STRUCTURES AND BIOGENESIS OF MANZAMINES AND RELATED ALKALOIDS†

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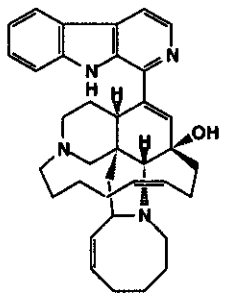
Abstract–Seven new manzamine-related alkaloids have been isolated together with known manzamine alkaloids from the Okinawan marine sponges of the genera *Ircinia* and *Amphimedon*. These alkaloids seem to be biogenetically related to manzamines A ~ C. We propose a plausible biogenetic path of manzamines A ~ C on the basis of the structures and ratios of all the manzamine-related alkaloids isolated from the *Amphimedon* sponge. The structures and biogenesis of other manzamine-related alkaloids from marine sponges are also described.

1. INTRODUCTION

In 1986 Higa and coworker isolated a novel cytotoxic β-carboline alkaloid, named manzamines A (**1**), from a marine sponge *Haliclona* sp. collected off Manzamo, Okinawa, and the structure including absolute configuration was established by X-ray analysis.[1] In the next year the isolation of manzamines B (**2**), C



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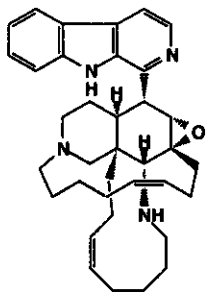

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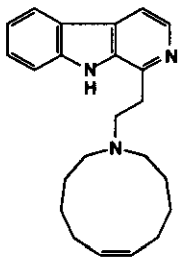

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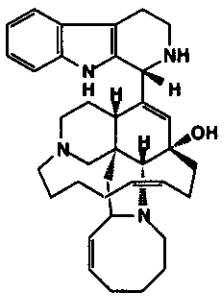

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†Dedicated to the memory of Emeritus Professor Shun-ichi Yamada

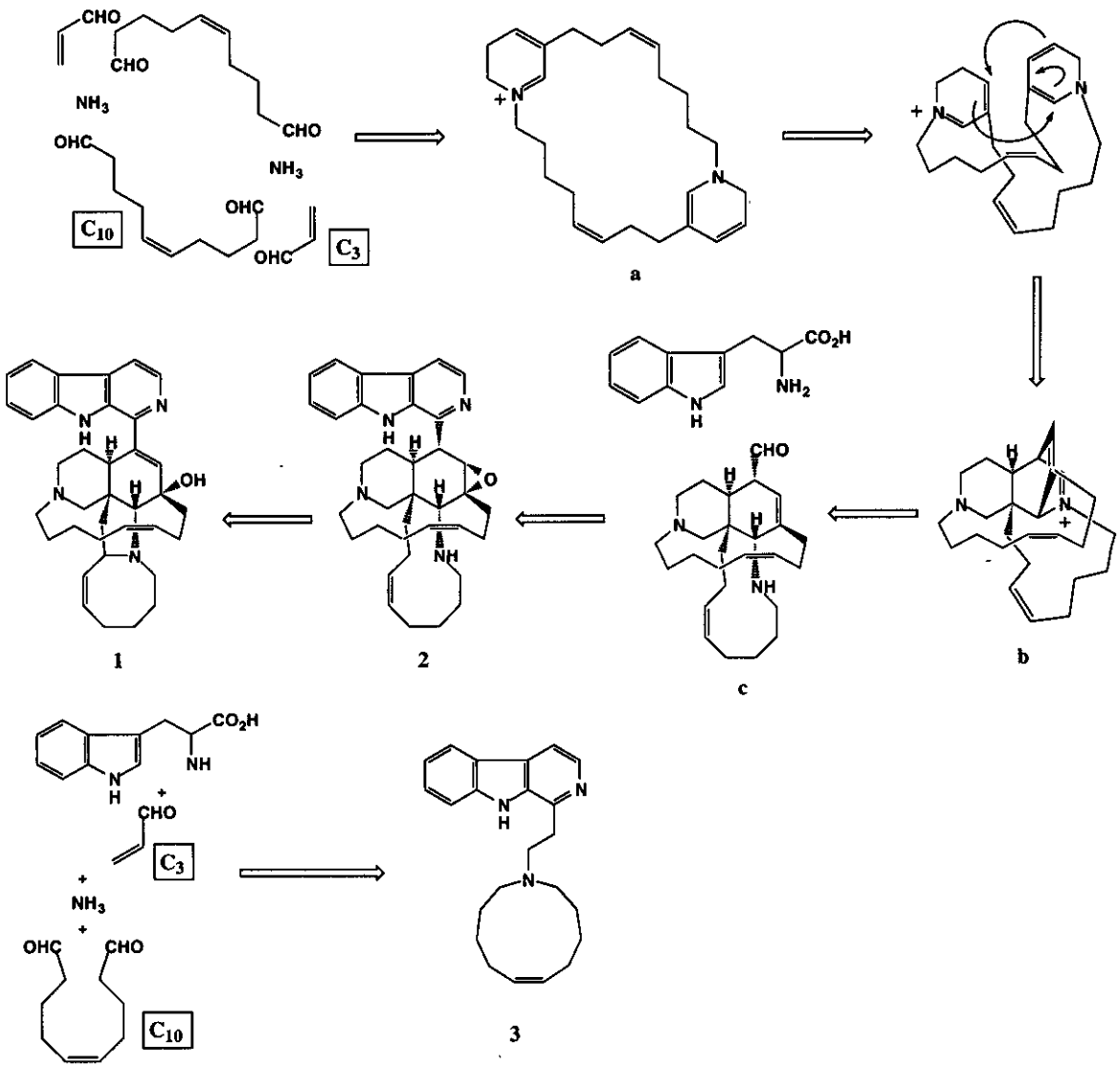
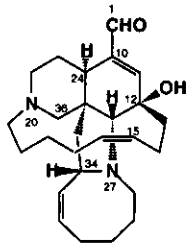


Figure 1. Biogenetic Path of Manzamines A ~ C (**1** ~ **3**) Proposed by Baldwin and Whitehead

(**3**), and D (**4**) from the *Haliclona* sponge was reported.[2,3] At almost the same time our group also isolated keramamines A and B (= manzamines A (**1**) and B (**2**), respectively) from an Okinawan marine sponge *Pellina* sp. independently.[4] The heterocyclic systems at C-1 of manzamines are classified into tthe following two types; one is represented by manzamines A (**1**) and B (**2**) possessing penta- and tetracyclic isoquinoline chromophores, respectively, while another group has an azacycloundecene ring such as manzamine C (**3**). These unusual ring systems have attracted great interest as one of the most challenging targets for total synthesis or for unprecedented biosynthetic path to be resolved.

In 1992 Baldwin and Whitehead proposed a biogenetic path for manzamines A ~ C (**1** ~ **3**) as shown in Figure 1.[5] The proposal suggested that *bis*-3-alkyldihydropyridine macrocycle (**a**), which can be derived from ammonia, a C_3 unit, and a C_{10} unit, might be converted through a Diels-Alder-type [4+2] intramolecular cycloaddition into a pentacyclic intermediate (**b**), which in turn led to manzamines A (**1**) and B (**2**) *via* a tetracyclic intermediate (**c**). Although the Baldwin's biogenetic path was elegant and fascinated many chemists, this proposal was only a hypothesis without any experimental basis. In the same year we have isolated two novel alkaloids, ircinals A (**5**) and B (**6**) from an *Ircinia* sponge,[6] which are very close to the Baldwin's intermiediate **c**. Subsequently our group has obtained a novel manzamine-related alkaloid, keramaphidin B[7] (**7**), which is quite similar to the Baldwin's intermediate **b**, keramaphidin C[8] (**8**) and keramamine C[8] (**9**), which seem to be biogenetic precursors of manzamine C (**3**), and ircinols A (**10**) and B[9] (**11**), which correspond to antipodes of the alcohol forms of ircinals A (**5**) and B (**6**), all isolated from an *Amphimedon* sponge. In this review we describe the isolation and structure elucidation of these manzamine-related alkaloids and plausible biogenetic path of manzamines A ~ C (**1** ~ **3**). Furthermore the strctures and biogenesis of other manzamine-related alkaloids reported by other groups are also described.



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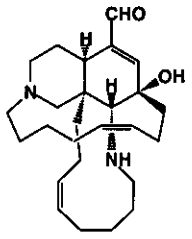

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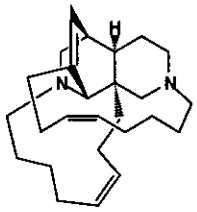

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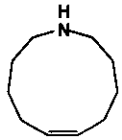

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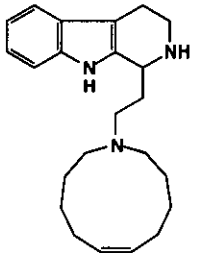

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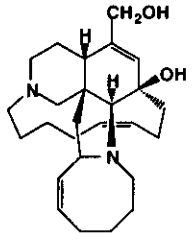

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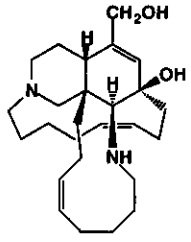

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2. IRCINALS A AND B

In 1991 we started searching for biogenetic precursors of manzamines A ~ C (**1** ~ **3**) in Okinawan marine sponges. During our preliminary screening of the sponge collection, we have found that the extract of a

marine sponge of the genus *Ircinia* (order Dictyoceratida, family Thorectidae), collected off Kise, Okinawa Island, contains some new manzamine-related alkaloids. EtOAc-soluble materials of the methanol extract of the sponge were repeatedly chromatographed on silica gel (hexane/acetone (4:1), $CHCl_3$/MeOH (95:5), and hexane/acetone (9:1)) to afford four new manzamine-related alkaloids, ircinals A (**5**, 0.0057 % wet weight) and B (**6**, 0.0020 %), manzamines H (**12**) and J (**13**) together with known alkaloids, manzamines A (**1**), B (**2**), and D (**4**).[6]

The ^1H and ^{13}C NMR data of ircinal A (**5**) resembled those of manzamine A (**1**) except for lacking the β-carboline moiety. The structure of ircinal A was elucidated to be **5** by analyses of the 2D NMR data (^1H-^1H COSY, HSQC, and HMBC spectra). Absolute configuration of ircinal A (**5**) was confirmed by the chemical correlation with manzamine A (**1**) (Figure 2). Pictet-Spengler cyclization of **5** with tryptamine afforded manzamine D (**4**), which was then transformed into manzamine A (**1**) through DDQ oxidation. The UV, IR , ^1H NMR, and EIMS spectra and $[\alpha]_D$ value of manzamine A derived from **5** were identical with those of natural manzamine A (**1**).

The ^1H and ^{13}C NMR spectra of ircinal B (**6**) were similar to those of **5** except for that the methine proton signal at C-34 of ircinal A (**6**) was not observed in the ^1H NMR spectrum of **6**. These results suggested

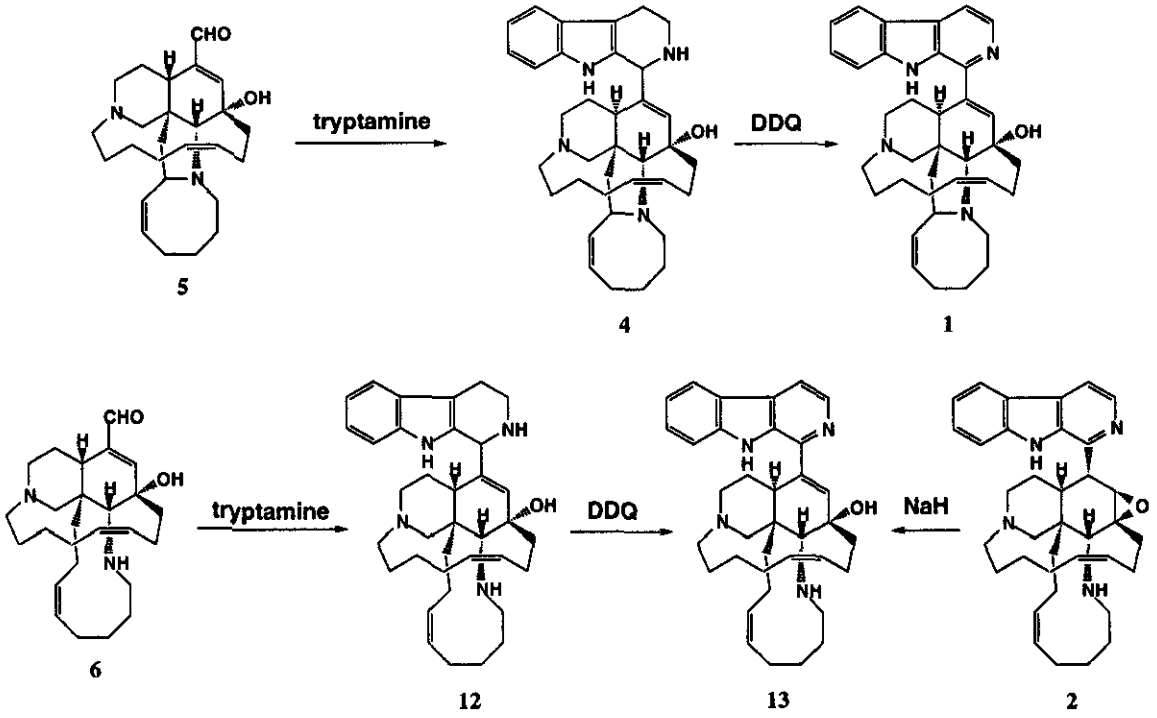


Figure 2. Chemical Correlation of Ircinals A (**5**) and B (**6**) with Manzamines A (**1**) and B (**2**)

that the structure of ircinal B was **6**, corresponding to the compound which the C-N bond between C-34 and N-27 in **5** was disconnected. The structure of **6** was established by the chemical correlation with manzamine B (**2**) as shown in Figure 2. Pictet-Spengler cyclization of **6** with tryptamine afforded manzamine H (**12**), which was then transformed into manzamine J (**13**) through DDQ oxidation. On the other hand, treatment of manzamine B (**2**) with NaH also gave manzamine J (**13**). The UV, IR, ^{1}H NMR, and EIMS spectra and $[\alpha]_D$ value of manzamine J (**13**) prepared from ircinal B (**6**) were identical with those of **13** derived from manzamine B (**2**).

Ircinals A (**5**) and B (**6**) correspond to the tetracyclic intermediate (**c**) in the biogenetic path proposed by Baldwin and Whitehead. Manzamines A (**1**) and B (**2**) may be biogenetically generated from ircinals A (**5**) and B (**6**) through Pictet-Spengler reaction with tryptamine or tryptophan followed by dehydrogenation such as the biomimetic chemical conversion as shown in Figure 2.

3. KERAMAPHIDIN B

Soon after the isolation of ircinals, we investigated extracts of the sponge *Amphimedon* sp. (order Hapaloscerida, family Niphatidae) collected off Kerama Islands, Okinawa, including manzamine-related alkaloids. The TLC pattern of the MeOH extract was different from that of the *Ircinia* sponge. EtOAc and *n*-BuOH-soluble materials of the MeOH extract were chromatographed on silica gel using several Et_2NH-containing solvent systems to afford four new alkaloids lacking a β-carboline moiety, keramaphidins B[7] (**7**, 0.0054 %, wet weight) and C[8] (**8**, 0.0022 %), and ircinols A[9] (**10**, 0.006 %) and B[9] (**11**, 0.0003 %), and four new β-carboline alkaloids, keramamine C[8] (**9**, 0.0026 %), manzamine L[10] (**14**, 0.0056 %), 6-hydroxymanzamine A[11] (= manzamine Y,[12] **15**, 0.005 %), and 3,4-dihydromanzamine A[11] (**16**, 0.002 %) together with known related compounds, manzamines A (**1**, 0.081 %), B (**2**, 0.0072 %), C (**3**, 0.002%), D (**4**, 0.012 %), and H (**12**, 0.0028 %), and ircinals A (**5**, 0.0009 %) and B (**6**, 0.0006 %), and 8-hydroxymanzamine A[13] (= manzamine G,[14] **17**, 0.002%).

The planar structure of keramaphidin B (**7**), $C_{26}H_{40}N_2$, was elucidated by detailed analyses of ^{1}H and ^{13}C NMR data aided with 2D NMR experiments (^{1}H-^{1}H COSY, HOHAHA, HMQC, HMBC, and HMQC-HOHAHA), paticularly HMBC and HMQC-HOHAHA experiments were very useful for assignment of connectivities *via* nitrogen atoms (N-2 and N-7) and of two aliphatic rings (C-11 to C-18 and C-19 to C-26), thereby leading to a gross structure of **7**, consisting an 1,4-etheno-2,7-decahydronaphthylidine core with two macrocyclic rings. Relative stereochemistry of the 1,4-etheno-2,7-

decahydronaphthylidine core and *cis*-geometries of two disubstituted double bonds (Δ^{15} and Δ^{23}) were deduced from analysis of the NOESY spectrum of **7**. The relative stereostructure was established by the X-ray analysis using a suitable crystal of **7** grown in acetonitrile (Figure 3). Interestingly, the X-Ray study revealed that the crystal of **7** was racemic though it possesses four asymmetric centers. The

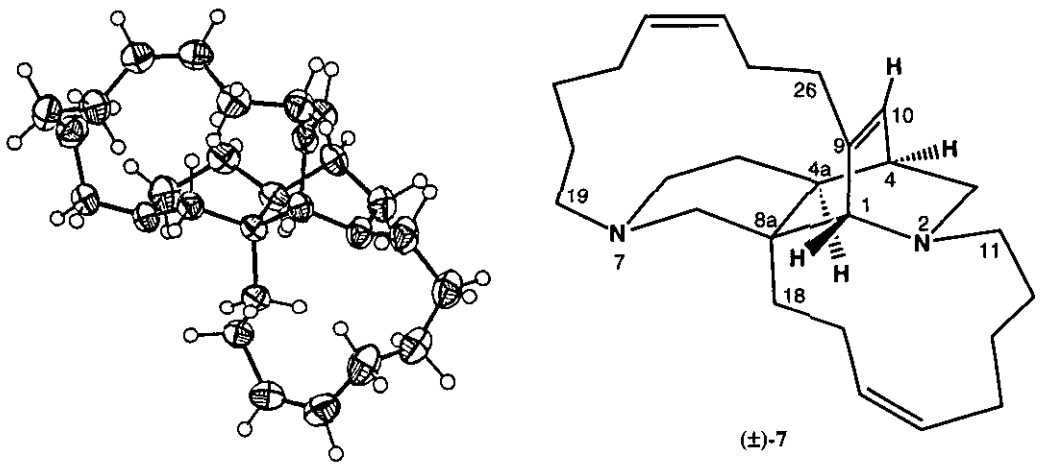


Figure 3. Perspective Drawing of X-ray Model for (±)-Keramaphidin B (**7**).

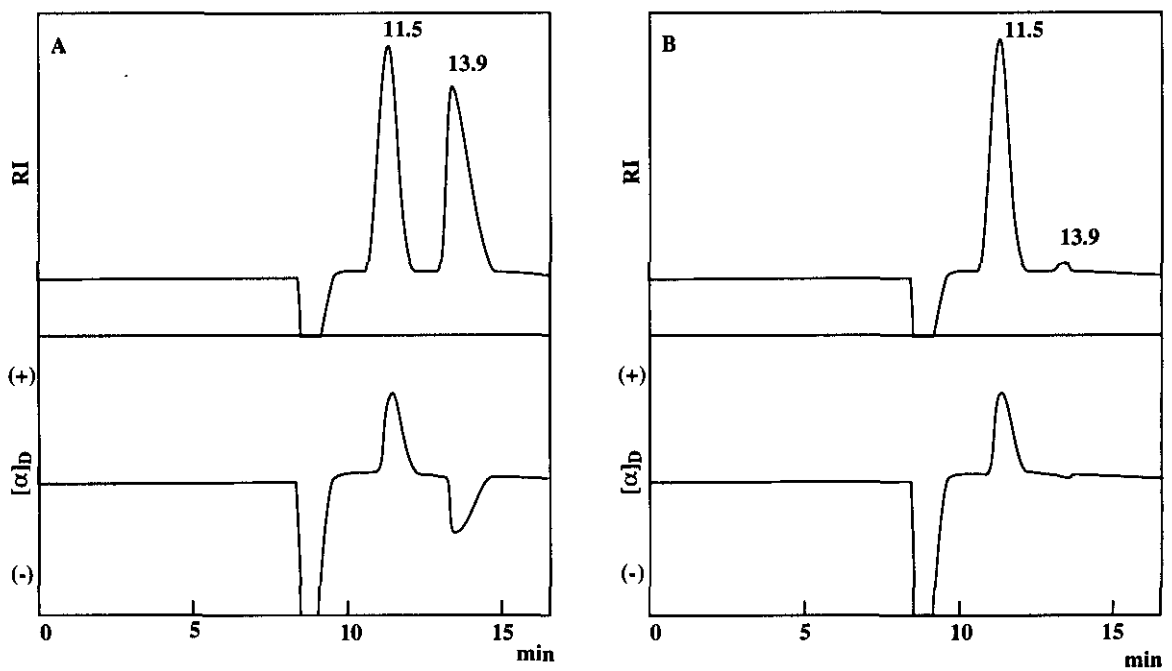


Figure 4. Chiral HPLC of Keramaphidin B (**7**) in Resolution of Crystals (A) and Filtrate (B).
Peaks: t_R 11.5 min, (+)-Keramaphidin B {(+)-**7**}: t_R 13.9 min, (-)-Keramaphidin B {(-)-**7**}; HPLC Condition: eluent, MeOH/H_2O (80:20); column, Chiralpak OP(+) (4.6 i.d. x 250 mm); flow rate; 0.3 mL/min; RI and $[\alpha]_D$ detection; sample injection, 50 μg/100 μL in MeOH.

structure of keramaphidin B (**7**) corresponds to that of the pentacyclic intermediate (**b**) proposed by Baldwin and Whitehead.

Keramaphidin B (**7**) was optically active ($[\alpha]_D^{20}$ +22.2°), while small crystal of **7** obtained from CH_3CN was racemic. Chiral resolution of this racemate was performed by HPLC using a column [Chiralpak OP(+)] packed with (+)-poly(diphenyl-2-pryridylmethyl methacrylate) and eluting with MeOH/H_2O as shown in Figure 4. Chiral HPLC analyses of the crystals and the filtrate of keramaphidin B (**7**) revealed that the ratio of (+)- and (-)-forms was *ca.* 1:1 for the crystals and 20:1 for the filtrate, respectively. On the other hand, the ratio of the crystal and the filtrate of keramaphidin B (**7**) was 5:95. These results suggested that (+)-keramaphidin B {(+)-**7**} was estimated to be *ca.* 97 % in this sponge.[10]

(+)-Keramaphidin B {(+)-**7**} was subjected to reduction with Pd/C, and then oxidation with OsO_4 to give two dihydroxy products (**18** and **19**) in the ratio of *ca.* 9:1 (Figure 5). Relative stereochemistry at C-9 and C-10 of **18** and **19** was elucidated from NOE data. Treatment of **18** with (*R*)-(-)- and (*S*)-(+)-α-

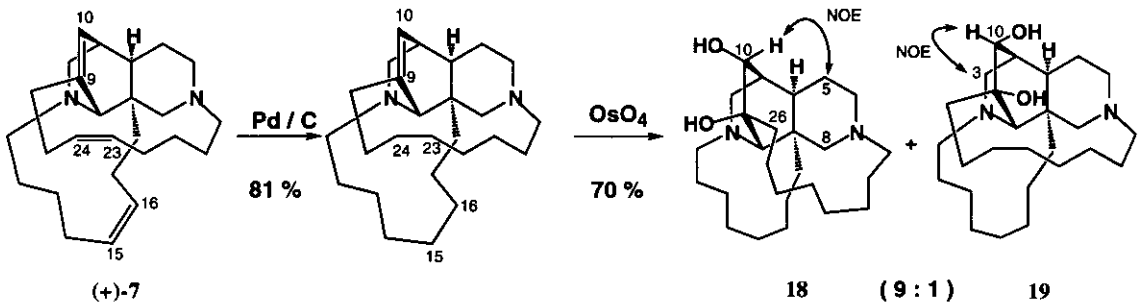


Figure 5. Conversion of (+)-Keramaphidin B {(+)-**7**} into its Dihydroxytetrahydro Derivative (**18**).

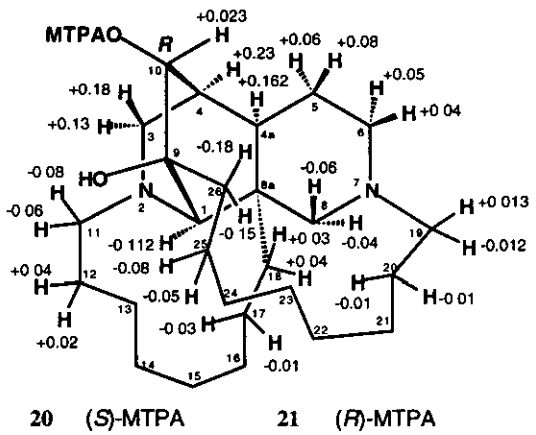


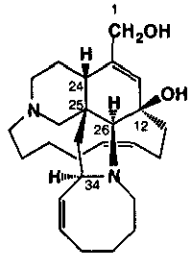
Figure 6. Δδ Values [Δδ (in ppm) = δ*S* -δ*R*] Obtained fro (*S*)- and (*R*)-MTPA Esters (**20** and **21**) of 9,10-Dihydroxy-15,16,23,24-tetrahydrokeramaphidin B (**18**).

methoxy-α-(trifluoromethyl)phenylacetyl chloride (MTPACl) gave the (*S*)- and (*R*)-MTPA esters (**20** and **21**), respectively. The ^{1}H chemical shift differences ($\Delta\delta = \delta_S - \delta_R$) were shown in Figure 6, indicating that the absolute configuration at C-10 of **18** was *R*. Thus the absolute configurations at C-1, C-4, C-4a, and C-8a of (+)-keramaphidin B {(+)-**7**} were concluded to be *R*, *S*, *R*, and *S*, respectively.[15]

4. IRCINOLS A AND B

Ircinols A (**10**) and B (**11**) were isolated from more polar fractions than those containing keramaphidin B (**7**) in the *Amphimedon* sponge. The ^{1}H and ^{13}C NMR data of ircinol A (**10**) were similar to those of ircinal A (**5**) except for the presence of an oxymethylene in **10** in place of the formyl group in ircinal A (**5**). Thus the structure of ircinol A was elucidated to be **10**, corresponding to the alcoholic form at C-1 of **5**. The structure elucidation of ircinol A (**25**) was further substantiated by chemical correlations with ircinal A (**5**). Treatment of **5**, which was simultaneously isolated from the *Amphimedon* sponge, with DIBALH afforded a reductive product (**22**) (Figure 7), of which spectral data were identical with those of ircinol A (**10**). However the sign of the optical rotation was opposite {**22**, $[\alpha]_D^{18}$ +20° (*c* 0.2, MeOH); **10**, $[\alpha]_D^{18}$ -19° (*c* 0.5, MeOH)}. This result revealed that ircinol A (**10**) was an enantiomer of the alcoholic form at C-1 of ircinal A (**5**), which has been shown to have the same absolute configuration as that of manzamine A (**1**).

^{1}H and ^{13}C NMR data of ircinol B (**11**) were similar to those of ircinal B (**6**). The structure of ircinol B (**11**) was confirmed by chemical correlation with ircinal B (**6**) isolated from the *Amphimedon* sponge. Reduction of **6** with DIBALH yielded a reductive product (**23**) (Figure 7), which showed identical spectral data with those of ircinol B (**11**) but the opposite sign of the optical rotation {**23**, $[\alpha]_D^{18}$ +4.2° (*c* 0.2, MeOH); **11**, $[\alpha]_D^{18}$ -2.8° (*c* 0.12, MeOH)}. Thus the absolute stereochemistry of ircinol B was concluded as shown in structure **11**.



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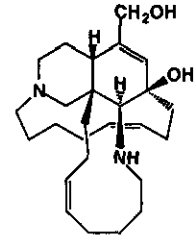

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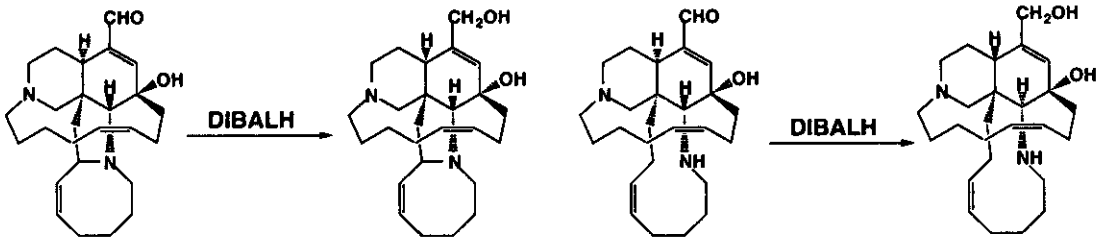

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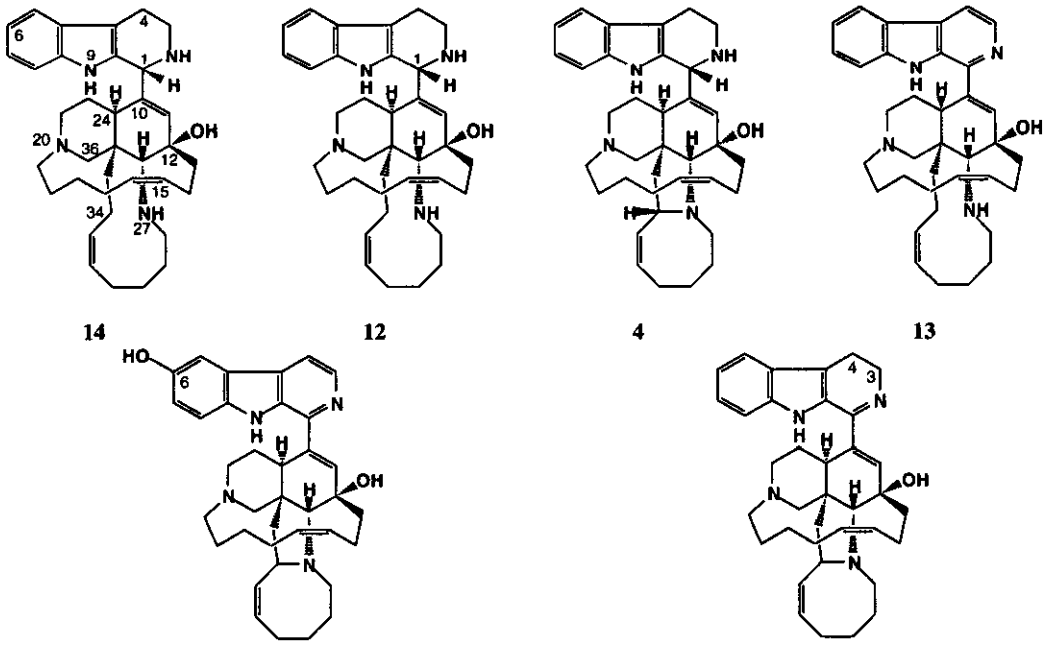
Figure 7. Conversion of Ircinals A (**7**) and B (**6**) into the Alcohol Forms (**22** and **23**).

5. OTHER MANZAMINE-RELATED ALKALOIDS FROM *AMPHIMEDON* SPONGE

Manzamine L[10] (**14**) was isolated from the fractions containing manzamines D (**4**) and H (**12**). Spectral data of manzamine L (**14**) were similar to those of manzamine H (**12**), and the structure of **14** was elucidated to be a stereoisomer at C-1 of **12** on the basis of conversion of **14** with DDQ into manzamine J (**13**). Absolute configurations at C-1 of manzamines D (**4**), H (**12**), and L (**14**) were deduced from the CD data (Figure 8) and the molecular mechanics calculations using Macro Model ver 5.0 (Figure 9) to be *R*, *R*, and *S*, respectively. Interestingly 1*S*-isomer of manzamine D has not been isolated from the



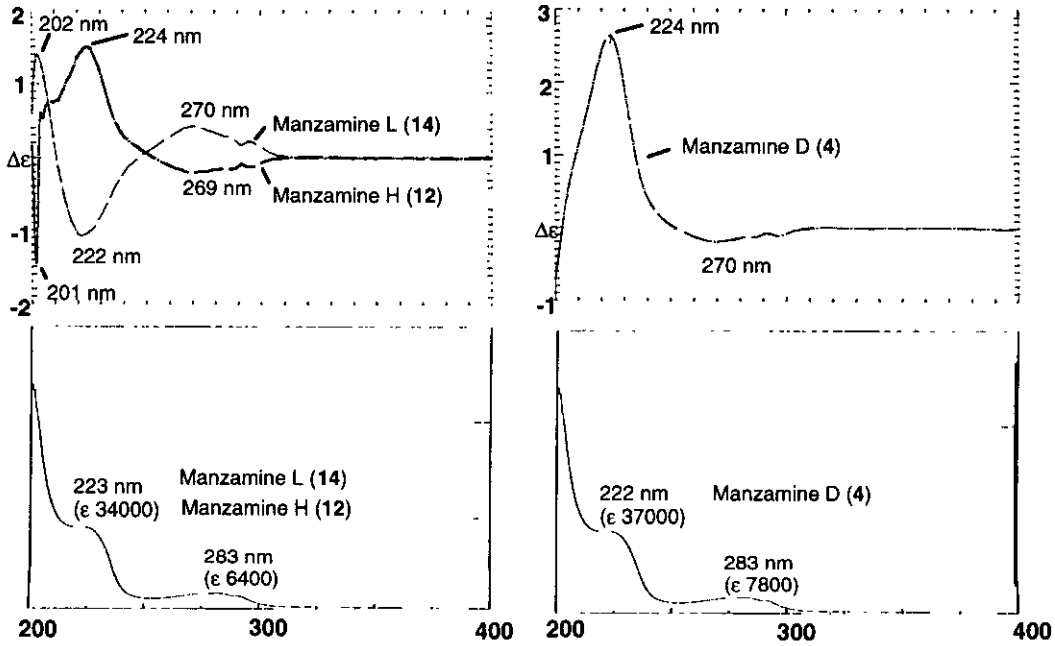


Figure 8. CD and UV Spectra of Manzamines D (**4**), H (**12**), and L (**14**)

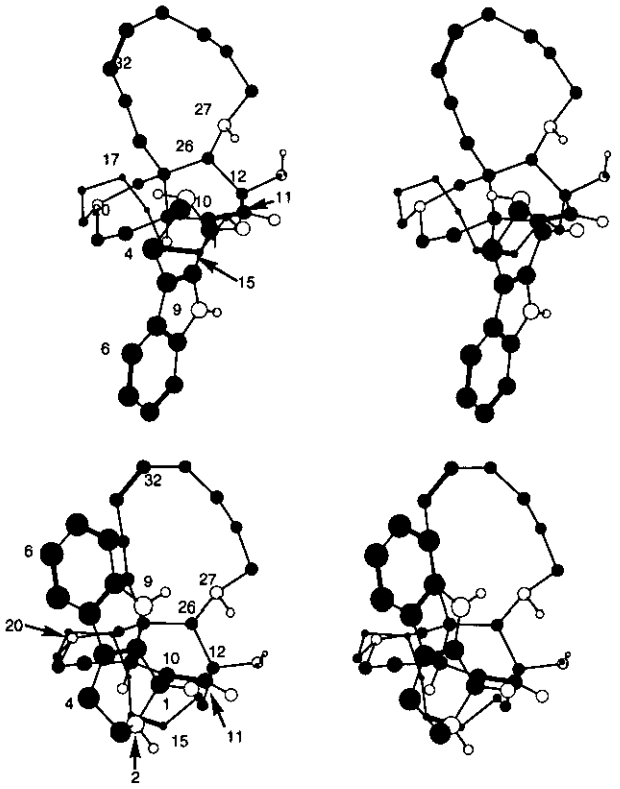


Figure 9. Streoviews of the Monte Carlo Lowest-Energy Conformations of Manzamines H (**12**, upper) and L (**14**, lower).

Amphimedon or *Ircinia* sponge, from the latter ircinals A (**5**) and B (**6**) and manzamines H (**12**) and J (**13**) were obtained. 6-Hydroxymanzamine A[11] (= manzamine Y, **15**) is the first manzamine congener with a hydroxy group at C-6, although 8-hydroxy analogues of manzamines such as manzamine F[17] (**25**) and 8-hydroxymanzamine A[13] (= manzamine G,[14] **17**) have been reported previously. On the other hand, 3,4-dihydromanzamine A[11] (**16**) is the first 3,4-dihydro analogue of manzamines and is easily converted into manzamine A (**1**) by daylight.

6. PLAUSIBLE BIOGENETIC PATH OF MANZAMINES A AND B

The *Amphimedon* sponge used revealed to contain several manzamine-related alkaloids with both of dextrorotation and raevorotation (Table 1). Minor enantiomer of keramaphidin B {(-)-**7**} is considered to possess the same configuration as most of manzamine-related alkaloids with dextrorotation represented by manzamines A (**1**) and B (**2**), while the major enantiomer {(+)-**7**} may be correlated to those with

Table 1 Yield and Optical Rotation of Manzamine-Related Alkaloids from the *Amphimedon* sponge.

Compound	Yield (%)[a]	$[\alpha]_D$ (degree)
Manzamine A (**1**)	0.081	+46
Manzamine B (**2**)	0.0072	+93
Manzamine D (**4**)	0.012	+44[b]
Ircinal A (**5**)	0.0009	+42
Ircinal B (**6**)	0.0006	+15
Ircinol A (**10**)	0.006	-19
Ircinol B (**11**)	0.0003	-2.8
Manzamine H (**12**)	0.0028	+21[b]
Manzamine L (**14**)	0.0056	-15[b]
6-Hydroxymanzamine A (**15**)	0.005	+139
3,4-Dihydromanzamine A (**16**)	0.002	+86
8-Hydroxymanzamine A (**17**)	0.002	+118

[a] These yields were based on wet weight of the sponge.
[b] These compounds have the same configurations as those of **1** and **2**.

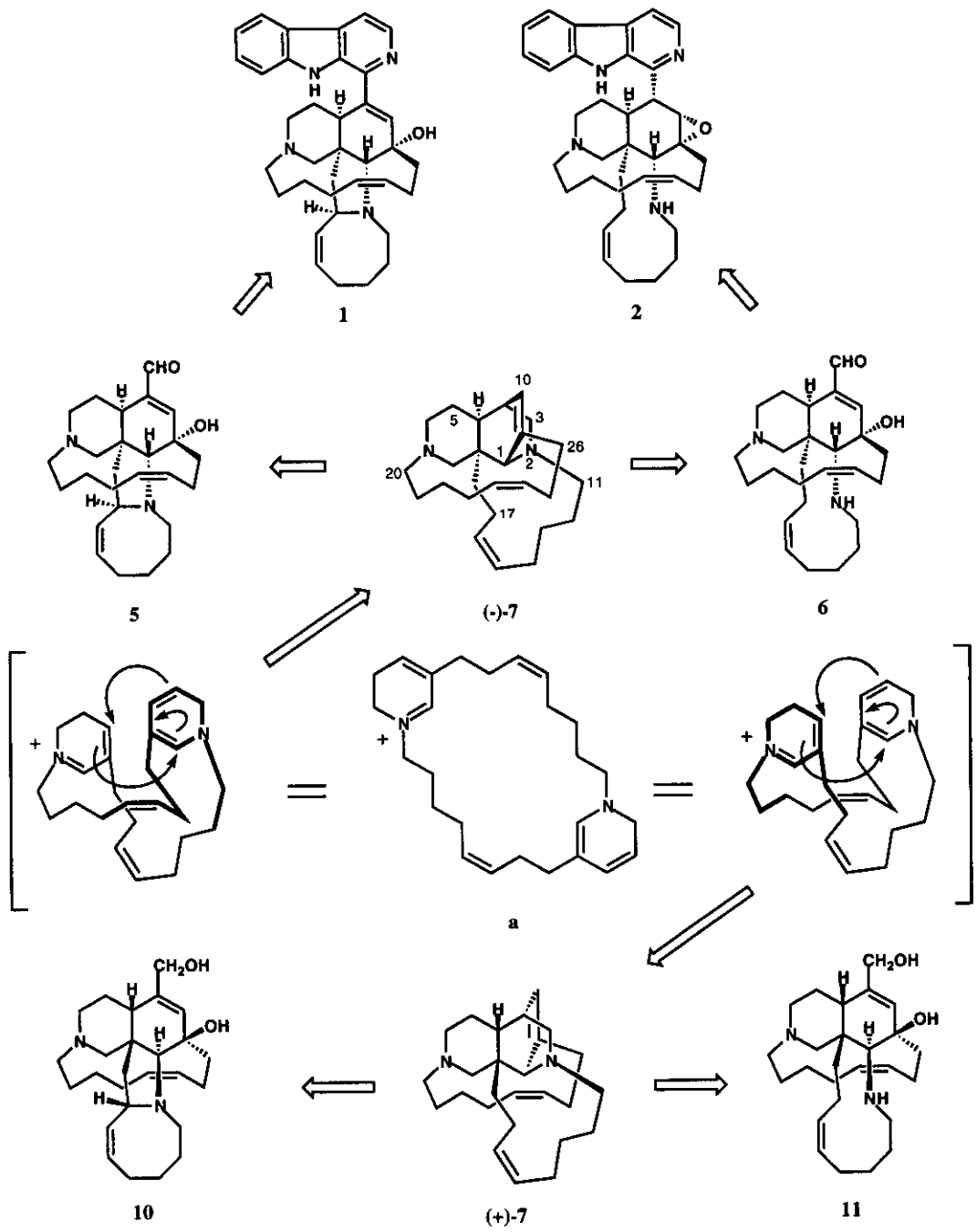


Figure 10. Plausible Biogenetic Path of Manzamines A (**1**) and B (**2**)

raevorotation like ircinols A (**10**) and B (**11**). Altogether the ratio of dextrorotatory vs. raevorotatory alkaloids in this sponge was found to be about 15:1. On the other hand, the ratio of (-)- and (+)-form of

keramaphidin B (**7**) was 3:97.

A plausible biogenetic path of manzamines A (**1**) and B (**2**) is shown in Figure 10, which was elucidated on the basis of the structures and ratios of all the manzamine-related alkaloids isolated from this sponge. The Baldwin's *bis*-3-alkyldihydropyridine (**a**) might be a biogenetic precursor of both enatiomers of keramaphidin B (**7**). The 2,3-iminium form of the (-)-enantiomer {(-)-**7**} may be hydrolyzed to generate (+)-ircinals A (**5**) or B (**6**), which are probably converted through Pictet-Spengler cyclization with tryptamine into manzamines D (**4**), H (**12**), and L (**14**), respectively, and then dehydrogenated to manzamines A (**1**) and B (**2**), respectively. On the other hand, the (+)-enantiomer {(+)-**7**} may be associated with some antipodes of ircinals and manzamines such as ircinols A (**10**) and B (**11**).

7. STRUCTURES OF KERAMAPHIDIN C AND KERAMAMINE C AND PLAUSIBLE BIOGENESIS OF MANZAMINE C

Keramaphidin C (**8**) and keramamine C (**9**) were obtained together with tryptamine from the *n*-butanol soluble material of the MeOH extract of the *Amphimedon* sponge by silica gel chromatography using $CHCl_3$/MeOH (95:5) and then organic layer of $CHCl_3$/MeOH/H_2O (6:1:1).[8] The strctures of keramaphidin C and keramamine C were easily established as **8** and **9**, respectively, by their NMR data. This is the first isolation of **8** from natural sources, although compound **8** has been synthesized as an intermediate in total synthesis of manzamine C (**3**) by Nakagawa and coworkers.[16]

Isolation of keramaphidin C (**8**) and keramamine C (**9**) together with manzamine C (**3**) and tryptamine seems to substantiate partly the biogenetic path of manzamine C (**3**), which may be derived from coupling of keramaphidin C (**8**) with tryptamine and a C_3 unit *via* keramamine C (**9**) (Figure 11). On the other hand, keramaphidin C (**8**) is probably generated from a C_{10} unit and ammonia.

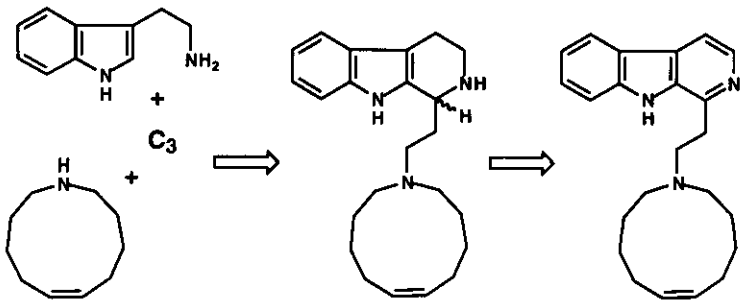
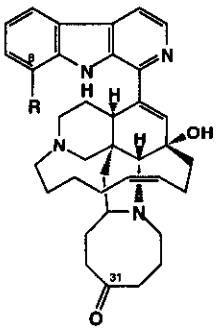


Figure 11. Plausible Biogenetic Path of Manzamine C (**3**)

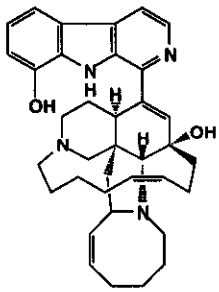
8. MANZAMINE-RELATED ALKALOIDS ISOLATED BY OTHER GROUPS

8-1 β-Carboline Alkaloids

Many manzamines and related alkaloids have been reported from several marine sponges so far; manzamines E (**24**) and F (**25**) from an Okinawan sponge *Xespongia* sp.,[17] 8-hydroxymanzamine A (= manzamine G, **17**) from an Indonesian sponge *Pachipellina* sp.,[13] xestomanzamines A (**26**) and B (**27**) and manzamines X (**28**) and Y (= 6-hydroxymanzamine A) from Oknawan sponges *Xestospongia* and *Haliclona* sp.,[12] respectively, 1,2,3,4-tetrahydro-8-hydroxymanzamine A (**29**) and its 2-*N*-methyl



24 R = H
25 R = OH



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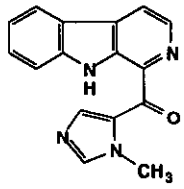

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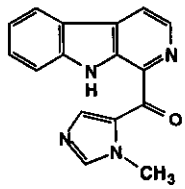

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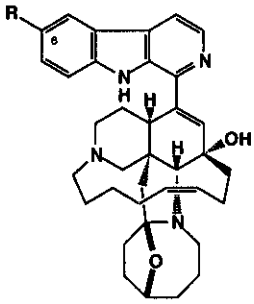
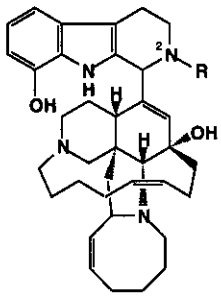
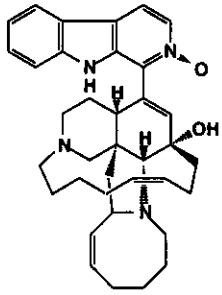


28 R = OH
31 R = H



29 R = H
30 R = CH_3



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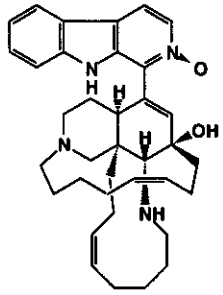

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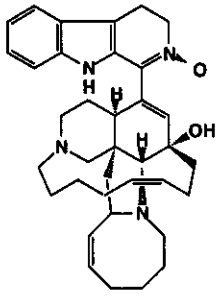

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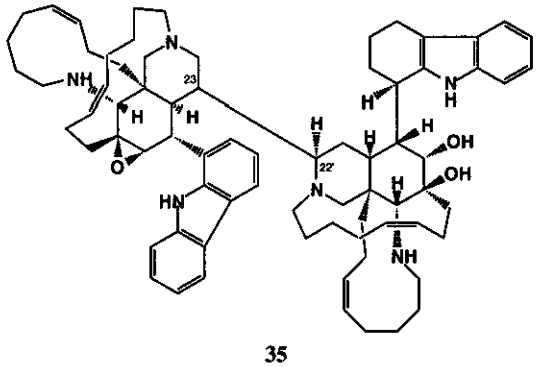
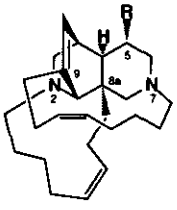


35

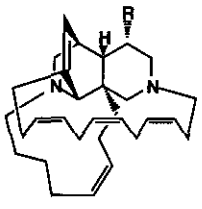
derivative (**30**) from Papua New Guinean sponges *Petrosia* and *Cribochalina* sp.,[18] and 6-deoxymanzamine X (**31**) and the three 1-*N*-oxide derivatives (**32** ~ **34**) from Philippine sponge *Xestospongia ashimorica*.[19] Unique β-carboline alkaloids, xestomanzamines A (**26**) and B (**27**) may be biogenetically derived from *N*-methylhistidine and tryptamine. More recently Scheuer *et al.* isolated the first manzamine dimer, named kauluamine (**35**), from an Indonesian sponge *Prianos* sp.[20]

8-2. Ingenamines, Ingamines, and Xestocyclamines

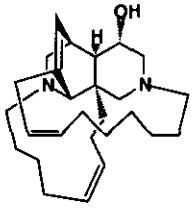
Several alkaloids similar to keramaphidin B (**7**) were reported from two groups independently just before or after isolation of **7**. Andersen's group isolated eight pentacyclic alkaloids, named ingenamine[21] (**36**), ingamines A (**37**) and B[22] (**38**), and ingenamines B ~ F[17] (**39** ~ **43**), from the sponge *Xestospongia ingens* collected in Papua New Guinea. Crews and coworker reported two new alkaloids, xestocyclamines A[19] (**44**) and B[20] (**45**), from a Papua New Guinean sponge *Xestospongia* sp. Ingenamine (**36**) corresponds to 5-hydroxy form of keramaphidin B (**7**). The skeletons of ingamines A



36 R = OH
7 R = H



37 R = OH
38 R = H



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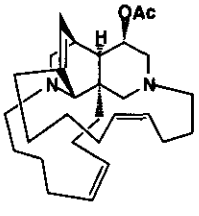

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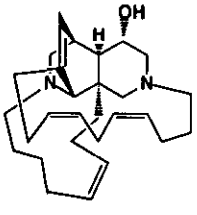

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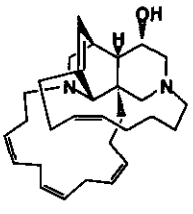
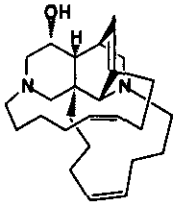


42 R = OH
43 R = H



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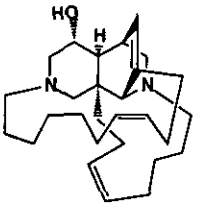

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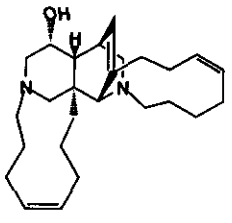
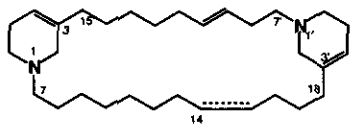


46

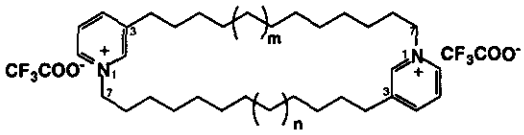
(**37**) and B (**38**) differ from those of ingenamine (**36**) and keramaphidin B (**7**) in having a C_{12} alkyl chain between N-7 and C-9 in place of the C_8 alkyl chain in **36** and **7**. Ingenamines B (**39**), C (**40**), and D (**41**) have C_9 or C_{10} alkyl chain between N-7 and C-9, while ingenamines E (**42**) and F (**43**) possess twelve carbon alkyl chain between N-2 and C-8a. If keramaphidin B (**7**) and ingenamine (**36**) are generated from a pair of symmetrical dialdehyde (C_{10} unit), C_3 units, and ammonia as Baldwin suggested, it may be explained that macrocyclic rings of ingamines A (**37**) and B (**38**) and ingenamines B ~ F (**39** ~ **43**) are derived from C_{11}, C_{12}, or C_{14} dialdehyde unit in addition to C_{10} dialdehyde unit. Absolute configurations of ingenamine (**36**), ingamine A (**37**), and ingenamine E (**42**), which were determined by application of modified Mosher method at the hydroxy group on C-6,[17] were the same as those of keramaphidin B (**7**). Xestocyclamine A (**44**) was revised to be the Δ_{14} isomer of **36** by reassignment of its 2D NMR data, although initial structure of xestocyclamine A was elucidated to be **46**. The structure of xestocyclamine B (**45**) corresponds to the 15,16-dihydro form of ingenamine D (**41**).

8-3. Halicyclamines and Cyclostellettamines

Some alkaloids from marine sponges, which were reminescent of the Baldwin's bisdihydropyridine macrocycle (**a**), have been reported. In 1989 from a sponge *Haliclona* sp. collected off the Uwa Sea, Japan, Fusetani *et al.* isolated new bistetrahydropyridine alkaloids, haliclamines A (**47**) and B (**48**) as cytotoxic constituents.[26] The structures consisted of two tetrahydropyridines linked through C_9 and C_{12} alkyl chains. Cyclostellettamines A ~ F[27] (**49** ~ **54**), isolated from the hydrophilic extracts of the sponge *Stelletta maxima* collected off the Sata Peninsula, Shikoku, Japan, were macrocyclic bispyridines linked through C_{12} ~ C_{14} alkyl chains.



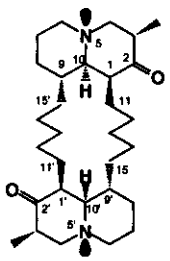
47
48: Δ^{14}



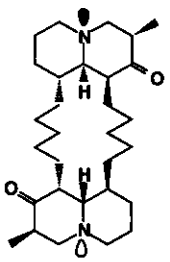
49 m = 1, n = 1 **52** m = 1, n = 3
50 m = 1, n = 2 **53** m = 2, n = 3
51 m = 2, n = 2 **54** m = 3, n = 3

8-4. Petrosins and Xestospongins

Unique bis-quinolizidine alkaloids, petrosin[28] (**55**) and petrosins A[29,30] (**56**) and B[29] (**57**) were isolated from the Papua New Guinean sponge *Petrosia serita*, and the C_2-synmetrical structure of petrosin (**55**) was established by X-Ray, while petrosin A (**56**) was elucidated as mesomeric.[30] In 1984 Nakagawa *et al.* reported isolation of novel macrocyclic 1-oxa-quinolizidine alkaloids, xestospongins A ~ D (**58** ~ **61**), from the Australian sponge *Xestospongia exigua*, and the structures were established on the basis of X-



55



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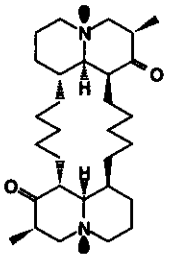

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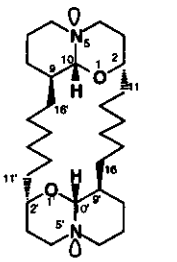

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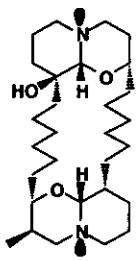

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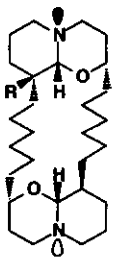
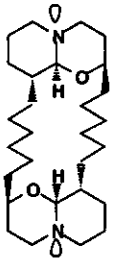
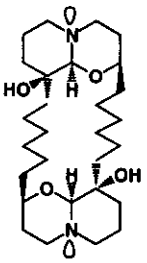


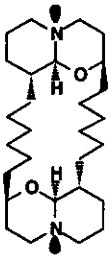
60 R = H
61 R = OH



(+)-62
((+)-62 : (-)-62 1 : 1)

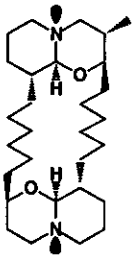


63



(-)-64
((+)-64 : (-)-64 3 : 7)

(+)-65
((+)-65 : (-)-65 3 : 2)



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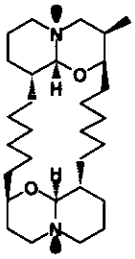

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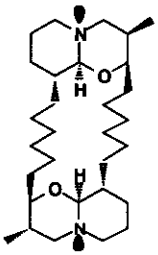
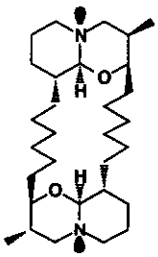
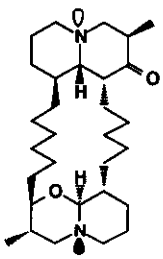


68



69



70

71

Ray analysis of xestospongin C (**60**).[31] In 1989 Kitagawa and coworkers isolated ten new alkaloids, araguspongines B ~ H and J[32] (**62** ~ **69**) and aragupetrosine A[33] (**70**), together with petrosin (**55**) and petrosin A (**56**) from an Okinawan sponge *Xstospongia* sp. Araguspongines are bis-1-oxa-quinolizidine alkaloids, while aragupetrosine A (**69**), having a quinolizidine and an 1-oxa-quinolizidine rings, is hybrid of petrosin (**55**) and araguspongin F (**65**). Araguspongines F (**66**), G (**67**), H (**68**), and J (**69**) were obtained as optically pure compounds, while araguspongines B (**62**), D (**64**), and E (**65**) were isolated as enantiomeric mixtures or mesomeric compounds. In 1986 an interesting biogenetic path for petrosin (**55**), petrosin A (**56**), and xestospongin A ~ D (**58** ~ **61**) was proposed by Cimino *et al.*,[34] although those

alkaloids were isolated from different genera of marine sponges. On the other hand, Kitagawa *et al.* indicated the biogenetic relationship between bisquinolizidine alkaloids and bis-1-oxa-quinolizidine alkaloids. The biogenetic path is shown in Figure 12; dimerization of two C_9-C_5N units (**d**) gives the macrocycle (**e**) followed by oxidation of C-12 and C-12' to afford the diketone compound (**f**). Araguspongines B ~ H and J (**62** ~ **69**) may be generated from **e** *via* pathway **A**). On the other hand, aragupetrosine A (**70**) and petrosins (**55** and **56**) were probably generated *via* pathway **B** and **C**, respectively. Both precursors **a** and **e** are similar to haliclamines A (**47**) and B (**48**) and cyclostellettamines A ~ F (**49** ~ **54**). Recently demethylxestospongin B (**71**) was isolated together with xestospongins B (**54**) and D (**56**) and araguspongin F (**64**) from a New Caledonian sponge *Xestospongia* sp.[35]

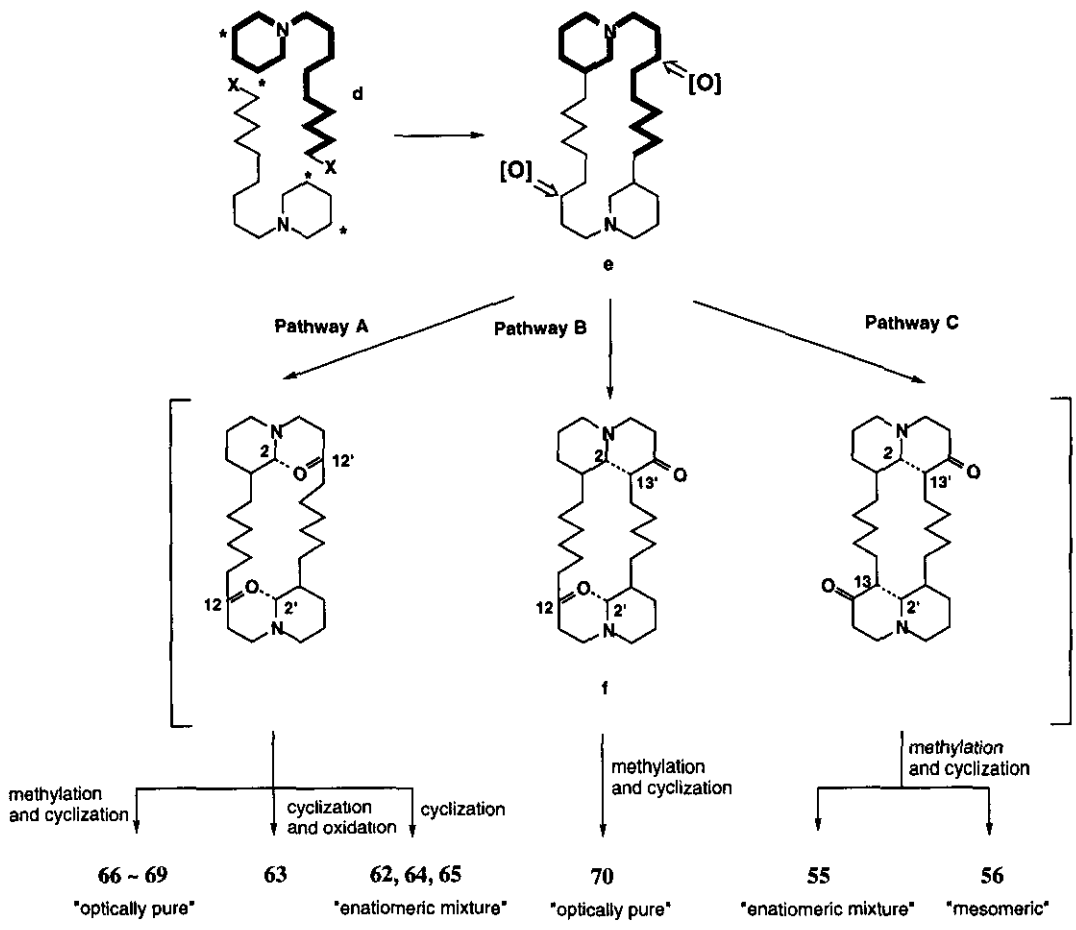
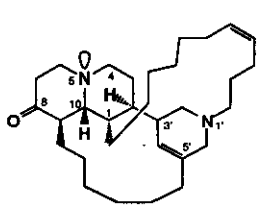


Figure 12. Biogenetic Path of Aragspongines and Petrosins Proposed by Kitagawa *et al.*

8-5. Sarains, Isosarains, and Saraines

The metabolic pattern of the Mediterranean sponge *Reniera sarai* is characterized by the presence of a series of unique complex polycyclic alkaloids. Cimino *et al.* reported the isolation of unprecedented alkaloids, sarains 1 ~ 3 (**72** ~ **74**), isosarains 1 ~ 3 (**75** ~ **77**), and saraines A ~ C (**78** ~ **80**).[34,36~41] Sarains 1 ~ 3[34,41] (**72** ~ **74**) possessed a *trans*-quinolizidine moiety linked to an unsaturated piperidine ring directly and by two linear alkyl chains, while isosarains 1 ~ 3[37,39,41] (**75** ~ **77**), obtained as minor constituents of the sponge, were isomers at C-1, C-2, and C-9 of sarains 1 ~ 3 (**72** ~ **74**), respectively. Saraines A (**78**), of which the structure was assigned on the basis of combination of X-Ray study of the acetyl derivative of **78**[36] and datailed spectral studies of **78** itself,[38] had unique pentacyclic core with two macrocyclic rings. More recently structures of saraines B (**79**) and C (**80**) and absolute streochemistry of **78** ~ **80** were determined.[40] The biogenetic path of sarain-related alkaloids (**72** ~ **80**) proposed by Cimino *et al.* is analogous with the Baldwin's proposal for manzamines (Figure 2). The retro-biosynthesis of sarains 1 ~ 3 (**72** ~ **74**) and isosarains 1 ~ 3 (**75** ~ **77**) (Figure 13a) proceeds through a partially reduced *bis*-3-alkylpyridine macrocycle which contains 10 carbons in an alkyl chain and 10, 11, and 12 carbons in



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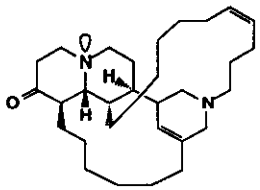

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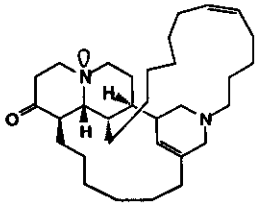

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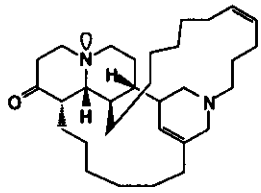

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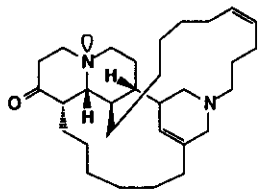

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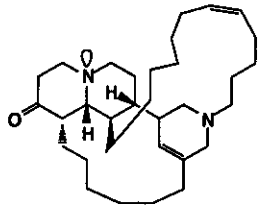

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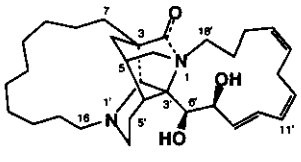

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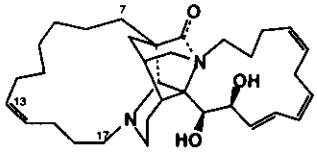

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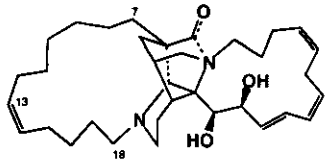

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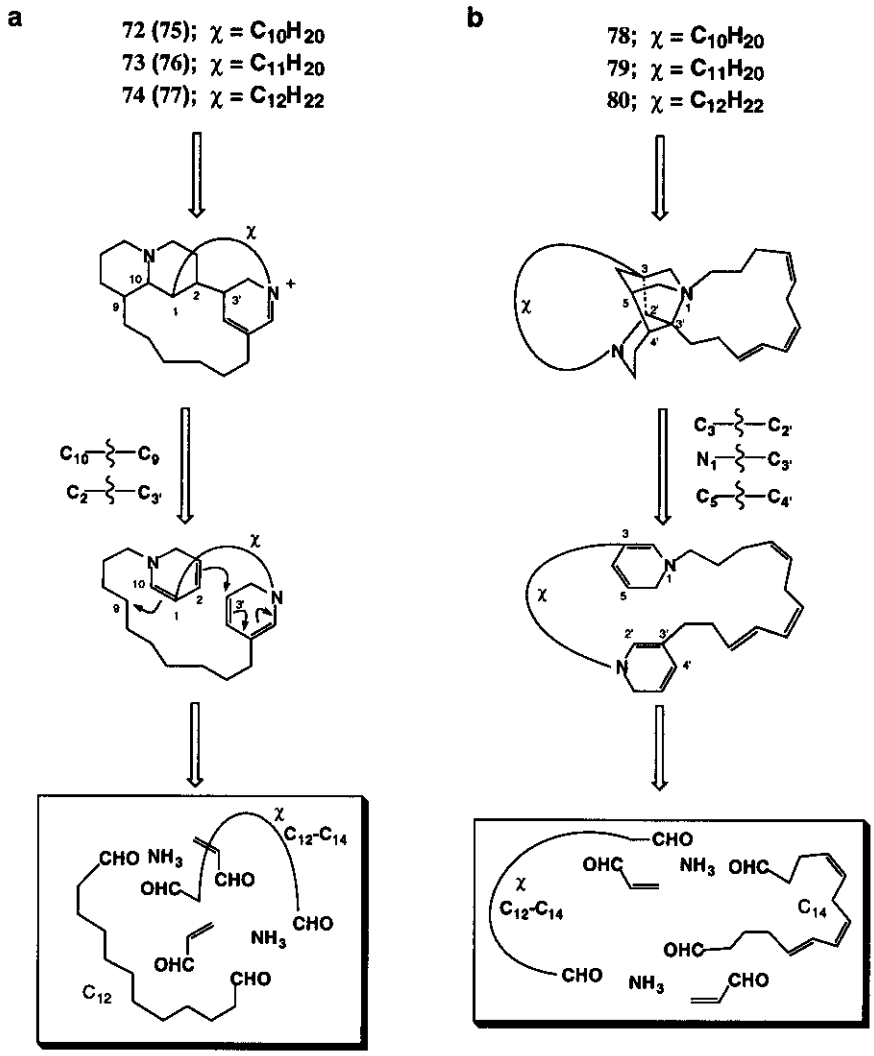


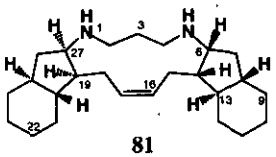
Figure 13. Retro-Biosynthetic Pathway of Sarains 1 ~ 3 (**72** ~ **74**), Isosarains 1 ~ 3 (**75** ~ **77**), and Saraines A ~ C (**78** ~ **80**) Proposed by Cimino *et al.*

another alkyl chain (***x***). These macrocycles may give sarains and isosarains through some intramolecular reaction.[41] On the other hand, macrocycles for saraines A ~ C (**78** ~ **80**) contain 12 carbons in an alkyl chain and 10, 11, and 12 carbons in another alkyl chain (***x***) (Figure 13b).[40]

8-6. Papuamine and Haliclonadiamine

Papuamine[42] (**81**) and haliclonadiamine[43] (**82**) were isolated from *Haliclona* sponges collected off Papua New Guinea and Palau, respctively. The structure of **81** was elucidated mainly by NMR data including

INADEQUETE studies, while the structure of **82** was established by X-Ray analysis of its diacetyl derivative. Haliclonadiamine (**82**) is an unsymmetrical diastereomer of papuamine (**81**). Recently Crews and Schmitz *et al.* proposed the biogenetical and taxonomic consideration of marine diamine-containing alkaloids, in which they suggested that papuamine (**81**) and haliclonadiamine (**82**) may be formed by condensation of ammonia, acrolein, and acyclic aldehyde, which are Baldwin's biosynthetic building blocks of manzamines.[18]



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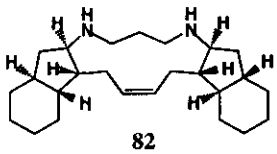

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8-7. Madangamine A and Halicyclamine A

A novel class of pentacyclic alkaloid, madangamine A[44] (**83**), was isolated by Andersen *et al.* from the Papua New Guinean sponge *Xestospongia ingens*, from which ingenamine (**18**) and ingamines A (**19**) and B (**20**) were also isolated. The proposed biogenesis for madangamine A (**83**) was outlined in Figure 14, which resembles partly the Baldwin's proposal for the biogenesis of manzamines. The ingenamine-type intermediate [= ingenamine F (**25**)], which may be generated from a bis-3-alkylpyridine macrocycle

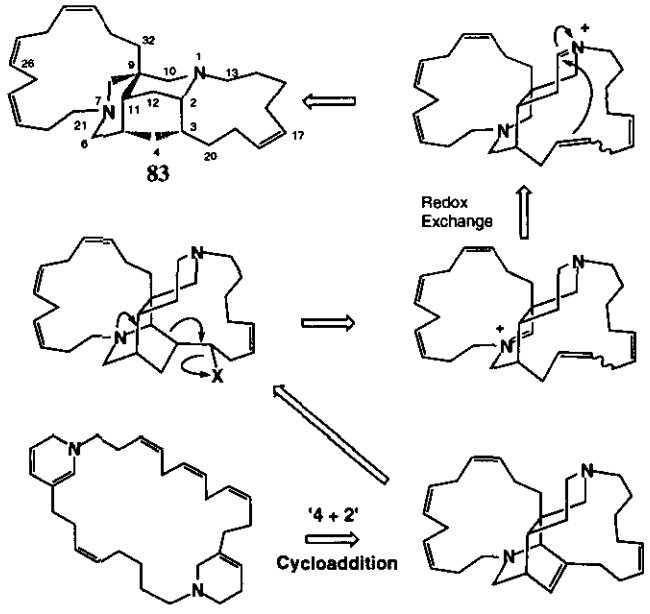

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Figure 14. Biogenesis for Madangamine A (**83**) Proposed by Andersen *et al.*

(i) similar to **a** (Figure 2) through "4+2" cycloaddition reaction, can undergo rearrangement to generate the madangamine A skeleton.

Crews and coworkers isolated a novel tetracyclic diamine alkaloid, named halicyclamine A (**84**), from an Indonesian sponge *Haliclona* sp., and elucidated the structure on the basis of spectroscopic data.[45] More recently isolation of haliclonacyclamines A (**85**) and B (**86**) from a *Haliclona* sponge collected off Great Barrier Reef was reported by Garson *et al.*, and the structure of **85** was assigned by X-Ray analysis.[46] The relative stereochemistry at C-2 in halicyclamine A (**84**) was different from those of haliclonacyclamines A (**85**) and B (**86**). Crews *et al.* also reported isolation of halicyclamine B (**87**) from an Indonesian *Xestospongia* sponge and structural determination based on X-Ray analysis.[47] The biogenetic path of these tetracylcic alkaloids is proposed by Garson *et al.* (Figure 15); cleverage of C-1–C-

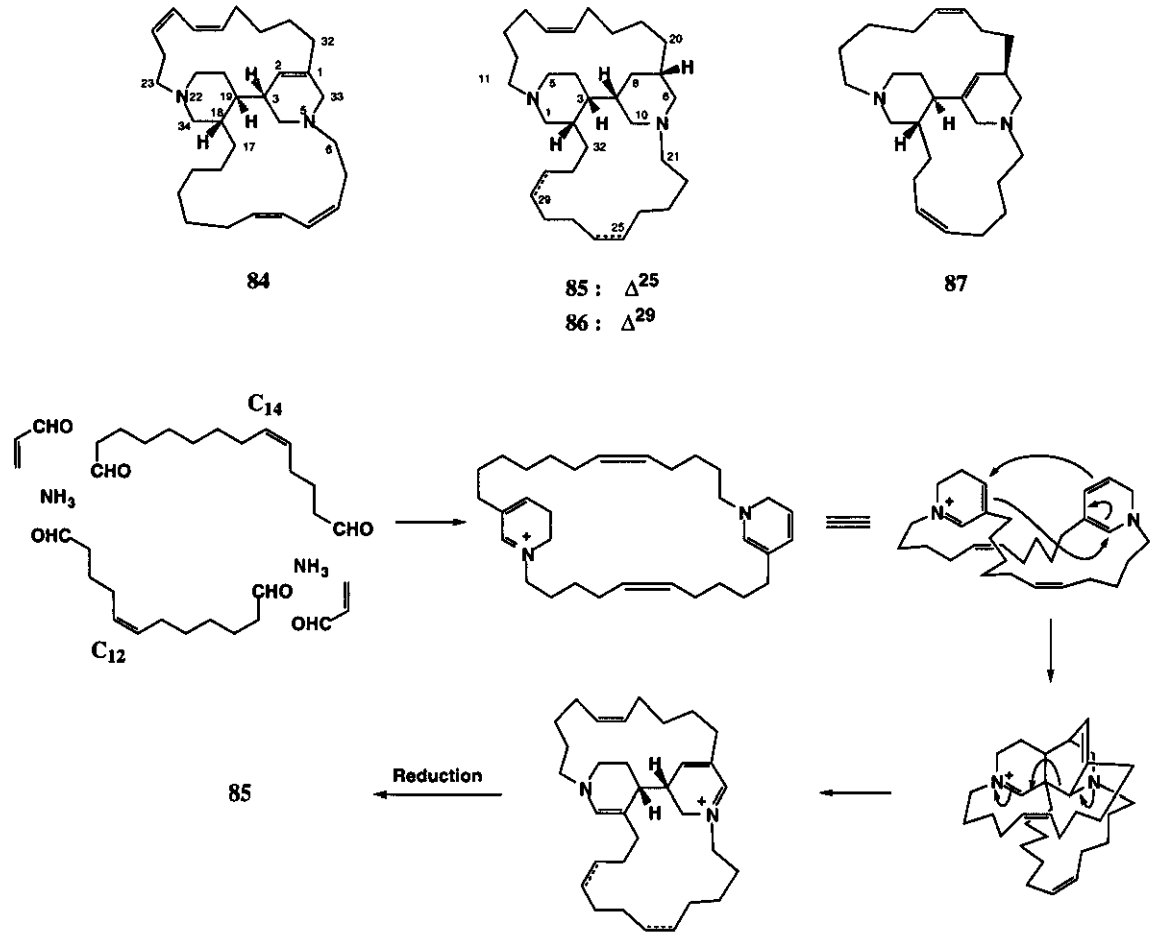


Figure 15. Biosynthetic Pathway for Haliclonacyclamine A (**85**) Proposed by Garson *et al.*

8a bond of Baldwins' pentacyclic intermediate (**b**) analog followed by reduction may give halicyclamine A (**84**) while haliclamine B (**87**) is probably derived from a homolog of **84** *via* 1,3-sigmatropic shift.

9. CHEMOTAXONOMY OF MANZAMINE-RELATED ALKALOIDS

Taxonomy of sponge materials containing manzamine-related alkaloids was shown in Table 2. This result indicates that all the alkaloids described in this review are obtained mainly from sponges belonging to two orders of Haplosclerida and Nepheliospongida except for sponges of genera *Ircinia*, *Prianos*, and *Stelletta*. Particularly the *Xestospongia* and *Haliclona* sponges are rich sources of manzamine-related alkaloids.

Table 2. Taxonomy of Sponges Containing Manzamine-Related Alkaloids.

Order	Family	Genus	Compounds	ref.
-----Subclass, Tetractinomorpha-----				
Chronistida	Stelletidae	*Stelletta*	**49, 50, 51, 52, 53, 54**	27
-----Subclass, Ceractinomorpha-----				
Dictyoceratida	Thorectidae	*Ircinia*	**1, 2, 4, 5, 6, 12, 13**	6
Nepheliospongida	Oceanapiidae	*Pellina*	**1, 2**	4
		Pachypellina	**1, 17**	13
	Nepheliospongiidae	*Petrosia*	**55, 56, 57**	28,29
			29, 30	18
		Xestospongia	**17, 24, 25**	14,17
			1, 24, 25, 28	12
			58, 59, 60, 61	31
			55, 56, 62, 63, 64, 65, 66, 67, 68, 69, 70	32,33
			54, 56, 64, 71	35
			44, 45	24,25
			7, 36, 37, 38, 39, 40, 41, 42, 43, 83	21,22,23,44
			87	45
Haplosclerida	Niphatidae	*Cribochalina*	**30**	18
		Amphimedon	**1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 15, 16, 17**	7,8,9,10,11
	Chalinidae	*Haliclona*	**1, 2, 3, 4**	1,2,3
			47, 48	26
			1, 2, 3, 15	12
			81	42
			81, 82	43
			84	45
			85, 86	46
		Reneira	**72, 73, 74, 75, 76, 77, 78, 79, 80**	35,36,37,40,41
Poecilosclerida	Desmacidonidae	*Prianos*	**35**	20

10. SYNTHETIC STUDY OF MANZAMINES

Synthetic studies of manzamines have been reported by several groups. The simplest manzamine C (**3**) has been synthesized by Nakagawa and coworkers in 1989 (Figure 16).[16,48] Manzamine C (**3**) was prepared through the key amidation using diphenylphosphoryl azide (DPPA) of azacycloundecene (**8**, = keramaphidin C), which was derived from coupling of a siloxyacetylide (**88**) and siloxyiodide (**89**), with the β-carboline potasium salts (**90**). The *trans* geometrical isomer (**91**), the unsaturated congener (**92**), and some derivatives possessing vairous azacycles[49] were also synthesized. Recently Gerlach *et al.* also reported synthesis of manzamine C (**3**).[50]

Several synthetic studies aimed at the total synthesis of most complicate manzamine A (**1**) have been reported in the last few years.[51-71] However total synthesis of the complete skelton of manzamines A (**1**) or B (**2**) has not been achieved yet. In 1993 Nakagawa *et al.* acheived the synthesis of tetracyclic core (**96**) of manzamine A (**1**) (Figure 17).[65] A key strategy of the synthesis is intermolecular Diels-Alder reaction between 3-substituted dihydropyridinone (**93**) and a siloxydiene (**94**) and amidation of **95** using pentafluorophenyl (PFP) ester method. More recently Pandit's group reported first synthesis of a

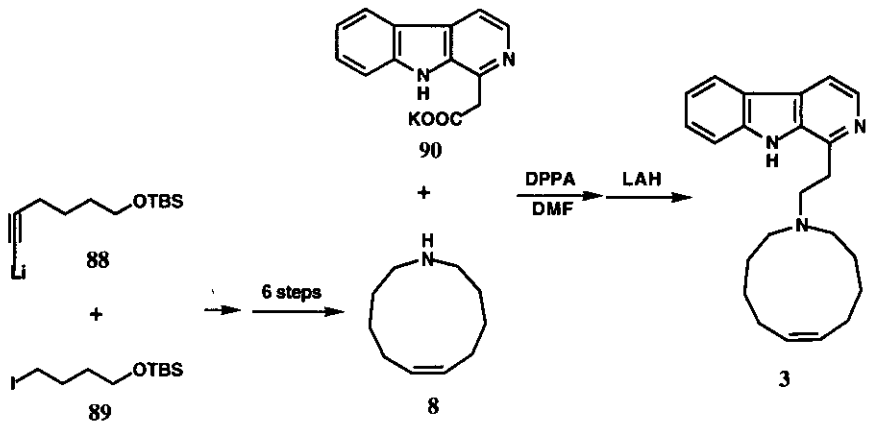
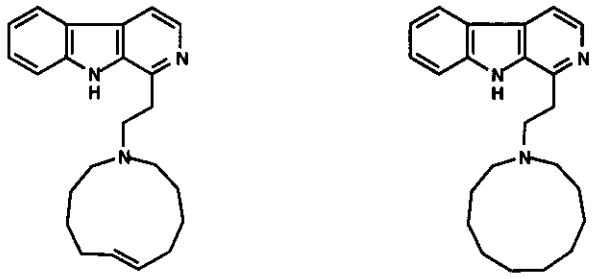


Figure 16. Synthetic Scheme of Manzamine C (**3**) by Nakagawa *et al.*



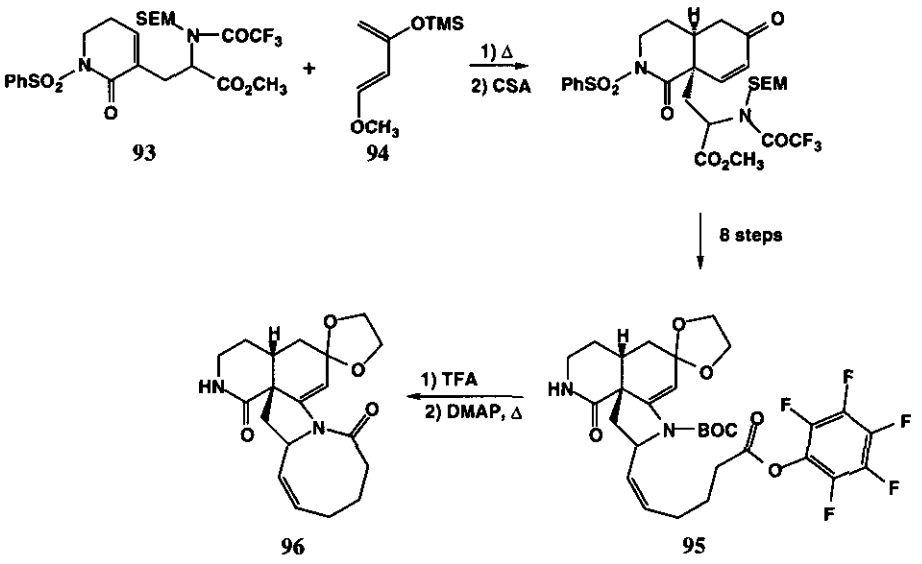


Figure 17. Synthetic Scheme of Tetracyclic Core of Manzamine A (**1**) by Nakagawa *et al.*

pentacyclic nuclei (**101**) of manzamine A (**1**).[71] The synthetic scheme is outlined in Figure 18. The tricyclic pyrrolo[2,3-*i*]isoquinoline system (**100**) was synthesized by intramolecular Diels-Alder reaction of **99**, which was prepared from the dehydropyperidine (**96**) and the amino ester (**97**),[51] the former was obtained in nine steps from L-serine,[54] *via* intermediates (**98a**) and (**98b**). Construction of the 13-membered and 8-membered rings was achived by a key metathesis cyclization of using Grubbs'es ruthenium carbene catalyst (**102**).[70] The transformation of oxidation states at C-10, C-11, C-28, and C-36 of **101** would lead to the skeleton of manzamine A (**1**).

10. CONCLUSION

Manzamines and related alkaloids are very interesting marine spongian metabolites possessing unusual ring systems which are challenging targets for total synthesis and for unprecedented biogenesis to be defined. Further progress in extensive studies on isolation, structure elucidation, biogenesis, total synthesis, and bioactivity is expected for these miracle compounds to be called manzamine family.

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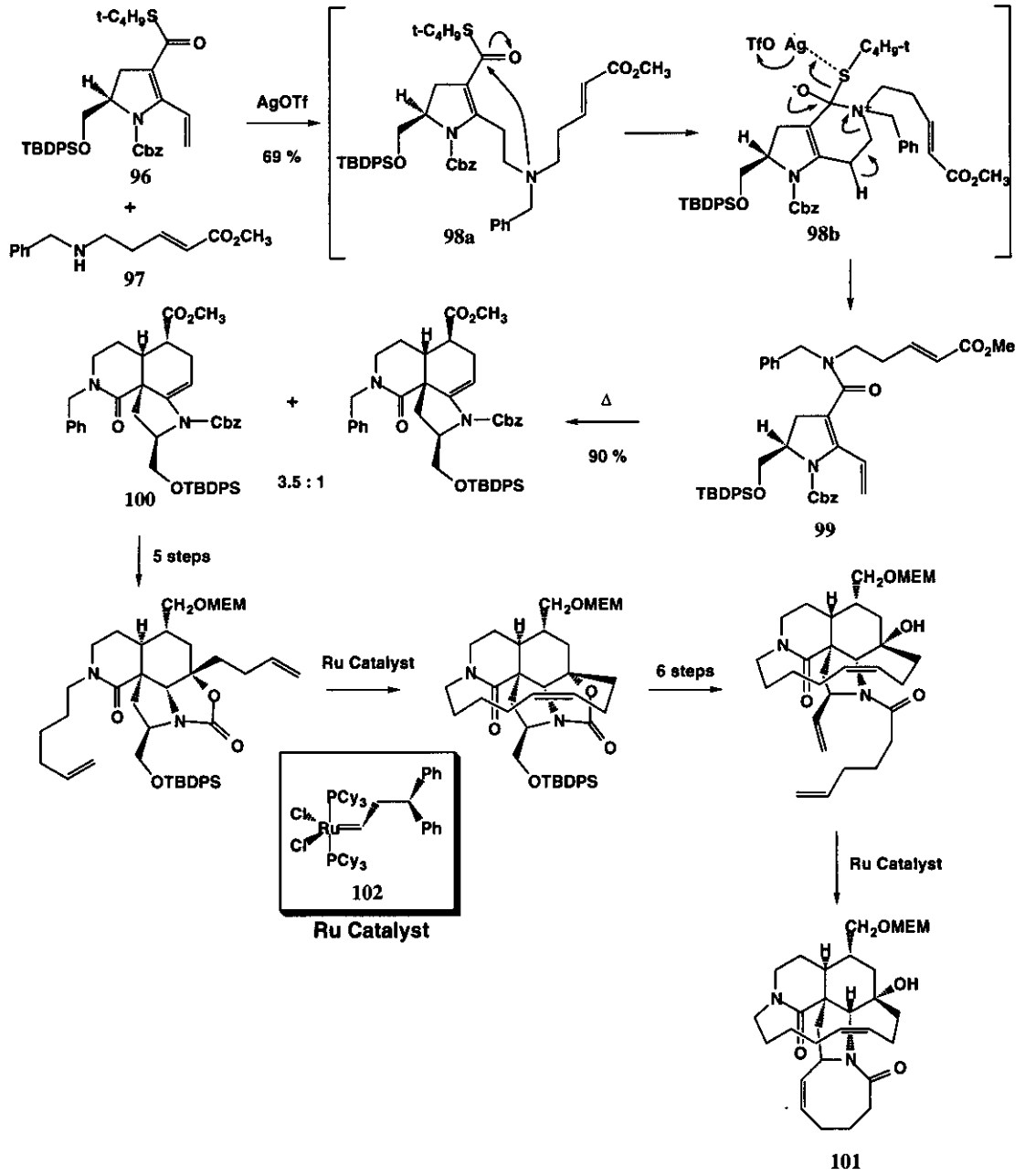

Figure 18. Synthetic Scheme of Pentacyclic Core of Manzamine A (**1**) by Pandit *et al.*

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