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Recent advances in stereoselective glycosylation through intramolecular aglycon delivery

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Methodology toward the stereoselective 1,2-*cis* glycoside linkage using intramolecular aglycon delivery (IAD) has been extensively developed. In the last two decades, progress has been made using various mixed acetal linkages and a number of glycosyl donor moieties to develop novel IAD strategies, mainly based on formation of acetal linkages. This account summarizes the newest naphthylmethyl (NAP) ether-mediated IAD as well as all the types of mediations for stereospecific construction of various 1,2-*cis* linkages, not only for β-mannopyranoside, but also for other linkages almost without exception, including β-L-rhamnoside.

1. Introduction

1,2-*Cis* glycosidic linkages, such as β-mannopyranoside, β-arabinofuranoside and α-glucopyranoside, are found in natural glycans, including glycoproteins, glycolipids, proteoglycans, microbial polysaccharides and bioactive natural products. While 1,2-*trans* isomers have been obtained stereoselectively through the effect of neighboring group participation of the C-2 substituent such as an acyl group, stereoselective synthesis of 1,2-*cis* glycosides is far less straightforward (Fig. 1).[1] Although the key factors that control the stereoselectivity of glycosylation are largely understood, strictly controlled formation of these 1,2-*cis* glycosides is generally difficult.[2]

To achieve this, a number of strategies have been explored.[3] Among them, approaches based on intramolecular aglycon delivery (IAD) are of special promise, because they are expected to guarantee the exclusive formation of 1,2-*cis* glycosides under kinetic control.[4] Thus, the stereoselectivity of glycosylation through IAD may well be independent of the structure of the acceptor. In the synthesis of complex molecules, tethering is an essential step to perform intramolecular reactions in a regio- and stereoselective manner.[5,6] In this context, various mixed acetal linkages and a number of glycosyl donor moieties for IAD have been developed as depicted in Fig. 2 and 3.

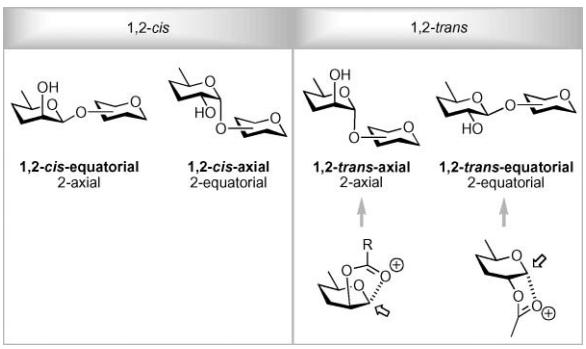

Fig. 1 Types of glycosidic linkages.

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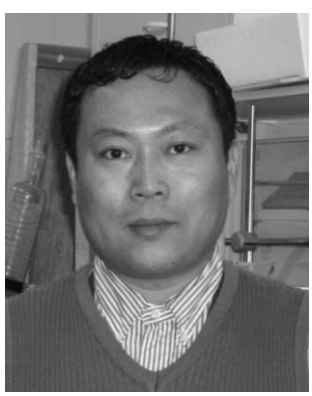

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Yong Joo Lee was born in Incheon, Korea. He obtained his Ph. D. from Yonsei University, Korea in 2006 under supervision of Professor Kwan Soo Kim. After working at the Center for Bioactive Molecular Hybrids as a researcher in the same University, he moved to RIKEN in 2007, and now he is a foreign postdoctoral researcher at RIKEN.

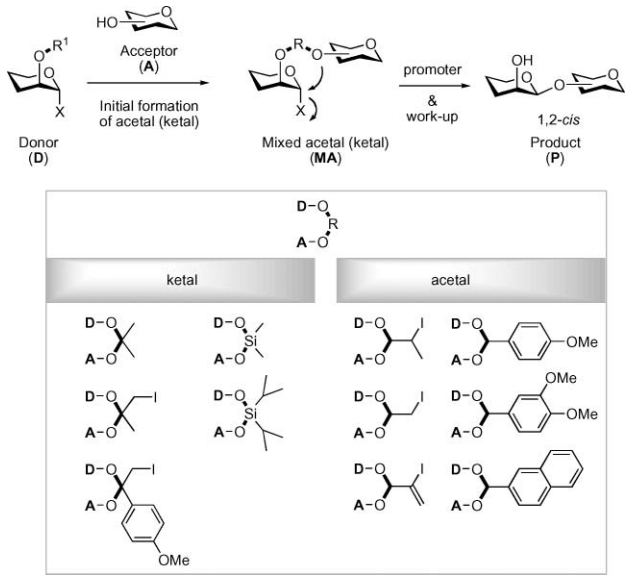

Fig. 2 Various types of tethers for IAD.

In the case of IAD with 2-axial-oriented substrates, *e.g.*, β-mannopyranosylation, the stereochemical outcome of IAD is clear since the pathway producing the corresponding α-glycosides is essentially prohibited. Namely, the axial orientation of the tether at the C-2 position guarantees the formation of the β-glycoside. The pathway toward 1,2-*trans*-furanosides through IAD is also disfavored, because it requires the intermediacy of a *trans*-fused [5,5,0] bicycle, although the radical reaction for the synthesis of *C*-glycosides through tethering reported by Stork *et al*.[7] was less selective than for pyranoside derivatives. On the other hand, the stereochemical outcome of 2-equatorial-oriented 1,2-*cis*-pyranosides, *e.g.*, α-glucopyranoside or α-galactopyranoside

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Yukishige Ito obtained his Ph. D. in 1982 from Faculty of Pharmaceutical Sciences, the University of Tokyo, under the direction of Professor Masaji Ohno. After two years postdoctoral training at Massachusetts Institute of Technology under direction of Professor Satoru Masamune, he joined RIKEN, starting his career in carbohydrate chemistry under the direction of Dr Tomoya Ogawa. In the same institute, he became independent as a chief scientist in 1998. He is also a director of the ERATO project of the Japan Science and Technology Agency (JST) (2009~) and holds appointments from Saitama University (1998~) and Rikkyo University (2004~) as a Visiting Professor. In 2008, he received Roy L. Whistler International Award in Carbohydrate Chemistry from the International Carbohydrate Organization (ICO).

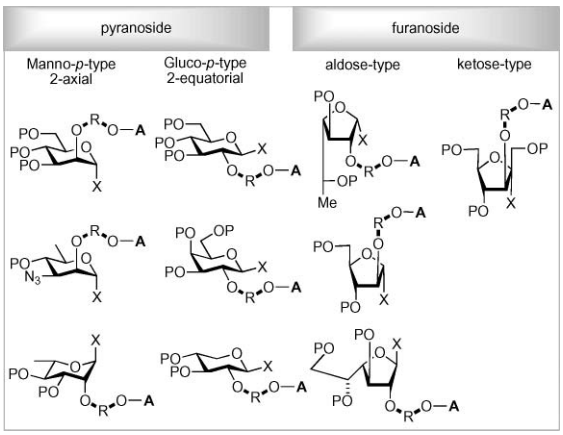


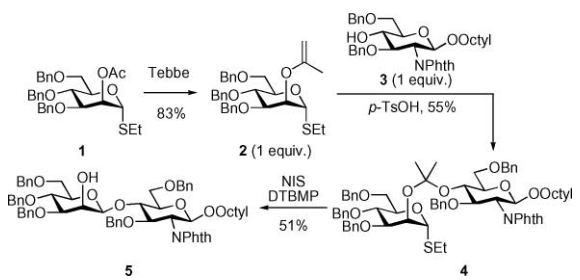
Fig. 3 Various mixed acetals sorted by donor moiety.

formation, is less obvious. In fact, formation of 1,2-*trans*-β-glucopyranoside was not completely prohibited (*vide infra*).[8]

2. Ketal type tethers

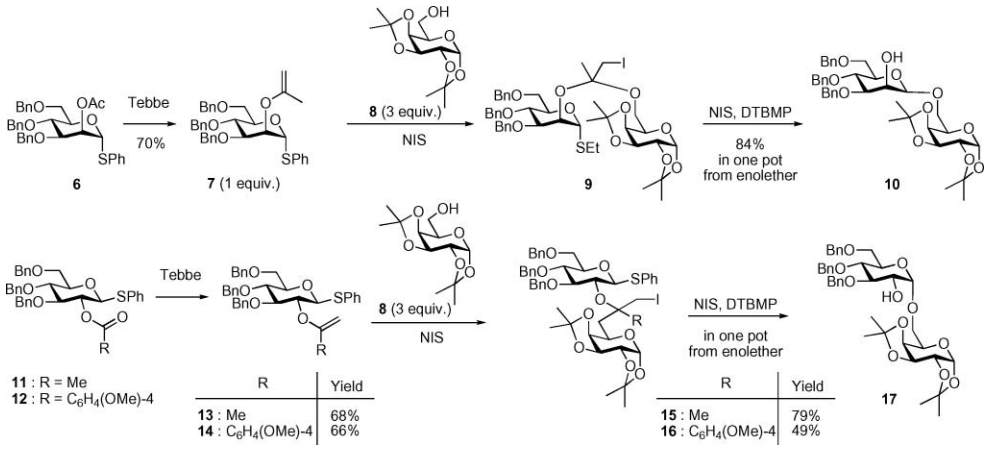
Dimethyl ketal (isopropylidene acetal)

The β-mannoside linkage is generally recognized as difficult to construct selectively. In 1991, Barresi and Hindsgaul[9,10,11] pioneered the intramolecular aglycon delivery approach, which was demonstrated to be promising for the exclusive synthesis of β-mannoside. Their strategy featured the initial formation of mixed dimethylketal **4** as the tethered intermediate. This step was achieved by the reaction between aglycon **3** and isopropenyl ether **2**, the latter of which was prepared from acetate **1** by Tebbe's exomethylenation (Scheme 1).[12,13] Subsequent thioglycoside activation by *N*-iodosuccinimide (NIS) gave disaccharide **5** in a highly stereocontrolled manner. The stereospecificity of the transfer was strictly controlled by a kinetically favored approach fixed by the acetal tether. Intriguingly, formation of methyl glycoside was not observed in the presence of 1 equiv. of MeOH, suggesting that aglycon transfer indeed proceeded intramolecularly. Enhancement of the yield was achieved by adding di-*t*-butylmethylpyridine (DTBMP), which presumably suppressed breakdown of the mixed ketal under acidic conditions.[12]



Scheme 1 IAD through dimethylketal-tethered intermediates.

Acetal-tethered intramolecular methods have been extended to other types of regio- and stereoselective reactions, such as cycloaddition.[14] In the case of isopropylidene acetal, the 5-membered intramolecular transfer system would be enhanced by a geminal dialkyl effect.[15] $Glc^{6\text{-}OH}$, $Glc^{4\text{-}OH}$ and $GlcNAc^{4\text{-}OH}$–GlcNAc derivatives have been used as acceptors.



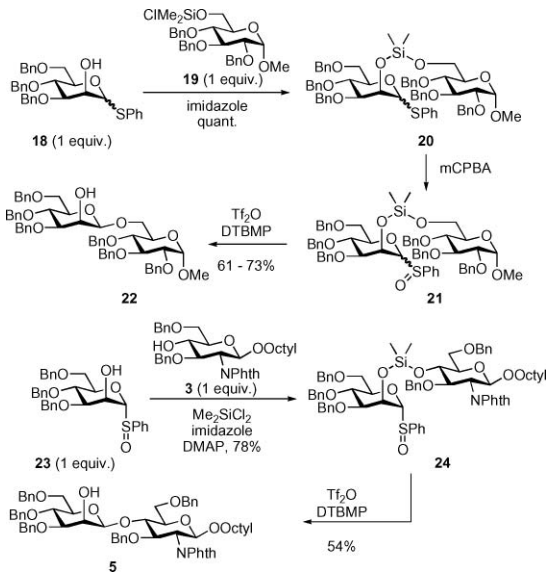
Scheme 2 IAD through 2-iodomethyl-1-methyl- and 2-iodomethyl-1-(4-methoxyphenyl)-ketal-tethered intermediates.

2-Iodomethyl-1-methyl- and 2-iodomethyl-1-(4-methoxyphenyl)-ketals

Fairbanks *et al.*[16,17] described the difficulty they encountered in the formation of a mixed acetal from isopropenyl ether and a series of primary alcohols, which resulted in the hydrolysis of isopropenyl ether. To circumvent this problem, they studied *N*-iodosuccinimide as an alternative electrophile for mixed acetal (ketal) formation from **9**, **15**, and **16** through iodoetherification of exomethylene compounds **7**, **13**, and **14**, which in turn were prepared from **6**, **11**, and **12**, respectively (Scheme 2). Subsequent intramolecular glycosylation with NIS and DTBMP proceeded cleanly, stereoselectively giving disaccharides corresponding to β-Man-(1→6)-Gal (**10**) and α-Glc-(1→6)-Gal (**17**) structures. The intramolecular nature of the reaction has been suggested by the reaction using phenyl 2,3,4,6-tetrabenzyl-1-thio-α-D-glucopyranoside under similar conditions, which resulted in the formation of a 1 : 1 mixture of α- and β-isomers, and by the competition reaction using 3 equiv. of MeOH, which gave the desired glycoside selectively. Even though the mixed ketals of primary and simple secondary alcohols were successfully formed with NIS, reactions with more hindered secondary alcohols were found to be sluggish. 4-Methoxybenzoate **12** was also examined as an alternative precursor of vinyl ether. However, the resultant mixed ketal **16** was revealed to be highly sensitive to hydrolysis. By avoiding purification of **16**, the desired glucoside **17** could be obtained in 49% yield.

Dimethylsilaketal

The versatility of silicon-tethered intramolecular reactions has been demonstrated in the regio- and stereoselective construction of various molecular architectures.[6,7] In 1992, Stork *et al.*[18,19] developed a strategy that employed silyl acetal as a tether for β-mannosylation (Scheme 3). Requisite silyl acetal **20** was obtained in nearly quantitative yield from phenyl 1-thio-3,4,6-tri-*O*-benzyl-mannoside (**18**) and chlorodimethylsiloxy derivative **19**. For the subsequent aglycon delivery, they employed Kahne's glycosylation conditions.[20] Thus, the phenylthio group of **20** was oxidized to give the sulfoxide **21**, which was subjected to activation with triflic anhydride and DTBMP (0.05 M in CH_2Cl_2). Desired β-mannopyranoside **22** was obtained in 73% and 61% yields

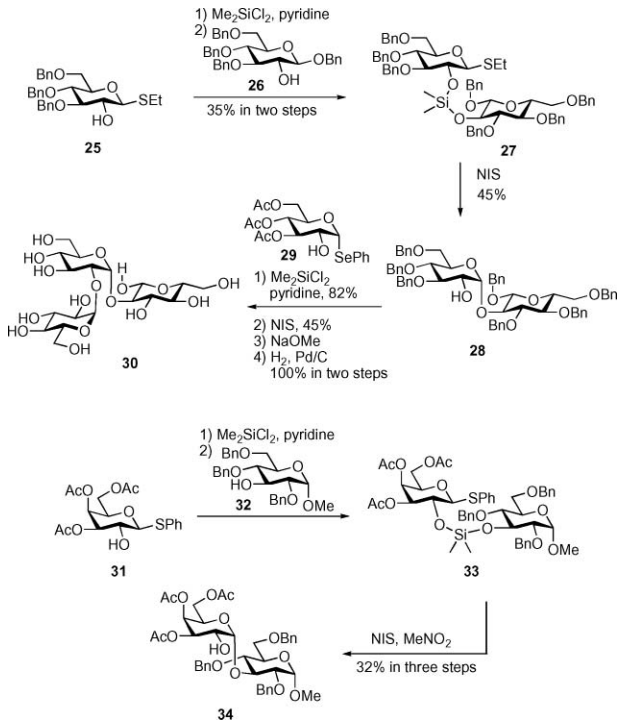


Scheme 3 IAD through dimethylsilaketal-tethered intermediates (1).

from α- and β-sulfoxide **21**, respectively. Alternatively, preformed phenyl sulfoxide **23** was used as a glycosyl donor, which gave the β-mannoside **5** through mixed silyl acetal **24**. It is noteworthy that sterically hindered acceptor **3** was glycosylated in a practically useful yield, giving biologically relevant disaccharide, β-Man-(1→4)-GlcN. In order to optimize the operational simplicity, their study was extended to the formation of the silyl acetal by treatment of an equimolar mixture of the donor and acceptor with 1 equiv. of dichlorodimethylsilane, thereby obviating the work-up and isolation of moisture-sensitive chlorodimethylsilyl ether.[18] This procedure was successfully applied to reactions with acceptors such as $Glc^{6\text{-}OH}$, $Glc^{4\text{-}OH}$, $Glc^{3\text{-}OH}$, $Glc^{2\text{-}OH}$, 6-deoxy$Glc^{4\text{-}OH}$, $Man^{6\text{-}OH}$, and $GlcNAc^{4\text{-}OH}$–GlcNAc.

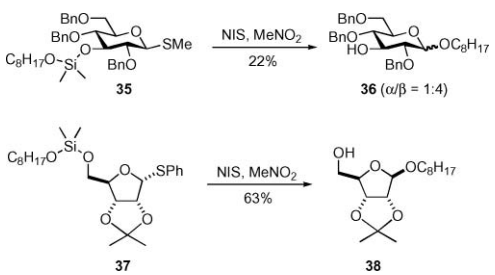
The silyl acetal-based IAD approach was also studied by Bols,[21] who reported the synthesis of 1,2-*cis*-α-glucoside in 1992. Further study clarified its practicality in the synthesis of α-glucoside **28** and α-galactoside **34** structures. Donor/acceptor combinations **25**/**26** and **31**/**32** gave these products through corresponding mixed acetals **27** and **33**, respectively. Disaccharide **28** was further reacted

with the selenoglycoside **29** to afford kojitriose-type trisaccharide **30** (Scheme 4).[22,23,24]



Scheme 4 IAD through dimethylsilaketal-tethered intermediates (2).

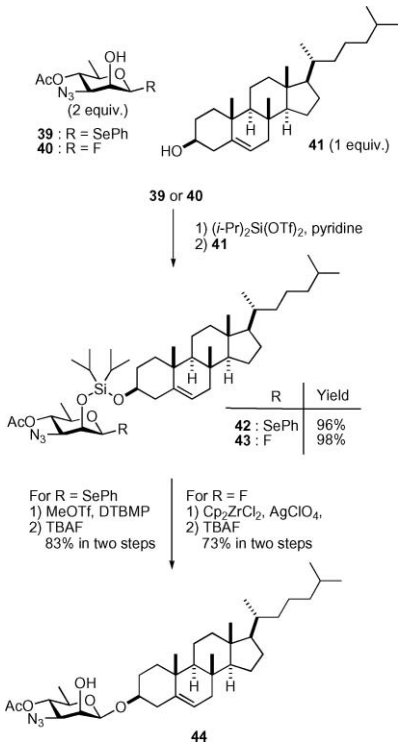
The Bols group broadened the scope of this strategy to long range intramolecular glycosylation. As a proof-of-concept study, glycosylation of a simple octanol as an acceptor was performed. Namely, IAD from the 3-position of glucosyl donor **35** was not completely selective, giving the octyl glycoside **36** as a mixture of stereoisomers. On the other hand, IAD from 5-*O*-tethered ribofuranosyl donor **37** achieved complete stereoselective formation of the 1,4-*cis* adduct **38** (Scheme 5).[25]



Scheme 5 IAD through dimethylsilaketal-tethered intermediates (3).

Diisopropylsilaketal

In order to introduce the β-glycoside of D-mycosamine, Rychnovsky and Packard[26] used an IAD approach that employed glycosyl sulfoxide, thioglycoside, selenoglycoside **39** and glycosyl fluoride **40**. As an acceptor substrate, cholesterol **41** was examined, giving cholesteryl 3,6-dideoxy-3-amino-β-D-mannoside derivative **44** stereoselectively in good yield. Employment of tethered intermediates diisopropylsilaketals **42** and **43** was proven to be highly satisfactory (Scheme 6).

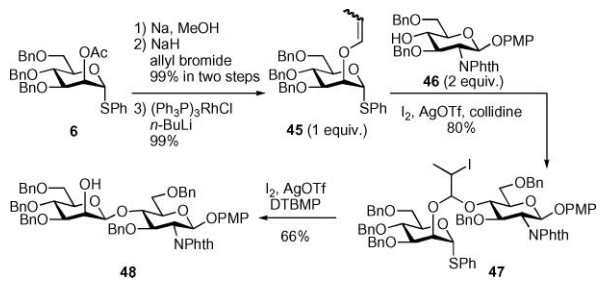


Scheme 6 IAD through diisopropylsilaketal-tethered intermediates.

3. Alkylidene acetal

2-Iodopropylidene acetal

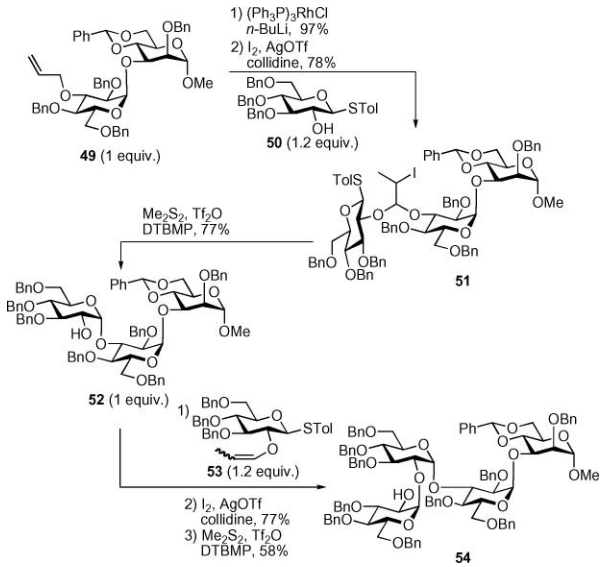
In order to maximize the efficiency of the bridged intermediate formation, intermediary of a less hindered alkylidene acetal was tested. Fairbanks *et al.*[27,28] investigated allyl ether as the precursor of enol ether, which was converted to the acetal with iodonium reagents (Scheme 7). To achieve this, the allyl ether obtained from acetate **6** was converted to 1-propenyl ether **45** by treatment with $(Ph_3P)_3RhCl$–^{n}BuLi.[29] The iodoethylidene mixed acetal formation with NIS proceeded smoothly. Alternatively, iodonium dicollidine triflate prepared *in situ* from I_2, AgOTf and collidine was also effective. Thus, the mixed acetal **47** was prepared from glucosamine derivative **46** in 80% yield, which in turn was subjected to IAD with I_2–AgOTf in the presence of DTBMP. The desired disaccharide β-Man-(1→4)-GlcNAc **48** was obtained in 66% yield.[30]



Scheme 7 IAD through 2-iodopropylidene-tethered intermediate.

Fairbanks also found that a combination of I_2–AgOTf in the presence of DTBMP was optimal for mixed acetal formation,[31] while the subsequent glycosylation was best achieved by Me_2S_2, Tf_2O and DTBMP.[32]

The allyl ether-mediated IAD was applied to the synthesis of the tetrasaccharide [α-Glc-(1→2)-α-Glc-(1→3)-α-Glc-(1→3)Man] (**54**), which corresponds to the non-reducing terminal structure of triglucosylated high mannose type oligosaccharide $Glc_3Man_9GlcNAc_2$, a biosynthetic precursor of *N*-linked glycoprotein glycans (Scheme 8).[33,34] Versatility of this approach was expanded to the so-called "iterative allyl IAD." Namely, coupling of disaccharide acceptor **49** with 2-hydroxy glucosyl donor **50** afforded trisaccharide **52** *via* mixed acetal **51**. This was followed by conversion to tetrasaccharide **54** through coupling with 2-*O*-(1-propenyl) glucosyl donor **53**.

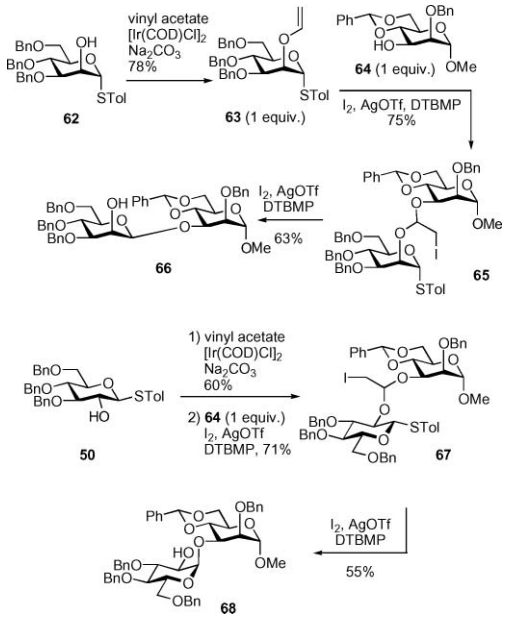


Scheme 8 Synthesis of Glc_3Man_1 using allyl ether-mediated IAD.

This approach was further applied to the synthesis of β-rhamnopyranoside **58** and α-glucofuranoside **61** which have a different configuration than the *gluco*-type donors. In these cases, 2 equiv. of allyl protected donors **55** and **59** were reacted with acceptors **56** and **8** and resultant mixed acetals **57** and **60** were subjected to IAD (Scheme 9).[35] As the acceptors, $Gal^{6\text{-}OH}$, $Glc^{6\text{-}OH}$, $Glc^{4\text{-}OH}$, $Glc^{2\text{-}OH}$–GlcMan, $Glc^{3\text{-}OH}$–Man, $Man^{6\text{-}OH}$, and $Man^{4\text{-}OH}$ derivatives were studied.

2-Iodoethylidene acetal

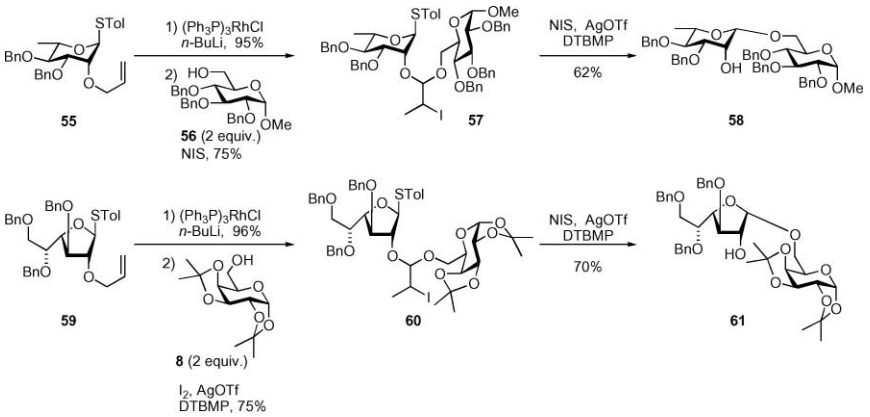
As a precursor to a tether with minimum steric hindrance, Fairbanks *et al.*[36] examined vinyl ethers. For example, **63** was prepared from alcohol **62** by Ishii's Ir-catalyzed transvinylation.[37] It was then linked with an acceptor **64** by the action of I_2–AgOTf in the presence of DTBMP, affording the iodoalkylidene acetal intermediate **65**. Subsequent IAD gave the β-mannopyranoside **66** as expected (Scheme 10). In a similar manner, synthesis of α-glucoside **68** was also realized stereoselectively from **50** and **64** through **67**. $Gal^{6\text{-}OH}$, $Glc^{6\text{-}OH}$, $Glc^{4\text{-}OH}$ and $Man^{4\text{-}OH}$ derivatives were also used as acceptors.



Scheme 10 IAD through 2-iodoethylidene-tethered intermediates.

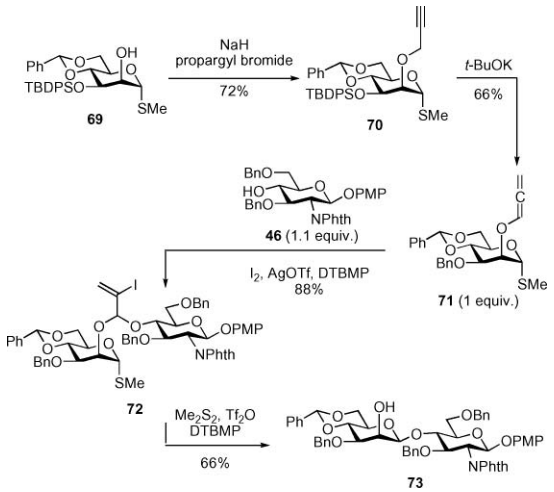
2-Iodo-2-propenylidene acetal

In a similar context as vinyl ethers, propargyl ether was examined by Fairbanks and Attolino.[38] Thiomannoside **70** obtained from corresponding alcohol **69** was isomerized to allenyl ether **71**, which was then converted to the 2-iodo-2-propenylidene mixed acetal **72** by reaction with acceptor **46** in the presence of I_2–AgOTf–DTBMP



Scheme 9 Application of allyl ether-mediated IAD to other glycosidic linkages.

(Scheme 11). Subsequent glycosylation with Me_2S_2, Tf_2O and DTBMP[39] gave disaccharide **73** in 66% yield. Although application to the fragment condensation was not successful,[40] β-Man-(1→2)-GlcNAc disaccharide **73** was successfully converted to *N*-linked glycan core pentasaccharide $Man_3GlcNAc_2$,[38,40] demonstrating its practicality in the synthesis of biologically relevant glycans.



Scheme 11 IAD through 2-iodo-2-propenylidene-tethered intermediates.

4. Benzylidene acetal

p-Methoxybenzylidene acetal

Soon after very early communications from Hindsgaul and Stork about the synthesis of β-mannoside, Ito and Ogawa also reported an alternative approach using Hindsgaul's chemistry. Our group developed an approach that took advantage of the characteristic reactivity of *p*-methoxybenzyl (PMB) ether[41] (Fig. 4).[42,43] Since PMB is a widely used hydroxy protective group, removable by DDQ in wet CH_2Cl_2, it was hoped that the reaction of a 2-*O*-PMB-protected mannosyl donor with an alcohol under anhydrous conditions would lead to a mixed acetal. Indeed, mixed acetal formation proceeded cleanly upon treatment of the donor–acceptor mixture with DDQ. Subsequent activation of the anomeric position (*e.g.* thioglycoside or fluoride) initiated the transfer of an aglycon from *p*-methoxybenzylidene acetal to

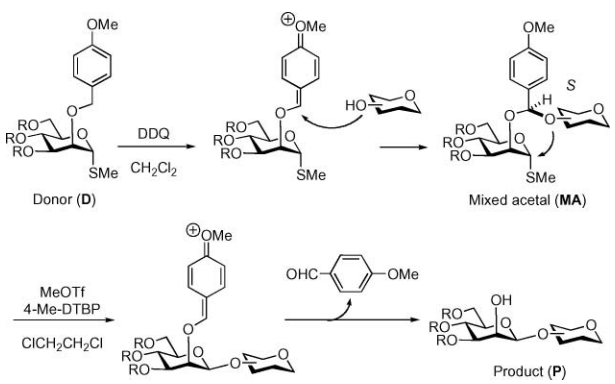


Fig. 4 IAD through 4-methoxybenzylidene-tethered intermediates.

Table 1 The results of IAD for fragment condensation

Entry	Donor (equiv.)	Acceptor (equiv.)	MA/%	product	yield/%
1	**74** (1.4)	**81** (1)	→	$Man_1GlcNAc_2$	60[a]
2	**77** (1.4)	**46** (1)	→	$Man_2^{(3)}GlcNAc_1$	53[a]
3	**77** (1.3)	**81** (1)	→	$Man_2^{(3)}GlcNAc_2$	55[a]
4	**79** (1)	**81** (1.3)	→	$Man_3GlcNAc_2$	37[a]
5	**78** [b](1)	**3** (1.2)	25	$Man_2^{(6)}GlcNAc_1$	28
6	**75**[c](1.2)	**82** (1)	38	$Man_1GlcNAc_2$	27
7	**78** [b](2)	**2** (1)	>10	$Man_2^{(6)}GlcNAc_1$	—
8	**76** [d](1.3)	**81** (1)	70	$Man_1GlcNAc_2$	32
9	**80** [e](1.5)	**46** (1)	64	$Man_3GlcNAc_1$	55
10	**80** [e](1.5)	**81** (1)	64	$Man_3GlcNAc_2$	<5

[a] Yield in two steps. [b] Obtained from corresponding acetate in 69% yield. [c] Obtained from corresponding acetate in 90% yield. [d] Obtained from corresponding propargyl ether in 66% yield. [e] Obtained from corresponding propargyl ether in 77% yield.

the anomeric position, giving the desired β-mannopyranoside (*vide infra*).

In this context, acceptors including glucosamine or chitobiose derivatives were tested in combination with mannosyl fluoride[41] and methyl thiomannoside[44] as the donors. Among reported variants of IAD to date, this approach seems to be most suitable for block condensation of oligosaccharide fragments (Fig. 5 and Table 1). Namely, IAD of 2-propenyl (**75**, **78**) and allenyl (**76**, **80**) donors with glucosamine (**46**, **3**) or chitobiose (**81**, **82**) acceptors provided ~10% and ~35% yields of β-mannoside, respectively. On the other hand, PMB-assisted IAD of mannosyl (**74**),[44] mannobiosyl (**77**)[45] and mannotriosyl (**79**)[46] donors with chitobiose acceptor **81** gave β-mannopyranosides in ~60% yields, which were then transformed to $Man_3GlcNAc_2$, a core pentasaccharide of *N*-glycans.[44,45,46] Conversion to bisecting and fucose-containing $FucMan_3GlcNAc_2$ *N*-glycans was also reported.[45]

Interestingly, formation of the mixed acetals was shown to be highly stereoselective. Configuration of the acetal carbon was assigned as *S* based on NMR and computational analyses.[47] Although this stereochemistry would seem to be inconsequential, our study revealed that the efficiency of IAD was sensitive to the configuration of the acetal carbon. In addition, NMR monitoring studies suggested that the nonhydrolytic pathway that liberated anisaldehyde from the intermediate cationic product was operative (Fig. 4).[48]

Efficiency of the PMB-assisted β-mannosylation was optimum when the 4,6-*O*-cyclic protective group was introduced (Fig. 5 and Table 2). For example, reaction of 4,6-*O*-cyclohexylidene protected mannosyl donor **85** with acceptor **46** gave the product in higher yield (83%) compared to 4,6-di-*O*-benzyl- (**83**), 4,6-*O*-benzylidene- (**74**), 4,6-*O*-isopropylidene- (**84**) and 4,6-tetraisopropyldisiloxanylidene (**86**) protected donors.[49] The β-Man*p* linkage, synthesized *via* PMB-mediated IAD, has also been converted to glycosphingolipid from *Protostomia phyla* reported by Takeda *et al.*[50,51]

Practicality of our approach was demonstrated in the context of synthetic studies toward glycoprotein glycans.[52,53] In particular, the comprehensive synthesis of high mannose type glycans has removed the long-standing difficulty arising from the heterogeneity of naturally occurring glycoproteins.[54] This achievement has enabled detailed analysis of glycoprotein processing events in the

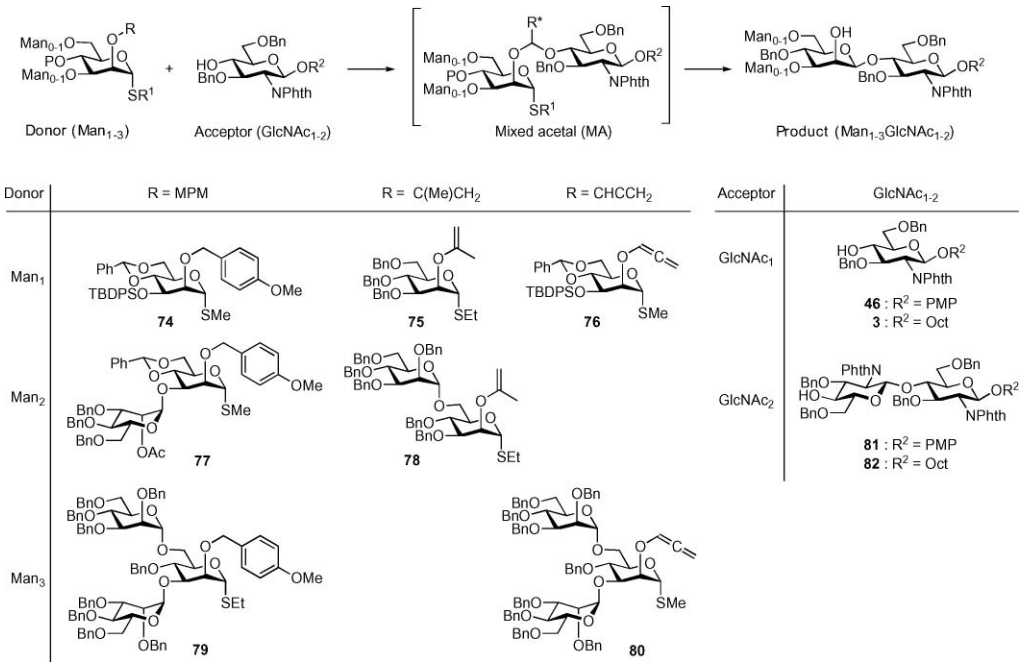
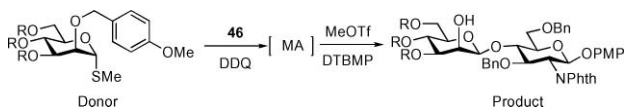
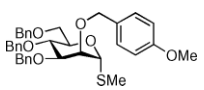
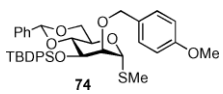
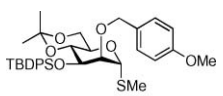
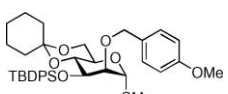
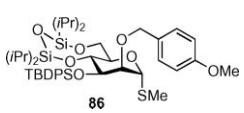


Fig. 5 IAD for fragment condensations.

Table 2 Effect of protective groups on PMB-mediated IAD with **46**

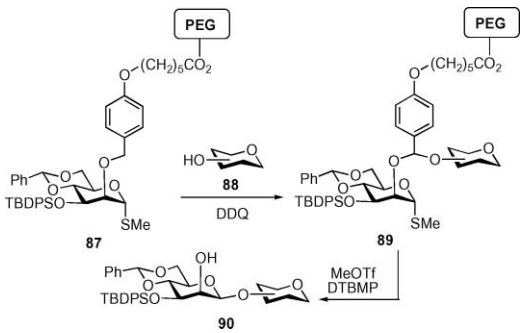


Entry	Donor	yield[a]/%
1		29
2		60
3		61
4		83
5		78

[a] Yield in two steps

endoplasmic reticulum (ER), which plays an important role in glycoprotein folding, degradation and transportation.

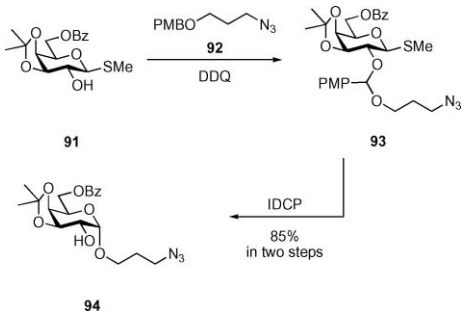
In addition, a polymer-supported variant of IAD was explored (Scheme 12).[55] In this case, thiomannoside **87** was connected to polyethylene glycol (PEG, MW ~5,000) *via* a *p*-alkoxybenzyl linker. The mixed acetal **89** was isolated by precipitation and unreacted acceptor **88** was removed at this stage. After IAD, resultant β-mannoside **90** was specifically released into the non-polymeric phase. The by-products were easily removed, because they remained bound to the polymer.



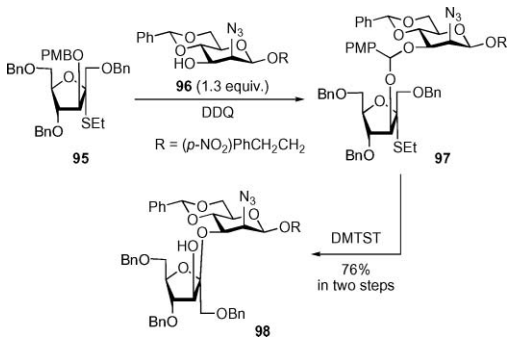
Scheme 12 Polymer-supported version of PMB-mediated IAD.

Field *et al.* applied PMB-assisted IAD to the construction of the 1,2-*cis*-α-linkage of Gal*p* (Scheme 13).[56] After formation of the mixed acetal **93** by the reaction between Gal*p* donor **91** and PMB-protected 3-azido-1-propanol **92**, subsequent IAD using iodonium dicollidine perchlorate (IDCP) was conducted.[57] In this particular case, this promoter was more effective than dimethyl(methylthio)sulfonium trifluoromethanesulfonate (DMTST)[58] or NIS,[16] stereoselectively affording the 1,2-*cis*-α-Gal*p* **94** after acidic work-up.

For the application of the PMB-mediated IAD to the 1,2-*cis*-furanosidic linkage, Krog-Jensen and Oscarson[59,60] reported stereospecific synthesis of β-fructofuranoside (β-Fru*f*) found in a capsular polysaccharide from *Haemophilus influenzae*. The intramolecular transfer from mixed acetal **97**, which was prepared from β-Fru*f* donor **95** and mannosamine derivative **96**, was activated by DMTST to give β-Fru*f* **98** (Scheme 14).



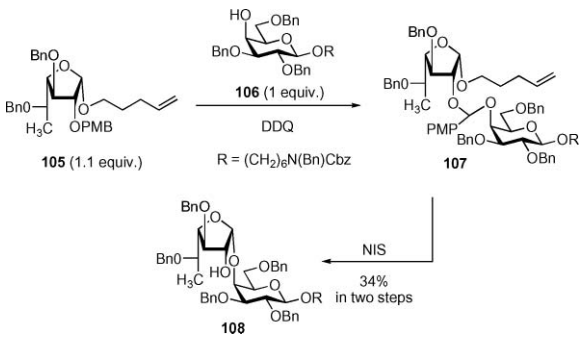
Scheme 13 PMB-mediated IAD for α-Gal*p*.



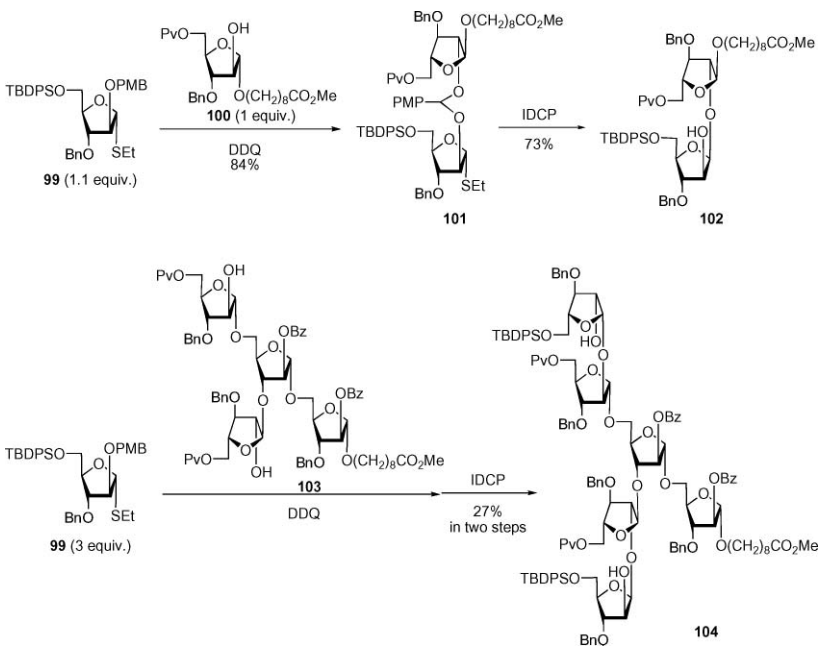
Scheme 14 PMB-mediated IAD for β-Fru*f*.

Mycobacterial cell walls consist of arabinogalactan (AG) and arabinomannan (AM), which are comprised of β-arabinofuranosides at the non-reducing terminal ends. To achieve the synthesis of this linkage stereoselectively, Prandi *et al.* applied the PMB-mediated IAD (Scheme 15).[61,62,63,64] Namely, 2-*O*-PMB-protected arabinofuranosyl donor (**99**) was treated with 5- or 2-OH (**100**) derivatives as acceptors[61,62] under oxidative conditions to give the mixed acetals (*e.g.* **101**) in good yield. Subsequent intramolecular glycosylation using IDCP as the activator specifically afforded the 1,5- and 1,2-linked (**102**) β-arabinofuranosides. The 1,2-linked arabinofuranoside was converted to the pentasaccharide fragment of arabinomannan.[63] For the synthesis of the terminal branching motif of AG, PMB-mediated β-arabinofuranosylation to tri- and tetrasaccharide (**103**) diols[63,64] was carried out to afford the bis-β-arabinofuranosylated penta- and hexasaccharide (**104**) motifs, respectively, however the yield of the products over two steps was only modest. As the authors pointed out, this reflects the limitation of the IAD approach for the construction of complex oligoarabinofuranosidic structures by simultaneous glycosylations at multiple sites.

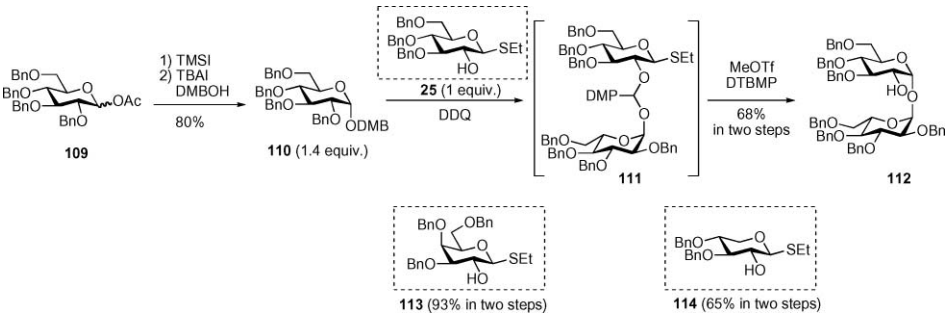
Ferriéres *et al.*[65] reported the synthesis of α-L-fucofuranoside (Fuc*f*) found in the polysaccharides produced by *Chaetoceros curvisetus* and *Eubacterium saburreum*. PMB-mediated IAD was applied to the stereoselective construction of this characteristic structure. By using the fucofuranosyl donor **105**, coupling with galactose acceptor **106** *via* mixed acetal **107** afforded the desired disaccharide **108**,[66] albeit in modest overall yield (Scheme 16).



Scheme 16 PMB-mediated IAD for α-Fuc*f*.



Scheme 15 PMB-mediated IAD for β-Ara*f*.



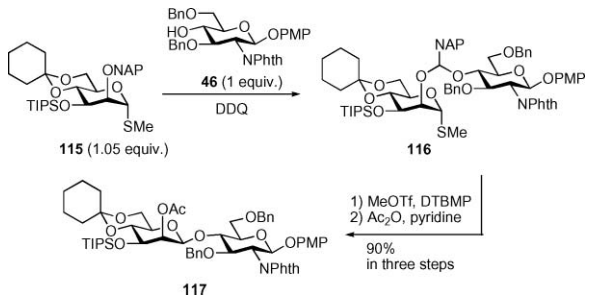
Scheme 17 DMB-mediated IAD.

Dimethoxybenzylidene acetal

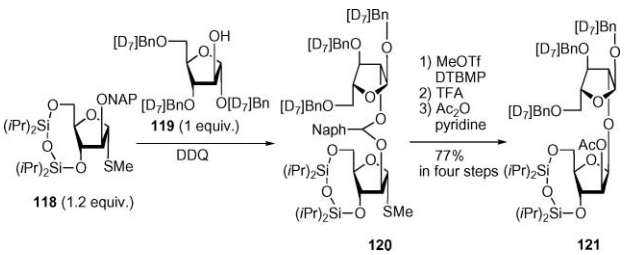
Bertozzi *et al.*[67,68] recently reported a cleverly designed synthesis of trehalose derivatives through IAD (Scheme 17). In this case, the use of a dimethoxybenzyl (DMB)[69,70,71] group was shown to be advantageous over PMB. Requisite α-glycoside **110** was obtained from anomeric acetate **109** *via* glycosyl iodide through *in situ* anomerization-type conditions. Mixed acetal **111** was obtained by coupling with 2-OH liberated thioglycoside **25**. Subsequent activation with MeOTf constructed the 1,1′-α,α-glycosidic linkage of **112**.

White *et al.* also reported their attempt to conduct DMB-assisted IAD for the synthesis of the antiparasitic agent Abermectin B_{1a}, which resulted in the hydrolysis of the DMB glycoside.[72]

DMB-assisted IAD was effectively applied to the stereospecific synthesis of glucosyl-, galactosyl- and xylosyl-trehaloses from **25**, **113** and **114**, respectively,[67] as well as *Mycobacterium tuberculosis* sulfolipid-1 containing glucosyl-trehalose.[68]



Scheme 18 NAP-mediated IAD for β-Man*p*.



Scheme 19 NAP-mediated IAD for β-Ara*f*.

Naphthylidene acetal

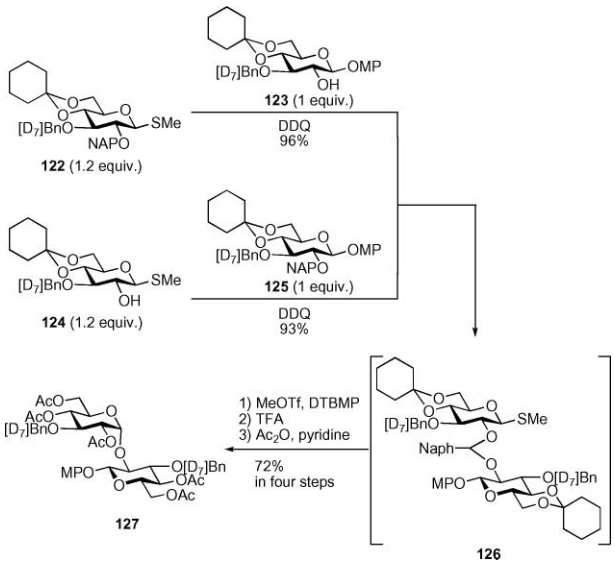
As an extension of the PMB-based strategy, our recent study has focused on the use of the 2-naphthylmethyl (NAP) group as a tether.[73] NAP ether has been gradually gaining popularity as a hydroxy protective group in natural product synthesis.[74] It is similar to PMB ether in that it is removable under oxidative conditions.[42,75,76] Therefore, we hoped that IAD using a 2-*O*-NAP-protected donor could be conducted in a similar manner as our previous version of IAD, which utilized the PMB group.[77,78]

In fact, the formation of the mixed acetal with 2-*O*-NAP-protected thiomannoside **115** and the acceptor **46** proceeded quantitatively. Subsequent IAD mediated by MeOTf–DTBMP cleanly gave β-Man*p*, which was isolated as **117** after acetylation (Scheme 18). As in the case of the 2-*O*-PMB carrying donor, the mixed acetal **116** was stereochemically homogeneous, most likely with the *S*-configuration. Gratifyingly, the efficiency of NAP-assisted IAD was clearly higher than the PMB-assisted reaction. Only 1.05 equiv. of the 2-*O*-NAP-protected Man donor **115** gave β-mannopyranoside **117** in 90% yield.

This approach was applied to the synthesis of β-Ara*f*. Thus, formation of the mixed acetal from Ara*f* donor **118** and Ara$f^{2\text{-OH}}$ acceptor **119** cleanly gave the mixed acetal **120** (Scheme 19). Subsequent IAD provided β-arabinofuranoside **121** in a satisfactory yield after acidic workup and acetylation. The anomeric configuration was unambiguously assigned by ^{1}H NMR. Its stereochemical homogeneity was rigorously confirmed by conducting the reaction using a perdeuterated benzyl ([D_7]Bn) protected Ara*f* derivative.[79,80]

To explore the applicability of our strategy to α-Glc formation, 2-*O*-NAP-protected Glc thioglycoside **122** was employed. The mixed acetal was smoothly formed both from 2-*O*-NAP-protected Glc donor **122** and Glc acceptor **123**, and from 2-*O*-unprotected donor **124** and 2-*O*-NAP-protected acceptor **125** (Scheme 20). The subsequent intramolecular glycosylation of mixed acetal **126** afforded the desired 1,2-*cis* glycoside, which was isolated as pentaacetate **127** after acidic treatment and acetylation. PMB ether- and 1-naphthylmethyl ether-mediated IADs were also examined in this case, however, the yields of mixed acetal formation were lower, being 69% and 67%, respectively.[73]

In a synthetic study on glucose-terminated high mannose type *N*-glycans, construction of α-Glc(1→2)-α-Glc(1→3)-α-Glc(1→3)Man has been problematic.[33,34,80,81] Our attempt to form α-Glc under the setting of NAP-assisted IAD encountered complications due to dimerization of the IAD product. Although acidic treatment and acetylation cleanly converted most of the products into **127**, the TBDPS and cyclohexylidene groups were inevitably lost. It is preferable to retain these protective groups in order to apply this method to the synthesis of higher oligomers. To achieve



Scheme 20 NAP-mediated IAD for α-Glc*p*.

this, nucleophilic quenching of cationic species was examined. As a result, addition of silyl hydrides, especially $(TMS)_3SiH$,[82] was found to be suitable. This reagent effectively reduced the benzylic cation of the IAD product, giving the glycoside product having both 2-*O*-NAP and 4,6-*O*-cyclohexylidene protection (Scheme 21 and Fig. 6). For example, IAD of 2-*O*-NAP-protected Glc donor **128** with $Glc^{2\text{-OH}}$ acceptor **123** gave α-glucoside **129** possessing the NAP ether (82%) as the sole product. That the NAP ether is regenerated is advantageous in several respects. Namely, it functions as an orthogonal protective group to cyclohexylidene as well as being the key functionality for subsequent IAD.

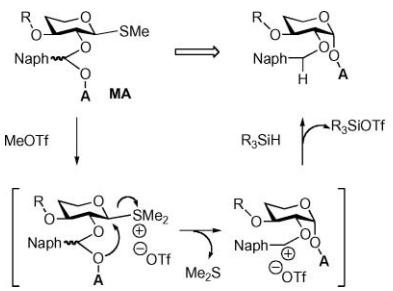
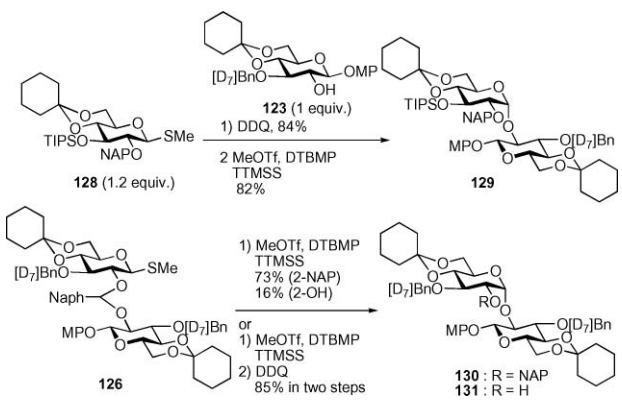


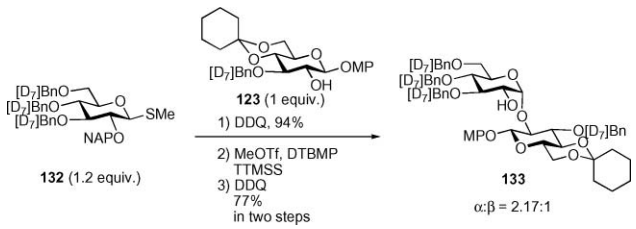
Fig. 6 Mechanism of NAP-mediated IAD using $(TMS)_3SiH$.



Scheme 21 NAP-mediated IAD using $(TMS)_3SiH$ (1).

In a similar manner, IAD of aforementioned **126** in the presence of $(TMS)_3SiH$ afforded α-glucoside with 2-*O*-NAP ether **130** in 73% yield, together with a smaller amount of hydrolyzed compound **131** in 16% yield (Scheme 21). In this case, treatment of the crude mixture with DDQ gave the sole product **131** in 85% yield.

On the other hand, IAD of 3,4,6-tri-*O*-benzyl-glucosyl donor **132** with $Glc^{2\text{-OH}}$ acceptor **123** was only marginally selective, giving **133** as a mixture ($\alpha{:}\beta = 2.17:1$) of anomers (Scheme 22), possibly because of the flexibility of the pyranose ring which might allow access from the α-direction. Therefore, cyclic protection at the 4,6-position of the donor appears to be important in order to achieve strictly controlled α-glycosylation.

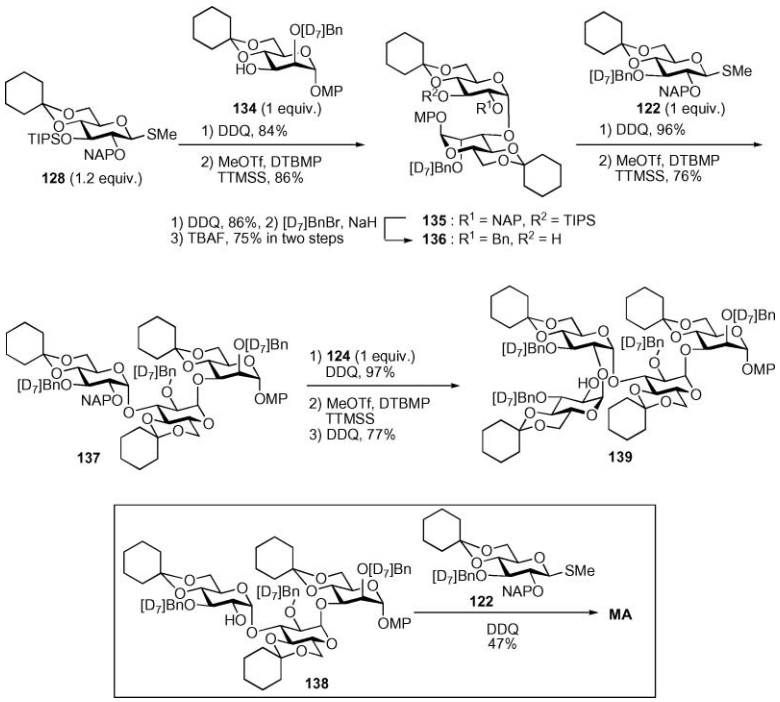


Scheme 22 NAP-mediated IAD for α-Glc*p* (2).

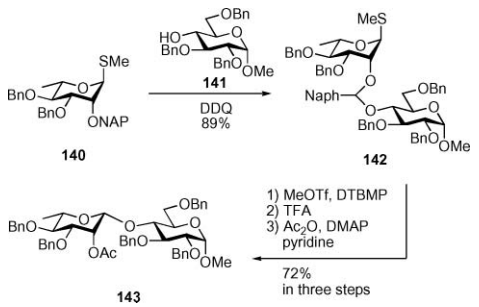
In order to demonstrate its practicality, NAP-IAD was applied to the construction of Glc_3Man_1, a tetrasaccharide carrying consecutive α-glucosidic linkages (Scheme 23). The first NAP-IAD of $Man^{3\text{-OH}}$ acceptor **134** with cyclohexylidene-protected Glc donor **128** afforded α-glucoside **135** in high yield with complete stereoselectivity. After a three-step conversion to $Glc^{3\text{-OH}}$–Man acceptor **136**, the second IAD with cyclohexylidene-protected Glc donor **122** afforded Glc_2Man_1 trisaccharide **137**. As for the third NAP-IAD, two approaches were compared: a mixed acetal formation between $Glc^{2\text{-OH}}$–GlcMan acceptor **138** (prepared from **137**) with 2-*O*-NAP-protected Glc donor **122** (Approach A) or 2-*O*-NAP-protected Glc_2Man_1 acceptor **137** with $Glc^{2\text{-OH}}$ donor **124** (Approach B). While Approach A afforded the mixed acetal only in modest yield (47%), Approach B resulted in nearly quantitative formation of the mixed acetal. Subsequent intramolecular glycosylation gave the tetrasaccharide **139** as the sole product in 77% yield. After conventional deprotection, the synthesis of Glc_3Man_1-OMP was accomplished in high yield with complete stereoselectivity.

Currently, β-L-rhamnopyranoside (β-L-Rha) is the most challenging glycosidic linkage to construct selectively. Although its difficulty derives from structural features similar to β-D-mannopyranosides (β-D-Man) (*i.e.*, equatorial, 1,2-*cis*),[83] the formation of this linkage is more difficult by far. Most significantly, the direct glycosylation strategy developed for β-D-Man is not effective for β-L-Rha, because the 6-deoxy structure of Rha excludes the 4,6-*O*-cyclic (*e.g.*, benzylidene) protection, which is essential for the stereoselective β-D-Man formation.[84] Application of NAP-mediated IAD to solve this problem was investigated.

Formation of the mixed acetal **142** from 2-*O*-NAP-protected L-Rha donor **140** and Glc acceptor **141**, followed by IAD under our standard conditions, afforded β-L-rhamnoside **143** in 72% yield as a single isomer after acidic treatment and acetylation (Scheme 24).[85]



Scheme 23 Synthesis of Glc_3Man_1 using NAP-mediated IAD.



Scheme 24 NAP-mediated IAD for β-L-Rha*p*.

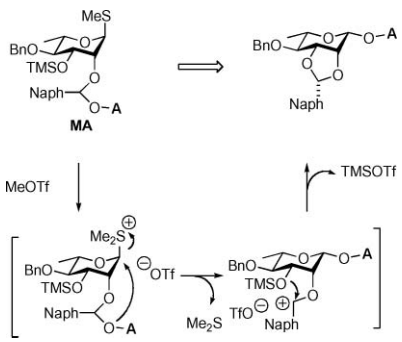
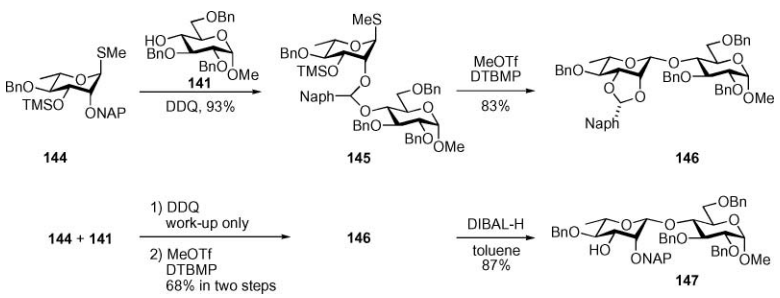


Fig. 7 Mechanism of NAP-mediated IAD for β-L-Rha*p*.

On the other hand, 3-*O*-TMS-protected donor MA **144** was converted to **145** (93%), which was subjected to treatment with MeOTf and DTBMP. In this case, the TMS ether intramolecularly trapped the transiently generated benzylic cation to give the naphthylidene cyclic acetal **146**[86] in 83% yield. Interestingly, stereochemistry of the cyclic acetal was exclusively *endo* (Scheme 25 and Fig. 7). A quite comparable yield of **146** was obtained when the mixed acetal was not isolated (Scheme 25). Acceptors that correspond to $Glc^{3\text{-OH}}$, $Man^{2\text{-OH}}$, $Rha^{4\text{-OH}}$, and $GlcNAc^{4\text{-OH}}$ were glycosylated successfully, providing disaccharides [β-L-Rha*p*(1 → 3)Glc], [β-L-Rha*p*(1 → 2)Man], [β-L-Rha*p*(1 → 4)Rha], and [β-L-Rha*p*(1→4)GlcN] in 64–71% yields, which will give access to components of various bacterial polysaccharides. In order to approach α-L-Rha*p*(1→3)-β-L-Rha*p*(1→4)Glc, the substructure of *Sphaerotilus natans* polysaccharide, β-L-Rha*p* naphthylidene



Scheme 25 Operationally more simple NAP-mediated IAD using crude mixed acetal for β-L-Rha*p*.

acetal of **146** was regioselectively opened with DIBAL-H to liberate the 3-OH **147** of β-L-Rha*p* (Scheme 25).

Conclusions

The IAD methodology through various mixed acetal linkages toward stereoselective 1,2-*cis* glycoside formation has been studied relatively extensively. Newer versions of IAD based on the formation of acetal linkages, such as iodoalkylidene type (2-iodopropylidene, 2-iodoethylidene and 2-iodopropenylidene) and benzylidene type (*p*-methoxybenzylidene, dimethoxybenzylidene and naphthylidene) acetals, afforded stereospecific constructions of various 1,2-*cis* glycosidic linkages such as β-mannopyranoside as well as other linkages including β-L-rhamnoside almost without exception. These methodologies have also been applied successfully to the synthesis of *N*-glycans for biological studies and the more difficult iterative 1,2-*cis* linkages such as α-Glc(1→2)-α-Glc(1→3)-α-Glc(1→3)Man (Glc_3Man_1), and the non-reducing terminal structure of tetradecasaccharide $Glc_3Man_9GlcNAc_2$, a common precursor of all *N*-linked glycans. Although IAD is an indirect method involving at least a two-step procedure including tethering and intramolecular glycosylation, it is one of the most specific methods to obtain 1,2-*cis*-glycoside linkages and can be used to synthesize various biologically active and complex glycans.

Acknowledgements

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