Lead Tetraacetate Oxidation of Humulene and Conformational Analysis of the Produced Humulatrienediols

Haruhisa SHIRAHAMA,* Kiyoharu HAYANO, Gurdial Singh ARORA, Eiji ŌSAWA and Takeshi MATSUMOTO

Department of Chemistry, Faculty of Science, Hokkaido University, Sapporo 060

(Received February 12, 1983)

Humulene was oxidized by lead tetraacetate in benzene to give 2,5,9-humulatrien-7-ol acetate and 1,5,9-humulatriene-3,7-diol diacetates. Conformational analysis of 1,5,9-humulatriene-3,7-diols was performed by NMR spectroscopy and molecular mechanics calculations.

Oxidation of the double allylic methylene group (C-8) of humulene (**1**) was previously attempted by Sukh Dev[1] in order to make a conversion of humulene to zerumbone (8-ketohumulene)(**2**). The oxidation seemed to be facile. However, even by using various reagents it was practically so difficult that the conversion was not fruitful. We also tried the oxidation of humulene and all of attempts at oxidizing C-8 methylene group of humulene were unsuccessful. The conversion to zerumbone was recently achieved through a roundabout way after all.[2] During these studies, a rather clean oxidation reaction of humulene by lead tetraacetate was realized.[3] The reaction could be applicable to syntheses and modifications of humulanoids.

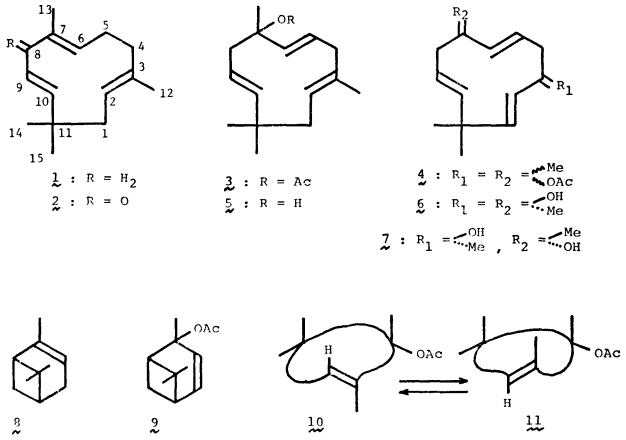
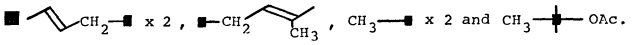


Fig. 1.

Humulene (1 mol) was treated with 1 mol of lead tetraacetate in benzene at 70 °C to give an acetate **3** (45%) and a diastereoisomeric mixture of diacetates **4** (23%). Oxidation with 3 mol of the reagent afforded the mixture of diacetates **4** exclusively. The ^{1}H NMR spectrum of the acetate **3** in the presence of a shift reagent (LIS-^{1}H NMR) (Table 1) showed that following partial structures were there in the molecule:



They led us readily to figuring formula **3**. The ^{13}C NMR and MS spectra also supported the formula. On treatment with $LiAlH_4$ the acetate **3** gave an alcohol **5** whose ^{1}H NMR spectrum was identical to that of the compound obtained also through oxidation of humulene by Matsubara *et al.*[3b,4]

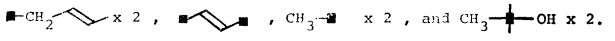
The mixture of diacetates **4** first seemed to be a single compound whose structure was presumed to be **4** by its ^{1}H NMR and molecular weight referring to the structure of monoacetate **3**. It was, however, found to be a mixture of two diacetates (1:1) after converting it to corresponding alcohols which could be separated by chromatography. Both diols **6** and

Table 1. ^{1}H NMR spectra of the compounds **3**, **6**, and **7** in the presence of Eu(fod)$_3$

Compound [Eu]/[S] proton	**3** 0.22 δ	**6** 0.30 δ	S[b]	**7** 0.44 δ	S[b]
14, 15	1.2(3H, s) 1.24(3H, s)	1.74(3H, s) 1.98(3H, s)	1.5 2.6	2.18(6H, s)	2.4
12[a]	1.8(3H, s)	3.85(3H, s)	8.8	4.70(3H, s)	8.1
13[a]	3.43(3H, s)	4.08(3H, s)	8.9	4.74(3H, s)	8.3
8	2.72(2H, d, J=7 Hz)	4.41(1H, dd, J=13, 9 Hz) 5.14(1H, dd, J=13, 5 Hz)	8.6 10.1	5.84(1H, dd, J=12, 7 Hz) 6.59(1H, dd, J=12, 7 Hz)	9.1 10.8
4	3.4(1H, dd, J=7, 14 Hz) 4.05(1H, dd, J=7, 14 Hz)	4.92(1H, dd, J=15, 10 Hz) 5.78(1H, dd, J=15, 5 Hz)	9.4 11.4	6.05(1H, dd, J=12, 6 Hz) 6.84(1H, dd, J=12, 6 Hz)	9.1 11.2
10	5.40(1H, dd, J=15 Hz)	6.74(1H, d, J=16 Hz)	5.3	7.18(1H, d, J=16 Hz)	5.1
9	5.82(1H, dt, J=15, 7 Hz)	7.13(1H, ddd, J=16, 9, 5 Hz)	5.1	7.70(1H, dt, J=16, 7 Hz)	6.8
1	2.1(2H, d, J=8 Hz)	8.33(1H, d, J=16 Hz)	8.9	8.63(1H, d, J=16 Hz)	8.3
6	7.29(1H, d, J=16 Hz)	7.88(1H, d, J=15 Hz)	9.6	9.26(2H, d, J=16 Hz)	8.3
2	5.40(1H, t, J=8 Hz)	7.9(1H, d, J=16 Hz)	10.0		
5	6.74(1H, dt, J=16, 7 Hz)	8.02(1H, ddd, J=15, 10, 5 Hz)	11.3	9.63(1H, dt, J=16, 6 Hz)	11.5
Ac	4.20(3H, s)				

a) Assignment to 12 and 13 alternates for **6** and **7**. b) LIS values=$\Delta\delta$/[Eu]/[substrate].

7 exhibited the same M^+ by high resolution MS and their ^1H NMR spectra were so similar that these were implied to be stereoisomers. LIS-^1H NMR revealed that the both diols **6** and **7** and the following structural fragments:



Assembling these parts on a humulene skeleton gave readily formula **6** or **7** except stereochemistry. Relative configuration of the two hydroxyl groups was deduced from LIS value ($\Delta\delta$/[Eu]/[Substrate]). The compound whose *gem*-dimethyl group shifted separately by addition of the shift reagent, namely, **6** was assigned to a *cis*-diol and the other one showing equivalent shift for each of the *gem*-dimethyl groups was allotted to a *trans*-diol.

The mode of lead tetraacetate oxidation of olefinic compounds is not uniform but the above reaction followed the one that exhibited by the oxidation of α-pinene (**8**→**9**).[5] Reaction of 6,7-double bond first took place and then the oxidation of 2,3-double bond followed. The ratio (1:1) of formation of the diastereoisomeric diacetates **6** and **7** could be regarded as a support[6] for equal existence of two stable conformers (**10** and **11**) of the acetate **3** because three *trans* double bonds must have been placed perpendicular to the 11-membered ring and attack of reagent must have been made from outside of the ring.

Conformational Analysis of 1,5,9-Humulatriene-3,7-diol. The coupling constants of methylene protons of **6** were not averaged and suggested that the compound existed either in a predominant conformation or in an equilibrium among several conformations. Strain energy and population for each of eight possible conformations[7] of **6** were thus estimated by means of molecular mechanics calculations.[8] Analysis of possible conformers for **6** followed our previous work[9] in which the conformations of humulene were fully analysed. Arrangement of three double bonds of **6** in cycloundecane ring was the same as those of humulene itself (1,4,8-undecatriene) and thus basic four conformations of humulene (CT, CC, TC, and TT)[9] were modified by proper substitutions (Fig. 2). Energy minimization of the eight conformers were successfully achieved to give their precise geometries and strain energies (Table 2). The conformation *RRR*-CC[10] was found to be most stable and the compound **6** was suggested to be equilibrated mostly among three conformers (*RRR*-CC, *SSS*-CC, and *RRS*-TC). The coupling constants (J_{AC}, J_{BC}, J_{DF}, and J_{EF}) (see Fig. 2) allotted to partial structures, $C(4)H_2C(5)H$= and $C(8)H_2$–$C(9)H$–, were

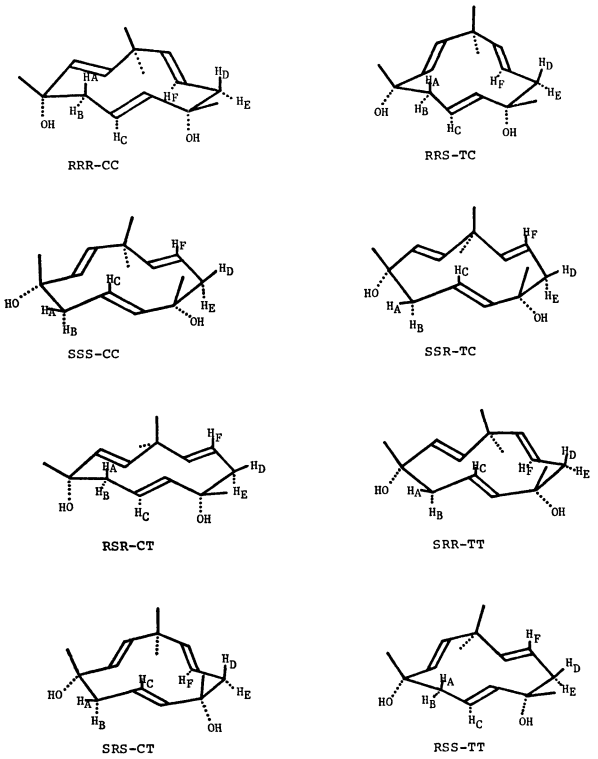


Fig. 2. Eight possible conformations of (3*S*,7*S*)-(*E*,*E*,*E*)-1,5,9-humulatriene-3,7-diol.

TABLE 2. DIHEDRAL ANGLES, RELATIVE STRAIN ENERGY, AND POPULATION FOR EIGHT POSSIBLE CONFORMATIONS OF (3*S*,7*S*)-(*E*,*E*,*E*)-1,5,9-HUMULATRIENE-3,7-DIOL

Dihedral angles	*RRR*-CC	*SSS*-CC	*RRS*-TC	*SSR*-TC	*RSR*-CT	*SRS*-CT	*RSS*-TT	*SRR*-TT
1-2=3-4	−175.3	176.7	−176.9	174.6	−174.2	174.4	−173.8	168.3
2=3-4-5	106.5	−97.2	114.0	−120.2	111.1	−100.8	114.8	−112.3
3-4-5-6	−45.9	40.2	−40.0	45.1	−36.6	33.4	−26.6	27.6
4-5-6-7	125.8	−124.4	110.7	−100.5	−91.4	99.1	−85.0	101.0
5-6=7-8	−174.6	175.8	−116.6	169.9	167.4	−168.6	168.7	−175.4
6=7-8-9	51.1	−49.7	75.8	−95.7	−70.3	64.0	−62.4	47.9
7-8-9=10	51.0	−51.0	−98.0	69.0	93.0	−100.0	−76.4	50.8
8-9=10-11	−174.7	175.3	170.6	−167.9	−169.9	170.7	169.7	−174.9
9=10-11-1	126.1	−124.1	−61.6	95.4	100.7	−89.1	−64.7	104.8
10-11-1-2	−47.1	−42.9	−41.7	37.4	−47.7	42.4	−35.7	27.8
11-1-2=3	106.2	−110.7	119.4	−109.0	120.9	−124.6	129.2	−113.3
2=3-4-OH	−12.2	146.5	−5.1	123.7	−8.1	142.7	−2.9	131.1
9=10-11-OH	8.1	119.7	−179.8	−22.8	−17.1	154.8	179.5	−14.5
Relative strain / kcal mol^{-1}	0.00	1.01	0.73	2.72	1.87	3.42	3.32	3.84
Population/%	65.2	11.8	19.0	0.7	2.8	0.2	0.2	0.1

Table 3. Dihedral angles calculated for $-CH_2-CH=$ moieties and estimated and observed J values

		H_A-4 -5-H_C	H_B-4 -5-H_C	H_D-8 -9-H_F	H_E-8 -9-H_F
RRR-CC	*a*	167.9	52.6	−172.6	68.7
	J	12	4	12	1
	J'	7.8	2.6	7.8	0.7
SSS-CC	*a*	−58.0	−172.9	−70.7	172.3
	J	3	12	1	12
	J'	0.4	1.4	0.1	1.4
RRS-TC	*a*	176.7	60.8	176.1	58.2
	J	13	3	13	3
	J'	2.5	0.6	2.5	0.6
SSR-TC	*a*	−57.7	−173.7	−52.0	−166.2
	J	3	12	4	12
	J'	0.0	0.1	0.0	0.1
RSR-CT	*a*	−178.4	63.2	−43.6	−158.5
	J	13	2	6	11
	J'	0.4	0.1	0.2	0.3
SRS-CT	*a*	−70.8	172.8	161.1	46.9
	J	1	12	11	6
	J'	0.0	0.0	0.0	0.0
RSS-CT	*a*	−169.9	71.7	−39.3	−152.8
	J	12	1	7	10
	J'	0.0	0.0	0.0	0.0
SRR-TT	*a*	−64.0	179.1	158.6	46.2
	J	2	13	10	6
	J'	0.0	0.0	0.0	0.0
	J_{calcd}	11.0	4.8	10.6	2.8
	J_{obsd}	10	5	9	5

a: Dihedral angles for the moieties indicated in the first line. *J*: *J* values estimated for the dihedral angles shown in the upper line. *J'*: Contributing fraction = *J* × population.

obtained from the estimated conformations referring Karplus relationship.[11] Weighted averages (sum of each conformer's *J* × population) of the calculated *J* values well coincided with observed values (Table 3).

The coupling constants of methylene protons of **7** were averaged and indicated that this compound was freely mobile and did not exist in a particular stable conformation. The different situation between the two diastereoisomers, **6** and **7**, may be readily understood since in **6** two methyl groups at C(3) and C(7) will take equatorial-like orientation while in **7** the both will take always opposite (equatorial- and axial-like) orientations each other.

Experimental

Melting point was uncorrected. IR spectra were measured with JASCO IR-S spectrometer. ^1H NMR and ^{13}C NMR spectra were recorded on a HITACHI R20B (60 MHz) and a JEOL JNM FX-100 (25 MHz) instrument using TMS as an internal standard respectively. High resolution mass spectra were measured on a JEOL JMS D-300 mass spectrometer.

*Lead Tetraacetate Oxidation of Humulene (**1**).* To a stirred mixture of $Pb(OAc)_4$ (1.2 g, 2.71 mmol) and dry benzene (20 ml) was added a solution of humulene (500 mg, 2.45 mmol) in benzene (10 ml) under argon. The mixture was stirred at 65—70 °C for 8 h and washed with water, aqueous $NaHCO_3$ solution and brine. The benzene solution was dried over Na_2SO_4 and evaporated under reduced pressure to leave paste. The crude product was chromatographed on a silica-gel column using hexane, 5% Et_2O-hexane and 13% Et_2O-hexane in turn as eluents to give an acetate **3** (289 mg, 45%) and a diasteroisomeric mixture of diacetates **4** (180 mg, 23%) which was not separable on TLC and VPC.

*(E,E,E)-2,5,9-Humulatrien-7-ol Acetate (**3**)*: IR (neat) 1745, 1245, and 965 cm^{-1}; ^1H NMR δ=1.0, 1.02, and 1.99 (each 3H, s), 1.59 (6H, s), 2.4—2.8 (3H, m), and 4.8—5.9 (5H, complex); ^{13}C NMR δ=17.6(q), 22.0 (q), 22.3 (q), 26.4 (q), 27.4 (q), 38.9 (s), 40.5 (t×2), 47.3 (t), 82.8 (s), 120.2 (d), 123.6 (d), 129.1 (d), 134.3 (d), 137.9 (s), 143.5 (d), and 169.6 (s). Found: *m/z* 262.1924. Calcd for $C_{17}H_{26}O_2$: M, 262.1926.

*(E,E,E)-1,5,9-Humulatriene-3,7-diol Diacetates (**4**)*: IR (neat) 1745, 1240, and 965 cm^{-1}; ^1H NMR δ=1.19 (6H, s), 1.51 (3H, bs), 1.58 (3H, s), 1.95, 1.96 (each 3H, s), and 4.9—5.7 (6H, complex). Found: *m/z* 320.2026. Calcd for $C_{19}H_{28}O_4$: 320.1980.

*(E,E,E)-2,5,9-Humulatrien-7-ol (**5**).* A solution of the acetate **3** (29 mg) in dry THF (1 ml) was stirred with $LiAlH_4$ (8 mg) at 0 °C under argon. The reaction was followed by TLC. After completion of the reaction, aqueous NH_4Cl solution was added and the mixture was extracted with ether three times. The combined extracts were dried (Na_2SO_4) and evaporated to leave an oil **5** (23 mg, 95%) which was purified by chromatography (silica gel, 5% AcOEt-hexane): IR (neat) 3420, 1660, 1110, and 965 cm^{-1}; ^1H NMR δ=1.03 and 1.37 (each 3H, s), 1.65 (3H, d, *J*=1 Hz), 1.94 (2H, d, *J*=8 Hz), 2.55 (2H, d, *J*=7 Hz), 5.05 (3H, m), 5.33 (1H, d, *J*=16 Hz), and 5.73 (1H, dt, *J*=16 and 7 Hz). Found: *m/z* 220.1815. Calcd for $C_{15}H_{24}O$: 220.1821.

*(E,E,E)-1,5,9-Humulatriene-*cis*-3,7-diol (**6**) and (E,E,E)-1,5,9-Humulatriene-*trans*-3,7-diol (**7**).* A solution of the diacetates **4** (40 mg) in dry THF (0.5 ml) was added to a well stirred slurry of $LiAlH_4$ (15 mg) and dry THF (0.5 ml) at 0 °C under argon. After completion of the reaction (checked by TLC), an excess of the $LiAlH_4$ was decomposed by addition of ice-water and extracted with EtOAc three times. The combined extracts were dried and evaporated to give 30 mg (quantitative) of paste which was shown to be a mixture (1:1) of two diols by its NMR spectrum. The mixture was separated by chromatography on a silica-gel column using a mixed solvent of hexane and ether (4:1) to afford a pair of diastereomeric diols **6** and **7**.

*Diol **6***: Mp 124—125 °C, IR ($CHCl_3$) 3640, 3480, 1090, and 970 cm^{-1}; ^1H NMR δ=1.18, 1.22, 1.28, and 1.35 (each 3H, s), 1.66—2.6 (6H, m), 5.08 and 5.46 (2H, ABq, *J*=16 Hz), and 5.1—5.5 (4H, m). Found: *m/z* 236.1772, Calcd for $C_{15}H_{24}O_2$: 236.1777.

*Diol **7***: Colorless oil, IR ($CHCl_3$) 3640, 3480, 1090, and 970 cm^{-1}; ^1H NMR δ=1.18 (6H, s), 1.27 and 1.33 (each 3H, s), 1.9—2.5 (6H, m), and 4.8—5.6 (6H, m). Found: *m/z* 236.1763. Calcd for $C_{15}H_{24}O_2$: 236.1777.

We thank Prof. Y. Matsubara (Kinki University) for sending ^1H NMR spectrum of compound **5**.

References

1) N. P. Damodaran and Sukh Dev, *Tetrahedron Lett.*, **1965**, 1977.

2) H. Shirahama, B. R. Chhabra, and T. Matsumoto,

Chem. Lett., **1981**, 717.

3) a) "Many of the reactions of lead tetraacetate with olefin systems are characterized by complex mixture of products which often render these reactions of little synthetic value." R. N. Butler, "Lead Tetraacetate" in "Synthetic Reagents," ed by J. S. Pizey, Ellis Horwood Ltd., Chichester, England (1977), Vol. 3, Chap. 4, p. 288; b) In fact, humulene gave many oxidation products by use of lead tetraacetate in acetic acid: H. Iwamuro, M. Hashimoto, and Y. Matsubara, *Nippon Nogei Kagaku Kaishi*, **55**, 793 (1981).

4) They have given the same structure as ours to their compound without showing any supporting data and without discussing the geometry of rearranged double bond (Δ^5).

5) G. H. Witham, *J. Chem. Soc.*, **1961**, 2232.

6) This is not real evidence, of course. However, a medium size cyclopolyolefin reserves often its stable conformation during the reactions. K. Takeda, *Tetrahedron*, **30**, 1525 (1974); J. K. Sutherland, *ibid*, **30**, 1651 (1974); P. D. Cradwick and G. A. Sim, *J. Chem. Soc., D*, **1971**, 31; F. H. Allen, E. D. Brown, D. Rogers, and J. K. Sutherland, *ibid*, **1967**, 1116; R. M. Gipson, H. W. Guin, S. H. Simonsen, C. G. Skinner, and W. Shive, *J. Am. Chem. Soc.*, **88**, 5366 (1966).

7) Their enantiomers were not considered.

8) Allinger's program "MMI" was used. QCPE 318. N. L. Allinger; J. T. Sprague, and J. Liljefors, *J. Am. Chem. Soc.* **96**, 5100 (1974); D. H. Wertz and N. L. Allinger, *Tetrahedron* **30**, 1579 (1974).

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

10) A prefix RRR represents the chiralities of the three double bonds, $\Delta^{1,2}$, $\Delta^{5,6}$, and $\Delta^{9,10}$, in this order. Conformations only for 3*S*,7*S*-diol were considered here.

11) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, Oxford (1969), Chap. 4-2.