Diethyl Ether–Boron Trifluoride (1/1) Induced Transannular Cyclization Reaction of Humulene 2,3-Epoxide

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The treatment of (6*E*, 9*E*)-2,3-epoxy-3,7,11,11-tetramethylcycloundeca-6,9-diene with $Et_2O{\cdot}BF_3$ produced four novel transannular cyclized compounds of (4*E*)-(1*S**, 8*S**, 9*S**)-8-acetoxy-6,6,9-trimethyl-2-methylenebicyclo[7.2.0]undec-4-ene (**13**), (2*Z*, 4*E*)-(1*S**, 8*S**, 9*S**)-8-acetoxy-2,6,6,9-tetramethylbicyclo[7.2.0]undeca-2,4-diene (**14**), (6*E*)-(1*R**, 2*R**, 3*S**, 10*R**)-3-acetoxy-2,5,5-trimethyl-9-methylenebicyclo[8.1.0]undec-6-ene (**15**), and (4*E*)-(1*S**, 2*S**, 8*S**, 9*S**)-2,8-diacetoxy-2,6,6,9-tetramethylbicyclo[7.2.0]undec-4-ene (**16**) together with three new acetates: (2*E*, 5*E*, 8*E*)-1-acetoxy-2,6,10,10-tetramethylcycloundeca-2,5,8-triene, (1*E*, 6*E*)-3,9-diacetoxy-2,5,5,9-tetramethylcycloundeca-1,6-diene, and (4*E*, 7*E*)-1-acetoxy-3,3,7-trimethyl-11-methylenecycloundeca-4,7-diene. The configurations of the bicyclo[7.2.0]undecane skeletons (**13**, **14**, and **16**) and **15** maintained the shape of TC and CT conformers of the original epoxide, respectively.

We have studied the transannular cyclization of humulene epoxides caused by a cleavage of the epoxide rings in connection with a biogenetic study of cyclic sesquiterpenes.[1—4] It is known that a medium-size cyclic olefin maintains its conformation through transannular cyclization to give a product whose conformation is very similar to that of the original olefin.[5] The cleavage reaction, followed by transannular cyclization of humulene 9,10-epoxide (**1**), proceeded under two different conditions [trimethylsilyl triflate (TMSOTf) in toluene and $Et_2O{\cdot}BF_3$ in Ac_2O]. As a result of this reaction, two compounds, **2** and **3**, whose configurations are similar to the two stable CT and CC conformers of the original epoxide, were obtained. Compounds **2** and **3** were converted to natural products: africanol (**4**) and bicyclohumulenone (**5**), respectively.[6] On the other hand, humulene 6,7-epoxide (**6**) was converted by a treatment with TMSOTf to a transannular cyclized product **7** that had the configuration of the most stable CT conformer of the original epoxide (Scheme 1).[7] Since the reaction of humulene 2,3-epoxide (**8**) has not been examined, a detailed study of the reaction of **8** in the $Et_2O{\cdot}BF_3/Ac_2O$ system is now described in this report.

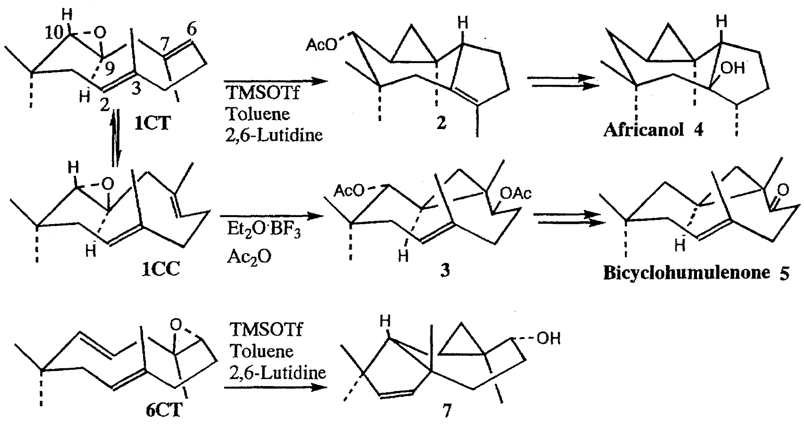
Experimental

Preparation of (6*E*, 9*E*)-2,3-Epoxy-3,7,11,11-tetramethylcycloundeca-6,9-diene (Humulene 2,3-Epoxide, 8).[8] To a solution of 7.6 g (37 mmol) of humulene **9** in 190 ml of dry dichloromethane chilled in an ice bath was slowly added *m*-chloroperbenzoic acid (12.9 g) in portions. The suspension was kept at 0 °C for 0.5 h, and then at room temperature for 1 h. The reaction mixture was washed once with a 10% $Na_2S_2O_3$ solution, twice with an aqueous NaOH solution (1 mol dm^{-3}), twice with water, and dried over Na_2SO_4. Removal of the solvent left a colorless viscous oil. Crystallization of the crude product from hexane yielded 8.6 g (97.8%) of pure (9*E*)-2,3;6,7-diepoxy-3,7,11,11-tetramethylcycloundec-9-ene (humulene 2,3;6,7-diepoxide, **10**, mp 102—104 °C).

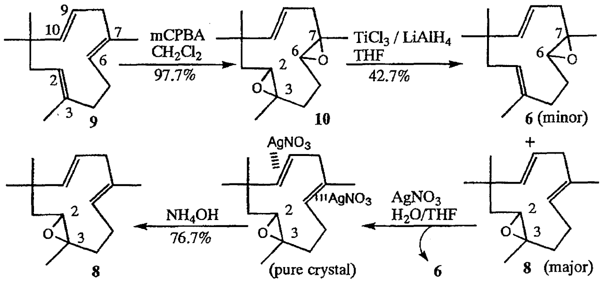
The reduction of **10** (7.53 g, 31.9 mmol) with Ti(II) reagent [prepared with $TiCl_3$ (5.17 g) and $LiAlH_4$ (2.55 g)] in dry THF (120 ml) at 10—20 °C for 40 min gave a mixture of **6**, **8**, **9**, and **10**, from which a chromatographic separation (eluting solvent, 10% EtOAc/hexane) produced 1.77 g (27.3%) of **9**, 3.0 g (42.7%) of a mixture of **6** and **8**, and 1.88 g (25%) of **10**.

To the stirred mixture of **6** and **8** was added an aqueous solution of $AgNO_3$ (9.6 g of $AgNO_3$ and 3.8 ml of water). After 5—10 min at room temperature under stirring, the mixture was solidified by the formation of a $AgNO_3$ complex of **8**. To the mixture was added 60 ml of dry THF; the complex was then crushed to a powder, which was collected by sucking filtration. After the complex was added to a mixture of aqueous ammonia and hexane, pure **8** was extracted three times with hexane. The extracts were washed twice with water, dried over Na_2SO_4, and concentrated in vacuo to yield 2.3 g (32% from **9**) of the starting material **8** (Scheme 2).

Diethyl Ether–Boron Trifluoride (1/1) Induced Reaction of 8. To a stirred solution of 1.6 g (7.27 mmol) of **8** in 33 ml of Ac_2O at −20 °C under an argon atmosphere was added 0.9 ml (7.27 mmol) of $Et_2O{\cdot}BF_3$. The mixture was kept at 0 °C until **8** was almost consumed. After stirring for 10 min, ice and water (about 30 ml) was added to the reaction mixture; Ac_2O as a solvent was then hydrolyzed to AcOH at room temperature for 0.5 h. The solution was diluted with 200 ml of water and extracted three times with benzene. The extracts were washed twice with water, three times with a saturated solution of $NaHCO_3$, once with a saturated solution of NaCl, and finally dried over Na_2SO_4. Removal of the solvent yielded a viscous oil, from which separation by silica-gel column chromatography (2.5% EtOAc/hexane) gave a mixture of five monoacetates (**11**, **12**, **13**, **14**, and **15**, 535 mg, 28.1%), a diacetate **16** (531 mg, 26.0%), and another diacetate **17** (384 mg, 13.8%). The two diacetates (**16** and **17**) were crystallized from hexane and the mixture of the five monoacetates was converted to the corresponding benzoates (**18**, **19**, **20**, **21**, and **22**).



Scheme 1. C and T symbols represent the same crossed and parallel arrangement as these of humulene (Scheme 5), respectively, that is, first C and second T symbols of **1CT** denote crossed arrangement of 2,3-double bond and 9,10-epoxide ring, and parallel arrangement of 2,3- and 6,7-double bonds, respectively.



Scheme 2.

Preparation of Benzoates (18, 19, 20, 21, and 22) from the Mixture of Monoacetates (11, 12, 13, 14, and 15). Hydrolysis of the mixture (**11**, **12**, **13**, **14**, and **15**) was carried out with 5 ml of a NaOH solution (1 mol dm^{-3}) in methanol (20 ml) under reflux for 12 h. The reaction mixture was concentrated in vacuo, diluted with 50 ml of water, and extracted three times with EtOAc. The extracts were washed twice with water, once with a saturated solution of NaCl, dried over Na_2SO_4, and concentrated under reduced pressure to afford a mixture of the corresponding alcohols. Chromatographic separation (5% EtOAc/hexane) of the alcohols left two mixtures, **A** (170 mg) and **B** (139 mg), of which esterification with benzoic anhydride (1.5 molar amounts) in pyridine (1 ml) at 80 °C for 3 d produced two mixtures, **C** and **D**, respectively. Mixture **C** was separated into **19** (57 mg, 2.4% from **8**), **20** (112 mg, 4.8% from **8**), and **21** (71 mg, 3.0% from **8**) by chromatography (eluting solvent, 10% EtOAc/hexane–20% EtOAc/benzene) over silica-gel impregnated with silver nitrate (10%). Mixture **D** was separated into **18** (51 mg, 2.1% from **8**) and **22** (153 mg, 6.5% from **8**) by HPLC using a column of μPORASIL (P/N 27477, Waters, 0.5% EtOAc/hexane).

(4*E*)-(1*S, 2*S**, 8*S**, 9*S**)-2,8-Diacetoxy-2,6,6,9-tetramethylbicyclo[7.2.0]undec-4-ene (16):** Mp 87—89 °C; IR (Nujol) 1710 cm^{-1}; ^{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); ^{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=O×2); HRMS Calcd for $C_{19}H_{30}O_4$: M, 322.2145. Found: *m*/*z* 322.2178.

(1*E*, 6*E*)-(3*S, 9*S**)-3,9-Diacetoxy-2,5,5,9-tetramethylcycloundeca-1,6-diene (17):** Mp 88—90 °C; IR (Nujol) 1728 cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz) δ = 0.90, 1.05 (each 3H, s, 5-Me_2), 1.26 (1H, d, $J_{4\alpha\beta}$ = 13.9 Hz, 4α-H), 1.37 (1H, dd, $J_{4\beta\alpha}$ = 13.9, $J_{4\beta-3\alpha}$ = 8.6 Hz, 4β-H), 1.41 (3H, s, 9α-Me), 1.42 (1H, m, 10-H), 1.82 (1H, bs, 2-Me), 1.96 (3H, s, OAc), 1.99 (1H, m, 11-H_2), 2.02 (3H, s, OAc), 2.53 (1H, dd, $J_{8\alpha\beta}$ = 11.9, $J_{8\alpha-7}$ = 5.2 Hz, 8α-H), 2.69 (1H, m, 10-H), 2.70 (1H, dd, $J_{8\beta-7}$ = 9.2, $J_{8\beta\alpha}$ = 11.9 Hz, 8β-H), 5.18 (1H, dd, $J_{1-11\alpha\beta}$ = 5.6, 9.6 Hz, 1H), 5.32 (1H, d, $J_{3\alpha-4\beta}$ = 8.6 Hz, 3α-H), 5.36 (1H, d, J_{6-7} = 16.2 Hz, 6-H), 6.04 (1H, ddd, $J_{7-8\alpha\beta}$ = 5.2, 9.2, J_{7-6} = 16.2 Hz, 7-H); ^{13}C NMR ($CDCl_3$, 270 MHz) δ = 17.86 (q, 2-Me), 18.39 (q, 9-Me), 21.24 (q, 5-Me), 21.42 (q, OAc), 22.23 (q, OAC), 22.59 (t, 11-C), 30.75 (q, 5-Me), 34.76 (t, 10-C), 36.14 (s, 5-C), 41.39 (t, 8-C), 42.43 (t, 4-C), 72.74 (d, 3-C), 87.26 (s, 9-C), 128.14 (d, 2-C), 131.07 (d, 7-C), 140.50 (d, 6-C), 140.63 (s, 2-C), 169.72 (s, C=O), 170.35 (s, C=O); HRMS Calcd for $C_{19}H_{30}O_4$: M, 322.2145. Found: *m*/*z* 322.2104.

(2*E*, 5*E*, 8*E*)-1-Benzoyloxy-2,6,10,10-tetramethylcycloundeca-2,5,8-triene (18): ^{1}H NMR ($CDCl_3$, 270 MHz), δ = 1.07 (3H, s, 10α or 10β-Me), 1.11 (3H, s, 10β or 10α-Me), 1.59 (3H, s, 2 or 6-Me), 1.73 (3H, s, 6 or 2-Me), 1.89 (1H, dd, $J_{11\beta-1\alpha}$ = 2.6, $J_{11\alpha\beta}$ = 13.5 Hz, 11β-H), 2.20 (1H, dd, $J_{11\alpha\beta}$ = 13.5, $J_{11\alpha-1\alpha}$ = 11.6 Hz, 11α-H), 2.28 (1H, ddd, $J_{4\alpha\beta}$ = 13.5, $J_{4\alpha-3}$ = 9.9, $J_{4\alpha-5}$ = 7.9 Hz, 4α-H), 2.54 (2H, d, J_{7-8} = 7.2 Hz, 7-H_2), 2.65 (1H, ddd, $J_{4\beta-3}$ = 6.6, $J_{4\beta-5}$ = 7.9, $J_{4\beta\alpha}$ = 13.5 Hz, 4β-H), 4.95 (1H, t, J_{5-4} = 7.9 Hz, 5-H), 5.21 (1H, d, J_{9-8} = 15.8 Hz, 9-H), 5.25 (1H, dd, $J_{1\alpha-11\alpha}$ = 11.6, $J_{1\alpha-11\beta}$ = 2.6 Hz, 1α-H), 5.32 (1H, dd, $J_{3-4\alpha}$ = 9.9, $J_{3-4\beta}$ = 6.6 Hz, 3H), 5.61 (1H, dt, J_{8-7} = 7.2, J_{8-9} = 15.8 Hz, 8-H), 7.04—8.05 (5H, m, benzoyloxy group); ^{13}C NMR ($CDCl_3$, 270 MHz) δ = 11.32 (q, 14 or 15-C), 17.90 (q, 15 or 14-C), 24.03 (q, 12 or 13-C), 28.99 (t, 11-C), 29.81 (q, 13 or 12-C), 36.98 (s, 10-C), 40.83 (t, 7 or 4-C), 41.85 (t, 4 or 7-C), 80.58 (d, 1-C), 120.88 (d, 8-C), 127.10 (d, 5 or 3-C), 128.27 (d, C×2), 129.51 (d, C×2), 130.76 (s), 130.96 (s, 2 or 6-C), 132.72 (d), 141.56 (d, 9-C), 141.65 (6 or 2-C), 165.79 (s, C=O); IR (neat) 1710 cm^{-1}; HRMS Calcd for $C_{22}H_{28}O_2$: M, 324.2080. Found: *m*/*z* 324.2081.

(4*E*, 7*E*)-1-Benzoyloxy-3,3,7-trimethyl-11-methylenecycloundeca-4,7-diene (19): ^{1}H NMR ($CDCl_3$, 270 MHz), $\delta = 0.99$, 1.09, 1.81 (each 3H, s), 1.76 (1H, dd, $J_{2\beta-1\alpha} = 6.3$, $J_{2\beta\alpha} = 14.3$ Hz, 2β-H), 1.86 (1H, dd, $J_{2\alpha-1\alpha} = 3.5$, $J_{2\alpha\beta} = 14.3$ Hz, 2α-H), 2.18—2.36 (4H, m, 9 and 10-H_2), 2.57 (1H, dd, $J_{6\alpha-5} = 6.3$, $J_{6\alpha\beta} = 13.2$ Hz, 6α-H), 2.68 (1H, dd, $J_{6\beta-5} = 9.2$, $J_{6\beta\alpha} = 13.2$ Hz, 6β-H), 4.98, 5.10 (each 1H, s, 15-H_2), 5.29 (1H, bt, $J_{8-9\alpha\beta} = 5.8$ Hz, 8-H), 5.44 (1H, d, $J_{4-5} = 16.7$ Hz, 4-H), 5.50 (1H, dd, $J_{1\alpha-2\alpha} = 3.5$, $J_{1\alpha-2\beta} = 6.3$ Hz, 1α-H), 5.85 (1H, ddd, $J_{5-6\alpha} = 6.3$, $J_{5-6\beta} = 9.2$, $J_{5-4} = 16.7$ Hz, 5-H), 7.43—8.00 (5H, m, benzoyloxy group); IR (neat) 1710 cm^{-1}; ^{13}C NMR ($CDCl_3$, 270 MHz) $\delta = 18.21$ (q, 7-Me), 22.93 (q, 3a or b-Me), 28.09 (t, 10 or 9-C), 29.72 (q, 3b or a-Me), 35.20 (t, 9 or 10-C), 36.26(s, 3-C), 40.76 (t, 6-C), 47.21 (t, 2-C), 74.23 (d, 1-C), 113.21 (t, 15-C), 127.08 (d, 8-C), 128.30 (d, C×2), 129.08 (d, 5-C), 129.56 (d, C×2), 130.80 (s), 132.72 (d), 139.41 (s, 7-C), 141.01 (d, 4-C), 150.49 (s, 11-C), 165.89 (s, C=O); HRMS Calcd for $C_{22}H_{28}O_2$: M, 324.2080. Found: *m/z* 324.2076.

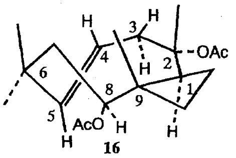
(4*E*)-(1*S, 8*S**, 9*S**)-8-Benzoyloxy-6,6,9-trimethyl-2-methylenebicyclo[7.2.0]undec-4-ene (20):** ^{1}H NMR ($CDCl_3$, 270 MHz) $\delta = 1.05$, 1.08, 1.31 (each 3H, s), 1.48 (1H, m, 10α or β-H), 1.65 (1H, m, 10β or α-H), 1.72 (1H, m, 11α or β-H), 1.95 (1H, m, 11β or α-H), 2.54 (1H, bt, $J_{3\alpha\beta} = J_{3\alpha-4} = 11.4$ Hz, 3α-H), 2.77 (1H, dd, $J_{1\alpha-11} = 11.4$, 11.7 Hz, 1α-H), 2.94 (1H, dd, $J_{3\beta\alpha} = 11.4$, $J_{3\beta-4} = 4.6$ Hz, 3β-H), 4.89, 5.08 (each 1H, s, 12-H_2), 5.21 (1H, d, $J_{8\alpha-7\beta} = 9.8$ Hz, 8α-H), 5.31 (1H, ddd, $J_{4-3\beta} = 4.6$, $J_{4-3\alpha} = 11.4$, $J_{4-5} = 16.3$ Hz, 4H), 5.74 (1H, d, $J_{5-4} = 16.3$ Hz, 5-H), 7.42—8.01 (5H, m, benzoyloxy group); IR (neat) 1710 cm^{-1}; ^{13}C NMR ($CDCl_3$, 270 MHz) $\delta = 16.89$ (q), 19.12 (t, 11-C), 28.34 (q), 28.99 (q), 31.20 (t, 10-C), 32.84 (s, 6 or 9-C), 43.78 (t, 3-C), 47.62 (d, 1-C), 48.39 (s, 9 or 6-C), 49.67 (t, 7-C), 81.28 (d, 8-C), 112.72 (t, 12-C), 127.0 (d, 4-C), 128.28 (d, C×2), 129.49 (d, C×2), 131.0 (s), 132.63 (d), 141.71 (d, 5-C), 145.0 (s, 2-C), 165.9 (s, C=O); HRMS Calcd for $C_{22}H_{28}O_2$: M, 324.2080. Found: *m/z* 324.2079.

(2*Z*, 4*E*)-(1*S, 8*S**, 9*S**)-8-Benzoyloxy-2,6,6,9-tetramethylbicyclo[7.2.0]undeca-2,4-diene (21):** ^{1}H NMR ($CDCl_3$, 270 MHz) $\delta = 1.07$, 1.11, 1.27 (each 3H, s), 1.67 (3H, bs, 2-Me), 1.51 (1H, ddd, $J_{10\alpha\beta} = 9.7$, $J_{10\alpha \text{ or } \beta-11} = 5.6$, 9.7 Hz, 10$\alpha$ or β-H), 1.56 (1H, dd, $J_{7\alpha\beta} = 12.9$, $J_{7\alpha-8\alpha} = 1.3$ Hz, 7α-H), 1.67 (1H, ddd, $J_{10\beta\alpha} = 9.7$, $J_{10\beta \text{ or } \alpha-11} = 8.2$, 9.7 Hz, 10$\beta$ or α-H), 1.86 (2H, m, 11-H_2), 2.03 (1H, dd, $J_{\beta-8\alpha} = 11.2$, $J_{7\beta\alpha} = 12.9$ Hz, 7β-H), 3.41 (1H, bt, $J = 9.2$ Hz, 1α-H), 5.35 (1H, dd, $J_{8\alpha-7\beta} = 1.3$, $J_{8\alpha-7\beta} = 11.2$ Hz, 8α-H), 5.63 (1H, d, $J_{5-4} = 15.9$ Hz, 5-H), 5.75 (1H, d, $J_{4-5} = 15.9$ Hz, 4-H), 5.81 (1H, bs, 3-H), 7.39—8.0 (5H, m, benzoyloxy group); IR (neat) 1710 cm^{-1}; ^{13}C NMR ($CDCl_3$, 270 MHz) $\delta = 16.1$ (q), 21.7 (t, 11-C), 22.3 (q, 2-Me), 25.6 (q), 27.9 (q), 30.8 (t, 10-C), 33.4 (s, 6 or 9-C), 49.0 (d, 1C), 49.3 (s, 9 or 6-C), 51.0 (t, 7-C), 81.2 (d, 8-C), 122.8 (d, 4 and 5-C), 123.5 (d, 3-C), 128.3 (d, C×2), 129.5 (d, C×2), 130.9 (s), 132.7 (d), 139.8 (s, 2-C), 165.9 (s, C=O); HRMS Calcd for $C_{22}H_{28}O_2$: M, 324.2080. Found: *m/z* 324.2077.

(6*E*)-(1*R, 2*R**, 3*S**, 10*R**)-3-Benzoyloxy-2,5,5-trimethyl-9-methylenebicyclo[8.1.0]undec-6-ene (22):** ^{1}H NMR ($CDCl_3$, 270 MHz) $\delta = 0.32$ (1H, m, 11α 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, benzoyloxy group); ^{13}C NMR ($CDCl_3$, 270 MHz) $\delta = 5.32$ (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, C×2), 129.47 (d, C×2), 131.05 (s), 132.69 (d), 143.04 (d, 6-C), 149.63 (s, 9-C), 165.48 (s, C=O); IR (neat) 1710 cm^{-1}; HRMS Calcd for $C_{22}H_{28}O_2$: M, 324.2080. Found: *m/z* 324.2086].

Results and Discussion

The preparation of humulene 2,3-epoxide (**8**) was achieved by the reduction of humulene 2,3;6,7-diepoxide with Ti(II) in dry THF.[8] The epoxide, contaminated with a small amount of humulene 6,7-epoxide, was purified by the formation of the silver nitrate adduct (crystals), followed by a treatment of the adduct with aqueous ammonia (Scheme 2). The epoxide **8** was mainly transformed into seven materials during the $Et_2O \cdot BF_3$-induced rearrangement. The products were separated to a mixture of five monoacetates (**11**, **12**, **13**, **14**, and **15**) and two diacetates (**16** and **17**) by silica-gel column chromatography. A stereostructural analysis of the obtained pure products was achieved by the ^{1}H–^{1}H COSY spectrum, which revealed the connectivity among various signals due to protons by reading the cross peaks, the C–H COSY spectrum, which was used to assign most of the peaks of ^{1}H NMR to the particular peak of ^{13}C NMR spectrum by picking out the cross peaks, and the NOESY or NOE spectrum, which showed spatially near protons to the particular proton. HRMS of the two diacetates showed the same molecular formula, $C_{19}H_{30}O_4$. The ^{1}H–^{1}H and C–H COSY spectra of **16** revealed the partial structures depicted in Fig. 1. These observations, together with a consideration of the reaction course, led to structure **16** for this diacetate. Furthermore, the NOESY spectrum, observed spatially its near protons with one another, indicated α-faced group of 1αH, 3αH, 5H, and 8αH, and β-faced group of 2βMe, 3βH, 4H, 6βMe, and 9βMe. Therefore, the stereochemistry of **16** was determined based on the above results (Fig. 1). An analysis of the COSY (^{1}H–^{1}H, and C–H) and ^{13}C NMR spectra of another diacetate also showed the presence of the following partial structures: ■–CH_2–CH(OAc)–■, –(CH_3)C=CH–CH_2–CH_2–■,



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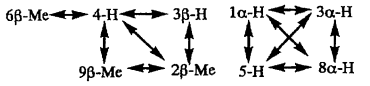
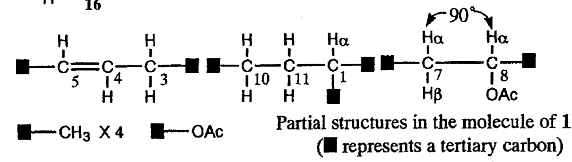
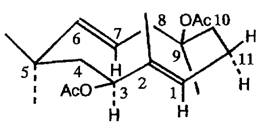


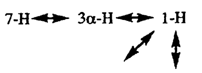
Results of NOESY studies of **16**.



Partial structures in the molecule of **16**.
(■ represents a tertiary carbon)



17



Results of NOE studies of **17**.

Fig. 1. Partial structures of **16**, and NOESY and NOE studies of **16** and **17**.

■–CH=CH–CH$_2$–■, ■–CH$_3$×3, and ■–OAc (■ shows a tertiary carbon), from which structure **17** was assembled. NOESY studies demonstrated the existence of the same α-faced group (1H, 7H, and 9αMe) with 3αH, from which the stereochemistry of **17** was displayed (Fig. 1). A mixture of monoacetates was converted to the corresponding benzoates (**18**, **19**, **20**, **21**, and **22**) by hydrolysis and benzoylation. The molecular formula of the five benzoates can be represented as $C_{22}H_{28}O_2$ based on the HRMS spectra. The NMR (^{1}H and ^{13}C) spectra of the first and second benzoates elucidated that these had three double bonds in an eleven-membered ring system. From the existence of partial structures (■–CH$_2$–CH(OCOC$_6$H$_5$)–■, –(CH$_3$)C=CH– ×2, and ■–CH=CH–CH$_2$–■, ■–CH$_3$ ×2, ■ represents a tertiary carbon), the structure of the first benzoate was determined to be **18** (Fig. 2). The observation of NOE of its three protons (8H, 1αH, and 3H) suggested a trans stereochemistry of its 2,3-double bond. Since the partial structures of the second benzoate were the same as that of **18**, except for –(CH$_3$)-C=CH– in **18** and –C=CH$_2$ in the benzoate, its structure was depicted as **19** (Fig. 2). The structure of the third benzoate was determined as formula **20**, based on a comparison of its NMR (^{1}H, ^{13}C, ^{1}H–^{1}H COSY, and C–H COSY) spectra with that of **16**; its configuration is shown in Fig. 3 based on an NOE observation of four protons (1αH, 3αH, 5H, and 8αH). The stereostructure of the fourth benzoate was also clarified as **21** by the existence of partial structures (shown by an analysis of its ^{1}H–^{1}H and C–H COSY spectra), a comparison of its NMR with those of **16** and **20**, and an NOE observation of three protons (1αH, 5H, and 8αH, Fig. 3). Stereostructural studies of the fifth benzoate were carried out based on the NMR (^{1}H–^{1}H and C–H COSY) spectra, and showed partial structures and a value of 0 Hz for the three coupling constants ($J_{3\alpha-4\alpha}$, $J_{3\alpha-2\alpha}$, and $J_{2\alpha-1\alpha}$) pictured in Fig. 4. A consideration of the possible combination of these fragments, probable reaction course and its NOE observation of several protons (β-faced group of 2βMe and 10βH, and α-faced group of 1αH, 3αH, 5αMe, and 7H) suggested that the stereostructure can be represented by **22** (Fig. 4). Therefore, the structures of the five monoacetates are according to formulas **11**, **12**, **13**, **14**, and **15** (Scheme 3).

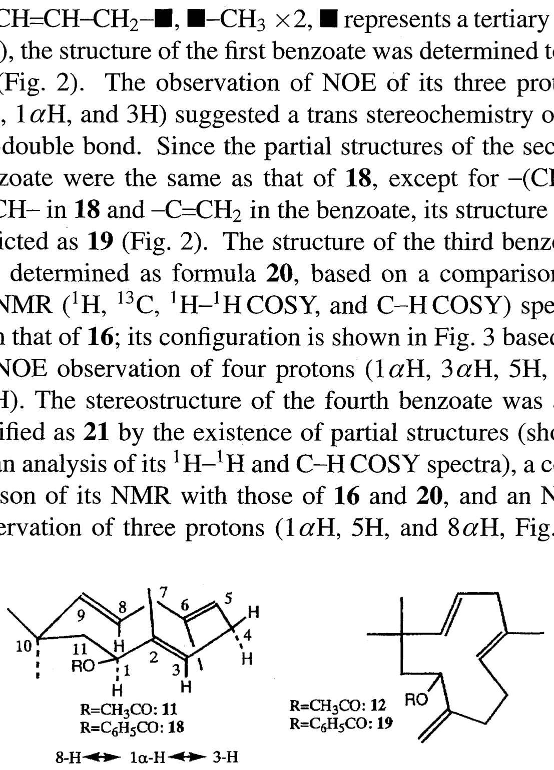
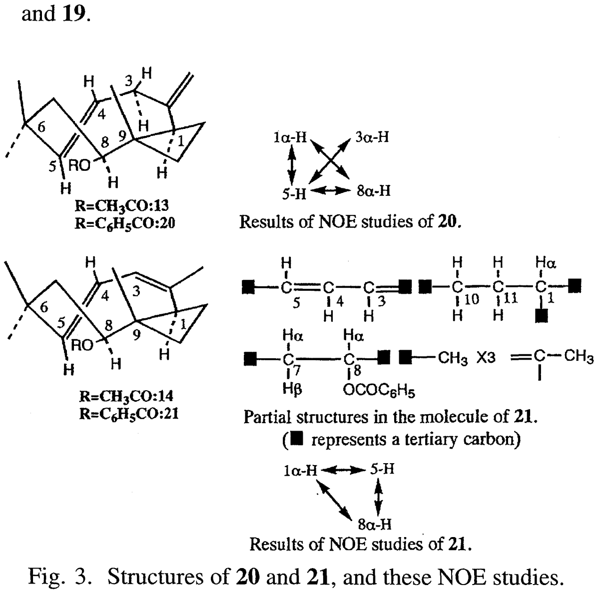


Fig. 2. Results of NOE spectrum of **18**, and structures of **18** and **19**.



Results of NOE studies of **20**.

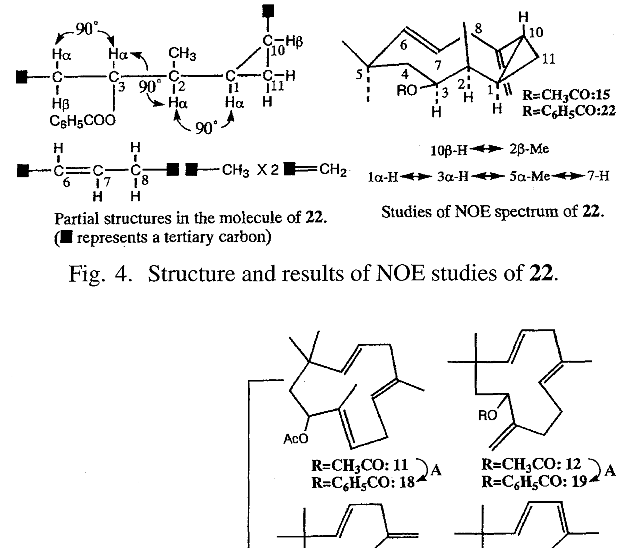
Partial structures in the molecule of **21**. (■ represents a tertiary carbon)

Results of NOE studies of **21**.

Fig. 3. Structures of **20** and **21**, and these NOE studies.

Two allylic acetates (**11** and **12**) were produced by the deprotonation of 12H and 4H (paths a and b in Scheme 4) of cation **I** generated from **8**, respectively. Concomitantly, an addition reaction of product **11** with acetic acid occurred on its 5,6-double bond to produce the diacetate **17**, due to a similar high reactivity of the bond to the 6,7-double bond of humulene (**9**) (Scheme 5).[9]

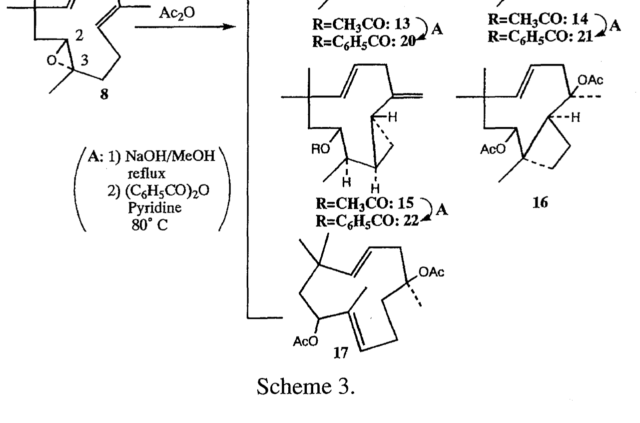
A transannular cyclization accompanied by the formation of a four-membered ring was observed in **13**, **14**, and **16**, whose conformations were very similar to that of the original epoxide (**8**). The conformation of **8** was represented by using the same C and T symbols as those of humulene (**9**). C and T denote the crossed and parallel arrangement of the



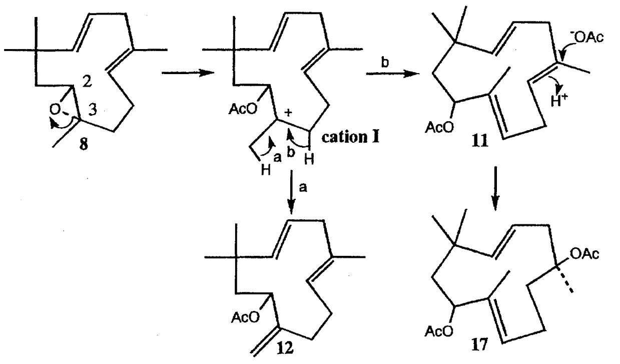
Partial structures in the molecule of **22**. (■ represents a tertiary carbon)

Studies of NOE spectrum of **22**.

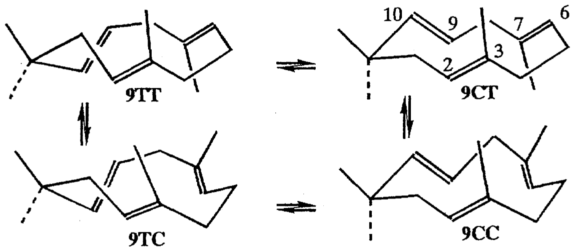
Fig. 4. Structure and results of NOE studies of **22**.



Scheme 3.



Scheme 4.



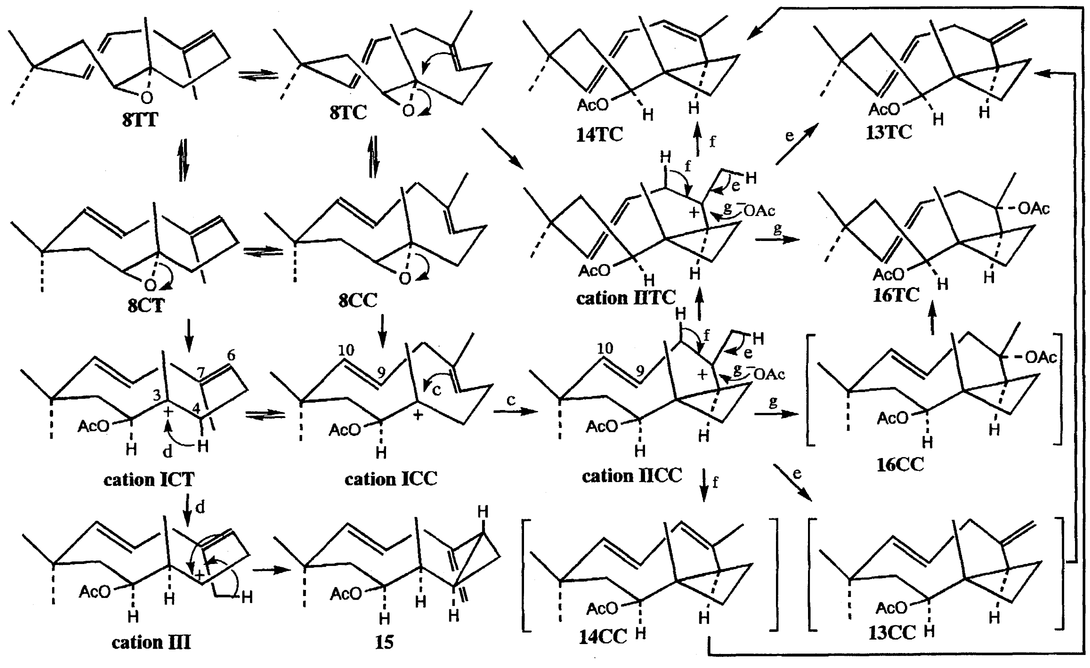
Scheme 5. C and T symbols denote crossed and parallel arrangement of two double bonds, respectively. First and second symbols in **9** mean arrangement of 2,3- and 9,10-double bonds, and of 2,3- and 6,7-double bonds, respectively.

double bond and epoxide ring, respectively. For instance, the first T and second C symbols in TC mean a parallel arrangement of the 2,3-epoxide ring and 9,10-double bond, and a crossed arrangement of the 2,3-epoxide ring and 6,7-double bond, respectively. Furthermore, the configuration of product and cation was also expressed using the same symbol as that of the epoxide (**8**). From the results of configurational studies (Figs. 1 and 3) of **16**, **20** (benzoate of **13**), and **21** (benzoate of **14**), three conceivable pathways (Scheme 6) of these formations from **8** were suggested, as follows: 1) Formation by deprotonations (paths e and f) and trapping with the acetate anion (path g) of cation **IITC** generated from **8TC** (**8TC**→cation **IITC**→**13TC**, **14TC**, and **16TC**); 2) Formation by deprotonations (paths e and f) and trapping with the acetate anion (path g) of cation **IITC** generated from **8CC** through a rotation of the 9,10-double bond of cation **IICC** (**8CC**→cation **ICC**→cation **IICC**→cation **IITC**→**13TC**, **14TC**, and **16TC**); and 3) Formation by the rotation of the 9,10-double bond after deprotonation (paths e and f) and trapping with the acetate anion (path g) of cation **IICC** generated from **8CC** (**8CC**→cation **ICC**→cation **IICC**→**13CC**, **14CC**, and **16CC**→**13TC**, **14TC**, and **16TC**).

Another transannular cyclization of the epoxide (**8**) was also carried out, and gave **15**, having a three-membered ring moiety. Since **15** kept its configuration, similar to that of the CT conformer of **8**, it can be explained based on the formation of cation **III** through a 1,2-shift of 4H from the α-side to the C(3) of cation **ICT** (path d in Scheme 6) generated from **8CT** and a following attack of the 6,7-double bond from the β-side to the C(4) of cation **III**.

The above-mentioned two transannular reactions are summarized in Scheme 6; these stereochemistries could be reasonably explained by assuming that the four stable conformers (CT, CC, TC, and TT) of humulene epoxides are very similar to those of humulene (**9**, Scheme 5).[10,11]

As described above, it was found that the epoxide **8**, as well as the other humulene epoxides (**1** and **6**), gave rise to a transannular cyclization reaction and produced **15** having the CT conformer configuration of the original epoxide.



Scheme 6.

Furthermore, the reaction of **8** formed **13**, **14**, and **16**, the configurations of which showed the shape of the TC conformer of **8**. No transannular cyclized compound of the TC form, except for the above-mentioned compounds **13**, **14**, and **16**, has been determined in the transannular cyclization reactions of the other humulene epoxides.

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