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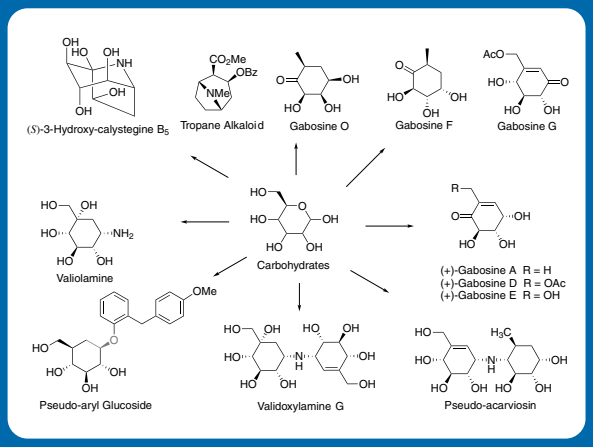

CONTENTS

Research Article

Carbocyclization of Carbohydrates to Hydroxylated Cycloalka(e)nes

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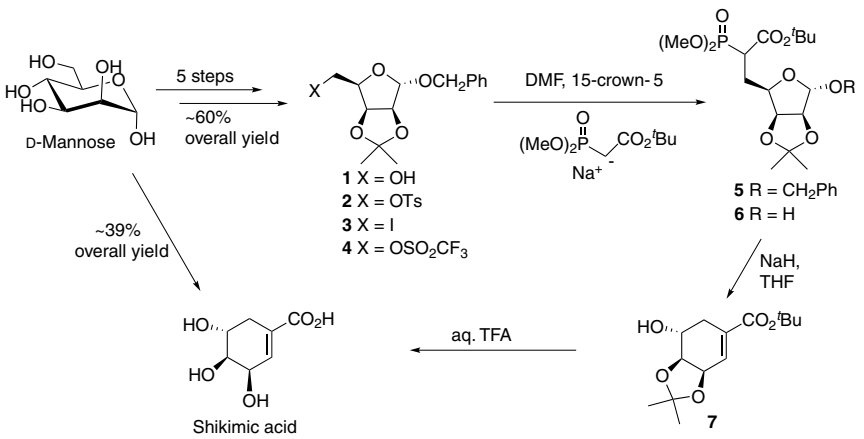
Abstract: Carbohydrates, inexpensive and rich in stereochemistry, are nature's gifts to the synthetic organic chemists. We have been conducting research on the carbocyclization of carbohydrates for many years, i.e. the conversion of simple, readily available monosaccharides into hydroxylated cycloalkanes 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).

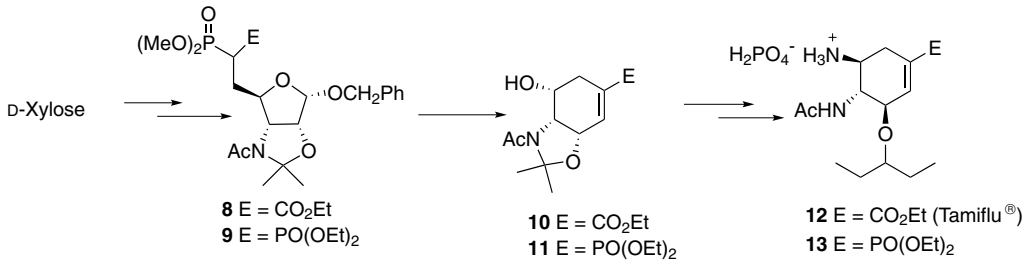
* Tamiflu® is a registered trademark of F. Hoffmann-La Roche, Ltd.

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.

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).

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?



Scheme 2. Synthesis of Tamiflu® and its phosphonate analog

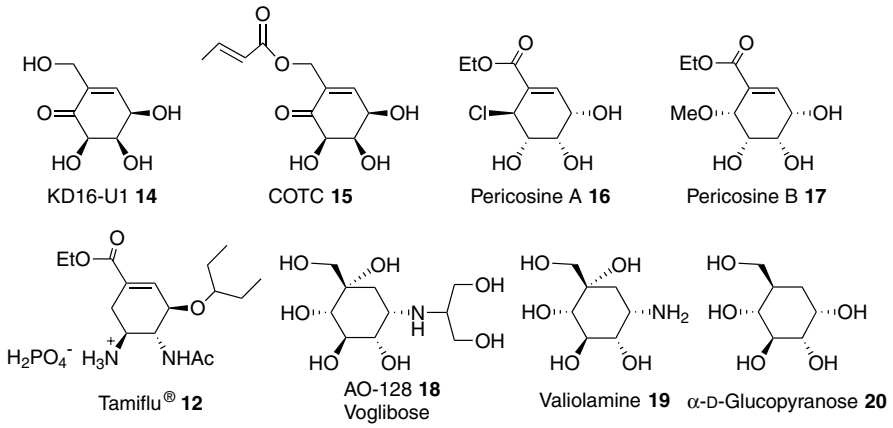


Figure 1. Bioactive hydroxylated cyclohexanes and cyclohexenes

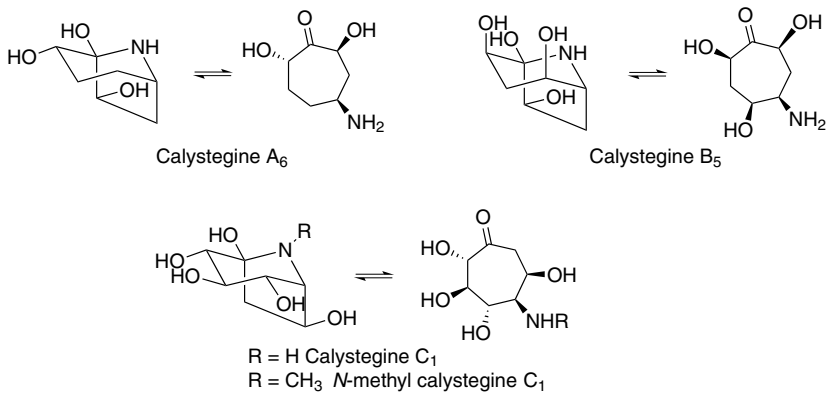


Figure 2. Structures of some calystegines

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]

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]

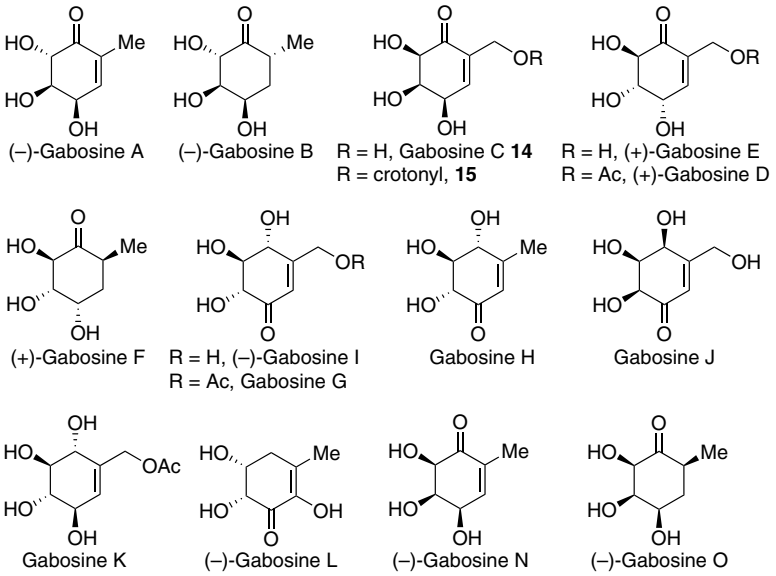
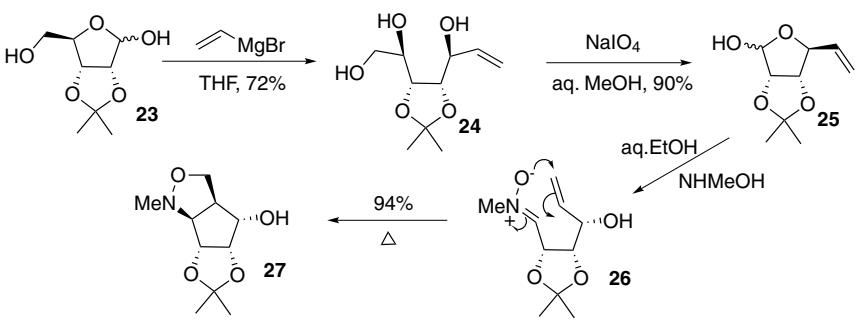


Figure 3. Gabosine family

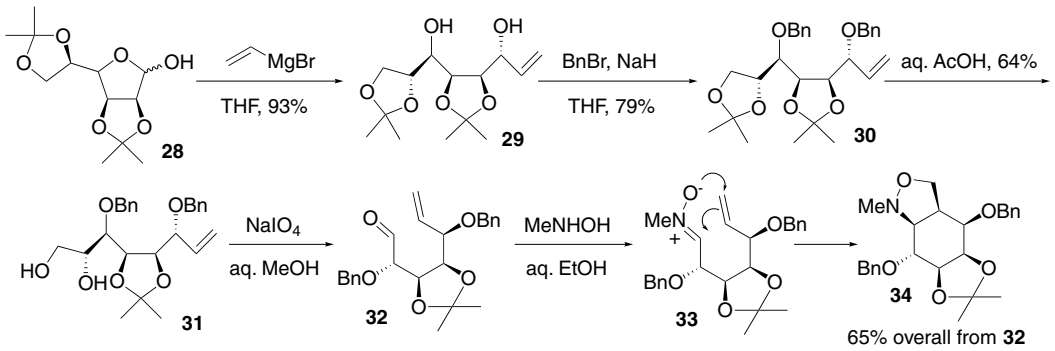


Scheme 3. Synthesis of a functionalized cyclopentane **27** from ribose

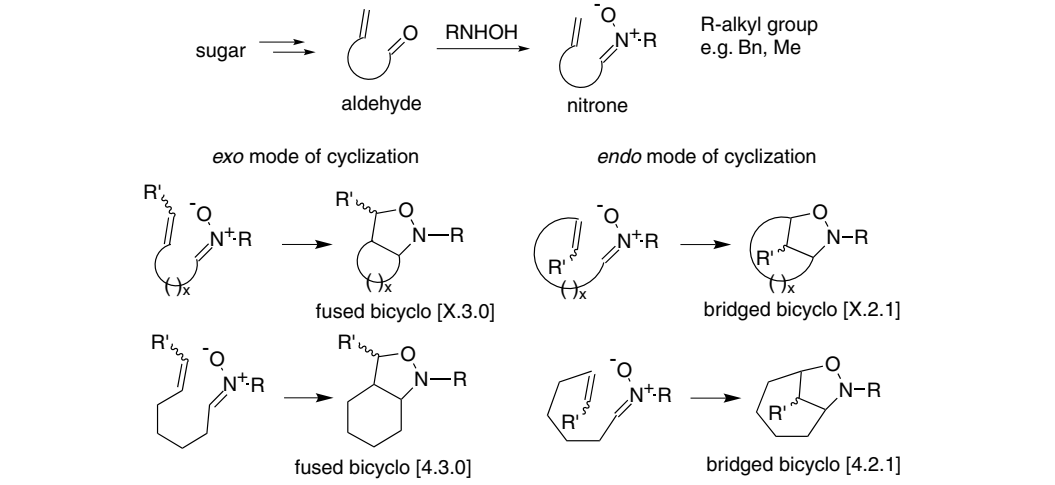
We had more interests in this INAC reaction because we reasoned that it could be controlled to provide 7-membered carbocycles. When a sugar molecule was elaborated to have a terminal alkene, on reaction with *N*-alkyl hydroxylamine, there would be two possible modes of INAC cyclization, the *exo* or 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.

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.

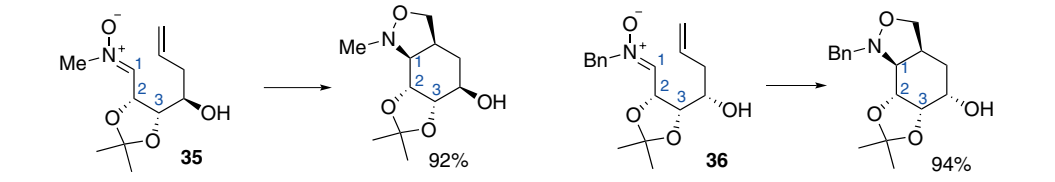
We reasoned that the mode of cyclization might be controlled by the blocking groups as they affect the orbital overlap between the nitrone and the alkene. Thus we investigated the effect of *trans*-diacetal blocking group on the regioselectivity of hept-6-enose. Epimeric nitrones **37** and **38** were readily prepared from D-arabinose involving glycosidation with benzyl alcohol, diacetalisation, debenzylation, Grignard



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



Scheme 5. INAC mode of cyclization

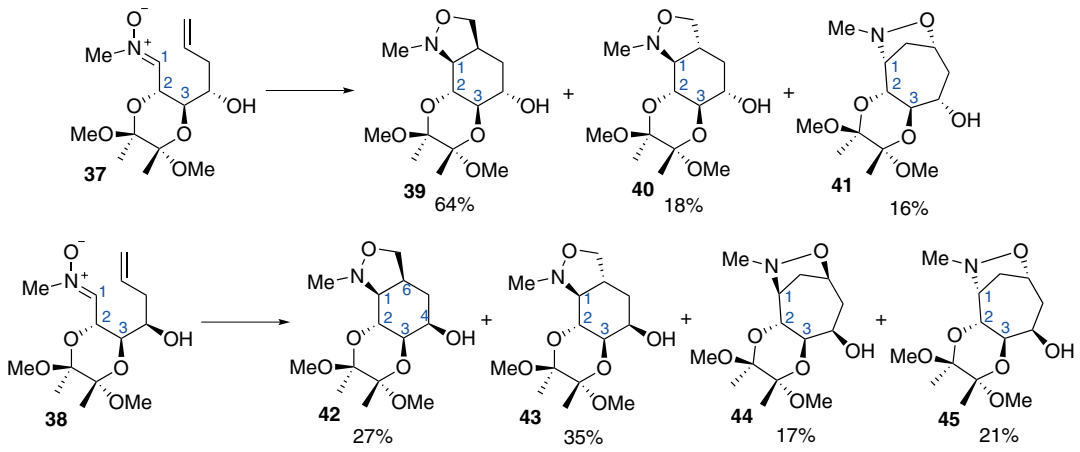


Scheme 6. INAC of hept-6-enoses with a *cis*-acetonide

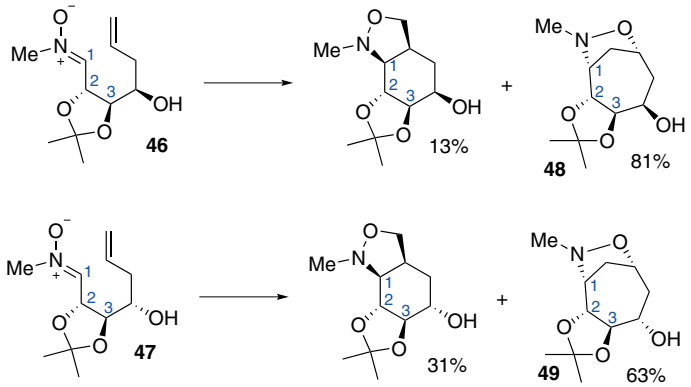
allylation, glycol cleavage oxidation and reaction with *N*-methyl hydroxylamine. Interestingly, nitrones **37** and **38** with a *trans*-diacetal blocking group (the diol moiety is *trans*) afforded *endo*-mode of cyclization products **41**, **44**, **45**, i.e., cycloheptane rings, for the first 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]

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]

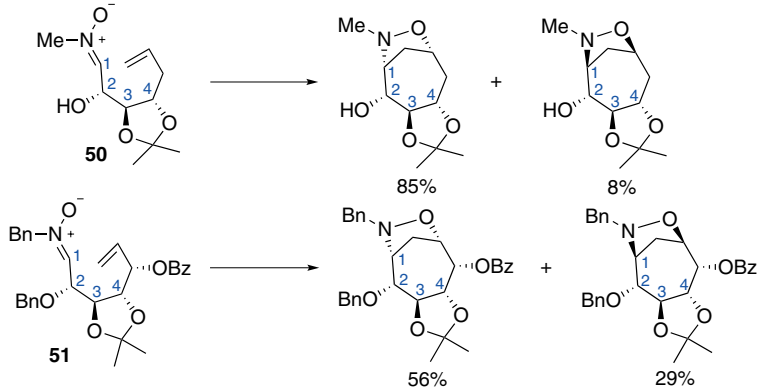
Hept-6-enose nitrones **50** and **51** with a 3,4-*trans*-acetonide were even more remarkable as only the *endo*-mode cycloheptanes were harvested in good yields (Scheme 9).[10]



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



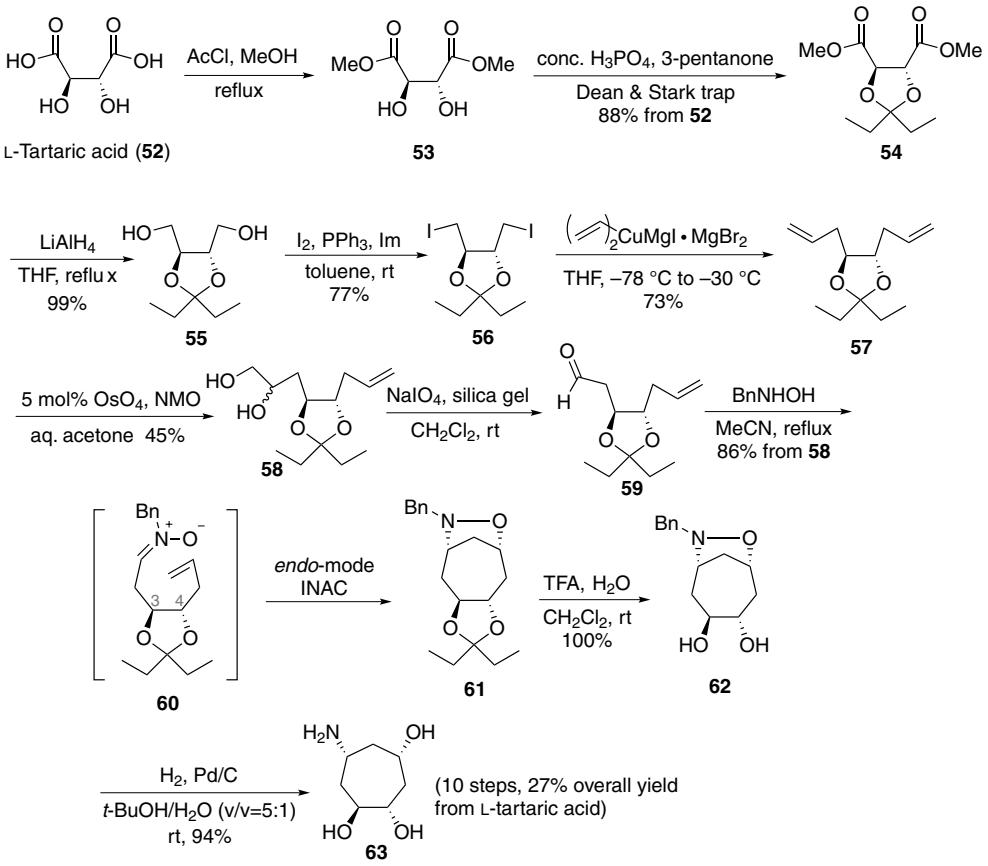
Scheme 8. INAC of hept-6-enoses with a 2,3-*trans*-acetonide



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

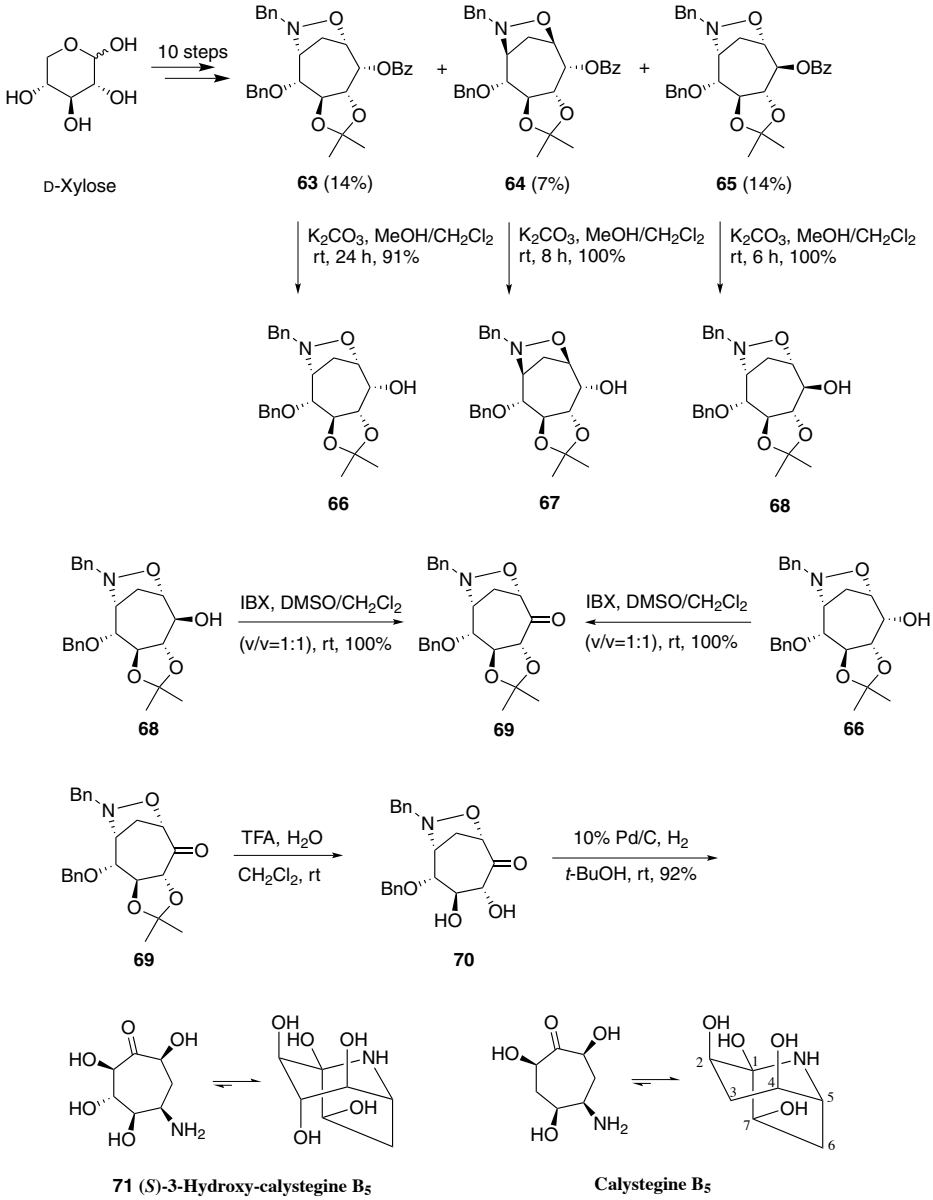
We were wondering if the stereochemistry of the C-2/C-5 hydroxyl groups might affect the regioselectivity of the INAC reactions. We thus constructed a hept-6-enose nitrone **60** with only a 3,4-*trans*-acetonide from L-tartaric acid using standard reactions (Scheme 10). Only a cycloheptane ring **61**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

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.

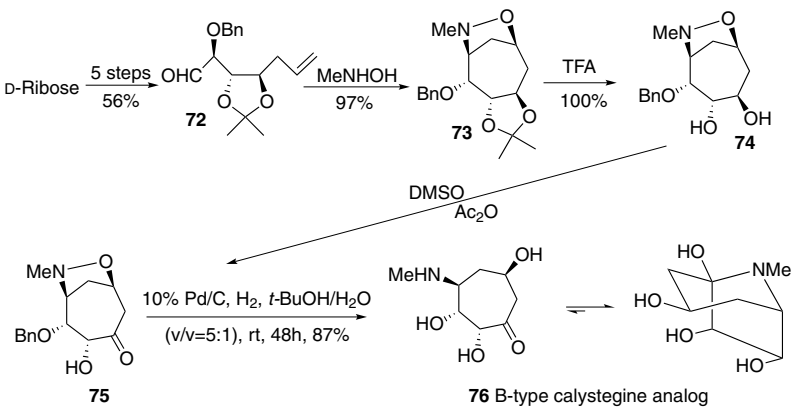


Scheme 10. INAC of hept-6-enose with only a 3,4-*trans*-acetonide

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 11. Synthesis of a calystegine B_5 analog



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.

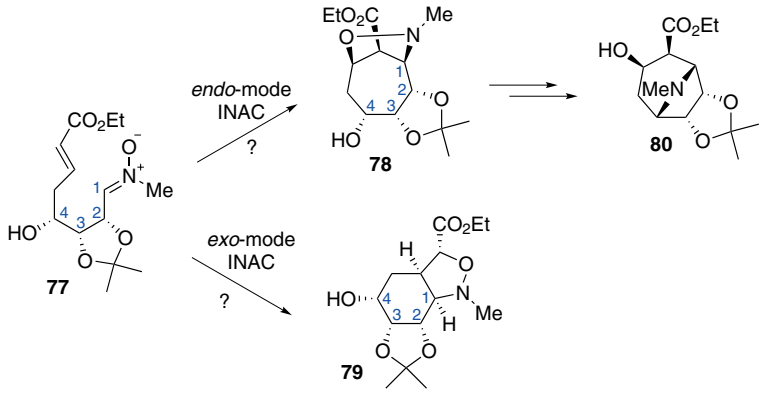
(A) Strategy towards tropane alkaloid 1: INAC of a Nitrone with a 2,3-*cis*-Isopropylidene as Blocking Group and an α,β-Unsaturated Ester as Dipolarophile

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.

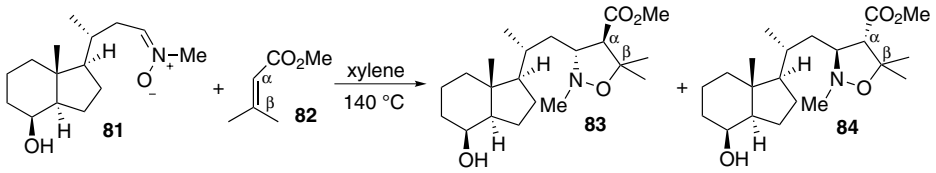
To our disappointment, the INAC of nitrone **85** produced only *exo*-mode cycloadducts **86** and **87**, 6-membered carbocycles. Hence it appears that steric control is more important than electronic control for the regioselectivity (*exo* versus *endo*) of INAC reactions of hept-6-enoses (Scheme 15).[11]

(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

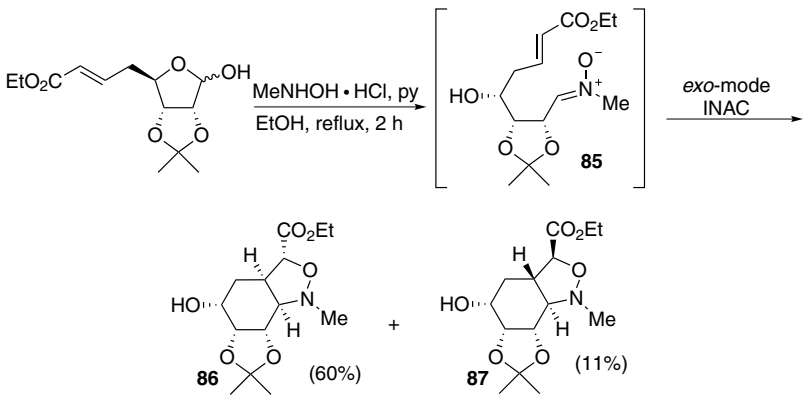
Since we had shown that 3,4-*trans*-acetonide would direct an *endo*-selective mode of cyclization, we devised a synthetic route towards tropane alkaloid **90** based on this key step as summarised in Scheme 16.



Scheme 13. Orbital controlled synthetic plan towards tropane alkaloid



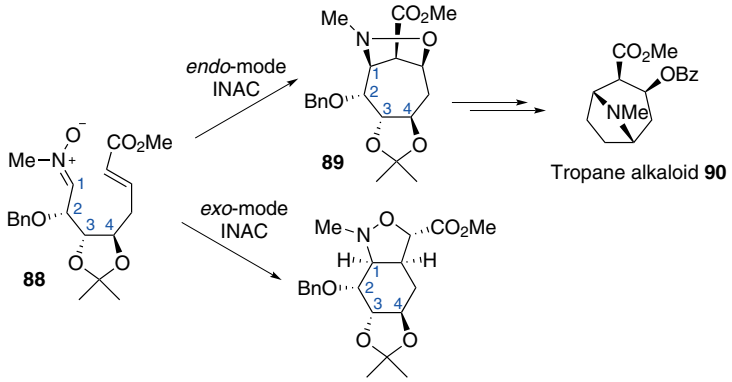
Scheme 14. Intermolecular cycloaddition of nitrone **81** and enoate **82**



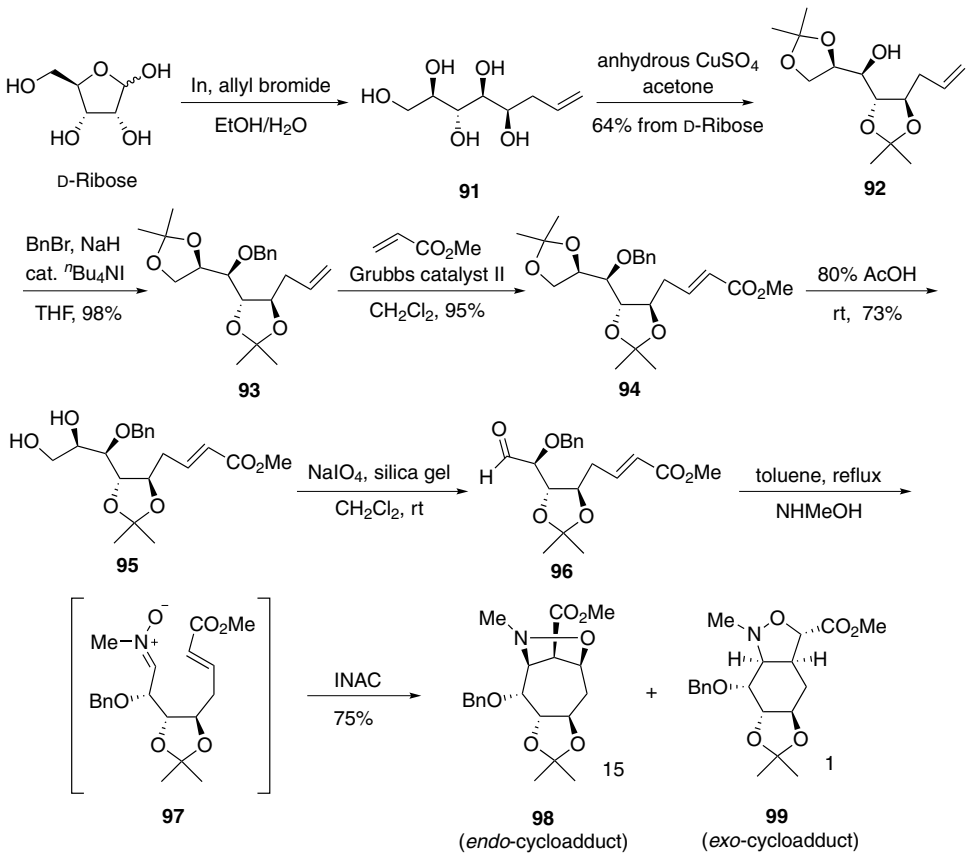
Scheme 15. INAC of enoate with a *cis*-acetonide

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]

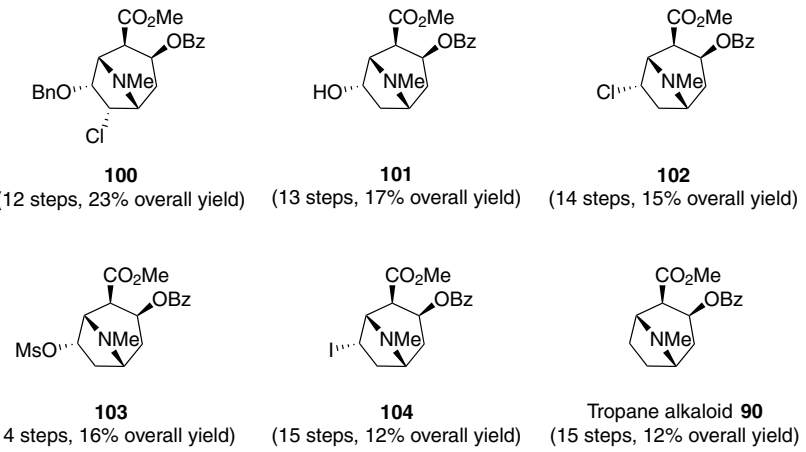
As the cycloheptane skeleton was installed correctly, cycloadduct **98** was converted into natural tropane alkaloid **90** and its analogs **100**–**104** as shown in Figure 4.[13]



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



Scheme 17. INAC synthetic route towards tropane alkaloid



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)

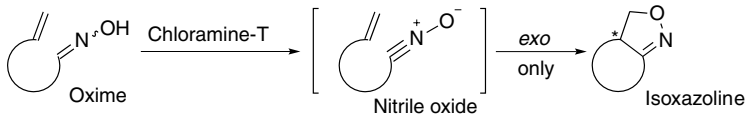
Figure 4. Tropane alkaloid **90** and its analogs

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

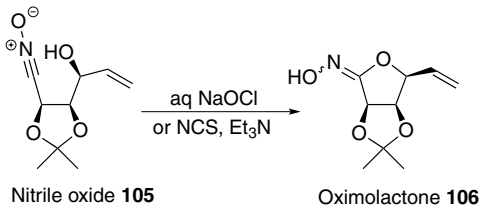
The use of chloramine-T in the conversion of ene-sugar oxime into a nitrile oxide and its subsequent INOAC reaction is known.[15] This cycloaddition shown in Scheme 18 can only be *exo*-mode as the *endo*-mode of cyclization would produce an impossible C=N bond at the bridge head position (Bredt's rule).[16]

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.

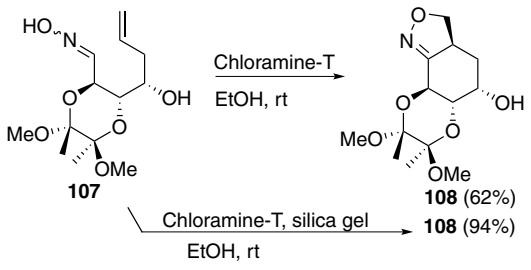
We found that adding flash chromatography silica gel to "buffer" the reaction medium dramatically increased the yield of the chloramine-T mediated INOAC reaction from 62 to 94% (Scheme 20).[17]



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



Scheme 19. Formation of oximolactone under basic conditions



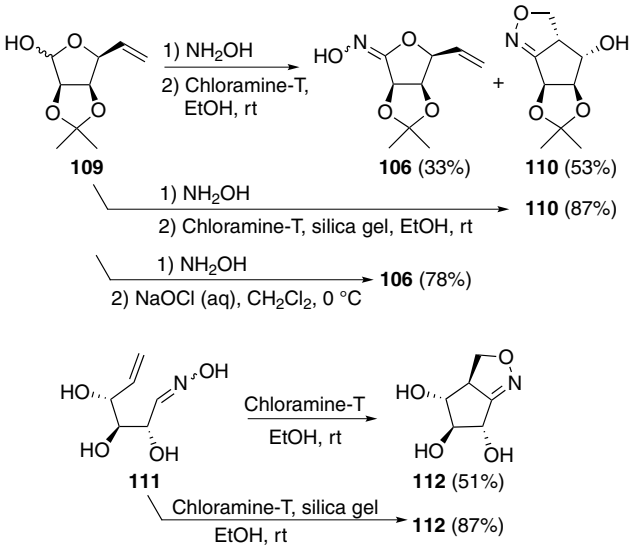
Scheme 20. INOAC with and without silica gel

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.

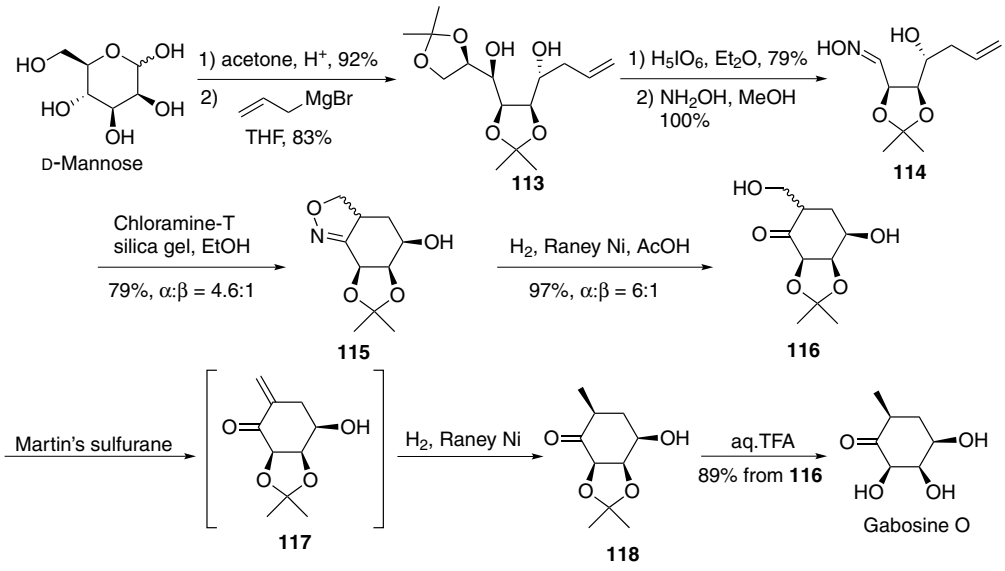
The silica gel mediated INOAC reactions were compatible with substrates containing unprotected hydroxyl groups, thus reducing masking/unmasking steps and rendering a synthesis shorter.[17]

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]

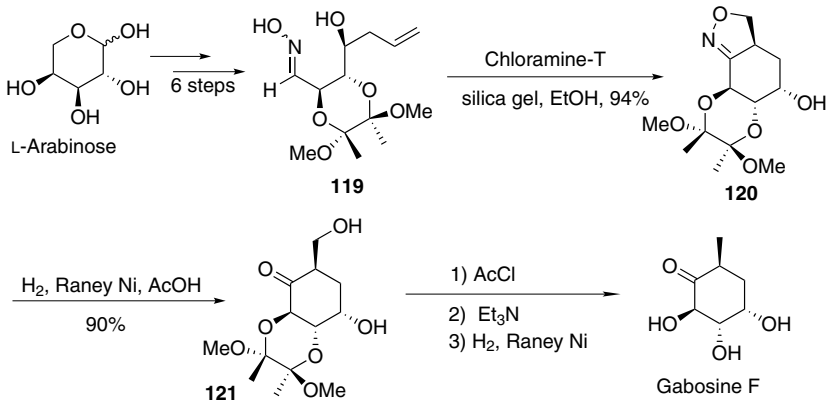
On the other hand, L-arabinose was transformed into oxime **119** with a free hydroxyl group. INOAC reaction of **120** furnished the 6-membered carbocycle in an excellent yield with the new C–C bond equatorially installed. Standard conversion afforded the target molecule gabosine F (Scheme 23).



Scheme 21. INOAC with and without silica gel



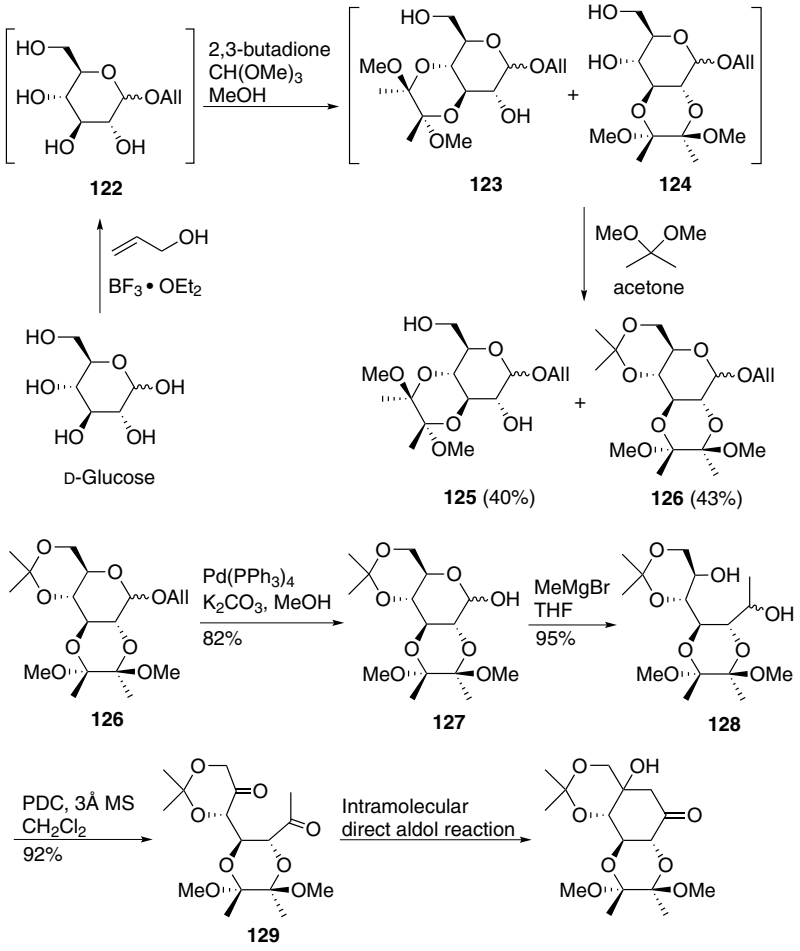
Scheme 22. Synthesis of gabosine O



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.

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]

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]

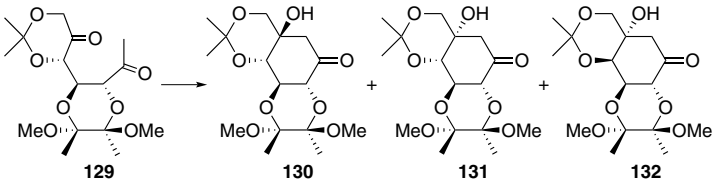
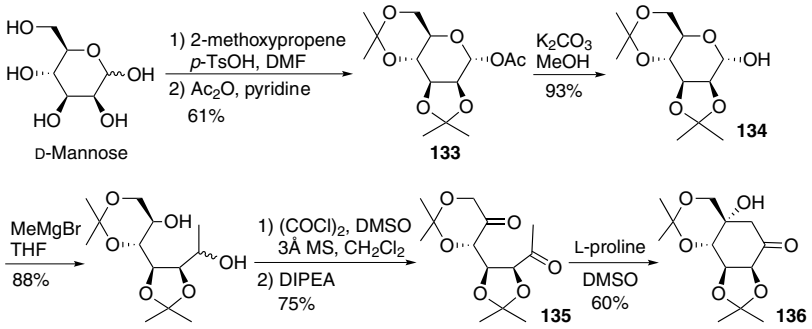
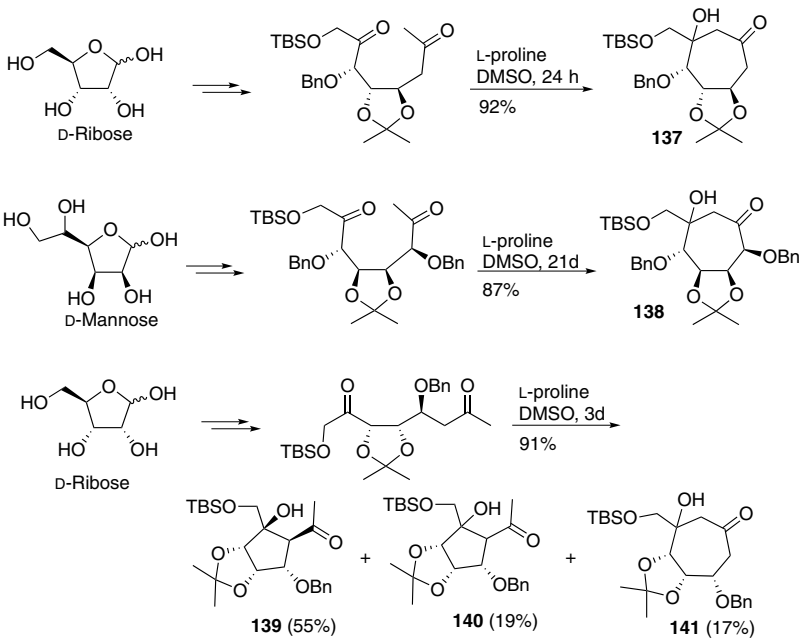


Table 1. Summary of direct aldolization conditions of 2,6-diketone **129**

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%**



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



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.

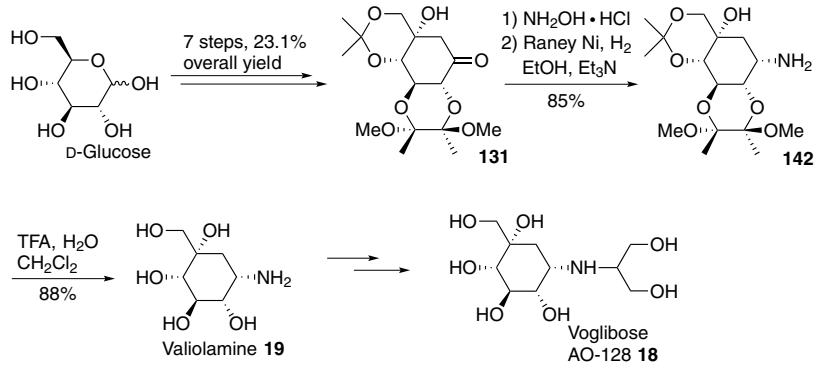
3a. Synthesis of Valiolamine and Voglibose (AO128)

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]

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.

Retrosythesis 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 27. Synthesis of valiolamine **19**

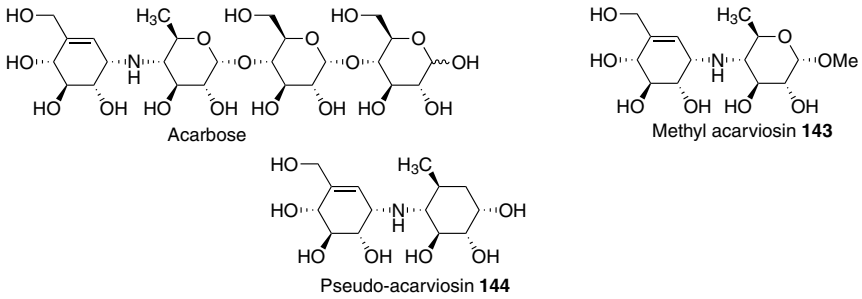
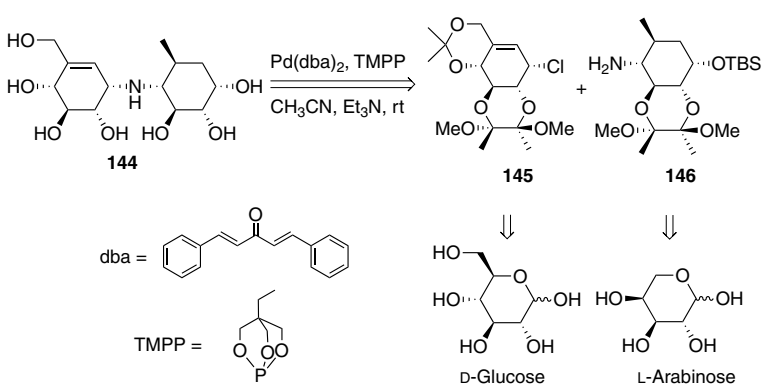


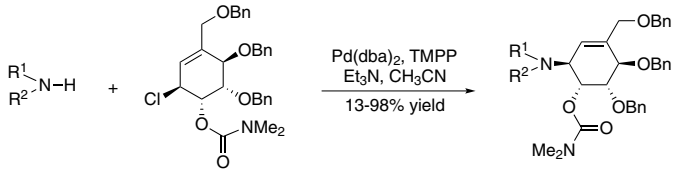
Figure 5. Acarbose and related compounds



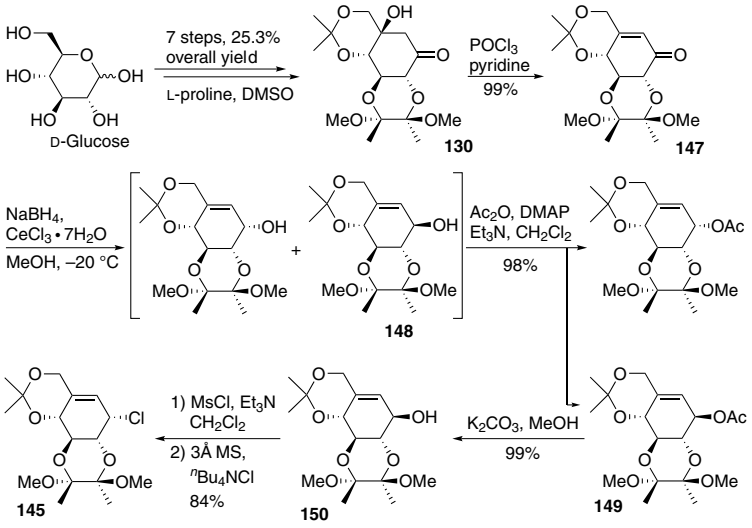
Scheme 28. Retrosynthetic analysis of pseudo-acarviosin **144**

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, allylic 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]

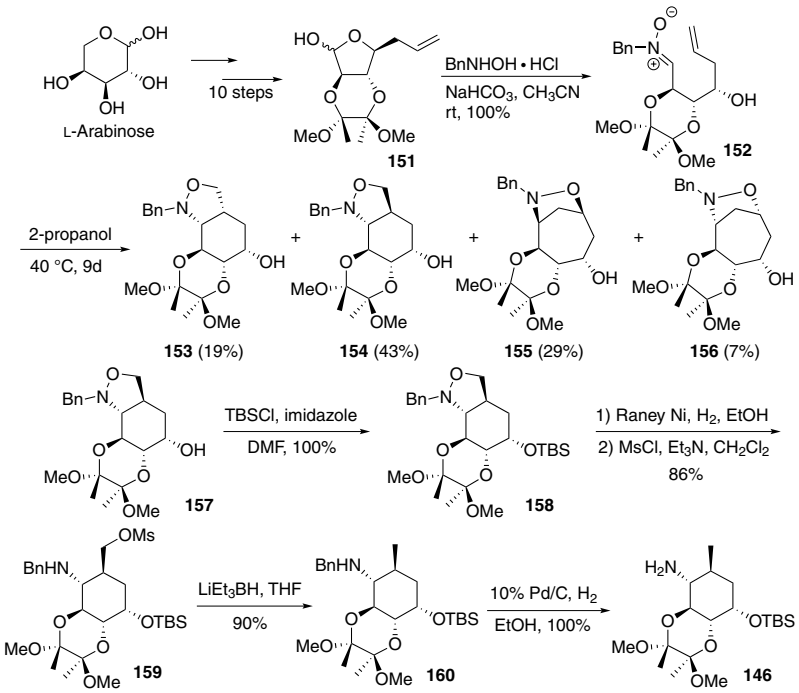
Since the coupling conditions were established, we started to construct the two coupling partners **145** and **146**. D-Glucose was converted into aldol **130** as said earlier.[19] Elimination of the alcohol in **130** followed by reduction of the ketone group in **147** produced allylic alcohol **148** 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 29. Successful coupling reactions when allylic chloride was used



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



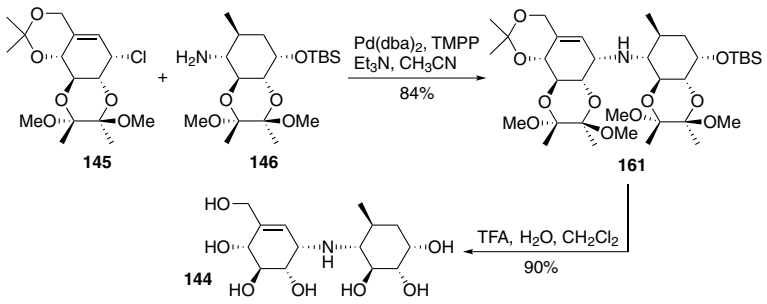
Scheme 31. Preparation of amine **146** from L-arabinose

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.

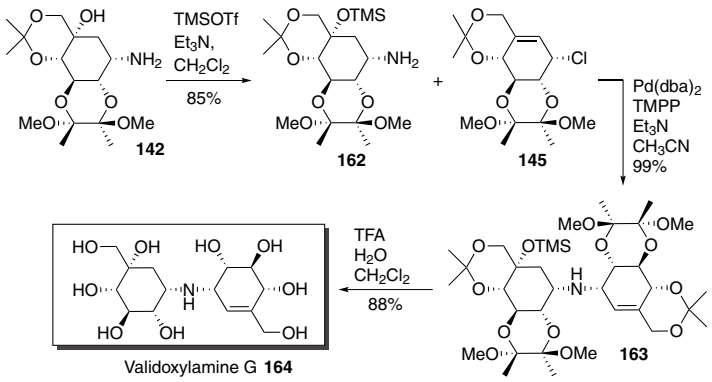
With the coupling partners in our hand, palladium catalysed allylic substitution of chloride **145** with amine **146** proceeded with retention of configuration to give the protected allylic amine **161** (Scheme 32). Hydrolysis gave the target molecule pseudo-acarviosin **144** which was shown to be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

3c. Synthesis of Validoxylamine G

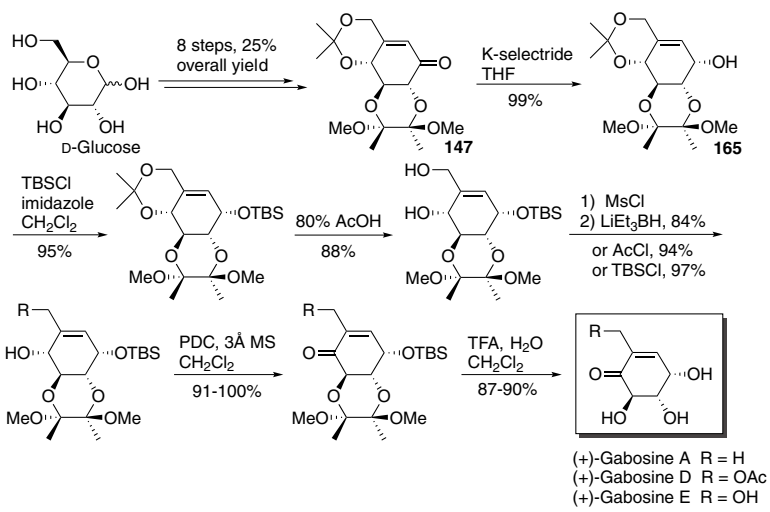
Capitalising on the palladium-catalysed allylic substitution reaction, the silyl ether **162** of the afore-prepared amine **142** and allylic chloride **145** (both are direct aldol products from D-glucose) were coupled together to form pseudo-glycosyl amine **163** which on complete acidic deprotection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



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



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



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

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]

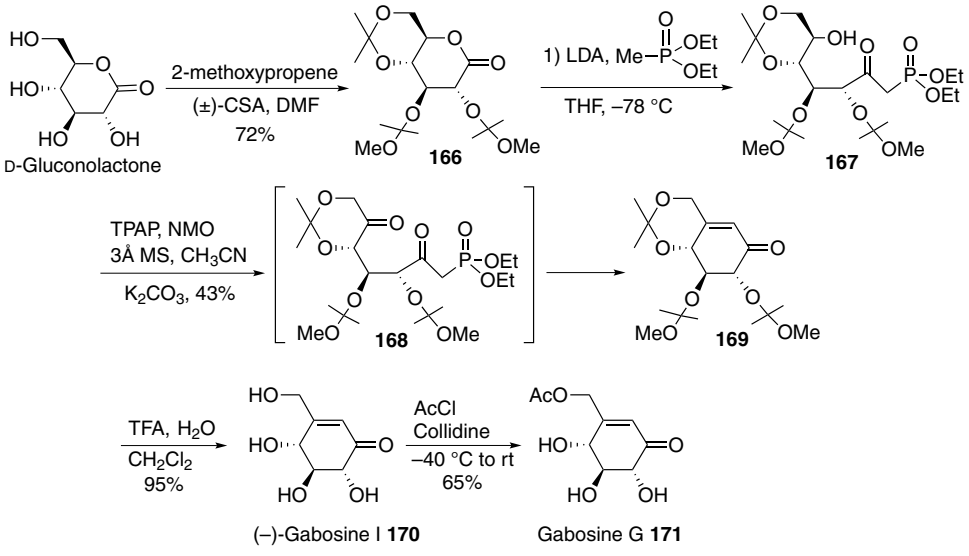
4. Carbocyclization of Carbohydrates *via* an Intramolecular Horner–Wadsworth–Emmons (HWE) Olefination

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]

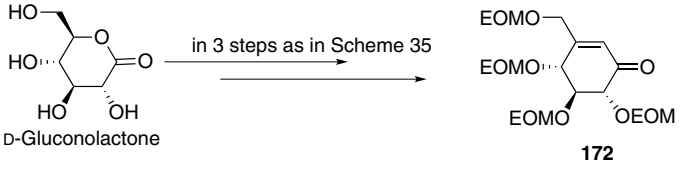
Since EOM protected cyclohexanone **172** could also be synthesized readily from D-gluconolactone (Scheme 36), application of this route to the syntheses of streptol and other gabosines were accomplished.[27,28] Exploiting this facile carbocyclization strategy, we embarked on the construction of sodium-dependent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

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]

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 35. Syntheses of gabosine I and G



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

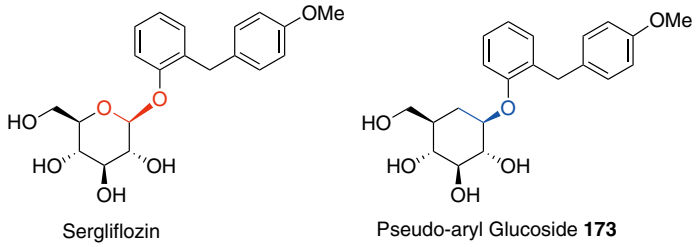
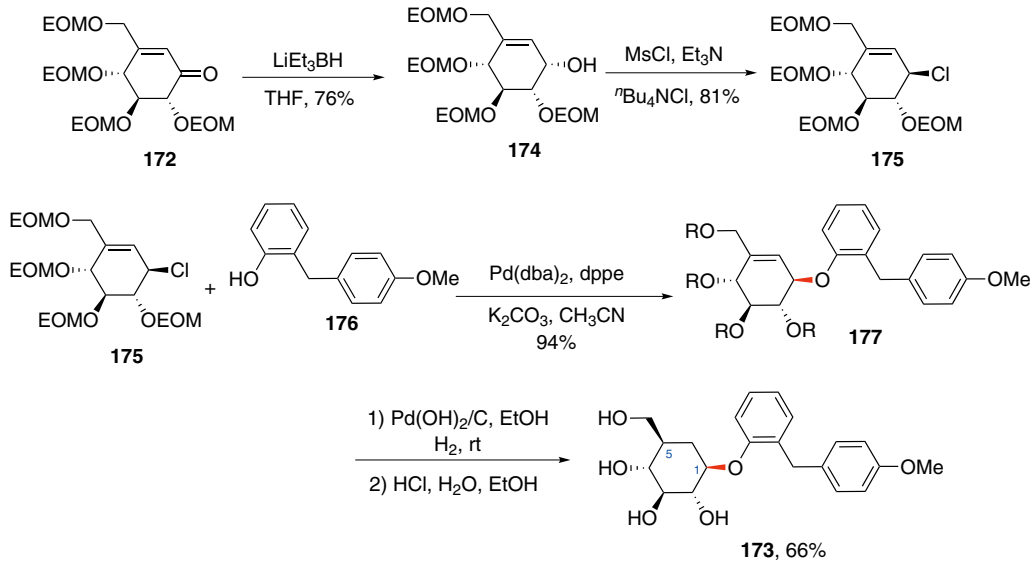


Figure 6. Structures of sergliflozin and pseudo-aryl glucoside **173**



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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Introduction of the author:

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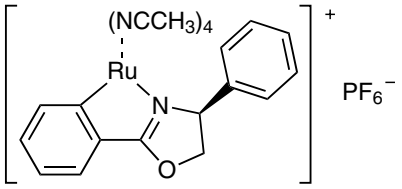
Professor Tony K. M. Shing obtained his first degree from the University of Hong Kong, his M.Sc. (analytical chemistry), Ph.D. (carbohydrate chemistry) and D.Sc. (organic synthesis) degrees from the University of London. After postdoctoral work at McGill University and Oxford University, Prof. Shing began his independent career at the University of Manchester England, as a New Blood Lecturer in 1984. He was visiting Associate Professor at the University of California, Irvine, before returning to Hong Kong in 1990. He joined the Department of Chemistry at the Chinese University of Hong Kong (CUHK) as a Lecturer, was promoted to Senior Lecturer in 1993, and to full Professor in 1996. In 2016 August, he retired from CUHK and joined Sophia University as an Invited Visiting Professor. Professor Shing moved to Keio University in October last year and is now a full Professor at the Department of Chemistry. He is also the Chairman of the Hong Kong Section of the Royal Society of Chemistry. His research interest is on the syntheses of organic molecules with chemotherapeutic potential, namely anti-cancer, anti-viral, or anti-diabetic activity.

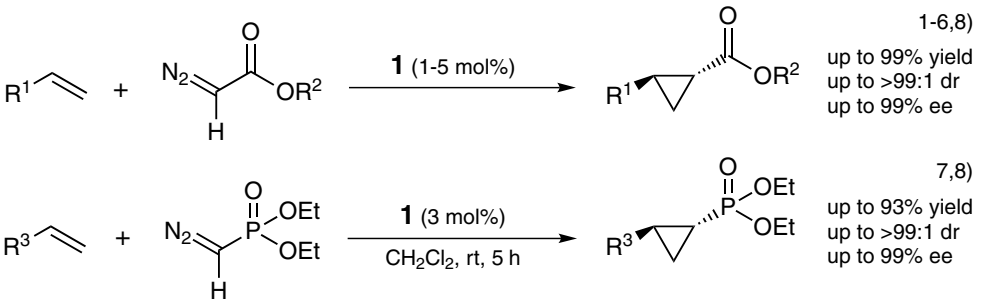
Chiral Ruthenium Complex for Enantioselective Cyclopropanations

R0196 Ru(II)-(*S*)-Pheox Catalyst (1) 200mg 1g

Ru(II)-(*S*)-Pheox Catalyst (**1**) is a chiral phenyloxazoline-ruthenium(II) complex, developed by Iwasa *et al*. **1** catalyzes highly enantioselective cyclopropanation of various olefins using diazoacetates[1-6,8] or diazomethylphosphonates.[7,8] **1** is a promising reagent for the synthesis of medicinally relevant optically active cyclopropane derivatives.



1



1-6,8)
up to 99% yield
up to >99:1 dr
up to 99% ee

7,8)
up to 93% yield
up to >99:1 dr
up to 99% ee

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Related Product

D5368 (*S*)-Pheox 1g 5g

Cylindrically Shaped Carbon Molecule : (6,6)Carbon Nanobelt

I1078 (6,6)Carbon Nanobelt Bis(tetrahydrofuran) Adduct (1) 10mg

Carbon nanobelts were proposed as general term for carbon molecules with a cylindrical structure consisting solely of fused benzene rings, first recorded and described in the literature in 1954.[1] Thereafter, various cylindrical shaped carbon molecules have been proposed, and many researchers have challenged their synthesis methods in part due to the difficulty and reproduceability.[2] After the discovery of carbon nanotubes in 1991,[3] carbon nanobelts were found to be a partial structure of the carbon nanotube wall and began to garner more and more attention. To date, there have been no effective syntheses of carbon nanobelts, largely in part due to the bent nature of each benzene unit.

Itami and Segawa *et al.* have succeeded in the first chemical synthesis of **1** in 2017. The synthetic method of converting of an unstrained cyclic molecule into a cylindrical shape structure from *p*-xylene can be completed in 11 steps.[4]

The cylindrical shape of **1** was confirmed by X-ray crystallography, and its fundamental optoelectronic properties were elucidated by ultraviolet-visible (UV) absorption and fluorescence spectroscopic studies. These analyses demonstrated the properties of the carbon nanobelt with respect to its electric conductivity, light absorption and emission. Raman spectroscopy further demonstrated that carbon nanobelts have characteristics very similar to that of (6,6)carbon nanotube.[4]

Carbon nanobelts are expected to open the path for the synthesis of single-structured carbon nanotubes and the development of new functional materials, which will likely be instrumental in the next generation nanocarbon science. One noteworthy property of **1** is that it exhibits red fluorescence, which can be applied toward electronic devices as light emitting materials and as organic semiconductors. Furthermore, if a single-structured carbon nanotube can be obtained by using carbon nanobelt as a template, a wide range of applications are expected to emerge such as a light weight and stretchable display, a power saving super-integrated CPU, and highly efficient batteries and solar cells.

Figure 1. (6,6)Carbon Nanobelt (**1**)

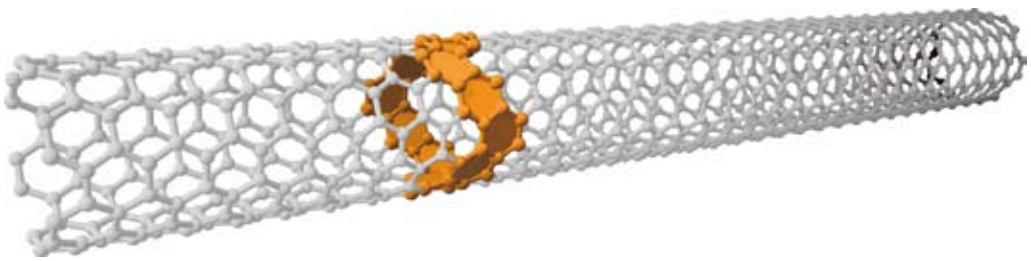
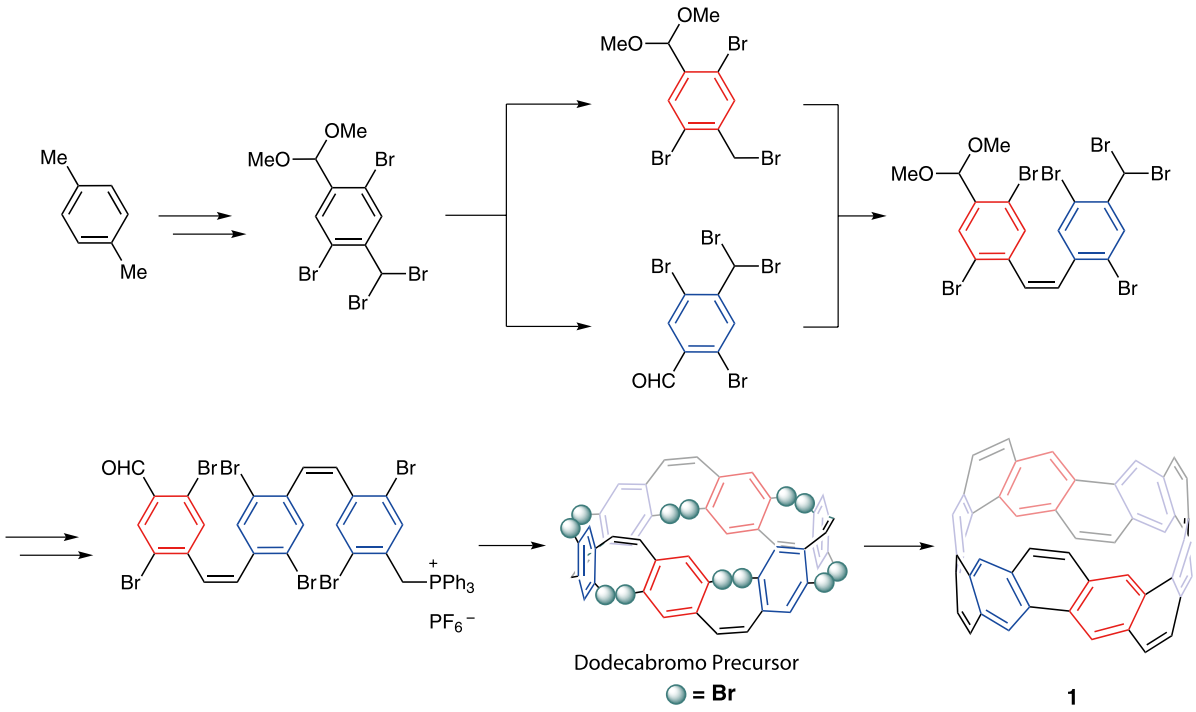


Figure 2. (6,6)Carbon Nanotube (Schematic Diagram)



Scheme 1.

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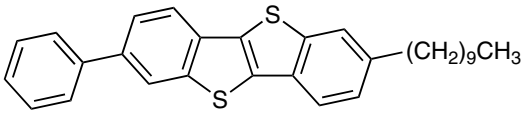
High-performance Liquid Crystalline Semiconductor Material: Ph-BTBT-10

D5491 Ph-BTBT-10 (1) **100mg 250mg**



Ph-BTBT-10 (**1**)

A liquid crystalline semiconductor material Ph-BTBT-10 (**1**) has been recently reported by Hanna *et al.*[1] as a p-type semiconductor material which possesses excellent transport properties. **1** exhibits an ultra-high mobility (μ_{max} = 14.7 cm^2/Vs) comparable to oxide-based semiconductors (IGZO), and remarkable air stability.[1] TCI has examined the fabrication and evaluation of **1**-based Organic Field-Effect Transistor (OFET) devices by vacuum deposition methods. Furthermore, TCI has investigated the vacuum-deposited thin film structure of **1** and the correlation between device performances and thin-film crystallinities through 2D grazing-incidence X-ray diffraction (2D-GIXD) analysis.[2,3]

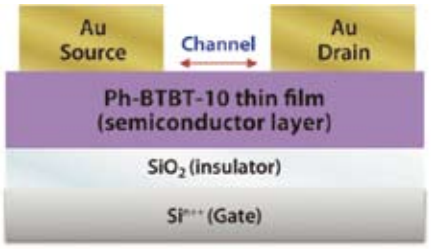


Figure 1. OFET device configuration

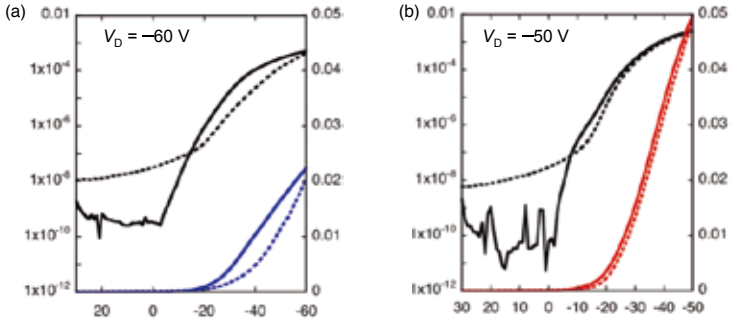


Figure 2. Transfer characteristics of Ph-BTBT-10 devices
(a) w/o annealing (ODTS) (b) annealing 120 °C 5 min (ODTS)

Table 1. OFET characteristics of vacuum deposition Ph-BTBT-10 devices

Compound	SAM	Annealing Temp. (°C)	Mobility (cm^2/Vs)	V_{th} (V)
Ph-BTBT-10 (**1**)	bare	w/o	0.87 ~ 0.91	-24
		120	4.24 ~ 4.86	-8
	ODTS	w/o	1.40 ~ 1.42	-23
		120	10.3 ~ 14.0	-22

The field-effect mobility of **1** was measured using top-contact thin-film field-effect transistor (FET) geometry (Figure 1). The performances of the OFET devices are summarized in Table 1 and Figure 2. All the devices exhibited pure typical p-channel FET characteristics. FET mobilities were quite dependent on the thermal annealing treatment regardless of the self-assemble-monolayer (SAM) (Figure 2). The device fabricated on bare substrate demonstrated good performance with a hole carrier mobility of 4.86 cm^2/Vs and threshold voltage (V_{th}) of -8 V. Moreover, although V_{th} increased (V_{th} = -22 V), the ODTS-treated devise exhibited a large increase in drain current (I_{DS}) and the highest transport performance with a hole carrier mobility of 14.0 cm^2/Vs.

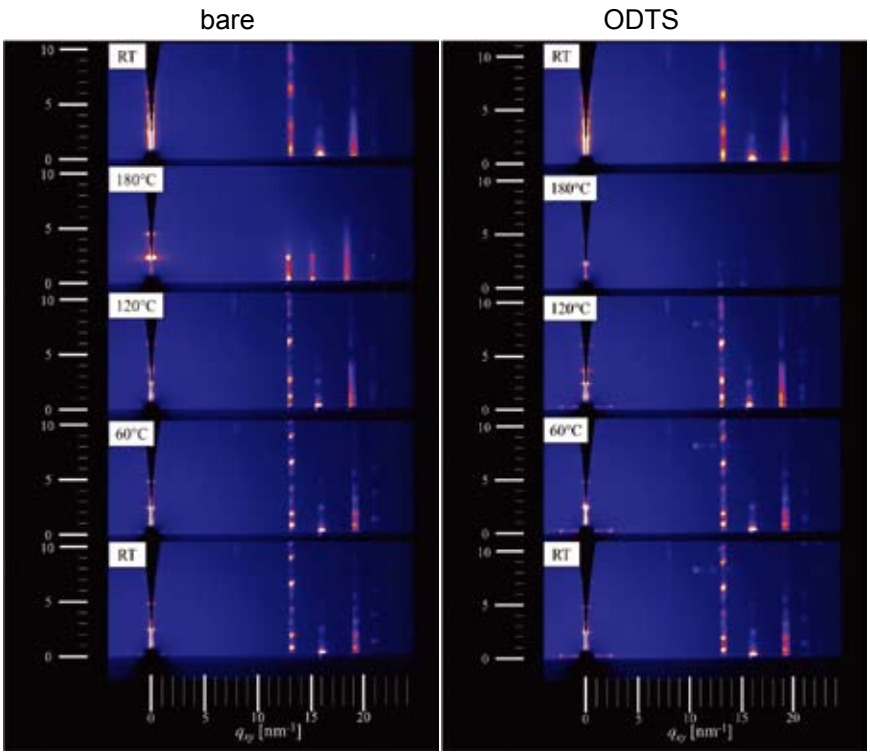


Figure 3. 2D-GIXD analysis (Thermal *in-situ* measurement)

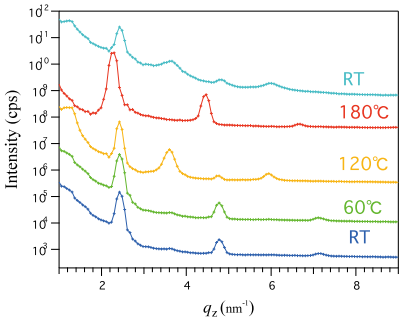


Figure 4. 2D-GIXD analysis (Out-of-plane, bare substrate)

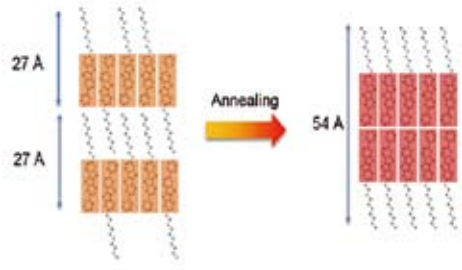


Figure 5. Phase transition Image of Ph-BTBT-10

Figure 3 and 4 show the thermal *in situ* 2D-GIXD data of 1-thin-film crystal structure.[2,3] The data at RT and 60 °C indicated a similar series of peaks assignable to a monolayer structure with a *d*-spacing of 27 Å. When the substrate temperature was increased to 120 °C, the diffraction peaks clearly changed, which suggests a transformation from a monolayer structure (d = 27 Å) to a bilayer structure with a *d*-spacing of 54 Å as shown in Figure 5. Since the phase transition temperature to the smectic E (SmE) mesophase is 144 °C,[1] a series of peaks assignable to SmE were observed when heated to 180 °C. In addition, a mixed layer of monolayer and bilayer structures appeared when the thin film of **1** was rapidly cooled from 180 °C to RT. This result indicates that the cooling speed might be a significant factor in forming a well-uniformed crystalline thin film structure.

Based on these results, **1** can be handled through vacuum deposition method, and the phase transition from the monolayer to the bilayer structure can occur in the same way in which it occurs for solution-processed thin films of **1**.[1] Finally, we demonstrated top-ranked FET performances via vacuum deposition process using our in-house equipment.

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We acknowledge Prof. Noriyuki Yoshimoto, Assist. Prof. Daiki Kuzuhara and Mr. Shimpei Miura (Iwate Univ.), Assist. Prof. Mitsuharu Suzuki (NAIST) and Dr. Tomoyuki Koganezawa (JASRI) for technical support in GIXD.
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Ready-to-use Substrate Solution for Peroxidas

A3176 AzBTS (Ready-to-use solution) [for ELISA] (1) 100mL
C3384 4-CN (= 4-Chloro-1-naphthol) (Ready-to-use solution) [for Western blotting] (2) 100mL

Peroxidase is an enzyme that catalyzes the oxidation of a given substrate mediated by hydrogen peroxide and is often used in biochemical experiments. **1** and **2** are available as follows.

1 is supplied as a ready-to-use solution for ELISA containing both 2,2'-azinobis(3-ethylbenzothiazoline-6-sulfonic acid ammonium salt) (AzBTS) and hydrogen peroxide. When **1** reacts with horseradish peroxidase (HRP), a green soluble reaction product appears. The absorbance of the reaction product is measured at 405 nm.

Direction for use
The following procedure is for a 96-well plate format.
1. Bring **1** to room temperature and mix gently.
2. Add 100 μL of **1** to each well.
3. Incubate the plate at room temperature for 30 minutes.
4. Within 1 hour from the start of the reaction, measure the absorbance of each well at 405 nm.

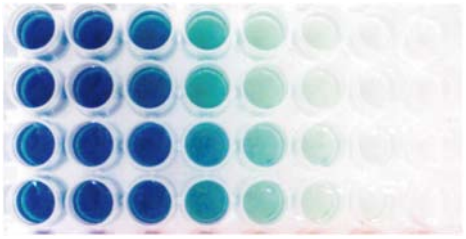

Figure 1. Example of use

2 is supplied as a ready-to-use solution containing both 4-CN (4-chloro-1-naphthol) and hydrogen peroxide for Western blotting. When **2** reacts with horseradish peroxidase (HRP), a blue-purple precipitate appears.

Direction for use
1. Incubate a blotting membrane with an HRP-conjugated antibody and then wash the membrane.
2. Incubate the washed membrane with **2** until color develops.
3. Dispose the solution and add deionized water to stop color development.

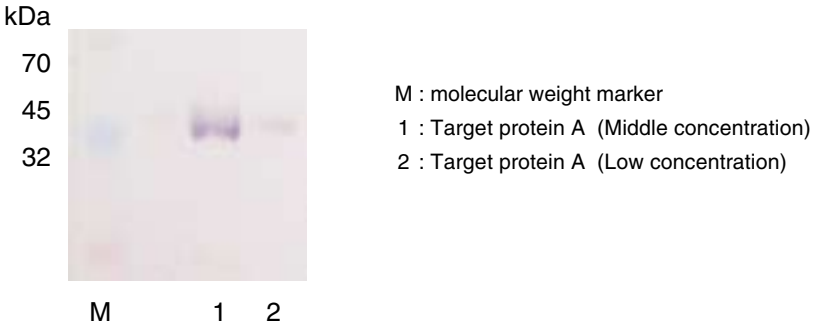

Figure 2. Example of Western blotting

These products are for research purpose only.

Reference
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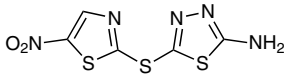
c-Jun N-terminal kinase (JNK) Inhibitor: SU 3327

A2940 SU 3327 (1) **20mg 100mg**



1

SU 3327 (**1**) is a JNK (c-Jun N-terminal kinase) inhibitor developed based on structure-activity relationship studies.[1] **1** inhibits activating transcription factor-2 (AFT-2) phosphorylation by JNK1 with IC_{50} = 0.7 μM in a substrate competitive manner. **1** also inhibits protein-protein interaction between JNK and JIP-1* with IC_{50} = 239 nM.

One of the important roles JNK plays is the induction of autophagy *via* stimulations as shown in Table 1. It has been demonstrated that acute ethanol treatment decreased autophagy in mouse models and the decrease in autophagy was prevented by **1**.[2]

* JIP-1: JNK-interacting proteins (JIP) were identified as JNK scaffold proteins.[3,4] JIP1 is a member of the JIP family and contains a JNK binding domain (JBD), an SRC homology (SH3) domain, and phosphotyrosine-binding (PTB) domain. JBD possesses the consensus sequence, R/KXXXXLXL.[5] The probe, pep-JIP1, used in the reference (1), contains the sequence.

Table 1. Autophagy by various stimuli implicating JNK

Stimulation	References
Neuronal excitotoxic stimuli	*Eur. J. Neurosci.* **2003**, *18*, 473.
Caspase inhibition	*Science* **2004**, *304*, 1500.
Starvation	*J. Immunol.* **2006**, *177*, 5163.
T-cell receptor activation	*J. Immunol.* **2006**, *177*, 5163.
Cytokine stimulation	*Immunol. Cell Biol.* **2006**, *84*, 448.
ER stress	*Mol. Cell. Biol.* **2006**, *26*, 9220.

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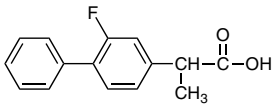
Cyclooxygenase (COX) Inhibitor: Flurbiprofen

F0371 Flurbiprofen (1) **5g 25g**



1

Flurbiprofen (**1**) functions as a cyclooxygenase (COX) inhibitors and inhibits COX-1 and COX-2 with the IC_{50}s of 0.1 μM and 0.4 μM, respectively.[1] **1** exists as a racemic mixture of their enantiomeric form and the *S*-isomer is a more potent inhibitor of COX isoenzymes than the *R*-isomer.[2,3] **1** is also widely known as a non-steroidal anti-inflammatory drug (NSAID).[1] Furthermore, **1** maintains the self-renewal and pluripotency of human embryonic stem cells.[4,5]

*Human recombinant COX-1 and COX-2 were used in the reference 1.

This product is for research purpose only.

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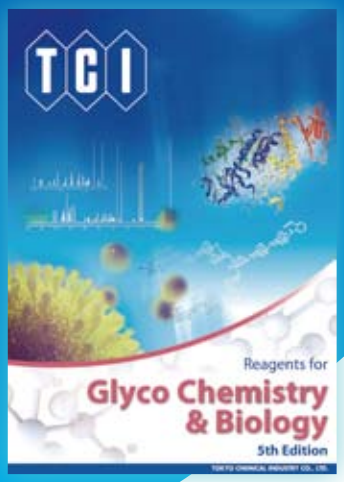

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