CHEMICAL REVIEWS

REVIEW

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2-Oxoglycosyl ("Ulosyl") and 2-Oximinoglycosyl Bromides: Versatile Donors for the Expedient Assembly of Oligosaccharides with β-D-Mannose, β-L-Rhamnose, *N*-Acetyl-β-D-mannosamine, and *N*-Acetyl-β-D-mannosaminuronic Acid Units

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CONTENTS

1. INTRODUCTION

Our methodical armory for the stereocontrolled synthesis of interglycosidic bonds has expanded dramatically over the past two decades, such that their synthesis has reached a level of sophistication that even exceedingly complex oligosaccharides are fairly well accessible—albeit in a substantial number of steps owing to protecting group manipulations and activation protocols.[1] Of the various interglycosidic connections to be constructed in these endeavors, the stereocontrolled generation of a β-1,2-*cis*-glycosidic linkage toward oligosaccharides with D-mannose, L-rhamnose, D-mannosamine, and D-mannosaminuronic acid as constituent sugars (Figure 1)—ubiquitous in nature and endowed with important biological activities[2]—is the most difficult. The reasons are obvious: operation of the anomeric effect and the steric repulsion exerted by the axial C-2 substituent toward equatorial entry of an *O*-nucleophile strongly favor the formation of α-1,2-*trans*-glycosidic linkages in standard glycosylation protocols.

The challenge to circumvent these adverse circumstances has resulted in a plenitude of direct and indirect strategies, the direct

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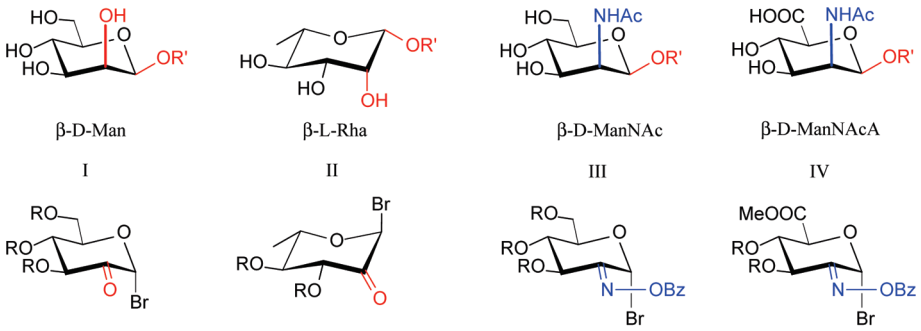


Figure 1. Structures of naturally occurring glycosides of β-D-*manno* and β-L-*rhamno* configurations (top) juxtaposed to 2-oxoglycosyl ("ulosyl") and 2-oximinoglycosyl donors (below) from which they may efficiently be generated in two simple steps: β-specific glycosidation and stereocontrolled reduction.

approaches generating the desired β-mannosidic bond in a single step, such as the insoluble silver salt-mediated coupling of α-mannosyl halides[3] and the preparatively more efficient 4,6-*O*-benzylidene-directed glycosylation via in situ generation of α-mannosyl triflates from their thio- or sulfoxidoglycosides.[4] The indirect approaches require either prior attachment of the acceptor to the mannosyl donor, such as the intramolecular aglycon delivery method,[5,6] or the correction of stereochemistry at C-2 in β-glucosides feasible by S_N2 displacement of a suitable leaving group placed at C-2[7] or by sequential oxidation/reduction with 2-*O*-unprotected β-D-glucosides.[8] These approaches have been well reviewed by Barresi and Hindsgaul,[9] Gridley and Osborn,[10] Pozsgay,[11] and El Ashry et al.,[12] adequately elaborating on their respective advantages and shortcomings. By contrast, the two-step ulosyl donor approach to β-D-mannosides and β-L-rhamnosides, introduced in 1983,[13] as well as the use of 2-oximinoglycosyl bromides for the generation of oligosaccharides containing *N*-acetyl-β-D-mannosamine (β-D-ManNAc) and *N*-acetyl-β-D-mannosaminuronic acid (β-D-ManANAc) units have, except for an early review,[14] only cursorily been treated or not covered at all.[15]

This review gives an overview on the present development of this approach with respect to the straightforward preparation of ulosyl and oximinoglycosyl bromides of types I–IV (Figure 1), the protocols for reaching high or exclusive β-selectivity in glycosidations as well as high *manno*-selectivity in the reduction of the respective 2-oxo- and 2-oximino-β-glycosides, and, most significant, their utilization for the assembly of oligosaccharides with β-D-mannose (β-D-Man), β-L-rhamnose (β-L-Rha), β-D-ManNAc, and β-D-ManNAcA units.

2. ULOSYL DONOR APPROACH TO β-D-MAN AND β-L-RHA LINKAGES

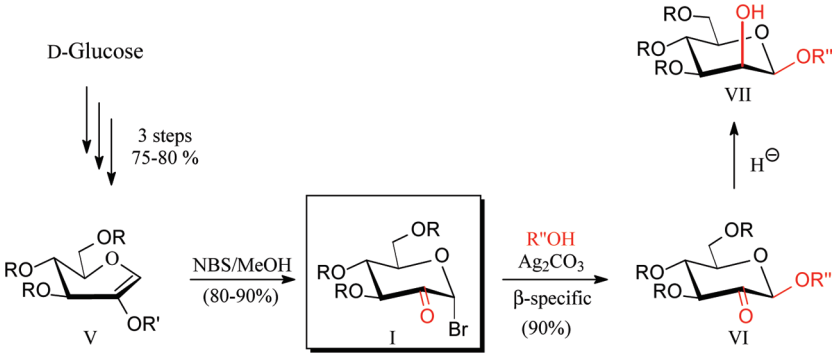
The essence of the ulosyl donor strategy to β-D-mannosides (or β-L-rhamnosides) comprises the four-step generation of 2-oxoglycosyl (glycos*ulosyl*) bromides of type I or II (Figure 1) from D-glucose (or 6-deoxy-L-glucose) via the respective 2-hydroxyglycal esters **V** and then their essentially β-specific insoluble silver salt-promoted glycosidation, **I** → **VI**, and highly *manno*-selective reduction of the resulting β-D-glycosid-2-uloses, **VI** → **VII** (Scheme 1).

The intrinsic preparative advantages of this methodology not only lie in the multigram accessibility of the ulosyl bromides and the exceedingly high level of β- as well as *manno*-selectivity in their two-step conversion to β-mannosides, but in the fact that, preparatively, those two steps can be merged into a consecutive one-pot procedure. As propitiously, the resulting β-D-mannosides **VII** carry a free 2-OH and hence are acceptor substrates for glycosylation with other donors, even with another ulosyl bromide toward (1→2)-β-D-mannopyranosyl oligomers.

2.1. Preparation of Ulosyl Donors

2.1.1. Ulosyl Bromides. Unlike the venerable acylated glycosyl bromides that were first prepared by Koenigs and Knorr

Scheme 1. Essentials of the Ulosyl Bromide Methodology



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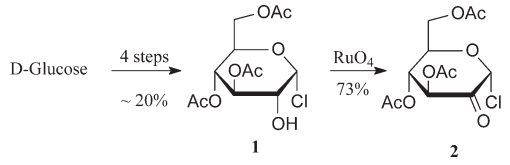
in 1900,[16] their 2-oxohexosyl ("ulosyl") analogues were not encountered until 73 years later, when Collins et al.[17] subjected the 2-*O*-unprotected hexosyl chlorides of D-glucose and D-galactose to a ruthenium tetroxide oxidation, e.g., **1** → **2** (Scheme 2). The somewhat intricate accessibility of **2** and its *galacto* analogue—five steps from the underlying sugar in modest overall yields (15−20%)—and their capricious obtention as gums, however, have not invited their utilization as glycosyl donors for the synthesis of oligosaccharides.

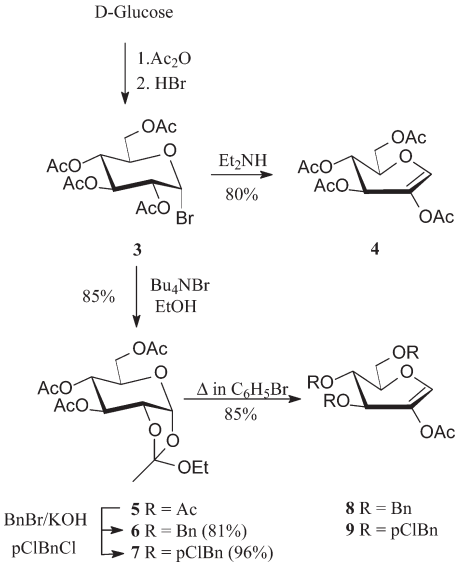
Scheme 2. Five-Step Sequence for the Generation of Acetylated Glycos-2-ulosyl Chlorides[17]



Only the elaboration of a simple, preparatively satisfactory access to their bromo analogues, the glycosulosyl bromides, from any of the common sugars[14] and the establishment of suitable conditions for β-specific glycosidation and *manno*-selective reduction[9] prompted their comprehensive use as indirect glycosyl donors for the straightforward synthesis of oligosaccharides containing β-D-mannose units.

Key intermediates for the efficient generation of glycos-2-ulosyl bromides are the 2-(acyloxy)glycals. In their ester-protected form, they are most readily accessible from any of the basic mono- or disaccharides in a large-scale adaptabe three-step procedure comprising acylation, bromination, and elimination of hydrogen bromide, as exemplified for the D-glucose case in Scheme 3. As the first two of these steps can be combined into a one-pot operation, the overall yields are in the 70% range.[18]

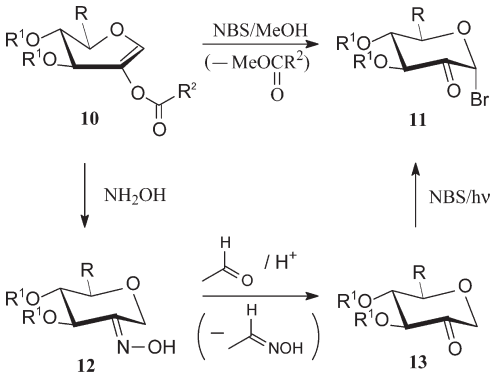
Scheme 3. Access to 2-Acetoxyglucals



In the case of 2-(acyloxy)glycals with benzyl protection, such as D-glucose-derived **8** or **9**, their acquisition requires a five-step sequence from a common sugar: conversion of acetobromoglucose **3** into the orthoester **5** by exposure to tetrabutylammonium bromide/ethanol in the presence of *s*-collidine,[19] followed by exchange of the *O*-acetyl groups by benzyl (→**6**) or *p*-chlorobenzyl (→**7**) residues and subsequent thermal fragmentation by refluxing in bromobenzene, the overall yields being in a preparatively satisfactory 60−65% range.[20,21]

The conversion of 2-(acyloxy)glycals into glycos-2-ulosyl bromides can be effected by either one of two ways (Scheme 4): a high-yield three-step procedure involving hydroxylaminolysis of the enediol ester group, **10** → **12**,[22] deoximination[23] (→**13**), and photobromination at the push−pull-substituted anomeric center, **13** → **11**,[24,25] or, alternately, via a straightforward one-step process simply comprising exposure of the respective 2-(acyloxy)glycal **10** in dichloromethane solution to a slight excess of *N*-bromosuccinimide or bromine in the presence of methanol (30 min at room temperature, rt)[13,26−32] or in the more reactive *O*-benzyl-protected cases with ethanol at 0 °C for 1−2 min.[20,21]

Scheme 4. Generation of Ulosyl Bromides from 2-(Acyloxy)glycals



R = CH_2OR^1, CH_3, H, COOMe;
R^1 = Ac, Bz, Piv, Bn;
R^2 = CH_3, Ph.

As amply demonstrated by the 20 presently known ulosyl bromides, all prepared by the one-step procedure **10** → **11** (Table 1, compounds **14**−**33**), the exceedingly mild conditions and the easily removable other reaction products—succinimide and methyl acetate or methyl benzoate—are as remarkable as the yields obtainable, which are in the 75−90% range. Equally important, this methodology tolerates essentially any blocking group pattern, is applicable to cellobiose- and lactose-derived hydroxyglycal esters, thus providing the cellobiosulosyl bromide **21** and lactosulosyl bromide **22** as particularly versatile disaccharide donors, and appears to be amenable to large-scale syntheses (reactions up to 20 mmol have been performed with no drop in efficiency).

Mechanistically, this one-step process, **10** → **11**, as exemplified with the 2-(benzoyloxy)-D-glucal tribenzoate **34** (Scheme 5), is thought to proceed via initial axial attack of a bromonium ion to a 2-bromobenzoxonium salt intermediate, **35**, in which the 2-*O*-acyl group is captured by methanol; the resulting formation of methyl benzoate and a bromide ion leaves behind the ion pair **36**, which combines to give ulosyl bromide **15**.[26] Substantiation for the C-2 capture of the bromonium ion from the axial face can be

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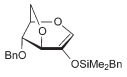
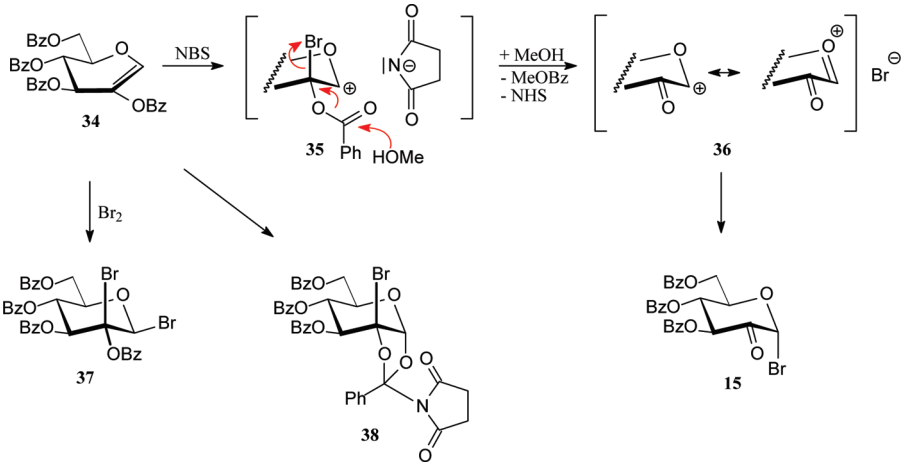
Table 1. Direct Conversion of Hydroxyglycal Esters into Glycosulosyl Bromides[a]

Educt	Hydroxy-glycal Ester	R	Product		Conditions[b]	Yield[c] (%)	Mp (°C)	$[\alpha]_D^{20}$ ($CHCl_3$)	Ref.
D-Glucose		Ac		**14**	a	92	syrup	+233.7	26
		Bz		**15**	a	89	134-135	+224.1	26
		Piv		**16**	a	85	125-126	+191.4	26
D-Glucose		Bn		**17**	a	96	syrup	+103.7	27
		All		**18**	a	90	syrup	+154.8	28
D-Glucose		Bn		**19**	b	92	syrup	+172	20
		p-ClBn		**20**	b	92	syrup	?	21
Cellobiose		βBz_4Glc		**21**	a	83	amorph.	+80.0	29
Lactose		βBz_4Gal		**22**	a	90	amorph.	+123.0	29
D-Glucuronic acid		Ac		**23**	a	66	syrup	+192.4	30
		Bz		**24**	a	70	171-173	+151.6	30
6-Deoxy-D-glucose		Me		**25**	a	76	125-126	+191.4	31
D-Xylose		H		**26**	a	81	syrup	+101.5	26
L-Rhamnose				**27**	a	75	123-124	-195.2	32
L-Rhamnose		Ac		**28**	b	98	syrup	-203.9	32
		Bz		**29**	b	95	syrup	-132.5	32
		Bn		**30**	b	87	syrup	-229.2	32
		pMeOBn		**31**	b	98	syrup	-196.4	32
D-Glucose				**32**	c	?	syrup	?	33
D-Galactose				**33**	a	79	62	+319.0	26

[a] Abbreviations: Ac = acetyl; Bz = benzoyl; Piv = pivaloyl (*t*BuCO); All = allyl; Bn = benzyl; *p*MeOBn = *p*-methoxybenzyl; β-Bz_4Glc = 2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl; βBz_4Gal = 2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranosyl. [b] Reagents and conditions: (a) NBS/CH_2Cl_2, MeOH, 30 min, rt; (b) NBS/CH_2Cl_2, EtOH, 2−15 min, 0 °C; (c) NBS/THF, −20 °C. [c] Yields based on the respective hydroxyglycal esters.

Scheme 5



derived from the course of the Br_2/CCl_4 bromination of **34**, delivering the 2-bromo-β-D-glucopyranosyl bromide **37** as the major product,[34] and from the NBS/CH_2Cl_2 bromination of **34** (in the absence of methanol), which led to the orthoester amide **38**,[35] which spontaneously elaborated the ulosyl bromide **15** on exposure to methanol.[36]

2.1.2. Anomerically Modified Ulosyl Donors. While the ulosyl bromides with a benzyl group protection pattern exhibit

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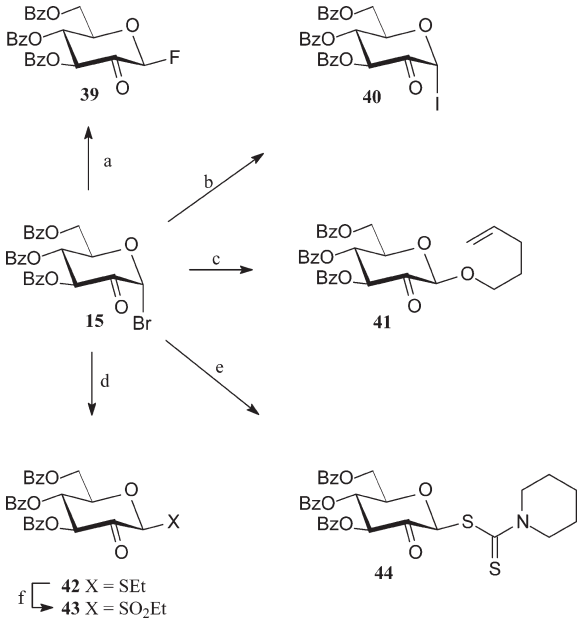
high anomeric reactivities, their peracylated analogues are stable substances, storable for weeks without noticeable decomposition; hence, they must be considered as comparatively unreactive glycosyl donors—a conclusion conforming with the preparative finding that the benzoylated ulosyl bromide **15** (cf. Table 1) may be recovered from a methanolic solution at ambient temperature, methanolysis only occurring on heating under reflux.[26] While acylated ulosyl bromides nevertheless proved to be a useful glycosyl donor when promoting glycosidations with insoluble silver salts (cf. section 2.2.1), they alternately may readily be transformed into a range of more reactive donor substrates, such as the β-fluoride **39**, the α-iodide **40**, the 4-pentenyl uloside **41**, and a number of thioglycosiduloses, e.g., the ethylthio **42**, its sulfone derivative **43**, and piperidinecarbodithioate **44** (Scheme 6), each obtainable in crystalline form and in high yields (80−95%).[26]

Except for the ulosyl iodide **40** though, which exhibits an approximately 10-fold higher anomeric reactivity than the bromide **15**, these modified ulosyl donors are of limited preparative utility in glycosylations as the β-selectivities attainable are distinctly lower than those obtained with the bromide or iodide (cf. section 2.2.1).

Scheme 6. Anomerically Modified Ulosyl Donors[a]



[a] Reagents and conditions: (a) AgF in $MeNO_2/CH_2Cl_2$, 30 min, −18 °C; 95%;[37] (b) NaI/Celite, $CHCl_3$, 7 h, reflux; 83%;[26] (c) silver aluminosilicate, 4-pentenol, 5 min, −18 °C → rt; 78%;[26] (d) in situ sodium piperidinedithioate/DMF, 10 min, −60 °C; 96%;[26] (e) EtSH/$(Me_2N)_2CO$, CH_2Cl_2, 6 h, rt; 75%;[26] (f) MCPBA, CH_2Cl_2, 0 °C → rt, 82%.[26]

2.2. Anomeric Selectivities in Ulosyl Bromide Glycosidations

As the glycos-2-ulosyl bromides listed in Table 1 lack a participating group next to the anomeric center, the stereochemical outcome of glycosidations strongly depends on the catalyst. As to be detailed in the sequel on the basis of comprehensive evidence, the use of insoluble silver salts, such as the classical silver carbonate,[16] silver silicate,[38] or silver aluminosilicate,[39] as the promoters invariably results in the formation of β-glycosiduloses with either high or complete stereoselectivitiy—obviously due to

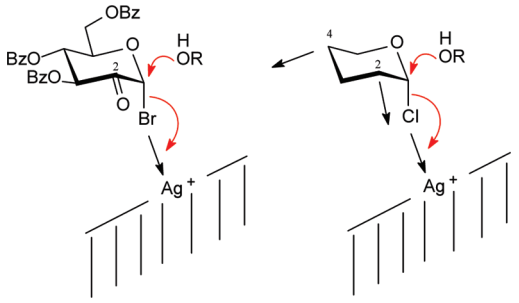


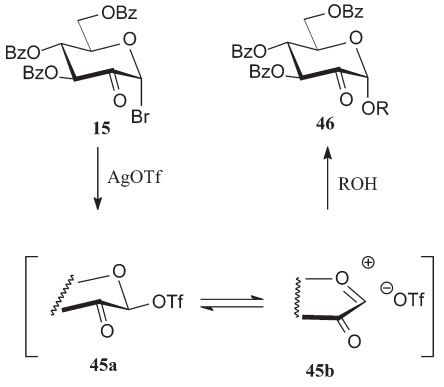
Figure 2. Electron-withdrawing substituents at C-2 and/or C-4 favor S_N2-type attack of the alcohol component in insoluble silver salt-promoted glycosidations, entailing high β-selectivities.

an essentially full suppression of oxocarbenium ion intermediates by the strong electron-withdrawing effect of the 2-carbonyl and, hence, a high if not exclusive displacement of the bromine by the alcohol (Figure 2, left).

Support for this mechanistic inference can be derived from the β-directional effects exerted by electron-withdrawing groups at C-2 (and C-4). In his lucid rationalizations on extensive experimental material, van Boeckel[40] came to the conclusion that OAc or N_3 groups at C-2 and/or C-4 impede the formation of an intermediate oxocarbenium ion at the anomeric center, thereby allowing the alcohol component to directly attack in an S_N2 mode and entailing high proportions of the β-glycoside (Figure 2, right). In analogous fashion, the work by Schuerch[41] on the glycosidation of α-D-mannosyl and α-L-rhamnosyl chlorides carrying electron-withdrawing 2-*O*-sulfonyl groups which give comparatively high β-selectivities finds a most plausible rationalization in the direct S_N2 displacement of the anomeric chloride (arrows in Figure 2, right). Accordingly, it is not necessary to invoke oxocarbenium ion intermediates twisted toward the boat conformation[42] to account for the observed stereoselectivities, inasmuch as such species, when formed, have a penchant to form α-glycosides.

The glycosidation of ulosyl bromides can also be conducted in a highly α-selective manner simply by mediating with *soluble* silver salts, most effective being silver triflate in CH_2Cl_2 at low temperature. Although less well studied than β-glycosylations, the respective α-glycosiduloses are generated with distinct preference (cf. section 2.2.2), the reaction, e.g., **15** → **46**, conceivably proceeding via a β-triflate, **45a**, stabilized by the inductive effect of the carbonyl group or an oxocarbenium ion pair, **45b** (Scheme 7).

Scheme 7



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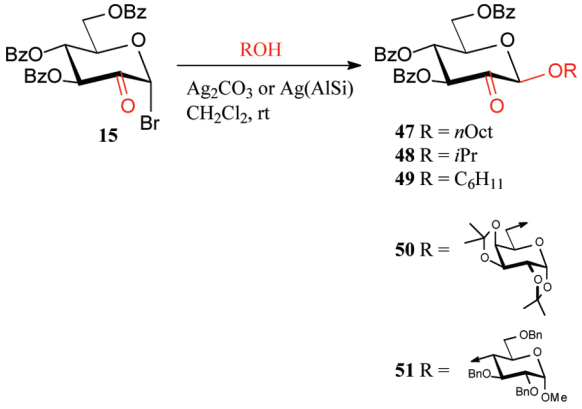
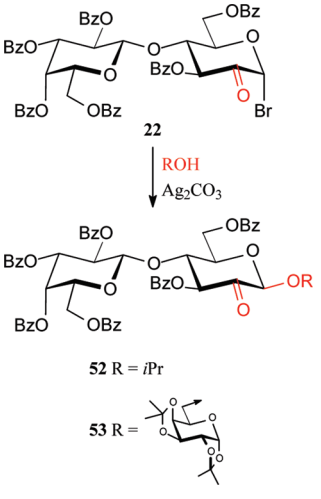
2.2.1. β-Selective Glycosidations. Although the *ester-protected ulosyl bromides* of Table 1 exhibit a lower anomeric reactivitiy than their benzylated analogues (vide infra), they nevertheless readily yield to *O*-glycosidations with high or exclusive β-selectivity when mediated by insoluble silver catalysts. The ulosyl bromide **15**, for example, afforded the β-glycosiduloses **48**,[26] **49**,[26] and **50**[43] simply by stirring in dichloromethane with silver carbonate in the presence of the respective alcohol (0.5−3 h, rt), the actual reaction time best being determined by thin-layer chromatography (TLC) monitoring. Using the highly active van Boeckel catalyst—i.e., silver(I) immobilized on a porous, amorphous aluminosilicate[39]—or Garegg's silver zeolite,[38] these reaction times may be substantially shortened, e.g., to 2 min, for the glycosylation of 1-octanol, **15** → **47**, whereas the comparatively unreactive 4-OH of methyl 2,3,6-tri-*O*-benzyl-α-D-glucoside required 16 h at rt to be glycosylated by **15** to the disaccharide **51**[43] (Scheme 8); in each case though, the couplings took an essentially β-specific course, so isolated yields were in the 80−90% range.[14,37,43]

Scheme 8



The disaccharide-derived ulosyl bromides **21** and **22** (cf. Table 1) are less reactive than the monosaccharide analogue **15**, as evidenced by the comparatively slow (12 h, 25 °C) glycosidation of lactulosyl bromide **22** with 2-propanol (→**52**, 90%[29]) and diacetonegalactose (→**53**, 62%[44]) (Scheme 9), no anomers being detectable by ^{1}H NMR in the reaction mixtures.

Scheme 9



These results amply show that despite the low anomeric reactivity of ulosyl bromides essentially β-specific glycosidations can readily be achieved with a variety of hydroxyl components—without the need to resort to anomerically modified donor substrates. If a higher anomeric reactivity is required though, the α-iodide **40**, readily prepared from the bromide **15** by refluxing in chloroform with sodium iodide adsorbed on Celite,[26] is the donor of choice (Figure 3). Iodine has an approximately 10 times higher reactivity than its bromide, as evidenced, e.g., by the Ag_2CO_3-induced conversion of **40** into isopropyl β-uloside **48**: alcoholysis occurs in a matter of 10 min—versus a 2 h reaction time in the case of α-bromide **15**.

The anomerically modified ulosyl donors **41**−**44** (Figure 3) appear to be of less utility, since their glycosidations require homogeneous Ag^+ catalysis, conditions that invariably result in the partial generation of α-glycosiduloses. Thus, the pentenyl uloside **41**, when activated as recommended[45] with NIS/TfOH or triethylsilyl triflate, rapidly reacts with 2-propanol (5 min at rt

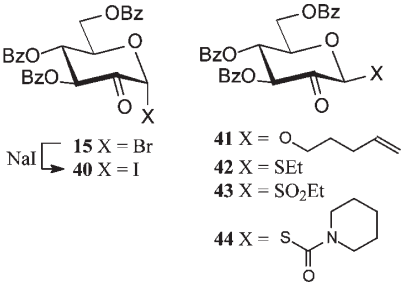


Figure 3. Reactivity-enhanced acylated ulosyl donors.

in CH_2Cl_2) to a 3:1 β/α mixture of isopropyl ulosides.[37] Similar limitations apply to the thioglycosiduloses **42**−**44**. When activated in situ with various catalyst systems, such as NIS/TfOH[46] in 1,2-dichloromethane (15 min, 0 °C) for **43** and methyl triflate[47] in dichloromethane (3 h, 25 °C) for **44**, the β-selectivities obtained are in the 2:1 to 5:1 range only.[37]

That ether-protected ulosyl bromides have higher anomeric reactivity than their ester analogues is already obvious from the fact that the benzylated ulosyl bromide **19** undergoes methanolysis on dissolution in methanol at room temperature, while its benzoylated analogue **15** can be quantitatively recovered from a methanol solution, alcoholysis occurring on heating only. Under standard Koenigs−Knorr conditions, β-specific alcoholysis is a matter of minutes with simple alcohols such as 2-propanol (→**54**) and diacetonegalactose (→**55**), whereas the moderately reactive hydroxyl groups in methyl 2,3-*O*-isopropylidene-α-L-rhamnoside (→**56**) or in methyl 2,3,6-tri-*O*-benzyl-α-D-glucoside (→**57**) require around 15 min at room temperature to effect the respective conversions[20,48] (Scheme 10). The same holds for the silver zeolite-promoted coupling of **19** with allyl 3,4,6-tri-*O*-benzyl-β-D-mannoside (→**58**).[21] In each case though, the couplings to the respective disaccharides **55**−**58** took an essentially β-specific course, resulting in yields in the 80−90% range.

The 6-deoxy-β-L-*arabino*-hexulosyl bromides **28**−**31** (Table 1), convenient donor substrates for the generation of β-L-rhamnosides (vide infra), similarly yield to β-specific glycosidation. As exemplified with the variably *O*-protected ulosyl donor **29** (Scheme 11), alcoholysis with 2-propanol (Ag_2CO_3 in CH_2Cl_2 at rt) or saccharidic alcohols such as diacetonegalactose and methyl 2,4-di-*O*-benzyl-α-L-rhamnoside (Ag^+/aluminosilicate,

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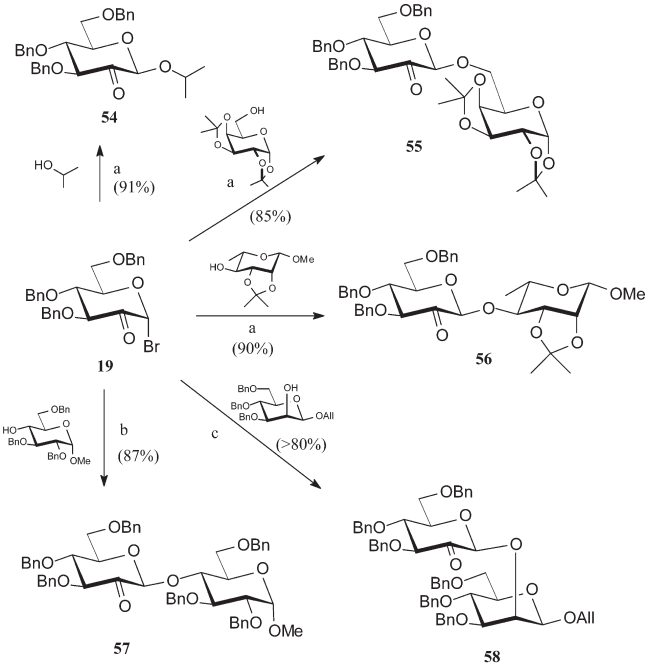
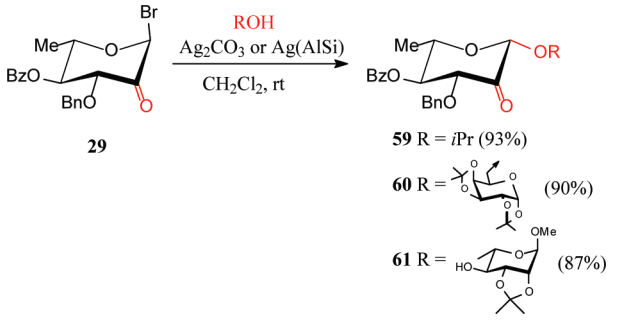
Scheme 10. Insoluble Silver Salt-Promoted β-Specific Couplings of Ulosyl Bromide 9 with Various Alcohols[a]



[a] Reagents and conditions: (a) Ag_2CO_3, acceptor alcohol, molecular sieves 4 Å, CH_2Cl_2, 5−15 min, rt;[20] (b) silver aluminosilicate, glycosyl acceptor, 20 min, rt;[48] (c) silver zeolite, mannosyl acceptor, 16 h, rt.[21]

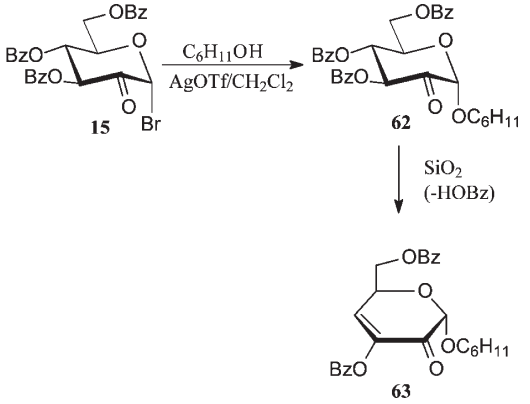
CH_2Cl_2, rt) are complete within 15−30 min, no α-anomeric products being detectable in the reaction mixtures by ^{1}H NMR or TLC. Accordingly, the yields of β-L-rhamnosiduloses **59**−**61** are excellent.[32]

Scheme 11



2.2.2. α-Selective Glycosidations. Of the several procedures evaluated with the benzoyl-protected ulosyl bromide **15**, moderately useful results are obtained with Lemieux's tetraethylammonium bromide-promoted in situ anomerization procedure or with silver triflate as the catalyst, each resulting in approximately 4:1 to 10:1 α/β mixtures. Silver triflate-induced glycosidation of **15** with cyclohexanol (30 min, rt), for example, gave the α-glycosidulose **62** nearly exclusively (TLC), yet only part could be secured from the anomeric mixture which fortuitously crystallized (34%) (Scheme 12); a further increase in yield was precarious because even brief contact with silica gel (flash chromatography) induced partial β-elimination of benzoic acid to the respective enolone ester **63**.[43]

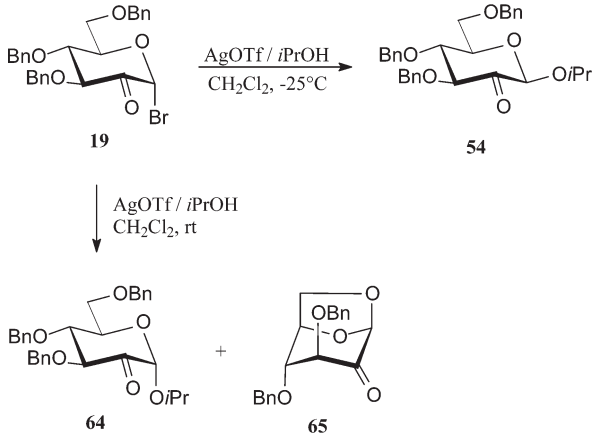
Scheme 12



In the case of the more reactive benzylated analogue **19**, exposure to 2-propanol in the presence of silver triflate (in CH_2Cl_2 at −25 °C, 10 min) led to the β-uloside **54** (78%). At ambient temperature though, and upon slow addition of 2-propanol to **19** and silver triflate in CH_2Cl_2, a 3:2 mixture of the α-anomer **64** and the 1,6-anhydrouloside **65** was obtained (Scheme 13), the latter through intramolecular participation of the C-6 oxygen and loss— formally—of benzyl bromide.[20]

Due to these preparative complications and the additional strategic disadvantage that α-D-glycosiduloses, on subsequent hydride reduction, provide α-D-glucosides which are more economically made from the parent sugar directly, α-selective glycosidations of ulosyl donors received no further attention.

Scheme 13



2.2.3. Glycosidations with Bifunctional Acceptors. When exposing ulosyl bromides in the presence of insoluble silver salts to bifunctional acceptors such as vicinal diols or their amino and thio analogues, the essentially β-specific glycosidation is followed by intramolecular hemiketalization with the 2-carbonyl. As exemplified by the Ag_2CO_3-promoted reaction of glycol[35,49] or (*R*,*R*)-1,2-cyclohexanediol[50] with ulosyl bromide **15**, β-glycoside formation with one OH entails intramolecular addition of the other at the carbonyl group to form the β-*cis*-annulated cyclohemiketals **66** and **67**, respectively (Scheme 14), the high yields (92 and 87%) emphasizing the extent of stereocontrol in the two consecutive reactions involved. Enjoying the thermodynamics derived from two anomeric effects and the

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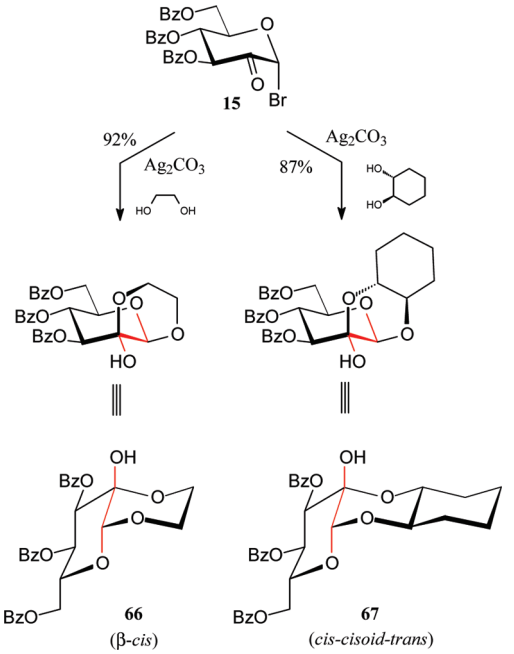
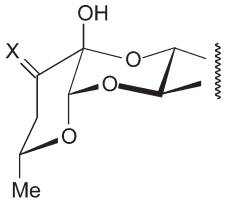
propensity to elaborate the sterically most favorably annulated dioxane ring, the second OH attacks the C═O of the glycosidulose intermediate from the axial (upper) face of the pyran ring to give products (**66** and **67**) in which the pyranoid ring oxygen and the ketalic OH at the ring junction are in the favorable *trans*-diaxial disposition (marked in red in Scheme 14). The alternate possibility—OH attack from the equatorial face—would lead to *trans*-connection of the dioxane ring in which stereoelectronic effects are distinctly less favorable.[49,50]

Scheme 14. Ulosyl Bromide Glycosidations with Glycols Entailing Cyclohemiketalization



The *cis*-linked trioxadecalin **66** and the *cis,cisoid,trans*-fused pyran−dioxane−cyclohexane tricycle **67** with their acetalic OH group at the ring junction contain the key structural and conformational features of the antibiotic spectinomycin and a series of cardioactive glycosides such as gomphoside. Each bear their steroidal respectively diaminoinositol aglycon in bisacetalic *cis*-annulation to a 4,6-dideoxy-D-hexos-2,3-diulose (Figure 4), which can be attached in a straightforward manner to the respective aglycon using the 6-deoxyulosyl bromide **27** (see section 2.5.3).

The "click-type" elaboration of a *cis*-joined pyranodioxane structure upon reaction of ulosyl bromides with 1,2-diols (Scheme 14) can equally well be accomplished with other 1,2-bifunctional compounds: 1,2-ethanedithiol and 2-mercaptoethanol, for example, smoothly formed the 1,4,5-triheterodecalins **68** and **69** simply on stirring ulosyl bromide **15** in dichloromethane in the presence of either silver carbonate or tetramethylurea (Scheme 15). Under the same conditions, 2-mercaptophenol, 1,2-dimercaptobenzene, and 2-aminophenol gave the respective benzo analogues **70**−**72**, while the reaction with 1,2-dihydroxybenzene required addition of base to proceed (→**73**), obviously due to the lower nucleophilicity of the phenolic OH groups as compared to aliphatic alcohols. In the case of 1,2-diaminobenzene though, elimination to the pyranobenzopyrazine **74** occurred during workup.[51]



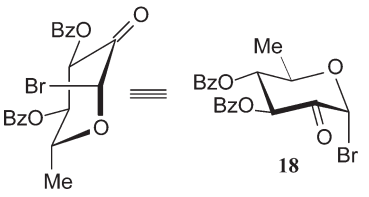
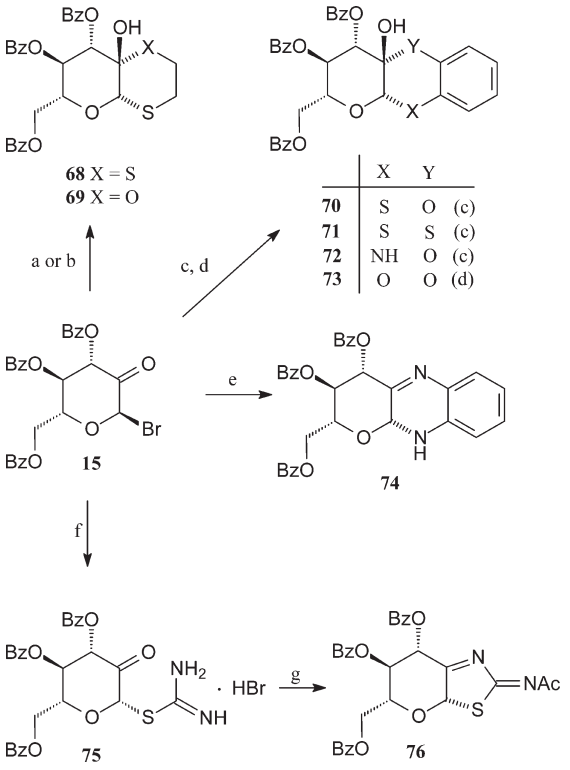


Figure 4. *cis*-Biacetal attachment of a 4,6-dideoxy-D-hexos-2,3-diulose onto the aglycon diols of spectinomycin and gomphoside.

As α-haloketones are known to readily react with thiourea to form aminothiazoles,[52] which are of interest as pharmaintermediates, ulosyl bromide **15** was exploited for the generation of enantiomerically pure pyranothiazolamines. Indeed, when equimolar parts of

Scheme 15. Enantiopure Fused *O*-, *S*-, and *N*-Heterocycles[a]



[a] Reagents and conditions: (a) Ag_2CO_3, ethanedithiol in CH_2Cl_2, 1 h, rt, →**68** (79%);[49] (b) ethanedithiol, TMU in CH_2Cl_2, 1 h, rt, →**68** (86%); with 2-mercaptoethanol, →**69** (92%);[51] (c) TMU in CH_2Cl_2, 1 h, rt, with 2-mercaptophenol, →**70** (97%); with 1,2-dimercaptobenzene, →**71** (80%); with 2-aminophenol, →**72** (60%);[51] (d) 1,2-dihydroxybenzene, TMU, Et_3N in CH_2Cl_2, 1 h, rt, →**73** (56%);[51] (e) 1,2-diaminobenzene, TMU in CH_2Cl_2, 1 h, rt, →**74** (75%);[51] (f) thiourea in Me_2CO, 15 min, rt, →**75** (88%);[49] (g) pyridine/Ac_2O, 20 min, 0 °C, →**76** (91%);[49] (TMU = 1,1,3,3-tetramethylurea).

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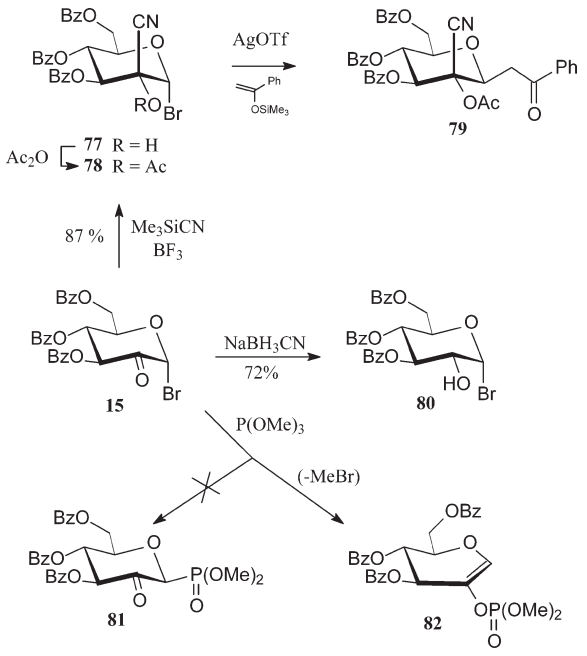
thiourea and **15** reacted in acetone solution at room temperature, the anomeric bromine was instantaneously displaced by sulfur to give the β-thioamidine, isolated as the hydrobromide **75** in 88% yield (Scheme 15). Removal of HBr by ion-exchange resin left the β-glycosidulose intact (TLC), yet quantitative ring closure was effected on acetylation to give the acetamidothiazole **76** in nearly quantitative yield.[49]

2.2.4. *C*-Glycosidations. Anomeric cyanation of an acylated glycosyl halide has undoubtedly been the most practical *C*-extension method in terms of simplicity of reagents, workup procedures, and yields.[53] However, exposure of ulosyl bromide **15** to Helferich cyanation conditions[53a] (mercuric cyanide in nitromethane for 1−2 d, rt) resulted in complex product mixtures; by contrast, reaction with trimethylsilyl cyanide/$BF_3 \cdot OEt_2$[53e] was instantaneous, yet the anomeric bromine was not replaced by cyanide, but the cyanohydrin **77**, isolable in 87% yield, was formed quantitatively (TLC).[35,54] (Scheme 16). Thus, of the two electrophilic carbons that may be attacked by cyanide—displacement of bromine at C-1 or carbonyl addition at C-2—the latter is strongly preferred, obviously due to the electron-withdrawing effect of the 2-carbonyl that diminishes the polarity of the C−Br bond.

Scheme 16



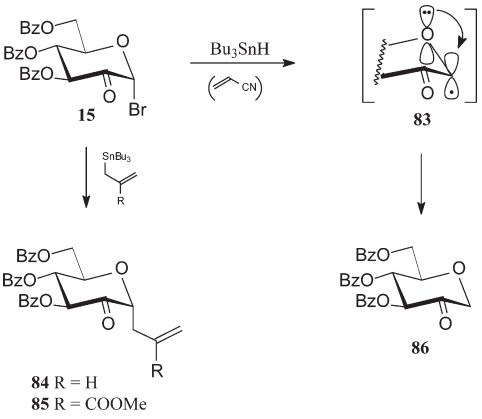
Accordingly, *C*-glycosidation via an electrophilic 2-oxoglycal intermediate requires prior carbonyl protection to avoid carbonyl addition of the *C*-nucleophile—the cyanohydrin **77** upon *O*-acetylation (→**78**) being one possibility. Indeed, on silver triflate-promoted reaction with the silylenol ether of acetophenone the β-phenacyl product **79** was obtained in high yield.[54]

The ambivalence of the two competing electrophilic centers in ulosyl bromides is similarly borne out in their reactions with a mildly reactive hydride reagent[55] and with trimethyl phosphite.[13] Exposure of **15** to acid-catalyzed cyanoborohydride reduction in dioxane at rt resulted in the formation of the glucosyl bromide **80** (72%), proceeding via nearly exclusive hydride addition to the carbonyl group from the side opposite the anomeric substituent (Scheme 16). Only with excess reductant and on extended reaction times did hydride addition and reductive dihydrobromination occur to then afford the 3,4,6-tribenzoate of 1,5-anhydroglucitol (60%).[55] Ulosyl bromides being α-haloketones as well, their reactions with phospites are doomed to proceed either to phosphonates of type **81** (Arbuzov reaction[56]) or to enol phosphates (Perkow reaction[57]). As shown by exposure of ulosyl bromide **15** to trimethyl phosphate, only the Perkow-type reaction takes place to the 2-phosporyloxyglucal ester **82** (Scheme 16), conceivably through attack at the anomeric carbon, the resulting trimethylphosphonium salt then being stabilized by consecutive excision of methyl bromide and C → O shift of the phosphoryl residue.[13]

The most commonly used approach for *C*-extensions via glycosyl radicals is their generation from glycosyl bromides with tributyltin hydride and AIBN as initiators and treatment with electron-deficient alkenes.[58] However, attempts to effect radical-induced coupling of ulosyl bromide **15** with acrylates or acrylonitrile under a variety of conditions failed, since the 2-oxoglycosyl radical **83** generated by $Bu_3SnH/h\nu$ or AIBN is quantitatively trapped by hydrogen even in acrylonitrile as the solvent, to afford the known[59] 1,5-anhydro-D-fructose tribenzoate **86**[54] (Scheme 17).

Reagents with inherent radical chain transfer,[60] e.g., allyltributylstannane in the presence of catalytic amounts of AIBN, reacted sluggishly with **15** to give the 1-*C*-(α-D-oxoglycosyl)propene **84** in modest yield (26%), whereas reaction of **15** with its 2-carbomethoxy analogue proceeded more uniformly to the 1-*C*-(α-D-oxoglycosyl)methacrylate **85** (57%).[54] In toto though, the "one-electron" *C*-extension of ulosyl bromides appears to be of limited preparative utility.

Scheme 17



C-Extensions of ulosyl bromides via nucleophilic anomeric carbons appear to be more promising, as their α-bromocarbonyl functionality is apt to yield to Reformatsky-type conditions, i.e., to generate enolate intermediate **87** on treatment with zinc in an inert solvent. Indeed, when **15** was treated with copper-activated zinc in THF, followed by addition of formaldehyde, a 1:1 mixture of α- and β-hydroxymethylation products was generated, of which the α-isomer **88** was isolable (35%), but difficult to purify, since extensive 3,4-elimination of benzoic acid occurred on elution from a silica gel toward the dihydropyranone **90** (Scheme 18). On brief treatment with $NaHCO_3$ in aqueous acetone, the conversion **88** → **90** can be effected quantitatively,[54] thus smoothly affording a versatile enantiopure C_7-building block.

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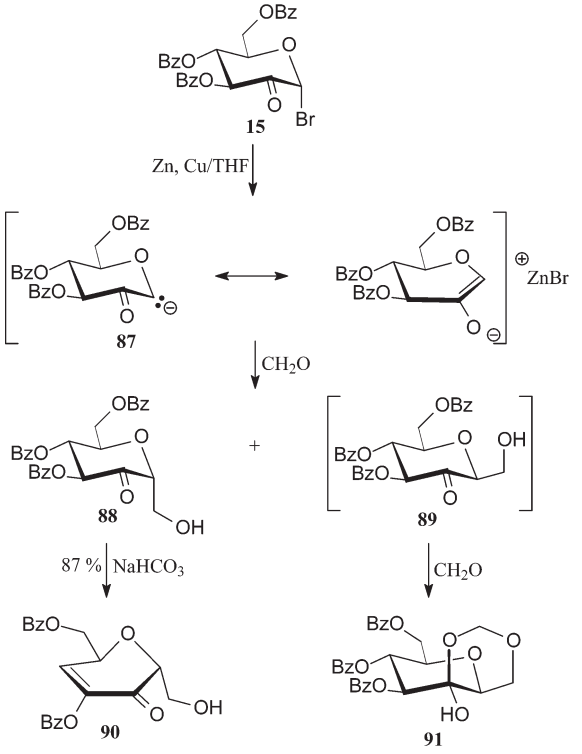
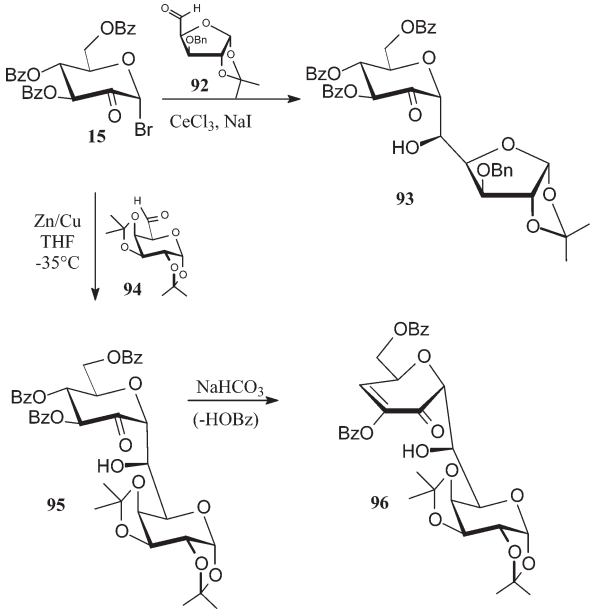
Scheme 18



Scheme 19



The β-anomer **89** cannot be isolated as such, but due to reaction with another formaldehyde molecule as the 1,3-*O*-methylene-bridged cycloacetal **91**.[54]

Trapping of the ulosyl bromide-derived enolate **87** with carbohydrate-based aldehydes smoothly leads to *C*-disaccharides (Scheme 19). Thus, D-xylose-derived aldehyde **92**, upon cerium-mediated generation of the enolate from ulosyl bromide **15**, gave a 2:1 mixture of α-adducts (58%), the major product being the 5*R* diastereomer **93**.[33] In the case of diacetonegalactose-6-aldehyde **94** and on Zn−Cu-promoted activation of **15**, an 8:1 mixture of two aldol adducts, **95** and its 6-epimer, was obtained in essentially quantitative yield.[33] As attempts toward purification of **95** on silica gel resulted in β-elimination of benzoic acid, the mixture was exposed to brief stirring with $NaHCO_3$ in aqueous acetone to give the beautifully crystalline *galacto*-dihydropyranone **96** in 73% yield.[54]

The α-stereocontrol observed in these aldol additions is noteworthy, given the fact that the cerium or zinc enolate intermediate shows neglible α,β-selectivity with formaldehyde (cf. Scheme 18) or acetaldehyde.[54]

2.3. β-Glycosidulose Reductions

2.3.1. *manno*-Selective Hydride Reductions. Ample evidence has accumulated[8,20,29,61] that β-glycosid-2-uloses ("β-ulosides") of D-*arabino* configuration—generated either by oxidation of 2-*O*-unprotected β-glucosides[8] or through glycosidation of ulosyl bromides (cf. section 2.2)—can be reduced by borohydride reagents to the respective β-D-mannosides with high preference. As the extent of *manno*-stereocontrol attainable in this reduction is crucial to the efficiency of the "ulosyl donor approach" to β-D-Man oligosaccharides, the different borohydride reagents have been studied in detail with the isopropyl β-D-*arabino*-hexosiduloses **48** and **54** as model compounds.[61] In the case of uloside **54**, carrying only *O*-benzyl blocking groups, the standard $NaBH_4$ reduction provides the β-D-mannoside **98** in a stereochemically uniform course and excellent yield, a result which is not further improved by using lithium tri-*sec*-butylborohydride in THF at −78 °C (entries 1−4 in Table 2).

With the more readily accessible, ester-protected isopropyl ulosides **48**, however, the steric outcome of the respective $NaBH_4$ reductions and those with $LiB(iBu)_3H$ or its K-analogue as well are distinctly different: 2:1 to 3:1 selectivities in favor of the mannoside **97** with $NaBH_4$ (entries 5 and 6) versus high, essentially complete, *manno*-stereoselectivities with the sterically bulky, *sec*-butyl-substituted borohydrides (entries 9 and 10).[61]

The essentially *manno*-specific course in the Selectride reductions of benzylated as well as acylated isopropyl ulosides, gratifyingly, is applicable to systems with larger anomeric residues. As borne out by the examples in Scheme 20 featuring octyl, cholestanyl, and a number of unwieldy glycoside residues, the 2:1 to 3:1 *manno*-selectivities of their $NaBH_4$ reductions are transformed into essentially stereospecific formation of the desired β-D-mannosides **101**−**105** when employing K- or L-Selectride in THF (Table 3).

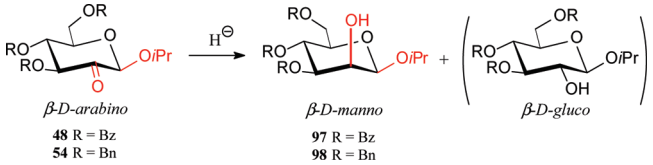
The same steric outcome is observed for thioglycosiduloses, e.g., **106**−**108**, which provide respective 1-thio-β-D-mannosides **109**−**111** in high yields (Scheme 21).[61] These are not only

Table 3. β-D-Mannosides 101−105 Obtained on Reduction of the Respective Ulosides with $NaBH_4$ and K- or L-Selectride[61]

	manno:gluco ratio		
educt	$NaBH_4$	Selectride	β-D-mannoside (isol yield, %)
47	3:1	50:1	**101** (88)
99	5:2	50:1	**102** (82)
15 (via **50**)	3:1	50:1	**103** (79)
15 (via **100**)	3:2	50:1	**104** (80)
15 (via **51**)	3:2	50:1	**105** (76)

dx.doi.org/10.1021/cr100444b |*Chem. Rev.* 2011, 111, 5569–5609

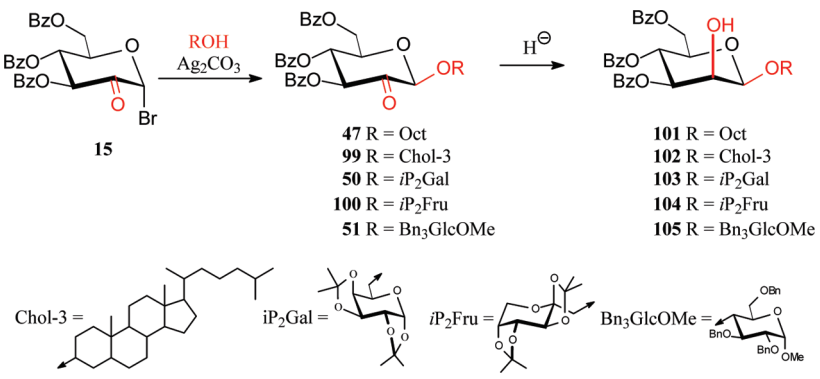
Table 2. Stereoselectivities of Hydride Reductions of Isopropyl β-D-*arabino*-Hexosid-2-uloses



entry	uloside	reagent[a]	solvent	temp (°C)	time (min)	ratio[b] *manno*:*gluco*	β-D-mannoside (isol yield, %)	ref
1	**54** (R = Bn)	$NaBH_4$	$MeOH/CH_2Cl_2$ (1:1)	rt	120	50:1	**98** (91)	20
2	**54** (R = Bn)	$NaBH_4$	$MeOH/CH_2Cl_2$ (1:1)	rt	20	50:1	**98** (90)	61
3	**54** (R = Bn)	$LiB(iBu)_3H$	THF	−78	1	50:1	**98** (86)	61
4	**54** (R = Bn)	$KB(iBu)_3H$	THF	−78	1	50:1	**98** (89)	61
5	**48** (R = Bz)	$NaBH_4$	$MeOH/CH_2Cl_2$ (1:1)	rt	20	3:1	[c]	61
6	**48** (R = Bz)	$NaBH_4$	CH_2Cl_2	rt	22 h	5:2	[c]	37
7	**48** (R = Bz)	$Zn(BH_4)_2$	DME	0	45	1:1	[c]	61
8	**48** (R = Bz)	Bu_4NBH_4	THF	rt	1	2:1	[c]	61
9	**48** (R = Bz)	$LiB(iBu)_3H$	THF	−78	1	50:1	**97** (85)	61
10	**48** (R = Bz)	$KB(iBu)_3H$	THF	−78	1	50:1	**97** (79)	61

[a] $LiB(iBu)_3H$ and $KB(iBu)_3H$ refers to lithium and potassium triisobutyl borohydride (i.e., L- and K-Selectride), respectively. [b] A 50:1 ratio signifies that no *gluco* isomer was detectable by ^1H NMR and TLC. All other ratios were determined by ^1H NMR. [c] Mixture of *manno* and *gluco* isomers not separated.

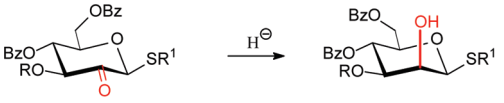
Scheme 20



useful mannosyl acceptors due to their free 2-OH, but donors as the *S*-aglycons can subsequently be activated under appropriate conditions.

In summation, essentially any 2-oxoglycoside of β-D-*arabino* configuration—generated either via the ulosyl bromide approach or via oxidation of 2-OH-free β-D-glucosides[8]—can be turned to preparative use for the expedient assembly of oligosaccharides with β-D-mannose units (section 2.4) or the synthesis of β-mannosylated noncarbohydrate natural products (section 2.5), a pertinent example being the synthesis of the fungal metabolite **115** (Scheme 22):[62] silver aluminosilicate-promoted glycosylation of the salicyclic acid derivative **112** followed by $NaBH_4$ reduction of the resulting β-glycosidulose to give the β-D-mannoside **113** with excellent stereoselectivity (78% yield over the two steps), subsequent removal of the isopropylidene group (→**114**), and hydrogenolysis, securing the natural product **115**.[62]

Scheme 21



	R	R^1
106	Bz	C_6H_5
107	Bn	Et
108	Bn	C_6H_5

	R	R^1	*manno*/*gluco*-ratio $NaBH_4$	*manno*/*gluco*-ratio Selectride	isol. yield (%)
109	Bz	C_6H_5	3:1	50:1	85
110	Bn	Et	15:1	50:1	78
111	Bn	C_6H_5	15:1	50:1	82

2.3.2. *gluco*-Selective Borane Reductions. On reduction of the carbonyl group in β-D-*arabino*-hexosiduloses with diborane in THF at room temperature, the selectivity is the reverse of that occurring with ionic borohydrides: β-D-glucosides are obtained with preferences that make the procedure preparatively useful. This steric course is exemplified by the borane reductions of the ulosides listed in Scheme 23, which give *gluco*:*manno* ratios from 7:1 to better than 20:1 and allow the isolation of the corresponding major products **116**−**120** in yields of 70−80%.[61]

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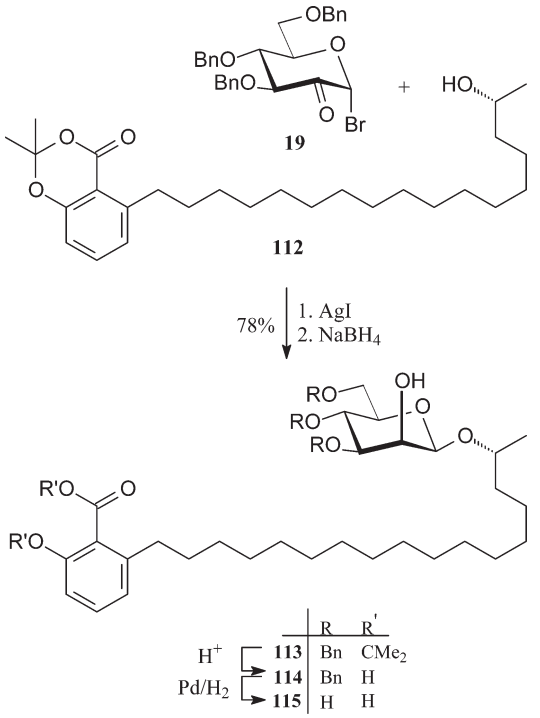
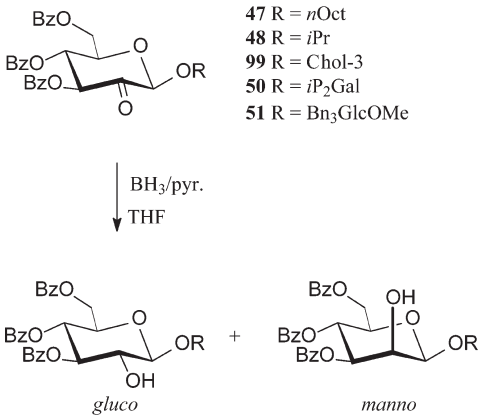
Scheme 22



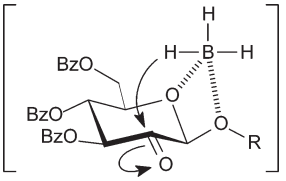
Scheme 23



	R	ratio *gluco*/*manno*	glucoside (yield, %)
116	*n*Oct	7:1	73
117	*i*Pr	11:1	82
118	Chol-3	10:1	76
119	iP_2Gal	8:1	72
120	Bn_3GlcOMe	>20:1	80

As these β-D-glucosides are obtained with free 2-OH groups, they are ideal glucosyl acceptors for the generation of oligosaccharides carrying 2-*O*-linked glucosyl residues.

In trying to rationalize this sterically reverse borane reduction course of 2-oxo-β-D-*arabino*-hexopyranosides, a preferential complexation of the neutral borane with the upper side (β-face) of the molecule appears most likely, such that not only the carbonyl oxygen is involved but due to the Lewis acid nature of borane the pyranoid ring oxygen and the anomeric oxygen are involved as well. This preorientation of the reducing agent to the uloside, as depicted in the following structure, obviously results in the preferential delivery of the hydride to the carbonyl carbon from the β-face to yield the β-D-glucosides:[61]

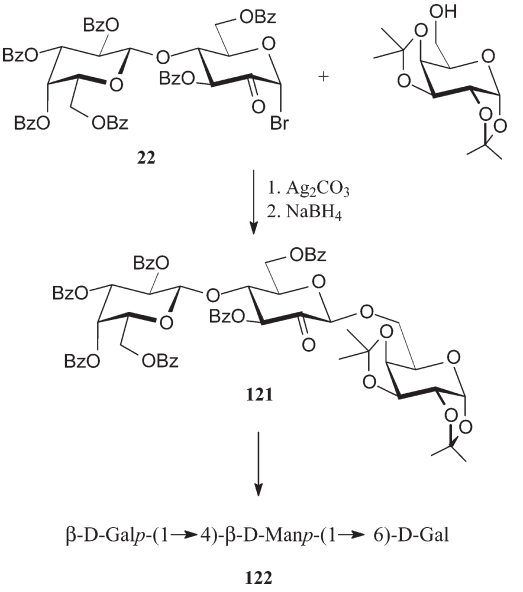


2.4. Assembly of β-D-Man and β-L-Rha Oligosaccharides via Ulosyl Bromides

The fairly extensive experimental material presented on the preparation of 2-oxoglycosyl (ulosyl) bromides (cf. section 2.1), their stereocontrolled β-glycosidation (section 2.2), and the highly *manno*-selective uloside reduction (section 2.3) has provided ample evidence on the salient utility of the *ulosyl donor approach* for the straightforward generation of β-D-mannosidic or β-L-rhamnosidic linkages. The following elaboration gives an overview on the presently realized applications of this methodology toward the assembly not only of oligosaccharides but of cardic glycosides and antibiotics as well (section 2.5).

2.4.1. Heterotrisaccharides with a Central β-D-Man Unit. The ready accessibility of the ulosyl bromides from the common disaccharides, such as lactose or cellobiose,[29] clearly suggested their utilization for the synthesis of trisaccharides with central β-D-mannose units. The lactosulosyl bromide **22**, for example, on silver carbonate-mediated glycosylation of diacetonegalactose and in situ exposure to $NaBH_4$ gave the trisaccharide **121** in an essentially stereospecific manner (Scheme 24), deblocking through standard procedures, affording the free Gal-β(1→4)-Man-β(1→6)-Gal trisaccharide **122** in a 66% yield over the four steps from **22**.[44]

Scheme 24



In a similar fashion, any of the common, readily available disaccharides can be used to generate a host of trisaccharides in a most expedient way, such as Glc-β(1→4)-Man-β-(1→*x*)Glyc

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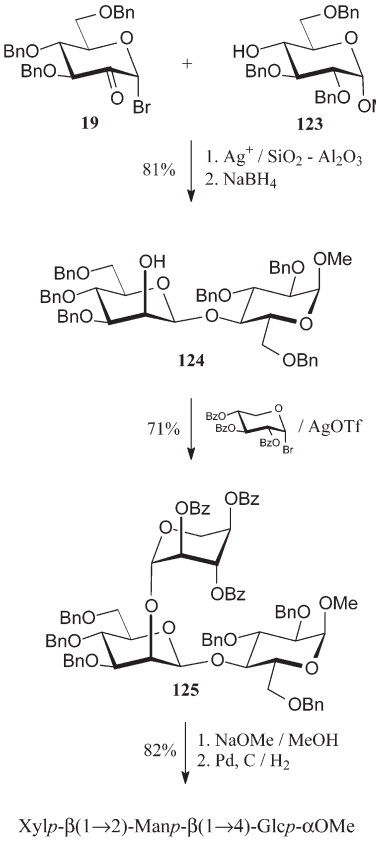
from cellobiose, Glc-α(1→4)-Man-β-(1→*x*)Glyc from maltose, Glc-β(1→6)-Man-β-(1→*x*)Glyc from gentiobiose, Glc-α-(1→6)-Man-β-(1→*x*)Glyc from isomaltose, and Gal-α(1→6)-Man-β-(1→*x*)Glyc from melibiose. Should there arise a demand for their availability, the method of choice for their preparation will be through their respective disaccharide-derived ulosyl bromides.

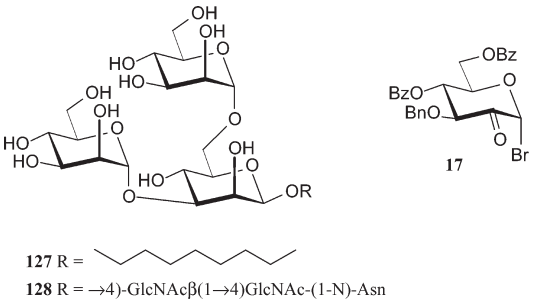
Analogously straightforward in terms of steps involved and yields attainable proved to be the synthesis of a Xyl-β(1→2)-Man-β(1→4)-Glc trisaccharide,[48] a component of glycosphingolipids from *Hyriopsis schlegelii*:[63] the readily accessible[64] methyl 2,3,6,-tri-*O*-benzyl-α-D-glucoside **123** was reacted with the equally benzyl-protected ulosyl bromide **19** employing silver aluminosilicate as the promoter (20 min at rt in CH_2Cl_2) to give upon in situ $NaBH_4$ reduction the mannosyl glucoside **124**. The 81% yield obtained thereby emphasizes the near diastereoselectivity over both the glycosylation and the subsequent reduction steps (Scheme 25). Favorably carrying a free 2-OH in the mannose portion, its xylosylation to **125** was effected smoothly using a standard procedure to give upon deprotection—Zemplén debenzoylation and hydrogenolysis of the benzyl groups—the target trisaccharide **126**.[48]

Scheme 25



This ulosyl bromide approach to trisaccharide **126** compares favorably with alternate syntheses advanced by Ogawa,[65] Kanie,[66] and Crich,[67] its major strength being the emergence of the β-D-mannose portion from the glycosylation/reduction sequence with an unprotected 2-OH, thereby minimizing protecting group manipulations.

2.4.2. 3,6-Branched β-D-Mannosides. A ulosyl bromide differently *O*-protected at the 3- and 6-positions, such as the 3-*O*-benzyl-4,6-di-*O*-benzoyl derivative **17** (cf. Table 1), appears well adapted to prepare β-D-mannosides branched at O-3, O-6, or at both. Indeed, the *N*-glycoprotein core trisaccharide **127**, carrying an octyl spacer instead of the common chitobiosyl moiety (**128**), can readily be assembled employing **17** as a most useful indirect β-D-mannosyl donor:[27]



Koenigs−Knorr glycosylation of 1-octanol followed by $NaBH_4$ reduction proceeded with near stereospecificity in either step to give the key octyl β-D-mannoside **129**. Its free 2-OH can directly be glycosylated with acetobromomannose (→**131**) to afford after deblocking the free mannobioside **132**. Alternately, the blocking group pattern in **129** can be varied by simple operations (for details see Scheme 26) to provide the octyl mannosides with free hydroxyl groups either at C-4 and C-6 (→**133**) or at C-3 (→**134**). When subjected to $HgBr_2$-promoted glycosylation with acetobromomannose, **133** gave the α(1→6)-linked mannobioside **137** in excellent O-6 regioselectivity (86% isolated yield), while **134**, upon mannosylation via the trichloroacetimidate method, afforded the α(1→3)-interconnected disaccharide **135** (76%). In turn, the 3,6-branched mannotrisaccharide **127** resulted from disaccharide **137** by acetylation of the 4-OH (→**138**), hydrogenolysis of its 3-*O*-benzyl group (→**139**), trimethylsilyl triflate-mediated mannosylation with the α-trichloroacetimidate (→**141**), and deblocking, each of the four steps performable in yields in the 80% range.[27]

By way of a preparative balance of this ulosyl bromide approach application, α(1→2)-, α(1→3)-, and α(1→6)-mannosylated β-D-mannosides such as **132**, **136**, and **140** are conveniently accessible from a single ulosyl bromide in yields of 35−40% over the five steps involved. Elaboration of 3,6-branched analogues, e.g., **127**, however, require another three steps, overall yields from the ulosyl donor being around 20%.

2.4.3. Di- and Trisaccharides with β-L-Rha Units. The sound accessibility of the 6-deoxy-α-L-*arabino*-hexosulosyl bromides **27**−**31** (cf. Table 1) urged their use as "indirect" β-L-rhamnosyl donors, inasmuch as the glycosylation/reduction sequence proceeds with nearly complete stereoselectivity in either of the two steps involved. As demonstrated with the ulosyl bromide **29** carrying different protecting groups at O-3 and O-4, and acceptors such as diacetonegalactose or a 4-OH-free 1,6-anhydro-D-glucose, silver aluminosilicate-mediated glycosylation and ensuing hydride reduction gave the galactosyl β-L-rhamnoside **142** and the L-rhamnosyl-β(1→4)-D-glucose **143** in yields of 85% and 78%, respectively (Scheme 27).[32] In an analogous manner, rhamnobiosides with β(1→2)-, β(1→3)-, and β(1→4)-intersaccharidic linkages could be effectively prepared by starting from ulosyl bromide **29** and the

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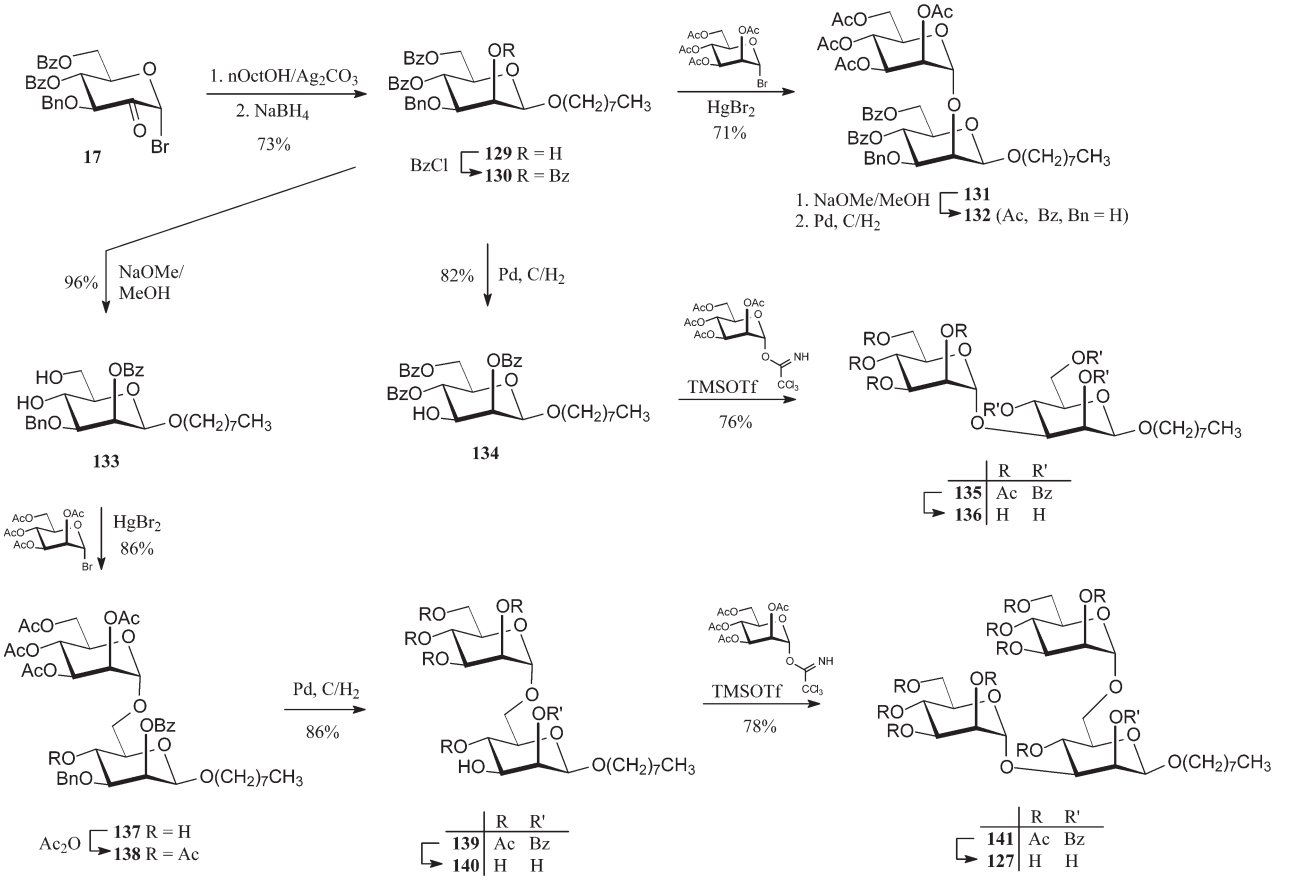
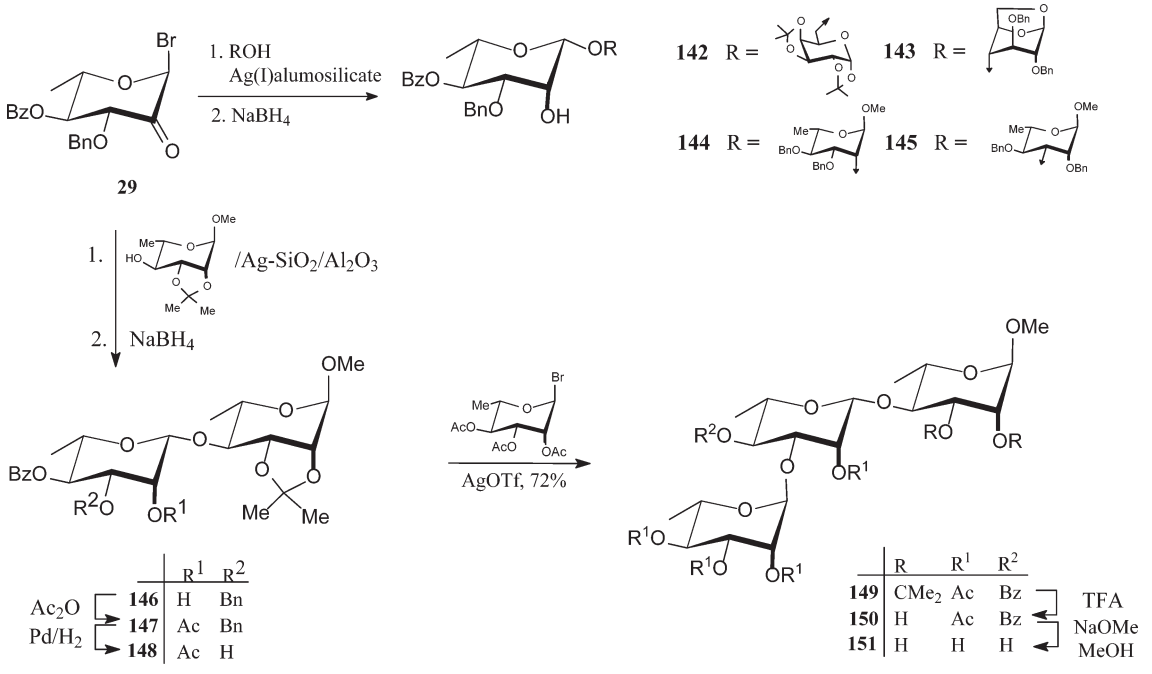
Scheme 26. β-D-Mannosides Branched at O-2, O-3, and O-6 or at O-3 and O-6[27]



correspondingly protected L-rhamnoside acceptors except for a free 2-OH (→**144**, 79%), 3-OH (→**145**, 77%), and 4-OH (→**146**, 80%) group.

Aside from the efficient generation of β-L-rhamnopyranosidic linkages, this approach has the advantage of providing the disaccharide with a free rhamnosyl 2-OH, ready for further

Scheme 27. Synthesis of Di- and Trisaccharides with β-L-Rhamnose Units[32]



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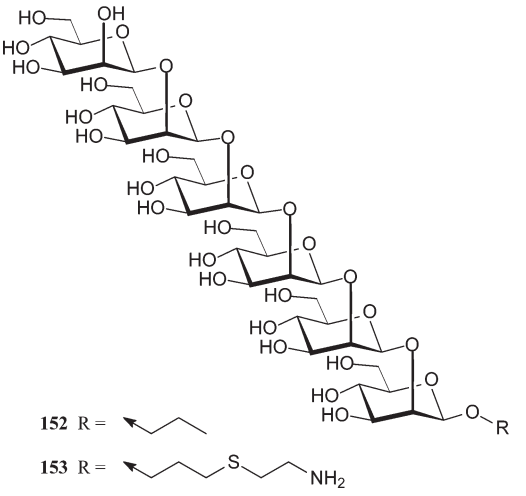
glycosylation. However, the rhamnotrisaccharide sequences found in the repeating units of *Klebsiella* and *Azotobacter vinelandii* polysaccharides[68] as well as in various lipopolysaccharides[69] have the third rhamnose unit attached at the 3-OH of a rhamnosyl-β(1→4)-rhamnoside, as in **151**.

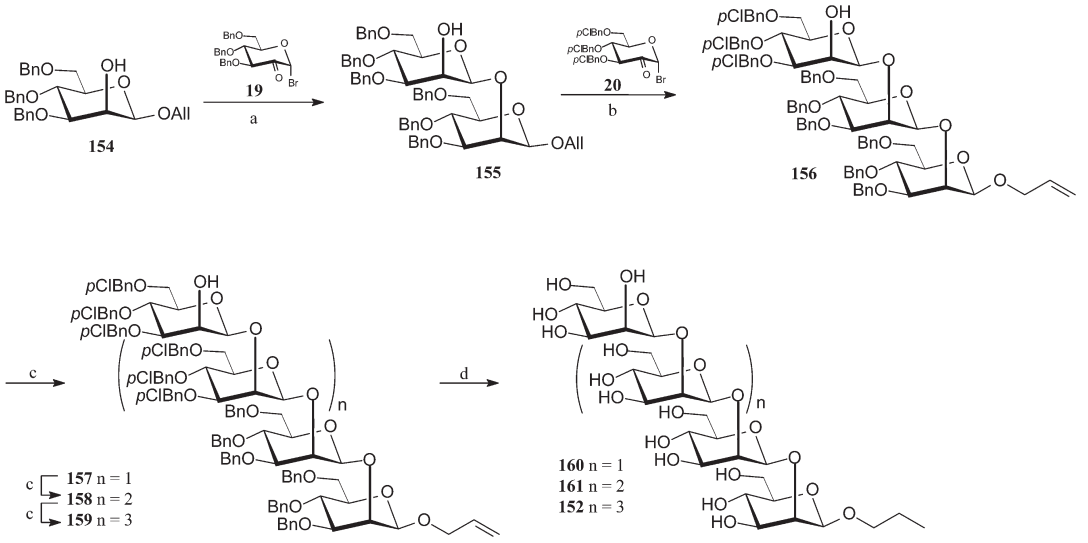
Thanks to the differentiated blocking group pattern at O-3 and O-4, though, further glycosyl residues may also be introduced at these positions. This option was demonstrated with the synthesis of rhamnotrisaccharide **151** (Scheme 27):[32] readily accessible rhamnobioside **146** was converted by acetylation (→**147**) and hydrogenolysis into an acceptor, **148**, with a free 3-OH (91% for the two steps). Silver triflate-promoted glycosylation with acetobromorhamnose smoothly gave the protected rhamnotrisaccharide **149** (82%) and, on consecutive removal of the blocking groups, the targeted lipopolysaccharide (LPS) repeating unit **151**. Thus, in a seven-step sequence based on the fairly well accessible, differentially *O*-protected α-L-rhamnosulosyl bromide **29**, a rhamnotrisaccharide with α(1→3)- and β(1→4)-intersaccharidic linkages can readily be assembled, with overall yields in the 45% range. Hence, the ulosyl donor approach to β-L-rhamno-oligosaccharides compares favorably with existing methodologies,[70] in its β-specific glycosylation even meeting Ziegler's strategy of intramolecular β-L-rhamnosylation through prelinked donor and acceptor substrates.[6]

2.4.4. β(1→2)-Oligomannosides. That higher oligomers of β(1→2)-mannopyranosides constitute essential parts of the heavily immunogetic cell wall glycoprotenis of *Candida albicans*[71] has stimulated substantial efforts toward their synthesis to study their unique immunological properties. Of the several practicable strategies developed,[72−75] the ulosyl bromide approach proved to be one of the most direct, as application of the two-stage glycosylation/reduction protocol generates a β-D-mannoside with a free 2-OH, ready for further glycosylation with a ulosyl bromide. So far, this approach has been carried up to hexasaccharides **152** and **153**:[21,72]



The synthesis of the first 1→2-linked β-mannosyl unit was accomplished by silver zeolite-mediated glycosylation of allyl 3,4,6-tri-*O*-benzyl-β-D-mannoside **154** with the equally benzyl-protected ulosyl bromide **19**, followed by reduction of the uloside with L-Selectride to give the mannobioside **155** in excellent yield after purification (Scheme 28). For introducing subsequent β-mannopyranosyl units though, obviously due to the lesser reactivity of the 2-OH in **155** as compared to **154**, stronger activation promoters, such as silver triflate with 2,6-di-*tert*-butyl-4-methylpyridine as an acid scavenger and acetonitrile as a participating solvent, had to be used, conditions that upon L-Selectride-mediated reduction of the product gave the trisaccharide in 45% yield, yet with the α-*gluco* epimer and the 3,4-di-*O*-benzyl-1,6-anhydro-β-D-mannose as side products (cf. Scheme 13). Nevertheless, use of the *p*-chlorobenzyl-protected ulosyl bromide **20** under these conditions—likely due to the increased stability of the protecting groups—successfully enabled attachment of the third (→**156**, 65%), fourth (→**157**, 48%), fifth (→**158**, 51%), and sixth (**159**, 48%) β-D-mannopyranosyl

Scheme 28. Generation of β-(1→2)-Mannooligosaccharides[a,21,72]



[a] Reagents and conditions: (a) silver zeolite, **19**, in CH_2Cl_2, 16 h, rt, then L-Selectride in THF, −78 °C, 5 min → rt, 78%; (b) **20**, AgOTF, D*t*BMP, CH_3CN, 1 h, rt, then L-Selectride in THF, −78 °C → rt, 65%; (c) **20**, AgOTF, D*t*BMP, *t*BuCN, 1 h, rt, then Selectride in THF, −78 °C → rt, →**157** (48%), **158** (51%), **159** (48%); (d) $H_2NNH_2 \cdot H_2O$ in EtOH/THF, then Pd/C, H_2, EtOH, 77−81%.

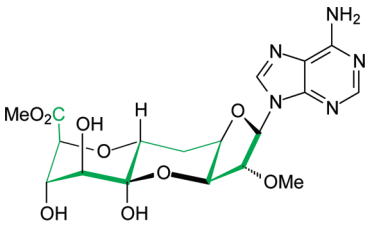
dx.doi.org/10.1021/cr100444b |*Chem. Rev.* 2011, 111, 5569–5609

residues, providing on hydrogenolysis over Pd/C and/or diimide the respective *manno*-oligosaccharides **160**, **161**, and **152** with a propyl group at the reducing end.[21,72]

Alternatively, to facilitate the conjugation of these oligosaccharides to protein carriers, the allyl group in **156**−**159** can smoothly and effectively be transformed into an amine-terminated aglyconic tether by photoaddition of 2-aminoethanethiol and subsequent deprotection. The resulting 3-[(2-aminoethyl)thio]propyl glycosides of type **153** were coupled to bovine serum albumin through diethyl squarate, showing conjugation efficiencies of 65−70%.[72]

2.5. Ulosyl Bromides in Synthesis of Antibiotics and Cardiac Glycosides

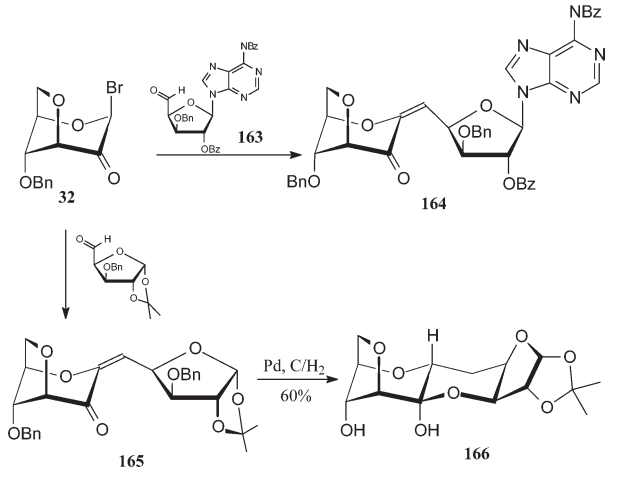
2.5.1. Approach to Herbicidins. In studies directed toward the total synthesis of herbicidins, exemplified by herbicidin B (**162**),[76] the 3,6-anhydro-bridged ulosyl bromide **32** has elegantly been used to elaborate analogues of its unusual C_{11} sugar component as well as of the corresponding adenine nucleoside.[33,77]



Herbicidin B (**162**)

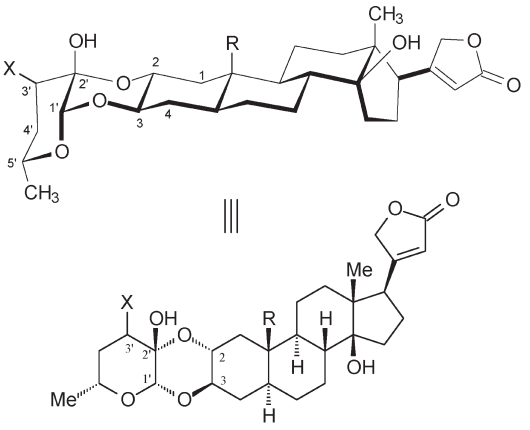
Upon $CeCl_3$−NaI-mediated activation of ulosyl bromide **32**, the resulting cerium enolate reacted smoothly with the arabinosyladenine-derived aldehyde **163** to give a 1:1 diastereomeric mixture of aldol adducts, which underwent dehydration to a single enone, **164** (Scheme 29).[33,77] This product, in fact, has all the essentials to elaborate the pyranopyran−furan scaffold of the undecosyladenine core of the herbicidines, as simultaneous saturation of the olefinic bond and removal of the benzyl groups by hydrogenation provide the stage for cycloacetal formation between the C-3-OH and the C-7-carbonyl. Although this conversion has not been carried out, it is realistic to expect a clean reaction, since the analogous aldol adduct **165**—only lacking the nucleobase—spontaneously formed the cycloacetal **166** on release of the C-3-OH by Pd,C/H_2 treatment.[78]

Scheme 29



2.5.2. Synthesis of Gomphoside. Whereas the cardiac glycosides from *Digitalis* and *Strophantus* species carry one to five sugar units linked through the 3-OH of the steroid aglycon,[79] those produced by plants from the milkweed family Asclepiadacea (Table 4) invariably contain a single sugar—the rare 4,6-dideoxy-D-hexos-2,3-diulose or its epimeric C-3 reduction products—in a unique "dioxanoid" attachment.[80,81] The common β-glycosidic bond to the steroidal 3-OH is complemented by a hemiacetal linkage between the 2-carbonyl group of the sugar and the 2-OH group of the aglycon to result in a *cis,cisoid,trans*-fusion of pyran, dioxane, and cyclohexane rings.

Table 4. Cardenolide Glycosides Isolated from the Milkweed Family Asclepiadaceae



Compound	3'-C—X	R	Ref.
Gomphoside (**167**)	—OH	Me	80
3'-*epi*-gomphoside	····OH	Me	81
3'-dehydrogomphoside	=O	Me	81
calactin	—OH	CHO	82
calotropin	····OH	CHO	82
uscharidine	=O	CHO	82

The 6-deoxy-D-glucose-derived ulosyl bromide **27** and its 3,4-elimination analogue, chloride **169** (Scheme 30), are particularly well adjusted for targeting natural products with dioxanoid sugar components. They not only contain the 2-carbonyl function, which is essential for generation of the cyclohemiacetal linkage, but in the case of **169** also an enol ester-protected carbonyl at C-3, thereby closely matching the tricarbonyl sugars in 3′-dehydrogomphoside and uscharidine (cf. Table 4). Furthermore, both donors are fairly well accessible from D-glucose through the 6-deoxy-2-hydroxyglucal ester **168**[83] (Scheme 30): ulosyl bromide **27** can be obtained in five large-scale adaptable steps from D-glucose[31] versus seven steps for its unsaturated chloro analogue **169**,[84] with overall yields of 42% and 25%, respectively.

As the feasibility of advancing from donors **27** and **169** to the cardenolide glycosides of Table 4 had been probed with

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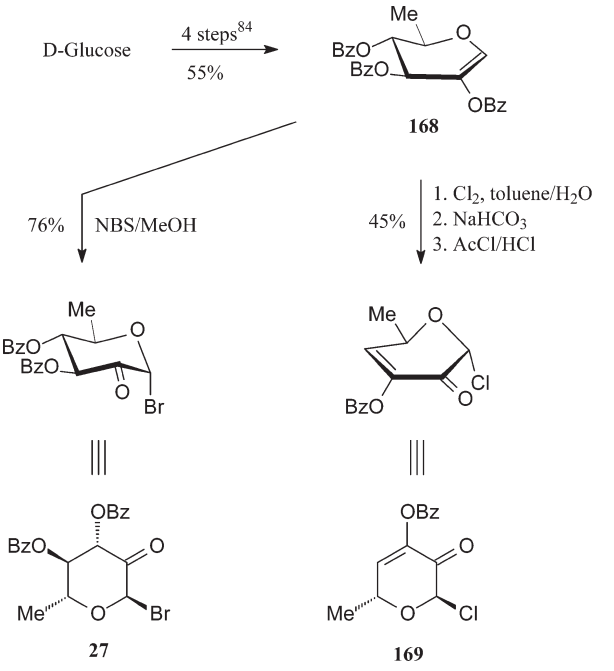
Scheme 30



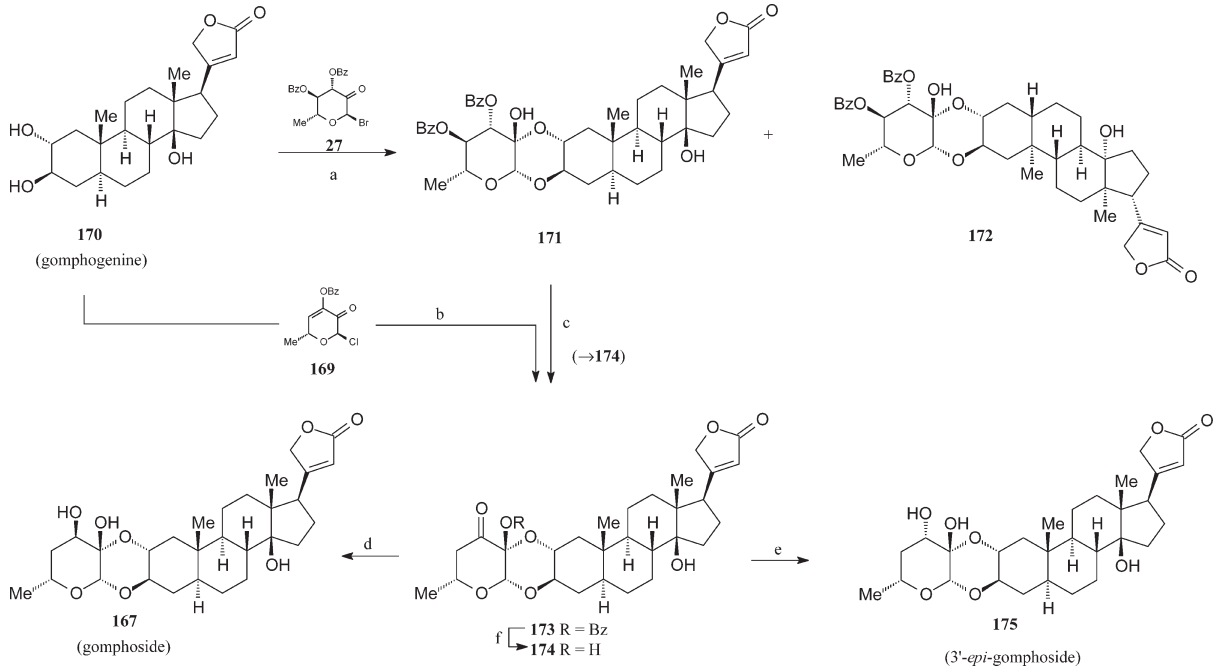
(*R*,*R*)-cyclohexane-1,2-diol as a model aglycon leading straightforwardly to the *cis*,*cisoid*,*trans*-fused pyran−dioxane−cyclohexane tricycle[50] (cf. section 2.2.3), the methodology was applied to gomphogenine **170**, the steroid aglycon of the gomphosides. Being an unsymmetrical diol, its Ag_2CO_3-mediated *O*-glycosylation with donors **27** and **169** gave approximate 3:1 mixtures of two products each, of which the major one turned out to be the 3-*O*-glycosylated and concomitantly hemiketalized compounds **171** and **173**, isolable in 61% and 54%, respectively[85] (Scheme 31). Thus, fortunately, the 3-OH of gomphogenine proved to be the more reactive of the two hydroxyls and, after β-glycosylation, spontantously "folds" into the natural *cis*,*cisoid*,*trans*-geometry.

De-*O*-benzoylation of **173** was readily effected by exposure to mild base to provide the 3′-dehydrogomphoside **174**, identical in all respects with the natural product derived from *Asclepias fruticosa*.[81] It could also be obtained from the ulosyl bromide glycosylation product **171** by stirring with nBu$_4$NOAc in anhydrous acetonitrile (81%)—conditions that not only initiate elimination of benzoic acid in the cycloacetal-opened form, but elicit a subsequent 3′-*O*-benzoyl → 2′-*O*-benzoyl group shift with seemingly exclusive preference for OH → C═O attack from the lower (axial) face of the pyran ring. Obviously, dipolar interactions are minimized thereby through *trans*-diaxial disposition of the pyran ring oxygen and the acetalic benzoyloxy group.

Gomphoside **167** and its 3′-epimer **175** could easily be secured from the 3′-dehydro derivative **174** by hydrogenation over either Rh/C (→**167**, 80%) or $NaBH_4$ (→**175**, 81%).[85]

2.5.3. Total Synthesis of Spectinomycin. The broad spectrum antibiotic spectinomycin **176**[86] can be perceived, in formal terms, to be a pseudodisaccharide in which a tricarbonyl sugar, the 4,6-dideoxy-D-*glycero*-hexose-2,3-diulose **177** designated actinospectose, is fused to *N*,*N*-methylated 1,3-diamino-*myo*-inositol actinamine **178** by both a β-glycosidic and a hemiketal linkage to form a pyran−dioxane−cyclohexane system in *cis*,*cisoid*,*trans*-arrangement. While actinamine **178** can readily be secured by acid hydrolysis of spectinomycin,[86b] and by a variety of syntheses,[87] the actinospectose portion does not survive the harsh acidic conditions required for cleaving the bisglycosidic linkage (6 M HCl, 6 h reflux) and is left as an intractable tar.

Scheme 31. Synthesis of Gomphosides[a]



[a] Reagents and conditions:[85] (a) **27** (2 equiv), Ag_2CO_3 (1 equiv), molecular sieves, CH_2Cl_2, 25 °C, 16 h, 61% (**171**), 14% (**172**); (b) **169** (1 equiv), Ag_2CO_3 (1 equiv), molecular sieves, CH_2Cl_2, 40 °C, 2 h, 54% (**173**); (c) nBu$_4$NOAc, MeCN/water (50:1), 25 °C, 15 h, 89% (**174**); (d) 5% Rh/C, MeOH/water (9:1), 25 °C, 24 h, 80%; (e) $NaBH_4$ (1 equiv), dry MeOH, 0 °C, 10 min, 81%; (f) K_2CO_3, MeOH, 25 °C, 10 min, 95%.

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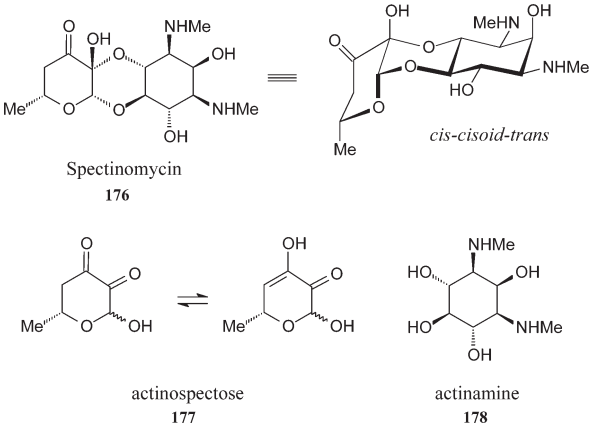
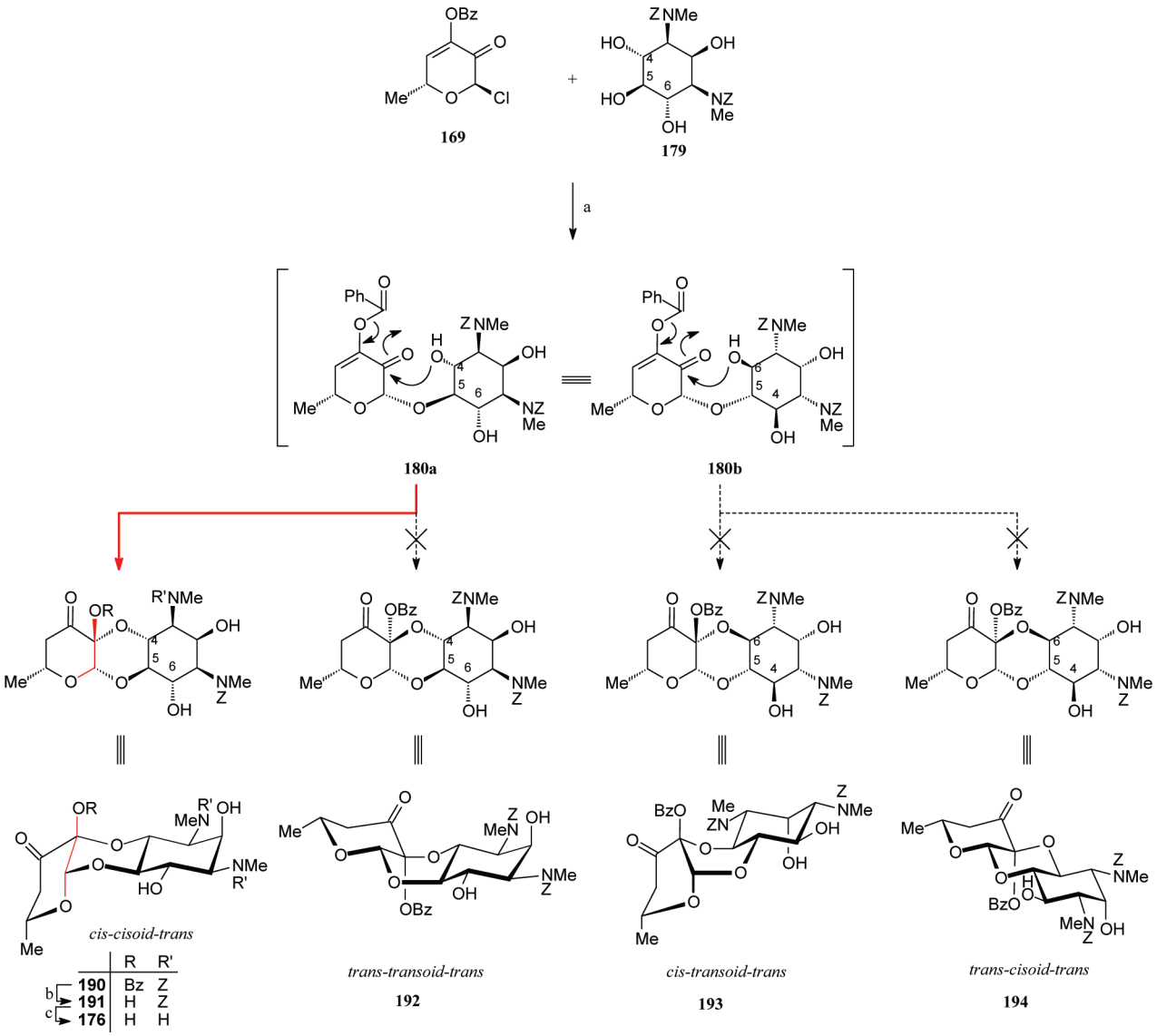
Toward a total synthesis of spectinomycin, the methodology developed for the dioxanoid annulation of ketosugars to cyclic 1,2-diols[49,50] (cf. section 2.2.3) and to gomphogenine (Scheme 31) was applied to *N,N*-bis[(benzyloxy)carbonyl]actinamine **179**, the aglycon of spectinomycin in a suitably *N,N*-protected form. As the bulky *N*-protecting groups impede glycosylation at the vicinal hydroxy groups through steric shielding,[89] a highly regioselective attack of ulosyl donor **27** or **169** at 3-OH was anticipated. However, the acceptor reactivitiy of this 3-OH proved to be considerably lower than that in cyclohexane-1,2-diol or in gomphogenine—seemingly due to the high oxygen substitution in its cyclohexane ring—entailing sluggish glycosylations when promoted with Ag_2CO_3. The more reactive silver aluminosilicate in THF/CH_2Cl_2 or in toluene effected β-selective *O*-glycosylation of **179** with either of the two donors, in the case of the unsaturated ulosyl chloride **169** directly leading to the 2′-*O*-benzoyl derivative of *N,N*-bis[(benzyloxy)carbonyl]spectinomycin **190**, isolable in 51% yield after the removal of 4-*O*- and 6-*O*-glycosylated analogues (ca. 5% each) (Scheme 32). Its deblocking



Scheme 32. Unique Stereocontrol in the Intramolecular Hemiketal Folding of Glycosidulose Intermediate 180 toward the *cis*, *cisoid*,*trans*-Fused Framework of Spectinomycin[a]



[a] Reagents and conditions: (a) silver aluminosilicate (1.2 equiv), toluene, 80 °C, 3 h, 51%; (b) K_2CO_3, MeOH, 25 °C, 10 min, 89%; (c) H_2, 5% Pd/C, *i*PrOH, 25 °C, 12 h, 90%. Z = (benzyloxy)carbonyl.

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by de-*O*-benzoylation (→**191**) and hydrogenolysis then smoothly provided the antibiotic **176**.[84,85]

While the regioselectivity and β-selectivity of the glycosylation reaction is already remarkable, the stereocontrol exercised in the hemiketal folding of the uloside intermediate (cf. arrows in **180a** and **180b**, Scheme 32) is even more so as it leads from a product with two stereogenic centers to one with altogether nine: enjoying the thermodynamics derived from two anomeric effects and the propensity to form the sterically most favorable linear-fused tricycle, the glycosidulose carbonyl in **180** is attacked with high, or exclusive, preference by the 5(*R*)-OH from the axial (lower) face of the pyran ring, elaborating **190** with a pyranoid ring oxygen and ketalic OBz in the favorable *trans*-diaxial disposition, as well as the chair conformations of the three rings (Scheme 32). By contrast, the alternate possibilities—4(*R*)-OH attack from the β (equatorial) face (**180a** → **192**) or of the 6(*S*)-OH in the two conceivable steric modes (**180b** → **193** or **194**)—invariably lead to thermodynamically less stable products because the central dioxane ring is forced into a boat conformation (**192** and **193**) or unfavorable dipolar interactions are operative (**192** and **194**).

In summary, the ulosyl donor approach, here applied to the well-accessible 3,4-unsaturated 2-ulosyl chloride **169**, could be exploited toward a concise, efficient synthesis of spectinomycin, the 10 steps required from D-glucose being performable in a 10.2% overall yield,[84,85] and with its spontaneous folding into the natural *cis*, *cisoid*,*trans*-geometry conceivably proceeds along lines possibly relevant to its biosynthesis.[88] In such, it compares most favorably with two other total syntheses requiring nine steps from L-glucose[89] (3% overall yield) or 23 from D-glucose[90] (~1%[91]).

3. OXIMINOGLYCOSYL DONOR APPROACH TO β-D-ManNAc, *N*-ACETYL-α-D-GLUCOSAMINE (α-D-GlcNAc), AND β-D-ManNAcA LINKAGES

N-Acetyl-β-D-mannosamine units are not as widespread in nature as their β-linked mannose counterparts yet are found as key constituents in the repeating units of various cell wall

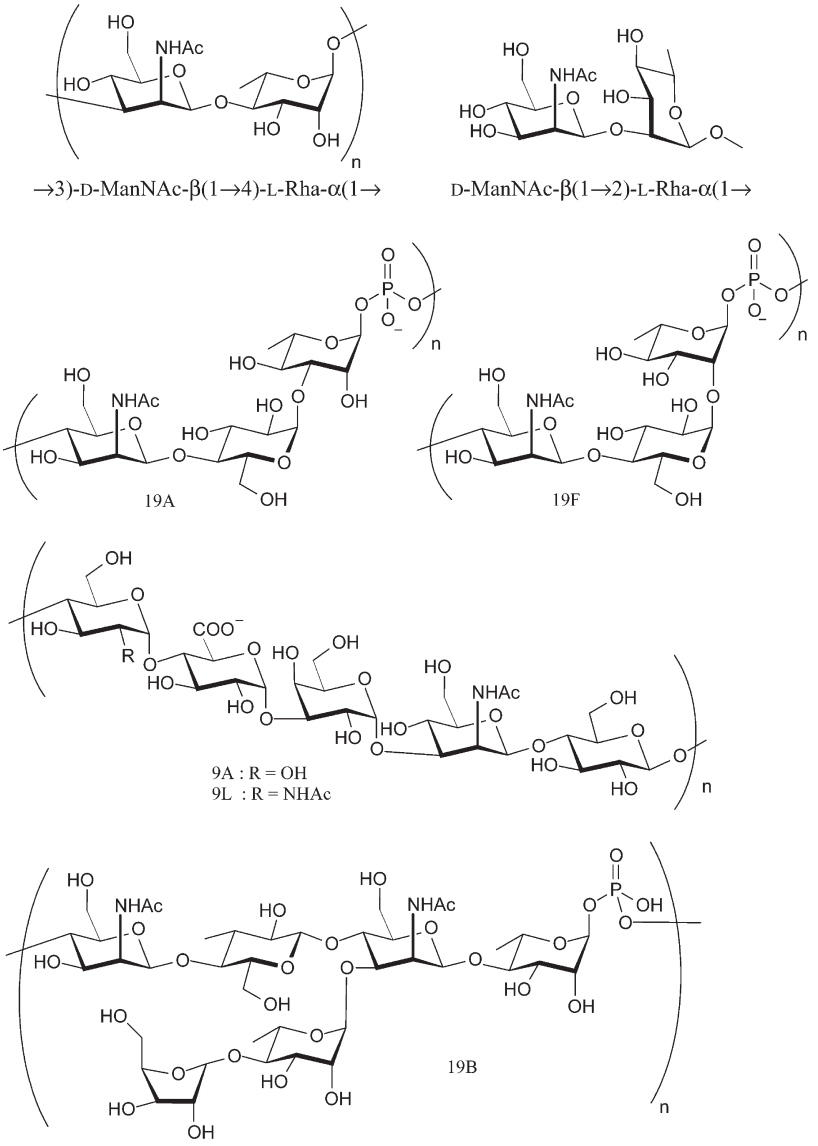

Figure 5. Disaccharide units found in the lipopolysaccharides of *P. cepacia*, *P. aeruginosa*, and *A. salmonicida* (top left) and *E. coli* (top right). Center and bottom: Repeating units of capsular polysaccharides of *S. pneumoniae* serotypes 19A, 19F, 9A, 9L, and 19B.

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lipopolysaccharides,[92] such as, for example, the opportunistic pathogens in *Pseudomonas cepacia*,[93] *Pseudomonas aeruginosa*,[94] and *Aeromonas salmonicida*[95] (Figure 5, top left) and in *Escherichia coli* serotype 01[96] (top right). Distinctly more significant with respect to their infectiousness and molecular complexity appear to be the repeating units with β-D-ManNAc components embodied in *Streptococcus pneumoniae* capsular *polysaccharides*,[97] most notably those displayed by the serotypes 9A,[98] 9L,[99] 19A,[100] 19B,[101] and 19F[102] (Figure 5).

Of similar relevance is the comparatively rare, yet salient occurrence of *N*-acetyl-β-D-mannosaminuronic acid as a conspicuous component of capsular polysaccharides in serious pathogenic bacteria[103−105] (Figure 6), most notably in *Streptococcus aureus*,[106] responsible for most hospital-related infections.

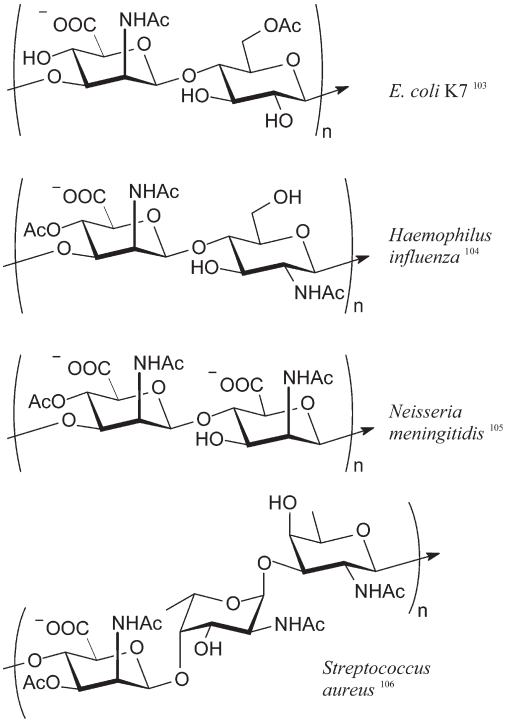


Figure 6. Repeating units in capsular polysaccharides of various pathogenic bacteria containing β-D-ManNAcA residues.

The eminent biological significance of these polysaccharides has prompted substantial efforts toward the synthesis of their repeating units, whereby elaboration of the β-D-ManNAc or β-D-ManNAcA portion invariably is the crucial step. It necessarily entails *indirect* donors since conceivable direct ones due to their axially oriented acetamido function unavoidably direct a glycosylation to either 1,2-oxazolines or α-glycosides. Thus, various indirect D-ManNAc donors have been used, such as the 2-azido-α-D-mannosyl bromides **196**,[107] **197**,[107] and **198**,[108] yet only the tri-*O*-benzyl compound **197**—its preparation from D-glucose requiring 11 steps with an overall yield of about 10%[107]—gave useful β-selectivities in glycosidations.[107] Another even more remote indirect strategy used donors of type **199**,[109] **200**,[110] **201**,[111] or **202**,[112] i.e., glucopyranosyl derivatives each with a selectively removable protecting group at O-2 (Figure 7). Although fairly well accessible, these donor substrates are burdened with the necessity—upon β-glycosidation—to convert the equatorial 2-*O*-acyl group into an axial acetamido function, a process requiring five steps each in either of the two procedures

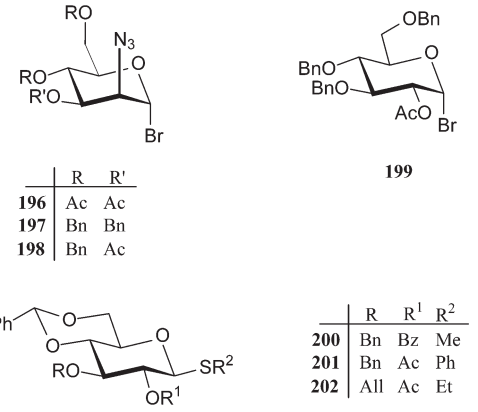
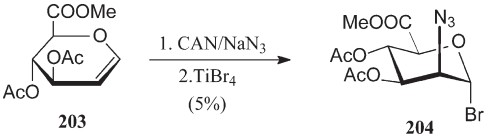


Figure 7. Indirect β-D-ManNAc donors.

employed: de-*O*-acylation → oxidation → oximation → reduction → *N*-acetylation sequence[113] or, alternatively, introduction of a 2-sulfonyl group upon deacetylation, followed by S_N2 displacement with azide, hydrogenation, and *N*-acetylation.[110−112] Although somewhat long, either approach provides fairly acceptable overall yields.

Similarly intricate in preparative terms are indirect β-D-ManNAcA donors on this basis. The 2-azidomannuronyl bromide **204**, for example, is an attractive candidate, yet its acquisition from glucuronal **203** (Scheme 33) in less than 5% yield over two steps[107]—the azidonitration involved is highly *gluco*-selective[114]—is preparatively as prohibitive as its sensitivity, resulting in substantial formation of side products during glycosylations.[115] The obvious alternative to elaborate a 2-azido- or 2-acetamido-β-D-mannoside via donors **196**−**202** and subject their 6-OH—after liberation—to catalytic oxidation[115,116] is similarly impractical in preparative terms due to the large number of steps involved.

Scheme 33

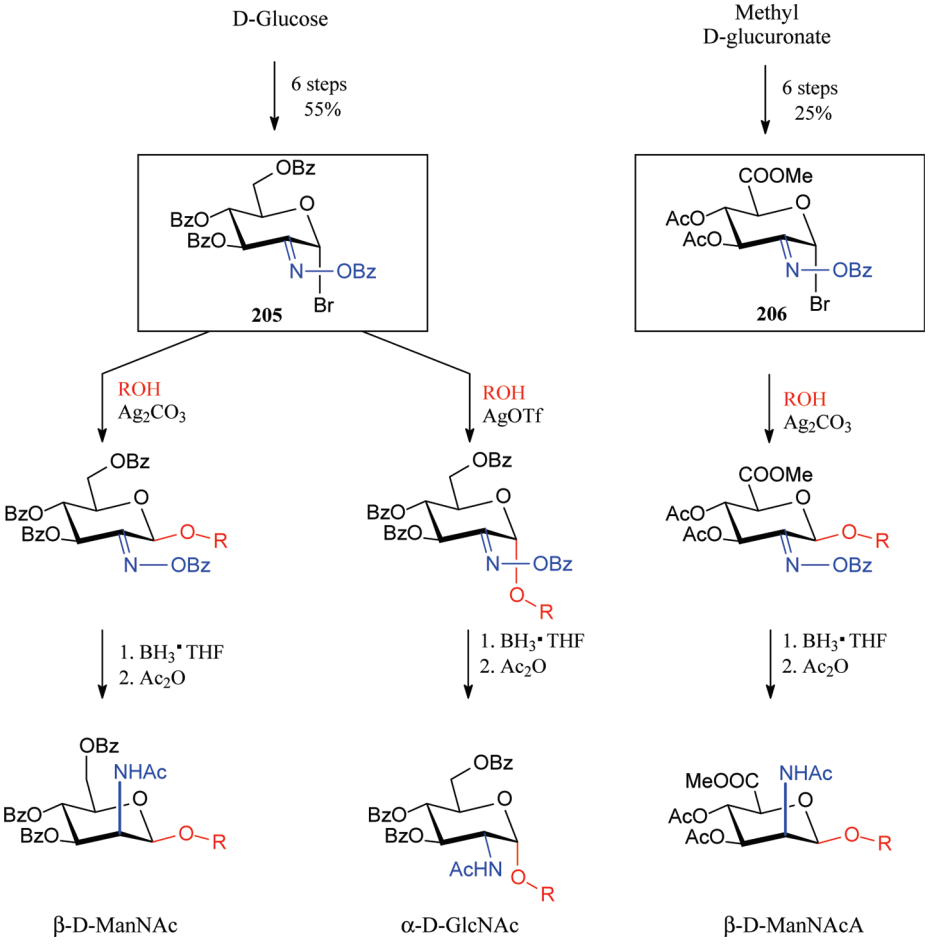


In comparing the accessibility of these indirect β-D-ManNAc and β-D-ManNAcA donors and the selectivities attainable in the β-glycosidation and ensuing steps, the 2-oximinoglycosyl bromide **205** and its 2-oximinoglycuronyl analogue **206**, as to be implemented below, not only are exceedingly well accessible, but due to essentially β-specific glycosidations and remarkably high *manno*-selectivities in the oxime reductions are the preparatively most efficient in terms of expenditure, overall yields, and large-scale adaptability. This oxime counterpart of the ulosyl donor approach, appropriately termed the *oximinoglycosyl donor strategy*, toward oligosaccharide assemblies with β-D-ManNAc, β-D-ManNAcA, and, by change of glycosylation selectivity, α-D-GlcNAc units (Scheme 34) is being elaborated in the sequel.

3.1. Preparation of 2-Oximinoglycosyl Bromides

Unlike ulosyl bromides that are accessible from hydroxyglycal esters in a high-yielding one-step process (cf. Scheme 2 and Table 1), acquisition of their 2-oximino analogues requires three steps (Scheme 35): hydroxylaminolysis of the enol ester function, **X** → **XI**, protection of the oxime OH by acylation (→**XII**), and photobromination of the proanomeric center (→**XIII**).

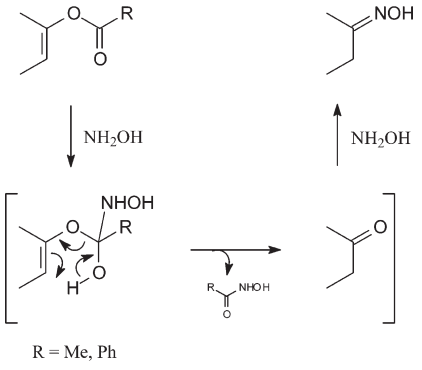
Scheme 34. Oximinoglycosyl Donor Approach to Oligosaccharides Containing β-D-ManNAc, α-D-GlcNAc, and β-D-ManNAcA Units



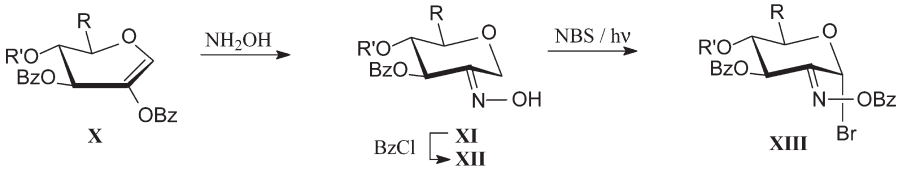
3.1.1. Hydroxylaminolysis. The first step, **X** → **XI**, is most readily accomplished by stirring the acetylated or benzoylated 2-hydroxyglycal ester with hydroxylamine in pyridine at rt or 70 °C or in 1:1 THF/acetate buffer, which exclusively cleaves the enediolic ester group (Scheme 36) to generate aceto- or benzohydroxyamic acid and the respective 1,5-anhydroketose, its carbonyl group then being captured by another hydroxylamine to the ketoxime **XI**.[22−24,29]

This delightful simple protocol is generally applicable to any hydroxyglycal ester, e.g., those listed in Table 5, and allows yields in the 75−90% range except for the glucuronal-derived case (56%, entry 8 in Table 5), where the carbomethoxy group is partially converted into the hydroxylamide.

Scheme 36. Hydroxylaminolysis of Enol Esters



Scheme 35. Generation of 2-Benzoximinoglycosyl Bromides from 2-Hydroxyglycal Esters



R = CH_2OBz, COOMe, CH_3, H
R' = Bz, βBz_4Gal, βBz_4Glc, αBz_4Glc

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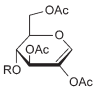
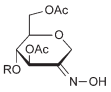
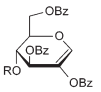
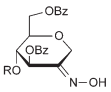
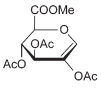
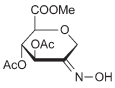
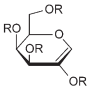
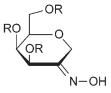
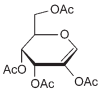
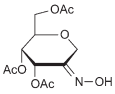
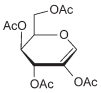
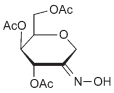
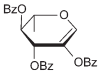
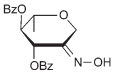
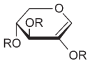
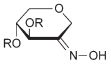
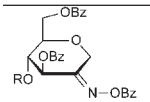
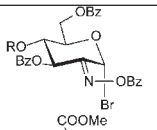
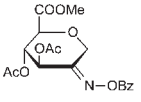
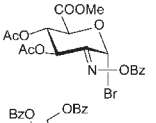
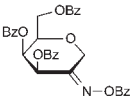
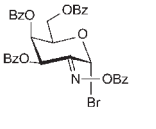
Table 5. Hydroxylaminolysis of 2-Hydroxyglycal Esters to 1,5-Anhydrohexos-2-ulose (*E*)-Oximes

Entry	Starting Sugar	Hydroxyglycal Ester[a]		1,5-Anhydro-ketose *E*-oxime	Configuration	Procedure[b]	Yield (%)	Ref.
1	D-Glucose		R = Ac		D-*fructo*	A (16 h)	86	22
2	Cellobiose		R = βAc$_4$Glc			A (24 h)	84	117
3	Maltose		R = αAc$_4$Glc			A (24 h)	79	117
4	D-Glucose		R = Bz			A (4 d) B (10 h)	93 93	22,24 24
5	Lactose		R = βBz$_4$Gal			B (20 h)	89	29
6	Cellobiose		R = βBz$_4$Glc		D-*fructo*	B (13 h)	76	29
7	Maltose		R = αBz$_4$Glc			B (20 h)	86	29
8	D-Glucurono-lactone				D-*fructo*	A (20 h)	56	118
9	D-Galactose		R = Ac		D-*tagato*	A (15 h)	82	119
10			R = Bz			A (20 h)	73	120
11	D-Allose				D-*psico*	C (6 h)	82	94
12	D-Gulose				D-*sorbo*	C (6 h)	80	119
13	L-Rhamnose				L-*rhamnulo*	A (5 d)	86	119
14	D-Xylose		R = Ac		D-*xylulo*	D (20 h)	76	119
15			R = Bz			B (12 h)	83	119

[a] Abbreviations: αAc$_4$Glc = 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl; βAc$_4$Glc = 2,3,4,6-tetra-*O*-acetyl-β-D-glucosyl; βBz$_4$Gal = 2,3,4,6-tetra-*O*-benzoyl-β-D-galactosyl; βBz$_4$Glc = 2,3,4,6-tetra-*O*-benzoyl-β-D-glucosyl; αBz$_4$Glc = 2,3,4,6-tetra-*O*-benzoyl-α-D-glucosyl. [b] Preparative procedures involved treatment of substrate with 3−3.5 molar equiv of hydroxylamine hydrochloride in the following systems: A, pyridine at rt; B, pyridine at 70 °C; C, 1:1 pyridine/EtOH, rt; D, 1:1 THF/acetate buffer (pH 4.5), rt.

Table 6. 2(*Z*)-Benzoximinoglycosyl Bromides Generated from 2-Hydroxyglycal Esters in the Three-Step Sequence Hydroxylaminolysis → *O*-Benzoylation → Photobromination (NBS/*hν* in CCl_4, 15−30 min Reflux)

Benzoyloxime	Oximinoglycosyl Bromide			Yield (%)	mp (°C)	$[\alpha]_D^{20}$ (CHCl$_3$)	Ref.	Overall Yield (%) from Hydroxyglycal Ester
		**205**	R = Bz	87	78-79	+261	25	74
		207	R = βBz$_4$Gal[a]	93	111-113	+80	29	75
		208	R = βBz$_4$Glc[a]	90	113-114	+174	29	77
		209	R = αBz$_4$Glc[a]	96	120-122	+182	29	75
		**206**		95	90-91	+341	118	52
		**210**		90	68-72	+239	120	53

[a] Abbreviations: βBz$_4$Gal = 2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranosyl; βBz$_4$Glc = 2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl; αBz$_4$Glc = 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranosyl.

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In all of these *1,5-anhydroketoximes* the oxime OH is directed toward the less substituted vicinal carbon as evidenced by the downfield chemical shift for the equatorially oriented H-1 when compared to the underlying ketose.[121] Thus, they have *E*-stereochemistry throughout, as indicated in Table 5, which de facto is retained in ensuing reactions such as *O*-benzoylation or photobromination (cf. below).

3.1.2. Photobromination. The photobromination of the ketoximes of Table 5 to the desired oximinoglycosyl bromides, i.e., utilizing the oximino function as the captive ("pull") element of a captodative system,[122] required blocking of the oxime hydroxyl group as *N*-bromosuccinimide is known to oxidize ketoximes to bromonitroso compounds,[123] while bromine in aqueous medium is a mild and efficient means for deoximation.[124] Although simple alkyl ethers of oximes survive NBS treatment,[125] as do acetyl groups in the majority of cases,[126] the benzoyl ester function appeared to be the group of choice or, alternatively, the *p*-nitrobenzoyl[25] or *p*-cyanobenzoyl or *p*-chlorobenzoyl[127] moieties.

Thus, ketoximes **XI** are converted under standard benzoylation conditions into the respective benzoyloximes **XII** as suitable substrates for the ensuing radical-induced bromination at their proanomeric centers. Indeed, when allowed to react with *N*-bromosuccinimide in refluxing tetrachloromethane under irradiation, they quickly elaborated the respective α-bromides **XIII** (Scheme 35), isolable in crystalline form and in nearly quantitative yields. The emergence of the α-bromides as the exclusive products infers that the intermediate anomeric radical—despite its delocalization over four bonds—retains the α-selectivity usually shown by nondelocalized anomeric radicals.[128]

While any of the 1,5-anhydroketoximes of Table 5 may be converted through this two-step benzoylation/photobromination protocol into the respective benzoximinoglycosyl bromides **XIII**, as of now, only those relevant for the generation of β-D-ManNAc and β-D-ManNAcA linkages have been prepared, i.e., donors **205**−**210** listed in Table 6. The efficiency with which this photobromination can be effected—isolated yields are consistently in the 90% range—is as remarkable as the obtention of the bromides in crystalline form and as bench-stable products.[25,29,118,120]

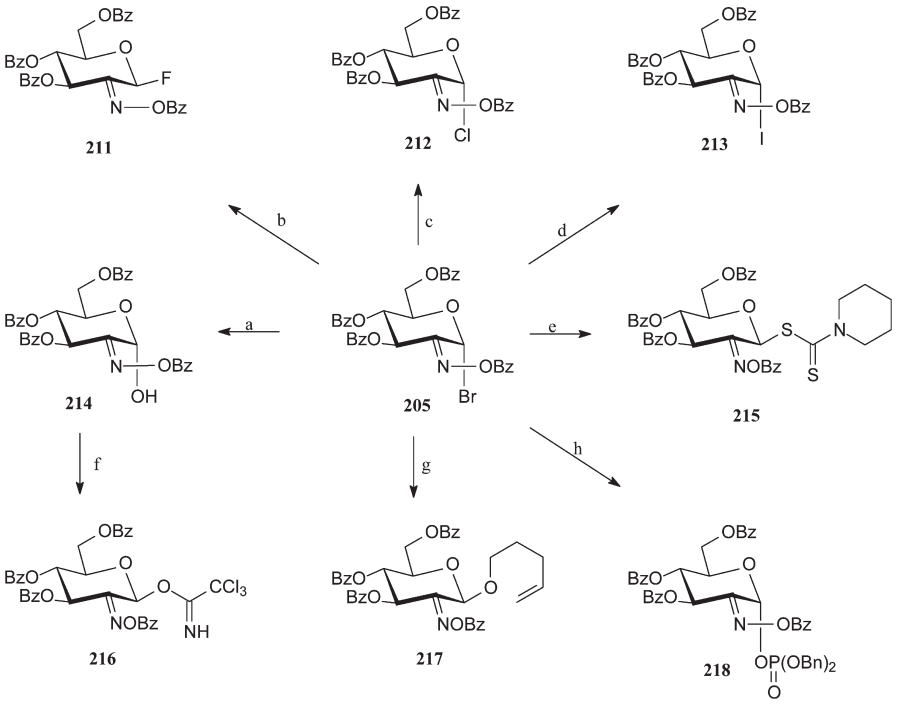
In terms of their preparative use as indirect donors for β-D-mannosamine or β-D-mannosaminuronic acid linkages, the overall yields for the three steps from the respective 2-hydroxyglycal esters are detrimental. They are listed in Table 6 (last column) and, with 75% yield, are most satisfactory for the β-D-ManNAc progenitors **205** and **207**−**209**.

The oxime stereochemistry of these 2-benzoximinoglycosyl bromides was found[121] to be the same as in the ketoximes—the *N*-OH or *N*-OBz group is directed toward C-1—even if their notation has to be *Z* due to priority reversal of the carbons vicinal to the oximino group. Thus, the conditions of benzoylation, those of photobromination, and those of Koenigs−Knorr-type glycosylations, as to be shown below, do not affect in any way the geometry at the oximino groups.

3.2. Anomerically Modified 2-Oximinoglycosyl Donors

The anomeric substituent in the 2-benzoximinoglycosyl bromides may readily be replaced by others with donor capabilities as shown for **205** in Scheme 37. Using standard methodologies, the β-fluoride **211**, α-chloride **212**, α-iodide **213**, β-dithiocarbamate **215**, and β-trichloroacetimidate **216** are obtained as stable, crystalline products in high yields. Exposure of **205** to

Scheme 37. Anomerically Modified Oximinoglycosyl Donors[a]



[a] Reagents and conditions: (a) acetone/water (10:1), tetramethylurea, 7 h, rt, 79%;[37] (b) AgF in MeCN, 20 min, rt, 60%;[26] (c) AgCl in MeCN, 2.5 h, rt, 76%;[37] (d) NaI in CH_2Cl_2/MeCN, 15 min, 0 °C, 84%;[26] (e) in situ sodium piperidinedithioate in DMF, 15 min, −60 °C, 74%;[26] (f) Cl_3CCN, DBU in CH_2Cl_2, 5 min, rt, 73%;[37] (g) 4-penten-1-ol, silver aluminosilicate in CH_2Cl_2, 3 min, rt, 69%;[26] (h) $(BnO)_2PO_2H$, Ag_2CO_3 in CH_2Cl_2, 2 h, rt, 65%.[26]

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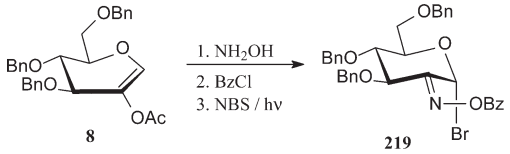
4-pentenol in the presence of silver aluminosilicate smoothly generated the β-pentenyl glycosidulose oxime **217**, whereas reaction with silver dibenzylphosphate elaborated the α-phosphate **218**.[26,37]

In *O*-glycosidations though, employing the established activation procedures, these anomerically modified donors provide few advantages over the bromide **205**. The couplings of dithiocarbamate **215** and trichloroacetimidate **216** with 2-propanol, for example, upon methyl triflate and trimethylsilyl triflate activation, respectively, resulted either in extensive decomposition (**215**) or in no reaction (**216**, 4 h, rt), while the NIS/AgOTf-mediated glycosidation of the pentenyl donor **217** proceeded rapidly (1 h, rt), yet with inadequate anomeric selectivity as the α:β ratio was near 1:1.[37] The α-iodide **213**, however, appears to be a preparatively quite useful alternative as it combines higher reactivity than the bromide **205** with equally high β-selectivity: the Ag_2CO_3-promoted glycosylations of cyclohexanol or diacetonegalactose, for example, were complete within 1−2 h versus 24 h in the case of **205**.[37]

A considerably more promising alternative toward improving the anomeric reactivity, albeit not realized yet, lies in the replacement of the benzoyl protecting groups in **205** by benzyl, inasmuch as the 2-acetoxyglucal precursor **8** is well accessible[20] (cf. Scheme 3) and should readily yield to the well-established three-step sequence hydroxylaminolysis → benzoylation → photobromination (Scheme 38). The resulting oximinoglycosyl bromide **219** is deemed to have a substantially higher reactivity than **205** aside from being sterically less congested and, hence, should be the donor of choice for glycosylations of notoriously unreactive acceptor hydroxyls.

Scheme 38

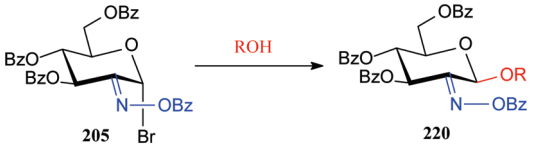


3.3. Stereocontrol in Glycosidations

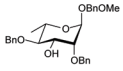
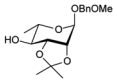
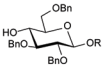
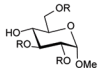
The 2-benzoximinoglycosyl bromides **205** and **207**−**209** of Table 5 are—like their 2-ulosyl analogues—crystalline, shelf-stable compounds of comparatively low anomeric reactivity. Nevertheless, their *O*-glycosidations can be conducted with preparatively useful selectivities of at least 20:1 to either α- or β-glycosidulose oximes by selection of the proper promoters and conditions.

3.3.1. β-D-Glycosidulose Oximes. When reacted with alcohols in the presence of silver carbonate or silver aluminosilicate and molecular sieve as a desiccant (CH_2Cl_2, rt), the 2-benzoximinoglycosyl bromides of α-D-*arabino* configuration (Table 6) invariably generate the β-D-*arabino*-glycosidulose oximes. As exemplified by the data collected in Table 7 for the D-glucose-derived bromide **205**, simple aliphatic alcohols and the diacetonegalactose 6-OH are smoothly glycosylated under these conditions to the respective β-glycosidulose oximes **220**, readily isolable in crystalline form each with yields in the 90% range (entries 1−3).[121,129] The 3-OH and 4-OH of otherwise benzyl-protected α-L-rhamnosides (entries 4 and 5) are similarly glycosylated by **205** with β-selectivities of 20:1 as determined by ^{1}H NMR,[130] the somewhat lower yields obviously being due to more expeditious isolation rather than a drop in anomeric selectivity. In the case of the 4-OH of protected glucosides as the alcohol components, an interesting reactivity pattern emerged:

Table 7. β-D-Glycosidulose Oximes of Type 220 Generated by Insoluble Silver Salt-Promoted Glycosidations of Oximinoglycosyl Bromide 205



α-D-*arabino* β-D-*arabino*

Entry	Acceptor alcohol[a]	Promotor[b]	Conditions (CH_2Cl_2, rt)	Isolated Yield (%)	Ref.
1	MeOH	Ag_2CO_3/I_2	24 h	93	129
2	*i*PrOH	Ag_2CO_3	2.5 h	89	121
3		Ag_2CO_3/I_2	24 h	94	129
4		Ag^+/AlSi	2.5 h	72	130
5		Ag^+/AlSi	3 h	50	130
6	 R = MBn[a]	Ag+/AlSi	2 d	85	131
7	R = $EtSiMe_3$[a]	Ag^+/AlSi	2.5 h	86	132
8	 R= Bn	Ag_2CO_3/I_2	2 d	55[c]	129
9	R = Bz	Ag_2CO_3/I_2	2 d	—	129

[a] Abbreviations: MBn = *p*-methoxybenzyl; $EtSiMe_3$ = 2-(trimethylsilyl)ethyl. [b] Ag^+/AlSi = silver aluminosilicate.[39] [c] Plus 18% **219**, the hydrolysis product of **205** (OH instead of Br), due to the sluggish reaction.

excellent anomeric stereocontrol and, hence, high yields with the β-glucosidic acceptors (entries 6 and 7)[131,132] versus moderate results only (55%) with the α-anomeric analogue (entry 8), the sluggish reaction resulting in partial hydrolysis of the bromide (→**214**, 18% isolated yield); the expectedly less reactive as well as sterically more congested 4-OH of methyl 2,3,6-tri-*O*-benzoyl-α-D-glucoside (entry 9), however, entirely failed to react under these conditions, revealing the limitations of the donor **205**.[129] Here, the use of the benzyl-protected donor **219** (Scheme 38) is likely to give more favorable results due to its expected substantially higher anomeric reactivity.

The conditions found efficient for the β-glycosidation of **205** work as effectively with disaccharidic oximinoglycosyl bromides. The lactose-derived **207**, for example, on silver carbonate-promoted coupling with benzyl or *p*-methoxybenzyl alcohol, cyclohexanol, or diacetonegalactose (CH_2Cl_2, rt, 1−2 d), provided the respectice β-glycosidulose oximes **221a**−**d** (Scheme 39) in crystalline form each and in yields around 80%.[29,44,133]

3.3.2. α-D-Glycosidulose Oximes. When the alcoholysis of oximinoglycosyl bromides such as **205** or the lactose-derived **207** is promoted by silver triflate (CH_2Cl_2, −78 °C → rt), invariably the respective α-glycosidulose oximes are generated with as high a preference as to be preparatively useful. Obviously, a double inversion occurs at the anomeric carbon, the Ag^+-assisted S_N2 displacement of the bromide by triflate being followed by ejection of the β-triflate moiety through the acceptor OH.

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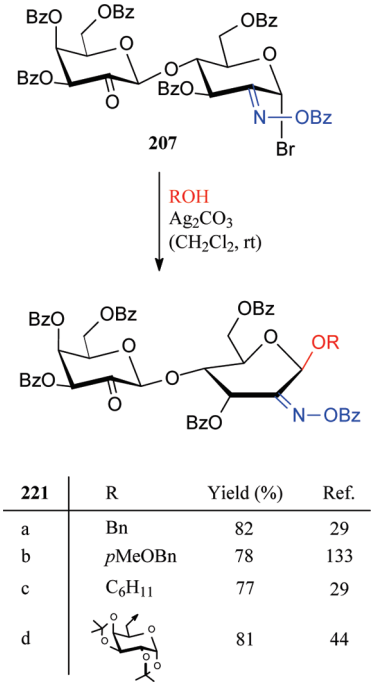
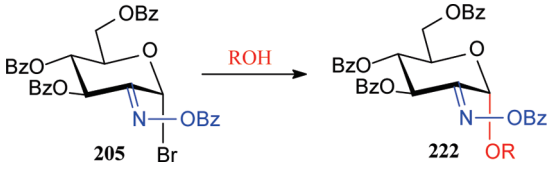
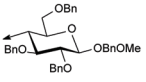
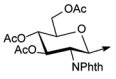
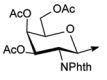
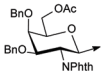
Scheme 39



221	R	Yield (%)	Ref.
a	Bn	82	29
b	*p*MeOBn	78	133
c	C_6H_{11}	77	29
d		81	44

Table 8. α-Linked Disaccharides of Type 222 Generated by AgOTf- or *s*-Collidine-Promoted Glycosidations of Oximinoglycosyl Bromide 205



Entry	R[a]	Conditions[a]	Yield (%)	Ref.
1		AgOTf / TMU, dioxane, rt, 20 h	77	44
2		*s*-collidine, dioxane, rt, 2 d	78	44
3		AgOTf / TMU, CH_2Cl_2, rt, 20 h	90	134
4		AgOTf / *s*-collidine, CH_2Cl_2, -78°C, 1.5 h	80	135
5		AgOTf / *s*-collidine, CH_2Cl_2, -78°C, 1.5 h	72	135
6		AgOTf / *s*-collidine, CH_2Cl_2, -78°C, 1.5 h	77	135

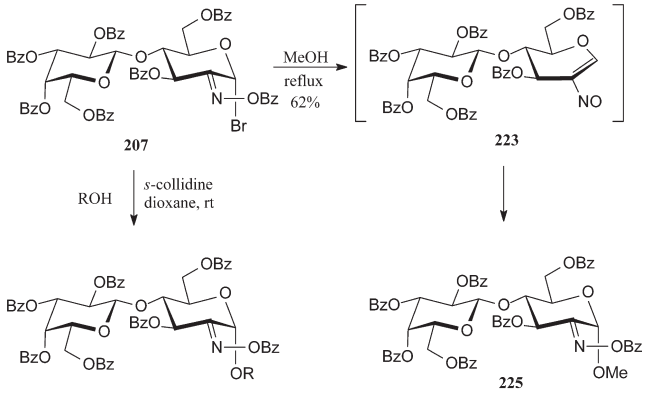
[a] Abbreviations: NPhth = phthalimido; TMU = *N*,*N*-tetramethylurea; *s*-collidine = 2,4,6-trimethylpyridine.

Ample evidence is provided by the results collected in Table 8.[44,134,135] Couplings of donor **205** with five relatively demanding glycosyl acceptors smoothly afford the α-linked disaccharides **222** in as high yields as to infer α/β-selectivities in the 15:1 to 20:1 range. The individual promoters and conditions employed vary such that AgOTf/tetramethylurea in dioxane or CH_2Cl_2 (entries 1 and 3), *s*-collidine in dioxane (entry 2), and the AgOTf/*s*-collidine combination in CH_2Cl_2 (entries 4−6) give equally efficient results. The advantage of using both, i.e., AgOTf and the sterically hindered pyridine base, appears to lie in the low reaction temperature (−78 °C) at which the glycosidations **205** → **222** are effected.

In the case of oximinolactosulosyl bromide **207**, reagents and conditions for accessing α-glycosidulose oximes have been studied in greater detail.[29,133] Surprisingly, high α-selectivity is already achieved by refluxing in methanol, yet not only α-glycosidation occurs but cleavage of the oxime ester function as well, to afford the α-D-lactosuloside oxime **225** (Scheme 40). Of the several reactions involved in this conversion, methanolysis is thought to be the first, since the resulting α-bromo oxime is expected[136] to dehydrobrominate to a nitrosoglycal intermediate of type **223**, which is known[137] to add alcohols with high α-preference. This course is substantiated by isolation of the anticipated intermediate and its conversion into the α-glycoside: treatment of **207** with base (*s*-collidine) in *N*,*N*-dimethylformamide readily delivered the 2-nitrosolactal ester **223** in dimeric form (67%) and was cleanly converted into α-lactosuloside oxime **225** (69%) on refluxing with methanol.

The in situ anomerization procedure[138] or variations thereof proved to be less propitious in achieving high α-selectivity in

Scheme 40

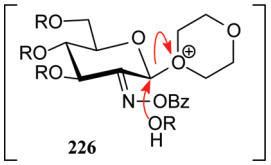


224	R	Yield (%)	Ref.
a	Bn	82	29
b	*p*MeOBn	78	133
c	C_6H_{11}	77	29

glycosidations of **207**. When exposed to tetraethylammonium bromide in CH_2Cl_2 at ambient temperature, a gradual decrease in rotation is observable (+180° → +80° in 2 d), indicating that α→β-anomerization does take place yet obviously leads to the still rather stable β-bromide. Correspondingly, reaction of **207** with simple alcohols in CH_2Cl_2 in the presence of tetraethylammonium bromide proceeds rather sluggishly, workup after 3 days providing glycosidic mixtures, e.g., of **225** and its β-anomer in α:β ratios of 4:1 to 3:1 only (^{1}H NMR). Use of the more reactive Helferich catalyst,[139] i.e., mercuric cyanide in dioxane or nitromethane, also favored α-glycosidation to the extent of a 3:1 to 4:1 selectivity at best.[29]

dx.doi.org/10.1021/cr100444b |*Chem. Rev.* 2011, 111, 5569–5609

Preparatively very useful α-selectivities of about 15:1 to 20:1 in glycosidations of **207** are readily reached not only with AgOTf in CH_2Cl_2 in the precence of tetramethylurea—in analogy to glycosidations of the monomeric **205** (cf. Table 7)—but also, somewhat surprisingly, by its exposure to alcoholysis in dioxane solution in the presence of a sterically hindered pyridine base such as *s*-collidine. Accordingly, on reaction with benzyl alcohols or cyclohexanol under such conditions (rt, 2 d), clean conversion into the respective α-D-lactuloside oximes **224a**−**c** is effected, yields of isolated crystalline products being around 80% (Scheme 40). The high α-selectivity, which on the basis of ^{1}H NMR data of mother liquors is better than 15:1, and the solvent dependency (in nitromethane approximate 1:1 mixtures of anomers accumulate) give reason for the assumption that the base-induced removal of the anomeric bromine is assisted by the dioxane oxygen to generate an intermediate β-dioxonium ion of type **226**, which subsequently undergoes S_N2 displacement by the alcohol.



226

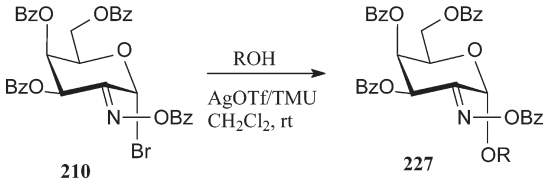
Despite the quite favorable, *sym*-collidine-promoted α-glycosidations **207** → **224a**−**c**, in the case of more complex, sugar-derived alcohol components, it appears more expedient to rely on AgOTf and AgOTf/*s*-collidine as the promoters as these gave excellent α-selectivities in the coupling of the monomeric oximinoglycosyl donor **205** with saccharidic acceptors (cf. Table 8).

Whereas the D-*arabino*-configurated oximinoglycosyl bromides can efficiently be directed toward either α- or β-glycosidulose oximes by proper choice of the promoter and conditions, their D-galactose-derived analogues of D-*lyxo* configuration, e.g., **210**, cannot, the axially oriented 4-*O*-benzoyl group obviously influencing the steric course of reactions at the anomeric center. Thus, exposure of **210** in CH_2Cl_2 at rt to silver triflate in the presence of tetramethylurea, molecular sieves, and the respective alcohol components (Scheme 41) gave rise to approximate 5:1 α/β mixtures, from which the preponderant α-glycosidulose oximes **227a**−**c** are isolable in moderate yields.[120] Experiments with diacetonegalactose as the acceptor revealed that, in solvents such as dioxane or acetonitrile, the anomeric selectivity deteriorates to a 3:2 and 2:1 α:β ratio of the disaccharide, while with Ag_2CO_3 as the promoter (CH_2Cl_2, rt, 2 d) a mixture of anomers was obtained with a 3:2 preponderance of the β-disaccharide.[120]

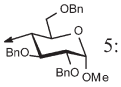
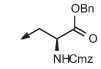
3.4. Oxime Reductions

Of the various protocols used to reduce sugar oximes to the corresponding amines, neither hydrogenation over Adams catalyst[140] or 10% palladium on charcoal[141] nor exposure to $LiAlH_4$ in THF[142] was appreciably selective, glycoside-2-ulose oximes, for example, consistently leading to glucosamine/mannosamine mixtures of varying ratios, irrespective of the anomeric configuration of the educt. In fact, the only effective reducing agent with respect to ease of application, rapid reactions, and high, in some cases even full, stereoselectivity proved to be the borane−THF complex,

Scheme 41



210 **227**

227	R	α:β ratio	isol. yield (%)
a		6:1	52
b		5:1	42
c		5:1	50

first applied by Lemieux for the reduction of oximino and acetyloximino groups in α-D-glycosidulose oximes to α-D-glucosamine derivatives.[143] Thereby, the reagent either is used in the form of a commercially available 1 M solution or is generated in situ from $LiBH_4$ and trimethylsilyl chloride in THF, a methodology originally introduced for the reduction of carboxyl, cyano, and nitro groups[144] and first applied to sugar oximes by Banaszek.[145]

Sterically, these oxime reductions are subject to anomeric stereocontrol, the hydride attack occurring with high preference or even exclusively from the face opposite the anomeric substituent. Thus, upon subsequent *N*-acetylation, β-D-ManNAc derivatives are obtained from β-D-*arabino*-glycosidulose oximes, while the α-D-*arabino*-analogues as consistently result in the α-D-GlcNAc epimers. These steric preferences are clearly borne out by the data collected in Tables 9 and 10. In the β-D-*arabino* → β-D-ManNAc cases, the anomeric stereocontrol of the reduction is well pronounced already with simple anomeric substituents such as methyl or cyclohexyl (Table 9, entries 1 and 2, yields of 88% and 82%, respectively), yet all the more with more bulky saccharidic residues (entries 3−9). Thereby, the uniformity of the steric course may at least in part result from the fact that the pyranoid ring in the β-D-*arabino*-glycosidulose oximes, on the basis of unusually small $J_{3,4}$ couplings of about 3 Hz,[29,44] is substantially flattended around C-2 (as indicated in the formula in Table 9), which is apt to facilitate the hydride attack from the α-face.

In the three α-D-*arabino*-configurated cases listed in Table 10, the BH_3 reduction is likewise endowed with high to excellent *gluco*-selectivity even though the isolated yields of the respective α-D-GlcNAc derivatives **229** are somewhat inferior. This is due, however, to the lability of the 3′- and 4′-*O*-benzoyl groups under the reduction conditions leading to partially de-*O*-benzoylated products. Thus, it is more opportune to subject the reaction mixture—after *N*-acetylation—to de-*O*-benzoylation under Zémplen conditions and characterize the disaccharides as such or as their peracetates.[135]

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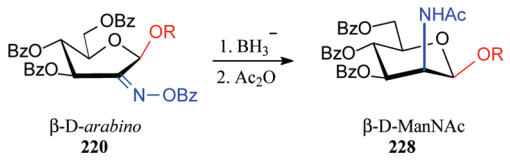
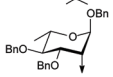
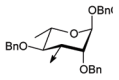
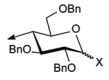
Table 9. Reduction of β-D-*arabino*-Glycosidulose Oximes Followed by *N*-Acetylation to β-D-ManNAc Derivatives 220−228



β-D-*arabino* **220** β-D-ManNAc **228**

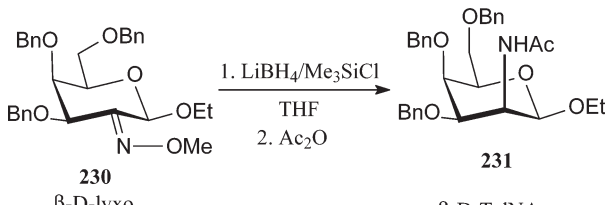
Entry	R[a]	Procedure[b]	Isolated Yield (%)	Ref.
1	Me	A	88	129
2	C_6H_{11}	B	82	146
3		A B	74 72	129 146
4		A	70	130
5		A	59	130
6		A	61	130
7	 X = αOMe	A	81	129
8	X = βOMBn	A	69	131
9	X = βOEtSiMe3	A	73	132

[a] Abbreviations: MBn = *p*-methoxybenzyl; $EtSiMe_3$ = 2-(trimethylsilyl)-ethyl. [b] Reagents and conditions: A, 1 M BH_3·THF, −10 °C → rt, 2.5 h, then Ac_2O; B, $LiBH_4/Me_3SiCl$, THF, −20 °C → rt, 3 h, then Ac_2O.

Excellent reduction results are similarly obtained with α- and β-lactuloside oximes **221** and **224**, respectively, providing an efficient entry into trisaccharides with a central β-D-ManNAc or α-D-GlcNAc moiety (vide infra, section 3.5.3.). In the D-*lyxo* series, however, only the β-anomers appear to be reduced with high selectivity, the hexosidulose oxime **230**, for example, exclusively forming the β-D-TalNAc derivative **231**, isolable in 80% yield[146] (Scheme 42).

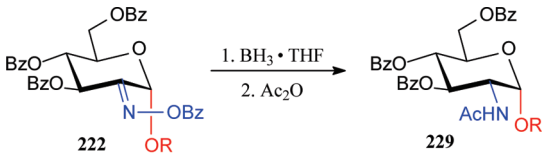
As would be expected on steric grounds, the borohydride reduction of α-D-*lyxo*-hexosidulose oximes is considerably less uniform, invariably giving—after *N*-acetylation—mixtures of the *N*-acetyl-α-D-talosamine (α-D-TalNAc) and *N*-acetyl-α-D-galactosamine (α-D-GalNAc) compounds in varying ratios, from which the major component, usually the

Scheme 42

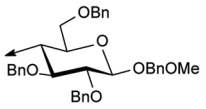
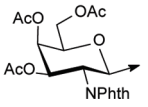


230 β-D-lyxo **231** β-D-TalNAc

Table 10. Reduction of α-D-*arabino*-Glycosidulose Oximes and Subsequent *N*-Acetylation to α-D-GlcNAc Derivatives



222 α-D-*arabino* **229** α-D-GlcNAc

Entry	R	Procedure[a]	Yield (%)	Ref.
1		A	53	146
2		A	55	134
3		B	60	145

[a] Reagents and conditions: A, BH_3·THF, −10 °C → rt, then Ac_2O; B, $LiBH_4/Me_3SiCl$, THF, −20 °C → rt, then Ac_2O.

α-D-talosaminide (Table 11, entries 1−5), can be separated in modest to good yield. A peculiar exception to these *talo*-selective reductions proved to be the *tert*-butyl α-D-*lyxo*-hexosidulose oxime (entry 6), which nearly exclusively formed the GalNAc derivative.

3.5. 2-Oximinoglycosyl Bromides in Oligosaccharide Synthesis

The convenient accessibility of mono- and disaccharide-derived 2-benzoximinoglycosyl bromides from the respective hydroxyglycal esters, combined with high diastereoselectivities in both the glycosidation and reduction steps (Scheme 35), amply demonstrates the salient synthetic protential of this "2-oximinoglycosyl bromide strategy" to the straightforward construction of oligosaccharides with either β-D-ManNAc or α-D-GlcNAc units as well as β-D-ManNAcA components. The experimental material to be presented below strongly emphasizes the conceptual and preparative utility of this approach.

3.5.1. β-D-ManNAc-L-rhamnoses. *N*-Acetyl-D-mannosaminyl-β(1→*x*)-L-rhamnoses have been identified as key disaccharide elements of various *O*-antigens of lipopolysaccharides known to be responsible for opportunistic infections. The β-D-ManNAc-(1→4)-L-Rha **232**, for example, represents a common core repeating unit of the *O*-antigen from the opportunistic pathogens *P. cepacia*[93] and *P. aeruginosa*,[94] as well as from *A. salmonicida*,[95] a lethal aquatic bacterium which causes the disease furunculosis in salmonoid fish. The respective

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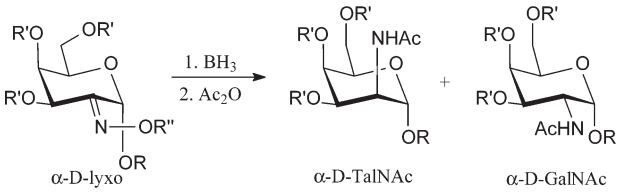
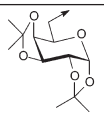
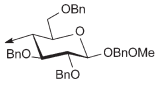
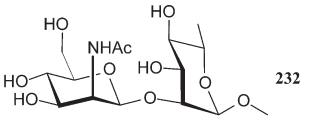
Table 11. Borohydride Reductions of α-D-*lyxo*-Hexosidulose Oximes



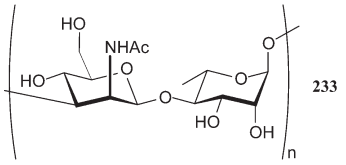
Entry	R	R'	R"	Reduction procedure[a]	Ratio *talo* : *galacto*	yield (*talo*)	Ref.
1		Bz	Bz	B	?	41	120
2		Bz	Bz	B	?	40	120
3	Me	Bn	Me[c]	A	6 : 1	68	146
4	Me	Ac	Me[c]	A	3 : 2	[b]	146
5	C_6H_{11}	Ac	Me[c]	A	2 : 1	69	146
6	tBu	Ac	Me[c]	A	1 : 19	74	146

[a] REagents and conditions: A, 1 M BH_3·THF, −10 °C → rt, 2.5 h, then Ac_2O; B, $LiBH_4/Me_3SiCl$, THF, −20 °C → rt, 3 h, then Ac_2O. [b] Mixture not separated. [c] Methoximes (R″ = Me) were prepared by reaction of the respective hexosid-2-uloses with methylhydroxylamine.

β(1→2)-isomeric disaccharide **233** is part of the *O*-antigen of *E. coli* O1A.[96]



D-ManNAc-β(1→2)-L-Rha-α(1→

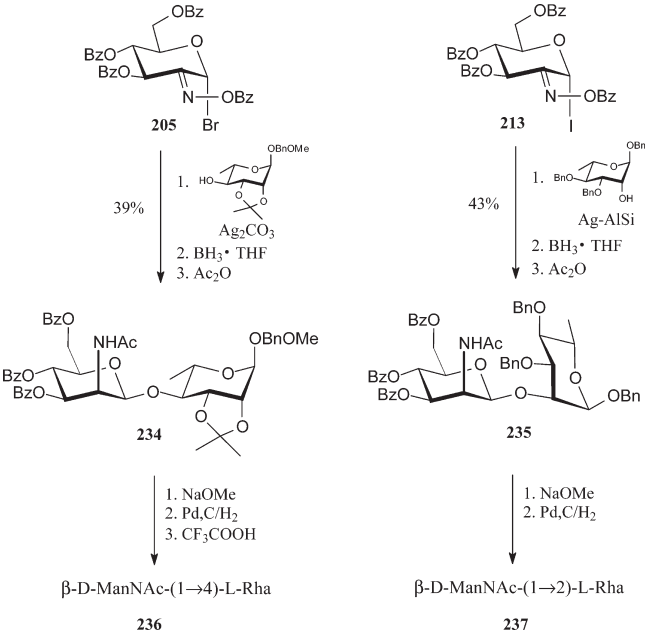


→3)-D-ManNAc-β(1→4)-L-Rha-α(1→

Utilization of the benzoximinoglycosyl bromide **205** as the β-D-ManNAc donor and suitably protected L-rhamnosyl acceptors resulted in concise, preparatively satisfactory syntheses of either of these disaccharides.[130] As detailed in Scheme 43, insoluble silver salt-promoted coupling of donor **205** or **213** with *p*-methoxybenzyl 2,3-*O*-isopropylidene-α-L-rhamnoside or alternately with a 2-OH-free analogue (1−3 h, rt, in CH_2Cl_2), followed by borane reduction and *N*-acetylation, afforded the β(1→4)- and β(1→2)-linked ManNAc-rhamnosides **234** and **235**; the glycosylation steps proceed with a 20:1 β-selectivity, the oxime reductions even in an essentially stereospecific manner.[130] The blocking group pattern in these disaccharides is flexible as they easily can be fully deprotected to the free disaccharide **236** or **237**, respectively, or alternately be modified for introduction of further glycosyl moieties.

An alternate means of constructing β-D-ManNAc-(1→4)-L-rhamnoside **236** has been devised via glycosylation of a 4-OH-free rhamnoside with 2-azidomannosyl bromide **197**.[147] However, this donor is difficultly accessible (11 steps from D-glucose in 10% overall yield[107]), must be used in situ due to its high sensitivity, and requires a 6-fold excess of the rhamnosyl acceptor to avoid loss of its 6-*O*-benzyl group toward formation of the

Scheme 43



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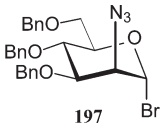
1,6-anhydro derivative.[147] The oximinoglycosyl donors **205** and **213**, by contrast, are comparatively well accessible, in 59% and 50% yield for the six and seven steps, respectively, from D-glucose,[26] are crystalline, storable compounds, and are glycosidated with 20:1 β-selectivities (vide supra, section 3.3.1).



197

3.5.2. Versatile *N*-Acetyl-β-lactosamine (β-LacNAc) Donors. *N*-Acetylated lactosamine (Gal-β(1→4)-GlcNAc or LacNAc) is a ubiquitous component of cell wall glycans, thereby invariably linked in β-attachment to the respective oligosaccharide assembly.[148] Readily accessible donors with which to introduce the β-LacNAc unit efficiently being highly desirable,[149] the well-accessible oximinolactosulosyl bromide **207**—six steps from lactose in 60% overall yield[29]—was evaluated toward this end, leading to the oxazoline **242** (Scheme 44) or, preparatively more important, to the *N*-(trichloroethoxy)carbonyl-protected lactosaminyl β-fluoride **245** and α-trichloroacetimidate **246** (Scheme 45) as most versatile β-LacNAc donors.

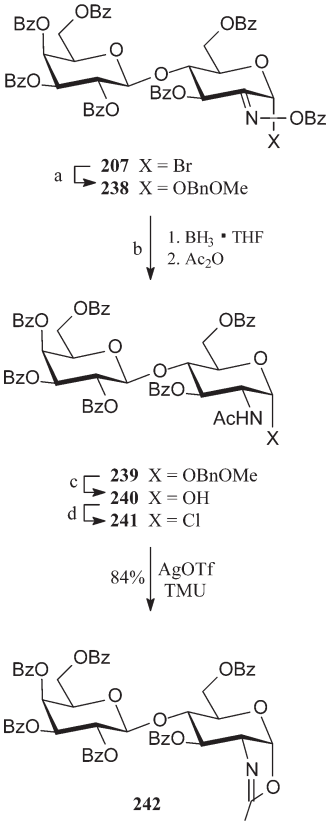
For reasons lying in the steric requirements for the oxime reduction—only α-glycosidulose oximes are reduced *gluco*-selectively—the lactose-derived donor **207** is only capable of introducing LacNAc residues in α-linkage (Scheme 45): α-glycosidation (→**238**) and successive borane and acetic anhydride treatment smoothly lead to the α-LacNAc derivative **239**.[133] Upon release of the anomeric OH by hydrogenolysis (→**240**) and exposure to $SOCl_2$, however, the α-LacNAc chloride **241** is obtained, readily convertible by AgOTf/TMU treatment into oxazoline **242**.[127]

The utility of 1,2-oxazoline **242** as a β-LacNAc donor has not explicitly been probed, yet its coupling with saccharidic acceptors is expected to occur in a way similar to that of its *O*-acetylated analogue[150] (**242** with acetyl instead of benzoyl protecting groups). However, the somewhat harsh coupling conditions required—e.g., *p*-toluenesulfonic acid in toluene−nitromethane at 60 °C[150b]—indicated donors of this type to be of limited general practicality.

More promising in this context proved to be the lactosaminyl donors **245**[151] and **246**[151,152] with the (trichloroethoxy)carbonyl (Troc) group for *N*-protection—a group known[154] to foster donor reactivity and β-glycosidation aside facile introduction and removal. Elaboration of the β-fluoride **245** from the oximinolactosulosyl bromide **207** required four standard operations (Scheme 45): α-selective glycosidation (→**244**), BH_3 reduction and *N*-Troc protection (→**243**), liberation of the anomeric center (→**213**), and fluorination with (dimethylamino)sulfur trifluoride (DAST), performable in an overall yield of 35%. The utility of this donor for β-glycosidation was verified by its $AgClO_4$-mediated β-coupling onto a 3-OH-free methyl galactoside, the resulting *O*-protected LacNAc-β(1→3)-galactoside **247**, obtained in 76% yield, being readily deprotected to the free trisaccharide **250**.[151]

Particularly well suited for β-glycosylation of saccharidic acceptors proved to be the lactosaminyl imidate **246**, readily prepared by exposure of the anomerically unprotected **244** to trichloroacetonitrile/K_2CO_3 (Scheme 45).

Scheme 44[a]



242

[a] Reagents and conditions: (a) *p*-MeOBnOH, *s*-collidine in dioxane, rt, 2 d, 82%;[133] (b) BH_3 in THF, −10 °C (30 min) → rt (2 h), then Ac_2O, 57%, plus 29% 3-de-*O*-benzoylated product;[133] (c) CAN in 9:1 acetonitrile/water, rt, 20 h, 79%;[127] (d) $SOCl_2$ in DMF, rt, 20 h, 72%;[127] (e) AgOTf, TMU in CH_2Cl_2, 20 h, rt, 84%.[127]

Boron trifluoride-mediated coupling with diacetonegalactose, for example (1.5 h at −20 °C in CH_2Cl_2), efficiently (82%) elaborated the *O*-protected LacNTroc-β(1→6)-Gal trisaccharide.[152]

Preparatively more significant appears to be the straightforward applicability of lactosaminyl donor **246** toward the acquisition of LacNAc-β(1→3)-L-fucosides, a trisaccharide sequence being part of *O*-linked chains of human clotting factor IX[155] and of proteoglycans of the marine sponge *Microciona prolifera*.[156] Accordingly, (TMS)OTf-mediated coupling of lactosaminyl donor **246** onto 3-OH-free, 2,4-*O*-benzyl-protected fucosides, followed by simple exchange of *N*-protection (Troc → Ac), smoothly afforded the LacNAc-fucosides **248** and **249** (Scheme 45, right entries) in yields of 57% and 49%, respectively, for the three steps involved. Simple Zemplén de-*O*-benzoylation and hydrogenolysis then led to the free trisaccharides **251**[153] and **252**, the latter with its 5-aminopentyl aglycon handle already ideally predisposed for conversion into BSA glycoconjugates.[151]

Preparative Utility of LacNAc Donors. The elaboration of the *N*-Troc-lactosaminyl donors **245** and **246** from lactose is admittedly somewhat lengthy as it requires 11 steps each, performable in overall yields of 20%[29,151] and 22%,[29,151,152] respectively. Nevertheless, these preparative results compare favorably with those attainable with other procedures for

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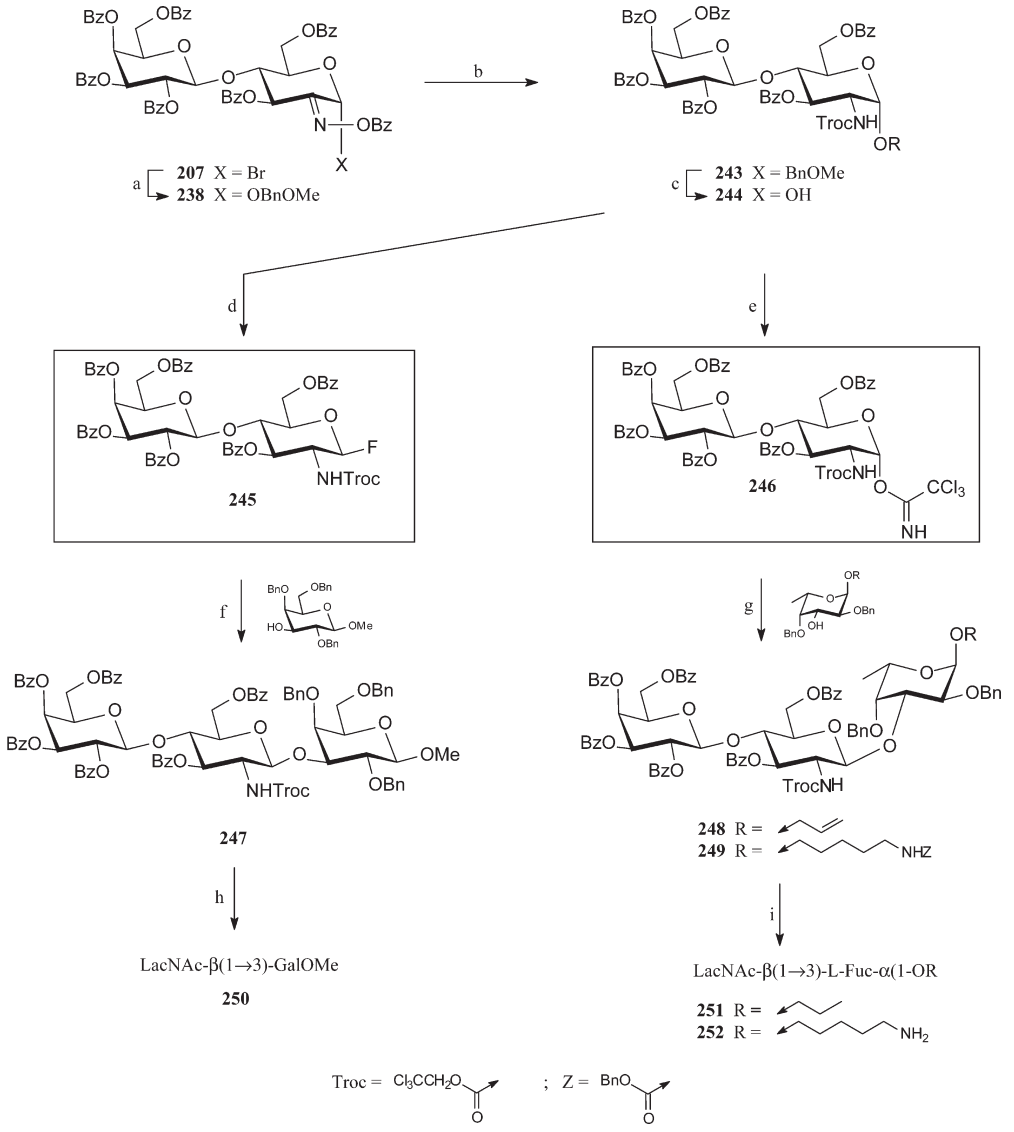
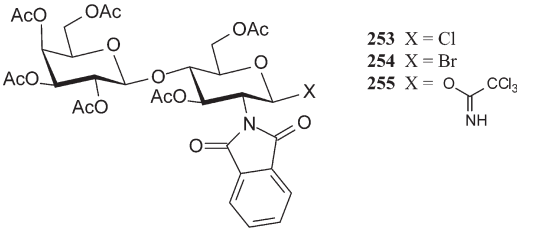
Scheme 45[a]



[a] Reagents and conditions: (a) *p*-MeOBnOH, *s*-collidine in dioxane, rt, 2 d, 82%;[152] (b) **238**, BH_3 in THF, −10 °C (0.5 h) → rt (2 h), then (2,2,2-trichloroethoxy)carbonyl chloride/Na_2CO_3, rt, overnight, 76%;[152] (c) DDQ/water in CH_2Cl_2, rt, overnight, 63%;[152] (d) (dimethylamino)sulfur trifluoride (DAST) in CH_2Cl_2, −30 °C → rt, 20 h, 89%;[152] (e) Cl_3CCN/K_2CO_3 in CH_2Cl_2, 3 h, rt, 98%;[151] (f) methyl 2,4,6-tri-*O*-benzyl-β-D-galactoside, $Cp_2ZnCl_2/AgClO_4$ in CH_2Cl_2, rt, overnight, 76%;[152] (g) →**248**: allyl 2,4-di-*O*-benzyl-α-L-fucoside, (TMS)OTf in CH_2Cl_2, 1 h at −20 °C, then Zn/HOAc and Ac_2O/pyridine, 57%;[153] →**249**: 5-[(benzyloxy)carbonyl]pentyl 2,4-di-*O*-benzyl-α-L-fucoside, (TMS)OTf in CH_2Cl_2, 45 min, −20 °C, then Zn/HOAc and Ac_2O/pyridine, 49%;[151] (h) Zn, HOAc, rt, then Ac_2O in MeOH, followed by debenzoylation (NaOMe/MeOH) and hydrogenolysis (Pd,C/H_2), 60%;[153] (i) NaOME/MeOH (2 d, 50 °C), then Pd,C/H_2 (24 h, rt) 74% (**251**);[153] 68% (**252**).[151]

the conversion of lactose into suitable lactosaminyl donors. Acquisition of the *N*-phthaloyl-protected β-chloride **253**, for example—by way of applying the nitrosochloride[157] and azidonitration[158] methodology to hexaacetyllactal—entails 10 and 11 steps, respectively, with overall yields being only 10% and 14%, respectively; the approach via lactose-derived galactosyl-β(1→3)-arabinose, involving an amino-cyanohydrin extension to the respective aminonitrile,[159] is shorter (eight steps), yet overall yields do not exceed 19%.[160] The same, 19% over eight steps, holds for the elaboration of the β-bromide **254** from lactose via an elegantly streamlined version of the azidonitration route,[161] while acquisition of the β-trichloroacetimidate **255** along the same route—12% over 10 steps from lactose[158,162]—is less efficient.



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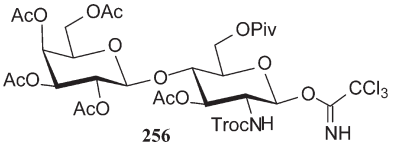
In summary, the preparatively most readily accessible β-lactosaminyl donors in terms of practicality of synthetic sequences and overall yields are the *N*-phthaloyl-protected β-chloride **253**, the respective bromide **254**, and the *N*-Troc-blocked fluoride **245** and imidate **246**, whereby the latter two have the distinct advantage that the *N*-Troc group is cleaner to remove than the venerable *N*-phthaloyl moiety.

Nonetheless, apparently unaware of the work on donors **245** and **246** by Ziegler[151] and Kaji et al.,[152] a decade later the LacNTroc β-imidate **256** was described by Matta et al.,[163] differing from **246** only in the acyl protecting pattern and the anomeric configuration. This donor, which on the basis of its NMR data may actually be the α-imidate,[164] was synthesized by joining suitably protected galactosyl and glucosamine derivatives entailing a total of 15 steps,[163] the overall yield of barely 10%, based on galactose and GlcNAc, being essentially half of that required for the acquisition of donor **246** from lactose (22% over 11 steps[151,152]). Notwithstanding, the fact that **256** could efficiently be applied to the synthesis of an allyl LacNAc-β(1→3)-L-fucoside by (TMS)OTf-mediated coupling onto a 3-OH-free fucose derivative[163] strongly emphasizes the prime utility of the *N*-Troc-protected lactosaminyl trichloroacetimidate for the expedient linking of the β-LacNAc block onto saccharidic acceptor substrates toward biologically important oligosaccharide assemblies.



256

3.5.3. β,α-Disaccharides Related to Tunicamycin. The tunicamycins comprise a family of closely related microbial metabolites inhibiting a variety of enzymatic processes toward the formation of phospholipid-linked intermediates.[165,166] Aside from being a uracil nucleoside and carrying various long-chain *N*-acyl appendages varying in length and degree of unsaturation, their most unique feature is the 11-carbon sugar tunicamine, of which the C_6-C_{11} portion can be seen as a D-GalNAc scaffold linked in β(1↔1)α-fashion to a GlcNAc residue (Figure 8).

The construction of the 11-carbon backbone of tunicamine already being a formidable challenge—several syntheses have been accomplished[167−171]—the stereocontrolled generation of the α,β-trehalose-type linkage between GlcNAc and tunicamine is another. In Suami's total synthesis of tunicamycin V,[167] this issue was addressed via a late-stage Koenigs−Knorr-type glycosidation encumbered with poor yield (18%) and difficulties in reproduction.[168] Myers et al. in their total synthesis[170] generated the crucial β,α-disaccharidic link at an early stage by trifluoromethanesulfonic acid-mediated coupling of a (*Z*)-azidoglucosyl trichloroacetimidate with an *N*-phthaloylgalactosamine derivative in a quite stereocontrolled manner—77% β,α-disaccharide aside 11% β,β-isomer—yet acquisition of the donor substrate (17% over six steps from triacetyl-D-glucal) is somewhat long.

Utilization of oximinoglycosyl bromide **205** as an indirect α-D-GlcNAc donor, accessible in 74% yield over three steps from 2-benzoyloxy-D-glucal tribenzoate,[22,25] proved to be a plausible alternative. Silver triflate/*s*-collidine-mediated glycosylation of the anomerically unprotected glucose derivatives **258**−**260** gave the α(1↔1)β-disaccharides **261**−**263** as the major products (Scheme 46), yet sizable amounts of the β,β-isomers **264**−**266** as well, their proportions being dependent on the C-2 substituent of the glucosyl acceptor: 3:2 to 3:1 in the case of 2-OAc or 2-NAc

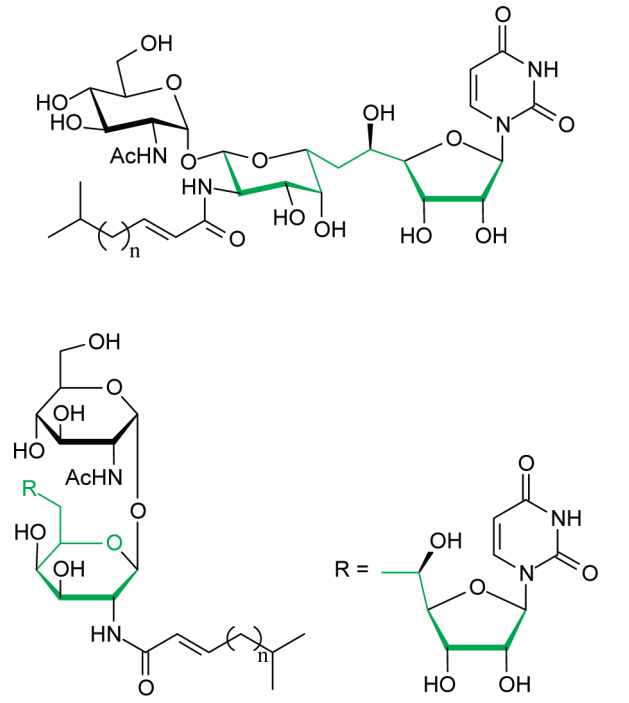
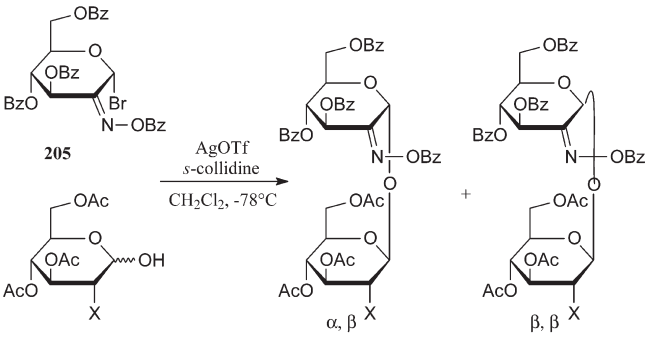


Figure 8. Tunicamycins in conventional representation (top) and in another accentuating the trehalose-type GlcNAc-α(1↔1)β-tunicamine scaffolds.

groups versus 40:1 with acceptor **260**, its bulky 2-*N*-phthaloyl moiety obviously directing the glycosylation to the α,β-isomer **263** (80%), the β,β-diastereomer **266** being barely isolable (2%).[135]

Scheme 46



258 X = OAc
259 X = NHAc
260 X = NPhth

261 X = OAc (38%)
262 X = NHAc (21%)
263 X = NPhth (80%)

264 X = OAc (29%)
265 X = NHAc (7%)
266 X = NPhth (2%)

Similar steric preferences are observed with the tunicamycin-related *N*-phthaloylgalactosamine acceptors **267** and **268**, which afforded the α,β-disaccharides **269** and **270** in preparatively useful yields (Scheme 47). Their convertibility into the GlcNAc-α(1↔1)β-GalNAc derivatives **271** and **272** was demonstrated by their $LiAlH_4-Me_3SiCl$ reduction followed by *N*-acetylation.[135,172]

Gratifyingly, this glycosylation procedure could readily be applied to the *N*,*O*-protected tunicamine derivative **273**, providing on coupling with oximinoglycosyl donor **205** the α,β-disaccharide **274** (46%)—all set to be transformed into the tunicamycins by *N*-glycosidation with bis(trimethylsilyl)uracil[173] and subsequent

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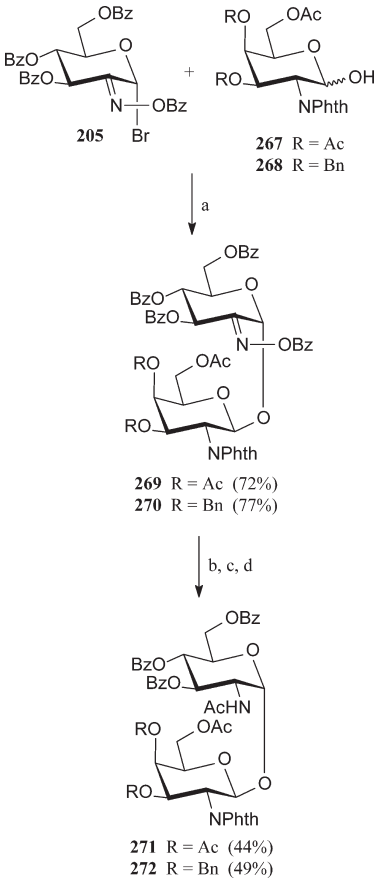
conversion by reduction, *N*-acetylation, and *N*-fatty acid acylations (Scheme 48). These concluding reactions though have not been implemented so far.

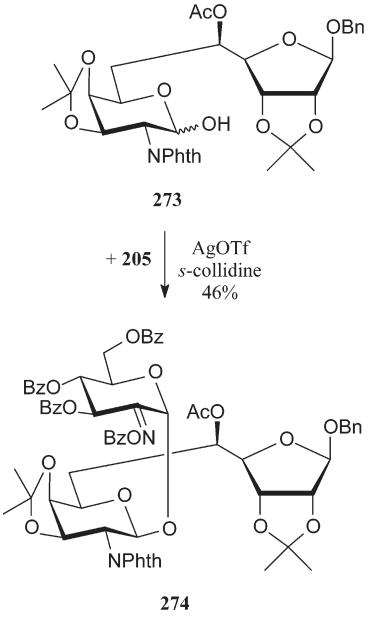
Scheme 47[a]



[a] Reagents and conditions: (a) AgOTf, *s*-collidine, molecular sieves in CH_2Cl_2, 1.5 h at −78 °C; (b) $LiAlH_4$−Me_3SiCl/THF, −20 → +40 °C; (c) K_2CO_3, MeOH; (d) Ac_2O/pyridine.

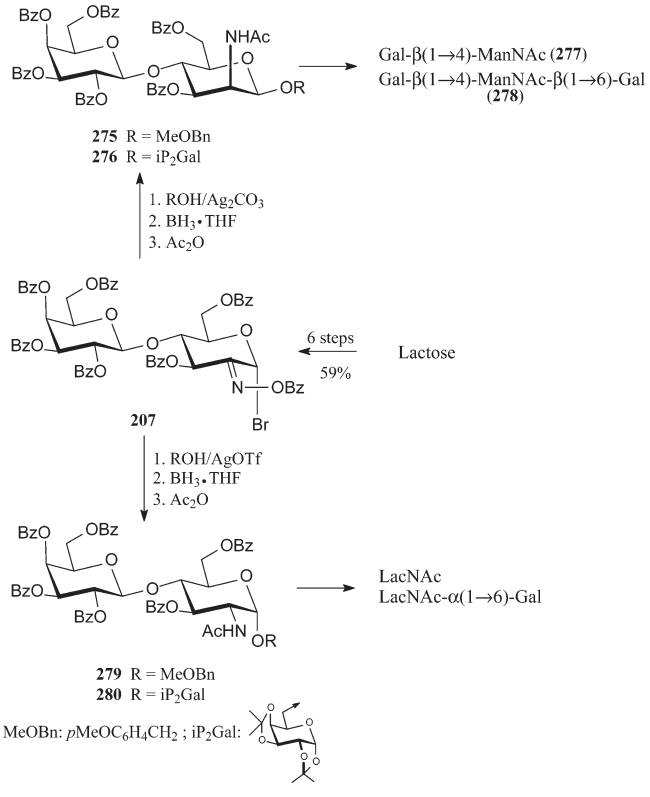
3.5.4. Trisaccharides with Central β-D-ManNAc and α-D-GlcNAc Units. The convenient accessibility of the 2-oximinoglycosyl bromides **207**−**209** from the common disaccharides lactose, maltose, and cellobiose (cf. Table 6) renders possible the straightforward generation of trisaccharides or higher oligosaccharides with internal β-D-ManNAc or α-D-GlcNAc residues, the product type being determined in the glycosylation step. As depicted in Scheme 49 for the lactose-derived donor **207**, silver carbonate-mediated glycosidation with *p*-methoxybenzyl alcohol or diacetonegalactose, followed by borane reduction and *N*-acetylation, afforded the Gal-β(1→4)-ManNAc derivative **275**[133] and its trisaccharide analogue **276**[44] in yields of 48% and 70%, respectively. Their blocking group pattern is such that deprotection may be readily achieved via standard protocols—Zémplén de-*O*-benzoylation, hydrogenolysis, hydrogenolysis for detachment of the *p*-MeOBn moiety, and trifluoroacetic acid for removal of the isopropylidene groups—to afford the respective free galactosyl-β(1→4)-*N*-acetylmannosamine **277** and its β(1→6)-galactosylated analogue **278** in yields around 90%.

Scheme 48



Preparatively more important appears to be the exploitation of the 2-oximinolactosulosyl bromide **207** as an indirect LacNAc donor, since α-selective glycosidation followed by reduction and *N*-acetylation necessarily leads to *N*-acetyllactosamine derivatives. Thus, silver triflate-mediated coupling of **207** with *p*-methoxybenzyl alcohol or diacetonegalactose smoothly and efficiently provided the LacNAc derivatives **279**[133] and **280**.[44]

Scheme 49



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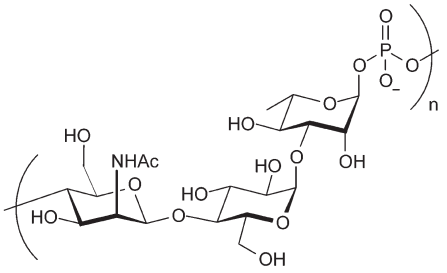
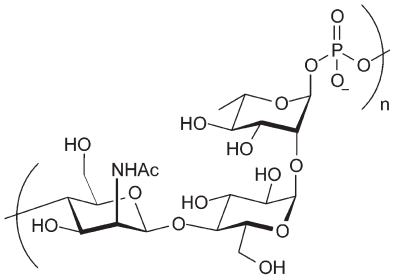
As these can easily be freed from their blocking groups via standard procedures, not only the LacNAc-α(1→6)-Gal trisaccharide becomes readily accessible, but LacNAc as well (Scheme 49). Thus, another, quite practical and, notably, large-scale-adaptable means for the acquisition of LacNAc from lactose is provided, comparing favorably with the various existing methodologies.[174]

In summary, oximinolactosulosyl bromide **207**, well accessible from lactose in a high-yielding six-step sequence,[22,25] is an ideal donor substrate for preparing oligosaccharide assemblies with either β-connected Gal-β(1→4)-ManNAc residues or α-coupled LacNAc units. In similar fashion, the equally well accessible maltose- and cellobiose-derived oximinoglycosyl bromides **208** and **209** (cf. Table 6) may expediently be used for introducing disaccharidic building blocks of the type Glc-α-(1→4)ManNAc-β(1→, Glc-β(1→4)ManNAc-β(1→, Glc-α-(1→4)GlcNAc-α(1→, and Glc-β(1→4)GlcNAc-α(1→ into oligosaccharide assemblies. Although none of these disaccharidic units have been encountered in nature so far, they are to gain importance in the preparation of mimics of the biologically relevant oligosaccharides for pharmaceutical evaluation toward unraveling structure−activity relationships.

3.5.5. *S. pneumoniae* Trisaccharides. The *S. pneumoniae* serogroup 19, including the two types 19A and 19F, is of particular clinical importance, since it is known to be a major pathogenic bacterium in penicillin-resistant *S. pneumoniae*-provoked pneumonia.[175] Its immunogenic specificity is embodied in cell-surface capsular polysaccharides consisting mainly of the β-D-ManNAc-containing trisaccharide repeating units **281**[100] and **282**[102] (Figure 9).



→4)-D-ManNAc-β(1→4)-D-Glc-α(1→3)-L-Rha-α(1→PO_4^-→
281



→4)-D-ManNAc-β(1→4)-D-Glc-α(1→2)-L-Rha-α(1→PO_4^-→
282

Figure 9. *S. pneumoniae* 19A (top) and 19F capsular polysaccharide repeating units.

Both trisaccharide components, as of now only lacking the phosphate residue, have expediently been synthesized by elaboration of the critical β-D-ManNAc portion from 2-benzoximinoglycosyl bromide **205** via 4-*O*-glycosylation of the central D-glucose unit and consecutive coupling with a 2-OH- and 3-OH-unprotected L-rhamnoside, respectively (Scheme 50).[131,132] The first coupling of **205** with the 4-OH-free glucoside **283**—intendedly carrying the easily acid-removable (trimethylsilyl) ethyl group at its anomeric center—was smoothly effected by silver aluminosilicate (3 h at rt in CH_2Cl_2) to afford the β(1→4) disaccharide **284** in high yield (86%)—ample evidence that the β-selectivity of the reaction is in the 20:1 range. The subsequent hydroboration similarly proceeded with high *manno*-selectivity, giving after *N*-acetylation the ManNAc-β(1→4)-Glc disaccharide **285** (77%), which via liberation of the anomeric center (→**286**) and DAST treatment was converted into fluoride **287**, obtained as a 1:3 α/β mixture. For attachment of the L-rhamnose units in either 1→2- or 1→3-linkage, the fluoride donor was exposed to correspondingly protected L-rhamnosyl acceptors in the presence of $AgClO_4/SnCl_2$ to effect α-glycosylation to trisaccharides **288a** (57%) and **288b** (30%) (Scheme 50).[132] The comparatively poor yield of the latter is attributable to the low reactivity of the rhamnose 3-OH and, hence, inadequate α-selectivity, as evidenced by obtention of substantial amounts (26%) of the β(1→3)-analogue of **289**.[132] Here the use of disaccharide donors other than the fluoride **287**, e.g., the respective imidate readily generated by exposure of **286** to trichloroacetonitrile/NaH or the equally well accessible sulfoxide, is likely to improve the attachment of the L-rhamnosyl residues.

In view of the various other strategies used for elaboration of the trisaccharide repeating units **289**[108,110,111,176−178] and **290**,[176,179] a comparative assessment of their practicality and overall efficiency is probably best done on the basis of how expediently the crucial β-D-ManNAc portion is incorporated.

Conversion of the 2-oximinoglycosyl bromide **205**, for example, into the ManNAc-β(1→4)-Glc derivative **285** is readily performed in three steps, comprising β-specific coupling with a 4-OH-free glucoside, subsequent highly *manno*-selective oxime reduction, and *N*-acetylation (63%; cf. Table 12). Comparable in efficiency are the likewise three steps required—β-glycosidation, hydrogenation, and *N*-acetylation—for generation of the ManNAc-β(1→4)-Glc scaffold from azidomannosyl bromides **196** and **197** used in Paulsen's approach,[176] even though they are less readily accessible[107] (Table 12). Distinctly less opportune proved to be the closely related donor **198** used in the Sugawara−Igarashi entry[108] as not only the donor is difficultly accessible, but the β-selectivities in coupling with the free 4-OH of an otherwise protected glucosyl-α(1→2)-rhamnoside are low, and hence, the yields are moderate: 33% with $AgClO_4$/2,4,6-collidine in diethyl ether and 17% with silver silicate in benzene/dichloromethane.

Considerably more remote indirect β-D-ManNAc donors used for elaboration of the disaccharide portion are the glucosyl derivatives **199**,[109] **200**,[110] and **201**.[111] Although fairly well accessible (Table 12), they are burdened with the necessity to convert their equatorial 2-*O*-acyl group into an axial acetamido function, a process feasible either by a de-*O*-acylation → oxidation → oximation → reduction → *N*-acetylation sequence[113] or, alternately, by introduction of a 2-sulfonyl group, S_N2 displacement by azide, hydrogenation, and *N*-acetylation[110,111]—a not

Scheme 50

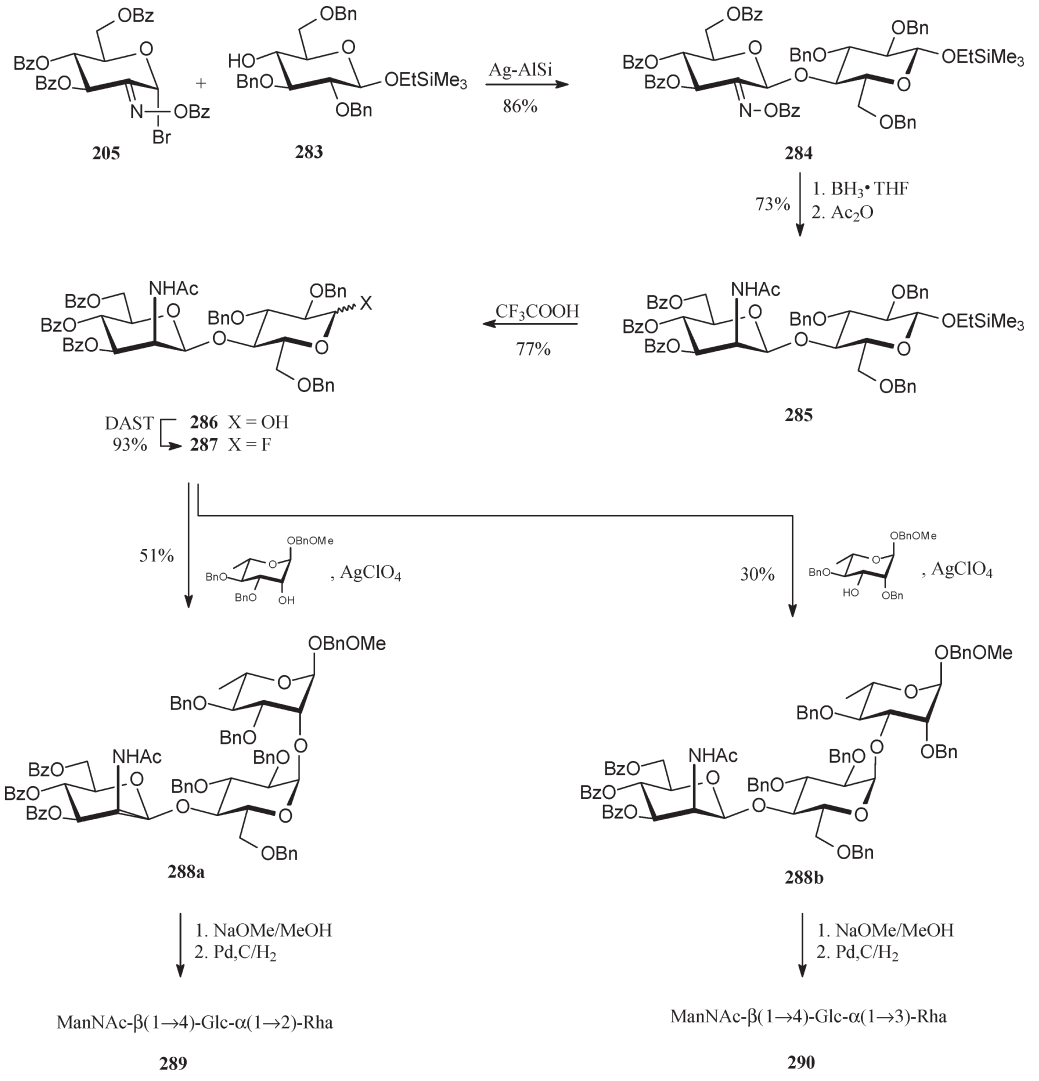
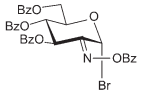
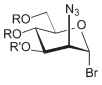
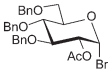
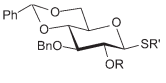


Table 12. Accessibility of Indirect β-D-ManNAc Donors from D-Glucose and Steps Required for Elaboration of the ManNAc-β(1→4)-Glc Scaffold toward Generation of the Trisaccharide Repeating Units of *S. pneumoniae*

Donor		R	R'	Steps required from D-Glucose	Overall Yield (%)	Ref.	Steps required to ManNAc-β(1→4)-Glc derivative	Yield (%)	Ref.
	**205**			6	59	25	3	63	132
	**196**	Ac	Ac	6	30	107	3	67	176
	197	Bn	Bn	11	10	107	3	45	176
	198	Bn	Ac	12	7	108	3	21	108
	**199**			5	33	109	6	35	113
	**200**	Bz	Me	8	17	110	7	43	110
	201	Ac	Ph	8	84	111	7	59	111

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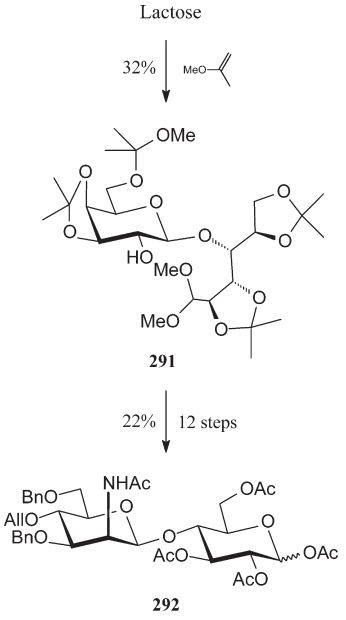
necessarily shorter reaction sequence. Neither approach provides acceptable overall yields.

Quite differently, Catelani's approach[178] starts from galactosyl-β(1→4)-glucoside **291** (Scheme 51), accessible from lactose by acetonation (32%).[180] Its conversion into the ManNAc-β(1→4)-Glc derivative **292**, however, entailed two inversions in the galactose part, at C-2 with introduction of the acetamido group and at C-4—transformations that were accomplished in 12 steps with the surprisingly high overall yield of 22% (85% per step).[181]

Scheme 51



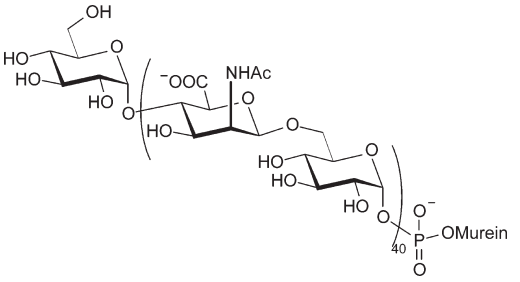
In summing up these preparative utility considerations on the various approaches toward the trisaccharide repeating units of *S. pneumoniae*, two emerge as the most expedient with respect to the number of steps involved and overall yields attainable for the elaboration of the β-D-ManNAc portion: the 2-azidomannosyl bromide **196** and the oximinoglycosyl bromide **205** (cf. Table 12).

Both, however, carry acyl protecting groups, which entail comparatively unreactive anomeric centers, and hence may engender difficulties with the glycosylation of notoriously unreactive acceptor hydroxyls. In such cases, it is advisible—despite several additional steps for their generation—to resort to the donor analogues with benzyl protection, such as the 2-azidomannosyl bromide **197** (Table 12) or the readily preparable (Scheme 38) oximinoglycosyl donor **219**.

Distinctly less favorable in terms of the number of steps required is the use of β-D-glucosyl derivatives of types **199**−**201** or the lactose-derived galactosylglucose **292** as rather remote β-D-ManNAc progenitors. Despite comparatively high yields in the individual steps involved, these approaches, aside from being somewhat long, appear to lack practicality in assembling more complex oligosaccharides with β-D-ManNAc units.

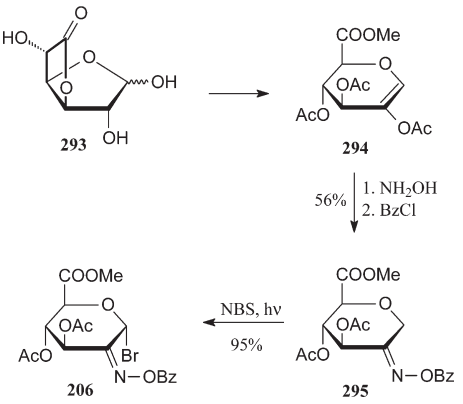
By contrast, the oximinogylycosyl donor strategy—and to a lesser extent also the azidomannosyl bromide approach—has the additional advantage to directly prepare ManNAc-α(1→4)-Glc analogues simply by changing the silver catalyst from silicate to triflate in the glycosidation step.

3.5.6. β-D-ManNAcA Disaccharides. 2-Acetamido-2-deoxy-β-D-mannuronic acid (β-D-ManNAcA) is an important structural unit of various bacterial capsular polysaccharides[105,106] and lipopolysaccharides.[92] It is also found in teichuronic acid,[182] a cell wall component from *Micrococcus luteus*, which is an acidic polysaccharide composed of a D-ManANAc-β(1→6)-D-Glc repeating unit, bound to a peptidoglycan (murein) through a phosphoric ester linkage:



The 2-oximinoglucuronyl bromide **206**, accessible from D-glucuronolactone **293** via hydroxylaminolysis of 2-acetoxyglucuronal **294**, benzoylation (→**295**), and photobromination (Scheme 52, 20% yield over the seven steps[118]) proved to be an efficient indirect glycosyl donor for the construction of β-D-ManNAcA-containing oligosaccharides.

Scheme 52



Employing silver aluminosilicate as the promoter (CH_2Cl_2, 2 h, rt), β-selectivities of better than 20:1 (^{1}H NMR) are obtained with acceptors such as Cbz-blocked aminoethanol (→**296**, 71%) or a 6-OH-free β-glucoside (→**300**, 88%) (Scheme 53). The subsequent, essentially *manno*-specific reduction and *N*-acetylation proceeded as smoothly to afford the β-D-ManNAcA derivatives **297** and **301**, the latter disaccharide constituting the repeating unit of the *M luteus* teichuronic acid in protected form. Both are well suited for the generation of glycolipids: In **297**, for example, palmitic acid can be attached to the aminoethanol spacer through Cbz hydrogenolysis (→**298**) and *N*,*N*-carbonyldiimidazole/triethylamine-mediated coupling (→**299**). In the ManNAcA-β(1→6)-Glc disaccharide **300**, the stearoyl residue was linked via the aminoethanol spacer to the anomeric position by acid removal of the 2-(trimethylsilyl)ethyl group (→**302**), fluorination with DAST (→**303**), and $Cp_2ZrCl_2/AgClO_4$-promoted glycosidation with (stearoylamino)ethanol (→**304**). Deblocking then provided the artificial glycolipid **306**.[118]

This oximinoglycuronyl donor approach to β-D-ManNAcA-containing oligosaccharides has major advantages over others.

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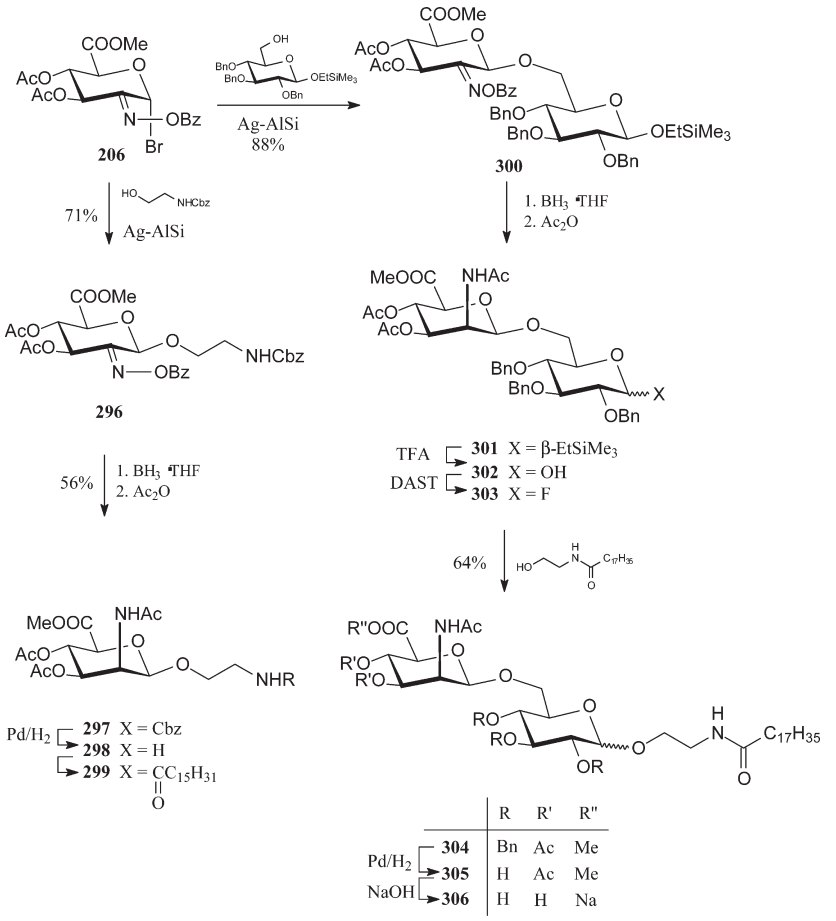
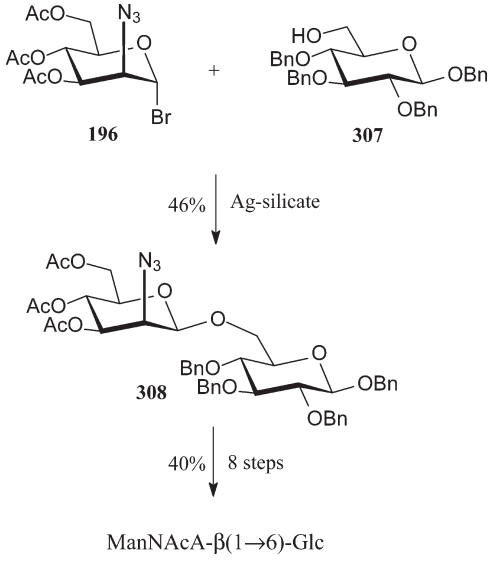
Scheme 53[a]



[a] Abbreviations: Ag-AlSi = silver aluminosilicate; $EtSiMe_3$ = 2-(trimethylsilyl)ethyl; TFA = trifluoroacetic acid; DAST = (dimethylamino)sulfur trifluoride.

Scheme 54



The 2-azidomannuronyl bromide **204**, for example, is well suited as an indirect β-D-ManNAcA donor, yet its acquisition from glucuronal **203** (Scheme 33) has less than 5% yield over two steps,[107] as the azidonitration involved is highly *gluco*-selective.[114] Similary impractical in preparative terms is the elaboration of the *N*-acetylmannosaminuronic part at the stage of disaccharide **308** synthesized by joining the fairly well accessible (Table 12) 2-azidomannosyl bromide with the 6-OH-free glucoside **307** (Scheme 54)—a coupling that due to low donor reactivity is devoid of selectivity (α:β ratio ∼1:1). Moreover, the conversion of **308** into β-D-ManNAccA-(1→6)-glucoside—via Pt/O_2 oxidation at C-6 and azide reduction as the key steps—requires another eight steps.[116]

4. CONCLUSION

The methodology reviewed here comprises the preparatively efficient conversion of cheap, basic mono- or disaccharides into 2-oxo- and 2-oximinoglycosyl bromides, which have proved to be surprisingly versatile glycosyl donors for the expedient construction of β-D-mannose-, β-L-rhamnose-, and β-D-mannosamine-containing oligosaccharides. This approach, comprising simple protocols, exellent β-selectivities, and high to excellent yields, aside from being readily amenable to large-scale preparations, has major preparative advantages over alternative methods. The synthesis of a sizable number of naturally occurring oligosaccharides containing β-D-Man, β-L-Rha, β-D-ManNAc, and β-D-ManNAcA units is testimony to the success of the methodologies developed.

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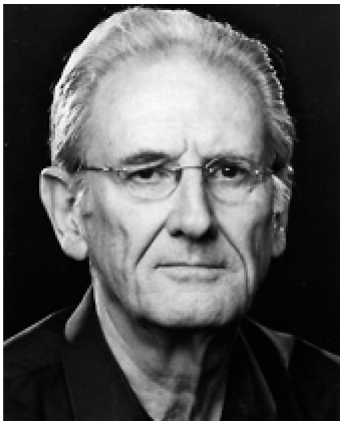
BIOGRAPHY



Frieder Lichtenthaler studied chemistry at the University of Heidelberg and received his doctorate there in 1959 with F. Cramer for work on the chemistry of enol phosphates. After three postdoctoral years at the University of California, Berkeley, studying the synthesis of nitrosugars with H. O. L. Fischer, he joined the faculty of the Technical University of Darmstadt, where he acquired his "Habilitation" in 1963 and was appointed Associate Professor in 1968 and Full Professor in 1972; in 2000 he was retired to Professor Emeritus, having mentored 74 Ph.D. students and 35 postdoctoral fellows. His research acitivities, documented in over 300 scientific papers, focused on the generation of enantiopure building blocks from sugars, their use in the synthesis of oligosaccharides and complex noncarbohydrate natural products, molecular modeling of chemical and biological properties of sugars, and extensive studies toward the utilization of carbohydrates as organic raw materials. He received an honorary doctoral degree from the Kossuth University, Debrecen (1993), and the SPRI Science Award of the Sugar Research Foundation, New Orleans (1994), and was elected Honorary Member of the Hungarian Academy of Sciences, Budapest (2004).

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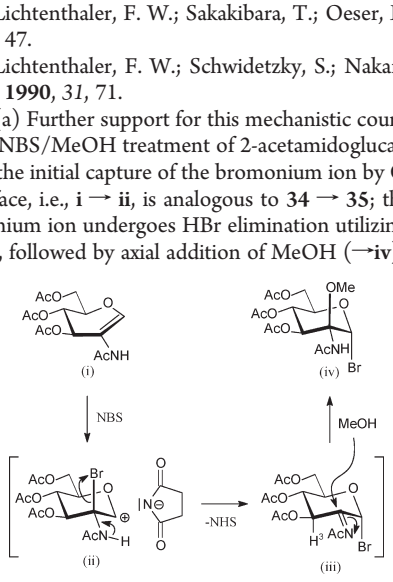

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