1電子移動反応の新展開

ー生理活性バイオマテリアルズ構築への利用ー

（課題番号　13640530 ）

平成１３年度～平成１４年度科学研究費補助金

（基盤研究（C）(2)）研究成果報告書

平成１５年３月

研究代表者　　依田秀実

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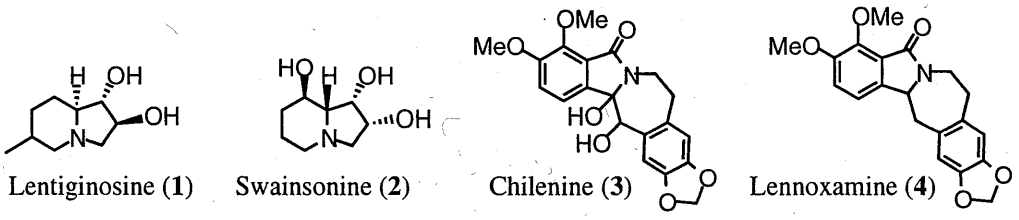
はしがき

連続不斉中心を有する多置換のアゼチジン（含窒素４員環）、ピロリジン（含窒素５員環）、あるいはインドリジジン系アルカロイド（含窒素ビシクロ[4,3,0]）は、その特異な構造と強力な抗腫瘍活性等を持つことから多くの研究者の注目を集めているが、その中でも水酸基による連続不斉中心化合物群は***alkaloidal sugar mimics*** として知られ、極めて取り扱いが困難にもかかわらず、様々な酵素(***glycosidases***)に対して協奏的あるいは逆行的に極めて強い阻害活性を示すため、重要な生体物質として周知されている。

そこで本申請では新たな研究の展開として、申請者によって新規に開発されたアミド系化合物のSmI_2による１電子移動反応を利用することによって、近年単離、発見され、これまでの間接的手法ではその基本骨格の構築が困難とされている種々の強い生理活性（抗腫瘍、抗菌、抗ガン活性等）を有したヒドロキシ置換インドリジジン、およびイソインドロベンズアゼピン系アルカロイド類の直接的な新構築方法を模索、検討し、実践的応用プロセスの開発を行うことを目的としている。

SmI_2を用いた１電子移動反応はこれまでに数多く報告されているが、極めて反応性の乏しいアミド化合物を用いる手法は、２例の単位反応が報告されているのみで生理活性物質構築への利用は皆無である。ところが本年（2000年）、申請者はこの反応性の低さを「イミド」とすることにより、初めてカルボニル化合物とのcross-coupling反応に成功し、合わせて立体選択性の極めて高い還元反応や脱酸素反応を報告している。一方その直後、フランスのNamyらはN-アシルラクタムが同様にSmI_2の存在下で、カルボニル化合物と開環をともなったcross-coupling反応を行うことを明らかにしている。そこで本申請では、新たなアミド系化合物を用いたSmI_2による１電子移動反応の開発を行うとともに、先に報告した新しい反応を利用し、これまでの手法では直接的な構築が困難であった***alkaloidal sugar mimics*** 群のうち、特に***glycosidase*** に強力な阻害作用を有し、つい最近抗HIVウィルス活性をも示すことが明らかにされたインドリジジン系化合物、Lentiginosine (**1**)やSwainsonine (**2**)、および植物ヘビノボラスより単離され、

強力かつすばやい健胃効果と消化促進作用を有するイソインドロベンズアゼピン系アルカロイド、Chilenine (3)やLennoxamine (4)の全構築への応用を目的とした。



Lentiginosine (1)　Swainsonine (2)　Chilenine (3)　Lennoxamine (4)

このような水酸基を含む複素環系生理活性天然物の多くは、われわれ生体系を維持、コントロールする重要な物質であるが、不安定な場合がほとんどであり、取り扱う研究室も極めて少なく、それぞれ独自の操作方法に関するknow-howを有している。本申請でもこれまでに蓄えたこれら不安定アルカロイドに関する知識を最大限利用し、加えて今回新しく開発したSmI_2による1電子移動反応に適用することにより、新しく、かつ極めて興味深い生理活性化合物の実践的構築法の確立を目指した。

まとめると、本報告書は次の六つの章より成り立っている。

第一章　Recent Advances in the Synthesis of Naturally Occurring Polyhydroxylated Alkaloids

第二章　SmI_2-promoted Tandem Desulfurization and Reductive Coupling Reactions of Aromatic Lactams with Carbonyl Compounds

第三章　A Novel Synthetic Approach to Isoindolobenzazepine Alkaloid, Chilenine, Employing SmI_2-mediated Pinacolic Coupling Reaction

この分野の研究は日進月歩極めて早い速度で進行しており、各種不斉反応への応用について詳細に研究されている。しかしながら、まだまだ満足のいく高度な合成手法の開発には至っていない。本研究では、上述した研究の方針により、さ

らなる選択性の追及と化学的手法による不斉反応の開発と、生理活性天然物の全合成を推す進めようと考えている。一つの分子中にたくさの作用点のある生物化学上の酵素を用いた反応に比し、その数の極めて少ない化学合成分子をいかに上手に構築し、鋭敏な化学的手法を用いてこれを凌ぐか、また、複雑な構造を持つ化合物上で、どのようにしたら期待するような完全なコントロールを行えるか、という観点を含めて、環境に配慮した新しい合成手法の開発は意義深いと考えられる。

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第３３回中部化学関係学協会支部連合秋季大会、2002.10.6.

目　次

Chapter 1

Recent Advances in the Synthesis of Naturally Occurring Polyhydroxylated Alkaloids

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Abstract:

A major fraction of the organic compounds isolated from nature are comprised of nitrogen, oxygen, or sulfur heterocycles. Nirogen-containing substances called alkaloids among them represent a majority of the important medicinal agents discovered in nature. The development of new synthetic methodology for the preparation of such alkaloids and the application of these methods to the synthesis of alkaloidal natural products continue to be an active and exciting area of research in organic chemistry. Especially, polyhydroxylated alkaloids possessing an azetidine-, pyrrolidine-, piperidine-, pyrrolizidine-, or indolizidine-ring structure have attracted a great deal of interest because of their applications from both a biological and a synthetic point of view. Since several reviews have already appeared concerning isolation, structural determination, total synthesis and biological aspects of these compounds independently, the scope of this review is to underline the most recent advances on the synthesis of monohydroxylated, dihydroxylated, and tri- or above hydroxylated bioligically active natural alkaloids containing the ring sturctures described above and related compounds according to those strategies involving prior construction of chiral pools (such as carbohydrates, amino acids, or tartaric acid)-derived crucial lactam intermediates suitable for further chemical elaboration.

Key Words

1) Natural product
2) Azetidine, pyrrolidine, indolizidine, pyrrolizidine alkaloids
3) Lactam
4) Deoxygenation
5) Stereoselective reduction
6) Carbohydrate
7) Tartaric acid
8) Amino acid

Abbreviations

Ac_2O	acetic anhydride
AIBN	azobisisobutyronitrile
$(Boc)_2O$	di-*t*-butyl dicarbonate
CAN	ammonium cerium(IV) nitrate
CbzCl	benzyl chloroformate
DHP	3,4-dihydro-2*H*-pyran
DMAP	*N,N*-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
LDA	lithium diisopropylamide
MCPBA	*m*-chloroperbenzoic acid
MOMCl	chloromethyl methyl ether
$MPMNH_2$	*p*-methoxybenzylamine
MsCl	methanesulfonyl chloride
NMO	4-methylmorpholine *N*-oxide
PCC	pyridinium chlorochromate
TBDPSCl	*t*-butyldiphenylsilyl chloride
TBSCl	*t*-butyldimethylsilyl chloride
TFA	trifluoroacetic acid
TIPSCl	triisopropylsilyl chloride
p-TsCl	*p*-toluenesulfonyl chloride
p-TsOH	*p*-toluenesulfonic acid

1. INTRODUCTION

A large number of polyhydroxylated alkaloids have been extracted from natural sources, mainly plants and microorganisms. An apparent joint structural property of the representatives of this group is that their nitrogen-containing four- (azetidine), five- (pyrrolidine), or six-membered (piperidine) ring, or their fused ring system (pyrrolizidine, indolizidine, and quinolizidine) built up from the above monocycles, is substituted with one or more hydroxyl functions. Many of these products display interesting biological activity as inhibitors of glycosidases [1]. Glycosidases are key enzymes in the biosynthesis and processing of glycoproteins, which are macromolecules involved in recognition (cell-cell, host-pathogene interactions) and in control of biological mechanisms and structures. Thus, substances able to inhibit the biosynthetic pathway of glycoproteins have become important as potential antibacterial [2], antiviral [3] , antitumoral [4], or antidiabetic [5] agents. These inhibitors have also shown potential in the treatment of obesity and hyperlipoproteinemia. Azasugars and polyhydroxyalkaloids have been the objects of intense synthetic efforts in the last decade [1,6] because of their close structural analogy to natural enzyme substrates. These endeavors have initially targeted natural products, generally employing natural sugars as starting materials, and have been extended to all the possible stereoisomers and analogues for studies of structure-activity relationships.

The present review is aimed at summarizing and discussing the synthetic strategies already employed for construction of the hydroxylated natural alkaloids and their structurally related analogues in this laboratory. For this purpose three types of reactions based on manipulation of the functionalized lactams derived from chiral pools have been selected as shown in Scheme 1; i. e., 1) *reduction-elimination* (for the synthesis of an azetidine alkaloid and related compounds), 2) *addition-deoxygenation* (for the synthesis of pyrrolidine and indolizidine alkaloids) and 3) *addition-(stereoselective)reduction* (also for the synthesis of pyrrolidine and indolizidine alkaloids). Recent example on the construction of the bicyclic ring system containing hydroxyl functions will be briefly discussed in order to illustrate new synthetic perspectives in pyrrolizidine (represented by alexine) chemistry.

Scheme 1.

2. REDUCTION-ELIMINATION (for the synthesis of an azetidine alkaloid and related compounds)

The starting materials of the synthetic procedures belonging to this group are amino acids. Because of its versatility as a chiral synthon and its availability, glutamic acid was selected and incorporated into the framework of a hydroxylated azetidine alkaloid in such a way that the asymmetric carbon of glutamic acid corresponds to the *N*-α-asymmetric center of the natural product. Before establishing the total synthesis of this alkaloid, we researched the development of an expeditious and practical process for the synthesis of acyclic amino alcohols, phytosphingosine and tetrahydroxy-LCB, featuring the *reduction-elimination* elaboration of the functionalized homochiral lactam derived from D-glutamic acid [7].

2.1. Synthesis of Phytosphingosine and Tetrahydroxy-LCB

Marine sponges contain unusual lipid components such as phospholipids with long-chain or branched fatty acids [8] and sterols with unconventional side chains [9]. In particular, sphingosine (**1**) and phytosphingosine (**2**) are major backbone building blocks of glycosphingolipids and phosphosphingolipids, important membrane constituents composed of ceramides and phosphorous or sugar residues [10] (Fig. (1)). They play a significant role in biological processes on cell surfaces [11]. The presence of phytosphingosine in mammalian tissues, for example, in kidney [12a] liver [12b], uterus [12c], intestine [12d], skin [12e], and blood plasma [12f] is also well known. In addition, due to the recent interesting discovery of protein kinase C inhibition by **1** [13], considerable attention has been focussed on the lipid parts of sphingolipids and indirect evidence led to the hypothesis that sphingolipid-derived products may function as second messangers [14]. Many synthetic strategies have appeared for the construction of such compounds [15], however, these generally require multistep reactions or

crucial techniques. Our method for the synthesis of phytosphingosine (**2**), tetrahydroxy-LCB **3a** of a new cerebroside recently isolated from the latex *Euphorbia characias* L. [16], and its (5*S*)-isomer **3b** through the same homochiral lactam intermediate is expeditious and practical.

Fig. (1).

Thus, hydroxylactam **4** easily obtained from D-glutamic acid was protected with TBSCl and $(Boc)_2O$, followed by olefination with selenoxide-elimination to afford the unsaturated lactam **5** as shown in Scheme 2. Dihydroxylation of **5** with OsO_4 and subsequent acetonide-protection proceeded smoothly, leading to the single product **6**. Treatment of **6** with tridecanylmagnesium bromide, followed by *reduction* of the corresponding tautomer of keto- and hydroxy pyrrolidine form [17] resulted in the preparation of the alcohol **7** as a diastereomeric mixture. Then, formation of thioimidazolide with (thiocarbonyl)diimidazole and successive *elimination* with Bu_3SnH under radical conditions [18] cleanly provided the deoxygenated product **8**. Finally, **8** was effected by simultaneous deprotection of TBS and Boc groups with TFA to complete the synthesis of **2**. Furthermore, the structure was confirmed by direct conversion from **7** to the known tetraacetate **9**.

Scheme 2.

On the other hand, the syntheses of (5*R*)-tetrahydroxy-LCB **3a** and its (5*S*)-stereoisomer **3b** of new cerebrosides were established as follows (Scheme 3); nucleophilic addition of acetylide anion to the common lactam **6** and then reduction afforded the two diastereomers of **10a** and **10b**, respectively. After silylation of the hydroxyl group in **10a** and **10b**, these were reduced effectively by partial hydrogenation over Lindlar's catalyst leading to the *cis*-olefinic **11a** and **11b**, since accompanying formation of small amounts of saturated products were observed in the

case of direct hydrogenation of **10**. Deprotection of **11a** and **11b** were submitted with TFA simultaneously as described above to produce the desired **3a** and **3b**, respectively. Those structures were characterized after derivatisation to the pentaacetate derivatives **12a** and **12b**.

Scheme 3.

2.2. Synthesis of an Azetidine Alkaloid, Penaresidin B

With the successful transformation method of the functionalized lactam **6** into the corresponding phytosphingosine (**2**) and its derivatives **3** in hand, application to the total synthesis of an azetidine alkaloid was carried out in a similar strategy along the *reduction-elimination* line [19].

Penaresidin A (**13**) and B (**14**), first isolated in 1991 from an Okinawan marine sponge *Penares* sp. by Kobayashi *et al.* [20], exhibit potent actomyosin ATPase-activating activity. After structural characterization as a mixture of the corresponding tetraacetyl derivatives, these were revealed to be the first sphingosine-derived alkaloids [7] possessing an azetidine ring. The syntheses of both a straight-chain analog by Kamikawa *et al.* [21] and three stereoisomers of **13** with (2***S***,3***R***,4***S***)-configurations of the azetidine ring and syn configuration between C-15 and C-16 of the side chain by Mori *et al.* [22] have been recently established [23] and, in addition, the initially proposed structure of penaresidin B was revised to be **14** [24] as shown in Fig. 2 and the absolute configuration at C-15 in **13** and **14** has been determined to be ***S*** [25].

Fig. (2).

Construction of the azetidine ring with the desired contiguous stereogenic centers and the total synthesis of penaresidin B (**14**) are accomplished as follows; homochiral *N*-Boc lactam **6** was

treated with the acetylide elaborated from D-leucine in 9 steps [26] via the acetylene zipper reaction [27], followed by *reduction* of the corresponding tautomer of ketoamide and hydroxy pyrrolidine form [17] to give the alcohol **15** as a diastereomer mixture (Scheme 4). Formation of thioimidazolide and successive radical *elimination* with Bu_3SnH [18] resulted in the clean preparation of **16**. After deprotection of the four hydroxyl groups of **16**, reprotection of the primary alcohol with TBDPSCl and the secondary ones with TBSCl brought about undesirable regioselectivity, leading to the mixture of alcohols **17** and **18** (2:98) in high yield. Fortunately, it has become apparent that the major product **18** was smoothly trasnformed into the desired **17** with 1,4-silyl rearrangement under basic conditions [28]. After chromatographic isolation of **17**, mesylation and cyclization with NaH were subsequently submitted to produce **19** with the azetidine ring containing the same contiguous configurations as those of natural one. Finaly, **19** was treated with Bu_4NF to give the *N*-Boc derivative **20** of penaresidin B (**14**) and the *N*-Boc group was removed to complete the synthesis of **14**. The structure was confirmed by conversion to the known tetraacetate **21** [24].

Scheme 4.

This process containing *reduction-elimination* of the lactam carbonyl function starting from D-glutamic acid to these membrane components represents a short and easily accessible alternative to existing synthetic methods of the long chain bases.

3. ADDITION-DEOXYGENATION (for the synthesis of pyrrolidine and indolizidine alkaloids)

The chirality inherent in carbohydrates is of greatest interest for the synthesis of naturally occurring compounds, and over the last two decades it has led to a rapidly growing speciality in the general field of organic synthesis and many elegant procedures employing carbohydrate precursors have been developed to carry out the asymmetric syntheses of important natural

products. Out of the large number of reported synthetic applications in this laboratory, this section will stress some aspects of the use of *addition-deoxygenation* reactions to the lactam-containing carbonyl function derived from carbohydrates for the total synthesis of pyrrolidine and indolizidine alkaloids.

3.1. Functionalization of Lactams to Highly Substituted Pyrrolidines

To begin with, a stereoselective route to enantiomerically and diastereomerically pure pentasubstituted pyrrolidines was researched by using reductive deoxygenation of quaternary α-hydroxy *N*-Boc pyrrolidine derivatives prepared from alkylation of the functionalized homochiral lactams [17]. As described in Scheme 5, **24** were prepared from commercially available 2,3,5-tri-*O*-benzyl-β-D-arabinofuranose (**22**) through successive amination and extremely stereoselective addition of Grignard reagents, followed by oxidative degradation with PCC [29]. Then, the compounds **24** were transformed into the desired *N*-Boc lactams **25** by 2 steps. Nucleophilic *addition* of Grignard reagent to **25a** thus obtained at low temperature interestingly afforded the labile quaternary α-hydroxy pyrrolidine **26a** which slowly tends to come to equilibrium with its open keto form **27a**. The mixture of **26a** and **27a** was submitted to reduction to give **28a** which was followed by cyclization, leading to the almost non-stereoselective diastereomer mixture of **29a** and **30a**. The newly created stereogenic centers of **29a** and **30a** were easily determined, since **30a** possesses a C_2-axis of symmetry.

Scheme 5.

Next, we investigated the direct Lewis acid-induced *deoxygenation* of quaternary **26a** [30]. When the Grignard adduct to **25a** was treated with Et_3SiH in the presence of Lewis acid, it afforded the deoxygenated pentasubstituted pyrrolidine **29a** exclusively. No other stereoisomer such as **30a** was observed and accompanying formation of small amounts of ketone **27a** resulted from equilibrium of **26a** and *N*-Boc deprotected lactam of **25a** were isolated. We further examined

the reactions employing other lactams. The results are summarized in Table 1. The reaction proceeded with exclusive stereoselectivity to yield the corresponding substituted pyrrolidines **29** in each case. *It is worth noting that no other diastereomeric compound was isolated and consequently it involves no separation of stereoisomers through the entire sequence until 1,2,3,4,5-pentasubstituted pyrrolidine **29** was synthesized from **22**.* We have considered that it would proceed through the attack of Et_3SiH to the *N*-acyliminium ion intermediate [31].

Table 1.

3.2. Synthesis of a Pyrrolidine Alkaloid, Preussin

Based on these synthetic considerations, the availability of that *addition-deoxygenation* strategy has been demonstrated by completion of the asymmetric synthesis of (+)-preussin [32], one of pyrrolidine alkaloids. Thus, (+)-preussin (L-657,398) (**31**) (Fig. (3)), an antifungal antibiotic first isolated in 1988 from fermentation broths of *Aspergillus ochraceus* ATCC 22947, has attracted considerable attention since this compound was shown to inhibit growth of the bacteria, *Candida*, and filamentous fungi, including *Trichophyton menta* and *Microsporum canis* [33]. On the other hand, recently we reported a novel and short synthetic strategy for the preparation of enantiomerically pure (-)-anisomycin [29c] employing the *cis*-selective lactam formation protocol [29]. In this connection it is noteworthy that **31** and its acetate ester show a broader spectrum of antifungal activity against both filamentous fungi and yeasts than the structurally related anisomycin [33].

Fig. (3).

As shown in Scheme 6, the benzyl protecting groups of the functionalized *N*-Boc lactam **25c** described above were removed with Pd(black). Then, highly regioselective acylation with PhOCSCl followed by radical deoxygenation [34] resulted in the preparation of **32**. This was silylated to give **33** and nucleophilic *addition* of nonylmagnesium bromide to **33** provided the labile quaternary α-hydroxy *N*-Boc intermediate. This was readily submitted to reductive *deoxygenation* with Et_3SiH in the presence of Lewis acid, cleanly leading to the pyrrolidine derivative **34** as a single stereoisomer with the desired ***R*** configuration. Finally, **34** was reduced effectively after desilylation to complete the total synthesis of (+)-preussin (**31**) [35].

Scheme 6.

This process, in which (+)-preussin is synthesized from 2,3,5-tri-*O*-benzyl-β-D-arabinofuranose, also involves no separation of stereoisomers throughout the entire sequence and provides a new synthetic strategy.

3.3. Synthesis of an Indolizidine Alkaloid, Lentiginosine

The second interesting presentation involving functionalization of carbohydrate precursors via *addition-deoxygenation* reaction was the synthesis of a dihydroxylated indolizidine alkaloid, (+)-lentiginosine [36]. As noted in the introduction, structurally complex alkaloidal sugar mimics with a nitrogen in the ring have been isolated from plants and microorganisms and inhibit various glycosidases in a reversible and competitive manner [1c,1f,37]. Since such glycosidase inhibitors proved to have the potential to produce antiviral, insect antifeedant, antidiabetic, and anticancer effects, as well as immune modulatory properties, they have held considerable interest in the context of stereoselective heterocyclic synthesis. Noteworthy members among this class of compounds are castanospermine (**35**), swainsonine (**36**) and deoxynojirimycin (**37**) (Fig. (4)) and these have also found use in anticancer, antiviral and antiretroviral research [4a,38]. An examination of the structural features of the known such azasugars that act as inhibitors of

glycosidases led to the establishment of a general empirical rule starting that a substance should possess at least three hydroxyl groups β to the amino moiety in order to display inhibitory activity [1a,1b,39]. The first compound that violated this rule was lentiginosine (**38**), an alkaloid isolated in 1990 from the spotted locoweed, *Astragalus lentiginosus var. diphysus* and assigned the *trans*-1,2-dihydroxyindolizidine structure [40]. Although we reported the first asymmetric synthesis of (+)-**38** [30b] starting from L-tartaric acid, due to impurities present in the natural alkaloid it was not until the inhibitory activities of (+)- and (-)-**38** were investigated in 1995 by Brandi and co-workers that the absolute stereochemistry of the natural **38** was determined unambiguously as shown in Fig. (4) [41,42]. In spite of its low degree of hydroxylation, **38** was found to be ca. twice as potent as castanospermine (**35**) also known to inhibit replication of human immunodeficiency virus (HIV) [3a,3d], in its inhibition of amyloglucosidases, making this compound the most potent inhibitor of this type of α-glucosidase [43].

Fig. (4).

Starting from the commercially available 1,2-*O*-isopropylidene-D-xylofuranose (**39**) as shown in Scheme 7, tribenzylether **40** was obtained through the successive reactions of benzylation and deprotection followed by benzylation again. Hydrolysis and amination of **40** with *p*-methoxybenzylamine gave the crude aminal **41** [17,29,32], which was subsequently reduced to lead to the amino alcohol intermediate. This was submitted to oxidative degradation with PCC [17,29,32] to provide the optically pure lactam **42**. Then, **42** was transformed into the desired *N*-Boc lactam **43a** by 2 steps. The bissilylated ether **43b** was also easily prepared through removal of benzyl groups followed by silylation. Nucleophilic *addition* with simple nonylmagnesium bromide to **43a** was at first investigated. The reaction performed at -78 °C afforded the labile quaternary α-hydroxypyrrolidine derivative **44a** rapidly, which readily underwent the reductive *deoxygenation* with Et_3SiH in the presence of Lewis acid [17,30,32] leading to the product **45a** with moderate diastereoselectivity (3.6:1). In this case accompanying formation of the keto-type of compound resulted from the ring-opening reaction was not observed. Furthermore, it became

apparent that a change from the benzyl substituents to the larger *t*-butyldimethylsilyl groups in **43** highly enhanced the stereoselectivity (11:1) to yield **45b** as a predominant product. However, no addition product was observed in the case of the reaction of **43** with the largest triisopropylsilyl groups in any conditions.

Scheme 7.

With the above stereochemical outcome in hand, the total synthesis of (+)-**38** was accomplished in a short number of steps as follows (Scheme 8); nucleophilic *addition* of the functionalized Grignard reagent to **43b** followed by the reductive *deoxgenation* provided the pyrrolidine derivative **47** with extremely high stereoselectivity (98:2). After separation of the major component, the benzyl substituent in **47** was replaced by the leaving group to give the corresponding tosylate **48**. Finally, **48** was subjected to deprotections and in turn cyclization under basic conditions to complete the total synthesis of (+)-lentiginosine (**38**).

Scheme 8.

In this way, efficient and novel synthetic pathways from carbohydrate-derived lactams to biologically active polyhydroxylated alkaloids have been established employing the *addition-deoxygenation* strategy as a key step, which will furthermore serve for the synthesis other natural products.

4. ADDITION-REDUCTION (for the synthesis of pyrrolidine and indolizidine alkaloids)

As has been detailed in the foregoing sections, the 'carbohydrate-precursor' presents definite stereochemical and operational advantages in dealing with targets containing multiple centers of

chirality and functionality, but by no means constitutes the ideal approach. The question is often asked concerning the wisdom and practicality in terms of cost and effort, of using a carbohydrate to generate a chiral unit or a target as a whole. For this reason, basically and logically more convenient methods have been desired. Among many 'chiral pools', tartaric acid has thus far proven to be one of the most pervasive and versatile compound for the stereoselective elaboration, and chirons derived from it are crucial intermediates for not only the synthesis of natural products, but also the development of therapeutically useful drugs. In this chapter, representative asymmetric syntheses of the major classes of nitrogen-containing mono- and bicyclic natural products have been demonstrated employing chiral lactams derived from tartaric acid based on novel *addition-(stereoselective)reduction* concept.

4.1. Synthesis of a Pyrrolidine Alkaloid, Codonopsinine

As the first example, the synthesis of a fully substituted pyrrolidine alkaloid was focussed. Codonopsinine (**49**) and codonopsine (**50**) (Fig. (5)), antibiotics first isolated in 1969 from *Codonopsis clematidea* by a Russian group [44] exhibit hypotensive pharmacological activity with no effect on the central nervous system observed in animal tests [45]. After structural characterization [46], these were revealed to be a new class of simple pyrrolidine alkaloids possessing 1,2,3,4,5-pentasubstituted structures. Further, in 1972 the relative stereochemistry of these alkaloids was elucidated by the same group [47] to be (**2*R***,3*S***,4*S***,5*S***) without absolute configuration based on analyses of ^{1}H NMR coupling constants using the Karplus equation. It was not until the synthesis of **49** with stereochemistry different to the naturally occurring form was accomplished in 1987 by Kibayashi *et al.* [48] that the absolute stereochemistry of the natural antibiotic **49** was determined unambiguously to be (**2*R*,3*R*,4*R*,5*R***). In addition, the structure of codonopsine (**50**) was confirmed by another group using X-ray crystallographic analysis of the chromatographically separated sample [49]. The four functional groups in the pyrrolidine ring of these compounds are situated in all *trans* positions.

Fig. (5).

The details of the preparation of the above mentioned codonopsinine (**49**) employing the *addition -(stereoselective)reduction* strategy cited in this section has been summarized as follows [50]; C_2-imide **52** obtained from D-tartaric acid (**51**) [30a], was treated with methylmagnesium bromide to give the quaternary α-hydroxylactam intermediate (Scheme 9). This readily underwent reductive deoxygenation with Et_3SiH leading to the single stereoisomer of the homochiral lactam **53** [30]. After exchange of the protecting groups in **53** to benzyl ethers to resist changes in pH, **54** thus obtained was transformed into the *N*-Boc lactam **55**. Nucleophilic *addition* of *p*-methoxyphenylmagnesium bromide to **55** easily afforded the labile quaternary α-hydroxypyrrolidine **56**. Since direct deoxygenation of **56** with Et_3SiH according to our communication [17,32] did not succeed in the preparation of the homochiral pentasubstituted pyrrolidine derivative (in this case the pyrrole-type elimination product was obtained in high yield), we examined *stereoselective reduction* leading to the corresponding alcohol **57a** with desired configuration. The results are indicated in Table 2. Whereas the reduction with $NaBH_4$ only gave the (**5*R***)-stereoisomer **57b** as a major product (entry 1) [51], reaction in the presence of $CeCl_3$ or $SmCl_3$ predominantly afforded the desired (**5*S***)-isomer **57a** (entries 7,8,10). The use of DIBALH [52] (entries 2,3) or $NaBH_4$ in the presence of other metal chlorides [53] (entries 4-6) brought about unsatisfactory stereoselectivities. After investigations under a variety of conditions employing $SmCl_3$ (entries 10-15), the best result (**95 : 5**) was observed under the conditions indicated in entry 14.

Scheme 9.

Table 2.

On the basis of these observations, mesylation and subsequent cyclization of pure **57a** were performed, smoothly leading to the optically pure pentasubstituted pyrrolidine derivative **58**

(Scheme 10) Finally, **58** was reduced after deprotection of the benzyl groups to complete the total synthesis of (-)-codonopsinine (**49**).

Scheme 10.

In addition to the synthesis of **49**, we briefly investigated the mechanistic origin of the asymmetric reduction of **56**. As shown in Fig. (6), it was apparent that Cram's non-chelation or five-membered chelation model favors production of the undesirable (**5*R***)-**57b**. Although the reasons why such an unusual stereoselective reduction was acomplished only by the use of $SmCl_3$ have not yet been clarified, under these conditions it could proceed through the predominant attack of H^- on the carbonyl function from the top face of the six-membered metal-chelate rather than five-membered one due to the shielding effect of the three large functional groups. This is the first report of the synthesis of the natural product **49** [54].

Fig. (6).

The *addition-(stereoselective)reduction* method using functionalized homochiral lactams via quaternary α-hydroxypyrrolidines described here could be regard as a useful strategy for the preparation of various analogues. In order to display its availability we researched the asymmetric total synthesis of the same type of polyhydroxylated pyrrolidine alkaloids.

4.2. Synthesis of a Pyrrolidine Alkaloid, Broussonetine C

Broussonetine C (**59**) and D (**60**) together with several structurally related compounds shown in Fig. (7) first isolated in 1997 by Kusano *et al* [55]. from the branch of *Broussonetia kazinoki* SIEB. (Moraceae) (whose branches, leaves, and fruits have been used as a diuretic, a tonic, and a suppressant for edema in Chinese folk medicine) were selected as a next target. These compounds exhibit unique β-galactosidase and β-mannosidase inhibitory activities, while their congeners inhibit other glycosidases. After structural characterization by the same group based on spectroscopic and chemical methods, these were revealed to be a new class of tetrahydroxylated pyrrolidine alkaloids possessing a 1,2,3,4-tetrasubstituted structure [56] situated in all *trans* positions similar to codonopsinine (**49**). Since the synthesis of this type of compounds poses interesting and often unsolved problems of stereocontrol, no report concerning the total synthesis of **59** or **60** has been appeared to date despite those pharmacological activities and interesting structural features. We express herein the details of the first asymmetric synthesis of **59** by means of requisite stereoselective reduction of a hydroxypyrrolidine intermediate elaborated along the line in this section [57].

Fig. (7).

TIPS-protected C_2-imide **52** mentioned above was treated with undecenylmagnesium bromide at ambient temperature to give the quaternary α-hydroxylactam intermediate, which underwent subsequently reductive deoxgenation with Et_3SiH [30], leading to the *trans*-substituted lactam **61** exclusively (96% d.e.) (Scheme 11). After oxidative cleavage of the olefinic part in **61** followed by the coupling reaction with the C_3-unit containing a hydroxyl function, **62** thus obtained was subjected to oxidation with PCC and then exchange of the TIPS-protecting groups to benzylethers resulted in the preparation of **63**. This was deprotected and transformed into the *N*-Boc lactam **64**. The second Grignard *addition* to **64** easily afforded the labile quaternary α-hydroxypyrrolidine [50], which was successively subjected to *reduction* with $NaBH_4$ in the presence of $CeCl_3$, fortunately providing the desired stereoisomer **65** as a sole product. Then, **65** was effected by the reactions of mesylation and cyclization, leading to the tetrasubstituted

pyrrolidine **66** with the desired configurations. The double bond in **66** was cleavaged and reduced to the primary alcohol. Finally, deprotection of the obtained product was at first performed with Pd (black) due to avoid the acetal formation, affording the debenzylated *N*-Boc ketal derivative **67** of broussonetine C (**59**). Then, removal of the resulted protecting groups in **67** was conducted under acidic conditions to complete the total synthesis of **59**, whose structure was characterized after derivarization to the pentaacetate **68**.

Scheme 11.

Thus, the first asymmetric synthesis of natural broussonetine C was achieved in 21% overall yield from C_2-imide through the successive reactions of *addition-(stereoselcetive)reduction*. This process will be also widely applicable to the synthesis of other broussonetine congeners.

4.3. Synthesis of an Indolizidine Alkaloid, 1-Deoxycastanospermine

The use of this *addition-(stereoselective)reduction* strategy in synthesis has been advantageous for construction of bicyclic pyrrolizidine- or indolizidine alkaloids. A third route affording 1-deoxycastanospermine, a derivative of castanospermine (**35**) and one of indolizidine alkaloids, was also based on a sequence of reactions starting from tartaric acid-derived homochiral lactam derivative [58].

As previously shown in Fig. (4) , castanospermine (**35**), swainsonine (**36**), deoxynojirimycin (**37**), and lentiginosine (**38**) have found use in anticancer, antiviral and antiretroviral research [4a,38]. Of all these molecules, **35** has been shown to inhibit replication of human immunodeficiency virus (HIV) [3] and is of particular interest in connection with chemotherapeutic intervention in the treatment of AIDS. The diverse array of potentially useful activities make it an inviting target for synthesis [59]. In particular the preparation of unnatural epimers and other structural analogs of **35** has genarated much interest since the biological

activity of these molecules varies substantially with the number, position and stereochemistry of the hydroxy groups into the indolizidine skeleton [60].

Thus, C_2-imide **52** was treated with Grignard reagent followed by the reductive deoxgenation, leading to the homochiral lactam **69** (Scheme 12). After exchange of the protecting group in **69** to benzyl and THP ethers, **70** thus obtained was transformed into the *N*-Boc lactam **71**. Nucleophilic *addition* of the second Grignard reagent to **71** easily afforded the labile quaternary α-hydroxypyrolidine [17,50,57], which was successively submitted to the *stereoselctive reduction* to give the desired (**3*S***)-stereoisomer **72** as a sole product [50]. The olefinic part in **72** was cleavaged after benzyl-protection to lead to the cyclized α-hydroxypiperidine (azasugar) derivative **74**. Interestingly, it became apparent that Lewis acid induced deoxgenation [17,30] of **74** cleanly resulted in the direct preparation of the *N*- and *O*-deprotected piperidine which was in turn isolated as the Cbz-derivative **75** in quantitative yield. Finally, **12** was subjected to cyclization followed by the simultaneous debenzylation to complete the total synthesis of 1-deoxycastanospermine **76**. The structure was characterized after derivatization to the known triacetate **77**.

Scheme 12.

4.4. Total Synthesis of a Tetrahydroxylated Pyrrolizidine Alkaloid, Alexine

Other important members among this class of compounds proved to have the potential to produce antiviral, insect antifeedant, antidiabetic, and anticancer effects as well as immune modulatory properties are alexine (**78**) [61], australine (**79**) [62], and casuarine (**80**) [63] containing a pyrrolizidine ring [64] (Fig. (8)). These display powerful glycosidase inhibitory properties and, in addition, exhibit viral and retroviral [65] including anti-HIV activity [66]. These are also a unique subset of pyrrolizidine alkaloids possessing five contiguous stereogenic centers, and the presence of a hydroxymethyl group adjacent to the ring nitrogen [C(3)] distinguishes this group from the larger class of necine bases which contain carbon substituents at C(1). However, despite interesting pharmacological activity and unique structural features, to our

knowledge, only one approach to the total synthesis of the parent alkaloid **78** of alexines has been reported to date based on an optical resolution method [67].

Fig. (8).

As the last presentation, this part will focuss on recent advances in the chemistry of a pyrrolizidine alkaloid, alexine (**78**), with particular attention to the method for construction of the functionalized pyrrolidine structure (**III**) via the use of chiral lactam intermediate (**II**) obtained from a carbohydrate precursor [68] (Fig. (9)).

Fig. (9).

The functionalized homochiral lactam **81** obtained from arabinofuranose derivative **22** [17,29,32] was cleavaged via dihydroxylation to give the aldehyde **82**, which was in turn subjected to $BF_3 \cdot OEt_2$-induced allylation at low temperature, leading to the corresponding desired allyl alcohol **83** predominantly (97:3) through attack on the carbonyl group from the less hindered face (Scheme 13). After removal of the *N*-MPM moiety and protection of the hydroxyl group in **83** with MOMCl, **84** thus obtained was submitted to oxidative cleavage again followed by reduction to the corresponding alcohol, which was stepwisely treated with DPSCl and $(Boc)_2O$ to give the *N*-Boc lactam **85**. Then, the second vinyl-Grignard *addition* to **85** easily afforded the labile quaternary α-hydroxypyrrolidine intermediate [50,57,58], which was subsequently effected by *stereoselective reduction* in the presence of $CeCl_3$ to provide the desired stereoisomer **86** with five contiguous stereogenic centers as a sole product.

In light of the above outcome, we turned our attention to the construction of pyrrolizidine ring system. Cyclization of **86** under basic conditions via mesylation was performed to yield the pyrrolidine derivative **87**. This was then successively effected by reactions of oxidative cleavage,

reduction, and MOM-protection to lead to the functionalized *N*-Boc derivative **88**. Construction of the bicyclic pyrrolizidine ring was accomplished under mild basic conditions after replacement of the silyl substituent in **88** by the leaving Ts-group followed by simultaneous deprotection of two hydroxyl and amino functions with conc. HCl, leading to the alexine dibenzyl derivative **89**. Finally, removal of the benzyl groups in **89** was performed with 10% Pd on carbon to complete the total synthesis of alexine (**78**).

Scheme 13.

As mentioned above, three elegant procedures such as 1) *reduction-elimination*, 2) *addition-deoxygenation* and 3) *addition-reduction* strategies employing lactams derived from amino acid, carbohydrate, or tartaric acid have been developed to carry out the asymmetric synthesis of bilogically active (poly)hydoxylated azetidine-, pyrrolidine-, indolizidine-, pyrrolizidine alkaloids and related substances. Programs completed are summarized in Scheme 14. These results will open the way to further exploitation with the use of chiral pool precursors and new development of these molecules in natural product chemistry.

Scheme 14.

5. CONCLUSIONS

An attempt has been made in this article to review the significant synthetic advances of (poly)hydroxylated alkaloids and those analogues which have been synthesized in this laboratory over the last 5 years. In addition to that, a brief catalog of the most important examples is provided along with key references to guide the reader to the original literature. As has been detailed in these sections, some strategies have enabled the efficient regio- and/or stereospecific

synthesis of this fully functionalized hydroxyl-containing alkaloid family. Furthermore, the growing number of revealed biological properties of these compounds will stimulate many new practical and ingenious synthetic routes. And it can be no doubt that the development of such new approaches will see further advances in synthetic methodology as well as application of that alkaloid chemistry in the near future.

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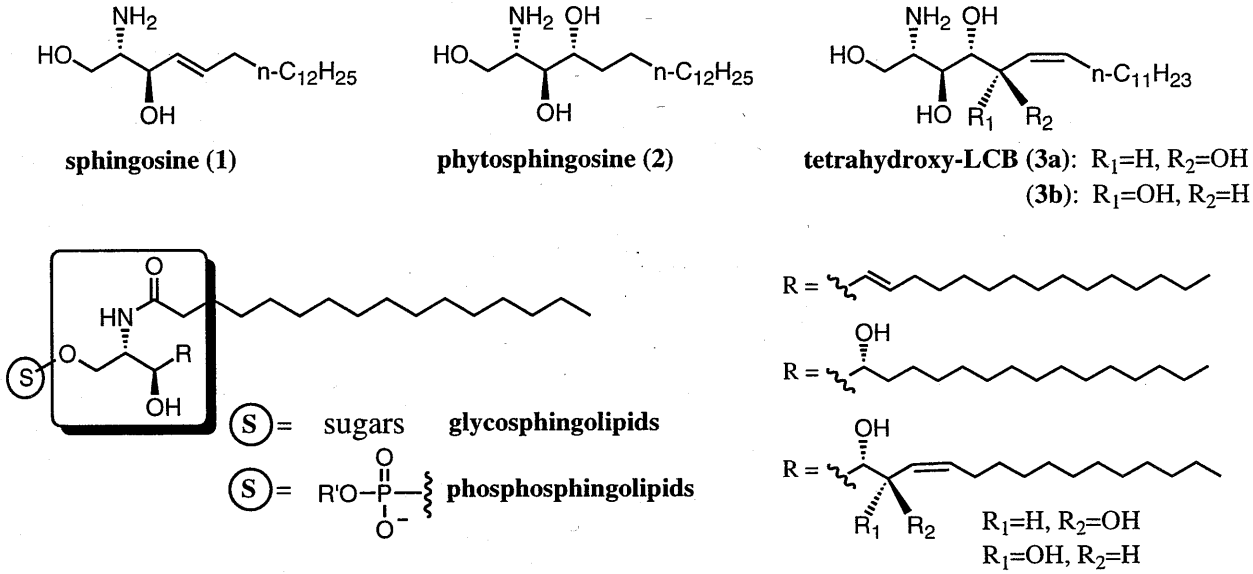


Fig. (1). Glyco- and phosphosphingolipids.

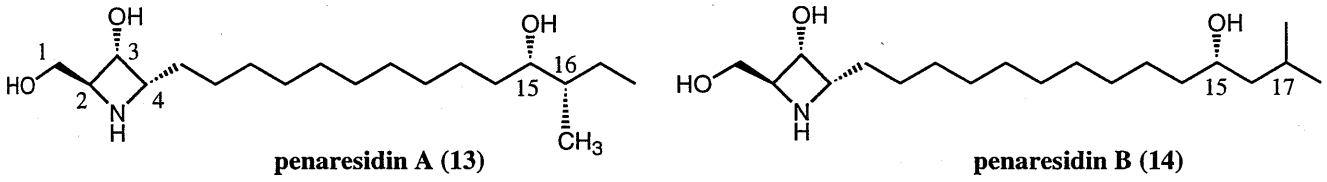
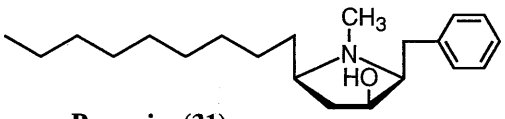
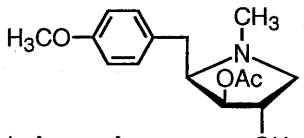


Fig. (2). Penaresidin A and B.

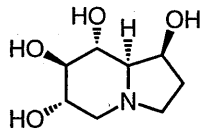


Preussin (31)

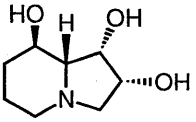


Anisomycin

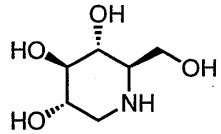
Fig. (3). Antifungal antibiotics.



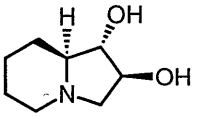
Castanospermine (35)



Swainsonine (36)

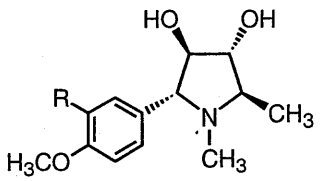


Deoxynojirimycin (37)



Lentiginosine (38)

Fig. (4). Representative glycosidase inhibitors.



Codonopsinine (49): R = H
Codonopsine (50): R = CH_3

Fig. (5). Codonopsinine and codonopsine.

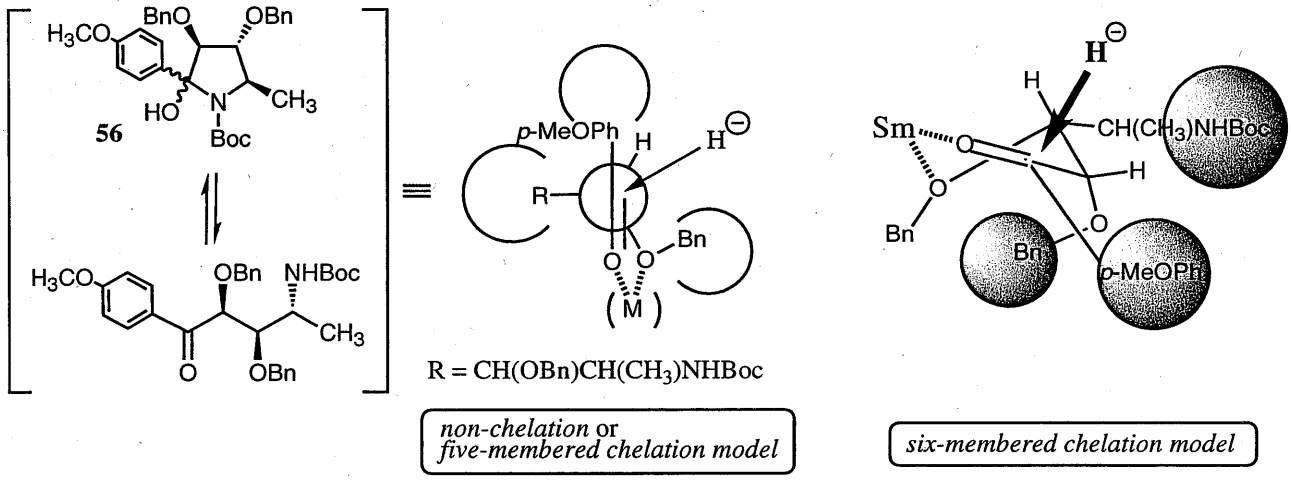
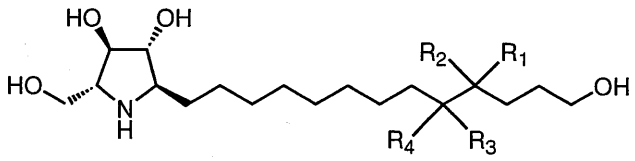
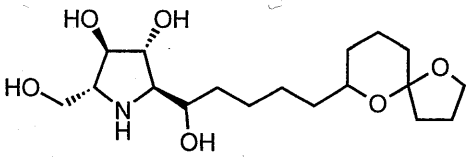


Fig. (6). Mechanistic origin of the stereoselective reduction.

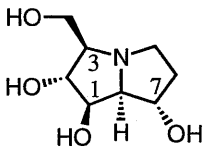


Broussonetine C (59): R_1,R_2=O, R_3=R_4=H
Broussonetine D (60): R_1=R_2=H, R_3,R_4=O

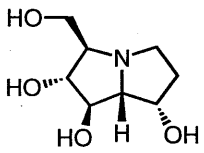


Broussonetine G

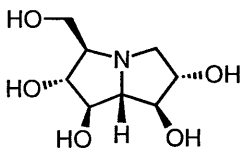
Fig. (7). Broussonetines.



(+)-Alexine (78)

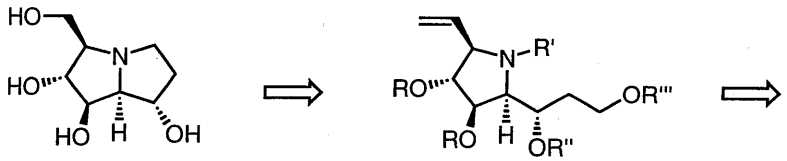


(+)-Australine (79)

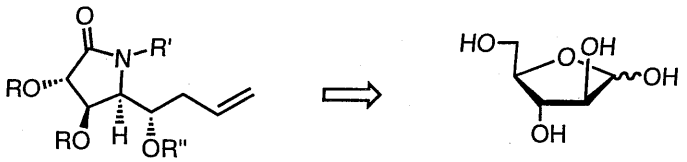


(+)-Casuarine (80)

Fig. (8). Alexine and its derivatives.

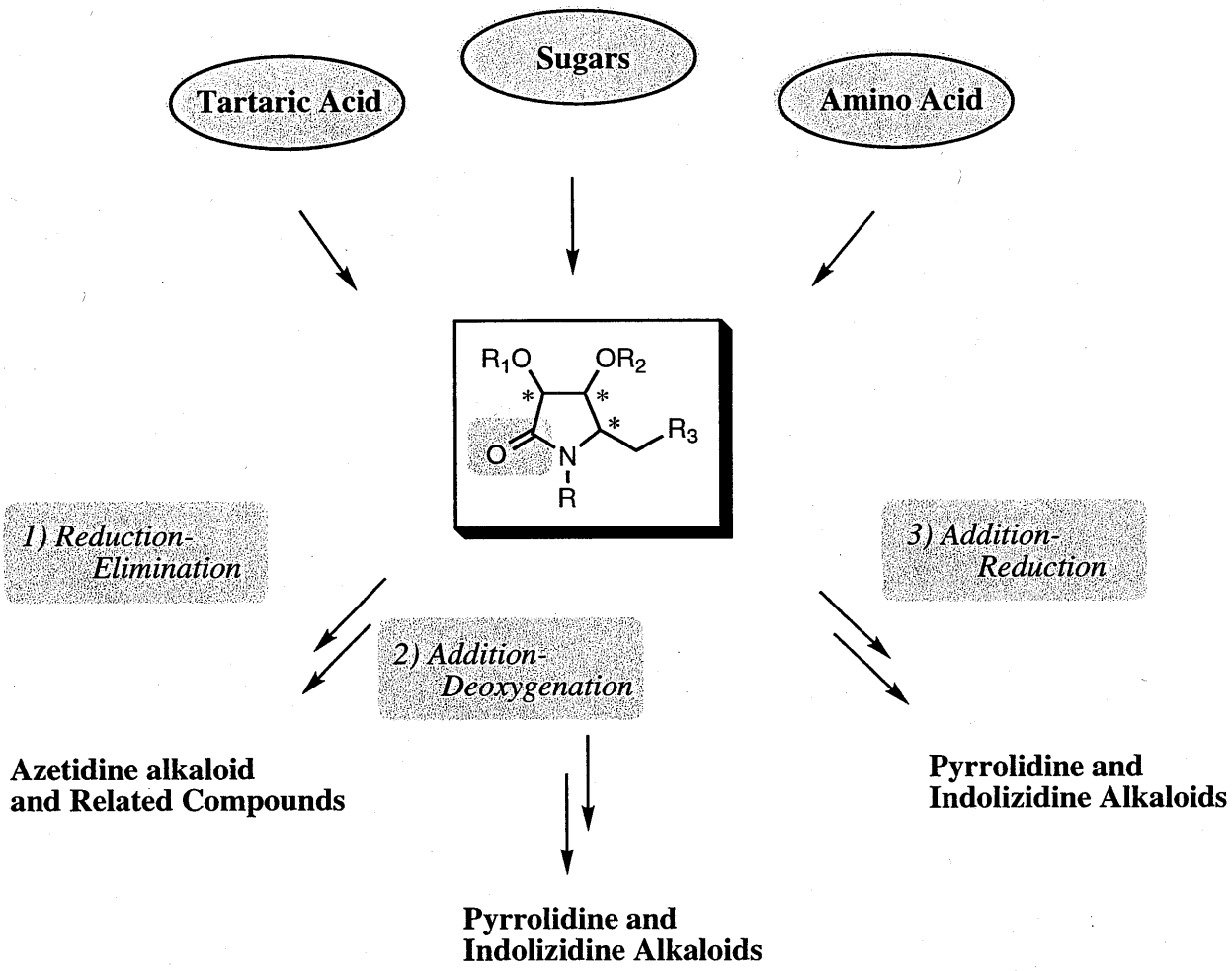


(+)-Alexine (78) **(III)**

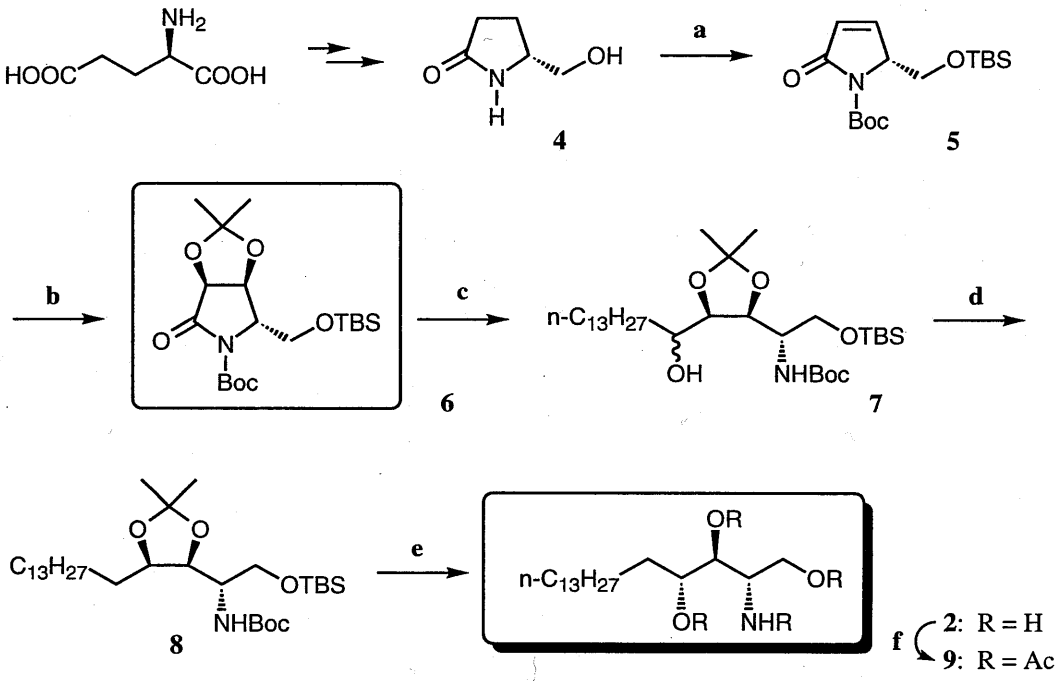


(II) **D-Arabinofuranose**

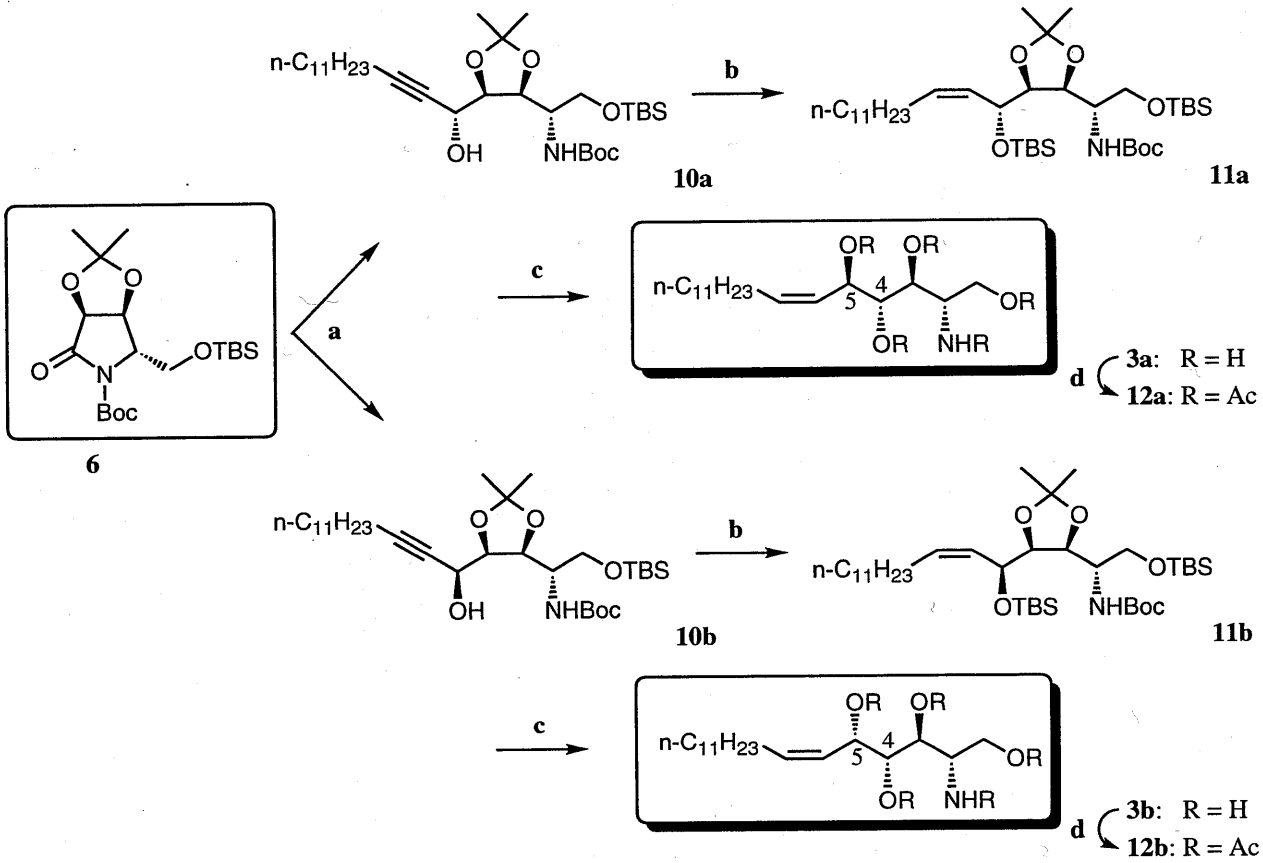
Fig. (9). Retrosynthetic pathway of alexine.



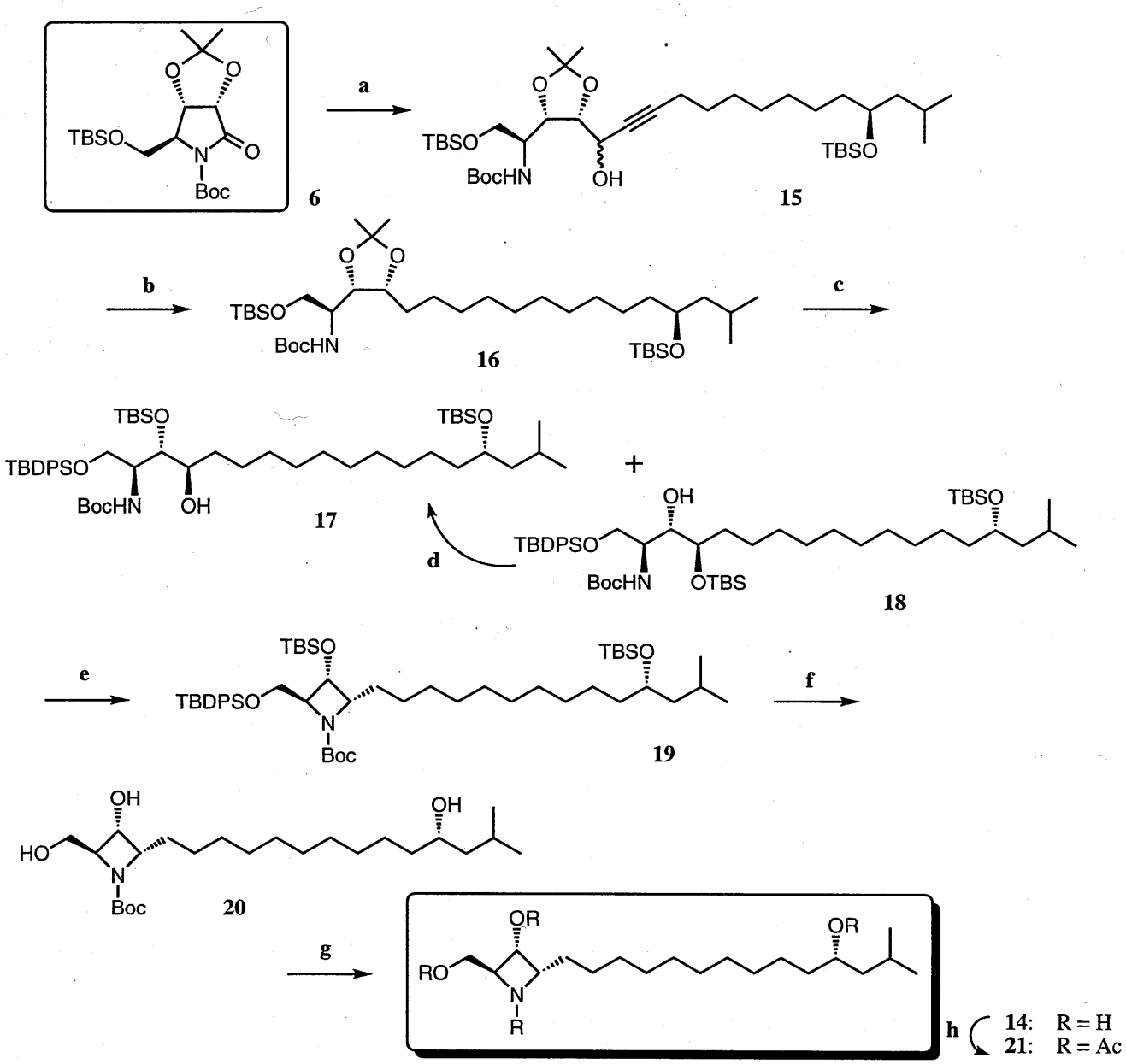
Scheme 1. Manipulation of functionalized lactams derived from chiral pools.



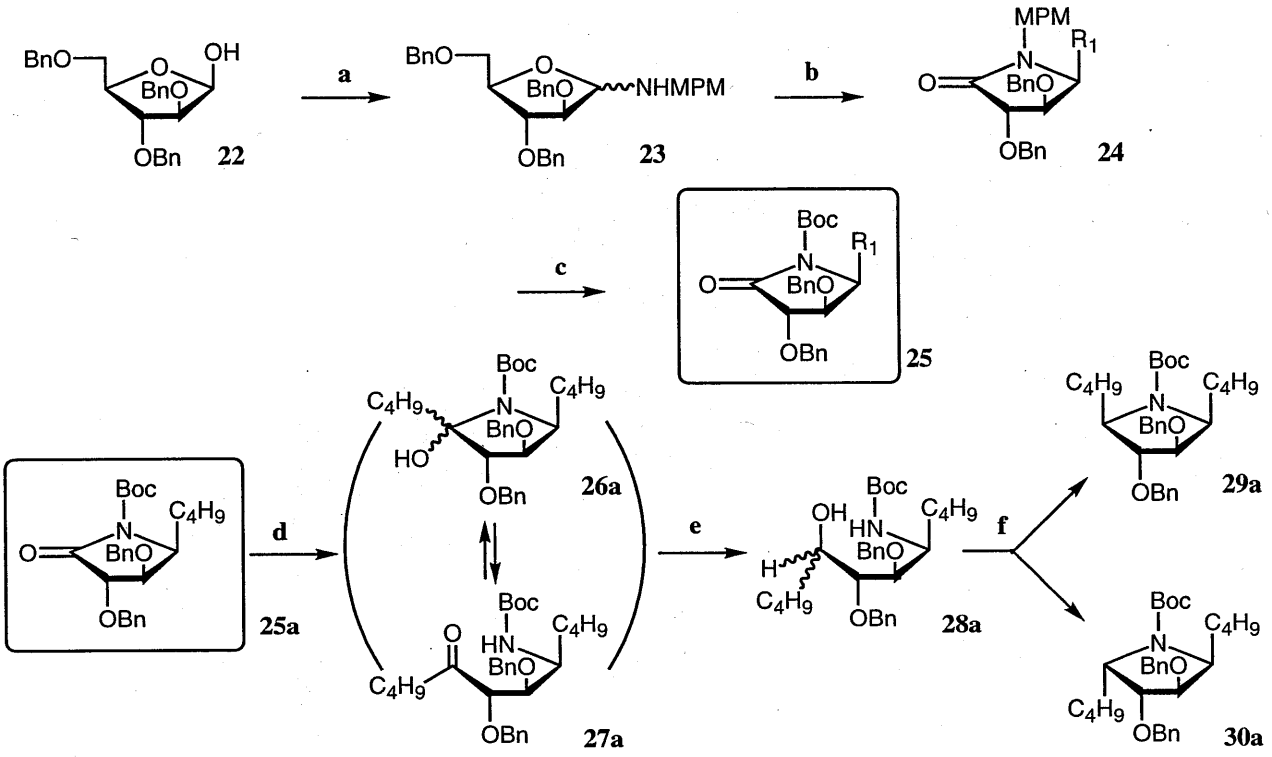
Scheme 2. Reagents and conditions: (a) 1, TBSCl, imidazole, DMF; 88%; 2, $(Boc)_2O$, Et_3N, DMAP, CH_2Cl_2; 90%; 3, LDA, THF, then PhSeBr, -78 °C; 4, MCPBA, -78 °C; (b) 1, OsO_4, NMO, acetone-H_2O (1:1); 55% (3 steps); 2, $(CH_3)_2C(OCH_3)_2$, *p*-TsOH; quant.; (c) 1, $C_{13}H_{27}MgBr$, -78 °C; 60%; 2, $NaBH_4$, EtOH; 88%; (d) 1, (thiocarbonyl)diimidazole, 50 °C; 98%; 2, Bu_3SnH, AIBN, toluene, 100 °C; 87%; (e) TFA-H_2O (9:1), then KOH, MeOH; quant.; (f) Ac_2O, pyridine, DMAP; 70%.



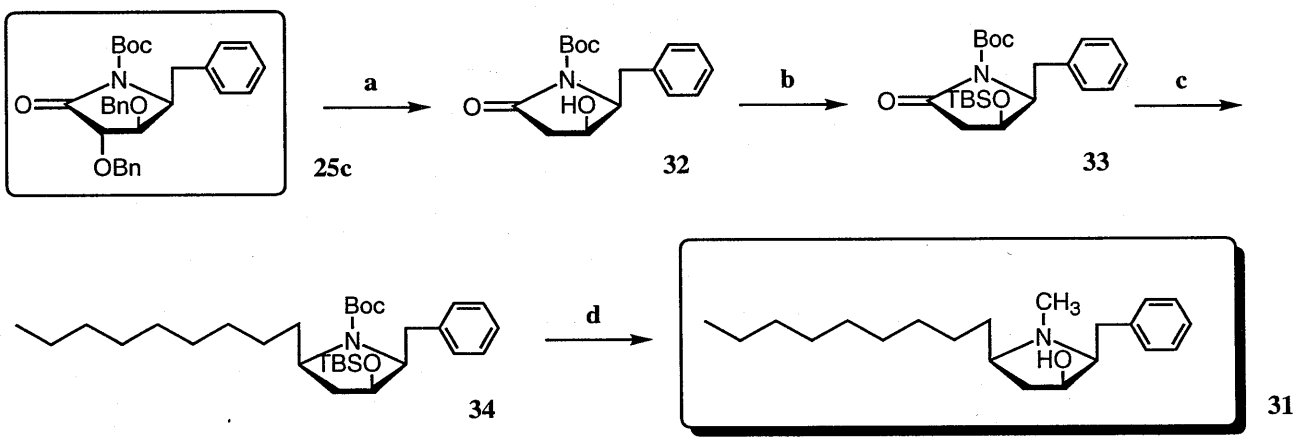
Scheme 3. Reagents and conditions: (a) 1, $C_{11}H_{23}C{\equiv}CLi$, THF, -78 °C; 2, $NaBH_4$, *i*-PrOH; **10a**: 59% (2 steps); **10b**: 22% (2 steps); (b) 1, TBSCl, imidazole, DMF; 2, H_2, Lindlar, quinoline, MeOH; **11a**: 60% (2 steps); **11b**: 67% (2 steps): (c) TFA-H_2O (9:1), then KOH, MeOH; (d) Ac_2O, Et_3N, DMAP; **12a**: 68% (2 steps); **12b**: 51% (2 steps).



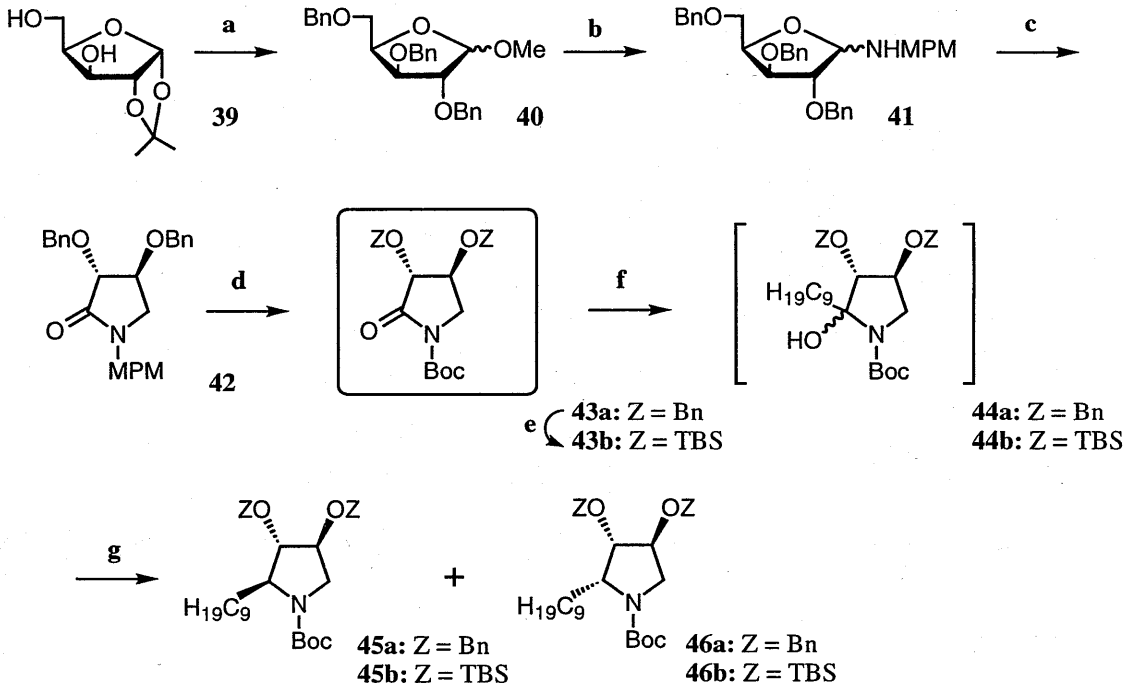
Scheme 4. Reagents and conditions: (a) 1, (*S*)-HC≡C$(CH_2)_7$CH(OTBS)CH_2CH$(CH_3)_2$, BuLi, THF, -78 °C; 2, $NaBH_4$, EtOH; 58% (2 steps); (b) 1, (thiocarbonyl)diimidazole, THF, 40 °C; 98%; 2, Bu_3SnH, AIBN, toluene, 95 °C; 70%; (c) 1, *p*-TsOH, MeOH; 63%; 2, TBDPSCl, Et_3N, CH_2Cl_2; 75%; 3, TBSCl, imidazole, DMF; 98% (**17** : **18** = 2 : 98); (d) NaH, THF, 35% (conv. 80%); (e) 1, MsCl, pyridine; 2, NaH, THF, 58% (2 steps); (f) Bu_4NF, THF, 79%; (g) 1, $BF_3 \cdot OEt_2$, CH_2Cl_2, -40～-30 °C; (h) Ac_2O, pyridine, CH_2Cl_2; quant. (2 steps).



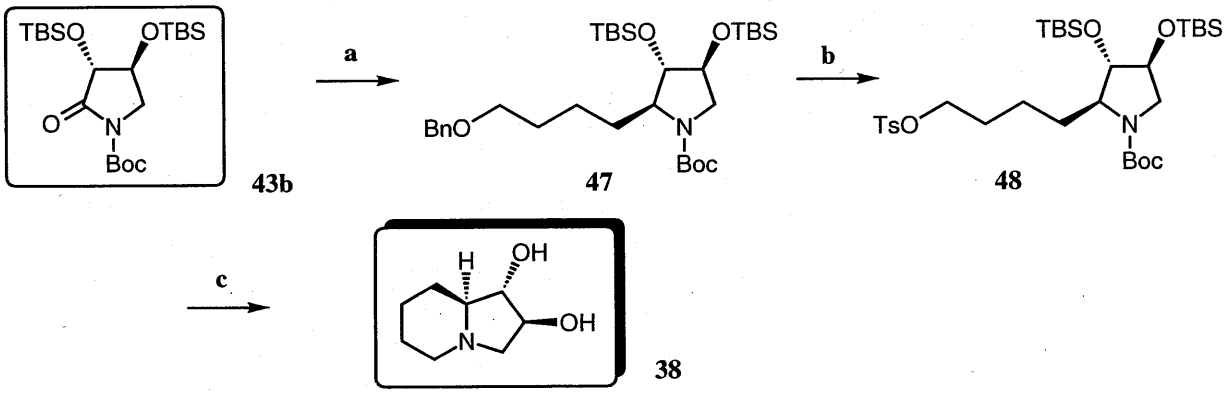
Scheme 5. Reagents and conditions: (a) $MPMNH_2$, CH_2Cl_2, MS 4A; quant.; (b) 1 R_1MgX, -78--30 °C, THF; 2 PCC, MS 4A, CH_2Cl_2; [R_1=C_4H_9: **24a**: 52%, R_1=C_9H_{19}: **24b**: 42%, R_1=Bn: **24c**: 51%, based on **22**] (c) CAN, CH_3CN-H_2O; 2 $(Boc)_2O$, Et_3N, DMAP, CH_2Cl_2; [R_1=C_4H_9: **25a**: 76%, R_1=C_9H_{19}: **25b**: 58%, R_1=Bn: **25c**: 76%] (2 steps); (d) C_4H_9MgBr, -78 °C, THF; (e) $NaBH_4$, EtOH; 73%; (2 steps); (f) 1 MsCl, Et_3N, CH_2Cl_2; 2 *t*-BuOK, THF; **29a**: 41% (2 steps); **30a**: 37% (2 steps).



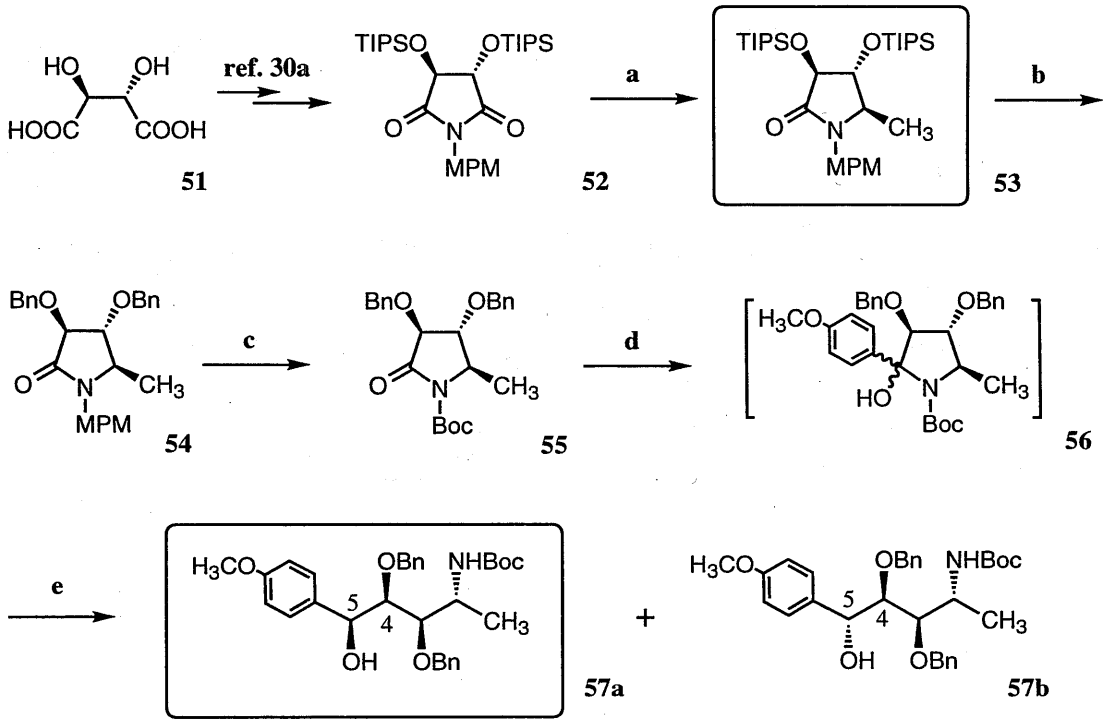
Scheme 6. Reagents and conditions: (a) 1 Pd(black), HCOOH, MeOH; quant.; 2 PhOCSCl, pyridine, DMAP, CH_3CN; 3 Bu_3SnH, AIBN, toluene, 90 °C; 72% (2 steps); (b) TBSCl, imidazole, DMF; 91%; (c) 1 $C_9H_{19}MgBr$, -78 °C, THF; 2 Et_3SiH, $BF_3{\bullet}OEt_2$, -40~-30 °C, CH_2Cl_2; 67% (2 steps); (d) 1 Bu_4NF, THF; 97%; 2 $LiAlH_4$, THF, 50 °C; 92%.



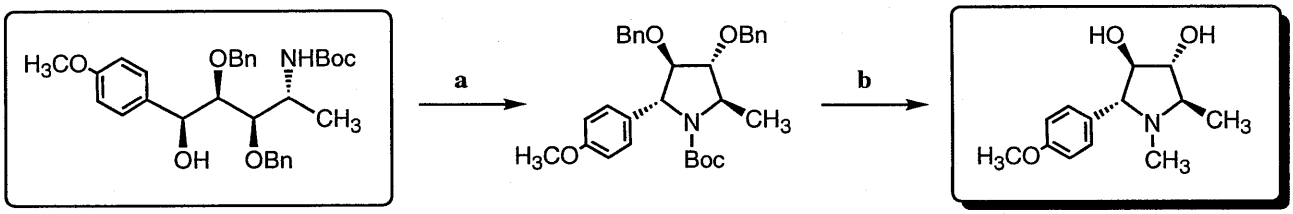
Scheme 7. Reagents and conditions: (a) 1, NaH, BnBr, THF; 93%; 2, conc. HCl, MeOH; 93%; 3, NaH, BnBr, THF; 98%; (b) 1, 80% CH_3COOH, 100 °C; 91%; 2, $MPMNH_2$, benzene-$CHCl_3$, 70 °C, MS 4A; quant.; (c) 1, $LiAlH_4$, THF; 83%; 2, PCC, MS 4A, CH_2Cl_2; 58%; (d) 1, CAN, CH_3CN-H_2O; 81%; 2, $(Boc)_2O$, Et_3N, DMAP, CH_2Cl_2; 96%; (e) 1, Pd (black), 4.4% HCOOH-CH_3OH, 40 °C; 96%; 2, TBSCl, imidazole, DMF; 94%; (f) $C_9H_{19}MgBr$, THF, -78 °C; (g) Et_3SiH, $BF_3 \cdot OEt_2$,CH_2Cl_2, -78 °C; **45a**: 47% (2 steps); **46a**: 13% (2 steps); **45b**: 55% (2 steps); **46b** 5% (2 steps).



Scheme 8. Reagents and conditions: (a) 1, $BnO(CH_2)_4MgBr$, THF, -78 °C; 2, Et_3SiH, $BF_3{\bullet}OEt_2$, CH_2Cl_2, -78 °C; 55% (2 steps); (b)1, Pd (black), 4.4% HCOOH-CH_3OH, 40 °C; 94%; 2, TsCl, pyridine; 70%; (c) $BF_3{\bullet}OEt_2$, CH_2Cl_2, -20 ~ 0 °C; 2, KOH, CH_3OH; 74% (2 steps).

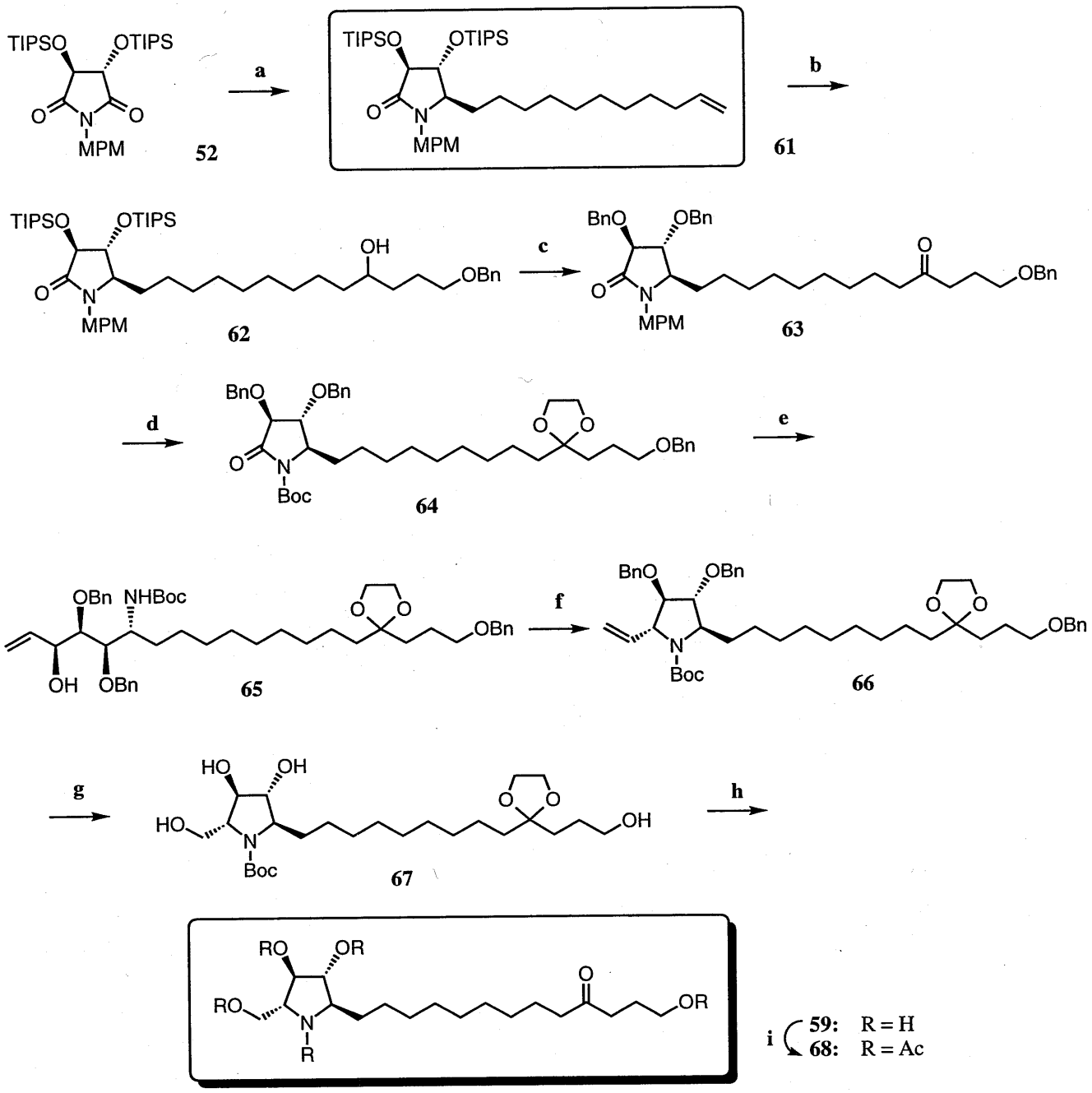


Scheme 9. Reagents and conditions: (a) 1, CH_3MgBr, THF, -78 - -10 °C; 91%; 2, Et_3SiH, $BF_3 \bullet OEt_2$, CH_2Cl_2, -78 °C; 98%; (b) 1, aqHCl, MeOH; 99%; 2, BnBr, Ag_2O, EtOAc; 75%; (c) 1, CAN, CH_3CN-H_2O (9:1); 90%; 2, $(Boc)_2O$, Et_3N, DMAP, CH_2Cl_2; 99%; (d) *p*-MeOPhMgBr, THF, -78 °C; (e) reducing agent (see Table 2).

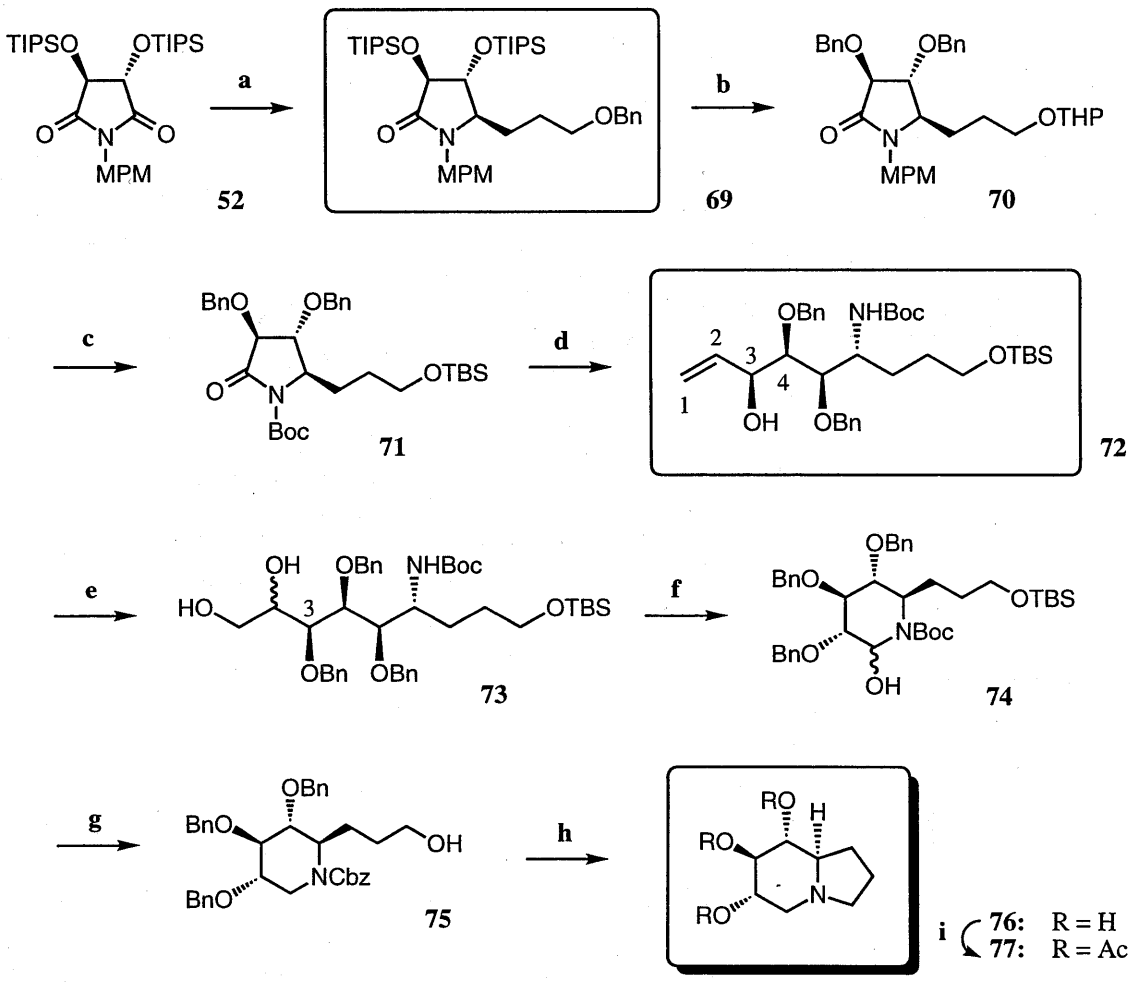


57a **58** **49**

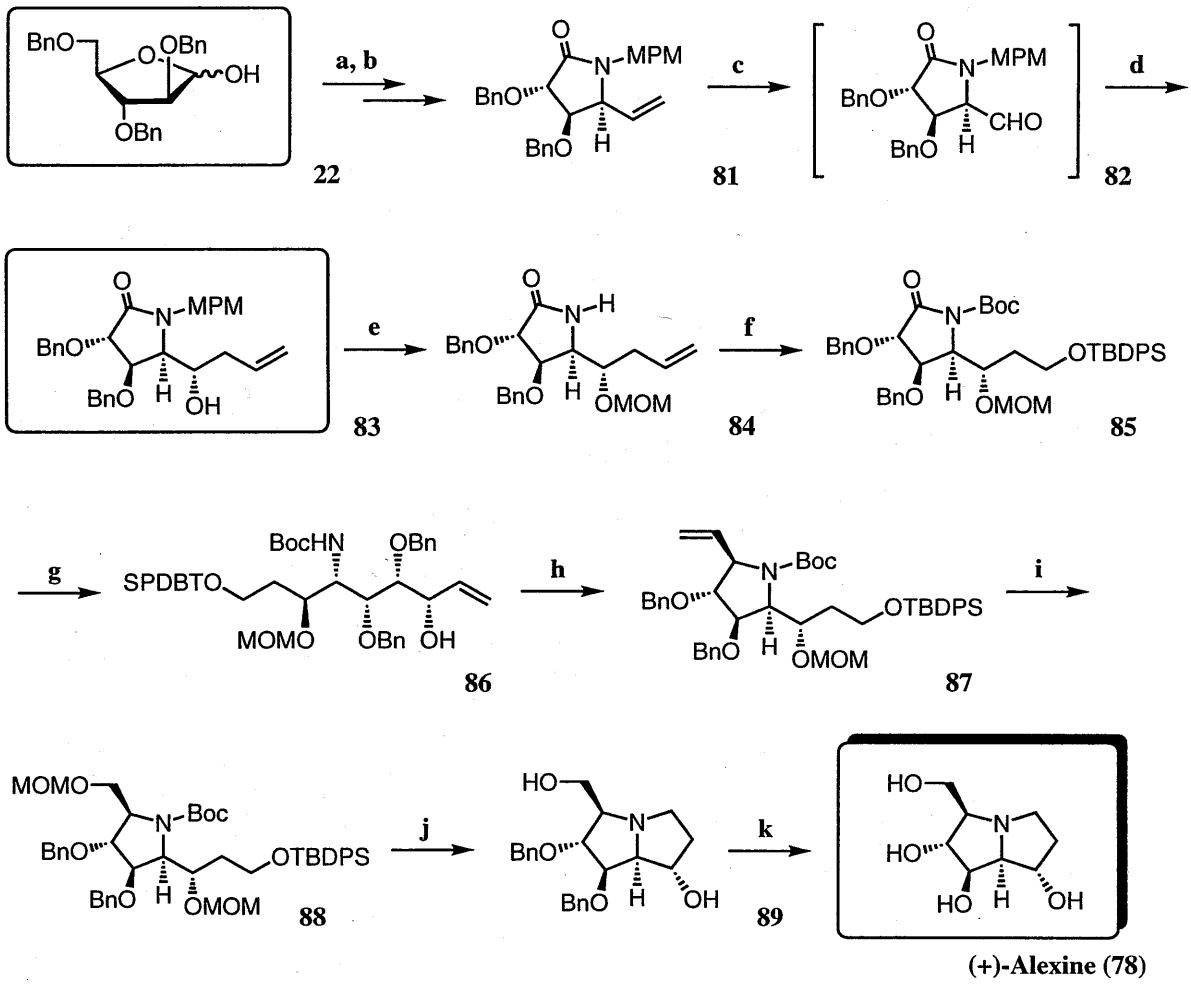
Scheme 10. Reagents and conditions: (a) 1, MsCl, Et_3N, CH_2Cl_2; 2, *t*-BuOK, THF; 92% (2 steps); (b) 1, Pd (black), 4.4% HCOOH-MeOH; 99%; 2, $LiAlH_4$, THF, reflux; 69%.



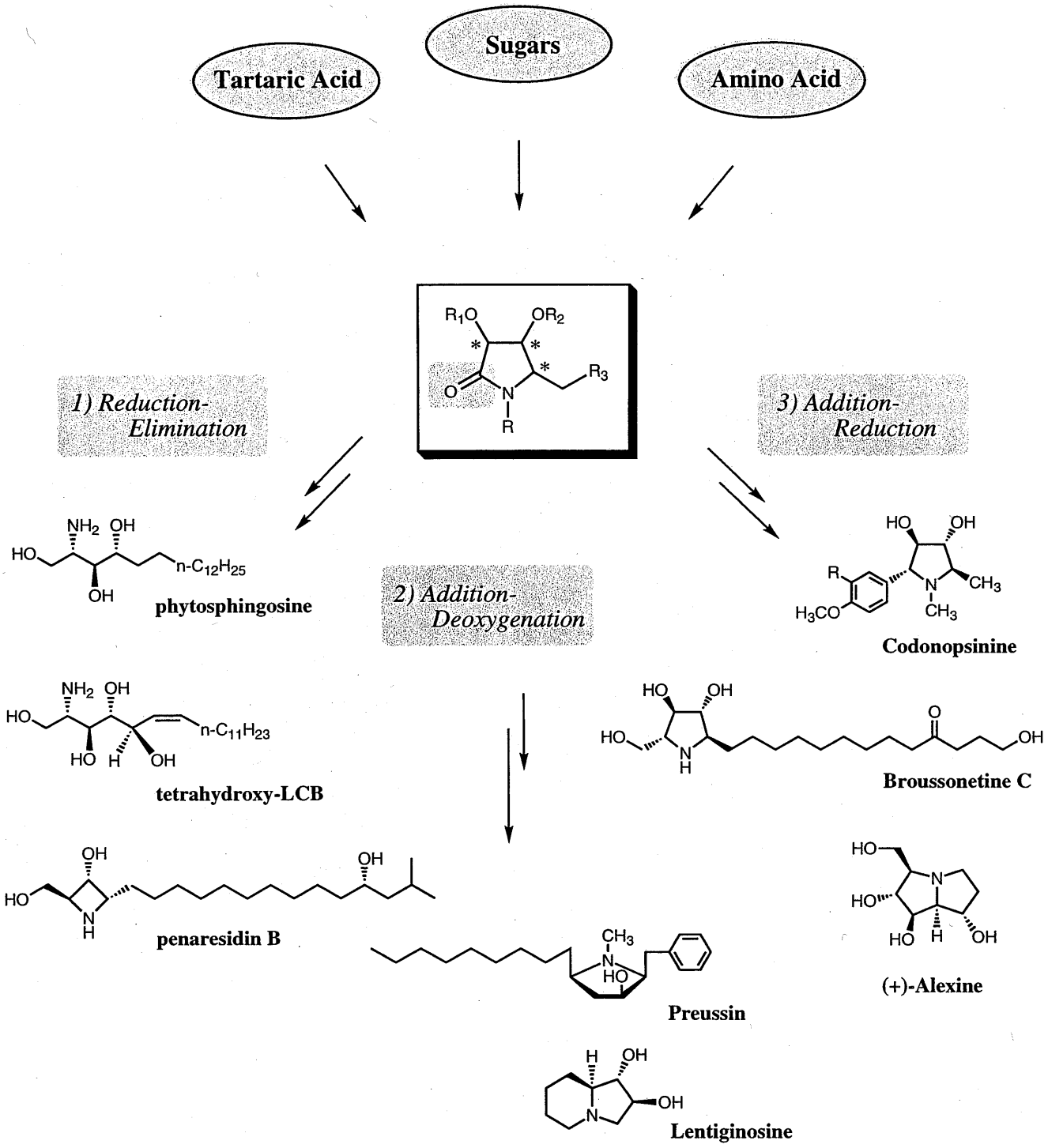
Scheme 11. Reagents and conditions: (**a**) **1**, undecenylmagnesium bromide, THF, rt; **2**, Et_3SiH, BF_3•OEt_2, CH_2Cl_2, -78~-50 °C; 83% (2 steps); (**b**) **1**, OsO_4, NMO, acetone-H_2O (1:1); 99%; **2**, $NaIO_4$, Et_2O-H_2O (1:1); **3**, benzyloxypropylmagnesium bromide, THF, 0 °C; 85% (2 steps); (**c**) **1**, PCC, CH_2Cl_2, MS 4A; 90%; **2**, Bu_4NF, THF; 92%; **3**, BnBr, Ag_2O, CH_3COOEt; 100%; (**d**) **1**, CAN, CH_3CN; 70%; **2**, $HOCH_2CH_2OH$, cat. *p*-TsOH, benzene, reflux; 96%; **3**, $(Boc)_2O$, Et_3N, DMAP, CH_2Cl_2; 100%; (**e**) **1**, vinylmagnesium bromide, THF, -78 °C; **2**, $NaBH_4$-$CeCl_3$, MeOH, -45 °C; 78% (2 steps); (**f**) **1**, MsCl, Et_3N, CH_2Cl_2, **2**, *t*-BuOK, THF; 92% (2 steps); (**g**) **1**, OsO_4, NMO, acetone-H_2O (1:1); 100%; **2**, $NaIO_4$, Et_2O-H_2O (1:1); **3**, $NaBH_4$, MeOH; 92% (2 steps); **4**, Pd (black), 4.4% HCOOH-MeOH; 83%; (**h**) conc. HCl, CH_3COOEt; (**i**) Ac_2O, pyridine, DMAP; 67% (2 steps).



Scheme 12. Reagents and conditions: (a) 1, $BnO(CH_2)_3MgBr$, THF, -78 - 0 °C; 2, Et_3SiH, $BF_3 \cdot OEt_2$, CH_2Cl_2, -78 °C; 96% (2 steps); (b) 1, Pd (black), 4.4% HCOOH-MeOH; 88%; 2, DHP, cat. *p*-TsOH, MeOH, CH_2Cl_2; 97%; 3, Bu_4NF, THF, quant.; 4, BnBr, Ag_2O, CH_3COOEt; 99%; (c) 1, cat. *p*-TsOH, MeOH; 77%; 2, CAN, CH_3CN-H_2O (9:1); 81%; 3, TBSCl, imidazole, DMAP, DMF; 72%; 4, $(Boc)_2O$, Et_3N, DMAP, CH_2Cl_2; quant.; (d) 1, vinylmagnesium bromide, THF, -78 °C; 2, $NaBH_4$-$CeCl_3$, MeOH, -18 °C; 86% (2 steps); (e) 1, BnBr, Ag_2O, CH_3COOEt; 87%; 2, OsO_4, NMO, acetone-H_2O (1:1); 88%; (f) $NaIO_4$, Et_2O-H_2O (1:1); 95%; (g) 1, Et_3SiH, $BF_3 \cdot OEt_2$, CH_2Cl_2, 0 °C; 99%; 2, CbzCl, $NaHCO_3$, CH_2Cl_2; 99%; (h) 1, MsCl, Et_3N, CH_2Cl_2; 2, Pd (black), 4.4% HCOOH-MeOH; 99% (2 steps); (i) Ac_2O, Et_3N, CH_2Cl_2; 80%..



Scheme 13. Reagents and conditions: (**a**) **1**, $MPMNH_2$, benzene-$CHCl_3$ (1:1), MS 4A, reflux; quant.; (**b**) **1**, vinylmagnesium bromide, THF, -78~-40 °C; 70%; **2**, PCC, MS 4A, CH_2Cl_2; 68%; (**c**) **1**, OsO_4, NMO, acetone-H_2O (1:1); 98%; **2**, $NaIO_4$, Et_2O-H_2O (2:1); (**d**) allyltrimethylsilane, BF_3•OEt_2, CH_2Cl_2, -78~-20 °C; 82% (2 steps); (**e**) **1**, CAN, CH_3CN-H_2O (9:1); 71%; **2**, MOMCl, *N,N*-diisopropylethylamine, CH_2Cl_2; 75%; (**f**) **1**, OsO_4, NMO, acetone-H_2O (1:1); 91%; **2**, $NaIO_4$, Et_2O-H_2O (2:1); **3**, $NaBH_4$, EtOH; 90% (2 steps); **4**, TBDPSCl, imidazole, DMF; quant.; **5**, $(Boc)_2O$, DMAP, Et_3N, CH_2Cl_2; 99%; (**g**) **1**, vinylmagnesium bromide, THF, -78 °C; **2**, $NaBH_4$-$CeCl_3$, MeOH, -45 °C; 66% (2 steps); (**h**) **1**, MsCl, Et_3N, CH_2Cl_2; **2**, *t*-BuOK, THF; 84% (2 steps); (**i**) **1**, OsO_4, NMO, acetone-H_2O (1:1); 92%; **2**, $NaIO_4$, Et_2O-H_2O (2:1); **3**, $NaBH_4$, EtOH; 74% (2 steps); **4**, MOMCl, *N,N*-diisopropylethylamine, CH_2Cl_2; 99%; (**j**), **1**, Bu_4NF, THF; quant.; **2**, *p*-TsCl, pyridine; 92%; **3**, conc.HCl, MeOH; **4**, K_2CO_3, MeOH; 94% (2 steps); (**k**) H_2, 10% Pd /C, EtOH; 70%.



Scheme 14. Synthesized natural hydroxylated alkaloids.

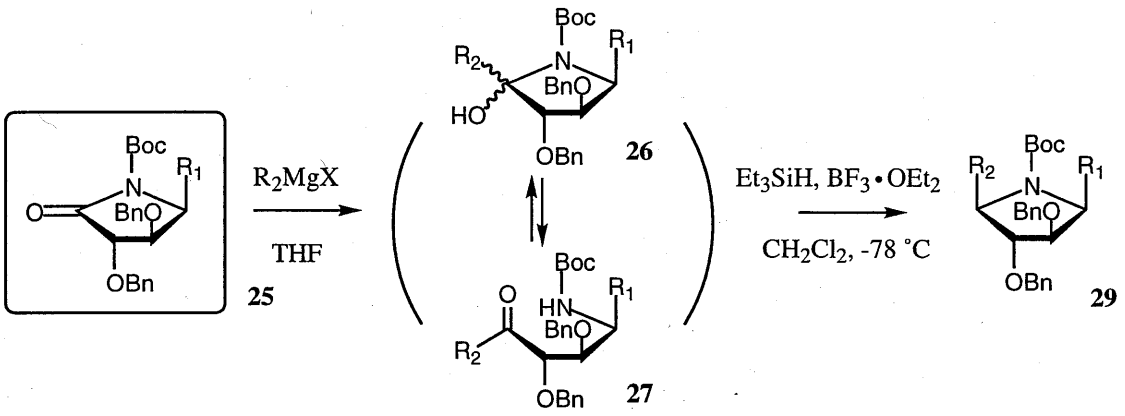


Table 1. Reductive Deoygenation of the Alkylated Products to 25[a)]

Entry	R_1	R_2	Yield[b)] of **27** (%)	Yield[b)] of **29** (%)	$[\alpha]_D$,deg[c)] (Temp./°C, c)
1	C_4H_9	C_4H_9	7 (**27a**)	65 (**29a**)	-20.0 (23, 1.24)
2	C_4H_9	C_9H_{19}	21 e) (**27b**)	52 (**29b**)	-17.2 (25, 1.70)
3	C_4H_9	$PhCH_2$	5 (**27c**)	52 (**29c**)	-2.40 (26, 0.99)
4	C_9H_{19}	C_4H_9	7 (**27d**)	72 (**29d**)	-16.7 (23, 2.10)
5	C_9H_{19}	C_9H_{19}	13 e) (**27e**)	62 (**29e**)	-16.6 (26, 1.82)
6	C_9H_{19}	$PhCH_2$	2 (**27f**)	59 (**29f**)	-5.70 (24, 1.21)
7	$PhCH_2$	C_4H_9	6 (**27g**)	63 (**29g**)	-24.2 (24, 1.38)
8	$PhCH_2$	C_4H_9 d)	-- f) (**27g**)	74 (**29g**)	-24.5 (26, 0.56)
9	$PhCH_2$	C_9H_{19}	8 (**27h**)	44 (**29h**)	-22.5 (23, 1.25)
10	$PhCH_2$	$PhCH_2$	-- f) (**27i**)	33 (**29i**)	-8.50 (26, 0.84)

a) 3 equiv. of Et_3SiH and 6 equiv. of $BF_3 \cdot OEt_2$ were used. b) Isolated yield. c) Measured in $CHCl_3$.
d) BuLi was used. e) Yield after reduction to alcohol with $NaBH_4$. f) Ketone form was not observed.

Table 2. Stereoselective reduction of the quaternary α-hydroxypyrrolidine (56)

Entry	Reagent	Additive[a] (equiv.)	Solvent	Temp. (°C)	Yield[b] (%)	Ratio of **57a** : **57b**[c]
1	$NaBH_4$	none	MeOH	18	86	17 : 83
2	DIBALH	$MgBr_2$ (2)	Et_2O	-78	69	61 : 39
3	DIBALH	$SmCl_3$ (2)	toluene	-78	90	73 : 37
4	$NaBH_4$	$MgCl_2$ (2)	MeOH	0	73	42 : 58
5	$NaBH_4$	$CaCl_2$ (2)	MeOH	0	82	67 : 33
6	$NaBH_4$	$MnCl_2$ (2)	MeOH	0	83	44 : 56
7	$NaBH_4$	$CeCl_3$ (2)	MeOH	0	87	80 : 20
8	**$NaBH_4$**	**$CeCl_3$ (2)**	**MeOH**	**-18**	**88**	**81 : 19**
9	$NaBH_4$	$CeCl_3$ (2)	MeOH	-78	90	68 : 32
10	**$NaBH_4$**	**$SmCl_3$ (2)**	**MeOH**	**0**	**90**	**92 : 8**
11	$NaBH_4$	$SmCl_3$(0.05)	MeOH	-18	90	68 : 32
12	$NaBH_4$	$SmCl_3$ (4)	MeOH	-18	89	82 : 18
13	$NaBH_4$	$SmCl_3$ (2)	*i*-PrOH	-18	72	86 : 14
14	**$NaBH_4$**	**$SmCl_3$ (2)**	**MeOH**	**-18**	**88**	**95 : 5**
15	$NaBH_4$	$SmCl_3$ (2)	MeOH	-78	89	80 : 20

a) Dried *in vacuo* at 140 °C. b) Isolated yield as a mixture of **57a** and **57b**. c) Determined by chiral HPLC (Daicel chiralpak AD).

Chapter 2

SmI_2-promoted tandem desulfurization and reductive coupling reactions of aromatic lactams with carbonyl compounds

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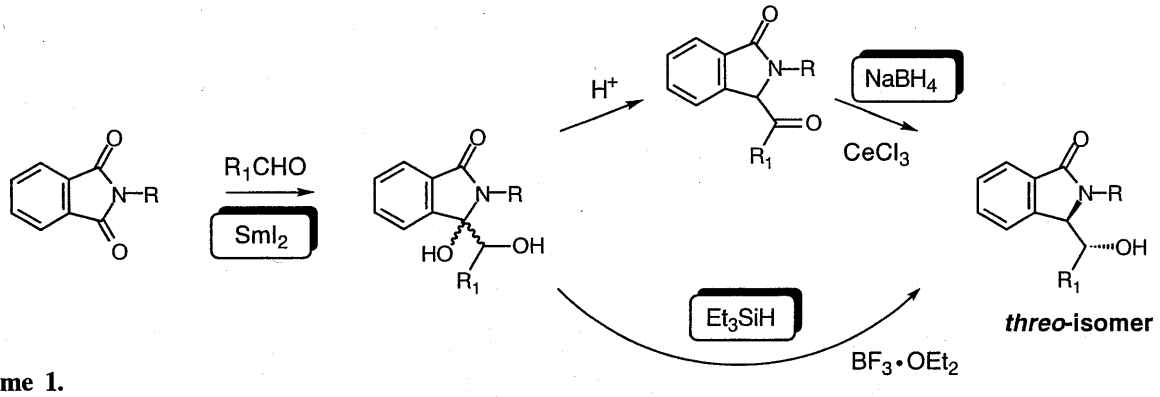
Abstract—Treatment of sulfur-substituted aromatic lactams with carbonyl compounds in the presence of samarium(II) diiodide was found to undergo novel tandem desulfurization and reductive coupling reactions to generate α-hydroxyalkylated lactams in high yield. Stereochemistry of the coupling products was researched and the results that decreasing the steric bulkiness of the *N*-substituents as well as raising the reaction temperature leads to an increase of the *erythro*-selectivity were observed. The mechanistic origins of this stereoselectivity are also briefly documented.

Since its introduction by Kagan and co-workers[1] SmI_2 has been extensively investigated as a powerful electron donor able to promote a wide range of reductions and coupling reactions.[2] Its use in synthesis has been especially advantageous for ring closure reactions and C-C bond formation such as hydroxyl-directed addition of carbonyl to C=C double bond and stereocontrolled intramolecular pinacol reactions.[2k,3] The reactions of acid chlorides[4] and acid anhydrides[5] with this reagent have also been researched. In addition, intramolecular and intermolecular Barbier-type reactions with haloalkanes toward the carbonyl group of ketones[6] and imides[7] have been reported. In this connection recent disclosures from this laboratory have demonstrated the first pinacolic cross-coupling reaction between phthalimides and carbonyl compounds and its application to two types of complete *threo*-selective reactions; $CeCl_3$-mediated reduction after dehydration of the coupling products is the first and the second one is direct Lewis acid–promoted deoxygenation of the coupling substrates with Et_3SiH as shown in Scheme 1.[8] Although significant progress, thus, has been made in advancing the versatility of samarium(II) compounds, the lack of studies concerning the reactivity toward simple amides is surprising except in some special cases.[9] This should be attributed to their low reactivity. Herein we report our successful efforts for the development of novel SmI_2-mediated tandem reaction of sulfur-substituted aromatic lactams with carbonyl compounds, leading to the α-hydroxyalkylated products with *erythro*-selectivity.



Scheme 1.

Initial experiments have been performed on a coupling reaction promoted by SmI_2 between γ-hydroxy-, phenylthio-, or phenylsulfonyl-substituted phthalides and iodobutane with a variety of additives such as HMPA, $CuCl_2$, $FeCl_3$, or NiI_2[6b,10] in expectation of new C-C bond formation.[11] The reactions, however, did not proceed under any conditions even in the use of excess SmI_2. Next, we examined the same type of reactions employing similarly sulfur-substituted *N*-benzyllactams **2**[12] prepared from imides **1** (Table 1) and iodobutane, which, in turn, changed the results and unexpectedly gave the desulfurized lactam alone in high yield (up to 89%) without coupling adducts.

With the above desulfurization method in hand, we researched the tandem reaction followed by C-C bond formation of **2** employing more reactive aldehyde than haloalkane. The results from our survey are summarized in Table 1. To begin with, treatment of *N*-benzyl-phenylthiolactam **2a** with heptanal in the presence of 2 equiv of SmI_2 at ambient temperature for 1 h rapidly provided the desired tandem reaction products **3** but in low yield (entry 1) due to the formation of the aldehyde-self-coupling compouds. The use of excess SmI_2 (3 equiv), however, had a dramatic effect on the rate, giving **3** in 86% isolated yield within 5 min (entry 3). The same beneficial results were again obtained in reaction employing the phenylsulfonyllactam **2b** (80% in entry 4). We were delighted to find that 5 equiv of this reagent (entry 5) could effect these reactions in excellent yield (98%) without byproducts except the aldehyde-dimerized substances. This procedure is also applicable for the production of a wide range of α-hydroxylalkylated lactams through replacement of the *N*-benzyl group by the larger diphenylmethyl (entry 7) or the smaller methyl functions (entries 8-13) together with a change from the sulfur- to the seleno-substituent in **2** (entry 6). Although the reason why such unusual desulfurization and subsequent

coupling reactions were observed in the use of lactams is not clarified at present, the presence of a nitrogen atom in the substrate has a decisive role and is indispensable for these reactions.

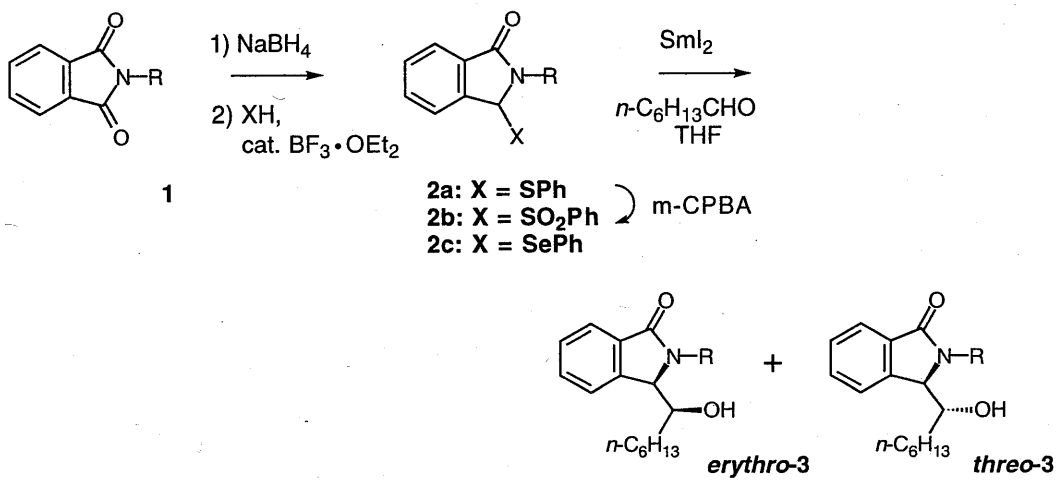


Table 1. SmI_2-promoted tandem reactions of lactams 2 with aldehyde[a]

entry	X	R	SmI_2, (equiv)	temp, °C	yield, %[b]	*erythro/threo*[c]
1	SPh	CH_2Ph	2.0	rt	22	---
2	SO_2Ph	CH_2Ph	2.0	rt	42	---
3	SPh	CH_2Ph	3.0	rt	86	83 / 17
4	SO_2Ph	CH_2Ph	3.0	rt	80	79 / 21
5	SO_2Ph	CH2Ph	5.0	rt	98	79 / 21
6	SePh	CH_2Ph	3.0	rt	58	---
7	SPh	$CHPh_2$	3.0	rt	39	55 / 45[d]
8	SPh	CH_3	3.0	-20	63	76 / 24[d]
9	SO_2Ph	CH_3	3.0	-20	69	68 / 32[d]
10	SPh	CH_3	3.0	0	71	82 / 18[d]
11	SO_2Ph	CH_3	3.0	0	73	84 / 16[d]
12	SPh	CH_3	3.0	rt	69	92 / 8[d]
13	SO_2Ph	CH_3	3.0	rt	90	92 / 8[d]

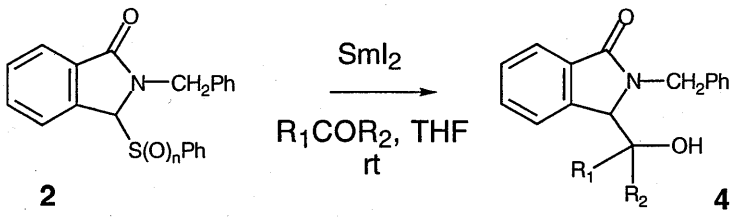
a) All reactions employed 3.0 equiv of heptanal.

b) Isolated yield.

c) Isolated ratio after chromatographic separation unless otherwise indicated and stereochemistry determined according to our preceding report.[8]

d) Determined by 1H NMR.

We further found that the use of both aliphatic (entries 1-4 shown in Table 2) and sterically more hindered aromatic ketones (entries 5,6) also underwent fast reactions (5 min) to afford the corresponding desulfurized coupling products with good to high yields in contrast to the fact that direct SmI_2-promoted reaction of phthalimides with ketones did not provide any desired coupling adduct.[8] This strategy will find convenient usage and proved to be a superior C-C bond formation method accompanying the desulfurization reaction.



2 **4**

Table 2. SmI_2-promoteda tandem reactions of lactams **2** with ketones[a]

entry	n	R_1	R_2	yield, %[b]
1	0	CH3	CH3	50
2	2	CH3	CH3	85
3	0	CH3	*n*-C3H7	71
4	2	CH3	*n*-C3H7	79
5	0	CH3	Ph	72
6	2	CH3	Ph	85

a) Reactions employed 3 equiv of SmI_2 and ketones, respectively.

b) Isolated yield.

In addition to the development of novel tandem reaction described here, we investigated the stereochemistry of these products, since the stereodefined construction of *threo*- or *erythro*-heterocyclic moieties with a hydroxyl-containing side chain attracts considerable attention due to their presence in the framework of natural products.[13]

It will particularly be of interest to note that decreasing the steric bulkiness of the *N*-substituents as well as raising the reaction temperature[14] up to rt led to an increase of the *erythro*-selectivity (from 55:45 to 92:8 as shown in Table 1) contrary to our previous *threo*-selective results[8] and the *erythro/threo* ratio of **3** is essentially independent of the leaving groups. The observed reverse stereochemical outcome of these reactions can be explained by consideration using the 6-membered SmI2-chelation models A and B[7b] containing nitrogen lone-paired electrons (Figure 1). In the thermodynamically stable former the reaction progressed through coupling of the radical produced by desulfurization with a carbonyl compound from the same face of the smaller *N*-methyl group and SmI_2, avoiding the mutual steric repulsion between *N*- and aldehyde-alkyl groups. On the other hand, the fact that the steric bulkiness of the *N*-substituents and raising the reaction temperature affect the *erythro*-selectivity reversely can be ascribed to the attack of the radical present in the other 6-membered conformational isomer (Model B) on the carbonyl group, in which the *N*-larger functions prefer to be equatorial. In this case coupling reactions resulted in a decrease of the *erythro*-selectivity, since the aldehyde-alkyl group constituting the chelation structure could occupy both sides.

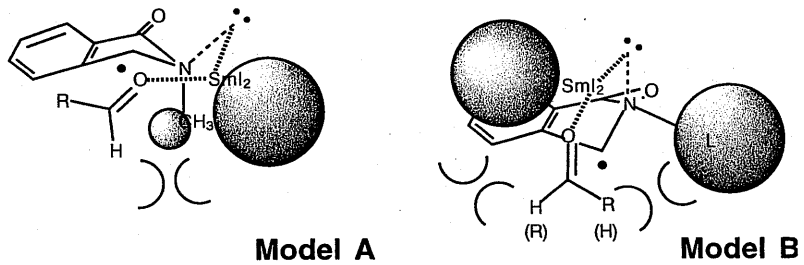


Figure 1. Potential stereocontrol elements.

In conclusion, we have developed synthetically useful tandem SmI_2-mediated desulfurization and reductive coupling reactions that employ commercially available reagents. In addition, the success of these reversely *erythro*-selective reactions together with our previous *threo*-selective results demonstrates the mechanistically fascinating duality of the lactam-employed coupling reactions for controlled carbon-carbon bond formation. Current efforts to expand the scope of coupling partners with this method as well as to elucidate the thermodynamic behavior and detailed mechanism of the reaction are in progress.

Ackowledgments

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Chapter 3

A novel synthetic approach to isoindolobenzazepine alkaloid, chilenine, employing SmI_2-mediated pinacolic coupling reaction

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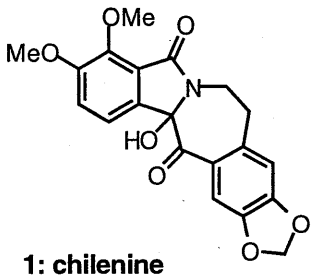
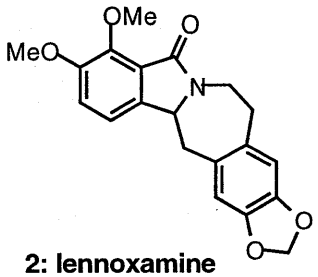
Abstract—Samarium(II) diiodide-mediated intramolecular reductive coupling reaction of phthalimides with *N*-formylated alkyl side chains is shown to afford dihydroxylated tricyclic lactams with 5-7 membered rings. This process was further applied for the preparation of an isoindolobenzazepine alkaloid, chilenine, by featuring the elaboration of the functionalized phthalimide derivative.

Chilenine (**1**) and lennoxamine (**2**) first found in the plants of the Chilean *Berberis* species, *Berberis empetrifolia* Lam and *Berberis darwinii* Hook, respectively, are a new class of alkaloids belonging to the aporhoedane series.[1] Although biogenetically related to protoberberines and usually classified as isoquinoline alkaloids, they are distinguished by the presence of an isoindolo[1,2-*b*][3]benzazepine unit embedded in their skeleton from the simple isoquinoline group. Due to the fact that their structures incorporating the 3*H*-3-benzazepine moiety and equally an isoindolinone ring system are architecturally sophisticated and possess the real and potential biological properties,[2] they have captured the interest as attractive and synthetically challenging targets.[3] Synthetic strategies described up to date, however, in general require multistep reactions or crucial techniques and were not necessarily satisfactory. On the other hand, as part of our work designed to explore the use of cyclic imides, we have demonstrated some significant stereoselective reactions[4] and their applications to the total syntheses of biologically active natural products.[5] In addition, recently novel and stereoselective methods for the preparation of hydroxylactams via reductive coupling reactions mediated by SmI_2 have also been developed in this laboratory.[6] The purpose of the present communication is to describe the result that *N*-functionalized phthalimide derivatives underwent fast SmI_2-induced intramolecular pinacol-type coupling reaction, which in turn made possible to provide a new expeditious and practical opportunity for the synthesis of an isoindolobenzazepine alkaloid, chilenine.

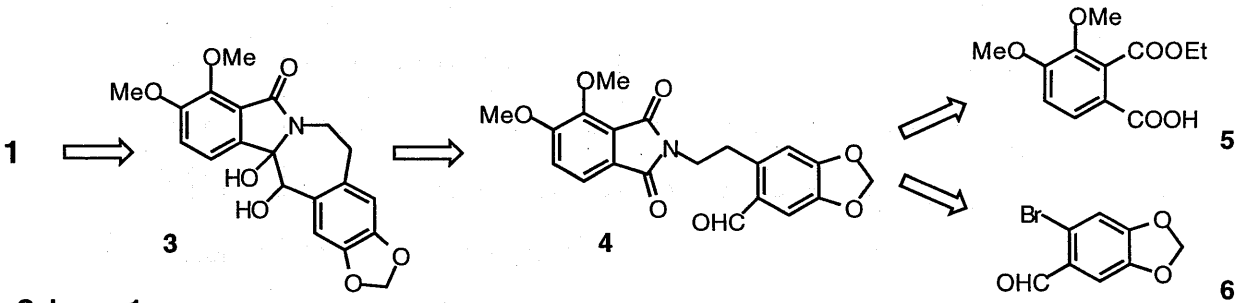


1: chilenine



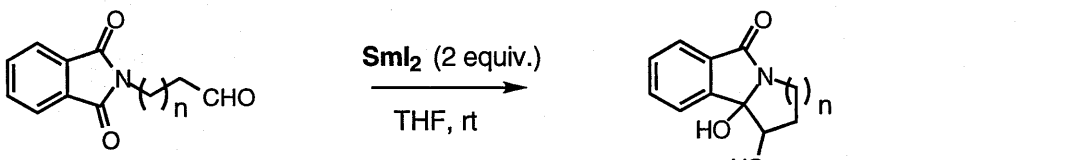
2: lennoxamine

In formulating the synthetic plan for chilenine (**1**), we envisioned that the benzazepine ring of significant precursor **3** would originate from the intramolecular coupling reaction of **4**, which could be divided into two known fragments, acid ester **5**[7] and bromopiperonal (**6**),[8] respectively (Scheme 1).



Scheme 1

In advance, initial experiments have been performed on the intramolecular coupling reaction in the presence of SmI_2 (2 equiv.) in THF at rt employing simple phthalimide derivatives **7**[9] with *N*-formylated alkyl substituents. As shown in Scheme 2, it became apparent that these conditions without additives brought about the desired dihydroxylated tricyclic lactams **8** with 5-7 membered rings in satisfactory yields, respectively.[10]



7a: n = 1
7b: n = 2
7c: n = 3

8a: n = 1 y. 86%
8b: n = 2 y. 79%
8c: n = 3 y. 63%

Scheme 2

With these results in hand, we next focussed our attention on the synthesis of **1**, an isoindolobenzazepine natural product. The results from our survey are summarized in Scheme 3.

To begin with, the ethylene acetal compound derived from bromopiperonal (**6**) was converted into **9** via aromatic allylation,[11] which underwent dihydroxylation and oxidative cleavage of the olefinic part followed by reduction to give the alcohol **10** in high yield after successive reactions of deacetalization, reduction, and MPM(*p*-methoxybenzyl)-protection. On the other hand, acid ester **5** was submitted to coupling reaction with MPM-amine to afford the cyclic imide directly, which was then deprotected with cerium ammonium nitrate (CAN), leading to the *N*H-imide **11**. Thus, reaction of **11** with the alcohol **10** prepared above under Mitsunobu conditions proved to yield the condensation product **12** in moderate yield. When the subsequent deprotection of the MPM-group in **12** was effected by the use of DDQ, it was apparent that the desired aldehyde intermediate **4** could be obtained directly. Finally, SmI_2-mediated intramolecular pinacolic reaction of **4** was performed to give the crucial coupling product **3** in 65% yield with fortunately complete regioselectivity. The ratio of the two diastereomers (*cis:trans* = 3:1) was easily determined by ^1H NMR.[12] Since both of these isomers of **3** has already been converted into **1** via the same enol acetate[12] by Danishefsky et al.[13] in high yield, the whole sequence of reactions constitutes, in a formal sense, a total synthesis of natural chilenine.

In summary, we have found SmI_2-mediated intramolecular coupling reaction of cyclic imides with aldehyde-alkyl side chains to give some isoindolone derivatives directly and accomplished the formal synthesis of chilenine natural alkaloid employing this procedure. This process provides an easily accessible alternative to existing synthetic methods of isoindoloazepine alkaloids.

Acknowledgments

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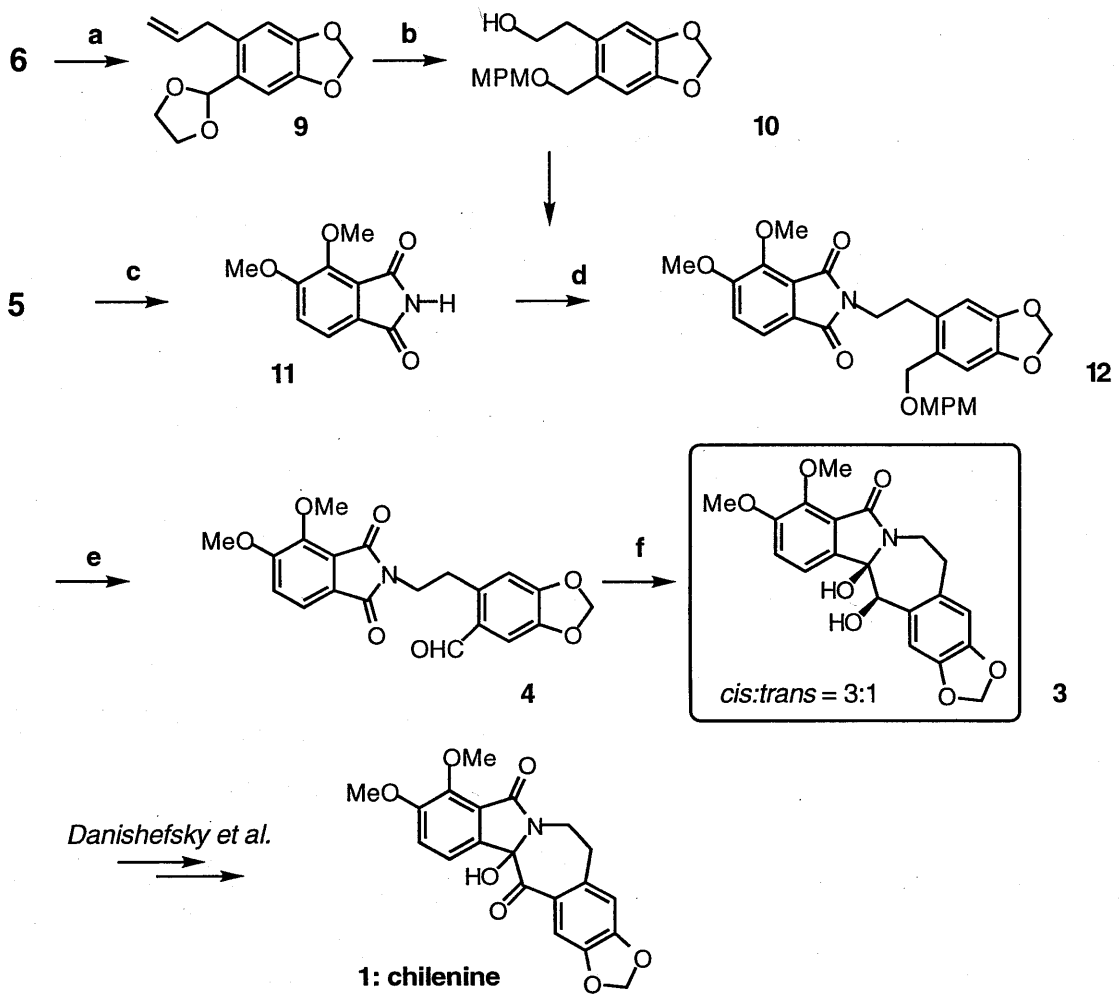

Scheme 3. Reagents and conditions: (**a**) **1**, $HO(CH_2)_2OH$, *p*-TsOH, toluene, reflux; quant.; **2**, BuLi, ether, -60 °C, then allyl bromide; 63%; (**b**) **1**, conc. HCl, ether; **2**, $NaBH_4$, MeOH; 78% (2 steps); **3**, MPMCl, Ag_2O, CH_3COOEt; 82%; **4**, OsO_4, NMO, acetone-H_2O (1:1), **5**, $NaIO_4$, ether-H_2O (1:1), -5 °C; **6**, $NaBH_4$, MeOH; 80% (3 steps); (**c**) **1**, $MPMNH_2$, DCC, CH_2Cl_2; 78%; **2**, CAN, CH_3CN-H_2O (9:1), -10 °C; 65%; (**d**) (**10**), DEAD, PPh_3, THF; 46%; (**e**) DDQ, CH_2Cl_2-H_2O (10:1), -10 °C; 54%; (**f**) SmI_2 (3 equiv.), THF; 65%.

Ackowledgments

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