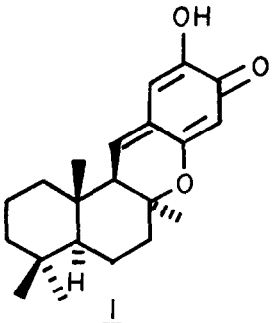
Tetrahedron Letters No. 18, pp 1525 - 1528, 1978. 0040-4039/78/0429-1525. $02.00/0.

THE TOTAL SYNTHESIS OF (±)-PUUPEHENONE

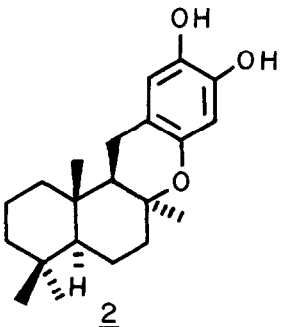
TRAMMELL, G.L.
Department of Chemistry, Miami University, Ohio, 45056, U.S.A.

(Received in USA 19th September 1977; received in UK for publication 6 March 1978)

Puupehenone (1) was isolated from a marine sponge of unknown genus collected near the Blowhole area of Oahu and the Needles of Lanai.[2] The structure and relative stereochemistry of puupehenone (1) were determined by a combination of chemical degradation and X-ray spectroscopy.[2] Both *in vivo* and *in vitro* assay showed puupehenone (1) to be active against a variety of bacteria.[2] Because of its biological activity and unique structure, the first total synthesis of puupehenone (1) was accomplished.



1



2

The first objective of the synthesis was the degradation product dihydropuupehenone (2), prepared by sodium borohydride reduction of 1.[2] It appeared that oxidation of catechol 2 to its o-quinone followed by tautomerization would yield puupehenone (1). Accordingly, polyene 3, containing all the carbon and oxygen atoms of 1, was prepared by alkylation of the lithium salt of sesamol (obtained by m-chloroperbenzoic acid oxidation of piperonal followed by hydrolysis) with farnesyl bromide (tetrahydrofuran, room temperature, 24 hours). Alkylation occurred exclusively on carbon to give 3 (40% after silica gel chromatography) and recovered sesamol. This abnormal C-alkylation was attributed to the disposition of the three oxygen atoms in sesamol, a conclusion supported by the exclusive O-alkylation of farnesyl bromide with lithium p-methoxyphenoxide under indentical conditions.

Cyclization of 3 with boron trifluoride etherate in methylene chloride gave the incompletely cyclized compound 4 [pmr ($CDCl_3$)δ 2.74 (2H, d of d,J=7, 7 Hz), 1.70 (3H,s), 1.37 (3H,s), 1.11 (6H,s), no olefinic H]. To prevent

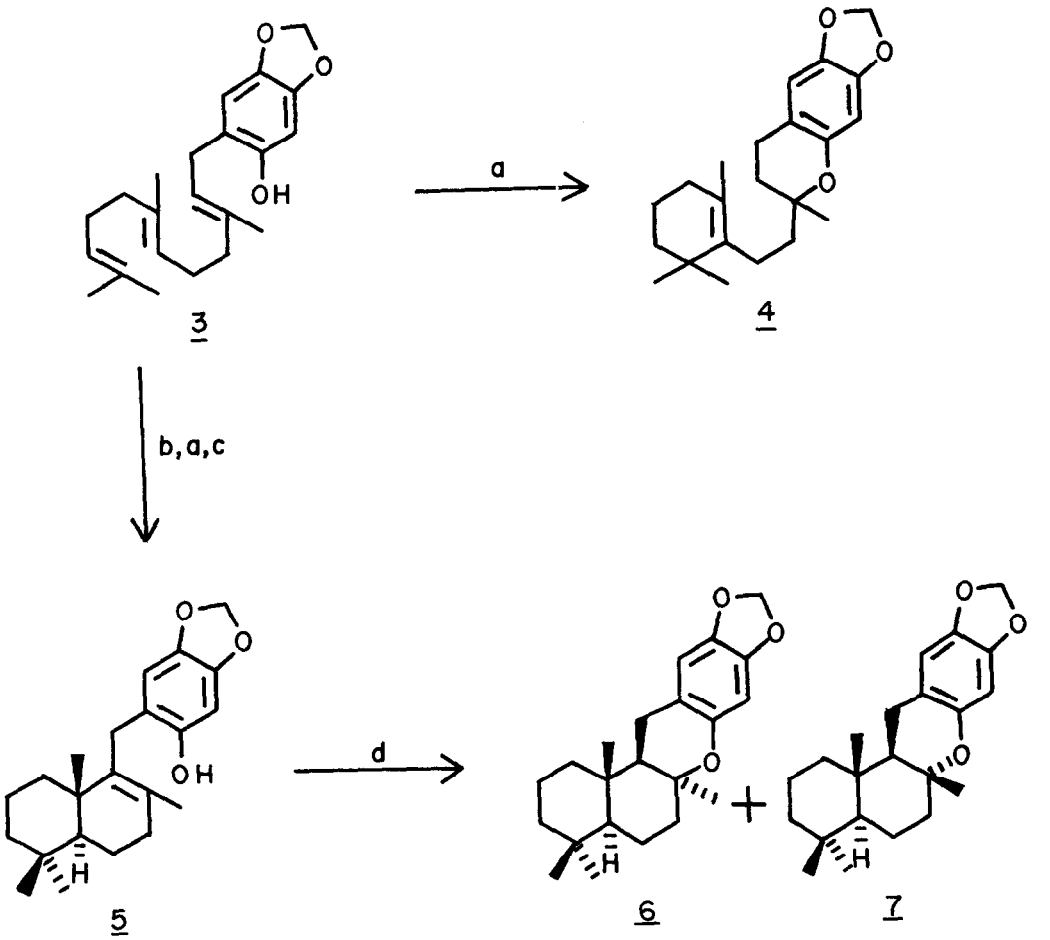
participation of the phenolic oxygen, 3 was acetylated. Cyclization of the acetate of 3 with boron trifluoride etherate followed by alkaline hydrolysis gave phenol 5 (40% overall) [ir (neat) 3400 cm^{-1}; nmr ($CDCl_3$)δ 1.58, 0.97, 0.98, and 0.85 (3H, singlets)]. No double bond isomers were detected in the nmr spectrum of the crude product. The trans-stereochemistry of 5 was assigned by the known stereochemical outcome of such cyclizations.[3,4]

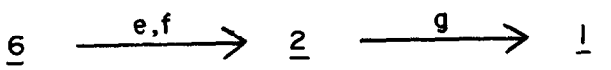
Treatment of phenol 5 with a catalytic amount of β-naphthalenesulfonic acid in methylene chloride gave two isomers, 6 and 7 (2.4:1 ratio), separable by column chromatography on Florisil (eluent: 20% benzene in hexane). Assignment of structure 6 to the major isomer was based on the downfield shift of the C-10 methyl group of 6 relative to 7 produced by the 1,3-diaxial disposition of methyl group and ether oxygen in 6.[5] This assignment was supported by subsequent conversion of 6 to puupehenone (1).

Cleavage of the methylenedioxy group of 6 was accomplished by the traditional method of halogenation with phosphorous pentachloride to give the geminal dichloride, hydrolysis of the crude product to the carbonate, and subsequent hydrolysis to the catechol 2,[6] identical with a sample prepared from natural puupehenone (1). Aerobic oxidation of catechol 2 in the presence of KOH[7] gave puupehenone (1) (identical to the authentic substance) in almost quantitiative yield.

We had hoped to affect cleavage and oxidation of 6 simultaneously using silver (II) oxide.[8] However, oxidative polymerization of puupehenone (1) was more rapid than oxidative cleavage of the methylenedioxy group and only highly polar red pigments were obtained along with starting material. It is interesting to note that a red pigment was isolated along with puupehenone and appears to be an oxidative dimer.[2] Other methods for nucleophilic dealkylation of 6 were unsuccessful in our hands (BCl_3,[9] lithium thioethoxide,[10] and trimethylsilyl iodide[11]).

Acknowledgement: We thank the Department of Chemistry at The University of Hawaii for support of this research. We also thank Professor Paul J. Scheuer for an authentic sample of puupehenone and Givaudan Corporation for a generous sample of farnesol. The assistance of Dr. P. Freeman in obtaining mass spectra is gratefully acknowledged.





a) BF_3 · etherate, CH_2Cl_2;
b) acetic anhydride, pyridine;
c) KOH, methanol;
d) β-naphthalenesulfonic acid CH_2Cl_2;
e) PCl_5, CH_2Cl_2, reflux;
f) H_2O, methanol, reflux;
k) KOH, methanol, O_2

REFERENCES

1. Address correspondence to Department of Chemistry, Miami University, Oxford, Ohio 45056.

2. B.N. Ravi, Ph.D. Thesis, The University of Hawaii at Manoa, Honolulu, Hawaii, 1976; P.J. Scheuer, presented in part at the 12th Regional Western Meeting of the American Chemical Society, Phoeniz, Arizona, November 1976.

3. G. Stork and A.W. Burgstahler, J. Am. Chem. Soc., 77, 5068 (1955); P.A. Stadler, A. Eschenmoser, H. Schinz, and G. Stork, Helv. Chim. Acta, 40, 2191 (1957).

4. R.W. Skeean, G.L. Trammell, and J.D. White, Tetrahedron Lett., 525 (1976)

5. N.S. Bhacca and D.H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry, Illustrations from the Steroid Field," Holden-Day, Inc., San Francisco, 1964, pp. 13-24.

6. J.S. Buck and F.J. Zimmerman in "Organic Syntheses," Coll. vol. 2, A.H. Blatt, Ed., John Wiley & Sons, Inc., New York, New York, 1943, pp. 549-550.

7. D.H.R. Barton and J.B. Hendrickson, J. Chem. Soc., 1028 (1956).

8. C.D. Snyder and H. Rapoport, J. Am. Chem. Soc., 94, 227 (1972).

9. S. Teite and J.P. O'Brien, J. Org. Chem., 41, 1657 (1976).

10. G.I. Feutrill and R.N. Mirrington, Tetrahedron Lett., 1327 (1970).

11. M.E. Jung and M.A. Lyster, J. Am. Chem. Soc., 99, 968 (1977).