Stereoselective Synthesis of the Novel Marine Diterpene (+)-Isoagatholactone

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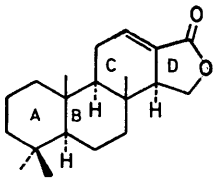
Summary The synthesis of (+)-isoagatholactone (**1**) from (+)-manool (**4**) *via* the key intermediate *ent*-methyl isocopalate (**2**) is described.

RECENTLY, several diterpenes which possess a novel skeleton have been isolated from some species of marine sponges.[1-3] Of this new group of natural products, isoagatholactone (**1**)[1] was the first member to be isolated and since it is also the simplest member of the group, it was of interest to study its chemical synthesis. In this connection, *ent*-methyl isocopalate (**2**) appeared to be an ideal precursor since it possesses the required absolute stereochemistry and, further, can be easily prepared by cyclization of *ent*-methyl copalate (**3**).[4]



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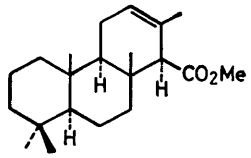

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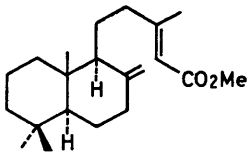

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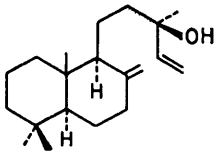

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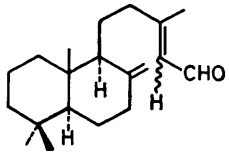
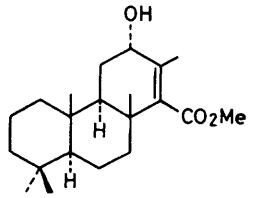


(5) (*E*)
(6) (*Z*)

Compound (**3**) was prepared from (+)-manool (**4**),[5] which, by the oxidative rearrangement induced by pyridinium chlorochromate[6] gave the *E*- and *Z*-aldehydes (**5**) and (**6**) in a 1:1 ratio, estimated by integration of the aldehyde proton signals in the ^{1}H n.m.r. spectrum. The mixture of aldehydes in methanol was submitted to manganese dioxide oxidation in the presence of HCN,[7] which produced a mixture of α,β-unsaturated methyl esters, from which pure *ent*-methyl copalate (**3**)‡ was obtained by careful silica-gel column chromatography. Acid-catalysed cyclization of compound (**3**) gave the isocopalate (**2**), m.p. 108—110 °C, $[\alpha]_D$ −60° ($CHCl_3$) (lit.,[4] m.p. 110—111 °C, $[\alpha]_D$ −55°).

Of the several alternative methods available to functionalize the allylic methyl group of compound (**2**), sensitized photo-oxygenation seemed the most attractive, even though it might be expected that the two allylic alcohols (**7**) and (**8**) should be produced.[8] An allylic rearrangement of the alcohol (**8**) with simultaneous lactonization followed by reductive opening of the lactone (**9**) to give the diol (**10**) and subsequent oxidation of the allylic alcohol would give isoagatholactone (**1**). Photo-oxygenation of compound (**2**) in a mixture of ethyl acetate–ethanol with methylene blue as sensitizer gave, after 14 h of irradiation with a Sylvania DYV-tungsten–halogen projector lamp and reduction of the initially formed mixture of hydroperoxides with trimethyl phosphite, a 2:1 mixture of the alcohols (**7**) and (**8**) in 50% yield (75% based on recovered starting material).



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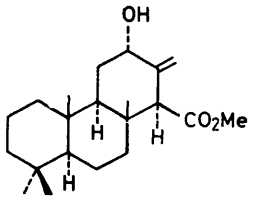

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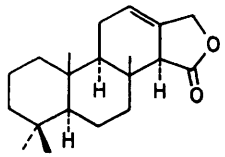

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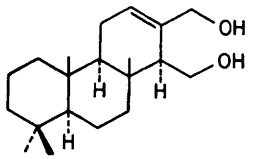

(10)

Both allylic alcohols were isolated by a careful silica-gel column chromatography and characterized. Treatment of the alcohol (**8**), m.p. 153—154·5 °C, $[\alpha]_D$ +43·4° ($CHCl_3$), with 6N aqueous sulphuric acid in dioxan (1:13, v/v) at 90 °C for 40 min afforded the lactone (**9**) in 56% yield, m.p. 162·5—164·5 °C, $[\alpha]_D$ +6·5° ($CHCl_3$), which on $LiAlH_4$ reduction in ether, gave the diol (**10**) in 72% yield,

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‡ Satisfactory spectroscopic data were obtained for all compounds.

m.p. 161—163 °C, $[\alpha]_D$ −36·3° ($CHCl_3$) (lit.,[1] m.p. 159—161 °C, $[\alpha]_D$ −16·5°). Finally, manganese dioxide oxidation of the diol (**10**) in dichloromethane produced compound (**1**) in 57% yield, m.p. 152—153·5 °C, $[\alpha]_D$ +7·2° ($CHCl_3$) (lit.,[1] m.p. 153—155 °C, $[\alpha]_D$ +6·3°). The i.r., ^1H n.m.r., and mass spectral data of compounds (**1**) and (**10**) are identical with those reported for (+)-isoagatholactone and its known degradation product, the diol (**10**).[1] The route described in this communication represents a simple synthetic entry into the D-ring system of this group of natural products.[2,3]

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