obtained for both OCH_3 signals in compounds **8** and **9** by subtracting the linewidth of the TMS resonance. Where available, the temperature dependence of the separation of OCH_3 signals in individual conformers was extrapolated from the region with resolved signals to higher temperatures. For simulation of lineshapes broadened by dynamic phenomena, the DNMR programme (Prof. G. Hägele, University Düsseldorf) was used. Standard procedures[29,30] were used for obtaining thermodynamic parameters.

Molecular modelling studies were performed using the programme Hyperchem 2 (Hypercube) on a PC Pentium 100 MHz computer. Scripts and macros were used to facilitate operations which were repeated many times. Results are presented in kJ mol^{-1}. The conjugate gradient method for minimizations was used to convergence (less than 0.2 kJ mol^{-1} RMS force). Force-field MM2+ was used for all computations. In the case of compound **2** and its stereoisomer **2a**, a count of 10 rotamers with random torsion angle (C-4)–(C-3)–O–H were manually created and optimized. In the case of stereoisomers **3** and **3a** with acetate group allowing many conformations, the simulated annealing was used for conformational analysis. A set of 80 structures was thus obtained for each stereoisomer from which the lowest-energy one for each rotamer was chosen. The same protocol was used for finding local and global minima in compounds **8** and **9**. The dependence of energy on torsion angle was calculated by systematic incrementation of torsion angle in the region of 0–360° in steps of 10° with high value of barrier in the dihedral term. The return to the geometry of starting conformer after 36 steps was carefully checked.

Oxidation of Allobetulone (**1**) with Chromium(VI) Oxide

Allobetulone (**1**; 5.0 g, 11.3 mmol) and chromium(VI) oxide (5.0 g, 50 mmol) were added to acetic acid (94 ml) and resulting mixture was heated in water bath to 70 °C for 3 h. After cooling to room temperature, the crystalline precipitate of 1β,3β;19β,28-diepoxy-3-hydroxy-1,2-seco-18α-oleanano-2,1α-lactone (**2**) was filtered under suction and washed twice with acetic acid and twice with ethanol. Yield 1.32 g (24%), m.p. 250–253 °C, $[\alpha]_D$ +79 (pyridine). IR: 3 272 (OH); 1 802 (O=C–O); 1 030 (C–O–C). MS: 486 (M^+, 1), 468 (0.1), 457 (1), 442 (1), 430 (3), 415 (5), 371 (4), 353 (2), 343 (7), 245 (6), 95 (100). ^{1}H NMR (400 MHz, $CDCl_3$): 0.80 s, 0.93 s, 0.93 s, 1.01 s, 1.03 s, 1.04 s, 1.18 s, 7 × 3 H (7 × CH_3); 1.82 m, 1 H; 3.26 s, 1 H (OH); 3.45 d, 1 H and 3.76 dd, 1 H, J_{gem} = 7.8 $J_{l.r.}$ = 1.6 (H_2-28); 3.51 s, 1 H (H-19α); 5.52 s, 1 H (H-1). For $C_{30}H_{46}O_5$ (486.7) calculated: 74.04% C, 9.53% H; found: 74.16% C, 9.38% H.

Acetate **3**: Compound **2** (1.6 g, 3.3 mmol) was acetylated by standing for 2 days with acetic anhydride (50 ml) in pyridine (50 ml) at ambient temperature. After the usual work-up and crystallisation from ethanol, 3-acetoxy-1β,3β;19β,28-diepoxy-1,2-seco-18α-oleanano-2,1α-lactone was obtained in the yield 1.4 g (80%). M.p. 225–229 °C (ethanol), $[\alpha]_D$ +82. IR: 1 806 (O=C–O); 1 763 (CH_3C=O); 1 037 (C–O–C). MS: 528 (M^+, 6), 510 (1), 499 (0.3), 484 (0.1), 469 (0.1), 457 (4), 440 (2), 412 (2), 397 (1), 384 (1), 369 (2), 353 (1), 341 (1), 323 (2), 83 (100). For NMR spectra, see Tables III and IV.

Methyl 19β,28-Epoxy-1,3-dioxo-1,2-seco-18α-oleanan-2-oate (**4**)

Compound **2** (2.0 g, 4.1 mmol) was poured into an ethereal solution of diazomethane (80 ml, prepared from 5.6 g of Diazald). The mixture was left aside with occasional shaking for 8 days at ambient temperature and then evaporated to dryness. Chloroform (5 ml) was

TABLE III

^{1}H chemical shifts and coupling constants (in parentheses) of compounds **3**, **4**, **6** and **7**. Chemical shift values marked with tilde (~) were obtained from 2D spectra. Assignment based on 2D correlations

Proton	**3**	**4**	**6**	**7**
1	5.62 s	9.33 s	–	–
3	–	–	4.65 s[a]	4.90 s[b]
5α	~1.26	2.40 dd (12.4, 2.7)	~1.54	~1.30
6a	~1.38	~1.65[c]	~1.50	~1.33
6b	~1.48	~1.27[d]	~1.56	~1.52
7a	~1.40	~1.48	~1.40	~1.32
7b	~1.40	~1.47	~1.50	~1.50
9α	1.85 m (ΣJ = 16.0)	1.85 dd (12.7, 2.8)	2.02 dd (12.2, 2.8)	2.09 dd (11.9, 2.6)
11a	~1.38	~0.96	2.50 dq (12.8, 2.9)[e]	2.25 dq (12.6, 3.2)[e]
11b	~1.40	~1.24	~1.40[f]	~1.37[f]
12α	~1.00	~0.90	~1.10	~1.15
12β	~1.65	~1.59	~1.68	~1.68
13β	~1.46	~1.49	~1.52	~1.54
15α	~1.05	~1.14	~1.13	~1.04
15β	~1.58	~1.52	~1.50	~1.53
16α	~1.42	~1.41	~1.41	~1.43
16β	~1.30	~1.31	~1.31	~1.30
18α	~1.47	~1.49	~1.52	~1.53
19α	3.51 s	3.50 s	3.56 s	3.56 s
21α	~1.23	~1.22	~1.23	~1.23
21β	~1.50	~1.50	~1.50	~1.50
22a	~1.32	~1.33	~1.34	~1.31
22b	~1.45	~1.44	~1.47	~1.48
23	1.04 s	1.10 s	1.17 s	0.94 s
24	1.06 s	1.20 s	1.01 s	1.19 s
25	1.16 s	1.13 s	1.36 s	1.28 s
26	1.00 s	1.01 s	1.04 s	1.04 s
27	0.94 s	0.97 s	0.95 s	0.94 s
28 (*pro-R*)	3.45 d (7.8)	3.45 d (7.8)	3.45 d (7.8)	3.45 d (7.8)
28 (*pro-S*)	3.75 dd (7.9, 1.7)	3.76 dd (7.8, 1.5)	3.77 dd (7.8, 1.9)	3.77 dd (7.8, 1.7)
29	0.80 s	0.79 s	0.80 s	0.80 s
30	0.93 s	0.93 s	0.94 s	0.94 s
OAc	2.15 s	–	–	–
OCH_3	–	3.86 s	3.79 s	3.80 s

[a] 3α; [b] 3β; [c] 6α; [d] 6β; [e] 11α; [f] 11β.

TABLE IV
^{13}C chemical shifts of compounds **3**, **4**, **6** and **7**. Assignment based on 2D correlations

Carbon	**3**	**4**	**6**	**7**
1	104.47	206.32	176.02	174.67
2	168.19	164.52	168.74	168.34
3	99.89	202.14	87.60	81.46
4	38.67	50.97	35.15	35.91
5	48.63	45.54	53.36	49.90
6	17.00	21.53	17.49	19.04
7	33.68	32.40	33.12	32.42
8	40.96[a]	39.34	41.35[a]	41.08[a]
9	42.06	39.96	44.32	44.00
10	41.84[b]	54.05	46.07	44.50
11	21.07	22.71	23.79	24.68
12	25.55	25.87	26.10[b]	26.16[b]
13	33.86	34.50	34.34	34.67
14	40.87[a]	41.10	41.13	40.72[a]
15	26.28	26.41	26.29[b]	26.40[b]
16	36.63	36.63	36.65	36.64
17	41.40[b]	41.45	41.37[a]	41.36
18	46.68	46.57	46.57	46.59
19	87.92	87.81	87.79	87.85
20	36.22	36.24	36.20	36.21
21	32.60	32.63	32.65	32.65
22	26.08	26.07	26.19[b]	26.17[b]
23	21.02	25.07	28.64	25.40
24	16.65	19.76	18.76	22.58
25	14.75	12.81	16.93	12.31
26	16.19	15.59	16.77	16.02
27	13.60	13.41	13.26	13.31
28	71.15	71.19	71.23	71.25
29	24.47	24.49	24.47	24.46
30	28.73	28.72	28.73	28.73
OAc	20.69	–	–	–
	167.74	–	–	–
OCH_3	–	52.35	52.04	52.02

[a,b] Signals marked with identical symbols may be interchanged.

added to the resulting material and the mixture was left overnight in the refrigerator. Unreacted starting lactone was filtered off, the filtrate was evaporated and crystallised from methanol. Yield 1.6 g (78%) of the title methyl ester **4**, m.p. 181–184 °C (methanol), $[\alpha]_D$ +14. IR: 2 812, 2 689 (HC=O); 1 738, 1 720, 1 716 (C=O); 1 254 (CO–O–C); 1 032 (C–O–C). MS: 500 (M^+, 2), 485 (0.3), 472 (9), 441 (5), 429 (4), 413 (3), 401 (1), 385 (5), 371 (17), 343 (22), 313 (6), 245 (6), 95 (100). For NMR spectra, see Tables III and IV.

Lactones **6** and **7**

Compound **2** (1.0 g, 2.1 mmol) was suspended in benzene (20 ml) and a solution of sodium hydroxide (200 mg, 5 mmol) in ethanol (1 ml) was then added. The resulting mixture was refluxed for 3 h, then poured into a 20% solution of hydrochloric acid (50 ml) and stirred with ether (100 ml) for 3 h. After the usual work-up an excess of an ethereal solution of diazomethane was added to the evaporation residue. Column chromatography on silica gel (100 g, eluant light petroleum–ether 1 : 1) led to subsequent elution of the following lactones:

*Methyl (3R)-1,3;19*β,*28-diepoxy-1-oxo-1,2-seco-18*α*-oleanan-2-oate* (**7**; 520 mg, 51%) m.p. 248–255 °C (methanol), $[\alpha]_D$ +90. IR: 1 761, 1 742 (C=O); 1 174. MS: 500 (M^+, 44), 470 (15), 446 (5), 429 (20), 341 (5), 302 (6), 295 (6), 278 (24), 271 (23), 119 (19), 95 (100). For NMR spectra, see Tables III and IV.

*Methyl (3S)-1,3;19*β,*28-diepoxy-1-oxo-1,2-seco-18*α*-oleanan-2-oate* (**6**; 360 mg, 35%), m.p. 284–287 °C (methanol), $[\alpha]_D$ +56. IR: 1 755, 1 738 (C=O); 1 175. MS: 500 (M^+, 30), 470 (14), 429 (17), 341 (5), 302 (5), 278 (12), 271 (14), 245 (5), 212 (20), 95 (100). For NMR spectra, see Tables III and IV.

The same mixture of lactones **6** and **7** in comparable yields was obtained from acetate **3** and methyl ester **4** under the reaction conditions and work-up described above.

A solution of dimethyl ester **8** (100 mg, 0.19 mmol) in ether (20 ml) was shaken with 10% hydrochloric acid (5 ml) and allowed to stand for 1 h at ambient temperature. Usual work-up and crystallisation from methanol gave lactone **6** (83 mg, 88%). Dimethyl ester **9** afforded under the same conditions lactone **7** (89 mg, 95%).

Dimethyl (3*S*)-19β,28-Epoxy-3-hydroxy-1,2-seco-18α-oleanan-1,2-dioate (**8**)

A solution of sodium hydroxide (11 mg, 0.28 mmol) in ethanol (2 ml) was added to the stirred suspension of lactone **6** (118 mg, 0.24 mmol) in benzene (1 ml). The mixture was stirred for 12 h at ambient temperature and then neutralised with ethanolic solution of citric acid. The mixture was extracted twice with 10 ml of ether, combined organic layers were dried with anhydrous sodium sulfate and then treated with excess of ethereal solution of diazomethane. The solvents were evaporated under reduced pressure and the solid was crystallised from the mixture of acetone and methanol. Yield of the title compound **8** was 69 mg (55%), m.p. 200–208 °C, $[\alpha]_D$ +38. IR: 3 534 (O–H); 1 730, 1 722 (C=O); 1 202. IR(OH): 3 610 (9.5, 16.6); 3 560 (40.0, 40.5); 3 531 (36.6, 43.0). MS: 532 (M^+, 2), 500 (18), 443 (19), 401 (37), 383 (12), 369 (10), 271 (15), 245 (14), 199 (26), 95 (100).^{1}H NMR (400 MHz, $CDCl_3$, 55 °C): 0.78 s, 0.79 s, 0.91 s, 0.92 s, 0.95 s, 0.99 s, 1.24 s, 7 × 3 H (7 × CH_3); 2.16 bd, 1 H, J = 12.0 (H-9α); 2.41 m, 1 H (H-5α); 2.65 d, 1 H, J = 8.2 (OH); 3.44 d, 1 H and 3.76 dd, 1 H, J_{gem} = 7.8 $J_{l.r.}$ = 1.6 (H_2-28); 3.49 s, 1 H (H-19α); 3.63 bs, 3 H (OCH_3); 3.76 s, 3 H (OCH_3); 4.03 d, 1 H, J = 8.2 (H-3). For other NMR spectra, see Tables V and VI.

TABLE V
^{1}H chemical shifts and coupling constants (in parentheses) of dimethyl esters **8** and **9** in $CDCl_2CDCl_2$ at 35 °C. Chemical shift values marked with tilde (~) were obtained from 2D spectra. Assignment based on 2D correlations

Proton	**8**	**9**
3	4.02 d (8.5)	3.91 bs
5α	2.33 bd (10.4)	2.15 bd (10.3)
6a	~1.51	~1.46
6b	~1.51	~1.46
7a	~1.45	~1.43
7b	~1.45	~1.44
9α	2.10 bd (10.8), 2.13 bd (11.0)	2.08 bd (11.0)
11α	~0.93	~0.92
11β	~1.35	~1.34
12α	~0.90	~0.90
12β	~1.57	~1.58
13β	~1.38	~1.38
15α	~1.10	~1.11
15β	~1.52	~1.53
16α	~1.39	~1.39
16β	~1.29	~1.29
18α	~1.44	~1.45
19α	3.46 bs	3.46 bs
21α	~1.22	~1.28
21β	~1.47	~1.46
22α	~1.31	~1.30
22β	~1.43	~1.44
23	0.87 s	0.98 s
24	0.75 bs	0.76 bs
25	1.21 s	1.20 bs
26	0.96 s	0.96 s
27	0.93 bs	0.93 s
28 (*pro-R*)	3.41 d (7.9)	3.41 bd (7.8)
28 (*pro-S*)	3.72 d (7.6)	3.72 bd (7.8)
29	0.77 s	0.77 s
30	0.90 s	0.90 s
C(1)–OCH_3	3.61 bs, 3.64 bs	3.60 s
C(2)–OCH_3	3.75 bs	3.80 bs
OH	2.67 d (8.2)	2.67 bs

TABLE VI
^{13}C chemical shifts of dimethyl ester **8** in $CDCl_2CDCl_2$ at 5, 35, 65 and 95 °C

Carbon	5	35	65	95
1	180.53, 179.29	180.45, 179.21	–	–
2	174.96	174.90	174.84	174.81
3	76.31, 76.15	76.60 b	77.03	77.42
4	41.61, 41.35	41.73, 41.49	41.74	41.92
5	46.59, 45.71	46.87, 46.01	–	–
6	20.39, 20.01	20.51, 20.19	20.53	20.71
7	32.22, 32.11	32.30 b	32.51	32.71
8	39.83, 39.80	39.96	40.13	40.32
9	47.64, 45.29	47.80, 45.39	–	47.17 b
10	52.02, 51.87	52.17 b	52.33	52.55
11	23.42, 23.07	23.51, 23.20	23.48	23.62
12	26.05	26.14	26.23	26.36
13	34.09	34.24	34.41	34.59
14	40.83	40.96	41.10	41.27
15	26.16	26.31	26.43	26.58
16	36.36	36.53	36.71	36.90
17	41.19	41.29	41.40	41.53
18	46.32	46.50	46.70	46.91
19	87.57, 87.52	87.65	87.75	87.88
20	35.97	36.04	36.13	36.25
21	32.41	32.59	32.77	32.97
22	25.89	26.01	26.14	26.30
23	21.09, 21.03	21.12	21.20	21.34
24	18.48, 18.28	18.79 b	19.22	19.63
25	14.99, 14.26	15.09 b, 14.24 b	–	14.63 b
26	15.07, 15.02	15.09	15.19	15.31
27	13.52, 13.33	13.42 b	13.46	13.51
28	70.85	70.94	71.04	71.18
29	24.34	24.40	24.47	24.57
30	28.70	28.76	28.83	28.91
C(1)–O**C**H_3	52.23, 52.20	52.06	51.92	51.84
C(2)–O**C**H_3	51.80	51.66	51.54	51.47

TABLE VII
^{13}C chemical shifts of dimethyl ester **9** in $CDCl_2CDCl_2$ at 5, 35, 65 and 95 °C. Chemical shift values marked with tilde (~) were obtained from 2D spectra.

Carbon	5	35	65	95
1	180.75, 179.08	~180.10	–	–
2	174.90, 174.79	174.76 b	174.69	174.63
3	76.74, 76.55	76.79	76.97	77.17
4	42.38, 42.25	42.38	42.47	42.58
5	46.54, 45.36	~46.83, ~45.73	–	–
6	21.09, 20.62	~20.90	21.02	21.12
7	32.20, 32.08	32.29	32.45	32.61
8	39.76	39.91	40.07	40.25
9	47.75, 45.30	~47.68, ~45.27	–	47.15
10	52.25, 52.12	52.27 b	52.45	52.65
11	23.39, 23.10	23.40	23.50	23.62
12	26.04 b	26.14	26.24	26.34
13	34.08 b	34.24	34.40	34.56
14	40.72	40.86	41.02	41.20
15	26.22 b	26.33	26.44	26.56
16	36.37 b	36.55	36.72	36.90
17	41.20	41.29	41.39	41.51
18	46.35 b	46.53	46.72	46.92
19	87.51 b	87.60	87.71	87.83
20	35.97	36.04	36.13	36.23
21	32.41 b	32.59	32.77	32.95
22	25.90 b	26.03	26.15	26.28
23	21.45, 21.37	21.42	21.44	21.47
24	19.71, 19.44	19.70	19.84	20.03
25	14.92, 14.21	~14.70	14.51 b	14.51
26	15.03 b	15.13	15.22	15.24
27	13.33, 13.20	13.28	13.31	13.34
28	70.85 b	70.95	71.04	71.15
29	24.32	24.38	24.45	24.52
30	28.69 b	28.75	28.82	28.88
C(1)–O**C**H_3	51.87, 51.74	51.68 b	51.57	51.48
C(2)–O**C**H_3	52.19, 51.98	52.04 b	51.90	51.78

Dimethyl (3*R*)-19β,28-Epoxy-3-hydroxy-1,2-seco-18α-oleanan-1,2-dioate (**9**)

The same procedure as in the case of preparation of compound **8** was applied to lactone **7** (185 mg, 0.37 mmol). Dimethyl ester **9** was formed as the sole product in yield 156 mg (79%), m.p. 103–106 °C (ether), $[\alpha]_D$ +12. IR: 3 540 (OH); 1 728, 1 722 (C=O); 1 190, 1 028 (C–O–C). IR(OH): 3 614 (10.9, 21.4); 3 558 (30.4, 33.4); 3 537 (43.8, 47.9). MS: 532 (M^+, 2), 514 (3), 500 (18), 443 (22), 413 (1), 401 (33), 383 (13), 369 (11), 355 (3), 341 (10), 271 (15), 245 (14), 199 (26), 95 (100). ^{1}H NMR (400 MHz, $CDCl_3$, 55 °C): 0.78 s, 0.79 s, 0.92 s, 0.95 s, 0.98 s, 1.00 s, 1.23 s, 7 × 3 H (7 × CH_3); 2.12 dd, 1 H, J_1 = 2.6, J_2 = 12.6 (H-5α); 2.65 bs, 1 H (OH); 3.44 d, 1 H and 3.76 dd, 1 H, J_{gem} = 8.0, $J_{l.r.}$ = 1.7 (H_2-28); 3.50 bs, 1 H (H-19α); 3.61 s, 3 H (OCH_3); 3.81 s, 3 H (OCH_3); 3.94 d, 1 H, J = 7.9 (H-3). For other NMR spectra, see Tables V and VII.

When a mixture of lactones **6** and **7** or compound **2** is subjected to the same reaction conditions and the work-up of reaction mixture as described for preparation of compounds **8** and **9**, chromatographically inseparable mixture of dimethyl esters **8** and **9** is obtained (in the case of compound **2** in ratio *ca* 1 : 1 according to ^{1}H NMR spectrum).

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