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A PARTIAL SYNTHESIS OF MARRUBIIN

L. Mangoni, M. Adinolfi, G. Laonigro and E. Doria
Istituto di Chimica Organica, Università di Napoli (Italia)

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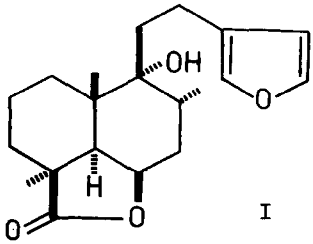
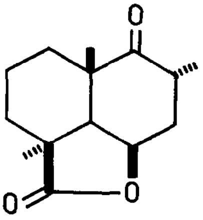
As an extension of our work (1) on the stereochemistry of marrubiin (I), we now report a partial synthesis of this compound from ketolactone (II) (2).

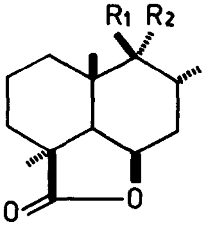
Through reaction with lithium acetylide-ethylendiamine adduct (3) in dioxane at room temperature ketolactone (II) was converted to a 5:1 mixture of two crystalline ethinyl carbinols.



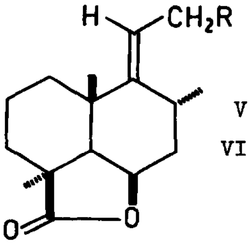
I



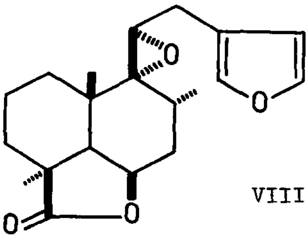
II



III R_1= OH R_2= C≡CH
IV R_1= C≡CH R_2= OH
V R_1= OH R_2= $CH{=}CH_2$



VI R= Br
VII R= β-furyl



VIII

As we can quite safely assume both the ethinylation to be not preceded by epimerization at C_8 and the attack from α-side to be the preferred one (4).

structures (III) and (IV) were respectively assigned to the major product m.p. 206°, $[\alpha]_D$ +16.6° (5) and to the minor isomer m.p. 209.5-210°, $[\alpha]_D$ +43.5° (*).

Catalytic hydrogenation of (III) over palladium/barium sulfate gave the ethylenic alcohol (V) m.p. 161-162°, $[\alpha]_D$ +26°. By reaction of (V) with phosphorous tribromide in pyridine (6) the primary allylic bromide (VI) m.p. 143.5-145°, $[\alpha]_D$ +70° was obtained, that with β-furyl-lithium (7) in tetrahydrofuran at -70° easily gave crystalline (VII) m.p. 94-96°, $[\alpha]_D$ +31.6°, identical with known anhydromarrubiin (8). Treatement of this with an ethereal solution of perphtalic acid in strictly controlled conditions followed by chromatography on alumina afforded besides to a rather large amount of unreacted (VII) a 6:1 mixture of epimeric epoxides, from which the more abundant α-epimer (VIII) m.p. 106-107°, $[\alpha]_D$ +5° was easily isolated. Reduction of the epoxide (VIII) with lithium in anhydrous ethylamine followed by chromatography on silicagel finally gave marrubiin (I) m.p. 159-160°, $[\alpha]_D$ +35°, identical in all respects with the natural product (IR, UV, NMR and mixed m.p.) in almost a 50% yield.

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(*) Satisfactory analyses were obtained for all compounds reported. Melting points were determined on a Kofler block and have not be corrected. Specific rotations were determined on chloroform solutions at room temperature.

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