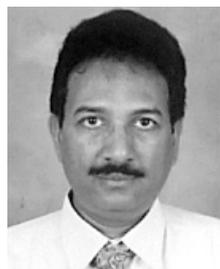


α -Trimethylsilylmethylamine Radical Cation in the Synthesis of Cyclic Amines and Beyond

Ganesh Pandey^{*a}, Debasis Dey, and Smita R. Gadre

Abstract: The evolution of chemistry associated with the photoinduced electron transfer (PET)-generated α -trimethylsilylmethylamine radical cation cyclization to a tethered olefin to synthesize cyclic amine structural frameworks is presented in chronological order. The importance of this interesting chemistry is demonstrated by the synthesis of several novel glycosidase inhibitors.

Keywords: α -Amine radical · Glycosidase inhibitors · 1-*N*-Iminosugars · Photoinduced electron transfer (PET) · α -Trimethylsilyl methylamine radical cation



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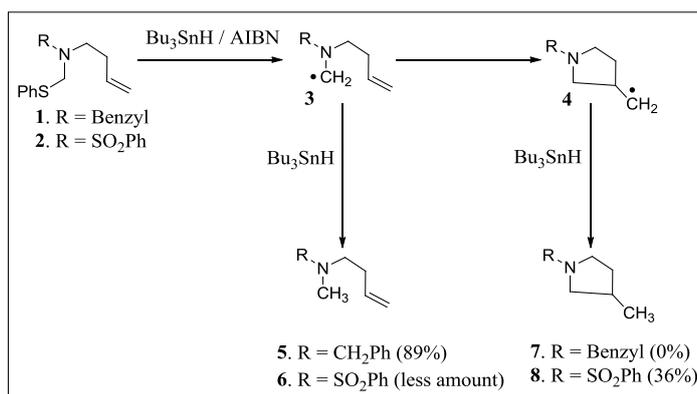
doctoral study (July 1980–May 1983) in the group of Prof. H. A. Morrison. On returning to India, initially he joined (September 1983) Panjab University, Chandigarh as a ‘Pool Officer’ and within a few months moved to IICT, Hyderabad (May 1984) and established his research group at IICT. He once again moved to National Chemical Laboratory, Pune (July 1991) where he is pursuing his research interests in the area of developing new synthetic strategies involving radical ions as reactive species and natural products syntheses. He is recipient of some of the most coveted awards and honors from India.

1. Introduction

Nitrogen-containing heterocycles, such as pyrrolidines, piperidines, pyrrolizidines, indolizidines and quinolizidines are ubiquitous in a large number of naturally occurring alkaloids and pharmaceuticals which are endowed with diverse biological activities.^[1] Bicyclic amines such as pyrrolizidines, indolizidines and quinolizidines are also present in a large number of alkaloids isolated from amphibian skin, which are known to display a variety of biological activities.^[2] Another class of cyclic amines such as polyhydroxy piperidine, pyrrolizidine, quinolizidine and indolizidine constitute a distinct subclass, well known for their glycosidase inhibitory activities.^[3] Glycosidase inhibitors are particularly important in biochemistry and pharmacology owing to their potent application in a variety of carbohydrate-mediated diseases such as HIV, diabetes, hepatitis, cancer, and viral infections such as influenza.^[4] Therefore, developing an efficient synthetic strategy to synthesize substituted cyclic amines^[5–9] has engaged organic chemists over the years.

Although free radicals have evolved as the most significant reactive intermediates, due to their versatility, predictability and functional group tolerance, in the construction of carbocyclic structural frameworks, cyclization of corresponding α -amine radicals, generated through conventional tributyl tin hydride from *N*-alkenyl-*N*-(phenylthio)methyl amines, to obtain cyclic amines failed.^[10] This failure was explained by hypothesizing its reduced radical character due to electronic assistance of nitrogen lone pair to the radical (Scheme 1).

The above result led us to envision that if a trimethylsilyl group is attached to the α -methylene position of a tertiary amine (**9**), a radical cationic species (**10**) generated on nitrogen would be delocalized between silicon and nitrogen through overlap between the filled C–Si σ -orbital and half-filled nitrogen orbital^[11] (Scheme 2) may undergo an S_N2 -type cyclization process to a tethered olefin producing a cyclic amine system as shown in Scheme 2.



Scheme 1. Reactivity of the merostabilized radical.

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2. Background of Concept

The above concept emerged from our broad interest in radical ion chemistry in general and *t*-amine radical cation in particular.^[12] The amine radical cations can be generated efficiently through a photoinduced electron transfer (PET) process, using 1,4-dicyanonaphthalene (DCN) as a light-harvesting electron acceptor, through the photoredox cycle shown in Fig. 1.

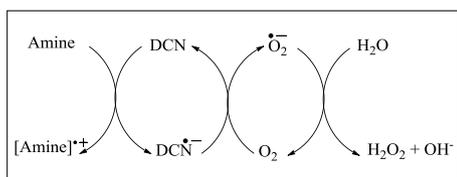


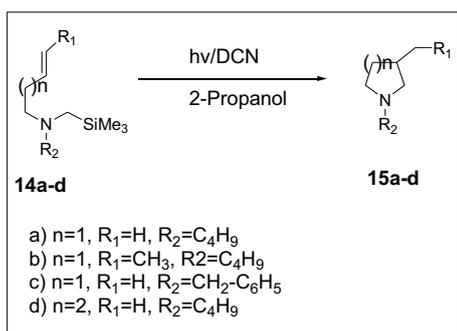
Fig. 1. Photoredox cycle for generating amine radical cations.

3. Results and Discussion

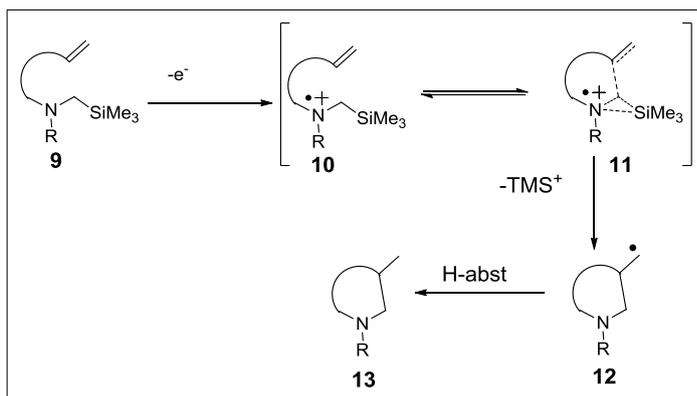
Our concept as outlined in Scheme 2 was vindicated when photolysis (450-W Hanovia lamp housed in a Pyrex vessel, >300 nm, 2 h), of a mixture of **14a–d** and 1,4-dicyanonaphthalene (DCN) in *iso*-propanol produced cyclic amines **15a–d** in high yields^[13] (Scheme 3). The reaction was found to be successful on a variety of substrates and the entire amount of DCN was recovered at the end of the reaction.

The most favourable *exo*-cyclization product was formed in each case. Although, according to Beckwith's radical cyclization guidelines,^[14] cyclization of **16** was supposed to produce exclusively **17a**, it produced a 1:1 diastereomeric mixture of **17a** and **17b**. Similarly **18** produced a 1:1 mixture of **19a** and **19b** (Scheme 4).

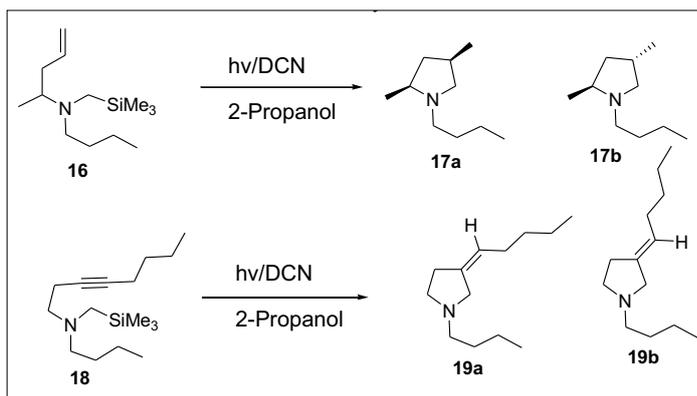
This unexpected cyclization result was explained by considering two easily interconvertible chair-like transition states (Fig. 2) where the energy barrier for interconversion was assumed to be very low.^[15,16] In order to support this explanation, cyclization of amines of type **20–23** were



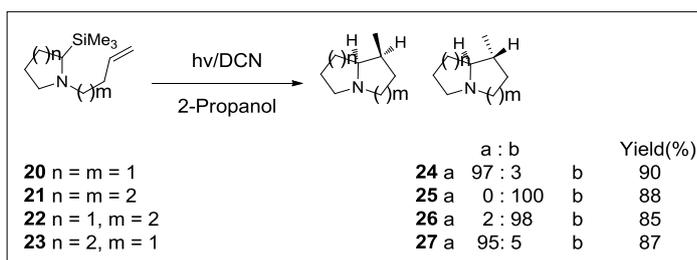
Scheme 3. Generation and reaction of α -trimethylsilyl-methylamine radical cations.



Scheme 2. Concept for the generation of an α -trimethylsilyl-methylamine radical cation.



Scheme 4. Stereochemical outcome of cyclization.



Scheme 5. Stereoselective construction of pyrrolizidine/indolizidine frameworks.

considered as in these cases interconversion would be restricted. The results are discussed in the next section.

4. Stereoselectivity in the Cyclization of Cyclic Amines

PET activation of cyclic amines **20–23** produced the corresponding bicyclic amines **24–27** with an interesting stereochemical outcome. For example, the 1,5/1,6-stereochemistry was found to be dependent on the ring size being formed. In case of **20** and **23** where the new ring formed was five-membered, 1,5-*cis* stereo-

chemistry was predominant whereas in the case of **21** and **22** where a six-membered ring is formed, 1,6-*trans* stereochemistry emerged (Scheme 5).

The 1,5-*cis* stereoselectivity for **24a** and **27a** was explained by invoking 'chair-like' transition states **28** analogous to the ring closure of 2-but-3-enylcycloalkyl radicals. Similarly, the emergence of *trans*-stereochemistry for **25b** and **26b** was visualized in terms of the 'chair-like' transition state **29** where effective overlap between the SOMO of the radical cation and olefin π -orbitals of olefin results in a 1,6-*trans*-stereochemistry (Fig. 3).^[17]

This stereochemical outcome provided

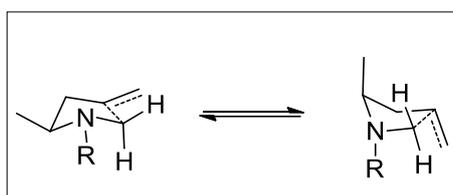


Fig. 2. Proposed transition state to explain the lack of stereoselectivity.

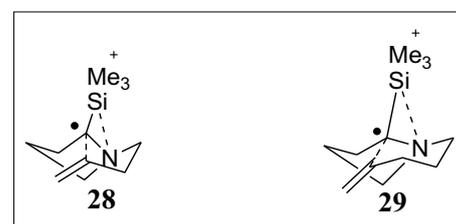


Fig. 3. Stereochemical rationalization.

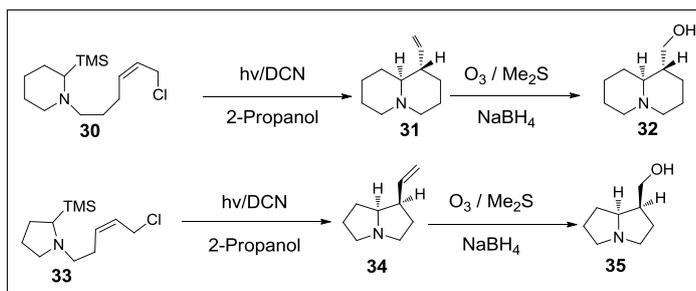
a general route towards synthesizing the azabicyclo[m.n.o]alkane skeleton, a prevalent structural framework in quinazolidine, indazolidine and pyrazolidine type of alkaloids.^[18] This strategy was utilized for the synthesis of racemic epilupinine^[19] (**32**) and isoretronecanol^[20] (**35**) as shown in Scheme 6. The synthesis of these two natural products substantiated the stereochemical outcome of such cyclizations.

Having established an efficient general strategy for the synthesis of mono- as well as bicyclic amines, we envisioned extending this powerful cyclization protocol for the synthesis of polyhydroxylated cyclic amines which are endowed with diverse biological activities.

5. Synthesis of Polyhydroxylated Piperidines

Polyhydroxylated piperidines (Fig. 4) have attracted considerable attention as glycosidase inhibitors.^[3] Glycosidase inhibitors are carbohydrate analogues where nitrogen atoms have replaced one or more of the oxygen atoms.^[21] These alkaloids are sugar mimics and are widespread in plants and microorganisms.^[22] The activities of these compounds are rationalized on the basis of their similarities with the shape and charge of the postulated oxocarbenium ion intermediate formed during the glycosidic bond cleavage by glycosidase enzymes.^[23] Such molecules have also been demonstrated to be a tool for studying various biological functions of oligosaccharides.^[24] These classes of compounds have gained widespread interest due to the postulation that they can be used as therapeutic agents in various carbohydrate-mediated diseases^[25] like AIDS, diabetes, cancer and some viral infections like influenza.

Due to diverse and interesting properties associated with these polyhydroxylated cyclic amines, it was not surprising that their syntheses had attracted considerable attention from chemists around the globe.^[26,27] The main challenge in their syntheses has been to construct the amino-methyl group in the piperidine ring vicinal to a stereocenter starting with the carbohydrates. Many interesting syntheses are reported to overcome this problem but a general approach towards this obstacle is still lacking. Based on our current strategy of α -trimethylsilylmethylamine radical cation cyclization, we envisaged a general strategy for the synthesis of both D- and L-type of 1-N-iminosugars as shown retrosynthetically in Scheme 7. We anticipated that the fully functionalized piperidine skeleton could be obtained from the suitably placed *exo*-cyclic olefinic bond as in **41**, easily obtainable by the PET cycliza-



Scheme 6. Synthesis of epilupinine and isoretronecanol.

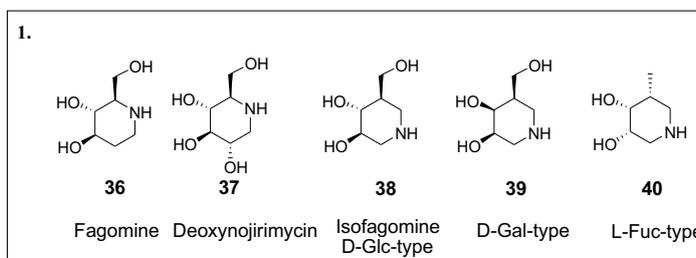
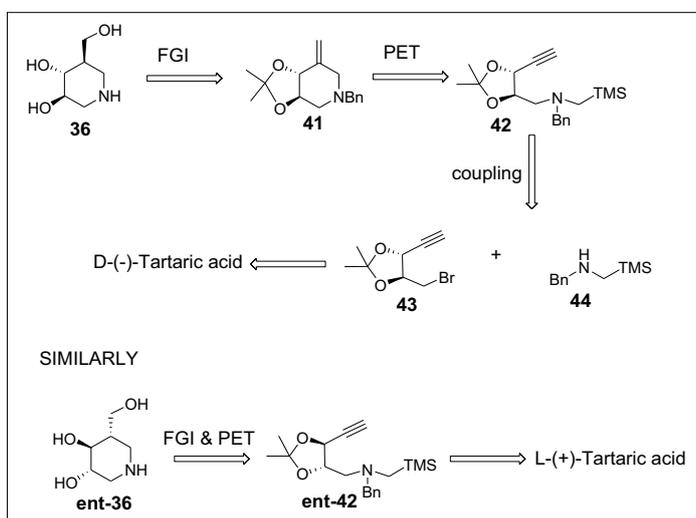
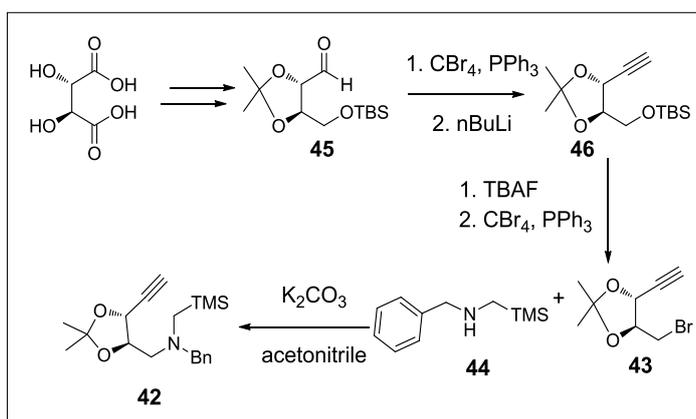


Fig. 4. Some important polyhydroxy piperidines.



Scheme 7. Retrosynthetic breakdown of polyhydroxylated piperidines.



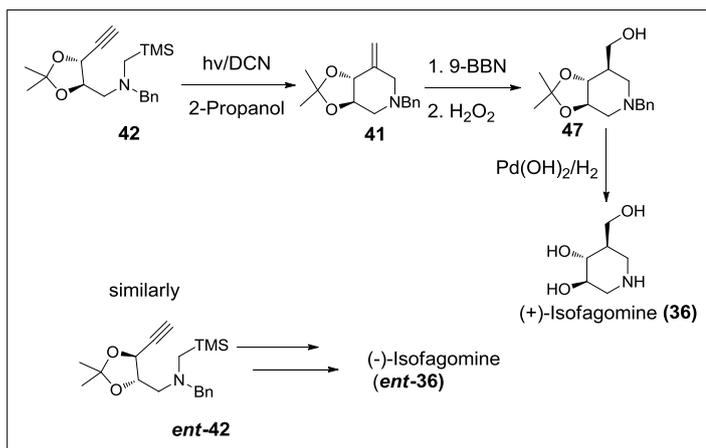
Scheme 8. Synthesis of the irradiation precursor for fagomine.

tion of **42**. Compound **42** could easily be assembled from an abundantly found natural chiral resource.

The key irradiation precursor **42** was easily prepared either from D-(-) or from L-(+)-tartaric acid by following the simple synthetic steps shown in Scheme 8.

The PET cyclization of **42** delivered **41** which on hydroboration using 9-BBN furnished **47** as a pure isomer. The *trans*-stere-

oselectivity for this reaction was assumed to arise due to severe steric interaction of the axial hydrogens of the acetone rings with the bulky 9-BBN moiety (Scheme 9). Finally debenzoylation of **47** by hydrogenolysis using Pearlman's catalyst produced (+)-isofagomine (**36**). Following a parallel protocol starting with L-(+)-tartaric acid, (-)-isofagomine (*ent*-**36**) was also synthesized.^[28]



Scheme 9. Synthesis of (+)-isofagomine and (-)-isofagomine.

droxylated piperidines in a straightforward manner. For example, des(hydroxymethyl) deoxymannojojirimycin (**54**) could be obtained by following the simple synthetic protocol as shown in Scheme 11. Synthesis of des(hydroxymethyl)deoxynojojirimycin (**53**) was also accomplished by inverting the stereochemistry of the free hydroxy group of *ent*-**60** by using standard Mitsunobu conditions (Scheme 12).^[36,37]

7. Synthesis and Evaluation of C(6) Homologues of 1-Deoxynojojirimycin as Specific Glycosidase Inhibitors

6. Developing a General Approach for the Syntheses of 1-*N*-Iminosugars

As the interest in azasugars grew rapidly, many interesting syntheses were reported.^[29] Therefore, we renewed our interest in the pursuit of synthesizing and evaluating novel azasugars as glycosidase inhibitors. The chiral pool approaches which were available at that time lacked a general strategy towards various targets as each time the starting materials required small or overall modification making synthetic process tedious.^[30,31]

A close assessment of all 1-*N*-azasugars uncovered a universal substitution pattern as shown in **48**. Altering the stereochemical pattern at C(3) and C(4) and the nature of the substituent at C(5) would lead to the synthesis of most of these compounds. Therefore, a general precursor of type **49** was envisaged to serve the purpose provided the correct stereochemistry at C(3) and C(4) and desired functionalization at C(5) was possible (Fig. 5). This led us to propose two specific precursors **41** and *ent*-**41** to synthesize D- and L-*threo* classes of 1-*N*-iminosugars, respectively.

Precursor **41** was utilized for the synthesis of two azasugars **50** ($K_i/\mu\text{M} = 96$, β -glucosidase) and **51** ($K_i/\mu\text{M} = 30$, β -glucosidase) which showed promising glycosidase inhibitory activity when tested against β -glucosidase enzyme (Scheme 10).

The success in achieving the synthesis of these important azasugars encouraged us to visualize the possibility of synthesizing some of the most important 3,4,5-piperidine triols (**52**, **53** and **54**, Fig. 6), isolated by Kusano and coworkers in 1995 from the extract of the plant *Eupatorium fortunei*.^[32] These polyhydroxy piperidines were considered as the derivative of deoxynojojirimycin and they exhibited moderate to good glycosidase inhibitory activity.^[33] These compounds were also known to be used in Chinese and Japanese folk medicine as diuretic, antipyretic, emmenagogue and antidiabetic agents. These triols were ini-

tially synthesized by Ganem *et al.*^[34] and other research groups.^[35]

It was anticipated that precursor **56** and *ent*-**56** would produce these polyhy-

By this time the potential of nojirimycin and its 1-deoxy analogues such as 1-deoxynojojirimycin and 1-deoxygalactonojojirimycin were established as strong α - and β -glucosidase inhibitors.^[38] Due to

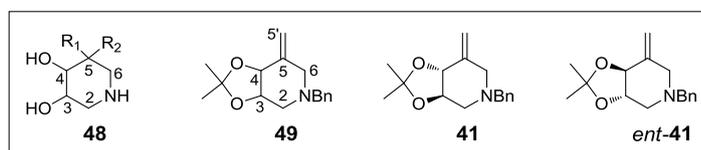
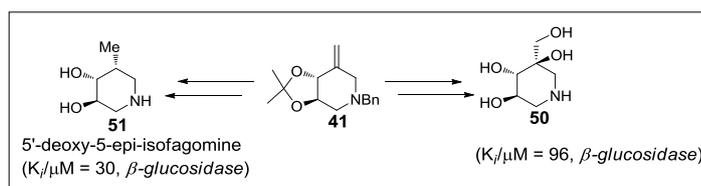


Fig. 5. General precursor of D- and L-*threo* classes of 1-*N*-iminosugars.



Scheme 10. Synthesis of 5'-deoxy-5-epi-isofagomine.

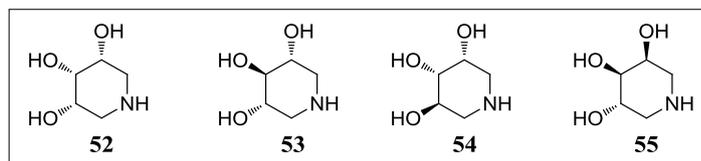
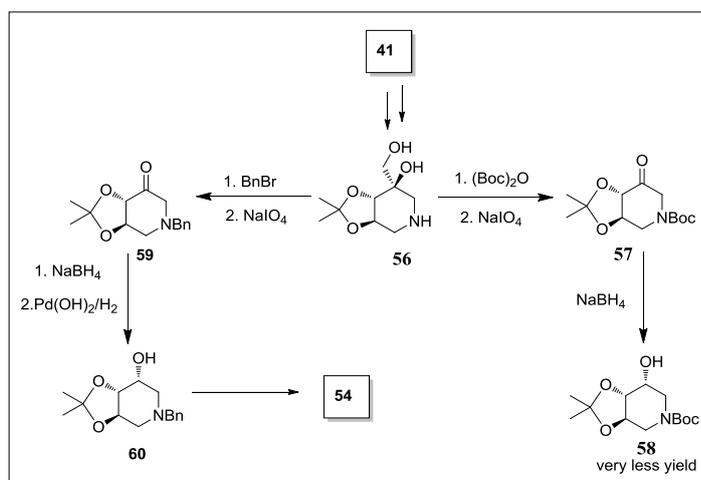
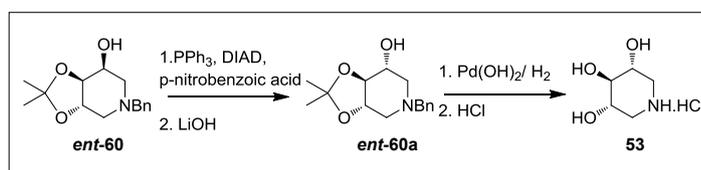


Fig. 6. Some of the most important 3,4,5-piperidine triols.



Scheme 11. The synthesis of the deoxymannojojirimycin derivative.



Scheme 12. Synthesis of des(hydroxymethyl) deoxynojojirimycin.

intense research activities in this field.^[39] two new azasugar-based medicines such as Miglitol (N-hydroxyethyl DNJ, Glyset or Diastabol)^[40] and Miglustat (N-nBuDNJ, Zavesca)^[41] for the treatment of type II diabetes and Gaucher's disease, respectively, were introduced. In order to discover a molecule with better glycosidase inhibitory activities, intense research activities^[41] continued towards synthesizing homoazasugar derivatives with (CH₂)-homologation at C(6) of 1-deoxyazasugars. However, the major challenge was to find a suitable route for the synthesis of polyhydroxy piperidines. As we had already established a novel route for the synthesis of polyhydroxy piperidine involving **41**, employing PET cyclization of suitably substituted α -trimethylsilylmethylamine, we turned our attention towards synthesizing C(6) homologues of 1-deoxy azasugars and evaluated their glycosidase inhibition activities.

Upon vigilant inspection it occurred to us that template **69**, where the strategic exocyclic double bond would enable proper functionalization, could serve as a transition point for the synthesis of all these important azasugars (Fig. 7). This intermediate could be synthesized effortlessly by the cyclization of **70** employing our newly developed protocol. The irradiation precursor **70** could be assembled together through reductive amination of a chiral fragment **71** which can be obtained from L-(+)-tartaric acid and **72**. Compound **72** was obtained from 3-aminopropanol utilizing known synthetic sequences.^[35a]

As anticipated the PET cyclization of **70** produced **69** (60% yield) smoothly. Dihydroxylation of **69** using OsO₄ produced **73** whose stereochemistry was confirmed through single crystal X-ray diffraction study (Scheme 13). Removal of all protecting groups generated **66**. Furthermore, sodium periodate cleavage of **66** produced the corresponding bicyclic ketone which upon reduction with sodium borohydride produced **74** as a pure diastereomer. The stereochemistry was confirmed by 2D NMR spectroscopy. The removal of acetonide group using aqueous hydrochloric acid produced tetrahydroxy azasugar **65** (K_i/ μ M = 1.7, α -galactosidase). Enantiomeric azasugars of the same series were also easily synthesized using D-(-)-tartaric acid.

While this study was in progress, it was noticed that there was increasing interest in the evaluation of glycosidase inhibitory activities of non-basic glyconolactams^[43] such as **75**, **76** and **77** (Fig. 8). The original mechanistic rationale for inhibitory activities of these molecules was attributed to the involvement of their tautomeric iminol form, however, later detailed studies suggested the inhibitory activities were solely due to hydrogen bonding.^[44]

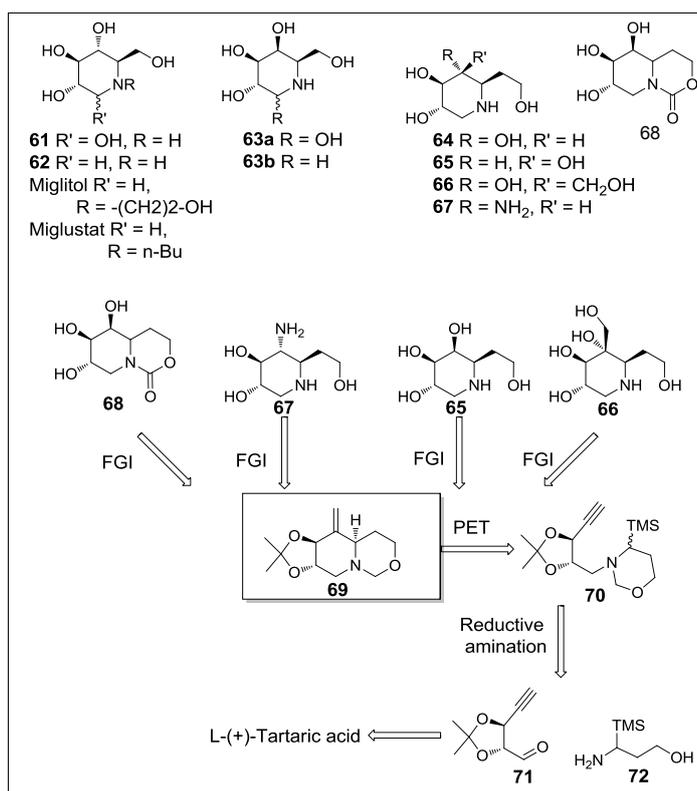
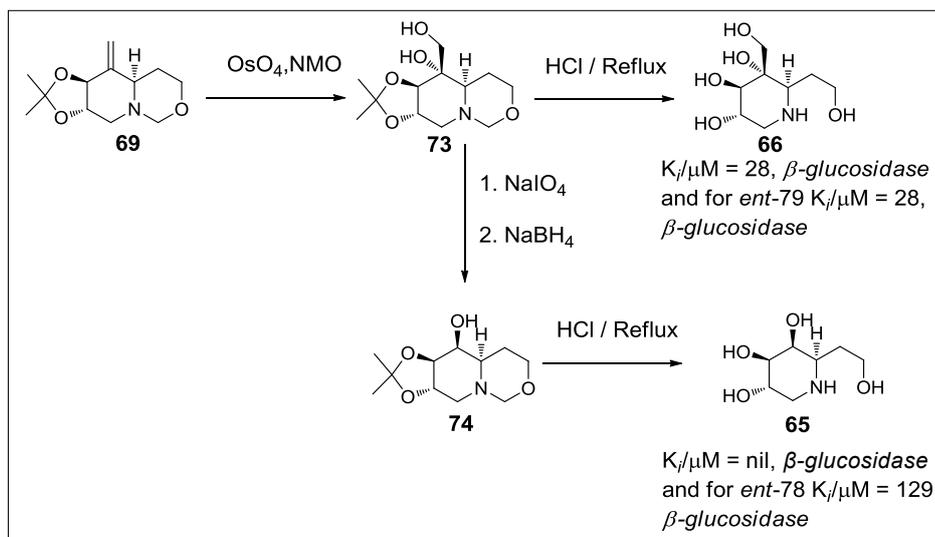


Fig. 7. Some important homologues of 1-deoxyojirimycin.



Scheme 13. Synthesis of azasugars.

Therefore, encouraged by these findings, we synthesized a new non-basic azasugar **68** from the intermediate **74** by following the reaction sequences outlined in Scheme 14. In continuation of our effort

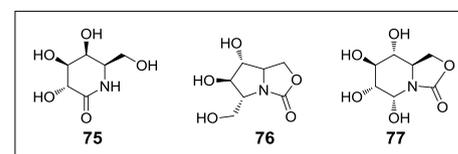
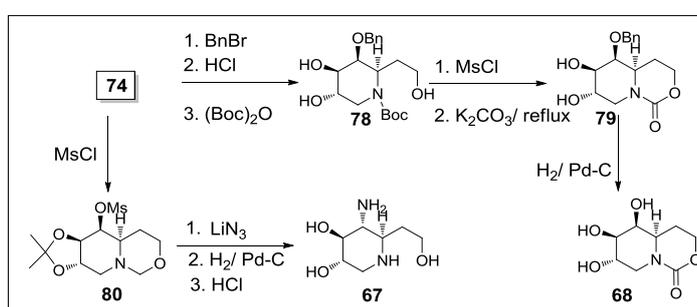


Fig. 8. Some non basic azasugars.



Scheme 14. Synthesis of non basic azasugars.

to synthesize novel azasugars, molecule **67** having a more basic amino functionality was also prepared.

By following identical protocols and starting with D-(–)-tartaric acid, the entire enantiomeric series was also prepared and evaluated. Compound **66** ($K_i/\mu\text{M} = 28$, β -glucosidase) and its enantiomer *ent*-**66** ($K_i/\mu\text{M} = 12$, β -glucosidase) showed modest specific inhibition against β -glucosidase and were found completely inactive for α -glucosidase. Compound *ent*-**65** ($K_i/\mu\text{M} = 129$, β -glucosidase) also showed moderate specific inhibition against β -glucosidase. Inhibitory activities of other synthesized compounds were not so encouraging.^[45]

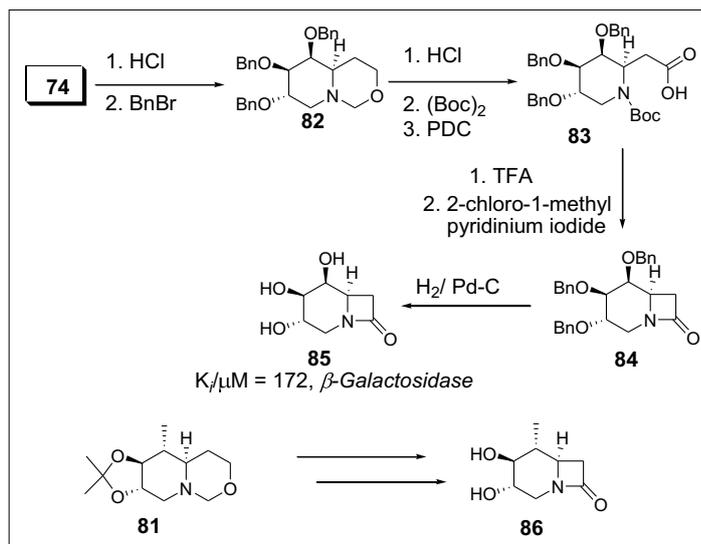
8. Synthesis of Conformationally Restricted Glycosidase Inhibitors

Taking a clue from the previous studies, it was envisioned that the conformationally constrained polyhydroxylated β -lactam-azasugar hybrid molecule of type **85** may be more potent as the β -lactam ring may compel the polyhydroxy piperidine ring to assume a nearly half chair conformation (mimic of the glycosidase inhibitor's transition state) and the carbonyl group may provide an additional H-bonding site to the enzyme. The synthesis of **85** was accomplished from **74** through simple synthetic transformations shown in Scheme 15. Similarly its corresponding enantiomer was also obtained from D-(–)-tartaric acid. The C(10) methylated analogue **86** was also synthesized from **81**.

The inhibitory activities of **85**, **86** and *ent*-**85** were studied against β -galactosidase (*Aspergillus oryzae*), α -galactosidase (coffee beans), β -glucosidase/ β -mannosidase (almonds), α -glucosidase (yeast) and α -mannosidase (jackbeans), however, unfortunately the activities were found to be poor except for **85** which showed moderate inhibition of β -galactosidase ($K_i/\mu\text{M} = 172$, β -galactosidase).^[46]

9. Synthesis of Castanospermine-type Azasugars

After having successfully used α -trimethylsilylmethylamine radical cation cyclization with tethered olefin to synthesize polyhydroxylated piperidines and their analogues, we turned our attention towards applying this strategy to synthesize the indolizidine class of polyhydroxylated 1-azabicyclo[4.3.0]nonane alkaloids such as castanospermine, swainsonine and other structurally related compounds (Fig. 9).^[47] The structural difference between these classes of compounds and 1-deoxyojirimycin is only the presence



Scheme 15. Synthesis of conformationally restricted polyhydroxy piperidines.

of an ethylene bridge between the nitrogen ring junction and the hydroxymethyl group. These compounds are known to exhibit glucosidase inhibitory activities and some of them have also shown antiviral properties.^[48] Since castanospermine on further study was found to cause osmotic diarrhoea^[49] attempts have been intensified to synthesize functional analogues of this molecule to overcome this problem. Therefore, various stereoisomers of castanospermine were synthesized,^[50] however, the synthetic steps were too long and low yielding. This encouraged us to take up a general route towards the synthesis of these compounds employing our cyclization strategy. It was anticipated that intermediate **96** can be utilized for various

structural manipulations by employing a simple synthetic sequence. This intermediate was easily synthesized by PET cyclization of **95** by following the reaction sequences outlined in Scheme 16. Further, functional group manipulations provided 1-deoxy-8-*epi*-castanospermine **91** in excellent yield. The corresponding amino analogue **93** was also synthesized from **98** as depicted in Scheme 16. Glycosidase inhibitory activities for compounds **91**, **92** and **93** were studied against different enzymes.

Disappointingly all compounds turned out to be inactive against α -glucosidase and α -/ β -mannosidases. 1-Deoxy-8-*epi*-castanospermine **91** showed nonspecific mild inhibition against α -galactosidase ($K_i/\mu\text{M}$

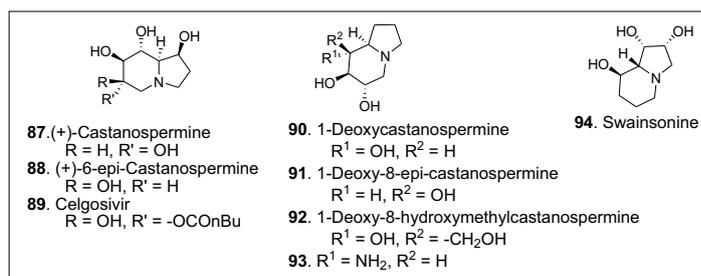
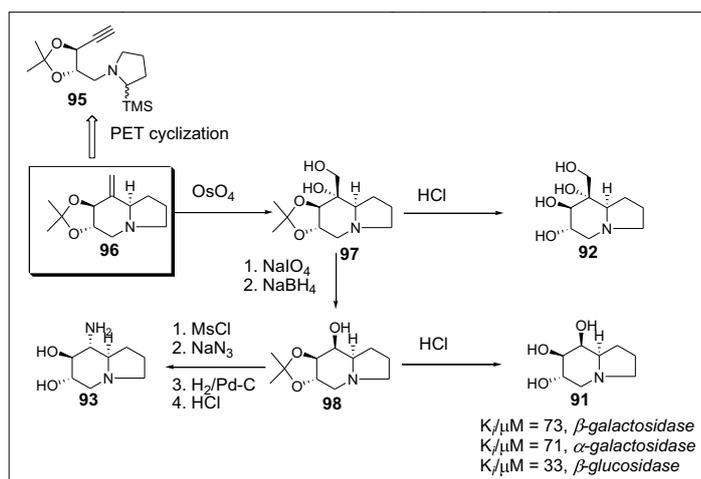


Fig. 9. Indolizidine class of azasugars.

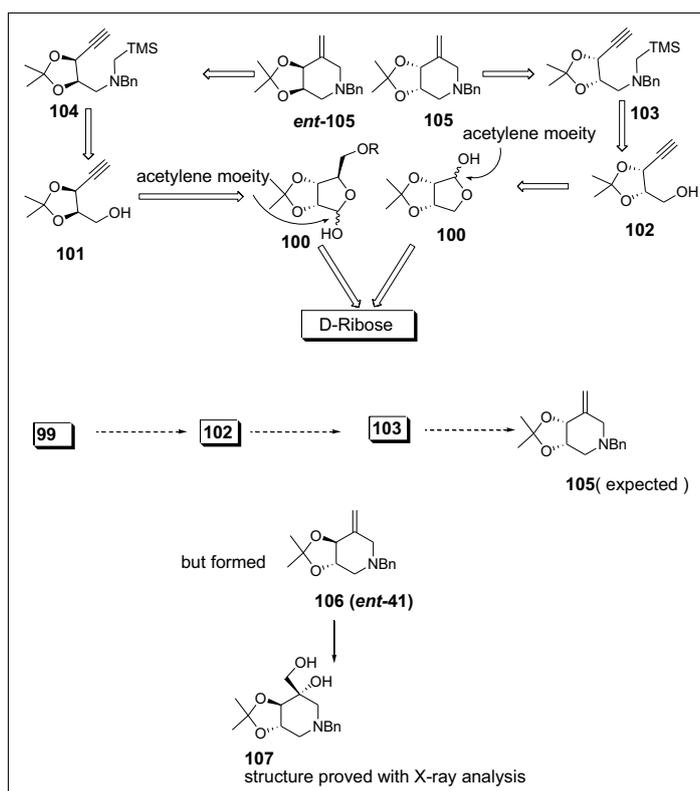


Scheme 16. Synthesis of the indolizidine class of azasugars (castanospermine type).

$\mu\text{M} = 71$, α -galactosidase), β -galactosidase ($K_i/\mu\text{M} = 73$, β -galactosidase) and β -glucosidase ($K_i/\mu\text{M} = 33$, β -glucosidase). We were also disappointed to find that 1-deoxy-8-hydroxymethylcastanospermine **92** and **93** displayed very weak inhibitory activity.^[51]

Although we synthesized various azasugars starting from tartaric acid where the stereochemistry of the two hydroxyl groups was *trans*, we also became interested in synthesizing another class of azasugars where two hydroxyl groups would be *cis*.^[32,52] Towards this end it was envisioned that there could be two enantiomeric intermediates **105** and *ent*-**105** (Scheme 17) which would lead to the synthesis of these azasugars. It was further hoped that these two intermediates would arise from the PET cyclization of **103** and **104**, respectively. We envisioned that these two irradiation precursors could be made available *via* regio- and stereoselective installation of an acetylenic moiety into D-ribose. In pursuit of the intermediate **105**, we prepared **99** by known literature procedures,^[53] and the acetylene moiety was installed using Ohira-Bestmann reagent to produce **102**. Coupling of **102** with benzylsilylmethylamine produced irradiation precursor **103**.

However, cyclization of **104**→**105** (60% yield) indeed, produced unexpectedly **106**, confirmed by the crystal structure of **107** produced by its dihydroxylation. Although, it was disappointing initially, this strategy provided intermediate **107** in only six steps compared to a previously described method from tartaric acid (11 steps). The scope of this protocol for synthesizing a number of new azasugar scaffolds was explored and results are summarized in Scheme 18.

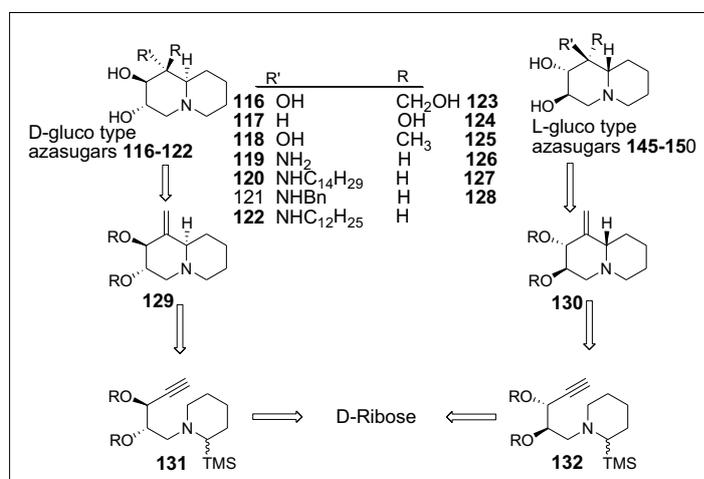
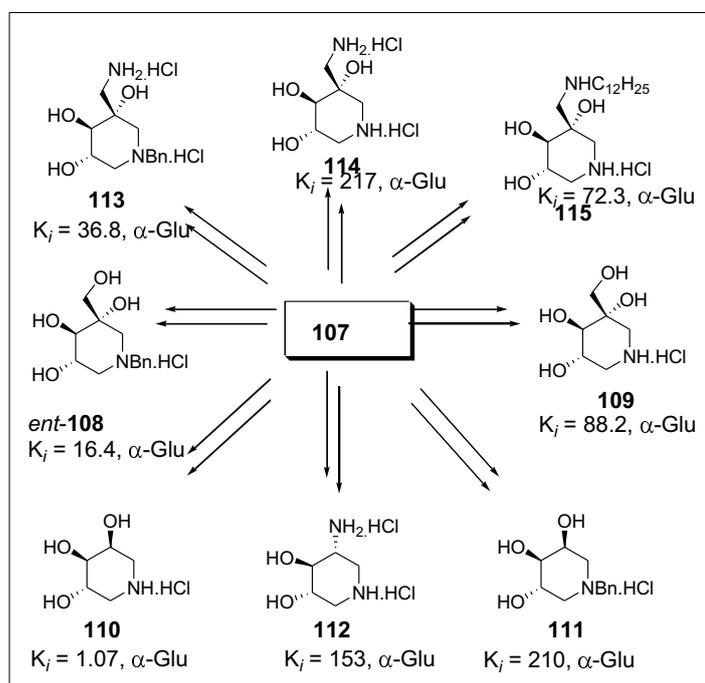


Scheme 17. Improved synthesis of polyhydroxy piperidine type azasugars.

The enzyme inhibition studies for these azasugars were carried out using β -galactosidase (*Aspergillus oryzae*), α -galactosidase (coffee beans), β -glucosidase/ β -mannosidase (almonds), α -glucosidase (yeast) and α -mannosidase (jackbeans) and all of them showed α -glucosidase specific activities.^[54] The best result was, however, obtained for compound **110** ($K_i/\mu\text{M} = 1.07$, α -glucosidase).

10. Synthesis of the Polyhydroxy Quinolizidine Class of Alkaloids

In order to evaluate further structure–reactivity relationships of azasugars possessing azabicyclo[4.4.0]nonane structural frameworks, compounds such as **116–128** were synthesized and evaluated from precursors **129** and **130** which were obtainable by the PET cyclization of **131** and **132**, respectively (Scheme 19). Enzyme inhibition studies were performed with these newly synthesized azasugars.^[55]



Scheme 19. Synthesis of quinolizidine class of azasugars.

Left: Scheme 18. Synthesis of analogues of polyhydroxy piperidine type azasugars.

11. Conclusion and Outlook

In summary, we have developed a new concept of α -trimethylsilylmethylamine radical cation, generated by photoinduced electron transfer processes, cyclization to tethered olefinic moiety for the synthesis of cyclic amines in general. The chemistry has been explored for the synthesis of stereoselectively substituted pyrrolidines, piperidines, pyrrolizidines, indolizidines and quinolizidines. New as well as known glycosidase inhibitors have been synthesized employing this strategy. It is hoped that this powerful strategy will increasingly find application in the synthesis of structurally complex natural products.

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