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SYNTHESES OF MACROCYCLIC TERPENOIDS BY INTRAMOLECULAR CYCLIZATION I. (±)-CEMBRENE-A, A TERMITE TRAIL PHEROMONE, AND (±)-NEPHTHENOL

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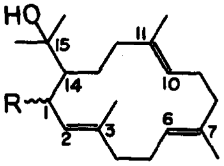
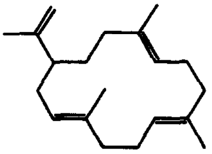
The most fundamental and important biogenetic pathway in sesquiterpenoids is the cyclization of acyclic carbonium ions (for example, the farnesyl cation) to form the monocyclic ions with 10- or 11-membered rings, which in turn undergo further transformation to polycyclic carbonium ions (1). This is clearly exemplified by the occurrence in nature of germacranes, humulanes and a vast variety of compounds which have biogenetically related carbon skeletons. Likewise in diterpenoids, the cyclization of the geranylgeranyl cation to the ion with 14-membered ring (cembrene cation) is one of the basic natural pathways, although this process is less predominant in diterpenoids than the one noted above in sesquiterpenoids.

Although some of such monocyclic terpenes have been synthesized, these syntheses usually employ either condensation of appropriate building blocks (2) or ring opening or [3,3]sigmatropic reactions of suitable cyclic precursors (3). It is thus evident that none of the approaches have followed the biogenetic pathway. In order to effect the biogenetic type synthesis of these macrocyclic terpenes, we have investigated the anion-induced cyclization of suitably functionalized acyclic terpenoids, since the cation-induced cyclization would unlike in nature be difficult to achieve with high selectivity (4). We have subsequently found that the reaction proceeded quite satisfactorily, offering a new, simple and specific method of synthesizing macrocyclic terpenoids. In this communication we report the successful application of the method to the synthesis of 14-membered ring diterpenes, nephthenol 1 (5) and cembrene-A 2 (6,7), the latter of which is known to be a trail-making pheromone of termites. Further-



1 : R=H

6 : R=SPh



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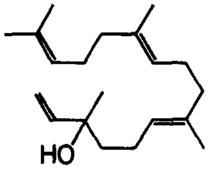

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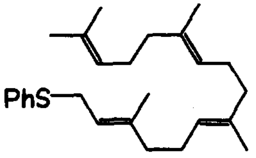

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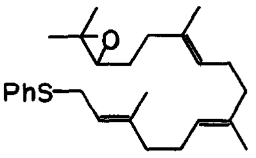

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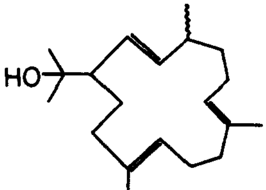

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more, our unequivocal synthesis established the all trans stereochemistry of the double bonds of these diterpenes.

trans, trans-Geranyllinalool **3** was converted (i, PBr_3: ii, PhS^-Na^+) to all trans-geranylgeranyl phenyl thioether **4** in 73% yield [oil: nmr ($CDCl_3$) 1.61 (4 Me, br.s), 1.68 (1 Me, br.s), 3.53 (2H, d, J=7.5), 4.9-5.2 (3H, m), 5.32 (1H, br.t, J=7.5), 7.1-7.4 (5H, m)]. Terminal epoxidation was performed by van Tamelen's method (8) (i, NBS in aqueous THF: ii, K_2CO_3 in absolute methanol) to give **5** (42%) [oil: nmr ($CDCl_3$) 1.26 (1 Me, s), 1.30 (1Me, s), 1.62 (4 Me, br.s), 2.68 (1H, t, J=6.0), 3.54 (2H, d, J=8.0), 5.0-5.3 (2H, m), 5.33 (1H, br.t, J=8), 7.1-7.4 (5H, m)].

The crucial step, the intramolecular cyclization, took place smoothly when the epoxide **5** was treated in large volume of dry THF with slight excess of n-butyl lithium at -78° in the presence of 1,4-diazabicyclo[2.2.2]octane under nitrogen (9,10) and, after alumina chromatography, monocyclic alcohol **6** was obtained in 62% yield (11) [oil: ms, m/e 398 (M^+), 59 (base peak): ir (neat) 3450, 1585 cm^{-1}: nmr ($CDCl_3$) 1.03 (1 Me, d, J=1.1, C_3-Me), 1.27 (2 Me, d, C_{15}=Me_2), 1.49 (2 Me, br.s, C_7-Me, C_{11}-Me), 3.86 (1H, dd, J=11, 6.5, H_1), 4.6-5.0 (2H, m, H_6, H_{10}), 5.09 (1H, br.d, J=11, H_2), 7.0-7.4 (5H, m, Ph)] (12).

Trans disposition of the C_2-C_3 double bond was established by the presence of nOe (12%) between C_1-H and C_3-methyl, and its absence between C_2-H and the methyl group. Desulfurization of **6** with lithium-ethylamine at -78° followed by a preparative tlc using silver nitrate-impregnated silica-gel afforded the alcohol **1** (30% yield) and **7** (20% yield). The mass, ir and nmr spectra of the former compound were practically identical with those of nephthenol (13) isolated from a soft coral (5), while those of the latter compound [ms, m/e 290 (M^+), 59 (base peak): ir (neat) 3430 cm^{-1}: nmr (CCl_4) 1.04 (3H, s), 1.05 (3H, d, J= 7), 1.08 (3H, s), 1.53 (3H, s), 1.59 (3H, s), 4.95 (1H, ddd, J=15.5, 9.0, 1.5), 4.8-5.5 (2H, m), 5.82 (1H, dd, J=15.5, 4.0)] suggest the structure **7** with the migrated double bond.

Furthermore, **1** was dehydrated with thionyl chloride in pyridine to give the tetraene **2** as a sole product in more than 95% yield. The synthetic **2** was identical in all respects except optical rotation with cembrene-A isolated by Birch from *Nasutitermes exitiosus* (Hill) (6) and by Dev from *Commiphora mukul* (Hook et Stocks) Engl. (7).

The configuration of the double bonds in these two natural products has not been elucidated. In light of our syntheses, starting from geranyllinalool of known configuration, and the nOe evidence on **6** all the trisubstituted double bonds in each compound are established to be in trans disposition.

Thus, anion-induced cyclization was proved to be an excellent method for the synthesis of macrocyclic terpenes. Application of the method to the synthesis of related systems is in progress.

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10) As far as we are aware, this is the first example of intramolecular reaction of the anion of allyl thioether. Intermolecular reaction of such an anion with epoxide has been used for the synthesis of Cecropia juvenile hormone [K. Kondo, A. Negishi, K. Matsui, D. Tunetomo and S. Masamune, J. Chem. Soc., Chem. Commun., 1311 (1972); P.L. Stotter and R.E. Hornish, J. Am. Chem. Soc., 95, 4444 (1973)].

11) The alcohol 6 shows no indication (tlc, nmr) for the presence of its epimer. The reaction mixture indicates no sign of the starting material 5 but the presence of more polar substances which have not been investigated further.

12) Assignment was established by nmdr. Irradiation at 5.09 ppm (H_2) collapsed the doublet at 1.03 ppm (C_3-Me) to a singlet and the double doublet at 3.86 ppm (H_1) to a doublet (J=6.5). Abnormal shielding of C_3-methyl is attributed to the anisotropic effect of phenyl group closely situated.

13) The spectra of natural nephthenol kindly supplied by Professor Schmitz indicates that it still contains a small amount of ketonic material. It is clear, however, that the synthetic nephthenol is identical with the major constituent of the substance from the natural source.