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SYNTHESIS AND ABSOLUTE CONFIGURATION OF (-)-D_3-TRITWISTANE, (-)-(1S,3S,6S,7S,10S,12S)PENTACYCLO[8.4.0.$0^{2,7}$.$0^{3,12}$.$0^{6,11}$]TETRADECANE

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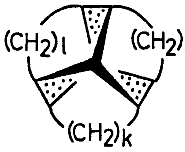
Diazomethane ring expansion of 12-acetoxy-C_2-bismethanotwistan-8-one (11) followed by the Wolff-Kishner reduction and the Jones oxidation gave C_2-methanoditwistan-4-one (14) whose incubation with Rhodotorula rubra afforded the (-)-enantiomer 16, which was converted into (-)-(1S,3S,6S,7S,10S,12S)-D_3-tritwistane (7).

Among the seven chiral pentacyclic hydrocarbons 1~7 with rigid conformation which can conceptually be generated by ring expansion of cubane, the five 1~5 have been prepared in optically active modifications in our laboratory and their absolute configurations as well as their absolute rotations were reported.1)

Conspicuous features in their chiroptical properties are; (a) the enantiomers with D_3-bicyclo[2.2.2]octane moiety with M-helicity (shown with dotting) are all levorotatory, and (b) their molecular rotations increase proportionally to the deviation from cubane.



1 k=0, l=m=1, (C_2)
2 k=0, l=1, m=2, (C_1)
3 k=0, l=m=2, (C_2)
4 k=l=m=1, (D_3)
5 k=l=1, m=2, (C_2)
6 k=1, l=m=2, (C_2)
7 k=l=m=2, (D_3)

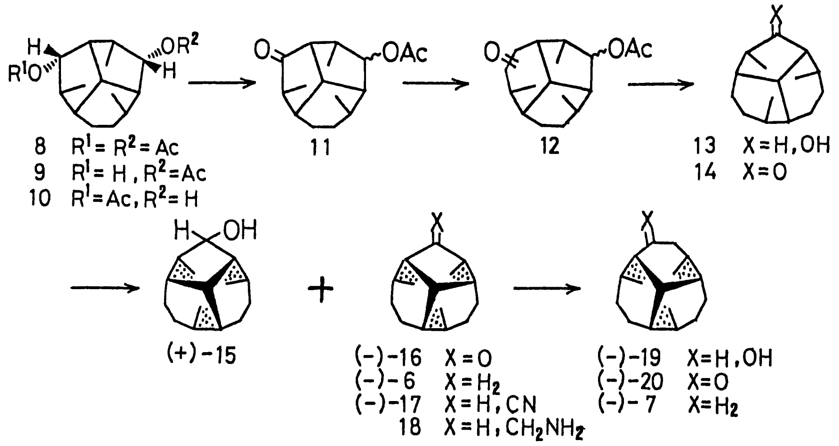
In this communication, we wish to report the syntheses of the remaining two, C_2-methanoditwistane (6) and D_3-tritwistane (7) in optically active modifications and the determination of their absolute configurations.

Partial hydrolysis of syn-8,12-diacetoxy-C_2-bismethanotwistane (8)1d) gave a mixture of the diastereomeric hydroxy-acetates 9 and 102); a crystalline isomer, mp 118~119 °C (22% yield)3) and an oily isomer, bp 145 °C (0.5 mmHg) (13% yield). Corey oxidation converted the crystalline hydroxy-acetate into the keto-acetate 11, mp 99~100 °C whose diazomethane ring expansion in ether to 12 followed by the Wolff-Kishner reduction provided C_2-methanoditwistan-4-ol (13), mp 111~112 °C (70% yield from 11), which was also obtained in a comparable yield from the oily hydroxy-acetate by the same sequence of conversions.

Racemic C_2-methanoditwistan-4-one (14), mp 119~120 °C secured from 13 by Jones oxidation was incubated with Rhodotorula rubra for 238 h at 30 °C, and chromatography of the metabolites afforded the (-)-ketone 16, mp 111~112 °C, $[\alpha]_D$ -37.0°4) (23% yield) and the (+)-alcohol 15, mp 99 °C, $[\alpha]_D$ +125.5° (10% yield).

The proposed microbial "C_2-ketone rule"5) predicts that the recovered (-)-

ketone 16 should be an M-ketone possessing the larger parts of molecule in upper-left and lower-right quadrants, and this was confirmed by its (+)-Cotton effect, [θ]$_{291}$ +1.39 x 10^3 (isooctane) establishing the (3S,5S) configuration around the carbonyl group. The observed enantiomer differential shift with Eu(TFC)$_3$ assigned 33% optical purity to the specimen of the (+)-alcohol 15, [α]$_D$ +125.5° indicating its absolute rotation [α]$_{D\ abs.}$ +377°, and the absolute rotation [α]$_{D\ abs.}$ -254° of the (-)-ketone 16 was obtained by LiAlH$_4$ reduction of the (-)-ketone 16, [α]$_D$ -37.0° to the (-)-alcohol 15, [α]$_D$ -54.7°. The Wolff-Kishner reduction of the (-)-ketone 16, [α]$_D$ -37.0° yielded (-)-C$_2$-methanoditwistane (6), mp 108~108.5 °C (racemic modification mp 95 °C)$^{1d)}$, [α]$_D$ -58.6° (CHCl$_3$) automatically assigning its (1S,3S,5S,6S,9S,11S) configuration and absolute rotation [α]$_{D\ abs.}$ -404°.



Final ring expansion of (-)-16, [α]$_D$ -112° (44% optical purity)$^{6)}$ was carried out via the (-)-nitrile 17, mp 63.5~64 °C which was prepared by reacting (-)-16 with tosylmethyl isocyanide (TosMIC). LiAlH$_4$ reduction of 17 to the amine 18 followed by the Demjanov rearrangement with nitrous acid yielded the ring-expanded (-)-alcohol 19 whose Jones oxidation to the (-)-ketone 20, mp 109~110 °C, [α]$_D$ -204° followed by the Wolff-Kishner reduction afforded (-)-D$_3$-tritwistane (7), mp 99~99.5 °C,$^{7)}$ [α]$_D$ -250° (CHCl$_3$). These chemical correlations allowed us to assign the (1S,3S,6S,7S,10S,12S) configuration to (-)-7 and to calculate its absolute molecular rotation [M]$_{D\ abs.}$ 1067° which can be compared with [M]$_{D\ abs.}$ 241° reported for D$_3$-trishomocubane (4).$^{1b)}$

References and Notes

1) a) M. Nakazaki and K. Naemura, J. Org. Chem., 42, 2985 (1977); b) M. Nakazaki, K. Naemura, and N. Arashiba, ibid., 43, 689 (1978); c) M. Nakazaki, K. Naemura, and S. Nakahara, ibid., 43, 4745 (1978); d) M. Nakazaki, K. Naemura, N. Arashiba, and M. Iwasaki, ibid., 44, 2433 (1979); e) M. Nakazaki, K. Naemura, Y. Kondo, S. Nakahara, and M. Hashimoto, ibid., in press.
2) This eventually supported the proposed syn-structure 8 with C$_1$ symmetry.
3) Satisfactory elemental analyses and spectral data were obtained for all new compounds reported in this communication.
4) Unless otherwise notified, the optical rotations reported in this communication refer to ethanolic solution.
5) M.Nakazaki, H. Chikamatsu, K. Naemura, M. Nishino, H. Murakami, and M. Asao, J. Org. Chem., 44, 4588 (1979).
6) Enzymatic oxidation of (±)-C$_2$-methanoditwistan-4-ol (13) mediated by horse liver alcohol dehydrogenase was carried out to afford the (-)-ketone 16 and the (+)-alcohol 15 of exceedingly high optical purities (100% and 77% respectively); M. Nakazaki, H. Chikamatsu, K. Naemura, Y. Sasaki, and T. Fujii, J. Chem. Soc., Chem. Commun., 1980, 626.
7) Preparation of the racemic modification, mp 100~102 °C, has been reported; K. Hirao and O. Yonemitsu, J. Chem. Soc., Chem. Commun., 1980, 423.

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