寄稿論文

Carbocyclization of Carbohydrates to Hydroxylated Cycloalka(e)nes

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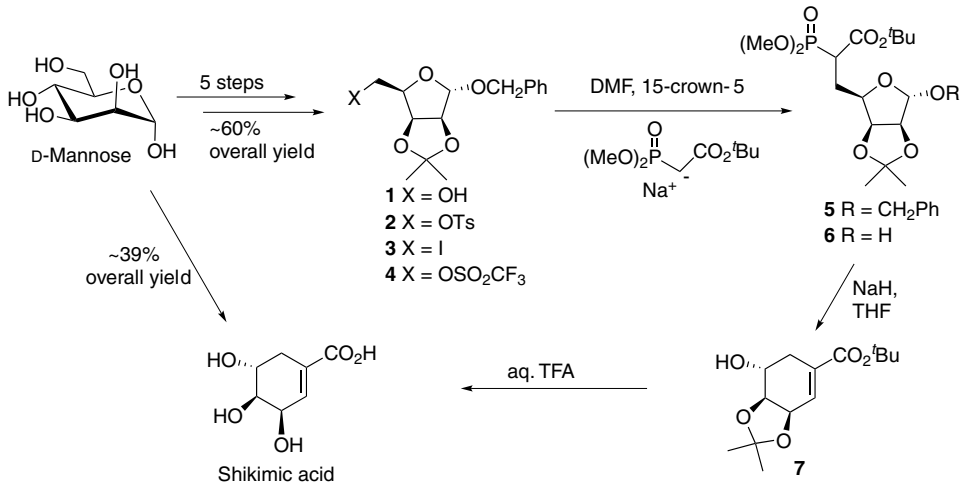
Abstract: Carbohydrates, inexpensive and rich in stereochemistry, are nature's gifts to the synthetic organic chemists. We have been conducting research on the carbocyclization of carbohydrates for many years, i.e. the conversion of simple, readily available monosaccharides into hydroxylated cycloalkanes and cycloalkenes with pharmaceutical potential. Several key reactions are presented in this Article to illustrate such facile transformation namely [π4s+π2s] cycloaddition - intramolecular nitrone-alkene and nitrile oxide-alkene cycloadditions, intramolecular direct aldol reaction and intramolecular Horner–Wadsworth–Emmons olefination. These protocols provide facile entries to 6 and 7-membered hydroxylated carbocycles in enantiomerically pure forms which then could be further elaborated into target molecules. Examples including calystegines, tropane alkaloid, cyclohexanyl and cyclohexenyl gabosines, cycloheptanones, valiolamine, validoxylamine G, pseudo-acarviosin, and a SGLT2 inhibitor are presented.

Keywords: carbohydrates, natural products, organic synthesis, pericyclic reactions, hydroxylated carbocycles

This review article describes our research efforts on finding a short, facile, and efficient way of transforming carbohydrates into hydroxylated carbocycles over a period of about 30 years. There are excellent reviews on the topic published elsewhere.[1]

The story begins when I was a postdoctoral fellow at Oxford working with Professor George Fleet in 1983. We were trying to synthesize shikimic acid from D-mannose using an intramolecular aldol condensation or a Wittig-type alkenation as the key step. Installing a phosphono-acetate moiety at the C-5 of the benzyl furanoside intermediate **1** to form the Wittig–Horner–Emmons precursor met with difficulty (Scheme 1).[2]

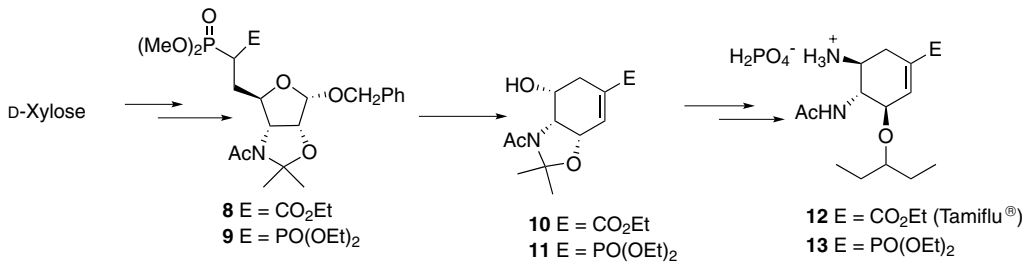
Simple S_N2 displacement reactions in carbohydrates are known to be sluggish/difficult due to the high concentration of oxygen functions (electron rich). Thus the derived standard electrophiles, 5-tosylate **2** and 5-iodide **3** were found to be inert towards substitution. We then attempted to use the 5-triflate **4** as a reactive leaving group (this was new at that time). Gratifyingly, the alkylation proceeded smoothly to give the Horner–Wadsworth–Emmons (HWE) alkenation precursor in a good yield. Subsequent unmasking the aldehyde function in **5** by hydrogenolysis afforded lactol **6** that was treated with base to give the cyclohexene motif, the protected shikimic acid **7**. Acid catalysed removal of the blocking groups in **7** furnished shikimic acid in an excellent overall yield.[2]



Scheme 1. Synthesis of shikimic acid

Up to date, this intramolecular HWE alkenation is still one of the most powerful strategies for the carbocyclization of sugar molecules. A notable example of using this strategy was demonstrated by Fang and co-workers[3] to synthesize anti-viral agent Tamiflu® **12** and its more potent phosphonate analog **13** in a similar manner (Scheme 2).

* Tamiflu® is a registered trademark of F. Hoffmann-La Roche, Ltd.



Scheme 2. Synthesis of Tamiflu® and its phosphonate analog

The reasons for researching on carbocyclization of carbohydrates are attributed to the fact that many biologically active molecules are hydroxylated cycloalkanes/alkenes. Carbohydrates are obvious starting materials that offer the most facile and economical way to approach these highly oxygenated carbocycles with defined stereochemistry.

Some hydroxlated cyclohexanes and cyclohexene are listed in Figure 1. They display a wide plethora of bioactivities including antibiotic, antitumor, antiviral, glycosidase inhibitory activities.

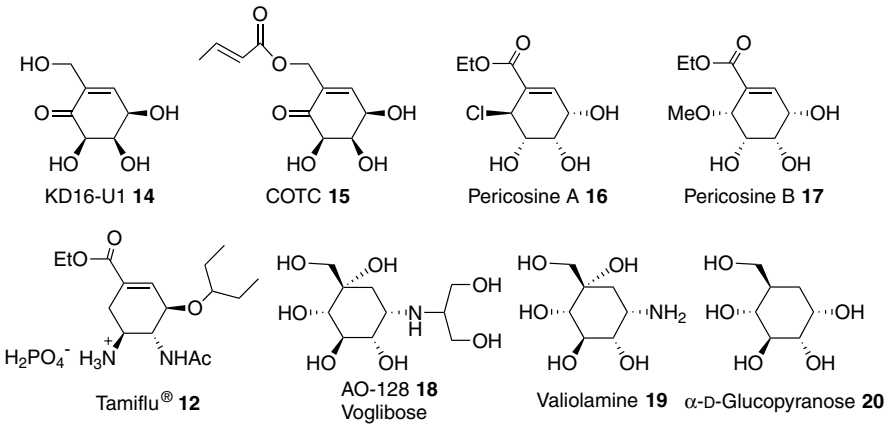


Figure 1. Bioactive hydroxylated cyclohexanes and cyclohexenes

Calystegines,[4] displayed specific glycosidase inhibition, are a group of bicyclic heterocycles which are in equilibrium with the open chain form, a hydroxylated gamma-amino cycloheptanone that are potentially accessible from carbohydrates (Figure 2).

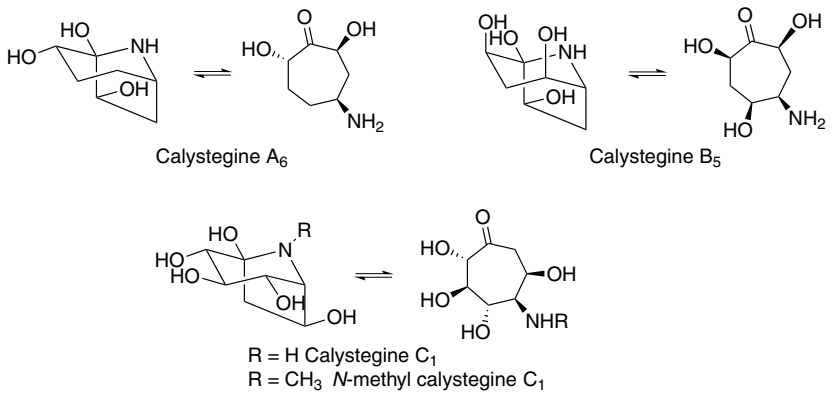


Figure 2. Structures of some calystegines

Gabosines are a group of hydroxylated cyclohexanones/cyclohexenones that display antibiotic, anticancer, and DNA binding properties (Figure 3).[5] All these compounds should in theory be approachable from sugars, but how could we effect the carbocyclization efficiently?

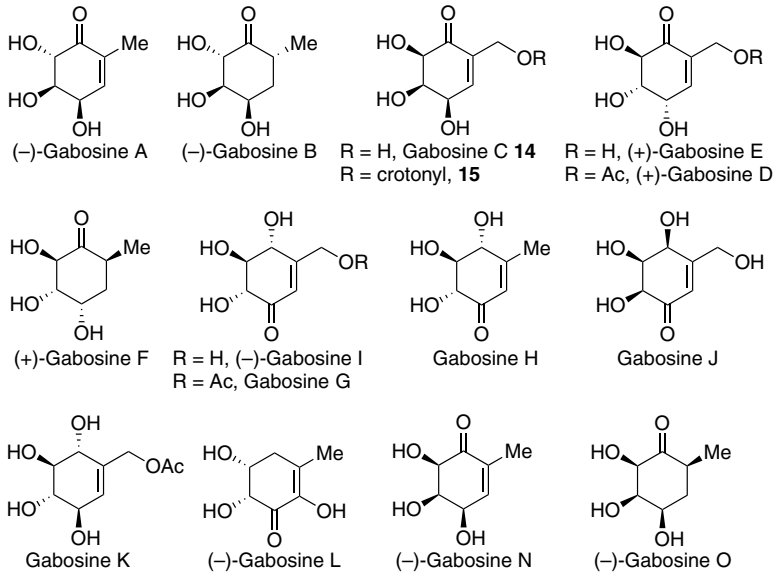


Figure 3. Gabosine family

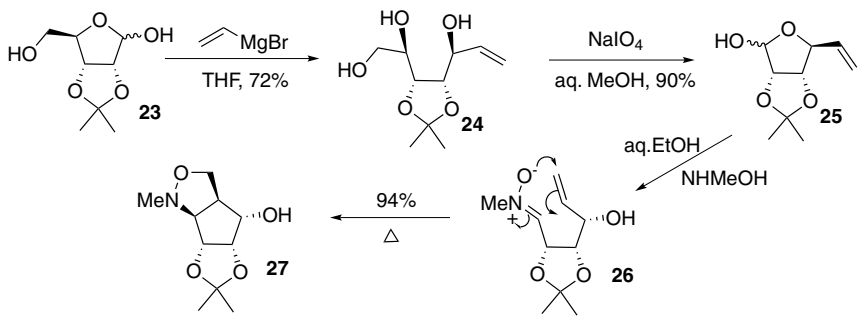
Towards that end, we have been investigating the following strategies for the carbocyclization of sugars:

1. Carbocyclization of Carbohydrates *via* an Intramolecular Nitrone-Alkene Cycloaddition (INAC)
2. Carbocyclization of Carbohydrates *via* an Intramolecular Nitrile Oxide-Alkene Cycloaddition (INOAC)
3. Carbocyclization of Carbohydrates *via* an Intramolecular Direct Aldol Addition of Sugar Diketone
4. Carbocyclization of Carbohydrates *via* an Intramolecular Horner–Wadsworth–Emmons (HWE) Olefination

From 1984, I started my independent research career at the University of Manchester and began to investigate the construction of carbocycles using an INAC reaction as the key step.

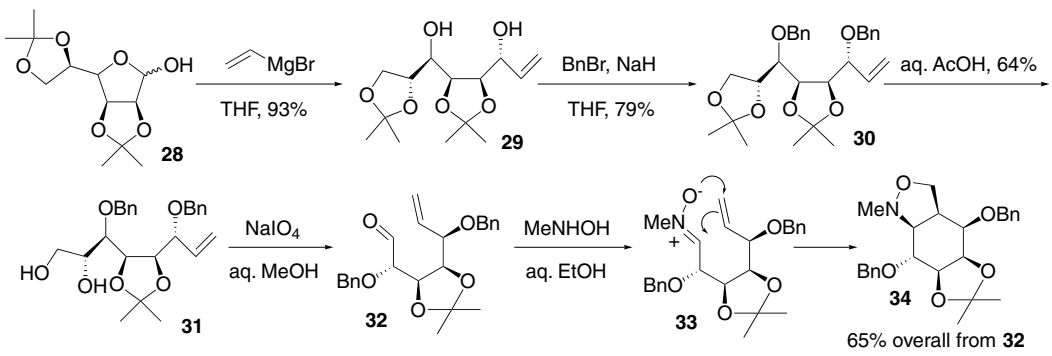
1 Carbocyclization of Carbohydrates *via* an Intramolecular Nitrone-Alkene Cycloaddition (INAC)

2,3-*O*-Isopropylidene D-ribose **23** underwent a chelation controlled Grignard vinylation to give triol **24** (Scheme 3). Glycol cleavage oxidation of the vicinal diol in **24** affoded lactol **25** which on heating with *N*-methyl hydroxylamine furnished a hydroxylated cyclopentane **27** smoothly. This is an extremely short approach towards 5-membered carbocycles and its application to the syntheses of carbocyclic nucleosides should have received more attention.[6]



Scheme 3. Synthesis of a functionalized cyclopentane **27** from ribose

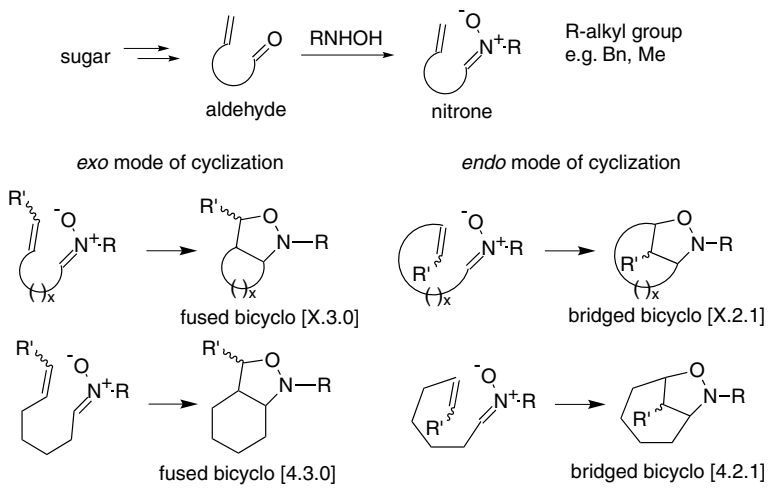
On the other hand, chelation controlled vinylation of diacetone mannose **28** gave allyl alcohol **29** stereoselectively which was protected as benzyl ether **30** (Scheme 4). Regioselective mild acid hydrolysis of the terminal acetonide was feasible as the *O*-8 was the least hindered and therefore protonated first. The resultant diol **31** was oxidatively cleaved to afford aldehyde **32** which was reacted with *N*-methyl hydroxylamine to give nitrone **33**. INAC occurred smoothly on heating to give cyclohexane **34** in good yield. In both cases, the new C–N bond is *anti* to the *O*-2 stereochemistry and the ring fusion is *cis*.[6]



Scheme 4. Synthesis of a functionalized cyclohexane **34** from mannose

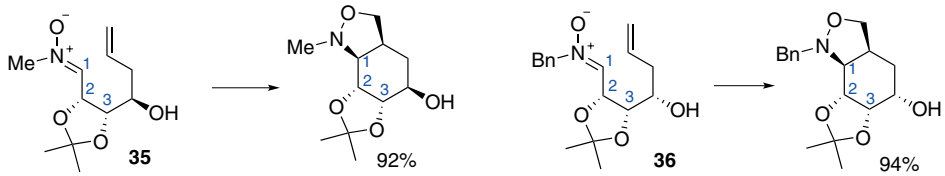
We had more interests in this INAC reaction because we reasoned that it could be controlled to provide 7-membered carbocycles. When a sugar molecule was elaborated to have a terminal alkene, on reaction with *N*-alkyl hydroxylamine, there would be two possible modes of INAC cyclization, the *exo* or the *endo* mode (Scheme 5), which leads to either a fused or a bridged isoxazolidine, respectively.[7] To be specific, a hept-6-

enose would provide either a fused bicyclo[4.3.0] system, i.e. a cyclohexane skeleton from an *exo*-mode or a bridged bicyclo[4.2.1] system, i.e. a cycloheptane skeleton from an *endo*-mode INAC cyclization. We were particularly intrigued by the potential formation of 7-membered carbocycles as there are few synthetic strategies towards cycloheptanes whereas the synthetic methods for the construction of 5- and 6-membered carbocycles are plentiful.



Scheme 5. INAC mode of cyclization

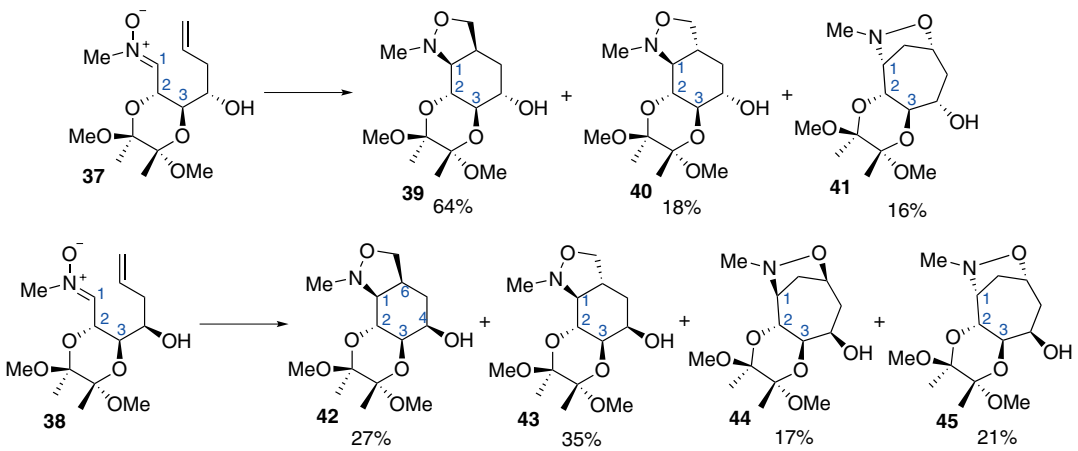
We realised that the formation of a cyclohexane skeleton *via* the *exo*-mode of cyclization of hept-6-enose is the usual regioselectivity outcome with conventional protecting groups like benzyl ether, silyl ether, acetonide, and esters *etc*. For examples, nitrone **35** and **36**, both with a *cis*-diol acetonide protecting group gave cyclohexane rings in high yields (Scheme 6).[8] The stereochemistry of 4-OH apparently had no effect on the regioselectivity.



Scheme 6. INAC of hept-6-enoses with a *cis*-acetonide

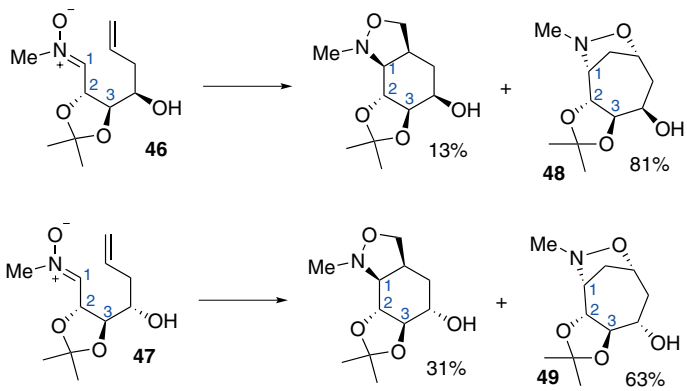
We reasoned that the mode of cyclization might be controlled by the blocking groups as they affect the orbital overlap between the nitrone and the alkene. Thus we investigated the effect of *trans*-diacetal blocking group on the regioselectivity of hept-6-enose. Epimeric nitrones **37** and **38** were readily prepared from D-arabinose involving glycosidation with benzyl alcohol, diacetalisation, debenzylation, Grignard allylation, glycol cleavage oxidation and reaction with *N*-methyl hydroxylamine. Interestingly, nitrones **37** and **38** with a *trans*-diacetal blocking group (the diol moiety is *trans*) afforded *endo*-mode of cyclization products **41**, **44**, **45**, i.e., cycloheptane rings, for the first time (Scheme 7). Another notable feature of this reaction is that a *trans*-fused

bicyclo[4.3.0] system, i.e. cyclohexane **40** and **43** were formed. The lower yield of *cis*-fused **42** and higher yield of *trans*-fused **43** is probably attributed to the 1,3 diaxial interaction between 4-OH and the 6-hydroxymethyl in **42**, this steric interaction is absent in the *cis*-cycloadduct **39**. The rigidity of the diacetal ring requires 2-O and 3-O in the *trans*-diequatorial dispositions, thus 4-OH and the 6-hydroxymethyl in **42** must be axial.[8]



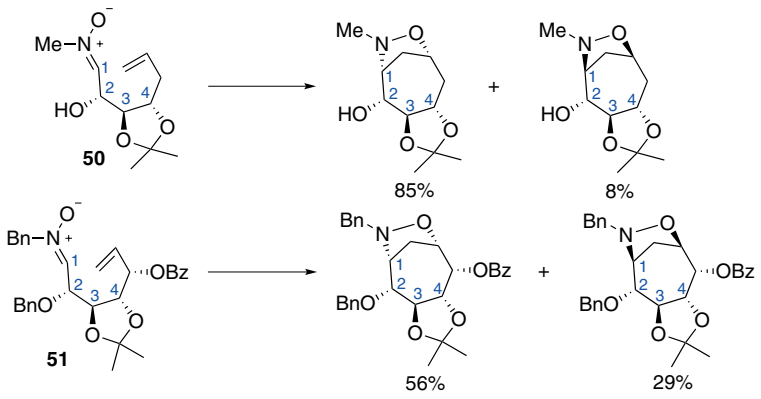
Scheme 7. INAC of hept-6-enoses with a *trans*-diacetal

We reasoned that cycloheptane ring might be more accommodating than 6-membered rings as far as ring strain is concerned. We therefore went on to study the effect of an acetonide with a *trans*-diol blocking group on the regioselectivity of nitrone cycloaddition of hept-6-enose (Scheme 8). Nitrones **46** and **47** with an acetonide of *trans*-2,3-diol provided *endo*-cycloadducts **48** and **49** as the major products for the first time.[9]



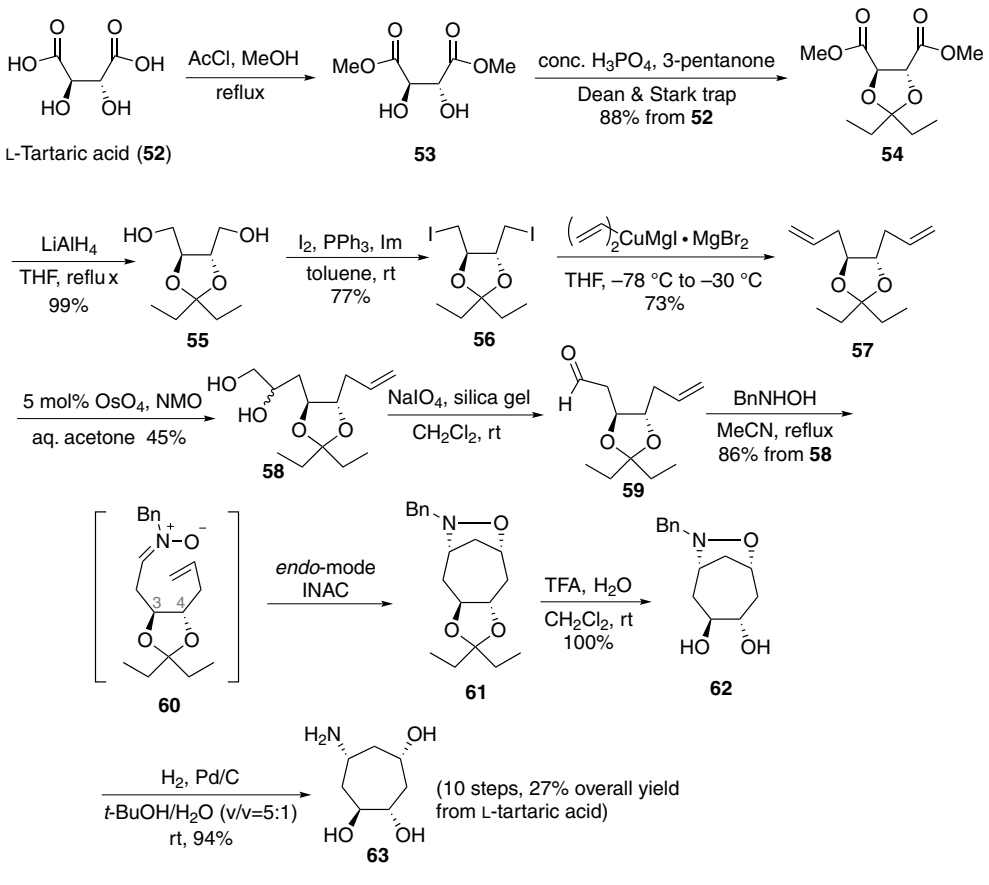
Scheme 8. INAC of hept-6-enoses with a 2,3-*trans*-acetonide

Hept-6-enose nitrones **50** and **51** with a 3,4-*trans*-acetonide were even more remarkable as only the *endo*-mode cycloheptanes were harvested in good yields (Scheme 9).[10]



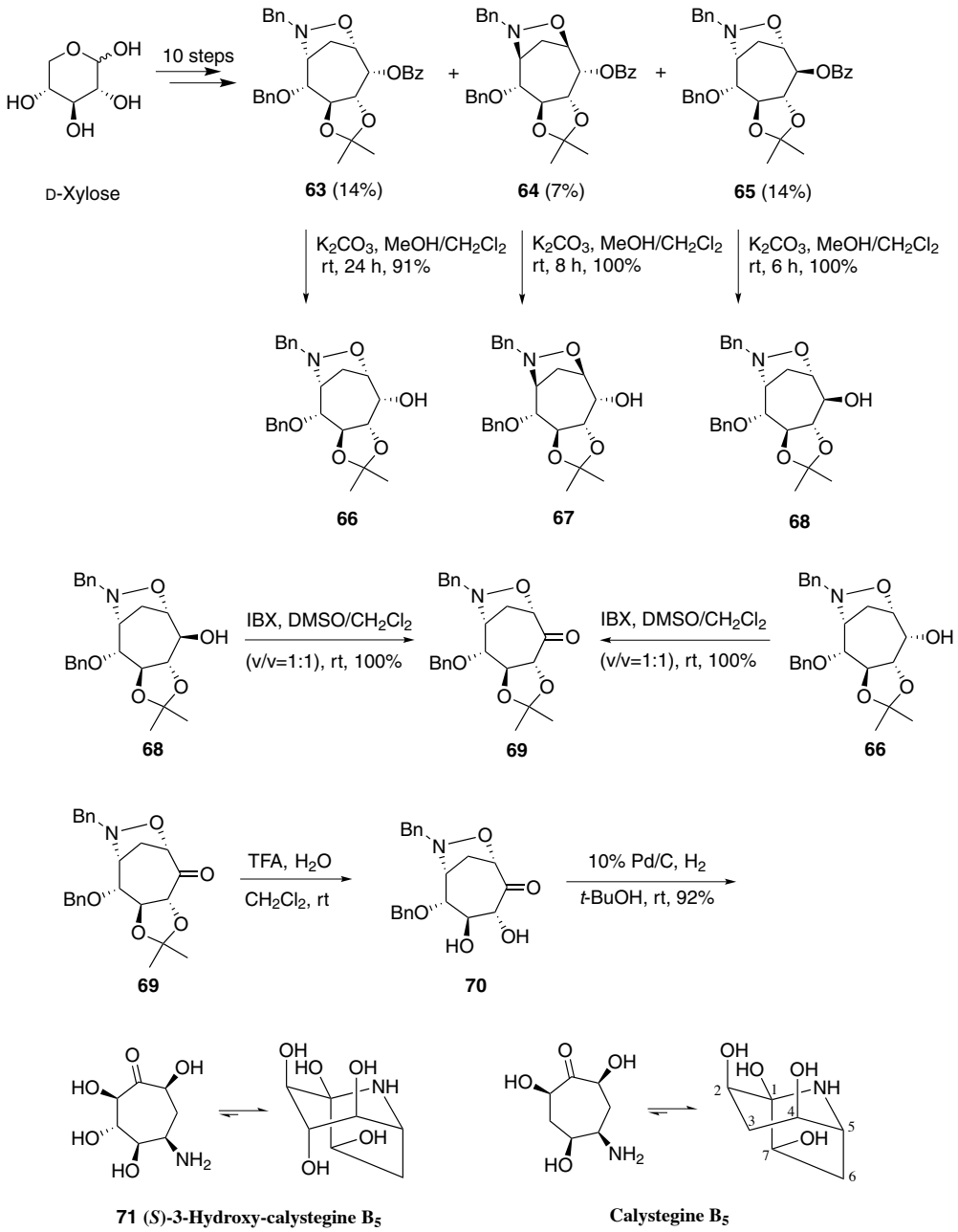
Scheme 9. INAC of hept-6-enoses with a 3,4-*trans*-acetonide

We were wondering if the stereochemistry of the C-2/C-5 hydroxyl groups might affect the regioselectivity of the INAC reactions. We thus constructed a hept-6-enose nitrone **60** with only a 3,4-*trans*-acetonide from L-tartaric acid using standard reactions (Scheme 10). Only a cycloheptane ring **61** was obtained, thereby confirming that the *endo*-mode of cyclization was controlled by the *trans*-acetonide ring.[11]



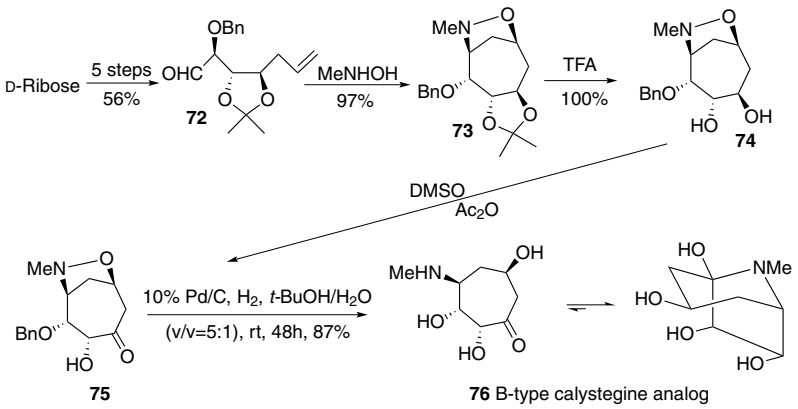
Scheme 10. INAC of hept-6-enose with only a 3,4-*trans*-acetonide

Since we have established that 7-membered cycloheptanes can be accessed *via* a *trans*-acetonide directed *endo*-selective INAC reactions of hept-6-enoses, we set out to synthesize calystegine analogs. In this way, D-xylose was transformed into cycloheptanes **63**, **64**, **65** with a 3,4-*trans*-acetonide (Scheme 11). Debenzoylation afforded the corresponding alcohols in which **66** and **68** were oxidized to the same ketone **69**. Acidic deacetonation of **69** followed by global hydrogenolysis furnished (*S*)-3-hydroxy-calystegine B_5 **71**.[10] We found that *tert*-butanol was a good solvent for hydrogenolysis of a *N*-benzyl group as no side products from *N*-alkylation was possible.



Scheme 11. Synthesis of a calystegine B_5 analog

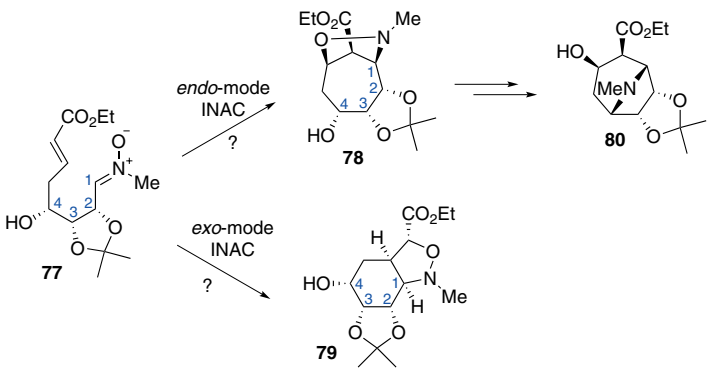
On the other hand, D-ribose was converted into aldehyde **72** which underwent *trans*-acetonide directed *endo*-selective INAC reaction to give cycloheptane **73** in an excellent yield (Scheme 12). Acid hydrolysis of the acetonide ring produced the diol **74** which underwent steric controlled regio-selective oxidation of the less hindered alcohol to give ketone **75**. Hydrogenolysis of the N–O bond afforded a B-type calystegine **76**.[10]



Scheme 12. Synthesis of a B-type calystegine analog

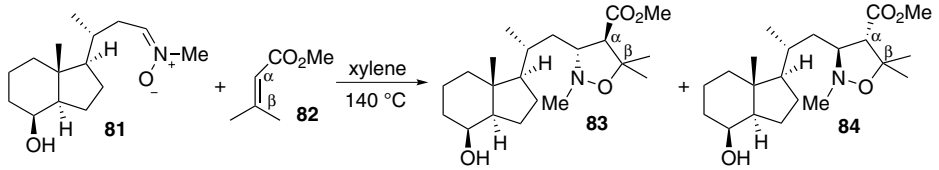
Then we investigated this *endo*-selective INAC approach towards syntheses of tropane alkaloid **90** and analogs.

(A) Strategy towards tropane alkaloid 1: INAC of a Nitrone with a 2,3-*cis*-Isopropylidene as Blocking Group and an α,β-Unsaturated Ester as Dipolarophile



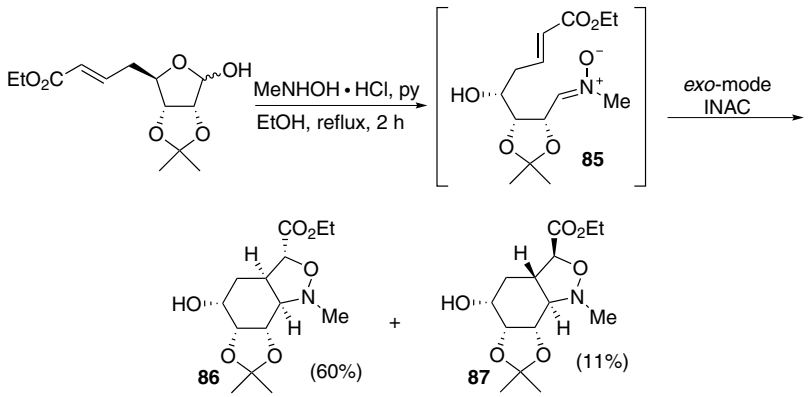
Scheme 13. Orbital controlled synthetic plan towards tropane alkaloid

Since the alkene moiety in **77** is an electrophilic alkene whereas the alkenes used in our INAC cyclization mode studies were simple nucleophilic alkenes, we were hoping that the electrophilic alkene of the enoate group in **77** might cause an *endo*-selective INAC reaction attributable to HOMO–LUMO reasons (Scheme 13). This proposal was supported by a precedent[12] that in the intermolecular nitrone-alkene cycloaddition of α,β-unsaturated ester **82**, and nitrone **81**, the new C–O was installed on the β-carbon in cycloadducts **83** and in **84** (Scheme 14). If this were applied to our INAC case, the *endo*-mode cyclization would have taken place. We were excited with this precedent and therefore proceeded with the synthesis.



Scheme 14. Intermolecular cycloaddition of nitrone **81** and enoate **82**

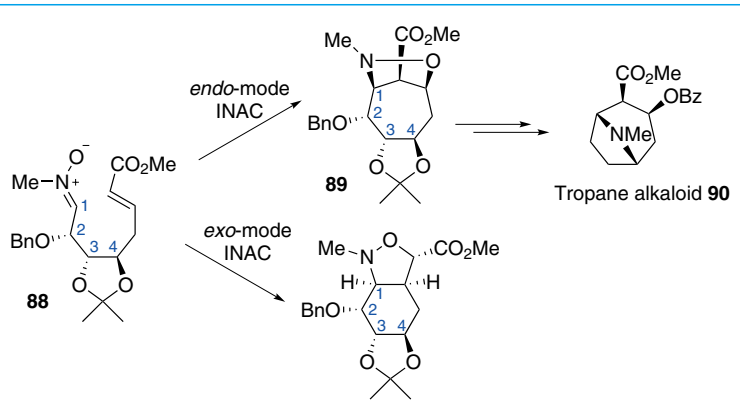
To our disappointment, the INAC of nitrone **85** produced only *exo*-mode cycloadducts **86** and **87**, 6-membered carbocycles. Hence it appears that steric control is more important than electronic control for the regioselectivity (*exo* versus *endo*) of INAC reactions of hept-6-enoses (Scheme 15).[11]



Scheme 15. INAC of enoate with a *cis*-acetonide

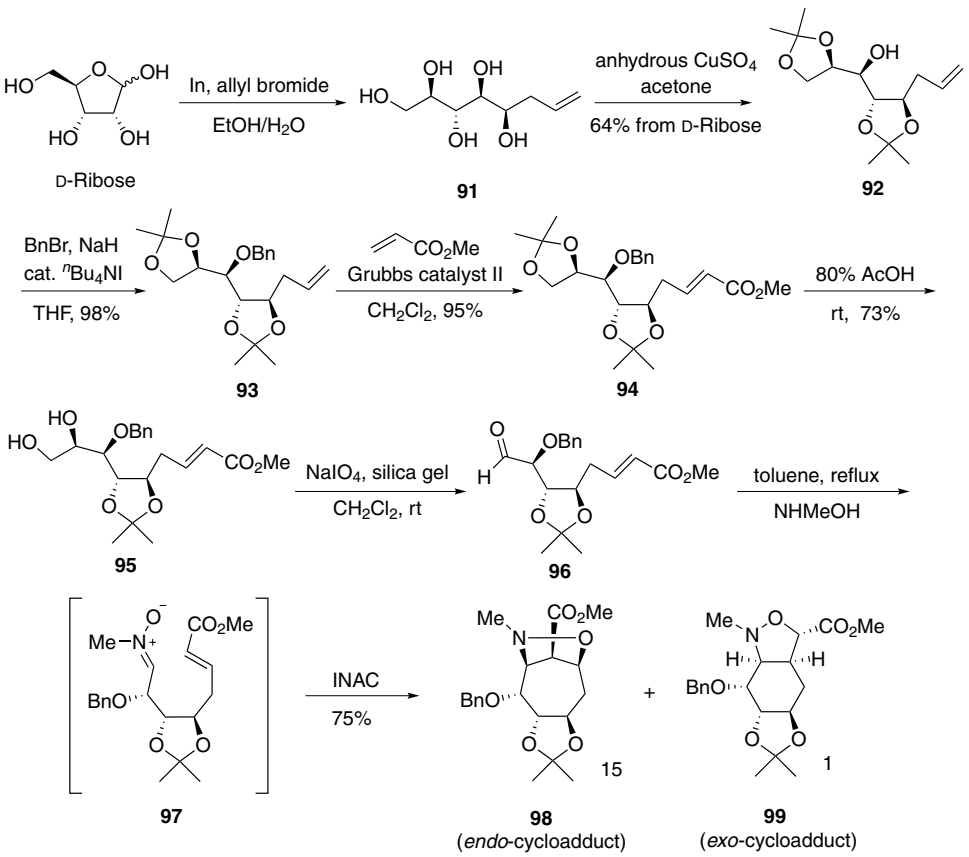
(B) Strategy towards tropane alkaloid 2: INAC of a Nitrone with a 3,4-*trans*-Isopropylidene as Blocking Group and an α,β-Unsaturated Ester as Dipolarophile

Since we had shown that 3,4-*trans*-acetonide would direct an *endo*-selective mode of cyclization, we devised a synthetic route towards cocaine based on this key step as summarised in Scheme 16.



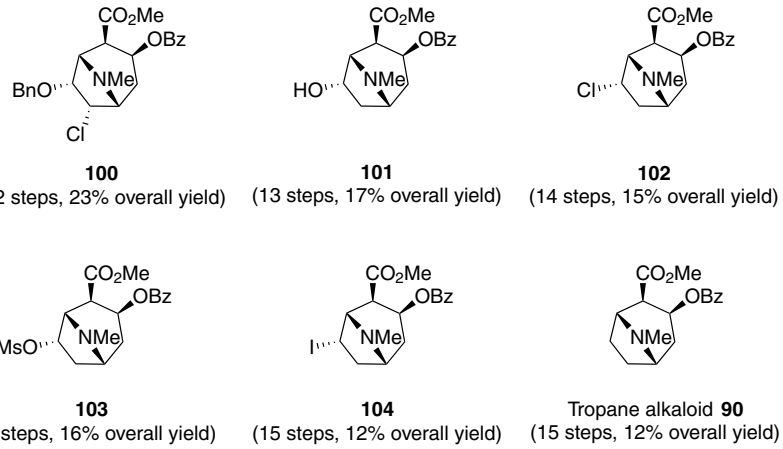
Scheme 16. Steric controlled synthetic plan towards tropane alkalovid **90**

Capitalising from our studies that 3,4-*trans*-acetonide would produce cycloheptane ring on INAC reactions of hept-6-enoses, we proceeded to prepare the nitrone **97** from ribose.[13] The known allyl alcohol **91** was readily obtained from D-ribose *via* a steric-controlled allylation (Scheme 17). Thermodynamic acetonation of **91** formed the 7,8-*O*-isopropylidene first as the primary 8-alcohol was the most reactive of all. Then an acetonide was formed between *O*-4,5 instead of *O*-5,6 because the substituents on the acetonide ring **92** were *trans* to each other. The diacetonide **92** was then transformed into diol **95** without incident. Glycol cleavage oxidation of **95** with silica supported $NaIO_4$ furnished aldehyde **96** smoothly. This solid-phase $NaIO_4$ reagent[14] is highly recommended as the operation is very simple and the aldehyde harvested is usually un-hydrated. INAC reaction of **97** did produce the desired cycloheptane derivative **98** as the major product.[13]



Scheme 17. INAC synthetic route towards tropane alkaloid

As the cycloheptane skeleton was installed correctly, cycloadduct **98** was converted into natural tropane alkaloid **90** and its analogs **100**–**104** as shown in Figure 4.[13]



100
(12 steps, 23% overall yield)

101
(13 steps, 17% overall yield)

102
(14 steps, 15% overall yield)

103
(14 steps, 16% overall yield)

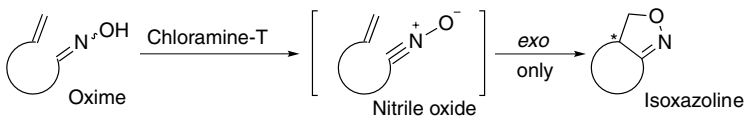
104
(15 steps, 12% overall yield)

Tropane alkaloid **90**
(15 steps, 12% overall yield)

Figure 4. Tropane alkaloid **90** and its analogs

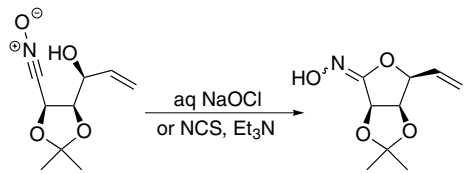
2 Carbocyclization of Carbohydrates *via* an Intramolecular Nitrile Oxide-Alkene Cycloaddition (INOAC)

The use of chloramine-T in the conversion of ene-sugar oxime into a nitrile oxide and its subsequent INOAC reaction is known.[15] This cycloaddition shown in Scheme 18 can only be *exo*-mode as the *endo*-mode of cyclization would produce an impossible C=N bond at the bridge head position (Bredt's rule).[16]



Scheme 18. Intramolecular nitrile oxide-alkene cycloaddition (INOAC)

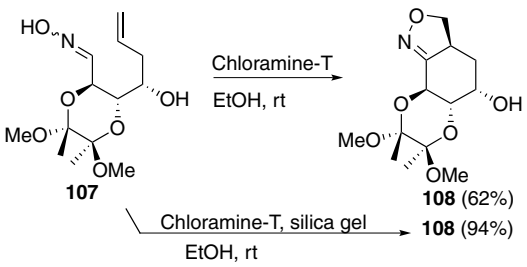
Common chemicals for the transformation of oxime into nitrile oxide include NaOCl, NaOCl/NEt_3 and *N*-chorosuccinimde/NEt_3.[16] Under the basic conditions, the free hydroxyl group in nitrile oxide **105** would attack the nitrile carbon to give oximolactone **106** and failed to produce a carbocycle. The hydroxy groups of the sugar have to be protected in order to achieve satisfactory yields. Thus, providing a mildly acidic environment for the INOAC reactions is crucial in achieving a fruitful carbocyclization without the formation of oximolactone.



Nitrile oxide **105** Oximolactone **106**

Scheme 19. Formation of oximolactone under basic conditions

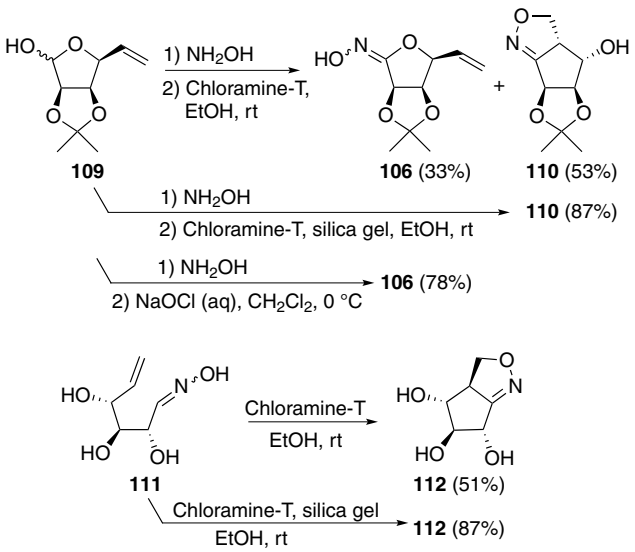
We found that adding flash chromatography silica gel to "buffer" the reaction medium dramatically increased the yield of the chloramine-T mediated INOAC reaction from 62 to 94% (Scheme 20).[17]



Scheme 20. INOAC with and without silica gel

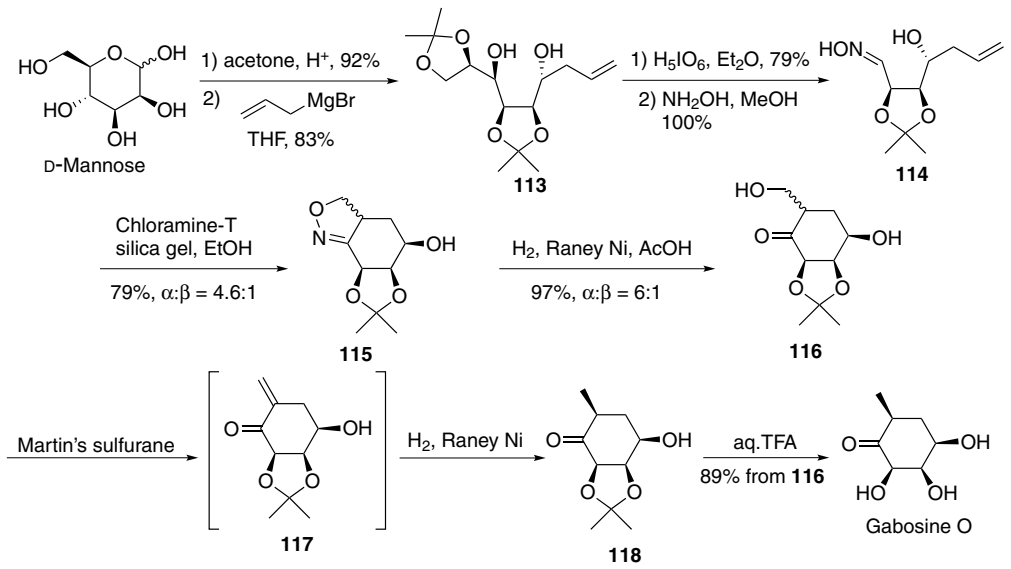
Towards the construction of 5-membered carbocycles, similar improvement in reaction yields were observed and examples are shown in Scheme 21. It is interesting to note that other acidic conditions attempted including the addition of acetic acid, benzoic acid, acetate buffer or phosphate buffer did not cause the INOAC to occur.

The silica gel mediated INOAC reactions were compatible with substrates containing unprotected hydroxyl groups, thus reducing masking/unmasking steps and rendering a synthesis shorter.[17]



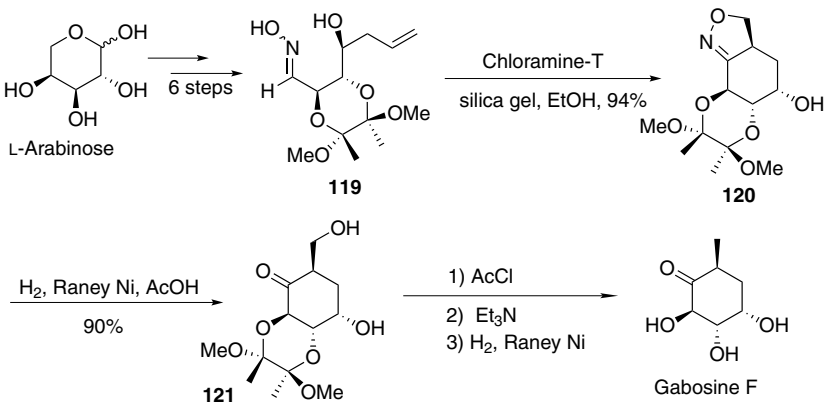
Scheme 21. INOAC with and without silica gel

We have applied this methodology to the construction of gabosine O and F.[18] Mannose was transformed readily into oxime **114** with a free hydroxyl group (Scheme 22). INOAC of **114** occurred smoothly to give a 6-membered carbocycle **115** which was hydrogenolysed, dehydrated, and then hydrogenated from the less hindered side to form ketone **118**. Acidic hydrolysis of the acetonide in **118** yielded the target molecule gabosine O.[18]



Scheme 22. Synthesis of gabosine O

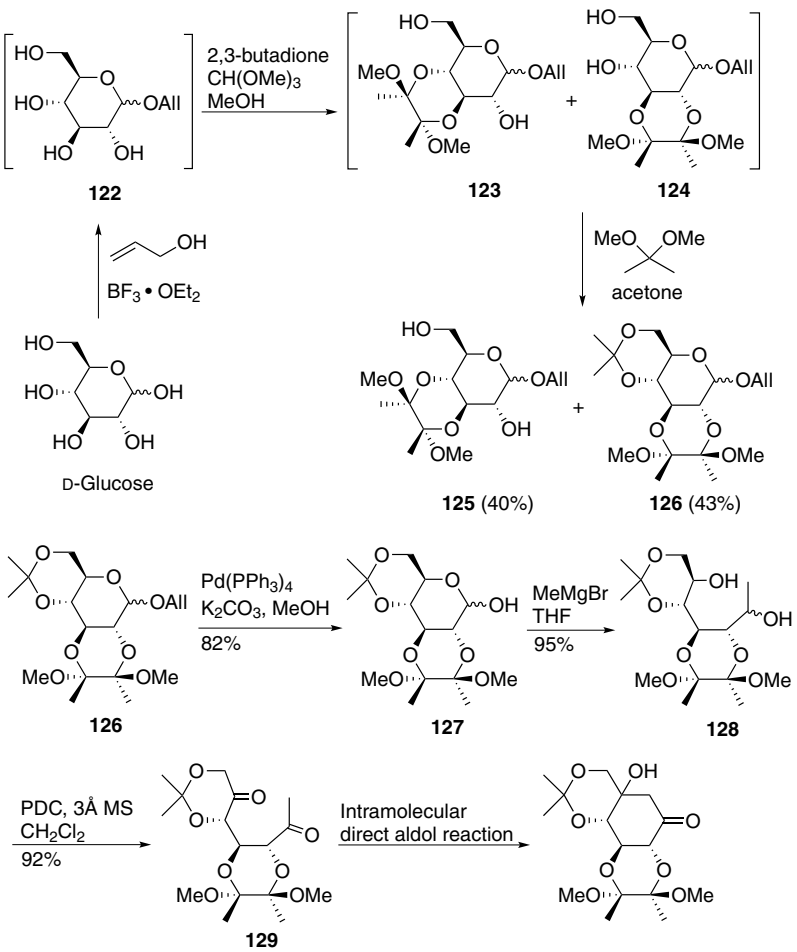
On the other hand, L-arabinose was transformed into oxime **119** with a free hydroxyl group. INOAC reaction of **120** furnished the 6-membered carbocycle in an excellent yield with the new C–C bond equatorially installed. Standard conversion afforded the target molecule gabosine F (Scheme 23).



Scheme 23. Synthesis of gabosine F

3 Carbocyclization of Carbohydrates *via* an Intramolecular Direct Aldol Addition of Sugar Diketone

First of all, we started our investigation on D-glucose since voglibose **18** and valiolamine **19** are obvious synthetic targets. Glycosidation of D-glucose with allyl alcohol and then diacetalization produced 2,3- **124** and 3,4-diacetals **123** which were readily separable upon acetonation to the 4,6-acetonide **126**.[19] Palladium catalysed deallylation of glycoside **126** gave lactol **127** which underwent Grignard methyl addition followed by PDC oxidation afforded the 2,6-diketone **129**. Intramolecular aldol addition reactions of **129** were carried out under various basic conditions and the best results are shown in Table 1.



Scheme 24. Preparation of 2,6-diketone **129** from D-glucose

The stereo-selective formation of a particular aldol product can be controlled by either L-proline, strong or weak amine base. It is noteworthy that all the direct aldol reactions are not reversible. The resistance towards a retro-aldol reaction is probably attributable to steric reasons.

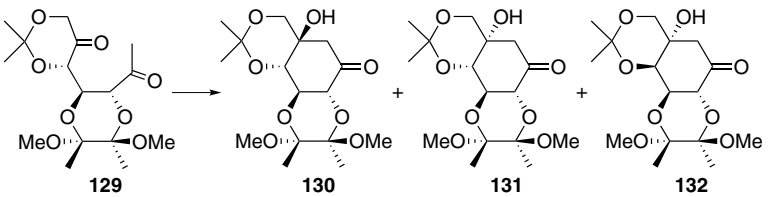
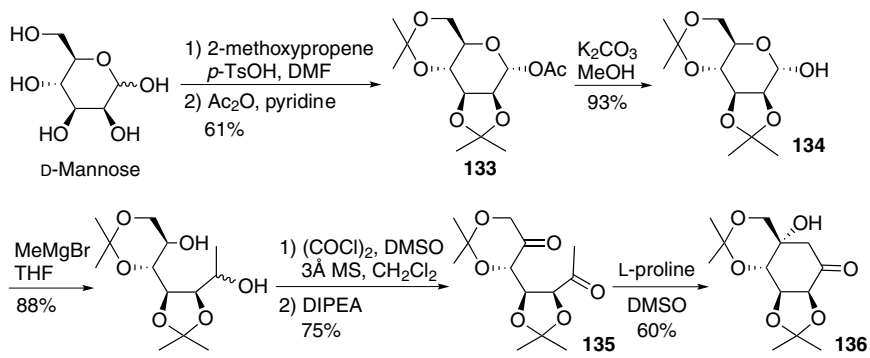


Table 1. Summary of direct aldolization conditions of 2,6-diketone **129**

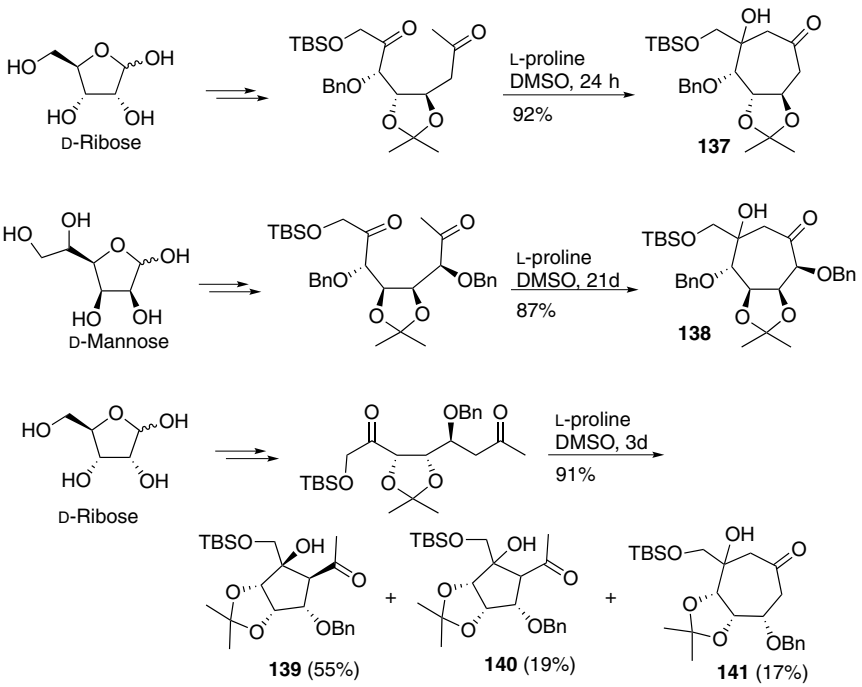
Entry	Conditions	Results		
		130	**131**	**132**
1	L-Proline (0.3 eq), DMSO	**82%**	8%	2%
2	KHMDS (1 eq), Toluene, -78 °C	–	**75%**	–
3	Et_3N (1.5 eq), CH_2Cl_2	–	–	**95%**

The preparation of mannose diketone **135** was executed in a similar manner (Scheme 25). Disappointingly, all strong and weak basic conditions failed to generate an aldol product with the exception of L-proline, which provided aldol **136** as the sole cyclohexanone in 60% yield.[19]



Scheme 25. Preparation of aldol **136** from D-mannose

We have also investigated an intramolecular direct aldolization of 2,7-diketones, in search for a synthetic avenue towards hydroxylated cycloheptanones. The 2,7-diketones were prepared from D-ribose or D-mannose using standard reactions and the results are summarized in Scheme 26.[20]

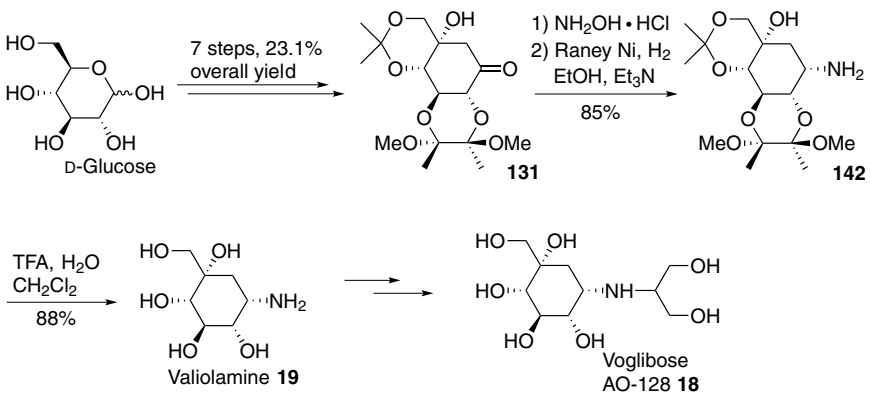


Scheme 26. Summary of direct aldolization of 2,7-diketones from ribose and mannose

Application of the versatile intramolecular direct aldolization strategy to synthesis was demonstrated by the following examples.

3a. Synthesis of Valiolamine and Voglibose (AO128)

D-Glucose was transformed smoothly into aldol **131** as stated above. Oximation of the ketone moiety in **131** followed by hydrogenation/hydrogenolysis furnished amine **142**. Acidic removal of the acetals in **142** provided vailolamine **19** which, reportedly, could be converted into the anti-diabetic agent voglibose (AO128) **18** (Scheme 27).[19]



Scheme 27. Synthesis of valiolamine **19**

3b. Synthesis of Pseudo-Acarviosin

Methyl acarviosin **143** was obtained from the natural anti-diabetic agent, acarbose, by acidic methanolysis (Figure 5). As methyl acarviosin is a stronger α-amylase inhibitor, we wanted to replace the sugar moiety in **143** with a cyclohexane to render the compound more stability in acid conditions. In search for an improved anti-diabetic drug, we proceeded to synthesize pseudo-acarviosin **144** for biological screening.

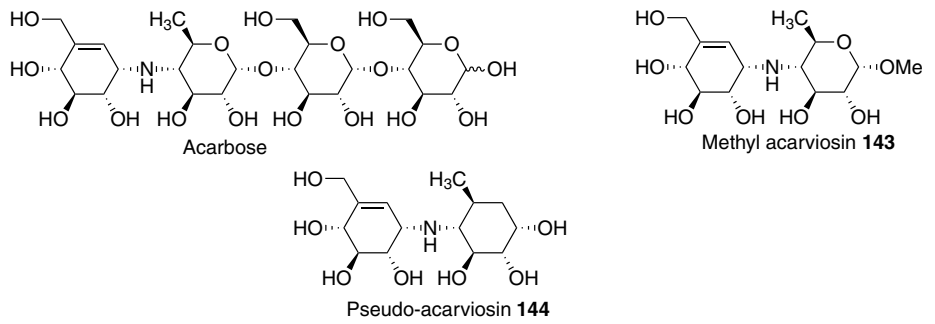
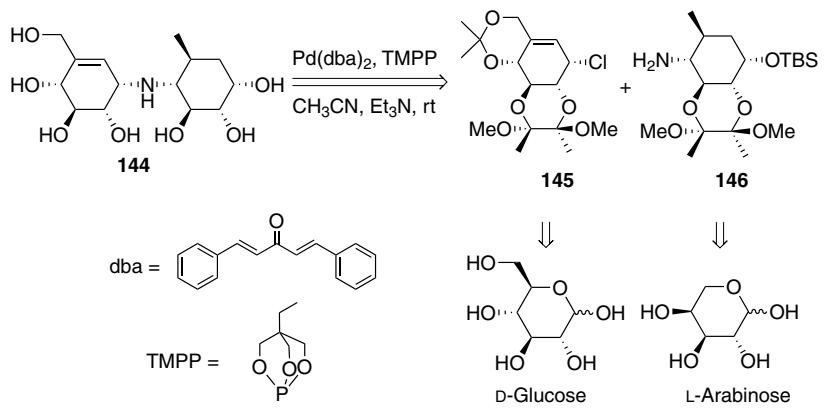


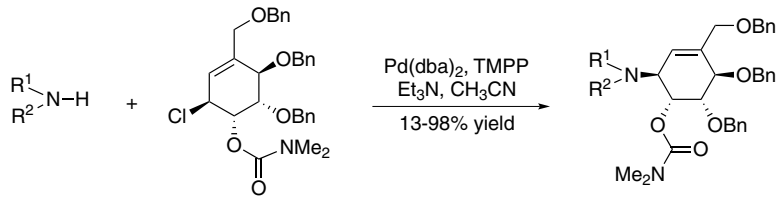
Figure 5. Acarbose and related compounds

Retrosynthesis of pseudo-acarviosin **144** *via* a palladium catalysed allylic substitution would give two fragments, an allylic chloride **145** and a cyclohexanyl amine **146**. Chloride **145** would be accessed from D-glucose *via* a direct aldol strategy while the amine **146** should be approached from L-arabinose through an INAC reaction.[21]



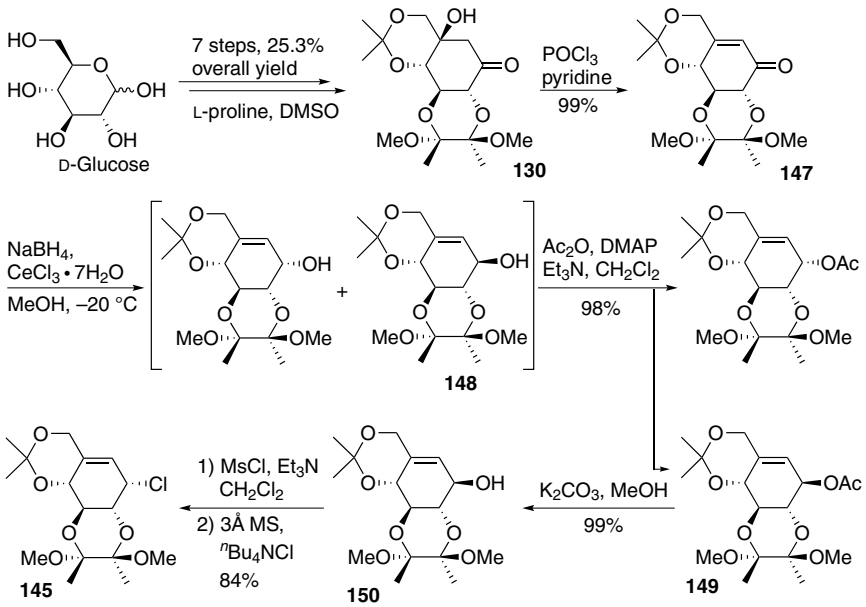
Scheme 28. Retrosynthetic analysis of pseudo-acarviosin **144**

The palladium-catalysed coupling plan is the result of a massive experimentation. We attempted a great many coupling reaction conditions between different partners, amine with mesylate, ketone, allylic epoxide, allyic cyclic sulphite, or allylic acetate.[22] As most of the electrophiles are unstable under the conditions and elimination is the major side-reaction, none of the coupling reactions gave the desired product except for using allylic chloride as the coupling partner shown in Scheme 29.[23]



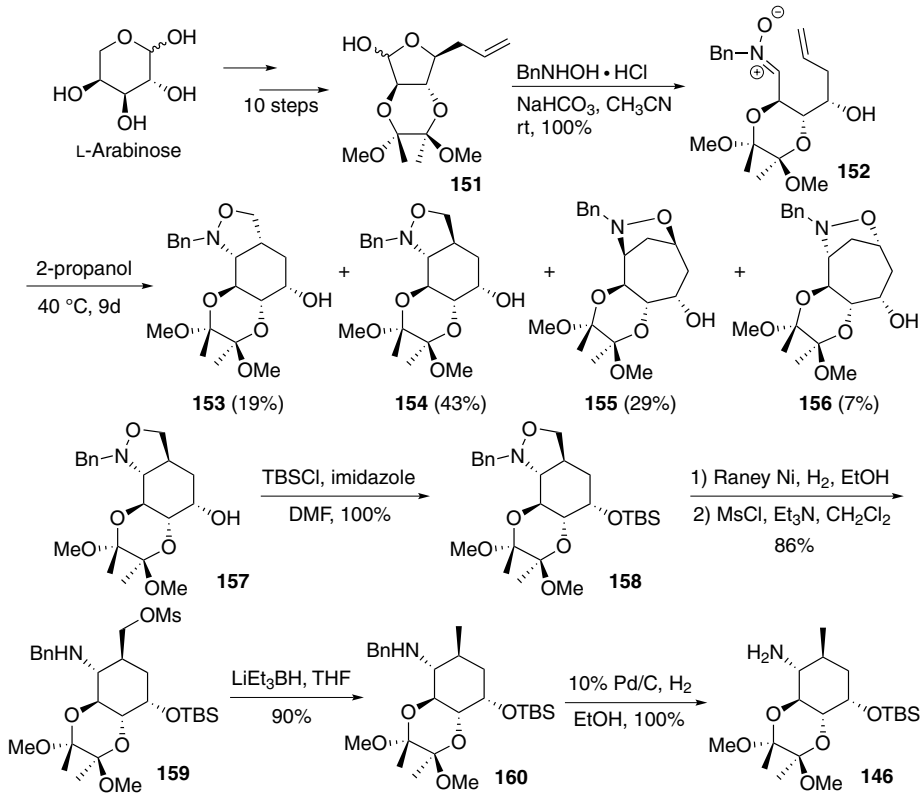
Scheme 29. Successful coupling reactions when allylic chloride was used

Since the coupling conditions were established, we started to construct the two coupling partners **145** and **146**. D-Glucose was converted into aldol **130** as said earlier.[19] Elimination of the alcohol in **130** followed by reduction of the ketone group in **147** produced allylic alcohol **148** which was separated from its epimer *via* an acetylation and deacetylation protocol. The isolated **148** was then transformed into the allylic chloride **145** by standard reactions (Scheme 30).



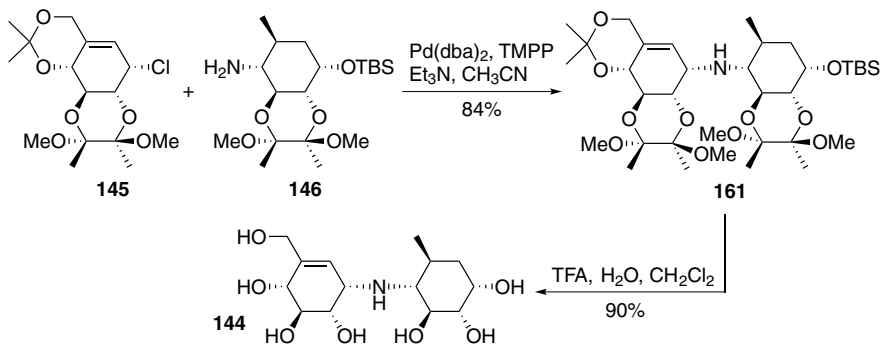
Scheme 30. Preparation of allylic chloride **145** from D-glucose

On the other hand, the amine coupling partner **146** was assembled from L-arabinose *via* an INAC reaction of a protected hept-6-enose **151** as the key step (Scheme 31).[21] The major *exo*-cycloadduct **154** with a *trans*-ring fusion was formed with the correct stereochemistry. It is noteworthy that the *trans*-fused *exo*-cycloadduct could only be harvested with the nitrone containing a *trans*-diacetal blocking group. The cycloadduct **154** was transformed readily into the cyclohexyl amine **146** using standard reactions with a good overall yield.



Scheme 31. Preparation of amine **146** from L-arabinose

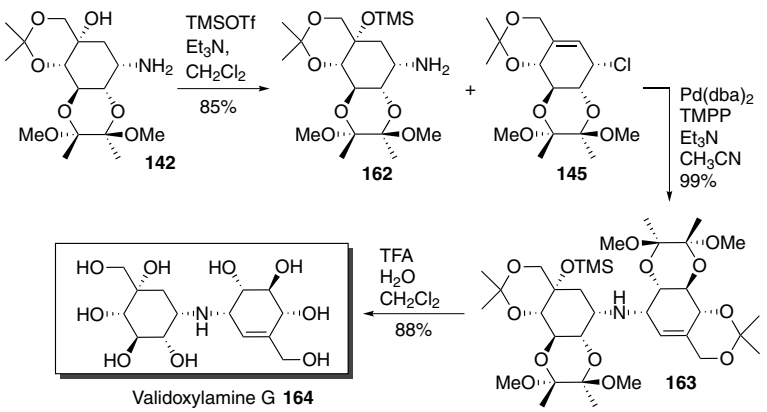
With the coupling partners in our hand, palladium catalysed allylic substitution of chloride **145** with amine **146** proceeded with retention of configuration to give the protected allylic amine **161** (Scheme 32). Hydrolysis gave the target molecule pseudo-acarviosin **144** which was shown to be a stronger sucrose and glucoamylase inhibitor than acarbose.[21]



Scheme 32. Synthesis of pseudo-acarviosin **144**

3c. Synthesis of Validoxylamine G

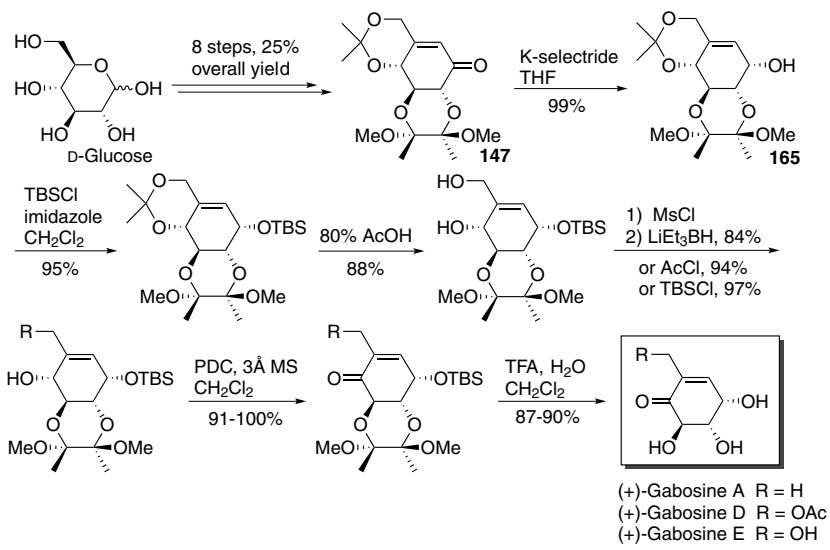
Capitalising on the palladium-catalysed allylic substitution reaction, the silyl ether **162** of the afore-prepared amine **142** and allylic chloride **145** (both are direct aldol products from D-glucose) were coupled together to form pseudo-glycosyl amine **163** which on complete acidic deprotection afforded validoxylamine G **164** in a good yield (Scheme 33).[19]



Scheme 33. Synthesis of validoxylamine G **164**

3d. Synthesis of Gabosines

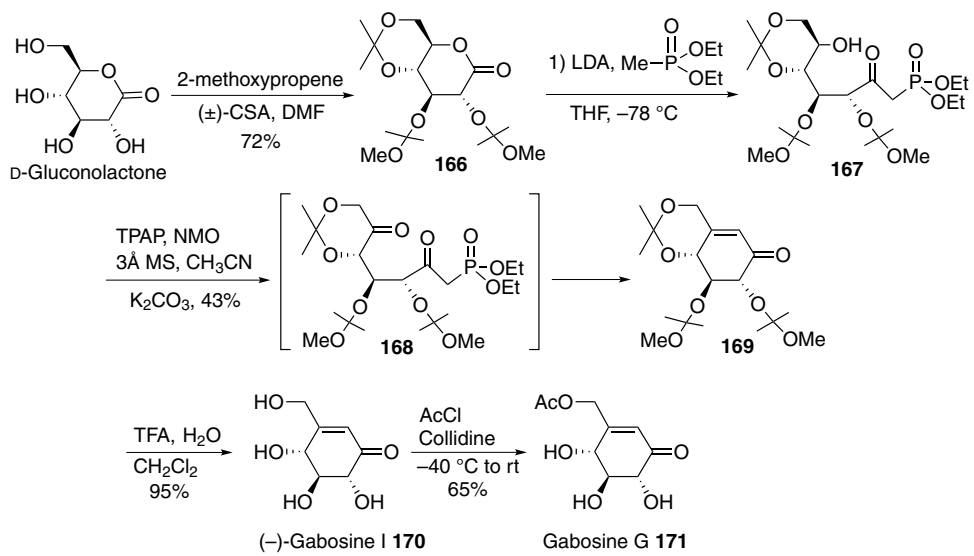
A number of gabosines were easily assembled from D-glucose *via* the direct aldol strategy. Only a few of them are illustrated here.[24,25] Thus the aforesaid enone **147** was regio- and stereo-selectively reduced to the α-allylic alcohol **165** in an excellent yield (Scheme 34). Functional group manipulation of **165** with standard reactions then furnished gabosine A, D, and E without incident.[25]



Scheme 34. Syntheses of gabosine A, D, and E

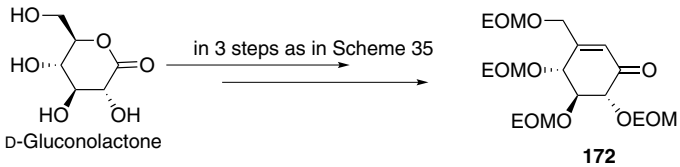
4 Carbocyclization of Carbohydrates *via* an Intramolecular Horner–Wadsworth–Emmons (HWE) Olefination

Intramolecular HWE olefination was introduced at the beginning of this article, interestingly, it is perhaps still the best strategy for a short and efficient carbocyclization of carbohydrate. Towards this end, we globally protected D-gluconolactone with 2-methoxypropene as mixed acetals **166** (Scheme 35).[26] Addition of methyl phosphonate carbanion followed by oxidation of the alcohol in **167** caused intramolecular HWE alkenation to proceed concomitantly to give the protected cyclohexanone **169** in just 3 steps from the free sugar! Acidic removal of the acetals afforded gabosine I **170** and regioselective acetylation at the primary alcohol provided gabosine G **171**. The relatively labile mixed acetal blocking groups were problematic, but we have circumvented this obstacle with ethoxymethyl (EOM) protecting group.[27]



Scheme 35. Syntheses of gabosine I and G

Since EOM protected cyclohexanone **172** could also be synthesized readily from D-gluconolactone (Scheme 36), application of this route to the syntheses of streptol and other gabosines were accomplished.[27,28] Exploiting this facile carbocyclization strategy, we embarked on the construction of sodium-dependent glucose cotransporter 2 (SGLT2) inhibitors.



Scheme 36. Synthesis of stable EOM blocked cyclohexanone **172**

Sergliflozin is a potent SGLT2 inhibitor, but was abandoned for further investigation because phenyl glycosides are prone to hydrolysis and therefore not suitable for development into useful medicine. Replacing the sugar moiety in sergliflozin with a pseudo-sugar unit would provide a stable "glycoside" **173** as the "glycosidic bond" is now an ether linkage (Figure 6).[29]

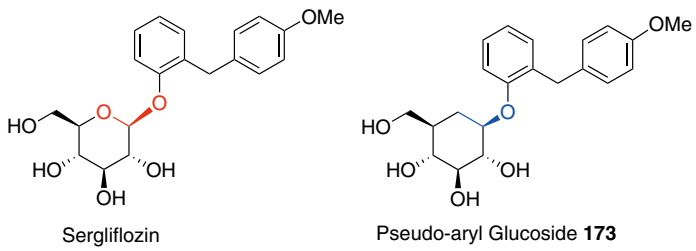
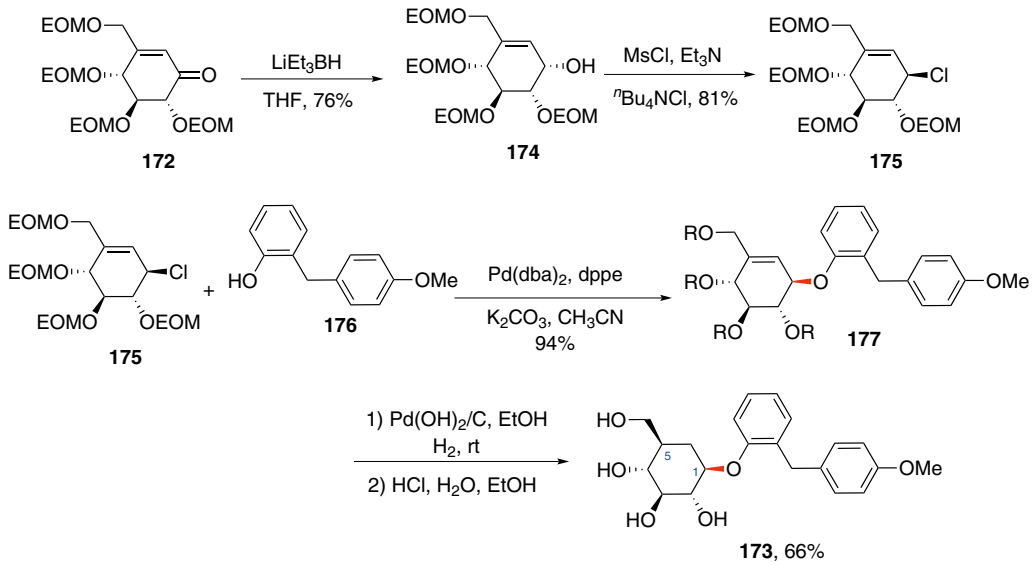


Figure 6. Structures of sergliflozin and pseudo-aryl glucoside **173**

The synthetic avenue towards pseudo glucopyranoside **173** is shown in Scheme 37. Regio- and stereo-selective reduction of **172** gave α-alcohol **174** which was activated and displaced with chloride to β-chloride **175**. Palladium catalysed allylic substitution of the allylic chloride **175** with phenolic alcohol **176** proceeded with retention of configuration to form allylic ether **177** in an excellent yield. Catalytic hydrogenation followed by acid removal of the EOM groups afforded the target molecule **173** which is a potent and selective SGLT2 inhibitor. Other analogs have also been made on extending this carbocyclization strategy.[30,31]



Scheme 37. Synthesis of pseudo-aryl glucopyranoside **173**

Conclusion

In this Article, transformation of carbohydrates into highly oxygenated cycloalkanes and cycloalkenes has been described using four synthetic strategies, namely intramolecular nitrone-alkene and nitrile oxide-alkene cycloadditions, direct aldol addition, and Horner–Wadsworth–Emmons (HWE) olefination. The latter strategy probably offers the most facile and efficient avenue to the pseudo-D-glucopyranose motif to date. The carbocyclized intermediates could then elaborated into various target molecules containing hydroxyl/amine functional groups of defined stereochemistry. Considering the low cost, availability in large quantities, and rich stereochemistry of sugar molecules, carbohydrates are perhaps the ideal starting materials for the construction of heavily oxygenated natural products or molecules with pharmaceutical implication. Research towards the syntheses of carbocyclic nucleosides should have received more attention.

Acknowlegments

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