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SYNTHESIS OF MACROCYCLIC TERPENOIDS BY INTRAMOLECULAR CYCLIZATION VI.

SYNTHESIS OF 3Z-CEMBRENE A AND CEMBRENENE

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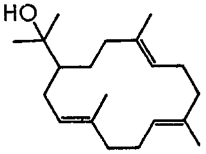
Abstract. Two 14-membered diterpenes, 3Z-cembrene A and cembrenene, isolated from a termite and a soft coral, respectively, were synthesized by the anion-induced cyclization of geranylgeranyl phenyl sulfide.

We describe herein the synthesis of two natural cembrenoids by the application of anion-induced cyclization of the acyclic precursor, the method we have developed previously for the synthesis of nephthenol (1), cembrene A (2)1) and hedycaryol2). The synthetic objects are 3Z-cembrene A (3) isolated by Meinwald et al. together with 2 from the frontal grand of the termite soldier, Cubitermes umbraus3), and cembrenene (4) found by Hayashi, et al. from the soft coral, Sinularia mayi4).



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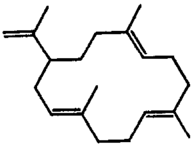

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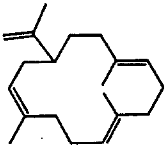

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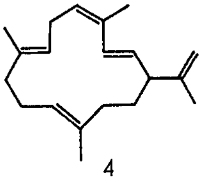

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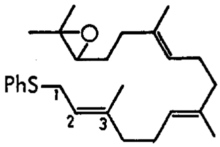
We started the re-examination of the anion-induced cyclization of 14,15-oxidogeranylgeranyl phenyl sulfide (5)1) since the geometrical isomerization of the 2E-double bond observed in the similar cyclization of oxidofarnesyl phenyl sulfide2) was not noted in this case. The thin-layer chromatography of the crude reaction product exhibited the presence of a small spot partly overlapped with the major one of the nephthenyl phenyl sulfide (6)1). The minor product was separated by repeated column chromatography using alumina to give besides 6 (62%) its isomer 7 (ca. 5%)5). 3Z-Geometry in 7 was secured by the observation of NOE (11%) between C_4-methyl (δ 1.58 ppm) and H_3 (δ 5.47 ppm). Desulfurization of 7 with Na t-BuOH THF at room temperature yielded 3Z-nephthenol (8)5) in 53% yield together with 1 (12%). The alcohol 8 was also obtained in 13% yield on desulfurization of 6 with Li/$EtNH_2$/EtOH6) in addition to the products reported previously1). Dehydration of 8 by $SOCl_2$ occurred very selectively to give a tetraene 35) (93% yield) whose PMR and CMR spectra are identical with those of natural 3Z-cembrene A.

For the synthesis of cembrenene (4), dehydration of the tetraenol 97) was attempted first, using $SOCl_2$ or $POCl_3$, only to yield a complex inseparable mixture in which the pentaene 10 is predominant. However, dehydration with $SOCl_2$ of the triene-diol 11, prepared from 6 by the way of [2,3]sigmatropic



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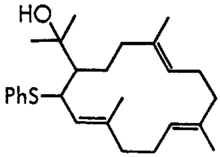

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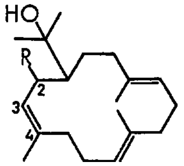
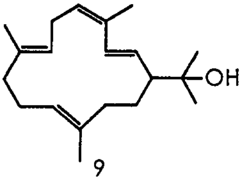


7: R=SPh

8: R=H

rearrangement of the corresponding sulfoxide$^{7)}$, afforded a mixture of hydrocarbons from which the pentaene 4$^{5)}$ was separated in 42% yield by chromatography using $AgNO_3$-impregnated SiO_2. Its IR and PMR spectra are identical with those of authentic cembrenene.



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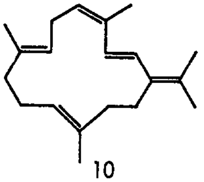

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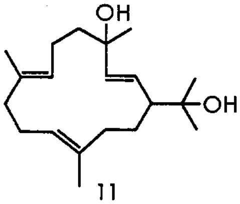

11

We thank Mr. I. Miura, Otsuka Pharmaceutical Co., Ltd., for the spectral identification of 3Z-cembrene A, and Dr. Y. Uchio, Hiroshima University, for the spectra of authentic cembrenene.

References and Notes

1) M. Kodama, Y. Matsuki and S. Itô, Tetrahedron Letters, 3065 (1975).

2) Idem, ibid., 1121 (1976).

3) D.F. Wiemer, J. Meinwald, G.D. Prestwich and I. Miura, J. Org. Chem., **44**, 3950 (1979).

4) Y. Uchio, H. Nabeya, M. Nakayama, S. Hayashi and T. Hase, Tetrahedron Letters, **22**, 1689 (1981).

5) 7; colorless oil, m/e 398 (M^+), 59 (b.p.), ν 3460 cm^{-1}, δ (CCl_4) 1.22 (3H, s), 1.34 (3H, s), 1.54 (3H, br.s), 1.58 (3H, br.s), 1.59 (3H, br.s), 4.45 (1H, d, J=10), 4.65-5.20 (2H, m), 5.47 (1H, d, J=10), 7.0-7.4 (5H, m). 8; colorless oil, m/e 290 (M^+), 59 (b.p.), ν 3450 cm^{-1}, δ (CCl_4) 1.11 (3H, s), 1.14 (3H, s), 1.52 (3H, d, J=1.5), 1.62 (3H, br.s), 4.70-5.10 (2H, m), 5.35 (1H, t, J=7.5). 3; m/e 272 (M^+), 68 (b.p.), ν 2920, 1640, 885 cm^{-1}, δ (CCl_4) 1.53 (3H, br.s), 1.64 (6H, br.s), 1.67 (3H, br.s), 4.64 (1H, m), 4.74 (1H, m), 5.03 (1H, m), 5.07 (1H, t, J=8), 5.28 (1H, t, J=7), CMR δ 15.5 (q), 15.7 (q), 18.7 (q), 22.4 (q), 24.7 (tx2), 29.8 (t), 30.8 (t), 31.1 (t), 36.0 (t), 40.2 (t), 45.5 (d), 111.0 (t), 125.0 (d), 125.1 (d), 125.3 (d), 133.1 (s), 133.2 (s), 134.4 (s), 148.7 (s). These PMR and CMR data are identical with those of authentic spectra supplied by Mr. I. Miura. The reported data$^{3)}$ seems to contain some errors. 4; m/e 270 (M^+), 133 (b.p.), ν (CCl_4) 3075, 1670, 1635, 965, 890 cm^{-1}, δ ($CDCl_3$) 1.53 (3H, br.s), 1.61 (3H, br.s), 1.72 (3H, br.s), 1.80 (3H, br.s), 4.70 (2H, br.s), 4.80-5.25 (2H, m), 5.24 (1H, dd, J=16, 9), 5.56 (1H, br.t, J=8), 6.18 (1H, d, J=16).

6) Similar isomerization has been observed by us in sesquiterpene series. See, M. Kodama, S. Yokoo, H. Yamada and S. Itô, Tetrahedron Letters, 3121 (1978).

7) M. Kodama, K. Shimada and S. Itô, Tetrahedron Letters, 2763 (1977).

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