

SYNTHESES OF MACROCYCLIC TERPENOIDS BY INTRAMOLECULAR CYCLIZATION III.
MODEL REACTIONS FOR THE SYNTHESIS OF CEMBRENE AND THUNBERGOL DERIVATIVES

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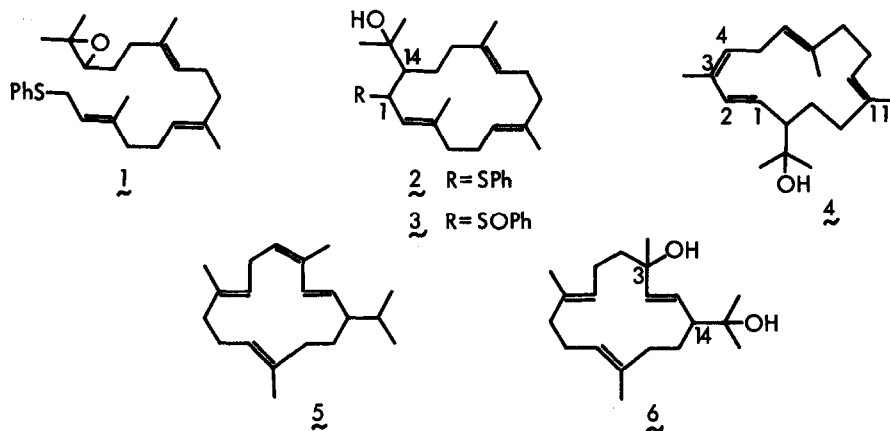
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In the previous paper (1), we have reported an efficient anion-induced intramolecular cyclization of the epoxy sulfide 1 leading to the fourteen-membered ring compound 2. We have extended our study starting from 2 to induce the other functionalities incorporated in the naturally occurring cembrenes. In this paper, we describe the facile formation of the 1,3-diene and 1-ene-3-ol systems via the sulfoxide 3. These reactions, combined with the intramolecular cyclization of the sulfenyl carbanion, constitute a convenient and useful route for the synthesis of cembrene (2), and thunbergol (3) and 4,8,13-duvatriene-1,3-diol (4).

Nephtenylphenyl sulfide 2 (1) was oxidized at 0°C in dilute methanol with 1 molar equivalent of NaO₄. Although the formation of two products were detected by thin-layer chromatography, both of them are rather unstable, and changed to the diene 4, colorless oil, in 70% yield during the isolation process at room temperature. The physical data of 4 are similar to those of cembrene 5 and establish its structure: ms: m/e 288 (M⁺), 59 (base peak), uv (MeOH): 240 (ε 12700), 246 (ε 12900), 256 nm (sh, ε 7800), ir (neat): 3425, 1662, 965 cm⁻¹, nmr (CCl₄): 1.08 (3H, s), 1.09 (3H, s), 1.50 (3H, br.s, C₁₁-Me), 1.59 (3H, br.s, C₇-Me), 1.77 (3H, t, J=1.2, C₃-Me), 3.04 (1H, ddd, J=14, 11, 6, H₅), 4.82 (1H, br.d, J=6, H₁₀), 4.95-5.2 (1H, m, H₆), 5.13 (1H, dd, J=15.4, 9.7, H₁), 5.52 (1H, dd, J=9.0, 6.2, H₄), 6.11 (1H, d, J=15.4, H₂). Two NOEs were observed between C₃-Me and H₄ (10%) and C₃-Me and H₂ (14%) indicating an S-cis conformation of the diene part.

These reactions indicated that the initial product was the mixture of diastereomeric sulfoxides 3, although not isolated, and sulfenic acid was eliminated during the isolation. The direction of deprotonation is highly selective providing a new and useful sequence for the specific synthesis of cembrene 5.



Since the isolation of sulfoxide $\underline{3}$ was unsuccessful, the reaction mixture of the above oxidation was directly treated with trimethylphosphite (0°C , 1 day). After chromatographic separation, the diol $\underline{6}$ was obtained in 92% yield. $\underline{6}$: colorless prisms, m.p. $111-112^{\circ}\text{C}$, ms: m/e 306 (M^+), 94 (base peak), ir (KBr): $3325, 972\text{ cm}^{-1}$, nmr (CCl_4): 1.04 (3H, s), 1.15 (3H, s), 1.28 (3H, s), 1.48 (3H, s), 1.53 (3H, s), 4.85-5.0 (1H, m), 5.05-5.25 (1H, m), 5.11 (1H, dd, $J=15.1, 9.1, \text{H}_1$), 5.71 (1H, d, $J=15.1, \text{H}_2$). The relative configuration of C_3 -hydroxyl and the substituent at C_{14} is assumed to be trans, since the substituents at C_1 and C_{14} in $\underline{2}$ should have trans configuration considering the stereochemistry of the cyclization, $\underline{1}$ to $\underline{2}$ (5) and the [2,3]sigmatropic rearrangement of sulfoxide is known to proceed in the retention of the configuration (6).

Synthesis of natural diterpenes using these reaction sequences is under current investigation.

References and Footnotes

- 1) M. Kodama, Y. Matsuki and S. Itô, Tetrahedron Letters, 3065 (1975).
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- 5) Although the configuration of $\underline{2}$ can not be deduced from the coupling constant, $J_{1,14}=6.5\text{ Hz}$, trans configuration is suggested considering the non-bonded interaction in the transition state of cyclization. Details will be reported in our forthcoming paper.
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