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# SYNTHETIC APPROACH TO GRAYANOTOXINS: A NEW METHOD FOR THE CONSTRUCTION OF THE A-HOMOGRAYANOTOXANE RING SYSTEM

Tetsuji Kametani,* Hiroo Matsumoto, Toshio Honda, and Keiichiro Fukumoto
Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan

Summary: The A-homograyanotoxane ring system was constructed by a thermolysis of benzocyclobutene, followed by a Wagner-Meerwein rearrangement of the resulting kaurane type of compound.

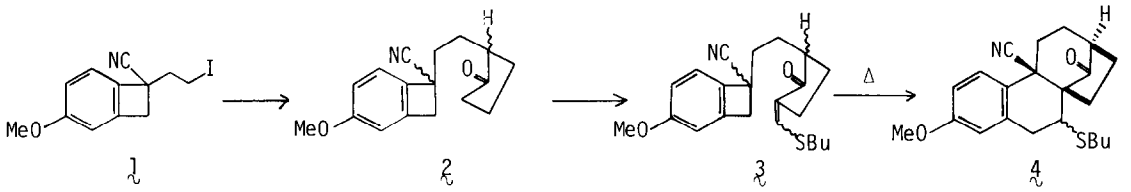
The tetracyclic diterpenoids related to grayanotoxins and asebotoxins are interesting substances because of their structural characteristics and biological activities.[1] The synthesis of grayanotoxin II has recently been achieved utilizing a photochemical rearrangement as a key reaction by Matsumoto.[2] We have also investigated a synthesis of grayanotoxanes[3] and here wish to report a new construction of grayanotoxane skeleton by an alternative approach which involves a thermolysis of a benzocyclobutene and Wagner-Meerwein rearrangement of a kaurane type of compound.

Condensation of the benzocyclobutenylethyl iodide[4] (1) with the pyrrolidine enamine of cyclopentanone gave the 2-substituted cyclopentanone (2),[5] which was converted into the key intermediate (3)[5] [in 64.6 % overall yield from 1; $\nu_{max}^{CHCl_3}$ 2240 and 1695 $cm^{-1}$; $\delta$ ($CDCl_3$) 3.18 and 3.30 (each 1H, d, J = 14 Hz, $ArCH_2$); m/e 369 ($M^+$)] by treatment with ethyl formate in the presence of sodium hydride and then with n-butyl mercaptan and p-toluenesulfonic acid. Heating the olefinic benzocyclobutene (3) in o-dichlorobenzene at 180° for 6 h in a current of nitrogen afforded in 70.7 % yield the tetracyclic compound (4)[5] having a kaurane system [mp 74 - 76°; $\nu_{max}^{CHCl_3}$ 2215 and 1750 $cm^{-1}$; m/e 369 ($M^+$)]. Reduction of 4 with sodium borohydride gave the corresponding alcohol (5)[5] [mp 157 - 160°; $\nu_{max}^{CHCl_3}$ 2215 and 3570 $cm^{-1}$; m/e 371 ($M^+$)], whose acetate (6)[5] [oil; $\nu_{max}^{CHCl_3}$ 2205 and 1725 $cm^{-1}$; m/e 413 ($M^+$)] showed the methyl resonance in acetoxyl group at 1.38 and the methine proton on $C_{14}$ at 4.70 as a broad doublet (J = 5 Hz). The stereochemical assignment of the structure 6 was well supported by these data.

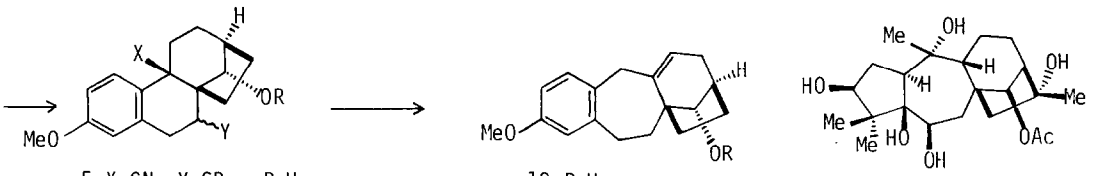
Desulfurization of 5 with Raney nickel, followed by the catalytic hydrogenation on 10 % palladium-carbon furnished the compound 7[5] [mp 170 - 171°; $\nu_{max}^{CHCl_3}$ 3550 and 2205 $cm^{-1}$; m/e 283 ($M^+$)], which was reduced with DIBAL into the corresponding aldehyde (8)[5] [ oil; $\nu_{max}^{CHCl_3}$ 3350 and 1710 $cm^{-1}$; $\delta$ 9.43 (1H, s, CHO); m/e 257 ($M^+$ - CHO)]. Sodium borohydride reduction of this aldehyde afforded the alcohol (9)[5] [oil; $\nu_{max}^{CHCl_3}$ 3560 $cm^{-1}$; $\delta$ ($CDCl_3$) 3.30 and 3.63 (each 1H, d, J = 14 Hz, $-CH_2OH$): m/e 288 ($M^+$)] in 24.2 % yield from 4.

The alcohol (9) thus obtained was treated with tosyl chloride in pyridine at room temperature to give in a quantitative yield a mixture of the rearranged compound (10)[5] and its tosylate (11)[5] in a ratio of 1:1, which was separated by silica gel chromatography. The former [mp 110 - 110°; $\nu_{max}^{CHCl_3}$ 3570 $cm^{-1}$; m/e 270 ($M^+$)] exhibited an olefinic proton at 5.50

as a distorted triplet ($J$ = 3 Hz) and benzylic methylene protons at 3.00 and 3.43 as a doublet ($J$ = 11 Hz). The tosylate (11), which was also obtained by treatment of 10 with tosyl chloride and pyridine, showed a proton on $C_{14}$ at 4.36 as a doublet ($J$ = 5 Hz) in addition to an olefinic proton [$\delta$ 5.35 (1H, distorted t, $J$ = 3 Hz)] and tosyl resonance [$\delta$ 2.45 (3H, s, Me), 7.30 and 7.75 (each 2H, d, $J$ = 8 Hz, ArH)]. These data indicated the products to have the structure 10 and 11, and ruled out other possible rearranged structure. A total synthesis of grayanotoxins along this line is in progress in this laboratory.




1 2 3 4




5 X=CN, Y=SBu, R=H
6 X=CN, Y=SBu, R=Ac
7 X=CN, Y=R=H
8 X=CHO, Y=R=H
9 X=$CH_2OH$, Y=R=H

10 R=H
11 R=Ts

grayanotoxin I

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5. All new compounds exhibited satisfactory spectroscopic and analytical data consistent with the structures.

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