Recent Advances in Synthesis of Bacterial Rare Sugar Building Blocks and Their Applications

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HIGHLIGHT

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Bacteria have unusual glycans on their surfaces which distinguish them from the host cells. These unique structures offer avenues for targeting bacteria with specific therapeutics and vaccines. However, the rare sugars are not accessible in acceptable purity and amounts by isolation from natural sources. Thus, procurement of orthogonally protected rare sugar building blocks through efficient chemical synthesis is regarded as a crucial step towards the development of glycoconjugate vaccines. This *Highlight* focuses on recent advances in the synthesis of the bacterial deoxy amino hexopyranoside building blocks and their applications to construct various biologically important bacterial *O*-glycans.

1. Introduction

Bacterial glycoproteins and oligosaccharides contain rare deoxy amino sugars which are not present on the human cell surface.[1-6] These important structural differences help to differentiate between the pathogen and the host cell and can be exploited for target specific drug discovery and carbohydrate based vaccine development.[7] However, these rare sugars are not available from natural sources. Chemical synthesis of orthogonally protected rare sugar building blocks has therefore received considerable attention.

The bacterial atypical sugars include, 2-acetamido-4-amino-2,4,6-trideoxy-D-galactose (AAT),[2] 2,4-diacetamido-2,4,6-trideoxy-D-galactose (DATDG),[3] bacillosamine (Bac),[4] *N*-acetyl fucosamine (FucNAc),[5] and D-xylo-6-deoxy-4-ketohexosamine (DKH)[6] (Fig 1). These sugars form key components of a variety of bacterial glycoconjugates (zwitterionic polysaccharides, glycoproteins and oligosaccharides). There is growing evidence that the ability of the pathogen to express these unusual sugars is linked with pathogenesis. A detailed account of the bacterial source, the type of sugars present and their associated disease is categorically presented in a recent review article by Dube and coworkers.[1a] In this *Highlight* we discuss the methods developed for chemical synthesis of the rare sugars. Application of the rare monosaccharide building blocks in the synthesis of various bacterial *O*-glycans is also presented.

The unusual deoxy amino sugars depicted in Fig. 1 share some common structural features such as, the presence of equatorially oriented C2-NHAc, C3-OH and C5-CH_3 groups. The structural variation of the C4 functionality alone results in several different sugars. For example, AAT bears an axial C4-NH_2 group, while DATDG and Bac have axial and equatorial C4-NHAc groups, respectively. DKH has a keto functionality at the 4-position. Owing to their biological importance, several routes starting from a variety of carbohydrates and non-carbohydrate precursors are reported in literature.

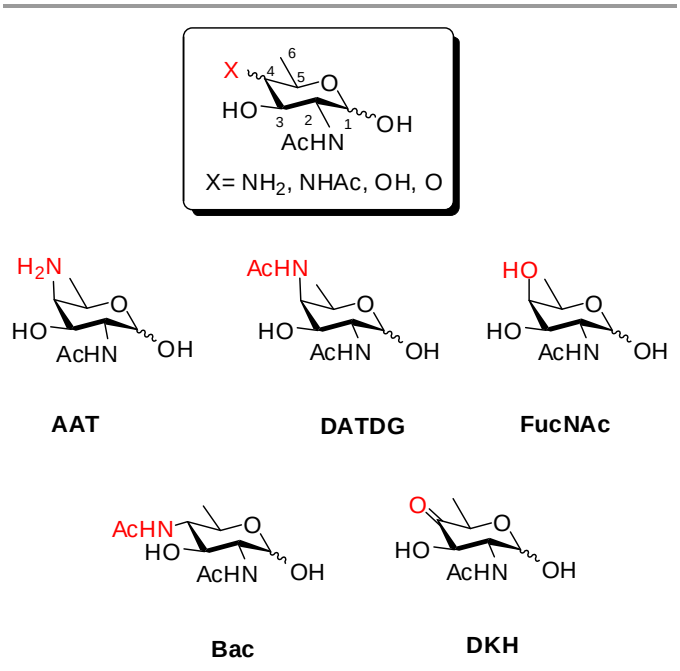

Fig. 1 Structures of various bacterial rare sugar building blocks.

2. Classical carbohydrate approaches

A number of reports for the synthesis of rare amino sugar building blocks using carbohydrate precursors have been

documented in literature. The key steps involved in these approaches are deoxygenation at C-6 position and incorporation of amine or hydroxyl functionality at C-4 and/or at C-2.

2.1 AAT and DATDG

D-Glucosamine (D-GlcNH_2) is the most suitable precursor for AAT and DATDG as the requisite equatorial C2 amino function is already in place. Not surprisingly, most synthetic procedures, for AAT and DATDG start from readily available D-GlcNH_2 (Fig 2, path A).[8-14] These methods typically involve a C-6 deoxygenation via conversion of C-6 hydroxyl to corresponding mesylate, iodide or bromide and their subsequent displacement with hydride. Introduction of amine functionality at C-4 position with inversion is usually achieved by S_N2 displacement of C-4 hydoxyl (Mitsunobu conditions), mesylate, tosylate or triflate with azide or phthalimide as nucleophiles. In 1984, Lönngren and coworkers accomplished the first synthesis of an orthogonally protected AAT building block by employing the corresponding 4,6-dimesylate to achieve these two steps.[9] van Boom and co-workers explored two different routes for the synthesis of AAT and DATDG building blocks starting from D-mannose by stepwise introduction of amine functionality at C-4 followed by at C-2 positions. In their first approach, D-mannosan was transformed into DATDG[15] via a multistep sequence involving 2,3-*O*-*p*-methoxy benzylidene acetal formation, triflation of 4-OH and azide displacement of C4 *O*-triflate, followed by regioselective oxidative ring opening of 2,3-*O*-*p*-methoxy benzylidene acetal at O2, and finally triflation of 2-OH and subsequent azide displacement of C2 *O*-triflate (Fig. 2, path B). For the synthesis of AAT derivative,[16] stereoselective reduction of C4-oxime of mannoside, followed by conversion to glycal derivative and subsequent azidonitration to install the C2-azide function was carried out

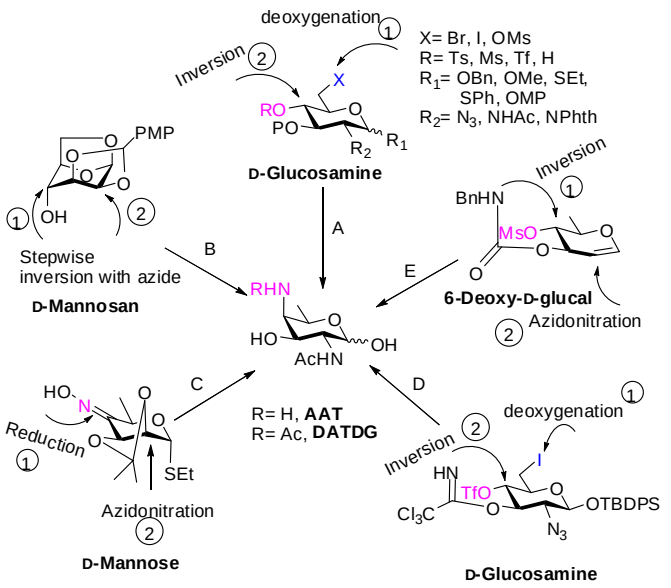

Fig. 2 Synthetic strategies employed for AAT and DATDG derivatives.

(Fig 2. path C). Recently, an intramolecular displacement strategy was employed to introduce amine functionality at C-4 position of hexopyranosides. van der Marel and co-workers[17] used 3-*O*-trichloroacetimidate to displace the C-4 triflate on 6-deoxy D-glucosamine scaffold to get to the oxazoline intermediate (Fig 2, path D) whereas Bundle and co-workers[18] used 3-*O*-benzyl carbamate to displace the C-4 mesylate of 6-deoxy-D-glucal (Fig 2, path E) followed by azidonitration to introduce the C2-azido functionality.

2.2 D-Fucosamine

The most suitable precursor for the synthesis of D-fucosamine is D-galactosamine, since it is the C-6 deoxy analogue of the

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Suvarn Kulkarni received his M.Sc. (1993) and Ph.D. (2001) in Organic Chemistry from University of Pune in 2001. After his Ph. D., he pursued his post-doctoral research in the laboratory of Professor Shang-Cheng Hung at Academia Sinica, Taipei on chemical synthesis of glycans via one-pot protection of sugars. In 2005, he moved to University of California Davis to work with Professsor Jacquelyn Gervay-Hague and was engaged in glycosyl iodide mediated one-pot synthesis of glycolipids.

He returned to India in late 2008 and held a faculty position at IACS Kolkata prior to joining the Indian Institute of Technology Bombay in 2009. He was promoted to Associate Professor in 2012. His current research interests include devising newer ways for efficient chemical synthesis of complex glycoconjugates implicated in various infectious diseases as well as cancer.

same. C-6 Deoxygenation of D-galactosamine derivative was carried out using Barton-McCombie procedure[19] or via reduction of C-6 iodide[20-23] with a hydride source (Fig 3, path A). Since D-galactosamine is quite expensive, D-glucosamine is more often employed instead for this purpose (Fig 3, path B). This transformation involves the preparation of C-6 bromide or mesylate and their displacement with hydride and followed by C-4 inversion of mesylate or triflate with benzoate as a nucleophile.[24-26] Carreira[27] and Shibaev[28] groups reported elegant procedures for the synthesis of D-fucosamine derivatives by aminohydroxylation or azidonitration of D-fucal, respectively (Fig 3, path C). More recently, Adamo and co-workers[29] carried out a double inversion at C-2 position of D-fucose (6-deoxy galactose) by oxidation-reduction, triflation and azide displacement of the 2-*O*-triflate to access the D-fucosamine derivative (Fig 3, path D).

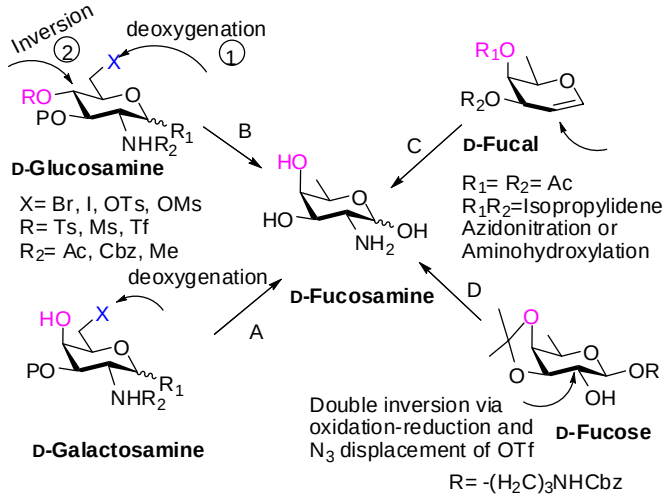

Fig. 3 Synthetic strategies for D-fucosamine derivatives.

2.3 D-Bacillosamine (Bac)

C-4 Inversion of D-fucosamine with amine source gives the access to Bac. Accordingly, transformation of D-glucosamine,[30,31] D-galactosamine[32] and D-fucal[33] to the corresponding D-fucosamine derivatives as described above, and subsequent nucleophilic displacement of their C-4 chloride, mesylate, tosylate or triflate derivatives with azide nucleophile afforded the D-bacillosamine derivatives (Fig 4, paths A, B and C). All the classical carbohydrate approaches described so far involve C-6 deoxygenation first and followed by C-4 inversion. Very recently, Imperiali and co-workers[34] employed a reverse approach via first carrying out a C-4 inversion on a D-galactosamine derivative with azide followed by C-6 iodide displacement with simultaneous reduction of the azido group under hydrogenation conditions (Fig 4, path D).

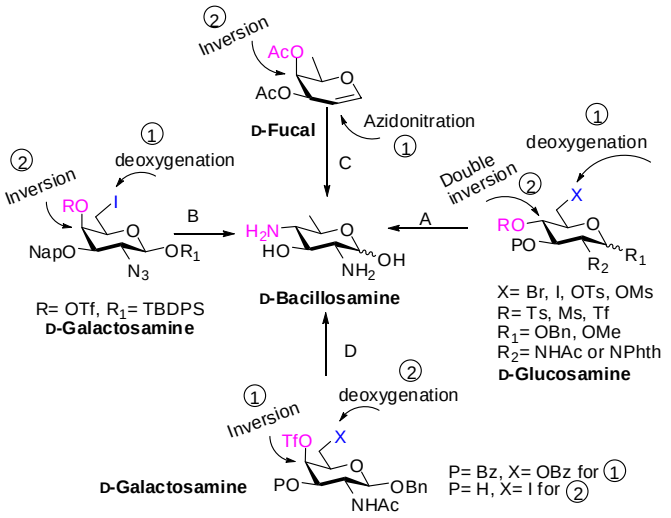

Fig. 4 Synthetic strategies for D-bacillosamine derivatives.

3. *De novo* approaches

Over the years, *de novo* approaches[35-46] have been extensively employed for the synthesis of variety of carbohydrates. Although most of the rare sugars can be accessed via classical carbohydrate approaches, this usually involves lengthy routes to obtain orthogonally protected building blocks, while shorter versions provide amino sugars bearing the participating groups at C-2 position which cannot be used for α-glycosylation. To overcome these problems, *de novo* approaches have been explored for synthesis of various rare sugars.

In 1994, a *de novo* route was first explored by Polt and co-workers[47] to synthesize *N*-methyl- D-fucosamine (Fig 5). In this method, O'Donnell's Schiff base **1** underwent chelation-controlled reduction-alkylation using Bu_2AlH-iBu_3Al/CH_3CH=CHLi to afford a *trans* alkene (dr = 20:1, separable by column), which was subjected to Sharpless dihydroxylation followed by acetylation to obtain the triacetate **2** in 70% yield over 2 steps. Reduction of the imine and its subsequent methylation in the presence of formaldehyde afforded the *N*-methyl derivative, which upon desilylation gave

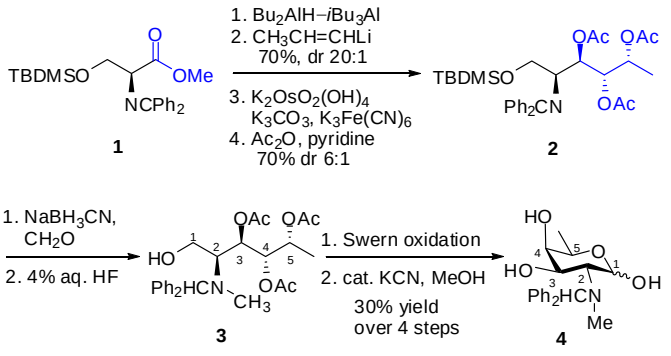

Fig. 5 *De novo* synthesis of *N*-methyl-D-fucosamine by Polt and co-workers.

the primary alcohol **3**. Oxidation of **3** and tandem cyclization under deacetylation conditions provided the *N*-methylfucosamine derivative **4**.

Quintela and co-workers[48,49] synthesized a D-fucosamine derivative by employing a *syn* Aldol type reaction between 1,3-dioxolane-4-carboxaldehyde **5** and lithiated Schöllkopf's bis-lactim ether **6** (Fig. 6). The so-formed alcohol intermediate **7** was methylated and a selective cleavage of the bis-lactim ether followed by Cbz protection of the formed amine afforded **8**. Subsequent acid hydrolysis of the isopropylidene group, in situ lactonization and partial DIBAL reduction of the lactone gave a mixture of the furanose and pyranose forms of D-fucosamine, which upon hydrogenolysis of the Cbz group gave D-fucosamine derivative **9** as a mixture of pyranose anomers.

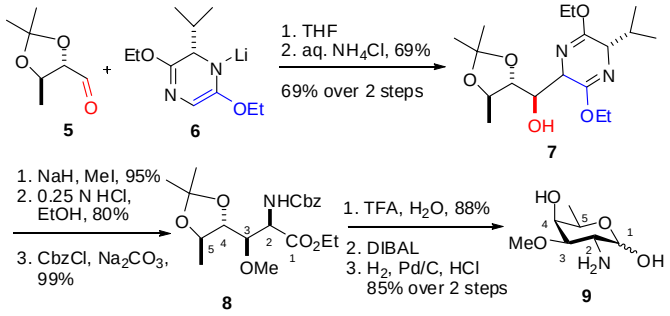

Fig. 6 *De novo* synthesis of D-fucosamine by Quintela and co-workers.

Recently, Seeberger and co-workers[50,51] developed an elegant and convenient method for the synthesis of AAT building block starting from commercially available *N*-Cbz-L-threonine **10** using Dieckmann cyclization as a key step (Fig 7). First, *N*-Cbz-L-threonine **10** was subjected to esterification and followed by *O*-acetylation to obtain acetate **11**, which underwent Dieckmann cyclization in the presence of LHMDS. The crude Dieckmann cyclization product was methylated using K_2CO_3/Me_2SO_4 to give methoxy enone **12**, which was

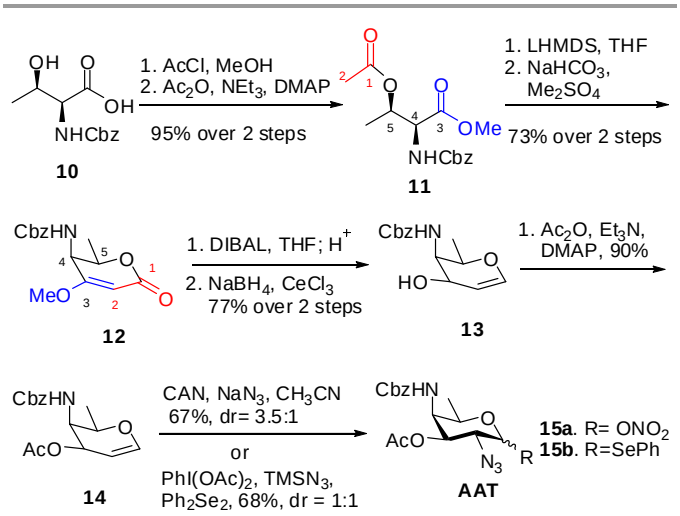

Fig. 7 *De novo* synthesis of orthogonally protected AAT building blocks by Seeberger and co-workers.

reduced with DIBAL in a 1,2-manner and the so-formed unstable intermediate was subjected to acidic work-up to obtain the rearranged α,β-unsaturated ketone intermediate. Reduction of the keto group under Luche conditions afforded glycal **13**. The free C3-OH group of glycal **13** was acetylated to afford **14**. The introduction of the equatorial azido group at C-2 was carried out under azidonitration and azidoselenation conditions. In both the cases, mixtures of inseparable diastereomers involving the configuration at C2 were obtained. For **15a**, the mixture was separated during conversion to both a glycosyl trichloroacetimidate and a glycosyl *N*-phenyltrifluoroacetimidate.

Seeberger's group developed yet another *de novo* route to synthesize D-fucosamine, Bac and DKH[52] starting from L-Garner aldehyde by using chelation-controlled organometallic additions (Fig 8). L-Garner aldehyde **16** was treated with propynyl magnesium bromide and the formed alkyne was selectively reduced with red Al to give the *trans* allylic alcohol which was subsequently *O*-alkylated to afford *E*-olefin **17**. The acetonide group in **17** was cleaved to free the primary hydroxyl, which was oxidized with DMP to generate aldehyde **18**. The key intermediate **18** was subjected to Sharpless dihydroxylation and the obtained product was cyclized to give the desired D-fucosamine derivative **19** as the major product (dr = 5:1, separable by column). The free 4-hydroxyl of **19** was oxidized with DMP to give the DKH derivative **20**. Alternatively, triflation of **19** and inversion with azide afforded D-bacillosamine **21**. Similar reaction sequence on the D-Garner aldehyde led to respective L-fucosamine derivative.[53]

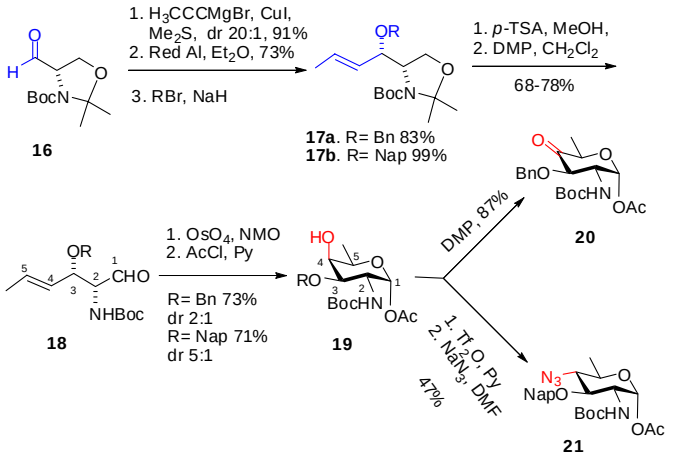

Fig. 8 Seeberger's *de novo* synthesis of orthogonally protected FucNAc, Bac and DKH.

Very recently, Schmid and co-workers[54] developed a convenient synthesis of a DATDG derivative starting from L-Garner aldehyde using the nitro Aldol reaction as a key step (Fig 9). L-Threonine **22** upon sequential esterification, *N*-bocylation, acetonide protection, reduction to primary alcohol and its oxidation gave L-Garner aldehyde derivative **23**, which was subjected to the nitro Aldol reaction with 2-nitroacetaldehyde diethylacetal to give key intermediate **24** in a

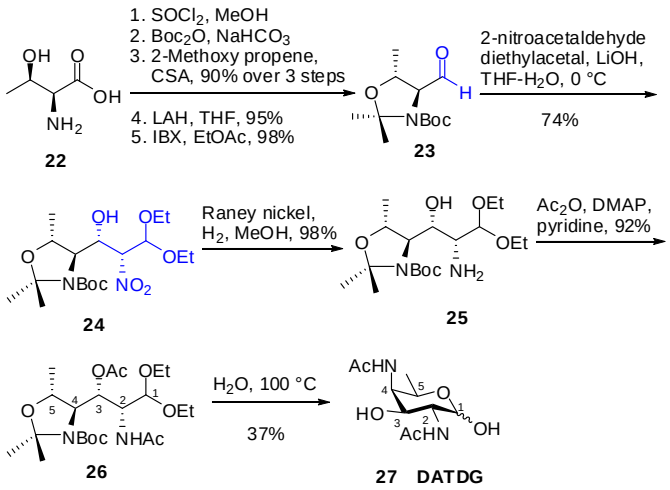

Fig. 9 *De novo* synthesis of DATDG by Schmid and co-workers.

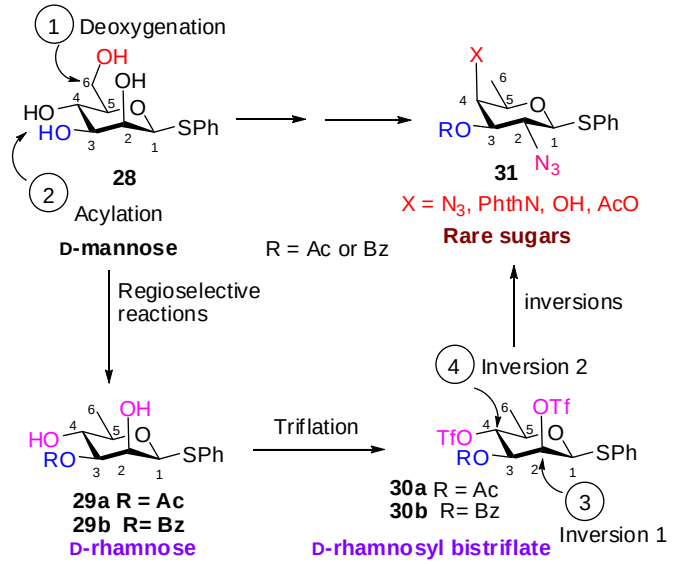

Fig. 10 Our strategy for the synthesis of rare sugar building blocks.

5:1 diastereomeric ratio. Raney nickel reduction of nitro group in **24** afforded amine **25** which was acetylated to give fully protected ketal **26**. Global deprotection with water at high temperature without any additional catalysts, and concomitant O to N acetate migration under the prevailing conditions directly furnished the DATDG derivative **27** in 37% yield.

4. Via a one-pot double serial and double parallel nucleophilic displacements of D-rhamnosyl 2,4-triflates

Methods developed for the synthesis of appropriately protected rare sugar building blocks through classical carbohydrate approaches are lengthy. *De novo* approaches on the other hand are novel and elegant but still involve separation of diastereomers. In the quest to develop a short and general protocol to access all the rare sugars, we embarked upon a systematic study to carry out nucleophilic displacements of *O*-triflates on the D-mannose scaffold. To begin with, we established conditions to efficiently transform β-D-thiomannoside into orthogonally protected D-glucosamine and D-galactosamine building blocks via stepwise serial inversion at C2 or C2 and C4, by azide and nitrite ions, respectively.[55] We envisioned that the study can be extrapolarated to synthesize rare sugars and that the methodology can be augmented to fit the one-pot paradigm. These efforts culminated into development of a divergent protocol for the synthesis of all rare sugar building blocks starting from a readily available β-D-thiomannoside **28** (Fig. 10). It was envisaged that through a regioselective C6-deoxygenation and O3-acylation, D-mannosyl tetraol **28** can be converted to D-rhamnosyl 2,4 diol **29**. Triflation and concomitant nucleophilic displacements of the resulting 2,4-bis-triflates **30** with various nucleophiles (N_3, PhthN, OH, OAc) would then afford all the rare sugar building blocks in a one-pot manner, if the desired regioselectivity could be attained by tuning reaction conditions. We anticipated that the C2-OTf in **30** being more accessible as compared to the C4-OTf would be more reactive due to stereoelectronic effects.

Accordingly, tosylation of β-D-thiomannoside **28** and its subsequent reduction with LAH afforded the D-rhamnosyl thioglycoside **33**, which upon regioselective 3-*O* acylation using dimethyltin dichloride as a catalyst furnished the requisite D-rhamnosyl 2,4 diols **29a** and **29b** in good yields (Fig. 11).

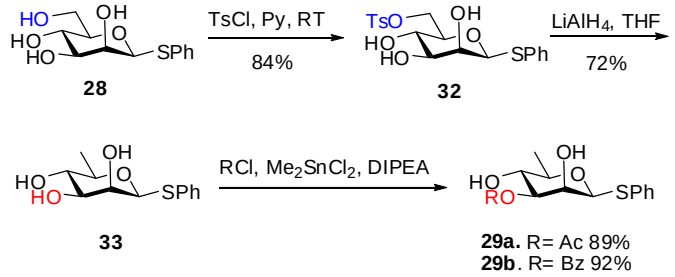

Fig. 11 Synthesis of D-rhamnosyl 2,4-diols.

With the 2,4-diols **29a/29b** in hand, we carried out sequential triflation and regioselective nucleophilic displacements of the D-rhamnosyl 2,4-bis-triflates **30** with various nucleophiles to access the rare sugar building blocks. The optimized reaction conditions and yields are depicted in Fig 12. The D-rhamnosyl 2,4 diols **29a** and **29b** were treated with Tf_2O, pyridine and the so formed 2,4-bis triflates **30a** and **30b** were as such treated with excess sodium azide to give DATDG derivatives **34** and **35** respectively in essentially one-pot manner (Fig. 12). A challenging task was to incorporate two different amine functionalities at C-2 and C-4 positions to obtain AAT derivative **36**. For this purpose, the D-rhamnosyl diol **29b** was converted into its bis triflate derivative **30b** and the regioselective C-2 OTf displacement was carried out at -30 °C using 1.0 equiv of $TBAN_3$. After the displacement of C2-OTf was complete, C4-OTf was displaced with phthalimide salt to afford AAT derivative **36** in 57% yield over 3 steps.

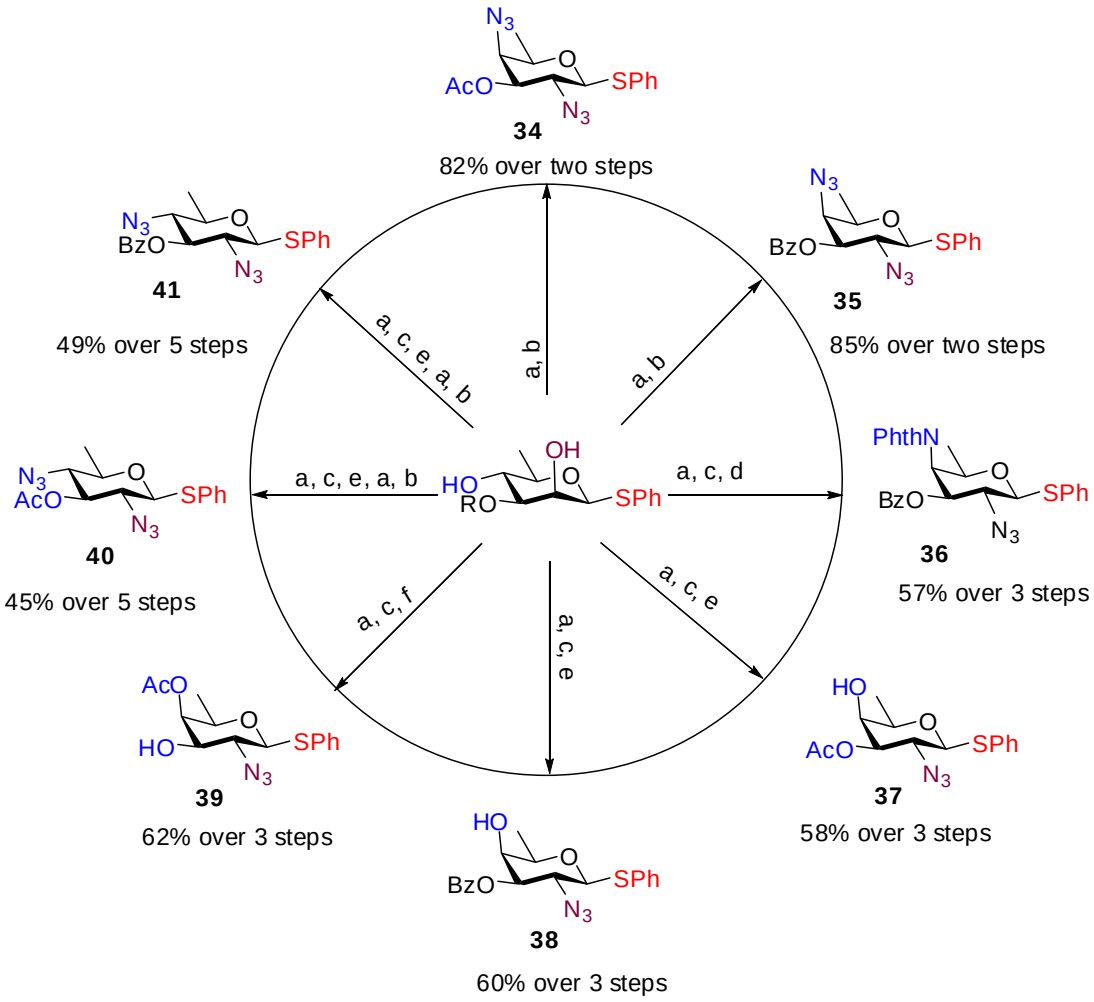

Fig. 12 Synthesis of various rare sugar building blocks.

To access the D-fucosamine derivatives **37** and **38**, first C2-OTf of **30a** and 3**0b** was selectively displaced with $TBAN_3$ and subsequently C4-OTf displacement with $TBANO_2$ was carried out again in essentially one-pot manner. For the synthesis of 3-hydoxy D-fucosamine derivative **39** we employed a different strategy, in which after the displacement of C2-OTf in **30a**, water was added and the reaction mixture was heated. Under the conditions, the O-3 acetate displaced the C4-OTf in an intra-molecular manner from the top face to give 3-hydroxy D-fucosamine derivative **39** in 62% yield over 3 steps. To synthesize the bacillosamine derivatives **40** and **41**, the 4-hydroxy fucosamine derivatives **37** and **38** were again treated with Tf_2O, pyridine and the 4-triflates were displaced with azide. In this way, by employing highly regioselective and one-pot, nucleophilic displacements of 2,4-bistriflates **30a** and **30b** as key steps, readily accessible β-D-thiomannoside **28** could be transformed into various rare sugar building blocks.[56,57] The strategy was also successfully extended to construct various orthogonally protected D-galacto configured glycosamine building blocks, which can be utilized for the synthesis of bacterial glycans.[58]

5. Applications to total synthesis of bacterial glycoconjugates

In 2007, van der Marel and co-workers[17] synthesized a fully protected tetrasaccharide repeating unit of zwitterionic polysaccharide A1 (ZPS A1) found in *Bacteroides fragilis*, in which the rare sugar AAT building block is attached to the D-galactosamine unit through α (1→4) linkage. As shown in Fig 13, using iterative dehydrative glycosylation conditions

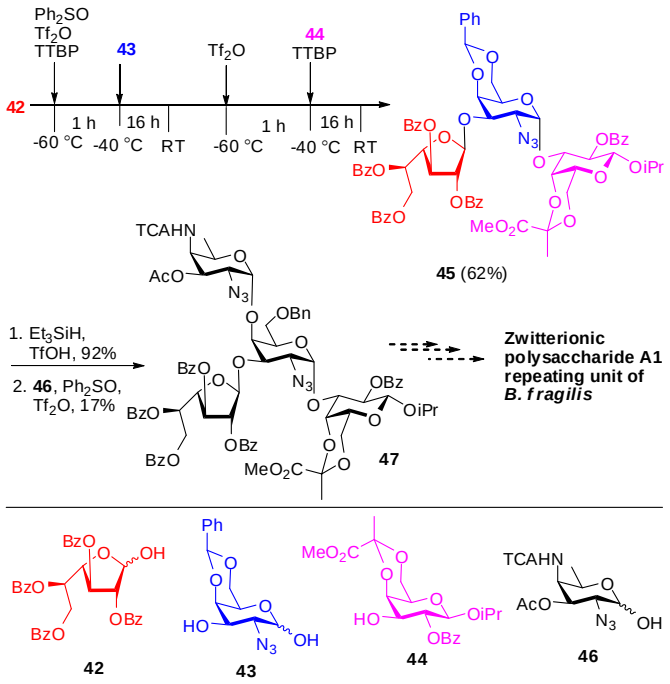

Fig. 13 Synthesis of ZPS A1 of *B. fragilis* by van der Marel and co-workers.

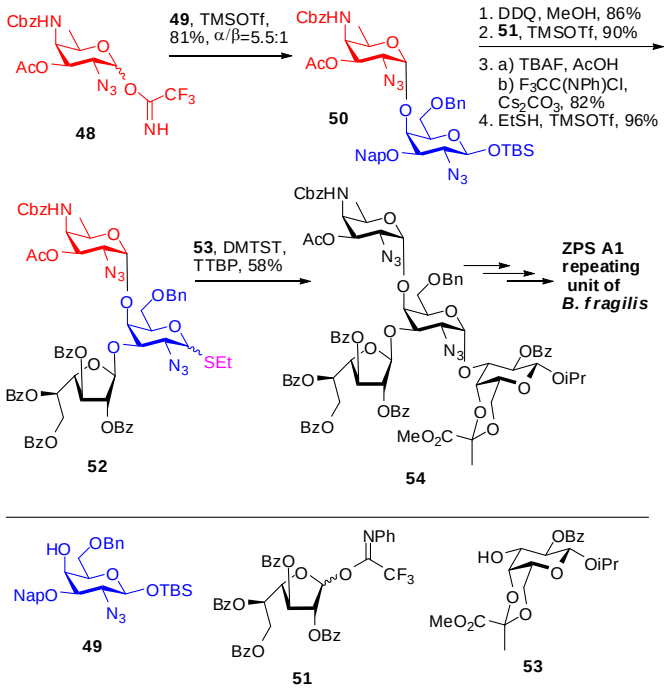

Fig. 14 Synthesis of ZPS A1 of *B. fragilis* by Seeberger and co-workers.

(hemiacetal, Ph_2SO and Tf_2O), trisaccharide **45** was assembled, in which the hemiacetal **42** was pre-activated and coupled with acceptor **43** to give the corresponding disaccharide donor which was sequentially activated by freshly added Tf_2O and coupled with acceptor **44** to give the desired trisaccharide **45** (62%) in a one-pot manner. Regioselective reductive benzylidene ring opening of **45** with Et_3SiH and TfOH gave its corresponding 4-hydroxy derivative and its coupling with pre-activated AAT donor **46** gave the tetrasaccharide repeating unit of *B. fragilis* in a low yield of 17%. In this synthesis, since the AAT donor is more difficult to prepare, the corresponding glycosylation was carried out at the late stage. The low yield in the glycosylation was attributed to the steric bias in the trisaccharide acceptor and the apparent low reactivity of AAT donor **46**. Very recently, the AAT building block **46** was also utilized for synthesis of all possible trisaccharide repeating units of the type 1 capsular polysaccharide of *Streptococcus pneumonia*, Sp1.[59]

Seeberger and co-workers[51] employed a convenient strategy to accomplish the total synthesis of ZPS A1 (Fig. 14). Through a systematic study, they found out that the coupling of AAT with D-galactosamine acceptor has to be performed at the initial stage and not at the late stage, to get better coupling yields. Accordingly, AAT imidate donor **48** was activated with TMSOTf and coupled with the D-galactosamine derived acceptor **49** to afford the desired key disaccharide **50** in good yields with a α/β ratio of 5.5:1. Cleavage of naphthyl group, incorporation of galactofuranside **51** at *O*-3 and anomeric functional group transformation afforded the trisaccharide **52**. Activation of thioglycoside **52** and its coupling with the acceptor **53** gave the required tetrasaccharide **54** repeating unit of *B. fragilis*.

Schmidt and co-workers[14] accomplished the total synthesis of the complex oligosaccharide (lipoteichoic acid) of *Streptococcus pneumoniae*. This complex lipoteichoic acid contains AAT building block which is attached to D-galactosamine through α (1→4) linkage similar to ZPS A1. The synthesis of key disaccharide **57** was achieved by the activation of imidate donor **55** with TMSOTf and its coupling with acceptor **56** in good yields (Fig. 15). The key disaccharide with the proper protecting groups was successfully utilized for the total synthesis of lipoteichoic acid **58** of *S. pneumoniae*.

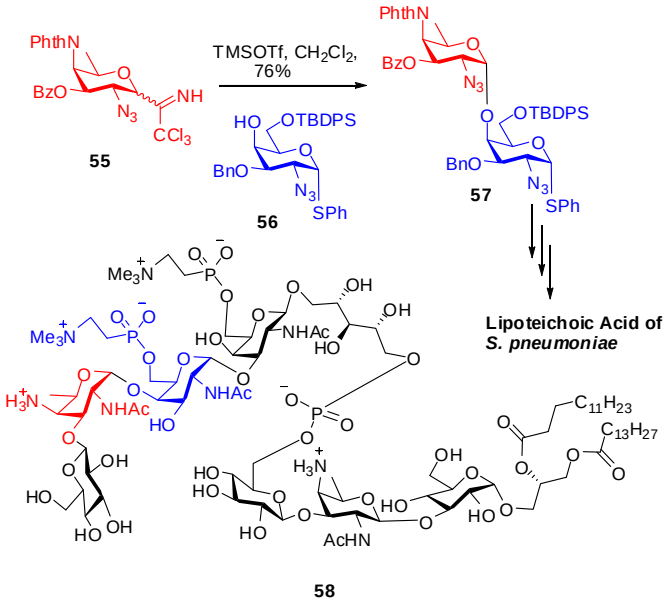

Fig. 15 Synthesis of lipoteichoic acid by Schmidt and co-workers.

Recently, Adamo and co-workers[29] developed a novel strategy for synthesis of rare D-and L-FucNAc building blocks and further employed these building blocks for the synthesis of repeating unit of capsular polysaccharide isolated from *Staphylococcus aureus* (Fig. 16). The crucial step in this synthesis was the α-fucosylation, which was achieved by coupling of donor **60** with acceptor **59** to obtain trisaccharide **61** in moderate selectivity (α/β 2.8:1). The undesired β-isomer was separated and the desired α-linked trisaccharide was subjected to global deprotection to afford the repeating unit of *S. aureus* **62**.

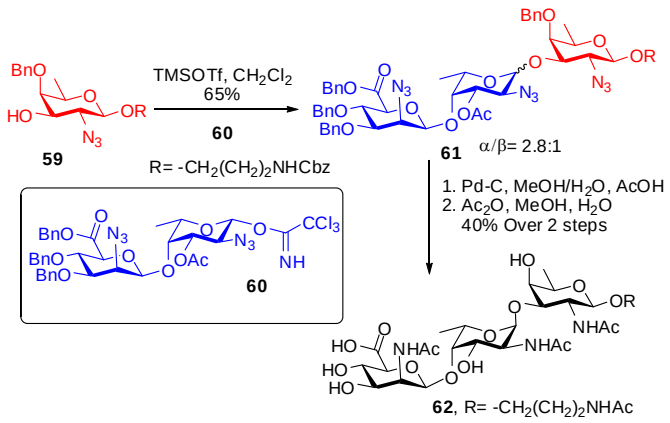

Fig. 16 Synthesis of the repeating unit of *S. aureus* by Adamo and co-workers.

In 2007, Ito and co-workers[60,61] synthesized the heptasaccharide **67** isolated from *C. jejuni*, which is composed of D-bacillosamine and repeating D-galactosamine building blocks with branched D-glucose (Fig 17). The key disaccharide **65** for this purpose was obtained by the coupling of glycosyl fluoride donor **63** with bacillosamine acceptor **64** and it was elaborated into heptasaccharide unit **67** of *C. jejuni* via step-wise glycosylations.

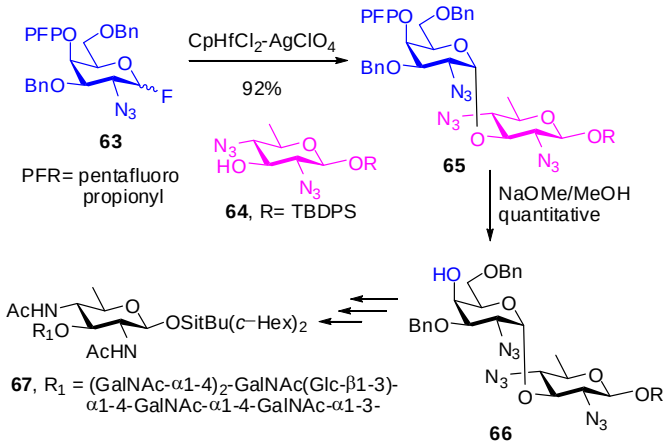

Fig. 17 Synthesis of heptasaccharide of *C. jejuni* by Ito and co-workers.

Having access to various rare sugar building blocks through our protocol, we accomplished the synthesis of key disaccharide **69** of ZPS A1 and the first total synthesis of the α-L-serine-linked trisaccharides **73** and **75** of *N. meningitidis*. The major challenge involved in the synthesis of disaccharide fragment of ZPS A1 is stereoselective α-coupling of AAT donor to the D-galactosamine acceptor. To achieve exclusive α-selectivity, first the thioglycoside AAT derivative **36** was converted to its corresponding glycosyl bromide, activated with AgOTf and coupled with the D-galactosamine acceptor **68** to give the disaccharide moiety **69**[56, 58] of ZPS A1 in 81% yield as a single α-isomer (Fig 18). A unique feature of this synthesis is that both the coupling partners **36** and **68** were derived from D-mannose as described earlier.

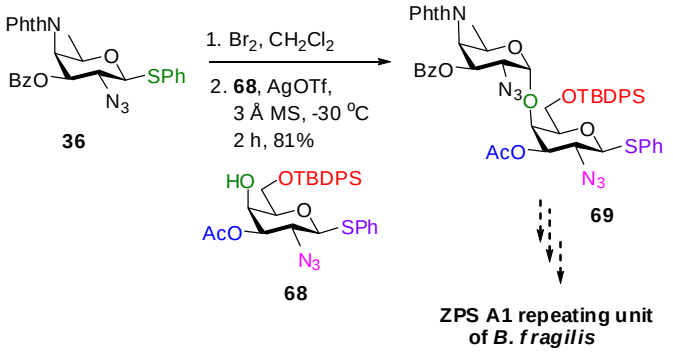

Fig. 18 Synthesis of key disaccharide of ZPS A1 of *B. fragilis*.

In 1995, Stimson *et al*.[3] isolated a glycoprotein from *N. meningitidis* and they proposed the structure of glycoprotein where a unusual trisaccharide Gal-(β 1-4)-Gal-(α 1-3)-2,4-diacetimido-2,4,6-trideoxyhexose [Gal(β 1-4)-Gal(α 1-3)-DATDH] is attached to the pili through L-serine. Since the configuration at C-4 position of the rare sugar (DATDH) was not defined, it was pertinent to synthesize both the variants of the trisaccharide. Having access to both the rare sugar building blocks (DATDG **34** and Bac **40**) through our protocol, we synthesized the L-serine linked trisaccharides **73**[56,57] and **75**[62] as shown in Fig 19. The major difficulties encountered in this synthesis are incorporation of successive α-glycosidic bonds. DATDG thioglycoside **34** was converted to its corresponding imidate, which was activated with TMSOTf and coupled with L-serine derivative **70** using THF as the participating solvent to furnish α-isomer **71**, exclusively (Fig. 19 A). However, coupling of bacillosamine derivative **40**, under the same conditions, afforded a mixture of α/β isomers (1.8:1). After trying several conditions, α-selectivity was finally achieved via an *in situ* anomerization protocol. Thus, thioglycoside **40** was converted to corresponding α-glycosyl bromide and reacted with acceptor **70** in the presence TBAI to afford α-product **74**, exclusively (Fig. 19 B). 3-*O*-Acetate in **71** and **74** was cleaved and the so formed 3-OH acceptors were individually coupled with β (1→4) digalactosyl chloride **72** using AgOTf as the promoter to give the trisaccharides **73** and **75**, respectively, in exclusive α-fashion. Global deprotection of the trisaccharides **73** and **75** afforded the final target molecules in good yields.

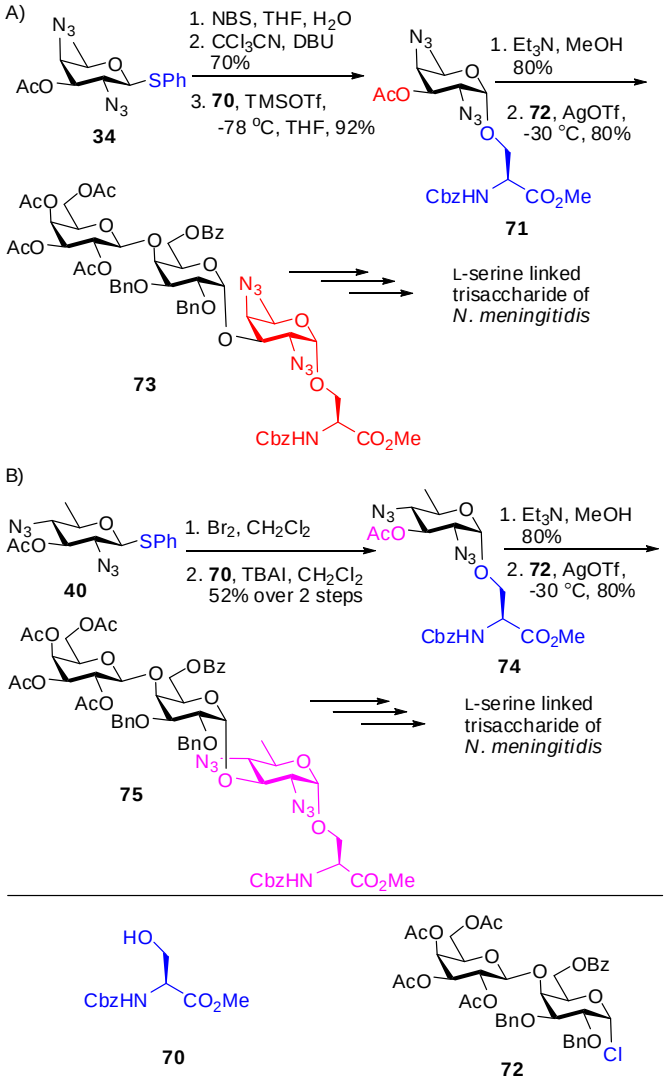

Fig. 19 Synthesis of L-serine linked trisaccharides of *N. meningitides.*

6. Outlook of the field

Although first synthesis of a rare sugar dates back to 1964, synthesis of bacterial glycans has received much attention in past few years. The recent protocols have opened up new doorways to access the orthogonally protected rare sugar building blocks in high yields. With ready availability of such monosaccharide blocks, the assembly of antigenic bacterial glycans can be carried out in an expedient manner. These advances together with the recent breakthroughs in immuno-glycobiology are expected to speed up the development of glycoconjugate vaccines and specific drugs for various infectious diseases.

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TOC abstract

The Highlight describes recent advances in the synthesis of the bacterial deoxy amino hexopyranoside building blocks and their applications to construct various biologically important bacterial O-glycans.

TOC Graphic