REVIEW

Recent advances in the construction of β-D-mannose and β-D-mannosamine linkages

Jonathan J. Gridley and Helen M. I. Osborn *

Department of Chemistry, University of Reading, Whiteknights, Reading, UK RG6 6AD.
Tel. +44 (0) 1189 875123; Fax: +44 (0) 1189 316331;
E-mail: jjgridley@currantbun.com; h.m.i.osborn@reading.ac.uk

Received (in Cambridge, UK) 25th January 2000
Published on the Web 25th April 2000

Covering: January 1993 to August 1999.

1 Glycobiology

Carbohydrates are one of the largest classes of naturally occurring substances, which have been attracting an increasing amount of attention from all corners of science. The role of carbohydrates in nature goes under the broad heading of "Glycobiology", an eye-opening subject encompassing many areas of interest, particularly to the synthetic organic chemist and more recently receiving attention from a therapeutic drug development aspect.[1] Carbohydrates are at the heart of a multitude of biological events in all living organisms, and are often found in conjunction with other large biomolecules such as lipids or proteins. The three major domains into which these huge glycoconjugates can be subdivided are glycoproteins, glycolipids and proteoglycans. To introduce the three subsets briefly:

1. Proteoglycans are composed of a protein portion to which is bound long sulfated carbohydrate chains. They make up the bulk matrix surrounding cells where they are responsible for integrity of connective tissue and the storage of biologically active compounds within the body.[2] Also, they are implicated in the mediation of a range of biological functions including formation of new blood vessels, blood clotting and regulation of gene expression.[3,4]
2. Glycolipids are oligosaccharides covalently linked to a fatty acid by means of either a sphingosine or inositol moiety and can be found anchored to the cell membrane. The glycal portion of the molecule protruding from the extracellular surface is accessible to carbohydrate-binding proteins.[2]
3. Glycoproteins along with glycolipids are know to act as sites for the binding of other large biomolecules such as hormones, antibodies, enzymes, bacterial toxins and cell surface proteins.[1,2,5a–i] The impact of protein glycosylation can be seen in the important physical properties imparted to the molecule, for example, protease resistance, conformational stability, charge and water-binding capacity.[5a] The number of monosaccharides and the possible ways of linking them together gives the glycal portion of glycoproteins immense diversity in structure compared with the protein, implicating them as the key elements in the complex subtleties involved in physiological and pathological processes of living organisms.[5a–i] Glycosylation of the protein is known to be species, cell and tissue specific.[5b,6] The existence of "microheterogeneity" adds further complexity in that discrete subsets of a glycoprotein, called glycoforms, with different physical and biochemical properties exist.[6] There are two main classes of glycoproteins, namely *N*-linked and *O*-linked glycoproteins. The classification depends on whether the oligosaccharide side chain is linked to the protein *via* serine or threonine amino acids (*O*-linked) or asparagine (*N*-linked). *S*-Linked, *P*-linked and the *C*-linked glycoproteins are less abundant.[7]

1.1 Natural occurrence of β-mannosides

1.1.1 *N*-Linked glycoproteins

1.1.1.1 Structure and diversity

In this review attention is focused on the *N*-linked glycoproteins which are a biologically important and widespread class of structures containing a β-linked mannopyranoside unit. They contain a universal (in all but a few exceptions)[8a] pentasaccharide core structure and an array of oligomer chains can be attached to this core. The oligomer chains have been classified into four groups according to their structure and point of attachment, they are commonly referred to as antennae (Fig. 1).[5c,d,8a,b] The four classes of *N*-linked glycoproteins are high-mannose, complex, hybrid and poly-*N*-acetyllactosamine (Fig. 1).[5d] The high-mannose glycans contain only α-linked mannose units in as many as three oligomer chains attached to the core. The complex-type contains as many as five oligomer

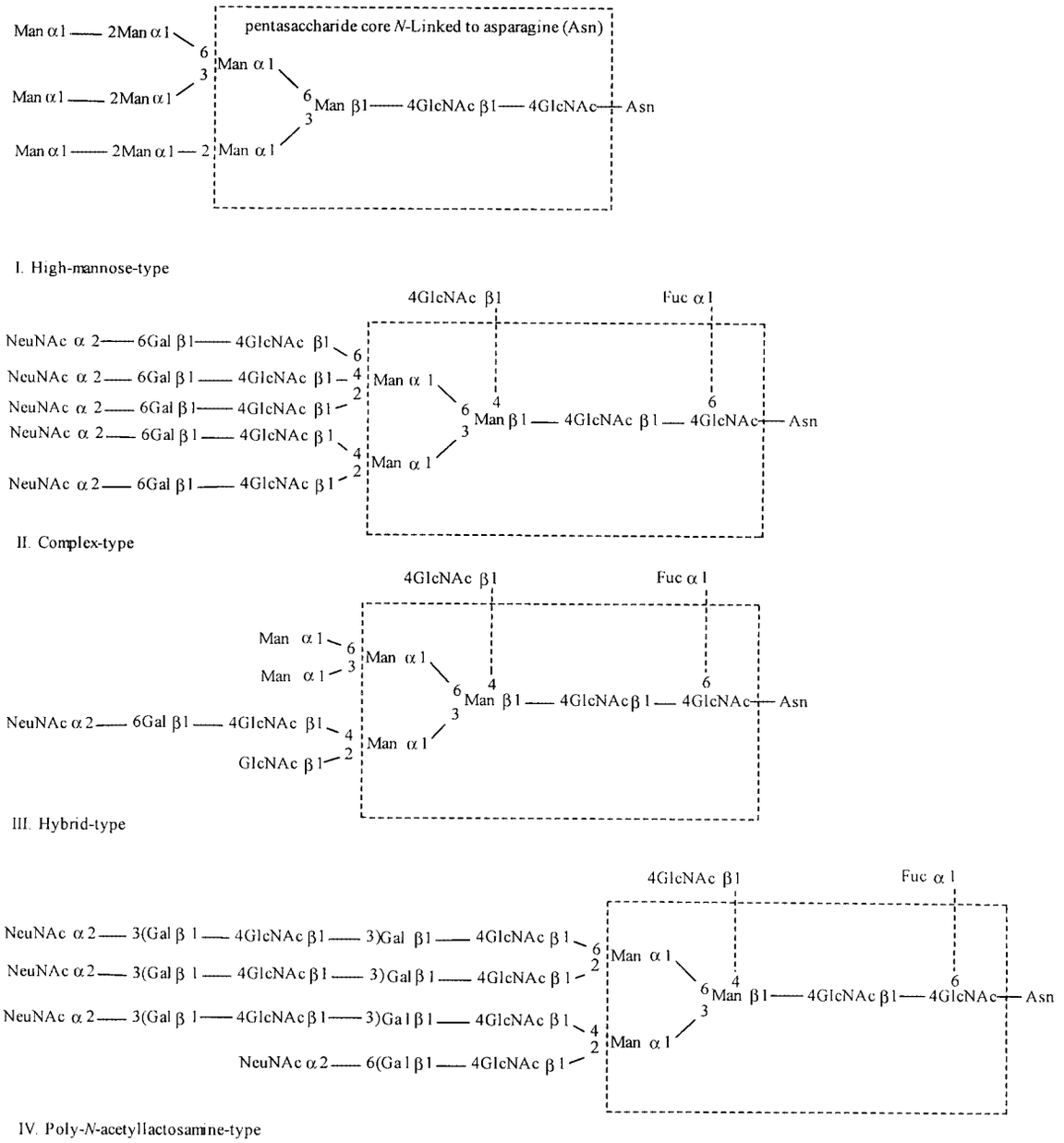
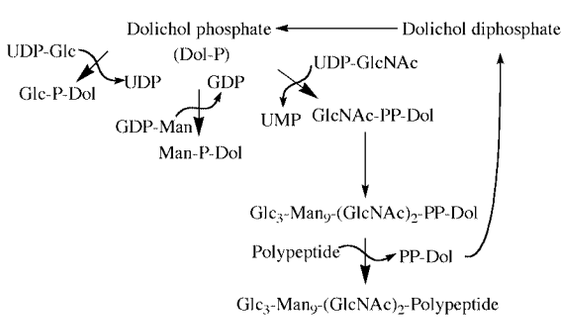


Fig. 1 Pentasaccharide core and antennae regions.

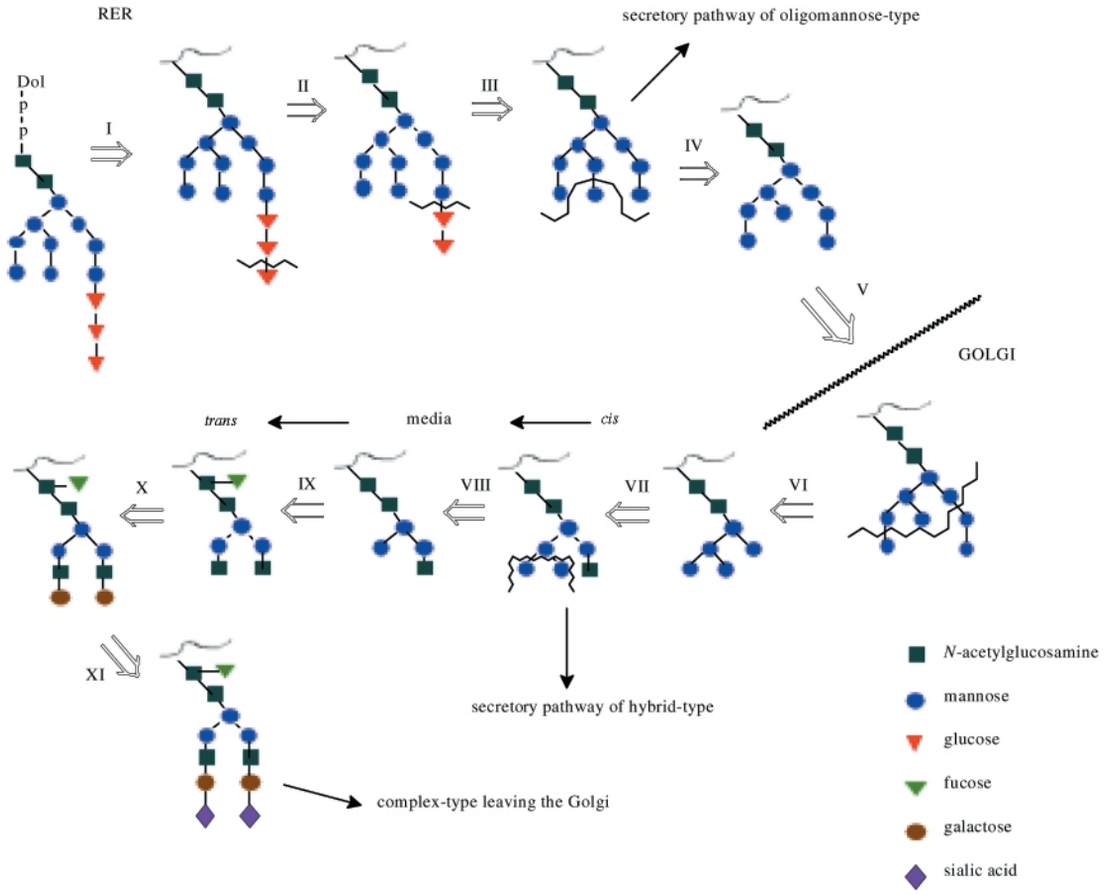
chains none of which contains mannose sugars. They are attached to a trimannose core through the reducing end of *N*-acetylglucosamine. The complex-type show the greatest diversity, this is seen in the number of chains, the variation of chain length, the presence or absence of a fucose residue and a "bisecting" GlcNAc residue, attached directly to the core region. The hybrid-type show characteristic features of both high mannose-type and complex-type glycans. Finally, the poly-*N*-acetyllactosamine *N*-glycans contain the repeating unit Gal(β1-4)GlcNAc(β1-3) in varying amounts, and may also be branched.



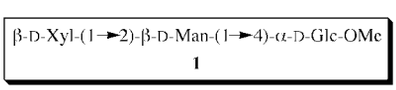
Scheme 1 Biosynthesis of dolichol-linked glycal precursor.

1.1.1.2 Origin and biosynthesis

The *N*-linked glycoproteins originate from the biosynthetic precursor dolichol phosphate linked glycal (Glc_3-Man_9-$(GlcNAc)_2$-PP-Dol). The enzyme-mediated assembly of this precursor occurs in the endoplasmic reticulum (ER) and is a stepwise process. The first seven sugars originate from nucleotide sugar units UDP-GlcNAc and GDP-Man. The next seven sugars are from the lipid linked intermediates, Dol-P-Man and Dol-P-Glc (from GDP-Man and UDP-Glc respectively), the general process[8b,9] is shown in Scheme 1. Once the lipid-donor reaches the rough endoplasmic reticulum (RER) the glycal can be transferred to the amide nitrogen of a specifically located asparagine unit (specifically when found in the peptide sequence Asn-Xxx-Ser/Thr, where Xxx can be any amino acid, although proline is unfavourable) in the protein backbone. This process is described as a co-translational modification, which is mediated by the enzyme oligosaccharyltransferase (OT). Next, a sequence of enzyme mediated events takes place that shapes the *N*-linked glycoprotein's development and contrives to give the numerous glycoforms. A number of factors, including, the cell, its internal and external environment, its origin, its devel-



Scheme 2 Oligosaccharide processing through the RER and Golgi in the development of *N*-linked glycoproteins. The whole process is catalysed by a number of enzymes: I. oligosaccharyltransferase, II. α-glucosidase 1, III. α-glucosidase 2, IV. ER α-1,2-mannosidase, V. transfer to Golgi, VI. Golgi α-mannosidase 1, VII. UDP-*N*-acetylglucosamine in the presence of *N*-acetylglucosaminyltransferase 1, VIII. Golgi α-mannosidase II, IX. UDP-*N*-acetylglucosamine in the presence of *N*-acetylglucosaminyltransferase 2 and GDP-fucose in the presence of fucosyltransferase, X. UDP-galactose in the presence of galactosyltransferase, XI. CMP-sialic acid in the presence of sialyltransferase.



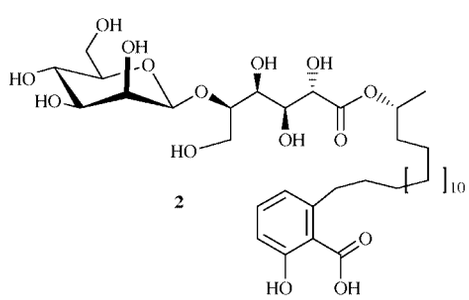
1

Fig. 2 Trisaccharide oligomer of glycosphingolipids of *Hyriopsis schlegelii*.

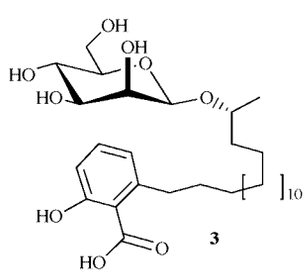
opment state, and its health (disease state) influence these events. Also, the specific order that the enzymes act on the glycoconjugate, the competing pathways (secretory pathway) and the 3D structure of the protein, all affect the biosynthesis of the *N*-linked glycoproteins.[5d,8b] The general development is described pictorially in Scheme 2.

1.1.2 Other natural sources of β-mannosides

There are a number of natural sources of β-linked mannosides outside of the *N*-linked glycoproteins and these have recently received attention from synthetic[10,11] and structural elucidation[12a–e] points of view. For example, trisaccharide **1** (Fig. 2) is a key component of the *Hyriopsis schlegelii* glycosphingolipid,[13a,b] recently synthesised by two groups.[14a–c] The fungal metabolite deacetyl-caloporoside **2** (Fig. 3) is a novel inhibitor of the $GABA_A$ receptor ion channel. Its mode of action and synthesis have received a great deal of attention from Tatsuta and Yasuda who reported its first total synthesis.[15] Similarly the salicylic acid derivative **3** (Fig. 3) is also an inhibitor of the $GABA_A$ receptor ion channel. Following its isolation in 1994, it was then synthesised by Fürstner *et al.*[16] Synthesis of the prodigious structure of Everninomicin 13,384-1, **4**, poses a great challenge (Fig. 4). It contains a β-linked mannose sugar (ring F) and the disaccharide unit FG was recently synthesised by Nicolaou *et al.*[17] The Everninomicins are a group of



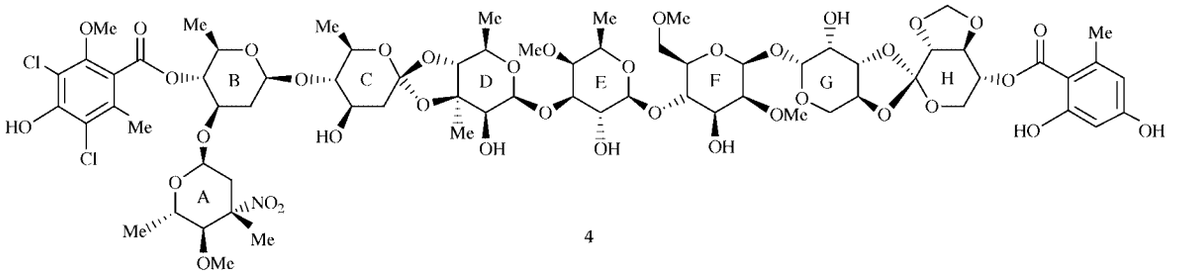
2



3

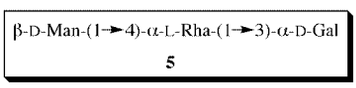
Fig. 3 Fungal metabolites **2** and **3** with $GABA_A$ ion channel receptor inhibiting properties.

complex carbohydrate antibiotics, which are active against a number of resistant Gram positive bacteria including the methicillin resistant *Staphylococci* and vancomycin resistant *Enterococci*. The bacterial *O-antigen* repeating unit **5** (Fig. 5) of *Salmonella* serogroup E_1 is a trisaccharide unit containing a β-(1-4)-mannose sugar linked to an L-rhamnose unit. It is an *O*-polysaccharide that is part of a family of *Salmonella* serogroups and its particular glycal region has recently been

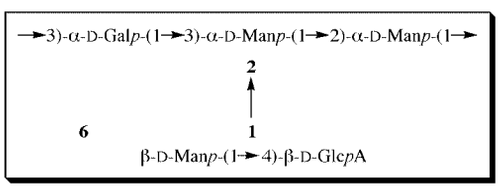


4

Fig. 4 Everninomicin 13,384-1.



I. Trisaccharide repeating unit of *Salmonella* serogroup E_1.



II. Repeating unit of the capsular polysaccharide from *Klebsiella* type 43.

Fig. 5

synthesised by chemoenzymatic methods.[18a,b] Finally, the β-mannose unit can be found in a number of serotypes of the capsular polysaccharides *Klebsiella*. Roy and co-workers[19] have recently published the synthesis of the disaccharide and trisaccharide units that make up the repeating pentasaccharide unit **6** of serotype 43 (Fig. 5).

1.2 Natural occurrence of β-mannosamines

The β-ManNAc unit is an integral part of a number of bacterial capsular polysaccharides and lipopolysaccharides. The synthesis[11] and structural determination[20a–e] of polysaccharides containing this unit is widespread in recent literature.

1.2.1 Capsular polysaccharides

Towards the beginning of the century the immunogenic properties of capsular polysaccharides were realised and put to use in human vaccines[21] in the form of whole cell preparations. As early as 1923 it was demonstrated that the capsular polysaccharides display type-specific immunogenic character. Since then the chemical structure and immunological properties of a multitude of bacterial species have become well known and this has been put to use in multivalent human vaccines.[21,22] The capsular polysaccharides are seen as the principle antigens in the majority of Gram positive and negative organisms. Their location on the outer surface of organisms implicates them in the stimulation of the human immune system against the invading organisms.[21] The Gram positive organisms *Nesseria meningitidis* and *Haemophilus influenzae* are responsible for several types of meningitis, one of the most serious is *Haemophilus influenzae* type b, for which the latest conjugate vaccines have proven successful in preventing disease in children.[23] The occurrence of the β-ManNAc unit in the capsular polysaccharide of *Haemophilus influenzae* is limited to serotypes d and e. However, it is far more prevalent in the capsular polysaccharides of the Gram positive organisms of *Streptococcus pneumoniae*. The *Streptococcus pneumoniae* organism is responsible for lower tract respiratory infection in adults and middle ear infection in children. There are 85 known serotypes of pneumococcal polysaccharides, 14 of which have been regularly used in multivalent vaccines in the fight against pneumonia. The use of only 14 serotypes comes from the cross-reactivity and cross-immunity[24a,b] shown by a number of serotypes, in which there is structural homology.[21] The serotypes most apparent in recent literature (from a synthetic and structural investigative aspect) are those of type 19A, B, C and F. Type 19F is a repeating trisaccharide (Fig. 6) which has recently been synthesised by Kaji *et al.*,[25] Nilsson and Norberg[23] and Russo and co-workers.[26]

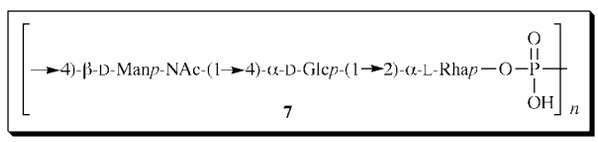


Fig. 6 The repeating unit of *Streptococcus pneumoniae* 19F polysaccharide.

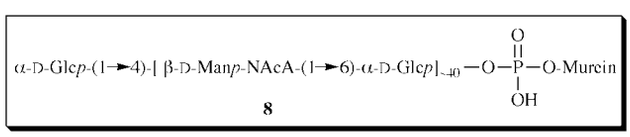


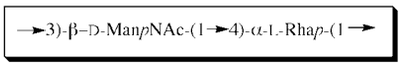
Fig. 7 The repeating unit of teichuronic acid, an acidic polysaccharide bound through a phosphoric diester linkage to murein.

1.2.2 Lipopolysaccharides

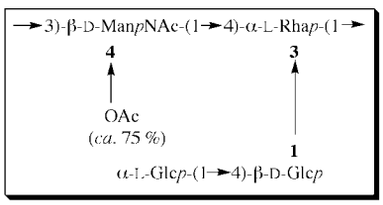
Apart from the capsular polysaccharides the most apparent source of the β-ManNAc unit is in naturally occurring lipopolysaccharides.[20a] Synthetic endeavours towards artificial glycolipids containing a β-D-mannuranic acid moiety can be found in the synthesis of teichuronic acid.[27a,b] This is a disaccharide repeating unit of an acidic polysaccharide constituent of the cell wall of a number of Gram positive bacteria. In *Micrococcus luteus* it is bound *via* a phosphoric diester linkage to a peptidoglycan, murein, **8** (Fig. 7). The *O*-antigens of several lipopolysaccharides are known for a number of Gram negative bacteria. *Pseudomonas cepacia* O5, *Pseudomonas aeruginosa* X and *Aeromonas salmonicida* all contain the ManNAc(β1-4)-L-Rha disaccharide unit, whereas *Escherichia coli* O1A contains the ManNAc(β1-2)-L-Rha disaccharide (Fig. 8).[28]

2 Synthetic approaches to β-mannosides and β-mannosamines

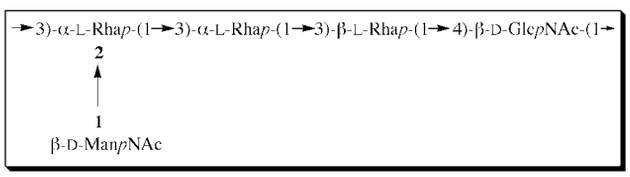
To date there has been an enormous amount of creative endeavour towards the synthesis of β-mannose and β-mannosamine linkages. Their synthesis poses one of the greatest challenges to the carbohydrate chemist. Despite all of the past examples in the literature no single universal method for the synthesis of these linkages exists. Previous attempts towards the synthesis of the β-mannose linkage have been well reviewed by Barresi and Hindsgaul,[10] Paulsen,[29a,b] Veeneman,[30] Kaji and Lichtenthaler[11] and others.[31a–f] The synthesis of the β-mannosamine linkage has been investigated to a lesser extent, and has recently been reviewed by Kaji and Lichtenthaler,[11] Veeneman[32] and Banoub.[31a] The difficulties in constructing these ubiquitous



I. *Pseudomonas cepacia* O5 *and Pseudomonas aeruginosa X* (Meitert).



II. *Aeromonas salmonicida*.

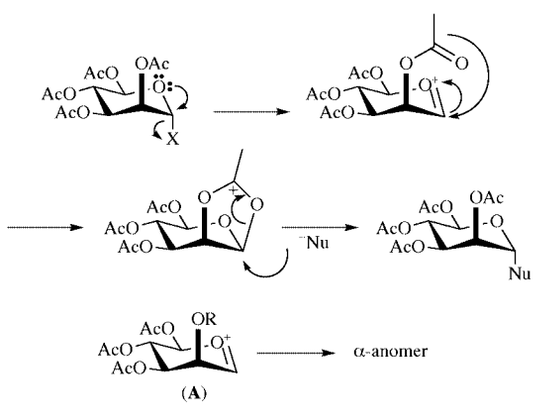


III. *Escherichia coli* O1A.

Fig. 8

linkages have been well documented in a number of the aforementioned reviews; but to summarise:

1. The location of an axial acyl protecting group at C-2 in mannose that can participate in the glycosidation reaction (neighbouring group participation) leads predominately to the α-mannosides (Scheme 3); this is opposite to glucose for which the equatorial acyl group participates to give predominantly the β-glucoside product.



Scheme 3 Neighbouring group participation in mannose sugars and oxonium ion (**A**) both deliever the α-anomer.

2. The anomeric effect in pyranosides can be seen as the propensity of an electronegative substituent to adopt an axial orientation. The axial conformer is stabilised by the $\pi \rightarrow \sigma^*$ interaction of the axial orientated lone pair of electrons of ring oxygen, with the antibonding orbital of the anomeric carbon bonded to an electronegative group. This therefore favours the α-mannoside and not the β-mannoside.[33]

Thus α-mannosides are thermodynamically and kinetically favoured, and are the major product when the oxonium ion **A** is an intermediate in the glycosidation reaction (Scheme 3).

The methodologies developed to date to overcome these problems and allow the synthesis of β-linked mannose and mannosamines units have shown varying degrees of success. They can be divided into several groups, some of which show overlap in their strategies:

1. Koenigs–Knorr coupling methods. Glycosidation using insoluble silver salt promoters to block the α-face of mannosyl halides and direct glycosidation to give β-linked mannose units.
2. Deprotection, oxidation and subsequent reduction of the C-2-OH of β-linked glucopyranosides, effecting epimerisation at C-2.
3. Utility of 2-oxo and 2-oximinoglycosyl halides.
4. Utility of intermolecular or intramolecular S_N2 reactions to facilitate displacement of a good leaving group at C-2 in β-linked glucopyranosides, effecting epimerisation at C-2.
5. Intramolecular aglycon delivery (IAD), including the first ever use of polymer supports to synthesise β-mannose linkages.
6. S_N2 displacement, with inversion of configuration of α-mannosyl triflate donors.
7. Application of β-mannosidases and immobilised recombinant β-mannosyltransferases.
8. Anomeric radical hydrogen abstraction giving rise to equatorial glycosides.
9. Dibutylstannylene complexes, involving locked anomeric configurations.
10. Utility of mannosyl fluoride donors.

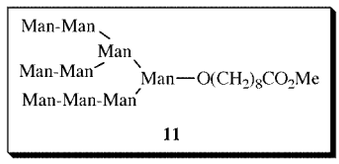
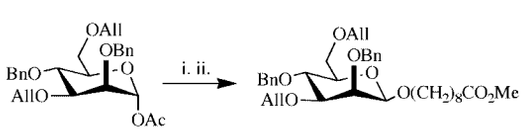


Fig. 9

Less successful methods also documented in the literature include the use of reductive cleavage of mannosyl anomeric orthoesters,[34a,b] bulky mannosyl donors,[15] peptide templates,[35] dimethylphosphinothioate[36]/phosphite[37] donors, and the use of α-mercaptopyrimidine mannosyl[38] donors.

2.1 Koenigs–Knorr coupling methods

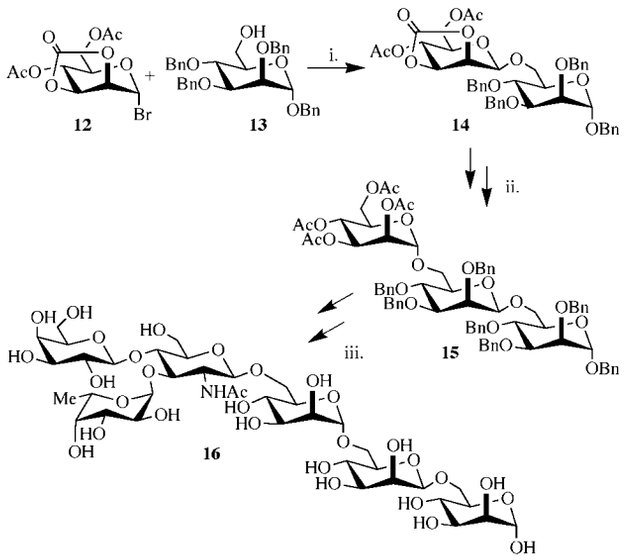
Previous β-mannoside formation using traditional and modified silver salts, has been well reviewed.[10,11] Ley and co-workers showed the direct coupling of an α-mannopyranosyl bromide **9** with a long chain alcohol, using silver silicate coupling over 3 days, to afford the β-anomer **10** in 79% yield (Scheme 4).[39] The β-mannosylation reaction is a key step prior to elaboration of the monosaccharide to afford a high mannose oligosaccharide **11**, of use for biological interaction studies. This example shows the best and the worst attributes of the Koenigs–Knorr mediated direct mannosylation reaction, that is, the reaction is slow, but excellent β-selectivity and good yields are obtained. High selectivity is generally only obtained with simple, reactive alcohol acceptors. For example, Ogawa and co-workers used silver silicate–alumina to couple an α-bromo mannoside with a 4-OH GlcNAc acceptor.[40] The anomeric ratio attained was poor at 8 : 7 in favour of the β-anomer, but the overall yield was an excellent 72%. The disaccharide was elaborated to afford the pentasaccharide core of the *N*-linked glycoproteins with three amino acid residues, Asp-Val-Thr.



Scheme 4 *Reagents and conditions*: i. $TiBr_4$, DCM, 3 h. ii. Ag-silicate, $HO(CH_2)_8CO_2Me$, 4 Å MS, 3 days, −40 to 0 °C, 79%.

However, Matta and co-workers have shown β-selective AgO mediated coupling of the α-bromo (C-2, C-3 cyclic carbonate) mannose derivative **12**, with the C-6-OH acceptor **13**, in a 78% yield.[41] Disaccharide **14** was then manipulated to give a free

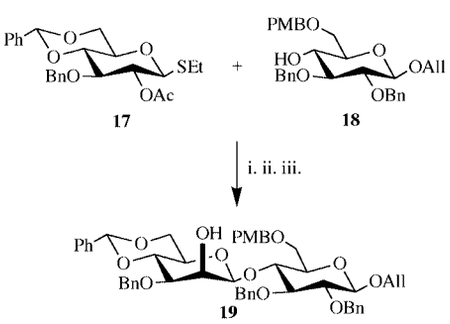
hydroxy at C-6 of the mannose unit, which was then coupled to a second mannose unit through an α-linkage using NIS–TfOH methodology. The Lewis^x determinant was coupled to the trimannose unit **15** with α-selectivity through the 6-position of the terminal mannose sugar, using NIS–TfOH. The hexasaccharide oligomer **16**, which contains the Lewis^x determinant can be envisaged as being useful in experiments to raise specific antibodies, which could then be used against tumour cells that possess the Lewis^x containing glycoprotein (Scheme 5).



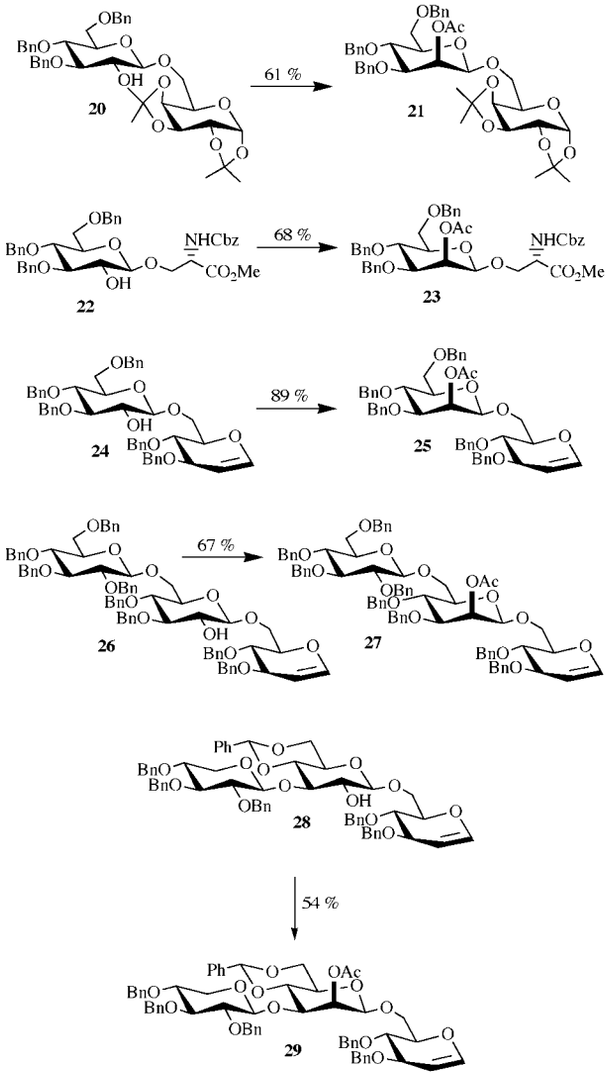
Scheme 5 *Reagents and conditions*: i. AgO, $CHCl_3$, 78%. ii. Elaboration through C-6. iii. Coupling of Lewis^x determinant, then global deprotection.

2.2 Deprotection, oxidation, and subsequent reduction of β-linked glucopyranosides

The trisaccharide unit β-D-Xyl(1-2)β-D-Man(1-4)GlcNPhth has been synthesised by Kerékgyárto *et al.*[42] Silver triflate was used to mediate the coupling of two glucose units, followed by the deprotection, oxidation and reduction of a C-2-OH of one of the glucose units. The reduction was effected with $NaBH_4$ in a solution of 2:1 propan-2-ol–dichloromethane, with a ratio of 7:3 in favour of the β-mannoside and overall yield of 91%. The β-selective coupling of a xylose residue was achieved once again using silver triflate in good yield. The synthesis of the β-mannoside disaccharide unit of *Klebsiella* type 43 (Fig. 5) was accomplished by Roy and co-workers,[19] utilising NIS–TfOH to couple glucopyranoside units **17** and **18** in 72% yield, followed by the three step protocol, as above, to give disaccharide **19** (Scheme 6). The three-step transformation was achieved in a very respectable 59% yield and **19** was then converted to the disaccharide unit highlighted in Fig. 5. Unlike the previous example, reduction with $NaBH_4$ was stereoselective and only the mannoside product was detected.

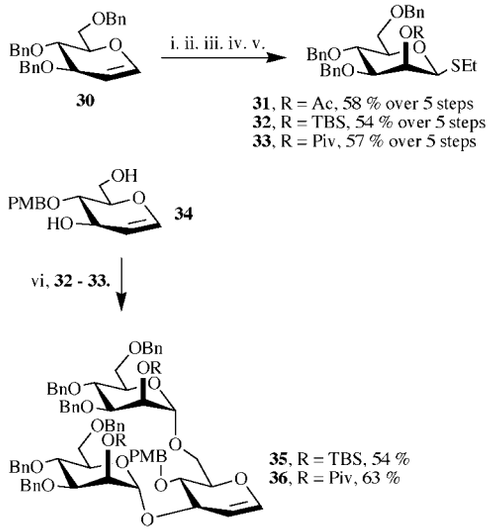


Scheme 6 *Reagents and conditions*: i. NIS, TfOH, MS, 4 Å MS, DCM, −25 °C, 72%. ii. NaOMe, MeOH, 95%. iii. DMSO, Ac_2O, 16 h, then $NaBH_4$, 5–10 °C, 5 h, 62% over two steps.



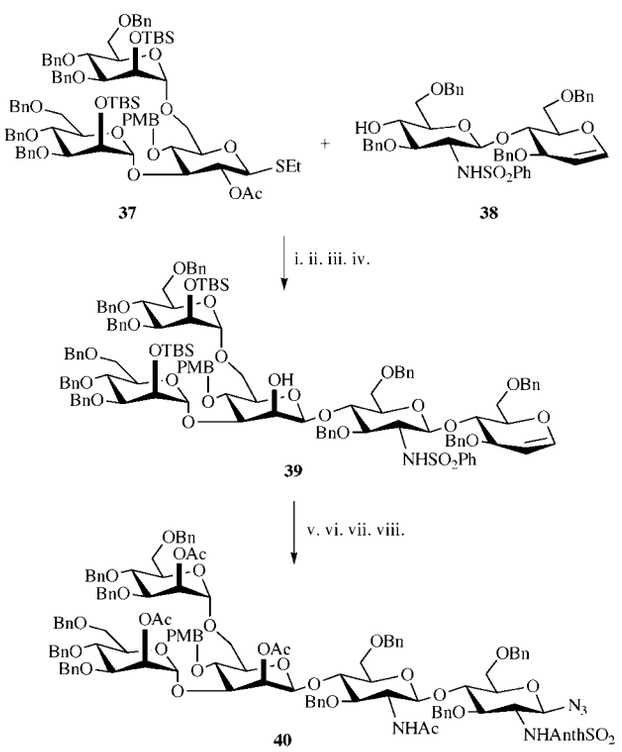
Scheme 7 *Reagents and conditions*: In each case, [O] then [H] then acetylation; i. DMSO, Ac_2O. ii. $NaBH_4$, DCM–MeOH. iii. Ac_2O.

Glycal chemistry has proved to be very useful in the synthesis of β-mannosides.[31b] The main protagonists in this area are Danishefsky, Liu, Seeberger and co-workers, who have developed an epoxidation, nucleophilic attack, oxidation, and reduction methodology.[43,44] Liu and Danishefsky showed that β-(1-6)-mannosidic linkages could be formed in reasonable yield, for a range of systems including hindered trisaccharide systems (Scheme 7). The method is only limited by the extent of branching that can be tolerated at the central glucose unit. A highly convergent glycal approach to the synthesis of a high mannose containing pentasaccharide core is illustrated below.[44] The synthesis of the thioethyl donor units **31**, **32** and **33** from readily available **30**, in respectable yield over five steps, is shown in Scheme 8. Dimannosylation of acceptor **34** with donors **32** and **33** is more practical than for **31** since the acetate derivative produces a large proportion of the orthoester. The trisaccharide unit **35** was used to synthesise the thioethyl donor **37**, since the selective removal of the TBS groups would allow for further elongation of the oligosaccharide domain. Coupling with a glycal chitobiose precursor **38**, followed by removal of the acetate at C-2, Dess–Martin oxidation and stereoselective reduction with L-Selectride afforded the β-mannoside **39** (in 71% over 3 steps) at the centre of a pentasaccharide oligomer unit. This result is exceptional, when the complex setting in which the key transformation to the β-mannoside takes place is considered, compared to recent literature, where the reduction surroundings are less complex.[10,11,42] Following exchange of protecting groups, the pentasaccharide was manipulated at the



Scheme 8 *Reagents and conditions*: i. DMDO. ii. EtSH, Cat. TFAA. iii. DMSO, Ac_2O, 72 h. iv. $NaBH_4$, MeOH. v. Ac_2O, pyridine, DMAP (**31**) or TBSOTf, Et_3N (**32**) or PivCl, DMAP (**33**). vi. MeOTf, 4 Å MS, DTBMP.

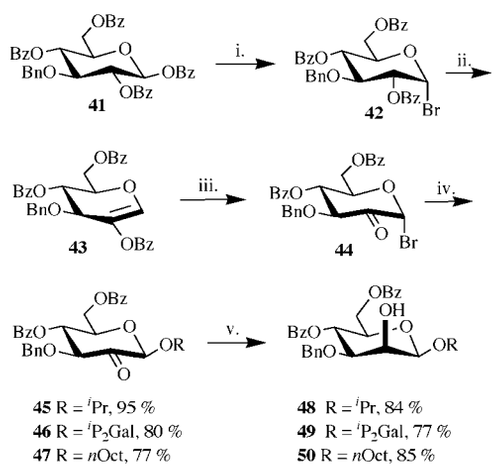
terminal glycal to give a terminal protected glucosamine unit **40**. The pentasaccharide system was now ready for coupling to an asparagine peptide (Scheme 9).



Scheme 9 *Reagents and conditions*: i. MeOTf, DTBP, 4 Å MS, 64%. ii. $LiAlH_4$, 86%. iii. Dess–Martin [O]. iv. L-Selectride, 83% over two steps. v. TBAF, 69%. vi. Ac_2O, Et_3N, 80%. vii. Na, naphthalene, 78%. viii. $I(coll)_2ClO_4$, anthracenesulfonamide, 4 Å MS, then $TBAN_3$, 67% over two steps.

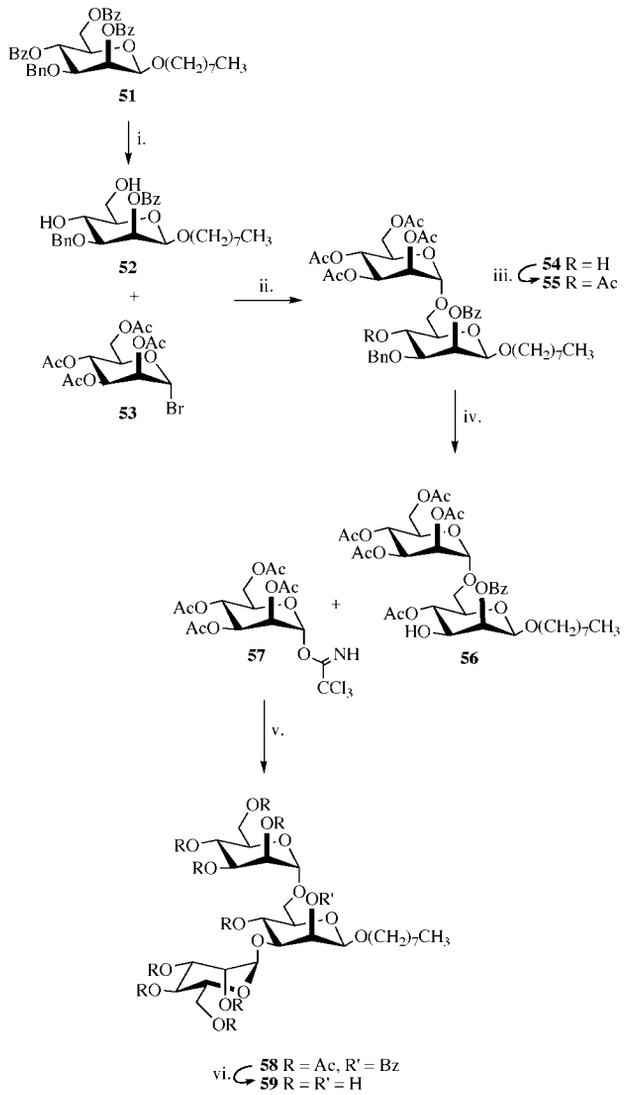
2.3 Utility of 2-oxo- and 2-oximinoglycosyl halides

Combination of strategies **2.1** and **2.2** has given risen to the use of 2-oxo-[10,11] and 2-oximinoglycosyl halides[11] as synthetic intermediates for constructing β-mannopyranoside and β-mannosamine linkages respectively. α-Ulosyl bromides react *via* an S_N2-type reaction under the Koenigs–Knorr conditions to afford β-linked units.[10] The S_N2 mechanism is attributed to the electron withdrawing effect of the 2-keto group and is aided by the co-ordination of silver salts, allowing the acceptor to access only the β-face. For example, ulosyl bromide **44** can be attained in six steps from diacetone-glucose *via* the glucopyranoside **41** in 49% overall yield. It is also sufficiently reactive to couple in high yield and with β-selectivity with reactive primary and secondary alcohols (Scheme 10). The reduction of the resultant β-linked ulose sugars with sodium borohydride is highly stereoselective (>20 : 1) when the substituent at C-3 is a benzyl group.[45] However, the protecting groups around the ulose sugar have a great influence on the stereoselectivity of the reduction. If the protecting group at C-3 is electron withdrawing, the selectivity of the reduction is greatly reduced; *e.g.* with C-3-*O*-pivaloyl (C-3-*O*-Piv), reduction affords β-linked Man : Glc in a ratio of 5 : 2. Mannoside **50** was benzoylated to afford **51** which was selectively debenzoylated to afford **52** and coupled with α-bromo mannoside **53** to give disaccharide **54**, in 73% yield over three steps. Acetylation of **54** was followed by debenzylation and coupling with the trichloroacetimidate donor **57** to afford trimannoside **58** (Scheme 11). Finally, global deacetylation gave trisaccharide **59** in 28% yield over four steps, thus showing the applicability of the ulosyl bromide method for constructing branched β-mannosides.[46] Lichtenthaler *et al.* have used ulosyl bromide donors for the synthesis of naturally occurring oligosaccharides, and this has allowed efficient synthesis of **1**, a trisaccharide component of the *Hyriopsis schlegelii* glycospingolipid, in 47% yield over four steps from 3,4,6-tri-*O*-benzyl-α-D-*arabino*-hexosyl bromide (Fig. 2).[14a] Fürstner *et al.* have also shown this approach to be very effective in the synthesis of the fungal metabolite **3** (Fig. 5), from 3,4,6-tri-*O*-benzyl-α-D-*arabino*-hexosyl bromide, in 59% yield over four steps.[16]

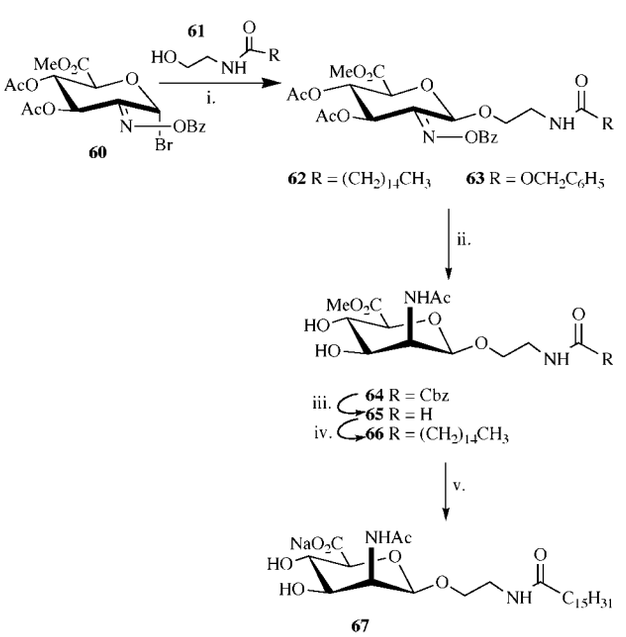


Scheme 10 *Reagents and conditions*: i. HBr. ii. DBU, 80% over two steps. iii. NBS, 96%. iv. ROH, Ag_2CO_3. v. $NaBH_4$. ^iP_2Gal = 1,2 : 3,4-diacetone-galactose.

In a similar fashion the 2-oximinoglycosyl halides have been shown to be effective for the synthesis of β-mannosamine derivatives. For example, donor **60** was synthesised in 21% yield over six steps from D-glucuronolactone and was shown to couple *N*-blocked 2-aminoethanols **61** in a β-selective manner using an insoluble salt promoter. When silver–aluminosilicate was used the reaction time was decreased to an acceptable two hours (Scheme 12, Table 1), with a reaction yield of 71% and high selectivity (20 : 1 in favour of β-anomer). The stereoselective reduction of oxime **63** was achieved in 56% yield to give the β-mannosamine **64**, whereas the reduction of **62** gave a complex mixture of unidentified products. This problem was overcome by manipulation of **64** to give the *N*-protected glycolipid with a longer aliphatic chain, subsequent saponification gave the required product **67** (Scheme 12).[27a] Similarly, Kaji and co-workers attached a second sugar unit to **60** *via* a (1-6)-linkage before carrying out the stereoselective reduction of the oxime to give β-mannosamine **70** in 74% yield, over two steps. Two *N*-blocked 2-aminoethanols **61** of differing length were



Scheme 11 *Reagents and conditions*: i. NaOMe, 96%. ii. $HgBr_2$, 86%. iii. Ac_2O, 53%. iv. H_2, Pd/C, 86%. v. TMSOTf, 73%. vi. NaOMe, 84%.



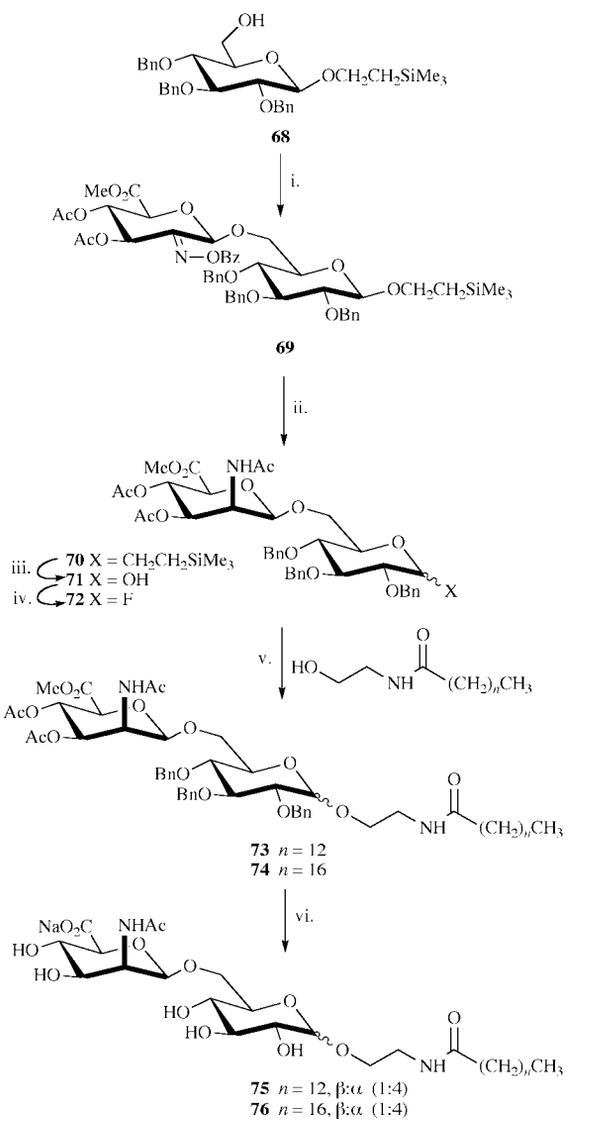
Scheme 12 *Reagents and conditions*: i. Promoter, DCM, 25 °C. ii. BH_3·THF, then Ac_2O, 56%. iii. MeOH, *p*-TsOH, H_2, Pd/C, 100%. iv. DMF, palmitic acid, *N*,*N*′-carbonyldiimidazole, TEA, 20 h, 57%. v. Saponification, 76%.

Table 1 Reaction of **60** with **61** (see Scheme 12)

Acceptor **61**, R	Promoter	*t*/h	Yield (%)	β : α ratio[a]
$(CH_2)_{14}CH_3$	Ag_2CO_3–I_2	48	30	20 : 1
$(CH_2)_{14}CH_3$	AgOTf–TMU[b]	24	47	2 : 1
$OCH_2C_6H_5$	Ag_2CO_3–I_2	48	60	20 : 1
$OCH_2C_6H_5$	Ag_2–aluminosilicate	2	71	20 : 1

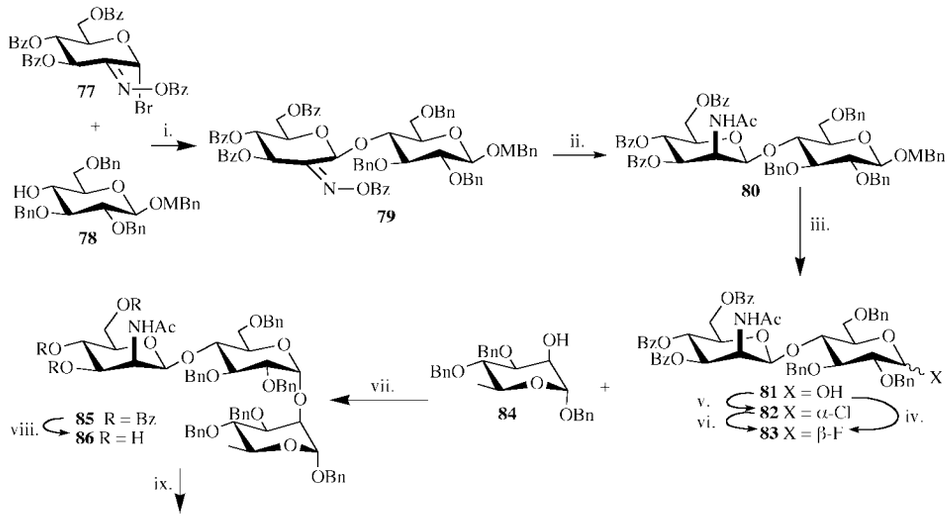
[a] Determined by ^{1}H-NMR of the reaction mixture. [b] 1,1,3,3-Tetramethylurea.

then coupled *via* the glucopyranoside unit to give **73** and **74**, both as anomeric mixtures (4 : 1 α : β). Saponification gave the required *N*-protected teichuronic acids (artificial glycolipids) **75** and **76** (Scheme 13). If active against immunological systems, monosaccharides and oligosaccharides containing the antigenic determinate teichuronic acid could have important roles to play as recognition markers in drug delivery systems (Fig. 7).[27a,b]



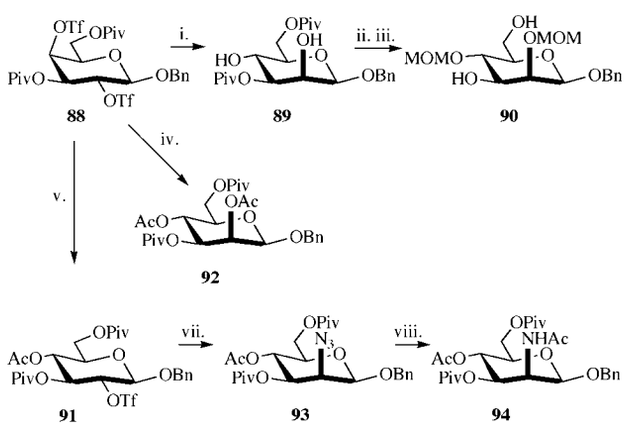
Scheme 13 *Reagents and conditions*: i. **60**, Ag–aluminosilicate, DCM, 2 h, 25 °C, 88%. ii. BH_3·THF, then Ac_2O, 84%. iii. CF_3CO_2H, 83%. iv. DAST, 98%. v. $n = 12$, promoter = $ZnCl_2$–$AgClO_4$, 62%. $n = 16$, promoter = Cp_2ZrCl_2–$AgClO_4$, 64%. vi. H_2, Pd/C, then saponification, $n = 12$, 79%, $n = 16$, 86%.

An important unit found within the antennae region of *N*-linked glycoproteins is the lactosamine unit. Kaji *et al*. have demonstrated an efficient preparation of benzoylated lactos-2-oximino bromide donors for the synthesis of Gal(β1-4)-



Scheme 14 *Reagents and conditions*: i. Ag_2CO_3–Ag, zeolite, 85%. ii. BH_3·THF, then Ac_2O, 69%. iii. DDQ, 44% (~20% recovery of **80**, 55%). iv. DAST, 72%. v. $SOCl_2$, DMF, 100%. vi. Ag–MeCN, 77%. vii. $AgClO_4$–$SnCl_4$, 51%. viii. NaOMe, 89%. ix. H_2, Pd/C, 94%.

GlcNAc(α1-OR) and more importantly Gal(β1-4)ManNAc-(β1-OR) saccharides.[47] The trisaccharide repeating unit of *Streptococcus pneumoniae* serotype 19F of the capsular polysaccharides has been synthesised using the synthetically accessible donor **77** (59% in 6 steps from D-glucose) and acceptor **78** (32% in 5 steps from acetobromo-α-D-glucose) (Fig. 6, Scheme 14). Kaji *et al.*[25] achieved β-selective glycosidation in 85% yield using $AgCO_3$–Ag-zeolite as promoters over 48 hours. Faster reaction times were observed with a different silver promoter but the yield was lower. The stereoselective reduction of oxime **79** was achieved in 69% yield to give the β-mannosamine disaccharide **80** in an overall yield of 35% based on the synthesis of **77** from D-glucose. Coupling of an L-rhamnose moiety through the anomeric centre of the glucopyranoside unit, with α-stereochemistry, followed by removal of the protecting groups gave trisaccharide **87** (6% over 14 steps, Scheme 14). Kaji *et al.* have also shown that the methodology is applicable to the synthesis of a number of other β-mannosamine linkages, particularly those found in the immunogenic determinants of *O*-antigens of lipopolysaccharides (Fig. 8). In a similar manner to that described above, but with much reduced glycosidation reaction times, the construction of ManNAc(β1-4)-L-Rha (13% overall yield from **77**), ManNAc(β1-3)-L-Rha (23% overall yield from **77**) and ManNAc(β1-3)-L-Rha (17% overall yield from iodide derivative of **77**) linkages has been possible.[28] A milder alternative reduction method for simple 2-oximinomonosaccharides has been presented by Banaszek *et al.*, using $LiBH_4$–Me_3SiCl.[48] The high yielding preparation of propen-2-yl 2-oxo and 2-oximino β-*C*-glycosides, followed by their stereoselective reduction to afford β-mannopyranoside and β-mannosamine derivatives respectively has recently been disclosed by Nicotra and co-workers.[49] These simple monosaccharides are of great pharmaceutical interest as potential inhibitors of biological processes.

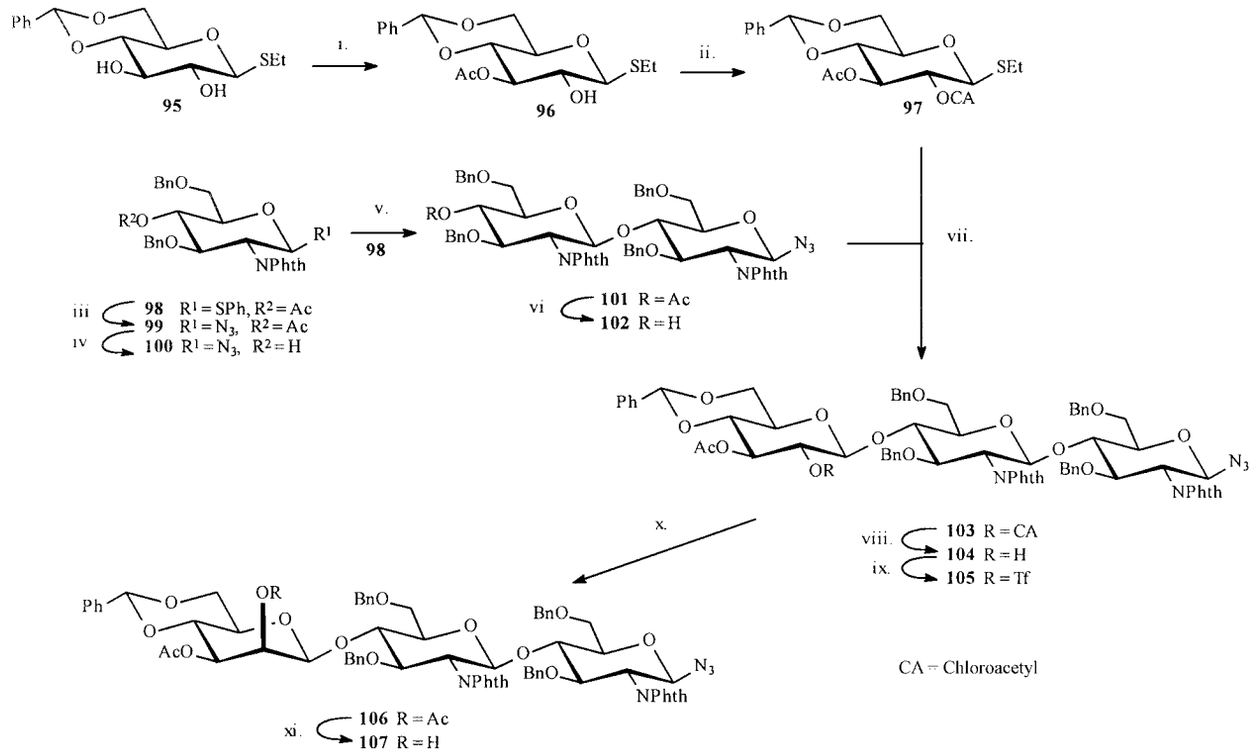


Scheme 15 *Reagents and conditions*: i. $CsOCOCF_3$, 18-crown-6, toluene, DMF, reflux, then aq. $NaHCO_3$, MeOH, 76%. ii. $CH_2(OMe)_2$, P_2O_5, DCE, 93%. iii. NaOMe, MeOH, 100%. iv. $CsOCOCF_3$, reflux, 94%. v. CsOAc, 18-crown-6, toluene, rt, 84%. vi. CsOAc, 18-crown-6, toluene, ultrasonication, 94%. vii. Bu_4NN_3, benzene, ultrasonication, 91%. viii. 5% Pd/C, benzene, then Ac_2O, 88%.

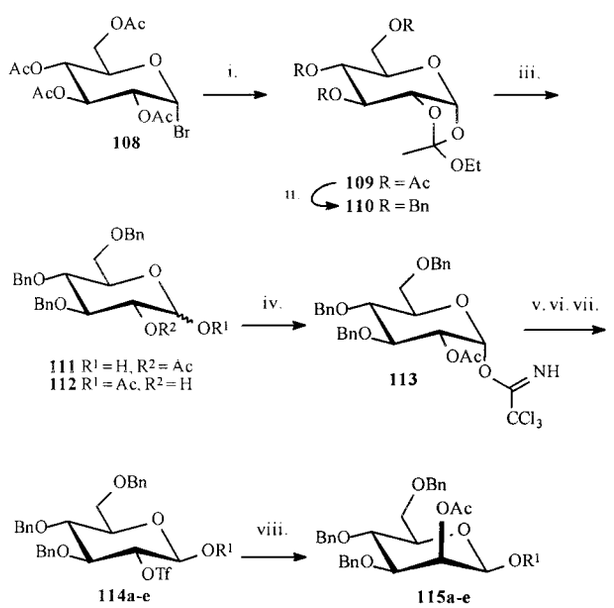
2.4 Utility of intermolecular or intramolecular S_N2 reactions

2.4.1 Intermolecular S_N2 reactions

The work of Sato *et al.* follows the innovative work by Miljkovic *et al.* and Davids *et al.*[10] Sato employed caesium acetate (CsOAc) to displace an equatorial triflate at C-2 in a β-glycopyranoside to afford the corresponding β-mannopyranoside. This methodology has been further exploited to install an axial azide group at C-2, thus giving rise to precursors to β-mannosamine units. The yields reported compare favourably to the pioneering work by Miljkovic *et al.* and Davids *et al.* (Scheme 15).[50a,b] Ajisaka and co-workers successfully synthesised the chitobiose containing core trisaccharide of the *N*-linked glycoproteins in a high yielding convergent manner.[51] The synthesis was based upon the β-selective coupling of three monosaccharides **97**, **98** and **100**, using NIS–TfOH. In each case neighbouring group participation of the C-2-Phth of the donor led to β-selective glycosidation in high yield. The key β-mannoside forming step was achieved by deprotection of a C-2-chloroacetate and conversion to the triflate species **105**. In a similar manner to Sato, using CsOAc, axial delivery of an acetate nucleophile was mediated by 18-crown-6 in toluene under sonication conditions, affording **106** in 80% yield over the three steps (Scheme 16). Ultrasound has been used by a number of groups to overcome unfavourable stereoelectronic interaction with the axially orientated lone pair of the ring oxygen. Consequently, improved yields in the S_N2 inversion reaction at C-2 have been observed. Fürstner *et al.* have coupled an armed trichloroacetimidate donor under catalytic Lewis acid conditions with reactive and sterically hindered acceptors to stereoselectively afford β-glucopyranosides (Scheme 17 and Table 2). The C-2-OAc derivatives were converted to C-2 triflates **114a**–**e**, which were treated with *n*-Bu_4NOAc in toluene under sonication conditions, to afford β-mannosides **115a**–**e** in excellent yields.[52] Previous groups have used CsOAc (with and without 18-crown-6) as an acetate nucleophile, but in this case *n*-Bu_4NOAc was found to have far superior reactivity. The



Scheme 16 *Reagents and conditions*: i. Lipase, vinyl acetate, 45 °C, 92%. ii. Chloroacetic anhydride, pyridine, DCM, 92%, (CA = chloroacetyl). iii. $TMSN_3$, NIS, TfOH, 88%. iv. NaOMe, MeOH–THF, 90%. v. NIS, TfOH, 92%. vi. NaOMe, MeOH–THF, 86%. vii. NIS, TfOH, 78%. viii. Thiourea, $NaHCO_3$, 90%. ix. Tf_2O, pyridine, 100%. x. CsOAc, 18-crown-6, toluene, ultrasonication, 89%. xi. NaOMe, MeOH–THF, 93%.



Scheme 17 *Reagents and conditions*: i. EtOH, *n*-Bu_4NBr, collidine, 85%. ii. BnBr, KOH, THF, 81%. iii. aq. HOAc, 1 h, 93%. iv. Cl_3CCN, Cs_2CO_3, DCM, 16 h, 92%. v. R^1-OH, **116a–e**, $BF_3{\cdot}Et_2O$ cat., DCM, hexane, −25 °C. vi. KOMe cat., MeOH, rt. vii. Tf_2O, DCM, pyridine, rt. viii. *n*-Bu_4NOAc, toluene, ultrasound, see Table 2.

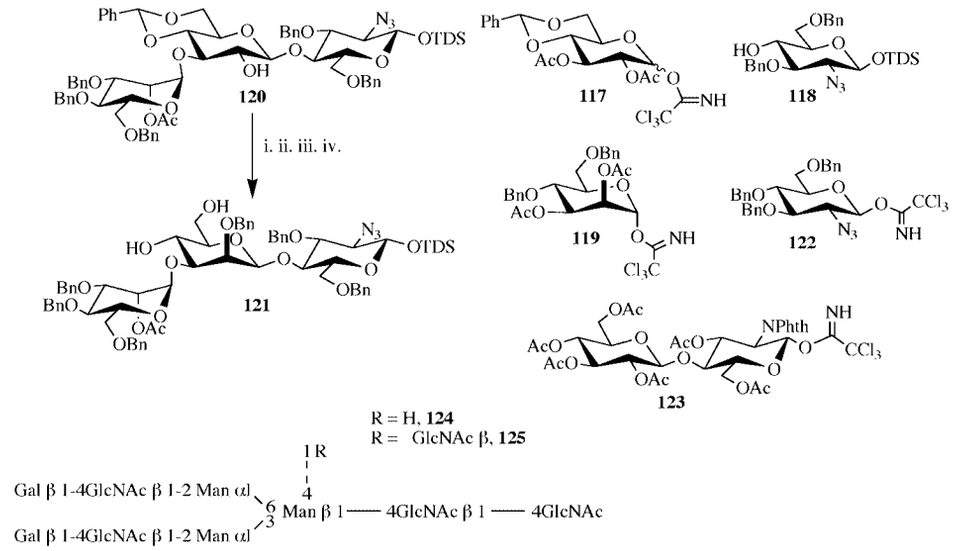
Table 2 Reaction of **114** and **113** with **116** (see Scheme 17)

R^1OH **116**	β-Glucoside **114** yield (%) from **113**	β-Mannoside **115** yield (%) from **114**
a	77	84[a]
b	73	84
c	73	87
d	55	82
e	71	92

[a] The β-glucoside was formed as a by-product (7%).

ultrasound-assisted substitution of a triflate with acetate has been found to also occur simultaneously in other areas of molecule **116e**.

Schmidt and Weiler have developed a versatile strategy for the synthesis of 9 and 10 unit oligomers of diantennary and bisected diantennary complex-type *N*-glycans, using five readily available building blocks.[53] The strategy uses trichloroacetimidate coupling chemistry and a minimal number of deprotection steps for which the yields are generally good. Units **117**, **118** and **119** are coupled sequentially to give trisaccharide **120** and the central benzylidene protected β-glucopyranoside unit is then converted into its C-2 epimer. Epimerisation by conversion of the C-2-OH to C-2-OTf, followed by treatment with tetrabutylammonium nitrite ($TBANO_2$), hydrolysis (53% yield compared to Ajiska's 89% over 2 steps), and finally benzyl protection of the remaining hydroxy groups furnished **121** (Scheme 18). A second unit of **119** can be regioselectively coupled to the primary hydroxy group of the β-mannoside, at which point a unit of **122** can be coupled at C-4 to give rise to the bisected structure. Addition of the two units of **123** to the C-2 positions of each of the mannose antennae, followed by a unit of **118** completes the diantennary and bisected diantennary structures. The overall yield is less than 1% for each of the 17 steps. The *N*-phthaloyl and azide groups are converted to NHAc and the remaining protecting groups are removed to give rise to oligosaccharides **124** and **125**, each in 21 steps from D-glucose.



Scheme 18 *Reagents and conditions*: i. Tf_2O, pyridine, −15 °C, 93%. ii. $TBANO_2$, MeCN, rt, 57%. iii. BnBr, NaH, TBAI, DMF, 71%. iv. EtSH, *p*-TsOH, DCM, 84%.

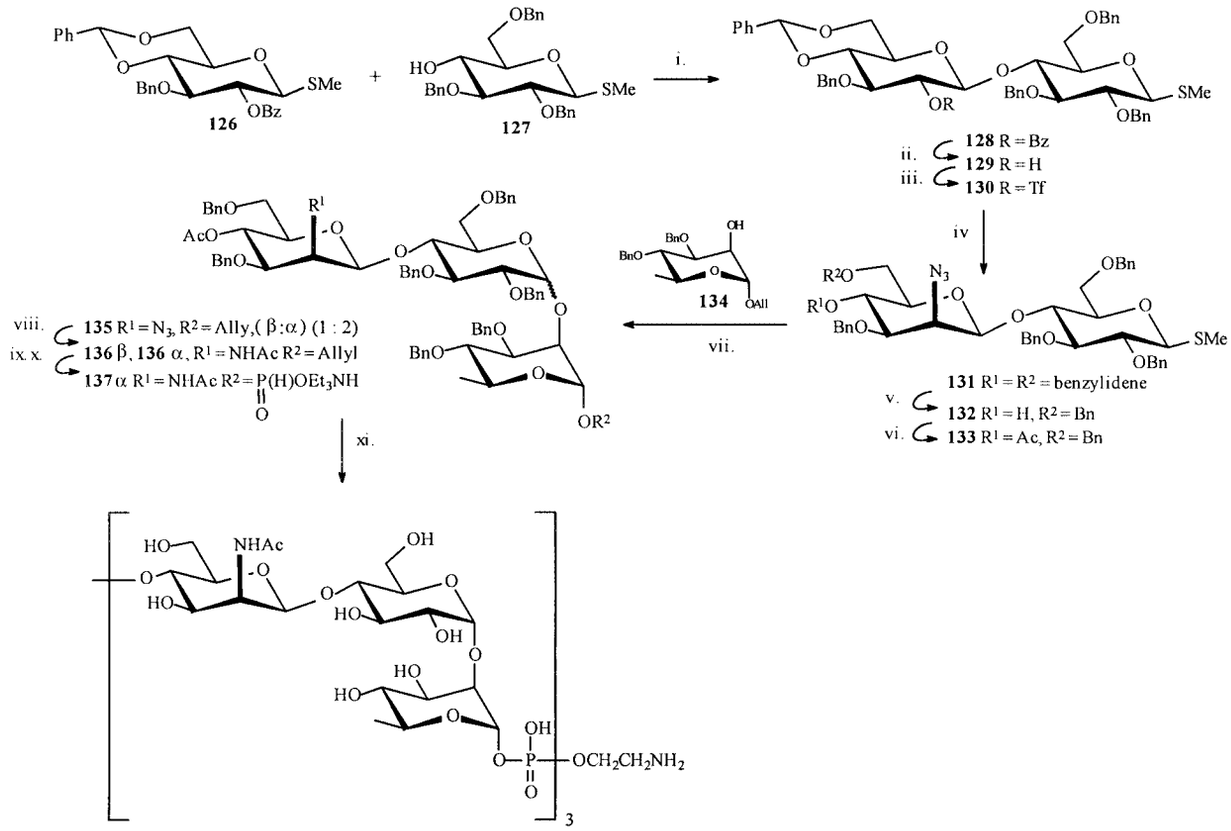
As noted earlier the use of azide as a nucleophile can lead to the β-linked mannazides, which can be converted to mannosamines. This allows alternative access to the trisaccharide repeating unit of *Streptococcus pneumonia* serotype 19F of the capsular polysaccharide, to that demonstrated by Kaji *et al.*[25] The use of silver triflate coupling to give disaccharide **128** as demonstrated by Nilsson and Norberg[23] and subsequent manipulation of the C-2 position in the donor portion of **128** to give the triflate, allows installation of an axial azide group to give the β-mannazide **131**. The benzylidene group is selectively cleaved by reduction to give the 6-*O*-benzyl ether. The 4-OH was then acetylated for later elaboration. Stereoselective coupling of the rhamnose sugar **134** is effected with MeOTf, favouring the α-anomer (2:1). Separation of the anomers was only possible after the azide had been converted to the NHAc, the α-trisaccharide was then taken through a number of steps to give the nonasaccharide **138**. The chemistry is effective in constructing the nonasaccharide unit, however, the efficiency of the overall synthesis suffers by the lack of complete stereocontrol in the coupling of the rhamnose unit, although the yield is greater than the steroselective coupling achieved by Kaji *et al.* (Scheme 19). In contrast to the two previously described methods Russo and co-workers report a reversal in the coupling strategy that proves to be quicker, higher yielding and stereoselective in the key glycosidation steps.[26] The more lengthy three step inversion of configuration method (similar to the method used by Nilsson and Norberg) is comparable to the stereoselective reduction of disaccharide oximes by Kaji *et al*. Overall, Russo and co-workers' method seems to be more effective than both those previously described (**143**, 37% yield, 12 steps from the thiophenyl diol precursor of **139**) and also allows for further manipulation of the saccharide, due to the orthogonal protection (Scheme 20).

2.4.2 Intramolecular S_N2 reactions

Unverzagt *et al.*[54a,b] built upon the innovative work of Kunz and Gunther[10] in the synthesis of a core-fucosylated biantennary octasaccharide from disaccharide **145**. Disaccharide **145** is constructed from two GlcNPhth units, one containing an anomeric fluoride, which acts as the donor and the other containing a hydroxy group at C-4. The acceptor displayed an anomeric azide that was later employed to allow coupling of an asparagine unit. Both monosaccharides originate from the common building block, ethyl 4,6-di-*O*-benzylidene-3-*O*-benzyl-1-thio-GlcNPhth. Scheme 21 outlines the intramolecular displacement of an equatorially disposed C-2-OTf by a C-3-carbamate, which is then hydrolysed to give the β-mannose diol trisaccharide **147**, available in 10 g quantities. The trisaccharide unit was carried forward through a number of high yielding steps to give the protected core-fucosylated biantennary octasaccharide **148** with an overall yield of 14%, from **145** (Fig. 10). Enzymatic development of the terminal sugar chains was then possible to afford sialylated diantennary *N*-glycan.[55a–c]

2.5 Intramolecular aglycon delivery (IAD)

In the early 1990s Stork *et al.* and Hindsgaul *et al.* reported the first stereocontrolled synthesis of β-mannosides *via* a temporary silicon tether.[10] Further investigation of this methodology led Stork *et al.* to modify the general protocol.[56] Whereas the initial procedure involved activation of the anomeric thiol to give an anomeric sulfoxide after silyl tethering of the acceptor, the modified procedure now involved attachment of the tether to the sulfoxide donor. This resulted in a more efficient route to a range of β-mannosides with good yields (Scheme 22 and Table 3). Ogawa and Ito *et al.* also reported an elaboration of their *p*-methoxybenzyl assisted IAD method for the stereocontrolled synthesis of β-mannosides. The coupling of trisaccharide donor **154**, with chitobiose acceptor **155** *via* the mixed acetal **156**, under the standard *p*-methoxybenzyl (PMB) assisted β-mannosylation conditions, followed by subsequent deprotection afforded the core pentasaccharide of *N*-linked glycoproteins **157**, in 33% yield from **154** (Scheme 23).[57] This methodology has also been applied to the coupling of monosaccharide and disaccharide donor units to reach the pentasaccharide core and bisecting hexasaccharide glycans.[58a–c] Moreover, Ito and Ogawa *et al.* adapted this method for synthesis on a polymer support, an unprecedented step in the synthesis of β-mannosides.[59] The β-linked products could be released from the polymer, whilst the impurities remained bound, allowing for easy purification (Scheme 24). Initially the linker-polymer bound donor was constructed in a similar manner to the 2-*O*-PMB derivatives, in six, moderate to high yielding steps (Scheme 25). The potential of the polymer support method was first investigated using **164** and **165a** (Scheme 26 and Table 4). Shifts in the ^{1}H-NMR indicated that the mixed acetal **166a** had been formed as one stereoisomer. This was precipitated with *tert*-butyl methyl ether (TBME) and treated as detailed in Scheme 26, followed by simple workup and chromatographic separation, to give exclusively the β-mannosides **167a** in a modest 50% yield.[59] The yields, although not exceptional, do show the potential to employ the

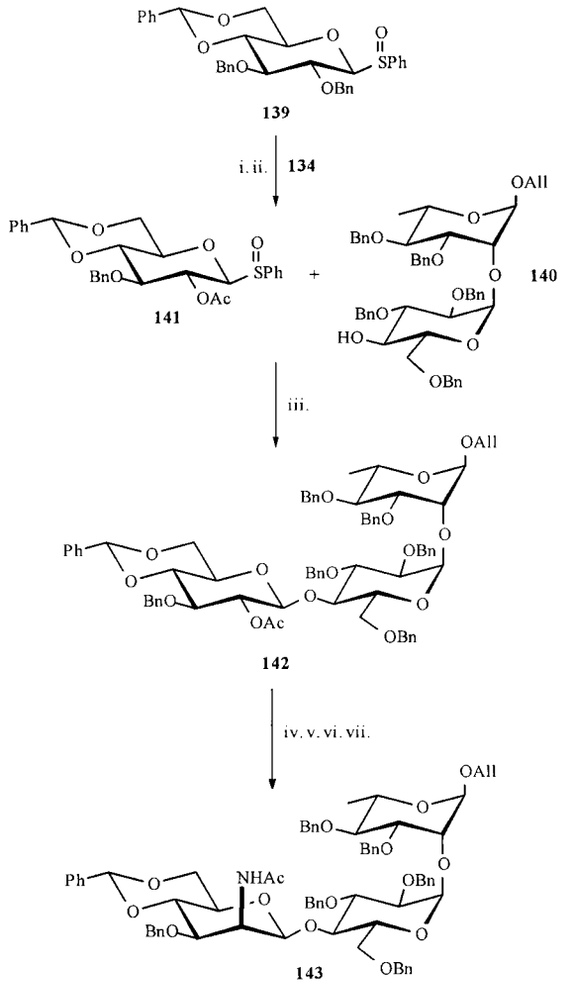


Scheme 19 *Reagents and conditions*: i. Br_2, 0 °C, 4 Å MS, DCM, then −40 °C, **127**, DTBMP, AgOTf, 66%. ii. MeOH, NaOMe, 40 °C, 2 h 45 min, Dowex 50 (H^+) resin, 96%. iii. DCM–pyridine (2:1), 0 °C, Tf_2O. iv. NaN_3, DMF, 70 °C, 4 h 30 min, 75%. v. $NaBH_3CN$, 3 Å MS, THF, fluoroboric acid, 81%. vi. Pyridine–acetic anhydride, 14 h, 94%. vii. **134**, 4 Å MS, DCM, MeOTf, 24 h, TEA, 87%, β:α ratio (32:68). viii. Ph_3P, DCM, 37 °C, 23 h, water, 10 h, 58% **136** α and 28% **136** β from **135** β/α. ix. **136** α, tris(triphenylphosphine)rhodium(I) chloride, EtOH, toluene, water, 4 h reflux, workup then 80% acetic acid, 80 °C, overnight, 80%. x. Pyridine, 2 M phosphorous acid, 2-chloro-5,5-dimethyl-2-oxo-1,3,2-dioxaphosphorinane, 54 h, rt to 40 °C, 17 h, 61%. xi. Elaboration of the trisaccharide to the nonasaccharide, by attachment of spacer group, stepwise oligomerisation and global deprotection.

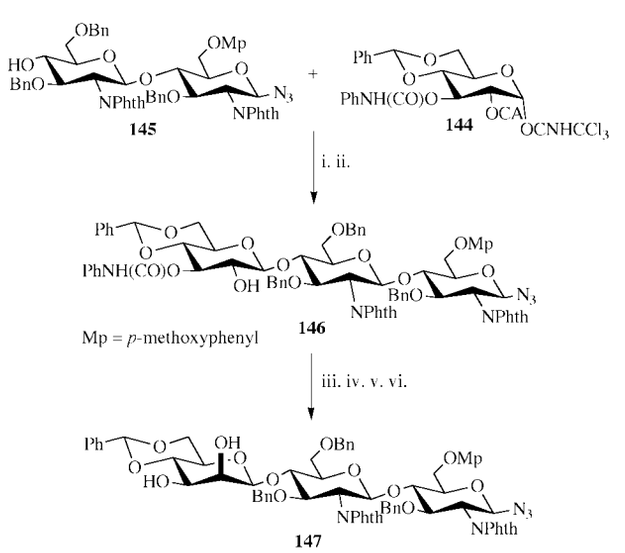
IAD method under solid phase controlled conditions. Following the IAD coupling procedure, **167c** was protected and coupled with monosaccharide **100** to give the orthogonally protected core trisaccharide of the *N*-linked glycoproteins, **169** (Scheme 27). Optimisation of the methodology was achieved by investigating the influence of the C-4 and C-6 protecting group(s) on the reaction. Previously it was discovered that the rigidity imposed on the sugar moiety by the 4,6-benzylidene aided the selective preparation of the β-mannoside by preventing oxonium ion formation.[60] This lead Ito and Ogawa *et al.* to employ a 4,6-*O*-cyclohexylidene moiety that holds the pyranosyl ring in a more rigid $^4C_1$ conformation. This gave rise to quantitative mixed acetal formation with acceptor **171** as illustrated by crude ^{1}H-NMR analysis. The mixed acetal **172** was activated in the usual manner to give rise to **174** in 83% yield. Similarly, the trisaccharide **175** was realised in an impressive 85% yield (Scheme 28).[60] The glycosidation yield of 61% for **176** with **171** compares favourably with that for the benzylidene derivative (60% yield),[58a] whereas **170** gave a yield of 83%, showing the favourable influence the greater rigidity of the cyclohexylidene ring has on the reaction (Scheme 29). When 4,6-*O*-disiloxanylidene and C-3-*O*-trimethyl silyl protecting groups were used as in **178**, the β-mannoside **181** was formed. The mixed acetal **179** was isolated in 96% yield following purification on Flurosil and the β-mannoside **181** was formed in 78% yield (Scheme 30). Similar transformations with the benzylidene derivative **182** gave a lower yield, 55% of **183**, showing how a larger/less rigid ring structure across the 4,6-positions is beneficial for the ring closure of **180** (Scheme 31). Further fine-tuning of the PMB-assisted β-mannosylation methodology was successful by using 4,6-*O*-cyclohexylidene **170** and silyl protected **178** mannosyl donors.[60] The latest investigations have addressed the stereochemical outcome of the tethering step and show that it proceeds with a high degree of diastereofacial selectivity.[61] Recently a number of modified IAD methods have been published that show moderate[62] to excellent[63] results, but to date none has proved as capable at forming β-mannosidic linkages as the PMB-assisted β-mannosylation methodology.

2.6 S_N2 displacement, with inversion of configuration of α-mannosyl triflate donors

Crich and Sun have developed a protocol for the synthesis of β-mannosidic linkages based on the sulfoxide glycosylation method of Kahne *et al.*[64] The methodology was limited to the use of armed but rigid glycosyl donors but the nature of the glycosyl acceptor could be varied (Scheme 32 and Table 5). Glycosidation with a range of glycosyl acceptors was investigated with β:α ratios as high as ≥20:1. Furthermore, yields of 80% could be achieved when the electron rich additive 1,4-dimethoxybenzene (DMB) was used, instead of benzene. Unfortunately, yields and selectivities dropped considerably when more sterically hindered donors were used, however, the β-mannoside was still favoured.[64] The yields, selectivities and breadth of applicability of this methodology were further improved by reducing the steric bulk at the C-2 position of the donor, using an anomeric phenyl sulfoxide group, and using dichloromethane as solvent. Excellent β-selectivities and yields were achieved when a range of donors were coupled with a primary acceptor, in addition, good results were obtained



Scheme 20 *Reagents and conditions*: i. DCM–Et_2O (1:1), 4 Å MS, −78 °C, Tf_2O, DTBMP, 5 h, 84%. ii. DCM, 0 °C, TfOH, 1 h, 80%. iii. DCM–Et_2O (1:1), 4 Å MS, −78 °C, Tf_2O, DTBMP, 3 h, 77%. iv. MeOH, NaOMe, rt, 98%. v. DMF, NaH, −40 °C, sulfonyldiimidazole, 5 h, 99%. vi. Toluene, Bu_4NN_3, reflux, Dean–Stark, 3 h, 97%. vii. Zn, 2% $CuSO_4$, THF–Ac_2O–AcOH (6:4:2), 2 h, 35 °C, 84%.



Scheme 21 *Reagents and conditions*: i. TMSOTf, 4 Å MS, DCM. ii. K_2CO_3, DCM, MeOH, 65% over two steps. iii. Tf_2O, pyridine, DCM, −20 °C. iv. Pyridine, DMF, 60 °C. v. AcOH, dioxane, H_2O, 0 °C. vi. NaOMe, MeOH, DCM, 62% over 4 steps.

when the less reactive C-4-OH rhamnose glycoside acceptor was employed. Coupling of the notoriously unreactive C-4-OH of a GlcNAc acceptor with the phenyl sulfoxide donor gave only

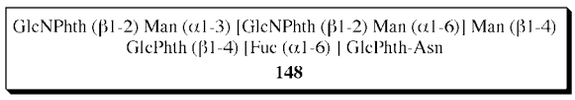
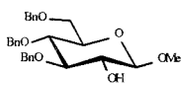
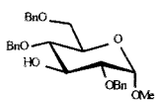
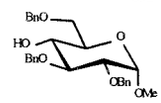
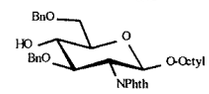
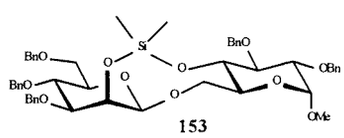


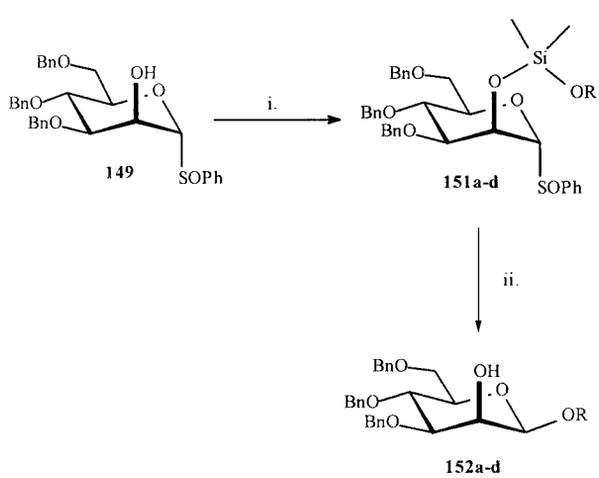
Fig. 10 The protected core-fucosylated biantennary octasaccharide.

Table 3 Reaction of **149** with **150** (Scheme 22)

ROH **150**		Tethering yield (%)	Glycosidation yield (%)	Overall yield (%)
a		84	65	55
b		88	82	72
c		98	12[a]	12
d		78	54	42

[a] The remaining material underwent 6-*O*-debenzylation to afford **153**.

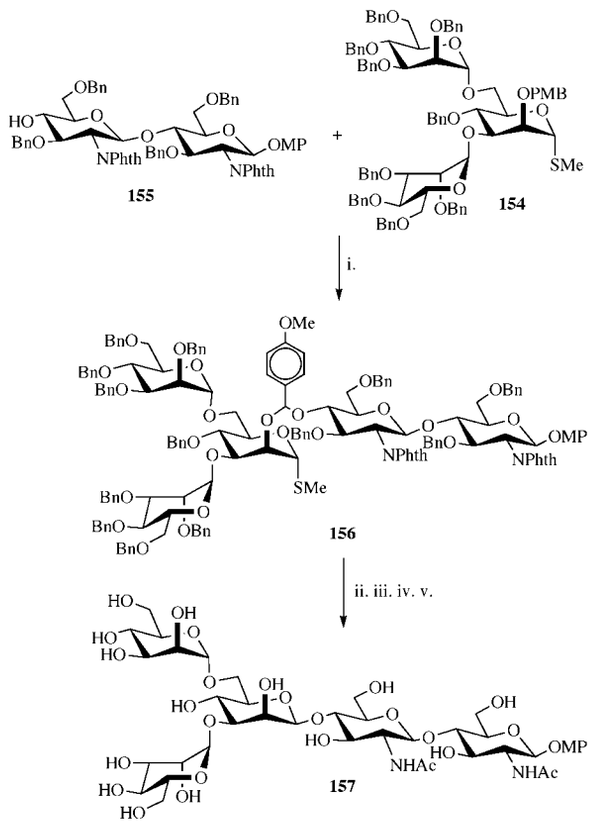




Scheme 22 *Reagents and conditions*: i. R-OH, **150a–d**, imidazole, DMAP, $(Me)_2SiCl_2$, THF. ii. Tf_2O, DTBP, Et_2O, DCM.

moderate to poor yield, but with an adequate β:α ratio (Table 6).[65] As mentioned previously, conformationally flexible donors that did not possess a 4,6-benzylidene protecting group gave poor β:α selectivities, due to their lack of resistance in forming an oxocarbenium cation intermediate.[65] Spectroscopic investigations using a phenyl sulfoxide donor determined that the α-mannosyl triflate was initially formed as the reactive glycosyl donor intermediate.[66] Interestingly, when sub-stoichiometric amounts of triflic anhydride were used complete consumption of the sulfoxide donor was observed, leading to the conclusion that the reaction by-product, benzenesulfenyl triflate (PhSOTf), was a very powerful electrophile towards sulfoxides. Indeed the potential of PhSOTf as a thiophilic reagent was further demonstrated by the clean conversion of simple thio-glycosides to glycosyl triflates with 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) at low temperature. This advanced methodology was found to be comparable in yield and selectivity with that of the

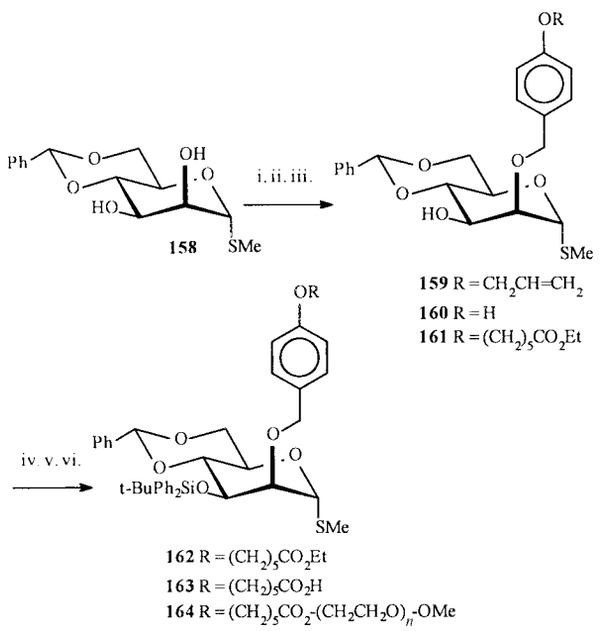
sulfoxide method previously described above (Table 7).[66,67a,b] This appears to be the first literature example of efficient and clean β-mannosylation of a tertiary alcohol.[67a,b] Armed with a versatile synthetic tool, Crich *et al.* demonstrated its utility for the synthesis of the trisaccharide component of the *Hyriospsis schlegelii* glycosphingolipid (Fig. 2), a difficult target which contains two β-linkages. Thus the allyl donor **195** was coupled with **196** in high yield and with good stereoselectivity (entry 8, Table 6). This was then deprotected at C-2 and successfully coupled to an α-bromo perbenzoylated xylose sugar (68%, 90% based on recovered starting material).[14b,c]



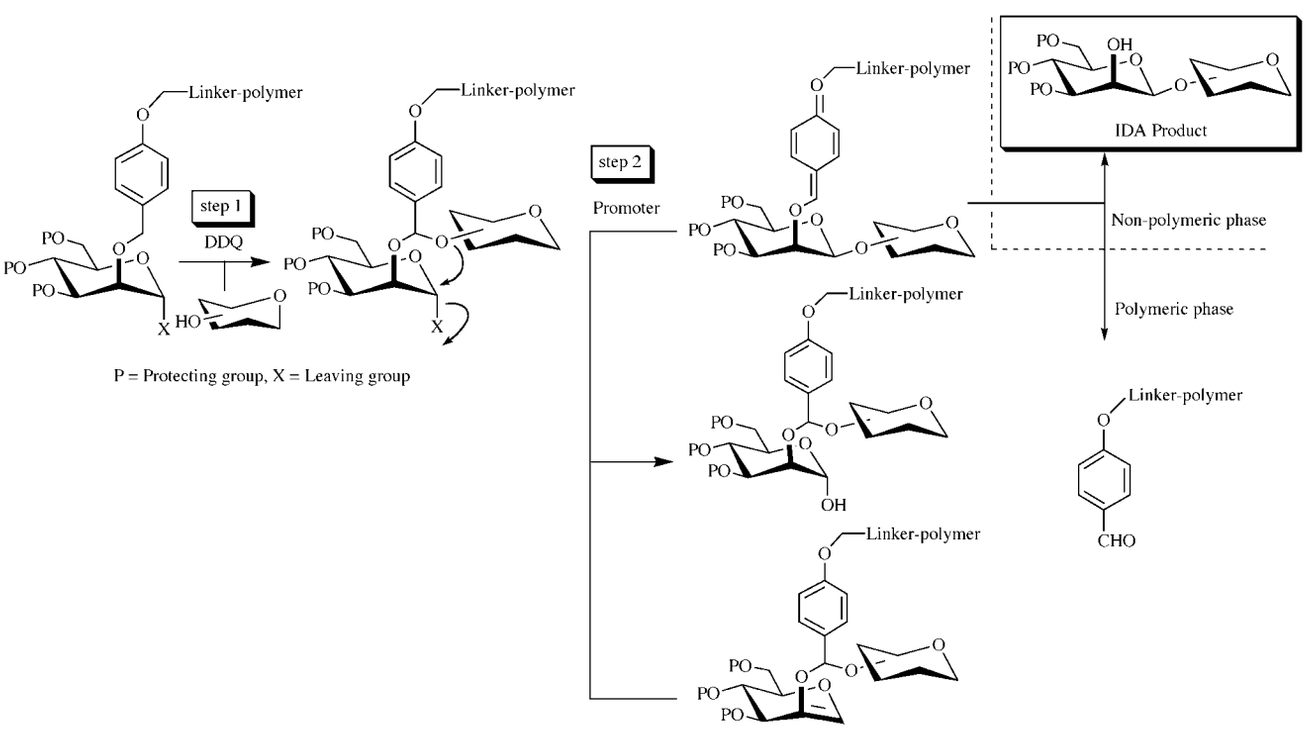
Scheme 23

2.7 Application of β-mannosidases and immobilised recombinant β-mannosyltransferases

In recent years the application of enzymes to solve problems in oligosaccharide synthesis has greatly advanced.[68a,b] The problems associated with enzymatic methods including the handling, acquisition of enzymes in appreciable quantities, cost and in many cases, poor yields[69a–c] have been overcome with rapid

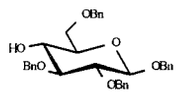
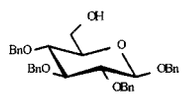
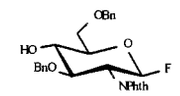
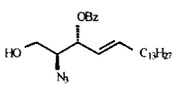


Scheme 25 *Reagents and conditions*: i. *p*-allyloxybenzyl chloride, aqueous NaOH, Bu_4NHSO_4, DCM, 43%. ii. $Pd(PPh_3)_4$, $NaBH_4$, THF. iii. $Br(CH_2)_5CO_2Et$, Cs_2CO_3, DMF, 79% over two steps. iv. TBSCl, imidazole, DMF, 81%. v. aqueous NaOH, *t*-BuOH. vi. PEG monomethyl ether, $EtO_2CN{=}NCO_2Et$, Ph_3P, DCM–THF, 80% over two steps. The latter yield was estimated based on ^{1}H-NMR analysis of **164** in the presence of *p*-nitrobenzaldehyde as an internal standard.

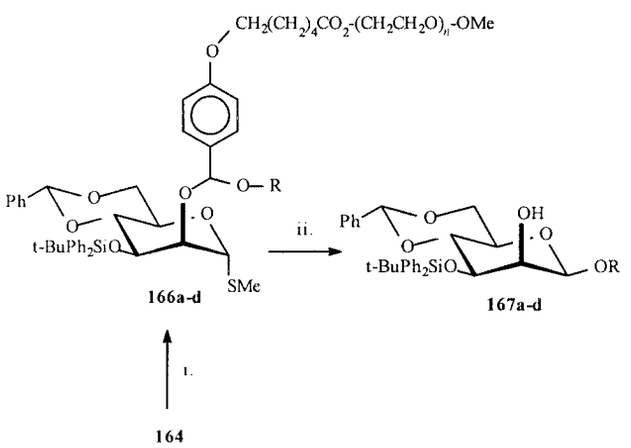


Scheme 24

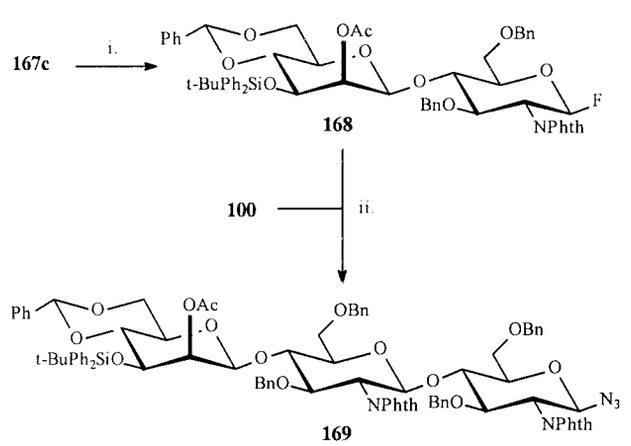
Table 4 Reaction of **164** with **165** (Scheme 26)

R-OH **165a–d** (equiv.)		*T*/°C	*t*/h[a]	Yield (%)[b]
a (2.6)[c,d]		40	21	50
a (2.0)		40	40	48
b (2.0)		20	8	43
c (1.9)[c]		40	120	37[e] (48[f])
d (2.3)		40	22	54

[a] Step ii. of Scheme 26. [b] Calculated based on **164**. [c] Performed in the presence of MeSSMe, 4 equiv. [d] Formation of the mixed acetal was confirmed by ^{1}H-NMR. [e] Isolated as corresponding acetate **168**. [f] Calculated based on consumption of **165c**.

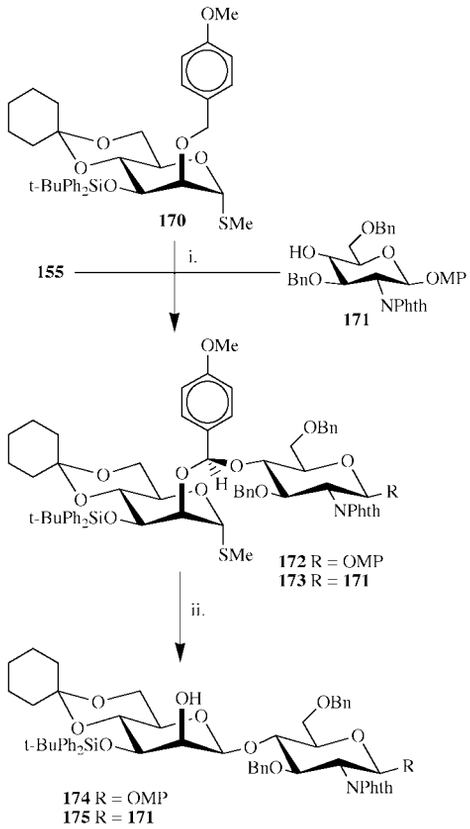


Scheme 26 *Reagents and conditions*: i. ROH, **165a–d**, DDQ, 4 Å MS, DCM, rt, 3 h. ii. MeOTf, DTBMP, 4 Å MS, DCE.

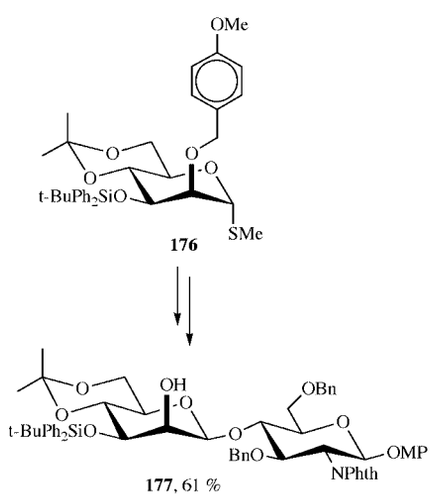


Scheme 27 *Reagents and conditions*: i. Ac_2O, pyridine. ii. Cp_2HfCl_2, AgOTf, DCE, 85%.

developments in biotechnology.[68a,b] One of the most difficult β-mannose linkages to synthetically construct is Man(β1-4)-GlcNAc. However, a number of groups have shown that an enzymatic approach can solve this problem. Crout and co-workers detail the purification of a β-mannosidase from *Aspergillus oryzae* and its application to the synthesis of the core trisaccharide **203** (Scheme 33). Although there is complete

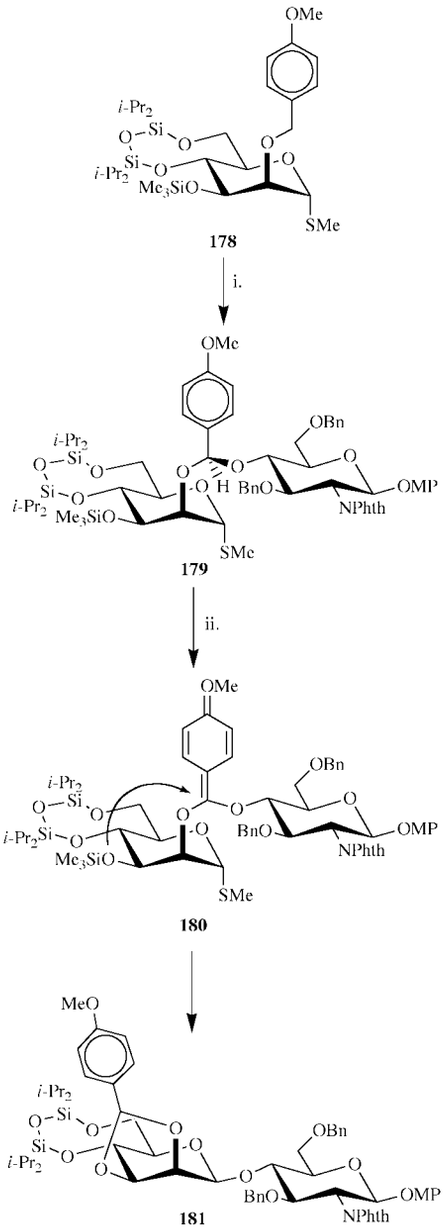


Scheme 28 *Reagents and conditions*: i. DDQ, 4 Å MS, DCM, rt, 2 h. ii. MeOTf, DTBMP, 4 Å MS, DCE, 45 °C, 24 h, **174** in 83% from **171** and **175** in 85% from **155**.

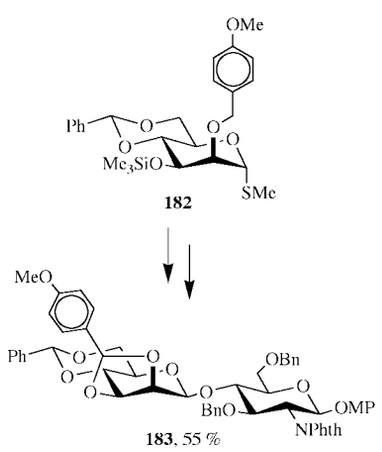


Scheme 29

regiocontrol and stereocontrol in the mannosylation reaction, the yields are relatively low. However no protection–deprotection manipulations are required.[70a,b] Flitsch and co-workers have recently published significant advances within enzyme oligosaccharide technology reporting modification of biocatalysts to efficiently synthesise the core region of the *N*-linked oligosaccharides. Over production in *Escherichia coli* of full-length and transmembrane-deleted yeast β-1,4-mannosyltransferases has allowed the recombinant enzyme to be prepared as a functionally pure immobilised biocatalyst (by nickel(II) chelation), with high activity.[71a–c] The enzyme analogue substrate used, phytanyl-pyrophosphoryl-α-*N*,*N*′-diacetylchitobioside (PPGn2) is chemically synthesised from chitobiose in 65% yield and mannosylated by the enzyme in yields of 60–80% (as determined by radiolabelling studies) (Scheme 34). The β-mannosylation yields are much higher than those reported by



Scheme 30 *Reagents and conditions*: i. **171**, DDQ, 4 Å MS, DCM, rt, 2 h, 96%. ii. MeOTf, DTBMP, 4 Å MS, DCE, 60 °C, 14 h, 78%.

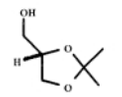
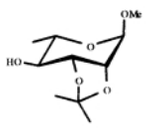
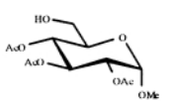
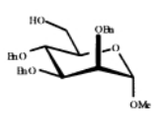


Scheme 31

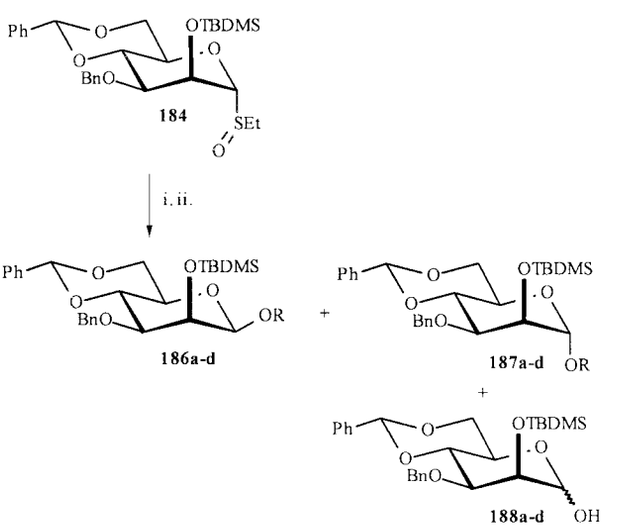
Crout and co-workers but the overall chemoenzymatic process is longer.

The application of mannosylating enzymes to synthesise the trisaccharide unit of the bacterial *O-antigen Salmonella* group

Table 5 Reaction of **184** with **185a–d** (Scheme 32)

ROH **185a–d**	Yield **186a–d** (%)	Yield **187a–d** (%)	Yield **188a–d** (%)
a 	80[a] (>20:1)	—	3
b 	50[a] (1.5:1)	33	10
c 	86[b] (10.7:1)	8	—
d 	84[b] (8.6:1)	10	—

[a] DMB added. [b] Benzene added.



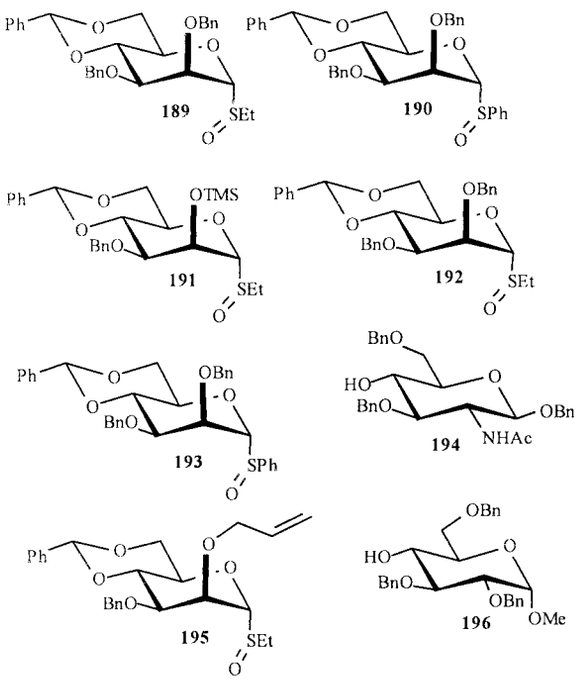
Scheme 32 *Reagents and conditions*: i. ROH, **185a–d**, Tf_2O, DTBMP, Et_2O, −78 °C. ii. ROH, −78 to 0 °C.

E_1, using recombinant β-1,4-mannosyltransferase ($ManT^{\beta 4}$) was recently reported by Thorson and co-workers (Fig. 5).[18a,b] The efficient five step chemical synthesis of **207** was then followed by an enzymatic β-mannosylation, mediated by a purified recombinant $ManT^{\beta 4}$, regioselectively and stereoselectively transferring a mannose unit from guanosine (α-D-mannosyl-5′-diphosphate)(GDP-α-D-Man) in 72% over 5 hours (Scheme 35).

2.8 Anomeric radical hydrogen abstraction

The application of an anomeric radical method to synthesise β-mannosides, as described by Crich and co-workers, is based on the knowledge that 1-alkoxy-1-glycosyl radicals are quenched along the axial direction by thiols and stannanes to give equatorial glycosides (Scheme 36).[72] Early investigations into the potential of this inversion employing a 1,5-hydrogen abstraction mechanism (Scheme 36), for the formation of disaccharide **209** (disaccharide **209** was formed in a 3:1 ratio α:β with no evidence of other unwanted by-products) showed the feasibility of this approach. A detailed study of the reaction pathways, the reaction conditions and substrate blocking pattern around the mannopyranoside ring to optimise and control the mannoside inversion process, has been reported.[73] An

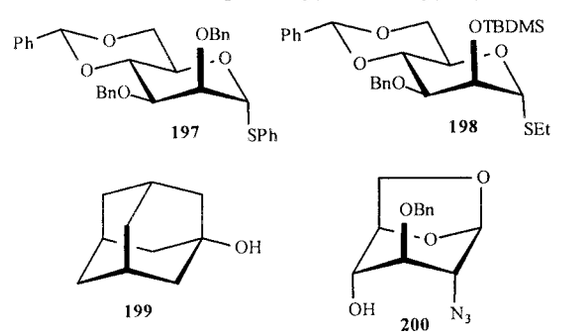
Table 6 Glycosidation of a range of glycosyl acceptors



Entry	Donor	Acceptor	β-Mannoside yield (%)	α-Mannoside yield (%)	β:α Ratio
1	**189**	**185c**	95	0	>25:1[a]
2	**190**	**185c**	95	0	>25:1[a]
3	**184**	**185b**	82	11	7.5:1[a]
4	**191**	**185b**	82	11	7.5:1[a]
5	**192**	**185b**	74	11	6.7:1[b]
6	**193**	**185b**	90	0	>25:1[a]
7	**193**	**194**	31	8	3.8:1[a]
8	**195**	**196**	87	7	12:1[a]

[a] DCM as solvent. [b] Et_2O as solvent.

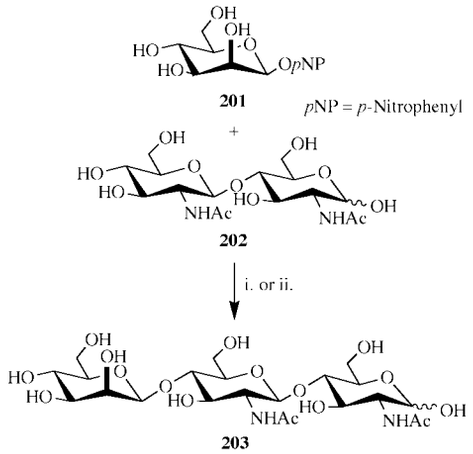
Table 7 Conversion of simple thio-glycosides to glycosyl triflates[a]



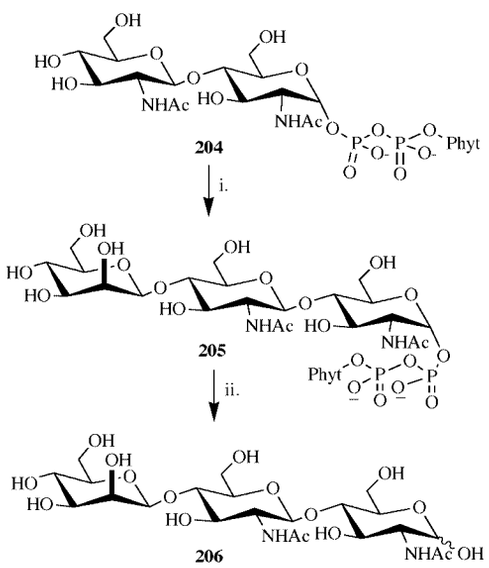
Entry	Donor	Acceptor	β-Mannoside yield (%)	β:α Ratio
1	**197**	**185b**	95	>25:1
2	**198**	**185b**	80	10:1
3	**197**	**199**	94	>25:1
4	**197**	**200**	85	5.1:1
5	**197**	**116d**	95	>25:1

[a] All reactions carried out in DCM.

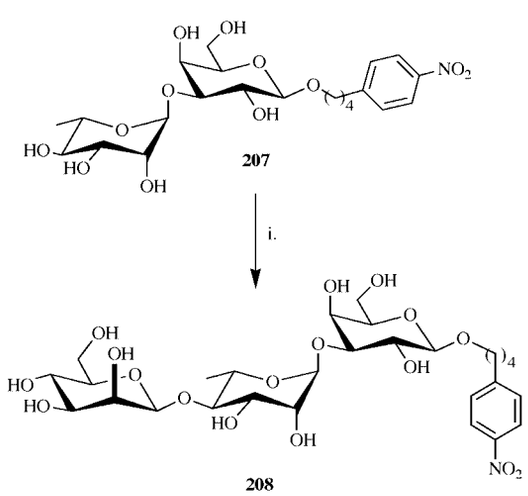
improvement in the methodology was achieved, using Barton's reductive decarboxylation of an anomeric 2-furyl substituent as a means of forming the 1-alkoxy-1-mannopyranosyl radical. The selectivity and yield in forming β-(1-6)-mannosidic linkages was improved to give disaccharide **210** in a reasonable 67% yield and ≥25:1 β:α ratio. To date the methodology has not



Scheme 33 *Reagents and conditions*: β-Mannosidase from i. *Helix pomatia*, 3%. ii. *Aspergillus oryzae*, 26%.

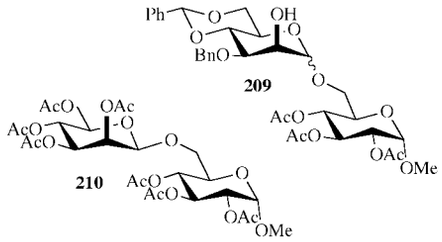


Scheme 34 *Reagents and conditions*: i. GDPMan, β-mannosyltransferase. ii. HCl, 80% overall yield.

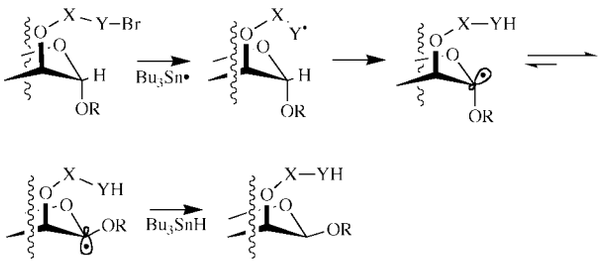


Scheme 35 *Reagents and conditions*: i. $ManT^{P4}$/GDP-Man, 72%.

been successfully extended to incorporate secondary glycosyl acceptors.[74] A 1,6-hydrogen abstraction method was developed and published at the same time by Curran and co-workers.[75] Curran and co-workers developed a number of useful functional groups call "**PRT**" groups, which act as **p**rotecting groups and **r**adical **t**ranslocators. In a similar manner to Crich and co-workers they were able to favour formation of the



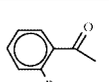
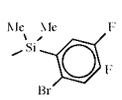
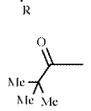
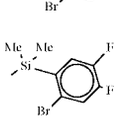
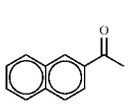
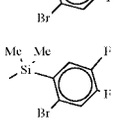
β-mannoside over the α-mannoside. Initial investigations with methyl 3-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside derivatives with a range of **PRT** groups at C-2 gave average to poor total yields and low β-selectivities. When the benzyl group at C-3 was replaced by an acyl group great improvements in selectivity and yield were observed. This improvement can be explained by an increase in the ratio of 1,6 : 1,5-hydrogen abstraction from ~0.6 for benzyl derivatives to ~1–2 for the acyl derivatives (Scheme 37 and Table 8).



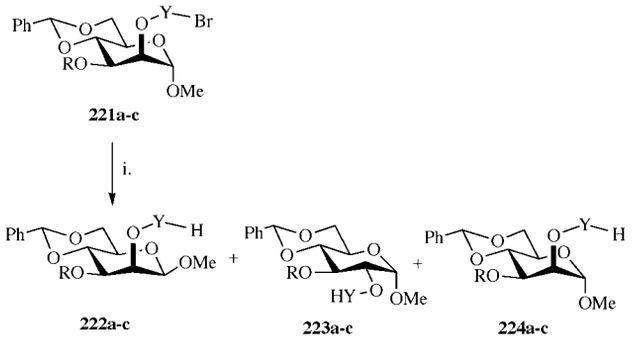
Scheme 36 *Reagents and conditions*: Inversion of α- to β-mannoside.

One final method of interest that is being developed by Shuto and co-workers involves the intramolecular radical cyclisation of vinylsilyl groups.[76] 1-Hydroxyethyl and 2-hydroxyethyl β-*C*-mannosides are synthesised through this process, *via* an initial 5-*exo*-cyclisation. In the presence of a high concentration of tributyltin hydride the 5-*exo*-radical is quenched and, following oxidative cleavage, the 5-*exo*-product affords 1-hydroxyethyl β-*C*-mannosides. If a low concentration of tributyltin hydride is used, rearrangement of the 5-*exo*-product occurs to give the 6-*endo*-product and, following oxidative cleavage, the 2-hydroxyethyl β-*C*-mannosides are formed.

Table 8 Hydrogen abstraction reactions of **221a–c** (Scheme 37)

221	R	Y–Br		Ratio of products[a] β-Mannoside : α-Glucoside : α-Mannoside	Yield (%)[b]
a			R = H	50 : 50 : 0	82
			R = F	52 : 37 : 11	72
b				53 : 33 : 14	75
c				58 : 42 : 0	68

[a] Determined by ^{1}H-NMR. [b] Total isolated yield.



Scheme 37 *Reagents and conditions*: i. Bu_3SnH, 0.05 M.

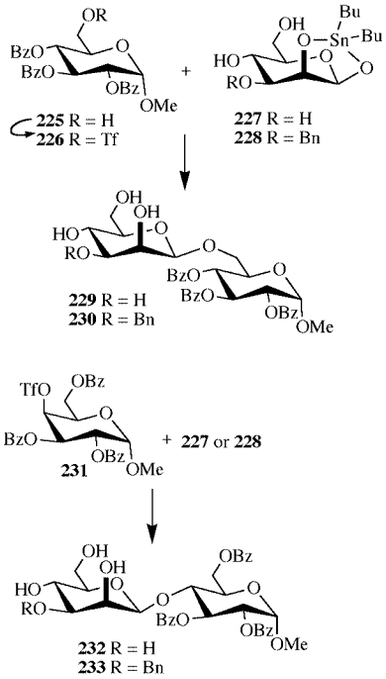
2.9 Dibutylstannylene complexes

Hodosi and Kovác have developed a method for coupling a primary glycosyl acceptor with an unprotected mannosyl donor *via* stannylene chemistry.[77] This effectively reverses the roles of the donor and acceptor. In this case the mannosyl moiety, which is generally employed as the donor, behaves as a nucleophile in the form of a tin acetal complex. This idea has previously been employed by Schuerch *et al.*, in the alkylation of the anomeric hydroxy group with simple alkyl halides.[10] The C-6 acceptor **225** is converted to a triflate species **226** and behaves as the donor in an S_N2 displacement reaction at C-6. This methodology does not allow formation of an oxonium ion intermediate at the anomeric centre of an activated donor, which is inherently responsible for non-specific glycosidation reactions in all but S_N2-type couplings (Scheme 38). An improvement in the methodology was achieved by varying the solvent. Thus in DMF the triflate species **226** was found to slowly convert to the C-6-aldehyde which restricted the yield. This was overcome by using acetonitrile (Table 9). Yields were further improved by using C-3-OBn 1,2-*O*-stannylene acetal-mannosyl derivative **228**, which prevents the 1,2-*O*-stannylene acetal from opening and forming the 2,3-*O*-stannylene acetal-mannosyl derivative **227a**. The 2,3-*O*-stannylene acetal-mannosyl derivative has been identified by the isolation and acetylation of **234** to give **235** (Scheme 39). Using this method, peracetylated β-D-mannose has been synthesised from D-mannose in excellent yield.[78] Moreover **233** has been elaborated to the tetrasaccharide **236** in good yield.[79] It is possible to couple two sugar moieties through both anomeric centres using stannylene chemistry as shown by Nicolaou *et al.*[17] Coupling a range of sugar donors with a perbenzylated stannylene acetal acceptor has given good yields and selectivities. The principle has been extended to the coupling of a second donor unit at C-2 of the

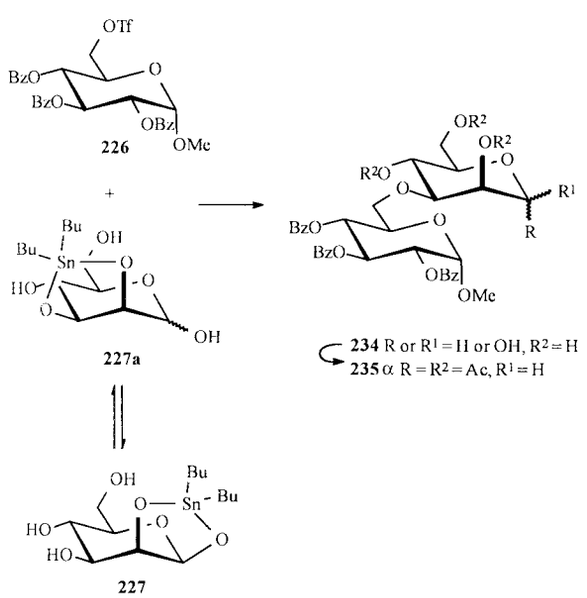
Table 9

Entry	Nu[a] (equiv.)	El[b] (equiv.)	Product	Yield (%)	Solvent	*T*/°C	Time	Salt (equiv.)
1	**227** (4)	**226** (1)	**229**	40	DMF	0, 25	4 h, 10 h	
2	**227** (3)	**226** (1)	**229**	57	CH_3CN	25	20 h	Bu_4NF (1)
3	**227** (6)	**231** (1)	**232**	40	DMF	25	5 d	
4	**227** (6)	**231** (1)	**232**	52	DMAA	25	3 d	
5	**227** (6)	**231** (1)	**232**	59	DMSO	25	2 d	
6	**228** (5)	**226** (1)	**230**	75	CH_3CN	25	14 h	Bu_4NF (1)
7	**228** (6)	**231** (1)	**233**	67	DMF	25	18 h	CsF (6)

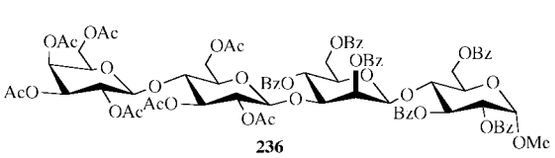
[a] Nucleophile. [b] Electrophile.



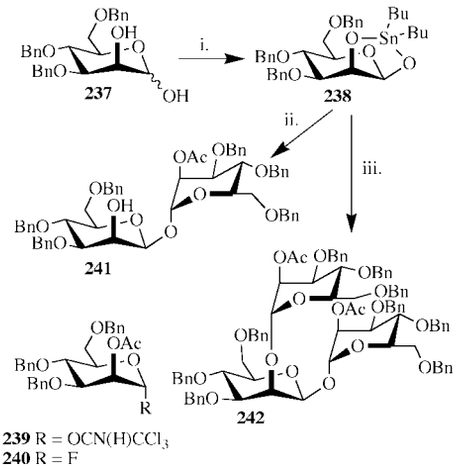
Scheme 38 See Table 9 for conditions and yields.



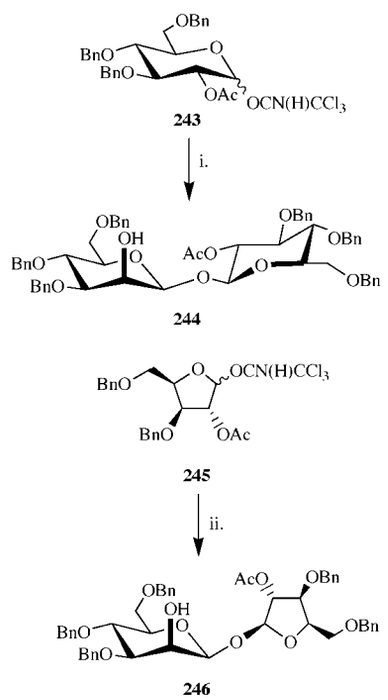
Scheme 39



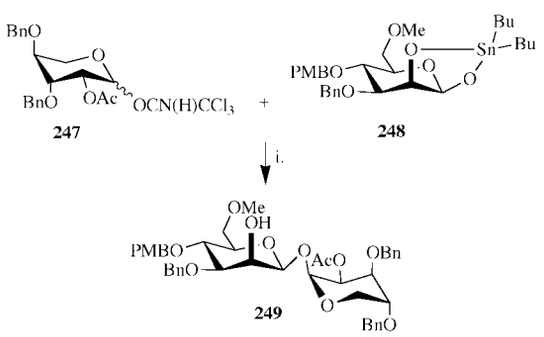
acceptor, forming a trisaccharide **242** (Scheme 40). By varying the conditions and the anomeric activating group of the donor, Nicolaou *et al.* have selectively accessed the disaccharide or trisaccharide with each glycosidic bond formed stereoselectively (Schemes 40 and 41). The methodology was used to construct the β-mannose linkage of the sugar unit labelled F in Everninomicin 13,384-1, **4**, in Fig. 6. Disaccharide **249** was successfully synthesised in 67% yield from donor **247** and stannylene **248**, using the TMSOTf-stannylene methodology (Scheme 42). The anomeric stereochemistry assignments were made on the basis of the C-1, H-1 coupling constants and the chemical shift of H-5 proton in the mannose moiety, appearing at δ ~3.4 ppm for the β-linked glycoside.



Scheme 40 *Reagents and conditions*: i. Bu_2SnO, MeOH, reflux. ii. **239**, TMSOTf, 0.5 equiv., Et_2O, 0 °C to 25 °C, 48 h, 66%. iii. **240**, TMSOTf, 1.2 equiv., Et_2O, 0 to 25 °C, 24 h, 84%.



Scheme 41 *Reagents and conditions*: i. **238**, 1.5 equiv., TMSOTf, 0.4 equiv., Et_2O, 0 to 25 °C, 48 h, 68%. ii. **238**, 1.5 equiv., TMSOTf, 0.5 equiv., Et_2O, 0 to 25 °C, 0.5 h, 72%, 8% trisaccharide.



Scheme 42 *Reagents and conditions*: i. **247**, 0.7 equiv., TMSOTf, 0.5 equiv., DCM, 0 to 25 °C, 67%.

2.10 Utility of mannosyl fluoride donors

Direct glycosylation of armed mannopyranosyl fluoride **250** with a range of primary acceptors gave rise to excellent yields and useful selectivities.[80] As entry **d** in Table 10 shows, no

Table 10 Utility of mannosyl fluoride donors (Scheme 43)

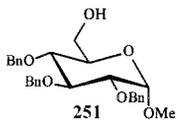
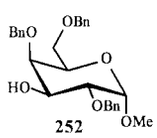
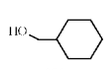
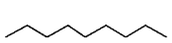
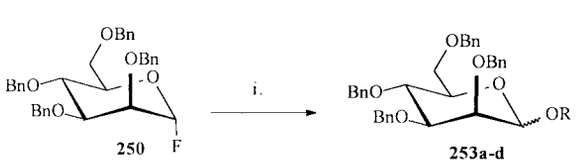
	ROH	Promoter (equiv.)	Co-promoter (equiv.)	Yield (%)	β : α Ratio
a	 **251**	$Sn(OTf)_2$ (1.2)	$La(ClO_4)_3 \cdot nH_2O$ (1.2)	85	71 : 29
		$Sn(OTf)_2$ (2.4)	$La(ClO_4)_3 \cdot nH_2O$ (1.2)	97	74 : 26
b	**116a**	$Sn(OTf)_2$ (2.4)	$La(ClO_4)_3 \cdot nH_2O$ (1.2)	99	75 : 25
c	**185d**	$Sn(OTf)_2$ (2.4)	$La(ClO_4)_3 \cdot nH_2O$ (1.2)	97	74 : 26
d	 **252**	$Sn(OTf)_2$ (2.4)	$La(ClO_4)_3 \cdot nH_2O$ (1.2)	99	49 : 51

Table 11 Utility of mannosyl fluoride donors with non-carbohydrate secondary alcohol acceptors [a]

250 $\xrightarrow{\text{i.}}$ **253a, e–h**

	ROH [b]	Yield (%)	β : α Ratio
a	251	84	73 : 27
e	 **254**	32 [c]	76 : 24
		99	83 : 17
f	 **255**	96	80 : 20
g	 **256**	97	81 : 19
h	 **257**	95	84 : 16

[a] i. ROH, **a**, **e–h**, SO_4–ZrO_2, 100 wt%, Et_2O, 5 Å MS, 100 wt%, 25 °C, 15 h. [b] Equiv. of acceptor. [c] No MS added.



Scheme 43 *Reagents and conditions*: i. ROH, **a–d**, promoters, MeCN–PhMe (1 : 4), 4 Å MS, −40 °C, 23 h.

β-selectivity is seen in reaction with a secondary sugar acceptor, plus the method seems limited to armed/reactive donors (Scheme 43 and Table 10). The promoters used to great effect are tin(II) triflate and lanthanum perchlorate, less effective promoters investigated by Shibasaki and co-workers include the rare earth salts.[81a,b] Toshima *et al.* have published similar examples of direct glycosylation with a range of acceptors that consist mainly of non-carbohydrate secondary alcohols (Table 11).[82] The method is most successful when carried out in diethyl ether, with 5 Å MS, using what has been described as a recyclable, environmentally compatible solid acid, namely sulfated zirconia (SO_4–ZrO_2).

3 Conclusion

The recent literature shows a vast amount of development of new and improved methods towards the synthesis of β-mannose and β-mannosamine linkages. The development of polymer-supported methodology and recombinant biocatalysts has allowed access to some difficult linkages, with high stereoselectivity, regioselectivity and practical yields. The synthesis of a number of naturally occurring β-mannose and β-mannosamine units is testimony to the success of the methodologies developed.

4 References

1 (*a*) J. Hodgson, *Biotechnology*, 1991, **9**, 609; (*b*) D. A. Cumming, *Glycobiology*, 1991, **1**, 115; (*c*) S. K. S. Shibahura, T. Usui, T. Kudo, A. Tamura, S. Gomi, Y. Ikedu, D. Ikeda and T. Takeuchi, *J. Antibiot.*, 1993, **46**, 531; (*d*) M. A. Fischl, L. Resnick, R. Coombs, A. B. Kremer, J. C. Pottuge, S. J. Fass, K. H. Fife, W. G. Powderly, A. C. Collier, R. L. Aspinall, S. L. Smith, K. G. Kowalski and C. B. Wallemark, *J. Acquired Immune Defic. Syndr.*, 1994, **7**, 139; (*e*) J. Ziegler, *J. Natl. Cancer Inst.*, 1996, **88**, 397; (*f*) J. C. McAuliffe and O. Hindsgaul, *Chem. Ind.* (*London*), 1997, 170.

2 E. F. Hounsell, *Chem. Soc. Rev.*, 1987, **16**, 161.

3 A. Varki, *Glycobiology*, 1993, **3**, 97180.

4 M. Ishihara, N. S. Fedarko and H. E. Conrad, *J. Biol. Chem.*, 1986, **261**, 13575.

5 (*a*) J. C. Paulson, *Trends Biol. Sci.*, 1989, **14**, 272; (*b*) H. Lis and N. Sharon, *Eur. J. Biochem.*, 1993, **218**, 1; (*c*) A. Kobata, *Acc. Chem. Res.*, 1993, **26**, 319; (*d*) R. A. Dwek, *Chem. Rev.*, 1996, **96**, 683; (*e*) L. A. Lasky, *Science*, 1992, **258**, 964; (*f*) Y. C. Lee and R. T. Lee, *Acc. Chem. Res.*, 1995, **28**, 321; (*g*) L. A. Lasky, *Annu. Rev. Biochem.*, 1995, **64**, 113; (*h*) W. I. Weis, *Annu. Rev. Biochem.*, 1996, **65**, 441; (*i*) T. A. Springer, *Nature* (*London*), 1990, **346**, 425.

6 P. Knight, *Biotechnology*, 1989, **7**, 35.

7 C. M. Taylor, *Tetrahedron*, 1998, **54**, 11313.

8 (*a*) J. Montreuil, *Adv. Carbohydr. Chem. Biochem.*, 1980, **37**, 157; (*b*) R. Kornfeld and S. Kornfeld, *Annu. Rev. Biochem.*, 1985, **54**, 631.

9 R. T. Schwarz and R. Datema, *Adv. Carbohydr. Chem. Biochem.*, 1983, **40**, 287.

10 F. Barresi and O. Hindsgaul, *Front. Nat. Prod. Res.*, 1996, **1**, 251.

11 E. Kaji and F. W. Lichtenthaler, *Trends Glycosci. Glycotechnol.*, 1993, **5**, 121.

12 (*a*) P. L. Hackland, H. Parolis and L. A. S. Parolis, *Carbohydr. Res.*, 1988, **172**, 209; (*b*) P. Edebrink, P. E. Janson, G. Widmal and W. Nimmich, *Carbohydr. Res.*, 1994, **257**, 107; (*c*) N. A. Paramonov, L. A. S. Parolis, H. Parolis, I. F. Boán, J. Antón and F. Rodríguez-Valera, *Carbohydr. Res.*, 1998, **309**, 89; (*d*) H. Rougeaux, P. Talaga, R. W. Carlson and J. Guezennec, *Carbohydr. Res.*, 1998, **312**, 53; (*e*) P.-A. Trinel, Y. Plancke, P. Gerold, T. Jouault, F. Delplace, R. T. Schwarz, G. Strecker and D. Poulain, *J. Biol. Chem.*, 1999, **274**, 30520.

13 (*a*) T. Hori, M. Sugita, S. Ando, M. Kuwahara, K. Kumauchi, E. Sugie and O. Itasaka, *J. Biol. Chem.*, 1981, **256**, 10979; (*b*) T. Takeda, N. Hada and Y. Ogihara, *Chem. Pharm. Bull.*, 1993, **41**, 2058.
14 (*a*) F. W. Lichtenthaler, T. Schneider-Adams and S. Immel, *J. Org. Chem.*, 1994, **59**, 6735; (*b*) D. Crich and Z. Dai, *Tetrahedron Lett.*, 1998, **39**, 1681; (*c*) D. Crich and Z. Dai, *Tetrahedron*, 1999, **55**, 1569.
15 K. Tatsuta and S. Yasuda, *Tetrahedron Lett.*, 1996, **37**, 2453.
16 A. Fürstner and I. Konetzki, *Tetrahedron*, 1996, **52**, 15071.
17 K. C. Nicolaou, F. L. van Delft, S. R. Conley, H. J. Mitchell, Z. Jin and R. M. Rodríguez, *J. Am. Chem. Soc.*, 1997, **119**, 9057.
18 (*a*) Y. Zhao, J. B. Biggins and J. S. Thorson, *J. Am. Chem. Soc.*, 1998, **120**, 12986; (*b*) M. Zhao and S. J. Thorson, *Carbohydr. Res.*, 1999, **319**, 184.
19 S. Sarbajna, A. K. Misra and N. Roy, *Synth. Commun.*, 1998, **28**, 2559.
20 (*a*) C. Lugowski and E. Romanowska, *Carbohydr. Res.*, 1983, **118**, 173; (*b*) H. J. Jennings, K.-G. Rosell and D. J. Carlo, *Can. J. Chem.*, 1980, **58**, 1069; (*c*) E. Katzenellenbogen and H. J. Jennings, *Carbohydr. Res.*, 1983, **124**, 235; (*d*) N. Ohno, T. Yadomae and T. Miyazaki, *Carbohydr. Res.*, 1980, **80**, 297; (*e*) L. M. Beynon, J. C. Richards and M. B. Perry, *Can. J. Chem.*, 1992, **70**, 218.
21 H. J. Jennings, *Adv. Carbohydr. Chem. Biochem.*, 1983, **41**, 155.
22 P. Smith, D. Oberhoizer, S. Hayden-Smith, H. J. Koornhof and M. R. Hillerman, *J. Am. Med. Assoc.*, 1977, **238**, 2613.
23 M. Nilsson and T. Norberg, *J. Chem. Soc., Perkin Trans. 1*, 1998, 1699.
24 (*a*) T. Krishnamurthy, C.-J. Lee, J. Henrichsen, D. J. Carlo, T. M. Stoudt and J. B. Robbins, *Infect. Immun.*, 1978, **22**, 727; (*b*) S. C. Szu, C.-J. Lee, J. C. Parke, Jr., G. Schiffman, J. Henrichsen, R. Austrian, S. C. Rastogi and J. B. Robbins, *Infect. Immun.*, 1978, **22**, 777.
25 E. Kaji, F. W. Lichtenthaler, Y. Osa, K. Takahashi and S. Zen, *Bull. Chem. Soc. Jpn.*, 1995, **68**, 2401.
26 E. Bousquet, M. Khitri, L. Lay, F. Nicotra, L. Panza and G. Russo, *Carbohydr. Res.*, 1998, **311**, 171.
27 (*a*) Y. Osa, E. Kaji, K. Takahashi, M. Hirooka, S. Zen and F. W. Lichtenthaler, *Chem. Lett.*, 1993, 1567; (*b*) Y. Osa, E. Kaji, K. Takahashi, M. Hirooka, S. Zen and F. W. Lichtenthaler, *Bull. Chem. Soc. Jpn.*, 1994, **67**, 1130.
28 E. Kaji, N. Anabuki and S. Zen, *Chem. Pharm. Bull.*, 1995, **43**, 1441.
29 (*a*) H. Paulsen, *Angew. Chem., Int. Ed. Engl.*, 1982, **21**, 155; (*b*) H. Paulsen, *Angew. Chem., Int. Ed. Engl.*, 1990, **29**, 823.
30 G. H. Veeneman, *Carbohydrate Chemistry*, Chapman and Hall, New York, 1998, p. 149.
31 (*a*) J. Banoub, *Chem. Rev.*, 1992, **92**, 1167; (*b*) S. J. Danishefsky and M. T. Bilodeau, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 1380; (*c*) K. Toshima and K. Tatsuta, *Chem. Rev.*, 1993, **93**, 1503; (*d*) G.-J. Boons, *Contemp. Org. Synth.*, 1996, 173; (*e*) P. J. Garegg, *Acc. Chem. Res.*, 1992, **25**, 575; (*f*) M. Shimizu, H. Togo and M. Yokoyama, *Synthesis*, 1998, 799.
32 G. H. Veeneman, *Carbohydrate Chemistry*, Chapman and Hall, New York, 1998, p. 161.
33 G.-J. Boons, *Carbohydrate Chemistry*, Chapman and Hall, New York, 1998, p. 10.
34 (*a*) H. Ohtake, T. Iimori and S. Ikegami, *Tetrahedron Lett.*, 1997, **38**, 3413; (*b*) H. Ohtake, T. Iimori and S. Ikegami, *Tetrahedron Lett.*, 1997, **38**, 3415.
35 R. J. Tennant-Eyles, B. G. Davis and A. J. Fairbanks, *Chem. Commun.*, 1999, 1037.
36 T. Yamanoi, K. Nakamura, H. Takeyama, K. Yanagihara and T. Inazu, *Bull. Chem. Soc. Jpn.*, 1994, **67**, 1359.
37 Y. Wantanabe, C. Nakamoto and S. Ozaki, *Synlett*, 1993, 115.
38 X. Ding, G. Yang and F. Kong, *Carbohydr. Res.*, 1998, **310**, 135.
39 P. Grice, S. V. Ley, J. Pietruszka, H. M. I. Osborn, H. W. M. Priepke and S. L. Warriner, *Eur. J. Chem.*, 1997, **3**, 431.
40 I. Matsuo, Y. Nakahara, Y. Ito, T. Nukada, Y. Nakahara and T. Ogawa, *Bioorg. Med. Chem.*, 1995, **3**, 1455.
41 R. K. Jain and K. L. Matta, *Carbohydr. Res.*, 1996, **282**, 101.
42 J. Kerékgyárto, J. G. M. van der Ven, J. P. Kamerling, A. Lipták and J. F. G. Vliegenthart, *Carbohydr. Res.*, 1993, **238**, 135.
43 K. K.-C. Liu and S. J. Danishefsky, *J. Org. Chem.*, 1994, **59**, 1892.
44 S. J. Danishefsky, S. Hu, P. F. Cirillo, M. Eckhardt and P. H. Seeberger, *Eur. J. Chem.*, 1997, **3**, 1617.
45 F. W. Lichtenthaler and T. Schneider-Adams, *J. Org. Chem.*, 1994, **59**, 6728.
46 F. W. Lichtenthaler, U. Kläres, Z. Szurmai and B. Werner, *Carbohydr. Res.*, 1998, **305**, 293.
47 E. Kaji and F. W. Lichtenthaler, *J. Carbohydr. Chem.*, 1995, **14**, 791.
48 A. Banaszek and W. Karpiesiuk, *Carbohydr. Res.*, 1994, **251**, 233.
49 L. Cipolla, L. Lay and F. Nicotra, *J. Org. Chem.*, 1997, **62**, 6678.
50 (*a*) K.-I. Sato and A. Yoshitomo, *Chem. Lett.*, 1995, 39; (*b*) K.-I. Sato, A. Yoshitomo and Y. Takai, *Bull. Chem. Soc. Jpn.*, 1997, **70**, 885.
51 I. Matsuo, M. Isomura, R. Walton and K. Ajisaka, *Tetrahedron Lett.*, 1996, **37**, 8795.
52 A. Fürstner and I. Konetzki, *Tetrahedron Lett.*, 1998, **39**, 5721.
53 S. Weiler and R. R. Schmidt, *Tetrahedron Lett.*, 1998, **39**, 2299.
54 (*a*) C. Unverzagt, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 1102; (*b*) J. Seifert and C. Unverzagt, *Tetrahedron Lett.*, 1996, **37**, 6527.
55 (*a*) C. Unverzagt, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 2350; (*b*) J. Seifert and C. Unverzagt, *Tetrahedron Lett.*, 1997, **38**, 7857; (*c*) C. Unverzagt, *Carbohydr. Res.*, 1998, **305**, 423.
56 G. Stork and J. J. La Clair, *J. Am. Chem. Soc.*, 1996, **118**, 247.
57 A. Dan, Y. Ito and T. Ogawa, *Tetrahedron Lett.*, 1995, **36**, 7487.
58 (*a*) A. Dan, Y. Ito and T. Ogawa, *J. Org. Chem.*, 1995, **60**, 4680; (*b*) A. Dan, Y. Ito and T. Ogawa, *Carbohydr. Lett.*, 1996, 496; (*c*) A. Dan, M. Lergenmüller, M. Amano, Y. Nakahara, Y. Ito and T. Ogawa, *Eur. J. Chem.*, 1998, **4**, 2182.
59 Y. Ito and T. Ogawa, *J. Am. Chem. Soc.*, 1997, **119**, 5562.
60 Y. Ito, Y. Ohnishi, T. Ogawa and Y. Nakahara, *Synlett*, 1998, 1102.
61 M. Lergenmüller, T. Nukada, K. Kuramochi, A. Dan, T. Ogawa and Y. Ito, *Eur. J. Org. Chem.*, 1999, 1367.
62 T. Ziegler, G. Lemanski and A. Rakoczy, *Tetrahedron Lett.*, 1995, **36**, 8973.
63 S. C. Ennis, A. J. Fairbanks, R. J. Tennant-Eyles and H. S. Yeates, *Synlett*, 1999, 1387.
64 D. Crich and S. Sun, *J. Org. Chem.*, 1996, **61**, 4506.
65 D. Crich and S. Sun, *J. Org. Chem.*, 1997, **62**, 1198.
66 D. Crich and S. Sun, *J. Am. Chem. Soc.*, 1997, **119**, 11217.
67 (*a*) D. Crich and S. Sun, *J. Am. Chem. Soc.*, 1998, **120**, 435; (*b*) D. Crich and S. Sun, *Tetrahedron*, 1998, **54**, 8321.
68 (*a*) C.-H. Wong, R. L. Halcomb, Y. Ichikawa and T. Kajimoto, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 412; (*b*) Manuscripts presented at 4th International Symposium on Biocatalysis and Biotransformations to appear in *J. Mol. Catal. B*: *Enzym.*
69 (*a*) T. Usui, M. Suzuki, T. Sato, H. Kawagishi, K. Adachi and H. Sano, *Glycoconjugate J.*, 1994, **11**, 105; (*b*) G. Vic, J. J. Hastings and D. H. G. Crout, *Tetrahedron: Asymmetry*, 1996, **7**, 1973; (*c*) N. Taubken and J. Thiem, *Glycoconjugate J.*, 1998, **15**, 757.
70 (*a*) S. Sing, M. Scigelova and D. H. G. Crout, *Chem. Commun.*, 1996, 993; (*b*) S. Sing, M. Scigelova and D. H. G. Crout, *J. Chem. Soc., Perkin Trans. 1*, 1999, 777.
71 (*a*) G. M. Watt, L. Revers, M. C. Webberley, I. B. H. Wilson and S. L. Flitsch, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 2354; (*b*) G. M. Watt, L. Revers, M. C. Webberley, I. B. H. Wilson and S. L. Flitsch, *Carbohydr. Res.*, 1998, **305**, 533; (*c*) G. M. Watt, L. Revers, R. M. Bill, I. B. H. Wilson and S. L. Flitsch, *Biochem. Biophys. Acta*, 1999, **1428**, 88.
72 J. Bruckova, D. Crich and Q. Yao, *Tetrahedron Lett.*, 1994, **36**, 6619.
73 J. Bruckova, D. Crich and S. Sun, *J. Org. Chem.*, 1996, **61**, 605.
74 D. Crich, J.-T. Hwang and H. Yuan, *J. Org. Chem.*, 1996, **61**, 6189.
75 N. Yamazaki, E. Eichenberger and D. P. Curran, *Tetrahedron Lett.*, 1994, **35**, 6623.
76 Y. Yahiro, S. Icikawa, S. Shuto and A. Matsuda, *Tetrahedron Lett.*, 1999, **40**, 5527.
77 G. Hodosi and P. Kovác, *J. Am. Chem. Soc.*, 1997, **119**, 2335.
78 G. Hodosi and P. Kovác, *Carbohydr. Res.*, 1997, **303**, 239.
79 G. Hodosi and P. Kovác, *Carbohydr. Res.*, 1998, **308**, 63.
80 W.-S. Kim, H. Sasai and M. Shibasaki, *Tetrahedron Lett.*, 1996, **37**, 7797.
81 (*a*) W.-S. Kim, S. Hosono, H. Sasai and M. Shibasaki, *Heterocycles*, 1996, **42**, 795; (*b*) W.-S. Kim, S. Hosono, H. Sasai and M. Shibasaki, *J. Org. Chem.*, 1995, **60**, 4.
82 K. Toshima. K.-I. Kasumi and S. Matsumura, *Synlett*, 1998, 643.