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Iodine : A Versatile Reagent in Carbohydrate Chemistry IV. Per-*O*-Acetylation, Regioselective Acylation and Acetolysis[1]

K.P. Ravindranathan Kartha* and Robert A. Field

School of Chemistry, The Purdie Building, University of St Andrews, St Andrews, Fife KY16 9ST, U.K.

Abstract: Iodine has been found to be an effective Lewis acid for promoting the per-*O*-acetylation of unprotected sugars. Under controlled conditions it can bring about regioselective acylation of carbohydrate derivatives. At higher concentration and with longer reaction times, iodine can effect the selective acetolysis of benzyl ether-protected primary hydroxyl groups. All of these reactions proceed in high yield, are easy to carry out and make use of readily available iodine, which is both cheap and easy to handle. © 1997 Elsevier Science Ltd.

Introduction

A wide variety of Lewis acids are in current use in the modern organic chemistry laboratory. However, cost, availability and ease of handling can limit the widespread application of many of these reagents. The Lewis acidity of iodine is well characterised; it interacts with electron-rich centres of solvents and reagents, and it has been used in many classes of reactions.[2] In carbohydrate chemistry,[3] iodine has been used to promote the formation and cleavage of isopropylidene acetals,[4] glycosylation reactions using reducing sugars[5] and the addition of alcohols to glycals.[6] We have recently exploited iodine as a promoter for the activation of 'armed' thioglycosides[3] and 'disarmed' glycosyl halides.[1] In this paper we present our observations on the ability of iodine to promote synthetically useful acyl transfer reactions.

A number of compounds have been widely accepted as effective catalysts (not withstanding the fact that some of them are employed in greater than catalytic quantities) for routine acylation reactions such as acetylation and benzoylation.[7] In spite of its toxicity and unpleasant odour, pyridine, which serves as both solvent and catalyst for the reaction, is by far the most widely used.[7] Another popular method uses sodium acetate in refluxing acetic anhydride to effect per-*O*-acetylation of reducing sugars.[7] Both of these procedures have their limitations; large volumes of pyridine or hot acetic anhydride are potentially troublesome. We reasoned that iodine might serve as a cheap and easy to handle reagent for the polarisation of acid anhydrides, and hence prove to be a practical promoter of acylation reactions (Figure 1).

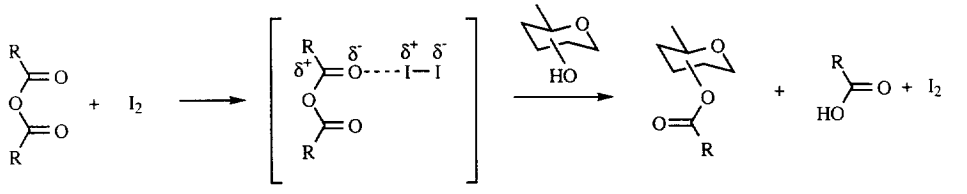


Figure 1 : Proposed Iodine-Promoted Acylation Reactions

Results and Discussion

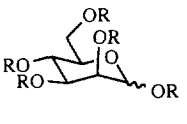
Per-O-acetylation

Results presented in Table 1 demonstrate that iodine can be used as an effective substitute for pyridine in the conversion of free aldoses and reducing disaccharides to their per-*O*-acetates. A typical procedure involves adding iodine to a suspension of the sugar in acetic anhydride at room temperature. The reaction is exothermic, hence in large scale preparations it is advisable to add the carbohydrate portionwise to a solution of iodine in acetic anhydride. However, on a small scale addition of iodine to the other reagents is convenient. Dissolution usually indicates completion of the reaction. Reaction rates and anomeric ratios of the per-*O*-acetate products

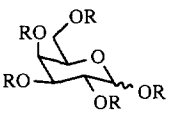
Table 1 : Iodine-Promoted Acetylation of Reducing Sugars

Sugar[a]	Iodine (mg/g sugar)	Reaction time	Yield (%)	Product	Ratio α:β
D-Mannose (**1**)	50	<1 min.	>98	Penta-*O*-acetate (**2**)	4:1
D-Galactose (**3**)	50	8 min.	>98	Penta-*O*-acetate (**4**)	19:1
D-Glucose (**5**)	50	30 min.	>98	Penta-*O*-acetate (**6**)	>25:1
D-Lactose (**7**)	50	4 min.	>98	Octa-*O*-acetate (**8**)	>30:1
D-Maltose (**9**)	50	10 min.	>98	Octa-*O*-acetate (**10**)	1:6.6
N-Ac-D-glucosamine (**11**)	250	2 days	>98	Tetra-*O*-acetate (**12**)	2.5:1
D-NANA Me ester (**13**)	250	very slow reaction		see Table 5	
D-NANA Me ester (**13**)	500	20 min.[b]	70	4,7,8,9-Tetra-*O*-acetyl NANA Me estrer (**14**)	not determined
D-NANA Me ester (**13**)	500	60 min.[b]	90	2,4,7,8,9-Penta-*O*-acetyl NANA Me ester (**15**)	1:3.5

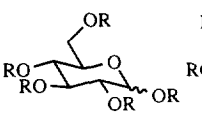
[a] Reactions carried out with 1 g of sugar in 5 ml acetic anhydride at RT. [b] At 35°C.



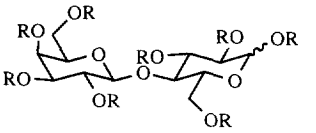
(**1**) R = H
(**2**) R = Ac



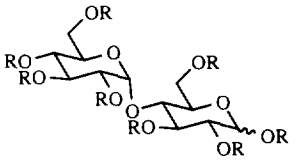
(**3**) R = H
(**4**) R = Ac



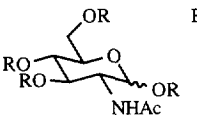
(**5**) R = H
(**6**) R = Ac



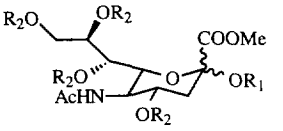
(**7**) R = H
(**8**) R = Ac



(**9**) R = H
(**10**) R = Ac



(**11**) R = H
(**12**) R = Ac



(**13**) $R_1 = R_2 = H$
(**14**) $R_1 = H$, $R_2 = Ac$
(**15**) $R_1 = R_2 = Ac$

were markedly dependent on the configuration and substitution of the sugar ring. Acetylation of mannose (**1**) using 50 mg iodine/g sugar (approximately 3.5 mol%) was typically complete within a minute. Under similar conditions galactose (**3**) and glucose (**5**) both underwent peracetylation at a slower rate than mannose, as did the reducing disaccharides lactose (**7**) and maltose (**9**). Neverthless, these reactions were complete in 4 - 30 min. depending upon the sugar. Comparison with literature data for ferric chloride-mediated acetylation of these sugars [8] reveals that iodine is a more potent promoter than ferric chloride, although anhydrous ferric chloride is generally accepted as a much stronger Lewis acid than iodine. Acetylation of mannose, for instance, was complete in less than one minute when 1.75 mol% of iodine was used (see below). In contrast, the same reaction using 8.8 mol% ferric chloride took 15 minutes to go to completion. In the case of disaccharides also, the iodine-promoted reaction proved faster than with ferric chloride, and undesirable side products arising from acetolysis of the inter-sugar glycosidic linkage were not observed.

Although the aldohexoses and disaccharides described above underwent smooth acetylation at low iodine concentrations, acetylation of *N*-acetyl glucosamine (**11**), in contrast, required two days for complete reaction, even at much higher iodine concentrations (250 mg/g sugar). Likewise acetylation of *N*-acetyl neuraminic acid methyl ester (**13**) at room temperature was extremely slow giving rise to only partially acetylated compounds even after extended periods of time. However increasing the concentration of iodine to 500 mg/g of the sugar and heating the reaction mixture for a short period gave the tetra-*O*-acetate (**14**) with 2-OH free in excess of 70% yield. This compound had previously been obtained in 31% yield after crystallization from a mixture of products formed by treatment of (**13**) with acetic anhydride in the presence of perchloric acid[9] (see Table 5 also). Prolonging the reaction resulted in the formation of the peracetylated product (**15**) in very good yield.

Acetylation rates are dependent on iodine stoichiometry (Table 2). Thus, increasing the iodine concentration markedly increased the rate of acetylation and rendered it increasingly exothermic. To some extent anomeric ratios of the per-*O*-acetate products were also dependent on iodine concentration. For mannose (**1**), galactose (**3**) and glucose (**5**) faster reactions gave higher ratios of the anomeric α-acetate.

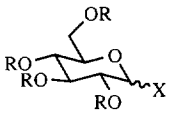
Table 2 : Dependence of the Rate of Acetylation on Iodine Stoichiometry

Sugar[a]	Iodine (mg/g sugar)	Reaction time	Yield (%)	Product	Ratio α:β
D-Mannose (**1**)	12.5	8 min.	>98	Penta-*O*-acetate (**2**)	2:1
D-Mannose (**1**)	25	<1 min.	>98	Penta-*O*-acetate (**2**)	2.5:1
D-Mannose (**1**)	50	<1 min.	>98	Penta-*O*-acetate (**2**)	4:1
D-Galactose (**3**)	25	45 min.	>98	Penta-*O*-acetate (**4**)	10:1
D-Galactose (**3**)	50	8 min.	>98	Penta-*O*-acetate (**4**)	19:1
D-Glucose (**5**)	10	120 min.	>98	Penta-*O*-acetate (**6**)	25:1
D-Glucose (**5**)	25	80 min.	>98	Penta-*O*-acetate (**6**)	25:1
D-Glucose (**5**)	50	30 min.	>98	Penta-*O*-acetate (**6**)	>25:1
D-Glucose (**5**)	100	2 min.	>98	Penta-*O*-acetate (**6**)	>30:1

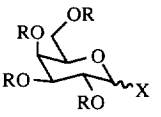
[a] Reactions carried out with 1 g of sugar in 5 ml acetic anhydride at RT.

Further, in some of the *gluco*- and *galacto*-configured compounds examined, the nature of the anomeric

substituent and its configuration were found to influence the rate of acetylation of the carbohydrate derivative (Table 3). The effect was once again more pronounced in the *galacto*-series. Thus, while methyl α-glucoside (**16**) underwent acetylation in less than 5 minutes under the conditions employed for the parent reducing sugar, methyl β-glucoside (**18**) remained largely unaffected over a period of several hours under the same conditions. Increasing the iodine concentration (Table 3), however, caused complete acetylation to occur. 2-(Trimethylsilyl)ethyl glucoside (**20**) likewise gave completely acetylated product (**21**) only on treatment with high concentrations of iodine. On the other hand, phenyl β-glucoside (**22**) gave its tetra-*O*-acetyl derivative (**23**) in 3 minutes under mild conditions. In the *galacto*-series, while methyl α-**D**-galactoside (**24**) reacted smoothly with acetic anhydride to give (**25**) under mild conditions, its β-analogue (**26**) reacted extremely sluggishly, even



(**16**) X = α-OMe, R = H
(**17**) X = α-OMe, R = Ac
(**18**) X = β-OMe, R = H
(**19**) X = β-OMe, R = Ac
(**20**) X = β-OTMSEt, R = H
(**21**) X = β-OTMSEt, R =Ac
(**22**) X = β-OPh, R = H
(**23**) X = β-OPh, R =Ac



(**24**) X = α-OMe, R = H
(**25**) X = α-OMe, R = Ac
(**26**) X = β-OMe, R = H
(**27**) X = β-OMe, R = Ac
(**28**) X = β-OTMSEt, R = H
(**29**) X = β-OTMSEt, R =Ac
(**30**) X = β-OPh*p*-NO_2, R = H
(**31**) X = β-OPh*p*-NO_2, R =Ac

Table 3 : Effect of Anomeric Substitution on the Rate of Iodine-Promoted Acetylation

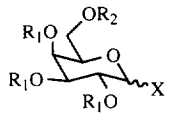
Sugar[a]	Iodine (mg/g sugar)	Reaction time	Yield (%)	Product	Ratio α:β
D-Glucose (**5**)	50	30 min.	>98	Penta-*O*-acetate (**6**)	>25:1
Me α-**D**-glucoside (**16**)	50	5 min.	>98	Tetra-*O*-acetate (**17**)	-----
Me β-**D**-glucoside (**18**)	50	very slow reaction[b]			
Me β-**D**-glucoside (**18**)	100	very slow reaction[b]			
Me β-**D**-glucoside (**18**)	300	6 h.	>98	Tetra-*O*-acetate (**19**)	-----
TMSEt β-**D**-glucoside (**20**)	300	15 min.	>98	Tetra-*O*-acetate (**21**)	-----
Ph β-**D**-glucoside (**22**)	50	3 min.	>98	Tetra-*O*-acetate (**23**)	-----
D-Galactose (**3**)	50	8 min.	>98	Penta-*O*-acetate (**4**)	19:1
D-Lactose (**7**)	50	4 min.	>98	Octa-*O*-acetate (**8**)	>30:1
Me α-**D**-galactoside (**24**)	100	5 min.	>98	Tetra-*O*-acetate (**25**)	-----
Me β-**D**-galactoside (**26**)	300	very slow reaction[b]		-----	-----
TMSEt β-**D**-galactoside (**28**)	300	very slow reaction[b]		-----	-----
p-NO_2Ph β-**D**-galactoside (**30**)	100	15 h.	>98	Tetra-*O*-acetate (**31**)	-----

[a] Acetic anhydride at a ratio of 5 ml/g sugar was used at RT. [b] Yield not determined.

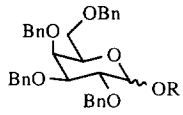
with a three-fold increase in iodine concentration. The β-glycoside (**28**) likewise proved very sluggish towards iodine-promoted acetylation. In contrast, lactose (**7**), which contains a β-1,4-linkage between the galactose anomeric centre and the glucose unit, was acetylated at a rate even faster than that of free reducing galactose (**3**). *p*-Nitrophenyl β-galactoside (**30**), on the other hand required prolonged reaction for complete formation of the

tetra-*O*-acetate (**31**).

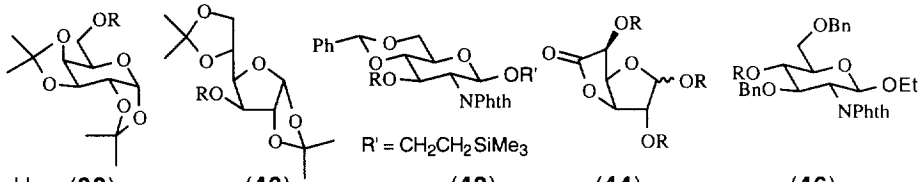
Having investigated the effect of anomeric protection on iodine-promoted acetylation, substitution at other sites was also considered (Table 4). Thus, the 6-*O*-benzyl derivative of (**24**), namely (**32**), underwent acetylation quickly and efficiently giving fully *O*-acetylated derivative (**33**) even faster than the conversion of (**24**) to (**25**). Cooling the reaction mixture on an ice-bath proved desirable in order to prevent complicating side reactions; marked differences in the rate of acetylation of the free hydroxyl groups and the acetolysis of the benzyl group at C-6 position in (**32**) were clearly evident. Similarly, although the TMSEt glycoside (**28**) proved sluggish towards iodine-promoted acetylation (Table 3) its 6-*O*-methoxybenzyl derivative (**34**) could be very effectively acetylated under mild conditions to give the tri-*O*-acetate (**35**). Significantly, the methoxybenzyl substituent at C-6 position, which is even more susceptible to acetolysis than a benzyl group, remained unaffected. Tetra-*O*-benzyl galactose (**36**) could likewise be acetylated under mild conditions to give (**37**) in excellent yield. Thus, substituents that are activating (electron releasing) in nature were found to enhance the rate of acetylation. More over, encouraged by the fact that groups that are susceptible to the usual Lewis acid [10] or sulphuric acid [11] catalyzed acetolysis survived the present conditions, other compounds having different acid labile substituents were also subjected to iodine-promoted acetylation (Table 4). Thus, five and six membered



(**32**) X = α-OMe, R_1 = H, R_2 =Bn
(**33**) X = α-OMe, R_1 = Ac, R_2= Bn
(**34**) X = β-OTMSEt, R_1 = H, R_2 = MBn
(**35**) X = β-OTMSEt, R_1 =Ac, R_2 = MBn



(**36**) R = H
(**37**) R = Ac



R = H (**38**) (**40**) (**42**) (**44**) (**46**)
R = Ac (**39**) (**41**) (**43**) (**45**) (**47**)

Table 4 : Effect of Protecting Groups on the Rate of Iodine-Promoted Acetylation

Sugar	Iodine (mg/g sugar)	Reaction time	Yield (%)	Product	Ratio α:β
Me 6-*O*-Bn-α-galactoside (**32**)	50	5 min.[a]	>95	2,3,4-Tri-*O*-acetate (**33**)	-----
β-Galactoside (**34**)	50	20 min.[a]	>95	2,3,4-Tri-*O*-acetate (**35**)	-----
Tetra-*O*-Bn galactose (**36**)	50	15 min.[a]	>95	1-Mono-*O*-acetate (**37**)	1:0.2
Diacetone galactose (**38**)	25	5 min.[a]	>98	6-Mono-*O*-acetate (**39**)	-----
Diacetone glucose (**40**)	25	5 min.[a]	>90	3-Mono-*O*-acetate (**41**)	-----
Benzylidene acetal (**42**)	100	slow reaction		3-Mono-*O*-acetate (**43**)[b]	-----
D-Glucurono-6,3-lactone (**44**)	50	10 min.[c]	>98	1,2,5-Tri-*O*-acetate (**45**)	7:1
Ethyl phthalimidoglucoside (**46**)	50	5 min.[c]	>95	4-Mono-*O*-acetate (**47**)	-----

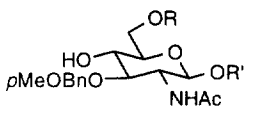
[a] Reaction carried out at ice-bath temperature. [b] Yield approx 30% in 24 h. [c] Reaction carried out at RT.

acetal functions as exemplified in compounds (**38**), (**40**) and (**42**) and the lactone ring in (**44**) proved remarkably stable to the iodine-acetic anhydride system. ^{1}H NMR spectra of (**39**) and (**41**) showed characteristic singlets amounting to three protons near 2 ppm due to the methyl protons of the acetyl goup. Moreover, on acetylation the hydroxyl proton signals originally present in the spectra of (**38**) and (**40**) disappeared as expected. Likewise, the spectrum of (**43**) showed the characteristic lowfield shift of the H-3 signal following acetylation,[12] and the appearence of a new singlet near 2 ppm was also apparent. The results obtained here on the stability of the acetal groups are in agreement with our previous observations on the compatibility of iodine with acid labile protecting groups.[3] The effect of the presence of deactivating (electron withdrawing) substituents adjacent to the site of acetylation on the sugar ring towards iodine-promoted acetylation was evident from the reaction of (**42**) with iodine-acetic anhydride wherein after 24 h. at room temperature only 30% of the 3-*O*-acetate (**43**) was formed. The benzylidene acetal, however, remained unaffected. On the other hand, though generally considered to be unreactive, the 4-OH in compound (**46**) bearing an activating group on the adjacent position was acetylated smoothly under mild conditions to give the monoacetate (**47**) in very high yield.

Regioselective acylation

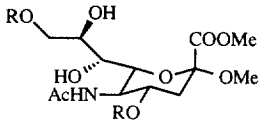
The resistance of *N*-acetylneuraminic acid methyl ester (**13**) and simple β-galactosides (**26**), (**28**) and (**30**) to iodine-promoted acetylation suggested that under controlled conditions *partial* acylation of some of these compounds might prove possible; our observations confirm this expectation (Table 5). Selective mono-*O*-acetylation of the primary alcohol of diol (**48**) gave (**49**) in good yield. The regiocontrol of the reaction is to be expected, and even warming the reaction mixture to 35°C to improve the reaction rate did not interfere with the selective reaction of the primary alcohol. Methoxybenzyl and the 2-(trimethylsilyl)ethyl groups that are prone to other acetolysis conditions once again proved compatible with the iodine-acetic anhydride system. The methyl glycoside of *N*-acetyl neuraminic acid methyl ester (**50**) was another important candidate that we wanted to examine for regioselective acetylation because of the importance of 4,9-di-*O*-acetate derivatives, such as (**51**), as a building block in glycoconjugate synthesis.[14] In accordance with the relative reactivities of the hydroxyl groups in (**50**) the 4,9-di-*O*-acetate (**51**) could be prepared in excellent yield by treating (**50**) with iodine in acetic anhydride at room temperature for a short period of time. The ^{1}H NMR spectrum of the di-*O*-acetate derivative (**51**) contained a low field ddd at 4.90 ppm with a spacing of about 4.9 Hz ($J_{3eq.,4}$) that is typical of the H-4 proton of α-linked sialic acid derivatives that are acetylated at the C-4 position. The double doublet at 2.66 ppm with coupling constants of 4.9 Hz ($J_{3eq.,4}$) and 13.0 Hz ($J_{3eq.,3ax.} = J_{3ax.,4}$) was also diagnostic. Synthesis of the TMSEt glycoside analogue of (**51**) from its respective precursor [corresponding to (**50**)] has previously been reported as a four step procedure.[14] On treatment with acetic anhydride containing iodine 3-*O*-benzyl glucose (**52**) gave the pyranosyl β-1,6-di-*O*-acetate (**53**) in excellent yield; it is not clear what governs the regio- and stereoselectivity of this process. Compound (**54**) on the other hand, when allowed to react with acetic anhydride in the presence of iodine under identical conditions gave an inseparable mixture of 3,6- and 4,6-di-*O*-acetates, (**55**) and (**56**) respectively in 0.5:1 ratio (by NMR) in 92% yield, the remaining material being the tri-*O*-acetate (**57**). Rendering the 3-OH group less reactive towards iodine promoted acetylation by placement of a phthalimido group at C-2 position in (**54**) is once again evident from the ratio of the regioisomers formed.

We next turned our attention to the possibility of carrying out regioselective (partial) benzoylation of unprotected hexopyranosides. Of particular interest was the 6-mono-*O*-benzoylation of unprotected galactoside

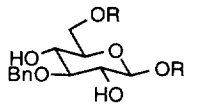


R' = $CH_2CH_2SiMe_3$

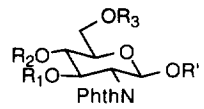
(48) R = H
(49) R = Ac



(50) R = H
(51) R = Ac

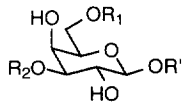


(52) R = H
(53) R = Ac

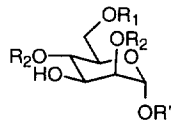


R' = $CH_2CH_2SiMe_3$

(54) $R_1 = R_2 = R_3 = H$
(55) $R_1 = R_3 = Ac$, $R_2 = H$
(56) $R_1 = H$, $R_2 = R_3 = Ac$
(57) $R_1 = R_2 = R_3 = Ac$



R' = $CH_2CH_2SiMe_3$
(28) $R_1 = R_2 = H$
(58) $R_1 = Bz$, $R_2 = H$



R' = Octyl
(59) $R_1 = R_2 = H$
(60) $R_1 = Bz$, $R_2 = H$
(61) $R_1 = H$, $R_2 = Bz$
(62) $R_1 = R_2 = Bz$

Table 5. Iodine-Promoted Regioselective Acylation of Sugar Derivatives

Sugar	Iodine (mg/g sugar)	Reaction time	Yield (%)	Product	Ratio α:β
TMSEt glycoside (**48**)[a]	200	15min.[b]	85	6-Mono-*O*-acetate (**49**)	-----
Me α-D-NANA Me ester (**50**)[a]	100	10 min.	90	4,9-Di-*O*-acetate (**51**)	-----
3-*O*-Bn-D-glucose (**52**)[a]	100	30 min.	90	1,6-Di-*O*-acetate (**53**)	0:1
Phthalimido glucoside (**54**)[a]	100	12h	92	Di-*O*-acetates (**55**) and (**56**)	-----
TMSEt β-D-galactoside (**28**)[c,d]	1:1	18 h.	70	6-Mono-*O*-benzoate (**58**)	-----
Octyl α-D-mannoside (**59**)[d,e]	1:1	18 h.	65	6-Mono-*O*-benzoate (**60**)	-----

[a] Reactions carried out at RT with 100 to 500 mg of sugar in 1 to 5 ml acetic anhydride. [b] Reaction carried out at 35°C. [c] Reaction carried out in DCM at RT. [d] With benzoic anhydride (4 mol equiv.). [e] Reaction carried out in 1,4-dioxane at RT.

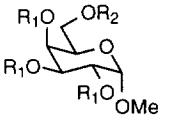
(**28**), an important step in the preparation of building blocks for the synthesis of α-2,3-sialylated glycoconjugates.[15] Our results show that the 6-*O*-benzoyl galactoside (**58**) can be prepared in a single step and in reasonably good yield (70%) using the iodine-promoted procedure. This compound has typically been synthesised in the past by a three step procedure from (**28**) involving 3,4-*O*-isopropylidenation, selective 6-*O*-benzoylation and subsequent de-*O*-isopropylidenation, or by the selective 3-*O*-benzylation of the 3,4-*O*-stannylene acetal followed by selective 6-*O*-benzoylation and finally hydrogenolysis to remove the benzyl group.[15] Performing the iodine / benzoic anhydride reaction in acetonitrile instead of dichloromethane led to a loss of regioselectivity, whereas in dioxane a faster reaction was observed that was accompanied by the formation of over benzoylated products in significant quantities (data not shown).

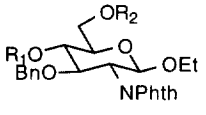
In connection with our work[16] on the enzymes involved in GPI anchor biosynthesis, we had a need to prepare partially protected mannoside (**62**). Using the ortho-ester chemistry developed by Oscarson,[17] the di-*O*-benzoate (**61**) is readily available, albeit in moderate yield, from the octyl mannoside (**59**). However, in our hands selective mono-*O*-benzoylation (benzoyl chloride/pyridine or benzoyl cyanide/pyridine at low temperarture) of the primary alcohol of (**61**) proved problematic due to competing over acylation giving rise to

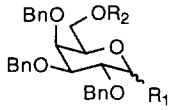
the per-*O*-benzoylated product. Therefore we reasoned that if the mannoside (**59**) could be transformed into its 6-*O*-benzoyl derivative (**60**) in good yield it might be possible to convert the latter to (**62**) in a one-pot, three step procedure. This would involve conversion of the benzoate (**60**) to the 2,3-*O*-ortho-ester followed by benzoylation of the 4-OH and subsequent regioselective ortho-ester rearrangement. Indeed it was observed that the 6-*O*-benzoate (**60**) could be prepared from the unprotected octyl mannoside (**59**) by the selective mono-*O*-benzoylation under conditions analogous to that employed for the preparation of the corresponding galactoside analogue (**58**) as described above and was successfully converted to (**62**).[18]

Acetolysis

Whilst investigating the acetylation of 6-*O*-benzyl galactoside (**32**) it became apparent that at ambient temperature iodine/acetic anhydride was capable of cleaving benzyl-protected primary alcohols, hence the complicating side reactions when exothermic acetylation reactions were allowed to progress in an uncontrolled manner. In fact it was observed that at ambient temperature when the acetylation of (**32**) was allowed to take place for 24 h. the sole product obtained was the tetra-*O*-acetate (**63**) (Table 6). Acetolysis of the aglycone group was not observed. Under similar conditions compound (**46**) having benzyl ether protection at C-3 and C-6 positions gave exclusively the primary acetate (**64**) with the benzyl-protected secondary alcohol intact. This







(32) R_1 = H, R_2 = Bn **(46)** R_1 = H, R_2 = Bn
(63) R_1 = R_2 = Ac **(64)** R_1 = R_2 = Ac

(36) R_1 =O H, R_2 = Bn
(65) R_1 = OAc, R_2 = Ac
(66) R_1 = β-SMe, R_2 = Bn
(37) R_1 = OAc, R_2 = Bn

Table 6. Iodine-Promoted Acetolysis of Sugar Benzyl Ethers

Sugar	Iodine (mg / g sugar)	Reaction time	Yield (%)	Product	Ratio α:β
Compound (**32**)	100	24 h.	>95	Tetra-*O*-acetate (**63**)	-----
Compound (**46**)	50	24 h.	>95	4,6-Di-*O*-acetate (**64**)	-----
Compound (**36**)	100	24 h.	>95	1,6-Di-*O*-acetate (**65**)	1:0.2
Compound (**66**)	50	5 min.[a]	>95	1-Mono-*O*-acetate (**37**)	>1:0.1
Compound (**66**)	100	1 h.[a]	>95	1,6-Di-*O*-acetate (**65**)	>1:0.1

[a] Reaction carried out at ice-bath temperature.

prompted us to investigate the possibility of selective acetolysis of the 6-*O*-benzyl group in poly-*O*-benzylated compounds (**36**) and (**66**) (Table 6). Treatment of (**36**) with iodine/acetic anhydride quickly gave the glycosyl acetate (see Table 4) which after subsequent acetolysis of the 6-*O*-benzyl group gave (**65**) in excellent yield. In the case of (**66**), as expected, acetolysis of the thiomethyl group preceded that of the 6-*O*-benzyl group, once again giving the glycosyl acetate derivative (**37**) (*cf.* Table 4). On continued reaction clean (**65**) was eventually obtained. Manipulation of the reaction conditions in favour of one or the other transformation as desired was

thus possible. We find that acetolysis reactions employing iodine/acetic anhydride are practically easier to carry out and control than the related procedures employing ferric chloride,[10] or concentrated sulfuric acid.[11]

Conclusions

We have demonstrated that iodine is an efficient promoter for acyl transfer reactions in carbohydrate chemistry, and offers scope for the practical synthesis of fully and partially protected carbohydrate building blocks.[19] The differences in the rate of acyl transfer reactions noted are dependent on a number of factors including sugar configuration, anomeric substitution, and the nature and position of protecting groups. Such rate differences might also be attributed to differences in solubility of the compounds concerned in acetic anhydride. Alternatively, advantageous (or disadvantageous) complexation of iodine, or iodine-derived species, to the sugar might explain these observations, although the molecular basis of such complexation events is not immediately obvious. In summary, iodine is a mild and practical alternative to many of the complex reagents currently used in acyl transfer / protecting group chemistry.

Experimental

General: All reagents (Aldrich) were used as purchased without further purification. Solvents used for reactions were dried by storing over activated molecular sieves (4Å). Reactions were monitored by TLC, which was performed with 0.2 mm Merck pre-coated silica gel 60 F_{254} aluminium sheets. Compounds were detected by dipping the TLC plates in an ethanolic solution of sulphuric acid (4% v/v) and heating. Sorbsil C60 40/60 A (Sorbsil Chromatography Media) was used for column chromatography. Hexane refers to a mixture of isomeric hexanes. Melting points (uncorrected) were determined on a Gallenkamp Melting Point Apparatus. Optical rotations were recorded on an Optical Activity Ltd. AA-1000 Polarimeter at room temperature (approximately 22 to 24°C.) for solutions in dichloromethane. ^{1}H NMR spectra were recorded at 300 MHz on a Brucker AM300 spectrometer in deuteriochloroform or methanol. Chemical shifts are expressed relative to that of the residual proton in the deuterated solvents (δ 7.25 and 3.35 for $CDCl_3$ and CD_3OD respectively). ^{13}C NMR spectra were recorded at 75.47 MHz. Assignments of resonances are based on published data. The anomeric ratio of products reported in Tables 1 to 6 were determined from their NMR spectra. Most of the compounds reported here have been reported previously, many are commercially available and therefore only spectral data for compounds that are otherwise significant are reported. NANA, TMSEt and DCM refer to *N*-acetyl neuraminic acid, 2-(trimethylsilyl)ethyl and dichloromethane respectively. RT refers to room temperature (approximately 20 to 24°C).

General Procedure for Acetylation/Acetolysis - The sugar was suspended in acetic anhydride (5 ml/g of sugar for acetylation and 10 ml/g of sugar for acetolysis, see Tables 1 to 6) and stirred. Iodine (10 to 500 mg/g sugar, see Tables 1 to 6) was added and stirring was continued until TLC showed the reaction to be complete. In small scale reactions the reaction mixture was diluted with DCM and was washed successively with dilute aqueous sodium thiosulphate and aqueous sodium carbonate solutions. The organic layer was then dried (Na_2SO_4) and concentrated to give the product. The products thus obtained were pure enough in most cases for use elsewhere directly or else were purified by column chromatography. In large scale acetylations the reaction mixture was poured into ice-cold dilute sodium thiosulphate solution with stirring. The products were allowed to crystallize in the refrigerator, and were separated by filtration.[7]

General Procedure for Partial Benzoylation - Iodine (1.1 to 1.2 mol equiv.) was added to a stirred

solution of the sugar and benzoic anhydride (4 mol equiv.) in dichloromethane/dioxane and stirring was continued until TLC indicated completion of the reaction. Excess benzoic anhydride was then destroyed by the addition of methanol. The resulting amber solution was then decolourized by stirring with Amberlite IRA-400 (OH^-) resin, and was concentrated under reduced pressure to a thick syrup. Products were subsequently isolated by column chromatography.

Typical Procedure: Acetylation of D-galactose (3). Iodine (50 mg) was added to a stirred suspension of galactose (1 g) in acetic anhydride (5 ml) at room temperature. In a couple of minutes the reaction mixture began to warm indicating the onset of acetylation, and thereafter the sugar started to go into solution quickly. A clear dark amber coloured solution was obtained in the next few minutes and TLC (ethyl acetate:hexane, 1:1, v/v) showed the presence of only the pentaacetate. The reaction mixture was then poured into a separating funnel containing DCM (50 ml), dilute aqueous sodium thiosulphate solution and crushed ice and was shaken thoroughly. The colourless organic layer thus obtained was then transferred to another separating funnel containing aqueous sodium carbonate solution. The residual aqueous layer in the first funnel was then extracted with DCM (x 2) and the organic extracts were combined and washed with sodium carbonate solution to neutrality. It was then dried (Na_2SO_4) and concentrated. A clear colourless syrup was obtained which crystallized on drying under high vacuum (yield, nearly quantitative). ^1H NMR spectrum of this product showed it to be α-**D**-galactopyranose pentaacetate (**4α**) containing 4 to 5% of the β-isomer. Recrystallization from ethanol gave pure α-anomer.[7]

Acetylation of **D**-mannose (**1**), **D**-glucose (**5**), **D**-lactose (**7**), **D**-maltose (**9**), *N*-acetyl-**D**-glucosamine (**11**), methyl (5-acetamido-3,5-dideoxy-**D**-glycero-**D**-galacto-2-nonulopyranosid)onate (**13**), methyl α-**D**-glucopyranoside (**16**), methyl β-**D**-glucopyranoside, (**18**), 2-(trimethylsilyl)ethyl β-**D**-glucopyranoside[13] (**20**) phenyl β-**D**-glucopyranoside (**22**), methyl α-**D**-galactopyranoside (**24**) and methyl β-**D**-galactopyranoside (**26**), 2-(trimethylsilyl)ethyl β-**D**-galactopyranoside[15] (**28**), *p*-nitrophenyl β-**D**-galactopyranoside (**30**), 2-(trimethylsilyl)ethyl 4,6-*O*-benzylidene-2-deoxy-2-phthalimido-β-**D**-glucopyranoside[13] (**42**), **D**-glucurono-6,3-lactone (**44**), ethyl 3,6-di-*O*-benzyl-2-deoxy-2-phthalimido-β-**D**-glucopyranoside (**46**) were carried out in the same way as described for the acetylation of **D**-galactose (**3**) under the conditions given in Tables 1 to 4. The products obtained were identical in all respects with the respective compounds prepared by standard method using acetic anhydride and pyridine or as given in the references shown. Selected NMR spectral data for the less common sugar derivatives are listed below.

Methyl (5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-glycero-D-galacto-2-nonulopyranosid)onate[9] (14) from (**13**). A mixture of methyl (5-acetamido-3,5-dideoxy-**D**-glycero-**D**-galacto-2-nonulopyranosid)onate[9] (**13**, 100 mg) and iodine (50 mg) in acetic anhydride (1 ml) was stirred at 35°C for 20 min. TLC (DCM:MeOH, 9.5:0.5, v/v) at this stage revealed complete disappearence of (**13**). Work up as described in the general procedure and purification by column chromatography (silica gel, 50 ml; eluent, DCM:MeOH, 9.6:0.4, v/v) gave a thick colourless syrup (yield, 107 mg, 70%) which crystallized on standing (mp. 173-175°C). ^1H NMR δ: 6.11, d, 1 H, 9.8 Hz, N*H*; 5.36, dd, 1 H, 2.2 Hz and 4.4 Hz, H-7; 5.22, m, 1 H, H-8; 5.03, ddd, 1 H, H-4; 4.93, broad s, 1 H, 2-*O*-*H*; 4.56, dd, 1 H, 2.5 Hz and 12.3 Hz, H-9a; 4.23, dd, 1 h, 2.2 Hz and 10.5 Hz, H-6; 4.07, q, 1 H, 9.8 Hz and 10.4 Hz, H-5; 4.00, dd, 1 H, 8.0 Hz, 12.3 Hz, H-9b; 3.81, s, 3 H, COOC*H*$_3$; 2.18, m, 2 H, H-3a and H-3e; 2.11. 2.07, 1.99 and 1.98, 4 s, 12 H, 4 x OCOC*H*$_3$ and 1.87, s, 3 H, NCOC*H*$_3$. ^{13}C NMR δ: 171.35, 171.06, 170.83, 170.31 and 170.19, 5 x *C*=O, 4 x O*C*OMe and 1 x NH*C*OMe; 168.98, C-1; 94.87, C-2; 71.69, C-8; 71.29, C-6; 69.17, C-4; 68.27, C-7; 62.56, C-9;

53.32, $COOCH_3$; 49.18, C-5; 36.12, C-3; 23.06, $NCOCH_3$ and 21.02, 20.84, and 2 x 20.75, 4 x $OCOCH_3$.

2-(Trimethylsilyl)ethyl 3-*O*-acetyl-4,6-*O*-benzylidene-2-deoxy-2-phthalimido-β-D-glucopyranoside (43) from **(42)**. Acetylation of **(42)**[13] (100 mg) carried out in acetic anhydride (1 ml) in the presence of iodine (10 mg) for 24 h. at room temperature followed by work up as described above and purification by colmn chromatography (silica gel, 50 ml; eluent, ethyl acetate:hexane, 2:3) gave the title compound (yield, 32.6 mg, 30%) as dry foam which on grinding was obtained as a white powder. mp., 103-104°C. $[\alpha]_D$, -20.7 (c, 1.5). ^1H NMR δ: 7.36 - 7.93, 4 m, 9 H, 9 aromatic *H*; 5.91, dd, 1 H, 8.8 Hz and 10.2 Hz, H-3; 5.7, s, 1 H, C*H*Ph; 4.50, d, 1 H, 8.4 Hz, H-1; 4.43, dd, 1 H, 4.3 Hz and 10.3 Hz, H-6a; 4.33, dd, 1 H, 8.4 Hz and 10.3 Hz, H-2; 3.97 and 3.57, 2 m, 2 H, $OCH_2CH_2SiMe_3$; 3.72 -3.91, m, 3 H, H-4, H-5 and H-6b; 1.91, s, 3 H, $OCOCH_3$; 0.7 - 0.95, m, 2 H, CH_2SiMe_3 and -0.10, 9 H, $Si(CH_3)_3$. ^{13}C NMR δ: 170.06, 167.96 and 167.43, 3 x *C*=O; 101.5, *C*HPh; 98.06, C-1; 68.62, C-6, 67.46, $OCH_2CH_2SiMe_3$; 55.36, C-2; 20.47, $OC(=O)CH_3$; 17.75, CH_2SiMe_3 and -1.63, $Si(CH_3)_3$. (Found: C, 62.58; H, 6.29; N, 2.55. $C_{28}H_{33}NO_8Si$ requires: C, 62.62; H, 6.16; N, 2.60%)

Ethyl 4-*O*-acetyl-3,6-di-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranoside (47) from **(46)**. Treatment of **(46)**[3] (250 mg) with iodine-acetic anhydride reagent under the conditions given in Table 4 gave **(47)** after work up and filtration through a column of silica gel (eluent, ethyl acetate:hexane, 1:3) as white crystals (yield, 258 mg, 95.6%). mp., 70-72°C. $[\alpha]_D$, +55.2 (c, 1.4). ^1H NMR δ: 6.80 - 7.80, 3 m, 14 H, 14 aromatic *H*; 5.18, d, 1 H, 8.5 Hz, H-1; 5.13, dd, 1 H, 9.1 Hz and 9.9 Hz, H-4; 4.62 and 4.35, 2 d, 2 H and 4.60, s, 2 H, 2 x CH_2Ph; 4.47, dd, 1 H, 9.1 Hz and 10.6 Hz, H-3; 4.29, dd, 1 H, 8.5 Hz and 10.6 Hz, H-2; 3.87 and 3.52, 2 m, 2 H, OCH_2Me; 3.77, m, 1 H, H-5; 3.65, d, 2 H, 4.6 Hz, H-6a and H-6b; 1.97, s, 3 H, $OCOCH_3$ and 1.02, t, 3 H, CH_3. ^{13}C NMR δ: 169.56,167.48 and 167.00, 3 x *C*=O; 97.80, C-1; 73.68 and 73.50, 2 x CH_2Ph; 69.64, C-6; 66.20, OCH_2Me; 20.80, $OCOCH_3$ and 14.89, CH_3. (Found: C, 68.81; H, 6.20; N, 2.42. $C_{32}H_{33}NO_8$ requires: C, 68.68; H, 5.94; N, 2.50%)

Acetylation of methyl 6-*O*-benzyl-α-D-galactopyranoside (32), 2-(trimethylsilyl)ethyl 6-*O*-*p*-methoxybenzyl-β-D-galactopyranoside (34), 2,3,4,6-tetra-*O*-benzyl-D-galactopyranose (36), 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (38), 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (40). Acetylation was carried out as described in the general procedure but at ice-bath temperature and under conditions of iodine concentration and reaction time as listed in Table 4. The acetylation products obtained from **(32)**,[20] **(36)**,[21] **(38)**[4] and **(40)**[4] were identical with the known methyl 2,3,4-tri-*O*-acetyl-6-*O*-benzyl-α-**D**-galactopyranoside[22] **(33)**, 1-*O*-acetyl-2,3,4,6-tetra-*O*-benzyl-**D**-galactopyranose[21] **(37)**, 6-*O*-acetyl-1,2:3,4-di-*O*-isopropylidene-α-**D**-galactopyranose[23] **(39)** and 3-*O*-acetyl-1,2:5,6-di-*O*-isopropylidene-α-**D**-glucofuranose[23] **(41)** respectively. The NMR spectral data for the tri-*O*-acetate **(35)**[24] obtained from **(34)**[24] is as follows. ^1H NMR δ: 7.21 and 6.87, 2 d, 4 H, C_6H_4; 5.45, near d, 1 H, H-4; 5.16, dd, 1 H, 7.88 Hz and 10.40 Hz, H-2; 5.01, dd, 1 H, 3.4 Hz and 10.3 Hz, H-3; 4.47, d, 1 H, H-1; 4.36 and 4.48, 2 d, CH_2 of the MBn group; 4.00 and 3.54, 2 m, 2 H, $CH_2CH_2SiMe_3$; 3.80, s, 3 H, OCH_3; 1.97, 2.04 and 2.06, 3 s, 9 H, 3 x $OCOCH_3$; 0.95, m, 2 H, CH_2SiMe_3 and -0.01, s, 9 H, $Si(CH_3)_3$.

2-(Trimethylsilyl)ethyl 2-acetamido-6-*O*-acetyl-2-deoxy-3-*O*-*p*-methoxybenzyl-β-D-glucopyranoside (49). A mixture of 2-(trimethylsilyl)ethyl 2-acetamido-6-*O*-acetyl-2-deoxy-3-*O*-*p*-methoxybenzyl β-**D**-glucopyranoside (**48**, 200 mg) and iodine (40 mg) in acetic anhydride (4 ml) was stirred at 35°C for 15 min. TLC (DCM:MeOH, 9.7:0.3, v/v) at this stage revealed conversion of the diol (**48**) to a faster moving compound. Work up as described above and purification by column chromatography (silica gel, 50 ml; eluent,

DCM:MeOH, 9.7:0.3) gave the title product as a white crystalline solid. mp., 114-117°C. $[\alpha]_D$, -50.1 (c, 0.9). ^{1}H NMR δ: 7.23 and 6.83, 2 d, 4 H, 4 aromatic *H*; 5.82, d, 1 H, 7.7 Hz, N*H*; 4.88, d, 1 H, 8.2 Hz, H-1; 4.65, q, 2 H, C*H*$_2$C$_6$H$_4$; 3.76, s, 3 H, Ph-OC*H*$_3$; 3.0, d, 1 H, O*H*; 2.06, s, 3 H, OCOC*H*$_3$; 1.91, s, 3 H, NCOC*H*$_3$; 0.90, m, 2 H, C*H*$_2$SiMe$_3$ and -0.02, s, 9 H, Si(C*H*$_3$)$_3$. ^{13}C NMR δ: 171.63 and 170.53, 2 x *C*=O; 99.13, C-1; 63.43, C-6; 57.51 and 55.20, C-2 and OCH$_3$; 23.60, NCO*C*H$_3$; 20.82, OCO*C*H$_3$ and -1.48, Si(*C*H$_3$)$_3$. (Found: C, 57.67; H, 7.91; N, 2.82. C$_{23}$H$_{37}$NO$_8$Si requires: C, 57.12; H, 8.11; N, 2.89%)

Methyl (methyl 5-acetamido-4,9-di-*O*-acetyl-3,5-dideoxy-D-glycero-α-D-galacto-2-nonulopyranosid)onate (51). Methyl (methyl 5-acetamido-3,5-dideoxy-D-glycero-α-D-galacto-2-nonulopyranosid)onate (**50**, 100 mg) was taken up in a round bottom flask and acetic anhydride (1 ml) was added to it followed by iodine (10 mg) and the mixture was stirred at room temperature for 10 min. when TLC (DCM:MeOH, 8:2, v/v) indicated complete conversion of (**50**) to a faster moving compound. Work up as described above and filtration through a short column of silica gel (eluent, DCM:MeOH, 8:2, v/v) gave the title compound after lyophilization from dioxan as a white powder (113 mg) in over 90% yield. $[\alpha]_D$, -25.7 (c, 0.9). ^{1}H NMR δ: 5.98, d, 1 H, 7.6 Hz, N*H*; 4.90, ddd, 1 H, 4.9 Hz, H-4; 3.84, s, 3 H, COOC*H*$_3$; 3.35, s, 3 H, OC*H*$_3$; 2.66, dd, 1 H, 4.9 Hz and 13.0 Hz, H-3e; 2.10 and 2.08, 2 s, 6 H, 2 x OCOC*H*$_3$ and 1.97, s, 3 H, NCOC*H*$_3$. ^{13}C NMR δ: 172.78, 172.27 and 171.22, 3 x *C*=O; 169.02, C-1; 98.51, C-2; 66.26, C-9; 53.40, 51.86 and 51.67, COO*C*H$_3$, O*C*H$_3$ and C-5; 36.92, C-3; 23.04, NCO*C*H$_3$ and 21.00 and 20.97, 2 x OCO*C*H$_3$. (Found: C, 48.82; H, 6.58; N, 2.94. C$_{17}$H$_{27}$NO$_{11}$ requires: C, 48.46; H, 6.46; N, 3.32%)

1,6-Di-*O*-acetyl-3-*O*-benzyl-β-D-glucopyranose (53). To 3-*O*-benzyl-D-glucose (**52**, 100 mg) added acetic anhydride (1 ml) followed by iodine (10 mg) and the mixture was stirred for about 30 min. at room temperature. TLC (ethyl acetate:hexane, 2:3, v/v) at this stage showed complete disappearence of (**52**) and the emergance of a faster moving compound. Work up and purification of the resulting colourless syrup obtained carried out as in the above using ethyl acetate:hexane (2:3, v/v) as the eluent gave pure (**53**) as a clear syrup. (Yield, 120 mg, 90%). $[\alpha]_D$, -17.4 (c, 1.0). ^{1}H NMR δ: 7.25 - 7.40, m, 5 H, C$_6$*H*$_5$; 5.49, d, 1 H, 8.1 Hz, H-1; 4.86, s, 2 H, C*H*$_2$Ph; 4.42 and 4.22, 2 dd, 2 H, H-6a and H-6b; 3.10 and 2.81, 2 d, 2 H , 2-*O*-*H* and 4-*O*-*H* and 2.10 and 2.06, 2 s, 6 H, 2 x OCOC*H*$_3$. ^{13}C NMR δ: 171.81, 169.49, 2 x O*C*OMe; 138.14, C-1 of Ph; 128.56, 128.46, C-2 to C-6 of Ph; 93.84, C-1; 83.55, C-3; 75.11, *C*H$_2$Ph; 62.79, C-6 and 20.89, and 20.73, 2 x OCO*C*H$_3$. (Found: C, 57.98; H, 6.68. C$_{17}$H$_{22}$O$_8$ requires: C, 57.62; H, 6.26%)

2-(Trimethylsilyl)ethyl 6-*O*-benzoyl-β-D-galactopyranoside (58). To a solution of 2-(trimethylsilyl)ethyl β-D-galactopyranoside[15] (**28**, prepared from 2-(trimethylsilyl)ethyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside[1] by Zemplen's transesterification with sodium methoxide in methanol) (140 mg, 0.5 mmol) in dry dichloromethane (4 ml) was added benzoic anhydride (452 mg, 2 mmol) and stirred at RT. Iodine (150 mg, 0.59 mmol) was then added and stirring continued for 18 h. at RT. Most of (**28**) had been disappeared by then (TLC, DCM:MeOH, 9.5:0.5, v/v). MeOH was then added and after stirring for some time the clear amber coloured solution was stirred with amberlite IRA-400 (OH^-) resin to yield a nearly colourless solution. The resin was then removed by filtration and washed with methanol. The filtrate was then concentrated under reduced pressure and the residue was chromatographed on a column of silica gel (100 ml) using DCM:MeOH, 9.5:0.5, v/v as the eluent. The product obtained (white solid, 135 mg, 70%) was homogeneous with that obtained by the three-step literature procedure as described by Murase, *et al.*[15]

***n*-Octyl 6-*O*-benzoyl-α-D-mannopyranoside (62).** *n*-Octyl mannopyranoside (**59**, prepared from *n*-

octyl 2,3,4,6-tetra-*O*-acetyl-α-**D**-mannopyranoside[1] by Zemplen's transesterification with sodium methoxide in methanol, 146 mg, 0.5 mmol) in dry dioxan (10 ml) was treated with benzoic anhydride (452 mg, 2 mmol) in the presence of iodine (150 mg, 0.59 mmol) for about 30 h. as described for the preparation of (**58**). Work up and purification by column chromatography in the same way gave the title product as a thick, colourless syrup (129 mg, 65%). $[\alpha]_D$, +23.2 (c, 1.0). ^{1}H NMR δ: 8.00, near t and 7.40 m, 5 H, OCOC$_6H_5$; 4.79, broad s, 1 H, H-1; 4.61, m, 2 H, H-6a and H-6b; 3.78 - 3.93, m, 4 H, H-2, H-3, H-4 and H-5, 3.60 and 3.32, 2 ddd, 2 H, OCH_2; 1.49, near t, 1 H, OCH$_2$CH_2; 1.20, m, 10 H, (CH_2)$_5$Me and 0.83, t, 3 H, CH_3. ^{13}C NMR δ: 166.93, *O*C*O*Ph; 99.68, C-1, 71.79, 70.79, 70.47 and 67.92, C-2 to C-5; 67.79, C-6; 64.60, OCH$_2$(CH$_2$)$_6$Me and 14.02, *C*H$_3$. (Found: C, 63.33; H, 8.31. C$_{21}$H$_{32}$O$_7$ requires: C, 63.62; H, 8.14%)

Acetolysis of methyl 6-*O*-benzyl-α-D-galactopyranoside (32), ethyl 3,6-di-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranoside (46), 2,3,4,6-tetra-*O*-benzyl-D-galactopyranose (36), methyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β–D-galactopyranoside (66). The acetolysis reactions were carried out as described in the general procedure under conditions of iodine concentration and reaction time as listed in Table 6. The product of acetolysis of (**32**) was identical with the acetylation product obtained from (**24**) (see Table 3) and was found to be the known methyl tetra-*O*-acetyl-α-**D**-galactopyranoside (**63**).[25]

Ethyl 4,6-di-*O*-acetyl-3-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranoside (64). Obtained from (**46**) as white crystals in more than 95% yield. mp. 104-105°C. $[\alpha]_D$, +48.0 (c, 1.2). ^{1}H NMR δ: 6.90 - 7.70, 2 m, 9 H, 9 aromatic *H*; 5.18, dd, 1 H, 9.0 Hz and 9.9 Hz, H-4; 5.15, d, 1 H, 8.4 Hz, H-1; 4.58 and 4.31, 2 d, 2 H, 12.0 Hz, CH_2Ph; 4.41, dd, 1 H, 8.9 Hz and 10. 7 Hz, H-3; 4.28 and 4.15, 2 dd, 2 H, H-6a and H-6b; 4.24, dd, 1 H, 8.5 Hz and 10.7 Hz, H-2; 3.78 and 3.47, 2 m, OCH_2Me; 3.75, m, 1 H, H-5; 2.03 and 2.10, 2 S, 6 H, 2 x OCOCH_3 and 1.01, t, 3 H, CH_3. ^{13}C NMR δ: 170 84 and 169.39, 2 x O(C=O)Me; 98.06, C-1; 77.00, C-3; 73.89, *C*H$_2$Ph; 71.99, C-5; 71.35, C-4, 65.17, O*C*H$_2$Me; 62.38, C-6; 55.44, C-2; 20.83, 2 x OCO*C*H$_3$ and 14.92, *C*H$_3$. (Found: C, 63.45; H, 5.66; N, 2.71. C$_{27}$H$_{29}$NO$_9$ requires: C, 63.40; H, 5.71; N, 2.74%)

1,6-Di-*O*-acetyl-2,3,4-tri-*O*-benzyl-D-galactopyranose (65) from (36): To 200 mg (0.37 mmol) of (**36**) were added 2 ml of acetic anhydride followed by 20 mg of iodine and the mixture was stirred at RT for 24 h. Work up carried out as given in the general procedure gave after filtration through a short column of silica gel (eluent, ethyl acetate:hexane, 1:5) pure (**65**) as a soft glassy solid (189 mg, 95.5%). ^{1}H NMR δ: (α- anomer) 7.25 - 7.45, m, 15 H, 3 x C$_6H_5$; 6.42, d, 1 H, 3.7 Hz, H-1; 5.02, 4.90, 4.80 and 4.63, 4 d, 4 H, and 4.72, q, 2 H, 3 x CH_2Ph; 4.21, dd, 1 H, 3.7 Hz and 9.8 Hz, H-2; 4.00- 4.15, m, 3 H, H-5, H-6a and H-6b; 3.95, near d, 1 H, H-4; 3.91, dd, 1 H, 2.7 Hz and 9.8 Hz, H-3 and 2.13 and 2.00, 2 s, 6 H, 2 x OCOCH_3. ^{13}C NMR δ: 170.46, 169.30, 2 x O*C*OMe; 138.44, 137.99, 137.87, 3 x C-1 of Ph; 90.62, C-1; 63.01, C-6 and 20.72, OCO*C*H$_3$. (Found: C, 69.99; H, 6.64. C$_{31}$H$_{34}$O$_8$ requires: C, 69.65; H, 6.41%)

Selective acetolysis of the thiomethyl group in (66): To a mixture of (**65**) (114.1 mg, 0.2 mmol) and acetic anhydride (2 ml) cooled in an ice-bath was added iodine (5.5 mg) and stirred for about 5 min. Work up and purification of the product as described above gave a thick syrup that was shown to be 1-*O*-acetyl-2,3,4,6-tetra-*O*-benzyl-α-**D**-galactopyranose (α-**37**) containing traces of the β-anomer (113 mg, 97%). Crystals of pure α-anomer was obtained from ether - hexane.[20]

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