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Synthesis and the Absolute Configuration of Panaxacol

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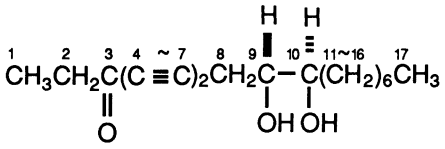
Panaxacol, a polyacetylene isolated from the callus of Panax ginseng, was synthesized from D-(-)-diethyl tartrate. The absolute configuration of panaxacol was determined to be 9R, 10R.

In the previous papers,[1-2] We have reported the isolation and structural elucidation of three new cytotoxic polyacetylenes (1, 2, and 3) and panaxydol (4)[3] from the callus of Panax ginseng C. A. Meyer.

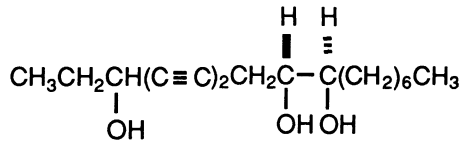
Although we have confirmed the relative configuration at C-9 and C-10 in panaxacol to be anti, the absolute configuration of panaxacol is not determined yet. Thus, we plan to establish the absolute configuration of panaxacol by synthesizing it using L-(+)- or D-(-)-diethyl tartrate as a chiral template.

D-(-)-diethyl tartrate was treated with 2,2-dimethoxypropane-camphorsulphonic acid to give an acetonide (5, 68.5%, 15% recovery of starting material), which was then converted into a diol (6, 77.3%)[4] by the action of $LiAlH_4$. Tosylation of 6 with tosyl chloride-pyridine (1.0 equiv.) gave a mixture of monotosylate(7, 54.5%)[5] and ditosylate (8, 14.8%) which was separated by silica gel column chromatography (hexane : AcOEt = 2 : 1).

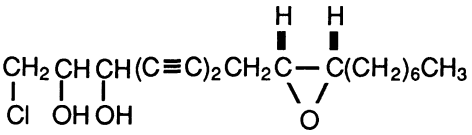
After protection of the hydroxyl group, 7 was treated with dihexyl copper lithium[6] and then 2 mol dm^{-3} HCl-MeOH (1 : 4) to afford a triol (9, 66.4%). Tosylation of 9 gave a diol-monotosylate (10, 43.6%) which was transformed to an acetonide by the method described in the case of 5. Coupling reaction of the acetonide and 1,3-heptadiyne-5-ol tetrahydropyranyl ether[7] in the presence of



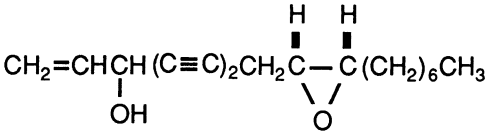
panaxacol (1)



dihydropanaxacol (2)



chloropanaxydiol (3)

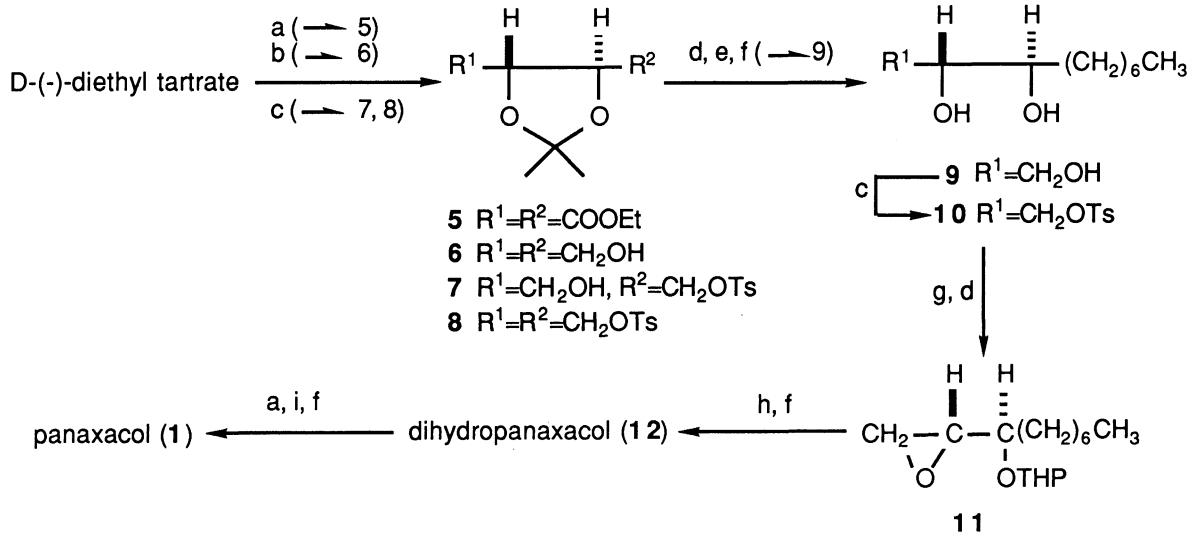


panaxydol (4)

n-BuLi-HMPA did not give any desired compound. Therefore, the compound (10) was converted into an epoxide (11) by usual means and then it was allowed to react with 1,3-heptadiyne-5-ol tetrahydropyranyl ether to give a coupling product which without purification was deprotected to afford a diastereomeric mixture of 9R,10R-dihydropanaxacol {12, 40%, $[\alpha]_D$ +12.3° (c 0.79, MeOH)}.

Similarly, the diastereomeric mixture of 9S,10S-dihydropanaxacol {$[\alpha]_D$ -17.0° (c 0.36, MeOH)} was synthesized from L-(+)-diethyl tartrate.

The diastereomeric mixture of dihydropanaxacol prepared from panaxacol by $NaBH_4$ reduction exhibited the positive optical rotation {$[\alpha]_D$ +13.5° (c 1.0, MeOH)}.



Scheme 1. (a) 2,2-dimethoxypropane-camphorsulphonic acid; (b) $LiAlH_4$; (c) p-TsCl-py; (d) dihydropyrane-camphorsulphonic acid; (e) $(C_6H_{13})_2CuLi$, -30 °C; (f) MeOH-HCl; (g) K_2CO_3; (h) $H(C \equiv C)_2CH(OTHP)Et$, n-BuLi-HMPA, -30 °C; (i) DMSO-$(COCl)_2$, -50 °C

Thus, the absolute configuration of panaxacol could be presumed to be the same as that of D-(-)-diethyl tartrate.

Finally, the glycol moiety of 12 was protected and then the hydroxyl group at C-3 was oxidized by Swern's method. Deprotection of the oxidation product and followed by purification using HPLC gave a solid which was identical with natural panaxacol in all respects including optical property.

Thus, the absolute configuration at C-9 and C-10 in panaxacol were confirmed as 9R and 10R. The biological activities of these polyacetylenes and of its relatives will be published elsewhere.

References

1) Y. Fujimoto and M. Satoh, Phytochemistry, 26, 2850 (1987).

2) Y. Fujimoto and M. Satoh, Chem. Pharm. Bull., 36, 4206 (1988).

3) J. Poplawski, J. T. Wrobel, and T. Glinka, Phytochemistry, 19, 1539 (1980).

4) M. Carmack and C. J. Kelley, J. Org. Chem., 33, 2171 (1968).

5) All new compounds described in the text gave satisfactory spectral data consistent with the assigned structures. Selected physical properties for 7: EI-MS (m/z): 301 $(M-Me)^+$(100), 285 $(M-CH_2OH)^+$; ^1H NMR (270 MHz, $CDCl_3$, δ): 1.33, 1.39 (3H each, s), 2.45 (3H, s), 3.63 (1H, dd, J=4.2, 12.0 Hz), 3.80 (1H, dd, J=3.7, 12.0 Hz), 3.81 (1H, m), 3.99 (1H, m), 4.04 (1H, m), 4.11 (1H, m), 7.36 (2H, d, J=8.3 Hz), 7.80 (2H, d, J=8.3 Hz); 9: mp 52-54℃. CI-MS: 191 $(M+1)^+$, EI-MS: 159 $(M-CH_2OH)^+$(17), 129 $(M-C_2H_5O_2)^+$(41), 111 $(M-C_2H_7O_3)^+$(100); IR ($CHCl_3$, cm^{-1}): 3400, 2930, 2850; ^1H NMR: 0.95 (3H, t, J=7.1 Hz), 1.2-1.4 (10H, brm, W1/2 = 25 Hz), 1.50 (2H, brm), 3.62 (2H, m), 3.75 (2H, m); ^{13}C NMR: 14.1, 22.7, 25.8, 29.4, 29.8, 31.9, 33.6, 64.5, 72.3, 74.4. 10; mp 63 ℃. CI-MS: 345 $(M+1)^+$; EI-MS: 173 $(M-OTs)^+$; IR ($CHCl_3$) : 3550, 2930, 2850,1730, 1600, 1460; ^1H NMR: 0.88 (3H, t, J=7.1 Hz), 1.2-1.4 (10H, brm, W1/2 = 25 Hz), 1.42 (2H, m), 2.46 (3H, s), 3.72 (2H, brm), 4.05 (1H, dd, J=5.6, 12.8 Hz), 4.12 (1H, dd, J=5.4, 12.8 Hz), 7.35 (2H, d, J=8.3 Hz), 7.80 (2H, d, J=8.3 Hz); ^{13}C NMR: 14.2, 21.8, 22.8, 25.7, 29.4, 29.6, 31.9, 33.5, 70.9, 71.6, 78.5, 128.0 (two carbons), 130.0 (two carbons), 132.6, 145.2 11; ^1H NMR: 0.88 (3H, t, J=7.3 Hz), 1.2-1.4 (10H, brm, W1/2 = 25 Hz), 1.60 (2H, m), 1.78 (1H, d, J=5.9 Hz, OH), 2.72 (1H, dd, J=2.7, 4.9 Hz), 2.83 (1H, dd, J=3.9, 4.9 Hz), 2.98 (1H, m), 3.44 (1H, m). 12; $[\alpha]_D$

+12.3°(c 0.79, MeOH); CI-MS: 281 $(M+1)^+$, IR ($CHCl_3$): 3500-3300, 2930, 2850, 2260, 1485; ^1H NMR: 0.89 (3H, t, J=7.0 Hz), 1.02 (3H, t, J=7.3 Hz), 1.2-1.4 (10H, brm, W1/2 = 25 Hz), 1.50 (2H, m), 1.74 (2H, m), 1.88 (1H, d, J=5.8 Hz, OH), 2.01 (1H, d, J=5.5 Hz, OH), 2.37 (1H, d, J=5.8 Hz, OH), 2.56 (1H, dd, J=6.4, 16.5 Hz), 2.59 (1H, dd, J=6.4, 16.5 Hz), 3.59 (1H, m), 3.64 (1H, m), 4.36 (1H, q, J=6.1 Hz); ^{13}C NMR: 9.4, 14.1, 22.7, 24.9, 25.6, 29.2, 29.6, 30.7, 31.8, 33.6, 64.0, 66.7, 69.6, 72.2, 73.2, 77.3, 77.5. panaxacol; $[\alpha]_D$ +18.3°(c 1.0, MeOH) (synthetic), $[\alpha]_D$ +19.5°(c 1.0, MeOH) (natural); CI-MS: 279 $(M+1)^+$, IR ($CHCl_3$): 3560, 3400, 2930, 2240, 1665; ^1H NMR: 0.89 (3H, t, J=7.1 Hz), 1.15 (3H, t, J=7.3 Hz), 1.2–1.4 (10H, brm), 1.51 (2H, m), 1.91 (1H, d, J=5.6 Hz, OH), 2.60 (2H, q, J=7.3 Hz), 2.64 (1H, dd, J=6.3, 17.6 Hz), 2.68 (1H, dd, J=5.9, 17.6 Hz), 3.59 (1H, m), 3.70 (1H, m).

6) Dihexyl copper lithium was prepared by the reaction of cuprous iodide and hexyl lithium. ex. g, C. R. Johnson and G. A. Dutra, J. Am. Chem. Soc., 95 7777 (1973).

7) The tetrahydropyranyl ether of 1,3-heptadiyne-5-ol was prepared by aldol condensatoin of diacetylene and propionaldehyde in the presence of n-BuLi-HMPA and followed by protection of resulting alcohol. 1,3-Heptadiyne-5-ol; ^1H NMR: 1.03 (3H, t, J=7.1 Hz), 1.76 (2H, m), 1.95 (1H, brs, OH), 2.20 (1H, d, J=1.0 Hz), 4.38 (1H, m); ^{13}C NMR: 9.2, 30.4, 63.6, 67.3, 68.2, 68.9, 77.1. 1,3-heptadiyne-5-ol tetrahydropyranyl ether; a mixture of diastereomers, exhibit two spots on TLC (silica gel, Rf 0.60 and 0.68, solvent; hexane : AcOEt = 5 : 1); CI-MS: 193 $(M+1)^+$. Preparation of diacetylene : L. Brandsma and H. D. Verkruijsse, "Studies in Organic Chemistry, Vol. 8, Synthesis of Acetylenes, Allenes and Cumulenes," Elsevier Scientific Publishing Co., Amsterdam, p.146 (1981).

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