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MONOEPOXIDATION OF HUMULENE 2,3-EPOXIDE TO HUMULENE 2,3;6,7-DIEPOXIDES. OBSERVATION OF THE ROTATION OF THE DOUBLE BOND PLANE BY ^{1}H NMR SPECTRAL ANALYSIS AND CONFORMATION

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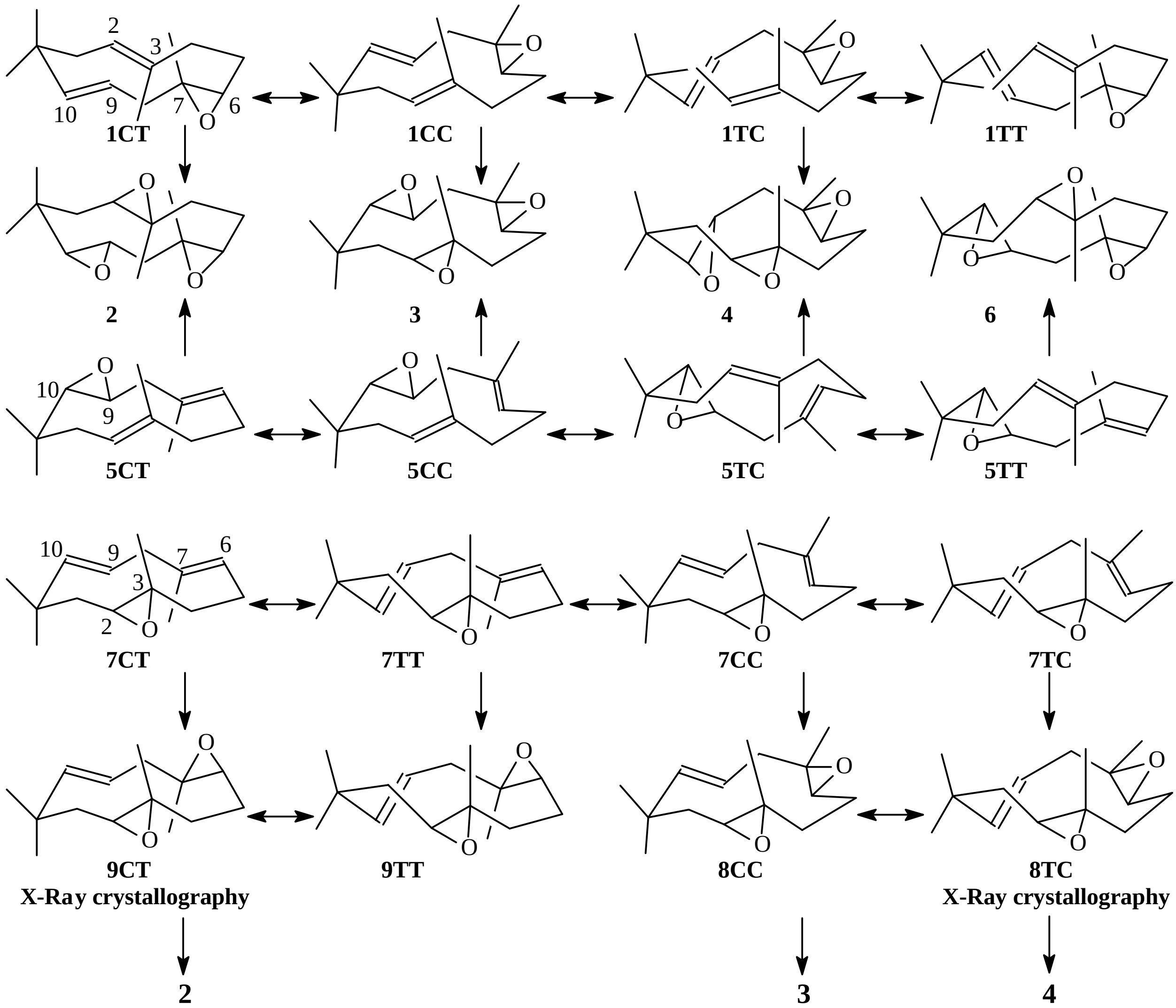
Abstract-The reaction of (6*E*,9*E*)-humulene 2,3-epoxide (**7**) with *m*-CPBA produced two known humulene 2,3;6,7-diepoxides (**8** and **9**), and careful analysis of the ^{1}H NMR of **7** at various temperatures suggested an equilibrium of four possible conformations, CT, CC, TC and TT, over 0°C together with free rotation of the 9,10-double bond plane in **8** at 85°C.

Recently, we reported that complete epoxidation[1] of humulene 6,7-epoxide (**1**) gave three humulene 2,3;6,7;9,10-triepoxides (**2**, **3** and **4**) originating from its three possible conformations, CT, CC and TC, and also that the epoxidation[2] of humulene 9,10-epoxide (**5**) produced a fourth triepoxide (**6**) corresponding to its TT conformation. In this paper, we describe the possible conformation of humulene 2,3-epoxide (**7**) in solution, based on the results of the epoxidation of its 6,7-double bond and measurement of the ^{1}H NMR spectrum in **7** at various temperatures. The epoxidation of **7** with *m*-chloroperbenzoic acid (*m*-CPBA) gave a mixture of the known two humulene 2,3;6,7-diepoxides (**8** and **9**, **8**:**9**=26:74, 99%). The ^{1}H NMR spectrum of **7** at -10°C below clearly showed the restriction of the free rotation of its 9,10-double bond plane at over 0°C. The free rotation of the 6,7- and 9,10-double bonds in a solution of **7** indicated the existence of the four possible CT, CC, TC and TT conformations. The spectrum in toluene-d_8 of the diepoxide (**8**) also showed the rotation of the 9,10-double bond plane at 85°C.

Humulene 2,3-epoxide (**7**) was prepared by reduction[3] of humulene 2,3;6,7-diepoxides. The epoxidation reaction of the 6,7-double bond in **7** produced two 2,3;6,7-diepoxides (99% yield) in a ratio of 26:74. These ^{1}H and ^{13}C NMR ($CDCl_3$) spectra were superimposable on those of the authentic samples (**8** and **9**) determined by X-Ray crystallography,[4,5] and therefore, these structures and conformations in the crystalline state were determined to be **8TC** and **9CT** depicted in Scheme 1. Because it has already been reported[1] that the epoxidation reaction of **8** and **9** in CH_2Cl_2 at 0 °C gave the two triepoxides (**3** and **4**, in the ratio **3**:**4** = 48:52) and only one (**2**) as shown in Scheme 1, respectively, the complete epoxidation reaction of **7** was formally represented as Scheme 1. The formation of two stereoisomers in the 2,3;6,7-diepoxide



Scheme 1.

shows that the 6,7-double bond plane in **7** rotates during the epoxidation reaction (CH_2Cl_2, 0°C~rt) and suggests that a broad triplet coupling pattern of hydrogen attached at the 6-position in the ^1H NMR spectrum (CD_3COCD_3, 24.1 °C) of **7** is the average of the possible conformation obtained by the rotation of the 6,7-double bond plane. The coupling pattern of 6-H did not change in the measurement of the ^1H NMR spectrum (CD_3COCD_3) of **7** at temperatures between 45 and –60 °C, but the doublet coupling pattern of hydrogen attached at the 8-position changed to a double-doublet at temperatures below -10°C as shown in Figure 1. With the alteration of the coupling pattern in 8-H_2, the double-triplet coupling pattern of 9-H changed to a double-double-doublet (Figure 2).

Thus, the chemical shift and magnetic equivalence of the methylene proton at the 8-position in **7** is produced by the free rotation of the 9,10-double bond plane at temperatures of 0°C or over. The free rotation is restricted at temperatures below -10°C, and the coupling pattern of the methylene proton is changed from the equivalent doublet to an unequivalent double-doublet. From the above results of the spectral analysis in **7**, it is thought that **7** is in equilibrium between the CT, CC, TC and TT conformations at high temperatures over 0°C and that the less stable TT conformation decreases on lowering the temperature, and the equilibrium then separates into two equilibra of CT←→CC and TC ←→TT due to the restriction of the rotation of the 9,10-double bond plane at temperatures below –10°C (Scheme 2).

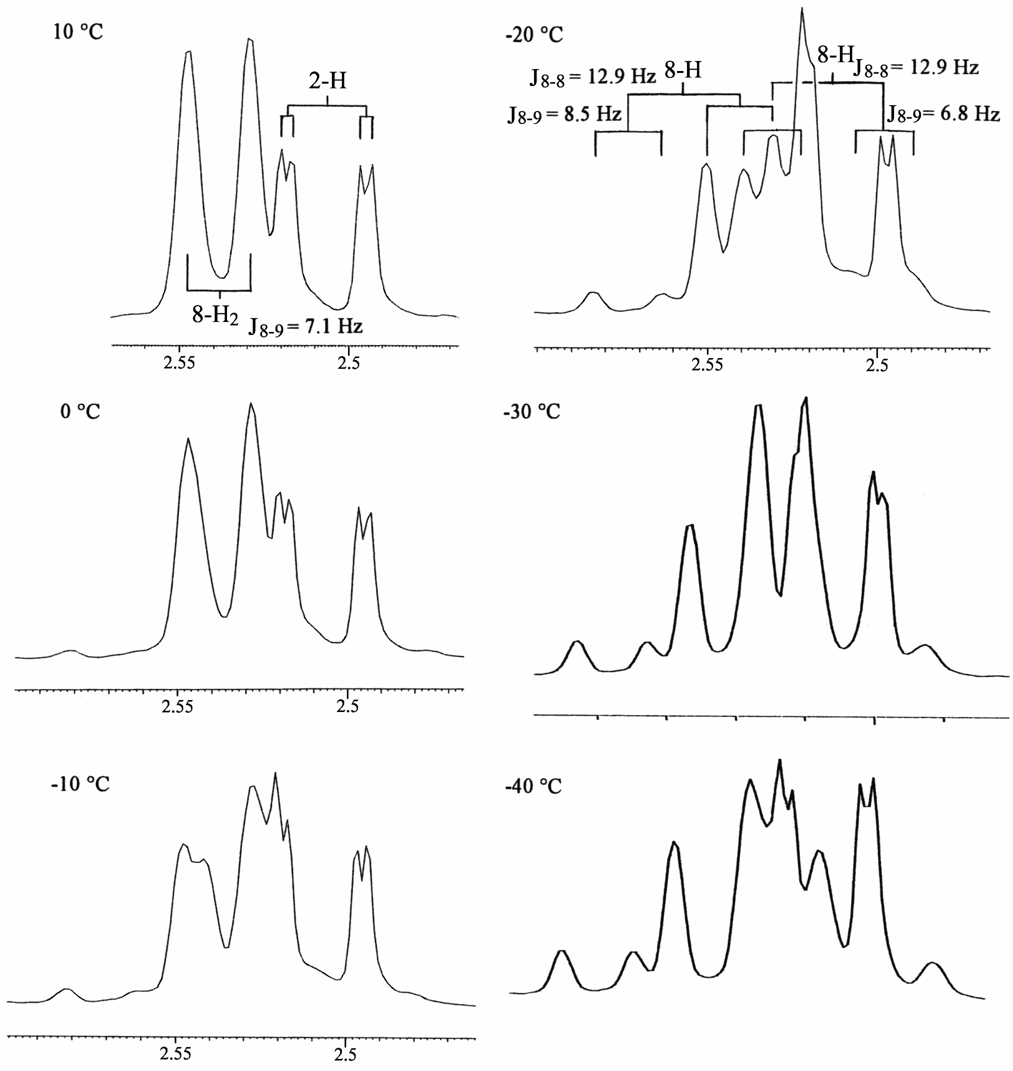


Figure 1. The change in coupling pattern of 8-H_2 in **7** at temperatures between 10 and -40 °**C**.

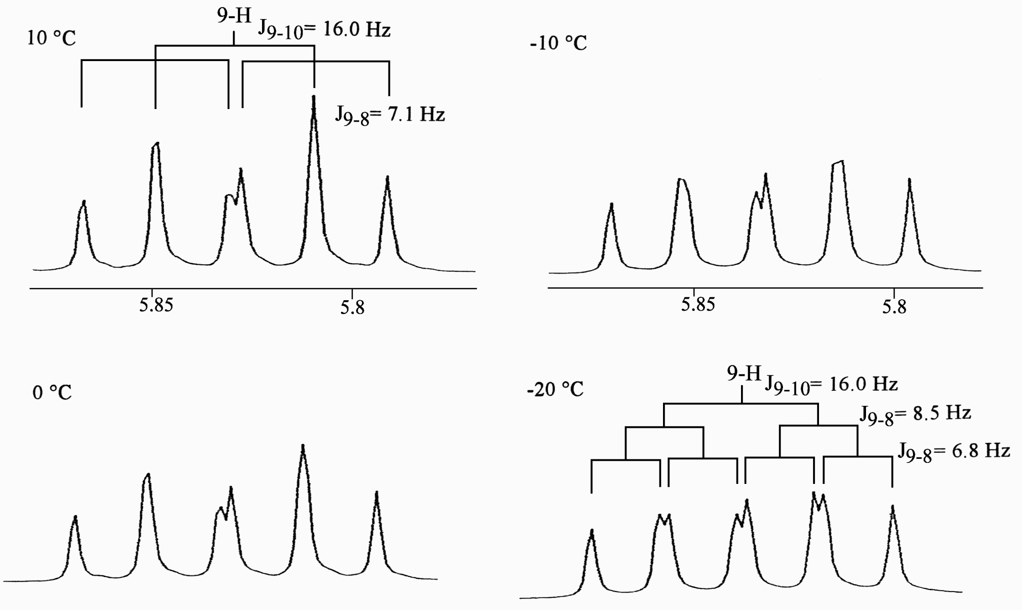
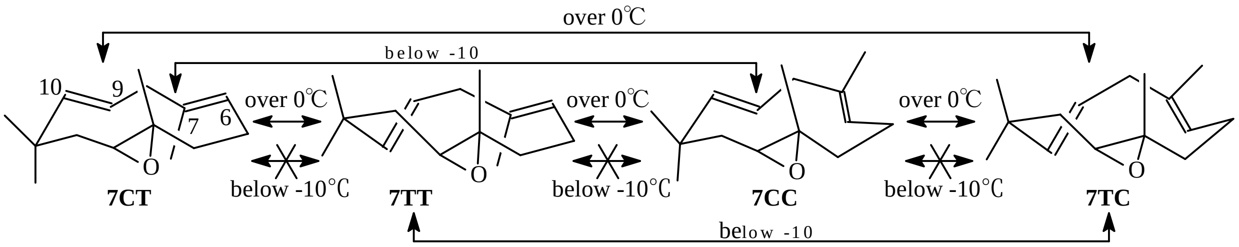


Figure 2. The change in coupling pattern of 9-H in **7** at temperatures between 10 and -20 °C.



Scheme 2.

The population of the four possible conformations in **7** was calculated by Conflex (extensive mode) with MM2[6] to give a ratio of CT:CC:TC:TT=15.8:7.7:71.8:4.7 at 25°C.[7] The calculated result shows that the TC and CT conformations are stabler than the CC and TT conformations and supports the equilibrium between the four possible CT, CC, TC and TT conformations at temperatures over 0°C. The stabler TC and CT conformations are also confirmed by the transannular cyclized products[3] of **7** and by X-Ray crystallography[4,5] of **8** and **9** (Scheme 1).

On the other hand, the ^{1}H NMR spectrum of **9** at temperatures between 45°C and -30°C did not show any change in the coupling pattern, but that of **8** at temperatures between 10°C and 95°C indicated that two different coupling constants and patterns of 8-αβH, 9-H and 10-H existed at 10°C in acetone-d_6 and that these differences disappeared completely at 85°C in toluene-d_8 as depicted in Figures 3 and 4. Two sets of the coupling pattern are represented as A and B in Figures 3 and 4. The coupling pattern A contained the long range coupling between 8-H and 7-CH_3 which presumably shows that of the TC conformation because the same long range coupling also exists in the spectrum of **4** produced from the TC conformation. The results of analysis in the spectrum shown in Figures 3 and 4 are the explicable configuration between 8-H_2 and the 9,10-double bond in the two TC and CC conformations of **8** (Figure 5). These above spectra lead us to think that **8** in solution is a mixture of the TC and CC conformations and that these proton peaks are an overlap of two spectra originated from the two conformations, but these can not be separated by HPLC (10% EtOAc/hexane) at rt.

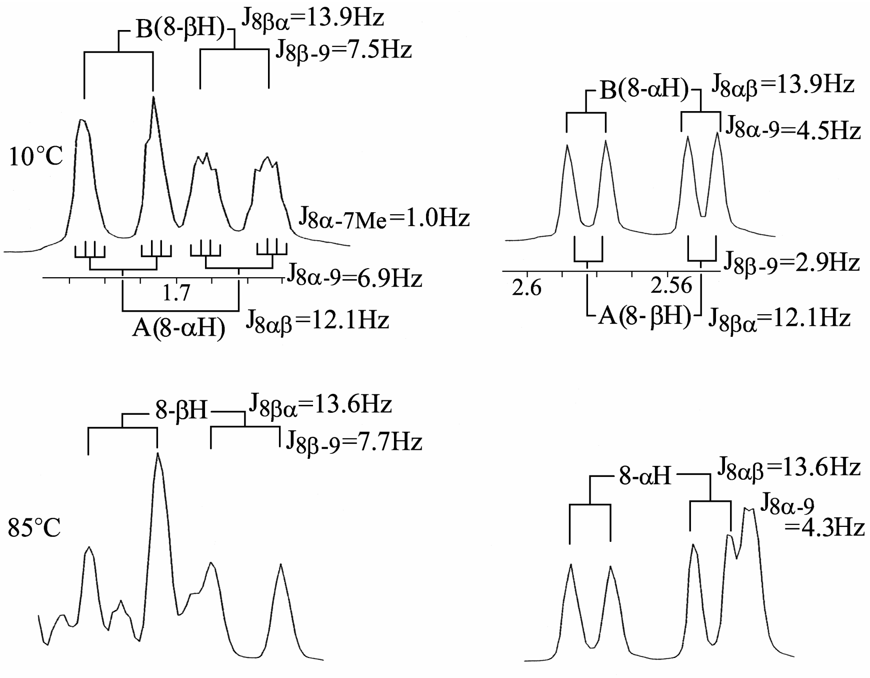


Figure 3. The coupling pattern of 8-αH and 8-βH in **8** at 10 (upper) and 85 °C (lower).

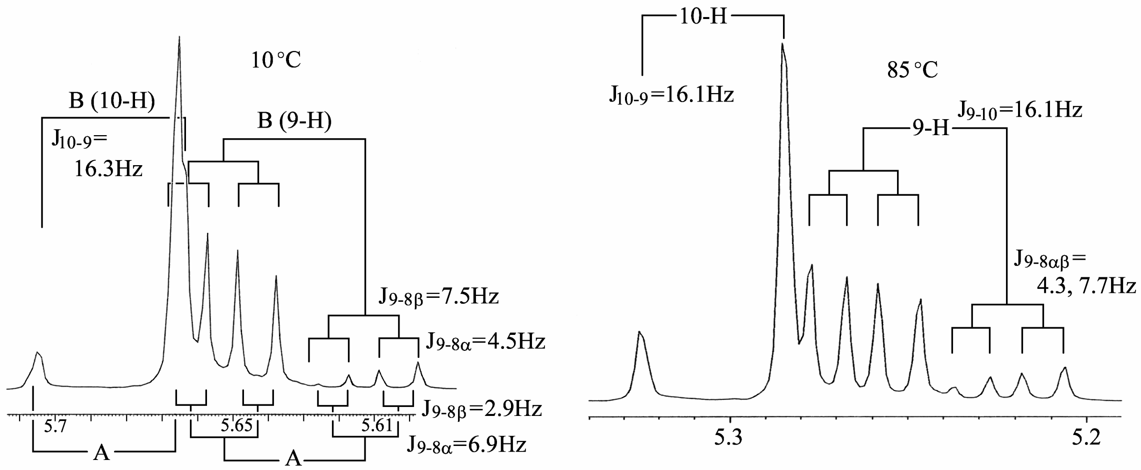
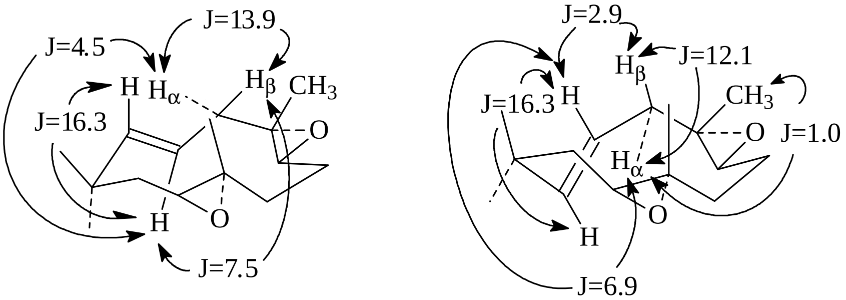


Figure 4. The coupling pattern of 9-H and 10-H in **8** at 10 (left) and 85 °C (right).



8CC **8TC**

Figure 5.

Thus, careful observation of the ^{1}H NMR spectrum in **7** clearly shows the free rotation of the 6,7- and 9,10-double bond planes at temperatures over 0°C together with the restriction of the free rotation of the 9,10-double bond plane at those below -10°C and the equilibrium of the four possible conformatons, CT, CC, TC and TT, over 0°C. Moreover, **8** appeared as a mixture of the two TC and CC conformations, which are in equilibrium at 85°C due to the rotation of the 9,10-double bond plane. The above clear result of the spectral measurement for the rotation of the double bond plane has never been observed in other humulene mono- and di-epoxides except for **7** and **8**.

EXPERIMENTAL

Melting points were determined in open capillaries and uncorrected. NMR spectra were measured using a JEOL ECP400 spectrometer. Chemical shifts were reported in δ units relative to internal Me_4Si. Pre-coated TLC plates (silica gel 60 F-254, Merck) were used for examining the reaction and separation in column chromatography. The silica gel column was prepared using silica gel 60, 70-230 mesh ASTM (Merck). HPLC was carried out using a model 6000A solvent delivery system (Waters) and a differential refractometer R 401 (Waters).

Preparation of (6E, 9E)-2,3-Epoxy-3,7,11,11-tetramethylcycloundeca-6,9-diene (Humulene 2,3-epoxide, 7) from Humulene 2,3;6,7-Diepoxides.[3] The reduction of humulene 2,3;6,7-diepoxides (3.77 g, 16.0 mmol) prepared from humulene and *m*-CPBA (2 eq) with Ti(II) reagent [prepared with $TiCl_3$ (2.58 g) and $LiAlH_4$ (1.77 g)] in dry THF (60 mL) at 10-20 °C for 35 min gave a mixture of **1**, **7**, humulene and the starting material, of which a chromatographic separation (eluting solvent, 10% EtOAc/hexane) produced 0.91 g (28.0%) of humulene, 1.42 g (40.5%) of a mixture of 6,7- and 2,3-epoxides (**1** and **7**), and 0.912 g (24.3%) of 2,3;6,7-diepoxides. To the stirred mixture of **1** and **7** was added an aqueous solution of $AgNO_3$ (4.54 g of $AgNO_3$ and 1.8 mL of water). After 5-10 min at rt under stirring, the mixture was solidified by the formation of an $AgNO_3$ complex of **7**. To the mixture was added 28 mL of dry THF and then the complex was crushed to a powder, which was collected by vacuum filtration. After the complex was added to a mixture of aqueous ammonia and hexane, pure **7** was extracted three times with hexane. The extracts were washed twice with water, dried over Na_2SO_4, and concentrated in *vacuo* to yield 1.06 g (30.2% from 2,3;9,10-diepoxides) of the starting material (**7**): ^{1}H NMR (CD_3COCD_3, 400 MHz, at 24.1 °C) δ 1.02 (3H, s, 11-Me), 1.09 (1H, ddd, $J_{4\alpha\beta}$=$J_{4\alpha\text{-}5\beta}$=12.4, $J_{4\alpha\text{-}5\alpha}$=6.7 Hz, 4-αH), 1.14 (3H, s, 3-Me), 1.19 (3H, s, 11-Me), 1.42 (1H, dd, $J_{1\beta\alpha}$=14.5, $J_{1\beta\text{-}2\alpha}$=9.2 Hz, 1-βH), 1.51 (1H, dd, $J_{1\alpha\beta}$=14.5, $J_{1\alpha\text{-}2\alpha}$=1.3 Hz, 1-αH), 1.70 (3H, br s, 7-Me), 1.96 (1H, ddd, $J_{4\beta\alpha}$=12.5, $J_{4\beta\text{-}5\beta}$=4.5, $J_{4\beta\text{-}5\alpha}$=2.8 Hz, 4-βH), 2.11 (1H, dddd, $J_{5\beta\alpha}$=$J_{5\beta\text{-}4\alpha}$=12.5, $J_{5\beta\text{-}4\beta}$=4.5, $J_{5\beta\text{-}6}$=8.0 Hz, 5-βH), 2.16 (1H, dddd, $J_{5\alpha\beta}$=12.5, $J_{5\alpha\text{-}4\alpha}$=6.7, $J_{5\alpha\text{-}4\beta}$=2.8, $J_{5\alpha\text{-}6}$=8.0 Hz, 5-αH), 2.50 (1H, dd, $J_{2\alpha\text{-}1\beta}$=9.2, $J_{2\alpha\text{-}1\alpha}$=1.3 Hz, 2-αH), 2.54 (2H, d, $J_{8\alpha\beta\text{-}9}$=7.1 Hz, 8-αβ$H_2$), 5.26 (1H, br t, $J_{6\text{-}5}$= 8.0 Hz, 6-H), 5.44 (1H, d, $J_{10\text{-}9}$=16.0 Hz, 10-H), 5.82 (1H, dt, $J_{9\text{-}8\alpha\beta}$=7.1, $J_{9\text{-}10}$=16.0 Hz, 9-H) ppm.

Preparation of a Mixture (**8** and **9**) of (9E)-(2S*, 3S*, 6S*, 7S*)- and (9E)-(2S*, 3S*, 6R*, 7R*)-2,3;6,7-Diepoxy-3,7,11,11-tetramethylcycloundec-9-enes (Humulene 2,3;6,7-Diepoxides) from **7**. To a solution of 0.5 g (2.27 mmol) of **7** in 15 mL of dry dichloromethane (CH_2Cl_2) chilled in an ice bath under an argon atmosphere was slowly added 1 molar amount of *m*-CPBA (0.45 g, minimum 70%) in portions in order to selectively oxidize its 6,7-double bond. The reactants were kept at 0 °C for 0.5 h and then stirred at rt for 1 h. The reaction mixture was washed once with 10% $Na_2S_2O_3$ solution, twice with an aqueous 4% NaOH solution, twice with water, and dried over Na_2SO_4. Removal of the solvent left a colorless viscous oil, of which a chromatographic separation gave a mixture of the humulene 2,3;6,7-diepoxides (**8** and **9**) (0.531 g, 99% yield in the ratio of **8**:**9** = 26:74). The ratio of **8**:**9** was calculated from the peak areas of HPLC using a 7.8 x 300 mm column of µPORASIL (Waters, 10% EtOAc/hexane).

Separation of the Mixture (**8** and **9**) into **8** and **9**. A 50% hexane solution of the above mixture (0.531 g, **8** and **9**) was separated into **8** (0.131 g, mp 66-69 °C) in 24.4% yield from **7** and **9** (0.364 g, mp 102-105 °C) in 67.9% yield from **7** by HPLC using a 7.8 x 300 mm column of µPORASIL (Waters, 10% EtOAc/hexane). Because the ^{1}H and ^{13}C NMR spectra of **8** and **9** in $CDCl_3$ were superimposable on those of the authentic samples,[4] the structure and stereochemistry of **8** and **9** were shown to be (9*E*)-(2*S**, 3*S**, 6*S**, 7*S**)- and (9*E*)-(2*S**, 3*S**, 6*R**, 7*R**)-humulene 2,3;6,7-diepoxides, respectively. The conformation in the crystalline states of **8** and **9** was also determined to be the TC and CT conformations, respectively. The ^{1}H NMR spectra of **8** and **9** in CD_3COCD_3 at rt were shown as follows.

8: ^{1}H NMR (CD_3COCD_3, 400 MHz, at 26.5 °C), δ 1.09, 1.15, 1.20 1.35 (each 3H, s), 1.26 (1H, ddd, $J_{4\alpha\text{-}5\alpha}$=4.0, $J_{4\alpha\text{-}5\beta}$=$J_{4\alpha\beta}$=13.5 Hz, 4-αH), 1.46 (1H, dddd, $J_{5\beta\alpha}$=14.8, $J_{5\beta\text{-}4\alpha}$=13.5, $J_{5\beta\text{-}4\beta}$=4.0, $J_{5\beta\text{-}6\alpha}$=10.1 Hz, 5-βH), 1.51 (1H, dd, $J_{1\beta\alpha}$=14.1, $J_{1\beta\text{-}2\alpha}$=9.2 Hz, 1-βH), 1.60 (1H, dd, $J_{1\alpha\beta}$=14.1, $J_{1\alpha\text{-}2\alpha}$=1.0 Hz, 1-αH), 1.71 (1H, dd, $J_{8\beta\alpha}$=13.9, $J_{8\beta\text{-}9}$=7.5 Hz, 8-βH and ddq, $J_{8\alpha\beta}$= 12.1, $J_{8\alpha\text{-}9}$= 6.9, $J_{8\alpha\text{-}7Me}$=1.0 Hz, 8-αH), 1.85 (1H, ddt, $J_{5\alpha\beta}$=14.8, $J_{5\alpha\text{-}4\alpha\beta}$=4.0, $J_{5\alpha\text{-}6\alpha}$=1.0 Hz, 5-αH), 2.11 (1H, dt, $J_{4\beta\alpha}$=13.5, $J_{4\beta\text{-}5\alpha\beta}$=4.0 Hz, 4-βH), 2.56 (1H, dd, $J_{8\alpha\beta}$=13.9, $J_{8\alpha\text{-}9}$=4.5 Hz, 8-αH and dd, $J_{8\beta\alpha}$= 12.1, $J_{8\beta\text{-}9}$= 2.9 Hz, 8-βH), 2.67 (1H, dd, $J_{6\alpha\text{-}5\beta}$=10.1, $J_{6\alpha\text{-}5\alpha}$=1.0 Hz, 6-αH), 2.73 (1H, dd, $J_{2\alpha\text{-}1\beta}$=9.2, $J_{2\alpha\text{-}1\alpha}$=1.0 Hz, 2-αH), 5.62 (1H, ddd, $J_{9\text{-}10}$=16.3, $J_{9\text{-}8\beta\alpha}$=7.5 and 6.9, $J_{9\text{-}8\alpha\beta}$=4.5 and 2.9 Hz, 9-H), 5.67 (1H, d, $J_{10\text{-}9}$=16.3 Hz, 10-H) ppm. The above NMR data of 8-αβH and 9-H in **8** were shown as an overlap of two spectra originated from the TC and CC conformations (Figures 3 and 4).

9: ^{1}H NMR (CD_3COCD_3, 400 MHz, at 26.8 °C), δ 1.06, 1.21, 1.28, 1.29 (each 3H, s), 1.07 (1H, ddd, $J_{4\alpha\beta}$=$J_{4\alpha\text{-}5\beta}$=13.2, $J_{4\alpha\text{-}5\alpha}$=5.5 Hz, 4-αH), 1.30 (1H, dddd, $J_{5\alpha\beta}$=14.1, $J_{5\alpha\text{-}4\alpha}$=5.5, $J_{5\alpha\text{-}4\beta}$=2.4, $J_{5\alpha\text{-}6\beta}$=10.6 Hz, 5-αH), 1.42 (1H, dd, $J_{1\beta\alpha}$=13.2, $J_{1\beta\text{-}2\alpha}$=9.2 Hz, 1-βH), 1.51 (1H, dd, $J_{1\alpha\beta}$=13.2, $J_{1\alpha\text{-}2\alpha}$=1.1 Hz, 1-αH), 1.57 (1H, dd, $J_{8\beta\alpha}$=11.9, $J_{8\beta\text{-}9}$=10.8 Hz, 8-βH), 2.00 (1H, ddd, $J_{4\beta\alpha}$=13.2, $J_{4\beta\text{-}5\beta}$=5.6, $J_{4\beta\text{-}5\alpha}$=2.4 Hz, 4-βH), 2.14 (1H, dddd, $J_{5\beta\alpha}$=14.1, $J_{5\beta\text{-}4\alpha}$=13.2, $J_{5\beta\text{-}4\beta}$=5.6, $J_{5\beta\text{-}6\beta}$=5.1 Hz, 5-βH), 2.47 (1H, dd, $J_{2\alpha\text{-}1\beta}$=9.2, $J_{2\alpha\text{-}1\alpha}$=1.1 Hz, 2-αH), 2.57 (1H, dd, $J_{8\alpha\beta}$=11.9, $J_{8\alpha\text{-}9}$=4.9Hz, 8-αH), 2.73 (1H, dd, $J_{6\beta\text{-}5\alpha}$=10.6, $J_{6\beta\text{-}5\beta}$=5.1 Hz, 6-βH), 5.44 (1H, d, $J_{10\text{-}9}$=15. 6 Hz, 10-H), 5.60 (1H, ddd, $J_{9\text{-}10}$=15.6, $J_{9\text{-}8\beta}$=10.8, $J_{9\text{-}8\alpha}$=4.9 Hz, 9-H) ppm.

*Sampling Method and Measurement of ^{1}NMR Spectra of **7**, **8** and **9** in Acetone-d_6 and **8** in Toluene-d_8 at Various Temperatures*. An acetone-d_6 solution containing 0.03% (v/v) of tetramethylsilane of 10 mg of **7**, **8** and **9** was placed in an NMR sample tube (ϕ=5 mm) through absorbent cotton till its height was 5 cm. The sample tube was cooled to 0 °C in an ice-bath, and argon gas was blown through the tube. After cooling the solution to 0 °C, a part 1 cm from the top of the tube was melted and closed with a gas burner. Furthermore, sampling of a toluene-d_8 solution of **8** was carried out in the same manner as described above.

The ^{1}H NMR spectra of **7**, **8** and **9** in acetone-d_6 and **8** in toluene-d_8 were measured at the following temperatures. **7**: 45, 35, 24.1, 10, 0, -10, -20, -30, -40, -50, -60 °C; **8**: (toluene-d_8) 95, 85, 75, 65, 55, (acetone-d_6) 45, 35, 26.8, 10, 0, -10, -20, -30 °C; **9**: 45, 35, 26.5, 10, 0, -10, -20, -30 °C. The results of the measurements at various temperatures are shown in the above text.

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7. Conflex (extensive mode) with MM2 in CAChe (Windows version 3.2, Oxford Molecular, Sony Tektronix) was used.