RECENT ADVANCES IN THE TOTAL SYNTHESIS OF INDOLIZIDINE IMINOSUGARS

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Abstract – The importance of sugar-mimic glycosidase inhibitors in biochemistry, medicinal chemistry, and in the various aspects of life processes presents a challenge. The structural diversity of their multichiral architecture has long intrigued synthetic chemists to develop novel approaches to this class of compounds. Since glycosidase inhibitors have shown remarkable therapeutic potential in treating various metabolic diseases, an impressive number of synthetic routes to such compounds and their derivatives have been recently developed. This report highlights recent developments in the synthesis of indolizidine iminosugars. Different synthetic strategies have been used such as ring-closing metathesis, dihydroxylation, asymmetric epoxidation, [3,3]-sigmatropic rearrangement, desymmetrization, and amination. The potential application of our amination methodology that uses chlorosulfonyl isocyanate (CSI) for producing a variety of polyhydroxylated alkaloids will be presented.

INTRODUCTION
Iminosugars (or azasugars) are structural analogues of carbohydrates in which the ring oxygen is replaced by a nitrogen atom. These iminosugars have been reported to inhibit various glycosidases in a reversible or competitive manner due to a structural resemblance to the sugar moiety of the natural substrate. Glycosidases are enzymes that are involved in a wide range of anabolic and catabolic processes that are based on molecular recognition. These biological processes include intestinal digestion, the biosynthesis of glycoproteins, and lysosomal catabolism of glycoconjugates. Since the majority of glycosidase
inhibitors have shown remarkable therapeutic potential in many diseases such as viral infections, diabetes mellitus, obesity, genetic disorders, and tumor metastasis, much attention has been directed at iminosugars as future drugs. For example, two N-alkylated derivatives of deoxynojirimycin, miglitol (Glyset™) and N-butyl-deoxynojirimycin (Zavesca™), are drugs for the treatment of type II diabetes mellitus and Gaucher’s disease, respectively.²

Over the past 40 years, more than 100 polyhydroxylated alkaloids have been isolated from both plants and microorganisms. Naturally occurring polyhydroxylated alkaloids with a nitrogen atom in the ring are divided into five structural classes: pyrrolidines, piperidines, pyrrolizidines, indolizidines, and nortropanes. These alkaloids bind directly or indirectly to the active sites of glycosidases, because of their structural resemblance to the corresponding natural substrates. The realization that these azasugars might have enormous therapeutic potential in many diseases has led to the development of an impressive number of synthetic routes to create such compounds.³

In 1966, nojirimycin (1, NJ) was discovered as the first natural polyhydroxylated alkaloid that mimics a sugar (Figure 1). It was isolated from a Streptomyces filtrate,⁴ and was found to be a potent inhibitor of α- and β-glucosidase.⁵ Mannojirimycin (2, manno-NJ) and galactonojirimycin (3, galacto-NJ), two other iminosugars containing the hydroxyl group at C-1, were also isolated from the fermentation broth of Streptomyces species. Mannojirimycin (2) was co-produced with nojirimycin by Streptomyces lavendulae SF-425,⁶ while galactonojirimycin (3) was isolated from Streptomyces lydicus PA-5726 as a potent β-galactosidase inhibitor.⁷ Since these iminosugars bearing a hydroxyl group at C-1 are fairly unstable, they are relatively difficult to isolate and handle, and are usually stored as bisulfite adducts.

The first 1-deoxy derivative, 1-deoxynojirimycin (4, DNJ), was first chemically synthesized from l-sorbofuranose⁸ by the reduction of 1.⁹ It was isolated from the roots of Mulberry trees¹⁰ and Streptomyces cultures.¹¹ This compound was found to be a potent inhibitor of α-glucosidases and other glycosidases.¹² The 2-epimer of 4, 1-deoxymannojirimycin (5, DMJ) was first isolated from the seeds of the legume Lonchocarpus sericeus found in the West Indies and tropical America. This compound showed strong inhibitory activities toward several mannosidases as shown in Figure 2.¹³
The first example of indolizidine alkaloids was swainsonine (6), isolated from the leaves of *Swainsona canescens* in 1979. Later it was also found in *Astragalus* spp., together with swainsonine *N*-oxide. The trihydroxylated indolizidine 6 has received much attention due to an effective α-mannosidase inhibitory action. It was also the first inhibitor to be selected for testing as an anticancer drug, reaching phase I clinical trials (Figure 3).

The tetrahydroxylated indolizidine, castanospermine (7), is a bicyclic analogue of deoxynojirimycin that has an ethylene bridge between the hydroxymethyl group and the nitrogen atom. It was first isolated in 1981 from the seeds of *Castanospermum australe* and its structure was confirmed by X-ray crystallography. Castanospermine was found to be a powerful inhibitor of human α- and β-mannosidases.

Lentiginosine (8) and 2-epi-lentiginosine (9), extracted from the leaves of *Astragalus lentiginosus* in 1990, are the first α-glucosidase inhibitors that have been found to possess only two hydroxyl groups. The biosynthetic origin of these dihydroxylated indolizidine alkaloids is related to other polyhydroxylated indolizidine alkaloids such as 6 and 7. Lentiginosine is a potent competitive inhibitor (IC_{50} 5μg/mL) of fungal amyloglucosidase, while the 2-epimer 9 has no activity toward any of the glycosidase that were tested.

Given the enormous therapeutic potential of iminosugars, the development of improved synthetic methodologies for their synthesis has become the objective of many synthetic chemists. This report highlights recent developments in the synthesis of indolizidine iminosugars according to the different synthetic strategies, i.e. ring-closing metathesis, dihydroxylation, asymmetric epoxidation,
[3,3]-sigmatropic rearrangement, desymmetrization, and amination. In addition, the potential application of our amination methodology that uses chlorosulfonyl isocyanate (CSI) to produce a variety of polyhydroxylated alkaloids will be described.

RESULTS AND DISCUSSION

Ring-Closing Metathesis

The last 13 years have witnessed considerable development of metathesis reactions and an explosion of their application in organic synthesis. Among them, ring-closing metathesis (RCM) has emerged as one of the most powerful methods for the preparation of carbocyclic and heterocyclic compounds (Figure 4).

In the construction of iminosugars, the RCM reaction is one of the most efficient strategies to construct the heterocycle with the formation of the double bond in the right position occurring simultaneously in a single step.

In the total synthesis of (−)-lentiginosine reported by Singh et al., the ring-closing metathesis was used as the key step for the construction of the indolizidine skeleton, as illustrated in Scheme 1. The synthesis of (−)-8 started with the diol 10, which was prepared from commercially available D-mannitol by a previously described method. The cleavage of the diol 10 with lead tetraacetate gave a crude aldehyde, which was reduced to the alcohol by treatment of sodium borohydride. The alcohol, without any purification, was converted into the azide 11 by treating its tosylate with sodium azide in DMF. The acetonide group of 11 was removed to give the diol 12 by treatment of trifluoroacetic acid in a mixture of THF and water.

The diastereoselective addition of allyltributyltin to the crude aldehyde, prepared from an oxidative cleavage of the diol 12 with lead tetraacetate, was carried out at −78 °C using SnCl₄ as a Lewis acid to give the homoallyl alcohol 13 with a high diastereoselectivity of 99:1. The highly selective addition of the allyl group to the Si-face of the aldehyde can be explained by a more rigid five-membered chelation-controlled transition state rather than a flexible six-membered half-chair transition state.
Treatment of the azido mesylate 14 with lithium aluminum hydride in THF gave the cyclized amine 15 in which an amine produced by reduction of the azide displaced the mesylate via the SN2 mechanism. The secondary amine 15 was converted into the acryl amide 16 using standard conditions. RCM was accomplished with an 85% yield in refluxing toluene in the presence of the 1st generation Grubbs catalyst to give 17. Finally, hydrogenation of 17 followed by the reduction of the crude amide with LiAlH4 furnished (–)-8 in quantitative yield.

Scheme 1. Reagents and conditions: (a) (i) Pb(OAc)4, CH2Cl2; (ii) NaBH4, EtOH; (iii) TsCl, Et3N, CH2Cl2; (iv) NaN3, DMF, 80 °C, 80% for 4 steps; (b) TFA, THF/H2O (4:1), 97%; (c) (i) Pb(OAc)4, CH2Cl2; (ii) SnCl4, allyltributyltin, CH2Cl2, 82% for 2 steps; (d) MsCl, Et3N, CH2Cl2, 92%; (e) LiAlH4, THF, 65 °C, 68%; (f) acryloyl chloride, Et3N, CH2Cl2, 85%; (g) 1st generation Grubbs catalyst (10 mol%), toluene, reflux, 86%; (h) (i) Pd/C, H2, MeOH; (ii) LiAlH4, THF, 97% for 2 steps

Génsisson and coworkers also employed the RCM reaction for straightforward synthesis of (–)-8 and of its pyrrolizidine analogue starting from chiral cis-α,β-epoxyamine 18,23 which is readily available from the corresponding chiral epoxy aldehyde, as shown in Scheme 2.24
opening of epoxide 18, butenyl moiety was introduced to give 20. The treatment of 20 with the second generation 1,3-bis(mesityl)-2-imidazolidinylidene substituted ruthenium Grubbs catalyst (2\textsuperscript{nd} generation Grubbs catalyst) was found to be superior to the first generation Grubbs catalyst in the formation of the tetrahydropyridine ring 21. The catalytic hydrogenation of 21 followed by the Appel cyclization gave (−)-8.

Scheme 2. Reagents and conditions: (a) H\textsubscript{2}SO\textsubscript{4}, 1,4-dioxane, reflux, 70%; (b) 4-butenyl trifluoromethanesulfonate, proton sponge, CH\textsubscript{2}Cl\textsubscript{2}, rt, 67%; (c) 2\textsuperscript{nd} generation Grubbs catalyst (8 mol%), toluene, 80 °C, 66%; (d) H\textsubscript{2}, Pd/C, MeOH, HCl, rt, 90%; (e) PPh\textsubscript{3}, CCl\textsubscript{4}, Et\textsubscript{3}N, rt, 68%

Cardona et al. also used the RCM reaction for the construction of the six-membered ring of (+)-lentiginosine 8.\textsuperscript{25} This strategy was based on a highly selective addition of vinylmagnesium bromide to nitron 22 derived from L-tartaric acid.

Scheme 3. Reagents and conditions: (a) vinylmagnesium bromide, Et\textsubscript{2}O, 96%; (b) In (18 mol%), Zn (400 mol%), MeOH, NH\textsubscript{4}Cl, reflux, 84%; (c) CH\textsubscript{2}=CHCH\textsubscript{2}CO\textsubscript{2}H, HOBt, DCC, 71%; (d) 1\textsuperscript{st} generation Grubbs catalyst (12 mol%), CH\textsubscript{2}Cl\textsubscript{2}, 60%; (e) (i) LiAlH\textsubscript{4}, THF, 62%; (ii) H\textsubscript{2}, Pd/C, MeOH, 90%; (iii) CF\textsubscript{3}CO\textsubscript{2}H, 74%
As shown in Scheme 3, the addition of 1.2 equiv. of vinylmagnesium bromide in Et₂O at room temperature provided 23 as a single diastereomer, which was derived from the preferred anti attack of the organometallic reagent with respect to the vicinal alkoxy group. After the reduction of hydroxylamine 23 using organoindium reagent,²⁶ the amine 24 was then coupled with but-3-enoic acid to yield amide 25. The RCM reaction of 25 was performed with the first generation Grubbs catalyst to give indolizidinone 26, which was transformed into the target (+)-lentiginosine (8) for two steps.

**Dihydroxylation**

Dihydroxylation reactions using osmium tetroxide (OsO₄) in the presence of N-methylmorpholine N-oxide (NMO) have found wide application in the synthesis of a large number of iminosugars. In recent work by Parsons and coworkers, a key step in the formal synthesis of (–)-8-epi-swainsonine was based on a diastereoselective dihydroxylation of a cyclic carbamate 27, as illustrated in Scheme 4.²⁷ The HOMO of 27 has an unsymmetrical π bond with higher electron density on the endo face of the bicyclic system. Therefore, cis-dihydroxylation of 27 using OsO₄ and NMO led to the formation of the endo diol 28 as a major product. After the acetonide protection of diol 28 followed by hydrolysis of carbamate, the resulting amine was protected using (Boc)₂O. The primary alcohol was oxidized using TPAP to give the aldehyde 29 in high yield.

**Scheme 4. Reagents and conditions:** (a) OsO₄ (5 mol%), NMO, acetone, H₂O, 85%; (b) (MeO)₂CMe₂, PPTS, acetone, reflux, 95%; (c) LiOH, EtOH, reflux; (d) (Boc)₂O, Et₃N, MeCN, 85% for 2 steps; (e) TPAP (5 mol%), 4Å MS, NMO, CH₂Cl₂, 98%; (f) vinylmagnesium bromide, THF, 85%; (g) TBSOTf, Et₃N, CH₂Cl₂, 98%; (h) ZnBr₂, CH₂Cl₂, 81%; (i) allyl bromide, K₂CO₃, THF, reflux, 91%; (j) 2nd generation Grubbs catalyst (20 mol%), CH₂Cl₂, reflux, 70%; (k) H₂, Pd/C, EtOAc, 54%
Addition of vinylmagnesium bromide to aldehyde 29 afforded allylic alcohol 30 as a single product. The stereoselectivity of this reaction can be explained by the chelation of the magnesium ion to both the aldehyde and Boc carbonyl groups. Silylation, deprotection of Boc group, and N-allylation provided the diene 31, which was converted into the indolizidine core 32 via RCM using the 2nd generation Grubbs catalyst followed by hydrogenation. Indolizidine 32 could be transformed into (−)-8-epi-swainsonine.

**Asymmetric Epoxidation**

A total synthesis of (−)-swainsonine (6) by a route involving the Sharpless asymmetric epoxidation to induce chirality was reported by Pyne et al., as shown in Scheme 5.  

![Scheme 5](image)

**Scheme 5.** Reagents and conditions: (a) (−)-DIPT (15 mol%), Ti(OiPr)₄ (15 mol%), t-BuOOH, 4Å MS, CH₂Cl₂, −15 °C, 52%; (b) (COCl)₂, DMSO, Et₃N, CH₂Cl₂, −50 °C, 94%; (c) methyltriphenylphosphonium bromide, KHMDS, toluene, rt, 67%; (d) allylamine, p-TsOH·H₂O (15 mol%), 105 °C, 88%; (e) (Boc)₂O, Et₃N, THF, rt, 98%; (f) 1st generation Grubbs catalyst (6.5 mol%), CH₂Cl₂, reflux, 95%; (g) NaH, THF, BnBr, n-Bu₄NI, rt, 74%; (h) TFA, anisole, CH₂Cl₂, rt, 88%; (i) CBr₄, PPh₃, Et₃N, CH₂Cl₂, 0 °C, 74%; (j) AD-mix-α, (DHQ)₂PHAL, t-BuOH, CH₃SO₂NH₂, 4 °C; (k) 2,2-dimethoxypropane, p-TsOH, CH₂Cl₂, rt, 50%

The (E)-allylic alcohol 33 under Sharpless catalytic asymmetric epoxidation conditions gave the corresponding (2R,3R)-epoxyalcohol 34 in 52% yield and in 92%ee. Swern oxidation and Wittig olefination afforded the chiral vinyl epoxide 35. Regioselective ring opening of vinyl epoxide 35 was
performed by heating with an excess amount of allylamine in the presence of \( p \)-TsOH to give the anti-amino alcohol 36 as a single diastereomer in 88% yield. After the Boc protection of the amine moiety, treatment with the 1st generation Grubbs catalyst furnished the 2,5-dihydropyrrole 37 in 94% yield for two steps. Standard protective group manipulations delivered the amino alcohol, which was cyclized under the Appel condition to give the indolizidine 38 in 74% yield. Dihydroxylation of 38 with AD-mix-\(\alpha\) or AD-mix-\(\beta\) provided \(\textit{syn}\)-diols with excellent diastereoselectivities of 92:2 or 95:5, respectively. The facial selectivity in the dihydroxylation can be explained by the addition of the bulky osmium reagent to the \(\alpha\)-face of the molecule. However, the attack from the \(\beta\)-face would be hindered by the pseudoaxial protons \(H_{8\alpha}\) and \(H_{3\beta}\), as shown in Figure 5. In contrast, a poor diastereoselectivity of 2:1 was obtained with the use of \(\text{OsO}_4\) and NMO. Finally, the removal of the protecting group of 39 gave \((-\)swainsonine (6).

![Figure 5](image)

In the light of this work, \((\)\(+\)\()\)-1,2-di-\(\textit{epi}\)-swainsonine was prepared from the 2,5-dihydropyrrole 37 in a similar way, just via reversing the order of the dihydroxylation and the cyclization reactions, as illustrated in Scheme 6.

![Scheme 6](image)

\textbf{Scheme 6. Reagents and conditions:} (a) \(\text{K}_2\text{OsO}_4\cdot2\text{H}_2\text{O}\) (7 mol%), NMO, acetone, H\(_2\)O, rt, 90%

This strategy shows an excellent diastereoselectivity of the dihydroxylation of 37 to give 40 as a sole diastereomer in 90% yield. The diastereoselectivity of the dihydroxylation can be explained by the steric hindrance of the C-2 substituent on 2,5-dihydropyrrole.
Sigmatropic Rearrangement

Ichikawa and coworkers demonstrated a total synthesis of (+)-lentiginosine (8) from L-tartaric acid as a starting material. Asymmetric addition of diethylzinc to the aldehyde, derived from the alcohol 41, afforded the chiral alcohol 42 (Scheme 7). Subsequent [3,3]-sigmatropic rearrangement of allyl cyanate 43 provided the isocyanate 45 with a high degree of enantioselectivity. Further manipulations including RCM of 47 afforded the tetrahydropyridine, which was finally converted into (+)-lentiginosine (8).

Scheme 7. Reagents and conditions: (a) 2-iodobenzoic acid, DMSO, 90%; (b) Et₂Zn, (S)-diphenyl(1-methylpyrrolidine-2-yl)methanol, 91%, 93:7 dr; (c) CCl₃CONCO, K₂CO₃, MeOH, H₂O, 95%; (d) PPh₃, CBr₄, Et₃N, –20 °C; (e) Cl₃CCH₂OH, 86%; (f) Zn, AcOH, THF; (g) NsCl, Et₃N, 87% for 2 steps; (h) 3-buten-1-ol, PPh₃, DEAD, 89%

In the total synthesis of (+)-lentiginosine (8), Spino et al. illustrated tandem Mitsunobu reaction and [3,3]-sigmatropic rearrangement of the allylic azide on chiral auxiliary to prepare a key azide intermediate, as shown in Scheme 8. The chiral auxiliary, p-menthane-3-carbaldehyde (48), prepared from menthone in enantiomeric enriched form, was used to induce stereochemistry, and to provide the required allylic azide. Treatment of the starting aldehyde 48 with a vinyllithium reagent afford the alcohol 49, which was then subjected to the Mitsunobu reaction condition to give the azide 50 in an excellent level of diastereoselectivity of 95:5. The stereochemical outcome can be explained by SN₂ displacement of the intermediate phosphonyloxy group by the azide group followed by a [3,3]-sigmatropic rearrangement to the thermodynamically favored regioisomer. After further manipulations, the diene 51 was subjected to
RCM using the Grubbs-Nolan catalyst\textsuperscript{31} to give pyrrolidine 52 in an excellent yield. Stereoselective epoxidation, removal of TBDPS group, and the introduction to the tosylate gave 53, which was cyclized to afford 54. Finally, regioselective ring opening of the epoxide provided (+)-lentiginosine (8).

\begin{center}
\textbf{Scheme 8.} Reagents and conditions: (a) IHC=CH(CH\textsubscript{2})\textsubscript{4}OTBDPS, t-BuLi, AlMe\textsubscript{3}, 56\%, 35:1 dr; (b) PPh\textsubscript{3}, DEAD, HN\textsubscript{3}, 98\%, 95>5 dr; (c) LiAlH\textsubscript{4}, Et\textsubscript{2}O, rt, 86-96\%; (d) K\textsubscript{2}CO\textsubscript{3}, MeCN, allyl bromide, 59\%; (e) (Boc)\textsubscript{2}O, Et\textsubscript{3}N, rt, 92\%; (f) Grubbs-Nolan catalyst (1 mol\%), CH\textsubscript{2}Cl\textsubscript{2}, 100\%; (g) Oxone\textsuperscript{®}, NaHCO\textsubscript{3}, CF\textsubscript{3}CO\textsubscript{2}H, MeCN, 0 °C, 89\%; (h) TBAF, THF, rt, 87\%; (i) TsCl, pyridine, CH\textsubscript{2}Cl\textsubscript{2}, rt, 85\%; (j) TFA, CH\textsubscript{2}Cl\textsubscript{2}, rt, then Et\textsubscript{3}N, 63\%; (k) H\textsubscript{2}SO\textsubscript{4}, dioxane, 71\%
\end{center}

**Desymmetrization**

A large number of groups have developed chemical or enzymatic resolutions as the key step in the synthesis of iminosugars. Silvani \textit{et al.} reported the resolution of pro-chiral diol 56 using \textit{Candida cylindracea} lipase and vinyl acetate in ionic liquid to give acetate 57, which was subsequent transformed into hydroxymethyl indolizidine 58 in nine steps including ring-closing metathesis and dihydroxylation, as shown in Scheme 9.\textsuperscript{32}

\begin{center}
\textbf{Scheme 9.} Reagents and conditions: (a) \textit{Candida cylindracea} lipase, CH\textsubscript{2}=CHOAc, ionic liquid, 40 °C, 90\%, 98\%ee
\end{center}
Takabe and coworkers also described enzymatic resolution for the synthesis of indolizidine alkaloid 62, as illustrated in Scheme 10. Maleic anhydride 59 was converted into the pyrrole 60 via the reaction with PMB-NH$_2$ and the Luche reduction. Lipase PS-D catalyzed kinetic resolution of 60 yielding the alcohol 61 with an excellent level of enantioselectivity (>99%ee). Conversion of the alcohol 61 to the indolizidine 62 was achieved in a further ten steps.

Scheme 10. Reagents and conditions: (a) lipase PS-D, CH$_2$=CHOAc, dioxane, rt, 49%, >99%ee

Amination

We recently reported a novel regioselective and diastereoselective amination of a variety of allylic ethers using chlorosulfonyl isocyanate (CSI) to give allylic amines. Moreover, we have demonstrated the application of this methodology to the total syntheses of (–)-cytoxazone, 35 1,4-dideoxy-1,4-imino-D-arabinitol (DAB1), 36 (–)-lentiginosine, 36 (2R,5S)-dihydroxymethyl-(3R,4R)-dihydroxyprrolidine (DGDP), 37 3-hydroxypipeolic acid, 38 (+)-deoxoprosophylline, 39 D-1-deoxynojirimycin, 40 D-1-deoxyxannojirimycin, 40 D-1-deoxyallonojirimycin, 40 aminocyclopentitols, 41 (+)-polyoxamic acid, 42 and lentiginosine analogues. 44

Our initial study focused on the regioselectivity and the diastereoselectivity of the reaction of anti-1,2-dibenzyl ether 63 with CSI. After the optimization of the reaction conditions under various solvents and temperatures, we found that treatment of the 1,2-anti-tribenzyl ether 63 with chlorosulfonyl isocyanate in toluene at 0 °C for 24 h, followed by the desulfonylation using an aqueous solution of 25% sodium sulfite yielded the 1,2-anti-amino alcohol 64 with an excellent diastereoselectivity of 26:1 in 84% yield, as shown in Scheme 11.

Scheme 11. Reagents and conditions: (a) CSI, Na$_2$CO$_3$, toluene, 0 °C, 24 h, then 25% aq. Na$_2$SO$_3$
Consistent with these observations, this study investigated the diastereoselectivity of the reactions between the cinnamylic polybenzyl ethers (63, 65, 67 and 69) and chlorosulfonyl isocyanate to give the corresponding allylic amine products (64, 66, 68 and 70).

![Scheme 12](image)

**Scheme 12.** Reagents and conditions: (a) CSI, Na₂CO₃, toluene, 0 °C, 24 h, then 25% aq. Na₂SO₃

As shown in Scheme 12, the anti-1,2-dibenzyl ethers 63 and 65 were converted to the anti-1,2-aminoalcohols 64 and 66 as the major products with excellent diastereoselectivities of 26:1 and 15:1, respectively. However, the syn-1,2-dibenzyl ethers 67 and 69 in toluene at 0 °C gave the corresponding syn-1,2-aminoalcohols 68 and 70 in a moderate yield with moderate diastereoselectivities of 4:1 and 3:1 in favor of the syn-isomer.

The observed diastereoselectivities of these reactions can be explained by the neighboring group effect, where the NHCbz group orientation retains its original configuration in benzyl ether via the double inversion of the configuration, as shown in Figure 6. As the polarity of the solvent decreased, the attack of the vicinal OBn (the neighboring group effect) became faster than nucleophilic attack, and the diastereoselectivity of 1,2-aminoalcohol increased. The increased anti-diastereoselectivity of 63 and 65 might have been caused by the decreased steric repulsion between the two bulky substituents, which were placed at the opposite face around the benzyloxonium ion intermediate (transition state A).
Based on the above results, the total synthesis of (–)-lentiginosine (8) was achieved from the benzylated pyranose 71 prepared from commercially available D-lyxose according to the methodology reported in the literature, as shown in Scheme 13.

The Wittig olefination of compound 71 followed by the exchange of the hydroxyl group to the bromine afforded the compound 63 in two steps. Treatment of the 1,2-anti-dibenzyl ether 63 with chlorosulfonyl isocyanate in toluene at 0 °C afforded the 1,2-anti-aminoalcohol 64 with an excellent diastereoselectivity.
of 26:1 in 84% yield. The intramolecular cyclization, the removal of Cbz protective group, and the N-alkylation provided the corresponding the pyrrolidine 72. Treatment of compound 72 with the 1st generation Grubbs catalyst in methylene chloride at reflux provided compound 73 in 10% yield. The yield of compound 73 was improved to 56% when the 2nd generation Grubbs catalyst in methylene chloride was used, but the reaction required 60 h to complete. The best result was obtained when compound 72 was treated with the 2nd generation Grubbs catalyst in toluene, which provided the indolizidine core 73 in 86% yield within 8 h. Finally, the palladium catalyzed hydrogenation of compound 73 afforded (−)-lentiginosine (8) in quantitative yield.

With this efficient route to (−)-lentigninosine, our attention was then focused on the synthesis of the pyrrolizidine alkaloid 76 via a parallel synthetic route (Scheme 14). N-Allylation of the pyrrolidine 74 under standard conditions (allyl bromide, K₂CO₃ and THF) followed by the ring-closing metathesis afforded the pyrrolizidine core 75, which was subjected to a catalytic hydrogenation condition to provide the pyrrolizidine alkaloid (1R,2R,7aR)-1,2-dihydroxy-pyrrolizidine (76) in quantitative yield.

According to previous works, we planned the introduction of N-alkylation and ring-closing metathesis for the synthesis of the pyrroloazepine core 78, which can be converted into (1R,2R,9aR)-octahydro-1H-pyrrolo[1,2]azepine-1,2-diol (83). However, the ring-closing metathesis of 77 was unsuccessful and led to the recovery of the starting material and a small amount of intermolecular olefination byproducts, as shown in Scheme 15. In view of these unsuccessful results, our attention was turned to the intermolecular metathesis reaction between the common intermediate 79 and the olefin 80.

![Scheme 14. Reagents and conditions: (a) allyl bromide, K₂CO₃, THF, 45 °C, 82%; (b) 2nd generation Grubbs catalyst (10 mol%), toluene, reflux, 57%; (c) (i) 10% Pd/C, H₂, 6 N HCl, EtOH; (ii) DOWEX-50Wx8 H⁺ form, (0.5 M NH₄OH eluent), 100%]

![Scheme 15. Ring-closing metathesis approach for the synthesis of 78]
After the optimization of the reaction conditions under various Grubbs catalysts, solvents and temperatures, we found that the treatment of 79 and 80 with 30 mol% of the 2nd generation Grubbs catalyst furnished the corresponding alkene 81 with 3:1 mixture of trans- and cis-isomers in 63% yield (Scheme 16). Treatment of 81 with tetrabutylammonium fluoride followed by the hydrogenation provided the trihydroxylated pyrrolidine alkaloid 82 in 72% yield. Finally, the Appel cyclization and the subsequent resin purification provided the 5,7-bicyclic dihydroxylated alkaloid 83.

Scheme 16. Reagents and conditions: (a) 2nd generation Grubbs catalyst (30 mol%), toluene, 100 °C, 48 h, 57%; (b) TBAF, THF, rt, 8 h, 76%; (c) (i) 10% Pd/C, H2, 6 N HCl, MeOH, rt, 24 h; (ii) DOWEX-50Wx8 H+ form, (0.5 M NH4OH eluent), 72%; (d) (i) PPh3, CCl4, Et3N, DMF, rt, 36 h; (ii) DOWEX-50Wx8 H+ form, (0.5 M NH4OH eluent), 51%

CONCLUSIONS

Iminosugars are a crucial class of compounds and many new methodologies have been developed for the total synthesis of natural and unnatural iminosugars. This account described the recent examples in the total synthesis of indolizidine iminosugars by well-precedented methodologies such as ring-closing metathesis, dihydroxylation, asymmetric epoxidation, [3,3]-sigmatropic rearrangement, desymmetrization, and amination. It is believed that these synthetic strategies can be applied to the preparation of a large range of polyhydroxylated alkaloids or other natural products containing a nitrogen atom in the ring. Even though many successful and efficient routes to iminosugars have been developed, as presented in this minireview, there is still a great deal of research remaining to improve these syntheses in a short, flexible, and highly stereospecific fashion.

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