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EPOXIDATION OF FOUR POSSIBLE CONFORMERS OF HUMULENE 9,10-EPOXIDE: FIRST ISOLATION OF 2R*, 3R*, 6S*, 7S*, 9S*, 10S*-HUMULENE 2,3;6,7;9,10-TRIEPOXIDE

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Abstract-The complete reaction of humulene 9,10-epoxide {((2E, 6E)-9,10-epoxy-3,7,11,11-tetramethylcycloundeca-2,6-diene, (1)) with m-CPBA produced a hitherto unknown 2R*, 3R*, 6S*, 7S*, 9S*, 10S*-humulene 2,3;6,7;9,10-triepoxide (6) together with three known humulene triepoxides (7, 8 and 9), in the ratio of 6 : 7 : 8 : 9 = 1.3 : 11.5 : 22.6 : 64.6. The configuration of 6 was determined by X-Ray crystallography (C15H24O3: space group P21/n with a = 14.147(4) Å, b = 8.419(3) Å, c = 12.238(4) Å, β = 102.10(3°), Z = 4). The new triepoxide (6) maintained configuration corresponding to the IT conformer, one of the four possible conformers of 1.

It has been considered that four configurations, (2R*,3R*,6S*,7S*,9S*,10S*)-, (2R*,3R*,6R*,7R*,9S*,10S*)-, (2S*,3S*,6S*,7S*,9S*,10S*)- and (2S*,3S*,6R*,7R*,9S*,10S*)-humulene 2,3;6,7;9,10-triepoxides (6, 7, 8 and 9), are derived from (2E,6E)-humulene 9,10-epoxide (1) by complete epoxidation of 2,3- and 6,7-double bonds via (2E)-humulene 6,7;9,10- and (6E)-humulene 2,3;9,10-diepoxides (2, 3, 4 and 5), because 1 can take four conformations, TC, CC, CT and TT due to the rotation of the 2,3- and 6,7-double bond planes1 as shown in Scheme 1. Indeed, we have previously described2,3 the existence of the three triepoxides (7, 8 and 9), the configurations of which correspond to the TC, CC and CT conformations, respectively, in the epoxidation reaction of another epoxide, (6E, 9E)-humulene 2,3-epoxide, but the last triepoxide (6) derived from the TT conformation, has not been detected and isolated until this work. The TT conformation itself and/or configuration originated from the TT conformation has neither been experimentally isolated nor confirmed in the case of following compounds; humulene,4 humulene mono-, di- and triepoxides,5 transannular cyclized compounds6 of humulene and the monoepoxides, and cyclohumulanoids.7 In the present study, we first isolated the new 2R*, 3R*, 6S*, 7S*, 9S*, 10S*-humulene 2,3;6,7;9,10-triepoxide (6) corresponding to the TT conformation as a minor product together with the three known triepoxides (7, 8, and 9),3 from the complete epoxidation of 1 with m-chloroperbenzoic acid (m-CPBA). The triepoxide (6) was separated by HPLC and isolated as a
single crystal, and its configuration was first determined by X-Ray crystallography.

**Scheme 1.** Four possible conformations of 1 and epoxidation products of 1. C and T denote crossed and parallel arrangement of 6,7- and 9,10-bonds against 2,3-bond, respectively. For example, first T and second T in TT represent parallel and parallel that of 9,10- and 2,3-bonds, and 6,7- and 2,3-bonds, respectively.

Epoxidation\(^8\) of one double bond in humulene 9,10-epoxide (1) with \(m\)-CPBA (1 eq) in dry dichloromethane (CH\(_2\)Cl\(_2\)) at 0 °C under an argon atmosphere and then chromatographic separation (SiO\(_2\), EtOAc / hexane = 1 / 9) gave an oily mixture (97%) of 2, 3, 4 and 5 \((2+3) : (4+5) = 59 : 41\); the ratio was calculated from the HPLC peak areas, Scheme 1), which was separated into an oily mixture (48.4 % from 1) of two 6,7;9,10-diepoxides (2+3) and a crystalline mixture (33.6 % from 1) of two 2,3;9,10-diepoxides (4+5) by HPLC using a 10 x 244 mm column of RP-18 (7 μm, Merck, H\(_2\)O / EtOH = 3 / 7). Furthermore, separation of the two mixtures (2 : 3 = 69 : 31 and 4 : 5 = 85 : 15; the ratios were calculated from the HPLC peak areas) by HPLC using two 10 x 250 mm columns of Inertsil SIL 100-5 (GL Sciences, Inc., EtOAc / hexane = 1 / 9) gave 2 (30.7 % from 1)\(^9\), 3 (14.4 % from 1)\(^9\), 4 (26.3 % from 1)\(^9\) and 5 (4.6 % from 1).\(^9\) Although the HRMS of 2 and 3 showed the same molecular formula, C\(_{15}\)H\(_{24}\)O\(_2\), and their COSY (H-H and C-H) spectra revealed the existence of the same partial structures (Figure 1), the \(^1\)H and \(^13\)C NMR spectra of 2 and 3 were different. From the results of the NOESY spectrum of 2, conformation of 2 was shown to be CT, and therefore, the CC or TT conformation\(^10\) was deduced for 3. The di-epoxides (4 and 5) differed from 2 and 3 in the \(^1\)H and \(^13\)C NMR spectra,\(^5\) but the HRMS of the diepoxides (4 and 5) also showed the same molecular formula, C\(_{15}\)H\(_{24}\)O\(_2\), as that of 2 and 3. Moreover, because the partial structures of 4 revealed by COSY (H-H and C-H) spectra were the same as those of 5 (Figure 2), 4 was thought to be a stereoisomer of 5. From the above results and the results (Figure 2) of the NOESY spectrum of 5, the structure and conformation of 5 were derived to be TC as depicted in Figure 2, and therefore, the CT or CC conformation\(^10\) was suggested for 4.
The epoxidation of the residual double bond in the above pure diepoxides (2, 3, 4 and 5) with \textit{m}-CPBA (1 eq) in CH$_2$Cl$_2$ at 0 °C under an argon atmosphere, followed by chromatographic separation (SiO$_2$, EtOAc / hexane = 3 / 17) yielded quantitatively a triepoxide mixture of 7 and 9 (7 : 9 = 14 : 86), 6 and 8 (6 : 8 = 5 : 95), 8 and 9 (8 : 9 = 15 : 85) and 6 and 7 (6 : 7 = 6 : 94) (Scheme 1). The ratio of these mixtures was calculated from the HPLC peak areas using two 10 x 250 mm columns of Inertil SIL 100-5 (GL Sciences, Inc., EtOAc / hexane = 1 / 3). Fractional crystallization of the mixture of 6 and 8, and 6 and 7 from benzene, combined with HPLC separation of these filtrates, produced 6 (4.7 % from 3) and 8 (93.8 % from 3), and 6 (4.8 % from 5) and 7 (90.5 % from 5). Fractional crystallization of the mixture of 7 and 9, and 8 and 9 from hexane, followed by HPLC separation of these filtrates, gave 7 (11.1 % from 2) and 9 (77.8 % from 2), and 8 (14.5 % from 4) and 9 (81.1 % from 4). $^{13}$C and $^1$H NMR spectra of 7, 8 and 9 were superimposable on those of known 2$^R$, 3$^R$, 6$^S$, 7$^S$, 9$^S$, 10$^S$-humulene 2,3,6,7,9,10-triepoxides, and therefore, these configurations were depicted as 7, 8 and 9 in Scheme 1. Although the HRMS of 6 showed the same molecular formula, C$_{15}$H$_{24}$O$_3$, as those of 7, 8 and 9, the triepoxide (6) differed from 7, 8 and 9 in these $^{13}$C and $^1$H NMR spectra. In order to determine the configuration of 6, a single crystal of 6 was supplied for X-Ray crystallography, which revealed its configuration, 2$^R$, 3$^R$, 6$^S$, 7$^S$, 9$^S$, 10$^S$-humulene 2,3,6,7,9,10-triepoxide, as depicted in Figure 3. Consequently, the complete epoxidation of 1 with \textit{m}-CPBA (2 eq) gave a mixture (97 % yield) of 6, 7, 8 and 9 in the ratio of 6 : 7 : 8 : 9 = 1.3 : 11.5 : 22.6 : 64.6.

Thus, the new triepoxide (6) maintained the configuration, 2$^R$, 3$^R$, 6$^S$, 7$^S$, 9$^S$, 10$^S$, originated
from the TT conformation, one of the four possible conformations of 1. It was shown experimentally that the triepoxide (6) was produced as a minor product via the TT conformer of 3 and 5 from 1 in the complete epoxidation reaction.

REFERENCES AND NOTES


8. It is possible that the epoxidation reaction of 1 gives the triepoxides as a minor product.

9. 2: oil; *1H NMR* (CDCl$_3$, 400 MHz), $\delta$ 0.64 (1H, dd, $J=10.3, 12.9$ Hz, 8$\beta$H), 0.78, 1.10, 1.39, 1.69 (each 3H, s), 1.35 (1H, m, 5H), 1.96 (1H, br d, $J=14.9$ Hz, 1$\alpha$H), 2.16 (1H, dd, $J=7.3, 13.3$ Hz, 4$\alpha$H), 2.22 (1H, d, $J=3$ Hz, 10H), 2.24 (1H, dd, $J=10.6, 14.9$ Hz, 1$\beta$H), 2.26 (1H, m, 4$\beta$H), 2.30 (1H, m, 5H), 2.48 (1H, dd, $J=4.6, 10.3$ Hz, 6H), 2.68 (1H, dd, $J=3, 12.9$ Hz, 8$\alpha$H), 2.80 (1H, dt, $J=3, 10.3$ Hz, 9H), 5.2 (1H, br d, $J=10.6$ Hz, 2H) ppm; *$^{13}$C NMR* (CDCl$_3$, 400 MHz) $\delta$ 15.2 (q, 3Me), 17.3 (q), 19.3 (q), 24.8 (t, 5C), 28.5 (q), 34.1 (s, 11C), 36.2 (t, 4C), 39.1 (t, 1C), 43.6 (t, 8C), 53.0 (d, 9C), 57.8 (s, 7C), 61.7 (d, 6C), 66.1 (d, 10C), 122.8 (d, 2C), 133.7 (c, 3C) ppm; HRMS (EI): m/z 236.1752 (M$^+$, C$_{15}$H$_{24}$O$_2$ requires 236.1777).

3: mp 69-71 °C; *1H NMR* (CDCl$_3$, 400 MHz), $\delta$ 0.77, 1.13, 1.20 (each 3H, s), 1.44(1H, dddd, $J=2.4, 7.2, 10.0, 14.5$ Hz, 5H), 1.54 (1H, dd, $J=8.3, 13.7$ Hz, 8H), 1.61 (3H, br s, 3Me), 1.92 (1H, br d, $J=15$ Hz, 1H), 2.00 (1H, dddd, $J=3.7, 7.2, 14.5$ Hz, 5H), 2.16 (1H, dd, $J=5.5, 13.7$ Hz, 8H), 2.22 (2H, dddd, $J=3.7, 7.0, 7.2, 9.7, 10.0$ Hz, 4H$_2$), 2.39 (1H, dd, $J=11.0, 15.0$ Hz, 1H), 2.48 (1H, d, $J=2.7$ Hz, 10H), 2.80 (1H, d, $J=2.4$ Hz, 6H), 2.82 (1H, ddd, $J=2.7, 5.5, 8.3$ Hz, 9H), 5.15 (1H, br d, $J=11$ Hz, 2H) ppm; *$^{13}$C NMR* (CDCl$_3$, 270 MHz) $\delta$ 16.1 (q, 3Me), 18.0 (q), 20.3 (q), 25.0 (t, 5C), 29.5 (q), 34.4 (s, 11C), 36.6 (t, 4C), 38.8 (t, 1C), 41.9 (t, 8C), 51.7 (d, 9C), 58.6 (s, 7C), 61.4 (d, 6C), 63.2 (d, 10C), 122.9 (d, 2C), 133.7 (s, 3C) ppm; HRMS (EI): m/z 236.1752 (M$^+$, C$_{15}$H$_{24}$O$_2$ requires 236.1777).

4: mp 66-69 °C; *1H NMR* (CDCl$_3$, 270 MHz), $\delta$ 0.84, 1.09, 1.25, 1.71 (each 3H, s), 1.15 (1H, dd, $J=14.0, 115.0$ Hz, 4$\beta$H), 1.57 (1H, dd, $J=7.6, 15.2$ Hz, 1$\beta$H), 1.63 (1H, dd, $J=9.9, 12.9$ Hz, 8$\beta$H), 1.68 (1H, dd, $J=1.3, 15.2$ Hz, 1$\alpha$H), 2.07 (1H, dddd, $J=5.2, 7.9, 13.6$ Hz, 5$\beta$H), 2.12 (1H, dddd, $J=1.8, 5.2, 15.0$ Hz, 4$\alpha$H), 2.30 (1H, dddd, $J=1.8, 7.9, 13.6, 14.0$ Hz, 5$\alpha$H), 2.36 (1H, d, $J=2.3$ Hz, 10H), 2.58 (1H, dd, $J=1.3, 7.6$ Hz, 2H), 2.68 (1H, dd, $J=3.6, 12.9$ Hz, 8$\alpha$H), 3.01 (1H, dddd, $J=2.3, 3.6, 9.9$ Hz, 9H), 5.28 (1H, t, $J=7.9$ Hz, 6H) ppm; *$^{13}$C NMR* (CDCl$_3$, 270 MHz) $\delta$ 16.4 (q), 17.79 (q), 18.2 (q), 23.4 (t, 5C), 29.0 (q), 33.2 (s), 38.3 (t, 4C), 38.7 (t, 1C), 41.5 (t, 8C), 56.5 (d, 9C), 61.0 (s), 61.6 (d, 2C), 65.4 (d, 10C), 125.5 (d, 6C), 132.6 (s, 7C) ppm; HRMS
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(El): m/z 236.1766 (M+, C15H24O2 requires 236.1777).
5: mp 85-87 ºC; 1H NMR (CDCl3, 270 MHz, δ 0.71, 1.14, 1.30, 1.77 (each 3H, s), 1.18 (1H, dd, J=4.7, 12.8 Hz, 4βH), 1.49 (1H, dd, J=5.2, 15.8 Hz, 1αH), 1.53 (1H, dd, J=3.0, 15.8 Hz, 1βH), 1.63 (1H, dd, J=9.9, 12.0 Hz, 8βH), 2.12 (1H, dd, J=3.3, 12.8 Hz, 5βH), 2.17 (1H, dt, J=12.8, 3.3 Hz, 4αH), 2.32 (1H, ddd, J=3.3, 4.7, 11.9, 12.8 Hz, 5αH), 2.66 (1H, dd, J=3.3, 12.0 Hz, 8αH), 2.67 (1H, d, J=2.7 Hz, 10H), 2.79 (1H, dd, J=3.0, 5.2 Hz, 2H), 2.90 (1H, ddd, J=2.7, 3.3, 9.9 Hz, 9H), 5.10 (1H, br d, J=11.9 Hz, 6H) ppm; 13C NMR (CDCl3, 270 MHz) δ 17.0 (q), 17.7 (q, 7Me), 22.9 (q), 24.6 (t, 5C), 26.8 (q), 32.5 (s, 11C), 40.9 (t, 1C), 43.3 (t, 8C), 54.8 (d, 9C), 60.2 (s, 3C), 60.4 (d, 2C), 64.7 (d, 10C), 127.9 (d, 6C), 131.2 (s, 7C) ppm; HRMS (El): m/z 236.1781 (M+, C15H24O2 requires 236.1777).

10. The preliminary X-Ray crystallography suggested that 3 and 4 held the CC and CT conformations in the crystalline state, respectively.

11.6: mp 147-149 ºC; 1H NMR (CDCl3, 400 MHz) δ 0.72, 1.15, 1.32, 1.35 (each 3H, s), 1.37 (1H, m, 5H), 1.43 (1H, dd, J=11.0, 14.2 Hz, 1H), 1.49 (1H, dd, J=9.6, 14.0 Hz, 8H), 1.83 (1H, m, 5H), 1.85 (1H, m, 4H), 2.01 (1H, m, 4H), 2.07 (1H, dd, J=3.1, 14.2 Hz, 1H), 2.35 (1H, dd, J=4.3, 14.0 Hz, 8H), 2.72 (1H, dd, J=2.5 Hz, 10H), 2.77 (1H, ddd, J=2.5, 4.3, 9.6 Hz, 9H), 2.92 (1H, ddd, J=3.1, 11.0 Hz, 2H), 2.94 (1H, m, 6H) ppm; 13C NMR (CDCl3, 400 MHz) δ 18.3 (q), 20.2 (q), 20.9 (q), 21.0 (t, 5C), 28.3 (q), 32.7 (s, 11C), 34.3 (t, 4C), 38.5 (t, 8C), 39.9 (t, 1C), 53.2 (d, 9C), 58.8 (s), 59.2 (d, 2 or 6C), 60.1 (s), 61.7 (d, 6 or 2C), 63.8 (d, 10C) ppm; HRMS (El): m/z 252.1722 (M+, C15H24O3 requires 252.1726). Anal. Calcd for C15H24O3: C 71.39; H 9.59. Found: C 71.29, H 9.57.

12. The X-Ray crystallography of a single crystal of 6 obtained by recrystallization from 20 % (v/v) EtOAc / hexane was carried out on a MAC Science MXC3k four-circle diffractometer with graphite-monochromatized MoKα radiation (λ=0.71073 Å) using the ω scan technique. A total of 3281 independent reflections was collected for compounds (6), and the structure was solved by direct methods. Crystal data: C15H24O3, F.W.=252.40, monoclinic, space group P21/n, a = 14.147(4) Å, b = 8.419(3) Å, c = 12.238(4) Å, β = 102.10(3)°, V = 1425.3(9) Å³, Z = 4, Dcalc = 1.176 g/cm³, μ(MoKα) = 0.075 cm⁻¹, R = 0.060, Rw = 0.069, 1793 observed reflections [I≥2σ(I)] used in the refinement.

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