TRANSFORMATION OF α-DIHYDROIONOL TO DIHYDROEDULAN AND THEASPYRANE BY PHOTOSENSITIZED OXYGENATION†

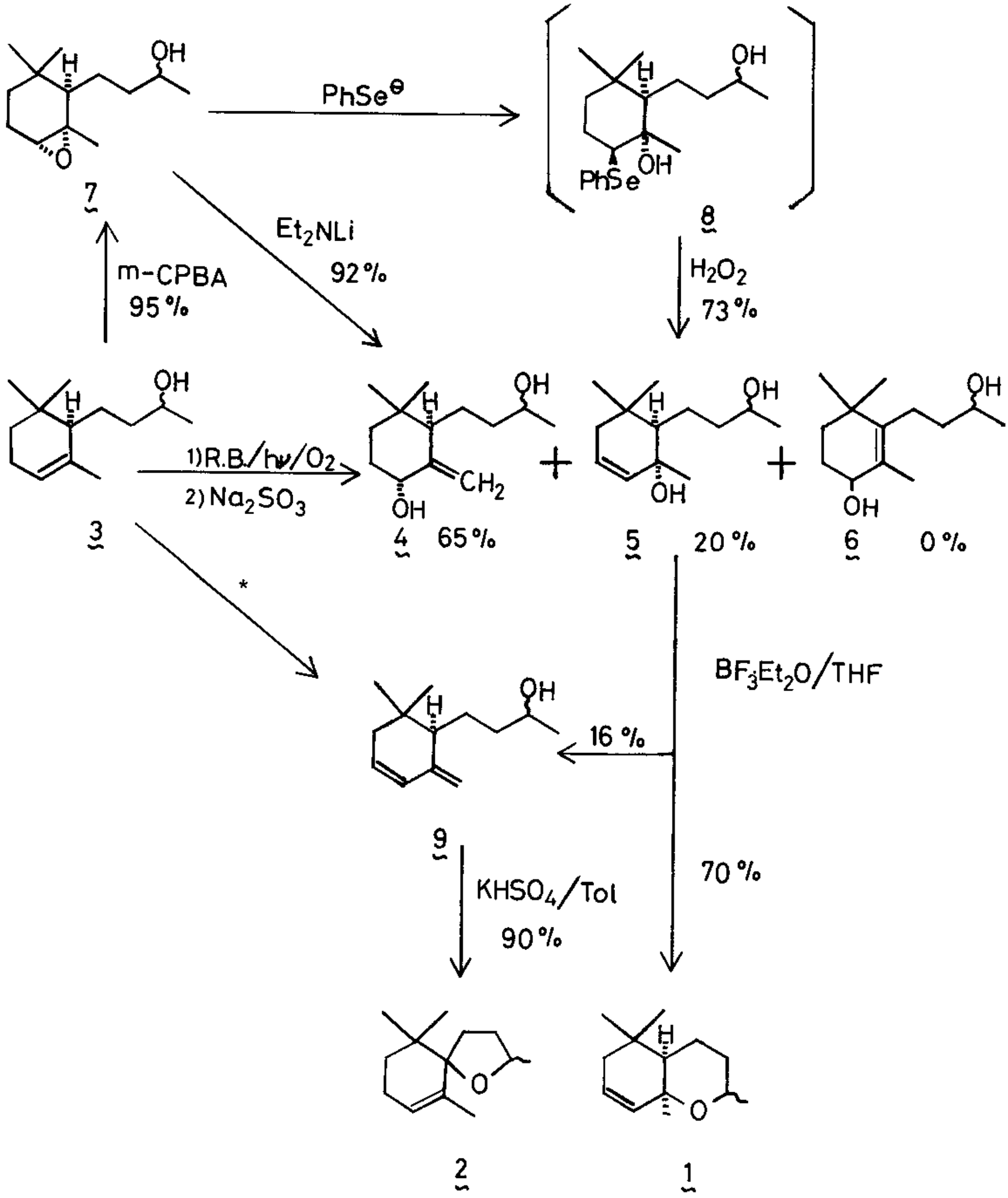
Hideki Okawara, Susumu Kobayashi, and Masaji Ohno*
Faculty of Pharmaceutical Sciences, University of Tokyo,
Bunkyo-ku, Tokyo 113, Japan

Abstract — Racemic dihydroedulan (1) and theaspyrane (2) have been synthesized starting with racemic α-dihydroionol (3) in a few steps using photosensitized oxygenation as the key step. Two isomeric hydroxy allyl alcohols 4 and 5 were obtained upon treatment with singlet oxygen and also prepared from an epoxide 7 by treatment with lithium diethylamide and organoselenium reagents, respectively. The allyl alcohol 5 afforded dihydroedulan (1) predominantly with BF_3 in THF and another allyl alcohol 4 was converted selectively to theaspyrane (2) through a diene 9.

Dihydroedulan (1) and theaspyrane (2) are components responsible for the unique flavor of the juice of the purple-skinned passionfruit Passiflora edulis Sims[1] and black tea aroma,[2] respectively, and they were obtained as an epimeric mixture isolated in a trace amount from nature. Therefore, it is very interesting and even important to approach such valuable flavors synthetically from a starting material readily available. Recently, multistep synthesis of 1 was achieved starting with 3-(4-oxo-2,2,6-trimethylcyclohex-5-enyl)propanenitrile[1] or α-ionone,[3] and synthetic studies on theaspyrane derivatives were extensively carried out.[4,5,6] However, a more efficient and practical route to these unique flavors was desired urgently. We report here a new, simple, and obviously more practical synthesis of an epimeric mixture of dihydroedulan and theaspyrane from the same starting material by photosensitized oxygenation.

---

† Dedicated to Emeritus Professor Dr. Hamao Umezawa, University of Tokyo and Director of Institute of Microbial Chemistry in Tokyo, on the occasion of his sixty-fifth birthday.



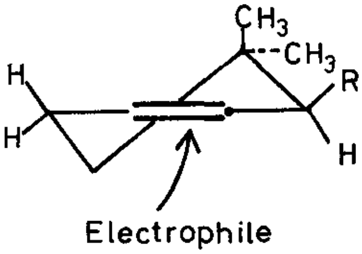
* 1) AcCl-Py 2) $^1O_2$ 3) Na_2SO_3 4) $POCl_3$
5) DBU 6) LAH

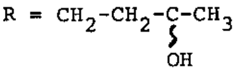
α-Dihydroionol (3) was chosen as the starting material for our synthesis, since it is readily available by reduction of α-ionone[7] and is considered to be a good candidate for the synthesis of 1 and 2 through ene-type reaction with singlet oxygen.[8] On treatment of 3 with dye-sensitized oxygen (rose bengal, high pressure mercury lamp) followed by reduction with Na_2SO_3, two isomeric hydroxy allyl alcohols 4 and 5 were obtained in 65 and 20% yields, respectively. Another possible isomer 6 was not confirmed to be formed. The result is interesting when compared with that of photooxygenation of limonene[9] and shows that steric hindrance at the transition state to form 4, 5 and 6 seems to be quite different from each other.

Protection of the hydroxyl group of 3 with bulky groups such as Ac, THP, CH_2Ph and COPh, did not change the ratio of the products 4 and 5, so it seems to be rather difficult to cause a significant difference in the steric effect from δ-position to the double bond.

The main product 4 was easily purified by distillation, showing bp 115~125°/0.7~0.9 mm: IR (neat) 3350, 1640, 900 cm^{-1}; NMR ($CDCl_3$) δ 0.72 and 0.96 (s, gem-dimethyl), 1.18 (d, J=6 Hz, HO-CH-CH_3) 4.7 and 5.2 (s, C=CH_2); MS m/e 211 (M^+-1), 195 (M^+-17), 177 (base peak, M^+-17-18). Furthermore, it was independently synthesized in two steps and in excellent yields through an epoxide 7, confirming the structure unanimously to be 4. The epoxide 7 was prepared in 95% yield by treatment of 3 with m-chloroperbenzoic acid, and afforded the allyl alcohol 4 with lithium diethylamide in 92% yield. The second product 5 was obtained in about 20% yield (GPC), and was rather hard to purify by fractional distillation simply due to its small scale (1~10g), but it was also independently synthesized easily from the epoxide 7. The epoxide 7 was treated with diphenyl diselenide and sodium borohydride, and followed by oxidative elimination with hydrogen peroxide,[10] affording an epimeric mixture of allyl alcohols 5 in 73% yield based on 7.

The epimeric mixture was separated by silica gel chromatography, affording two crystalline allyl alcohols in about 1 to 1 ratio: 5a; mp 94~94.5°, Rf 0.369 (tlc) and 5b; mp 90.5~92°, Rf 0.333.[11] Both of them gave expected analytical data and similar ^1H- and ^{13}C-NMR and IR spectra and showed the following mass spectra: m/e 212 (M^+), 194 (M^+-18), 179 (M^+-18-15), and 95 (base peak). Therefore, it is remarkable that products by photooxygenation and through epoxidation are essentially identical and consist of only two diastereomers. These results suggest that addition of electrophiles such as singlet oxygen and peracid occurred stereoselectively. A survey using Dreiding model strongly prefers that electrophiles more easily attack from the less hindered side or the side of the tertiary hydrogen as shown in the Figure. The *cis* relation between the hydroxyl group and the tertiary hydrogen of 5 is also reasonably supported by easy transformation to dihydroedulan[1,12] with *cis* junction, as demonstrated by Prestwich *et al.*[1] Such discussion can be applied also to the stereochemistry of 5.





$R = CH_2-CH_2-\underset{OH}{C}-CH_3$

The reaction conditions which effect ring closure to lead 1 and/or 2 has been found to be most critical and subtle. Firstly, 4 was directly treated with various acids in various solvents. In the case of $BF_3 \cdot Et_2O$-benzene and $KHSO_4$-toluene, the formation of 1 and 2 were scarcely confirmed by GPC (5~6% yield), and other acids (HCl, H_3PO_4, CF_3SO_3H, and p-toluene sulfonic acid) afforded only intractable materials. Next, another transformation was investigated. A diene compound 9 was prepared from acylated dihydroionol by successive treatment with singlet oxygen, $POCL_3$-Py., DBU and removed of the protective group with LAH. It was purified by distillation, showing bp 139°/0.6 mm; NMR ($CDCl_3$) δ 0.85 and 0.95 for gem-Me, 1.15 (d, *J*=6 Hz, HO-CH-$\underline{CH_3}$), 4.7 and 4.85 for $C=CH_2$, 5.8 (m, 2H, -CH=CH-); IR (neat) 3425, 1640, 1600 and 880 cm^{-1}; UV_{max} (EtOH) 233 nm (ε, 24750); MS m/e 194 (M^+), 79 (base peak). The diene 9 thus obtained afforded exclusively an epimeric mixture of theaspyrane (2) in 90% yield by treatment with $KHSO_4$ in boiling toluene. However, it was interestingly recognized that a mixture of 1, 2, and 9 (a ratio of 2, 5, and 2, respectively) was obtained with H_3PO_4 in n-hexane at room temperature and even dihydroedulan (1) itself was transformed at the same condition to an equilibrium mixture of 1, 2, and 9 in a ratio of about 1, 3, and 4, respectively. This finding is striking since 1 is so sensitive to such a mineral acid, and suggests that such acid-catalyzed ring closure will not be used in the latter stage of synthesis of 1.

When the isomeric mixture 4 and 5 was treated with $BF_3 \cdot OEt_2$ in tetrahydrofuran at room temperature, the formation of an epimeric mixture of 1 was recognized in about 12% yield by GPC and most of 4 was recovered. This result seemed to show that only the allyl alcohol 5 was converted into 1, implying also that a *cis*-fused system such as dihydroedulan could be favorably formed if a cyclohexenol type compound with proper stereochemistry is employed. Since the allyl alcohol 5 was easily obtained from the epoxide 7 in pure form and has the desired cis stereochemistry, each of the crystalline epimers has been subjected to acid-treatment with $BF_3 \cdot OEt_2$ in tetrahydrofuran. The products were carefully analyzed by GPC using a capillary column.[7] Surprisingly, each of the epimers 5a and 5b mentioned previously was transformed to their corresponding epimers of the dihydroedulan in 70% yield along with the diene 9 in 16% yield. The present study have shown that α-dihydroionol (3) is an useful starting material and photosensitized oxygenation or formation of the allyl alcohols 4 and 5 is an effective methodology for the synthesis of bicyclo compounds containing ether linkage such as dihydroedulan and theaspyrane.

The stereochemical problems and characterization of each epimer of 1, 2, 4, and 5 are now under careful investigation and the results will be published in the near future.

Reference and Notes

1. G. D. Prestwich, F. B. Whitfield and G. Stanley, *Tetrahedron*, 1976, **32**, 2945.
2. W. Renold, R. Näf-Müller, U. Keller, B. Willhalm, and G. Ohloff, *Helv. Chim. Acta*, 1974, **57**, 1301 and references cited therein.
3. H. Eto, M. Iguchi, and K. Ina, "21st Symposium on the Chemistry of Terpenes, Essential Oils, and Aromatics", Osaka, 1977 abstract p. 175.
4. Y. Nakatani and T. Yamanishi, *Tetrahedron Letters*, 1969, 1995.
5. G. Ohloff, V. Rautenstrauch, and K. H. Scholte-Elte, *Helv. Chim. Acta*, 1973, **56**, 1503.
6. R. Kaiser, A. Kappeler, and D. Lamparsky, *Helv. Chim. Acta*, 1978, **61**, 387.
7. α-Dihydroionol, kindly supplied by Soda Perfume Company, was obtained by catalytic reduction of α-ionone followed by $NaBH_4$ reduction, and it was confirmed to be an epimeric mixture (about 1 to 1) by gas phase chromatography (GPC) using a capillary column (30m, FFAP).
8. G. Ohloff, *Pure and Applied Chemistry*, 1975, 481.
9. G. O. Schenk, K. Gollnick, G. Buchwald, S. Schroeter, and G. Ohloff, *Ann. Chem.*, 1964, **674**, 93.
10. K. B. Sharpless and R. F. Lauer, *J. Am. Chem. Soc.*, 1973, **95**, 2697.
11. Recrystallized from n-hexane and a mixed solvent of ether and n-hexane in a ratio of 3 to 1 was used as eluent.
12. Acid-catalyzed ring closure is considered to be synchronized (SN_2 type reaction) and *cis*-dihydroedulan is most perferably formed.[1]
13. The stereochemical problems involved in the present research will be mentioned in the next paper in detail.
14. W. S. Johnson, P. J. Neustadter, and K. K. Schmiegel, *J. Am. Chem. Soc.*, 1965, **87**, 5148.

15. This research was financially supported by Grants-in-aid for General Scientific Research (No. 347115) from the Ministry of Education, Science and Culture of Japan.

Received, 1st October, 1979