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ACID CLEAVAGE OF HUMULENE 9,10-EPOXIDE. ANOMALOUS PRODUCTS AND EFFECTS OF STRAIN ON THE REACTION COURSE

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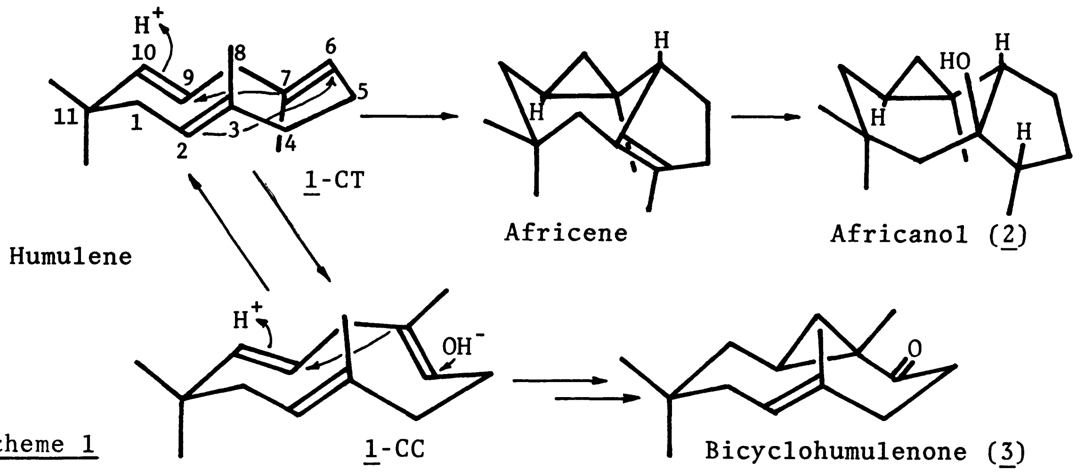
Summary On treatment of humulene 9,10-epoxide with $BF_3 \cdot OEt_2$ in AcOH, seemingly anomalous products 6-acetoxy-7-hydroxy-2,9-humuladiene and 6-acetoxy-2,7(13),9-humulatriene were obtained together with known compounds 2,9-diacetoxy-1,5,8,8-tetramethylbicyclo[8,1,0]undec-5-ene, 9-acetoxy-1,5,8,8-tetramethyltricyclo[8,1,0,0^{2,6}]undec-4ene and -5ene. The reaction course was well explained by the strain energy of four possible intermediates expected at the first stage of the transannular reaction.

Our current interest1) in biogenetic like cyclization of humulene (1) led us to examine the fate of humulen-9-yl cation generated by cleavage of humulene-9,10-epoxide (4).2) Humulene has been shown to have two stable conformations,3) CT and CC, from which two skeletally different cyclohumulanoids, africanol (2) and bicyclohumulenone (3) are biosynthetically derived1a) (Scheme 1). The chemical cleavage reactions under different conditions (TMSOTf in toluene and $BF_3 \cdot OEt_2$ in Ac_2O) of the epoxide 4 gave actually the two skeletally different compounds 9 and 11 which were converted to the two natural products, 3 and 2, respectively.1a)



Scheme 1

We wish to describe here the acid treatment of the humulene epoxide 4 under more polar conditions, which gave two anomalous acetates 14 and 16 together with 9 and 11, and a probable explanation of the reaction course.

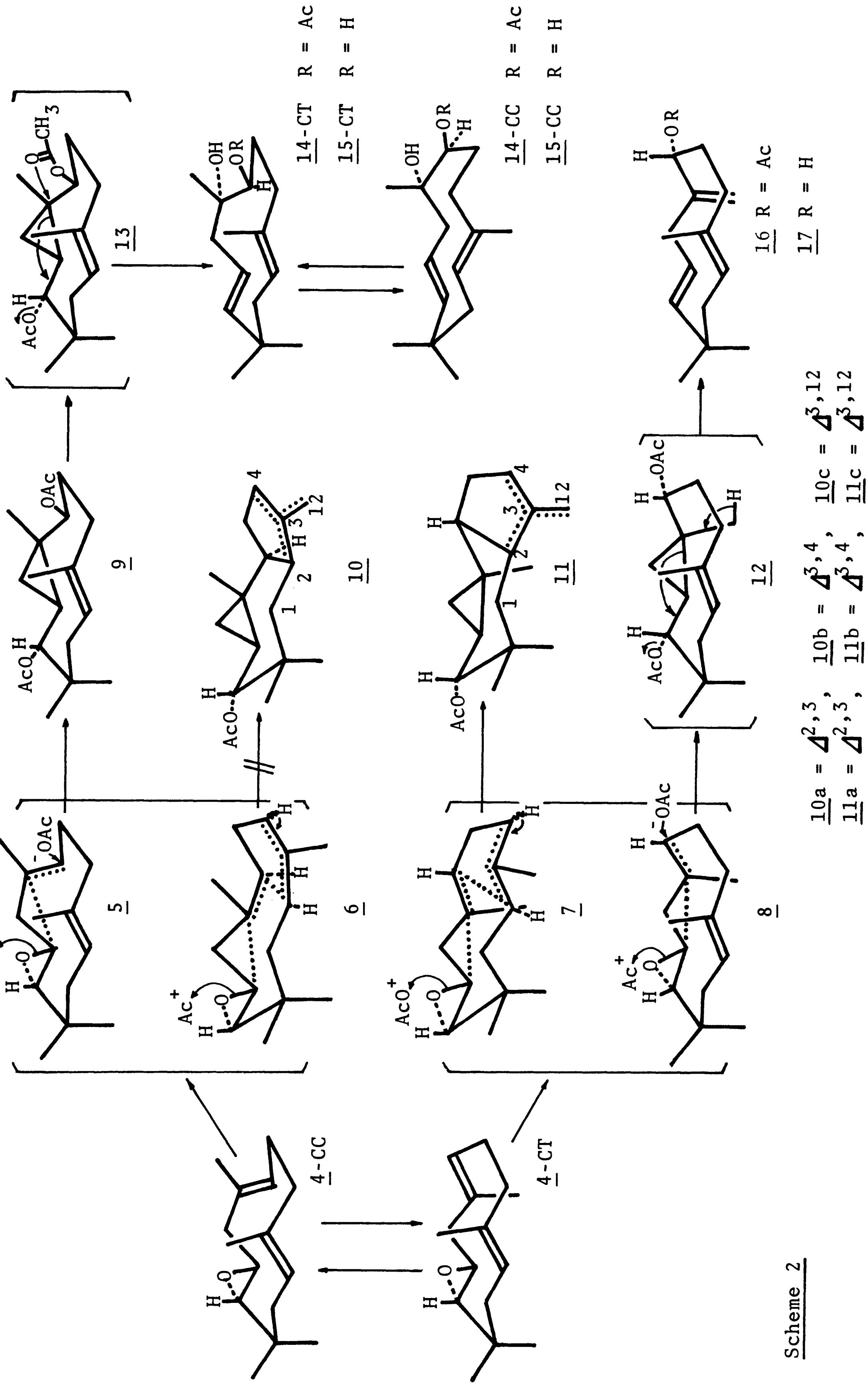
The epoxide 4 was treated with 1 eqv. of $BF_3\cdot OEt_2$ in AcOH under argon at ambient temperature for 15 min to give five compounds, 9[1a,4] (17.6%),[5] 14[4] (33.3%)[5] and a mixture of 11a,[1a,4] 11b[1a,4] and 16[4,6] (26,8%,[5] ratio[8]= 1:1:0.7). Prolongation of reaction time and/or using excess of $BF_3\cdot OEt_2$ increased the yield of 14 and decreased 9. Since 9 gave 14 under the same reaction conditions, 9 was probably an intermediate to 14. The diol monoacetate 14 was converted to a diol 15[9] which was identical with the product yielded by oxidation of humulene with OsO_4. It is interesting to note that both 9,10- and 6,7-epoxide[10] gave a common diol 15 by acid cleavage.[9] The stereostructure of 9 shows that 9 must be derived from the CC conformer of 4. Therefore, 14 is a CC mediated product. On the contrary, the acetate 16 was considered to be brought from 4-CT through a hypothetical intermediate 12 because even a small amount of 16 could not be obtained from 9 under the above reaction conditions. Since the tricyclic compounds 11a and 11b must originate from CT conformer of 4, the four pairs of conformer-product relationship is summarized as shown in Scheme 2.

In the above reaction mixture, the tricyclic compound 10 originating from 4-CC could not be identified. These results seem to be explicable on the basis of strain energy calculations of the expected initial products 9, 10, 11 and 12 (Table). It should be noted that the reaction in toluene (TMSOTf) and in Ac_2O ($BF_3\cdot Et_2O$) afforded selectively 4-CT and 4-CC mediated products respectively,[1a] while in AcOH the reaction proceeded through both the conformers. For the formation of 9, 12 and their related compounds (i.e. 14 and 16), the presence of a nucleophile such as AcO^- is necessary. In the reaction in toluene, since only weak nucleophile such as TfO^- is present, the C-6 cationic center would attack the intramolecular nucleophile C(2)=C(3), leading to either 10 or 11. Since 10 is calculated to be less stable than 11, only the latter is produced. In the reaction in Ac_2O, where highly nucleophilic AcO^- is available, the preferred reaction must be substitution leading to either 9 or 12. The acetate 9, calculated to be more stable than 12, becomes the main product. In the $AcOH/BF_3\cdot Et_2O$ system, the main nucleophilic species is much less reactive AcOH, and attack of the internal (C=C) and external (AcOH) nucleophiles to the cationic center (C-6) may take place to give 11 and 9, respectively.[11]

References and Notes

1) a) H. Shirahama, K. Hayano, Y. Kanemoto, S. Misumi, T. Ohtsuka, N. Hashiba, A. Furusaki, S. Murata, R. Noyori, and T. Matsumoto, Tetrahedron Lett., 21, 4835 (1980); b) S. Misumi, Y. Ohfune, A. Furusaki, H. Shirahama, and T. Matsumoto, ibid, 1976, 2865; c) Review for our works: H. Shirahama, Y. Ohfune, S. Misumi, and T. Matsumoto, J. Synth. Org. Chem., Japan, 36, 569 (1978), in Japanese.

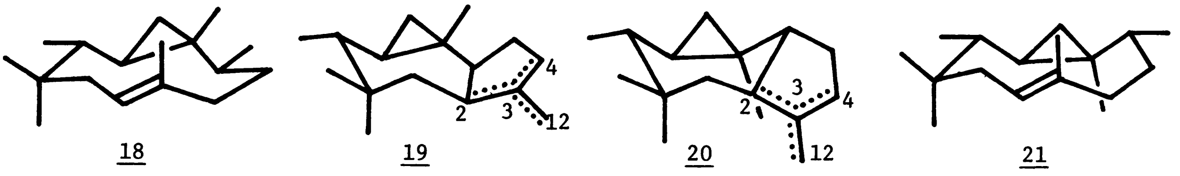
2) A. Sattar, J. Forrester, M. Moir, J.S. Roberts, and W. Parker, Tetrahedron Lett., 1976, 1403.


4-CC
4-CT
5
6
7
8
9
10
11
12
13
14-CT R = Ac
15-CT R = H
14-CC R = Ac
15-CC R = H
16 R = Ac
17 R = H
10a = Δ2,3, 10b = Δ3,4, 10c = Δ3,12
11a = Δ2,3, 11b = Δ3,4, 11c = Δ3,12
Ac+
AcO+
OAc
AcO
OR
OH
CH3
H
1
2
3
4
12

Scheme 2

Table Strain energy estimated by molecular mechanics calculations[12)]

compounds	18	19			20			21
		a	b	c	a	b	c	
strain, kcal/mol	46.8	52.85	50.19	52.89	42.66	42.51	47.04	49.00



18 19 20 21

a = $\Delta^{2,3}$, b = $\Delta^{3,4}$, c = $\Delta^{3,12}$

Model compounds of 9, 10, 11 and 12, in which acetoxyl groups are replaced by methyl groups.

3) H. Shirahama, E. Ōsawa, and T. Matsumoto, J. Am. Chem. Soc., 102, 3208 (1980).

4) Spectral data of all compounds are consistent with the structures depicted in the Scheme 2. NMR spectra were measured in CCl_4. 11a: δ 0.4~0.7 (3H, m), 0.84, 089, 0.93 (each 3H, s), 1.64 (3H, bs), 1.98 (3H, s), 4.57 (1H, m), 11b: δ 0.63 (3H, m), 0.88, 1.02, 1.08 (each 3H, s), 1.62 (3H, bs), 2.04 (3H, s), 4.55 (1H, dd, J=5.5, 2.5 Hz; virtual coupling), 5.28 (1H, bs). 14: δ 1.40 (6H, s), 1.19 (3H, s), 1.59 (3H, bs), 2.05 (3H, s), 5.10 (4H, m). 16: δ 1.05, 1.11 (each 3H), 1.61 (3H, bs), 1.96 (3H, s), 4.75~5.2 (5H, m). 9:See ref. 1a.

5) Estimation from vpc charts.

6) Acetate 16 was converted to the known humulenol-II (17).[7,10)]

7) J.M. Greenwood, M.D. Solomon, J.K. Sutherland, and A. Torre, J. Chem. Soc., C, 1968, 3004.

8) Estimation from nmr spectrum.

9) M.A. McKervey and J.R. Wright, Chem. Commun., 1970, 117; M. Namikawa, T. Murae, and T. Takahashi, Bull. Chem. Soc. Jpn., 51, 3616 (1978).

10) N.P. Damodaran and S. Dev, Tetrahedron, 24, 4113, 4123, 4133 (1968).

11) The most straightforward informations regarding the observed solvent dependence of product distribution should be available from the presumed transition states 5~8. Since the present version of MMI is not parameterized for half-bonds, we assumed they are close enough to the primary products 9~12, respectively. We restricted the comparison among the calculated stabilities within two pairs of closely related structure, 9/12 and 10/11.

12) The strain energies of the model compounds 18, 19, 20 and 21 for the compounds 9, 10, 11 and 12 respectively were calculated using Allinger's program (MMI, QCPE 318). For similar model calculations, see ref. 13.

13) P. Müller and J.C. Perlberger, J. Am. Chem. Soc., 98, 8407 (1976).

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