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SYNTHETIC APPROACH TO GRAYANOTOXINS AND ASEBOTOXINS: A NEW CONSTRUCTION OF THE A-HOMOGRAYANOTOXANE RING SYSTEM

TETSUJI KAMETANI*, HIROO MATSUMOTO, and TOSHIO HONDA
Hoshi College of Pharmacy, Ebara 2-4-41, Shinagawaku, Tokyo 142, Japan

KEIICHIRO FUKUMOTO
Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan

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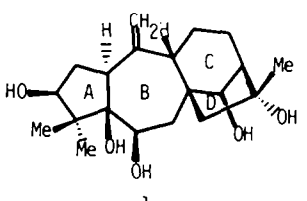
Abstract-The tetracyclic compounds (3 and 4) corresponding to A-homograyanotoxane system were synthesised by a thermolysis of the benzocyclobutene (8), followed by a Wagner-Meerwein rearrangement of the kaurane type of compounds (15 and 16).

Diterpenoids related to the grayanotoxane ring system which is consisted of a perhydroazulene skeleton fused with a bicyclo[3.2.1]octane system are the interesting substances because of their structural characteristics and of biological activities.[1] Although the synthesis of grayanotoxin II (1) has recently been achieved by Matsumoto,[2] studies concerning with the synthetic approach to asebotoxanes are not so much.[3,4] Major obstacles in synthesis are the construction of hydroazulene and bicyclo[3.2.1]octane parts. We have been investigating a development of a new conctruction of the route for a synthesis of grayanotoxanes and reported benzohydroazulene (2) corresponding to A/B/C ring part of grayanotoxanes.[5] Now our attention has been focused on a synthesis of the B/C/D ring part consisting of a bicyclo[3.2.1]-octane system, and here report a new construction of the A-homograyanotoxane system (3 and 4) by a thermolysis of benzocyclobutene and a Wagner-Meerwein rearrangement of the resulting kaurene type of compounds, whose methods were developed in our laboratory.[5-7]

Chart 1



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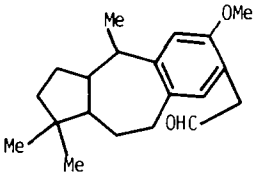
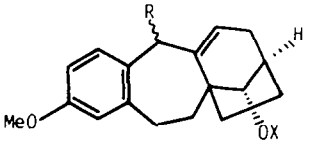


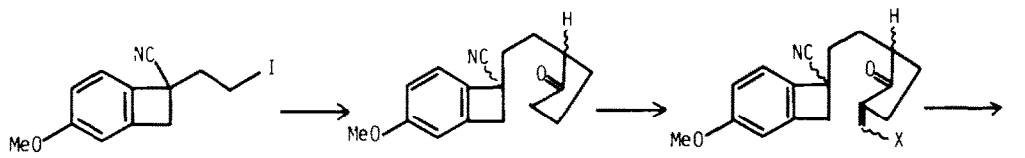
2



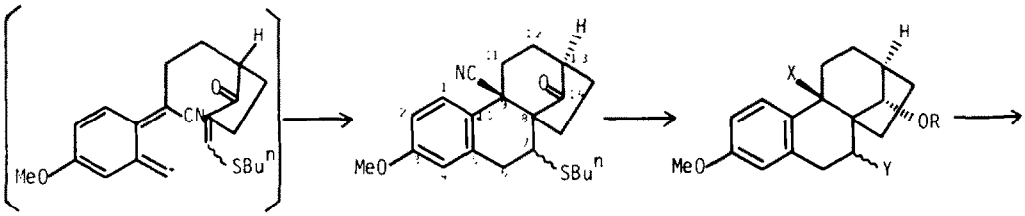
3 R=X=H
4 R=Me, X=Ts
17 R=H, X=TS

Condensation of 2-(1-cyano-4-methoxybenzocyclobutenyl)ethyl iodide (5)[8], a synthon containing the A ring and a part of the B and C rings, with the pyrrolidine enamine of cyclopentanone, a synthon for the D ring, as usual gave the 2-benzocyclobutenylethylcyclopentanone (6) which has all the carbon atom in the grayanotoxane framework. This was converted into the key intermediate (8) [$\nu_{max.}$ ($CHCl_3$) 1695 cm^{-1} and δ ($CDCl_3$) 3.18 and 3.30 (each 1H, d, J 14 Hz, $ArCH_2$)] by a treatment with ethyl formate in the presence of sodium hydride and then the resulting hydroxymethine (7) with n-butyl mercaptan and p-toluenesulphonic acid in 64.6 % overall yield from 5. Heating the olefinic benzocyclobutene (8) in o-dichlorobenzene at 180° for 6 hr in a current of nitrogen gave in 70.7 % yield, via o-quinodimethane (9), the tetracyclic compound (10)[9] having a kaurane system which showed the presence of cyclopentanone system at 1750 cm^{-1} in its IR spectrum. Reduction of 10 with sodium borohydride afforded the alcohol (11) [$\nu_{max.}$ ($CHCl_3$) 3570 cm^{-1}], which was treated with acetic anhydride and pyridine to yield the corresponding acetate (12) [$\nu_{max.}$ ($CHCl_3$) 1720 cm^{-1}]. The NMR spectrum of 12 revealed the methyl resonance in acetoxyl group at an abnormally high field (δ 1.38) and the methine proton of C_{14} position at δ 4.70 as a broad doublet. The former fact shows that the relative configuration of the cyano group and the C_{13}-hydrogen is trans as shown in 12. This stereochemistry is supported by the second effect in Woodward-Hoffmann rule[10] which considers the role of the cyano function on the o-quinodimethane system. The latter data in NMR spectrum indicate methine proton at C_{14} position to be coupled with the proton at C_{12} position in long-range manner, thus showing the C_{14}-hydroxyl group to be an α orientation[7]. Treatment of the alcohol (11) with Raney nickel[11] in acetone at 60° for 4 hr, followed by the catalytic hydrogenation on 10 % palladium-carbon in ethanol gave the desulphurized product (13), which was reduced with DIBAL at room temperature into the corresponding aldehyde (14) [$\nu_{max.}$ ($CHCl_3$) 1710 cm^{-1} and δ ($CDCl_3$) 9.43] in 31.4 % overall yield from 11. Sodium borohydride reduction of this aldehyde afforded in 90 % yield the alcohol (15) [δ ($CDCl_3$) 3.58 and 3.63 (each 1H, d, J 14 Hz, $-CH_2OH$)].

Chart 2



5 6 7 X=OH 8 X=SBu^n



9 10 11 X=CN, Y=SBu^n, R=H
12 X=CN, Y=SBu^n, R=Ac
13 X=CN, Y=R=H
14 X=CHO, Y=R=H
15 X=CH_2OH, Y=R=H
16 X=CH<Me/OH, Y=R=H

5 or 4

The alcohol (15) thus obtained was treated with p-toluenesulphonyl chloride in pyridine at room temperature for 5 hr to give in 59 % yield the expected rearranged compound (3) in addition to its tosylate (17) in 29.5 % yield, and the both was easily separated by silica gel column chromatography. The former product [$\nu_{max.}$ ($CHCl_3$) 3570 cm^{-1} and m/e 270 (M^+)] exhibited an olefinic proton at 5.50 as a distorted doublet and benzylic methylene protons at 3.30 and 3.43 as a doublet having J 11 Hz. The tosylate (17), which was also obtained by treatment of 3 with p-toluenesulphonyl chloride and pyridine as usual, showed a methine proton on C_{14} at 4.36 as a doublet in addition to an olefinic proton at 5.35 as a distorted doublet and tosyl resonance. These NMR spectral data indicated the products to have the structure 3 and 17, and ruled out other possible rearranged structures.

By having the result in hand that the aromatic ring is preferred to migrate, a synthesis of the C_{10}-methylated compound (4) was investigated by the same method as follows.

Grignard reaction of the aldehyde (14) with methylmagnesium iodide in ether at room temperature for 0.5 hr gave in 66.3 % yield the alcohol (16) which was subjected to Wagner-Meerwein rearrangement with an excess of p-toluenesulphonyl chloride in pyridine at 70° for 17 hr to afford the A-homograyanotoxane (4) as a stereoisomeric mixture at C_{10} position in 50.2 % yield.

Thus, we could succeed in developing a new route for a construction of a A-homograyanotoxane ring system.

EXPERIMENTAL

IR spectra were obtained with a Hitachi 260-10 spectrophotometer, NMR spectra with JEOL-PMX-60 spectrometer ($SiMe_4$ as internal reference), and mass spectra with Hitachi M-52G and JEOL-JMS-01SG-2 spectrometers.

2-[2-(1-Cyano-4-methoxybenzocyclobutenyl)]ethylcyclopentanone (6). — A mixture of pyrrolidine enamine of cyclopentanone (20 g), 2-(1-cyano-4-methoxybenzocyclobutenyl)ethyl iodide (5)[8] (25 g) and dry benzene (200 ml) was refluxed for 15 hr. After addition of water (15 ml), the resulting mixture was refluxed for 0.5 h and then treated with 10 % H_2SO_4 (5 ml). The organic layer was separated and the aqueous layer was extracted with ether. The combined organic layers were washed with 5 % aq. $Na_2S_2O_3$ soln and dried (Na_2SO_4). Evaporation of the solvent left a yellow oil, which was chromatographed on silica gel (220 g) using benzene to give the 2-benzocyclobutenylethylcyclopentanone (6) (28 g, 93.2 %) as a colorless oil (Found: C, 75.55; H, 6.99; N, 4.95. $C_{17}H_{19}NO_2$ requires C, 75.81; H, 7.11; N, 5.20 %); IR $\nu_{max.}$ ($CHCl_3$) 2230 (CN) and 1735 cm^{-1} (CO); NMR ($CDCl_3$) δ 3.17 and 3.65 (each 1H, d, J = 14 Hz, $ArCH_2$) and 3.73 (3H, s, OCH_3); MS m/e 269 (M^+).

5-[(n-Butylthio)methylene]-2-[2-(1-cyano-4-methoxybenzocyclobutenyl)ethyl]cyclopentanone (8). — To a soln of 6 (10 g) and NaH (50 % in oil, 1.96 g) in dry benzene (150 ml) was added a soln of ethyl formate (3 g) in dry benzene (30 ml) with stirring at room temp. After being stirred at room temp for 1 hr, water (50 ml) was added to the reaction mixture. The resulting aqueous layer was acidified with 10 % HCl and extracted with ether. The ethereal extract was washed with water and dried (Na_2SO_4). Removal of the solvent afforded the crude formyl derivative (7) (8.9 g) which was used for the next reaction without purification: IR ν_{max} ($CHCl_3$) 1670 cm^{-1}; NMR ($CDCl_3$) δ 10.03 (1H, br s). A soln of the crude 7 (8.9 g), n-butyl mercaptan (3.2 g), a catalytic amount of p-toluenesulphonic acid and dry benzene (200 ml) was refluxed for 2 hr in a current of N_2. After the reaction had been cooled to room temp, 10 % NaOH soln was added to it. The resulting mixture was extracted with ether and the extract was washed with water and dried (Na_2SO_4). Evaporation of the solvent left a reddish gum, which was chromatographed on silica gel (200 g) using benzene to give the thiomethylene derivative (8) (9.5 g, 69.3 %) as a colorless oil (Found: C, 71.25; H, 7.48; N, 3.55. $C_{22}H_{27}NO_2S$ requires C, 71.50; H, 7.37; N, 3.79 %); IR $\nu_{max.}$ ($CHCl_3$) 2240 (CN) and 1695 cm^{-1} (CO); NMR ($CDCl_3$) δ 3.18 and 3.50 (each 1H, d, J = 14 Hz, $ArCH_2$), 3.73 (3H, s, OCH_3) and 7.23 (1H, br s, $=CH-SBu$); MS m/e 369 (M^+).

7-n-Butylthio-9-cyano-6,7,8,9,11,12,13a,14-octahydro-3-methoxy-8β,13β-ethanophenanthren-14-one (10). — A soln of 8 (4.6 g) in o-dichlorobenzene (460 ml) was heated at 180° for 6 hr in a current of nitrogen. After evaporation of the solvent, the residue was chromatographed on

silica gel (140 g) using n-hexane-AcOEt (v/v 10 : v/v) to give the tetracyclic compound (10) (3.25 g, 70.7 %) as colorless needles, mp 74 ∿ 76° (ether-n-hexane) (Found: C, 71.60; H, 7.39; N, 3.64. $C_{22}H_{27}NO_2S$ requires C, 71.50; H, 7.37; N, 3.79 %); IR $\nu_{max.}$ ($CHCl_3$) 2215 (CN) and 1750 cm^{-1} (CO); NMR ($CDCl_3$) δ 3.43 (2H, br s, $ArCH_2$) and 3.77 (3H, s, OCH_3); MS m/e 369 (M^+).

7-n-Butylthio-9β-cyano-6,7,8,9,11,12,13α,14β-octahydro-14α-hydroxy-3-methoxy-8β,13β-ethanophenanthrene (11). — To a soln of 10 (3 g) in MeOH (100 ml) was added in saml1 portions $NaBH_4$ (0.5 g) with stirring at room temp, and then the mixture was stirred for 1 hr at the same temp. After evaporation of MeOH, the residue was decomposed with water and extracted with ether. The extract was washed with water, dried (Na_2SO_4) and evaporated to give the alcohol (11) (2.67 g, 89 %) as colorless needles, mp 157 ∿ 160° (n-hexane) (Found: C, 71.05; H, 8.00; N, 3.60. $C_{22}H_{29}NO_2S$ requires C, 71.12; H, 7.87; N, 3.77 %); IR $\nu_{max.}$ ($CHCl_3$) 3570 (OH) and 2215 cm^{-1} (CN); MS m/e 371 (M^+).

The acetate (12) (6 mg, colorless oil) was prepared from 11 (10 mg) by treatment with acetic anhydride (0.1 ml) and pyridine (0.2 ml) for 48 hr at room temp; IR $\nu_{max.}$ ($CHCl_3$) 2205 (CN) and 1720 cm^{-1} (CO); NMR ($CDCl_3$) δ 1.38 (3H, s, $-OCOCH_3$) and 4.70 (1H, br d, J = 5 Hz, $-CH-OCOCH_3$); MS m/e 418 (M^+) (Found: M^+ 413.2019. $C_{24}H_{31}NO_3S$ requires M 413.2024).

9β-Cyano-6,7,8,9,11,12,13α,14β-octahydro-14α-hydroxy-3-methoxy-8β,13β-ethanophenanthrene (13). — A mixture of 11 (210 mg), Raney Ni[11] (3.5 g) and Me_2SO (30 ml) was heated at 60° for 6 hr with stirring. After filtration of Raney Ni, the solvent was distilled off to give 9β-cyano-8,9,11,12,13α,14β-hexahydro-14α-hydroxy-3-methoxy-8β,13β-ethanophenanthrene (160 mg, 50.3 %) as colorless crystals, mp 98 ∿ 101° (ether-n-hexane) (Found: C, 74.00; H, 6.81; N, 4.55. $C_{18}H_{19}NO_2 \cdot 0.5\ H_2O$ requires C, 74.44; H, 6.94; N, 4.82 %); IR $\nu_{max.}$ ($CHCl_3$) 3570 (OH), 2210 (CN) and 1625 cm^{-1} (C = O); NMR ($CDCl_3$) δ 5.73 (1H, d, J = 10 Hz, -CH = CH-); MS m/e 281 (M^+).

A mixture of the olef n (80 mg) and 10 % Pd-C (80 mg) in EtOH (10 ml) was shaken in a current of H_2 at room temp for 4 hr. After filtration of Pd-C, EtOH was removed in vacuo to give 13 (76 mg, 94.5 %) as colorless needles, mp 170 ∿ 171° (ether-n-hexane) (Found: C, 76.00; H, 7.70; N, 4.73. $C_{18}H_{21}NO_2$ requires C, 76.29; H, 7.47; N, 4.94 %); IR $\nu_{max.}$ ($CHCl_3$) 3550 (OH) and 2210 cm^{-1} (CN); MS m/e 283 (M^+).

9β-Formyl-6,7,8,9,11,12,13α,14β-octahydro-14α-hydroxy-3-methoxy-8β,13β-ethanophenanthrene (14). To a soln of the nitrile (13) (30 mg) in dry benzene (3 ml) was added DIBAL (0.5 ml; 25 wt % solution in toluene) in one portion at room temp with stirring and the mixture was stirred for 14 hr at room temp. After addition of an excess of 10 % NH_4Cl soln, the reaction mixture was further stirred for 2 hr and then extracted with CH_2Cl_2. The extract was washed with water, dried (Na_2SO_4), and evaporated to leave a gum, which was subjected to silica gel (2 g) column chromatography using n-hexane-AcOEt (v/v 9 : 1) as an eluant to give the aldehyde (14) (20 mg, 66 %) as a colorless oil (Found: C, 75.30; H, 7.80 $C_{18}H_{22}O_3$ requires C, 75.49; H, 7.74 %); IR $\nu_{max.}$ ($CHCl_3$) 3560 (OH) and 1710 cm^{-1} (CO); NMR ($CDCl_3$) δ 9.43 (1H, s, -CHO); MS m/e 257 (M^+-CHO).

6,7,8,9,11,12,13α,14β-Octahydro-14α-hydroxy-9β-hydroxymethyl-3-methoxy-8β,13β-ethanophenanthrene (15). — $NaBH_4$ (10 mg) was added to a soln of the aldehyde (14) (20 mg) in MeOH (5 ml) and the mixture was stirred at room temp for 1 hr. After evaporation of MeOH, the residue was decomposed with water and extracted with CH_2Cl_2. The extract was washed with water and dried (Na_2SO_4). Evaporation of the solvent left a colorless gum, which was chromatographed on silica gel (1 g) using CH_2Cl_2 as an eluant to give the alcohol (15) (18 mg, 89.5 %) as a colorless oil (Found: M^+ 288.1699. $C_{18}H_{24}O_3$ requires M 288.1724); IR $\nu_{max.}$ ($CHCl_3$) 3560 cm^{-1} (OH); NMR ($CDCl_3$) δ 3.30 and 3.63 (each 1H, d, J = 14 Hz, $-CH_2OH$).

Wagner-Meerwein Rearrangement of 15. — To a soln of the alcohol (15) (20 mg) in pyridine (0.3 ml) was added p-toluenesulphonyl chloride (20 mg) and the mixture was allowed to stand for 5 hr at room temp. The resulting mixture was poured into water and extracted with CH_2Cl_2. The extract was washed in 5 % HCl and water. After drying (Na_2SO_4) the solvent was removed by distillation to give an oil, which was subjected to silica gel (3 g) column chromatography. The first n-hexane-AcOEt (v/v 1 : 1) eulant gave the A-homograyanotoxane (3) (7 mg, 59 %) as colorless needles, mp 110 - 11 (MeOH) (Found: C, 78.10; H, 8.26. $C_{18}H_{22}O_2 \cdot 0.25\ H_2$ requires C, 78.60; H, 8.20 %), IR $\nu_{max.}$ ($CHCl_3$) 3570 cm^{-1} (OH); NMR ($CDCl_3$) δ 3.00 and 3.43 (each

1H, d, J = 11 Hz, $ArCH_2C=$) and 5.50 (1H, distorted t, J = 3 Hz, >C=CH-); MS m/e 270 (M^+) (Found: M^+ 270.1645. $C_{18}H_{22}O_2$ requires M 270.1620).

The second n-hexane-AcOEt (v/v 3 : 7) eluant afforded the tosylated product (17) (6 mg, 29.5 %) as colorless crystals, mp 125~127° (MeOH) (Found: C, 69.91; H, 6.87. $C_{25}H_{28}O_4S \cdot 0.25\ H_2O$ requires C, 69.98; H, 6.69 %); NMR ($CDCl_3$) δ 2.45 (3H, s, CH_3Ar), 4.36 (1H, d, J = 5 Hz, >CH-OTs), 5.35 (1H, distorted t, J = 3 Hz, >C=CH-) and 7.30 and 7.75 (each 2H, d, J = 8 Hz, ArH); MS m/e 424 (M^+). (Found: M^+ 424.1711. $C_{25}H_{28}O_4S$ requires M 424.1708).

Tosylation of 3.— A mixture of 3 (3 mg), p-toluenesulphonyl chloride (3 mg) and pyridine (0.1 ml) was allowed to stand at room temp for 1 hr, and worked up as the above rearrangement to give the tosylated product 17 (6 mg, 91 %), which was identical with 17, prepared directly from 15, in spectral and chromatographical comparison.

6,7,8,9,11,12,13α,14β-Octahydro-14α-hydroxy-9β-(2-hydroxyethyl) 3-methoxy-8β,13β-ethanophenanthrene (16).— A soln of aldehyde (14) (20 mg) in dry ether (10 ml) was added dropwise to MeMgI [prepared from Mg (7 mg) and MeI (50 mg) in dry ether (10 ml)] with stirring at room temp, and the mixture was stirred for 0.5 hr at room temp. The reaction mixture was decomposed with an excess of 10 % NH_4Cl soln and filtered. The organic layer was separated and the aqueous layer was extracted with ether. The organic layer and the extract were combined, washed with water, and dried (Na_2SO_4). Evaporation of the solvent gave an oil, which was purified with silica gel thick layer chromatography using n-hexane-AcOEt (v/v 1 : 1 ; Rf 0.43) to afford 16 (14 mg, 66.3 %) as a colorless oil (Found: C, 74.58; H, 8.30. $C_{19}H_{26}O_3 \cdot 0.24\ H_2O$ requires C, 74.35; H, 8.62 %); IR $\nu_{max.}$ ($CHCl_3$) 3565 (OH) cm^{-1}; NMR ($CDCl_3$) δ 0.83 and 0.95 (ratio 1 : 1; 3H, d, J = 7 Hz, CH_3-CH), and 4.0 (1H, broad, CH_3-CH-OH). The separtion of stereoisomer could not be achieved.

Wagner-Meerwein Rearrangement of 16.— A mixture of the alcohol (16) (11 mg), p-toluenesulphonyl chloride (17 mg) and pyridine (0.3 ml) was heated at 70° for 17 hr, and worked up as above rearrangement to give the crude oil, which was subjected to silica gel thick layer chromatography using n-hexane-AcOEt (v/v 1 : 1; Rf 0.61) to afford 4 (8 mg, 50.2 %) as a colorless oil (Found: M^+ 438.1835 $C_{26}H_{30}O_4S$ requires M 438.1863); NMR ($CDCl_3$) δ 1.30 and 1.42 (ratio 1 : 2, 3 H, d, J = 7 Hz, CH_3CH), 2.43 (3H, s, $ArCH_3$), 3.68 (3H, s, OCH_3), 3.93 ~ 4.38 (1H, CH-OTs), 5.27 (1H, broad, >C=CH), and 7.33 and 7.80 (each 2H, d, J = 8 Hz, ArH).

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