Tetrahedron Vol. 47, No. 38, pp. 8067-8078, 1991
Printed in Great Britain

0040-4020/91 $3.00+.00

A Total Synthesis of Manzamine C and Its Geometrical Isomer†

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(*Received in Japan* 1 *July* 1991)

Key Words: β-carboline; azacycloundecene; manzamine C; geometrical isomer; dihydromanzamine C

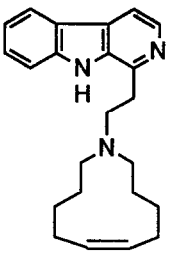
Abstract: *Manzamine C (1) has been synthesized from silyloxyacetylene (3) along the line : 4→5→8→18→1 The overall yield is 21 %. The β-carboline segment (11) was obtained by the Bischler-Napieralski reaction of 14 followed by dehydrogenation. By the similar procedure, the trans isomer (2) and dihydromanzamine C (21) have been synthesized*

INTRODUCTION

Manzamines have been a growing family of novel oncolytic marine alkaloids isolated from several Okinawan marine sponges by Higa and coworkers [1] since 1986. Nakamura and coworkers [2] have independently isolated two alkaloids (keramamine A and B) from different sponges which are ultimately identical with Higa's manzamine A and F. Because of their intriguing structural features coupled with significant biological activities, these alkaloids have attracted considerable interests from both synthetic and biosynthetic points of view. Among these, manzamine C (**1**) is the simplest member of the six congeners known, which is essentially a novel β-carboline alkaloid bearing unprecedented azacycloundecene ring. Quite interestingly, it was found that this simplest manzamine is equally potent in antitumor activity as the more complex congener such as manzamine B.

† Dedicated to Professor Emeritus Yoshio Ban on the occasion of his 70th birthday.

At the very beginning of our synthetic studies toward various manzamines, we have initiated the efficient synthesis of **1** [3] and related compounds with the aim of uncovering the factors involved in its activity. Described herein is the full detail of the synthesis of **1** and also the preparation of its geometrical isomer (**2**) and the saturated congener (**21**), whose biological profiles are of special interest.



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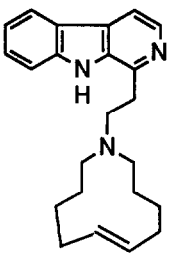

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Scheme 1

RESULTS AND DISCUSSION

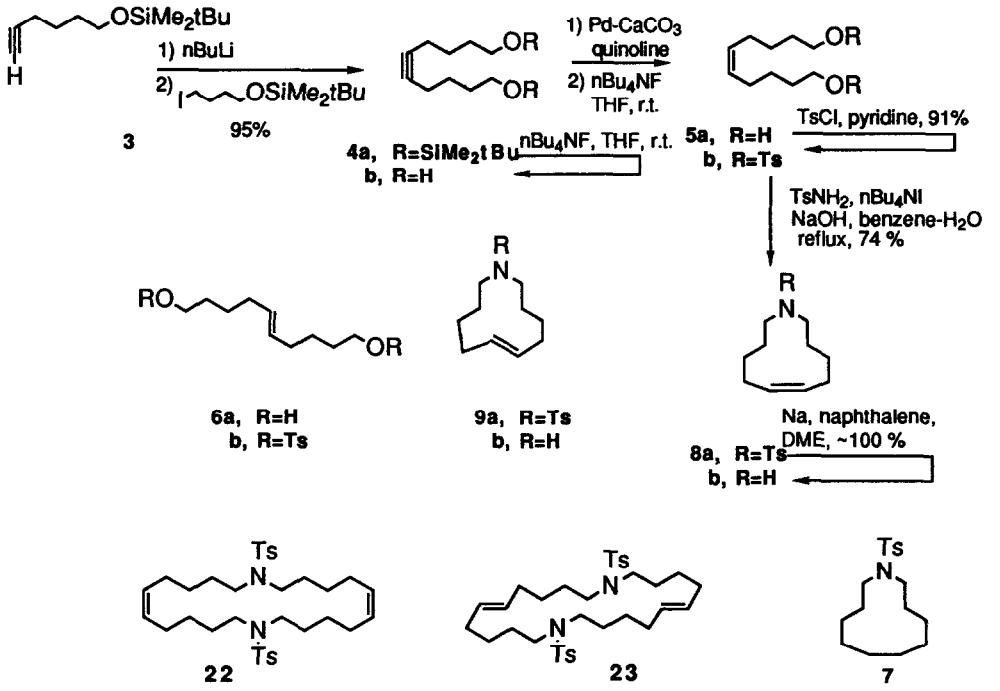
Azacycloundecene Ring Construction

The primary and most obvious task of the present synthesis is an expedient preparation of the requisite 6(*Z*)- or 6(*E*)-azacycloundecene ring system, which constitutes the lower portion of **1** and **2**. Toward the construction of this substructure, the known silyloxyacetylene (**3**) [4] was alkylated with 1-iodo-4-*tert*-butyldimethylsilyloxybutane by conventional way [5] to afford the key intermediate acetylene (**4a**) (95 %). For the preparation of natural *cis*-azacycloundecene, **4a** was subjected to hydrogenation in the presence of Lindlar catalyst to furnish the *cis* diol (**5a**) (71 %) after desilylation and purification by silica gel column chromatography. A small amount of the *trans* isomer (**6a**) (2 %) was also obtained together with 1,10-decanediol (0.7 %). On the other hand, this *trans* diol (**6a**) was prepared quite effectively by the following sequence of reactions: desilylation of **4a** and subsequent reduction of the diol (**4b**) by $LiAlH_4$ in diglyme [6]. **6a** was now obtained as a waxy solid in 89 % yield from **4a** along with a small amount of the *cis* isomer (**5a**) (2 %). The structures of these isomers (**5a** and **6a**) were originally deduced from the reaction conditions employed and unequivocally determined from the spectroscopic grounds. Especially IR spectrum of **6a** showed the characteristic strong absorption at 965 cm^{-1} due to the *trans* disubstituted olefin, which is completely absent in the *cis* isomer (**5a**).

For the crucial azacycloundecene ring construction, each diol was converted to the corresponding tosylates (**5b, 6b**). It was already known that azacycloundecane ring (ie. **7**) was constructed from the reaction of 1, 10-dibromodecane and tosylamide ($TsNH_2$) under phase-transfer conditions,[7] although the yield was not satisfactory and undesired dimeric product was formed predominantly. To our delight, however, with our own substrate (**5b** or **6b**) which contains internal olefin, this protocol was quite effective to furnish the desired azacycloundecene ring predominantly. Thus, N-tosyl-6(*Z*)-azacycloundecene (**8a**) was obtained in up to 74 % yield from **5b** by heating with $TsNH_2$, n-Bu_4NI and NaOH in benzene-H_2O for 4 h with the formation of a trace of dimeric product (**22**, 1 %). For the structural confirmation **8a** was unequivocally transformed to the known saturated azacycle (**7**) by usual hydrogenation. On the other hand, N-tosyl-6(*E*)-azacycloundecene (**9a**)

was obtained in a slightly lower yield (61 %) from the same reaction conditions along with the undesirable dimeric compound (**23**, 22 %). These N-tosylazacycloundecenes (**8a** and **9a**) were fully characterized by the spectral data and elemental analysis.

Reductive removal of the N-tosyl group of **8a** by heating with excess Red-Al in toluene provided the corresponding amine (**8b**) in 58 % yield. However, liberation of the free amines (**8b** and **9b**) from these N-tosylazacycloundecene (**8a** and **9a**) was almost quantitatively carried out by treating the amides in dimethoxyethane with sodium naphthalenide [8]. Free amines (**8b** and **9b**) were obtained as a colorless oil after purification by silica gel column chromatography, in quantitative yields, respectively.



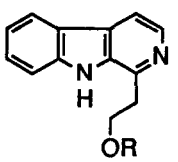
Scheme 2

β-Carboline Segment Synthesis

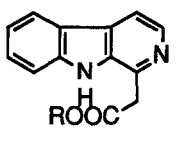
Having established an expedient procedure for the construction of azacycloundecene ring, we next turned our attention to the preparation of the other half of **1** and **2**. The β-carboline derivatives (**10a**, **11a** and **11b**) were selected as the obvious targets. Fortunately, the alcohol (**10a**) has already been isolated from the plant *Soulamea fraxinifolia* and well characterized spectroscopically [9]. Toward this alkaloid, we initially examined the typical Pictet-Spengler reaction of tryptamine with the aldehyde (**12**). It was found, after several experiments, that the purity of the aldehyde was a key factor to successful conversion. Thus, tryptamine was stirred with aldehyde (**12**) in CH_2Cl_2 followed by a brief treatment with CF_3COOH at room temperature to furnish the desired tetrahydro-β-carboline (**13**) in 60 % yield. Prolonged reaction did not give any better results. To our further disappointment, the next aromatization reaction was found to be quite difficult to

conduct. Typical aromatization conditions (DDQ, 5 % Pd-C) gave only a trace of product and even under the best conditions found (10 % Pd-C, *p*-cymene), the desired β-carboline (**10a**) was obtained in low yield ranging from 10-20 % after usual desilylation.

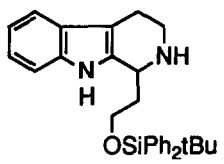
In order to explore more efficient route to **10a**, next efforts were devoted to the more promising Bischler-Napieralski reaction of the readily available amide (**14b**). Reaction of **14b** in $POCl_3$ at room temperature cleanly furnished the corresponding enaminoester (**15b**) in 61 % yield. In the presence of some co-solvent, this reaction was found to be quite sluggish. The structure of **15b** was unequivocally determined on the basis of its ^1H NMR spectrum, in which characteristic one olefinic proton (δ 4.90) and two NH protons (δ 8.15, 8.29) indicated the presence of an exocyclic double bond. We tentatively assigned its stereochemistry as shown (Z) [10]. Next, the aromatization reaction was most effectively carried out by brief heating of **15** with excess 10 % Pd-C in *p*-cymene to give **11**. In contrast to the unsuccessful case mentioned above, a reproducible yield (67 %) was obtained in this aromatization reaction. Under more specified conditions (NBS/CH_2Cl_2; S8[11]), 200 °C), only a decomposition of the starting material was observed. Through the same sequence of reactions starting with tryptamine and methyl malonyl chloride, a substantial quantity of the ester (**11a**) was obtained and $LiAlH_4$ reduction of these ester (**11a** or **11b**) now gave the alcohol (**10a**) as colorless prisms, mp 195.5-197.0 °C (reported [9] mp 192 °C), after recrystallization from MeOH.



10a, R=H
b, R=SiPh$_2$tBu
c, R=Ms



11a, R=Me
b, R=Et
c, R=K



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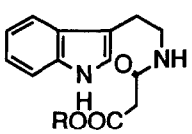
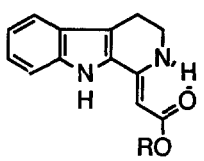
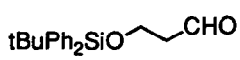


14a, R=Me
b, R=Et



15a, R=Me
b, R=Et



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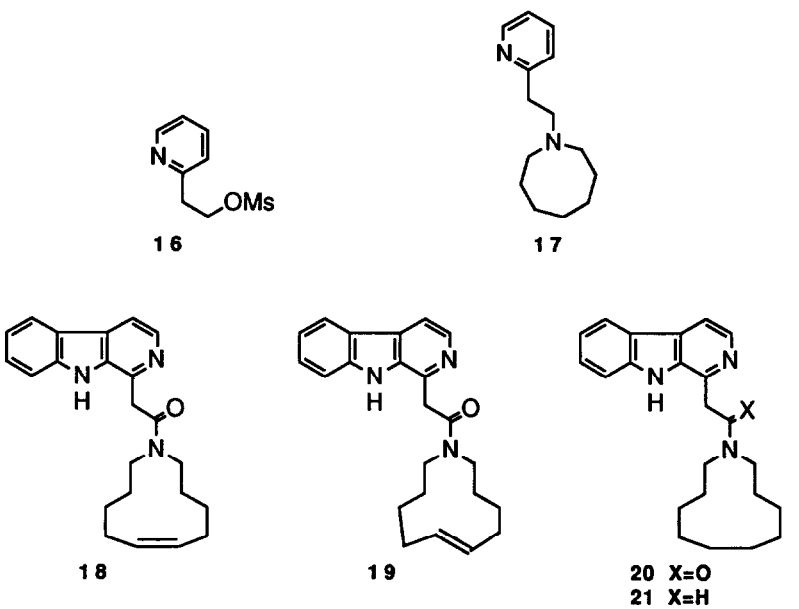
Scheme 3

Synthetic Entry into Manzamine C (1), its trans Isomer (2) and 21

With both segments (**8b**, **9b** and **10a**, **11**) in hand, stage was then set for the final conjunction of each component to the target manzamine C (**1**) and further to its analog. We initially surveyed the possibility of carrying out this transformation *via* the mesylate (**10c**). Model studies indicated that satisfactory transformation of the simple mesylate (**16**) to the desired amine (**17**) was realized by heating with azacyclooctane in the presence of K_2CO_3. Thus, more complex mesylate (**10c**) was heated with the above-prepared 6(Z)-azacycloundecene (**8b**) in CH_3CN for several hours. From the dark reaction mixture, manzamine C (**1**) was isolated, after tedious chromatography, only in poor yield (10 %) as a yellow amorphous. To secure the

quantity of **1**, we next examined the reaction of the ester (**11**) and the amine (**8b**), which proved to be practical and reproducible. Thus, the amide (**18**) was obtained in 68 % yield from **11b** after heating **11b** and **8b** in toluene for 7 days. However, remarkable improvement for this condensation was found when the potassium salt (**11c**) was treated with the amine (**8b**) in DMF employing diphenylphosphoryl azide (DPPA) [12] as a condensing agent together with Et_3N, giving the corresponding amide (**18**) in 87 % yield. Likewise, **19** and **20** were obtained from the corresponding amines (**9b** and azacycloundecane) in 88 % and 67 % yields, respectively. Reduction of the amide (**18**) with $LiAlH_4$ afforded **1**, which could be crystallized initially from ether-CH_2Cl_2 to afford slightly yellow crystals (mp 79.0-83.0 °C). Further recrystallization from $CHCl_3$-CH_3CN gave colorless prisms (mp 90.0-92.0 °C) which were completely identical with the natural product (**1**). $LiAlH_4$ reduction of **19** and **20** afforded the *trans* manzamine C (**2**), mp 145-145.5 °C and the saturated congener (**21**), mp 151-153 °C, respectively. The synthetic manzamine C (**1**), its *trans* isomer (**2**), and **21** are now under evaluation for their biological activity.



Scheme 4

EXPERIMENTAL

Melting points were determined with Yamato MP-1 and Yanagimoto micro melting point apparatus, and are uncorrected. UV spectra were recorded on a Hitachi 323 spectrophotometer. IR spectra were obtained with a Hitachi 260-10 spectrophotometer. Mass spectra (MS) were recorded on a Hitachi M-60 or a JMS-HX 100 mass spectrometer. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on JEOL JNM-FX 270, JNM-GX 270, and JNM-GSX 500 apparatus. All chemical shifts are reported downfield from an internal Me_4Si standard and given as δ values (ppm). Microanalyses were performed on a Perkin-Elmer 240 C, H, and N analyzer. Unless otherwise noted, UV spectra (l in nm) refer to a solution in 95 % EtOH, IR spectra to KBr or NaCl disks, and ^{1}H NMR spectra to

solutions in $CDCl_3$. Chromatographic purification refers to column chromatography using Merck silica gel 60 (70-230 Mesh) unless otherwise noted.

1,10-Bis-(*tert*-butyldimethylsilyloxy)-5-decyne (4a) To a stirred solution of the acetylene (3) (azeotropically dried with benzene, 3.5 g, 16.4 mmol) in THF (30 mL) was added n-BuLi (1.5 M sol in hexane, 14 mL) at ca. -10 °C under Ar atm. The resulting mixture was kept stirring for 0.5 h under these conditions to give a deep yellow solution. To this lithium acetylide solution was added dropwise the 1-iodo-4-*tert*-butyldimethylsilyloxy butane [3] (5.7 g, 1.8 mmol) in 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (Aldrich, 28 mL) and the resulting mixture was kept stirring at -10 °C for 0.5 h and at rt for 1 h. The mixture was quenched with saturated NH_4Cl (10 mL) and extracted with AcOEt:hexane=1:1. Usual workup and chromatography (560 g, AcOEt:hexane=1:40) of the residue yielded the acetylene (4a) (6.2 g, 95 %) as a colorless oil: IR 1100, 765 cm^{-1}; ^1H NMR δ 0.05 (s, 12 H, $SiCH_3$), 0.89 (s, 18 H, tBu), 1.55 (m, 4 H, CH_2), 1.60 (m, 4 H, CH_2), 2.16 (t, *J*=5.0 Hz, 4 H, C≡C-CH_2), 3.62 (t, *J*=6.0 Hz, 4 H, OCH_2); MS *m/z* (relative intensity), 341 (5), 147 (100); HRMS Calcd for $C_{18}H_{37}O_2Si_2$ (M-*t*-Bu) *m/z* 341.2331, Found 341.2356.

5(*Z*)-Decene-1,10-diol (5a) Method i: To a stirred solution of the acetylene (4a) (1.1 g, 2.6 mmol) in AcOEt (30 mL) under N_2 atm was added a AcOEt solution of quinoline (0.2 mL of 50 mg/mL solution) and Pd-$CaCO_3$ (44 mg) in one portion at rt. Then N_2 balloon was replaced with H_2 balloon and pre-existed N_2 gas was exchanged by H_2. The mixture was further kept stirring at rt for 2 h. After careful TLC analysis, the mixture was diluted with AcOEt (30 mL) and filtered to remove the catalyst. Concentration of the filtrate gave crude olefin, which was subjected to the next desilylation without purification. Thus, to a stirred solution of the crude olefin (1.0 g) in THF (15 mL) was added tetrabutylammonium fluoride (TBAF) (1 M in THF solution, 5 mL, 5 mmol) at rt. After stirring at rt for 12 h, the mixture was concentrated. Purification of the residue by flash chromatography (silica gel, Fuji-BW-300, 60 g, AcOEt:hexane=1:2) gave *cis* diol (5a) (321 mg, 71 %) as a colorless oil along with isomeric *trans* diol (6a) (9 mg, 2 %) and decanediol (3 mg, 0.7 %). 5a: IR 3300, 1650, 1060, 1000 sh cm^{-1}; ^1H NMR δ 1.43 (m, 4 H, C=C-CH_2), 1.50 (s, 2 H, OH), 1.57 (m, 4 H, CH_2), 2.07 (m, 4 H, CH_2), 3.65 (t, *J*=6.6 Hz, 4 H, OCH_2), 5.38 (m, 2 H, HC=CH); MS *m/z* (relative intensity) 172 (M^+, 0.6); HRMS Calcd for $C_{10}H_{18}O$ (M-H_2O) *m/z* 154.1358, Found 154.1351.

Method ii: Crude product obtained after hydrogenation (4.80 g) was taken up into MeOH (250 mL) and Amberlyst 15 (500 mg) was added at rt. The mixture was stirred at rt for 45 h and concentrated after removing insoluble Amberlyst. Crude residue thus obtained was purified by column chromatography (silica gel, Fuji-BW-300, 75 g, AcOEt:hexane=1:2) gave 5a (1 90 g, 94 % from 4a).

5(*E*)-Decene-1,10-diol (6a) To a stirred solution of the acetylene (4a) (1.7 g, 4.2 mmol) in THF (25 mL) was added TBAF (1 M solution in THF, 10 mL, 10 mmol) at rt and the resulting mixture was kept stirring for 48 h. After evaporation of the solvent, crude residue was directly chromatographed on silica gel (Fuji-BW-300, 200 g, AcOEt:hexane=1:2) to afford decyne-1,10-diol (4b) (550 mg) as a waxy solid. A stirred mixture of THF (1 mL), diglyme (6 mL), and $LiAlH_4$ (500 mg, 13.1 mmol) was heated under N_2 and a low boiling fraction (THF) was distilled off. A solution of the acetylene (4b) (500 mg, 2.9 mmol) in diglyme (1 mL) was slowly added to this magnetically stirred mixture cooled at -10 °C. Then the temperature was raised and kept at 140 °C for 8 h. The reaction mixture was slowly hydrolyzed with 10 % NaOH. The aqueous slurry was extracted with CH_2Cl_2 (150 mL) and this extracts were washed with brine, dried ($MgSO_4$), and evaporated. Purification of the crude residue (2.2 g) by chromatography (25 g, hexane:AcOEt=1:1) provided the *trans* diol (6a) (450 mg, 89 %) and a trace of *cis* diol (5a) (2 %). 6a: IR 3300, 2925, 2850, 1475 sh, 1450, 1430, 1375, 1060, 965 cm^{-1}; ^1H NMR δ 1.42 (m, 4 H, CH_2), 1.57 (m, 4 H, CH_2), 2.01 (m, 4 H, C=C-CH_2), 3.63 (t,

J=6.6 Hz, 4 H, OCH_2), 5.41 (m, 2 H, HC=CH); MS *m/z* (relative intensity) 172(M^+, 0.6); HRMS Calcd for $C_{10}H_{20}O_2$ *m/z* 172.1464, Found 172.1470.

1,10-Bis(*p*-toluenesulfonyloxy)-5(*Z*)-decene (5b) To an ice-cooled stirred solution of the diol (**5a**) (1.8 g, 10.3 mmol) in pyridine (20 mL) was added TsCl (9.8 g, 51.5 mmol) and the whole was kept stirring at this temperature for 2 h The mixture was diluted with ether (100 mL) and H_2O (50 mL). Workup gave crude residue (10.5 g), which was purified by flash chromatography (silica gel, Fuji-BW-300, 100 g, AcOEt:hexane=1:4) to give the *cis* ditosylate (**5b**) (3.5 g, 99 %): IR 1595, 1350, 1198, 1185, 930 cm^{-1}; ^1H NMR δ 1.36 (m, 4 H, CH_2), 1.62 (m, 4 H, CH_2), 1.95 (m, 4 H, C=C-CH_2), 2.45 (s, 6 H, $ArCH_3$), 4.02 (t, *J*=6.3 Hz, 4 H, OCH_2), 5.27 (m, 2 H, CH=CH), 7.35 (d, *J*=8.0 Hz, 4H, ArH), 7.78 (d, *J*=8.0 Hz, 4 H, ArH); MS *m/z* (relative intensity) 308 (1.9), 136 (100); HRMS Calcd for $C_{17}H_{24}O_3S$ (M-TsOH) *m/z* 308.1447, Found 308.1414.

1,10-Bis(*p*-toluenesulfonyloxy)-5(*E*)-decene (6b) **6b** was obtained as a colorless oil (3.7 g, 95 %) according to the same procedure as described for **5b** starting from **6a** (1.5 g, 8.8 mmol), pyridine (7 mL), and TsCl (4.3 g, 22.6 mmol): IR 1600, 1360, 1190, 1180, 960 sh, 940 cm^{-1}; ^1H NMR δ 1.35 (m, 4 H, CH_2), 1.62 (m, 4 H, CH_2), 1.91 (m, 4 H, CH_2), 2.45 (s, 6 H, $ArCH_3$), 4.01 (t, *J*=6.3 Hz, 4 H, OCH_2), 5.28 (m, 2 H, HC=CH), 7.35 (d, *J*=8.0 Hz, 4 H, ArH), 7.78 (d, *J*=8.2 Hz, 4 H, ArH); MS *m/z* (relative intensity) 482 (M^+, 0.4); HRMS Calcd for $C_{17}H_{24}O_3S$ (M-TsOH) *m/z* 308.1447, Found 308.1515.

N-(*p*-Toluenesulfonyl)-6(*Z*)-azacycloundecene (8a) To a mixture of the ditosylate (**5b**) (880 mg, 1.9 mmol) in benzene (1450 mL) and H_2O (37 mL) was added *n*-Bu_4NI (994 mg, 2.6 mmol), $TsNH_2$ (566 mg, 3.3 mmol), and NaOH (16 g) at rt. The whole mixture was then gently refluxed (bath temp. 100 °C) for 4 h with mechanical stirring and the organic layer was separated. Aqueous layer was further extracted with ether (15 mL x 3) and the combined organic layer was washed with brine (100 mL x 2), dried ($MgSO_4$) and evaporated. Purification of the crude product (1.9 g) by flash chromatography (silica gel, Fuji-BW-300, 120 g, AcOEt:hexane=1:7) gave **8a** (442 mg, white powder, 74 %) as a less polar major product along with small amount of more polar dimer (**22**, 13 mg, white powder, 1 %) and recovered starting material (8 mg, 1 %). **8a**: mp 117.5-119.0 °C (hexane); IR 1600, 1330, 1160 cm^{-1}; ^1H NMR δ 1 56 (m, 4 H, CH_2), 1.67 (m, 4 H, CH_2), 2.29 (d-like, 4 H, CH_2), 2.42 (s, 3 H, $ArCH_3$), 3.14 (t, *J*=6.5 Hz, 4 H, NCH_2), 5.37 (m, 2 H, HC=CH), 7.28 (d, *J*=8.0 Hz, 2 H, ArH), 7.67 (d, *J*=8.0 Hz, 2H, ArH); ^{13}C NMR δ 21.47, 24.79, 25.87, 26.33, 50.60, 127.18, 129.56, 130.71, 136.67, 142.91; MS *m/z* (relative intensity), 307 (M^+, 26.3); HRMS Calcd for $C_{17}H_{25}NO_2S$ *m/z* 307.1608, Found 307.1603.; Anal. Calcd for $C_{17}H_{25}NO_2S$: C, 66.41; H, 8.20; N, 4.56. Found: C, 66.40; H, 8.18; N, 4.48. **22**: mp 141.0~141.5 °C (hexane-AcOEt); IR 2970, 2890, 1610, 1475, 1355, 1155 cm^{-1}; ^1H NMR δ 1.34 (m, 8 H, CH_2), 1.53 (m, 8 H, CH_2), 2.02 (q-like, 8 H, CH_2), 2.41 (s, 6 H, $ArCH_3$), 3.04 (t, *J*=7.4 Hz, 8 H, NCH_2), 5.34 (m, 4 H, HC=CH), 7.28 (d, *J*=8.2 Hz, 4 H, ArH), 7.66 (d, *J*=8.2 Hz, 4H, ArH); ^{13}C NMR δ 21.47, 26.53, 26.90, 28.78, 48.86, 127.11, 129.59, 129.75, 136.70, 142.96; MS *m/z* (relative intensity), 614 (M^+, 0.1); Anal. Calcd for $C_{34}H_{50}N_2O_4S_2$: C, 66.41; H, 8.20; N, 4.56. Found: C, 66 33; H, 8.22; N, 4.43.

N-(*p*-Toluenesulfonyl)-6(*E*)-azacycloundecene (9a) **9a** was obtained as white crystals (138 mg, 61 %) along with **23** (22%), starting from **6b** (322 mg, 0.7 mmol), $TsNH_2$ (214 mg, 1.3 mmol), *n*-Bu_4NI (356 mg), and NaOH (6 g) in benzene (550 mL) and H_2O (14 mL), according to the same procedure as described for **8a**. **9a**: mp 102.5-103.5 °C (hexane); IR 1600, 1335, 1160, 995, 925, cm^{-1}; ^1H NMR δ 1.28 (m, 4 H, CH_2), 1.44 (m, 4 H, CH_2), 2.08 (m, 4 H, CH_2), 2.41 (s, 3 H, $ArCH_3$), 3.22 (t, *J*=8.0 Hz, 4 H, NCH_2), 5.39 (m, 2 H, HC=CH), 7.25 (d, *J*=6.9 Hz, 2 H, ArH), 7.68 (d, *J*=8.5 Hz, 2 H, ArH); ^{13}C NMR δ 21.47, 23.03, 25.00, 34 49, 44.57, 126.95, 129.50, 130.68, 138.52, 142.70; MS *m/z* (relative intensity) 307 (M^+, 28.0); HRMS Calcd for $C_{17}H_{25}NO_2S$ *m/z* 307.1608, Found 307.1611; Anal. Calcd for $C_{17}H_{25}NO_2S$: C, 66.41; H, 8.20; N, 4.56. Found. C, 66.64; H,

8.21; N, 4.51. **23**: mp 148.0~148.5 °C (hexane-AcOEt); IR 2975, 2800, 1615,1485, 1350, 1170 cm^{-1}; ^1H NMR δ 1.34 (m, 8 H, CH_2), 1.52 (m, 8 H, CH_2), 1.98 (q-like, 8 H, CH_2), 2.42 (s, 6 H, $ArCH_3$), 3.04 (t, *J*=7.6 Hz, 8 H, NCH_2), 5.33 (m, 4 H, HC=CH), 7.28 (d, *J*=8.1 Hz, 4 H, ArH), 7.67 (d, *J*=8.1 Hz, 4H, ArH); ^{13}C NMR δ 21.47, 26.13, 27.57, 31.73, 48.11, 127.12, 129.58, 130.45, 136.83, 142.93; MS *m/z* (relative intensity), 614 (M^+, 0.1); Anal. Calcd for $C_{34}H_{50}N_2O_4S_2$: C, 66.41; H, 8.20; N, 4.56. Found: C, 66.43; H, 8.18; N, 4.42.

6(Z)-Azacycloundecene (8b) Method i: To a stirred solution of the tosylamide (**8a**) (489 mg, 1.6 mmol) in toluene (8 mL) was added at rt Red-Al (70 % in toluene solution, 2.3 mL, ca. 10 eq.) under Ar atm. The mixture was heated under reflux for 12 h. The mixture was diluted with CH_2Cl_2 (10 mL) followed by addition of 10 % NaOH (2 mL). Extraction with CH_2Cl_2 (200 mL) and usual workup gave crude residue. Purification by chromatography (13 g, CH_2Cl_2:AcOEt:Et_3N=4:4:1) afforded the amine (**8b**) (141 mg, 58 %) as a colorless oil: IR 3300 br, 1650 cm^{-1}; ^1H NMR δ 1.54 (m, 8 H, CH_2), 2.28 (m, 4 H, CH_2), 2.68 (m, 4 H, NCH_2), 5.36 (m, 2 H, HC=CH); MS *m/z* (relative intensity) 153 (M^+, 30); HRMS Calcd for $C_{10}H_{19}N$ *m/z* 153.1519, Found 153.1530.

Method ii: A solution of sodium naphthalenide in DME [8] was prepared by adding DME (6 mL) to a mixture of sodium (0.17 g, 7.0 mmol) and naphthalene (1.2 g, 10 mmol) and stirring the resulting mixture at rt for 2 h. A solution of the tosylamide (**8a**) (200 mg, 0.7 mmol) in DME (12 mL) was cooled to -78 °C. The sodium naphthalenide solution (ca. 2 mL) was added dropwise to the well stirring tosylamide solution until a light blue color persisted. The reaction mixture was stirred at -78 °C for 1 h and quenched by addition of saturated $NaHCO_3$ (1 mL). Anhydrous K_2CO_3 (6 g) was added, and the mixture was stirred at rt for 6 h. The mixture was filtered and the precipitates were rinsed with ether. The combined filtrates were concentrated *in vacuo*, and the residue was chromatographed (8 g, CH_2Cl_2:Et_2O:Et_3N=7:2:1) to give **8b** (102 mg, ~100 %) as a colorless oil.

6(*E*)-Azacycloundecene (9b) **9b** was obtained as a colorless oil (153 mg, ~100 %) starting from **9a** (307 mg, 1.0 mmol) using the same procedure as described for **8b** (Method ii). **9b**: IR 3450, 980, cm^{-1}; ^1H NMR δ 1.51 (d, *J*=2.7 Hz, 8 H, CH_2), 2.03 (d, *J*=4.1 Hz, 4 H, CH_2), 2.59 (t, *J*=5.5 Hz, 4 H, NCH_2), 5.59 (m, 2 H, HC=CH); MS *m/z* (relative intensity) 153 (M^+, 17); HRMS Calcd for $C_{10}H_{19}N$ *m/z* 153.1519, Found 153.1505.

1-(2-Hydroxyethyl)-β-carboline (10a) To a stirred suspension of $LiAlH_4$ (270 mg, 7.1 mmol) in THF (20 mL) was added a solution of the β-carboline (**11b**) (280 mg, 1.1 mmol) in THF (20 mL) at rt and the resulting mixture was kept stirring at rt for 2 h. The mixture was quenched by addition of brine (2 mL) and stirred for 0.5 h. Dilution with AcOEt (~30 mL) and addition of Na_2SO_4 powder led to clear organic phase. Filtration with repeated washing gave crude product after evaporation of the dried (MgSO4) solvent. Purification by chromatography (30 g, $CHCl_3$:AcOEt:MeOH=7:2:1) gave the alcohol (**10a**) (220 mg, 93 %), mp 178-182 °C, as a slightly yellow solid, which could be recrystallized from MeOH to furnish colorless prisms: mp 195.5-197.0 °C (reported [9] mp 192 °C (MeOH)) ; UV 214, 235, 240, 250, 282, 288, 336, 350; IR 3400, 3175, 750 cm^{-1}; ^1H NMR δ 3.33 (t, *J*=5.3 Hz, 2 H, CH_2), 4.10 (bs, 1 H, OH), 4.25 (t, *J*=5.3 Hz, 2 H, OCH_2), 7.30 (t-like, 1 H, ArH), 7.53 (t-like, 1 H, ArH), 7.54 (m, 1 H, ArH), 7.86 (d, *J*=5.2 Hz, 1 H, ArH), 8.12 (d, *J*=7.8, 1 H, ArH), 8.35 (d, *J*=5.2 Hz, 1 H, ArH), 8.63 (bs, 1 H, NH); MS *m/z* (relative intensity) 212 (M^+, 40); Anal. Calcd for $C_{13}H_{12}N_2O$: C, 73.57; H, 5.70; N, 13.20. Found C, 73.53; H, 5.76; N, 13.15.

N-(Indol-3-yl-ethyl)-2-methoxycarbonylacetamide (14a) To a stirred and cooled (0 °C) solution of tryptamine (8 g, 50.0 mmol) was added simultaneously and slowly over a period of 30 min a solution of methyl malonyl chloride (7.5 g, 54.8 mmol) in CH_2Cl_2 (100 mL) and aqueous NaOH solution (NaOH: 3 g + H_2O: 100 mL) with vigorous stirring. The resulting mixture was kept stirring at rt for 1 h. After TLC analysis (CH_2Cl_2:AcOEt=3:1), the mixture was diluted with CH_2Cl_2 (50 mL) and 5 % HCl (10 mL)

was added. Acidic aqueous layer was separated and organic layer was washed with saturated $NaHCO_3$ (10 mL x2) and dried. Evaporation of the solvent gave crude material (12.0 g) which was purified by chromatography (100 g, CH_2Cl_2:AcOEt=4:1) to afford the ester-amide (**14a**) (9.9 g, 76 %) as a slightly yellow oil: IR 3350, 3300, 1730, 1650, 1550, 1200, 1100, 740 cm^{-1}; ^1H NMR δ 2.91 (t, *J*=6.6 Hz, 2 H, CH_2), 3.02 (m, 2 H, CH_2), 3.48 (m, 2 H, N-CH_2), 3.82 (s, 3 H, CH_3), 6.64 (d, *J*=2.2 Hz, 1 H, NH), 7.11 (m, 1 H, ArH), 7.21 (m, 1 H, ArH), 7.34 (m, 1 H, ArH), 7.51 (m, 1 H, ArH), 7.76 (s-like, 1 H, ArH), 8.78 (s, 1 H, NH); MS *m/z* (relative intensity) 260 (M^+, 0.3). By the same procedure, starting with tryptamine (2.5 g, 15.6 mmol) and ethyl malonyl chloride (3.5 g, 27.2 mmol), 4.0 g (93 %) of **14b** was obtained as a yellow oil: IR 3400 sh, 3300, 1730, 1660, 1550 cm^{-1}; ^1H NMR δ 1.23 (t, *J*=7.5 Hz, 3 H, CH_3), 2.98 (t, *J*=7.0 Hz, 2 H, CH_2), 3.24 (s, 2 H, CH_2), 3.61 (q, *J*=7.0 Hz, 2 H, N-CH_2), 4.12 (q, *J*=7.5 Hz, 2 H, OCH_2), 7.00~7.20 (m, 4 H, ArH, NH), 7.35 (d, *J*=7.5 Hz, 1 H, ArH), 7.59 (d, *J*=7.5 Hz, 1 H, ArH), 8.35 (s, 1 H, NH); MS *m/z* (relative intensity) 274 (M^+, 10).

1(Z)-(Ethoxycarbonylmethylidene)-tetrahydro-β-carboline (15b) The amide ester (**14b**) (4.3 g, 15.6 mmol) in $POCl_3$ (25 mL) was stirred at rt for 12 h . Excess $POCl_3$ was evaporated *in vacuo* and the residue was carefully basified with saturated $NaHCO_3$ and extracted with CH_2Cl_2. Usual workup gave crude product (4.1 g) which was purified by chromatography (260 g, CH_2Cl_2:AcOEt=10:1) to give **15b** as a yellow oil (2.5 g, 61 %): IR 3330, 1635, 1600, 1535, 740 cm^{-1}; ^1H NMR δ 1.30 (t, *J*=7.0, 3 H, CH_3), 2.99 (t, *J*=6.9 Hz, 2 H, CH_2), 3.56 (dt, *J*=2.47, 6.87 Hz, 2 H, NCH_2), 4.17 (q, *J*=7.14 Hz, 2 H, OCH_2), 4.90(s, 1 H, C=CH), 7.14 (t-like, 1 H, ArH), 7.28 (m, 1 H, ArH), 7.36 (d-like, 1 H, ArH), 7.57 (d-like, 1 H, ArH), 8.15 (bs, 1 H, NH), 8.29 (bs, 1 H, NH); MS *m/z* (relative intensity) 256 (M^+, 25).

1-Methoxycarbonylmethyl-β-carboline (11a) To a preheated (~40 °C) solution of the enaminoester (**15a**) (2.0 g, 8.3 mmol) in *p*-cymene (70 mL) was added 10 % Pd-C (3.0 g) in one portion and the mixture was immediately heated to 160-170 °C (bath temp.) for 10 min with vigorous stirring. After TLC analysis, the mixture was cooled to rt and diluted with AcOEt (~100 mL) and filtrated to remove the catalyst. Combined AcOEt filtrates were evaporated (bath temp. ~70 °C). Purification of the residue by chromatography (200 g, CH_2Cl_2→CH_2Cl_2:AcOEt=1:1) afforded the β-carboline (**11a**) (1.3 g, 67 %) as a yellow caramel: IR 3050, 1730, 1622, 1560, 1500, 1475, 1450, 1430, 1320, 1240, 1200, 740 cm^{-1}; ^1H NMR δ 3.70 (s, 3 H, CH_3), 4.23 (s, 2 H, CH_2), 7.29 (m, 1 H, ArH), 7.54 (m, 2 H, ArH), 7.90 (d, 1 H, ArH), 8.11 (d, *J*=7.6 Hz, 1 H, ArH), 8.39 (d, *J*=5.3 Hz, 1 H, ArH), 9.43 (s, 1 H, NH); MS *m/z* (relative intensity) 242 (M^+, 45).

1-Ethoxycarbonylmethyl-β-carboline (11b) **11b** was prepared in 32 % overall yield starting from tryptamine and ethyl malonyl chloride, according to the same reaction sequence as described for **11a**, **11b**: IR 3500-2500 br, 1730, 1630, 750 cm^{-1}; ^1H NMR δ 1.26 (t, *J*=7.1 Hz, 3 H, CH_3), 4.19 (m, *J*=7.1 Hz, 4 H, CH_2), 7.29 (m, 1 H, ArH), 7.54 (m, 2 H, ArH), 7.90 (d, *J*=5.3 Hz, 1 H, ArH), 8.12 (m, 1 H, ArH), 8.39 (d, *J*=5.3 Hz, 1 H, ArH), 9.29 (s, 1 H, NH); MS *m/z* (relative intensity) 254 (M^+, 75.5); HRMS Calcd for $C_{15}H_{14}N_2O_2$ *m/z* 254.1056, Found 254.1041.

Preparation of the model compound (17) To a cooled (0 °C) solution of 2-hydroxyethylpyridine (2.46 g, 20 mmol) and triethylamine (4.20 ml, 30 mmol) in CH_2Cl_2 (50.0 mL) was added MsCl (2.3 ml, 30 mmol) and the resulting mixture was kept stirring for 15 min. The mixture was then diluted with saturated $NaHCO_3$ and CH_2Cl_2 and extracted with CH_2Cl_2. Organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvents gave crude residue (5.10 g), which was purified by column chromatography (200g, CH_2Cl_2:AcOEt=10:1) to afford the mesylate (**16**, 3.87 g, 96.3 %) as a yellow oil; **16**: IR 3020, 2945, 1595, 1570, 1480, 1350, 1180 cm^{-1}; ^1H NMR δ 3.00 (s, 3 H, CH_3), 3.30 (t, *J*=7.0 Hz, 2 H, CH_2), 4.75 (t, *J*=7.0 Hz, 2 H, O-CH_2), 7.20~7.35 (m, 2 H, ArH), 7.70 (t, *J*=7.0 Hz, 1 H, ArH), 8.60 (d-like, 1 H, ArH). A mixture of **16** (730 mg, 3.64 mmol),

azacyclooctane (453 mg, 4 mmol) and K_2CO_3 (1.60 g, 12 mmol) in CH_3CN (12 ml) was heated at 100 °C for 5 h. After dilution with CH_2Cl_2, the mixture was filtered to remove insoluble precipitates and the filtrate was concentrated to give crude residue (1.17 g), which was purified by column chromatography (50 g, CH_2Cl_2:AcOEt:MeOH=7:2:1) to afford **17** (757 mg, 86.8 %) as a yellow oil; **17**: 2910, 2850, 2800, 1590, 1570, 1475, 1440, 1360, 1100 cm^{-1}; ^1H NMR δ 1.75 (brs, 10 H), 2.70 (m, 4 H), 2.80~3.05 (m, 4 H), 7.10 (m, 1 H, ArH), 7.20 (d, *J*=6.0 Hz, 1 H, ArH), 7.60 (t, *J*=6.0 Hz, 1 H, ArH), 8.55 (d-like, 1 H, ArH); MS *m/z* (relative intensity) 218 (M^+, 5).

N-(1-β-Carbolinylacetyl)-6(Z)-azacycloundecene (18)

Method i: **18** from **11a** A mixture of the β-carboline methylester (**11a**) (132 mg, 0.5 mmol) and 6(*Z*)-azacycloundecene (**8b**) (79 mg, 0.5 mmol) in toluene (5 mL) was heated under reflux for 132 h. Evaporation of the solvent and purification by flash chromatography (silica gel, Fuji-BW-300, 20 g, CH_2Cl_2:AcOEt=12:1) afforded the amide (**18**) (87 mg, 46 %) as a slightly yellow amorphous solid along with the recovered methyl ester (**11a**) (15 mg, 11 %). **18**: IR 3450, 1625, 740 cm^{-1}; ^1H NMR δ 1.46 (m, 4 H, CH_2), 1.67 (m, 4 H, CH_2), 2.19 (m, 4 H, CH_2), 3.33 (m, 2 H, NCH_2), 3.56 (m, 2 H, NCH_2), 4.26 (s, 2 H, CH_2), 5.34 (m, *J*=5.7 Hz, 2 H, HC=CH), 7.26 (m, 1 H, ArH), 7.54 (m, 2 H, ArH), 7.87 (d, *J*=5.2 Hz, 1 H, ArH), 8.09 (d, *J*=9.0 Hz, 1 H, ArH), 8.33 (d, *J*=5.2 Hz, 1 H, ArH), 10.14 (s, 1 H, NH); MS *m/z* (relative intensity) 361 (M^+, 23.7); HRMS Calcd for $C_{23}H_{27}N_3O$ *m/z* 361.2156, Found 361.2142.

18 from **11b** Similar treatment of β-carboline ethyl ester (**11b**) (470 mg, 2.0 mmol) and 6(*Z*)-azacycloundecene (**8b**) (250 mg, 1.6 mmol) in toluene (5 mL) for 7 days gave **18** (400 mg, 68 %) along with the recovered ethyl ester (**11b**) (80 mg, 17 %).

Method ii: **18** from **11c** To a solution of **11b** (169 mg, 0.7 mmol) in EtOH (5 mL) was added KOH (0.086 g, 1.3 mmol) in H_2O (1 mL). The reaction mixture was stirred at rt for 2 h and concentrated *in vacuo*. The residue (**11c**) was further evaporated by vacuum pump for 2~3 h at rt. To the residue was added DMF (10 mL), **8b** (102 mg, 0.7 mmol), DPPA (0.3 mL, 1.4 mmol) and triethylamine (0.2 mL, 1.4 mmol). After 12 h of stirring at rt, the reaction mixture was basified with 10 % NaOH and extracted with AcOEt and benzene (3:1). The organic layer was washed with water, dried over sodium sulfate, and stripped off the solvent to furnish a residue (620 mg) which was purified by flash chromatography (silica gel, Fuji-BW-300, 20 g, AcOEt) to yield **18** (202 mg, 87 %) as a colorless amorphous solid.

19 and 20 from 11c The amides (**19** and **20**) were prepared from **11c** (254 mg) and the corresponding amines, (**9b**) (153 mg, 1.0 mmol) and azacycloundecane[7] (146 mg, 0.9 mmol) according to the method described for **18**, in 88 % and 67 % yields, respectively. **19**: IR 3400, 1640, 990, 750 cm^{-1}; H NMR δ 1.32 (m, 4 H, CH_2), 1.65 (m, 4 H, CH_2), 2.13 (s-like, 4 H, CH_2), 3.39 (m, 2 H, NCH_2), 3.52 (m, 2 H, NCH_2), 4.22 (s, 2 H, CH_2), 5.40 (dd, *J*=5.6, 6.4 Hz, 2 H, HC=CH), 7.26 (m, 1 H, ArH), 7.54 (m, 2 H, ArH), 7.87 (d, *J*=5.5 Hz, 1 H, ArH), 8.10 (d, *J*=5.5 Hz, 1 H, ArH), 8.33 (d, *J*=5.2 Hz, 1 H, ArH), 10.07 (s, 1 H, NH); MS *m/z* (relative intensity) 361 (M^+, 20.7); HRMS Calcd for $C_{23}H_{27}N_3O$ *m/z* 361.2156, Found 361.2172.
20: IR 3450, 1625, 740 cm^{-1}; ^1H NMR δ 1.43 (m, 12 H, CH_2), 1.83 (m, 4 H, CH_2), 3.32 (t, *J*=5.9 Hz, 2 H, N-CH_2), 3.60 (t, *J*=5.9 Hz, 2 H, N-CH_2), 4.29 (s, 2 H, $COCH_2$), 7.26 (m, 1 H, ArH), 7.55 (m, 2 H, ArH), 7.87 (d, *J*=5 3 Hz, 1 H, ArH), 8.11 (d, *J*=7.8 Hz, 1 H, ArH), 8.33 (d, *J*=5.5 Hz, 1 H, ArH), 10.18 (s, 1 H, NH); MS m/z (relative intensity) 363 (M^+, 33.7); HRMS Calcd for $C_{23}H_{29}N_3O$ *m/z* 363.2313, Found 363.2320.

Manzamine C (1) from the Mesylate (10c) To a stirred solution of the alcohol (**10a**) (150 mg, 0.7 mmol) in CH_2Cl_2 (7 mL) was added at 0 °C triethylamine (0.5 mL) and MsCl (0.3 mL) and the whole was kept stirring for 0.5 h. Dilution with ether (30 mL)

and saturated $NaHCO_3$ (20 mL) followed by usual workup gave crude product, which was purified by chromatography (50 g, CH_2Cl_2:AcOEt:MeOH=7:2:1) to afford the mesylate (**10c**) (110 mg, 54 %) as a yellow amorphous solid: IR 3500-2500 br, 1630, 1350, 1170 cm^{-1}; ^1H NMR δ 3.16 (s, 3 H, CH_3), 3.39 (m, 2 H, CH_2), 4.81 (t, *J*=6.4 Hz, 2 H, O-CH_2), 7.29 (m, 1 H, ArH), 7.57 (m, 2 H, ArH), 7.86 (m, 1 H, ArH), 8.07 (d, *J*=7.9 Hz, 1 H, ArH), 8.33 (t, *J*=5.5 Hz, 1 H, ArH), 10.24 (s, 1 H, NH). A mixture of the mesylate (**10c**) (110 mg, 0.4 mmol), 6(Z)-azacycloundecene (**8b**) (ca. 1.5 g, 1.0 mmol), and K_2CO_3 (150 mg, 1.1 mmol) in CH_3CN (3 mL) was heated at 100 °C for 3 h. After dilution with CH_2Cl_2, the mixture was filtrated to remove insoluble precipitates. Concentration of the filtrate gave crude residue which was purified by chromatography (7 g, CH_2Cl_2:AcOEt:MeOH=7:2:1) to give manzamine C (**1**) (14 mg, 10 %) as a yellow amorphous solid. UV: 214, 234, 239 sh, 248 sh, 282 sh, 288, 335, 349; IR 3000, 2910, 1630, 1440, 1425, 740 cm^{-1}; ^1H NMR δ 1.52 (m, 4 H, CH_2), 1.77 (m, 4 H, CH_2), 2.32 (m, 4 H, CH_2), 2.85 (t-like, *J*=7.5, 7.5 Hz, 4 H, NCH_2), 2.92 (dd-like, *J*=5.2, 5.2 Hz, 2 H, CH_2), 3.31 (dd-like, *J*=5.2, 5.2 Hz, 2 H, N-CH_2), 5.48 (m, 2 H, HC=CH), 7.25 (m, 1 H, ArH), 7.51 (m, 2 H, ArH), 7.81 (d, *J*=5.5 Hz, 1 H, ArH), 8.11 (d, *J*=7.9 Hz, 1 H, ArH), 8.26 (d, *J*=5.2 Hz, 1 H, ArH), 12.72 (s, 1 H, NH) ; ^{13}C NMR δ 23.33, 24.93, 26.03, 34.46, 48.97, 52.77, 111.89, 113.10, 119.14, 121.71, 121.97, 127.70, 128.34, 130.98, 135.56, 137.46, 140.75, 145.50; MS *m/z* (relative intensity) 347 (M^+, 3.5); HRMS Calcd for $C_{23}H_{29}N_3$ *m/z* 347.2364, Found 347.2392.

Manzamine C (1) from the Amide (18) To a cooled and stirred solution of the amide (**18**) (336 mg, 0.9 mmol) in THF (60 mL) was added $LiAlH_4$ (170 mg, 4.5 mmol) and the mixture was kept stirring at rt for 0.5 h. The mixture was then quenched by careful addition of 10 % NaOH and stirring was continued to obtain a clear organic layer. The mixture was extracted with CH_2Cl_2 (~200 mL) and dried over anhydrous K_2CO_3. Evaporation of the solvent gave crude product which was purified by flash chromatography (silica gel, Fuji-BW-300, 12 g, Et_2O:MeOH=40:1→8:1) to give manzamine C (**1**) (148 mg, 46 %) as a yellow caramel. Recrystallization of this material from ether-CH_2Cl_2 afforded slightly yellow prisms, mp 79-83 °C. Further recrystallization from CH_3CN-$CHCl_3$ finally furnished colorless prisms of mp 90.0-92.0 °C.

Manzamine C *trans* isomer: N-(1-β-Carbolinylethyl)-6(*E*)-azacycloundecene (2) To a solution of **19** (300 mg, 0.8 mmol) in THF (50 mL) was added $LiAlH_4$ (360 mg, 9.7 mmol). The mixture was stirred at rt for 1 h and concentrated *in vacuo*. The residue was basified with 10 % NaOH and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried, and evaporated. The residue (350 mg) was chromatographed [(silica gel, flash column, Fuji-BW-300, 20 g, CH_2Cl_2:AcOEt:MeOH=7:2:1) and (Merck-aluminiumoxide-90, 20 g, CH_3CN)] to give **2** (122 mg, 42 %): mp 145-145.5 °C (from 50% CH_2Cl_2 in CH_3CN); IR 3600-3000 br, 1615, 975, 740 cm^{-1}; ^1H NMR δ 1.39 (s-like, 4 H, CH_2), 1.68 (s-like, 4 H, CH_2), 2.19 (s-like, 4 H, CH_2), 2.84 (t-like, *J*=8.0 Hz, 4 H, N-CH_2), 2.92 (m, 2 H, NCH_2), 3.33 (t-like, *J*=5.2 Hz, 2 H, NCH_2), 5.51 (t-like, *J*=4.1 Hz, 2 H, HC=CH), 7.26 (m, 1 H, ArH), 7.51 (m, 2 H, ArH), 7.81 (d, *J*=5.5 Hz, 1 H, ArH), 8.11 (d, *J*=5.5 Hz, 1 H, ArH), 8.26 (d, *J*=5.5 Hz, 1 H, ArH), 12.74 (s, 1 H, NH); ^{13}C NMR δ 22.97, 23.75, 29.89, 34.64, 50.26, 59.76, 111.81, 113.69, 119.53, 121 31, 121.60, 128.16, 129.31, 130.91, 133.51, 136.84, 140.45, 144.74; MS *m/z* (relative intensity) 347 (M^+, 0.8); HRMS Calcd for $C_{23}H_{29}N_3$ *m/z* 347.2364, Found 347.2353.

Dihydromanzamine C (21) Dihydromanzamine C (**21**) was prepared from **20** (217 mg, 0.6 mmol) by a similar method as described for the preparation of **1** and **2** in 62 % yield as pale yellow prisms: mp 151-153 °C (from 50 % CH_2Cl_2 in CH_3CN); IR 3500-3000 br, 745 cm^{-1}, ^1H NMR δ 1.52 (m, 16 H, CH_2), 2.64 (m, 4 H, CH_2), 2.99 (t, *J*=6.6 Hz, 2 H, N-CH_2), 3.32 (t, *J*=6.6 Hz, 2 H, N-CH_2), 7.26 (m, 1 H, ArH), 7.54 (m, 2 H, ArH), 7.81 (d, *J*=5.2 Hz, 1 H, ArH), 8.11 (d, *J*=7.7 Hz, 1 H, ArH), 8.34 (d, *J*=5.2 Hz, 1 H, ArH), 10.14 (s, 1 H, NH); MS *m/z* (relative intensity) 349 (M^+, 4.7); HRMS Calcd for $C_{23}H_{31}N_3$ *m/z* 349.2520, Found 349.2524.

Acknowledgments

We thank Prof. T. Higa, Ryukyu University for sending us data of various manzamines. Finantial support by a Grant-in-Aid for Scientific Research (62470134, 01870092) from the Ministry of Education, Science and Culture, is gratefully acknowledged. We also thank Mr. T. Kuramochi and Mrs. S. Imamoto of The Chemical Analysis Center of our University for Mass spectral measurement and microanalysis.

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