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Recent advances in β-L-rhamnosylation

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L-Rhamnose forms the key components of important antigenic oligo- and polysaccharides of a variety of pathogens. Obtaining 1,2-*cis* stereoselectivity in the glycosylation of L-rhamnoside is quite challenging due to the unavailability of neighboring group participation and disfavoring of the anomeric effect and stereoelectronic effect of the substituents on the C-2 axial position. Nevertheless, various methodologies have been developed exploiting diverse pathways for obtaining β-stereoselectivity in the glycosylation of L-rhamnose. This review describes the recent advances in β-L-rhamnosylation and its applications in the total synthesis of β-L-rhamnose-containing biologically important oligosaccharides.

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1. Introduction

Cell-surface carbohydrates in the form of glycoconjugates (glycolipids, glycoproteins and oligosaccharides) play important

Diksha Rai

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Suvarn S. Kulkarni

Suvarn S. Kulkarni is a Professor in the Department of Chemistry at the Indian Institute of Technology Bombay, India. After receiving his Ph.D. in Organic Chemistry from the University of Pune in 2001, he pursued his postdoctoral research in the laboratory of Professor Shang-Cheng Hung at the Academia Sinica on chemical synthesis of complex glycans via *one-pot protection of sugars. In 2005, he moved to the University of California, Davis to work with Professor Jacquelyn Gervay-Hague and was engaged in glycosyl iodide mediated one-pot synthesis of glycolipids. He returned back to India in late 2008 and held a faculty position at IACS Kolkata prior to joining the Indian Institute of Technology Bombay in 2009. His current research interests include devising newer ways for efficient chemical synthesis of complex glycoconjugates implicated in various infectious diseases for the development of vaccines, therapeutics, and diagnostics. His group actively pursues the development of one-pot methods for the synthesis of a variety of bacterial rare D/L-sugars and their stereoselective assembly into biologically important complex bacterial oligosaccharides and is also involved in the total synthesis of diverse trehalose glycolipids and oligosaccharides of mycobacterial origin* via *regioselective functionalization of trehalose.*

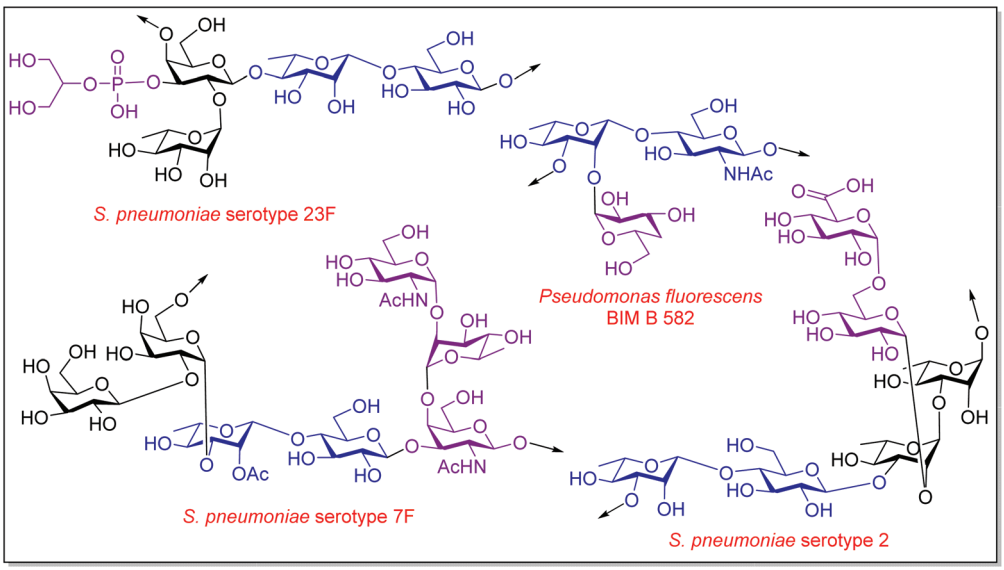


Fig. 1 Representative examples of β-L-rhamnose linked antigenic oligosaccharides.

roles in a variety of life processes such as viral and bacterial entry, cell–cell communication and immune response.[1] Over the past few years, there has been a remarkable advance in the chemical synthesis of complex glycans[2] and their application in the development of carbohydrate-based vaccines[3] and therapeutics.[4] Various naturally occurring antigenic carbohydrate polysaccharides are composed of L-rhamnose.[5] Although L-rhamnose is found to be mostly linked in an α-fashion, the β-rhamnosidic linkage is frequently encountered in glycans of pathogenic bacteria, for example, *Pseudomonas fluorescens* BIM B-582,[6] *Streptococcus pneumoniae* serotypes 23F,[7] 7F[8] and type 2[9] (Fig. 1) *Salmonella* serogroup,[10] *Shigella boydii* type 18,[11] *Vibrio cholerae*[12] and others.

In glycosylation reactions, the reactivity of sugar building blocks depends on the substituents of various hydroxyl groups and their relative orientation.[13] Although, the stereoselective formation of most of the glycosidic linkages has been worked out, the 1,2-*cis* stereoselectivity in glycosylation to obtain β-D-mannosides and to a greater extent β-rhamnoside poses a different level of challenge.[14,15] While the α-glycosylation in the case of L-rhamnose sugar can be achieved with ease due to the neighboring group participation of the C2 group, the same makes β-L-rhamnosylation difficult. In addition, the disfavoring anomeric effect and stereoelectronic effect from the C2 axial protecting group of the donor owing to its 1,2-*cis* relationship with the incoming glycosyl acceptor makes it even more challenging.[16–18] Moreover, while β-mannosylation can be achieved by the employment of a benzylidene protected D-mannosyl thioglycoside,[19] such conformational disarming is not possible in L-rhamnose due to the lack of the OH group at the C6 position. Thus, β-L-rhamnosylation is very demanding and attracts attention towards the development of new methods.

2. Early studies on β-L-rhamnosylation

Over the past four decades, carbohydrate chemists have been involved in devising novel methods for installing β-rhamnosidic linkages. The key intermediates employed in the early studies, on achieving β-selective rhamnosylation, from 1980 to 2003 are shown in Fig. 2. The early studies have been thoroughly reviewed by El Ashry in 2008.[14] A brief account is presented in this section for the sake of continuity. In 1980, Bundle and coworkers used 2,3-*O*-cyclohexylidine protection on the α-bromo-rhamnoside donor to synthesize β-L-rhamnoside products.[20] They observed good to moderate yields and selectivity after screening the donor with several model acceptors under standard Koenigs–Knorr reaction conditions. Although, good results were obtained with more reactive primary acceptors as well as L-rhamnosyl 3-OH and 4-OH acceptors, low selectivity and yields were observed in the case

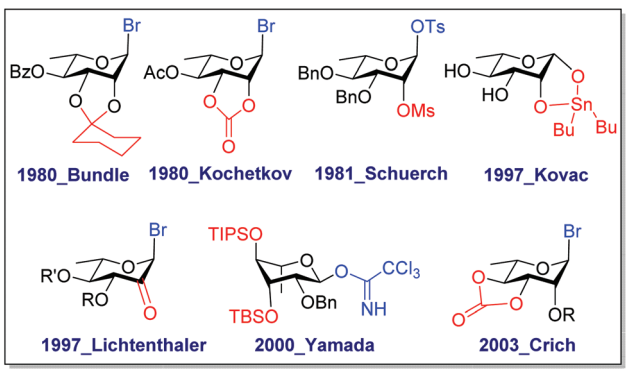


Fig. 2 Key intermediates employed in early studies on β-L-rhamnosylation.

of a less nucleophilic Glu-4-OH acceptor. Around the same time, Kochetkov and coworkers[21] employed a 2,3-*O*-carbonate protecting group on glycosyl bromide and carried out the glycosylation in the presence of silver oxide to install the desired *β*-L-rhamnosidic linkages. In 1981, Schuerch showed that the interaction of opposite dipoles of the reactive leaving group at C1 and the electron withdrawing *O*-methylsulfonyl group at the C2 position drives the system towards the formation of a *β*-L-rhamnoside product.[22]

In 1997, Kovac introduced a unique method of 1,2-*O*-*cis*-stannylene acetals to afford the 1,2-*cis* glycoside product.[23] With time, various other methods evolved, for example, the ulosyl bromide approach by Lichtenthaler for an efficient *β*-rhamnosidic linkage.[24] The glycosylation with iso-propanol under standard Koenigs–Knorr conditions and subsequent reduction of the carbonyl group at the C2 position transformed *β*-ulosyl glycoside to *β*-L-rhamnoside. In 2011, Lichtenthaler reviewed the studies on the ulosyl bromide approach to achieve *β*-D-mannosides and *β*-L-rhamnosides.[25]

In 2000, Yamada[26] showed the use of a 'super-armed' donor and subsequent ring flipping of a reactive L-rhamnose sugar moiety from $^1C_4$ to $^4C_1$ conformation. With the tuning of reaction conditions, it was observed that the *β*-L-rhamnoside product predominates over the *α*-product at lower temperature under the TIPSOTf promoter conditions with the silyl ether protected super armed donors. In 2003, Crich and coworkers expanded the 3,4-*O*-carbonate effect on *β*-L-rhamnosylation under homo- and heterogeneous glycosylation conditions compared to 2,3-*O*-carbonates which are applicable only under heterogeneous conditions (with insoluble silver salts).[27] They showed that *β*-selectivity was due to the electron withdrawing effect of the carbonate group present on the rhamnose sugar at the 3,4-*O*-position and its inability to participate in glycosylation *via* NGP.

3. Recent developments in *β*-L-rhamnosylation

In recent years, several groups have developed methods leading to *β*-L-rhamnosylation *via* direct as well as indirect routes. A schematic overview indicating the study rationale of each approach is given in Fig. 3. The indirect methods include the IAD approach *via* an allyl and naphthylmethyl tether mechanism (Fairbanks & Ito)[28–30] and hydrogen bond mediated aglycon delivery (HAD) by using a picolinyl and picoloyl protecting group (Demchenko).[33] Few direct methods for *β*-L-rhamnosylation include the Au(I) catalyzed glycosylation reaction proposed by B. Yu[39] and the boronic and borinic acid catalyzed glycosylation by Toshima and Takahashi.[42]

In this review, we discuss the recent developments in the field of *β*-L-rhamnosylation and its application to the total synthesis of synthetically challenging and biologically important oligosaccharides, starting from 2004.

3.1 Intra-molecular aglycon delivery (IAD)

In 2004, Fairbanks and coworkers explored the concept of intramolecular aglycon delivery (IAD) and observed an excellent selectivity using a C2-*O*-allyl protecting group in the L-rhamnosyl thioglycoside donor.[28] The C2-*O*-allyl donor **1** was first treated with Wilkinson's catalyst and *n*-BuLi resulting in alkene isomerization followed by treatment with NIS and glucosyl acceptor **2** to obtain the mixed acetal intermediate **3** (Scheme 1). The tethering of allyl ether with the hydroxyl group of the glucosyl acceptor was achieved in 75% yield.

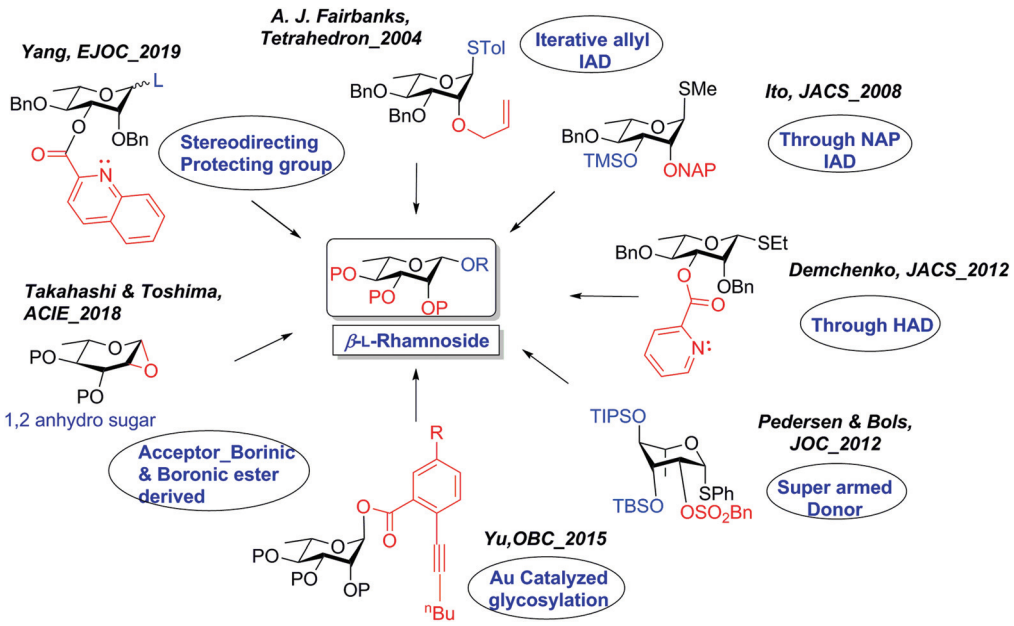
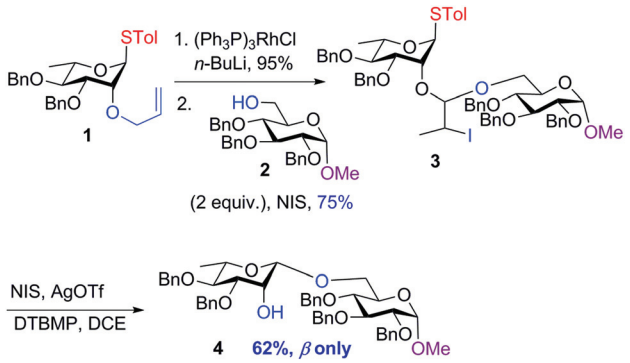


Fig. 3 Schematic outline of the development of β-L-rhamnosylation.

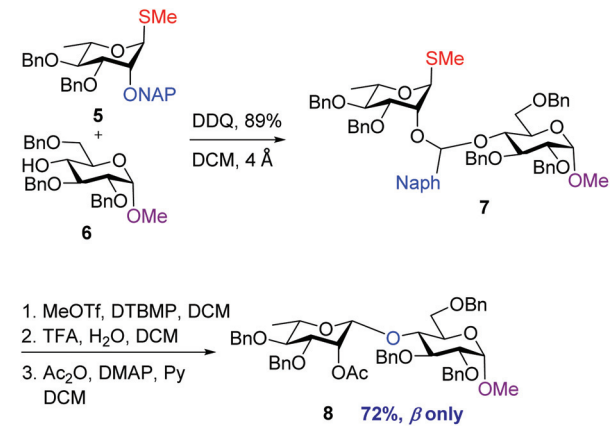


Scheme 1 β-L-Rhamnosylation using allyl mediated IAD.

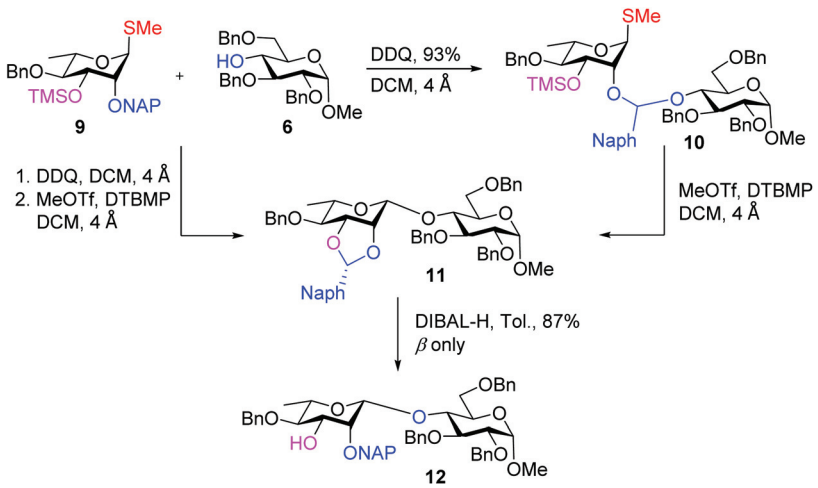
Subsequently, the resulting intermediate was treated under NIS and AgOTf reaction conditions to give β-L-rhamnosylated disaccharide **4** in 62% yield. The reaction worked well on other acceptor derivatives like Gal-6-OH, Glc-6-OH, Glc-2-OH and Man-4-OH and Man-6-OH. The methodology offered excellent selectivity but moderate overall yields. The observed stereoselectivity in IAD glycosylation reactions depends upon the steric crowding of glycosyl donors and acceptors. Thus, it was observed that in the case of sterically crowded secondary alcohol acceptors, glycosylation yields were low.

A further improvement in β-L-rhamnosylation using the IAD approach was achieved by Ito and coworkers in 2008, by employing 2-naphthyl methyl ether tether. They conducted extensive studies on C2-*O*-naphthyl methyl ether protected L-rhamnosyl donors using a variety of acceptors to form mixed acetals.[29,30] They noted that unlike allyl mediated IAD, their approach is more advantageous and rewarding in terms of high yield and excellent selectivity with primary as well as secondary acceptors. As an example, the C2-*O*-naphthyl methyl rhamnosyl donor **5** and Glu-4-OH acceptor **6** underwent oxidative coupling using DDQ to form mixed acetal derivatives **7**, which on purification gave an excellent yield of 89% (Scheme 2). The resulting acetal was further treated with methyl triflate (MeOTf) and DTBMP to afford the corresponding β-L-rhamnoside which upon acidic treatment followed by acetylation furnished disaccharide **8** in 72% yield, as a sole isomer.

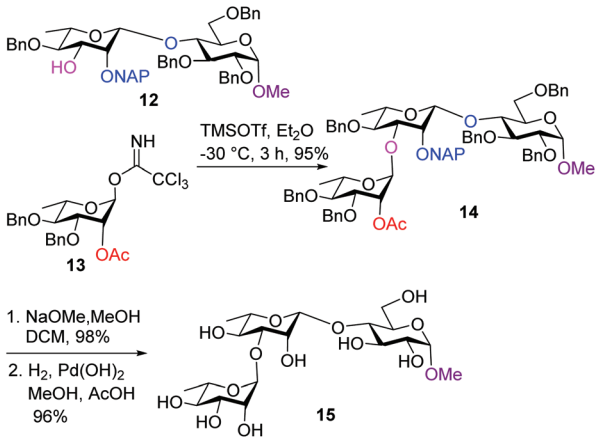
Later, the same group showed the efficacy of the naphthyl methyl ether tether IAD approach with a 3-*O*-TMS protecting group in a stepwise as well as in a one-pot manner without purification of the mixed acetal intermediate. The yield was observed to be comparable in both cases. But the advantageous side of the TMS protecting group lies in the *in situ* formation of naphthylidene acetal **11** by trapping the benzylic cation generated in the reaction medium.[31] Accordingly, 3-*O*-TMS, 2-*O*-NAP donor **9** was glycosylated with the Glu-4-OH acceptor **6** following the former glycosylation conditions (stepwise as well as one-pot) to afford compound **11** which upon reduction with DIBAL-H, provided disaccharide **12** in 87% yield (Scheme 3).



Scheme 2 β-L-Rhamnosylation facilitated by NAP mediated IAD.



Scheme 3 Straightforward β-rhamnosylation *via* NAP-mediated IAD.



Scheme 4 Synthesis of trisaccharide **15** of *S. natans*.

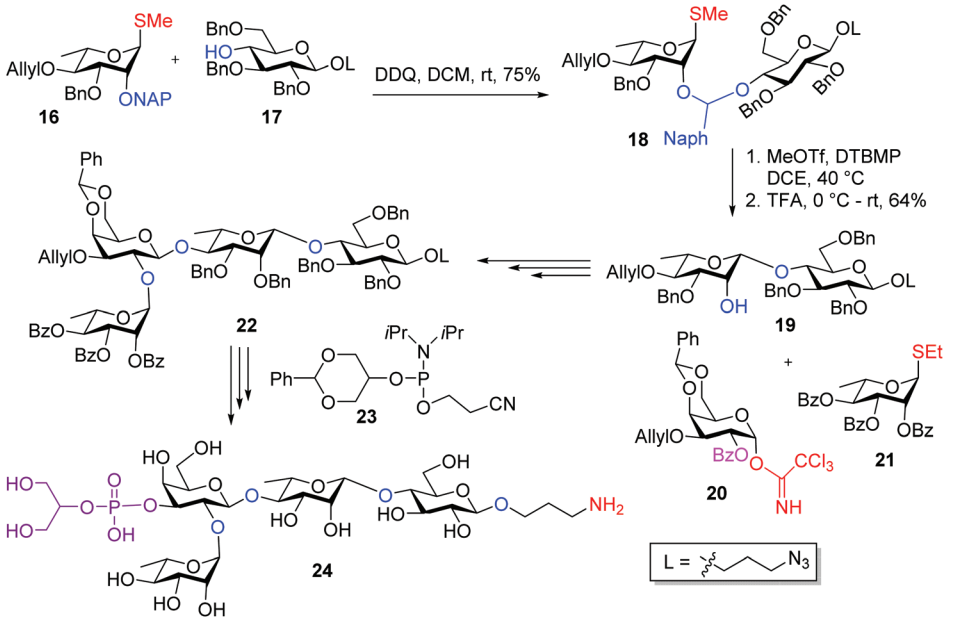
After the successful synthesis of *β*-L-rhamnoside **12**, Ito and coworkers showed the applicability of the method by the synthesis of trisaccharide **15**, which is a linear backbone of *Sphaerotilus natans* polysaccharide (Scheme 4). The glycosylation of disaccharide acceptor **12** with imidate donor **13** under TMSOTf and Et_2O conditions furnished fully protected trisaccharide **14** in an excellent yield of 95%, which upon global deprotection afforded the desired trisaccharide **15** in 94% yield.[29]

The versatility and exclusive stereoselectivity of the above-mentioned approach paved the way to the total synthesis of many complex oligosaccharides. For instance, Guo *et al.* successfully synthesized a tetrasaccharide repeating unit of a capsular polysaccharide of *Streptococcus pneumoniae* serotype 23F by a linear assembly of glycosyl donors and acceptors. The challenging *β*-L-rhamnosidic linkage in the tetrasaccharide moiety was achieved by applying Ito's methodology of NAP-ether mediated IAD approach (Scheme 5). The other linkages were easily installed with the help of neighboring group participation at the C2 position.[32]

Thus, C2-*O*-naphthyl methyl donor **16** and Glu-4-OH acceptor **17** were first treated with DDQ to provide mixed acetal **18** in 75% yield as a 10 : 1 diastereomeric mixture. The desired disaccharide was then formed by using Ito's standard glycosylation reaction conditions, which on TFA catalyzed denaphthylation afforded disaccharide **19** in a stereoselective manner in 67% yield over two steps (Scheme 5). Unlike other linkages, the formation of a *β*-L-rhamnosidic linkage has to be ascertained from its ^{13}C–^{1}H coupling constant of anomeric carbon in ^{13}C NMR and NOESY correlations between H-1 and H-5. Accordingly, the *β*-linkage of disaccharide **19** was confirmed by a coupling constant value J_{C1-H1} 162 Hz. Disaccharide **19** upon protecting group moderation and sequential assembly of monosaccharide units **20** and **21** fashioned tetrasaccharide **22**. The installation of a phosphoglycerol moiety by the phosphoramidite method on **22** and global deprotection afforded target tetrasaccharide repeating unit **24** having a free amino propyl linker at the reducing end to facilitate the conjugation for immunological studies.

3.2 Hydrogen bond-mediated aglycon delivery (HAD)

The IAD approach for the successful synthesis of a *β*-L-rhamnosidic linkage was soon followed by Demchenko's hydrogen bond-mediated aglycon delivery where picolinyl (Pic) and picoloyl (Pico) groups are installed on hydroxyls at different positions of glycosyl donors.[33] The 1,2-*cis* selectivity in the rhamnosyl moiety was achieved by the use of a picoloyl protecting group at the 3-O position to facilitate the *β*-facial attack during



Scheme 5 Synthesis of the repeating unit **24** of *Streptococcus pneumoniae* serotype 23F.

the course of glycosylation *via* the H-bond tether mechanism between the glycosyl donor and acceptor. Demchenko and coworkers screened a variety of donors and acceptors, such as *β*-rhamnosides, *β*-mannosides, and *α*-glucosides, for establishing their methodology. In the case of rhamnosyl sugar derivatives, the picoloyl group at the 3-O position facilitated the hydrogen bonding between C-3-*O*-picoloyl (N of picoloyl group) and H of the acceptor (Fig. 4). When the donor is activated by a Lewis acid to form an oxocarbenium ion intermediate, the C-3-*O*-picoloyl protecting group coordinates with H of the acceptor from the same side (*β*-side) of the picoloyl group, thereby enforcing the acceptor to attack from the *β*-facial side to give 1,2-*cis* stereoselectivity.

Thus, the glycosylation of 3-*O*-picoloyl L-rhamnosyl donor **25a** and Glu-6-OH acceptor **2** under DMTST activation conditions could successfully produce the difficult *β*-linked rhamnoside **26** ($\alpha/\beta > 1:25$) in 93% yield (Scheme 6).[33]

There are several examples of important antigenic oligosaccharides present in nature having *β*-L-rhamnosidic linkages, which are synthetically challenging. Recently, few groups have applied the picoloyl group for HAD mediated *β*-rhamnosylation to synthesize biologically important target molecules. Notably, Seeberger and coworkers completed the total synthesis of a complex hexasaccharide repeating unit of *Streptococcus pneumoniae* type 2.[34] They used C-3-*O*-picoloyl rhamnosyl donor **25b** with 4-OH glucosyl acceptor **27** under NIS and TfOH activation conditions at 0 °C to obtain *β*-linked disaccharide **28** (α/β 1 : 3) in 53% yield (Scheme 7). Although Pico mediated glycosylation did not give good selectivity and yield, the desired disaccharide could be separated by column chromatography. With this crucial *β*-disaccharide fragment **28**, they assembled disaccharide units **28**, **29** and **30** *via* a [2 + 2 + 2] approach to obtain the fully protected hexasaccharide moiety, which upon further deprotection afforded the desired target molecule **31**.

Kulkarni and coworkers in 2018 demonstrated the utility of the HAD approach by using the C-3-*O*-picoloyl group in the L-rhamnosyl donor for the total synthesis of the trisaccharide repeating unit of *Pseudomonas fluorescens* BIM B-582.[35] For that, they glycosylated L-rhamnosyl donor **32** with 4-OH glucosamine acceptor **33** under NIS/TfOH promotion conditions to obtain disaccharide **34** (α/β = 1 : 8.4) in 80% yield (Scheme 8). With the help of silica gel column purification, the separated single *β*-isomer of disaccharide **34** was glycosylated with 4-deoxy D-xylo-hexose sugar **35** to furnish a fully protected trisaccharide, which on global deprotection provided a target trisaccharide molecule **36**.

On similar lines, Misra and coworkers in 2019 accomplished the total synthesis of the pentasaccharide repeating unit of *O*-antigenic polysaccharide *Shigella boydii* type 18 in a one-pot manner.[36] The group has also shown sequential glycosylation by an assembly of monosaccharide sugar units **37–40** to obtain fully protected tetrasaccharide. Then, they performed the challenging glycosylation of C3-picoloyl protected rhamnosyl donor **25b** *via* the HAD-mediated approach. Here, tetrasaccharide acceptor **41** was coupled with L-rhamnosyl donor **25b** under NIS/$HClO_4$-SiO_2 activation conditions to give the desired pentasaccharide **42** in 74% yield with full control of *β*-stereoselectivity, which upon global deprotection furnished the target molecule **43** in 62% overall yield (Scheme 9).

As an extension of Demchenko's picoloyl mediated HAD approach for *β*-L-rhamnosylation, recently in 2019, Yang and coworkers experimented with the stereo-directing effect of an ester group at the C-3 position of an L-rhamnosyl donor. In sharp contrast to the Pico group, the strategy applied on L-rhamnosyl moieties having a C3-Lev or aryl carbonyl group conferred high *α*-selectivity in excellent yields. On the other hand, the same C3 stereo-directing effect with a substituted picoloyl protecting group showed a powerful impact on *β*-L-rhamnosylation.[37]

In support of their proposed strategy, glycosylation was performed with several donors **44a–d** and reactive primary acceptor **45** under NIS/TfOH conditions to furnish disaccharide **46** (Scheme 10), from which donor **44a** emerged to be more suitable among the others to obtain the finest *β*-selectivity (α/β = 1 : 14) and good yield. Therefore 4-nitro picoloyl substituted

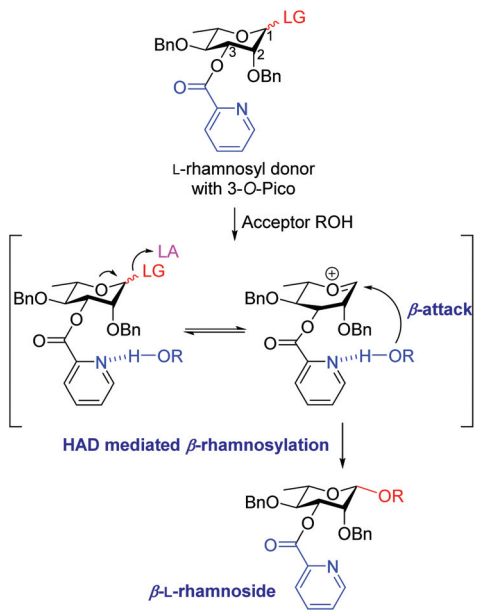
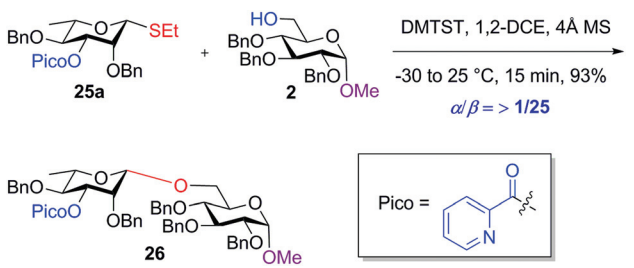
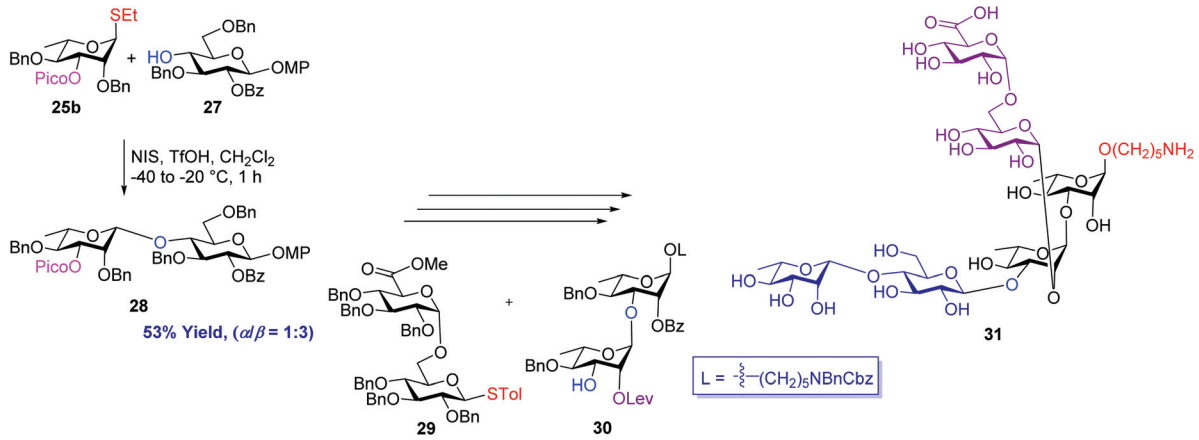


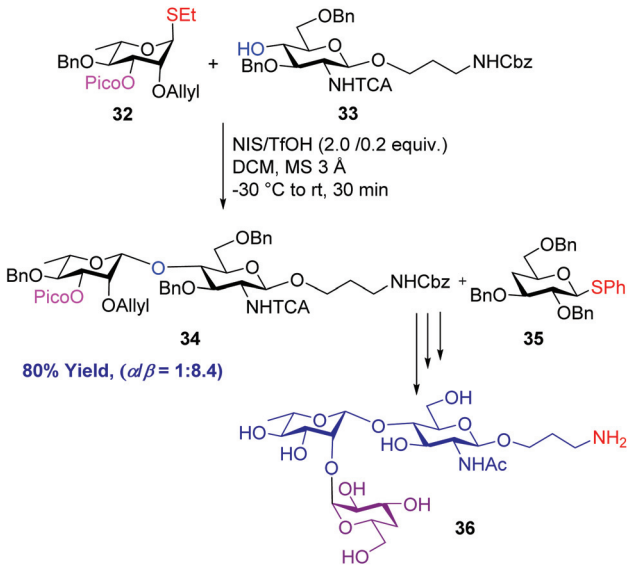
Fig. 4 Picoloyl protecting group effect on *β*-L-rhamnosylation.



Scheme 6 Picoloyl HAD-mediated β-L-rhamnosylation.



Scheme 7 Synthesis of trisaccharide repeating unit **31** of *Streptococcus pneumoniae* type 2.



Scheme 8 Synthesis of trisaccharide repeating unit **36** of *Pseudomonas fluorescens* BIM B-582.

rhamnosyl donor **44a** was taken as a standard to perform glycosylation with various primary and secondary acceptors (Table 1). The selectivity was found to be excellent in the case of reactive primary and secondary acceptors like **47b**, **47d** and **47f**, whereas low selectivity was observed for acceptors of poor nucleophilicity. With these results, the group showed the application of their methodology to the synthesis of trisaccharide **15** corresponding to the substructure of *S. natans* polysaccharide (Scheme 11). Accordingly, they performed glycosylation of 3-OBz protected rhamnosyl donor **50** with disaccharide acceptor **49** to generate a fully protected trisaccharide which upon global deprotection gave target molecule **15**.

Recently in 2020, Mandal and coworkers explored the effect of the picoloyl protecting group at the C2- and C3-position of the rhamnosyl donor in *N*-benzoyl glycine and Schreiner's thiourea co-catalyzed glycosylation reaction.[38] They examined several reactions with 2-*O*-/3-*O*-picoloyl protected rhamnosyl donors with different kinds of model acceptors under mild reaction conditions. The best selectivity was found with 2-*O*-picoloyl protected imidate donor **51** giving **53** in 82% yield (α/β = 1 : 20). At the same time, 3-*O*-picoloyl protected imidate donor **52** under identical reaction conditions delivered **54** in modest (α/β = 1 : 2.5) selectivity (Scheme 12).

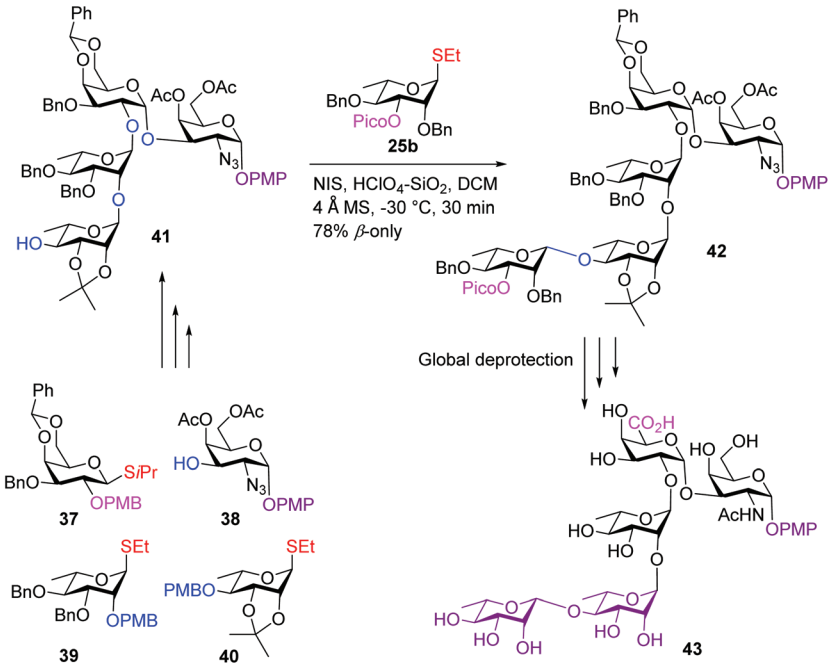
3.3 Gold catalyzed glycosylation

In 2015, Yu and coworkers explored the Au(I) catalyzed S_N2 type glycosylation reaction using a 2-alkynyl benzoate α-rhamnosyl donor. For this, they performed a number of glycosylation reactions with various substituted donors and acceptors. Through these studies, the electron withdrawing substitution at the O4 position and the 4-nitro group on the aryl ring of the donor proved to be a better choice for 1,2-*cis* selectivity with primary and secondary acceptors.[39] Donor **55** was glycosylated with acceptors **45** and **59** under $Ph_3PAuCl/AgBAr_4^F$ catalyzed reaction conditions to provide disaccharides **56** and **60** respectively in ~1 : 14 (α/β) selectivity with an excellent yield of 95% (Scheme 13). For secondary acceptors, the best selectivity was obtained in the case of 4-nitro substituted donor **55a** with acceptor **57** which gave **58** with 1 : 8 (α/β) selectivity in 71% yield.

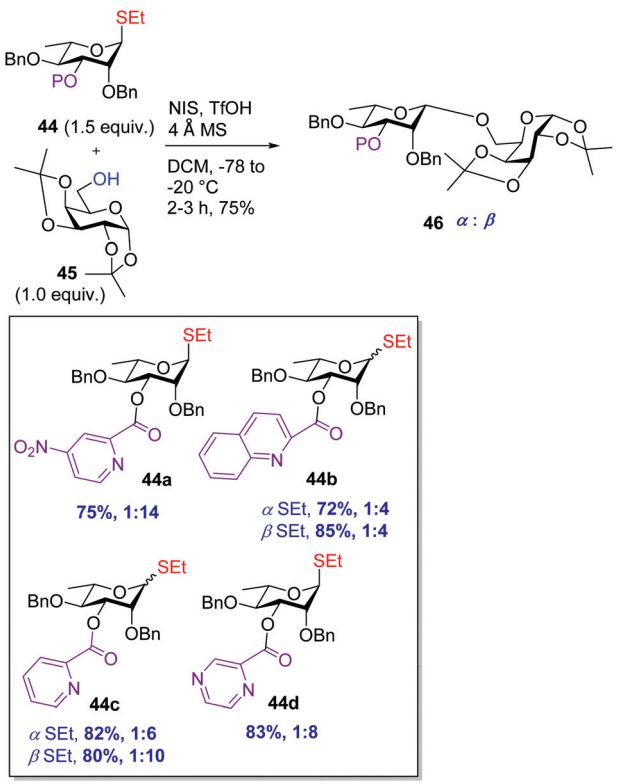
Furthermore, they showed the one-pot anomerization of donor **55** to perform the aforementioned glycosylation reaction *via* an S_N2 manner. Accordingly β-rhamnoside donor **55b** was anomerized to α-rhamnosyl donor **55a**, which upon glycosylation with cholesterol acceptor **61** delivered disaccharide molecule **62** with 1 : 10.5 (α/β) selectivity (Scheme 14).

3.4 Other effects

(a) Protecting group. Bols and Pedersen studied the effect of changing the protecting groups of L-rhamnosyl sugars on 1,2-*cis* selectivity. The group introduced the idea of 'super-armed' donor for β-selectivity in L-rhamnosylation. Earlier, these types of protecting groups were applied by Yamada and coworkers *via* the S_N2 glycosylation mechanism to obtain β-

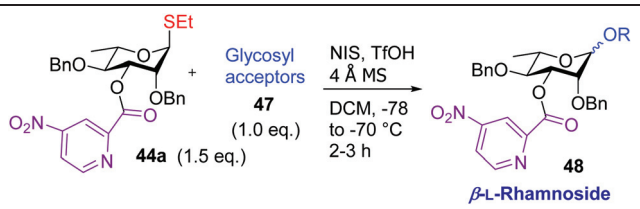


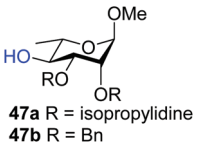
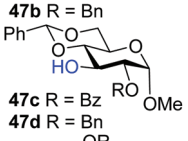
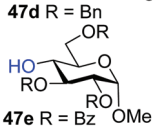
Scheme 9 Synthesis of a pentasaccharide repeating unit **43** of *O*-antigen *Shigella boydii* type 18.



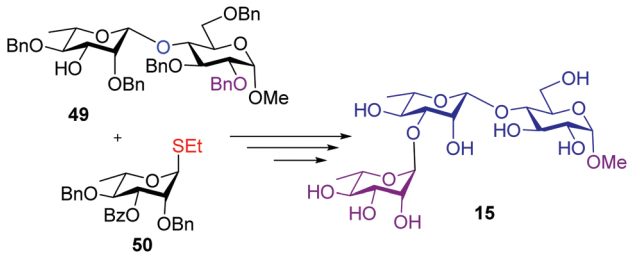
Scheme 10 β-L-Rhamnosylation with several donors **44a–d** using a C3 stereo-directing effect.

Table 1 Stereo-directing β-L-rhamnosylation with various acceptors **47a–f**

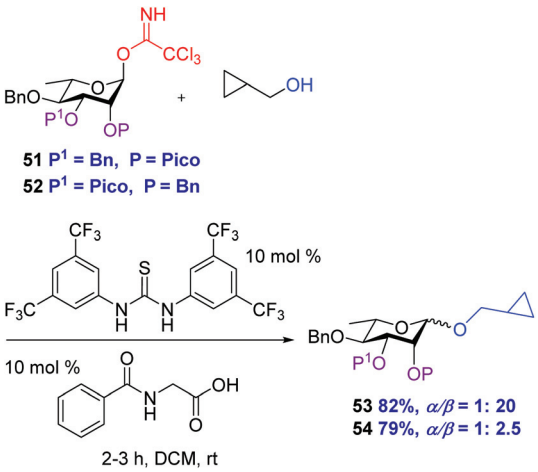


Entry	Acceptor	Yield (%)	α/β
1	 **47a** R = isopropylidine **47b** R = Bn	**48a** 87% **48b** 83%	1 : 1.1 1 : 15
2	 **47c** R = Bz **47d** R = Bn	**48c** 91% **48d** 91%	1 : 1 1 : 15
3	 **47e** R = Bz **47f** R = Bn	**48e** 88% **48f** 88%	1 : 2 1 : 15

rhamnosides in good to moderate yields and selectivities, especially in the case of less nucleophilic secondary acceptors.[26] Bols and coworkers performed several model glycosylation reactions with reactive aliphatic alcohols and observed that the selectivity was poor towards β-L-rhamnosylation.[40] However, on tuning protecting groups and reaction conditions, they proposed that electron withdrawing non-participating groups at the C2 position such as the benzyl sulfonyl moiety

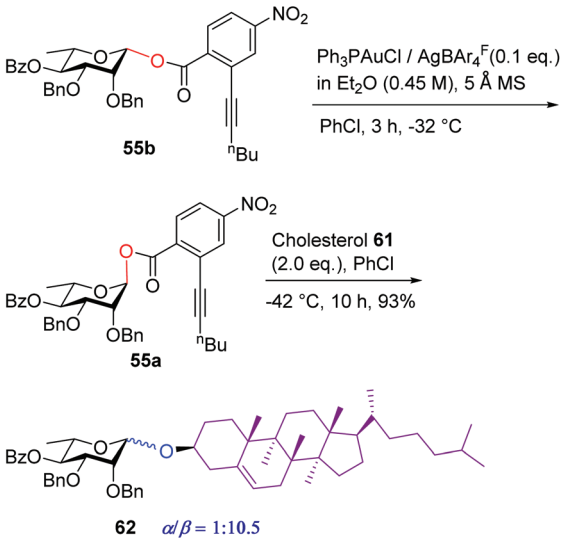


Scheme 11 Synthesis of trisaccharide **15** of *S. natans*.



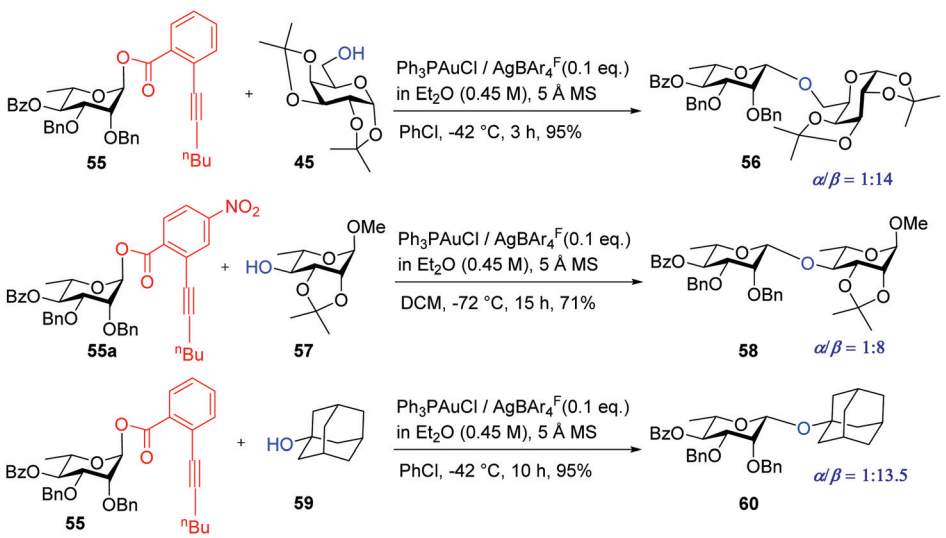
Scheme 12 *N*-Benzoyl glycine/Schreiner thiourea catalyzed *β*-L-rhamnosylation of 2*O*-Pico/3*O*-Pico donor with a model acceptor.

permit the selectivity towards *β*-L-rhamnosides at a lower temperature (−78 °C). As shown in Table 2, donors **63a–d** when glycosylated with a cyclohexanol acceptor under NIS/TfOH conditions at −78 °C allowed limited selectivity and moderate yield.



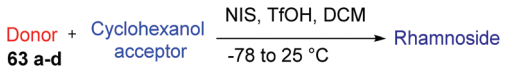
Scheme 14 One-pot anomerization and β-L-rhamnosylation.

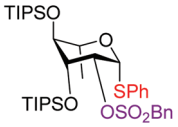
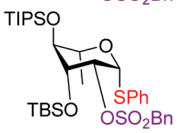
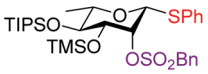
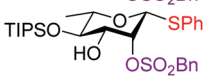
(b) Solvent. In addition, recently Pedersen and coworkers reported a reversal of the solvent participation effect during glycosylation. They observed a reversed effect where ethereal solvents like Et_2O and THF worked in favor of *β*-selectivity whereas CH_3CN and EtCN solvents led to the predominant formation of an *α*-isomer.[41] They screened several reactions by varying the solvent and temperature and found the best *β*-selectivity in L-rhamnoside in DCM solvent and with thiophene additive at very low temperature (−78 °C). The glycosylation was done with donor **64** and acceptor **65**, under given reaction conditions (Scheme 15) to obtain *β*-L-rhamnoside **66** in 92% and 1 : 3.3 (*α*/*β*) selectivity. However, earlier Crich and coworkers have observed enhanced *β*-selectivity in L-rhamnosylation while using 5% acetonitrile in a dichloromethane solvent system.[15c]

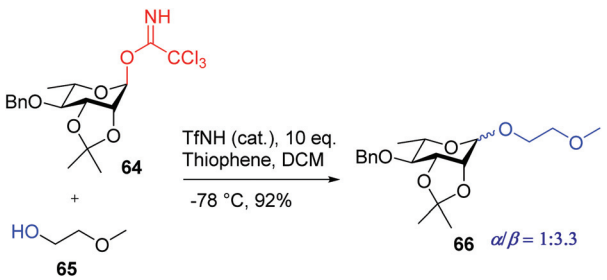


Scheme 13 *β*-L-Rhamnosylation using *O*-hexynylbenzoate donors with various model acceptors.

Table 2 β-L-Rhamnosylation using super-armed donors



Entry	Donor	Yield	α/β
1		62%	1 : 1
2		83%	1 : 1.5
3		62%	1 : 2
4		43%	1 : 1.5



Scheme 15 Solvent and additive effect on stereo-selective glycosylation.

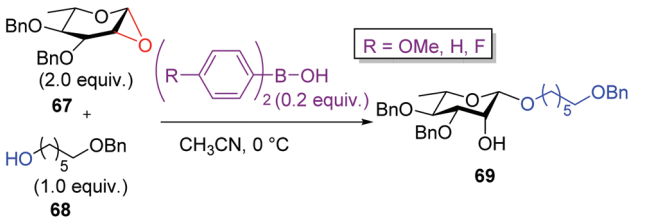
3.5 Organoboron catalyzed glycosylation

In 2018, the Takahashi and Toshima group put forward an excellent strategy for β-L-rhamnosylation using organo-boron catalyzed S_Ni-type glycosylation under very mild conditions.[42] The group employed 1,2-anhydro sugar **67** and performed the borinic acid catalyzed stereospecific glycosylation reaction with a simple alcohol. On screening with various substituted boronic acids they observed that the best is the one with fluoro substitution which gave a β-product in 94% yield within 1 h (Table 3).

The mechanistic studies provided support to their proposed strategy for obtaining 1,2-*cis* selectivity. The borinic/boronic ester derived glycosyl acceptors would coordinate with 1,2-anhydro sugar which would deliver β-L-rhamnoside *via* the S_Ni type mechanism (Fig. 5). So, finally with this mechanistic understanding, they moved forward to show further glycosylation of 1,2-anhydro sugar with primary and secondary glycosyl acceptors (Scheme 16).

The 1,2-anhydro sugar derivative **67** was glycosylated under borinic acid catalyzed glycosylation reaction conditions with

Table 3 Borinic acid catalyzed glycosylation reaction



Entry	Borinic acid	Time (h)	Yield (%)	α/β
1	R = OMe	24	82	β
2	R = H	24	87	β
3	R = F	24	92	β
4	R = F	1	94	β

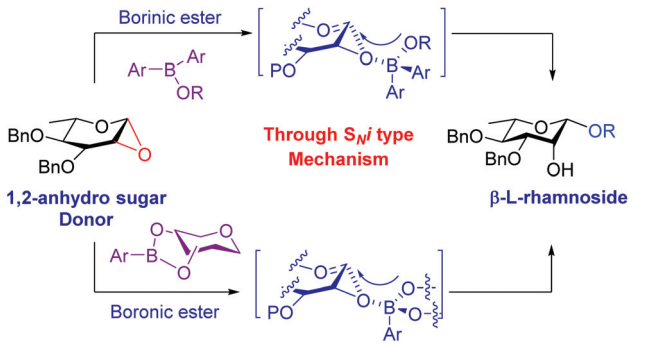
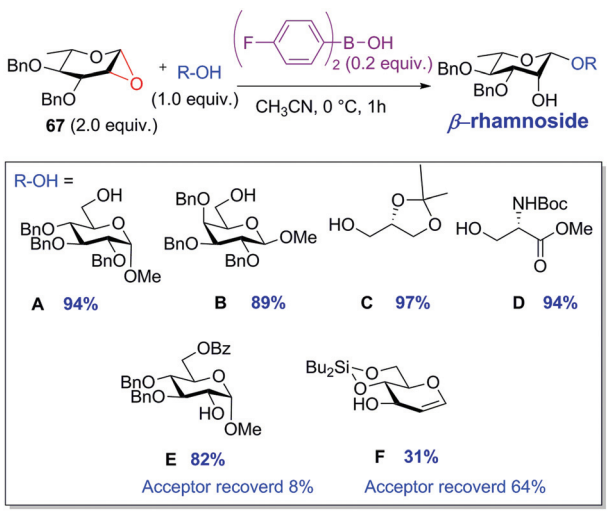
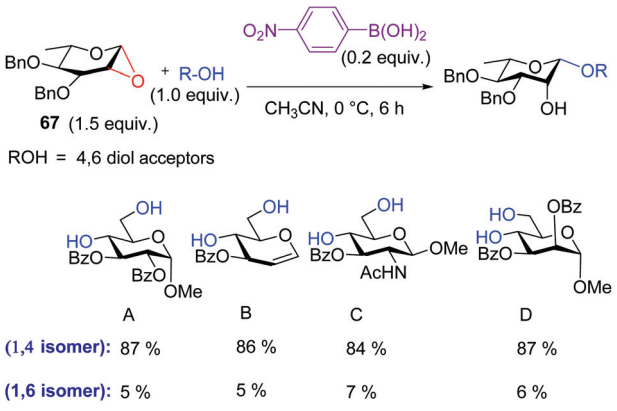


Fig. 5 Mechanistic view on borinic/boronic acid catalyzed β-L-rhamnosylation.



Scheme 16 Borinic acid catalyzed glycosylation with various acceptors.

various acceptors **A** to **F** (Scheme 16) and they observed that yield and selectivity were excellent in the case of primary acceptors but secondary acceptors were low yielding resulting

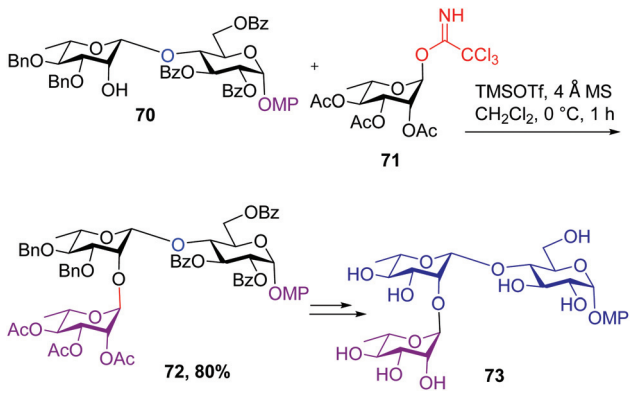


Scheme 17 Synthesis of β-L-rhamnoside with a 4,6-diol acceptor.

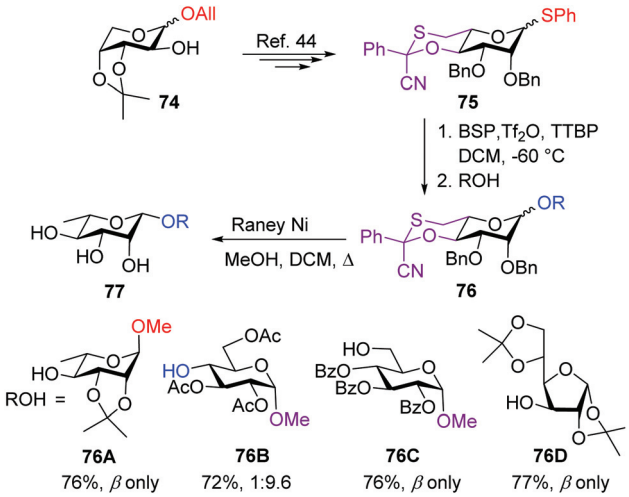
in their recovery during the course of glycosylation reaction. For example, with acceptors **E** and **F**, glycosylation yields were 82% and 31% with the recovered acceptor being 8% and 64%, respectively.

To overcome the shortcomings of this strategy, the authors further tried glycosylation with stoichiometric amounts of boronic acid derived acceptors but with no significant improvement. Later, they performed the glycosylation of 1,2-anhydro sugar **67** with 4,6-diol acceptor derivatives **A–D** (Scheme 17) and surprisingly they found the β-1-4-linked rhamnosides as a major product and the β-1-6-isomer as the minor one (Scheme 17). To probe this unexpected result, the group conducted extensive studies on the above observed regioselectivity *via* the ^{13}C kinetic isotope effect (KIE) and DFT calculations. It was concluded that in the course of glycosylation, the β-1-4 transition state is more exposed and as a result it is kinetically more favored than the corresponding β-1-6 transition state.[42]

Finally, to showcase the applicability of the proposed mechanism, the group carried out the total synthesis of trisaccharide repeating units of important pathogen *S. pneumoniae*.[43] For this, the β-linked disaccharide acceptor **70** was coupled with imidate donor **71** under TMSOTf promotion conditions at 0 °C to furnish fully protected trisaccharide **72** in 80% yield which upon global deprotection provided target molecule **73** (Scheme 18).



Scheme 18 Synthesis of a trisaccharide repeating unit of *S. pneumoniae* serotypes 7B, 7C and 7D.



Scheme 19 Synthesis of β-L-rhamnoside from β-L-mannoside.

3.6 From β-L-mannose to β-L-rhamnoside

In 2009, Crich and Li showed the synthesis of β-L-rhamnoside from β-L-mannoside.[44] This was successfully achieved by the coupling of 4-*O*-6-*S*-cyanobenzylidine protected 6-thiomannopyranosyl donor **75** to the corresponding acceptors **A–D** under BSP/triflic anhydride reaction conditions at −60 °C, facilitating the formation of a β-L-mannoside **76** product, which underwent RANEY® Ni catalyzed reduction to give β-L-rhamnoside **77** (Scheme 19). Substituted L-mannoside donor **75** in turn was synthesized from L-arabinose **74** *via* a multi-step transformation.[44]

4. Summary and outlook

The installation of a β-rhamnosyl linkage has been one of the most challenging problems in oligosaccharide synthesis. In this review, we have outlined the entire spectrum of the development of methodologies for β-L-rhamnosylation over the past 15 years, starting from IAD and HAD approaches, S_N2 type glycosylations, and to the most recent advances using organocatalyzed S_Ni-type glycosylation. Each of these methods have their own advantages and disadvantages. For example, Ito's NAP mediated IAD procedure allows facile installation of β-L-rhamnosidic linkages in high selectivity but requires the use of hazardous MeOTf. Likewise the use of a 3-*O*-Pico group bearing donors gives easy access to β-L-rhamnosides and although the selectivity is not exclusive, it was observed that the isomers can be separated by column chromatography. Similarly S_N2 glycosylations using α-alkynyl benzoates and borinic acid mediated S_Ni glycosylations are promising approaches which can be further tuned for excellent selectivity and yields. These novel methods have enabled the total syn-

thesis of a variety of biologically important and synthetically challenging oligosaccharides. The limitations and drawbacks of the proposed methods especially in the case of less nucleophilic secondary acceptors open up avenues for continued study in β-L-rhamnosylation.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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