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Syntheses of Some 6-Oxa- and 2,8-Dioxabicyclo[3.2.1]octanes in Connection with the Daphniphyllum Alkaloids

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In connection with the daphniphyllum alkaloids, some 6-oxa- and 2,8-dioxabicyclo[3.2.1]octanes, which are included as a partial structure of daphmacrine and codaphniphylline, have been synthesized starting from geraniol.

Previously, we could isolate a number of novel alkaloids from the plant *Daphniphyllaceae.*[1] From a structural point of view, these alkaloids, which are biosynthesized from six mevalonate via squalene, are classified into six types of nitrogen heterocyclic skeletons. Among them, remarkable variations in the remaining partial structure except for the main nitrogen heterocyclic skeleton are found in the group of daphniphylline-type alkaloids, in which codaphniphylline (**1**) and daphmacrine (**2**) are included. As a part of our synthetic study on these alkaloids, we wish to describe the syntheses of some 6-oxa- and 2,8-dioxabicyclo[3.2.1]octanes starting from geraniol.

The known monoacetate (**3**)[2] derived from geraniol in three steps was treated with PhCOCl–pyridine in dichloromethane (room temp, 3 h) in order to differentiate the two original allylic hydroxyl groups, giving rise to the corresponding benzoate (**4**), in quantitative yield, which was further converted into a desired cyclization product (**5**) in four steps, as follows.

The benzoate (**4**) was treated with $Hg(OCOCF_3)_2$ (1.5 equiv) in nitromethane under argon (−15 °C, 3 h) and then stirred with aqueous sodium chloride (room temp, 20 h) to give the corresponding organomercury chloride (**6**),[3] which was directly subjected to reductive demercuration with $NaBH_4$ in *N,N*-dimethylformamide with oxygen bubbling (0 °C, 30 min)[4] and then oxidized with pyridinium chlorochromate (PCC) in dichloromethane (room temp, 4 h) to afford the cyclohexanone derivative (**5**) in 60% overall yield from **4**. The ketone (**5**) was hydrolyzed with saturated methanolic ammonia (0 °C, 5 h) to afford a diol (**7**) in 89% yield, which was further oxidized with pyridinium dichromate (PDC) in *N,N*-dimethylformamide (0 °C, 1 h) to give an aldehyde (**8**) in 85% yield. The resulting aldehyde was treated with 1,2-ethanedithiol–BF_3 etherate to afford the corresponding thioacetal (**9**), which was hydrolyzed with K_2CO_3 in methanol (0 °C, 2 h) to give a dihydroxy compound (**10**), in 84% overall yield. Furthermore, the compound (**10**) was oxidized with PDC in *N,N*-dimethylformamide (room temp, 1 h) to give rise to a desired lactone (**11**) [mp 162—164 °C, IR (film) 1780 and 1715 cm^{-1}] in 54% yield. On $NaBH_4$ reduction in ethanol–dioxane (1:1) (0 °C, 2 h) followed by acetylation with Ac_2O–pyridine, the resulting lactone (**11**) was readily converted into an acetate (**12**), mp 146.5—147.5 °C, in 78% overall yield, in which the newly formed acetoxyl group must be in an axial configuration, as judged from its ^1H NMR spectrum [δ=4.91(1H, br s)].

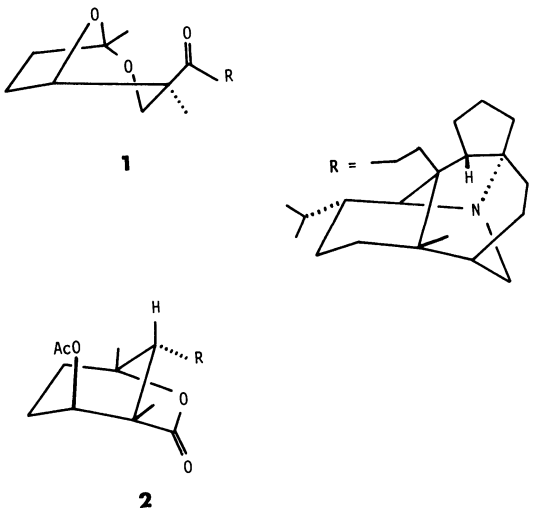

Fig. 1. Structures of codaphniphylline (**1**) and daphmacrine (**2**).

In the next step, the lactone (**12**) was successively treated with thallium trinitrate (TTN) (2.2 equiv) in chloroform–methanol (1:1) (room temp, 1 h),[5] trifluoroacetic acid (TFA) in chloroform containing a small amount of water (0 °C, 1 h), and SiO_2 (room temp, overnight) to afford an acid (**13**) which on methylation with MeI–K_2CO_3 in *N,N*-dimethylformamide (0 °C, 4 h) was converted into the corresponding ester (**14**) [IR (film) 1665 and 1625 cm^{-1}] in 48% overall yield from **12**. In the above procedure, the desired aldehyde (**15**) is too unstable to be separable and seems to be simultaneously converted into the α,β-unsaturated aldehyde (**13**), which has been also produced on exposure to K_2CO_3 in methanol. Finally, this ester (**14**) was successfully converted into the desired 2,8-dioxabicyclo[3.2.1]octane derivative (**16**) which has the same oxygen heterocyclic skeleton

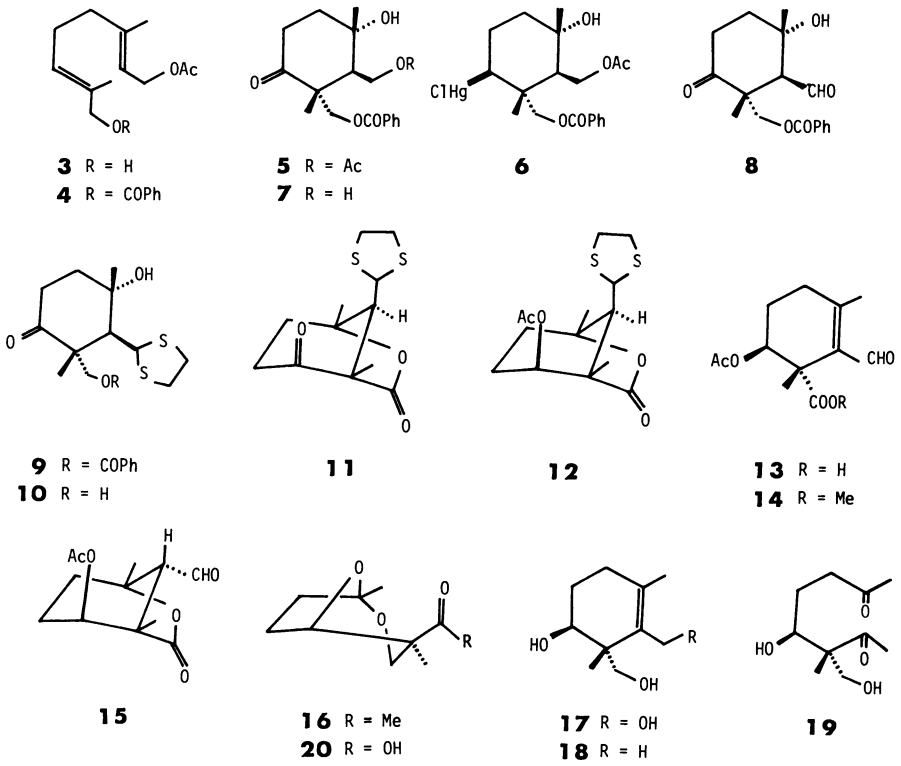

Fig. 2.

as that of codaphniphylline (**1**), as follows.

The ester (**14**) was reduced with excess $NaBH_4$ in ethanol (room temp, overnight) to afford a triol (**17**) and the acetate which on ammonolysis at 0 °C for 2 d afforded **17** in almost quantitative yield. Thus, the total yield of **17** from **14** was 69%. The triol so far obtained was subjected to hydrogenolysis using Pd–C in methanol (room temp, 1.5 h) to give a diol (**18**), mp 104—104.5 °C, in 87% yield. In the last step, on ozonization of **18** in methanol (−60 °C, 30 min) followed by reduction with excess Me_2S, the resulting diketone (**19**) was spontaneously cyclized to the desired acetal (**16**), in 72% yield, having the same oxygen heterocyclic skeleton as that of codaphniphylline (**1**), as judged from its ^1H NMR spectrum [δ=3.49 (1H, d, J=12 Hz), 4.27 (1H, dd, J=12, 2 Hz), and 4.68 (1H, m)], which was similar to that of the degradation product (**20**) of daphniphylline [δ=3.63 (1H, d, J=12 Hz), 4.30 (1H, dd, J=12, 2 Hz), and 4.77 (1H, m)].[6]

On the basis of biogenetic consideration of these daphniphyllum alkaloids, which are biosynthesized from squalene,[1] these two 6-oxa- and 2,8-dioxabicyclo-[3.2.1]octanes have been synthesized. Further synthetic study on the nitrogen heterocyclic moiety of these alkaloids are in progress.

Experimental

All the melting points were obtained on a Mitamura Riken melting point apparatus and uncorrected. IR spectra were recorded on a JASCO Model A-202 spectrophotometer. ^1H NMR spectra were obtained on a Varian EM-390 NMR spectrometer (90 MHz) using tetramethylsilane as an internal standard. Coupling constants are given in Hz (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet). High resolution mass spectra were obtained on a Hitachi M-80 GC-MS spectrometer operating with an ionization energy (70 eV). Preparative and analytical TLC were carried out on silica-gel plates (Kieselgel 60 F_{254}, E. Merck A. G. Germany) using UV light and/or 5% molbdophosphoric acid in ethanol for detection, unless otherwise stated.

Benzoylation of 3. A solution of **3** (3.0 g) and benzoyl chloride (3.5 ml) in CH_2Cl_2 (30 ml) containing pyridine (2.3 ml) was stirred at room temperature for 3 h. The resulted mixture was partitioned between EtOAc and water, and the organic layer was washed successively with 2M HCl (1 M=1 mol dm^{-3}) and aqueous $NaHCO_3$, and then dried over anhydrous Na_2SO_4. After evaporation of the solvent, the residue was chromatographed on silica gel (200 g) using hexane–EtOAc (5:1) as eluent to give the benzoyl derivative (**4**) as an oil (4.5 g): IR (film) 1730, 1720, 1600, and 1580 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.75 (6H, s), 2.07 (3H, s), 2.14 (4H, complex), 4.57 (2H, d, J=7 Hz), 4.71 (2H, s), 5.2—5.6 (2H, complex), 7.3—7.6 (3H, complex), and 7.95—8.15 (2H, complex); Found: m/z 316.1677. Calcd for $C_{19}H_{24}O_4$: M, 316.1673.

Cyclization of the Benzoate (4) to the Cyclohexanone Derivative (5). To a solution of $Hg(OCOCF_3)_2$ (4.0 g) in CH_3NO_2 (50 ml) at −20 °C under argon was added a solution of **4** (2.0 g) in CH_3NO_2 (10 ml). The mixture was stirred at approximate −15 °C for 3 h, and then excess

aqueous NaCl was added. After stirring at room temperature for 20 h, the reaction mixture was extracted with $CHCl_3$. The organic extract was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to leave an oil (3.9 g), which was dissolved in DMF (16 ml), and a 4 ml portion of the solution was gradually added to a solution of $NaBH_4$ (112 mg) in DMF (15 ml) with oxygen bubbling. After being reacted at 0 °C for 30 min, precipitated mercury was filtered off using Celite. The filtrate was partitioned between EtOAc and 2M HCl. The organic layer was washed with aqueous $NaHCO_3$ and dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. The remaining DMF solution was submitted to the same procedure as above. The combined product was dissloved in CH_2Cl_2 (50 ml), and oxidized with PCC (3.5 g) at room temperature for 4 h. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give a brownish residue, which was chromatographed on silica gel (150 g) using $CHCl_3$–EtOAc (4:1) as eluent to afford **5** as an oil (1.3 g): IR (film) 3450, 1710br., 1595, and 1575 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.21 (3H, s), 1.42 (3H, s), 1.99 (3H, s), 2.0—3.0 (5H, complex), 4.16 (1H, dd, J=12, 5 Hz), 4.45 (1H, dd, J=12, 5 Hz), 4.50 (1H, d, J=11 Hz), 4.72 (1H, J=11 Hz), 7.3—7.6 (3H, complex), and 7.9—8.1 (2H, complex); Found: m/z 349.1627. Calcd for $C_{19}H_{25}O_6$: M+1, m/z 349.1649.

Hydrolysis of 5 to the Diol (7). The ketone (**5**) (0.17 g) was treated with saturated methanolic ammonia (10 ml) at 0 °C for 5 h, and then this mixture was concentrated under reduced pressure to leave an oil, which was purified by preparative TLC [hexane–EtOAc (1:1)] to give the desired diol (**7**) (0.11 g) and the starting material (**5**) (0.03 g). **7** as an oil: IR (film) 3450, 1705, 1595, and 1580 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.10 (3H, s), 1.52 (3H, s), 1.9—2.1 (2H, complex), 2.2—2.7 (3H, complex), 3.9—4.05 (2H, complex), 4.45 (2H, s), 7.3—7.6 (3H, complex), and 7.85—8.05 (2H, complex); Found: m/z 307.1534. Calcd for $C_{17}H_{23}O_5$: M+1, m/z 307.1543.

Oxidation of the Diol (7) with PDC. A mixture of **7** (36 mg) and PDC (89 mg) in DMF (1 ml) was stirred at 0 °C for 1 h. The reaction mixture was directly submitted to preparative TLC [hexane–EtOAc (1:1)] to yield the aldehyde (**8**) (11 mg) in addition to the starting material (**7**) (23 mg). **8** as an oil: IR (film) 3450, 1715, 1625, 1600, 1580, and 1550 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.22 (3H, s), 1.40 (3H, s), 2.0—2.7 (3H, complex), 2.8—3.2 (3H, complex), 4.53 (1H, d, J=11 Hz), 5.01 (1H, d, J=11 Hz), 7.3—7.6 (3H, complex), 7.9—8.1 (2H, complex), and 9.67 (1H, d, J=4 Hz); Found: m/z 305.1387. Calcd for $C_{17}H_{21}O_5$: M+1, m/z 305.1387.

Protection of the Aldehyde (8) with 1,2-Ethanedithiol. To a solution of **8** (41 mg) in CH_2Cl_2 (2 ml) were added 1,2-ethanedithiol (34 µl) and $BF_3 \cdot OEt_2$ (14 µl), and the mixture was stirred at 0 °C for 5.5 h. The resulting mixture was washed with aqueous $NaHCO_3$, and then dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by preparative TLC [hexane–EtOAc (1:1)] to give the thioacetal (**9**) (44 mg): Mp 125—127.5 °C (from hexane–EtOAc); IR (film) 3400, 1710, 1600, and 1580 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.25 (3H, s), 1.53 (3H, s), 1.5—2.2 (5H, complex), 3.0—3.4 (4H, complex), 4.25 (1H, d, J=12 Hz), 4.41 (1H, d, J=12 Hz), 4.52 (1H, d, J=12 Hz), 7.3—7.65 (3H, complex), and 8.0—8.15 (2H, complex); Found: m/z 381.1219. Calcd for $C_{19}H_{25}O_4S_2$: M+1, m/z 381.1193.

Hydrolysis of the Thioacetal (9). A solution of **9** (0.15 g) and K_2CO_3 (64 mg) in MeOH (7 ml) was stirred at 0 °C for 2 h. The reaction mixture was quenched with H_2O and worked up as usual to give a crude product, which was purified by preparative TLC using hexane–EtOAc (1:1) to give a diol (**10**) (0.1 g) as a crystalline solid: ca. 123 °C; IR (film) 3350 and 1695 cm^{-1}; ^1H NMR ($CDCl_3$+D_2O) δ=1.26 (3H, s), 1.56 (3H, s), 1.5—2.2 (5H, complex), 3.0—3.4 (4H, complex), 3.45 (1H, d, J=11 Hz), 3.91 (1H, d, J=11 Hz), and 4.41 (1H, d, J=12 Hz); Found: m/z 246.0734. Calcd for $C_{11}H_{18}O_2S_2$: M−CH_2O, m/z 246.0747.

Oxidation of the Diol (10) with PDC. A mixture of **10** (22 mg) and PDC (0.15 g) in DMF (1 ml) was stirred at room temperature for 1 h. The resulting brown solution was passed through a short silica-gel column [hexane–EtOAc (1:2)] and purified by preparative TLC [hexane–EtOAc (1:2)] to afford the lactone (**11**) (7.1 mg) and the starting diol (**10**) (8.7 mg). **11**: Mp 162—164 °C (from hexane–EtOAc); IR (film) 1780 and 1715 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.48 (3H, s), 1.77 (3H, s), 2.1—2.4 (2H, complex), 2.5—2.65 (2H, complex), 2.73 (1H, d, J=10 Hz), 3.0—3.4 (4H, complex), and 4.24 (1H, d, J=10 Hz); Found: m/z 272.0513. Calcd for $C_{12}H_{16}O_3S_2$: M, m/z 272.0539.

Reduction of the Lactone (11) Followed by Acetylation. A mixture of **11** (45 mg) and $NaBH_4$ (7 mg) in EtOH (1 ml) and dioxane (1 ml) was stirred at 0 °C for 1 h and then worked up as usual to give a hydroxy compound (38 mg): Mp 125.5—127 °C (from hexane); IR (film) 3450 and 1755 br. cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.48 (3H, s), 1.63 (3H, s), 1.7—2.1 (4H, complex), 2.27 (1H, d, J=10 Hz), 3.0—3.3 (4H, complex), 3.37 (1H, br.s), and 5.23 (1H, d, J=10 Hz); Found: m/z 274.0694. Calcd for $C_{12}H_{18}O_3S_2$: M, m/z 274.0695.

This compound (28 mg) was dissolved in excess Ac_2O–pyridine and allowed to stand at room temperature overnight, and then worked up as usual to afford the acetate (**12**) (30 mg): Mp 146.5—147.5 °C (from hexane); IR (film) 1770 and 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.40 (3H, s), 1.65 (3H, s), 1.6—2.1 (4H, complex), 2.14 (3H, s), 2.26 (1H, br.d, J=12 Hz), 3.1—3.4 (4H, complex), 4.94 (1H, br.s), and 5.02 (1H, d, J=12 Hz); Found: m/z 316.0813. Calcd for $C_{14}H_{20}O_4S_2$: M, m/z 316.0802.

Formation of the α,β-Unsaturated Aldehyde (14). A mixture of **12** (19 mg) and TTN (58 mg) in $CHCl_3$ (0.5 ml) and MeOH (0.5 ml) was stirred at room temperature for 1 h. After filtration of salt precipitated, the filtrate was partitioned between $CHCl_3$ and H_2O, and the organic layer was dried over anhydrous Na_2SO_4 and then concentrated under reduced pressure. The residue was treated with TFA (0.5 ml) in $CHCl_3$ (0.5 ml) containing small amount of H_2O at 0 °C for 1 h. The mixture was diluted with $CHCl_3$ and neutralized with aqueous $NaHCO_3$. The organic layer was dried over anhydrous Na_2SO_4 and then concentrated under reduced pressure to leave a syrup, which was charged on silica-gel plates and kept at room temperature overnight. Development of the plate using $CHCl_3$–MeOH (4:1) afforded a crude product, which on methylation with MeI (6 µl)–K_2CO_3 (11 mg) in DMF (0 °C, 4 h) led to the ester (**14**) (7.1 mg) as an oil: IR (film) 1730, 1665, and 1625 cm^{-1};

^{1}H NMR ($CDCl_3$) δ=1.35 (3H, s), 1.55—2.65 (4H, complex), 2.04 (3H, s), 2.18 (3H, S), 3.60 (3H, s), 5.19 (1H, m), and 10.00 (1H, s); Found: *m/z* 254.1114. Calcd for $C_{13}H_{18}O_5$: M, *m/z* 254.1152.

Formation of the Triol (17). To a solution of **14** (15 mg) in EtOH (1 ml) was added $NaBH_4$ (13 mg) at 0 °C, and then the reaction temperature was gradually elevated to room temperature. After being stirred at room temperature overnight, the mixture was neutralized with AcOH and then concentrated under reduced pressure to leave a syrup, which was passed through a short silica-gel column [hexane–acetone (3:1)] to give the triol (**17**) (4.4 mg) and the acetate (4.4 mg). The latter was directly treated with mathanolic ammonia at 0 °C for 2 d to afford **17** (3.3 mg) as a syrup: IR (film) 3380 cm^{-1}; ^{1}H NMR ($CDCl_3$+D_2O) δ=0.85 (3H, s), 1.77 (3H, s), 1.4—2.3 (4H, complex), 3.67 (2H, d, *J*=1.5 Hz), 4.02 (1H, d, *J*=12 Hz), ca. 4.0 (1H, overlapped with the doublet), and 4.29 (1H, d, *J*=12 Hz); Found: *m/z* 186.1261. Calcd for $C_{10}H_{18}O_3$: M, *m/z* 186.1255.

Hydrogenolysis of the Triol (17). The triol (**17**) (5.3 mg) in MeOH (1 ml) was hydrogenated over catalyst 10% Pd–C at room temperature for 1.5 h. After filtration of the catalyst, the filtrate was concentrated under reduced pressure and then directly separated by a short silica-gel column using hexane–acetone (5:1) to afford **18** (2.6 mg) and the unreacted **17** (2.0 mg). **18**: Mp 104–104.5 °C (from hexane–EtOAc); IR (film) 3400 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ= 1.02 (3H, s), 1.61 (6H, s), 1.7—2.2 (4H, complex), 3.52 (1H, d, *J*=11 Hz), 3.74 (1H, d, *J*=11 Hz), and ca. 3.75 (1H, overlapped with the doublet); Found: *m/z* 170.1286. Calcd for $C_{10}H_{18}O_2$: M, *m/z* 170.1305.

Ozonization of the Diol (18). Ozone was passed through a solution of **18** (20 mg) in MeOH (5 ml) at −60 °C for 30 min. After excess ozone was purged with N_2, the reaction solution was treated with excess Me_2S as usual, and then concentrated under reduced pressure. The residue was purified by preparative TLC [hexane–EtOAc (1:1)] to give the acetal (**16**) (14 mg), and the starting material (2 mg) was recovered. **16** as an oil: IR (film) 1710 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.85 (3H, s), 1.48 (3H, s), 1.8—2.1 (4H, complex), 2.39 (3H, s), 3.49 (1H, *d*, *J*=12 Hz), 4.27 (1H, dd, *J*=2, 12 Hz), and 4.68 (1H, m); Found: *m/z* 184.1087. Calcd for $C_{10}H_{16}O_3$: M, *m/z* 184.1097.

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