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IN VITRO CONVERSION OF HUMULENE TO $\Delta^{8(13)}$-CAPNELLENE. CYCLOPROPANE SLIDING REACTION

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Summary: Tricyclic epoxide 7, derived from humulene 6,7-epoxide, underwent unusual rearrangement on treatment with TMSOTf to give an apparently methyl group migrated product 8 which was converted to a irregular isoprenoid hydrocarbon $\Delta^{8(13)}$-capnellene.

Capnellene (1) is the parent hydrocarbon of several oxygenated capnellanoids and is found in the soft coral Capnella imbricata.$^{1)}$ It is suggested that capnellene originates biogenetically from humulene whose C-13 methyl group moves from C-7 to C-8 during a cyclization reaction.$^{2)}$ However, the mechanism for this migration is not yet well understood. We should like to describe here chemical conversion of humulene to $\Delta^{8(13)}$-capnellene$^{3)}$ through an apparent methyl group migration.

Humulene 6,7-epoxide (2) had been nicely converted to tricyclic alcohol 3$^{4)}$ and the double bond of 3 has been hydrogenated ($H_2/PtO_2/AcOEt$) to give crystalline alcohol 4$^{5)}$ (mp 94～94.5°, 99%). Ketone 5$^{5)}$ (mp 45～45.5°), obtained 97%) by Jones oxidation of 4, was converted to tricyclic olefin 6$^{5)}$ by use of Shapiro's method$^{6)}$ (1. $TsNHNH_2/EtOH/pTsOH$/rfl./1 h, 2. n-BuLi/THF/rt/40 min; 85%). Oxidation of 6 with mCPBA ($CH_2Cl_2/NaHCO_3$aq/0°/2 h)$^{7)}$ gave a stereoisomeric mixture of epoxides 7$^{5)}$ (7a:7b=9:1 (vpc); almost quantitative) which was not stable enough to be separated through a silica gel column. α-Configuration of the oxirane ring of major product 7a was suggested by the configuration of the hydroxyl group of alcohols 8 and 9 given by the next reaction. The stereoisomeric mixture of epoxides 7 was subjected to rearrangement by treatment with TMSOTf$^{8)}$ in toluene at room temperature and desilylation with 1N-HCl to give three compounds, 8$^{5)}$ (mp 79～80°, 55%), 9$^{5)}$ (mp 81～82°, 24%) and 10$^{5)}$ (mp 63～64°, 8%). Structure of the main product 8 was deduced from nmr studies involving extensive decoupling experiment in the presence of $Eu(fod)_3$ and measurement of lanthanide induced shift values of several protons (Fig 1. Table 1). Migration of the methyl group could be explained by a process involving cyclopropane sliding mechanism$^{9)}$ (Scheme 2). On oxidation with pyridinium chlorochromate on alumina$^{10)}$, the alcohols 9 and also 10 afforded ketone 11$^{5)}$ (97% from 9 and 98% from 10) which gave back exclusively one of the original alcohols, **10** (99%), on reduction with L-selectride (THF/-78°). Ketone **12**[5] obtained by OsO_4-$NaIO_4$ oxidation of benzyl derivative of **9** (77% from **9**) exhibited the presence of a cyclobutanone (1785 cm^{-1}) in its IR spectrum. These observations and consideration of reaction course together with their nmr spectra suggested the structure of alcohols **9** and **10** for these alcohols.

The position of C-13 methyl group of **8** was properly arranged for conversion to capnellene. The double bond of **8** was saturated ($H_2/PtO_2/EtOH$;→**13**[5], mp 78∼79°, 98%) and the hydroxyl group of the saturated alcohol **13** was inverted to β-(**14**,[5] mp 71∼72°) by successive oxidation (Jones Reagent; **15**,[5] 98%) and reduction (L-selectride/THF/-78°, 97%). Rearrangement of the β-alcohol **14** to capnellene skeleton was accomplished by solvolysis of its mesylate (1. 2 eq MsCl/CH_2Cl_2/DMAP/0°→rt/20 min, 2. NaOAc/AcOH/70∼80°/6 h) and a mixture of acetate **16**[5] (42%) and olefin **19**[5] (51%) was obtained. The acetate **16** was converted to the olefin **19** by elimination of the acetoxyl group (1. $LiAlH_4/Et_2O$:→**17**,[5] mp 76∼77°, 99%; 2. MsCl/DMAP; 3. Basic Alumina: **19**, 77% from **17**). The ketone **18**[5] furnished through oxidation of alcohol **17** exhibited the presence of cyclopentanone in its ir spectrum (1745 cm^{-1}).

Isomerization of the olefin **19** into Δ^{7}-capnellene[11] **20** was carried out employing rhodium catalyst[12] ($RhCl_3$/EtOH/rfl/15 min, 92%). The spectral data of **20** coincided with those reported in literature.[11] Transposition of the double bond of **20** from endo- to exo-position was achieved by treatment of tertiary alcohols (**21** and **22**), prepared from **20** (1. mCPBA/CH_2Cl_2/$NaHCO_3$aq/0°/2 h,[7] 2. $LiAlH_4$/THF/rt/10 h, **21**[5] (α-OH)[13] (mp 87∼87.5°, 50%), **22**[5] (β-OH)[13] (23%)), with a mixture (1:1) of 1,1,2,3,3,3-hexafluoropropyl diethyl amine and 1,2,3,3,3,-pentafluoropropenyl diethyl amine (HFPDEA).[14] Refluxing a mixture of α-alcohol **21** and 5 equivalents of HFPDEA in THF for 2 h afforded 50% of $\Delta^{8(13)}$-capnellene **1** and 37% of original Δ^{7}-capnellene **20**. A similar treatment of β-alcohol **22** yielded 17% of **1** and 73% of **20**. Synthetic $\Delta^{8(13)}$-capnellene **1** was spectrally identical with the natural product.

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References and Notes

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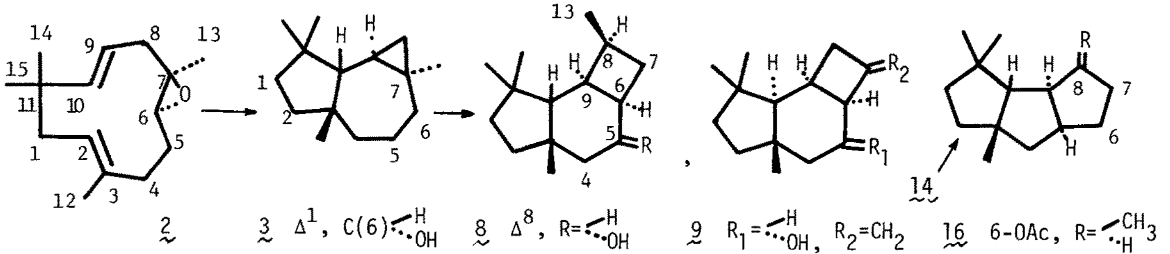
Scheme 1



2

3 Δ^1, C(6)${<}^{H}_{\cdots OH}$

4 C(6)${<}^{H}_{\cdots OH}$

5 C(6)=0

6 · Δ^5

7 · 5,6-epoxy

7a · 5,6-α-epoxy

8 Δ^8, R=${<}^{H}_{\cdots OH}$

13 R=${<}^{H}_{\cdots OH}$

14 · R=${<}^{OH}_{\cdots H}$

15 R=0

9 R_1=${<}^{H}_{\cdots OH}$, R_2=CH_2

10 R_1=${<}^{OH}_{\cdots H}$, R_2=CH_2

11 · R_1=0, R_2=CH_2

12 R_1=${<}^{H}_{\cdots OBz}$, R_2=0

16 6-OAc, R=${<}^{CH_3}_{\cdots H}$

17 6-OH, R=${<}^{CH_3}_{\cdots H}$

18 6=0, R=${<}^{CH_3}_{\cdots H}$

19 Δ^6, R=${<}^{CH_3}_{\cdots H}$

20 Δ^7, R=—CH_3

21 R=${<}^{CH_3}_{\cdots OH}$

22 R=${<}^{OH}_{\cdots CH_3}$

1 R=CH_2

Scheme 2

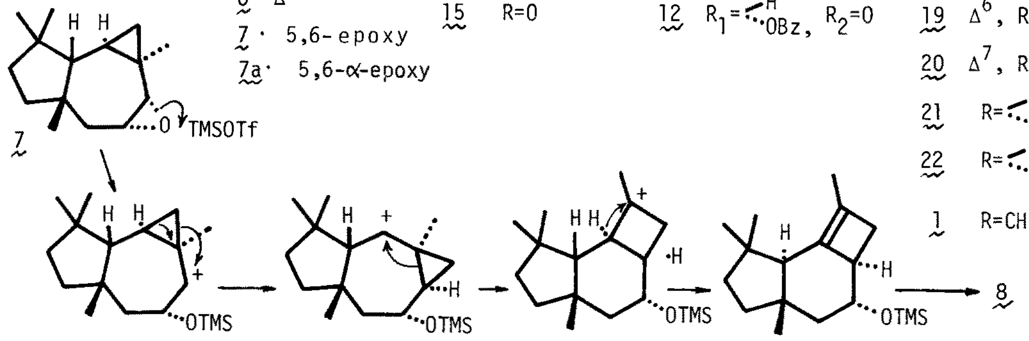
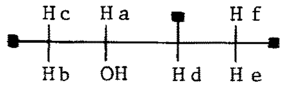


Fig. 1.

The following partial structure of 8 was revealed by nmr studies Chemical shifts and coupling constants are shown below. (60 and 100 MHz, $CDCl_3$, Eu(fod)$_3$, Eu/8=0.38)



a(5β) 11.97, b(4α) 7.70, c(4β) 6.67, d(6α) 8.28, e(7α) 5.49, f(7β) 4.97. J(ab)=11, J(ac)=4, J(ad)=9, J(bc)=12, J(de)=0, J(df)=4 Hz.

Table 1.

Lanthanide induced shift values (Δδ/([Eu]/[substrate])) for protons of alcohol 8.

5β	21.9	12 Me	3.89
6α	14.8	14(15) Me	2.33
4α	13.9	13 Me	2.11
4β	12.7	15(14) Me	1.78
7α	8.33		
7β	5.89		

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5) Pertinent spectral data for all of new compounds are given below. Nmr spectra were measured in $CDCl_3$.

4 ir(nujol) 3260, 3086/cm, nmr δ 0.09~0.95(3H, m), 0.99, 1.09(each 3H, s), 1.01(6H, s), 3.34(1H, dd, J=10, 6.5 Hz)

5 ir(CCl_4) 1714, 1679/cm, ir(KBr) 1703/cm, nmr δ 0.94, 1.29(each 3H, s), 1.07(6H, s).

6 ir(neat) 3015, 3060/cm, nmr δ 0.55~0.93(3H, m), 1.00, 1.10(each 3H, s), 1.11(6H, s), 5.60(2H, m)

7a nmr δ 0.1~0.9(3H, m), 1.08, 1.10, 1.13, 1.17(each 3H, s), 3.02(1H, ddd, J=9, 4.5, 3.5 Hz), 3.04(1H, d, J=3.5 Hz).

8 ir(nujol) 3380/cm, nmr δ 0.97, 0.99, 1.01(each 3H, s), 1.57(3H, bs), 3.48(1H, ddd, J= 11, 9, 4 Hz).

9 ir(nujol) 3370, 3090, 880/cm, nmr δ 0.84, 1.00, 1.18(each 3H, s), 3.90(1H, ddd, J=11.5, 8, 5 Hz), 4.75, 4.92(each 1H, bs).

10 ir(nujol) 3410, 3070, 888/cm, nmr δ 0.78, 1.00, 1.13(each 3H, s), 3.99(1H, ddd, J=11, 7, 5 Hz), 4.94(2H, bs).

11 ir(neat) 3090, 1714, 886/cm, nmr δ 0.76, 1.02, 1.25(each 3H, s), 2.20(1H, dd, J=13.5, 1 Hz), 2.62(1H, d, J=13.5 Hz), 4.87, 4.98(each 1H, bs).

12 ir(neat) 1785/cm, nmr δ 0.94, 1.07, 1.09(each 3H, s), 4.50, 4.70(each 1H, ABd, J=12 Hz), 7.30(5H, s).

13 ir(nujol) 3360/cm, nmr δ 0.82, 0.98, 1.16(each 3H, s), 1.01(3H, d, J=6.5 Hz), 3.73(1H, ddd, J=11.5, 8, 3.5 Hz).

14 ir(nujol) 3300/cm, nmr δ 0.76, 0.93, 1.16(each 3H, s), 1.00(3H, d, J=6 Hz), 3.87(1H, m)

15 ir(neat) 1717/cm, nmr δ 0.93, 1.00, 1.12(each 3H, s), 0.95(3H, d, J=6 Hz), 2.14, 2.34 (each 1H, ABd, J=12 Hz).

16 ir(neat) 1745, 1244/cm, nmr δ 0.95(3H, d, J=6 Hz), 0.95, 0.99, 1.14, 1.98(each 3H, s), 4.80(1H, bt, J=3 Hz).

17 ir(nujol) 3360/cm, nmr δ 0.97, 1.00, 1.12(each 3H, s), 0.95(3H, d, J=7 Hz), 3.93(1H, bt, J=3 Hz).

18 ir(neat) 1745/cm, nmr δ 1.01(6H, s), 1.22(3H, d, J=6 Hz), 1.47(3H, s).

19 ir(neat) 3020/cm, nmr δ 0.96(6H, s), 1.06(3H, d, J=7 Hz), 1.08(3H, s), 5.48(2H, m)

21 ir(nujol) 3340/cm, nmr δ 1.00(6H, s), 1.20, 1.30(each 3H, s)

22 ir(neat) 3515/cm, nmr δ 0.95, 1.06(each 3H, s), 1.22(6H, s).

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13) Configuration of the hydroxy group was determined by the lanthanide induced shift nmr spectrum of **21**. At Eu(fod)$_3$/**21**=0.4, δ 8.88(1H, t, J=6 Hz, S=15.0, 9α), 7.44 (1H, ddd, J=12, 8, 1 Hz, S=13.5, 7α), 6.98(1H, ddddd, J=9, 8, 6, 3, 1 Hz, S=10.3, 5α), 6.95 (3H, s, S=12.4, 13Me), 6.46(1H, ddt, J=10, 8, 9 Hz, S=10.3, 6α), 5.44(1H, dt, J=12, 9 Hz, S=8.6, 7β), 4.70(1H, d, J=6 Hz, S=7.5, 10β), 3.88(1H, ddt, J=10, 9, 1 Hz, S=5.6, 6β), 3.45 (1H, dd, J=13, 8 Hz, S=3.9, 4α), 3.24(1H, dd, J=13, 3 Hz, S=3.9, 4β), 2.70(3H, s, S=3.75, Me), 2.56(3H, s, S=3.33, Me), 2.24(3H, s, S=2.78, Me)

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