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ARTICLE TYPE

Glyconanosynthons as powerful scaffolds and building blocks for the rapid construction of multifaceted, dense and chiral dendrimers

René Roy*and Tze Chieh Shiao

This review represents the first of its kind in that it is mainly devoted to the use of carbohydrates as both scaffolds and buildings for the construction of a wide range of novel, dense, and chiral dendrimers. It deviates from several previous reviews describing solely carbohydrates as functional surface groups, mostly devoted to biological applications. A brief overview of the most recent synthetic strategies in dendrimer design will be presented for the purpose of comparing their differences, similitudes, and advantages. A particular emphasis will be devoted to the general family of core molecules or scaffolds possessing a large number of functional groups from which, carbohydrates clearly emanate for their wide structural diversities, abundant chiral centers, and the relative ease with which their functional groups can be selectively manipulated. This beneficial characteristic relies on the fact that carbohydrates exist in enantiomeric states, several conformations, anomeric configurations, range of functional groups, and as three to seven carbon units.

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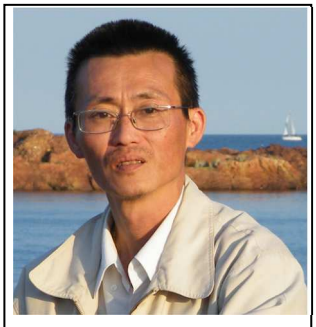
1. Introduction

Generally, synthetic strategies toward dendrimers' design have largely suffered from the self imposed limitations of using the same repeating moieties during the layer by layer syntheses.[1-6] This has greatly diminished the potential to include diversified biophysical properties between each dendrimer generation.

René Roy

Prof. René Roy holds a Canadian Research Chair in the Department of Chemistry of the Université du Québec à Montréal. He has more than 40 years of experience in carbohydrate chemistry. After is Ph. D., from the Université de Montréal, he joined the National Research Council of Canada in Ottawa where he was acquainted with immunochemistry. He has been at the University of Ottawa from 1985-2002. He was the recipient of the 2003 Melville L. Wolfrom Award from the ACS Division of Carbohydrate Chemistry for his contributions to the design glycodendrimers. He has published over 310 publications and has contributed to the development of two commercial carbohydrate-based vaccines against meningitis. His actual interests are in multivalent carbohydrate protein interactions and medicinal chemistry.



Tze Chieh Shiao

Tze Chieh Shiao was born in Taiwan (R. O. C.) in 1965. He grew up in Argentina. He started his study in medicine at Universidad de Buenos Aires (UBA) from 1986 to 1988. He also obtained an informatic diploma at the same time. In 1989, he turned back to Taiwan and obtained his certificate in administration (M. B. A.) at the University of Taiwan in 1991. He then moved with his family to Québec (Canada) in 1992. He return to University 2000 and obtained his B Sc in Biochemistry and M Sc in Chemistry (honour) at Université du Québec à Montréal (Canada) in 2009 under the supervision of Prof. René Roy. He then became the assistant of Prof. René Roy. His main research interests are carbohydrate-based synthetic vaccines and glycochemistry. He has over 44 publications to date.

In addition, this trend has been exacerbated by using simple AB_2-type repeating units, thus greatly limiting the accelerated expansion of the number of surface functionalities. Notably however, this limited approach has been recently diversified by a strategy that has been described as "onion peel", because each dendrimer layer can be prepared from a different chemical entity.[7-8]

Nevertheless, dendrimers are efficiently synthesized using two fundamentally different approaches. In the classical one, they are built "inside out" from the core molecules, a strategy that was coined "divergent method" (Fig. 1).[1] In the most recent design, dendrimers are built from the "outside in", through the intermediacy of dendrons or wedges. The strategy was thus coined "convergent method".[2] The number of surface groups accessible by both methods is following the mathematical growth equation: $Z = N_A \cdot N_B^{Gn}$, wherein Z is the number of surface group at final generation G_n, N_A is the number of functional group of the core molecule (scaffold), N_B is the number of functional groups of the repeating residues, whereas G_n is the generation number.[1] As can be seen from this equation, when the scaffold contains three functional groups, and the repeating units as two functions, G3 would have 24 surface groups (Fig. 1).

This trend holds for both divergent and convergent methods as long as the repeating units are kept constant. If however, different building blocks are used to construct dendrimers, a new equation should be used in which additional terms should be included to account for the different functional group number introduced as building blocks from one layer to the next. Hence, it follows that $Z = N_A \cdot N_B^{Gn} \cdot N_C^{Gm}$ and so on, each time a new dendrimer layer is brought in. For instance, a core molecule with a valency of three (A_3), followed by the first and second generation built from AB_2 blocks, and capping with an AB_3 block will provide a G3 dendrimer with 36 surface groups instead of the usual 24 originating from the one described above. Therefore, the "onion peel"[7-8] methodology offers several unprecedented advantages over the more classical approaches.[1-6]

The above combined strategies have also been elegantly applied to afford the next block dendrimer generations such as layer-block, segment-block, surface-block ("Janus dendrimers"), and amphiphilic self-assembling Janus glycodendrimers.[9] Multivalent heterobifunctional dendrimers with either alternating or randomly distributed surface groups have similarly been added to the arsenal of sophistication that are finding applications in photochemistry, electrochemistry, biology, and catalysis.

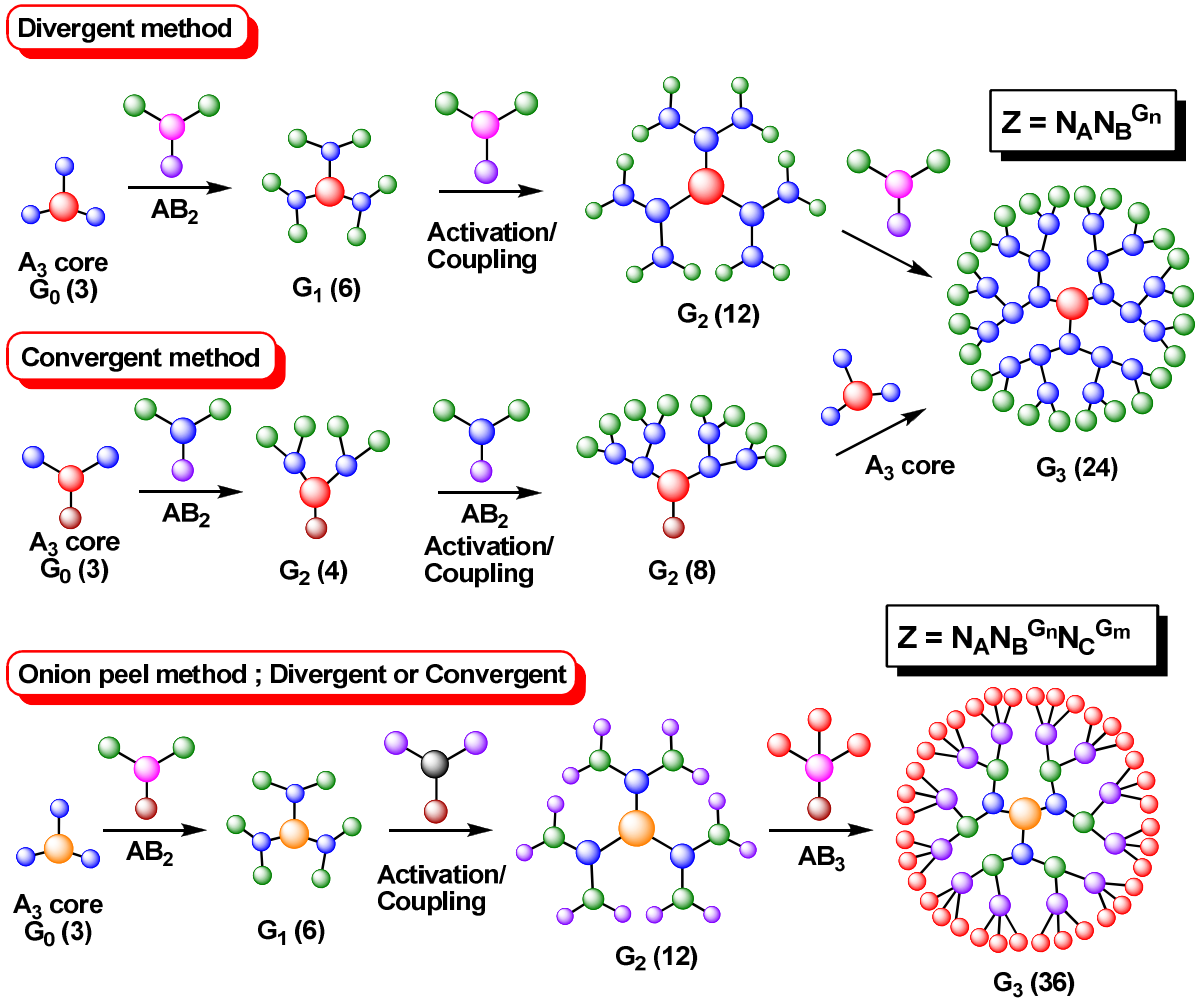


Fig. 1 Schematic representation of common strategies used to build dendrimers including the novel "Onion peel" approach that allows faster surface group increase together with bringing biophysical versatility in between dendrimer generations. Numbers in parentheses refer to those of the functional groups at the periphery.

In addition, the efficiency to rapidly provide dendrimers of higher generations greatly depends on accelerated methodologies.[4] This can be readily achieved by: 1) choosing appropriate building blocks (ideally with a large number of surface groups – ("multivalent scaffolds"); 2) by limiting the number of reactions involved at each cycle; 3) by using one-pot methodologies. Moreover, multivalent intermediates have been obviously considered to reach the above goals, however, they can only be considered as advanced dendrons. Their syntheses have been associated to: 1) hypermonomer strategy; 2) double stage convergent growth; and 3) double exponential growth.

Adding chemoselective and orthogonal reactions to the above methodologies has also greatly advanced the art of making monodisperse macromolecules such as dendrimers.[1-6] True hypercore building blocks have however scarcely been used as "seed molecules" to initiate dendrimer syntheses, although an exhaustive review has been dedicated to AB_3 cores by Newkome and Shreiner.[10]

2. Multivalent dendrimer cores

This section will first concentrate on higher valency-containing starting materials A_4 and above up to A_{12} found in fullerenes and cucurbit[6]urils. An emphasis will then be dedicated to sugars as elegant and versatile monomeric moieties since they can add several structural elements usually absent from conventional scaffolds.[11-14]

Fig. 2 illustrates some of the most common multivalent A_n (n > 3) scaffolds that have been used to synthesize dendrimers. The most common belongs to the A_4 family (**1-6**).[15-16] For instance, several of which such as 1,2,4,5-tetrasubstituted benzenes (**1**), 1,3,6,8-substituted pyrenes (**2**), and tetraphenylethylenes (**3**) possesses aromatic cores that have found values as photochemical probes. Pentaerythritol (**4**), 1,3,5,7-tetrasubstituted adamantanes (**5**), and cyclen (**6**, 1,4,7,10-tetraza-cyclododecane)[17] represent the non-aromatic congeners that have found numerous applications in

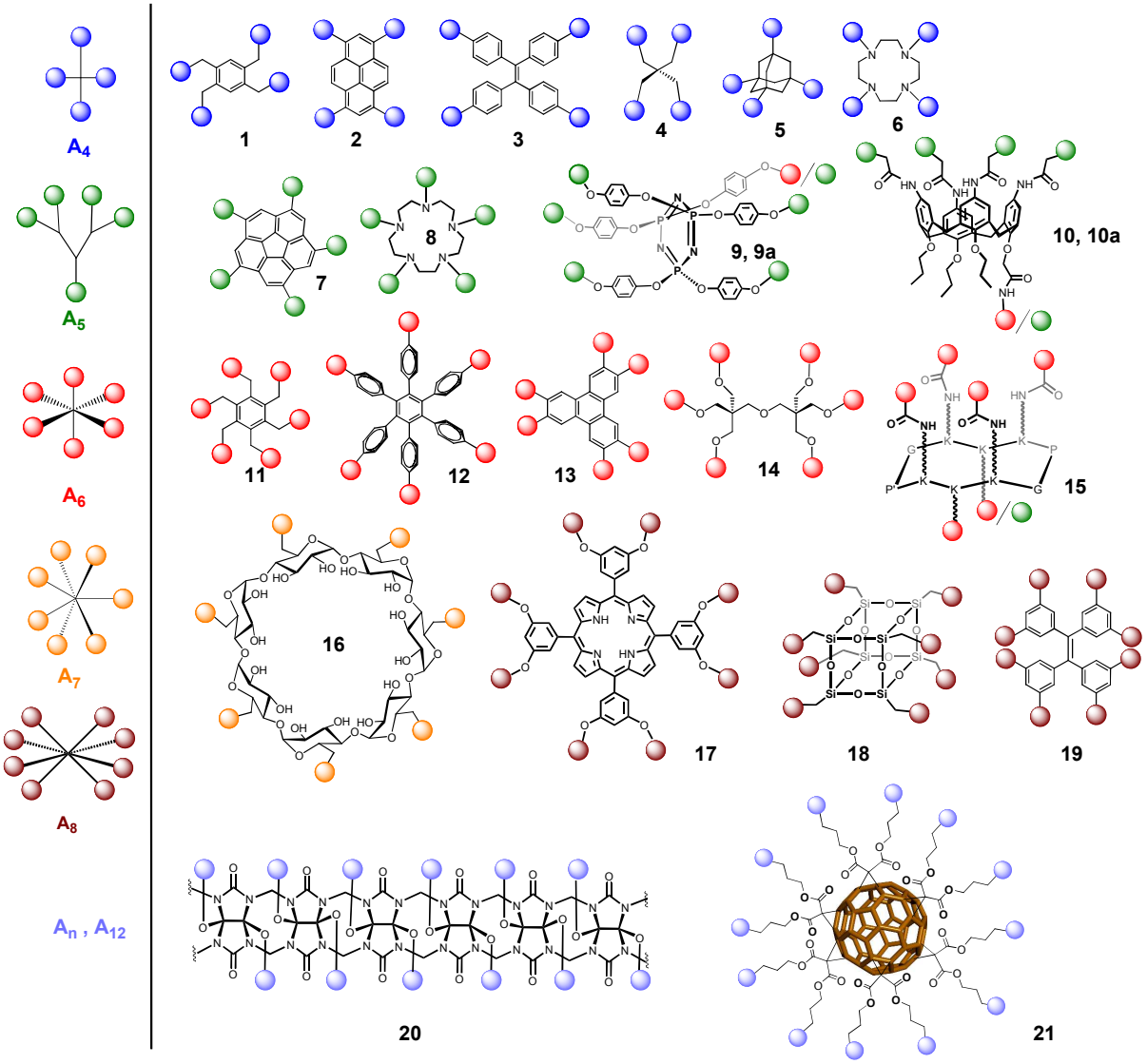


Fig. 2 Overview of the main multivalent scaffolds used in designing dendritic architectures

glycodendrimer chemistry and in supramolecular assembly. Dendrimer cores harbouring five accessible functionalities (A_5) such as the five-fold C_5-symmetric pentasubstituted corannulene (**7**)[18] and pentacyclen (**8**, 1,4,7,10,13-pentaazacyclopentadecane),[17] which belongs to the family of azamacrocycles, have not been frequently employed. Note however, that they are commercially available and an elegant kilogram scale synthesis of the corannulenes above has been described.[19] However, the most common of which, the cyclotriphosphazenes (**9**)[20] and the calix[4]arenes (**10**)[21] have been the subject of several publications in the field. Hexameric core **9** in particular has been mainly popularized by the group of Majoral *et al.*,[20] whereas the aromatic scaffolds **10** has been described in details by the Italian group headed by Ungaro *et al.*,[21] respectively. It is also noteworthy to mention that each of the above A_n multivalent dendrimer precursors can also be partially modified to provide lower $A_{n-1}B$ building blocks such as A_5B monomers (**9a**, **10a**). In fact, this approach has provided exciting entries into higher monomeric dendrons onto which were anchored probes or other functional groups, as well as serving as intermediates toward greatly accelerated dendrimer syntheses with a large number of surface functionalities at low generation. For instance, when cyclotriphosphazene **9a** (red-ending ball) was covalently ligated to its hexameric core (**9**), dendrimer having 30 surface functional groups can be readily prepared at G1.[20] The strategy was also elegantly applied for the synthesis of cationic and fluorescent "Janus" dendrimers (not covered herein[11]).

A_6 scaffolds illustrated in Fig. 2 also constitute useful building blocks for the rapid construction of heavily dense dendrimers in general, including glycodendrimers. Amongst these, building blocks **12**,[15] **14**, and **15**[22] have been predominantly well exploited toward sugar exposed glycodendrimers. Cyclic peptide **15** is particularly appealing since the various surface functionalities have been orthogonally protected to afford multivalent hybrid structures that have found applications in cancer vaccines.[23]

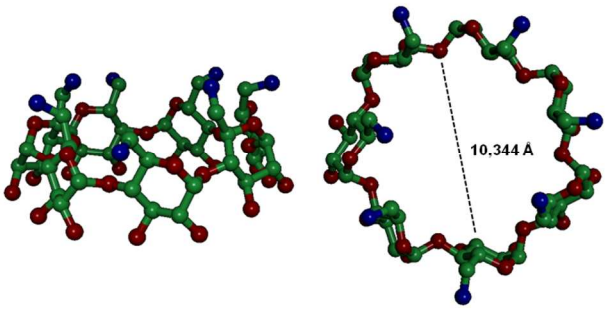


Fig. 3 A_7 Cone-shaped γ-cyclodextrin (**16**) with its seven primary hydroxyl groups (blue) and 10,344Å cavity for inclusion complexes and drug delivery has been extensively used as dendrimer scaffold.

Of general interest for this review, is the family of cyclodextrins that exist as 6-, 7, and 8-membered rings, commonly referred to as α-, β-, and γ-cyclodextrins, respectively.[24] Keeping in mind the context of this review, the A_7 case (β-cyclodextrin (**16**), has already 21-exposed hydroxyl groups that can be selectively manipulated since it contains seven readily accessible primary hydroxyl groups and fourteen secondary OHs, among which, the hydroxyls on position two of the sugar rings are also chemoselectively accessible with strong bases by virtue of their lower pKa values (Fig. 3). In addition, analogously to the cucurbit[*n*]uril family of ≥ A_{12} (**20**)[25] building blocks, they form stable inclusion complexes, useful for small drug delivery. This is due to the fact that sugars possess hydrophobic side (see below).

T-Symmetrical C_{60} fullerene derivatives (A_{12}, **21**), pioneered by the Nierengarten's group, also comprise a powerful family of potent building block assets since they possess their own intrinsic photochemical properties that are being successfully applied in glycobiology (Fig. 4).[26]

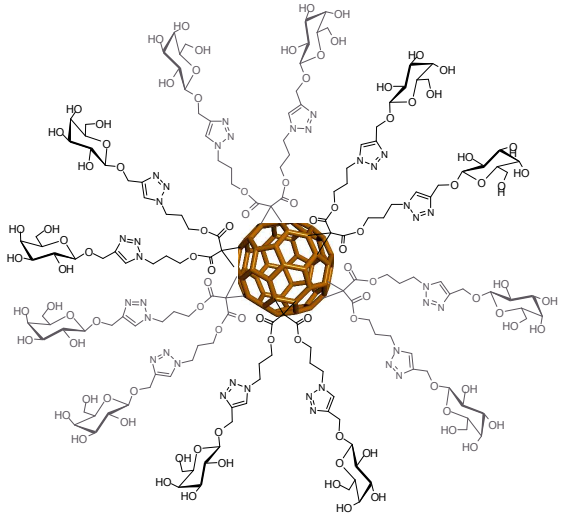


Fig. 4 Example of a polyol C_{60} fullerene (A_{12}, **21**) with surface exposed β-D-galactopyranosides represents a molecule harbouring 48-OH groups.

3. Sugars as highly versatile, multivalent building blocks for dendrimer syntheses

3.1 Classical glycodendrimers

Classically, most carbohydrate-containing dendrimers, coined glycodendrimers, were built with the sugar residues exposed at the surface for biological interaction studies with their cognate protein receptors.[11-16] This has given rise to an astonishing expansion of the "glycoside cluster effect" that has been later associated to "multivalent glycoside effect".[27] By virtue of this effect, binding associations with proteins were shown to be exponentially better than what would have been predicted from the sum of the individual monovalent binding interactions. Typical glycodendrimer structures are illustrated in Fig. 5. Multiple forms and strategies were creatively designed for their syntheses, several of which using the above multivalent scaffolds. As this review is principally devoted to describe the usefulness of sugars as scaffolds, rather than exposed surface groups, a brief overview of their valuable properties will be first discussed.

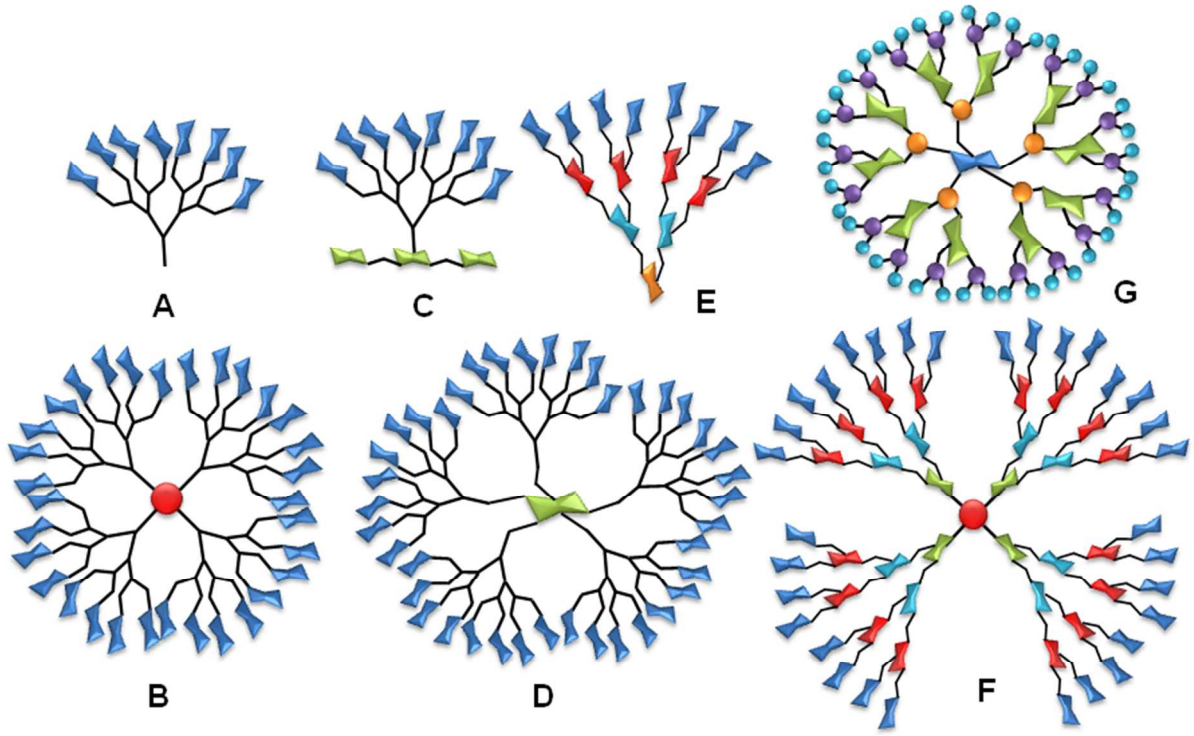


Fig. 5 Classical examples of synthetic dendrons and dendrimers that contain sugars at the periphery only (**A**, **B**), sugars as both the core and the surface groups (**C**, **D**), and sugars at all three positions: *i.e*. the core, the repeating units and the surface groups (**E**, **F**). The recent examples (**G**) represented by the "onion peel" strategy is of particular interest because the sugars constitute the integral parts of the building blocks/and or the repeating units.

3.2 Sugars: a brief overview

Carbohydrate chemistry (glycochemistry) has usually been considered as a specialized topic from the organic chemistry community. For some, it is an "art" and this assessment is probably through since it necessitates special skills for manipulating these water-soluble molecules that possess so many exposed hydroxyl groups. Moreover, single carbohydrate moiety may exist in two anomeric configurations (α or β), in both enantiomeric forms, as open chain as well as in five or six membered rings (furanoses and pyranoses) (Fig. 6). Several structures already exist in naturally oligomeric forms such as cellobiose, maltose, trehalose, and lactose in addition to cyclodextrins.

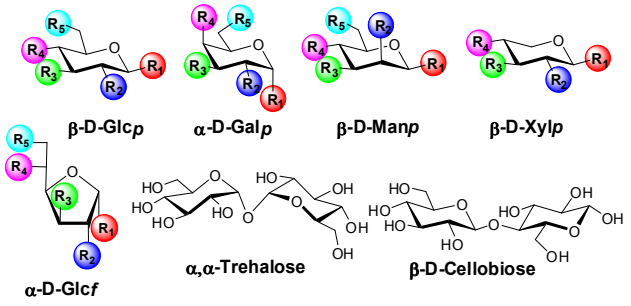


Fig. 6 Carbohydrates are chiral molecules that exist in multiple conformational and configurational states with a range of OH-groups oriented in a wide range of relative stereochemistry.

However, it is these intrinsic complexities that should make them so attractive for the construction of dendrimers. For example, if we consider a β-D-glucopyranoside residue (**β-D-Glc*p***, Fig. 6), all of its five substituents are oriented equatorially, that is, the molecule is somewhat planar in respect to the six-membered ring backbone. In addition, once the hydroxyl functions are derivatized, even partially, the compounds become soluble in most organic solvents. Also, an important but hidden behaviour of carbohydrates, even in their fully unprotected version, is that they can induce CH-π stacking interactions with most proteins (Fig. 7) that greatly depends upon the anomeric configurations and the relative OH group stereochemistry.[28] This important property has been advantageously taken into consideration for the inclusion of hydrophobic drugs (Roy, unpublished data). We coined this behaviour as the "glycodendritic box".

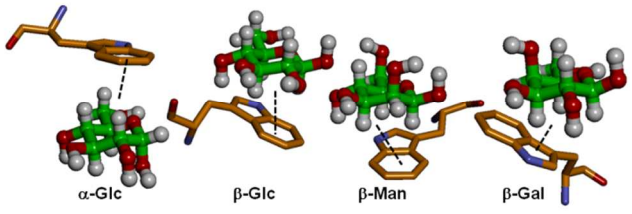


Fig. 7 Sugars have "hidden" hydrophobic sides capable of CH-π stacking.

Importantly as well, when considering using sugars as dendrimer moieties, not all hydroxyl groups need to be used equally. In fact, if we consider again the **β-D-Glc*p*** moiety, basically an A_5 scaffold, its specific and readily accessible anomeric position (R_1, Fig. 6) can be selectively manipulated in order to incorporate a different functionality which can make it as a useful source of AB_4 building block. In other words, it becomes a dendron.

Furthermore, a few commercially available sugars exist with built-in functionalities. This is particularly the case with D-glucosamine, better known as its glucosamine sulfate derivative, a **β-D-Glc*p*** analog having an amine group as R_2. Analogously, D-glucuronic acid has a carboxylic acid as R_5 (Fig. 6). Although these naturally occurring derivatives represent useful candidates, they have been seldom used in dendrimer chemistry.

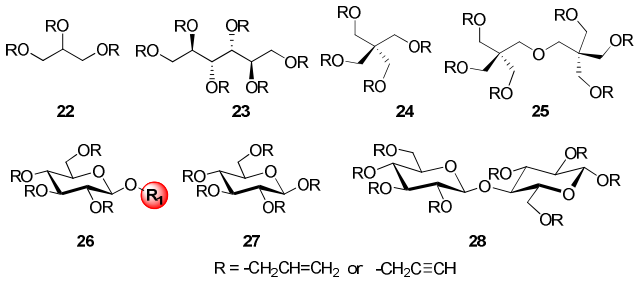


Fig. 8 Representative examples of sugars and polyols frequently encountered as scaffolds and building blocks in dendrimer syntheses.

Moreover, a clear strategic advantage of carbohydrates as building blocks is the fact that their multiple hydroxyl groups are fundamentally different from one another. For instance, the C1 anomeric hydroxyls (R_1 in Fig. 6) are essentially hemiacetals which makes this position particularly and selectively prone to chemical modifications. Its stereochemistry can be relatively well controlled by directly using Fischer type glycosidations (thermodynamic) onto reducing sugars, thus giving rise to α-glycosides (axial). Alternatively, the β-anomers (equatorial) can be obtained using anchimeric group participation with esters such acetates and benzoates on C2, at least with D-glucosides and D-galactosides. The art of sugar chemistry thus consists in mastering, almost case by case, how sugars (D-, L-, pentoses, aldoses, etc) behave in each of the above circumstances. Secondly, the reactivity of the primary hydroxyl groups (R_5) comes next simply because they are less hindered. Finally, some secondary hydroxyls are either axial (more hindered) than their equatorial (less hindered) equivalent. These properties can be fully exploited in the context of dendrimer chemistry.

3.3 Sugars and polyols as dendrimer scaffolds

As mentioned above,[11-16] sugars and naturally occurring polyols such as glycerol, pentaerythritol, dipentaerythritol and even alditols like mannitol, glucitol, xylitol, etc. constitute valuable building blocks and scaffolds as they can be readily modified by simple etherification under alkali conditions with, for example, allyl and propargyl bromides (Fig. 8). Notice again that the selective manipulation of the anomeric position, such as in **26**, provides the versatile starting materials for both divergent and convergent dendrimer syntheses as they represent valuable A_4B molecules. When the same sugar (ex. **27**) is entirely substituted with identical reactive functions, it becomes a versatile A_5 core.

3.4 The versatility of sugar chemistry

Modern "click chemistry" such as the copper-catalyzed azide-alkyne cycloaddition (CuAAC),[29] thiol-Ene (TEC), and thiol-Yne (TIC)[30] have not escaped the attention of glycochemists. So they too have been extensively used in constructing dendrimers. Although most examples in the following sections have been dedicated to synthesized "classical glycodendrimers",[11-16] we purposely selected to arrest their description at the functional level wherein the final surface group modification is left open. This approach will better allowed the practitioners in both fields (carbohydrates – dendrimers) to merge their creativity toward the construction of novel architectures encompassing original structural moieties.

3.4.1. D-Glucopyranoside scaffolds

Since click chemistries are so powerful, the necessary sugars harbouring fully substituted alkenes and alkynes have been frequently encountered. Their preparations are straightforward and again, their access depends on whether α- or β-glycosides are requested. Fig. 9 illustrates classical cases for the syntheses of the fully allylated (**35**)[31] or propargylated (**36**)[32] β-D-glucopyranoside precursors. Although the example below starts from a peracetylated glucosyl bromide (**29**) and gave **31** in excellent yield under Helferich conditions, a more practical approach consists in using a peracetylated sugar (**30**) under Lewis acid-catalyzed conditions. Similarly, the latter has been used for the preparation of the corresponding propargyl β-D-glucopyranoside **33** using propargyl alcohol. Catalytic transesterification under the so-called Zemplén conditions (NaOMe, MeOH) afforded tetrols **32** or **34**, respectively, which upon etherification with either allyl or propargyl bromides gave **35** or **36**, respectively.

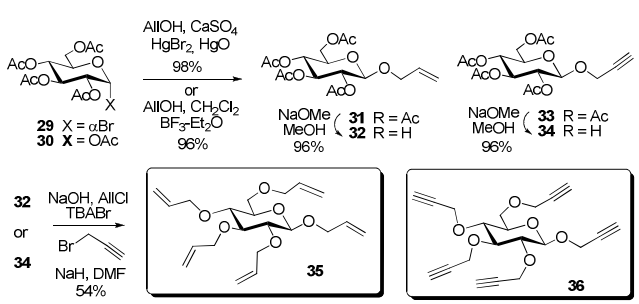
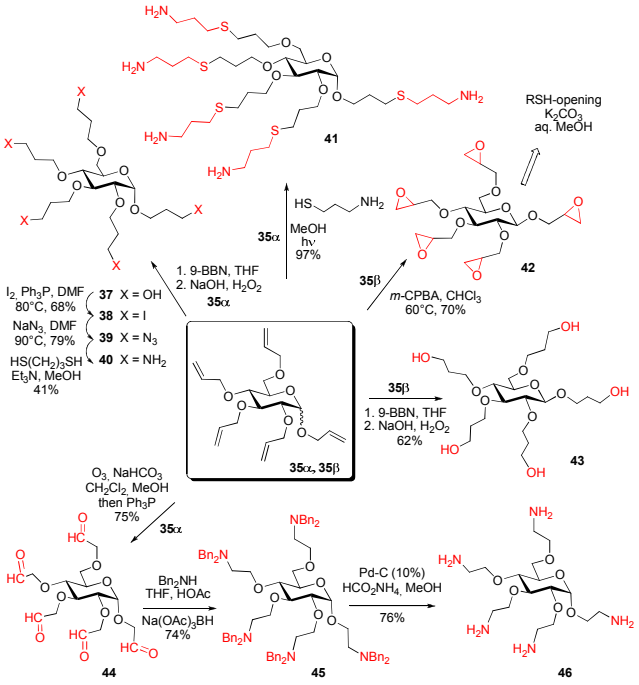


Fig. 9 Typical syntheses of β-D-glucopyranosides and their polyallylated and propargylated derivatives.

These useful compounds were readily transformed into a wide panel of intermediates for the successful completion of various multivalent functionalities that have been so common in dendrimer syntheses (Fig. 10).

For instance, taking perallylated α- or β-D-glucopyranosides (**35α**, **35β**) as case study, it can be readily seen that they constitute versatile precursors toward constructing dendron and dendrimer precursors (scaffolds) having a large number of typical surface functionalities exposed. Thus, oxidative hydroboration of both anomers **35α** and **35β** have been an important source of chiral polyols **37**[33] and **43**,[31] respectively. In turn, pentahydroxylated intermediate **37** has been successfully transformed into a range of derivatives that included periodide **38** (I_2, Ph_3P, 80%) followed by azide **39** (NaN_3, DMF, 79%) by simple nucleophilic S_N2 substitution. The latter (**39**) was next transformed into amine **40** by a Staudinger transformation with 1,3-propanedithiol in 41% yield.[33]



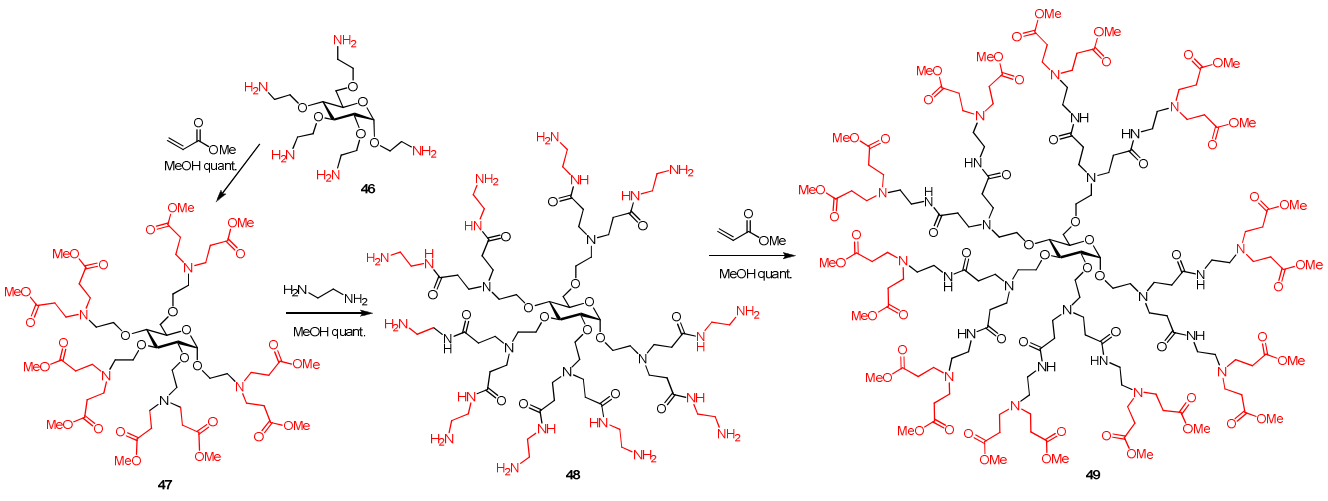


Fig. 10 Synthetic modifications at the origin of versatile carbohydrate building blocks.

Alternatively, allyl ethers can be treated with cysteamine hydrochloride under radical conditions (photolytic or AIBN-catalyzed) to afford extended pentaamine derivatives such as **41** in excellent yield (Fig. 10).[33] Note that pentaamine **40** stands for a shorter homolog of amine **41**. Moreover, perallylated sugars have also been suitably transformed into the next higher generations by using sugars bearing either a thiol at the anomeric position or in the extended aglycones. Conversely, *meta*-chloroperbenzoic acid (*m*-CPBA) epoxidation of **35β** gave the pentaepoxide **42** which represent a useful precursor for ring opening with various nucleophiles, including thiols.[34]

Additional useful transformations of perallylated sugars were based on ozonolysis of, for example **35α** (O_3, Ph_3P) to provide pentaaldehyde **44** which, upon reductive amination with dibenzylamine and sodium triacetoxyborohydride gave **45** (74%) followed by catalytic transfer hydrogenation (Pd-C, HCO_2NH_4, MeOH) to give shorter pentaamine homolog **46** (76%).[35] Intermediate polyadldehyde **44** could not be readily characterized as it is constituted of several hydrate and hemiacetal forms, a behaviour typical in carbohydrate chemistry. In addition, reductive amination of **44** with benzylamine rather than dibenzylamine inevitably afforded complex mixtures of cyclic amines resulting from the reduction of intramolecular imine intermediates. Interestingly, reduction of pentaaldehyde **44** also gave the shorter penta-(2-hydroxyethyl) analog (not shown).[33] Furthermore, pentaamine **40** was shown to react with isothiocyanates to give thioureas in excellent 80% yield.[36]

Fig. 11 PAMAM-type dendrimer syntheses based on an α-D-glucopyranoside backbone.

It is worth mentioning that the above polyamines (**40**, **41**, **46**) represent important starting materials for the synthesis of higher dendritic PAMAM-type polyamines. For example, penta-(2-aminoethyl) glucoside **46** has been elegantly and efficiently treated with a large excess of methyl acrylate to give decamethyl ester **47** (Fig. 11).[35] Following its sequential and successive treatment, as per PAMAM dendrimers, decaamine **48** and 20-mer ester **49** were quantitatively generated.

As mentioned above, equivalent A_4B systems can be effortlessly synthesized from sugars having different functionalities in the aglycones (Fig. 12). Thus, tetrallylated 6-bromohexyl glucoside **50**[36] has been transformed into a tetramannosylated glycocluster such as in **51** (R = sugar) using photolytic thiol-ene reaction in 40% yield.

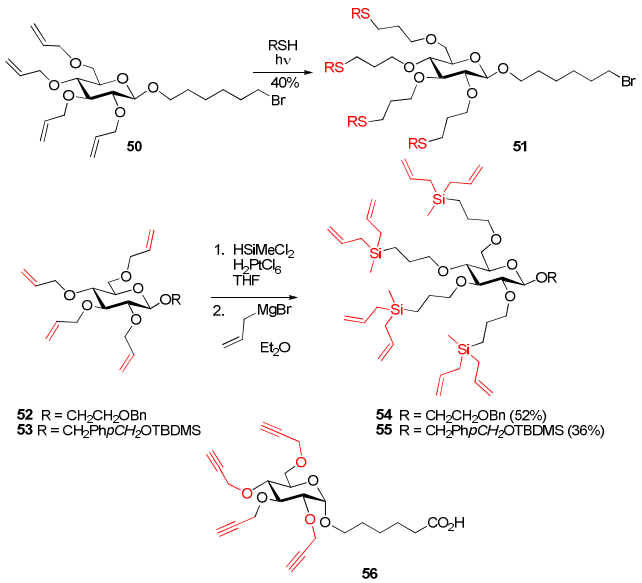


Fig. 12 Typical perallylated and propargylated A_4B sugar scaffolds synthesized around glucopyranosides.

Unfortunately, this strategy and analogous ones described below have not been extensively pursued until now toward the syntheses of higher dendrimer generations (Roy, unpublished data). Carbosilane dendrimers having a carbohydrate core have been similarly investigated,[37] albeit in low overall yields (Fig. 12). Hence, tetraallylated β-D-glucopyranosides **52** and **53** were submitted to a hydrosilylation-Grignard addition sequence ($HSiMeCl_2$, $H_2PtCl_6{\cdot}6H_2O$/*i*-PrOH, THF; AllylMgBr, Et_2O) to give the next higher homologs **54** and **55**, respectively. Although this strategy has not been exploited further, it can be suitably adapted to that of other carbosilane-based dendrimer syntheses.[38] An analogous A_4B system incorporating tetrapropargyl ethers such as in **56** has also been generated.[39] This interesting scaffold was efficiently utilized for the development of a potent self-adjuvanting lipopeptide vaccine comprising four copies of a group A streptococcal B cell epitope using click chemistry. The aglycone bearing a carboxyl was further transformed with an additional promiscuous T-helper cell epitope.[39]

3.4.2. D-Galactopyranoside scaffolds

As mentioned, β-D-glucopyranosides have their five substituents equatorially distributed while its α-D-congener has the aglycone in the axial orientation, thus providing a break in the overall geometrical architecture. In addition, except for the readily accessible primary C-6 hydroxyl group, the remaining equatorially oriented tetraol cannot be so easily and chemoselectively manipulated. However, this is not the case with other sugars such as galactopyranosides (Gal) and mannopyranosides (Man) that contain at least one more hindered axial hydroxyl (C-4 for Gal and C-2 for Man). As a matter of fact, this particularity has also not been sufficiently exploited (see section 3.5). Nevertheless, the strategies described for the glucosides above have been successfully applied for the Gal and Man congeners. Fig. 13 nicely illustrates such transformations. For instance, NHBoc-ending peracetylated α-D-galactopyranoside **57**,[40] obtained from its corresponding allyl glycoside by a thiol-ene reaction with NHBoc-cysteamine derivative, can be efficiently perpropargylated using conventional conditions to afford **58** in 51% yield. Compound **58** has been further transformed by classical CuAAC into biotinylated tetra-antennary carbohydrate probes used for magnetic relaxation switches. Methyl α-D-galactopyranoside **59** on the other hand has served as a precursor for esterification with Boc_2-aminooxyacetic acid **60** under conventional peptide coupling conditions to afford tetraaminooxy derivative **61** that was used toward the syntheses of carbopeptides using chemoselective oxime ligation with aldehydo-peptides.[41]

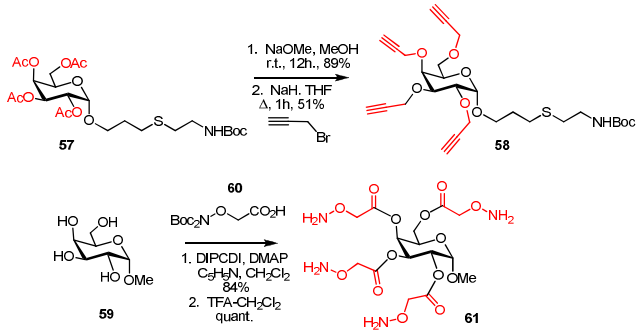


Fig. 13 α-D-Galactopyranosides A_4B systems.

Another useful 2-azidoethyl α-D-galactopyranoside scaffold (**62**) has also been elegantly used toward the synthesis of a carbohydrate-based HIV-1 vaccine (Fig. 14).[42] To this end, azido tetraol **62** was perallylated in 88% yield using conventional conditions (allyl bromide, NaH, DMF) to give tetrallyl ether **63**. Staudinger ligation of **63** with NHBoc-protected 6-aminohexanoic acid gave **64** that undergone clean photoinduced thiol-ene reaction upon treatment with excess cysteamine to provide **65** (82%). Further derivatization of **65** with the succinate active ester of 6-maleimidohexanoic acid (**66**) gave the interesting tetravalent Michael acceptor **67** in a moderate 44% yield. Thiol-ending multiantennary $Man_9GlcNAc_2Asn$ derivative, serving as HIV-1 B-cell epitope, and further coupling with a T-helper cell peptide epitope afforded the desired vaccine. Given the importance of maleimide-bearing intermediates in Diels-

Alder coupling toward dendron and dendrimer syntheses,[43] compound **67** may represent a versatile carbohydrate-based A_4B scaffolds toward other dendrimer building blocks.

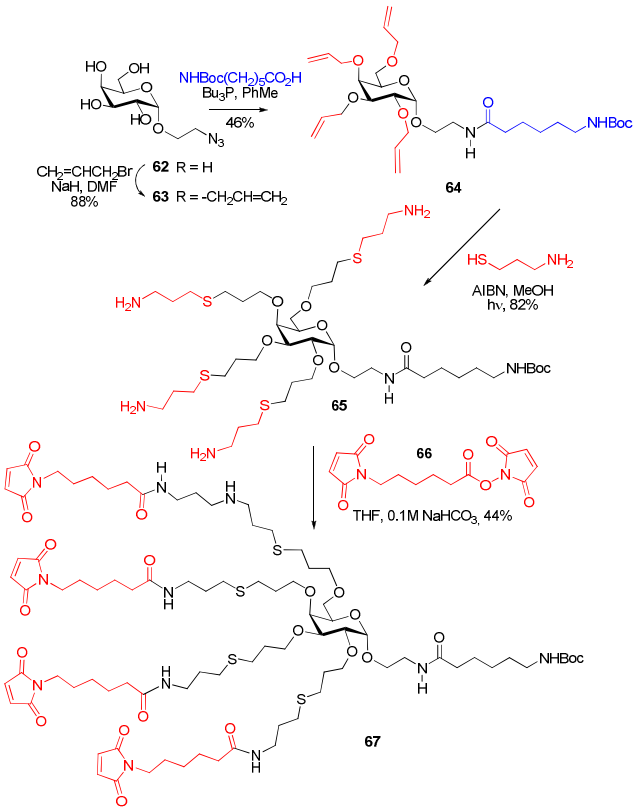


Fig. 14 Potent A_4B galactopyranoside building blocks harbouring allyl (**64**), amine (**65**), or maleimide (**67**) functionalities.

3.4.3. α-D-Mannopyranoside scaffolds

An interesting series of papers have dealt with the syntheses of glycodendrimers as multivalent bacterial lectin inhibitors and in sensitive DNA-based microarrays using a panel of highly functionalized scaffolds described in Fig. 2.[44] As this review focus essentially on sugars as building blocks, the discussion will be limited to the key example described in Fig. 15, although glucoside (Glc) and galactoside (Gal) were also used as scaffolds in place of the mannopyranoside illustrated. The chemical expansion of the sugar backbone was efficiently built using solid phase oligonucleotide synthesis (SPOS) by standard phospho di- and tri-ester chemistry on glass beads.

The key precursor was the known propargyl α-D-mannopyranoside **68** that has ultimately served as an anchoring motif to both the exposed sugar residues and to the oligonucleotides to be hybridized on the pre-sensitized glass slides. Thus, alkyne **68** (or their Glc or Gal analogs) was treated with azido-functionalized glass-beads under CuAAC conditions to give **69**. Phosphoramidite couplings on the four exposed hydroxyl groups of the mannopyranoside-anchored intermediate **69** were done with either *bis*-pent-4-ynyl phosphoramidite (**70**) or an analogous monovalent 2-cyanoethyl *N*, *N*-diisopropyl phosphoramidite (not shown) using 5-benzylmercaptotetrazole (BMT) as the coupling

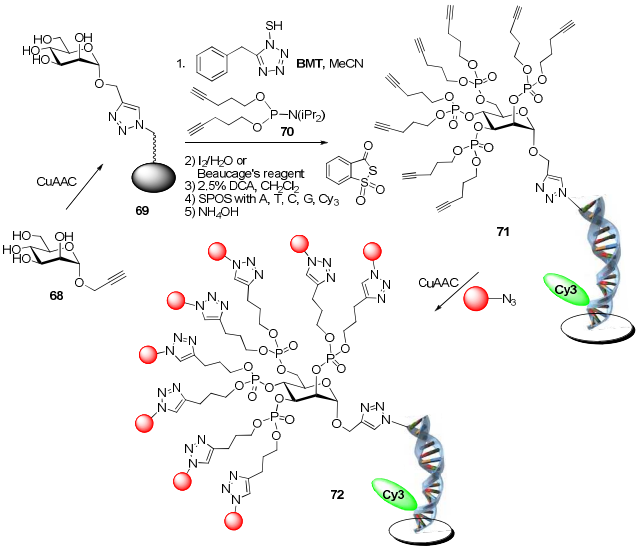


Fig. 15 SPOS syntheses of octapropargylated mannoside scaffolds.

reagent. The resulting octa-propargylated mannopyranoside scaffold (or tetra-propargylated, not shown) were then subjected to SPOS after oxidation by I_2 or Beaucage's reagent (3-*H*-1,2-benzodithiol-3-one-1,1-dioxide) to provide **71** after labelling with cyanine dye (Cy_3). Finally, coupling with various sugar azides using the CuAAC method and hybridization on the glass slides gave **72**.

3.5 Partial modifications of sugar derivatives

Sugars, by virtue of their several useful and distinct functional groups, constitute versatile scaffolds in dendrimer syntheses. When left unprotected at the end of the dendrimer scaffolding and or layer build-up, the variously positioned hydroxyl, amine, and carboxylic groups constitute useful appendages for the incorporation of electrochemical, photophysical, biological, and medicinal probes. In addition, when few hydroxyl groups are left behind, they would confer dendrimers with increased water-solubility, an important property toward biological applications. This section will exemplify a few case studies to demonstrate how these essentially carbohydrate-specfic properties can be advantageously utilized for dendrimer construction.

Fig. 16 illustrates the synthesis of PAMAM-type amino- and carboxyl-terminated dendrimers using D-glucuronic acid derivative **73** that can be readily transformed into an A_2B sugar amino acid using classical carbohydrate and peptide chemistry. Thus, an anomeric β-azide functionality can be introduced onto peracetylated **73** using $TMSN_3$ and a Lewis acid ($SnCl_4$) to provide azido acid **74** in 53% yield (Fig. 16).[45] Peptide coupling (DIC, HOBt) between acid **74** and Newkome-type A_3B amine **75** afforded azido tricarboxylate **76** in 79% yield. This compound was intended to serve toward the synthesis of a glycopeptide mannodendron useful as inhibitor in the adhesion of uropathogenic *E. coli* to epithelial cells. Alternatively, orthogonally protected amino diacid derivatives **77** and **78** were coupled (HATU, DIPEA) to provide 6-amino derived tetraester **79** in 79% yield. NHBoc deprotection of **79** (TFA, Me_2S) and

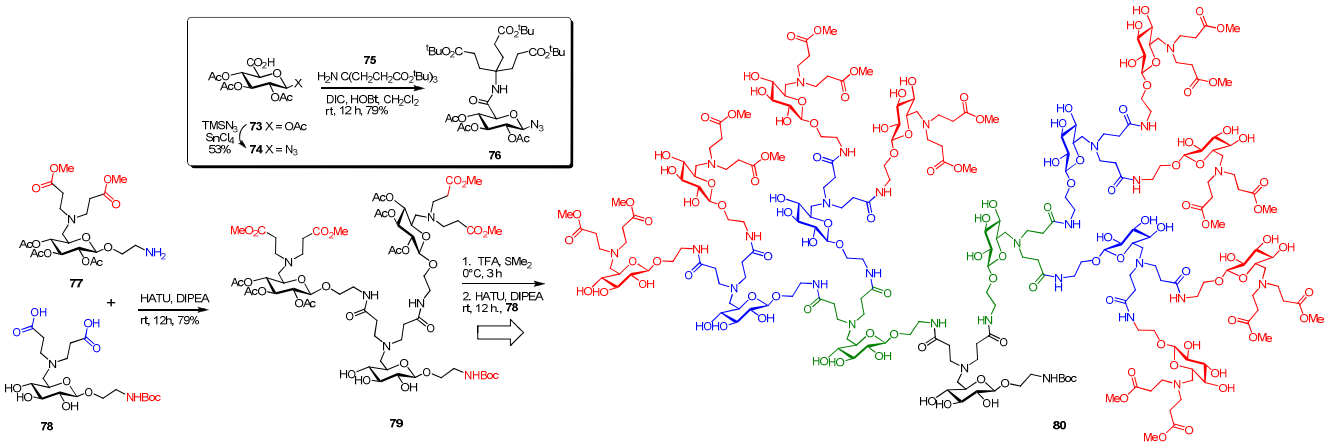


Fig. 16 Application of the PAMAM-dendrimer synthetic strategy using partially modified sugar derivatives (β-D-glucopyranosides) modified at C-6.

further iterative coupling with diacid **78** as above and repetition of the sequence gave glycopeptide dendron **80** possessing 16-esters and an NHBoc-protected amine at the focal point.

Selectively positioned 3,6-diallylated mannopyranoside **81** has also nicely served as scaffold for the synthesis of dendritic chiral polyols having free hydroxyl groups in the inner layers as well as the outer layer (Fig. 17).[46] To this end, mild oxidative hydroboration (9-BBN, THF) of **81** followed by a buffered peroxide treatment (NaOAc, 30% H_2O_2) to keep the benzoate esters intact gave diol **82** in 69% yield. α-Stereoselective mannosylation of **82** with trichloroacetimidate donor **83** catalyzed by TMSOTf provided tetraallyl intermediate **84** (79%). Reiteration of the oxidative hydroboration process gave tetraol **85** (40%) having six masked benzoates which upon further mannozylation as above and deprotection afforded glycodendron **86**. It has to be kept in mind however that such a sequence can be an excellent strategy to generate perallylated dendrons that are nowadays so usefully derivatized by thiol-ene chemistry. It would still provide dendrons with plenty of OH groups in their interior.

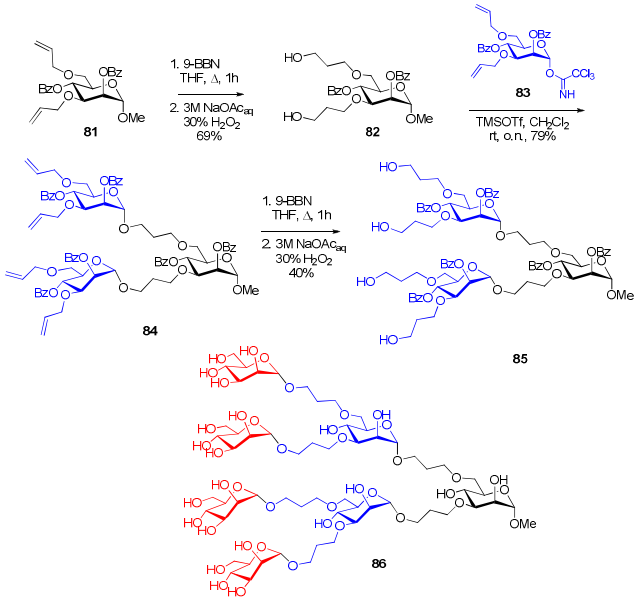


Fig. 17 Reiterative synthesis of perallylated dendrimers having free inner hydroxyl groups.

Another interesting application of selectively protected carbohydrate derivatives has been described for the synthesis of multichromophoric sugars for fluorescence photoswitching (Fig. 18).[47] Hence, multichromophoric methyl α-D-glucopyranoside **93** bearing three dicyanomethylenepyran (DCM) fluorophores and one diarylethene (DAE) photochrome has been prepared by the CuAAC method. Toward this goal, O-6 trityl protected glucoside **87** was tripropargylated (propargyl bromide NaH, DMF, Bu_4NI) to give precursor **88** which upon treatment with DCM-azide **89** under CuAAC gave **90**. Trityl group deprotection under *in situ* generated HCl (AcCl, MeOH), followed by mesylation (MsCl, Et_3N, DCM), and azide substitution afforded **91**. Second CuAAC coupling with propargylated DAE (**92**) delivered photoswitch **93** in 66% yield. Interestingly and as expected, the fluorescence of **93** was switched off upon UV irradiation. A nearly 100% Förster-type resonance energy transfer (FRET) from all three DCM moieties to a single DAE (in its close form) was achieved. Again, given that the anomeric position could have been derivatized with an appropriate functional group, the strategy opens the door for further expansion.

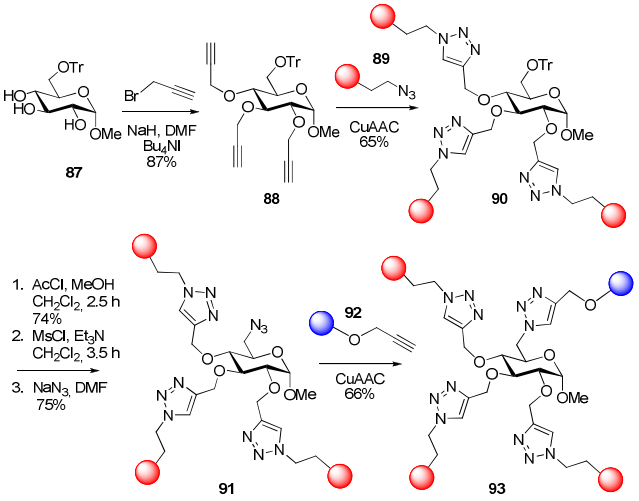


Fig. 18 Multichromophoric sugar for fluorescence photoswitching. Red balls represent dicyanomethylenepyran fluorophores (DCM) while the

blue ball corresponds to a diarylethene photochrome (DAE).

The versatility of selective sugar manipulations between a glucoside and a galactoside derivative has been further substantiated with the following example (Fig. 19).[48a] Readily accessible methyl 4,6-*O*-benzylidene-α-D-glucopyranoside acetal **94** can be propargylated under usual conditions to give 2,3-di-*O*-propargyl glucoside **95** which upon acetal hydrolysis (aq. AcOH, 94%) and subsequent etherification with bis(2-chloroethyl) ether gave orthogonally protected dichloride **96** (54%). An analogous reaction sequence was also performed on galactoside 2,6-diol **97** to give 2,6-di-*O*-propargylated intermediate **98** which upon etherification as above afforded precursor **99**. CuAAC coupling of either glucoside **96** or galactoside **99** using a stable copper catalyst ($(EtO)_3P$-CuI)[48b] in refluxing toluene with a family of azides gave triazole dichlorides **100a** or **101a** in 80 and 94% yields, respectively. Subsequent substitution of chlorides by azides gave intermediates **100b** and **101b**, suitable for the next CuAAC.

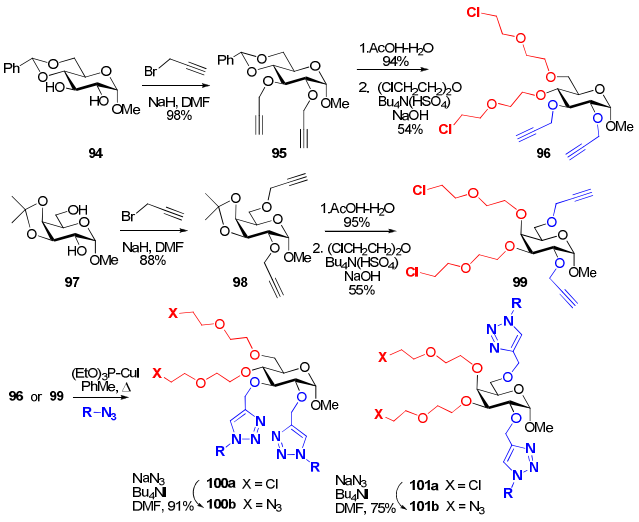


Fig. 19 Practical entries into combined azido-triazole functionalities can be achieved from suitably and orthogonally protected glucoside and galactoside acetals.

Another representative approach toward orthogonally protected A_3BC sugars has been described in which an azide functionality was introduced together with TMS-protected alkynes. The readily available levoglucosan 2,3,4-triol **102** was efficiently transformed into its tripropargylated ether **103** using standard conditions (Fig. 20).[49] Protection of the terminal alkynes with TMS derivative was performed using TMSCl, AgOTf, and DBU as a base to give key intermediate **104**. Careful ring opening of the intramolecular 1,6-anhydro group was next achieved using $TMSN_3$ and the Lewis acid TMSOTf to afford azido alcohol **105** in 82% yield in high diastereoselectivity. The conditions were chosen as to avoid the intramolecular azide-alkyne 1,2-cycoaddition. Sequential CuAAC treatment of azide **105** with an external alkyne gave **106** regioselectively in 69% yield. The final step involved a combined one pot TMS deprotection–CuAAC triazole formation using TBAF, $CuSO_4 \cdot 5H_2O$, sodium ascorbate, Na_2CO_3, in DMF-water and microwave (100ºC, 1h) to give hybrid triazole **107** in 63% yield.

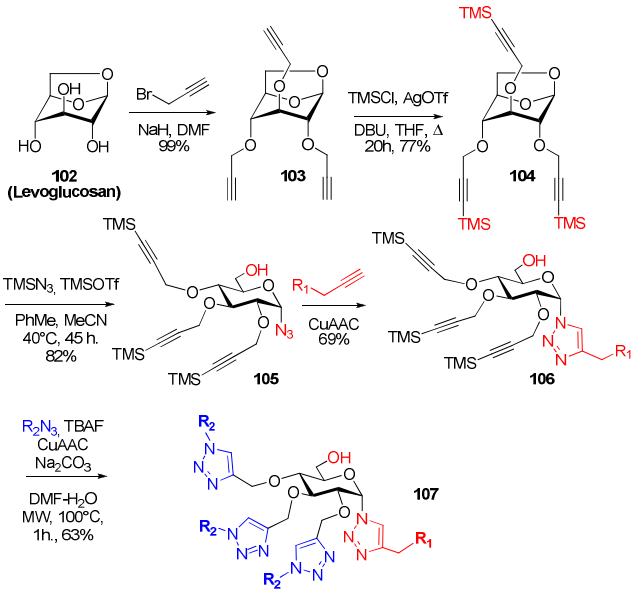


Fig. 20. Orthogonally-protected A_3BC azido-TMS-protected alkyne involving versatile levoglucosan (**102**) as a source of glucoside 2,3,4-triol.

3.6 Oligomeric sugar scaffolds

Disaccharides like cellobiose, lactose, melibiose, trehalose, and their higher homologues also represent useful candidates toward dendritic G0 scaffolds. For example, they can be readily transformed into A_8 core such as the perallylated (**108**, **115**) and the perpropargylated (**114**) melibiose and trehalose derivatives (Fig. 21).[50] Moreover, octameric core **108** can be hydroborated similarly to its glucoside analog **35** (Fig. 9) with 9-BBN to give octaol **109** and further transformed into a plethora (see Fig. 10) of functionalized precursors such as **110-112** frequently encountered in dendrimer syntheses.[50] To this end, stereoregular polyol **109** was converted to it's per bromide derivative **110** in 63% yield (CBr_4, Ph_3P). The bromides were then almost quantitatively substituted with a phthalimide functionality to afford **111** that was deprotected to the polyamine **112** by hydrazinolysis in 58% yield. Of particular interest, oactaamine **112** was next converted in excellent yield (94%) to perester **113** using conjugate Michael addition with methyl acrylate analogously to the one used in PAMAM dendrimer synthesis (Fig. 21).

Besides the A_8-type trehalosides **108** and **114**, which are somewhat crowded by virtue of being α,α-1,1-linked (and kinked), perallylated melibioside **115** and raffinose **116** can be equally synthesized.[51] Note that **116** represent an interestingly dense A_{11} monomer core that has been fully allylated under the usual conditions (allyl bromide, NaH, DMF) in 69% yield. In addition, besides **108**, oxidative hydroboration of **115** and **116** gave the corresponding polyols (not shown). These three polyols were successfully glycosylated to next polyols level in moderate to excellent yields. Also of interest is the synthesis of the A_7B-type azido cellobioside **117** (Roy, unpublished data) that serve as an excellent inter-layer building block for the rapid synthesis of highly functionalized dendrimers within low generation.

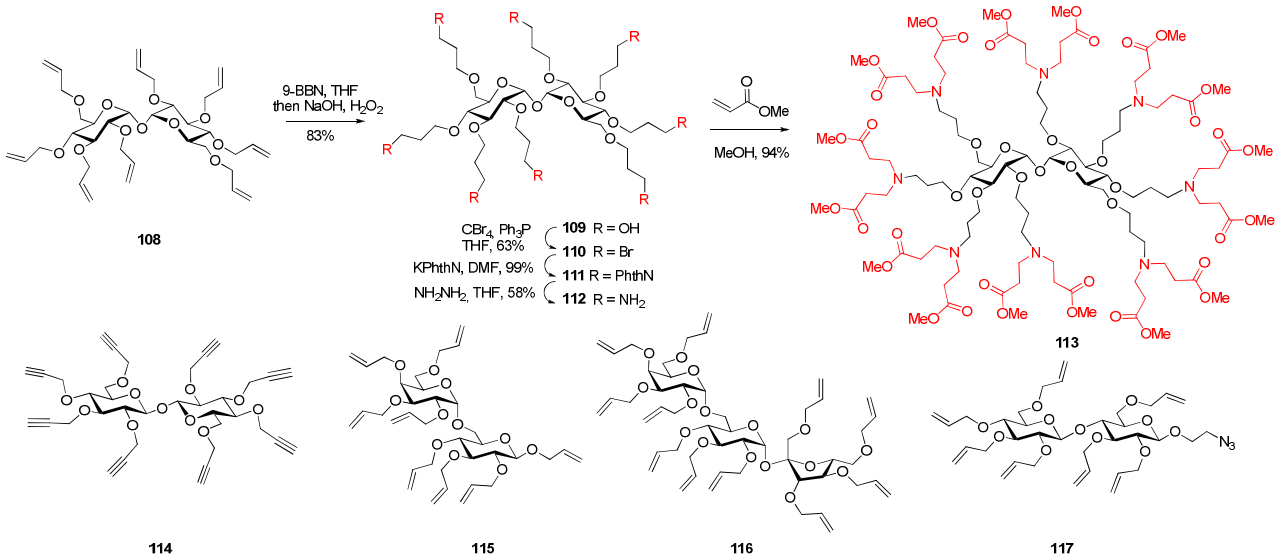


Fig. 21 Synthesis of G0 and G1 dendrimers using naturally occurring disaccharides and trisaccharides as A_8 core.

Another helpful entry into multivalent sugar scaffolds has been described in which cyclic oligo-(1→6)-β-D-glucosamine core were prepared, albeit using lengthy reaction sequences (Fig. 22).[52]

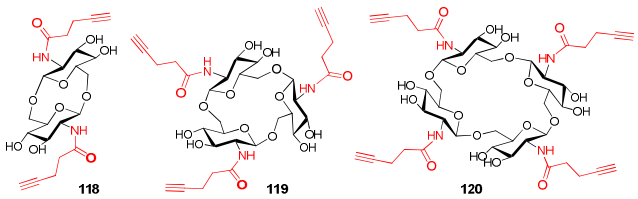


Fig. 22 Per propargylated cyclic oligo-(1→6)-β-D-glucosamine core used as scaffolds.

A family of two to seven monosaccharide units were thus assembled to afford polyamino compounds varying in both their degree of branching and the positioning of the amino groups to be elongated. For instance, compounds **118-120** were synthesized and further transformed into valuable glycoclusters using CuAAC chemistry.

As mentioned above, sugars can be easily and partially modified to provide suitably derivatized intermediates with strategically positioned functionalities such as azides and alkynes. This also holds for more complex oligosaccharides (Fig. 23).[48a]

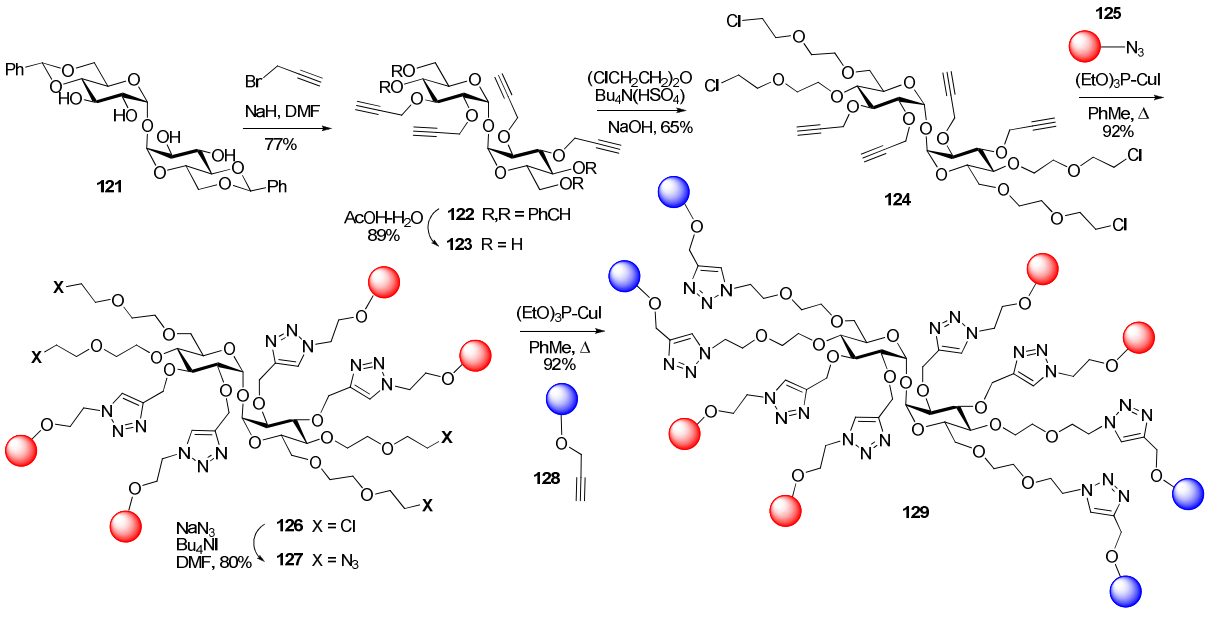


Fig. 23 Examples of orthogonally functionalized trehaloside disaccharide that can undergo regioselective CuAAC coupling.

In this regard, trehalose dibenzylidene acetal **121** was symmetrically propargylated to give tetrapropargyl ether at positions 2,3- and 2',3'(**122**) (77%). Aqueous acid hydrolysis of the benzylidene acetal (HOAc-H_2O) gave tetraol **123** (89%) that was next etherified at the 4,6- and 4',6'-positions under phase transfer catalysis with bis(2-chloroethyl) ether and tetrabutylammonium hydrogensulfate (50% aq NaOH, $Bu_4N(HSO_4)$) to afford tetrachloride **124** in 65% yield. The reaction sequence is thus analogous to the one described above for the monosaccharide analogs (Fig. 19). A first CuAAC sequence using the reactive copper catalyst ((EtO_3P)-CuI)[48b] in refluxing toluene and azide **125** uneventfully furnished tetra"clicked" intermediate **126** in 92% yield. Chloride to azide substitution gave **127** that undergone a second CuAAC with propargyl ether **128** to give hybrid glycocluster **129** (92%).

3.7 Cyclodextrin scaffolds

Undoubtedly, β-cyclodextrin (cyclomaltoheptaose) has been the most heavily used multivalent sugar scaffold for the syntheses of highly versatile and multifunctional dendrimers.[24, 53] It possesses a total of 21-regioselectively accessible hydroxyl groups (Fig. 24). Thus, it constitutes a valuable A_{21}-type core molecule. In addition, as stated, it can accommodate small hydrophobic moieties in its interior cavity of 10.3 Å (see Fig. 3), including adamantanes. It's seven primary hydroxyl groups, most readily accessible (**130**) and exposed at the top of the cone-shaped architecture, have offered several opportunities toward various chemical manipulations. For instance, the C-6 primary hydroxyls

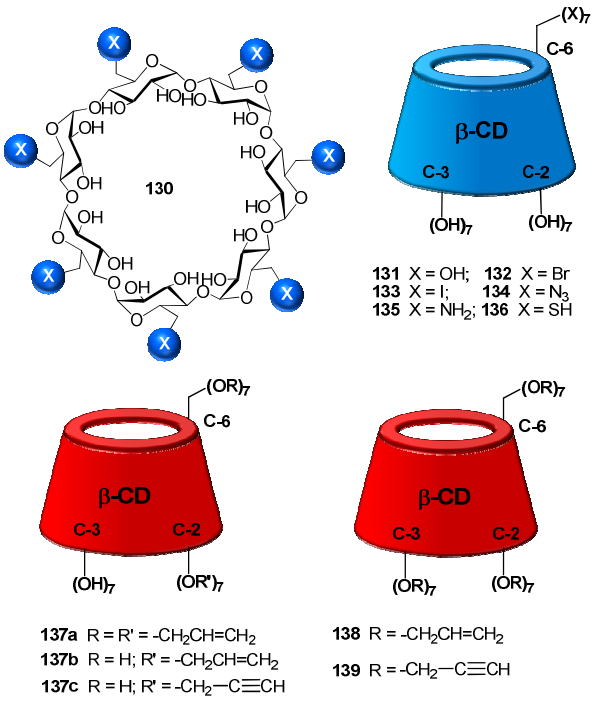


Fig. 24 Typical structures of modified β-cyclodextrin extensively used as scaffolds in dendrimer syntheses. It possesses 21 distinct OH functionalities.

can be easily transformed into heptakis(6-bromo-6-deoxy)cyclomaltoheptaose (**132**) using NBS, Ph_3P, DMF.[53a] Alternatively, the corresponding heptakis iodide (**133**) can also be similarly prepared with I_2, Ph_3P in DMF. From the above two key precursors, heptakis azide (**134**) or heptakis thiol (**136**) can be reached by nucleophilic displacement. Obviously, heptakis azide **134** has been an excellent precursor for varied CuAAC reactions. Per(C-6) amino β-cyclodextrin (**135**) has been obtained by simple reduction of azide **134**. Additionally, substitution of either the perbromide (**132**) or the periodide (**133**) by cysteamine afforded the homologous per(C-6)-cysteaminyl amine derivative (not shown).

Equally interesting, access to more substituted β-cyclodextrins with 14- (**137**) and 21- (**138**, **139**) typical functionalities encountered in dendrimer synthesis can also be achieved. Toward this goal, base-catalyzed allylation/propargylation of the less hindered primary hydroxyl groups together with the most acidic secondary C-2 hydroxyls gave access to **137a**[53d,e] affording the fully substituted versions harbouring 21-allyl (**138**) or 21-propargyl (**139**) groups. By blocking the primary C-6 hydroxyl groups with TBDMS-ethers, it is also possible to prepare heptakis (C-2) allyl /propargyl ethers (**137b,c**). Of particular interest in glycodendrimer syntheses, these CD-derivatives have been further transformed into highly branched structures using CuAAC, isothiocyanate, thiol-ene and thiol-yne couplings.

4. Miscellaneous contributions

This section will described less commonly used glyconanosynthons as building blocks. Doubly branched sugar thiourea-based dendrons have been efficiently synthesized up to the G2 generation using iterative coupling strategies (Fig. 25).[54a] The methodology simply relied on bisazido glucose isothiocyanate **140** that was treated with 2,3-bisamino acetamide **141** in pyridine for 2 h to give tetraazide **142** in 77% yield. Note that both **140** and **141** came from the same glucose precursor. De-*O*-acetylation under Zemplén conditions, followed by Staudinger reduction of azide groups was done in high yields using 1,3-propanedithiol (MeOH, Et_3N, 18 h., 95%).

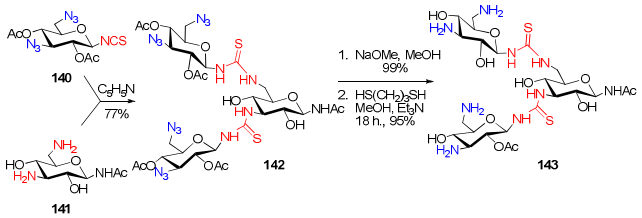


Fig. 25 Thioureas-linked dendrons using bisazido sugar precursors.

Another valuable, but lengthy reaction sequence, has led to an interesting A_3B building block starting from *myo*-inositol **144** (Fig. 26).[54b] Inositols are not fundamentally members of the sugar family but their structural polyol motifs resemble those of carbasugars. In the example below, one of the stereocenter of the starting *myo*-inositol was inverted to a *scyllo*-inositol

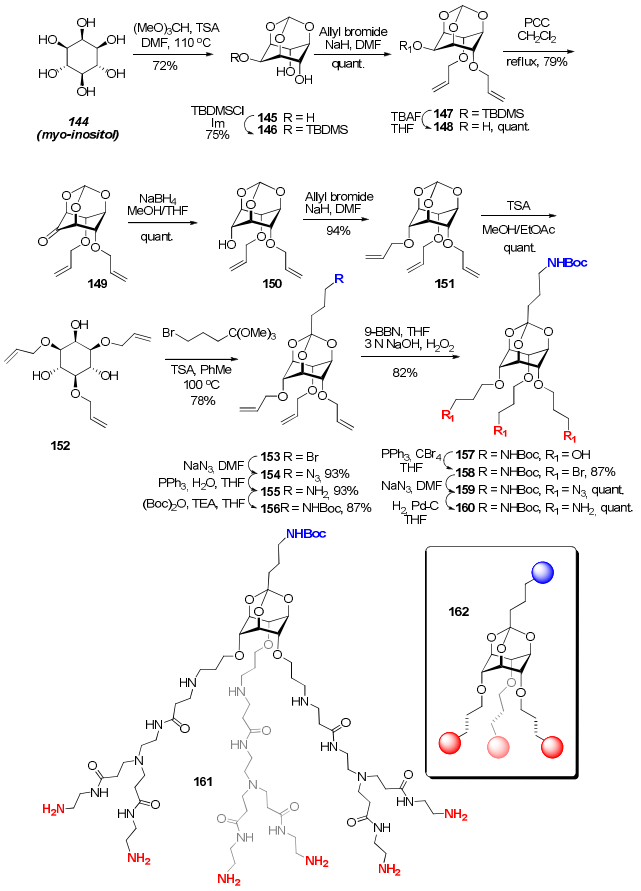


Fig. 26 Synthetic sequence leading to a PAMAM-type symmetrical A_3B scaffold starting from readily available *myo*-inositol.

diastereoisomer in order to obtain a symmetrical scaffold (**162**) for a probe attachment leading to atomic force microscopy (AFM) measurements of protein-multivalent carbohydrate binding interactions. To this end, three of the hydroxyl groups of hexaol **144** facing the same side of the molecule were blocked as an orthoformate ($(MeO)_3CH$, TSA) to afford **145** in 72% (Fig. 26). A sequence of selective equatorial OH protection as a TBDMS ether (**145**), perallylation (**147**), deprotection with TBAF (**148**), oxidation/reduction, and allylation again gave the desired intermediate **151** in a good overall yield. After hydrolysis, the orthoformate group of **151** was exchange with a variant incorporating trimethyl 4-bromoorthobutyrate to provide the bidirectional key intermediate **153** in which the two functional groups have been independently and orthogonally manipulated. The ensuing functional group interconversion ultimately led to triamine **160** that can then be treated as a PAMAM-type core to give **161** and its higher generation members (up to 12 amines). The final attachment of sugar residues (not shown) was accomplished using thiourea linkages.

A practical application of sugars as scaffolds certainly resides in polypropargylated building blocks such as the all-equatorial glucoside derivative **36** (Fig. 27)[54c] and previous discussions above. Thus, treatment with a 3-azido-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-galactofuranose (**163**) under click chemistry using CuI and DIPEA led to the fully acetal-protected intermediate which upon acid hydrolysis liberated glycocluster **164** in 61% yield. Because **164** is a strong copper chelator, notably the authors have conducted exhaustive measurement and considerable efforts to remove residual traces of copper.

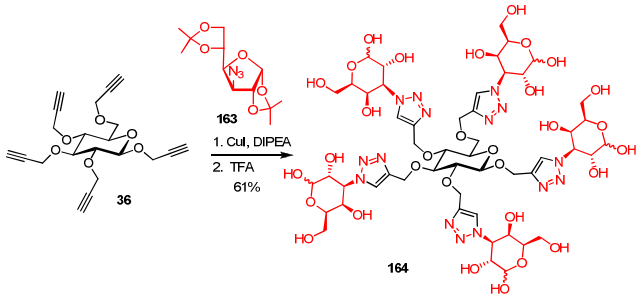


Fig. 27 CuAAC attachment of an azido furanose derivative (**163**) onto a pentapropargylated (**36**) glucoside scaffold affording 20-OHs groups at the G1 level.

In a similar approach toward achieving chiral dendrimers, glucofuranose acetal (**165**) was etherified (NaH, THF) at its C-3 position using 1,3,5-tris-bromoethylbenzene **166** to afford G1 building block **168** in 60% yield (Fig. 28).[54d] In parallel and for the purpose of a convergent strategy, alcohol **165** was also etherified with nitro dibromide **167** to give dendron **170** (60%).

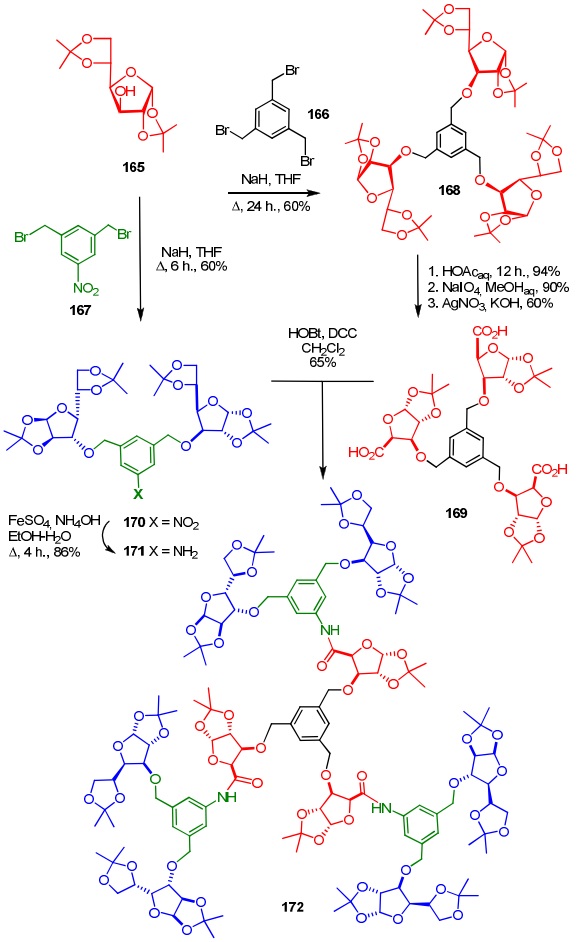


Fig. 28 Convergent synthesis of chiral dendrimers using sugar residues.

Functional group interconversion of both fragments afforded acid **169** and amine **171** ready for amide coupling under standard conditions (HOBt, DCC) which gave G3 glycodendrimer **172** in 65% yield. It is however important to mention that both dendrimers **164** and **172** possess reducing sugar functionalities that are usually not very stable under both acid and particularly under basic conditions (peeling off reactions).

An appealing approach rapidly and efficiently leading to chiral polyols has been accomplished true which sugar epoxides have been treated under either acid or base-catalyzed conditions to give hyperbranched structures with good to moderate polydispersity (Fig. 29).[54e] As an example, D-mannitol epoxide **173** was converted to polyol **174**.

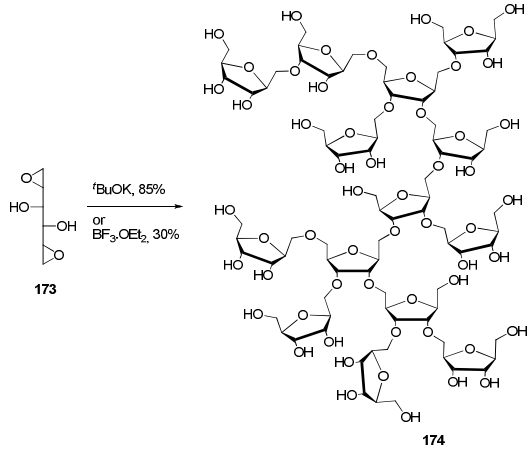


Fig. 29 Single step synthesis of hyperbranched chiral polyols using either acid or base-catalyzed ring-opening of sugar epoxide.

Using the appealing strategy based on "onion peel"[7-8] construction of dendrimers described earlier together with using sugars as multifunctional building blocks; Roy *et al*. recently described the rapid synthesis of surface-bound polyols encompassing 128-OH groups at the G3 level only.[7] Toward this goal, an A_4B sugar monomer (**175**) was synthesized from D-glucose (Fig. 30). Functional group interconversion efficiently led to orthogonal scaffold **177** which, upon treatment under basic conditions (NaOMe, MeOH) with A_4 core **178** provided dendrimer **179** harbouring 16-allyl functionalities in 89% yield. Photoinduced thiol-ene of the perallylated compound **179** with thioacetic acid gave **180** that underwent a second iterative cycle with chlroacetylated sugar **177** to give perallylated intermediate **181** containing 64-alkene groups. Final capping with thioglycerol **182** under the common radical process afforded G3 polyol **183** having 128 hydroxyl groups at the periphery.

Although perpropargylated sugars such as **36** have been previously used to construct multivalent sugars, they have not yet been fully exploited for the systematic elaboration of dendrimers of higher generations. Ongoing activities in the author's laboratory are met to reach this objective. For instance, when compound **36** was treated under standard CuAAC conditions with azide **175** followed by the photoinduced thiol-ene reaction with thioglycerol **182**, an accelerated entry into polyol **184** has been efficiently accomplished (Fig. 31). The interesting feature of such compounds, and by virtue of the inherent chirality of the sugar residues, is that the resulting five triazole moieties were all found in chemically different environment, as seen from the five distinct

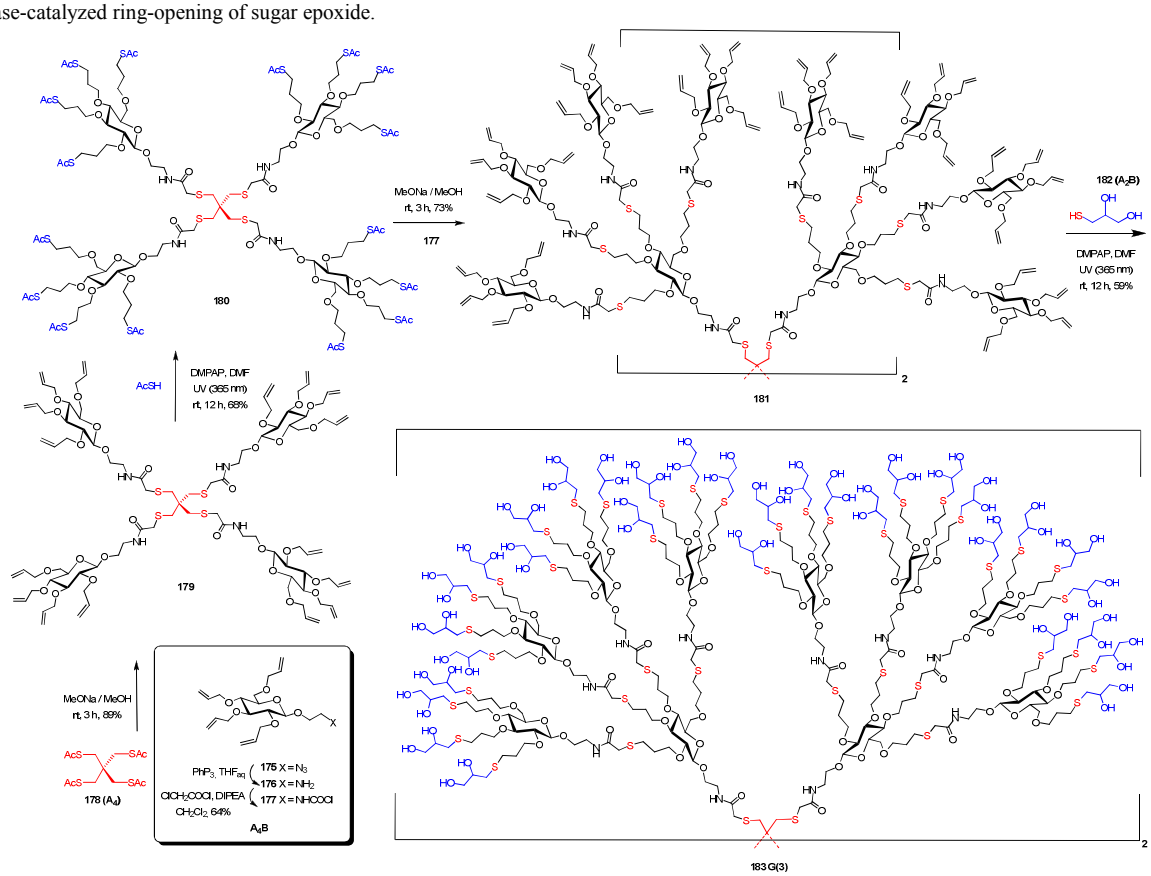


Fig. 30 Novel polyol dendrimer having 128-exposed OH groups reached at the G3 level.

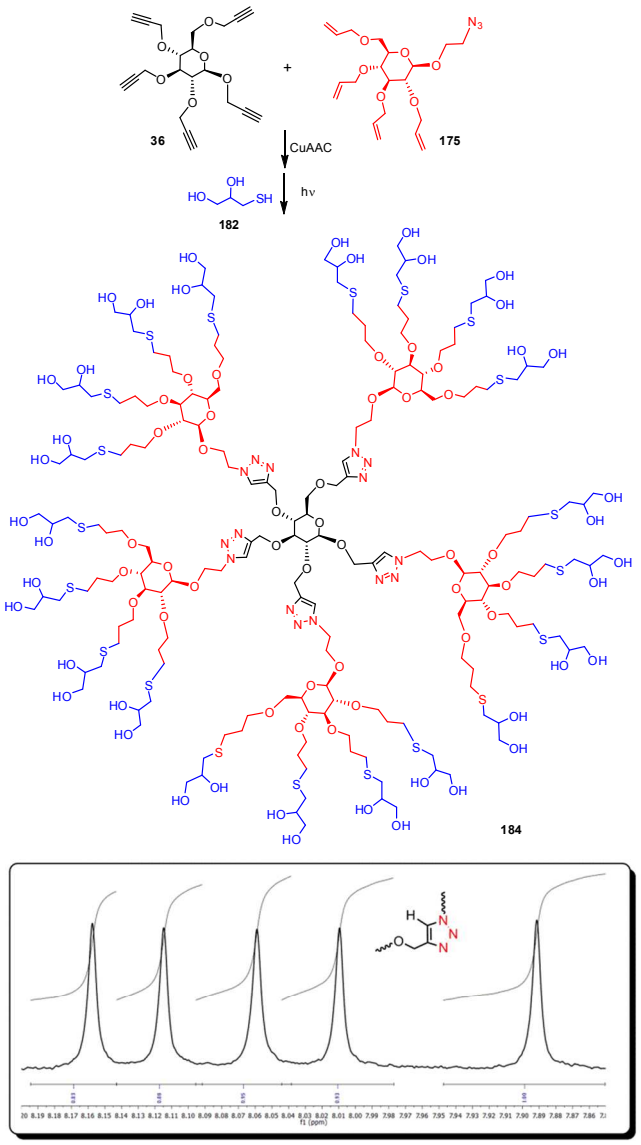


Fig. 31 Combining two glyconanosynthons as both a core and as a repeating scaffold and further capping with a polyol can afford a compact and densily functionalized dendrimer at low generation. By virtue of its chirality, each triazole sub-structure was shown to be distinct by NMR spectroscopy.

signals of the triazole protons in the ^{1}H-NMR spectrum of **184** (Fig. 31) (Roy, unpublished data). Note again that, albeit just a G2 dendrimer, compound **184** bears 40-OH groups that can be further derivatized. Work is in progress to fully exploit this novel approach.

5. Summary and outlook

Carbohydrates clearly represent underexploited building blocks toward the rapid syntheses of chiral, functionally dense, and versatile dendrimers. Their occurrence in various natural states, conformation, and anomeric configurations confer their high potential. The fact that each family member has its own peculiar stereochemistry allows for the facile manipulations of its multiple hydroxyl groups. The necessary chemistry involved to further expand their oligomeric structures into complex oligosaccharides is also well developed and handy. Hence, glyconanosynthons offer several advantages not yet accessible from other, more conventional building blocks and scaffolds.

This review has highlighted progresses encountered for their involvement into complex nanomaterial architectures. Of particular interest was the fact that well known chemistry, already in use toward most common dendrimers such as PAMAMs, can also be accomplished with sugars, thus providing additional features not yet fully exploited. When combined with the introduction of an "onion peel"[7-8] synthetic strategy for the layer-by-layer changes in repeating units, glyconanosynthons constitute helpful molecular structural design worth further exploring.

Although most glycodendrimers described to date were intended to expose the biologically relevant sugar head groups to their cognate protein receptors such as bacterial and mammalian lectins, it remains that the very polyhydroxylated nature of the surface groups could still be further transformed into useful chemical entities. The fact that they can be built using both convergent and divergent approaches should also facilitate their usage by the dendrimer community.

In addition, since a few specific hydroxyl groups can be left intact during the build-up processes which can be deprotected only at the final stage, offers clear advantages for biological applications or introduction of probes of different nature. This aspect has similarly culminated in a larger exploitation of cyclodextrins that represent a valuable family of three members (α-, β-, and γ-CDs) having respectively, 18-, 21- or 24- hydroxyl groups, the primary position of which being more readily accessible to derivatization. Their cone shape and small hydrophobic cavities make them resemble calix[n]arenes and cucurbit[n]urils.

Asymmetric catalysis represents an important topic in modern organic chemistry and the intrinsic stereochemistry imparted by sugar derivatives may additionally offer several interesting opportunities. In fact, although single carbohydrate derivatives have been successfully used as chiral ligands in asymmetric catalysis,[55a] particularly as phosphine ligands, their incorporation within dendritic architectures is clearly underexploited. Actually, just a few examples has been described,[55b] but without any demonstrated asymmetry.

In conclusion, sugars have been clearly demonstrated as valuable building blocks for complex dendrimer syntheses. The chemistry involved in their manipulations is common to most synthetic organic chemists which should widen their manifestation in the field of dendrimer synthesis. It is the hope that this review is encouraging.

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Key learning points

(1) Dendrimers are more rapidly constructed with multivalent scaffolds as both building blocks and repeating units.

(2) Carbohydrates constitute such multivalent building blocks but with added chirality.

(3) Most of the chemistry used to synthesized "classical dendrimers" has been applied to carbohydrate-based dendrimers.

(4) Not all functionalities on the sugars need to be used in the dendrimer buil-up.

(5) Naturally occurring carbohydrate oligomers and cyclodextrins represent versatile higly multivalent scaffolds.

