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SYNTHESIS OF (+)-β-EUDESMOL

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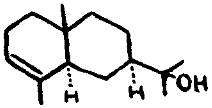
Eudesmol has long been recognised as being a mixture of two isomers, α- and β-, formulated on degradative evidence as (1) and (2) respectively.[1] A third isomer, γ-eudesmol (3), is also present in some samples of commercial eudesmol.[2]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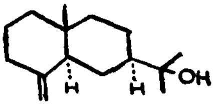
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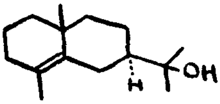
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The constitution assigned to γ-eudesmol has been confirmed by total synthesis.[3] The relative stereochemistry (2) for β-eudesmol has been deduced from chemical studies,[4] and this has been confirmed recently by an elegant stereoselective synthesis of racemic β-eudesmol.[5] It has also been proved, by correlation with intermediates in steroid

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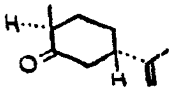
synthesis of known absolute configuration, that (2) represents (+)-β-eudesmol.[6]

We describe here a total synthesis of (+)-β-eudesmol by a stereoselective route. A Robinson-Mannich condensation between (-)-dihydrocarvone, of established stereochemistry (4),[7] and nascent methyl vinyl ketone (from 4-diethylaminobutan-2-one methiodide and methylsulphinyl carbanion[8] in dimethyl sulphoxide) afforded the *cis*-2-decalone (5), the stereochemistry at the ring junction being assigned from a knowledge of the steric course of the reaction.[9] ORD measurements



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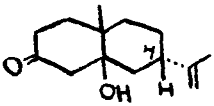

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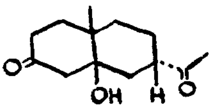

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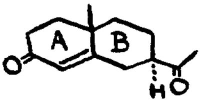
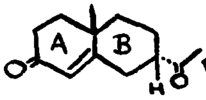


(7)

on (5) indicated the rings were fused in the non-steroidal conformation,[10] further evidence for this being the chemical shift (δ = 1.18 ppm, relative to TMS = 0) of the angular methyl protons in the N.M.R. spectrum of (5).[11] Ozonolysis of (5) in chloroform led to the diketo-alcohol (6), which on acid dehydration afforded the octalone (7). During the dehydration step an inversion occurred at $C_{(7)}$,[12] for the ORD curve of the product was very similar to that of cholest-4-en-3-one[13] and quite different from those of *epi*-α-cyperone[13] and 8-*iso*testosterone,[13], suggesting that ring B in (7) is a chair, with the acetyl substituent equatorial and β. If ring B of the uninverted structure (8) were a chair the acetyl group would be axial, but it is almost certain that this ring is a boat with the $C_{(7)}$-substituent boat-equatorial (cf. *epi*-α-cyperone[14]). The correctness



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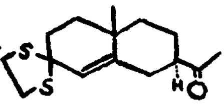

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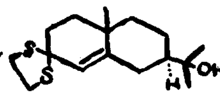

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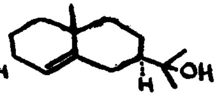
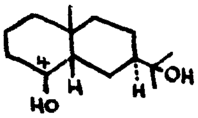


(11)

of this configurational assignment was corroborated by the subsequent steps in the synthesis. Reaction of (7) with ethanedithiol resulted in a preferential attack[15] of the conjugated keto-group with the formation of the monodithioketal (9), the ORD curve of which was closely similar to that of cholest-4-en-3-one dithioketal.[16] Treatment of (9) with magnesium methyl iodide gave the tertiary alcohol (10), which on desulphurisation with sodium and liquid ammonia[17] afforded nor-γ-eudesmol (11). The ORD curve of this product was closely similar to that of γ-eudesmol (3).[3] Hydroboration of (11) under carefully defined conditions[18] yielded a mixture of the diols (12) and (13), which was oxidised directly with Jones reagent[19] to a mixture of the corresponding 4-ketones, homogenised[20] on basic alumina to the crystalline *trans* ketol (14). This compound proved to be identical in every respect with the ketol obtained by ozonolysis of



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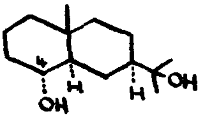

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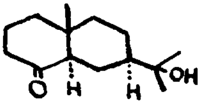

(14)

commercial eudesmol.[4,21] Finally, a Wittig reaction between (14) and methylenetriphenylphosphorane in dimethyl sulphoxide solution[22] afforded (+)-β-eudesmol, purified by chromatography and sublimation, and identical in all respects with natural (+)-β-eudesmol (2).

This synthesis is also a total synthesis of cryptomeridiol[23] and neointermedeol,[24] which have been synthesised from (+)-β-eudesmol.

All the new compounds described have satisfactory spectral properties and analyses.

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