

BIOMIMETIC TRANSFORMATIONS OF GERMACRADIENES.

STEREOSPECIFIC CONVERSION OF HEDYCARYOL PHENYL SULFIDES TO CADINANES

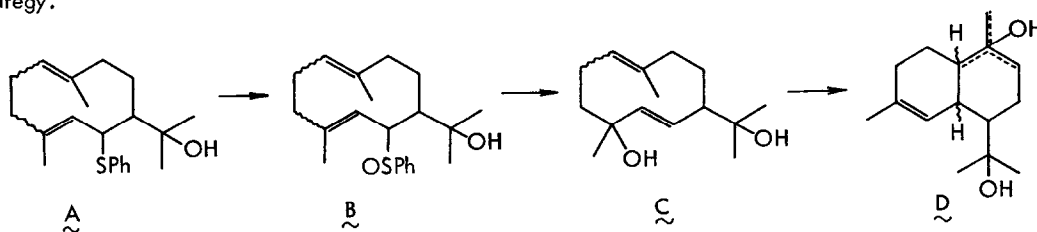
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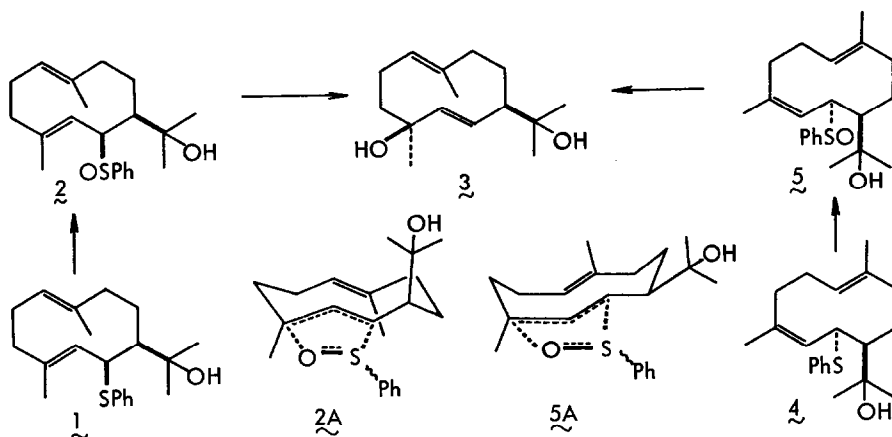
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Abstract. E,E- and 2Z,6E-hedycaryol phenyl sulfides were converted by [2,3]sigmatropy of their sulfoxides to the same allyl alcohol which in turn afforded cadinane derivatives stereospecifically by the action of acids.

In the previous paper¹⁾ we reported unexpected cyclizations of isomeric hedycaryol phenyl sulfides to eudesmane carbon skeleton. Since our original aim was to achieve the transformation of germacra- dienes to cadinane carbon skeleton and to observe its stereochemical requirement, we next tried an alternative route, A → D, using the same sulfides. In this communication we describe the stereospecific transformation of E,E- and 2Z,6E-hedycaryol phenyl sulfides to cadinane derivatives based on the strategy.

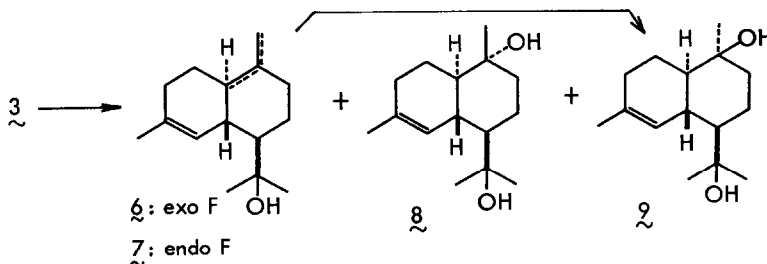


When E,E-hedycaryol phenyl sulfide 1^{1,2)} was oxidized with NaO₄ (dil. MeOH, 0°, 20 hrs), two isomeric sulfoxides, 2a and 2b³⁾, were obtained in 59% and 34% yields, respectively. From spectral data it is clear that they are configurational isomers on sulfur. The mixture 2a+2b, when treated with Et₂NH in refluxing MeOH, yielded a single allyl alcohol 3 (72% yield from 1) after 10 days. Similar oxidation of the 2Z,6E-isomer 4²⁾ and the rearrangement (Et₂NH, room temp. 18 hrs) of the unstable sulfoxide mixture 5 resulted gave the same allyl alcohol 3 (65% yield from 4) as a single product. The facts that the PMR spectrum of 3 indicates E-configuration of the newly-formed disubstituted double bond (J=16.0 Hz) and that the same alcohol 3 is obtained as a single product culminated in the assignment of configuration in 3, when the stereochemical course of the [2,3]sigma-



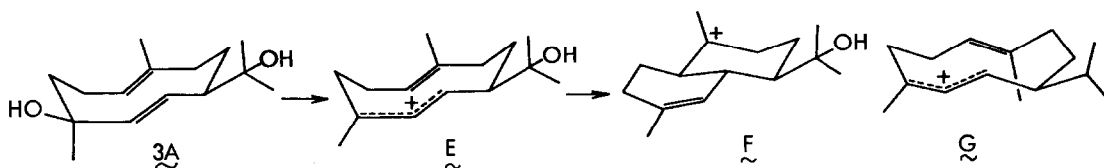
tropic rearrangement of a sulfoxide (perpendicular disposition of the cleaving C-S bond and the plane of the double bond)⁴⁾ is taken into consideration. Transition states of the rearrangement can be depicted as shown (2A and 5A)⁵⁾ for each case.

The allyl alcohol 3 thus obtained always gave four products, the dienols 6 and 7, and the diols 8 and 9, on treatment with various acids. For example, with 3N-H₂SO₄ (aq. acetone, 0°, 50 min) yields of 6+7 (1:1, mixture), 8 and 9 were 15%, 81% and trace, respectively, and with 10% HClO₄ (aq. dioxane, 0°, 20 min), they are 24%, 33% and 25%, respectively. With p-TsOH (refluxing ether, 18 hrs) 6, 7 and 8+9 were formed in 44%, 42% and 13% yield, respectively.

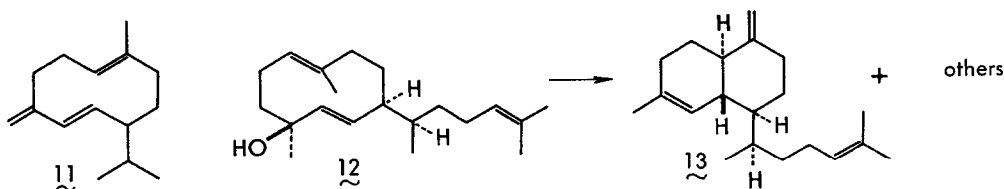


While the structure of 9 was unequivocally established by X-ray crystallographic analysis⁶⁾, that of 6 was confirmed by its conversion (oxymercuration and reduction) to 9 and that of 7 by the chemical correlation with δ -cadinene 10⁷⁾ utilizing the following reaction sequences; 1) SOCl₂/Py, ii) 9-BBN, H₂O₂, iii) MsCl/Py, iv) LiAlH₄. The structure of 8 was based on the spectral evidences: Large chemical shift differences between NMR spectra of 8 and 9 are observed only for one methyl group³⁾ (PMR: $\Delta\delta=0.11$ ppm, CMR: $\Delta\delta=7.9$ ppm) suggesting 8 to be epimeric only at a carbinyl carbon. Thus, all the products were shown to have an identical carbon skeleton corresponding to natural cadinenes and cadinols.

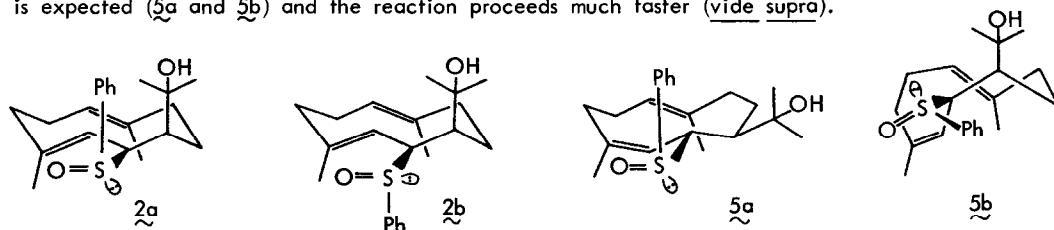
The configuration of the products $\underline{6}$ - $\underline{2}$ suggests only one conformation $\underline{3A}$ to be involved to give the bicyclic cation \underline{E} . In this conformation, the allylic hydroxyl group is equatorially oriented and suited for elimination (maximum overlap between the developing carbonium p-orbital and π -electron of the neighboring double bond) and the carbon atoms are suitably located for the formation of Z-double bond and the C-C bond. Therefore the entire sequence $\underline{3A} \rightarrow \underline{E}$ may well be a concerted process.



The present results show a marked contrast to the acid-catalyzed cyclization of germacrene D $\underline{11}$ ⁷⁾, where products with both cadinane and muurolane carbon skeletons were resulted in 52% and 15% yields, respectively, along with other products. In the light of stereospecific cyclization revealed in the present study, intervention of two conformational species \underline{E} (without OH) and \underline{G} in the allylic ion should be considered in the cyclization of $\underline{11}$. The present results also shed light to the undetermined stereochemistry of obscuronatin $\underline{12}$ isolated from a soft coral⁸⁾. Since $\underline{12}$ has been converted to biflora-4,10(19),15-triene $\underline{13}$ ⁹⁾ with the cadinane stereochemistry, $\underline{12}$ is most likely to possess the configuration identical with $\underline{3}$ ⁸⁾.



Finally we suggest stereochemistry of the sulfoxides $\underline{2a}$ and $\underline{2b}$ as shown on the following basis. The [2,3]sigmatropic reaction is much slower for $\underline{2a}$ than for $\underline{2b}$ and when the reaction with the mixture was stopped after 3 days, pure $\underline{2a}$ was recovered in 20% yield in addition to $\underline{3}$ (54%). The difference in the reaction rate is rationalized⁵⁾ in terms of a steric compression between phenyl group and the bulky $-\text{CMe}_2\text{OH}$ in the transition state of $\underline{2a}$ but not $\underline{2b}$. In the sulfoxide mixture $\underline{5}$ no such compression is expected ($\underline{5a}$ and $\underline{5b}$) and the reaction proceeds much faster (*vide supra*).



We are grateful to Dr. H. Nishimura, Hokkaido University, for the spectra of cadinane derivatives.

References and Notes

- 1) M. Kodama, K. Shimada and S. Itô, Tetrahedron Letters, 22, 1523 (1981).
- 2) M. Kodama, Y. Matsuki and S. Itô, ibid., 1121 (1976).
- 3) Properties and spectra of new compounds are listed. 2a: m.p. 121-122°, m/e 346 (M⁺), 81 (b.p.), ν (KBr) 3340, 1012 cm⁻¹, δ (CCl₄) 1.16 (3H, s), 1.28 (3H, s), 1.42 (3H, br.s), 1.64 (3H, br.s), 4.05 (1H, d, J=10.0), 4.60 (1H, m), 4.77 (1H, d, J=10.0), 7.4-7.6 (5H, m), 2b: m.p. 129-130°, m/e 346 (M⁺), 59 (b.p.), ν (KBr) 3400, 1015 cm⁻¹, δ (CCl₄) 1.35 (3H, s), 1.44 (6H, br.s), 1.57 (3H, br.s), 3.78 (1H, br.d, J=10), 4.84 (1H, m), 5.33 (1H, d, J=10.0), 7.4-7.6 (5H, m), 3: oil, m/e 238 (M⁺), 59 (b.p.), ν (oil) 3400 cm⁻¹, δ (CDCl₃) 1.10 (3H, s), 1.16 (3H, s), 1.21 (3H, s), 1.56 (3H, br.s), 4.9-5.5 (3H, m), δ (CDCl₃+Eu(fod)₃) 6.41 (1H, d, J=16.0), 7.21 (1H, dd, J=16.0, 10.5), 4: m.p. 107-108°, m/e 220 (M⁺), 159 (b.p.), ν (KBr) 3300, 885, 878 cm⁻¹, δ (CDCl₃) 1.19 (3H, s), 1.23 (3H, s), 1.70 (3H, br.s), 4.57 (1H, br.s), 4.65 (1H, br.s), 6.17 (1H, br.s), 7: oil, m/e 220 (M⁺), 159 (b.p.), ν (oil) 3380 cm⁻¹, δ (CDCl₃) 1.25 (3H, s), 1.31 (3H, s), 1.68 (6H, br.s), 5.71 (1H, m), 8: m.p. 136-137°, m/e 238 (M⁺), 59 (b.p.), ν (KBr) 3380, 820 cm⁻¹, PMR δ (CDCl₃) 1.12 (3H, s), 1.24 (6H, s), 1.68 (3H, br.s), 6.15 (1H, br.s), CMR δ (CDCl₃) 20.7 (q), 22.7 (t), 24.1 (q), 24.1 (q), 27.1 (t), 30.6 (t), 32.1 (q), 40.8 (d), 42.3 (t), 49.8 (d), 52.9 (d), 72.1 (s), 74.2 (s), 124.7 (d), 134.3 (s), 9: m.p. 140°, m/e 220 (M⁺-H₂O), 59 (b.p.), ν (KBr) 3380 cm⁻¹, PMR δ (CDCl₃) 1.23 (3H, s), 1.25 (6H, s), 1.68 (3H, br.s), 6.17 (1H, br.s), CMR δ (CDCl₃) 22.6 (t), 24.0 (q), 24.2 (q), 25.0 (t), 28.6 (q), 30.6 (t), 32.0 (q), 38.6 (d), 40.5 (t), 47.9 (d), 53.0 (d), 70.4 (s), 74.5 (s), 125.1 (d), 133.6 (s).
- 4) Inter al., R.W. Hoffmann, Angew. Chem. Intern. Ed., 18, 563 (1979).
- 5) The conformation of the rear side of the molecules is tentative.
- 6) The crystal belongs to orthorhombic system with two independent molecules in an unsymmetrical unit of cell dimensions a=18.382, b=9.539, c=16.157 Å, space group Pna2₁. The structure was solved by the direct method and refined by block-diagonal least-squares method using 2964 reflections. Anisotropic temperature factors were given for nonhydrogen atoms to yield R=0.098. Since the structure determination was our primary concern, no further refinement was attempted.
- 7) H. Nishimura, H. Hasegawa, A. Seo, H. Nakano and J. Mizutani, Agric. Biol. Chem., 43, 2397 (1979).
- 8) Y. Kashman and A. Groweiss, J. Org. Chem., 45, 3814 (1980). Authors state that PMR spectrum of their product overlaps almost completely with that of 13.
- 9) D.F. Wiemer and J. Meinwald, G.D. Prestwich, B.A. Solheim and J. Clardy, J. Org. Chem., 45, 191 (1980).

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