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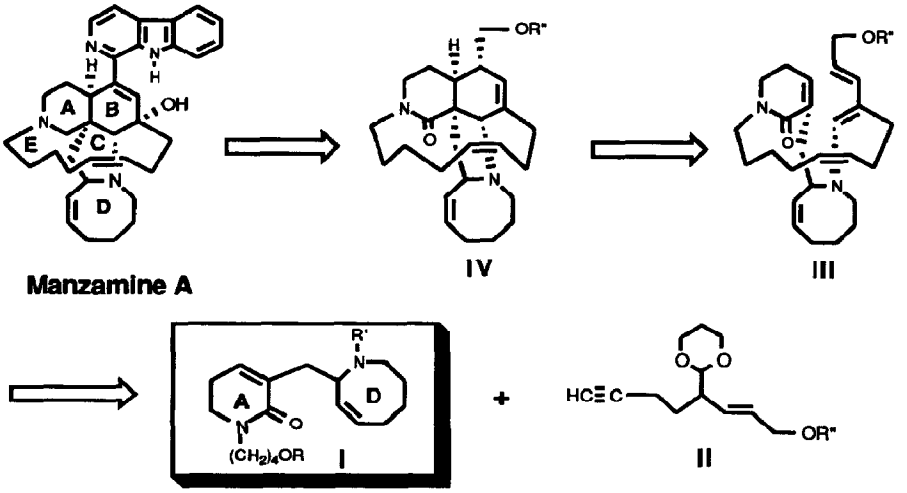
Synthetic Studies on Manzamine A: Construction of a Key Bicyclic AD Ring Subunit I

Shouming Li, Seiji Kosemura, and Shosuke Yamamura*

Department of Chemistry, Faculty of Science and Technology, Keio University, Hiyoshi, Yokohama 223, Japan

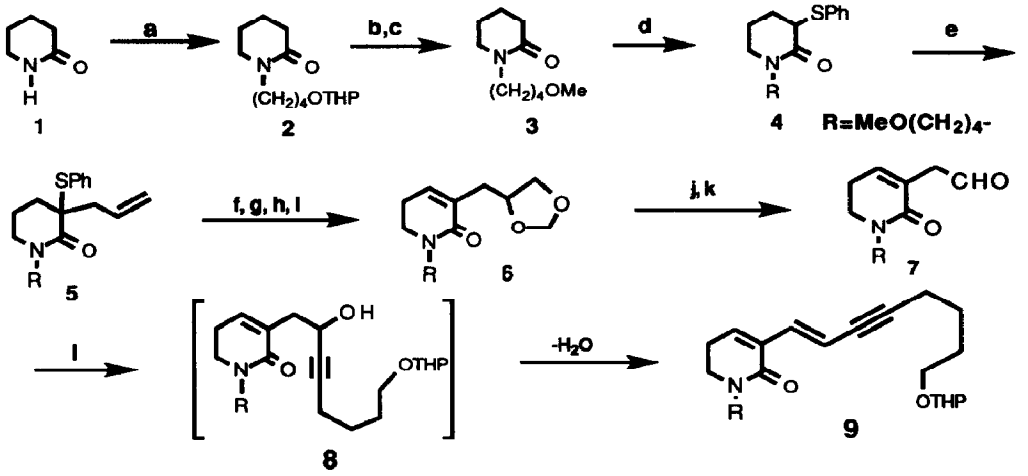
Abstract: A preparation of key intermediate, bicyclic AD ring subunit I was achieved in our new route to the total synthesis of manzamine A.

In 1986, Higa reported the isolation of manzamine A from marine sponges found off the coast of Okinawa, which has a unique structure and exciting biological activity.[1] The complex and unusual structure of manzamine A is really a challenge for total synthesis, and several groups around the world have devoted themselves to develop its construction.[2] At the beginning, the investigations were focused on the production of a simple tricyclic ABC ring subunit which contains all of the five stereogenic carbons,[2a,c,g,3] and there have recently been four laboratories to get the complex ABCD core structure of manzamine A successfully.[4] However, the total synthesis of the more complicated manzamine A has not been reported up to now. Through a detail analysis of the structure of manzamine A, whose biogenesis has been reported,[5] we wish to construct its framework IV firstly with an intramolecular Diels-Alder reaction of intermediate III outlined in Scheme 1 in which the stereochemistry will be controlled, followed by approaching to manzamine A. Bicyclic AD ring subunit I becomes a key precursor to the compound IV through III, then to manzamine A in our strategy, and we describe its synthesis in this paper.



Scheme1.

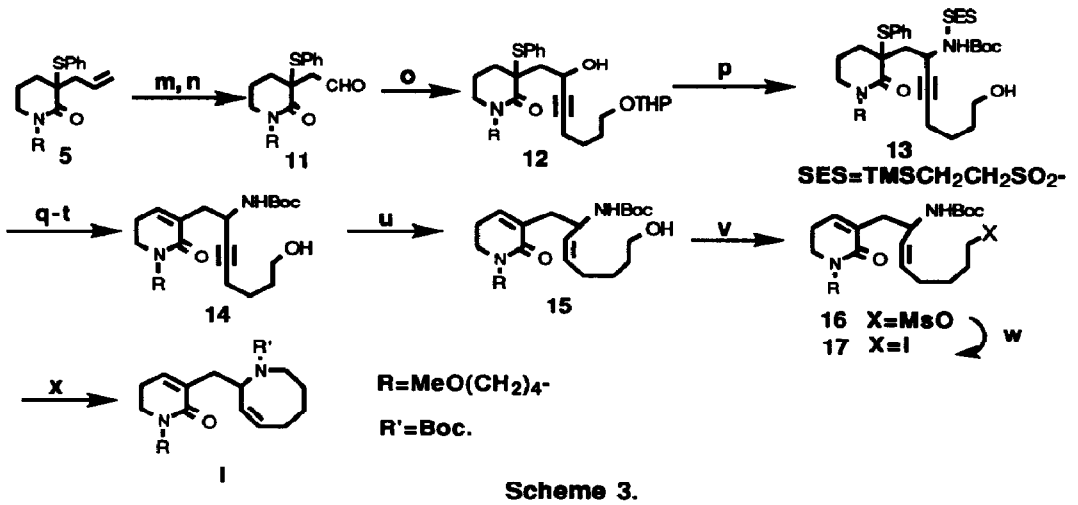
In our pathway approaching to the compound I, δ-valerolactam **1** was chosen as a starting material, and its alkylation with 2-(4-chlorobutoxy)pyran under usual condition proceeded to give a N-substituted lactam **2**[6] in 88% yield[7] (Scheme 2). The THP group was transformed into the more stable methyl ether **3**[6] in excellent overall yield[8] because we would introduce other protective groups in following-up steps and need to remove them selectively. Compound **4**[6] was obtained by sulfidation of lactam **3** treated with LDA and PhSSPh in THF at -75 °C in good yield,[9] followed by allylation of sulfide **4** to give olefin **5**[6] in excellent yield. Subsequent dihydroxylation and protection of the derived diol yielded ketal, desulfinylation of which via oxidation with $NaIO_4$ then heated in benzene[9] formed a desired inner cyclic olefin **6**[6] in 84% overall yield from **5**. However, no positive result was obtained when m-chloroperbenzoic acid was used as an oxidant here. Although aldehyde **7**[6] was obtained easily in excellent yield, following nucleophilic addition to the CO group with $LiC{\equiv}C\text{-}(CH_2)_4\text{-}OTHP$ in THF at -78 °C did not produce an expected alcohol **8**, and only compound **9**[6] was given by spontaneous dehydration of intermediate **8** due to forming a stable large conjugated system.



Scheme 2.

(a) $Cl(CH_2)_4OTHP$, KOH,TBAB, THF, 88%; (b) PPTS, EtOH, 93%; (c) MeI, KOH, DMSO, TBAB, ~100%; (d) LDA,HMPA,$(PhS)_2$,THF, -75°C,79%;(e) $KN(TMS)_2$, $CH_2{=}CHCH_2Br$, THF, -75°C, 95%; (f) OsO_4,NMO; (g) pTsOH, $CH_3C(MeO)_2CH_3$, CH_3COCH_3 ; (h) $NaIO_4$, MeOH, H_2O; (i) PhH, reflux, 84% in 4 steps from **5**;(j) pTsOH,MeOH;(k)$NaIO_4$,THF,H_2O,87% in 2 steps from 6;(l)$CH{\equiv}C(CH)_4OTHP$,BuLi,THF,-78°C.

From conjugated energy, we thought that the dehydration of **8** would not occur spontaneously if large conjugated system like **9** was not constructed. Just as we considered, aldehyde **11**,[6] which was prepared by oxidation cleavage of double bond from **5**, was successfully converted into desired alcohol **12**[6] by nucleophilic addition with $LiC{\equiv}C\text{-}(CH_2)4\text{-}OTHP$ in THF at -75 °C in 55% overall yield from **5** (Scheme 3). Here, the aldehyde is not stable and its desulfidation takes place easily to give a conjugated aldehyde. It is impossible to purify **11** by using silica gel TLC plates or column. Treatment of **12** with imide, SESNHBOC which was readily obtained under mild condition in excellent yield,[10] under typical Mitsunobu system afforded an amine derivative **13**[6] in 88% yield (a mixture of isomers).[11]



Scheme 3.

(m) OsO_4, NMO; (n) $NaIO_4$, THF, H_2O; (o) BuLi,$CH{\equiv}C(CH_2)_4OTHP$, THF, -75°C, 55% in 3 steps from **5** (p) Ph_3P, DEAD, SESNHBoc, THF, 88%; (q) $^nBu_4NF$, THF; (r) pTsOH, MeOH; (s) $NaIO_4$, MeOH, H_2O; (t) PhH, reflux, 54% in 4 steps from 13; (u) 5% $Pd/BaSO_4$, quinoline,H_2, 91%; (v) MsCl, Et_3N, CH_2Cl_2, 93%; (w) NaI, CH_3COCH_3, > 77%; (x) $KOBu^t$, THF, -60°C, 85%.

Removal of both protective groups SES and THP was easily carried out under mild conditions, followed by conversion of sulfide to endo-olefin **14** in 54% overall yield from **13**. With Lindlar's catalyst, **14** was reduced to give **15** in 91% yield. Here, we wish to construct compound I by intramolecular nucleophilic substitution. When we treated methyl sulfonic acid ester **16**,[6] prepared by mesylation of **15** in 93% yield, with $KOBu^t$ and BuLi in THF from -78 °C to room temperature respectively, no desired compound I was formed. However, we could successfully synthesize key precursor, bicyclic AD ring subunit to manzamine A by treatment of iodide **17**[6] with $KOBu^t$ in THF at -60 °C in 85% yield. The structure of intermediate I was well confirmed by IR, NMR (^1H and ^{13}C including NOE experiments) and HRMS.[13]

In summary, the bicyclic AD ring subunit of manzamine A was successfully synthesized, and further studies directed towards the total synthesis of manzamine A are currently underway based on Scheme 1.

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13. Selected data for I: $C_{23}H_{38}N_2O_4$ [m/z 406.2788 (M^+)]; IR (film) 3050, 1690, 1670, 1625,1480 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.30 (1H, m), 1.43 (9H, s), 1.61 (4H, complex), 1.74 (1H, br), 1.99 (3H, br), 2.25 (4H, complex), 2.64 (1H, dd, J = 5.3, 4.4 Hz), 3.02 (1H, br), 3.22 (1H, br), 3.32 (3H, s), 3.29 (3H, m), 3.36 (2H, t, J = 5.8 Hz), 3.59 (1H, m), 4.95 (1H, s), 5.29 (1H, d, J = 11.7 Hz), 5.63 (1H, m), 6.21 (1H, br); ^{13}C-NMR (100 MHz, $CDCl_3$ at 50 °C) δ: 24.90, 24.90, 24.51, 25.77, 27.00, 28.59, 34.35-35.41 (br)*, 43.23, 45.38, 46.78, 54.67 (br)*, 58.39, 72.36, 79.00, 129.99 (br), 130.75 (br)*, 132.74 (br), 132.81-135.15 (br)*, 155.48, 164.81.
    * These signals varied with temperature, indicating that two stereoisomers are in an equilibrium.

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