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SOME TRANSFORMATIONS OF EPISIDERIDIOL IN THE SYNTHESIS OF NATURALLY OCCURRING TETRACYCLIC KAURENE DITERPENES

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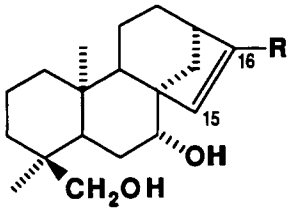
The diterpenes *ent*-7β,17,18-trihydroxykaur-15-ene [**1**] (sinfernol), *ent*-15β,16β-epoxy-7β,17,18-trihydroxykaurane [**2**] (epoxysinfernol), and *ent*-7β,15β,18-trihydroxykaur-16-ene [**3**] (canditriol) are the constituents present in the aerial part of *Sideritis infernalis* (1), a species endemic to the Canary Islands.

In a continuation of our studies on the partial synthesis of compounds with a kaurene skeleton (2–4) we report here their partial synthesis starting from the more readily available *ent*-7β,18-dihydroxykaur-15-ene [**4**] (5) (episideridiol).

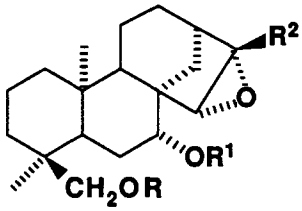
For the introduction of an oxygen function into C-15, the photosensitized oxygenation of *ent*-kaur-15-ene derivatives has been useful (4). To synthesize canditriol [**3**] we applied this procedure to episideridiol [**4**]. This was subjected to direct photo-oxygenation in the presence of haematoporphyrin in dry pyridine to yield **3** as the main product together with traces of **1**. Alternatively, canditriol [**3**] was prepared in the following manner: Reaction of **4** with *m*-chloroperbenzoic acid gave *ent*-15β,16β-epoxykaurane-7β,18-diol [**5**] (ucriol) a diterpene from *Sideritis syriaca* whose structure is well defined (6). The epoxide ring of **5** was cleaved with boron trifluoride-ether complex in DMSO to yield compound **3** identical (mp, ir, ^{1}H nmr) with naturally occurring canditriol.

These results confirm the stereochemistry at C-15 of compound **3**, because it is known that in these reactions the hydroxyl formed has the α stereochemistry (7).

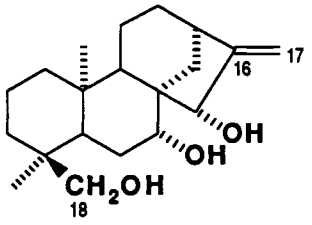
In order to obtain a suitable derivative for the synthesis of sinfernol [**1**], the episideridiol [**4**] was subjected to allylic bromination with *N*-bromosuccinimide to yield 17-bromoepisideridiol [**6**], whose structure is supported by its ^{1}H-



1 R=CH_2OH
4 R=Me
6 R=CH_2Br



2 R=R^1=H, R^2=CH_2OH
5 R=R^1=H, R^2=Me
7 R=R^1=Ac, R^2=CH_2OAc



3

nmr spectrum. By hydrolysis with aqueous K_2CO_3 the allylic alcohol **1**, identical to the natural product, was obtained with high yield. This was treated with *m*-chloroperbenzoic acid to form epoxysinfernol [**2**].

The latter compound was acetylated with Ac_2O/pyridine to give **7** identical with the acetylated natural product.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Melting points were determined on a Kofler block and are uncorrected. Mass spectra were run on a Hitachi Perkin-Elmer RMU-6L (70 eV) spectrometer. ^{1}H-nmr spectra were measured on a Varian EM 360 spectrometer, TMS as internal standard; ir spectra (Nujol) were taken with a Perkin-Elmer 257 spectrophotometer.

PARTIAL SYNTHESIS OF CANDITRIOL.—*Photo-oxygenation of episideridiol* [**4**].—Episideridiol (150 mg, 0.4 mmol) and haematoporphyrin (6 mg) in dry pyridine (15 ml) were irradiated with four fluorescent tubes (Philips TL 4W/33) and oxygenated for 95 h.

The solution was concentrated in vacuo at 40°, and a solution of KI (350 mg) and HOAc (0.1 ml) in EtOH (10 ml) was added and kept at room temperature overnight. The solution was evaporated, and the residue was extracted with Et_2O (3 × 10 ml). The combined Et_2O solution was washed with aqueous sodium thiosulfate and H_2O, dried, and evaporated to give a residue (130 mg) that was chromatographed on a Si gel column. Elution with cyclohexane-EtOAc (3:1) gave unchanged episideridiol (35 mg, 17.3%); elution with cyclohexane-EtOAc (1:3) gave *ent*-7β,15β,18-trihydroxy-kaur-16-ene [**3**] (canditriol) (85 mg, 53.8%), mp 221–223° (EtOAc); ^{1}H-nmr and ms data identical with those reported by Fernandez *et al.* (1).

Elution with cyclohexane-EtOAc (1:6) gave *ent*-7β,17,18-trihydroxykaur-15-ene [**1**] (sinfernol) (6 mg, 3.8%), identified by tlc and ir spectrum.

Epoxidation of **4**: ent-*15β,16β-epoxykaurane-7β-18-diol* [**5**] *(ucriol) and rearrangement of* **5**.—Episideridiol [**4**] was transformed, as described previously (6), into ucriol [**5**]. The epoxide **5** (80 mg, 0.25 mmol) dissolved in dry DMSO (10 ml) was treated with freshly distilled boron trifluoride-Et_2O complex (2 drops) and heated at 100° for 20 h.

The solution was diluted with H_2O and extracted with Et_2O. Evaporation of the solvent left a residue (65 mg, 81.25%) which was separated by chromatography on a Si gel column [cyclohexane-EtOAc (3:7)] giving pure **3**, mp 218–220° from EtOAc [lit. (1) mp 220–222°].

The spectroscopic data were identical with those of the natural canditriol.

REACTION OF *N*-BROMOSUCCINIMIDE WITH EPISIDERIDIOL [**4**].—A solution of **4** (200 mg, 0.66 mmol) and *N*-bromosuccinimide (150 mg, 1 mmol) in dry CCl_4 was heated under reflux for 2 h and then kept for 4 h at room temperature. The succinimide was removed and washed with CCl_4, and the combined filtrates were concentrated in vacuo to yield 17-bromoepisideridiol [**6**] (176 mg, 70%), mp 138–140° from petroleum ether (35–50°); ir ν max cm^{-1} 3260 (OH), 1635 (C=C), 830 (C=CH); ms *m/z* [M]$^+$ 384 and 382; ^{1}H nmr ($CDCl_3$) δ 0.76 (3H, s, 4α-Me), 1.08 (3H, s, 10α-Me), 3.00 and 3.46 (2H, 2d, J = 11.0 Hz, 4β-CH_2OH), 3.76 (1H, br, W½ = 12 Hz, H-7β), 4.10 (2H, d, J_{allyl} = 0.5 Hz, CH_2Br on C-16), 5.18 (1H, br, W½ = 4.5 Hz, H-15).

HYDROLYSIS OF 17-BROMOEPISIDERIDIOL [**6**]: SINFERNOL [**1**].—Compound **6** (100 mg, 0.26 mmol) was heated under reflux with K_2CO_3 (110 mg) and H_2O (20 ml) for 6 h. The cooled mixture was extracted with EtOAc, and the residue was chromatographed on Si gel. Elution with light petroleum ether-EtOAc (1:1) gave *ent*-7β,17,18-trihydroxykaur-15-ene [**1**] (80 mg, 95.7%), mp 224–226° from EtOAc; ^{1}H-nmr data identical with those described by Fernandez *et al.* (1).

EPOXIDATION OF **1**: EPOXYSINFERNOL [**2**].—A solution of **1** (100 mg, 0.31 mmol) and *m*-chloroperbenzoic acid (250 mg, 1.45 mmol) in CH_2Cl_2 (6 ml) was stirred at room temperature (18°) for 24 h.

The reaction mixture was then washed with 5% aqueous $NaHCO_3$, and the CH_2Cl_2 was evaporated. Cc of the obtained residue [Si gel, eluent Et_2O-EtOAc (3:7)] gave **2** (75 mg, 71.5%), mp 232–234° from EtOAc; ir ν max cm^{-1} 3380–3260 (OH); ms *m/z* [M − CH_2OH]$^+$ 305; ^{1}H nmr (pyridine) δ 0.92 (3H, s, 4α-Me), 1.08 (3H, s, 10α-Me), 3.40 and 3.68 (2H, 2d, J = 11 Hz, 4β-CH_2OH), 3.88 (1H, br, W½ = 16.0 Hz, H-7β), 3.68 (1H, s, H-15 on epoxy ring), 4.40 and 4.0 (2H, 2d, J = 12 Hz, 16β-CH_2OH).

Ac_2O-pyridine treatment of **2** yielded the triacetate **7** with physical and spectroscopic data identical with those of the natural product (1).

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