

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

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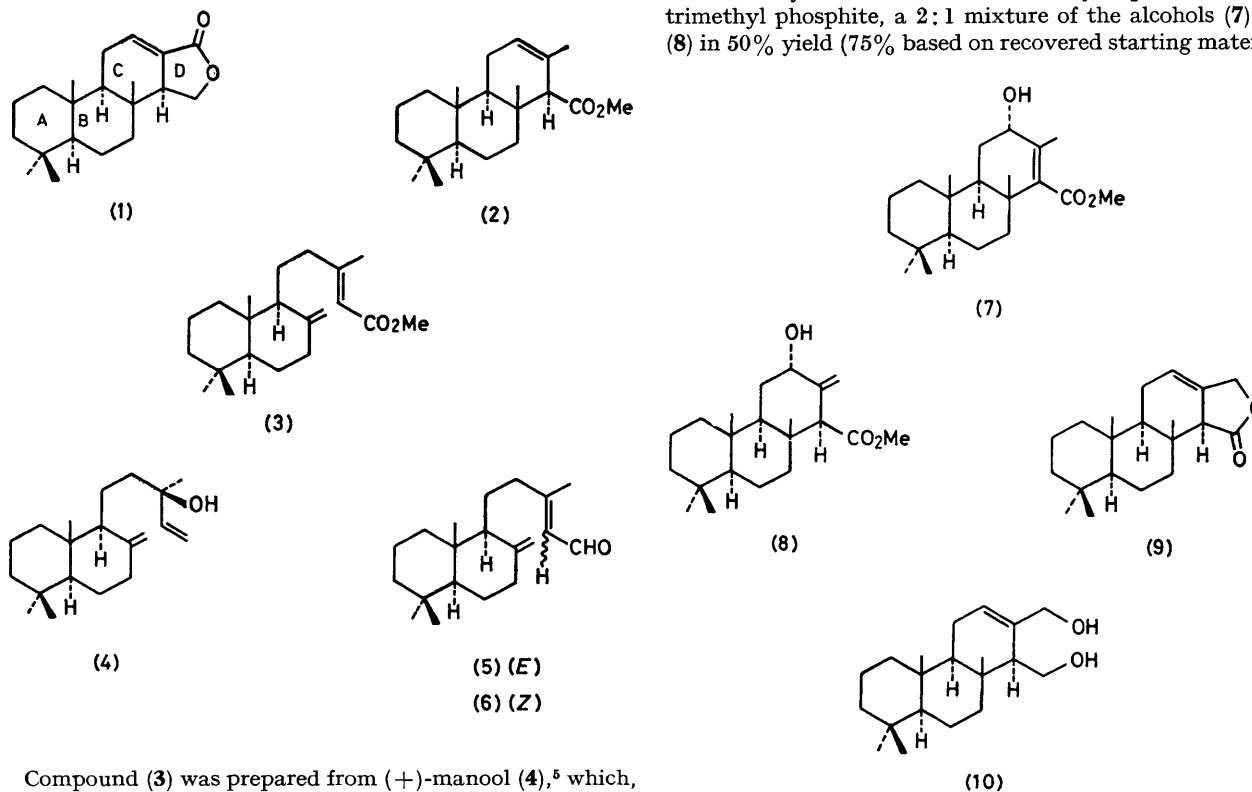
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**Summary** The synthesis of (+)-isoagatholactone (**1**) from (+)-manool (**4**) via the key intermediate *ent*-methyl isocopalate (**2**) is described.

RECENTLY, several diterpenes which possess a novel skeleton have been isolated from some species of marine sponges.<sup>1-3</sup> Of this new group of natural products, isoagatholactone (**1**)<sup>1</sup> 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**).<sup>4</sup>

column chromatography. Acid-catalysed cyclization of compound (**3**) gave the isocopalate (**2**), m.p. 108–110 °C,  $[\alpha]_D -60^\circ$  (CHCl<sub>3</sub>) (lit.,<sup>4</sup> m.p. 110–111 °C,  $[\alpha]_D -55^\circ$ ).

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.<sup>8</sup> 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).



Compound (**3**) was prepared from (+)-manool (**4**),<sup>5</sup> which, by the oxidative rearrangement induced by pyridinium chlorochromate<sup>6</sup> gave the *E*- and *Z*-aldehydes (**5**) and (**6**) in a 1:1 ratio, estimated by integration of the aldehyde proton signals in the <sup>1</sup>H n.m.r. spectrum. The mixture of aldehydes in methanol was submitted to manganese dioxide oxidation in the presence of HCN,<sup>7</sup> which produced a mixture of  $\alpha,\beta$ -unsaturated methyl esters, from which pure *ent*-methyl copalate (**3**)<sup>‡</sup> was obtained by careful silica-gel

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,  $[\alpha]_D +43.4^\circ$  (CHCl<sub>3</sub>), with 6*N* 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,  $[\alpha]_D +6.5^\circ$  (CHCl<sub>3</sub>), which on LiAlH<sub>4</sub> 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,  $[\alpha]_D -36.3^\circ$  ( $\text{CHCl}_3$ ) (lit.,<sup>1</sup> m.p. 159—161 °C,  $[\alpha]_D -16.5^\circ$ ). Finally, manganese dioxide oxidation of the diol (**10**) in dichloromethane produced compound (**1**) in 57% yield, m.p. 152—153.5 °C,  $[\alpha]_D +7.2^\circ$  ( $\text{CHCl}_3$ ) (lit.,<sup>1</sup> m.p. 153—155 °C,  $[\alpha]_D +6.3^\circ$ ). The i.r., <sup>1</sup>H 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**).<sup>1</sup> The route described in this communication represents a simple synthetic entry into the D-ring system of this group of natural products.<sup>2,3</sup>

We thank Dr. Ferdinand Näf (Firmenich S.A.) for a generous gift of (+)-manool, Professors J. D. McChesney (University of Mississippi) and A. J. Marsaioli for helpful discussions, FINEP (Financiadora de Estudos e Projetos) for financial support, and the Universidad Nacional de Rosario (Argentina) for a leave of absence to M. G. S.

(Received, 3rd March 1981; Com. 242.)

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