5,9-Dihydroxy-4,8,11,11-tetramethyltricyclo[6.3.0.0^{2,4}]undecane. Acid-catalyzed Cyclization Product of 6,7-Epoxyhumula-2,9-diene[1]

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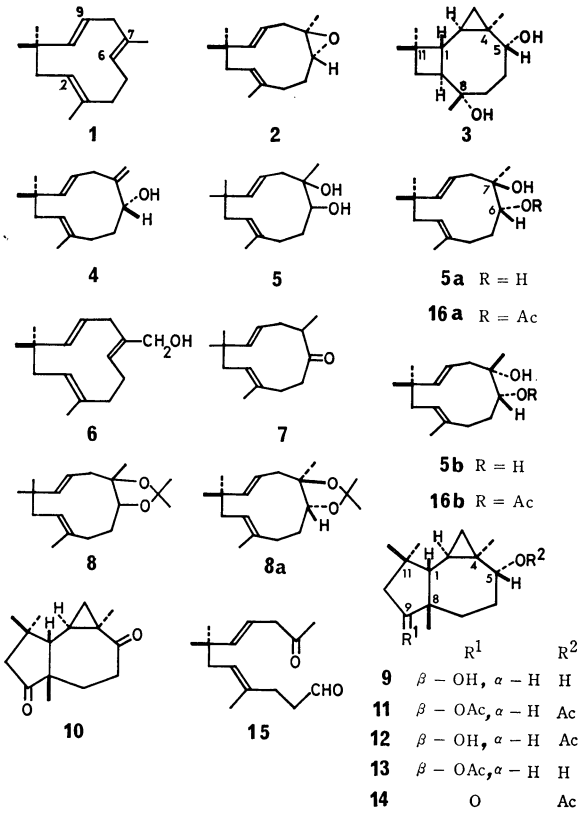
6,7-Epoxyhumula-2,9-diene (**2**) was treated with 1.8 M sulfuric acid–acetone (1: 1) to yield a new tricyclic diol, 5,9-dihydroxy-4,8,11,11-tetramethyltricyclo[6.3.0.0^{2,4}]undecane (**9**; diol B), together with tricyclohumuladiol (**3**; diol A), humulenol-II (**4**), a diol C (**5b**), a diol D (**5a**), and an acetonide (**8a**). The same reaction at 0° gave only **3**. Tricyclohumuladiol (**3**) was shown to be a key intermediate in the reaction of **2** to form **4**, **5a**, **5b**, **8a**, and **9**.

Cyclization of humulene (**1**) and its derivatives has been the subject of a number of studies in connection with the biogenesis of sesquiterpenes.[2] Treatment of 6,7-epoxyhumula-2,9-diene[3] (**2**; 1,2-humulene epoxide;[4] humulene epoxide-II[5]) with 20% sulfuric acid in acetone at room temperature has been reported[4] to give a complex mixture of products containing tricyclohumuladiol (**3**),[6-9] humulenol-II (**4**),[5,6b] and an unsaturated diol (**5**).[4] In this reaction, **4** was suggested to be formed directly from **2** or by acid-catalyzed decyclization of **3**.[4] It has also been reported[7] that tricyclohumuladiol (**3**) affords humulenol-II (**4**), an alcohol (**6**), humuladienone (**7**),[9] and an acetonide (**8**) on treatment with sulfuric acid in acetone at room temperature. In the present paper, the formation of a diol (**9**) with a new skeletal structure of 4,8,11,11-tetramethyltricyclo[6.3.0.0^{2,4}]undecane in the cyclization of **2** is described.

Treatment of 6,7-epoxyhumula-2,9-diene (**2**)[3-5,11] with 1.8 M sulfuric acid and acetone (1: 1) at 0 °C for 30 min gave tricyclohumuladiol (**3**;[6-9,11] diol A) as a sole product (yield: >95%). Further continuation of the reaction at room temperature for 7 h resulted in the formation of a mixture of at least seven products, which was subjected to separation by crystallization, column chromatography, and/or preparative gas chromatography to give the acetonide (**8**;[7,11] y: 10%), humulenol-II (**4**;[5,6b,11] y: 9%), tricyclohumuladiol (**3**; y: 4%), a diol B (**9**;[11] y: 25%), a diol C (**5b**;[11] y: *ca.* 4%), a diol D (**5a**;[11] y: 7%), and a diol E (y: *ca.* 4%). The same mixture of products was formed when tricyclohumuladiol (**3**) was treated with 1.8 M sulfuric acid in acetone (1: 1) (at room temperature, 7 h).



	R^1	R^2
9	β – OH, α – H	H
11	β – OAc, α – H	Ac
12	β – OH, α – H	Ac
13	β – OAc, α – H	H
14	O	Ac

The elementary analysis of the diol B (**9**; mp 171.5—172 °C) fitted best for the molecular formula $C_{15}H_{26}O_2$ (M^+ at *m/e* 238.1861). The PMR and IR spectra showed the presence of four tertiary methyl groups, a trisubstituted cyclopropane ring, and hydroxyl group(s). A diol nature with two secondary hydroxyl groups was shown for **9** by oxidation with chromium trioxide–pyridine complex in dichloromethane (Ratcliffe's procedure[12]) to yield a diketone (**10**). The IR (1740 and 1680 cm^{-1}; no hydroxyl absorption) and UV (λ_{max} 212 nm, ε 2200) spectra of **10** suggested the presence of a five-membered ring ketone and a six- or larger-membered ring ketone conjugated with the cyclopropane ring.[6] Acetylation of **9** with acetic anhydride in pyridine at room temperature gave a diacetate (**11**) and two monoacetates (**12** and **13**). One (**12**) of the monoacetates was treated with chromium trioxide in pyridine to yield a keto acetate (**14**), whose IR spectrum (1742 cm^{-1}) indicated the presence of a five-membered ring ketone. The hydroxyl and acetoxyl groups of the monoacetate (**12**) must be located on a five-membered ring and on a carbon adjacent to the cyclopropane ring, respectively. Lanthanide induced shift (LIS) technique using Eu(fod)$_3$-d_{27} as a shift reagent coupled with double irradiation was applied for PMR measurements of **12** to show the presence of the partial structures **A**, **B**, and **C** (*cf.* Table 1). It was suggested from the large LIS value observed for the proton (H_h) that the hydroxyl group in **A** and the proton (H_h) in **C** are located closely to each other. The results described above

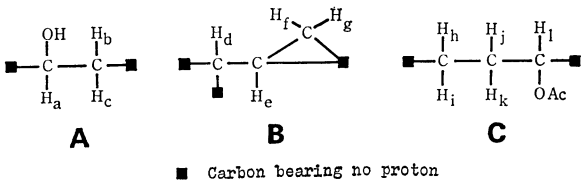


Table 1. Lanthanide induced shift values and coupling constants for the protons of the diol B monoacetate (**12**)

Protons	a	b	c	d	e	f	g	h	i	j	k	l
S[a]	24.7	19	13.7	6.3	5	3	3	15.5	8	8	5	6.3
Coupling constants (Hz)	$J_{a,b}=11$ $J_{a,c}=8$ $J_{b,c}=13$			$J_{d,e}=10$ $J_{e,f}=J_{e,g}=9$ $J_{f,g}=6$				$J_{h,i}$ or $J_{h,j}=10$ $J_{k,i}$ and/or $J_{k,j}=12$ $J_{h,k}=0$; $J_{j,l}=7$ $J_{k,l}=10$				
Methyls	$C_{(4)}$–CH_3		$C_{(8)}$–CH_3	$C_{(11)}$–CH_3		$C_{(11)}$–CH_3		$C_{(5)}$–$OCOCH_3$				
S[a]	2.0		12.5	4.3		3.2		2.7				

a) S: the slopes of shift values plotted against the molar ratio of [Eu(fod)$_3$-d_{27}]/**12** for a *ca.* 2%w/v soln of **12** in $CDCl_3$.

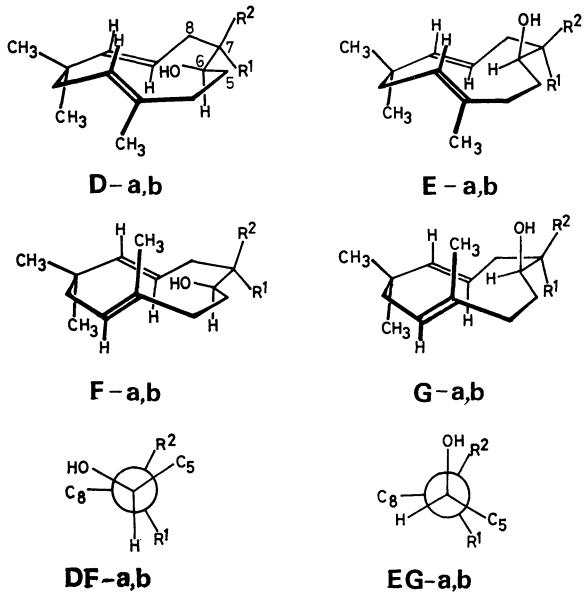
along with the evidence that the diol B was formed by acid-catalyzed rearrangement of tricyclohumuladiol (**3**) led to the structure of 5,9-dihydroxy-4,8,11,11-tetramethyltricyclo[6.3.0.0^{2,4}]undecane for the diol B (**9**). The large LIS value observed for the methyl group at C-8 of **12** showed that the C-9 hydroxyl group and the C-8 methyl group are in *cis* relationship for **9** and **12**.

The molecular formula of $C_{15}H_{26}O_2$ was given for both the diol C (**5b**; mp 182—183 °C) and the diol D (**5a**; a colorless oil). The diol D was treated with acetone in the presence of cupric sulfate to yield the known acetonide (**8**).[7] Acid hydrolysis of **8** gave the diol D. The diol D was also obtained on treatment of humulene [**1**; (2*E*,6*E*,9*E*)-3,7,11,11-tetramethylcycloundeca-2,6,9-triene)][3,13] with osmium tetroxide.[14] When the diol D as well as the diol C was oxidized with periodate, the same keto aldehyde (**15**) was formed. Therefore, the structure of (2*E*,9*E*)-6,7-dihydroxyhumula-2,9-diene[3] was confirmed for both the diols C (**5b**) and D (**5a**), which must be the diastereomers at C-7.

The presence of four preferred conformational isomers (**D**—**G**) could be suggested for each of the diols (**5a** and **5b**) based on an examination by the Dreiding model. The Newman projection about the bond axis $C_{(6)}$–$C_{(7)}$ for **D** and **F** is shown as in **DF**, and that for **E** and **G** as in **EG**. The presence of an intramolecular O–H···π hydrogen-bonding[15] could be expected for **D** and **F** for both the *trans*-diol ($R^1=CH_3$, $R^2=OH$) and the *cis*-diol ($R^1=OH$, $R^2=CH_3$). An intramolecular O–H···O hydrogen-bonding could be formed in **E** and **G** for the *trans*-diol; no formation of this hydrogen-bonding is expected for **D**—**G** for the *cis*-diol. The IR spectrum of the diol C (2.6 mM soln in carbon tetrachloride) showed the absorptions at 3640, 3625, and 3605 cm^{-1} due to a free secondary hydroxyl, a free tertiary hydroxyl, and an intramolecular O–H···π hydrogen-bonded hydroxyl group,[15] respectively, while the spectrum of the diol D (2.6 mM soln in carbon tetrachloride) indicated an absorption at 3588 cm^{-1} due to an intramolecular O–H···O hydrogen-bonded hydroxyl group in addition to the bands at 3642, 3627, and 3603 cm^{-1} (Fig. 1). The *trans*-diol (**5a**) and the *cis*-diol (**5b**) structures are suggested for the diol D and the diol C, respectively. The structure (**8a**) follows for the acetonide (**8**) of the diol D.

These results received support from the following observations. (i) The rate of the periodate cleavage of the *trans*-diol (**5a**) was found to be greater than that of the *cis*-diol (**5b**). This could be interpreted by the proximity of the two hydroxyl groups for **5a** shown as in **E-a**, **G-a**, and **EG-a**; the two hydroxyl groups are rather alienated to each other in **D**—**G** for **5b**. (ii) The formation of the acetonide (**8a**) from the *trans*-diol (**5a**) can be explained on the basis of the conformations **E-a** and **G-a**, while the corresponding acetonide could not be obtained from the *cis*-diol (**5b**). (iii) The R_f value on TLC for **5a** was observed higher than that for **5b**; this could be due to the formation of an intramolecular hydrogen-bonding in **5a**. (iv) In the IR spectrum of the monoacetate (**16a**) prepared from **5a**, the carbonyl absorption due to the acetoxyl group appears at the lower wave-number (1710 cm^{-1}). The presence of an intramolecular hydrogen-bonding between the C-7 hydroxyl group and the acetoxyl group at C-6 is suggested for **16a** which could adopt the conformations **E-a** and **G-a** (OAc in place of $C_{(6)}$–OH). (v) A *cis*-addition of osmium tetroxide to the (6*E*)-olefinic linkage of humulene (**1**) would lead to the *trans*-diol (**5a**).

In the mass spectra of the diol B (**9**) and its related compounds (**11**—**14**), the peaks due to cleavages **a**, **b**,



a $R^1=CH_3$, $R^2=OH$ (**5a**: *trans*-diol)
b $R^1=OH$, $R^2=CH_3$ (**5b**: *cis*-diol)

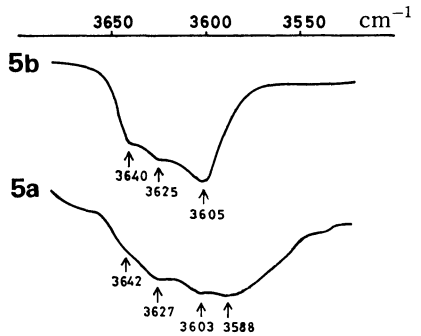
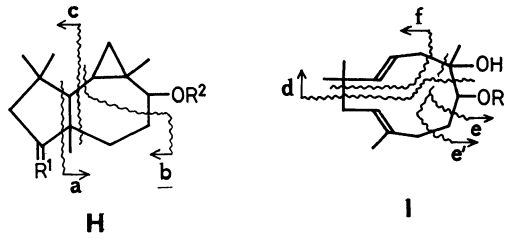


Fig. 1. IR Spectra of the diol D (**5a**) and the diol C (**5b**) in CCl_4 (2.6 mM soln for both compounds).

and **c** were observed (*cf.* **H**). The fragment ions due to fissions **d**, **e**, **e'**, and **f** were observed for the diols C (**5b**), D (**5a**), and their derivatives (**16a**, **b**) (*cf.* **I**).



Finally, both the reaction of the epoxide (**2**) (Fig. 2) and the rearrangement of tricyclohumuladiol (**3**) (Fig. 3) were examined by a time-dependent product analysis (GLC). An initial formation of **3** and the subsequent

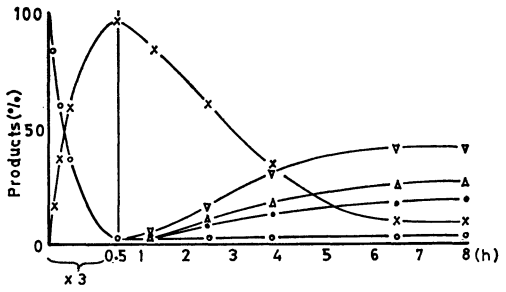


Fig. 2.

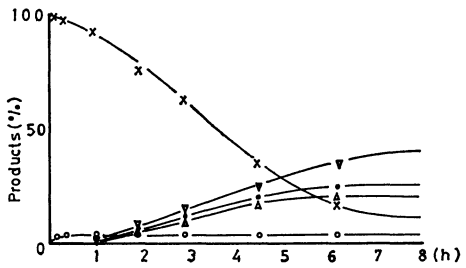
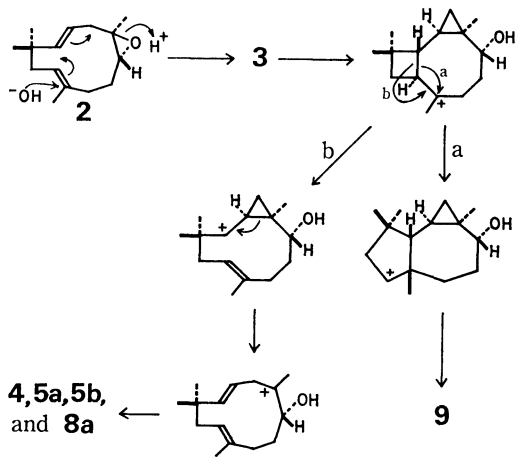


Fig. 3.

Figs. 2 and 3. Time-dependent product analysis for the reaction of the epoxide (**2**) (Fig. 2) and the rearrangement of tricyclohumuladiol (**3**) (Fig. 3): **2** (-○-), **3** (-×-), **4** (-△-), **8a** (-▽-), and **9** (-●-). The formation of the diol C (**5b**) was detected. However, this could not be registered in Figs. 2 and 3 due to a small quantity of **5b** formed. The diol D (**5a**) could not be detected due to decomposition of this compound under the conditions employed [column: SP-1000 (10%); 180—220 °C].



Scheme 1.

formation of a series of products (**4**, **5b**, **8a**, and **9**) in consumption of **3** were shown (Fig. 2). These results and the product isolation experiments (*vide supra*) indicate that tricyclohumuladiol (**3**) is a key intermediate in the reaction of **2** to form **4**, **5a**, **5b**, **8a**, and **9**. The sequence of the acid-catalyzed cyclization and the subsequent rearrangement of 6,7-epoxyhumula-2,9-diene (**2**) could be interpreted as in Scheme 1.[16]

Experimental

All mps were measured on a Mel-temp capillary melting point apparatus (Laboratory Devices) and uncorrected. IR spectra were measured on Hitachi EPI-G2, JASCO IRA-2, JASCO DS-402G spectrometers, and UV spectrum on a Hitachi EPS-2 spectrometer. Mass (MS) spectra were run on a Hitachi RMU-6-Tokugata mass spectrometer and high resolution mass spectra on a Hitachi RMH-2 mass spectrometer operating at 70 eV. The relative intensity observed in low resolution mass spectra was expressed in % in the parentheses. PMR spectra were taken using a Hitachi R-20B (60 MHz), or a JEOL FX-60 spectrometer, using TMS as an internal standard. Gas chromatography (GLC) was carried out using Shimadzu GC-6A equipped with a hydrogen flame ionization detector. Analytical TLC was carried out on Kieselgel GF_{254}(Merck) in 0.25 mm thickness and preparative TLC on Kieselgel PF_{254}(Merck) in 0.5 mm thickness. Wakogel C-200 (Wako) was used for column chromatography.

6,7-Epoxyhumula-2,9-diene (2). 6,7-Epoxyhumula-2,9-diene (**2**)[11] was prepared from humulene (**1**) by treatment with pervanadic acid (H_2O_2–V_2O_5)[17] in acetone according to the procedure described by Damodaran *et al.*[5]

Treatment of 6,7-Epoxyhumula-2,9-diene (2) with Sulfuric Acid in Acetone. To a solution of the epoxide (**2**; 100 mg) in acetone (10 ml) cooled to 0 °C was added 1.8 M sulfuric acid (10 ml) with stirring. The solution was stirred at 0 °C for 1 h and then at room temperature for 7 h. The reaction mixture was neutralized with aqueous sodium hydroxide solution and extracted thrice with ether after acetone was removed. The combined ethereal solutions were washed with brine, dried over sodium sulfate, and evaporated. Crystals (17 mg; **9**; *diol B*) separated from the residual oil (98 mg) were filtered and washed with a small amount of ether. The filtrate gave another crop of crystals [6 mg; a mixture of diols B, C, and E], which was collected by filtration. Evaporation of the filtrate gave a residue (75 mg), which was dissolved in hexane–ether (4: 1), passed through a column of silica gel (7 g), and

eluted with the following solvents (each fraction, 5 ml). Hexane–ether (7: 3), frs 1—4; hexane–ether (1: 1), frs 5—14; ether, frs 15—50. On evaporation, fractions 9—14 gave a *diol D* (**5a**; 4 mg), fractions 17—23 a mixture of diols B, C, and E (12.5 mg), fractions 24—30 a *diol C* (**5b**; 1 mg), fractions 31—36 a mixture (*ca.* 1: 1) of diols C and A (2 mg), fractions 37—43 a *diol A* (**3**; *tricyclohumuladiol*;[6-9] 2 mg), and fractions 44—47 a mixture (*ca.* 1: 1) of diol A and an unidentified product (2 mg). Fractions 3—8 were combined and the solvents were distilled off. The residue (44 mg) was dissolved in hexane and further chromatographed on a column of silica gel (8 g) using the following solvents as eluent (each fraction, 8 ml). Hexane, frs 1—6; hexane–ether (19: 1), frs 7—14; hexane–ether (9: 1), frs 15—31; ether, frs 32—36. On removal of the solvents, fractions 10—12 afforded an *acetonide* (**8a**; 14 mg; yield 10%), fractions 13—15 the starting material (**2**; 1 mg), fractions 25—28 *humulenol-II* (**4**;[5,6,11] 9 mg; y: 9%), and fraction 34 a mixture (*ca.* 1: 1) of diol D and another unidentified product (6 mg). From the mixture containing diols B, C, and E mentioned above, the diol C (R_t 15 min) and the *diol E* (R_t 10.3 min) were separated by means of preparative GLC [column, SP-1000 (10%), 4 (mm)×2 (m); 220 °C; N_2 flow rate, 50 ml/min]. The total yields for each of the diols A—E were estimated to be 4, 25, 4, 7, and 4%, respectively.

When the reaction (at 0 °C) was interrupted after 30 min, the diol A (**3**) was obtained as a sole product (y: >95%); a part of the starting material (**2**; <5%) left unchanged.

Characterization of the diols B, C, D, and E and the acetonide are as follows. *5,9-Dihydroxy-4,8,11,11-tetramethyltricyclo[6.3.0.0^{2,4}]undecane (**9**; Diol B).* The diol B (**9**) crystallized from benzene as colorless needles, mp 171.5—172 °C; IR (Nujol) 3280, 3050, 1380, 1365, 1350, 1260, 1055, 1045, 1035, 925, 910, and 880 cm^{-1}; PMR ($CDCl_3$) δ 0.16—0.63 (3H, m), 0.90, 1.03, 1.05, 1.12 (each 3H, s), 3.4 and 3.8 (each 1H, m); Found: C, 75.31; H, 11.02%. Calcd for $C_{15}H_{26}O_2$: C, 75.58; H, 10.99%; MS *m/e* 238.1861 (9%; M$^+$; calcd for $C_{15}H_{26}O_2$: 238.1931), 223.1684 [11%; $(M-CH_3)^+$], 220.1795 [13%; $(M-H_2O)^+$], 205.1585 [20%; $(M-H_2O-CH_3)^+$], 202.1658 [9%; $(M-2\times H_2O)^+$], 152.1229 [22%; **a** and/or (**b**−2H); $C_{10}H_{16}O$], 150.1083 [38%; (**a**−2H); $C_{10}H_{14}O$], 138.0976 (84%; $C_9H_{14}O$), 125.0963 [71%; (**c**−H); $C_8H_{13}O$], 121.1014 (73%; C_9H_{13}), 109.0886 (100%; C_8H_{13}), and 107.0833 (91%; C_8H_{11}).

Diol C (5b). The diol C (**5b**) crystallized from ethyl acetate as colorless needles, mp 182—183 °C; IR (Nujol) 3380, 1150, 980, and 860 cm^{-1}; PMR (CD_3OD) δ 1.04, 1.09, 1.31, and 1.66 (each 3H, s); MS *m/e* 238.2004 (3%; M$^+$; calcd for $C_{15}H_{26}O_2$: 238.1931), 220.1765 [3%; $(M-H_2O)^+$], 205.1450 [2%; $(M-H_2O-CH_3)^+$], 138.1037 (53%; $C_9H_{14}O$), 125.0959 [35%; (**d**−H); $C_8H_{13}O$], 109.0951 (57%; C_8H_{13}), 95.0853 (53%; C_7H_{11}), 87.0419 [23%; (**e′**−H); $C_4H_7O_2$], and 83.0831 [100%; (**f**+H); C_6H_{11}].

Diol D (5a). The diol D (**5a**) is a colorless oil, IR (liquid) 3400, 1040, 980, 910, 875, and 860 cm^{-1}; PMR ($CDCl_3$) δ 1.05 (3H, s), 1.11 (6H, s), 1.60 (3H, s), 3.68 (1H, *t*-like, J=*ca.* 4.5 Hz), and 4.8—5.6 (3H); MS *m/e* 238.2026 (4%; M$^+$; calcd for $C_{15}H_{26}O_2$: 238.1931), 220.1813 [6%; $(M-H_2O)^+$], 205.1552 [5%; $(M-H_2O-CH_3)^+$], 138.1053 (35%; $C_9H_{14}O$), 125.0946 [36%; (**d**−H); $C_8H_{13}O$], 109.1018 (74%; C_8H_{13}), 95.0853 (87%; C_7H_{11}), 87.0421 [19%; (**e′**−H); $C_4H_7O_2$], 83.0848 [100%; (**f**+H); C_6H_{11}], and 74.0359 [46%; **e**; $C_3H_6O_2$].

Diol E. The diol E is a crystalline compound, mp 131.5—132 °C; IR (Nujol) 3320, 1380, 1362, 1110, 1080, 928, and 868 cm^{-1}; PMR ($CDCl_3$) δ 0.82, 0.97, 1.11, 1.15 (each 3H, s), and 3.77 (1H, m); MS M$^+$ at *m/e* 238. The structure of the diol E remains undetermined due to paucity of this compound.

Acetonide (8a). The acetonide (**8a**) was obtained as a colorless oil, IR (liquid) 1250, 1095, 1085, 1050, 995, 970, and 860 cm^{-1}; PMR (CCl_4) δ 1.03, 1.06, 1.10, 1.28, 1.33 (each 3H, s), 1.63 (3H, br s), 3.88 (1H, dd, J=2, J=7 Hz), and 4.8—5.5 (3H) [lit,[7] 1.04 (6H, s), 1.08 (3H, s), 1.28, 1.34 (each 3H, s), 1.60 (3H, d, J=1 Hz), 3.92 (1H, m), and 5.10 (3H, m)], PMR ($CDCl_3$) δ 1.07 (3H, s), 1.11 (6H, s), 1.37, 1.44 (each 3H, s), 1.64 (3H, d, J=1 Hz), 4.01 (1H, dd, J=2, J=7 Hz), and 4.8—5.5 (3H); MS[7] (indirect) M$^+$ at *m/e* 278 ($C_{18}H_{30}O_2$).

Time-dependent Product Analysis of the Reaction of 6,7-Epoxyhumula-2,9-diene (2) with Sulfuric Acid in Acetone by Means of GLC. Sulfuric acid (8 ml; 1.8 M soln) was added to a solution of the epoxide (**2**: 60 mg) in acetone (8 ml) at 0 °C, and the reaction was allowed to proceed at 0 °C for 30 min and then at room temperature for 7.5 h. Product analysis was carried out as follows. A part of the solution (0.5 ml) was separated from the reaction mixture. To this solution was added a 10% aqueous sodium hydroxide solution (0.4 ml) and the resulting mixture was extracted four times with dichloromethane (total 5 ml). The dichloromethane solution was washed with brine, dried over magnesium sulfate, and evaporated to give a residue, which was dissolved in acetone (1.5 ml) and subjected to an examination by GLC [column, SP-1000 (10%), 4 (mm)×2 (m); 180—220 °C (temperature elevated at the rate of 5 °C/min); N_2 flow rate, 55 ml/min] (Fig. 2). The retention times under these conditions for **2**, **3**, **4**, **5b**, **8a**, and **9** were 5.6, 15.2, 8.2, 17.4, 4.8, and 24.6 min, respectively.

Product Analysis of the Reaction of Tricyclohumuladiol (3) with Sulfuric Acid in Acetone by Means of GLC. To a solution of tricyclohumuladiol (**3**: diol A; 71 mg) in acetone (9 ml) was added 1.8 M sulfuric acid (9 ml) with stirring at 0 °C. The reaction was allowed to proceed at room temperature for 8 h. Product analysis was effected as mentioned above. The result is shown as in Fig. 3.

Oxidation of the Diol B (9). Chromium trioxide (52 mg) was added to a mixture of pyridine (75 mg) and dichloromethane (1.3 ml) with stirring for 15 min. To the solution, the diol B (20 mg) in dichloromethane (2 ml) was added. The reaction mixture was stirred at room temperature for 40 min. The organic solution was separated by decantation and the residue was washed thoroughly with ether. The combined solution was evaporated *in vacuo* and the residue was extracted with ether. The ethereal layer was washed with 1% aqueous sodium hydroxide solution, brine, and dried over sodium sulfate. Evaporation of the solvent gave a residue which was dissolved in hexane, passed through a column of silica gel (5 g), and eluted with hexane–ether (2: 3) (each fraction, 3 ml). Fractions 5 and 6 gave a dione and fractions 8—13 a crude mixture of monoketones and the dione. This mixture was further subjected to separation by preparative TLC to afford the dione and a mixture of monoketones. *5,9-Dioxo-4,8,11,11-tetramethyltricyclo[6.3.0.0^{2,4}]undecane* (10; total 7.5 mg), a colorless oil; IR (CCl_4) 1740, 1710, 1680, 1380, and 1345 cm^{-1}; IR (liquid) 1735, 1700, 1670, 1380, 1345, 1275, 1230, and 895 cm^{-1}; UV (EtOH) λ_{max} 212 nm (ε 2200); PMR ($CDCl_3$) δ 1.11, 1.20, 1.22, 1.34 (each 3H, s), 2.30 (2H, d, J=*ca.* 1 Hz), and 2.56 (2H, dd, J=5, J=7 Hz); MS *m/e* 234.1612 (35%; M$^+$; calcd for $C_{15}H_{22}O_2$: 234.1618), 219.1394 [9%; $(M-CH_3)^+$], 151.1130 [94%; (**a**+H) and/or (**b**−H); $C_{10}H_{15}O$], 123.0805 [31%; (**c**−H); $C_8H_{11}O$], 109.1031 (100%; C_8H_{13}), and 69.0335 (66%; C_4H_5O); GLC R_t=10.8 min [column, SP-1000 (10%); 220 °C; N_2 flow rate 90 ml/min], R_t=4.0 min [column, Dexsil-300GC (5%); 170 °C; N_2 flow rate, 50 ml/min].

Acetylation of the Diol B (9). A solution of the diol B (**9**; 33 mg) in pyridine was treated with acetic anhydride at room temperature for 30 min. Methanol was added to decompose an excess of acetic anhydride. The solvents were evaporated under reduced pressure to give an oily residue, which was dissolved in hexane–ether. Crystals (7 mg; diol B) separated from the solution were removed by filtration and the filtrate was passed through a column of silica gel (5 g). Elution with hexane–ether (3: 2; each fraction, 5 ml) gave a *diacetate* (**11**; 8 mg; from frs 1—4), mp 88.5—90.5 °C (crystallized from hexane), IR (Nujol) 3050, 1735, 1245, 1040, and 980 cm^{-1}; PMR ($CDCl_3$) δ 0.35—0.63 (3H), 1.02, 1.04, 1.10, 1.16, 2.02, 2.05 (each 3H, s), 4.50 (1H, dd, J=7.5, J=10 Hz; H–C–OAc), and 4.82 (1H, dd, J=7.5, J=11 Hz; H–C–OAc); MS *m/e* 322.2155 (1%; M^+; calcd for $C_{19}H_{30}O_4$: 322.2142), 280.2031 [5%; $(M-CH_3CO+H)^+$], 263.2007 [17%; $(M-AcOH+H)^+$], 262.1904 [5%; $(M-AcOH)^+$], 220.1824 [17%; $(M-AcOH-CH_3CO+H)^+$], 205.1581 [18%; $(M-AcOH-CH_3CO-CH_3+H)^+$], 203.1774 [23%; $(M-2\times AcOH+H)^+$], 202.1709 [46%; $(M-2\times AcOH)^+$], 187.1482 [46%; $(M-2\times AcOH-CH_3)^+$], 162.1407 (100%, $C_{12}H_{19}$), 135.1164 [49%; (**a**—AcOH+H) and/or (**b**—AcOH—H); $C_{10}H_{15}$], 133.1015 [51%; (**a**—AcOH—H); $C_{10}H_{13}$], 109.1020 (66%; C_8H_{13}), and 107.0861 [80%; (**c**—AcOH—H); C_8H_{11}]. Fractions 5 and 6 yielded a *monoacetate* (**12**; 5 mg), a colorless oil, IR (liquid) 3420, 3050, 1735, 1720 (sh), 1380, 1365, 1250, and 1030 cm^{-1}; PMR ($CDCl_3$) δ *ca.* 0.4 (2H, m), 0.62 (1H, br s), 1.00 (3H, s), 1.06 (6H, s), 1.15, 2.05 (each 3H, s), 3.88 (1H, dd, J=8, J=11 Hz; H–C–OH), and 4.53 (1H, dd, J=7, J=10 Hz; H–C–OAc); MS *m/e* 280.2032 (3%; M^+; calcd for $C_{17}H_{28}O_3$: 280.2036), 265.1812 [2%; $(M-CH_3)^+$], 262.1926 [2%; $(M-H_2O)^+$], 238.1912 [7%; $(M-CH_3CO+H)^+$], 220.1818 [22%; $(M-AcOH)^+$], 205.1585 [33%; $(M-AcOH-CH_3)^+$], 202.1696 [23%; $(M-AcOH-H_2O)^+$], 180.1513 (54%; $C_{12}H_{20}O$), 162.1414 (60%; $C_{12}H_{18}$), 135.1109 [75%; (**a**—AcOH+H) and/or (**b**—H_2O—H); $C_{10}H_{15}$], 133.1002 [43%; (**a**—AcOH—H); $C_{10}H_{13}$], 125.0967 [75%; (**c**—H); $C_8H_{13}O$], 121.0984 (83%; C_9H_{13}), 109.1017 (83%; C_8H_{13}), and 107.0859 [100%; (**c**—H_2O—H); C_8H_{11}]. Fractions 7—11 were combined and the solvents were evaporated to give a residue, which was subjected to separation by silica gel dry column chromatography [9 g; elution with hexane–ether (1: 1); each fraction 2.3 ml]. Fractions 16—18 gave **12** (5 mg) and fractions 22—30 afforded another *monoacetate* (**13**; 3.8 mg), an amorphous solid, IR (Nujol) 3300, 1730, 1245, and 1030 cm^{-1}; PMR ($CDCl_3$) δ 0.2—0.7 (3H), 0.97, 1.02, 1.10, 1.15, 2.04 (each 3H, s), 3.38 (1H, m), and 4.82 (1H, dd, J=8, J=11 Hz); MS *m/e* 280.2120 (0.2%; M^+; calcd for $C_{17}H_{28}O_3$; 280.2036), 262.1938 [1%; $(M-H_2O)^+$], 220.1823 [5%; $(M-AcOH)^+$], 205.1591 [5%; $(M-AcOH-CH_3)^+$], 202.1722 [5%; $(M-AcOH-H_2O)^+$], 187.1482 (8%; $C_{14}H_{19}$), 135.1128 [16%; (**a**—H_2O+H) and/or (**b**—AcOH+H); $C_{10}H_{15}$], 133.1013 [16%; (**a**—H_2O—H); $C_{10}H_{13}$], 109.1027 (26%; C_8H_{13}), and 107.0866 [30%; (**c**—AcOH—H); C_8H_{11}], and 55.0563 (100%; C_4H_7).

Oxidation of the Monoacetate (12). The monoacetate (**12**; 4.7 mg) in dichloromethane (*ca.* 0.1 ml) was added to a solution prepared from chromium trioxide (11.1 mg), pyridine (18.5 mg), and dichloromethane (0.25 ml). The mixture was stirred at room temperature for 1 h. The reaction mixture was worked up as before to give a keto acetate (**14**; 2.1 mg), a colorless oil; IR (liquid) 3050, 1742, 1736, 1380, 1370, and 1250 cm^{-1}; MS *m/e* 278.1859 (15%; M^+; calcd for $C_{17}H_{26}O_3$: 278.1879), 236.1759 [8%; $(M-CH_3CO+H)^+$], 221.1534 [19%; $(M-CH_3CO-CH_3+H)^+$], 218.1654 [20%; $(M-AcOH)^+$], 203.1439 [22%; $(M-AcOH-CH_3)^+$], 152.1211 (43%; **b**; $C_{10}H_{16}O$), 134.1094 [99%; (**a**—AcOH); $C_{10}H_{14}$], 123.0855 [47%; (**c**—H), $C_8H_{11}O$], 119.0861 [87%; (**a**—AcOH—CH_3); C_9H_{11}], 109.1013 (79%; C_8H_{13}), and 94.0782 (100%; C_7H_{10}).

Acetonization of the Diol D (5a). To a solution of the diol D (**5a**; 19.5 mg) in acetone (0.5 ml) containing a trace of sulfuric acid, was added anhydrous cupric sulfate (40 mg) and the mixture was stirred vigorously at room temperature for 18 h. Cupric sulfate was separated by filtration and washed with acetone. The combined acetone solution was neutralized with powdered calcium hydroxide. After filtration, the solvent was removed to give a residue, which was chromatographed on a column of silica gel (5 g). Elution with hexane–ether (17: 3; each fraction, 2.5 ml) gave an acetonide (8.7 mg; from frs 4—7), whose spectral data were identical with those of the acetonide (**8a**).

Acid Hydrolysis of the Acetonide (8a). A mixture of the acetonide (**8a**; 52 mg), methanol (3 ml), and 0.5 M hydrochloric acid (1.5 ml) was stirred at room temperature for 7 h. The reaction mixture was neutralized with aqueous sodium hydroxide solution and extracted with ether after methanol was removed. The ethereal solution was washed with brine, dried over sodium sulfate, and evaporated to give a residue (37 mg), which was chromatographed on a column of silica gel (5 g; elution with hexane–ether (1: 2); each fraction, 5 ml). Fractions 13—21 yielded the diol D (**5a**; 26 mg).

Treatment of Humulene (1) with Osmium Tetroxide. To a solution of humulene (**1**; 54 mg) in dry ether (5 ml) was added osmium tetroxide (67 mg) in dry ether (1.5 ml) under nitrogen atomosphere and the reaction mixture was left for 14 h at room temperature in the dark. A solution of sodium sulfite (470 mg) in water (5 ml) and ethanol (2.5 ml) was added to the reaction mixture and refluxed for 4 h under nitrogen atmosphere in the dark. The precipitate was removed by filtration and washed with hot ethanol. The combined solution was concentrated under reduced pressure, and extracted with ether. The ethereal solution was washed with brine, dried over sodium sulfate, and the solvent was evaporated to give a residue (40 mg), which was chromatographed on a column of silica gel (5 g; elution with hexane–ether (1: 2); each fraction 2.5 ml). Fractions 7—11 gave a diol (27.3 mg) which was identified to be the diol D (**5a**).

Periodate Oxidation of the Diol C (5b). A solution of the diol C (**5b**; 5.3 mg) in methanol (5 ml) was treated with 22.6 mM aqueous potassium periodate solution (2 ml) at room temperature for 28 h. Aqueous sodium arsenite solution (5 ml; 26.3 mM soln) and 20% aqueous potassium iodide solution (1 ml) were added and the resulting mixture was titrated with iodine solution; it was shown that *ca.* 0.65 equivalent mole of periodate was consumed. After the titration was effected, the mixture was extracted with dichloromethane. The organic layer was washed with brine, dried over sodium sulfate, and the solvent was evaporated. Crystals (2.6 mg; **5b**; diol C) separated from the residual oil were filtered. The residue was then passed through a column of silica gel (1 g) and eluted with hexane–ether (1: 1) to give a *keto aldehyde* (**15**; 0.4 mg), a colorless oil, IR (liquid) 2720, 1720, 1380, 1360, 1160, and 975 cm^{-1}; PMR ($CDCl_3$) δ 0.99 (6H, s), 1.62 (3H, br s), 1.98 (2H, d, J=7 Hz), 2.14 (3H, s), 2.43 (4H), 3.11 (2H, d, J=6 Hz), 5.18 (1H, t, J=7 Hz), 5.49 (2H, d, J=2 Hz), and 9.75 (1H, br s); MS *m/e* 218 [0.3%; $(M-H_2O)^+$], 207 [0.3%; $(M-CHO)^+$], 193 [0.6%; $(M-CH_3CO)^+$], 178 (15%), 125 (45%), and 43 (100%); GLC R_t=6.2 min [column, SP-1000 (10%); 220 °C; N_2 flow rate, 55 ml/min], R_t=7.7 min [column, Dexsil-300GC (5%); 200 °C; N_2 flow rate, 53 ml/min].

Periodate Oxidation of the Diol D (5a). A solution of the diol D (**5a**; 6.5 mg) in methanol (3 ml) was treated with

24.2 mM aqueous potassium periodate solution (2 ml) at room temperature for 24 h; *ca.* 1.1 equivalent mole of periodate was consumed. Treatment of the reaction mixture as described above afforded a keto aldehyde (**15**; 5 mg), whose spectral data and chromatographic (TLC and GLC) properties were identical with those of the keto aldehyde obtained from the diol C (**5b**).

Acetylation of the Diol C (5b). A solution of the diol C (**5b**; 11.7 mg) in pyridine was acetylated with acetic anhydride at room temperature for 2 days. Treatment as usual gave an oily product, which was passed through a silica gel dry column [5 g; elution with hexane–ether (2: 3)] to yield a *monoacetate* (**16b**; 7.4 mg), an amorphous solid, IR (liquid) 3450, 1730, 1710 (sh), 1380, 1373, 1260 (sh), 1245, 1025, 980, 875, and 800 cm^{-1}; PMR ($CDCl_3$) δ 1.07, 1.16, 1.23, 1.64, 2.10 (each 3H, s), and 4.9—5.5 (4H); MS *m/e* 280 (1%; M^+; $C_{17}H_{28}O_3$), 262 [1%; $(M-H_2O)^+$], 220 [5.5%; $(M-AcOH)^+$], 202 [4%; $(M-AcOH-H_2O)^+$], 138 (18%), 129 [1.5%; (**e**′−H)], 125 [100 %; (**d**–H)], 116 (40%; **e**), 109 (36%), 95 (73%), 83 [50%; (**f**+H)], 74 (30%), and 68 (70%). Further purification was not effected due to paucity of the material.

Acetylation of the Diol D (5a). The diol (**5a**; 15.5 mg) in pyridine was acetylated with acetic anhydride at room temperature for 16 h. The usual treatment gave a product which was passed through a silica gel dry column (5 g) and eluted with hexane–ether (2: 3) to afford a *monoacetate* (**16a**; 6.2 mg), mp 132.5—133.0 °C (crystallized from hexane); IR (Nujol) 3450, 1740 (sh), 1710, 1260, 1240 (sh), 1035, 990, 965, and 880 cm^{-1}; PMR ($CDCl_3$) δ 1.07, 1.14, 1.18, 1.63, 2.11 (each 3H, s), and 4.7—5.7 (4H); MS *m/e* 280 (1%; M^+; $C_{17}H_{28}O_3$), 262 [2%; $(M-H_2O)^+$], 220 [5%; $(M-AcOH)^+$], 205 [2%; $(M-AcOH-CH_3)^+$], 202 [5%; $(M-AcOH-H_2O)^+$], 138 (32%), 129 [16%; (**e**′−H)], 125 [65%; (**d**–H)], 116 (71 %; **e**), 109 (45%), 95 (100%), 83 [59%; (**f**+H)], and 68 (96%).

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