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CARBOHYDRATE-BASED DESIGNER MOLECULES

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Carbohydrates, one of the basic building blocks in nature's arsenal, is relatively less explored for therapeutic applications than others like amino acids and nucleotides. However, the structural and functional diversities of carbohydrate molecules and their myriad possible concoctions provide unlimited challenges and opportunities to chemists. With the advent of new techniques, like combinatorial chemistry and high throughput screening processes, chemists are now in a position to reap the fullest benefits of these multifaceted building blocks to create diversities emulating nature's principles. Concerted efforts of chemists worldwide in this direction will hopefully provide crucial leads in discovering new drugs and materials.

Key Words: Carbohydrates; Peptidomimetics; Sugar amino acids; H-bonding; Conformation; NMR

Introduction

Carbohydrates and amino acids constitute two important classes of building blocks used by nature to build its vast repertoire of biomolecules. Carbohydrates present in nucleotides, glycopeptides and glycolipids play very important roles in various biological processes, especially in cell-cell recognition processes.[1] However, unlike peptides and oligonucleotides, solid-phase synthesis of oligosaccharides have not yet achieved enough efficiency for generating oligosaccharide-based libraries due to their structural diversities arising out of variations in their sequences, position and configuration of linkages and heterocyclic ring sizes.[2] If efficiently exploited these diversities can lead to libraries of astronomically large number of carbohydrate-based structures since carbohydrates carry much more information per unit mass than do either nucleotides or amino acids. Carbohydrates also play very important role in cell-cell recognition processes. Many pathogens use carbohydrate-binding proteins to attach themselves to cell surfaces and initiate disease. Oligosaccharides and sugar molecules may have potential therapeutic values against many of these diseases.[3] Combinatorial libraries of novel carbohydrate-based molecules may find useful applications in new drug discoveries in the coming years.[4] In the last 10-15 years, large number of publications appeared from various groups on a variety of carbohydrate-based molecules.[5] In this article, we describe some recent developments in the wide-ranging applications of such carbohydrate-based building blocks in designing new molecular entities.

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Peptidomimetic Studies Based on Sugar Amino Acids and Related Building Blocks

In order to improve the therapeutic efficacy of peptides, it is important to deliver them efficiently to the target site.[6] The transport of peptides across the cell membranes through hydrophobic barriers assumes to be very important.[7] Attachment of fatty acid moieties to the *C*- or *N*-termini of peptides will increase their membrane permeability.[8] Towards this goal, novel *O*-acylated glucose-derived furanoid sugar amino acids[9] **1-3** have been developed as peptide building blocks.[10] To find out their effects on peptide conformation di-*O*-myristoylated building block **3** was incorporated into Leu-enkephalin, replacing the Gly-Gly portion, resulting in the Leu-enkephalin analog **4**.

Extensive NMR studies, in combination of constrained molecular dynamics (MD) simulation studies revealed a well defined β-turn structure of **4** in DMSO-d_6 with an intramolecular 10-membered hydrogen bond between PheNH → Tyr^5C=O (Fig.1). These results are in contrast to the free-hydroxyl-containing Leu-enkephalin analog **5**, which is characterized by an unusual pseudo β-turn with a 9-membered hydrogen bond between LeuNH → sugarC3-OH in DMSO-d_6.[11] These results clearly show that protection/deprotection of

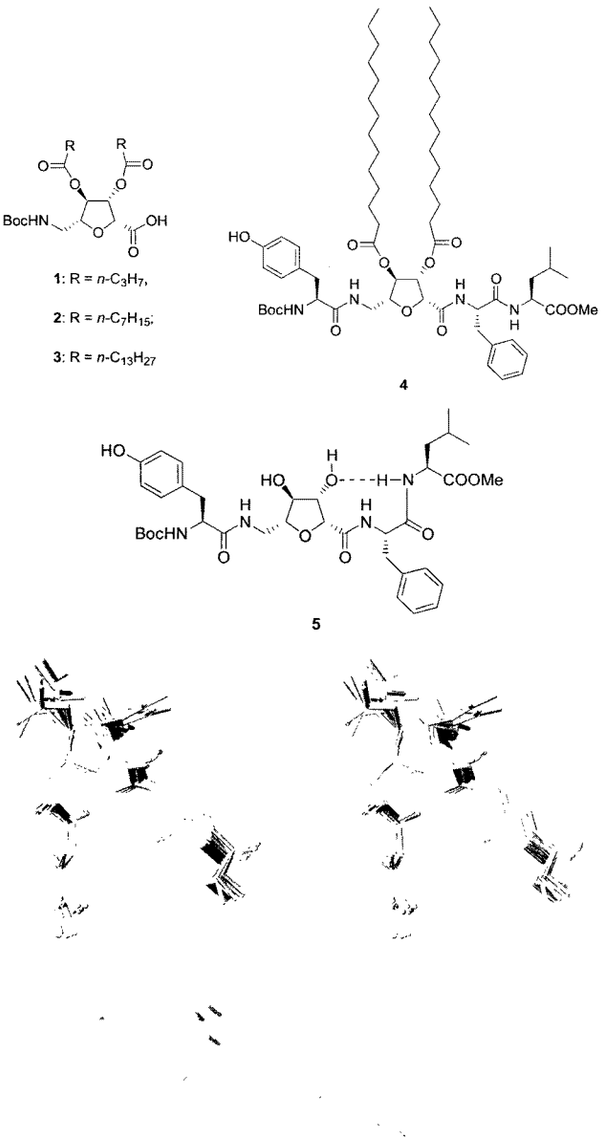
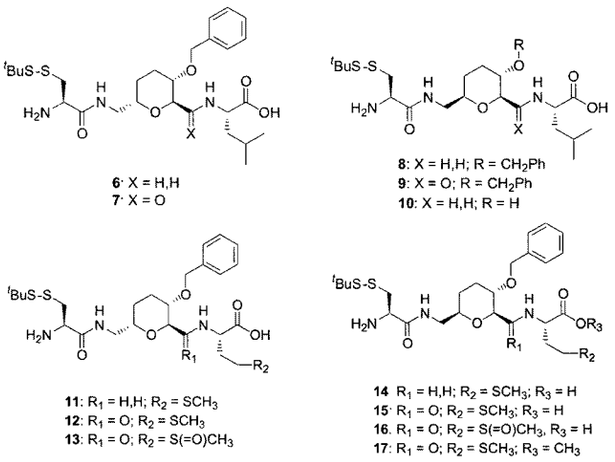


Fig. 1 top: Stereoview of the 12 backbone-superimposed energy-minimized structures of 4, sampled during 20 cycles of the 120 ps constrained MD simulations following the Simulated Annealing protocol. For clarity in viewing, only the backbones are shown here omitting the amino acid side-chains, fatty acid chains and all hydrogens except the amide protons; bottom: full view of one of the energy minimized structures sampled during MD studies.

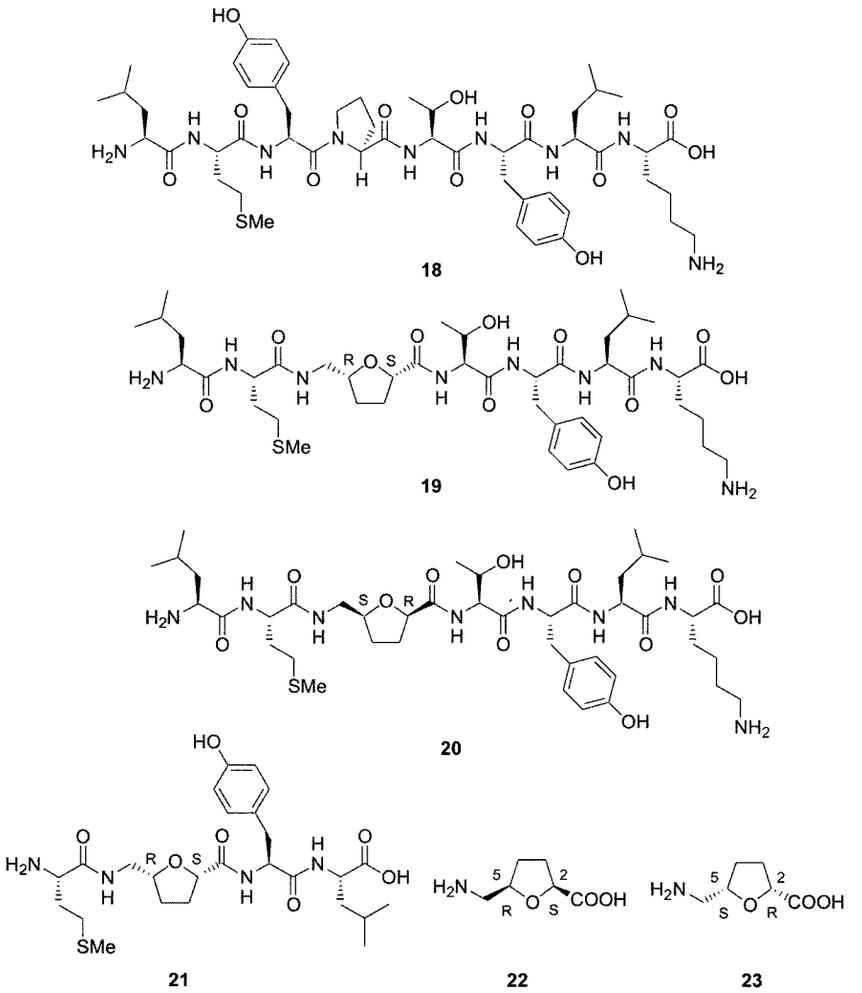
hydroxyl groups of sugar amino acids have profound effect on the overall conformation of peptides.

Protein farnesyl transferase (PFT) and protein geranylgeranyl transferase-1 (PGGT-1) catalyze the isoprenylation at the *C*-terminal of the Ca_1a_2X motif of the protein, is the essential step for the formation of mature Ras, a small GTP-binding protein. Ras plays key role in various biological processes. Extensive investigations have shown that inhibition of PFT and PGGT-1 is essential for the treatment of cancer.[12] With this aim, Marel et al synthesized novel set of protein prenyl transferase (PFT and PGGT-1) inhibitors **6–17**. These analogs **6–17** were obtained by incorporating the benzyl protected sugar amino acid, replacing the central dipeptide a_1a_2 of simple tetrapeptide Ca_1a_2X sequence and evaluated their selectivity and inhibitory potency against PFT and PGGT-1. Analog **15** was found to be a selective and potent PFT inhibitor (IC_{50} = 250 ± 20 nM), whereas analog **9** was the most active PGGT-1 inhibitor (IC_{50} = 14 mM), with no high selectivity for both enzymes. Compound **17** selectively inhibited protein farnesylation in cultured cells.[13]



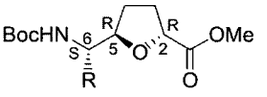
Vasoactive intestinal peptide (VIP), a 28 amino acid containing neuropeptide has wide-ranging biological activities.[14] It was shown that VIP acts as a growth factor and plays a dominant role in the sustained or indefinite proliferation of cancer cells. Therefore attention was made for the development of VIP receptor binding inhibitors.[15] A known VIP receptor binding inhibitor, octapeptide **18**,[16] was chosen as a target to develop its peptidomimetic analogs.

Several 3,4-dideoxy furanoid sugar amino acid-based VIP receptor binding inhibitors **19–21** have been developed.[17] The design was envisaged by studying the conformational analysis of the octapeptide **18**. Analogs **19** and **20** were synthesized by replacing the Tyr-Pro segment of octapeptide



18 by (2*S*,5*R*)-dideoxy furanoid sugar amino acid **22** and its enantiomer **23**, respectively. Detailed conformational analysis of analogs **19** and **20** in DMSO-d_6, displayed a β-turn structure having a 10-membered hydrogen bond between ThrNH → MetC=O and this conformational behavior is similar to that of the native octapeptide **18** (Figure 2). Although both building blocks **22** and **23** induced similar β-turn structures in peptides **19** and **20**, the turn induced by **23** was more pronounced than its antipode **22**. It is interesting that even a shorter peptide **21** exhibited a similar β-turn structure stabilized by a 10-membered hydrogen bond between TyrNH → MetC=O. These results suggest that a *syn* relationship between C2-H and C5-H of furanoid sugar amino acid building blocks **22** and **23** are responsible for getting folded conformation.[17]

Introduction of chirality at the C6-position of the sugar amino acid building blocks will not only influence the conformational behavior of the resulting peptides, but will also allow manipulation of their hydrophobicity/hydrophilicity. In this connection, a series of C6-substituted 3,4-dideoxy furanoid sugar amino acid building block **24** have been developed that were synthesized from chiral *N*,*N*-dibenzylaminoaldehydes and glyceraldehyde acetonide.[18]



24

a: R = Me; **b**: R = CH_2Ph
c: R = $CHMe_2$; **d**: R = CH_2OBn

With a similar goal, Overhand and co-workers prepared the C7-substituted pyranoid sugar amino acid **25** via diastereoselective sulfinimine chemistry. To check whether these δ-substituted analogs can be readily incorporated into oligomeric sequences,

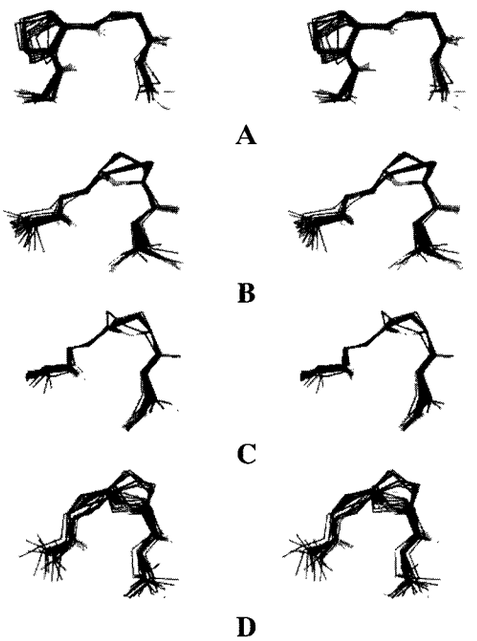
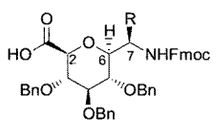


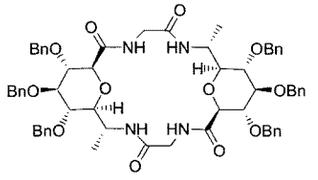
Fig. 2 Stereo views of the H-bonded regions of 25 superimposed energy-minimized structures of **18-21** (**A-D**, respectively) sampled during 50 cycles of the 300 ps constrained MD simulations following the Simulated Annealing protocol.

the authors constructed a cyclic tetramer **26** of compound **25a** by solid phase approach using Wang resin.[19]



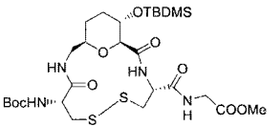
25

a: R = Me; **b**: R = CH_2Ph
c: R = $CHMe_2$; **d**: R = Ph



26

It is well known that turns, a common secondary structure in proteins, are involved in a myriad of biological processes such as protein folding, receptor binding, antibody recognition, and post-translational modification in proteins.[20] It is, therefore, not surprising that the reverse-turn peptidomimetics are extensively studied to explore the structure-function relationship of ligands and receptors.[21] To this end, Overhand's group synthesized pyranoid sugar amino acid based cyclic β-turn mimetics **27** and **28**. These mimetics were designed by analyzing the known proteins having a Cys-AA-AA-Cys tetrapeptide sequence with a disulfide linkage. A well-designed pyranoid sugar amino acid was used to replace the AA-AA segment of the tetrapeptide sequence to install the β-turn. They have further mimicked the disulfide linkage of cyclic peptide **27** with a rigid non-natural acetylene bridge following ring-closing alkyne metathesis (RCAM). Structural analysis of **27** and **28** through 2D NMR measurements established the presence of β-turn as major structural motif in both cyclic peptides.[22]



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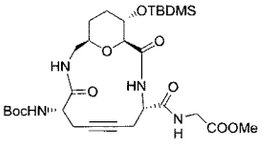
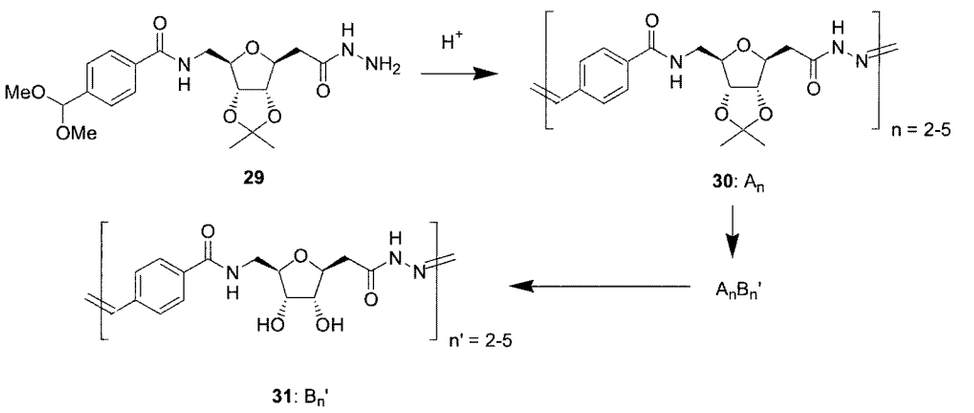


28

Dynamic combinatorial chemistry,[23] a target-driven approach, relies on reversible connections between a set of basic building blocks. In this way the best ligand to the receptor will be selectively amplified from a set of available components. Poulsen and co-workers utilized the concept of dynamic combinatorial chemistry for the preparation of cyclic oligomers of furanoid sugar amino acid.[24] The *N*- and *C*-termini of the sugar amino acid repeating unit was functionalised with a dimethoxy acetal protected aldehyde and a hydrazide, respectively. When this functionalised building block **29** was treated with acid, it generated the aldehyde and subsequent hydrazone exchange to form cyclic oligomers **30** or **31**. The authors further demonstrated that the formation of hydroxyl protected/deprotected cyclic oligomers could be obtained by simply altering the amount of the acid catalyst employed.[24]

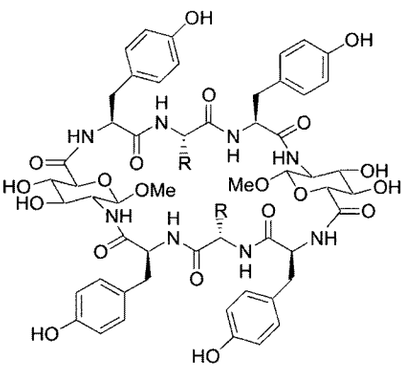
Nilsson *et al.* reported three cyclic sugar amino acid/amino acid hybrids **32–34** as novel artificial biomimetic receptors. It was envisaged that these C_2-symmetric macrocyclic peptides with a polar sugar amino acid together with nonpolar amino acids enable interactions with both hydrophilic and hydrophobic regions of a ligand. The binding properties of cyclic peptides **33** and **34** towards *p*-nitrophenyl glycosides, nucleotides, aromatic amino acids, aromatic amines and purines were examined in water using NMR titrations. The binding studies shown that these macrocyclic peptides were bound, though weak but specific to some purine derivatives.[25]

The naturally occurring C_2-symmetric cyclic decapeptide gramicidin S (GS) with a sequence of *cyclo*(^{D}Phe-Pro-Val-Orn-Leu)$_2$ has potent antimicrobial activity. GS has two type II' β-turns



29 **30**: A_n **31**: B_n'

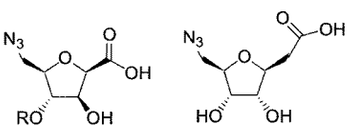
A_nB_n'



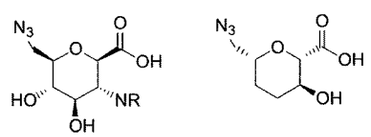
32: R = tyrosine side chain
33: R = CH_2CH_2COOH
34: R = $CH_2CH_2CH_2NHC(NH)NH_2$

induced by ^{D}Phe-Pro segment with four interstrand hydrogen bonds between the Leu and Val residues.[26] Despite having potent biological activity, its usage is restricted due to toxicity against human erythrocytes.[27] Therefore it is prerequisite to improve the therapeutic value of GS. In this line, Overkleeft's group produced a series of GS analogs **39** and **40** using solid-phase peptide protocol. They have incorporated either one or both nonproteinogenic sugar amino acids **35–38** into the turn region of GS by replacing the ^{D}Phe-Pro portion and carried out their structural studies and biological activity. The wealth of NMR data revealed that these peptides **39** and **40** prevalently adopt a β-sheet structure. The antimicrobial activity and hemolytic activity of peptides **39** and **40** showed a limited therapeutic value.[28]

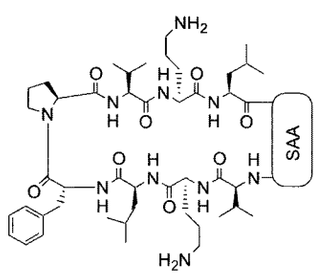
Overhand *et al.*[29] prepared morpholine amino acids from sugar amino acids **41** or **43**. They have prepared a series of ε-morpholine amino acids **42** based on oxidative cleavage of vicinal diol of sugar amino acid followed by double reductive amination



35: R = Piv **36**

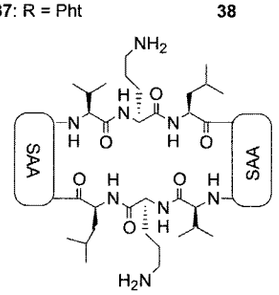


37: R = Pht **38**



39

a: SAA = **35**; R = H
b: SAA = **36**
c: SAA = **37**; R = H_2
d: SAA = **38**



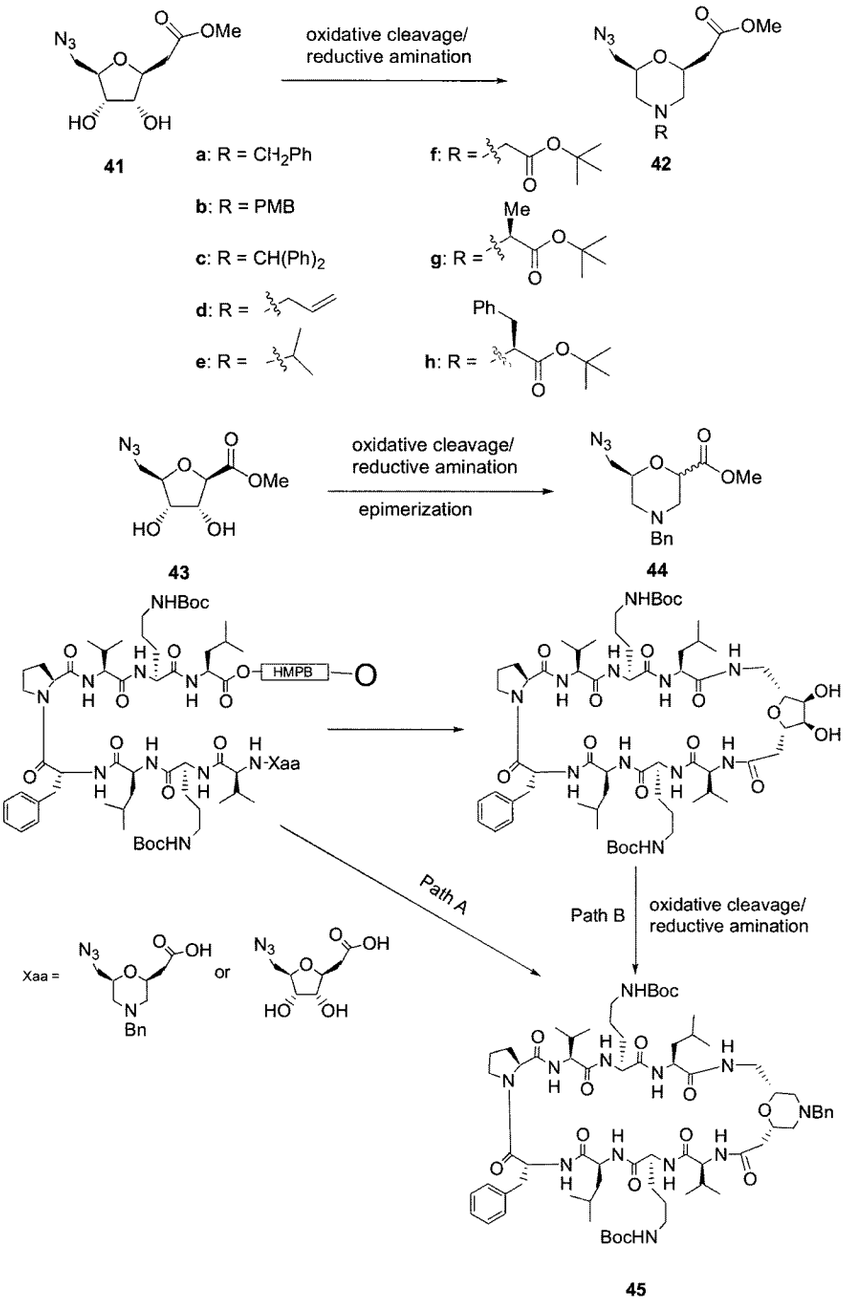
40

a: SAA = **35**; R = H
b: SAA = **36**
c: SAA = **37**; R = H_2
d: SAA = **38**

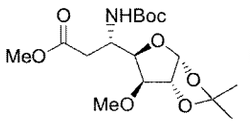
of the resulting dialdehyde. However, this strategy was suffered by epimerization during the synthesis of δ-morpholine amino acid **44**.

The application of morpholine amino acids was demonstrated by incorporating into the turn region of the gramicidin S (GS), using solid-phase peptide synthesis. The GS analog **45** was synthesized by two ways: direct introduction of morpholine building block **42a** (path A) or through oxidative cleavage/ reductive amination procedure (path B). ^{1}H NMR studies have shown that the Boc-deprotected version of GS analog **45** adopts a β-sheet structure, which is reminiscent to the native gramicidin S.[29]

Sharma and co-workers synthesized linear oligomers **48–53** in solution phase from a new class of *C*-linked carbo-β^3-amino acids **46** and **47**. CD spectra and 2D NMR studies revealed that alternating chirality of the epimeric *C*-linked carbo-β^3-amino acids has a determinant role in the formation of right-handed mixed helices in these peptides **48–53**. In $CDCl_3$, even a tripeptide **48** displayed an unprecedented 12/10 helical structure. Exceptional



stability and organization was observed in peptide **49** and **50** with the presence of 12/10 and 12/10/12/10 helical pattern, respectively. Though peptide **51** does not show any ordered structure, tetrapeptide **52** and hexapeptide **53** were characterized by a novel 10/12/10 and a propagated 10/12/10/12/10 helix, respectively. These studies are indicating that β-amino acid **47** ("*R*" at amine center) participate in 12-membered hydrogen bond while its epimer **46** ("*S*" at amine center) take part in 10-membered H-bond. These mixed helical structures were preserved predominantly in peptides **48–50**, **52** and **53** even in polar DMSO-d_6 solvent.[30]



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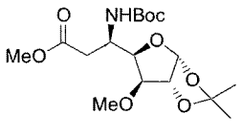
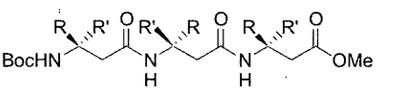
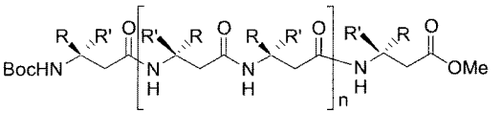


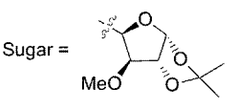
47



48 R = Sugar, R' = H; **51** R' = Sugar, R = H



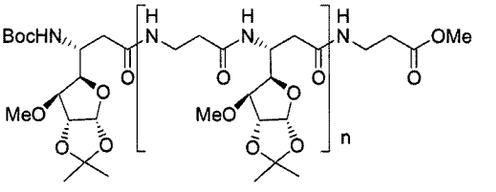
n = 1; **49** R = Sugar, R' = H; **52** R' = Sugar, R = H
n = 2; **50** R = Sugar, R' = H; **53** R' = Sugar, R = H



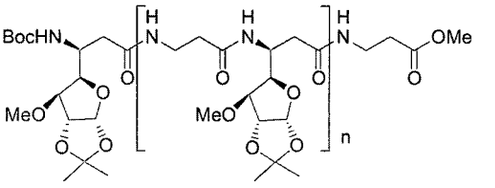
The same group subsequently prepared linear peptides **54–61** containing the alternative epimeric *C*-linked carbo-β[3]-amino acids **46** or **47** and β-hGly units. CD and NMR spectroscopic techniques were employed to study the conformational behavior of these peptides **54–61**. These studies revealed that peptide **54** in $CDCl_3$, exhibited right-handed 12/10 helical structure and peptide **55** displayed a propagated right-handed 12/10/12/10 helix. In peptide **56**, no definitive structure could be obtained due to averaging coupling constants, but peptide **57** was characterized by an unprecedented left-handed 12/10/12/10 helical structure in $CDCl_3$.

As expected, NMR studies of peptides **58** and **59** in $CDCl_3$ confirmed the presence of a right-handed 10/12/10/ and 10/12/10/12/10 helical structure, respectively. Though the signatures for helical structure were observed in peptide **60**, the structure was not assigned due to weak NOEs. However, in peptide **61** an unprecedented left-handed 10/12/10/12/10 helix conformation was observed.[31]

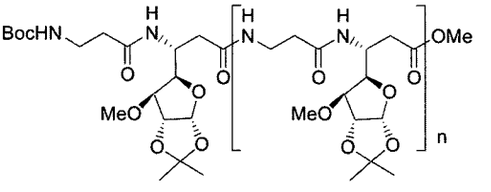
Chandrasekhar *et al.* synthesized linear homooligomers **62** of furanoid *cis*-b-sugar amino acid **63** in solution phase. Circular dichroism (CD) and extensive NMR investigations together with restrained molecular dynamics calculations revealed that even a tetramer in $CDCl_3$, adopts a right-handed 14-helical structure having hydrogen bond between $NH_i \rightarrow C{=}O_{i+3}$. The increase in the length of the peptide from tetramer to octamer, increased the organization and stability of 14-helix.[32]



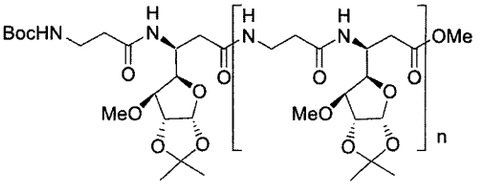
54: n = 1; **55**: n = 2



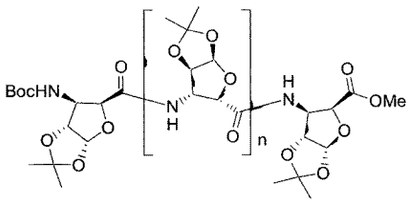
56: n = 1; **57**: n = 2



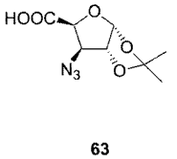
58: n = 1; **59**: n = 2



60: n = 1; **61**: n = 2

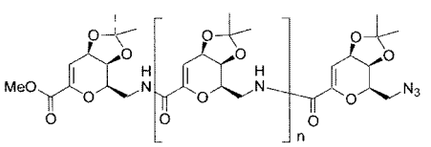


62: n = 2, 4, 6

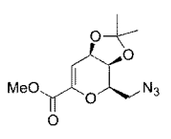


63

Jones and co-workers[33] reported a new class of peptidomimetic **64** comprising an unsaturated sugar amino acid building block **65**. It was envisaged that the double bond at the α-position of this building block would allow further conformational constraints in peptidomimetic **64**. Though it was not fully confirmed, IR and NMR studies showed a well-organized secondary structure (Fig. 3) in tetramer **64**.



64: n = 2



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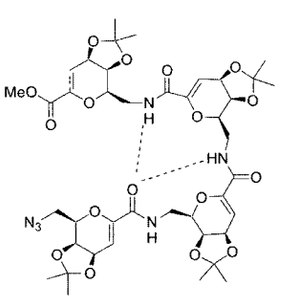
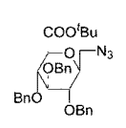


E

Fig. 3 Proposed secondary structure of tetramer **64** (**E**)

In order to mimic the structures and functions of biopolymers, Xie et al prepared linear homooligomers **68** and **69** in solution phase from pyranoid sugar amino acids **66** and **67**, respectively.[34]



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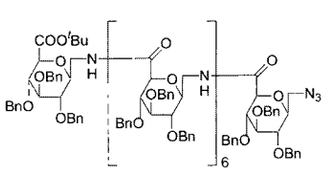

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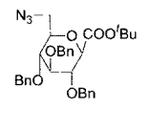

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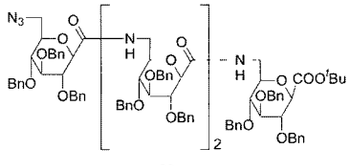
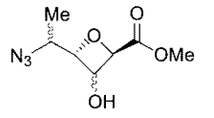


69

A new entry toward the δ-sugar amino acid dipeptide isosteres was prepared by Fleet's group.[35] They have synthesized a series of oxetane δ-amino acid scaffolds **70** and **71**, that can be considered as D/L-Ala-D-Ser and Gly-L-Ser dipeptide isosteres, respectively.



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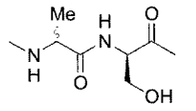
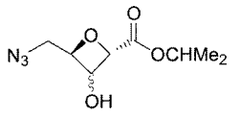


D/L-Ala-D-Ser



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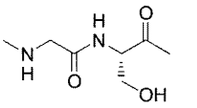
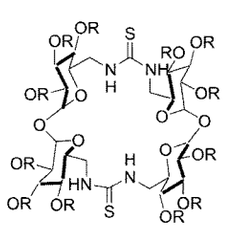


Gly-L-Ser

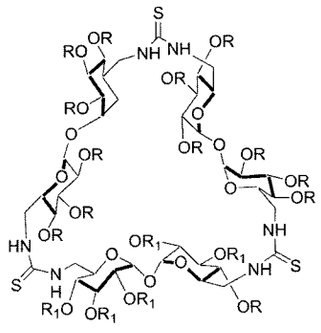
Cyclic Oligosaccharides with Linkage of Achiral Thiourea Functional Group

Fernandez group has reported[36] a special class of carbohydrate based cyclic oligomers, cyclotetrahalins (CTs) **72–74** where the classical *O*-glycosidic intersaccharide linkages has been replaced by achiral thiourea functional group. In these oligosaccharides (called reverse CD's) the β face of the monosaccharide constituents (i.e., H-1, H-2 and H-4) is oriented toward the inside of a convex cavity.

NOE experiments in **73** indicate close contacts between the H-1/ H-1′, H-5/ H-5′ and H-5/ H-1 protons of the magnetically non-equivalent D-glucopyranose moieties of the acylated trehalose fragments, which lead the CT to be a structurally rigid scaffold. D_3 symmetric **74**, a truncated-cone structure having limited flexibility in the semi-rigid thiourea segment binds benzoate anion in water with an association constant of 8 ± 2 M^{-1} for tetrabutyl ammonium benzoate.

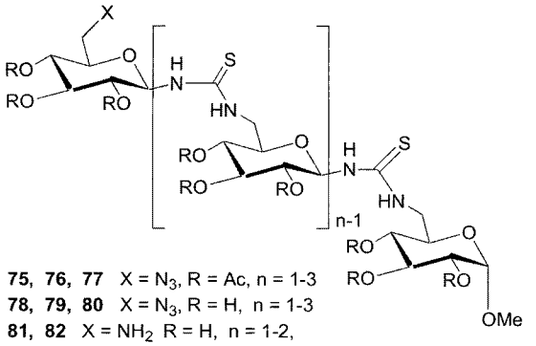


72 : R = H

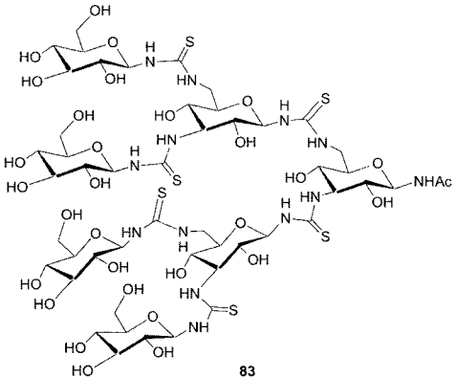


73 : R = Ac, R_1 = H
74 : R = R_1 = H

The same group has also reported[37] the development of thiourea-linked glycooligomers in linear, dendritic and branched form. By using sugar azido (carbamate) isothiocyanates as the key templates they prepared the neutral carbamate architectures, β-(1→6) disaccharides, trisaccharides, tetrasaccharides (compound **75–82**), second generation dendritic, β-(1→6), β-(1→3) heptamer **83**. They have also prepared pseudoheptasaccharide **84**, which mimics the branching pattern of a naturally occurring phytoalexin elicitor-active β-glucan. Disaccharide **75** can be involved in phosphate ester binding in aqueous solution against the sodium salt of dimethyl phosphate and phenyl phosphate. It forms 1:1 complexes in both cases with association constants of 2.5 ± 0.2 and 39 ± 3 M^{-1}, respectively.



75, 76, 77 X = N_3, R = Ac, n = 1-3
78, 79, 80 X = N_3, R = H, n = 1-3
81, 82 X = NH_2 R = H, n = 1-2,



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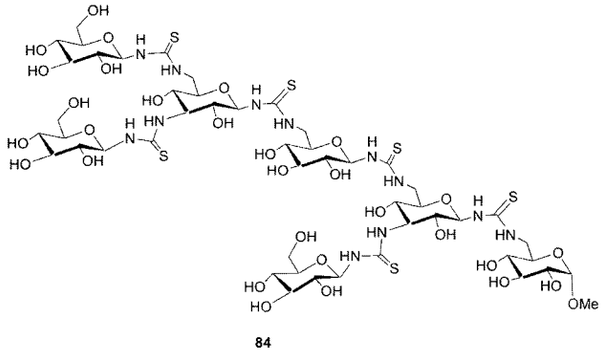


84

Modified Cyclodextrin Architecture

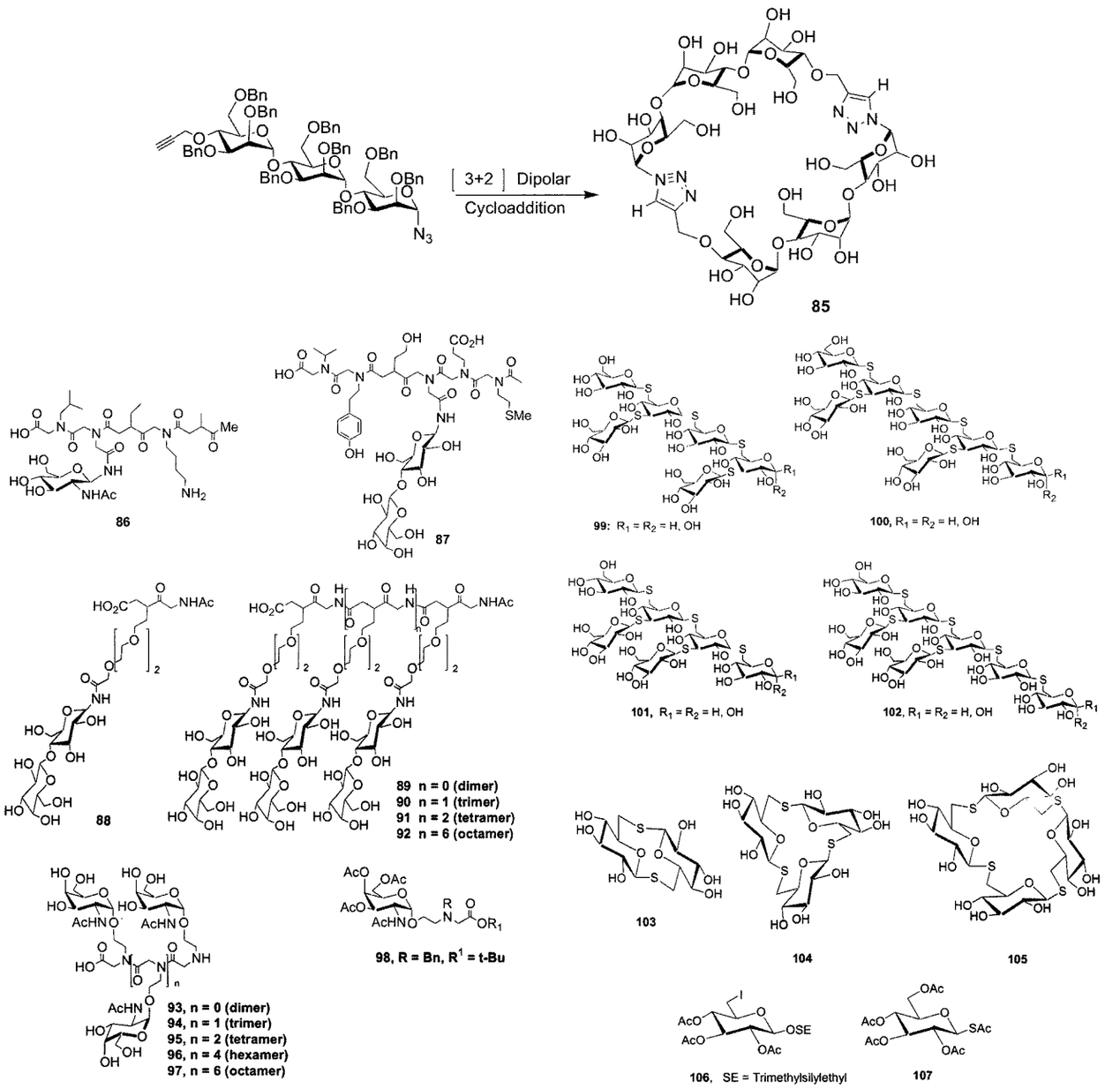
Recently Mary S Gin *et al.* has synthesized[38] modified cyclodextrin analogues **85**, which contains two triazole rings in the macrocycle. Taking alkynyl-azido trisaccharides as the starting material they have cyclodimerized it through [3+2] Huisgen cyclization. The macrocycle **85** exhibits association characteristics with the hydrophobic fluophore 8-anilino-1-naphthalenesulfonate (K_a = 38 ± 10 M^{-1}) which is comparable to that of β-CD (K_a = 71 ± 4 M^{-1}).

N-Linked-Glycopeptoids as New Glucopeptidomimetics

Glycopeptides are in recent focus of potential pharmaceutical applications.[39,40] Unfortunately, glycopeptides, like their peptide counterparts, are metabolically unstable. In order to apply mimetic concepts to glycopeptides, Rene Roy and coworkers reported a number of "glycopeptoid" libraries representing *N*-linked and *O*-linked glycans. They have replaced the sequence NH_2-Leu-Asn (D-GlcNAc)-Phe-Lys-Ala-OH from a glycopeptide by *t*-BuO_2CCH_2-Nleu-Nasn-(D-GlcNAc)-Nphe-Nlys-Nala-N-Ac **86**, an asparagine linked N-acetylglucosaminide *N*-linked pentapeptoid mimic.[41] They reported another *N*-linked glycopeptoid **87** bearing a lactosyl residue[42] along with combinatorial structures of conformationally flexible multivalent *N*-linked lactose **88–92** containing glycopeptoids having triethylene glycol spacers between the sugar residues and the peptide backbones. Each of these isomers offers the possibility of exploring complex clustered receptors.[43] Besides, they also prepared a library of oligomeric glycopeptiods **93–97** as a mimic, which bears the cancer related T_N-Antigen.[44] In order to prepare these oligomers, the key intermediate building block **98** was prepared from which both amino ester and *N*-protected acid were derived.

Oliosaccharides exclusively in Thioglycosidic Linkages

Jacques Defaye group reported[45] varieties of oligosaccharides exclusively through thio-glycosidic linkages. They carried out the synthesis of sulfur-linked analogues of nigerose, laminarobiose, laminaratriose, gentiobiose, gentiotriose and laminaran trisaccharide Y. Later they synthesized[46] *S*-linked pentathio analogue **99** of the elicitor-active



3I, 3^{IV}-di-β-D-glucopyranosylgenetitetraose, the homologous hexathioheptasaccharide **100**, as well the isomeric pentathiohexasaccharide **101** and hexthioheptasaccharide **102**. All bear the trisaccharide epitope at the non-reducing end and so represent potentially enzymatically stable phytoalexin-elicitor analogues.

Cyclic Oligosaccharides: β-1,6-Thio-Linked Cycloglucopyranoside

Hindsgaul's group prepared cyclic oligosaccharides of D-glucopyranosides (**103–105**) with exclusively thioglycosidic linkages.[47] Taking **106** and **107** as the starting materials they prepared linear thiooligosaccharides architecture as the key intermediate which bears an iodo group at C-6 of the nonreducing sugar unit and a thioacetyl group at the anomeric center of the reducing sugar unit. During macrocyclisation of the corresponding oligomers through base-promoted intramolecular S_N2 glycosylation yields were found to be 92-95%.

Conclusions

Carbohydrates are being increasingly utilized as multifunctional molecular scaffolds in wide-ranging applications. Sugar amino acids, for example, have

emerged as excellent building blocks in peptidomimetic studies, capable of inducing secondary structures in peptides. The various functional groups on each of these sugar amino acids, especially their amino and carboxyl termini, can serve as adapters for solid-phase synthetic methods providing opportunities to create libraries of multifaceted molecules that may emulate diversities of biopolymers. Besides, the cyclic oligomers developed by manys groups employing various sugar rings can be moulded to build predisposed cavities of precise dimensions that are expected to provide useful tools as novel synthetic receptors to study diverse molecular recognition processes. The nonproteinogenic properties of these designer carbohydrate-based molecules will make compounds having them physiologically more stable. Optimum utilization of the molecular diversities of carbohydrate molecules and the efficiency and speed of solid-phase chemistry will lead to the development of more and more bioactive molecules. As the demand for discovering new molecules is increasing day by day, the need to explore new methods to create them at much faster rate is felt today more than ever before. The diversities of carbohydrate molecules provide chemists the opportunities to create novel "Designer Molecules" that hold lots of promises for the future.

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