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(Z,E,E)-HUMULENE. CONFORMATIONAL ANALYSIS AND TRANSANNULAR CYCLIZATION

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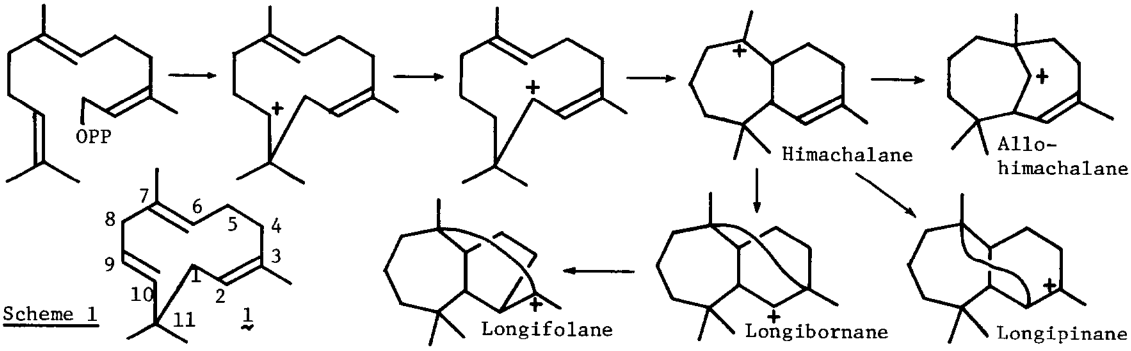
Summary: Geometries and populations for four possible conformers of (Z,E,E)-humulene (**1**) were obtained by molecular mechanics calculations. Treatment of **1** with mercury salt gave 3,7-epoxy-3,6-secoprotoilludane (**3**) and 9,10-epoxide of **1** afforded tetramethylbicyclo[7.2.0]-undecadienols (**10**,**11**) on treatment with TMSOTf.

Not a small number of sesquiterpenes having versatile carbon framework such as himachalane, longipinane, longibornane and so forth have been considered to be biogenetically derived from cis-farnesyl pyrophosphate through a protonated form of (Z,E,E)-humulene (**1**) (Scheme 1).[1] However, no information about **1** has been available since it has not been found in nature and not synthesized so far. Recently we reported the first synthesis of this biogenetically important compound.[2] In this paper we wish to describe conformational analysis and chemical cyclization of **1**.

Conformational analysis of **1** was carried out in the same procedure as that used in the analysis of (E,E,E)-humulene (**2**).[3] The results obtained by molecular mechanics calculations[4] were shown in Table 1. Among four strain minimum conformers, TT, CT, TC and CC,[5] only small differences of strain were observed and every conformer was supposed to be present in a conformational equilibrium mixture. (Z,E,E)-Humulene was revealed to be a little more strained than its (E,E,E)-isomer referring to their averaged heats of formation (6.41 and 4.42 Kcal/mol respectively). Separated signals due to gem-dimethyl group (δ 1.03 and 1.05) in the ^1H NMR spectrum (400 MHz) suggested that ring inversion was restricted at room temperature and (Z,E,E)-humulene could be resolvable. Vicinal J values assigned to three fragments, -C(1)H_2-C(2)H=, -C(4)H_2-C(5)H_2-C(6)H= and C(8)H_2-C(9)H= well coincided with values calculated by the Karplus equation based on the dihedral angles in the four strain minimum conformers (Table 2).



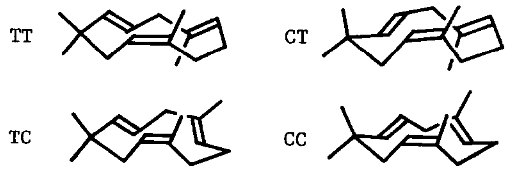
Scheme 1

Cyclization reaction of **1** was performed by mercuric salt. Oxymercuration-demercuration of **1** (1. 170 mg **1**/850 mg $Hg(NO_3)_2 \cdot xH_2O$/4 ml THF-H_2O (1:1)/rt/30 min. 2. 95 mg $NaBH_4$ at pH 10/0 °C /30 min→rt/1.5 h) followed by chromatographic purification gave a crystalline ether **3** (185 mg, 57%, mp 40-41 °C) whose configuration was disclosed as follows. High resolution MS showed molecular formula $C_{15}H_{26}O$ and IR absorption (1050 cm^{-1}) revealed that the oxygen formed ether function. Extensive decoupling experiments in ^1H NMR (400 MHz) indicated the existence of moieties shown in Fig 1a which reminded us of ether **4** previously obtained by us in the similar treatment of **2**.[7)] However, ^1H NMR of **3** was clearly different from that of the ether **4**. Taking accounts of the vicinal coupling J_{2-9}=6 Hz, the five membered ring should be fused to the bicyclo[3.3.1]nonane framework in <u>cis</u> manner. Calculated[8)] dihedral angles for **3**[9)] well suited the observed J values (Table 2).

Another cyclization reaction of (Z,E,E)-humulene ring was achieved with epoxide **5** which was prepared from (Z,E,E)-humulen-12-al 6,7-epoxide (**9**)[2)] through four steps (**9**→**8**:[6)] mCPBA, 91%;→**7**:[6)] $NaBH_4$, 96%;→**6**:[6)] $TiCl_3$/LAH, 82%;→**5**:[6)] MsCL/collidine/LiCl, $LiAH_4$, 95%). Treatment of the epoxide **5** with TMSOTf (1: 53 mg **5** / 2 ml toluene/0.08 ml 2,6-lutidine/80 mg TMSOTf/10 ml hexane/-20 °C/1.5 h. 2: 0.15 g KF/5 ml MeOH) followed by chromatographic separation of the products employing $AgNO_3$ inpregnated silica gel afforded crystals A (21 mg, 40%; mp 87-88 °C) and paste B (18 mg, 34%). Both of the products have the same molecular formula $C_{15}H_{24}O$ (high resolution MS) and showed an absorption band due to a hydroxy group in IR(3650 cm^{-1}). They showed ^1H NMR peak, a doublet, assigned to a proton α to an hydroxy group (H+OH) also in common. The compound A displayed in ^1H NMR an olefinic methyl group and an exomethylene group, while B exhibited two olefinic methyl groups. These observations suggested that the oxirane ring of **5** was cleaved between C(9) and the oxygen and one of two double bonds (Δ^2 or Δ^6) in humulene ring probably attacked at C(9) to form a new bond. Thus A could be represented by the formula **10** or **12** and B by **11** or **13**. Collins oxidation of A and B gave ketones C and D respectively whose IR indicated the presence of a carbonyl group in a larger than six membered ring (C: 1700, D: 1715 cm^{-1}). Extensive decoupling experiment in ^1H NMR at 400 MHz revealed the existence of three moieties (Fig 1b) in C and four moieties (Fig 1c) in D. These NMR data demonstrated clearly that structure of C should be depicted by **14**, consequently A by **10** except the stereochemistry at C(6) and B must be figured as **15** hence D as **11**. Stereochemistry of **14**, namely of **10**, could not be determined straightforword since the coupling constant between two protons arranged vicinally on cyclobutane remains always around 7 Hz regardless of their geometrical relationship (<u>cis</u> or <u>trans</u>). It was then

<u>Table 1</u>

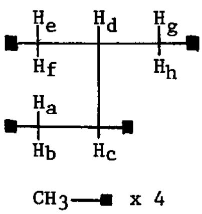
		TT	CT	TC	CC
Dihedral angles	1--2==3--4[a)]	0.3[b)]	1.8	-1.2	0.7
	2==3--4--5	117.4	117.5	104.4	112.8
	3--4--5--6	-59.0	-56.9	-63.1	-63.8
	4--5--6==7	-90.4	-107.2	120.2	105.2
	5--6==7--8	163.2	168.8	-174.1	-164.5
	6==7--8--9	-86.2	-48.9	39.9	78.9
	7--8--9==10	82.9	-38.5	51.9	-87.4
	8--9==10--11	-165.4	176.2	-169.1	166.0
	9==10--11--1	97.0	-126.7	106.9	-99.5
	10--11--1--2	55.9	65.8	51.5	66.4
	11--1--2==3	-116.5	-104.8	-120.0	-117.5
ΔH_f[c)]		6.29	6.36	6.42	6.71
populations (%)		31.4	27.9	25.2	15.5



a) The symbol == denotes a double bond.
b) A positive dihedral angle in an assembly 1-2-3-4 denotes a clockwise rotation of plane 2,3,4 with respect to the reference plane 1, 2,3 when viewing the assembly from 2 to 3.
c) Heats of formation in Kcal/mol (25 °C, gas).

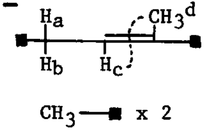
determined as follows. Precise geometries and strain energies of four strain minimum conformations[10)] possible for each of cis and trans isomers (about C(6)/C(9)) of 14 were obtained by molecular mechanics calculations.[8)] The observed coupling constants of all of vicinal protons fitted unambiguously to those calculated for the trans isomer (Table 2).

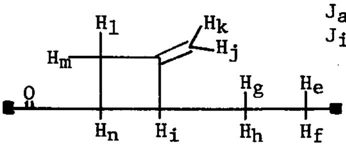
Fig 1 a



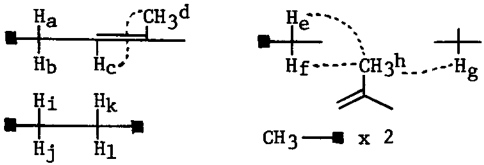
Me=0.96, 1.10(x2), 1.13, a=1.38, b=1.74, c=1.86, d=2.69, e=1.71, f=1.14, g=1.51, h=1.31
J_{ab}=12, J_{ac}=6, J_{bc}12, J_{cd}=6, J_{de}=8, J_{df}=1.5, J_{ef}=13, J_{dg}=7, J_{dh}=13, J_{gh}=13, J_{hi} (long range)=2

b





c



Me=0.99, 1.17, a=2.59, b=1.80, d=1.51, e=2.0～2.18, f=2.42, g=3.99, i=1.65, j=2.25, k=2.0～2.18, l=2.16
J_{ab}=13, J_{ac}=11, J_{bc}=6, J_{ef}=12, J_{ij}=13, J_{ik}=8, J_{il}=2, J_{jk}=0, J_{jl}=9

Me=0.89, 1.15, a=1.61, b=2.55, c=5.20, d=1.45, e=2.55, f=1.57, g=1.47, h=1.85, i=2.85, j ⟷ k=4.74 ⟷ 4.73, l=3.16, m=2.39, n=3.10
J_{ac}=12, J_{bc}=6, J_{eg}=6, J_{eh}=12, J_{fg}=2, J_{fh}=6, J_{gh}=12, J_{gi}=12, J_{hi}=6, J_{ij}=2, J_{ik}=2, J_{im}=2, J_{in}=7, J_{jl}=2, J_{jm}=2, J_{kl}=2, J_{km}=2, J=$_{lm}$=14, J_{ln}=7, J_{mn}=7

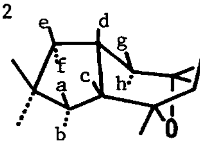
Broken lines(-----) show the presence of spin coupling which were revealed by decoupling experiments but J value could not be determined.

Table 2 Calculated and observed J values of vicinal protons for compounds 1, 3 and 10

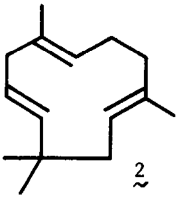
For 1	J_{calcd} TT	CT	TC	CC	J_{av}*	J_{obs}	For 14	$J_{av-calcd}$*,10) trans	cis†	J_{obs}	For 3	J_{calcd}	J_{obs}
H-C(1)-C(2)-H	3	5	2	3	3.3	4	H-C(1)-C(2)-H	10.4	7.5	12	a-C-C-c	5	6
H'-C(1)-C(2)-H	12	10	12	12	11.5	12	H'-C(1)-C(2)-H	5.4	9.6	6	b-C-C-c	13	12
H-C(4)-C(5)-H	3	3	3	2	2.8	3	H-C(4)-C(5)-H	5.1	7.3	6	c-C-C-d	7	6
H-C(4)-C(5)-H'	12	12	12	12	12.0	12	H-C(4)-C(5)-H'	2.9	6.2	2	d-C-C-e	11	8
H'-C(4)-C(5)-H	3	3	3	3	3.0	3	H'-C(4)-C(5)-H	10.0	4.4	12	d-C-C-f	0	1.5
H'-C(4)-C(5)-H'	3	3	2	2	2.5	-	H'-C(4)-C(5)-H'	5.1	7.3	6	d-C-C-g	6	7
H-C(5)-C(6)-H	10	12	2	3	7.4	8	H-C(5)-C(6)-H	4.6	12.0	6	d-C-C-h	11	13
H'-C(5)-C(6)-H	6	3	12	11	7.4	8	H'-C(5)-C(6)-H	12.2	3.5	12			
H-C(8)-C(9)-H	7	0	11	10	6.6	7							
H'-C(8)-C(9)-H	9	9	3	6	7.0	7							

† configurational relations at C(6)/C(9).

* Calculated J values for each conformer multiplied by population of the conformer and all of the values for four conformers were added to give weighted averages of calculated J values.



3'



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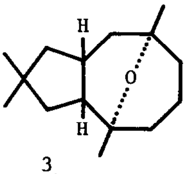
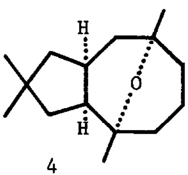


3



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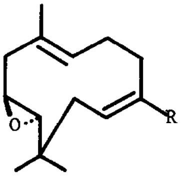
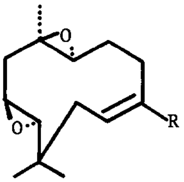
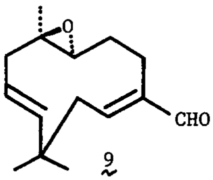


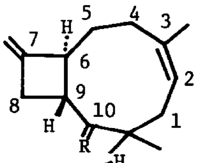
5 R=CH_3
6 R=CH_2OH



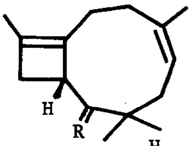
7 R=CH_2OH
8 R=CHO



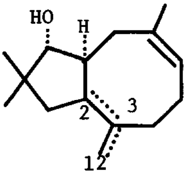
9



10 R= H ··OH 14 R=O



11 R= H ··OH 15 R=O



12 Δ3,12
13 Δ2,3

In both of the above transannular cyclization, biogenetic like 1,3-hydride shift (from C(1) to C(10)) was not observed. Mercuric salt induced transannular cyclization of 1 proceeded in a similar manner as observed in the case of 2. Difference of the geometry of C(2) double bond in the starting material resulted in the difference in stereochemistry of the product (see 3 and 4). The reaction of the epoxide 5 initiated by oxirane ring cleavage demonstrated a new mode of cyclizations, that is, formation of C(6)-(9) bond. The product 10 must have stemed from TT and/or CC coformers of 5. The bicyclic skeleton obtained here has not been found in nature yet but it might be found in future if (*Z*,*E*,*E*)-humulene is operative in cyclohumulanoid biosynthesis.

References and Notes

1) W. Parker, J. S. Roberts, R. Ramage, Quart. Rev., 21, 331 (1967); T. K. Devon, A. I. Scott, "Handbook of Nat. Occurr. Compd." vol. II, Academic, New York, 1972, p 57.
2) H. Shirahama, G. S. Arora, T. Matsumoto, Chem. Lett., 281 (1983).
3) H. Shirahama, E. Ōsawa, T. Matsumoto, J. Am. Chem. Soc., 102, 3208 (1980).
4) The program MMI (QCPE 318) was used. N. L. Allinger, J. T. Sprague, J. Liljefors, J. Am. Chem. Soc., 96, 5100 (1974).
5) Nomenclature: see ref. 3.
6) Satisfactory spectroscopic (IR, MS, NMR) data were obtained for all the new compound. NMR spectra were listed as follows. The spectra were measured in CDCl$_3$.
   5: δ 0.67(3H, s), 1.13(3H, s), 1.69(6H, s), 2.45(1H, d, J=3), 2.95(1H, ddd, J=9, 4, 3), 5.17(1H, bt, J=8), 5.38(1H, bd, J=12).
   6: δ 0.70(3H, s), 1.18(3H, s), 1.70(3H, d, J=1), 2.42(1H, d, J=2.5), 2.98(1H, ddd, J=9, 4, 2.5), 4.07(2H, bs), 5.16(1H, bt, J=8), 5.70(1H, dd, J=12, 3).
   7: δ 0.75(3H, s), 1.18(3H, s), 1.38(3H, s), 4.10(bs), 5.63(bt, J=10).
   8: δ 0.88(3H, s), 1.24(6H, bs), 6.58(1H, bd, J=12), 9.40(1H, s).
   10: δ 0.88, 1.12(each 3H, s), 1.25(1H, b), 1.62(2H, bm), 1.69(3H, bs), 2.00(3H, bs), 2.28 (2H, bs), 2.58(2H, bm), 2.73(1H, ddt, J=16, 8, 2), 3.36(1H, d, J=8), 4.68(1H, q, J=2), 4.71(1H, q, J=2), 5.29(1H, bt, J=8).
   11: δ 0.90, 1.07(each 3H, s), 1.63(6H, bs), 1.90(1H, bd, J=12), 1.94(1H, dd, J=14, 8), 2.14(1H, bd, J=12), 2.40(4H, m), 2.73(2H, m), 3.31(1H, d, J=10), 5.23(1H, dd, J=12, 4).
7) S. Misumi, T. Ohtsuka, H. Hashimoto, Y. Ohfune, H. Shirahama, T. Matsumoto, Tetrahedron Lett., 35 (1979).
8) The program MM2' was used. This was originally made by Allinger and improved by C. Jaime and E. Ōsawa, Tetrahedron in press.
9) The 9-oxabicyclo[3.3.1]nonane part can take chair-chair, chair-boat and boat-boat conformations but the population of 3' was so predominant (99%) that only 3' was taken into account.
10) The combination of two factors determining the conformation of 14 (direction of Δ^2 double bond plane and a dihedral angle around C(4)-C(5)) claimed four conformations for each of the *cis* and *trans* isomers. But one of them had so shallow energy minimum that it changed easily to the more stable conformer during calculations8) and three conformers for each of *cis* and *trans* isomers were obtained. (To be published in detail.)

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