# A FORMAL TOTAL SYNTHESIS OF DACTYLOL

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Summary: The tetracyclic epoxide **16** was prepared in stereocontrolled fashion from 4,4-dimethylcyclohexanone, the key steps being Saegusa ring expansion of its silyl enol ether to **5**, ortho ester Claisen rearrangement of **7**, and cyclization of **9** without rupture of the three-membered ring. Epoxide **16** had previously been transformed into dactylol, thus completing the formal total synthesis.

Dactylol (**1**), an irregular isoprenoid sesquiterpene alcohol isolated in 1978 from the Caribbean sea hare *Aplysia dactylomela*,[1] belongs to an expanding family of architecturally related natural products that also includes poitediol (**2**)[2,3] and precapnelladiene (**3**).[4,5] Structurally, these substances feature a functionalized cyclooctane ring annealed to a smaller cycle; consequently, they can be regarded as lower homologues of the ophiobolins.[6]
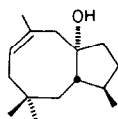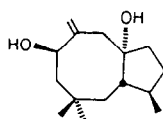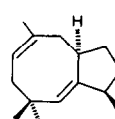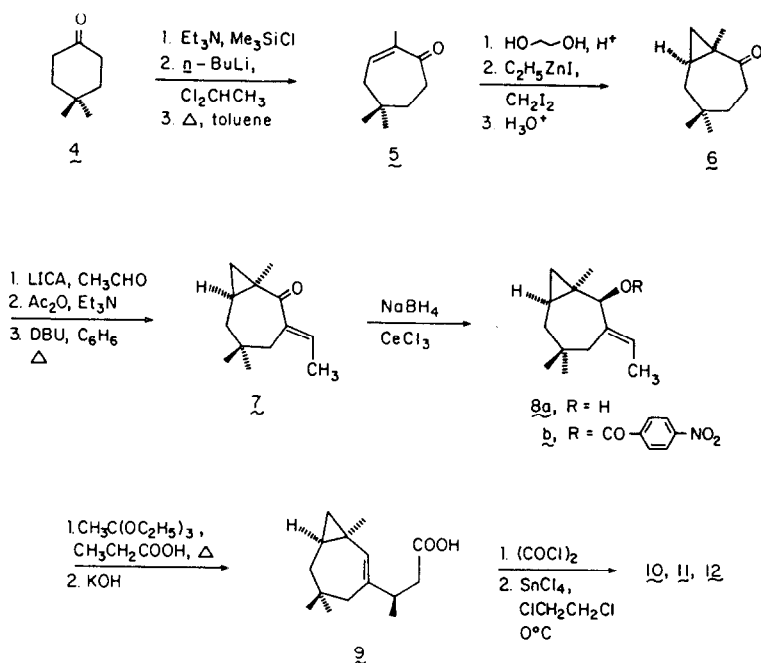

The arrangement of atoms in **1-3**, including appropriate interlocking of the chiral centers, can in principle be accommodated by several tactical approaches. As concerns the scheme described herein, an africane nucleus[7] is first elaborated. Since epoxide **16** has previously been converted in two steps to **1**,[8] a formal total synthesis of dactylol has been successfully achieved.[9]

4,4-Dimethylcyclohexanone (**4**), obtained by hydrogenation[10] of the readily available α,β-unsaturated ketone,[11] was efficiently (71% overall) ring expanded to cyclohepte-

none 5[12] by the Saegusa procedure.[13] The stage was now set for introduction of the cyclopropane ring. Of the several methods examined, the most expedient consisted of ketalization (83%, no double bond migration), Simmons–Smith cyclopropanation (92%),[14] and hydrolytic removal of the ethylenedioxy group (100%).

With the seven-membered ring now fully elaborated, efforts were next focused on appropriate cyclopentannulation in the vicinity of the carbonyl group *without cleavage of the conjugated cyclopropane unit*. Aldol condensation of the lithium enolate of 6 with acetaldehyde produced a β-hydroxy ketone (79%), which was directly acetylated (96%) and subjected to β-elimination (93%). The anti stereochemistry of the ethylidine methyl group in 7 was ascertained on the basis of the chemical shift of its olefinic proton (δ 6.83).[15]

Reduction of 7 with the Luche reagent[16] gave rise predominantly to β-alcohol 8a. This relevant stereochemical issue was elucidated by X-ray crystal structure analysis of the p-nitrobenzoate (8b).[17] This result reveals that the α face of the carbonyl carbon is more sterically accessible, a fact that will be used to advantage subsequently. Heating of 8a with triethyl orthoacetate in the presence of propionic acid delivered a stereochemically homogeneous ester (72%) whose saponification furnished 9. The configuration of the side-chain methyl group has been inferred from the usual stereoelectronic considerations.[18] With
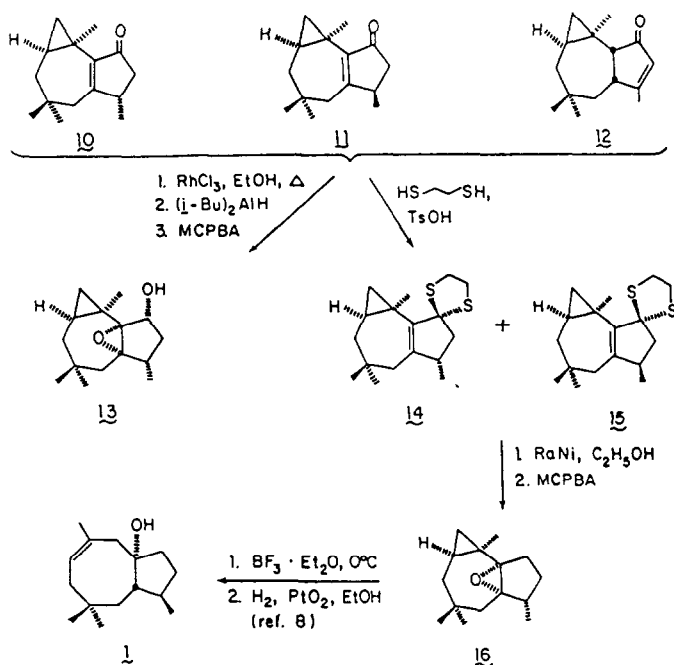
9 in hand, the acid chloride was prepared and this intermediate was exposed to the action of stannic chloride in anhydrous 1,2-dichloroethane solution at 0°C. As anticipated, a mixture of cyclopentenones (96%) resulted: 10 (12%), 11 (24%), 12 (64%). The structural assignments to these isomers follow from their respective spectral properties, the independent conversion of 10[19] to epoxy alcohol 13, and confirmatory X-ray analysis of this tetracyclic compound.[20]

Chromatographic separation of the trio of enones proved not to be necessary, since standard dithioketalization proceeded to give an 83:17 mixture of 14 and 15. Only after sequential Raney nickel desulfurization and epoxidation was silica gel chromatography deployed. The peracid likewise approached the π bond from the α face to deliver predominantly epoxide 16 (27.2% overall), whose high field ^{1}H NMR spectrum was identical to that provided by Professor Matsumoto. The facility with which 16 undergoes Lewis acid-catalyzed isomerization with cleavage of both three-membered rings has been earlier detailed by the Matsumoto group.[9]

Thus, it is now possible to view 5/8-fused sesquiterpenes such as 1-3 as being usefully accessible from perhydroazulenoid precursors. This principle apparently already operates in nature, with humulene serving as the starting point of biosynthetic construction.[9,21]

References and Notes

(1)   Schmitz, F. J.; Hollenbeak, K. H.; Vanderah, D. J. *Tetrahedron* **1978,** *34,* 2719.

(2)   Isolation: Fenical, W.; Schulte, G. R.; Finer, J.; Clardy, J. *J. Org. Chem.* **1978,** *43,* 3630.

(3)   Synthesis: Gadwood, R. C.; Lett, R. M; Wissinger, J. E. *J. Am. Chem. Soc.* **1984,** *106,* 3869.

(4)   Isolation: Ayanoglu, E.; Gebreyesus, T.; Beechan, C. M.; Djerassi, C. *Tetrahedron* **1979,** *35,* 1035.

(5)   Synthesis: (a) Kinney, W. A.; Coghlan, M. J.; Paquette, L. A. *J. Am. Chem. Soc.* **1984,** *106,* 6868; **1986,** *108,* in press.   (b) Mehta, G.; Narayana Murty, A. *J. Chem. Soc., Chem. Commun.* **1984,** 1058.

(6)   (a) Paquette, L. A.; Andrews, D. R.; Springer, J. P. *J. Org. Chem.* **1983,** *48,* 1148. (b) Paquette, L. A.; Colapret, J. A.; Andrews, D. R. *Ibid.* **1985,** *50,* 201 and references cited therein.

(7)   (a) Tursch, B.; Braekman, J. C.; Daloze, D.; Fritz, P.; Kelecom, A.; Karlsson, R.; Losman, D. *Tetrahedron Lett.* **1974,** 747.   (b) Karlsson, R. *Acta Cryst.* **1976,** *B32,* 2609.   (c) Dartayet, G. H.; Catalán, C. A.; Retamar, J. A.; Gros, E. G. *Phytochemistry* **1984,** *23,* 688. (d) Kashman, Y.; Bodner, M.; Finer-Moore, J. S.; Clardy, J. *Experentia* **1980,** *36,* 891.   (e) Braekman, J. C.; Daloze, D.; Tursch, B.; Hull, S. E.; Declercq, J. P.; Germain, G.; Van Meerssche, M. *Ibid.* **1980,** *36,* 893.   (f) Shirahama, H., et al. *Tetrahedron Lett.* **1980,** 4835. (g) Shirahama, H.; Hayano, K.; Ohtsuka, T.; Osawa, E.; Matsumoto, T. *Chem. Lett.* **1981,** 351.

(8)   Hayasaka, K.; Ohtsuka, T.; Shirahama, H.; Matsumoto, T. *Tetrahedron Lett.* **1985,** 873.

(9)   For an alternative synthesis of dactylol, see Gadwood, R. C. *J. Chem. Soc., Chem. Commun.* **1985,** 123.

(10) Bordwell, F. G.; Wellman, K. M. *J. Org. Chem.* **1963,** *28,* 1347.

(11) Flaugh, M. E.; Crowell, T. A.; Farlow, D. S. *J. Org. Chem.* **1980,** *45,* 5399.

(12) All new compounds exhibited compatible infrared, proton/carbon magnetic resonance, and mass spectroscopic or combustion analysis data. Yields refer to isolated chromatographically homogeneous materials.

(13) Ito, Y.; Fujii, S.; Nakatsuka, M.; Kawamoto, F.; Saegusa, T. *Org. Synth.* **1980,** *59,* 113.

(14) Sawada, S.; Inouye, Y. *Bull. Chem. Soc. Jpn.* **1969,** *42,* 2269.

(15) (a) Crandall, J, K.; Arrington, J. P.; Hen, J. *J. Am. Chem. Soc.* **1967,** *89,* 6208.   (b) Paquette, L. A.; Eizember, R. F. *Ibid.* **1967,** *89,* 6205.   (c) Yanami, T.; Miyashita, M.; Yoshikoshi, A. *J. Chem. Soc., Chem. Commun.* **1979,** 525

(16) Luche, J.-L. *J. Am. Chem. Soc.* **1978,** *100,* 2226.

(17) Korp, J. D.; Bernal, I. private communication.

(18) Hill, R. K. in "Asymmetric Synthesis, Volume 3", Morrison, J. D., Ed., Academic Press, Inc: New York, 1978, Chapter 8.

(19) Ketone **10** materializes as the major product from the RhCl$_3$-promoted isomerization of **10-12** in ethanol at 100°C (sealed tube).

(20) Springer, J. P. private communication.

(21) Fujita, T.; Ohtsuka, T.; Shirahama, H.; Matsumoto, T. *Tetrahedron Lett.* **1982,** 4091.