A SYNTHESIS OF (±)-PHORACANTHOLIDE M

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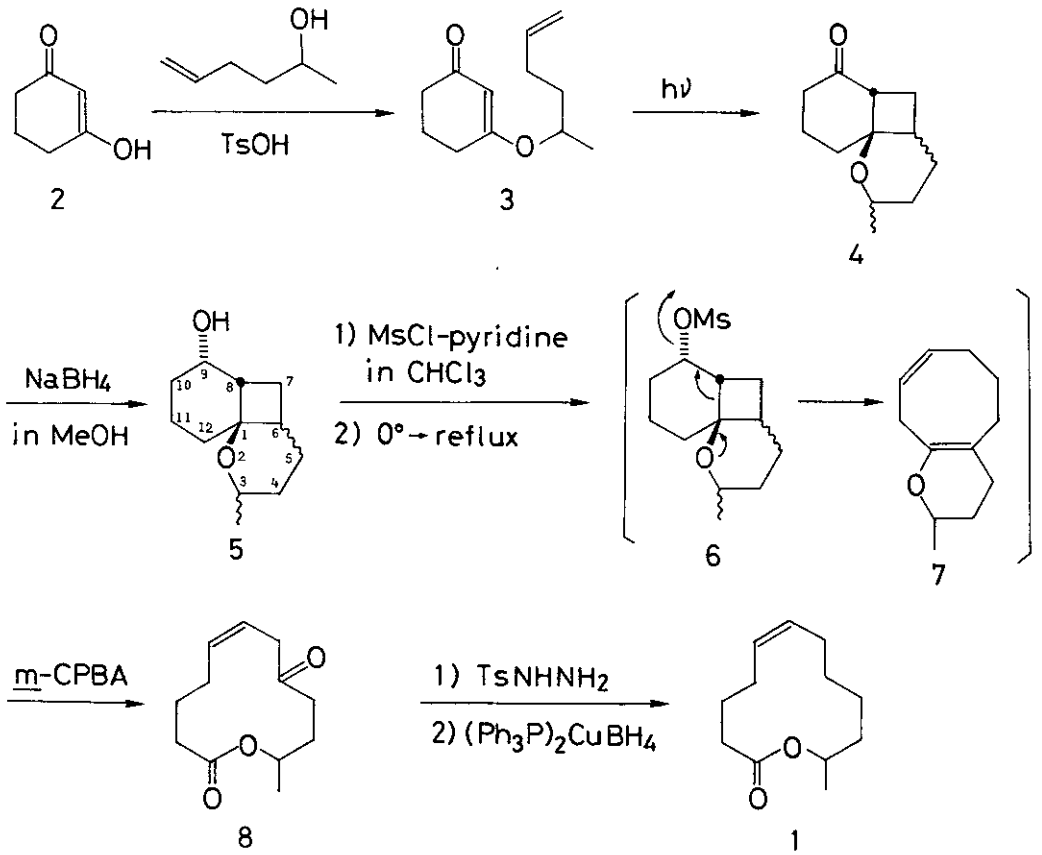
Abstract —— (±)-Phoracantholide M was synthesized by a route involving an intramolecular photo[2+2]cycloaddition of 3-(5-hexenyl-2-oxy)-2-cyclohexen-1-one.

Phoracantholide M (1) is one of the macrolides isolated from Phoracanta synonyma.[1] The first total synthesis has been accomplished by Gerlach et al.[2] We now wish to describe the synthesis of this macrolide by a route involving an intramolecular photo[2+2]cycloaddition of 3-(5-hexenyl-2-oxy)-2-cyclohexen-1-one (3).[3] Starting material (3)[4] was prepared in 70% yield from cyclohexane-1,3-dione (2) and 5-hexen-2-ol by refluxing in benzene in the presence of p-toluenesulfonic acid. Irradiation of (3) in cyclohexane with a 300 W high-pressure mercury lamp through a Pyrex filter under nitrogen atmosphere for a period of 24 h afforded, after column chromatography on alumina, 78% yield of the photo-adduct.[5] The adduct was assigned the structure (4) by analogy with the results of an analogous photo-addition of 3-(4-pentenyloxy)-5,5-dimethyl-2-cyclohexen-1-one.[3] Sodium boro-hydride reduction of (4) in methanol at 0°C afforded the alcohol (5)[6] in 87% yield, which was treated with 1 molar equiv. of methanesulfonyl chloride in chloroform in the presence of 2 molar equiv. of pyridine at 0°C for 15 min and then at reflux for 4 h giving the dihydropyran (7).[7] Due to its lability, (7) was directly oxidized with m-chloroperoxybenzoic acid (m-CPBA)[8] in methylene chloride at 0°C to give the keto-lactone (8),[9] m.p. 85-86°C, in 58% overall yield [from (5)]. The facile fragmentation of the mesylate (6) is presumably attributed to the anti-periplanar arrangement of the C-OMs bond and C_1-C_8 bond.[10,11] In fact analysis of the nmr spectrum of the alcohol (5) using a shift reagent [Eu(fod)$_3$] revealed that the signal of the proton attached to the hydroxyl group appeared as double



triplets with $J_{8,9}=J_{9,10eq}=6$ Hz and $J_{9,10ax}=12$ Hz. An inspection of a molecular model revealed that such coupling pattern would occur only if the C_9-H and the bridgehead proton (C_8-H) were cis to each other and the hydroxyl group equatorial. This stereochemistry is attained by approach of hydride from the less hindered exo-face of the cis-fused bicyclo[4.2.0]octane system in (4) and accounts for the formation of the cis-olefin.[10]

Removal of the ketonic group of (8) was effected by treating (8) with tosylhydrazine in methanol followed by refluxing the tosylhydrazone in chloroform with bis(triphenylphosphine)copper (I) tetrahydroborate.[12,13] The crude product was purified by silica gel column chromatography to give (1) in 30% yield as an oil, which was identical with racemic (1) in both the ir and nmr spectra.[2]

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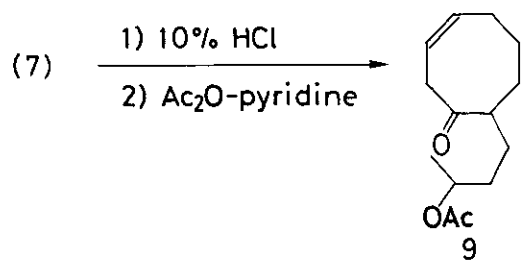
4. Compound (3): a colorless oil, bp 123-125°C (0.1 mmHg); ir ($CHCl_3$) 1635, 1595, cm^{-1}; nmr ($CDCl_3$) δ 1.27 (d, 3H, J=6 Hz), 1.4-2.7 (m, 10H), 4.27 (sextet, 1H, J=6 Hz), 4.8-5.2 (m, 2H), 5.30 (s, 1H), 5.5-6.0 (m, 1H); uv (EtOH) λ_{max} 251 nm (log ε 3.93).
5. Compound (4): a colorless oil; ir ($CHCl_3$) 1690 cm^{-1}; nmr ($CDCl_3$) δ 0.9-2.5 (m, 13H), 1.13 (d, 3H, J=6 Hz), 3.2-3.9 (m, 2H). Glc analysis of the product showed that it consisted of essentially one isomer.
6. Compound (5): low melting crystals; ir (CCl_4) 3620, 3400 cm^{-1}; nmr ($CDCl_3$) δ 1.13 (d, 3H, J=6 Hz), 0.9-2.4 (m, 14H), 3.0-3.35 (m, 1H, H-8), 3.5-4.0 (m, 2H, H-9 and -3).
7. The dihydropyran structure was confirmed by conversion of (7) to 2-(3-acetoxybutyl)-6-cyclooctenone (9). Thus, the crude product (7) was treated with 10% hydrochloric acid at room temperature for 1 h followed by acetylation with acetic anhydride in pyridine at room temperature overnight to give (9) in 69% yield. [Compound (9): a colorless oil; ir (neat) 1720, 1690 cm^{-1}; nmr ($CDCl_3$) δ 1.20 (d, 3H, J=6 Hz), 1.4-1.9 (m, 6H), 2.00 (s, 3H), 2.0-2.7 (m, 7H), 4.7-5.0 (m, 1H, CHOAc), 5.5-5.9 (m, 2H, CH=CH)].



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9. Compound (8), mp 84.5-85.5°C; ir (KCl) 1715 cm^{-1}; nmr ($CDCl_3$) δ 1.22 (d, 3H, J=6 Hz), 1.4-2.65 (m, 10H), 2.91 (dd, 1H, J=5 and 13.5 Hz, H-7), 3.37 (dd, 1H, J=9.5 and 13.5 Hz, H-7), 4.7-5.2 (m, 1H, H-11), 5.2-6.0 (m, 2H, H-5 and -6).

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11. The mesylate of a major alcohol derived from 11,11-dimethyl-2-oxatricyclo-[6.4.0.$0^{1,6}$]dodecan-9-one[3] was found to be stable under the same conditions used for the conversion of (6) to (7). The axial configuration of the mesyloxyl group was assigned on the basis of the nmr spectrum showing that the signal of the proton attached to the mesyloxyl group appeared as a quartet with J=6 Hz.

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13. Use of sodium borohydride (in methanol) or cyanoborohydride (in THF-methanol) instead of this reagent did not give satisfactory results.

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