CHEMISTRY LETTERS, pp. 281-282, 1983.

PREPARATION OF (*Z*,*E*,*E*)-HUMULENE. AN IMPORTANT INTERMEDIATE FOR BIOGENESIS OF POLYCYCLIC SESQUITERPENES

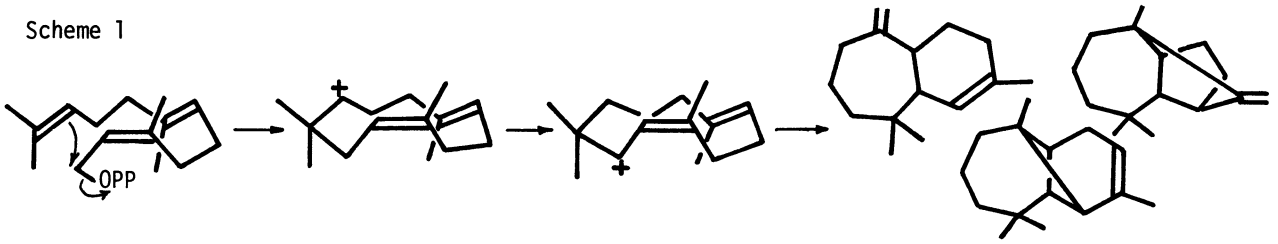
Haruhisa SHIRAHAMA,* Gurdial S. ARORA, and Takeshi MATSUMOTO
Department of Chemistry, Faculty of Science, Hokkaido University, Sapporo 060

Summary: (*Z*,*E*,*E*)-Humulene was prepared from (*E*,*E*)-6,7-epoxyhumula-2,9-dien-12-ol which was obtained from (*E*,*E*,*E*)-humulene 6,7-epoxide by oxidation with SeO$_2$-t-BuOOH.

Since Hendrickson's pioneering work$^{1)}$ suggested stereochemical course of sesquiterpene biogenesis, several groups of sesquiterpenes such as himachalene, longifolene, longipinene and so on have been considered to be derived from *cis*-farnesyl pyrophosphate through a protonated form of (*Z*,*E*,*E*)-humulene (Scheme 1). However, no information about the (*Z*,*E*,*E*)-humulene (6) has been available since it has not been found in nature and not synthesized so far. We would like to describe the first synthesis of the biogenetically important compound 6. The procedure consists of stereochemical inversion of Δ^2-double bond of natural (*E*,*E*,*E*)-humulene caused by selenium dioxide-t-butyl hydroperoxide oxidation of its allylic C-12 Me group$^{2)}$ and reduction of the allylic hydroxymethyl back to the original methyl group. This procedure must be generally useful$^{3)}$ for *trans* to *cis* inversion of double bonds bearing a methyl group in medium rings such as humulene, germacrene$^{4)}$ and other similar compounds.

Humulene 6,7-epoxide (1)$^{5)}$ was oxidized (1.2 mmol 1/1.2 mmol SeO$_2$/3 mmol t-BuO$_2$H/CH$_2$Cl$_2$/rt/6 h)$^{6)}$ to give three compounds (2: 60.7%, 3: 5.3%, 4: mp 100 102 °C; 19.6%).$^{7,8)}$ Aldehyde 4 was mostly isomerized to 3 on treatment with t-BuOK (DMSO/rt/30 min) and 3 was converted (LiALH$_4$/THF) to 2 quantitatively and thus yield of 2 was raised to 85% after all. Stereochemistry of Δ^2-double bond of 2 was inferred by the NMR spectrum. The signals due to C(2)-H of (*E*,*E*,*E*)-humulene and its oxygenated derivatives at hand showed always a triplet or a double doublet whose two coupling constants were fairly close while the corresponding signals of 2 showed a clearly separated double doublet (J=12 and 4 Hz). Moreover the spectrum of 2 at 400 Mz showed existence of two conformers (ca. 2:1) since two sets of signals inferring structure 2 were observed at r.t. and the two sets of signals combined to a broad signal at elevated temperature and exhibited again the same spectrum as original one after cooling. Such conformational separation was not observed in the spectra of (*E*,*E*,*E*)-humulene series. Restricted ring inversion of the (*Z*,*E*,*E*)-humulene ring could be realized by molecular model studies. Epoxide 2 was converted to olefinic alcohol 5$^{8)}$ (0.5 mmol 2/0.9 mmol LiAlH$_4$/0.19 mmol TiCl$_3$/THF/0 °C/15 min/under Ar,$^{9)}$ 90% yield) which was further reduced to (*Z*,*E*,*E*)-

Scheme 1



humulene (6)[8] (γ-collidine/LiCl/DMF/MsCl/0 °C/1.5 h,[10] and then $LiAlH_4$/THF/rt/overnight, 62.5% yield). ^1H and ^{13}C NMR spectra of 6 suited well to the assigned structure.

References 1) J. B. Hendrickson, Tetrahedron, 7, 82 (1959).

2) B. R. Chhabra, K. Hayano, T. Ohtsuka, H. Shirahama, T. Matsumoto, Chem. Lett., 1981, 1703.

3) Several methods are known[a] for inversion of double bond geometry. However, application of these methods to several methylsubstituted double bonds in medium rings gave usually poor results in our experience. Photochemical inversion of double bond geometry is a good method to make isocaryophyllene from caryophyllene[b] but irradiation of humulene did not give (Z,E,E)-humulene.[c] a) P. B. Dervon, M. A. Shippey, J. Am. Chem. Soc., 98, 1265 (1976), references cited threin. b) K. H. Schulte-Elte, G. Ohloff, Helv. Chim. Acta, 51, 548 (1968). c) E. J. Corey, E. Hamanaka, J. Am. Chem. Soc., 89, 2758 (1967).

4) Stereochemical inversion of a double bond in germacranoids were reported: M. Haruna, K. Ito, J. Chem. Soc., Chem. Commun., 1981, 483.

5) N. P. Damodaran, S. Dev, Tetrahedron, 24, 4123 (1968).

6) M. A. Unbreit and K. B. Sharpless, J. Am. Chem. Soc., 99, 5526 (1977).

7) Our assignment previously given to the oxidation product obtained from 1 under similar conditions[2] (trans Δ^2-) should be revised to cis-alcohol 2.

8) Satisfactory spectroscopic (IR, MS, NMR) data were obtained for all the new compounds except 3 which could not be obtained in good purity. NMR spectra were listed as follows. The spectra were measured in $CDCl_3$ Except those of 2 which were obtained in nitrobenzene-d_5 at 23 °C.

2: a) 1.05; 1.09; 1.32 (each 3H, s), 2.79 (1H, dd, J=11, 3), 4.39; 4.25 (2H, ABq, J=13), 5.49 (2H, bs), 5.76 (1H, dd, J=12, 4). b) 1.03; 1.08; 1.25 (each 3H, s), 2.72 (1H, dd, J=11, 3), 4.10; 4.20 (2H, ABq, J=13), 5.28 (1H, ddd, J=16, 8, 4), 5.36 (1H, d, J=16), 5.58 (1H, dd, J=12, 4).

4: 1.20; 1.21; 1.23 (each 3H, s), 5.24 (1H, d, J=16), 5.40 (1H, ddd, J=16, 10, 6), 6.28 (1H, t, J=8), 10.06 (1H, s).

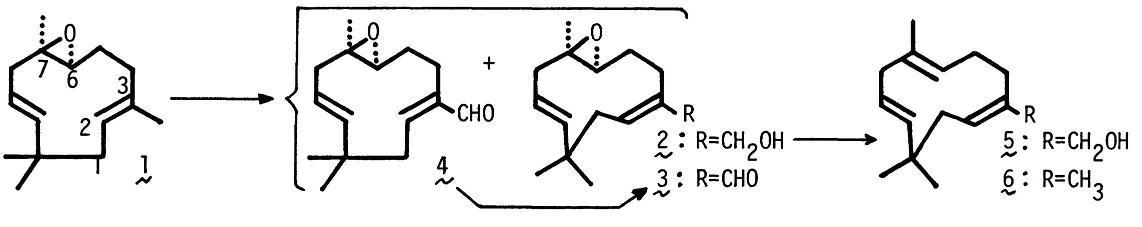
5: 1.06; 1.09; 1.56 (each 3H, s), 3.96; 4.13 (2H, ABq, J=12), 5.02 (1H, bt, J=8), 5.30 (1H, d, J=16), 5.48 (1H, dd, J=12, 4), 5.57 (1H, bt, J=16, 8).

6: 1.03; 1.05; 1.67 (each 3H, s), 1.58 (3H, d, J=1.5), 1.68 (1H, bd, J=13), 1.79 (1H, dt, J=12, 3), 1.90 (1H, t, J=13), 2.12 (1H, hidden), 2.22 (1H, tdd, J=13, 8, 2), 2.23 (1H, td, J=12, 3), 2.50 (2H, d, J=7), 5.03 (1H, bt, J=8), 5.18 (1H, bd, J=13), 5.33 (1H, d, J=16), 5.57 (1H, dt, J=16, 7).

^{13}C NMR: 16.30q, 22.37q, 22.88q, 24.34t, 27.53q, 30.26t, 36.60s, 40.23t, 42.08t, 121.85d, 123.70d, 124.89d, 133.57s, 138.59s, 141.58d.

9) J. E. McMurry, M. P. Fleming, J. Org. Chem., 40, 2555 (1975). The ratio $LiAlH_4/TiCl_3$ was modified in order to give best yield in this reduction. Otherwise it gave a mixture of hydrocarbons whose structure were obscrure.

10) E. W. Collington, A. I. Meyers, J. Org. Chem., 36, 3044 (1971).



(Received December 13, 1982)