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LETTERS

Synthetic Studies on Manzamine A: Construction of the Tetracyclic ABCE Ring Substructure I

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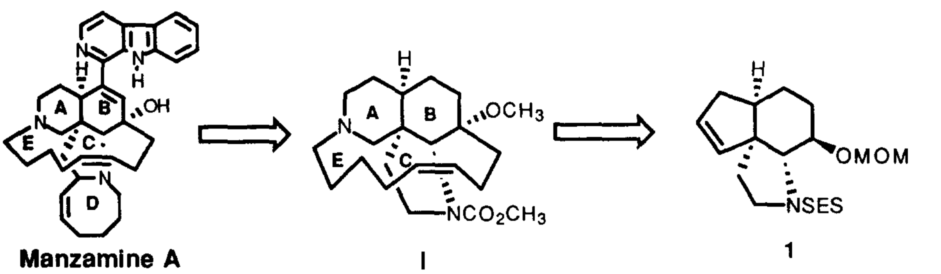
Abstract : The synthesis of the tetracyclic ABCE ring, which bears the crucial 13-membered azacycle, of manzamine A is described.

Manzamine A, isolated from the Okinawa marine sponge *Haliclona sp.* by Higa in 1986[1] and independently by Nakamura in 1987 from the marine sponge *Pellina sp.*,[2] is one member of manzamines which are a new group of complex β-carboline alkaloids that display antitumor and antibacterial activities. Its unique nitrogen heterocycle containing 5-, 6-, 8-, and 13-membered rings as well as the β-carboline moiety is a challenging synthetic target. The majority of published works is focused on the assembly of the pyrrolo [2,3-i] isoquinoline core, tricyclic ABC ring subunit[3] and tetracyclic ABCD ring subunit.[4] To our knowledge, only Pandit's group[5] has reported a synthesis of the tetracyclic ABCE ring bearing the 13-membered azacycle which we consider to be the key factor, for the total synthesis of manzamine A.



Scheme 1.

We have previously published the preparation of the core subunit, tricyclic ABC ring of manzamine A.[3h] In this letter, we disclose a route to the synthesis of an advanced intermediate I containing the 13-membered ring E, completely different from other synthetic methods,[3,4] as shown in Scheme 1.

The double bond of the compound **1**, whose synthesis has been described in our previous work,[3h] was cleaved by ozone in CH_2Cl_2 at -78°C to give an ozonide intermediate which was reduced with $NaBH_4$, followed by treatment with Ac_2O to get diacetate **2**,[6] as shown in Scheme 2. The protective group MOM of **2**

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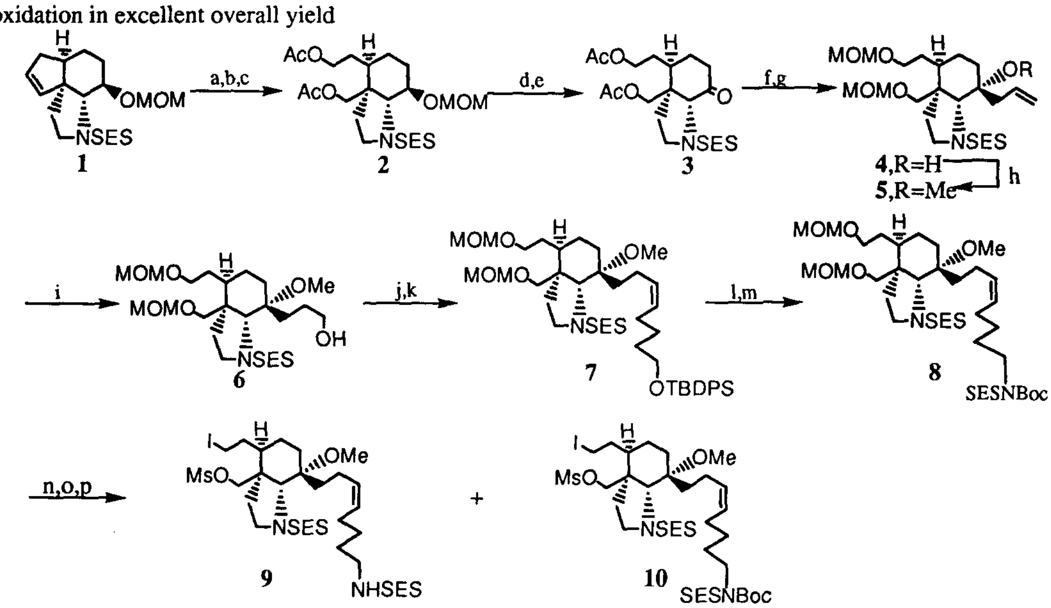
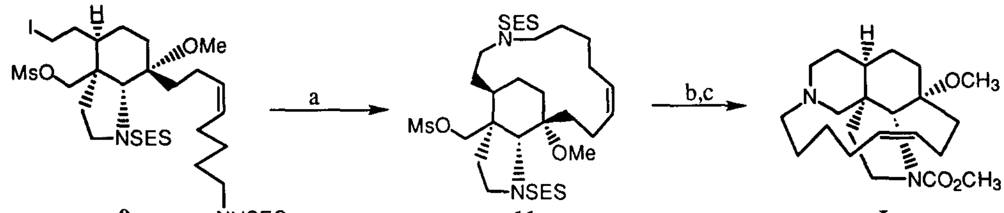
was removed with TFA in CH_2Cl_2 and the resulting alcohol was transformed into ketone **3** by Swern oxidation in excellent overall yield



a) O_3, CH_2Cl_2, -78°C, then Me_2S; b) $NaBH_4$, MeOH; c) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 58% in 3 steps; d) TFA, CH_2Cl_2; e) Swern Oxid., 92% in 2 steps; f) CH_2=$CHCH_2MgCl$, THF, -78°C; g) MOMCl, $^{i}Pr_2NEt$, CH_2Cl_2, 52% in 2 steps; h) NaH, MeI, 15-C-5, THF, rt, 84%; i) BH_3ÅEMe_2S, THF, 0°C; H_2O_2, NaOH, 79%; j) Swern Oxid.; k) Ph_3P=$CH(CH_2)_4OTBDPS$, THF, -78°C~rt, 83% in 2 steps; l) TBAF, THF, rt, 84%; m) SESNHBoc, DEAD, Ph_3P, THF, rt, 98%; n) PTSA, MeOH, 50°C; o) MsCl, Et_3N, CH_2Cl_2, 0°C; p) NaI, Aceone, rt, 63% in 3 steps.

Scheme 2

The nucleophilic addition of allyl magnesium chloride to the carbonyl of the ketone **3** gave the desired top-face adduct. Under the above reaction conditions, the diacetyl groups were also removed and the resulting diol was furnished with MOMCl again to afford olefin **4**,[6] which was recrystallized from a mixed solvent of hexane and chloroform to give colorless crystals (m.p. 92-3°C) whose structure was unambiguously determined by an X-ray crystallographic analysis (Fig.).[7] The tertiary hydroxy group of the olefin **4** was protected with a methyl group to yield methyl ether **5**[6] in good yield. The hydroboration-oxidation of **5** produced primary alcohol **6**[8] which was converted into aldehyde by Swern oxidation, followed by Wittig olefination[9] using phosphorane Ph_3P=$CH(CH_2)_4OTBDPS$[10] to form cis-olefin **7**.[6] The elimination of the protective group TBDPS of **7** was completed by reaction with TBAF in THF and the resulting free primary hydroxy group was converted into another function group containing a nitrogen atom by the Mitsunobu reaction[11] using SESNHBoc to generate carbimide **8**[6] in almost quantitative yield. The compound **8** was hydrolyzed with PTSA in methanol and the resulting products were mesylated with methanesulfonyl chloride in CH_2Cl_2, followed by treatment with NaI in acetone to only give a mixture of monoiodo-substituted major product **9** and a small amount of **10**[6] after overnight.



9 **11** **I**

a) Cs_2CO_3, DMF, 50°C, 82%; b) TBAF, THF; c) $ClCO_2Me$, Et_3N, CH_2Cl_2, 57% in 2 steps.

Scheme 3

The treatment of the iodide **9** with Cs_2CO_3 in DMF at 50°C afforded aza-macrocyclic compound **11**[6,12] (Scheme 3). Both the SES protective groups of the macrocycle **11** were eliminated with TBAF in THF at 55°C and the resulting amino group on the macrocycle spontaneously attacked the mesylate group to close the six-membered ring and another amino group on the five-membered ring was treated with methyl chloroformate in CH_2Cl_2 to offer the tetracyclic ABCE ring substructure **I**.[13]

In summary, the tetracyclic ABCE ring substructure **I** bearing the 13-membered azacycle E, that is the key factor for the total synthesis of manzamine A, was successfully synthesized. Further studies towards the total synthesis of manzamine A are currently under way.

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6. The spectral data for the new compounds cited herein are in accord with the structure assigned.
7. Tables of atomic parameters, bond lengths and bond angles have been deposited with Cambridge Crystallographic Data Centre. Crystal data for 4 ($C_{23}H_{45}NO_7SiS$) are as follows: monoclinic, $P2_1/a$, a=11.626(3), b=8.078(4), c=30.408(4) Å, β=92.00(2)°, V=2854.0(16) Å^3, Z=4, R=0.083 for 2902 reflections.

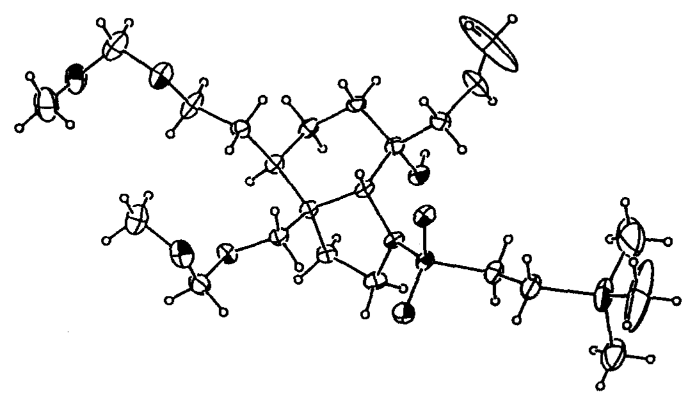

Fig. The ORTEP Drawing of 4.

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10. The synthesis of the phosphorane:

$$HO(CH_2)_5OH \xrightarrow{a,b,c} TBDPSO(CH_2)_5I \xrightarrow{d,e} Ph_3P{=}CH(CH_2)_4OTBDPS$$

a) TBDPSCl, imidazole, DMF; b) TsCl, Et_3N, CH_2Cl_2; c) NaI, acetone; d) Ph_3P, PhH; e) $KN(TMS)_2$, THF, -78°C.

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13. The target tetracyclic compound I was characterized by HRMS, IR, ^{1}H-NMR and ^{13}C-NMR spectra. Selected data for the subunit I: $C_{22}H_{36}N_2O_3$[m/z 376.2724(M$^+$)]; IR(film): 2950, 2860, 1700cm^{-1}; ^{1}H-NMR(270MHz, $CDCl_3$) δ(ppm): 1.24(3H, m), 1.38(1H, m), 1.53(5H, m), 1.81(6H, m), 2.02(3H, m), 2.54(1H, q, J=10.6), 2.73(1H, d, J=14.3), 2.89(2H, br, t, J=13.6), 3.10(3H, s), 3.15(3H, m), 3.31(2H, t, 10.3), 3.72(3H, s), 3.94(1H, s), 5.41(2H, m); ^{13}C-NMR(270Hz, $CDCl_3$) δ(ppm): 22.7, 23.0, 23.2, 24.6, 26.3, 27.0, 29.7, 33.9, 34.0, 39.2, 41.4, 44.2, 47.5, 50.16, 50.22, 52.8, 54.7, 61.1, 78.2, 130.8, 132.9, 156.5.