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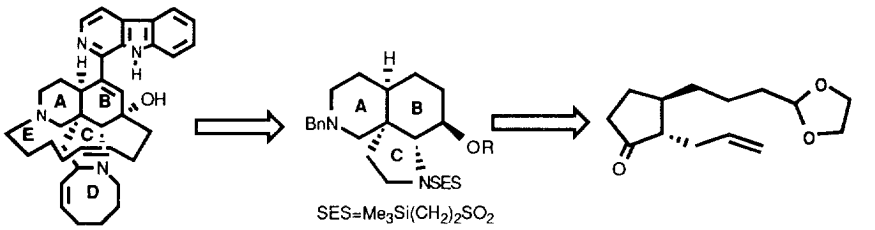
Synthetic Studies on Manzamine A: Construction of the Tricyclic ABC Ring Subunit I

Shouming Li, Shigeru Ohba, Seiji Kosemura, and Shosuke Yamamura*

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

Abstract: A model synthesis of the tricyclic ABC ring subunit **I** of manzamine A is described.

Manzamine A is a structurally complex polycyclic alkaloid with cytotoxic, antileukemic and antibacterial activities[1] and its unique structure and significant biological activity have stimulated many synthetic studies, culminating in the syntheses of several fragments and subunits. From a view of the papers published, there are two main strategies, Diels-Alder reaction[2a-k] and asymmetric synthesis,[2l-q] involved in the approach to the total synthsis of manzamine A. Generally, the tricyclic ABC subunit of manzamine A was chosen as the first synthetic target because it consists of all of five stereogenic carbons. In a previous paper,[3] we tried the Diels-Alder reaction route, and herein we wish to report a synthesis of the tricyclic ABC ring subunit I approaching to manzamine A as outlined in Scheme 1.

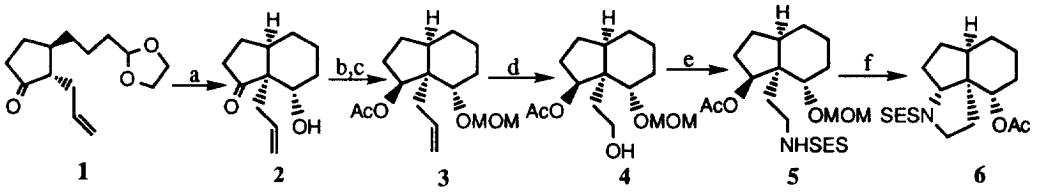


Manzamine A **Subunit I** **1**

Scheme 1.

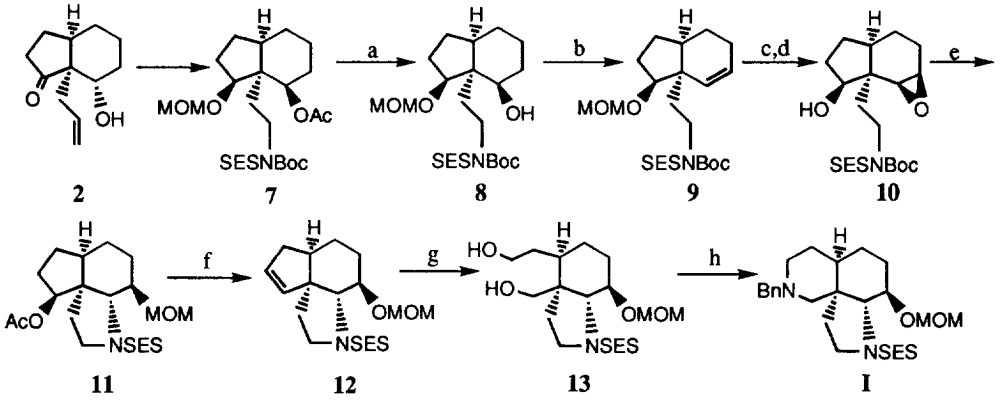
In the synthesis of the subunit **I** (Scheme 2), compound **1** was chosen as a starting material,[4] which was synthesized with the conjugated addition of a Grignard reagent, derived from the reaction of 2-(3-chloropropyl)-1,3-dioxolane with magnesium, to cyclopentenone followed by allylation. Treatment of **1** with hydrochloric acid[5] induced sequential acetal hydrolysis and intramolecular aldol condensation, thus giving the bicyclic annulation product **2** in 78% yield (α isomer was the major product).[6] The hydroxyl group on **2** was first protected with MOMCl, then the carbonyl was reduced with $NaBH_4$ to give an alcohol (only the β isomer formed in this case), which was acetylated to produce acetate **3**.[6] Subsequent dihydroxylation, oxidative cleavage and reduction of **3** afforded alcohol **4**[6] in almost quantitive overall yield. After the treatment of **4** with SESNHBoc under Mitsunobu conditions,[7] the protective group Boc of the resulting product was removed with $MgCl_2$ in reflux CH_3CN[8] to give amide **5**.[6] In the Mitsunobu step, the yield was

not satisfactory due to steric hindrance. When we attempted to eliminate the protective group MOM with TFA in CH_2Cl_2, an unexpected result was obtained. The reaction probably underwent a six-membered cyclic intermediate (Fig. 1 in ref. 9) to form tricyclic compound **6**,[6] which was recrystallized from a mixed solvent of hexane and chloroform to give colourless crystals(m.p. 103-5°C) whose structure was unambiguously determined by an X-ray crystallographic analysis (Fig. 2).[9]



(a) 2N HCl, CH_3COCH_3, 78%; (b) MOMCl, $^iPr_2NEt$, CH_2Cl_2,75%; (c) $NaBH_4$, MeOH; Ac_2O Et_3N, CH_2Cl_2, ~100% in 2 steps; (d) OsO_4, NMO, CH_3COCH_3:H_2O=10:1; $NaIO_4$, THF; $NaBH_4$, MeOH, 99% in 3 steps;'(e) SESNHBoc, Ph_3P, DEAD, THF, 52%; $MgCl_2$, CH_3CN reflux, 86%; (f) TFA, CH_2Cl_2, 81%.

Scheme 2.



(a) 2N LiOH(aq.), MeOH, 94%; Boc_2, Et_3N, CH_2Cl_2, 96%; (b) MsCl, Et_3N, CH_2Cl_2; DBU, PhH, 60°C, 85%; (c) p-TsOH, MeOH, 90%; (d) $VO(acac)_2$, TBHP, PhH, reflux, 69%; (e) Ac_2O Et_3N, DMAP, CH_2Cl_2; $MgCl_2$, CH_3CN, reflux; MOMCl, $^iPr_2NEt$, CH_2Cl_2, 69% in 3 steps (f) 2N LiOH(aq.), MeOH; MsCl, Et_3N, CH_2Cl_2; DBU, PhH, reflux, 57% in 3 steps; (g) O_3, CH_2Cl_2, -78°C and then Me_2S; $NaBH_4$, MeOH, 67% in 2 steps; (h) MsCl, Et_3N, CH_2Cl_2; $BnNH_2$, KF, and DMF, ~60°C, 87% in 2 steps.

Scheme 3.

Although we tried many conditions to deprotect the MOM group of **5**, the results were unsatisfactory, so we made some changes in our strategy (Scheme 3). Bicyclic compound **7**[6] was derived from **2** in several steps[10] which were similar to the reactions in Scheme 2. Herein the α-hydroxyl group of **2** was converted to its β isomer because of poor yields in some steps when the α-isomer was used. In 2N LiOH aqueous solution, both groups Ac and Boc on **7** were eliminated, and the resulting amide was protected with Boc_2O again to create alcohol **8**.[6] Olefin **9**[6] was prepared by successive mesylation and de-mesylation of **8**[11] in 85% yield. The methoxymethyl ether **9** was deprotected and the resulting homoallylic alcohol was epoxidized to produce **10**[6] in 69% yield.[12,2m] For the epoxide **10**, sequential acetylation of the hydroxyl group, cleavage of the Boc group to close the five-membered ring spontaneously, and protection of the afforded alcohol as a methoxymethyl ether gave the tricyclic compound **11**[6] in 69% yield in 3 steps from **10**. Ester **11** was hydrolyzed and the resulting alcohol was converted to olefin **12**[6] in 57% overall yield,[11] with which we tried to cleave the double bond several times using different methods, but no positive result was obtained. Finally, we found that O_3 was a proper cleaving reagent only in dry CH_2Cl_2 at -78 °C. After the oxidation of **12** with ozone followed by addition of Me_2S, the resulting dialdehyde was reduced with $NaBH_4$ to afford diol **13**[6] in 67% yield. After its mesylation, conversion of diol **13** to the subunit **I**[13] was accomplished in 87% yield using $BnNH_2$ and KF in DMF at ~60 °C.[14]

In summary, the tricyclic ABC ring subunit **I** was successfully synthesized. It is our hope that the functional groups on compoud **13** will prove suitable for introduction of the 13-membered ring azacycle E which is a key factor in the total synthesis of manzamine A.

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9. Tables of atomic parameters, bond lengths and bond angles have been deposited with The Cambridge Crystallographic Data Centre. The Crystal data for **6** ($C_{18}H_{33}NO_4SiS$) are as follows: monoclinic, P2/c; a = 10.134 (2), b = 20.269 (1), c = 10.457 (1) Å; β = 97.57 (1)°, V = 2129.2 (6) Å^3; R = 0.055 for 2637 reflections.

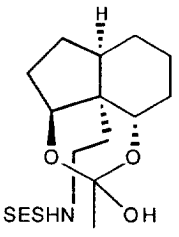


Fig. 1.

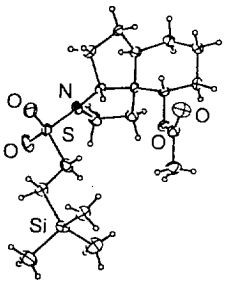
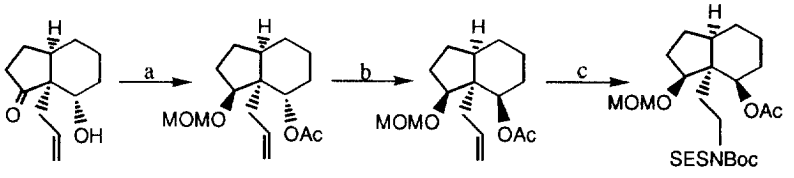


Fig. 2. The ORTEP Drawing of 6.

10. The conversion of **2** to **7**:



2 **7**

(a) Ac_2O, Et_3N, DMAP, CH_2Cl_2; $NaBH_4$, MeOH; MOMCl, $^iPr_2NEt$, CH_2Cl_2;
(b) 2NLiOH(aq.), MeOH; Swern Oxid.; $NaBH_4$, MeOH; Ac_2O, Et_3N, DMAP, CH_2Cl_2;
(c) OsO_4, NMO, $NaIO_4$, THF; $NaBH_4$, MeOH; SESNHBoc, Ph_3P,DEAD, THF.

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13. The target tricyclic compound **I** was characterized by HRMS, IR, and ^{1}H NMR spectra. Selected data for the subunit **I**: $C_{25}H_{42}N_2O_4SiS$ [m/z 494.2439(M^+)]; IR(film): 3060, 2950, 1640, 1490 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ: 0.03 (9H, s), 1.05 (2H, m), 1.57 (9H, m), 1.85 (2H, m), 2.14 (2H, m), 2.93 (3H, m), 3.32 (2H, m), 3.37 (3H, s), 3.70 (3H, m), 4.71 (2H, s), 7.29 (5H, m).
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