# Transannular Cyclization Reaction of Humulene 2,3-Epoxide. Formation of a Compound Shaping TC Conformer

Kiyoharu Hayano* and Haruhisa Shirahama†
*Chemistry Laboratory, Hokkaido College of Education, Ainosato, Sapporo 002*
†*School of Science, Kwansei Gakuin University, Uegahara, Nishinomiya 662*

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Treatment of humulene 2,3-epoxide (**5**) with boron trifluoride etherate at 0° C gave (6E)-(1R*,2R*,3S*,10R*)-3-acetoxy-2,5,5-trimethylbicyclo[8.1.0]undeca-6,9(15)-diene and (4E)-(1S*,2S*,8S*,9S*)-2,8-diacetoxy-2,6,6,9-tetramethylbicyclo[7.2.0]undec-4-ene which corresponded to the transannular bond formation products shaping the CT and TC conformers of **5**, respectively.

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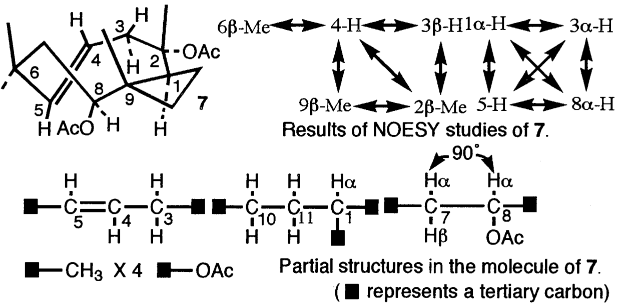
We previously reported that humulene (**1**) has four strain minimum conformers, CT, CC, TT, and TC in the following population, 52%, 37%, 11%, and 0.2%, respectively.[1,2] From our studies on the cleavage reactions of humulene 9,10-epoxide (**2**) using TMSOTf/toluene and $BF_3 \cdot OEt_2/Ac_2O$, africanol (**3**) and bicyclohumulenone (**4**) were obtained through the conformationally selective transannular cyclization of the most stable two conformers, CT and CC, respectively (Scheme 1).[3-5] In other word, the two stable conformers, CT and CC, were frozen in the molecules of **3** and **4**. The less stable two conformers, TC and TT, have not been trapped so far. In this report we describe the formation of a compound shaping TC conformer, (4E)-(1S*, 2S*, 8S*, 9S*)-2,8-diacetoxy-2,6,6,9-tetramethylbicyclo[7.2.0]undec-4-ene (**7**), together with a frozen CT conformer, (6E)-(1R*, 2R*, 3S*, 10R*)-3-acetoxy-2,5,5-trimethylbicyclo[8.1.0]undeca-6,9(15)-diene (**6**), as a result of the cleavage reaction of humulene 2,3-epoxide (**5**)[6] employing the $BF_3 \cdot OEt_2/Ac_2O$ system.

Treatment of the epoxide **5** at 0 °C for 25 min with 0.76 eq. of $BF_3 \cdot OEt_2$ in $Ac_2O$ under argon gave a crude monoacetate **6** (8.2%), a crystalline diacetate **7** (13.3%, mp 87-89°), unchanged **5** (20%), and a complex mixture of more polar compounds (39%). Two COSY (H-H and C-H) and $^{13}C$ DEPT spectra of the diacetate showed the existence of the partial structures depicted in Figure 1. The possible combination of these fragments, probable reaction course and NOESY studies (Figure 1) suggested that the stereostructure of the diacetate was represented by formula **7**.[7]

The crude monoacetate product was subjected to hydrolysis, benzoylation, and separation by HPLC (μPORASIL: 5% EtOAc/hexane) to afford a benzoate **8** (4.6% from **5**)[8]. The high resolution mass and IR spectra of this compound showed the molecular formula $C_{22}H_{28}O_2$ and C=O absorption band (1740 $cm^{-1}$), respectively. H-H and C-H COSY studies of the benzoate **8** revealed the existence of the partial structures depicted in Figure 2 and showed value of 0 Hz for three coupling constants ($J_{3\alpha-4\beta}$, $J_{3\alpha-2\alpha}$, and $J_{2\alpha-1\alpha}$). On the bases of these results, three dihedral angles of 3αH-4βH, 3αH-2αH, and 2αH-1αH were expected to be about 90° by the Karplus relation and coincided with those deduced from the molecular model of **8**, of which the NOE analysis supported its configuration shown in Figure 2. Therefore, the structure and configuration of the monoacetate containing three-membered ring are expressed by formula **6**.

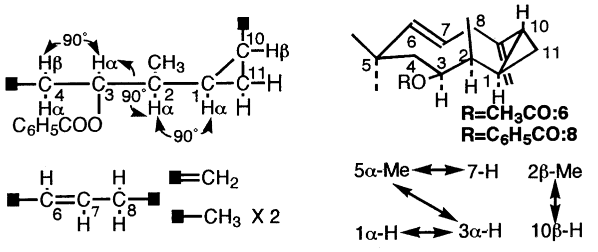
Assuming the four stable conformers, CT, CC, TC, and TT, also to be effective for the epoxide **5** like humulene (**1**) itself, compound **7** should be obtained by the transannular cyclization of **5** CC followed by rotation of the disubstituted 9,10-double bond. The stereochemistry of the present transannular reaction is reasonably postulated as Scheme 2. Compound **7** is the first compound shaping TC conformer of humulene.



Results of NOESY studies of **7**.

Partial structures in the molecule of **7**.
(■ represents a tertiary carbon)

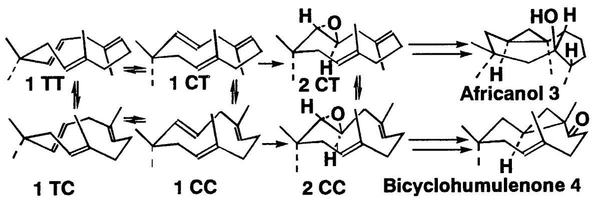
**Figure 1.**



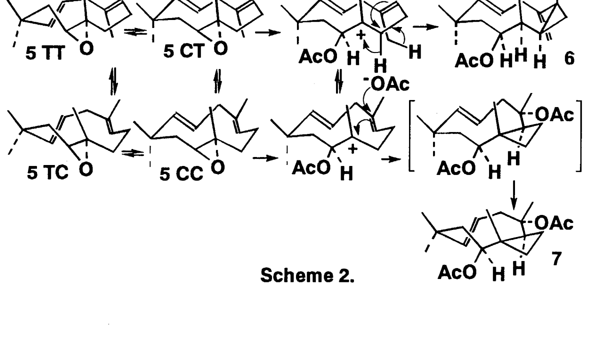
Partial structures in the molecule of **8**.
(■ represents a tertiary carbon)

Studies of NOE spectrum of **8**.

**Figure 2.**



**Scheme 1.**



**Scheme 2.**

## References and Notes

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7 $^1$H NMR ($CDCl_3$, 270 MHz) δ 1.07 (3H, 6β-Me), 1.16 (3H, s, 9β-Me), 1.21 (3H, s, 6α-Me), 1.16 (1H, d, $J_{7\alpha\beta}$=14.2 Hz, 7α-H), 1.39 (1H, dd, $J_{10\beta\alpha}$=18.2, $J_{10\beta-11\beta}$=8.6 Hz, 10β-H), 1.43 (3H, s, 2β-Me), 1.53 (1H, m, 11β-H), 1.55 (1H, m, 10α-H), 1.76 (1H, m, 11α-H), 1.92, 1.96 (each 3H, s, 2α and 8β-OAc), 2.00 (1H, dd, $J_{7\beta\alpha}$=14.2, $J_{7\beta-8\alpha}$=9.2 Hz, 7β-H), 2.61 (1H, dd, $J_{3\beta\alpha}$=11.6, $J_{3\beta-4}$=4.6 Hz, 3β-H), 2.78 (1H, dd, $J_{3\alpha\beta}$=11.6, $J_{3\alpha-4}$=11.2 Hz, 3α-H), 2.97 (1H, dd, $J_{1\alpha-11\alpha\beta}$=7.9, 11.5 Hz, 1α-H), 4.88 1H, d, $J_{8\alpha-7\beta}$=9.2 Hz, 8α-H), 5.28 (1H, ddd, $J_{4-3\beta\alpha}$=4.6, 11.2, $J_{4-5}$=16 Hz, 4-H), 5.86 (1H, d, $J_{5-4}$=16 Hz, 5-H) ppm; $^{13}$C NMR ($CDCl_3$, 270 MHz) δ 18.09 (q, 9β-Me), 18.42 (t, 10-C), 21.15, 22.39 (each q, 2 and 8-OAc), 22.67 (q, 2β-Me), 28.43 (q, 6α-Me), 29.04 (q, 6β-Me), 31.36 (t, 11-C), 32.83 (s, 6-C), 42.91 (t, 3-C), 49.15 (s, 9-C), 49.27 (d, 1-C), 49.45 (t, 7-C), 80.43 (d, 8-C), 92.60 (s, 2-C), 124.44 (d, 4-C), 144.94 (d, 5-C), 169.88 (s, C=Ox2) ppm; HRMS Calcd for $C_{19}H_{30}O_4$: M, 322.2145. Found: m/z 322.2178.

8 $^1$H NMR ($CDCl_3$, 270 MHz) δ 0.32 (1H, m,11$_\alpha$ or β-H), 0.57 (1H, m, 1α-H), 0.75 (3H, d, $J_{2\alpha-12}$=7.3 Hz, 2β-Me), 0.78 (1H, m, 11β or α-H), 1.07 (3H, s, 5β-Me), 1.07 (1H, m, 10β-H), 1.19 (3H, s, 5α-Me), 1.51 (1H, d, $J_{4\alpha\beta}$=14.5 Hz, 4α-H), 2.14 (1H, dd, $J_{4\beta\alpha}$=14.5, $J_{4\beta-3\alpha}$=8.9 Hz, 4β-H), 2.34 (1H, q, $J_{12-2\alpha}$=7.3 Hz, 2α-H), 2.75 (1H, dd, $J_{8\beta\alpha}$=12.8, $J_{8\beta-7}$=9.6 Hz, 8β-H), 2.95 (1H, dd, $J_{8\alpha\beta}$=12.8, $J_{8\alpha-7}$=4.6 Hz, 8α-H), 4.71 and 4.52 (each 1H, s, 15-$CH_2$), 5.20 (1H, d, $J_{3\alpha-4\beta}$=8.9 Hz, 3α-H), 5.26 (1H, ddd, $J_{7-8\alpha}$=4.6, $J_{7-8\beta}$=9.6, $J_{7-6}$=15.8 Hz, 7-H), 5.43 (1H, d, $J_{6-7}$=15.8 Hz, 6-H), 7.40-8.04 (5H, m, benzoyloxyl group) ppm; $^{13}$C NMR ($CDCl_3$, 270 MHz) δ 5.32 (q, 11-C), 9.29 (q, 12-C), 18.76 (d, 1-C), 22.80 (q, 5α-Me), 28.80 (d, 10-C), 31.32 (q, 5β-Me), 35.42 (s, 5-C), 38.10 (d, 2-C), 42.10 (t, 8-C), 45.28 (t, 4-C), 77.65 (d, 3-C), 106.99 (t, 15-C), 123.52 (d, 7-C), 128.27 (d, Cx2), 129.47 (d, Cx2), 131.05 (s), 132.69 (d), 143.04 (d, 6-C), 149.63 (s, 9-C), 165.48 (s, C=O) ppm; IR (Neat) 1710 cm$^{-1}$; HRMS Calcd for $C_{22}H_{28}O_2$: M, 324.2090. Found: m/z 324.2086.