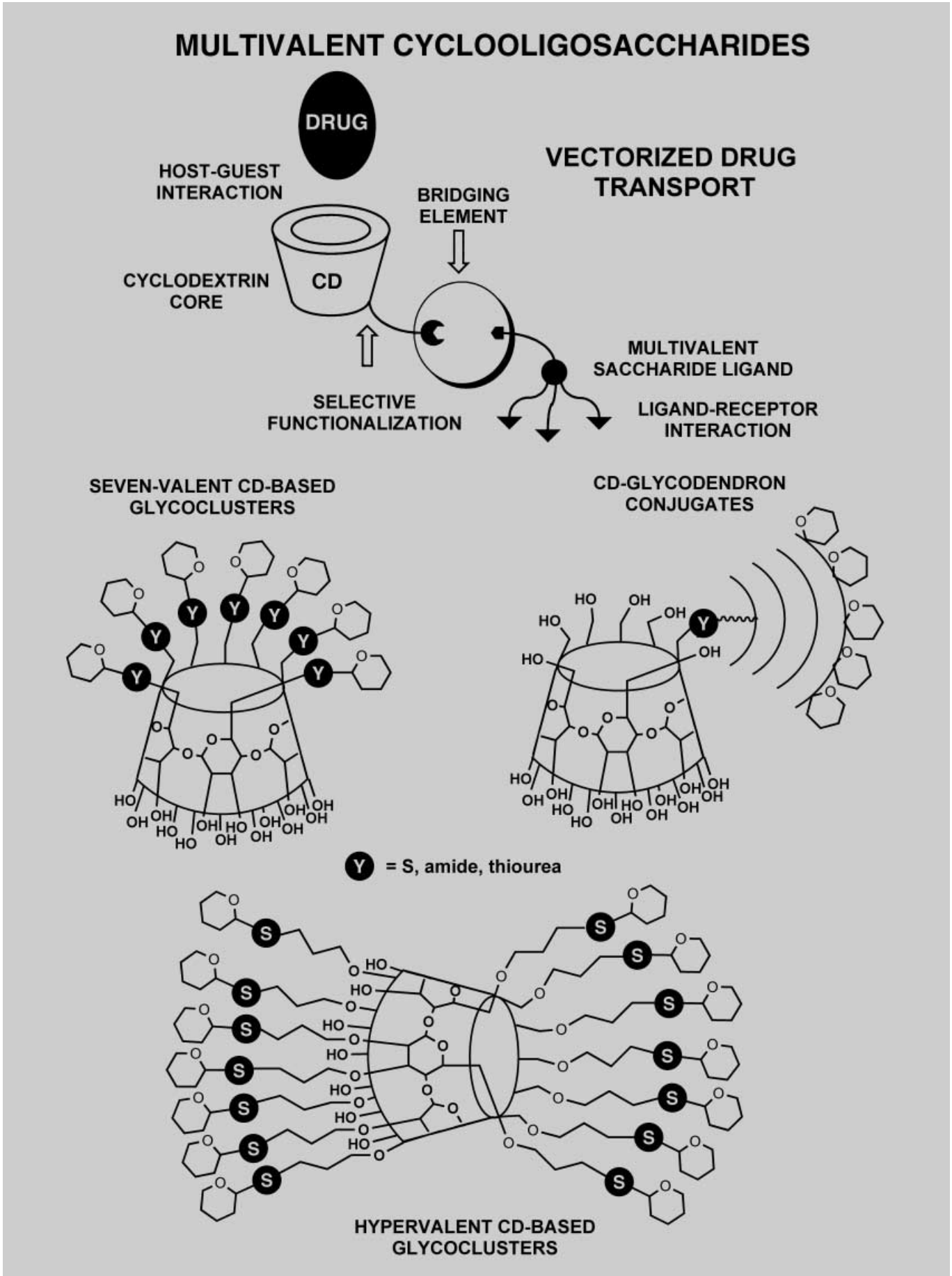

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Multivalent Cyclooligosaccharides: Versatile Carbohydrate Clusters with Dual Role as Molecular Receptors and Lectin Ligands

Carmen Ortiz Mellet,[b] Jacques Defaye,[c] and José M. García Fernández*[a]

Dedicated to Professor Derek Horton on the occasion of his 70th birthday

Abstract: Results obtained over the past decade towards the preparation of multitopic carbohydrate architectures combining the molecular inclusion capabilities of cyclomaltooligosaccharide receptors (cyclodextrins, CDs) and the recognition properties of saccharide ligands towards biological receptors are discussed. The potential of these new sugar-based "intelligent" transporters for site specific delivery of therapeutics is outlined.

Keywords: cyclodextrins · drug delivery · glycoclusters · glycodendrimers · multivalency · receptors

Introduction

Protein–carbohydrate interactions play an essential role in biological communication. Numerous normal and pathological processes including fertilization, infection, the inflammatory response, cell adhesion, and metastatic spreading, are mediated by such recognition events. Although the intrinsic binding ability of monovalent protein–carbohydrate interactions is low, presentation of carbohydrates epitopes in multivalent arrays results usually in highly specific and effective ligands.[1] This specificity suggests a potential utility of synthetic multiantennated saccharide derivatives as carriers in drug or probe delivery to target sites and as inhibitors of undesired carbohydrate–receptor associations.[2] Multivalent carbohydrate scaffolds built on conformationally defined rigid macrocycles, such as cyclopeptides,[3] azacrown ethers,[4] macrocyclic polyesters[5] or calixarenes,[6] have proven already particularly useful in the design of both efficient ligands for pharmacologically relevant receptor proteins (lectins) and valuable tools for exploring the mechanisms by which multivalent saccharide ligands interact. Cyclodextrins (cyclomaltooligosaccharides, CDs)[7] offer unique features toward these goals since they are essentially biocompatible, non-immunogenic carbohydrates of natural origin with high symmetry, and a variety of selectively functionalized derivatives are accessible from the commercially available cyclic hexa-, hepta- and octamer (α-, β- and γ-CD, respectively). Moreover, their truncated cone-shaped hydrophobic cavity can include other organic molecules of appropriate size that, eventually, can be solubilized and stabilized in water. Multivalent cyclodextrin conjugates may, therefore, form ternary lectin–carbohydrate cluster–guest complexes through simultaneous host–guest complexation at the CD cavity and carbohydrate–protein interaction at the carbohydrate cluster moiety (Figure 1).

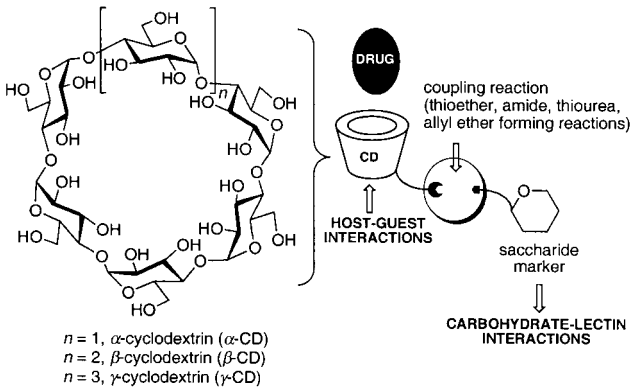

Figure 1. Full-carbohydrate, site-specific drug delivery systems based on the cyclodextrin core.

In this article, we will summarize the progress that has been made towards the design of saccharide-bearing cyclomaltooligosaccharides for encapsulation, cell recognition and molecular delivery. For reasons of applicability, most of these results focus on cyclomaltoheptaose (β-CD), the most interesting CD representative from the commercial point of view.

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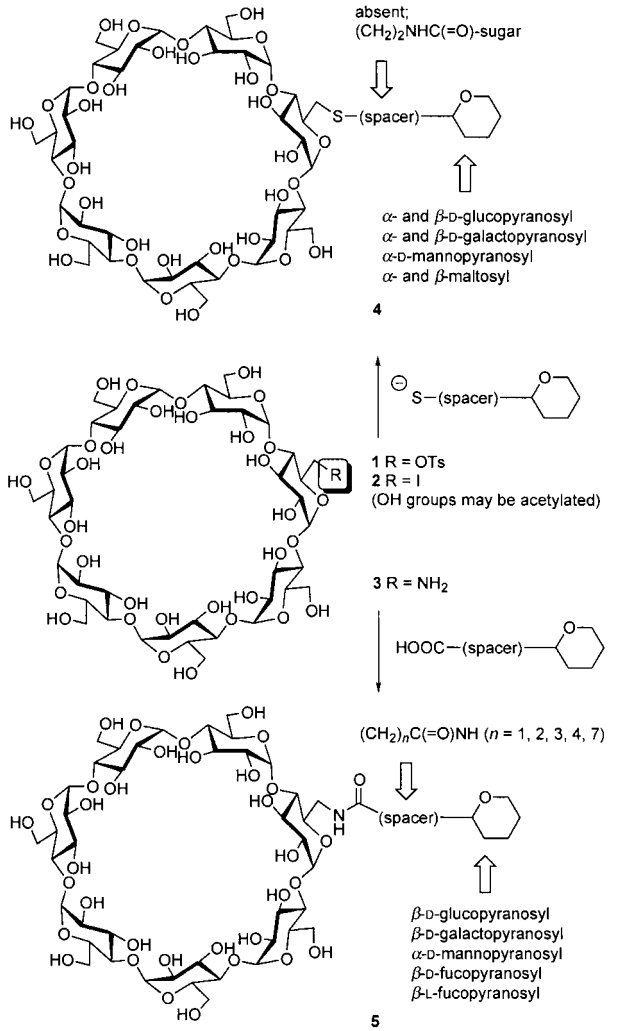
Emphasis is placed on the versatility of the synthetic approaches and the lectin binding and drug inclusion capabilities of the resulting conjugates.

Discussion

Monovalent cyclodextrin neoglycoconjugates: The key precursor for the preparation of monobranched β-CD neoglycoconjugates is 6^I-deoxy-6^I-*O*-*para*-tolylsulfonylcyclomaltoheptaose (**1**), for which we have recently reported an improved one-step synthesis from β-CD.[8] Its reactivity was first exploited by Defaye's group in the preparation of 6^I-*S*-glycosyl-6^I-thiocyclomaltoheptaose (**4**) by use of the sodium salt of 1-thio-α- and β-D-glucopyranose as the nucleophile[9] and was further extended to the synthesis of the analogous monovalent α- and β-thiomaltosyl β-CD conjugates[10] (Scheme 1).

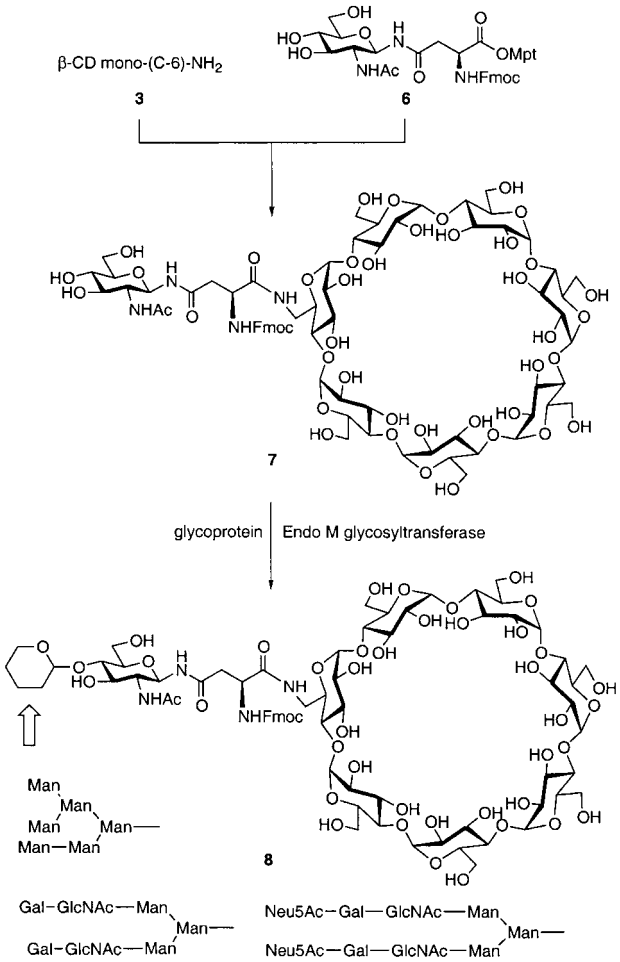


Scheme 1. General synthetic scheme for the preparation of monovalent β-CD neoglycoconjugates through thioether[9–12] and amide bond-forming reactions.[13, 14]

Driguez et al. have used a similar approach that employs the peracetylated mono-(C-6)-iodo β-CD derivative **2** as a precursor, which was obtained from the monotosylate **1**.[11] The peracetylated 1-thioglycose (β-D-glucopyranose, β-D-galactopyranose, α-D-mannopyranose) is then used as the nucleophile. More recently, Hattori et al.[12] have reported the incorporation of a spacer arm between the CD core and the saccharide marker by: i) reacting lactonolactone and cysteamine; and ii) introducing the resulting galactosyl-gluconoamide ethanethiol fragment at the 6^I position of β-CD following the above general synthetic pathway (Scheme 1).

A second general approach for the preparation of monovalent β-CD-neoglycoconjugates consists in the amidation reaction between 6^I-amino-6^I-deoxycyclomaltoheptaose (**3**), readily available from **1** via the corresponding azide, and saccharide markers bearing a carboxylic acid functionality to give adducts **5**. This strategy has been widely developed by the groups of Parrot-Lopez[13] and Hattori[14] (Scheme 1).

The above-mentioned groups have reported an interesting extension of the amide-bridging approach that combines: i) amidation of the mono-(C-6) amine **3** with a carboxylic acid armed *N*-acetylglucosamine derivative (e.g. **6**); and ii) enzymatic glycosyl transfer to the glucosamine moiety in the β-CD-conjugate.[15, 16] The preparation of mono-branched β-CD derivatives that incorporate complex natural oligosaccharides of the high-mannose, asialo- and sialo-complex type (**8**), as depicted in Scheme 2, illustrates the potential of the chemoenzymatic strategy. Oligosaccharide transfer from ovalbumin or human transferring glycoproteins to acceptor **7** was



Scheme 2. Chemo-enzymatic synthesis of monovalent β-CD conjugates.[16] Fmoc: Fluorenyloxycarbonyl; Mpt: dimethylphosphinothioyl.

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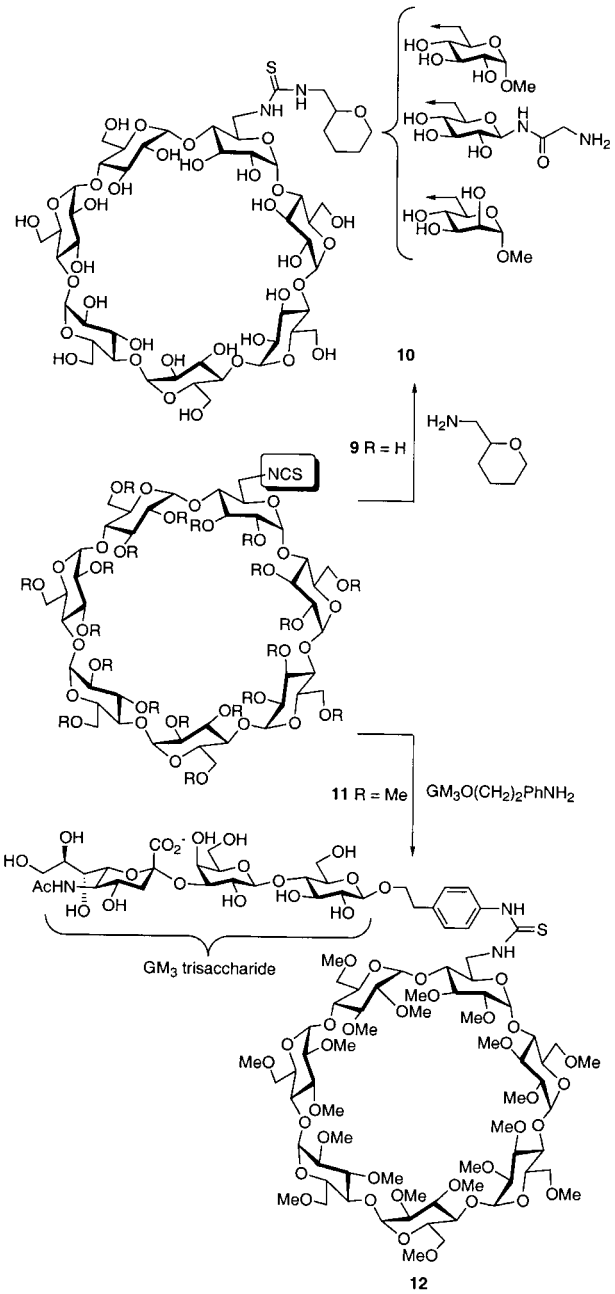
catalyzed by the endo-β-*N*-acetylglucosaminidase of *Mucor hiemalis* (Endo M).

As an alternative to the amidation reaction, we reported in 1996[17] the preparation of thiourea-bridged β-CD-neoglycoconjugates **10** by reaction of 6^I-deoxy-6^I-isothiocyanatocyclomaltoheptaose (**9**), obtained by isothiocyanation of **3** with thiophosgene, with aminodeoxy sugars. Recently, Haque and Diakur[18] have used the corresponding per-*O*-methyl derivative **11** in the conjugation with the ganglioside GM_3 trisaccharide, a tumor associated antigen (**12**) (Scheme 3). The reverse coupling of mono-(C-6)-amino β-CD **3** with per-O-protected glycosyl isothiocyanates proved more convenient for the synthesis of (1 →6)-thiourea-linked conjugates.[19] The methodology is compatible with the presence both of alkyl and aryl spacer arms, giving access to a virtually unlimited number of structures. Moreover, the thiourea-bridged adducts exhibited a dramatic increase in water solubility (up to 40-fold) as compared with the native β-CD, even when incorporating hydrophobic substituents, and a significant decrease in the hemolytic character (up to eight-fold), while keeping the inclusion capabilities of the cyclodextrin core. The scope of the thiourea-bridging strategy, actually one of the most conventional methodologies in neoglycoconjugate preparation,[20] for the design and synthesis of multivalent cyclooligosaccharides will be further illustrated in the following sections.



Scheme 3. Synthesis of monovalent β-CD conjugates through the thiourea-bridging strategy.[17–19]

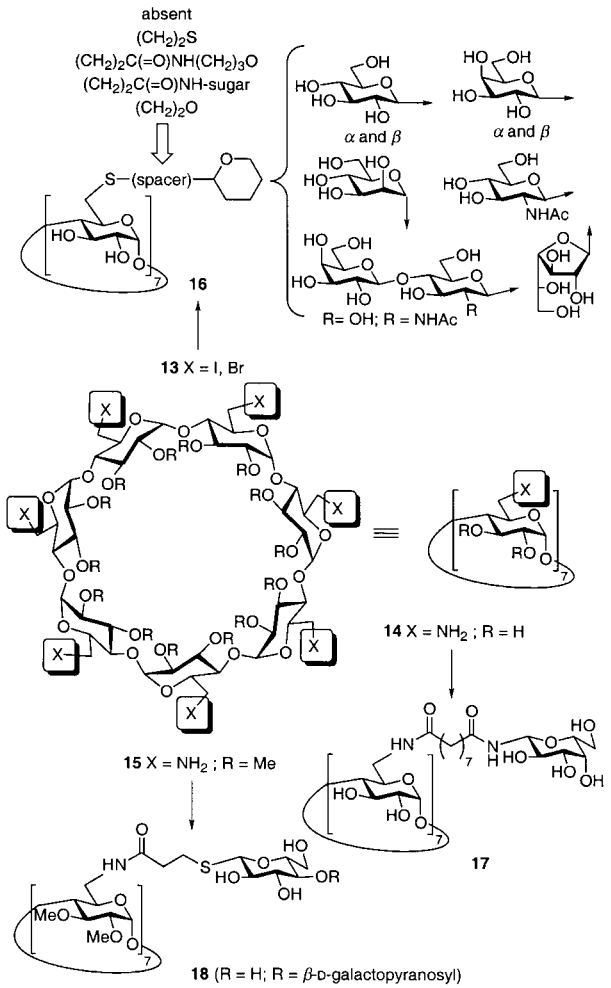
Multivalent polysubstituted cyclodextrin neoglycoconjugates: The need for a multivalent presentation of the saccharide markers to attain biologically relevant carbohydrate–lectin binding affinities has stimulated the preparation of well-defined β-CD polyconjugates. For practical reasons, (C-6)-heptabranched derivatives have been privileged. Highly efficient coupling reactions are a prerequisite for such prospect, since partial substitution would lead to a mixture of undersubstituted regioisomers from which purification of the desired per-(C-6) substituted compound becomes a difficult task.

Basically, the preparation of per-(C-6) substituted β-CD derivatives bearing carbohydrate appendages relies on the same synthetic methodologies commented above for the synthesis of monovalent conjugates, that is, thiol displacement of a good leaving group (I or Br; **13**), amidation of the per-(C-6)-amino β-CD (**14**), or reaction of the latter with sugar isothiocyanates. The development of very efficient procedures for the preparation of the key per-(C-6)-halo β-CD precursors has been, not surprisingly, a turning point in the chemistry of these derivatives.[21]

The groups of Defaye[10] and Driguez[11b, 22] have been instrumental in the development of per-(C-6)-thioglycosylated β-CD neoglycoconjugates (**16**). The thiolates of the corresponding 1-thioglycopyranoses were first used as the nucleophiles. Alternatively, a variety of spacer arms bearing a terminal thiolate functionality were introduced[12, 22, 23] (Scheme 4).

Parrot-Lopez's[13c] and Stoddart's groups[24] have exploited the amidation approach for the synthesis of heptavalent conjugates (**17**, **18**) using carboxylic acid derivatives of D-galactose, D-glucose or lactose and the heptaamine **14** or its per-(2,3-di-*O*-methyl) derivative **15** as the coupling precursors (Scheme 4). The reverse strategy using the heptacarboxylate resulting from oxidation of the primary hydroxyl groups of β-CD in reaction with saccharide-derived amines has also been attempted. Yet, a mixture of undersubstituted compounds was obtained from which no pure compound could be isolated.[25]

Recently, the groups of Santoyo-González, Vargas-Berenguel and Roy[26] have reported some modifications of this general scheme aimed at diversifying the nature of the linkers while keeping the coupling efficiency, including: i) the use of sugar derived thiouronium salts as nucleophilic agents instead of the corresponding thiolates; ii) the preparation of the heptakis(6-chloroacetamido-6-deoxy)cyclomaltoheptaose **19** (Figure 2) and its use as precursor in coupling reactions with



Scheme 4. General synthetic scheme for the preparation of heptavalent β-CD neoglycoconjugates through thioether[10, 11b, 12, 22, 23] and amide bond-forming reactions.[13c, 24]

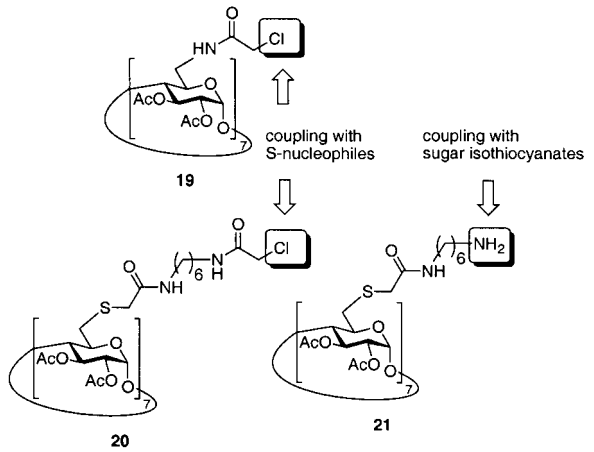
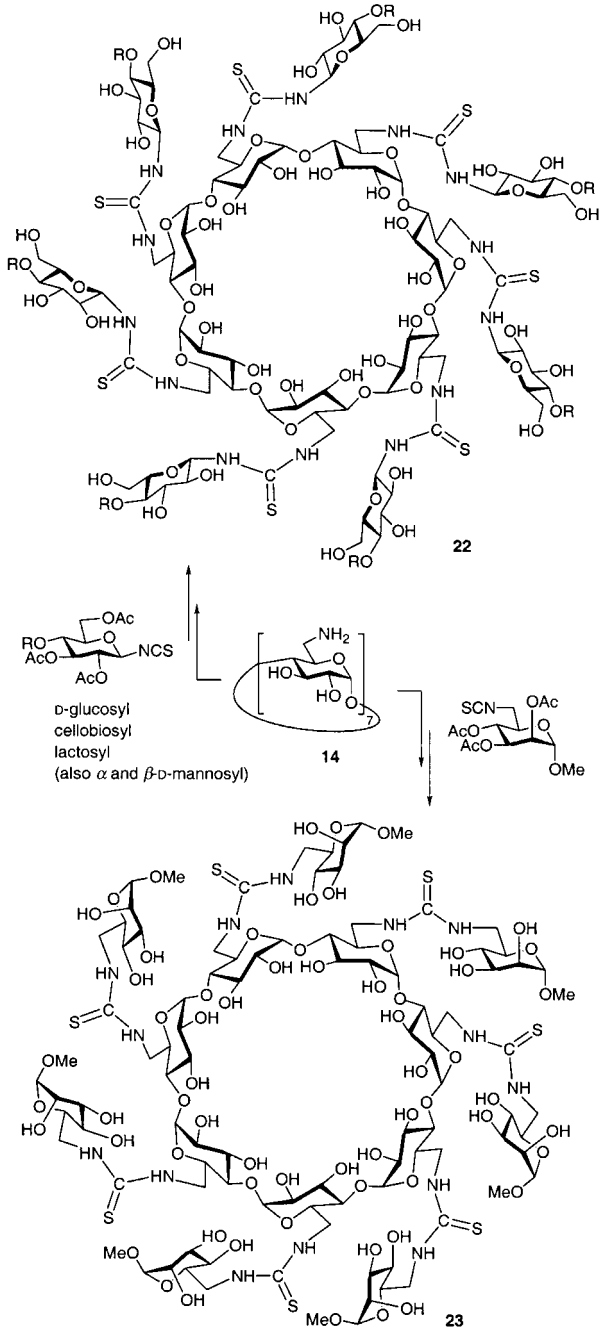


Figure 2. Spacer-containing β-CD derivatives for the synthesis of heptavalent glycoclusters.[26]

the aforementioned nucleophiles; and iii) the synthesis of the per-(C-6)-thioether β-CD derivatives **20** and **21**, bearing a terminal chloro or amino group that can be used in coupling reactions with sugar thiols or isothiocyanates, respectively. All approaches require, however, the protection of the hydroxyl groups both in the β-CD precursor and in the functionalized saccharide marker.

In our laboratories, we have focused our approach on the thiourea-bridging strategy for the preparation of heptavalent β-CD glycoclusters.[19] The reaction of the per-(C-6)-amino β-CD **14** (Scheme 5) with mono- as well as disaccharide glycosyl isothiocyanates proceeded smoothly and with total chemoselectivity in water/acetone at pH 8 ($NaHCO_3$) to afford the target heptaconjugates (e.g. **22** and **23**) in high yields. Although some deacetylation of the adduct may occur, purification from the unreacted precursors was readily achieved at this stage by conventional column chromatog-



Scheme 5. General synthetic scheme for the preparation of heptavalent β-CD neoglycoconjugates through the thiourea-bridging strategy.[19]

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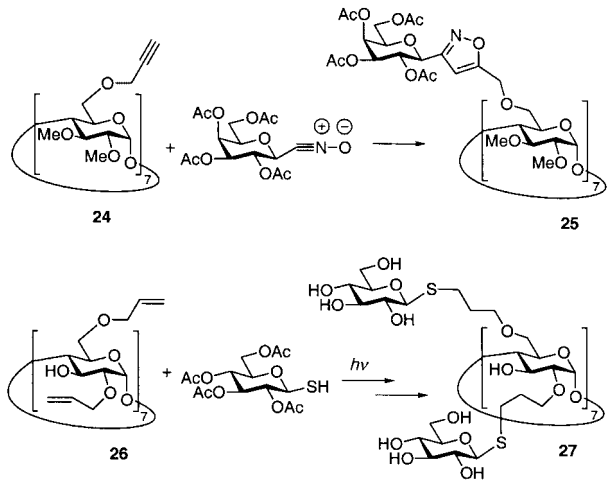
raphy, an important aspect since the purification step is frequently quite troublesome with CDs.

Two examples of β-CD glycoclusters that differ from the aforementioned (C-6)-S or -N-substituted β-CD conjugates by exploiting the reactivity of unsaturated β-CD ether derivatives have been recently reported. Santoyo-González et al.[27] described the preparation of an heptavalent neoglycoconjugate having heterocyclic linkers (**25**) by the 1,3-dipolar cycloaddition of 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl nitrile oxide and the per-(2,3-di-*O*-methyl-6-*O*-propargyl)-β-CD **24** (Scheme 6). Stoddart and Fulton[28] prepared the per-(6-*O*-allyl-2,3-di-*O*-methyl-)-β-CD derivative and carried out the photochemical addition of 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranose to the double bonds. Interestingly, this strategy was also extended to β-CD derivatives per-O-allylated at O-2 and per-(di-O-allylated) at O-2 and O-6 positions (**26**), resulting in the first examples of an heptavalent β-CD neoglycoconjugate branched at the secondary face and of a 14-valent (**27**) β-CD conjugate (Scheme 6).



Scheme 6. Synthesis of multivalent β-CD neoglycoconjugates from unsaturated ether derivatives.[27, 28]

Lectin-binding and inclusion ability of monovalent versus multivalent polysubstituted cyclodextrin neoglycoconjugates: β-CD neoglycoconjugates bearing biorecognizable saccharide markers have been shown to bind to complementary lectins in vitro. Thus, D-galactopyranosyl ligands bind to the cell wall lectin of *Kluyveromyces bulgaricus* (KbCWL),[13, 15, 29] *Arachis hypogea* (peanut),[26b] *Ricinus communis*[11b] and *Griffonia simplicifolia* I (GSI) lectins;[25] D-glucopyranosyl ligands to *Pisum sativum* (pea) lectin;[26a] D-mannopyranosyl ligands to *Pisum sativum*[60] and *Concanavalia ensiformis* (concanavalin A, Con A) lectins;[14, 16, 25, 26a] *N*-acetylglucosamine and *N*-acetyllactosamine ligands to *Triticum vulgaris* (WGA, wheat germ agglutinin)[23a, 23b, 25, 26a] and *Erythrina corallodendron* (EcorL) lectins.[23b, 25] Multivalent polysubstituted conjugates are generally bound with much higher association constants. The increment in binding efficiency depends on the length and the nature of the linker, being usually higher for neoglycoconjugates having long spacers between the external saccharide markers and the β-CD core. It must be noticed, however, that lectin binding results are also highly dependent on the evaluation method, which hampers a reliable comparison of literature data.

In order to assess the structural requirements for efficient binding of CD-centered glycoclusters to specific lectins, we have undertaken a systematic evaluation of a number of thiourea-bridged mannose-β-CD conjugates using the enzyme-linked lectin assay (ELLA) and Con A as the model lectin. Both monovalent and heptavalent adducts have been considered (e.g. **28**–**30**) in comparison with model compounds lacking the CD moiety.[19b] Our interest was to pinpoint the possible effect of the CD moiety and the thiourea linkers on the carbohydrate–protein recognition process. Several interesting conclusions have been drawn: i) the thiourea linker slightly decreases the binding efficiency in comparison with the conventional O-glycosidic linkage and totally abolishes the anomeric specificity (in contrast with the known 40-fold higher affinity for the α-anomer in the *O*-mannoside series); ii) the β-CD aglycon in monovalent conjugates interacts with the protein stabilizing the complex by about -0.35 kcal; iii) surprisingly, heptasubstitution at the primary hydroxyls rim with mannopyranosylthioureido ligands totally abolishes Con A binding, probably due to unfavorable steric interactions. This is a rather rare example of a virtually complete inhibition of binding upon multiplication of the putative recognition epitope for a given lectin. It may be interpreted as an indication that the mechanism of transmission of biological information by expression of cell surface carbohydrates might probably be more complex than the off/on (low density–high density) model previously considered. The expected higher-than-seven-fold increase in binding efficiency was observed after intercalation of a C_5 spacer (Figure 3).

Only a few data on the inclusion ability of β-CD neoglycoconjugates are available in the literature. Defaye and coworkers[10] have shown that the stability of inclusion complexes of monovalent (C-6)-S-linked β-CD neoglycoconjugates is strongly dependent both on the inclusion dynamic and on the possibility of complex stabilization. Complexes involving guest molecules entering the cavity through the narrower rim may experience some decrease in the association constant as compared to the corresponding native β-CD due to the steric hindrance imposed by the substituent. No significant difference was observed, however, for molecules entering the cavity through the wider secondary hydroxyl groups rim. Complex stabilization through hydrogen bonding by unsubstituted primary hydroxyl groups may then be operative. On the other hand, per-(C-6)-substitution may drastically affect the formation and stability of inclusion complexes. Thus, for guest molecules entering the cavity through the primary hydroxyl groups face, the association constant will be expected to drastically decrease. Interestingly, the opposite effect has been observed for the complexation of the anticancer drug doxorubicin with a heptalactosyl β-CD conjugate of type **16** having flexible spacer arms, which has been ascribed to the induced fit of the heptavalent glycocluster around the guest molecule.[12]

Beyond polysubstitution—CD-scaffolded glycodendrons: From the above data, it can be concluded that heptasubsti-

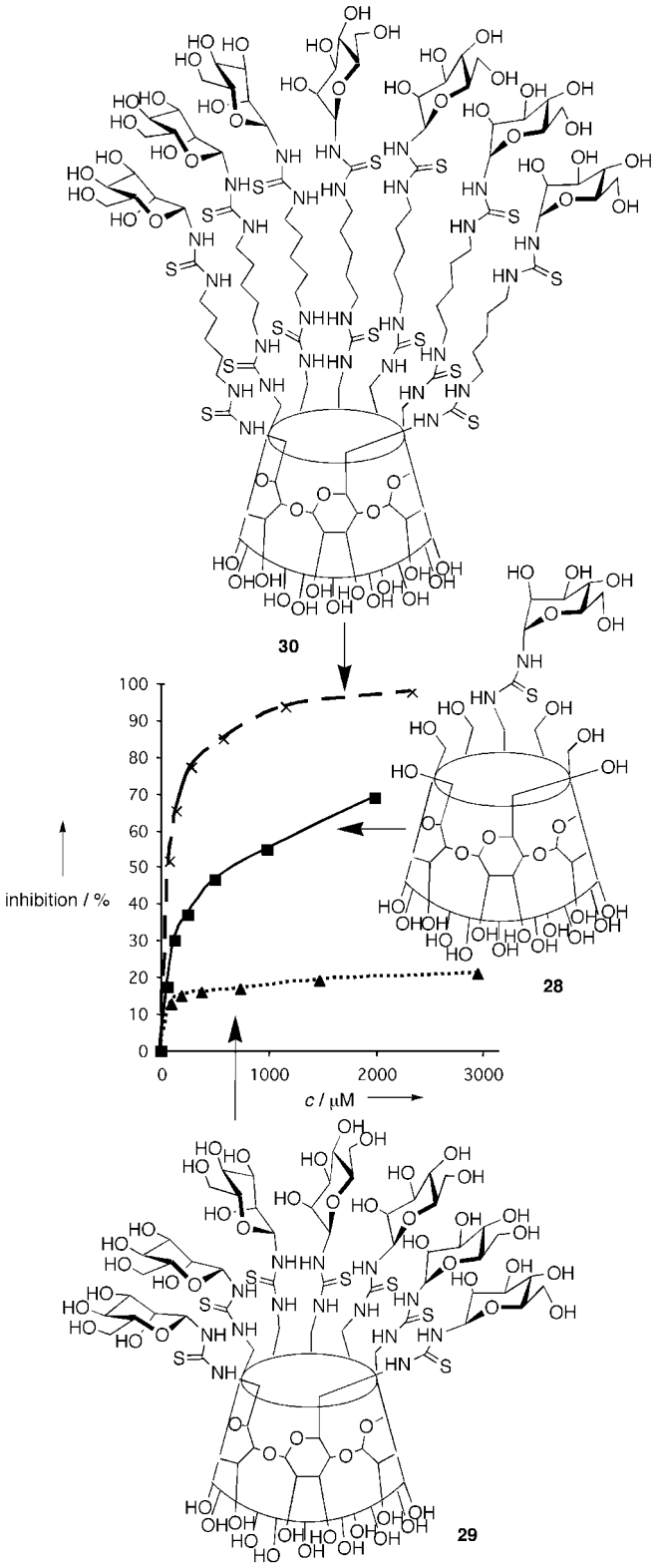
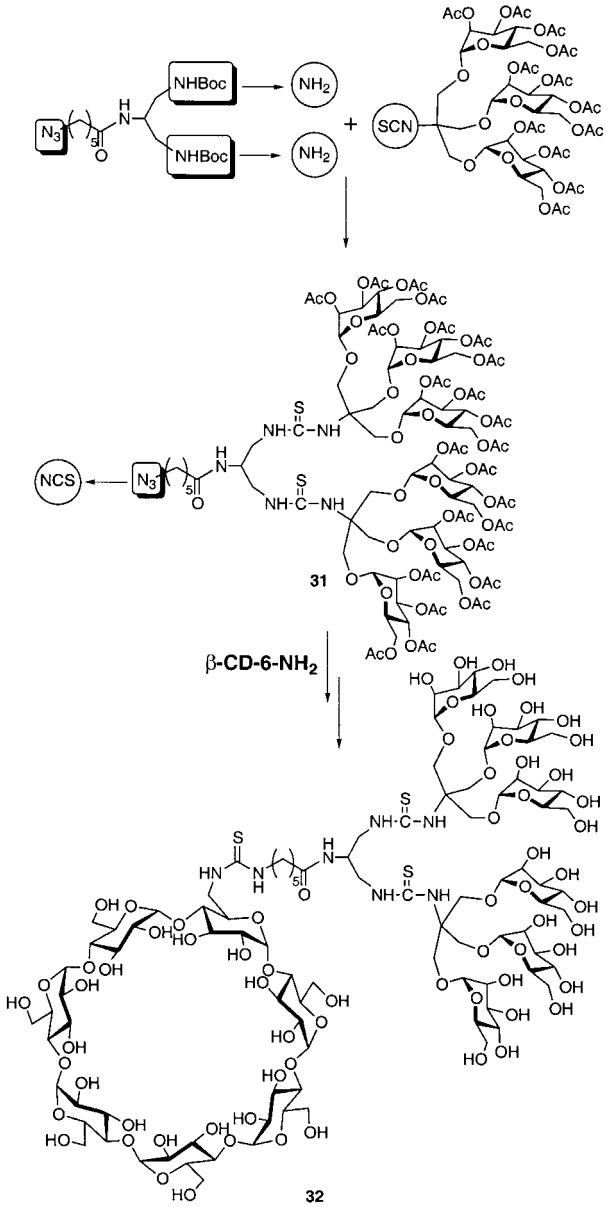


Figure 3. Comparative ELLA data for mannosylated β-CDs towards concanavalin A (Con A). The mannosyl residues have the α-anomeric configuration in the monovalent derivative **28** and a random 1:1 α:β distribution in the heptavalent counterparts **29** and **30**.[19b]

tution at the primary hydroxyl groups rim of β-CD with incorporation of saccharides markers has beneficial effects from the biological standpoint as compared with monovalent conjugates, provided that long enough spacer arms are used to warrant the accessibility of the glycocluster structure to carbohydrate–lectin recognition events. Yet, heptasubstitution may also impair inclusion and stabilization of potential guests.

Ideal CD carriers for use in drug targeting should combine both the advantages of monosubstitution regarding efficient inclusion capabilities and a multivalent display of the required saccharide epitope to comply with the need of high biological receptor binding efficiency. Towards this goal, we have recently reported the preparation of β-CD-scaffolded glycodendrons (e.g. **32**) as a new class of multivalent monosubstituted β-CD neoglycoconjugates.[8b] A modular strategy for the preparation of isothiocyanate-armed mannosyl-coated dendritic wedges (e.g. **31**) was devised and these structures were attached to the β-CD monoamine **3** in a final step (Scheme 7).



Scheme 7. Convergent synthesis of glycodendron-bearing architectures based on the β-CD core.[8b]

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Evaluation of the Con A binding ability by ELLA for a series of mono- to hexavalent derivatives indicated a dramatic increase in binding efficiency for the higher-valent conjugates (up to 16-fold in a molar basis for hexavalent as compared to monovalent). Moreover, solubilization experiments using the anticancer drug Taxotère as model guest indicated solubility values similar to those previously encountered for monovalent monobranched β-CD conjugates, about 20% higher as compared with per-(C-6) substituted analogues.

Concluding Remarks and Future Directions

From the present body of information, it appears that combination of the ability to form host–guest inclusion complexes characteristic of CDs and the biorecognition capabilities of oligosaccharide appendages makes CD neoglycoconjugates promising candidates both as site-specific drug delivery systems and valuable tools to expand the current notions of carbohydrate–protein interactions. Efficient and high yielding synthetic methodologies involving a limited number of protection/deprotection sequences have been settled, opening the way to unlimited possibilities of biorecognition structures which could result from the combination of chemical and enzymatic methods as well. Forthcoming architectures include polyconjugates from selectively functionalized CDs (e.g. **33**),[30] hypervalent CDs (**34**),[31] for which new supramolecular properties could result from the presence of the cavity-like dendritic wedge, and multivalent dimeric CD conjugates (**35**),[32] designed for the efficient transport of molecules forming 2:1 host–guest sandwich-type complexes (Figure 4). The ability of multivalent CD-conjugates to interact simultaneously with both a specific lectin and a drug has already been proven by surface plasmon resonance (SPR).[12, 33] The field seems now mature for the development of specific applications in the biological and biomedical areas.

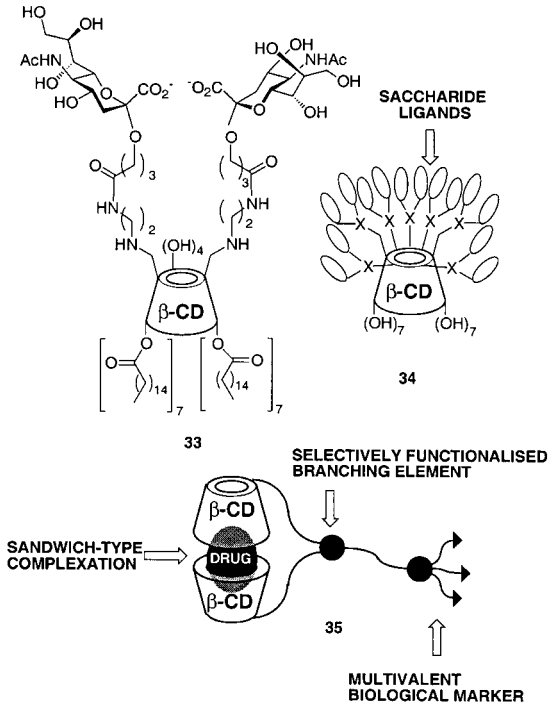

Figure 4. New multivalent cyclodextrin architectures: defined diantennated conjugates (e.g. **33**),[30] hyperbranched CDs (**34**)[31] and dimeric multivalent conjugates (**35**).[32]

Acknowledgements

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