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SYNTHESIS AND REACTIONS OF 18β-GLYCYRRHETALDEHYDE

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Abstract—18β-Glycyrrhetaldehyde has been prepared by two methods and its synthetic potential has been studied. In spite of some steric hindrance, it reacts on the whole quite normally. The aldehyde has been used for the preparation of derivatives with side-chains at C-20 which resemble those in the corticoid hormones.

Amongst the triterpenoid acids occurring in nature, 18β-glycyrrhetic acid (**1**) appears to have the most pronounced pharmacological effects, as many recent papers describe the medicinal use of glycyrrhetic acid and its simple derivatives.[1]

It seemed that 18β-glycyrrhetaldehyde (**2**) should be a suitable starting material for the preparation of derivatives with side-chains at C-20β that have possible biological interest.

Glycyrrhetaldehyde is unknown but 11-deoxoglycyrrhetaldehyde had been prepared by Ruzicka[2] using Rosenmund's method, and by Brieskorn[3] through LAH reduction of O-acetyl-glycyrrhetamide in low yield.*

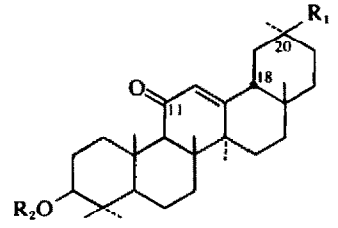
We have obtained glycyrrhetaldehyde in two ways: reduction of the thioester **5** with partly deactivated Raney nickel or, more conveniently, by the McFayden reaction. It is noteworthy that the latter method which is supposed to apply particularly to aromatic compounds,[4] gives about the same yield as the reduction of **5**.

Other attempts at the preparation of **2**, such as Brown's reduction of **4** with $LiAl(O\text{-}t\text{-}Bu)_3H$[5] or the oxazoline method[6] failed.

The aldehyde **2** is rather inactive and fails to give certain typical aldehyde reactions, e.g. with sodium diethyl oxalo-fluoroacetate[7] or methylsulphonodimethylphosphonomethane.[8] Even the reactions which have given positive results, demanded stringent conditions. Obviously this low reactivity is due to steric hindrance caused by the 20α-methyl and the *cis*-junction between rings D and E.

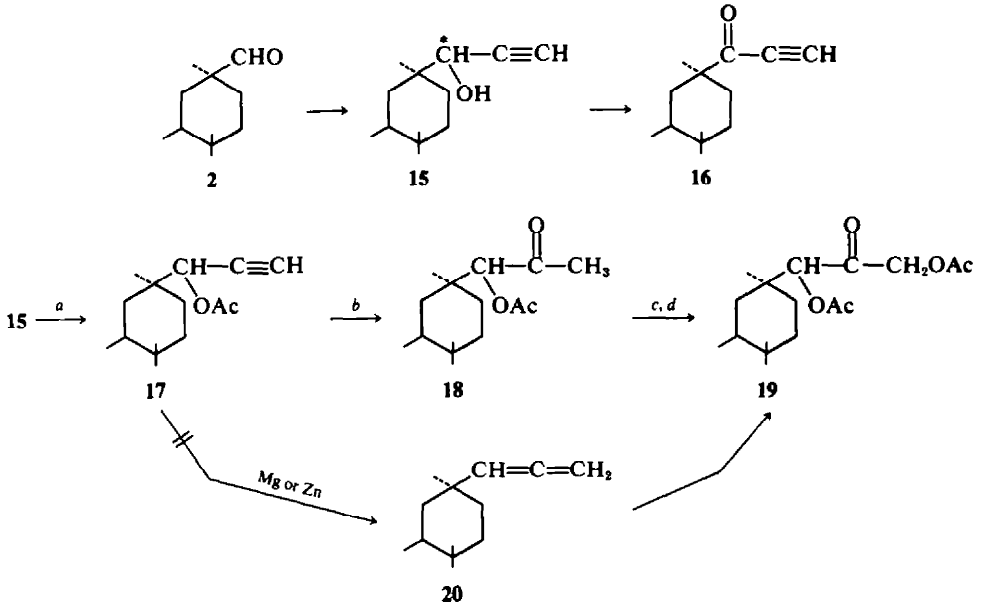
The aldehyde **2** reacts with triethyl phosphonoacetate, to give in good yield 20β-(*trans*-2-carbethoxyvinyl)-olean-12-en-11-on-3β-yl acetate (**7**), which could be hydrolyzed to the corresponding acid **8**. Another phosphonate which gave a positive reaction was diethyl *p*-bromophenylthiomethanephosphonate[9] which gave 20β-(*trans*-2-[*p*-bromophenylthio] vinyl)-olean-12-en-11-on-3β-ol (**9**).

Since steroids with acetylenic side chain often have interesting biological properties, we have prepared some acetylenic derivatives of glycyrrhetic acid. Compound **2** reacted with methylene-triphenylphosphorane in DMSO at 50° to give (after reacetylation) 20β-vinyl-olean-12-en-11-on-3β-yl acetate (**10**) which was brominated, using pyridine perbromide hydrobromide to 20β-(α,β-dibromoethyl)-olean-12-en-11-on-3β-yl acetate (**11**). The dehydrobromination of **11** was accomplished with methylsulphinyl carbanion in DMSO.[10] When the reaction was carried out at room temperature, the main product was 20β-(β-bromovinyl)-olean-12-en-11-on-3β-ol (**12**), whilst at 55° the desired 20β-



1:	$R_1 = COOH$	$R_2 = H$
2:	$R_1 = CHO$	$R_2 = Ac$
3:	$R_1 = CHO$	$R_2 = H$
4:	$R_1 = COCl$	$R_2 = Ac$
5:	$R_1 = COSCH_2C_6H_4Cl(p)$	$R_2 = Ac$
6:	$R_1 = CONHNHTs$	$R_2 = Ac$
7:	$R_1 = CH{=}CHCOOEt$	$R_2 = Ac$
8:	$R_1 = CH{=}CHCOOH$	$R_2 = H$
9:	$R_1 = CH{=}CHSC_6H_4Br(p)$	$R_2 = H$
10:	$R_1 = CH{=}CH_2$	$R_2 = Ac$
11:	$R_1 = CHBr\text{-}CH_2Br$	$R_2 = Ac$
12:	$R_1 = CH{=}CHBr$	$R_2 = H$
13:	$R_1 = C{\equiv}CH$	$R_2 = Ac$
14:	$R_1 = \overset{*}{C}H{-}C{\equiv}CH$ (OH)	$R_2 = H$

*The UV spectrum reported by Brieskorn for his compound (λ max = 286 mμ) seems to indicate that it is the 9,11-dehydro-11-deoxo-glycyrrhetaldehyde.



ethynyl-olean-12-en-11-on-3β-yl acetate (**13**) was obtained after reacetylation.

By direct reaction of **3** with ethynylmagnesium bromide, a mixture of two substances was obtained, which was separated by repeated preparative TLC. The compounds proved to be the epimeric 30-(3-hydroxy-1-propyn-3-yl)-olean-12-en-11-on-3β-ols (**14**). The ORD spectra of the two epimers exclude the possibility that epimerization at the sensitive centre at C-18 had taken place: Djerassi[11] has shown that derivatives of 18α-olean-12-en-11-one have negative rotation values in the 390-350 mμ region. Both our epimers have in this region positive values which are typical of the *cis*-junction between rings D and E. No attempts have yet been made to determine the absolute configuration of C-30 in these epimers.

Because of the steric hindrance from the two Me groups at C-4 one can apply ethynylmagnesium bromide also to **2** without fear of an attack on the acetyl group at C-3. 30-(3-Hydroxy-1-propyn-3-yl) olean-12-en-11-on-3β-yl acetate (**15**) is formed. When **15** is oxidized with chromic acid-sulphuric acid, 3-0-acetyl-glycyrrhetyl ethynyl ketone **16** is obtained.

In order to obtain corticoidal side chains, we studied the reaction values traced by the above formulae.

It is noteworthy that the hydratation of the acetylenic bond requires the OH group at C-30 to be acetylated to **17**, which undoubtedly is also a mixture of epimers. Hydratation yielded the two C-30 epimers of 20β-(1-acetoxy-2-oxo-1-propyl)-olean-12-en-11-on-3β-yl acetate (**18**) which were separated easily by preparative TLC.

The NMR spectrum of the more polar epimer of **18** has clearly three singlets at δ = 2·04, 2·12 and 2·16 ppm assigned to the 3-Ac, the 30-Ac and the Me ketone groups, respectively; it further shows peaks at δ = 5·18 and 5·76 ppm, for the C-30 H atom and the C-12 vinylic proton. After bromination of the methyl ketone the peak at 2·16 ppm disappeared: the bromomethyl ketone (—$COCH_2Br$) resonates as a singlet at 3·98 ppm, whilst the C-30 and C-12 H atoms absorb at 5·43 and 5·53 ppm respectively. On replacing the bromine by the acetoxy group to give **19**, the methylene is more shielded, apparently because of the mesomeric effect of the O atom[12]; thus it now resonates at a higher field (δ = 3·33 ppm). The 3–O and the new 32–O acetyl groups of the 20β-(1,3-diacetoxy-2-oxo-1-propyl)-olean-12-en-11-on- β-yl acetate (**19**) resonate at 2·00 and 2·10 ppm, respectively. The C-30 and C-12 H atoms, resonate at the same place as in the bromo compound.

Crabbe's pathway[13] for the construction of a corticoid side chain from **17** by reaction with Zn or Mg and OsO_4 oxidation of the corresponding allene **20** proved ineffective, the starting material being recovered quantitatively.

Also our attempts to introduce an acetoxy group in **18** directly by lead tetraacetate (with or without BF_3–OEt_2)[14] failed. A very complex mixture was obtained in which **19** was not present.

EXPERIMENTAL

18β-Glycyrrhetic acid was kindly supplied by Dr. D. Gredinger of "Chemicals and Phosphates Ltd.", Haifa, Israel. NMR spectra were measured with a Varian HA-

[a]Ac_2O-Py [b]$HgCl_2$-dioxane-H_2O [c]Pyridine hydrobromide perbromide [d]NaOAc-DMF.

100 instrument, $CDCl_3$ serving as solvent, TMS as internal standard and $CHCl_3$ as lock signal. Optical rotations were determined in chloroform with a Perkin-Elmer 141 polarimeter. IR spectra in Nujol mulls and m.ps on a Thomas-Hoover capillary apparatus. The term "treated in the usual way" refers to the treatment of extracts and indicates that they were washed with water till neutral, dried with $MgSO_4$ and evaporated to dryness *in vacuo*. Merck silica gel 70–325 mesh was used for column chromatography. Merck silica gel GF254 for analytical Tlc and Merck PF254 for preparative Tlc.

3-O-*Acetyl-glycyrrhetaldehyde* **2**.

Method A. S-p-*Chlorobenzylthioester of 3-O-acetyl-glycyrrhetic acid* (**5**)

To a suspension of NaH (1·44 g) (50% in oil, washed with hexane) in 50 ml dry THF, *p*-chlorobenzylmercaptan (5·0 g) was added and the mixture refluxed with stirring for 30 min. Then **4**[15] (5 g) in 100 ml THF was added and the mixture refluxed for 2·5 hr, poured into water, extracted with chloroform, washed with a 10% NaOHaq and treated as usual. The residue was recrystallised from CH_2Cl_2-MeOH; m.p. 255°; yield, 4·95 g (81%). IR $\tilde{\nu}$ = 1740, 1690, 1660 cm^{-1}; $[\alpha]_D^{25} = \perp 127{\cdot}0°$ (c = 1·0). (Found: C, 71·8; H, 7·9; S, 5·0. $C_{39}H_{53}SClO_4$ requires: C, 71·8; H, 8·1; S, 4·9%).

3-O-*Acetyl-glycyrrhetaldehyde* (**2**). Raney Ni (32 g) was partly deactivated by refluxing it with 60 ml acetone for 15 min. To the resulting suspension, **5** (3·7 g) in 100 ml THF was added with efficient stirring, and the mixture refluxed for 7 hr. The Ni was filtered off and washed with chloroform, and the filtrate treated as usual. The residue was chromatographed on a column of silica gel and eluted with benzene, which yielded some unchanged starting material. Elution with 5% ether in benzene gave about 1·0 gr of **2** (40%), from EtOAc, m.p. 265°; IR: ν = 1740; 1720; 1660 cm^{-1}; $[\alpha]_D^{25} = \perp 120{\cdot}0°$ (c = 1·0); NMR: δ = 1·40, 1·17, 1·14, 0·99, 0·89, 0·89, 0·81 ppm (for Me-26, 27, 25, 29, 23, 24 and 28 respectively[16])*; 2·05 ppm for Ac group, 4·55 ppm (q, for H-3); 9·43 ppm (s, for the aldehyde proton). (Found: C, 77·5; H, 9·5. $C_{32}H_{48}O_4$ requires: C, 77·4; H, 9·7%).

Method B: α-(3-O-*Acetyl-glycyrrhetyl*)-β-*tosylhydrazine* (**6**). To a cold soln of tosylhydrazine (8 g) in 20 ml pyridine a soln of **4** (15·9 g) in 40 ml THF-pyridine was added slowly. The mixture was left for 24 hr at room temp, poured into dil HCl, extracted with chloroform and treated as usual. The crude product was pure enough for the next step. An analytical sample was obtained by recrystallisation from benzene-hexane; m.p. 245°; yield, quantitative; IR: $\tilde{\nu}$ = 3320, 3260, 1730, 1690, 1650 cm^{-1}; $[\alpha]_D^{25} = \perp 134{\cdot}8°$ (c = 1·0). (Found: C, 69·0; H, 8·4; S, 4·4; N, 4·2. $C_{39}H_{58}SN_2O_6$ requires: C, 68·8; H, 8·2; S, 4·7; N, 4·1%).

Glycyrrhetaldehyde (**3**)

5 Na_2CO_3(5g) was added in one portion to a suspension of **6** (10 g) in 120 ml ethylene-glycol at 160°. After 30 sec the mixture was poured on ice, extracted with chloroform and treated as usual. The residue was recrystallised several times from MeOH, m.p. 286°; yield, 3·4 g (50%). IR: $\tilde{\nu}$ = 3620, 1740, 1660 cm^{-1}; $[\alpha]_D^{25} = \perp 147{\cdot}0°$ (c = 1·0). (Found: C, 79·0; H, 9·9. $C_{30}H_{46}O_3$ requires: C, 79·3; H, 10·1%).

The crude **3** can be reacetylated in 80% yield by treatment with excess Ac_2O-pyridine at 100° for 20 min. After another 12 hr at room temp the mixture is poured into dil HCl, extracted with chloroform and treated as usual. After chromatography as described in Method A, pure **2** is obtained.

20β-(trans-2-*Carbethoxyvinyl*)-*olean*-12-*en*-11-*on*-3β-*yl acetate* (**7**). 50% NaH (400 mg) (washed with hexane) in 10 ml toluene was added to triethyl phosphonoacetate in 70 ml of the same solvent. After the evolution of H_2 had ceased, **2** (1·8 g) in 20 ml toluene was added, the mixture refluxed for 6 hr under N_2, poured into 100 ml 10% $NaHCO_3$aq, extracted with chloroform and treated as usual. The residue was chromatographed on silica gel and eluted with 2% ether in benzene; m.p. 284°, yield 1·4 g (68%); IR: $\tilde{\nu}$ = 1740, 1730, 1650 cm^{-1}; $[\alpha]_D^{25} = \perp 197{\cdot}0°$ (c = 1·0); NMR: δ = 1·39, 1·17, 1·14, 1·03, 0·89, 0·89 and 0·83 ppm (for Me-26, 27, 25, 29, 23, 24 and 28, respectively); 3·90 ppm (q, 2H—$COOCH_2CH_3$); 4·53 (q, H-3); 5·60 (s, 12-H); 5·75 and 6·88 ppm (two d, olefinic protons, J = 16 Hz). (Found: C, 76·2; H, 9·5. $C_{38}H_{54}O_5$ requires: C, 76·3; H, 9·5%).

20β-(trans-β-*Carboxyvinyl*)-*olean*-12-*en*-11-*on*-3β-*ol* (**8**). To a soln of KOH (2·5 g) in 50 ml MeOH-dioxane, **7** (1·2 g) was added and the mixture refluxed for 5 hr under N_2, poured into dil HCl and treated as usual. The residue was recrystallised from benzene/hexane; m.p. 273°; yield 0·9 g (85%); IR: $\tilde{\nu}$ = 3400, 1700, 1660 cm^{-1}; $[\alpha]_D^{25} = \perp 55{\cdot}3°$ (c = 1·0); NMR: δ = 5·33 ppm (H-12), 5·80 and 7·02 (two d, olefinic protons, J = 16 Hz). (Found: C, 77·2; H, 9·8. $C_{32}H_{48}O_4$ requires: C, 77·4; H, 9·7%).

20β-(trans-2-p-*Bromophenylthio vinyl*)-*olean*-12-*en*-11-*on*-3β-*ol* (**9**). A soln of **3** (0·5 g) and diethyl *p*-bromophenylthio-methane-phosphonate (2·04 g) in 50 ml dry DMF was added to a suspension of 50% NaH (0·3 g) (washed with hexane) in 4 drops t-amyl alcohol. The mixture was kept at 120° for 24 hr under N_2, poured into dil HCl and treated as usual. The residue was triturated with MeOH; m.p. 230°; yield 0·3 g (43%); IR: $\tilde{\nu}$ = 3500, 1650, 1600 cm^{-1}; $[\alpha]_D^{25} = \perp 165{\cdot}0°$ (c = 1·0); UV: λ_{max}^{EtOH} = 251 mμ ($\epsilon = 1{\cdot}98 \times 10^4$), 274 mμ ($1{\cdot}74 \times 10^4$); NMR: δ = 1·38, 1·14, 1·14, 1·14, 1·01, 0·85 and 0·81 ppm (for Me-26, 27, 25, 29, 24, 23 and 28 respectively), 3·23 ppm (for H-3), 5·73 ppm (s, H-12), 5·60 and 6·20 ppm (two d, J = 11 Hz) AB spectrum for 4 aromatic protons (δA = 7·47, δB = 7·30; J = 11 Hz). (Found: Br, 12·6; S, 5·2. $C_{37}H_{51}BrO_2S$ requires: Br, 12·5; S, 5·0%).

20β-*Vinyl-olean*-12-*en*-11-*on*-3β-*yl acetate* (**10**). To a methylene-triphenylphosphorane soln (prepared from 14 g methyltriphenylphosphonium bromide in 80 ml DMSO and 1·5 g NaH (50%) according to Corey[17]), **2** (1·3 g) was added and the mixture stirred at 50° for 24 hr under N_2, poured into water, extracted with chloroform and treated as usual. The crude product was chromatographed on a silica gel column and eluted with 2% ether in benzene. After reacetylation the product was purified by preparative TLC, benzene as eluent; m.p. 272°; yield, 800 mg (60%); IR: $\tilde{\nu}$ = 1740, 1655 cm^{-1}; $[\alpha]_D^{25} = \perp 132{\cdot}0°$ (c = 1·0); NMR: δ = 1·39, 1·17, 1·15, 0·91, 0·89, 0·89, 0·82 ppm (for Me-26, 27, 25, 29, 24, 23 and 28 respectively), 2·05 ppm (3-acetyl group), 4·52 (q, H-3), 5·59 (s, H-12) and two multiplets at 5·07 and 5·66 ppm (for three olefinic protons, at C-30 and C-31). (Found: C, 80·0; H, 10·0. $C_{33}H_{50}O_3$ requires: C, 80·2; H, 10·1%.)

20β-(α,β-*Dibromoethyl*)-*olean*-12-*en*-11-*on*-3β-*yl acetate* (**11**). A mixture of **10** (640 mg), pyridine hydrobromide perbromide (500 mg) and 20 cc AcOH was heated at 40–50° for 2 hr in a N_2 atmosphere, poured into water,

*The various substituents at C-3 and C-30 are helpful for assignments of the Me groups.[16]

extracted several times with chloroform and treated as usual. The crude product (830 mg, 85%) is pure enough for the next step. An analytical sample was recrystallised from acetone-hexane, m.p. 240°; IR: $\tilde{\nu}$ = 1720, 1660 cm^{-1}; $[\alpha]_D^{25} = \perp 125{\cdot}0°$ (c = 1·0). (Found: C, 59·7; H, 7·5; Br, 24·2. $C_{33}H_{50}Br_2O_3$ requires: C, 60·5; H, 7·6; Br, 24·5%.)

20β-Ethynyl-olean-12-en-11-on-3β-yl acetate (**13**). Dry DMSO (60 ml) and 50% NaH ((400 mg), washed with hexane) were heated at 70° in a N_2 atmosphere till all the NaH had dissolved. The soln was cooled, and **11** (700 mg) in 10 ml dry DMSO was added. The mixture was kept at 60° for 12 hr and then poured into water, extracted with chloroform and treated as usual. The crude product was purified by preparative TLC, 4% MeOH in benzene serving as eluent. The product may be recrystallised from acetone-hexane; yield 300 mg (60%); m.p. 210°; IR: $\tilde{\nu}$ = 3250, 2100, 1700, 1660 cm^{-1}; $[\alpha]_D^{25} = \perp 103{\cdot}2°$ (c = 1·0); NMR: δ = 5·65 ppm (δ, H-12); 2·12 ppm (3-acetyl group). (Found: C, 80·6; H, 9·5; mol. wt. 492 (mass spectrum). $C_{33}H_{48}O_3$ requires: C, 80·5; H, 9·7%; mol. wt. 492).

When the reaction was carried out at room temp for 3 hr, **12** was formed, m.p. 90°, 20% yield, IR: $\tilde{\nu}$ = 3400, 1660 cm^{-1}; NMR: δ = 5·66 ppm (s, H-12); 5·47 (d, J = 6 Hz, 2H of CHBr = CH—). (Found: Br, 15·0. $C_{31}H_{47}BrO_2$ requires: Br, 15·1%).

30-(3-Hydroxy-1-propyn-3-yl)-olean-12-en-11-on-3β-ol (**14**). To a tenfold excess of a soln of ethynylmagnesium bromide[18] in 100 ml THF, **3** (1·5 g) in 20 ml THF was added. The mixture was stirred at room temp for 24 hr under N_2, poured into HCl and treated as usual. The residue was separated by repeated preparative TLC, using 7% MeOH in benzene as eluent. In this way, two epimers of **14** could be separated. The yield of the less polar epimer (**14a**) was 500 mg (32%); m.p. 282°; IR: ν = 3500, 3300, 1650 cm^{-1}; $[\alpha]_D^{25} = \perp 80{\cdot}4°$ (c = 1·0); NMR: δ = 1·37, 1·13, 1·13, 1·00, 0·98, 0·87, 0·81 ppm (for Me-26, 27, 25, 29, 24, 23 and 28 respectively), 3·23 (H-3), 5·62 (s, H-12), 2·47 (d, J = 2 Hz, acetylenic proton), 4·64 ppm (d, J = 2 Hz, proton at C-30 α-to acetylene); ORD (C, 0·2; dioxane); 25°; Φ420 = ⊥1005°; Φ390 = ⊥1200°; Φ380 = ⊥1100°; Φ370 = ⊥1415°; Φ360 = ⊥1030°; Φ350 = ⊥2060°; Φ347·5 = ⊥ 1965°; Φ260 = ⊥ 17250°; Φ210 = −27800°. (Found: C, 79·7; H, 10·0; mol. wt. 480 (mass spectrum). $C_{32}H_{48}O_3$ requires: C, 80·0; H, 10·0%; mol. wt. 480).

The yield of the more polar epimer (**14b**) was 415 mg (27%); m.p. 170°; IR: $\tilde{\nu}$ = 3400, 3300, 1650 cm^{-1}; $[\alpha]_D^{25} = \perp 126{\cdot}5°$ (c = 1·0); NMR: δ = 1·38, 1·14, 1·14, 1·01, 0·99, 0·87, 0·81 ppm (for Me-26, 27, 25, 29, 24, 23 and 28 respectively), 3·22 (H-3), 5·65 (s, H-12), 2·45 (d, J = 2 Hz, acetylenic proton), 4·61 ppm (d, J = 2 Hz, proton at C-30, α-to acetylene); ORD (c, 0·2, dioxane); 25°; Φ420 = ⊥1175°; Φ390 = ⊥1510°; Φ380 = ⊥1440°; Φ368 = ⊥1740°; Φ362 = ⊥1650°; Φ350 = ⊥2350°; Φ347·5 = ⊥2310°; Φ260 = ⊥16800°; Φ210 = −23000°. (Found: C, 79·8; H, 10·0; mol. wt. 480 (mass spectrum). $C_{32}H_{48}O_3$ requires: C, 80·0; H, 10·0%; mol. wt. 480).

30-(3-Hydroxy-1-propyn-3-yl)olean-12-en-11-on-3β-yl acetate (**15**). Analogously **15** can be prepared from **2** (1·1 g) by reaction with ethynylmagnesium bromide and purified by preparative TLC (5% MeOH in benzene). 530 mg (46%) of **15**, m.p. 259°, was thus obtained, accompanied by 170 mg (16%) of **14**. We did not separate the two epimers of **15**, IR: $\tilde{\nu}$ = 3520, 3300, 1725, 1650 cm^{-1}; $[\alpha]_D^{25} = \perp 92{\cdot}0°$ (c = 1·0). (Found: C, 77·8; H, 9·2; mol. wt. 522 (mass spectrum). $C_{34}H_{50}O_4$ requires: C, 78·2; H, 9·6%; mol. wt. 522).

15 was acetylated at C-30 in quantitative yield to give **17** by the procedure described for **2**; m.p. 276°; IR: ν = 3250, 2120, 1745, 1720, 1660 cm^{-1}; $[\alpha]_D^{25} = \perp 117{\cdot}3°$ (c = 1·0). (Found: C, 76·8; H, 9·2. $C_{36}H_{52}O_5$ requires: C, 76·6; H, 9·2%).

3-0-Acetyl-glycyrrhetyl ethynyl ketone (**14**). A suspension of **15** (150 mg) in 15 ml acetone was stirred with CrO_3 (25 mg), 5 ml water and 3-4 drops of conc H_2SO_4 at 0° under N_2 for 4 hr and then for 2 more hr at room temp. The mixture was poured into water, extracted with chloroform and treated as usual. Two compounds were separated by preparative TLC (6% MeOH in benzene). One of them, 57 mg (40%), proved to be the starting material (**15**); the second, 60 mg (41%), m.p. 272°, was the desired ketone; IR: $\tilde{\nu}$ = 3210, 2080, 1725, 1670, 1650 cm^{-1}; $[\alpha]_D^{25} = \perp 115{\cdot}0$ (c = 1·0). UV λ_{max}^{EtOH} = 249 mμ ($\epsilon = 1{\cdot}12 \times 10^4$), 308 mμ ($2{\cdot}6 \times 10^2$); NMR: δ = 5·62 ppm (s, H-12); 4·48 (q, H-3); 3·23 (s, acetylenic proton); 2·03 (s, acetyl group). (Found: C, 78·3; H, 9·0; mol. wt. 520 (mass spectrum). $C_{34}H_{48}O_4$ requires: C, 78·5; H, 9·2%; mol. wt. 520).

20β-(1-Acetoxy-2-oxo-1-propyl)-olean-12-en-11-on-3β-yl acetate (**18**). A mixture of **17** (1·05 g), $HgCl_2$ (2·5 g) and 100 ml dioxane-water (1 : 1) was refluxed for 7 hr, poured into water, extracted with chloroform and treated as usual. The two epimeric products **18** were separated by repeated preparative TLC (2% MeOH in benzene). The yield of the less polar component (**18a**) was 370 mg (35%); m.p. 252° (from acetone); IR: $\tilde{\nu}$ = 1745, 1725, 1720, 1655 cm^{-1}; $[\alpha]_D^{25} = \perp 100{\cdot}0°$ (c = 1·0); NMR: δ = 5·44 ppm (s, H-12), 5·21 ppm (s, H-30), 4·52 ppm (q, H-3), 2·19, 2·12 and 2·04 ppm (for methyl ketone group and acetyl groups at C-30 and at C-3, respectively). (Found: C, 74·3; H, 8·9; mol. wt. 582 (mass spectrum). $C_{36}H_{54}O_6$ requires: C, 74·2; H, 9·3%; mol. wt. 582).

The more polar isomer (**18b**) melted at 246°; yield, 420 mg (40%); IR: $\tilde{\nu}$ = 1740, 1730, 1710, 1655 cm^{-1}; $[\alpha]_D^{24} = \perp 95{\cdot}3°$ (c = 1·0); NMR: δ = 5·76 ppm (s, H-12), 5·18 ppm (s, H-30), 4·52 ppm (q, H-3), 2·16, 2·12 and 2·04 ppm (methyl ketone group and acetyl groups at C-30 and C-3, respectively). (Found: C, 73·4; H, 8·9; mol. wt., 582 (mass spectrum). $C_{36}H_{54}O_6$ requires: C, 74·2; H, 9·3%; mol. wt. 582).

20β-(1,3-Diacetoxy-2-oxo-1-propyl)-olean-12-en-11-on-3β-yl acetate (**19**). **18b** (250 mg), dry THF (25 ml), pyridine hydrobromide perbromide (250 mg) and $AlCl_3$ (9 mg) were stirred at room temp under N_2 for 3 days. The mixture was filtered and evaporated to dryness. The crude bromoketone was dissolved in 10 ml dry DMF, which contained 0·5 gr dry NaOAc, and stirred at 90–100° for 12 hr. The product was then poured into dil HCl, extracted with chloroform and treated as usual. After purification by preparative TLC using 3% MeOH in benzene as eluent, 50 mg (23%) of **19** was obtained; m.p. 150°; IR: $\tilde{\nu}$ = 1745, two shoulders at 1740 and 1735, 1670 cm^{-1}; $[\alpha]_D^{25} = \perp 290{\cdot}0°$ (c = 1·0); For NMR see the theoretical part. (Found: C, 71·4; H, 8·9. $C_{38}H_{56}O_8$ requires: C, 71·3; H, 8·8%).

REFERENCES

[1]More than 350 papers dealing with biological tests of glycyrrhetic acid and its derivatives have been published in the recent literature

[2]L. Ruzicka and A. Marxer, *Helv. Chem. Acta* **22**, 195 (1939)

[3]C. H. Brieskorn and H. Sax, *Arch. Pharm.* **303**, 901 (1970)

[4]*Organic Reactions* Vol. **8**, p. 232 (1954)

[5]H. C. Brown and R. F. McFarlin, *J. Am. Chem. Soc.* **78**, 252 (1956)

[6]I. C. Nordin, *J. Heterocyclic Chem.* **3**, 531 (1966)

[7]E. D. Bergmann and I. Shahak, *J. Chem. Soc.* 4033 (1961)
[8]I. Shahak and J. Almog, *Synthesis* 170 (1969)
[9]I. Shahak and J. Almog, *Ibid*, 145 (1970)
[10]J. Klein and E. Gurfinkel, *Tetrahedron* **26**, 2127 (1970)
[11]C. Djerassi, J. Osiecki and W. Closson, *J. Am. Chem. Soc.* **81**, 4587 (1959)
[12]L. M. Jackman and S. Sternell, *Application of NMR Spectroscopy in Organic Chemistry* (2nd Ed.) Pergamon Press (1969)
[13]M. Biollaz, W. Haefliger, E. Velarde, P. Crabbe and J. H. Fried, *Chem. Comm.* 1322 (1971)
[14]J. D. Cocker, H. B. Henbest, G. H. Phillips, G. P. Slater and D. A. Thomas, *J. Chem. Soc.* 6 (1965)
[15a]S. Rozen, I. Shahak and E. D. Bergmann, *Synthesis* 701 (1972); [b]S. Rozen, I. Shahak and E. D. Bergmann, *Israel J. Chem.* **9**, 185 (1971)
[16a]J. Karliner and C. Djerassi, *J. Org. Chem.* **31**, 1945 (1966); [b]M. Mousseron-Canet, F. Crouzet and J. P. Chabaud, *Bull. Soc. Chim. Fr.* 4668 (1967)
[17]E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.* **84**, 866 (1962); **87**, 1345 (1965)
[18]*Org. Syntheses* Coll. Vol. **4**, p. 792.