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SYNTHESIS OF MACROCYCLIC TERPENOIDS BY INTRAMOLECULAR CYCLIZATION IV[1].

SYNTHESIS OF 6Z-HEDYCARYOLS

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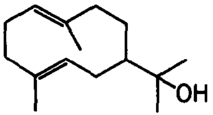
Recently, we have reported the successful synthesis of natural hedycaryol 1 (2E,6E-isomer) and 2Z,6E-hedycaryol 2[2] as well as nephthenol and cembrene-A[3], utilizing the anion-induced cyclization of the epoxy phenyl sulfides of corresponding acyclic precursors, and demonstrated the reaction sequence be a convenient and efficient general route to macrocyclic terpenes. Because of recent mechanistic interest on the reactions of cyclodecadienes, in particular germacradienes[4], we have synthesized two remaining (2E,6Z- and 2Z,6Z-) isomers, 3 and 4, of hedycaryol, by the same reaction sequence. We have also found some abnormal behavior of the synthetic intermediates, revealing the strain in the ring system.



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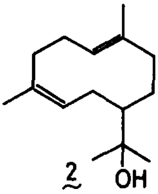

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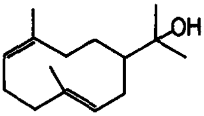

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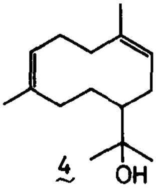

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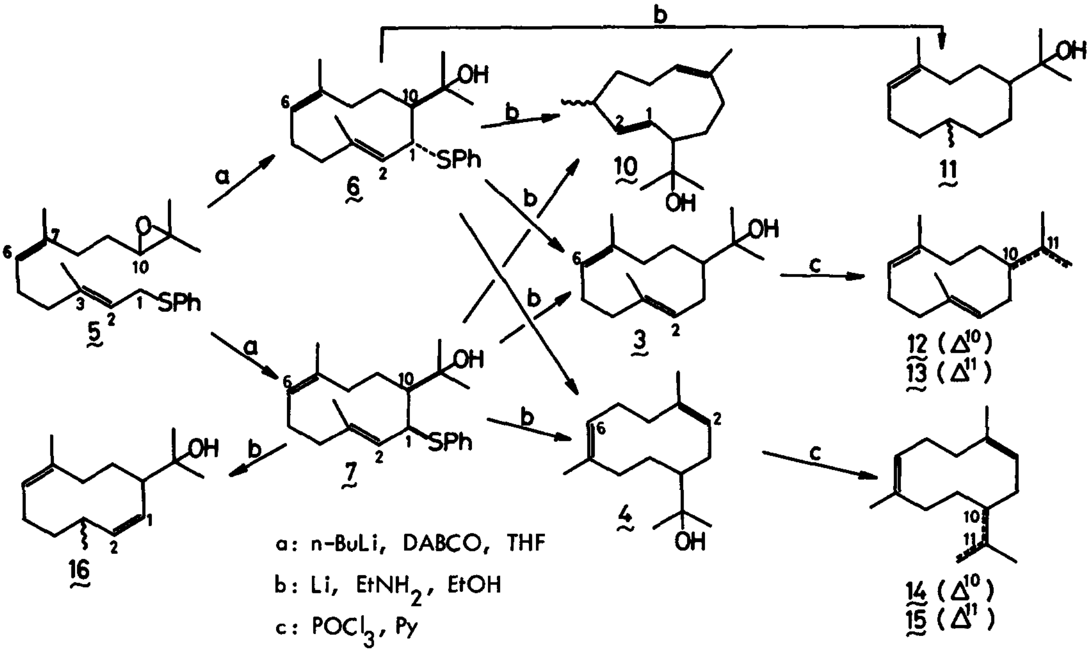
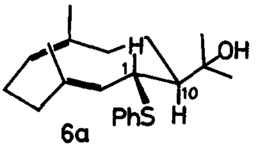
2E,6Z-Farnesyl phenyl sulfide[5], prepared in 70% yield by known procedure[3] from 6Z-nerolidol[6], was converted to the epoxy phenyl sulfide 5 in 39% yield by the successive treatment with NBS and anhydrous Na_2CO_3. The 2E,6Z-geometry of 5 was confirmed by the presence of NOE between C_7-Me (δ 1.67) and H_6 (δ 5.05) (20%), and C_3-Me (δ 1.55) and H_1 (δ 3.45) (9%).

When the epoxy phenyl sulfide 5 was treated at -78° with n-BuLi in anhydrous tetrahydrofuran in the presence of diazabicyclooctane, the instant formation of the corresponding anion was observed. Gradual warming of the reaction mixture to room temperature induced slow cyclization[7], and, after alumina chromatography, two monocyclic products 6 and 7 were obtained in 35% and 15% yield, respectively. [6: colorless

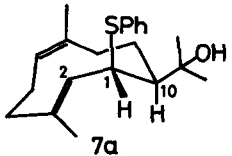


a: n-BuLi, DABCO, THF
b: Li, $EtNH_2$, EtOH
c: $POCl_3$, Py

oil, m/e 330 (M^+), 81 (base peak), 59 (95%); ν 3450 cm^{-1}; δ 1.26 (6H, s), 1.36 (3H, d, J=1.5, C_3-Me), 1.57 (3H, br.s, C_7-Me), 3.73 (1H, dd, J=11, 10, H_1), 5.00 (1H, br.t, J=8, H_6), 5.26 (1H, ddd, J=11, 1.5, 1.5, H_2), 7.1-7.5 (5H, m), 7: colorless oil, m/e 330 (M^+), 59 (base peak); ν 3460 cm^{-1}; δ 1.30 (3H, s), 1.39 (3H, s), 1.58 (3H, br.s), 1.66 (3H, br.s), 4.40 (1H, d, J=8, H_1), 5.0-5.2 (1H, m, H_6), 5.52 (1H, br.d, J=8, H_3), 7.0-7.3 (5H, m)]. However, unlike in the previous cases2,3), they are not the geometrical isomers but diastereomers, both having 2E,6Z-germacradiene skeleton, as was verified by the NOE measurement [6: C_7-Me→ H_6 (25%), C_3-Me→ H_1 (9%); 7: C_7-Me, C_3-Me→ H_6 (16%), H_1 (12%), H_2 (0%)]. Using the NOE data, and coupling constants, $J_{1,2}$ (11 Hz and 8 Hz, respectively) and $J_{1,10}$ (10 Hz and 0 Hz, respectively), the conformations 6a and 7a can be deduced for these compounds.



6a



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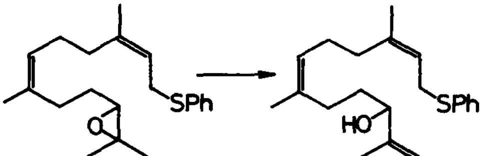

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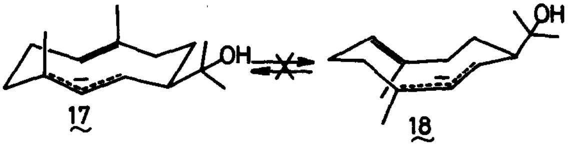
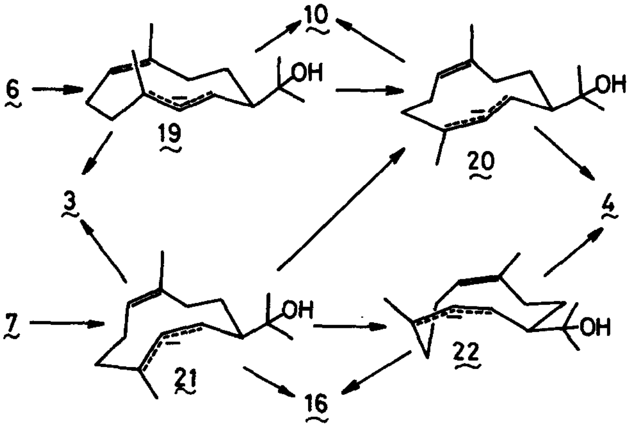
The likewise cyclization of epoxy-2Z,6Z-farnesyl phenyl sulfide 8, prepared in the same reaction sequence from 2Z,6Z-farnesol8), afforded the acyclic allyl alcohol 9, no cyclization being achieved [9: ν 3410, 896 cm^{-1}; δ 1.71 (9H, br.s), 3.50 (2H, d, J=7.5), 3.94 (1H, t, J=6), 4.79 (1H, br.s), 4.91 (1H, br.s), 5.17 (2H, m), 7.1-7.4 (5H, m)].

Desulfurization reaction of 6 and 7 followed again a different course from the previous cases[2]. The reaction of 6 with Li in ethylamine at -78° in the presence of ethanol afforded the desired 3 (33%) and 4 (16-22%) in a single reaction together with the products of allylic rearrangement 10 (14-22%) and further reduction 11 (15% yield), all of which were separated by chromatography on $AgNO_3$-impregnated silica-gel. While the structures of 10 and 11 were deduced from their spectra, that of 3 was verified by its spectra [m/e 204 (M^+-H_2O), 59 (base peak); ν 3370 cm^{-1}; δ 1.14 (6H, s), 1.60 (3H, t, J=1.5), 1.65 (3H, d, J=1.5), 4.95-5.2 (2H, m), NOE C_7-Me→H_6 (17%), and C_3-Me→H_2 (0%) measured in the presence of Eu(fod)$_3$], and its dehydration ($POCl_3$/Py) to the germacra-2,6,10-triene 12[9] and -2,6,11-triene 13. The structure of 4 was based on its spectra [colorless oil, m/e 204 (M^+-H_2O), 59 (base peak); ν 3400 cm^{-1}; δ 1.17 (6H, s), 1.60 (6H, br.s), 5.1-5.4 (2H, m)] including NOE measurements in the presence of Eu(fod)$_3$[10], and its conversion to 3 on UV irradiation in acetone. Dehydration of 4 gave two new trienes 14 and 15 in 1:2 ratio[11]. Desulfurization of 7 afforded 16[11] (37% yield) in addition to 3 (9%), 4 (12%) and 10 (7%).

As is reported[2], 2E,6E-isomer yielded 2E,6E-hedycaryol and 1E,6E-isomer, while 2Z,6E-isomer gave 2Z,6E-hedycaryol. Although the site of double bond in the products would be subjected to the kinetic control of proton attack on the intervening allylic anion, the geometry of the resulted double bond would reflect the conformation of the anion. The above results for two 6E-isomers therefore can be explained by the single anion 17 and 18, respectively, and disclosed no interconversion between them.





The facts that 6 yielded a pair of geometrical isomers 3 and 4, and that 7 gave 3 and 4, and 10 and 16 revealed the intervention of more than one allylic anion (19 and 20 from 6, and 20, 21 and perhaps 22 from 7), though the precise reaction pathways are not established[12]. These behavioral difference in the isomeric hedycaryol phenyl sulfides may reflect the strain inherent in each ring system.

Although 3 and 4 thus obtained have not yet been found in nature, sesquiterpenes of these carbon frame works are known[13] and some possess interesting biological activities. The transannular reactions of these hedycaryol isomers are in progress.

References and Notes

1) Part III of the series; M. Kodama, K. Shimada and S. Itô, Tetrahedron Letters, 2763 (1977).

2) M. Kodama, Y. Matsuki and S. Itô, ibid., 1121 (1976). E,E-Hedycaryol detected in this paper was later isolated by preparative TLC on $AgNO_3$-impregnated silica-gel and identified rigorously.

3) Idem, ibid., 3065 (1975). Close examination of the cyclization products revealed the formation of 2Z, 6E,10E-nephthenol phenyl sulfide (5%) in addition to the isomer (62%) reported.

4) K. Takeda, Tetrahedron, 30, 1525 (1974) and references cited therein. K. Takeda and I. Horibe, J. Chem. Soc., Perkin I, 870 (1975). P.S. Wharton and R.A. Kretchmer, J. Org. Chem., 33, 4258 (1968), K. Morikawa and Y. Hirose, Tetrahedron Letters, 869 (1969).

5) All new compounds gave correct elemental analyses and satisfactory spectra. The spectra were measured under the following conditions: MS (m/e) at 70 eV, IR (ν) liquid film, PMR (δ) in CCl_4.

6) A. Ofner, W. Kimel, A. Holmgren and F. Forrester, Helv. Chim. Acta, 42, 2577 (1959).

7) Fading rate of the color was much slower in this case than the previous cyclizations[2,3].

8) R.B. Bates, D.M. Gale and B. Gruner, J. Org. Chem., 28, 1086 (1963).

9) K. Takeda, I. Horibe and H. Minato, J. Chem. Soc., Chem. Commun., 87 (1971).

10) The following values were obtained: δ 1.76 (3H, br.s)→ δ 5.45 (1H, br.t, J=8) (4%) and δ 6.3 (1H, m) (5%); δ 2.10 (3H, br.s)→ δ 5.45 (7%). Although assignment of each methyl and vinyl protons is impossible, the result indicates both vinyl protons be cis to methyl groups.

11) 14: colorless oil, m/e 204 (M^+), 121 (base peak); ν 1645 cm^{-1}; δ 1.55-1.75 (12H, m), 2.72 (2H, br.d, J=8), 5.0-5.4 (2H, m), 15: colorless oil, m/e 204 (M^+), 93 (base peak); ν 1645, 886 cm^{-1}; δ 1.60 (6H, br.s), 1.72 (3H, t, J=1.0), 4.65 (2H, br.s), 4.85-5.25 (2H, m), 16: colorless oil, m/e 222 (M^+), 149 (base peak), 59 (98%); ν 3400 cm^{-1}; δ 0.97 (3H, d, J=7), 1.15 (6H, s), 1.75 (3H, br.s), 5.17-5.58 (3H, m); δ ($Eu(fod)_3$) 5.62 (1H, dd, J=11, 11), 6.12 (1H, dd, J=11, 11).

12) The difference in the formation ratio between two reactions revealed that though interconvertible, these conformers 19-22 are not in full equilibrium during the reaction.

13) 2E,6Z-Configuration: N.H. Fischer, R. Wiley and J.D. Wander, J. Chem. Soc., Chem. Commun., 137 (1972), S. Neidle and D. Rogers, ibid., 140 (1972), W. Herz and P.S. Kalyanaraman, J. Org. Chem., 40, 3486 (1975), N.H. Fischer, R. A. Wiley, D.L. Perry and K.D. Haegele, ibid., 41, 3956 (1976). 2Z,6Z-Configuration: F. Bohmann and D. Ehlers, Phytochem., 16, 137 (1977).

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