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Synthesis of the Tetracyclic ABCE Ring Subunit I, Bearing the 13-Membered Azacycle, of Manzamine A#

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Abstract: The tetracyclic ABCE ring, which bears the crucial 13-membered azacycle, of manzamine A has been synthesized through the corresponding bicyclic BC ring subunit as a promising synthetic intermediate.

Introduction

Since the discovery and structure elucidation of manzamine A in 1986 [1], it has attracted the interest of many groups worldwide to undertake its total synthesis in view of its complex structure and significant biological activities. The unique nitrogen heterocyclic structure of manzamine A contains 5-, 6-, 8-, and 13-membered rings as well as the β-carboline moiety. The majority of published works is focused on the assembly of the pyrrolo[2, 3 -i]isoquinoline core structure, the tricyclic ABC ring subunit [2-9], and the tetracyclic ABCD ring subunit [10-13] of manzamine A. To our knowledge, only Pandit's group has reported a synthesis of the tetracyclic ABCE ring bearing the 13-membered azacycle, which must be a key factor for the total synthesis of manzamine A, *via* the metathesis cyclization using the ruthenium catalyst [14].

Results and Discussion

We have previously published the preparation of the tricyclic ABC ring subunit of manzamine A [9], and in this paper, we will further disclose the synthesis of an advanced intermediate, the tetracyclic ABCE ring subunit **I** of manzamine A by means of a newly developed synthetic method, which is completely different from others, as outlined in Scheme 1.

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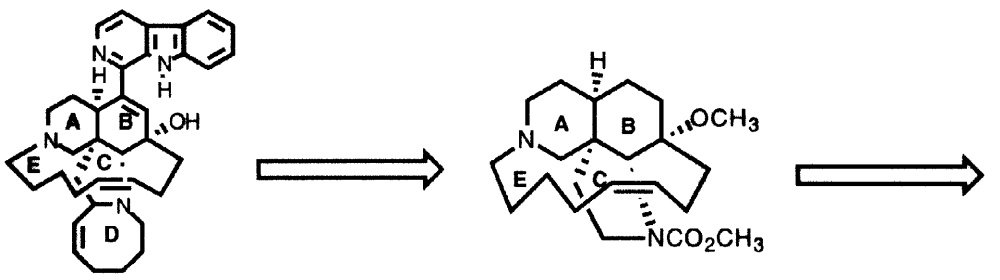
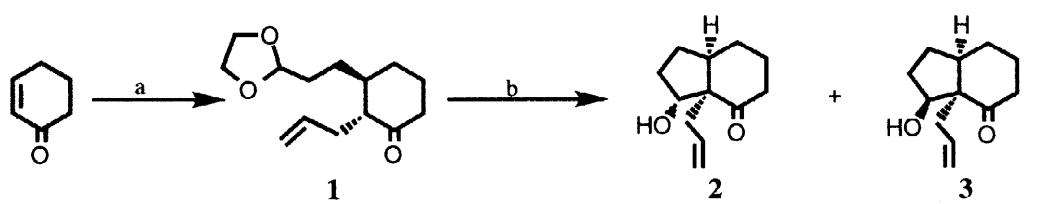
Here, we designed another efficient synthetic route to the synthesis of the tetracyclic ABCE ring subunit I from a starting material, cyclohexenone, because the original synthetic route to the construction of the tricyclic ABC ring subunit [9] took longer, and the epoxidation of the homoallylic alcohol using a catalytic amount of the transition metal vanadium was not easily controlled.



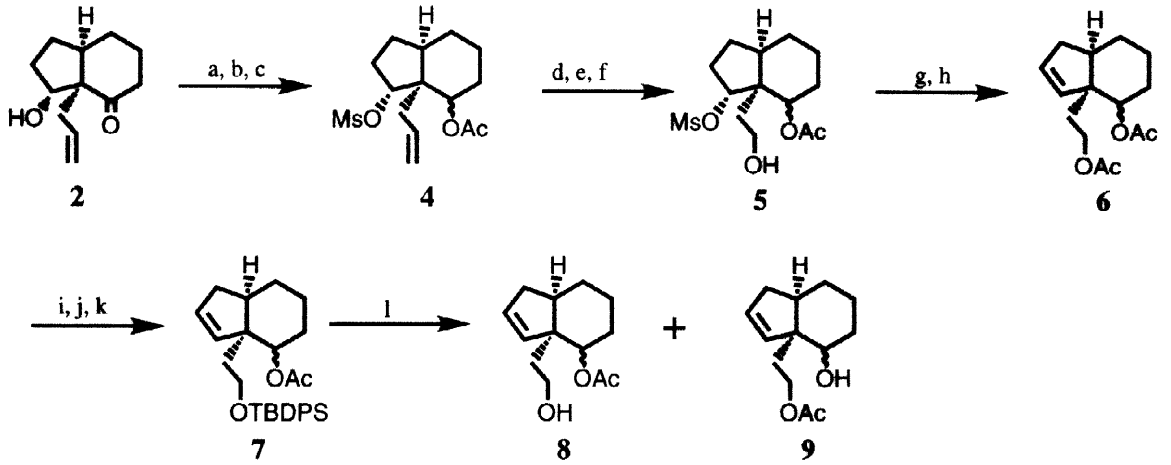
Scheme 1

The *trans*-adduct **1** was stereoselectively prepared by the conjugated nucleophilic addition of a Grignard reagent [15], derived from the reaction of 2-(2-bromoethyl)-1,3-dioxolane with magnesium, to cyclohexenone, followed by allylation of the resulting enolate with allyl bromide, as shown in Scheme 2. Treatment of **1** with 2N aqueous HCl induced sequential acetal hydrolysis and intramolecular aldol condensation, thus giving the bicyclic annulation product, a mixture of diastereoisomers **2** and **3** in a ca. 3:2 ratio [16, 17]. The isomers **2** and **3** could be simply separated by column chromatography.



a) 2-(2-bromoethyl)-1,3-dioxolane, Mg, THF, rt; $CuBr{\cdot}Me_2S$, Me_2S, -75 °C HMPA, Allyl bromide, -75 °C~ rt; b) 2N HCl, acetone, 50 °C; 61% overall yield (**2**:**3**=3:2).

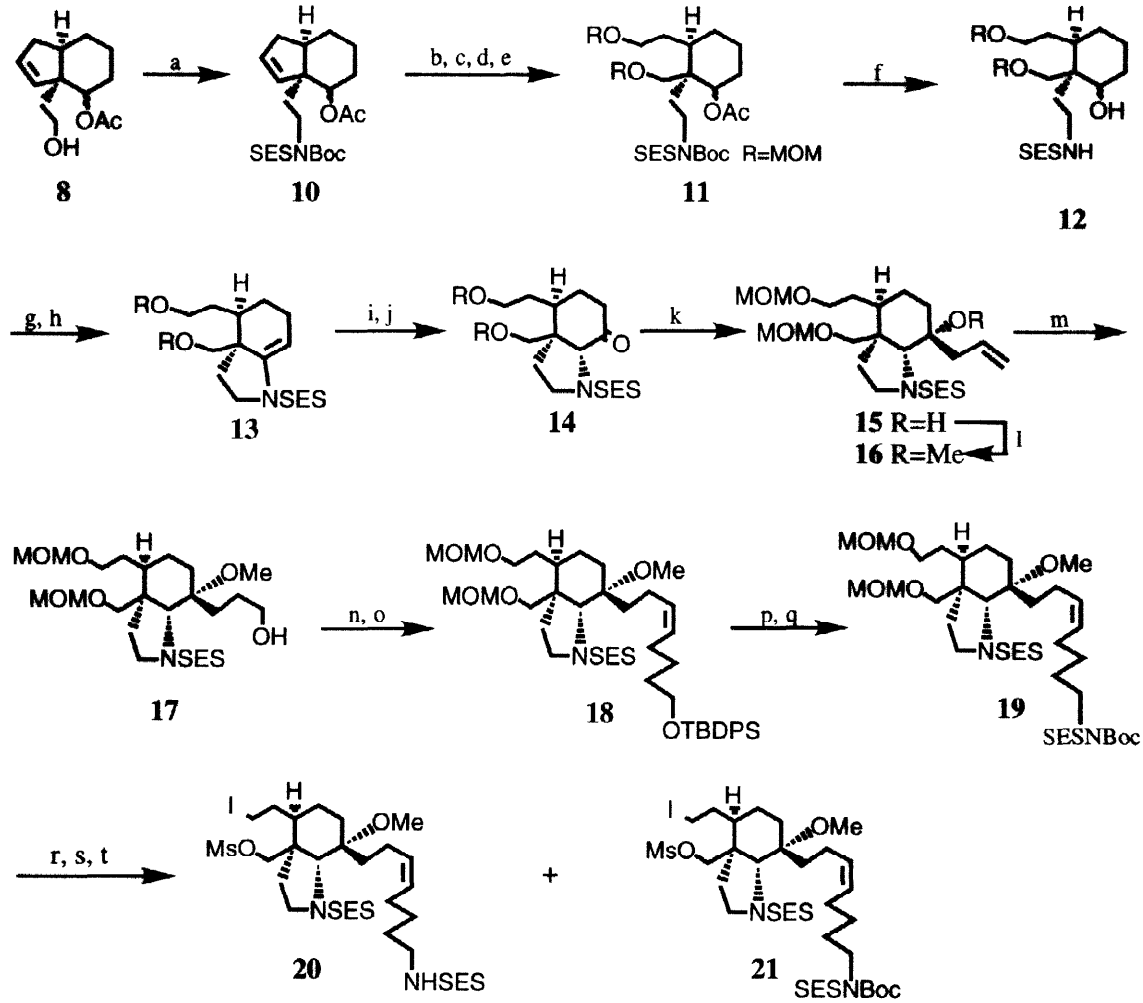
Scheme 2



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; f) $NaBH_4$, MeOH, -40 °C, 67% in 3 steps; g) Ac_2O, DMAP, Et_3N, CH_2Cl_2, ice-bath; h) DBU, Toluene., reflux, 60% in 2 steps; i) 0.5N LiOH, MeOH, rt; j) TBDPSCl, imidazole, DMF, rt; k) Ac_2O, DMAP, Et_3N, CH_2Cl_2, rt; l) TBAF, THF, rt.

Scheme 3

At first, the α-isomer **2** was chosen as the starting material to synthesize the tetracyclic ABCE ring subunit **I**. The alcohol **2** was mesylated with methanesulfonyl chloride in dichloromethane and the resulting product was reduced with sodium borohydride in methanol, followed by acetylation with acetic anhydride in dichloromethane to give compound **4** in more than 60% overall yield. Subsequent dihydroxylation, oxidative cleavage and reduction of **4** afforded alcohol **5**. The compound **5** was stable and the hydroxy group did not attack the mesylate group to close a 5-membered ring since both the hydroxy and mesylate groups were at the same side. However, the major product was a ring-closure compound when we attempted to remove the mesylate group with DBU to generate olefin. Therefore, we first attempted to protect the hydroxy group of **5** and then eliminate the mesylate group. The results were not satisfactory after the hydroxy group was treated with TBDPSCl and dihydropyran, respectively. After many trials were carried out, we found that the best result was obtained when the hydroxy group was only protected with an acetyl group. The hydroxy group of **5** was acetylated with acetic anhydride, followed by treatment with DBU [18] to give olefin **6** in 60% overall yield. With **6** in hand, we tried to cleave the primary acetyl group selectively; unfortunately, the results proved that there was low selectivity between the primary and secondary acetyl groups. Both acetyl groups were eliminated with 0.5N aqueous 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**. When the group TBDPS was deprotected with TBAF in THF, a mixture of primary alcohol **8** and secondary alcohol **9** was produced in 41 and 33% overall yield from **6**, respectively. The alcohol **9** was probably formed by the acetyl group on the secondary hydroxy group at the α-position shifting to the resulting primary hydroxy group under the reaction conditions due to crowded space.



a) SESNHBoc, Ph3P, 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-Crown-5- ether, THF, rt, 79% in 2 steps; m) BH_3•Me_2S, THF, 0 °C; H_2O_2, NaOH, 79%; n) Swern Oxid.; o) Ph_3P=$CH(CH_2)_4OTBDPS$, THF, -78 °C ~ rt, 83% in 2 steps; p) TBAF, THF, rt, 84%; q) SESNHBoc, DEAD, Ph_3P, THF, rt, 98%; r) PTSA, MeOH, 50 °C s) MsCl, Et_3N, CH_2Cl_2, 0 °C; t) NaI, CH_3COCH_3, rt, 63% in 3 steps.

Scheme 4

Conversion of the alcohol **8** into carbamate **10** was carried out under the Mitsunobu conditions using SESNHBoc [19, 20] (Scheme 4). Here, the endo-double bond could be cleaved to open the 5-membered carbon ring by sequential treatment with OsO_4 and $NaIO_4$. The resulting dialdehyde was reduced with sodium borohydride, followed by protection with MOMCl to afford **11** in 65% overall yield from **8**. After both protective groups Ac and Boc of **11** were eliminated with 2N aqueous LiOH in methanol, we wished to transform **12** into a ketone by oxidation and then close five-membered azacycle by acid-promoted

dehydration other than by the metal catalytic epoxidation of the homoallyl alcohol as we described previously [9]. The alcohol **12** was oxidized with PCC in dichloromethane, followed by treatment with CSA in chloroform under reflux to give the desired cyclic ene-sulfonamide **13**. Both protective MOM groups were unaffected under these conditions. Without purification, the ene-sulfonamide **13** was dihydroxylated with OsO_4, followed by acid-catalyzed dehydration and rearrangement of the resulting diol, to provide ketone **14** [2] in 36% overall yield from **12**. Nucleophilic addition of allylmagnesium chloride to the carbonyl of **14** stereoselectively gave a top-face adduct [14] **15** which could be recrystallized from a mixed solvent of hexane and chloroform to give colorless crystals whose structure was unambiguously determined by X-ray crystallographic analysis (Fig. 1).

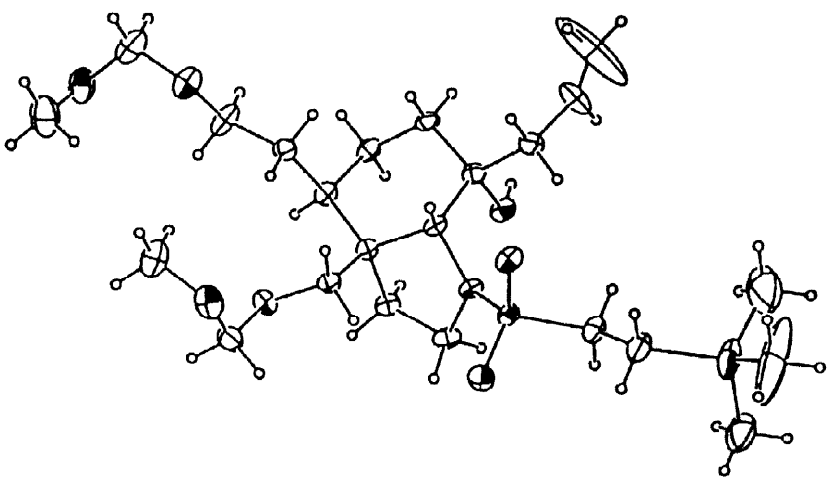
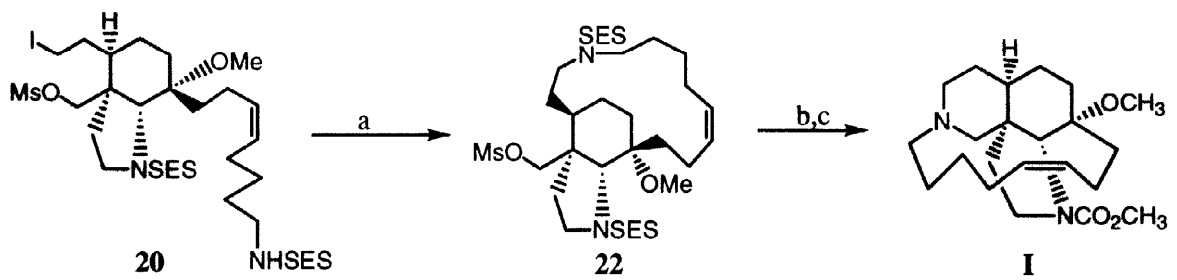


Fig. 1 The ORTEP Drawing of 15

With **15** in hand, we attempted to protect the tertiary hydroxy group with a protective group which could be easily eliminated, but the results were not satisfactory because of high steric hindrance. Fortunately, protection could be accomplished with methyl iodide by using sodium hydride as a base in the presence of 15-crown-5 ether to afford methyl ether **16**. Hydroboration of **16** was carried out by treatment with borane-dimethylsulfide [21], followed by oxidation with H_2O_2 to produce primary alcohol **17** in good yield. After **17** was oxidized under the Swern conditions, the Wittig olefination of the resulting aldehyde with triphenylphosphorane $Ph_3P{=}CH(CH_2)_4OTBDPS$ [22], gave the desired *cis*-olefin **18** in very good yield. Conversion of **18** into **19** was completed by removal of the protective group TBDPS with TBAF in dry THF, followed by treatment of the resulting alcohol with SESNHBoc under the Mitsunobu conditions [19, 20]. Herein, we wished to find a deprotective reagent to effectively remove the protective groups Boc and both MOM of **19**. After some trials were carried out, we found *p*-toluenesulfonic acid to be a good reagent. Although the protective group Boc was also cleaved under the reaction conditions, longer time was needed to eliminate the protective group Boc and the product seemed to decompose slowly. Thus, it was important to control the reaction time so that the best result could be obtained. Without purification after the deprotection

of **19** with *p*-toluenesulfonic acid in methanol, the resulting products were mesylated with methanesulfonyl chloride in dichloromethane, followed by treatment with sodium iodide in acetone to give a mixture of monoiodo-substituted **20** and a small amount of **21**. Initially, we anticipated that on eliminating the protective group SES, the resulting amino group would simultaneously attack both functional groups iodo and mesylate to close the 6-membered A ring and 13-membered E ring. When the sulfonamide **20** was treated with TBAF in THF or CsF in DMF [23], unfortunately, no desired ring-closure product was yielded although the protective group SES was cleaved. Therefore, we decided to make the ring-closure step by step, first to close the 15-membered ring *via* nucleophilic substitution of a nitrogen anion and then to eliminate both protective groups SES with TBAF. The resulting amino group on the macrocycle would spontaneously attack the mesylate group to close the 6-membered ring (Scheme 5).



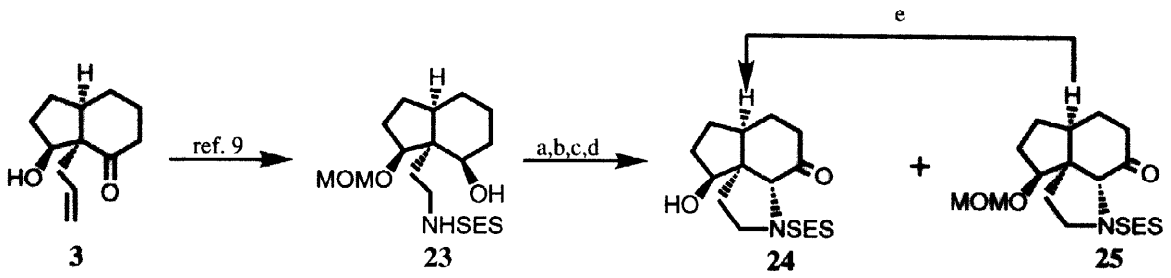
a) Cs_2CO_3, DMF, 50 °C, 82%; b) TBAF, THF; c) $ClCO_2Me$, Et_3N, CH_2Cl_2, 57% in 2 steps.

Scheme 5

When the sulfonamide **20** was treated with some bases, such as KOBu^t, NaH and $KN(TMS)_2$, the expected product was not formed. Finally, we found that the desired macrocyclic compound **22** could be obtained in good yield by treatment with Cs_2CO_3 in DMF [24]. Both protective SES groups of **22** were cleaved with TBAF [23] and the resulting amino group on the macrocycle spontaneously replaced the mesylate group to close the 6-membered ring A, thus also giving the 13-membered ring E simultaneously. Another amino group on the 5-membered C ring was treated with methyl chloroformate to afford the desired tetracyclic ABCE ring subunit **I**, bearing the 13-membered azacycle E.

In the above, we discussed the synthesis of the tetracyclic ABCE ring subunit **I** of manzamine A from the α-isomer **2**. Now we wish to convert the β-isomer **3** into the α-isomer **2** so that both the isomers can be used to synthesize the subunit **I**. Many attempts were carried out, but unfortunately we could not find a method to effectively complete the transformation. Thus, we developed another way for the construction of the compound **15** from the β-isomer **3**, leading to the synthesis of subunit **I**, as outlined in Scheme 6.

Conversion of **3** into **23** was easily carried out in high yield according to the synthetic method we developed [9] (Scheme 3). The alcohol **23** was also oxidized with PCC in dichloromethane, followed by the acid-promoted dehydration with CSA to give the cyclic ene-sulfonamide intermediate. Epoxidation of the resulting ene-sulfonamide with magnesium monoperoxyperphthalate in methanol, followed by the acid-



a) PCC, CH_2Cl_2, NaOAc, rt; b) CSA, $CHCl_3$; c) MMPP, MeOH, rt;d) CSA, $CHCl_3$; e) PTSA, MeOH, 85%.

Scheme 6

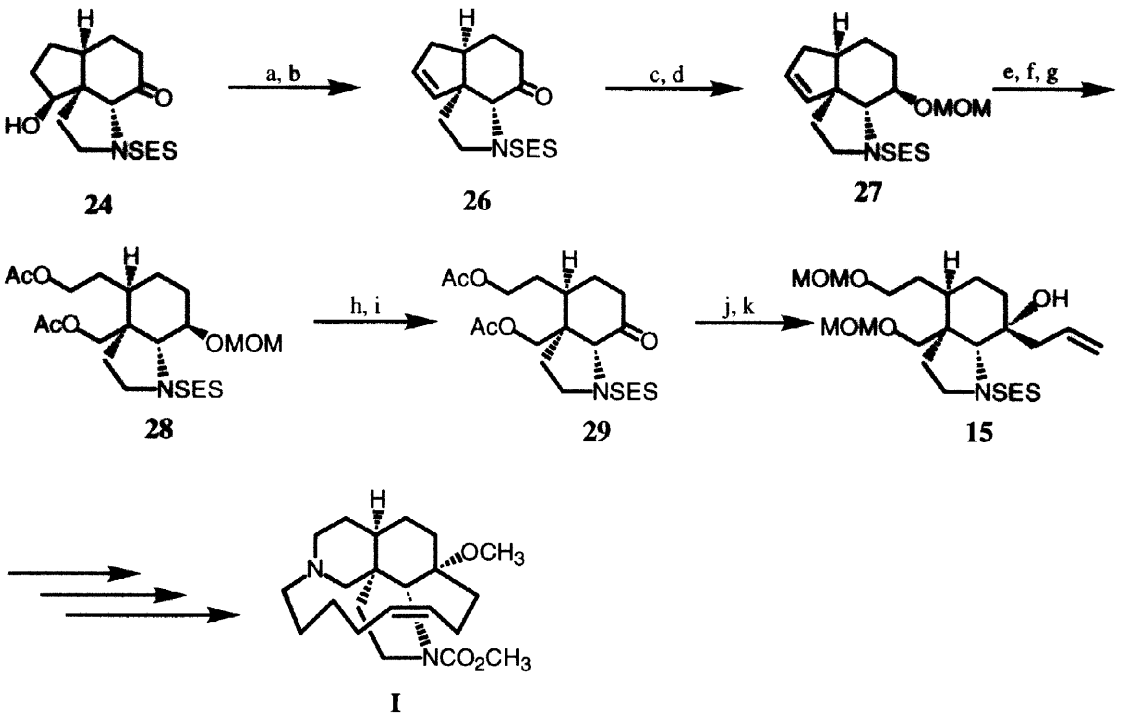
catalyzed rearrangement with CSA [7], afforded ketones **24** and **25**. The ketone **25** was transformed into **24** by deprotection of the MOM group with *p*-toluenesulfonic acid in methanol in 85% yield.

Conversion of **24** into **26** was carried out by mesylation with methanesulfonyl chloride, followed by elimination with DBU [18] (Scheme 7). **26** was then reduced with sodium borohydride, followed by protection with MOMCl to provide compound **27**. The double bond of **27** was cleaved with ozone to give an ozonide intermediate which was reduced with sodium borohydride, followed by acetylation with acetic anhydride to give diacetate **28** which was deprotected with TFA in dichloromethane, followed by Swern oxidation of the resulting alcohol to afford ketone **29** in excellent overall yield. Although the nucleophilic addition of allyl magnesium chloride to the carbonyl of the ketone **29** stereoselectively afforded the desired top-face adduct [14], both acetate groups were also removed simultaneously under the reaction conditions. Reprotection of the resulting diol with MOMCl generated the compound **15**. The synthesis of the tetracyclic ABCE ring subunit **I** can proceed from the compound **15** as we just described in Scheme 5.

In conclusion, we have designed a new route towards the total synthesis of manzamine A and successfully synthesized the tetracyclic ABCE ring, bearing the 13-membered azacycle, which is a key factor for the total synthesis of manzamine A, from the α- and β-isomers (**2** and **3**) readily derived from cyclohexenone as the starting material.

Experimental Section

General. All melting points are uncorrected. Infrared (IR) spectra were recorded on a Jasco A-202 spectrophotometer and are recorded in cm^{-1}. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on JNM-EX 270 and JNM-α 400 instruments. They were also used for recording carbon nuclear magnetic resonance (^{13}C-NMR) spectra. Chemical shifts are given in ppm downfield from tetramethylsilane (TMS). Coupling constants are given in Hz. ^{1}H-NMR shift correlation spectroscopy (COSY), double resonance and ^{1}H-^{13}C correlation experiments were occasionally used for signal assignments. HRMS measurements were performed on a Hitachi M-80 instrument. THF was distilled from sodium metal and dichloromethane was distilled from phosphorous pentoxide. Benzene was dried over sodium metal.



a) MsCl, Et_3N, CH_2Cl_2; b) DBU, PhH; c) $NaBH_4$, MeOH; d) MOMCl, $^iPr_2NEt$, CH_2Cl_2; e) O_3, CH_2Cl_2, -78 °C, then Me_2S; f) $NaBH_4$, MeOH; g) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 58% in 3 steps; h) TFA, CH_2Cl_2; i) Swern Oxid., 92% in 2 steps; j) CH_2=$CHCH_2MgCl$, THF, -78 °C; k) MOMCl, $^iPr_2NEt$, CH_2Cl_2, 52% in 2 steps.

Scheme 7

Reactions requiring an inert atmosphere were run under argon. Column chromatography was performed using 70-230 mesh silica gel.

(1*R*,9*R*)-9-Hydroxy-1-prop-2-enylbicyclo[4.3.0]nonan-2-one (2) and (9*S*,1*R*)-9-Hydroxy-1-prop-2-enylbicyclo[4.3.0]nonan-2-one (3). To a stirred mixture of 6.15 g (0.26 mol) of magnesium in 350 ml of dry THF under argon was slowly added a solution of 30 ml (0.26 mol) of 2-(2-bromoethyl)-1,3-dioxolane in 100 ml of dry THF to keep the reaction temperature at lower than 30.°C. And then, the resulting mixture was stirred at room temperature overnight and then cooled to -75 °C. A solution of 11.7 g of copper(I) bromide-dimethyl sulfide in 100 ml of dry dimethyl sulfide was added dropwise over 2 hours and stirred for an additional 2 hours at -75 °C. A solution of 12.4 ml (0.13 mol) of hexenone in 50 ml of dry THF was added dropwise over 1 hour, and the resulting mixture was stirred for an additional 5 hours at -75 °C. Next, 100 ml of dry HMPA and 53 ml of dry allyl bromide were added, respectively, at -75 °C and the resulting mixture was gradually warmed to room temperature under stirring overnight. The reaction was quenched with saturated aqueous ammonium chloride and the mixture was extracted with ethyl acetate. The combined extracts were washed with brine, dried over sodium sulfate and concentrated *in vacuo*. The residue was

subjected to silica gel column chromatography, eluting with hexane-ethyl acetate (3:2), to give the desired conjugated adduct **1**.

To a solution of the above adduct **1** in 250 ml of acetone was added 35 ml of 2N aqueous HCl and the resulting mixture was stirred at 50 °C overnight. The reaction mixture was cooled to room temperature and extracted with ethyl acetate. The combined extracts were washed with saturated aqueous sodium bicarbonate and brine, dried over sodium sulfate, concentrated *in vacuo* and chromatographed, eluting with hexane-ethyl acetate (3:2), to afford 15.3 g of the alcohol **2** and **3** (**2:3**=3:2) in 61% overall yield as a light yellow oil. The spectral data for the α isomer **2**: IR(film) 3450, 3055, 2930, 1690 cm^{-1}; ^{1}H-NMR(270 MHz, $CDCl_3$), δ 5.62(1H, m), 5.03(2H, m), 4.50(1H, t, J=5.6), 2.67(1H, dd, J=6.93, 4.19), 2.40(2H,m), 2.30(2H, m), 1.84(5H, m), 1.72(2H, m), 1.35(1H, m); ^{13}C-NMR(270 MHz, $CDCl_3$): δ 22.3, 26.6, 29.7, 31.0, 36.4, 39.4, 43.4, 42.0, 75.4, 117.6, 134.4, 216.0; HRMS(M^+) calcd. for $C_{12}H_{18}O_2$ 194.1305, found 194.1269. The spectral data for the β-isomer **3**: ^{1}H-NMR(270 MHz, $CDCl_3$), δ 5.83(1H, m), 5.05(2H, m), 3.89(1H, t, J=6.93), 2.40(3H, m), 2.20(2H, m), 1.92(4H, m), 1.61(4H, m); ^{13}C-NMR(270 MHz, $CDCl_3$): δ 220.0, 133.3, 118.2, 80.8, 59.9, 42.6, 40.6, 40.5, 31.1, 26.3, 26.2, 21.7.

(1*S*,9*R*)-9-(Methylsulfonyloxy)-1-prop-2-enylbicyclo[4.3.0]non-2-yl acetate (4). To a solution of 20.0 g (0.10 mol) of the alcohol **2** and 57.4 ml of triethylamine in 200 ml of dichloromethane was added another solution of 16 ml (0.21 mol) of methanesulfonyl chloride in 50 ml of dichloromethane dropwise at -30 °C. And then, the resulting mixture was stirred under argon in an ice-bath for 5 hours. The reaction was quenched with saturated aqueous sodium bicarbonate and the aqueous phase was extracted twice with ethyl acetate and the combined organics were washed with brine, dried over sodium sulfate and concentrated *in vacuo* to give crude mesylate.

To a solution of the above mesylate in 80 ml of methanol was added sodium borohydride in batches at -20 °C ~ -10 °C until the starting material was totally exhausted. Saturated aqueous ammonium chloride was then added and the resulting mixture was extracted three times with ethyl acetate. The combined extracts were washed with brine, dried over sodium sulfate and concentrated *in vacuo* to leave crude alcohol which is a mixture of α and β isomers.

A solution of the above alcohol, 43 ml of triethylamine and 2.0 g of 4-dimethylaminopyridine in 200 ml of dichloromethane was cooled to 0 °C and another solution of 20 ml of acetic anhydride in 50 ml of dichloromethane was added dropwise at 0 °C. And then, the resulting mixture was stirred in an ice bath overnight. The reaction was quenched with saturated aqueous ammonium chloride and the mixture was extracted three times with ethyl acetate. The combined extracts were washed with brine, dried over sodium sulfate, concentrated *in vacuo* and chromatographed, eluting with hexane-ethyl acetate (1:1), to give 19.5 g of the acetate **4** in 60% overall yield as a light yellow oil. IR(film) 3050, 2930, 1740, 1640 cm^{-1}; HRMS(M^+) calcd. for $C_{15}H_{24}O_5S$ 316.1293, found 316.1342.

(1*S*,9*R*)-1-(2-Hydroxyethyl)-9-(methylsulfonyloxy)bicyclo[4.3.0]non-2-yl acetate (5). To a solution of 19.5 g (61.7 mmol) of **4** in 80 ml of a mixed solvent (acetone:water=10:1) in an ice bath were added 14.0 g of 4-methylmorpholine *N*-oxide and 3 ml of osmium tetroxide in *t*-butanol (0.2 M), respectively, and the resulting mixture was stirred in the ice bath until the starting material was exhausted completely. Sodium

hydrogen sulfite was added and the mixture was stirred for an additional hour. Water was added and the mixture was extracted three times with ethyl acetate. The combined extracts were washed successively with 5% aqueous acetic acid, saturated sodium bicarbonate and brine, dried over sodium sulfate and concentrated *in vacuo* to give crude diol.

A solution of the above diol in 350 ml of THF was cooled in an ice bath and another solution of 26.4 g of sodium periodate in 150 ml of water was added dropwise below -5 °C The resulting mixture was stirred in the ice bath for 1 hour and ethyl acetate was added. The aqueous phase was extracted twice with ethyl acetate and the combined organics were washed with brine, dried over sodium sulfate and concentrated *in vacuo* to leave crude aldehyde.

To the above aldehyde was added 100 ml of methanol and the resulting mixture was cooled to -40 °C. Sodium borohydride was then added in batches under stirring until the aldehyde was reduced completely. The reaction was quenched with saturated aqueous ammonium chloride, and the mixture was warmed to room temperature and extracted three times with ethyl acetate. The combined extracts were washed with brine, dried over sodium sulfate and concentrated *in vacuo*. The residue was subjected to silica gel column chromatography, eluting with hexane-ethyl acetate-methanol (5:10:1), to give 13.2 g of the corresponding alcohol in 67% overall yield as a pale yellow oil.

To a solution of 13.0 g (40.6 mmol) of the above alcohol **5**, 18.3 ml of triethylamine and 1.0 g of 4-dimethylaminopyridine in 80 ml of dry dichloromethane in an ice bath was dropwise added another solution of 8.5 ml of acetic anhydride in 20 ml of dichloromethane, and the resulting mixture was stirred in the ice bath overnight. The reaction was quenched with saturated aqueous sodium bicarbonate and the aqueous layer was extracted twice with ethyl acetate. The combined organics were washed with brine, dried over sodium sulfate and concentrated *in vacuo* to give the corresponding diacetate. IR(film) 2930, 1740 cm^{-1}; HRMS(M^+) calcd. for $C_{16}H_{26}O_7S$ 362.1370, found 362.1396.

2-((1*S*)-2-Acetyloxybicyclo[4.3.0]non-8-enyl)ethyl acetate (6). A mixture of **5** and 18.1 ml of 1,8-azabicyclo[5.4.0]undec-7-ene in 90 ml of dry toluene was stirred under argon under reflux for 24 hours and then cooled to room temperature. The solvent was evaporated under reduced pressure and the residue was chromatographed, eluting with hexane-ethyl acetate (1:1), to afford 6.6 g of **6** in 60 % overall yield as a light yellow oil. IR(film) 2930, 1740 cm^{-1}; HRMS(M^+) calcd. for $C_{15}H_{22}O_4$ 266.1478, found 266.1516.

(3a*S*)-3a-(2-Hydroxyethyl)-4,5,6,7,3a,7a-hexahydroinden-4-yl acetate (8) and 2-((3a*S*)-2-Hydroxybicyclo[4.3.0]nonyl)ethyl acetate (9). To a solution of 3.56 g (13.4 mmol) of **6** in 80 ml of methanol was added 53.5 ml of 0.5N aqueous lithium hydroxide and the resulting mixture was stirred at room temperature for 4 hours. The mixture was extracted three times with ethyl acetate. The combined extracts were washed with brine, dried over sodium sulfate and concentrated *in vacuo* to leave the corresponding diol.

To a solution of the above diol in 30 ml of dry dimethylformamide was added 1.44 g of imidazole and 3.5 ml of *t*-butyldiphenylsilyl chloride respectively, and the resulting mixture was stirred at room temperature overnight. Ethyl acetate was added and the mixture was washed with water and brine, dried over sodium sulfate and concentrated *in vacuo* to provide the corresponding silylate.

To a solution of the above silylate in 60 ml of dry dichloromethane in an ice bath was added 6.7 ml of dry triethylamine, 0.59 g of 4-dimethylaminopyridine and 3.2 ml of acetic anhydride, respectively, and the resulting mixture was stirred in the ice bath for 6 hours. Saturated aqueous ammonium chloride was added and the mixture was extracted with ethyl acetate. The combined extracts were washed with brine, dried over sodium sulfate, concentrated *in vacuo* and chromatographed, eluting with hexane-ethyl acetate (4:1), to afford 6.47 g of **7** as a colorless oil.

To a solution of 6.47 g of **7** in 60 ml of dry THF under argon was added 21 ml of tetrabutylammonium fluoride in THF (1.0 M) and the resulting mixture was stirred at room temperature for 2 hours. The solvent was evaporated under reduced pressure and the residue was subjected to silica gel column chromatography, eluting with hexane-ethyl acetate (1:2), to give 1.23 g of **8** and 1.0 g of **9** in 41 and 33% overall yield from **6**. IR(film) 3300,2930, 1740 cm^{-1}; HRMS(M^+) calcd. for $C_{13}H_{20}O_3$ 224.1467, found 224.1411.

(3a*S*)-3a-{2-[(tert-Butoxy)-N-(2-trimethylsilylethylsulfonyl)carbonylamino]ethyl}-4,5,6,7,3a,7a-hexahydroinden-4-yl acetate (10). A mixture of 1.9 g (8.48 mmol) of **8**, 3.5 g of *t*-butyl 2-(trimethylsilyl)ethanesulfonylcarbamate (SESNHBoc) and 8.0 g of triphenylphosphine in 45 ml of dry THF under argon was cooled to 0 °C and 1.2 ml of diethyl azodicarboxylate was added and the resulting mixture was stirred in an ice bath for half an hour and at room temperature overnight. The solvent was removed under reduced pressure and the residue was chromatographed, eluting with hexane-ethyl acetate (4:1), to give 4.4 g of **10**. IR(film) 2930, 1730 cm^{-1}; HRMS(M^+) calcd. for $C_{21}H_{37}NO_4SiS$ 427.2185, found 427.2210.

(2*R*)-2-{2-[(tert-Butoxy)-N-(2-trimethylsilylethylsulfonyl)carbonylamino]ethyl}-3-[2-(methoxymethoxy)ethyl]-2-[(methoxymethoxy)methyl]cyclohexyl acetate (11). To a solution of 4.4 g of **10** in 35 ml of a mixed solvent (acetone:water=10:1) in an ice bath were added 4.5 g of 4-methylmorpholine *N*-oxide and 0.5 ml of osmium tetroxide in *t*-buthanol (0.2 M) respectively, and the resulting mixture was stirred in the ice bath for 3 days. Sodium hydrogen sulfite was added and stirred for an additional hour. The solid was dissolved with water and the aqueous phase was extracted with ethyl acetate. The combined extracts were washed successively with 5% aqueous acetic acid, saturated aqueous sodium bicarbonate and brine, dried over sodium sulfate and concentrated *in vacuo* to afford the crude corresponding diol.

A solution of the above diol in 40 ml of THF was cooled to 0 °C and another solution of 3.9 g of sodium periodate in 24 ml of water was added. The resulting mixture was stirred in an ice bath for 1 hour and water was added to dissolve the solid produced in the reaction. The aqueous phase was extracted with ethyl acetate and the combined organics were washed with brine, dried over sodium sulfate and concentrated *in vacuo* to leave the crude corresponding dialdehyde.

To a solution of the above dialdehyde in 15 ml of methanol was added sodium borohydride in batches at -40 °C ~ 0 °C until the starting material was reduced completely. Saturated aqueous ammonium chloride was added to decompose excess amount of sodium borohydride and the mixture was extracted with ethyl acetate. The combined extracts were washed with brine, dried over sodium sulfate and concentrated *in vacuo* to give the crude corresponding diol.

To a solution of the above diol in 65 ml of dry dichloromethane were added 4.4 ml of diisopropylethylamine and 2.0 ml of chloromethyl methyl ether, respectively, and the resulting mixture was

stirred at room temperature for 10 hours. Ethyl acetate was added and the mixture was washed with brine, dried over sodium sulfate and concentrated *in vacuo*. The residue was subjected to chromatography, eluting with hexane-ethyl acetate (1:1), to give 3.4 g of **11** in 65% overall yield. IR(film) 2930,1730 cm^{-1}; HRMS(M^+-AcOH) calcd. for $C_{25}H_{49}NO_8SiS$ 551.2865, found 551.2945.

N-(2-{(1*R*)-2-Hydroxy-6-[2-(methoxymethoxy)ethyl]-1-[(methoxymethoxy)methyl]c yclohexyl} -ethyl)(tert-butoxy)-N-(ethylsulfonyl)carboxamide (12). A solution of 3.4 g (5.5 mmol) of **11** in 25 ml of methanol was cooled to 0 °C and 16 ml of 2N aqueous lithium hydroxide was added. The resulting mixture was stirred at room temperature for 24 hours and extracted three times with ethyl acetate. The combined extracts were washed with brine, dried over sodium sulfate and concentrated *in vacuo*. The residue was subjected to silica gel column chromatography, eluting with hexane-ethyl acetate-methanol (5:10:1), to provide 1.8 g of **12** in 68% yield. IR(film) 3550, 3300, 2930 cm^{-1}; HRMS(M^+) calcd. for $C_{20}H_{43}NO_7SiS$ 469.2503, found 469.2526.

(6*S*)-9-Aza-9-(2-trimethylsilylethylsulfonyl)-5-[2-(methoxymethoxy)ethyl]-6-[(methoxymethoxy)-methyl]bicyclo[4.3.0]nonan-2-one (14). To a solution of 0.23 g of pyridinium chlorochromate and 0.23 g of sodium acetate in 2.5 ml of dry dichloromethane under argon was added another solution of 0.25 g (0.53 mmol) of **12** in 1.5 ml of dry dichloromethane slowly, and the resulting mixture was stirred at room temperature for 1 hours. Ether was added and the suspension was filtered through a hyflo-supercell bed. The filtrate was evaporated under reduced pressure to leave the corresponding ketone.

A mixture of the above ketone and 10 mg of 10-camphorsulfonic acid in 5 ml of chloroform was stirred at 50 °C for 3 hours and then cooled to room temperature. Ethyl acetate was added and the mixture was washed with saturated aqueous sodium bicarbonate and brine, dried over sodium sulfate and concentrated *in vacuo* to give the crude **13**.

To a solution of **13** in 2 ml of a mixed solvent (acetone:water=10:1) in an ice bath were added 0.2 g of 4-methylmorpholine *N*-oxide and 0.2 ml of osmium tetroxide in *t*-butanol (0.2 M), respectively, and the resulting mixture was stirred in the ice bath for 2 days. Sodium hydrogen sulfite was added and the mixture was stirred for an additional hour and water was added to dissolve the solid. The aqueous phase was extracted three times with ethyl acetate and the combined organics were washed successively with 5% aqueous acetic acid, saturated aqueous sodium bicarbonate and brine, dried over sodium sulfate and concentrated *in vacuo* to afford the crude corresponding diol.

A mixture of the above diol and 10 mg of 10-camphorsulfonic acid in 5 ml of chloroform was stirred at room temperature for 7 hours. Ethyl acetate was added and the mixture was washed with saturated aqueous sodium bicarbonate and brine, dried over sodium sulfate and concentrated *in vacuo*. The residue was subjected to silica gel column chromatography, eluting with hexane-ethyl acetate (1;1), to give 90 mg of **14** in 36% overall yield from **12** as a colorless viscous oil. IR(film) 2930, 1730 cm^{-1}; ^{1}H-NMR(270 MHz, $CDCl_3$), δ 4.62(2H, s), 4.58(2H, d, J=1.65), 4.51(1H, s), 3.58(4H, m), 3.43(2H, m), 3.38(3H, s), 3.33(3H, s), 3.11(2H, t, J=9.24), 2.45(2H, m), 2.14(1H, m), 1.88(3H, m), 1.66(3H, m), 1.09(2H, m), 0.05(9H, s); ^{13}C-NMR(270 MHz, $CDCl_3$), δ 210.0, 96.4, 95.9, 69.0, 68.6, 65.1, 55.2, 52.9, 48.4, 46.3, 39.4, 37.1, 33.6, 29.8, 25.8, 9.5, -2.4; HRMS(M^+) calcd. for $C_{20}H_{39}NO_7SiS$ 465.2154, found 465.2213.

(1*S*,5*R*)-7-Aza-7-(2-trimethylsilylethylsulfonyl)-5-methoxy-2-[2-(methoxymethoxy)ethyl]-1-[(methoxymethoxy)methyl]-5-prop-2-enylbicyclo[4.3.0]nonane (16).

To a solution of 90 mg (0.19 mmol) of **14** in 2 ml dry THF under argon was slowly added 0.19 ml (0.38 mmol) of allylmagnesium chloride in THF (2.0 M) at -78 °C, and the resulting mixture was stirred at this temperature for 2 hours. The reaction was quenched with saturated aqueous ammonium chloride and the mixture was extracted three times with ethyl acetate. The combined extracts were washed with brine, dried over sodium sulfate and concentrated *in vacuo* to leave a residue.

To a solution of the above residue and 50 µl of dry 15-crown-5 ether in 3 ml of dry THF under argon was added 30 mg of sodium hydride (60%) and the resulting mixture was stirred at room temperature for 1 hour. 0.25 ml of methyl iodide was then added and the mixture was stirred at room temperature for 14 hours. After excess amount of sodium hydride was decomposed with methanol, saturated aqueous ammonium chloride was added and the mixture was extracted twice with ethyl acetate. The combined extracts were washed with brine, dried over sodium sulfate, concentrated *in vacuo* and chromatographed, eluting with hexane-ethyl acetate (1:1), to afford 78 mg of **16** in 79% overall yield. IR(film) 3050, 2950 cm^{-1}; ^{1}H-NMR(270 MHz, $CDCl_3$), δ 5.94(1H, m), 5.07(2H, dd, J=7.92, 16.17), 4.60(4H, m), 3.98(1H, s), 3.50(4H, m), 3.37(3H, s), 3.35(3H, s), 3.31(2H, m), 3.19(3H, s), 2.98(2H, t, J=7.92), 2.39(2H, d, J=7.26), 2.11(1H, m), 1.95(2H, m), 1.72(3H, m), 1.42(3H, m), 1.11(2H, m), 0.04(9H, s); ^{13}C-NMR(270 MHz, $CDCl_3$), δ 134.3, 118.1, 96.9, 96.3, 79.0, 70.9, 66.5, 65.1, 55.6, 55.1, 49.4, 49.0, 48.7, 47.6, 39.7, 34.7, 34.3, 30.7, 24.4, 21.2, 10.2, -2.03; HRMS (M^+) calcd. for $C_{24}H_{47}NO_7SiS$ 521.2839, found 521.2813.

(1*S*,5*R*)-7-Aza-7-(2-trimethylsilylethylsulfonyl)-5-(3-hydroxypropyl)-5-methoxy-2-[2-(methoxymethoxy)ethyl]-1-[(methoxymethoxy)methyl]bicyclo[4.3.0]nonane (17). A solution of 0.14 g (0.27 mmol) of **16** in 6 ml of dry THF under argon was cooled in an ice bath and 0.3 ml of borane-dimethyl sulfide in THF (2 M) was added. The resulting mixture was stirred at room temperature for 1.5 hours and then cooled to 0 °C. After excess amount of the borane was decomposed with 0.3 ml of ethanol, 0.3 ml of 6N aqueous sodium hydroxide and 0.3 ml of hydroperoxide (30%) were added respectively. The mixture was stirred at 50 °C for 1 hour. Ethyl acetate was added and the organic layer was washed with brine, dried over sodium sulfate, concentrated *in vacuo* and chromatographed, eluting with hexane-ethyl acetate (1:3), to give 0.11 g of **17** in 79% yield as a colorless oil. IR(film) 3500, 2930 cm^{-1}; ^{1}H-NMR(270 MHz, $CDCl_3$), δ 4.59(4H, s), 4.01(1H, s), 3.59-3.43(6H, m), 3.38(3H, s), 3.36(3H, s), 3.30(2H, m), 3.16(3H, s), 3.02(2H, m), 2.13(1H, s, br), 1.98-1.64(9H, m), 1.45(4H, m), 1.09(2H, t, J=9.24), 0.04(9H, s); ^{13}C-NMR(270 MHz, $CDCl_3$), δ 98.4, 97.8, 79.1, 72.6, 68.0, 64.2, 61.8, 57.1, 56.6, 50.6, 50.5, 49.8, 49.0, 36.2, 35.5, 32.5, 31.1, 29.2, 25.4, 22.5, 11.6, -0.91; HRMS (M^+) calcd. for $C_{24}H_{49}NO_8SiS$ 539.2946, found 539.2974.

5-*t*-Butyldiphenylsilyloxypentan-1-ol. To a solution of 10 ml (95.6 mmol) of 1,5-pentanediol in 150 ml of dry dimethylformamide were added 3.93 g of imidazole and 10 ml (38.5 mmol) of *t*-butyldiphenylsilyl chloride, respectively, and the resulting mixture was stirred at room temperature overnight. Water was added and the mixture was extracted with ethyl acetate. The combined extracts were washed with brine, dried over sodium sulfate, concentrated *in vacuo* and chromatographed, eluting with hexane-ethyl acetate (1:1), to give

the corresponding mono-protective product 9.87 g in 75 % yield as a colourless oil. IR(film) 3350, 3080, 2930, 1580 cm^{-1}; ^{1}H-NMR(270 MHz, $CDCl_3$), δ 7.66(4H, m), 7.38(6H, m), 3.68(2H, t, J=6.27), 3.62(2H, t, J=6.27), 1.50(6H, m), 1.06(9H, s); ^{13}C-NMR(270 MHz, $CDCl_3$), δ 135.5, 133.7, 129.0, 127.4, 63.6, 62.1, 32.1, 26.7, 21.8, 19.5, 19.0.

5-*t*-Butyldiphenylsilyloxy-1-iodopentane. To a solution of 3.42 g (10 mmol) of 5-*t*-butyldiphenylsilyloxypentan-1-ol in 10 ml of dichloromethane were added 1.4 ml of triethylamine and 1.19 g (10 mmol) of *p*-toluenesulfonyl chloride, respectively, and the resulting mixture was stirred at room temperature for 12 hours. Saturated aqueous sodium carbonate was added and the mixture was extracted with ethyl acetate. The combined extracts were washed with brine, dried over sodium sulfate and concentrated *in vacuo* to leave the corresponding tosylate.

A mixture of the above tosylate and 10.0 g of sodium iodide in 30 ml of acetone was stirred at room temperature for 12 hours. Ethyl acetate was added and the mixture was washed with brine, dried over sodium sulfate and concentrated *in vacuo*. The residue was subjected to silica gel column chromatography, eluting with hexane-ethyl acetate (7:3), to afford 3.4 g of the desired iodide in 73% overall yield as a colorless oil. IR(film) 3080, 2930, 1580 cm^{-1}; ^{1}H-NMR(270 MHz, $CDCl_3$), δ 7.67(4H, m), 7.38(6H, m), 3.67(2H, t, J=5.94), 3.17(2H, t, J=6.92), 1.78(2H, q, J=7.26), 1.50(4H, m), 1.06(9H, s); ^{13}C-NMR(270 MHz, $CDCl_3$), δ 135.3, 133.6, 129.4, 127.5, 63.3, 32.9, 31.2, 26.8, 26.6, 19.0, 6.8.

(5-*t*-Butyldiphenylsilyloxypentanyl)triphenylphosphonium iodide. A mixture of 1.0 g of the above iodide and 0.58 g of triphenylphophine in 10 ml of dry benzene under argon was stirred at 60 °C overnight and then cooled to room temperature. After the solvent was removed under reduced pressure, the solid was washed with ether completely and dried under argon *in vacuo* at 100 °C for 3 hours to give 1.5 g of the phosphonium iodide in 96% yield as a white solid. mp. decomposed; ^{1}H-NMR(270 MHz, $CDCl_3$), δ 7.62(9H, m), 7.58(6H, m), 7.51(4H, m), 7.29(6H, m), 3.53(2H, br), 3.51(2H, t, J=6.27), 1.56(6H, m), 0.88(18H, s).

(1*S*,5*S*)-5-[(3*Z*)-8-(t-Butyldiphenylsilooxy)oct-3-enyl]-7-aza-7-(2-trimethylsilylethylsulfonyl)-5-methoxy-2-[2-(methoxymethoxy)ethyl]-1-[(methoxymethoxy)methyl]bicyclo[4.3.0]nonane(18). To a solution of 0.25 ml of oxalyl chloride in 10 ml of dry dichloromethane under argon was added 0.44 ml of dry dimethyl sulfoxide at -78 °C and the resulting mixture was stirred at this temperature for 20 minutes. Another solution of 0.11 g (0.21 mmol) of **17** in 6 ml of dry dichloromethane was added and the mixture was stirred at -78 °C for an additional half an hour. Next, 0.92 ml of dry triethylamine was added and the reaction mixture was stirred until the reaction temperature of the cooling bath was gradually elevated to -50 °C. The reaction was then quenched with saturated aqueous ammonium chloride and the mixture was extracted three times with ethyl acetate. The combined extracts were washed with brine, dried over sodium sulfate and concentrated *in vacuo* to leave the crude corresponding aldehyde.

To a solution of 0.56 g (0.79 mmol) of the above phosphonium iodide in 3 ml of dry THF under argon was added 1.6 ml (0.79 mmol) of potassium bis(trimethylsilyl)amide in toluene (0.5 M) at -78 °C and the resulting mixture was stirred at -78 °C for 40 minutes. Another solution of the above aldehyde in 2 ml of dry

THF was then added and the reaction temperature was elevated gradually up to room temperature under stirring overnight. The reaction was then quenched with saturated aqueous ammonium chloride and the mixture was extracted three times with ethyl acetate. The combined extracts were washed with brine, dried over sodium sulfate and concentrated *in vacuo*. The residue was subjected to silica gel column chromatography, eluting with hexane-ethyl acetate (2:1), to afford 0.15 g of **18** in 83% overall yield as a pale yellow oil. IR(film) 3050, 2930 cm^{-1}; ^{1}H-NMR(270 MHz, $CDCl_3$), δ 7.66(4H, m), 7.36(6H, m), 5.32(2H, t, J=5.28), 4.62(2H, s), 4.61(2H, s), 4.03(1H, s), 3.66(2H, t, J=6.27), 3.50(4H, m), 3.38(3H, s), 3.36(3H, s), 3.32(2H, m), 3.16(3H, s), 2.95(2H, dt, J=2.64, 9.24), 2.03(7H, m), 1.59(12H, m), 1.08(2H, m), 1.04(9H, s), 0.04(9H, s); ^{13}C-NMR(270 MHz, $CDCl_3$), δ 135.5, 134.1, 129.8, 129.6, 129.5, 127.5, 97.0, 96.4, 79.3, 71.1, 66.6, 65.0, 63.9, 55.6, 55.2, 49.6, 49.1, 48.6, 47.8, 35.1, 34.7, 34.4, 32.2, 31.1, 27.0, 26.8, 26.0, 24.5, 22.4, 21.7, 19.2, 10.3, -2.0

N-(8-{(2*S*,6*S*)-9-Aza-9-(2-trimethylsilylethylsulfonyl)-2-methoxy-5-[2-(methoxymethoxy)ethyl]-6-[(methoxymethoxy)methyl]bicyclo[4.3.0]non-2-yl}(5Z)oct-5-enyl)(tert-butoxy)-N-(2-trimethylsilylethylsulfonyl)carboxamide (19). To a solution of 34 mg (0.04 mmol) of **18** in 1 ml of dry THF under argon was added 0.08 ml of tetrabutylammonium fluoride in THF (1.0 M) and the resulting mixture was stirred at room temperature for 2 hours. The solvent was evaporated under reduced pressure and the residue was purified on TLC plate, eluting with hexane-ethyl acetate (1:2), to provide 22 mg of the corresponding alcohol in 92% yield. IR(film) 3500, 2930 cm^{-1}; ^{1}H-NMR(270 MHz, $CDCl_3$), δ 5.34(2H, m), 4.60(4H, s), 4.03(1H, s), 3.65(2H, t, J=6.27), 3.51(4H, m), 3.39(3H, s), 3.37(3H, s), 3.34(2H, m), 3.18(3H, s), 2.93(2H, m), 2.05(7H, m), 1.54(12H, m), 1.07(2H, m), 0.04(9H, s); ^{13}C-NMR(270 MHz, $CDCl_3$), δ 129.8, 129.6, 97.0, 96.4, 79.2, 71.1, 66.6, 64.8, 62.6, 55.6, 55.1, 49.6, 49.1, 48.5, 47.7, 35.0, 34.6, 34.3, 32.2, 31.0, 26.8, 25.8, 24.3, 22.4, 21.5, 10.2, -2.0

A solution of 22 mg (36.2 μmol) of the above alcohol, 21 mg (72.5 μmol) of *t*-butyl 2-(trimethylsilyl)ethanesulfonylcarbamate (SESNHBoc) and 47 mg of triphenylphosphine in 1 ml of dry THF under argon was cooled to 0 °C and 30 μl of diethyl azodicarboxylate was added slowly. The resulting mixture was stirred in an ice bath for half an hour and then at room temperature overnight. The solvent was removed under reduced pressure and chromatographed, eluting with hexane-ethyl acetate (2:1), to give 31 mg of **19** in 98% yield. IR(film) 2930, 1740 cm^{-1}; ^{1}H-NMR(270 MHz, $CDCl_3$), δ 5.32(2H, m), 4.61(4H, s), 4.02(1H, s), 3.57(5H, m), 3.38(3H, s), 3.34(3H, s), 3.36(5H, m), 3.17(3H, s), 2.95(2H, m), 2.08(3H, m), 1.91(3H, m), 1.68(6H, m), 1.52(9H, s), 1.43(3H, m), 1.31(4H, m), 1.09(2H, m), 0.95(2H, m), 0.06(9H, s), 0.04(9H, s); ^{13}C-NMR(270 MHz, $CDCl_3$), δ 151.7, 130.0, 129.2, 97.0, 96.4, 84.0, 79.3, 71.1, 66.6, 64.9, 55.6, 55.2, 50.7, 49.6, 49.1, 48.6, 47.8, 46.9, 35.1, 34.7, 34.4, 31.1, 29.9, 28.0, 26.8, 26.7, 24.4, 22.4, 21.6, 10.4, 10.3, -1.95, -2.03

((1*S*,5*S*)-5-{(3Z)-8-[(2-Trimethylsilylethylsulfonyl)amino]oct-3-enyl}-7-aza-7-(2-trimethylsilylethylsulfonyl)-2-(2-iodoethyl)-5-methoxybicyclo[4.3.0]nonyl)methyl methylsulfonate20). A mixture of 79 mg (91 μmol) of **19** and 60 mg of *p*-toluenesulfonic acid in 2 ml of methanol was stirred at 50 °C for 24 hours and cooled to room temperature. Ethyl acetate was added and the mixture was washed with saturated

aqueous sodium bicarbonate and brine, dried over sodium sulfate and concentrated *in vacuo* to leave a residue.

To a solution of the above residue in 6 ml of dry dichloromethane under argon was added 0.15 ml of dry triethylamine and 50 µl of methanesulfonyl chloride, respectively, at -50 °C and the reaction temperature was gradually elevated to -10 °C under stirring for 11 hours. The reaction was then quenched with saturated aqueous ammonium chloride and the mixture was extracted twice with ethyl acetate. The combined extracts were washed with brine, dried over sodium sulfate and concentrated *in vacuo* to afford the corresponding dimesylate.

To a solution of the dimesylate in 1 ml of acetone was added 0.1 g of sodium iodide and the mixture was stirred at room temperature for 27 hours. The solvent was removed under reduced pressure and the residue was chromatographed, eluting with hexane-ethyl acetate (2:1), to give 41 mg of **20** in 52% overall yield. IR(film) 3300, 2930 cm^{-1}; ^{1}H-NMR(270 MHz, $CDCl_3$), δ 5.32(2H, m), 4.09(1H, d, J=10.25), 4.05(1H, s), 3.96(1H, d, J=10.25), 3.55(1H, m), 3.37(2H, m), 3.17(3H, s), 3.08(3H, m), 3.06(3H, s), 2.95(4H, m), 2.29(1H, m), 2.03(3H, m), 1.89-1.20(15H, m), 1.04(4H, m), 0.03(18H, s); ^{13}C-NMR(270 MHz, $CDCl_3$), δ 129.8, 129.5, 85.1, 79.4, 71.8, 64.5, 64.2, 50.3, 48.7, 47.8, 43.1, 38.0, 37.0, 35.1, 34.4, 29.9, 26.7, 26.5, 23.5, 22.4, 20.3, 14.1, 10.6, 10.3, 6.1.

The macrocyclic compound 22. To a solution of 5 mg (5.7 µmol) of **20** in 3 ml of dry dimethylformamide was added 4 mg (12.3 µmol) of cesium carbonate and the resulting mixture was stirred at 60 °C for 30 hours. The solvent was evaporated under reduced pressure and chromatographed, eluting with hexane-ethyl acetate (3:2), to afford 4 mg of **22** in 82% yield. IR(film) 2930, 1460 cm^{-1}; ^{1}H-NMR(400 MHz, $CDCl_3$), δ 5.42(1H, m), 5.20(1H, m), 4.04(2H, d, J=10.26), 4.00(1H, s), 3.46(2H, m), 3.21(4H, m), 3.13(3H, s), 3.05(3H, s), 2.97(2H, m), 2.85(2H, m), 2.37(1H, m), 2.15(3H, m), 2.01(2H, m), 1.84(3H, m), 1.59(5H, m), 1.49(2H ,m), 1.31(3H, m), 1.05(4H ,m), 0.03(18H, s); ^{13}C-NMR(270 MHz, $CDCl_3$), δ 133.2, 130.1, 79.6, 71.7, 61.0, 50.0, 48.4, 48.3, 47.5, 46.5, 44.9, 37.1, 32.9, 31.1, 27.4, 26.7, 26.0, 25.2, 23.1, 22.3, 16.5, 10.4, 10.3, -2.0; MS(M^+) m/z 742, 674, 608, 542, 503, 429, 371, 321, 225, 166, 99, 67.

The tetracyclic ABCE ring subunit I. To a solution of 5.5 mg (7.4 µmol) of **22** in 1 ml of dry THF under argon was added 0.1 ml of tetrabutylammonium fluoride in THF (1.0 M) and the resulting mixture was stirred under reflux for 4.5 hours and then cooled to room temperature. The solvent was removed under reduced pressure to give a residue.

To a solution of the above residue and 50 µl of dry triethylamine in 0.7 ml of dry dichloromethane under argon was added 10 µl of methyl chloroformate at -50 °C and the reaction temperature was gradually elevated to room temperature under stirring overnight. Saturated aqueous sodium bicarbonate was added and the mixture was extracted twice with ethyl acetate. The combined extracts were washed with brine, dried over sodium sulfate and concentrated *in vacuo*. The residue was separated on TLC plate, eluting with hexane-ethyl acetate-methanol (5:10:1), to afford 1.6 mg of the subunit **I** in 57% overall yield. IR(film) 2950, 2860, 1700 cm^{-1}; ^{1}H-NMR(270MHz, $CDCl_3$), δ 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 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. HRMS(M^+) calcd. for $C_{22}H_{36}N_2O_3$ 376.2724, found 376.2724.

(1*S*,12*S*,5*R*)-4-Aza-4-(2-trimethylsilylethylsulfonyl)-12-hydroxytricyclo[7.3.0.0<1,5>]dodecan-6-one (24) and (1*S*,12*S*,5*R*)-4-Aza-4-(2-trimethylsilylethylsulfonyl)-12-(methoxymethoxy)tricyclo-[7.3.0.0<1,5>]dodecan-6-one (25). To a solution of 1.78 g of pyridinium chlorochromate and 1.78 g of sodium acetate in 15 ml of dry dichloromethane was added another solution of the crude **23**, which was prepared from 1.16 g (4.11 mmol) of 2β-acetoxy-1α-allyl-6α-hydro-9β-methoxymethoxybicyclo[4, 3, 0]nonane in 5 steps, in 10 ml of dry dichloromethane slowly, and the resulting mixture was stirred at room temperature for 2 hours. Ether was added and the suspension was filtered through a hyflo-supercell bed. The filtrate was evaporated under reduced pressure to leave the corresponding ketone.

A mixture of the above ketone and 0.3 g of 10-camphorsulfonic acid in 20 ml of chloroform was stirred at ~ 55 °C overnight and then cooled to room temperature. Chloroform was added and the mixture was washed with saturated aqueous sodium bicarbonate and brine, dried over sodium sulfate and concentrated *in vacuo* to give the corresponding cyclic ene-sulfonamide.

To a solution of the above ene-sulfonamide in 20 ml of methanol was added 1.2 g of magnesium monoperoxyperphthalate, and the resulting mixture was stirred at room temperature for 28 hours. Ethyl acetate was added and the mixture was washed with brine, dried over sodium sulfate and concentrated *in vacuo* to afford the crude corresponding epoxide.

A mixture of the above epoxide and 0.5 g of 10-camphorsulfonic acid in 20 ml of chloroform was stirred at 50 °C for 14.5 hours. The solvent was evaporated under reduced pressure and the residue was subjected to silica gel column chromatography, eluting with hexane-ethyl acetate (2:1) to provide 0.44 g of **24** and 0.32 g of **25** in 30 and 19% yield in 9 steps respectively. The spectral data for **24**: IR(film) 3300, 2950, 1740 cm^{-1}; ^{1}H-NMR(270 MHz, $CDCl_3$), δ 4.82(1H, s), 3.84(1H, s, br), 3.65(1H ,dt, J=9.90, 7.59), 3.35(1H, t, J=7.92), 3.10(2H, m), 2.51(1H, m), 2.21(1H, m), 1.89(8H, m), 1.55(dt, J=9.90, 13.2), 1.11(2H, m), 0.06(9H, s); ^{13}C-NMR(270 MHz, $CDCl_3$), δ 169.2, 65.8, 59.1, 52.0, 49.3, 45.5, 41.7, 36.6, 36.5, 32.2, 29.1, 28.7, 9.6, -2.3; HRMS (M^+-H_2O) calcd. for $C_{16}H_{27}NO_3SiS$ 341.1413, found 341.1479. The spectral data for **25:** ^{1}H-NMR(270 MHz, $CDCl_3$), δ 5.00(1H, s), 4.72(2H, q, J=6.93), 3.70(1H, s, br), 3.54(1H, m), 3.40(3H, s), 3.36(1H, m), 3.18(2H, m), 2.50(1H, m), 2.23(3H, m), 1.79(3H, m), 1.61(3H, m), 1.15(2H, m), 0.05(9H, s).

To a solution of 0.3 g of **25** in 2 ml of methanol was added 20 mg of *p*-toluenesulfonic acid, and the resulting mixture was stirred at 50 °C for 12 hours. The solvent was removed *in vacuo* and the residue was chromatographed, eluting with hexane-ethyl acetate (2:1), to give 0.23 g of **24** in 85% yield.

(1*S*,5*R*)-4-Aza-4-(2-trimethylsilylethylsulfonyl)tricyclo[7.3.0.0<1,5>]dodec-11-en-6-one (26). To a solution of 0.5 g (1.39 mmol) of **24** in 10 ml of dry dichloromethane was added 0.48 ml of dry triethylamine and 0.21 ml (2.79 mmol) of methanesulfonyl chloride respectively at -40 °C, and the temperature of the resulting mixture was gradually elevated to room temperature under stirring for 7.5 hours. The reaction was then quenched with saturated aqueous ammonium chloride and the mixture was extracted with ethyl acetate. The combined extracts were washed with brine, dried over sodium sulfate and concentrated *in vacuo* to leave the corresponding mesylate.

A solution of the above mesylate and 0.5 ml of 1,8-diazabicyclo[5.4.0]undec-7-ene in 15 ml of dry benzene under argon was stirred at 60 °C for 13 hours. The solvent was removed under reduced pressure and the residue was chromatographed, eluting with hexane-ethyl acetate (1:1), to afford 0.36 g of **26** in 76% overall yield. IR(film) 3070, 2970, 1740 cm^{-1}; ^{1}H-NMR(400 MHz, $CDCl_3$): δ 5.84(2H, s), 4.31(1H, s), 3.63(1H, m), 3.45(1H, t, J=8.79), 3.18(2H, t, J=12.18), 2.73(1H, dd, J=8.81, 17.1), 2.53(1H, dt, J=4.86, 17.58), 2.31(2H, m), 2.11(1H, m), 2.01(1H, m), 1.84(3H, m), 1.14(2H, m), 0.06(9H, s); ^{13}C-NMR(270 MHz, $CDCl_3$), δ 209.1, 133.7, 129.9, 61.2, 49.9, 46.5, 41.7, 38.1, 36.8, 36.6, 27.4, 9.9, -2.13; HRMS (M^+) calcd. for $C_{16}H_{27}NO_3SiS$ 341.1562, found 341.1480.

(1*S*,5*R*,6*R*)-4-Aza-4-(2-trimethylsilylethylsulfonyl)-6(methoxymethoxy)tricyclo[7.3.0.0<1,5>]dodec-11-ene (27). To a solution of 0.15 g (0.44 mmol) of **26** in 1.5 ml of methanol was added sodium borohydride in batches at -20 °C ~ -10 °C until the starting material was reduced completely. Saturated aqueous ammonium chloride was added, and the mixture was extracted with ethyl acetate. The combined extracts were washed with brine, dried over sodium sulfate and concentrated *in vacuo* to leave a residue.

A mixture of the above residue and 0.22 ml of diisopropylethylamine in 2.5 ml of dry dichloromethane was cooled in an ice bath and 0.10 ml of chloromethyl methyl ether was then added. The resulting mixture was stirred at room temperature overnight and quenched with saturated aqueous ammonium chloride. The mixture was extracted with ethyl acetate and the combined extracts were washed with brine, dried over sodium sulfate, concentrated *in vacuo* and chromatographed, eluting with hexane-ethyl acetate (2:1), to give 0.16 g of **27** in 94% overall yield. IR(film), 3050, 2950, 1450 cm^{-1}; ^{1}H-NMR(270 MHz, $CDCl_3$), δ 5.77(2H, s), 4.70(2H, d, J=1.65), 3.81(1H, m), 3.57(2H, m), 3.36(3H, s), 3.31(3H, m), 3.01(3H, m), 2.40(1H, dd, J=7.92, 18.15), 2.18(2H, m), 1.94-1.50(6H, m), 1.05(2H, m), 0.04(9H, s); ^{13}C-NMR(270 MHz, $CDCl_3$), δ 135.8, 129.3, 95.7, 76.8, 67.0, 56.8, 55.3, 48.8, 46.5, 40.7, 36.9, 34.7, 25.5, 22.6, 10.0, -1.8; HRMS(M^+) calcd. for $C_{18}H_{33}NO_4SiS$ 387.1897, found 387.1708.

[(1*S*,5*R*,6*R*)-2-(2-Acetyloxyethyl)-7-aza-7-(2-trimethylsilylethylsulfonyl)-5-(methoxymethoxy)-bicyclo[4.3.0]nonyl]methyl acetate (28). A solution of 0.2 g (0.52 mmol) of **27** in 3 ml of dry dichloromethane under argon was cooled to -78 °C and ozone was then introduced at this temperature until the starting material was oxidized completely. Dimethyl sulfide was added and the resulting mixture was stirred under argon at -78 °C for 1 hour and at room temperature for 2 hours. The solvent was evaporated under reduced pressure to give the corresponding ozonide.

To a solution of the above ozonide in 3 ml of methanol was added sodium borohydride in batches at 0 °C ~ room temperature until the ozonide was reduced totally. Excess amount of sodium borohydride was decomposed by addition of saturated aqueous ammonium chloride and the mixture was extracted with ethyl acetate. The combined extracts were washed with brine, dried over sodium sulfate and concentrated *in vacuo* to provide the corresponding diol.

To a solution of the above diol and 0.7 ml of dry triethylamine in 7 ml of dry dichloromethane were added 34 mg of 4-dimethylaminopyridine and 0.35 ml of acetic anhydride, respectively, at -40 °C, and the resulting mixture was stirred in an ice bath overnight. Saturated aqueous ammonium chloride was added and the mixture was extracted with ethyl acetate. The combined extracts were washed with brine, dried over

sodium sulfate, concentrated *in vacuo* and chromatographed, eluting with hexane-ethyl acetate (2:1), to afford 0.15 g of the diacetate **28** in 58% overall yield. IR(film) 2950, 1740 cm^{-1}; ^{1}H-NMR(270 MHz, $CDCl_3$), δ 4.61(2H, q, J=6.27), 4.28-4.03(5H, m), 3.68(2H, m), 3.34(3H, s), 3.32(1H, m), 2.92(2H, m), 2.05(3H, s), 2.03(3H, s), 1.89-1.30(9H, m), 1.03(2H, m), 0.02(9H, s); ^{13}C-NMR(270 MHz, $CDCl_3$), δ 170.8, 170.5, 95.3, 72.1, 63.7, 62.5, 62.2, 55.2, 47.5, 47.1, 47.0, 34.3, 30.4, 29.5, 25.3, 21.0, 20.9, 9.9, -0.18; HRMS(M^+-AcOH) calcd. for $C_{20}H_{37}NO_6SiS$ 447.2108, found 447.2053.

[(1*S*,6*R*)-2-(2-acetyloxyethyl)-7-aza-7-(2-trimethylsilylethylsulfonyl)-5-oxobicyclo[4.3.0]nonyl]-methyl acetate (29). To a solution of 12 mg (23.7 μmol) of **28** in 1 ml of dichloromethane was added 0.1 ml of trifluoroacetic acid and the resulting mixture was stirred at room temperature for 2 hours. The reaction was quenched with saturated aqueous sodium bicarbonate and the mixture was extracted three times with ethyl acetate. The combined extracts were washed with brine, dried over sodium sulfate and concentrated *in vacuo* to give a residue.

A solution of 30 μl of oxalyl chloride in 2.0 ml of dry dichloromethane under argon was cooled to -78 °C and 48 μl of dry dimethyl sulfoxide was then added. The resulting mixture was stirred at -78 °C for 30 minutes and another solution of the above residue in 1.5 ml of dry dichloromethane was added and stirred for an additional 30 minutes at -78 °C Next, 102 μl of dry triethylamine was added and the reaction mixture was stirred until the temperature of the cooling bath was elevated gradually up to -30 °C. The reaction was quenched with saturated aqueous ammonium chloride and the mixture was extracted twice with ethyl acetate. The combined extracts were washed with brine, dried over sodium sulfate and concentrated *in vacuo*. The residue was purified on TLC plate, eluting with hexane-ethyl acetate (1:1), to afford 10 mg of **29** in 92% overall yield. IR(film) 2950, 1740 cm^{-1}; ^{1}H-NMR(270 MHz, $CDCl_3$), δ 4.36(1H, s), 4.26-4.05(4H, m), 3.66(1H, dt, J=9.57, 8.24), 3.48(1H, m), 3.03(2H, dd, J=7.59, 10.23), 2.52(2H, m), 2.12(3H, s), 2.05(3H, s), 2.03(2H, m), 2.01-1.59(5H, m), 1.12(2H, dt, J=7.26, 8.91), 0.07(9H, s); ^{13}C-NMR(270 MHz, $CDCl_3$), δ 208.5, 170.5, 170.2, 69.7, 65.6, 62.2, 52.1, 49.2, 46.7, 39.7, 37.3, 34.6, 29.3, 25.7, 20.8, 10.2, -0.18; HRMS (M^+) calcd. for $C_{20}H_{35}NO_7SiS$ 461.1902, found 461.1949.

(6*S*,2*R*)-9-Aza-9-(2-trimethylsilylethylsulfonyl)-5-[2-(methoxymethoxy)ethyl]-6-[(methoxy-methoxy)methyl]-2-prop-2-enylbicyclo[4.3.0]nonan-2-ol (15).

A solution of 70 mg (0.15 mmol) of **29** in 5 ml of dry THF under argon was cooled to -78 °C and 0.38 ml (0.75 mmol) of allylmagnesium chloride in THF (2 M) was then added slowly. After the resulting mixture was stirred at -78 °C for 1 hour, saturated aqueous ammonium chloride was added and the mixture was extracted three times with ethyl acetate. The combined extracts were washed with brine, dried over sodium sulfate and concentrated *in vacuo* to leave a residue.

To a solution of the above residue in 3 ml of dichloromethane in an ice bath were added 0.23 ml of diisopropylethylamine and 0.1 ml of chloromethyl methyl ether and the resulting mixture was stirred at room temperature overnight. Saturated aqueous ammonium chloride was added and the mixture was extracted twice with ethyl acetate. The combined extracts were washed with brine, dried over sodium sulfate, concentrated *in vacuo* and chromatographed, eluting with hexane-ethyl acetate (1:1), to provide 40 mg of **15** in 52% yield as a white solid which was recrystallized from a mixed solvent of hexane and chloroform to

give colorless needles. mp. 92-3 °C; IR(film) 3500, 3050, 2950 cm^{-1}; ^{1}H-NMR(270 MHz, $CDCl_3$), δ 5.86(1H, m), 5.12(2H, dd, J=7.92, 14.85), 4.62(2H, s), 4.60(2H, s), 3.88(1H, s), 3.52(4H, m), 3.38(3H, s), 3.35(3H, s), 3.29(2H, m), 3.02(2H, m), 2.36(2H, m), 2.08(2H, m), 1.91(4H, m), 1.42(3H, m), 1.10(2H, m), 0.06(9H, s); ^{13}C-NMR(270 MHz, $CDCl_3$), δ 133.3, 118.0, 96.4, 95.8, 73.0, 69.2, 65.8, 64.8, 55.1, 54.6, 48.6, 47.6, 47.0, 45.9, 33.1, 32.7, 29.8, 28.9, 20.0, 9.5, -2.5; HRMS (M^+) calcd. for $C_{23}H_{45}NO_7SiS$ 507.2683, found 507.2766. Crystal data for **15** ($C_{23}H_{45}NO_7SiS$) 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.

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