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SYNTHESIS OF MACROCYCLIC TERPENOIDS BY INTRAMOLECULAR CYCLIZATION VII. TOTAL SYNTHESIS OF (±)-CUBITENE

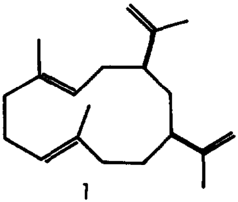
Mitsuaki Kodama, Toshiya Takahashi, Tsutomu Kojima and Shô Itô

Department of Chemistry, Tohoku University

Sendai 980, Japan

Abstract Stereoselective total synthesis of (±)-cubitene, a diterpene isolated from termite soldiers, and its stereoisomer has been achieved utilizing the anion-induced intramolecular cyclization.

Frontal gland secretions of termite soldiers are known to play an important role in the defence against potential predators. Cubitene (**1**) is a novel diterpene isolated as one of the major components of the defensive secretion of East African termites, *Cubitermes umbratus*, and was shown to possess the irregular isoprenoid structure with cis-oriented isopropenyl groups on a twelve-membered ring[1]. In addition to our recent synthesis of 3Z-cembrene A (**2**)[2], another component of the defensive secretion, we achieved the stereoselective synthesis[3] of ±**1** and its stereoisomer, trans-cubitene, applying the anion-induced intramolecular cyclization reaction developed by us for the synthesis of macrocyclic terpenoids[4].



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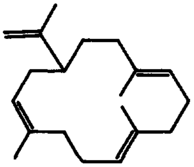

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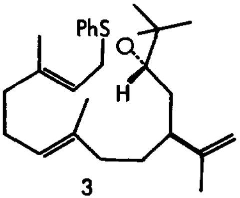

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The epoxy phenylthio ether **3**, the key intermediate for our synthetic strategy, was constructed in a stereo-controlled fashion as shown in Chart 1. 10,11-Oxido-E,E-farnesyl phenyl sulfide **4**[4b] was converted in two steps to the aldehyde **5** [ν 1710 cm^{-1}, δ 9.58 (1H, t-like)][5] in 84% overall yield. Wittig reaction of **5** in benzene at room temperature afforded the unsaturated ester **6** [ν 1705 cm^{-1}, δ 1.80 (3H, br.s), 6.59 (1H, br.t, J=6.7)] (97%) which was reduced to the allylic alcohol **7** [δ 3.87 (2H, br.s)] in 85% yield. Reaction of **7** with the chloroacetal[6] **8** in the presence of a catalytic amount of 2,4-dinitrophenol at 140°C yielded the chloroketone **9**, the Claisen rearrangement product, in 61% yield.[7] DIBAL reduction of **9** at -78°C produced a mixture of chlorohydrins **10** and **11** quantitatively their ratio being ca. 10 : 1[8]. These chlorohydrins were easily separated by flash column chromatography (n-hexane-ether, 15 : 1). Although the relative stereochemistry of **10** and **11** was not determined at this stage, the major product **10** was found to have the desired stereochemistry (*vide infra*). Each chlorohydrin was converted to the corresponding epoxides 3 (99%) and 12 (99%) by conventional base treatment. Thus, desired epoxide 3 was synthesized in highly stereoselective manner.

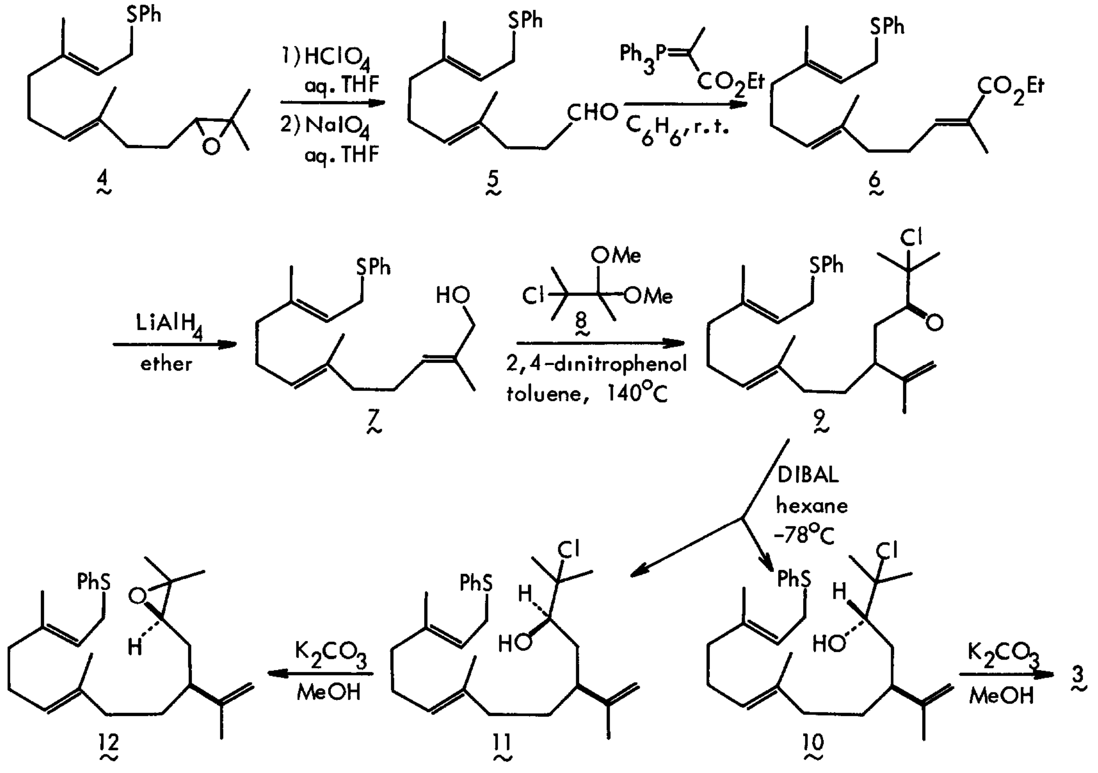

Chart 1

When the epoxide 3 in dry THF was treated with n-BuLi in the presence of 1,4-diazabicyclo[2.2.2]-octane initially at -78°C (70 min.), then at 0°C (overnight), two cyclization products 13a and 13b[9)] (ratio=ca. 2:3) were formed in 73% yield as shown in chart 2. In contrast, cyclization of the epoxide 12 under the same condition yielded essentially the single product 14[7)], m.p. 89-91°C, in almost the same yield. Although stereochemical relationship of 13a and 13b is not clear, desulfurization of the mixture afforded a single alcohol 15 (93%) indicating that these are epimeric regarding phenylthio group. The fact that CMR spectrum of 15 showed methyl signals at 14.69 and 15.01 ppm[10)] revealed that both double bonds in the ring remain E-configuration and therefore no isomerization of C_2-C_3 double bond occurred during the cyclization and desulfurization steps. Dehydration of 15 with $SOCl_2$ in pyridine afforded the tetraene 1 (61% yield after purification by $AgNO_3$-impregnated silica-gel chromatography), which showed superimposable PMR and CMR spectra with those of natural cubitene[1,11)]. Using the same sequence of reactions, another cyclization product 14 was converted to the tetraene 17, trans-cubitene, via the alcohol 16 in 66% overall yield. E-configuration of C_2-C_3 double bond in these products was evidenced again by the chemical shifts of methyl groups in CMR spectra.

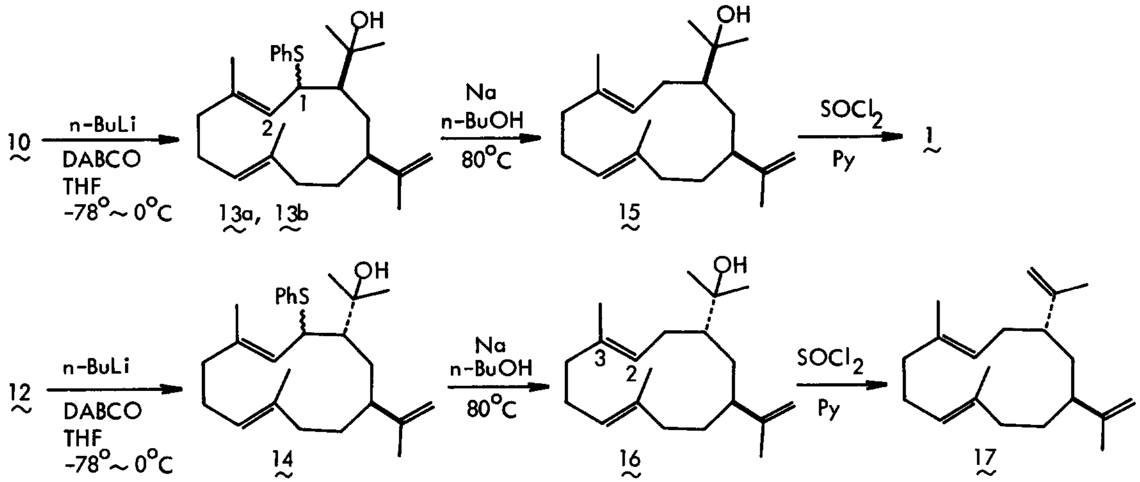

Chart 2

Acknowledgement We are deeply indebted to Professor G. D Prestwich, State University of New York, for the spectra of cubitene and Dr. H Tsuruta, Takasago Perfumery Co., Ltd., for generous gift of nerolidol.

References and Notes

1) G.D Prestwich, D.F. Wiemer, J. Meinwald and J. Clardy, J Am. Chem. Soc., **100**, 2560 (1978).

2) K. Shimada, M. Kodama and S. Itô, Tetrahedron Letters, **22**, 4275 (1981)

3) For non-stereoselective synthesis of cubitene, see O.P. Vig, S.S. Bari, I.R. Trehan and R. Vig, Indian J. Chem., **19B**, 446 (1980).

4) a) M. Kodama, Y. Matsuki and S. Itô, Tetrahedron Letters, 3065 (1975), b) Idem, ibid., 1121 (1976), c) M. Kodama, S. Yokoo, H. Yamada and S. Itô, ibid , 312 (1978).

5) IR spectra were measured in neat liquid. PMR and CMR spectra were taken in CCl_4 and $CDCl_3$ solutions, respectively, unless otherwise stated.

6) L. Werthemann and W S Johnson, Proc. National Acad. Sci , **67**, 1468, 1810 (1970).

7) Spectral data of selected key compounds are listed. 9 m/e 434, 432 (M^+), 135 (b.p.), ν 1718, 892 cm^{-1}, δ 1.59 (6H, br.s), 1.62 (6H, br.s), 1.68 (3H, br.s), 3.46 (2H, d, J=7.5), 4.70 (2H, br.s), 5.02 (1H, m), 5.27 (1H, br.t, J=7.5), 7.0-7.3 (5H, m). 10 m/e 436, 434 (M^+), 135 (b.p.), ν 3550, 890 cm^{-1}, δ 1.51 (6H, s), 1.58 (6H, br s), 1.68 (3H, br s), 3.35-3.55 (1H, m), 3.46 (2H, d, J=7.5), 4.73 (2H, br s), 5.02 (1H, m), 5.25 (1H, br t, J=7.5), 7.0-7.3 (5H, m). 11 m/e 436, 434 (M^+), 95 (b.p.), ν 3470, 890 cm^{-1}, δ 1.51 (3H, s), 1.52 (3H, s), 1.58 (9H, br.s), ca. 3.35 (1H,dd, J=10, 2.5), 3.46 (2H, d, J=7.5), 4.66-4.83 (2H, m), 5.02 (1H, br.m), 5.26 (1H, br.t, J=7.5), 7.0-7.3 (5H, m). 3 m/e 398 (M^+), 135 (b.p.), ν 1641, 890 cm^{-1}, δ 1.20 (3H, s), 1.22 (3H, s), 1.58 (6H, br.s), 1.66 (3H, br.s), 2.49 (1H, t, J=6.0), 3.45 (2H, d, J=7.5), 4.69 (2H, br.s), 5.00 (1H, m), 5.24 (1H, t, J=7.5), 7.0-7.3 (5H, m). 12 m/e 398 (M^+), 71 (b.p.), ν 1640, 890 cm^{-1}, δ 1.18 (3H, s), 1.22 (3H, s), 1.59 (6H, br s), 1.64 (3H, br.s), 2.46 (1H, dd, J=7.5, 4.5), 3.47 (2H, d, J=7.5),

4.74 (2H, br.s), 5.02 (1H, m), 5.25 (1H, br.t, J=7.5), 7.0-7.3 (5H, m). **14**: m/e 398 (M^+), 231 (b.p.), ν 3490, 1640, 895 cm^{-1}, δ 1.21 (3H, s), 1.33 (3H, s), 1.54 (3H, br.s), 1.57 (3H, br.s), 1.76 (3H, br.s), 4.31 (1H, br.d, J=9.5), 4.71 (2H, br.s), 4.8-5.0 (1H, m), 5.47 (1H, br.d, J=9.5), 7.0-7.3 (5H, m), CMR; δ 15.21 (q), 16.25 (q), 19.32 (q), 26.18 (t), 26.37 (t), 28.40 (q), 29.57 (q), 31.53 (t), 36.88 (t), 39.69 (t), 41.32 (d), 49.09 (d), 51.37 (d), 73.70 (s), 110.51 (t), 126.25 (d), 126.57 (d), 128.73 (dx2), 129.83 (dx2), 132.45 (d), 132.64 (s), 134.27 (s), 135.97 (s), 148.90 (s). **15** m/e 290 (M^+), 272 (b.p.), ν 3380, 1639, 885 cm^{-1}, δ 1.14 (3H, s), 1.18 (3H, s), 1.54 (6H, br.s), 1.62 (3H, br.s), 4.63 (2H, br.s), 4.69 (2H, br.s), 4.86 (1H, m), 5.08 (1H, br.t, J=7.5), CMR; 14.69 (q), 15.01 (q), 17.89 (q), 25.07 (t), 27.55 (q), 28.00 (t), 28.13 (q), 31.27 (t), 31.46 (t), 36.62 (t), 40.21 (t), 41.45 (d), 45.43 (d), 73.63 (s), 112.15 (t), 125.46 (d), 127.09 (d), 132.77 (s), 133.69 (s), 148.63 (s). **16** m/e 290 (M^+), 272 (b.p.), ν 3400, 1640, 880 cm^{-1}, δ 1.22 (6H, s), 1.58 (6H, br.s), 1.67 (3H, br.s), 4.66 (2H, br.s), 4.83 (1H, br.dd, J=6, 7.5), 5.22 (1H, br.t, J=7.5), CMR; δ 15.14 (q), 17.04 (q), 19.13 (q), 25.65 (t), 26.63 (q), 27.02 (q), 27.55 (t), 30.81 (t), 36.16 (t), 37.99 (t), 39.30 (t), 40.28 (d), 48.76 (d), 73.57 (s), 110.25 (t), 125.85 (d), 127.61 (d), 133.23 (s), 134.53 (s), 149.81 (s). **17**: m/e 272 (M^+), 244 (b.p.), ν 1640, 880 cm^{-1}, δ ($CDCl_3$) 1.61 (9H, br.s), 1.70 (3H, br.s), 4.61 (2H, br.s), 4.66 (2H, br.s), 4.90 (1H, br dd, J=6, 7.5), 5.27 (1H, br.t, J=7.5), CMR, δ 15.14 (q), 16.58 (q), 19.00 (q), 20.50 (q), 25.72 (t), 28.26 (t), 34.53 (t), 36.49 (t), 39.49 (t), 40.60 (t and d), 44.98 (d), 108.03 (t), 110.19 (t), 126.12 (d), 127.03 (d), 133.75 (s), 134.40 (s), 149.75 (s), 151.90 (s).

8) The ratio was determined by HPLC analysis (Micropack SI-5, n-hexane-ether, 97:3), using the UV intensity at 260 nm. $NaBH_4$ reduction in MeOH gave the same products quantitatively, but the ratio varied from 2:1 (at 0°C) to 5:1 (at -50°C). These results are rather unexpected in view of the poor 1,3-asymmetric induction in LAH reduction (J.D. Morrison and H.S. Mosher, Asymmetric Organic Reactions, Prentice-Hall, New Jersey, 1971, p. 108).

9) PMR spectrum of the mixture showed two sets of a doublet of doublets and a doublet due to H_1 and H_2 [**12a** 3.93 (dd, J=11.3, 6.0), 5.19 (d, J=11.3), **12b** 4.04 (dd, J=10.5, 4.5), 5.35 (d, J=10.5)] together with complicated methyl and olefinic proton signals.

10) J.B. Stothers, Carbon-13 NMR Spectroscopy, Academic Press, New York, 1972; p. 433.

11) Although natural cubitene has m.p. 33.5-34°C[1)], synthetic ±**1** remains viscous liquid (a racemic mixture) despite of various effort.

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