Tetrahedron Letters No.55, pp. 5785-5786, 1968. Pergamon Press. Printed in Great Britain.

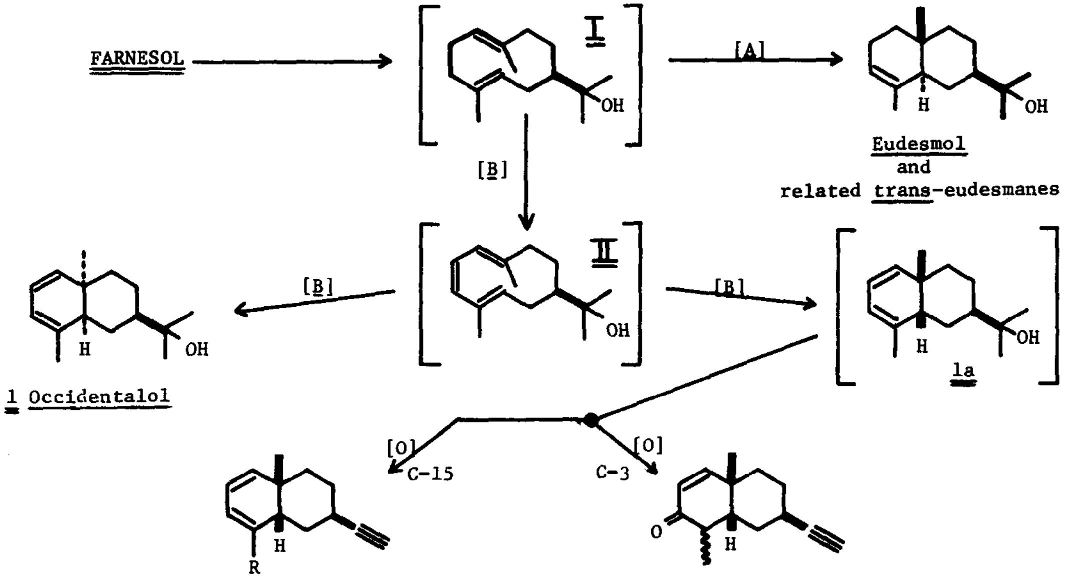
A HYPOTHESIS FOR THE FORMATION OF *CIS*-FUSED EUDESMANE-TYPE SESQUITERPENES

Alfred G. Hortmann

Department of Chemistry, Washington University, St. Louis, Missouri 63130

(Received in USA 27 July 1968; received in UK for publication 15 October 1968)

The prophetic proposals of Ruzicka have provided an outline for the probable biogenesis of several major classes of terpenes;(1a) additional considerations concerning the stereochemical course of sesquiterpene biosynthesis have been presented by Hendrickson.(1b) The biogenesis of the usually *trans*-fused eudesmane-type sesquiterpenes is believed to involve an *in vivo* transformation (Route [*A*]) which resembles, formally, proton-initiated transannular cyclization of a *trans,trans*-cyclodeca-1,5-diene such as *I*; similar *in vitro* processes have been observed.(1b) This scheme has also been extended(1c) to account for the genesis of the *cis*-fused eudesmadiene, occidentalol (**1**).(2) Recently, several *nor*-eudesmanes (**2**, **3**, **4**, **5**, and others) have been isolated from *Chamaecyparis Formosensis* Matsum.(3) Compounds **1**, **2** and **3** each possess a 1,3-diene system and a *cis* ring-fusion, two features which, to this author's knowledge, have not been observed to occur either alone or together in any other eudesmane;(4) the cooccurrence of **4**, **5**



2 Dehydrodihydrochamaecynenol (R=CH_2OH)

3 Dehydrodihydrochamaecynenal (R=-CHO)

4 Chamaecynone (4α-methyl)

5 Isochamaecynone (4β-methyl)

and related ketones with 2 and 3 in the same plant suggests that all of these compounds arise *via* oxidation of a common intermediate, the presently unknown 5β,10β-occidentalol, 1a (or a related *nor*-structure). These observations, taken with the established structure of 1 (which also possesses a rarely-observed configurational relationship between its C-7 and C-10 substituents), suggests the hypothesis that a unique biosynthetic route exists for the formation of *cis*-fused eudesmanes. Such a pathway (Route [B]) might involve either enzymatic hydroxylation-dehydration(5) or direct dehydrogenation of I to yield II; once formed, this *trans,cis,trans*-cyclodecatriene might undergo further enzymatically-controlled, or facile non-enzymatically-controlled, valence tautomerism to one or both possible *cis*-fused occidentalols (1 and/or 1a).(6-10)

REFERENCES

1. a) L. Ruzicka, *Experientia*, **9**, 357 (1953); A. Eschenmoser, L. Ruzicka, O. Jeger and D. Arigoni, *Helv. Chim. Acta*, **38**, 1890 (1955). b) J.B. Hendrickson, *Tetrahedron*, **7**, 82 (1959). c) E. von Rudloff and G.V. Nair, *Can. J. Chem.*, **42**, 421 (1964).

2. Revised structure: A.G. Hortmann and J.B. De Roos, manuscript submitted to *J. Org. Chem.*

3. T. Asao, S. Ibe, K. Takase, Y.S. Cheng and T. Nozoe, *Tetrahedron Letters*, 3639 (1968) and references cited.

4. *Cf.* G. Ourisson, S. Munavelli, and C. Ehret, *International Tables of Selected Constants*, Vol. 15, pp 13-14, 22, 25-26. Pergamon Press, Oxford, 1966. See also G.L. Chetty, V.B. Zalkow, and L.H. Zalkow, *Tetrahedron Letters*, 3223 (1968).

5. Sesquiterpenes having a ten-membered ring oxygenated at C-3 are known, *e.g.* N.H. Fischer and T.J. Mabry, *Chem. Comm.*, 1235 (1967); N.H. Fischer, T.J. Mabry, and H.B. Kagan, *Tetrahedron*, **24**, 4091 (1968).

6. The stereochemical outcome observed for such a thermally-induced process *in vitro* is found to be as proposed here in those cases where it has been examined.(7,8,9,10) Although it would appear that the Woodward-Hoffmann rules apply in these cases, the validity of theories of this type for systems having little symmetry is questionable (M.J.S. Dewar, *Tetrahedron Supplement*, **8**, 75 (1966)).

7. E.J. Corey and A.G. Hortmann, *J. Am. Chem. Soc.*, **85**, 5736 (1965).

8. E. Havinga and J.L.M.A. Schlatmann, *Tetrahedron*, **16**, 146 (1961) and references cited; E. Vogel, W. Grimme and E. Dinne, *Tetrahedron Letters*, 391 (1965); E.N. Marvell, G. Caple and B. Schatz, *ibid.*, 385 (1965).

9. Studies presently in progress in This Laboratory (A.G. Hortmann, J.E. Martinelli and M. Tio; see also Y. Wang, M. A. Thesis, Washington Univ., 1966) indicate that, in experiments similar to those described in ref. 7, 1 and 1a can be obtained, presumably by recyclization of II, in a *ca.* 1:1 ratio *via* photolysis of "*trans*-occidentalol"; preliminary observations in a very closely-related system also indicate that a photochemical diene-triene equilibrium is detectable at -70° and that thermally-induced recyclization of the cyclodecatriene to both possible *cis*-fused decalins is rapid well below 0°.(10)

10. The course of such a non-enzymatically-controlled process of low $\Delta F^{\ddagger}$ might still be sterically-controlled *in vivo* as a result of the asymmetric environment provided by the enzyme responsible for the formation of triene II; this assumes that, subsequent to the formation of II, the residence time of II on the surface of this enzyme (which presumably would have a similar attraction for the π-bonds and/or the 7β substituents of both I and II) is long when compared with the rate of uncatalyzed cyclization of II.