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STEREOSPECIFIC TOTAL SYNTHESIS OF (-)-γ_2-CADINENE

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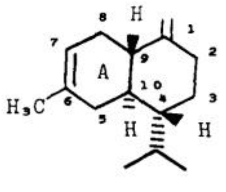
The recent publication of Kelly and Eber[1] of a total synthesis of (±)-γ_2-cadinene prompts us to report our own stereospecific total synthesis of the natural (-)-γ_2-cadinene (1).[2a,b] The sesquiterpene, which occurs in North Indian vetiver oil from Vetiveria zizanioides (L.) Nash,[3] is stereochemically correlated with (+)-cadinene dihydrochloride (2) and is of biogenetic interest[4a,b] since it belongs to the unusual antipodal series among the cadalenic natural products. The new synthesis is shorter and somewhat more direct than that reported for the racemic analogue.

In the present work, the dextrorotatory methylene ketone 3, which has been prepared by stereospecific total synthesis,[5] was quantitatively converted with excess methyllithium to a mixture of tertiary alcohols in which the axial epimer 4[6] was expected to preponderate. It has been pointed out that in addition reactions between methyllithium and substituted cyclohexanones, the alkyllithium reagent approaches preferentially from the least hindered equatorial side of the ketone group.[7,8] Such addition should proceed from the β side of the ketone function in compound 3 to give the 6β-methyl-6α-hydroxy isomer, 4. In accord with this, the crude carbinol on mild treatment with thionyl chloride in pyridine[9a,b] yielded directly, after distillation in vacuo followed by argentic layer chromatography,[10] (-)-γ_2-cadinene (1) as the main olefinic product [26% from the methylene ketone 3; $[\alpha]_D^{22}$ -4.9° ($CHCl_3$);[11] $\nu_{max}^{CCl_4, CS_2}$ (cm^{-1}) 3080 (m), 1770 (w), 1640 (s), 1390 (s), 1370 (s), 882 (vs), 832 (w), 790 (s); nmr



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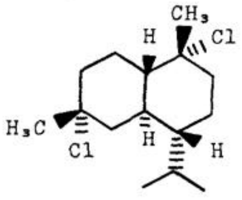

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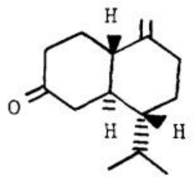

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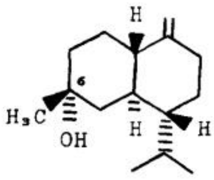

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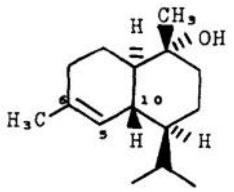

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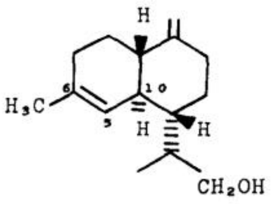

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(Varian A-60-A, $\delta_{TMS}^{CDCl_3}$ Kontes micro apparatus) 5.48 (1H, broad multiplet, vinylic H), 4.69, 4.57 (1H each, both broad singlets, terminal methylene), 1.67 (3H, singlet, vinylic methyl), 0.93 and 0.73 (3H each, both doublets, J=6.5 Hz, isopropyl group); uv (EtOH), no maxima in 400-215 mμ region]. The ir and nmr spectra of 1 were virtually identical with those of (±)-γ_2-cadinene.[12]

The formation of the double bond in a 6,7-trans-decalin position in preference to the 5,6-position[13,14] has been explained in terms of steric[15] and hyperconjugative[16] effects. That the double bond is actually located in the 6,7-position was confirmed by the nmr spectrum, which in agreement with that reported for (±)-γ_2-cadinene[1] showed the presence of a non-geminal vinylic proton at δ5.48 as an unresolved multiplet, instead of a characteristic singlet[17] for a C_5 vinylic proton, such as that shown, for example, by α-cadinol[18] (5) and khusol[19] (6).

The gross structure of the synthetic product 1 was confirmed by ready conversion with hydrogen chloride in ether at -15° to (+)-cadinene dihydrochloride (2), $[\alpha]_D$ +37°, m.p., and mixed m.p. with an authentic sample,[20] 116-117°.

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REFERENCES AND FOOTNOTES

1. R. B. Kelly and J. Eber, *Can. J. Chem.*, **48**, 2246 (1970).
2. a) C. C. Kartha, P. S. Kalsi, A. M. Shaligram, K. K. Chakravarti and S. C. Bhattacharyya, *Tetrahedron*, **19**, 241 (1963); b) T. Sakai, K. Yoshihara and Y. Hirose, *Bull. Chem. Soc. Japan*, **41**, 1945 (1968).
3. The name of the plant from which the Vetiver oils are obtained is frequently misspelled and is often attributed to an incorrect authority (see for example, reference 2a). Since chemically distinct races of the species have been reported,[4a] and the biogenetic implications involved are under study,[4a,b] correct nomenclatural procedures would seem especially important. The essential oil is obtained from *Vetiveria zizanioides* (L.) Nash. The species was originally described by Linnaeus in 1771 as *Phalaris zizanioides* and was transferred to the genus *Vetiveria* by Nash in 1903. For a complete synonymy see A. S. Hitchcock, "Manual of the Grasses of the United States," 2nd edition, revised by Agnes Chase, 979, U. S. Govt. Print. Off., 1950. We are indebted to Professor John Burk, of the Smith College Department of the Biological Sciences, for this information.
4. a) N. H. Andersen, *Phytochemistry*, **9**, 145 (1970); b) *ibid*., *Tetrahedron Letters*, 4651 (1970).
5. M. D. Soffer and L. A. Burk, *Tetrahedron Letters*, 211 (1970).
6. Found for the crude tertiary alcohol **4**: $\nu_{max}^{CCl_4}(cm^{-1})$ 3610 (sharp, m), 3080 (m), 1645 (s), 890 (vs), no absorption for a ketone group.
7. D. B. Bigley, N. A. J. Rogers and J. A. Barltrop, *Chem. Ind*., 558 (1958).
8. W. J. Houlihan, *J. Org. Chem*., **27**, 3860 (1962).
9. a) R. R. Smolders, *Can. J. Chem*., **42**, 2836 (1964); b) For the correct structure and stereochemistry of the δ-cadinol described, and its derivatives,

see B. A. Nagasampagi, L. Yankov and Sukh Dev, *Tetrahedron Letters*, 1913 (1968); R. R. Smolders, *Ing. Chim.*, **49**, 244 (1967) [*C. A.*, **69**, 3030v (1968)]; L. Westfelt, *Acta Chem. Scand.*, **24**, 1618 (1970).

10. Brinkman 2 mm. F-254 silica gel plate impregnated with silver nitrate; developing solvent, anhydrous benzene.

11. The present value for the optical rotation differs considerably from the one value reported previously.[2a] The previous product was isolated directly from the essential oil by stepwise column chromatography on alumina with no further purification, except by distillation over sodium. Since the natural sesquiterpene is not available at this time, a direct comparison with the synthetic compound is not possible. We thank Dr. K. K. Chakravarti[2a] for the foregoing information and for his cooperation.

12. We are indebted to Dr. R. B. Kelly for making available to us copies of the ir and nmr spectra of the racemic product.[1]

13. D. H. R. Barton, A. da S. Campos-Neves and R. C. Cookson, *J. Chem. Soc.*, 3500 (1956).

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16. D. A. H. Taylor, *Chem. Ind.*, 250 (1954).

17. The difference in the splitting pattern is due to the fact that the dihedral angle between the vinylic proton at C_5 and the single allylic proton at C_{10} is almost 90°. [M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959)].

18. W. G. Dauben, B. Weinstein, P. Lim and A. B. Anderson, *Tetrahedron*, **15**, 217 (1961); see also reference 9b.

19. P. S. Kalsi, K. K. Chakravarti and S. C. Bhattacharyya, *Tetrahedron*, **19**, 1073 (1963).

20. M. D. Soffer and G. E. Günay, *Tetrahedron Letters*, 1355 (1965).