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BORJATRIOL, A NEW DITERPENOID FROM *SIDERITIS MUGRONENSIS*, BORJA (LABIATAE)

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Abstract – A new diterpene, borjatriol, isolated from the aerial parts of *Sideritis mugronensis*, Borja, is a derivative of manoyl oxide. Its structure, 6S,14R,15-trihydroxy-8α,13-epoxy-labdane (**1**), as well as the preferred conformation of ring C, has been established on the basis of chemical and spectroscopic data.

Sideritis mugronensis, Borja (Labiatae) is a perennial herbaceous shrub growing in the south-east of the Iberian Peninsula. The sole diterpenic component isolated from the ether extract of the plants is a new compound $C_{20}H_{36}O_4$ (borjatriol) (**1**).†

The IR spectrum of I exhibits strong —OH absorption and no —CO— bands. Acetylation of I yields a triacetate (**2**), the IR spectrum of which is devoid of —OH adsorptions. It seems plausible that the fourth oxygen atom is involved in a ether linkage.

The NMR spectrum of **2** is very informative. At δ 4·95 there is a 2H complex signal corresponding to protons geminal to acetoxyl groups. Between δ 4·60 and 3·85 there are eight lines, the AB part of an ABX system ($J_{AX} = 9{\cdot}33$ Hz, $J_{BX} = 2{\cdot}66$ Hz, $J_{AB} = 12$ Hz). The chemical shift and the integration (2H) of the eight lines pattern suggests it originates in two protons of an acetylated primary alcohol. Three acetoxyl groups appear at δ 2·01, 2·05 and 2·09. In the upper region of the spectrum five methyl singlets at δ 1·31, 1·24, 0·86, 0·79 and 0·78 are observed. Double resonance experiments show that X part of the ABX system is located at δ 4·95; irradiation of this complex signal collapses the AB pattern to a clean quartet ($J_{AB} = 12$ Hz) centered at δ 4·26; similarly irradiation at the latter frequency sensibly narrows the complex signal appearing at δ 4·95. It is then obvious the presence of a —CHOAc—CH_2OAc system at the borjatriol triacetate.

The presence of five methyl singlets, two of them (at δ 1·31 and 1·24) attached to carbon atoms bearing an ethereal oxigen,[1] taken in conjunction with the tricyclic nature of borjatriol (suggested by its molecular formula and absence of unsaturations) pointed toward a structural hypothesis based on the labdane skeleton with an 8,13-cyclic ether and two hydroxyl groups on the ethyl side chain. This structure is represented by **1** with the third hydroxyl group located at the carbocyclic system. The corroboration of these hypothesis and the justification of the absolute stereochemistry of borjatriol are discussed below.

The presence of a —CHOH—CH_2OH side chain attached to C-13 system responsible for the ABX pattern found in the NMR spectrum of **2** is substantiated by the products obtained treating borjatriol with HIO_4 in ethanol solution. Formaldehyde is formed (characterized as the dimedone derivative); and a hydroxyaldehyde **3** is isolated as well. The aldehydic proton of **3** appears as a singlet at δ 9·49 proving the fully-substituted nature of C-13.

Borjatriol treated with acetone/$CuSO_4$ is transformed smoothly in a hydroxyacetonide (**4**) which, acetylated at the usual manner, yields a monoacetate **5**. The NMR spectrum of **5** shows a 1H complex signal at δ 4·72 assigned to the proton geminal to the acetoxyl group. The protons implied at the acetonide grouping (3H) appear accumulated at δ 3·90.

When the hydroxyaldehyde **3** is subjected to Huang-Minlon reduction the main product is an alcohol **6**. The NMR spectrum of **6** exhibits six methyl singlets at 1·24, 1·21, 1·14, 0·87, 0·81 and 0·78. The three signals appearing at lower field correspond to methyl groups linked to C-8 and C-13, the sites of attachment of the ether bridge.

Several compounds possessing the carbocyclic system represented by formula **1**, are known differing in the stereochemistry of the A/B ring junction and/or the stereochemistry of the C-8, C-9 and C-13 assymmetric centres.[2–6] Our first goal was to try to correlate borjatriol with one of the known variations of the same skeleton.

The reaction of the hydroxyacetonide **4** with tosyl chloride gives the tosylate **7**, easily transformed into the benzylthioether **8** by reaction with benzylmercaptan and metallic sodium in DMF solution. Desulfuration of **8** with Raney Ni gives

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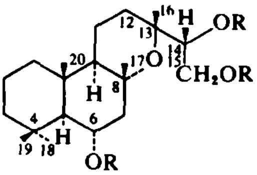
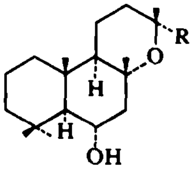
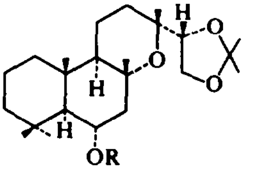
†We have followed the numbering system of E. Fujita, *Bull. Inst. Chem. Res., Kyoto Univ.*, **48**, 294 (1970).



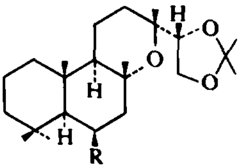
1 $R=H$
2 $R=Ac$



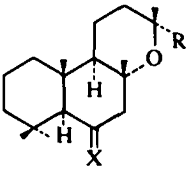
3 $R=-CHO$
6 $R=-CH_3$



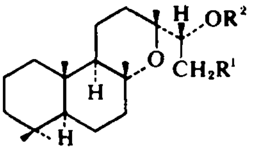
4 $R=H$
5 $R=Ac$
7 $R=-SO_2-C_6H_4-CH_3$
27 $R=-CH_2-C_6H_5$
29 $R=-CO-C_6H_5$



8 $R=-S-CH_2-C_6H_5$
9 $R=H$



10 $R=-CHO, X=H_2$
11 $R=-COOH, X=H_2$
12 $R=-COOCH_3, X=H_2$
13 $R=-CH=N-NH-CO-NH_2, X=H_2$
14 $R=-CH=CH_2, X=H_2$
21 $R=CH_3, X=O$
22 $R=CO_2H, X=O$



15 $R^1=-OH; R^2=H$
16 $R^1=-OSO_2-C_6H_4-CH_3; R^2=H$
17 $R^1=-S-CH_2-C_6H_5; R^2=H$
18 $R^1=R^2=H$
19 $R^1=H; R^2=-CO-C_6H_5$

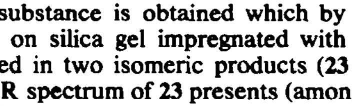
9, subjected to HIO_4 oxidation yields the aldehyde 10. Oxidation of 10 with Jones' reagent provides the acid 11. The m.ps of the acid 11, its methyl ester 12 and the semicarbazone 13 of the aldehyde 10 are identical with those described for the corresponding derivatives of manoyl oxide 14. The IR spectra and $[\alpha]_D$ values are also identical as well.[1,2]

The preceding results define as *trans-anti-trans* the relative stereochemistry of the A, B and C ring junctions and as *cis* the relationship of the methyl groups attached to C-8 and C-13. Since the absolute stereochemistry of manoyl oxide has already been established[2] these results also define the absolute stereochemistry of the carbocyclic skeleton of borjatriol as depicted in 1. It remains to define the absolute stereochemistry of the secondary alcohol on C-14 and the position and configuration of the other secondary hydroxyl group.

Absolute stereochemistry of C-14. Compound 9 treated with HCl in methanol solution yields quantitatively the diol 15, which under controlled conditions can be transformed into the monotosylate 16 and benzylthioether 17. Desulfuration (Raney/Ni) of the last compound affords the alcohol 18.

Two different methods, Horeau's method of partial resolution[7,8] and the "benzoate rule",[9] when applied to the alcohol 18 define as 14R the absolute stereochemistry of this carbon atom (see Experimental).

Position and configuration of the secondary —OH on the carbocyclic system. Oxidation (Py/CrO_3) of the hydroxyacetonide 4 yields a product 20 which shows two distinct signals at δ 2·42 (1H, singlet) and δ 2·55 (2H, AB quartet, $J_{AB} = 14$ Hz). The same signals appear at the NMR spectra of the ketone 21 and the ketoacid 22. They are indicative of a partial structure such as:

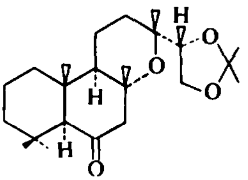


$$\begin{array}{cccccccc} & & C & & C & & C & \\ & & | & & | & & | & \\ C & - & C & - & CH & -CO-CH_2- & C & -O- \\ & & | & & & & | & \\ & & C & & & & C & \end{array}$$

which is compatible only with positions C-6 or C-11 for the carbonyl group.

When compound 3 is reduced (Huang-Minlon conditions), besides the expected product 6, another substance is obtained which by chromatography on silica gel impregnated with $AgNO_3$, is resolved in two isomeric products (23 and 24). The NMR spectrum of 23 presents (among others) signals due to an olefinic proton (triplet with further unresolved long range couplings at δ 5·23, J = 6 Hz) and to methyl groups (2 $-CH_3$) attached to olefin carbon atoms at δ 1·67. In addition there are a methyl group attached to carbon atom bearing an oxygen atom (δ 1·13) and three other methyl singlets at 0·88 (1 $-CH_3$) and δ 0·81 (2 $-CH_3$). The first two signals require the grouping $-CH_2-CH=C(CH_3)_2$.

On the other hand the NMR spectrum of 24



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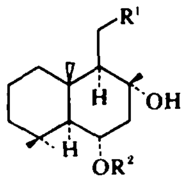
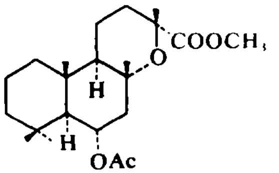


23 R^1= —CH=C(CH$_3$)$_2$; R^2=H
24 R^1= —CH$_2$—C(CH$_3$)=CH$_2$; R^2=H
25 R^1= —CH$_2$—CH(CH$_3$)$_2$; R^2=H
26 R^1= —CH$_2$—CH(CH$_3$)$_2$; R^2=Ac



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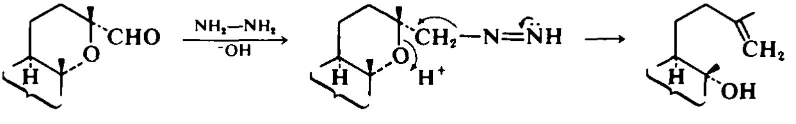
present five methyl singlets, one of which only is attached to double bond, while there is a new signal at δ 4·72 (slightly broaden 2H singlet), assigned to a terminal methylene (IR absorptions at 3080, 1648 and 880 cm^{-1}), and requiring the grouping —C(CH$_3$)=CH$_2$.

Compounds 23 and 24 confirm the attachment of the ethyl side chain to the same carbon atom that bears the ether linkage since they arise by fragmentation of 3 under the conditions of the Wolff-Kishner reaction[10] (Scheme).



SCHEME

The newly formed olefinic linkage is located at $\Delta^{12(13)}$ and $\Delta^{13(14)}$ respectively and there is a hydroxyl group attached at C-8 in both products. Accordingly the catalytic hydrogenation of 23 and 24 afford the same product 25 which acetylated at room temperature gives a monoacetate 26 with residual —OH absorption (3500 cm^{-1}) in its IR spectrum.

The NMR spectra of 23 and 24 show a —C$\underline{H}$-(OH)— signal analogous in position and shape to the one observed in compounds with intact ring C (such as 6). This observation and the multiplicity observed for the olefinic proton of 23 definitely excludes position C-11 as the location of the alcohol group. It is then located at C-6. This conclusion is supported by the fact that both 20 and 21 present a negative Cotton effect ($[\Phi]_{304}$ −7,315° and $[\Phi]_{304}$ −8,600°) compatible with position C-6 of the borjatriol skeleton.[11,12] The average width of the proton geminal to the —OH group is ~ 17 Hz indicating an axial configuration. Reduction (NaBH$_4$) of the C-6 keto group (in 20) takes place with considerable difficulty affording a product identical to the natural compound 4. Apparently the reduction takes place from the more hindered side implying that factors related to the "product development control" are prevailing.

The equatorial configuration assigned to the C-6 —OH group is supported by other observations. The NMR spectrum of the benzylthioether 8 presents a C-6 proton signal at δ 2·93 as a narrow multiplet ($W_{1/2}$ = 6 Hz). This is in accordance with an inversion of the C-6 configuration during the S_N2 reaction leading to 8. That there is an inversion at C-6 and not a mere change of conformation in ring B is consistent with the observation of a broad multiplet at δ 3·27 ($W_{1/2}$ = 17 Hz) in the NMR spectrum of the benzylether 27 (prepared from compound 4 by the action of benzyl chloride and KOH). The similar sterical size of the benzyl and benzylthioether exclude the possibility of ring B adopting a different conformation in both compounds. (Unfortunately we failed to prepare the epimeric benzylether on C-6 by reaction of the tosyl derivative with benzyl alcohol in basic media).

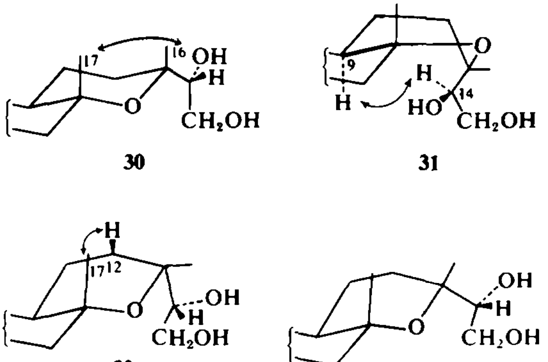
Identical conclusion regarding the configuration of C-6 is reached with the single product obtained by the Meerwein-Ponndorf-Verley reduction of 22. This product once methylated and acetylated yields 28, the NMR spectrum of which shows the C-6 proton as a multiplet ($W_{1/2}$ = 18 Hz) at δ 4·94. It is quite reasonable the obtention of the equatorial epimer as the sole reaction product due to the considerable eclipsing that would appear between the axial (β) epimer and the axial methyl groups (C-17, C-19 and C-20).

Final proof came from the application to product 4 of Horeau's method[13] and the "benzoate rule".[9] In both cases the results obtained define as 6S the configuration at this carbon atom, requiring an equatorial (α) —OH. The same conclusion is reached considering the molecular rotations of 4 (+34°), 5 (+118°) and 20 (−114°) in comparison with analogous steroidal C-6 alcohols.[14]

Therefore borjatriol is 6S,14R,15-trihydroxy-8α,13-epoxylabdane 1.

Conformational analysis of ring C. Dreiding models of the borjatriol molecule makes highly improbable ring C in the chair conformation since there are strong interactions between the C-16 and

C-17 methyl groups (**30**, Figure). The two possible boat conformations (**31** and **32**, Figure) can also be excluded on the basis of the intrinsic instability of these conformations and the strong interactions existing between C-14 and C-9 proton (**31**) and between the βH of C-12 and C-17 (**32**). It seems logical to assume for ring C a twisted boat conformation (such as **33**, Figure) where most interactions are minimized. In agreement with this assumption the molecular amplitudes of the ORD curves of compounds **20** and **21** are a $= -175$ and a $= -190$ respectively implying that in the case of **20** there is an extra contribution into the positive octant, a situation compatible with conformation **33** (see Fig 1).[15]



30 **31**

32 **33**

Fig 1.

Borjatriol is the first diterpene isolated from plants of the *Sideritis* genera presenting a normal (steroid-like) A/B ring junction since up to now all the products isolated presented an antipodal fusion of these rings.[16–26]

EXPERIMENTAL

All m.ps were determined in a Kofler apparatus and are uncorrected. Refractive indexes were measured in a Karl Zeiss refractometer. The optical rotations were measured using a Perkin Elmer 141 Polarimeter with 1 dm cells. The IR spectra were recorded with a Perkin Elmer 257 Spectrophotometer, neat or in KBr disc. The NMR spectra were performed on a Perkin Elmer R-12 Spectrometer, in $CDCl_3$ solution using TMS as an internal standard. Elemental analyses were carried out in this laboratory using an automatic analyzer. Column chromatography separations were carried out on silica gel (Merck) (0·02–0·5 mm) and preparative layer chromatography (plc) was carried out on silica gel $6OPF_{254}$ (Merck) support (20 × 20 cm and 2 mm thick).

Extraction of borjatriol (**1**). Dried and finely divided plants (*S. mugronensis*, 1·73 kg) were Soxhlet extracted with pet ether (b.p. 50–70°, 16 l) during 72 hr. The pet ether extract, concentrated to 700 ml, was extracted (4 × 500 ml) with 90% aqueous MeOH. The methanolic extract was concentrated (0·5 1), diluted with H_2O (2 1) and extracted with $CHCl_3$ (8 × 250 ml). The chloroform solution, once evaporated, leaves a residue (19·3 g) that purified by column chromatography (eluant, $CHCl_3$: MeOH 9 : 1) gave **1** (10·9 g) an amorphous solid; it sublimes at 180° and 0·2 mm/Hg as an amorphous solid that softens at 184–190° and melts (decomp) at 285°; $[\alpha]_D^{20°}$ $-2·3°$ (*c* 1·47, $CHCl_3$); IR: ν_{max}^{KBr} 3410, 3000, 2950, 2880, 1465, 1390, 1207, 1125, 1105, 1075, 1045, 995, 960 and 895 cm^{-1}. NMR (δ): Complex signal between 3·15 and 4·40 (4H; C-6, C-14 and C-15 protons), C-methyl singlets at 1·27, 1·21, 0·87, 0·80 and 0·77. (Found: C, 70·67; H, 10·83; $C_{20}H_{36}O_4$ requires: C, 70·54; H, 10·66%).

Borjatriol triacetate (**2**). The triol **1** (200 mg) was dissolved in Py/Ac_2O at room temperature during 48 hr. The triacetate **2** crystallized from aq. EtOH, m.p. 121·5–122·5°; $[\alpha]_D^{20°}$ $+50·4°$ (*c* 1·42, $CHCl_3$); IR: ν_{max}^{cKBr} 2960, 1740, 1290 and 1235 cm^{-1}. NMR (δ): 4·95 (2H, C-6 and C-14), 4·26 (2H, AB part of the ABX system, $J_{AB} = 12$ Hz, $J_{AX} = 9·33$ Hz, $J_{BX} = 2·66$ Hz, C-15), 2·09, 2·05 and 2·01 (—O—CO—CH_3 singlets), 1·31, 1·24, 0·86, 0·79 and 0·78 (C—Me singlets). (Found: C, 67·03; H, 9·37; $C_{26}H_{42}O_7$ requires: C, 66·92; H, 9·07%).

Hydroxyaldehyde **3**. The triol **1** (174 mg) was dissolved in ethanol (20 ml), to this solution 0·1N aq ethanolic HIO_4 (30 ml) was added. The mixture was left at room temperature in the dark during 24 h. The soln was made alkaline with saturated aq $NaHCO_3$ and extracted with chloroform. The aqueous phase was distilled in part. The distillate was used to prepare the dimedone derivative of formaldehyde, m.p. 191–191·5°[27] (from EtOH: H_2O). (Found: C, 70·08; H, 8·54; $C_{17}H_{24}O_4$ requires: C, 69·83; H, 8·27%).

Evaporation of the $CHCl_3$ extract yields **3** (135 mg). M.p. 120–122° (n-hexane); $[\alpha]_D^{20°}$ $+22·0°$ (*c* 0·3, $CHCl_3$); IR: ν_{max}^{KBr} 3560, 3530, 3460, 2705, 2680 and 1748 cm^{-1}. NMR (δ): 9·49 (iH, s, C-14), 3·65 (1H, m, $W_{1/2}$ 17 Hz, C-6), C—Me singlets at 1·26, 1·23, 0·88 and 0·80 (2 —CH_3). (Found: C, 73·99; H, 10·35; $C_{19}H_{32}O_3$ requires: C, 73·98; H, 10·46%).

Hydroxyacetonide **4**. Borjatriol **1** (500 mg) was dissolved in anhydrous acetone (200 ml) and $CuSO_4$ (3 g) was added to the soln. The mixture was heated under reflux for 48 hr. The reaction product **4** was crystallized from n-hexane. M.p. 161–162°; $[\alpha]_D^{20°}$ $+8·9°$ (*c* 1·36, $CHCl_3$); IR: ν_{max}^{KBr} 3600, 1210 and 860 cm^{-1}. NMR (δ): 3·93 (3H, m, C-14 and C-15), 3·50 (1H, m, $W_{1/2}$ 17 Hz, C-6), C—Me singlets at 1·41, 1·34, 1·27 (2 —CH_3), 0·88, 0·81 and 0·79. (Found: C, 72·78; H, 10·26; $C_{23}H_{40}O_4$ requires: C, 72·59; H, 10·6%).

Horeau's method[8]. The hydroxyacetonide **4** (41·3 mg) was dissolved in pyridine (2 ml) containing 0·380 mmol of (±)-α-phenylbutyric anhydride. The solution was left 16 hr at room temp. $\alpha_1 = +0·691$; $\alpha_2 = +1·012$; $\alpha_1 - 1·1\alpha_2 = -0·422$. Optical yield: 16%. Configuration: 6S.

Acetyl derivative **5**. The hydroxyacetonide **4** (50 mg) was acetylated at the usual manner (Py/Ac_2O) giving monacetate **5**; m.p. 98–100° (aq EtOH); $[\alpha]_D^{20}$ $+28·8°$ (*c* 0·4, $CHCl_3$); IR: ν_{max}(neat) 1740, 1240 and 855 cm^{-1}. NMR (δ): 4·72 (1H, m, $W_{1/2}$ 17 Hz, C-6), 3·90 (3H, m, C-14 and C-15), 2·02 (3H, s, —O—CO—CH_3), C—Me singlets at 1·37, 1·30 (2 —CH_3), 1·21, 0·86 and 0·79 (2 —CH_3). (Found: C, 71·13; H, 10·27; $C_{25}H_{42}O_5$ requires: C, 71·05; H, 10·02%).

Huang-Minlon reduction of **3**: *Compounds* **6**, **23** *and* **24**. A triethyleneglycol solution (60 ml) containing **3** (1·05 g), 85% hydrazine hydrate (20 ml) and absolute ethanol (20 ml) was kept at 180° during 2 hr; KOH (4 g) were then added maintaining the same temp during 1 hr. Excess hydrazine was distilled off and the temperature slowly raised to 220° for 3 hr. Once cooled, it was diluted with H_2O and extracted with $CHCl_3$. TLC showed two spots. "Dry column" chromatography[28,29] gave the two components with C_6H_6 : EtOAc (3 : 1). The less polar component (310 mg) was the alcohol **6**. m.p. 130·5–132° (n-hexane); $[\alpha]_D^{20}$ + 8·7° (*c* 1·13, $CHCl_3$); IR: ν_{max}^{KBr} 3480 cm^{-1}. NMR (δ); 3·60 (1H, m, $W_{1/2}$ 18 Hz, C-6), C-Me singlets at 1·24, 1·21, 1·14, 0·87, 0·81 and 0·78. (Found: C, 76·91; H, 11·81; $C_{19}H_{34}O_2$ requires: C, 77·49; H, 11·64%).

The most polar component (500 mg) gave two spots on $AgNO_3$ – impregnated silica gel plates with C_6H_6 : EtOAc. Using the same solvent system both products were separated on PLC, giving **23**: M.p. 60–65° aq EtOH; $[\alpha]_D^{20}$ + 5·1° (*c* 0·7, $CHCl_3$); IR: ν_{max}^{KBr} 3360, 3040 and 840 cm^{-1}. NMR (δ): 5·23 (1H, t, J = 6 Hz, C-12), 3·50 (1H, m, $W_{1/2}$ 18 Hz, C-6), 1·67 (6H, s, C-14 and C-16 Me), 1·13 (3H, s, C-17 Me), C-Me singlets at 0·88 and 0·81 (2 —CH_3). (Found: C, 72·90; H, 11·46; $C_{19}H_{34}O_2.H_2O$ requires: C, 73·03; H, 11·61%). **24**: M.p. 79–81° (n-hexane); $[\alpha]_d^{20}$ + 3·4° (*c* 0·5, $CHCl_3$); IR: ν_{max}^{KBr} 3375, 3080, 1648 and 880 cm^{-1}. NMR (δ): 4·72 (2H, broad singlet, $>C{=}CH_2$), 3·46 (1H, m, $W_{1/2}$ 18 Hz, C-6) 1·75 (3H, broad singlet, $CH_3{-}\overset{|}{C}{=}C<$), 1·10 (3H, s, C-17 Me), C-Me singlets at 0·88 and 0·80 (2 —CH_3). (Found: C, 77·37; H, 11·31; $C_{19}H_{34}O_2$ requires: C, 77·49; H, 11·64%).

Tosyl derivative **7**. The hydroxyacetonide **4** (700 mg) was dissolved in anhydrous pyridine (60 ml). To this solution, cooled to 0°, was added to p-toluenesulfonyl chloride (1 g) and the mixture left at room temperature during 5 days, diluted with water, and extracted with $CHCl_3$. **7** crystallized from aq EtOH, m.p. 133–136°; $[\alpha]_D^{20}$ + 64·7° (*c* 0·34, $CHCl_3$); IR: ν_{max}^{KBr} 3080, 3060, 1600, 1185, 1170 and 660 cm^{-1}. NMR (δ): 7·62 (4H, A_2B_2 aromatic system, J = 8 Hz), 4·28 (1H, m, $W_{1/2}$ 19 Hz, C-6), 3·5 (3H, m, C-14 and C-15), 2·43 (3H, s, Me-Ph), C-Me singlets at 1·34, 1·28 (2 —CH_3), 1·12, 0·86, 0·78 and 0·76. (Found: C, 67·46; H, 8·52; S, 5·85; $C_{30}H_{46}O_6S$ requires: C, 67·39; H, 8·67; S, 5·99%).

Benzylthioether **8**. A mixture of benzylmercaptan (2·1 g) in DMF (4 ml) and metallic sodium (0·19 g) was heated, with stirring under N_2 atmosphere, till the sodium dissolved. To this soln the monotosylate **7** (534 mg) in DMF (16 ml) was added. The temperature was raised to 150° and kept there for 10 hr. Once cooled it was diluted with water and extracted with chloroform. TLC indicated a single product that did not crystallize even after purification on PLC. **8**: n_D^{16} 1·5401; $[\alpha]_D^{20}$ + 45° (*c* 0·12, $CHCl_3$); IR: ν_{max}(neat) 3095, 3070, 1603 and 757 cm^{-1}. NMR (δ): 7·30 (5H, m, aromatic protons), 4·06 (3H, m, C-14 and C-15), 3·73 (2H, s, —S—CH_2—Ph), 2·93 (1H, m, $W_{1/2}$ 6 Hz, C-6), C-Me singlets at 1·38 (2 —CH_3), 1·32, 1·29, 0·86 and 0·75 (2 —CH_3). (Found: C, 74·14; H, 9·53; S, 6·41; $C_{30}H_{46}O_3S$ requires: C, 74·03; H, 9·53; S, 6·58%).

Desulfuration of **8** *to give* **9**. To an ethanol solution of **8** (300 mg) Raney Ni (3 g) was added. The mixture was heated under reflux for 10 hr. Filtration and evaporation yielded **9**, purified by PLC: n_D^{16} 1·5044; $[\alpha]_D^{20}$ + 25° (*c* 0·1, $CHCl_3$); IR: ν_{max}(neat) 2920, 1460, 1375, 1070 and 855 cm^{-1}. NMR (δ): 3·93 (3H, m, C-14 and C-15), C-Me singlets at 1·39, 1·31, 1·27 (2 —CH_3), 0·85, 0·78 and 0·76.

8α,13-epoxy-15-nor-labdan-14-al **10**. To an ethanol solution (10 ml) of **9** (185 mg), 0·3N aq ethanolic HIO_4 (20 ml) was added. The reaction mixture was left at room temperature 48 hr, made alkaline with saturated aqueous $NaHCO_3$, diluted with water and extracted with $CHCl_3$. The residue, purified by PLC was a syrup **10**, n_D^{16} 1·5039; $[\alpha]_D^{20}$ + 34·6° (*c* 0·3, $CHCl_3$); IR: ν_{max} (neat) 2690, 1743 cm^{-1}. NMR (δ): 9·57 (1H, s, C-14), C-Me singlets at 1·29, 1·22, 0·86 and 0·79 (2 —CH_3).

Semicarbazide of **10**. Semicarbazide hydrochloride (10 mg) in pyridine (0·2 ml) and a solution of **10** (8 mg) in EtOH (3 ml) were mixed and heated on a water bath during 1 hr. The semicarbazide **13** crystallized from EtOH : H_2O. Single product by TLC; m.p. 225–227° (lit[2] m.p. 225–227·5°).

8α,13-epoxy-15-nor-labdan-14-oic acid **11**. Jones' reagent was added dropwise to a cooled (0°) acetone solution of **10** (120 mg) until reaction was complete. The soln was left 2 hr at room temp. Excess reagent was destroyed adding ethanol and the soln was diluted with water and extracted with $CHCl_3$. The residue was crystallized from aq MeOH yielding **11** (112 mg), m.p. 47–50° (drying 24 hr at 40° and 0·05 mm/Hg raised the m.p. to 97–98°); $[\alpha]_D^{20}$ + 41·5° (*c* 0·54, $CHCl_3$); IR: ν_{max}^{KBr} 3330–2650, 1780, 1720^2 cm^{-1}. NMR (δ): 9·23 (1H, broad singlet, —COOH), C-Me at 1·45, 1·31, 0·86 and 0·79 (2 —CH_3). (Found: C, 74·02; H, 10·39; $C_{19}H_{32}O_3$ requires: C, 73·98; H, 10·46%). (Lit[2] m.p. 45–47° and 97–98°; $[\alpha]_D$ + 42°; identical IR spectra).

8α,13-epoxy-15-nor-labdan-14-oic methyl ester **12**. The methyl ester **12** was prepared treating an ether solution of **11** with diazomethane. Crystallization of the residue from MeOH : H_2O yields **12**, m.p. 85–86°; $[\alpha]_D^{20}$ + 9·0° (*c* 1·21, $CHCl_3$); IR: ν_{max}^{KBr} 1750 and 1155 cm^{-1}. NMR (δ): 3·73 (3H, s, —$COOCH_3$), C-Me singlets at 1·37, 1·25, 0·86 and 0·79 (2 —CH_3). (Found: C, 74·61; H, 10·81; $C_{20}H_{34}O_3$ requires: C, 74·49; H, 10·63%). (Lit[1,2] m.p. 84–85°; $[\alpha]_D$ + 9°, + 14°; identical IR spectra).

Diol **15**. To a methanol solution (100 ml) of **9** (850 mg) was added conc HCl (14 drops). The mixture was heated on a water bath during 40 min, then diluted with water and extracted with $CHCl_3$. The chloroform extracts were washed with aq $NaHCO_3$, dried and evaporated. The residue was purified on PLC ($CHCl_3$: MeOH; 97 : 3) yielding **15** (600 mg), m.p. 126–129° (EtOH : H_2O); $[\alpha]_D^{20}$ − 4·2° (*c* 0·42, $CHCl_3$); IR: ν_{max}^{KBr} 3460, 3420, 1120 and 1034 cm^{-1}. NMR (δ): 3·70 (AB part) and 3·12 (X part) of an ABX system (3H, C-14 and C-15; J_{AB} = 12 Hz, J_{AX} = 5·33 Hz, J_{BX} = 3·33 Hz), C-Me singlets at 1·29, 1·25, 0·86, 0·79 and 0·77. (Found: C, 73·78; H, 11·13; $C_{20}H_{36}O_3$ requires: C, 74·02; H, 11·18%). Acetylation of **15** at room temperature (Py/Ac_2O) yielded the *diacetate*, m.p. 70·5–71·5° (EtOH : H_2O); $[\alpha]_D^{20}$ + 33·5° (*c* 0·9, $CHCl_3$); IR: ν_{max}^{KBr} 1743, 1270 and 1220 cm^{-1}. NMR (δ): 4·30 (AB part) and 5·00 (X part) of an ABX system (3H, C-14 and C-15) (J_{AB} = 12 Hz, J_{AX} = 8·6 Hz, J_{BX} = 2·6 Hz), 2·08 and 2·01 (6H, s,s, 2 —O—CO—CH_3), C-Me singlets at 1·24 (2 —CH_3), 0·86, 0·78 and 0·76. (Found: C, 70·26; H, 9·64; $C_{24}H_{40}O_5$ requires: C, 70·55; H, 9·87%).

Monotosyl derivative of **15**. A pyridine solution (14·5 ml) of **15** (483 mg) and tosyl chloride (473 mg) was left 60 hr at room temp. After purification on PLC the monotosylate **16** (480 mg) was obtained as a syrup, n_D^{10} 1·5365; $[\alpha]_D^{20}$ + 16·3° (*c* 0·38, $CHCl_3$); IR: ν_{max}(neat) 3530, 3080, 1600, 1190, 1178, 755 and 665 cm^{-1}. NMR (δ): 7·61 (4H, A_2B_2 system, J = 8·6 Hz, aromatic protons), 4·16 and 3·38 (3H, ABX system, J_{AB} = 10·6 Hz, J_{AX} = 6·6 Hz, J_{BX} = 4·0 Hz), 2·46(3H, s, CH_3-Ph), C-Me singlets at 1·23, 1·18, 0·85, 0·78 and 0·75.

Benzylthioether derivative of **15**. Compound **16** (450 mg) was treated under the same conditions described for the preparation of **8**. The product **17** was purified by PLC (solvent $CHCl_3$). It was a syrup (260 mg): n_D^8 1·5580; $[\alpha]_D^{20}$ +22·0° (*c* 0·23, $CHCl_3$); IR: ν_{max}(neat) 3500, 3090, 3070, 1603, 1493, 760 and 700 cm^{-1}. NMR (δ): 7·32 (5H, m, aromatic), 3·78 (2H, s, —S—CH_2—Ph), 3·33 (1H, q, X part; J_{AX} = 7·3 Hz, J_{BX} = 4·6 Hz, C-14), 2·58 (2H, m, AB part, C-15), C-Me singlets at 1·22, 1·11, 0·84, 0·76 and 0·73.

Desulfuration of **17**. The desulfuration was carried out with **17** (240 mg) and Raney Ni (1 g) in the usual manner, giving **18** (170 mg), m.p. 56–57° (n-hexane); $[\alpha]_D^{20}$ −1·5° (*c* 0·4, $CHCl_3$); IR: ν_{max}^{KBr} 3590 and 3460 cm^{-1}. NMR (δ): 3·35 (1H, q, J = 6·3 Hz, C-14), 1·04 (3H, d, J = 6·3 Hz, C-15 Me), C-Me singlets at 1·27, 1·13, 0·86, 0·80 and 0·78. (Found: C, 77·91; H, 11·75; $C_{20}H_{36}O_2$ requires: C, 77·86; H, 11·76%).

Application of Horeau's method[8] *to* **18**. A mixture of (±)-α-phenylbutyric anhydride (0·38 mmol) and **18** (38·3 mg) in pyridine solution (2 ml) was kept at room temperature during 16 hr. $\alpha_1 = +0{\cdot}238$; $\alpha_2 = -0{\cdot}055$; $\alpha_1 - 1{\cdot}1\alpha_2 = +0{\cdot}298$. Optical yield: 11·4%. Configuration: 14R.

Benzoyl derivative of **18**. A pyridine solution (1·5 ml) of **18** (42 mg) was mixed with benzoyl chloride (40 mg). The mixture was heated 2 hr on a water bath. The solvent was evaporated and the residue was purified by PLC (C_6H_6:EtOAc, 95:5) giving **19** as a syrup, n_D^8 1·5308; $[\alpha]_D^{20}$ −2·1° (*c* 0·82, $CHCl_3$); IR: ν_{max}(neat) 3100, 3070, 1720, 1605, 1585, 1275, 755 and 710 cm^{-1}. NMR (δ): 8·10 (2H, m, aromatic), 7·35 (3H, m, aromatic), 5·02 (1H, q, J = 6·3 Hz, C-14), 1·27 (3H, d, J = 6·3 Hz, C-15 Me), C-Me singlets at 1·27 (2 —CH_3), 0·86, 0·79 and 0·77.

Application of the "benzoate rule"[9]: **19** $[M]_D$ −8·65°; **18** $[M]_D$ −4·62°; $\Delta[M]_D$ = −4·03°. Absolute stereochemistry: 14R.

Ketoacetonide **20**. To a suspension of CrO_3 (1 g) in pyridine (10 ml) was added **4** (300 mg) in pyridine solution (10 ml). The mixture was left 72 hr at room temp. The solution was diluted with water and extracted with ether. The ether extract was dried and evaporated and the residue was purified on PLC (EtOAc). The purified product **20** crystallized from ether: n-hexane, (220 mg), m.p. 179–181°; $[\alpha]_D^{20}$ −30·2° (*c* 0·45, $CHCl_3$); IR: ν_{max}^{KBr} 1723, 1205 and 860 cm^{-1}. NMR (δ): 4·03 (3H, m, C-14 and C-15), 2·55 (2H, AB quartet, J = 14 Hz, C-7), 2·42 (1H, s, C-5), C-Me singlets at 1·49, 1·40, 1·34, 1·31, 1·00 and 0·84 (2 —CH_3). ORD (*c* 0·093, MeOH): $[\Phi]_{304}$ −7,315°; $[\Phi]_{264}$ +10,170°; (a = −175). (Found: C, 73·19; H, 10·41; $C_{23}H_{38}O_4$ requires: C, 72·97; H, 10·12%).

Ketone **21**. Compound **6** (100 mg) in acetone solution was treated with excess Jones' reagent during 1 hr. **21** crystallized from EtOH:H_2O (80 mg), m.p. 148–149°; $[\alpha]_D^{20}$ −68·5° (*c* 0·56, $CHCl_3$); IR: ν_{max}^{KBr} 1730, 1130 and 830 cm^{-1}. NMR (δ): 2·36 (2H, AB quartet, J = 14 Hz, C-7), 2·42 (1H, s, C-5), C-Me singlets at 1·49, 1·27 (2 —CH_3), 1·00 and 0·83 (2 —CH_3). ORD (*c* 0·093, MeOH): $[\Phi]_{304}$ −8,600°; $[\Phi]_{264}$ + 10,365°; (a = −190). (Found C, 77·82; H, 11·00; $C_{19}H_{32}O_2$ requires: C, 78·03; H, 11·03%).

Ketoacid **22**. An acetone solution (20 ml) of the hydroxyaldehyde **3** (250 mg) was treated with Jones' reagent at the usual manner. **22** (210 mg), m.p. 184–185° aq EtOH; $[\alpha]_D^{20}$ −5·8° (*c* 0·36, $CHCl_3$); IR: ν_{max}^{KBr} 3250, 1765, 1710 and 998 cm^{-1}. NMR (δ): 10·3 (1H, broad signal, —COOH), 2·65 (2H, AB quartet, J = 12·6 Hz, C-7), 2·51 (1H, s, C-5), C-Me singlets at 1·52, 1·46, 1·08 and 0·89 (2 —CH_3). (Found: C, 70·62; H, 9·64; $C_{19}H_{30}O_4$ requires: C, 70·77; H, 9·38%). The methyl ester derivative of **22** was a solid m.p. 155–156·5° (EtOH:H_2O; $[\alpha]_D^{20}$ −42·1° (*c* 0·68, $CHCl_3$); IR: ν_{max}^{KBr} 1737, 1720 and 1280 cm^{-1}. NMR (δ): 3·72 (3H, s, —$COOCH_3$), 2·57 (2H, AB quartet, J = 14 Hz, C-7), 2·42 (1H, s, C-5), C-Me singlets at 1·46, 1·43, 1·02 and 0·85 (2 —CH_3). (Found: C, 71·12; H, 9·86; $C_{20}H_{32}O_4$ requires: C, 71·39; H, 9·59%).

Compound **25**. Hydrogenation (Pd/C) of **23** (and **24**) in EtOH soln at room temp and atmospheric pressure gave the same dihydroderivative **25**, m.p. 113–115° (EtOH:n-hexane); $[\alpha]_D^{20}$ −7·8° (*c* 0·51, EtOH); IR: ν_{max}^{KBr} 3430 cm^{-1}. NMR (δ): 3·48 (1H, m, $W_{1/2}$ 18 Hz, C-6), 0·88 (6H, d, J = 6 Hz, isopropyl group), C-Me singlets at 1·11 (C-17), 0·88, 0·80 and 0·79. (Found: C, 76·51; H, 12·53; $C_{19}H_{36}O_2$ requires: C, 76·97; H, 12·24%).

Compound **26**. **25** (100 mg) was acetylated (Py/Ac_2O) in the usual manner. The acetyl derivative **26** was a syrup, $[\alpha]_D^{20}$ −5·8° (*c* 0·38, $CHCl_3$); IR: ν_{max}(neat) 3490, 1720 and 1253 cm^{-1}. NMR (δ): 4·72 (1H, m, $W_{1/2}$ 18 Hz, C-6), 0·87 (6H, d, J = 6 Hz, isopropyl group), C-Me singlets at 1·13 (C-17), 0·87 and 0·82 (2 —CH_3). (Found: C, 74·41; H, 11·30; $C_{21}H_{38}O_3$ requires: C, 74·51; H, 11·32%).

Benzylether **27**. To a toluene solution (10 ml) of benzyl chloride (2 ml) and compound **4** (190 mg) was added powdered KOH (1 g). This solution was refluxed with vigorous stirring during 16 hr. It was diluted with water and extracted with $CHCl_3$. The residue **27**, after purification on PLC (C_6H_6:EtAcO, 9:1), is a syrup, n_D^{14} 1·5250; $[\alpha]_D^{20}$ +1·5° (*c* 1·2, $CHCl_3$); IR: ν_{max}(neat) 3100, 3070, 1650, 1608, 1497, 1075 and 735 cm^{-1}. NMR (δ): 7·34 (5H, m, aromatic), 4·74 (2H, AB quartet, J = 12 Hz, Ph—CH_2—O—), 3·92 (3H, m, C-14 and C-15), 3·27 (1H, m, $W_{1/2}$ 18 Hz, C-6), C-Me singlets at 1·42, 1·35, 1·33, 1·30, 0·85, 0·78 and 0·76. (Found: C, 76·61; H, 10·00; $C_{30}H_{48}O_4$ requires: C, 76·55; H, 9·85%).

$NaBH_4$ *reduction of* **20**. To an ethanol soln (20 ml) of **20** (81 mg), $NaBH_4$ (150 mg) was slowly added at room temp. The reaction was completed after 11 hr. The product obtained is identical with compound **4**.

Meerwein-Ponndorff reduction of **22**. A soln of **22** (130 mg) in absolute EtOH (10 ml) was mixed with NaOEt in EtOH (10 ml). The mixture was heated for 20 hr under N_2. It was diluted with water, made acid with 6N HCl and extracted with $CHCl_3$. The residue of the chloroform extract was treated with CH_2N_2 yielding a product, m.p. 112–113° (EtOH:H_2O); $[\alpha]_D^{20}$ +9·7° (*c* 0·39, $CHCl_3$); IR: ν_{max}^{KBr} 3500, 1730 and 1099 cm^{-1}. NMR (δ): 3·72 (4H, —$COOCH_3$ singlet superimposed on C-6), C-Me singlets at 1·37, 1·24, 0·88 and 0·80 (2 —CH_3). (Found: C, 70·80; H, 10·39; $C_{20}H_{34}O_4$ requires: C, 70·97; H, 10·13%).

This product (59 mg) was acetylated at the usual manner yielding **28** (47 mg) as a syrup: $[\alpha]_D^{20}$ +44·6° (*c* 0·65, $CHCl_3$); IR: ν_{max}(neat) 1745, 1730 and 1250 cm^{-1}. NMR (δ): 4·94 (1H, m, $W_{1/2}$ 18 Hz, C-6), 3·71 (3H, s, —$COOCH_3$), 2·07 (3H, s, CH_3CO—O—), C-Me singlets at 1·30, 1·27, 0·87, 0·80 and 0·78. (Found: C, 69·52; H, 9·71; $C_{22}H_{36}O_5$ requires: C, 69·44; H, 9·54%).

Benzoyl derivative of **4**. To a pyridine solution (3 ml) of **4** (120 mg) was added benzoyl chloride (0·3 ml) and the mixture was heated on a water bath for 3 hr. The solvent was evaporated and the residue was purified on PLC (C_6H_6:EtOAc) leading to **29**, m.p. 80–85° (EtOH:H_2O); $[\alpha]_D^{20}$ +60° (*c* 1·9, $CHCl_3$); IR: ν_{max}^{KBr} 3100, 1722, 1605, 1587, 1275 and 710 cm^{-1}. NMR (δ): 8·05 (2H, m, aromatic), 7·50 (3H, m, aromatic), 4·97 (1H, m, $W_{1/2}$ 18 Hz, C-6), 3·88 (3H, m, C-14 and C-15), C-Me singlets at 1·47, 1·36, 1·28, 1·22, 0·88, 0·83 and 0·79. (Found: C, 74·58; H, 9·40; $C_{30}H_{44}O_5$ requires: C, 74·34; H, 9·15%).

Application of the "benzoate rule"[29]: **29** $[M]_D$ +290°; **4** $[M]_D$ +34°; $\Delta[M]_D = +256°$. Absolute stereochemistry: 6S.

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