Correlation of the Diterpenoids Sideritol and Jativatriol

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The diterpenoids jativatriol (**1**) and sideritol (**2**) have been correlated by transformation of each into *ent*-17-noratis-13-en-1,16-dione (**9**). In the case of jativatriol, a simple procedure is described for transforming the *ent*-15-beyerene derivative into an *ent*-13-atisene derivative.

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On a établi une corrélation entre les diterpénoides jativatriol (**1**) et sidéritol (**2**) en les transformant chacun en *ent*-nor-17 atizène-13 dione-1,16 (**9**). Dans le cas du jativatriol, on décrit une procédure simple pour transformer le dérivé *ent*-beyérène-15 en dérivé *ent*-atizène-13.

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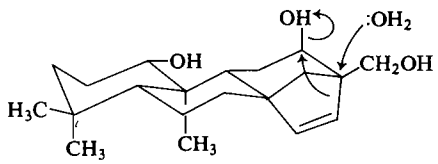
Jativatriol (**1**) (1) and sideritol (**2**) (2) are diterpenoids isolated from *Sideritis angustifolia* Lag. (family *Labiatae*). Sideritol is the first reported diterpenoid of the *ent*-atisane type which does not contain nitrogen as well as the first reported *ent*-atis-13-ene derivative. As noted previously (2) sideritol may be biogenetically related to jativatriol. Rearrangement of the latter as indicated by the arrows in **1** leads to **2**. Conceivably both compounds originate from a common intermediate arising from oxidation of the *ent*-beyer-15-ene skeleton at C-12. In this paper we describe two methods by which jativatriol has been transformed into a derivative of sideritol, confirming our previous conclusions regarding the relationship of these two compounds. In particular, this work firmly establishes the location of the secondary hydroxyl at C-1 in sideritol, a point which had previously been inferred from chemical and spectroscopic data but not directly proven.



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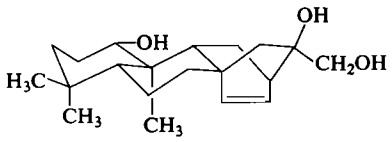

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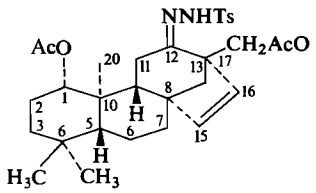
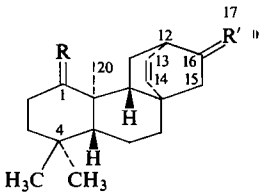
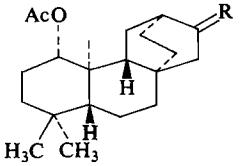
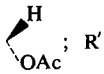
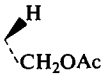


3

The transformation of an *ent*-15-beyerene derivative to an *ent*-13-atisene derivative by reductive rearrangement of a 12-tosylhydrazone has recently been reported (3). This same procedure has now been applied to the tosylhydrazone **3** derived (see Experimental) from jativatriol (**1**). The product proved to be a mixture of C-16 epimers, *ent*-1β,17-diacetoxy-16*S*-atis-13-ene (**4**) and ent-1β,17-diacetoxy-16*R*-atis-13-ene (**5**). The stereochemistry at C-16 in these epimers was established by comparing the chemical shifts of the —CH_2OAc protons in **4** and **5** with their respective dihydro deriva-





4 R =  ; R′ = 

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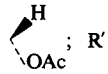
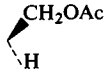
5 R =  ; R′ = 

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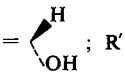
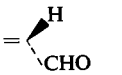
8 R =  ; R′ = 

9 R = O; R′ = O

tives **6** and **7**. The large downfield shift (0.33 p.p.m.) observed for these protons as we go from **4** to **6** indicates that in **4** the acetoxymethyl is *endo* to the double bond (4) and thus has the *ent*-16*S* configuration. In agreement with this result the observed effect (upfield shift of 0.04 p.p.m.) between **5** and **7** indicates the *ent*-16*R* configuration in **5**.

A simpler method of effecting the rearrangement of jativatriol (1) to an *ent*-13-atisene derivative has also been discovered. When a solution of jativatriol in aqueous methanolic HCl is heated under reflux for several hours the aldehyde **8** (as a mixture of C-16 epimers) is obtained in 70% yield. The n.m.r. spectrum of this mixture shows aldehydic signals at δ 9.75 and 9.35 in the ratio of 1:3. Repeated recrystallization from hexane–acetone afforded the epimer displaying the δ 9.35 signal, assigned the stereochemistry shown in **8** on the basis of the upfield shift of the aldehydic signal relative to that of the minor epimer. This assignment was confirmed by reduction ($NaBH_4$) of **8** and subsequent acetylation to give compound **4**.

Oxidative decarbonylation (5) of **8** gave a compound which without further characterization was oxidized with Jones' reagent to the diketone **9**. Oxidation of sideritol (**2**) with excess Jones' reagent gave, in high yield, the same diketone (**9**), thus completing the correlation of the two series and firmly establishing the location of an oxygen function at C-1 in sideritol.

Experimental

Solutions were dried over anhydrous sodium sulfate. Melting points were determined in a Kofler apparatus and are uncorrected. The optical rotations were measured with a Perkin Elmer 141 polarimeter with 1-dm cells. Infrared spectra were recorded on a Perkin Elmer Model 257 spectrometer. Nuclear magnetic resonance spectra were measured using a Perkin Elmer Model R-12 spectrometer or a Varian XL-100 spectrometer in $CDCl_3$ solution and with tetramethylsilane as internal standard and are quoted as δ (number of protons, description of signal assignment). Elementary analyses were carried out in the Instituto de Química Orgánica, Madrid, with the aid of an automatic analyser. Silica gel Merck (60 PF_{254}) was used for preparative layer chromatography.

Preparation of ent-1β,17-Diacetoxy-15-beyeren-12-tosylhydrazone (3)

To a solution of jativatriol-1-monoacetate (1 g), obtained from jativatriol triacetate as described in ref. 1, in anhydrous pyridine (5 ml) was added acetic anhydride (5 ml). The solution was allowed to stand 30 min at 0° and then poured into water and extracted with chloroform. The chloroform layer was dried, filtered, and evaporated leaving a residue which on t.l.c. shows two components. The less polar of these corresponded to jativatriol triacetate, while the other, isolated by preparative t.l.c. (eluent benzene – ethyl acetate 1:1), is a mixture (700 mg) of 1,17- and 1,12-jativatriol diacetates (4:3 ratio according to n.m.r. data). This mixture was dissolved in acetone (20 ml) and mixed with Jones' reagent (1.5 ml). The oxidation was allowed to proceed for 2 h at room temperature. Two products were obtained and these were separated by preparative t.l.c. (eluent benzene – ethyl acetate 3:2):

ent-1β,17-Diacetoxy-15-beyeren-12-one (380 mg): m.p. 145–147° (from aqueous EtOH); $[\alpha]_D^{22}$ −238.1° (*c* 0.44, $CHCl_3$); i.r. (KBr) cm^{-1}: 3080 (olefinic CH); 2980, 2970, 2940, 2920, 2860 (CH stretching vibrations); 1735 (ester); 1710 (ketone); 1235 (C—O of ester); 761 (*cis*-1,2-disubstituted olefin); n.m.r. (δ): 5.91 (2H, AB quartet, *J* 6 Hz, olefinic H-15 and H-16), 4.47 (1H, multiplet, $w_{1/2}$ 18 Hz, axial H-1), 4.19 (2H, AB quartet, *J* 11.3 Hz, H-17), 2.02 and 2.00 (3H each, singlets, two —$OCOCH_3$), C—Me singlets at 0.94, 0.91, and 0.87.

Anal. Calcd. for $C_{24}H_{34}O_5$: C, 71.61; H, 8.51. Found: C, 71.87; H, 8.43.

ent-1β,12α-Diacetoxy-15-beyeren-17-oic acid (290 mg): m.p. 189–191° (from *n*-hexane); $[\alpha]_D^{22}$ −10.0° (*c* 1.43, $CHCl_3$); i.r. (KBr) cm^{-1}: 3400–2550, 1705 (—COOH); 3060, 762 (olefin); 1740, 1240 (—OAc); n.m.r. (δ): 8.85 (1H, broad signal, —COOH), 5.96 (2H, AB quartet, *J* 6 Hz, olefinic H-15 and H-16), 5.30 (1H, multiplet, $w_{1/2}$ 8 Hz, equatorial H-12), 4.58 (1H, multiplet, $w_{1/2}$ 18 Hz, axial H-1), 2.04 and 2.01 (3H each, singlets, two —$OCOCH_3$), three C—Me singlets accumulated at 0.87 (9H).

Anal. Calcd. for $C_{24}H_{34}O_6$: C, 68.87; H, 8.19. Found: C, 68.97; H, 8.08.

To a solution of the above ketone (300 mg) in absolute ethanol (4 ml) was added tosylhydrazide (167 mg). The solution was then heated under reflux for 10 h. A crystalline precipitate appears on cooling. Crystallization from aqueous ethanol affords pure **3** (360 mg), m.p. 164–167°; $[\alpha]_D^{22}$ −112.3° (*c* 0.52, $CHCl_3$); i.r. (KBr) cm^{-1}: 3110 (—NH—); 3060, 3030, 1600, 758, 738, 685 (aromatic and olefinic); 1720, 1240 (—OAc); 1623 (>C=N—); 1165 (—Ts); n.m.r. (δ): 7.55 (4H, A_2B_2 system, *J* 8.6 Hz, aromatic protons), 5.78 (2H, AB quartet, *J* 6 Hz, olefinic H-15 and H-16), 4.42 (1H, multiplet, $w_{1/2}$ 18 Hz, axial H-1), 4.24 (2H, AB quartet, *J* 12 Hz, H-17), 2.42 (3H, singlet, CH_3—Ph), 2.19 and 1.98 (3H each, singlets, —$OCOCH_3$ on C-17 and C-1 respectively), C—Me singlets at 0.90, 0.86, and 0.85.

Anal. Calcd. for $C_{31}H_{42}O_6N_2S$: C, 65.24; H, 7.42; N, 4.91; S, 5.60. Found: C, 65.41; H, 7.35; N, 4.82; S, 5.71.

$NaBH_4$ Reduction of 3: Compounds 4 and 5

Sodium borohydride (200 mg) was slowly added to a solution of **3** (350 mg) in a 1:1 (v/v) mixture of dioxane – absolute ethanol (10 ml). The solution was then allowed to stir at room temperature for 4 h, diluted with water, and extracted with chloroform. The residue obtained by evaporation of the solvent was then separated into two components by preparative t.l.c. (eluent benzene – ethyl acetate 85:15).

ent-1β,17-Diacetoxy-16*S*-atis-13-ene (**4**): Less polar component, crystallizes from MeOH (133 mg), m.p. 123–125°; $[\alpha]_D^{20}$ +7.3° (*c* 0.72, $CHCl_3$); i.r. (KBr) cm^{-1}: 3040, 3000, 2960, 2930, 2880, 2855, 1728, 1250, 725, 710; n.m.r. (δ): 5.98 (2H, multiplet, olefinic H-13 and H-14), 4.60 (1H, apparent doublet of doublets, axial H-1), 3.61 (2H, doublet, *J* 7.3 Hz, H-17), 2.42 (1H, multiplet, $w_{1/2}$ 12 Hz, allylic H-12), 2.01 and 1.99 (3H each, singlets, two —$OCOCH_3$), C—Me singlets at 0.88, 0.83, and 0.76.

Anal. Calcd. for $C_{24}H_{36}O_4$: C, 74.19; H, 9.34. Found: C, 74.11; H, 9.41.

ent-1β,17-Diacetoxy-16*R*-atis-13-ene (**5**), more polar component, thick oil (49 mg): $[\alpha]_D^{20}$ +30.7° (*c* 0.26, $CHCl_3$); i.r. (NaCl) cm^{-1}: 3030, 2950, 2855, 1740, 1243, 720; n.m.r. (δ): 6.09 (2H, multiplet, olefinic H-13 and H-14), 4.55 (1H, apparent doublet of doublets, axial H-1), 3.99 (2H, octet, J_{gem} 10.6 Hz, J_{vic} 6.6 Hz, H-17), 2.37 (1H, multiplet, $w_{1/2}$ 12 Hz, allylic H-12), 2.04 and 1.99 (3H each, singlets, two —$OCOCH_3$), C—Me singlets at 0.87, 0.83, and 0.78.

ent-1β,17-Diacetoxy-16S-atisane (6)

A solution of compound **4** (100 mg) in EtOH (20 ml) was hydrogenated at room temperature and atmospheric pressure over Pd/C (10%) for 16 h. Filtration and evaporation of the solvent leaves a residue (**6**; 100 mg) which crystallizes from aqueous EtOH, m.p. 99–101°; $[\alpha]_D^{20}$ −45.8° (*c* 0.58, $CHCl_3$); i.r. (KBr) cm^{-1}: 2990, 2950, 2900, 2880, 2855, 1735, 1723, 1250, 1220; n.m.r. (δ): 4.60 (1H, apparent doublet of doublets, axial H-1), 3.94 (2H, doublet, *J* 7.6 Hz, H-17), 2.02 and 1.99 (3H each, singlets, two —$OCOCH_3$), C—Me singlets at 1.11 (3H, H-20) and 0.85 (6H, two Me on C-4).

Anal. Calcd. for $C_{24}H_{38}O_4$: C, 73.80; H, 9.81. Found: C, 73.65; H, 9.80.

ent-1β,17-Diacetoxy-16R-atisane (7)

Compound **5** (40 mg) was hydrogenated in the same manner as described for **4** to give **7** (40 mg): m.p. 98–100° (aqueous EtOH): $[\alpha]_D^{20}$ +1.7° (*c* 0.46, $CHCl_3$); i.r. (KBr) cm^{-1}: 2990, 2965, 2920, 2860, 1750, 1245; n.m.r. (δ): 4.55 (1H, apparent doublet of doublets, axial H-1), 3.95 (2H, doublet, *J* 7.5 Hz, H-17), 2.03 and 2.00 (3H each, singlets, two —$OCOCH_3$), C—Me singlets at 1.11 (3H, H-20), and 0.84 (6H, two Me on C-4).

Anal. Calcd. for $C_{24}H_{38}O_4$: C, 73.80; H, 9.81. Found: C, 73.91; H, 9.68.

Rearrangement of Jativatriol (1) into ent-1β-Hydroxy-16S-atis-13-en-17-al (8)

To a solution of jativatriol (**1**, 400 mg) in absolute MeOH (10 ml), concentrated HCl was added (1.1 ml). The solution was heated under reflux for 7 h, cooled, diluted with water, and extracted with $CHCl_3$. The residue obtained by evaporation of the solvent is a complex mixture from which the main product (280 mg) can be separated by preparative t.l.c. (eluent benzene–ethyl acetate 4:1). Repeated crystallization of the major fraction from *n*-hexane affords pure **8**, m.p. 121–123°; $[\alpha]_D^{22}$ +14° (*c* 0.8, $CHCl_3$); i.r. (Nujol) cm^{-1}: 3535 (—OH); 3065, 3030, 720, 700 (olefin); 2760, 2730, 1716 (—CHO); n.m.r. (δ): 9.35 (1H, doublet, *J* 2 Hz, —*CH*O), 5.96 and 5.92 (1H each, doublet, *J* 4 Hz, H-13 and H-14 olefinic protons), 3.25 (1H, quartet, $J_{aa'}$ 9 Hz, $J_{ae'}$ 5 Hz, axial H-1), 2.86 (1H, multiplet, $w_{1/2}$ 12 Hz, allylic H-12), 2.54 (1H, multiplet, $w_{1/2}$ 20 Hz, H-16), C—Me singlets at 0.86, 0.80, and 0.66. Double resonance shows that the aldehyde proton (9.35 δ) is coupled to a complex signal at δ 2.54. Similarly the olefinic signal appears as a singlet when the allylic proton (δ 2.86) is irradiated. This last proton appears as a quartet (*J* 3.5 Hz) when the olefinic signal is irradiated.

Anal. Calcd. for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. Found: C, 79.55; H, 9.93.

The n.m.r. spectrum of the major fraction before crystallization shows aldehydic signals at 9.75 and 9.35 δ (1:3 ratio). The signal at 9.75 indicates the presence of the *ent*-16*R* isomer in this mixture. These isomers are not distinguished by t.l.c.

Preparation of 4 from 8

An ethanolic solution of compound **8** (50 mg) was reduced with $NaBH_4$ in the usual manner. The crude reduction product was acetylated (Py/Ac_2O) at room temperature to give compound **4**, identical (m.p., m.m.p., i.r., n.m.r., and $[\alpha]_D$) with that described above.

Preparation of ent-17-Noratis-13-en-1,16-dione (9) from 8

To a solution of **8** (47 mg) in DMF (15 ml) was added 1,5-diazabicyclo[4.3.0]non-5-ene (1.5 ml) and cupric acetate – 2,2′-bipyridyl complex (1:1; 9 mg). The solution was heated to 40° and dry air bubbled through the solution for 20 h. The reaction mixture was then diluted with water and extracted with ethyl ether. The residue obtained by evaporation of the ether is predominantly a single product (t.l.c.). This residue was oxidized by the Jones' method and the major component

(**9**) was separated by preparative t.l.c. Compound **9** (20 mg) crystallizes from aqueous EtOH, m.p. 137–138°; $[\alpha]_D^{22}$ +160° (*c* 0.38, $CHCl_3$); i.r. (KBr) cm^{-1}: 3050, 740 (olefin); 3000, 2960, 2860, 1720, 1710 (ketones); n.m.r. (δ): 6.15 (2H, multiplet, H-13 and H-14 olefinic protons), 3.07 (1H, multiplet, $w_{1/2}$ 9 Hz, allylic H-12), C—Me singlets at 1.07, 1.01, and 0.98; mass spectrum *m/e* (% of base peak): 286 (8, calcd. for $C_{19}H_{26}O_2$: 286.1933; found: 286.1944), 244 (36), 139 (100), 91 (35), 41 (34).

Anal. Calcd. for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.48; H. 9.03.

*Preparation of **9** from Sideritol (**2**)*

An acetone solution of compound **2** (70 mg) was oxidized with excess Jones' reagent for 12 h. A single product was obtained (61 mg) identical in all respects with compound **9** prepared from jativatriol.

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