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CYCLIZATION REACTION THROUGH OXIRANE RING CLEAVAGE OF 9,10-EPOXYHUMULA-2,6-DIEN-13-AL. SELECTIVE FORMATION OF 3,6-SECOPROTOILLUDANE AND BICYCLOHUMULANE SKELETONS

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9,10-Epoxyhumula-2,6-dien-13-al gave 3,6-secoprotoilludane derivatives by treatment with TMSOTf and a bicyclohumulane derivative by $BF_3 \cdot OEt_2$ selectively in each case.

Recently biosynthetically patterned selective conversions of humulene 9,10-epoxide (1) to africanol (3) and bicyclohumulenone (4) were performed by trimethylsilyl triflate (TMSOTf) and $BF_3 \cdot OEt_2$ respectively by us[1] (Scheme 1). In these conversions, the reactions were initiated by attack of 6,7-double bond to C(9) cationic center to furnish cyclopropane derivatives. Among increasing number of cyclohumulanoids, gem-dimethylcyclopentane derivatives, such as illudins (5), coriolins (6) and pentalenolactones (7), which are constructed through C-C bond formation between C(2) and C(9) of humulene, are more common[2] and physiologically active, however. Formation of the C(2)-C(9) bond induced by cleavage of oxirane ring of humulene 9,10-epoxide was therefore attempted (path a of Scheme 2).

In order to achieve attack of 2,3-double bond to the C(9) cationic center, prevention of the attack of 6,7-double bond should be effective. 9,10-Epoxyhumula-2,6-dien-13-al (2) seemed to be suitable for this purpose.

The aldehyde 2[3] (mp 126-127°) was prepared from the epoxide 1 by SeO_2/$^tBuO_2H$ (45%)[4]. Geometry of the 6,7-double bond of 2 was confirmed as Z by reduction of 2 to the original epoxide 1 (1. $LiAlH_4$, 2. $MsCl/Et_3N/CH_2Cl_2$, 3. $LiAlH_4$). The epoxyaldehyde 2 was then treated with TMSOTf[5] in toluene at -20° for 2 h and the resulting mixture was desilylated with 0.1N-HCl/MeOH. The product was chromatographed on silica gel column to give two crystalline

hydroxy-aldehydes 13[3] (mp 119-120°; 31%) and 14[3] (mp 90-91°; 47%). The structure of 13 was revealed by coincidence of its acetate 15 with the compound derived from a known secoprotoilludane 17[6]. The other hydroxy-aldehyde 14 was also assigned to the hydroxysecoprotoilludadienal structure, since 14 showed in its nmr spectrum a doublet at δ 3.22 (J=8.5) due to a proton α to a hydroxyl group and the corresponding ketone 16[3] obtained by Collins oxidation of 14 exhibited an ir absorption at 1745 cm^{-1} due to a five membered ketone. E-Geometry of the 6,7-double bond of both aldehydes 13, 14 was uncovered in their nmr spectra by a triplet peak (J=5~7 Hz) due to an olefinic proton β to aldehyde group, since it was known that an trans-cyclooctene showed a double doublet peak (J=5, 11 Hz) due to an olefinic proton, while cis-isomer exhibited a triplet peak[7]. The geometry was probably changed through a species 18. The cyclization was thus successfully achieved as expected and gave synthetically useful functionalized 3,6-secoprotoilludane derivatives selectively.

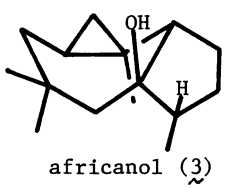
Contrary to the above results the aldehyde 2 was converted to a mixture of two cyclopropane derivatives 11[3] (mp 128-130°, 42%) and 9[3] (oil, 15%) on treatment with $BF_3 \cdot OEt_2$ in a mixture of Ac_2O and AcOH (5:1)[8] at -40° for 40 min and subsequent refluxing with Na_2CO_3 in MeOH-H_2O for 12 h. Structures of 11 and 9 were revealed by careful analysis of their nmr spectra and configurations were confirmed by close similarity of the spectra of 12[3] (acetate of 11) and 9 to those of the known compounds 10 and 8 respectively. A crude product of the BF_3-cleavage reaction showed nmr singlet signals at δ 6.7 and 6.8 before alkaline hydrolysis. This implied initial formation of the diacetylhydrate form ($-CH(OAc)_2$) of the aldehyde 2 and its subsequent cyclization. Therefore cyclopropane formation took place selectively in the same manner as observed in the previous reaction[1] of 1.

The reactions described here, are a further, but still rare example of reagent-dependent, regio- and stereoselective cyclization of humulene to skeletally different cyclohumulanoids.

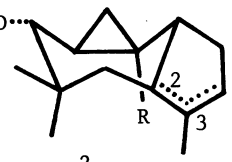
References

1) H. Shirahama, K. Hayano, Y. Kanemoto, S. Misumi, T. Ohtsuka, N. Hashiba, K. Furusaki, S. Murata, R. Noyori, T. Matsumoto, Tetrahedron Lett., 21, 4835 (1980).

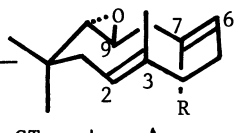
Scheme 1



africanol (3)



8 Δ^2, R = CH_3
9 Δ^3, R = CHO



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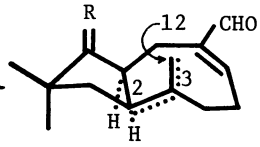
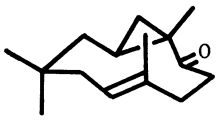
Scheme 2

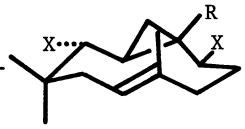
path a



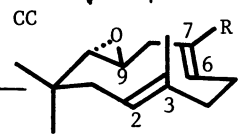
13 Δ^2, R = H, OH
14 $\Delta^{3,12}$, R = H, OH
15 Δ^2, R = H, OAc
16 $\Delta^{3,12}$, R = O



bicyclo-humulenone (4)



10 R = CH_3, X = OAc
11 R = CHO, X = OH
12 R = CHO, X = OAc



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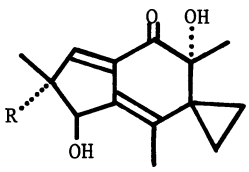
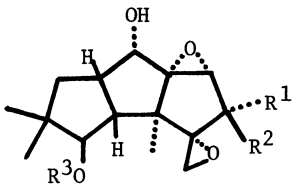
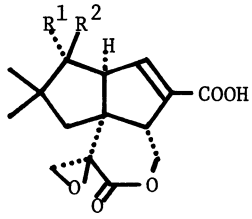
humulene 9,10-epoxide (1)
1 R = CH_3
2 R = CHO



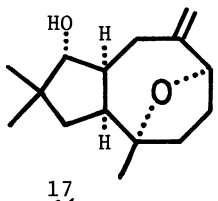
illudin (5)
M R = CH_3
S R = CH_2OH



coriolin (6)
A R^1= R^2= O, R^3= H
B R^1= OH, R^2= H, R^3= COC_7H_{15}
C R^1= R^2= O, R^3= $COCHOHC_6H_{13}$



pentalenolactone (7)
G R^1= R^2= O
H R^1= OH, R^2= H



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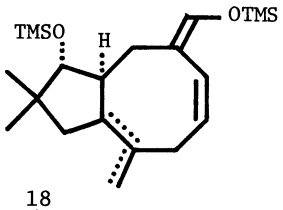

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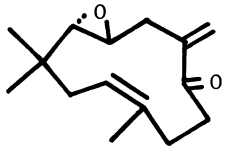

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2) See the footnote 5 of ref. 1.

3) Satisfactory spectral data were obtained for all new compounds. Nmr data are shown below. Unless otherwise stated, the nmr spectra were obtained on a 60 MHz instrument.

2: δ 0.71, 1.07 (each 3H, s), 1.54 (3H, bs), 5.0 (1H, dd, J=4, 9.5 Hz), 6.43 (1H, t, J=8.5 Hz), 10.1 (1H, s).

9: (400 MHz) δ 0.92 (1H, t, J=13 Hz), 0.95, 1.02 (each 3H, s), 1.07 (1H, dd, J=5, 7 Hz), 1.35 (1H, td, J=6, 9 Hz), 1.44 (1H, btd, J=10, 13 Hz), 1.63 (1H, t, J=7 Hz), 1.64 (3H, bs), 1.79 (1H, dd, J=3, 13 Hz), 2.23 (1H, bdd, J=10, 16 Hz), 2.78 (2H, bm), 3.32 (1H, d, J=9 Hz), 5.38 (1H, bs), 9.02 (1H, d, J=1.5 Hz).

11: (400 MHz) δ 1.06 (3H, s), 1.07 (3H, s), 1.34 (1H, dd, J=5.9 Hz), 1.52 (3H, bs), 1.65 (1H, dd, J=5, 7 Hz), 1.79 (1H, ddd, J=5, 8, 9 Hz), 1.83 (1H, bd, J=14 Hz), 1.93 (1H, tdd, J=3, 6, 14 Hz), 2.12 (1H, dt, J=3, 14 Hz), 2.21 (1H, dd, J=12, 14 Hz), 2.33 (1H, bd, J=14 Hz), 2.66 (1H, ddt, J=3, 11, 14 Hz), 2.87 (1H, bd, J=11 Hz), 3.36 (1H, d, J=5 Hz), 5.33 (1H, bd, J=12 Hz), 9.48 (1H, d, J=1.5 Hz).

12: (100 MHz) δ 0.92, 1.14, 1.56, 2.00, 2.05 (each 3H, s), 4.20 (1H, bd, J=10 Hz), 4.9 (1H, d, J=8 Hz), 5.37 (1H, bd, J=12 Hz), 9.36 (1H, s).

13: δ 0.9, 1.0 (each 3H, s), 1.58 (3H, bs), 6.66 (1H, t, J=5 Hz), 9.4 (1H, s).

14: δ 0.94, 1.10 (each 3H, s), 3.22 (1H, d, J=8.5 Hz), 4.85, 5.06 (each 1H, bs), 6.77 (1H, t, J=6.5 Hz), 9.37 (1H, s).

15: δ 0.89, 0.98, 2.15 (each 3H, s), 1.59 (3H, bs), 4.45 (1H, d, J=10 Hz), 6.60 (1H, t, J=5 Hz), 9.37 (1H, s).

16: δ 1.12, 1.16 (each 3H, s), 4.86, 4.94 (each 1H, s), 6.65 (1H, t, J=7 Hz), 9.30 (1H, s).

19: δ 0.69, 1.02 (each 3H, s), 1.61 (3H, bs), 5.0 (1H, dd, J=3, 9 Hz), 5.39, 5.78 (each 1H, s).

4) Besides 15% of ketone 19[3] was obtained. Oxidation with SeO_2-silica gel/$^tBuO_2H$ gave 9,10-epoxyhumula-2,6-dien-13-ol and -12, 13-diol in 4:6 ratio. See B. R. Chhabra, K. Hayano, T. Ohtsuka, H. Shirahama, T. Matsumoto, Chem. Lett., 1981, 1703.

5) R. Noyori, S. Murata, M. Suzuki, Tetrahedron, 23, 3899 (1981).

6) K. Sakai, T. Ohtsuka, S. Misumi, H. Shirahama, T. Matsumoto, Chem. Lett., 1981, 355. The conversion of 17 to 15 was carried out by the following series of reactions: 1. Me_3SiCl/imidazole, 2. Li/$EtNH_2$/THF, 3. CH_3I/NaH, 4. 1N-HCl/MeOH, 5. Ac_2O/Pyr, 6. $^tBuO_2H/SeO_2/CH_2Cl_2$, 7. HCO_2H. The procedure will be described in a full paper.

7) K. Hayano, Y. Ohfune, H. Shirahama, T. Matsumoto, Helv. Chim. Acta, 64, 1347 (1981).

8) The reaction employing Ac_2O singly as a solvent gave a complex mixture from which 18% of 11 was solely isolated.

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