

Synthesis and biological activity of naturally occurring α -glucosidase inhibitors

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In addition to their clinical importance in the treatment of type II diabetes, α -glucosidase inhibitors have attracted considerable attention from the synthetic community because of their profound effect on an array of cellular processes, including *N*-linked glycoprotein processing and maturation, oligosaccharide metabolism, and cell–cell and cell–virus recognition. Over the past decade, a number of structurally novel naturally occurring α -glucosidase inhibitors which do not conform to the classical iminosugar mold have been identified, including zwitterionic thiosugars and marine organosulfates. While these natural products are important leads in the development of new classes of glucosidase inhibitors, they have also attracted considerable attention as synthetic targets in of themselves. This article reviews the recent literature concerning the synthesis of these emerging natural product families, as well as the preparation of those polyhydroxylated alkaloids more traditionally associated with anti- α -glucosidase activity. 176 references are cited.

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1 Introduction

Glycosidase enzymes catalyze the hydrolysis of glycosidic linkages by releasing monosaccharides from the non-reducing end of an oligosaccharide or glycoconjugate, and are implicated in an array of vital biological processes.¹ Inhibitors of these enzymes, both natural and synthetic, have attracted considerable attention from the synthetic community because of their profound effect on *N*-linked glycoprotein processing and maturation, oligosaccharide metabolism, and cell–cell and cell–virus recognition.² Their modulation of such biochemical processes has not only led to a deeper understanding of the role that glycosidases play in living organisms,³ but is also the basis of a number of therapeutic agents. Glycosidase inhibitors are clinically utilized as anti-hyperglycemic⁴ and anti-influenza⁵ agents and have potential for the treatment of viral,⁶ bacterial, and fungal infections,⁷ as well as a range of other ailments, including Gaucher's disease,⁸ cystic fibrosis,⁹ and metastatic cancer.¹⁰

Notwithstanding the remarkable progress made in this field since the mid-1970s, the ubiquitous distribution of glycosidases and the non-drug-like properties of iminosugars have ensured a continuing need to identify ever more potent and selective inhibitors as well as develop efficient synthetic routes to them.¹¹ During the past decade, a number of structurally novel inhibitors which do not conform to the classical iminosugar mold have been identified, namely zwitterionic thiosugars and marine organosulfates. While these natural products are important leads in the development of new types of α -glucosidase inhibitors, they have attracted considerable attention as synthetic targets in of themselves. The purpose of this article is to review the recent literature (2005 through to the end of 2009) concerning the synthesis of these emerging families of

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inhibitors as well as advances in the preparation of alkaloid natural products more traditionally associated with α -glucosidase inhibition. Furthermore, since such information directly impacts synthetic chemists who work in the field, our discussion will also encompass issues pertaining to structural revision.

2 Mechanism and inhibition of enzyme-mediated glycosidase hydrolysis

α -Glucosidase enzymes selectively catalyse the hydrolysis of α -glucosidic linkages and, together with α -glucosidases in general, can be subdivided into two mechanistic classes, namely configuration-retaining and configuration-inverting, depending on the stereochemical outcome at the anomeric center of the

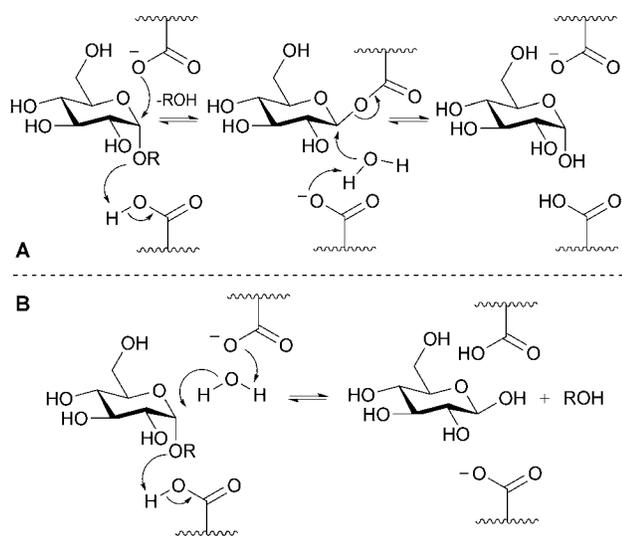


Fig. 1 Catalytic mechanisms for configuration-retaining (A) and configuration-inverting (B) α -glycosidase enzymes according to Koshland.¹³

monosaccharide, which departs upon hydrolysis (Fig. 1).¹² The active sites of glycosidase enzymes typically house two carboxylic acid-bearing residues (Asp or Glu) which are responsible for the mediation of hydrolysis, although the protonation state, relative location and mechanistic role of these groups differs for inverting and retaining glycosidases.

In configuration-retaining enzymes, the carboxylate residues are positioned approximately 5.5 Å apart and mediate a double displacement process involving a covalent enzyme-glycosyl intermediate (Fig. 1, A). In this case, one residue adopts the role of general acid catalyst, protonating the glycosidic oxygen atom, while the other simultaneously acts as a nucleophile, attacking the anomeric center to produce the covalent intermediate. In the second step, the free carboxylate anion deprotonates an incoming water molecule, which then attacks the anomeric center to displace the enzyme carboxylate group. The carboxylate residues within the active site of configuration-inverting glycosidases are further apart (10.5 Å), enabling simultaneous binding of the substrate and water, which undergo reaction *via* a single-step displacement (Fig. 1, B). In this case, one carboxylate group is deprotonated in the resting state and plays the role of general base by deprotonating the water molecule while it attacks the anomeric center. Concomitant with this process, the carboxylic acid protonates the glycosidic oxygen atom, resulting in a transition state with substantial oxocarbenium ion character (Fig. 2).

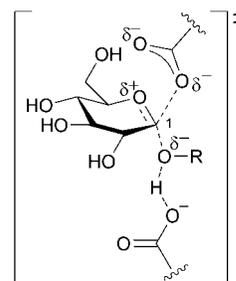


Fig. 2 Structure of the oxocarbenium ion-like transition state involved in the S_N2 -type hydrolysis mediated by stereoretaining α -glucosidases.



Duncan Wardrop

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Samantha Waidyarachchi

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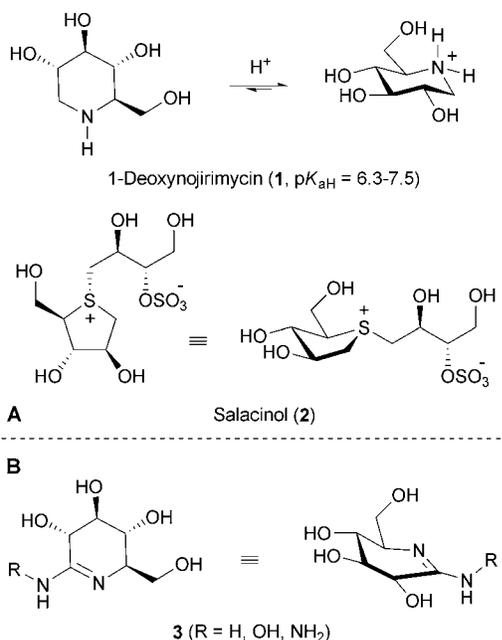


Fig. 3 Electrostatic and structural mimicry of the oxocarbenium-like transition state are among the factors believed to be responsible for the biological activity of iminosugar α -glucosidases inhibitors and their surrogates. A. Mimicry of the positive charge at the endocyclic oxygen atom. B. Mimicry of the half-chair structure adopted in the transition state associated with stereoretaining α -glucosidases.

Since the positive charge at the anomeric center in the transition state shown in Fig. 2 is substantially shared with endocyclic oxygen, the C1–O bond has significant double bond character. As a consequence, the ground-state chair conformation of the glycosyl ring is distorted into a boat or half-chair as the transition state is approached. Although the designation of glycosidase inhibitors as transition state mimics remains a topic of much debate,¹⁴ electrostatic (Fig. 3A) and structural (Fig. 3B) mimicry of these transient species have proven to be particularly effective strategies in the design of such inhibitors.

In the case of iminosugars (2-aza sugars), such as 1-deoxynojirimycin (**1**), the presence of an endocyclic nitrogen protonated under physiological conditions is believed to emulate the positive charge on the ring oxygen at the transition state, but not the flattened conformation.^{15,16} Similar arguments have also been posited in the case of the zwitterionic α -glucosidase inhibitor salicinol (**2**), in which a sulfonium center appears to behave as a surrogate for the developing positive on the endocyclic oxygen (see Section 4).¹²⁰ Isoiminosugars (1-aza sugars) are also believed to derive their inhibitory activity through electrostatic mimicry, although in these systems, the protonated nitrogen plays the role of the positively charged anomeric center.¹⁷ With regard to structural mimicry, inhibitors such as nojirimycin derivatives **3**,¹⁸ which adopt a distorted half-chair conformation, are believed to derive a significant portion of their binding properties from structural mimicry of the glycosidase transition state. While electrostatic charge is clearly a further factor in the activity of amidine derivative **3** ($X = H$), which is protonated under physiological conditions, Ganem, in light of the activity of the nonbasic amidoxime **3** ($X = OH$), has suggested that adoption of

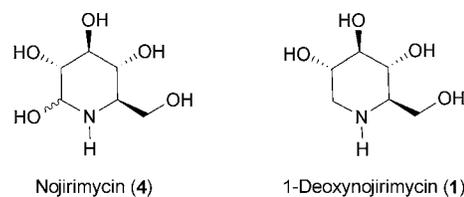


Fig. 4 Structure of the inaugural iminosugar glycosidase inhibitors nojirimycin (**4**, NJ) and 1-deoxynojirimycin (**1**, DNJ).

the flattened anomeric conformation of the glucosyl intermediate may be more important for transition state binding than achieving the full charge of the glucopyranosyl cation.

3 Iminosugars

Since the discovery of nojirimycin (**4**) in 1967 (Fig. 4),¹⁹ iminosugar-based glycosidase inhibitors have been the subject of intense scrutiny,²⁰ not only for their profound effect on glycosidases but for their inhibition of other carbohydrate-processing enzymes, including glycosyltransferases,²¹ glycogen phosphorylases,²² and nucleoside phosphorylases.²³ The role played by α -glucosidase inhibitors in the development of this field has been particularly important in light of their clinically proven value in the treatment of type II diabetes⁴ and hereditary lysosomal storage diseases.⁸

Notwithstanding a remarkable degree of constitutional diversity, iminosugars can generally be categorized as belonging into one of five major structural groups, namely piperidines (**5**), pyrrolidines (**6**), pyrrolizidines (**7**), indolizidines (**8**) and nortropanes (**9**) (Fig. 5). While a majority of the several hundred known iminosugar inhibitors are synthetic in origin, in almost all cases the basis for their design is, to some degree, structurally attributable to alkaloidal natural products.²⁰

3.1 Piperidines

Polyhydroxylated piperidines constitute the largest subgroup of α -glucosidase inhibitors among which (+)-1-deoxynojirimycin (DNJ, **1**) and its analogues have been the most intensively studied (Fig. 4). Isolated from both plant and microbial sources,²⁴ DNJ displays inhibitory activity against a variety of α - and β -glucosidase enzymes in a reversible or competitive manner.²⁵ Notably, the synthesis of this compound, first reported by Paulsen in 1966,²⁶ actually predates its isolation from natural sources by at least a decade. Given the central importance of deoxynojirimycin

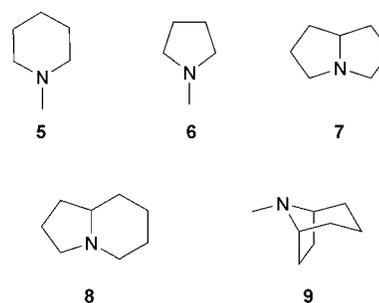
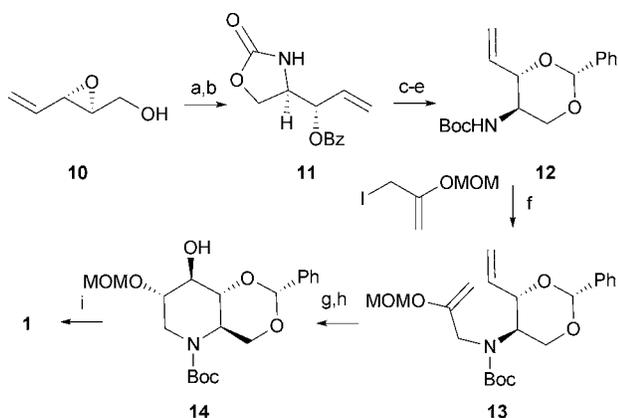


Fig. 5 Skeletal frameworks most commonly found in naturally occurring iminosugar glycosidase inhibitors and their synthetic derivatives.

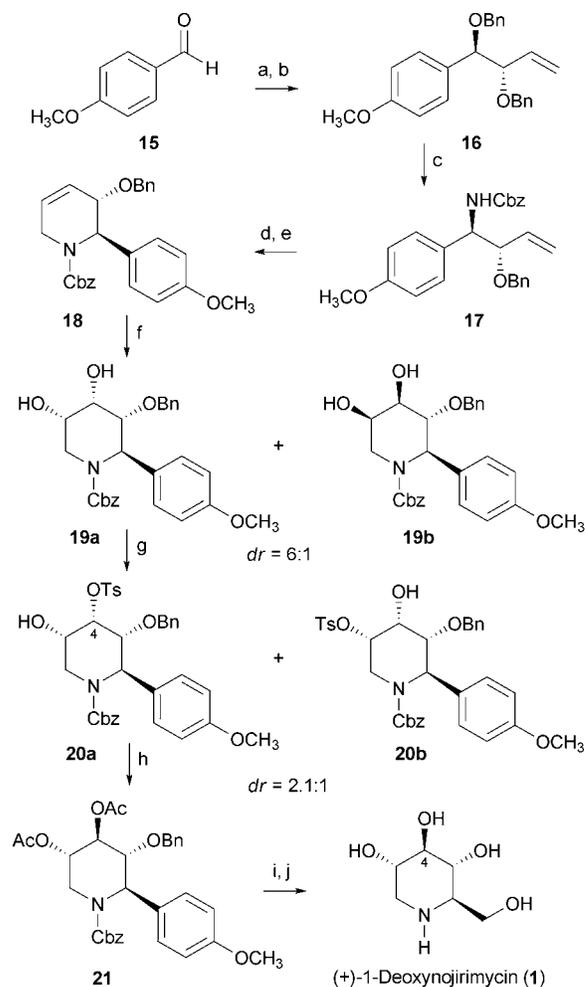


Scheme 1 Poisson's synthesis of (+)-1-deoxynojirimycin [(+)-DNJ]. *Reagents and conditions:* (a) BzNCO, Et₂O, 0 °C; (b) K₂CO₃, C₁₂H₂₅NMeCl, 20 °C, 6 h, 77%; (c) Boc₂O, Et₃N, DMAP, CH₂Cl₂, rt, 90 min; (d) NaOEt, EtOH, 0 → 20 °C, 1 h; (e) PhCH(OMe)₂, CSA, 20 °C, 6 h, 77% (3 steps); (f) NaH, DMF, 0 °C, 2 h, 82%; (g) Hoveyda–Grubbs II catalyst, benzoquinone, PhCH₃, heat, 87%; (h) BH₃·SMe₂, THF, NaBO₃·H₂O, 0 → 20 °C, 70%; (i) HCl, EtOH, reflux, 18 h, 100%.

as a template in the development of glycosidase inhibitors, it is not surprising that more than forty years after its isolation, this simple yet important molecule remains a popular synthetic target. To date, more than 30 total syntheses of 1-deoxynojirimycin have been reported.²⁷

Recently, Poisson and co-workers have reported the development of a highly stereocontrolled synthesis of (+)-1-deoxynojirimycin (**1**), which features the use of a novel one-pot enol ether metathesis–hydroboration sequence to establish the all-*trans* cyclic triol (Scheme 1).²⁸ The high diastereoselectivity of the hydroboration step in this case is notable in light of Takahata's earlier observation that dihydroxylation of related metathesis products proceeded with moderate selectivity.²⁹ In Poisson's route, treatment of (2*S*,3*S*)-epoxyalcohol **10** with benzoyl isocyanate generated the corresponding benzoylcarbamate which, upon exposure to base under biphasic conditions, underwent regioselective epoxide opening and intramolecular benzoyl migration to yield oxazolidinone **11**.³⁰ After conversion of this material to diene **13**, ring-closing metathesis (RCM) using the Hoveyda–Grubbs II catalyst generated the corresponding piperidine. Hydroboration–oxidation of this cyclic enol ether then furnished *trans* diol derivative **14** as a single diastereomer (*dr* > 95 : 5) in good overall yield. Finally, treatment with ethanolic HCl afforded (+)-1-deoxynojirimycin (**1**) in 11 linear steps and with an overall yield of 24%.

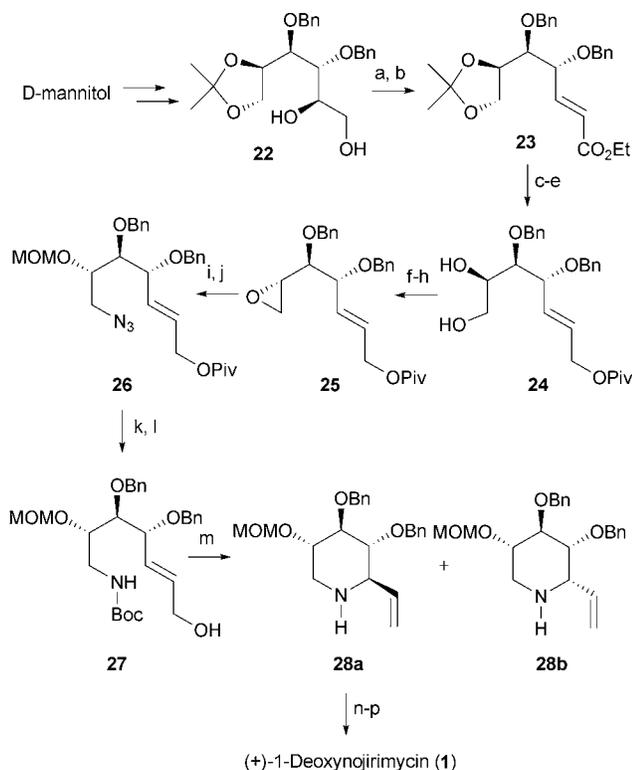
Jung and co-workers have also gainfully employed RCM to access the piperidine ring of DNJ (**1**) and two of its stereoisomers (Scheme 2).³¹ Commencing from *p*-anisaldehyde (**15**), Roush *anti*- α -silylallylation employing Brown's diisopinocampheyl auxiliary,³² Tamao–Fleming oxidation and subsequent di-*O*-benzylation provided *anti*-1,2-dibenzyl ether **16** with excellent stereocontrol. Diastereoselective and regioselective benzylic amination of **16** was now accomplished by treatment with chlorosulfonyl isocyanate, which following *in situ* de-*N*-sulfonylation, afforded **17** in high yield. *N*-Allylation and RCM using Grubbs' 1st-generation catalyst provided alkene **18**, which upon dihydroxylation using the Upjohn procedure, was converted to



Scheme 2 Jung's synthesis of (+)-DNJ. *Reagents and conditions:* (a) allyl (diisopropylamino)dimethylsilane, *n*-BuLi, TMEDA, β -methoxy-B(Ipc)₂, BF₃·OEt₂, Et₂O, –78 °C, 3 h; then KF, KHCO₃, 30% H₂O₂, THF, MeOH, rt, 20 h, 52%; (b) NaH, BnBr, THF, DMF, rt, 11 h, 99%; (c) chlorosulfonyl isocyanate, Na₂CO₃, PhCH₃, –78 °C, 24 h; then Na₂SO₃, rt, 24 h, 90%, *dr* = 50 : 1; (d) NaH, allyl bromide, THF, DMF, rt, 2 h, 100%; (e) Grubbs' 1st-generation catalyst, CH₂Cl₂, rt, 4 h, 91%; (f) cat. OsO₄, NMO, Ac₂O–H₂O (4 : 1), 75%, *dr* = 6 : 1; (g) TsCl, Et₃N, DMAP, CH₂Cl₂, rt, 2 h, 99%, *dr* = 2.1 : 1; (h) Ac₂O, DMAP, Et₃N, CH₂Cl₂, rt, 2 h, 99%; (i) CsOAc, DMF, 60 °C, 4 h, 74%; (j) cat. RuCl₃, NaIO₄, H₂O–MeCN–EtOAc (2 : 1 : 1), rt, 4 h; (k) BH₃·THF, THF, 0 °C, 24 h, 52% (2 steps); (l) 6 M HCl, MeOH, reflux, 12 h; (m) Dowex-50WX8 (H⁺ form, 0.5 M NH₄OH), 94% (2 steps).

a separable mixture of *cis*-diols **19**. Monotosylation of **19a** now proceeded with modest selectivity at the equatorially-positioned C4 hydroxyl group to provide a mixture of compounds **20a** and **20b**. After acetylation of the remaining hydroxyl group in **20a**, stereoinversion at C4 was accomplished by treatment with caesium acetate in DMF. Sharpless oxidative degradation of the *p*-methoxyphenyl substituent in **21**, reduction of the resulting carboxylic acid and sequential ester hydrolysis then provided DNJ (**1**).

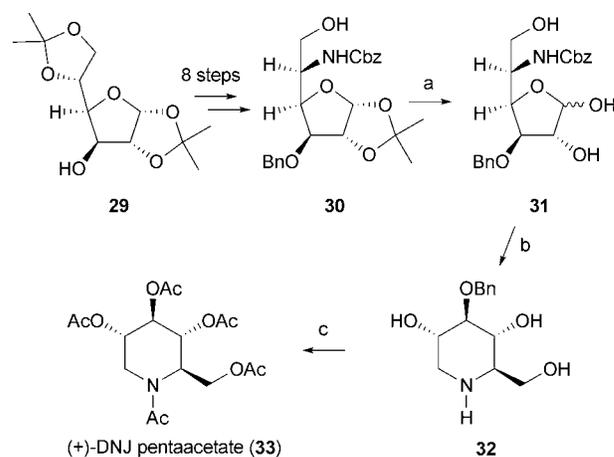
In contrast to the work of both Poisson and Jung, Hirai's synthesis of DNJ (**1**) employs the palladium(II)-catalyzed cyclization of an allylic alcohol to construct the piperidine ring



Scheme 3 Hirai's synthesis of (+)-DNJ. *Reagents and conditions:* (a) NaIO_4 , $\text{Et}_2\text{O-H}_2\text{O}$, 0°C , 79%; (b) $(\text{Et}_2\text{O})\text{P}(\text{O})\text{CH}_2\text{CO}_2\text{Et}$, NaH , THF , 0°C , 89%; (c) DIBAL-H , THF , -78°C , 94%; (d) PivCl , pyridine, THF , 0°C , 93%; (e) $\text{HCl-H}_2\text{O}$ (1 : 9), THF , 40°C , 95%; (f) BzCl , pyridine, CH_2Cl_2 , rt, 78%; (g) TsCl , pyridine, CH_2Cl_2 , rt, 85°C ; (h) K_2CO_3 , MeOH , rt, 68%; (i) NaN_3 , NH_4Cl , 15-crown-5, DMF , 55°C , 76%; (j) MOMCl , $i\text{-Pr}_3\text{NEt}$, rt, 99%; (k) LiAlH_4 , Et_2O , 0°C ; (l) $(\text{Boc})_2\text{O}$, Na_2CO_3 , CH_2Cl_2 , rt 75% (2 steps); (m) $\text{PdCl}_2(\text{MeCN})_2$ (10 mol%), THF , rt, 76%; (n) O_3 , $\text{CH}_2\text{Cl}_2\text{-MeOH}$, -78°C ; then NaBH_4 , -78°C , rt, 94%; (o) $\text{HCl-H}_2\text{O}$ (1 : 9), MeOH , 70°C , 90%; (p) H_2 , Pd/C , 12 M HCl-EtOH , rt, 92%.

(Scheme 3).³³ Starting from **22**, this D-mannitol derivative was converted to unsaturated ester **23** through oxidative cleavage of the 1,2-diol and a Horner–Wadsworth–Emmons reaction. Reduction of the ester, pivaloylation of the resulting allylic alcohol, and hydrolysis of the acetonide group provided diol **24** in high overall yield. After selective benzylation of the primary alcohol, the secondary alcohol was transformed to a tosylate ester, which upon exposure to K_2CO_3 in methanol, afforded **25**. Ring opening of this epoxide with sodium azide in DMF generated a β -hydroxy azide which was *O*-alkylated with MOMCl to yield compound **26**. Reduction of the azide group with LiAlH_4 and *N*-(*tert*-butyloxy)carbonylation of the amine afforded key intermediate **27**. Treatment of **27** with catalytic $\text{PdCl}_2(\text{MeCN})_2$ now mediated cyclization to furnish the all-equatorially-substituted piperidine **28** in good yield, albeit with modest diastereoselectivity ($\text{dr} = 2 : 1$). After separation, ozonolysis of the vinyl group of **28a**, reductive workup and subsequent removal of the Cbz, MOM and *O*-benzyl protecting groups provided DNJ (**1**).

Mandal and co-workers have reported an 11-step synthesis of (+)-DNJ pentaacetate (**33**) which centers on generation of piperidine ring through the reductive amination of latent aldehyde **31** (Scheme 4).³⁴ This key intermediate was prepared from



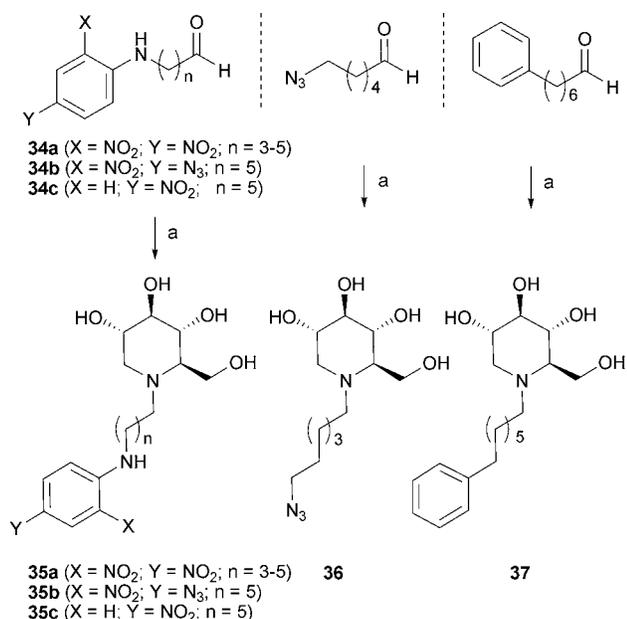
Scheme 4 Mandal's synthesis of (+)-DNJ pentaacetate. *Reagents and conditions:* (a) $\text{TFA-H}_2\text{O}$ (3 : 2), rt, 5 h, 89%; (b) H_2 , Pd/C (10 mol%), MeOH , 24 h, 45%; (c) H_2 , $\text{Pd}(\text{OH})_2/\text{C}$, MeOH , 6 h; then Ac_2O , pyridine, rt, 12 h, 70% (2 steps).

α -D-glucofuranose **29** by way of **30**. After removal of the acetonide group in **30**, catalytic hydrogenation over Pd/C in MeOH resulted in removal of the Cbz group and concomitant intramolecular reductive amination. Hydrogenolysis of the remaining benzyl ether in **32** was accomplished using Pearlman's catalyst and provided (+)-DNJ pentaacetate (**33**).

While 1-deoxyojirimycin (**1**) exhibits potent anti-glycosidase activity *in vitro*, its low *in vivo* efficacy, which stems in part from its pronounced hydrophilicity, has stimulated much interest in the preparation of more “drug-like” derivatives with improved pharmacokinetic properties. In particular, alkylation of the ring nitrogen has been found to both enhance the uptake of this iminosugar into mammalian cells and modify its specificity of inhibition *in vitro*. It is notable, in this context, that the iminosugar-based drugs which have to date reached the clinical marketplace are both *N*-alkylated derivatives of DNJ: *N*-(2-hydroxyethyl)-DNJ (Miglitol®/Glyset®) is approved for the control of diabetes mellitus type 2, while *N*-butyl-DNJ (Zavesca®) is indicated for Gaucher's disease, a glycolipid lysosomal storage disorder.^{4,8}

Fleet's pioneering studies of *N*-alkylated DNJ derivatives³⁵ has revealed that increases in *N*-alkyl chain length have a profound effect on endoplasmic reticulum (ER) α -glucosidase I inhibition.³⁶ It has been suggested that this effect is related to the hydrophobicity of the alkyl chain and its localization within the ER membrane. Studies by Asano also indicate that the conformation of the *N*-alkyl chain plays a role in the activity of these inhibitors.³⁷ In order to further understand the factors that govern iminosugar entry to the ER and potential binding partners, Fleet and co-workers have recently prepared the photolabile DNJ derivatives **35b** and **36** shown in Scheme 5 and employed these compounds in an affinity labelling study.³⁸

Reductive alkylation of DNJ (**1**) with aldehydes **34a-c**, in the presence of NaBH_3CN and acetic acid in methanol provided the target compounds in good to excellent yield (Scheme 5). Biological testing of these products against ER α -glucosidases I and II revealed that compounds **35a** ($n = 5$), **35b**, and **36** have increased potency over *N*-butyl-DNJ. Most notably, aryl azide **35b** not only proved to be a highly potent inhibitor of α -glucosidase I (IC_{50} , 17



Scheme 5 Fleet's synthesis of photosensitive *N*-alkyl-DNJ derivatives. Reagents and conditions: (a) DNJ (1), NaCNBH₃, AcOH, MeOH, rt.

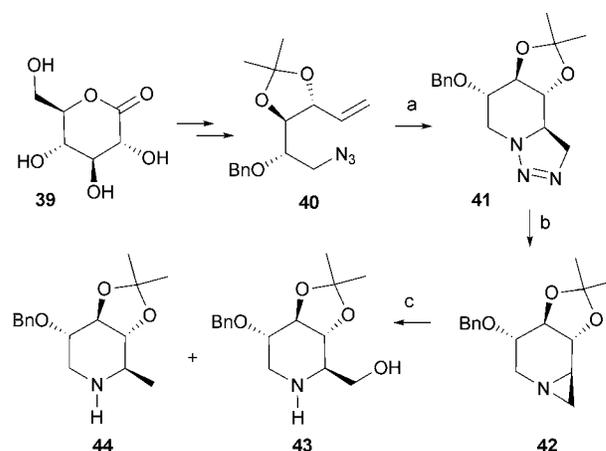


Fig. 6 Butters' *N*-alkyl and *N*-aryllalkyl analogues of the naturally occurring glycosidase inhibitor 1-deoxynojirimycin.

nM), but also inhibited cellular ER α -glucosidases with equal potency.

Butters has recently extended the study of *N*-alkylated DNJ derivatives through the preparation of a library of substrates in which an alkyl chain of 1 to 6 carbons provides a flexible linker between DNJ and phenyl, cyclohexyl or cyclopentyl groups (Fig. 6).³⁹ Utilizing the reductive amination coupling strategy previously outlined, compounds **38a–e** were prepared from DNJ and the requisite aldehydes. Employing a free oligosaccharide (FOS) assay, these iminosugars were evaluated for their activity against ER α -glucosidase I in cells. These studies revealed that maximal glycosidase inhibitory activity was observed where the linker was comprised of 4–6 carbon atoms and a phenyl group.

Murphy and Zhou have reported the use of an intramolecular Huisgen 1,3-dipolar cycloaddition reaction to simultaneously generate the piperidine ring and establish the C5 center of DNJ (Scheme 6).⁴⁰ Upon heating, unsaturated azide **40**, which was obtained in 6 steps from *D*-glucono- δ -lactone (**39**),⁴¹ underwent [2 + 3] cycloaddition to yield acid-sensitive triazoline **41** with excellent stereocontrol, albeit in moderate yield. Treatment of **41** with silica gel led to extrusion of dinitrogen and the formation of bicyclic aziridine **42**, which was of sufficient stability to be isolated but not fully characterised. Hydrogenation of **42** over Pd/C led to ring opening and the formation of an inseparable mixture of DNJ derivatives **44** and **43**. Notably, Murphy has found that



Scheme 6 Murphy and Zhou's route to (+)-DNJ derivatives. Reagents and conditions: (a) DMF or PhCH₃, 110 °C, 55%; (b) silica gel, PhCH₃, 20 °C, 35%; (c) 10% Pd/C, EtOAc, 20 °C, 78%, **44**:**42** = 1 : 1.5.

42 can be intercepted with a range of nucleophiles, including acetate, azide and thiophenol, thus offering convenient, one-pot access to a range of usefully functionalized DNJ derivatives.

Employing the diastereoselective aldol additions of metalated bislactim ethers to matched and mismatched erythrose or threose

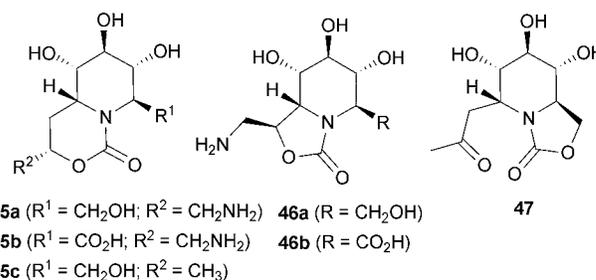
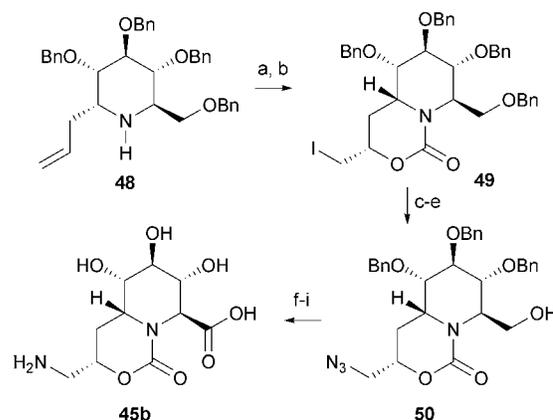


Fig. 7 Structure of Cipolla's nojirimycin (NJ)-based α -glucosidase inhibitors.



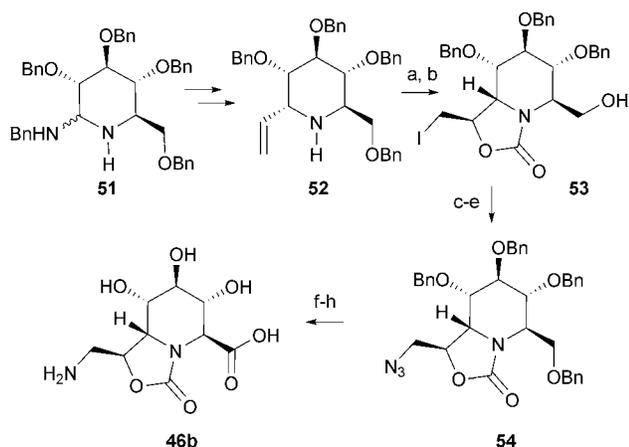
Scheme 7 Cipolla's route to conformationally restricted bicyclic nojirimycin derivatives. Reagents and conditions: (a) CbzCl, DIPEA, MeCN, 58%; (b) I₂, CH₂Cl₂, 0 °C, 92%; (c) NaN₃, *n*-Bu₄NI, CH₂Cl₂, 88%; (d) Ac₂O, TFA, 72%; (e) MeOH, cat. Na, 95%; (f) IBX, DMSO; (g) NaPO₄H₂·2H₂O, NaClO₂, CH₃CN, 72% (2 steps); (h) H₂, Pd(OH)₂/C, AcOH, acetone-H₂O, 100%.

acetanilides, Ruiz and Ojea have developed a general strategy for the preparation of 1,5-iminohexitols related to 1-deoxynojirimycin.⁴²

In an effort to access nojirimycin analogues with a flattened-chair conformation resembling the glycosidase transition state, Cipolla and co-workers have prepared a small library of conformationally restricted bicyclic nojirimycin (NJ) derivatives, which incorporate functional groups capable of being protonated under physiological conditions, including amines, ureas, cyclic carbamates and guanidines (Fig. 7).⁴³

Employing α -C-allyl nojirimycin derivative **48**, introduction of a conformationally rigidifying 1,3-oxazinan-2-one ring was accomplished through halofunctionalization of the corresponding Cbz derivative (Scheme 7). Iodocyclization in this case was readily effected by treatment with I₂, which furnished iodide **49** as a single diastereomer in excellent yield. Functionalization of the oxazinanone ring was now accomplished through a sequence of nucleophilic substitution and regioselective de-O-benzylation to yield primary alcohol **50**. Sequential oxidation and hydrogenolysis then afforded bicyclic NJ derivative **45b**. Employing the same strategy, α -C-vinyl nojirimycin derivative **51** was converted to **46b**, the oxazolidinone analogue of compound **45b** (Scheme 8). Through minor modification of the strategies outlined in Schemes 7 and 8, a range of other bicyclic NJ analogs were also accessed. While these novel nojirimycin-derived bicycles failed to display appreciable antibacterial activity, a number of the cyclic carbamate derivatives did prove to be inhibitors of α -glucosidase in the μ M range.

In 2000, Asano and co-workers reported the isolation of a novel family of α -1-C-alkylated analogues of 1-deoxy-homonojirimycin and fagomine (1,2-dideoxynojirimycin) from *Adenophora triphylla*⁴⁴ and *Lobelia sessilifolia*. (Fig. 8).⁴⁵ From among this series of alkyliminosugars, 1-O- β -D-glucopyranosyl-5-deoxyadenophorine (adenophorine (**55**)) and α -1-deoxy-1-C-methylhomonojirimycin (adenophorine (**56**)) were found to be α -glucosidase inhibitors.



Scheme 8 Cipolla's route to conformationally restricted bicyclic nojirimycin derivatives. *Reagents and conditions:* (a) CbzCl, DIPEA, MeCN, 58%; (b) I₂, CH₂Cl₂, 0 °C, 84%; (c) NaN₃, *n*-Bu₄NI, CH₂Cl₂, 97%; (d) Ac₂O, TFA, 74%; (e) MeOH, cat. Na, 78%; (f) IBX, DMSO; (g) NaPO₄H₂·2H₂O₂, NaClO₂, CH₃CN, 83% (2 steps); (h) H₂, Pd(OH)₂/C, AcOH, acetone-H₂O (1 : 1), 100%.

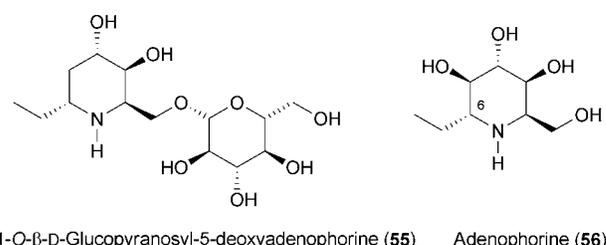
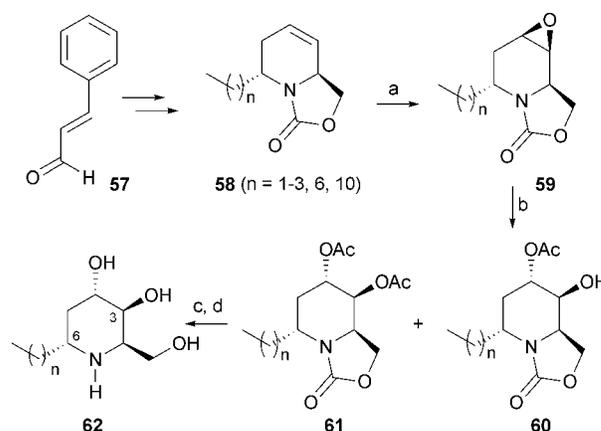


Fig. 8 Examples of naturally occurring α -1-C-alkylated 1-deoxy-iminosugar glycosidase inhibitors.

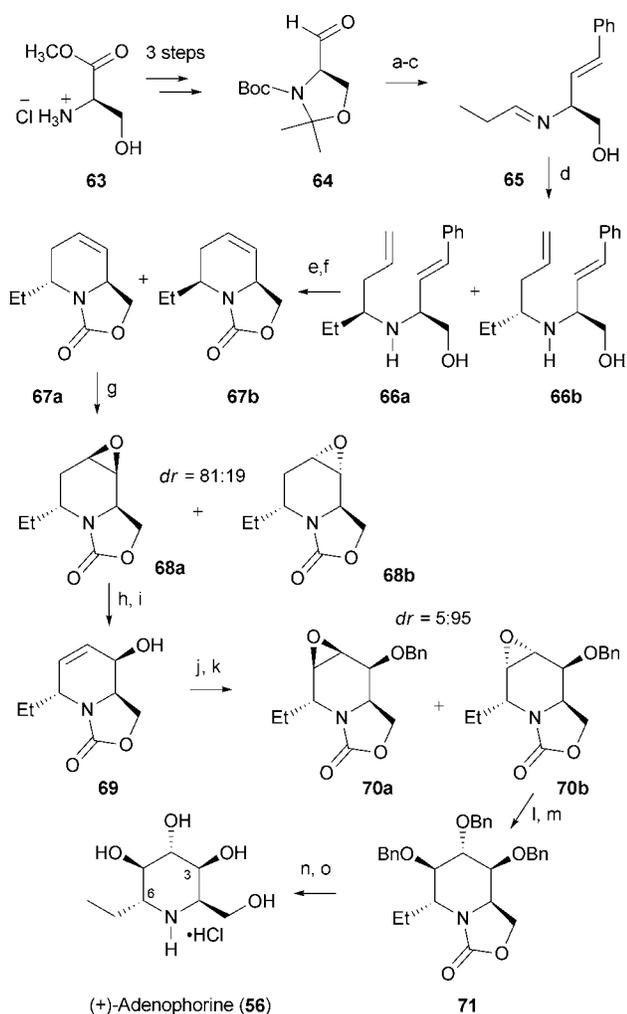


Scheme 9 Lebreton's synthesis of 5-deoxyadenophorine analogues. *Reagents and conditions:* (a) *m*-CPBA, NaH₂PO₄, CH₂Cl₂, 0 °C → rt, 72 h, 54–93%; (b) AcOH, 100 °C, 17 h; (c) K₂CO₃, MeOH, rt, 3 h, 50–70% (2 steps); (e) 8 M NaOH–H₂O–MeOH, 95 °C, 24 h, 66–74%.

of these systems is of note and has stimulated considerable interest.

Having previously completed the total synthesis of **55** in 2004,⁴⁶ Lebreton and co-workers have recently reported the preparation of a series of racemic 5-deoxyadenophorine analogues from 1-C-alkyl tetrahydropyridine **58** ($n = 1–3, 6, 10$) (Scheme 9).⁴⁷ These 1,6-disubstituted piperidines were expediently accessed from *trans*-cinnamaldehyde (**57**) through a six-step sequence involving formation of the tetrahydropyridine ring by RCM. From **58**, the *trans*-3,4-diol stereodiad was introduced *via* diastereoselective alkene epoxidation (*dr* = 85 : 15) and subsequent ring opening in acetic acid, which proceeded with complete regioselectivity to provide **60** and **61**. After saponification of this mixture, hydrolysis of the oxazolidinone under more stringent conditions (NaOH, 95 °C) furnished 5-deoxyadenophorine analogues **62**. The corresponding *cis*-3,4-iminosugar series was also accessed through dihydroxylation of **58** rather than epoxidation. Preliminary biological evaluation of these novel iminosugar analogues revealed them to be weak α -glucosidase inhibitors, although two *cis*-substituted compounds with C₇ and C₁₁ sidechains were found to be potent β -glucosidase inhibitors ($K_i = 60 \mu$ M).

In related work, Lebreton has also completed the first total synthesis of the natural product (+)-adenophorine (**56**) (Scheme 10).⁴⁸ After conversion of (+)-Garner's aldehyde (**64**) to imine **65**, addition of allylmagnesium bromide proceeded with reasonable diastereoselectivity to generate **66b**, thereby establishing the C₆ stereocenter of the target. After protection of these 1,2-amino



Scheme 10 Lebreton's total synthesis of (+)-adenophorine. *Reagents and conditions:* (a) diethyl benzylphosphonate, *n*-BuLi, THF, -78°C \rightarrow rt, 14 h, 75%; (b) 12 M HCl, MeOH, reflux, 4 h, 98%; (c) EtCHO, MgSO₄, THF, rt, 12 h; (d) allylmagnesium bromide, THF, Et₂O, $-78 \rightarrow -10^{\circ}\text{C}$, 6 h, 87%, *dr* = 87 : 13; (e) CDI, Et₃N, CH₂Cl₂, 18 h, 88%; (f) Grubbs' 2nd-generation catalyst (5 mol%), CH₂Cl₂, reflux, 1 h, **67a** (74%), **67b** (9%); (g) DMDO, acetone, rt, 4 h, **68a**, 60%; (h) Ph₂Se₂, NaBH₄, EtOH, rt, 12 h, 72%; (i) 50% H₂O₂, THF, rt, 2 h, 63%; (j) BnBr, NaH, THF, rt, 12 h; (k) *m*-CPBA, CH₂Cl₂, rt, 72 h, **70b** (60%, 2 steps); (l) 1 M H₂SO₄, H₂O-dioxane (1 : 1), 80 $^{\circ}\text{C}$, 12 h; (m) BnBr, NaH, DMF, rt, 2 h, 60% (2 steps); (n) 8 M NaOH, MeOH, 95 $^{\circ}\text{C}$, 48 h, 76%; (o) H₂, Pd(OH)₂, HCl, EtOH, rt, 24 h, 100%.

alcohols, formation of tetrahydropiperidine **70a** was accomplished by ring-closing metathesis of the oxazolidinone mixture and chromatographic separation. The C3–C5 stereotriad present in adenophorine was now introduced in stepwise fashion *via* alkene epoxidation, regioselective ring opening to generate an allylic selenide, and selenoxide elimination to yield **69**. *O*-Benzoylation of this allylic alcohol and *exo*-face epoxidation using *m*-CPBA generated **70a** with excellent facial control (*dr* = 95 : 5). Solvolysis of this epoxide proceeded with complete regiocontrol to yield **71**, after bis-*O*-benzoylation. Saponification of the oxazolidine ring and hydrogenolytic removal of the benzyl ethers then completed the synthesis of (+)-adenophorine (**56**).

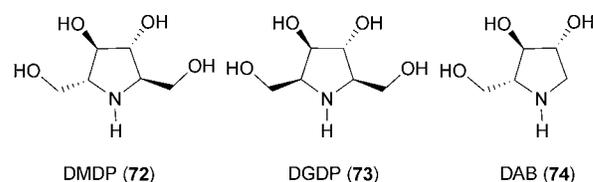
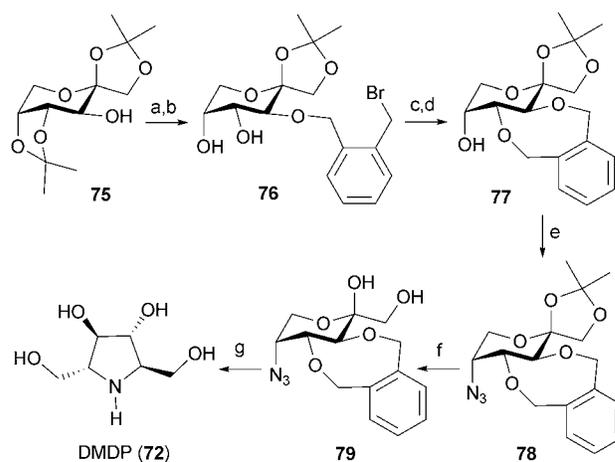


Fig. 9 Naturally occurring polyhydroxylated pyrrolidine-based glycosidase inhibitors: DMDP, DGDP and DAB.

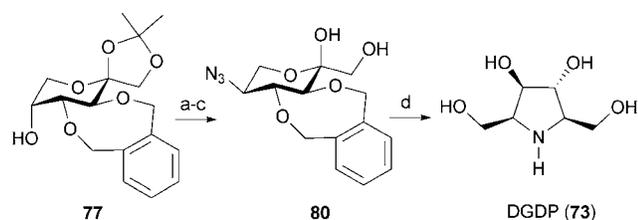
3.2 Pyrrolidines

Polyhydroxylated pyrrolidine alkaloids, including 2,5-dideoxy-2,5-imino-D-mannitol (DMDP, **72**), 2,5-dideoxy-2,5-imino-D-glucitol (DGDP, **73**), 1,4-dideoxy-1,4-imino-D-arabinitol (DAB-1, **74**) are widespread, naturally occurring secondary sugar mimics, many of which have been found to be specific inhibitors of plant and mammalian glucosidases as well as antiviral agents (Fig. 9).⁴⁹

Numerous syntheses of these targets have been reported in the literature,⁵⁰ and while carbohydrates are appealing points of departure in these undertakings, the issue of regiocontrol as it pertains to hydroxyl group protection has proven to be a recurring challenge. In an effort to obviate this problem, Mellet and Fernandez have recently developed a method to selectively mask 1,2-diols as cyclic *o*-xylylene ethers and have successfully utilized this protecting group strategy in the total synthesis of DMDP (**72**) and DGDP (**73**) (Scheme 11).⁵¹ Commencing from protected D-fructose derivative **75**, alkylation of the free hydroxyl group with α,α' -dibromoxylene and selective hydrolysis of the 4,5-*O*-isopropylidene group provided **76**. Treatment with sodium hydride in DMF then mediated ring closure to form *o*-xylylene ether **77** which, through double inversion, was converted to azide **78** in excellent overall yield. The synthesis of DMDP (**72**) was completed efficiently by removal of the acetonide group and submission of 1,2-diol **79** to catalytic hydrogenation. In the presence of HCl, this process resulted in hydrogenolysis of the cyclic ether, azide reduction and, ultimately, stereoselective reductive amination of the latent γ -amino ketone.

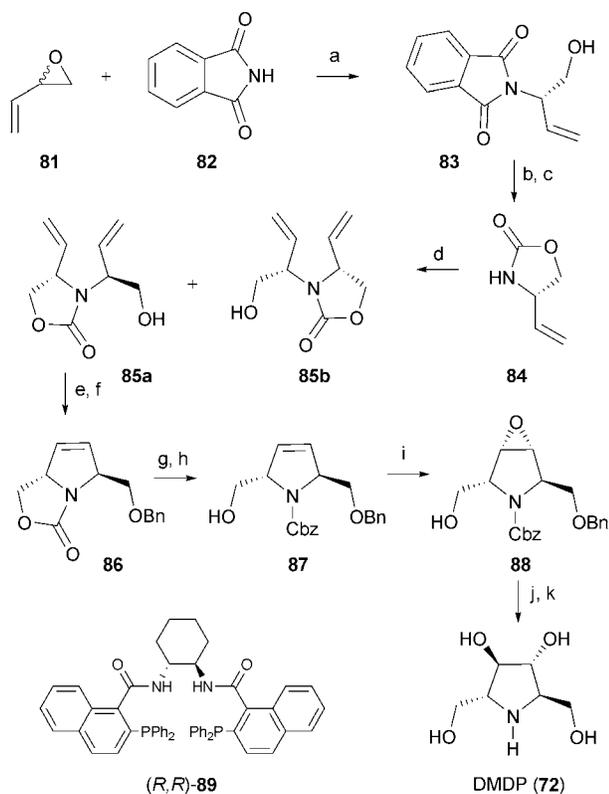


Scheme 11 Mellet and Fernandez's synthesis of DMDP. *Reagents and conditions:* (a) α,α' -dibromoxylene, NaH, DMF, rt, 20 min, 91%; (b) 60% aq. AcOH, 45 $^{\circ}\text{C}$, 2 h, 87%; (c) NaH, DMF, rt, 15 min, 93%; (d) I₂, PPh₃, imidazole, PhCH₃, 80 $^{\circ}\text{C}$, 16 h, 98%; (e) NaN₃, DMF, 80 $^{\circ}\text{C}$, 12 h, 91%; (f) TFA–H₂O (9 : 1), rt, 30 min, 98%; (g) H₂ (4 bars), Pd/C, HCl, MeOH–H₂O, 24 h, 95%.



Scheme 12 Mellet and Fernandez's synthesis of DGDP. *Reagents and conditions:* (a) Tf_2O , pyridine, CH_2Cl_2 , rt, 1 h; (c) NaN_3 , DMF, rt, 3 h, 83% (2 steps); (c) $\text{TFA-H}_2\text{O}$ (9 : 1), rt, 30 min, 98%; (d) H_2 (4 bars), Pd/C, HCl, $\text{MeOH-H}_2\text{O}$, 24 h, 95%.

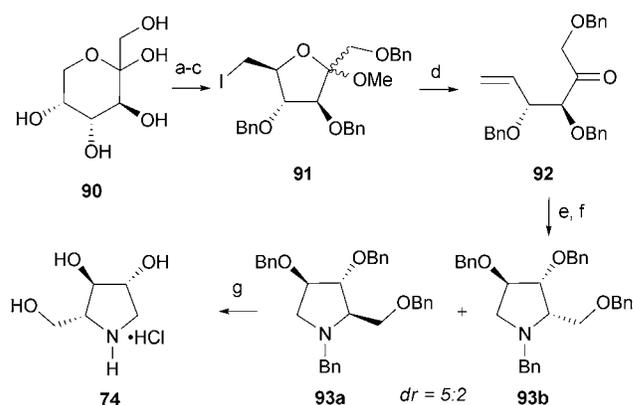
Mellet and co-workers have also adapted their route to DMDP (**72**) for the preparation of DGDP (**73**) (Scheme 12). In this case, activation of the secondary hydroxyl group in **77** as a triflate ester and stereoinversion with azide provided diastereomer **80**. Conversion of this material to the hydrochloride salt of DMDP (**73**) was accomplished as before, *via* acetone hydrolysis and global reduction.



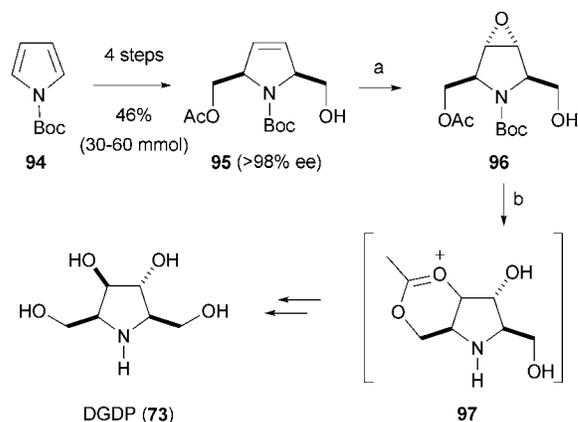
Scheme 13 Trost's synthesis of DMDP. *Reagents and conditions:* a) $[(\eta^3\text{-C}_3\text{H}_5)_3\text{PdCl}_2]$ (0.4 mol%), (*R,R*)-**89** (1.2 mol%), Na_2CO_3 (1 mol%), CH_2Cl_2 , rt, 99%, ee = 94%; (b) ethylenediamine, EtOH, reflux, 84%; (c) triphosgene, NaHCO_3 , toluene- H_2O (1 : 1), 0 °C, 85%; (d) butadiene monoxide, $[\text{Pd}_2\text{dba}_3]\cdot\text{CHCl}_3$ (1 mol%), (*R,R*)-**89** (1.5 mol%), DBU (1 mol%), CH_2Cl_2 , rt, 91%, dr = 93 : 7; (e) NaH, BnBr, TBAI, THF, rt, 84%; (f) Grubbs' second-generation catalyst (1.2 mol%), CH_2Cl_2 , 40 °C, 91%; (g) NaOH, EtOH- H_2O (3 : 1), reflux; (h) BnOCOC_2Cl , NaHCO_3 , Na_2CO_3 , H_2O , 0 °C, 99%, (2 steps); (i) MeReO_3 (5 mol%), $\text{CO}(\text{N-H}_2)_2\cdot\text{H}_2\text{O}_2$, CH_2Cl_2 , rt, 76%, dr > 25 : 1; (j) TFA, THF, H_2O , 65 °C, 72%; (k) H_2 , Pd/C, HCl, MeOH, 96%.

The first report of a catalytic enantioselective synthesis of DMDP (**72**) was made in 2006, by Trost and co-workers,⁵² who employed consecutive palladium-catalysed dynamic kinetic asymmetric transformations (DYKAT) to generate *trans*-2,5-dihydropyrrole **86**, a key intermediate for the preparation of a number of alkaloids (Scheme 13). In this case, *N*-alkylation of phthalimide (**82**) with butadiene oxide (**81**) proceeded with excellent regio- and enantioselectivity to form **83**. After a two-step conversion of this material to oxazolidinone **84**, a second Pd-catalyzed DYKAT reaction with butadiene oxide yielded a chromatographically separable mixture of dienes **85**. *O*-Benzoylation, ring closure using Grubbs' second-generation catalyst, oxazolidinone hydrolysis and *N*-protection then provided dihydropyrrole **87**. Hydroxyl-directed epoxidation of this alkene using catalytic methyltrioxorhenium led to the formation of **88** which, upon acid-mediated epoxide ring opening and hydrogenolysis, afforded DMDP (**72**) in 11 steps and 22% overall yield.

Employing a chiral-pool approach, Madsen and Lauritsen have reported a concise approach to DAB (**74**) which features the



Scheme 14 Madsen and Lauritsen's synthesis of DAB. *Reagents and conditions:* (a) MeOH, H_2SO_4 , rt; (b) I_2 , PPh_3 , imidazole, THF, 65 °C; (c) $\text{BnOC}(\text{NH})\text{CCl}_3$, TfOH, dioxane, 0 °C; (d) Zn, THF, H_2O , ultrasound, 40 °C; (e) O_3 , MeOH, CH_2Cl_2 , -78 °C, then Me_2S , rt; (f) BnNH_2 , NaCNBH_3 , AcOH, 3 Å MS, THF, rt, **93a** (44%, two steps); (g) H_2 , Pd/C, HCl, MeOH, rt, 74%.



Scheme 15 Donohoe's synthesis of DGDP. *Reagents and conditions:* (a) CF_3COCH_3 , Oxone, NaHCO_3 , $\text{CH}_3\text{CN-H}_2\text{O}$, EDTA, 0 °C, 94%; (b) $\text{BF}_3\cdot\text{OEt}_2$, CH_2Cl_2 , 0 °C → rt; then MeOH, 78%.

zinc-mediated fragmentation of iodofuranoside **91** (Scheme 14).⁵³ D-Fructose (**90**) was converted to **91** via a sequence of Fischer glycosylation with methanol, selective iodination of the primary alcohol and per-*O*-benzylation using Bundle's reagent. Upon sonication in the presence of zinc, **91** underwent reductive fragmentation to afford unsaturated ketone **92** in good yield. In order to complete the synthesis of DAB, this alkene was ozonized and the resulting 1,4-dicarbonyl compound subjected to reductive amination with benzylamine in the presence of NaBH₃CN and acetic acid. Unfortunately, this cyclization proceeded with poor diastereoselectivity and yielded *N*-benzyl-DAB derivative **93a** and its *L*-xylo epimer **93b** in a 5 : 2 ratio. After chromatographic separation, hydrogenolysis of **93a** gave the hydrochloride salt of DAB (**74**) in seven steps and 11% overall yield from D-fructose.

Donohoe and co-workers has developed an elegant and highly efficient synthesis of (+)-DGDP (**73**)⁵⁴ which makes use of their well-established methodology involving the partial Birch reduction of heterocycles (Scheme 15).⁵⁵ In this work, preparation of DGDP commenced from enantiopure monoacetate **95**, which was obtained from *N*-Boc pyrrole (**94**) in four steps. Epoxidation of this pyrroline using methyltrifluoromethyl dioxirane proceeded efficiently with excellent facial selectivity to yield **96**. Lewis acid-mediated ring opening of this epoxide now proceeded with complete regio- and stereocontrol as a result of the participation of the proximal *O*-acetyl group. Concomitant loss of the *N*-Boc group and methanolysis of the putative dioxonium ion intermediate **97** then provided DGDP (**73**) in 6 steps and 34% overall yield.

3.3 Pyrrolizidines

Noteworthy members of this family of plant-derived, polyhydroxylated natural products include (+)-australine (**98**), (+)-casuarine (**99**), hyacinthacine A₂ (**100**), hyacinthacine A₁ (**101**) and (+)-alexine (**102**) (Fig. 10). Notwithstanding their unifying pyrrolizidine core structure, these alkaloids display a diverse range of differing biological activities, for which reason they remain popular synthetic targets. (+)-Australine (**98**), isolated from *Castenosperme australe* by Moleneux and co-workers,⁵⁶ is among of the most important members of this group of compounds, since it not only potently inhibits α -amylglucosidase and glycoprotein processing,⁵⁷ but displays anti-HIV activity.⁵⁸

Trost and co-workers have reported an elegant synthesis of australine (**98**) which features the Pd-catalyzed DYKAT reaction of oxazolidinone **104** with butadiene oxide (Scheme 16).⁵⁹ Notably, this *N*-alkylation proceeded with excellent (catalyst-controlled) diastereoselectivity to provide **105** in near-quantitative yield. Ring-closing metathesis of this material using Grubbs' second-generation catalyst then furnished 3-pyrroline **106** which, after protection of the primary alcohol, underwent regioselective hydroboration–oxidation to generate the primary alcohol. The remaining alkene was epoxidized with methyl trifluoromethyl dioxirane and compound **107** then solvolyzed in benzyl alcohol to provide **108**, the product of oxazolidinone hydrolysis and epoxide ring-opening. Having established all stereocenters of the target, the synthesis of australine hydrochloride (**109**) was completed by formation of the pyrrolizidine ring system and removal of the benzyl ethers using PdCl₂ as the hydrogenation catalyst and source of HCl.

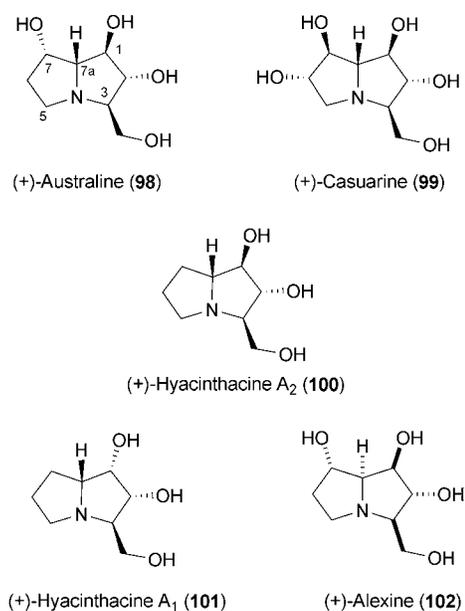
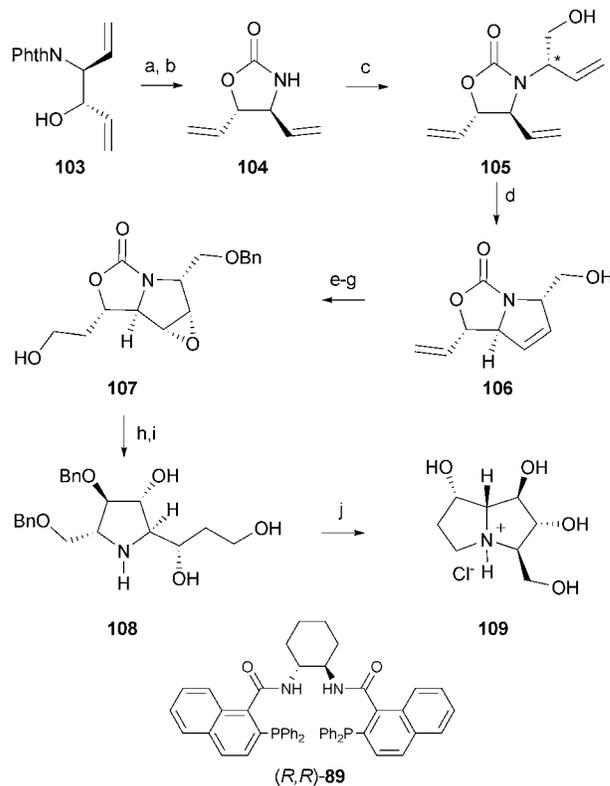
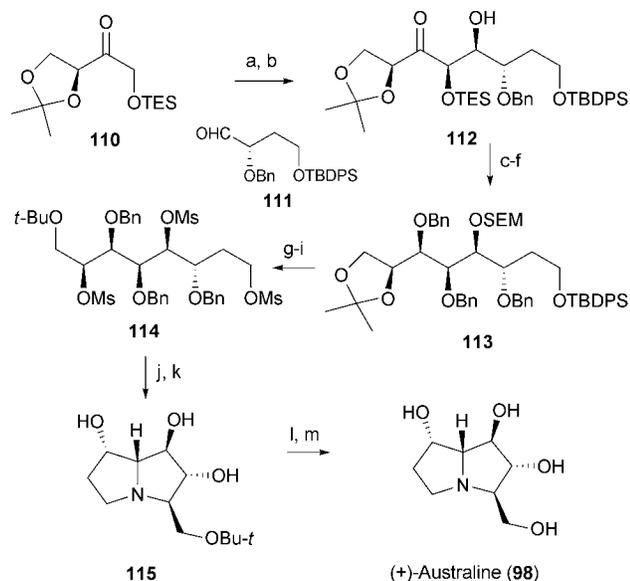


Fig. 10 Structures of selected, naturally occurring C3-alkylated pyrrolizidine alkaloids, which display α -glucosidase inhibitory activity.



Scheme 16 Trost's total synthesis of (+)-australine. Reagents and conditions: (a) H₂N(CH₂)₂NH₂, EtOH, 96%; (b) triphosgene, pyridine, CH₂Cl₂, 78%; (c) [Pd₂dba₃]-CHCl₃ (0.5 mol%), (*R,R*)-**89** (1.5 mol%), DBU (10 mol%), CH₂Cl₂, 99%, dr = 95 : 5; (d) Grubbs' second-generation catalyst (1 mol%), CH₂Cl₂, 77%; (e) BnOC(NH)CCl₃, TFOH, 94%; (f) 9-BBN, THF; NaBO₃·H₂O, H₂O, 74%; (g) Oxone, CF₃COCH₃, NaHCO₃, MeCN–H₂O, EDTA, 0 °C, 67%; (h) Dowex 1X8-50, BnOH, 100 °C, 51%; (i) MsCl, Et₃N, CH₂Cl₂, 74%; (j) H₂, PdCl₂, MeOH, 98%.

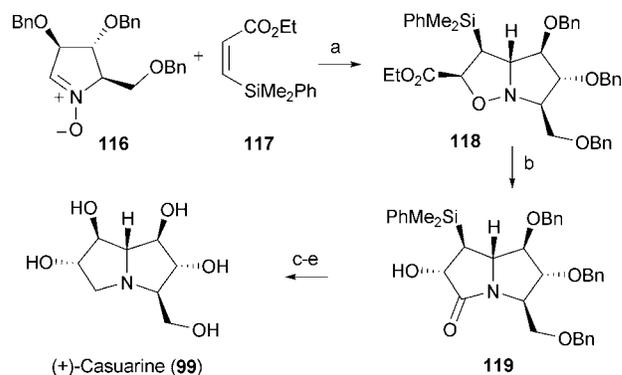


Scheme 17 Marco and Falamor's total synthesis of (+)-australine. *Reagents and conditions:* (a) (cyclohexyl)₂BCl, Et₃N, Et₂O, 0 °C; (b) **113**, 72%; (c) SEMCl, *i*-Pr₂NEt, CH₂Cl₂, rt, 24 h, 75%; (d) LiBH₄, Et₂O, -90 °C, 80%; (e) DDQ, THF-H₂O, rt, 24 h, 74%; (f) BnBr, NaH, THF, 4 h, 40 °C, 80%; (g) MeMgBr, PhCH₃-Et₂O, 16 h, 77%; (h) TBAF, THF, rt, 1 h, 97%; (i) MsCl, Et₃N, CH₂Cl₂, rt, 2 h; (j) BnNH₂, NaI, DMSO, 80 °C, 24 h, 60% (2 steps); (k) H₂, Pd(OH)₂, rt, 2 d; (l) TFA, CH₂Cl₂, rt, 15 h; (m) NH₄OH, 78% (3 steps).

A stereocontrolled, convergent synthesis of (+)-australine (**98**) has also been reported by Marco, Falomir and co-workers, who employ an aldol-based strategy to rapidly establish the 5 stereocenters present in the target molecule (Scheme 17).⁶⁰ In this endeavour, the *Z*-boron enolate derived from *L*-erythrulose derivative **110** underwent reaction with α -alkoxyaldehyde **111** to generate adduct **112** as a single diastereoisomer. After protection of the secondary alcohol and *syn*-selective reduction of the ketone, a series of protecting and functional group manipulations led to trimesylate **114**. Generation of the bicyclic pyrrolizidine system **115** was now accomplished by means of a three-step sequence of S_N2 displacements, triggered by benzylamine. Notably, this process also leads to the concomitant *N*-benzylation of the putative quaternary ammonium ion intermediate. The synthesis of (+)-australine (**98**) was completed by hydrogenolysis of the benzyl ether and acid-catalyzed removal of the *tert*-butyl ether. Employing this aldol strategy, Marco and co-workers have recently completed the stereoselective synthesis of hyacinthacine A₂, hyacinthacine A₃ and 5-*epi*-hyacinthacine A₃.⁶¹

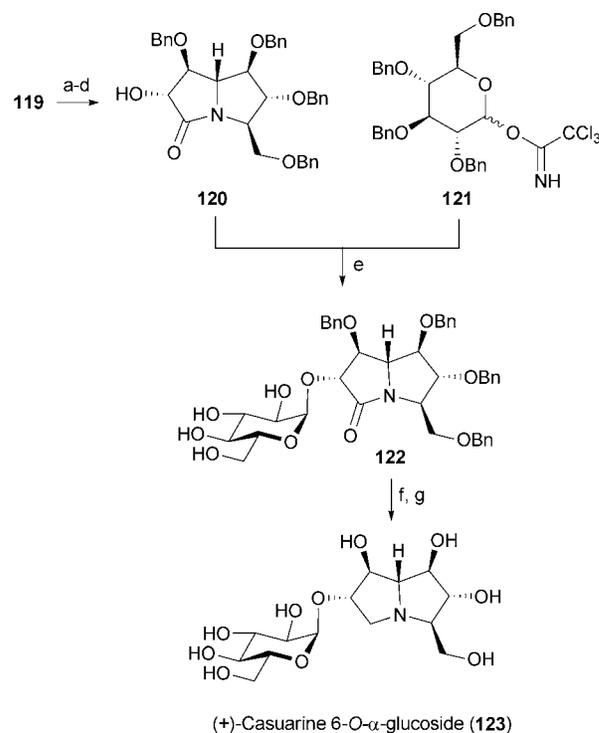
Using the zinc-mediated fragmentation strategy developed for their synthesis of 1,4-dideoxy-1,4-imino-D-arabinitol (DAB), Madsen and Lauritsen have reported a formal synthesis of australine (**98**), which features generation of the pyrrolizidine core structure through the transannular ring closure of an eight-membered aminoepoxide.⁵³ This approach has also been gainfully exploited by Madsen and co-workers in their 2009 synthesis of castanospermine (*vide infra*).

Isolated from the bark of *Casuarina equisetifolia* and from the leaves of *Eugenia jambolana*, (+)-casuarine (**99**) and its 6-*O*- α -glucoside **123** were originally found to be specific inhibitors of



Scheme 18 Goti's total synthesis of (+)-casuarine. *Reagents and conditions:* (a) CH₂Cl₂, rt, 36 h, 79%; (b) Zn, AcOH-H₂O, 60–65 °C, 5 h, 93%; (c) Hg(CF₃CO₂)₂, AcOH, AcOOH, CHCl₃, 76%; (d) LiAlH₄, THF, reflux, 78%; (e) H₂, Pd/C, MeOH, HCl, 100%.

fungal glucoamylase from *Aspergillus niger* (IC₅₀ = 0.7 and 1.1 μ M, respectively).⁶² These important alkaloids have most recently been prepared by Goti and co-workers, who employed a stereoselective nitron-alkene cycloaddition to establish the C6, C7 and C7a stereocenters of the pyrrolizidine framework in a single step (Scheme 18).⁶³ Thus, reaction of nitron **116** with disubstituted (*Z*)-vinylsilane **117** proceeded with the anticipated regioselectivity to yield **118**.⁶⁴ Reductive cleavage of this isoxazolidine with Zn in acetic acid afforded lactam **119** which,

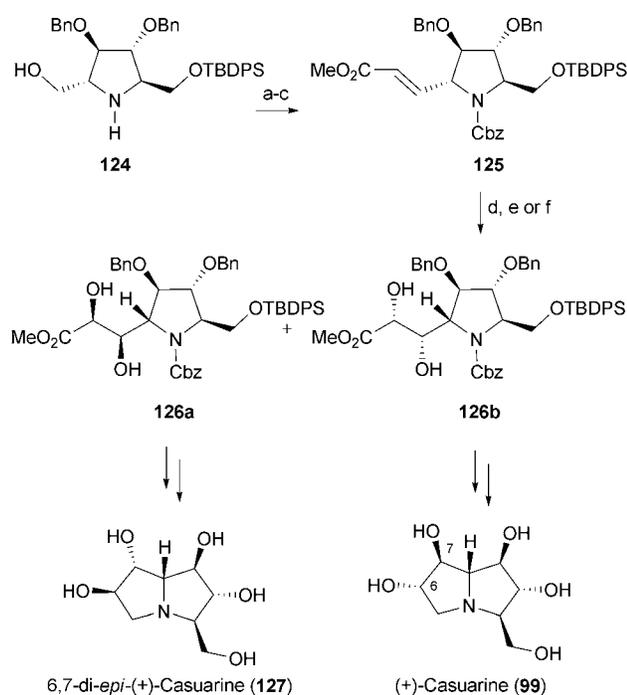


Scheme 19 Goti's synthesis of (+)-casuarine 6-*O*- α -glucoside. *Reagents and conditions:* (a) Ac₂O, pyridine, rt, 15 h, 100%; (b) Hg(CF₃CO₂)₂, AcOH, AcOOH, CHCl₃, 82%; (c) BnOC(=NH)CCl₃, CF₃SO₃H, Et₂O, rt, 3 h; (d) Ambersep 900 (OH⁻ form), MeOH, rt, 15 h, 75% (2 steps); (e) TMSOTf, Et₂O, -20 °C, 40 min, 72%; (f) LiBH₄, BH₃·THF, THF, 23 °C, 3 d, 68%; (g) H₂, Pd/C, MeOH, HCl, 77%.

through Tamao–Fleming oxidation of the C–Si bond, lactam reduction and catalytic hydrogenolysis, was converted to casuarine (**99**).

Goti's synthesis of casuarine glucoside **123** commenced from lactam **119**, which was advanced through 4 steps to compound **120**, as shown in Scheme 19. Glycosylation of this secondary alcohol using trichloroacetamide glycosyl donor **121** was mediated by catalytic TMSOTf and proceeded diastereoselectively to provide α -anomer **122** in high yield. Finally, reduction of **122** with excess of LiBH₄ in combination with BH₃·THF and subsequent hydrogenolysis generated target **123**. Inhibition and docking studies subsequently carried out on casuarine (**99**) by Rose with the N-terminal domain of human intestinal maltase-glucoamylase (ntMGAM) have shown this is compound to a potent inhibitor with a K_i of 0.45 μ M.⁶³ While glucoside **123** was found to be a significantly less active inhibitor of ntMGAM, it is a very potent ($K_i = 12$ nM) inhibitor of Tre37A, a periplasmic trehalase from *Escherichia coli*.

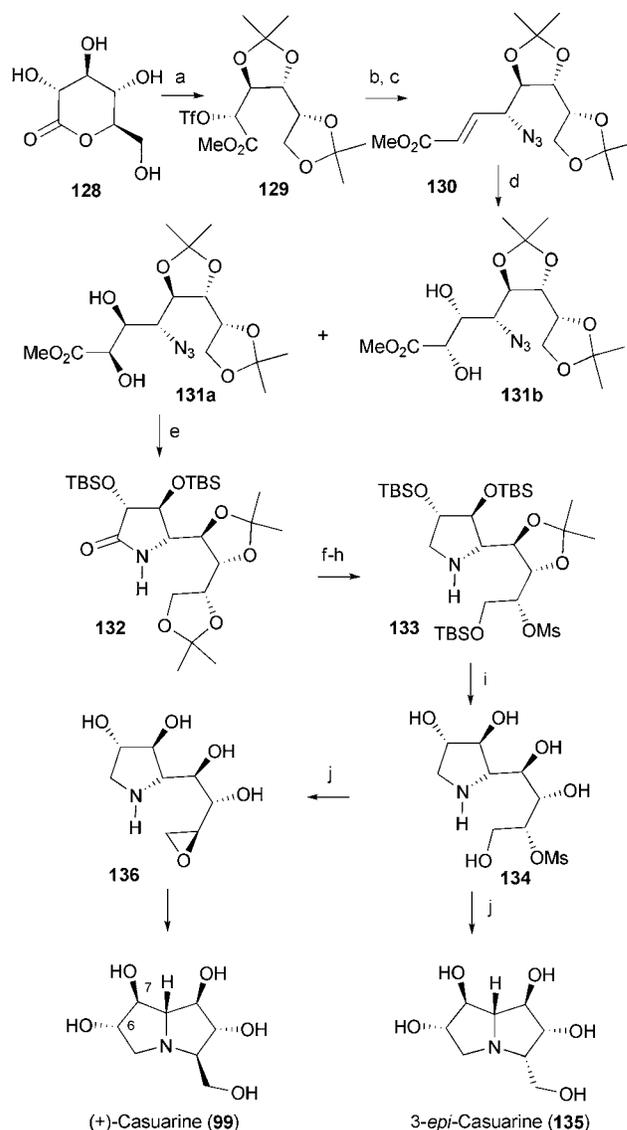
Utilizing DMDP derivative **124** as their starting point, Izquierdo and co-workers have developed a concise stereoselective route to (+)-casuarine (**99**) and its 6,7-bis-*epi* isomer **127** (Scheme 20).⁶⁵ Advanced intermediate **124** was converted to **125**, following a three-step sequence of carbamate protection, primary alcohol oxidation and Wittig homologation. Dihydroxylation of this unsaturated ester then served to introduce the C6 and C7 stereocenters of the target molecule, although the diastereoselectivity in this case proved to be rather low (dr = 2.2 : 1) and highly



Scheme 20 Izquierdo's total synthesis of 6,7-bis-*epi*-(+)-casuarine and (+)-casuarine. *Reagents and conditions:* (a) CbzCl, K₂CO₃, acetone, rt, 3 h, 93%; (b) TPAP, NMO, 4 Å MS, CH₂Cl₂, rt, 1 h; (c) Ph₃P=CHCO₂Me, CH₂Cl₂, rt, 48 h, 85% (2 steps); (d) OsO₄, NMO, acetone–H₂O (8 : 1), rt, 30 h, 88%, dr = 1 : 1 (e) DHQ-CLB, NMO, acetone–H₂O (5 : 1), rt, 48 h, 85%, dr = 1 : 2.2; (f) DHQD-CLB, NMO, acetone–H₂O (5 : 1), rt, 48 h, 92%, dr = 2 : 1.

dependant on the method/ligands employed. After separation of **126a** and **126b**, ring closure, lactam reduction, and further protecting group manipulations individually generated (+)-casuarine (**99**) and 6,7-bis-*epi*-casuarine (**127**).

In 2006, Fleet and co-workers reported the isolation and total synthesis of the naturally occurring β -glucosidase inhibitor 3-*epi*-casuarine (**135**) (Scheme 21).⁶⁶ In addition, these authors also adapted this synthetic route to encompass casuarine (**99**) itself. Embarking from D-gluconolactone (**128**), this inexpensive starting material was converted through a five-step, four-pot sequence to allylic azide **130** on a multigram scale. In common with



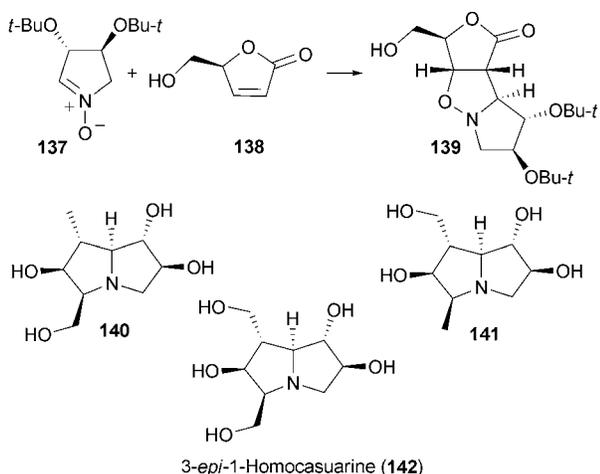
Scheme 21 Fleet's total synthesis of (+)-casuarine and 3-*epi*-casuarine. *Reagents and conditions:* (a) Me₂C(OMe)₂, *p*-TsOH, MeOH; then (CF₃SO₂)₂O, pyridine, CH₂Cl₂, 72%; (b) NaN₃, DMF, 97%; (c) DIBAL-H, –78 °C; then Ph₃P=CHCO₂Me, PhCH₃, 75% (2 steps); (d) OsO₄, NMO, *t*-BuOH–H₂O, 72%; (e) H₂, Pd/C, THF; then PhCH₃, heat; then TBSCl, imidazole, THF, 70% (3 steps); (f) 60% AcOH, H₂O–MeOH, 69%; (g) TBSCl, pyridine; then MeSO₂Cl, Et₃N, CH₂Cl₂, 66%; (h) BH₃·THF, THF, 57%; (i) CF₃CO₂H–H₂O (9 : 1); (j) NaOAc, H₂O, 89% (2 steps).

Izquierdo's casuarine synthesis, introduction of the C6/7 stereodiad was accomplished through dihydroxylation, which gave a 4 : 1 mixture of **131a** and **131b**. Isomer separation was achieved in this case, after azide reduction, lactamization and diol silylation. Through a number of steps, compound **132** was converted to pentahydroaminomesylate **134**, which upon exposure to sodium acetate underwent cyclization to yield 3-*epi*-casuarine (**135**) with a 6% overall yield. In this case, a small quantity (<5%) of casuarine (**99**) was also isolated and is thought to arise through the competitive formation and cyclization of epoxide **136**.

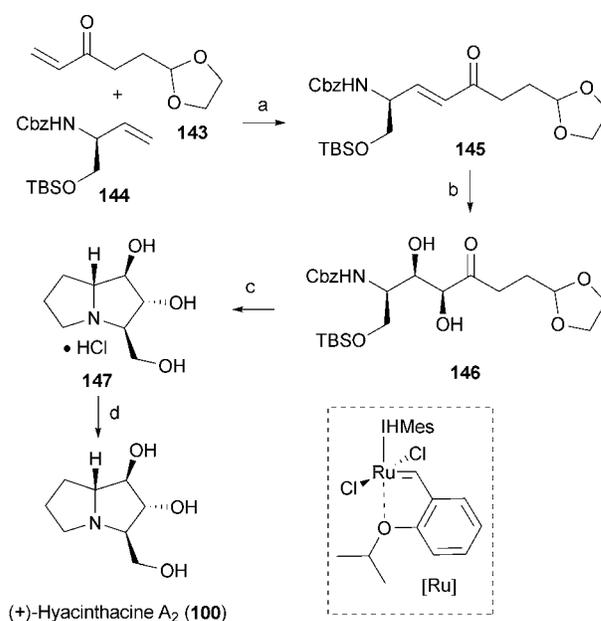
3-*epi*-Casuarine has also attracted the attention of Chmielewski and co-workers, who have recently developed a [2 + 3]-cycloaddition-based route to 3-*epi*-1-homocasuarine (**142**) and analogues, **140** and **141** (Scheme 22).⁶⁷ The key transformation in this work involves the 1,3-dipolar cycloaddition of nitron **137** and 2(5*H*)-furanone **138**, which proceeds with complete diastereo- and regioselectivity.⁶⁸ Through a sequence featuring lactone reduction, N–O bond scission and intramolecular alkylation of the nitrogen atom, **139** was converted to **140**, **141** and **142**.

Isolated from the bulbs of the grape hyacinth (*Muscari armeniacum*) by Asano co-workers, hyacinthacine A₂ (**100**) is a selective inhibitor of amyloglucosidase (*Aspergillus niger*) with an IC₅₀ value of 8.6 μM.⁶⁹ Blechert and co-workers have developed a short and convergent synthesis of **100** in which the *trans*-fused pyrrolizidine core is constructed through a double reductive cyclization (Scheme 23).⁷⁰ Assembly of the skeleton of **100** commenced with the stereoselective cross-metathesis (CM) of enone **143** and vinylglycine derivative **144** and using the Hoveyda–Blechert ruthenium catalyst. Sharpless enantioselective dihydroxylation of the resulting enone was followed by a one-pot, three-step hydrogenation procedure to generate hydrochloride salt **147**. Treatment with Amberlite (OH[−] form) then afforded hyacinthacine A₂ (**100**) in 39% yield. Blechert has also employed the CM reaction of a 2-vinyl-3-alkoxyproline derivative in the preparation of 7*a-epi*-7-deoxycasuarine.⁷¹

The total synthesis of (+)-hyacinthacine A₂ (**100**) has also been reported by Py, who has made use of a SmI₂-induced reductive coupling reaction to simultaneously assemble the carbon framework and establish the C7*a* stereocenter of the target



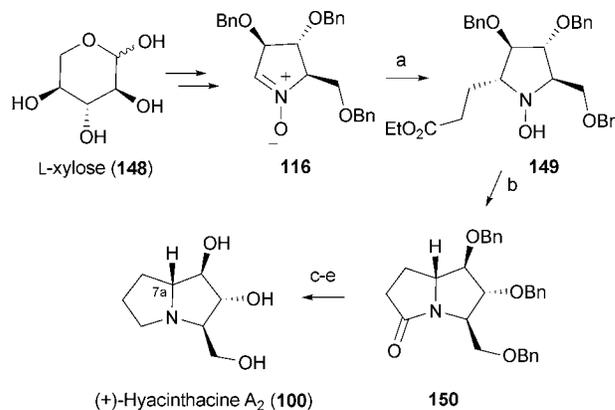
Scheme 22 Chmielewski's 1,3-dipolar cycloaddition strategy for the preparation of 3-*epi*-1-homocasuarine and analogues.



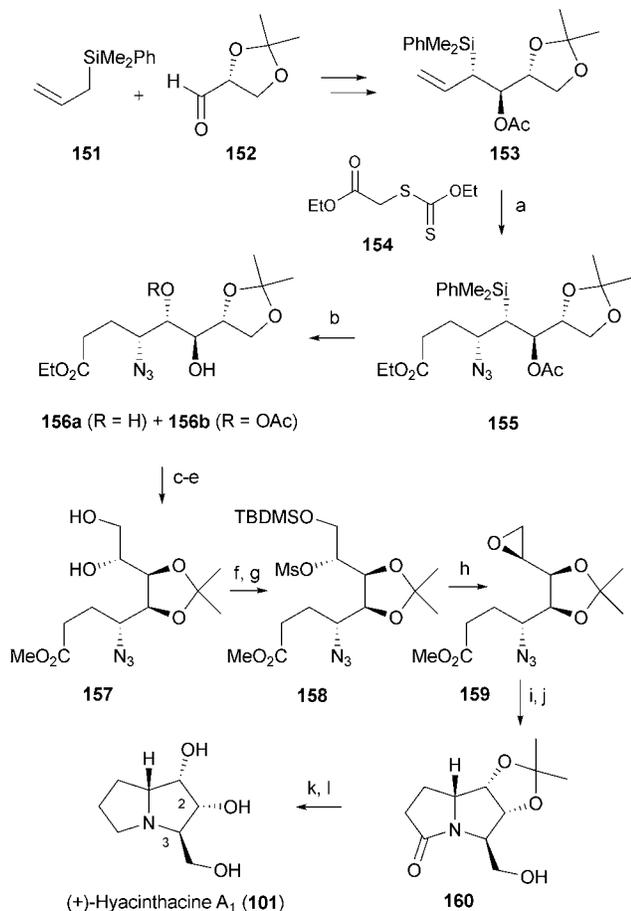
Scheme 23 Blechert's total synthesis of hyacinthacine A₂. *Reagents and conditions:* (a) [Ru] (10 mol%), CH₂Cl₂, reflux, 3 d, 73%; (b) AD-mix β, NaHCO₃, MeSO₂NH₂, K₂OsO₄·2H₂O, *t*-BuOH–H₂O, 1 h, 67%; (c) H₂ (4 bars), Pd/C (10 mol%), MeOH, 3 d; cat. HCl; H₂ (4 bars), 3 d; (d) Amberlite IRA, NH₄OH, 39% (4 steps).

molecule (Scheme 24).⁷² In this regard, treatment of nitron **116** with SmI₂ generated an α-azanucleophile,⁷³ which underwent stereoselective addition to ethyl acrylate to generate **149** (dr = 9 : 1). From this intermediate, the synthesis of hyacinthacine A₂ was completed through N–O bond scission, lactamization, lactam reduction and hydrogenolytic cleavage of the benzyl protecting groups. The overall yield of **100** from L-xylose was 19%.

Differing from hyacinthacine A₂ in the relative configuration at the C1 stereocenter, hyacinthacine A₁ (**101**) has proven to be a similarly popular synthetic target (Scheme 25). In this regard, the total synthesis of **101** reported by Landais and Renaud is



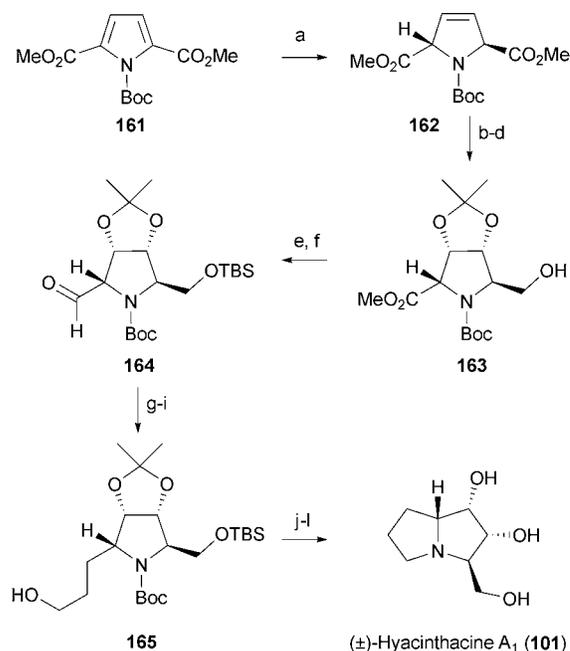
Scheme 24 Py's total synthesis of (+)-hyacinthacine A₂. *Reagents and conditions:* (a) ethyl acrylate, SmI₂, H₂O, THF, −78 °C, 3 h, 64%, dr = 90 : 10; (b) SmI₂, THF, −78 °C rt, 24 h; K₂CO₃, EtOH, H₂O, 59% (2 steps), dr = 90 : 10; (c) LiAlH₄, THF, 66 °C, 1 h, 79%; (d) H₂, Pd/C, MeOH, THF, 6 M HCl, rt, 4 d; (e) Dowex 1X8, 79% (2 steps).



Scheme 25 Renaud's total synthesis of (+)-hyacinthacine A₁. *Reagents and conditions:* (a) **154**, (Bu₃Sn)₂, *t*-BuON=NO*t*-Bu, benzene, pyrSO₂N₃, 60 °C, 84%, (*synlanti* 85 : 15); (b) AcOOH, AcOH, KBr, AcONa, 0 °C → rt, 84%; (c) Dowex 1X10, MeOH, rt; (d) Me₂C(OMe)₂, *p*-TsOH, CH₂Cl₂, rt, 12 h; (e) Zn(NO₃)₂·6H₂O, CH₃CN, 50 °C, 6 h, 55% (3 steps); (f) TBSCl, pyridine, rt, 5 h; (g) MsCl, pyridine, rt, 3 h, 84% (2 steps); (h) TBAF, THF, rt, 2 h; then K₂CO₃, MeOH, rt, 12 h, 70%; (i) H₂, Pd/C, MeOH, rt, 2 h; (j) Et₃N, MeOH, reflux; (k) LiAlH₄, THF, reflux, 1 h; (l) HCl, MeOH then Dowex 1X10 (OH⁻ form), 65% (2 steps).

notable not only for being the first but also for its reliance upon the diastereoselective, radical carboazidation reaction of allylsilane **153** to establish the C2/3 stereodiad.⁷⁴ Having served its purpose, to effect 1,2-stereocontrol, the PhMe₂Si group was now removed *via* Tamao–Fleming oxidation to generate **156a** and **156b**, which through saponification and deacetalization were converted to **157**. A number of protecting group manipulation steps then led to epoxide **159**, which upon hydrogenation and treatment with base, underwent 5-*exo*-tet cyclization to generate pyrrolizidinone **160**. Reduction of the lactam with LiAlH₄ and deacetalization then provided hyacinthacine A₁ (**101**) in 13 steps and 8% overall yield.

Published shortly after the Landais and Renaud report, Donohoe's flexible synthesis of (±)-hyacinthacine A₁ (**101**) and related targets centers around the stereodivergent generation and functionalization of 3-pyrrolines (Scheme 26).⁷⁵ In the case of **101**, partial Birch reduction of pyrrole **161** in ammonia generated *trans*-**162**. Poli dihydroxylation (OsO₄, Me₃NO), diol protection

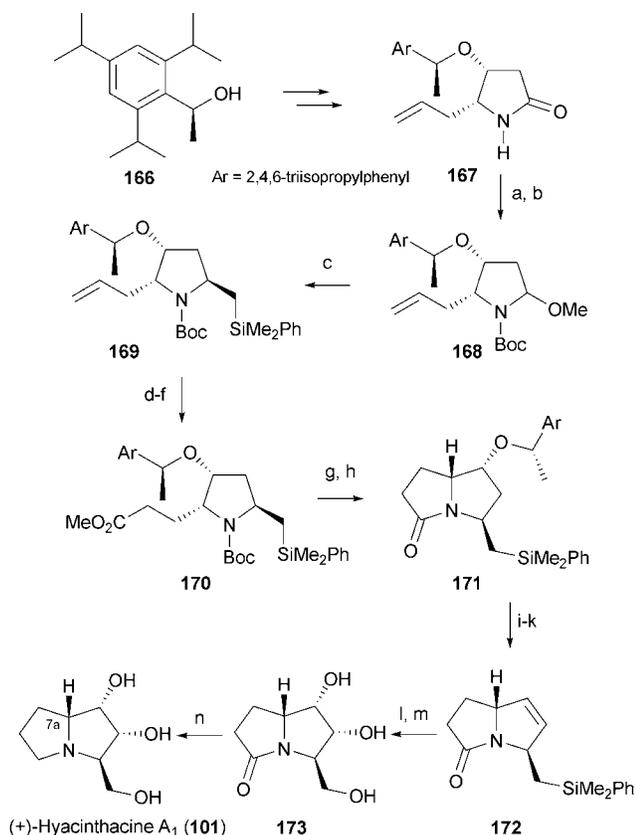


Scheme 26 Donohoe's total synthesis of (±)-hyacinthacine A₁. *Reagents and conditions:* (a) Li, NH₃, -78 °C, isoprene, NH₄Cl, 73%; (b) cat. OsO₄, CH₂Cl₂, Me₃NO, 95%; (c) dimethoxypropane, *p*-TsOH, acetone, 94%; (d) NaBH₄, MeOH–THF; (e) TBSCl, imidazole, DMF, 85% (2 steps); (f) DIBAL-H, CH₂Cl₂, -40 °C, 97%; (g) Ph₃P=CHCO₂Me, toluene, 110 °C, 100%; (h) H₂, Pt₂O, MeOH, rt, 100%; (i) DIBAL-H, CH₂Cl₂, -78 °C → rt, 93%; (j) MsCl, pyridine, 0 °C; (j) TESOTf, 2,6-lutidine, CH₂Cl₂, -78 °C → rt, 91% (2 steps); (k) (COCl)₂, MeOH, rt, 89%.

and reduction of the more accessible ester group yielded **163** which, by way of a 3-step sequence, was homologated to compound **165**. Activation of this primary alcohol *via* methanesulfonylation and removal of the *N*-Boc group then triggered ring closure to form the pyrrolizidine ring. Finally, global deprotection using HCl in MeOH generated racemic hyacinthacine A₁ (**101**) in high yield. Donohoe has subsequently extended this chemistry to the enantioselective preparation of a number of other pyrrolizidine natural products, including 2,3,7-tri-*epi*-australine and (+)-hyacinthacines A₆ and A₇, as well as (+)-hyacinthacine A₁ itself.⁷⁶

In common with the work of Landais and Renaud, Delair's synthesis of hyacinthacine A₁ (**101**) also employs a dimethylphenylsilyl substituent as an agent of stereocontrol and a surrogate hydroxyl group (Scheme 27).⁷⁷ The central theme of this work is the establishment of the C7a stereocenter through an enantioselective dichloroketene-enol ether [2 + 2] cycloaddition which was used to access **167** (*vide infra*).⁷⁸ From this point, introduction of the C3 stereocenter was accomplished by *N*-protection, lactam reduction and reaction of **168** with magnesio(dimethylphenylsilylmethyl)cuprate. After generating pyrrolizidine **171**, removal of the chiral auxiliary and dehydration generated **172**. A sequence of dihydroxylation and Tamao–Fleming oxidation now generated triol **173**, which was reduced with borane to provide (+)-hyacinthacine A₁ (**101**).

Chandrasekhar's enantioselective synthesis of hyacinthacine A₁ (**101**)⁷⁹ is notable both for its use of a stereoretentive, Pd-catalysed epoxide ring-opening reaction and the generation of



Scheme 27 Delair's total synthesis of (+)-hyacinthacine A₁. *Reagents and conditions:* (a) Boc₂O, DMAP, Et₃N, 85%; (b) LiEt₃BH; then *p*-TsOH, MeOH, 84%; (c) PhMe₂SiCH₂MgCl, CuBr·SMe₂, BF₃·OEt₂, 96%, dr = 6 : 1; (d) Sia₂BH; H₂O₂; (e) Dess–Martin periodinane, CH₂Cl₂; (f) NaClO₂, CH₂N₂, 67% (3 steps); (g) TMSOTf; (h) toluene, heat, 63% (2 steps); (i) TFA, 87%; (j) KH, CS₂, MeI, (k) heat, 72% (2 steps); (l) cat. OsO₄, NMO, acetone, 99%; (m) HBF₄·OMe₂, KF; *m*-CPBA, 82%; (n) BH₃·SMe₂, 78%.

the pyrrolizidine ring system in a five-step, one-pot “domino” hydrogenation (Scheme 28). Commencing from compound **175**, this (+)-diethyl tartrate derivative was converted in six steps and high overall yield to **177**. Treatment of this γ,δ -epoxyester with TMSN₃ in the presence of catalytic Pd(PPh₃)₄ now mediated ring opening with double inversion of configuration at the γ position to yield *syn* azido alcohol **178**.⁸⁰ After protecting of the alcohol as a MOM ether, the acetonide group of **179** was hydrolyzed and the primary hydroxyl group selectively silylated to provide **180**. To accomplish pyrrolizidinone formation, **180** was converted to the corresponding mesylate and this material hydrogenated over Pd/C to yield **181**. Removal of the *O*-protecting groups and lactam reduction using LiAlH₄ then provided (+)-hyacinthacine A₁ (**101**) in 14 steps and 8.5% overall yield from **175**.

Isolated from the leguminous plant *Alexa leiopetala* by Asano and co-workers,⁸¹ (+)-alexine (**102**) is a potent glycosidase inhibitor and also the first pyrrolizidine alkaloid to be found with a C3 carbon substituent. Despite its biological activity, alexine has, until recently, proven to be a less popular synthetic target than other members of the pyrrolizidine family. Notably therefore, Yoda and co-workers have developed a unified, carbohydrate-based approach to (+)-alexine (**102**) and its C7 epimer,

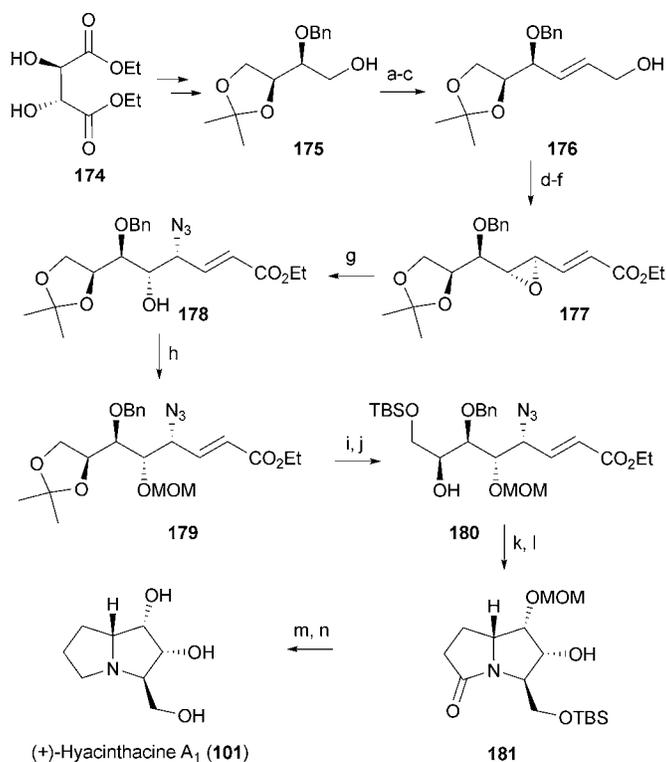
which in common with Py's hyacinthacine A₂ synthesis, employs L-xylose as its source of asymmetry (Scheme 29). This synthesis commences from 2,3,5-tri-*O*-benzyl-L-xylose (**182**), which after conversion to the corresponding furanosylamine underwent vinyl addition to furnish **183** as a single diastereomer. A series of protecting group manipulations then provided alkene **184**, which was cleaved *via* Lemieux–Johnson oxidation to the corresponding aldehyde. A second substrate-controlled (Cram) vinyl addition then established the final stereocenter, albeit with the undesired stereochemistry. Inversion of the hydroxyl-bearing stereocenter in **185** was achieved through a cycle of TPAP oxidation and chelation-controlled Luche reduction. From **186**, the remainder of the synthesis involved a series of protecting group manipulations, to enable the formation of pyrrolidine **187**, and *N*-alkylative ring closure of this intermediate to generate alexine (**102**). As the synthesis of (–)-7-*epi*-alexine did not require stereoinversion at **185**, Yoda's route to this compound involved two fewer steps than that to alexine.

Of the pyrrolizidine syntheses reported during the period under review, Somfai's non-carbohydrate-based approach to (+)-alexine (**102**), is of particular note for the rapidity and stereoselectivity with which the tetrasubstituted pyrrolidine subunit of the target is established (Scheme 30).⁸² The key transformation of this synthesis is in fact the first and involves the diastereoselective, Lewis-acid-promoted [3 + 2] annulation of *N*-Ts- α -aminoaldehyde **189** and 1,2-bis(silyl)propene **190**. Having established 4 of 5 stereocenters in the target molecule, conversion of **191** to aldehyde **192** now set the stage for introduction of the final chiral center, which was accomplished *via* Sakurai–Hosomi allylation in the presence of TiCl₄. After bis-*O*-benzylation of the resulting diol, sequential Lemieux–Johnson oxidation and *in situ* reduction generated **194** efficiently. Reductive cleavage of the sulfonamide protecting group was followed by a sequence of Appel cyclization⁸³ and Tamao–Fleming oxidation to yield pyrrolizidine **196a** together with its *N*-oxide **196b**. Hydrolysis of **196a** and subsequent hydrogenolysis with **196b** furnished (+)-alexine (**102**).

3.4 Indolizidines

Isolated from the seeds of the Moreton Bay chestnut tree (*Castanospermum australe*),⁸⁴ the indolizidine alkaloid (+)-castanospermine (**205**) displays an impressive range of biological activities which stem from its potent inhibition of endoplasmic reticulum α -glucosidase I as well as glucosidase II, and intestinal maltase and sucrase.⁸⁵ Importantly, castanospermine exhibits activity against a range of human viral pathogens, including parainfluenza, dengue virus, HSV-2 and HIV-1.⁸⁶ Adding further impetus to the development of synthetic routes to **205**, castanospermine has most recently been found to inhibit the Rho/Ras-glycosylating action of *Clostridium difficile* toxin B,⁸⁷ the major virulence factor of this bacteria and the causative agent of antibiotic-associated pseudomembranous colitis.⁸⁸

In view of the biological activity associated with **205**, it is understandable that this alkaloid and its derivatives remain popular synthetic targets.⁸⁹ The self-evident stereochemical relationship between (+)-castanospermine (**205**) and D-glucose (**197**), which share four stereocenters, have made this carbohydrate a popular starting point for the preparation of **205**. In this regard, Murphy and Cronin have reported the total synthesis of



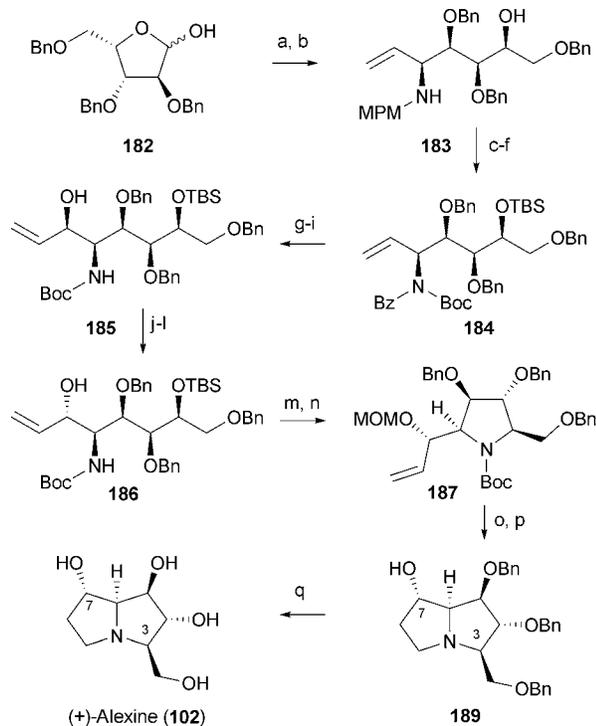
Scheme 28 Chandrasekhar's total synthesis of (+)-hyacinthacine A₁. *Reagents and conditions:* (a) IBX, EtOAc, reflux, 3 h; (b) Ph₃P=CHCO₂Et, CH₂Cl₂, 0 °C → rt, 30 min, 90% (2 steps); (c) DIBAL-H, THF, -10 → 0 °C, 1 h, 96%; (d) (-)-DET, Ti(O-*i*-Pr)₄, TBHP, CH₂Cl₂, -23 °C, 10 h, 93%, dr > 98%; (e) IBX, EtOAc, reflux, 3 h; (f) Ph₃P=CHCO₂Et, benzene, 0 °C → rt, 10 min, 90% (2 steps); (g) TMSN₃, Pd(PPh)₄ (10 mol%), THF, 12 h, rt; (h) MOMCl, DIPEA, CH₂Cl₂, rt, 48 h, 77%; (i) PPTS, MeOH, rt, 24 h, 74%; (j) TBSCl, imidazole, CH₂Cl₂, rt, 30 min, 78%; (k) MsCl, Et₃N, CH₂Cl₂, -10 °C, 10 min, 88%; (l) H₂, Pd/C, EtOH, rt, 12 h; then K₂CO₃, EtOH, H₂O, reflux, 2 h, 65%; (m) PTSA, MeOH, rt, 12 h; (n) LiAlH₄, THF, reflux, 2 h, 58% (2 steps).

(+)-castanospermine (**205**) and 1-*epi*-castanospermine (**206**) from 6-deoxyhex-5-enopyranosyl azide **198** (Scheme 31).⁹⁰ Since this substrate houses all but one of the stereocenters present in the piperidine ring of **205**, the initial stages of the synthesis focused upon a) introduction of the C5 methoxy group required for the antepenultimate reductive amination cascade and b) two-carbon homologation. The former task was accomplished through formation and ring opening of spiroepoxide **199** to primary alcohol **200**, while homologation was completed by aldol condensation of aldehyde **201**. Unfortunately, both processes displayed marginal diastereoselectivity and offered access to intermediate **202b** in very low overall yield. Nonetheless, the rapidity with which castanospermine was subsequently accessed is worthy of note: high-pressure hydrogenation of **202b** under acidic conditions provided indolizidine **203** as a single isomer! After temporary silylation of the free hydroxyl groups, reduction with LiAlH₄ generated (+)-castanospermine (**205**). (+)-1-*epi*-Castanospermine (**206**) was prepared in similar fashion, albeit in higher overall yield, from compound **204**.

Also employing D-glucose as the starting point of their 2009 synthesis of (+)-castanospermine (**205**), Madsen and co-workers exploit the transannular cyclization of an nine-membered amino epoxide to generate the indolizidine core of this alkaloid (Scheme 32).⁹¹ After conversion of α-D-glucopyranoside (**207**) to 6-iodopyranoside **208**, zinc-mediated fragmentation provided unsaturated aldehyde **209**, which was subjected to reductive

amination with homoallylamine using NaCNBH₃ and then *N*-acylated to yield **210**. Cyclization of this 1,10-diene now proceeded at high dilution in the presence of the Hoveyda–Blechert ruthenium catalyst to provide azonine **211a** together with azocine **211b**. This byproduct likely arises as a result of Ru-mediated alkene isomerisation and subsequent elimination of propene during metathesis.⁹² After diastereoselective alkene epoxidation, transannular cyclization was triggered through treatment with KO-*t*-Bu and proceeded to furnish strained azetidines **212a** and indolizidines **212b**. Hydrogenolysis of the latter product provided (+)-castanospermine (**205**) in 9 steps and 27% overall yield from **197**. Although prior to the timeframe of this review, the RCM–transannular epoxide ring opening approach to bicyclic alkaloids was first reported by White and co-workers, who employed this strategy in the synthesis of (+)-australine.⁹³

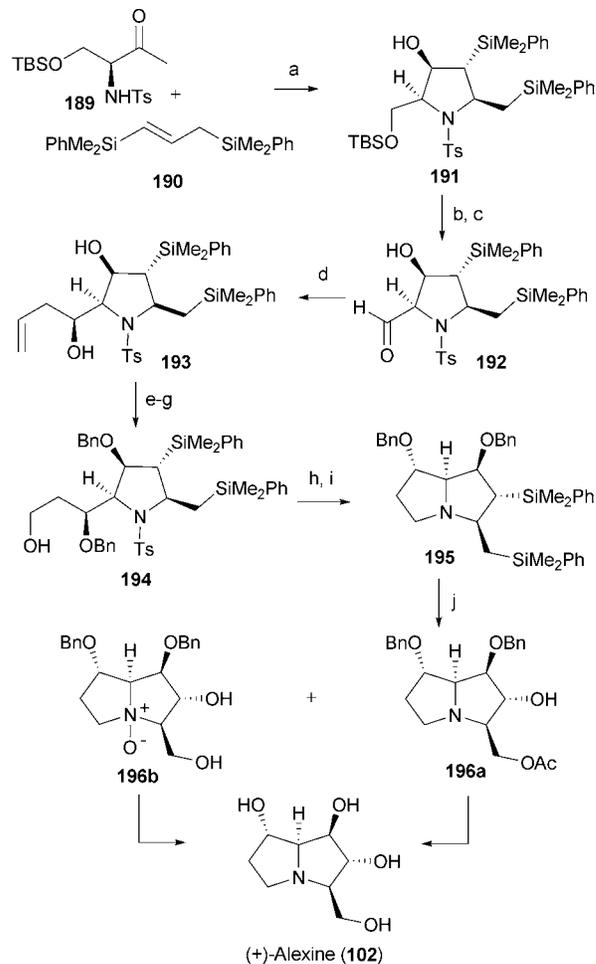
While a significant proportion of castanospermine syntheses rely on reductive amination to establish one or both of the C–N bonds within this target, Dhavale's approach to **205** is notable in that it employs a 5-*endo* alkene aminomercuration to accomplish this task while simultaneously creating the pyrrolidine ring (Scheme 33).⁹⁴ From D-glucose-derived nitron **213**, diastereoselective 1,3-addition of vinylmagnesium bromide preferentially generated D-*gluco*-*N*-allylamine **214b**, which after separation, was converted to **216**. Although vinyl addition to this aldehyde proceeded with acceptable diastereoselectivity (dr = 3 : 1), the major product of this reaction proved to bear the undesired 5*R*,6*R*



Scheme 29 Yoda's total synthesis of (+)-alexine. *Reagents and conditions:* (a) MPMNH₂, 4 Å MS, PhCH₃, reflux; (b) vinylmagnesium chloride, THF, -78 → 0 °C, 2 h, 75% (2 steps); (c) BzCl, CH₂Cl₂, rt, 3 h, 89%; (d) CAN, MeOH, 0 °C → rt, 4 h, 86%; (e) TBSCl, imidazole, DMF, rt, 12 h, 89%; (f) (Boc)₂O, Et₃N, DMAP, CH₂Cl₂, rt, 12 h, 92%; (g) (Me₂N)₂C=NH₂, 130 °C, 8 h, 98%; (h) OsO₄, NMO, acetone, 12 h, 94%; (i) NaIO₄, THF-H₂O (1 : 1), 4 h; then vinylmagnesium chloride, THF, -78 °C, 95% (2 steps); (j) TPAP, NMO, 4 Å MS, CH₂Cl₂, rt, 12 h, 92%; (k) NaBH₄, CeCl₃·H₂O, MeOH, -45 °C, 2 h, 80%; (l) MOMCl, *i*-Pr₂NEt₂, 12 h, 96%; (m) Bu₄NF, THF, 3 h, 91%; (n) MsCl, Et₃N, CH₂Cl₂, rt, 12 h; then *t*-BuOK, THF, rt, 12 h, 87% (2 steps); (o) 9-BBN, 30% H₂O₂, 3 M NaOH, THF, 97%; (p) MsCl, Et₃N, CH₂Cl₂; then BF₃·OEt₂, CH₂Cl₂, -20 °C, 84% (2 steps); (q) Pd/C (10 mol%), HCO₂NH₄, MeOH, reflux, 2 h, 83%.

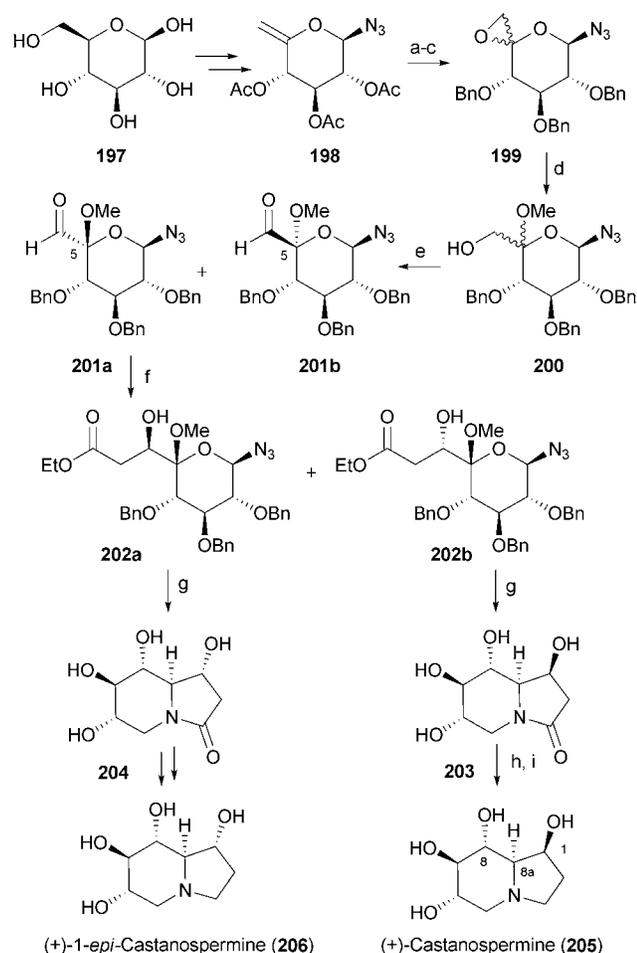
configuration. Facial selectivity in this case was rationalized in terms of the Felkin-Anh transition state model. Moving forward from **217a**, hydrolysis of the oxazolidinone ring now yielded the β-hydroxy-γ-alkenylamine, which upon treatment with mercury(II) acetate underwent 5-*endo*-trig-aminomercuration to form pyrrolidine **218**, after *in situ* reduction with NaBH₄. Correction of the C1 (castanospermine) stereocenter was now brought about by formation and reduction of ketone **219**, which generated **220** with high diastereoselectivity. Finally, a sequence of acetonide deprotection and hydrogenation generated the indolizidine ring and provided castanospermine (**205**). Dhavale has subsequently adapted this synthetic strategy to the preparation of two new C1 epimeric hydroxymethyl castanospermine congeners that display potent immunomodulatory activity.⁹⁵

In an extension of their work on the application of the Petasis borono-Mannich reaction⁹⁶ to the preparation of alkaloids,⁹⁷ Pyne and co-workers have reported the use of this remarkable transformation in an 11-step step of (+)-castanospermine (**205**) (Scheme 34).⁹⁸ In this regard, three-component condensation of L-xylose, allylamine and an (*E*)-vinyl boronic acid proceeded



Scheme 30 Somfai's total synthesis of (+)-alexine. *Reagents and conditions:* (a) MeAlCl₂, CH₂Cl₂, -78 °C, 57%, dr > 40 : 1; (b) AcOH, THF, H₂O, 96%; (c) TEMPO, NaOCl, KBr, CH₂Cl₂-H₂O, 99%; (d) allyltrimethylsilane, TiCl₄, -78 °C, 70%, dr > 95 : 5; (e) BnBr, KHMDS, THF, -78 °C, 85%; (f) OsO₄, NaIO₄, pyridine, CH₃CN-H₂O; (g) NaBH₄, 0 °C, MeOH, 72%; (h) Na⁺ C₁₀H₈⁻, DME, -60 °C, 99%; (i) CBr₄, Ph₃P, Et₃N, CH₂Cl₂, 64%; (j) Hg(OTf)₂, AcO₂H, AcOH, **196a** (41%), **196b** (21%), (k) LiOH, THF, H₂O, 90%; (l) H₂, Pd/C, EtOH, 70%.

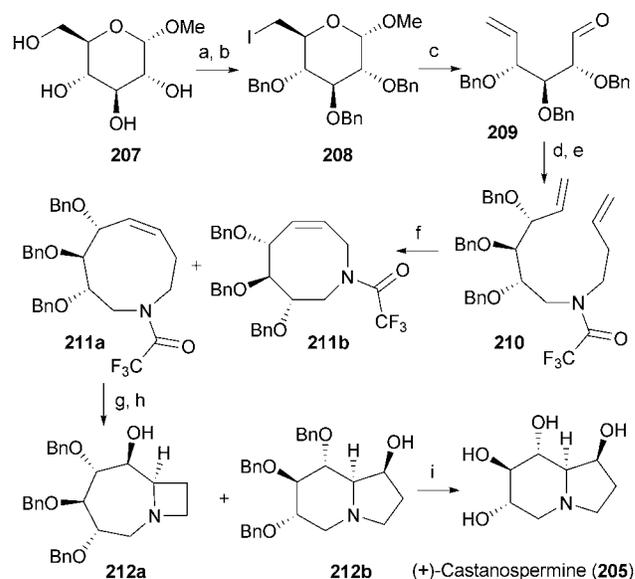
with complete diastereocontrol to yield **221**.⁹⁹ The 1,2,3-triol remaining after chemoselective formation of oxazolidinone **222** was differentially alkylated to provide compound **223b**, whose formation was accompanied by significant quantities of oxazirone **223a**, the product of acyl migration. RCM of this mixture using Grubbs' second-generation catalyst and separation of the resulting 3-pyrroline products gave **224** in 38% overall yield from the 1,6-diene. *syn*-Dihydroxylation of this cyclic alkene now proceeded from the *endo* face, under stereoelectronic control,¹⁰⁰ to generate the corresponding 1,2-diol from which the extraneous C2 (castanospermine) hydroxyl group was removed through formation and regioselective reduction (NaBH₄, DMA) of cyclic sulfate **225**. After solvolysis of the trityl group, oxazolidinone **226** was saponified to form **227a**, a process which unexpectedly gave rise to furan **227b**. Notwithstanding the routine appearance of this penultimate transformation, cyclization of **227a** to generate the indolizidine ring system was found to



Scheme 31 Murphy's total synthesis of (+)-castanospermine and (+)-1-*epi*-castanospermine. *Reagents and conditions:* (a) NaOMe, MeOH, rt, 1 h; (b) BnBr, DMF, 0 °C, 3 h; (c) CF₃(CO)CH₃, Oxone, NaHCO₃, Na₂EDTA, CH₃CN, H₂O, 0 °C, 1.5 h; (d) CSA, MeOH, 10 min, >95% (2 steps); (e) TPAP, NMO, CH₂Cl₂, 4 Å MS, rt, 15 h, **201a** (46%), **201b** (21%); (f) LDA, EtOAc, THF, -78 °C → rt, 1.5 h, **202a** (35%), **202b** (16%); (g) H₂ (500 psi), Pd(OH)₂, MeOH, HCO₂H, rt, 48 h; (h) TMSOTf, pyridine, 2,6-lutidine, 0 °C → rt, 12 h; (i) LiAlH₄, THF, rt, 16 h, 53% (2 steps).

be decidedly challenging. While recourse to an Appel reaction (Ph₃P/CBr₄) was unsuccessful, use of Mitsunobu's conditions produced **228b** in only 25% yield together with oxepane **228a** and furan **228c**. Nonetheless, hydrogenolysis of the benzyl ethers in **228b** furnished (+)-castanospermine (**205**) in near-quantitative yield.

The Petasis reaction has also been employed by Wong and co-workers, who recently reported its use in a highly concise route to 5- and 6-membered iminocyclitols.¹⁰¹ In this case, condensation of polyhydroxyl dialdehydes with ammonia and styrylboronic acid triggers sequential borono-Mannich reactions which lead to the formation of bis-vinylated iminocyclitols with excellent diastereoselectivity. Ozonolytic cleavage of these dienes and reductive workup then provides the corresponding iminocyclitols in high overall yield. Wong, in light of the unexpected diastereoselectivity of the Mannich reaction, has proposed that this condensation

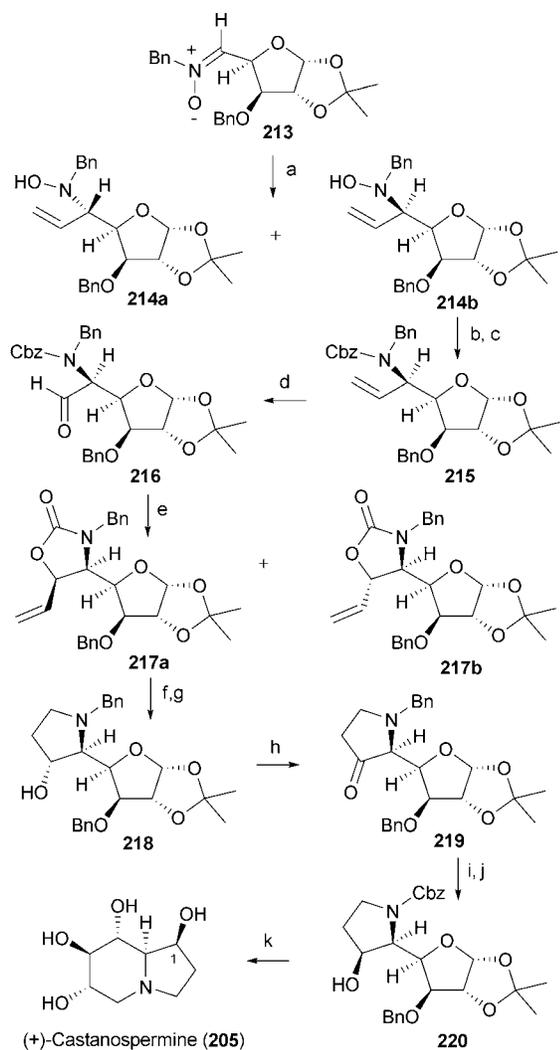


Scheme 32 Madsen's total synthesis of (+)-castanospermine. *Reagents and conditions:* (a) I₂, PPh₃, imidazole, THF, 65 °C, 87%; (b) BnOC(NH)CCl₃, TfOH, *p*-dioxane, 22 °C, 90%; (c) Zn, THF-H₂O, ultrasound, 40 °C, 90%; (d) homoallylamine, 4 Å MS, AcOH, NaCNBH₃, THF, 0 → 22 °C, 89%; (e) (CF₃CO)₂O, Et₃N, CH₂Cl₂, 0 °C, 93%; (f) Grubbs' 1st-generation catalyst, benzene, 80 °C, **211a** (78%), **211b** (7%); (g) CF₃COCH₃, Oxone, NaHCO₃, Na₂EDTA, CH₃CN-H₂O, -10 → 0 °C; (h) KO-*t*-Bu, H₂O, Et₂O, 0 → 22 °C, **212a** (15%), **212b** (44%); (i) H₂, Pd/C, HCl-MeOH, 22 °C, 94%.

proceeds *via* formation of a boronate ester and the cyclization of a five- or six-membered cyclic iminium ion intermediate.

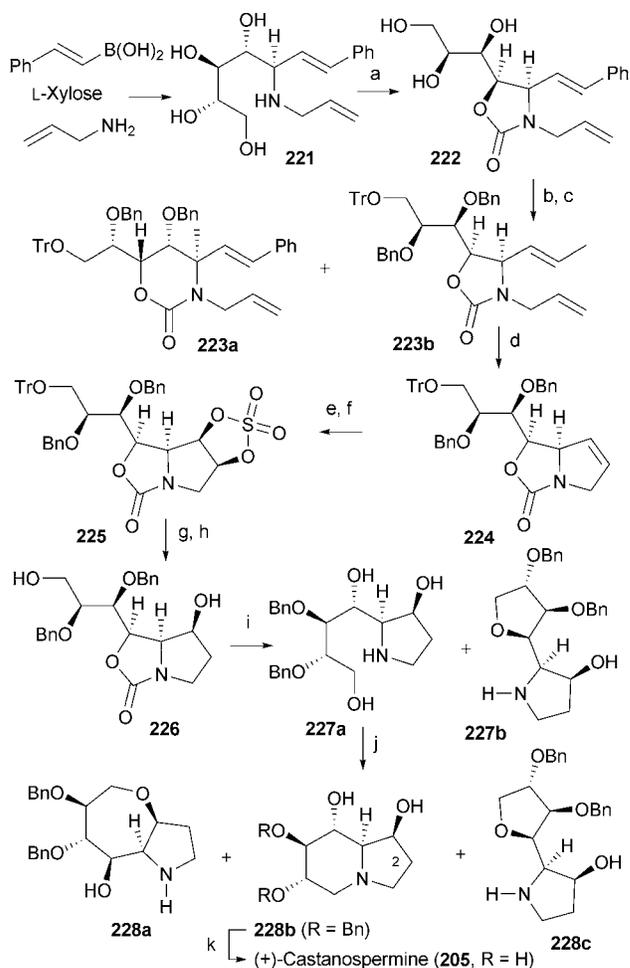
Poisson and co-workers recently reported total synthesis of (+)-castanospermine stands in contrast to the majority of existing routes to this natural product in that it does not rely on a starting material chosen from the chiral pool (Scheme 35).¹⁰² Rather, these authors employ the [2 + 2] cycloaddition of dichloroketene to chiral enol ether **229** in order to establish the C1 and C8a stereogenic centers of the target. Asymmetric induction (*dr* = 96 : 4) in this case was mediated by the (*R*)-sterical [1-(2,4,6-triisopropylphenyl)ethanol] alkene substituent.¹⁰³ From cyclobutanone **230**, regioselective Beckmann ring expansion, reductive dechlorination and allylic oxidation provided γ -lactam **231** in high overall yield. After *O*-silylation of **231** and *N*-alkylation using **232**, RCM of 1,7-diene **233** generated compound **234**. Introduction of the *trans-trans* triol array was now accomplished by hydroboration-oxidation of this enol ether, which afforded a mixture of products **235a** and **235b**, which were each isolated as single diastereomers (*dr* > 95 : 5). In the case of **235b**, a sequence of diol protection, lactam reduction and global protecting group/auxiliary removal now provided (+)-castanospermine (**205**), which was also accessed more directly from **235a**, through acid hydrolysis.

Arguably, the most unique non-chiral pool synthesis of castanospermine (**205**) published during the review period originates from the laboratory of Mariano, who employs a photochemical electrocyclic ring contraction to prepare a carbocyclic substrate from which the piperidine ring of **205** is accessed *via* a ring rearrangement reaction (RRM) (Scheme 36).¹⁰⁴ Photocyclization of pyridinium chlorate (**236**) in water results in the formation of



Scheme 33 Dhavale's total synthesis of (+)-castanospermine. *Reagents and conditions:* (a) vinylmagnesium bromide, TMSOTf, THF, -78°C , 2 h, 90%; (b) Zn, Cu(OAc)₂, AcOH, 80°C , 1 h, 88%; (c) NaHCO₃, CbzCl, MeOH–H₂O, 3 h, 92%; (d) NMO, K₂OsO₄·2H₂O, acetone–H₂O (8 : 1), 12 h; then NaIO₄, acetone–H₂O (9 : 1), 6 h, 84% (2 steps); (e) vinylmagnesium bromide, THF, -50°C , 1 h; then KOH–H₂O (2 : 3), MeOH, 90°C , 10 min, 77%; (f) KOH–H₂O (2 : 3), MeOH, 90°C , 48 h, 98%; (g) Hg(OAc)₂, THF–H₂O (1 : 1), NaBH₄, 3 h, 74%; (h) Swern oxidation, 85%; (i) NaBH₄, MeOH–H₂O, -60°C , (10 : 1); (j) NaHCO₃, CbzCl, MeOH–H₂O (9 : 1), 3 h, 70% (2 steps); (k) TFA–H₂O (3 : 2), 2.5 h, rt; then H₂ (80 psi), Pd/C (10 mol%), MeOH, 12 h, 85%.

bicyclic aziridinium ion **237**, which undergoes solvolysis to provide 4-amino-3,5-cyclopentenediol **238a**. As part of an earlier synthesis of the iminosugar swainsonine, Mariano developed a route to enantiomerically enriched **239** from **238a** using a sequence involving enzymatic desymmetrization and alcohol inversion.¹⁰⁵ Employing this advanced building block, treatment with the Grubbs' second-generation catalyst in the presence of ethylene triggered a highly selective RRM reaction to yield allyl-tetrahydropyridine **240** in excellent yield. After hydroxyl-directed epoxidation of the alkene *endo* face, *trans*-diaxial opening of epoxide **241** under mild conditions and per-*O*-benzylation provided **242**. In preparation for the formation of

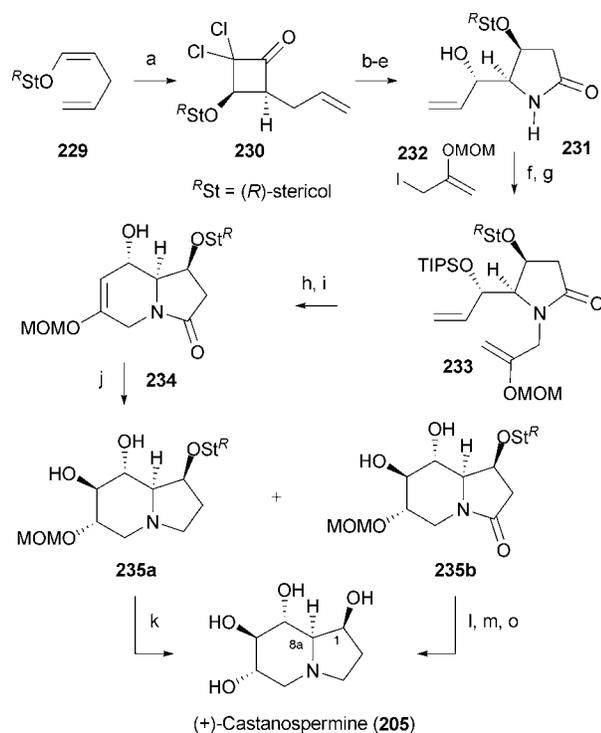


Scheme 34 Pyne's total synthesis of (+)-castanospermine. *Reagents and conditions:* (a) (Cl₃CO)₂CO, Et₃N, THF, rt, 10 h, 53%; (b) TrCl, pyridine, rt, 20 h, 87%; (c) NaH, BnBr, Bu₄NI, THF, 50°C , 4 d; (d) Grubbs' second-generation catalyst, CH₂Cl₂, reflux, 48 h, 88%; (e) K₂OsO₄·2H₂O, NMO, acetone–H₂O, rt, 48 h, 84%, dr = 83 : 17; (f) SOCl₂, Et₃N, CH₂Cl₂; then RuCl₃, NaIO₄, 64%; (g) NaBH₄, DMA, rt, 16 h; (h) H₂SO₄, H₂O, THF, rt, 20 h, 63%; (i) NaOH, H₂O, MeOH, 110°C , 2 h; (j) DIAD, Ph₃P, THF, $0-5^{\circ}\text{C}$, 48 h, **228a** (11%), **228b** (25%), **229c** (22%); (k) H₂, PdCl₂, MeOH, rt, 1 h; DOWEX-1 (OH⁻ form), 95%.

the pyrrolidine ring, this material was now submitted to hydroboration–oxidation, which fortuitously also served to remove the *N*-acetyl group. Mitsunobu cyclization followed by hydrolysis of the resulting alcohol formed (+)-castanospermine (**205**).

4 Sulfonium-sulfate thiosugars

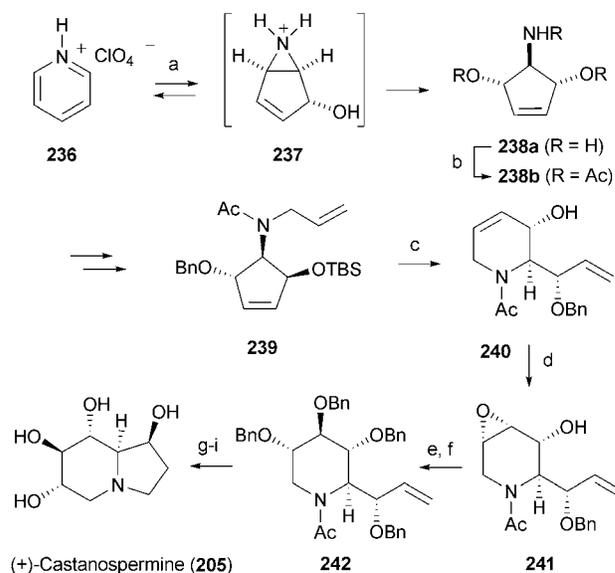
Iminosugars such as castanospermine (**205**) are believed to derive their glycosidase binding properties from an ability to mimic the charge and, to some degree, the structure of the oxocarbenium ion-like transition state involved in glycoside hydrolysis (Fig. 11). A requirement for this transition state mimicry is protonation of the ring nitrogen atom within the active site of the enzyme, where electrostatic interaction between the inhibitor ammonium ion and the carboxylate residue(s) have been proposed to play a key



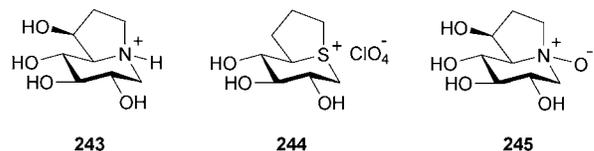
role in the activity of iminosugars. Prior to the review period, as part of an effort to design synthetic glycosidase inhibitors which carry a permanent positive charge, Pinto reported the synthesis of the sulfonium-ion castanospermine analogue **244** and found this compound to be a functional inhibitor of glucoamylase.^{106,107} Interestingly, this approach to inhibitor design has not always met with success, as in the case of **245**, the *N*-oxide analogue of castanospermine, which Wong and co-workers have shown to be a weak glycosidase inhibitor in comparison with the natural product.¹⁰⁸

As previously noted for 1-deoxynojirimycin (**1**), synthetic chemistry has often pre-empted the isolation of natural products with anti-glycosidase properties. A particularly notable case in this regard has been Pinto's castanospermine studies, which were dramatically validated by Yoshikawa's discovery, beginning in 1997, of a series of naturally occurring glycosidase inhibitors that encompass a zwitterionic sulfonium-sulfate structure (Fig. 12).¹⁰⁹

Isolated from the aqueous extracts of the roots and stems of *Salacia reticulata* and related plant species, salicinol (**2**),¹¹⁰ kotalanol (**247**),¹¹¹ salaprinol (**248**),¹¹² and ponkoranol (**249**)¹¹² are structurally related in having a 1,4-anhydro-4-thio-D-arabinitol "head" unit and a polyhydroxylated acyclic "tail" of varying length. Immediately attracting the attention of synthetic and medicinal chemists, these novel natural products were found to inhibit intestinal α -glucosidases with potencies surpassing that



Scheme 36 Mariano's total synthesis of (+)-castanospermine. *Reagents and conditions:* (a) hv, H₂O, 45–70 °C, 48 h; (b) NaHCO₃; then AcCl, pyridine, rt, 24 h, 22% (two steps); (b) Grubbs' 2nd-generation catalyst, CH₂=CH₂, CH₂Cl₂, reflux, 16 h, 93%; (c) VO(acac)₂ (10 mol%), *t*-BuOOH, 0 → 25 °C, 5 h, 50%; (d) NaOBz, H₂O, 130 °C, 12 h, 55%; (e) BnBr, NaH, DMF, 0 °C, 2.5 h, 94%; (f) BH₃·THF, THF, 0 °C, 3 h; then 30% H₂O₂, 25 °C, 3 h, 31%; (g) PPh₃, DEAD, THF, 25 °C, 12 h, 93%; (h) H₂, PdCl₂, MeOH–EtOAc (1 : 1), 25 °C, 4 h, 91%.



of voglibose and ascarbose. Furthermore, human clinical trials on patients with type-2 diabetes mellitus, conducted with extracts of *S. reticulata*, have shown this herbal preparation to be an effective treatment with minimal side effects.¹¹³ While the specific mode of action of **2** and related natural products has yet to be fully delineated, recent co-crystallographic studies of the *N*-terminal domain of human intestinal maltase-glucoamylase (ntMGAM) by Rose and Pinto¹¹⁴ suggest that in common with protonated iminosugars, these permanently charged species may mimic the oxocarbenium ion-like transition state of the glycosidase-mediated hydrolysis reaction.

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4.1 Salacinol

Salacinol (**2**), the first of the sulfonium-sulfate inhibitors to be discovered, was isolated by Yoshikawa and co-workers in 1997 from the dried roots and stems of *Salacia reticulata* (*Kotala himbutu* in Sinhalese), a large climbing plant found throughout the forests of Southern India and Sri Lanka (Fig. 13).¹¹⁰ Extracts of this herb, prepared by soaking the bark and roots in water overnight, have long been employed in traditional Indian, or

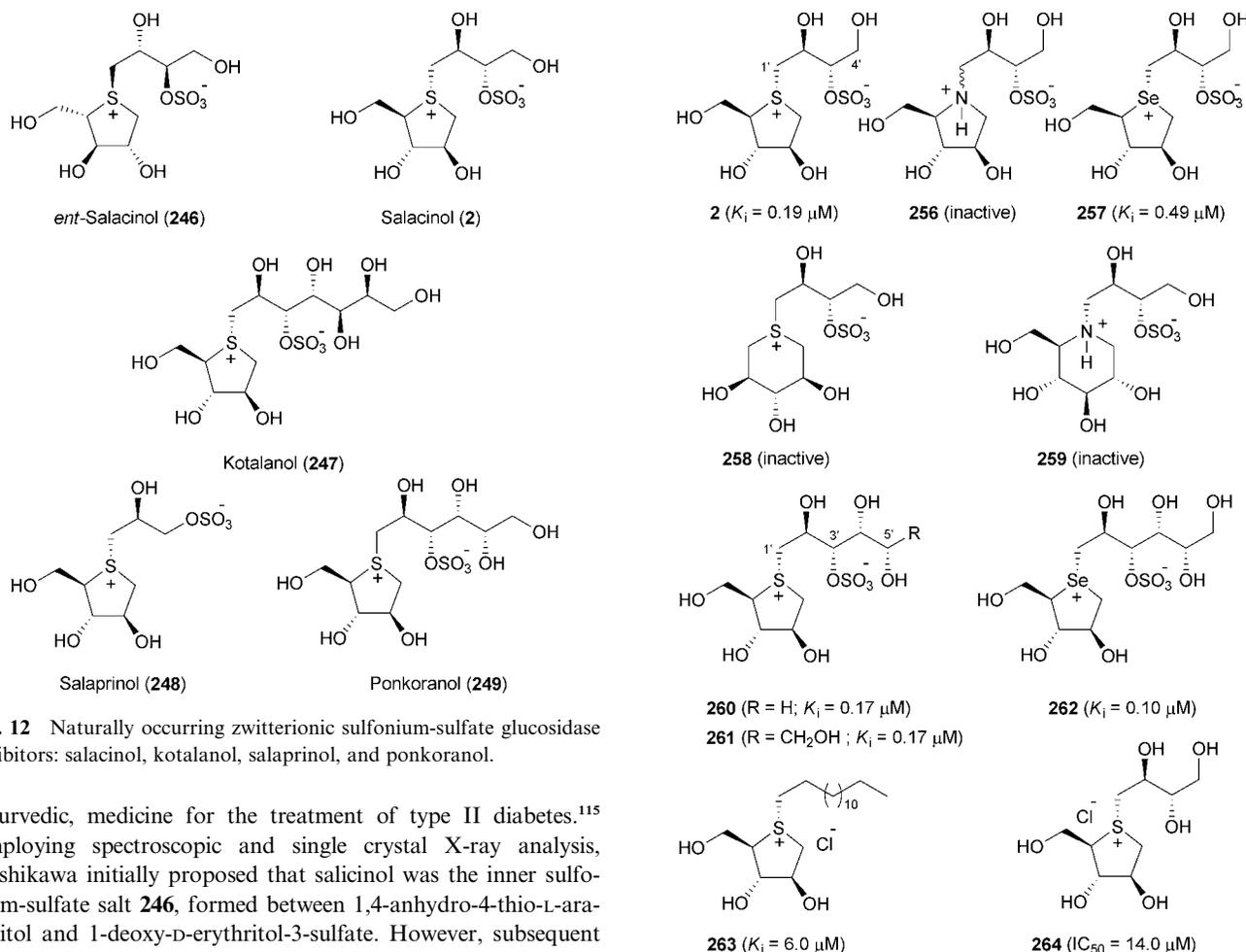


Fig. 12 Naturally occurring zwitterionic sulfonium-sulfate glucosidase inhibitors: salacinol, kotalanol, salaprinol, and ponkoranol.

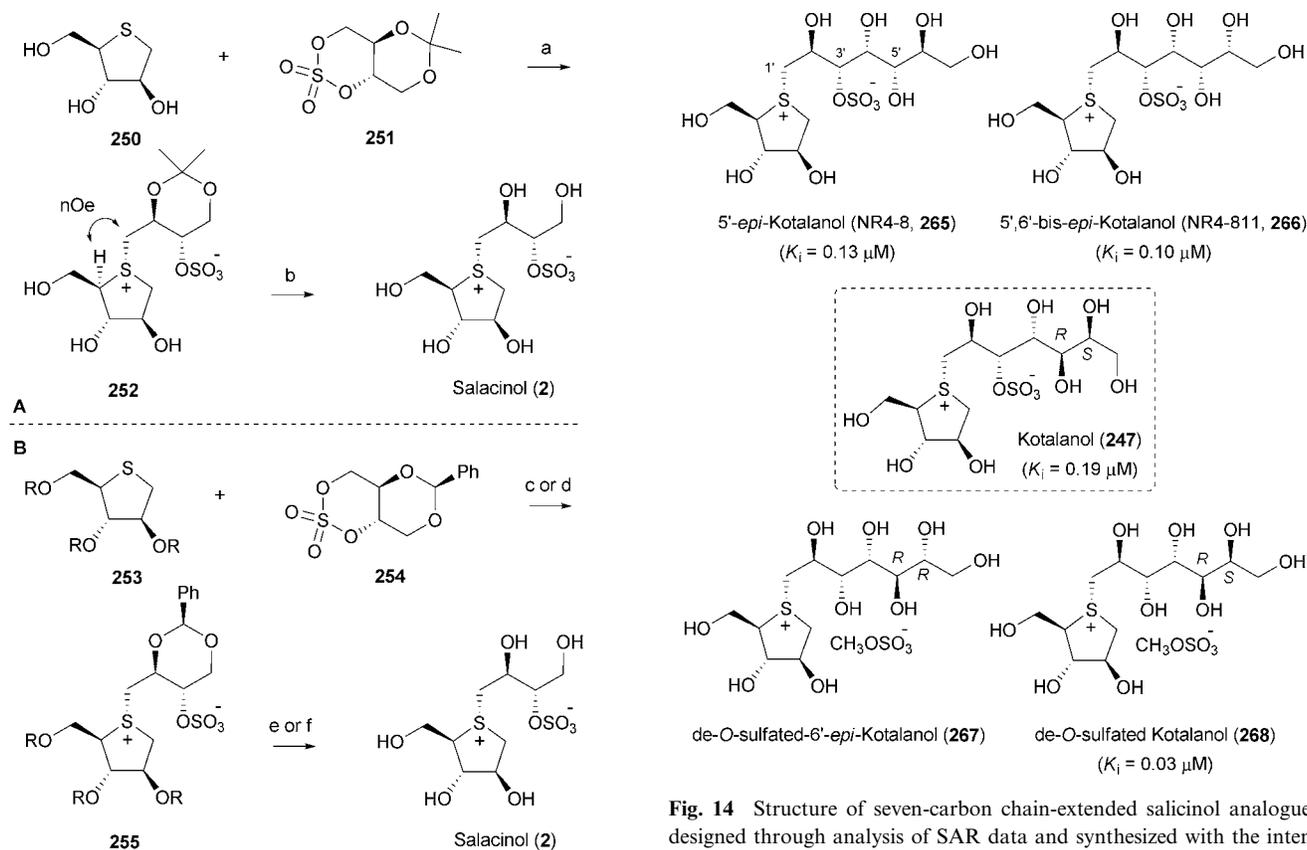
Ayurvedic, medicine for the treatment of type II diabetes.¹¹⁵ Employing spectroscopic and single crystal X-ray analysis, Yoshikawa initially proposed that salicinol was the inner sulfonium-sulfate salt **246**, formed between 1,4-anhydro-4-thio-L-arabinitol and 1-deoxy-D-erythritol-3-sulfate. However, subsequent degradation studies conducted on kotalanol (**247**) led to a stereochemical revision and the reassignment of the structure of salicinol as D-arabinitol derivative **2**.¹¹⁶ *In vitro* analysis of **2** has revealed this compound to be an inhibitor of several rat intestinal α -glucosidases, including maltase, sucrase and isomaltase ($K_i = 0.31$, 0.32 and $0.47 \mu\text{M}$, respectively).^{110,116}

The first total synthesis of salicinol (**2**) was reported in 2000 by Yuasa, who generated this sulfonium-sulfate inner salt through *S*-alkylation of 1,4-anhydro-4-thio-D-arabinitol (**250**) with **251**, the cyclic sulfate derivative of isopropylidene-D-erythritol (Scheme 37A).¹¹⁷ Reaction at the *S*-center in this case proceeded with complete diastereoselectivity to generate α -isomer **252**, which was hydrolyzed to provide salicinol in reasonable overall yield. Implementing a similar strategy, but employing *O*-benzyl protecting groups in the 1,4-anhydro-4-thio-arabinitol unit **253**, Pinto concurrently developed a synthetic route to **2** (Scheme 37B).¹¹⁸ While *S*-alkylation of **253** ($R = \text{Bn}$) with **251** in acetone proved to be inefficient, Snider and Pinto, through use of 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) as the reaction medium, have subsequently optimized the yield of this step. In the case of *p*-methoxybenzyl (PMB)-protected **253** ($R = \text{PMB}$), a quantitative yield of **255** ($R = \text{PMB}$) was obtained.¹¹⁹ Finding the hydrogenolytic removal of the protecting groups from this sulfonium salt prone to catalyst poisoning, simultaneous removal of the benzylidene acetal and the *p*-methoxybenzyl ethers was conveniently accomplished by solvolysis in aqueous trifluoroacetic acid.

Fig. 13 Structure of salicinol and selected analogues together with their respective K_i values against recombinant human maltase glucoamylase (MGA).

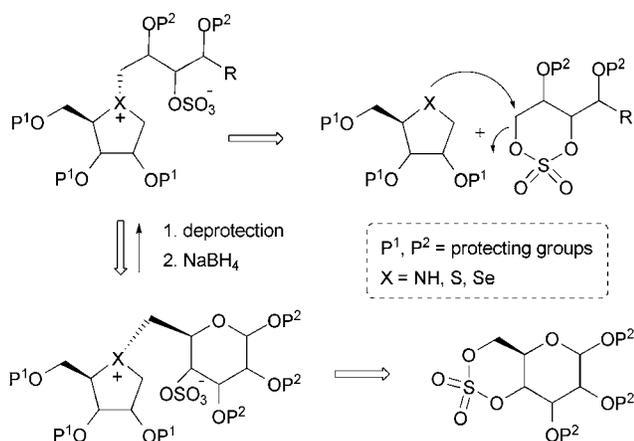
The biological activity of salicinol (**2**), its unique structure, and the rapidity with which analogues of this natural product can be prepared through recourse to the strategies outlined in Scheme 38, have spurred the groups of Pinto, Muraoka, Yoshikawa and Leamire to conduct extensive structure-activity studies. Since a full discussion of this recently reviewed field is beyond the scope of this article,^{120,121} we will limit our commentary to the salient findings of these studies (Fig. 14).

While Pinto¹²² and Muraoka¹²³ have found ghavamiol (**256**), the nitrogen analogue of salicinol (**2**), to be a weak inhibitor of a number of α -glucosidases,¹²⁴ the selenium homologue,¹²⁵ blintol (**257**), displays potent activity against recombinant human maltase glucoamylase (MGA), a key intestinal α -glucosidase involved in the breakdown of glucose oligosaccharides.¹²⁶ Employing the strategy outlined in Scheme 38, Pinto¹²⁷ and Lemaire¹²⁸ have also independently examined a series of ring analogues of salicinol in order to probe the influence of ring size, substitution and stereochemistry. Notably, both groups have found that departure from the D-arabinitol configuration of the heterocyclic ring, ring expansion (as in the case of **258**),¹²⁸ or removal of the C4 hydroxymethyl group from **2** results in loss of activity. The importance of the five-membered heterocyclic ring



Scheme 37 Yuasa's (A) and Pinto's (B) total syntheses of the naturally occurring α -glucosidase inhibitor salicinol. *Reagents and conditions:* (a) DMF, 45 °C, 13 h, 61%; (b) 0.01% HCl, 40 °C, 4 h, 75%; (c) **253** (R = Bn), K_2CO_3 , acetone, 75 °C (sealed tube), overnight, 33%; (d) **253** (R = PMB) HFIP, K_2CO_3 , 55 °C, overnight, >99%; (e) **255** (R = Bn), H_2 (52 psi), Pd/C, AcOH– H_2O (4 : 1), 67%; (f) **255** (R = PMB), TFA– H_2O (10 : 1), rt, 30 min, 86%.

to the activity of **2** is further underscored by the findings of Lemaire¹²⁹ and Pinto¹³⁰ that six-membered deoxynojirimycin-salicinol analogues **259** modeled on migitol are largely inactive towards a range of glucosidases.



Scheme 38 Regioselective, alkylative ring opening of 1,3-cyclic sulfates with hetero-1,4-anhydroalditols offers an expedient and flexible strategy for the preparation of ring and chain-extended analogues of salicinol.

Fig. 14 Structure of seven-carbon chain-extended salicinol analogues designed through analysis of SAR data and synthesized with the intention of determining the stereochemistry of the naturally occurring α -glucosidase inhibitor kotalanol (**247**). Respective K_i values for inhibition of recombinant human maltase-glucoamylase (MGA) are shown.¹¹⁴

Since kotalanol (**247**), which houses a longer side chain than salicinol, is a more potent glucosidase inhibitor,¹¹¹ considerable attention has been paid to the preparation of chain-extended analogs of salicinol (**2**) and blintol (**257**). In this regard, Pinto and co-workers have conducted a systematic examination of salicinol homologues possessing 5- and 6-carbon side chains with varying stereochemistry and discovered a number of inhibitors of MGA, including **260**,¹³¹ **261** and **262**,¹³² which match or exceed the inhibitory activity of salicinol and kotalanol. These studies have revealed that in the series shown, the *S*-configuration at C2' and *R*-configuration at C4' are critical for activity, while the relative configuration of the sulfate-bearing C3' stereocenter is unimportant. Intriguingly, simple *S*-alkylated sulfonium salts of 1,4-anhydro-4-thio-*D*-arabinitol, as exemplified by **263**, are also inhibitors of MGA.^{133,134} Pinto's findings in this regard appear to be in accord with those of Muraoka and co-workers, who, finding that neosalicinol (**264**) (the de-*O*-sulfonated derivative of salicinol) displays comparable activity against rat intestinal maltase to the natural product itself ($IC_{50} = 9.6 \mu M$), concluded that the *O*-sulfate anion is unnecessary for inhibitory activity.¹³⁵

4.2 Kotalanol

In addition to salicinol (**2**), the aqueous extracts of *Salacia reticulata* have yielded a number of other bioactive components, including kotalanol (**247**),¹¹¹ which displays more potent α -glucosidase

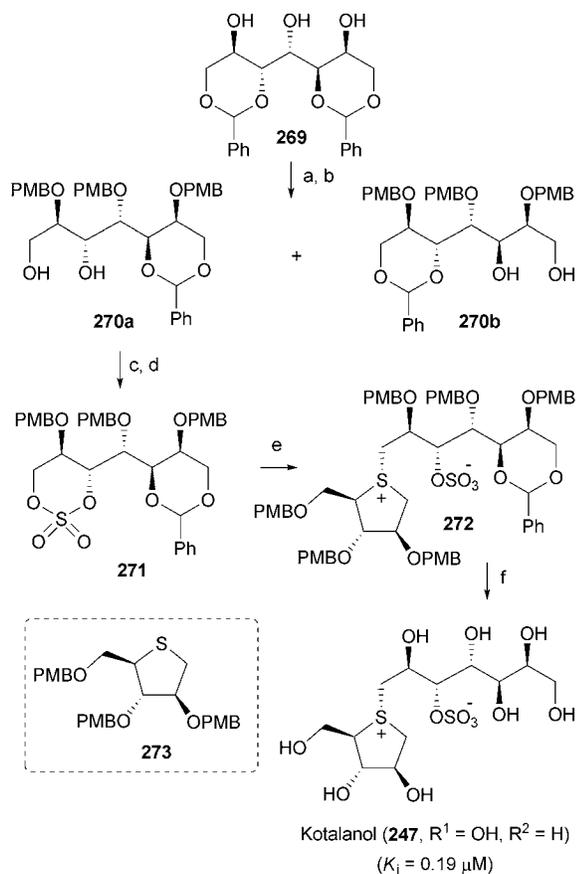
inhibitory activity (K_i : maltase, 0.23 $\mu\text{g/mL}$; sucrase, 0.18 $\mu\text{g/mL}$) than **2** (K_i : maltase, 0.31 $\mu\text{g/mL}$; sucrase, 0.32 $\mu\text{g/mL}$) (Scheme 39). From a structural perspective, **247** differs from salicinol in that it bears a heptitol rather than an alditol side chain and consequently has three additional stereocenters. Although the stereochemistry of the 1-deoxy-4-thiopento-furanosyl moiety was originally determined by Yoshikawa through degradation studies,¹¹¹ the absolute stereochemistry of the heptitol side chain and *S*-stereocenter of **247** remained unknown until 2008–2009, when Pinto published two reports concerning the structural elucidation and total synthesis of this medicinally important natural product.

Pinto's initial efforts to determine the side-chain stereochemistry of kotalanol (**247**) focused on establishing the common stereochemical motif necessary for inhibitory activity against recombinant human maltase-glucoamylase (MGA) (Fig. 14).¹³⁶ Through examination of a library of existing five- and six-carbon salicinol analogues, it was determined that compounds bearing the *S*-configuration at C2' and C5', and the *R*-configuration at C4', were most active. Based on this bioassay-guided analysis, chain-extended salicinol analogues **265** and **266** were selected as potential kotalanol candidates and synthesized. Unfortunately, while the inhibitory activity of these compounds was found to be

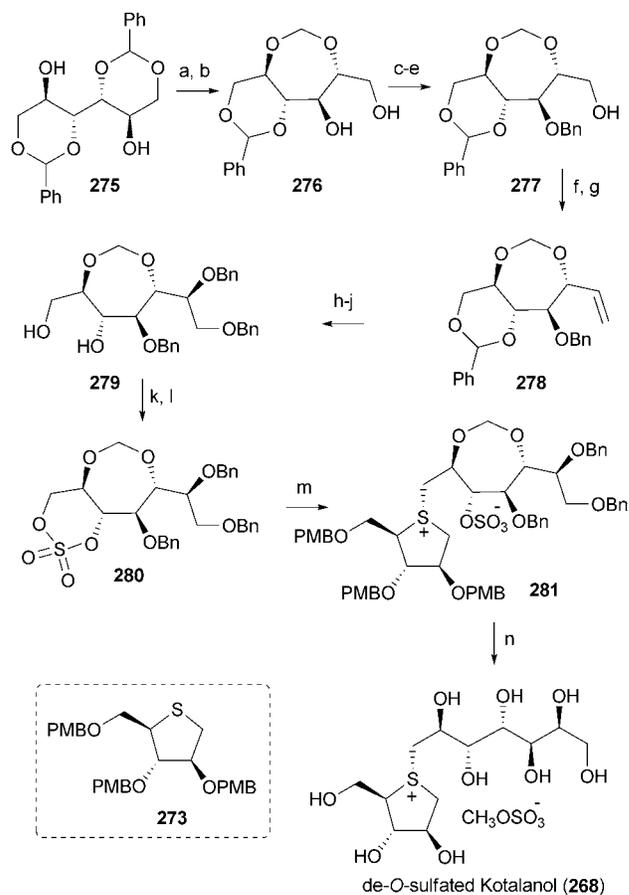
comparable to kotalanol, small discrepancies between the ^1H and ^{13}C NMR spectral data of these synthetic products and **247** indicated that neither was kotalanol. On the basis of detailed analysis of NMR data collected from **265** and **266**, Pinto concluded that the configuration at C5' in the natural product was in fact *R*.

In light of these findings, Pinto and co-workers have recently synthesized the de-*O*-sulfated C6' epimers **267** and **268** from D-mannitol (for details, see Section 4.3) and found the physical data collected from the latter compound to closely match that reported for naturally derived de-*O*-sulfonated kotalanol. Having thus formally confirmed the elusive structure of kotalanol by inference, Pinto prepared the natural product itself from D-perseitol,¹³⁷ a heptitol found in various parts of the avocado plant and its fruit (Scheme 40).

Commencing from D-perseitol derivative **269**,¹³⁸ *O*-benzylation and hydrolysis of this bis-benzylidene acetal generated a near-equal



Scheme 39 Pinto's total synthesis of kotalanol. *Reagents and conditions:* (a) PMBCl, NaH, DMF, 0 °C \rightarrow rt, 2 h; (b) *p*-TSA, MeOH, rt, 30 min, **270a** (44%), **270b** (34%); (c) SOCl₂, Et₃N, CH₂Cl₂; (d) NaIO₄, RuCl₃, CCl₄-CH₃CN, 77% (2 steps); (e) **273**, HFIP, K₂CO₃, 75 °C, 7 d, 69%; (f) TFA, CH₂Cl₂, H₂O, rt, 2 h, 93%.



Scheme 40 Pinto's total synthesis of de-*O*-sulfonated kotalanol. *Reagents and conditions:* (a) CH₂Br₂, NaOH-H₂O; (b) *p*-TSA, MeOH, 70 °C, 2 h, 65% (2 steps); (c) TBSCl, imidazole, DMF, 0 °C, 2 h; (d) BnBr, NaH, rt, 1 h; (e) TBAF, THF, rt, 20 h, 62% (3 steps); (f) Dess-Martin periodinane, CH₂Cl₂, NaHCO₃, rt, 15 min; (g) CH₃PPh₃Br, *n*-BuLi, THF, -78 °C \rightarrow rt, overnight, 56% (2 steps); (h) AD-mix β , *t*-BuOH-H₂O (1 : 1), 0 °C, 7 d, 64%; (i) BnBr, NaH, DMF, rt, 2 h; (j) *p*-TSA, MeOH, rt, 24 h, 77% (2 steps); (k) SOCl₂, Et₃N, CH₂Cl₂, 0 °C, 45 min; (l) NaIO₄, RuCl₃, CCl₄-CH₃CN (1 : 1), H₂O, rt, 2 h, 64% (2 steps); (m) **273**, HFIP, K₂CO₃, 75 °C, 7 d, 61%; (n) BCl₃, CH₂Cl₂, -78 °C \rightarrow rt, 12 h, 61%.

mixture of **270a** and **270b**, which were separated chromatographically. Moving forward with **270a**, this 1,3-diol was converted to the corresponding cyclic sulfate **271** and coupled with PMB-protected 1,4-dideoxy-1,4-imino-L-arabinitol **273** in HFIP to generate sulfonium ion **272** as a single diastereomer. Simultaneous removal of seven protecting groups using aqueous TFA then provided kotalanol (**247**) in high yield. The apparent simplicity of Pinto's synthetic route to kotalanol belies both the complexity of the underlying structural elucidation problem, which remained unresolved for more than a decade, and the fact that, before the preparation of the natural product itself was possible, the synthesis of a sizeable library of salicinol and kotalanol analogues was necessary.

4.3 De-*O*-sulfonated kotalanol

Since it has been estimated that salicinol and kotalanol only account for approximately 10% of the α -glucosidase inhibitory activity associated with the water-soluble extracts of *Salicia* spp., the search for other bioactive constituents in these herbal medicine has not abated. In this regard, Ozaki and co-workers recently reported the isolation of further α -glucosidase inhibitor from *S. reticulata* and assigned its structure as the unusual 13-membered cyclic sulfoxide **274** (Fig. 15).¹³⁹ Subsequent reevaluation of Ozaki's data by Koshikawa and co-workers has led to the conclusion that this compound is in fact de-*O*-sulfated kotalanol (**268**),¹⁴⁰ which Koshikawa has previously prepared *via* the desulfonation of kotalanol.¹⁴¹ Structural ambiguity notwithstanding, Ozaki has not only shown that **268** is the most potent inhibitor of rat intestinal α -glucosidase isolated from *Salicia* spp. to date, but also displays anti-hyperglycemic activity *in vivo*: administration of **268** to rats leads to significant lowering of postprandial (post-meal) glucose levels through inhibition of intestinal maltase and sucrase.¹⁴² More recent studies by Rose and Pinto have revealed that **268** is also a potent inhibitor of human intestinal maltase-glucoamylase (MGAM).¹¹⁴

With the exception Koshikawa's degradation study noted above, to date only one total synthesis of de-*O*-sulfonated kotalanol (**268**) has been reported, by Pinto and co-workers, who prepared this compound as part of their recent structural elucidation of kotalanol (**247**). In this case, synthesis commenced from di-*O*-benzylidene-D-mannitol (**275**), which underwent bis-*O*-alkylation with dibromomethane under phase transfer conditions to provide a C_2 -symmetric 1,3-dioxepane derivative. Methanolysis of a single benzylidene acetal under acid conditions then generated 1,3-diol **276**, which through a succession of

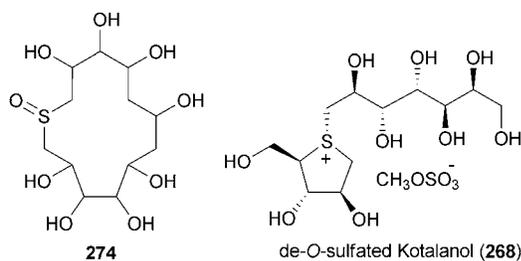


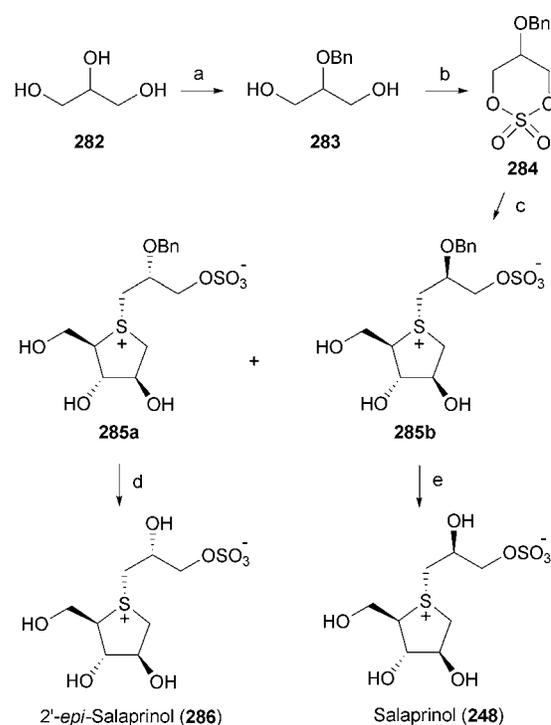
Fig. 15 Initially proposed and reassigned structures of the naturally occurring α -glucosidase inhibitor de-*O*-sulfonated kotalanol.

silylation, *O*-benzylation and desilylation was converted to primary alcohol **277**. Dess–Martin oxidation and Wittig homologation of the aldehyde generated terminal alkene **278**. Introduction of the C6' stereocenter of the target was accomplished by Sharpless asymmetric dihydroxylation using AD-mix β , which proceeded to generate a 7 : 1 mixture of diastereomeric diols. After chromatographic separation, the major product was bis-*O*-alkylated and the remaining benzylidene acetal hydrolyzed to provide **279**.

Conversion of 1,3-diol **279** to the corresponding cyclic sulfate now set the stage for coupling with **273**, which proceeded slowly (7 d) in HFIP to generate sulfonium salt **281** as a single α -isomer. In light of the stability of the 1,3-dioxepane ring towards aqueous TFA, simultaneous removal of all protecting groups and desulfonation was now carried out with BCl_3 , which furnished de-*O*-sulfated kotalanol as the methyl sulfate salt **268**.

4.4 Salaprinol

Isolated from the methanolic extract of the roots and stems of the Sri Lankan plant *Salacia prinoides*, salaprinol (**248**) is the least structurally complex of the zwitterionic thiosugar α -glucosidase inhibitors discovered to date (Scheme 41).¹⁴¹ Confirmation of the structure and stereochemistry of this natural product has been accomplished by Muraoka, through total synthesis and single crystal X-ray analysis.¹⁴³



Scheme 41 Muraoka's synthesis of 2'-*epi*-salaprinol and salaprinol. *Reagents and conditions*: (a) (i) TrCl , pyridine, rt, 24 h; (ii) BnBr , NaH , DMF, 0°C \rightarrow rt; (iii) H_2SO_4 , 1,4-dioxane, reflux, 2 h, 90% (3 steps); (b) SOCl_2 , Et_3N , CH_2Cl_2 , 0°C , 10 min; then NaIO_4 , RuCl_3 , NaHCO_3 , CCl_4 - CH_3CN (1 : 1), H_2O , 0°C \rightarrow rt, 30 min, 93% (2 steps); (c) 1,4-anhydro-4-thio-D-arabinitol (**250**), K_2CO_3 , HFIP, 65 – 70°C , 60 h, 43%; (d) H_2 , Pd/C , 80% AcOH , rt, <86%; (e) H_2 , Pd/C , 80% AcOH , rt, 87%.

Synthesis of **248** commenced from glycerol (**282**), which through a 3-step, one-pot sequence involving 1,3-di-*O*-tritylation, *O*-benzylation and solvolysis, was converted to 2-*O*-benzyl-glycerol (**283**) (Scheme 41). This 1,3-diol was then converted to *meso* cyclic sulfate **284**, which underwent slow *S*-alkylation with unprotected 1,4-anhydro-4-thio-*D*-arabinitol (**250**) exclusively from the α -face to generate a 10 : 1 mixture of C2'-epimers. After partial separation, hydrogenolytic de-*O*-benzylation of **285a** and **285b** provided 2'-*epi*-salaprinol (**286**) and salaprinol (**248**), respectively.

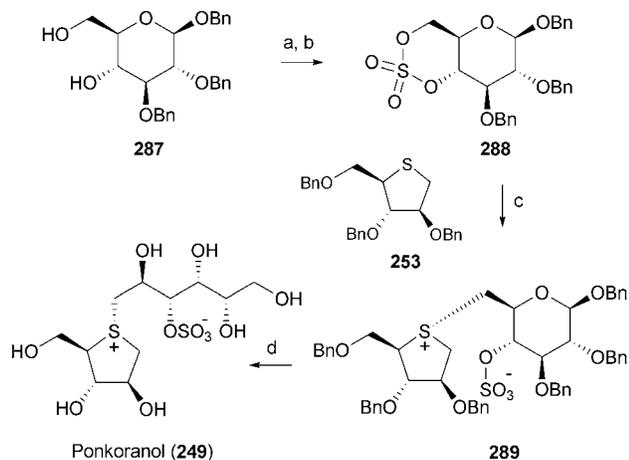
4.5 Ponkoranol

Ponkoranol (**249**), a six-carbon chain homologue of salacinol (**2**) initially isolated from *Salacia reticulata* by Kitamura,¹⁴⁴ who named it reticulanol, has more recently been found to occur in *Salacia prinoides* by Yoshikawa. In common with other members of the thiosugar sulfonium sulfate family, ponkoranol inhibits maltase, sucrase and isomaltase with IC₅₀ values in the low micromolar range.¹⁴⁵ To date, a single synthesis of **249** has been reported, by Pinto and co-workers who, while conducting SAR studies on salacinol, prepared this compound prior to the original report of its isolation (Scheme 42).¹³¹

Preparation of **249** was accomplished by the regioselective alkylation of thioether **253** with cyclic sulfate **288**, which was prepared from *D*-glucopyranoside **287** through the two-step method developed by Sharpless.¹⁴⁶ Alkylation of **288** proceeded slowly in HFIP to generate sulfonium salt **289** as a single *trans* isomer, albeit in moderate yield. A sequence of hydrogenolytic debenylation and reduction of the resulting mixture of hemiacetal anomers with NaBH₄ then generated ponkoranol (**249**).

4.6 Neosalacinol

Neosalacinol (**291**) and salicinol (**2**) were recently isolated from the medicinal plant *Salacia oblonga* by Asano and co-workers (Scheme 43). On the basis of NMR spectroscopic analysis, mass spectrometry and a degradation study, the identity of **291** was established as a de-sulfonated derivative of salicinol and

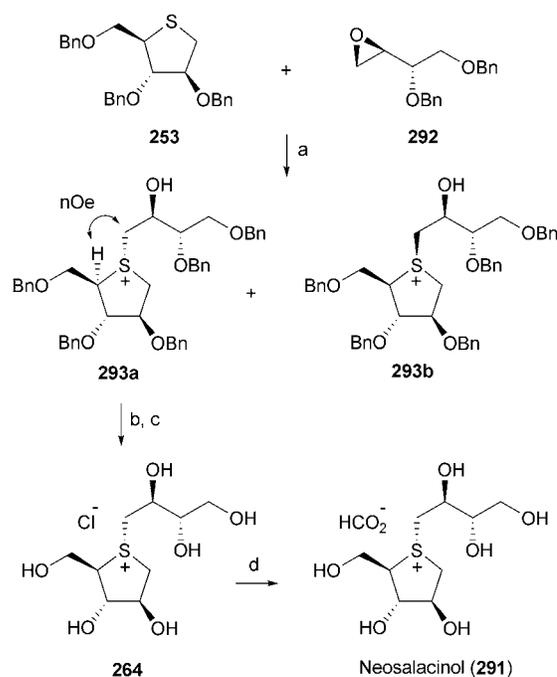


Scheme 42 Pinto's total synthesis of ponkoranol. *Reagents and conditions:* (a) SO₂Cl₂, Et₃N, CH₂Cl₂, rt, 80%; (b) NaIO₄, RuCl₃·H₂O (cat.), CCl₄-CH₃CN (1 : 1), rt, 15 min; (c) HFIP, 70 °C, 42 h, 50%; (d) H₂ (1 atm), Pd/C, AcOH, 22 h; then NaBH₄, H₂O, rt, 20 min, 64%.

formulated its structure in terms the sulfonium-alkoxide zwitterion **290** (Fig. 16).¹⁴⁷ Subsequent synthetic studies by Muraoka have revealed that while **291** is indeed de-*O*-sulfo-salicinol, it is not an inner salt.¹⁴⁸ Confusion regarding its ionic structure aside, compound **291** is notable in that it displays differential activity with respect to salicinol. Of these two molecules, **291** is the more potent inhibitor of rat intestinal isomaltase (IC₅₀ = 0.64 μM), while **2** is more active against maltase (IC₅₀ = 0.5 μM) and human lysosomal α -glucosidase, an essential mediator in the breakdown of glycogen to glucose.

In order to clarify the structure of this highly potent glucosidase inhibitor, Muraoka has developed a synthetic route to **291**, which involves the acid-catalyzed reaction of thioether **253** with epoxide **292**. In what is likely a reflection of the smaller size of this electrophile, in comparison with cyclic sulfates, *S*-alkylation in this case proceeded to generate a mixture of β -hydroxylated sulfonium salts (dr = 9 : 1) in favor of the *anti*-isomer. After chromatographic separation, **293a** was subjected to ion exchange (BF₄⁻ → Cl⁻) and hydrogenolysis to yield sulfonium chloride **263**. Treatment with Dowex 1-X2 (HCO₂⁻ form) then generated formate salt **291**, whose spectroscopic data was in accord with that of the original isolate.

Muraoka has also prepared neosalicinol through the methanolysis of salicinol itself (Scheme 44). In common with Asano,¹⁴⁷ heating **2** in 5% methanolic HCl was found to generate the methyl sulfate salt in high yield. Ion exchange with Dowex 1-X2 (HCO₂⁻ form) then generated formate salt **291**, which was identical to synthetic material. Whether neosalicinol is simply an artifact of the isolation of salicinol is a question which, as yet, remains unanswered.



Scheme 43 Muraoka's total synthesis and structural reassignment of neosalicinol (de-*O*-sulfo-salicinol). *Reagents and conditions:* (a) HBF₄·OMe₂, CH₂Cl₂, -60 °C, 90%, dr = 9 : 1; (b) IRA-400J (Cl⁻ form), MeOH-H₂O, rt, 95%; (c) H₂, Pd/C, AcOH-H₂O (4 : 1), 50–60 °C, 90%; (d) Dowex 1-X2 (HCO₂⁻ form), H₂O.

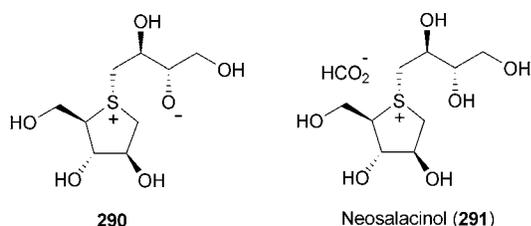
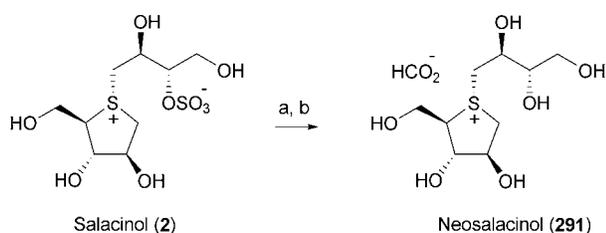


Fig. 16 Initially proposed and reassigned structures of the α -glucosidase inhibitor neosalacinal.



Scheme 44 Muraoka's synthesis of de-*O*-sulfated salacinal through salacinal degradation. *Reagents and conditions:* (a) MeOH–HCl (95 : 5), reflux, 1 h, 88%; (b) Dowex 1-X2 (HCO₂⁻ form), H₂O, 82%.

5 Carbasugars

First synthesized by McCasland and co-workers in 1966, carbasugars (or pseudosugars) are carbocyclic analogues of monosaccharides in which the ring-oxygen atom has been replaced by a methylene group.¹⁴⁹ In common with deoxynojirimycin, this seminal synthetic work actually predates, by seven years, the discovery of the first carbasugar natural product, 5a-carba- α -D-galactopyranose (**294**) (Fig. 17).¹⁵⁰ While rarely found in

Nature alone, carbasugars and in particular aminocyclitols more commonly occur as components of more complex natural products, as exemplified by the aminoglycoside antibiotic validamycin (**297**).¹⁵¹ Within the scope of the current review, the aminocyclitols valienamine (**295**), valioline (**296**), validamine (**299**) and their derivatives voglibose (**298**) and acarbose (**300**) are of particular note since they are potent α -glucosidase inhibitors. Indeed, acarbose and voglibose, which are respectively marketed as Precose[®] and Basen[®], are approved for the clinical treatment of type II diabetes. The obvious importance of aminocyclitols coupled with their limited availability from natural sources has motivated a considerable amount of work directed towards their preparation.¹⁵²

5.1 Valienamine

Found as a subunit of a number of pseudo-oligosaccharides and pseudo-aminosugars, including acarbose, adiposins, amylostatin and trestatins,¹⁵¹ the potent α -glucosidase inhibitor and antibiotic valienamine (**295**) was originally obtained from the microbial deglycosylation of validoxylamine A with *Pseudomonas denitrificans*.¹⁵³ Since its isolation in 1972, several elegant syntheses of this aminocyclitol have reported, many of which employ D-glucose or its derivatives as the starting point. In this vein, Kim and Jeon have developed a concise, nine-step synthesis of pentaacetate (**307**) from tetra-*O*-benzyl-D-glucose (**301**), which utilizes RCM to establish the cyclohexenyl ring (Scheme 45).¹⁵⁴ Treatment of **301** with ethanethiol and TFA yielded hydroxy dithioacetal **302**, which underwent Albright–Goldman oxidation (Ac₂O–DMSO) to yield the corresponding ketone. Wittig methylenation, thioacetal hydrolysis and addition of vinylmagnesium bromide to the aldehyde generated **304** as an inseparable mixture of diastereomers. RCM of these 1,7-dienes proceeded in the presence of Grubbs'

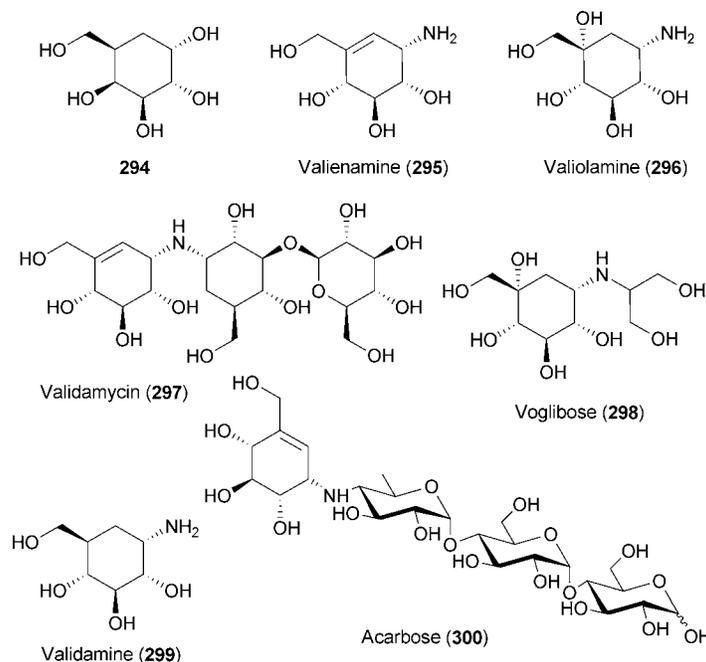
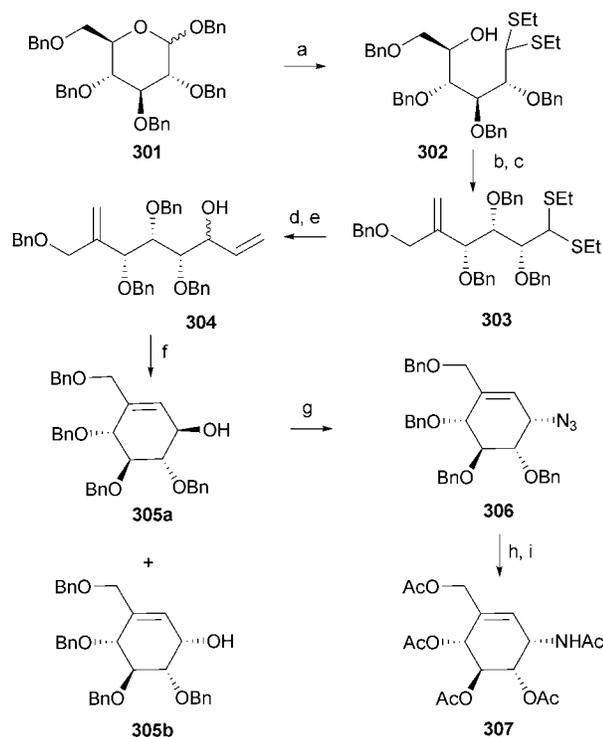


Fig. 17 Examples of naturally occurring carbasugar α -glucosidase inhibitors and the antibiotic validamycin.

second-generation catalyst to yield cyclohexenes **305a** and **305b** in a 2.4 : 1 ratio. After separation, **305a** underwent substitution with DPPA–NaN₃ to form **306**, which through stepwise reduction, debenzoylation and peracetylation was converted to valienamine pentaacetate (**307**) with an overall yield of 14.5%.

The use of a D-glucose-derived starting material and ring-closing metathesis also features prominently in Cumpstey's formal synthesis of valienamine (**295**), although in this case the use of ethanethiol and mercury salts is avoided by the direct addition of vinylmagnesium bromide to glucose derivative **308** (Scheme 46).¹⁵⁵ The mixture of 1,5-diols generated in this reaction were separated, the major product **309b** selectively monoalkylated with 3,4-dimethoxybenzyl chloride and the product transformed to **311** and byproduct **310**, which arises as a result of benzoylation of the non-allylic hydroxyl group of **309b**. Wittig methylenation of **311** furnished 1,7-diene **312**, which underwent RCM to form **313**, after removal of the pivalate ester. Since Fukase has previously converted **313** to valienamine (**295**) via a three-step sequence, preparation of **313** represents a formal synthesis of this natural product.¹⁵⁶

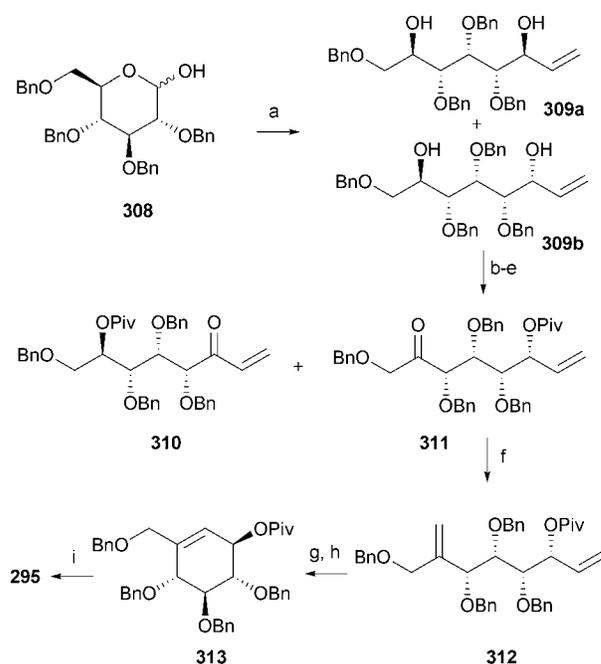
Employing C₂-symmetric L-tartrate derivative **314**, Yan and co-workers have developed a route to (+)-valienamine pentaacetate (**307**) and several other important C₇N aminocyclitols that is notable for both its brevity and the use of a [3,3]-sigmatropic rearrangement to control introduction of the C1 amine group (Scheme 47).¹⁵⁷ The cyclohexenyl ring of **307** was established in



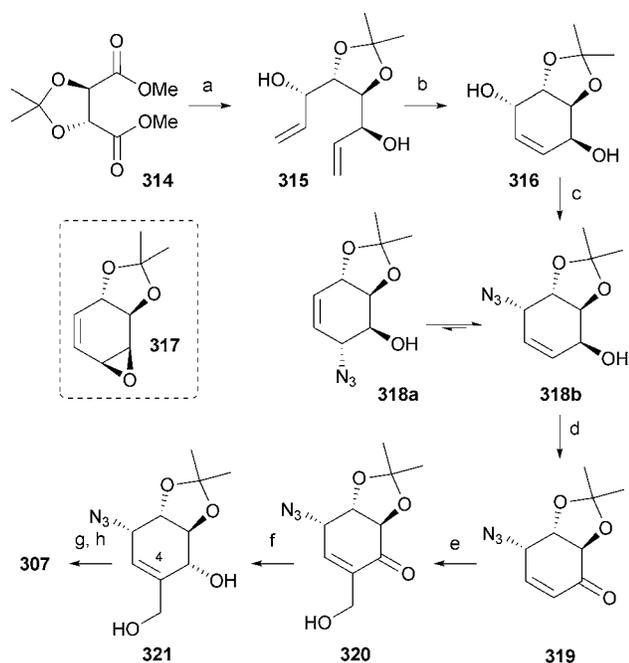
Scheme 45 Jeon and Kim's synthesis of valienamine pentaacetate. *Reagents and conditions:* (a) EtSH, TFA, rt, 12 h, 77%; (b) DMSO, Ac₂O, rt, 12 h, 94%; (c) Ph₃PCH₃Br, *t*-BuOH, 88%; (d) HgCl₂, HgO, CH₃CN–H₂O, 80–90 °C; (e) vinylmagnesium bromide, THF, –78 °C, 79% (2 steps); (f) Grubbs' 2nd-generation catalyst, CH₂Cl₂ (0.05 M), reflux, **305a** (61%), **305b** (25%); (g) DPPA, DBU, PhCH₃, 0 °C; NaN₃, 40 °C, 83% (2 steps); (h) Ph₃P, NH₄OH, pyridine, rt, 80%; (i) Na/NH₃, THF, –78 °C; (j) Ac₂O, pyridine, 71% (two steps).

this case through reduction of **314**, double diastereoselective addition of divinylzinc to the dialdehyde and RCM metathesis of the resulting 1,7-diene to form **316**. Base-mediated monotriflation of this diol now generated epoxide **317**, which upon treatment with azide underwent ring opening at the allylic position to generate **318a**. When conducted at 90 °C, **318a** underwent rearrangement to 1,4-azido alcohol **318b**, in which the azide substituent is in a pseudoequatorial rather than axial orientation. After introduction of the C4 hydroxymethyl group via formation and Baylis–Hillman reaction of **319**, chelation-controlled reduction of **320** provided **321**, which was converted to **307**, the pentaacetate derivative of valienamine, by azide reduction, deacetalization and peracetylation.

In contrast to the two other syntheses of valienamine (**295**) reported during the review period, Krishna's recent preparation of this natural product and its C4 epimer does not involve cyclohexene formation via RCM, but rather a ring-closing enyne metathesis reaction (RCEYM) (Scheme 48).¹⁵⁸ The substrate for this cyclization (**325**) was prepared from L-serine derivative **322** through a nine-step sequence featuring Sharpless asymmetric dihydroxylation and Carreira asymmetric alkynylation. In the presence of Grubbs' second-generation catalyst and ethylene, **325** underwent cyclization to form a 1-vinylcyclohex-1-ene, which upon oxidative cleavage of the 1,4-diene and enal reduction provided **326**. Global deprotection, accomplished by treatment of **326** with TFA in CH₂Cl₂, then provided valienamine, which was isolated as its pentaacetate derivative **307**.



Scheme 46 Cumpstey's synthesis of valienamine. *Reagents and conditions:* (a) vinylmagnesium bromide, THF, 0 °C, **309a** (29%), **309b** (65%); (b) 3,4-dimethoxybenzyl chloride, DMF, NaH, 0 °C, 57%, regioselection = 10 : 1; (c) PivCl, pyridine, DMAP, 93%; (d) CAN, MeCN–H₂O, 0 °C → rt, 74%; (e) COCl₂, DMSO, Et₃N, CH₂Cl₂, –60 °C, **310** (7%), **311** (81%); (f) PPh₃CH₃Br, THF, NaHMDS –78 °C, 63%; (g) Grubbs' 2nd-generation catalyst, PhCH₃, 60 °C, 65%; (h) NaOMe, MeOH, 40 °C, 99%; (i) 3 steps described in ref. 156.

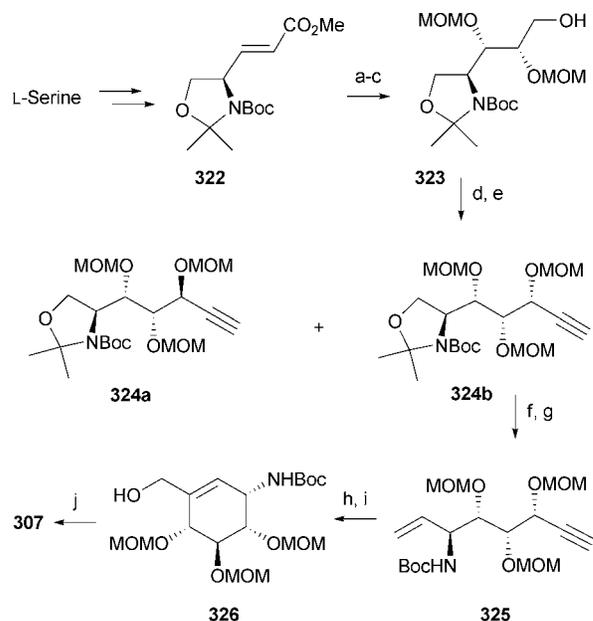


Scheme 47 Yan's synthesis of valienamine pentaacetate. *Reagents and conditions:* (a) DIBAL-H, $-78\text{ }^{\circ}\text{C}$; then ZnCl_2 , vinylmagnesium bromide, 83%; (b) Grubbs' 2nd-generation catalyst, CH_2Cl_2 , reflux, 2 h, 70%; (c) PhNTf_2 , NaH, DMF, $25\text{ }^{\circ}\text{C}$, 15 min; NaN_3 , $\text{EtOH-H}_2\text{O}$, $90\text{ }^{\circ}\text{C}$, 12 h, 70%; (d) Dess–Martin periodinane, CH_2Cl_2 , $25\text{ }^{\circ}\text{C}$, 3 h, 96%; (e) HCHO, NaHCO_3 , $\text{THF-H}_2\text{O}$, imidazole, $25\text{ }^{\circ}\text{C}$, 18 h, 80%; (f) NaBH_4 , $\text{CeCl}_3\text{-MeOH}$, $-78\text{ }^{\circ}\text{C}$, 20 min, 80%; (g) LiAlH_4 , Et_2O , $0\text{ }^{\circ}\text{C}$, 1 h; then $\text{AcOH-H}_2\text{O}$, $0 \rightarrow 50\text{ }^{\circ}\text{C}$; (h) Ac_2O , pyridine, 50% (2 steps).

5.2 Valiolamine and voglibose

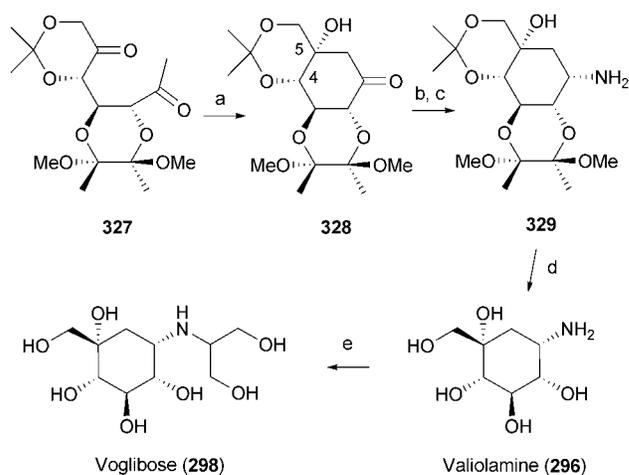
Voglibose (**298**, Basen[®]), an *N*-alkylated glycerol derivative of valiolamine (**296**), is a potent inhibitor of intestinal α -glucosidase, which delays the absorption of carbohydrates and thereby prevents hyperglycemia and the host of disorders associated with this condition.¹⁵⁹ This compound is currently employed in Japan, China and Korea for the management of type II diabetes.¹⁶⁰ During the review period, Shing and Cheng reported a synthesis of valiolamine, validoxylamine G and a formal synthesis of voglibose, which utilizes a stereoselective intramolecular aldol reaction to generate the common carbocyclic skeleton of these targets (Scheme 49).¹⁶¹

The key step in this work involves the highly stereoselective KHMDS-mediated cyclization of 1,5-diketone **327** (prepared in 6 steps and 30% yield from *D*-glucose) to form **328** (Scheme 49). Notably, the stereochemical outcome of this transformation was found to be remarkably sensitive to the identity of the base employed – *L*-proline led to the formation of the C5 epimer of **328**, while *D*-proline generated the C4 epimer. From **328**, reductive amination of the corresponding oxime generated valiolamine (**296**) with excellent stereocontrol, after removal of the acetal protecting groups. Since reductive amination of **296** with 1,3-dihydroxyacetone in the presence of sodium cyanoborohydride leads to the formation of voglibose (**298**), this work represents a formal synthesis of this medically important target molecule.¹⁵⁹ Shing and co-workers have also utilized the



Scheme 48 Krishna's synthesis of valienamine pentaacetate. *Reagents and conditions:* (a) AD-mix α , OsO_4 , MeSO_2NH_2 , *t*-BuOH– H_2O , $0\text{ }^{\circ}\text{C}$, 16 h, 84%; (b) MOMCl, DIPEA, CH_2Cl_2 , $0\text{ }^{\circ}\text{C} \rightarrow \text{rt}$, 17 h, 93%; (c) LiAlH_4 , THF, $0\text{ }^{\circ}\text{C} \rightarrow \text{rt}$, 1 h, 75%; (d) COCl_2 , DMSO, Et_3N , $-78\text{ }^{\circ}\text{C}$; then TMS-acetylene, *n*-BuLi, $-78\text{ }^{\circ}\text{C}$, 4 h; $\text{Zn}(\text{OTf})_2$, (–)-*N*-methylphedrine, Et_3N , PhCH_3 , 86%, dr = 98 : 1; (e) MOMCl, DIPEA, CH_2Cl_2 , $0\text{ }^{\circ}\text{C} \rightarrow \text{rt}$, 8 h; (f) $\text{CuCl}_2\cdot\text{H}_2\text{O}$, MeCN, $0\text{ }^{\circ}\text{C}$, 0.5 h, 92%; (g) Swern oxidation; then $\text{Ph}_3\text{PCH}_3\text{I}$, *t*-BuOK, THF, $0\text{ }^{\circ}\text{C}$, 8 h, 64%; (h) Grubbs' 2nd-generation catalyst (10 mol%), PhCH_3 , $110\text{ }^{\circ}\text{C}$, 12 h, 92%; (i) OsO_4 , NMO (0.5 eq), acetone– H_2O (4 : 1), 5 h; NaIO_4 , MeOH– H_2O (9 : 1), $0\text{ }^{\circ}\text{C}$, 5 min, 62% (3 steps); (j) TFA, CH_2Cl_2 , $0\text{ }^{\circ}\text{C}$, 4 h; (k) Ac_2O , pyridine, DMAP, CH_2Cl_2 , rt, 14 h, 68% (two steps).

synthetic strategy outlined in Scheme 49 for the preparation of pseudoacarviolin, a pseudo-1,4'-*N*-linked disaccharide with potent anti α -glucosidase (sucrase and glucoamylase) activity.¹⁶²



Scheme 49 Shing's synthesis of valiolamine and formal synthesis of voglibose. *Reagents and conditions:* (a) KHMDS (1 eq), PhCH_3 , $-78\text{ }^{\circ}\text{C}$, 75%; (b) $\text{NH}_2\text{OH}\cdot\text{HCl}$, NaHCO_3 , MeOH; (c) H_2 , RANEY[®] Ni, EtOH, Et_3N , 85% (2 steps); (d) TFA, H_2O , CH_2Cl_2 , 88%; (e) 1,3-dihydroxyacetone, $\text{Na}(\text{CN})\text{BH}_3$, 2 M HCl–DMF, $50\text{--}60\text{ }^{\circ}\text{C}$, 15 h, 73% (ref. 159).

6 Marine organosulfates

While the overwhelming majority of naturally occurring glucosidase inhibitors have to date been isolated from terrestrial plant sources, during the last decade there has been increasing interest in the discovery of inhibitors from marine organisms.¹⁶³ Of particular note in this regard has been the work of Fusetani and collaborators who, while screening Japanese marine invertebrates for drug candidates,¹⁶⁴ discovered a number of novel α -glucosidase inhibitors which bear scant resemblance to iminosugars (Fig. 18).¹⁶⁵ Members of this group, which include the penarolides (**330** and **331**),¹⁶⁶ penasulfate A (**332**)¹⁶⁷ and the schulzeine family (**333–336**),¹⁶⁸ are structurally related in that they each comprise an alkaloid or amino acid residue coupled with an *O*-sulfated long-chain fatty acid through an amide group.

6.1 Penarolide sulfates

Isolated from a marine sponge *Penares* sp. collected in the waters off Hachijo-jima Island, penarolide sulfate A₁ (**330**) and A₂ (**331**) are structurally unique 30- and 31-membered macrolides which encompass a trisulfated, lipophilic chain encircled by a proline residue.¹⁶⁶ These compounds inhibit α -glucosidase with IC₅₀ values of 1.2 and 1.5 μ g/mL making them approximately 30–40 times more active than 1-deoxynojirimycin (**1**). In common with a number of other sulfated natural products,¹⁶⁹ the penarolides also display anti-thrombin activity.

To date, a single total synthesis of the penarolides has been reported, by Mohapatra and co-workers, who employed an intramolecular Sonogoshira coupling reaction to establish the 30-atom macrolide ring of penarolide A₁ (**330**) (Schemes 50–53).¹⁷⁰ In this highly convergent approach, synthesis of the C1–C18 carboxylic acid subunit **342** commenced from dodecane-1,12-diol (**337**), which was converted *via* a three-step sequence to **338** (Scheme 50). Sharpless asymmetric dihydroxylation of this *E,E*-dienoate proceeded with complete regiocontrol to provide **339**, which was then converted to **340** through a succession of diol protection, reduction and Sharpless asymmetric epoxidation. After conversion of **340** to the corresponding alkyl chloride, treatment with *n*-BuLi generated propargylic alcohol **341**. Oxidative debenzoylation followed by stepwise oxidation of the primary alcohol then generated C₁₈ acid **342**.

The C19–C30-proline subunit **348** was prepared from known aldehyde **343**, which was converted to **344** in a single step *via* a Corey–Chakovsky reaction (Scheme 51). Hydrolytic kinetic resolution of this epoxide, using (*R,R*)-salen-Co(III)OAc, then provided **346** which through alkylative ring opening and coupling with *N*-Boc-L-proline was converted to **348**. Introduction of the (*E*)-vinyl iodide moiety necessary for macrocyclization was accomplished by debenzoylation, oxidation and Takai olefination which, after removal of the Boc group, furnished fragment **349**.

With both subunits of penarolide A₁ assembled, carbodiimide-mediated coupling of **349** and **341** proceeded in high yield to provide ester **350**, which underwent intramolecular Sonogashira cross-coupling to generate macrocycle **351** in 35% yield (Scheme 52). Reduction of the enyne group, through hydrogenation over RANEY® Ni, and global deprotection under acidic conditions now provided triol **352** which, upon treatment with pyridine–

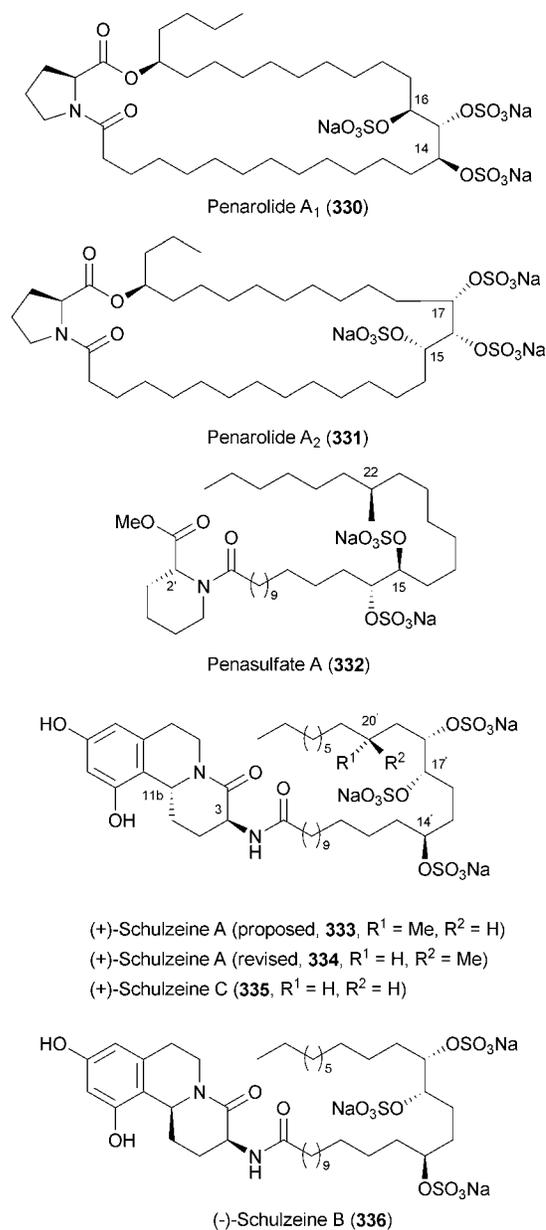
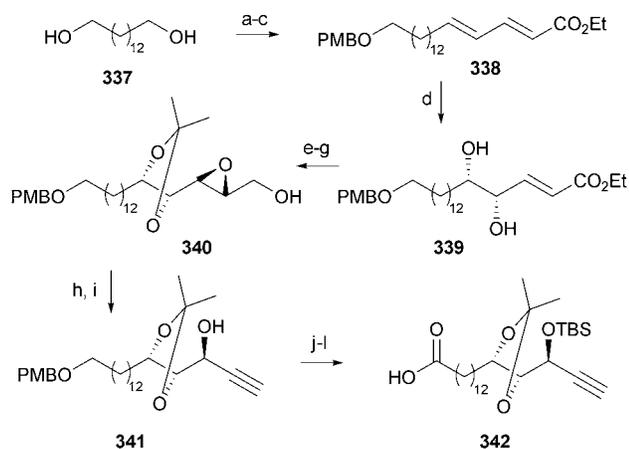


Fig. 18 Structure of organosulfate α -glucosidase inhibitors isolated from marine invertebrates.

sulfur trioxide complex, was converted to penarolide A₁ (**330**). The importance of the organosulfate groups to the biological activity of the penarolides and related natural products is underscored by Mohapatra's finding that while also an α -glucosidase inhibitor, compound **352** is significantly less active than the natural product itself.

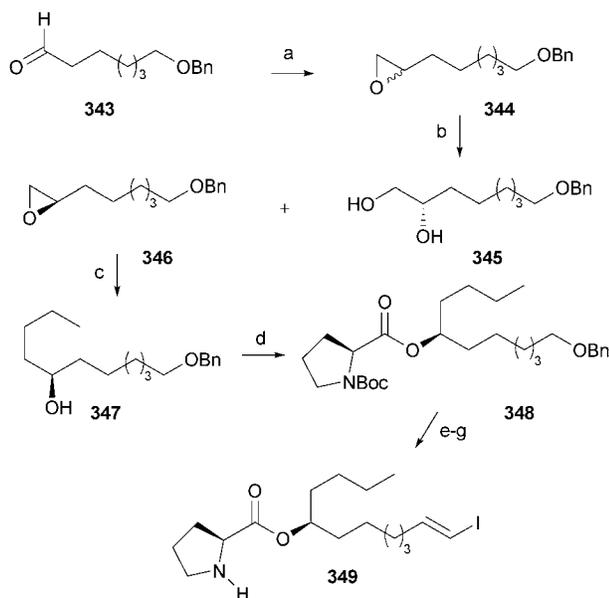
6.2 Schulzeines

The schulzeines (**333–336**), isolated by Fusetani and co-workers from extracts of the marine sponge *Penares schulzei*, not only represent a new class of marine alkaloids, but also display potent α -glucosidase-inhibitory activity (IC₅₀ = 48–170 nM) (Fig. 18).¹⁶⁸ The structure of each of the three members of this family was

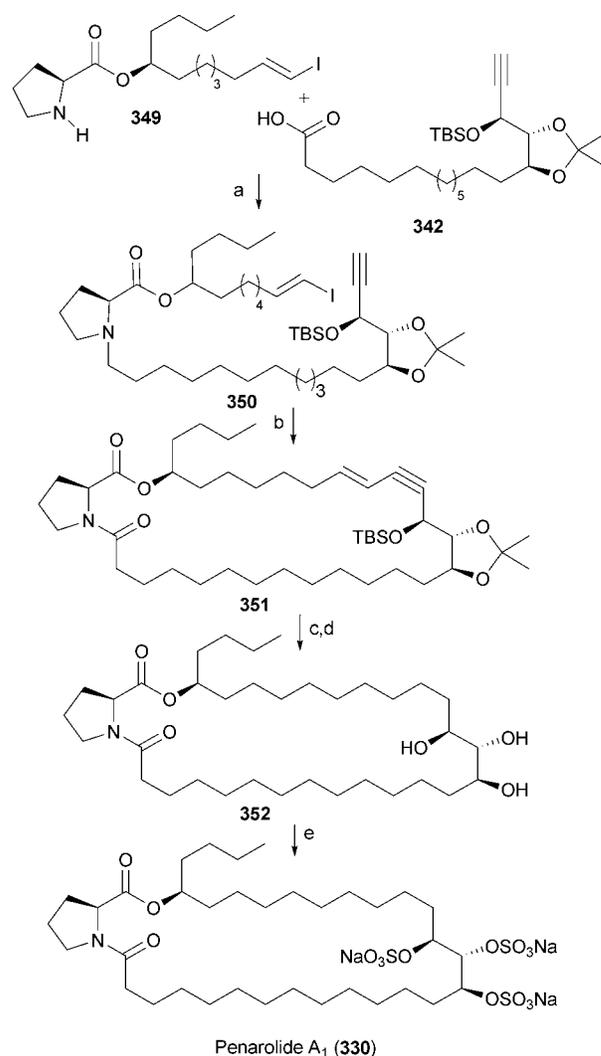


Scheme 50 Mohapatra's total synthesis of penarolide A₁: Preparation of the C1–C18 subunit. *Reagents and conditions:* (a) PMBBr, NaH, THF–DMF, 90%; (b) IBX, DMSO, 95%; (c) ethyl 4-(dimethylphosphono)crotonate, LiHMDS, THF, –78 °C, 83%; (d) AD-mix α , MeSO₂NH₂, *t*-BuOH, H₂O, 70%, ee = 98.4%; (e) 2,2-dimethoxypropane, TsOH, CH₂Cl₂, 96%; (f) DIBAL-H, CH₂Cl₂, –78 °C, 85%; (g) D-(–)-DIPT, Ti(O-*i*-Pr)₄, *t*-BuOOH, 4 Å MS, CH₂Cl₂, –20 °C, 67%, dr >95 : 5; (h) Ph₃P, CCl₄, NaHCO₃, reflux, 90%; (i) *n*-BuLi (3 eq), THF, –30 °C, 72%; (j) TBSCl, imidazole, CH₂Cl₂, 94%; (k) DDQ, CH₂Cl₂, buffer (pH = 7), 76%; (l) IBX, DMSO, 95%; NaClO₂, NaH₂PO₄·H₂O, 2-methyl-2-butene, *t*-BuOH, H₂O, 88%.

elucidated through a combination of spectral analysis and chemical degradation, while absolute configuration was determined by modified Mosher analysis of the fragments obtained upon acidic hydrolysis of the lipid side chains. Although total synthesis has subsequently confirmed the assignments originally made for



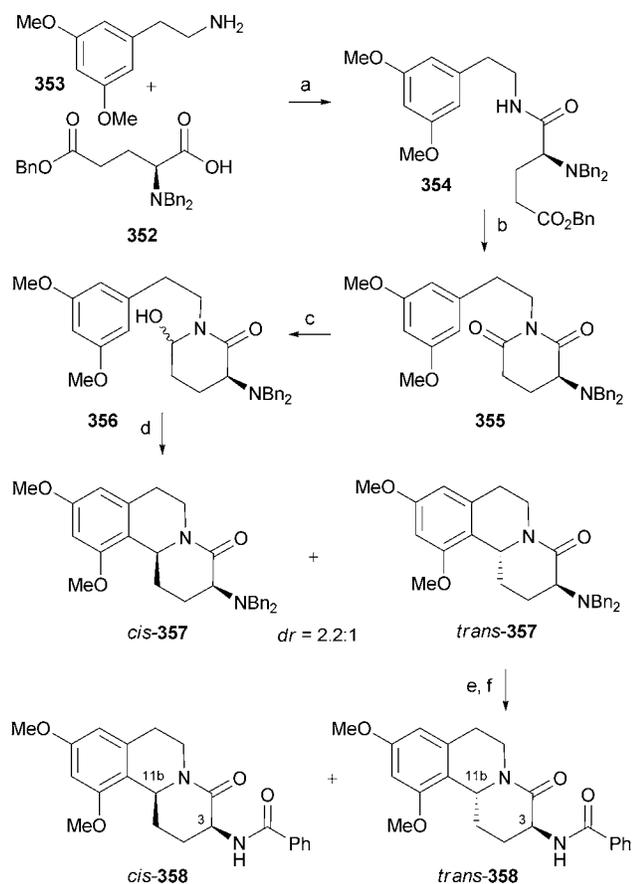
Scheme 51 Mohapatra's total synthesis of penarolide A₁: Preparation of the C19–C30–proline subunit. *Reagents and conditions:* (a) Me₃SO⁺ I[–], NaH, DMSO, 84%; (b) (*R,R*)-salen-Co(III)OAc (0.5 mol%), H₂O, **344** (47%), ee = 98.8%; (c) PrMgBr, CuCN, THF, 78%; (d) *N*-Boc-L-proline, EDC, DMAP, CH₂Cl₂, 95%; (e) H₂, Pd/C, EtOAc, 87%; (f) IBX, DMSO, 90%; (g) CrCl₂, CHI₃, THF, 90%; (h) 4 M HCl–EtOAc, 81%.



Scheme 52 Mohapatra's total synthesis of penarolide A₁. *Reagents and conditions:* (a) EDC, HOBT, CH₂Cl₂, 96%; (b) Pd(PPh₃)₄, CuI, Et₂NH, 35%; (c) H₂, RANEY® Ni, EtOH, 92%; (d) TsOH, MeOH, 82%; (e) SO₃·pyr, DMF, rt, 36 h; H₂O, 0 °C, 30 min; NaHCO₃, 0 °C, 84%.

schulzeine B (**336**) and C (**335**), Wardrop and Bowen have demonstrated that the stereochemical assignment made for the C20' stereocenter for schulzeine A (**334**) should be revised (*vide infra*). In light of their bioactivity and structural novelty, the schulzeines have garnered significant interest from the synthetic community, with three total syntheses of various members of this family having been published since their isolation in 2004.

First to report a study directed towards the synthesis of the schulzeines, Kuntiyong and co-workers have developed a short route to the *cis* and *trans*-3-aminobenzo[*a*]quinolizidine ring systems common to this group (Scheme 53).¹⁷¹ The key step in this endeavour involves the Pictet–Spengler reaction of α -hydroxy- δ -lactam **356**, which was assembled from L-glutamic acid derivative **352** and 2-(3,5-dimethoxyphenyl)ethylamine (**353**). While Lewis-acid-mediated ring closure of **356** led to the formation of tricycles *cis*-**357** and *trans*-**357** in excellent yield, the diastereoselectivity of this process proved to be disappointingly low (dr = 2.2 : 1). Nonetheless, chromatographic separation of these C11b epimers



Scheme 53 Kuntiyong's synthesis of the schulzeine benzo[*a*]quinolizidine subunits. *Reagents and conditions:* (a) DCC, DMAP, CH₂Cl₂, 63%; (b) LiAlH₄, THF, 53%; (c) DIBAL-H, PhCH₃, -78 °C, 75%; (d) TMSOTf, CH₂Cl₂, 0 °C, 95%, *dr* = 2.2 : 1; (e) H₂, Pd/C, MeOH, rt; (f) BzCl, pyridine, CH₂Cl₂, 0 °C, 94% (2 steps).

was accomplished after de-*O*-benzylation and conversion to the corresponding benzamide derivatives **358**.

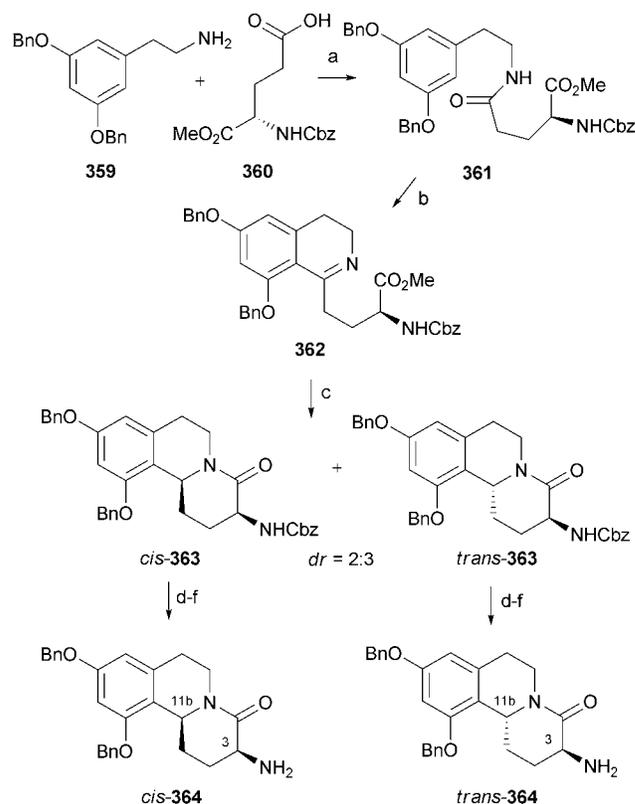
Employing a convergent strategy, Gurjar and co-workers were the first to complete the total synthesis of schulzeine B (**336**) and C (**335**) (Schemes 54–56).¹⁷² In this case, a Bischler–Napieralski rather than a Pictet–Spengler reaction was utilized in the construction of the tetrahydroisoquinoline “head” subunit. Reaction of *L*-glutamate derivative **361** with POCl₃ generated 3,4-dihydroisoquinoline **362** which, upon treatment with NaCNBH₃ in the presence of acetic acid, underwent non-selective reduction to form C11a epimers *cis*-**363** and *trans*-**363**. While these diastereomers proved to be chromatographically separable, the lack of orthogonality between the Cbz and *O*-benzyl groups and the need to access protected amines *cis* and *trans*-**364** now necessitated exchange of the carbamate group. For each isomer, this was accomplished by hydrogenolysis in the presence of Boc₂O, bis-*O*-benzylation of the free catechol and solvolysis of the *N*-Boc group.

The unbranched C₂₈ side chain common to both schulzeine B and C (but not A) was assembled from 1,12-dodecanedicarboxylic acid (**365**) and undecan-1-al (**366**), which were respectively converted to phosphonate **367** and aldehyde **368** (Scheme 55). Horner–Wittig–Emmons reaction of these fragments then

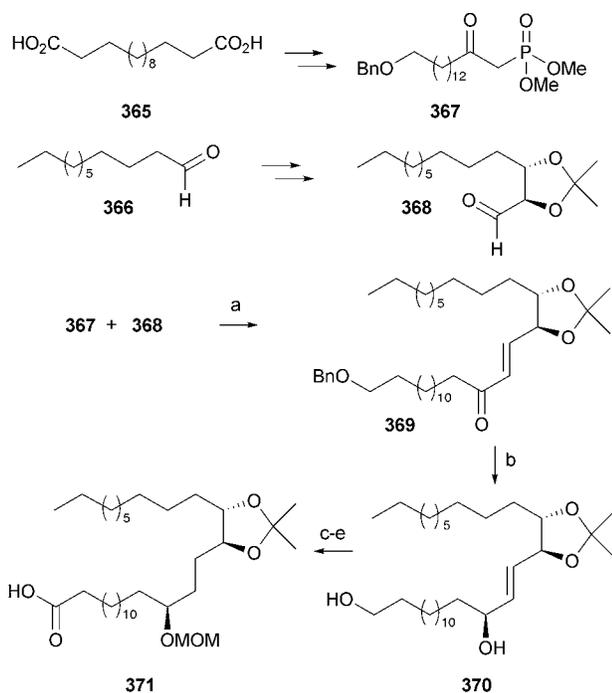
generated *E*-enone **369**. Having established the absolute configuration of the C17' and C18' stereogenic centers through Sharpless asymmetric dihydroxylation, the remaining chiral center at C14' was installed through stoichiometric reduction with (*S*)-(-)-BINAL-H. After separation of the minor diastereomer (*dr* = 11 : 1), allylic alcohol **370** was converted to the saturated C₂₈ carboxylic acid **371** through a sequence of *O*-protection, hydrogenolysis/hydrogenation and oxidation.

Gurjar's route to schulzeine B (**336**) was completed through carbodiimide-mediated coupling of carboxylic acid **371** and amine *cis*-**364** to provide **372** (Scheme 56). After simultaneous removal of the acetonide and MOM protecting groups with trimethylsilyl iodide, the resulting triol was persulfated by treatment with SO₃·pyridine complex in DMF and the benzyl ethers removed to provide schulzeine B (**337**) in high yield. Following the same sequence of reactions, (+)-schulzeine C (**335**) was also prepared from *trans*-**364**. In both cases, Gurjar found that the spectral and analytic data for these synthetic products match closely that reported for the natural products themselves.

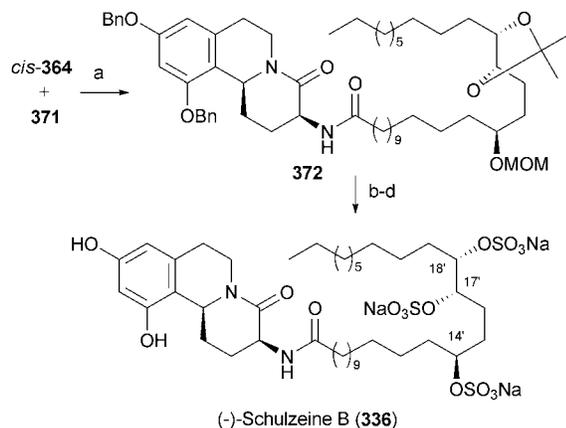
In 2009, Romo and Liu reported the second enantioselective synthesis of schulzeine B (**336**) and C (**335**) (Schemes 57 and 58),¹⁷³ their strategy in this case being notably different from other routes to these targets in not employing *L*-glutamate for construction of the tetrahydroisoquinoline subunit. In this



Scheme 54 Gurjar's synthesis of the schulzeine benzo[*a*]quinolizidine subunits. *Reagents and conditions:* (a) EDC, HOBt, CH₂Cl₂, 0 °C → rt, 15 h, 84%; (b) POCl₃, CHCl₃, 70 °C, 3 h; (c) NaCNBH₃, AcOH–CH₂Cl₂, 0 °C, 1 h; then aq. NaHCO₃, rt, 3 h, *cis*-**363** (26%, 2 steps), *trans*-**363** (39%, 2 steps); (d) H₂, Pd/C, Boc₂O, MeOH; (e) BnBr, Cs₂CO₃, BuNI, DMF, 0 °C, 1 h; (f) 3 M HCl–EtOAc, rt, 3 h, *cis*-**364** (84%, 3 steps), *trans*-**364** (84%, 3 steps).



Scheme 55 Gurjar's synthesis of the side chain common to schulzeine B and C. *Reagents and conditions:* (a) DBU, LiCl, CH₃CN, rt, 1 h, 95%; (b) (*S*)-(-)-BINAL-H (100 mol%), THF, -78 °C, 3 h, 84%, dr = 11 : 1; (c) MOMCl, DIPEA, rt, CH₂Cl₂, 2 h, 97%; (d) H₂, Pd(OH)₂/C, EtOAc, 6 h, 80%; (e) IBX, DMSO, rt, 3 h; (f) NaClO₂, NaH₂PO₄·2H₂O, *t*-BuOH-H₂O, 0 °C, 2 h, 2-methyl-2-butene, 88% (2 steps).

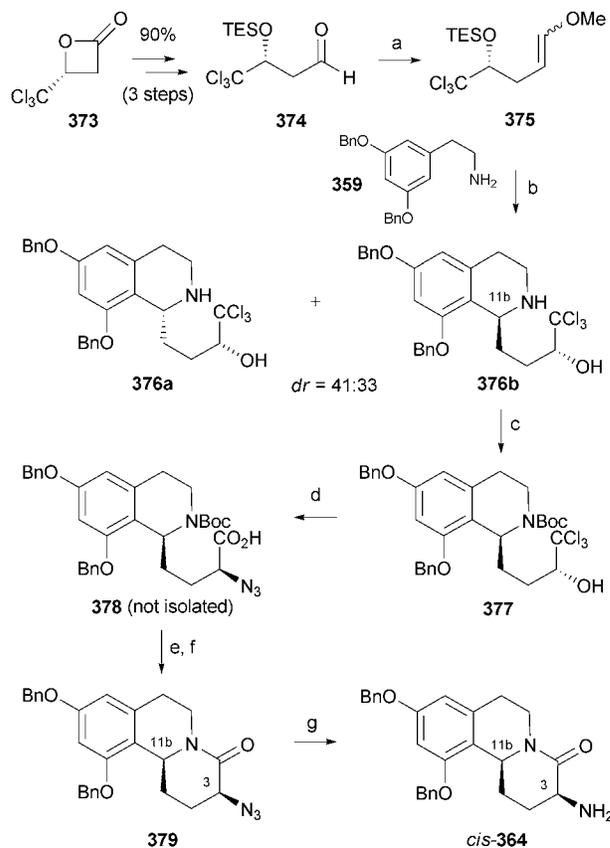


Scheme 56 Gurjar's total synthesis of (-)-schulzeine B. *Reagents and conditions:* (a) EDC, HOBT, Et₃N, CH₂Cl₂, rt, 15 h, 72%; (b) TMSI, CH₂Cl₂-CH₃CN, 0 °C, 1 h, 47%; (c) SO₃·pyr, DMF, rt, 30 h; then NaHCO₃, 96% (d) H₂, Pd/C, MeOH, rt, 3 h, 83%.

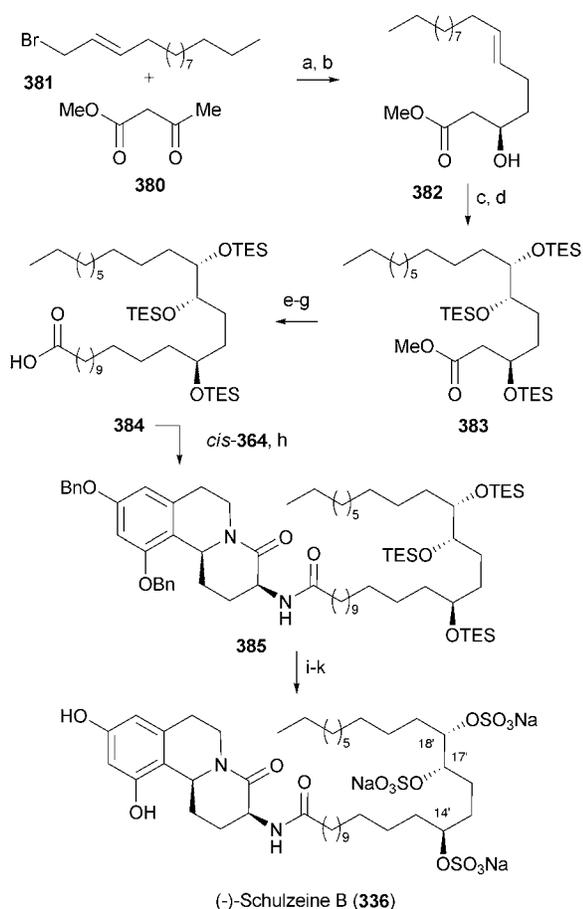
approach, trichloromethyl-β-lactone (**373**) was converted *via* a straightforward, four-step protocol to vinyl ether **375** which, through recourse to a Corey-Link reaction (**377** → **378**),¹⁷⁴ was employed as a bis-homoserine aldehyde equivalent.¹⁷⁵ Cyclization of **375** with phenylethylamine **359** under Pictet-Spengler conditions (AcOH, 100 °C) proceeded in high yield to provide **376a** and **376b**, albeit with negligible diastereoselectivity. After chromatographic separation, these tetrahydroisoquinolines were individually carried forward to tricyclic subunits of schulzeines C

and B, respectively. In this case of schulzeine B, *N*-protection of **376b** and treatment NaOH/NaN₃ led to the formation of α-azido acid **378** which, without isolation, was converted to *trans*-benzo[*a*]quinolizidine **379**. Selective reduction of the azide was now carried out using Ph₃P and provided *cis*-**364** suitably protected for coupling with the side chain.

Commencing with the alkylation of methyl acetoacetate (**380**) with allylic bromide **381**, Romo's preparation of the schulzeine B/C side chain **384** entailed introduction of the C14' stereogenic center, through Noyori hydrogenation of the resulting β-keto ester and dihydroxylation of compound **382** (Scheme 58). Employing Sharpless asymmetric conditions, dihydroxylation of this substrate proceeded with high diastereoselectivity to establish the C16'/17' diol system. After persilylation of the triol generated in this reaction, the remainder of the C₂₈ chain was introduced through partial reduction of the ester, Wittig olefination and simultaneous hydrogenation/hydrogenolysis to yield **384**. Carbodiimide-mediated coupling of this carboxylic acid with amine *cis*-**364** proceeded in moderate yield to provide **385**. Transformation to (-)-schulzeine B (**336**) was then accomplished through removal of the triethylsilyl groups, persulfation using pyridine-sulfur trioxide complex and hydrogenolysis. Following



Scheme 57 Romo's synthesis of the schulzeine benzo[*a*]quinolizidine subunits. *Reagents and conditions:* (a) Ph₃P⁺ CH₂OMeI⁻, LiHMDS, THF, 84%, *Z/E* = 3 : 2; (b) **359**, AcOH, 100 °C, 24 h, **376a** (41%), **376b** (33%); (c) Boc₂O, CH₂Cl₂, Et₃N, 92%; (d) NaOH, NaN₃, DME-H₂O (1 : 1); (e) TFA, CH₂Cl₂, 0 °C; (f) Et₃N, DPPA, DMF, 47% (3 steps, 1 pot); (g) PPh₃, THF-H₂O, 93%.



Scheme 58 Romo's total synthesis of (–)-schulzeine B. *Reagents and conditions:* (a) NaH, *n*-BuLi, THF 76%; (b) (*R*)-(BINAP)RuBr₂ (5 mol%), H₂ (6 atm), MeOH, 80 °C, 10 min, 70–90% (99% brsm), dr > 95 : 5; (c) AD-mix α , MeSONH₂, *t*-BuOH–H₂O (1 : 1), 76% (95% brsm), dr > 19 : 1; (d) TESCl, CH₂Cl₂, Et₃N, 98%; (e) DIBAL-H, CH₂Cl₂, –78 °C, 97%; (f) BnO₂C(CH₂)₉CH₂PPH₃Br, KHMDS, THF, 95%; (g) H₂, Pd/C, 2,6-lutidine, EtOH, 95%; (h) EDCI, HOBT, Et₃N, DMF, 65%; (i) AcOH, THF–H₂O, 99%; (j) SO₃·pyr, DMF, 0 → 23 °C; (k) H₂, Pd/C, MeOH, 82% (2 steps).

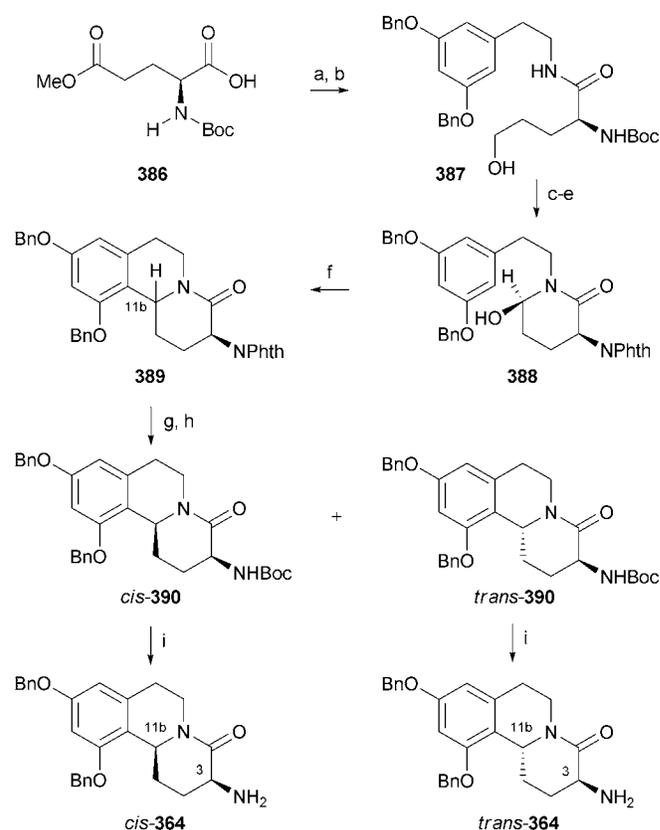
the same sequence of steps, but employing *trans*-364 in place of *cis*-364, (+)-schulzeine C (335) was also prepared.

The first total synthesis of schulzeine A (334) was reported in 2009 by Wardrop and Bowen, who in addition to preparing schulzeine B (336) and C (335), demonstrated that the absolute configuration originally assigned to the C20' stereocenter of this natural product should be revised (Schemes 59–61).¹⁷⁶ While employing L-glutamate in the preparation of the benzo[*a*]quinolizidine subunit (as in the work of Kuntiyong and Gurjar), Wardrop's overall synthetic strategy differs from that of Gurjar and Romo in that introduction of the C17' and C18' stereogenic centers occurs after coupling of the alkaloid and side chain subunits.

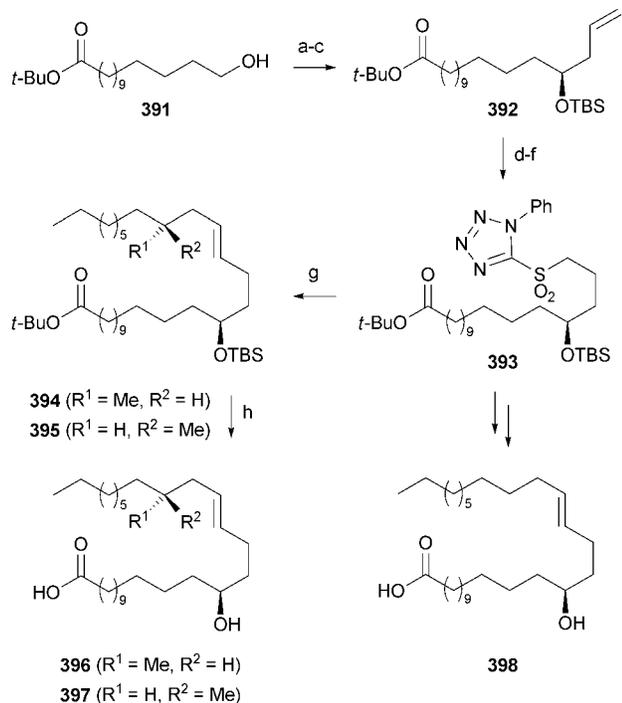
Preparation of the aminobenzo[*a*]quinolizidine subunits present in schulzeine A, B and C commenced with the assembly of cyclization precursor 388 from L-glutamic acid γ -methyl ester 386 and 2-[3,5-bis(benzyloxy)phenyl]ethylamine (359) (Scheme 59). Unanticipated interference of the *N*-Boc group during the

subsequent Pictet–Spengler reaction mandated the exchange of this carbamate for a more robust *N*-phthalimide group. This task was accomplished by treatment of 387 with ethereal HCl and *N*-phthaloylation of the resulting primary amine with *N*-(ethoxycarbonyl)phthalimide. Oxidation of the primary alcohol, under Swern conditions, then generated α -hydroxy- δ -lactam 388, which arises from cyclization of the unstable aldehyde. Exposure of 388 to a range of Pictet–Spengler promoters, including BF₃·Et₂O, acetic or trifluoroacetic acid, led to the selective formation of *cis*-389 (C11b-H₉) with a *cis/trans* selectivity ranging from 2 : 1 to 9 : 1. While *cis* and *trans*-389 proved to be inseparable by flash chromatography, diastereomer separation was achieved after hydrazinolysis of the phthalimide group and formation of carbamates *cis* and *trans*-390. Treatment of these individual diastereomers with TFA then afforded *trans*- and *cis*-364, the benzo[*a*]quinolizidine subunits required for the synthesis of schulzeines A and C, and schulzeine B, respectively.

Wardrop's construction of the two distinct schulzeine C₂₈ trisulfate sides began from ω -hydroxy ester 391, which was converted to 392 through a sequence of oxidation, Keck enantioselective allylation and silylation (Scheme 60). After introduction of a 1-phenyl-1*H*-tetrazol-5-yl sulfone group, assembly



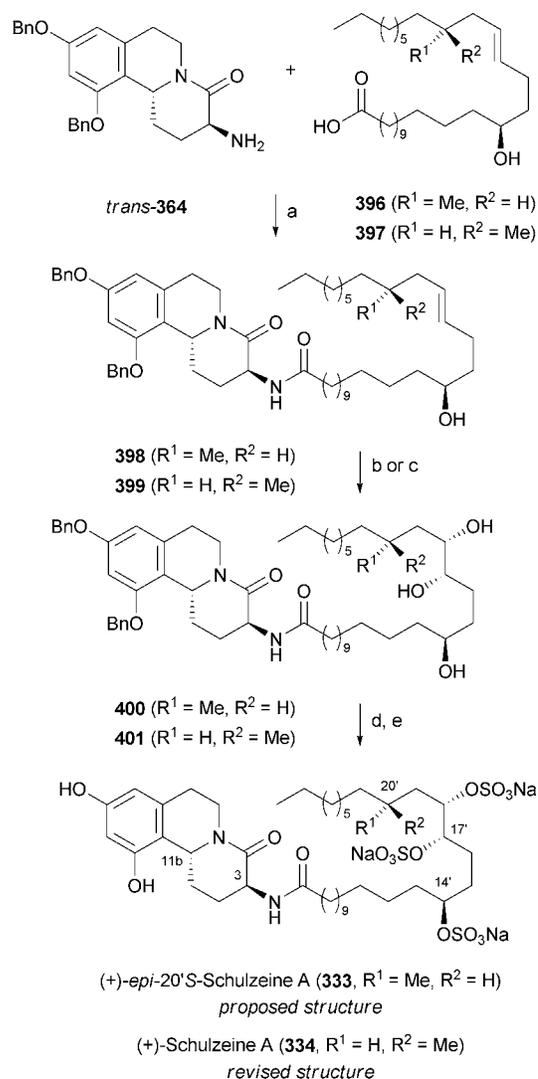
Scheme 59 Wardrop's synthesis of the schulzeine benzo[*a*]quinolizidine subunits. *Reagents and conditions:* (a) *i*-BuOCOCI, NMM, CH₂Cl₂, DMF, –35 °C, 15 min; then 2-[3,5-bis(benzyloxy)phenyl]ethylamine, DMF, CH₂Cl₂, rt, 12 h; (b) NaBH₄, LiCl, THF, MeOH, 0 °C, 5.5 h; (c) 1 M HCl in Et₂O, CH₂Cl₂, rt, 2 h; (d) PhthNCOOEt, Na₂CO₃, THF, rt, 16 h; (e) Swern oxidation; (f) AcOH, CH₂Cl₂, rt, 2 h; (g) H₂NNH₂, EtOH, rt, 24 h; (h) Boc₂O, CH₂Cl₂, rt, 1 h, *cis*-390 (57%), *trans*-390 (26%); (i) TFA, CH₂Cl₂, 0 °C, 1 h, *cis*-364 (98%), *trans*-364 (85%).



Scheme 60 Wardrop's synthesis of the schulzeine A, B and C side chain subunits. *Reagents and conditions:* (a) Moffat–Swern oxidation; (b) (*R*)-(+)-1,1'-bi-2-naphthol (10 mol%), Ti(*O-i-Pr*)₄, 4 Å MS, CH₂Cl₂, reflux 1 h; then -78 °C, allyl tri-*n*-butylstannane, -20 °C, 5 d, 75% (2 steps), ee > 98%; (c) TBSCl, imidazole, CH₂Cl₂, 0 °C → rt, 18 h, 97%; (d) 9-BBN, THF, 0 °C → rt, 14 h; then H₂O₂, NaOH, B(OH)₃, rt, 1 h, 94%; (e) 1-phenyl-1*H*-tetrazole-5-thiol, DIAD, Ph₃P, THF, 0 °C → rt, 12 h, 91%; (f) (NH₄)₆Mo₇O₂₄·4H₂O (20 mol%), H₂O₂, EtOH, 0 °C → rt, 14 h, 99%; (g) KHMDS, DME, -60 °C, 30 min, then (*S*)-3-methylundecanal, -60 °C → rt, 16 h, **394** (45%, dr > 20 : 1); KHMDS, DME, -60 °C, 30 min, then (*R*)-3-methylundecanal, -60 °C → rt, 16 h, **395** (75%, dr > 20 : 1); (h) HF, TBAF, THF, rt, 48 h; 1 M NaOH–EtOH–THF, reflux, 48 h, **396** (70%), **397** (84%).

of the complete lipid subunit was accomplished using the Julia–Kocienski protocol. In the case of schulzeine A (**332**, proposed), this involved reaction of the anion of **393** with (*S*)-3-methylundecanal to give **394**, while **398**, the less complex side chain of schulzeine B (**336**) and C (**335**), was generated from **393** and undecanal. In each case, alkene formation proceeded with high selectivity for the required *E*-isomer. Deprotection of **394**, through sequential exposure to HF–TBAF and aqueous NaOH, then provided carboxylic acid **396**. Compound **397**, the C20' epimer of **396**, was subsequently prepared in similar fashion from (*R*)-3-methylundecanal.

Synthesis of the compound proposed by Fusetani to be schulzeine A (**333**, 20'-*epi*-schulzeine A) was now completed by first coupling fragments *trans*-**364** and **396** to provide **398** (Scheme 61). Introduction of the C17'/18' diol was carried out *via* reagent-controlled Sharpless asymmetric dihydroxylation, which provided **400** with reasonable diastereoselectivity. Persulfation of this triol, using sulfur trioxide–pyridine complex in DMF, and hydrogenolysis of the benzyl ethers now provided 20'-*epi*-schulzeine A (**333**). At this stage, discrepancies between the ¹H and ¹³C NMR spectral data of this material and those collected from the



Scheme 61 Wardrop's total synthesis of (+)-schulzeine A and (+)-*epi*-20'*S*-schulzeine A. *Reagents and conditions:* (a) (i) EDC, CH₂Cl₂, rt, 16 h, **398** (73%), **399** (80%); (b) AD-mix α, MeSO₂NH₂, *t*-BuOH–*t*-BuOMe–H₂O–THF (1 : 1 : 1 : 1), 0 °C, 18 h, **400** (83%, dr = 4 : 1); (c) AD-mix α, MeSO₂NH₂, *t*-BuOH–*t*-BuOMe–H₂O (1 : 1 : 1), 0 °C, 48 h, **401** (77%, dr = 91 : 9); (d) SO₃·pyr, DMF, rt, 2 h; (e) H₂, Pd/C, EtOH, rt, 8 h, **333** (88%, two steps); **334** (75%, two steps).

natural product suggested that the original stereochemical assignment at C20' required re-evaluation and prompted the authors to prepare the C20' epimer of **333**, *i.e.* schulzeine A (**334**). From (*S*)-3-methylundecanal, compound **332** was accessed by way of carboxylic acid **397**, alkene **399** and triol **401**. The ¹H and ¹³C NMR spectra of synthetic **333** were found to be consistent with those reported by Fusetani for natural schulzeine A, thus supporting the premise that the stereochemistry at C20' should be reassigned as the *R*-configuration.

Following the same strategy employed in the assembly of schulzeine A and its C20' epimer, the total syntheses of schulzeine B (**336**) and schulzeine C (**335**) were also completed. In the case of schulzeine B, this involved the use of amino-benzo[*a*]quinolizidine *cis*-**364**.

7 Conclusions

As is clear from this review, interest in the total synthesis of natural products which display anti- α -glucosidase activity has not waned in the last five years, reflecting the importance of such compounds in both medical and chemical research. With regard to alkaloid-based inhibitors, few natural product types have provoked such intense and sustained interest in their preparation, and while the majority of this work has been focused on the application and evaluation of synthetic methodology, an increasing number of studies employ total synthesis as a means to an end, beyond simply accessing the natural product. This focus on function rather than preparation has been particularly prevalent in the thiosugar area, where the therapeutic potential of compounds such as salicinol demands a deeper understanding of their mode of action.

Future goals for this field of research include the discovery, synthesis and development of new inhibitors, which display increased potency and, above all, inter-glycosidase selectivity. In this context, the schulzeines and related organosulfates are of particular interest in light of their biological activity and, as yet, unknown mode of action. In addition to providing a means with which to accomplish these goals, synthetic chemistry has also played a pivotal role in the structural determination of a number of natural products, including kotalanol, its de-*O*-sulfonated derivative and schulzeine A. The knowledge gained from the total synthesis of these and other natural product targets will continue to be of central importance in the future discovery and development of α -glucosidase inhibitors.

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