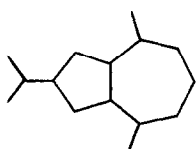


STEREOCHEMICAL RELATIONSHIPS IN SPIROVETIVANE SESQUITERPENES: THE TOTAL SYNTHESIS OF HINESOL

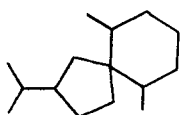
James A. Marshall and Stephen F. Brady*
Department of Chemistry, Northwestern University
Evanston, Illinois 60201

(Received in USA 14 February 1969; received in UK for publication 11 March 1969)

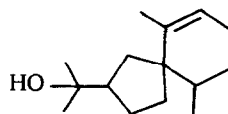
Recent synthetic and degradative studies (1) have necessitated a structural revision of the entire class of vetivane sesquiterpenes whereby the previously accepted bicyclo[5.3.0]-decane carbon framework (I) must be discarded in favor of the spiro[4.5]decane system (II). This revision creates some intriguing stereochemical problems, particularly with regard to spirovetivanes (2) such as hinesol (III) (3) which possess asymmetric centers in both rings. Solutions to these problems hold important biogenetic implications for this unusual class of terpenes and at the same time challenge current chemical methodology. This report outlines a solution based on synthesis which has been successfully applied to hinesol.



Vetivane (I)

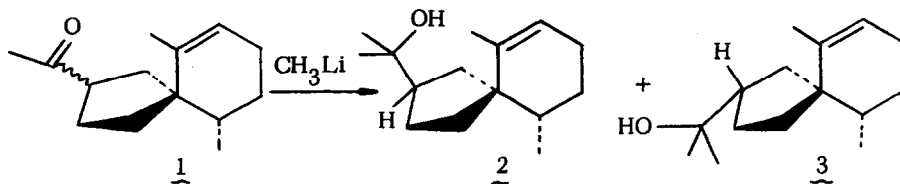


Spirovetivane (II)



Hinesol (III)

In connection with a total synthesis of β -vetivone (4) we prepared a mixture of the alcohols 2 and 3 from the corresponding acetyl derivative 1. One of these alcohols must be racemic hinesol; the other, on biogenetic grounds, may be agarospirol (5). However, both epimers exhibited nearly identical properties and the stereochemistry of the isopropylol grouping could not be ascertained. We therefore undertook an unequivocal synthesis of alcohol 2.

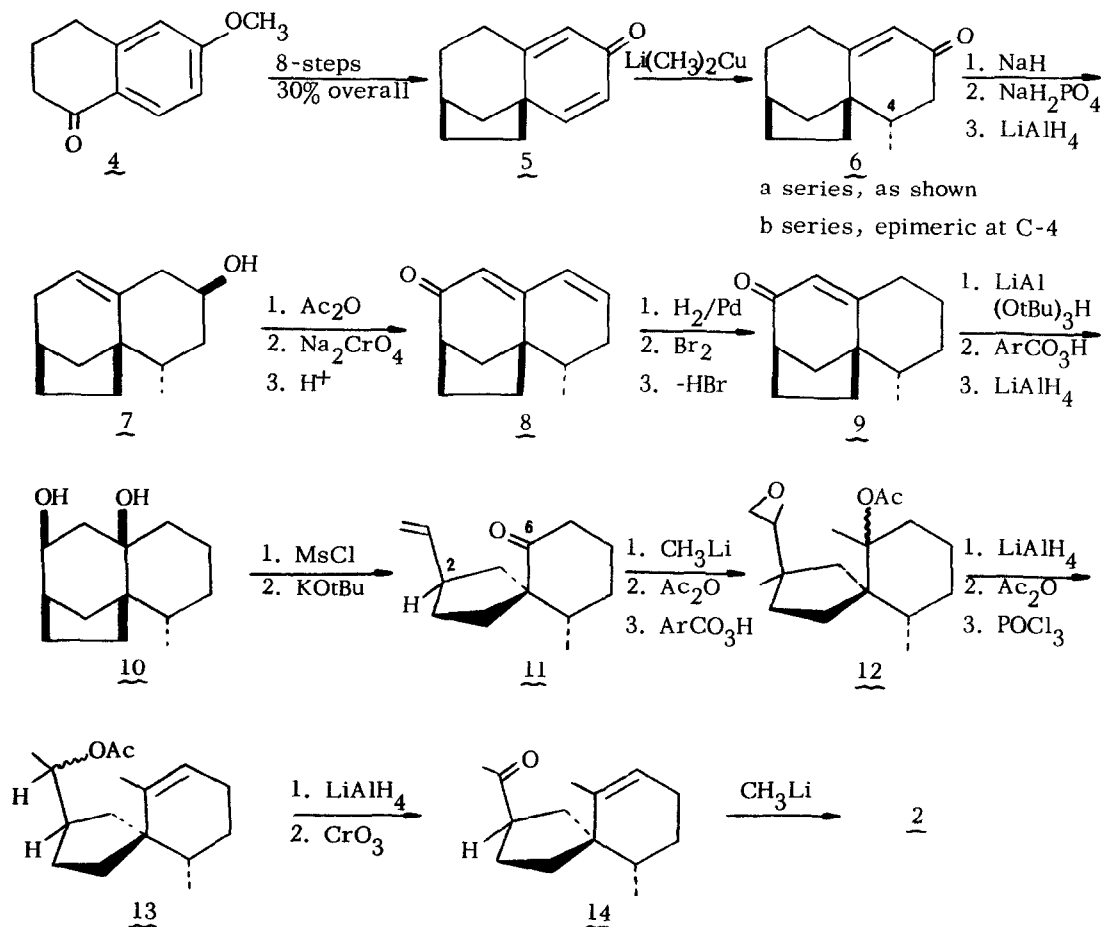


* National Institutes of Health Postdoctoral Fellow, 1967-1969.

Our synthetic scheme (Chart I) takes advantage of the unambiguous stereochemical arrangement of the tricyclic enone 6 to ensure an eventual cis relationship between the C-2 substituent and C-6 of the spiro system (cf. 11). This relationship seemed a priori the more likely one for hinesol on biogenetic grounds.

The tricyclic dienone 5 was prepared from 6-methoxy-1-tetralone (4) by an improved variation of Masamune's (6) route. Addition of lithium dimethylcopper (7) afforded the conjugated ketone 6 as a 1:4 mixture of anti (a series) and syn (b series) isomers (8). The stereochemistry of these adducts was unequivocally established through single crystal X-ray structure analysis (9) of the p-bromophenylurethane derivative of homoallylic alcohol 7b.

Chart I



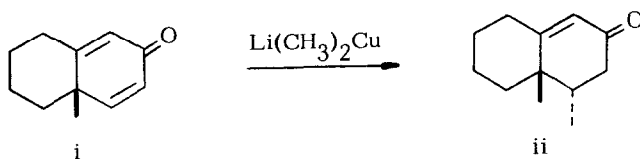
Dropwise addition of the enolate derived from the 1:4 mixture of enones 6a and 6b to aqueous sodium dihydrogen phosphate followed by reduction of the resulting β,γ -unsaturated ketone with lithium aluminum hydride and oxidation of the acetate derivative of the derived alcohol 7 afforded, after treatment with acid, the dienone 8 (50% overall yield) as a 1:4 mixture of the anti (8a) and syn (8b) isomers. Hydrogenation of the minor component 8a (purified via preparative gas chromatography) afforded a mixture (cis-trans) of saturated ketones which yielded (35% overall) the enone 9a upon bromination-dehydrobromination (10). Reduction with $\text{LiAl}(\text{O}t\text{Bu})_3\text{H}$ followed by epoxidation of the resulting allylic alcohol and reduction of the epoxide with LiAlH_4 gave the diol 10a. Selective esterification with methane-sulfonyl chloride followed by basic fragmentation (11) of the diol monomesylate thus secured afforded the unsaturated ketone 11a (60% overall yield: $\lambda_{\text{max}}^{\text{film}}$ 3.24, 5.87, 6.08, 10.01 and 10.95 μ). Addition of methylolithium, acetylation of the resulting tertiary alcohol, and epoxidation of the vinylic grouping led to the epoxy acetate 12a in nearly quantitative yield. Reduction of the epoxide with LiAlH_4 , selective acetylation of the resulting diol and dehydration of the tertiary alcohol thus secured afforded the unsaturated acetate 13a (60% yield). Cleavage of the acetate grouping followed by oxidation of the derived alcohol yielded ketone 14 which, in turn, was converted to racemic hinesol upon treatment with ethereal methyl-lithium.

Application of the above scheme to the epimeric dienone 8b led to an unsaturated alcohol (2b) whose spectral and chromatographic properties were virtually indistinguishable from those of hinesol. However, the derived acetates showed distinctly different gas chromatographic retention times with the acetate from alcohol 2a being identical with authentic hinesol acetate.

References

1. J. A. Marshall, N. H. Andersen, and P. C. Johnson, *J. Am. Chem. Soc.*, **89**, 2748 (1967); J. A. Marshall and P. C. Johnson, *ibid.*, **89**, 2750 (1967).
2. Since many of the vetivanes are no longer skeletally related to vetivazulene, it would seem desirable to have some other family name for those sesquiterpenes. We propose the name "spirovetivanes" for the vetivone-related natural products with a spiro[4.5]-decane carbon skeleton.
3. I. Yosioka and T. Kumura, *Chem. Pharm. Bull. Japan*, **13**, 1430 (1965).
4. J. A. Marshall and P. C. Johnson, *Chemical Communications*, 391 (1968).
5. K. R. Varma, M. L. Maheshwari, and S. C. Bhattacharyya, *Tetrahedron*, **21**, 115 (1965). See, H. C. Barrett and G. Büchi, *J. Am. Chem. Soc.*, **89**, 5665 (1967) for a configurational correction which bears on the proposed biogenetic relationship of agarospirol and agarofuran.
6. S. Masamune, *J. Am. Chem. Soc.*, **83**, 1009 (1961).

7. Cf. J. A. Marshall and N. H. Andersen, *J. Org. Chem.*, **31**, 667 (1966); H. O. House, W. L. Respass, and G. M. Whitesides, *ibid.*, **31**, 3128 (1966).
8. This stereochemical result is surprising in view of the fact that 10-methyl-1(9),3-hexal-2-one (i), the bicyclic analog of dienone 5, affords *trans*-4,10-dimethyl-1(9)-octal-2-one (ii) in over 90% yield upon treatment with lithium dimethylcopper (P. C. Johnson, unpublished results).



Studies aimed at resolving this apparent disparity are in progress.

9. We are deeply grateful to Professor R. E. Ireland and Dr. J. Bordner of the California Institute of Technology for carrying out this analysis.
10. Cf. J. A. Marshall and N. H. Andersen, *J. Org. Chem.*, **31**, 667 (1966). Under identical conditions the major dienone 8b afforded the enone 9b in 85% overall yield.
11. Cf. R. B. Clayton, H. B. Henbest, and M. Smith, *J. Chem. Soc.*, 1982 (1957); J. A. Marshall, G. L. Bundy, and W. I. Fanta, *J. Org. Chem.*, **33**, 3913 (1968).