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DESIGN OF CONFORMATIONALLY LOCKED INOSITOLS AND HEXOSES THROUGH CARBOCYCLIC ANNULATION

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By conceptualizing the tactic of carbocyclic ring annulation, a new family of bicyclic, conformationally locked, bipolarofacial inositols has been designed. These trans-fused annulated inositols, based on decalin and hydrindane frameworks exist in unnatural axial-rich conformations. For example, bicyclic myo-inositol exist in (5a/1e) conformation compared to the (5e/1a) conformation present in the parent myo-inositol. The carbocyclic ring annulation stratagem has been extended to carbohydrates, thereby resulting in the synthesis of novel annulated glucose and gulose, which are locked in unnatural axial rich conformation. The synthetic sequence towards these novel inositol and hexose entities has emanated from simple and readily available aromatic precursors like indane, tetralin and naphthalene. These annulated inositols and hexoses show a columnar arrangement of molecules in the solid state, the O-H...O hydrogen bonds defining a channel-like architecture with a hydrophobic (annulus) exterior and a hydrophilic interior (inositol/ sugar moiety).

Key Words: Annulation; Cyclitols; Axial-rich; Carbohydrates; Conformational analysis; Dihydroxylation; Myo-inositol

Introduction

Carbohydrates and inositols are important and ubiquitous biomolecules. Carbohydrates as part of glyconjugates like the glycoproteins, glycolipids, etc are key elements in a repertoire of life sustaining processes in the biological system like cell-cell recognition, cell growth, cell development, cell-cell adhesion, inflammation, and metastasis. Carbohydrate recognition events have been implicated in the progression of a number of diseases, as the cell surface carbohydrates are known to mediate pathogen binding.[1,2] Despite this realization of the fundamental and central role of the carbohydrates in a repertoire of biological events, full exploration of the carbohydrate based therapeutics has been lacking until recently. This can be largely attributed to the sheer structural complexity associated with oligosaccharides and lack of proper analytical tools to study minuscule quantities of carbohydrates regulating biological events among other things. However, the recent advances in the synthesis of carbohydrates and availability of new structural tools and analytical techniques has stimulated development of new carbohydrate based therapeutics and vaccines based on carbohydrate-carbohydrate and carbohydrate-protein interactions. Furthermore, the discovery of diverse biological roles for oligosaccharides and glycoconjugates is fueling interest in the development of chemical entities (*carbohydrate mimics*) that can mimic the carbohydrates involved in various signaling and recognition events, but with improved physicochemical properties with regard to the stability, specificity, affinity and synthetic availability.[1,2]

Closely related to carbohydrates are the inositols **1** (perhydroxylated cyclohexanes) and their phosphate derivatives which regulate a wide range of biological processes. Among the nine known stereoisomeric inositols, *myo*-inositol **2** is the most abundant and its trisphosphate, [Ins(1,4,5)P_3] **3** acts as a *second messenger* in the intracellular signal transduction pathway that regulates the release of calcium ions from intracellular stores, which in turn initiates a large number of cellular responses.[3] In addition, inositols are also involved in insulin stimulation, intracellular trafficking of vesicles and covalent anchoring of proteins to membranes. The recognition of the fundamental cellular role played by *myo*-inositol phosphates has led to extensive biochemical investigations to unravel the details of the complex pathway involving them. However,

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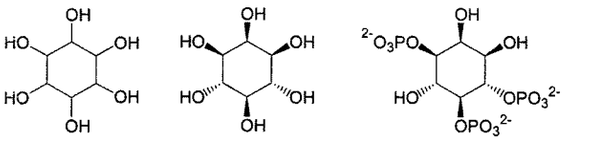
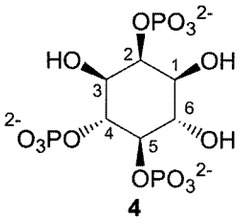


therapeutic potential of the inositol signaling pathway remains largely unexplored. In this context, the synthetic analogues of inositols with novel structural attributes may have interesting biological role to play. Such unnatural entities could help explore the structural requirements for binding to and activating the receptor.[4] Besides, such synthetic entities can also find applications as therapeutic agents. In this regard, conformationally constrained analogues of inositols may offer interesting prospects as they can be used to gauge the spatial requirements for effective protein-substrate interactions and provide insights into structure-activity relationships.

Conformationally Restricted Inositols

The quest for the new synthetic analogues of inositols has been extensive and attempts towards generation of inositol analogues have largely centered on ring modification, side arm and phosphate variations. Structure-activity investigation have showed that all the high-affinity agonists of $Ins(1,4,5)P_3$ receptor must contain groups equivalent to the vicinal 4R,5R-trans-diequitorial bisphosphate, Fig. 1.[3e,h] On this premise, a variety of inositols phosphate analogues were designed and synthesized retaining the phosphates at 4- and 5- position, but none could match the affinity of $Ins(1,4,5)P_3$ itself. . For example, the $Ins(2,4,5)P_3$ **4** was recognized by IP_3Rs, but with some 25-fold lower affinity than $Ins(1,4,5)P_3$.[3e]

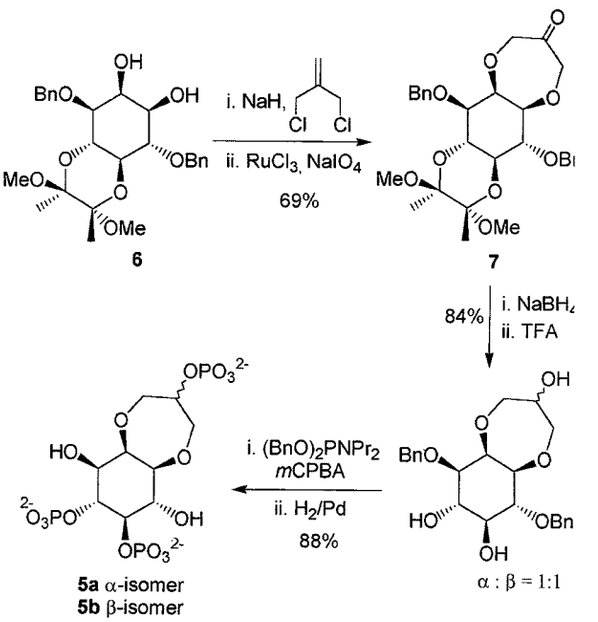
Besides the inositol variants derived from phosphate variations, there have been persistent efforts to generate structurally modified, particularly



4
D-*myo*-inositol-2,4,5-trisphosphate
Ins(2,4,5)P3

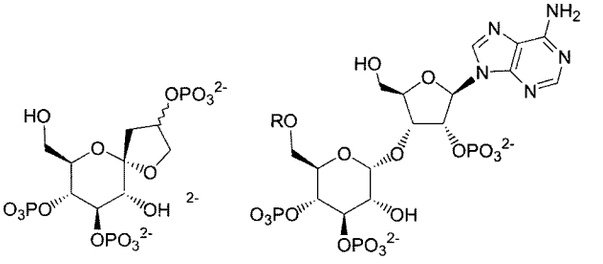
Fig. 1

conformationally restricted analogues.[3e,h] With the aim of decreasing the conformational mobility of the phosphate groups, Potter *et al.*, synthesized two bicyclic inositol variants **5a** and **5b** Scheme 1.[5] Synthesis of these bicyclic inositol phosphates commenced from the appropriately protected myo-inositol derivative **6** and the cis-diol moiety in it was protected using 3-chloro-2-chloromethyl-1-propene to deliver **7** and subsequent synthetic maneuvers furnished the bicyclic trisphosphates **5a, b** Scheme 1. Disappointingly, none of these bicyclic analogues showed any encouraging affinities towards $Ins(1,4,5)P_3$ receptors.



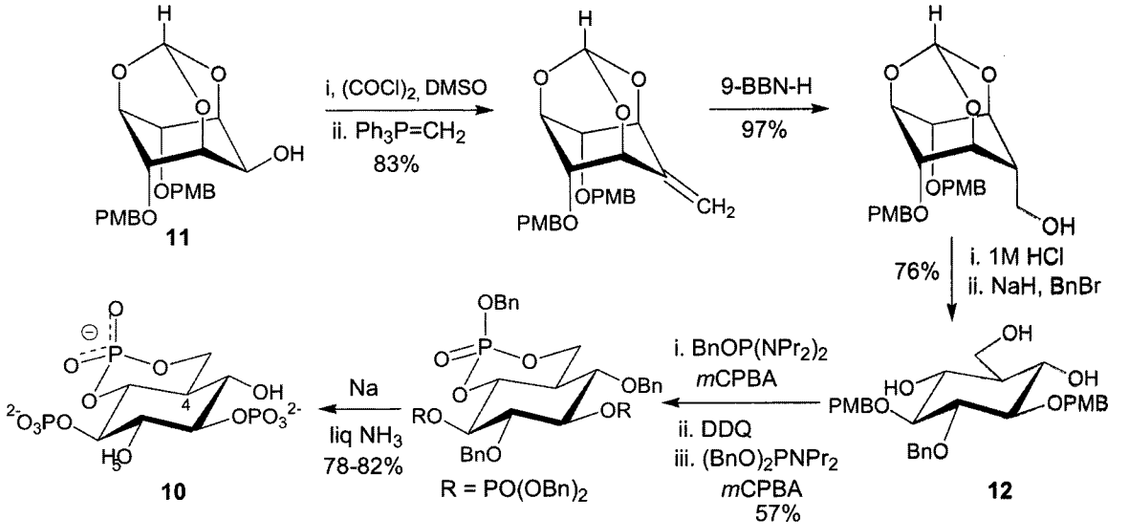
Scheme 1

van Boom *et al.* synthesized two glucose based, spiro-fused bicyclic analogues, "spirophostins" **8a, b**,[6] as conformationally restricted analogues of adenophostins A **9**[7] (a naturally occurring fungal metabolite, which exhibited high affinity for the inositol receptors) but these structural entities showed affinities about 20 fold lower than $Ins(1,4,5)P_3$.



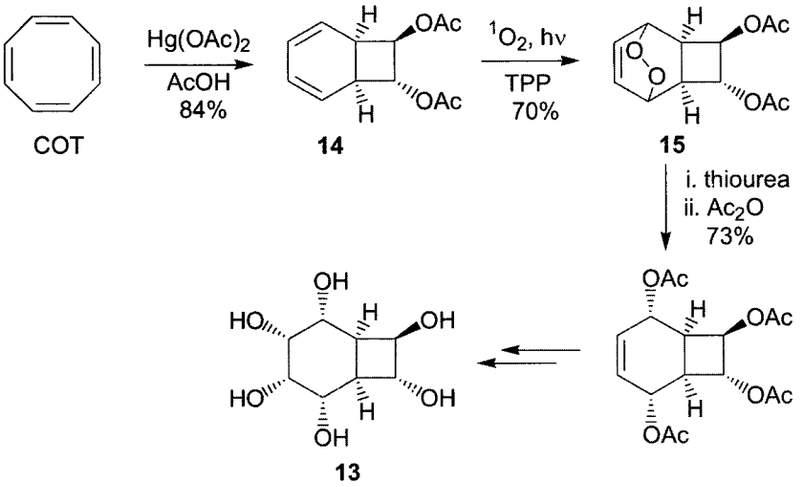
Potter *et al.* synthesized conformationally restricted cyclic phosphate analog of Ins(1,4,5)P_3, **10**, constraining the one phosphate group, thereby arresting the inositol moiety in a chair conformation.[8] Synthesis of **10** commenced from the inositol orthoformate derivative **11** and a sequence of protection/deprotection protocols led to the diol **12**. Further, sequential phosphorylation led to cyclic phosphate ester **10**, Scheme 2. However, the analog **10** was found to be weak agonist of Ins(1,4,5)P_3R. diacetoxydiene **14** which in turn was readily obtained from cyclooctatetraene (COT). The endo-peroxide **15** was reduced and the resulting diol was protected. Stereoselective dihydroxylation generated the oxygenation pattern in **13**.

In search for a suitable agonist for Ins(1,4,5,6)P_4 and antagonists for Ins(3,4,5,6)P_4, which regulate the trans-epithelial chloride secretion and transcription events, Schultz *et al.* have synthesized a bicyclic oxepin **16** and a tricyclic analogue **17**

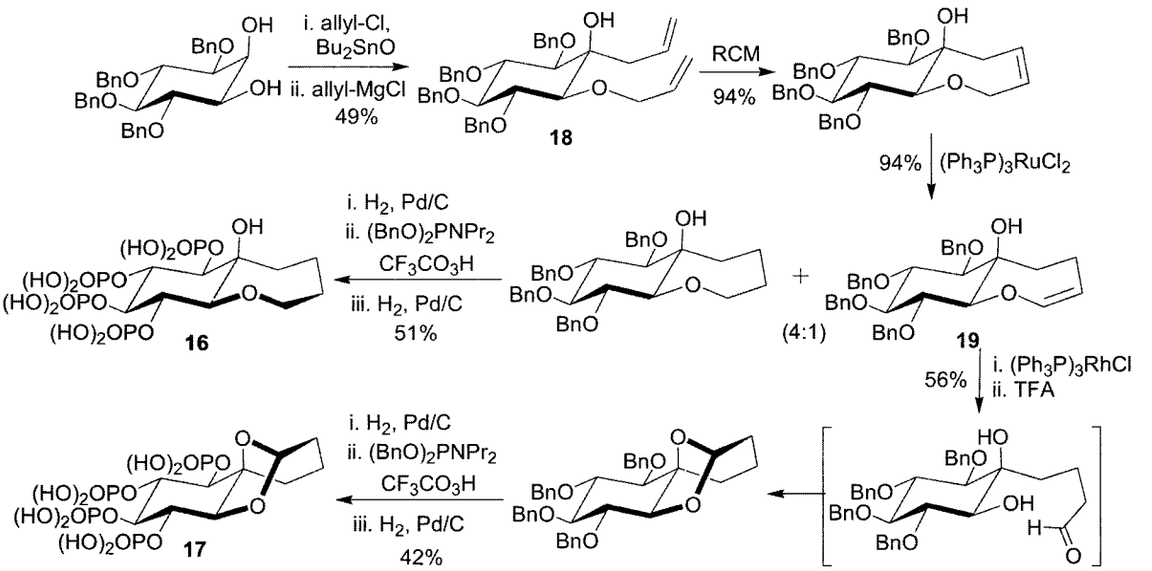


Scheme 2

Recently, Balci *et al.* reported a new structural variant of the inositols, namely bis-homoinositol **13**, Scheme 3.[9] The six-four ring fused bicyclic inositol was synthesized via a singlet oxygen mediated oxyfunctionalisation protocol on of the $InsP_4$.[10] The synthetic sequence, depicted in Scheme 4, emanated from suitably protected myo-inositol precursor and involved ring closing metathesis on the bis-allylated inositol derivative **18** as the key step. The tricyclic analogue **17** was



Scheme 3

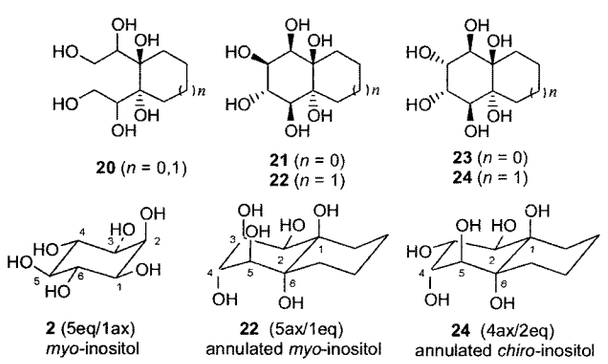


Scheme 4

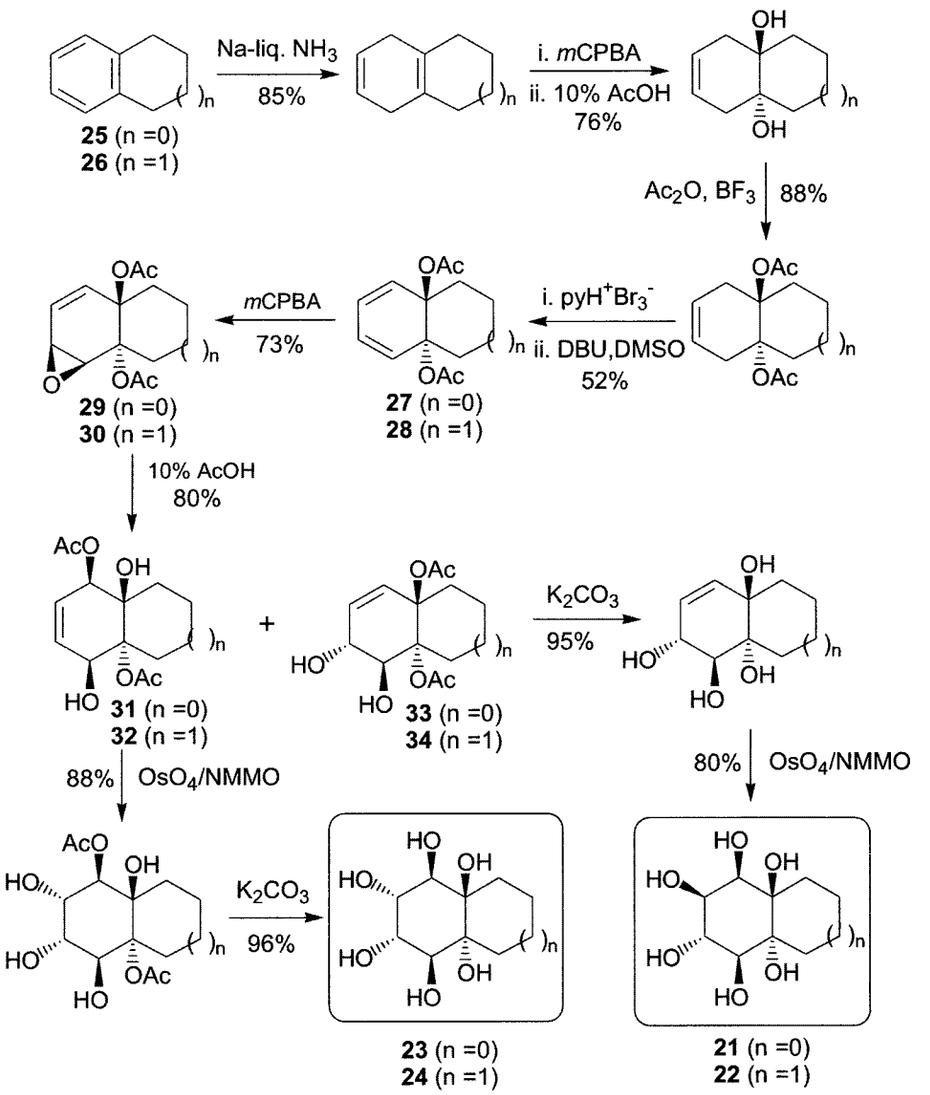
synthesized, from the double bond migrated compound **19**, which on oxidative cleavage and intramolecular acetalization furnished tricyclic framework.

Carbocyclic Ring Annulated Inositols

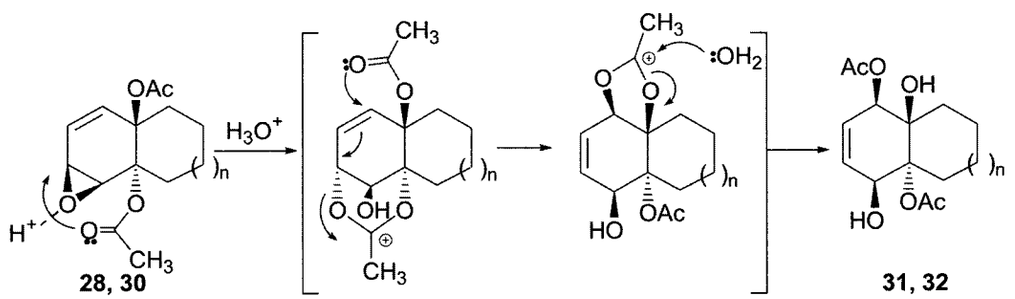
To access a brand new family of conformationally locked inositols we have conceived of novel variants like **20**, wherein a cycloalkane (5- and 6- membered) ring was appended, in trans fashion, to the inositol moiety.[11] A notable feature of such entities is that the *trans*-ring fusion locks the inositol moiety in an unnatural *axial-rich* conformation, while retaining the natural configuration of the parent inositol. In addition, the hydrophobic ring annulus present in **20** could also serve as a handle to fine tune the hydrophobic-hydrophilic balance in the polar inositols. The efficacy of this approach has been demonstrated through the synthesis of annulated myo-inositols **21**, **22** and chiro-inositols **23**, **24**. Parent myo-inositol **2** is known to exist in a stable conformation (1a/5e) with one axial and five equatorially disposed hydroxyl groups. However, the annulated myo-inositol **22** has been shown to exist in an axial-rich conformation, with five hydroxyl groups in axial orientation (5a/1e). Similarly, the annulated chiro-inositol **24** has a four axial and two equatorial (4a/2e) hydroxyl disposition, quite in contrast to the parent chiro-inositol having two axial-four equatorial hydroxyl disposition (2a/4e) in its stable conformation.[11] Our synthesis of the newly conceived ring annulated inositols commenced from readily available aromatics like indane **25** and tetralin **26**, through the intermediacy of annulated trans-cyclohexadiene diol (trans-CHD) derivatives like **27** and **28** as depicted in Scheme 5.



The trans-cyclohexadiene diol (trans-CHD) derivatives **27** and **28** are versatile, readily available building blocks for a wide variety of synthetic maneuvers and herein we detail their elaboration to a range of inositols. Monoepoxides **29**, **30** derived from trans-CHD derivatives **27**, **28**, on acid catalyzed cleavage led to a deep-seated rearrangement ("acetate dance", Scheme 6) to give cis-1,4-diol derivatives **31**, **32** and trans-1,2-diols **33**, **34**, respectively. The trans-diols **31**, **32** were further elaborated to the chiro-inositol **23**, **24**, respectively, through dihydroxylation and functional group alterations. In a similar manner, trans-diols **33**, **34** led to the annulated myo-inositols **21**, **22**, respectively, Scheme 5.



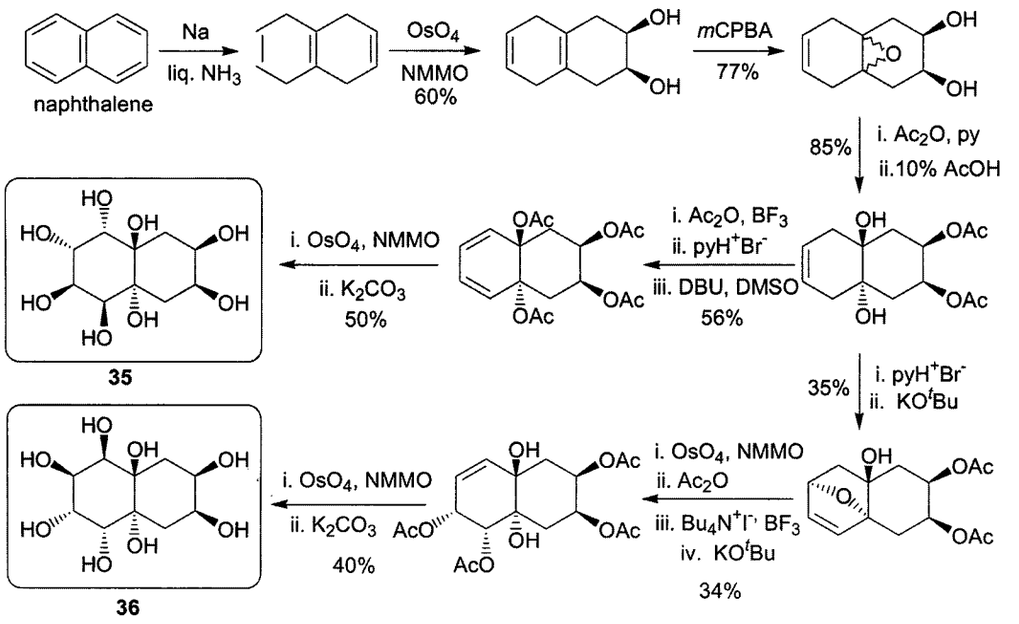
Scheme 5



Scheme 6

Following a modified approach, involving sequential oxyfunctionalization maneuvers, synthesis of annulated chiro-inositol **35** and neo-inositol **36**, with two additional hydroxyl functionalities on the cyclohexane annulus, starting from naphthalene has been realized, Scheme 7.[12]

The new inositols **35**, **36** due to trans fusion of the cyclohexane annulus, were also locked in unnatural axial-rich conformations, while retaining the natural configuration of the parent inositols. It



Scheme 7

is expected that the two additional hydroxyl groups in the annulated ring as in **35**, **36** can act as promoters of additional binding interactions along with the inositol core. The availability of novel bicyclic inositols with chemo-differentiated hydroxyl groups and novel spatial orientations augurs well for implementing phosphate variations and subsequent biological evaluation. Efforts along these lines could be quite rewarding.

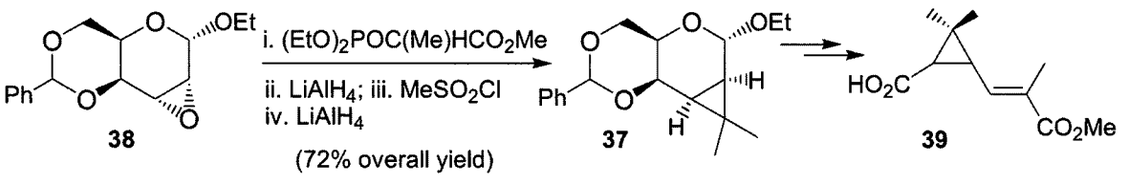
Annulated Carbohydrates

In recent years, carbohydrates have been extensively used as 'chirons' and as chiral auxiliaries ("*chirality transfer agents*") in a variety of enantioselective syntheses. However, given the central role of carbohydrates in a variety of cellular processes, structurally modified carbohydrates, particularly hexoses, can serve as interesting scaffolds for biochemical applications. Considerable efforts have been devoted to access a range of functionally and ring modified hexoses. In this context, carbocyclic ring annulation offers an interesting variant to design conformationally restricted and functionally modified hexoses with fine tuning of the hydrophilic-hydrophobic balance.

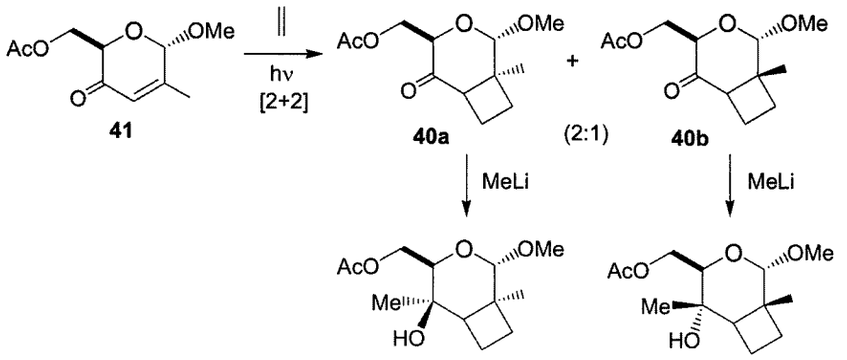
Several strategies based on inter- and intramolecular Diels-Alder reactions, Robinson annulation, radical cyclization, aldol condensation and other methods have been devised to gain access to mono- and bis-annulated hexoses. A few notable strategies adopted by different research groups for this purpose are discussed here.

The research group of Fraser-Reid has reported annulated pyranosides, with ring annulation varying from cyclopropane to the cyclohexane ring and each of these annulated entities has been utilized for the synthesis of various natural products.[13] The basic strategy in this case was to fuse a carbocyclic ring to the hexopyranoside to give the annulated sugar and then cleave the sugar ring to leave behind the carbocycle, with the transfer of chirality from the sugar moiety to the carbocylic portion. Along these lines, the cyclopropanated pyranoside **37**, obtained from epoxide **38**, was exploited towards enantiospecific synthesis chrysanthemum dicarboxylic acid **39**, Scheme 8.[13e,f] The cyclobutane annulated hexoses **40a,b** were obtained by photochemical [2+2] cycloaddition of ethylene to the enone **41**, Scheme 9.[13c] The conformationally immobile cyclohexano-annulated pyranoside **42** were obtained through the Diels-Alder reaction of the butadiene and carbohydrate derived enone **41**, Scheme 10.[13b,d] Cyclopentane annulated sibling **43** was obtained from the cyclohexenyl furanose **44** by oxidative cleavage of the cyclohexenyl ring in **42** followed by Dieckmann cyclisation, Scheme 10.[13b]

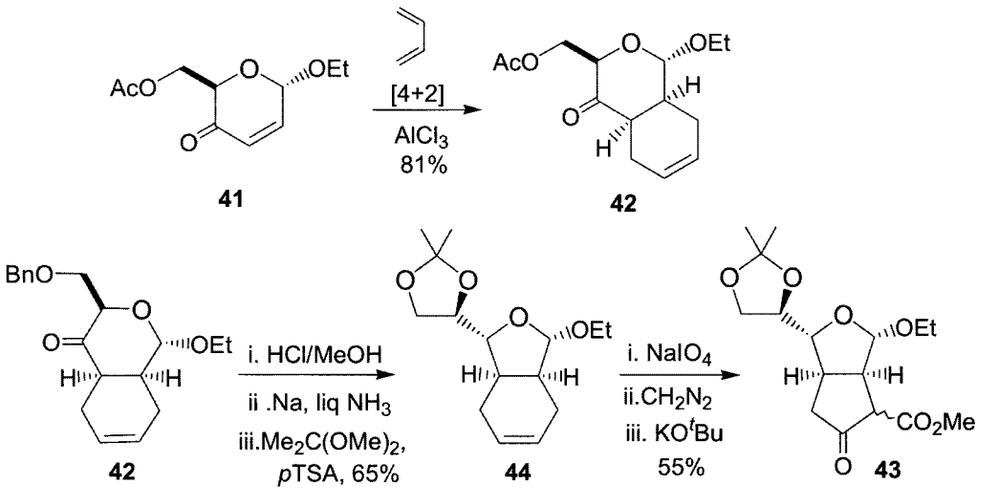
Marco-Contelles and coworkers have documented the synthesis of rigid, polyfunctionalised annulated furanoses, **45**, **46** and



Scheme 8



Scheme 9

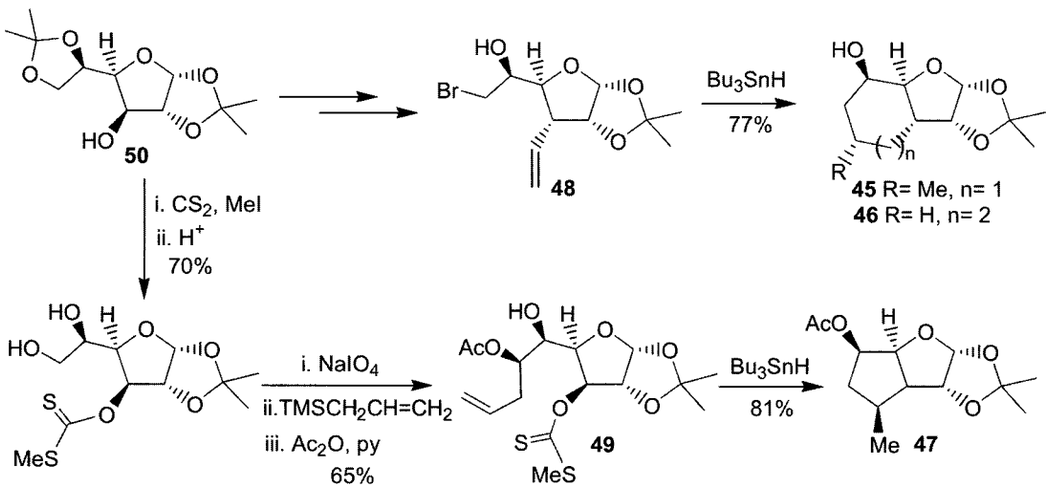


Scheme 10

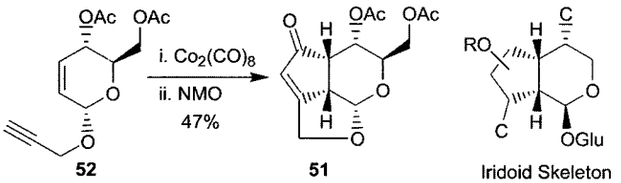
47 obtained through diastereoselective free-radical cyclisation of suitable chiral haloalkenes **48** or dithiocarbonate **49**, derived from diacetone glucose **50**, Scheme 11.[14] The same research group, in their efforts towards iridoid class of natural products, have generated a range of the cyclopentane annulated pyranosides like **51**, Scheme 12. The annulation in these systems was achieved *via* a Pauson-Khand reaction of conveniently functionalized 1,6-enynes like **52** on carbohydrate template derived from the D-glucal derivatives.[10a]

Sinou *et al.* have reported the synthesis of the *bis*-annulated pyranoside **53, 54** *via* a palladium acetate mediated 5-*exo*-trig cascade cyclization protocol on a bis-*O*-allylated carbohydrate template **55, 56** respectively (Scheme13).[16] The *O,O-bis*-allylated **55** and *N, O-bis*-allylated pyranoside **56** were readily obtained from the *O*-allylated glycal **57**.

An intramolecular Horner-Wadsworth-Emmoms olefination of appropriate vicinal β-ketophosphonate of pyranoside **58, 59** was adopted by Ermolenko *et al.* for the construction of cyclopentane **60** and cyclohexane annulated pyranoside **61**.[17] The phosphonates **58, 59** were obtained β-epoxide **62**, Scheme 14.



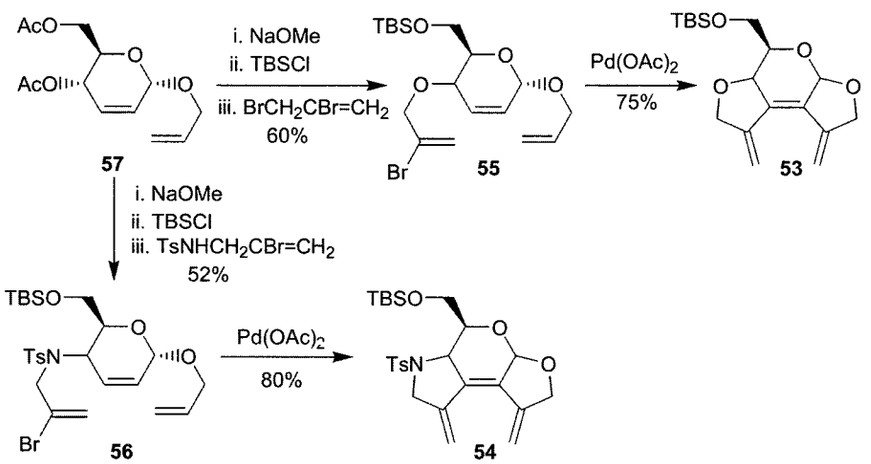
Scheme 11



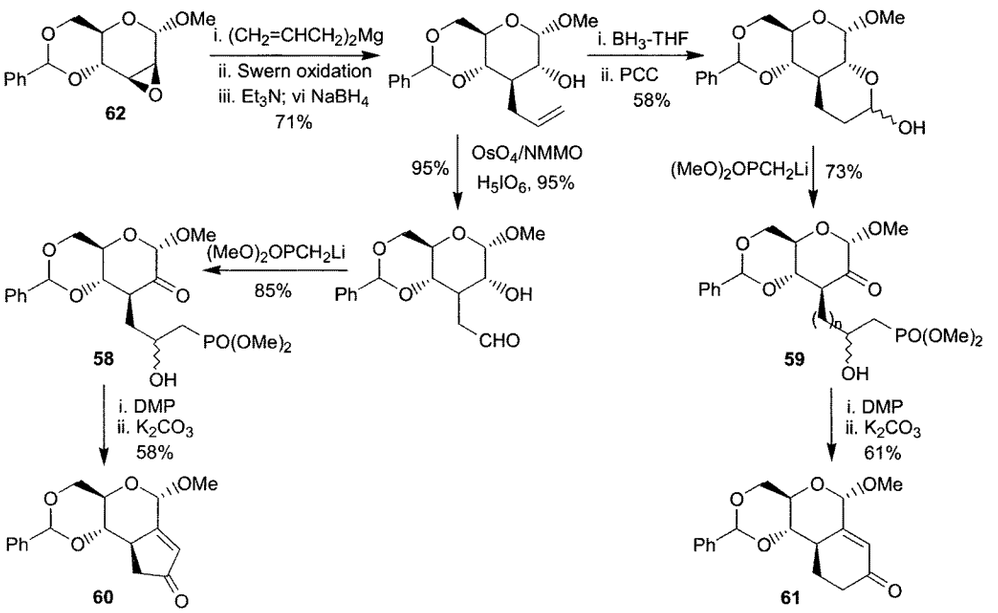
Scheme 12

Jenkins *et al.* have generated a range of annulated carbohydrates starting from conveniently protected carbohydrates using different strategies for generating the annulus.[18] The annulated appendage was introduced using (a) Robinson annulation protocol on the pyranoside **63** derived ketone derivative **64**,[18h] (b) intramolecular aldol based cyclopentaannulation of a glucose–derived diketone **65** to give enone **66**,[18e,f] (c) intramolecular [2+2] photoannulation catalysed by copper (I) triflate of dienes **67** on a carbohydrate scaffold to access tricyclic pyranoside **68**,[18a,c] and more recently (d) ring-closing metathesis (RCM) approach to the stereoselective preparation of enantiomerically pure annulated carbohydrates (**69-70**),[18b,d] Scheme 15. The RCM protocol to generate the bicyclic sugar entities **70** has been extended by Ghosh *et al* for the construction of cyclic ether annulation on to furanosugar to give **71**, Scheme 16. The synthesis of **71** started from O-allylated precursor **72**, obtained from diacetone glucose **50**.[19]

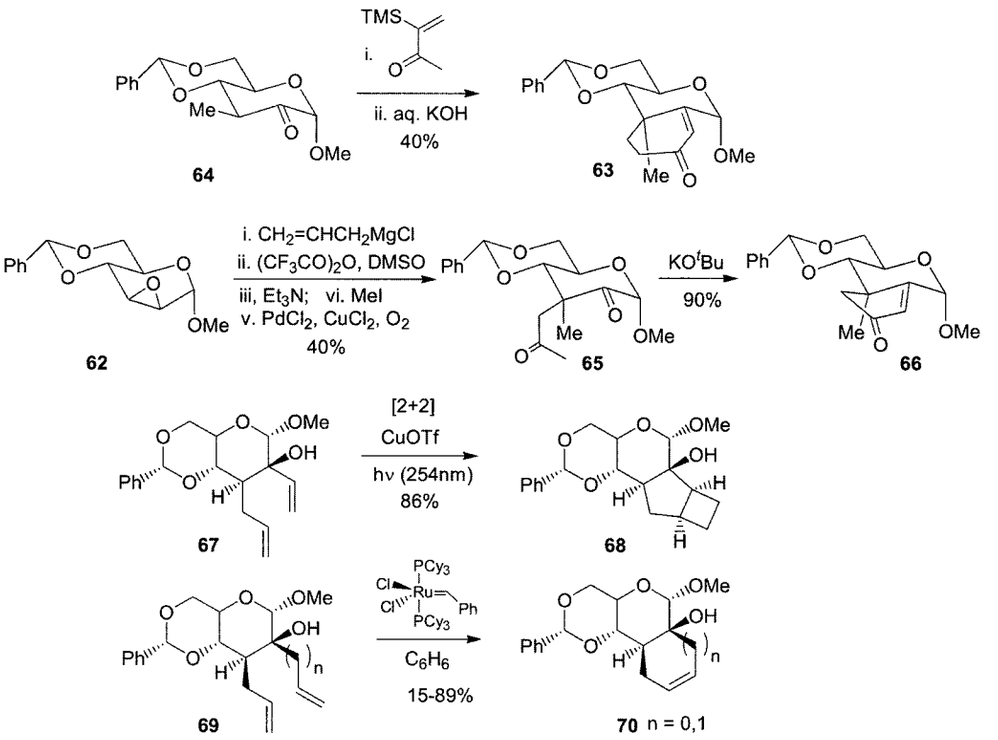
Cyclopropanated and spirocyclopropane-annulated sugar derivative, as well as their nucleosides, are of potential interest with regard to their physiological activity. The high strain energy of the cyclopropane moiety was expected to induce enhanced reactivity in such compounds and their



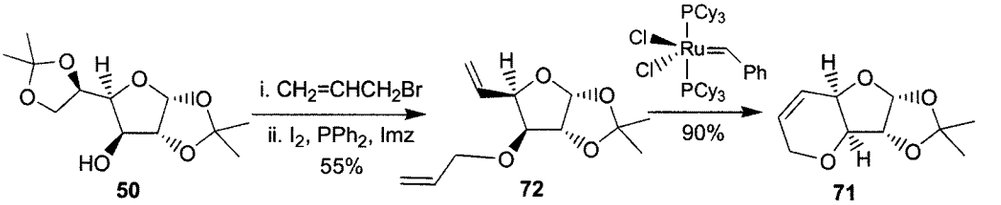
Scheme 13



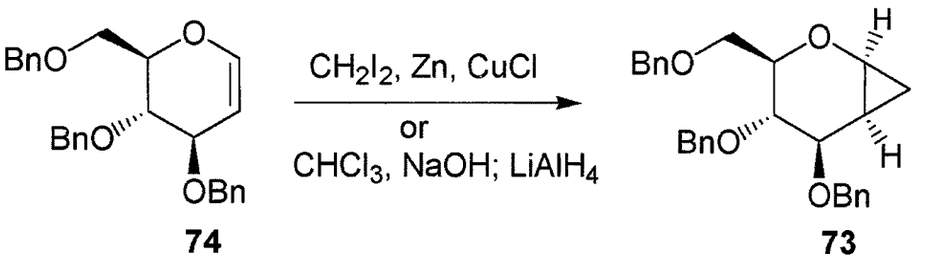
Scheme 14



Scheme 15



Scheme 16



Scheme 17

metabolic intermediates.[20] In this context, Nagarajan *et al* have synthesized a range of 1,2-cyclopropanated-sugar derivative **73** from tribenzylated glycal **74** adopting the Simmons-Smith protocol or the dichlorocarbene addition-dehalogentation for the introduction of the cyclopropane ring, Scheme 17.[21] de Meijere and co-workers have synthesized spirocyclopropane-annulated hexopyranoside derivatives **75**, using high-pressure-induced inverse-electron-demand hetero-Diels-Alder reaction to realize the pyran moiety in **76**, Scheme 18.[22] These novel constructs were evaluated against various glycosidases, but did not elicit any glycosidase inhibitory activity.

Recently, Sinay *et al.* have applied the strategy of conformational locking to carbohydrates to ascertain the active conformation of the L-iduronic acid, a typical monosaccharide component of heparin, responsible for the antithrombotic activity of the latter.[23] They synthesized three pentasaccharides in which the single L-iduronic residue was conformational locked, either in $^1C_4$, $^4C_1$ or $^2S_0$ form and they have shown the skew-boat conformation of L-iduronic acid governs the antithrombotic activity of heparin, Fig. 2.

Nielsen and co-workers have introduced novel 3',4'-*trans*-linked bicyclic nucleosides **77, 78** with sugar moiety locked in an S-type conformation, wherein the annulation was achieved by cyclic ether formation or ring-closing metathesis methodology, Scheme 19.[24] The synthesis emanated

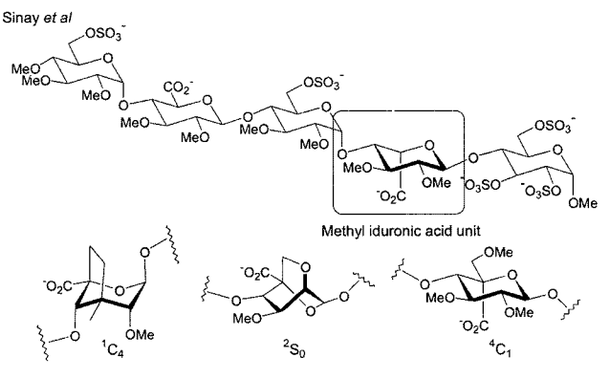
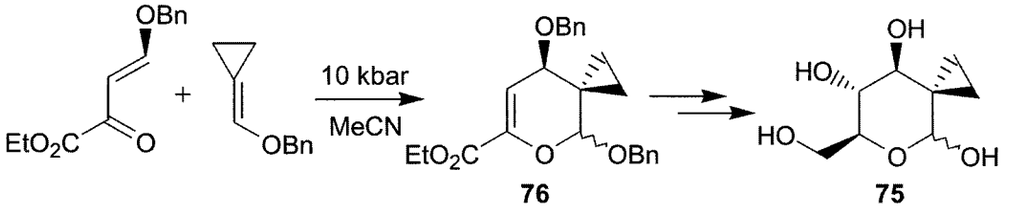


Fig. 2

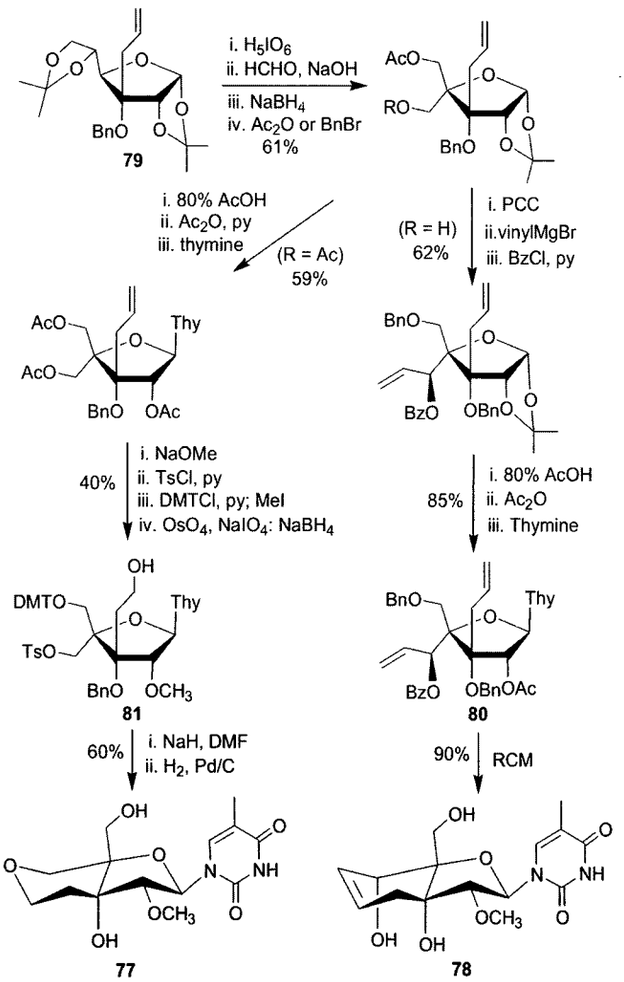
from the allylated *bis*-acetone glucose derivative **79**, which was elaborated to the alcohol **80** and diene **81**, which served as suitable precursors for generation of **77** and **78**, respectively.

Carbocyclic Ring Annulated Hexoses ("New sugars")

Having tasted the success in carbocyclic annulation tactic to generate *axial-rich* and conformationally restricted inositols, it was of immediate interest to extend the same strategy to hexose sugars. Thus, cyclohexane ring annulation, in *trans* fashion, to the carbohydrate moiety, could lead to a range of annulated carbohydrates **82 a-d** (*"new sugars"*), wherein the sugar moiety is locked in an unnatural, axial-rich conformation, while retaining its natural configuration.[25] Consequently, a *trans*-cyclohexane ring annulation to β-glucose **83**, having an all



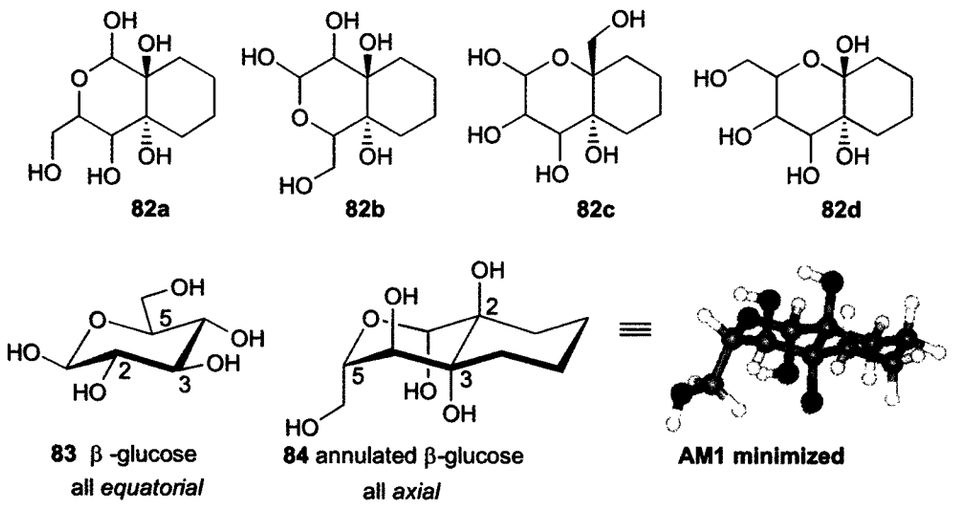
Scheme 18

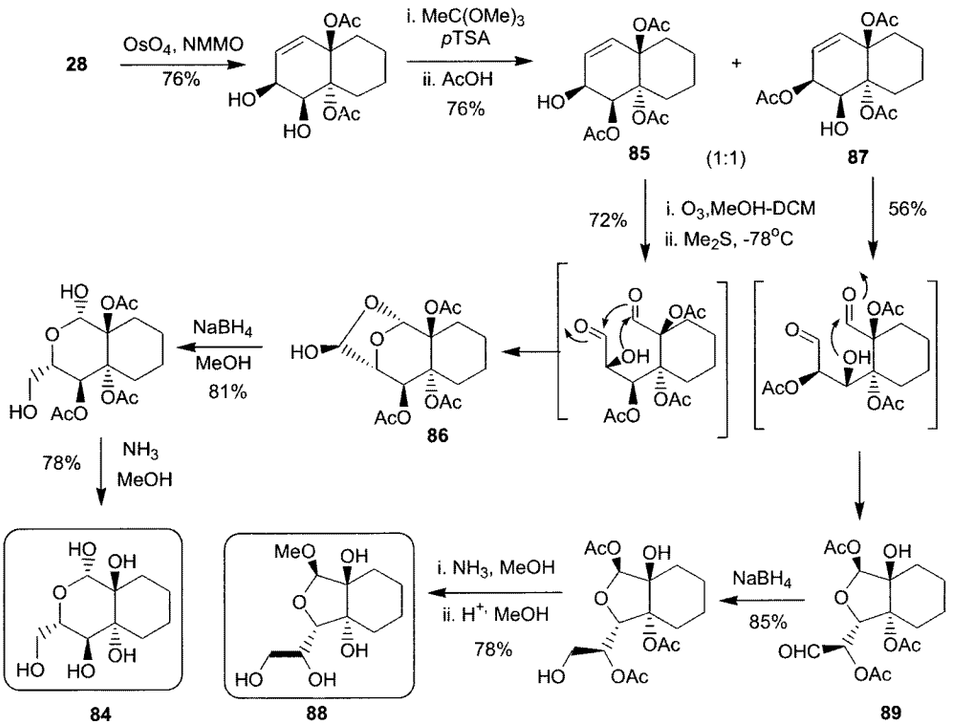


Scheme 19

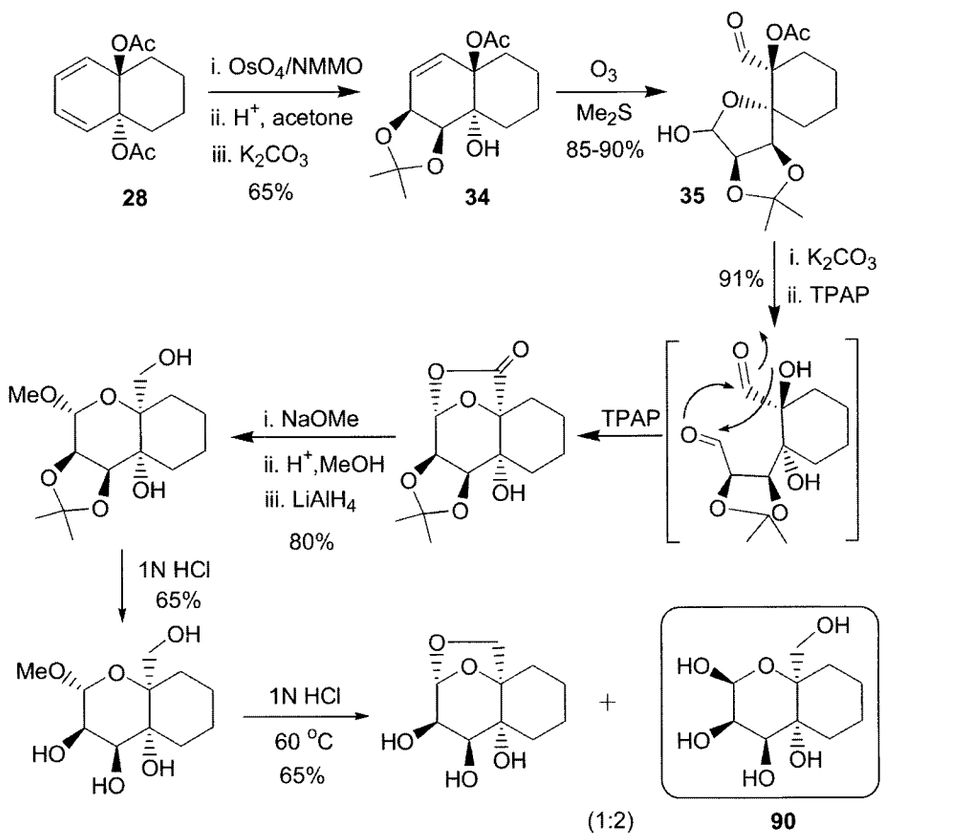
equatorial stable conformation, would result in a conformation having all the substituents in axial-disposition as in **84**. It was therefore decided to undertake a synthesis of annulated β-glucose **84** and this endeavor also commenced from the annulated *trans*-cyclohexadiene diol (*trans*-CHD) derivative **28**, which had proved its efficacy towards the synthesis of annulated inositols (*vide supra*). As depicted in Scheme 19, the allylic alcohol **85** derived from the *trans*-CHD derivative **28** was subjected to ozonolytic cleavage, with concomitant intramolecular acetalization to generate the pyran moiety bearing tricyclic acetal **86**, which after a sequence of protection-deprotection maneuvers was elaborated the annulated β-glucopyranose **84**. In another structural variation, following essentially a similar synthetic sequence, the homoallylic alcohol **87**, also derived from **28,** was elaborated to the annulated α- glucofuranose **88**, through ozonolytic cleavage of the double bond and intramolecular acetalization serving as the key step to realize the glucofuran moiety as in **89**, Scheme 20.

Additionally, the carbocyclic ring annulation strategy effectively used to generate conformationally constrained sugar variants was also employed to generate carbohydrate diversity. This was exemplified through synthesis of the two annulated gulopyranosides **90** and **91** differing only in the site of the ring annulation on the sugar moiety. A notable feature was that the synthesis of both 90 and 91 emanated from the same trans-CHD 28, making it a truly versatile building block, Schemes 21 and 22. The synthesis of annulated gulose derivative **91** employed a modified ozonolysis protocol and led to chemo-differentiated termini which on further intramolecular acetalization generated the pyran moiety of **92**, Scheme 22.

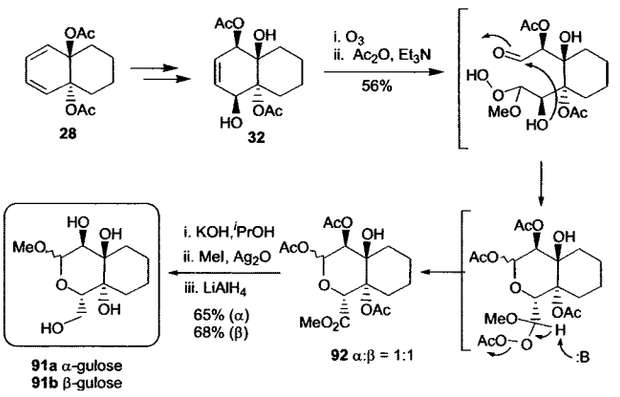




Scheme 20



Scheme 21



Scheme 22

Solid State Architecture of Annulated Inositols and Sugars: Evidence for Bipolarofaciality

Even though the solubility of annulated inositols and sugars in water showed little difference from that of the parent cyclitols and carbohydrates, the effect of appending a hydrophobic moiety to an otherwise polar inositol or sugar was observed most dramatically in the aggregation behavior of these molecules in the solid state. In fact a ubiquitous feature observed in the packing of cyclohexaannulated inositols and sugars in the crystalline phase is the formation of fascinating channel like architecture, formed by a hydrophobic exterior and an extensively O-H...O hydrogen bonded hydrophilic interior (Fig. 3). Interestingly enough such a phase separation disappears completely in case of cyclopentaannulated inositols.

An obvious explanation to this phenomenon lies in the fine modulation of the hydrophilic character of the cyclitols by a subtle alteration in the size of the hydrocarbon annulus. It was possible to quantify approximately this contribution from the hydrophobic appendage by a close examination of effective change in the polar surface area (PSA) of the cyclitols as brought about by a change in the size of the hydrocarbon ring (Table I). A map of the molecular lipophilic potential (MLP) surface showed too the trend in the modulation of the hydrophilic surface brought about by hydrophobic appendage (Fig. 4).

Besides demonstrating the capability of a hydrocarbon annulus to fine tune the hydrophilic

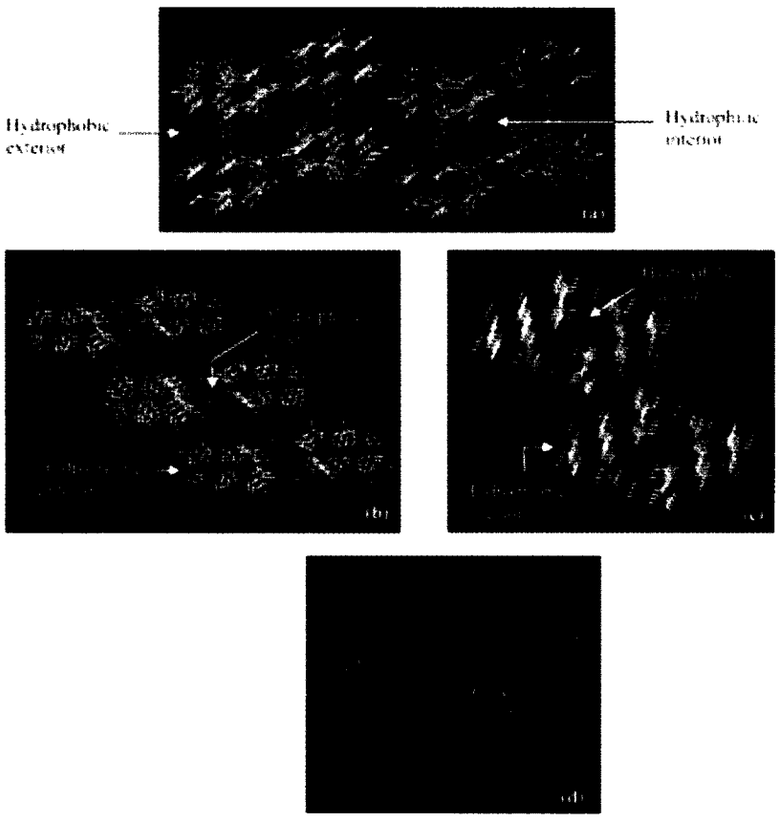
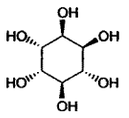
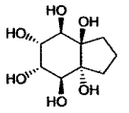
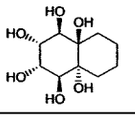


Fig. 3 Packing diagrams of (a) cyclohexaannulated chiro- inositol, (b) cyclohexaannulated myo- inositol and (c) cyclohexaannulated methyl-a-gulopyranoside showing the channel like architecture, and (d) cyclopentaannulated chiro- inositol.

Table I
Variation in the Effective Surface Area for the Parent and Anulated chiro *Inositols.*

	Molecular surface (Å^2)*	PSA (Å^2)	Ratio (polar : non-polar surface)
	331.3	254.5	**3.31**
	360.0	197.1	**1.20**
	373.0	194.2	**1.09**

*All molecular surface calculations were performed using the software VEGA online (http://galaxy.farma.unimi.it/vegawe/desktop.htm) using the atomic co-ordinates of the respective molecules as determined by X-ray crystallography as the input.

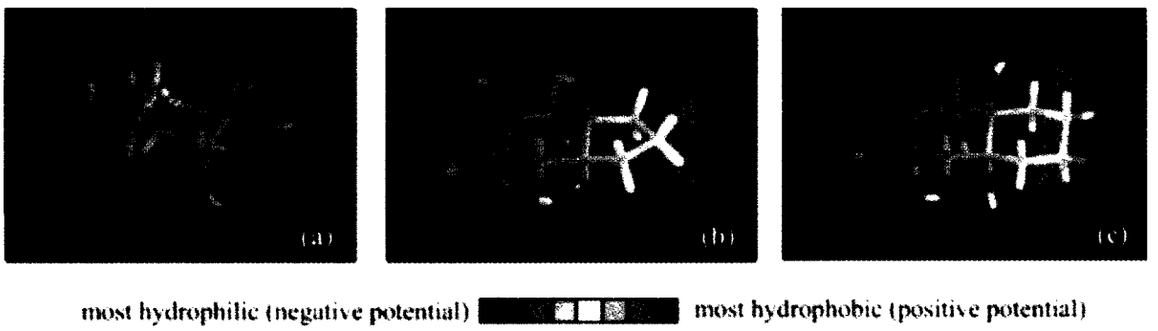


Fig. 4. Relative molecular lipophilic surface of (a) natural chiro-inositol, (b) cyclopentaannulated chiro-inositol and (c) cyclohexaannulated chiro- inositol. The standard MLP coloring scheme has been followed. Molecular surfaces were mapped using Chemscape Chime© (version 2.6 SP3), MDL Information System Inc. (http://www.mdlchime.com)

character of cyclitols, the solid state architecture of cyclohexaannulated inositols and sugars also bears evidence to their bipolarofacial character, a feature that distinguishes them from their non-annulated congeners. In fact it is the manifestation of this bipolarofacial behavior and the greater populace of axially locked hydroxyl groups that can be observed in the channel like solid state architecture of annulated inositols and sugars.

Conclusion

The tool of cycloalkane ring annulation to lock inositols and hexose sugars in unnatural, axial rich conformations has been conceptualized to create new polycyclitols. trans-Cyclohexadienediols (trans-CHDs), derived from simple aromatic precursors like tetralin, naphthalene and indane have served as starting materials for the synthesis of annulated inositols and carbohydrates through stereocontrolled oxyfunctionalization protocols. Synthesis of regioisomeric variants of annulated gulopyranoses highlights the efficacy of ring annulation strategy for generating carbohydrate diversity. The annulated carbohydrate and inositol entities prepared by us exhibit biploarofacial architecture in the solid state, further testifying to the fine tuning of the hydrophilic-hydrophobic balance in them. It is interesting to speculate on the nature of the oligosaccharides derived from the axially rich, annulated hexoses which are bound to unleash some interesting physico-chemical properties.

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