Stereoselective synthesis of (±)epihinesol (agarospirol)[1]

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An efficient stereoselective synthesis of (±)epihinesol (**1**) (agarospirol) is described.

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Current interests in degradative and synthetic studies on spiro[4.5]decane sesquiterpenes (1) prompt us to report a total synthesis of epihinesol **1** (1*c*, *d*).

The readily available keto ester **2** (2) was first converted into the dienone **4** (b.p. 65–68 °C (0.8 mm); ν_{max} 1665 cm^{-1}; τ 4.09 (1H, broad singlet), 4.56 (1H, singlet), 4.64 (1H, multiplet), 7.91 (3H, doublet, J = 1.5 Hz), and 8.80 (3H, doublet, J = 7 Hz); λ_{max} (EtOH) 273 mμ (ε = 16 300)) via the corresponding ketal ester and ketal alcohol **3** in 72% overall yield.

Michael addition with sodiomalonate followed by hydrolysis decarboxylation and reesterification with diazomethane gave the enone ester **5** (65% overall yield from **4**).

After protection of the ketonic carbonyl which was accompanied by migration of the double bond, the resulting ester was hydrolyzed to the crystalline acid (m.p. 72–73 °C). Conversion to the diazoketone **6** was then accomplished by standard procedures.

Copper-catalyzed internal cyclization (3) of the diazoketone **6** proceeded in a highly stereoselective manner to give **7***a* (10%) and *b* (90%)[4] (40% overall yield from **5**).

On being subjected to the following sequence of reactions: carbomethoxylation (→ **8**), borohydride reduction (→ **9**), Grignard reaction (→ **10**) and aqueous acid treatment, the mixture **7***a* and *b* gave the spiroketone **11** (m.p. 65–66 °C). Crude spiroketone **11** was further reduced to the diol **12** (m.p. 118–120 °C) which can be conveniently purified by direct crystallization (40% overall yield from **7***a* and *b*). The diol **12** was then converted in a quantitative yield into the monoacetate **13** (m.p. 79–80 °C).

Hydrogenolysis of the allylic acetate grouping (4) and specific reduction of the cyclopentene double bond was realized in a single operation giving epihinesol **1** almost quantitatively by treatment of **13** with lithium in ethylamine (5). Analogous reduction of the diol **12** also gave epihinesol (**1**), albeit in inferior yield (*ca.* 55%). The synthetic acetate **14** was found to be identical in all respect with an authentic sample of epihinesol acetate (1*a*, *b*).[5,6]

All new compounds reported in this communication gave satisfactory elemental analysis and spectroscopic data.

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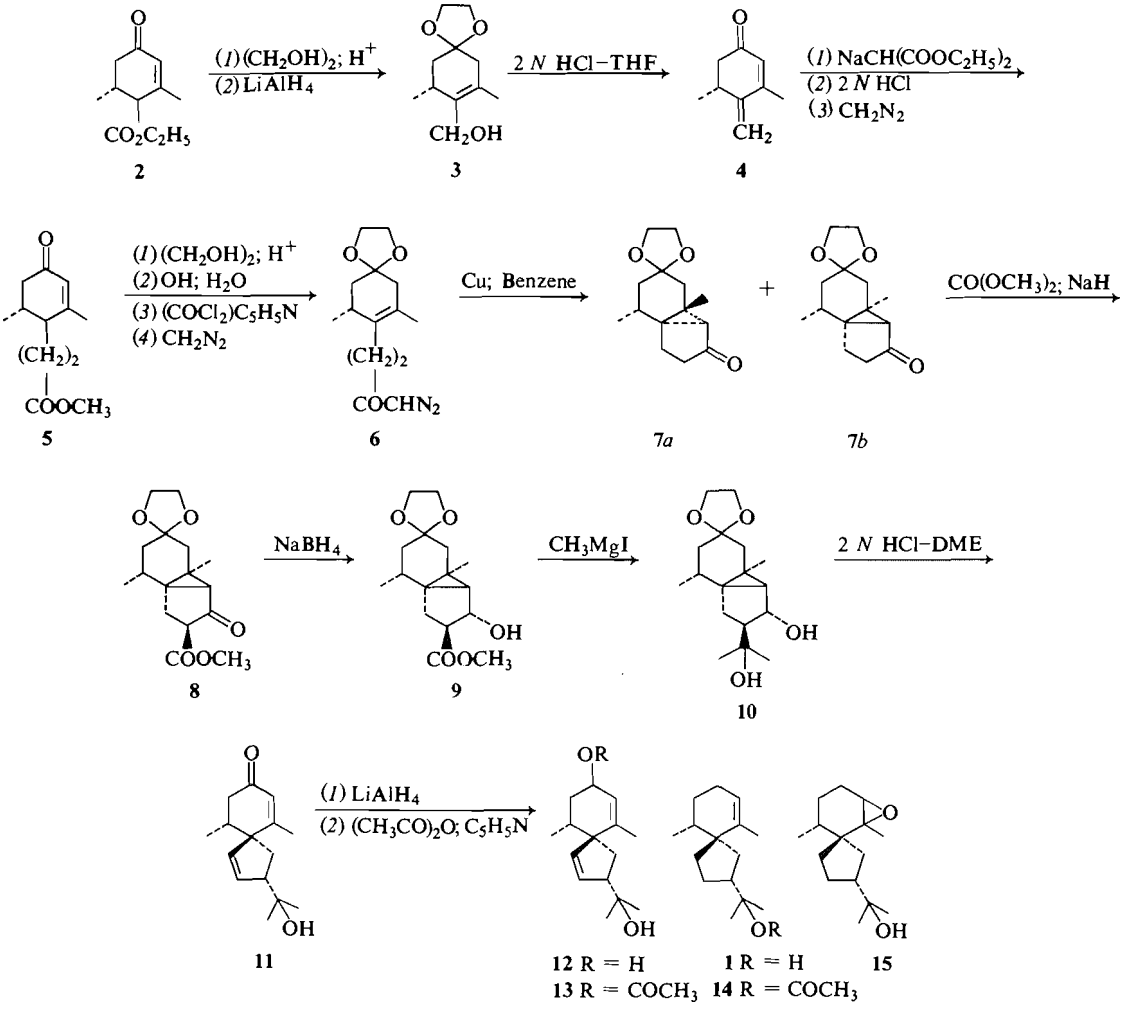
[4]Assignment of stereostructures of the two chromatographically separated isomers 7*a* and 7*b* will be presented in details in our forthcoming full publication. Professor G. Stork has kindly informed us that the identical reaction (**6** → 7*a*, *b*) has been carried out in his laboratories and similar conclusions were reached (P. McCurry (7)).

[5]We thank Professor James A. Marshall who kindly made this identification.

[6]Epihinesol (isopropylol epimer of hinesol) could very well be identical to agarospirol (1*d*) on the basis of biogenetic considerations (6). This conjecture is now strengthened by the identity of the n.m.r. spectrum of the crystalline epoxide **15** (m.p. 94–95 °C) with agarospirol epoxide. We thank Professor S. C. Bhattacharyya for this identification. However, the n.m.r. spectrum of our synthetic epihinesol differs from the one recorded in Bhattacharyya's paper in such a way that we suspect the natural "agarospirol" used by the Indian workers was probably contaminated. This was further hinted by our experience of quantitative epoxidation of epihinesol to a single product. We have not been able to secure a sample of authentic agarospirol.



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