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# BIOGENETIC TYPE SYNTHESIS OF (±)-CONCINNDIOL AND (±)-APLYSIN 20[1]

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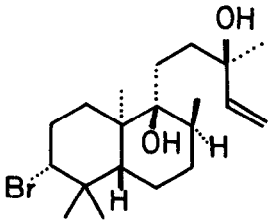
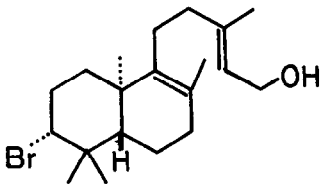
Summary: Based on the biogenetical consideration, the titled natural products were synthesized via the common intermediate (7).

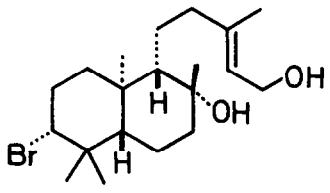
Concinndiol (1)[2] and aplysin 20 (2)[3] are the typical bromine containing diterpenoids, originated from marine organisms. Each structure was unequivocally established by X-ray crystallographic analysis. These natural products are considered to be biosynthesized from geranylgeraniol or its biogenetical equivalent by bromonium ion induced cyclization through the common intermediate (3)[4]. In connection with our continuous efforts toward the bromine containing cyclic terpenoids, we have further explored the reactivity of 2,4,4,6- tetrabromocyclohexadienone (4, TBCO) and found that $CH_3CN$ controlls unusually the reaction of polyenes. When methyl geranylgeranate (5) was treated with TBCO in $CH_3CN$, the monocyclic bromide (6) was formed in more than 50% yield. 6 was transformed into the cyclopentene derivatives by treatment with AgOAc in AcOH[5]. After treatment with AgOAc, the reaction mixture was submitted to the detailed chromatography, resulting in the isolation of the bicyclic ester (7) in 20% yield in addition to the rearranged products[6].



(1)



(3)



(2)

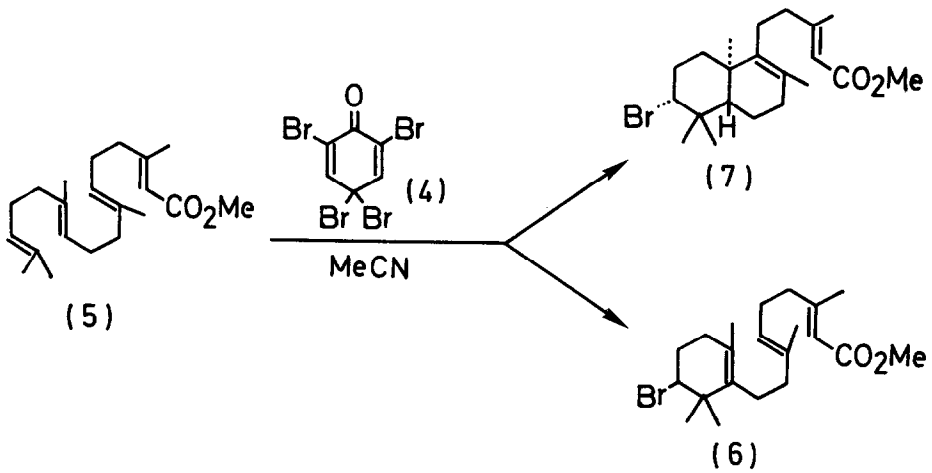
The structure of 7 was confirmed by transforming it into the known compound (7, H instead of Br)[7] in 70% yield by the reductive removal of the bromine atom with $Bu_3SnH$ and catalytic amounts of AIBN.

This paper deals with the simple, biogenetic type synthesis of (±)-concinndiol (1) and (±)-aplysin 20 (2) from the bicyclic ester (7). The tertiary hydroxyl group attached on the ring carbon of 1 and 2 was elaborated

by hydride reduction of the corresponding epoxides (8 and 9). On the basis of stereoelectronic effects, the preferential axial attack was expected, leading to the regioselective ring opening of each epoxide[8].

The bicyclic ester (7)[9] was subjected to the action of 1.2 mol eq of m-chloroperbenzoic acid in the presence of $NaHCO_3$ (1.5 eq) in $CH_2Cl_2$ at room temperature, providing a 2:1 mixture of two epoxides (8 and 9) in 80% yield, which was separated by a conventional silica gel column chromatography. The relative stereochemistry of the epoxide ring with respect to the angular methyl group was deduced on the basis of steric effect of the methyl group,i.e., the epoxide ring is anti orientation to the angular methyl in the major product (8). This deduction was supported by $^1H$ NMR spectrum. The chemical shifts of $C_8$ and $C_{10}$ methyls of the minor epoxide (9) were observed at relatively lower field as compared with those of the major one (8)[10]. Treatment of the minor epoxide (9) with excess of $AlH_3$ in ether at -78°C for 1.5 h gave the allyl alcohol (9, $CH_2OH$ instead of $CO_2Me$) quantitatively, while prolonged treatment first at -78°C and then at 0°C for 24 h afforded a single diol in 80% yield.

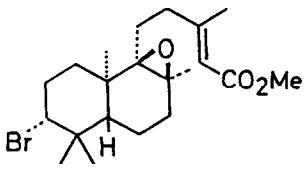
Identity of the diol with aplysin 20 (2) was secured by comparison of $^1H$-NMR, IR ($CHCl_3$) and Mass spectra.



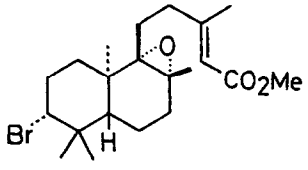

The conversion of the major epoxide (8) to (±)-concinndiol (1) was executed as follows. Reduction of the ester group with $AlH_3$ (excess) at -78°C gave the allyl alcohol (10) quantitatively, which was transformed into the thiophenyl ether (11) in 85% yield by two step sequence: (1) MsCl (2.2 eq)/LiCl (2 eq)/γ-collidine (2.2 eq) in DMF (0°C, 5 h)[11] and (2) PhSH (excess)/NaH (2 eq) in DMF (0°C, 30 min). Oxidation of the thiophenyl ether with 1.1 eq of $NaIO_4$ in MeOH overnight at room temperature followed by treatment with $P(OMe)_3$ (2 eq) in MeOH at room temperature for 3 days[12] provided the rearranged product (12) in 69% yield as a 1:1 diastereomeric mixture. Without any purification, the mixture was submitted to the action of $AlH_3$ (excess) in ether

at 0°C for 1.5 h, resulting in the formation of a diastereomeric mixtue of the diols. Assisted presumably by the intramolecular hydrogen bonding between the two hydroxyl groups in each molecule, separation of the diastereomers was achieved easily by a silica gel column chromatography, providing two crystalline diols in 30% respective yields. $^{1}H$ NMR spectrum of one isomer was completely in accord with concinndiol (2)[13].

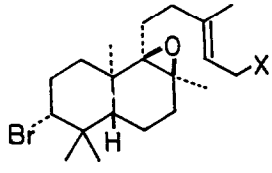
As described above, we have succeeded in the biogenetic type synthesis of (±)-concinndiol and (±)-aplysin 20 although it is necessary to explore the suitable conditions to execute the preferential preparation ofthe ester (7). The total synthesis of (±)-aplysin 20 was recently reported by Masamune's group[14].



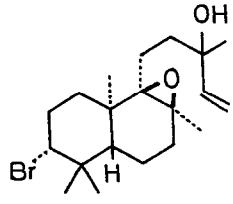

(8)




(9)




(10) X = OH
(11) X = SPh




(12)

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1. This constitutes part 44 of the series of cyclization of polyenes. Part 43, M. Aoki, T. Kato, Y. Uchio, M. Nakayama, and M. Kodama, Bull. Chem. Soc. Jpn., accepted for publication (1984).
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3. Y. Yamamura and Y. Hirata, Bull. Chem. Soc. Jpn., 44, 2560 (1971).
4. W. Fenical, "Marine Natural Products: Chemical and Biological Perspectives, vol II (ed. P. J. Scheuer)", Academic Press, New York, 1978, p 223.
5. T. Kato, M. Mochizuki, T. Hirano, S. Fujiwara, and T. Uyehara, Chem. Commun., in the press (1984).
6. It was difficult to separate 6 and 7 by the conventional chromatography, while 7 and the rearranged cyclopentene derivatives were easily separated by silica gel column chromatography.
7. G. Cimino, D. de Rosa, S. de Stefano, and L. Minale, Tetrahedron, 30, 645 (1974).
8. P. Deslongchamp, "Organic Chemistry Series, vol 1, (ed. J. E. Baldwin): Stereoelectronic Effects in Organic Chemistry", Pergamon Press, Oxford, 1983, p 165.
9. Only one enantiomer of dl-form was described in all the synthetic compounds.
10. Otherwise stated, $^{1}H$ and $^{13}C$ NMR spectra were recorded with Varian EM 390 (90 MHz) and JEOL FT 90Q (90 MHz) spectrometers.

11. E. W. Collington and A. I. Meyers, J. Org. Chem., 36, 3044 (1971).
12. D. A. Evans, G. C. Andrews, T. T. Fujimoto and D. Wells, Tetrahedron Lett., 1385; 1389 (1973).
see also; M. Kodama, K. Shimada and S. Ito, Tetrahedron Lett., 2763 (1977).
13. The synthesized compounds have the following physical data.
7, mp 99-100°C; $^1$H NMR (δ, $CDCl_3$) 0.96 (3H, s), 1.00 (3H, s), 1.09 (3H, s), 1.58 (3H, s), 2.18 (3H, d, 1.5 Hz), 3.67 (3H, s), 3.96 (1H, m), and 5.64 (1H, bs) ppm; $^{13}$C NMR (δ, $CDCl_3$) quaternary carbons at 167.1, 160.3, 138.3, 127.2, 39.7, and 39.1: tertiary carbons at 114.7, 69.1, and 52.5: secondary carbons at 41.5, 38.3, 33.8, 31.2, 26.3, and 19.4: methyls at 50.7, 30.4, 20.5, 20.0, 18.9 and 18.3 ppm.
8, mp 129-130°C; $^1$H NMR (δ, $CDCl_3$) 0.94 (3H, s), 1.03 (3H, s), 1.05 (3H, s), 1.20 (3H, s), 2.12 (3H, d, 1.5 Hz), 3.64 (3H, s), 3.93 (1H, dd, 11.1, 7.2 Hz), and 5.59 (1H, bs) ppm; $^{13}$C NMR (δ, $CDCl_3$) quaternary carbons at 167.0, 160.0, 70.5, 62.5, 39.2, and 38.7: tertiary carbons at 115.0, 68.3 and 43.5: secondary carbons at 37.5, 35.8, 30.5, 29.1, 24.6 and 18.7: methyls at 50.8, 30.7, 21.7, 19.1, 18.0 and 17.0 ppm.
9, oil; $^1$H NMR (δ, $CDCl_3$) 0.90 (3H, s), 1.04 (3H, s), 1.10 (3H, s), 1.29 (3H, s), 2.16 (3H, d, 1.5 Hz), 3.66 (3H, s), 3.93 (1H, m), and 5.62 (1H, bs) ppm; $^{13}$C NMR (δ, $CDCl_3$) quaternary carbons at 167.0, 159.5, 71.3, 64.8, 40.2, and 38.8: tertiary carbons at 115.1, 67.9, and 54.3: secondary carbons at 38.4, 37.8, 35.7, 31.8, 29.3, and 18.4: methyls at 50.9, 30.4, 21.1, 18.9, 18.9, and 17.0 ppm.
9 ($CH_2OH$ instead of $CO_2Me$), oil; $^1$H NMR (δ, $CDCl_3$) 0.90 (3H, s), 1.05 (3H, s), 1.10 (3H, s), 1.29 (3H, s), 1.66 (3H, bs), 3.94 (1H, m), 4.12 (2H, d, 7.0 Hz), and 5.36 (1H, t, 7.0 Hz) ppm.
10, oil; $^1$H NMR (δ, $CDCl_3$) 0.94 (3H, s), 1.02 (3H, s), 1.05 (3H, s), 1.20 (3H, s), 1.67 (3H, bs), 3.96 (1H, dd, 9.5, 6.8 Hz), 4.11 (2H, d, 6.8 Hz), and 5.35 (1H, t, 6.8 Hz) ppm; $^{13}$C NMR (δ, $CDCl_3$) quaternary carbons at 139.3, 70.8, 62.4, 39.2, and 38.6: tertiary carbons at 123.2, 68.5, and 43.5: secondary carbons at 59.1, 36.0, 35.8, 30.7, 29.1, 25.0, and 18.7: methyls at 30.7, 21.7, 18.0, 17.0, and 16.5 ppm.
12, oil; $^1$H NMR (δ, $CCl_4$, 60 MHz) 0.90 (3H, s), 1.07 (6H, s), 1.14 and 1.20 (total 3H, each s), 1.25 (3H, s), 3.97 (1H, m), 5.03 (1H, d, 10 Hz), 5.22 (1H, d, 18 Hz), and 5.86 (1H, dd, 18, 10 Hz) ppm.
(±)-Concinndiol (1); mp,102-103°C, $^1$H NMR (δ, $CDCl_3$) 0.86 (3H, d, 6.0 Hz), 0.97 (6H, s), 1.08 (3H, s), 1.28 (3H, s), 4.02 (1H, m), 5.06 (1H, dd, 10.5, 1.3 Hz), 5.18 (1H, dd, 17.5, 1.3 Hz), and 5.88 (1H, dd, 17.5, 10.5 Hz) ppm.
(±)-13-Epiconcinndiol, mp 94-95°C; $^1$H NMR (δ, $CDCl_3$) 0.86 (3H, d, 6.0 Hz), 0.93 (3H, s), 0.96 (3H,s), 1.07 (3H, s), 1.29 (3H, s), 4.01 (1H, m), 5.07 (1H, dd, 11.4, 1.7 Hz), 5.18 (1H, dd, 17.8, 1.7 Hz), and 5.82 (1H, dd, 17.8, 11.4 Hz) ppm.
(±)-Aplysin 20 (2), mp 157-158°C; $^1$H NMR (δ, $CDCl_3$) 0.97 (3H, s), 1.01 (3H, s), 1.09 (3H, s), 1.16 (3H, s), 1.70 (3H, bs), 3.97 (1H, dd, 10.8, 5.7 Hz), 4.14 (2H, d, 6.2 Hz) and 5.39 (1H, t, 6.2 Hz) ppm; $^{13}$C NMR (δ,$CDCl_3$ +$CD_3OD$ (4:1)) quaternary carbons at 139.6, 72.7, 39.9 and 39.2: tertiary carbons at 123.4, 70.0, 58.9 and 56.7: secondary carbons at 58.9, 43.5, 42.2, 40.8, 30.7, 24.0 and 20.0: methyls at 30.7, 30.4, 18.4, 16.4 and 15.2 ppm.
14. The authors thank to professor A. Murai of Hokkaido University for his sending the manuscript of the synthesis of (±)-aplysin 20 prior to publication; thanks are also due to professors A. Murai and J. J. Sims for their sending the copies of physical data of aplysin 20 and concinndiol, respectively.

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