Tetrahedron Letters,Vol.30,No.47,pp 6549-6550,1989   0040-4039/89 $3.00 + .00
Printed in Great Britain   Pergamon Press plc

A TOTAL SYNTHESIS OF MANZAMINE C

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Summary: *Manzamine C (1) was synthesized by the conjunction of 6-(Z)-azacycloundecene (**9**) and 1-substituted β-carboline derivatives (**10** or **13**)*

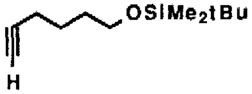
Manzamine C (**1**) is the simplest member of the novel oncolytic marine alkaloids manzamines, recently isolated from Okinawan marine sponges by Higa and his co-workers[1]. Besides being a novel β-carboline alkaloid bearing unprecedented azacycloundecene ring, it still possesses potent antitumor activity. At the outset of our synthetic challenge towards various manzamines, we have initiated the synthesis of **1** and related compounds with the aim of uncovering the factors involved in its activity.

An expedient preparation of the required 6-(Z)-azacycloundecene ring, the lower portion of **1**, was the first task. The silyloxyacetylene (**2**)[2] was alkylated by conventional way with t-$BuMe_2SiOCH_2(CH_2)_2CH_2I$ [2] and hydrogenated in the presence of Lindlar catalyst, furnishing the desired *cis*-diol (**3**, 64.5% from **2**) after desilylation. On the other hand, the *trans*-diol (**4**, 35% from **2**) was also prepared predominantly from **2** via hydrostannation and subsequent alkylation[3] with t-$BuMe_2SiOCH_2(CH_2)_2CH_2I$.

Crucial azacycloundecene ring formation *via* the *cis*-ditosylate (**5**) was conducted under phase-transfer conditions ($TsNH_2$, NaOH, nBu_4NI, benzene, reflux, 4h)[4] to afford the desired product (**6**, 73%, mp 107.5~109 °C; ^{1}H-NMR(δ): 5.37*m*, 3.14*t*, 2.30*m*, 1.67*m*, 1.56*m*) along with small amount of the dimeric product (~2%). The *trans*-ditosylate (**7**) was also successfully converted to **8** (63%, mp 102.5~103.5 °C; ^{1}H-NMR(δ): 5.38*m*, 3.22*t*, 2.08*m*, 1.44*m*, 1.28*m*) by the same conditions. Reaction of **6** with Red-Al gave free 6-(Z)-azacycloundecene (**9**, ~60%).

1-(2-Hydroxyethyl)-β-carboline (**10**), another segment of **1** was elaborated in the following two different ways. Pictet-Spengler reaction of tryptamine and t-$BuMe_2SiOCH_2CH_2CHO$ (CF_3COOH, CH_2Cl_2, rt.) followed by aromatization (Pd/C) and desilylation afforded **10** albeit in poor yield. More conveniently and effectively, tryptamine was treated with $ClCOCH_2COOEt$ to give **11** (98%), which was subjected to Bischlar-Napieralski cyclization ($POCl_3$), furnishing the enaminoester (**12**, 70%). Subsequent aromatization gave the β-carboline ester (**13**, 70%; Pd/C, *p*-cymene) and reduction of which now afforded a substantial amount of **10** (98% ; mp 195~197°C, MeOH), identical with those isolated from *Soulamea fraxinifolia* [5].

Finally, conjunction of each component was carried out in the following two ways. In the first attempt, **10** was converted to its mesylate, which was heated with the amine (**9**) in CH_3CN.



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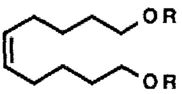

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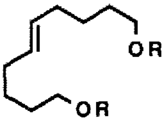
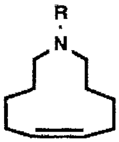
5; R=Ts



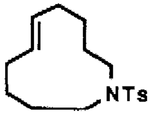
4; R=H

7; R=Ts



6; R=Ts

9; R=H



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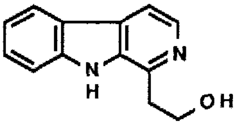

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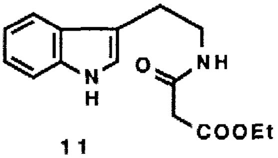

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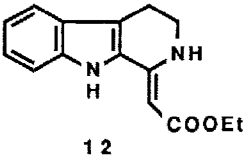

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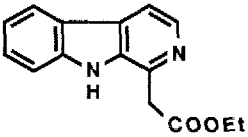

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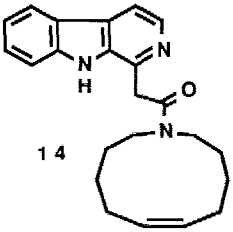

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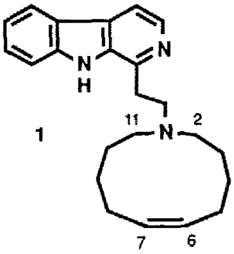

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From the dark reaction mixture, manzamine C (**1**) was isolated only in poor yield (~20%) as non-crystalline oil. To secure the quantity of **1**, we next examined the reaction of the ester (**13**) and the amine (**9**), which gave the amide (**14**) in 52% yield (toluene, reflux). Reduction of **14** with $LiAlH_4$ now afforded enough quantity of **1** (65%, mp 79-83°C, ether-CH_2Cl_2), identical in both ^{1}H-NMR and ^{13}C-NMR with those reported by Higa et al$^{1)}$.

Acknowledgements

We thank Prof. T. Higa, Ryukyu University for sending us spectral data of various manzamines. Finantial support by a Grant-in-Aid for Scientific Research (62470134, 01870092) from the Ministry of Education, Science and Culture, is gratefully acknowledged.

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(Received in Japan 26 August 1989)