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Challenges in the stereocontrolled syntheses of β-rhamnosides

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1. Introduction

The most fundamental process in glycoscience is the development of stereocontrolled and efficient methodologies for forming glycosidic bonds.[1–7] This is a consequence of the structural and functional diversities of glycoconjugates in nature. Protein- and lipid-bound saccharides play essential roles in many molecular processes impacting eukaryotic biology and disease.[8] Carbohydrates have also shown a tendency to elicit T-independent immune responses, and the pneumococcal capsular polysaccharide-protein conjugate vaccines containing a rhamnoside moiety are being developed to provide better anamnestic responses and offer better protection to infants.[9] Consequently, studies of the chemistry and biology of carbohydrates and their conjugates[9,10] are growing from day to day. The importance of the β-rhamnosidic linkages stems from the wide distribution of rhamnosides in nature as a component in the repeating unit of antigenic bacterial polysaccharides, oxopolysaccharides, and lipopolysaccharides;[10–20] the most abundant[11–29] L-enantiomers and particularly the β-L-rhamnopyranosyl moieties play important roles in the propagation of disease states,[11–13] in addition to their frequent occurrence in natural products.[30–39] The synthesis of the β-rhamnosides is problematic, as in the case of β-mannosides. These aspects have attracted our attention and have prompted us to review the methods of synthesis and of assigning the configuration of the β-rhamnosides, particularly the stereocontrolled procedures, which can bypass the problem of their formation.

2. 1,2-*cis*- and 1,2-*trans*-Rhamnoside

In general, the predominant pyranose conformation of L- or D-rhamnose is the chair conformation with more equatorial substituents. Thus, the $^1C_4$ conformations of L-rhamnose and its glycosides are the most predominant over the $^4C_1$ conformations. This can be attributed to the presence of one axial hydroxyl group in the $^1C_4$ conformations, whereas the $^4C_1$ conformations have two axial hydroxyl groups. The reverse situation holds for D-rhamnose, where the $^4C_1$ conformation is the more predominant.

The majority of rhamnose derivatives found in nature exist as glycoconjugates in which the rhamnose is joined with the aglycone via 1,2-*cis* (β) or 1,2-*trans* (α) glycosidic linkages. Such linkages would generate a more axial substituent at the anomeric center, as in the α-L-rhamnosides. However, sometimes the chair conformation with more axial substituents, which is known as an axial-rich conformation, can result (Fig. 1). This is known as conformational flip, which can be due to various factors such as the facilitation of attraction between a positive charge on the aglycone part and the lone pair of electrons on the ring oxygen, the repulsion of 1,2-*trans*-disilyloxy groups when their bulkiness is sufficient to induce flipping (see Scheme 14, and Ref. 67), and the preference of a C-5 aliphatic substituent to be in an equatorial position.[40]

3. Assignment of configuration at the anomeric center

The difficulties of forming a 1,2-*cis* (β) linkage in the O-rhamnosylation reactions are well known and the rhamnosyl donor

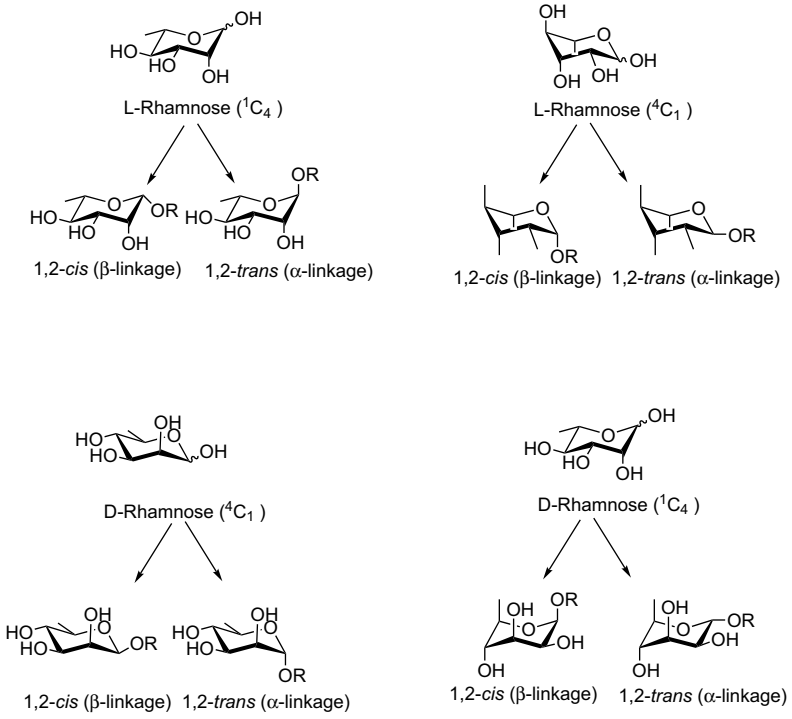


Figure 1.

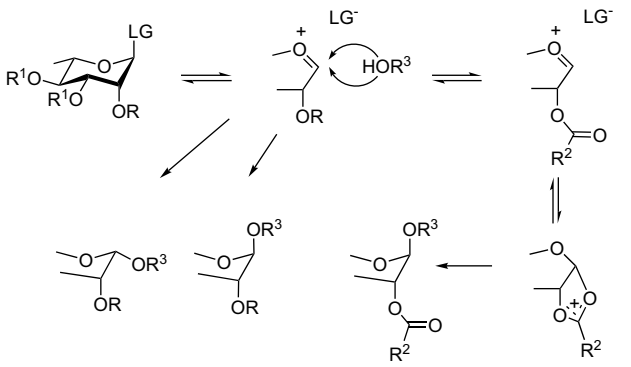


Figure 2.

shows a high selectivity.[41] Steric hindrance by the axial 2-O substituent and the stereoelectronic effect in both L- and D-rhamnose cause this selectivity. Figure 2 shows the trends of the rhamnosyl donor toward glycosylation. A positive charge will be created upon exit of the anomeric leaving group (LG) whereby an ion pair could be formed and, based on its tightness, the attack will be from different sites. On the other hand, when the substituent on 2-O is an acyl group, a neighboring-group participation could be formed whereby the attack of the alcohol would be from the α-site.

The assignment of configuration at the anomeric center of β- and α-rhamnoside has been mostly based on the value of the $^1J_{CH}$ coupling at the anomeric position.[42] The β-rhamnosides have values for such coupling in the range 152.3–159.8 Hz, whereas the α-rhamnosides have $^1J_{CH}$ values in the range 167.2–172.3 Hz. On the other hand, the $^3J_{H1,H2}$ coupling constants are not usually suitable for use, due to their close similarity (3 and <1 or 0 Hz, respectively) for the β- and α-rhamnoside.[43] The ^{1}H NMR assignments of the β- and α-rhamnopyranoside suggested that both possess the $^1C_4$ conformation, because their H-1 and H-2 coupling constants ruled out an axial–axial relationship that should exist in the respective $^4C_1$ conformation. In additions their H-4, H-5 coupling constant demonstrated an axial–axial coupling of the $^1C_4$ conformation (Fig. 2).

The mass spectra of methyl triacetyl-α-L-rhamnoside (i) and its β-anomer (ii) differed only in peak intensities and showed characteristic peaks at *m*/*z* 303 (M−1), 273 (M−OMe), and 244 (M−AcOH). For the α-anomer i, the peak at *m*/*z* 273 was found to be stronger than that for ii, and this was attributed to the sterically unfavorable axial methoxy group at C-1, which facilitated its elimination.[44]

4. Possible retrosynthetic approaches

The different strategies for elaborating the β-rhamnosidic linkage are collected in Figure 3 (for the L-series) and Figure 4 (for the D-series), which show in a retrosynthetic manner the different donors B–H and J,K required for generating this linkage to give the β-L-rhamnopyranoside A or the β-D-rhamnopyranoside I, respectively. The 2-O position in an L-rhamnosyl donor will have a tuning effect on the direction of rhamnosylation by its attachment to a non-participating group P, which could be benzyl, alkylidene or carbonate, as presented in B1–B4. The sulfonate group as in C and the electron-withdrawing group as in D were also precursors. The anomeric oxygen may be masked in a β-oriented manner to be an alkylating agent as in E. Reduction of the β-ulosyl bromide and inversion of the α-rhamnosidic linkage as well as an intramolecular glycosidation method via different pre-organized linkers as in F–H, respectively, were also used (Fig. 3).

The β-D-rhamnosidic (6-deoxy-β-D-mannoside) linkages were reported via modification of β-D-mannosides by deoxygenation and

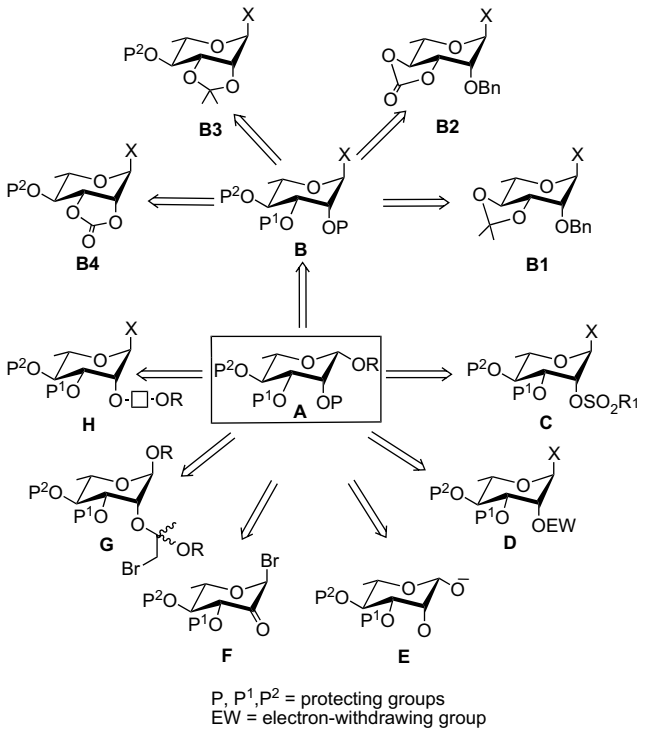


Figure 3.

reductive cleavage of their 4,6-acetals, as represented by J and K, respectively (Fig. 4). The different strategies for the syntheses of β-D-mannosides were recently reviewed.[1]

5. Syntheses of β-rhamnosides

One of the most important challenges in carbohydrate chemistry is the formation of 1,2-*cis* glycosides in the mannosyl and rhamnosyl series.[1–7] This can be viewed as a problem of the twins, mannose and rhamnose, in that they have a cis relation at the glycosidic bond and the functional group at C-2, but they are different at C-6. Rhamnose has a 6-deoxy function, which prohibits its disarming,[6] but mannose has a 6-OH that can be disarmed. Moreover, such a deoxy function influences the separation of the ion pair, which could be formed during the glycoside bond formation, thus reflecting its effect on the rhamnosylation step. Conformational and solvent effects in addition to activation of the anomeric center of the donor play an important role on the stereochemical outcome from the glycosidation reactions. The synthetic approaches for forming the linkage in the rhamnose series can be divided into five methods, within which the intermolecular methods can be subdivided into nine methods.

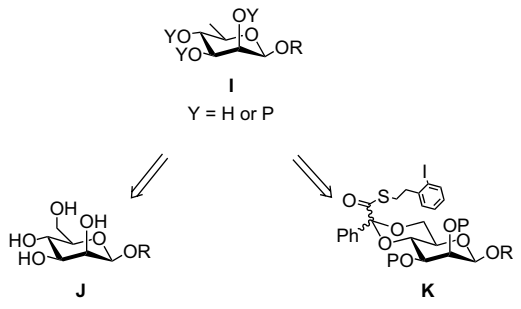
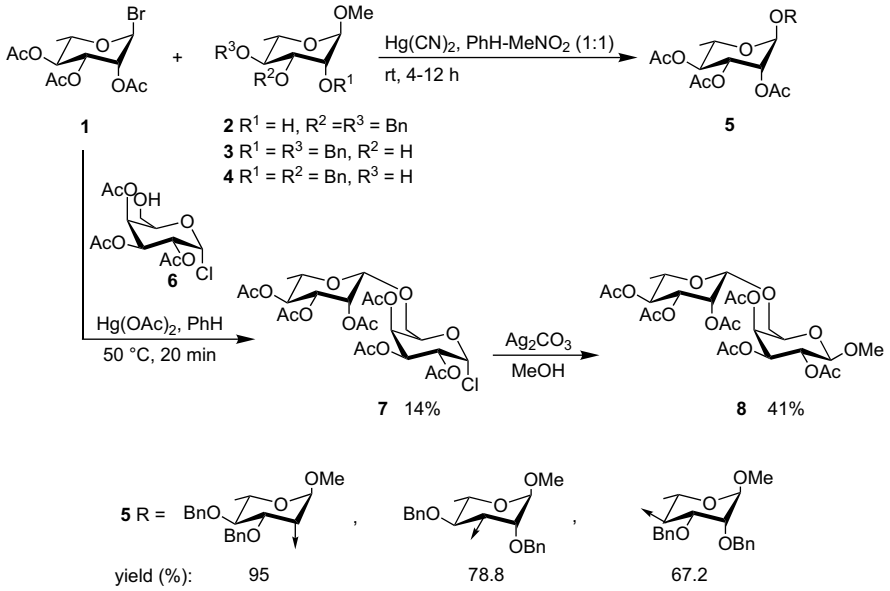


Figure 4.



Scheme 1.

5.1. Intermolecular glycosidation methods

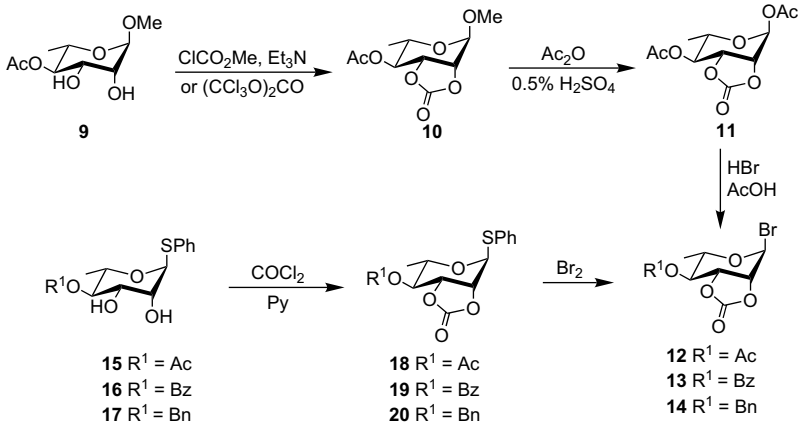
5.1.1. Role of participating group on O-2

Participation of the 2-acetyloxy group in a glycosyl donor, during the glycosyl bond formation, is a well-known phenomenon and leads usually to the 1,2-*trans* glycosides, the α-products in rhamnosides (Fig. 2). Thus, when the glycoside synthesis is supported by neighboring group participation, the α-glycosidic bond has been selectively obtained as a result of trans opening of the formed acetoxonium ion ring. Consequently, the method has been extensively used for the syntheses of α-glycosidically linked oligosaccharides of L-rhamnose, because they occur in the repeating units of a very wide range of lipopolysaccharides.[5]

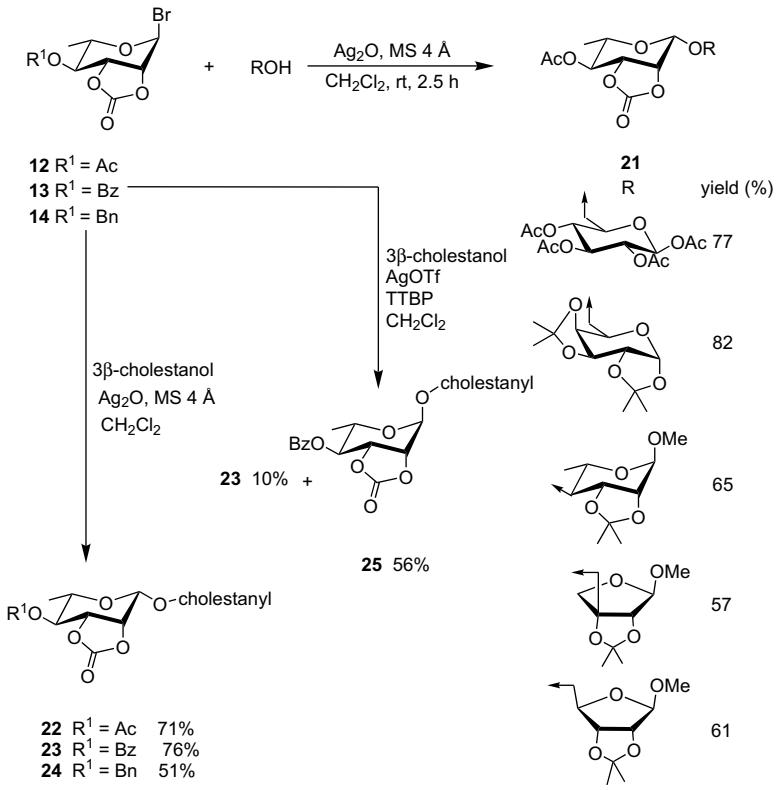
Reaction of 2,3,4-tri-*O*-acetyl-α-L-rhamnosyl bromide (**1**) with partially protected acceptors **2**–**4** gave the respective α-linked disaccharides **5**.[45] However, rhamnosylation of 2,3,4-tri-*O*-benzyl-D-rhamnopyranose with α-acetobromo-L-rhamnopyranose (**1**) followed by deprotection gave a mixture of β-D-rhamnopyranosyl-α-L-rhamnopyranoside and α-D-rhamnopyranosyl-α-L-rhamnopyranoside.[45] On the other hand, an earlier study of the reaction of **1** with **6** gave the β-linked disaccharide **7**, methanolysis of which gave **8**[46] (Scheme 1).

5.1.2. Role of 2,3-O-carbonate groups

Modifying or eliminating the neighboring-group effect of the 2-O substituent led to a preferential formation of the 1,2-*cis*-rhamnosides. The classical methods have used rhamnosyl halides as donors and insoluble heavy-metal salts as catalytic supports.[47] The mechanism for this class of reactions has included the formation of a rhamnosyl carbenium ion-insoluble support ion pair after activation of the donor. Subsequent attack by the nucleophilic hydroxyl group then occurs preferentially from the least hindered β-face, leading to a β-linkage. When the reaction was carried out heterogeneously, anomerization of the α-halide to the reactive β-halide has been limited and the reaction of the α-halide, therefore, proceeds with inversion. The glycosyl donor, 4-*O*-acetyl-2,3-*O*-carbonyl-α-L-rhamnosyl bromide (**12**), was prepared by the reaction of **9** with methyl chloroformate in the presence of triethylamine[48] or triphosgene[49] to give the cyclic carbonate **10** in 87 and 97% yield, respectively. Acetolysis of **10** gave the α,β-L-rhamnopyranose **11** in 90% yield with an α/β ratio of 4:1, from which the α-anomer was isolated in 60% yield.[48] Reaction of **11** with HBr/AcOH afforded the bromide **12** in 98% yield.[48] Alternatively, the bromides **12**–**14**[50] were prepared from the corresponding thiophenyl rhamnosides **18**–**20** upon reaction with bromine. The latter carbonates were prepared from diols[51] **15**–**17** by the action of phosgene (Scheme 2).



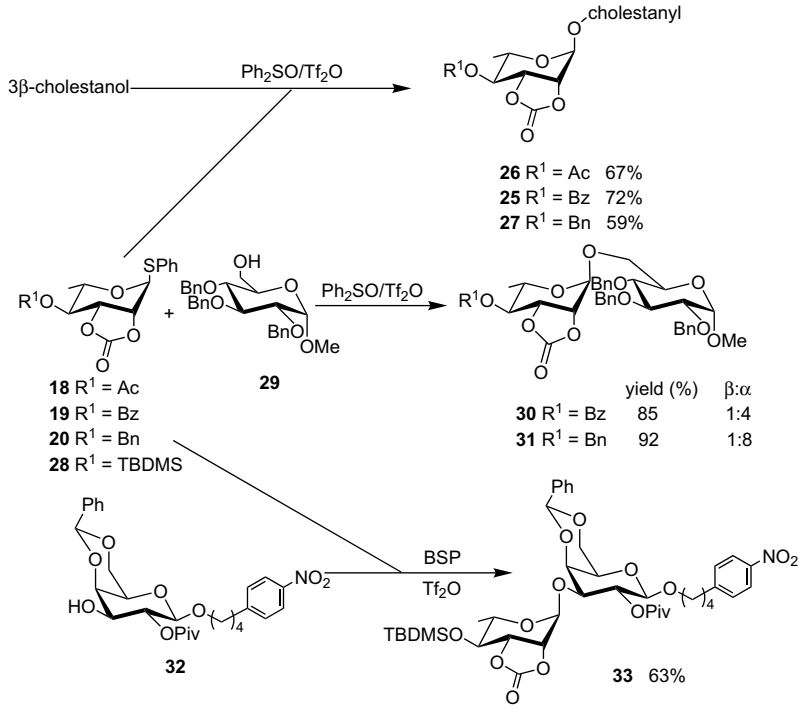
Scheme 2.



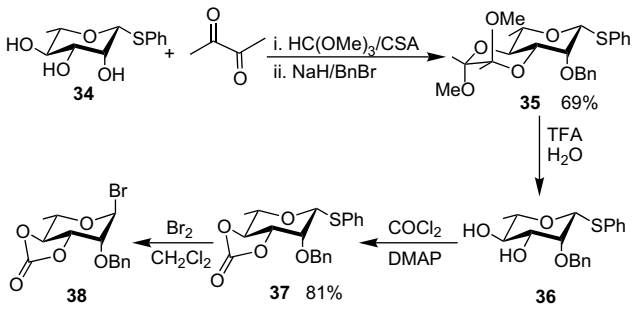
Scheme 3.

Historically, the 2,3-*O*-cyclic carbonate is one of the earliest protecting groups for the 2- and 3-vicinal hydroxyl functions in the mannosyl and rhamnosyl donors to direct the glycosidic bond toward the β-orientation, with high diastereoselectivity in the presence of an insoluble silver salt.[1,52] When a heterogenous insoluble silver oxide promoter was used, the 4-*O*-acetyl-2,3-*O*-carbonyl-α-L-rhamnosyl bromide **12** led to a β-selective coupling to give the disaccharides **21**.[48,49] 3-*O*-(β-L-Rhamnosyl)-β-D-rhamnoside was also synthesized.[48]

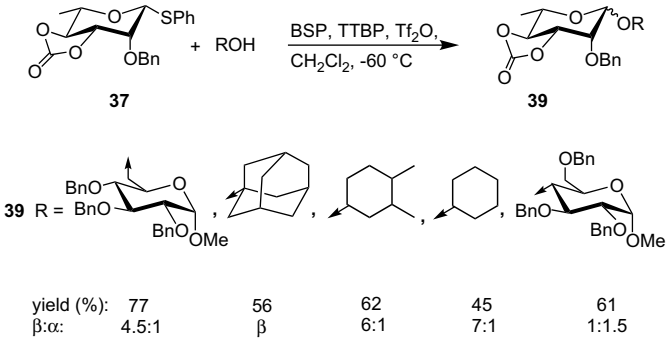
Similarly, the coupling of rhamnosyl bromides **12**–**14** with 3β-cholestanol in the presence of silver oxide gave the respective β-rhamnosides **22**–**24**. On the other hand, when the same coupling of **13** was carried out in the presence of silver triflate/tri-*tert*-butylpyrimidine (TTBP), a homogeneous soluble promoter system,



Scheme 4.



Scheme 5.



Scheme 6.

the β-rhamnoside **23** was formed in only 10% yield, whereas the α-anomer **25** was formed in 56% yield. Deprotection of the acetyl and carbonate groups by NaOMe and subsequent de-isopropylidenation, by careful treatment with a cation exchange resin (H^+) in methanol, of the furanoide derivatives of **21** gave an apiose-containing disaccharide fragment of rhamnogalacturonan-II,[49] β-L-Rha*p*-(1→3′)-β-Api*f*-OMe (92%), and β-L-Rha*p*-(1→5)-β-D-Rib*f*-OMe (68%) (Scheme 3).

In a homogeneous solution, the carbonate is highly α-selective. This is due to the half-chair conformation adopted by triflate donors, upon activation, that reduced the energy gap between the oxacarbenium ion conformation and the covalent triflate, thereby encouraging the α-face-selective process.[50] Thus, Crich deduced that the 2,3-*O*-carbonate is highly α-directing under his coupling conditions, whereas the β-selectivity was facilitated in the presence of a silver oxide promoter.[50] The α-face may be shielded by the absorption of the bromide on the promoter surface. Thus, the phenyl thiorhamnosides **19** and **20** were coupled with **29** under Crich conditions to give, selectively, the respective α-glycosides **30** and **31** in high yield; the expected selectivity[53] based on the finding that the β-directing influence of the 4,6-*O*-benzylidene group to provide β-mannosides is completely over-ridden by a 2,3-carbonate in the donor.[54] A similar coupling of the thiorhamnosides **18**–**20** with β-cholestanol gave the corresponding α-rhamnosides **26**, **25**, and **27**, respectively. In addition, **28** gave the α-rhamnosyl derivative **33** upon coupling with **32** in the presence of 1-benzenesulfinylpiperidine (BSP) and Tf_2O (Scheme 4).

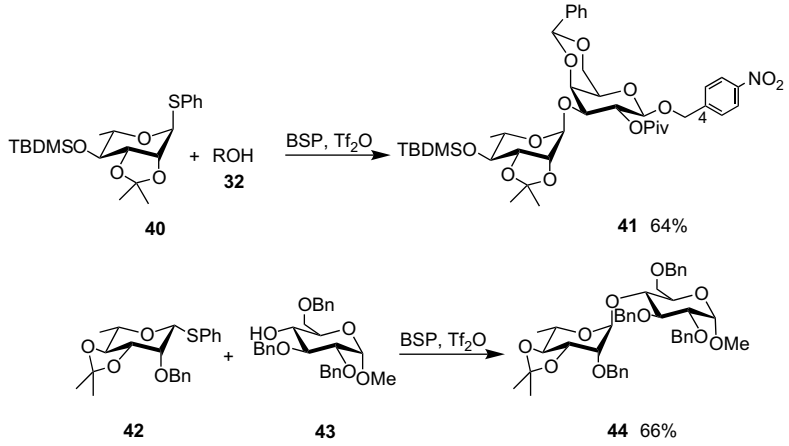
5.1.3. Role of 3,4-O-carbonate groups

When a cyclic carbonate protecting group has been located at the 3,4-*O*-position of a rhamnosyl donor, a β-directing effect was found in both homogenous and heterogenous conditions. This enforcement of β-glycosylations has been attributed to the combination of the strongly electron-withdrawing ability of the cyclic carbonate, which destabilizes the positive charge on C-1 derived by expulsion of the anomeric leaving group and its cyclic nature, which prevents neighboring-group participation.[50] Thus, the donors **37** and **38** were prepared[50] from the thiophenyl rhamnoside **34** by reaction with diacetyl in the presence of trimethyl orthoformate and camphorsulfonic acid (CSA) followed by benzylation to give **35**, the acid treatment of which gave **36** that, upon reaction with phosgene, gave **37**. The latter compound was converted into **38** upon reaction with bromine (Scheme 5).

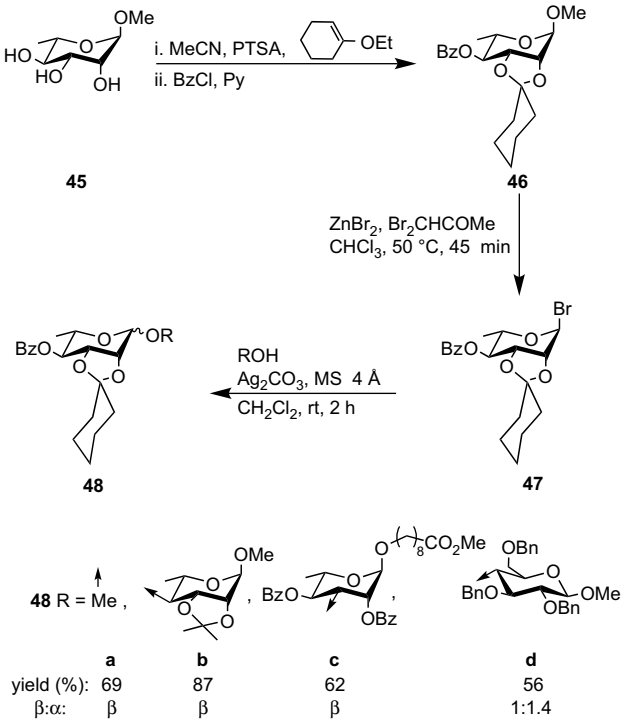
Coupling of glucose-6-OH as an acceptor with phenyl thiorhamnoside **37**, using a 1-benzenesulfinylpiperidine, 2,4,6-tri-*tert*-butylpyrimidine, and triflic anhydride (BSP/TTBP/Tf_2O)-mediated system, exhibited a significant β-selectivity to give **39** in 77% yield with a β/α ratio of 4.5:1; the anomeric selectivity was reduced, due to the less reactive nature of the acceptor. On the other hand, coupling of **37** to a tertiary alcohol, adamantanol, formed the β-anomer as the only detected coupling product in 56% yield[50] (Scheme 6). The use of 5% acetonitrile or propionitrile in dichloromethane increased the β-selectivity of a number of L-rhamnopyranosylations under the above reaction conditions.[50]

5.1.4. Role of 2,3- and 3,4-O-alkylidene groups

Comparable results to those shown by using the 2,3-*O*-carbonate group for the formation of the α-rhamnosidic linkage were also found upon using the 2,3-*O*-isopropylidene derivative **40** with acceptor **32**, whereby **41** was the only found anomer.[55] Similarly, the reaction of 3,4-*O*-isopropylidene acetal donor **42** with the 4-OH glucoside acceptor **43** was found to be completely α-selective,[50] to give **44** (Scheme 7). This led to the conclusion that the β-selectivity of the 3,4-*O*-carbonate cannot be due to a conformational effect arising from the cyclic nature of the protecting group.

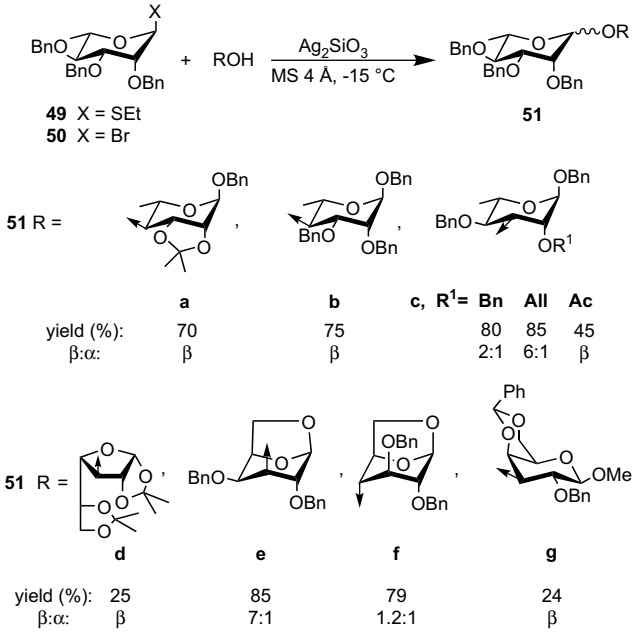


Scheme 7.



Scheme 8.

The 2,3-*O*-cyclohexylidene moiety has also been used as a non-participating protecting group. Thus, the donor cyclohexylidene rhamnosyl bromide **47** was prepared by acetalation of methyl α-L-rhamnopyranoside (**45**) with 1-ethoxycyclohexene followed by benzoylation[56] to give **46** that, upon bromination, afforded **47**. Reaction of **47** with partially protected acceptors under standard Koenigs-Knorr conditions using silver carbonate and molecular sieves (4 Å) in CH_2Cl_2 afforded, stereoselectively, the β-glycosides **48a–c**, whereas a mixture of the αβ anomers of **48d** was obtained. The lower ratio of the β-rhamnoside in **48d** has been attributed to the low reactivity of the 4-OH group in the respective acceptor.[56]



Scheme 9.

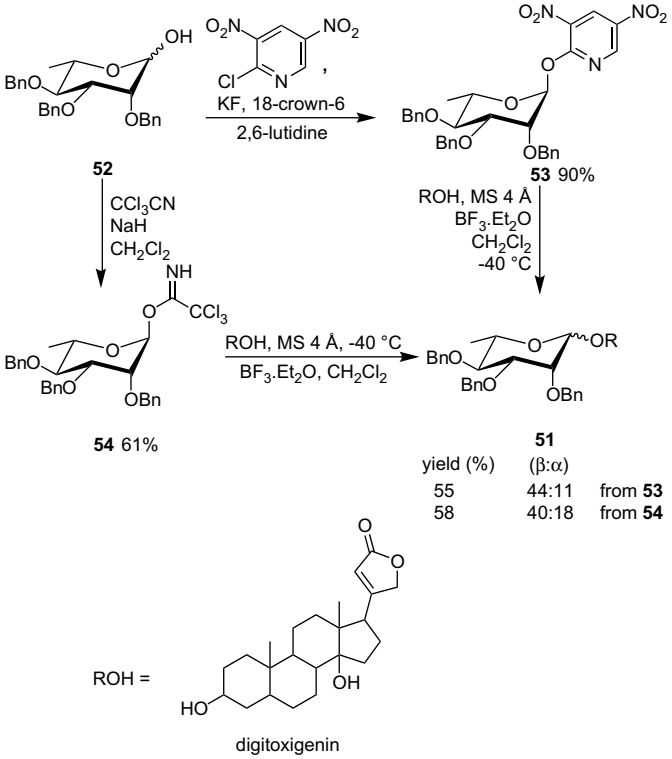
The removal of the protecting groups can be readily accomplished; TFA was used to hydrolyze the acetal group (Scheme 8).

5.1.5. Role of benzyl groups on O-2

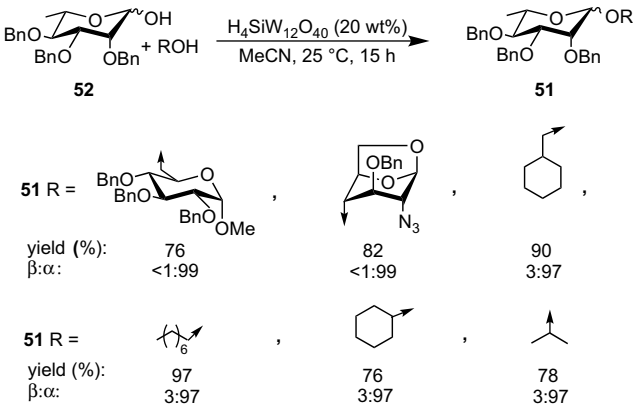
Intermolecular glycosidation of 2,3,4-tri-*O*-benzyl-α-L-rhamnopyranosyl bromide **50**, synthesized from the corresponding thioglycoside **49**, with saccharides containing reactive hydroxyl groups in the presence of silver silicate as a catalyst gave the β-glycosidically linked disaccharides **51a–g** with good selectivity. The solvent has an important effect on the anomerization during the coupling reaction. When dichloromethane was used as the solvent, the acceptors (ROH) with R=**a**, **b**, **c** (R^1=Ac), and **d** gave only the β-linked disaccharides, whereas, in toluene, a mixture of the α and β glycosides resulted from the acceptors with R=**c** and **e**.[57] On the other hand, coupling of **50** with the anhydro-sugar acceptor ROH (R=**f**) in CH_2Cl_2 at room temperature afforded the β- and α-rhamnoside disaccharides in 43 and 36% yield, respectively.[58,59] On coupling of ethyl 2,3,4-tri-*O*-benzyl-1-thio-α-L-rhamnopyranoside (**49**) with the acceptor ROH (R=**g**) in the presence of methyl triflate in dichloromethane, the β-linked disaccharide **51g** was obtained, from which the benzyl and benzylidene protecting groups were removed to afford the respective methyl glycoside[22] (Scheme 9).

Among the studies on cardiac glycosides, donors with non-participating benzyl groups in conjunction with 3,5-dinitro-pyrid-2-yl or trichloroacetimidate as leaving groups at the anomeric center, as in **53** and **54**, were prepared from 2,3,4-tri-*O*-benzyl-L-rhamnose **52**. Coupling of **53** or **54** with digitoxigenin in the presence of BF_3/Et_2O gave regioselectively the β-rhamnoside **51** (Scheme 10). The deprotected β-anomer showed good hog kidney Na^+, K^+-dependent ATPase inhibition (IC_{50} 4.79×10^{-9} M).[60] The 5′-Me and 4′-OH groups appear to have a predominant role in binding to the Na^+, K^+-ATPase receptor. The relative configuration of the OH group also contributes to the binding.[60]

The dehydrative glycosidation of 2,3,4-tri-*O*-benzyl-L-rhamnose **52** with alcohols, in the presence of the heteropolyacid $H_4SiW_{12}O_{40}$, gave the corresponding *O*-glycosides **51** that mainly contained the



Scheme 10.



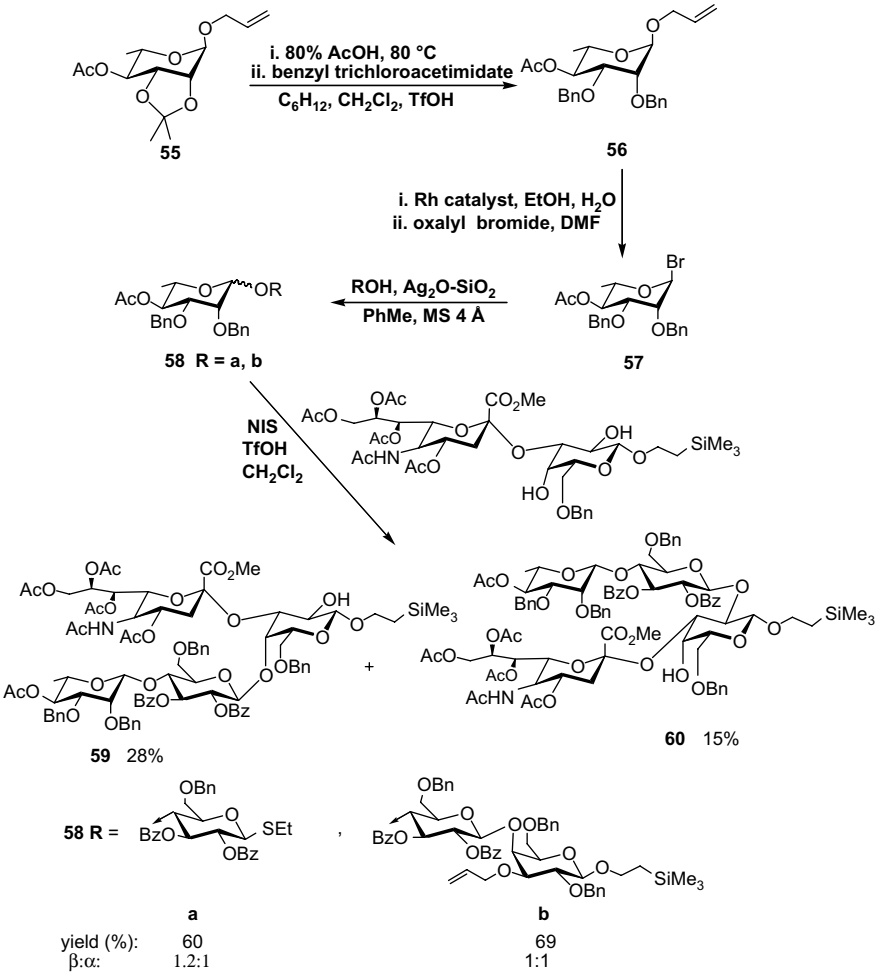
Scheme 11.

α-anomers with very minor amounts of the β-anomers[61] (Scheme 11). The heteropolyacid was considered to function as an activating agent of the anomeric hydroxyl group of the glycosyl donor and a dehydrating agent for the resulting water from the glycosidation. The ratio of the β-anomer and the yield changed by altering the heteropolyacid, but this cannot be considered as a suitable method for the synthesis of β-rhamnosides.

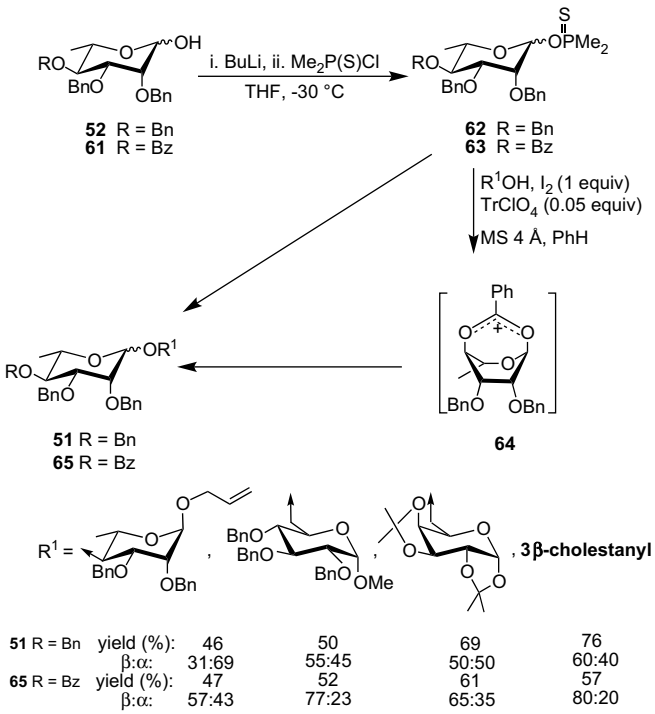
The rhamnosyl bromide **57**, having non-participating groups on O-2 and O-3, whereas the O-4 has a temporary acetyl group, was also used as a donor in the presence of silver silicate. It was synthesized in 35% yield from the 4-*O*-acetyl derivative **56**, prepared from allyl 2,3-*O*-isopropylidene-α-L-rhamnopyranoside **55**. Coupling of the rhamnosyl bromide **57** with mono- and disaccharide acceptors gave an α,β-mixture of the respective oligosaccharides **58a**,**b**. Further coupling of **58a** with a disaccharide-2,4-diol acceptor gave a mixture of the 4-*O*-regioisomer **59** in 28% yield and the 2-*O*-isomer **60** in 15% yield (Scheme 12). Deprotection of **58a** gave a single repeating unit of the type VIII group B *Streptococcus* (GBS) capsular polysaccharide required for developing vaccines for GBS infections.[62]

Rhamnosyl derivatives having non-participating 2,3-di-*O*-benzyl groups and a 4-*O*-benzyl or a 4-*O*-benzoyl group in conjunction with a dimethylphosphinothioate group on O-1, have been used to synthesize β-rhamnosides. Thus, the donors **62** and **63** were prepared by the reaction of the corresponding rhamnose derivatives **52** and **61** with dimethylphosphinothioyl chloride in the presence of butyllithium in tetrahydrofuran.[63,64] Coupling of **62** and **63** with several alcohols in the presence of iodine and catalytic amount of triphenylmethyl perchlorate, as an activator, in benzene gave the β-rhamnopyranosides **51** and **65**, respectively, in moderate yields. The presence of a 4-*O*-benzoyl group in **63** led to the β-linked disaccharides in higher selectivity than that from the donor **62** with a 4-*O*-benzyl group. This has been attributed to the formation of the 1,4-*O*-benzylidene-type cation intermediate **64** (Scheme 13). The catalyst and its ratio with respect to the reactants as well as the solvent played a role in the stereoselectivity.

When *tert*-butyldimethylsilyl (TBS) and *tert*-butyldiphenylsilyl (TPS) groups were introduced on the 3-OH and 4-OH groups, respectively, of L-rhamnose, in addition to the non-participating



Scheme 12.



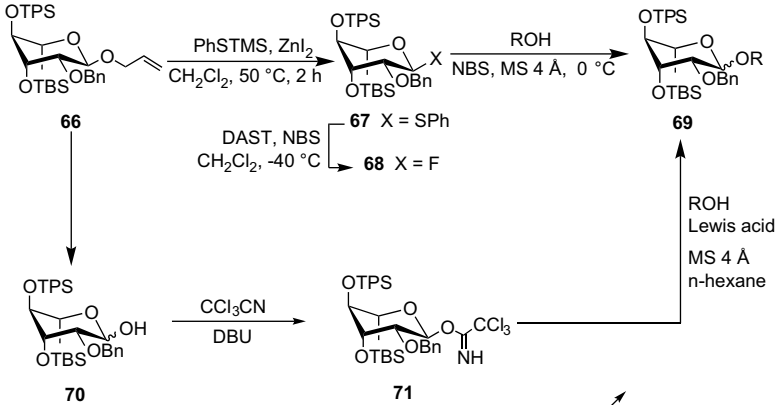
51 R = Bn	yield (%):	46	50	69	76
	β:α:	31:69	55:45	50:50	60:40
65 R = Bz	yield (%):	47	52	61	57
	β:α:	57:43	77:23	65:35	80:20

Scheme 13.

group on 2-OH, a flipping of the natural ring conformation occurred, whereby the $^4C_1$ conformation was adopted.[65,66] Thus, the α-selectivity of the general rhamnosylation reactions has been changed, leading to an increase in the β-rhamnosides. The glycosyl donors **67** and **68** were synthesized[67] from the corresponding allyl rhamnoside **66** by treatment with PhSTMS and ZnI_2 to give **67** followed by treatment with diethylaminosulfur trifluoride (DAST) and NBS to give **68**. The trichloroacetimidate **71** was prepared from **70**. Rhamnosylation of R-OH carried out with phenyl 1-thiorhamnoside **67** or rhamnosyl fluoride **68**, having a $^4C_1$ conformation, in the presence of *N*-bromosuccinimide gave **69**.[66] Similarly, a β-selective rhamnosylation was also accomplished by using the trichloroacetimidate **71**[65] (Scheme 14). Different acid catalysts were used on the rhamnosylation of **71** with cyclohexylmethanol, but those, which gave higher yields and/or higher β-selectivities were boron trifluoride etherate (BF_3/Et_2O), triethylsilyl triflate (TESOTf), *tert*-butyldimethylsilyl triflate (TBSOTf), and tri-*iso*-propylsilyl triflate (TIPSOTf).

A rhamnosyl bromide **72** with an allyl group on 2-O has been used in the rhamnosylation of benzyl rhamnoside **73** under catalysis by silver silicate in CH_2Cl_2 to afford mainly the β-rhamnobioside derivative **74** (73%). This compound was *O*-deacetylated and coupled with 2,3,4-tri-*O*-benzyl-α-L-rhamnosyl bromide **50** to afford **75** (72%) with β-glycosidic linkages of all monosaccharide units.[26] Similarly, the rhamnotrioside derivative **78** was prepared by using benzyl 3,4-di-*O*-benzyl-α-L-rhamnopyranoside **76** as an acceptor at O-2, the reaction of which with **72** in the presence of silver silicate gave only the β-glycosidically linked disaccharide **77**, deacetylation of which and further reaction with **50** gave **78** in 70% yield. Deblocking of **78** gave the respective trisaccharide,[5,68] a repeating unit of *Shigella flexneri* serotype 6 (Scheme 15).

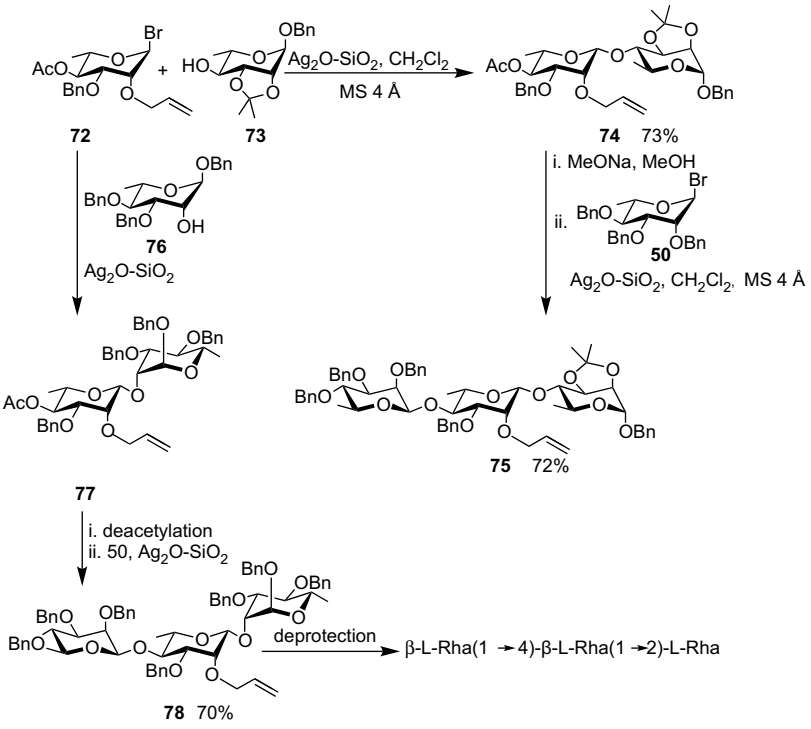
A surprising ring fission of the rhamnopyranose ring in **79** to the rhamnofuranosyl halide **80** has taken place by acetolysis of the *O*-*tert*-butyl residue of the rhamnopyranoside **79** with trifluoroacetic acid/acetic anhydride followed by treatment with titanium tetrabromide. The disaccharide **80** can be considered as the kinetic product of dealkylation of the 1-OH group in the rhamnopyranoside unit, with spontaneous ring scission to the unusual furanosyl form, followed by acetolysis and then bromination. Stereoselective coupling of the glycosyl donor **80** with a 3-deoxy-D-lyxo-heptulosaric acid acceptor **81** in the presence of mercuric cyanide afforded exclusively the β-rhamnofuranoside **82** in high yield. The



69 R=		Me		
X = SPh	yield (%):	64	81	73
	β:α:	63:37	63:37	50:50
X = F	yield (%):	–	–	84
	β:α:	–	–	43:57

X = OC(NH)CCl3	Lewis acid	yield (%)	(β:α)
	$MgBr_2.Et_2O$	55	(28:72)
	$AlCl_3$	61	(40:60)
	$BF_3.OEt_2$	97	(57:43)
	TMSOTf	70	(49:51)
	TESOTf	72	(54:46)
	TBSOTf	72	(59:41)
	TIPSOTf	72	(68:32)

Scheme 14.

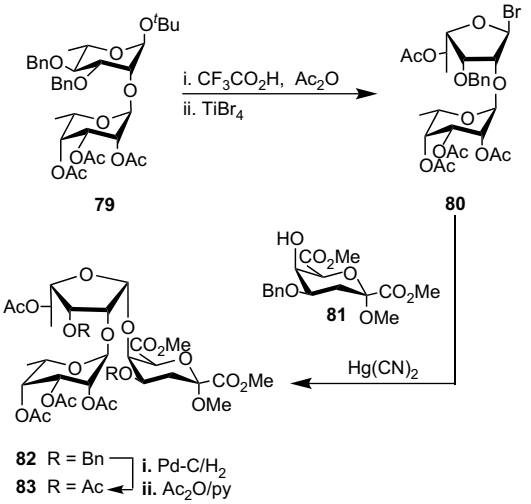


Scheme 15.

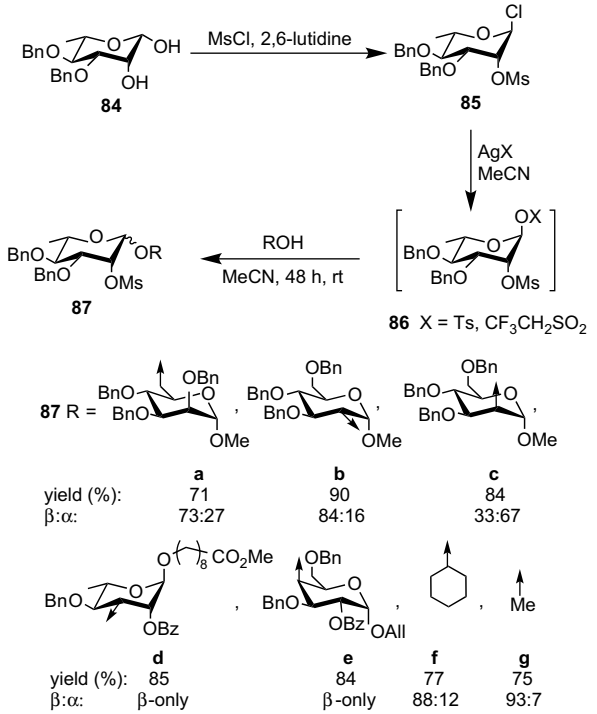
unexpected formation of the interglycosidic β-linkage was confirmed from an X-ray crystal structure determination of the corresponding acetate **83**[69] (Scheme 16).

5.1.6. Role of sulfonyl groups on O-2

The presence of a sulfonyl group on 2-O of rhamnosyl or mannosyl donors has played an important role in directing the formed glycosidic bond toward a β-configuration.[1,6,70] This was explained to be a result of the interaction of opposing dipoles of strongly electronegative non-participating substituents on O-2 and a highly reactive electronegative leaving group on C-1. Such a situation could direct the influence of the 2-*O*-sulfonyl group to stabilize the α-mannosyl[1,70–72] and α-rhamnosyl sulfonate esters and lead to glycosylation from the β-site. Thus, treatment of 1-*O*-tosyl derivative **86** (X=Ts) with methanol or cyclohexanol afforded mainly the β-anomers, along with small amounts of the α-anomers. The reaction was more stereoselective and also faster when the 1-*O*-(2,2,2-trifluoroethylsulfonyl) (tresyl) derivative **86** (X=$CF_3CH_2SO_2$) was used instead of the 1-*O*-tosyl derivative.[70] The tresyl donor **86** was prepared by the reaction of rhamnosyl chloride **85** with silver 2,2,2-trifluoroethanesulfonate in acetonitrile. The chloride **85** was prepared by the reaction of 3,4-di-*O*-benzyl rhamnose **84** with mesyl chloride. The syntheses of disaccharides containing



Scheme 16.

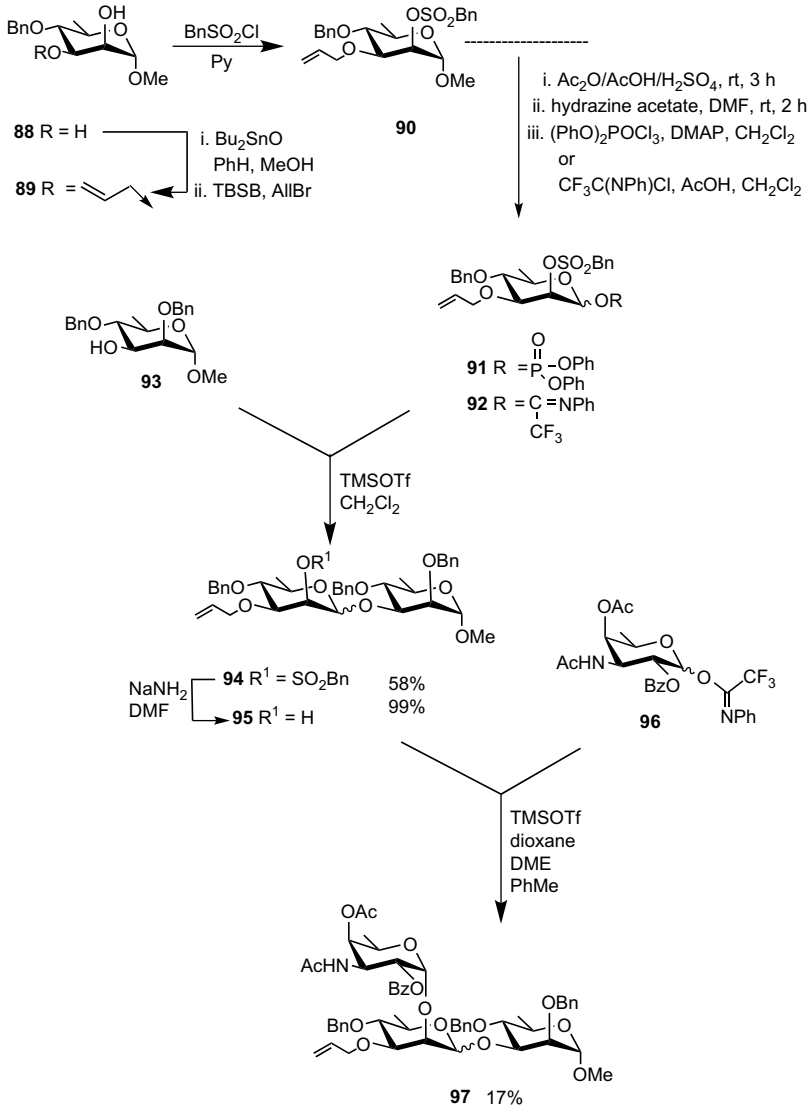


Scheme 17.

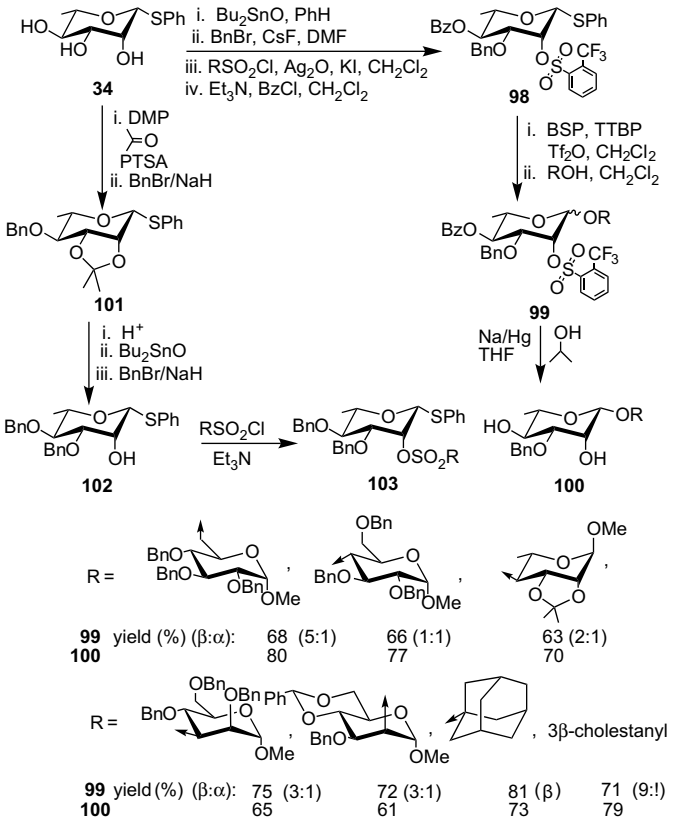
β-L-rhamnosidic bonds linked at the primary and secondary positions of the aglycons were carried out with the tresyl derivative **86** in acetonitrile at room temperature for 48 h to afford a mixture of α/β anomers of disaccharides **87a**–**g**. The α anomers in the case of aglycons **87** (R=**d** and **e**) were formed in a very small proportion and could not be isolated in the pure state[70] (Scheme 17).

The trisaccharide repeating unit of the O-antigen of the lipopolysaccharide from *Xanthomonas campestris pv.campestris* 8004, a pathogen of cruciferous crops, has a β-D-rhamnoside linkage. Its synthesis has been accomplished by the selective allylation of **88** to give **89**, benzylsulfonylation of which gave **90**, which was hydrolyzed and converted into the donors **91** and **92**. Sequential β-D-rhamnosylation of **93** with a 2-*O*-benzylsulfonyl-*N*-phenyltrifluoroacetimidate donor **92** gave **94** that, upon debenzylsulfonylation of the β-anomer, gave **95**, coupling of which with a D-Fuc*p*3NAc thioglycoside donor **96** gave **97** that was deprotected to give the target trisaccharide[73] (Scheme 18).

The ability of a number of 2-*O*-sulfonates to promote the β-glycosylation of 3β-cholestanol has been studied by the Crich group.[74] The β-thiorhamnosides rather than their α-analogues were selected as precursors for the donors because of the instability of the 2-*O*-sulfonates of the α-thioglycosides. Thus, **34** was converted into the 4-*O*-benzyl derivative **101**, which, upon de-isopropylidenation and selective benzylation, gave **102** that subsequently sulfonylated to give the respective 2-*O*-sulfonate **103** (R=*p*-C_6H_4–Br, *p*-C_6H_4–F, *p*-C_6H_4–CN, *p*-C_6H_4–CF_3, CH_2CF_3). Their coupling with 3β-cholestanol under the Crich protocol for activation of the donor indicated that the optimal donor was the *p*-trifluoromethylbenzenesulfonate, which gave the product in 75% yield with a β/α ratio of 5.5:1. A further increase in the β-selectivity could be obtained by using the 4-*O*-benzoyl donor **98**, which was prepared by regioselective 3-O monobenzylation of **34** through treatment with dibutyltin oxide and then benzyl bromide, followed by sulfonylation at O-2 and then benzoylation at O-4 (Scheme 19). The *o*-trifluoromethylbenzenesulfonate **98** rather than the β-isomer was selected as a donor, because of the instability of the respective *para*-substituted isomer. Activation of the 2-*O*-sulfonyl-protected rhamnosyl thioglycoside **98** with a combination of 1-benzenesulfinylpiperidine (BSP) and triflic anhydride in the presence of 2,4,6-tri-*tert*-butylpyrimidine (TTBP), followed by addition of the acceptor alcohols, yielded the respective mixture of anomeric rhamnopyranoside disaccharides **99**. Reaction of their β-anomers with sodium amalgam afforded their corresponding desulfonylated and debenzoylated glycosides **100**. β-Rhamnosylation with donors having 4-*O*-benzoyl protecting groups revealed a significant increase in the selectivity; the more highly disarmed

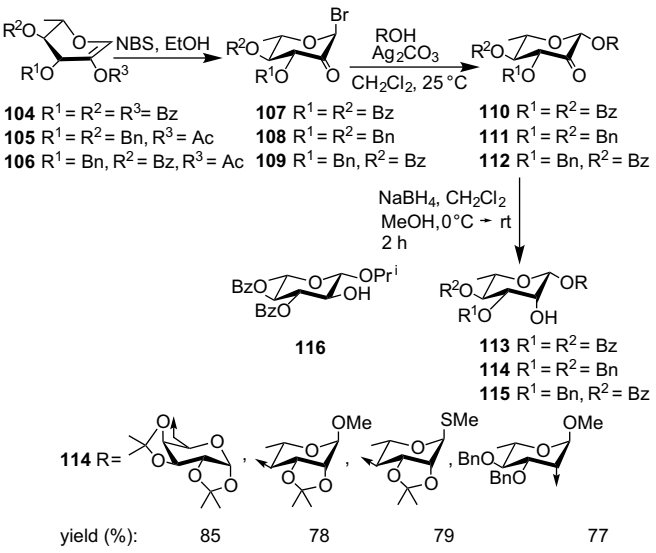


Scheme 18.



Scheme 19.

system proceeded well with primary and more reactive secondary acceptors, while, with glucose 4-OH acceptor, which has a less reactive secondary hydroxyl group, the β-selectivity was decreased. It was also reported that β-rhamnosylation with a tertiary alcohol, 1-adamantanol, was extremely β-selective.[74]



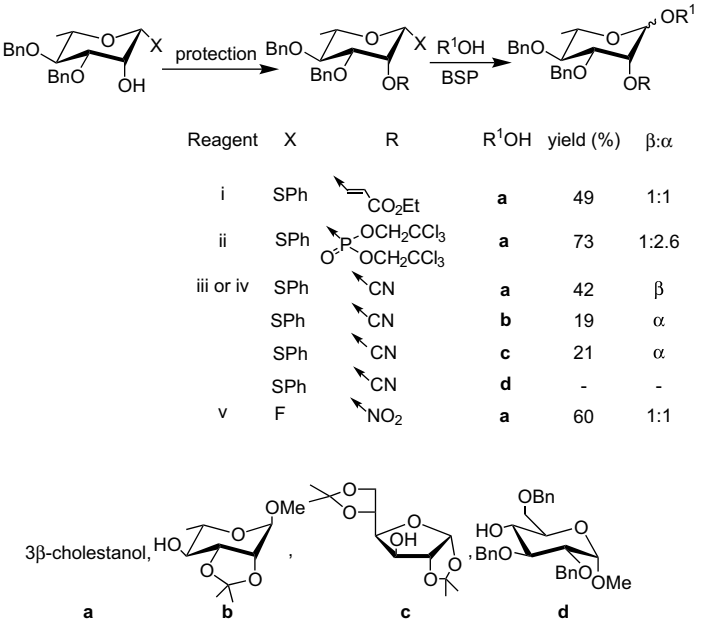
Scheme 21.

5.1.7. *Variable electron-withdrawing groups at O-2*

The potential of non-participating, electron-withdrawing groups at O-2, other than the sulfonate groups, as β-directing groups in the rhamnose series has been examined[75] and the results are shown in Scheme 20.

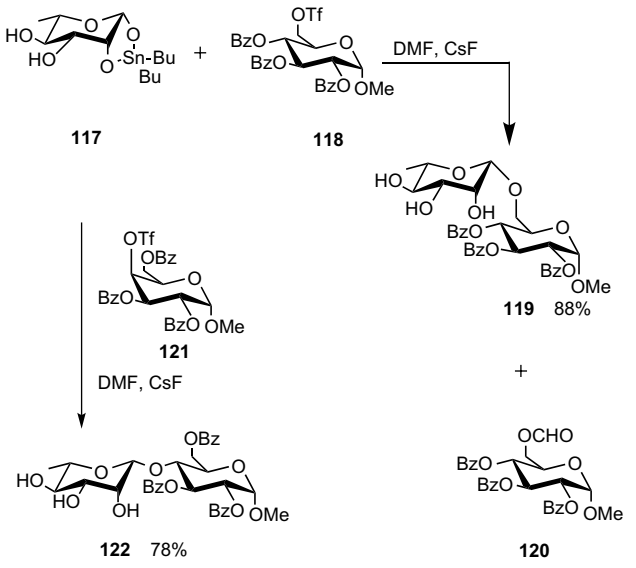
5.1.8. *Ulosyl bromide approach*

This is an indirect approach for the β-L-rhamnosyl donors.[76–79] The ulosyl bromides[76] **107**–**109** can be accessed from the readily available 2-acyloxy-L-rhamnals **104**–**106**. Glycosidation of ulosyl bromides was found to have a high potential to form the β-linkages under standard Koenigs-Knorr conditions. No α-anomeric products were detectable in the reaction mixture and the β-ulosides **110**–**112** were isolated in 80–90% yields.[77,78] The selectivities obtained in the carbonyl reductions of glycosiduloses **110**–**112** (R=*i*-Pr) were found



i. Ethyl propiolate/N-methylmorpholine. ii. Bis(2,2,2-trichloroethyl) phosphorochloridate. iii. Potassium hexamethyldisilazide, then BrCN. iv. Trichloroacetyl isocyanate, then dehydration with Ph_3P/CBr_4. v. HNO_3, Ac_2O.

Scheme 20.



Scheme 22.

to be dependent upon the nature of the 3-O-protection, as in the case of β-mannosyl donors.[79] Thus, reduction of uloside **110** by $NaBH_4$ gave a 3:1 mixture of the L-rhamno **113** and 6-deoxy-L-*gluco* epimer **116**, whereas reduction of 3-*O*-benzylated compound **111** or **112** gave essentially β-L-rhamnosides **114** and **115**, respectively[77] (Scheme 21).

5.1.9. Anomeric O-alkylation via locked anomers

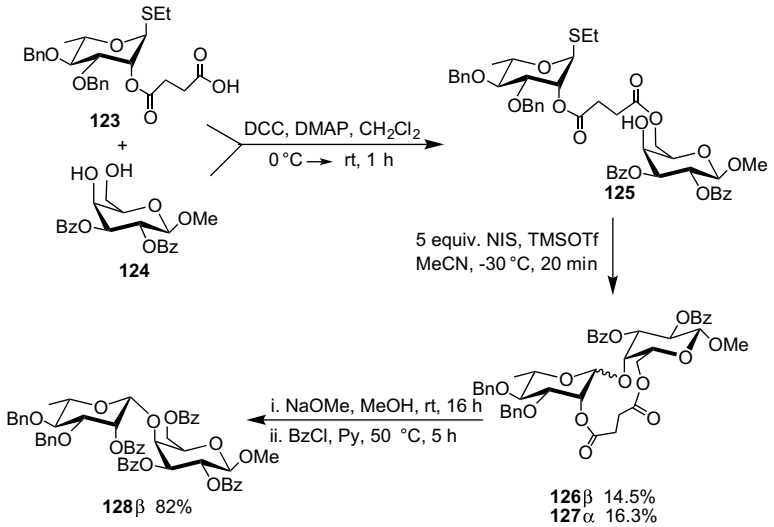
Kovac found that 1,2-*O*-*cis*-stannylene acetals of sugars are powerful nucleophiles capable of displacing good leaving groups in carbohydrates via an S_N2 mechanism and also make the protection of hydroxyl groups in the glycosyl donor unnecessary. Thus, glycosylation of the 1,2-*O*-*cis*-stannylene acetal of L-rhamnose (**117**) with the primary triflate **118** in DMF at 25 °C gave the β-L-rhamnopyranoside **119** in about 50% yield, in addition to the formation of **120** in about 25% yield, as a result of the reaction of **118** with DMF. When the same reaction was performed in the presence of CsF and a high proportion of **117** at low temperature, the yield of the disaccharide **119** increased to 88%. On the other hand, the reaction of **117** with less reactive secondary triflate **121**, at 25 °C for 2.5 h, gave the disaccharide **122** in 78% yield with complete inversion of configuration in the electrophile **121**; no 4-*O*-formylated derivative was isolated[80,81] (Scheme 22).

5.2. Intramolecular aglycon delivery

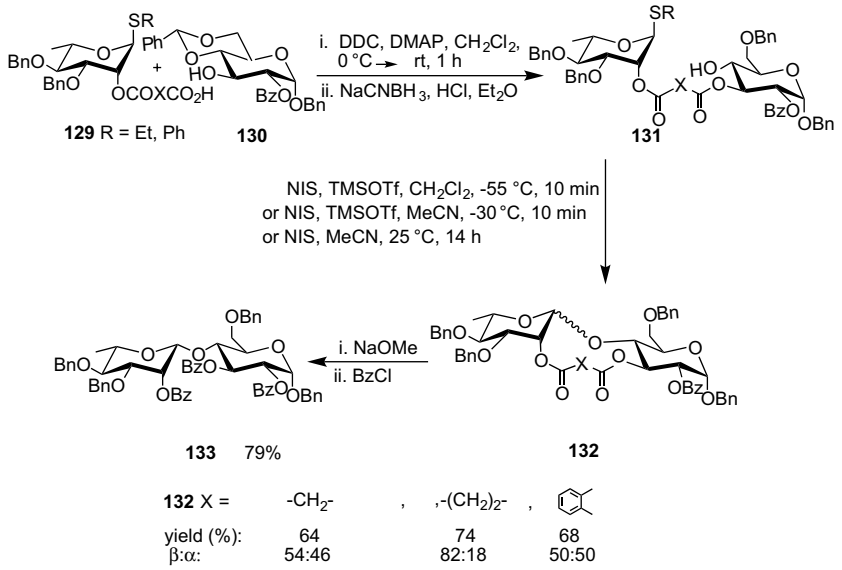
In order to achieve such intramolecular glycosidation processes, the donor and the acceptor have to be linked by a spacer, as reported by Ziegler.[82,83] Thus, ethyl 3,4-di-*O*-benzyl-1-thio-α-L-rhamnopyranoside was treated with succinic anhydride to give the 'spacer-modified' glycosyl donor **123** that, upon regioselective condensation with partially benzoylated galactoside **124**, afforded the pre-arranged spacer disaccharide **125**, intramolecular (1→4) glycosidation of which using NIS/TMSOTf gave a mixture of β and α cyclized anomers **126** and **127** in about 31% yield. The succinoyl group of **126** can be cleaved and the product was benzoylated to give the β-rhamnoside **128**[82] (Scheme 23).

Similarly, the glycosyl donors **131** were prepared from the respective 2-*O*-carboxyalkanoyl or -aroyl derivatives of 3,4-dibenzyl-1-thio-α-L-rhamnosides **129** by reaction with benzyl 2-*O*-benzoyl-4,6-*O*-benzylidene-α-D-glucopyranoside (**130**) followed by regioselective reduction of the benzylidene ring. Cyclization of the pre-arranged glycosides **131** afforded the 2,3′-bridged α and β-(1→4)-linked disaccharides **132** upon intramolecular glycosylation under various conditions. An excellent β-selectivity of the intramolecular glycosidation resulted when *N*-iodosuccinimide in acetonitrile was used as an activator[82] and this was enhanced with trimethylsilyl trifluoromethanesulfonate (TMSOTf) as a catalyst at low temperature. The ^1H NMR spectrum of the malonyl-bridged disaccharides **132** β (X=CH_2) showed the presence of a 3:1 mixture of two products, which could not be separated by chromatography and were postulated as a mixture of conformers. The anomeric selectivity of the glycosylation was strongly influenced by the nature of the alkanoyl and aroyl bridges and its position at the rhamnosyl residue, in addition to the solvent used for the coupling. It was found that compound **131** having a more rigid bridge (malonyl and phthaloyl groups) gave significantly lower portions of the desired β-coupled disaccharides, while the best result was obtained with succinoyl pre-arranged glycosides. The succinoyl pre-arranged glycoside **131** having a thiophenyl group afforded the respective cyclic disaccharide **132** (90%) with an excellent β-selectivity (β/α=84:16).

Compound **132** β [X=$(CH_2)_2$] was transformed into the disaccharide **133** by deacylation followed by rebenzoylation.[83] Although an α-directing participating acyl group was present at



Scheme 23.

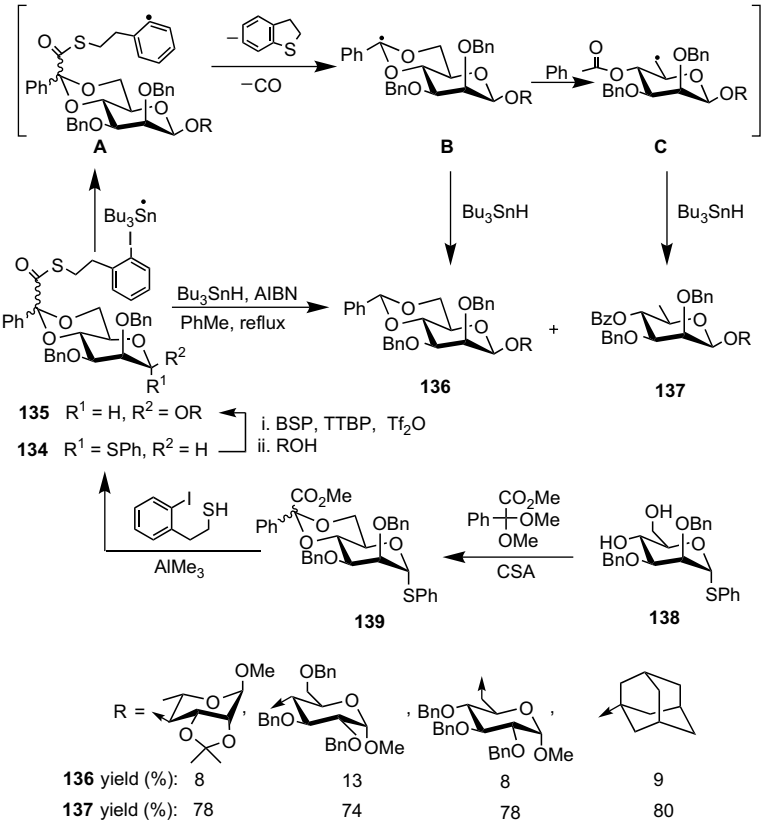


Scheme 24.

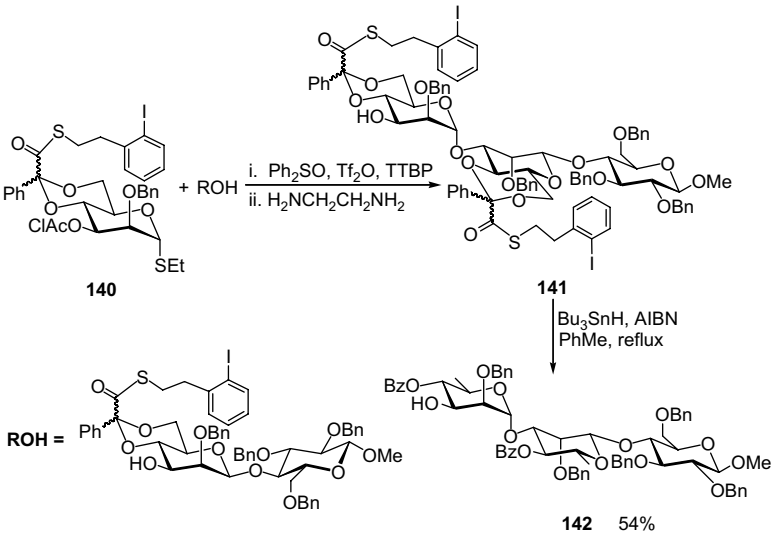
position-2 of the rhamnosyl residue, the pre-arrangement of the two glycosides forced the glycosylation toward a 1,2-*cis* selective coupling.[82] A lower yield of the conversion of the pre-arranged glycoside **125** to **126** and **127** (Scheme 23) was observed, which was attributed to the less-favored larger ring formed, compared to the respective 2:3′-bridged (1→4)-linked disaccharide analogue **132** (Scheme 24).

5.3. Reductive cleavage of 4,6-acetals of mannopyranosides

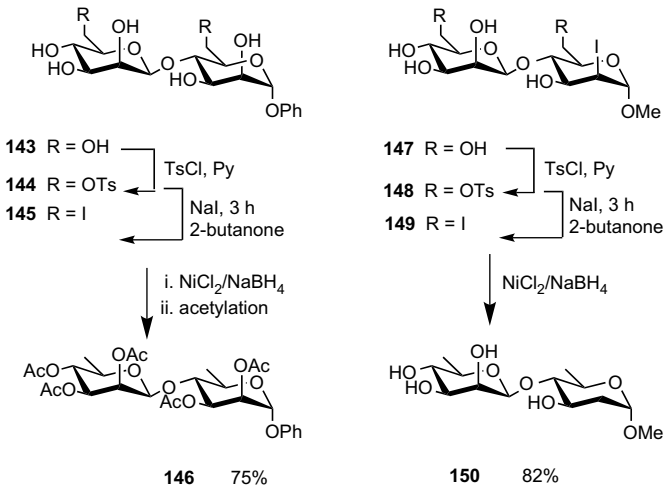
Regioselective reductive radical cleavage of the 4,6-acetal **135** by tributyltin hydride and 2,2′-azobisisobutyronitrile (AIBN) in toluene at reflux gave the β-D-rhamnosides **137**, rather than the alternative 6-*O*-benzoyl-4-deoxy-type products, in addition to the byproducts, 4,6-*O*-benzylidene-protected β-mannosides **136**, via



Scheme 25.



Scheme 26.



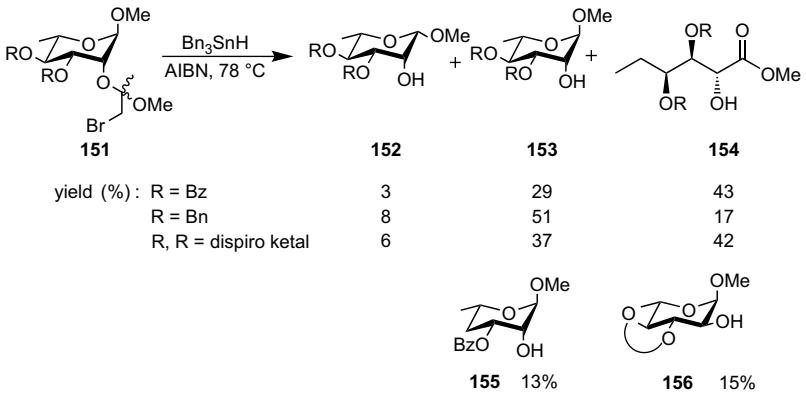
Scheme 27.

intermediates A, B, and C.[84,85] The starting compound **135** was prepared by the action of *N*-benzenesulfinylpiperidine (BSP), 2,4,6-tri-*tert*-butylpyrimidine (TTBP), and triflic anhydride on the corresponding phenyl α-thioglycoside of **134** at −60 °C in CH_2Cl_2. The latter compound was prepared from **138** by conversion into **139** and then into **134** (Scheme 25).

Using the above stereoselective glycosylation radical fragmentation route, the synthesis of trisaccharide **142** was achieved from the diacetal **141**, in which both the β-D and α-D-rhamnopyranosyl units were obtained in a single step in 54% isolated yield via a double radical fragmentation of the modified benzylidene acetals.[85] The diacetal **141** was prepared from the reaction of the 3-*O*-unprotected rhamnosyl acceptor (ROH) with the activated thioglycoside **140**, followed by deacetylation with ethylenediamine (Scheme 26).

5.4. Modification of β-mannosides

Since D-rhamnosides are 6-deoxy-D-mannosides, their synthesis can be expected to proceed via deoxygenation at the 6-position of the mannosides. Thus, selective tosylation of β-mannobiosides **143** and **147** at the 6-positions yielded the ditosylates **144** and **148** in 62 and 67% yields, respectively, which, in turn, gave the corresponding iodo derivatives **145** and **149** in 80 and 86% yields. Subsequent



Scheme 28.

reduction of **145** and **149** using nickel chloride and sodium borohydride gave β-D-rhamnobioside acetate **146** and the 2-deoxy derivative **150**,[86,87] respectively (Scheme 27).

5.5. Inversion of α-rhamnosidic linkages

Inversions of α- to β-rhamnoside have been described to take place under photochemical conditions, in addition to fragmentation at the anomeric radicals that resulted in the formation of ring-opened products Thus, addition of tributyltin hydride to the mixed acetal **151**, readily prepared from **153** and 1,2-dibromo-2-methoxypropane at reflux in benzene, gave the β-rhamnosides **152** and the α-rhamnosides **153**, in addition to the fragmentation products **154**. Unexpected byproducts, α-rhamnosides **155** and **156**, were detected in 13 and 15% yields and resulted from attack of the stannyl radical on the carbonyl oxygen of the benzoyl ester in the substrate at C-4, followed by fragmentation and 1,4-hydrogen atom abstraction, respectively[88] (Scheme 28).

6. Conclusions

The tuning of substituents and the activation processes of the rhamnosyl donors are essential requirements for the orientation of the rhamnosidic bond during the glycosidation reactions. The syntheses of β(1,2-*cis*)-rhamnosides require the absence of a neighboring-group effect and the projection of the leaving group in a trans-orientation (α) with respect to O-2 or the formation of an intimate ion pair, upon activation, to be substituted by the nucleophilic oxygen acceptor from the least hindered β-face to give the β-linkage. The heterogenous activation of the donor limited the anomerization of the leaving group in the donor. Although the 2,3-*O*-carbonate function has a β-orienting influence when the leaving group on C-1 is a bromine atom and the promoter is silver oxide, the situation has been reversed to be highly α-selective upon changing the leaving group to triflate in homogenous solution. This has been attributed to the adoption of the 1-*O*-triflate-formed donor of a half-chair conformation, in which the energy gap between the carbenium ion and the covalently bound triflate can allow the α-face for coupling. The α-face is shielded by the adsorption of the leaving group on the surface of the promoter. The 3,4-*O*-carbonate-group influence on the β-selectivity has been due to a conformational effect. The presence of a bulky silyl group on the 3-OH and 4-OH groups as well as a non-participating group on the 2-OH moiety gave rise to a flipping of the conformation to the $^4C_1$ conformer, leading to an increase of the β-rhamnosides. The presence of a sulfonyl group on 2-OH led to a stabilization of the reactive leaving group on C-1 in the α-position, thus providing a glycosylation from the β-site. Although there are valuable methods for the synthesis of β-rhamnosides, there is still a need for a generalized method for achieving such linkages.

Acknowledgements

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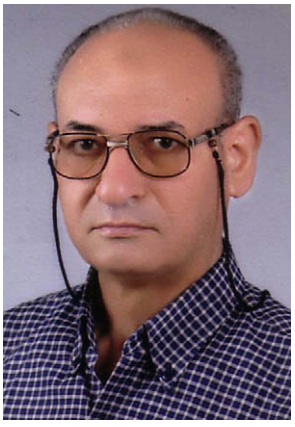

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