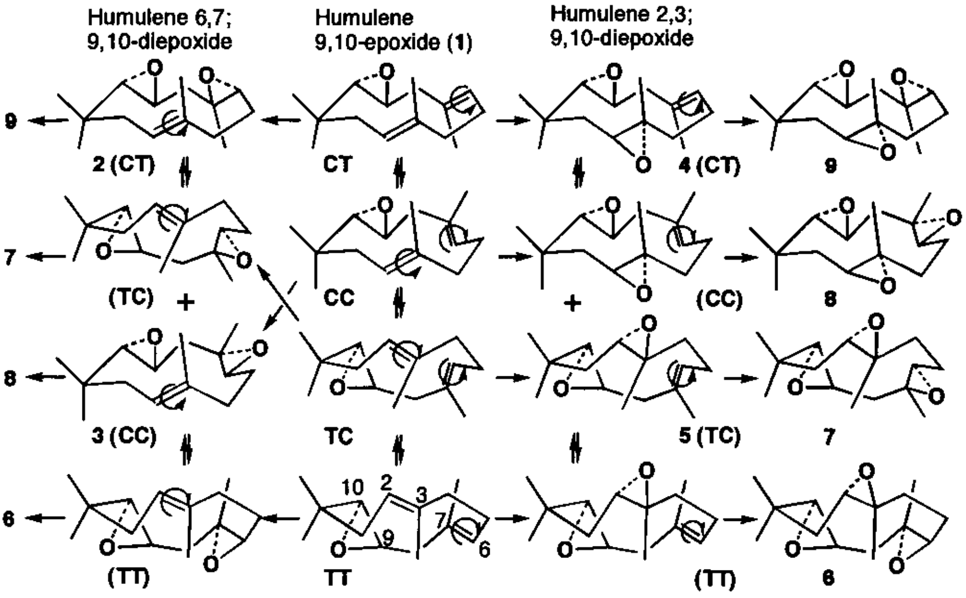
EPOXIDATION OF FOUR POSSIBLE CONFORMERS OF HUMULENE 9,10-EPOXIDE: FIRST ISOLATION OF *2R**, *3R**, *6S**, *7S**, *9S**, *10S**-HUMULENE 2,3;6,7;9,10-TRIEPOXIDE

Kiyoharu Hayano*, Nobue Ito, Makoto Sato, Masayuki Takishima†, and
Katsura Mochizuki†

Chemistry Laboratory, Hokkaido College of Education, Ainosato, Sapporo 002-8502, Japan, †Department of Chemistry, Yokohama City University, Kanazawa-ku, Yokohama, 236-0027, Japan

Abstract-The complete reaction of humulene 9,10-epoxide {(2*E*, 6*E*)-9,10-epoxy-3,7,11,11-tetramethylcycloundeca-2,6-diene, (**1**)} with *m*-CPBA produced a hitherto unknown 2*R**, 3*R**, 6*S**, 7*S**, 9*S**, 10*S**-2,3;6,7;9,10-triepoxy-3,7,11,11-tetramethylcycloundecane (**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 ($C_{15}H_{24}O_3$: space group $P2_1/n$ with $a = 14.147(4)$ Å, $b = 8.419(3)$ Å, $c = 12.238(4)$ Å, $\beta = 102.10(3)°$, $Z = 4$). The new triepoxide (**6**) maintained configuration corresponding to the TT conformer, one of the four possible conformers of **1**.

It has been considered that four configurations, (2*R**,3*R**,6*S**,7S*,9*S**,10*S**)-, (2*R**,3*R**,6*R**,7*R**, 9*S**,10*S**)-, (2*S**,3*S**,6*S**,7*S**,9*S**,10*S**)- and (2*S**,3*S**,6*R**,7*R**,9*S**,10*S**)-humulene 2,3;6,7;9,10-triepoxides (**6**, **7**, **8** and **9**), are derived from (2*E*,6*E*)-humulene 9,10-epoxide (**1**) by complete epoxidation of 2,3- and 6,7-double bonds *via* (2*E*)-humulene 6,7;9,10- and (6*E*)-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 planes[1] as shown in Scheme 1. Indeed, we have previously described[2,3] 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, (6*E*, 9*E*)-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 compounds[6] of humulene and the monoepoxides, and cyclohumulanoids.[7] In the present study, we first isolated the new 2*R**, 3*R**, 6*S**, 7*S**, 9*S**, 10*S**-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 agaist 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_2Cl_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_2O / 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 ^1H 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 diepoxides (**4** and **5**) differed from **2** and **3** in the ^1H 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**.

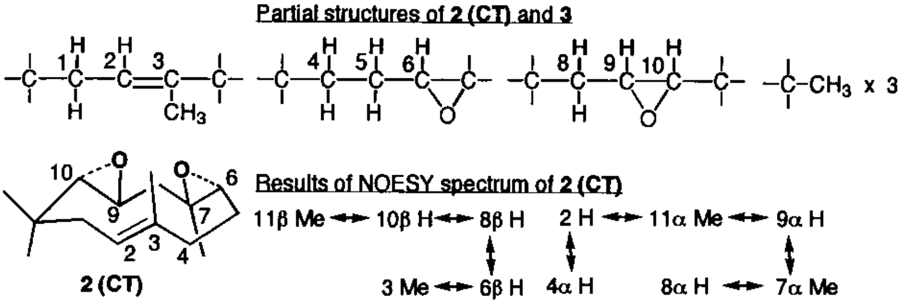


Figure 1. Partial structures of **2 (CT)** and **3**, and results of NOESY spectrum of **2 (CT)**.

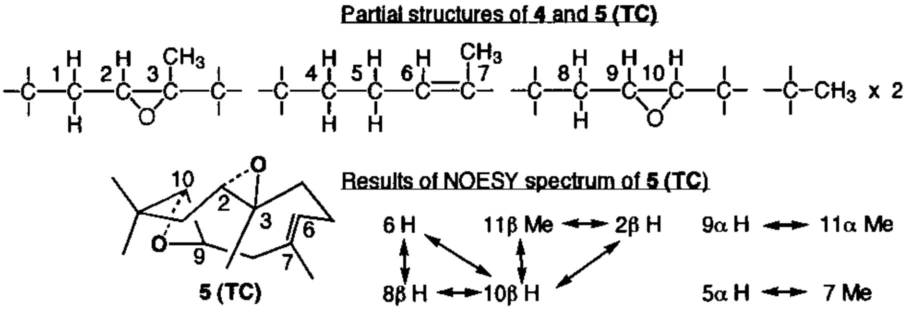


Figure 2. Partial structures **4** and **5 (TC)**, and results of NOESY spectrum of **5 (TC)**.

The epoxidation of the residual double bond in the above pure diepoxides (**2**, **3**, **4** and **5**) with *m*-CPBA (1 eq) in CH_2Cl_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 Inertsil 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*R**, 7*R**, 9*S**, 10*S**-, 2*S**, 3*S**, 6*S**, 7*S**, 9*S**, 10*S**- and 2*S**, 3*S**, 6*R**, 7*R**, 9*S**, 10*S**-humulene 2,3;6,7;9,10-triepoxides,[3] 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.[3,11] In order to determine the configuration of **6**, a single crystal of **6** was supplied for X-Ray crystallography,[12] 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 *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

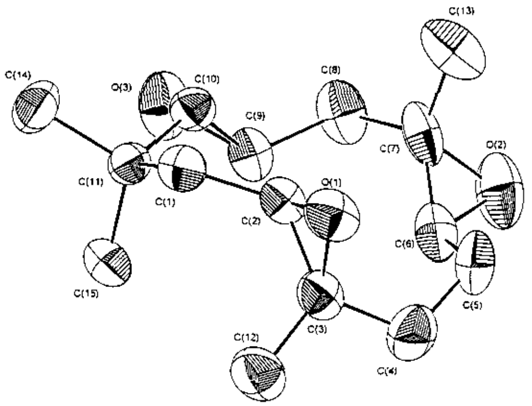


Figure 3. Perspective view of **6**. Hydrogen atoms were omitted.

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

1. H. Shirahama, E. Osawa, and T. Matsumoto, *J. Am. Chem. Soc*, 1980, **102**, 3208.
2. K. Hayano, T. Shinjo, and K. Mochizuki, *Heterocycles*, 1996, **43**, 523.
3. K. Hayano and K. Mochizuki, *Heterocycles*, 1997, **45**, 1573.
4. X-Ray crystallography of humulene $AgNO_3$ complex: R. P. Hildebrand and M. D. Sutherland, *Austral. J. Chem.*, 1961, **14**, 272; J. A. Hartsuck and I. C. Paul, *Chem. and Ind.*, 1964, 977; J. M. Greenwood, J. K. Sutherland, and A. Torre, *Chem. Comm.*, 1965, 410; A. T. McPhail and G. A. Sim, *J. Chem. Soc. B*, 1966, 112; F. H. Allen and D. Rogers, *J. Chem. Soc. B*, 1968, 1047.
5. Humulene 2,3-epoxide: Ref. 2; K. Hayano and H. Shirahama, *Nippon Kagaku Kaishi*, 1995, 291; B. R. Chhabra, H. Shirahama, and T. Matsumoto, *Chem. Ind. (London)*, 1981, 539. 6,7-Epoxide: N. P. Damodaran and S. Dev, *Tetrahedron*, 1968, **24**, 4123. 9,10-Epoxide, 2,3;9,10-diepoxide and 6,7;9,10-diepoxide: A. Sattar, J. Forrester, M. Moir, J. S. Roberts, and W. Parker, *Tetrahedron Lett.*, 1976, 1403; K. C. Lam, R. T. Foster, and M. L. Deinzer, *J. Agric. Food Chem*, 1986, **34**, 763. 2,3;6,7-Diepoxide: Ref. 2; M. E. Cradwick, P. D. Cradwick, and G. A. Sim, *J. Chem. Soc., Perkin II*, 1973, 404. 2,3;6,7;9,10-Tiepoxide: Ref. 3; F. Sorm, J. Mleziva, Z. Arnold, and J. Pliva, *Coll. Czech. Chem. Comm.*, 1949, **14**, 699.
6. Humulene cyclization with acid: W. G. Dauben, J. P. Hubbell, and N. D. Vietmeyer, *J. Org. Chem.*, 1975, **40**, 479; G. Mehta and B. P. Singh, *Tetrahedron Lett.*, 1975, 3961; D. Baines, J. Forrester, and W. Parker, *J. Chem. Soc., Perkin Trans. I*, 1974, 1598; Y. Naya and Y. Hirose, *Chem. Lett.*, 1973, 133 and 727; J. M. Greenwood, M. D. Solomon, K. J. Sutherland, and A. Torre, *J. Chem. Soc. C*, 1968, 3004; F. H. Allen and D. Rogers, *Chem. Comm.*, 1966, 582. Humulene monoepoxides cyclization: K. Hayano and H. Shirahama, *Bull. Chem. Soc. Jpn.*, 1996, **69**, 459; *Chem. Lett.*, 1995, 867; *Chem. Lett.*, 1993, 1151; H. Shirahama, K. Hayano, G. S. Arora, T.

Ohtsuka, Y. Murata, and T. Matsumoto, *Chem. Lett.*, 1982, 1417; H. Shirahama, S. Murata, T. Fujita, B. R. Chhabra, R. Noyori, and T. Matsumoto, *Bull. Chem. Soc. Jpn.*, 1982, **55**, 2691; H. Shirahama, K. Hayano, Y. Kanemoto, S. Misumi, T. Ohtsuka, N. Hashiba, A. Furusaki, S. Murata, R. Noyori, and T. Matsumoto, *Tetrahedron Lett.*, 1980, **21**, 4835; I. Bryson, J. A. Mlotkiewics, and J. S. Roberts, *Tetrahedron Lett.*, 1979, 3891.

7. H. Seto and H. Yonehara, *J. Antibiotics*, 1980, **33**, 92; D. E. Cane, T. Rossi, and J. P. Pachlatko, *Tetrahedron Lett.*, 1979, 3639; A. Matsuo, H. Nozaki, M. Nakayama, Y. Kushi, S. Hayashi, T. Komori, and N. Kamijo, *J. Chem. Soc., Chem. Comm.*, 1979, 174; H. Shirahama, E. Osawa, and T. Matsumoto, *Tetrahedron Lett.*, 1978, 1987; D. E. Cane and B. R. Nachbar, *J. Am. Chem. Soc.*, 1978, **100**, 3208; errata, 1979, **101**, 1908; F. Bohlmann and C. Zdero, *Phytochem.*, 1978, **17**, 1669; H. Shirahama, Y. Ohfune, S. Misumi, and T. Matsumoto, *J. Synth. Org. Chem. Jpn.*, 1978, **36**, 569; B. Tursh, J. C. Braekman, D. Daloze, P. Pritz, A. Kelecom, R. Karlsson, and D. Losman, *Tetrahedron Lett.*, 1974, 747; W. Parker, J. S. Roberts, and R. Ramage, *Quart. Rev.*, 1967, **21**, 331.
8. It is possible that the epoxidation reaction of **1** gives the triepoxides as a minor product.
9. **2**: oil; ^{1}H NMR ($CDCl_3$, 400 MHz), δ 0.64 (1H, dd, *J*=10.3, 12.9 Hz, 8βH), 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, 1αH), 2.16 (1H, dd, *J*=7.3, 13.3 Hz, 4αH), 2.22 (1H, d, *J*=3 Hz, 10H), 2.24 (1H, dd, *J*=10.6, 14.9 Hz, 1βH), 2.26 (1H, m, 4βH), 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, 8αH), 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) δ 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; ^{1}H NMR ($CDCl_3$, 400 MHz), δ 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, ddd, *J*=3.7, 7.2, 14.5 Hz, 5H), 2.16 (1H, dd, *J*=5.5, 13.7 Hz, 8H), 2.22 (2H, ddddd, *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) δ 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; ^{1}H NMR ($CDCl_3$, 270 MHz), δ 0.84, 1.09, 1.25, 1.71 (each 3H, s), 1.15 (1H, dd, *J*=14.0, 115.0 Hz, 4βH), 1.57 (1H, dd, *J*=7.6, 15.2 Hz, 1βH), 1.63 (1H, dd, *J*=9.9, 12.9 Hz, 8βH), 1.68 (1H, dd, *J*=1.3, 15.2 Hz, 1αH), 2.07 (1H, ddd, *J*=5.2, 7.9, 13.6 Hz, 5βH), 2.12 (1H, ddd, *J*=1.8, 5.2, 15.0 Hz, 4αH), 2.30 (1H, dddd, *J*=1.8, 7.9, 13.6, 14.0 Hz, 5αH), 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, 8αH), 3.01 (1H, ddd, *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) δ 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

(EI): m/z 236.1766 (M^+, $C_{15}H_{24}O_2$ requires 236.1777).

5: mp 85-87 °C; ^{1}H NMR ($CDCl_3$, 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, dddd, *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; ^{13}C NMR ($CDCl_3$, 270 MHz) δ 17.0 (q), 17.7 (q, 7Me), 22.9 (q), 24.6 (t, 5C), 26.8 (q), 32.5 (s, 11C), 38.4 (t, 4C), 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 (EI): m/z 236.1781 (M^+, $C_{15}H_{24}O_2$ 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 °C; ^{1}H NMR ($CDCl_3$, 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, d, *J*=2.5 Hz, 10H), 2.77 (1H, ddd, *J*=2.5, 4.3, 9.6 Hz, 9H), 2.92 (1H, dd, *J*=3.1, 11.0 Hz, 2H), 2.94 (1H, m, 6H) ppm; ^{13}C NMR ($CDCl_3$, 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 (EI): m/z 252.1722 (M^+, $C_{15}H_{24}O_3$: requires 252.1726). *Anal.* Calcd for $C_{15}H_{24}O_3$: 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 **6**: $C_{15}H_{24}O_3$, F.W.=252.40, monoclinic, space group $P2_1/n$, a = 14.147(4) Å, b = 8.419(3) Å, c = 12.238(4) Å, β = 102.10(3)°, V = 1425.3(9) Å^3, Z = 4, D_{calc} = 1.176 g/cm^3, μ(MoKα) = 0.075 cm^{-1}, R = 0.060, Rw = 0.069, 1793 observed reflections [$I \geq 2\sigma(I)$] used in the refinement.

Received, 28th May, 1998