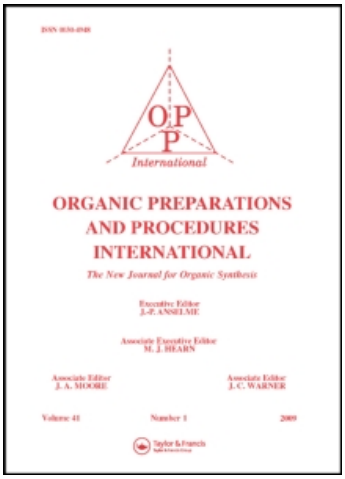

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A NEW REDUCTION OF THE ENONE SYSTEM OF 18B-GLYCYRRHETIC ACID

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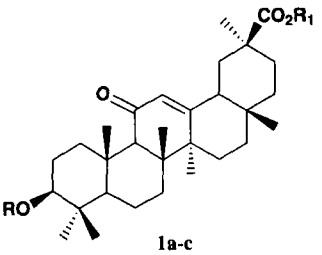
Carbenoxolone (**1c**) is a well known antiulcer drug[1] whose therapeutic use has, however, been discontinued owing to mineralocorticoid side-effects. A higher degree of separation between antiulcer activity and undesirable effects on electrolyte balance in rats was obtained[2] by chemical modification of ring C of the triterpene framework of **1c**, namely with the synthesis of the $\Delta^{9,11}$ derivative **2c** (deloxolone).[3] In order to easily provide larger amounts of deloxolone, so far obtained only by Wolff-Kishner reduction of methyl 3β-acetoxy-12-oxoolean-9(11)-en-30-oate (**3**),[4] we needed a new and more expeditious synthesis from 18β-glycyrrhetic acid (**1a**). This required an accurate reexamination of the behavior of the highly hindered enone system of **1a**, whose double bond resisted all the previously attempted reductions.

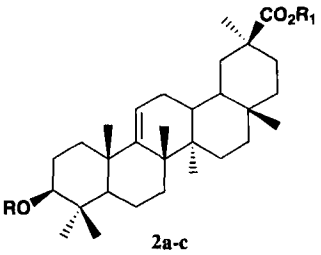
According to the literature, catalytic hydrogenation of **1a** afforded the 11-deoxoderivative **4a**[5] and treatment with sodium in alcohol gave the 9(11),12-diene **5**[6] or the 11,13(18)-diene **6a**.[7] These dienes arose also from the borohydride reduction[8] of **1a,** while with diborane, 3β,11β-dihydroxy-olean-12-en-30-oic acid (**4b**) was produced.

In our hands $NaBH_4$ reduction of **1a** gave an epimeric mixture of the intermediate allylic alcohols **4b,c**. After treatment with diazomethane and column chromatography, the pure 11β-hydroxy derivative **4d** and the 11α isomer **4e** were obtained in a ratio 5:1. We also noticed that the crude reaction mixture can be cleanly and selectively dehydrated to 3β-hydroxyolean-9(11),12-dien-30-oic acid (**5**) by refluxing in tetrahydrofuran in the presence of a catalytic amount of conc. HCl, or to heteroannular diene **6b** by refluxing in a 4:1 mixture of acetic acid-conc. HCl. Therefore, it seems that the formation of **5** is a kinetically controlled process, while **6b** is formed under thermodynamic control, as suggested by the conversion of **5** into **6b** under forcing conditions.[9]

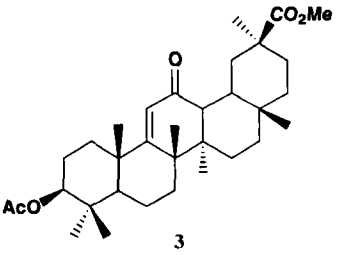
Treatment of a solution of **1a** in hexamethylphosphoric triamide (HMPT) containing *t*-butyl alcohol with an excess of lithium at room temperature, resulted in a nearly quantitative formation of the deoxo derivative **4a**. Although fission of carbon-oxygen bond by using such or similar reducing systems has been already reported,[10] this is the first instance in which a ketone deoxygenation takes place. Furthermore, this system provides an effective reduction[11] of the heteroannular diene **6a** to the 13(18)-unsaturated derivatives **7.** Reduction of glycyrrhetic acid (**1a**) with lithium and ammonia has been reported to proceed slowly or not at all;[12] in our hands, such reaction also presented some



1a-c



2a-c



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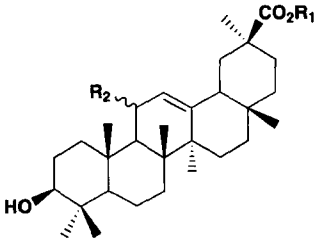
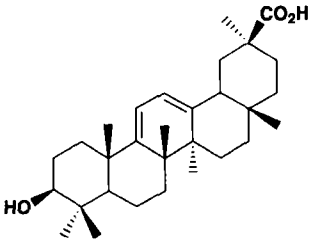
a) R = R' = H; b) R = Ac, R' = H; c) R = $CO(CH_2)_2CO_2Na$, R' = Na



	R_1	R_2
4a	H	H
4b	H	β-OH
4c	H	α-OH
4d	Me	β-OH
4e	Me	α-OH



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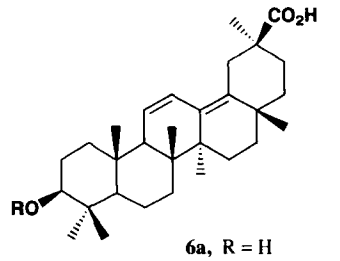
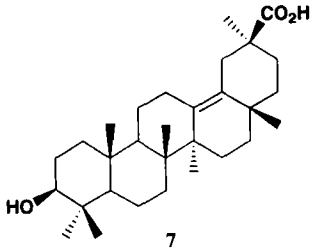
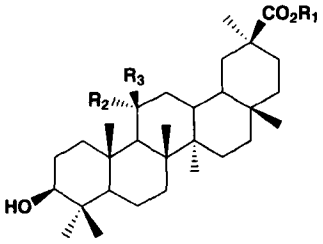


6a, R = H
6b, R = Ac



7



	R_1	R_2	R_3
8a	H	OH	H
8b	H	H	OH
8c	Me	OH	H
8d	Me	H	OH
8e	H	=O	
8f	H	H	H

difficulties owing to the poor solubility of glycyrrhetic acid. In fact, the customary procedure, i.e. addition of the metal to a solution of the substance in liquid ammonia containing a co-solvent and/or a proton donor, gave a complex mixture in which allylic alcohols **4b,c** predominated. In contrast, when an anhydrous solution of **1b**[13] in tetrahydrofuran was added at low temperature to an excess of lithium in liquid ammonia followed by quenching with 2-propanol and ammonium chloride, the reaction was successful affording mainly a mixture of the desired saturated alcohols **8a** and **8b** in a ratio 5:1. When refluxed in a 4:1 mixture of acetic acid-conc. hydrochloric acid, both alcohols **8a** and **8b** provided the desired 3β-acetoxyolean-9(11)-en-30-oic acid (**2b**) in excellent yield, thus affording a very good alternative entry to this structure, suitable also for easy scale-up.

To provide the saturated ketone **8e**, the 3-*O*-trimethylsilyl ether of **1a** was reduced with lithium and ammonia under the same conditions, but using an acetone-NH_4Cl quenching. Compound

8e was obtained in 70% yield along with a small amount of alcohol **8a**. Reduction of ketone **8e** by a modified Wolff-Kishner procedure[14] led to 3β-hydroxyolean-30-oic acid (**8f**) in which the ring C is fully saturated. The configuration at C-11 of the epimers **4b,c**, **4d,e** and **8a,b** follows from the position and the width at half height ($W_{1/2}$, *Table 1*) of the ^{1}H-NMR signal for the 11-proton and from the known absolute configuration at C-9. According to Bhacca *et al.*,[15] the 11-hydroxy configuration is α for compounds **4c, 4e**, **8a** and β for **4a**, **4d** and **8b**. Since the proton at position 13 in compounds **1** and **2a** was shown to be β by X-ray analysis,[16] the same configuration may be also assigned to compounds **8a,f** which are chemically related to **2a**. All the products were colorless solids.

TABLE 1. Resonances and $W_{1/2}$ for Protons at C11 in ^{1}H NMR Spectra

Compound	Configuration of 11-H	(ppm)	$W_{1/2}$ (Hz)
4d	(eq)	4.33	11.5 ($J_{9,11}$=5.0 $J_{11,12}$=4.0)
4e	(ax)	4.18	14.5 ($J_{9,11}$=8.5 $J_{11,12}$=3.5)
8a (methyl ester)	(ax)	4.13	28.5
8b (methyl ester)	(eq)	4.45	9.0

EXPERIMENTAL SECTION

Mps were taken on a Büchi capillary apparatus and are uncorrected; maximal temperatures of 300-320° were achievable and compounds that did not melt in this range are reported as mp. >300°. IR spectra were determined on a Perkin Elmer 177 spectrophotometer as mineral oil mulls. ^{1}H-NMR spectra were recorded on a Perkin Elmer 60 MHz R-12B spectrometer for solutions in $CDCl_3$. Chemical shifts are reported in parts per million (δ) downfield from internal tetramethylsilane. Mass spectra were obtained on a Varian MAT-12 mass spectrometer (at 70 eV) and UV spectra on a Beckman 3600 spectrophotometer for solution in methanol. Optical rotations were measured on a Perkin Elmer 141 polarimeter in tetrahydrofuran unless otherwise specified. Column chromatography was performed over silica gel 60 (E. Merck) using methylene chloride with increasing proportions of tetrahydrofuran as eluting system. Methyl esters were made by treating a suspension of the acid in methylene chloride with an excess of ethereal diazomethane. Acetates, unless otherwise specified, were prepared using acetic anhydride in pyridine at room temperature. Usual work up refers to acidification with conc. hydrochloric acid to pH 2 followed by extraction with ethyl acetate. The ethyl acetate was back-washed with water before evaporation *in vacuo*. **CAUTION**: HMPT is a carcinogen. Avoid inhalation or contact with skin. Use only in a chemical fume hood.

Preparation of Methyl 3β,11β-Dihydroxyolean-12-en-30-oate (4d). Glycyrrhetic acid (**1a**, 2.5 g, 5.3 mmol), sodium borohydride (12.5 g, 330 mmol) and sodium hydroxide pellets (1.25 g, 31 mmol) were dissolved in a mixture of tetrahydrofuran (100 mL) and of water (100 mL). The heterogeneous mixture was refluxed for 4 h. The organic layer was poured into a 5% aqueous solution of NaH_2PO_4 (500 mL) and extracted with ethyl acetate. The crude product was methylated with diazomethane and chromatographed affording 2.0 g (77%) of the 11β-epimer **4d**, mp. 199-200°, lit.[8] mp. 105°; $[\alpha]_D$ +146.9 (c = 0.8, $CHCl_3$), lit.[8] $[\alpha]_D$ +181.4. ^{1}H NMR: δ 5.4 (1H, d, 4.0 Hz, 12-H), 4.33 (1H, q, $W_{1/2}$

11.5 Hz, 11-H), 3.70 (3H, s, $COOCH_3$), 3.25 (1H, m, $W_{1/2}$ 19.5 Hz, 3H), 1.40, 1.22, 1.12, 1.10, 1.00 (each 3H, s), 0.83 (6H, s).

Anal. Calcd. for $C_{31}H_{50}O_4$: C, 76. 50; H, 10.36. Found C, 76.54; H, 10.35

Further elution gave 360 mg (14%) of the 11α epimer **4e,** mp. 214-215°, lit.[16] mp. 258°; $[\alpha]_D$ +89.7 (c = 1, $CHCl_3$). ^1H NMR: δ 5.36 (1H, d, J 3.5 Hz, 12-H), 4.18 (1H, dd, J 3.5 and 8.5 Hz, 11-H), 3.70 (3H, s, $COOCH_3$), 3.26 (1H, m, $W_{1/2}$ 19.5 Hz, 3-H), 1.23, 1.13, 1.06 (each 3H, s), 1.02, 0.81 (each 6H, s).

Anal. Calcd. for $C_{31}H_5O_4$: C, 76.50; H, 10.36. Found : C, 76.71: H, 10.28

Preparation of 3β-Hydroxyolean-9(11),12-dien-30-oic Acid (5). A solution of crude 3β,11-dihydroxyolean-12-en-30-oic acids (**4d,e**, 0.5 g, 1 mmol) in tetrahydrofuran (10 mL) containing a drop of conc. hydrochloric acid was refluxed for 8 h then evaporated to dryness. Column chromatography gave 450 mg (98%) of **5**, mp. > 300°, $[\alpha]_D$ +374.0 (c = 1). UV λ_{max}: 280 nm (log ε 3.95).

Anal. Calcd. for $C_{30}H_{46}O_3$: C, 79.24; H, 10.20. Found: C, 79.05; H, 10.08

Preparation of 3-Acetoxyolean-11,13(18)-dien-30-oic Acid (6b). A mixture of crude 3β,11-dihydroxyolean-12-en-30-oic acids (**4b,c**, 1 g, 2.2 mmol), 40 mL of acetic acid and 10 mL of conc. hydrochloric acid was refluxed for 2 h, poured into water (200 mL) and filtered. Column chromatography afforded 770 mg (71%) of **6b**, mp. >300°, $[\alpha]_D$ -32.8 (c = 1.18); UV λ_{max} : 258, 248 and 240 nm; ^1H NMR δ: 6.40 (1H, dd, J 3.0 and 10.0, 11-H), 5.62 (1H, d, J 10.0 Hz, 12-H), 4.56 (1H, m, $W_{1/2}$ 19.5 Hz, 3-H) 2.05 (3H, s, CH_3COO), 1.11 (6H, s), 0.99, 0.94 (each 3H, s), 0.88 (6H, s), 0.72 (3H, s).

Anal. Calcd. for $C_{32}H_{48}O_4$: C, 77.37; H, 9.74. Found C, 77.22; H, 9.53

The same product was obtained by refluxing a solution of **5** (500 mg, 1.1 mmol) in acetic acid (50 mL) and conc. hydrochloric acid (10 mL) for 4 h. Yield: 80 mg (15%), mp. > 300°, after purification by preparative tlc.

Preparation of 3β-Hydroxyolean-11,13(18)-dien-30-oic Acid (6a). A solution of the above acetate **6b** (500 mg, 1 mmol) in 95% ethanol (25 mL) containing potassium hydroxide (250 mg, 4.5 mmol) was refluxed for 6 h. The reaction mixture was concentrated under reduced pressure and poured into water. Work up as usual afforded 450 mg (98%) of **6a**, mp. > 300°, $[\alpha]_D$ -41.3 (c = 1.06) .

Anal. Calcd. for $C_{30}H_{46}O_3$: C, 79.24; H, 10.20. Found: C, 79.32; H, 10.28

Preparation of 3β-Hydroxyolean-12-en-30-oic Acid (4a). To a solution of glycyrrhetic acid (**1a**) (1 g, 2.1 mmol) in 80 mL of hexamethylphosphoric triamide containing 2 mL of *t*-butyl alcohol, lithium wire (300 mg, 43 mmol) cut into small pieces was added at room temperature under vigorous stirring . The deep blue color appeared after about 30 minutes and the temperature rose to 60°. After the blue color vanished (~ 4 h), the solution was poured into 300 mL of water. Usual work-up and subsequent column chromatography afforded 800 mg (82%) of **4a**, mp. > 300°, $[\alpha]_D$ +118.5 (c = 1.36), mass spectrum: m/z 456 (M^+).

Anal. Calcd. for $C_{30}H_{48}O_3$: C, 78.89; H, 10.59. Found: C, 78.75; H, 10.81

The corresponding methyl 3β-acetoxyolean-12-en-30-oate showed mp. 263-264°, (lit.[8] mp. 262-263·); $[\alpha]_D$ +118.7 (c = 1.07) (lit.[8] $[\alpha]_D$ +112.3).

Preparation of 3β-Hydroxyolean-13(18)-en-30-oic-Acid (7). To a solution of the diene **6a** (5 g, 11

mmol) in 400 ml of hexamethylphosphoric triamide containing 15 mL of *t*-butyl alcohol, lithium shots (1.5 g, 2.2 mol) were added all at once and the resulting mixture was vigorously stirred till the deep blue colour disappeared. The solution was then poured into water (1.5 L) and worked-up as usual. Column chromatography afforded 4.5 g (90%) of the product **7**, mp. > 300°, $[\alpha]_D$ -23.1 (c = 1.02); mass spectrum: m/z = 456 (M^+).

Anal. Calcd. for $C_{30}H_{48}O_3$: C, 78.89; H, 10.59. Found: C, 78.81; H, 10.75

The corresponding methyl ester had mp. 244-246° (lit.[17] 245-246°).

Preparation of 3β,11α-Dihydroxyolean-30-oic Acid (8a) and 3β,11β-Dihydroxyolean -30-oic Acid (8b). A solution of 3-*O*-acetylglycyrrhetic acid (**1b**) (15 g, 29.3 mmol) in 300 mL of anhydrous tetrahydrofuran was added over 1 h to a solution of lithium (5 g, 7.2 mol) in 1.5 L of distilled ammonia at -78°. The mixture was stirred for 2 h then 100 mL of 2-propanol were added over 45 min, the temperature being maintained below -70°. At the end of the addition cooling was removed and, when the blue colour vanished, 50 g of ammonium chloride were added and ammonia allowed to evaporate overnight. The crude product was dissolved in tetrahydrofuran (200 mL) containing few drops of conc. hydrochloric acid and the solution was refluxed for 1 h (to transform allylic alcohols into the diene **5**, then evaporated to dryness. The product thus obtained was chromatographed affording 9.4 g (68%) of the 11α epimer **8a**, mp. > 300°, $[\alpha]_D$ +25.7 (c = 1.06). ^{1}H NMR (of the corresponding methyl ester **8c**): δ 4.13 (1H, m, $W_{1/2}$ 28.5 Hz, 11-H), 3.66 (3H, s, $COOCH_3$), 3.23 (1H, m, W_ 18.0 Hz, 3-H), 1.33, 1.13, 1.05, 1.03, 0.99, 0.90, 0.80 (each 3H, s).

Anal. Calcd. for $C_{30}H_{50}O_4$: C, 75.90; H, 10.62. Found: C, 75.81; H, 10.68

Further elution gave 1.9 g (14%) of the 11β epimer **8b** mp. > 300°, $[\alpha]_D$ +48 (c = 1.34). ^{1}H NMR (of the corresponding methyl ester **8d**) δ: 4.45 (1H, m, $W_{1/2}$ 9.0 Hz, 11-H), 3.67 (3H, s, $COOCH_3$), 3.22 (1H, m, $W_{1/2}$ 18.0 Hz, 3-H), 1.40 (3H, s), 1.34 (6H, s), 1.14 (3H, s), 0.98 (6H, s), 0.80 (3H, s).

Anal. Calcd. for $C_{30}H_{50}O_4$: C, 75.90; H, 10.62. Found: C, 75.74; H, 10.53

Preparation of 3β-Acetoxyolean-9(11)-en-30-oic Acid (2b). A mixture of the diol **8a** (2.7 g, 5.7 mmol), acetic acid (108 mL) and conc. hydrochloric acid (27 mL) was heated at 90° for 1 h, poured into water (200 mL) and filtered. Column chromatography afforded 2.3 g (81%) of **2b**, mp. 305-307°, $[\alpha]_D$ +84.6 (c = 1.04). ^{1}H NMR: δ 5.36 (1H, m, $W_{1/2}$ 9.0 Hz, 11-H), 4.52 (1H, m, $W_{1/2}$ 19.5 Hz, 3-H), 2.04 (3H, s, CH_3COO), 1.24, 1.22, 1.17, 0.96 (each 3H; s), 0.87 (9H, s).

Anal. Calcd. for $C_{32}H_{50}O_4$: C, 77.05; H, 10.11. Found: C, 77.01; H, 9.93

Preparation of 3β-Hydroxy-11-oxoolean-30-oic Acid (8e). A solution of 3β-trimethylsilyloxy-11-oxoolean-12-en-30-oic acid (10 g, 18.4 mmol) in 300 mL of anhydrous tetrahydrofuran was added over 1 h to a solution of lithium (5 g, 0.72 mol) in 1.5 L of distilled ammonia at -78°. The mixture was stirred for 1 h then 200 mL of acetone were added over about 45 min, the temperature being kept below -70°. At the end of the addition cooling was removed and the reaction treated as described above, thus affording, after chromatography, 6 g (69%) of the ketone **8e** mp. > 300°, $[\alpha]_D$ +24.9 (c = 1.02).

Anal. Calcd. for $C_{30}H_{48}O_4$: C, 76.22; H, 10.24. Found: C, 76.38; H, 10.06

Further elution gave 300 mg (3.4%) of the diol **8a**, identical with an authentic sample.

Preparation of 3β-Hydroxyolean-30-oic Acid (8f). A mixture of 3β-hydroxy-11-oxoolean-30-oic acid (**8e**, 4.5 g, 9.5 mmol), 98% hydrazine hydrate (57 mL, 1.17 mol), hydrazine dihydrochloride (10.8 g, 103 mmol) and 250 mL of triethylene glycol was heated at 140° for 24 h. After adding potassium hydroxide pellets (25 g, 446 mmol), the temperature was raised to 230° distilling off the low-boiling material. After 6 h the reaction mixture was poured into 1.5 L of water. Usual work-up afforded 4 g (92%) of the compound **8f**, mp. > 300°, $[\alpha]_D$ +39.0 (c = 0.97). IR 3430 and 1705 cm^{-1}. *Anal* .Calcd. for $C_{30}H_{50}O_3$: C, 78.55; H, 10.99. Found: C, 78.42; H, 10.83

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