

## LINKIOL, A NEW SESQUITERPENE FROM *FERULA LINKII*\*

ANTONIO G. GONZÁLEZ,† BRAULIO M. FRAGA,† MELCHOR G. HERNÁNDEZ,† JAVIER G. LUIS,†  
 RAFAEL ESTEVEZ,‡ JUAN L. BÁEZ‡ and MANUEL RIVERO‡

†Department of Organic Chemistry and Biochemistry, University of La Laguna, Instituto de Productos Naturales Orgánicos, CSIC, Tenerife, Canary Isles; ‡Escuela Universitaria de Ingeniería Técnica Industrial, Las Palmas de Gran Canaria, Spain

(Revised received 27 July 1976)

**Key Word Index**—*Ferula linkii*; Umbelliferae; daucane sesquiterpenes; linkiol.

**Abstract**—A new sesquiterpene ester, linkiol with a daucane skeleton was isolated from *Ferula linkii*.

Continuing with our work on the chemistry of the Umbelliferae, we have studied *Ferula linkii*, a plant endemic to the Canary Isles [1]. From this species we have isolated a new sesquiterpene ester, linkiol (1).

Linkiol (1),  $C_{20}H_{34}O_4$ , showed bands characteristic of alcohol and ester groups in its IR spectrum. By hydrolysis it gave a sesquiterpene alcohol 2,  $C_{15}H_{28}O_3$ , with an IR spectrum in which signals typical of hydroxyls were noted. In the NMR spectrum this product presented a triplet at  $\delta$  3.65 ( $W_{1/2}$  12 Hz) characteristic of a proton geminal to an equatorial alcohol, two singlets at 1.02 and 1.25 resulting from tertiary methyls and a triplet at 9.05 (6H) due to the methyls of an isopropyl group. Equilibration with  $D_2O$  caused three hydroxyl hydrogens to disappear.

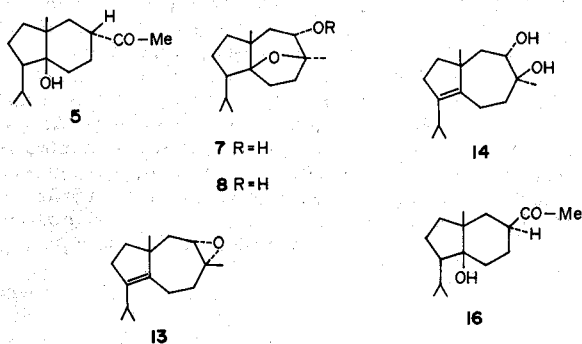
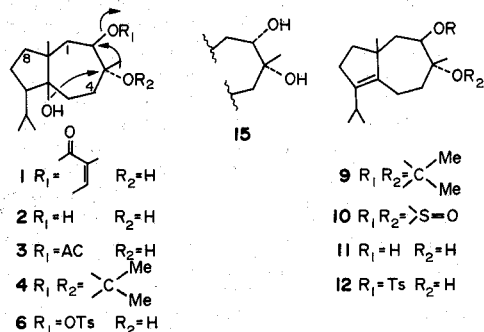
Mild acetylation yielded the monoacetate 3. The geminal proton to the acetate seemed, in the NMR spectrum, to be a quartet centred at 4.95. By treatment of 2 with acetone in anhydrous  $CuSO_4$ , acetonide 4 was obtained. Dehydration of this latter with thionyl chloride gave compound 9 with a tetrasubstituted double bond. A mixture of azulenoids was obtained from dehydrogenation with Se.

The above chemical and spectroscopic information suggests that this alcohol had an  $\alpha,\gamma$ -dimethyl-isopropylbicyclo-5,3,0-decane skeleton with one secondary and two tertiary alcohol groups. It could also be assumed from the NMR data and acetate formation described above that one of the latter was geminal to a methyl group, while the other was sited in such a way that on dehydration it gave a compound with a  $=C-CH(Me)_2$  grouping since in the NMR spectrum of 9 the proton of the isopropyl group appeared as a multiplet centred at  $\delta$  2.68. Since jaeschkeanadiol (17) [2], a sesquiterpene with a daucane skeleton, and its esters have been isolated from other species of *Ferula* [2], [3], it seemed reasonable to expect our product to have this type of skeleton.

A secondary alcohol group with the attributes described above can be found in a daucane structure at C-3, C-6 or C-10, and a tertiary at C-2 or C-4. As the

isopropyl group in the alcohol's NMR spectrum was not in the same position as the equivalent group in jaeschkeanadiol (17), which has a hydroxyl at C-10, we can assign position C-6 to the second tertiary alcohol, while the formation of acetonide points to the secondary hydroxyl being located at C-2 or C-4.

In order to distinguish correctly between these two positions and to relate our product to one already known, we treated alcohol 2 with tosyl chloride in pyridine, obtaining the tosylate 6 and miniscule quantities of ketone 5 and a compound identified with daucol (7) [4-6], which was produced by solvolysis of the tosyl-



\*Part 15 in the series 'Constituents of the Umbelliferae'. For Part 14, see A. G. González, E. D. Chico, J. R. Luis and F. Rodríguez Luis, *Anal. Quím.* (in press).

ate in the reaction medium. When the tosylate was solvolysed with methanolic KOH, daucol (7) was obtained in pure form. In view of these products and the reaction mechanism, we could then determine the structure and stereochemistry of the carbon skeleton of sesquiterpene 2, the position and stereochemistry of the tertiary hydroxyls and the location of the secondary alcohol at C-2.

Thus, only the stereochemistry of the secondary alcohol group remained to be solved. The NMR spectrum suggested that this hydroxyl was equatorial, but this molecule may adopt two conformations in which the hydroxyl, being equatorial, can be  $\alpha$  or  $\beta$ . Alcohol 2 differs from the triol 15, obtained from carotol by treatment with potassium permanganate [4, 7–11], and, hence, must be  $\beta$ . Moreover, when the tosylate obtained from the triol 15 was solvolysed, ketone 16 and not daucol (7) was obtained. The result of this solvolysis fits in with the *trans* and *cis* stereochemistry of the hydroxyl group at C-2 and C-3 for both the alcohols 2 and 15.

The solvolysis of the tosylate 6 to give daucol must be achieved through an epoxide, because when the tosylate of diol 11, which does not have a hydroxyl at C-6, was solvolysed under the same conditions as 6, the epoxide 13 was obtained. Perchloric acid catalysed opening of the epoxide gave a single *trans* diaxial diol 14.

Diol 11 could be obtained both by hydrolysis of the dehydrated acetonide or by treatment of the alcohol 2 with thionyl chloride in pyridine, followed by basic hydrolysis of the sulphite formed.

The acid which esterifies to alcohol 2 forming linkiol was identified as angelic acid from its spectroscopic data. Thus, the MS spectrum of linkiol (1) showed a  $M^+$  at *m/e* 338 and other prominent peaks at *m/e* 238 ( $M^+ - 100$ ), 83 (base peak) and 55. These fragments are typical of the cleavage of esters of angelic, tiglic, and senecioic acids. In the NMR spectrum of linkiol, a quartet appeared at  $\delta$  6.12, a chemical shift typical of the vinyl proton of angelic acid [12].

## EXPERIMENTAL

*Mp*'s are uncorr. Optical activities were taken in  $\text{CHCl}_3$ , NMR spectra on a 60 MHz instrument in  $\text{CDCl}_3$  with TMS as internal reference except where otherwise indicated. Column and dry column chromatography was performed on Si gel 0.2–0.5 and 0.063–0.2 mm respectively.

*Isolation of linkiol.* Air-dried roots of the plant *Ferula linkii* Webb (3.1 kg), collected at San Mateo (Gran Canaria, Canary Isles), were finely cut and Soxhlet extracted several times with EtOH. Combined filtered cold extracts were concentrated *in vacuo* and extracted with  $\text{C}_6\text{H}_6$ . Chromatography, with  $\text{C}_6\text{H}_6$  as eluent, gave linkiol (11 g).

*Linkiol (1).* *Mp* 123–125° ( $\text{C}_6\text{H}_6$  [ $\alpha$ ]<sub>D</sub> – 17 (*c* 0.28); (found: C 71.02; H 9.99.  $\text{C}_{20}\text{H}_{34}\text{O}_4$  requires: C 70.97; H 10.12%); IR  $\nu_{\text{max}}$   $\text{cm}^{-1}$ : 3400, 1700, 1660, 1270, 1170; NMR:  $\delta$  0.93 (3H, s), 0.95 (6H, t, *J* 6 Hz), 1.24 (3H, s), 1.83 (3H, s), 5.00 (1H, q, *J* 4 Hz, *J* 10 Hz), 4.10 (1H, q); MS *m/e* (%): 338 ( $M^+$ ), 320, 305, 302, 277, 267, 265, 254, 238, 220, 212, 209, 194, 193, 167, 156, 154 (100), 151, 140, 136, 83.

*Alcohol (2).* By saponification of linkiol with 5% KOH in MeOH, the alcohol 2 was obtained: *mp* 84–85° [ $\alpha$ ]<sub>D</sub> – 33 (*c* 0.26); IR  $\nu_{\text{max}}^{\text{CHCl}_3}$   $\text{cm}^{-1}$ : 3600, 1760, 1380, 1050, 1020, 930; NMR:  $\delta$  0.95 (6H, t), 1.03 (3H, s), 1.25 (3H, s), 3.65 (1H, t,  $W_{1/2}$  12 Hz); MS *m/e* (%): 256 ( $M^+$ ), 238, 223, 212, 209, 195, 194, 185, 183, 172 (100), 151. *Monooacetate (3)* obtained in the usual way: *mp* 114–117°; NMR:  $\delta$  0.92 (9H, t,  $W_{1/2}$  12 Hz), 1.20 (3H, s), 2.07 (3H, s), 4.95 (1H, q, *J* 4 Hz, *J* 10 Hz).

*Tosylation of 2.* A mixture of 2 (560 mg) and *p*-toluene-sulfonyl chloride (1.25 g) in dry pyridine was left at room temp. for 70 hr. It was then diluted with cold  $\text{H}_2\text{O}$  and extracted as usual. Dry column chromatography of the residue, eluted with petrol–EtOAc (1:1) gave ketone 5 (20 mg), daucol (7) (30 mg) and the tosylate (6) (410 mg). *Ketone (5).* NMR:  $\delta$  0.90 (3H, s), 0.95 (6H, t), 2.15 (3H, s); MS *m/e* (%): 238 ( $M^+$ ) 223, 210, 195, 154, 140, 126, 113, 97 (100). *Daucol (7):* *mp* 118–119° (petrol) [ $\alpha$ ]<sub>D</sub> – 14° (*c* 0.14) (Lit. [9] *mp* 118° Lit [4] [ $\alpha$ ]<sub>D</sub> – 17); NMR ( $\text{CCl}_4$ ):  $\delta$  0.78 (3H, d), 0.98 (3H, d), 1.04 (3H, s), 1.28 (3H, s), 3.62 (1H, q); MS *m/e* (%) 238 ( $M^+$ ), 221, 195, 176, 151 (100), 135, 132, 121, 107. *Daucol acetate:* NMR ( $\text{CCl}_4$ ) 4.82 (1H, q). *Tosylate 6:* NMR:  $\delta$  0.82 (3H, s), 0.90 (6H, t), 1.18 (3H, s), 2.44 (3H, s), 4.68 (1H, q), 3.37 and 3.84 (each 2H, d, *J* 9 Hz); MS *m/e* (%) 440 ( $M^+$ ), 422, 404, 362, 279, 249, 231, 191, 221, 203, 149, 139.

*Solvolysis of tosylate.* The tosylate 6 (100 mg) was treated with methanolic KOH (3%) (50 ml) at room temp. for 1 hr and extracted in the usual way, giving daucol (7).

*Hydroxyacetone 4.* The triol 2 (830 mg) was dissolved in dry  $\text{Me}_2\text{CO}$  (50 ml), and  $\text{CuSO}_4$  (5 g) was added. The mixture was heated under reflux for 24 hr. The reaction product was chromatographed on  $\text{SiO}_2$ , using petrol–EtOAc (4:1) as eluent. The end-products were a dehydrated acetonide (9) (80 mg), the hydroxyacetone (4) (600 mg) and unaltered alcohol 2 (180 mg). *4:* *mp* 155–156° (petrol) [ $\alpha$ ]<sub>D</sub> – 10° (*c* 1.5); NMR 0.98 (3H, s), 1.00 (6H, t), 1.18 (3H, s), 1.35 (3H, s), 1.42 (3H, s), 3.71 (1H, q); MS *m/e* (%): 296 ( $M^+$ ), 281, 221, 203, 149, 139.

*Dehydration of the acetonide.* Hydroxyacetone 4 (160 mg) was dissolved in dry  $\text{C}_2\text{H}_5\text{N}$  (3 ml), and  $\text{SOCl}_2$  (0.35 ml) was added dropwise to this soln which was left for 90 min, then dil with  $\text{H}_2\text{O}$  and extracted in the normal way, giving the dehydrated acetonide 9; NMR:  $\delta$  0.95 (6H, t), 0.97, 1.20, 1.31, 1.41 (each 3H, s), 2.68 (1H, m,  $W_{1/2}$  20 Hz), 3.64 (1H, q); MS *m/e* (%): 278 ( $M^+$ ), 263, 220, 203, 167 (100), 149, 148, 136, 121.

*Hydrolysis of dehydrated acetonide 9.* To a soln of 9 (130 mg) in MeOH (20 ml) was added conc HCl (0.15 ml) and the mixture was refluxed for 40 min. The soln was neutralized with

0.87 (3H, s), 0.97 (6H, t), 1.23 (3H, s), 2.62 (1H, m), 3.44 (1H, t); MS *m/e* (%): 238 ( $M^+$ ), 223, 205, 196, 178, 149, 133, 121, 107, 105, 93.

*Treatment of the alcohol with  $\text{SOCl}_2$ .* The triol (2) (60 mg) was dissolved in  $\text{C}_2\text{H}_5\text{N}$  (12 ml) at 0° and  $\text{SOCl}_2$  added dropwise. The mixture was left for 1 hr, then poured over water-ice and extracted as usual, forming the sulphite (10); NMR:  $\delta$  0.87 (3H, s), 0.98 (6H, t), 1.30 (3H, s), 2.60 (1H, m), 4.56 (1H, q).

*Hydrolysis of the sulphite 10.* (630 mg) was dissolved in methanolic KOH (5%) (20 ml) and left for 14 hr. The diol 11 was obtained.

*Tosyl derivative of 11.* The diol 11 (90 mg) was dissolved in dry  $\text{C}_2\text{H}_5\text{N}$  (3 ml) plus *p*-toluene-sulfonyl chloride (200 mg), the mixture was left at room temp for 24 hr, at the end of which time it was diluted with  $\text{H}_2\text{O}$  and extracted in the standard way. TLC showed two spots. Dry column chromatography gave the tosylate 12 (80 mg) and unaltered product 11 (20 mg). *Tosylate 12* NMR (90 Hz):  $\delta$  0.88 (3H, s), 0.97 (6H, q), 1.24 (3H, s), 2.44 (3H, s), 2.55 (1H, m), 4.45 (1H, q), 7.33 and 7.79 (each 2H, d, *J* 9 Hz); MS *m/e* (%) 392 ( $M^+$ ), 374, 349, 220, 205, 202, 193, 187, 177, 175, 159, 149, 147, 145, 135, 134, 133, 107, 105, 93, 91 (100).

*Solvolysis of tosylate 12.* The tosylate (300 mg) was treated with methanolic KOH (3%) (15 ml) at room temp. for 45 min and, extracted in the usual way, gave the epoxide 13: NMR (90 Hz):  $\delta$  0.89 (3H, d), 0.98 (3H, d), 1.08 (3H, s), 1.37 (3H, s), 2.70 (2H, m); MS *m/e* (%) 220 ( $M^+$ ), 205, 187, 177, 159, 149, 135, 134, 133, 122 (100), 119, 107.

*Diol 14.* The epoxide 13 (200 mg) in THF (25 ml) was stirred with aq. 3% perchloric acid (10 ml) at room temp. for 5 hr. The usual work-up gave the diol 14; *mp* 82–84° (petrol); NMR:  $\delta$  0.87, 0.85, 1.05 and 1.10 (each 3H, s), 2.65 (1H, m), 3.69 (1H, q); MS *m/e* (%): 238 ( $M^+$ ), 223, 205, 195, 177, 135, 133, 121, 119, 117, 115, 107, 105, 93, 91 (100).

*Tosylation of triol 15.* Triol 15 (80 mg) was treated as described above (tosylation of 2), yielding the ketone 16 (25 mg), the tosyl-

ate (35 mg) and unchanged triol (30 mg). *Ketone 16*; NMR:  $\delta$  0.99 (6H, t), 1.03 (3H, s), 2.14 (3H, s). *Tosylate of 15*; NMR:  $\delta$  0.85, 0.93, 1.00 and 1.22 (each 3H, s), 2.45 (3H, s), 4.68 (1H, q), 7.33 and 7.80 (each 2H, d,  $J$  9 Hz). The tosylate was solvolysed by the same process as **6** and also yielded ketone **16**.

*Acknowledgements*—We thank Prof Herout (Organic Chemistry Institute, Prague) for samples of daucol and triol **15**.

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