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Trimethylsilyl Triflate Induced Reaction of Humulene 6,7-Epoxide. Cyclization to 5-Hydroxy-4,8,11,11-tetramethyltricyclo[6.3.0.0^{2,4}]undec-9-ene

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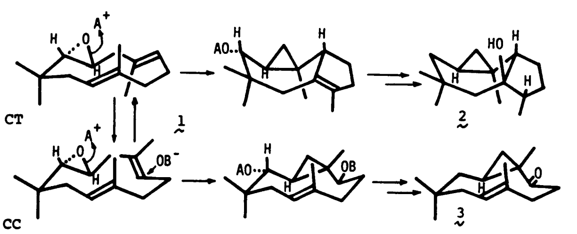
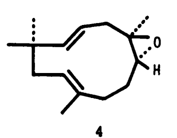
Synopsis. Humulene 6,7-epoxide was converted by treatment with trimethylsilyl triflate to 5-hydroxy-4,8,11,11-tetramethyl[6.3.0.0^{2,4}]undec-9-ene in 81% yield.

Recently we reported a conversion of humulene 9,10-epoxide (**1**) to africanol (**2**) and bicyclohumulenone (**3**) through a "conformationally selective reaction"1) (Scheme 1). The conversion means achievement of a high grade simulation of cyclohumulanoid biosynthesis.1) In this paper we would like to describe a conversion of humulene 6,7-epoxide (**4**) by means of trimethylsilyl triflate (TMSOTf)2) into a tricyclic alcohol, 5-hydroxy-4,8,11,11-tetramethyltricyclo[6.3.0.0^{2,4}]undec-9-ene (**5**) in good yield. The transannular cyclization (**4**→**5**) was first described by Takahashi *et al.*3) who treated **4** with sulfuric acid and obtained a hydrated form of **5**, namely, **7** in 25% yield with several other products. Our reaction was quite clean and gave **5** as an essentially sole product.



Scheme 1.1)



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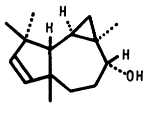

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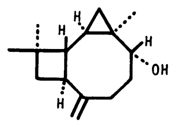

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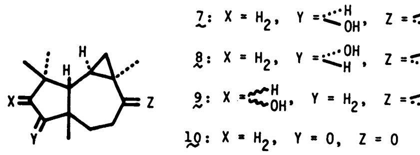
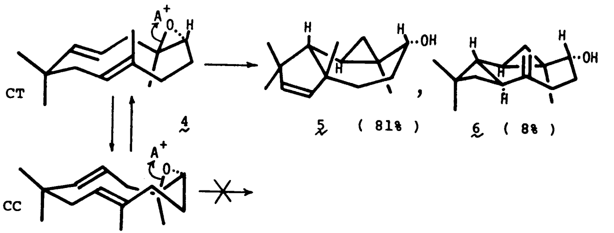


The epoxide **4**4) was treated with TMSOTf in toluene at −78 °C to give a crystalline mass. Chromatographic separation of the products gave tricyclic alcohol **5** in 81% yield accompanied by a small amount (8%) of another tricyclic alcohol **6**. The alcohol **6** was previously obtained by acid treatment of a tricyclohumuladiol by Naya and Kotake.5)

The compound **5** exhibited the same molecular weight as that of the original epoxide ($M^+=220$) and an OH band (3300 cm^{-1}) in its Mass and IR spectra respectively. The NMR spectrum displayed signals at δ 0.1—0.8 (3H, m, cyclopropane), 1.00, 1.10, 1.12, 1.14 (each 3H, s, Me×4), 3.39 (1H, dd, J=6, 10 Hz, H+OH), 5.24 (2H, s, olefinic). These observations together with consideration of the reaction course led to structure **5** for this compound. Stereochemistry of **5** was determined through its chemical conversion to known compounds. Treatment of **5** with B_2H_6 in THF followed by oxidation with H_2O_2 gave a mixture to alcohols which was separated by column chromatography into three diols **A**, **B**, and **C** in 39, 14, and 12% respectively. The IR and NMR spectra of diol **C** were superimposable with those of compound **7** which was previously obtained by Takahashi *et al.*3) by the reaction of **4** with H_2SO_4 in acetone. On oxidation with Collins reagent diols **B** and **C** gave the same diketone **10**3) and diol **A** yielded a new diketone **11**. Therefore, the configuration of **B** is represented by the formula **8** and that of **A** by **9**. The original olefinic alcohol is hence formulated as **5**.

Humulene is at equilibrium between two strain minimum conformers, CT and CC.6) Assuming that these two stable conformers are effective for the epoxide **4**, the stereochemistry of the present transannular reaction was reasonably figured as Scheme 2, based on the configuration of the products **5** and **6**.



Scheme 2.

Experimental

All melting points were uncorrected. IR spectra were recorded on a JASCO IR-S spectrometer. NMR spectra were measured with HITACHI R-20B (60 MHz) and JEOL JNM PS-100 (100 MHz) instruments in $CDCl_3$ using TMS as an internal standard. Mass spectra were obtained on a HITACHI M-52 spectrometer.

TMSOTf Induced Cyclization of Humulene 6,7-Epoxide (4). A solution of TMSOTf (1.86 ml) and 2,6-lutidine (1.39 ml) in toluene (40 ml) was stirred and cooled at −78 °C under argon. To this solution was added a solution of **4** (2.324 g) in toluene (12 ml) by portions. The mixture was stirred at this temperature for 5 h till the epoxide **4** was completely consumed. After removal of the cooling bath, DBU (2.8 ml) was added and the mixture was stirred for 2 h at room temperature. By addition of 1 mol dm^{-3} HCl the mixture was neutralized at

0 °C and extracted with hexane four times. The combined extracts were evaporated *in vacuo* to leave a brown mass which was dissolved in MeOH (10 ml). Mixing the solution with 1 mol dm^{-3} HCl (0.5 ml) for a few minutes effected desilylation. The methanol was removed and the residue was extracted with $CHCl_3$ four times. The combined extracts were dried and evaporated to leave a crystalline mass (2.331 g) which was subjected to silica gel chromatography. Elution of the column with 2.5% AcOEt–hexane afforded tricyclohumulenol (**6**)[5] (186 mg, 8%) first and then 5-hydroxy-4,8,11,11-tetramethyltricyclo[6.3.0.0^{2,4}]undec-9-ene (**5**) (1.822 g, 81%); mp 120—122 °C. Spectral data were described in the text.

Found: C, 81.75; H, 10.95%. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98%.

Hydroboration-Oxidation of **5**. To a solution of borane–THF (1.5 ml, 1 mol dm^{-3}) was added **5** (220 mg) in THF (3 ml) under argon at 0 °C. After standing for 3 h at 0 °C, the reaction mixture was quenched by the successive addition of ice, NaOH aq (10 ml, 3 mol dm^{-3}) and H_2O_2 (1.5 ml, 30%). The reaction mixture was stirred at room temperature for further 1.5 h till the oxidation was complete. After usual workup it gave a colorless liquid (200 mg) which was chromatographed on a column of $AgNO_3$ impregnated silica gel. Elution with hexane–ether (7 : 3) gave successively three crystalline diols, A (93 mg, 39%), B (33 mg, 14%), and C (29 mg, 12%). Further elution with ether gave a mixture which was not studied. Diol **C** showed the IR and NMR spectra superimposable with those of an authentic sample of **7**.[3]

Diol A (9): Mp 150 °C; IR 3200—3400 cm^{-1}; NMR δ 1.02 (9H, s), 1.08 (3H, s), 3.40 (1H, t, J=6 Hz), 3.86 (1H, dd, J=8, 6 Hz).

Found: C, 75.57: H, 11.17%. Calcd for $C_{15}H_{26}O_2$: C, 75.58; H, 11.00%.

Diol B (8): Mp 140 °C; IR 3200—3400 cm^{-1}; NMR δ 0.95, 1.05, 1.12, 1.20 (each 3H, s), 3.38 (1H, dd, J=10, 7 Hz), 3.70 (1H, br).

Found: C, 75.65; H, 11.44%. Calcd for $C_{15}H_{26}O_2$: C, 75.58; H, 11.00%.

Collins Oxidation of Diol A (9), B (8), and C (7). To a solution of dry pyridine (1 ml) in dry dichloromethane (15 ml) at 0 °C was added dry chromium trioxide (600 mg) under argon. The temperature of the mixture was raised to room temperature and the solution was stirred until it colored wine-red (20 min). At the end of this period a solution of diol *A* (**9**, 150 mg) in dry dichloromethane (5 ml) was added dropwise. A tarry black deposit separated immediately. After stirring for 20 min, the reaction mixture was worked up as usual and evaporation of the solvent gave a crystalline diketone (**11**); mp 149 °C. IR 1693, 1735, 1450 cm^{-1}; NMR δ 1.00, 1.12, 1.18, 1.32 (each 3H, s), 2.25 (2H, s).

Found: C, 76.86; H, 9.47%. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46%.

Oxidation of Diol B (8) in the same manner gave an oily diketone whose IR and NMR spectra were superimposable with those of an authentic sample of **10**.[3]

Diol C (7) was converted to the same diketone (**10**) by the same procedure as above.

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