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SYNTHESIS OF MACROCYCLIC TERPENOIDS BY INTRAMOLECULAR CYCLIZATION II
GERMACLANE-TYPE SESQUITERPENES

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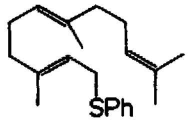
In the previous paper (1), we have described the biogenetic-type synthesis of diterpenes with a fourteen-membered ring, cembrene-A and nephthenol, exemplifying usefulness of the anion-induced intramolecular cyclization in the synthesis of macrocyclic terpenoids. We have applied the general reaction sequence to the synthesis of sesquiterpenes, where this type of cyclization is more important biogenetic pathway than in diterpenes. This communication deals with a convenient and highly selective synthesis of sesquiterpenes with ten-membered ring which would be quite laborious to construct by other methods (2).

trans,trans-Farnesyl phenyl sulfide 1 (3) was converted (i NBS, ii Na_2CO_3) to the epoxide 2 in 54% yield [colorless oil; nmr: 1.26 (3H, s), 1.30 (3H, s), 1.60 (6H, br.s), 2.69 (1H, t, J=6.0), 3.54 (2H, d, J=8.0), 5.2 (1H, br.m), 5.33 (1H, br.t, J=8), 7.0-7.4 (5H, m)] (4).

Cyclization of 2 was performed using *n*-butyl lithium in the presence of 1,4-diazabicyclo[2.2.2]-octane. Contrary to the previous case (1), however, the reaction afforded, after chromatographic separation, two isomeric hydroxy thioethers 3 and 4 in 35% and 25% yield, respectively. 3: colorless oil; ms: m/e 330 (M^+), 59 (base peak); ir: 3500, 1650, 1585 cm^{-1}; nmr: 1.15 (3H, s), 1.36 (3H, s), 1.49 (3H, d, J=1.0, C_3-Me), 1.60 (3H, d, J=1.0, C_7-Me), 4.13 (1H, dd, J=9.0, 2.5, H_1), 4.75-5.0 (1H, m, H_6), 5.12 (1H, br.d, J=9, H_2), 7.0-7.3 (5H, m, Ph). 4: colorless oil; ms: m/e 330 (M^+), 59 (base peak); ir: 3450, 1650, 1593 cm^{-1}; nmr: 1.27 (3H, s), 1.36 (3H, s), 1.48 (3H, d, J=1.0, C_7-Me), 1.64 (3H, d, J=1.0, C_3-Me), 3.31 (1H, d, J=11.5, H_1), 5.05-5.25



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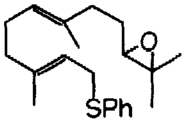

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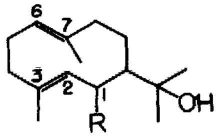

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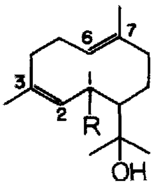
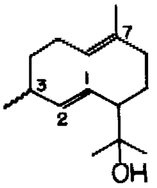
5: R= H



4: R= SPh

8: R= H



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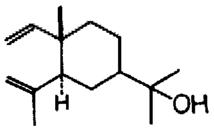

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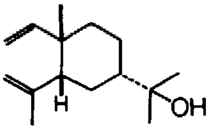

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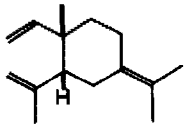

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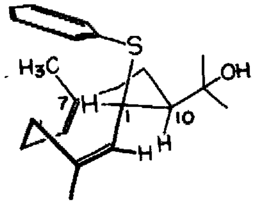

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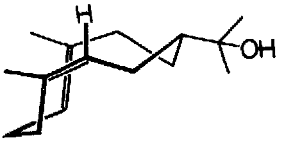

B

(1H, br.t-like, H_6), 5.58 (1H, br.d, J=11.5, H_2), 7.1-7.5 (5H, m, Ph). The structure assignment of 3 was based on the spectral properties described, nmdr experiments and the formation of levulinic acid on ozonolysis.

The alcohol 3 was desulfurized with lithium-ethylamine at -78° to give an inseparable mixture of two isomeric alcohols 5 and 6 in quantitative yield. The presence of hedycaryol (*trans,trans*-hedycaryol) 5 (5) in the mixture was shown by the ir and nmr spectra and its conversion to elemol 7 on thermolysis (170°) of the mixture (5:6=2 : 3) (6). The thermolysis offered a good method to obtain the pure alcohol 6 as colorless oil, whose structure was deduced from the following spectral data: ms: m/e 220 (M^+), 59 (base peak); ir: 3400, 1665 cm^{-1}; nmr: 0.91 (3H, d, J=6.8, C_3-Me), 1.01 (3H, s), 1.05 (3H, s), 1.50 (3H, br.s, C_7-Me), 4.7-5.1 (3H, complex); nmr (CCl_4+ $Eu(fod)_3$): 6.02 (dd, 1H, J=15.5, 9.5, H_1), 5.72 (1H, dd, J=15.5, 9.3, H_2).

The byproduct 4 of the cyclization reaction has the same functionality with 3 as is shown by the spectra. Cis disposition of C_2-C_3 double bond was concluded from the observation of nuclear

Overhauser effect (16%) between H_2 and C_3-methyl signals. The geometry depicted as A is the only conformation for **4** which accommodates the characteristic nmr features *i.e.*, i) appearance of H_1 signal as a doublet (J=11.5 Hz, showing coupling only with H_2) and ii) the appearance of H_1 (δ 3.31 ppm) and C_7-methyl (δ 1.48 ppm) at higher field than normal (Their assignment was based on nmdr experiments). Apparently the dihedral angle H_1-C_1-C_{10}-H_{10} is ~90° and H_1 and C_7-methyl group are in the shielding region of the C_6-C_7 double bond and the phenyl group, respectively.

Desulfurization of **4** by the same procedure described above yielded 2-*cis*-6-*trans*-hedycaryol **8** in 83% yield together with a trace amount of **6**. **8** : colorless oil; ms: m/e 220 (M^+), 59 (base peak); ir: 3375, 1665 cm^{-1}; nmr: 1.13 (3H, s), 1.14 (3H, s), 1.67 (6H, br.s), 5.25 (2H, br.t, J=~7). Although **8** has not been found in nature yet, its carbon skeleton, 2-*cis*-6-*trans*-germacradiene, is found in several terpenoids, such as heliangine, provincialin and peucephyllin (7). Furthermore, the carbon skeleton is known to be a precursor of cadinenes, amorphenes and other related terpenes (8).

On thermolysis at 200° (9), **8** underwent a Cope rearrangement to give *cis*-elemol **9** in 60% yield [colorless prisms; m.p. 38-40°; ms: m/e 220 (M^+), 59 (base peak); ir: 3380, 1635, 895 cm^{-1}]. Nmr spectrum of **9** exhibited signals assignable to a vinyl group [ABX-type, AB part: eight lines at δ 4.7-5.1, X part: six lines at δ 5.95-6.45, ν_A=4.93, ν_B=4.97, ν_X=6.22, J_{AB}=1.59, J_{AX}=17.45, J_{BX}=10.85 (10)], an exo-methylene group (δ 4.60, 4.72) and four methyl groups [δ 0.99 (3H, s), 1.14 (6H, s), 1.65 (3H, m)]. For the structure determination, **9** was converted to *cis*-α-elemene **10** with thionyl chloride in pyridine. The resulted **10** was shown to be identical (ir, nmr and glc) with the specimen obtained previously by Takeda, *et al.* (11). Although the relative configuration of dimethylcarbinyl side chain in **9** is not established, α-configuration is preferred because the most favored conformation (B) in the transition state for Cope rearrangement is derived only from this configuration.

Thus, although not isolated, synthesis of hedycaryol was achieved and the anion-induced cyclization was again proved to be useful method to construct macrocyclic terpenes. Further study on 2-*cis*-6-*trans*-hedycaryol is in progress.

We are deeply indebted to Dr. K. Takeda, Shionogi Research Laboratory, for the identification of *cis*-α-elemene, to Dr. Y. Fukazawa, Tohoku University, for the computer analysis and to Takasago Perfumery Co., Ltd., for the gift of *trans*-nerolidol.

References and Footnotes

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

2) Three syntheses of the sesquiterpenoids of this type have been achieved but all involved multistep processes and none followed biogenetic pathway (Cf. ref. 1).

3) J.F. Biellmann and J.B. Ducep, *Tetrahedron*, **27**, 5861 (1971). We have obtained this compound from *trans*-nerolidol in 71% yield *via trans,trans*-farnesylbromide.

4) All compounds described herein gave correct elemental analyses. Ir and nmr spectra are referred to neat liquid and carbontetrachloride solution, respectively.

5) R.V.H. Jones and M.D. Sutherland, *Chem. Commun.*, 1229 (1968).

6) At this temperature, **6** was shown to be stable, while hedycaryol is known to undergo Cope rearrangement to elemol (5).

7) H. Morimoto, Y. Sanno and H. Oshio, *Tetrahedron*, **22**, 3173 (1966); W. Herz and I. Wahlberg, *J. Org. Chem.*, **38**, 2485 (1973); M.J. Begley, G. Pattenden and T.J. Mabry, *Tetrahedron Letters*, 1105 (1975).

8) *Inter al.*, G. Rücker, *Angew. Chem. Internat. Edit.*, **12**, 793 (1973).

9) At this temperature, *cis,trans*-germacradienes are known to undergo the rearrangement (11).

10) Analysis was performed by Dr. Y. Fukazawa, Tohoku University, using Swalen's program [J.D. Swalen and C.A. Reilly, *J. Chem. Phys.*, **37**, 21 (1962)].

11) K. Takeda, I. Horibe and H. Minato, *J. Chem. Soc.*, Perkin I, 2212 (1973).