

SYNTHESIS OF MACROCYCLIC TERPENOIDS BY INTRAMOLECULAR CYCLIZATION VIII.

SYNTHESIS OF CEMBRA-3E,7E,11E,15(17)-TETRAEN-trans-16,2-OLIDE

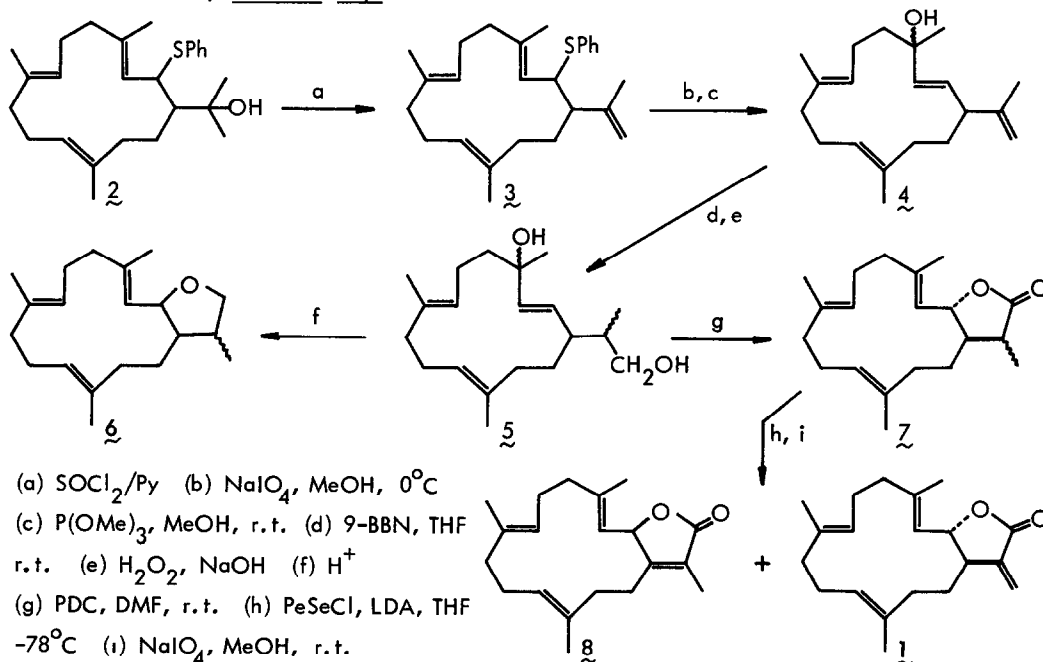
Mitsuaki Kodama, Toshiya Takahashi and Shô Itô

Department of Chemistry, Tohoku University

Sendai 980, Japan

Abstract A synthesis of the naturally-occurring title compound has been accomplished. It represents the first success in the synthesis of the naturally-occurring cembranolides.

Cembrene-based diterpenoids have attracted much attention recently, because they abound in marine invertebrates as well as in insects, both stimulating sources of investigation, and many of them show interesting biological activities¹⁾. However, all the biologically active cembranes from marine sources possess with few exceptions, a lactone—especially an α -methylene lactone—function in the molecule. Although a few efficient methods for the construction of cembrane carbon skeleton have been developed by us²⁾ and other groups³⁾, none of these lactones (cembranolide) has been synthesized. We now wish to report the first successful synthesis of a cembranolide, *i.e.* cembra-3E,7E,11E,15(17)-tetraen-trans-16,2-olide **1**, recently isolated from the soft coral, *Sinularia mayi*⁴⁾.



Nephtenol phenyl sulfide **2**, now available in large quantity by the method developed by us²⁾, was first dehydrated to the tetraene **3**. Periodate oxidation of **3** to the mixture of sulfoxides followed by [2,3]-sigmatropic rearrangement⁵⁾ yielded the allylic alcohol **4**⁶⁾ in 67% overall yield. Hydroboration using 9-BBN took place selectively at isopropenyl group to afford the diol **5**⁶⁾ (diastereomeric mixture) in 81% yield. The diol **5** is sensitive to acid and, when exposed to dilute acids or subjected to Jones' oxidation, gave the ether **6**⁶⁾ in good yield. However, on pyridinium dichromate (PDC) oxidation, **5** afforded the desired lactone **7**^{6,7)} (ca 1:1 mixture of diastereomers) in 37% yield along with the ether **6** (17%). Phenylselenylation of **7** followed by oxidative deselenylation afforded the α -methylene- γ -lactone **1**, m.p. 53-54.5°C⁸⁾, and its isomer **8**⁶⁾ in 60% and 12% yields, respectively. Identity of thus obtained **1** with natural product⁴⁾ was confirmed by the comparison of their PMR and CMR spectra.

The authors thank Dr. M. Nakayama, Hiroshima University, for the spectra of natural **1**.

References and Notes

- 1) W. Fenical in "Marine Natural Products", ed. by P.J. Scheuer, Academic Press, New York (1978), Vol.2, Chapter 3, B. Tursch, J.C. Braekman, D. Dalozze and M. Katsin, *ibid.*, Vol.2, Chapter 4.
- 2) M. Kodama, Y. Matsuki and S. Itô, *Tetrahedron Letters*, 3065 (1975)
- 3) W.G. Dauben, G.H. Beasley, M.D. Broadhurst, B. Muller, D.J. Peppard, P. Pesnelle and C. Suter, *J. Am. Chem. Soc.*, **97**, 4973 (1975), T. Kato, T. Kobayashi and Y. Kitahara, *Tetrahedron Letters*, 3299 (1975), H. Takayanagi, T. Uyehara and T. Kato, *J. Chem. Soc., Chem. Comm.*, 359 (1978), K. Toma, E. Miyazaki, T. Murae and T. Takahashi, *Chemistry Letters*, 863 (1982).
- 4) Y. Uchio, S. Eguchi, M. Nakayama and T. Hase, *Chemistry Letters*, 277 (1982).
- 5) D.A. Evans and C.C. Andrews, *Acc. Chem. Res.*, **7**, 147 (1974).
- 6) Spectral data of selected key compounds **4** m/e 288 (M^+), 79 (b.p.), ν (oil) 3425, 1640, 890 cm^{-1} , δ ($CDCl_3$) 1.34 (3H, s), 1.56 (3H, br.s), 1.62 (3H, br.s), 1.69 (3H, br.s), 4.66 (2H, br.s), 4.9-5.3 (2H, m), 5.31 (1H, dd, $J=15.6, 7.8$), 5.75 (1H, d, $J=15.6$). **5** m/e 306 (M^+), 288 (b.p.), ν (oil) 3370 cm^{-1} , δ ($CDCl_3$) 0.79 and 0.93 (3H, d, $J=7.5$), 1.34 (3H, s), 1.54 (3H, br.s), 1.62 (3H, br.s), 3.3-3.6 (2H, m), 4.9-5.3 (2H, m), 5.23 (1H, dd, $J=15.2, 9$), 5.73 (1H, d, $J=15.2$). **6** m/e 288 (M^+ , b.p.), δ ($CDCl_3$) 0.95 and 1.05 (3H, d, $J=7$, ca 1:1), 1.59 (6H, br.s), 1.68 (3H, br.s), 3.40 (0.5H, dd, $J=9, 6$), 3.43 (0.5H, dd, $J=8, 4.5$), 3.83 (0.5H, dd, $J=9, 7$), 3.95 (0.5H, dd, $J=8, 6$), 4.25 (1H, dd, $J=9, 7.5$), 4.8-5.2 (3H, m). **7** m/e 302 (M^+ , b.p.), ν (oil) 1766 cm^{-1} , δ ($CDCl_3$) 1.17 and 1.30 (3H, d, $J=7$, ca 1:1), 1.58 (6H, br.s), 1.72 (3H, m), 4.62 (0.5H, dd, $J=9, 7.5$), 4.79 (0.5H, dd, $J=9.7, 5.5$), 4.8-5.2 (2H, m), 5.13 (1H, br.d, $J=9$). **8** m/e 330 (M^+), 173 (b.p.), ν (oil) 1755 cm^{-1} , δ ($CDCl_3$) 1.60 (3H, br.s), 1.63 (3H, br.s), 1.79 (3H, br.s), 1.83 (3H, br.s), 4.83 (1H, br.d, $J=9.5$), 4.8-5.2 (2H, m), 5.47 (1H, br.d, $J=9.5$).
- 7) An isomer of **7** showed H_2 signal with $J_{1,2}=7.5$ Hz in the PMR spectrum, implying it to be a cis-fused lactone. However, since PDC oxidation of **7** yielded no detectable amount of cis lactone, **7** must have been an epimeric mixture on the methyl group. Thus, the lactonization must have proceeded stereoselectively.
- 8) Natural compound is reported as an oil in ref. 4.