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CONTROL ELEMENTS IN THE INTRAMOLECULAR DIELS-ALDER REACTION: SYNTHESIS OF α-EUDESMOL

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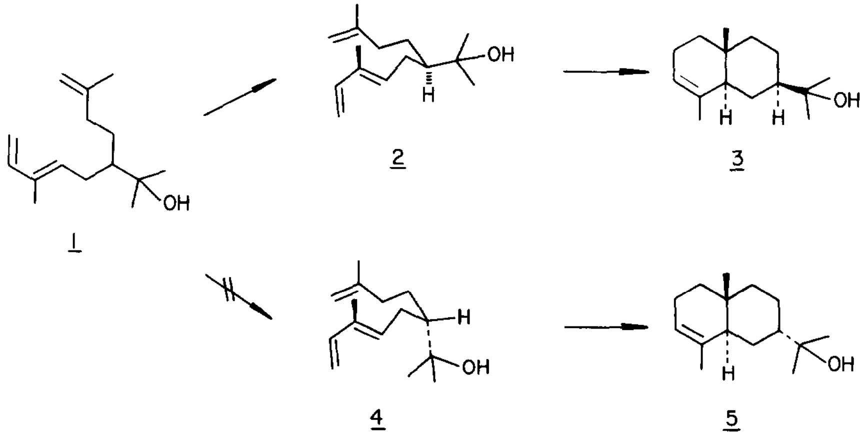
SUMMARY: Triene 1 undergoes cyclization with substantial 1,3 and 1,4 chiral induction to give largely trans, equatorial α-eudesmol 3.

The crystalline sesquiterpene alcohol eudesmol was the object of several early investigations. Although Ruzicka demonstrated in 1932 (1) that the natural material was a mixture of isomers, in varying proportion depending on the source from which it was isolated, it was not until 1956 (2) that pure α- and β-eudesmol were isolated and characterized. While two (3,4) stereocontrolled syntheses of β-eudesmol have been accomplished, the only route to α-eudesmol in the literature (3) starts from (+)-cyperenone. We report a direct, stereoselective preparation of α-eudesmol 3 (5), based on an intramolecular Diels-Alder cyclization (6).



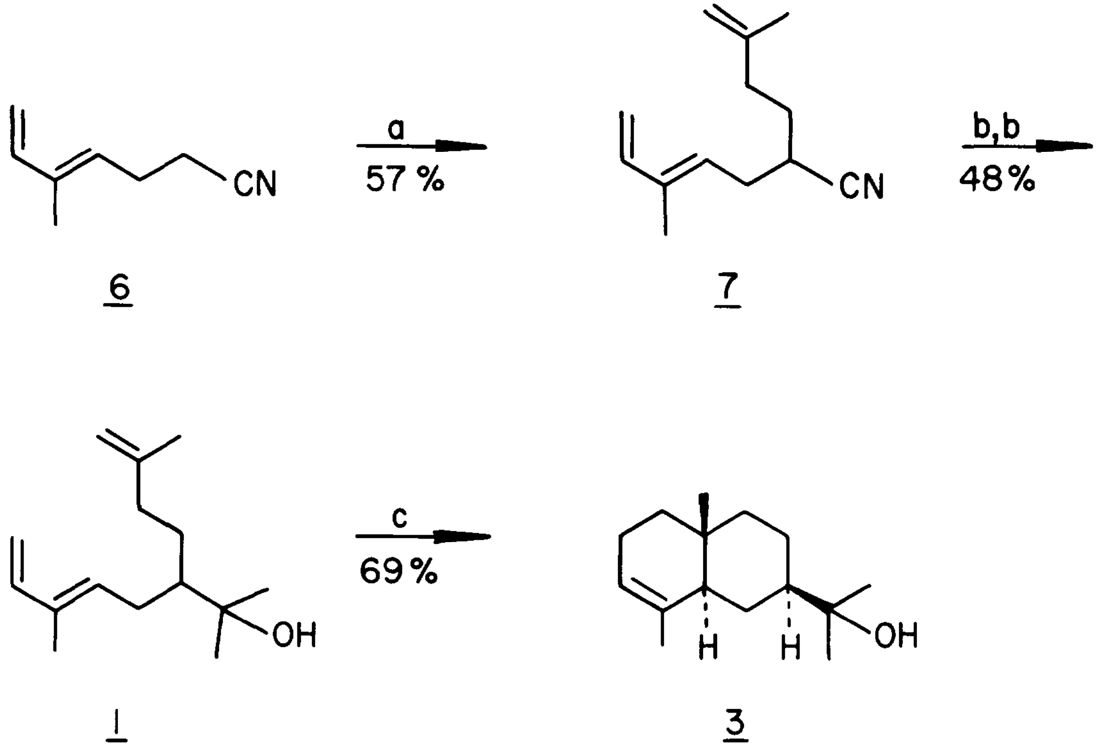
The key intermediate in the synthesis is triene 1. While it was known that trienes of this substitution pattern cyclize to give largely the trans product (7), it was less obvious how much influence a substituent on one of the methylenes bridging the diene and the dienophile would have on the stereochemical course of the cyclization. While one would expect equatorially-substituted transitions state conformation 2 to be favored over axially-substituted transition state conformation 4 (8), the elevated temperature required to achieve cyclization combined with the lack of rigidity in the system left the degree of stereocontrol in the course of the cyclization substantially in question. In the event, we have shown 3 to indeed be the dominant product of the cyclization.

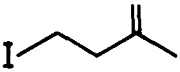
Triene 1 is easily prepared (Scheme) by sequential addition of methyl lithium to nitrile 2, itself readily available by alkylation of cyanodiene 6 (9,10) with 1-iodo-3-methyl-3-butene (11,12). On thermolysis (sealed tube) 1 was smoothly converted to a mixture that showed two components on TLC, Rf (10% EtOAc/hexane) = 0.28 and 0.35. The more polar component was isolated by column chromatography using TLC mesh silica gel. It showed one component on GC (6 ft. 1/8" 3% OV-17, 25 ml/min, 155., retention time 4.1 min.) This synthetic material (mp = 72-75.) was identical (TLC, GC/MS, ^{1}H NMR) with α -eudesmol isolated from the oil of Eucalyptus macarthurii.

GC analysis of the reaction mixture before chromatography showed, in addition to unreacted triene (2.1 min) four components (2.6, 2.8, 3.4 and 4.1 min) in a ratio of 5:9:4:82. The major component corresponds to α -eudesmol, isolated above. The three minor components, apparently (GC/MS) the other three eudesmol isomers, elute together on column chromatography, Rf = 0.35. We are currently investigating the separation and individual characterization of these minor products.

The degree of stereocontrol evidenced in this cyclization is remarkable. The applicability of this approach to the preparation of a wide variety of terpenoid natural products should be apparent. In particular, it should be noted that the asymmetric center originally present in 1 cleanly induces the relative stereochemistry of the ring fusion centers as they are formed. Given the relative ease with which acyclic fragments can be prepared enantiomerically pure (13), it should also be apparent that such intramolecular Diels-Alder reactions hold great promise for the enantioselective preparation of carbocyclic natural products (14).

SCHEME



a) LDA, THF, -78°; I, HMPA, -78° → RT. b) MeLi/Et_2O, 0°; HCl, H_2O, RT. c) $PhCH_3$, methylene blue, 195°, 68h.

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References and Notes

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5. Since α-eudesmol is smoothly converted to β-eudesmol on ultraviolet irradiation (ref 2), this work could be considered to be a formal total synthesis of the latter isomer also.

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9. M. Julia, S. Julia, B. Stalla-Bourdillon and C. Descoins, Bull. Soc. Chim. Fr. 2533 (1964).

10. The starting cyanodiene is a 70/30 mixture of E and Z isomers, which mixture is carried through the synthetic scheme. Only the E isomer undergoes cyclization,and yields are reported on that basis.

11. The iodo olefin was prepared by NaI/acetone exchange on the known bromide: P.-E. Sum and L. Weiler, Can. J. Chem. 57, 1475 (1979).

12. All new compounds were homogenous by TLC and gave ^{1}H NMR, IR and mass spectra consistent with the assigned structure.

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14. An elegant illustration of just such an enantioselective approach to a carbocyclic natural product recently appeared: K.C. Nicolaou, D.P. Papahatjis, D.A. Claremon and R.E. Dolle, III, J. Am. Chem. Soc. 103, 6967 (1981).

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