Pergamon

Tetrahedron Letters 39 (1998) 2597–2600

TETRAHEDRON LETTERS

Synthetic Studies on Manzamine A: An Efficient Synthesis of the Bicyclic Compound Leading to the Formation of the Tetracyclic ABCE Ring Subunit I (I)

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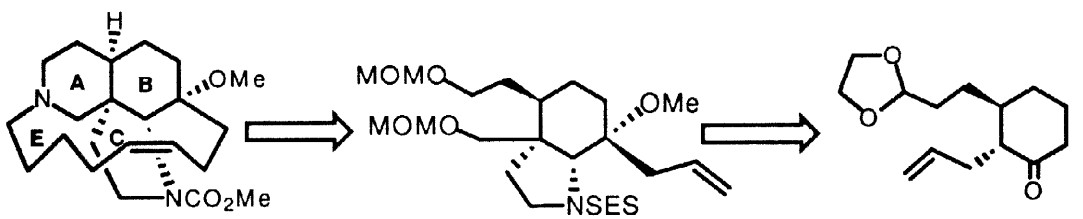
Received 26 December 1997; revised 29 January 1998; accepted 30 January 1998

Abstract : An efficient synthesis of the bicyclic key intermediate leading to the formation of the tetracyclic ABCE ring of manzamine A has been carried out.

Since the discovery and structure elucidation of manzamine A in 1986,[1] many groups around world[2] have been promoted to undertake its synthesis in view of its unique structure and significantly biological activities. We have previously published a route to the synthesis of the tetracyclic ABCE ring subunit I bearing a 13-membered azacycle of manzamine A.[3] In this letter, we wish to report an efficient synthesis of the desired bicyclic compound **II**, a synthetic precursor of the tetracyclic ABCE ring subunit **I**, with a more easily prepared starting material **1**, as shown in Scheme 1.



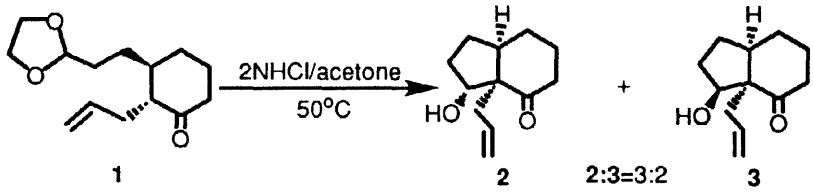
I **II** **1**

Scheme 1

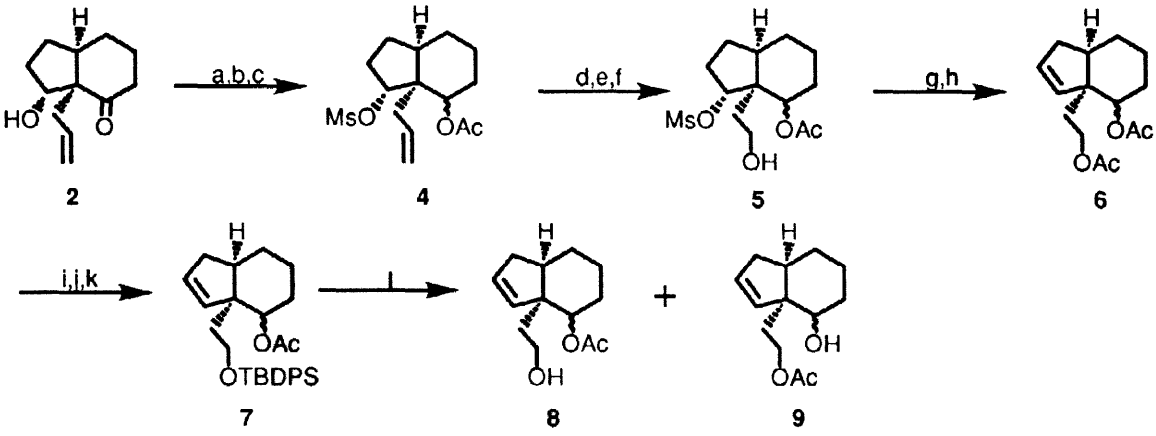
The starting material **1** was synthesized with the conjugated addition of a Grignard reagent,[5] derived from the reaction of 2-(2-bromoethyl)-1,3-dioxolane with magnesium, to cyclohexenone, followed by allylation in high yield. Treatment of the starting material **1** with 2N HCl in acetone[6] at 50°C produced a mixture of diastereoisomers **2**[5] and **3**[5] in a ca. 3:2 ratio, as shown in Scheme 2, which could be separated by column chromatography.

We decided to attempt the synthesis of the tetracyclic ABCE ring **I** from the α-isomer at first, as

0040-4039/98/$19.00
PII: S0040-4039(98)00278-0



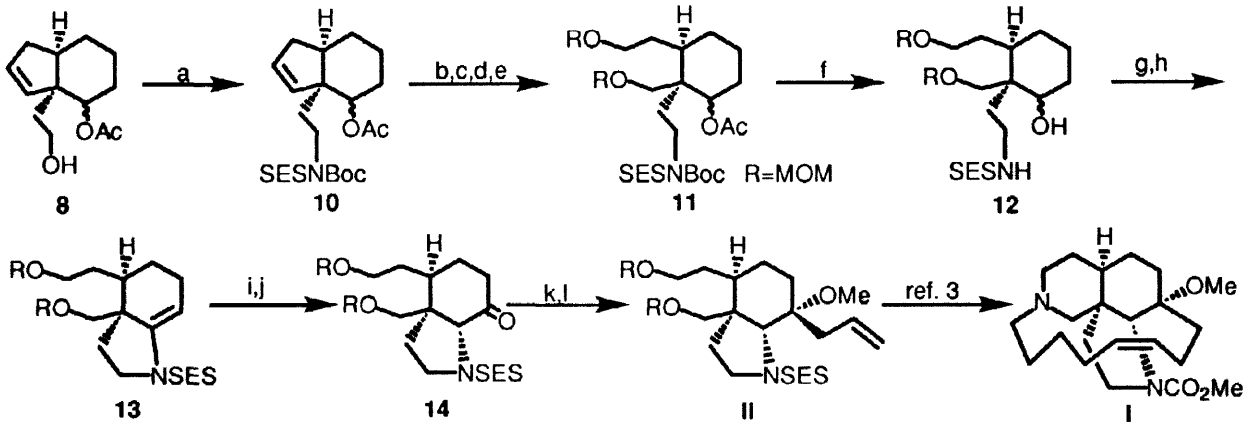
Scheme 2



a) MsCl, Et_3N, CH_2Cl_2, 0°C; b) $NaBH_4$, MeOH, -10°C; c) Ac_2O, DMAP, Et_3N, CH_2Cl_2, 60% in 3 steps; d) OsO_4, NMO; e) $NaIO_4$, THF, ice-bath; f) $NaBH_4$, MeOH, -40°C, 67% in 3 steps; g) Ac_2O, DMAP, Et_3N, CH_2Cl_2, ice-bath; h) DBU, Tol., refux, 60% in 2 steps; i) 2NLiOH, MeOH, rt; j) TBDPSCl, imidazole, DMF, rt; k) Ac_2O, DMAP, Et_3N, CH_2Cl_2, rt; l) TBAF, THF, rt.

Scheme 3

outlined in Scheme 3. The alcohol **2** was mesylated with methanesulfonyl chloride in dichloromethane and the resulting product was reduced with sodium borohydride in methanol, followed by acetylation of the produced alcohol with acetic anhydride in dichloromethane to give compound **4**[4] in more than 60% overall yield. Subsequent dihydroxylation, oxidative cleavage and reduction of **4** afforded an alcohol **5**[4] in 67% yield. The hydroxy group of **5** was acetylated with acetic anhydride, followed by treatment with DBU[7] in benzene to form olefin **6**[4] in 61% yield. At first, we wished to selectively remove the primary acetyl group of **6**, however, a number of trials failed to produce satisfactory results. Both the acetyl groups of **6** were cleaved with 0.5N LiOH in methanol, followed by selective protection of the resulting primary hydroxy group with TBDPSCl and the secondary hydroxy group with acetic anhydride to generate compound **7**.[4] When we deprotected the TBDPS group of **7** with TBAF in THF at room temperature, a mixture of primary alcohol **8**[4] and secondary alcohol **9**[4] was obtained in 41 and 33% yields from **6** respectively. The alcohol **9** was probably formed by a part of the acetyl group on the secondary hydroxy group shifting onto the resulting primary hydroxy group under the reaction due to the crowded space.



a) SESNHBoc, Ph_3P, DEAD, THF, rt; b) OsO_4, NMO; c) $NaIO_4$, THF; d) $NaBH_4$, MeOH; e) MOMCl, $^iPr_2NEt$, CH_2Cl_2, 65% in 5 steps; f) 2N LiOH, MeOH; g) PCC, NaOAc, CH_2Cl_2; h) CSA, $CHCl_3$; i) OsO_4, NMO; j) CSA, $CHCl_3$, 36% in 4 steps; k) CH_2=$CHCH_2MgCl$, THF, -78°C; l) NaH, MeI, 15-C-5 ether, THF, rt, 79% in 2 steps.

Scheme 4

The treatment of the primary alcohol **8** with SESNHBoc under the Mitsunobu condition[8] generated carbimide **10**.[4] Subsequent dihydroxylation, oxidative cleavage and reduction of the double bond on the carbimide **10**, followed by protection of the resulting diol with MOMCl yielded compound **11**[4] in 65% overall yield from **8**. Both the protective groups Boc and Ac of **11** were removed with 2N LiOH in methanol to offer compound **12**[4] in 78% yield. The alcohol **12** was converted into ketone with PCC in dichloromethane, followed by acid-catalyzed dehydration which afforded ene-sulfamide **13**.[4] Dihydroxylation of this intermediate using OsO_4, followed by acid-promoted dehydration and rearrangement of the resulting diol gave ketone **14**[4,2b] in 36% overall yield from **12**. The nucleophilic addition of allyl magnesium chloride to the carbonyl of the ketone **14**,[3] followed by protection of the resulting tertiary hydroxy group with methyl iodide yielded the desired compound **II**.[4] The synthesis of the tetracyclic ABCE ring subunit **I** could be completed according to the reference 3 from **II**.

In summary, a shorter approach to the synthesis of the desired bicyclic compound II which had been successfully converted into the tetracyclic ABCE ring subunit **I**, bearing the 13-membered azacycle, of manzamine A was developed with the starting material prepared easily. Further studies towards the total synthesis of manzamine A are currently under way.

Acknowledgment: This research was financially supported by a Grant-in-Aid from the Ministry of Education, Science and Culture which is gratefully acknowledged. We are also indebted to the Fujisawa

Foundation for a fellowship to S.L. and would like to thank Dr. S. Kosemura for his taking the 400MHz NMR and MS spectra.

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