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Synthesis of L-hexoses and their related biomolecules

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Carbohydrates either conjugated or as free entities are major players in numerous biological processes. The desire to comprehend the nature of their functions and further develop therapeutic and diagnostic applications has fuelled the recent upsurge in the glycoscience field. Mainly accessed through chemical synthesis, homogeneous and well-defined sugar constructs are on high demand for structure–activity evaluation. Although the D-sugars, particularly the D-hexoses, have dominated the carbohydrate landscape, L-hexoses also attracted attention because they are known components of important polysaccharides, antibiotics, and other natural products. Nonetheless, the L-hexose-based materials needed for making building blocks for sugar assemblies are rare and are usually expensive if commercially available. Thus, intense efforts were focused on the development of innovative and reliable methods for the acquisition of L-hexoses and their derivatives. This review outlines several efficient and cost-effective routes for the chemical syntheses of L-hexoses, particularly focusing on approaches that utilize commercially abundant sugars as starting materials. A sampling of the applications of the generated L-hexoses in preparing biologically relevant compounds is also provided.

1 Introduction

There is great diversity and complexity in carbohydrates—the most abundant biopolymer in Nature.[1] While traditionally acknowledged as key structural supports and energy storage molecules, recent advances have also identified them as potent mediators and modulators of cellular activities. More than 50% of proteins carry one or more sugar structures[2] that, in turn, impinge on the various aspects of the protein character such as

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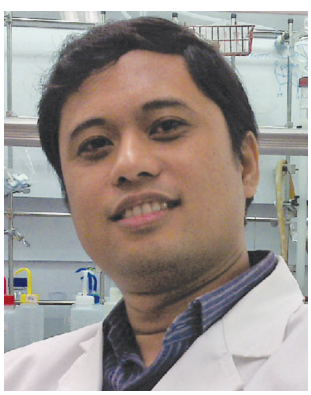


Medel Manuel L. Zulueta

Medel Manuel L. Zulueta earned his BS Chemistry degree at the Polytechnic University of the Philippines in 1997. After a few years in the private sector, he undertook graduate studies at the University of the Philippines and got the opportunity as an exchange student under Prof. Shang-Cheng Hung at the Genomics Research Center, Academia Sinica in Taiwan. He received his PhD in Chemistry in 2011. He is currently working with Prof. Shang-Cheng Hung in Academia Sinica as a post-doctoral fellow. His research interest is focused on the development of strategies for the chemical synthesis of oligosaccharides, particularly heparin and heparan sulphate.

Yong-Qing Zhong

Yong-Qing Zhong was born in Taiwan and obtained his bachelor's degree in chemistry at National Central University in 2005. He is currently a PhD student at National Tsing Hua University in Taiwan under the guidance of Prof. Shang-Cheng Hung. His doctoral research is focused on the development of efficient strategies for the synthesis of heparin and heparan sulphate libraries.

folding, targeting, trafficking, biological function, stability, and immunogenicity.[3] Sugars are also found conjugated to lipids anchored at plasma membranes[4] and as components of several natural products profoundly contributing to potency.[5] Cell-surface carbohydrates have pivotal roles in recognition, adhesion, and signalling that affect numerous biological processes from fertilization to development and from bacterial and viral infections to immune response. Such plethora of functions emerges from the exquisite structural complexity that these materials are able to exploit.[6] Individual sugar units are polyhydroxylated and bear multiple chiral centres. Numerous positions in their furanosidic or pyranosidic rings are amenable to linkage with another unit to form polymers that may be linear or branched. As a result, carbohydrate polymers hold extensive structural information density, beating nucleic acids and proteins by a long shot. Altogether, these findings fuelled the growth of glycobiology as they seek to unravel the intricacies of sugar functions and further provide inspirations for the development of novel diagnostic and pharmaceutical agents.[7]

Natural sugar constructs are generated using a non-template-driven process and are often heterogeneous, complicating isolation and purification.[6] Thus, chemical synthesis remains the most common source of pure well-defined carbohydrate structures for evaluating structure–activity relationships.[8] The relative ease of preparation of these compounds is dependent, in part, on the ready access to monosaccharide building blocks in the form of glycosyl donors and acceptors. Present in most oligo- and polysaccharides, D-sugars, particularly D-hexoses, are widely accessible. As for the L-form sugar units, only L-arabinose, L-fucose (6-deoxy-L-galactose), and L-rhamnose (6-deoxy-L-mannose) can be obtained in ample quantities from natural sources. The prevalence of these monosaccharides gave way to the straightforward preparation of corresponding building blocks for oligosaccharide assembly. In addition to their applications in sugar synthesis, they have been conveniently explored as chiral sources and as asymmetric catalysts in organic reactions.[9]

Shang-Cheng Hung

Shang-Cheng Hung obtained his PhD from National Tsing Hua University of Taiwan in 1992. After postdoctoral research with Prof. Andrew Streitwieser at University of California, Berkeley, and Prof. Chi-Huey Wong at Scripps Research Institute, he started his independent research at the Institute of Chemistry, Academia Sinica in 1998. In 2005, he moved to the Department of Chemistry, National Tsing Hua University. He is currently a Distinguished Research Fellow at the Genomics Research Center, Academia Sinica. His research focuses on carbohydrate chemistry and chemical biology, including the synthesis of heparin oligosaccharides and mycobacterial cell envelope components together with their bioevaluation.

L-Hexoses have also attracted significant attention despite their limited natural occurrence. Numerous biologically potent compounds contain L-hexoses within their structure (Fig. 1). For instance, the repeating disaccharide units (**1** and **2**) of heparin, heparan sulphate, and dermatan sulphate glycosaminoglycans include L-iduronic acid.[10] These polyanionic polysaccharides act as binding sites for various proteins, dynamically affecting the biological activity of the ligand. Here, L-iduronic acid, which assumes several conformations in solution, provides added flexibility to the polymer and, thus, is commonly situated at protein binding sites. Alginates (**3**), the polysaccharide from brown algae and some bacterial species, include blocks of D-mannuronic acids and L-guluronic acids as well as regions with mixed units.[11] High levels of L-guluronic acid within the polymer confer increased selective binding capability to metal ions affecting gel formation, stability, and immunogenicity. L-Altruronic acid, on the other hand, is a key feature in the tetrasaccharide repeating units of the *Proteus mirabilis* O10 (**4**)[12] and *Aerococcus viridans* var. homari[13] capsular polysaccharides. Moreover, the extracellular polysaccharides of *Butyrivibrio fibrisolvens* strain CF3 carry L-altrose as a typical component.[14] Meanwhile, L-galactose occurs in the A side chain of the pectic polysaccharide rhamnogalactorunan II (**5**).[15] L-Mannose together with L-rhamnose are structural components of the related capsular polysaccharides S-88 (**6**), S-130, and S-198 from *Sphingomonas*, which possess diverse industrial and food applications.[16] The carbohydrate component of the potent antitumour antibiotic bleomycin A_2 (**7**) comprises D-mannose $\alpha1\rightarrow2$-linked to L-gulose.[17] This moiety plays a crucial role in cell-surface recognition and is associated with the metal-binding domain of the molecule. Conversely, the antibiotics neomycin B (**8**),[18] adenomycin,[19] and capuramycin,[20] possess the sugars 2,6-diamino-2,6-dideoxy-L-idose, L-gulosamine, and 3-*O*-methyl-L-talofuranosyluronamide, respectively. Apoptolidin A (**9**), a macrolide with attached 6-deoxy-L-glucose from *Nocardiopsis* species, is a selective inducer of apoptosis in tumour cells.[21] The sulphated glycopeptidolipid from the *Mycobacterium avium* cell wall (**10**) has a 6-deoxy-L-talose residue.[22] Some terpenoids were also found conjugated to L-sugars such as L-idose from *Aster spathulifolius* Maxim (**11**)[23] and L-galactose from the marine octocoral *Muricea cf. purpurea*.[24] Natural compounds aside, the evident absence of chiral specificity in mammalian taste buds allowed L-sugars such as L-glucose and L-fructose to be explored as potential noncaloric sweeteners.[25] Their use, however, was primarily curtailed by the cost of preparation of these simple compounds. Phenolic conjugates of L-iduronic acid and L-mannose are utilized as substrates for measuring the activity of L-iduronidase[26] and the commercial naringinase,[27] respectively. Carbohydrate constructs that are mirror images of natural D-sugar-dominated structures are also being explored to further understand the interactions with protein and other biomolecules including their potential in evading antibody detection and enzyme degradation.[28]

With the need becoming more evident, particularly as building blocks in oligosaccharide assembly, various synthetic approaches were conceived to gain access to the rare L-hexoses.[29] The novel strategies advanced by several groups include *de novo*

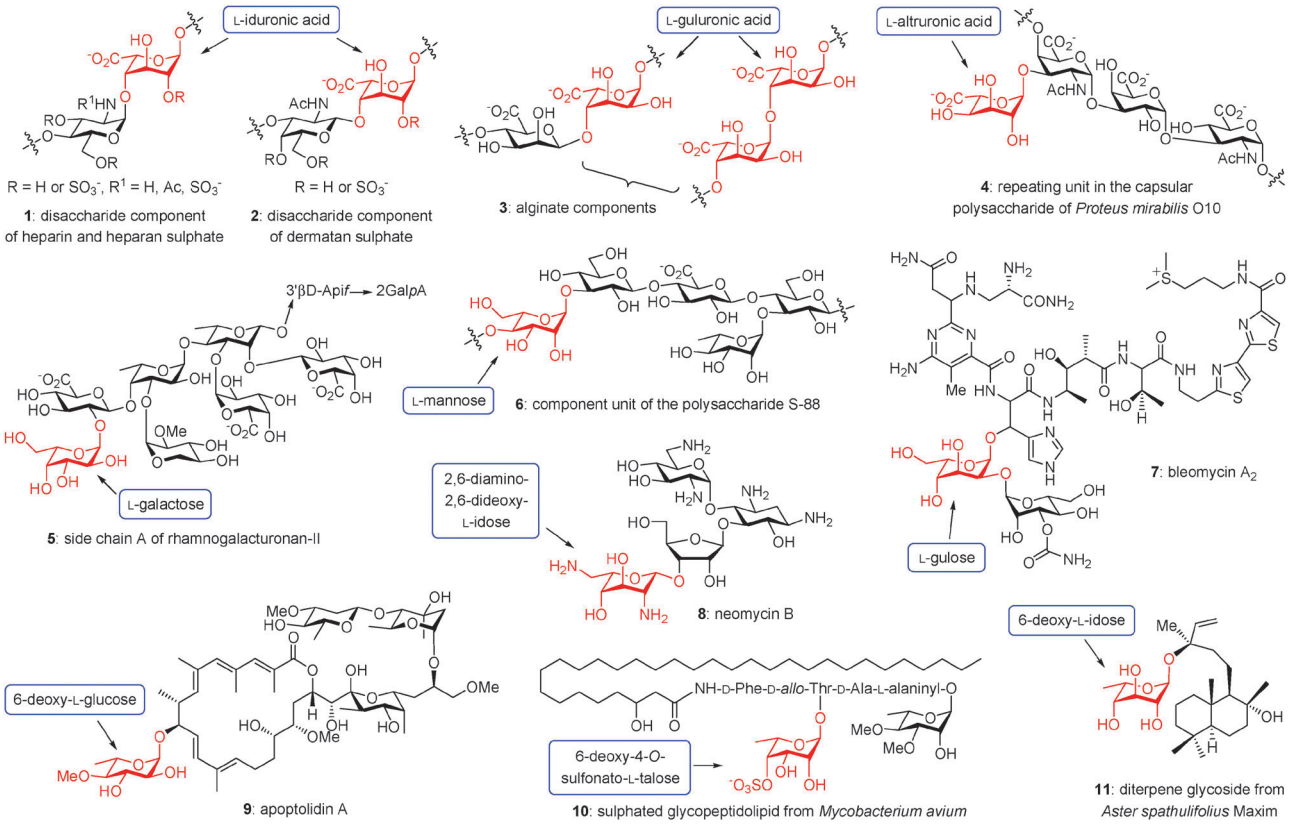


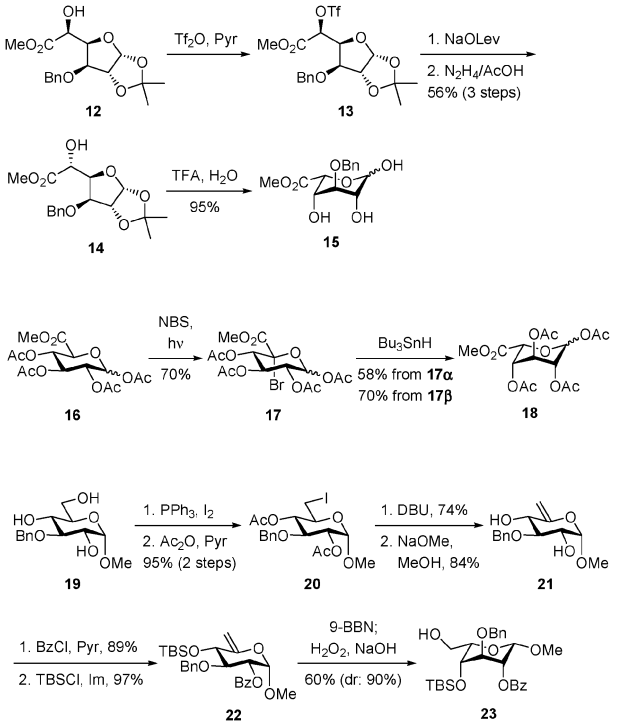
Fig. 1 Some natural compounds that have L-hexoses in their structures.

syntheses from non-sugar starting materials,[30–33] multicarbon elongation of shorter monosaccharides,[34] elaboration of the more abundant D- and L-sugar forms, and enzymatic synthesis.[35] As the topic became the subject of numerous intense investigations, we focused this review on the preparation of L-hexoses using the abundant pentoses and hexoses as starting materials. In such cases, the synthetic routes are relatively simple, convenient, and cost effective, enabling large scale preparations to be carried out. Because most chiral centres in the starting materials are already in place, these routes are largely straightforward and, although they still pose some concerns and an area for improvement, issues on reaction stereoselectivity are minimal. Many of the L-form products are also judiciously decorated with protecting groups suitable for their target application. Finally, we also present some synthetic examples that utilize L-hexose building blocks in the assembly and total synthesis of biologically relevant compounds.

2 Epimerisations

Hexoses mainly differ in the stereochemistry of one or more hydroxyl (or amine) groups. Epimerisation can, therefore, be devised to access many rare L-hexoses from their readily available D- and L-configured counterparts. This convenient and practical route has been extensively applied, with several distinct strategies available.

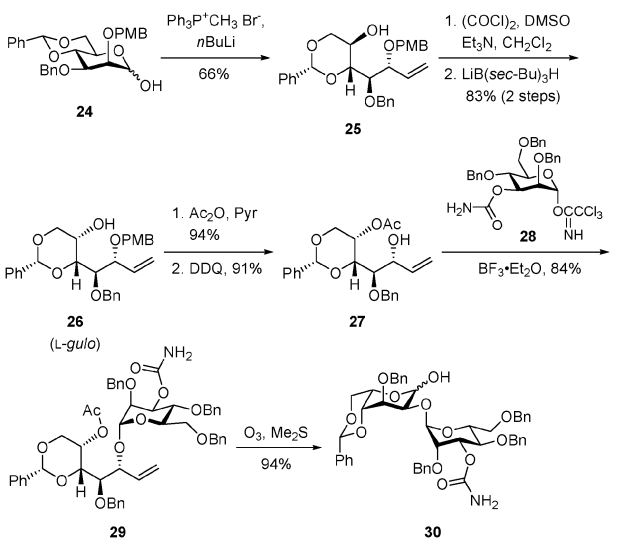
The orientation of the oxygen substituent at the C-5 position is what separates the realms of D- and L-hexoses. Plain D-hexoses have an *R*-configured C-5, whereas, in L-hexoses, C-5 is *S*-configured. Consequently, a C-5 inversion would convert the very abundant D-glucose into the rare L-idose and for that matter, D-mannose into L-gulose and D-galactose into L-altrose. The preparations of L-idose and L-iduronic acid building blocks, often demanded by the synthesis of chemically pure glycosaminoglycan analogues,[36] were mostly carried out in this manner. A representative sampling of the strategies involving the C-5 epimerisation of D-*gluco* compounds towards the L-*ido* configuration is shown in Scheme 1. The S_N2 substitution of the 5-triflate derivative of the uronate **12** generated the L-*ido* isomer. Cleavage of the levulinate (Lev) ester furnished the alcohol **14** and, by further acid hydrolysis of the isopropylidene protection, provided the triol **15**.[37] As often is the case with an unprotected 5-hydroxyl, freeing the anomeric position of the generated L-hexofuranoside leads to the formation of a mixture of furanosyl and pyranosyl products that have to be dealt with to avoid complications in the succeeding steps. Consequently, some groups implemented the epimerisation of the C-5 stereocentre without opening the pyranose ring of the D-sugar. Wong and co-workers performed free radical bromination at the C-5 position of the pyranose **16** using *N*-bromosuccinimide (NBS) in refluxing CCl_4 under UV light.[38] A dibutyltin hydride-mediated reduction at C-5 delivered the L-iduronate **18** as the major product, of which the orientation of the anomeric acetate displayed an influence on yield. Compound **19**, on the other hand, was first converted into the 6-iodide **20** and, then, into the *exo*-glycal by elimination of HI through the assistance of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).[39] Hydroboration of **22** with 9-borabicyclo[3.3.1]nonane (9-BBN) produced the L-idose



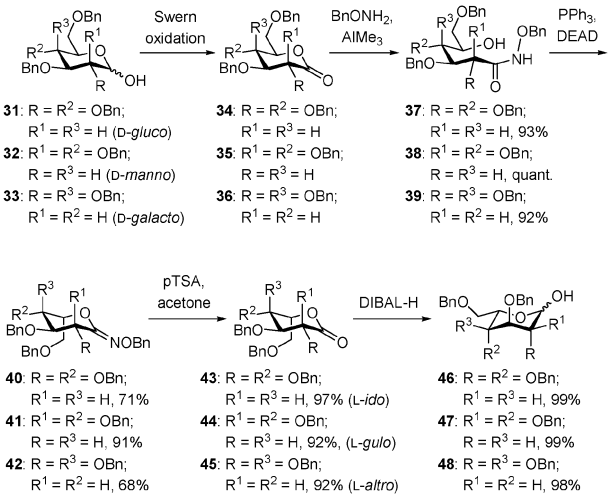
Scheme 1 Examples of procedures in transforming D-*gluco* into the L-*ido* configuration.

derivative **23** in 60% yield and 90% facial selectivity. Replacement of the *tert*-butyldimethyl silyl (TBS) and benzoyl groups reduced the diastereoselectivity of the addition process.

The preparation of the L-gulose derivative by Kobayashi *et al.*[40] through epimerisation at the C-5 position of D-mannose is illustrated in Scheme 2. Phosphonium ylide treatment of the hemiacetal **24** led to the hydroxyolefin **25**. Swern oxidation of this 5-alcohol formed the dioxanone, which was stereoselectively reduced by L-selectride to afford the L-*gulo* compound **26** in 83% yield over two steps as a single isomer. Further acetylation, *p*-methoxybenzyl (PMB) deprotection using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), and subsequent glycosylation with the mannosyl donor **28** supplied the adduct **29**. Upon ozonolysis, the disaccharide **30**, which carries the backbone of the bleomycin carbohydrate moiety, was obtained.

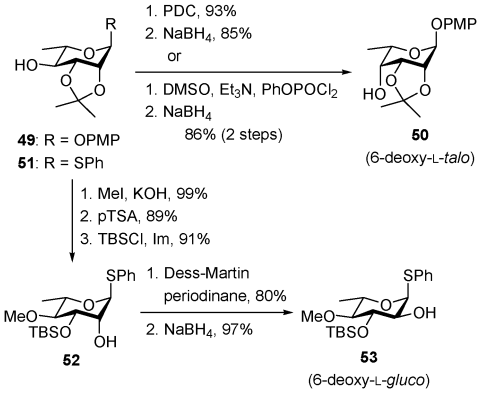


Scheme 2 Epimerisation of D-mannose into L-gulose and the preparation of the disaccharide moiety of bleomycin.

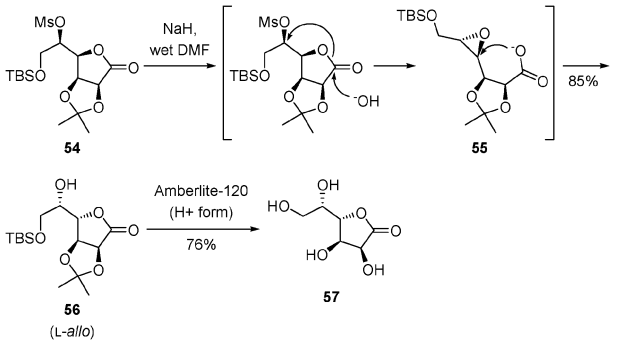


Scheme 3 C-5 epimerisation through δ-hydroxybenzyloxamate.

Ikegami's group carried out the epimerisation at C-5 of D-glucose, D-mannose, and D-galactose *via* δ-hydroxyalkoxamine (Scheme 3).[41] The D-glyconolactones **34–36**, obtained from the hemiacetals **31–33**, were exposed to *O*-benzylhydroxylamine and $AlMe_3$ to form the desired benzyloxamines **37–39** in excellent yield. In the presence of PPh_3 and diethylazodicarboxylate (DEAD) in THF, *O*-cyclisation appeared more favoured than the competing *N*-cyclisation with elimination of triphenylphosphine oxide and epimerisation at C-5. The so-formed oximes **40–42** were, then, transformed to the corresponding L-glyconolactones **43–45** upon acid hydrolysis. Reduction with diisobutylaluminium hydride (DIBAL-H) provided the hemiacetals having the L-*ido* (**46**), L-*gulo* (**47**), and L-*altro* (**48**) configurations. Different alkoxamines, protecting groups, and reaction solvent influence the *N*-/*O*-cyclisation ratio. Thus, by a judicious selection of parameters, L-iminosugars can also be effectively prepared using this route.



Scheme 4 Preparation of the 6-deoxy-L-hexose from L-rhamnose.

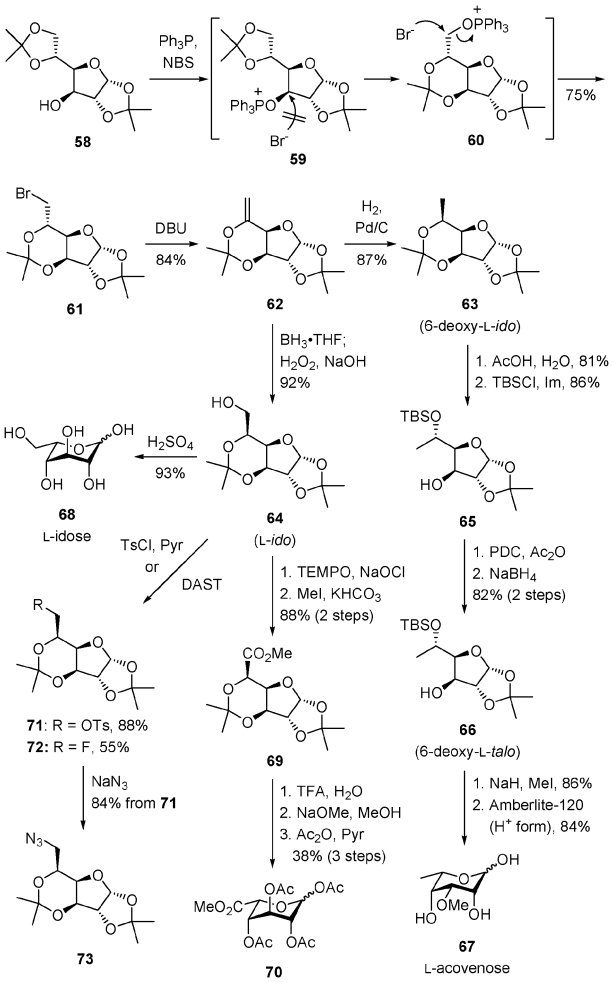


Scheme 5 Double inversion in D-mannose.

The relative availability of L-rhamnose makes it a suitable starting material to access some important 6-deoxy-L-hexoses through plain epimerisation. For example, 6-deoxy-L-talose building blocks required for the synthesis of several natural products were readily prepared from L-rhamnose (Scheme 4). In the synthesis carried out by Zhang's group,[42] the 1,2-isopropylidene-protected *p*-methoxyphenyl (PMP) rhamnoside (**49**) was subjected to pyridinium dichromate (PDC) or Pfitzner–Moffatt oxidation at C-3 to form the ketone, which was treated with $NaBH_4$ to acquire the desired 6-deoxy-L-talose derivative **50**. Conversely, the 6-deoxy-L-glucose donor used for the total synthesis of apoptolidin A and its analogues was prepared by Koert *et al.* from L-rhamnose.[43] Here, the properly protected 2-alcohol **52** was first prepared from the thiorhamnoside **51**. To secure the desired L-*gluco*-configured **53**, C-2 was oxidised with Dess–Martin periodinane followed by hydride addition. In both of these cases, the highly stereoselective reduction steps were likely influenced by steric factors.

Shih and Tseng were able to perform two-fold inversions at the adjacent C-4 and C-5 stereocentres in a D-mannose backbone, leading towards the L-allose derivative (Scheme 5).[44] The D-mannonolactone **54**, readily attainable from D-mannose, was treated with sodium hydride in a 4 : 1 DMF–water mixed solvent. The hydroxide ion generated *in situ* was presumed to bring about the S_N2 displacement of the mesylate group at C-5 by the so-formed oxide at C-4, generating the epoxide **55**. A second displacement at C-4 by the resultant carboxylate furnished compound **56** with an L-*allo* backbone. 1,4-L-Allonolactone (**57**) was afforded after acid exposure of **56**.

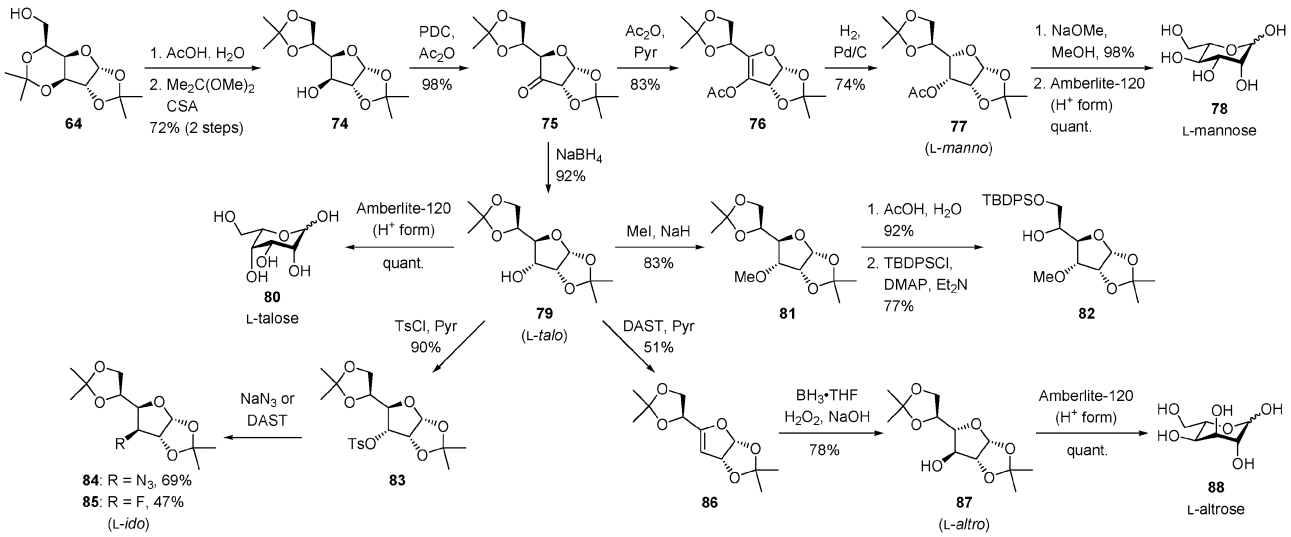
Our efforts in attaining various L-hexoses relied on multiple epimerisations starting from the commercially abundant diacetone D-glucose (**58**), with the first epimerisation carried out at C-5 to form the L-*ido* derivative (Scheme 6).[45] Treatment of **58** with PPh_3 and NBS enabled the formation of the 6-bromide **61** possessing 1,2;3,5-di-*O*-isopropylidene groups locked in a *cis–anti–cis* fused tricyclic core. Here, the 3-oxyphophonium intermediate **59** likely forms first, but the acetonide transfer from the 5,6- to 3,5-position apparently occurs faster than the S_N2 displacement by the bromide ion. The alternative and less sterically hindered substitution at the C-6 position of **60** is, hence, more favoured as evidenced by the isolation of compound **61** in 75% yield. Facile dehydrobromination by DBU delivered the enol ether **62**. Both agents in the palladium-catalysed hydrogenation and hydroboration attacked



Scheme 6 Entry to the L-hexoses from D-glucose.

stereoselectively the less congested *Re*-face of the compound **62** alkene function to furnish the respective L-*ido* products **63** and **64**. It should be mentioned that the same transformations and selectivity has been observed when a benzylidene acetal protects the 3,5-*O* position instead of isopropylidene.[45d,e,46] Following the regioselective 3,5-*O*-isopropylidene ring cleavage and 5-*O*-silylation of **63**, a next round of epimerisation, this time at the 3-*O* position of the 6-deoxy-L-*ido* compound, was carried out. Consequently, PDC oxidation and, then, $NaBH_4$ reduction provided the desired 6-deoxy-L-*talo* compound **66** in high yield. The sugar L-acovenose (**67**) was obtained after 3-*O*-methylation and acidic deprotection. L-Idose (**68**) was accessed from compound **64** after a simple acid hydrolysis. Moreover, further functionalization at C-6 of **64** can be readily carried out. For instance, 2,2,6,6-tetramethyl-1-piperidinyloxyl (TEMPO) free radical oxidation allowed the acquisition of L-iduronate **69** following methyl ester formation. This compound can be re-protected in 3 steps to get the tetraacetate **70**. The free 6-hydroxyl group also permits replacement with other functionalities such as fluoride (compound **72**) or azide (compound **73**).

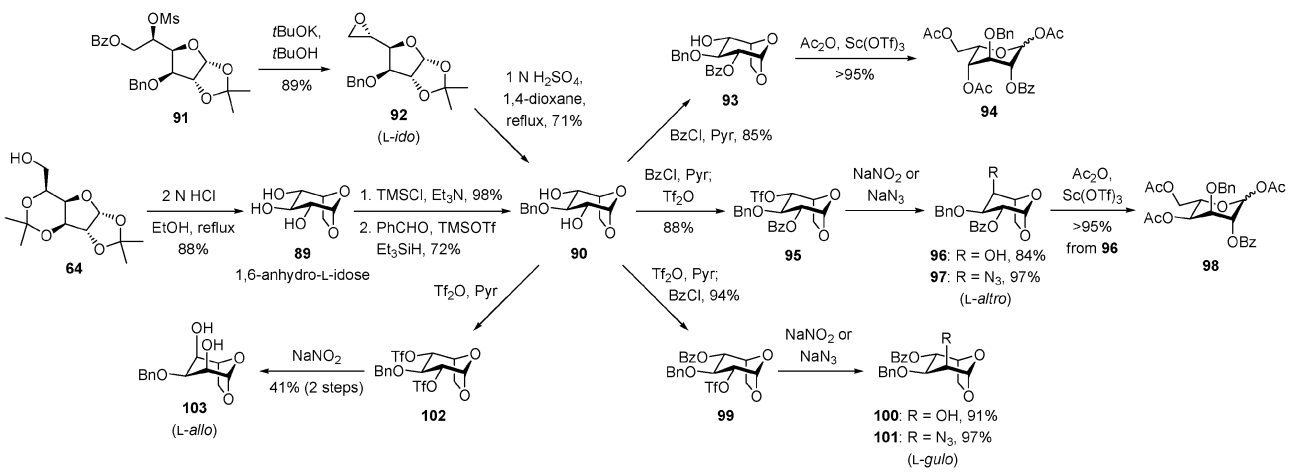
To enable the epimerisation at other positions of the L-idose derivative **64**, regioselective hydrolysis and 5,6-*O*-isopropylidenation were implemented, generating the 3-alcohol **74** (Scheme 7).



Scheme 7 Preparation of various L-hexoses from L-idose.

To get L-mannose from L-idose, inversions of stereochemistry at C-3 and C-4 positions are needed. Accordingly, **74** was oxidised by PDC to procure the ketone **75**, wherein the enol ether **76** was easily produced by acetic anhydride treatment. The L-*manno*-configured **77** was acquired after hydrogenation. Subsequent deacetylation and acetal hydrolysis produced L-mannose (**78**). On reduction with $NaBH_4$, **75** was alternatively transformed into compound **79**, which furnished L-talose (**80**) on acid hydrolysis of the diacetonide. Compound **79** is also a suitable precursor for the L-talose building block **82** designed for the synthesis of capuramycin. The required transformations, which included 3-*O*-methylation, regioselective isopropylidene deprotection, and silylation, were all carried out in high yields. The 3-hydroxyl of the L-talose derivative **79** further allows conversion back to the L-*ido* form. Hence, through the tosylate **83**, the L-*ido* 3-fluoro and 3-azido compounds **84** and **85** were, respectively, formed *via* S_N2 substitution under the agency of NaN_3 or diethylaminosulphur trifluoride (DAST). To access L-altrose, the C-3 and C-4 positions in **79** need to be inverted. Exposure to DAST supplied the enol ether **86** and the ensuing hydroboration gave the L-altro-configured **87**. Cleavage of the isopropylidene acetals led to L-altrose (**88**).

The L-idose derivative **64** was also shown to directly form 1,6-anhydro-L-idose (**89**) under reflux conditions with an acid (Scheme 8). This fruitful transformation has enabled a separate epimerisation route towards the preparation of L-*altro*, L-*allo*, and L-*gulo* derivatives from 1,6-anhydro-L-idose.[45d,e,47] The rigid structure of the 1,6-anhydro ring generally forces the L-hexose to assume an atypical conformation that profoundly affects the reactivity of the substituent oxygens. This, together with the decrease in the hydroxyl groups that need to be protected, made 1,6-anhydrosugars as valuable building blocks in carbohydrate synthesis.[48] Per-trimethylsilylation and reductive 3-*O*-benzylation of **89** produced the diol **90**. Alternatively, **90** was also obtained from the mesylate **91**, itself likewise derived from starting material **58**.[49] Here, treatment with potassium *tert*-butoxide cleaves the benzoyl group at O-6 and the alkoxide formed attacks C-5 on the backside to afford the L-*ido*

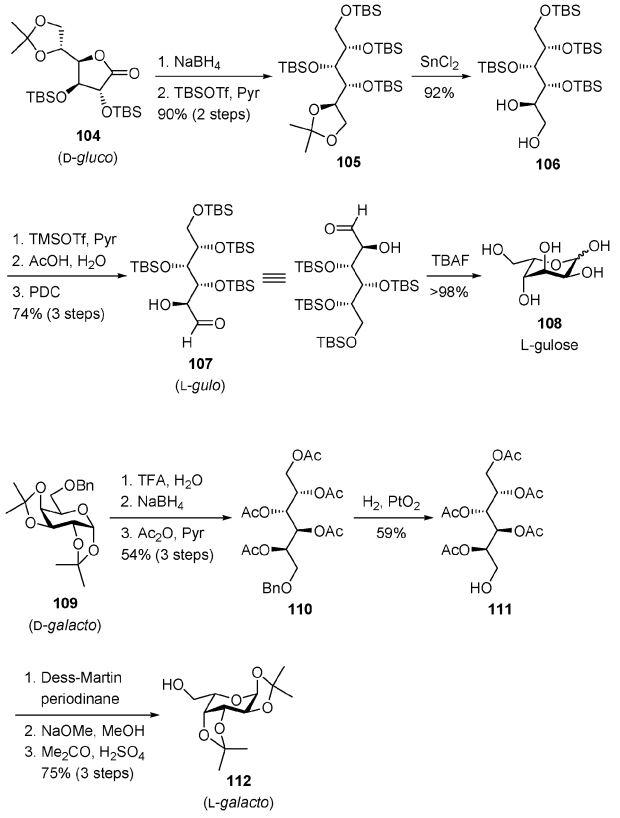


Scheme 8 Synthesis of L-hexoses through 1,6-anhydrohexopyranoses.

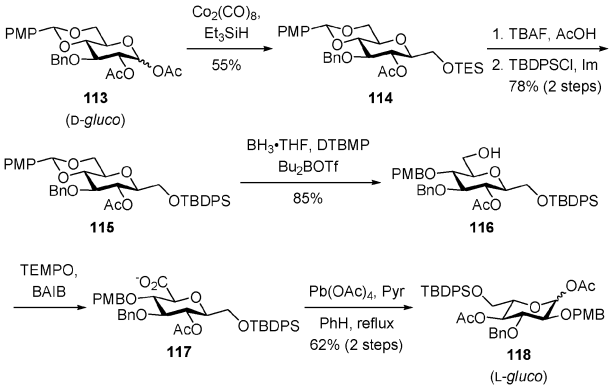
epoxide **92**. Reflux together with H_2SO_4 in 1,4-dioxane supplied the target compound **90**. The control in reactivity was demonstrated by regioselective 2-*O*-benzoylation acquiring the 4-alcohol **93** in 85% yield. An efficient method developed by our group opens the anhydro-ring using metal triflate-mediated acetolysis.[50] Thus, the triacetate **94** was procured under $Sc(OTf)_3$ catalysis in excellent yield. In a separate report, Wong *et al.* showed that the same ring opening can be facilitated by a nucleophilic sulphur reagent such as trimethyl(methylthio)silane in the presence of trimethylsilyl triflate (TMSOTf).[51] Taking the differences in reactivity between hydroxyl groups even further, consecutive one-pot benzoylation and triflation supplied the product **95**, which was treated with either $NaNO_2$ or NaN_3 to form the alcohol **96** or the azido **97** in the L-*altro*-configuration. Again, acetolysis facilitated by $Sc(OTf)_3$ efficiently led to the L-altrose triacetate compound **98**. Knowing that L-gulose is a C-2 epimer of L-idose, we followed the reverse order of reagent addition to **90** in one pot to get the 2-triflate **99**, which was treated similarly to **95** to form the L-*gulo* derivatives **100** and **101**. A double triflation of **90** equally granted access to the L-*allo* diol **103**.

3 Head-to-tail inversions

Four D-hexoses, namely, D-glucose, D-galactose, D-gulose, and D-allose, have an *R*-configured C-2. Consequently, an exchange of oxidation states between C-1 and C-6 in these sugars should make C-2 become the new C-5 in *S*-configuration. Under this premise, reduction of the aldehyde function at C-1 to a primary alcohol and oxidation of the C-6 alcohol to an aldehyde in D-glucose, D-galactose, D-gulose, and D-allose would generate L-gulose, L-galactose, L-glucose, and L-allose, respectively. Scheme 9 illustrates two examples applying this notion.



Scheme 9 Examples of C-1-to-C-6 inversion.



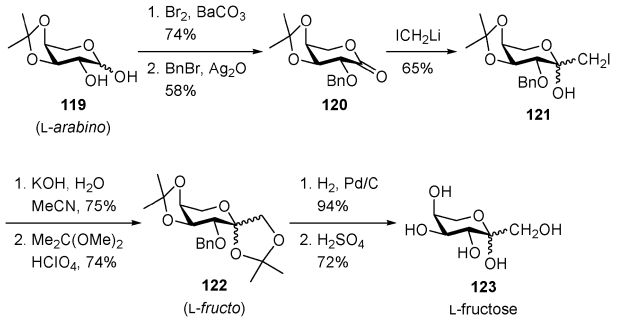
Scheme 10 C-1-to-C-5 inversion involving a β-C-glucoside.

The D-glucono-1,4-lactone **104** was first reduced using $NaBH_4$ and the generated diol was protected with TBS to afford the tetrasilylated **105**.[52] Chemoselective cleavage of the isopropylidene group was implemented using $SnCl_2$ leading to the diol **106**, which was re-protected with trimethylsilyl (TMS) groups. After cleavage of the primary TMS ether under mildly acidic conditions, the exposed alcohol was oxidised to furnish the aldehyde **107** carrying the L-*gulo* configuration. L-Gulose (**108**) was obtained after complete removal of all silyl groups. L-Xylose was also obtained from compound **106** upon treatment with Dess–Martin periodinane followed by full desilylation.

To access the L-galacto derivative **112**,[53] the diacetonide in the 6-*O*-benzylated D-galactose **109** was first cleaved to expose the aldehyde, which was reduced with $NaBH_4$. The pentaacetate **110**, acquired after per-acetylation, was subjected to hydrogenolysis to afford the alcohol **111**. Oxidation of the primary alcohol to the aldehyde, followed by deacetylation and diisopropylidene installation supplied the target L-hexose **112**.

The presence of latent symmetry at C-2, C-3, and C-4 positions in D-glucose could also be exploited in a strategy that follows the switching of the C-1 and C-5 positions (Scheme 10). Thus, Li and co-workers conceived an approach to L-glucose involving the β-C-glycoside **114** prepared from the D-glucosyl acetate **113** using $Co_2(CO)_8$-catalysed silyloxymethylation.[54] After installation of the more stable *tert*-butyldiphenylsilyl (TBDPS) in place of the triethylsilyl (TES) group, the regioselective 6-O ring opening of the *p*-methoxybenzylidene acetal led to the 6-alcohol **116**. Subsequent treatment with TEMPO in the presence of [bis(acetoxy)iodo]benzene (BAIB) fashioned the carboxylate **117**, which is amenable to oxidative decarboxylation. Accordingly, reflux with lead tetraacetate in a benzene–pyridine mixed solvent completed the C-1-to-C-5 switch and provided the L-glucosyl acetate **118**. The resultant compound holds orthogonal protecting groups that are very useful in sugar assembly.

Another approach that interchanges the C-1 and C-5 positions through a glycal intermediate is described in Section 5.



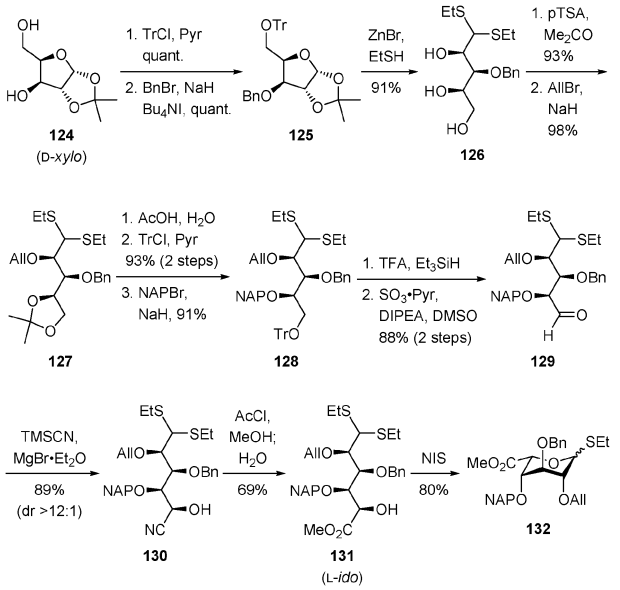
Scheme 11 Preparation of L-fructose from L-arabinose.

4 Through pentoses

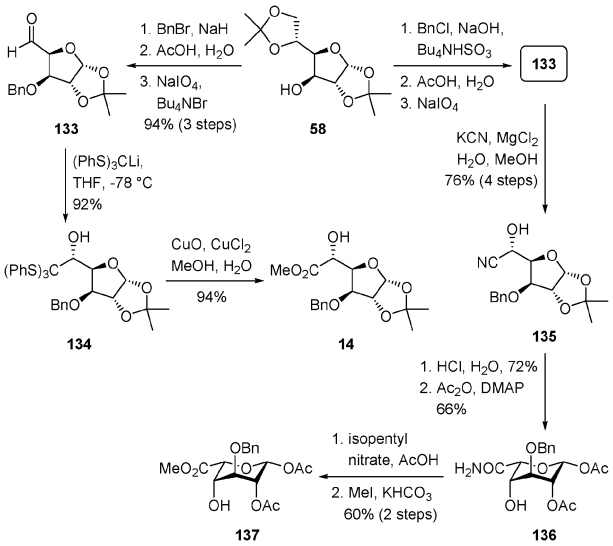
The homologation of pentoses to hexoses is traditionally carried out using the Kiliani–Fischer synthesis *via* a cyanohydrin, albeit with poor stereoselectivity. Conversely, there are several recent strategies that follow the pentose elongation process precisely targeting L-hexoses with good to exceptional selectivity. Some prominent examples are herein described.

The preparation of L-fructose by iodomethylation of L-arabino-1,5-lactone was described by Bessières and Morin (Scheme 11).[55] Lactone **120** was first prepared from the hemiacetal **119**. The iodide **121**, generated upon treatment with ICH_2Li, was converted to the primary alcohol by S_N2 substitution. The ensuing diol was protected with an acetonide to get compound **122**, which already holds an L-*fructo* configuration. Subsequent debenzylation and acid hydrolysis supplied the desired L-fructose (**123**).

L-Iduronate building blocks carrying orthogonal protecting groups were fashioned by Seeberger *et al.* from D-xylose (Scheme 12).[56] In contrast to the typical cyanohydrin formation, which occurs at C-1 of the pentose, the cyanide group was added, in this case, to the aldehyde group that was formed at the C-5 position. Following tritylation and benzylation of the diol **124**, the thioacetal **126** was synthesized using $ZnBr_2$ and a large excess of ethanethiol. Various manipulations of this triol were then carried out to afford the orthogonally protected **128** (NAP: 2-naphthylmethyl, All: allyl). The trityl (Tr) group in compound **128** was next removed and the resulting alcohol was subjected to Parikh–Doering oxidation to access the aldehyde **129**. Using $MgBr{\cdot}Et_2O$ as a chelate activator, the cyanide addition occurred in excellent yield and diastereoselectivity for the L-*ido*-configured cyanohydrin **130**. Transformations under successive methanolic HCl (Pinner reaction) and hydrolysis provided the methyl ester **131**, which cyclised to the pyranose form **132** after *N*-iodosuccinimide (NIS) treatment.



Scheme 12 Synthesis of L-iduronate from D-xylose.

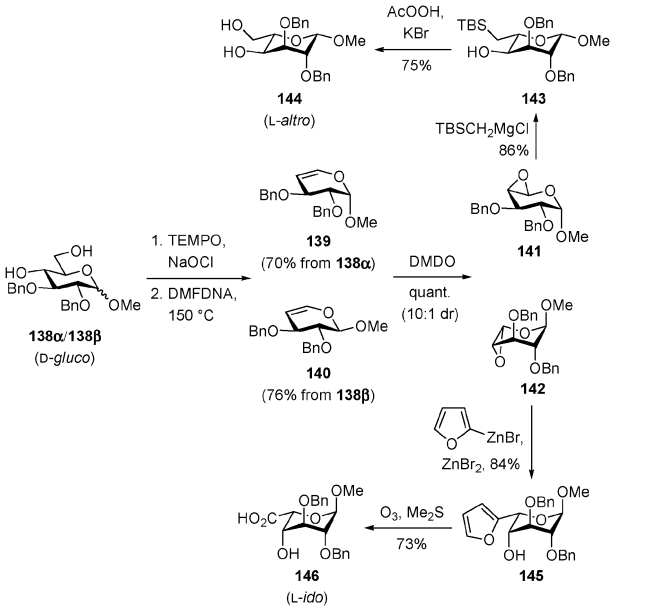


Scheme 13 Synthesis of L-iduronate through D-*xylo* dialdose.

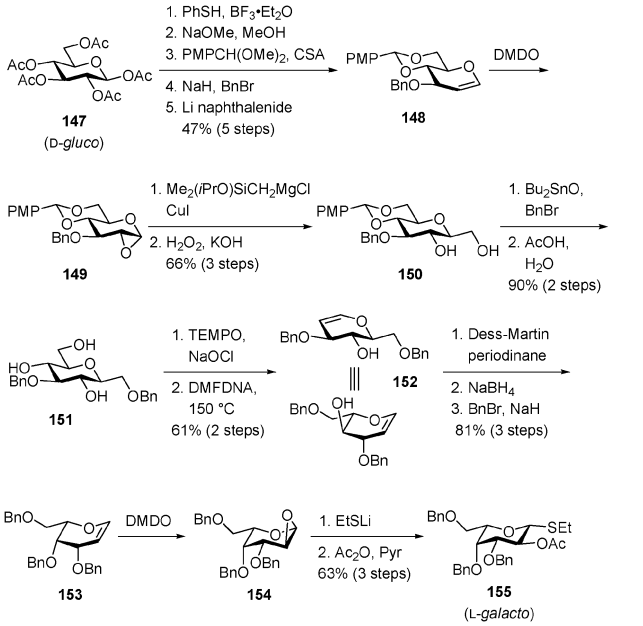
An aldehyde function at the C-5 position of a D-*xylo* compound could also be accessed from diacetone D-glucose (**58**) (Scheme 13). Accordingly, 3-*O*-benzylation, 5,6-*O*-isopropylidene cleavage, and periodate oxidation handily gave the D-*xylo* dialdose **133**. In a procedure developed by Bonnaffé,[57] the steric bulk of the carboxylic acid equivalent tris-(phenylthio)methyllithium was instrumental in favouring the L-*ido* configuration and providing compound **134** in complete stereoselectivity. The orthothioesters were effectively transformed to the methyl ester **14** in the presence of CuO and $CuCl_2$. Gardiner's group,[58] on the other hand, performed cyanide addition with $MgCl_2$ to shift the stereoselectivity towards L-idose (about 90% de). The compound formed after acid-mediated uronamide formation and acetal hydrolysis was diacetylated to obtain the pyranose **136**. Further transformation to the carboxylic acid and esterification led to the L-iduronate **137**.

5 Through unsaturated pyranosides

Approaches towards L-hexoses were also developed using intermediates with unsaturated pyranosides directly prepared from D-hexoses. These strategies, mainly introduced by Wei *et al.*,[28b,59] involve stereoselective epoxidation of 4-deoxypentenosides and glycals followed by nucleophilic attack in *syn* or *anti* manner. Moreover, D-glycals require a switch between C-1 and C-5 after nucleophilic addition in order to arrive at the proper L-configuration. The route



Scheme 14 Preparation of L-hexoses through a 4-deoxypentenoside intermediate.



Scheme 15 Synthesis of L-galactose derivative through a D-glucal intermediate.

leading to the L-sugar also allows for the introduction of unnatural C-5 substituents simply by the choice of nucleophile.

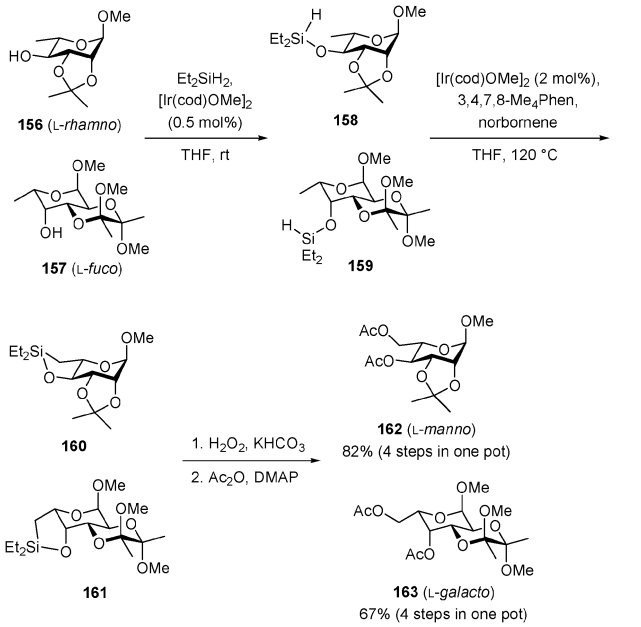
Scheme 14 describes the alternate transformations of 4-deoxypentenosides used for the preparation of L-hexoses.[59a,c] The D-glucosyl diol **138** is amenable to TEMPO oxidation towards the carboxylate, which was then refluxed with dimethylformamide dineopentyl acetal (DMFDNA) to enable decarboxylative elimination generating the pentenosides **139** and **140**. The separate exposure of these pentenosides to dimethyldioxirane (DMDO) furnished the epoxides **141** and **142**. As exhibited in these examples, the steric environment, particularly the substituent at C-1, has profound influence on the orientation of the formed epoxide. An S_N2-type *anti*-addition of a silylated nucleophile at the less hindered C-5 position in the epoxide **141** led to the L-configured 4-alcohol **143**. Tamao–Fleming oxidation delivered the L-altrose derivative **144**. Conversely, a C-5 *syn*-addition of a nucleophile is required for the epoxide **142** to guarantee the L-configuration. In this case, the addition of 2-furylzinc bromide, prepared by addition of zinc bromide to an *n*BuLi-treated furan, proceeded with high *syn*-stereoselectivity to obtain compound **145**. The L-iduronic acid derivative **146** was obtained after ozonolysis.

Glycals have been effectively utilized as building blocks in oligosaccharide assembly.[60] The facile manipulation of the double bond function and ready availability of C-5 decarboxylation methods also provide access to L-hexoses that are difficult to obtain using 4-deoxypentenosides. For instance, the D-glucal **148**, generated from the pentaacetate **147** in 5 steps, was converted to the L-galactose derivative **155** (Scheme 15).[28b,59b] The route towards L-glucose is also evident using this strategy. Accordingly, epoxidation of **148** fashioned compound **149**, with the orientation of oxirane group guided by the steric bulk of other ring substituents. The anti-attack by a silyl methyl nucleophile followed by Tamao–Kumada oxidation produced the diol **150**. After benzylation of the exposed primary alcohol, a similar oxidation–decarboxylative elimination sequence switched the C-1 and C-5 positions effectively generating the L-glycal **152**. Successive C-4 epimerisation, benzylation, epoxidation, thioethyl addition, and acetylation effectively delivered the target thiogalactoside **155**.

6 Hydroxylation of 6-deoxy-L-hexoses

As already stated, two 6-deoxy-L-hexoses (*i.e.*, L-rhamnose and L-fucose) are more accessible than the rest of the L-hexoses. Such availability provides a convenient opportunity for the direct synthesis of their rare fully hydroxylated counterparts. However, activation of the inherently unreactive primary C–H bond in the presence of multiple functional groups that are found in carbohydrates is a challenge. Recently, Simmons and Hartwig disclosed an approach in site-selective functionalisation of primary methyl groups that requires an iridium catalyst and a free γ-hydroxyl as a directing group.[61] Shortly after, the group led by Bols applied this method for generating the respective derivatives of L-mannose and L-galactose from L-rhamnose and L-fucose, respectively (Scheme 16).[62]

To primarily provide for the specific γ-hydroxyl needed by this approach, the methyl L-rhamnoside **156** and methyl L-fucoside **157** were first prepared from the free sugars. The isopropylidene and butane-2,3-diacetal protecting groups were particularly chosen to evaluate the regioselectivity of C–H bond activation. Treatment of these 4-alcohols with diethylsilane (Et_2SiH_2) and 0.5 mol% $[Ir(cod)OMe]_2$ (cod: 1,5-cyclooctadiene) at room temperature led to the (hydrido)silyl ethers **158** and **159**. After removal of the solvent and excess silane reagent *in vacuo*, more iridium catalyst (up to 2 mol%), the ligand 3,4,7,8-tetramethyl-1,10-phenanthroline (3,4,7,8-Me_4Phen), and norbornene were added together with the solvent. The iridium-catalysed C–H activation occurred at high temperature (120 °C), enabling the formation of the cyclic silyl ethers **160** and **161**. Subsequent



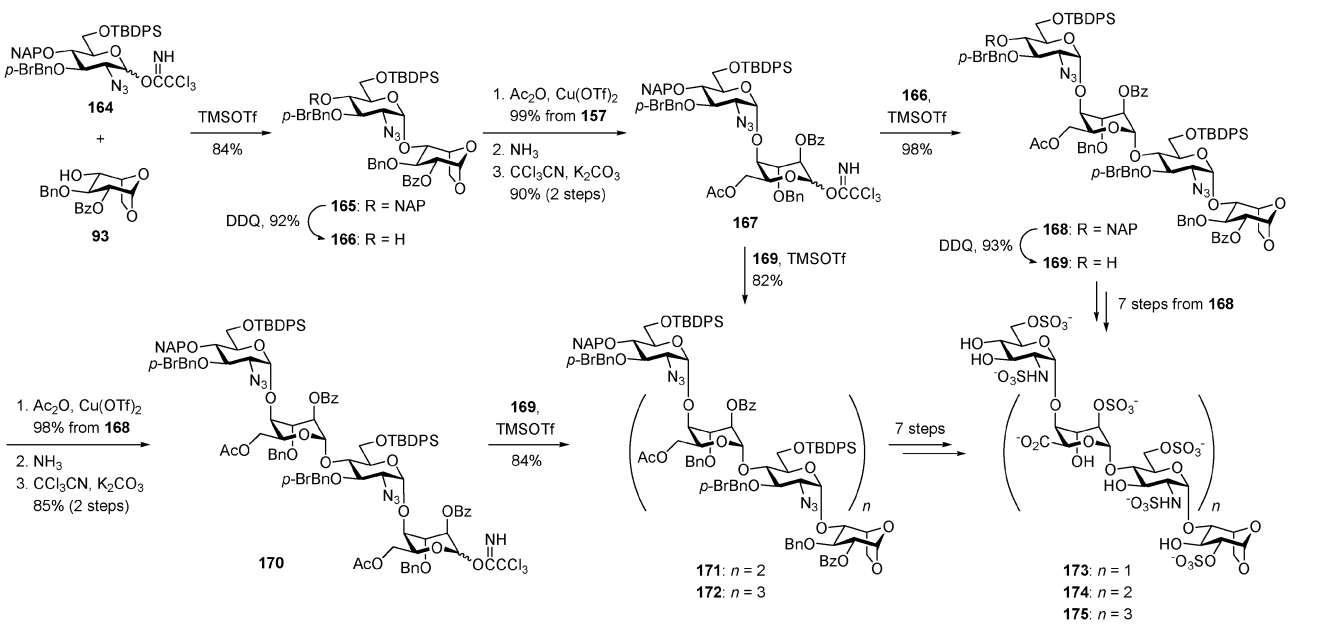
Scheme 16 Synthesis of L-mannose and L-galactose from L-rhamnose and L-fucose, respectively, by primary C–H bond activation.

Tamao–Fleming oxidation resulted in the L-mannosyl and L-galactosyl 4,6-diols, which were further acetylated to afford the fully protected derivatives **162** and **163**. The whole four-step procedure was achieved in one pot and in 82% and 67% overall yields for the synthesised L-*manno* and L-*galacto* compounds. The other methyl groups were left untouched during the process.

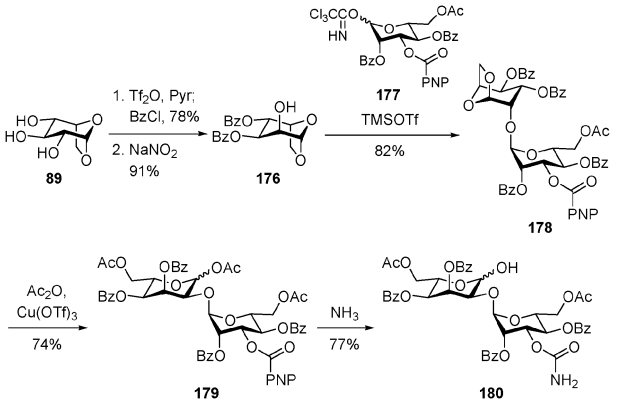
7 Some applications in sugar assembly

As a testament to the simplicity and convenience offered by the transformation routes, the more common pentoses and hexoses remain the principal source of L-hexose building blocks needed for the assembly of oligosaccharides and other complex sugar-containing molecules. *De novo* strategies, with their wealth of fascinating chemistry, found worth primarily in accessing rare sugar and sugar-like backbones within natural product structures.[29] The furfural-based method by O'Doherty *et al.*[32a,b] appears to be the only *de novo* approach to L-hexoses that has so far demonstrated extensions toward the preparation of oligosaccharides.[63] Typical at the course of the L-hexose preparation, suitable protecting groups are installed to accommodate subsequent manipulation and coupling. Hereafter are some examples of sugar assembly and synthesis that involve L-hexoses.

The biological activities of heparin and heparan sulphate are subject of keen investigations and the chemical synthesis of these sugars received considerable attention.[36] To supply well-defined oligosaccharides for evaluation, we have carried out the synthesis of several heparin- and heparan sulphate-based analogues that hold regular[49a,c,64] and irregular[65] repeating disaccharide units. Key to these preparations is the 1,6-anhydro-β-L-idopyranosyl 4-alcohol **93**. Condensation of this acceptor with the D-glucosaminyl donor **164** led to the disaccharide **165** in 84% yield and exclusive α-stereoselectivity (Scheme 17). The anhydro ring of the L-idose moiety could be easily manipulated through acetolysis, anomeric deacetylation, and trichloroacetimidation to generate the disaccharide donor **167**. We also demonstrated that, following acetolysis of the anhydro ring, treatment with trimethyl(4-methylphenylthio)silane and ZnI_2 could yield the corresponding thioglycoside donor without affecting other protecting groups.[64] The trichloroacetimidate **167** was then coupled to the acceptor **166**, which was acquired from **165** by exposure to DDQ, to afford the tetrasaccharide **168** in excellent yield and stereoselectivity. In this case, the 2-*O*-benzoyl group in the L-idose unit of the donor provided neighbouring group assistance to promote 1,2-*trans* glycosylation. Further deprotection



Scheme 17 Preparation of heparin analogues.



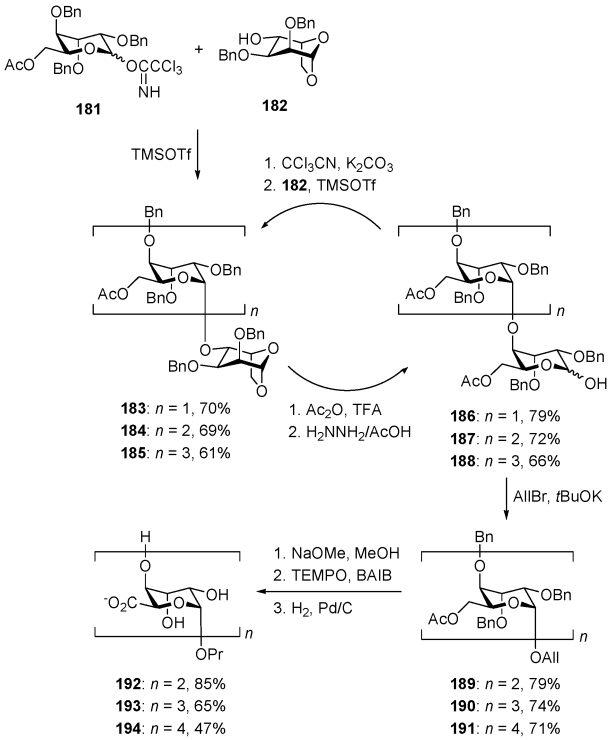
Scheme 18 Preparation of the disaccharide unit of bleomycins.

of the NAP group to form the tetrasaccharide acceptor **169**, manipulation of the anhydroidose to form the tetrasaccharide donor **170**, and [2 + 4]- and [4 + 4]-glycosylations supplied the fully protected hexasaccharide **171** and octasaccharide **172**. A series of seven functional group transformation steps eventually furnished the heparin-like tetra-, hexa- and octasaccharides **173–175**. Here, the benzoyl, acetyl, and benzyl groups confer protections to the L-idose hydroxyls that were later sulphonated, oxidised, and left unprotected, respectively.

The disaccharide moiety possessing the backbone of the sugar unit in bleomycins was prepared using the 1,6-anhydro-L-gulose derivative **176** (Scheme 18).[45e] This compound was prepared using standard procedures from 1,6-anhydro-L-idose (**89**). Coupling of **176** with the D-mannosyl trichloroacetimidate **177** gave the disaccharide **178** in 82% yield. Treatment with $Cu(OTf)_2$ and Ac_2O produced the triacetate **179**, which was subjected to ammonialysis to acquire the sugar unit **180** that can be used in bleomycin preparation.

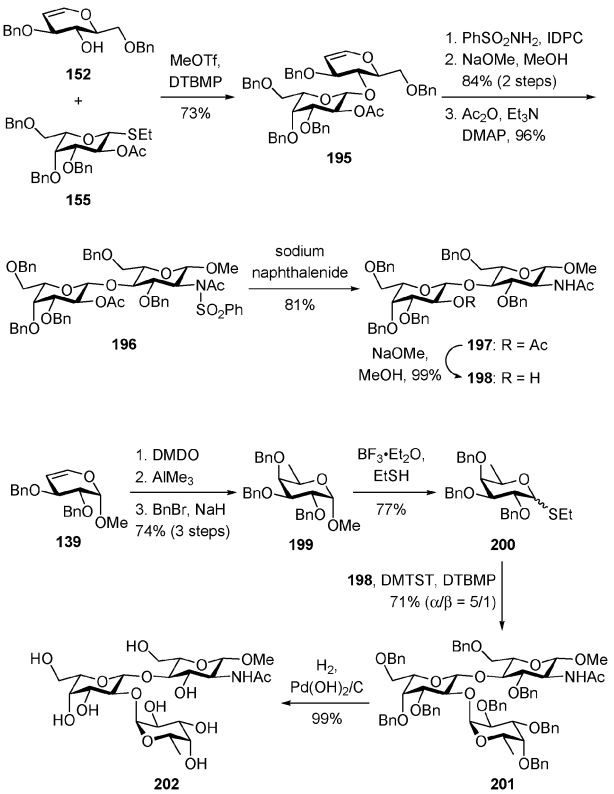
Alginate oligosaccharides with L-guluronic acid repeating units have also been prepared.[66] In our case,[66b] the monosaccharide building blocks **181** and **182**, which were both acquired in 4 steps from 1,6-anhydro-L-gulose, were coupled under the agency of TMSOTf to procure the desired α-disaccharide **183** together with its β-isomer in 70% and 17% yields, respectively (Scheme 19). Cycles of acetolysis, anomeric deacetylation, trichloroacetimidate formation, and glycosylation of the acceptor **182** ultimately delivered the hemiacetals **186–188**. Highly stereoselective α-allylations were successfully implemented *via* Williamson etherification with allyl bromide and potassium *tert*-butoxide as reagents. The so-formed compounds **189–191** were converted to the alginate di-, tri-, and tetrasaccharides **192–194** by Zemplén deacetylation, TEMPO oxidation, and hydrogenolysis.

With the hope that the mirror image counterparts of natural sugar constructs may provide important biological activities, Wei and co-workers synthesised the trisaccharide mirror image of the H-type II blood group determinant (Scheme 20).[28b] The L-glucal **152** and the L-galactoside donor **155** were condensed in the presence of MeOTf and 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) to afford compound **195** in 73% yield. *N*-Sulfonylaziridine formation (IDPC: iodonium di-*sym*-collidine perchlorate) at the α-face of the L-glucal unit followed by displacement with



Scheme 19 Preparation of alginate oligosaccharides.

NaOMe furnished the compound which produced the *N*-acetyl lactosamine derivative **196** after acetylation. Further treatment



Scheme 20 Preparation of the H-type II blood group determinant mirror image trisaccharide.

with sodium naphthalenide provided the acetamide **197**, which was deacetylated to afford the 2′-alcohol **198**. Meanwhile, the methyl D-fucoside **199** was prepared from the 4-deoxypentenoside **139**. Herein, the addition of the methyl group at the C-5 position occurred in a *syn* manner similar to that with 2-furylzinc bromide. Compound **199** was then transformed into the thioglycoside **200** using $BF_3{\cdot}Et_2O$ and EtSH. The subsequent glycosylation of the acceptor **198** upon activation of **200** with dimethylsulfonium triflate (DMTST) supplied the fully protected disaccharide **201**. Global hydrogenolysis fashioned the target trisaccharide **202**.

8 Conclusions

As the vital roles played by sugars in biological systems continue to be unravelled, the demand for chemically pure and defined carbohydrate constructs needed to understand structure–function relationships will remain high. The versatile, simple, and often cost-effective protocols in accessing L-hexose derivatives described here, as well as future improvements thereof, should provide suitable building blocks for the assembly of sugars and other natural products. Current approaches to L-hexoses from abundant pentoses and hexoses also benefit heavily from the rapid advances in mainstream carbohydrate chemistry, allowing for convenient integration in oligosaccharide preparation. The unusual sugar skeletons found in natural products, on the other hand, offer enduring challenges that are bound to keep carbohydrate chemists occupied in the years to come. These endeavours should further advance glycobiology as a whole and hopefully lead to novel and interesting pharmaceuticals of tomorrow.

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