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Minireview

Intramolecular aglycon delivery

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Abstract—A Minireview with 51 references covering the two-step tethering and intramolecular glycosylation process termed intramolecular aglycon delivery (IAD). Specifically, glycosylation reactions where the tethered oxygen acts as nucleophile are covered. In the majority of cases, tethering to O-2 of a glycosyl donor ensures formation of a 1,2-*cis* glycoside after intramolecular glycosylation.

Keywords: Intramolecular aglycon delivery; Glycosylation; Tethering; 1,2-*cis* Glycosides; Beta-mannosides

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1. Introduction

The idea of using the stereochemistry at the 2-position to induce stereoselectivity in the glycosylation reaction is well established in carbohydrate chemistry: ester protecting groups at C-2 take part in a neighbouring group participation process in glycosylation reactions, resulting in 1,2-*trans* products. In a complementary approach, the stereochemistry at C-2 can be used to dictate a 1,2-*cis* outcome from a two-step tethering–glycosylation process called intramolecular aglycon delivery (IAD) (Fig. 1). In the first step, the aglycon is tethered to the glycosyl donor by a temporary tether; this Minireview covers specifically those intramolecular glycosylation reactions where the oxygen that is to be glycosylated is the same one as that used for tethering. The aglycon is normally tethered to the 2-position of the donor, ensuring a 5-membered ring transition state in a subsequent intramolecular glycosylation step, and complete stereocontrol for the formation of the 1,2-*cis* product. Loss of the tether gives the glycoside with OH-2 free. This Minireview brings together IAD reactions reported in the literature 1992 to date, ordered after tethering method. Some aspects have also been covered in earlier reviews.[1,2]

2. Acid-catalysed acetal tethering

Hindsgaul and Barresi introduced the concept of intramolecular aglycon delivery, demonstrating it for the

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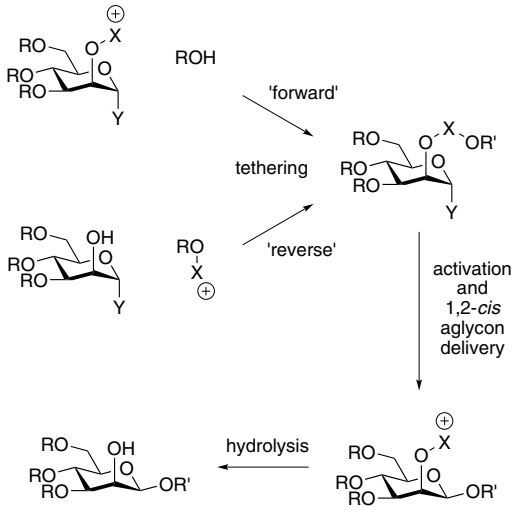
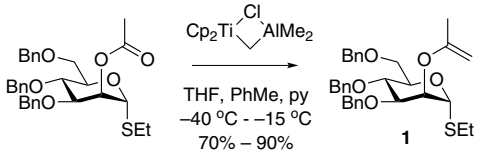


Figure 1. The intramolecular aglycon delivery concept for the formation of β-mannosides.

synthesis of β-mannosides using a mixed acetal tether.[3] Tethering was carried out using acid-catalysed (with CSA or TsOH) addition of the aglycon alcohol to an enol ether (e.g., **1**), which had been formed by the action of the Tebbe reagent on a mannose-2-*O*-acetate (Scheme 1).

Tethering under these conditions gave a reasonable yield of the mixed acetal from a primary alcohol **2** and an unhindered (i.e., monosaccharide) donor bearing the enol ether **1** (Table 1, entry 1). The reaction is very sensitive to steric effects, however, and increasing the bulk either of the alcohol (secondary alcohols **3**, **4** and disaccharide alcohols **5**) or of the enol ether component (di- **6** or trisaccharide **7** donors) caused significant decreases in the yield of mixed acetal formation (Table 1, entries 2–8).[3–5] The reaction time was also found to be critical: longer reaction times led to scrambling and formation of undesired symmetrical acetals, meaning that great care was needed to reproduce the optimum couplings. Furthermore, the stability of the mixed acetals was found to be rather low for the sterically hindered examples, meaning that they must be stored in basic solution to avoid decomposition.

Upon treatment with NIS, the mixed acetals underwent an intramolecular glycosylation to give the β-mannosides as sole glycosylated products in all cases. The isopropylidene tether was lost to give a free OH-group at C-2. No α-products were formed in any of the glycosylation reactions examined. Addition of a hindered base, 2,6-di-*tert*-butyl-4-methyl-pyridine (DTBMP), was found to increase the glycosylation yields, possibly by stopping the breakdown of mixed acetals. Other, less hindered, bases were not compatible with the glycosylation. More sterically hindered systems gave lower glycosylation yields, and also longer reaction times. Some competition experiments with the addition of external methanol (1 equiv) to glycosylation reactions were also carried out, from which it was concluded that the glycosylation was indeed intramolecular, and was S_N2-like.[5] Activation of mixed acetals **8** with NBS gave a major glycosylated product in which a presumed intermediate carbocation had been trapped by succinimide to give a mixed *N*,*O*-acetal **9**, along with a minor amount of the glycoside with OH-2 free **10** (Scheme 2).[5] Attempts at a convergent approach to the *N*-glycan core pentasaccharide with its key β-*manno* linkage were not successful with this early methodology.



Scheme 1.

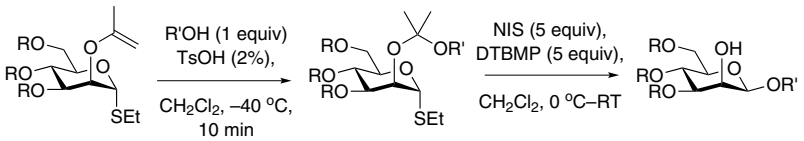
3. Silicon tethering

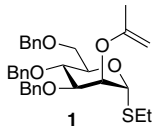
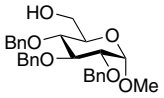
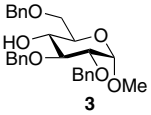
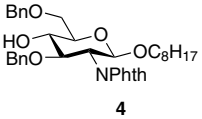
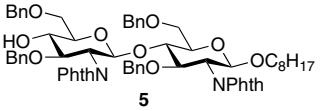
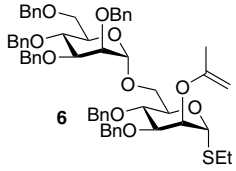
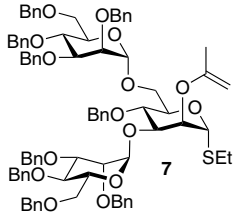
Stork introduced silicon-tethered IAD using mannosyl sulfoxides as donors.[6] The tethering–glycosylation procedure was as follows: A dimethylchlorosilyl ether (2.5 equiv) derived from the aglycon alcohol was coupled to OH-2 of a mannose thioglycoside **12** (1 equiv), to give mixed silyl acetals in essentially quantitative yield after chromatography. The tethered intermediates were oxidised to the glycosyl sulfoxides, which, upon activation with triflic anhydride in the presence of the hindered base DTBMP underwent intramolecular glycosylation to give the β-mannosides. No α-anomers were seen, and this process was reported for methanol, isopropanol and two primary carbohydrate alcohols **2** and **11** (Scheme 3). The process gave β-mannosides in similar yields starting from either the α- or β-configured thiomannoside donor.

A subsequent article described a modified tethering procedure where equimolar amounts of the donor **13** and acceptor alcohols were mixed with 1 equiv Me_2SiCl_2 to give the tethered intermediates.[7] Oxidation of the thioglycoside to the sulfoxide was carried out prior to tethering in this procedure.

The tethering and glycosylation worked well for a number of primary **2** and secondary **4**, **14**–**16** carbohydrate alcohols (Table 2), but a limitation was found in the form of an O-4 glucose aglycon **3**. In this case, the major product from the glycosylation was formed by attack by O-6 at the anomeric position with concomitant 6-O-debenzylation to give a (β1→6)-linked glycoside **17** (Fig. 2) as the major product (82%) along with 12% of the (β1→4)-linked compound. The same side reaction was seen to a lesser extent with a glucosamine acceptor **4**.

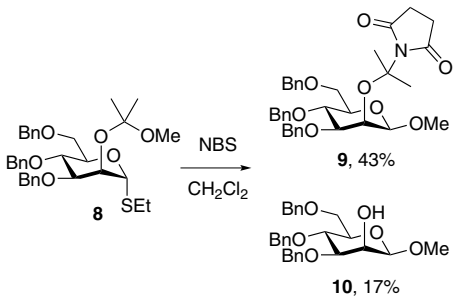
Table 1. Hindsgaul's acid-catalysed tethering and glycosylations



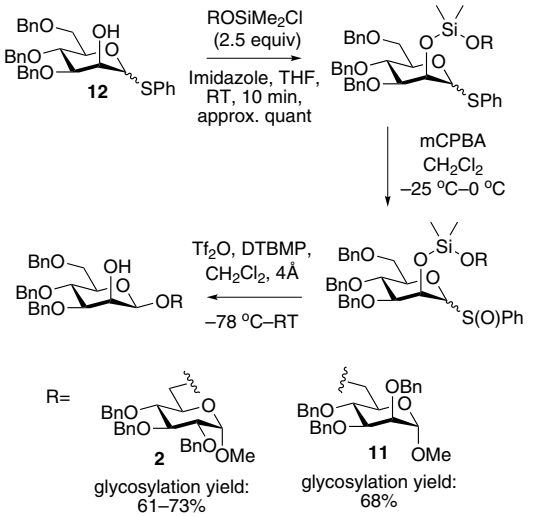
Entry	Donor	Acceptor R′OH	Yield of mixed acetal (%)	Yield of β-mannoside (%)
1	 **1**	 **2**	74	61[3,5]
2	**1**	 **3**	57	77[4,5] 42[a,3]
3	**1**	 **4**	55	51[4,5] 27[a,4]
4	**1**	 **5**	38	27[5]
5	 **6**	**4**	25	28[5]
6	**6**	**5**	8[b]	Not attempted[5]
7	 **7**	**2**	No product	[5]
8	**7**	**3**	No product	[5]

[a] Yield without DTBMP.
[b] Reaction carried out in the presence of $CaSO_4$.

Bols independently investigated silicon-tethered IAD, working in the *gluco* and *galacto* series. Using an acetate-protected α-thioglucoside donor **19**, he found that primary, secondary and tertiary alcohols underwent tethering and 1,2-*cis* glycosylation (promoted by NIS/TfOH) to give the α products in essentially the same yields, ruling out significant steric effects (Table 3).[8,10] He went on to investigate the formation of disaccharides from primary **21** and secondary **15**,**22** aglycon alcohols.[9,11] Glycosylation of the secondary alcohol **15** was low yielding, apparently due to hydrolysis of the tether. Omitting the acid from the activation mixture and carrying out the reaction at 100 °C in nitromethane gave a better yield of the α-glucoside (Table 3, entry 5). Switching to an armed donor **20** and carrying out the glycosylation at RT gave a better yield of the disaccharide



Scheme 2.



Scheme 3.

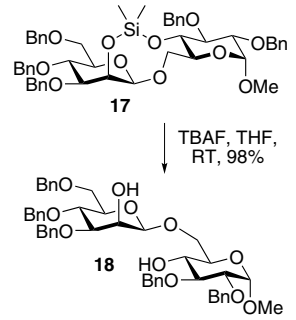
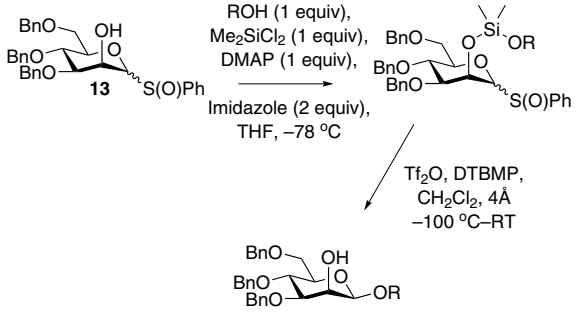


Figure 2.

Table 2. Stork's silicon-tethered β-mannosylation



Entry	Alcohol ROH	Tethering yield (%)	Glycosylation yield (%)
1	**2**	89	92
2	**14**	84	65
3	**15**	88	82
4	**3**	98	12
5	**16**	60	48
6	**4**	78	54

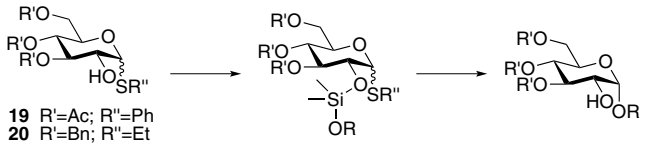
product derived from an unreactive aglycon **22** (Table 3, entries 7 and 8). For all these glycosylation reactions the α-glucoside was the only glycosylated product. Bols also tested a *galacto* donor **23**, and was able to glycosylate a secondary carbohydrate alcohol **15** (Scheme 4).[9,11] In addition to disaccharide **25**, a by-product **24** was formed due to debenzylation, which, in contrast to Stork's observation, seemed to be formed *after* glycosylation. Leaving the corresponding glucosylation reaction (from **15** and **19**) for a longer time gave an analogous debenzylated product.

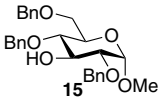
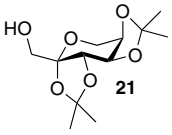
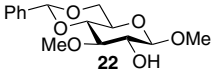
The intramolecular nature of the silicon-tethered α-glucosylation was investigated with a competition experiment, which gave α-glucosides due to intramolecular glycosylation predominating over glucosides derived from an external nucleophile.[10] An intermolecular glycosylation under the same conditions gave an α/β mixture, albeit with a preponderance of the α anomer. Some other anomeric leaving groups were also investigated without success: piperidine or methylpiperidinium glycosides bearing a silyl-tethered alcohol at C-2 did not undergo glycosylation, while a glycosyl chloride gave a 1:1 α/β mixture of glycosides.[10]

Bols used the silicon-tethered α-glucosylation for the preparation of kojitriiose (Scheme 5).[12] The first tethering step (between **20** and **26**) is rather low yielding, but tethering and glycosylation yields for the formation of the trisaccharide **29** are at least as good as for the formation of the disaccharide **27**. A selenoglycoside donor **28** is used in this synthesis. In the same paper, the synthesis of sucrose was attempted, but the tethered intermediates (Fig. 3) did not undergo glycosylation to give the corresponding disaccharides.[12]

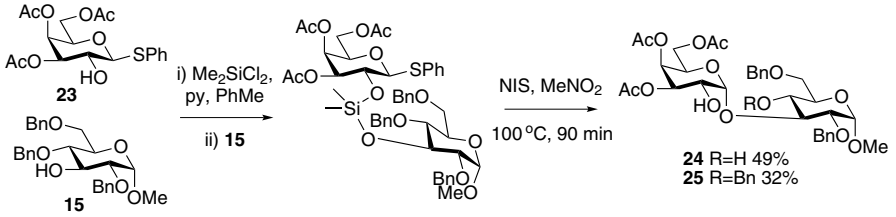
Bols and Hansen investigated whether the silyl-tethered IAD concept could be extended to alcohols other than OH-2 of the glycosyl donor.[13] Octanol was tethered to glucose thioglycosides at OH-3, OH-4 and OH-6, to give **30**–**32**, and to a ribofuranose derivative at OH-5 to give **33**. Activation by NIS in nitromethane gave octyl glycosides in variable yields (Scheme 6). Activation of the material tethered at OH-3 **30** gave an anomeric mixture of glycosides **34**, while for the other

Table 3. Bols' silicon-tethered synthesis of α-glucosides

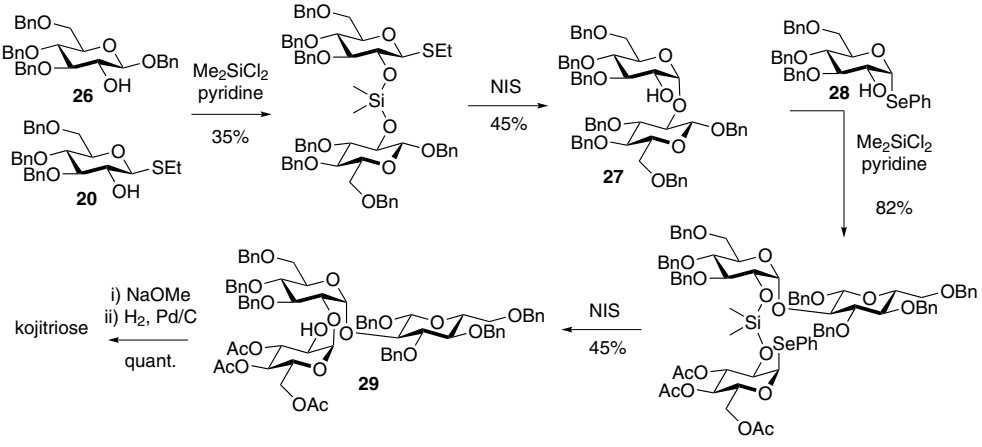


Entry	Donor	Acceptor	Tethering method	Tethering yield (%)	Glycosylation method	Glycosylation yield (%)
1	**19**	$C_8H_{17}OH$	R	75	A	59[8,10]
2	**19**		R	74	A	62[8,10]
3	**19**	^{t}BuOH	R	76	A	61[8,10]
4	**19**	PhOH	R	54	A	72[8,10]
5	**19**	 **15**	R	66	A B	19[9,11] 74[9,11]
6	**19**	 **21**	F	72	B	85[9,11]
7	**19**	 **22**	F	76	B	39[9,11]
8	**20**	**22**	F	93	C	67[11]

Tethering conditions, R: $ROSiMe_2Cl$ (2–3 equiv), py, THF, 2 h, rt; F: $SiMe_2Cl_2$ (5 equiv), py, PhMe; remove excess $SiMe_2Cl_2$; ROH (0.67 equiv). Glycosylation conditions, A: NIS (2.5 equiv), TfOH (0.2 equiv), DCM, 10 min, rt; B: NIS (2.5 equiv), $MeNO_2$, 100 °C; C: NIS (2.5 equiv), $MeNO_2$, rt.



Scheme 4.



Scheme 5.

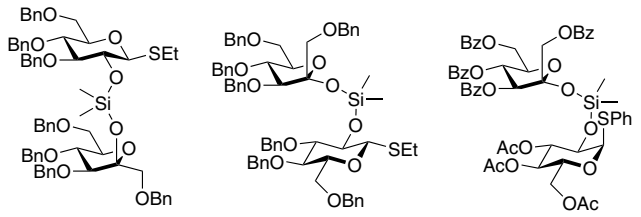


Figure 3.

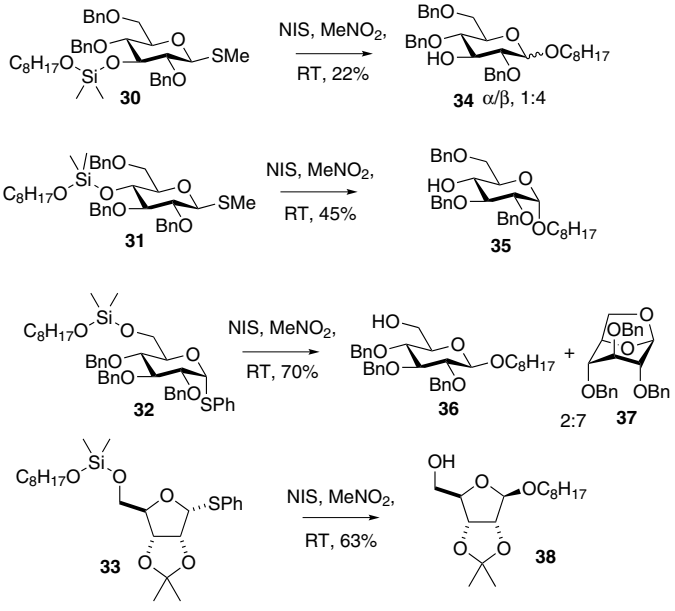
examples investigated, only the glycoside formally *cis* to the tethering OH-group was formed (i.e., **35**, **36**, **38**), although for the O-6-tethered material **32**, competing 1,6-anhydrosugar **37** formation reduced the yield of glycoside.

Rychnovsky and Packard examined IAD as a possible method for the formation of β-mycosamine linkages.[14] An efficient 1,2-*cis* glycosylation method was needed for a total synthesis of a macrolide antibiotic, where mycosamine is found β-linked to a macrolide core. Cholesterol was used as a model acceptor, and various glycosyl donors, i.e., glycosyl sulfoxide **39**, thioglycoside **40**, selenoglycoside **41** and glycosyl fluoride **42**, were examined (Scheme 7). Dimethylsilyl and diisopropylsilyl tethers were tested. Activation of the different donors **43**–**46** under appropriate reaction conditions resulted in glycosylation, and the silicon tether stayed in place, trapped by different nucleophiles (e.g., SPh, OH or F) depending on the reaction conditions. Cleavage of the tether gave the β-glycoside **47** as the only glycosylated product in all cases. Despite this successful formation of β-mycosamine linkages, the method was not used in the macrolide synthesis due to acid-lability of the macrolide aglycon.

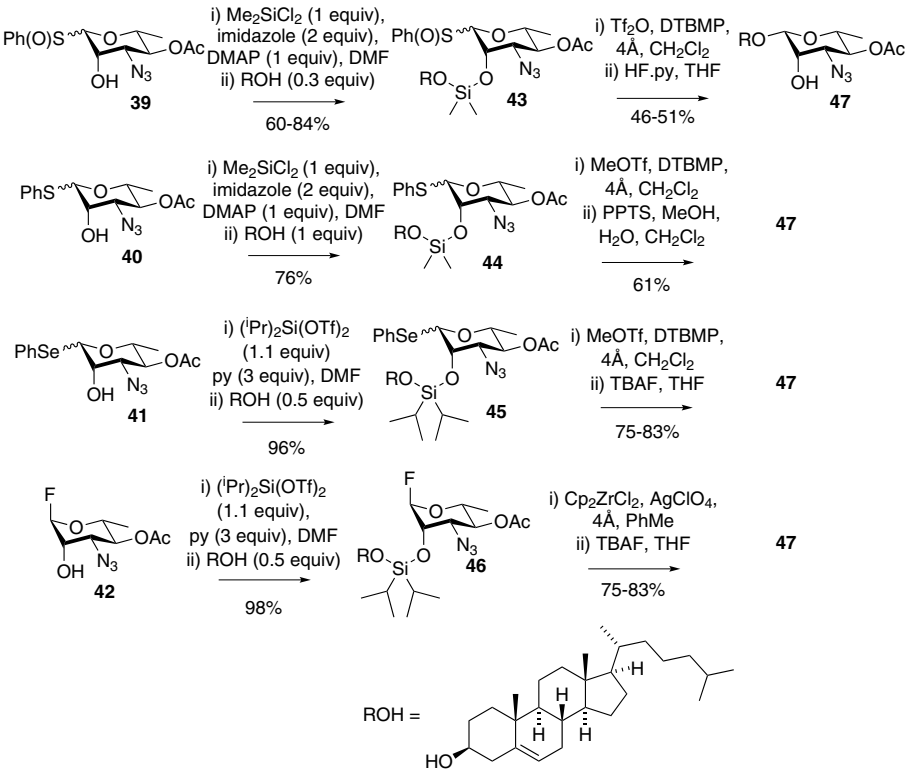
Skrydstrup and co-workers developed a method for dialkyl silaketal synthesis for alkyl groups other than methyl.[15] *n*-Pentenyl chlorodialkylsilyl ethers (e.g., **49**) could be prepared and distilled. Addition of one alcohol **48** gave a silaketal **50** that was stable enough to be purified by chromatography. Subsequent activation of the *n*-pentenyl group with an iodonium source enabled the addition of a second alcohol **2** to give a mixed silaketal **51** (Scheme 8). The preferential activation of the *n*-pentenyl silyl ether in the presence of an *n*-pentenyl glycoside introduced the possibility for one-pot tethering and glycosylation, but no results from any such studies have been reported.

4. Oxidative tethering: PMB and modified PMB acetals

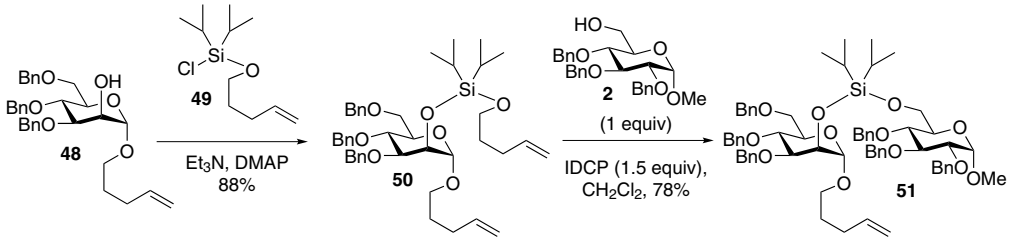
In 1994, Ogawa and Ito introduced a tethering method for use in IAD based on the commonly used *para*-methoxybenzyl (PMB) ether protecting group, and used this for the synthesis of β-mannosides, focussing on the core structure of *N*-glycans in particular.[16] Oxidation of a PMB group generates an oxycarbenium ion that can be captured by an alcohol to give a mixed acetal. When the PMB group is at C-2 of a glycosyl donor, and the alcohol is an appropriate aglycon, the resulting mixed acetals can undergo an intramolecular glycosylation reaction to give the 1,2-*cis* glycoside products. The first paper describes the use of mannosyl fluorides **52** as donors.[16] Tethering mediated by DDQ in DCM was universally high yielding, for primary **53**, secondary **54** and glucosamine (OH-4) **55** alcohols. So efficient was the tethering reaction that chromatographic purification



Scheme 6.



Scheme 7.



Scheme 8.

of the mixed acetals was not necessary before glycosylation. Activation of the glycosyl fluorides by AgOTf, $SnCl_2$ in the presence of DTBMP gave the 1,2-*cis* glycosides as the sole glycosylated products (Table 4). The tether was lost under the reaction conditions to give the glycoside with OH-2 free. The β-mannoside derived from **54** was converted into a glycosphingolipid **56** (Fig. 4).

In subsequent papers from the Ito/Ogawa group, α-methyl thioglycosides **57**, **58**, **61**, **63**–**67** were used as glycosyl donors (Table 5).[17–27] Tethering proceeded very efficiently using a slight excess of either donor or acceptor (typically 1.1–1.4 equiv relative to the other component) to give mixed acetals, which were either purified by size-exclusion chromatography or used crude in the next step. Activation with MeOTf, DTBMP, 4 Å in DCE or DCM gave the β-mannosides exclusively. (DTBMP is necessary to avoid the widespread decomposition during the reaction.) The focus is almost entirely on the formation of the Man(β1→4)GlcNAc linkage found in the core pentasaccharide of *N*-glycans. A [2+3] block approach assembles this pentasaccharide in a single step (Table 5, entry 6).[18] More efficiently, a [2+2] block approach (Table 5, entry 4) can be followed by glycosylation of mannose to give again the core pentasaccharide.[17]

A great increase in efficiency in the glycosylation reaction was seen when O-4 and O-6 were constrained by a

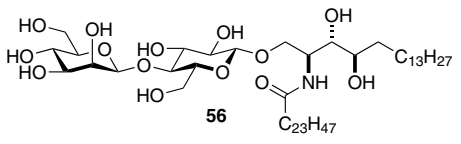


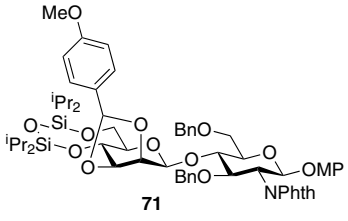
Figure 4.

cyclic protecting group (compare, e.g., Table 5, entries 1, 7, 12–14).[19] This effect was ascribed to the increasing ring-rigidity of the system forcing an S_N2-like reaction (and hence suppressing side reactions). Cyclohexylidene protection was found to have the most beneficial effect, and formation of the Man(β1→4)GlcNAc(β1→4)GlcNAc trisaccharide by IAD with this protecting group on the donor **64** raised the efficiency of the two-step tethering–glycosylation sequence to a highly optimised 85% (Table 5, entry 8).

Interestingly, the cyclic silyl protected donor **67** also glycosylated with high efficiency, despite the low rigidity imparted by this protecting group. Also notable is that in this reaction, the PMB tether is retained in the product **71** as a 2,3-cyclic acetal with loss of the TMS protection from O-3 (Fig. 5).

The fate of the tether in other glycosylation reactions was addressed by Ito:[24] NMR experiments revealed that *para*-methoxybenzaldehyde was formed during the reaction, i.e., that water and an aqueous work-up were not required for its formation. Furthermore, that an oxycarbenium ion derived from the tether (Fig. 6) was not formed after glycosylation in sufficient concentration as to be detectable by ^{1}H NMR spectroscopy. Some questions about this mechanism remain.

In contrast to the tethering systems discussed up until this point (Sections 2 and 3), when a PMB acetal is used as a tether, a new stereogenic centre is created during the tethering process, so that in theory two diastereomeric mixed acetals could be formed in a tethering reaction. During the normal tethering process (Tables 4 and 5), however, only one diastereomer is seen. Ito and Ogawa showed that in a reverse tethering approach, where the PMB ether is attached to the aglycon (i.e., at the position to be glycosylated) and tethered to a glycosyl fluoride with free OH-2, the mixed acetal can be formed, but



71

Figure 5.

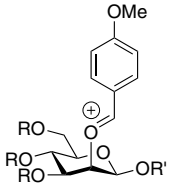
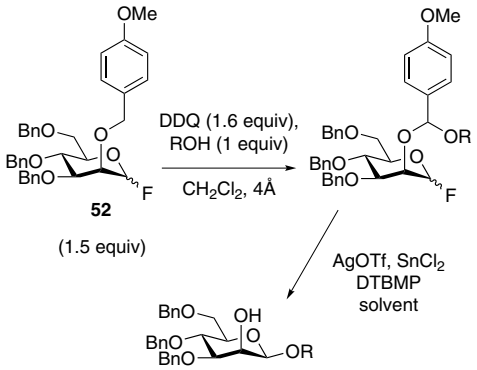
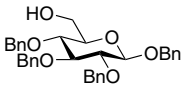
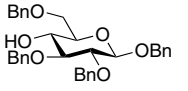
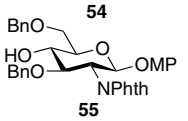


Figure 6.

Table 4. Ogawa's PMB-mediated β-mannosylation using fluorides as glycosyl donors



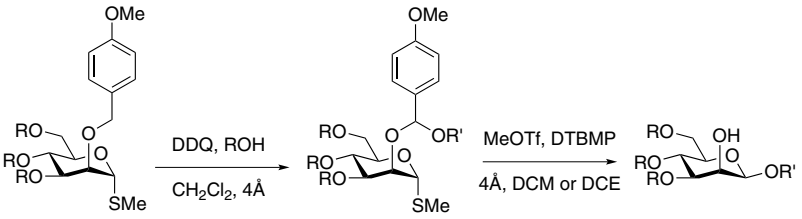
Entry	Acceptor ROH	Yield of β-mannoside (%)
1	 **53**	65–74
2	 **54**	45–52
3	 **55**	40

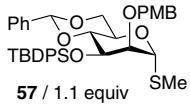
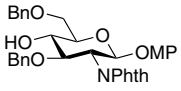
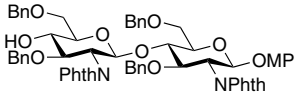
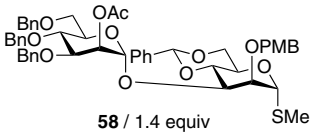
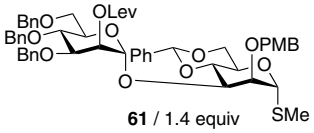
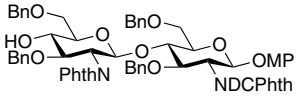
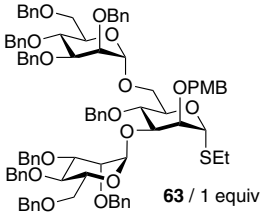
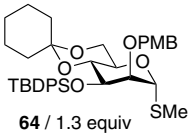
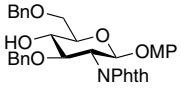
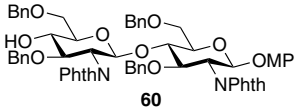
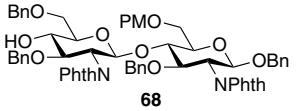
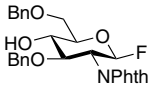
as a different diastereomer (i.e., opposite configuration at the new centre) or a mixture of diastereomers (Scheme 9).[21] The origin of the stereoselectivity is obscure, but it seems that the reaction operates under kinetic control. NOE measurements and computational studies were used to deduce the configuration at the newly formed stereogenic centre (from the forward tethering approach shown in Tables 4 and 5), which was assigned as *S*.

In some cases, the glycosylation of the two diastereomers proceeded in similar yields, which broadens the scope of PMB–IAD,[21] while in other cases significant differences in the yields and reaction rates of glycosylation of different diastereomers were seen. For example, *S* diastereomer **75** (derived from a 'forward' tethering of **64** and **73**) gave a significantly better glycosylation yield of β-mannoside **77** than did the *R* diastereomer **76** (derived from 'reverse' tethering of **72** and **74**) (Scheme 10),[24] which means that this behaviour can vary from case to case.

The Ito group went on to use IAD as a key step in the synthesis of many larger *N*-linked glycan structures: the β-mannosylation of a GlcNAc(β1→4)GlcNAc disaccharide **68** was a key step in the synthesis of a sialylated complex-type undecasaccharide (Table 5, entry 9).[22] A similar β-mannosylation of another GlcNAc(β1→4)GlcNAc disaccharide **70** was a key step in the synthesis of a $Glc_1Man_8GlcNAc_2$ undecasaccharide involved in

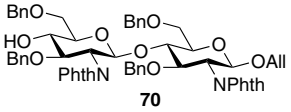
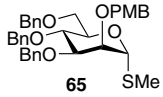
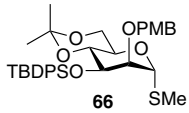
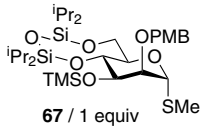
Table 5. Ogawa and Ito's synthesis of *N*-glycan oligosaccharides by PMB–IAD



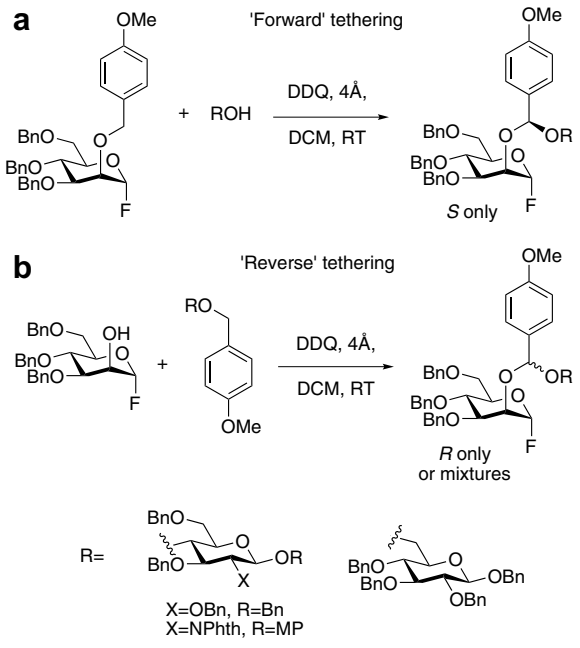
Entry	Donor	Acceptor	Yield of β-mannoside (%)
1	 **57** / 1.1 equiv	 **55** / 1 equiv	60[17]
2	**57**/1.4 equiv	 **60** / 1 equiv	60[17]
3	 **58** / 1.4 equiv	**55**/1 equiv	53[17,20]
4	**58**/1.3 equiv	**60**/1 equiv	49[17] 55[21]
5	 **61** / 1.4 equiv	 **62** / 1 equiv	39[21]
6	 **63** / 1 equiv	**60**/1.3 equiv	37[18]
7	 **64** / 1.3 equiv	 **55** / 1 equiv	83[19]
8	**64**	 **60**	85[19]
9	**64**	 **68**	78[22]
10	**64**	 **69**	83[26,27]

(*continued on next page*)

Table 5 (*continued*)

Entry	Donor	Acceptor	Yield of β-mannoside (%)
11	**64**	 **70**	74[25]
12	 **65**	**55**	29[19]
13	 **66**	**55**	61[19]
14	 **67** / 1 equiv	**55**/1.3 equiv	78[a,19,23]

[a] The product (**71**) from this reaction retains the PMB tether (Fig. 5).

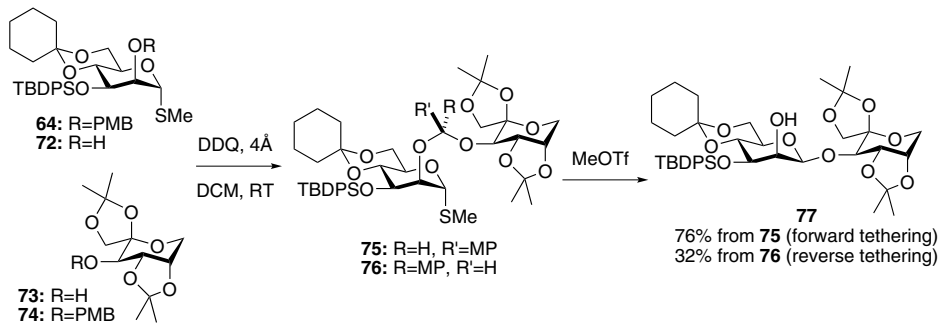


Scheme 9.

N-glycan biosynthesis (Table 5, entry 11).[25] The homologues $Glc_{1-3}Man_9GlcNAc_2$ were synthesised using β-mannosylation of a monosaccharidic GlcNAc fluoride **69** (Table 5, entry 10).[26,27]

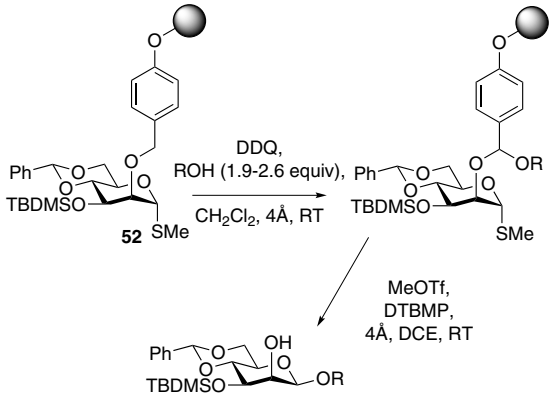
A solid-phase approach to IAD was also investigated.[28] This was based on attachment of the tether to the solid phase (via a *para*-alkyloxybenzyl ether) and was termed a gatekeeper approach, as by-products still containing the tether would be retained on the solid phase, while the desired product would be released into solution. Tethering and glycosylation of various acceptors (**53**, **54**, **69**, **78**) using this method gave the β-mannosides as almost exclusive reaction products, making chromatographic purification very simple (Table 6). Using a glycosyl fluoride **69** as acceptor (Table 6, entry 3) demonstrates compatibility with an orthogonal approach to oligosaccharide synthesis (See also Table 5, entry 10 for a solution-phase example.).

Meanwhile, the PMB tethering system was tested in the synthesis of other 1,2-*cis* glycosides (i.e., not exclusively β-mannosides) by other groups. In 1996, Oscarson and Krog-Jensen reported the successful application of



Scheme 10.

Table 6. Solid-phase 'Gatekeeper' approach to β-mannoside synthesis



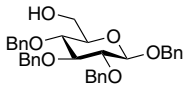
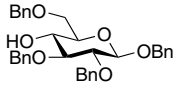
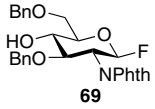
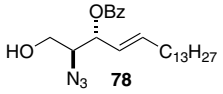
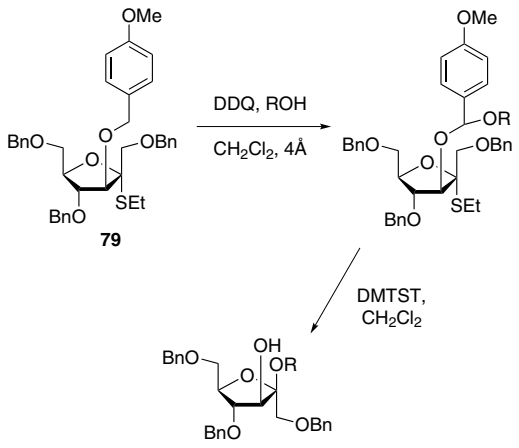
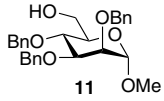
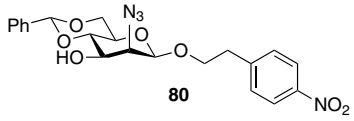
Entry	Acceptor ROH	Yield of β-mannoside (%)
1	 **53**	43
2	 **54**	48–50
3	 **69**	37
4	 **78**	54

Table 7. Oscarson's β-fructofuranoside synthesis using IAD



Entry	Acceptor	Yield of β-fructofuranoside (%)
1	 **11**	77
2	 **80**	76

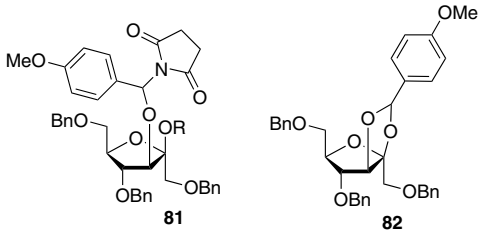


Figure 7.

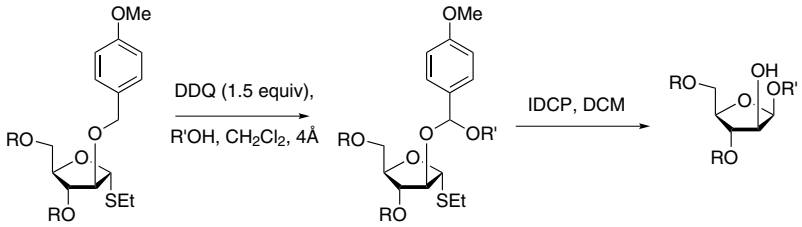
IAD to the synthesis of β-fructofuranosides, which are common in nature, but difficult to synthesise stereoselectively.[29] Using an α-thioethyl fructofuranoside with PMB protection at C-2 **79** as donor, the method was tested with a model primary alcohol **11** and a secondary alcohol **80** relevant for the synthesis of a polysaccharide from *Haemophilus influenzae* type E. Tethering following the Ogawa procedure cleanly gave the mixed acetals. Glycosylation of the crude mixture with DMTST in DCM gave the 1,2-*cis* glycosides in high yield as the sole glycosylated products (Table 7).

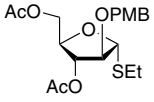
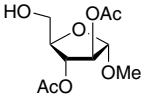
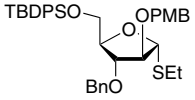
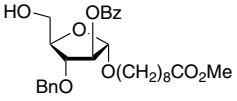
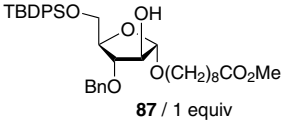
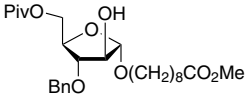
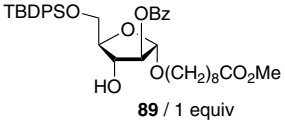
A screen of different promoters and glycosylation solvents for the glycosylation reaction was also made.[30] Activation with NIS resulted in glycosylation, but also in the formation of succinimide-trapped material **81** (*N*,*O*-acetals) that could not be hydrolysed (Fig. 7). IDCP and IDCT gave the β-fructofuranosides in slightly lower yields than DMTST. It is perhaps interesting to note that that no base (DMTBP) or sieves were used in these glycosylations. Using the β-thioglycoside donor in the glycosylations also gave the glycosides, albeit in slightly lower yield than for the α-donor **79** (45% for the primary, 54% for the secondary). Oscarson and Krog-Jensen also introduced the 'reverse approach' tethering (as discussed earlier) to the acetal tethers;[30] reverse-tethered materials gave β-fructofuranosides again in slightly lower yields (53% for the primary, 57% for the secondary alcohol).

Trying this method with ethanol as aglycon gave unexpected complications.[30] The mixed acetal (obtained by the reverse tethering approach) gave, after activation with DMTST, loss of EtOH and the formation of a cyclic PMB acetal **82** as the major product. NIS gave only glycosylated but succinimide-trapped material (**81**). IDCP gave the desired β-fructofuranoside with OH-2 free in good yield (76%).

The Prandi group have used PMB IAD to construct β-arabinofuranoside linkages as found in mycobacterial cell wall polysaccharides.[31–34] Tethering of methanol or various arabinofuranoside alcohols **85**–**89** to 2-*O*-PMB protected donors **83** or **84** under standard oxidative

Table 8. β-Arabinofuranosylation with PMB IAD



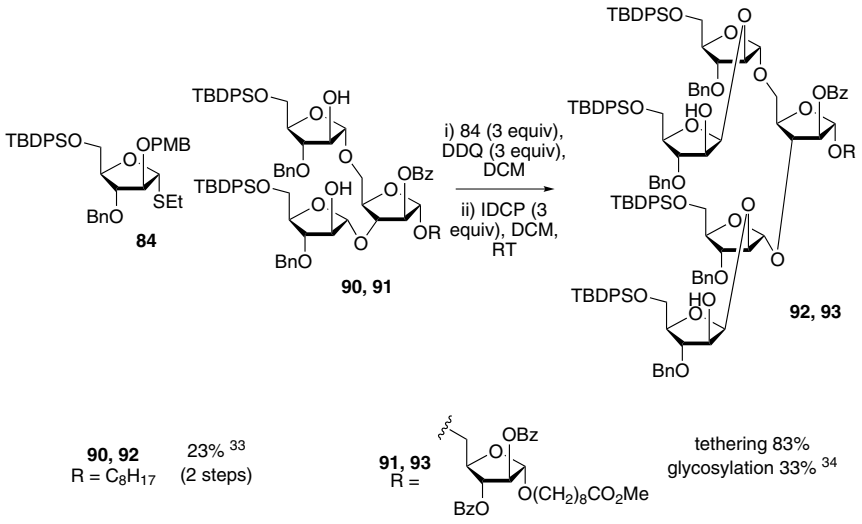
Entry	Donor	Acceptor R′OH	Tethering yield (%)	Yield of β-glycoside (%)
1	 **83** / 1 equiv	MeOH 1 equiv		51[b,31] (2 steps)
2	**83**/1 equiv	 **85** / 1.1 equiv	71	74[b,31]
3	 **84** / 1.1 equiv	 **86** / 1 equiv	66	79[a,33,34]
4	**84**/1.1 equiv	 **87** / 1 equiv	75	70[34]
5	**84**/1.1 equiv	 **88** / 1 equiv	84	74[32,34]
6	**84**/1.1 equiv	 **89** / 1 equiv		74[a,33] (2 steps)

[a] Yield after hydrolysis of trapped materials with DDQ and wet MeCN.
[b] Glycosylation carried out with IDCP and catalytic TMSOTf.

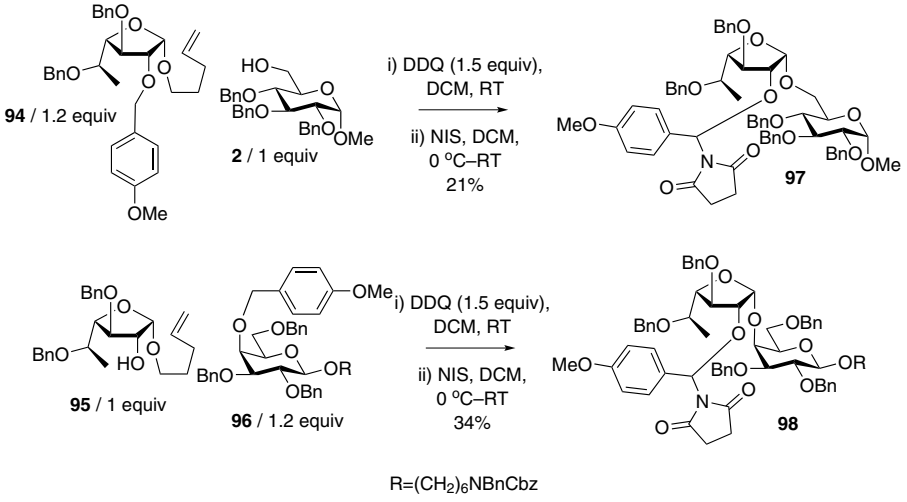
conditions gave the intermediate acetals, which were purified by silica gel chromatography. Activation with IDCP/Me_3SiOTf in DCM gave the β-arabinofuranosides as the exclusive glycosylated products (Table 8). Interestingly, Prandi and co-workers successfully cleaved *para*-methoxybenzaldehyde derivatives after the glycosylation reaction by treatment with catalytic DDQ in wet acetonitrile.[33,34] The disaccharides formed were elaborated into bigger arabinan fragments. Prandi and co-workers also attempted bis-β-arabinosylations using tri-[33] **90** and tetrasaccharide[34] **91** acceptors (Scheme 11). Tethering to the PMB-functionalised donor **84** gave good yields of the mixed acetals, but the glycosylation yields were disappointing, even though the desired bis-β-arabinosylated penta- **92** or hexasaccharides **93** were the only bis-glycosylated products seen.

Ferrieres and co-workers also examined PMB IAD in a furanose context.[35] They were interested in the synthesis of a cell-surface polysaccharide antigen from *Eubacterium saburreum* T19 containing unusual α-D-fucofuranosides bound to D,D-heptoses. They examined the glycosylation of primary and secondary model carbohydrate alcohols using *n*-pentenyl glycosides as glycosyl donors, a first in an IAD context (Scheme 12).

Forward tethering of a primary alcohol **2** and 2-*O*-PMB protected donor **94** gave the mixed acetals, while with an axial alcohol (corresponding to **96**), attempted forward tethering was very slow; however, a reverse tethering approach (**95** + **96**) was successful. Attempted



Scheme 11.



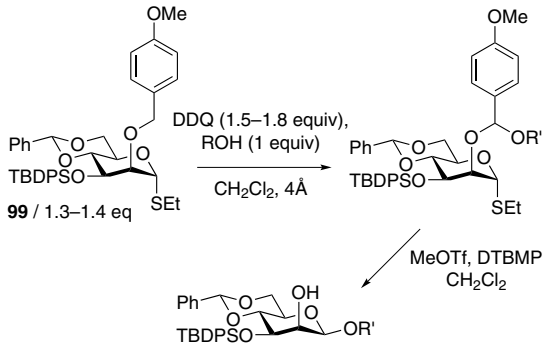
Scheme 12.

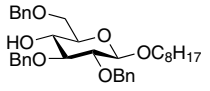
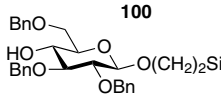
n-pentenyl glycoside activation with NIS/TMSOTf or NIS/Sn(OTf)$_2$ gave general degradation. Activation with NIS alone resulted in glycosylation, but the major glycosylated products were the succinimide-trapped *N*,*O*-acetals **97** and **98**. The *N*,*O*-acetal was cleaved along with the other protecting groups in **98** by hydrogenation; subsequent peracetylation allowed characterisation confirming that the glycosylation had resulted in 1,2-*cis* glycoside formation.

Takeda and co-workers used PMB IAD for the synthesis of Man(β1→4)Glc linkages in the synthesis of oligosaccharides from invertebrate glycosphingolipids, i.e., cholinephosphoryl(→6)GlcNAc(β1→3)Man(β1→4)Glcβ from *Ascaris suum*,[36] and GlcNAc(β1→3)Man(β1→4)-Glc(β1→)Cer and GalNAc(β1→4)GlcNAc(β1→3)Man-(β1→4)Glc(β1→)Cer from *Lucilia caesar*.[37] Standard oxidative tethering of acceptor alcohols **100** and **101** to donor **99** gave the mixed acetals in almost quantitative yield, and subsequent activation of the thioglycoside gave only β-mannosides (Table 9). No explanation for the rather modest glycosylation yields was given.

Bertozzi and co-workers were interested in a high yielding and stereoselective route to symmetrical and unsymmetrical α,α-trehaloses for the synthesis of glycolipids from *Mycobacterium tuberculosis*.[38,39] They modified the PMB approach to use the more electron-rich 3,4-dimethoxybenzyl group (DMB) as a tether. Attaching this to the anomeric position as a glycoside (i.e., a 'reverse' tethering) locked the α anomeric configuration of the acceptor (i.e., **102**, **103**) during an intramolecular glycosylation reaction. A higher yield over the two-step tethering–glycosylation procedure was obtained using this tether than with the usual PMB approach (Table 10, entry 1). Unsymmetrical trehaloses were also built

Table 9. β-Mannosylation en route to invertebrate glycosphingolipids



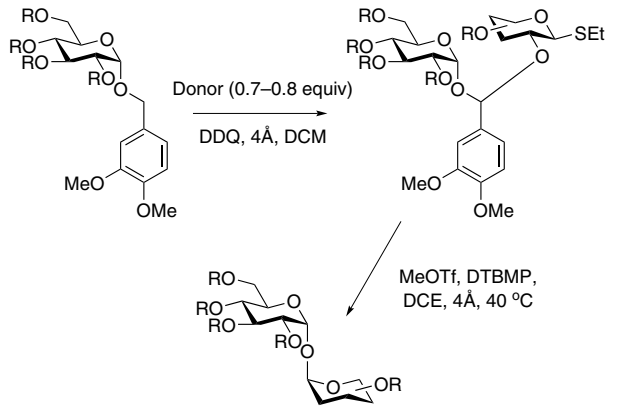
Entry	Acceptor	Yield of β-mannoside (%)
1	 **100**	35[36]
2	 **101**	37[37]

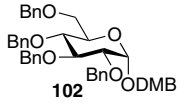
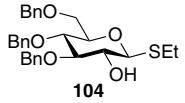
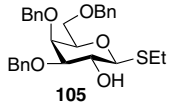
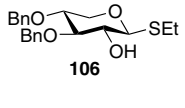
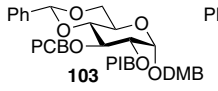
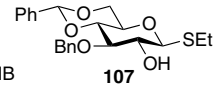
by this method, and in all cases the α,α-trehalose was the only disaccharide product: no α,β or β,α, or β,β products were formed (Table 10).

5. Iodonium tethering: acetals derived from substituted and unsubstituted vinyl ethers

The Fairbanks group have investigated a number of IAD systems all based on electrophilic tethering to enol ethers to give mixed carbon acetals, similar to the original Hindsgaul system (Section 1).[2] This work began with the observation that acid tethering onto the *gluco* vinyl ether **109** (derived from the corresponding acetate by Tebbe methylenation 68%) failed, giving only the product of hydrolysis. Tethering to **109** with NIS at low temperature worked well for primary and simple secondary alcohols in THF or dichloroethane, but not dichloromethane, to give mixed ketals, which could be isolated as diastereomeric mixtures by silica gel chromatography (Table 11).[40,41] Activation of the ketals with NIS in the presence of DTBMP gave high yields of the 1,2-*cis* glycosides in DCM or DCE, while in THF the glycosylations worked less well. The use of NIS both for tethering and for activation of the glycosyl donor opened the opportunity for a one-pot tethering–glycosylation reaction. Treating *gluco* donor **109** with diacetone galactose **110** and NIS (3 equiv) overnight gave an α-glycoside **112**, but the acetal was retained at C-2, trapped by excess alcohol present (Fig. 8). The O-2 acetals could be hydrolysed using an ion-exchange resin to give the desired glycoside with OH-2 free as a single anomer. While only α glycoside was formed in one-pot tethering–glycosylations in DCM or DCE, when ether was used, traces of β anomer were seen, suggesting that in some solvents, intermolecular glycosylation can compete with the intramolecular process.

Table 10. Bertozzi's DMB-mediated IAD for the synthesis of trehaloses



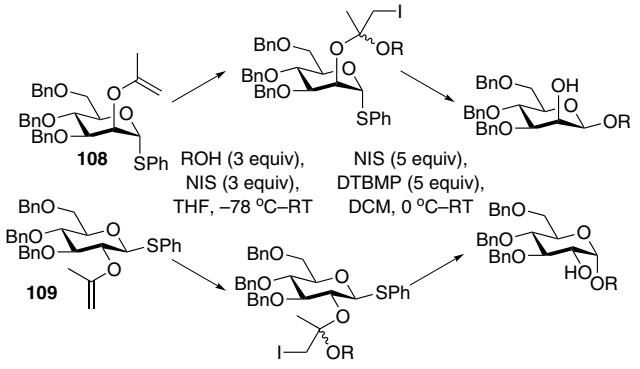
Entry	Acceptor	Donor	Yield of trehalose (%)
1	 **102**	 **104**	68[38] (40)[a,38]
2	**102**	 **105**	93[38]
3	**102**	 **106**	65[38]
4	 **103**	 **107**	ca. 60[39]

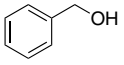
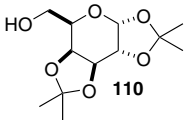
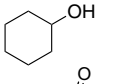
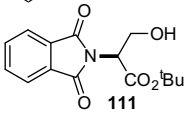
PCB, *para*-chlorobenzyl; PIB, *para*-iodobenzyl; DMB, 3,4-dimethoxybenzyl.
[a] Reaction carried out with a PMB tether.

A similar set of reactions was carried out in the *manno* series (enol ether **108** from Tebbe reaction on the acetate, 70%), with the formation exclusively of 1,2-*cis* glycosides, that is, β-mannosides, in all cases (Table 11). A one-pot tethering–glycosylation of primary alcohol **110** gave the β-mannoside following hydrolytic work-up. It was demonstrated that addition of methanol to a tethered glycosylation reaction did not result in the formation of methyl glycosides, indicating that the reaction is intramolecular.

Fairbanks and co-workers also examined a hybrid tether incorporating a PMB unit **112** (Fig. 9), but using NIS for tethering:[41] This was formed by the action of Tebbe reagent on a 2-*O*-*para*-methoxybenzoate protecting group. Mixed ketals derived from this tether were

Table 11. Iodonium-mediated tethering and intramolecular glycosylation



Entry	Acceptor ROH	Yield of mixed acetals (%)		Yield of 1,2-*cis* glycoside (%)	
		gluco	*manno*	*gluco*	*manno*
1	MeOH	96	92	75	70
2		76	66	75	88
3	 **110**	82	95	86 (68)[a]	63 (84)[a]
4		82	76	65	>99
5	 **111**	56		55	

[a] Reaction yields from one-pot reactions.

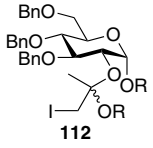


Figure 8.

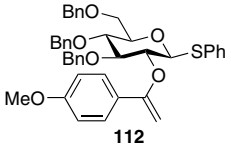
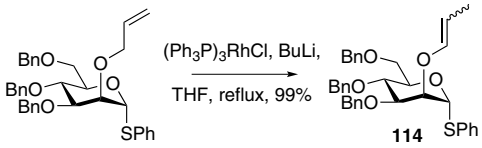


Figure 9.

very unstable and did not survive aqueous work-up. A one-pot approach was also tested: this worked well only for very simple alcohols: methanol and diacetone galactose **110** gave only α glycosides, but for cyclohexanol an α/β mixture was isolated, indicating that intermolecular glycosylation competes effectively with intramolecular glycosylation in this system.



Scheme 13.

In a second generation approach, enol ethers (e.g., **114**) were derived from isomerisation of 2-*O*-allyl protected glycosyl donors in an extremely efficient reaction mediated by a catalyst derived from the action of BuLi on Wilkinson's catalyst (Scheme 13).[42–48] The resulting prop-1-enyl ethers allowed more efficient tethering of primary and secondary carbohydrate alcohols than had been seen for the prop-2-enyl ethers: treatment of the *manno* thiophenyl donor **114** with NIS and the alcohols at low temperature in either THF or DCE in the presence of 4 Å sieves gave high yields of the mixed acetals (as a diastereomeric mixture that could be isolated by chromatography—these acetals were more stable than the ketals derived from the prop-2-enyl ethers) for all but the most unreactive secondary alcohols (Table 12).[42,43] Here, competitive tethering of succinimide produced undesired *N*,*O*-acetals **118** (Fig. 10).

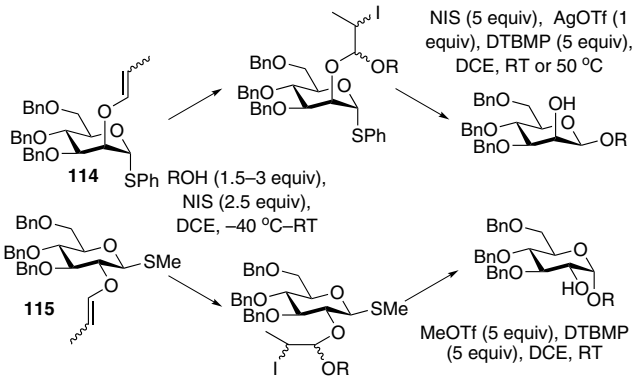
The problem of competitive tethering of succinimide was solved by the use of 'IDCT' generated in situ from I_2, AgOTf and collidine. Using this electrophile with a rather less nucleophilic counter-ion, the tethering yield of hindered alcohol **55** could be increased to 80%.

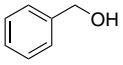
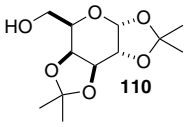
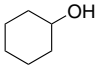
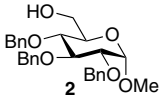
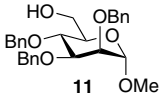
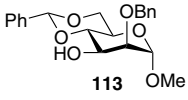
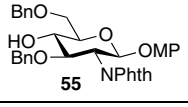
Treatment of the *manno* mixed acetals with NIS/AgOTf in the presence of DTBMP (the role of the base was investigated: reactions were cleaner but slower in the presence of the DTBMP, while with collidine or pyridine the reaction was killed altogether) resulted in glycosylation to give the β-mannosides as single anomers—the glycosylation reactions were noticeably slower than for the Hindsgaul-like system (Table 11). In addition to the disaccharide with mannose OH-2 free, 'trapped materials' where the tether was retained and another nucleophile present in the reaction mixture (e.g., alcohols or succinimide, cf. Fig. 8) was trapped were seen. These acetals could be hydrolysed by treatment with TFA to give further glycoside with OH-2 free.

For *gluco* **115** and *manno* **117** thiomethyl donors, NIS tethering of primary carbohydrate alcohols (**2**, **11**, **110**) also gave the mixed acetals in high yield, but for secondary carbohydrate alcohols (**55**, **113**), the tethering reaction was rather sluggish and the reactions were stopped before completion to avoid activation of the thiomethyl glycoside. Thiomethyl glucosides and mannosides were both activated most efficiently with MeOTf in the presence of DTBMP, again followed by a hydrolytic work-up to destroy any trapped materials and release further glycosylated product.

A *gluco* selenomethyl glycoside **116** was found to be unsuitable as a donor in this form of IAD as the reactiv-

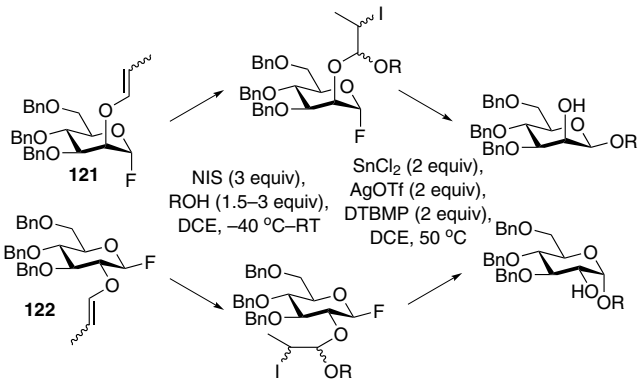
Table 12. Fairbanks' allyl-derived IAD with thioglycoside donors

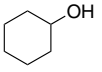
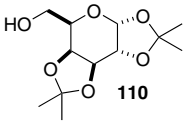
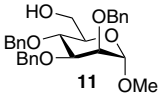
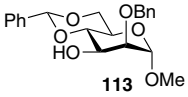
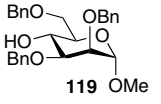
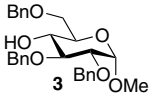
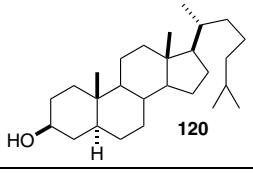


Entry	Acceptor ROH	Yield of mixed acetals (%)		Yield of 1,2-*cis* glycoside (%)	
		gluco	*manno*	*gluco*	*manno*
1	MeOH	98 (36)[a]	93	65	77
2		95	>99 (85)[b]	67	76
3	 **110**	85	95 (80)[b]	70	81 (55)[b]
4		80	76	77	68
5	 **2**	90	36	65	74
6	 **11**	—	63	—	72
7	 **113**	22	85 (55)[b]	—	89
8	 **55**	—	9 (80)[c]	—	60[d]

[a] Reaction carried out with the corresponding *gluco* selenophenyl glycosyl donor **116**.
[b] Reaction carried out with the corresponding *manno* thiomethyl glycosyl donor **117**.
[c] Tethering using IDCT.
[d] Using mixed acetals derived from IDCT tethering.

Table 13. Allyl-derived IAD with glycosyl fluorides



Entry	Acceptor ROH	Yield of mixed acetals (%)		Yield of 1,2-*cis* glycoside (%)	
		gluco	*manno*	*gluco*	*manno*
1	MeOH	99	97	89	76
2		99	99	66	70
3	 **110**	91	98	63	61
4	 **11**	79	80	46	75
5	 **113**	52	83	66	55
6	 **119**	—	37	—	50
7	 **3**	39	—	45	—
8	 **120**	68	72	87	59

ity difference between enol ether and anomeric leaving group was so low that even for methanol as nucleophile, anomeric activation competed effectively with NIS-mediated tethering, meaning that only low yields of mixed acetals could be isolated.

In contrast to the earlier results, attempted one-pot reactions using excess alcohol (i.e., diacetone galactose **110** or cyclohexanol) with a *manno* thiomethyl donor **117** gave anomeric mixtures of products, suggesting that intermolecular reaction successfully competes with intramolecular glycosylation in the allyl-derived IAD

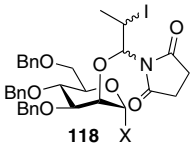
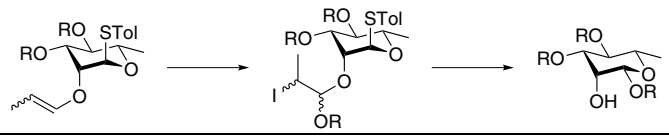
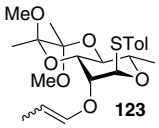
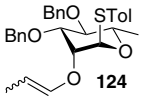
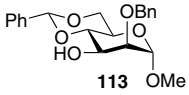
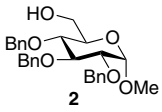
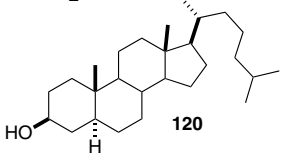

118

Figure 10.

Table 14.



Entry	Donor	Acceptor	Yield of mixed acetals (%)	Yield of 1,2-*cis* glycoside (%)
1	 **123**	MeOH	96[a]	29
2	 **124**	MeOH	88[a]	54
3	**124**	 **113**	82[b]	No disaccharide isolated
4	**124**	 **2**	75[a]	62
5	**124**	 **120**	69[b]	29

[a] Tethering carried out with NIS, ROH (1.5–2 equiv).
[b] Tethering carried out with I_2, AgOTf, DTBMP, ROH (1.05 equiv).

system. However, the intermolecular reaction could be suppressed by using an excess of the glycosyl donor (thus removing all acceptor alcohol from the system) and so the stereospecific reaction was the only operational pathway and the β-mannosides formed exclusively.[42,43] A competition reaction was carried out in which methanol was added as an external nucleophile to the glycosylation reaction of mixed acetals derived from the tethering of benzyl alcohol to manno donor **114**. The benzyl β-mannoside was formed along with both methyl α and β mannosides, confirming that in this system alcohol present in the reaction mixture can successfully compete with an intramolecular process.

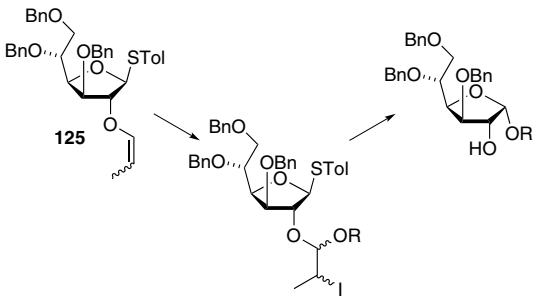
Fairbanks and co-workers went on to examine the use of glycosyl fluorides as donors in both the *gluco* and *manno* series;[44,45] this anomeric leaving group should be completely orthogonal to the tether, thus avoiding competitive activation. Standard NIS tethering to donors bearing isomerised allyl groups at O-2 (**121** and **122**) gave very good yields of the mixed acetals for primary carbohydrate alcohols, and improved yields for secondary carbohydrate alcohols. Tethering is slightly less efficient in the *gluco* series than the *manno* series (Table 13). The formation of some succinimide-tethered *N*,*O*-acetals (cf. Fig. 10) was seen for the more hindered alcohols.

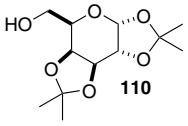
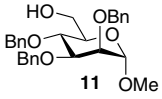
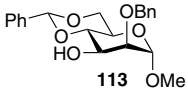
Efficient activation was carried out using a $SnCl_2$/AgOTf/DTBMP promoter system in DCE, though this required heating to proceed at a useful rate. Thus, *gluco*-tethered materials gave exclusively the α-glucosides after activation and acidic work-up, while *manno*-tethered materials gave the β-mannosides after similar activation and acidic work-up. Investigation of the by-products formed in these reactions revealed that they were enol ethers, and were cleaved by wet NIS to give increased yields of the 1,2-*cis* glycosides.

An improved tethering procedure was reported based on a mixture of I_2, AgOTf and DTBMP.[46] This allowed the tethering of hindered substrates in good yields using approximately equimolar quantities of reactants and reagents, which had not been found with NIS-mediated tethering. More mechanistic studies were reported: crossover experiments in both thioglycoside and glycosyl fluoride systems gave no crossover products, meaning that for these systems the allyl IAD is almost certainly entirely intramolecular.[46]

In addition to the synthesis of β-mannopyranosides and α-glycopyranosides, the formation of β-rhamnosides (Table 14) and α-glucofuranosides (Table 15) using allyl IAD was investigated.[47] Tethering of various alcohols to donors **123**, **124** and **125** using NIS or the I_2/AgOTf/DTBMP combination gave good yields of the mixed acetals. However, glycosylation in both of these systems was found to be quite low yielding, but still stereospecific—i.e., only the 1,2-*cis* glycosides were formed in all cases except for one: the attempted β-rhamnosyla-

Table 15.

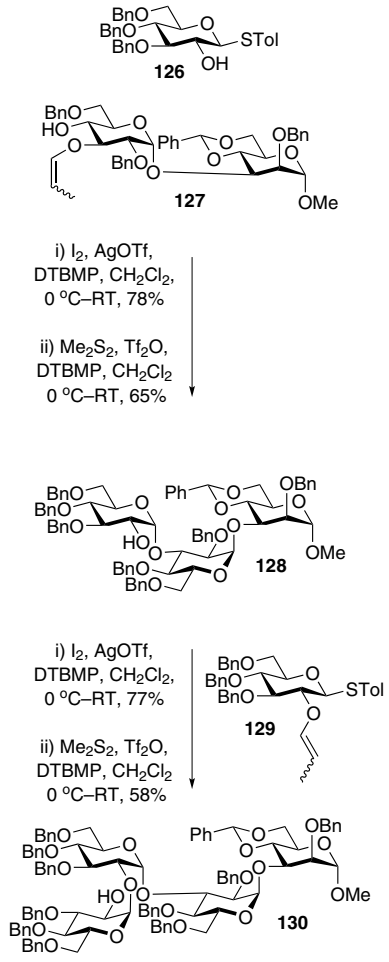


Entry	Acceptor ROH	Yield of mixed acetals (%)	Yield of 1,2-*cis* glycoside (%)
1	 **110**	75[a]	70[c]
2	 **11**	53[a] 64[b]	39[c]
3	 **113**	88[b]	32[d]

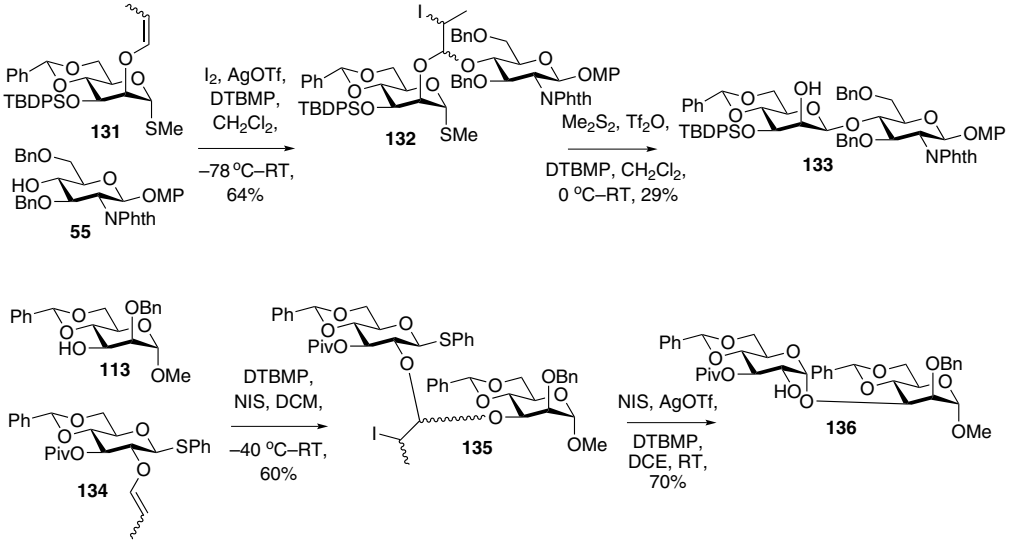
[a] Tethering carried out with NIS, ROH (2 equiv).
[b] Tethering carried out with I_2, AgOTf, DTBMP, ROH (1.05 equiv).
[c] Glycosylation with NIS, AgOTf, DTBMP.
[d] Glycosylation with DMTST, DTBMP.

tion of a secondary carbohydrate alcohol (**124** + **113** Table 14, entry 3), where no product could be isolated.

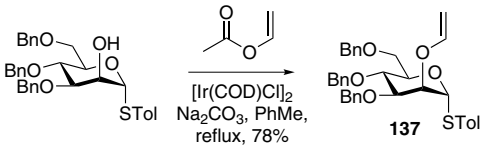
The terminal Glc_3Man tetrasaccharide of the tetradecasaccharide precursor to all *N*-linked glycoproteins was assembled using a so-called iterative allyl IAD approach (Scheme 14).[48] Reverse tethering of disaccharide acceptor **127** to donor **126** and subsequent optimised glycosylation using Me_2S_2/Tf_2O/DTBMP gave the tri-



Scheme 14.



Scheme 15.



Scheme 16.

saccharide **128** in good yield and with complete stereocontrol. The tethering and glycosylation operations were also carried out in one pot, but this gave the α-linked trisaccharide in a lower yield (35% vs 51% for the two-step approach). The trisaccharide **128** was tethered to another donor **129** and glycosylated under the same conditions to give the diastereomerically pure tetrasaccharide **130**. The yields here for tethering and glycosylation remain on the same level for the synthesis of tri- and tetrasaccharides as for the synthesis of disaccharides.

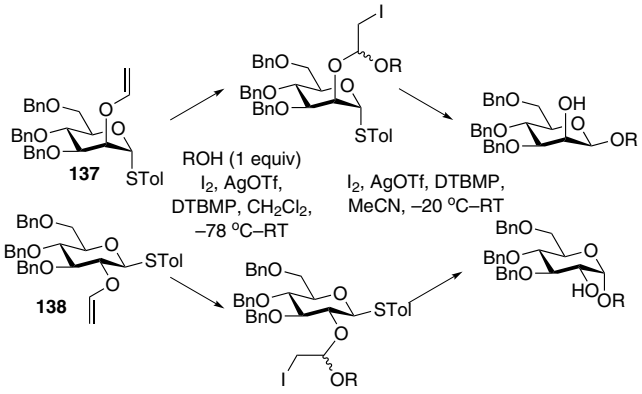
The effect of the protecting group pattern on the donor was investigated (Scheme 15). 4,6-Benzylidene protection did not appear to have a detrimental effect on α-glucosylation:[47] mixed acetals **135** (derived from aglycon **113** and benzylidene-protected donor **134**) were activated to give the α-glucoside **136** in 70% yield. In contrast, mixed acetals **132** derived from benzylidene-protected manno donor **131** underwent intramolecular glycosylation to give the β-mannoside **133** in a lower yield than for the corresponding benzyl ether protected system (cf. Table 12, entry 8).[50]

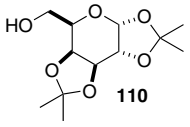
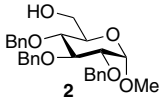
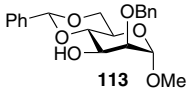
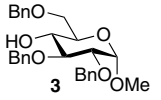
A further method that was investigated was based on tethering to unsubstituted vinyl ethers.[43,49] Vinyl ethers **137** and **138** were synthesised (60–78%) by iridium-catalysed vinylation of donors with OH-2 free (Scheme 16).[49]

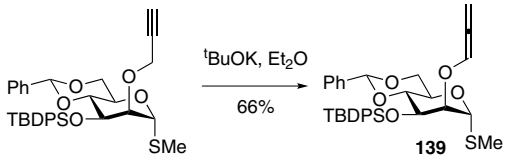
Mixed acetal formation with I_2/AgOTf/DTBMP as iodonium source and 1 equiv alcohol was quite efficient, and higher yielding than the corresponding yields in the allyl ether-derived system (Table 16). Intramolecular glycosylation of mixed acetals derived from **138** and **110** was low yielding with a variety of different promoters (16–51%). The best result (51%) was obtained using the same iodonium source as for tethering, now with acetonitrile as solvent. Various α-glucosides and β-mannosides were synthesised in this way, with a TFA work-up to hydrolyse trapped O-2 acetals derived from the tether after glycosylation to achieve optimum yields. In all cases, the 1,2-*cis* glycosides were the only glycosides seen.

In the Fairbanks group's latest venture into IAD, they investigated the use of propargyl ethers as a tethering device:[50,51] these were isomerised under basic conditions to give allenyl ethers (e.g., **139**, Scheme 17). A possible advantage of such a tethering mode would be that a carbocation produced following intramolecular glycosylation would be better stabilised than in the corresponding allyl case (compare with PMB- and DMB-derived tethers in Section 4). The potential to synthesise the *N*-glycan pentasaccharide core using this approach was investigated.

Table 16. IAD with unsubstituted vinyl ethers and thioglycoside donors



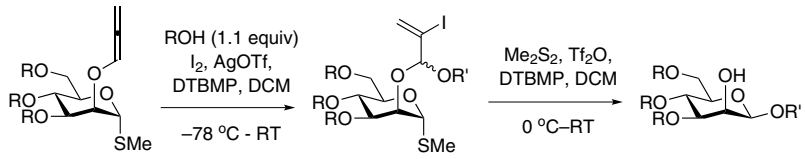
Entry	Acceptor ROH	Yield of mixed acetals (%)		Yield of 1,2-*cis* glycoside (%)	
		gluco	*manno*	*gluco*	*manno*
1	 **110**	90	86	51	65
2	 **2**	81	79	78	79
3	 **113** OMe	71	75	55	63
4	 **3**	57	60	33	52

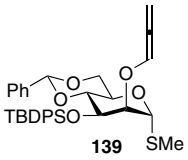
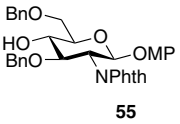
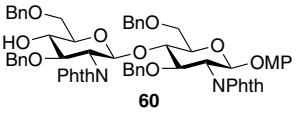
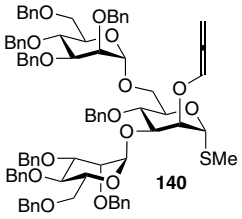


Scheme 17.

Iodonium tethering of mono- **55** or disaccharide **60** acceptors to mono- **139** or trisaccharide **140** donors worked generally well with the I_2/AgOTf/DTBMP reagent to give the mixed acetals, which were purified by flash chromatography on silica gel, in good yield (Table 17). The glycosylation reaction was, however, variable. Glycosylation worked well for the formation of a disaccharide (Table 17, entry 1), representing an improvement over the equivalent allyl reaction: the Man(β1→4)GlcNAc disaccharide could be synthesised in this way and the pentasaccharide core elaborated by a linear sequence. However, for more convergent

Table 17. IAD with allenyl ethers derived from isomerisation of propargyl ethers



Entry	Donor	Acceptor	Yield of mixed acetals (%)	Yield of β-mannoside (%)
1	 **139**	 **55**	88	81
2	**139**	 **60**	70	32
3	 **140**	**55**	64	<55
4	**140**	**60**	64	<5

approaches (i.e., [1+2], [3+1] and [3+2] Table 17, entries 2-4), the glycosylation yields dropped off rapidly, meaning that propargyl IAD does not appear to be suitable for convergent oligosaccharide synthesis.

6. Conclusions and outlook

The reactions described in this Minireview show that the intramolecular aglycon delivery method can be used for the synthesis of a range of different 1,2-*cis* glycosides with complete stereocontrol. Many protocols have been developed for efficiently tethering donor and acceptor together, some very recently. As with most glycosylation reactions, choice of protecting group pattern, solvent and promoter is important for the outcome of glycosylation. A general drop-off in yields of IAD in block approaches to oligosaccharides may mean that IAD is more suitable for stepwise linear synthesis.

Note added in proof

Ito and co-workers have just described the synthesis of β-rhamnosides by IAD with a new tethering technique based on oxidative activation of a 2-*O*-napthyl ether.[52]

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