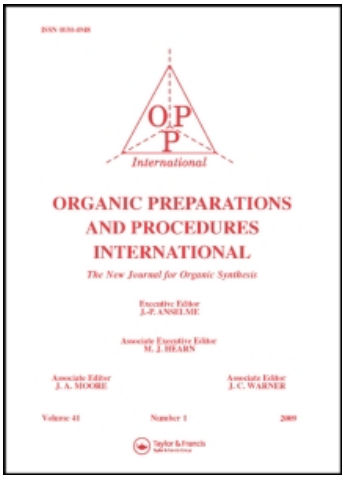

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INTRODUCTION

Marine natural product chemistry is a rapidly growing interdisciplinary science. The fascinating structures of marine secondary metabolites often have no terrestrial counterpart, and these molecules have attracted biological, ecological, pharmacological and chemically oriented research groups worldwide. In the last two decades interest has focused on metabolites isolated from marine invertebrates, particularly sponges and tunicates.[1] This review focuses on the biosynthesis, as well as biomimetic and synthetic approaches to a growing subset of unique marine sponge alkaloids which possess a common *bis*-pyridine macrocycle as the biosynthetic precursor. Many of these alkaloids possess significant biological activity including cytotoxicity, antifungal and vasodilative activity, and protein kinase C inhibition. The literature is surveyed from the onset of research in the area in the late 1980's until the middle of 1997. After reviewing the proposed biogenetic origin of these alkaloids, a short chapter on biomimetic syntheses follows. Biomimetic strategies can be attractive for the synthesis of complex alkaloid skeletons. Additionally, these strategies may support some of the hypotheses regarding the biosynthetic pathway. The discussion in the synthesis chapter focuses on the overall strategy and the key reactions in the approaches. If there is more than one published total synthesis or synthetic approach to an alkaloid, studies are described in chronological order.

I. PROPOSED ALKALOID BIOGENESIS

During a search for new bioactive marine natural products, Higa and coworkers isolated the cytotoxic alkaloid manzamine A (**1**) (Fig. 1) from a marine sponge (*Haliclona sp.*).[2] The unusual structure of manzamine A, consisting of a complicated array of 5-, 6-, 8-, and 13-membered rings prompted the statement, "... its provenance is problematical as there appears to be no obvious biogenic path."

In 1992, Baldwin and Whitehead[3] suggested *bis*-dihydropyridine macrocycle **2** as a key biogenetic precursor to manzamines A (**1**) and B (**3**)[4] (Fig. 1). According to this insightful proposal, macrocycle **2** undergoes the biological equivalent of a [4+2]-cycloaddition reaction[5] to give an initial

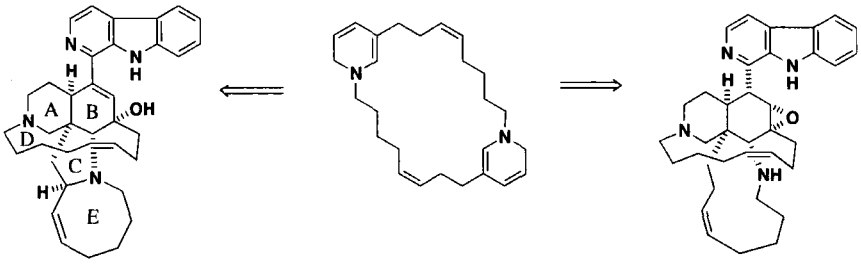


Figure 1

pentacyclic intermediate which has all the manzamine stereocenters intact. This biogenetic pathway reveals a "hidden symmetry" in the manzamine alkaloids which was not previously recognized. Furthermore, it has now become apparent that a number of structurally diverse alkaloids probably result from precursors similar to macrocycle **2**, some of which are structurally identical to intermediates in the Baldwin and Whitehead proposed biogenesis. Figure 2 serves to compactly illustrate the

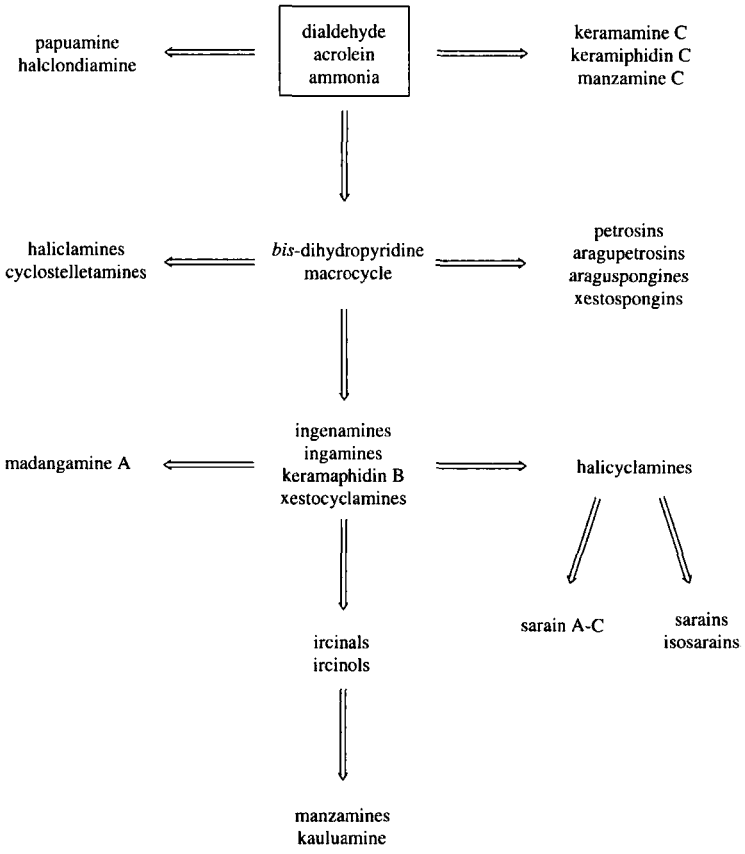
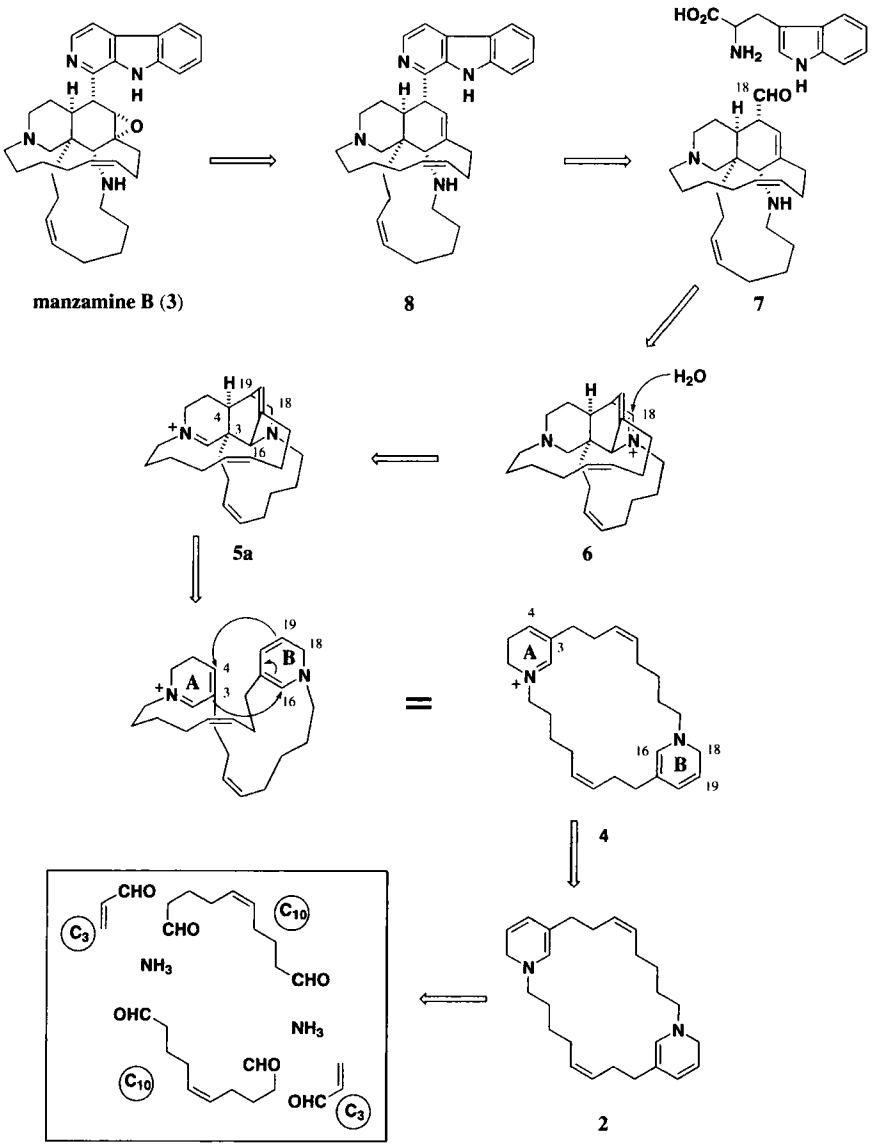


Figure 2

interrelationships among this group of alkaloids. Although to date no experimental studies supporting the biosynthetic proposal exist, the large number of recently isolated natural products belonging to this class do lend support to this logical and compelling postulate.

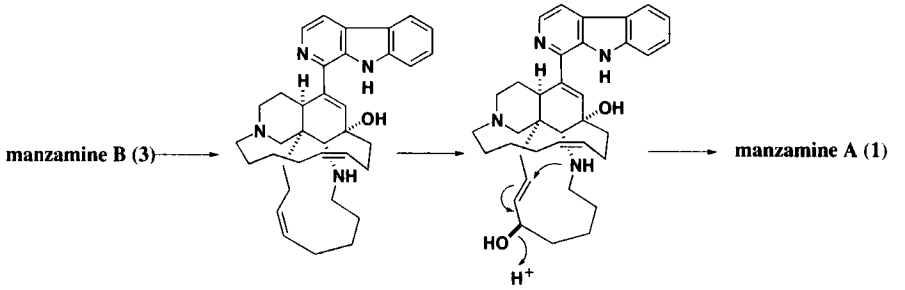
1. Manzamines A and B

bis-Dihydropyridine macrocycle **2** was proposed as a key intermediate, formed by the reductive coupling of two C_3 (acrolein) and two C_{10} (symmetrical dialdehyde) units with two equivalents of ammonia (Scheme 1).[3] Tautomerization of one of the dihydropyridine units in **2** leads to macrocycle



Scheme 1

4. Inspection of **4** reveals that dihydropyridine ring **B** can act as a diene and dihydropyridine ring **A** as a dienophile. **A** and **B** thus undergo an intramolecular [4+2]-like cycloaddition to provide pentacyclic iminium salt **5a**, where C-19 becomes attached to C-4 and C-16 to C-3. Redox exchange between the two piperidine rings of **5a** would then lead to new iminium salt **6**. Hydrolytic ring opening of **6** provides aldehyde **7**. Condensation of **7** with tryptophan through C-18, followed by oxidation, leads to β-carboline **8**. Selective epoxidation of **8** at the trisubstituted olefin produces manzamine B (**3**). Manzamine A (**1**) is related to manzamine B (**3**) by a *trans*-eliminative epoxide opening and allylic oxidation of a double bond, followed by ring closure to form an 8-membered ring (Scheme 2).



Scheme 2

2. Ircinals A and B/Ircinols A and B

Ircinal A (**9**) and B (**10**) (Scheme 3) are cytotoxic alkaloids which were discovered by Kobayashi and coworkers in 1992.[6] The similarities between the ircinals and the tetracyclic aldehyde **7** (Scheme 1) provided the first evidence to support the Baldwin/Whitehead proposed biosynthesis for the manzamines. It is generally presumed that aldehyde **7** is an intermediate in the biosynthesis of ircinal A (**9**) and B (**10**).

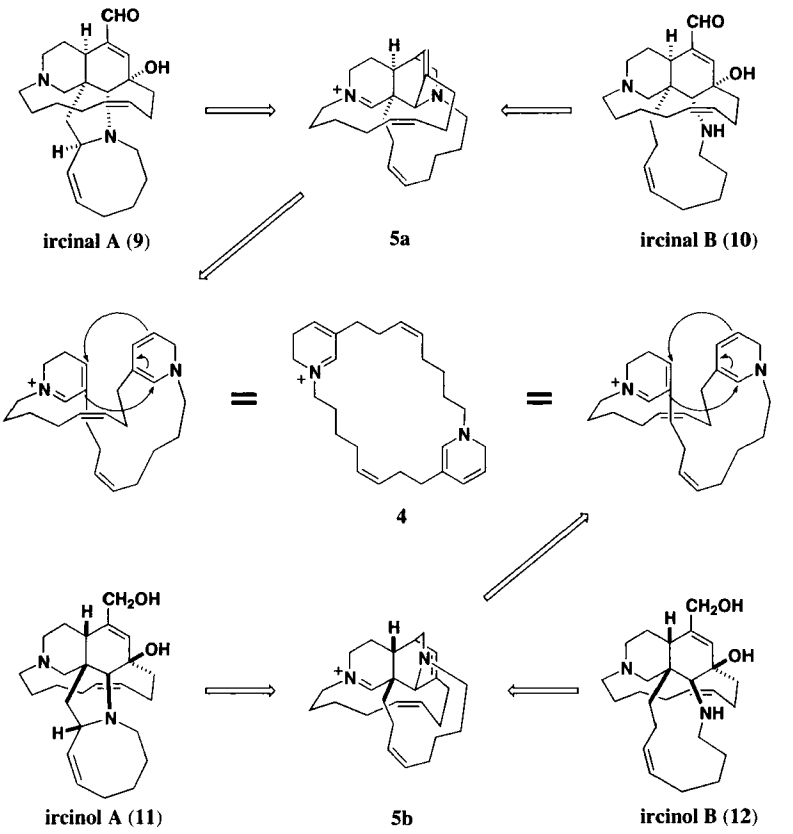
Interestingly, ircinol A (**11**) and B (**12**) were discovered to be antipodal to ircinal A (**9**) and B (**10**).[7] Therefore, it was proposed[7] that the biological [4+2]-cycloaddition is not enantiospecific and that the ircinols arise from **5b**, the enantiomer of the cycloadduct **5a** proposed in the Baldwin/Whitehead hypothesis (Scheme 3), in a manner analogous to the biosynthesis of ircinal A (**9**) and B (**10**).

3. Papuamine/Haliclonadiamine

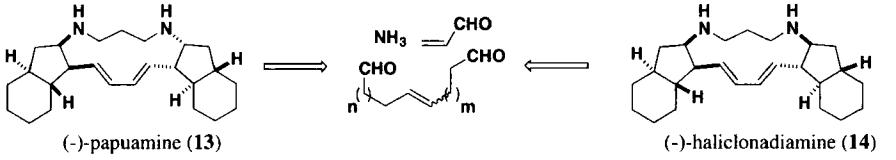
(-)-Papuamine (**13**)[8] and (-)-haliclonadiamine (**14**)[9] (Scheme 4) are pentacyclic alkaloids which were isolated from a *Haliclona* marine sponge. It is presumed[10] that, like the *bis*-dihydropyridine macrocycles, **13** and **14** are the condensation products of a linear dialdehyde and acrolein with ammonia. To date, however, no more detailed biosynthesis of these compounds has been proposed. Although these two alkaloids are probably not *bis*-pyidine derived, they do appear to fall into the same biogenetic class as the other compounds in this review.

4. Keramamine C/Keramaphidin C/Manzamine C

Manzamine C (**15**),[4] keramamine C (**16**), and keramiphidin C (**17**)[11] (Scheme 5) are compounds which also appear to be the result of a condensation between a dialdehyde and acrolein



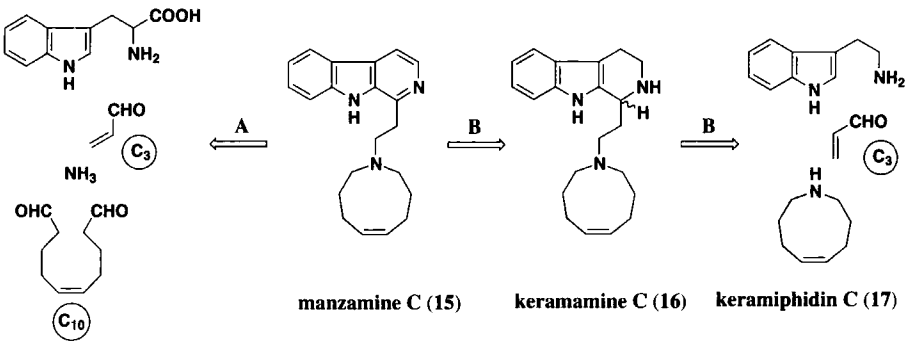
Scheme 3



Scheme 4

with ammonia. The first biosynthetic proposal for manzamine C (**15**) (path **A**, Scheme 5) was made by Baldwin and Whitehead along with their hypothesis for the biosynthesis of manzamines A and B.[3] Therefore, condensation of a C_{10} symmetrical dialdehyde and a C_3 unit with ammonia, followed by cyclization with tryptophan, leads directly to manzamine C (**15**). More recently, the isolation of keramiphidin C (**17**) and keramamine C (**16**) led Kobayashi and coworkers to propose a slightly modified biogenesis (path **B**, Scheme 5).[11] According to the Kobayashi proposal, keramiphidin C (**17**) is generated from the coupling of a C_{10} dialdehyde unit with ammonia. Keramiphidin C (**17**) then undergoes a condensation with a C_3 unit, followed by a Pictet-Spengler type cyclization with tryptamine, to

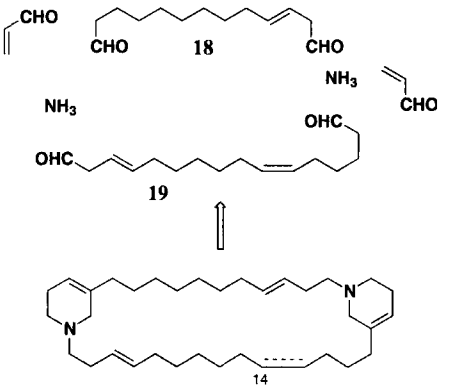
form keramamine C (**16**) which is oxidized to manzamine C (**15**). Additionally, the Kobayashi group has isolated tryptamine from the source of keramphidin C (**17**) and keramamine C (**16**).



Scheme 5

5. Haliclamine/Cyclostellettamines

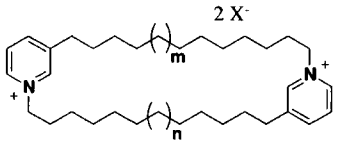
Variation in chain length and degree of unsaturation in the dialdehyde unit can lead to a number of related *bis*-dihydropyridine alkaloids. Reductive coupling of dialdehydes **18** and **19** and two C_3 acrolein units with two equivalents of ammonia, followed by partial reduction of both dihydropyridine moieties leads to haliclamine B (**20**) (Scheme 6).[12] Further reduction of the *cis* double



halicyclamine A (21)
Δ^{14} : halicyclamine B (20)

Scheme 6

bond leads to haliclamine A (**21**). In addition to reduced *bis*-dihydropyridine macrocycles, natural products in which the dihydropyridine units have been oxidized have also been isolated. Such is the case with cyclostellettamines A-F (**22-27**) (Fig. 3).[13]



cyclostellettamine A (m = 1, n = 1) (**22**)
cyclostellettamine B (m = 1, n = 2) (**23**)
cyclostellettamine C (m = 2, n = 2) (**24**)
cyclostellettamine D (m = 1, n = 3) (**25**)
cyclostellettamine E (m = 2, n = 3) (**26**)
cyclostellettamine F (m = 3, n = 3) (**27**)

Figure 3

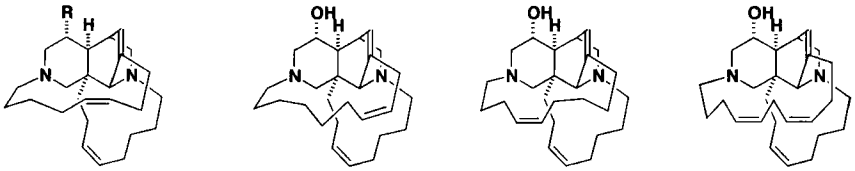
6. Petrosins/Aragupetrosins/Araguspongines/Xestospongins

Oxidation of the alkyl chains of *bis*-dihydropyridine macrocycles, followed by a Mannich-like cyclization onto an iminium salt by either an oxygen or a carbon nucleophile leads to the aragupetrosines,[14] araguspongines,[15] petrosins,[16] and xestospongins.[17] A biosynthetic proposal which generates each of these classes of alkaloids is shown in Scheme 7.[14,18] Starting from iminium salt **28**, oxidation of both alkyl connecting chains at the γ-position leads to diketone **29**. Methylation and Mannich-type cyclizations with both oxygen and carbon nucleophiles provides aragupetrosine A (**30**). Rotation of the alkyl chains of **29**, followed by nucleophilic attack by the ketone oxygen, leads to (+)-xestospongin A (**31**). Methylation and imine attack by oxygen provides (+)-araguspongine H (**32**). Rotation of the alkyl chains, followed by two Mannich cyclizations, leads to petrosin A (**33**).

With eight stereogenic carbons and two rigid sp^3 nitrogen lone pairs, there are a vast number of alkaloid stereoisomers possible within this class. The alkaloids shown in Scheme 7 are representative of the three main configurational series which have been isolated to date.

7. Ingenamines/Ingamines/Keramaphidin B/Xestocyclamines

Intramolecular cycloaddition reactions of partially reduced *bis*-dihydropyridine macrocycles with varying alkyl chain lengths and degrees of unsaturation lead to a class of pentacyclic compounds collectively known as the ingenamine alkaloids.[19] Interestingly, this class of alkaloids was anticipated by Baldwin and Whitehead in their proposal for the biogenic origin of manzamines A (**1**) and B (**3**).[3] In fact, the alkaloid keramiphidin B (**34**)[20] (Fig. 4) has a framework which is identical to the cycloadduct **5a** from the Baldwin/Whitehead hypothesis (Scheme 3).



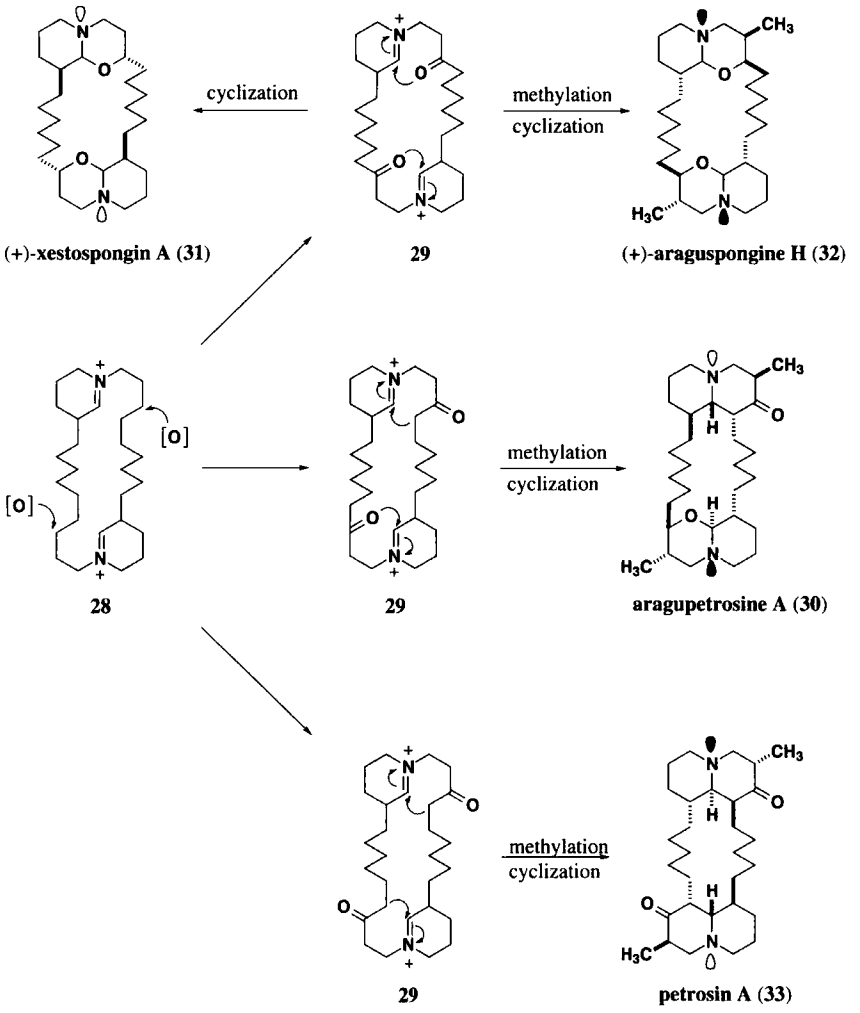
keramiphidin B R=H (34)
ingenamine R=OH (35)

ingenamine B (36)

ingenamine C (37)

ingenamine D (38)

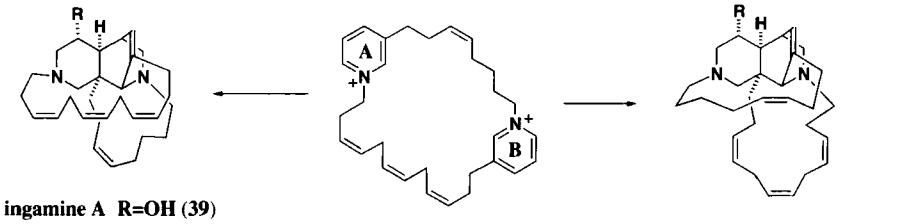
Figure 4



Scheme 7

In addition to keramiphidin B (**34**), a number of related alkaloids have been isolated. Ingenamine (**35**),[21] ingenamine B (**36**),[19] ingenamine C (**37**),[19] and ingenamine D (**38**)[19] (Fig. 4) all presumably arise *via* a similar biogenetic pathway. Additionally, the related alkaloids xestocyclamine A and B[22] have also been described, and were found to be inhibitors of protein kinase C.

Interestingly, ingamine A (**39**)[19] and B (**40**)[23] and ingenamine E (**41**) and F (**42**)[19] all appear to originate from a common *bis*-dihydropyridine macrocycle (**43**) (Scheme 8). If a partially reduced ring **B** acts as the diene and a partially reduced ring **A** is the dienophile in the biological Diels-Alder cycloaddition the ingamine A (**39**) and B (**40**) skeletons are formed. Conversely, if a partially reduced ring **A** acts as the diene and a reduced ring **B** becomes the dienophile in the [4+2]-cycloaddition the ingenamine E (**41**) and F (**42**) systems are generated.

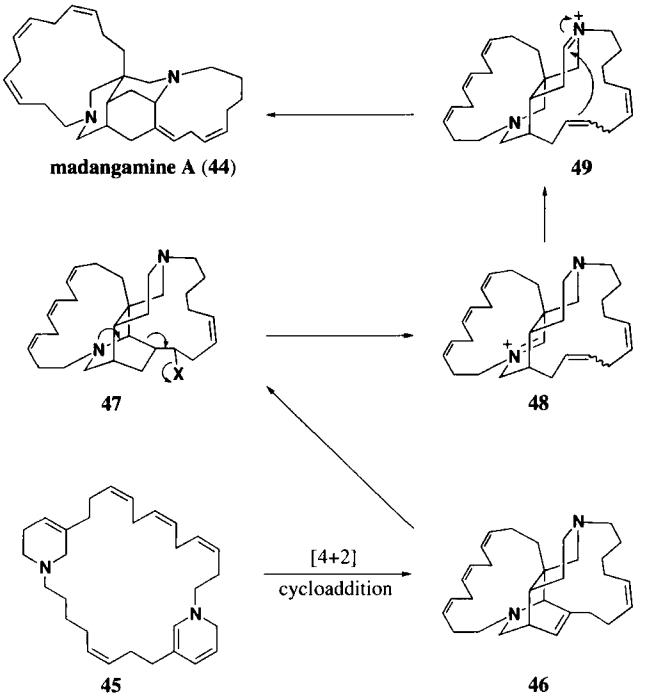


Scheme 8

Several recent studies have shown the absolute configuration of a number of the ingenamine alkaloids to be antipodal to manzamine A (**1**) and B (**3**).[19,24] The antipodal ingenamines and ircinols A (**11**) and B (**12**) raise some interesting questions regarding the nature of biological [4+2]-cycloadditions.[5] Kong and Andersen have suggested that perhaps there are enantiomeric enzymes capable of catalyzing this intramolecular condensation.[19]

8. Madangamine A

Several alkaloids, including the previously discussed ircinals, ircinols, and manzamines, are directly descended from ingenamine-like precursors. Additionally, the marine alkaloid madangamine A (**44**) (Scheme 9) presumably arises from an ingenamine-like precursor.[25] Starting from partially

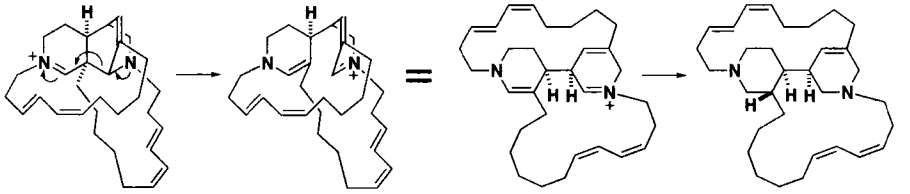


Scheme 9

reduced *bis*-dihydropyridine macrocycle **45**, a [4+2]-cycloaddition provides ingenamine-like adduct **46**. Adduct **46** has a skeleton which is identical to ingenamine F (**42**). Allylic activation leads to pentacyclic intermediate **47**, which then undergoes a fragmentation to provide tetracyclic iminium intermediate **48**. Redox exchange between the two piperidine rings leads to **49**, which undergoes a Mannich-like trapping of the iminium salt with an olefinic moiety, followed by oxidation, to provide the natural product.

9. Halicyclamine A

Fragmentation at a different location of an ingenamine-like cycloadduct leads to the natural product halicyclamine A (**52**)[26] (Scheme 10). Iminium forming fragmentation of ingenamine-like pentacycle **50** as shown leads to tetracyclic salt **51**. Reduction of the iminium salt and enamine then leads to halicyclamine A (**52**).[27]



50 **51** **halicyclamine A (52)**

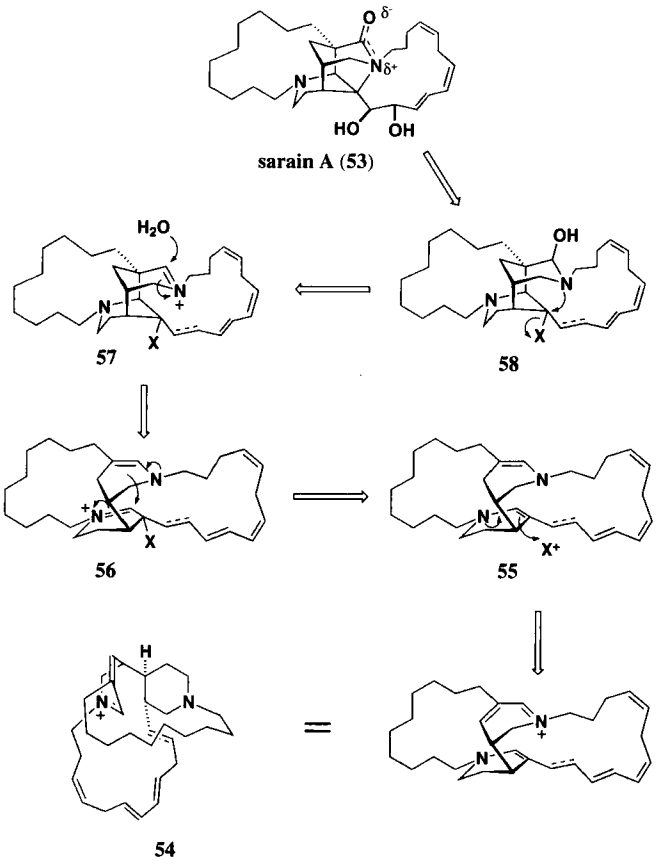
Scheme 10

10. Sarain A

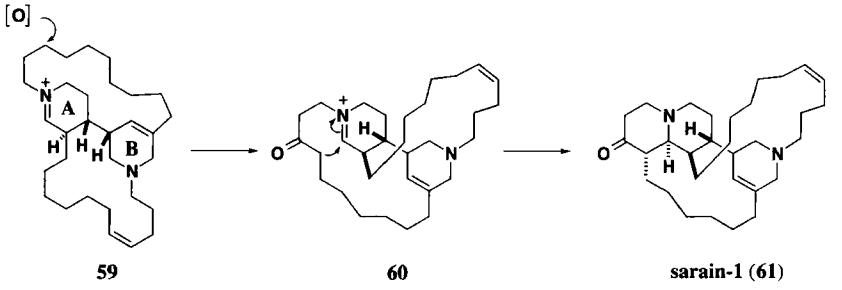
The relationship between the manzamines and sarain A (**53**)[28] (Scheme 11) is not immediately obvious. Upon closer inspection, however, it becomes apparent that sarain A (**53**) can be rationalized as deriving from a precursor similar to one producing the halicyclamines. Starting from halicyclamine-like compound **54**, reduction of the iminium salt leads to **55**. Iminium salt formation in the opposite piperidine ring and olefin activation provides **56**. Mannich-like bond formation leads to pentacyclic intermediate **57**. Hydrolysis of the iminium functionality in **57** gives amino alcohol **58**. Nucleophilic attack by nitrogen to form the final bond, followed by dihydroxylation of an olefin ultimately provides the zwitterionic natural product sarain A (**53**).[29]

11. Sarains/Isosarains

Sarain-1 (**61**)[30] is another alkaloid which appears to arise from a halicyclamine-related precursor (Scheme 12). Starting from halicyclamine-like iminium salt (**59**), oxidation at the γ-position of the alkyl chain followed by a rotation of piperidine ring B leads to ketone **60**. Intramolecular Mannich cyclization of **60** provides sarain-1 (**61**)[31].



Scheme 11



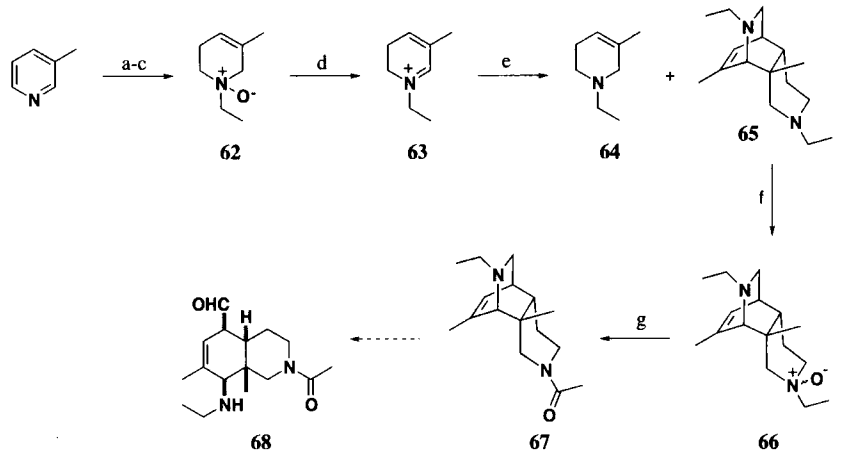
Scheme 12

II. BIOMIMETIC APPROACHES

The novel cytotoxic alkaloids keramaphidin B (**34**),[20] isolated from the Okinawan marine sponge *Amphimedon sp.*, and halicyclamine A (**52**) produced by a *Haliclona* sponge[26] have been the object of biomimetic approaches by two groups.

1. Baldwin Approach to Keramaphidin B and Halicyclamine A.

Baldwin and coworkers have investigated biogenetically patterned synthetic approaches to the ring systems of alkaloids **34** and **52**.[32-34] Their approach began by exploring a biomimetic [4+2]-cycloaddition model system in order to gain access to the tricyclic core of keramiphidin B (**34**).[32] It is envisaged that subsequent manipulations of keramaphidin B could lead to the ircinal and eventually the manzamine ring systems. Starting from 3-methylpyridine (Scheme 13), treatment with

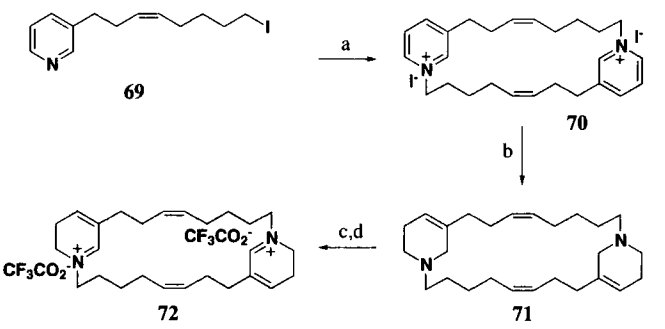


a) CH_3CH_2Br, acetone, reflux, 86%; b) $NaBH_4$, H_2O, CH_3OH, 55%; c) *m*-CPBA, CH_2Cl_2, 87%; d) $(CF_3CO)_2O$, CH_2Cl_2, 100%; e) pH 8.3 TRIS/HCl buffer, rt, 18 h; $NaBH_4$, H_2O, CH_3OH; 10% of **65** from **63**; f) *m*-CPBA, CH_2Cl_2, 75%; g) $(CH_3CO)_2O$, CH_2Cl_2, -78°-rt, 50%.

Scheme 13

bromoethane, followed by $NaBH_4$ reduction and subsequent *N*-oxide formation with *m*-CPBA gave compound **62** in 41% overall yield. Treatment of **62** with trifluoroacetic anhydride provided dihydropyridinium salt **63**. Stirring salt **63** in pH 8.3 TRIS/HCl buffer, followed by $NaBH_4$ reduction, led to tetrahydropyridine **64** as the major product, along with the desired tricycle **65** in 10% yield from **63**. Subsequent modifications of the route have led to the desired tricycle in up to 30% yield. *N*-Oxide **66**, formed by treatment of **65** with *m*-CPBA, was then exposed to acetic anhydride to give acetamide **67**. It is expected that subsequent clevage of the N1-C6 bond would furnish amino aldehyde **68** possesing the perhydroisoquinoline framework of the ircinals and manzamines. However, no work towards this goal has been presented to date.

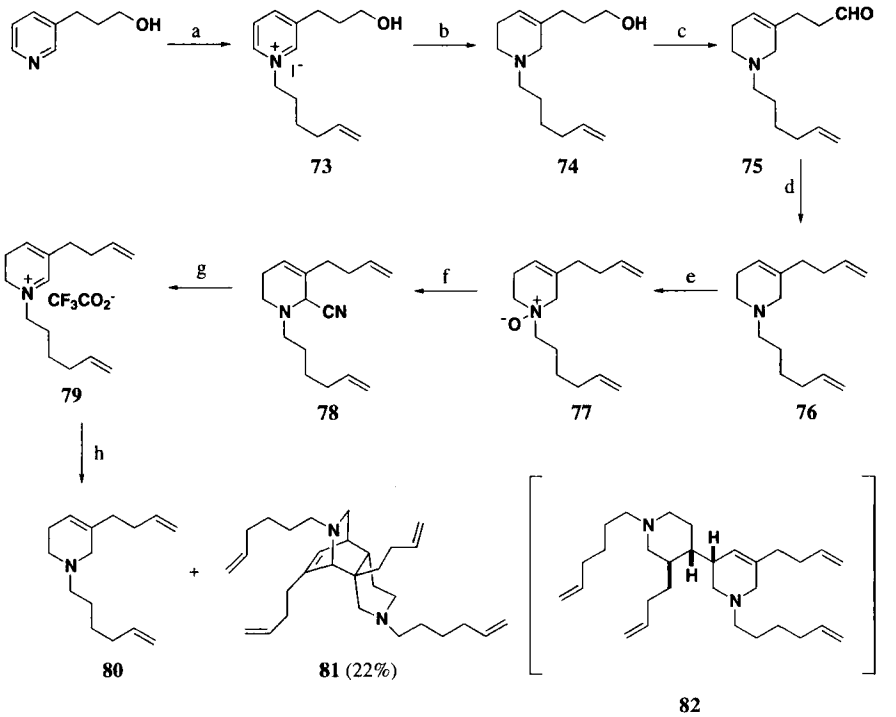
Baldwin's next system involved the synthesis of a *bis*-dihydropyridine macrocycle similar to that implicated in the biosynthesis of the manzamines. Starting from iodide **69**, cyclodimerization in refluxing acetone gave *bis*-pyridine macrocyclic salt **70** in 44% yield (Scheme 14).[33] $NaBH_4$ reduction of **70** led to *bis*-tetrahydropyridine **71**, which was then oxidized with *m*CPBA, followed by treatment with trifluoroacetic anhydride to give *bis*-dihydropyridinium salt **72**. The behavior of this compound under the conditions for the [4+2]-cycloaddition reaction have yet to be reported.



a) 40 mM in acetone, reflux, 96 h, 40-44%; b) $NaBH_4$, H_2O, MeOH, 66%;
c) *m*-CPBA, CH_2Cl_2, 100%; d) $(CF_3CO)_2O$, CH_2Cl_2, 100%.

Scheme 14

The most recent approach reported by Baldwin *et al.* is outlined in Scheme 15.[34] Starting with 3-pyridinepropanol, reaction with 6-iodohex-1-ene gave pyridinium salt **73**, and $NaBH_4$ reduction led to tetrahydropyridine **74**. Swern oxidation of **74** then provided aldehyde **75**, and



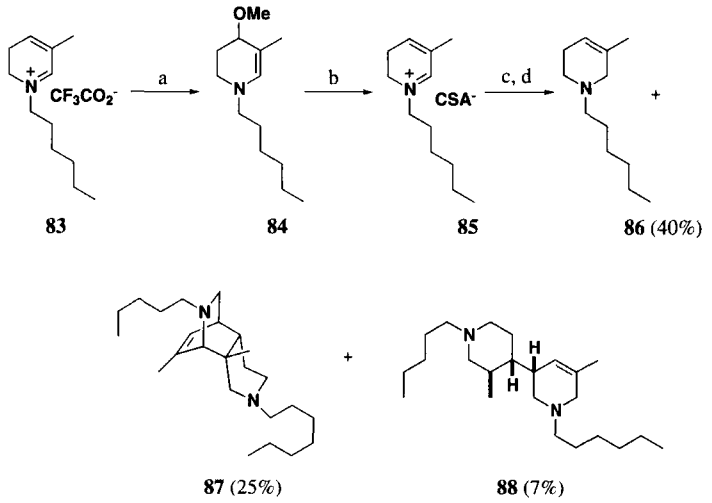
a) 6-iodohex-1-ene, PhMe, Δ, 100%; b) $NaBH_4$, MeOH, -78-0°, 93%;
c) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, -78°, 98%; d) methyltriphenylphosphonium bromide, *n*-BuLi, THF, 90%;
e) *m*-CPBA, CH_2Cl_2, 0°, 100%; f) TFAA, CH_2Cl_2, 0°; KCN, H_2O, pH 3-4, 87%; g) $AgOCOCF_3$, EtOH
h) H_2O, EtOH, TRIS, pH 8.3, 1 h; $NaBH_4$, MeOH, -78°-rt.

Scheme 15

subsequent Wittig olefination gave tetrahydropyridine **76**. Oxidation of **76** with *m*-CPBA led to *N*-oxide **77**, which upon exposure to trifluoroacetic anhydride, followed by *in situ* trapping of the intermediate iminium ion, provided α-amino nitrile **78**. Treatment of **78** with $AgOCOCF_3$ then provided dihydropyridinium salt **79**. [4+2]-Cycloaddition of salt **79** was performed in 1:1 ethanol/water buffered to approximately pH 8.3 at room temperature for one hour. The crude reaction mixture was then cooled to -78° and reduced with $NaBH_4$ in methanol to provide tetrahydropyridine **80** as the major product along with the desired cycloadduct **81** (22% yield from **79**). It was found that when the $NaBH_4$ reduction was performed at room temperature, small quantities of halicyclamine-like bicycle **82** were also formed. The Baldwin group is currently investigating the use of ring-closing metathesis to form keramaphidin B (**34**) from intermediate **81**.

2. Das Approach to Keramaphidin B and Halicyclamine A

Das and coworkers have investigated a model synthesis for keramiphidin B (**34**) and halicyclamine A (**52**) which is very similar to the Baldwin approach.[35] The key difference involves the conditions under which the [4+2]-cycloaddition takes place. The Das synthesis begins with dihydropyridinium salt **83** (Scheme 16) which upon treatment with NaOMe provides tetrahydropyridine **84**. Subsequent exposure of this intermediate to one equivalent of camphorsulfonic acid gave



a) NaOMe, 80%; b) camphorsulfonic acid, MeOH, 100%; c) 0.6 eq Et_3N, CH_2Cl_2, 2 h; d) $NaBH_4$, *i*-PrOH.

Scheme 16

dihydropyridinium salt **85**. It might be noted that it was found that the camphorsulfonic acid derived dihydropyridinium salts were obtainable in pure form, whereas the corresponding trifluoroacetic acid salts were consistently contaminated with trifluoroacetic acid. Treatment of salt **85** with 0.6 equivalents of triethylamine in CH_2Cl_2 for two hours, followed by $NaBH_4$ reduction in *iso*propanol provided tetrahydropyridine **86** in 40% yield, in addition to keramiphidin-like compound **87** and halicyclamine analog **88** in 25% and 7% yields, respectively

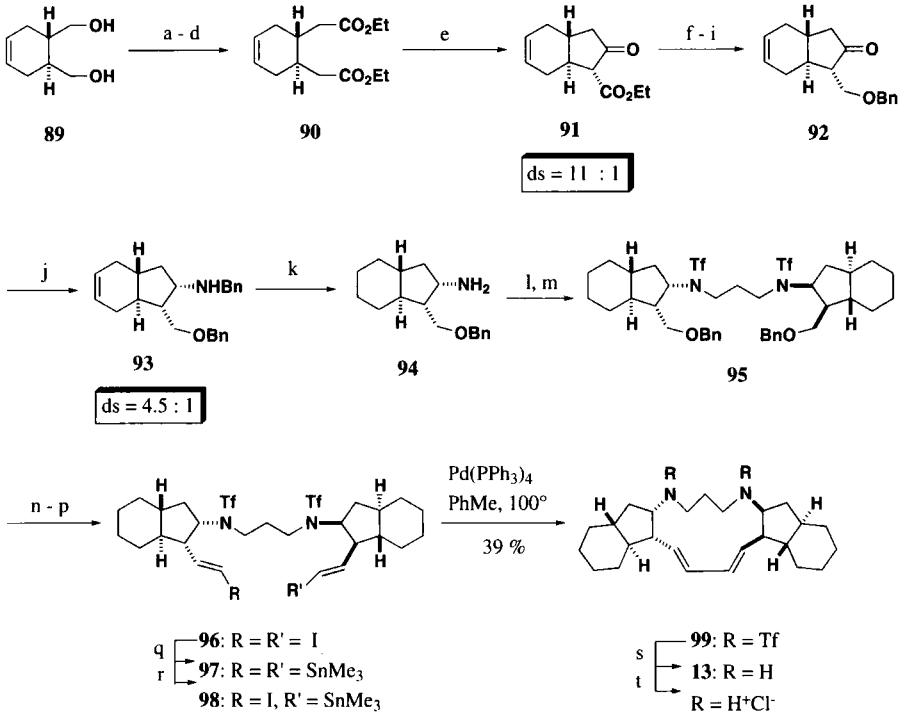
III. SYNTHETIC APPROACHES

1. Papuamine (13) and Haliclonadiamine (14)

The unusual pentacyclic alkaloid papuamine (**13**), isolated in 1988 by Scheuer and coworkers from the sponge *Haliclona sp.* collected off the coast of Papua New Guinea,[8] and haliclonadiamine (**14**), which was found, along with minor amounts of **13**, to be the major alkaloid of the marine sponge *Haliclona sp.* collected near Palau,[9] have been the object of several recent exercises in total synthesis. Both alkaloids display significant inhibitory activity against the growth of *Candida albicans, Bacillus subtilis* and *Staphylococcus aureus.* Papuamine also shows antifungal activity against *Trichophyton mentagrophytes.*

a. Barrett Total Synthesis of Papuamine

The first total synthesis of papuamine (**13**), achieved by Barrett and coworkers,[36] started from enantiomerically pure (+)-diol **89**, which was prepared by a Diels-Alder reaction of di-(-)-menthyl fumarate with 1,3-butadiene, and subsequent reductive cleavage of the chiral auxiliary (Scheme 17). The diol was homologated to diester **90**, followed by Dieckmann cyclization under thermodynamic control to give β-ketoester **91** as 11:1 mixture of diastereomers in 95% yield. Ketalization of the carbonyl group with ethylene glycol caused equilibration, changing the ratio to 22:1 in favor of the desired α-isomer. After reduction of the ester moiety, protection of the resulting alcohol as the benzyl ether, and subsequent removal of the ketal gave ketone **92** in high overall yield. Reductive amination of **92** with benzylamine and $NaBH(OAc)_3$ provided a 4.5:1 selectivity for *cis* secondary amine **93**. Selective *N*-deprotection of **93** with concurrent alkene reduction to compound **94** was achieved with Pd/C and ammonium formate. After protection of the amine **94** as its trifluoromethanesulfonamide, coupling with 1,3-dibromopropane catalyzed by KI gave the *bis*-hydrindane system **95** in 90% yield. For the initially planned macrocyclization *via* a *bis*-vinylstannane homocoupling, **95** was homologated to the *bis*-(E)-vinyl iodide **96** by debenzylation, Swern oxidation, and subsequent treatment with iodoform/$CrCl_2$. After *bis*-stannylation to compound **97** using hexamethylditin and Li_2CO_3 under $PdCl_2(PPh_3)_2$ catalysis, the planned Pd(0)-catalyzed homocoupling unfortunately failed. The problem was solved by desymmetrization of **97** by treatment with 1 equivalent of iodine to obtain iodostannane **98** in 44% yield, along with recovered staring material (24 %) and recyclable diiodide **96** (24 %). An intramolecular Stille coupling of **98** successfully gave the central 13-membered ring, affording **99** in 39% yield. The total synthesis was completed by reductive removal of the nitrogen protecting groups to obtain (+)-papuamine (**13**) and the corresponding dihydrochloride. At this point it was found that the (+)-diol **89** had led to the unnatural enantiomer of **13** (synthetic **13**: $[\alpha]_D$ +138.6 (c 0.34, MeOH); natural **13**: $[\alpha]_D$ -140 (c 1.3, MeOH)), thereby establishing the absolute stereochemistry of papuamine.

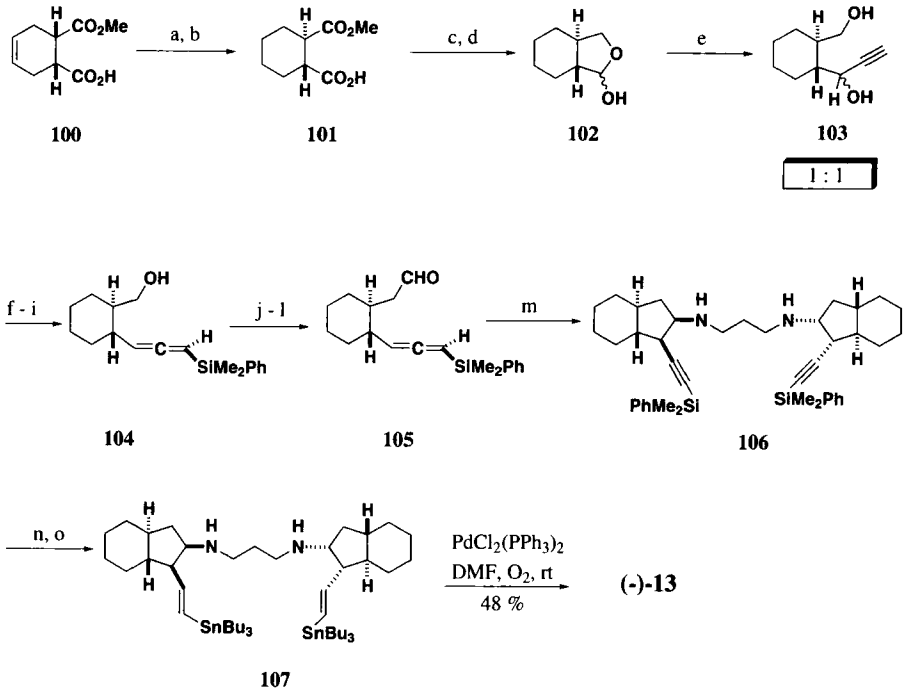


a) TsCl, pyr, 83%; b) NaCN, EtOH, heat, 95%; c) KOH, H_2O, heat, 95%; d) EtOH, H_2SO_4, 99%;
e) NaH, THF, heat, 95%; f) $HO(CH_2)_2OH$, *p*-TsOH, PhH, molecular sieves, heat, 100%;
g) $LiAlH_4$, Et_2O, 99%; h) NaH, BnBr, DMF, 92%; i) dil. HCl, THF, 25-60°, 97%;
j) $BnNH_2$, AcOH, $NaBH(OAc)_3$, THF, 85%; k) NH_4HCO_2, 10% Pd/C, MeOH, heat, 86%;
l) Tf_2O, Et_3N, CH_2Cl_2, - 78°; m) 1,3-dibromopropane, K_2CO_3, cat. KI, MeCN, heat, 90%;
n) H_2, 10% Pd/C, EtOH, 95%; o) Swern oxidation; p) CHI_3, $CrCl_2$, dioxane/THF, 71% over 2 steps;
q) $((CH_3)_3Sn)_2$, Li_2CO_3, $PdCl_2(PPh_3)_2$, THF, 60°, 51%; r) I_2, Et_2O, 44%;
s) $LiAlH_4$, Et_2O, heat, 42%; t) MeOH, H_2O, HCl.

Scheme 17

b. Weinreb Total Synthesis of (-)-Papuamine

Weinreb and Borzilleri employed a novel intramolecular imino ene reaction as a pivotal step in the synthesis of (-)-(**13**) (Scheme 18).[37] A notable feature of this sequence is the stereoselective formation of four stereocenters in a single operation. Again, an enantiopure starting alcohol ester was arbitrarily chosen, since the absolute stereochemistry of papuamine was not known at the time work was initiated. Acid ester **100** was prepared by PLE catalyzed partial hydrolysis of the corresponding *meso* diester. After hydrogenation of the double bond, the correct *trans*-stereochemistry was set by base-induced epimerization to yield **101**. Two step reduction of **101** led to lactol **102**. Addition of ethynylmagnesium bromide to the lactol produced a separable 1:1 mixture of propargyl alcohols **103**. Assembly of the requisite imino ene reaction precursor was accomplished by a stereospecific $SN^{2'}$ *anti* addition of a silyl cuprate reagent to the protected propargyl acetate derived from (*R*)-diol **103**.



a) 10% Pd/C, EtOH, H_2, 99%; b) NaOMe, MeOH, reflux, 96 %; c) Na/NH_3, EtOH, 70%;
d) DIBALH, PhMe, - 78°, 95%; e) ethynylmagnesium bromide, THF, 0°, 95%;
f) Ph_3CCl, DMAP, Et_3N, DMF, 45°, 95%; g) Ac_2O, DMAP, Et_3N, CH_2Cl_2, rt, 999%;
h) $Me_2PhSiLi$, CuCN, THF, - 78°, 88%; (i)*p*-TsOH, MeOH, rt, 97%; (j) MsCl, Et_3N, CH_2Cl_2, rt, 99%;
k) KCN, DMSO, 45°, 70%; (l) DIBALH, PhMe, -78°-0°, 77%;
m) 1,3-diaminopropane, PhMe, reflux, 70%; n) TBAF, THF, 74%; o) Bu_3SnH, AIBN, THF, reflux, 80%.

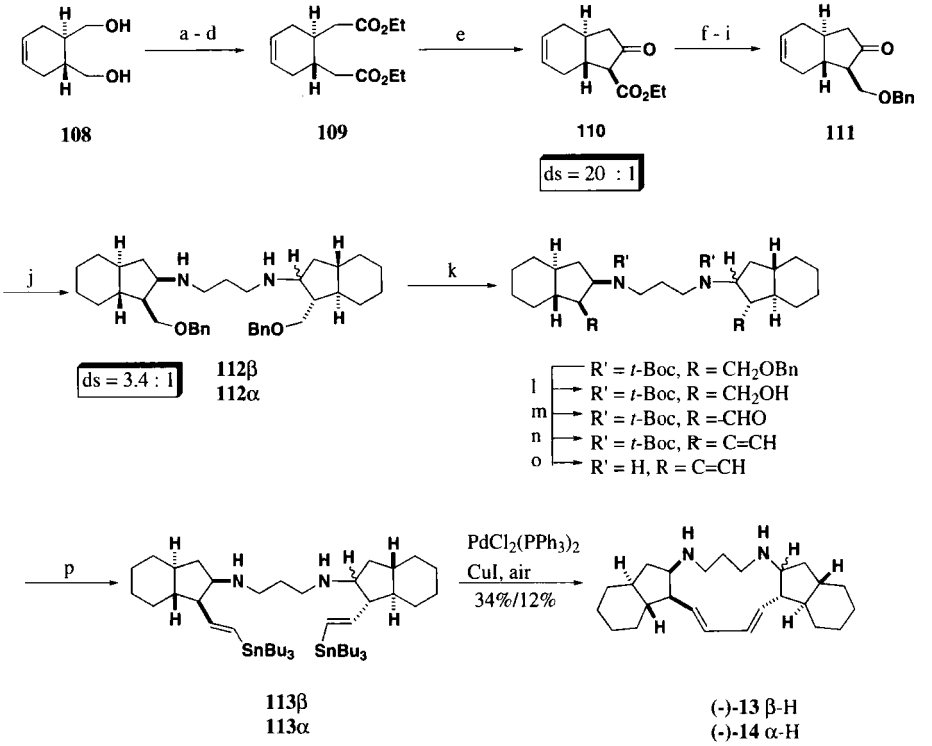
Scheme 18

Homologation of the primary alcohol group of **104** led to allenylsilane aldehyde **105**. Reaction of this aldehyde with 0.5 equivalents of 1,3-diaminopropane in refluxing toluene yielded tetracycle **106** as a single isomer. This cyclization is believed to occur by a concerted double pericyclic ene reaction between the *bis*-imine, generated from two equivalents of aldehyde **105** and one equivalent of the diamine, and the allenylsilane moieties. Desilyation of **106** with TBAF and subsequent tributyltin hydride addition produced *bis*-(*E*)-vinylstannane **107**. Finally, intramolecular homocoupling of **107** was achieved under Pd^{II} catalysis to afford (-)-papuamine (**13**) in reasonable yield without the need of any *N*-protection or desymmetrization process. Comparison of the optical rotation of natural and synthetic papuamine unambiguously confirmed the absolute stereochemistry of the alkaloid.

c. Heathcock Total Syntheses of Papuamine and Haliclonadiamine

The Heathcock group assembled the alkaloid framework in a fashion analogous to the Barrett approach by employing ketone **111** in a reductive amination sequence (Scheme 19).[38] Thus, enantiopure (-)-diol **108** was obtained by an asymmetric Diels-Alder reaction of di-(+)-menthyl

fumarate and 1,3-butadiene. Preparation of ketone **111** was accomplished in a straightforward manner as shown in Scheme 19. Dieckmann cyclization of diester **109** proceeded with a 20:1 selectivity.



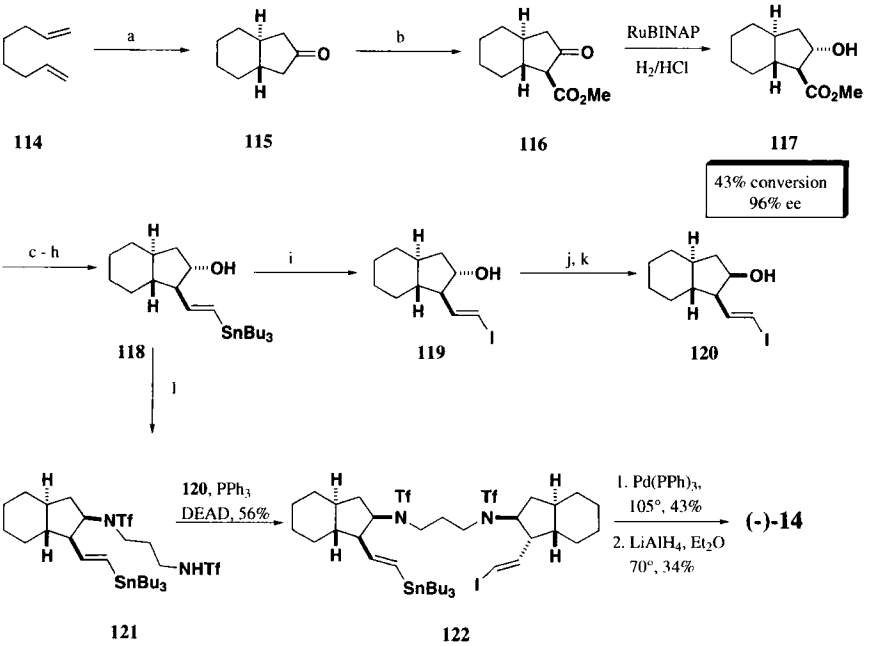
a) MsCl, Et_3N, CH_2Cl_2, 96%; b) KCN, DMSO, heat, 99%; c) KOH, $HO(CH_2)_2OH$, H_2O, 160°, 92%; d) EtOH, H_2SO_4, 98%; e) KH, THF, 0°, 98%; f) $HO(CH_2)_2OH$, *p*-TsOH, PhH, heat, 81%; g) $LiAlH_4$, Et_2O, 0°, 100 %; h) NaH, BnBr, THF, rt, 89%; i) PPTS, acetone/water, heat, 97%; j) 1,3-diaminopropane, $NaBH(OAc)_3$, dichloroethane/HOAc,rt, 58%; k) (*t*-Boc)$_2O$, CH_2Cl_2, rt, 95%; l) H_2, Pd/C, EtOH, 100%; m) TPAP, NMO, CH_2Cl_2, rt, 92%; n) $N_2CHPO(OMe)_2$, KO-*t*-Bu, THF, -78°- rt, 95 %; o) TFA, CH_2Cl_2, 93 %/92%; p) Bu_3SnH, AIBN, PhMe, heat, 93 %/43 %.

Scheme 19

Reductive amination of **111** with 1,3-diaminopropane gave the tetracyclic diamines **112β/112α** in a 3.4:1 ratio favoring the symmetrical structure **112β**. The lack of stereocontrol in this reaction in fact made it possible to prepare both alkaloids, since haliclonadiamine (**14**) is epimeric to papuamine at the center involved (*vide infra*). After Boc-protection of the nitrogen atoms, the protected primary alcohol groups of **112** were converted to the (*E*)-stannanes **113β/113α** in four steps as shown. It is noteworthy that the tin hydride addition to the minor *bis*-alkyne occurred in only 43% yield in contrast to 93% yield for the symmetrical case. Oxidative homocoupling of both *bis*-stannanes **113β/113α** with Pd^{II}/Cu^{+} in the presence of oxygen finalized the syntheses of both alkaloids in moderate yields (34 and 12%, respectively).

d. Taber (-)-Haliclonadiamine Synthesis

Taber and Wang reported a facile entry to the *trans*-fused alkaloid 6/5-ring system by cyclozirconation of 1,7-octadiene (**114**), followed by CO insertion of the zirconacycle to produce ketone **115** in good yield (Scheme 20).[39] Carbomethoxylation of **115** gave racemic keto ester **116**.



a) Cp_2ZrCl_2, *n*-BuLi/75°/CO, -78°/HOAc, 79%; b) $(MeO)_2CO$, NaH, DME, 69%;
c) TBDMSCl, imid. CH_2Cl_2, rt; d) DIBALH, CH_2Cl_2, -78°, 83% over 2 steps; e) Swern oxidation;
f) dimethyl-(1-diazo-2-oxopropyl)phosphonate, K_2CO_3, MeOH, 88% over 2 steps; g) H^+, MeOH, rt, 95%;
h) Bn_3SnH, AIBN, PhMe, 100-105°, 87%; i) I_2, Et_2O, 96%; j) *p*-$NO_2C_6H_4CO_2H$, PPh_3, DEAD, PhH, rt, 82%;
k) K_2CO_3, MeOH, 96%; l) N,N'-*bis*-triflyl-1,3-diaminopropane, PPh_3, DEAD, PhH, rt, 66%.

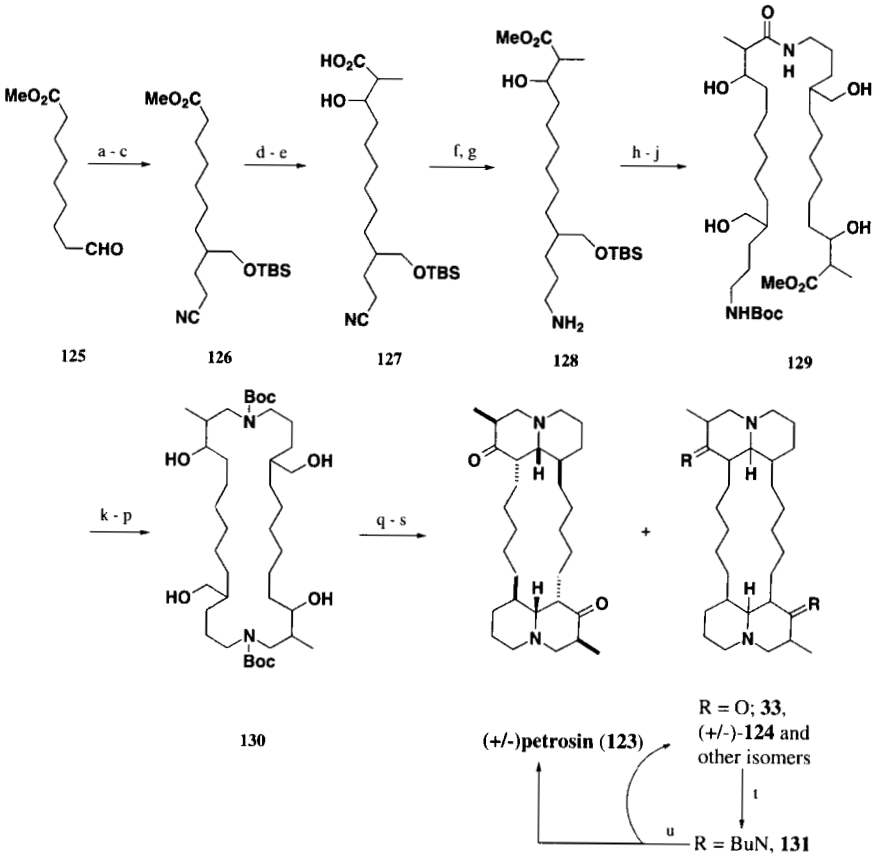
Scheme 20

Kinetic resolution of **116** by catalytic hydrogenation using (*S*)-Ru-BINAP/H_2 in MeOH/HCl gave enantiopure hydroxyester **117** in 43% yield. It was found that the amount of HCl used is crucial for the course of the reaction. By adding more than 10% HCl, the other enantiomer of **116** was also reduced to produce a mixture of diastereomers. Ester **117** was then homologated to (*E*)-vinylstannane **118** in 6 straightforward steps. It was planned to effect the intramolecular cyclization to produce (-)-haliclonadiamine (**14**) by a Stille coupling of an iodostannane as described by Barrett (Scheme 17). Therefore, stannane **118** was subjected to a Mitsunobu coupling with 2 equivalents of *N,N'-bis*-triflyl-1,3-diaminopropane to give monoalkylated diamide **121** with inversion of stereochemistry. A portion of stannane **118** was converted to iodide **119**, and the alcohol functionality was then inverted by a Mitsunobu reaction with 4-nitrobenzoic acid, followed by ester cleavage to yield *cis*-alcohol **120**. Finally, **120** and **121** were coupled under Mitsunobu conditions to obtain iodostannane **122** with the

correct haliclonadiamine stereochemistry in 56% yield. Stille coupling of **122** followed by reductive removal of the triflamide groups gave (-)-**14** in moderate overall yield.

2. Total Synthesis of the Petrosins

The three ichthyotoxic *bis*-quinolizidine alkaloids petrosin (**123**), petrosin A (**33**), and petrosin B (**124**) were isolated from the sponge *Petrosia seriata*, collected near Papua New Guinea.[16] The mixture of petrosins was found to be toxic to the fish *Lebistes reticulatus*. A rather unusual fact is that alkaloid **123** was isolated as a racemate. It had been postulated that racemization of **123** occurred by a post-biosynthetic process by simple enolizations and by retro-Mannich/Mannich and iminium ion/enamine equilibria for the remote stereocenters.[40] Petrosin A (**33**) is an achiral *meso* compound,



a) pyrrolidine, K_2CO_3/acrylonitrile, CH_3CN/H_2O, 73%; b) $NaBH_4$, MeOH, 100%; c) TBSCl, imid., DMF, 95%; d) DIBALH, CH_2Cl_2, -95°, 80%; e) propionic acid, 2 eq. LDA, THF, 77%; f) CH_2N_2, ether, 100%; g) H_2, PtO_2, EtOAc, HOAc, 97%; h) **127**, DCC, HOBT, THF, 70%; i) H_2, PtO_2, EtOH, HCl; j) $(Boc)_2O$, dioxane, H_2O, 90% over 2 steps; k) NaOH, MeOH, THF; l) DCC, C_6F_5OH, THF; m) 6 N HCl, dioxane; n) dioxane, pyridine, 90°, high dilution, 78% over 4 steps; o) $LiAlH_4$, THF; p) $(Boc)_2O$, dioxane, H_2O, 90% over 2 steps; q) Dess-Martin periodinane, CH_2Cl_2; r) 1 N HCl, EtOH, H_2O; s) 0.2 N HOAc, EtOH, 62% over 3 steps; t) butylamine, molecular sieves; u) propylammonium acetate, dichloroethane/H_2O, 80% over 2 steps.

Scheme 21

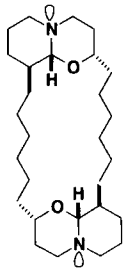
whereas **124** shows optical activity. The Heathcock group proposed a synthesis of the petrosins by a double Mannich cyclization without regard to stereochemistry in order to prove the hypothesis regarding post-biosynthetic equilibration.

Ester aldehyde **125** was cyanoethylated, and reduction of the aldehyde and subsequent alcohol protection as the TBS ether provided nitrile **126** (Scheme 21). Further homologation of **126** to hydroxy acid **127** was accomplished by addition of the dianion of propionic acid to the aldehyde derived from **126** by DIBALH reduction. A portion of **127** was converted to amino ester **128** in high overall yield. DCC/HOBT coupling of **127** and **128**, followed by nitrile reduction and Boc protection, produced amide **129**.

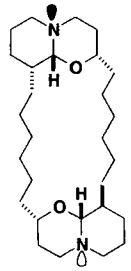
Macrocyclization was achieved using a pentafluorophenyl ester activating group to yield the macrolactam in 78% yield over 4 steps. Both amide linkages were reduced to the secondary amines and were subsequently protected as *t*-butyl carbamates **130**. All four alcohol groups were then oxidized with Dess-Martin periodinane. After acidic removal of the Boc groups, Mannich cyclization was induced with 0.2 M acetic acid to provide a petrosin mixture in 62% yield from precursor **130**. Racemic petrosin (**123**) crystallized directly from the mixture, whereas petrosin A (**33**) and (+/-)-petrosin B (**124**) were isolated by chromatography from the mother liquor. Direct acid induced epimerization of the alkaloids did not occur as anticipated. However, the corresponding *N*-butyl imines **131** could be equilibrated to produce additional racemic petrosin (**123**).

3. Syntheses of (+)-Xestospongin A (31) and (-)-Xestospongin C (132)

The C_2-symmetric xestospongin A (**31**) and its epimer (-)-xestospongin C (**132**) were originally isolated from the marine sponge *Xestospongia exigua* in 1984 (Fig. 6).[17]



(+)-xestospongine A = (+)-araguspongine D (31)



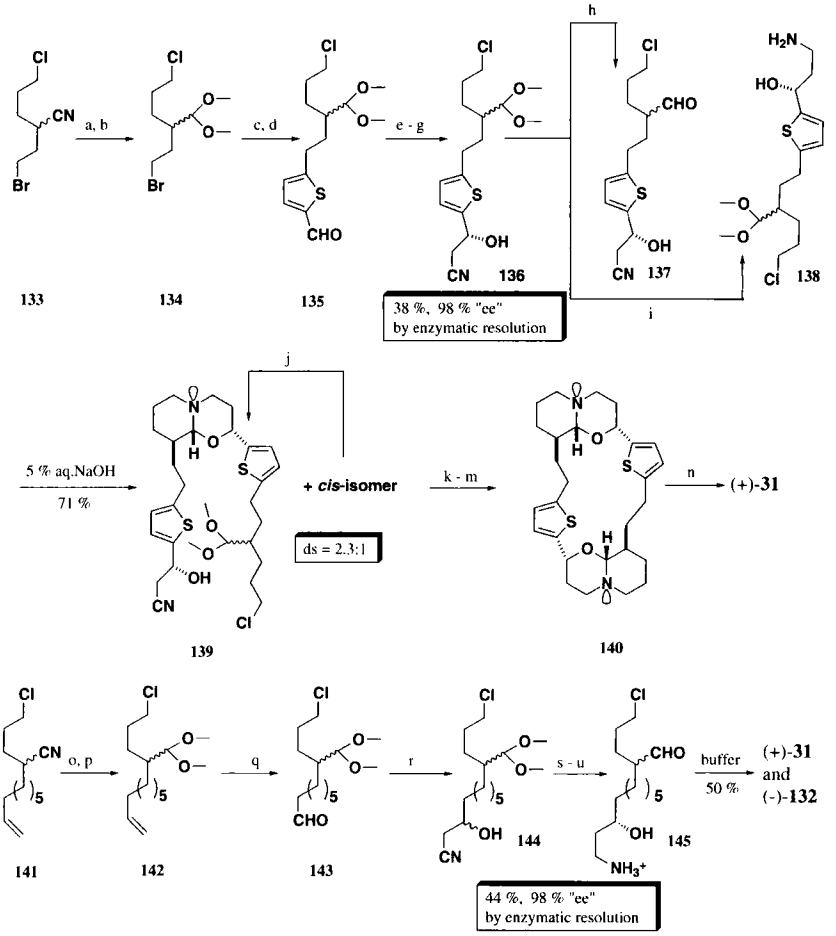
(-)-xestospongine C = (-)-araguspongine E (132)

Figure 6

These alkaloids possess vasodilative and cytotoxic properties. It has been found by analysis of the single crystal X-ray-structure of **132** that the two parent oxaquinolizidine ring systems can access both *trans*- and *cis*-decalin-like conformations *via* nitrogen atom inversion. In addition, the hexamethylene chains on each ring system can have *trans*- or *cis* orientations. The structure of **31** was assigned by spectroscopic comparison with data from **132**. Subsequently, in 1989 Kitagawa *et al.* described the isolation of araguspongines A-H and J from the sponge *Xestospongia sp.*[15] They and

Hoye[18] found that araguspongine D is identical to **31** and araguspongine E is identical to **132**. Interestingly, araguspongine D, as well as araguspongines B and E, were isolated as racemates. In 1996 Pettit and coworkers reported the isolation of racemic xestospongin D from the Singapore marine sponge *Niphates sp.*[41] Several strategies dealing with the synthesis of the basic alkaloid skeleton of the xestospongins, in particular involving construction of 2- and 2,9-substituted 1-oxaquinolizidines, have been published.[42] Hoye and coworkers completed an elegant total synthesis of **31** in 1994 and also described a simplified strategy for the synthesis of both alkaloids **31** and **132** in 1996.[43]

In the first approach racemic nitrile **133** was reduced and further transformed to acetal **134** (Scheme 22). A two-step homologation of **134** with 2-lithiothiophene and subsequent formylation



a) DIBALH, CH_2Cl_2, -78°, 92%; b) $HC(OMe)_3$, $CeCl_3$, MeOH, 98%; c) 2-lithio thiophene, THF, 0°- rt, 76%;
d) *n*- BuLi, DMF, -78°, 84%; e) lithioacetonitrile, THF, -78°, 96%; f) Ac_2O, pyridine, rt, 92%;
g) PS-30 from *Pseudomonas fluorescens*; h) TFA, H_2O, DMSO, 65°, 99%; i) $LiAlH_4$, Et_2O, 0°- rt, 92%;
j) Et_3N, $CDCl_3$, 80°; (k) $LiAlH_4$, Et_2O, 0°- rt, 78%; (l) TFA, H_2O, DMSO, 80°; (m) 5% NaOH, high dilution, 70%;
n) RaNi, H_2, EtOH; o) DIBALH, CH_2Cl_2, -78°, 86%; p) $HC(OMe)_3$, $CeCl_3$, MeOH, 97%;
q) O_3, CH_2Cl_2, MeOH, -78°/DMS, 79%; r) lithioacetonitrile, THF, -78°, 98%;
s) lipase SP-435, isopropenyl acetate, hexane, 65°; t) $LiAlH_4$, Et_2O, 0°- rt, 87%; (u) TFA, H_2O, DMSO, 80°.

Scheme 22

with DMF gave aldehyde **135**. Addition of lithioacetonitrile to **135**, followed by alcohol acetylation, provided a diastereomeric mixture of racemic acetates. Enzymatic resolution of these esters provided (*R*)-alcohol **136** in 38% yield with an ee ≥ 98% with respect to the carbinol center, along with 45% of recovered (*S*)-acetate.

Taking advantage of the symmetry of xestospongin A, one portion of **136** was hydrolyzed to aldehyde **137**, while some was reduced to amino alcohol **138**. Condensation of **137** and **138** provided a 2.3:1 mixture of *trans*- and *cis*-1-oxaquinolizidines **139**. The *cis*-isomer could be further equilibrated in the presence of triethylamine, presumably *via* an iminium/enamine equilibrium, to the thermodynamically more stable *trans*-isomer. It should be noted that the desymmetrized carbinol center controls the relative and absolute stereochemistry during the cyclization. For the closure of the other termini, **139** was further functionalized by nitrile reduction and acetal cleavage. Raising the pH to liberate the free amine from its "protected" ammonium salt, the macrocyclic *bis*-thiophene **140** was obtained in 70% yield under high dilution conditions. The cyclization could also be performed at higher concentration by addition of the ammonium salt to buffer solutions in a pH-range of 6-8 in comparable or slightly increased yields. Reductive desulfurization of **140** with Raney nickel afforded (+)-xestospongine A (**31**) in enantiomerically pure form.

In the second Hoye approach, total syntheses of **31** and **132** were also achieved without the rigid thiophene "linchpins". Thus, nitrile **141** was converted to acetal **142** in the same manner as for the synthesis of **134** (Scheme 22). Ozonolysis of the terminal olefin and homologation of the resulting aldehyde **143** produced racemic hydroxy nitrile **144**. Resolution of **144** with Lipase SP-435 by transesterification with vinyl acetate resulted in 44% isolated yield (≥ 98% ee) after two cycles. Nitrile reduction and acetal cleavage provided amino alcohol **145**. Cyclization occurred smoothly in a pH buffer to produce (+)-**31** and (-)-**132** in 50% yield in a 2.1-2.5:1 ratio.

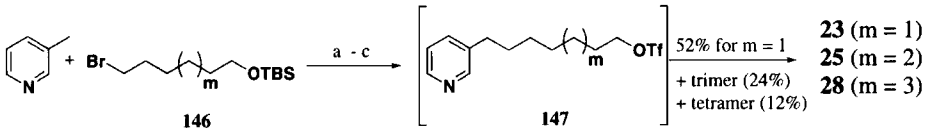
4. Approaches to the Cyclostellettamines

The cyclostellettamines were discovered in 1994 while screening sponge extracts for muscarinic receptor antagonists.[13] The hydrophilic extract of the sponge *Stellatta maxima* collected off the coast of Japan is the source of these alkaloids. Cyclostellettamines A-F (**22-27**) are cyclic *bis*-pyridinium salts which differ only in the length of the linking alkyl chains. Recently Faulkner isolated a polymeric pyridinium alkaloid from the Micronesian sponge *Callyspongia fibrosa* which was an activator of EGF (epidermal growth factor).[44] In order to try to establish the structure of the active compound, cyclostellettamines A, C and F (**22**, **24**, and **27**, respectively) and trimers/tetramers thereof were synthesized, thus unintentionally preparing natural products which were not known at the time. However, the structure of the EGF active compound still remains unsolved.

a. Faulkner Synthesis

3-Picoline was deprotonated with LDA and monoalkylated with TBS-protected bromo alcohols **146** (m=1-3) (Scheme 23). TBAF deprotection produced the corresponding alcohols, which were converted to their triflates **147** at -42°. Upon warming the mixture of crude triflates to room tempera-

ture, cyclostellettamines A, C and F (**22**, **24** and **27**) were formed in reasonable yields along with minor amounts of trimeric and tetrameric polypyridinium salts.

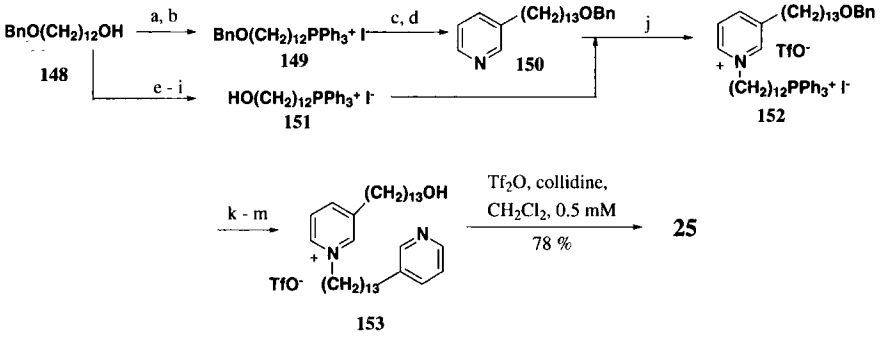


a) LDA, THF, -78°, 62-96%; b) TBAF, THF, rt, 92-100%; c) Tf_2O, diisopropylethylamine, - 42°-rt.

Scheme 23

b. Anan Synthesis

The Anan synthesis of cyclostellettamine C (**24**) relied on a stepwise ring construction, which could lead in principle to all the alkaloids of this class.[45] The synthesis began with monobenzylated 1,12-dodecadiol **148** (Scheme 24) which was converted to the corresponding phosphonium iodide **149** and combined with nicotinaldehyde to supply pyridine **150** after hydrogenation of the double bond. Compound **148** was also converted to the hydroxy phosphonium iodide **151** in 5 steps. Treatment of **151** with Tf_2O, followed by addition of **150**, furnished pyridinium salt **152**. Repeating the sequence of Wittig reaction and hydrogenation led, after debenzylation with TMSI, to alcohol **153**. Intramolecular *N*-alkylation of **153** was achieved by triflate formation under high dilution conditions to give cyclostellettamine C (**24**) in 78% yield.



a) I_2, imid. PPh_3 , PhH, rt,100%; b) PPh_3, PhMe, 88%; c) nicotinaldehyde, *n*-BuLi, THF, -20°, 85%;
d) H_2, Pd/C, EtOH, 90%; e) AcCl, Et_3N, CH_2Cl_2; f) H_2, Pd/C, EtOH, 95%; g) I_2, imid., PPh_3, PhH, rt, 98%
h) PPh_3, PhMe, 95%; i) NaOH, MeOH, 97%; j) Tf_2O, collidine, CH_2Cl_2, 68%;
k) nicotinaldehyde, NaH, THF, 43%; l) H_2, Pd/C, EtOH, 36%; m) TfOH, CH_2Cl_2/TMSI, rt, 81%.

Scheme 24

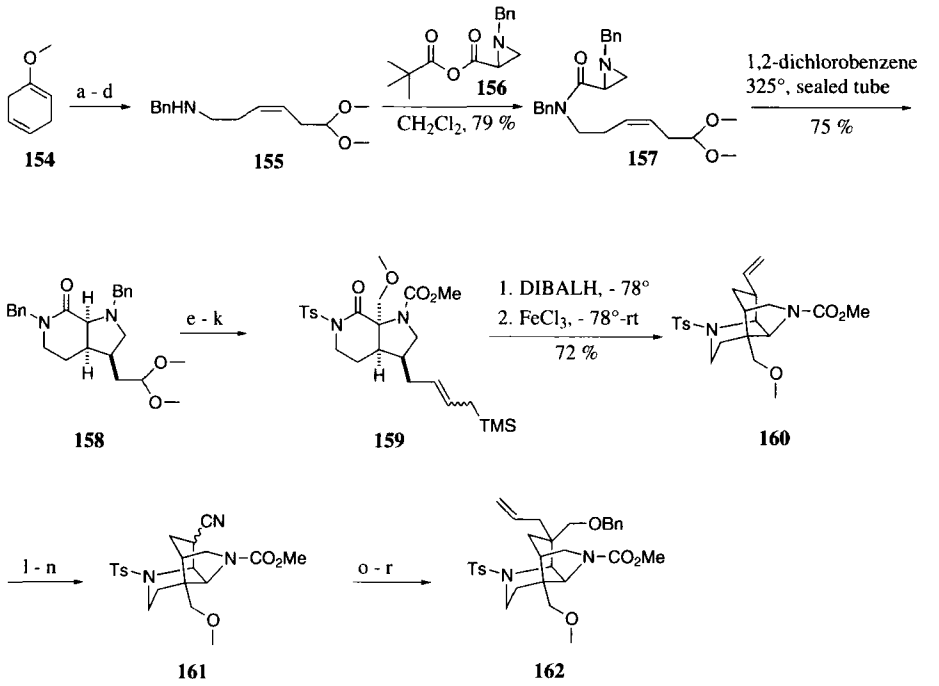
5. Approaches to Sarain A (53)

Sarain A (**53**) is an alkaloid isolated in 1989 from the sponge *Reneria sarai* collected in the bay of Naples.[28] Interestingly, **53** features a rather uncommon zwitterionic structure which arises from a proximal tertiary amine-aldehyde interaction. Two approaches towards this alkaloid have been published to date. The Weinreb group accomplished a synthesis of the tricyclic core based on an

azomethine ylide/olefin [3+2]-cycloaddition and an intramolecular allylsilane addition to an *N*-sulfonyliminium ion complex.[46] Heathcock devised a similar strategy also based on a [3+2]-cycloaddition.[47] Unfortunately, a subsequent intramolecular Mannich reaction for the formation of the tricyclic core failed in this approach (*vide infra*). However, this group successfully accomplished a model study for the construction of the 14-membered "eastern" ring containing the diol, the two *cis*- and the *trans* double bond.

a. Weinreb Approach

The Weinreb group has developed an efficient way to build the 5/6 *cis*-fused ring system **158** as depicted in Scheme 25.[46c] Thus, 1-methoxy-1,4-cyclohexadiene (**154**) was converted in four



a) O_3, -78° /DMS/PPTS, MeOH; b) $LiAlH_4$; c) MsCl, pyridine, 71% over 3 steps;
d) $BnNH_2$, DME, reflux, 69%; e) LHMDS, MOMBr, 70%; f) Na, NH_3, *t*-BuOH, THF, 65%;
g) LHMDS, TsCl, 86%; h) H_2, $Pd(OH)_2$; i) $ClCO_2Me$, pyridine; j) TsOH, acetone, H_2O, 85% over 3 steps;
k) Ph_3PMe^+ Br^-, *n*-BuLi/iodomethyltrimethylsilane, *n*-BuLi, THF, 52%; l) OsO_4, NMO;
m) NH_2OH•HCl, pyridine; n) phosgene, rt, 87% over 3 steps; o) KHMDS, 18-crown-6, allylbromide, 62%;
p) DIBALH, -78°; q) $NaBH_4$; r) BnBr, TBAI, KH, 64% over 3 steps.

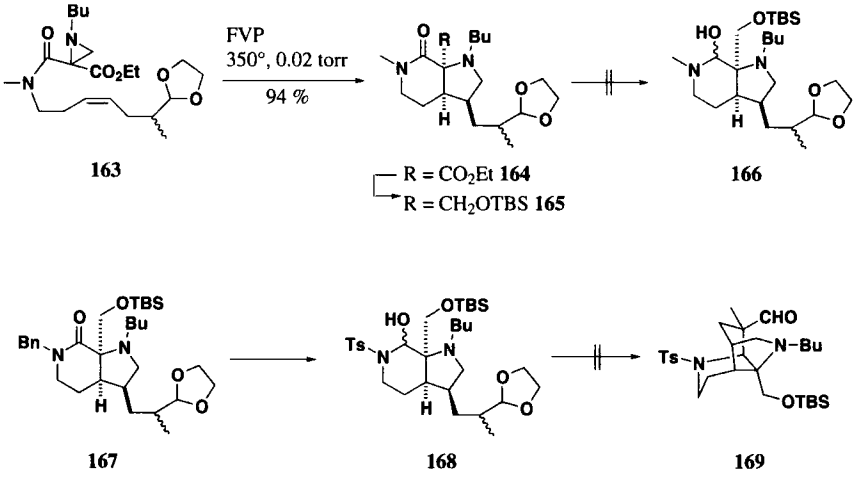
Scheme 25

steps to homoallylamine **155**. *N*-Acylation with the mixed anhydride **156** provided amide **157**. Thermolysis of **157** at 325° afforded bicyclic system **158** in 75% yield *via* an azomethine ylide/olefin [3+2]-cycloaddition. After stereoselective introduction of a methoxymethyl group and protecting group manipulation of **158**, the allylsilane **159** was synthesized by Wittig reaction of the corresponding aldehyde with a trimethylsilylethylidene phosphorane. The same allylsilane moiety could

also be introduced into the aldehyde by vinyl Grignard addition, followed by acetylation and higher order silyl cuprate addition in comparable yields. DIBALH reduction of **159** furnished an *N*-tosyl hemiaminal, which upon treatment with anhydrous $FeCl_3$ produced the tricyclic structure **160** as a single isomer in 72% yield *via* allylsilane addition to an intermediate *N*-sulfonyliminium. OsO_4 catalyzed cleavage of the terminal olefin, followed by oxime formation and subsequent dehydration gave nitrile **161** in good overall yield. Stereoselective installation of the quaternary center needed for construction of the "western" macrocyclic ring could be achieved by alkylation of **161** with allyl bromide, eventually leading to tricycle **162**.

b. Heathcock Approach

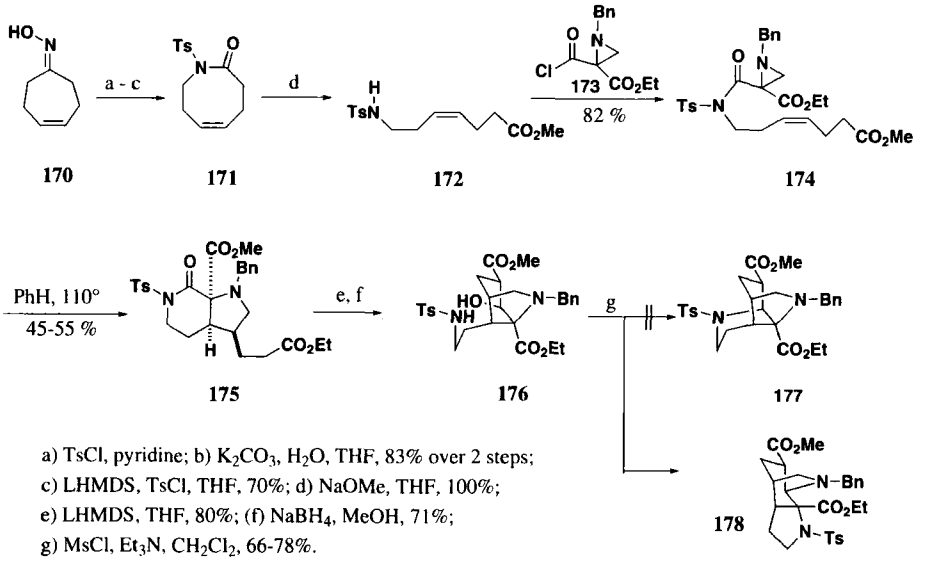
The approach by the Heathcock group also employed a [3+2]-cycloaddition to construct a *cis*-fused bicyclic system.[47] Doubly activated cyclization precursor **163** produced the desired bicyclic compound **164** upon flash vacuum pyrolysis in excellent yield (Scheme 26). However, reduction of lactam **165** with various reducing agents did not provide the hemiaminal necessary for the planned intramolecular Mannich reaction. Instead, lactam **165** was overreduced to the tertiary amine. Therefore, this system was abandoned and the Weinreb sulfonyliminium system was adopted. Indeed, after exchange of the benzyl group of **167** to the corresponding *N*-tosyl amide, the *N*-tosyl carbinolamine **168** could be generated. However, attempted acid-induced Mannich cyclization of this intermediate failed.



163 **166** **167** **168** **169**

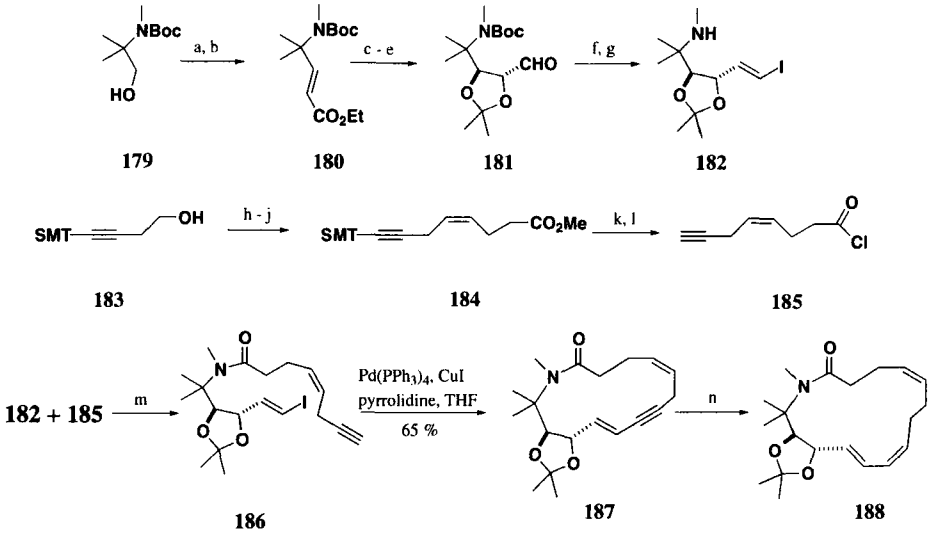
Scheme 26

In a revised strategy it was planned to form the tricyclic core by an intramolecular 1,4-addition of an amine to an unsaturated ester (Scheme 27). Beckmann rearrangement of oxime **170** furnished azacyclooctene **171** after *N*-tosylation of the lactam. Base-induced ring opening produced ester **172**, which was acylated with aziridine acid chloride **173** to yield the requisite cycloaddition precursor **174**. Thermally induced [3+2]-cycloaddition of **174** gave the desired bicyclic amide **175**, which upon treatment with lithium hexamethyldisilazide rearranged to a β-keto ester. Subsequent



Scheme 27

sodium borohydride reduction furnished β-hydroxy ester **176**. Mesylation of **176** did not induce the 1,4-addition reaction to tricycle **177**. Rather, rearranged product **178** was isolated, presumably *via*



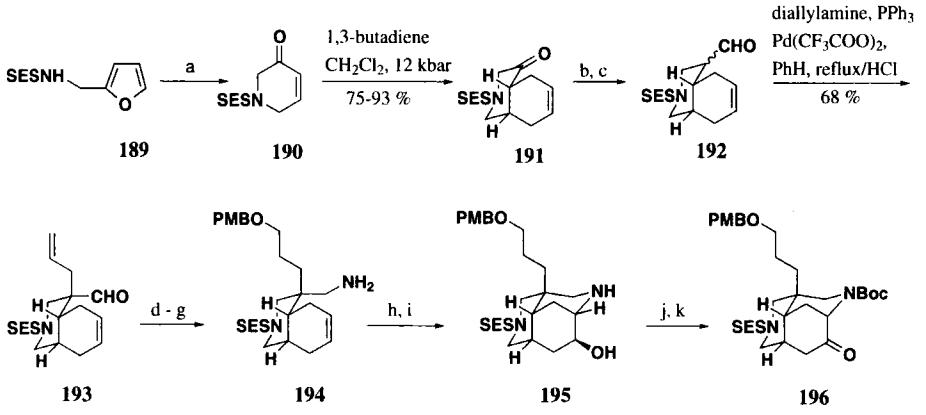
Scheme 28

aziridinium ion formation between the mesylate and the benzylamine portion of the molecule, followed by ring opening by the *N*-tosyl amide.

Heathcock and coworkers have also described a model study for the 14-membered ring of sarain A beginning with Boc protected amino alcohol **179** (Scheme 28). Ester **180** was obtained after oxidation and a subsequent Wadsworth-Emmons-Horner reaction. The diol was synthesized by OsO_4 catalyzed dihydroxylation of the olefin in **180**, and was protected as the acetonide. Subsequent reduction provided aldehyde **181** which was homologated to (*E*)-vinyl iodide **182**. The C-8 fragment **185** was synthesized in 5 steps starting from alcohol **183** using a Wittig reaction to build the internal (*Z*)-olefin. Acylation of **182** with **185** gave amide **186** and Pd^0-catalyzed ring closure furnished macrocycle **187** in good yield. The sequence was finalized by hydrozirconation/hydrolysis of the internal alkyne to generate triene **188**.

6. Approach to Madangamine A (44)

Madangamine A (**44**) is a pentacyclic alkaloid isolated from the sponge *Xestospongia ingens* in 1994.[25] The alkaloid shows cytotoxic activity toward several tumor cell lines. Weinreb and coworkers recently reported an approach to the tricyclic core of the alkaloid.[48] The synthesis began with SES-protected furfurylamine **189** which underwent ring expansion to a hemiaminal by treatment with *m*-chloroperbenzoic acid (Scheme 29). *In situ* reduction with triethylsilane/BF_3•Et_2O afforded



a) *m*-CPBA, CH_2Cl_2, 0°-rt/BF_3•Et_2O, Et_3SiH, 0°, 68-85%; (b) TosMIC, KO-*t*-Bu, MeOH, DME, -30-0°, 68%;
c) DIBALH, PhMe, -78-0°, 90%; d) NH_2OCH_2Ph•HCl, pyridine, CH_2Cl_2, 0°-rt, 97%;
e) disiamylborane, THF, 0°/H_2O_2, NaOH, 84%; (f) NaH, 4-$MeOC_6H_4CH_2Cl$, THF, reflux, 73%;
g) $LiAlH_4$, THF, -78° to rt, 74%; h) $Hg(CF_3COO)_2$, THF, 0°; i) $NaBH_4$, O_2, $(CF_3)CHOH$, rt, 39%;
j) $(Boc)_2O$, pyridine, 0°, 69%; (k) Swern oxidation, 95%.

Scheme 29

enone **190**. Diels-Alder reaction of **190** with 1,3-butadiene under high-pressure conditions gave *cis*-decalone system **191** in good yield. In order to synthesize the required quaternary center, **191** was homologated by nitrile formation and subsequently reduced to aldehyde **192**, which was isolated as 1:1 mixture of diastereomers. Pd^0-catalyzed aza-Claisen rearrangement of the corresponding diallyl

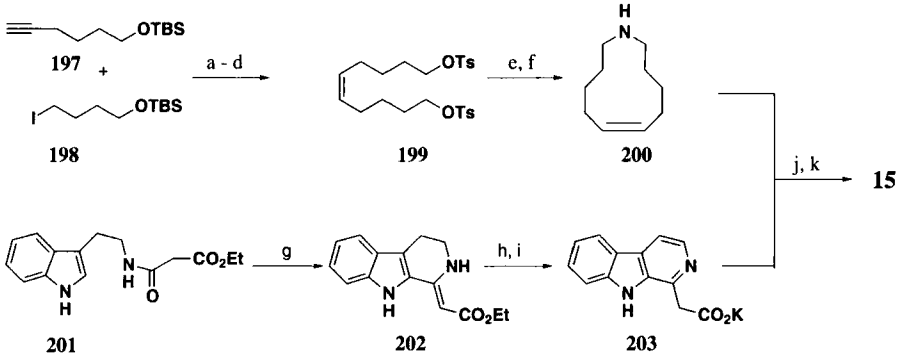
enamine provided aldehyde **193** as a single diastereomer after acidic work-up. The required madangamine A stereochemistry was confirmed by single-crystal X-ray of a derivative of **193**. *O*-Benzyloxime formation from **193**, followed by hydroboration of the terminal olefin, protection of the resulting alcohol as the PMB ether and subsequent reduction furnished amino alkene **194**. Hg^{2+}-mediated electrophilic cyclization of **194**, followed by oxidative cleavage of the organomercury intermediate, led to tricyclic amino alcohol **195** as a single isomer. Boc protection and subsequent Swern oxidation provided tricyclic ketone **196** which is expected to be a key intermediate in a total synthesis of the alkaloid.

7. Total Syntheses of Manzamine C (15)

The manzamines were originally discovered as a novel class of alkaloids isolated from three different genera of marine sponges by two independent groups.[2,4,49] There are also a variety of manzamine A congeners, such as manzamine B, E, F, X, and Y, which differ in the oxidation stage of the skeleton.[50] An Indonesian *Prianos sp.* yielded an unusual manzamine dimer, kauluamine.[51] Due to their challenging structures and potent cytotoxic activity, these β-carboline alkaloids have received attention by many synthetic organic chemists from around the world. Manzamine C (**15**) represents the simplest member of the alkaloid class, but shows equally potent antitumor activity to congeners of the manzamine group. Two total syntheses of manzamine C have been reported.[52-53] In addition, Nakagawa and coworkers have contributed a simple SAR study of manzamine C congeners with regard to their cytotoxic activity.[54]

a. Hino Total Synthesis

The Hino synthesis of manzamine C (**15**) is based on the assembly of two segments: a 6-(*Z*)-azacycloundecene system and a β-carboline segment.[52] The route to the macrocycle began with the alkylation of alkyne **197** with iodide **198** (Scheme 30). *bis*-tosylate **199** was obtained after hydrogenation over Lindlar catalyst, deprotection and subsequent tosylation of the diol. The crucial cyclization



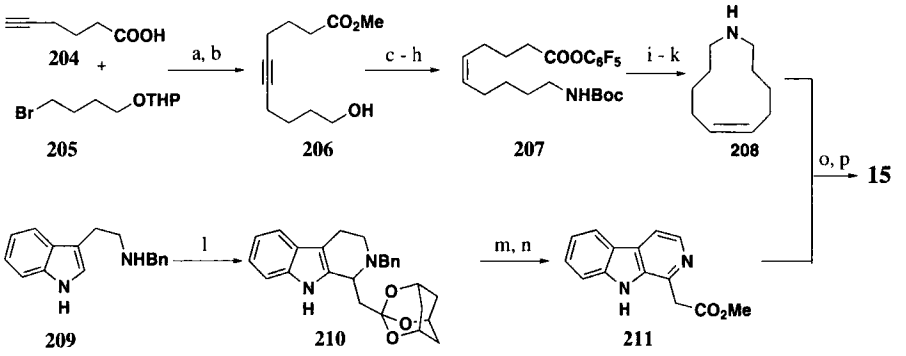
a) *n*-BuLi, 95%; b) $Pd/CaCO_3$, quinoline, H_2; c) TBAF, THF, rt, 71% over 2 steps; d) TsCl, pyridine, 91%; e) $TsNH_2$, TBAI, NaOH, benzene, H_2O, reflux, 74%; f) Na, naphthalene, DME, 100%; g) $POCl_3$, rt, 61%; h) 10% Pd/C, *p*-cymene, 67%; i) KOH; j) DPPA, DMF, NEt_3, 87%; k) $LiAlH_4$.

Scheme 30

of **199** with *p*-toluenesulfonamide proceeded smoothly under phase transfer conditions. Desulfonylation with sodium naphthalenide furnished the azacycloundecene **200** in 74% overall yield. Only traces of a dimeric compound could be detected in the cyclization reaction. Interestingly, cyclization of 1,10-dibromodecane with *p*-toluenesulfonamide under the same conditions gave predominantly dimeric product. The β-carboline moiety was synthesized by $POCl_3$ induced cyclization of tryptamine amide **201** to afford enamino ester **202**. Aromatization of **202** with Pd/C in *p*-cymene gave β-carboline **203** after ester hydrolysis. The best results for coupling the two segments were achieved with diphenylphosphoryl azide (DPPA). Reduction of the amide function afforded the natural product **15**.

b. Gerlach Total Synthesis

Scheme 31 outlines the Gerlach synthetic approach, which is similar to the Hino strategy. Thus alkylation of alkyne **204** with bromide **205** supplied hydroxy ester **206** after removal of the THP



a) *n*-BuLi, THF, HMPA, -45-0°; (b) MeOH, H_2SO_4, 70% over 2 steps; c) TsCl, pyridine, 0°; d) NaN_3, DMSO, rt, 75% over 2 steps; e) $Pd/CaCO_3$, H_2, cyclohexane, rt, 86%; f) 1 N KOH, reflux; g) (*t*-Boc)$_2$O, 83% over 2 steps; h) C_6F_5OH, *N*-(3-(dimethylamino)propyl)-*N*-ethylcarbodiimide•HCl, CH_2Cl_2, rt, 78 %; i) CF_3COOH, 0°; (j) DMAP, THF, reflux, high dilution, 93% over 2 steps; k) $LiAlH_4$, THF, reflux, 92% ; l) $TOACH_2CHO$, PhH, reflux, 89%; m) 10% Pd/C, mesitylene, reflux, 89%; n) 0.2 N H_2SO_4, reflux/MeOH, reflux, 90%; o) DMAP, mesitylene, reflux, 73%; p) $LiAlH_4$, THF, rt, 56%.

Scheme 31

protecting group. The synthesis of the azacycloundecene was performed *via* macrolactamization of amino ester **207**, which was obtained from **206** in six straightforward steps. After deprotection of **207** with TFA, reaction of the amino ester with DMAP under high dilution provided amine **208** in 93% yield. The β-carboline moiety was prepared by a modified Pictet-Spengler reaction of tryptamine derivative **209** and a suitably protected formylacetic acid equivalent to afford amine **210**. Aromatization and deprotection, followed by ester formation supplied ester **211** in good yield. Condensation of **208** with **211**, and subsequent reduction of the resulting amide, afforded the natural product manzamine C (**15**).

8. Synthetic Approaches to Manzamine A (1)

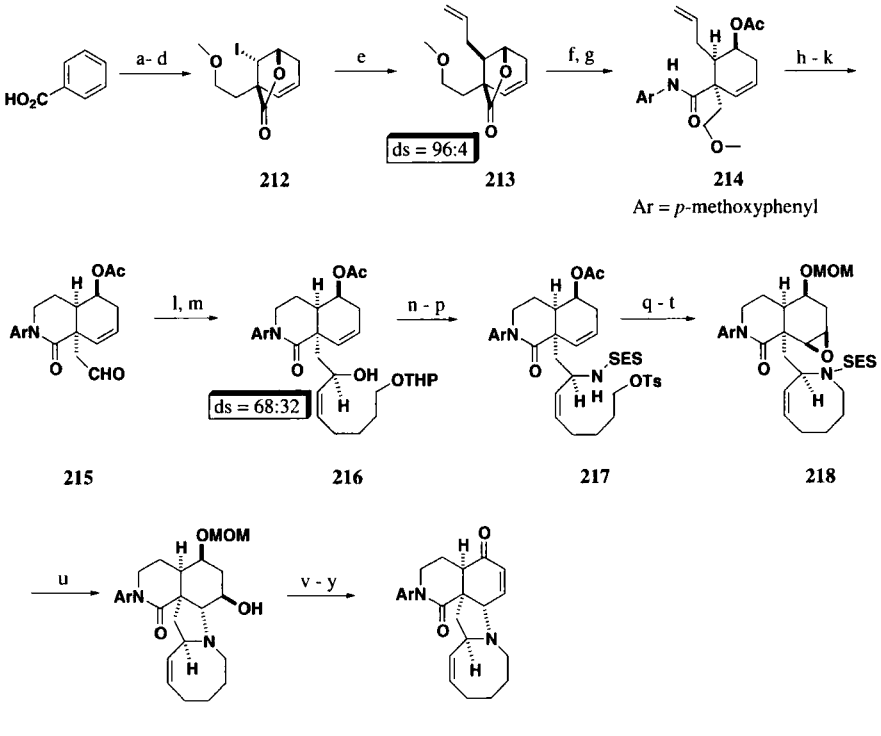
The first isolated manzamine, manzamine A (**1**), has been the subject of intensive synthetic investigations owing to its potent antitumor activity and unique molecular structure, containing 5-, 6-,

8-, and 13-membered rings as well as a β-carboline moiety. The majority of published synthetic approaches have focused on the construction of the tricyclic A/B/C ring system bearing all five stereocenters. In this review the approaches are categorized by strategies based on cycloadditions as a key step *vs* those which are not based on such an assembly. However, despite considerable progress no total synthesis of manzamine A has been achieved to date.

a. "Non-Cycloaddition" Approaches to Manzamine A

i. A/B/C/D Ring System Synthesis by Hart

The route described by Hart and coworkers towards racemic manzamine A features a diastereoselective radical allylation, azocine formation by intramolecular *N*-alkylation and an intramolecular amine addition to an epoxide as pivotal steps.[55] The synthesis began with benzoic acid which was converted to iodolactone **212** in 70% yield over four steps using a reductive alkylation/halolactonization sequence (Scheme 32). Allylation of **212** with allyltributylstannane/AIBN



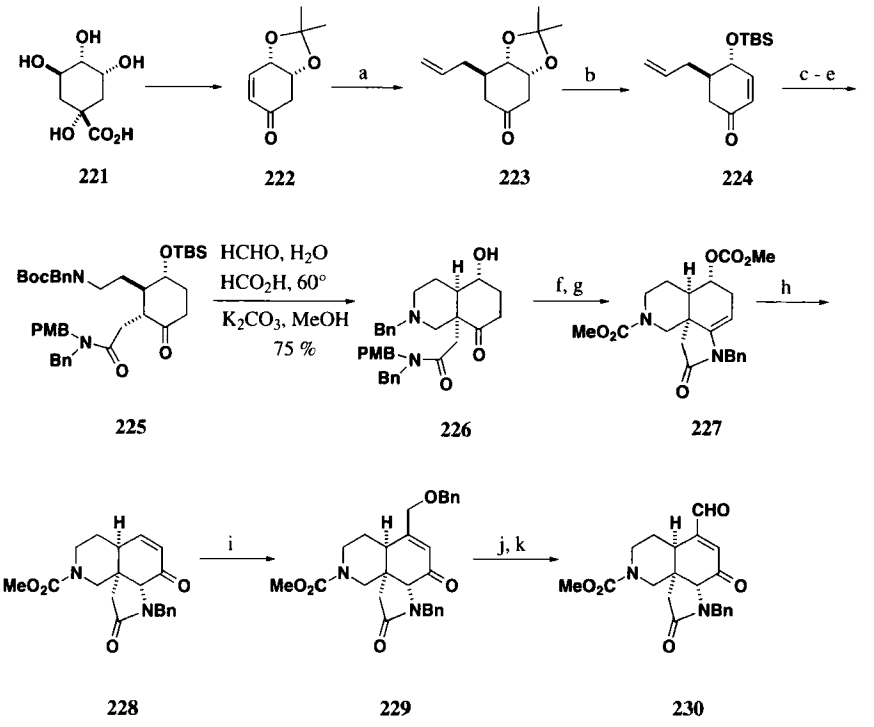
a) Li, NH_3; b) $Br(CH_2)_2OMe$; c) $(PhO)_2PON_3$, Et_3N, pyrrolidine; d) I_2, THF, H_2O, 70% over 4 steps; e) CH_2=$CHCH_2SnBu_3$, AIBN, PhH, reflux, 68%; f) *p*-$MeOC_6H_4NHMgBr$; g) Ac_2O, DMAP, pyridine, 91% over 2 steps; h) OsO_4, $NaIO_4$; i) $NaCNBH_3$, CF_3COOH, 65%; j) BBr_3 ; k) Swern oxidation, 77%; l) $LiCC(CH_2)_4OTHP$, 63%; (m) Pd/$BaSO_4$, pyridine, H_2, 100%; n) SESNHBoc, PPh_3, DEAD; o) CH_3SiCl_3, NaI, CH_3CN; p) TsCl, Et_3N, DMAP, CH_2Cl_2, 74% over 3 steps; q) KH, TBAI, 18-C-6, PhMe, reflux, 0.005 M solution, 91%; r) LiOH; s) $VO(acac)_2$, *t*-BuOOH, heat, 64% over 2 steps; t) MOMCl, diisopropylethylamine, 86%; u) CsF, DMF, heat, 72%; v) Ac_2O, DMAP, NEt_3, 93%; w) Me_3SiCl, NaI, CH_3CN, 65%; x) Swern oxidation; y) basic alumina, 100% over 2 steps.

Scheme 32

gave **213** with 96:4 stereoselectivity with inversion of configuration in the major isomer. Ring opening of **213** with the magnesium salt of *p*-anisidine served to introduce the A-ring nitrogen atom, and subsequent alcohol acetylation provided **214**. The A-ring was closed by oxidative cleavage of the terminal olefin to the aldehyde and subsequent intramolecular reductive amination, followed by manipulation of the side chain to obtain aldehyde **215**. Addition of a 6-carbon lithium acetylide to **215** resulted in a 68:32 mixture of diastereomeric alcohols, which could be separated after hydrogenation to the allylic alcohols, providing the requisite isomer **216**. Mitsunobu reaction of **216** with a mixed acyl sulfonyl imide gave intermediate **217** after removal of the Boc and THP protecting groups and conversion of the resulting alcohol to the sulfonamide. It should be noted that the conversion of **216** to **217** proceeded with retention of configuration, presumably *via* a double inversion process involving neighboring group participation. Treatment of **217** with potassium hydride under high dilution caused azocine formation in 91% yield. After deacetylation, face selective epoxidation of the homoallylic alcohol was achieved with $VO(acac)_2$/*t*-BuOOH. Reprotection of the acetate as a MOM ether provided **218**. The C-ring was then built by deprotection of the SES sulfonamide with CsF, which was accompanied by epoxide opening to produce the A/B/C/E ring system **219**. Manipulation of the oxidation state of the B-ring gave enone **220**.

ii. Overman A/B/C Ring Synthesis

An enantioselective approach to manzamine A by Overman *et al.* started from inexpensive D-(-)-quinic acid as the source of chirality and used a Mannich cyclization as the key step.[56] D-(-)-quinic acid (**221**) was transformed to enone **222** in four steps on a 100 g scale (Scheme 33). Stereoselective addition of an allylstannane to **222** in the presence of TBSOTf gave **223** after an acidic work-up. Further conversion of the acetonide functionality of **223** was carried out with DBU/TBSCl to afford protected allylic alcohol **224** in a single step. The side chain for the eventual construction of the C-ring was then installed by stereoselective alkylation of **224** with an *N,N*-disubstituted iodoacetamide, followed by reduction of the enone to yield the corresponding α-substituted ketone. The A-ring nitrogen atom was introduced by oxidative cleavage of the terminal olefin, followed by reductive amination with benzylamine and Boc-protection to produce **225**. The key Mannich cyclization was efficiently accomplished by the action of aqueous formaldehyde in formic acid on **225** to stereospecifically give the A/B system **226** in 75% yield. After debenzylation of **226** and removal of the PMB group, acid catalyzed dehydration proceeded smoothly to give tricyclic enamide **227**. Enamide **227** was then manipulated to elaborate the skeleton by one carbon to introduce the required aldehyde functionality. Thus, **227** was epoxidized, and subsequent acid catalyzed rearrangement followed by β-elimination gave enone **228**. Benzyloxymethyl homocuprate 1,4-addition to the enone was accomplished in the presence of TMSCl leading to **229**. Selective benzyl ether cleavage of **229**, followed by Dess-Martin oxidation, furnished the target enal **230**.



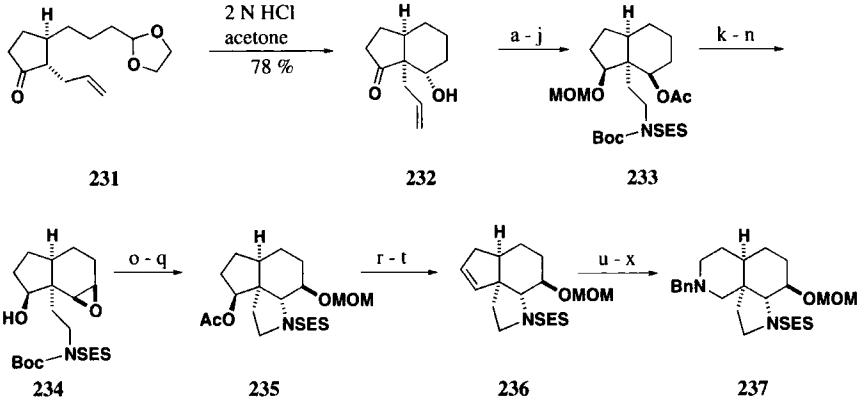
a) (n-Bu)$_3$SnCH$_2$CH=CH$_2$, TBSOTf, -78°-rt/p-TsOH, acetone, 88%; b) TBSCl, DBU, PhH, reflux, 84%; c) ICH$_2$CONBnPMB, LHMDS/Na$_2$S$_2$O$_4$, 75%; d) OsO$_4$, NaIO$_4$; e) BnNH$_2$, NaBH(OAc)$_3$, (Boc)$_2$O, 75% over 2 steps; f) ClCO$_2$Me, PhH, reflux; g) CAN, H$_2$O, MeOH/CSA, CHCl$_3$, 50°, 82% over 2 steps; h) MMPP, MeOH, rt/CSA, CHCl$_3$, 50°, 59%; i) (BnOCH$_2$)$_2$CuLi, TMSCl, THF, -78-0°/Pd(OAc)$_2$, CH$_3$CN, 80°, 55%; j) BCl$_3$, -78-0°/MeOH, -78-0°;
k) Dess-Martin oxidation, 65% over 2 steps.

Scheme 33

iii. A/B/C Subunit Synthesis by Yamamura

Yamamura *et al.* reported a synthesis of the tricyclic A/B/C ring system which is depicted in Scheme 34.[57] Bicyclic alcohol **232** was prepared by an intramolecular aldol condensation of **231** (ratio of diastereomers not given), which was derived in two steps from cyclopentenone. Alcohol **232** was converted over 9 steps to a doubly-protected triol, and the C-ring nitrogen was then introduced by a Mitsunobu reaction using SESNHBoc to generate **233**. Note that the original α-hydroxyl group of **232** was inverted to the β-isomer because of poor yields in some steps with the sterically more hindered α-isomer. Epoxidation of **233** was achieved in 4 steps: **233** was deacetylated, and subsequent mesylation and elimination supplied the corresponding alkene, which was epoxidized to give **234** after removal of the MOM group. Sequential reacetylation of **234** and cleavage of the Boc group resulted in spontaneous formation of the pyrrolidine C-ring. MOM protection of the alcohol then furnished sulfonamide **235**. In the last part of the synthesis, the cyclopentane ring of **235** had to be transformed into the required piperidine A-ring. Thus, elimination of the acetate gave alkene **236**, and the double bond was

cleaved by ozonolysis. Subsequent reduction of the resulting dialdehyde to the diol, dimesylation and treatment with benzylamine/KF gave racemic amine **237**. Due to the extensive use of protection/deprotection procedures, the synthesis of **237** required approximately 27 steps starting from cyclopentenone.

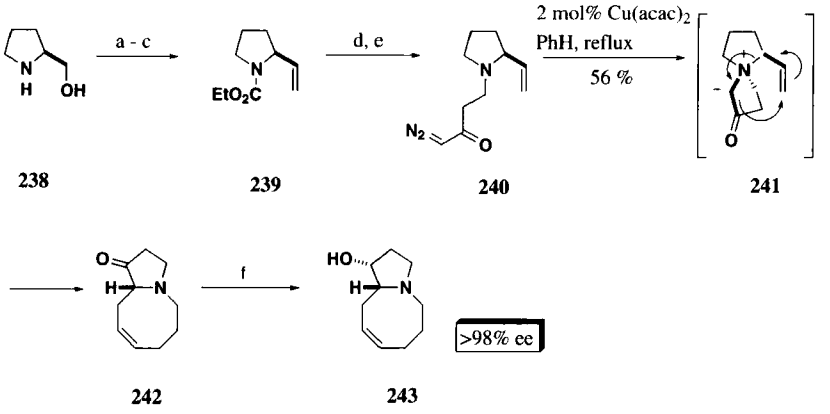


a) Ac_2O, Et_3N, DMAP, CH_2Cl_2; b) $NaBH_4$, MeOH; c) MOMCl, diisopropylethylamine;
d) 2 N LiOH, MeOH; e) Swern oxidation; f) $NaBH_4$, MeOH; g) Ac_2O, Et_3N, DMAP, CH_2Cl_2;
h) OsO_4, NMO, $NaIO_4$, THF; i) $NaBH_4$, MeOH; j) SESNHBoc, PPh_3, DEAD, THF;
k) 2 N LiOH, MeOH, 94%; l) $(Boc)_2O$, Et_3N, CH_2Cl_2/MsCl, Et_3N/DBU, PhH, 60°, 85%;
m) *p*-TsOH, MeOH, 90%; n) $VO(acac)_2$, TBHP, PhH, reflux, 69%; o) Ac_2O, Et_3N, DMAP, CH_2Cl_2;
p) $MgCl_2$, CH_3CN, reflux; q) MOMCl, diisopropylethylamine, CH_2Cl_2, 69% over 3 steps;
r) 2 N LiOH, MeOH; s) MsCl, NEt_3, CH_2Cl_2; t) DBU, PhH, reflux, 57% over 3 steps;
u) O_3, CH_2Cl_2, -78°/DMS; v) $NaBH_4$, MeOH, 67% over 2 steps; w) MsCl, Et_3N, CH_2Cl_2;
x) $BnNH_2$, KF, DMF, 60°, 87% over 2 steps.

Scheme 34

iv. Clark C/E Ring Synthesis

An enantioselective synthesis of the manzamine azabicylo[6.3.0]undecene system has been achieved by Clark and Hodgson using a rearrangement of a spiro-fused ammonium ylid derived from a copper carbenoid.[58] The synthesis started from (*S*)-prolinol (**238**) as chiral source (Scheme 35), which was converted in three steps to vinyl pyrrolidine **239**. The acyl pyrrolidine **239** was deprotected and alkylated with 4-bromo-1-diazobutan-2-one to supply cyclization precursor **240**. Reaction of **240** with a catalytic amount of $Cu(acac)_2$ in refluxing benzene produced ketone **242** in 56% yield. The enantiomeric excess of this product was determined to be ≥98% by reduction of **242** to alcohol **243** and subsequent NMR analysis of the Mosher ester. The reaction is presumed to have occurred by a [2,3]-sigmatropic rearrangement of spiro-fused ammonium ylide **241** with efficient transfer of stereochemical information, even though the original stereogenic center is lost in the process.



238 239 240 241

242 243

a) $ClCO_2Et$, NaOH, 0°-rt, 88%; b) SO_3•pyridine, Et_3N, DMSO, CH_2Cl_2, 0°, 81%;
c) $Ph_3PMe^+ Br^-$, NaH, DMSO, 0°-rt, 78%; d) H_2NNH_2•H_2O, KOH, $HO(CH_2)_2OH$, reflux;
e) $Br(CH_2)_2COCHN_2$, Et_3N, EtOAc, 60°, 55% over 2 steps; f) L-Selectride, THF, 0°, 75%.

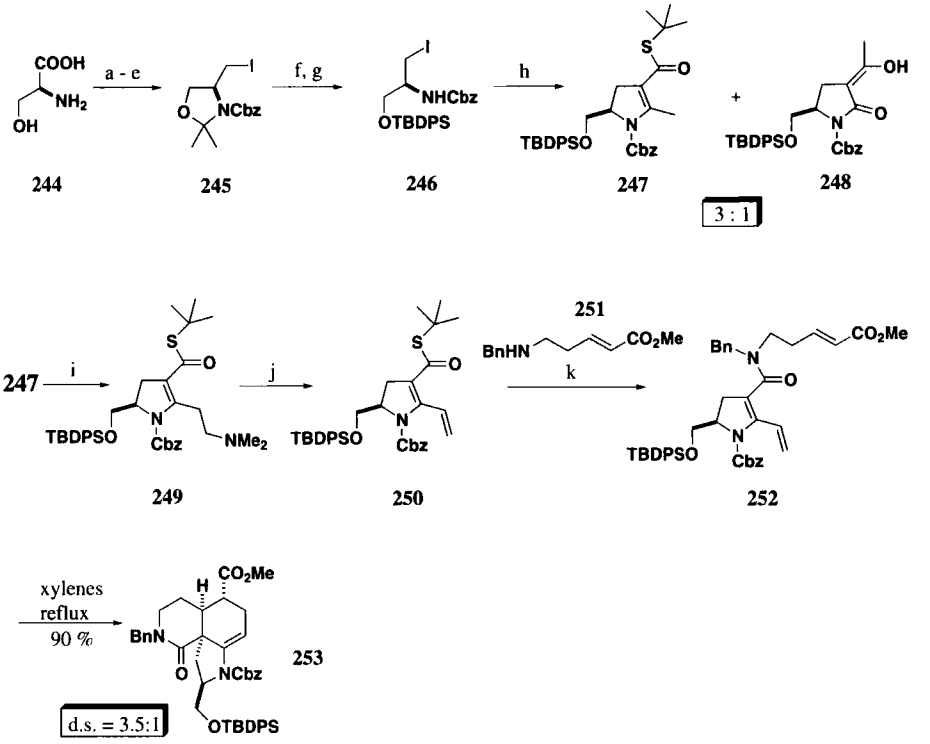
Scheme 35

a. Manzamine A Approaches Based Upon Cycloaddition Strategies

i. Approaches by Pandit to the A/B/C, A/B/C/E/β-Carboline, and A/B/C/D Segments

In an initial series of publications Pandit and coworkers assembled an enantiopure A/B/C segment of manzamine A (**1**) by an intramolecular [4+2]-Diels-Alder strategy.[59] The absolute chirality was provided by inexpensive L-serine, which was also used as a chiral anchor to control the stereochemistry of the cycloaddition. Thus, cyclization of *Z*-diene **252** (Scheme 36) created the alkaloid tricyclic core and three new chiral centers in a single step. The Pandit group was also able to synthesize the 8-membered ring by a lactamization approach and introduce the β-carboline portion *via* a Pictet-Spengler reaction (Scheme 37). Furthermore the challenging unsaturated 13-membered ring could be constructed using ring closing metathesis (RCM) methodology (Scheme 38).[60]

Thus, L-serine (**244**) was converted in five high yielding steps to iodide **245**, which after protecting group manipulation gave iodo carbamate **246** (Scheme 36). The C-ring was built by reaction of **246** with *t*-butyl acetothioacetate/sodium hydride, followed by acid catalyzed dehydration to provide thioester **247** along with 1,3-diketone **248** in a 3:1 ratio in 67% combined yield. The thioester functionality was chosen as a latent reactive acylating agent (*vide infra*). Introduction of a vinyl group into **247** to produce the diene moiety for the cycloaddition proved to be difficult. However, it was discovered that **247** could be converted to an *O*-silylketene acetal which upon *in situ* reaction with Eschenmoser salt produced amine **249** regioselectivly. Quaternization of **249**, followed by DBU treatment furnished diene **250**. Easily prepared amine **251** was then reacted with thioester **250** in the presence of thiophilic silver triflate to afford cyclization precursor **252** in 69% yield. Thermally induced Diels-Alder reaction of enantiopure **252** gave the desired tricyclic compound **253** as a 3.5:1 ratio of



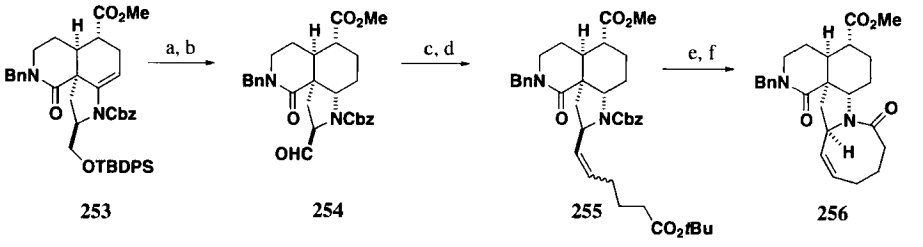
a) $SOCl_2$, MeOH; b) CbzCl, $NaHCO_3$, 95% over 2 steps; c) 2,2-dimethoxypropane, *p*-TsOH, 99%;
d) $Ca(BH_4)_2$, EtOH/THF, 99%; e) PPh_3, I_2, imid., 85%; f) 12 N HCl, acetone, 99%;
g) TBDPSCl, imid., DMF, 90%; (h) *t*-butyl acetothioacetate, NaH/*p*-TsOH, quinoline, 67%;
i) TMSOTf, Et_3N, $CH_2{=}N(CH_3)_2^+ I^-$, CH_2Cl_2, 0°, 85%; j) MeI, CH_3CN/DBU, CH_2Cl_2, 89%;
k) AgOTf, diisopropylethylamine, CH_3CN, 69%.

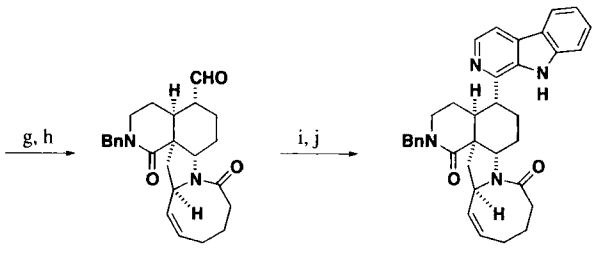
Scheme 36

diastereomers in 90% combined yield. The stereochemistry of the major isomer was unambiguously confirmed by X-ray analysis of a derivative.

The E-ring and β-carboline moiety could then be attached to tricycle **253** (Scheme 37). Thus, **253** was converted to aldehyde **254**, in which the ene carbamate functionality in the B-ring was reduced. Elongation of the aldehyde with a Wittig phosphonium ylide then gave alkene ester **255**. Subsequent deprotection and lactamization provided azocine **256**. Finally, aldehyde **257** was prepared from ester **256** and Pictet-Spengler reaction with tryptamine, followed by DDQ-mediated aromatization produced β-carboline **258**.

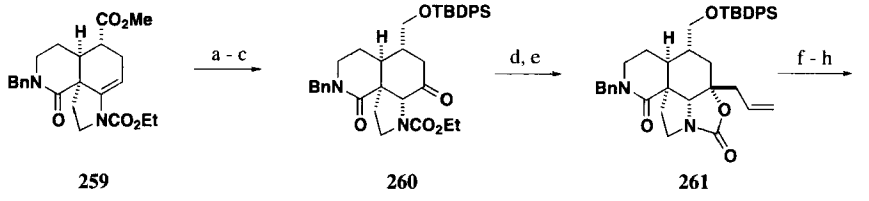
Pandit and coworkers have also accomplished a synthesis of the 13-membered manzamine A D-ring (Scheme 38).[60] Compound **259**, lacking the hydroxymethyl substituent in the C-ring, was transformed into ketone **260** by osmium tetroxide-mediated dihydroxylation of the ene carbamate, followed by acid catalyzed dehydration. Unfortunately, various homoallylic nucleophiles did not add

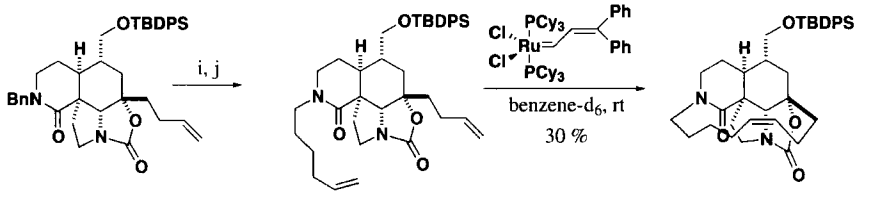




a) $NaCNBH_3$, HCl; b) Dess-Martin oxidation, 43% over 2 steps; c) $Ph_3P^+(CH_2)_4COOH\ Br^-$, KHMDS; d) isobutene, H^+, 46% over 2 steps; e) HBr, AcOH; f) TBTU; g) DIBALH; h) Dess-Martin oxidation; i) tryptamine, HCl; j) DDQ.

Scheme 37





a) $LiBH_4$; b) TBDPSCl, imid. DMF, 70% over 2 steps; c) OsO_4, pyridine/H^+, 66%; d) CH_2=$CHCH_2MgCl$, THF, 60%; e) NaH, THF, 93%; f) 9-BBN/H_2O_2; g) Dess-Martin oxidation; h) Ph_3P=CH_2, 48% over 3 steps; i) Li, NH_3/Bn_2O; j) $I(CH_2)_4CH$=CH_2, KOH, DMSO, 77%.

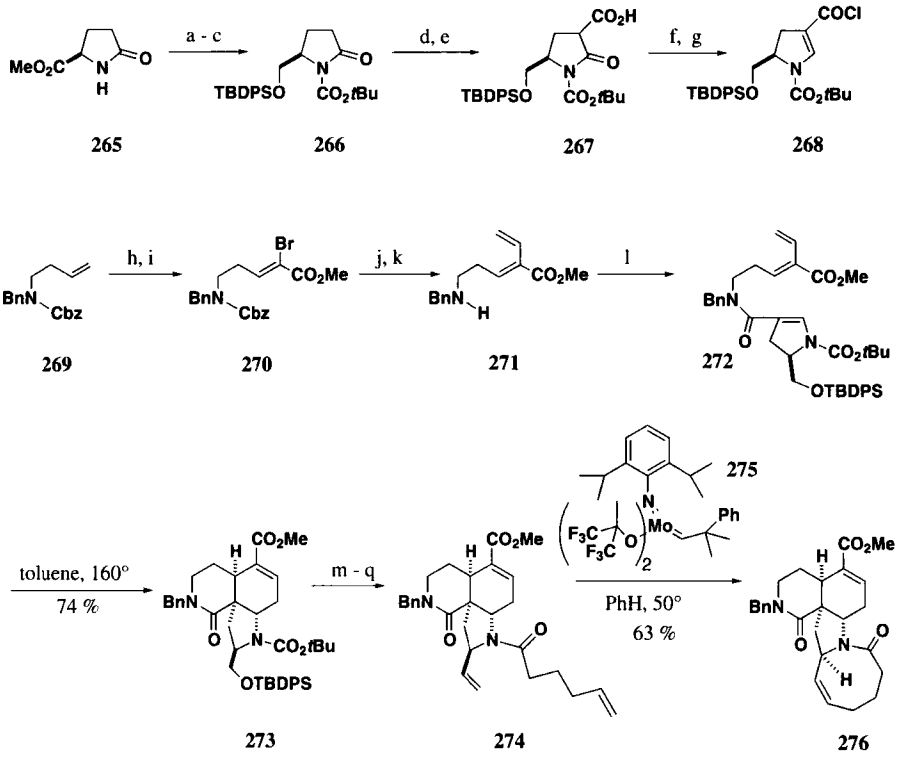
Scheme 38

to the carbonyl group of **260**, presumably due to steric hindrance. However, the desired product **262** could be prepared in a 4 step sequence *via* **261** by addition of allyl Grignard reagent, hydroboration,

Dess-Martin oxidation and subsequent Wittig reaction with methylenetriphenylphosphorane. Debenzylation of **262**, followed by alkylation with 1-iodo-5-hexene, furnished the di-olefin **263** required for the RCM reaction. Reaction of **263** in the presence of a ruthenium based RCM catalyst indeed provided the tetracyclic manzamine A A/B/C/D skeleton **264** as a single isomer in 30 % yield.

ii. A/B/C/E Ring Synthesis by Martin

An enantioselective approach to a tetracyclic fragment of manzamine A by Martin and coworkers relies on an intramolecular [4+2]-cycloaddition using a vinylogous imide as the dienophilic partner (Scheme 39)[61], a reaction which was previously disclosed as a useful process in synthesis of



a) $LiBH_4$, THF, rt, 80%; b) TBDPSCl, imid. DMF, rt, 95%; c) $(t\text{-Boc})_2O$, Et_3N, DMAP, CH_2Cl_2, 94%;
d) CbzCl, LHMDS, THF, -78°, 93%; e) H_2, 10% Pd/C, EtOAc, rt, 90%; f) $NaBH_4$, HCl, EtOH, -10°, 84%;
g) $(COCl)_2$, CH_2Cl_2, rt, 100%; h) O_3, CH_2Cl_2, - 78°/Zn, HOAc, -78°- rt, 93%;
i) $Ph_3P{=}CBrCO_2Me$, THF, rt, 92%; j) $Pd(PPh_3)_4$, $CH_2{=}CHSnBu_3$, PhMe, 100°, 82%;
k) TMSI, CH_2Cl_2, 0°, 77%; l) **268**, Et_3N, CH_2Cl_2, 90%; m) TMSI, 0°, 65%;
n) $CH_2{=}CH(CH_2)_3COCl$, Et_3N, CH_2Cl_2, 70%; o) HF/pyridine, CH_2Cl_2, 0°, 90%; p) Swern oxidation, 80%;
q) $Ph_3P{=}CH_2$, THF, 0°-rt, 75%.

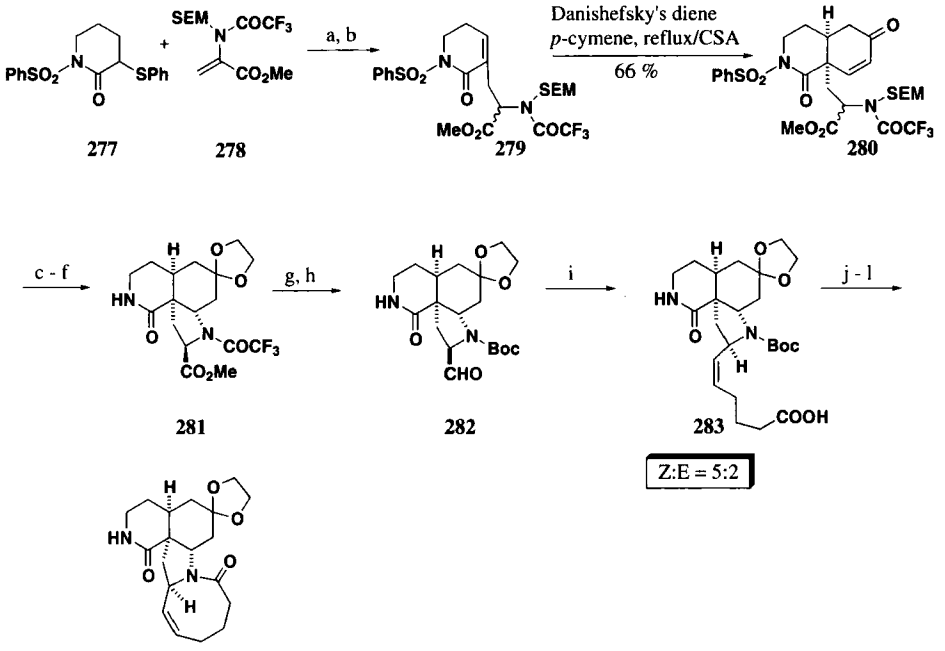
Scheme 39

several other types of alkaloids.[62] As in the Pandit approach, Martin and coworkers started with an enantiomerically pure C-ring precursor, in this case methyl D-pyroglutamate (**265**). Manipulation of the oxidation state and the protecting groups of **265** led to lactam **266**, which was then converted to

268 by acylation, reduction, dehydration and acid chloride formation. The diene **271** was prepared from homoallyl carbamate **269** by ozonolysis, stereoselective Wittig reaction and subsequent Stille coupling of bromoalkene **270** with tributylvinylstannane, followed by carbamate cleavage. Amide formation between **268** and **271** provided cyclization precursor **272** which was heated in toluene to afford the tricyclic compound **273** in 74% yield, thus creating three new stereocenters. It is believed that the dienophile participates as the electron rich component of an inverse demand Diels-Alder reaction, since the same cycloaddition without the ester group in the diene was much slower.[63] Finally, the E-ring was assembled by means of an RCM reaction. Compound **273** was converted in standard fashion to di-olefin **274** which upon exposure to the molybdenum-based Shrock catalyst **275** furnished the tetracyclic product **276** in good yield.

iii. Synthesis of an A/B/C/E Segment by Nakagawa

The entry to the tricyclic A/B/C system by Nakagawa *et al.* involved an intermolecular Diels-Alder reaction between a racemic dihydropyridinone and Danishefsky's diene, followed by intramolecular 1,4-addition of an amine to an α,β-unsaturated ketone (Scheme 40).[64] Thus, Michael



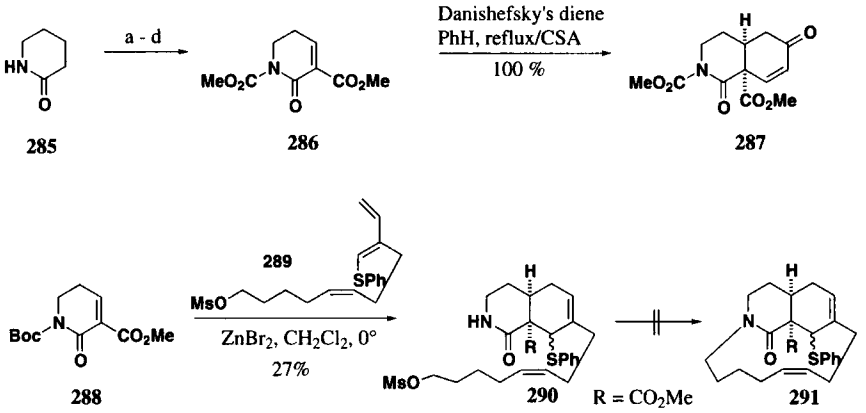
a) KHMDS, -78°, 100%; b) *m*-CPBA, CH_2Cl_2; c) CF_3COOH, CH_2Cl_2, rt, 77%;
d) DABCO, DME, rt, 85%; e) $HO(CH_2)_2OH$, PPTS, PhH, reflux, 96%/ recrystallization;
f) Na, anthracene, DME, -60°, 92%; g) $LiBH_4$, $B(OH)_3$, THF, rt/$(Boc)_2O$, NaOH, rt, 87%;
h) PCC, Al_2O_3, CH_2Cl_2, rt, 67%; i) $Ph_3P{=}CH(CH_2)_3COOK$, PhMe, rt;
j) C_6F_5OH, DCC, rt, 91% over 2 steps; (k) CF_3COOH, CH_2Cl_2, rt;
l) DMAP, dioxane, 80-90°, 58% over 2 steps.

Scheme 40

addition of α-thioketone **277** to amido acrylate **278** gave dienophile **279** after oxidation and subsequent elimination of the thiophenol portion. Thermally induced cycloaddition of **279** with Danishefsky's diene provided *cis*-fused isoquinoline **280** as a 1:1 mixture of diastereomers. The SEM group was removed by treatment with trifluoroacetic acid and the second key cyclization was accomplished by brief treatment of the trifluoroacetamide with DABCO to provide tricycle **281** after further manipulation of the protecting groups. Wittig homologation of derived aldehyde **282** proceeded in high yield giving olefin **283** with a 5:2 *Z/E* selectivity. Finally, azocine formation was performed by lactamization of **283** to afford racemic tetracyclic compound **284**.

iv. Simpkins A/B Ring Synthesis

The Simpkins approach to the *cis*-fused A/B manzamine A substructure is closely related to the Nakagawa approach described in Section 8.2c (Scheme 41).[65] Dienophile **286** was prepared from



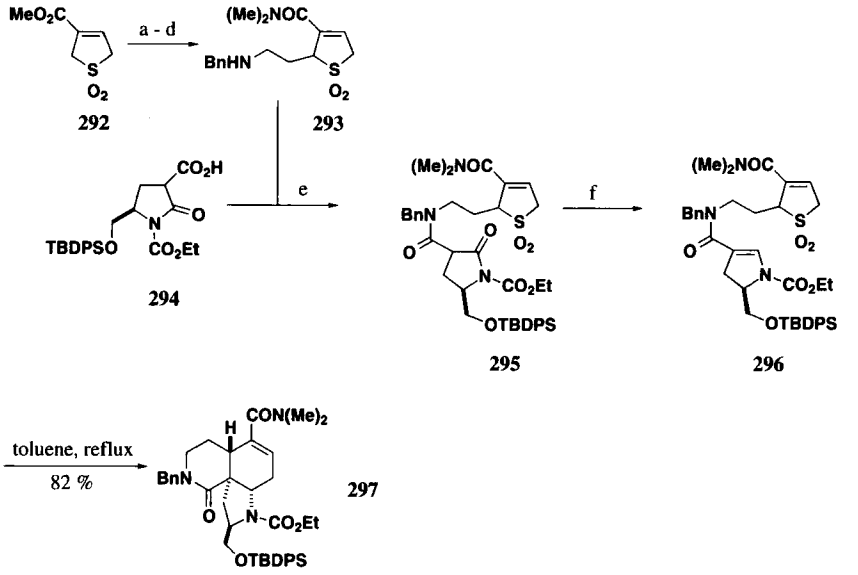
a) $ClCO_2Me$, NaH, CH_2Cl_2, 65%; b) $ClCO_2Me$, LDA, THF, 70%; c) PhSeCl, NaH, THF; d) H_2O_2, CH_2Cl_2, 92% over 2 steps.

Scheme 41

δ-valerolactam (**285**) in four steps. Subsequent thermally induced intermolecular [4+2]-cycloaddition of **286** with Danishefsky's diene, followed by an acidic work-up gave isoquinoline **287** in quantitative yield. In an attempt to synthesize a more highly functionalized intermediate which included a sidechain for the construction of the 13-membered D-ring, Boc-protected dienophile **288** was treated with diene **289** in the presence of zinc bromide at 0°. However, cycloadduct **290** was only isolated in poor yield, and furthermore the strategy has been thwarted by difficulties carrying out an intramolecular *N*-alkylation of **290** to produce **291**.

v. A/B/C Subunit Synthesis of Leonard

The Leonard synthetic plan is closely related to the Martin strategy described in Section 8.2b. but differs by the incorporation of the diene moiety into a sulfolene ring, which was anticipated to undergo a tandem SO_2 extrusion/Diels-Alder cyclization (Scheme 42).[66] Thus, commercially available sulfolene **292** was prenylated, converted to the *N,N*-dimethylamide, ozonized and reductively



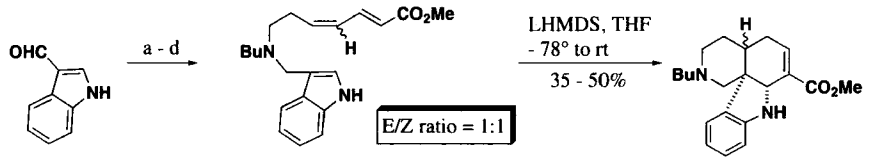
a) prenyl bromide, BuLi, THF, 84%; b) LiOH, H_2O, THF/DCC, Me_2NH•HCl, Et_3N, 80%; c) O_3, CH_2Cl_2, -78°/DMS, 94%; d) $BnNH_2$•HCl, $NaCNBH_3$, MeOH, 72%; e) carbonyldiimidazole, CH_2Cl_2, 65%; f) $LiBHEt_3$, THF/MsCl, Et_3N, 82%.

Scheme 42

aminated with benzylamine to furnish amine **293**. Acid **294** was prepared as described by Martin, but imide carbonyl reduction followed by dehydration on this stage failed. However, after carbonyldiimidazole-mediated coupling of **293** and **294** to give amide **295**, selective reduction was accomplished with $LiBHEt_3$ followed by *in situ* mesylation and elimination giving **296**. Thermally induced cycloaddition of **296** gave *trans*-isomer **297** as single isomer in 82% yield. This undesired result, which contrasts with that of Martin (Scheme 39), was explained by the different intermediate diene geometry and substitution pattern relative to **272**.

vi. Markó A/B/C Model Studies

This approach was originally planned as an intramolecular [4+2]-cycloaddition of dienoate **299** (Scheme 43).[67] Indole-3-carboxaldehyde (**298**) was reacted with butylamine followed by



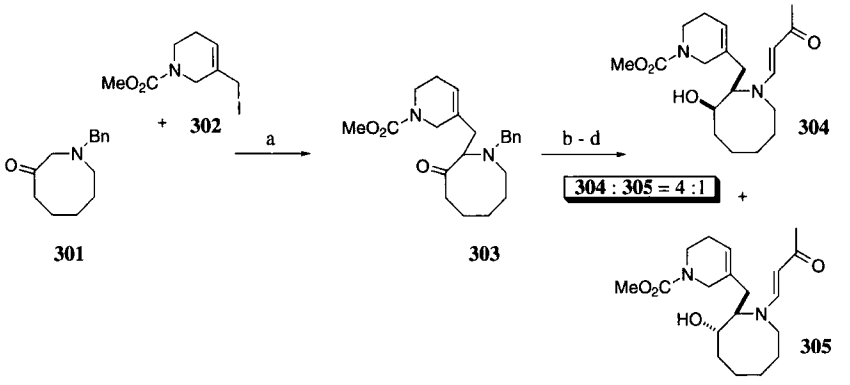
a) $BuNH_2$, PhH, reflux; b) $NaBH_4$, EtOH, rt, 75-80% over 2 steps; c) acrolein, DBU, THF, 0°; d) $(MeO)_2POCH_2CH{=}CHCOOMe$, KO-*t*-Bu, THF, rt, 75% over 2 steps.

Scheme 43

reduction of the imine with sodium borohydride, and subsequent Michael-like elongation with acrolein and reaction with phosphonocrotonate provided dienoate **299** as a 1:1 mixture of *E/Z* isomers. However, no Diels-Alder cycloaddition took place under either thermal or high-pressure conditions, or in the presence of a Lewis acid. Alternatively, it was found that treatment of **299** with 1 equivalent of lithium hexamethyldisilazide at low temperature gave tricycle **300** in moderate yield as a 1:1 mixture of diastereomers. Markó has suggested that tetracycle **300** forms *via* an indolyl anion conjugate addition to the dienoate moiety, followed by an intramolecular imino-aldol reaction.

vii. Winkler A/B/C/D/E Ring Synthesis

The Winkler approach is based on an intramolecular vinylogous amide [2+2]-cycloaddition/retro-Mannich fragmentation/Mannich cyclization cascade.[68] This approach allows a concise and convergent assembly of the ring system with high levels of asymmetric induction. As in the above Diels-Alder based strategies, a single stereogenic center could be used here to establish all of the relative stereochemical relationships. The initial photosubstrate was obtained by alkylation of azocine **301** with allylic iodide **302** to form ketone **303** (Scheme 44). Reduction of **303**, followed by debenzylation and formation of the vinylogous amide by treatment with sodio formylacetone, gave compounds **304** and **305** in a 4:1 ratio and 54% overall yield.

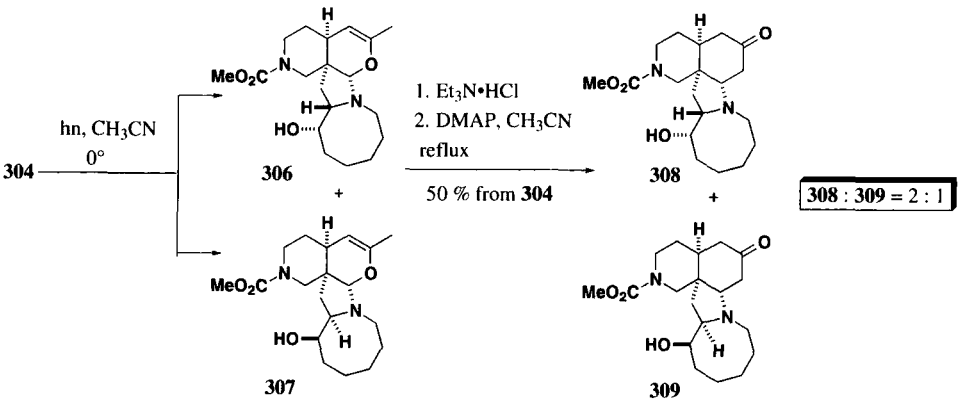


a) LHMDS, THF, 53%; b) $NaBH_4$, Et_2O, 92%; c) H_2, Pd; d) sodio formylacetone, 54% over 2 steps.

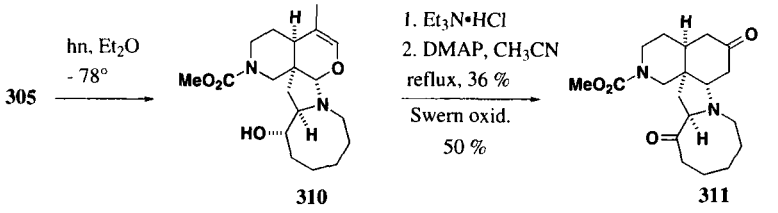
Scheme 44

When the major *cis*-isomer **304** was irradiated, the two hemiaminals **306** and **307** could be formed in a 2:1 ratio (Scheme 45). The initial [2+2]-cycloaddition of **304** is presumed to lead to a 1-amino-2-acetyl cyclobutane derivative, which undergoes retro Mannich fragmentation and subsequent hemiaminal formation. Exposure of the mixture of hemiaminals **306** and **307** to triethylamine hydrochloride, followed by DMAP led to the rearranged β-aminoketones **308** and **309**, in which the latter minor isomeric product represents the correct manzamine A stereochemistry.

On the other hand, irradiation of the minor *trans*-isomer **305** under modified conditions, and rearrangement under the conditions described above, provided a single isomeric cycloadduct **310** with the correct stereochemistry, which could be oxidized to the corresponding ketone **311** (Scheme 46).

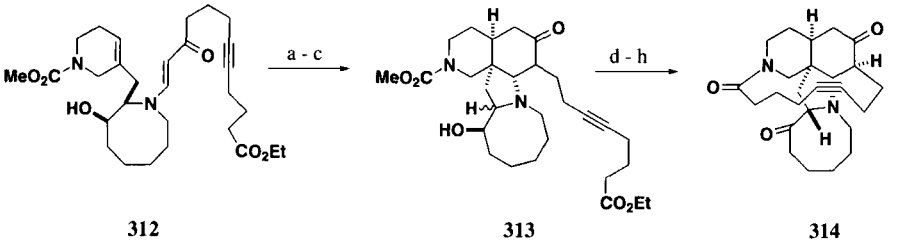


Scheme 45



Scheme 46

The extension of these results to the synthesis of the pentacyclic manzamine A system was also achieved as shown in Scheme 47. Thus, advanced photosubstrate **312** gave tetracycle **313** *via* the above methodology. Subsequent macrolactamization furnished pentacyclic alkyne **314** in reasonable overall yield.



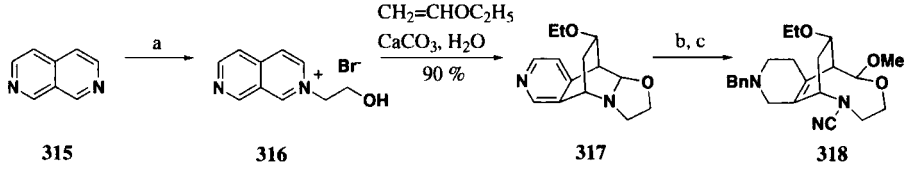
a) hn; b) Et_3N•HCl; c) DMAP, 37% over 3 steps; d) Swern oxidation; e) LiOH;
f) C_6F_5OH, DCC, 65% over 3 steps; g) CF_3COOH; h) diisopropylethylamine, 50% over 2 steps.

Scheme 47

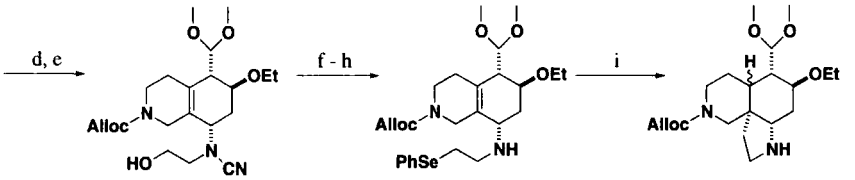
viii. Langlois A/B/C Subunit Synthesis

The approach by Langlois and coworkers relies on a Bradsher intermolecular [4+2]-cycloaddition between hydroxyethyl pyridinium salt **316** and ethyl vinyl ether as depicted in Scheme 48.[69]

2,7-Naphthyridine (**315**) was alkylated with 2-bromoethanol to furnish quaternary salt **316**. Subsequent cycloaddition in water at room temperature gave bridged oxazolidine **317** in 90% yield. Cyanogen bromide-mediated ring expansion of **317** furnished acetal **318** after reduction of the pyridine moiety. Exchange of the benzyl group to the allyloxy carbamate and methanolysis of the acetal produced alcohol **319**. Further transformation of **319** led to selenide **320**, which underwent tributylstannane/AIBN mediated radical cyclization to yield tricyclic compound **321**, but unfortunately as a 1:1 mixture of diastereoisomers in 80% yield.



315 **316** **317** **318**



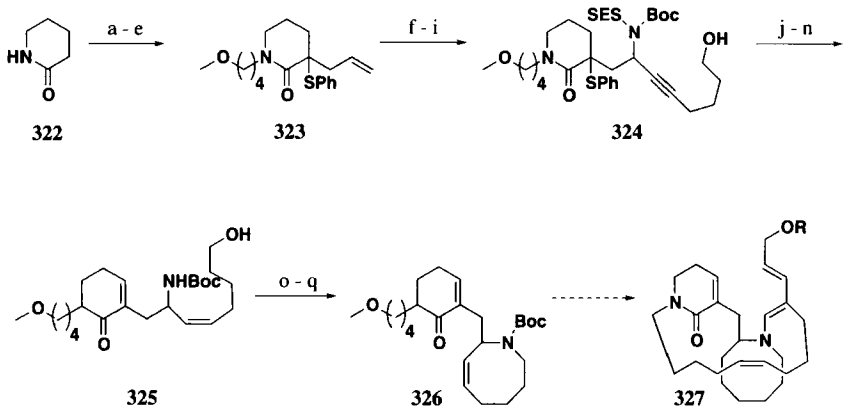
319 **320** **321**

a) $Br(CH_2)_2OH$, EtOH, 80%; b) BrCN, $NaHCO_3$, MeOH, 50%; c) BnBr, MeOH/$NaBH_4$, MeOH, 50 %; d) AllocCl, CH_2Cl_2; e) *p*-TsOH, MeOH, 80% over 2 steps; f) MsCl, Et_3N, LiBr, CH_2Cl_2; g) PhSeNa, THF; h) *p*-TsOH, MeOH, 80% over 3 steps; i) Ph_3SnH, AIBN, PhMe, 80%.

Scheme 48

ix. Yamamura A/E Segment Synthesis

The pivotal step in the synthetic plan evaluated by the Yamamura group is an intramolecular [4+2] cycloaddition to construct the B-ring of manzamine A, having the eight-membered ring already installed.[70] However, it is yet to be proven if the key cycloaddition can be realized on a highly functionalized triene such as **327** (Scheme 49). The synthesis of racemic precursor **326** began with δ-valerolactam (**322**). Introduction of a protected four carbon chain required three steps. Subsequent thiophenylation and allylation provided amide **323**. In a series of standard reactions **323** was converted *via* imide **324** to alcohol carbamate **325**. Alcohol **325** was then transformed to the corresponding iodide, which upon base treatment underwent intramolecular alkylation to produce azocine **326** in 85% yield.



a) $Cl(CH_2)_4OTHP$, KOH, TBAB, THF, 88%; b) PPTS, EtOH, 93%; c) MeI, KOH, DMSO, TBAB, 100%; d) LDA, HMPA, $(PhS)_2$, THF, -75°, 79%; e) KHMDS, $CH_2{=}CHCH_2Br$, THF, -75°, 95%; f) OsO_4, NMO; g) $NaIO_4$, THF, H_2O; h) *n*-BuLi, $HCC(CH_2)_4OTHP$, THF, -75°, 55% over 3 steps; i) Ph_3P, DEAD, SESNHBoc, THF, 88%; j) TBAF, THF; k) *p*-TsOH, MeOH; l) $NaIO_4$, MeOH, H_2O; m) PhH, reflux, 54% over 4 steps; n) 5% $Pd/BaSO_4$, quinoline, H_2, 91%; o) MsCl, Et_3N, CH_2Cl_2, 93%; p) NaI, acetone, 77%; (q) KO-*t*-Bu, THF, -60°, 85%.

Scheme 49

IV. SUMMARY

The clever 1992 proposal by Baldwin and Whitehead for the biosynthesis of manzamine implicated a *bis*-pyridine macrocycle as a key biogenic precursor. This proposal predicted the existence of several intermediates in the formation of manzamine. The subsequent discovery of a number of alkaloids which closely resemble these intermediates provides compelling evidence supporting the original Baldwin/Whitehead hypothesis. The concise method by which these alkaloids are generated in nature has led to testing of biomimetic strategies leading towards total synthesis of some members of this class. Clearly more work needs to be done in this arena. Additionally, the structural novelty and complexity of this class of alkaloids has provided impetus for development of elegant new synthetic methods and strategies for total synthesis. We anticipate that this area will remain active for years to come.

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REFERENCES

1. D. J. Faulkner, *Chem. Rev.*, **93**, 1671 (1993).

2. R. Sakai, T. Higa, C. W. Jefford and G. Bernardinelli, *J. Am. Chem. Soc.*, **108**, 6404 (1986).

3. J. E. Baldwin and R. C. Whitehead, *Tetrahedron Lett.*, **33**, 2059 (1992).

4. a) R. Sakai, S. Kohmoto, T. Higa, C. W. Jefford and G. Bernardinelli, *ibid.*, **28**, 5493 (1987); b) T. Ichiba, R. Sakai, S. Kohmoto, G. Saucy and T. Higa, *ibid.*, **29**, 3083 (1988).

5. *Cf.* S. Laschat, *Angew. Chem. Int. Ed. Engl.*, **35**, 289 (1996).

6. K. Kondo, H. Shigemori, Y. Kikuchi, M. Ishibashi, T. Sasaki and J. Kobayashi, *J. Org. Chem.*, **57**, 2480 (1992).

7. M. Tsuda, N. Kawasaki and J. Kobayashi, *Tetrahedron*, **50**, 7957 (1994).

8. B. J. Baker, P. J. Scheuer and J. N. Shoolery, *J. Am. Chem. Soc.*, **110**, 965 (1988).

9. E. Fahy, T. F. Molinski, M. K. Harper, B. W. Sullivan, D. J. Faulkner, L. Parkanyi and J. Clardy, *Tetrahedron Lett.*, **29**, 3427 (1988).

10. P. Crews, X. C. Cheng, M. Adamczeski, J. Rodriguez, M. Jaspars, F. J. Schmitz, S. C. Traeger and E. O. Pordesimo, *Tetrahedron*, **50**, 13567 (1994).

11. M. Tsuda, N. Kawasaki and J. Kobayashi, *Tetrahedron Lett.*, **35**, 4387 (1994).

12. N. Fusetani, K. Yasumuro, S. Matsunaga and H. Hirota, *ibid.*, **30**, 6891 (1989).

13. N. Fusetani, N. Asai, S. Matsunaga, K. Honda and K. Yasumuro, *ibid.*, **35**, 3967(1994).

14. M. Kobayashi, K. Kawazoe and I. Kitagawa, *ibid.*, **30**, 4149 (1989).

15. M. Kobayashi, K. Kawazoe and I. Kitagawa, *Chem. Pharm. Bull. Jpn*, **37**, 1676 (1989).

16. a) J. C. Braekman, D. Daloze, P. Macedo de Abreu, C. Piccinni-Leopardi, G. Germain and M. Van Meerssche, *Tetrahedron Lett.*, **23**, 4277 (1982); b) J. C. Braekman, D. Daloze, N. Defay and D. Zimmerman, *Bull. Soc. Chim. Belg.*, **93**, 941 (1984); c) J. C. Braekman, D. Daloze, G. Cimino and E. Trivellone, *ibid.*, **97**, 519 (1988). Petrosin and petrosin A have also been isolated from the sponge *Xestospongia sp.*[14]

17. M. Nakagawa, M. Endo, N. Tanaka and L. Gen-Pei, *Tetrahedron Lett.*, **25**, 3227 (1984).

18. a) T. R. Hoye, J. T. North and L. J. Yao, *J. Org. Chem.*, **59**, 6904 (1994); b) T. R. Hoye, J. T. North and L. J. Yao, *Ibid.*, **60**, 4958 (1995).

19. F. Kong and R. J. Andersen, *Tetrahedron Lett.*, **51**, 2895 (1995).

20. J. Kobayashi, M. Tsuda, N. Kawasaki, K. Matsumoto and T. Adachi, *ibid.*, **35**, 4383 (1994).

21. F. Kong, R. J. Andersen and T. M. Allen, *ibid.*, **35**, 1643 (1994).

22. J. Rodriguez, B. M. Peters, L. Kurz, R. C. Schatzman, D. McCarley, L. Lou and P. Crews, *J. Am.*

Chem. Soc., **115**, 10436 (1993); J. Rodriguez and P. Crews, *Tetrahedron Lett.*, **35**, 4719 (1994).

23. F. Kong, R. J. Andersen and T. M. Allen, *Tetrahedron*, **50**, 6137 (1994).

24. a) J. Kobayashi, N. Kawasaki and M. Tsuda, *Tetrahedron Lett.*, **37**, 8203 (1996); b) M. Tsuda, K. Inaba, N. Kawasaki, K. Honma and J. Kobayashi, *Tetrahedron*, **52**, 2319 (1996).

25. F. Kong, R. J. Andersen and T. M. Allen, *J. Am. Chem. Soc.*, **116**, 6007 (1994).

26. M. Jaspars, V. Pasupathy and P. Crews, *J. Org. Chem.*, **59**, 3253 (1994).

27. Halicyclamine B, a closely related compound, has also been described:

B. Harrison, S. Talapatra, E. Lobkovsky, J. Clardy and P. Crews, *Tetrahedron Lett.*, **37**, 9151 (1996).

28. a) G. Cimino, C. A. Mattia, L. Mazzarella, R. Puliti, G. Scognamiglio, A. Spinella and E. Trivellone, *Tetrahedron*, **45**, 3863 (1989); b) G. Cimino, G. Scognamiglio, A. Spinella and E. Trivellone, *J. Nat. Prod.*, **53**, 1519 (1990).

29. Sarains B and C have also been described: Y. Guo, A. Madaio, E. Trivellone, G. Scognamiglio and G. Cimino, *Tetrahedron*, **52**, 8341 (1996) and references cited therein.

30. G. Cimino, S. DeStefano, G. Scognamiglio, G. Sodano and E. Trivellone, *Bull. Soc. Chim. Belg.*, **95**, 783 (1986).

31. Isosarains have also been isolated: G. Cimino, A. Spinella and E. Trivellone, *Tetrahedron Lett.*, **30**, 133 (1989).

32. J. E. Baldwin, T. D. W. Claridge, F. A. Heupel and R. C. Whitehead, *ibid.*, **35**, 7829 (1994).

33. J. E. Baldwin, T. D. W. Claridge, A. J. Culshaw, F. A. Heupel, S. Smrckova and R. C. Whitehead, *ibid.*, **37**, 6919 (1996).

34. J. E. Baldwin, L. Bischoff, T. D. W. Claridge, F. A. Heupel, D. R. Spring and R. C. Whitehead, *Tetrahedron*, **53**, 2271 (1997).

35. L. Gil, X. Baucherel, M. T. Martin, C. Marazano and B. C. Das, *Tetrahedron Lett.*, **36**, 6231 (1995).

36. a) A. G. M. Barrett, M. L. Boys and T. L. Boehm, *J. Chem. Soc., Chem. Commun.*, 1881 (1994); b) A. G. M. Barrett, M. L. Boys and T. L. Boehm, *J. Org. Chem.*, **61**, 685 (1996).

37. a) R. M. Borzilleri, S. M. Weinreb and M. Parvez, *J. Am. Chem. Soc.*, **116**, 9789 (1994); b) R. M. Borzilleri, S. M. Weinreb and M. Parvez, *ibid.*, **117**, 10905 (1995).

38. T. S. McDermott, A. A. Mortlock and C. H. Heathcock, *J. Org. Chem.*, **61**, 700 (1996).

39. D. F. Taber and Y. Wang, *J. Am. Chem. Soc.*, **119**, 22 (1997).

40. R. W. Scott, J. R. Epperson and C. H. Heathcock, *ibid.*, **116**, 8853 (1994).

41. G. R. Pettit, B. Orr, D. L. Herald, D. L. Doubek, L. Tackett, J. M. Schmidt, M. R. Boyd, R. K. Pettit and J. N. A. Hooper, *Bioorg. Med. Chem. Lett.*, **6**, 1313 (1996).

42. a) T. R. Hoye and J. T. North, *Tetrahedron Lett.*, **31**, 4281 (1990); b) L. Börjesson, I. Csöregh and C. J. Welch, *J. Org. Chem.*, **60**, 2989 (1995); c) K. H. Ahn and S. J. Lee, *Tetrahedron Lett.*, **33**, 507 (1992); d) L. Börjesson and C. J. Welch, *Tetrahedron*, **48**, 6325 (1992).

43. a) T. R. Hoye, J. T. North and L. J. Yao, *J. Am. Chem. Soc.*, **116**, 2617 (1994); b) T. R. Hoye, Z. Ye, L. J. Yao and J. T. North, *ibid.*, **118**, 12074 (1996).

44. M. T. Davies-Coleman and D. J. Faulkner, *J. Org. Chem.*, **58**, 5925 (1993).

45. H. Anan, N. Seki, O. Noshiro, K. Honda, K. Yasumuro, T. Ozasa and N. Fusetani, *Tetrahedron*, **52**, 10849 (1996).

46. a) J. Sisko and S. M. Weinreb, *J. Org. Chem.*, **56**, 3210 (1991); b) J. Sisko, J. R. Henry and S. M. Weinreb, *ibid.*, **58**, 4945 (1993); c) J. R. Henry, K. Samizu and S. M. Weinreb, unpublished results.

47. a) B. R. Henke, A. J. Kouklis and C. H. Heathcock, *J. Org. Chem.*, **57**, 7056 (1992); b) D. A. Griffith and C. H. Heathcock, *Tetrahedron Lett.*, **36**, 2381 (1995); c) C. H. Heathcock, M. Clasby, D. A. Griffith, B. R. Henke and M. J. Sharp, *Synlett*, 467 (1995).

48. N. Matzanke, R. J. Gregg and S. M. Weinreb, *J. Org. Chem.*, **62**, 1920 (1997).

49. H. Nakamura, S. Deng, J. Kobayashi, Y. Okimuzi, Y. Tomotake, T. Matsuzaki and Y. Hirata, *Tetrahedron Lett.*, **28**, 621 (1987).

50. a) M. Kobayashi, Y.-J. Chen, S. Aoki, Y. In, T. Ishida and I. Kitagawa, *Tetrahedron*, **51**, 3727 (1995); b) R. A. Edraga, P. Proksch, V. Wray, L. Witte, W. E. G. Müller and R. W. M. Van Soest, *J. Nat. Prod.*, **59**, 1056 (1996).

51. I. Ohtani, T. Ichiba, M. Isobe, M. Kelly-Borges and P. J. Scheuer, *J. Am. Chem. Soc.*, **117**, 10743 (1995).

52. a) Y. Torisawa, A. Hashimoto, M. Nakagawa and T. Hino, *Tetrahedron Lett.*, **30**, 6549 (1989); b) Y. Torisawa, A. Hashimoto, M. Nakagawa, H. Seki, R. Hara and T. Hino, *Tetrahedron*, **47**, 8067, (1991).

53. W. Nowak and H. Gerlach, *Liebigs Ann. Chem.*, 153 (1993).

54. Y. Torisawa, A. Hashimoto, M. Okouchi, T. Iimori, M. Nakasawa, T. Hino and M. Nakagawa, *Bioorg. Med. Chem. Lett.*, **6**, 2565 (1996).

55. a) D. J. Hart and J. A. McKinney, *Tetrahedron Lett.*, **30**, 2611 (1989); b) J. A. Campbell and D. J. Hart, *ibid.*, **33**, 6247 (1992).

56. T. M. Kamenecka and L. E. Overman, *ibid.*, **35**, 4279 (1994).

57. S. Li, S. Ohba, S. Kosemura and S. Yamamura, *ibid.*, **37**, 7365 (1996).

58. J. S. Clark and P. B. Hodgson, *ibid.*, **36**, 2519, (1995).

59. a) K. M. J. Brands and U. K. Pandit, *ibid.*, **30**, 1423 (1989); b) K. M. J. Brands and U. K. Pandit, *Heterocycles*, **30**, 257 (1990); c) K. M. J. Brands, A. A. P. Meekel and U. K. Pandit, *Tetrahedron*, **47**, 2005 (1991).

60. a) U. K. Pandit, *J. Heterocycl. Chem.*, **31** 615, (1994); b) B. C. Borer, S. Deerenberg, H. Bieräugel and U. K. Pandit, *Tetrahedron Lett.*, **35**, 3191 (1994).

61. S. F. Martin, Y. Liao, Y. Wong and T. Rein, *ibid.*, **35**, 691 (1994).

62. a) S. F. Martin, T. Chou and C. Tu, *ibid.*, 3823 (**1979**); b) S. F. Martin, C. Tu and T. Chou, *J. Am. Chem. Soc.*, **102**, 5274 (1980); c) S. F. Martin, S. A. Williamson, R. P. Gist and K. M. Smith, *J. Org. Chem.*, **48**, 5170 (1983).

63. S. F. Martin, T. Rein and Y. Liao, *Tetrahedron Lett.*, **32**, 6481 (1991).

64. a) Y. Torisawa, M. Nakagawa, H. Arai, Z. Lai, T. Hino, T. Nakata and T. Oishi, *ibid.*, **31**, 3195 (1990); b) M. Nakagawa, Z. Lai, Y. Torisawa, and T. Hino, *Heterocycles*, **31**, 999 (1990); c) Y. Torisawa, M. Nakagawa, T. Hosaka, K. Tanabe, Z. Lai, K. Ogata, T. Nakata, T. Oishi and T. Hino, *J. Org. Chem.*, **57**, 5741 (1992); d) M. Nakagawa, Y. Torisawa, T. Hosaka, K. Tanabe, F. Tavet, M. Aikawa and T. Hino, *Heterocycles*, **35**, 1157 (1993); e) M. Nakagawa, Y. Torisawa, T. Hosaka, K. Tanabe, T. Da-te, K. Okamura and T. Hino, *Tetrahedron Lett.*, **34**, 4543 (1993); f) Y. Torisawa, T. Hosaka, K. Tanabe, N. Suzuki, Y. Motohashi, T. Hino and M. Nakagawa, *Tetrahedron*, **52**, 10597 (1996); g) Y. Torisawa, M. A. Ali, F. Tavet, A. Kageyama, M. Aikawa, N. Fukui, T. Hino and M. Nakagawa, *Heterocycles*, **42**, 677 (1996).

65. a) D. de Oliveira Imbroisi and N. S. Simpkins, *Tetrahedron Lett.*, **30**, 4309 (1989); b) D. de Oliveira Imbroisi and N. S. Simpkins, *J. Chem. Soc., Perkin Trans. 1,* 1815 (1991).)

66. a) J. Leonard, S. P. Fearnley and D. M. B. Hickey, *Synlett*, 272 (1992); b) J. Leonard, S. P. Fearnley, M. R. Finlay, J. A. Knight and G. Wong, *J. Chem. Soc., Perkin Trans. 1*, 2359 (1994).

67. a) I. E. Markó and A. Chesney, *Synlett*, 275 (1992); b) I. E. Markó, J. M. Southern and H. Adams, *Tetrahedron Lett.*, **33**, 4657 (1992).

68. a) J. D. Winkler, M. G. Siegel and J. E. Stelmach, *ibid.*, **34**, 6509 (1993); b) J. D. Winkler, C. M. Bowen and F. Liotta, *Chem. Rev.*, **95**, 2003 (1995).

69. E. Magnier, Y. Langlois and C. Mérienne, *Tetrahedron Lett.*, **36**, 9475 (1995).

70. S. Li, S. Kosemura and S. Yamamura, *ibid.*, **35**, 8217 (1994).

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