Review

Development of New Synthetic Methods and Its Application to Total Synthesis of Nitrogen-Containing Bioactive Natural Products

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A group of naturally occurring substances containing nitrogen is widely distributed in plants as well as in fungi, animal, marine organisms, and insects, and many exhibit significant biological activity. These natural products with a huge variety of chemical structures include antibiotics, antitumor agents, immunostimulants, drugs affecting the cardiovascular and central nervous systems, analgesics *etc*. The diverse activities and low natural abundance of this group of natural products when coupled with their molecular complexity warrant development of new and efficient synthetic methods and strategy for the total synthesis of these products, in particular alkaloids. The purpose of this review is to describe some of our achievements in the total synthesis of the naturally-occurring bases including the Dendrobatid alkaloids pumiliotoxin B and allopumiliotoxin A, the anitibiotic streptazolin, the tricyclic marine alkaloids isolated from the ascidians such as fasicularin, lepadiformine, and cylindricine C, and the dimeric monoterpene alkaloid incarvillateine as well as the formal total synthesis of the spirocyclic marine alkaloids halichlorine and pinnaic acid, which are isolated from the Japanese marine sponge and the Okinawan bivalve, respectively.

Key words nitrogen-containing bioactive natural product; total synthesis; new synthetic method; Dendrobatid alkaloid; marine alkaloid; incarvillateine

1. Introduction

A group of naturally occurring substances containing nitrogen is widely distributed in plants as well as in fungi, animal, marine organisms, and insects and many exhibit significant biological activity. These natural products with a huge variety of chemical structures include antibiotics, antitumor agents, immunostimulants, drugs affecting the cardiovascular and central nervous systems, analgesics *etc*. Because of these diverse activities, these compounds have attracted the attention of synthetic, medicinal, pharmaceutical, and organic chemists. In this regard, it can be said that alkaloids and related compounds, as synthetic targets, have contributed to the growth and development of modern organic synthesis. As the presence of these products in natural sources is in very low concentration, need has been felt for obtaining such products in large quantities in order to assess their physiological properties and understand the mechanism of their activities. It appears that the sole solution to this problem resides in total synthesis. Natural products isolated from sources that are not readily cultivated or cultured have presented and still present a challenge in chemical synthesis, which can play a vital role in situation where that particular molecule is needed to answer a specific question.

For more than three decades, research efforts in our laboratory have been directed toward the development of new synthetic methods and strategy for the total synthesis of the nitrogen-containing natural products, in particular alkaloids. The purpose of this article is to review some of our achievements in the total synthesis of the naturally-occurring bases including the Dendrobatid alkaloids pumiliotoxin B and allopumiliotoxin A, the anitibiotic streptazolin, the tricyclic marine alkaloids isolated from ascidians such as fasicularin, lepadiformine, and cylindricine C, and the dimeric monoterpene alkaloid incarvillateine as well as the formal total synthesis of the spirocyclic marine alkaloids halichlorine and pinnaic acid, which are isolated from the Japanese marine sponge and the Okinawan bivalve, respectively.

2. Total Synthesis of Pumiliotoxin A Class Dendrobatid Alkaloids

Neotropical poison-dart frogs of the Dendrobatidae family have been a rich source of a remarkable variety of alkaloids with structurally unique features and biological significance.[1—4] During the past 30 years, more than 500 alkaloids of over 20 structural classes have been detected in skin extracts from Dendrobatidae and hence are referred to as "dendrobatid alkaloid". The pumiliotoxin A alkaloids, one of the major classes of the dendrobatid alkaloids, are a group of more than 40 alkaloids characterized by the 6-alkylidene-8-hydroxy-8-methylindolizidine ring system, which have cardiotonic and myotonic activity apparently enhancing the sodium channel function.[3] They have been divided into two subclasses, the pumiliotoxins (**1**) and the allopumiliotoxins (**2**) (Fig. 1). Around the late 1980s, an international treaty to protect endangered species was enacted[5] that has prevented the collecting of the Dendrobatid frogs whose habitat is Cen-

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tral and South America. In this respect, the inability to obtain sufficient material from natural sources for detailed pharmacological evaluation makes the synthesis of the pumiliotoxin A alkaloids an important and urgent goal.[6,7]

2.1. Synthesis of (+)-Pumiliotoxin 323 A (Pumiliotoxin B)[8,9] Our initial synthetic target was pumiliotoxin B (**7**). The synthesis began with carbonyl addition of the allenylsilane to the ketone,[10,11] which was performed using the trifluoroacetate salt **11** of (*S*)-2-acetylpyrrolidine and the protected allenylsilane **12** (Chart 1). The reaction proceeded cleanly by using hafnium(IV) chloride ($HfCl_4$) to afford the homopropargylic alcohol **14** as a single diastereomer in excellent yield (95%). The α-facial selectivity realized in the propargylation of **11** can be rationalized by invoking a Lewis acid-chelate cyclic intermediate **13** (Cram's α-chelation model). In this case, $HfCl_4$ was found to be the most effective Lewis acid for the nucleophilic addition.[12] After Boc protection of the amino group in **14**, radical hydrostannylation using triethylborane and triphenyltin hydride proceeded with complete *trans* selectivity to give **15** with the (*Z*)-3′-stannyl alkene. Upon exposure of **15** to *N*-iodosuccinimide, iodolysis took place with complete retention of the (*Z*)-configuration to afford the vinyl iodide **16**. Palladium-catalyzed carbonylation of **16** smoothly occurred when treated with carbon monoxide and tributylamine in the presence of catalytic $Pd(OAc)_2$ (2 mol%) and PPh_3, furnishing the lactone **17**.

N-Boc deprotection of **17** with trifluoroacetic acid followed by DIBAL reduction gave the diol **18**, which underwent smooth intramolecular cyclodehydration (CBr_4, Ph_3P)[13] to construct the (*Z*)-alkylideneindolizidine skeleton, and then was converted to the homoallylic iodide **20** (Chart 2). In the critical cross-coupling reaction between **20** and the (*E*)-vinyl iodide **22** for the synthesis of pumiliotoxin B (**7**), one potential problem associated with the transition metal-catalyzed homoallyl–alkenyl coupling would be the tendency of the homoallylic compounds to undergo β elimination. This problem was overcome by Negishi[14] who adapted homoallylic organozincs to palladium-catalyzed cross-coupling with alkenyl halides to effect the construction of 1,5-dienes. In view of these results, we explored the use of the organozinc for the cross-coupling reaction.[15,16] Due to the difficulty usually associated with preparation of a homoallylzinc species by direct zinc insertion to the corresponding halides, the homoallylic iodide **20** was subjected to halogen–metal exchange with *t*-BuLi at −110 °C, followed by transmetalation with $ZnCl_2$. Subsequent one-pot treatment of the resulting homoallylzinc reagent **21** with the vinyl iodide **22** in the presence of 10 mol% of $Pd(PPh_3)_4$ in benzene at room temperature afforded the cross-coupled product with complete retention of configuration of the stereocenter(s) and (*Z*)-

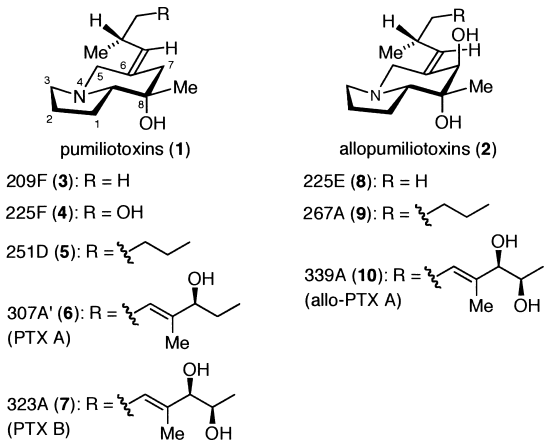

Fig. 1. Representative Pumiliotoxin (PTX) A Class Alkaloids

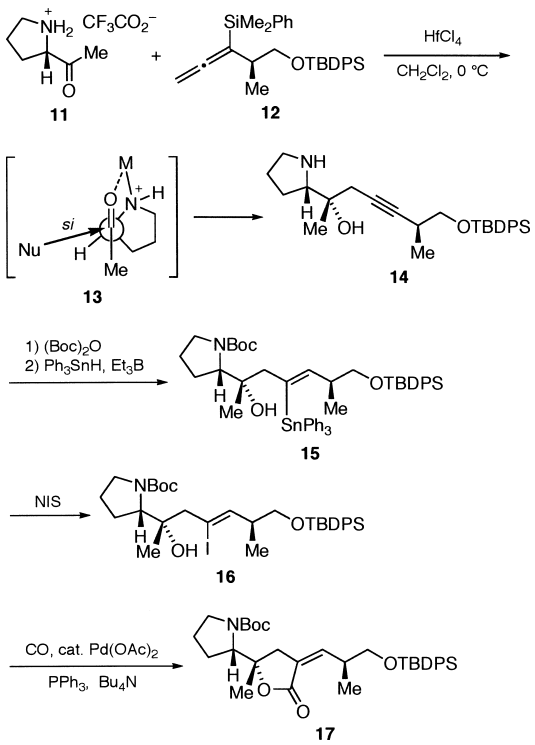

Chart 1

Chihiro Kibayashi was born in 1939 in Keijo (now Seoul), then part of Japan, and brought up in Tokyo. He graduated from Tokyo College of Pharmacy in 1962 and then received both a Master of Pharmacy and his Ph.D. from Tohoku University under the supervision of the late Prof. Tetsuji Kametani. He became Assistant Professor at the Tokyo College of Pharmacy (now Tokyo University of Pharmacy and Life Science) in 1972, and Associate Professor there in 1975. Since 1985 he has been Professor of Organic Chemistry at Tokyo University of Pharmacy and Life Science. Prof. Kibayashi was awarded the Academic Award of the Senji Miyata Foundation in 1994 and the Pharmaceutical Society of Japan Award in 2005. His research interests involve development of synthetic methodology, asymmetric synthesis, and natural products synthesis.

Chihiro Kibayashi

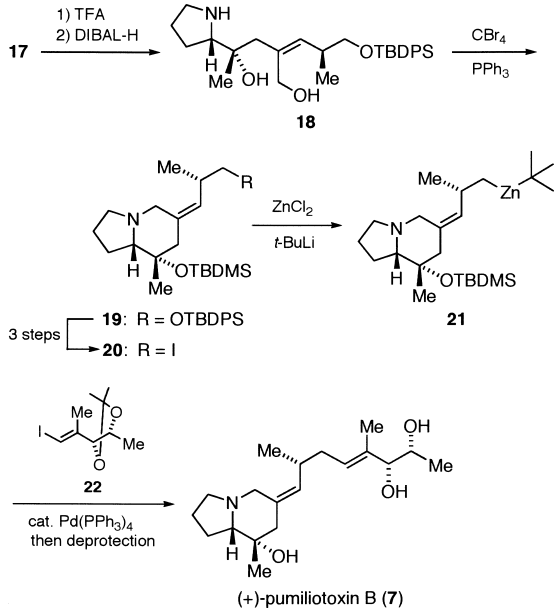

Chart 2

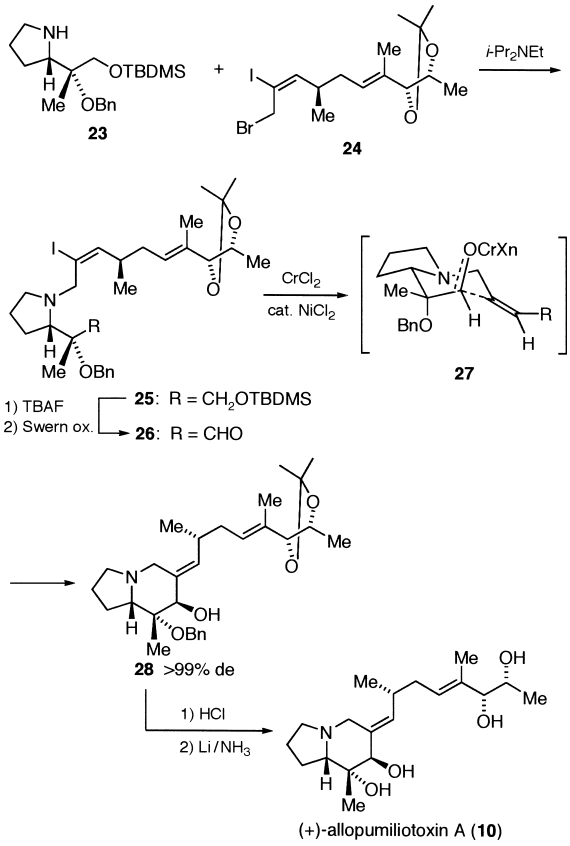

Chart 3

geometry. Finally, removal of the TBDMS and acetonide protecting groups provided (+)-pumiliotoxin B (**7**).[17]

2.2. Synthesis of (+)-Allopumiliotoxin 339A (Allopumiliotoxin A)[18—20] The allopumiliotoxin class dendrobatid alkaloids (**2**) are hydroxy congeners of the pumiliotoxin class (**1**) and possess a vicinal diol group in the indolizidine ring. They are the most complex members of the pumiliotoxin A alkaloid group. In studies aimed at developing another approach to the alkaloids of the pumiliotoxin A family, we next targeted the total synthesis of allopumiliotoxin A (**10**), which is the most complex member of this family,[1—4] utilizing the intramolecular chromium-mediated cyclization based on the Nozaki–Kishi reaction[21—23] that generates the indolizidines framework, installs the (*E*)-alkylidene side chain, and establishes the C-7 hydroxy stereochemistry in a single operation. Thus, *N*-allylation of the pyrrolidine **23** with the alkenyliodide side chain fragment **24**, elaborated from the D-4-deoxythreose derivative in eleven steps, afforded **25**, which was converted to the (*E*)-iodoalkenyl aldehyde **26** (Chart 3). On treatment of **26** with nickel(II) and chromium(II), intramolecular coupling proceeded with virtually complete stereoselection to give the C-7 axial alcohol **28** as a single isomer. The excellent stereoselection observed in the formation of the C-7 stereocenter was attributed to reaction through a chair-like transition state **27**. The cyclization conformer **27** avoids the allylic 1,3-strain between the quasi equatorial chromium alkoxide and the alkene and, more importantly, the steric hindrance and electrostatic repulsion between the benzyloxy and the chromium alkoxide group bearing a partial negative charge. Finally, cleavage of the isopropylidene group and subsequent reductive cleavage of the benzyl group provided (+)-allopumiliotoxin A (**10**).[24—26]

3. Total Synthesis of (+)-Streptazolin[27]

Streptazolin (**37**), first isolated from cultures of *Streptomyces viridochromogenes*,[28] is a unique antibiotic which possesses the structural feature of an unusual ring system, hexahydropyrindine, employing an internal carbamate unit and an exocyclic ethylidene side chain. This antibiotic has been claimed to be unstable and readily polymerizes during the isolation and purification although it may be kept for some time in diluted solution at low temperature. While **37** exhibits limited antimicrobial activities, some Diels–Alder adducts with naphthoquinone have been reported to have striking bacterial, fungicidal, protozoacidal, and antitumor activity as effective as adriamycin on leukemia L1210 cells as well as improvement of the chemical stability.[29] In view of the unique structural feature and promising pharmacological activity profile, this antibiotic has posed an interesting challenge.[30,31]

Mitsunobu coupling of the cyclic imide **29**, prepared from L-tartaric acid,[32] with (*Z*)-4-(trimethylsilyl)-3-butenol (**30**) provided the *N*-butenylimide **31**, which was converted to the indolizidinone **32** by intramolecular cyclization of the intermediate *N*-acyliminium ion generated *via* $NaBH_4$ reduction of the one of the carbonyls, acetylation of the hydroxy group, and treatment with $BF_3 \cdot Et_2O$ (Chart 4). The partial reduction of the tertiary amide moiety in **32** using the aluminum complex from DIBAL-H and butyllithium[33] yielded the amino aldehyde **33** which was protected with the ethoxycarbonyl group. After conversion of **33** to the enyne **34**, palladium-catalyzed bicyclization[34] was carried out using *N*,*N*′-bis(benzylidene)ethylenediamine (BBEDA) as the ligand for the construction of the (*Z*)-ethylidene pyrindine **35**. With correct (*Z*)-ethylidene stereochemistry and the configuration at all stereocenters in hand, the remaining problem was the isomerization of the 1,4-diene in **35** to the 1,3-diene. Thus, **35** was treated with triiron dodecacarbonyl in 1,2-dichloroethane (re-

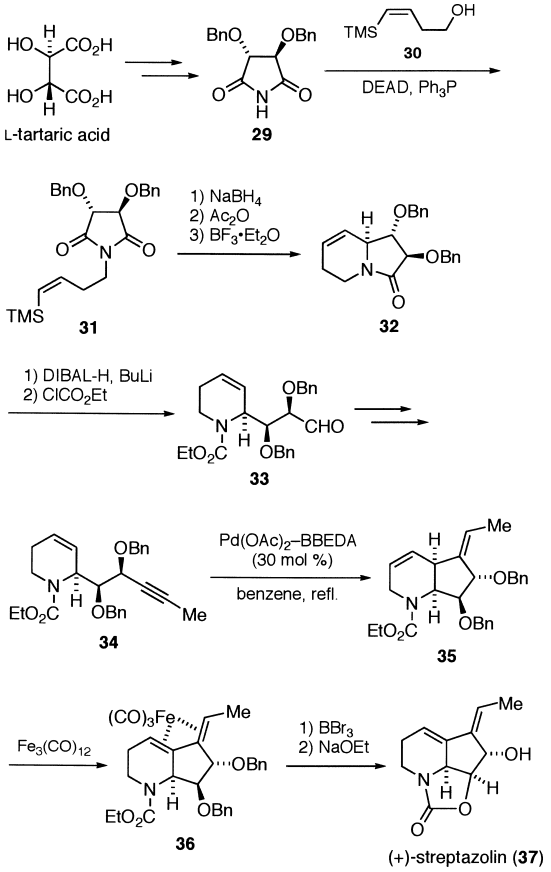

Chart 4

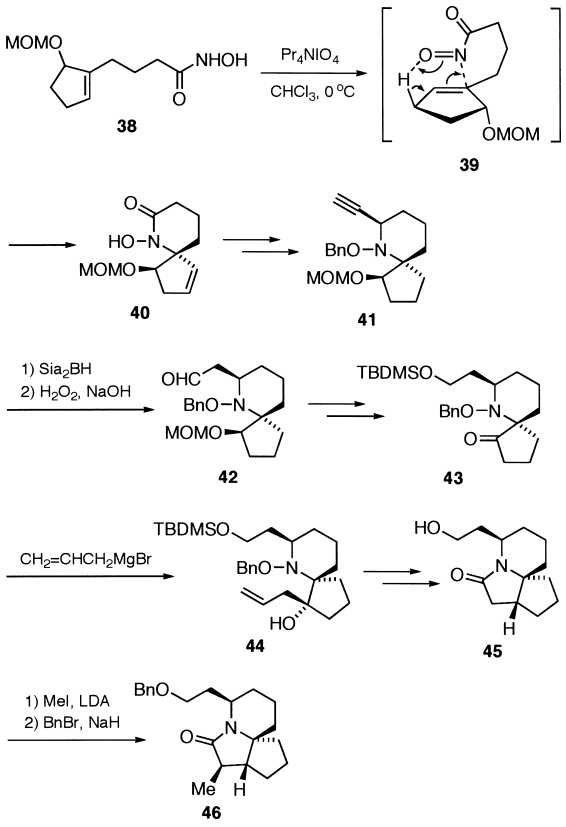

Chart 5

flux, 5 h) to provide the stable tricarbonyl(η^4-1,3-diene)iron complex **36** as a yellow crystalline compound (mp 68 °C). This complexation is very advantageous because of the stabilization of the conjugated diene system. Removal of the $Fe(CO)_3$ fragment and the benzyl protecting groups was performed simultaneously by exposure of **36** to BBr_3 (CH_2Cl_2, −90 °C), and the glycol obtained was treated with sodium methoxide in methanol at reflux to provide (+)-streptazolin (**37**).

4. Formal Syntheses of Halichlorine and Pinnaic Acid[35,36]

Halichlorine (**55**) is a novel marine alkaloid isolated in 1996 by Uemura and co-workers from the Japanese sponge *Halichondria okadai* KADOTA.[37,38] The structurally related natural product pinnaic acid (**51**) was isolated by the same research group from the Okinawan bivalve *Pinna muricata*.[39] The absolute configuration of halichlorine (**55**) was determined by chemical correlation of a degradation product.[38] This group of natural products share in common a 6-azaspiro[4.5]decane ring system. The unique structures and potentially valuable biological activities of these alkaloids have prompted intense synthetic interest culminating in several routes to the core azaspirodecane system.[40] The total syntheses of halichlorine (**55**) and pinnaic acid (**51**) were recently achieved by Danishefsky's group,[41—45] leading to revision of the structure originally proposed for pinnaic acid and establishment of the relative and absolute stereochemistry of these alkaloids **55** and **51**.

In our synthetic approach, we envisioned that synthesis of the azaspirodecane core of **55** and **51** would be accessible by utilizing methodology based on intramolecular ene reactions[46] of acylnitroso compounds, although these interesting reactions have found limited application in natural products synthesis compared with the corresponding Diels–Alder cycloadditions.[47] Thus, the hydroxamic acid **38** was subjected to the oxidative conditions using tetrapropylammonium periodate in $CHCl_3$ at 0 °C. Under these conditions, the desired acylnitroso species **39** was generated, and it underwent spontaneous ene reaction to give directly the spiro compound **40** as a single diastereomer in good yield (82%) (Chart 5). Remarkable facial stereoselectivity in this reaction is understandable on the basis that the nitroso group approaches the less hindered face of the cyclopentene ring. The next task was to introduce a two-carbon side chain at the eventual C-5 position. To this end, the *N*-hydroxy group was benzylated, and treatment with lithium acetylide–ethylenediamine complex served to introduce an alkynyl unit (**40**→**41**). The terminal acetylene was converted into a formylmethyl unit by hydroboration, and the resulting aldehyde **42** was transformed into the spirocyclic ketone **43**. Addition of allylmagnesium bromide to **43** occurred exclusively on the pro-*R* face of the carbonyl, as the other face is obstructed by the benzyloxy group, leading to the tertiary alcohol **44** in almost quantitative yield. After elaboration of **44** into the tricyclic lactam **45**, LDA-mediated methylation with iodomethane was performed to give a mixture of C-14 epimers favoring (15 : 1) the desired epimer, which was protected by *O*-benzylation to form **46**.

Attempts were made to open the lactam **46**, but no reaction was observed with $LiNH_2BH_3$.[48] Even prolonged exposure

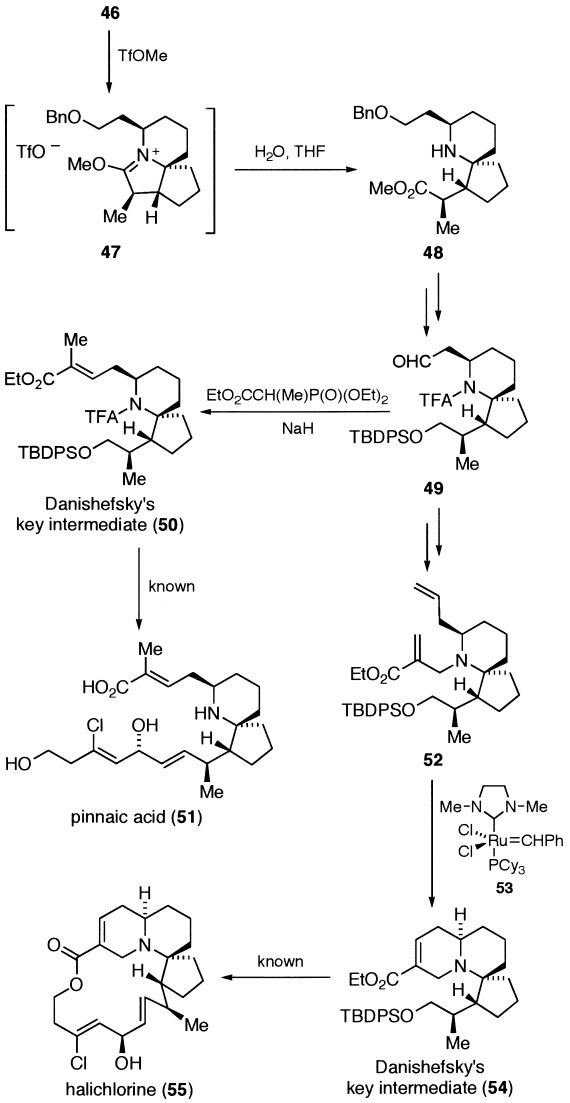

Chart 6

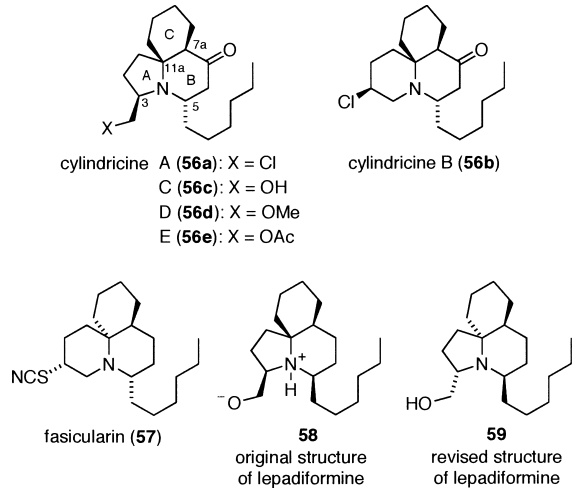

Fig. 2. Representative Tricyclic Marine Alkaloids Isolated from the Ascidians

(40 h) to refluxing aqueous KOH led to recovery of **46**. The corresponding *O*-methyl lactam (Me instead of Bn in **46**) was also not opened by heating in concentrated hydrochloric acid. The lactam **46** was eventually opened by *O*-methylation with methyl triflate and hydrolysis of the intermediate iminium ion **47** to produce **48** (Chart 6). Horner–Emmons–Wadsworth olefination of the aldehyde **49**, derived from **48**, yielded the TBDPS-protected Danishefsky key intermediate **50**. Since **50** previously has been converted to pinnaic acid (**51**),[44,45] a formal synthesis of racemic **51** was thus achieved.

Our attention was next directed toward the synthesis of the azaspirocyclic quinolizididine **54**, the ethyl ester analogue of the Danishefsky key intermediate in the total synthesis of halichlorine.[41—43] Thus, the aldehyde **49** was converted to the diene **52** by sequential Wittig methylenation, *N*-deprotection with $NaBH_4$, and introduction of the alkenyl chain into the secondary amine with the allylic bromide. It is noteworthy that the hindered nitrogen in the secondary amine can be alkenylated with a reactive allyl unit. Ring-closing metathesis of the diene **52** was almost quantitative with the Grubbs II catalyst **53** affording **54**, which is the racemic version of an intermediate in the Danishefsky routes[42] to halichlorine (**55**).

5. Total Syntheses of Tricyclic Marine Alkaloids

Ascidians have been proven to be a particularly rich source of a variety of structurally fascinating and bioactive nitrogen compounds.[49—54] Since the first members were reported in 1993, 11 cylindricines A—K have been identified from the Tasmanian ascidians *Clavelina cylindrica* as new marine alkaloids[55—57] with a tricyclic ring system unprecedented among natural products, possessing a perhydropyrroloquinoline or a perhydropyridoquinoline. Shortly after the first isolation of cylindricines A (**56a**) and B (**56b**)[55] the isolation and structure elucidation of a closely related marine alkaloid, named lepadiformine, from the ascidian *Clavelina lepadiformis* collected in the Mediterranean near Tunisia[58] in 1994 and later from *Clavelina moluccensis* found along the Djibouti coast[59] was reported by Biard and co-workers. It was found to be moderately cytotoxic toward various tumor cell lines *in vitro*. Moreover, a recent study indicated that lepadiformine is very active in the cardiovascular system *in vivo* and *in vitro* and suggested that it has antiarrhythmic properties.[59] On the basis of extensive spectral analysis, this alkaloid was assigned the unusual zwitterionic structure **58**.[58] Although its specific rotation value in a chloroform solution was reported to be zero, it is believed that lepadiformine is not racemic. In addition to these tricyclic alkaloids, fasicularin (**51**) was discovered in 1997 by Patil and co-workers[60] from the Micronesian ascidian *Nephteis fasicularis*, which has selective activity against a DNA repair-deficient organism and is cytotoxic to Vero cells. The structure and relative stereochemistry of **57** were deduced on the basis of NMR studies, though the absolute configuration is still unknown.

When our project toward the total synthesis of lepadiformine and related tricyclic alkaloids started in 1997, while approaches for the total syntheses of cylindricines A, D, and E (**56a**, **d**, **e**)[61] had been developed, no synthetic investigations had been reported on lepadiformine as well as fasicularin. We have achieved the first total synthesis of racemic fasicularin and lepadiformine, the latter of which led to a revision of the proposed structure **58** of lepadiformine to **59**.[62,63] We also have achieved the enantioselective synthesis of

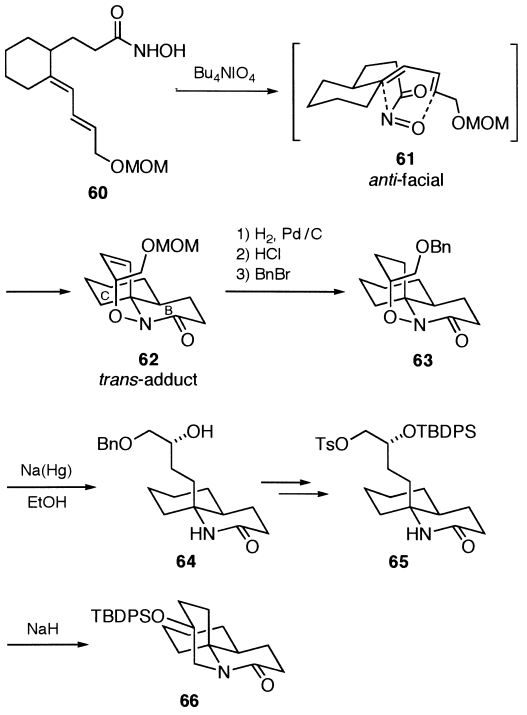

Chart 7

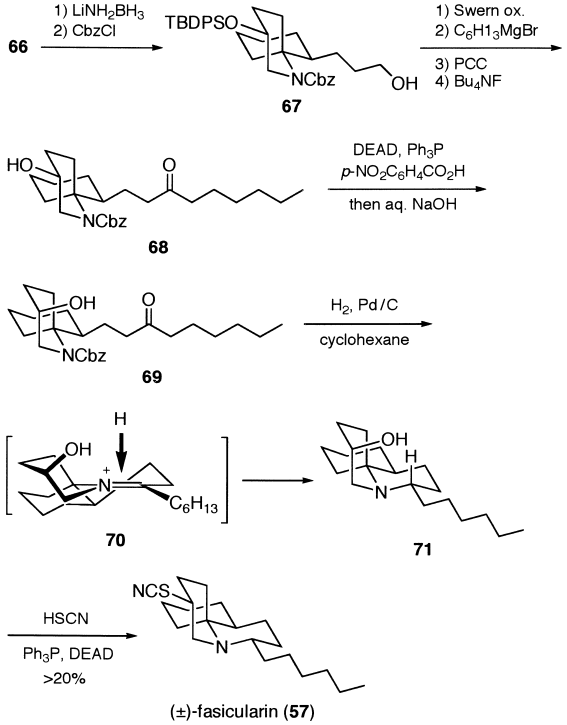

Chart 8

(−)-lepadiformine[64,65] that allowed us to assign the 3*S*,5*R*,7a*S*,11a*S* configuration for the natural product.[66,67]

5.1. Synthesis of (±)-Fasicularin[63] We began our approach to the synthesis of fasicularin (**57**) with the intramolecular hetero-Diels–Alder reaction of the acylnitroso compound. Upon oxidation of the hydroxamic acid **60** with Pr_4NIO_4, the in situ generated acylnitroso compound was subjected to intramolecular [4+2] cycloaddition *via* an antifacial conformer **61**, in which the tethering side chain is equatorially disposed, affording predominantly the *trans*-fused adduct **62** (Chart 7). This compound was converted to **63** and subjected to N–O bond cleavage with sodium amalgam to give the bicyclic lactam **64**. Cyclization of the tosylate **65**, derived from **64**, to the tricyclic lactam **66** was accomplished using sodium hydride in THF at reflux.

Since attempts to introduce the hexyl side chain into the lactam ring in **66** were unsuccessful, ring-opening of the lactone ring was deemed necessary for the attachment of the hexyl side chain. Thus, **66** was exposed to $LiNH_2BH_3$ leading to reductive ring-opening,[48] and it underwent subsequent N-protection to give the alcohol **67** (Chart 8). Swern oxidation of **67** followed by sequential addition of the hexyl Grignard reagent, PCC oxidation, and removal of the silyl protecting group provided the hydroxy ketone **68**. Subsequent inversion of configuration at the secondary alcohol center in **68** using the Mitsunobu procedure[68] led to the epimerized alcohol **69**. We first examined the reductive cyclization of **69** in ethanol, which proceeded under the hydrogenolytic conditions with palladium on carbon to provide a 1 : 1.7 mixture of the tricyclic products **71** and its 6-epi isomer favoring the undesired latter isomer. This result indicates that the use of a polar solvent does not lead to face selectivity of the hydrogenation in the desired sense, presumably due to the competitive association of the solvent molecule with the metal surface,[69] which diminishes the directing effect of the hydroxy group in the iminium intermediate **70**. We envisaged the hydrocarbons as a nonpolar solvent, which do not compete for binding sites of the catalytic surface, thus enforcing the hydroxyl group–catalyst association and thereby favoring formation of the desired 6α-hexyl isomer **71**. Accordingly, the catalytic hydrogenation of **69** was carried out using cyclohexane, whereby the stereochemical outcome of the cyclization was found to be reversed as expected, affording the desired 6α-hexyl isomer **71** which predominated in a ratio of 5.2 : 1, over its 6-epi isomer. Treatment of **71** with the isothiocyanatophosphonium salt[70,71] resulted in no reaction (at −45 °C to room temperature) or formation of a small amount of the isothiocyanate (at 60 °C); however, Mitsunobu condensation (Ph_3P, DEAD, benzene)[72] with thiocyano acid (HSCN) proceeded with complete inversion of configuration at the reaction center to provide (±)-fasicularin (**57**), albeit in low yield (20%) and with concomitant formation of an elimination product (54%) and an isothiocyanate (2%). The synthetic material of (±)-**57** so obtained showed ^{1}H- and ^{13}C-NMR spectra in full agreement with those of natural fasicularin, which verified the structure and relative stereochemistry proposed in the literature[60] for the natural product.

5.2. Synthesis of (±)-Lepadiformine[63] While our research program to explore the synthesis of lepadiformine was ongoing, Weinreb *et al.*[73,74] reported the synthesis of the putative structure **58** of lepadiformine and found their synthetic material to be different from natural lepadiformine. At the same time, Pearson *et al.*[75,76] described the synthesis of a series of tricyclic amino alcohols constituting the *cis*-perhydroquinoline ring system which corresponds to three of the four possible diastereo isomers of **58** at C-3 and C-5; however, none of these compounds was found to be compatible with lepadiformine. These results called into question the validity of the published structure of lepadiformine and also ruled out

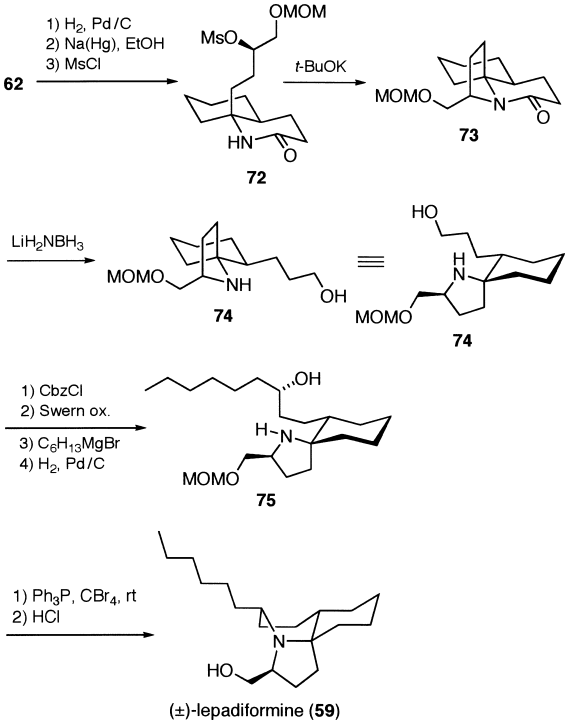

Chart 9

the possibility that lepadiformine consists of the *cis*-perhydroquinoline ring system, suggesting that it might be attributed to a structure like **59** constituting the *trans*-fused perhydroquinoline ring system as in fasicularin. We therefore envisioned that compound **59** could be constructed by utilizing the above-described cycloadduct **62**, the intermediate for the synthesis of fasicularin, as the starting material having the *trans*-fused octahydroquinolinone unit.

To investigate this approach, **62** was subjected to olefin hydrogenation followed by reductive cleavage of the N–O bond and mesylation to give the mesylate **72**, which upon treatment with *t*-BuOK furnished the tricyclic lactam **73** (Chart 9). Reductive lactam ring-opening of **73** using $LiNH_2BH_3$[48] and subsequent manipulation of the resulting azaspirocyclic alcohol **74** afforded **75**. Exposure of **75** to CBr_4 and Ph_3P led to smooth dehydrocyclization[13] with complete inversion of the configuration at C-3′ to the tricyclic amine, which was subjected to deprotection of the MOM protecting group and subsequent basic treatment to provide (±)-**59** as an oil. Further treatment of this material with methanolic HCl followed by evaporation of the solvent resulted in the hydrochloride salt of (±)-**59** as a solid. This provided single crystals from recrystallization in ether, thus allowing structural assignment to be unambiguously secured by X-ray analysis (Fig. 3),[77] which revealed the stereochemistry of (±)-**58**·HCl with the B ring in a somewhat unusual boat (twist-boat) form with the preferred adoption of an equatorial orientation of the hexyl side chain. Although both ^{1}H- and ^{13}C-NMR spectral data for synthetic (±)-**59** as the free base were distinctly different from those published[58] for natural lepadiformine, measurement of the ^{1}H- and ^{13}C-NMR spectra of the synthetic hydrochloride salt (±)-**59**·HCl allowed direct comparison with the spectra on natural lepadiformine kindly provided by Professor Biard, revealing an exact match. This finding strongly

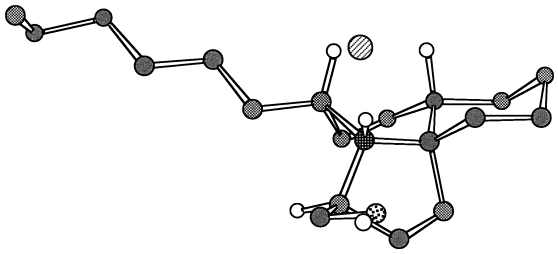

Fig. 3. The X-Ray Structure (Chem3D Representation) of Synthetic (±)-Lepadiformine Hydrochloride [(±)-**59**·HCl]

implies that the structure of natural lepadiformine reported in the literature[58] was actually that of the hydrochloride salt of structure **59**; this is understandable since natural lepadiformine was isolated *via* evaporation of an HCl extract.[58] These results therefore clearly indicate that structural formula **58** involving the zwitterionic structure originally assigned[49—54] to natural lepadiformine should be revised to **59** as shown. Interestingly, the HCl salt of synthetic racemic **59** is crystalline, whereas natural lepadiformine (also the hydrochloride) is an oil.

5.3. Synthesis of (−)-Lepadiformine[64,65] After the above establishment of the relative stereochemistry of lepadiformine, two syntheses of racemic lepadiformine were reported by Weinreb[78] and Funk[79] based on spirocyclization of an allylsilane–*N*-acyliminium ion and amidoacrolein-derived Diels–Alder reaction, respectively. However, because the natural product is not crystalline and its crystalline derivatives could not be prepared, efforts to obtain an X-ray structure of natural lepadiformine for the determination of the absolute configuration have so far been unsuccessful.[77] This prompted us to undertake the enantioselective synthesis of lepadiformine and to determine the absolute configuration of the natural product.

A crucial element in our approach to the target compound was the *N*-acyliminium-ion-initiated olefin cyclization to elaborate the azaspirocyclic core. *N*-Acyliminium ion–olefin cyclizations, which lead to spirocyclic compounds, were initially developed by Speckamp *et al.*[80—82] and Evans *et al.*,[83] and recently applied successfully in Weinreb's lepadiformine synthesis.[78] Described herein is a new variant of the *N*-acyliminium-ion-initiated intramolecular spirocyclization in which a conjugated diene was exploited as a π nucleophile and has been proved to be quite effective for the highly stereoselective and extremely short approach to **59**.

When a solution of **76** in toluene–THF (95 : 5) was treated with formic acid at 0 °C for 2 h, *in situ*-generation of the *N*-acyliminium ion followed by spirocyclization proceeded with synchronous formation of the new C–O bond at C-3′ leading to exclusive preferential formation of the (6*S*)-azaspirocyclic isomer **78** in 88% yield (Chart 10). Notably, the spirocyclization of **76** *via* the formation of the *N*-acyliminium ion **77**, which bears a conjugated diene, proceeded quite smoothly and was completed in a short time, in marked contrast to the case with the reported spirocyclization of *N*-acyliminium ions bearing nonconjugated olefins, which requires long reaction time.[84]

The formate ester **78**, which is epimeric at C3′, thus obtained underwent basic hydrolysis and then MnO_2 oxidation to form the α,β-conjugated ketone **79**. (*S*)-BINAL-H reduc-

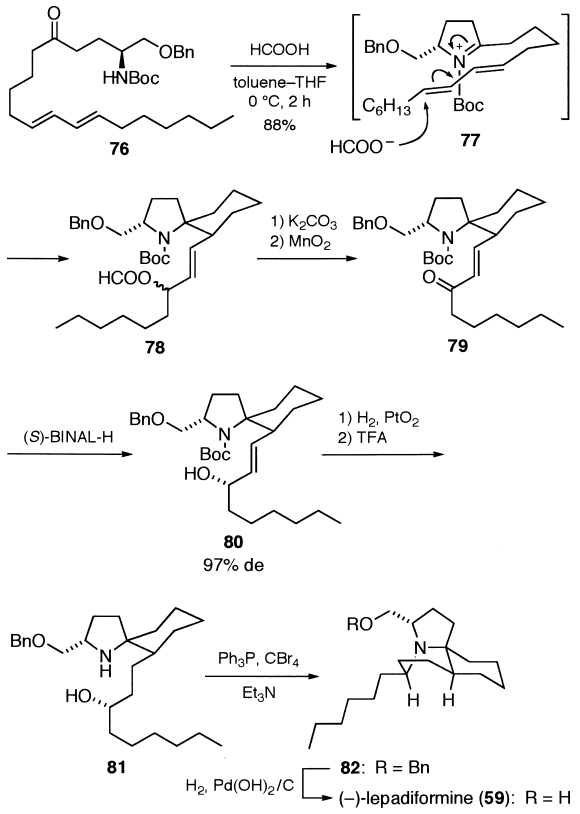

Chart 10

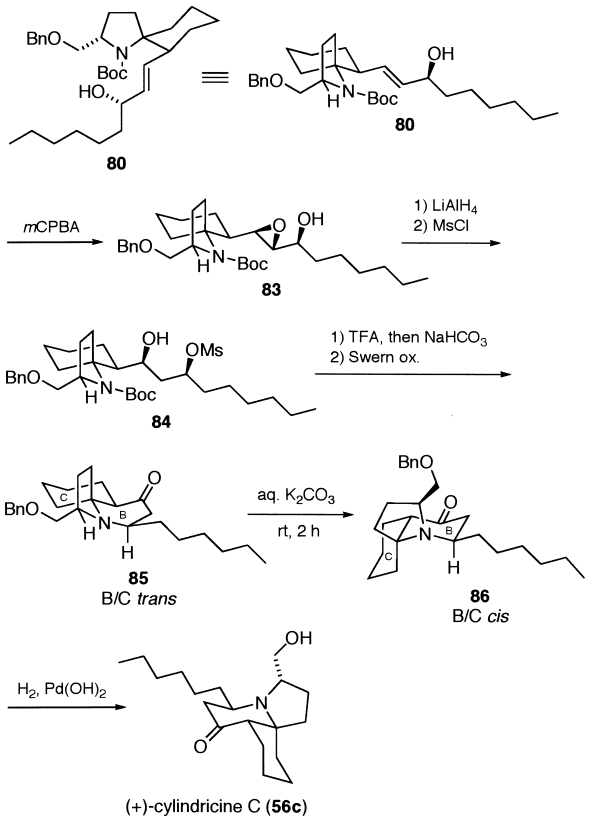

Chart 11

tion[85] provided the (3′*S*)-alcohol **80** (97% de), which then underwent hydrogenation over PtO_2 followed by removal of the Boc protecting group. The resultant amino alcohol **81** was subjected to cyclodehydration using CBr_4 and PPh_3[13] to give the tricyclic amine **82** with complete inversion of the configuration at C-3′. Hydrogenolytic removal of the benzyl protecting group of **82** furnished lepadiformine (**59**) whose spectral properties were identical in all respects with those of an authentic sample of racemic lepadiformine (±)-**59** previously prepared[63] by us. The optical rotation of synthetic alkaloid **59** was measured: $[\alpha]_D^{28}$ −15.0° (c=0.37, MeOH) for the free base (oil) and $[\alpha]_D^{26}$ +2.6° (c=0.54, $CHCl_3$) for the hydrochloride salt (colorless gum). Although comparison of the optical rotation of our synthetic sample with that of the natural product was impossible since the rotation of the natural product (actually the hydrochloride salt[63]) had been reported[49—54] to be zero, synthetic (−)-**59** proved to be identical with natural lepadiformine, kindly provided by Professor Biard, on the basis of their chromatographic behavior on the HPLC chiral phase.[64] This allowed the absolute configuration of the natural product to be assigned as 3*R*,5*S*,7a*R*,11a*R*.[86]

5.4. Synthesis of (+)-Cylindricine C[63] Having developed an extremely efficient approach to lepadiformine (**59**) utilizing the spirocyclic alcohol **80** stereoselectively derived from the enone **79**, we next attempted to exploit this intermediate **80** for the synthesis of the related marine alkaloid cylindricine C (**56c**).[87—92]

Cylindricine C (**56c**), possessing the perhydropyrroloquinoline framework, is intimately related to lepadiformine (**59**) differing structurally only in the *cis*/*trans* stereorelationship of the B/C ring system and the functionality at C-7. While the synthesis of both enantiomers of cylindricine C has been achieved,[87—89] the absolute configuration of natural cylindricine C remains unassigned since the optical rotation of the natural product has not been determined and no sample remains of the isolated cylindricine C. Biogenetically, it can be envisaged that both ascidian alkaloids **56c** and **59** presumably arise from an amino acid-derived azaspirocyclic compound, corresponding to the A/C ring of these alkaloids, by closure of the B ring (bond formed C-7—C-7a). Consequently, we assumed that the correct absolute stereochemistry for natural cylindricine C is defined by **56c**, which is epimeric with the natural lepadiformine (**59**) at C-7a.

Oxidation of the olefin in the unsaturated alcohol **80** with *m*CPBA stereoselectively afforded the *syn*-hydroxy epoxide **83** (68% yield) (Chart 11) along with the *anti*-hydroxy epoxide (14% yield). Reductive ring-opening of the epoxide **83** with $LiAlH_4$ proceeded regioselectively to give the 1,3-diol, which was regioselectively mesylated to form **84**. After deprotection of the Boc group in **84**, treatment with aqueous $NaHCO_3$ resulted in smooth ring closure (room temperature, 30 min), affording the tricyclic amino alcohol, which was oxidized under Swern conditions to form the tricyclic ketone **85**. To define the conformation of **85** including the *trans*-1-azadecalin B/C ring system, molecular mechanics (MM2) calculations using CAChe mechanics program (version 4.0) were carried out, showing that the piperidone ring (B ring) of **85** is in the boat conformation at lowest energy (Fig. 4). On the other hand, MM2 calculations on its C-7a epimer **86** which possesses the *cis*-fused BC ring system with a chair–chair conformation indicated that **86** is more stable by 5.5 kcal/mol than **85** in their optimized structures. These cal-

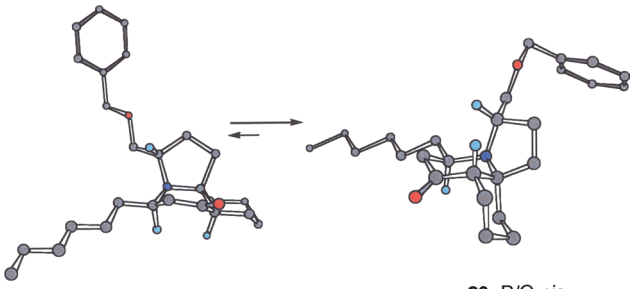

Fig. 4. Energy-Minimized Structures of **85** and **86** (CaChe 4.0 MM2 Calculation)

culations suggested that **85** would easily epimerize to provide the more thermodynamically stable **86** having the stereochemistry required for the structure of cylindricine C. Thus, upon exposing **85** to aqueous K_2CO_3 in methanol at room temperature for 2 h, complete epimerization at C-7a occurred to form **86** as a single isomer. Finally, the benzyl group of **86** was removed by hydrogenolysis to give (+)-cylindricine C (**56c**).

5.5. Synthesis of (−)-Fasicularin[65] Encouraged by the results described above, we next explored the possibility of extending the conjugate spirocyclization methodology to the enantioselective synthesis of fasicularin (**57**). As described above, the total synthesis of (±)-fasicularin was first reported by us in 2000.[63] After this report, the second synthesis of (±)-**57** using a 2-amidoacrolein Diels–Alder cycloaddition has been published by Funk and Maeng,[93] and more recently the formal construction of **57** starting from (*S*)-5-hydroxy-2-piperidone has been reported by the Dake group.[94] However, these syntheses[63,93] suffered from very poor overall yields (0.9% and 2.4%), mainly due to difficulty in incorporation of the thiocyanato group in the final step which was performed by a Mitsunobu procedure (HSCN, Ph_3P, DEAD) that we have exploited previously[63] or an SN2 displacement of the mesylate by Bu_4NSCN[93] resulting in very low yield (20%) of fasicularin in each case. Thus, there is a great need to develop a new thiocyanation method that can overcome such problem.

Our synthesis started with the spirocyclic ketone **79**, which was used as a common intermediate in the synthesis of (−)-lepadiformine (**59**) and (+)-cylindricine C (**56c**). Thus, **79** was subjected to reduction with (*R*)-BINAL-H to give the (3′*R*)-alcohol **87** with 9 : 1 diastereoselectivity (Chart 12). Hydrogenation of olefin, followed by deprotection of the amino group, cyclocondensation (Ph_3P, CBr_4),[13] and hydrogenolytic removal of the benzyl group provided the tricyclic amino alcohol **88**. Upon exposing **88** to NH_4SCN under the Mitsunobu conditions, a 1 : 1 mixture of (−)-fasicularin (**57**) and **89** was obtained in 94% combined yield. When a solution of the latter product **89** in acetonitrile was allowed to stand at room temperature for 72 h, (−)-fasicularin was further obtained in 91% yield. Formation of fasicularin was thus attained in remarkably high combined yield of 90% from the tricyclic amino alcohol **88**. Fasicularin so obtained, having spectral properties in agreement with those previously reported,[60,63] proved to be enantiomerically pure by chiral HPLC analysis (Dicel Chiralpak AD column) in

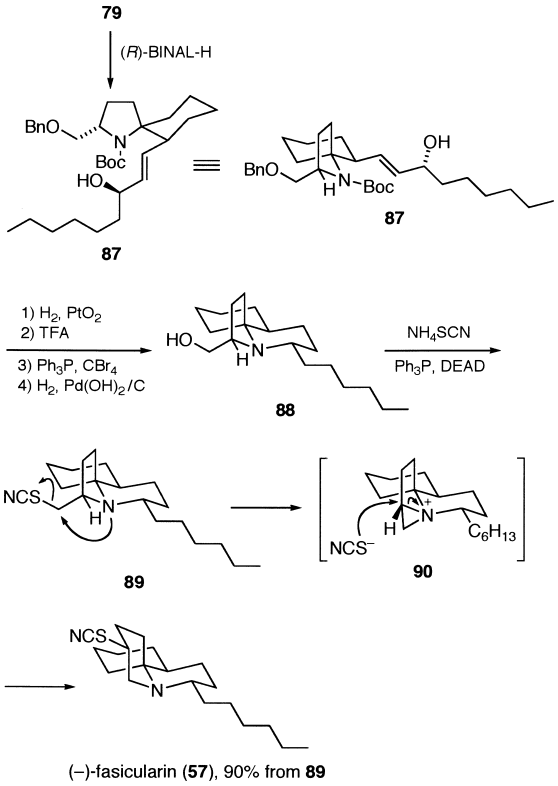

Chart 12

comparison with (±)-**57** previously obtained by us,[63] and was found to have $[\alpha]_D^{21}$ −4.4 (MeOH). The present fasicularin formation can be rationalized by considering the initial formation of the aziridinium ion **89** that undergoes nucleophilic attack of thiocyanate ion with subsequent expansion reaction of the aziridine.

The first enantioselective total synthesis of (−)-fasicularin (**57**) was thus accomplished in nine steps with an overall yield of 41% from the common intermediate **79**. Although the absolute configuration and the optical rotation of fasicularin have not yet been determined (no literature data are available) and no original natural sample remains,[95] since the optical rotation value for **57** was first obtained by the present synthesis, determination of the absolute configuration of fasicularin will become possible by re-isolation of the natural product and optical rotation measurement.

6. Total Synthesis of Incarvillateine[96,97]

Incarvillateine (**91**) is a member of a new class of monoterpene alkaloids carrying a characteristic cyclobutane ring (Fig. 5), first isolated from the aerial parts of *Incarvillea sinensis* LAM., which is a wild plant distributed in the northern area of China, that has been traditionally used in treating rheumatism and relieving pain as an ancient Chinese crude drug designated as "Jiaohao".[98] This compound has been found to show potent analgesic activity in a formalin-induced pain model in mice and this action was in part blocked by naloxone, indicating a partial interaction with a central opioid mechanism.[99] In subsequent tests on mice, it was observed that the analgesic effect of **91** was significantly blocked by theophylline, an adenosine receptor antagonist, suggesting that the potent antinociceptive action of **91** is

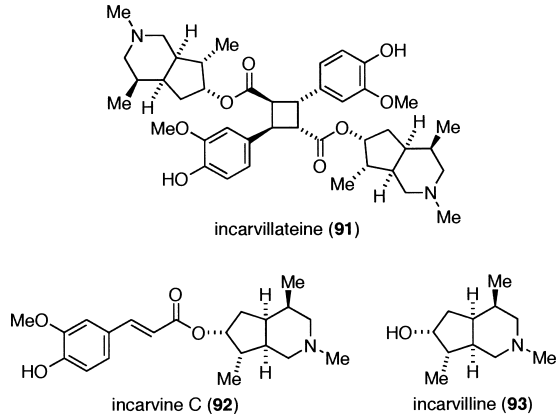

Fig. 5. Structures of Incarvillateine and Related Alkaloids

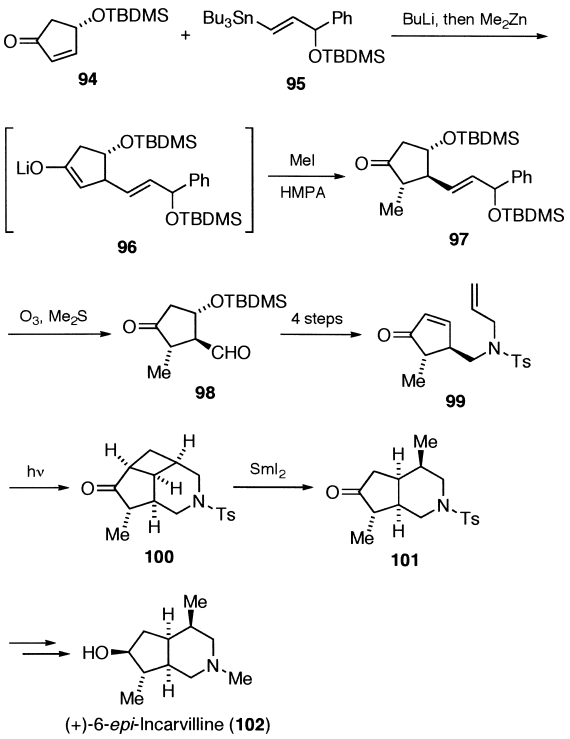

Chart 13

mainly mediated *via* an adenosine receptor mechanism rather than an opiate receptor mechanism.[100] Structure–activity relationship studies suggested that the cyclobutane moiety of **91** plays an important role in expression of antinociceptive action because incarvine C (**92**)[101] and incarvilline (**93**),[102] isolated from the same plant, and related compounds lacking the cyclobutane ring exhibited no or weak activity.[103]

The potential usefulness of **91** as a nonopioid analgesic agent and its unusual structural features have prompted us to initiate an effort directed toward its synthesis. The synthesis started with the three-component coupling reaction[104] using the cyclic enone **94**. Thus, the (*E*)-alkenylstannane **95** was subjected to transmetalation to generate the corresponding zincate, which was allowed to react with the (*S*)-enone **94**, followed by quenching of the resulting enol **96** with iodomethane to give 2,3,4-trisubstituted cyclopentanone **97** (Chart 13). Although **97** was an inseparable 1 : 1 mixture of diastereomers epimeric at the stereogenic center bearing the

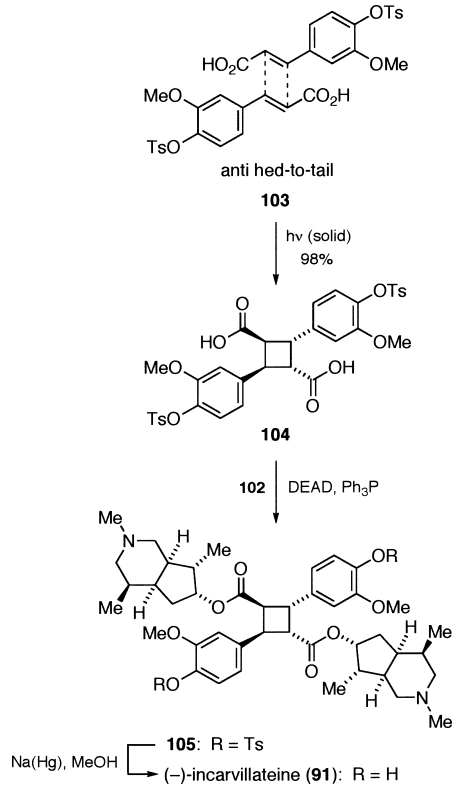

Chart 14

siloxy group on the olefinic side chain, the reaction proceeded with complete all-*trans* stereoselection. Ozonolysis of **97** and further manipulation of the resulting aldehyde **98** produced the *N*-allyl enone **99** as a single stereoisomer, which upon UV irradiation underwent intramolecular [2+2] cycloaddition[105] to afford the cyclobutyl ketone **100**. The *cis*-perhydro-2-pyrindine **101** obtained by reductive cyclobutane ring-opening of **100** with samarium(II) iodide[106] was converted into (+)-6-*epi*-incarvilline (**102**) in five steps involving stereoselective reduction of the ketone with $NaBH_4$.

UV irradiation of the ferulic acid **103** in the solid state led stereospecifically to anti head-to-tail [2+2] photodimerization.[97,107] Condensation of the resulting α-truxillic acid **104** with 2 equiv of the above-described (+)-6-*epi*-incarvilline (**102**) under Mitsunobu conditions, followed by deprotection of the tosyl groups provided (−)-incarvillateine (**91**) (Chart 14). The completion of the first total synthesis of incarvillateine firmly established the structure and absolute stereochemistry of this interesting antinociceptive monoterpene alkaloid as **91**.

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