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Minireview

Synthesis of carbasugar-containing non-glycosidically linked pseudodisaccharides and higher pseudooligosaccharides

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ABSTRACT

This minireview covers synthetic methods towards carbasugar-containing non-glycosidically linked pseudodisaccharides or higher pseudooligosaccharides. Carbocyclic pyranose mimetics (saturated or unsaturated between C-5 and C-5a) are linked by ether, thioether or amine bridges to carbohydrates or other carbasugars.

Contents

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1. Introduction

This minireview concerns the synthesis of carbasugar-containing non-glycosidically linked pseudodisaccharides (or higher pseudooligosaccharides) in which a carbocyclic pyranose mimetic, either saturated or unsaturated between C-5=C-5a, is linked at C-1 to a carbohydrate (or other carbasugar) by a one-atom nitrogen, oxygen or sulfur bridge. Formal replacement of a ring-oxygen by a methylene group to give saturated carbadisaccharides is conceptually the simplest modification that leads to a hydrolytically stable pseudodisaccharide of this type (Fig. 1a). Exchange of the inter-glycosidic oxygen for nitrogen or sulfur and introduction of unsaturation between C-5 and C-5a are further modifications that have been studied.

Several N-linked pseudooligosaccharides containing carbocyclic valienamine, valiolamine or validamine moieties occur naturally, and some of these are shown in Figure 1.[1] Some motivation for their synthesis was found in the desire to prove the structures proposed following isolation. The biological activity, in particular glucosidase inhibitory activity, of some of these natural structures has prompted the synthesis of analogues to help understand their biological mode of action or to try to alter or improve specificity and affinity for a glucosidase or other glycosidase of interest.[2,3] Carbasugar pseudooligosaccharides have also been shown to interact with other carbohydrate-binding proteins; some ether-linked carbasugar pseudodisaccharides have been found to act as substrates for glycosyltransferases;[2] some have been found to bind to lectins.[4] The assessment of biological activity of the pseudodisaccharide derivatives is not covered here, and neither are deprotection reactions; the interested reader is referred to the original articles or to review articles aimed more at these aspects.[2,3,5] The synthesis of

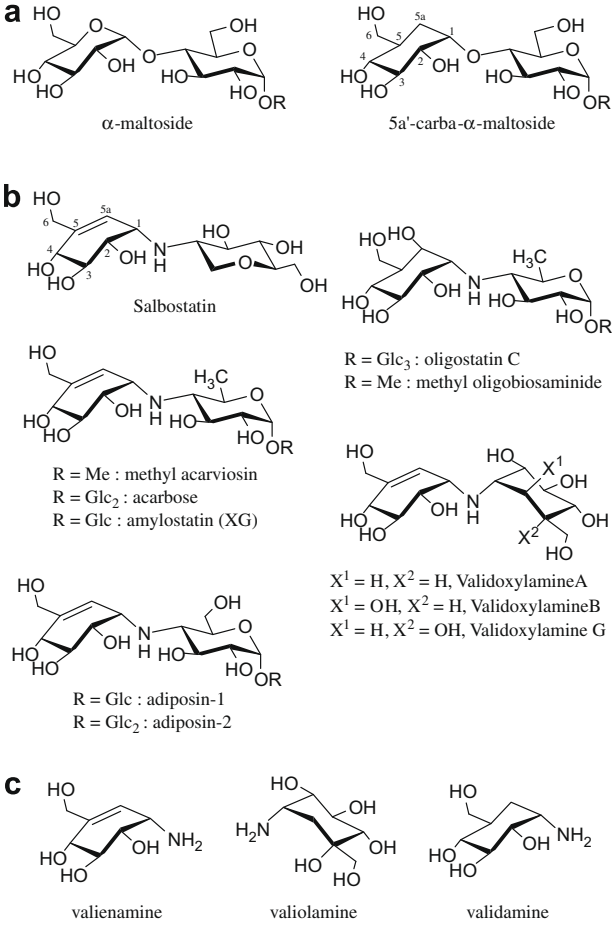


Figure 1. (a) A disaccharide and its O-linked carbasugar analogue; (b) some naturally occurring carbasugar-containing pseudosaccharide structures; and (c) carbocyclic amine substructures. This paper uses standard carbohydrate numbering for carbasugars reflecting their homomorphic relationships to glycosides.

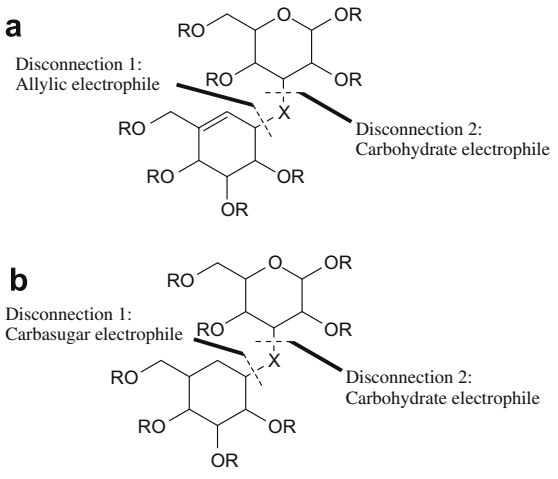


Figure 2. Retrosynthetic disconnection of carbasugar pseudodisaccharides.

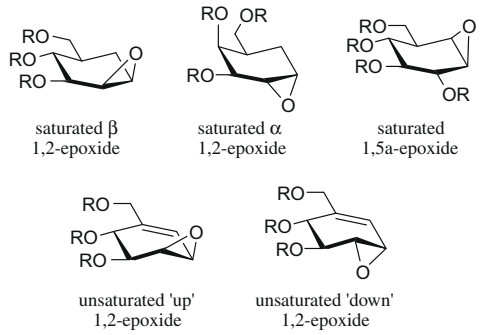


Figure 3. Main classes of carbasugar epoxides.

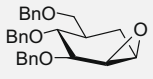
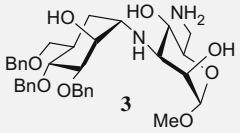
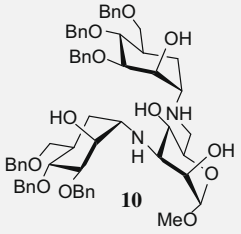
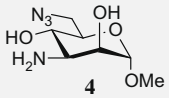
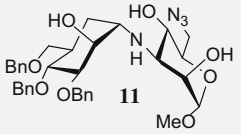
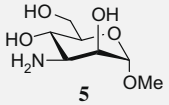
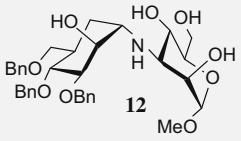
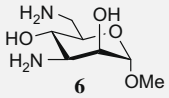
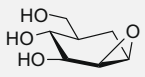
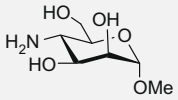
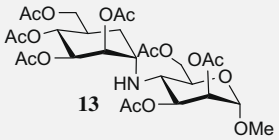
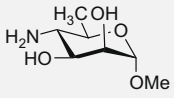
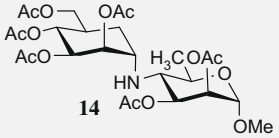
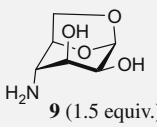
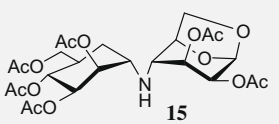
the carbasugar building blocks has been reviewed elsewhere,[5,6] so is not included here. The focus of this minireview is on the chemistry leading to such pseudodisaccharide structures; usually by coupling of a carbasugar to a carbohydrate, and where necessary followed by further modification.

The chemistry used to link a carbasugar to a carbohydrate by ether, thioether or secondary amine bridges is quite different from that used to synthesise a glycosidic bond. S_N reactions have been used for the synthesis of O- and S-linked pseudodisaccharides, while both S_N reactions and reductive amination have been used for the synthesis of N-linked pseudodisaccharides. The bridging bond may be disconnected retrosynthetically to give a carbasugar C-1 electrophile and a carbohydrate nucleophile or to give a carbasugar C-1 nucleophile and a carbohydrate electrophile (Fig. 2).

The two disconnections are similar, but even discounting the vagaries of real systems, they are non-equivalent. The C-1 position is allylic in C-5=C-5a unsaturated systems. The enhanced reactivity of the allylic electrophiles in S_N reactions[7] may make carbasugar electrophiles (disconnection 1 in Fig. 2a) a better choice than non-carbasugar electrophiles (disconnection 2). However, such an allylic carbasugar electrophile could also be prone to a favourable elimination reaction leading to a conjugated diene.

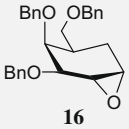
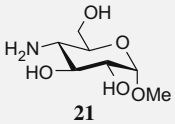
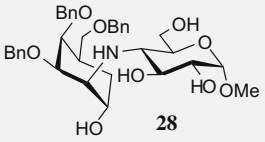
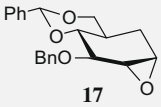
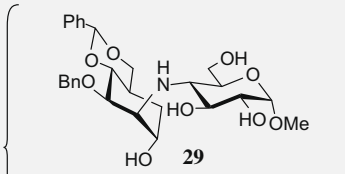
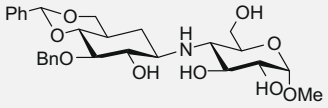
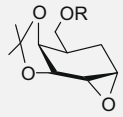
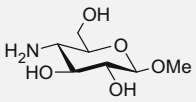
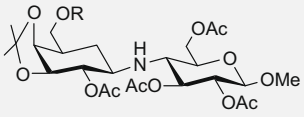
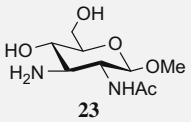
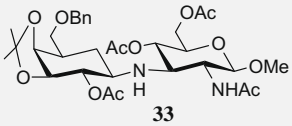
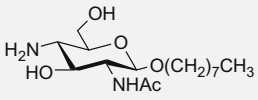
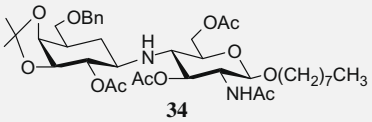
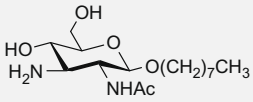
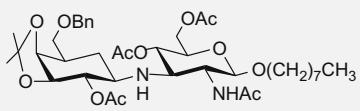
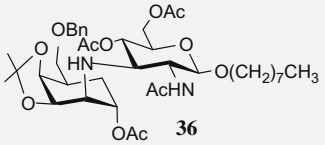
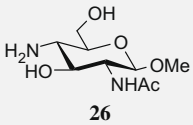
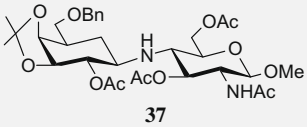
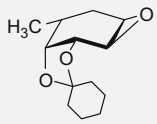
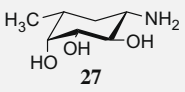
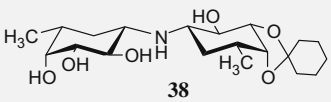
S_N reactions on carbohydrates (at carbons other than the anomeric carbon) are difficult: the many electron-withdrawing groups on the ring destabilise potential carbocations making S_N1 reactions very unusual away from the anomeric centre. S_N2 reactions are disfavoured by the presence of electron-withdrawing groups in the β-position to a leaving group (cf. disconnections 2 in Fig. 2a and b).[8] C-1 of a carbasugar is flanked by an alien methylene group (C-5a) that does not bear an electron-withdrawing oxygen, which means that it may be more electrophilic in S_N2 reactions than a carbon in a carbohydrate flanked by two carbons each bearing an electron-withdrawing oxygen functionality. Stereoelectronic factors are also important, with, for example, the Fürst–Plattner favoured *trans*-

Table 1
Synthesis of 1,2-*trans* α-*manno* imino-linked pseudodisaccharides and pseudotrisaccharides by opening of saturated β-*manno* 1,2-anhydro carbasugars

Entry	Epoxide	Amine	Conditions/*t*	Product	Yield	Ref.
1	 **1** (1.1 equiv.)	 **3**	A/5 days	 **10**	70%	10
2	**1** (1.5 equiv)	 **4**	A/6 days	 **11**	61%	10
3	**1** (1.5 equiv)	 **5**	A/6 days	 **12**	95%	10
4	**1** (2.2 equiv)	 **6**	A/5 days	**10**	72%	10
5	 **2**	 **7** (1.3 equiv.)	i) B/24 h ii) Acetylate	 **13**	59%	11
6	**2**	 **8** (1.5 equiv.)	i) B/24 h ii) Acetylate	 **14**	56%	11
7	**2**	 **9** (1.5 equiv.)	i) B/3 days ii) Acetylate	 **15**	68%	11

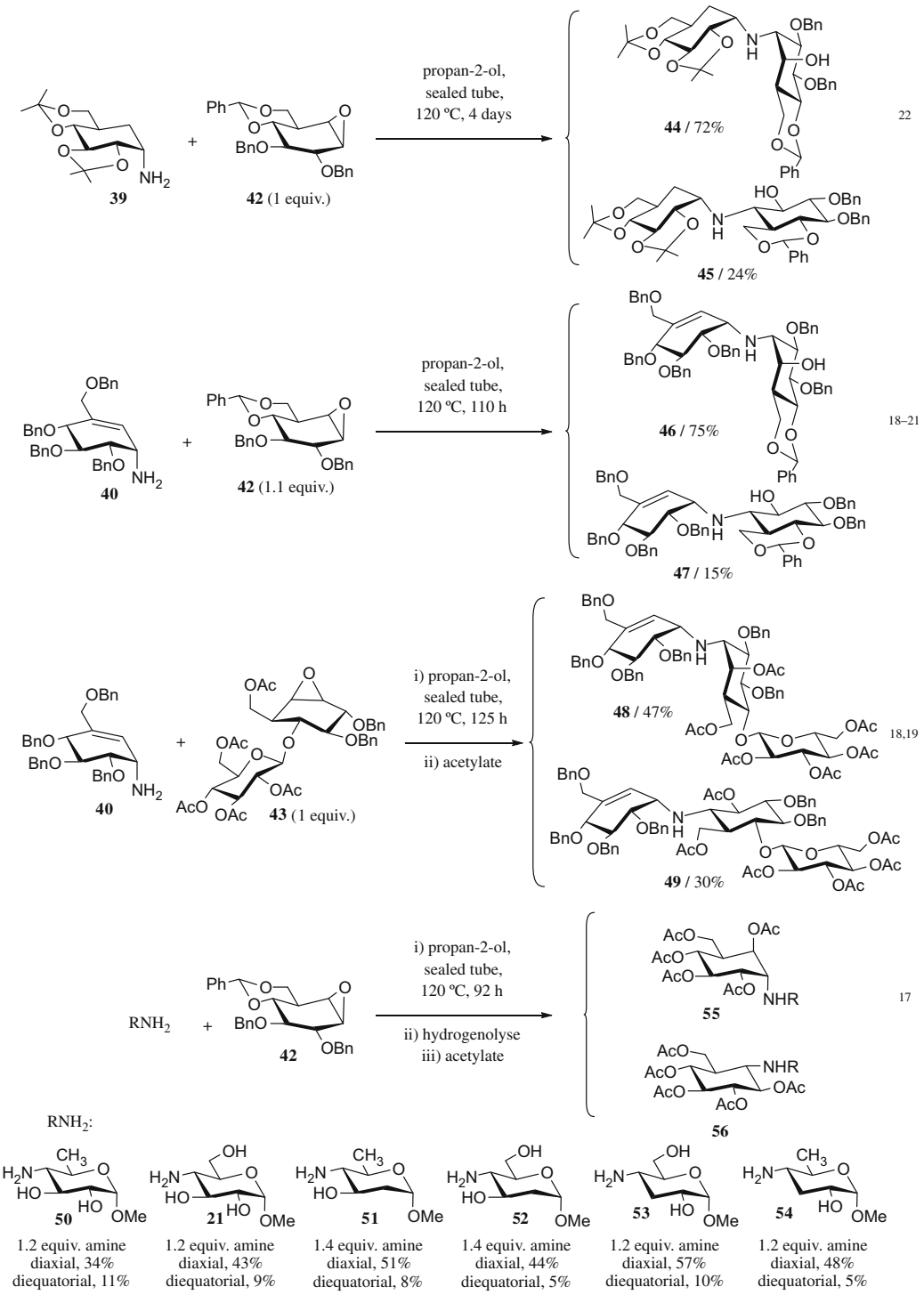
Reaction conditions: (A) propan-2-ol, sealed tube, 120 °C; (B) propan-2-ol/DMF, sealed tube, 100–120 °C.

Table 2
Synthesis of 1,2-*trans* β-*gluco* and β-*galacto* N-linked pseudodisaccharides by opening of saturated α-*gluco* or -*galacto* 1,2-anhydro carbasugars

Entry	Epoxide	Amine	*t*	Product	Yield	Ref.
1	 **16**	 **21**		 **28**	40%	12
2	 **17**	**21**		 **29**  **30**	ca 30% ca 30%	12
3	 **18**, R = Bn **19**, R = TBDMS	 **22** (1.3 equiv.)	i) 2 Weeks ii) Acetylate	 **31**, R = Bn **32**, R = TBDMS	**31**/66% **32**/51%	12
4	**18** (1.5 equiv)	 **23**	i) 3 Weeks ii) Acetylate	 **33**	24%	15
5	**18** (10 equiv)	 **24**	i) 3 Weeks ii) Acetylate	 **34**	38%	14
6	**18** (2 equiv)	 **25**	i) 3 Weeks ii) Acetylate	 **35**  **36**	38% 24%	14
7	**18** (1.1 equiv)	 **26**	i) 2 Weeks ii) Acetylate	 **37**	25%	13
8	 **20** (1.5 equiv.)	 **27**		 **38**	40%	16

Reaction conditions: propan-2-ol, sealed tube, 120 °C.

diaxial products tending to dominate in epoxide-opening reactions.[9] Alternative disconnections where the bridging C–X bonds are formed *before* formation of the carbasugar ring have also been put into practice.



Scheme 1. Synthesis of pseudodisaccharides and pseudotrisaccharides from 1,5a-epoxides.

2. N-Linked[†]

2.1. Epoxide and aziridine opening

The coupling of amines and epoxides is a synthetic strategy that has been used very widely by the Ogawa group and others for the synthesis of N-linked pseudodisaccharide or higher pseudooligosaccharide structures. Carbasugar epoxides that have been opened by amines to form a new C–N-bond at the carbasugar C-1 may be divided into four types: saturated 1,2-epoxides with α and β configurations, saturated 1,5a-epoxides, and finally C-5=C-5a unsaturated 1,2-epoxide derivatives (Fig. 3).

The coupling reactions of saturated epoxides take place under rather forcing reaction conditions: elevated temperatures, typically 120 °C in alcoholic solvents, in a sealed tube for several days. β-*manno*-Configured 5a-carba-1,2-epoxides (**1** and **2**) were opened

[†] It is noteworthy that nitrogen atoms bridging two secondary carbons in N-linked pseudodisaccharide structures tend to be resistant towards acylation.

stereospecifically and with excellent regioselectivity by carbohydrate amines (**3**–**9**) to give good yields of α-*manno*-configured imino-linked pseudodisaccharides and pseudotrisaccharides (**10**–**15**; Table 1).[10,11] Tribenzylated (**1**) and unprotected (**2**) epoxides have both been used. The reaction was efficient enough for a branched pseudotrisaccharide (**10**) to be formed (Table 1, entry 1).[10] Indeed, a monomeric substrate with two amino groups (**6**) reacted with two equivalents of epoxide (**1**) to give the same pseudotrisaccharide in good yield (Table 1, entry 4).[10]

The formation of regioisomeric products from β-*manno* 1,2-carbasugar epoxides has not been reported. This may be due to the following factors: Attack at C-1 (to give α-*manno*-configured carbasugar pseudodisaccharides) results in *trans*-diaxial opening as favoured by the Fürst–Plattner guidelines, so is stereoelectronically favourable; C-1 is flanked by an electron-rich methylene group whereas C-2 is flanked by a carbon bearing an electron-withdrawing group, so S_N2 is electronically favoured at C-1 over C-2; the groups flanking C-1 are smaller than those flanking C-2 so attack at C-1 may be favoured also from a steric point of view.

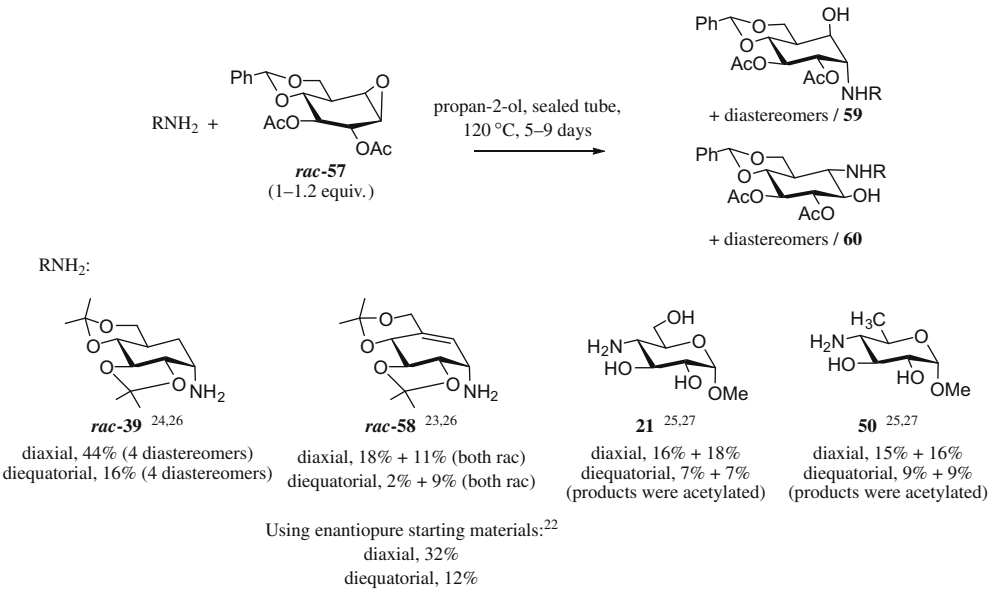
The reactions of α-*gluco* or α-*galacto* carbasugar epoxides (**16**–**20**) with amines (**21**–**27**) to give epoxide-opened coupling products (**28**–**38**; Table 2)[12–16] are reported to be generally slower than those for the carbamannosides, and the yields tend to be lower. Regioselectivity is an issue in such reactions and regioisomeric mixtures of products were formed in some cases (Table 2, entries 2 and 6).[12,14] A benzylated α-*galacto* epoxide (**16**) ring-opened with the attack only at C-2 (*trans*-diaxial product (**28**); Table 2, entry 1), a benzylidene-protected *gluco* 1,2-epoxide (**17**) gave a mixture of the products of C-2 attack (**29**) and C-1 attack (**30**) (Table 2, entry 2), while 3,4-isopropylidene-protected *galacto* derivatives (**18** and **19**) gave mostly or exclusively C-1 attack (Table 2, entries 3–7). A 3,4-cyclohexylidene 6-deoxygalacto epoxide (**20**) also gave exclusive C-1 attack (Table 2, entry 8), leading to the formation of a 1,1-linked di-L-fucoside (**38**).[16]

The α-*gluco/galacto* type epoxides shown in Table 2 must open to give *trans*-diequatorial products if a carbadisaccharide is to result from attack at C-1. Fürst–Plattner favoured *trans*-diaxial opening would arise from a C-2 attack, which would not lead to a carbadisaccharide product. The generally slower reactions and lower yields in this series than in the α-*manno*-forming reactions can be put down to the conflict between the sterically and intrinsically electronically favoured attack at C-1 (both due to C-1 being flanked by the small and relatively electron-rich methylene group) and the energetically demanding stereoelectronic requirement to reach a far-from-ground-state conformation at the transition state to enable *trans*-diaxial opening before reverting to a more favoured diequatorial ground state again for the product.

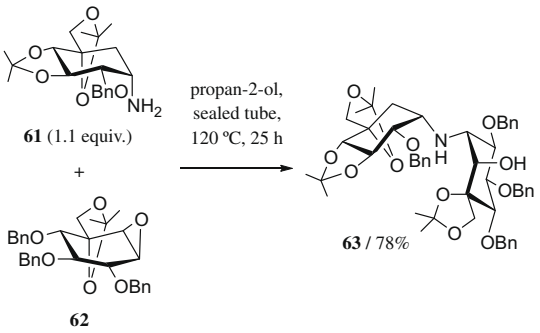
A carbasugar 1,5a-epoxide (**42**) has been opened regioselectively by various amines (**21**, **39**, **40**, **50**–**54**) with attack at C-1 to give the *trans*-diaxial opening products (**44**, **46**, **55**) as major products along with the C-5a-substituted *trans*-diequatorial opening products (**45**, **47**, **56**) as minor products (Scheme 1).[17–22] A slightly lower regioselectivity was seen when the pseudodisaccharide epoxide **43**, which is not conformationally locked by the presence of a 4,6-benzylidene acetal, was opened with amine **40** to give pseudotrisaccharides **48** and **49**.[18,19] A racemic 1,5a-epoxide (*rac*-**57**) was opened by enantiopure amines (**21** and **50**) to give coupling products as regioisomeric mixtures with the diaxially opened compounds (**59**) as major components and diequatorial compounds (**60**) as minor products (Scheme 2).[23–27] When racemic mixtures of both epoxide and amine components (*rac*-**39** and *rac*-**58**) were used, all eight possible products were formed (two diastereomeric pairs of enantiomeric products arising from each of diaxial and diequatorial opening), the difficult separation of which may account for the lower product yields.

The lower regioselectivity for diaxial opening for these 1,5a-epoxides than was seen for the 1,2-carbasugar epoxides may possibly be explained as follows: In the 1,5a-epoxides, the flanking atom C-2 bears an electron-withdrawing oxygen atom, whereas C-5 does not. This may favour S_N2 attack at C-5a over C-1 from an electronic point of view. Attack at C-1 leading to the *trans*-diaxial product is favoured stereoelectronically, so these opposing arguments may result in the observed mixtures of products. When the C-5-oxygenated 1,5a-epoxide **62** was opened by amine **61**, only one product (**63**) was reported (Scheme 3).[22] The increased steric bulk at C-5 and the addition of an electron-withdrawing group at C-5 would both tend to favour attack at C-1 over C-5a.

The axial OH-5a has been removed to give a methylene group by two routes as shown in Scheme 4 (forming **65**–**67**). First, the C-5a hydroxyl group in **46** was converted into a good leaving group, which then suffered intramolecular attack by the N-1 to give the aziridine. This aziridine was ring-opened by a sulfur



Scheme 2. Synthesis of pseudodisaccharides from racemic 1,5a-epoxides. (Mixtures of stereoisomers were formed. Only one diastereomer of each regioisomer is shown).



Scheme 3. Opening a 1,5a-epoxide with oxygen functionality at C-5.[22]

nucleophile to give the *trans*-diaxial-opened thioether. Reductive cleavage of the thio group with Raney nickel gave the C-5a methylene group (**65**).[20,21] Alternatively, conversion of OH-5a (in **44** and **63**) into dithiocarbonates, followed by radical reduction with tributyltin hydride, gave the C-5a-methylene carbasugars (**66** and **67**).[22] The axial OH-5a group has been used as a handle for the introduction of C-5=C-5a unsaturation (Scheme 4). Chlorination of the alcohol (**64**) with sulfuryl chloride or thionyl chloride gave the *axial* chloride, along with aziridine by-products. On treatment with DBU, HCl was eliminated across C-5=C-5a to give the valienamine derivative (**68**), along with aziridine by-products.[22,24,26]

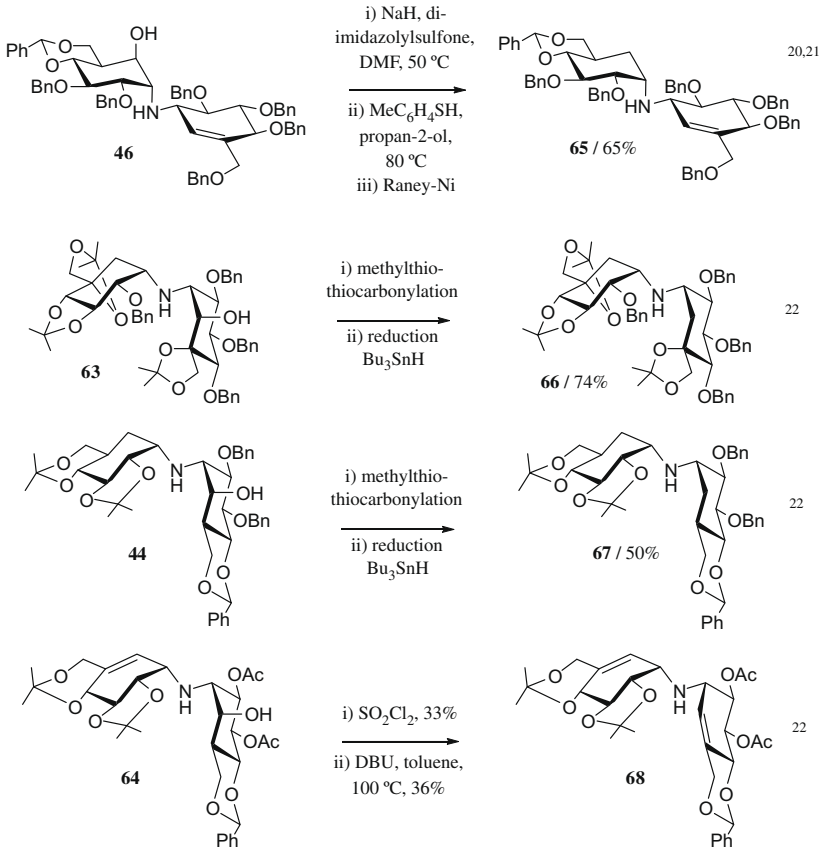
An unsaturated epoxide with the β-*lyxo* configuration (**69**) has been opened regioselectively at the allylic position (C-1) to give the 1,2-*trans* products with α-*lyxo* configuration (**72**–**78**; Table 3).[10,11,28,29] Using a racemic carbasugar (*rac*-**69**) as starting material resulted in diastereomeric mixtures of products, i.e., **72a**,**b** from the 4-amino-4-deoxyglucose **21** and **73a**,**b** from the 4-amino-4,6-dideoxyglucose **50** (Table 3, entry 1),[28] while the enantiomerically pure carbasugar (**69**) coupled with various carbohydrate amines to give the pseudodisaccharides in good yield (Table 3, entries 2–5).[11,29] A branched pseudotrisaccharide (**78**) was formed in a single step from monomeric components, a diamine (**6**) and two equivalents of epoxide (**69**), although here a mixture of products was seen, possibly due to acyl migration (Table 3, entry 6).[10] Much lower reaction temperatures (50–70 °C) were used for opening C-5=C-5a-unsaturated epoxides than for the corresponding saturated derivatives (where 120 °C was typically used), presumably due the intrinsically higher reactivity of an allylic epoxide.

The racemic α-*xylo*-configured unsaturated carbasugar donor (**79**) reacted with amines with the attack only at the allylic centre (i.e., C-1) to give, after acetylation, the 1,2-*trans* iminocarbadisaccharide coupling products (**82**–**85**) as diastereomeric mixtures (Scheme 5).[28,30] Again, lower reaction temperatures (45–55 °C) were used for the coupling reactions of this allylic epoxide.

Ogawa and Tsunoda approached carbasugar analogues of aminosugar disaccharides by *aziridine* opening.[31] They used 2,4-dinitrophenyl carbasugar aziridines with α-*gluco* (**86**) or α-*xylo* (**87**) configuration. A fully protected aziridine derivative (the 3,4,6-triacetate of **86**) failed to react to any great extent, while the reaction between the unprotected carbasugar aziridine (**86**) and amine **21** showed no regioselectivity, and the products of attack at both C-1 (**89**) and C-2 (**88**) were seen, along with the product of intramolecular attack by OH-6 (**90**) (Scheme 6).

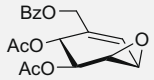
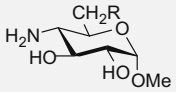
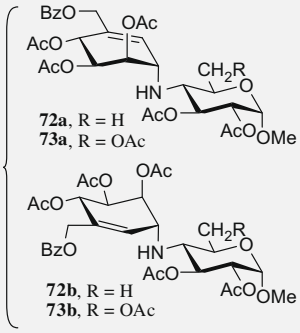
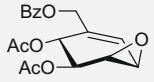
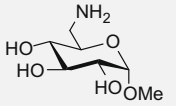
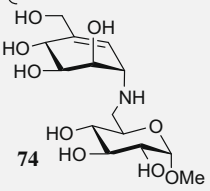
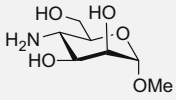
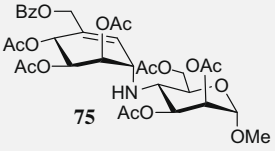
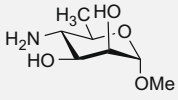
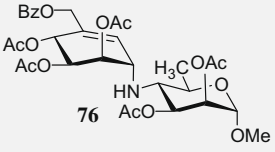
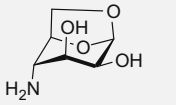
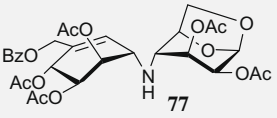
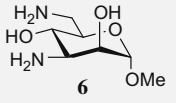
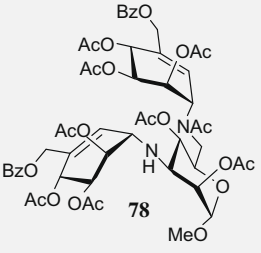
A (racemic) 5,6-unsaturated derivative (**87**) reacted with amine **21** with better regioselectivity for C-1 attack. The resulting pseudodisaccharide **91a** was refunctionalised at C-5a–C-6 to give either the valiolamine-like **93** or valienamine-like **94** pseudodisaccharides (Fig. 4).

The complementary strategy for the synthesis of N-linked pseudodisaccharides by epoxide opening is to condense a



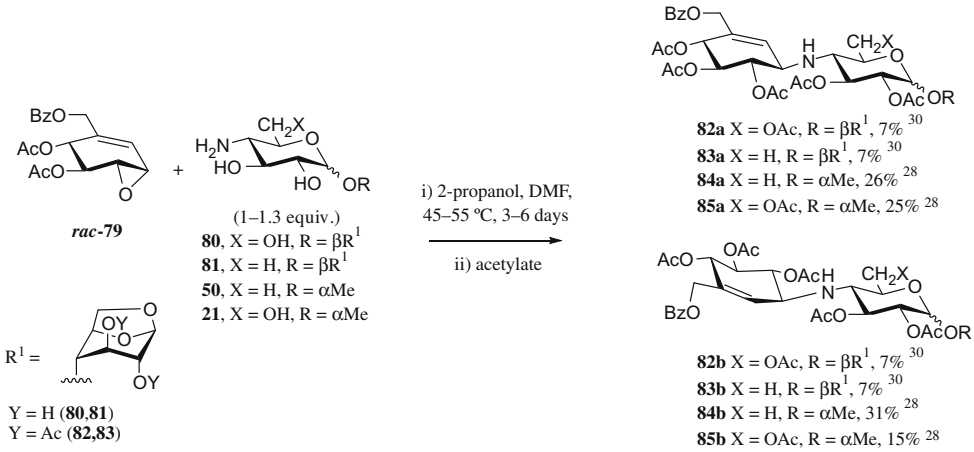
Scheme 4. Modification of pseudodisaccharides: deoxygenation of C-5a to achieve valienamines and saturated carbasugars.

Table 3
Formation of pseudodisaccharide and pseudotrisaccharide from 'up' type unsaturated donors

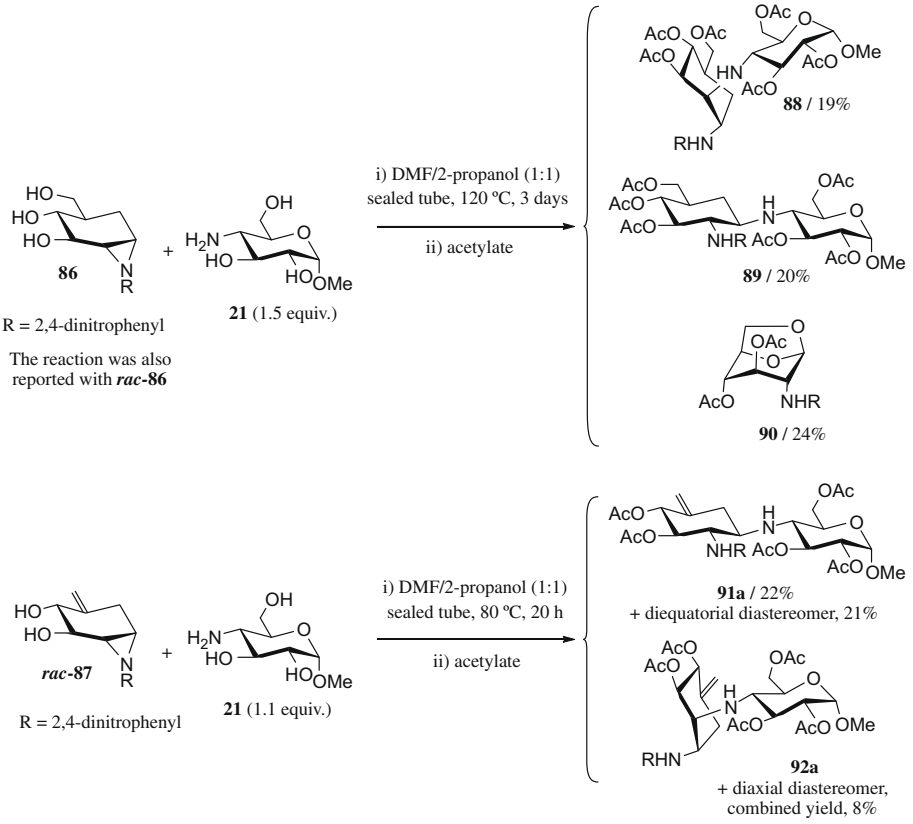
Entry	Epoxide	Amine	Conditions	Product	Yield	Ref.
1	 ***rac*-69**	 (1–1.3 equiv.) **21**, R = OH **50**, R = H	i) 2-Propanol, 50 °C, 5–7 days ii) Acetylate	 **72a**, R = H **73a**, R = OAc **72b**, R = H **73b**, R = OAc	**72a**, 46% **73a**, 10% **72b**, 31% **73b**, 7%	28
2	 **69**	 **70** (2.8 equiv.)	i) 2-Propanol, 60 °C, 48 h ii) Deprotect	 **74**	78%	29
3	**69**	 **7** (1.3 equiv.)	i) 2-Propanol, 60 °C, 48 h ii) Acetylate	 **75**	74%	11
4	**69**	 **8** (1.5 equiv.)	i) 2-Propanol, 50 °C, 3 days ii) Acetylate	 **76**	68%	11
5	**69**	 **9** (1.5 equiv.)	i) 2-Propanol, 70 °C, 3 days ii) Acetylate	 **77**	64%	11
6	**69** (2.3 equiv)	 **6**	i) 2-Propanol, 50 °C, 1 week ii) Acetylate	 **78**	34%	10

carbasugar C-1 amine with an appropriate epoxide (disconnection 2 in Fig. 2). The majority of reactions published in this area have been aiming for a (1→4)-linkage to a carbohydrate with *gluco* stereochemistry, no doubt because this is the configuration in many naturally occurring pseudooligosaccharides (cf. Fig. 1). The epoxides that have been studied that lead to such an outcome may be split into two types; both have *galacto* stereochemistry and both rely on regioselective attack at C-4 to give the 4-amino-4-deoxyglucose derivatives. In the first type, the carbohydrate ring-conformation is not locked by a 1,6-anhydro bridge; the epoxide-opened product will adopt a $^4C_1$ conformation and hence *trans*-diequatorial ring-opening with attack at C-4 will give the *gluco* configuration. In the second type, 1,6-anhydrosugars are locked in a 'ring-flipped' conformation and attack at C-4 gives the *gluco* epoxide-opened product with a *trans*-diaxial configuration and $^1C_4$ conformation.

Conformationally unlocked galacto 3,4-epoxides: Opening the 3,4-epoxides (**97**–**99**) with enantiopure carbasugar C-1 amines (**58**, **95** **96**) gave the 4-substituted glucose (**104**–**107**) and 3-substituted gulose (**112**–**115**) derivatives with varying regioselectivity (Table 4, entries 1–4).[32–35] Ogawa et al. noted that a slightly better regioselectivity for the desired diequatorial (i.e., *gluco*) product was seen when a C-6 hydroxyl group was present in the epoxide than



Scheme 5. Formation of pseudodisaccharides and pseudotrisaccharides from 'down' type unsaturated donors. The products may be C-6 acetates or C-6 benzoates depending on the work-up before separation of diastereomers.



Scheme 6. Aziridine opening approach to carbasugar pseudodisaccharides.[31]

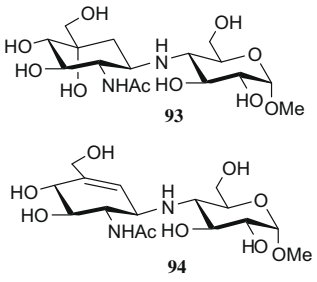
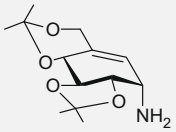
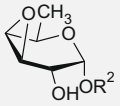
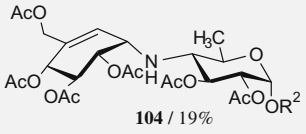
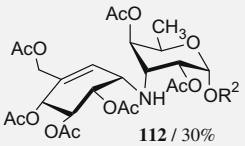
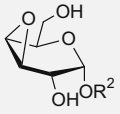
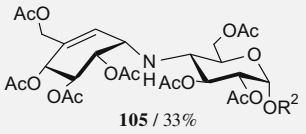
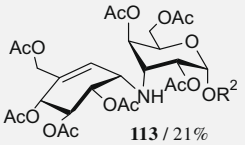
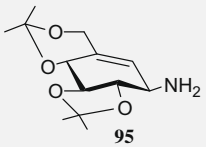
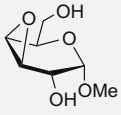
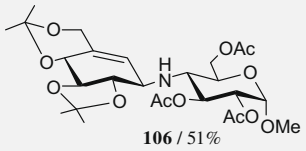
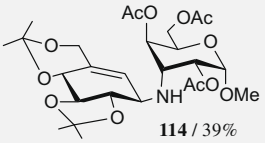
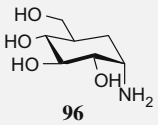
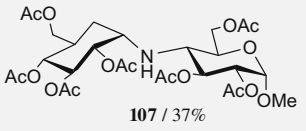
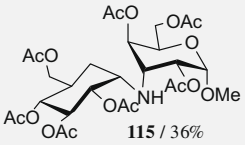
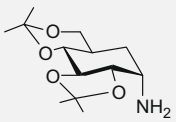
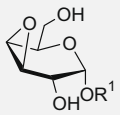
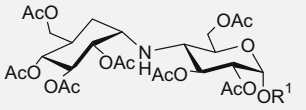
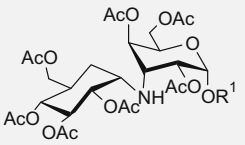
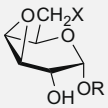
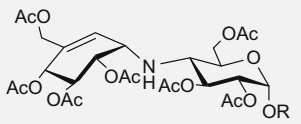
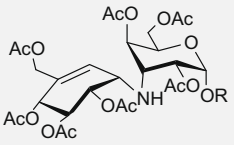


Figure 4. Valiolamine **93** and valienamine **94** derivatives formed from **91a**.[31]

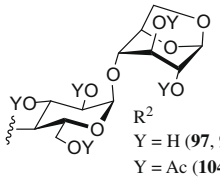
when such a group was absent.[33,34,38] However, the regioselectivity of these reactions was usually quite poor and significant amounts of both regioisomers were formed. The total yield of epoxide-opened products can be high, however.

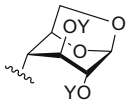
Similar coupling reactions between racemic carbasugar amine nucleophiles (*rac*-**39** and *rac*-**58**) and *galacto* 3,4-epoxides (**100**–**103**) gave the coupling products (**108**–**111**, **116**–**119**) (Table 4, entries 5 and 6).[36–38] Each reaction gave a mixture of four products; the two regioisomers were both formed as diastereomeric mixtures. Again the regioselectivity was poor, but better regioselectivity was seen with a free OH-6 in the epoxide than when this was absent. A number of related deoxygenated derivatives were investigated (not shown).[39]

Table 4
Formation of N-linked pseudodisaccharides and pseudooligosaccharides by reaction of carbasugar amines with *galacto* 3,4-epoxides

Entry	Amine	Epoxide	Conditions	Product/yield	Ref.
1	 **58** (1.2 equiv.)	 **97**	i) Propan-2-ol, DMF (1:1) 120 °C, 70 h ii) H^+ iii) Acetylate	 **104** / 19%  **112** / 30%	32,33
2	**58** (1.2 equiv)	 **98**	i) Propan-2-ol, DMF (1:1) 120 °C, 67 h ii) H^+ iii) Acetylate	 **105** / 33%  **113** / 21%	32,33
3	 **95**	 **99** (1.2 equiv.)	i) Propan-2-ol, DMF (1:1) 120 °C, 67 h ii) Acetylate	 **106** / 51%  **114** / 39%	34
4	 **96**	**99** (1 equiv)	i) Propan-2-ol, 120 °C, 6 days, sealed tube ii) Acetylate	 **107** / 37%  **115** / 36%	35
5	 ***rac*-39**	 **100** (1 equiv.)	i) Propan-2-ol, DMF 120 °C, 67 h ii) H^+ iii) Acetylate	 **108a** / 22% + diastereomer/25%  **116a** / 26% + diastereomer/26%	36
6	*rac*-**58**	 **99** R = Me, X = OH **102** R = R^1, X = OH **103** R = R^1, X = H (1–1.2 equiv.)	i) Propan-2-ol, DMF 120 °C, 40–60 h ii) H^+ iii) Acetylate	 **109a** / R = Me, X = OAc/17% [36] + diastereomer/20% **110a** / R = R^1, X = OAc/13% [36,37] + diastereomer/14% **111a** / R = R^1, X = H/6% [38] + diastereomer/6%	 **117a** / R = Me, X = OAc/20% [36] + diastereomer/18% **118a** / R = R^1, X = OAc/21% [36,37] + diastereomer/16% **119a** / R = R^1, X = H/24% [38] + diastereomer/32%	

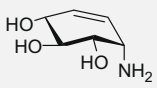
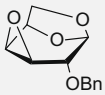
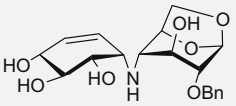
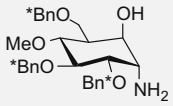
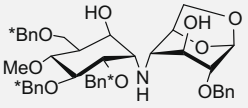
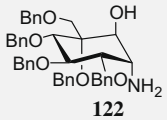
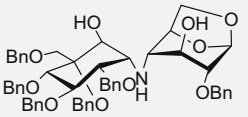
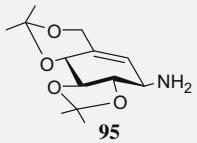
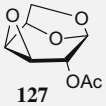
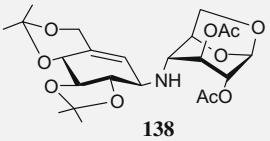
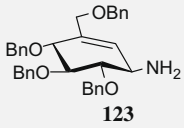
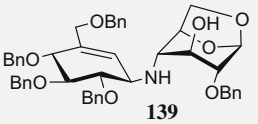
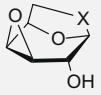
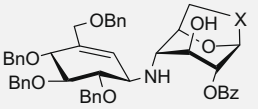
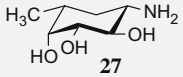
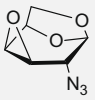
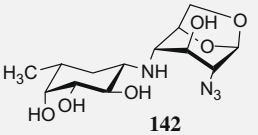
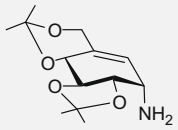
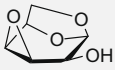
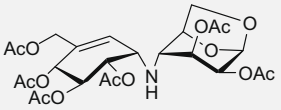
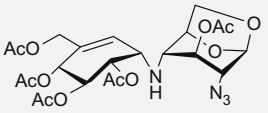
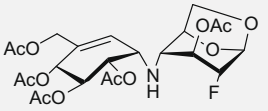
Note: when a racemic starting material was used, each regioisomer was formed as a mixture of diastereomers; only one diastereomer is shown.


R^2
Y = H (**97**, **98**)
Y = Ac (**104**, **105**, **112**, **113**)


R^1
Y = H (**100**, **102**, **103**)
Y = Ac (**108**, **110**, **111**, **116**, **118**, **119**)

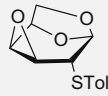
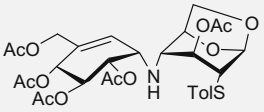
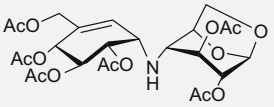
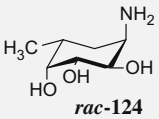
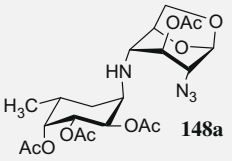
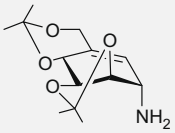
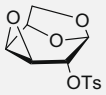
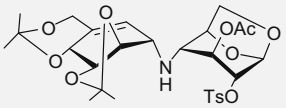
Conformationally locked 1,6-anhydro galacto 3,4-epoxides: 1,6-Anhydrosugar epoxides (**126**–**133**) were opened by carbasugar C-1 amines (**27**, **28**, **95**, **120**–**123**) with excellent regioselectivity to give the *trans*-diaxial products, i.e., the 4-substituted *gluco*-configured compounds (**135**–**146**), in good yields (55–93%; Table 5, entries 1–11).[16,40–46] The reactions seem to be sensitive to steric considerations: A more hindered amine (**121**) reacted more slowly than a less hindered amine (**120**) (cf. Table 5, entries 1

Table 5
Formation of N-linked pseudodisaccharides by reaction of carbasugar amines with 1,6-anhydrosugar *galacto* 3,4-epoxides

Entry	Amine	Epoxide	Conditions	Product	Yield	Ref.
1	 **120**	 **126** (2.5 equiv.)	*n*-BuOH, 110 °C, 20 h	 **135**	76%	40
2	 **121**	**126** (3.1 equiv)	*n*-BuOH, 110 °C, 30 h	 **136**	72%	40
3	 **122**	**126** (4.6 equiv)	1-Propanol, 90 °C, 30 h	 **137**	55%	41
4	 **95**	 **127**	i) Coupling ii) Acetylate	 **138**	70%	42
5	 **123**	**126** (2.3 equiv)	i) BuOH, 110 °C, 72 h	 **139**	67%	43,44
6	**123**	 **128**, X = S **129**, X = Se (2 equiv.)	i) BuOH, 100 °C, 2.5 days ii) BzCl, py	 **140**, X = S **141**, X = Se	**140**, 30% **141**, 41%	45
7	 **27**	 **130** (1.6 equiv.)	i) Propan-2-ol, 120 °C, 2 weeks	 **142**	93%	16
8	 **58**	 **131** (1.2 equiv.)	i) Propan-2-ol, 120 °C, 10 days ii) H^+ iii) Acetylate	 **143**	51%	46
9	**58**	**130** (1.2 equiv)	i) Propan-2-ol, 120 °C, 4 days ii) H^+ iii) Acetylate	 **144**	61%	46
10	**58**	 **132** (3 equiv.)	i) Propan-2-ol, 120 °C, 7 days ii) H^+ iii) Acetylate	 **145**	14%	46

(*continued on next page*)

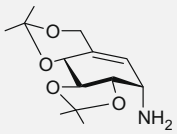
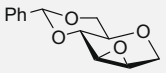
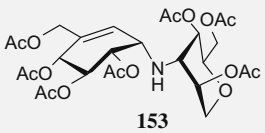
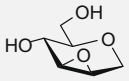
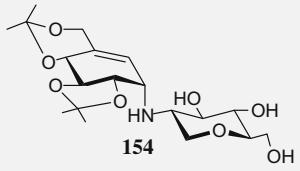
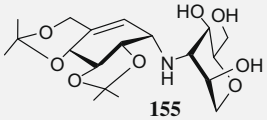
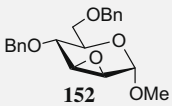
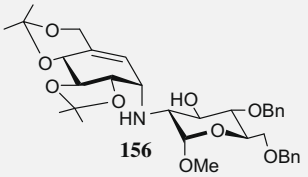
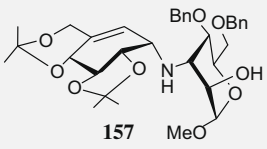
Table 5 (*continued*)

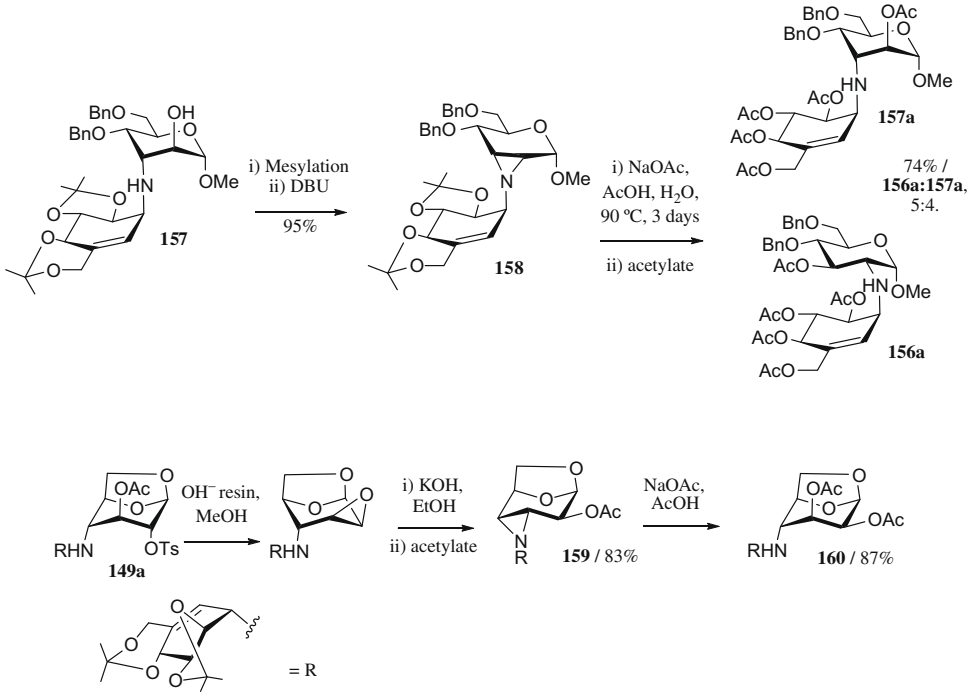
Entry	Amine	Epoxide	Conditions	Product	Yield	Ref.
11	**58**	 **133** (1.6 equiv.)	i) Propan-2-ol, 120 °C, 3 days ii) H^+ iii) Acetylate	 **146**	71%	46
12	*rac*-**58**	**127**	i) Propan-2-ol, 120 °C ii) H^+ iii) Acetylate	 **147a**	48% +diastereomer, 48%	42.[a]
13	 ***rac*-124**	**130** (1.6 equiv)	i) Propan-2-ol, 120 °C, 1 week ii) H^+ iii) Acetylate	 **148a**	44% +diastereomer, 48%	47.[a]
14	 ***rac*-125**	 **134**	i) Propan-2-ol, DMF (1:1) 70 °C, 7 days ii) Acetylate	 **149a**	20% +diastereomer, 19%	48.[a]

$Bn^* = CD_2Ph$.

[a] Racemic starting material was used, so two diastereomeric products were formed from *trans*-diaxial opening after attack at the epoxide C-4 (only one is shown).

Table 6
Formation of N-linked pseudodisaccharides by reaction of carbasugar amines with *manno* 2,3-epoxides

Entry	Amine	Epoxide	Conditions	Product	Yield	Ref.
1	 **58**	 **150** (1.3 equiv.)	i) Propan-2-ol, 120 °C, 8 days ii) H^+ iii) Acetylate	 **153**	89%	50
2	**58**	 **151** (1.3 equiv.)	Propan-2-ol, 120 °C, 4 days	 **154**  **155**	58% 25%	49,50
3	**58** (1.2 equiv)	 **152**	Propan-2-ol, 120 °C, 5 days	 **156**  **157**	6% 66%	51



Scheme 7. Modifications after pseudodisaccharide formation.[48,51]

and 2),[40] and OH-5a-protected analogues of the nucleophile **122** failed to give any reaction with epoxide **126** (cf. Table 5, entry 3).[41]

Some similar coupling reactions between racemic starting materials (*rac*-**58**, *rac*-**124** and *rac*-**125**) and epoxides (**127**, **130**, **134**) have also been reported. The reactions proceeded with excellent diastereoselectivity, but pairs of diastereomeric products were formed (Table 5, entries 12–14).[42,47,48]

manno 2,3-Epoxides: The discovery of the antibiotic Salbostatin, consisting of valienamine (1→2)-linked to glucose, has led to the synthesis of this compound and some analogues.[49,50] A 4,6-benzylidene-protected *manno*-configured 2,3-anhydrosugar (**150**) was ring-opened with a protected valienamine (**58**), resulting in exclusive formation of the undesired diaxial 3-amino-3-deoxyaltrose (**153**) (Table 6, entry 1). The regioselectivity could be switched to some extent by removing the benzylidene acetal. The unprotected epoxide (**151**) reacted with the amine nucleophile (**58**) to give a regioisomeric mixture of pseudodisaccharides with selectivity for the diequatorial 2-amino-2-deoxyglucose compound (**154**) over the diaxial 3-amino-3-deoxyaltrose (**155**). The unprotected epoxide was also found to be more reactive, so reducing the reaction time (Table 6, entry 2). The major product (**154**) of this reaction was converted into salbostatin.

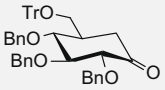
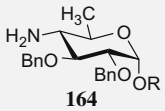
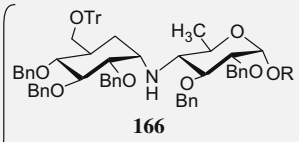
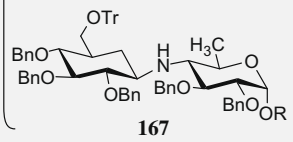
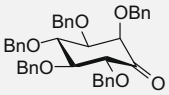
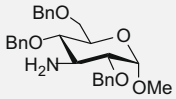
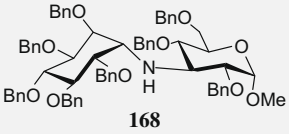
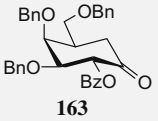
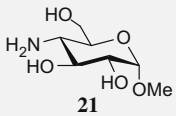
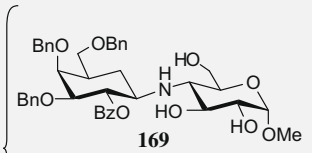
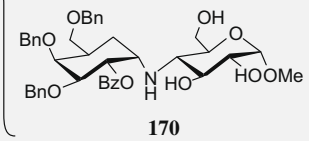
A benzylated 2,3-epoxide (**152**) was ring-opened with the protected valienamine **58** with the aim of synthesising a pseudodisaccharide consisting of valienamine (1→2)-linked to glucose as a potential inhibitor of α-glucosidase I,[51] but the required 2-substituted glucose derivative (**156**) was formed in very poor yield, the major product being the 3-amino-3-deoxyaltrose (**157**) (Table 6, entry 3). Analogues of the epoxide (**152**) with different protecting-group patterns, with 4,6-benzylidene protection or with OH-4 and OH-6 free, gave exclusive formation of the undesired 3-amino-3-deoxyaltrose by attack at C-3. Hence, a strategy to isomerise the 3-amino-3-deoxyaltrose product (**157**) into a 2-amino-2-deoxyglucose derivative was developed. The free OH-2 in **157** was converted into a sulfonate, and treatment with a base gave the aziridine (Scheme 7).[51] Heating this aziridine (**158**) with sodium acetate in acetic acid gave a mixture of the two regioisomeric products (**156a** and **157a**). The regioselectivity was very low, but the desired 2-amino-2-deoxyglucose (**156a**) was formed in slight excess over the undesired 3-amino-3-deoxyaltrose. A related modification transformed a conformationally locked 3-amino-3-deoxyglucose pseudodisaccharide (**149a**) into a 3-amino-3-deoxymannose (**160**) (Scheme 7).[48] Epoxide formation, rearrangement to the aziridine and opening with sodium acetate in acetic acid, which in this case proceeded with excellent regioselectivity for the diaxial product, resulted in overall inversion at C-2.

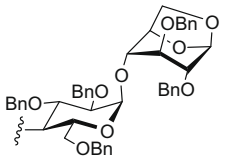
2.2. Reductive amination

Reductive amination is the textbook method for secondary amine formation, but it has not been widely used for the synthesis of imino-linked pseudodisaccharides. An obvious conceptual disadvantage of this method over S_N2-type reactions such as epoxide opening is that the reaction will be stereoselective to a greater or lesser degree: two diastereomeric products can be formed, which is not the case with stereospecific epoxide opening. On the other hand, *regio*selectivity should not be a problem for reductive amination.

Kuzuhara and co-workers reported a reductive amination between a carbasugar C-1 ketone (**161**) and a 4-amino-4,6-dideoxyglucose derivative (**164**) (Table 7, entry 1).[52,53] The stereoselectivity in the reduction step was in favour of the α product (**166**), which was formed in 30% yield, along with the β product (**167**, 4%). Direct reduction products (carbasugar C-1 alcohols) were obtained in 50% combined yield. The attempted reverse coupling between a carbasugar C-1 amine and a trisaccharide C-4 ketone failed, giving the *galacto*-configured product in 1% yield as sole pseudotetrasaccharide, along with unidentified by-products (not shown). Haines and Carvalho used reductive amination to link a 3-amino-3-deoxyglucose (**165**) to an inositol-derived ketone (**162**) in an attempt to synthesise an inhibitor of α-glucosidase II

Table 7
Reductive amination with carbasugar C-1 ketones

Entry	Ketone	Amine	Conditions	Product	Yield	Ref.
1	 **161** (2 equiv.)	 **164**	$NaBH_3CN$, pH 6.2, 4 Å	 **166**  **167**	30% 4%	52,53
2	 **162**	 **165**	i) Benzene, 4 Å, rt, 70 h ii) $NaBH_3CN$, DMF, rt, 70 h, 100 °C, 1 h	 **168**	61%	54,55
3	 **163**	 **21**	$NaBH_3CN$, MeOH, reflux, 12 h	 **169**  **170**	23% 25%	12

R = 

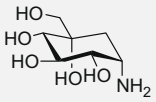
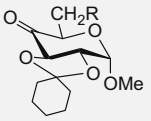
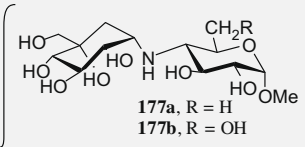
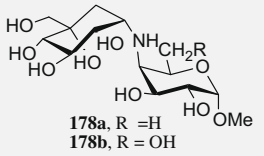
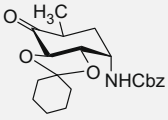
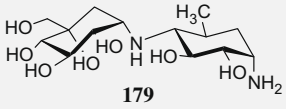
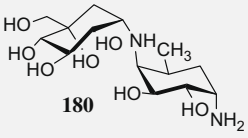
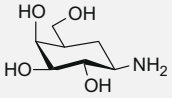
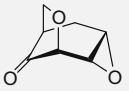
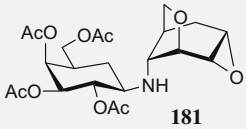
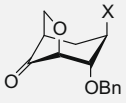
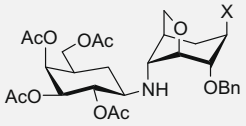
(Table 7, entry 2).[54,55] The optimised conditions required pre-formation of the imine and cyanoborohydride reduction in a second step and gave the desired pseudodisaccharide (**168**) in 61% yield. Attempted reductive amination between the same inositol ketone (**162**) and a 2-amino-2-deoxyglucose failed, however. Imine formation was very sluggish and on heating, an aromatic elimination product was obtained. Ogawa et al. described a reductive amination for the formation of an N-linked lactose analogue (**169**) by the reaction of a 4-amino-4-deoxyglucose (**21**) with a carbasugar C-1 ketone (**163**) (Table 7, entry 3), but the diastereoselectivity of the reduction was low, with the α-linked compound (**170**) formed in approximately the same amount as the desired β product.[12] Stick and co-workers attempted a reductive amination between an α,β-unsaturated carbasugar C-1 ketone and a carbohydrate C-4 amine, but no coupling product was obtained.[56]

Examples of successful couplings between carbasugar C-1 amines and carbohydrate ketones are known. Horii et al. reported the synthesis of some carbasugar (1→4)-linked pseudodisaccharides by this strategy with unprotected carbasugar C-1 amines.[57] A *xylo*-hexoside-4-ulose derivative (**173a**) was reductively condensed with a carbasugar C-1 amine (**171**) to give pseudodisaccharide products (**177a** and **178a**) in a reasonable yield and with good diastereoselectivity for the *gluco* configuration (**177a**) (Table 8, entry 1). The yield of the coupled products (**177b** and **178b**) was much lower when the 6-hydroxylated analogue (**173b**) was used. Using a carbasugar C-1 amine (**171**) and carbasugar C-4 ketone (**174**), the yield of pseudodisaccharides became very low and no selectivity between the *gluco* (**179**) and *galacto* (**180**) products was seen (Table 8, entry 2). Ogawa et al. used an unprotected β-*galacto* C-1 amine (**172**) as coupling partner with conformationally locked carbasugar C-4 ketones (**175** and **176a–c**).[58] These reactions gave the pseudodisaccharides (**181** and **182a–c**) in respectable yields and with good diastereoselectivities (Table 8, entries 3 and 4).

2.3. Alkylation: halide or sulfonate displacement

Direct S_N2 alkylation is not usually a recommended method for the synthesis of secondary amines. However, in the systems described below, overalkylation has not been described and it is unlikely to be a problem, due to the low nucleophilicity of the secondary amine nitrogen for both steric and electronic reasons. This approach has been used in a few cases to access imino-linked pseudodisaccharides. In fact, some of the first syntheses of N-linked carbasugar pseudodisaccharides were achieved by alkylation of amines with carbasugar allyl bromides (Scheme 8).

Table 8
Reductive amination with carbasugar C-1 amines

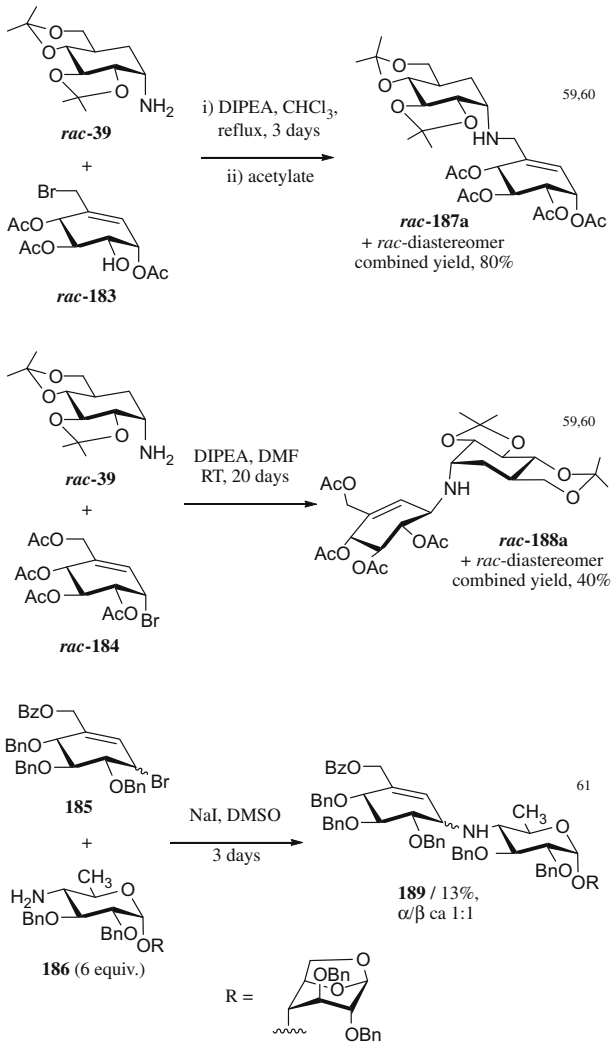
Entry	Amine	Ketone	Conditions	Product	Yield	Ref.
1	 **171**	 **173a**, R = H **173b**, R = OAc (1.7–2 equiv.)	i) $NaBH_3CN$, HCl, DMF, 65 °C, 18 h ii) Deprotect	 **177a**, R = H **177b**, R = OH  **178a**, R = H **178b**, R = OH	**177a**, 43% **177b**, 12% **178a**, 7% **178b**, 4%	57
2	**171**	 **174** (1.3 equiv.)	i) $NaBH_3CN$, HCl, DMF, 65 °C, 18 h ii) Deprotect	 **179**  **180**	8% 7%	57
3	 **172**	 **175** (2 equiv.)	i) HCl, MeOH, H_2O, $NaBH_3CN$, $MgSO_4$, reflux, 19 h ii) Acetylate	 **181**	47%	58
4	**172**	 **176a**, X = OMe **176b**, X = $O(CH_2)_7CH_3$ **176c**, X = N_3	i) HCl, MeOH, H_2O, $NaBH_3CN$, $MgSO_4$, reflux, 19 h ii) Acetylate	 **182a**, X = OMe **182b**, X = $O(CH_2)_7CH_3$ **182c**, X = N_3	**182a**, 60% **182b**, 41% **182c**, 50%	58

The allylic nature of the bromides presumably enhances their reactivity to the extent that an alkylation reaction is possible; S_N2 displacement of carbohydrate halides is not normally straightforward.

Ogawa et al. coupled together two racemic carbasugar derivatives, giving four stereoisomeric products (two diastereomeric pairs of enantiomers). A primary allylic bromide (*rac*-**183**) reacted with a carbasugar C-1 amine (*rac*-**39**) to give the coupled products (*rac*-**187**) in good combined yield, but separation resulted in some losses (the isolated yields of the separated diastereomers were 19% and 27%).[59,60] Note that the nitrogen in the products was not acetylated. An α C-1 allylic bromide (*rac*-**184**) coupled with the carbasugar C-1 amine (*rac*-**39**) to give the β products (*rac*-**188**, as a mixture of two diastereomers, both racemic, combined yield 40%), i.e., with inversion of configuration at C-1. Heating the reaction mixture resulted in degradation, so the reaction was conducted at rt. But the β-bromide (C-1 epimer of *rac*-**184**) also gave the same β-configured amine products (*rac*-**188**); neighbouring group participation or epimerisation of the bromide to the (presumably) more reactive α-isomer are possible explanations. Sulfonamide or trifluoroacetamide nucleophiles failed to give coupling products with these allylic bromides.

Kuzuhara and co-workers coupled an enantiopure carbasugar C-1 bromide (**185**) with a 4-amino-4-deoxyglucose disaccharide (**186**).[61] They found that the C-1 conformation of the bromide was not stable under the reaction conditions, and therefore used an α,β-mixture of bromides, which gave an α,β-mixture of products (**189**). The reaction conditions used here involved the addition of sodium iodide; the conditions used by Ogawa et al. ($^iPr_2NH$ (sic), DMF) reportedly failed to give the coupling product.

Stick et al. formed carbasugar pseudodisaccharides by coupling of unsaturated carbasugar C-1 amines (**123**, **190** and **191**) with axial C-4 or C-3 carbohydrate triflates (**192**–**197**). Straightforward displacement in *N*,*N*′-dimethyl-2-imidazolidinone (DMI) as solvent gave the *xylo*- or *gluco*-configured all-equatorial products (**199**–**204**) stereospecifically with inversion of configuration (Table 9).[56,62–65] It was important to have a neighbouring benzoate protecting group and not a benzyl ether for good yields to be obtained. The 2,3-dibenzylated triflate (analogous to **193**) gave essentially only the elimination products with amine **123**.[66] In most cases



Scheme 8. Alkylation of amines using carbasugar allylic bromides.[59–61] (**187** and **188** were formed as mixtures of two diastereomers, both of which were racemic. Only one diastereomer is shown.)

where a neighbouring benzoate was present, the coupled products (**199**–**203**) were obtained in reasonable yield (43–56%, Table 9, entries 1–5),[56,62–64] but a pseudotetrasaccharide (**205**) was only formed in very low yield by attempted coupling of a carbasugar amine (**123**) with a trisaccharide triflate (**128**) (Table 9, entry 6).[65]

2.4. Palladium-catalysed allylic coupling

The allylic nature of the C-1 position in C-5=C-5a unsaturated carbasugars opens the way for a transition-metal-catalysed allylic amination reaction for the synthesis of N-linked pseudodisaccharides.

Shing et al. developed this idea, using C-5=C-5a unsaturated carbasugars bearing chloride at C-1 (**209**–**212**) as the electrophilic coupling partner and other C-1 or C-4 amino carbasugars (**58**, **125** and **206**–**208**) as nucleophiles (Table 10).[67–69] Pseudodisaccharides (**214**–**218**) were formed with retention of configuration at the allylic carbasugar C-1 and with minimal elimination by-products (**219** and **220**) under the optimised conditions (i.e., with a palladium catalyst and a phosphonate ligand). The yield of elimination by-products was minimised by using acetal protecting groups rather than benzyl ethers on the electrophiles (cf. Table 10, entries 2 and 3).[67] Outstanding yields of pseudodisaccharide intermediates for syntheses of 'pseudoacarviosin'[68] (a carbasugar analogue of acarviosin) and validoxylamine G[69] were obtained by this method (Table 10, entries 4 and 5).

2.5. Intramolecular reaction

Knapp et al. described intramolecular strategies for N-substituted C-5=C-5a unsaturated carbasugar synthesis.[70] Only one example of the formation of a pseudodisaccharide by such a method has been described, however. A carbasugar precursor allylic alcohol (**221**) was coupled to a carbohydrate isothiocyanate (**222**) to give a carbonimidothioate (**223**) (Scheme 9). On heating, this compound underwent a 3,3-sigmatropic shift to form the N–C-1 bond. The reaction product was a thiocarbamate, which was deprotected under dissolving metal conditions to give the free amine (**224**). While this strategy worked well to form a (1→6)-linked derivative, an analogous reaction to form a (1→4)-linked glucose pseudodisaccharide failed, possibly owing to the increased steric hindrance around the secondary carbon of the amine.

3. O-Linked

3.1. Triflate displacement

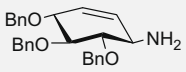
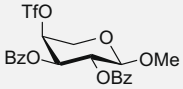
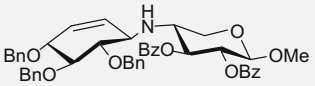
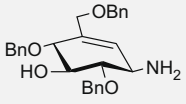
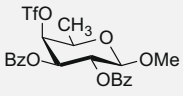
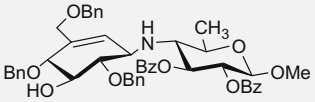
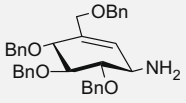
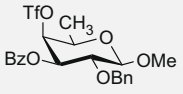
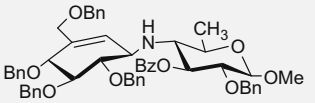
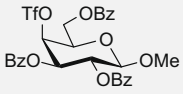
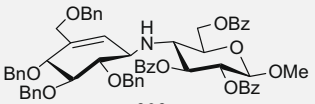
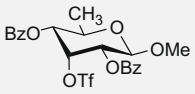
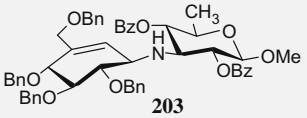
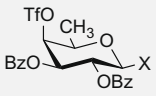
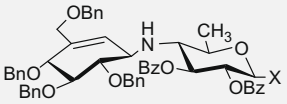
Ether-linked pseudodisaccharides have been synthesised by S_N2 reaction between carbasugar C-1 alcohols and carbohydrate triflates. The alkoxide nucleophile is a strong base, so potential competing elimination reactions must be minimised.

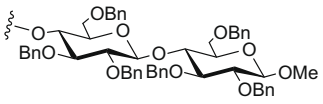
Paulsen et al. identified triflates that can be used to synthesise 6-substituted glucose (**236**–**238**) and 4-substituted glucose (**239**–**243**) pseudodisaccharides.[71] The displacement of the primary *gluco* triflate (**233**) by alkoxides derived from various carbasugar C-1 alcohols (**225**–**227**) took place in THF at rt, giving the ether-linked (1→6)Glc pseudodisaccharides (**236**–**238**) in excellent yield (Table 11, entries 1–3).[71] The alkoxides were generated from the alcohols and NaH, but KO*t*Bu could also be used in combination with 18-crown-6.

The synthesis of pseudodisaccharides containing 4-substituted glucose was more difficult; the reaction products are *sec*–*sec* ethers, and S_N2 is expected to be more difficult at a secondary than a primary carbon, while competing elimination does not suffer the same steric constraint. A galactose 4-triflate in the $^4C_1$ conformation (**245**; Fig. 5) gave only the product of elimination. Therefore, the conformationally locked ($^1C_4$) 1,6-anhydrogalactose derivative (**234**) with an *equatorial* C-4 triflate was used instead; here the antiperiplanar relationship of H and OTf is avoided, thus disfavouring a competing elimination pathway. Yields of pseudodisaccharide coupling products in THF were low, but adding DMF or HMPA as co-solvent gave better yields, and some ether-linked pseudodisaccharides (**239**–**243**) could be synthesised from the corresponding alcohols (**225** and **228**–**231**) by this method (Table 11, entries 4–8).[71,41] In my laboratory, we synthesised a pseudodisaccharide based on 3-substituted glucose (**244**) by coupling of a carbasugar C-1 alcohol (**232**) with an *allo* 3-triflate (**235**) (Table 11, entry 9).[72]

The yields for the synthesis of (1→6)- and (1→4)-linked compounds, at least, are high, and apparently independent of the structure of the nucleophile, from which we may infer that this approach may be used to synthesise other carbasugar pseudodisaccharides linked (1→4) or (1→6) to glucose. This approach to pseudodisaccharides requires triflates that will not easily undergo 1,2-elimination even under strongly basic conditions, so if further such carbohydrate triflates are discovered, the method may be extended to other linkages.

Table 9
Formation of N-linked pseudodisaccharides and pseudotetrasaccharides by reaction of carbasugar C-1 amines with carbohydrate triflates

Entry	Amine	Triflate	Conditions	Product	Yield	Ref.
1	 **190** (2.5 equiv.)	 **192**	DMI, 60 °C, 20 h	 **199**	56%	62
2	 **191** (2.5 equiv.)	 **193**	DMI, rt, 4 days	 **200**	36%	63
3	 **123** (2 equiv.)	 **194**	DMI, rt, 5 days	 **201**	43%	56
4	**123** (2.1 equiv)	 **195**	DMI, rt	 **202**	41%	64
5	**123** (2.5 equiv)	 **196**	DMI, rt, overnight	 **203**	55%	64
6	**123** (2.5 equiv)	 **197**, X = H **198**, X = X^1	DMI, 50–60 °C, 20 h	 **204**, X = H **205**, X = X^1	**204**, 20% **205**, 4%	65

X^1 = 

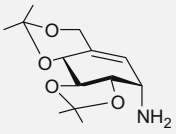
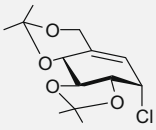
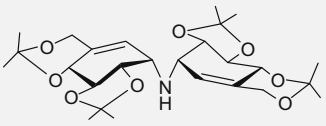
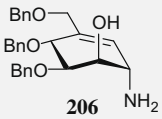
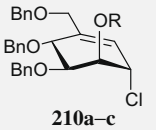
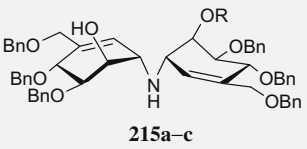
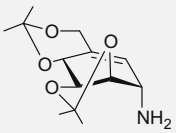
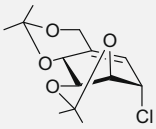
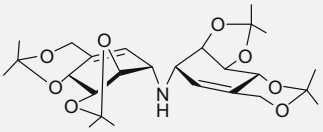
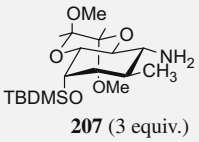
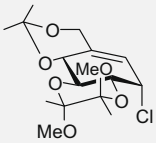
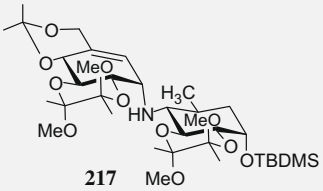
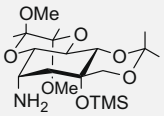
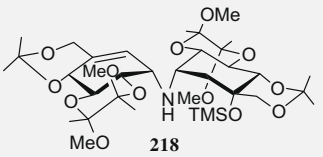
3.2. Epoxide opening

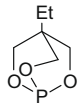
Ogawa et al. have shown that epoxide opening can be used to form ether-linked pseudodisaccharides and pseudotrisaccharides. Lewis acid catalysis promoted a coupling reaction between a β-*manno*-configured carbasugar 1,2-epoxide (**1**) and a primary carbohydrate alcohol (**246**) to form an ether-linked carbasugar pseudodisaccharide (**252**) (Table 12, entry 1), but a secondary carbohydrate alcohol (**249**) failed to open the epoxide under these conditions.[73] Efficient coupling could, though, be achieved under basic conditions; heating the epoxide (**1**) with the alcohol (**249**) in DMF with excess base gave the *sec–sec* ether (**255**) in 35% yield. Running the reaction in the presence of a crown-ether gave a higher yield of the pseudodisaccharide (Table 12, entry 4).[10,73] Two β-*manno*-configured carbasugar 1,2-epoxides (**1** and **258**) were used, and these coupled with primary or secondary carbohydrate alcohols, (**247**–**251** and **259**–**268**) to give the corresponding pseudodisaccharides (**253**–**255**, **257** and **269a**–**k**) or pseudotrisaccharide (**256**) in good yields and with excellent regioselectivity for the *trans*-diaxial-opening products (Table 12, entries 12–17).[10,12–14,35,73–79]

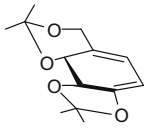
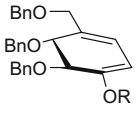
A branched pseudotrisaccharide (**256**) was formed by this method using a pseudodisaccharide alcohol (**250**) as a nucleophile (Table 12, entry 5),[10,73] but when the diol **247** was used as a nucleophile, only the primary alcohol reacted, giving a pseudodisaccharide product (**253**) and none of the pseudotrisaccharide (**256**; Table 12, entry 2).[10]

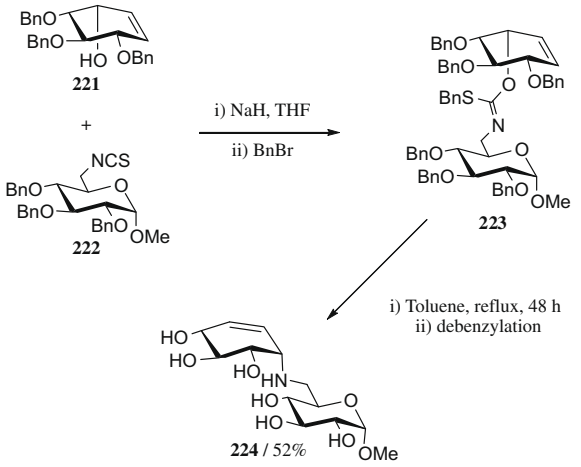
The products of these epoxide-opening reactions all have the α-*manno* configuration. Attempts to obtain β-*gluco*- or β-*galacto*-configured carbasugar pseudodisaccharides by analogous *trans*-diequatorial opening of the corresponding α-carbasugar epoxides with alcohol nucleophiles failed, which contrasts with the results with amines, where imino-linked pseudodisaccharides could be formed from such epoxides (vide supra). Only complex mixtures of elimination products were seen when α-*gluco* and α-*galacto* 1,2-epoxides (**16**–**18**) were heated with alcohols and base in DMF. Even a simple model alcohol, octanol, gave the coupling product in only 5% yield.[12,13] A procedure was developed to access ether-linked carbasugar pseudodisaccharides with configurations other than α-*manno*, based on epimerisations of either C-1 or C-2, or both (Scheme 10).[12–14,75–79] Oxidation of the free carbasugar OH-2 (**269**) gave the C-2 ketone (**270**), which could be epimerised at C-1 under basic conditions to give a mixture of α- and β-carbahexuloses (**270** and **271**), which were separated, and which usually contained the β isomer (**271**) as the major component. Reduction of the α-configured C-2 ketone (**270**) gave then mixtures of *gluco* (**272**) and *manno* (**269**)-configured α-linked carbasugar pseudodisaccharides, while reduction of the β-configured C-2 ketone (**271**) gave mixtures of the *gluco*

Table 10
Formation of N-linked pseudodisaccharides by palladium catalysis

Entry	Amine	Electrophile	Conditions	Product	Yield	Ref.
1	 **58** (4.4 equiv.)	 **209**	$Pd(dba)_2$, TMPP. MeCN, Et_3N, rt	 **214**	78% +**219**/15%	67
2	 **206**	 **210a–c**	$Pd(dba)_2$, TMPP. MeCN, 50 °C	 **215a–c**	**a**, R = Ac; 42% +**220**/38% **b**, R = $CONMe_2$; 50% +**220**/30% **c**, R = MOM; 57% +**220**/24%	67
3	 **125** (2.4 equiv.)	 **211**	$Pd(dba)_2$, TMPP. MeCN, Et_3N, rt	 **216**	94%	67
4	 **207** (3 equiv.)	 **212**	$Pd(dba)_2$, TMPP. MeCN, Et_3N, rt	 **217**	84%	68
5	 **208** (3.8 equiv.)	**212**	$Pd(dba)_2$, TMPP. MeCN, Et_3N, rt	 **218**	99%	69

TMPP (trimethylolpropane phosphite): 

Elimination products:  **219**  **220a–c**

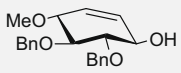
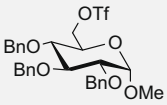
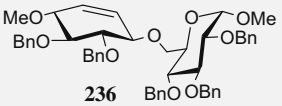
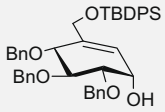
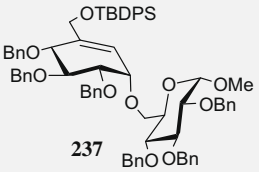
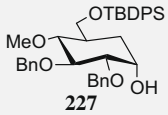
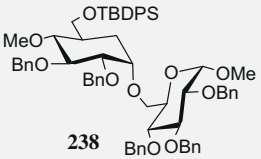
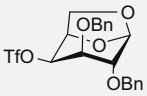
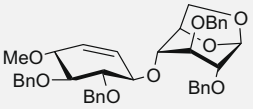
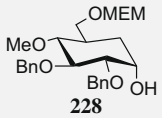
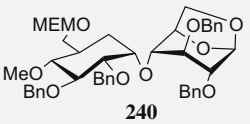
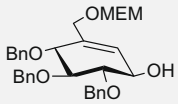
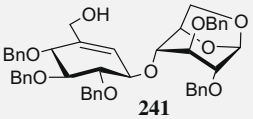
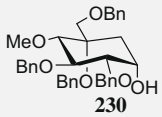
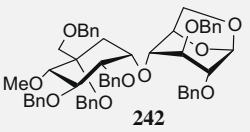
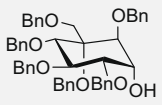
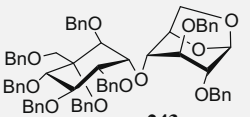
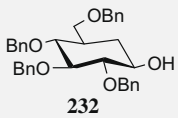
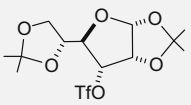
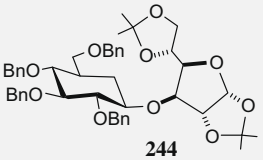


Scheme 9. Intramolecular amino delivery reaction for the synthesis of an N-linked pseudodisaccharide.[70]

(**273**) and *manno* (**274**) β-linked carbasugar pseudodisaccharides; different reduction conditions often gave different diastereoselectivities, as shown in Scheme 10. Further protecting group manipulation and inversion of configuration at C-4 by S_N2 reaction or oxidation–reduction gave *galacto*-configured carbasugars (not shown).[12–14,75,78] The C-2 epimerisation (*manno* **254**→*gluco* **275**) has also been demonstrated with a different protecting-group pattern (Scheme 11). Carbaglucosamine derivatives were accessible from sulfonation of OH-2 and S_N2 displacement with nitrogen nucleophiles. This substitution worked better for β-*manno*-configured starting material than α-*manno*, with elimination dominating in the latter case.[77] Introduction of C-5=C-5a unsaturation into an ether-linked carbasugar was also achieved at the pseudodisaccharide level (not shown).[35]

Ogawa has suggested that the β-*talo*-configured 1,2-epoxide **276** (Fig. 6) could be used to avoid *some* of the extensive post-processing necessary to achieve α-*galacto*-configured ether-linked carbasugar pseudodisaccharides, but no detailed results from coupling with this epoxide are given.[76]

Table 11
Ether-linked pseudodisaccharide synthesis by triflate displacement

Entry	Alcohol	Triflate	Conditions	Product	Yield	Ref.
1	 **225**	 **233** (1.2 equiv.)	NaH, THF, 0 °C to rt, 2 h	 **236**	84%	71
2	 **226**	**233** (1.3 equiv)	NaH, THF, 0 °C to rt, 12 h	 **237**	88%	71
3	 **227**	**233** (1.5 equiv)	NaH, THF, 0 °C to rt, 12 h	 **238**	86%	71
4	**225**	 **234** (1.3 equiv.)	NaH, HMPA, 0 °C to rt, 12 h	 **239**	90%	71
5	 **228**	**234** (2 equiv)	NaH, THF, HMPA, 0 °C to rt, 24 h	 **240**	88%	71
6	 **229**	**234** (2 equiv)	i) NaH, HMPA, 0 °C to rt, 12 h ii) HCl, MeOH	 **241**	88%	71
7	 **230**	**234** (2 equiv)	NaH, THF, HMPA, 0 °C to rt, 12 h	 **242**	87%	71
8	 **231**	**234** (2.7 equiv)	NaH, THF, HMPA, 0 °C to rt, 17 h	 **243**	89%	41
9	 **232**	 **235** (2 equiv.)	NaH, DMF, rt	 **244**	34%	72

3.3. Other methods for ether-linked carbadisaccharide synthesis

Two approaches to carbasugar pseudodisaccharides where the carbasugar is assembled *after* attachment to a carbohydrate component are described in this section. These approaches are quite different to the other work described in this minireview in that they completely remove the need to form an ether bond between two sterically encumbered and electronically unreactive partners (a carbasugar and a carbohydrate); the linkage is put in place at an earlier stage, either as a glycoside or as an ester.

Sinaÿ has developed modifications of the Ferrier II rearrangement where the glycosidic substituent is retained. The reaction has been applied to the synthesis of pseudodisaccharides, and the carbocycles elaborated to give carbadisaccharides. Hence, disaccharides were modified to give *exo*-glycals (**277**), which rearranged upon treatment with TIBAL to give pseudodisaccharides (**278**) (Scheme 12).[80]

The reaction worked well for a range of (1→6)- or (1→4)-linked compounds, but debenzylation was a competing reaction when the anomeric substituent was an α-methyl glucoside (**278a**,**b**). The reaction was diastereoselective and the products with an axial

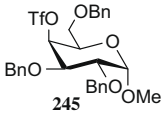


Figure 5. An ineffective carbohydrate triflate.

C-1 orientation were formed. The reaction also worked in a bis manner to give a pseudodisaccharide (not shown)[81] and even in a tris manner to give a pseudotrisaccharide (**279**→**280**) in 33% yield (Scheme 12).[82] Modification at C-5 of a pseudodisaccharide (**281**) obtained by this method gave a carbaidopyranoside pseudodisaccharide (**284**) (Scheme 13).[83]

C-6-Deprotected carbaidopyranosides have been converted to carbaglucopyranosides by an oxidation–epimerisation–reduction sequence, although this has only been shown on a *glycosidically linked* pseudodisaccharide (**285**→**286**) as yet (Scheme 14).[84]

Treatment of the *exo*-glycal rearrangement precursors with trimethylaluminium instead of TIBAL gave a rearrangement to cyclohexane products with no debenzylation observed.[85] Here though, a methyl group was added from the reagent (rather than a hydride from TIBAL), giving a carbahexopyranose (**287**), again with stereoselectivity for the C-1-axial product (Scheme 15).

Secondly, Mootoo and co-workers have also developed a route based on post-conjugation carbasugar synthesis, and demonstrated this principle for the synthesis of a carbagalactoside (Scheme 16).[86] The acyclic compound **288** is a carbasugar precursor. This was coupled to a carbohydrate alcohol by esterification. Tebbe methylenation gave the enol ether (**289**), which, upon activation with methyl triflate, underwent a cyclisation reaction to give the carbocyclic enol ether (**290**). This was then hydrated to give the carbasugar pseudodisaccharide (**291**). The method has only been demonstrated for a single example of an ether-linked carbadisaccharide, but a glycosidically linked compound was also made in the same way starting from a hemiacetal (not shown).

4. S-Linked

Reports of thioether-linked carbasugar pseudodisaccharides are scarcer than those of their amine- or ether-linked counterparts. The higher nucleophilicity and lower basicity of sulfur compared to oxygen mean that thioetherification reactions are less likely to suffer from elimination than are the corresponding etherifications. However, due to the very limited results in this area, it is difficult to draw extensive conclusions.

4.1. Epoxide opening

Ogawa and co-workers synthesised thioether-linked carbasugar pseudodisaccharides by epoxide opening.[35] Opening a 1,2-epoxide (**292**) with a thiol generated and activated in situ by treatment of the thioacetate (**293**) with 2-aminoethanethiol and 1,4-dithioerythritol gave the α-*manno* derivative (**294**), i.e., the *trans*-diaxial opening product, in excellent yield and with excellent regioselectivity (Scheme 17). The α-*manno*-configured carbasugar was converted to the required α-*gluco* compound by oxidation of the free OH-2, followed by reduction of the resulting ketone to give a thioether-linked carbamaltose (**295**) (Scheme 17). Opening a carbasugar 1,5a-epoxide (**296**) with a glucose C-4 thiol nucleophile (from **293**) gave the 5a-hydroxy α-*gluco*-configured carbasugar pseudodisaccharide (**297**) resulting from attack at C-1 of the epoxide and *trans*-diaxial opening. This compound was converted into the required α-*xylo* C-5=C-5a unsaturated carbasugar pseudodisaccharide (**298**) by chlorination of the free hydroxyl group (OH-5a, to give an axial chloride with overall retention of configuration) followed by basic elimination.

4.2. Triflate displacement

Triflate displacement strategies have also been used to synthesise thioether-linked carbasugar pseudodisaccharides.

Stick et al. coupled the carbasugar C-1 thiol of a C-5=C-5a unsaturated carbapentose derivative (**299**) with a pentose C-4 triflate (**192**), which gave the thioether carbasugar pseudodisaccharide (**300**) with inversion of configuration at C-4 (Scheme 18).[62] My group used the opposite strategy, with displacement of a β-*gluco*-configured carbasugar C-1 triflate (**301**) by C-3 thiols with *gluco* (**302**) or *manno* (**303**) configuration giving, with inversion of configuration at C-1, the α-*gluco* thioether carbasugar pseudodisaccharides (**304** and **305**) (Scheme 19).[87]

5. Summary, conclusions and outlook

In this final section, different useful routes to each of the synthesised linkages are compared. It is assumed that the required nucleophiles/electrophiles are accessible. This identifies those areas where methodology exists for the formation of a given stereochemical linkage as well as those areas where more work is required.

5.1. Carbasugar electrophiles

This section summarises those reactions in which the new C–X bond is the carbasugar C-1–X bond, corresponding to disconnection 1 in Scheme 2.

5.1.1. 5a-Carba-α-mannopyranosides

N, O and S-linked pseudodisaccharides are all accessible by condensation of a carbasugar 1,2-epoxide with a nucleophile: amines (yields are good, 56–95%; Table 1) for N-linked pseudodisaccharides; alcohols (yields are reasonably high, 36–82%; Table 12) for O-linked pseudodisaccharides or thiols (only one example known, Scheme 17) for S-linked pseudodisaccharides. The synthesis is efficient in that the α-mannosides are obtained directly in the condensation, and the *trans*-diaxial ring-opening attack at C-1 is favourable, so good regioselectivity is always seen.

5.1.2. 5a-Carba-α-glucopyranosides

Carbasugar 1,5a-epoxides are opened by amines to give 5a-hydroxy-5a-carba-α-glucosides with good regioselectivity for diaxial opening but rather low yields (34–57%) of coupling product. Competing formation of diequatorial product accounts for the lower yields in these reactions (Scheme 1). Such compounds have been deoxygenated at C-5a to give N-linked carba-α-*gluco* pseudodisaccharides (Scheme 4). Analogous epoxide opening has also been demonstrated for a thiol nucleophile (Scheme 17), but not for alcohol nucleophiles.

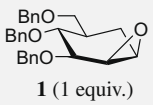
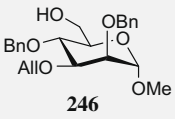
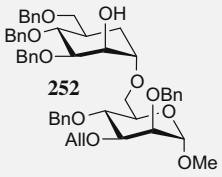
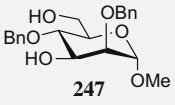
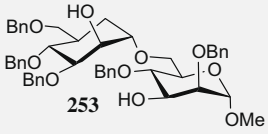
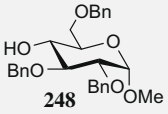
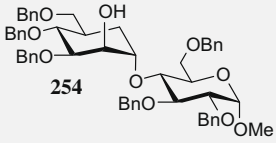
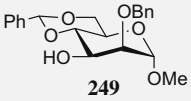
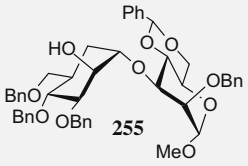
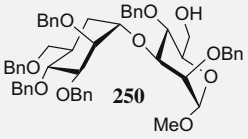
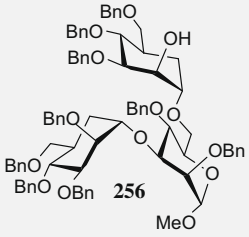
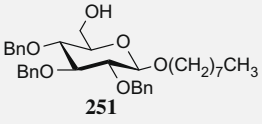
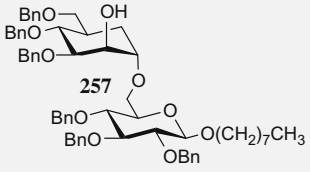
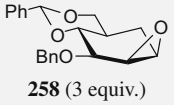
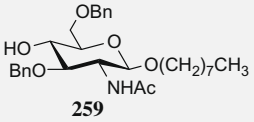
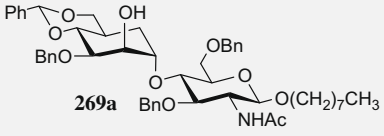
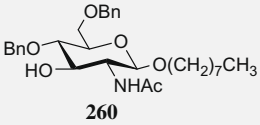
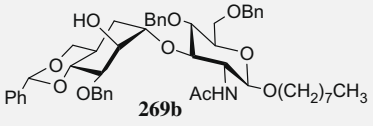
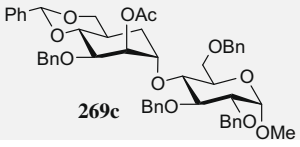
O-Linked carba-α-glucosides are available from the carba-α-mannosides by a two-step oxidation–reduction sequence to achieve epimerisation at C-2 (Schemes 10 and 11).

S-Linked carba-α-glucosides have been synthesised in two ways: either by coupling of a carba-β-glucose 1-triflate and carbohydrate C-3 thiols (Scheme 19); or by C-2 epimerisation of the first-formed carba-α-mannoside by an oxidation–reduction sequence (Scheme 17).

5.1.3. 5a-Carba-α-*xylo*-hex(5,5a)enopyranosides

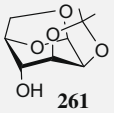
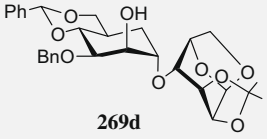
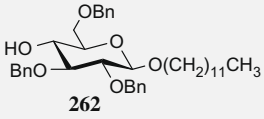
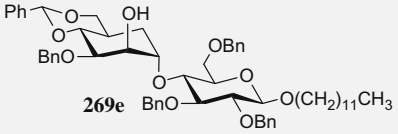
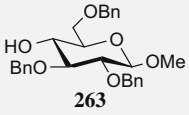
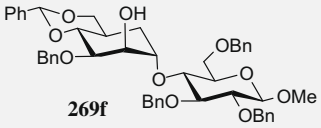
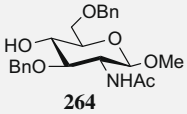
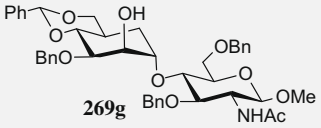
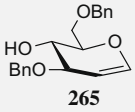
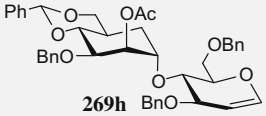
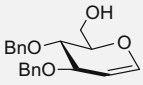
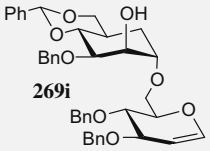
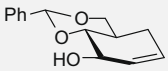
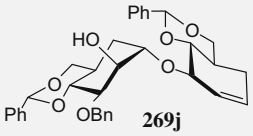
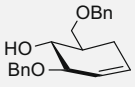
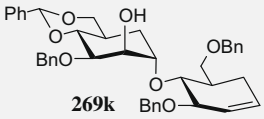
β-*lyxo*-Type unsaturated donors are opened by amine attack exclusively at C-1 to give good yields of N-linked α-*lyxo*

Table 12
Formation of pseudodisaccharides and pseudotrisaccharides by opening of 1,2-epoxides

Entry	Epoxide	Alcohol	Conditions	Product	Yield	Ref.
1	 **1** (1 equiv.)	 **246**	A	 **252**	37% (58% alcohol recovered)	73
2	**1** (2 equiv)	 **247**	B, 70 °C, 2 h	 **253**	65%	10
3	**1** (1 equiv)	 **248**	B, 70 °C, 4 h	 **254**	45% (46% alcohol recovered)	35,73
4	**1** (2.8 equiv)	 **249**	B, 70 °C, 2 h	 **255**	64% (27% alcohol recovered)	10,73
5	**1** (3 equiv)	 **250**	B, 70 °C, 2 days	 **256**	44%	10,73
6	**1** (2.4 equiv)	 **251**	B, 70 °C, 2 h	 **257**	82%	74
7	 **258** (3 equiv.)	 **259**	B, 70 °C, 3–26 h	 **269a**	66%	14,75
8	**258** (3 equiv)	 **260**	B, 80 °C, 3 days	 **269b**	36–48%	14,75
9	**258** (2 equiv)	**248**	i) B, 50 °C, overnight ii) Acetylate	 **269c**	60%	76

(*continued on next page*)

Table 12 (*continued*)

Entry	Epoxide	Alcohol	Conditions	Product	Yield	Ref.
10	**258**	 **261**	B, 80 °C, 6 h	 **269d**	52%	77
11	**258** (2 equiv)	 **262**	B, 50 °C, overnight	 **269e**	84%	78
12	**258** (2.5 equiv)	 **263**	B, 70 °C, 3 h	 **269f**	70%	12,13
13	**258** (2.3 equiv)	 **264**	B, 70 °C, 25 h	 **269g**	68%	13
14	**258** (1.5 equiv)	 **265**	i) B, 60 °C, 27 h ii) Acetylate	 **269h**	44%	79
15	**258** (1.5 equiv)	 **266**	B, 60 °C	 **269i**	56%	79
16	**258** (1.5 equiv)	 **267**	B, 60 °C, 16 h	 **269j**	45%	79
17	**258** (1.5 equiv)	 **268**	B, 60 °C	 **269k**	17%	79

Reaction conditions: (A) $BF_3{\cdot}OEt_2$ in CH_2Cl_2, −150 °C; and (B) NaH, DMF, 15-crown-5, 50–80 °C.

unsaturated pseudodisaccharides (2-*epi*-valienamine derivatives) with yields between 64% and 78% (Table 3).

Very good results for α-*lyxo* unsaturated pseudodisaccharide formation have been obtained by palladium-catalysed nucleophilic substitution of allylic C-1 α-chlorides with retention of configuration. Acetal-protecting groups are necessary for excellent yields (Table 10).

5.1.4. 5a-Carba-α-*xylo*-hex(5,5a)enopyranosides

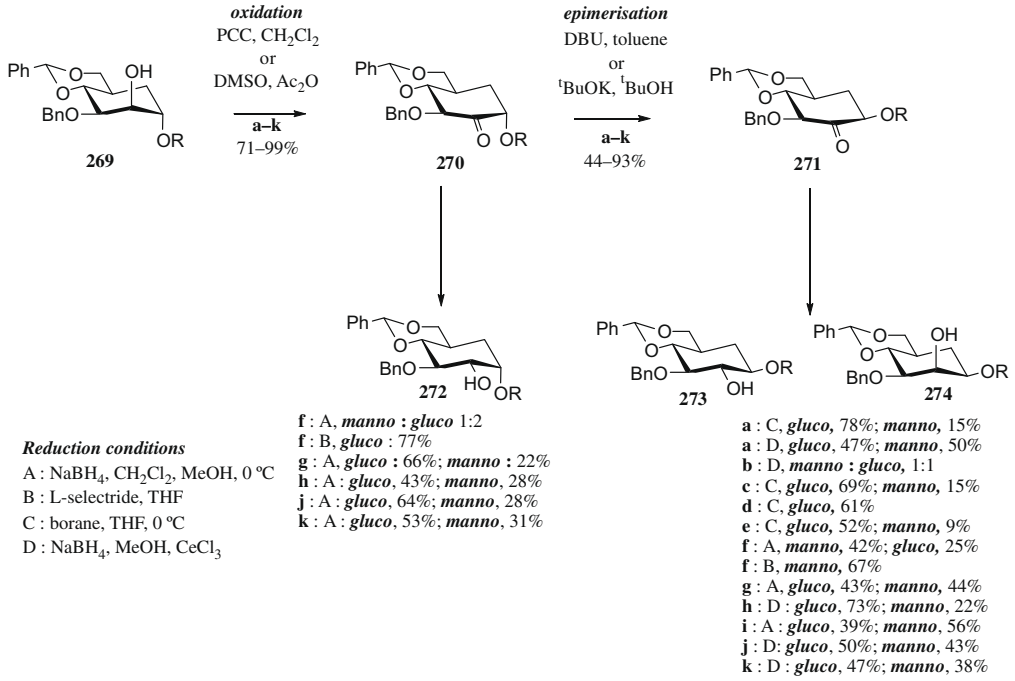
Very good results for the formation of N-linked carba-α-*xylo* pseudodisaccharides (valienamine derivatives) have been obtained by palladium-catalysed nucleophilic substitution of allylic C-1 α-chlorides with retention of configuration. Again, acetal protecting groups are necessary for the obtention of excellent yields (Table 10).

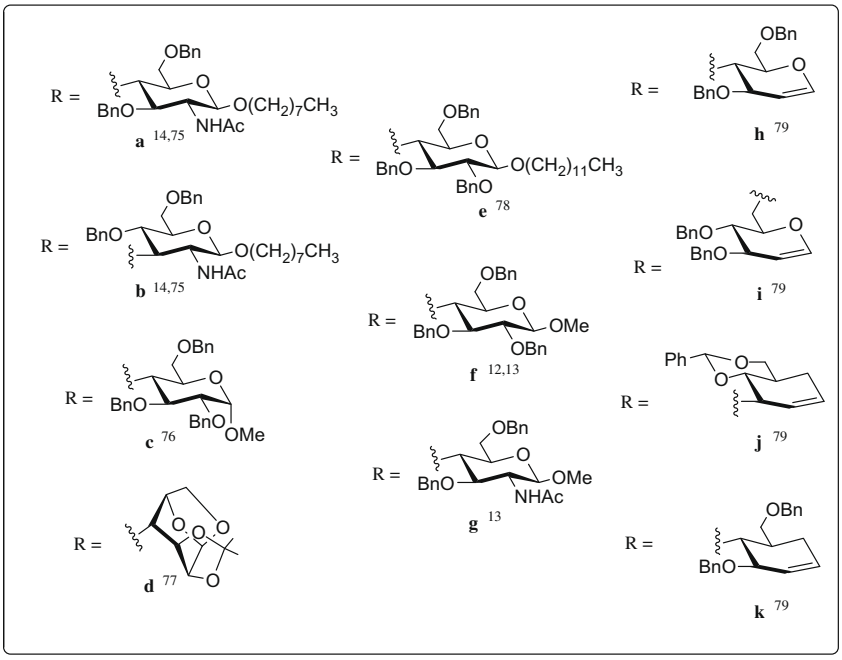
5.1.5. 5a-Carba-β-mannopyranosides

O-Linked compounds are available from the α-mannosides by multistep epimerisation at C-1 (Scheme 10). N-Linked and S-linked examples are not known.

5.1.6. 5a-Carba-β-galactopyranosides

N-Linked compounds are available directly by attack of a carbohydrate amine at C-1 of a carbasugar 1,2-epoxide, but regioselectivity can be problematic (Table 2). Product yields are lower than those for the formation of carba-α-mannosides, being between 24% and 66%. O-Linked compounds have only been synthesised by extensive modification of carba-α-mannosides at the pseudodisaccharide level, that is, epimerisation of the carbamannose at C-1, C-2 and C-4;[12–14,75,78] or by Mootoo's post-conjugation carbasugar assembly (Scheme 16).

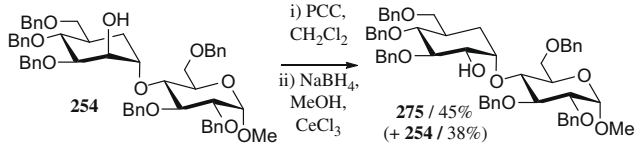




Scheme 10. Epimerisation of C-1 and/or C-2 after pseudodisaccharide formation.

5.1.7. 5a-Carba-β-glucopyranosides

For the synthesis of N-linked pseudodisaccharides by opening of 1,2-carbasugar epoxides by amines, the regioselectivity is not as good as that for the synthesis of carba-α-mannosides, but attack at C-1 has been observed (only one example; Table 2). O-Linked pseudodisaccharides are available from the carba-α-mannosides by the well-worked-out sequence of double epimerisation at C-1 and C-2 (Scheme 10).



Scheme 11. Epimerisation of C-2 after pseudodisaccharide formation.[35,73]

5.2. Carbasugar nucleophiles

This section summarises those reactions in which the new C–X bond is not the carbasugar C-1–X bond, corresponding to disconnection 2 in Scheme 2.

5.2.1. 4-Substituted glucose

For the formation of N-linked pseudodisaccharides, conformationally unlocked *galacto* 3,4-epoxides give mixtures of

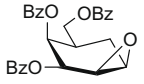


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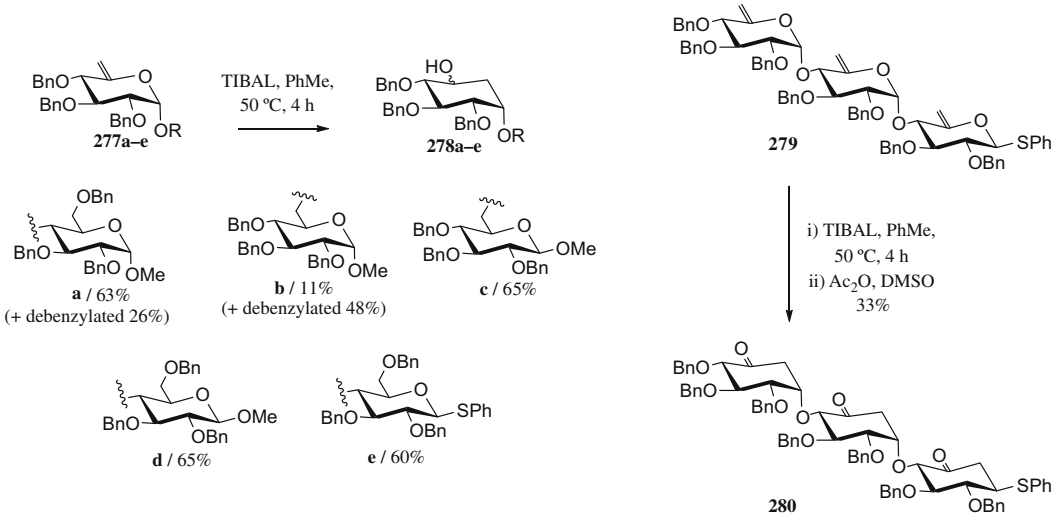
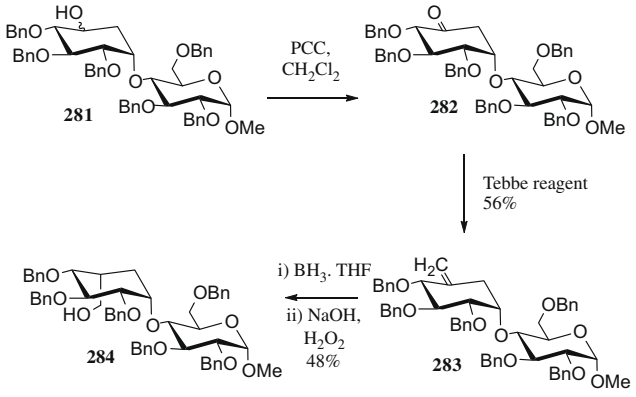
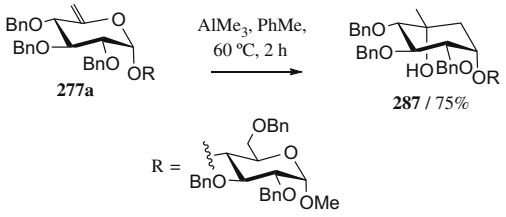
Figure 6. A β-*talo* epoxide proposed by Ogawa.



Scheme 12. Glycoside to pseudodisaccharide and pseudotrisaccharide rearrangements.

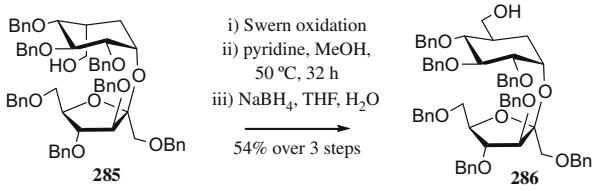


Scheme 13. Conversion of pseudodisaccharides into carbaidose-containing carbadisaccharides.

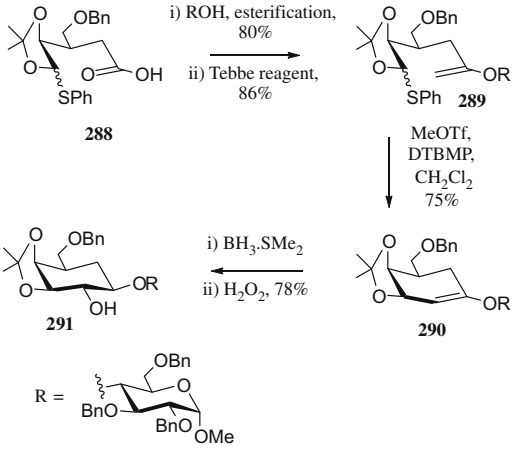


Scheme 15. Glycoside to pseudodisaccharide rearrangement.

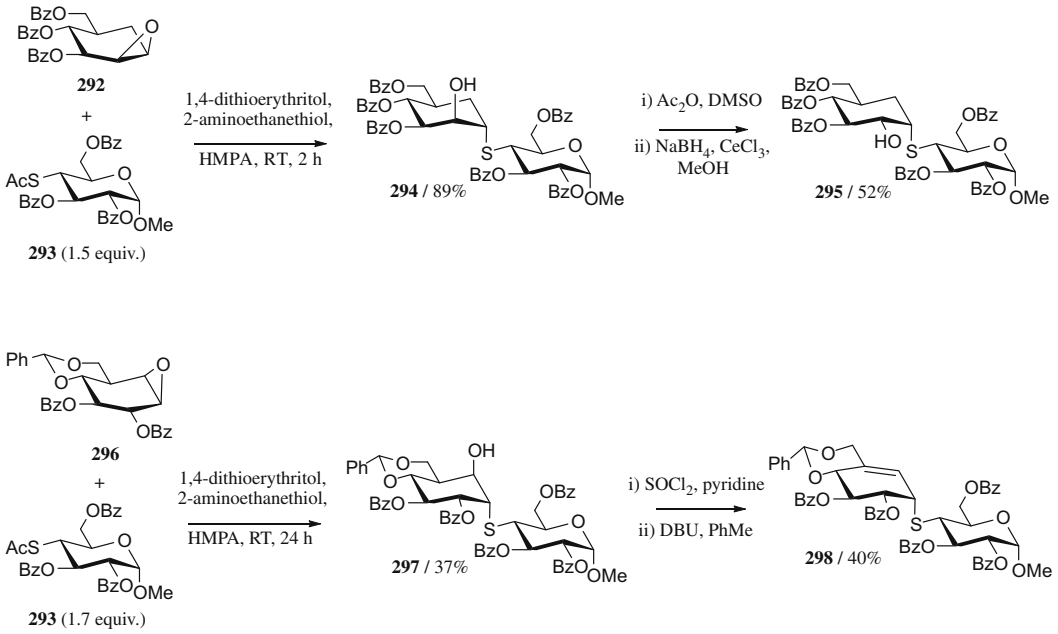
regioisomers when attacked by carbasugar C-1 amines (Table 4). The yields of the diequatorial *gluco*-configured coupled products are between 19% and 37%. Conformationally locked (1,6-anhydro) *galacto* 3,4-epoxides give much better regioselectivity when attacked by carbasugar C-1 amines (Table 5). The yields of the diaxial *gluco*-coupled product are typically 47–76%. N-Linked pseudodisaccharides have also been satisfactorily formed by the displacement of *galacto* C-4 triflates with vicinal benzoate protection: 45–55% yields have been obtained with β-valienamine N-1 nucleophiles, forming (1→4)Glc linkages with inversion of configuration at C-4 (Table 9).



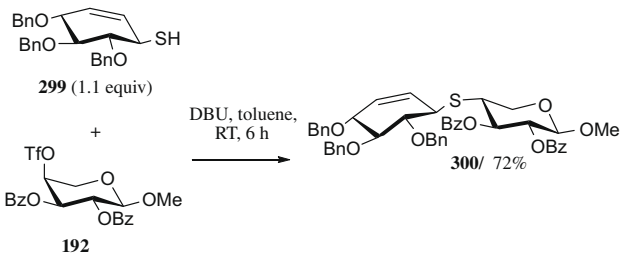
Scheme 14. C-5 (*ido*→*gluco*) Epimerisation of a glycosidically linked carbadisaccharide.



Scheme 16. Formation of a β-*galacto* carbasugar pseudodisaccharide by post-conjugation carbocylisation.

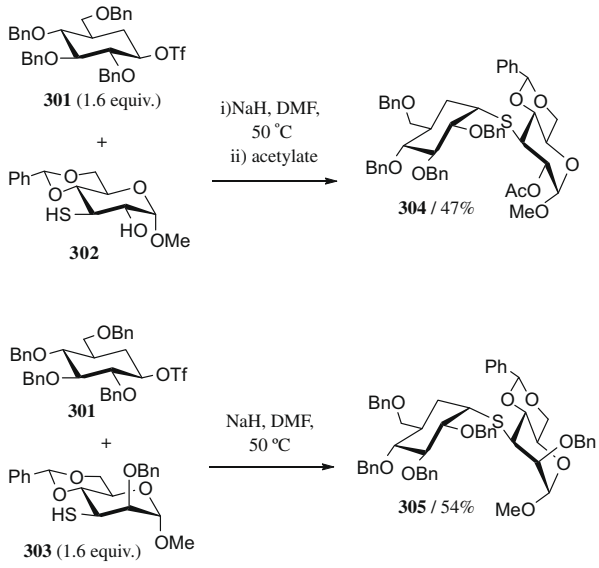


Scheme 17. Epoxide opening to form the carbasugar C-1–S bond, and modification of carbasugar pseudodisaccharides.[35]



Scheme 18. C-1–S bond formation by S_N2 reaction between carbasugar C-1 thiol and carbohydrate C-4 triflate.[62]

An electrophile, a 1,6-anhydrosugar *galacto* C-4 triflate (**234**), has been identified that leads to O-linked (1→4)Glc derivatives with carbasugar C-1 alcohol nucleophiles (Table 11). HMPA is needed as solvent for good yields.



Scheme 19. C-1–S bond formation by S_N2 reaction between carbasugar C-1 triflate and carbohydrate C-3 thiols.[87]

5.2.2. 3-Substituted glucose

An electrophile, an allofuranose C-3 triflate (**235**), has been identified that leads to an O-linked (1→3)Glc derivative with a carbasugar C-1 alcohol nucleophile (only one example; Table 11). An N(1→3)-linked glucose derivative is formed by S_N2 reaction of a benzoate-protected *allo* triflate (**196**) and a carbasugar N-1 amine nucleophile (only one example; Table 9).

5.2.3. 2-Substituted glucose

Conformationally unlocked *manno*-configured 2,3-epoxides have been used to synthesise N(1→2)-linked glucose derivatives (Table 6). The regioselectivity for the diequatorial 2-amino-2-deoxyglucose derivative over the diaxial 3-amino-3-deoxyaltrose is better when the epoxide is not conformationally locked by a 4,6-benzylidene acetal. A 3-amino-3-deoxyaltrose pseudodisaccharide was converted into the 2-amino-2-deoxyglucose isomer after coupling (Scheme 7).

5.2.4. 6-Substituted glucose

A glucose C-6 triflate (**233**) has been identified that leads to O-linked (1→6)Glc derivatives with carbohydrate C-1 alcohol nucleophiles (Table 11).

5.2.5. 4-Substituted mannose

An N-linked derivative was formed from a 4-substituted glucose pseudodisaccharide by multistep epimerisation (only one example, Scheme 7).

5.2.6. 4-Substituted xylose

An S-linked xylose derivative was formed by direct S_N2 displacement of a C-4 triflate with a thiol nucleophile (only one example, Scheme 18).

5.3. Conclusions and outlook

Many synthetic routes to non-glycosidically linked carbasugar pseudodisaccharides and pseudooligosaccharides have been

explored. The chemistry summarised here that leads to this group of structures is diverse, and includes different coupling reactions associated with each of nitrogen, oxygen and sulfur nucleophiles. The presence of C-5=C-5a unsaturation in the ring can be important in enhancing the reactivity of an electrophile (e.g., in epoxide opening) or introducing new reactivity (e.g., in palladium coupling). The reactions often appear to suffer from sensitivity to the sterically crowded and electron-poor nature of both nucleophile and electrophile, so that chemistry that may work well on simple systems can fail here.

The coupling reactions can be classified as indirect routes, which rely on post-coupling modification (e.g., epimerisation or reduction) to get the carbasugar or carbohydrate into its final form, and direct routes, where this is not necessary. Direct routes simplify already complex reaction sequences, and so such methods would be preferable for all linkages. Such direct routes exist in some cases. For example, the synthesis of α-*manno*-configured carbasugars with N-, S- or O-linkages by a one-step 1,2-epoxide opening seems apparently generally applicable.

Some other direct routes, such as the palladium-catalysed coupling routes to N-linked α-*gluco* carbasugar pseudodisaccharides and the formation of 4-O-substituted glucose derivatives by triflate displacement, are also apparently very efficient but maybe somewhat less explored. It would be desirable to see the development of direct coupling routes for those cases where none exists already. For example, new shorter and general routes to O-linked α- and β-*galacto* or N-linked α-*galacto* derivatives would be welcome. The biological activity of at least O- and N-linked carbasugar pseudodisaccharides justifies the further exploration of this type of structure, and hopefully in the future, efficient coupling methods for the synthesis of all the relevant linkages can be found.

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