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Manzamine Alkaloids, Syntheses and Synthetic Approaches.

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1. Introduction

During the last decade nitrogeneous marine natural products have appeared as compounds of increasing importance. Marine alkaloids represent about 25% of reported marine natural products and 54% of these alkaloids are extracted from sponges[1]. Among these compounds, β-carboline alkaloids, such as eudistomine and manzamine alkaloids have received special attention due to their biological activities; particularly to their cytotoxicity and/or antitumor activities. Several excellent reviews concerning marine alkaloids have been published[1]. The aim of the present review, following a brief introduction to the isolation and structural elucidation and possible biogenesis of manzamine alkaloids, is to present from a strategic point of view the various syntheses or synthetic approaches developed in this field by a number of research groups.

2. Isolation, structure determination.

Manzamine alkaloids are a growing family of β-carboline alkaloids characterized by a large membered ring, the presence of one or two additional nitrogens and, for the most complex members like manzamine A **1**, by a complex array of rings of varying sizes. Manzamine A **1**, the prototype of this group, was first reported as the hydrochloride salt by Higa[2] from a sponge of the genus *Haliclona*. This new alkaloid displayed a significant *in vitro* activity having particularly an IC_{50} of 0.07 μg/mL on P388 mouse leukaemia cells. Independently, the

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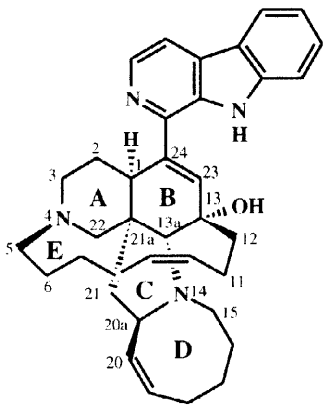
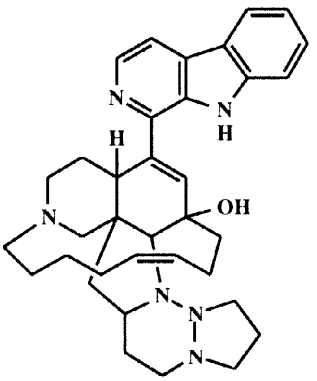
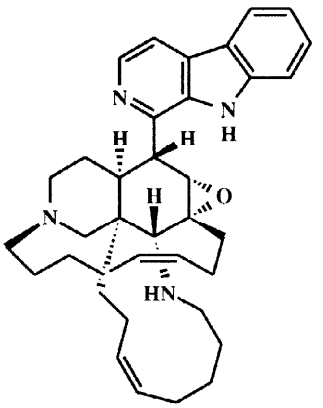
Nakamura group[3] described the same alkaloid extracted from *Pellina* sp, under the name of keramamine A together with another alkaloid keramamine B **2**. Subsequently, the Higa group isolated and characterized two additional alkaloids from *Haliclona*, manzamine **B 3** and manzamine C **4**[4] (Figure 1).



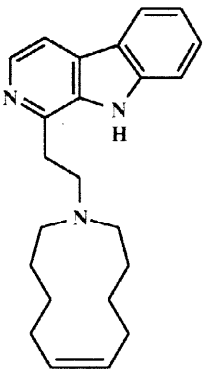
manzamine A **1**
(keramamine A)



keramamine B **2**
(proposed structure)



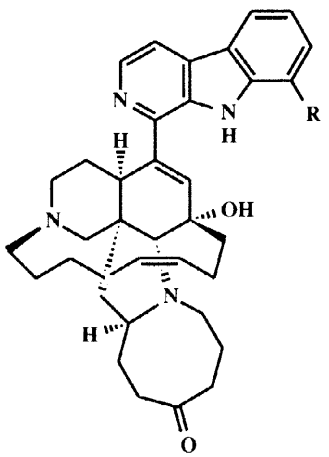
manzamine B **3**



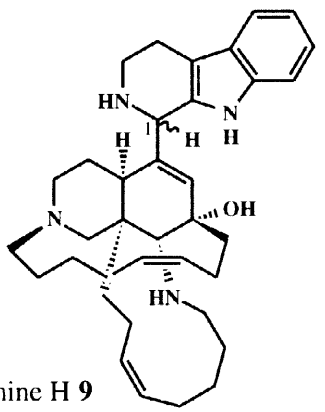
manzamine C **4**

Figure 1

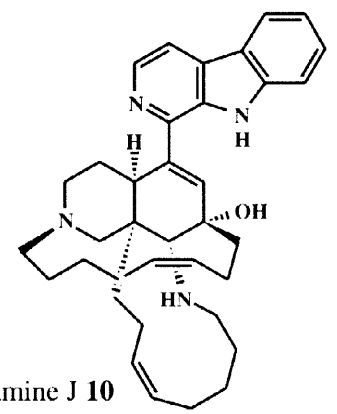
A third sponge species, *Xestonpongia* sp. contained related alkaloids, manzamines E **5** and F **6** which retain the general framework of manzamine A **1** with additional functionality either on the carboline unit or on the eight-membered ring (Figure 2).



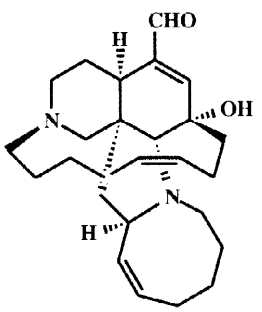
R= H : manzamine E **5**
R= OH : manzamine F **6**
(revised structure for **2**)



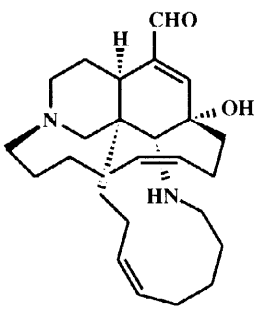
1*R* : manzamine H **9**



manzamine J **10**



ircinal A **7**

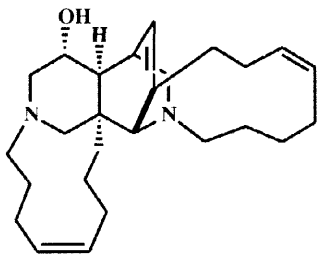


ircinal B **8**

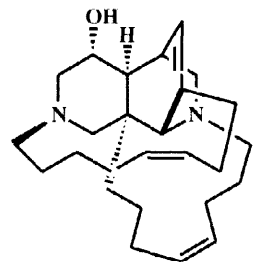
Figure 2

The identity between manzamine F **6** and the former keramamine B **2** was also established by Higa[5]. Four years later, the Kobayashi group[6] isolated and characterized four new alkaloids ircinal A **7** and B **8** together with manzamines H **9** and J **10**. A Pictet-Spengler condensation of ircinal A **7** and B **8** with tryptamine followed by DDQ oxidation afforded respectively manzamine A **1** and manzamine J **10**. This later alkaloid was also obtained after treatment of manzamine B **3** with sodium hydride. Isolation of ircinals A **7** and B **8** as well as these chemical correlations with manzamines gave further insight into a possible biogenetic pathway. Alkaloids **7**, **8** and **9** exhibited cytotoxicities against L1210 murine leukaemia cells with IC_{50} values in the range of 1.3 to 2.6 μg/mL.

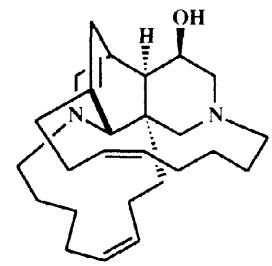
The same year of 1992, J. E. Baldwin[7] proposed a clever biogenetic pathway in which manzamine A **1**, B **3** and C **4** could result from the condensation of the same precursors a C10 dialdehyde unit, propenal and ammonia (*vide infra*). This hypothesis has been indirectly supported by the isolation[8] from *Xestospongia* sp. of xestocyclamine A **11**. This alkaloid, which is a strong protein kinase C inhibitor, could be derived from intermediates proposed in the scheme for manzamine biogenesis. The discovery[9] by the Andersen group of ingenamine A **12** and ingamine A **13** and B **14** from the marine sponge, *Xestospongia ingens*, afforded further evidence for Baldwin's biogenetic pathway (Figure 3).



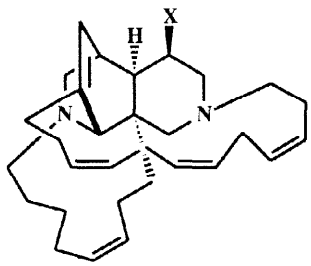
xestocyclamine A **11**
(proposed structure)



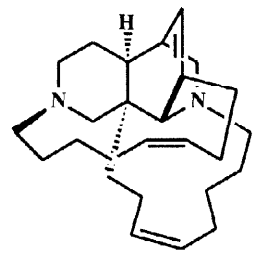
xestocyclamine A **18**
(revised structure)



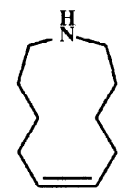
ingenamine A **12**



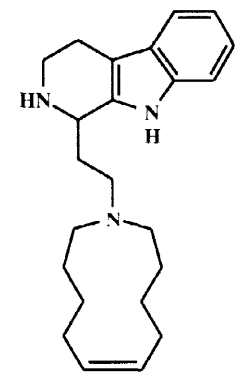
X = OH ingamine A **13**
X = H ingamine B **14**



keramaphidin B **15**
(isolated as racemic mixture)



keramaphidin C **16**



keramamine C **17**

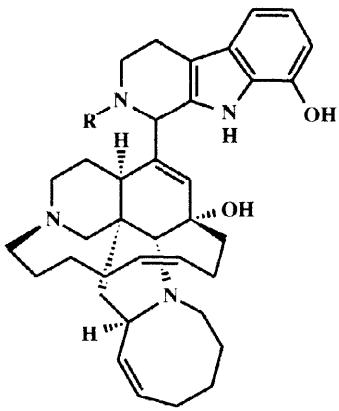
Figure 3

Keramaphidin B **15**, a novel cytotoxic alkaloid extracted from *Amphimedon* sp., appeared also as a cornerstone in the biogenesis of manzamine alkaloids[10]. Interestingly this alkaloid was isolated as the racemic mixture. The significant cytotoxicity of this alkaloid against P388 murine leukaemia (IC_{50} 0.28 μg/mL) and KB human epidermoid carcinoma cells (IC_{50} 0.3 μg/mL) showed that the presence of β-carboline unit, a possible

intercalant in the DNA groove, is not necessary for cytotoxic activity. Ircinals A **7** and B **8** are other examples to support this remark. Two new alkaloids keramaphidin C **16** and keramamine C **17** structurally related to manzamine C **4** were later isolated from the same sponge, *Amphimedon* sp[11]. Crews revised the previously proposed structure for xestocyclamine A **11**[12]. In the revised structure **18**, xestocyclamine is structurally related to keramaphidin B **15**.

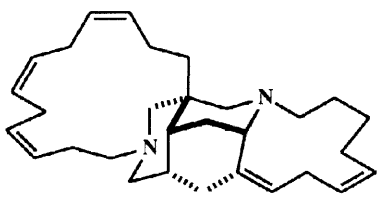
The same group[13] isolated two alkaloids structurally derived from manzamine A **1**, 1,2,3,4-tetrahydro-8-hydroxymanzamine A **19** and the corresponding *N*-methylated derivative **20**. They also proposed a general pathway for the biogenesis of marine sponges alkaloids including not only the manzamine family, but also papuamine **21**, madangamine **22** and cyclostellettamines **23**. All these nitrogeneous metabolites could be derived from dialdehyde units, propenal and ammonia as previously proposed by Baldwin (Figure 4).

Further studies concerning the alkaloidal fraction of *Haliclona* sp. allowed isolation and characterization of halicyclamine A **24**[14] (Figure 4).

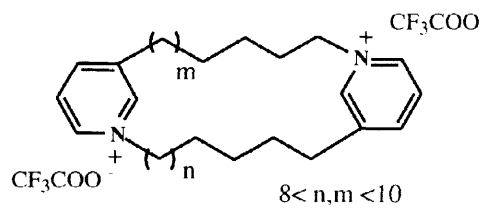


papuamine **21**

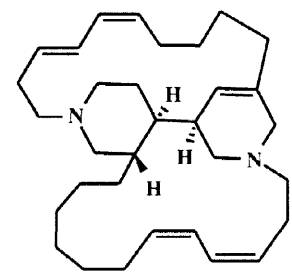
R =H : 1,2,3,4-tetrahydro-8-hydroxymanzamine A **19**
R = Me : *N*-methyl-1,2,3,4-tetrahydro-8-hydroxymanzamine A **20**



madangamine **22**



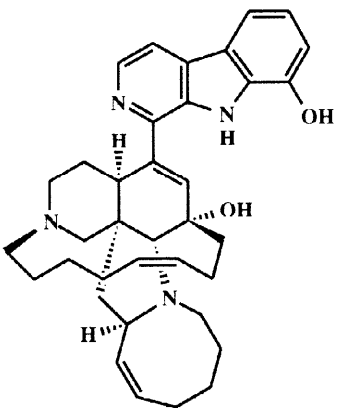
cyclostellamines **23**



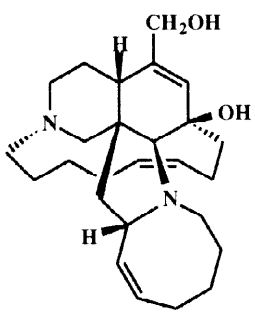
halicyclamine A **24**

Figure 4

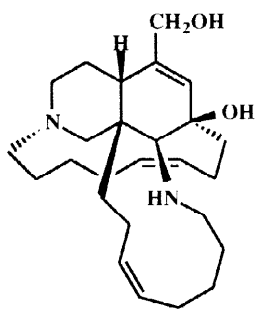
Manzamine A **1** and 8-hydroxymanzamine A **25** were isolated by Scheuer's group[15] from an undescribed sponge *Pachypellina* sp.. Kobayashi and co-workers[16] found two new alkaloids in the sponge *Amphimedon* sp., ircinols A **26** and B **27** which proved to be *antipodal* with ircinal A **7** and B **8** extracted previously from the same organism. This is a rare example of both enantiomeric forms isolated from the same organism. From the same sponge *Amphimedon*, two manzamine derivatives were also isolated, 6-hydroxymanzamine A **28** and 3,4-dihydromanzamine A **29**[16] (Figure 5).



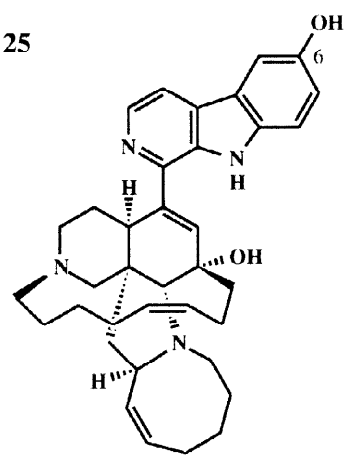
8-hydroxymanzamine A **25**
(manzamine G)



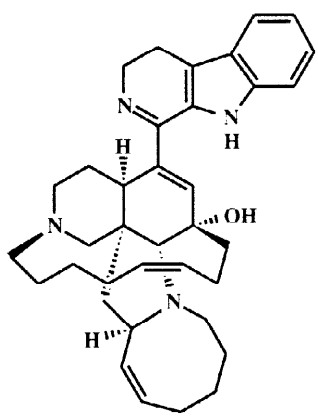
ircinol A **26**



ircinol B **27**



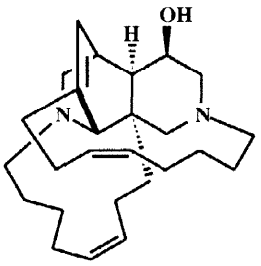
6-hydroxymanzamine A **28**
(manzamine Y)



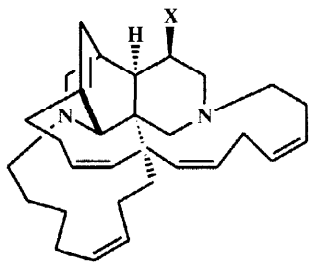
3,4-dihydromanzamine A **29**

Figure 5

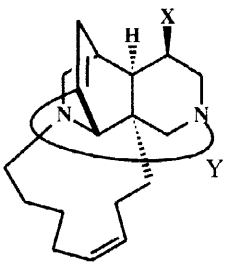
Five new minor alkaloids were isolated and characterized by Andersen[18] from *Xestospongia ingens*. Ingenamines B to F **30** to **34** presented structural variation in the macrocycles and substitution on the perhydro-2,7-naphthyridine unit. Ingenamine **12**, ingamines A **13** and B **14** belong to the same antipodal series which includes ircinols A **26** and B **27**. The antipodal series is represented by xestocyclamine A **11**, ircinals A **7** and B **8** and manzamines (Figure 6).

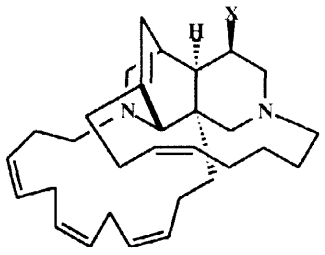


ingenamine A **12**



X = OH ingamine A **13**
X = H ingamine B **14**





ingenamines

B **30** X= OH Y= 

C **31** X= OAc Y= 

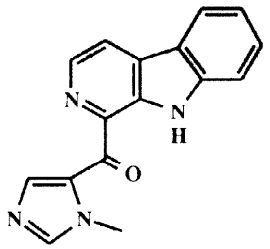
D **32** X= OH Y= 

E **33** X= OH

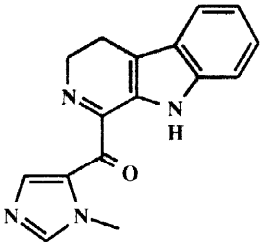
F **34** X= H

Figure 6

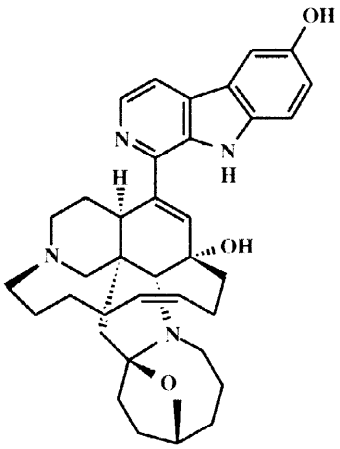
Subsequently, two new β-carboline alkaloids xestomanzamines A **35** and B **36** were isolated from *Xestospongia* sp., together with an additional member of the manzamine group, manzamine X **37** which contains an additional tetrahydrofuran ring[19]. The first dimeric structure in this type of alkaloids has been identified from the Indonesian sponge *Prianos* sp. and was named kauluamine **38**. This alkaloid results from an enamine-iminium C-C bond formation between C3 and C2' of two units derived from manzamine B **3**[20] (Figure 7).



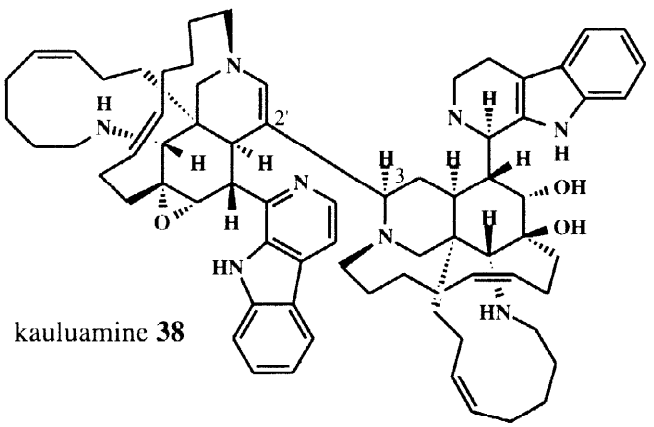
xestomanzamine A **35**



xestomanzamine B **36**



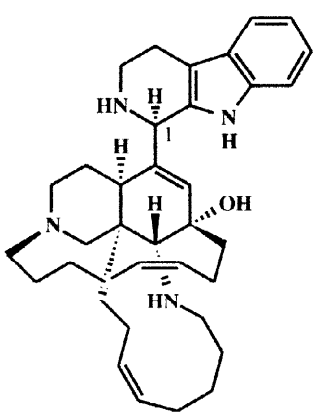
manzamine X **37**



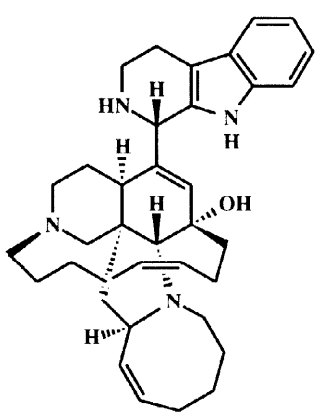
kauluamine **38**

Figure 7

Keramaphidin B **15** previously isolated as mixture of enantiomers, has been resolved using chiral HPLC. A ratio of 20:1 between the two enantiomers was obtained. In the same publication[21], isolation from the sponge *Amphimedon* sp. and structural elucidation of manzamine L **39** is reported. DDQ oxidation of **39** afforded manzamine J **10** (Figure 8).



manzamine L **39** (1*S*)



manzamine D **40** (1*R*)

Figure 8

The absolute configuration at C1 (*S*) in manzamine L **39** was deduced from circular dichroism measurements. The same technique made it possible to attribute the reverse configuration (1*R*) for manzamine

H **9** and manzamine D **40**[21]. The absolute configuration of the major and minor enantiomers of keramaphidin B **15** was deduced after dihydroxylation and esterification of both enantiomers with (+)-MTPA and (-)-MTPA chlorides[22]. The minor enantiomer **15** possesses the same absolute configuration as the major manzamine alkaloids ircinals A **7** and B **8** and manzamines A **1** and B **3**. The major enantiomer presents the same absolute configuration as ircinols A **26** and B **27**. These observations concerning the absolute configurations of manzamines and related alkaloids are summarized in figure 9.

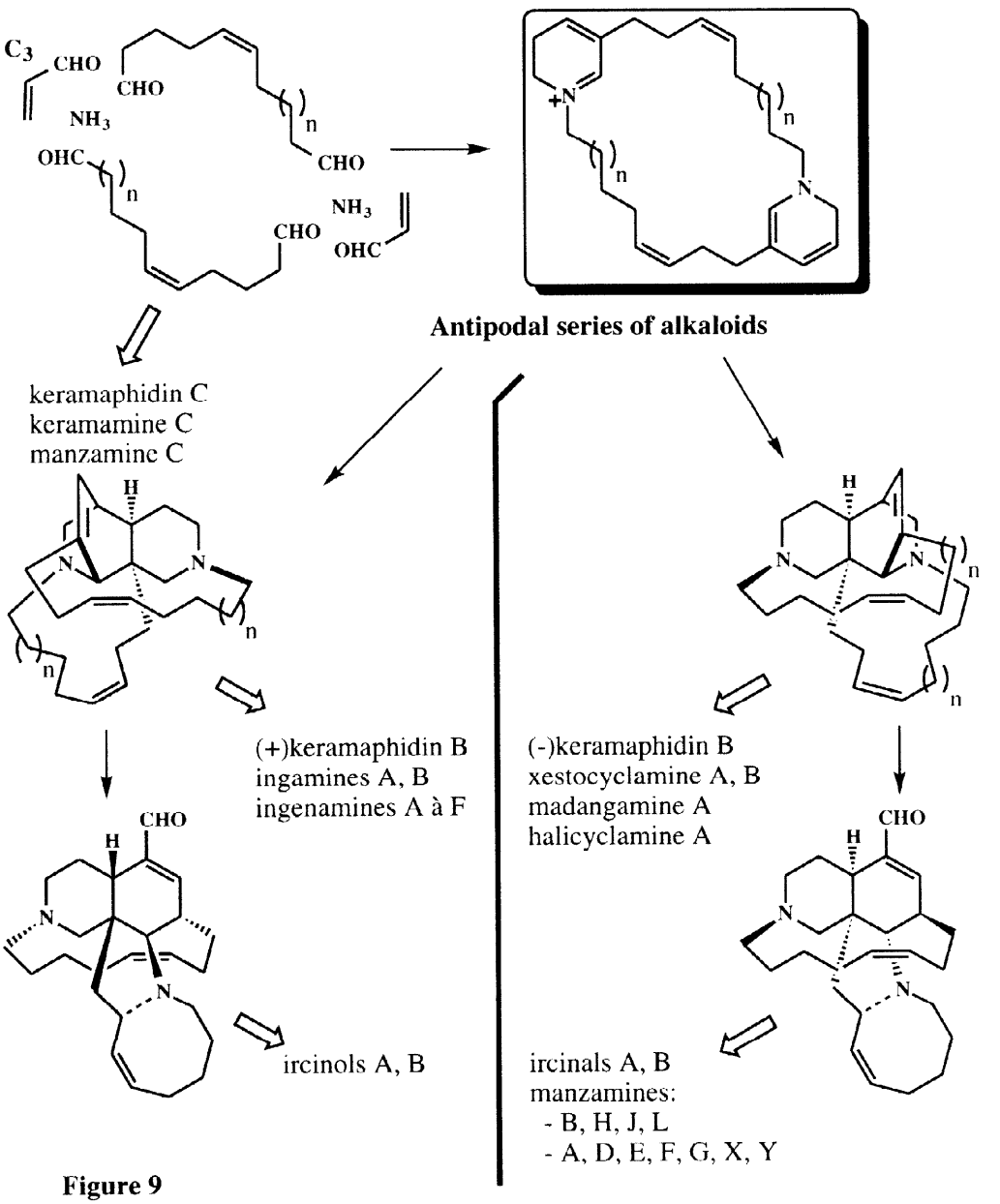
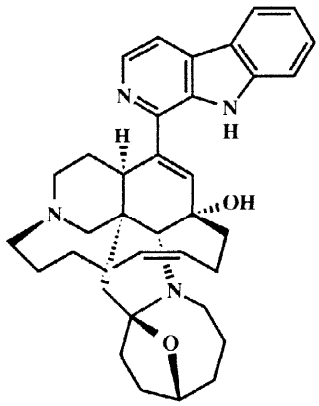


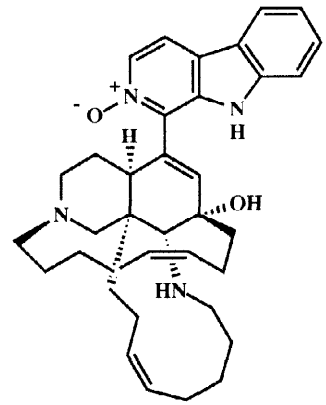
Figure 9

Analysis of the marine sponge *Xestospongia ashmorica* afforded four new manzamine congeners : 6-deoxymanzamine X **41**, and the *N*-oxides of manzamine J **42**, of 3,4-dihydromanzamine A **43** and of manzamine A **44**[23]. Other known manzamine alkaloids were also isolated from the same sponge. A new β-carboline alkaloid **45** extracted from *Hyrtios erecta* containing an imidazolium unit was named

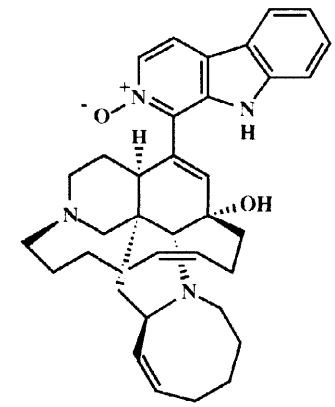
hyrtiomanzamine[24]. However, there is no evidence that this compound, as xestomanzamines A **35** and B **36**[19], is biogenetically related to manzamine alkaloids. Quite recently, a novel manzamine related alkaloid, nakadomarin A **46**, was isolated from another Okinawan sponge *Amphimedon* sp. (SS-264) by the Kobayashi group[25]. The unique structure of this alkaloid was deduced on the basis of NMR spectroscopic data. This alkaloid showed cytotoxicity against murine lymphoma L1210 cells (IC_{50} 1.3 μg/mL) as well as anti-fungal and antibacterial activity against a Gram positive bacterium. From a biogenetic point of view, nakadomarin A **46** could well be derived from ircinal A **7** after B-ring fragmentation and recyclisations (Figure10).



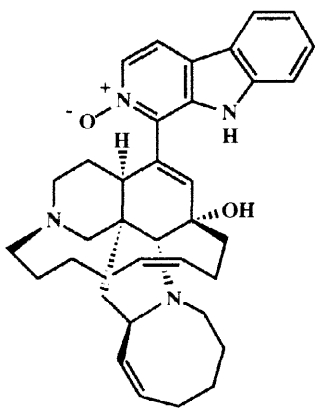
6-deoxymanzamine X **41**



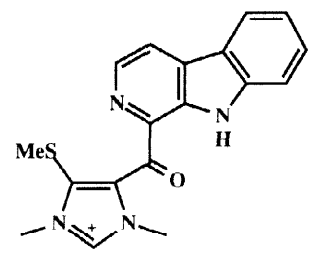
manzamine J *N*-oxide **42**



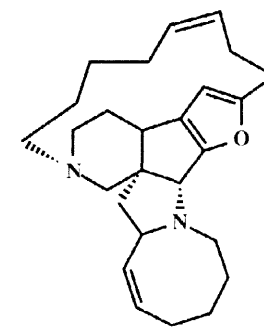
3,4-dihydromanzamine A *N*-oxide **43**



manzamine A *N*-oxide **44**



hyrtiomanzamine **45**

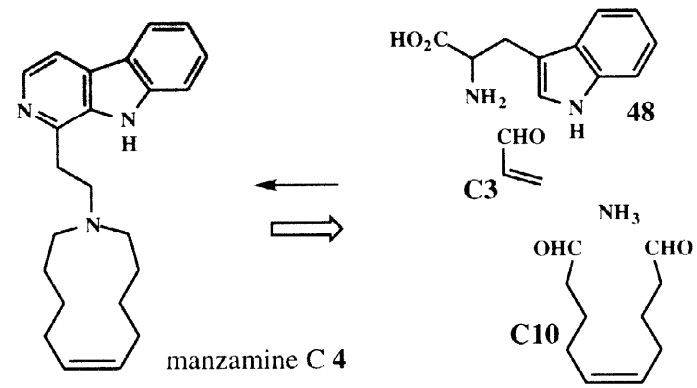


nakadomarin A **46**

Figure 10

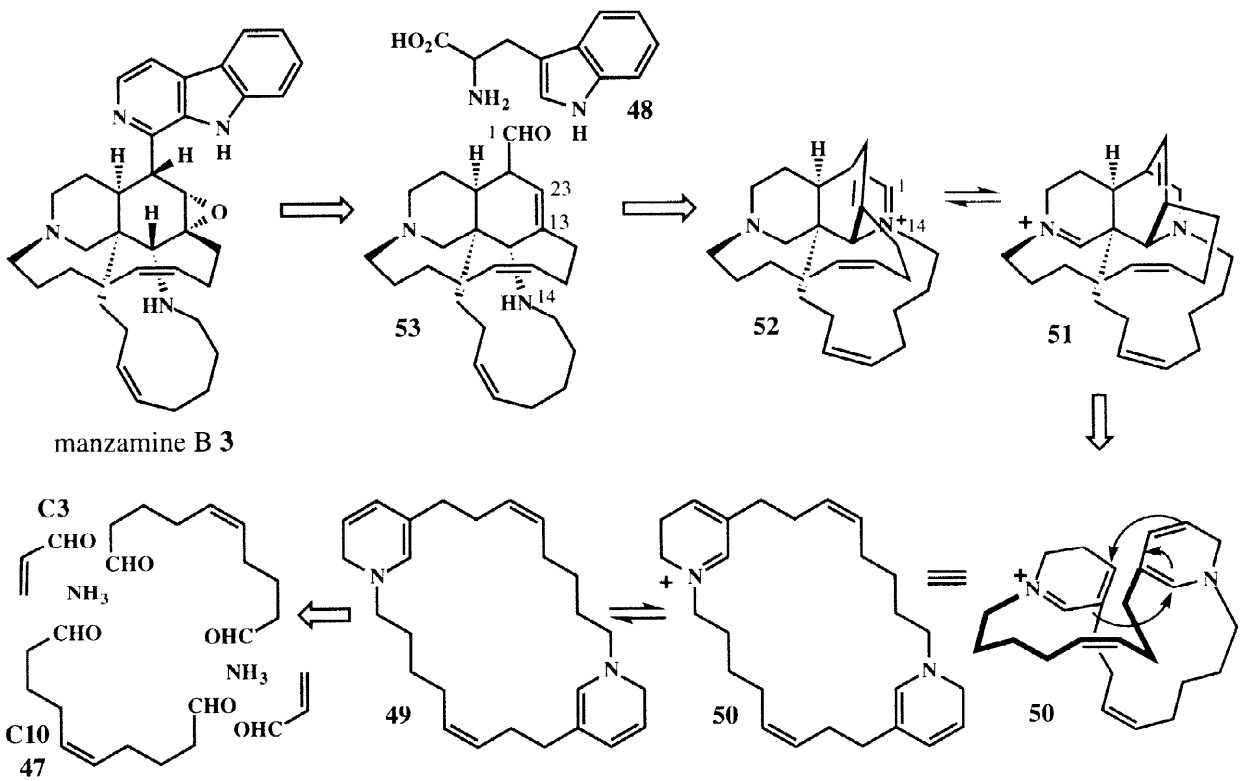
3. Biogenetic Hypothesis.

In 1992, Baldwin and Whitehead[7] proposed a biogenetic pathway for the possible elaboration of manzamines A **1**, B **3** and C **4** in sponges. It was suggested that the simplest structure, manzamine C **4**, could result from the condensation (*Z*)- dec-5-ene-1,10-dial **47**, ammonia, propenal and tryptophan **48** according to scheme 1.



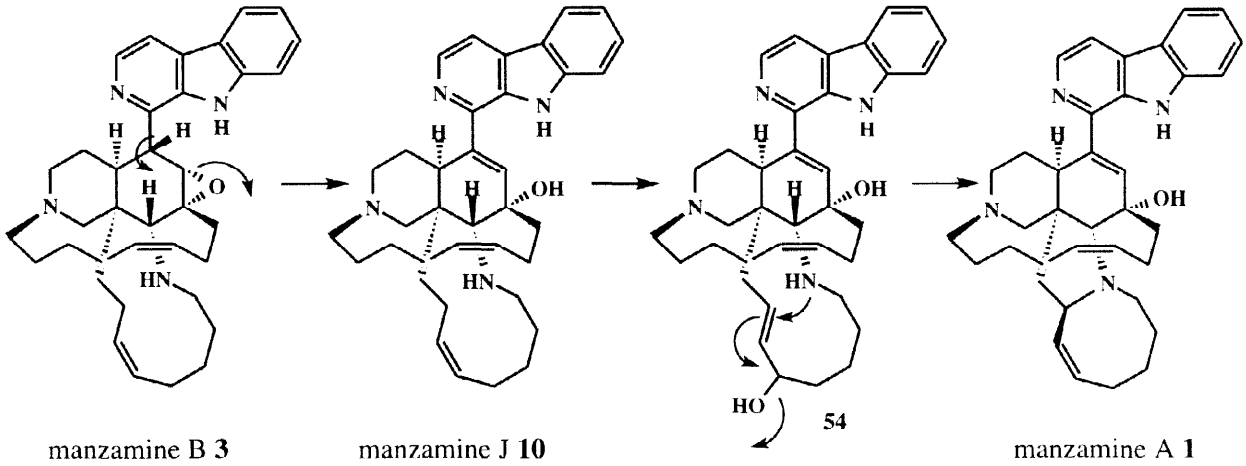
Scheme 1

The same components, by a combination of aldol and Michael type condensations, could lead to a bis dihydropyridine unit **49** which, after tautomerism, could be subject to a transannular Diels-Alder type cycloaddition affording compound **51**. Iminium equilibrium affords a new intermediate **52**, and hydrolysis of the iminium moiety gives rise to the aldehyde derivative **53**. Pictet-Spengler condensation with tryptophan **48**, decarboxylation and aromatization of the carboline moiety, and epoxidation of C13-C23 double bond, affords manzamine B **3** (Scheme 2).



Scheme 2

Epoxide cleavage, allylic hydroxylation and SN' substitution could give rise to manzamine A **1** (Scheme 3).

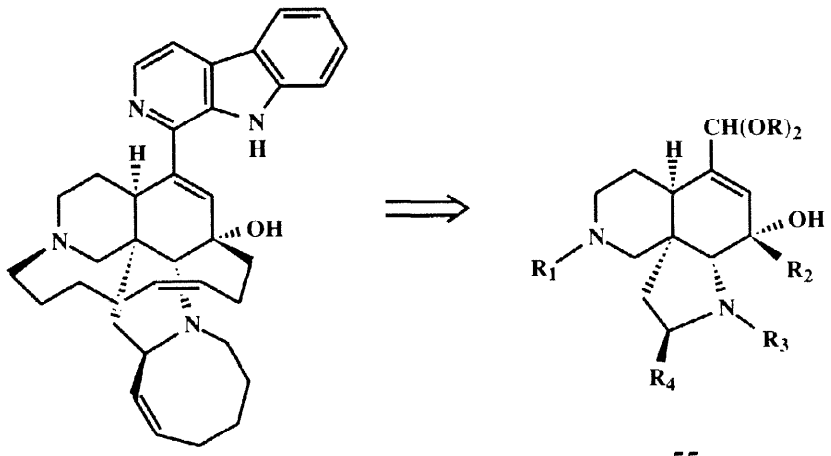


Scheme 3

Support for this hypothesis has been provided by the subsequent isolation of alkaloids like keramaphidin B **15**[10], ircinals A **7** and B **8**[6] which appear to be possible biogenetic intermediates in this scheme. Moreover, as an extension of the Baldwin proposal, a related possible biogenetic scheme has been also used for other families of marine sponge alkaloids, papuamines, haliclamines, cyclostellettamines, madangamines, sarains[13] and halicyclamine **24**[14]. Common synthetic precursors, ammonia, propenal and an unsaturated dialdehyde unit, were proposed as starting material in these biogenetic hypotheses.

4. Manzamime A, synthetic approaches.

As a consequence of their original structures and of their cytotoxic activities manzamine alkaloids, especially manzamine A **1**, rapidly became the subject of numerous synthetic studies. Two total syntheses of manzamine C **4** have been already published (*vide infra*), but the total synthesis of manzamine A **1** itself has still not been achieved, although very advanced pentacyclic synthetic intermediates have been obtained. In the present review, the synthetic approaches towards **1** will be presented from a strategic point of view. The preliminary common goal of nearly all these syntheses is the tricyclic core **55** of manzamine A **1** (Scheme 4).



manzamine A **1** **55**

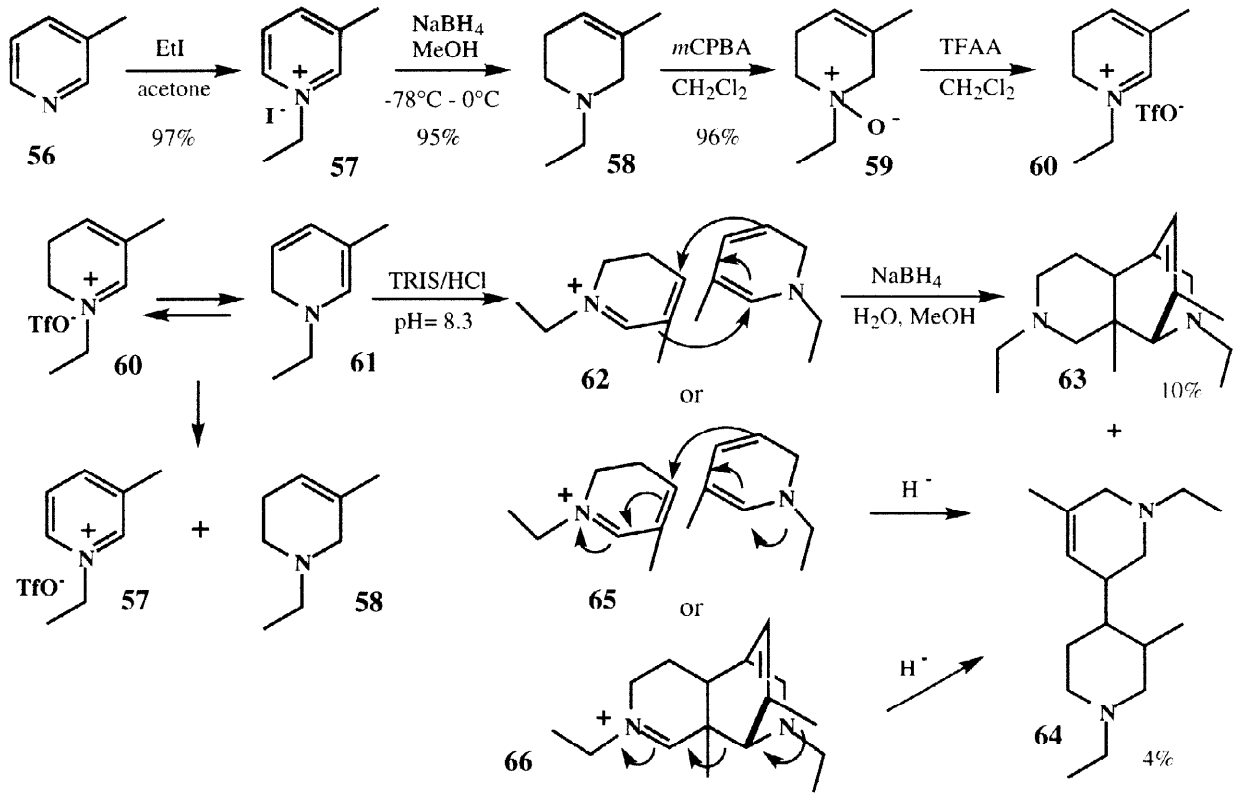
Scheme 4

To date five different strategies have been explored :

- biomimetic approaches.
- radical cyclisation and photochemical approaches.
- ionic cyclisation approaches.
- intermolecular Diels-Alder type cycloadditions approaches.
- intramolecular Diels-Alder cycloadditions approaches.

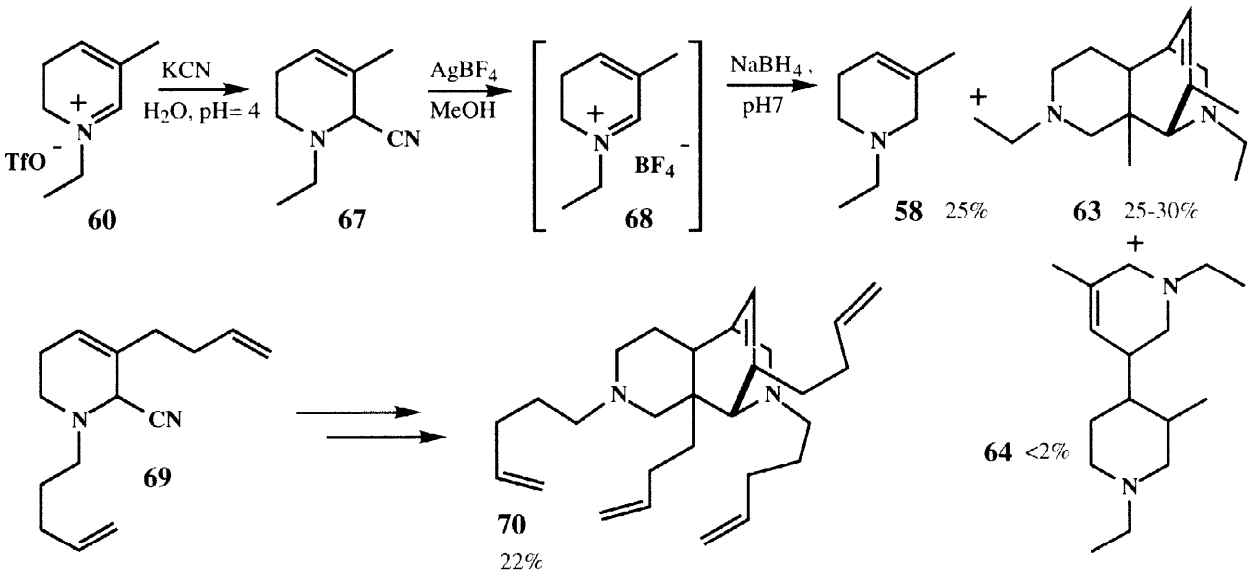
A. Biomimetic approaches.

Biomimetic syntheses or hemisyntheses proved to be in the past a very efficient way for natural products elaboration[26]. In order to implement their biogenetic proposal, Baldwin's group[27] studied the possible intramolecular Diels-Alder type cycloaddition between a 3-substituted 5,6-dihydropyridinium salt and 1,6-dihydropyridine. Classical preparation of 1,2,5,6-tetrahydropyridine afforded compound **58**. *N*-oxidation followed by treatment with trifluoroacetic anhydride under modified Polonovski conditions[28] gave rise to the conjugated iminium salt **60**. This salt was obtained in high overall yield from 3-methylpyridine **56**. Subsequent treatment of **60** in a pH 8.3 buffer solution induced an equilibrium between conjugated iminium **60** and dienamine **61**. Intermolecular Diels-Alder type cycloaddition between these two species gave rise to a tricyclic iminium intermediate **66** which is reduced *in situ* affording compound **63** in 10% yield with a small amount of the product **64** (4%). The formation of **64** can be explained either by a direct 1,4 nucleophilic attack of dienamine **61** on the iminium salt **60** as depicted in **65** or by a retro-Mannich type reaction from the tricyclic iminium intermediate **66** (Scheme 5). However, the major product in this reaction is the tetrahydropyridine **58**. This compound can result from a direct reduction of unreacted iminium **60** or by an oxido-reduction process, from the reduction of pyridinium salt **57**.



Scheme 5

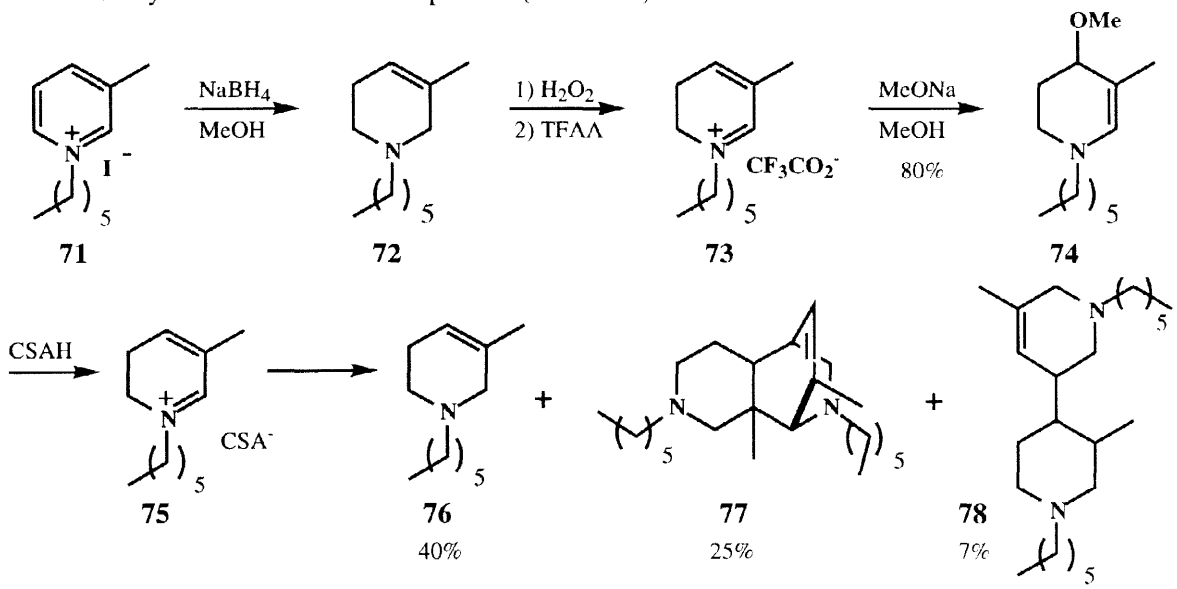
The chemical stability of iminium species **60** is clearly one of the major problems of this reaction. The use of a stable equivalent of **60** such as α-aminonitrile **67** which regenerates **60** in the presence of silver ions, led to an increased yield of 25-30% for "adduct" **63** (Scheme 6).



Scheme 6

This reaction has been subsequently extended to the more functionalized tetrahydropyridine derivative **69**. Thus, the tricyclic compound **70** is obtained in 22% yield, by the same sequence of reactions. The molecule **70** can be considered as a synthetic precursor of keramaphidin B **15**.

Independently, Marazano and coworkers[29] developed a parallel biomimetic approach. Pyridinium salt **71** was chosen as the starting material, classical *N*-oxidation followed by a modified Polonovsky reaction afforded the conjugated iminium species **73**. In this report, 1,4,5,6-tetrahydropyridine derivative **74**, which was isolated in a good overall yield, was used as a precursor of the dihydropyridinium species. Thus, treatment of **74** with camphorsulfonic acid afforded the anticipated iminium species **75**, which after treatment with triethylamine and reduction with sodium borohydride, led to a mixture of three products **76**, **77** and **78** in almost the same yields as in the Baldwin process (Scheme 7).

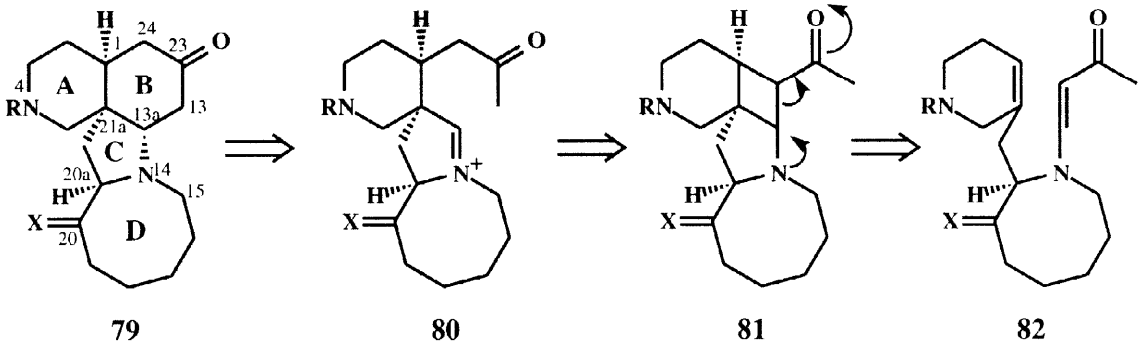


Scheme 7

These biomimetic studies allow the preparation of model compounds in a few steps which are synthetic precursors of the keramaphidin B **15** group and subsequently of manzamine group alkaloids. In addition, these reactions gave rise to halicyclamine A **24** synthetic intermediates. These observations support also the proposed biogenetic scheme.

B. Radical cyclisation and photochemical approaches.

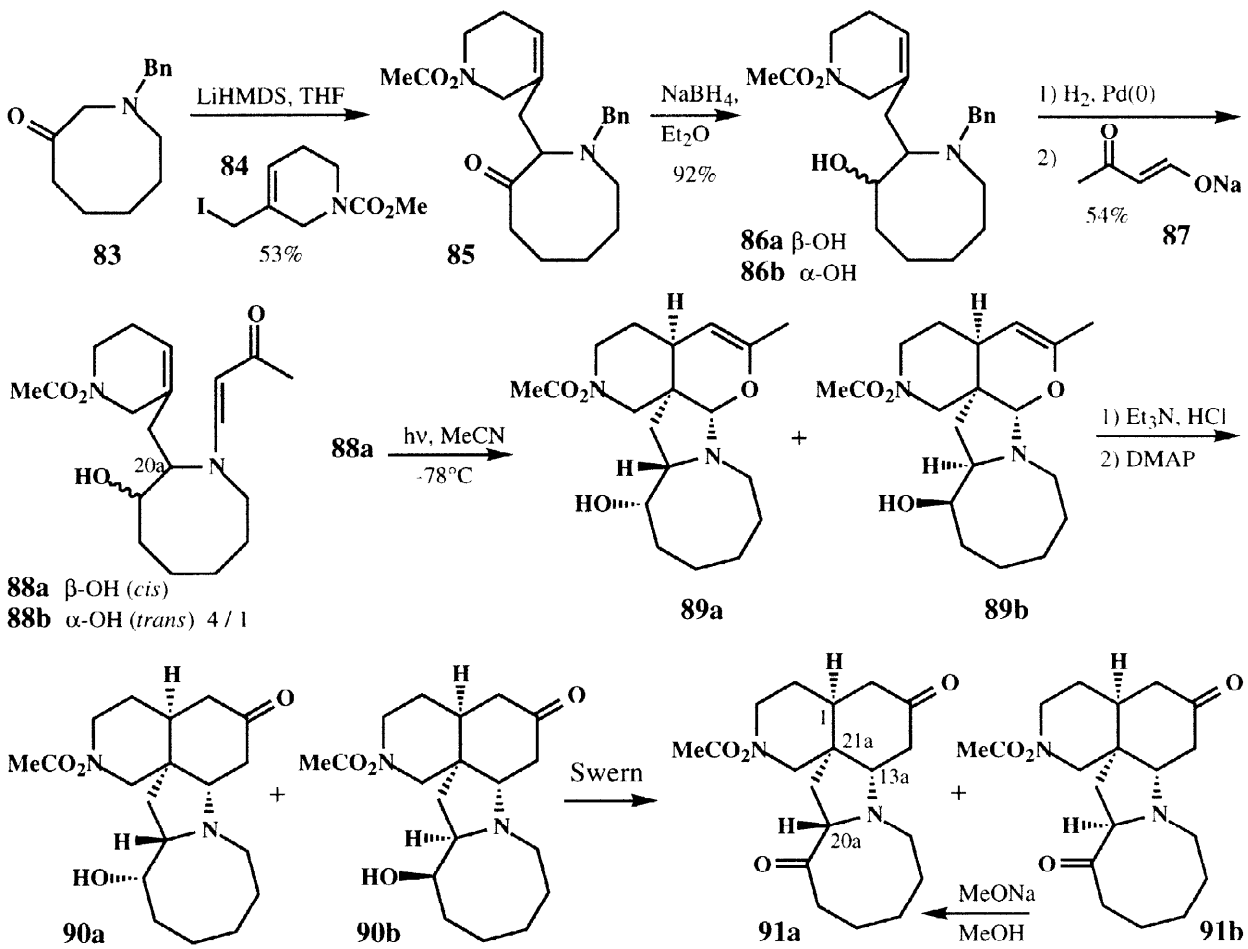
Winkler and coworkers[30] described in 1993 a convergent approach towards an ABCD tetracyclic precursor of manzamine A **1**. This synthesis was based on the use of a [2+2] photocyclisation followed by a retro-Mannich-Mannich cyclisation as depicted in retrosynthetic scheme 8.



79 80 81 82

Scheme 8

Azocinone **83**, prepared by a Dieckmann cyclisation, was regioselectively alkylated with the tetrahydropyridine derivative **84**, itself obtained in 5 steps from 3-hydroxymethylpyridine (Scheme 9).



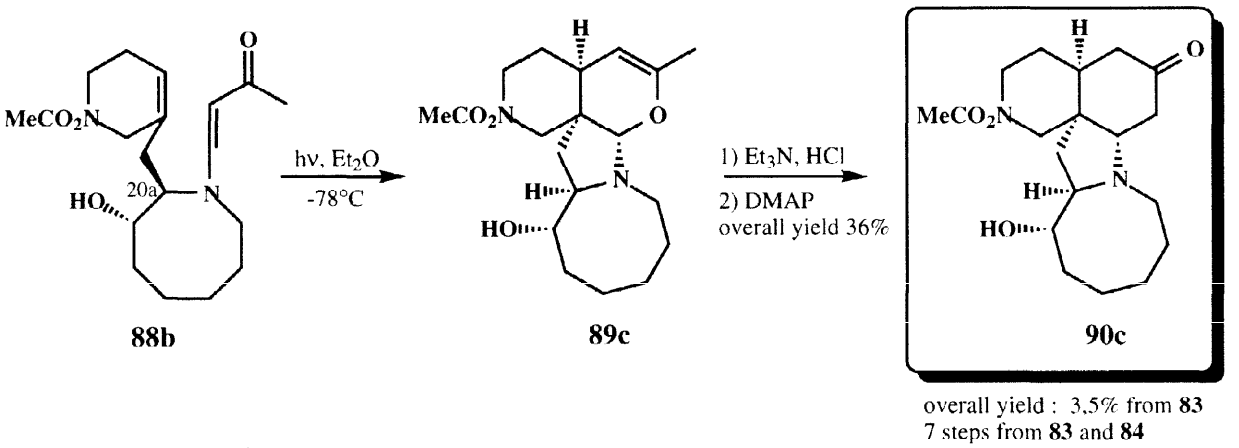
83 **84** **85** **86a** **86b** **87** **88a** **88b** **89a** **89b** **90a** **90b** **91a** **91b**

Scheme 9

The resulting azocinone **85** was reduced with sodium borohydride affording alcohols **86a** and **86b** as a mixture of diastereomers in a four to one ratio respectively. After separation and debenzylation, without

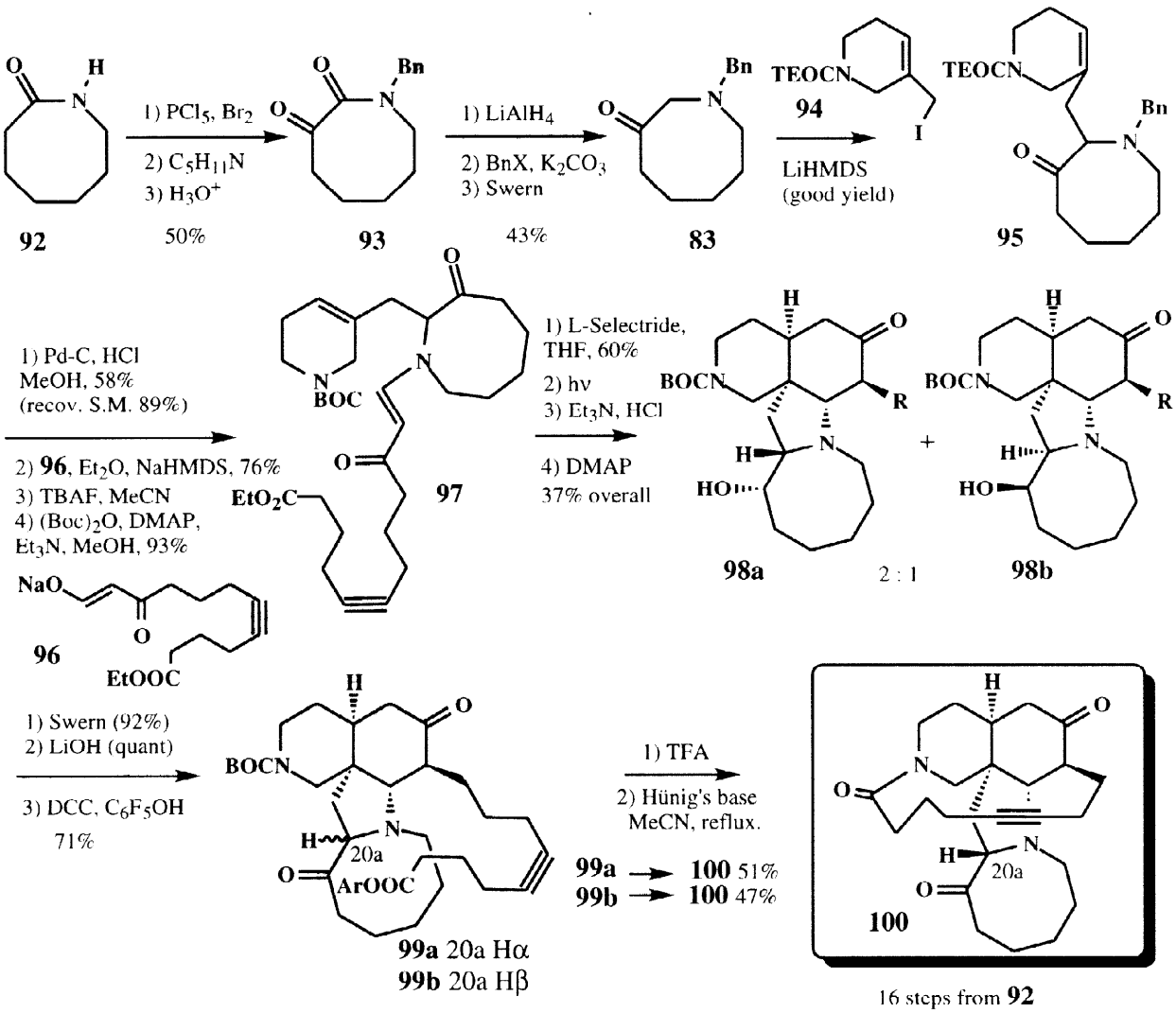
hydrogenation of the trisubstituted double bond, the resulting secondary alcohols were condensed with sodioformylacetone **87** and afforded diastereomeric derivatives **88a** and **88b**. UV irradiation of **88a** in acetonitrile followed by a treatment of the resulting mixture of aminals **89a** and **89b** with triethylamine hydrochloride and refluxing in the presence of one equivalent of DMAP afforded a mixture of isomeric alcohols **90a** and **90b**. Swern oxidation followed by equilibration with sodium methoxide in methanol gave rise to a single keto derivative **91a**. X-Ray analysis of this compound made it possible to attribute the natural relative configurations at C1, C13a and C21a and the reverse configuration at C20a (manzamine numbering).

The same sequence of reactions applied to the minor alcohol **88b** afforded stereoselectively the ABCD tetracyclic compound **90c** with natural relative configurations for all the asymmetric centers. This compound was obtained in 3.5% overall yield from azocinone **83**. The same group reported an asymmetric synthesis of an eight-membered ring precursor of the D-ring of manzamine A **1**[31] (Scheme 10).



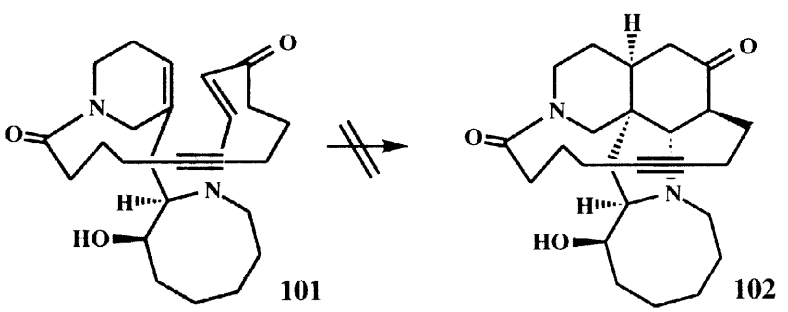
Scheme 10

More recently[32], the same strategy has been applied to the synthesis of an advanced pentacyclic intermediate. Accordingly, lactam **92** was transformed in six steps into azocinone **83**. Alkylation of **83** with the iodo tetrahydropyridine derivative **94** was followed by debenzylation and condensation of the resulting product with enolate **96**. Nitrogen protecting group interconversion (trimethylsilylethyloxycarbonyl (TEOC) to *tert*-butyloxycarbonyl) gave rise to the anticipated compound **97** bearing a nine carbon appendage for further thirteen-membered ring elaboration. Stereoselective reduction of the keto group was followed by the crucial photocyclisation-retro-Mannich-Mannich cascade reactions which led to the formation of two separable tetracyclic compounds **98a** and **98b**. Swern oxidation, saponification and esterification with pentaflurophenol afforded respectively **99a** and **99b**. Each compound was subjected to a high dilution macrolactamisation in the presence of the Hünig's base in refluxing acetonitrile, after acidic cleavage of the *tert*-butyloxycarbonyl nitrogen protecting group. Each isomer afforded the same pentacyclic compound **100** bearing the unnatural relative configuration at C20a (manzamine numbering) (Scheme 11).



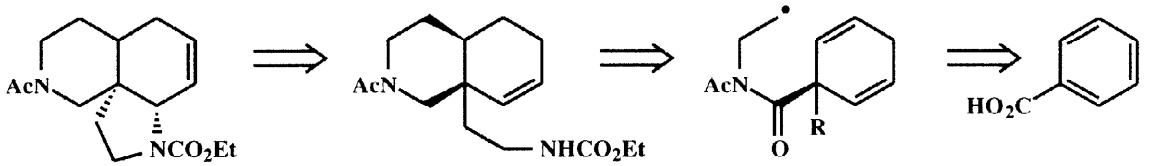
Scheme 11

Winkler and co-workers also studied an alternative tactic, depicted in Scheme 12, in which the large membered lactam was introduced before the photocyclisation step. Unfortunately this reaction didn't afford the expected compound **102**.



Scheme 12

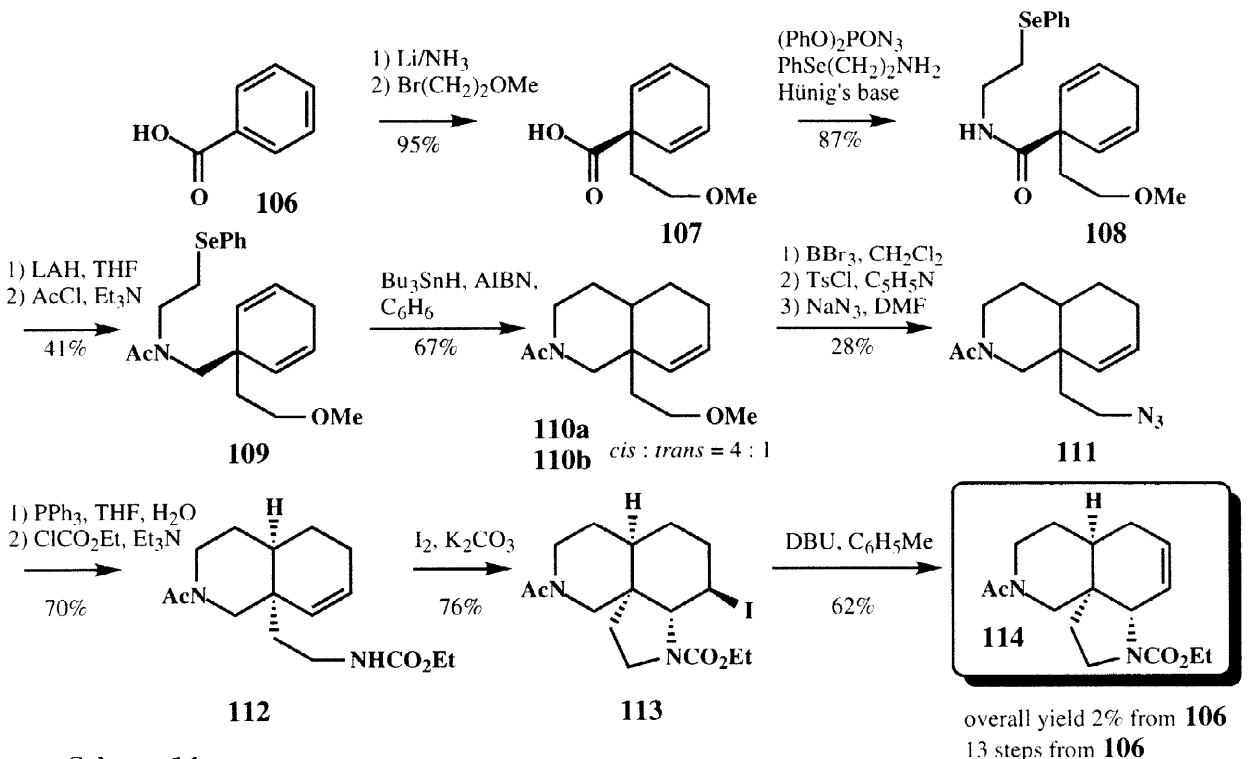
A strategy using a radical cyclisation affording an hexahydroisoquinoline derivative (retrosynthetic scheme 13) was studied by Hart and co-workers[33].



103 **104** **105** **106**

Scheme 13

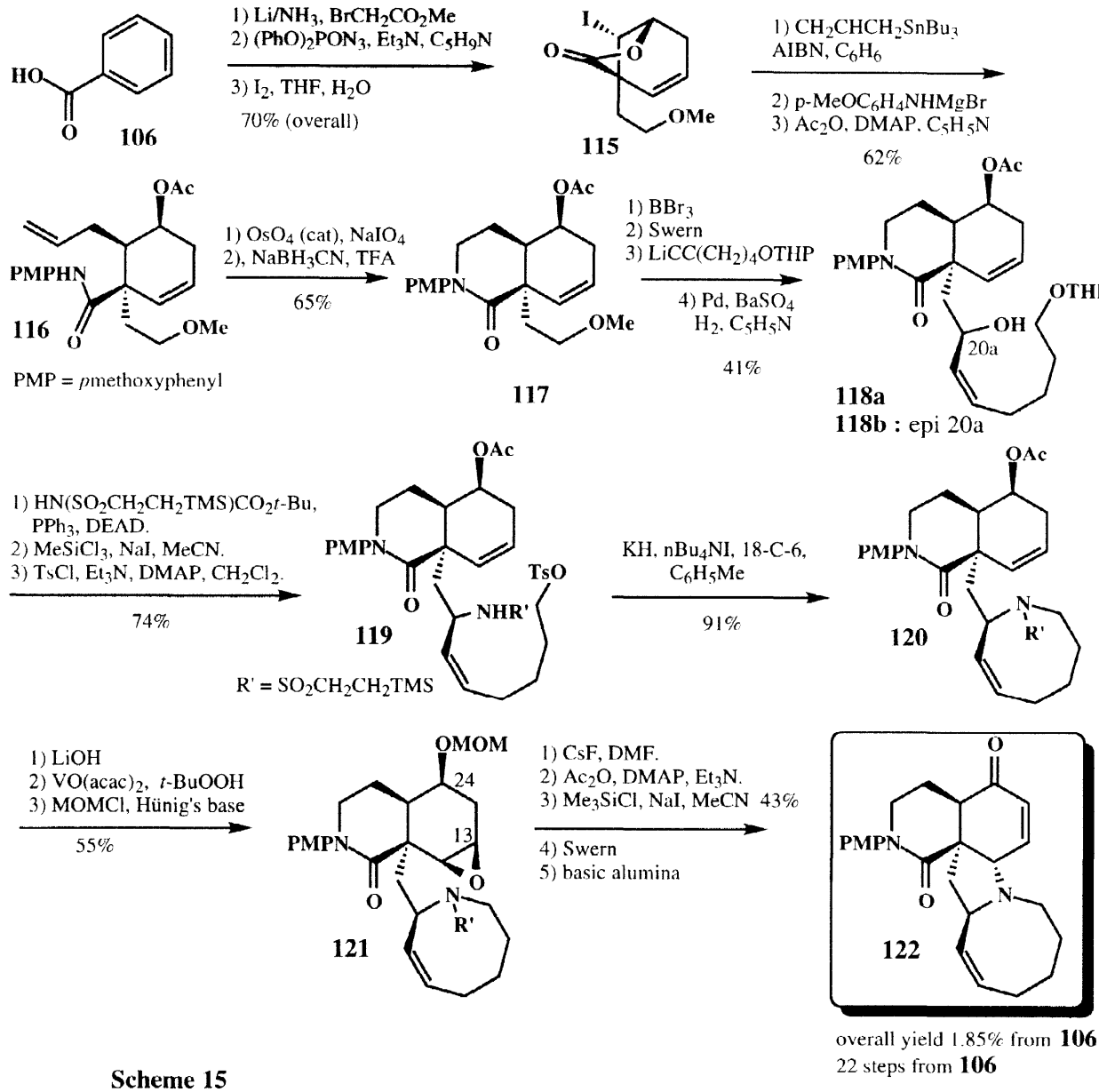
Birch reduction of benzoic acid **106**, followed by alkylation with 2-bromo-1-methoxyethane afforded **107**. Condensation with 2-(phenylseleno)ethylamine, reduction with lithium aluminium hydride and *N*-acylation gave rise to compound **109**. The crucial radical cyclisation was performed by slow addition of tri-*n*-butyltin hydride and AIBN to a refluxing solution of compound **109** in benzene. An inseparable mixture of *cis* and *trans* isomeric compounds **110a** and **110b** was obtained in a 4:1 ratio. Cleavage of the methoxy ether was performed with boron tribromide and the resulting alcohol was tosylated. The leaving group was then substituted with sodium azide affording pure azide derivative **111** after separation from the diastereomeric mixture. Compound **111** was transformed into carbamate **112**. Iodine initiated ring closure gave rise to the tricyclic compound **113**. Subsequent elimination of iodine afforded the tricyclic derivative **114** (Scheme 14).



Scheme 14

The same group developed another approach to the ABCD tetracyclic core of manzamine A in which they used as before benzoic acid as the starting material[34]. However, in this synthesis a radical cyclisation was not used for ring closure. The six-membered ring cyclisation resulted from a nucleophilic attack of an amino group on an aldehyde followed by a reduction of the imine intermediate. Overman followed the same strategy for A ring formation (*vide infra*, scheme 19).

Accordingly, Birch reduction-alkylation and iodolactonisation afforded lactone **115** in good overall yield (Scheme 15). Keck alkylation with allyl tributyltin, nucleophilic attack of the lactone intermediate with 4-methoxyaniline and acetylation afforded compound **116**. Six-membered ring closure was achieved after dihydroxylation-sodium periodate cleavage followed by sodium cyanoborohydride reduction of the imine intermediate. Thus compound **117** was isolated in good overall yield. In this new approach, the stereoselectivity at the six-six ring junction was secured at an early stage of the synthesis and was the result of the *trans* iodolactonisation. Appendages for five-membered and eight-membered ring elaboration were introduced in a second set of reactions. Thus, boron tribromide ether cleavage, as previously, Swern oxidation and lithium acetylide nucleophilic attack gave rise to an isomeric mixture of acetylenic alcohols which were purified after reduction. Isomeric allylic alcohols **118a** and **118b** were obtained in 68 and 32% yields respectively. The stereochemical assignments were based on X-ray analysis of **118a**. Treatment of **118a** under Mitsunobu conditions with a sulfonylurethane derivative as a nucleophilic equivalent of ammonia, followed by cleavage of tetrahydropyranyl protecting group with trichloromethylsilane-sodium iodide, and by tosylation of the resulting alcohol afforded tosylate **119**. It is worthy of note that the Mitsunobu type reaction occurred with retention of configuration, perhaps with participation of the carbonyl lactam. Eight-membered ring formation was performed under high dilution and afforded compound **120** in high yield. A diastereoselective epoxidation directed by the secondary alcohol was achieved after saponification of the acetate group. Reprotection of alcohol as the MOM-ether afforded compound **121**. Deprotection of the 2-trimethylsilylethanesulfonyl group with cesium fluoride in DMF was followed by a nucleophilic attack of secondary amino group on the epoxide and gave rise to the five-membered ring. In the final steps, the secondary alcohol at C13 was acetylated, cleavage of the MOM protecting group and Swern oxidation of alcohol at C24 (manzamine A numbering) was followed by acetate group elimination. Accordingly, tetracyclic compound **122** bearing a C13-C23 double bond for further functionalisation was obtained.

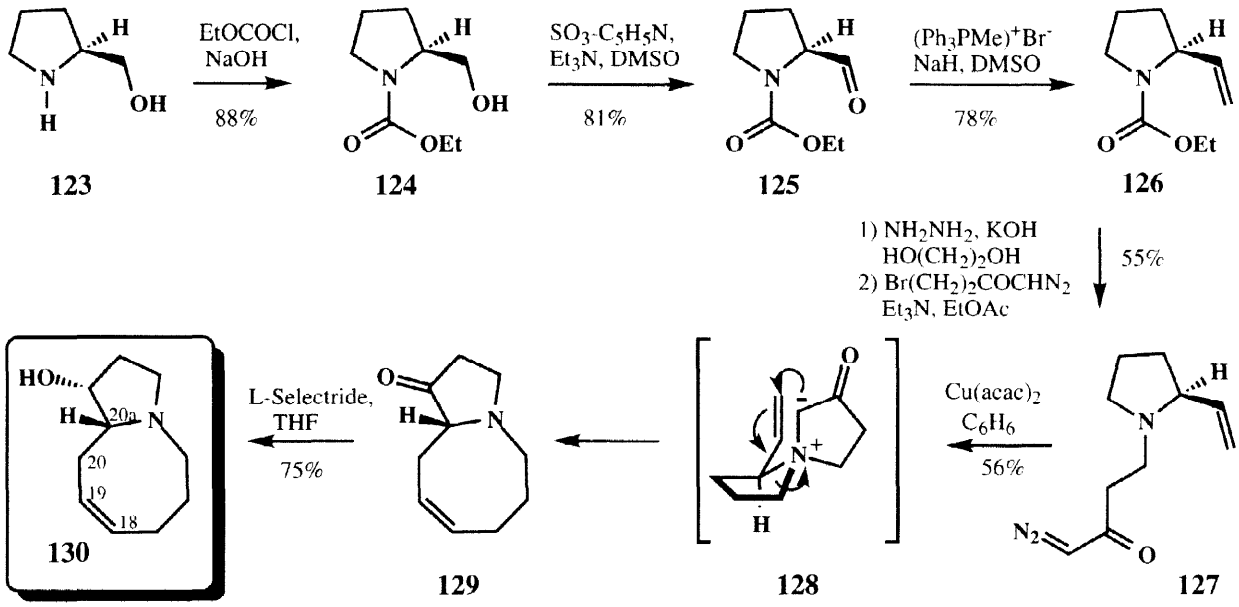


Scheme 15

C. Ionic cyclisation approaches.

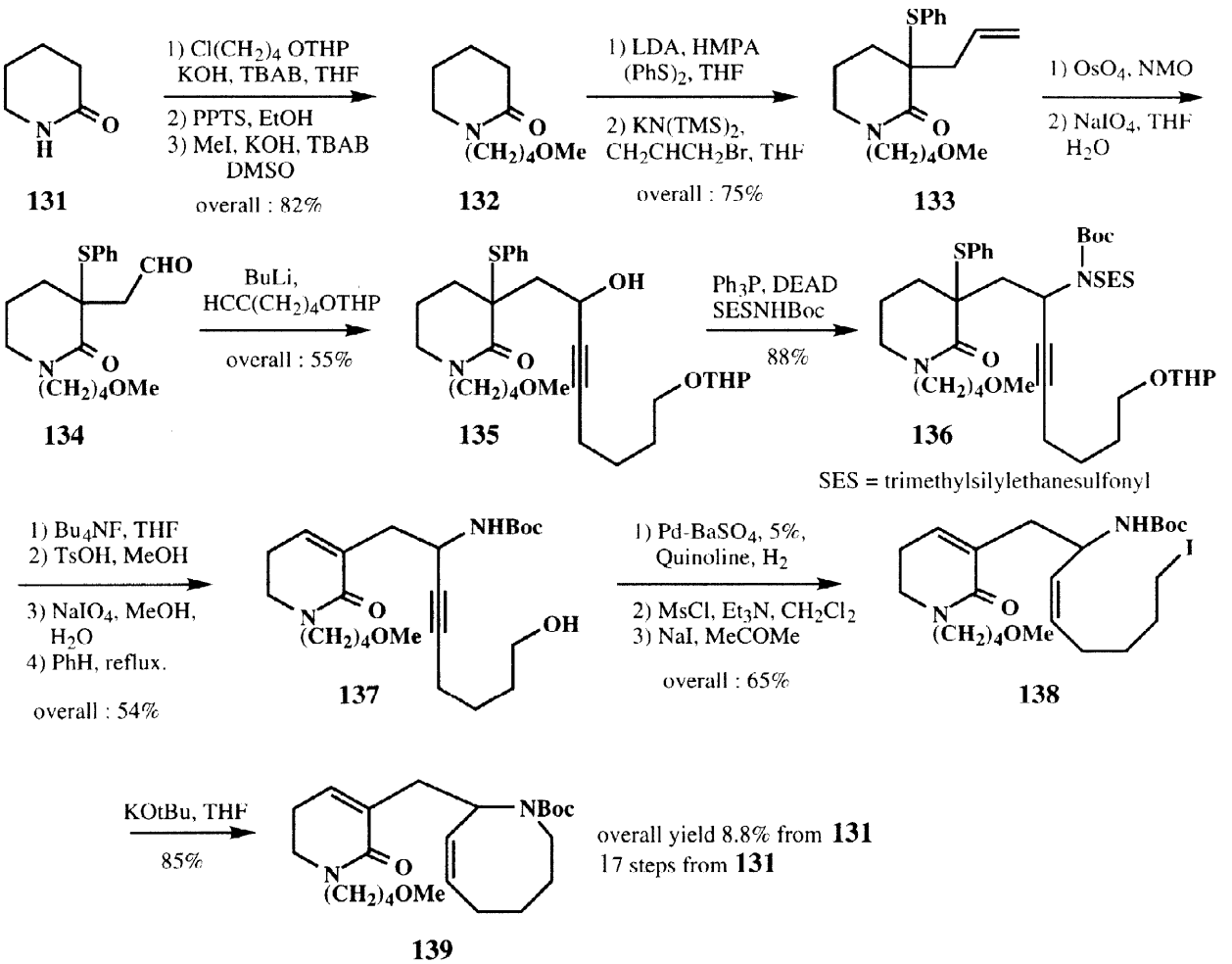
In an enantioselective synthesis of the CD ring system of manzamine A **1**, J. S. Clark and co-workers[35] developed a strategy based on the [2,3] sigmatropic rearrangement. This synthesis used (*S*)-prolinol **123** as starting material. Vinyl pyrrolidine **126** was obtained in three steps from **123** in good overall yield. Hydrazine cleavage of the urethane unit was followed by *N*-alkylation with a bromodiazoketone. The crucial step occurred in the presence of copper acetylacetonate and afforded compound **129** which resulted from a rearrangement of ylide intermediate **128**. L-selectride reduction of the keto group in **129** gave rise to alcohol **130** the optical purity of which (up to 98%) was estimated after Mosher ester formation. However compound **130** has the

unnatural configuration at C20a and a *Z* double bond at C18-C19 and not at C19-C20 as in manzamine A **1**. But this particular regioisomerism can be useful for manzamines E **5** or F **6** syntheses (Scheme 16).



Scheme 16

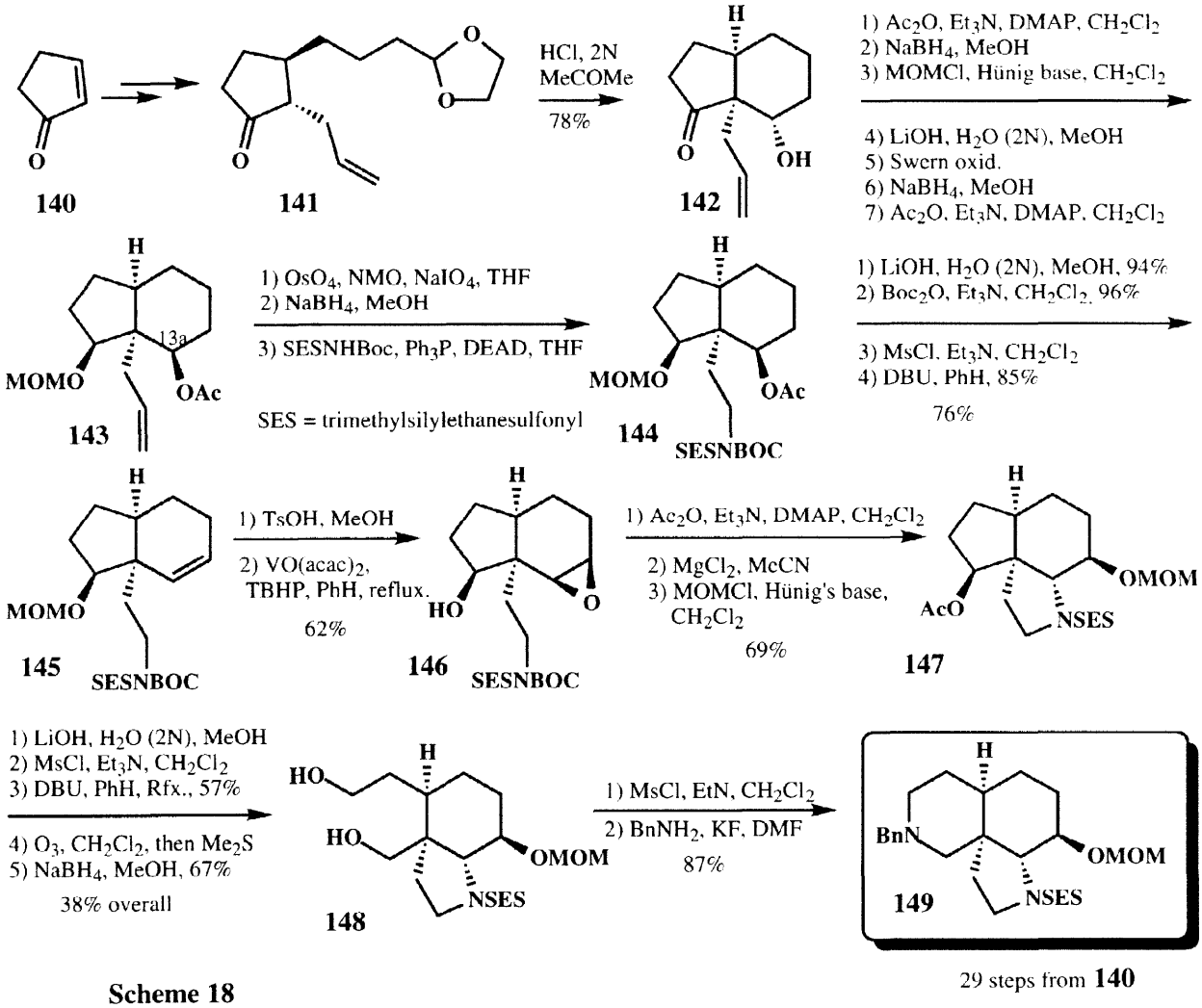
The Yamamura group developed two synthetic approaches to manzamine A **1**. In the first one[36] a bicyclic AD ring subunit was elaborated for further intramolecular Diels-Alder cycloaddition. Thus, piperidone **131** was *N*-alkylated with 4-chlorobutanol tetrahydropyranyl derivative. The acetal protecting group exchanged for the more stable methoxy ether. The resulting lactam **132** was sequentially alkylated with diphenyldisulfide and allylbromide affording compound **133**. Dihydroxylation and oxidative cleavage gave rise to the aldehyde derivative **134** which was in turn alkylated with an acetylide giving rise to compound **135**, bearing all carbons necessary for eight-membered ring formation. Nitrogen was introduced by a Mitsunobu reaction using a protected equivalent of ammonia as a nucleophile. The resulting piperidone **136** was submitted to a four steps sequence : deprotection of the trimethylsilylethanesulphonyl (SES) group and of the tetrahydropyranyl group, oxidation of the thioether and elimination of the resulting sulfoxide. α,β-Unsaturated lactam **137** was then isolated. Reduction of triple bond with Lindlar catalyst and nucleophilic displacement of primary alcohol with iodine afforded compound **138**. High yield eight-membered ring formation was promoted by potassium *tert*-butoxide and gave rise to the bicyclic compound **139** bearing the AD rings of manzamine A **1** (Scheme 17).



Scheme 17

A completely different approach was developed by the same group in a synthesis of the ABC tricyclic core of manzamine A **1**[37]. Accordingly, cyclopentenone **140** was dialkylated in a conjugate addition-alkylation sequence affording ketone **141**. An acid catalyzed aldol condensation gave rise to bicyclic ketol **142**. Acetylation, reduction of the carbonyl group and protection of the resulting alcohol as the MOM-ether was followed by a three step sequence of reactions which gave rise to compound **143** after epimerisation at C13a (yield not indicated). This epimerisation was made necessary because side reactions or poor yields were observed in the C13a α-alcohol series. It is also possible that the subsequent elimination giving rise to compound **145** (*vide infra*) was only possible in the β-hydroxy series. This point was not discussed by the authors. The allylic appendage in **143** was transformed into a primary alcohol by a classical sequence : dihydroxylation, sodium periodate oxidative cleavage, and reduction of the resulting aldehyde. A Mitsunobu reaction used in the previous synthesis allowed introduction of nitrogen and afforded compound **144**. Saponification of acetate group produced also cleavage of the *N*-Boc protecting group which was reintroduced before mesylation of the secondary alcohol. Elimination of the mesylate intermediate gave rise to compound **145**. As in a previous approach (*vide supra*, scheme 15), a hydroxyl-directed epoxidation was performed and afforded stereoselectively epoxide derivative **146**. Reacetylation of the secondary alcohol and cleavage of the *N*-Boc protecting group with magnesium chloride in acetonitrile was followed by a spontaneous five-membered

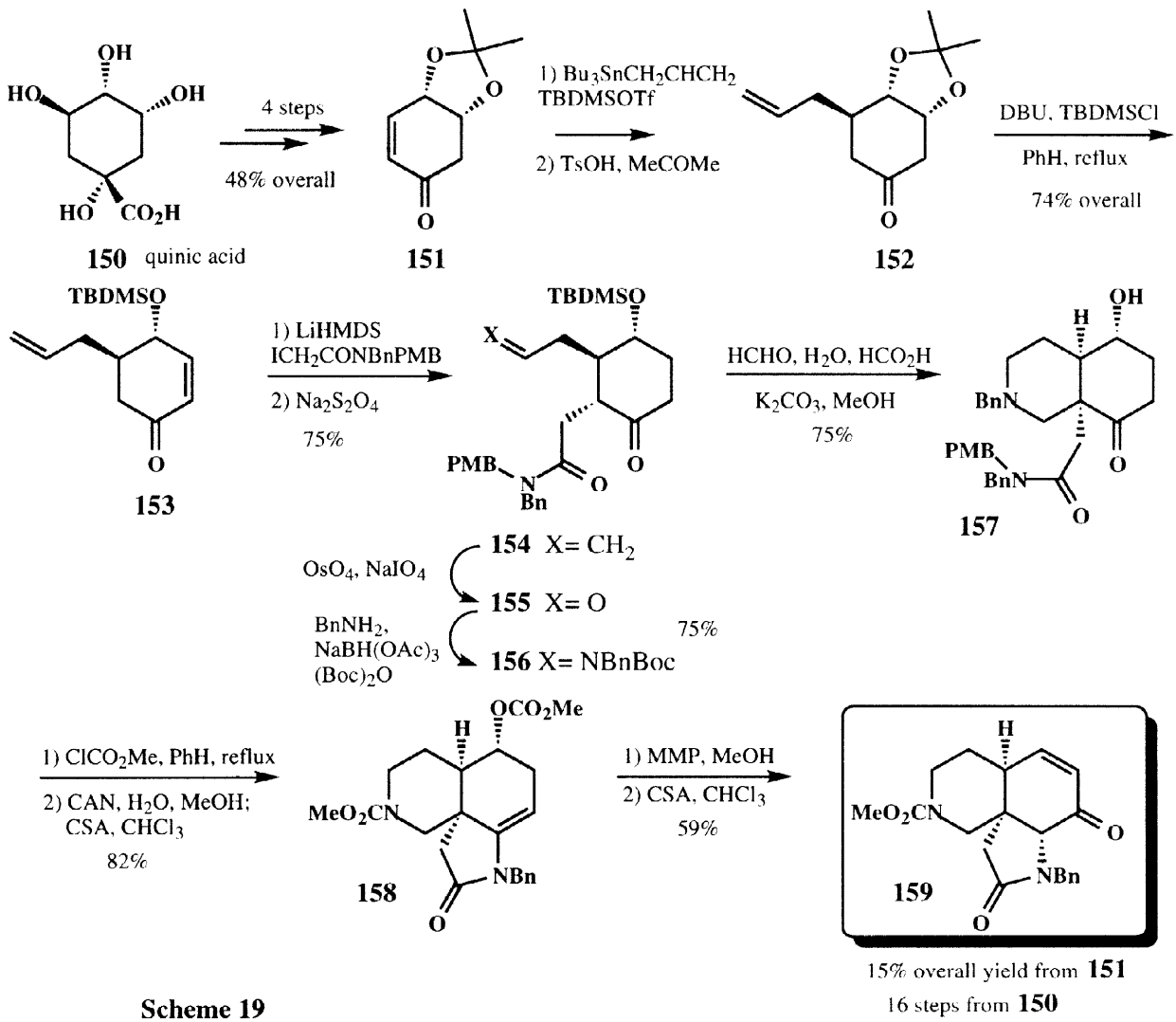
ring formation. Protection of the resulting secondary alcohol gave rise to compound **147**. Saponification of acetate, mesylation and elimination afforded the corresponding alkene derivative. Ozonolysis of the double bond followed by treatment with dimethylsulfide led to a dialdehyde intermediate which was reduced to the diol derivative **148**. In a final sequence, the corresponding ditosylate was treated with benzylamine and gave rise to the tricyclic derivative **149** in twenty nine steps from cyclopentenone **140** (Scheme 18).



Scheme 18

Overman and co-workers[38] reported a short enantioselective synthesis of the ABC tricyclic core of manzamine A **1**. Their strategy was based on use of the chiral pool. Thus, in this synthesis quinic acid **150** was used as starting material. This compound was transformed into ketone **151** in four steps (48 % overall) according to previous work described by Trost[39] and Danishefsky[40]. Conjugate addition of allyltributyl stannane assisted by *tert*-butyldimethylsilyl triflate followed by hydrolysis of the enoxisilane intermediate afforded the cyclohexenone derivative **152**. DBU promoted elimination, followed by protection of the remaining alcohol with *tert*-butyldimethylsilyl chloride gave rise to compound **153**. Highly stereoselective alkylation of the kinetic enolate of **153** with *N*-(*p*-methoxybenzyl)-*N*-(benzyl)iodoacetamide was followed by a conjugate reduction of the enone moiety with sodium dithionite affording the cyclohexanone derivative **154**.

The allylic side chain was then oxidatively cleaved by the osmium tetraoxide-sodium periodate couple of reagents and the resulting aldehyde intermediate was submitted to a reductive amination. After protection of the benzylamino group with $(Boc)_2O$, compound **156** was isolated in good overall yield. The key step in this synthesis, a Mannich cyclisation, afforded stereoselectively the bicyclic derivative **157**. Thus, after acidic cleavage of the *N*-Boc protective group, the following reactions were explained as iminium formation by condensation with formaldehyde followed by an intramolecular Mannich reaction with an axial attack of an enol intermediate on the iminium salt. The alternative sequence starting with an aldol condensation followed by a nucleophilic attack of nitrogen would have probably given rise to a mixture of stereoisomers or to the reverse stereoselectivity at ring junction (Scheme 19).

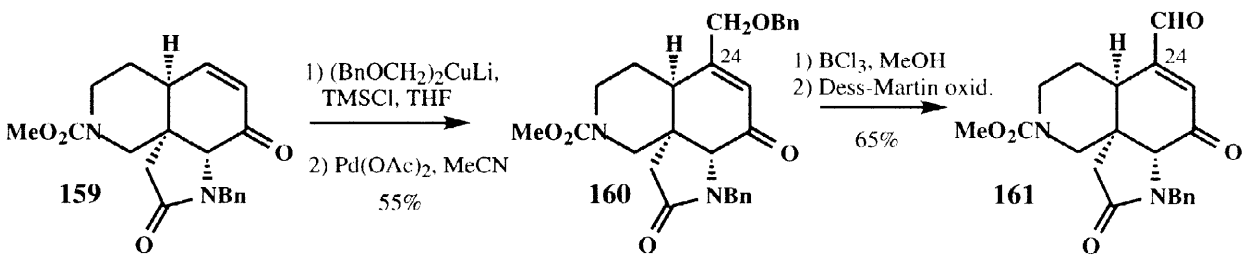


Scheme 19

Reprotection of the secondary alcohol as the carbonate followed by oxidative cleavage of the *p*-methoxybenzyl group afforded the tricyclic compound **158** after keto-amide condensation and acidic treatment promoting dehydratation of the aminal intermediate. In the last steps of this synthesis, epoxidation of the enamine double bond was followed by an acidic treatment, which induced both rearrangement of epoxide and

β-elimination of the protected alcohol, and gave rise to compound **159**. A single crystal X-ray analysis confirmed the configurations in compound **159**.

Several conjugate additions on enone **159** followed by oxidation of the enoxysilane intermediate were also studied; particularly, compound **160** bearing a benzyloxymethyl group at C24 is useful for further synthetic elaboration. This compound, after boron trichloride ether cleavage and Dess-Martin oxidation, afforded **161** bearing a formyl group at C24 suitable for Pictet-Spengler condensation with tryptamine (Scheme 20). This synthesis of a tricyclic core of manzamine A **1** is short, efficient in term of overall yield and afforded an enantiomerically pure synthetic intermediate.

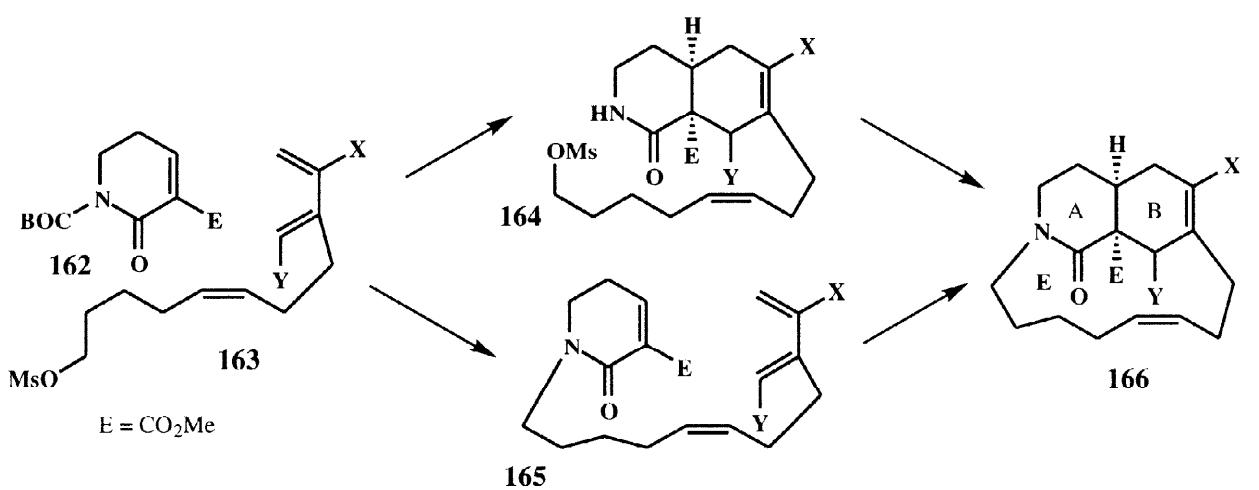


Scheme 20

D. Intermolecular Diels-Alder cycloaddition approaches.

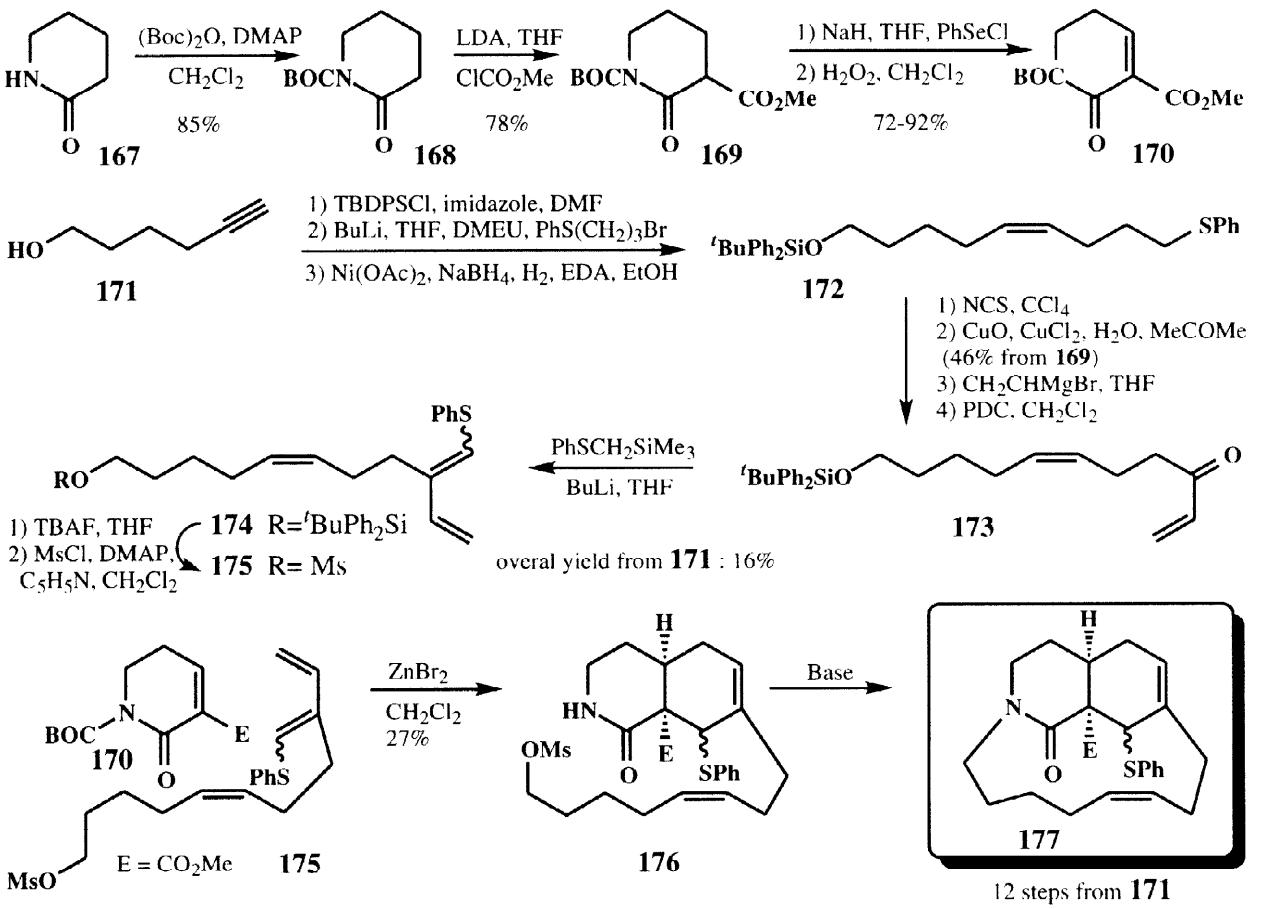
Diels-Alder cycloadditions in their intermolecular or intramolecular versions have been used by seven different groups and allowed the synthesis of several advanced intermediates in the synthesis of manzamine A **1**.

Simpkins and co-workers[41 42] studied a synthetic approach to the AB ring of manzamine A **1** which was initially designed to be used in either an intermolecular or intramolecular Diels-Alder strategy. In this second version an ABE tricyclic derivative should be obtained in a concise sequence of reactions (Scheme 21)



Scheme 21

Dienophile **170** was obtained in a five step synthesis from piperidone **167**. Protection of the nitrogen as a urethane, followed by a methoxycarbonylation of the lactam enolate afforded lactam ester **169**. Introduction of the 3,4 double bond was achieved by phenylselenation, oxidation to selenoxide and elimination giving rise to α,β-unsaturated lactam **170**. Various Diels-Alder cycloadditions were studied with dienophile **170** with electron rich dienes. It appeared from these studies that the best results were obtained with mild Lewis acid catalysts such as zinc bromide with both 2-trimethylsilyl butadiene and 1-thiophenylbutadiene. Thermal reactions gave poor yields except with the Danishefsky's diene which afforded quantitatively the expected adduct after refluxing in benzene[41] (Scheme 22).

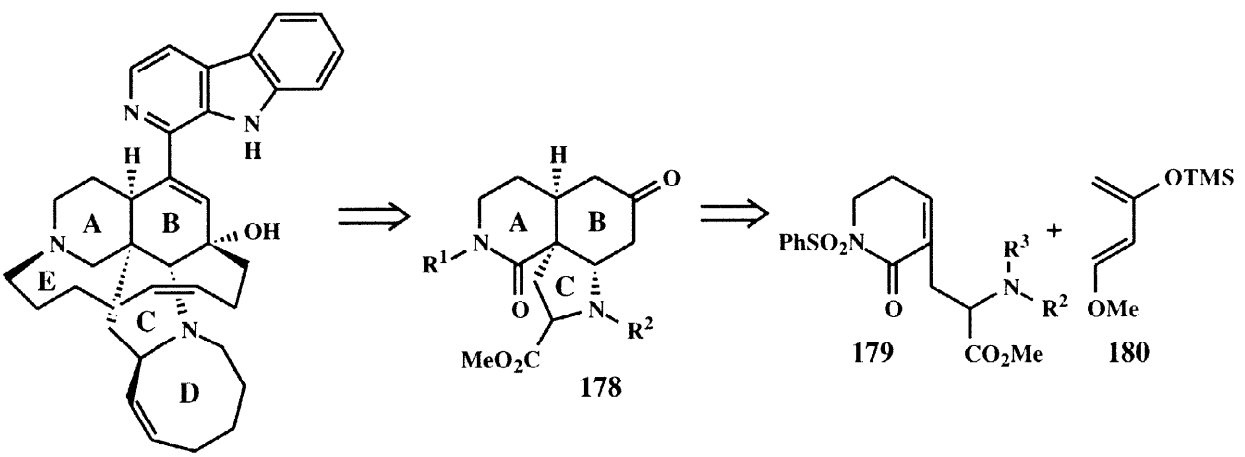


Scheme 22

Diene **175**, necessary for future thirteen-membered ring elaboration, was prepared from hex-5-yn-1-ol **171**. After protection of the primary acohol, the acetylenic moiety was alkylated with 3-bromopropyl phenyl sulfide in a mixture of THF and *N,N'*-dimethylethyleneurea (DMEU) and the resulting compound was selectively reduced into a *Z*-alkene **172** with nickel boride under hydrogen in presence of ethylenediamine. The thioether was transformed to the carbonyl product in two steps, oxidation with *N*-chlorosuccinimide followed by hydrolysis of α-chlorothioether intermediate with a mixture of copper oxide and cupric chloride. The resulting aldehyde was in turn treated with vinylmagnesium bromide. Oxidation of the formed allylic alcohol

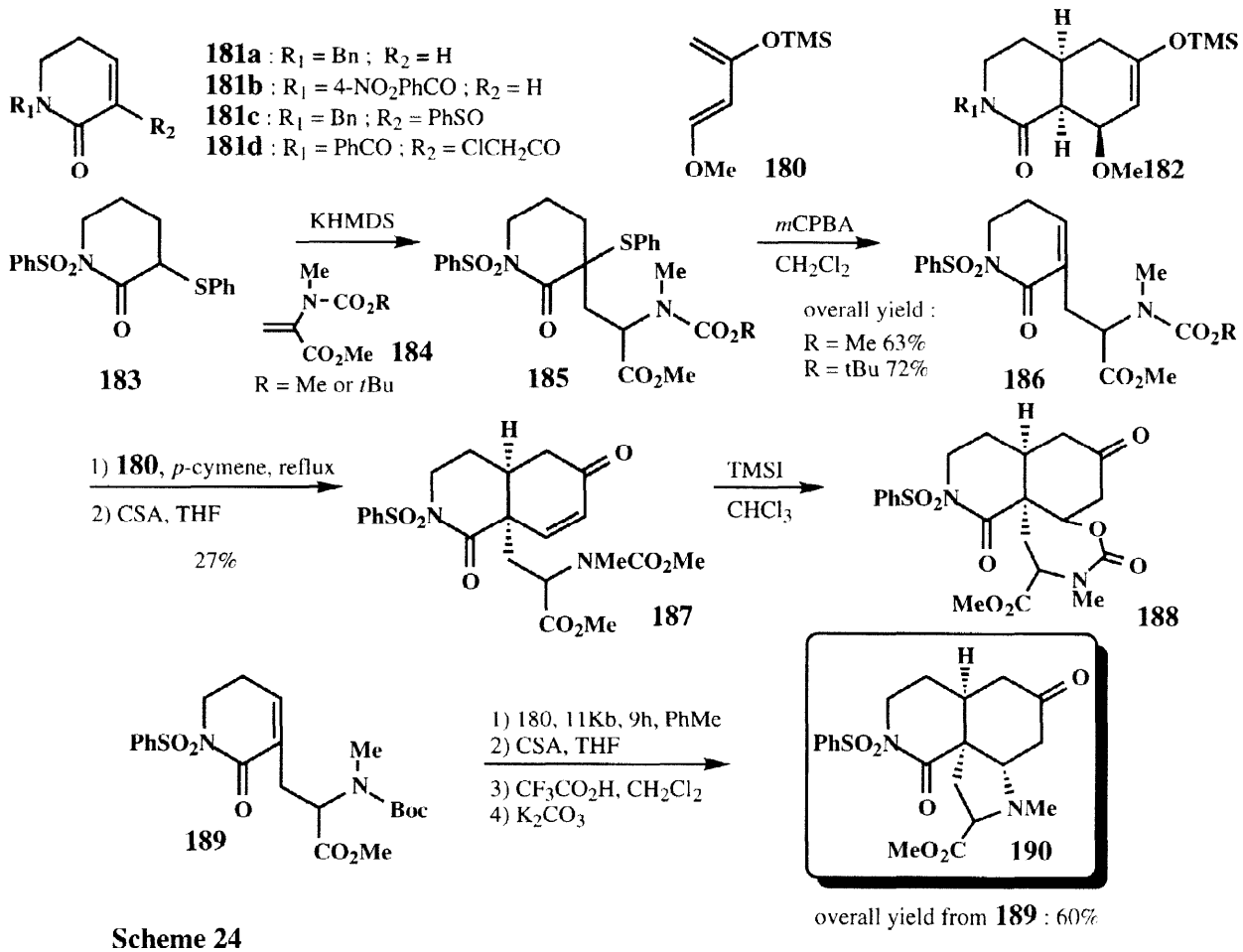
with pyridinium dichromate gave rise finally to the α,β-unsaturated ketone **173**. A Peterson type olefination was used to introduce the second double bond. Thus condensation of the anion of phenylthiomethyltrimethylsilane with ketone **173** afforded diene **174** (geometrical configuration of thioenol ether was not indicated) with a small amount of a Michael addition product. For further *N*-alkylation, the protected primary alcohol was changed to the mesylate **175**. The best results in cycloaddition were obtained with an excess of diene **175** and zinc bromide as catalyst. The main difficulty arose from the poor stability of the *N*-Boc protective group in the dienophile. Nevertheless, the remaining thirteen-membered ring formation was studied with adduct **176** obtained in 27 % yield. The results were also rather frustrating and small amounts of product to which structure **177** was tentatively assigned were isolated with other products resulting probably from a lactam *O*-alkylation. The alternative intramolecular Diels-Alder may be more efficient, but the preparation of a trienic precursor such as **165** was for the moment thwarted by the difficult *N*-alkylation of *N*-Boc deprotected lactam **170** with diene **175**.

The Diels-Alder strategy developed by the Nakagawa and Hino's group outlined in scheme 23 starts also with a dihydropyridone as diene, but in this approach this unit is substituted by an appendage which permits introduction of the five-membered ring C and of the eight-membered ring D.



Scheme 23

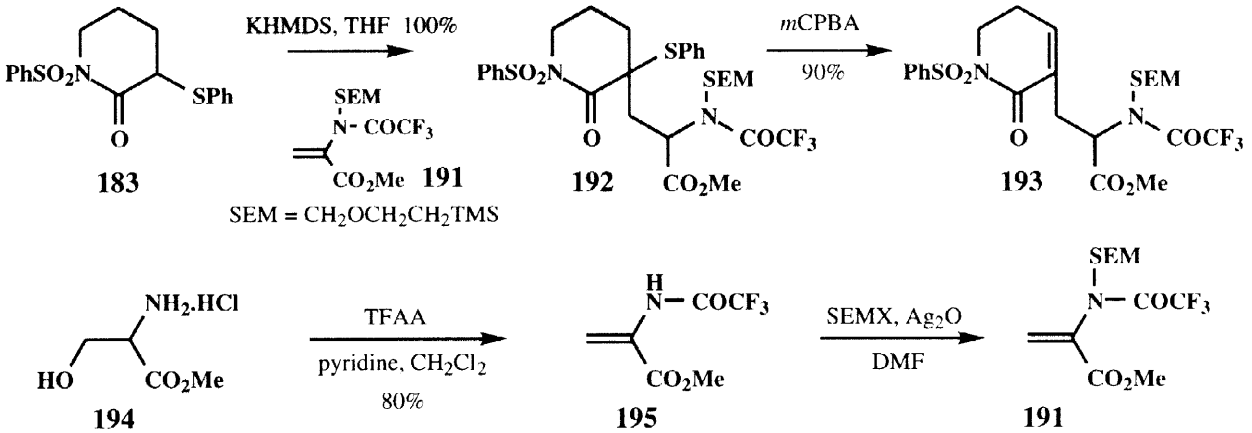
In a preliminary study[43], the reactivity of various dihydropyridones **181a-d** in Diels-Alder reactions with Danishefsky diene **180** were examined (Scheme 24). When the double bond of the dienophile was only conjugated with a simple lactam as in **181a** the cycloaddition failed under thermal conditions or in presence of Lewis acid catalyst. The presence of an electron withdrawing group at nitrogen was crucial from a reactivity point of view as observed with the *N*-4-nitrobenzoyl derivative **181b**. The presence of another electron withdrawing group at C3, as also observed by Simpkins (*vide supra*), increased the reactivity of the dienophile. However, with compound **181c**, an aromatized B-ring was obtained after purification on silica gel. An extensive study of this type of cycloaddition, including molecular orbital calculations, with various dihydropyridones was published subsequently by the same group. The influence of the substituent at nitrogen was emphasized and the presence of a *N*-phenylsulfonyl group which was systematically used in the following syntheses was recognized as quite positive[44].



Scheme 24

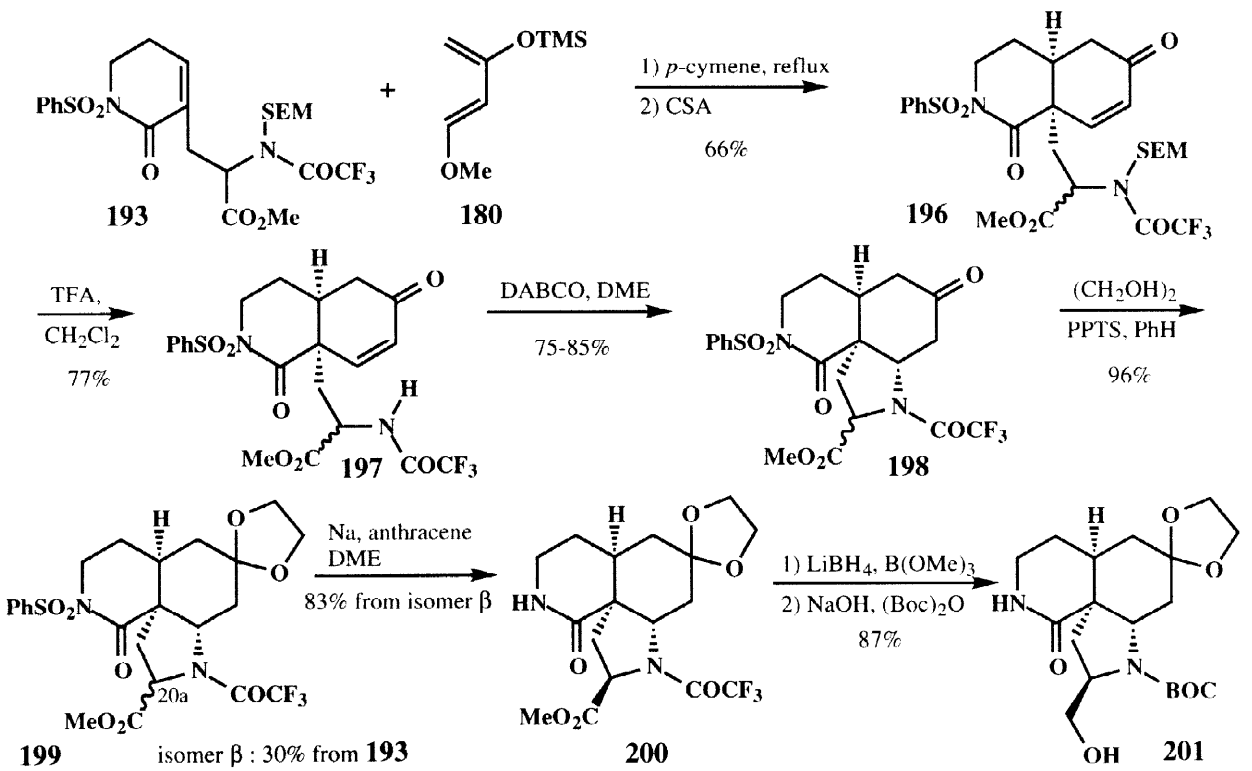
Following this strategy, the synthesis of the tricyclic ABC core of manzamine A **1** was undertaken. Lactam **183** was alkylated with the Michael acceptor **184** (methyl or *tert*-butyl ester). Sulfoxide elimination gave rise in good overall yield to lactams **186**. However cycloadditions of lactam **186** methyl ester with diene **180** under thermal conditions followed by acidic treatment gave adduct **187** in poor yield. The following deprotection of nitrogen gave an unexpected compound **188**. For this reason, other protective groups at nitrogen were also studied. Thus, with dienophile **189**, Diels-Alder cycloaddition gave better results under high pressure. After acidic cleavage of the *N*-Boc protective group followed by a Michael addition, the tricyclic compound **190** was isolated as a mixture of epimeric compounds at C20a in good overall yield[45,46] (Scheme 24). Relative configurations in compound **190** were established by X-ray analysis.

Alkylation of 3-phenylthiotetrahydrodropyridone **183** proved to be highly dependent on the nature of the electrophilic counterpart[47]. A systematic study of Michael addition with several dehydroalanine derivatives and other Michael acceptors made it possible to obtain lactam **192** in quantitative yield for instance with acrylate **191** bearing both an electron releasing group and an electron withdrawing group at nitrogen. As above, oxidation-elimination afforded dienophile **193** in high overall yield. The preparation of dehydroalanine **191** was achieved in two steps from serine methyl ester hydrochloride **194** (Scheme 25).



Scheme 25

Dihydropyridone **193** was then subjected to thermal Diels-Alder cycloaddition with Danishefsky's diene **180** and afforded compound **196** after acidic hydrolysis. Trifluoroacetic acid SEM deprotection and conjugate addition afforded a tricyclic compound **198** (Scheme 26)[48].

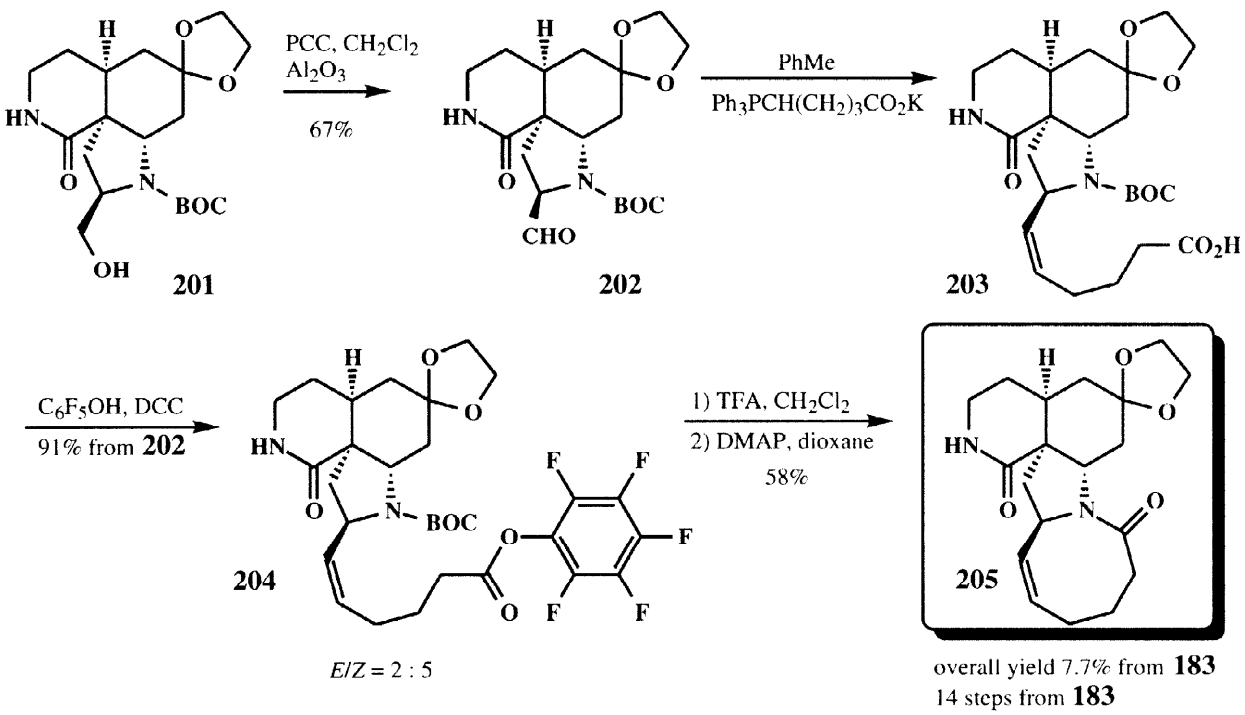


Scheme 26

In this compound, the pyrrolidine nitrogen is trifluoroacetylated which allowed theoretically deprotection and alkylation for eight-membered ring formation. After protection of the keto group as dioxolane, the mixture of diastereomers at C20a was separated and the *N*-phenylsulfonyl group was cleaved with sodium-

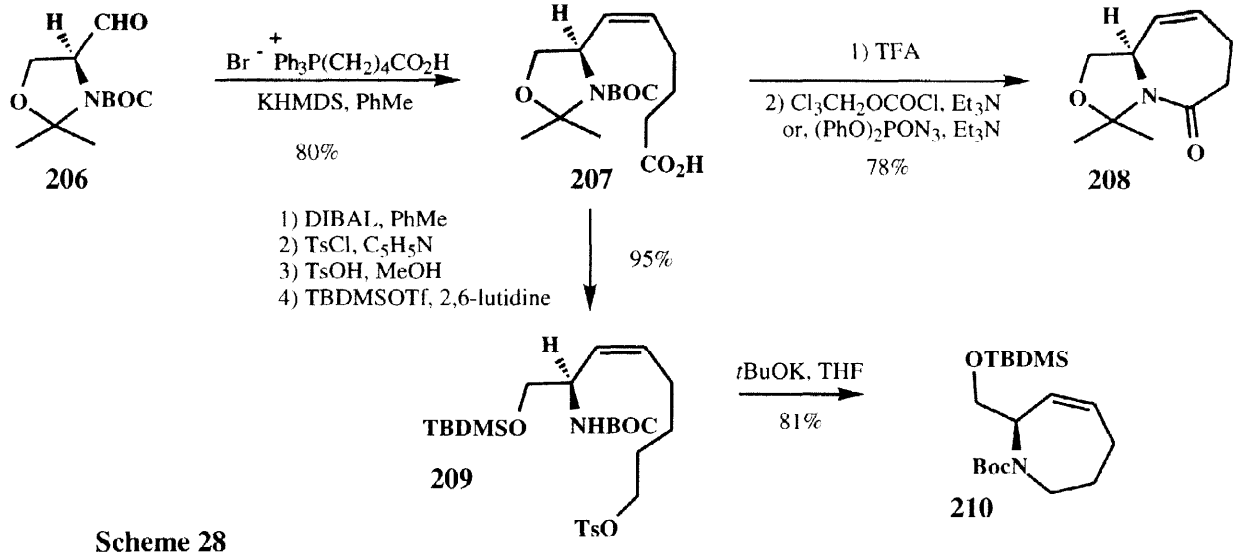
anthracene. The ester and *N*-trifluoroacetyl groups were simultaneously and respectively reduced and cleaved and the resulting secondary amine was reprotected with a *tert*-butyloxycarbonyl group. The tricyclic compound **201** bearing all the functionalities for eight-membered ring formation was thus obtained.

PCC oxidation of the primary alcohol in compound **201** gave rise to the corresponding aldehyde derivative **202** which was subjected to a Wittig olefination and afforded compound **203**. Esterification of acid **203** with pentafluorophenol led to the corresponding ester **204** which appeared to be a 2 to 5 mixture of *E* and *Z* isomers. In a model study the Wittig reaction was much more selective affording a 1 to 10 *E* : *Z* mixture. The crucial cyclisation was performed, after Boc deprotection, with 4-dimethylaminopyridine in dioxane and afforded the pentacyclic compound **205** in 58% yield (Scheme 27). The same cyclisation giving rise to a bicyclic model was performed in 83% yield. This intermolecular Diels-Alder strategy described by the Nakagawa's group allowed the preparation of a pentacyclic advanced intermediate in the synthesis of manzamine A **1** in fifteen steps and in a good overall yield from compound **183**[48, 49].



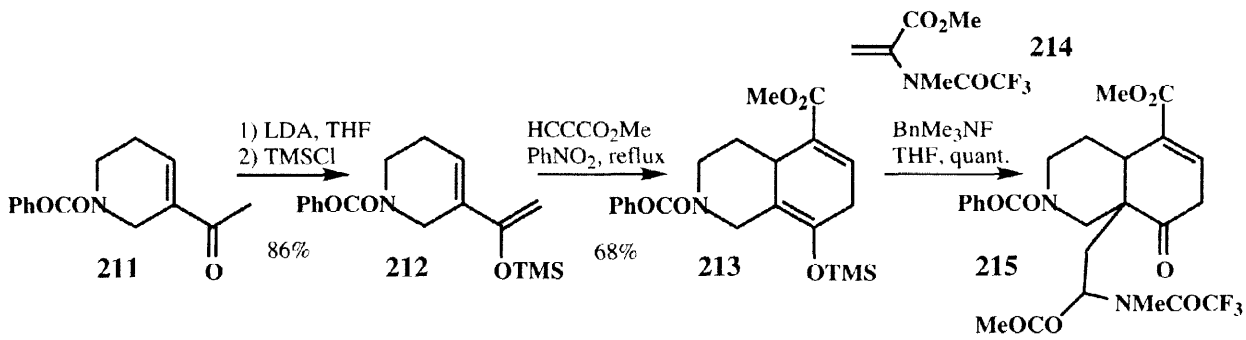
Scheme 27

Related studies have also been published by the same group. Thus a synthesis of optically active azocine started with the Garner aldehyde **206** which is prepared from L-serine. Wittig olefination in the presence of the potassium salt of hexamethyldisilazane afforded stereoselectively the *Z* acid derivative **207**. Deprotection of the *N*-*tert*-butyloxycarbonyl and cyclisation with trichloromethylchloroformate-triethylamine or with diphenyl phosphorylazide-triethylamine gave rise to azocinone **208**. In an alternative pathway, acid **207** was reduced with DIBAL and tosylated giving rise after acidic hydrolysis and subsequent protection of the alcohol to **209**. This was followed by a cyclisation induced with potassium *tert*-butoxide and led to azocine **210**[50]. However, both azocine derivatives **208** and **210** are of reverse absolute configuration at C20a (manzamine numbering) (Scheme 28).



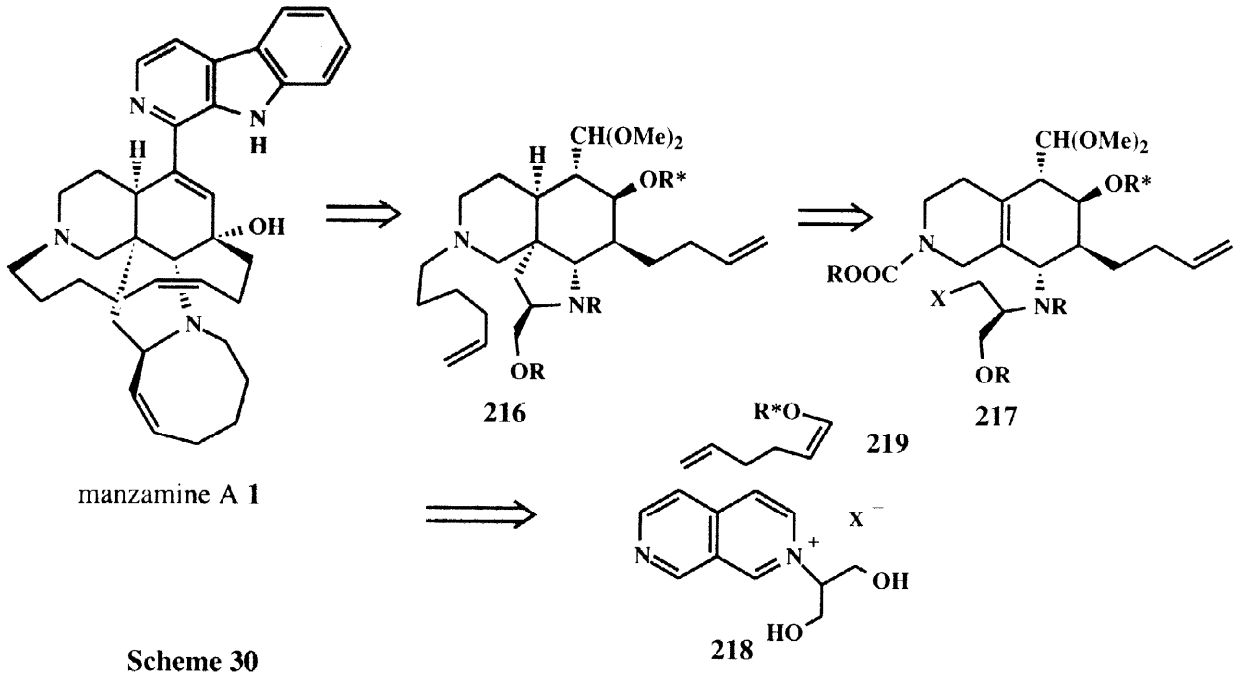
Scheme 28

An alternative synthesis of octahydroquinoline derivative starting with arecolone **211** has also been developed. Deprotonation of arecolone **211** and silylation of the resulting enolate gave the diene **212**. Diels-Alder cycloaddition with methyl propiolate in refluxing nitrobenzene afforded adduct **213**. The presence of the silylenol ether in **213** allowed a direct Michael addition with various acrylate derivatives. Thus, acrylate **214** led quantitively to compound **215**[51](Scheme 29).



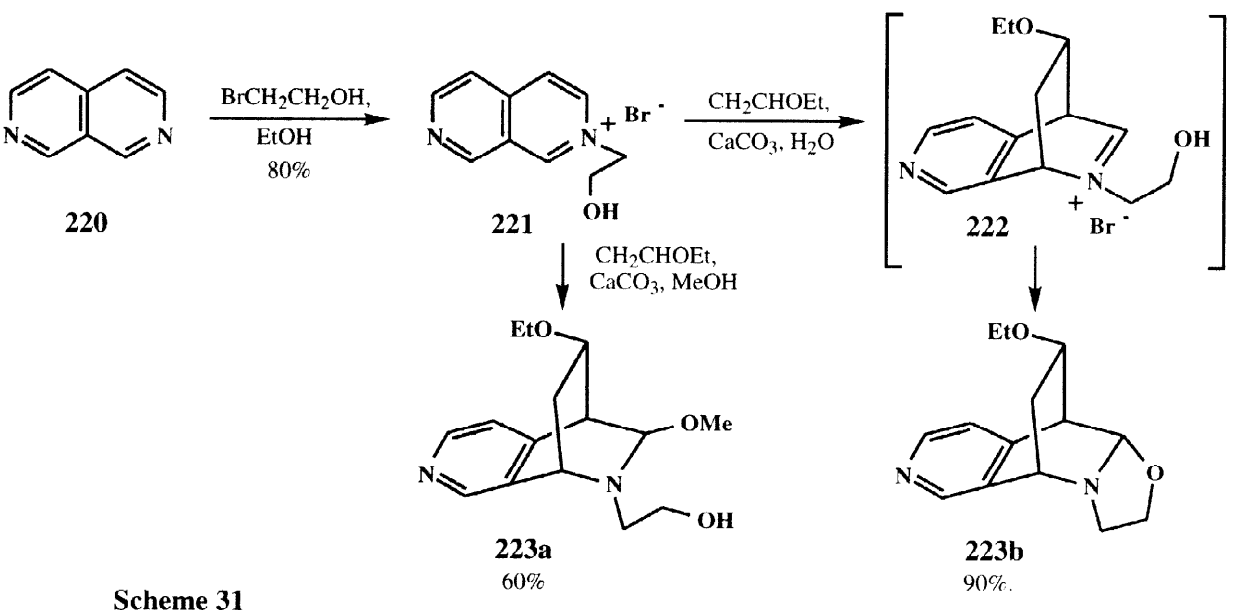
Scheme 29

A strategy using an inverse electron demanding Diels-Alder cycloaddition, the Bradsher cycloaddition, has been studied in our group. This strategy allowed a convergent and short access to functionalized octahydroquinolines such as **217** bearing all the appendages for further five, eight and thirteen-membered ring elaboration as depicted in retrosynthetic scheme 30.



Scheme 30

In a preliminary study the feasibility of this approach has been tested in the synthesis of a tricyclic core model of manzamine A **1**. Accordingly, 2,7-naphthyridine **220**, prepared according literature procedure (three steps, overall yield : 36 %) was *N*-alkylated with bromoethanol (Scheme 31).

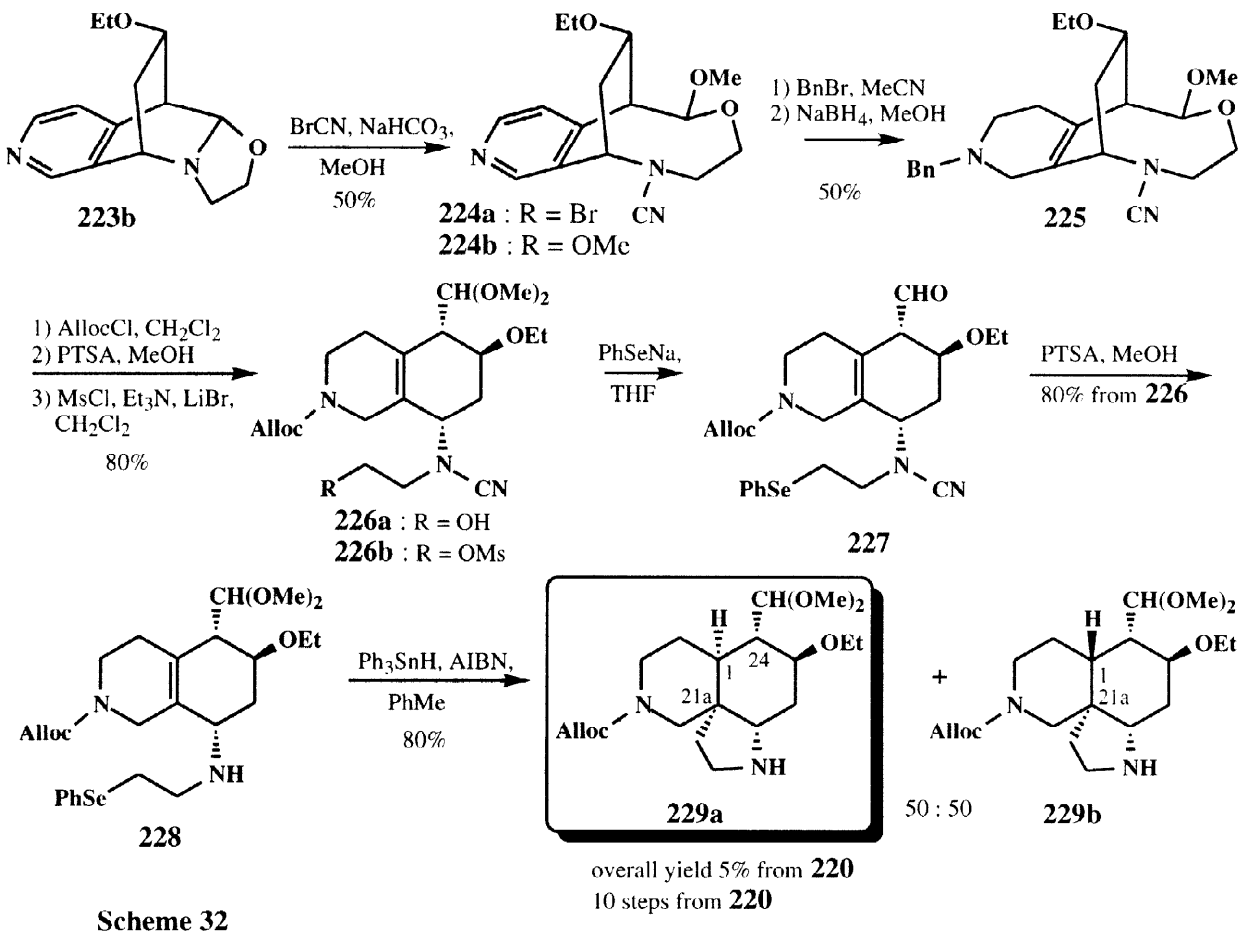


Scheme 31

The resulting naphthyridinium salt **221** was submitted to various Bradsher cycloaddition conditions. In methanol, the iminium intermediate **222** was trapped by the solvent as the nucleophile affording compound **223a.** But it was observed that in water the expected adduct **223b** was obtained in high yield without side reactions. As in the previous examples of Bradsher cycloaddition, the reaction which is not truly concerted, is

highly *exo* selective. This particular selectivity is due to both electronic and steric factors during the second carbon carbon bond formation.

Bradsher adduct **223b** was subsequently treated with cyanogen bromide in order to differentiate between the two basic nitrogens. Compound **224b** which resulted from a bromine-methoxyl exchange was isolated in moderate yield due to competitive attack of cyanogen bromide on the pyridine ring. *N*-alkylation with benzyl bromide was followed by classical pyridinium salt reduction. However here again a moderate yield was obtained for compound **225**. This is due to an unexpected poor regioselectivity during the reduction. In order to work with less polar products, the *N*-benzyl group was exchanged for a carbamate and then the cyclic acetal was methanolyzed. This cleavage gave rise to a primary alcohol which was in turn mesylated affording **226b**. Substitution of this group by phenylselenyl anion afforded the corresponding selenoether **227** in which the acetal group was also cleaved. Reprotection of the aldehyde was followed by a radical cyclisation which afforded in good yield compounds **229a** and **229b** in a 50 : 50 ratio (Scheme 32)[52]. The lack of stereoselectivity at this stage which is probably due to the presence of the acetal group at C24 (manzamine numbering) led us to study an alternative tactic.



Scheme 32

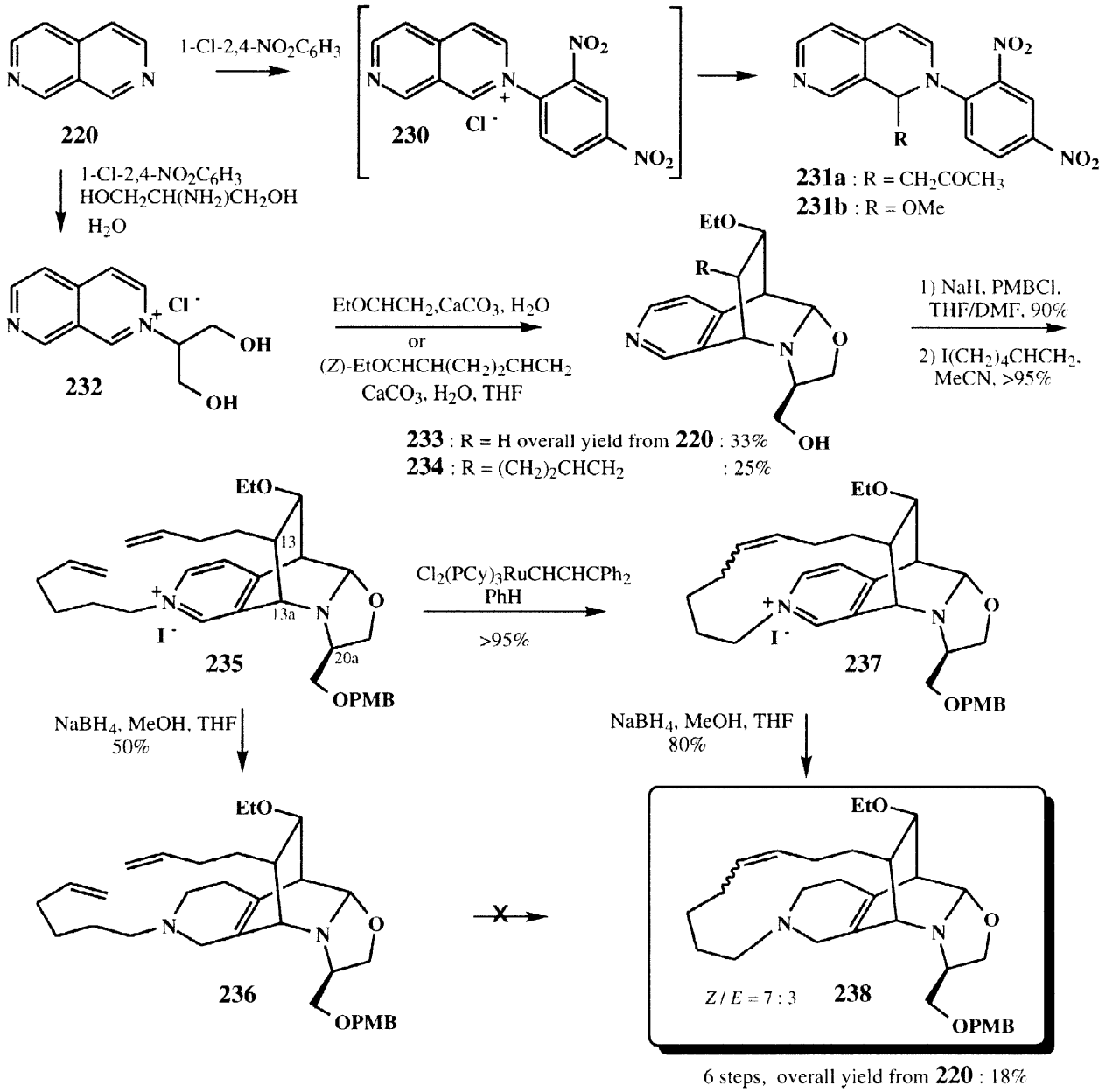
It was anticipated that a change to the order of introduction of the rings, namely the thirteen-membered ring formation before the five-membered ring formation, could have positive consequences upon the stereoselectivity of this latter cyclisation. Thus, in this hypothesis, the presence of the large thirteen-membered

ring should hinder the upper face of the molecule and favour the formation of a *cis* ring junction for cycles A and B during the radical cyclisation. In order to model a synthetic intermediate bearing all the appendages for five-membered and eight-membered ring elaboration, the synthesis of the naphthyridinium salt **232** was first investigated (Scheme 33).

Despite numerous attempts, direct *N*-alkylation of 2,7-naphthyridine with various 2-halogeno-1,3-propanediol derivatives was unsuccessful. The use of an indirect method, the Zincke reaction, brought a solution to this problem. The first studies using classical Zincke conditions were rather frustrating. Only side products were isolated such as compounds **231a** or **231b** resulting from a nucleophilic attack on the iminium intermediate **230** by the solvent, acetone or methanol used during purification. It turned out that the high reactivity of the naphthyridinium salt **230** was advantageous if the electrophile chlorodinitrobenzene and the nucleophile 2-aminopropanediol are introduced at the same time. Moreover, here again, the use of water as solvent overcame the side reaction, nucleophilic attack from the solvent. Under these conditions, the naphthyridinium salt intermediate **232** was obtained as a mixture with excess of aminodiol. This mixture was used without further purification in a Bradsher cycloaddition and afforded compound **233** with ethylvinylether as dienophile or the more functionalized adduct **234** with (*Z*)-1-ethoxy hexa-1,5-diene. The overall yield of 25% in this latter case although appearing modest includes in fact three steps. This sequence allowed also a short synthesis of compound **234** bearing all appendages for further cyclisations. The relative configurations in **234** were established after nOe experiments and by X-ray analysis of a single crystal of this compound. It is noteworthy that this reaction allowed the control of configuration at C20a and consequently a differentiation of the two appendages which are necessary for eight-membered and five-membered ring formation from the prochiral precursor **232** (Scheme 33).

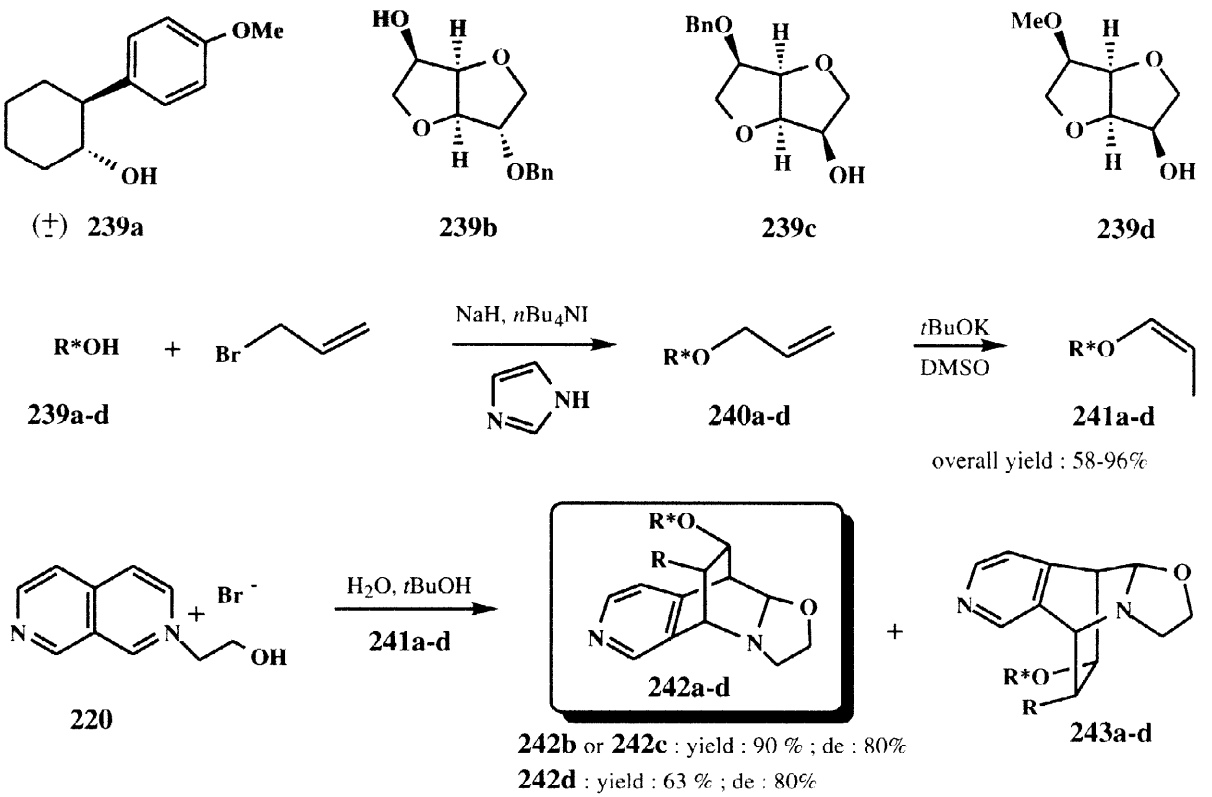
Before proceeding with a metathesis study, alcohol in **234** was protected as the *p*-methoxybenzyl ether and *N*-alkylated with a six-carbon unit giving rise in high yield to the salt **235**. This regioselective *N*-alkylation was made possible by the presence of the PMB protective group which precluded any alkylation of oxazolidine nitrogen. In a first attempt, salt **235** was reduced and the resulting compound **236** was subjected without result to metathesis reaction conditions in the presence of the Grubbs catalyst. The failure of this reaction was not completely unexpected because it was already known that this catalyst is sensitive to polar groups such as nitrogen. In contrast fortunately, the same reaction was nearly quantitative with the less basic salt **235**. Compound **237** resulting from this metathesis was reduced with sodium borohydride and afforded compound **238**. Careful NMR studies showed it to be a 7 to 3 mixture of *Z* and *E* isomers. This compound was obtained in a short six step sequence in 18% overall yield from 2,7-naphthyridine **220** (Scheme 33)[53].

Asymmetric synthesis of compound **238** is currently under study before testing the five-membered ring cyclisation.



Scheme 33

In this context, an asymmetric version of the Bradsher cycloaddition has been also studied. A known sequence was suitable for the synthesis of enantiomerically pure enol ethers. Thus, an optimized preparation of various chiral allylic ethers was followed by base induced isomerization affording in high yield enol ethers **241a-d** (Scheme 34).



Scheme 34

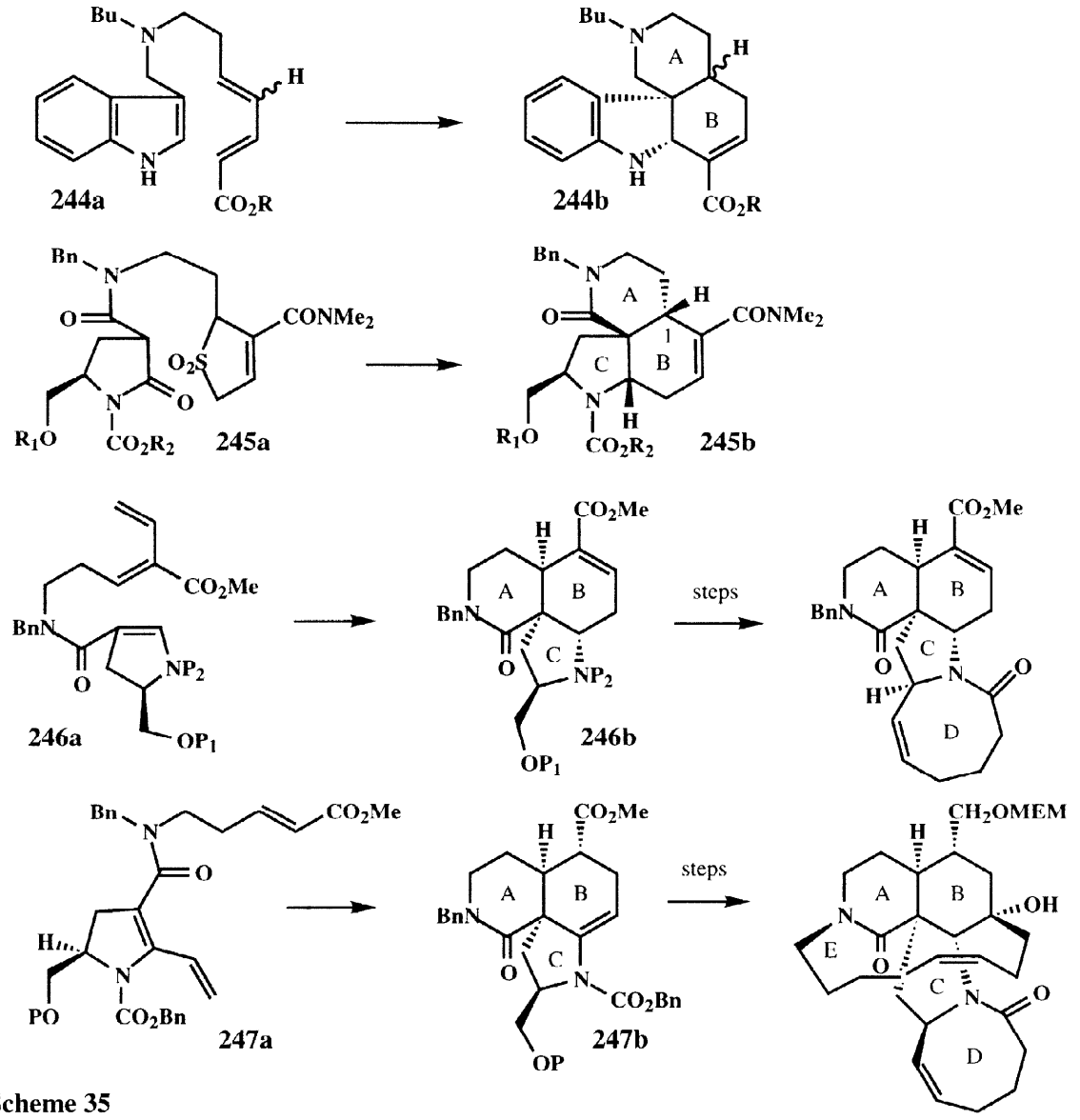
This sequence is rather general but, only enol ethers giving good results in asymmetric Bradsher cycloaddition are indicated in the scheme. Enol ethers **241b**, **241c** and **241d** derived respectively from isosorbide and isomannide afforded Bradsher adducts in good yields and with an interesting diastereoselectivity. These products were purified by crystallization. The direction of the asymmetric induction was established after X-ray analysis of a single crystal of adduct **242d**. The absolute configuration does agree with absolute configuration of manzamine alkaloids[54]. Extension of this asymmetric Bradsher cycloaddition to naphthyridinium salt **232** is currently under study.

E . Intramolecular Diels-Alder cycloaddition approaches.

This strategy which has been followed by four groups afforded in some cases very advanced intermediates in the total synthesis of manzamine A **1**. From a strategic point of view, it is interesting to compare the different pathways.

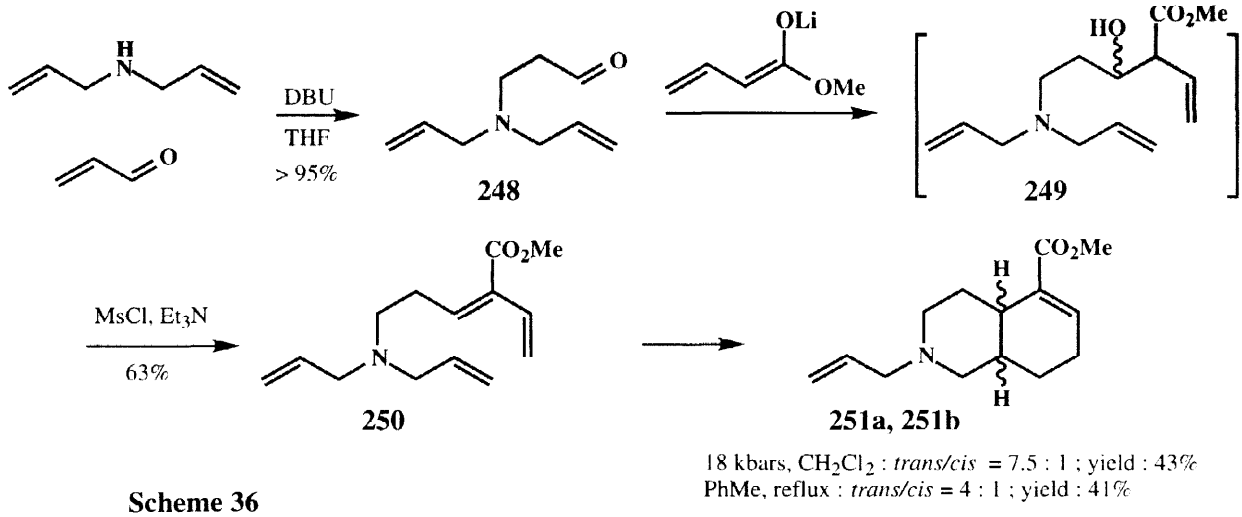
All of these intramolecular Diels-Alder reactions (IMDA) were designed to obtain the ABC tricyclic core of the alkaloid at an early stage. Trienes **244a**, **245a**, **246a** and **247a** were respectively used by the groups of Marko, Leonard, Martin and Pandit affording adducts **244b-247b** bearing various functional groups. In two cases, with adducts **246b** and **247b**, advanced tetracyclic or pentacyclic intermediates were synthesized. In the three first examples, the diene unit is the precursor of the B ring and the dienophile is included in a

dihydropyrrole ring. Pandit used a different strategy in which, for **247a**, the dienic moiety included the dihydropyrrole unit and the dienophile was located on the acyclic appendage. Interestingly, the three asymmetric syntheses used the chiral pool. A proline derivative was incorporated as a precursor of the C ring and played the role of chiral inductor in the Leonard and Martin syntheses whereas Pandit introduced chirality using (L)-serine as the starting material (Scheme 35).



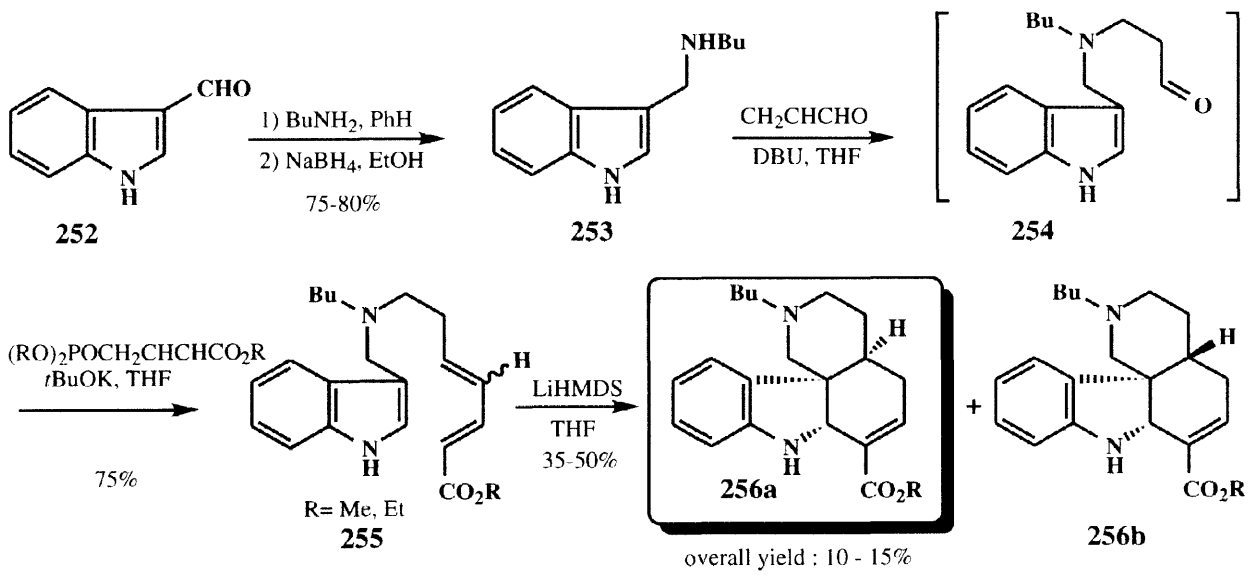
Scheme 35

In preliminary studies Marko and co-workers[55,56] showed that the unstable β-aminoaldehydes can be prepared and subjected to other reactions provided they remain in solution. Thus β-aminoaldehyde **248** prepared by Michael addition of diallylamine on propenal was subjected to an aldol condensation followed by *in situ* dehydration and afforded triene **250**. This compound under high pressure or under thermal conditions gave rise to hexahydroquinoline derivatives **251**. The *trans* isomer remains the major adduct with the varying reaction condition (Scheme 36).



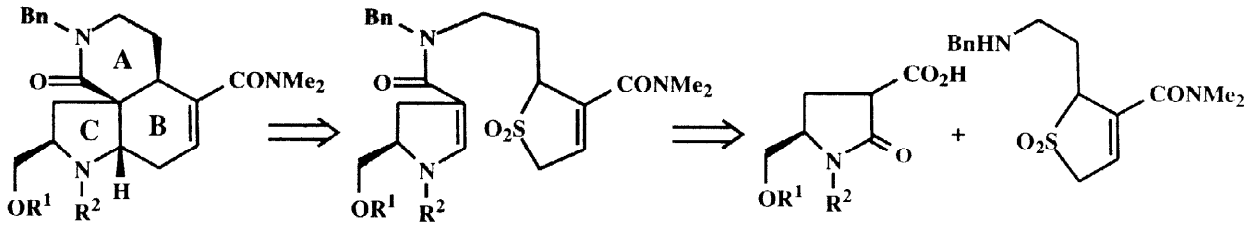
Scheme 36

Another kind of intramolecular Diels-Alder cycloaddition was developed with an indole as the dienophile and as a model of the C-ring of manzamine A **1**. Gramine derivative **253** was obtained in two steps from 3-formyl indole **252**. Michael addition followed by a Wittig-Horner reaction afforded compound **255** as a 50 : 50 mixture of *Z* and *E* isomers. Cyclisation under thermal conditions was unsuccessful, but interestingly, it was observed that, in the presence of LiHMDS, a smooth annulation took place giving rise to the tetracyclic compound **256** as a 50 : 50 mixture of *cis* and *trans* isomers (Scheme 37)[57]. The mechanism of this reaction was interpreted as a nucleophilic conjugate attack of indole anion on the dienic system followed by imine enolate aldol type condensation.



Scheme 37

The strategy developed by Leonard and coll. used a sulpholene derivative as a masked dienic precursor and a proline derivative as the dienophile and asymmetric precursor of the C-ring (retrosynthetic scheme 38).

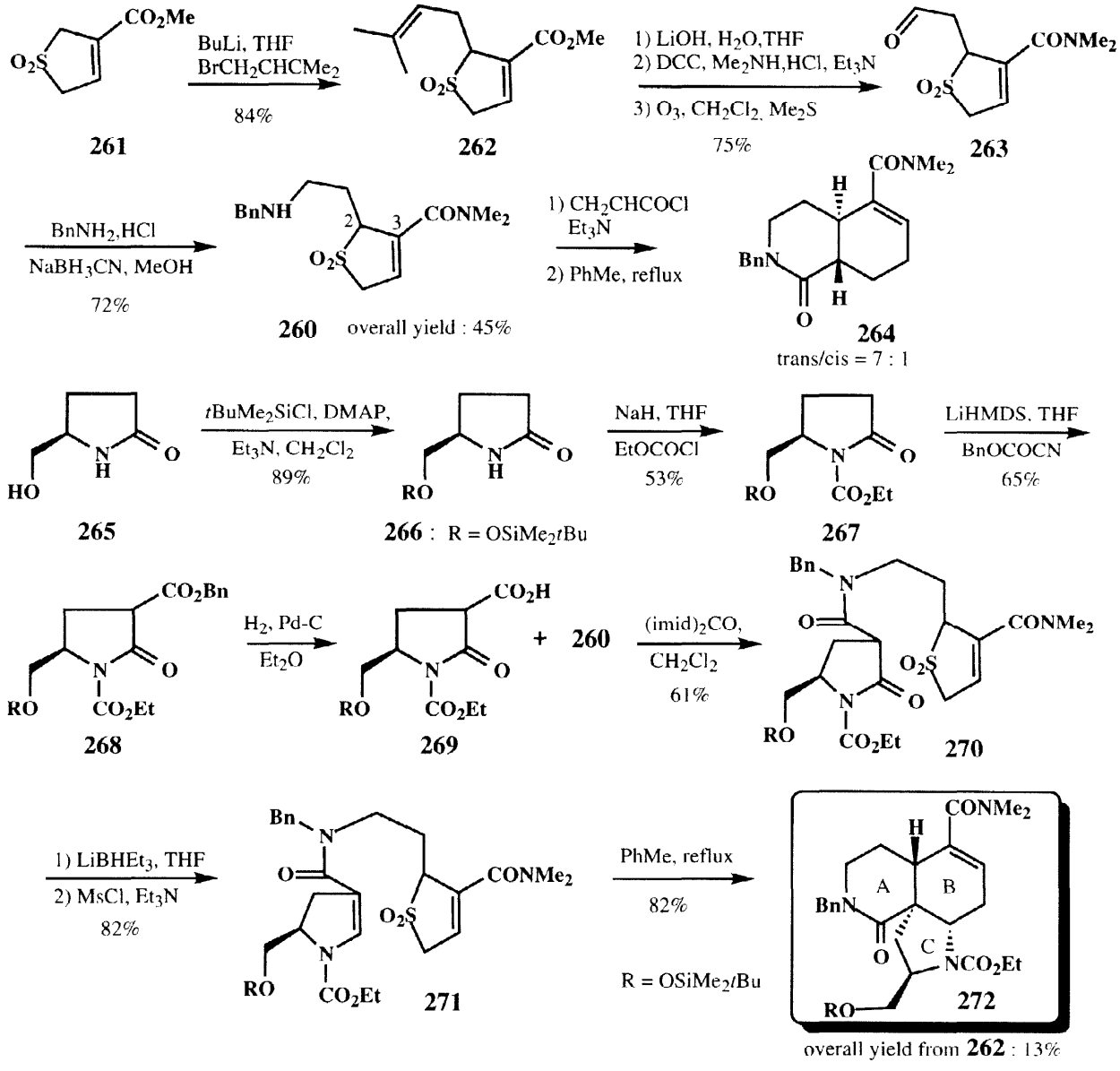


257 258 259 260

Scheme 38

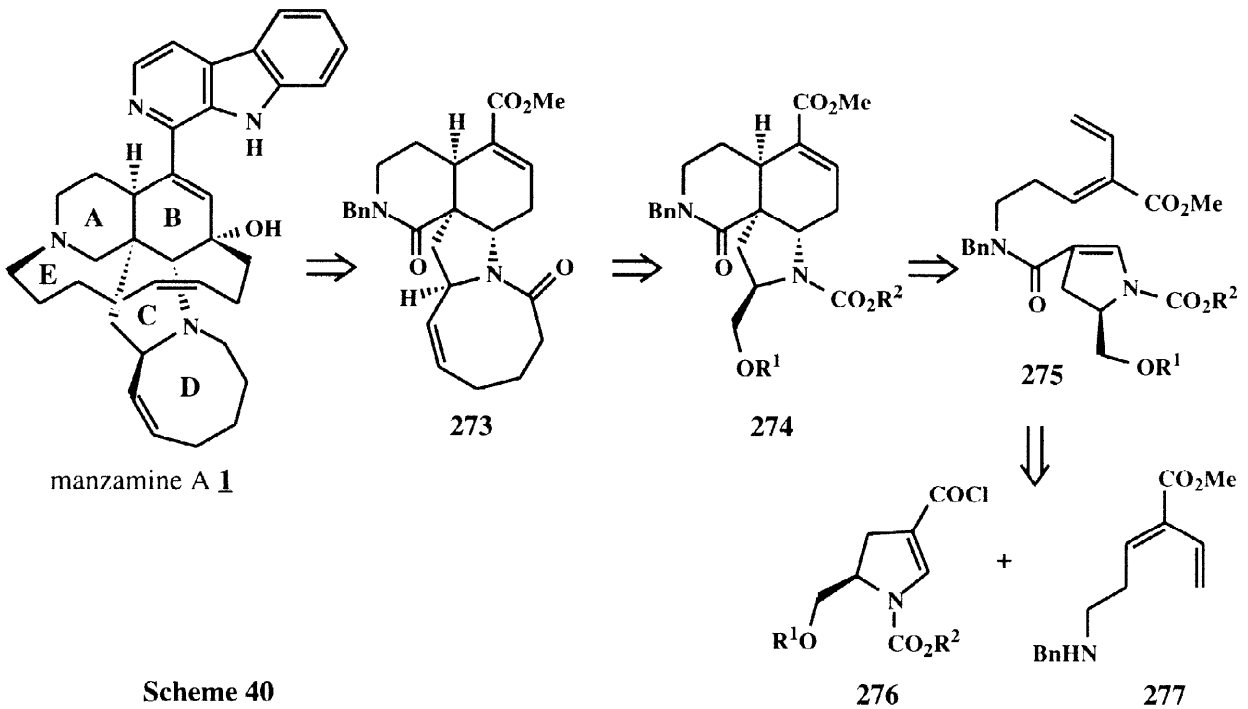
The feasibility of this strategy was first studied on a model affording the bicyclic core of manzamine A **1**[58]. Double deprotonation of the sulfolene ester **261** allowed a high yield regioselective alkylation. In order to preclude lactamisation with additional nitrogen during the subsequent steps, the methyl ester was changed to a dimethylamido group and the side chain was ozonolyzed giving rise to aldehyde **263**. Reductive amination with benzylamine afforded compound **260**. Acylation with propenoyl chloride followed by a thermal Diels-Alder cycloaddition of the resulting triene afforded adduct **264** as a 7:1 mixture of *exo* and *endo* isomers. This particular *exo* selectivity apparently did not result from an equilibrium after cycloaddition. Nevertheless, equilibration under basic conditions afforded a 1 : 1 mixture of *trans* and *cis* isomers.

The same strategy has been also applied to a more functionalized triene derivative designed to lead to the ABC tricyclic core of the alkaloid by an asymmetric intramolecular Diels-Alder cycloaddition[59]. Accordingly, pyroglutaminol **265** was doubly protected by silylation of the primary alcohol and *N*-acylation. Deprotonation of the resulting lactam **267** and *C*-acylation of the enolate with benzylcyanoformate, which gave better yield than the classical chloroformates, afforded lactam ester **268**. Hydrogenolysis of the benzylic ester was followed by condensation with the previously prepared aminosulfolene **260**. The dienophile unit was then introduced in two steps in high yield. Selective reduction of the pyrrolidone carbonyl with lithium triethylborohydride afforded an aminal intermediate, which after mesylation and elimination, gave rise to the dihydropyrrole derivative **271**. After thermal extrusion of sulfur dioxide, the intramolecular Diels-Alder reaction afforded in 82 % yield adduct **272** as the only isolated isomer. This product was obtained with an excellent diastereoselectivity, the facial differentiation due to the protected hydroxymethyl side chain being particularly efficient. However, if one can consider this cycloaddition as an inverse electon demand Diels-Alder reaction, the observed *endo* selectivity (with respect to the dihydropyrrole ring) afforded a *trans* AB ring junction. This result is consistent with studies by Martin (*vide infra*) who observed the reverse stereoselectivity starting with a *E* diene and not a *Z* diene as used in the Leonard approach (Scheme 39).



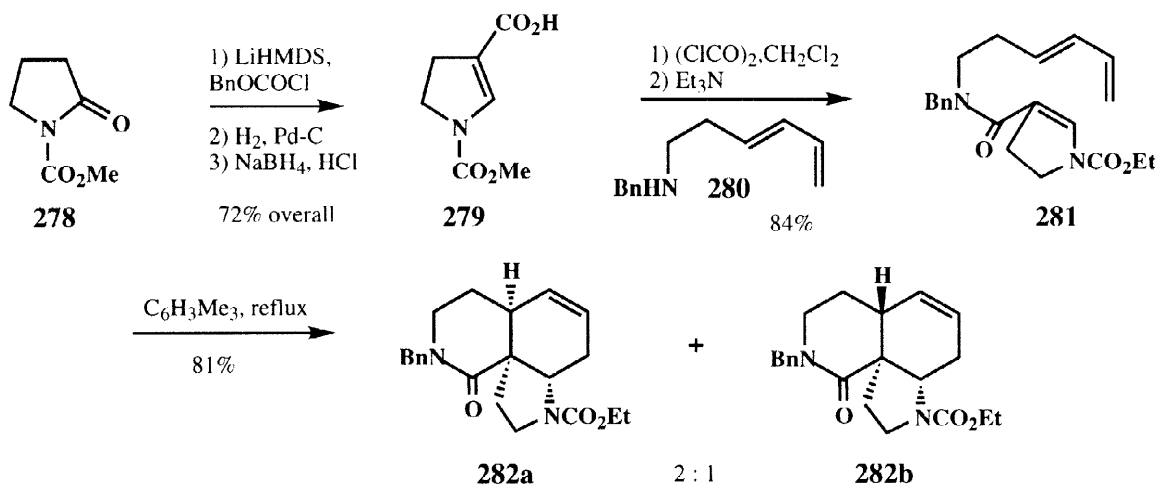
Scheme 39

Martin and co-workers studied independently the same type of strategy, but in a preliminary study with unsubstituted *E* diene, they obtained a mixture of *endo* and *exo* adducts, the requisite *endo* adduct being the major compound. As outlined in the retrosynthetic scheme 40, they applied the same scheme to the more elaborate compound **275**. They obtained with excellent stereocontrol adduct **274** which was subsequently transformed into a ABCD tetracyclic core **273** of manzamine A **1** after olefin metathesis (Scheme 40).



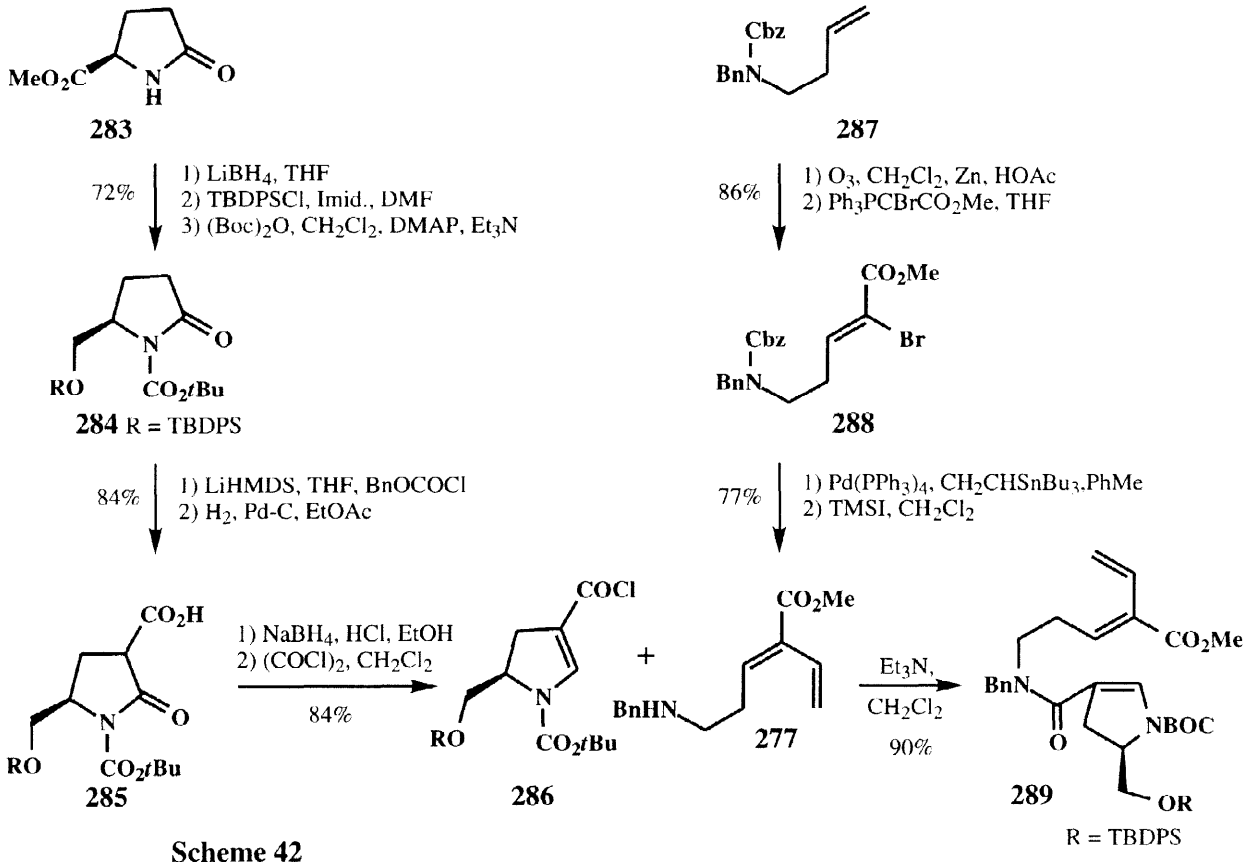
Scheme 40

The feasibility of an intramolecular Diels-Alder cycloaddition between an unfunctionalized diene and a vinylogous imide was investigated[60]. After deprotonation, lactam **278** was acylated with benzylchloroformate. Deprotection of the benzylic ester by hydrogenolysis and sodium borohydride reduction in acidic medium of the carbonyl lactam gave rise to the acid derivative **279**. The corresponding acid chloride was in turn treated with *E*-aminodiene **280** and furnished the triene **281**. A thermal Diels-Alder cycloaddition afforded a 2 : 1 mixture of *endo* and *exo* adducts **282a**-**282b**. A better *endo* selectivity was observed by catalysis with ethyldichloroaluminium which provided a mixture of 5.7 to 1 of the same isomers (Scheme 41). The influence of the configuration of the diene moiety was also studied. With a *Z*-diene a mixture 4 to 1 of **282a** and **282b** was obtained but the major compound was an adduct arising from an isomeric triene after 1,5-hydrogen shift.



Scheme 41

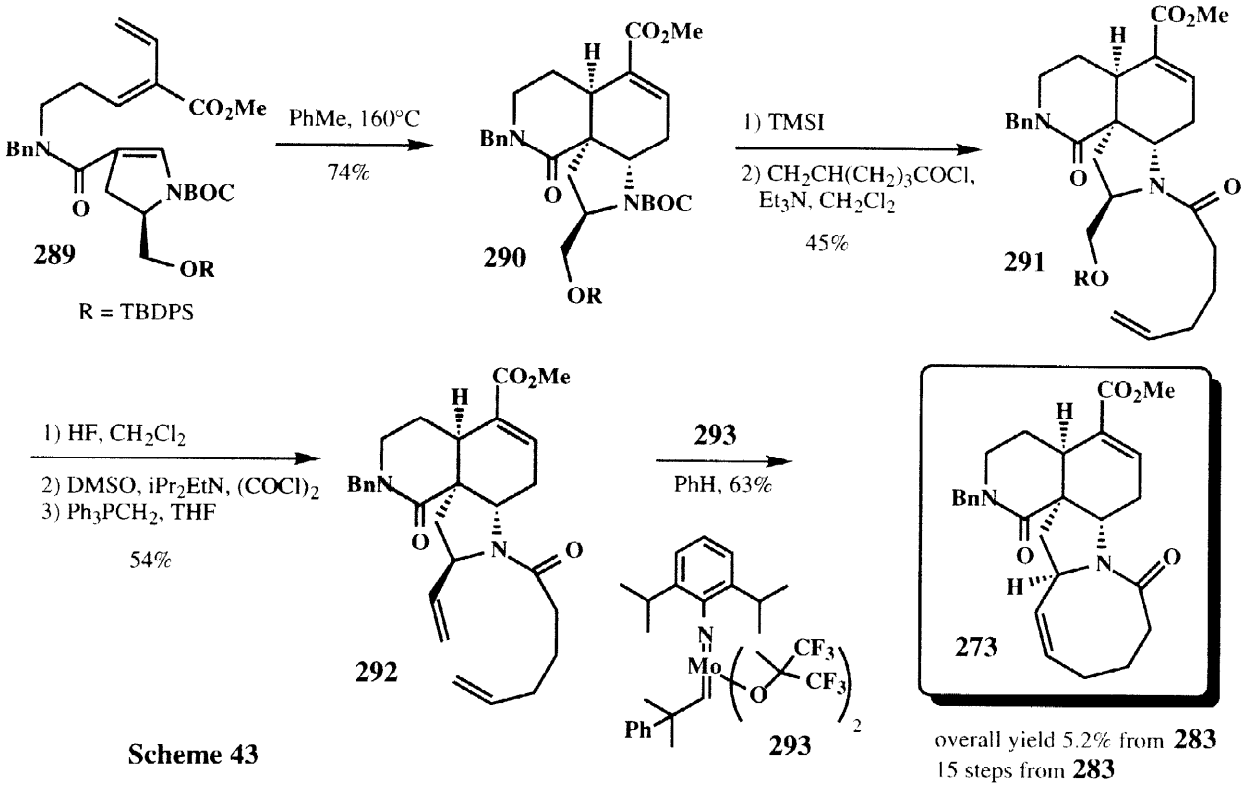
The enantiomerically pure tetracyclic ABCE subunit of manzamine A **1** has also been constructed by the same group using a related strategy[61]. The dienophilic partner was prepared from methyl pyroglutamate **283**. Reduction of the ester group followed by protection of the resulting primary alcohol and *N*-acylation furnished compound **284**. Introduction of carboxylic unit at C3 as above afforded acid lactam **285**. Sodium borohydride reduction in presence of hydrochloric acid generated a vinylogous imide derivative subsequently transformed into the acid chloride **286** in high overall yield. The dienic unit was obtained stereoselectively in four steps. Accordingly, the *N,N*-diprotected aminobutene **287** was subjected to ozonolysis followed by a stereoselective Wittig olefination affording compound **288**. A Stille coupling allowed the stereoselective introduction of a vinyl group and furnished the *E*-diene **277** after urethane cleavage with trimethylsilyl iodide. *N*-Acylation of **277** with acid chloride **286** gave rise to the anticipated triene **289**, the substrate for the intramolecular Diels-Alder cycloaddition (Scheme 42).



Scheme 42

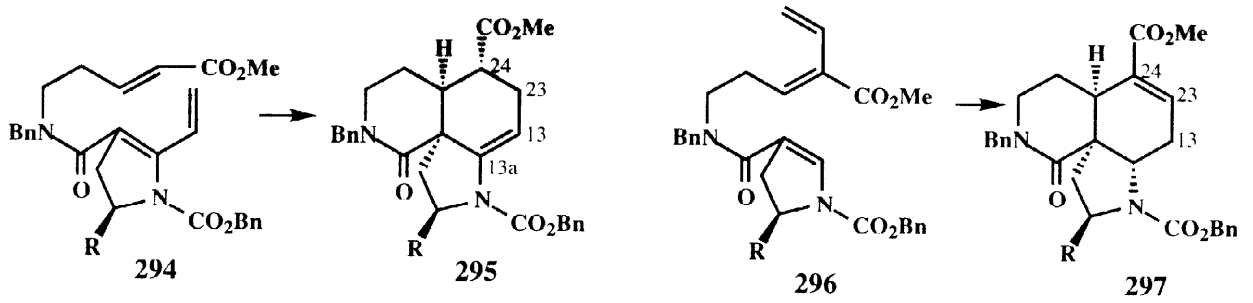
Under thermal conditions, the adduct **290** was obtained in high yield as a single isomer (Scheme 43). The configurations in the tricyclic compound **290** were established after NMR studies and confirmed by comparison with other tricyclic derivatives characterized by X-ray analysis. The eight-membered ring formation was then addressed. The Grubbs metathesis offered a nice opportunity for such a cyclisation[62]. This reaction has become of increasing importance in natural products synthesis and allowed the development of original strategies[63]. Thus, trimethylsilyl iodide cleavage of the *tert*-butyloxycarbonyl group and acylation with the suitable acid chloride for eight-membered ring formation afforded compound **291**. This sequence of reactions

was followed by functional group transformation of the hydroxymethylene appendage. Deprotection, oxidation and Wittig reaction furnished compound **292** ready for metathesis. This reaction was performed with the molybdenum Grubbs catalyst which is less sensitive to the presence of various functional groups than the ruthenium catalyst. Under these conditions, the enantiomerically pure tetracyclic compound **273** was obtained in fifteen steps for the longer sequence and in high overall yield from methyl pyroglutamate **283**.



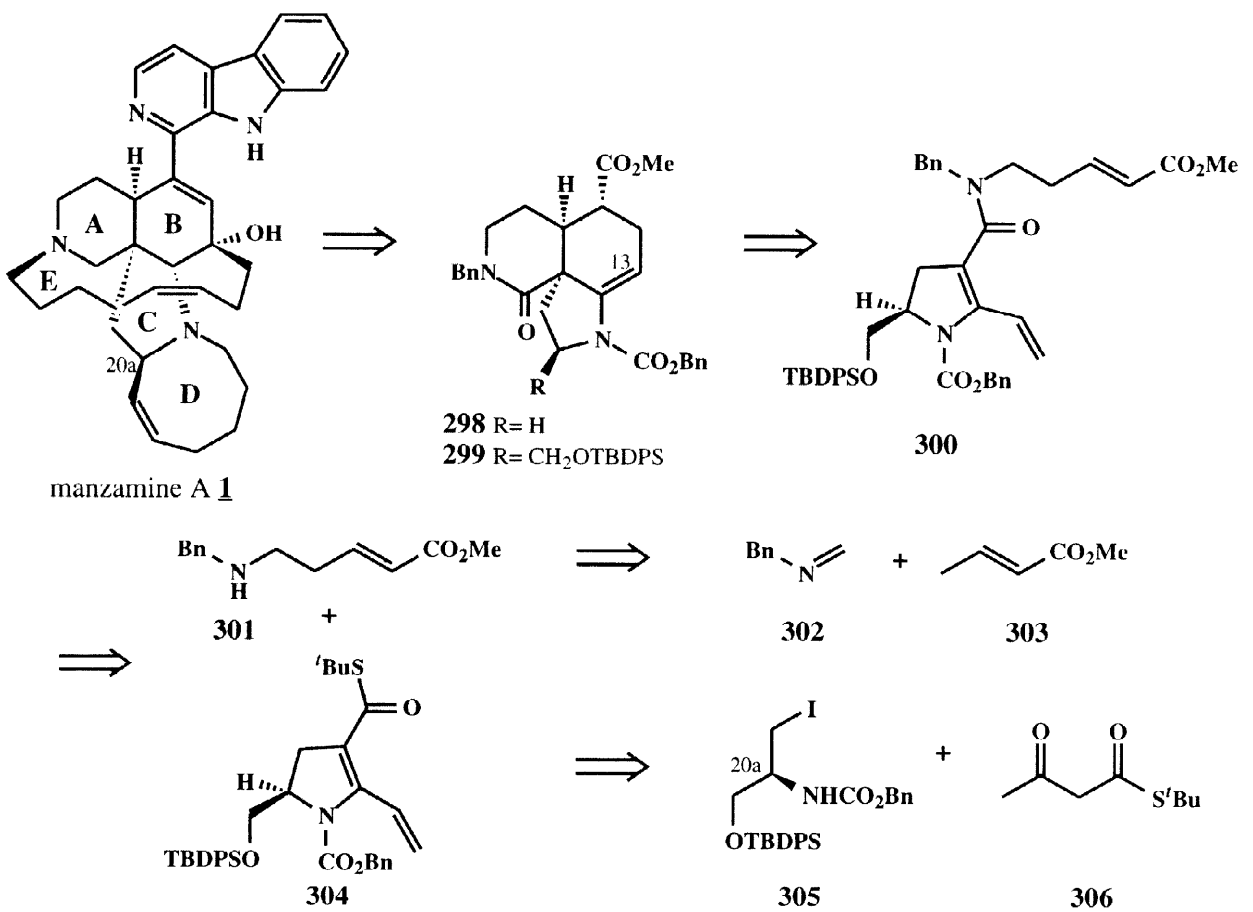
Scheme 43

In comparison with the preceding intramolecular Diels-Alder strategies, Pandit and co-workers chose the second alternative for preparing the tricyclic core of manzamine A **1** as illustrated in scheme 44. Triene **294** was used for this purpose and furnished the tricyclic intermediate **295**. This compound is characterized by the presence of C13-C13a double bond which allowed further functionalization at C13 and introduction of a C4 unit for thirteen-membered ring formation. Following this strategy, Pandit's group achieved the synthesis of the most advanced intermediate for manzamine A **1** synthesis. However, the introduction of the C23-C24 double bond which is obtained directly by the intramolecular cycloaddition in the Martin's approach, for instance in compound **297**, is delayed until the end of the synthesis in Pandit's strategy and has not been solved at present (Scheme 44).



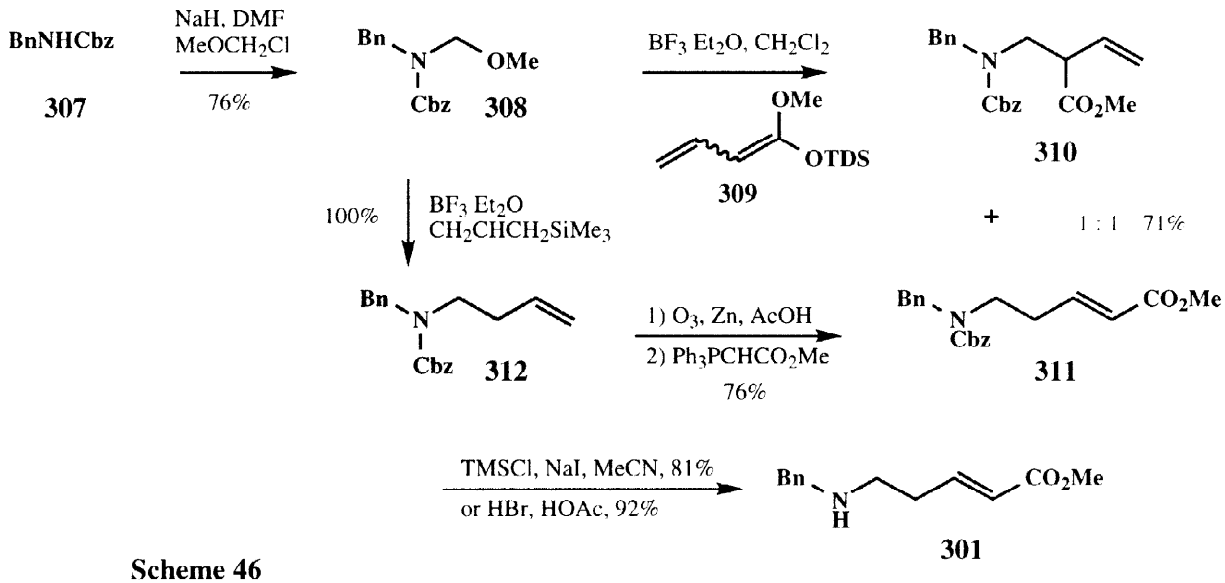
Scheme 44

Retrosynthetic analysis of the Pandit approach is presented in scheme 45. Chirality is introduced by using an iodoaminoalcohol compound **305** which is prepared from L-serine. This compound contains the asymmetric centre of the future C20a and the two appendages for five-membered and eight-membered ring elaboration. The dihydropyrrole unit **304** is constructed from **305**, which differs from the Martin and Leonard approaches which start from a proline derivative. As discussed above, functionalization at C13 in compound **299** was followed by thirteen-membered and eight-membered ring formation (Scheme 45).



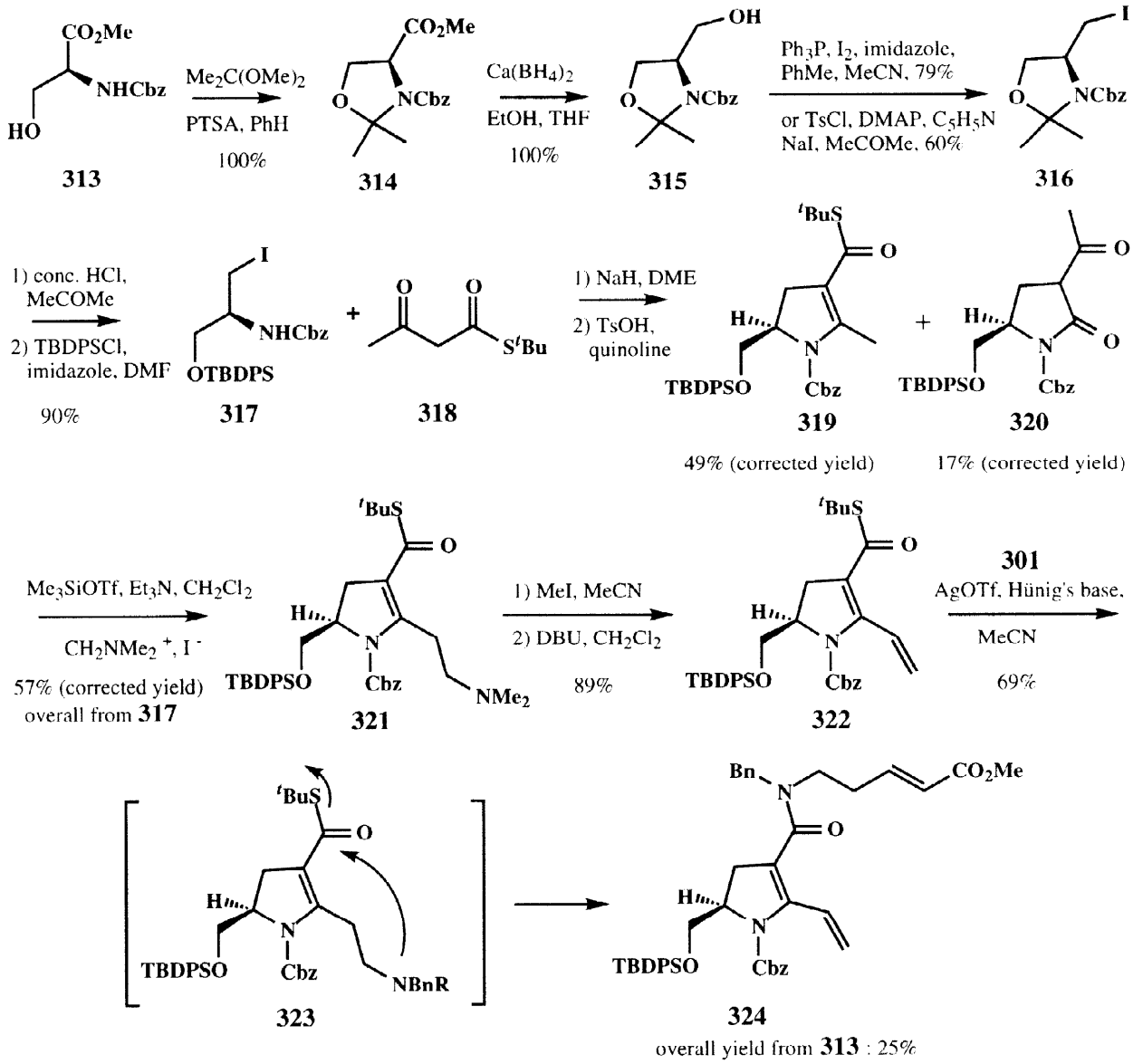
Scheme 45

The requisite dienophile was prepared either by a Mukaiyama-type iminium alkylation which furnished compound **311** along with the α-regioisomer **310**. A more efficient pathway was developed subsequently. Sakurai type alkylation with allylsilane afforded compound **312**. Ozonolysis of **312** and Wittig olefination of the resulting aldehyde gave rise unequivocally to compound **311**. The benzyloxycarbonyl group was deprotected either with trimethylsilyl iodide or with hydrobromic acid affording aminoester **301** (Scheme 46)[64, 65].



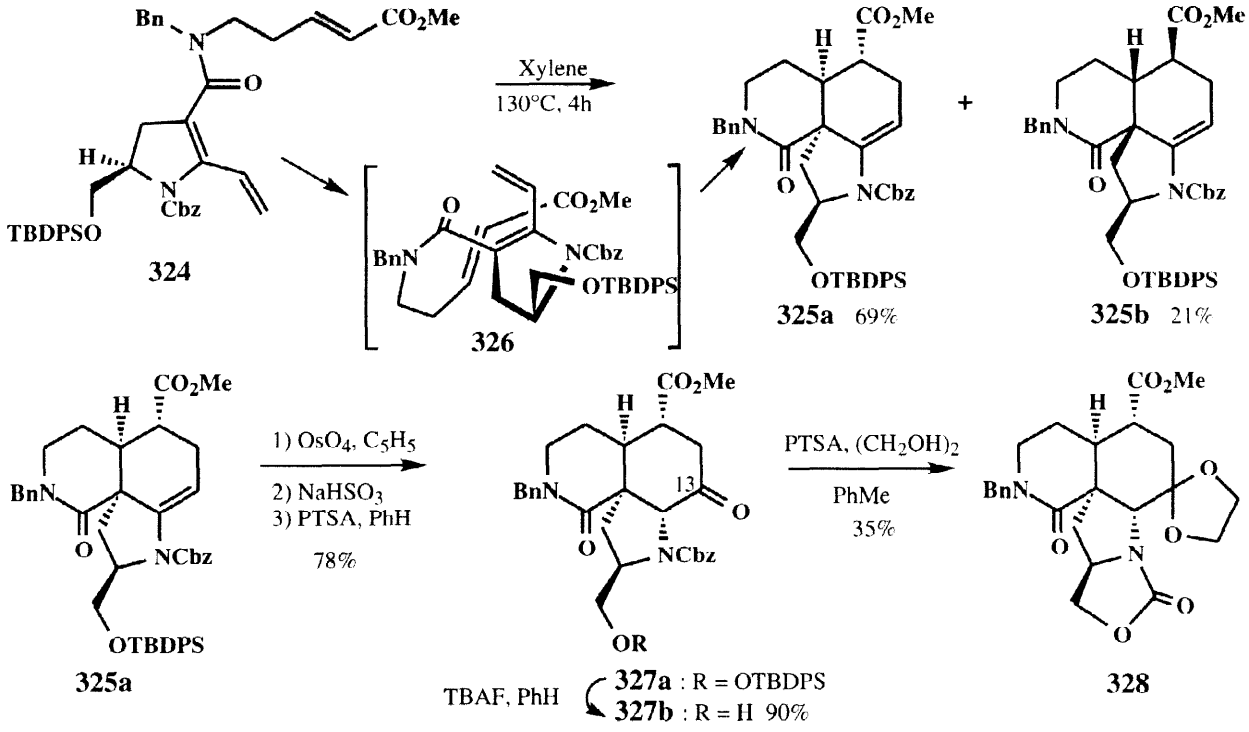
Scheme 46

On the other hand, *N*-benzyloxycarbonyl methyl serinate **313** protected as an oxazolidine derivative **314**, was reduced with calcium borohydride and furnished the primary alcohol **315** (Scheme 47). Substitution with iodine affording **316** was followed by acidic hydrolysis of the oxazolidine moiety and protection of the generated primary alcohol as the *tert*-butyldimethylsilyl ether. The iodo derivative **317** obtained by this sequence of reactions was reacted with *tert*-butyl acetylthioacetate **318**. The resulting product was cyclized in acidic medium and furnished a mixture of two pyrollidine derivatives **319** and **320** in moderate yields. However, unreacted iodo derivative **317** was recovered. A vinylogous Mannich type reaction under Mukaiyama conditions was used for methyl side chain elongation. In this reaction, a conjugate trialkylsilyl *tert*-butylthioketene acetal intermediate was alkylated on the γ carbon with Eschenmoser's reagent and furnished compound **321**. Classical Hofmann elimination gave rise to compound **322** bearing the dienic moiety necessary for IMDA. Introduction of the dienophilic counterpart resulted from silver ion-assisted acylation of aminoester **301** with the thioester group in **322**. It was subsequently recognized that this acylation is not direct but proceeds *via* a Michael addition on the vinylic side chain, giving rise to intermediate **323**, followed by an intramolecular nucleophilic attack of nitrogen on the thioester group[65, 66].



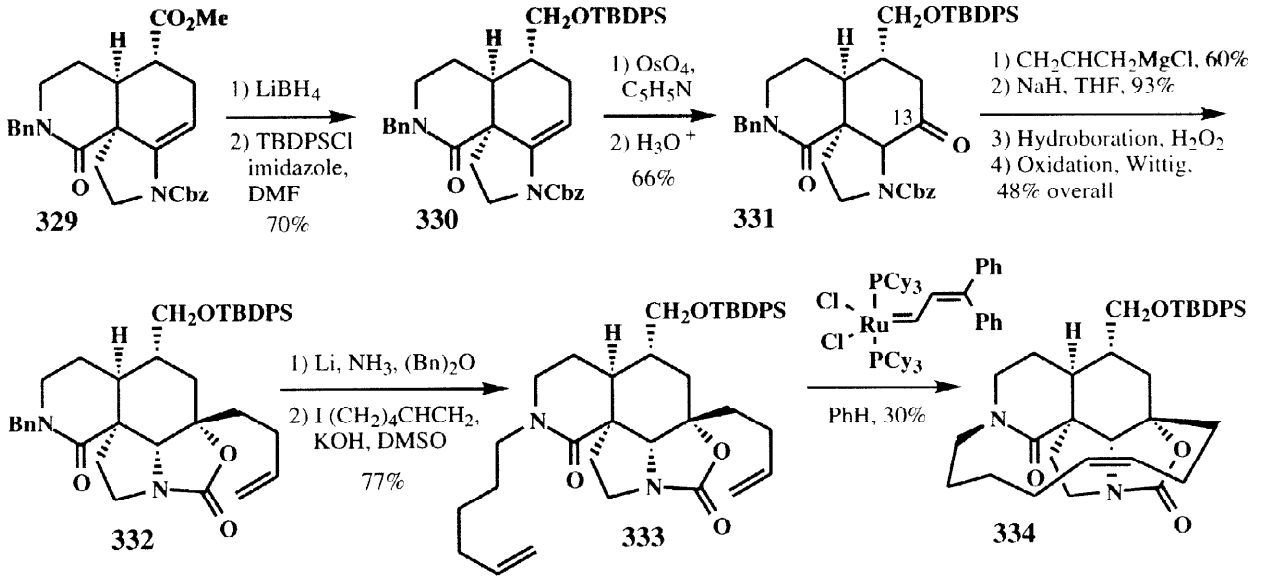
Scheme 47

With preparation of the trienic derivative **324** achieved, the IMDA reaction was performed under relatively mild conditions. A mixture of two adducts **325a** and **325b** was obtained (Scheme 48). The major compound **325a** resulting from transition state **326** presents the absolute configurations of manzamine A **1**. It is worthy of note that the diastereoselectivity is lower than in the other preceeding IMDA cycloadditions. Adduct **325a** after osmium tetraoxide hydroxylation, followed by a dehydration of the hydroxyl in the resulting aminal group afforded compound **327a** in which a keto group has been introduced at C13. Absolute configurations were determined by an X-ray analysis of crystalline derivative **328** which was prepared in two steps from **327a**[65, 66].



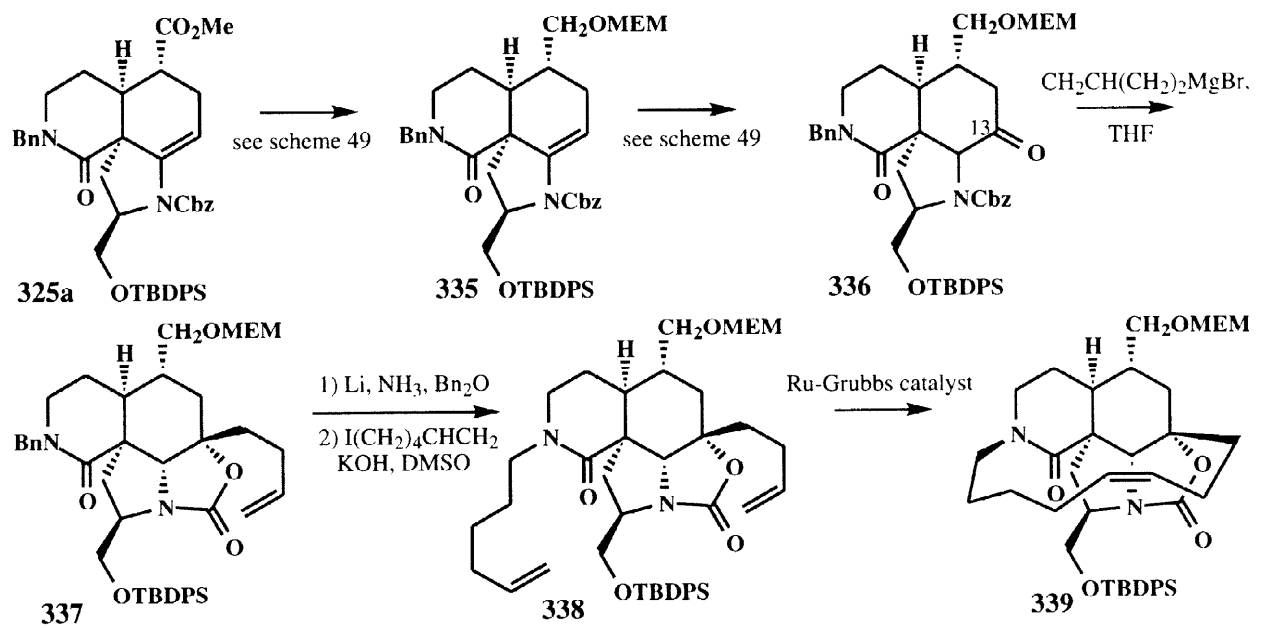
Scheme 48

A non asymmetric synthesis of the ABCE ring system of manzamine A **1** was described as an extension of this strategy (Scheme 49). Compound **329** resulting from the same kind of IMDA was functionalized at C13 as above furnishing the tricyclic derivative **331**. The low reactivity of the keto group at C13 precluded a direct alkylation with a butenyl Grignard reagent. Fortunately, the same type of alkylation can be performed with the more reactive allylmagnesium chloride. Internal protection of the resulting tertiary alcohol furnished a tetracyclic derivative. A one carbon chain elongation was then achieved in 48% overall yield in three steps *via* hydroboration, oxidation and Wittig olefination, but the experimental conditions were not indicated. Then, debenzylation was followed by a *N*-alkylation with iodohexene giving rise to compound **333** ready for metathesis. This reaction was performed with the ruthenium Grubbs catalyst and furnished compound **334** in 30% yield for this step[67]. This result contrasts with the high yield observed with salt **235** (Scheme 33) and is probably due to a template positive effect due to the presence of a [2.2.2] tricyclic framework in **235** (*vide supra*).



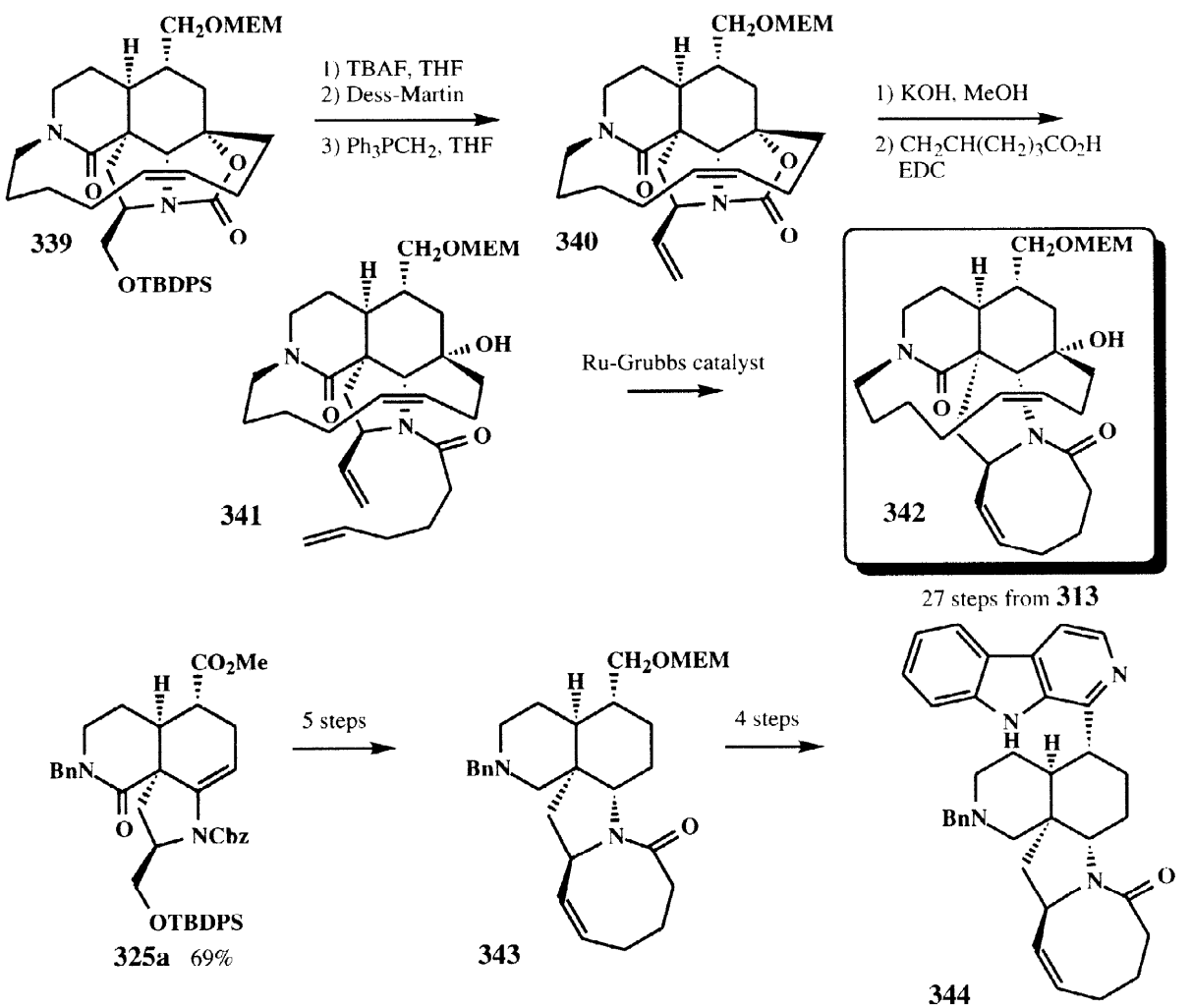
Scheme 49

A quite similar sequence was followed in the enantiomerically pure series. However this sequence has been published for the moment without experimental details and yields are not indicated. Accordingly, ketone **336** obtained as above was directly alkylated with a butenyl Grignard unit without problem of reactivity seen for the non-asymmetric series. This particular point was not discussed by the authors. *N*-Benzyl hydrogenolysis followed by realkylation afforded compound **338** which was submitted as above to a ruthenium Grubbs cyclisation and afforded compound **339** (Scheme 50)[68,69].



Scheme 50

With compound **339** in hand, the last eight-membered ring synthesis was addressed (Scheme 51). Deprotection of the primary alcohol at C20 was followed by a Dess-Martin oxidation giving rise to an aldehyde which was submitted to a Wittig olefination. The resulting compound **340** was in turn saponified and *N*-acylated with hexenoic acid. As in the Martin synthesis, the Grubbs catalyst promoted the eight-membered ring formation, but, in the present case, the ruthenium catalyst was used instead of the molybdenum one in the Martin approach. Yields for this sequence of reactions are not indicated. However, after metathesis, compound **342**, the most advanced ABCDE pentacyclic intermediate in the synthesis of manzamine A **1**, was isolated for the first time[68]. In related studies, Pandit and co-workers also prepared the ABCD tetracyclic compound **343** and studied the coupling reaction with tryptamine. Compound **344** bearing a carboline unit was thus obtained[69,70].

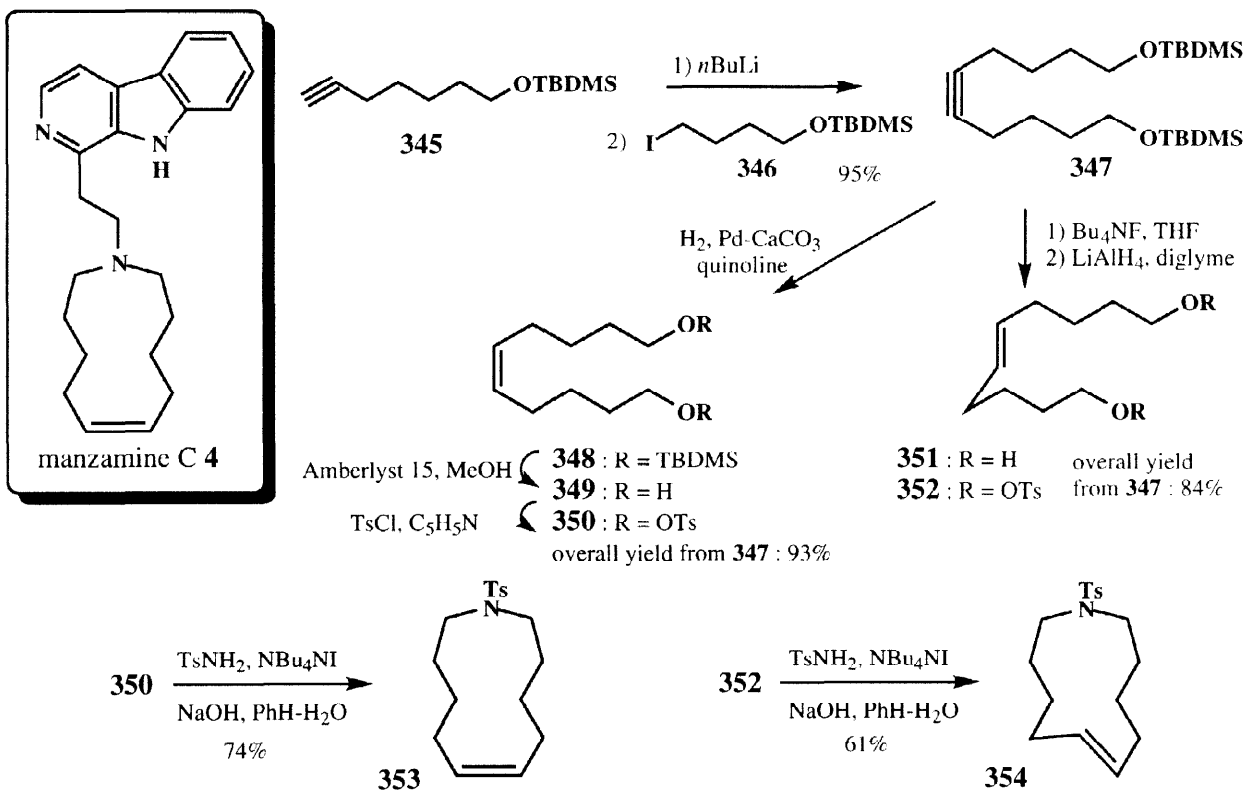


Scheme 51

5- Manzamine C syntheses.

Manzamine C **4**, despite its rather simple structure, retains a part of the cytotoxic activity found in manzamine A **1**. Therefore, from a structure-activity point of view, the synthesis of manzamine C **4** and of related analogues is also of interest.

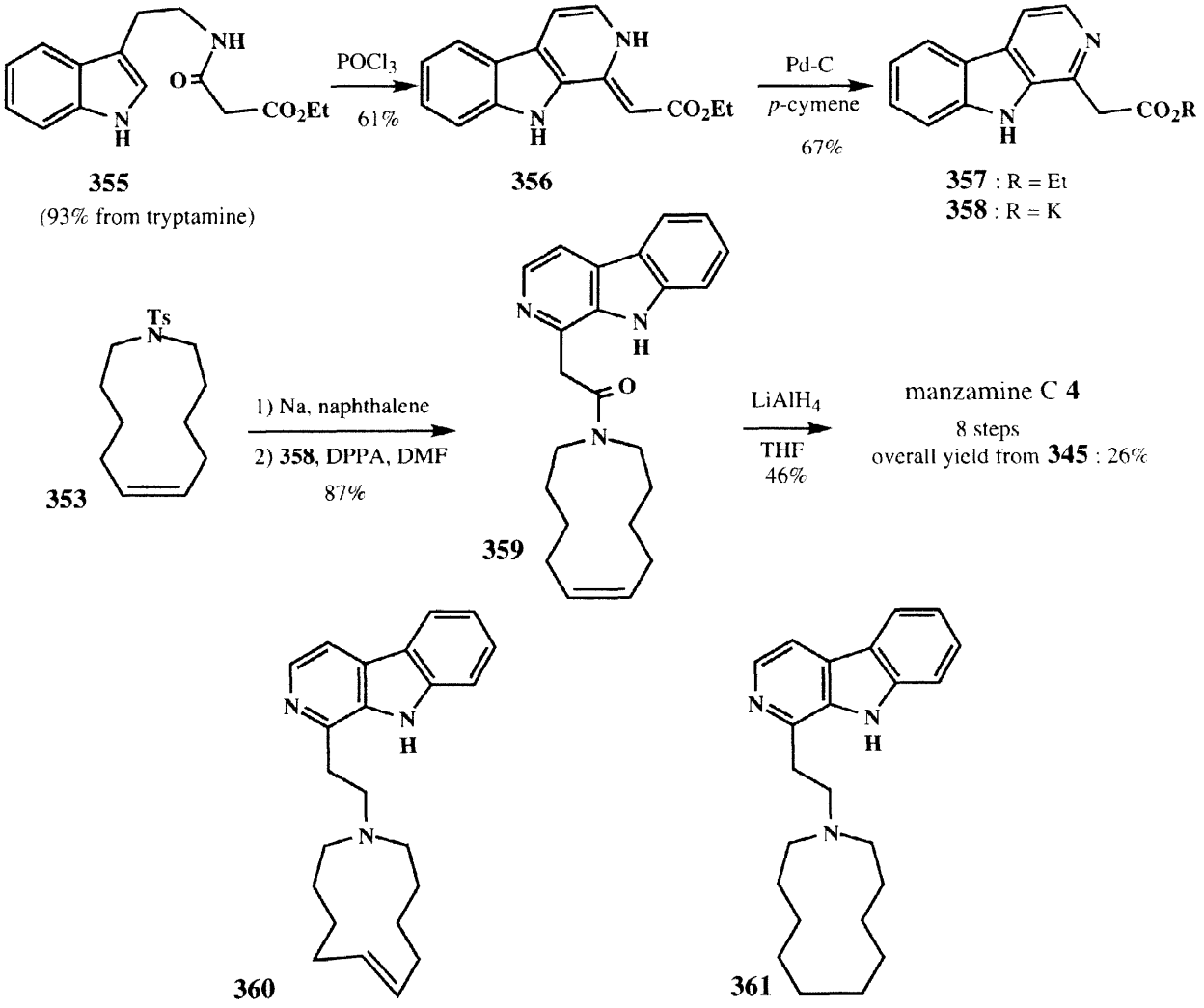
Two syntheses of this alkaloid have been already described. The first synthesis was achieved by the Nakagawa group[71] (Scheme 52). The known silyloxyacetylene **345** was alkylated with 1-iodo-4-*tert*-butyldimethylsilyloxybutane **346** and afforded the protected diol acetylenic derivative **347**. Hydrogenation of **347** in presence of Lindlar catalyst furnished stereoselectively the *Z* alkene **348** which was deprotected and tosylated to give rise to the ditosylate **350**. On the other hand, the *E* diol **351** was obtained after desilylation of **347** followed by reduction with lithium aluminium hydride in diglyme. After being converted to the ditosylate **352**, both ditosylates **350** and **352** were treated under phase transfer conditions with tosylamine and afforded the *N*-tosyl-6-(*Z*) or (*E*)-azacycloundecene **353** and **354** in 74 and 61% yields respectively.



Scheme 52

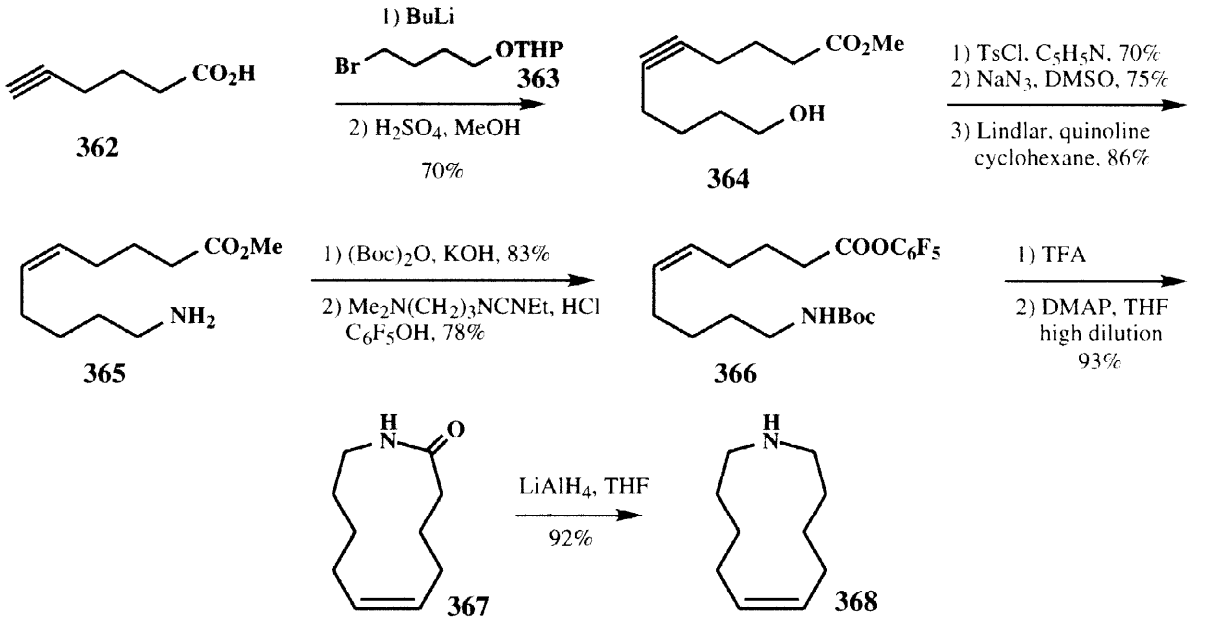
After disappointing results with a Pictet-Spengler cyclisation followed by aromatisation of the resulting tetrahydrocarboline derivative, a route using the Bischler-Napieralsky reaction was explored (Scheme 53). Thus, amide **355** furnished carboline derivative **356** after treatment with phosphorus oxychloride. Aromatization was performed with Pd-C in *p*-cymene and afforded the carboline derivative **357**. The best method for coupling compounds **353** and **354** was obtained by a condensation reaction in the presence of diphenylphosphoryl azide (DPPA) between the potassium salt **358** and the secondary amine resulting from a

sulfonyl group cleavage in compound **353**. The corresponding amide **359** was isolated in 87% yield. Reduction of the amide in **359** furnished manzamine C **4**. The same sequence afforded the *E* isomer **360** of manzamine C **4**, and after reduction of the double bond, dihydromanzamine C **361**.



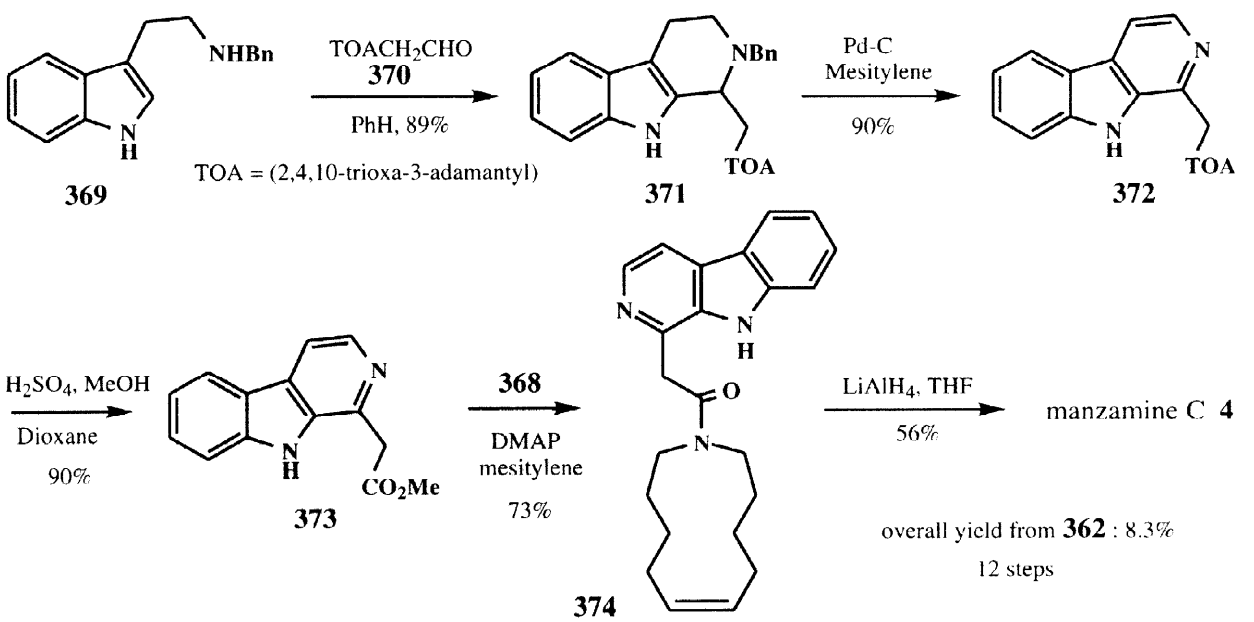
Scheme 53

A different synthetic pathway was followed by Gerlach[72] in the second synthesis of manzamine C **4**. The eleven-membered ring resulted from macrolactamisation under high dilution and the β-carboline unit was obtained after a Pictet-Spengler cyclisation (Scheme 54). The synthesis started with 5-hexynoic acid **362** which after deprotonation of acetylenic moiety, alkylation and esterification furnished compound **364**. Tosylation, nucleophilic substitution with sodium azide and simultaneous reduction of this group and of the triple bond with Lindlar catalyst afforded the aminoester **365**. Nitrogen protection, saponification and esterification with pentafluorophenol gave rise to the ester urethane **366**. Macrolactamization was performed after Boc acidolysis in presence of 4-dimethylaminopyridine under high dilution and furnished in good yield the anticipated lactam **367**. Final reduction with lithium aluminium hydride afforded (*Z*)-1-aza-6-cycloundecene **368**.



Scheme 54

The carboline unit was prepared by Pictet-Spengler condensation between *N*-benzyl tryptamine **369** and the aldehyde derivative **370** bearing a carboxylic group protected as the adamantyl orthoester. The resulting tetrahydro-β-carboline **371** was aromatized in high yield with palladium on charcoal and afforded carboline **372**. Methanolysis of the orthoester furnished methyl ester **373** which in turn reacted with the eleven-membered ring amine **368**. After hydride reduction, manzamine C **4** was isolated (Scheme 55).

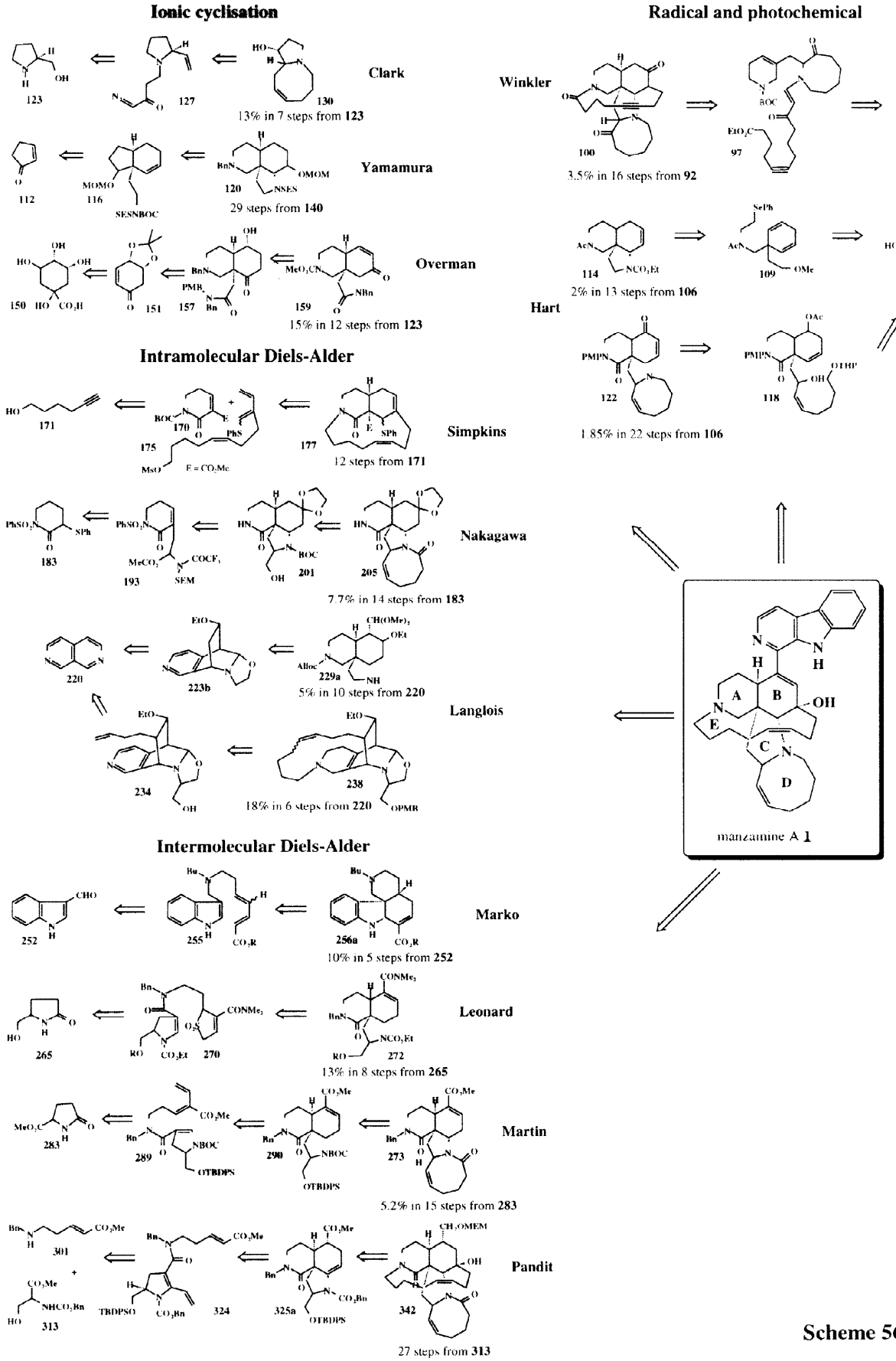


Scheme 55

A structure-activity relationship study of manzamine C **4** and analogues has been published more recently by the Nakagawa group[73]. This work emphasized the importance of the eleven-membered ring for a broad and effective activity against various kind of tumour cells. On the other hand the double bond either *Z* or *E* does not seem to play a particular role in cytotoxicity.

6 - Conclusion.

Despite the fact that the total synthesis of manzamine A **1** has yet to be achieved, the original structure of this recently discovered family of alkaloids and their cytotoxicity has induced a lot of synthetic studies using various strategies which are summarized in the general scheme 56. Cycloadditions play a preeminent role in these synthetic studies, but alternative strategies based for instance, on [2+2] cycloaddition or Mannich cyclisations are also quite efficient. Biomimetic syntheses, however, still at an early stage, may prove to be versatile giving rise not only to manzamine type alkaloids, but also to related alkaloids in this series.


Ionic cyclisation
Clark
13% in 7 steps from 123
Yamamura
29 steps from 140
Overman
15% in 12 steps from 123
Intramolecular Diels-Alder
Simpkins
12 steps from 171
Nakagawa
7.7% in 14 steps from 183
Langlois
5% in 10 steps from 220
18% in 6 steps from 220
Intermolecular Diels-Alder
Marko
10% in 5 steps from 252
Leonard
13% in 8 steps from 265
Martin
5.2% in 15 steps from 283
Pandit
27 steps from 313
Radical and photochemical
Winkler
3.5% in 16 steps from 92
Hart
2% in 13 steps from 106
1.85% in 22 steps from 106
manzamine A 1

Scheme 56

Acknowledgements : The authors thank Dr. Michael Gray for his suggestions and for the improvement of the english manuscript and MRES and Bourses Lavoisier for grants to E.M..

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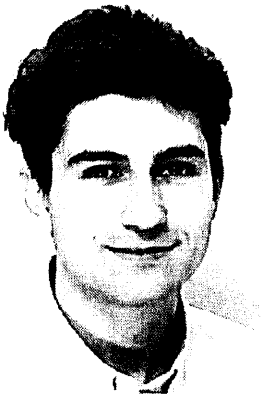
Biographical sketch

Yves Langlois



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Yves Langlois was born in 1938 in Paris. He prepared his thesis at the Ecole Supérieure de Chimie Organique et Minérale (ESCOM) under the guidance of Professor Pierre Mastagli. After two years at the Commissariat à l'Energie Atomique (CEA), he joined the Institut de Chimie des Substances Naturelles (CNRS) at Gif sur Yvette in 1968. He was appointed Professor at the Université de Paris-Sud at Orsay in 1988.

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