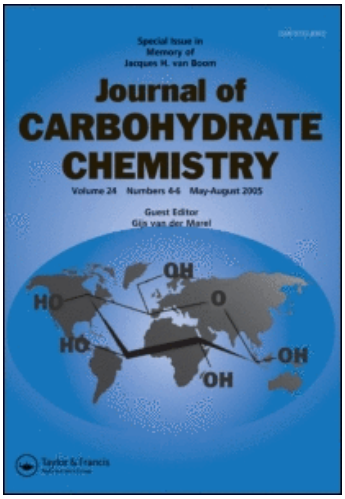

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A New Procedure for Highly Regio- and Stereoselective Iodoacetoxylation of Protected Glycals and α-1,2-Cyclopropanated Sugars

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A New Procedure for Highly Regio- and Stereoselective Iodoacetoxylation of Protected Glycals and α-1,2-Cyclopropanated Sugars

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Protected glycals and α-1,2-cyclopropanated sugars were converted in high yields and selectivities in less than 2 h at low temperatures to 2-deoxy-2-iodoglycosyl acetates or novel 2-deoxy-2-iodomethylglycosyl acetates using the simple, inexpensive reagent mixture of ammonium iodide, hydrogen peroxide, and acetic anhydride/acetic acid in acetonitrile. The protected glycals gave rise to 2-deoxy-2-bromoglycosyl acetates when ammonium bromide was used instead of the iodide, although longer reaction times were required and selectivities were inferior. Other simple olefins such as styrene and indene were also converted to their corresponding 1,2-*trans*-iodoacetates.

Keywords Glycals, 2-Iodoglycosides, Iodoacetates, 1,2-Cyclopropanated sugars

INTRODUCTION

Unsaturated sugars such as the glycals and 1,2-cyclopropanated derivatives are versatile building blocks for the synthesis of oligosaccharides, glycosides,

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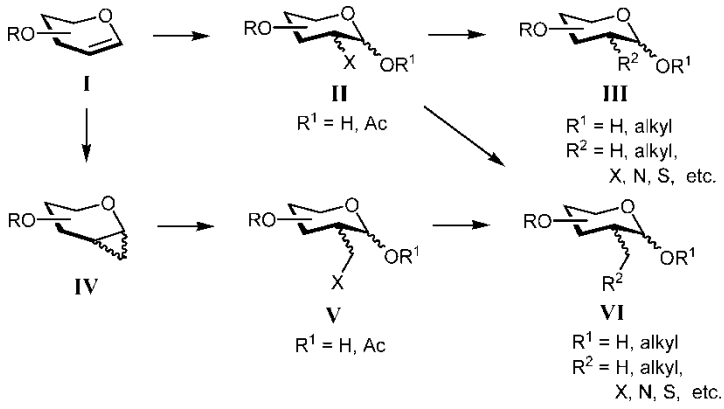
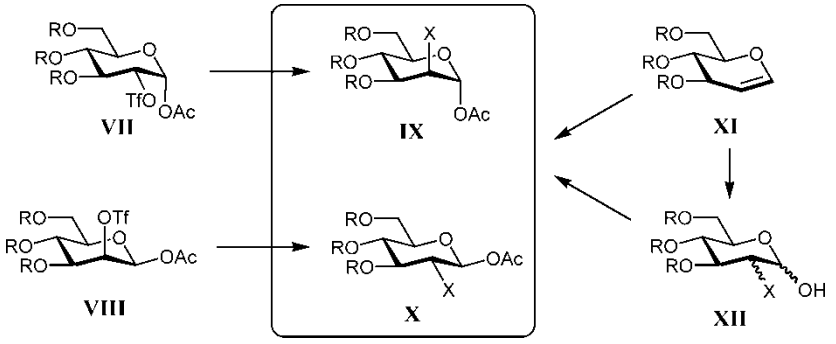


Scheme 1: Transformations and synthetic utility of glycals and 1,2-cyclopropanated sugars.

and modified sugars.[1–3] As summarized in Scheme 1, the α- or β-1,2-cyclopropanated sugars **IV** can be prepared stereoselectively from the glycals **I**, and all can be readily converted to the corresponding haloglycosyl acetates or halohydrins (**II** and **V**). These are in turn useful intermediates for producing a variety of sugar derivatives: the 1-acetates are glycosyl donors in their own right, or could be easily converted to other donors for preparation of glycosides **III** or **VI**, with the 2-iodo substituent (in **II**) known to provide stereodirecting anchimeric assistance in glycosylation reactions. In addition, the iodo- or bromo-substituents are amenable to reductive cleavage to give 2-deoxyglycosides or 2-*C*-methyl glycosides, and while it is known that 2-haloglycosides have limited utility in nucleophilic substitution reactions, the primary halides in the 2-halomethyl substituents of **V** could be precursors for further elaboration or extension of the C-2 side chain. Finally, the halogenated sugars also provide the basis for radical-mediated introduction of alkenyl substituents.

It was our efforts in this latter context[4] together with our interest in developing environmentally benign synthetic protocols[5] that led to an investigation of an alternative method for the preparation of 2-deoxy-2-iodoglycopyranosyl acetates from protected glycals, reported briefly in a preliminary publication.[6] We have now further explored the scope and limitations of this procedure, demonstrating its effectiveness on a wider range of glycal substrates and 1,2-cyclopropanated sugars, its compatibility with acid-sensitive benzylidene protecting groups, and the effective functionalization of a few simple noncarbohydrate olefinic substrates. Herein we report the results along with full experimental conditions and spectroscopic data of the compounds prepared.

The existing synthetic approaches to the 2-deoxy-2-iodoglycopyranosyl acetates can be divided into three categories, summarized for the gluco- and manno- cases in Scheme 2. The first, involving displacement of



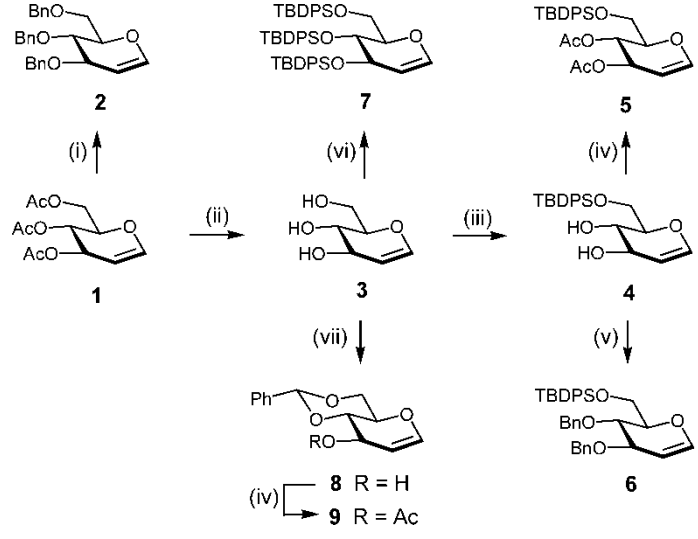
Scheme 2: Existing synthetic approaches to 2-deoxy-2-iodoglycopyranosyl acetates.

2-triflates from otherwise protected glycosyl acetates **VII** and **VIII,**[7] provides access in good yields to the desired products **IX** and **X**, but relies on selective preparation and careful handling of the moderately stable 2-triflates. The second category proceeds via formation of iodohydrins **XII** from glucals **XI** followed by acetylation to give mixtures of iodoacetates **IX** and **X**.[1,8] In most cases this is limited by the low diastereoselectivity of the iodohydrin formation, although in one instance[9] the exclusive formation of 3,4,6-tri-*O*-acetyl-2-deoxy-2-iodo-α-D-mannose has been reported. The third category provides direct access to the iodoacetates **IX** and **X** from glucals **XI** using, in most cases, a source of electrophilic iodine together with acetic acid as solvent or cosolvent.[2,3] A useful addition to this latter category, and of relevance to our consideration of synthetic protocols with low environmental impact, is Kirschning's use of polymer-supported reagents for haloacetoxylation, which work efficiently when applied to glycals.[10] Yields in all these methods are generally good to excellent, and product selectivities range from a modest ~2:1 to the synthetically useful ~11:1 in favor of the α-*manno*-configuration, achieved with the CAN/NaI/AcOH procedure.[2] The regio- and stereoselectivities have been extensively discussed, with the observed α-*manno*-selectivities rationalized in terms of the favored irreversible formation of the bridged iodonium intermediate on the β-face, due to its steric demands and its tendency not to equilibrate to oxocarbenium and other intermediates as is the case for the corresponding bromonium or chloronium species. Concerted α-face nucleophilic attack at the anomeric carbon and cleavage of the C-1 to iodine bond leads to the formation of α-*manno*-derivatives. In contrast, selectivity in favor of the *gluco*-isomer results when *tert*-butyldiphenylsilyl protecting groups are used, and has been explained[11] in terms of the preference in this glycal for the $^5H_4$ conformation, which minimizes significant steric interactions of the bulky silyl groups but also restricts access of the electrophile to the β-face of the glucal.

RESULTS AND DISCUSSION

Our approach to the direct halo-acetoxylation of glycals centered on the generation of iodonium ion equivalents through the oxidation of readily available iodide salts. The synthetic possibilities of iodination of organic substrates with halide salts in the presence of hydrogen peroxide and a catalyst have been highlighted,[1,12,13] and we have shown previously that under these conditions glycals are readily converted to iodohydrins or methyl-2-deoxy-2-halo-glycosides, the latter with methanol as solvent. While this heterogeneously catalyzed procedure is attractive, expansion of the synthetic utility by attempting direct glycosylations by combining glycals with more complex glycosyl acceptors in the reaction mixture in non-nucleophilic solvents was not successful. The halohydrins can, of course, be activated further in an additional step to produce glycosyl donors, but it was recognized that a simple, efficient method for direct and highly stereoselective conversion to 2-iodo-glycosyl acetates would provide synthetically useful intermediates for the preparation of C-2 modified glycosides.

To this end a series of protected glucals were prepared from tri-*O*-acetyl-D-glucal (**1**) as outlined in Scheme 3. These were chosen in order to evaluate not only the tolerance of the protecting groups to the reaction conditions, but also the steric and stereoelectronic impact of electron-withdrawing (acetyl), electron-donating (benzyl, silyl), sterically demanding (bulky silyl), and



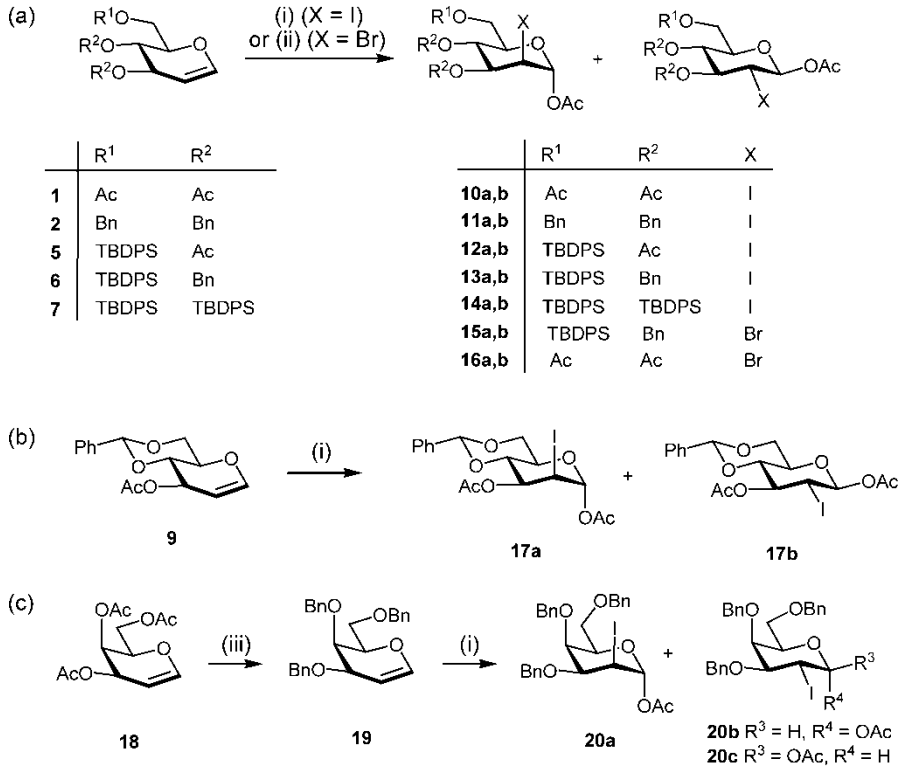
Scheme 3: (i) 50% aq NaOH, *t*-BuOH, *n*-Bu_4NHSO_4, 50°C, then BnCl, 4.5 h, 50%; (ii) cat. NaOMe in MeOH, rt, 0.5 h, 91%; (iii) TBDMSCl (1.1 equiv.), imidazole, DMF, rt, 1 h, 66%; (iv) Ac_2O, DMAP, Et_3N, rt, 1 h, 90%; (v) NaH, *n*-Bu_4NI, BnBr in THF, rt, 15 h, 70%; (vi) TBDMSCl (3.1 equiv.), imidazole, DMF, rt, 15 h, 85%; (vii) $PhCH(OMe)_2$, TsOH, DMF, rt, 15 h, 41%.

conformationally restrictive (4,6-*O*-benzylidene) groups on the reaction outcomes. Benzylated glucal **2** was prepared directly in a one-pot procedure from **1**.[14a] Deacetylation of **1** gave glucal **3**, which, upon treatment with one equivalent of TBDPSCl, gave the 6-*O*-silyl derivative **4,** which was converted to either its acetylated (**5**),[14b,c] benzylated (**6**),[14b,c] or silylated (**7**)[14b] form by standard methods. Glucal **3** was also converted to its 4,6-*O*-benzylidene derivative **8** and acetylated to give **9**.[14d,e]

In a first attempt at direct oxidative iodination/acetylation (Scheme 3), we treated tri-*O*-acetyl-D-glucal (**1**) and tri-*O*-benzyl-D-glucal (**2**) with NH_4I and 50% aqueous H_2O_2 in acetic acid, using conditions reported to achieve easy iodination of phenol[15,16] and also analogous to those reported by Barluenga et al.[1] The desired 2-iodoacetates were indeed formed but were accompanied by significant amounts of the corresponding iodohydrins. However, addition of acetic anhydride to the reaction mixture ensured clean and selective conversion to the iodoacetates **10a**,**b** or **11a**,**b**, while the further modification of introducing acetonitrile as solvent with concomitant reduction of the amounts of Ac_2O and AcOH allowed for lowering of the reaction temperature without the solution freezing. The latter modification followed observations that low temperatures favored high stereoselectivities. Further optimizations established that little more than one equivalent each of the iodide and the oxidant H_2O_2 was sufficient to realize full conversion of substrates in most instances, thus demonstrating excellent atom economies in this reaction.

A full summary of the transformations of the glycals is presented in Scheme 4 and Table 1. These results show the effective conversion of a range of protected glucals (**1**, **2**, **5**, **6**, **7**, and **9)** and a benzylated galactal (**19**)[14a] to the corresponding 2-deoxy-2-iodoglycosylacetates. In all cases complete conversion of the starting glycal was achieved, and products were identified by ^1H and ^{13}C NMR spectroscopy after chromatographic separation.

In reactions of protected glucals, only the 1,2-*trans* addition products were detected, and in accordance with previous findings[2] the α-manno products predominated except in the case of the per-*O*-silylated derivatives **14** (Table 1, entry 5).[2] Interestingly, the highest selectivity toward the α-manno product was observed when the bulky silyl group was present only on O-6 (substrates **5** and **6**), while protection as a conformationally constrained 4,6-*O*-benylidene acetal (**9**) led to loss of selectivity, although the *manno*-product still predominated and 1,2-*trans* addition took place exclusively. The product distribution in the reaction of benzylated galactal **19** was similar to previously reported results, with a 3:1 ratio of the *talo*- to *galacto*-isomers. The α-*talose* **20a** was the major product, representing concerted β-face addition of the iodonium species and α-attack by the nucleophile, while the mixture of *galacto*-isomers formed as minor products attested to a different mechanism involving approach of the electrophile from the α-face and an oxocarbenium ion intermediate.



	R1	R2
1	Ac	Ac
2	Bn	Bn
5	TBDPS	Ac
6	TBDPS	Bn
7	TBDPS	TBDPS

	R1	R2	X
10a,b	Ac	Ac	I
11a,b	Bn	Bn	I
12a,b	TBDPS	Ac	I
13a,b	TBDPS	Bn	I
14a,b	TBDPS	TBDPS	I
15a,b	TBDPS	Bn	Br
16a,b	Ac	Ac	Br

Scheme 4: (i) NH_4I, H_2O_2, Ac_2O, AcOH/CH_3CN (1:1), 0°C → rt, <2 h; (ii) NH_4I, H_2O_2, Ac_2O, AcOH/CH_3CN (1:1), 60°C, 15 h; (iii) 50% aq NaOH, *t*-BuOH, *n*-Bu_4NHSO_4 in benzene, 50°C; then BnCl in benzene over 4.5 h, 54%.

The reaction conditions were notably tolerant of a range of protecting groups, including the acid-sensitive benzylidene acetal (reaction (b) in Scheme 4). The selectivities and yields in this mild procedure compared very favorably with reported methods, with those obtained with benzyl or silyl protecting groups being the best yet reported. Interestingly, formation of silylated 2-iodo derivatives **14a**,**b** using NIS in AcOH required heating at 100ºC for 10 min,[11] whereas in the protocol described here the reaction proceeded at room temperature within 2 h. In general, we observed that selectivities were dependent on temperature, with lower temperatures favoring *α-manno* selectivity, although cooling below 0ºC led to unacceptably slow reactions.

The possibility of using this methodology for bromoacetoxylation reactions was demonstrated by replacement of NH_4I with NH_4Br in reactions of acetylated and benzylated glucals **1** and **6** (Scheme 4 and entries 6 and 7 in Table 1), with the bromoacetoxylation being less stereoselective as expected from earlier findings. NaI was also evaluated as an iodide source instead of NH_4I in the

Table 1: Yields and selectivities in the iodoacetoxylation of protected glucals (see Scheme 3).

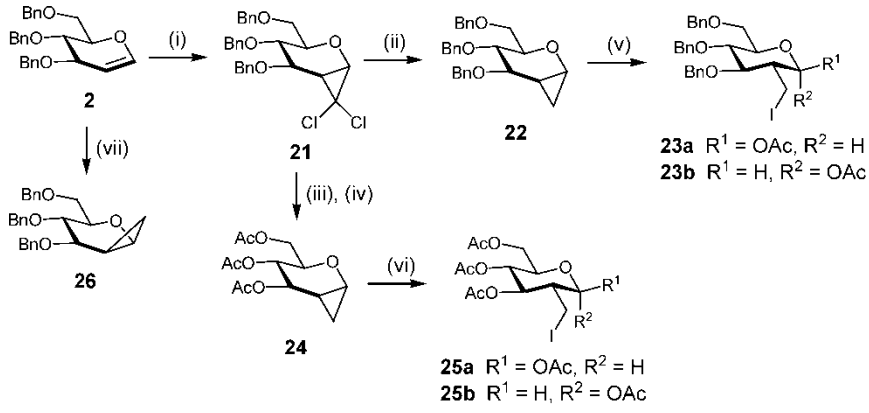
Entry	Substrate	Products	Yield (%)	Ratio[a]
1	**1**	**10a**, **10b**	85	83:17
2	**2**	**11a**, **11b**	100	91:9
3	**5**	**12a**, **12b**	100	93:7
4	**6**	**13a**, **13b**	95	93:7
5	**7**	**14a**, **14b**	94	17:83
6	**6**	**15a**, **15b**	70	25:75
7	**1**	**16a**, **16b**	82	60:40
8	**9**	**17a**, **17b**	88	66:34
9	**19**	**20a**, **20b**, **20c**	96	75:5:20
10	**22**	**23a**, **23b**	100	60:40
11	**24**	**25a**, **25b**	96	66:34
12	**27**	**28**	90	—
13	**29**	**30**	67	—

[a]Determined from ^{1}H NMR of the reaction products before separation.

conversion of acetylated glucal **1** to **10a**,**b**. In this instance, an improved stereoselectivity of 7:1 in favor of **10a** was observed but the yield (64% overall) was inferior and the ^{1}H NMR spectrum of the reaction products provided evidence for inseparable, hitherto unidentified products.

The final set of substrates examined for reactivity under these iodoacetoxylation conditions were the protected α-1,2-cyclopropanated sugars **22** and **24** and their β-counterpart **26**. Benzylated derivative **22** was prepared from benzylated glucal **2** using the dichlorocarbene methodology described by Nagarajan.[17] The preparation of acetylated derivative **24** from acetylated D-glucal has been reported, but yields are low and limited spectroscopic data provided for the product.[18] We found that a more efficient preparation of this compound was achieved by subjecting benzyl-protected dichlorocyclopropanated derivative **21** to Ca/NH_3 reduction followed by immediate acetylation.[19] The structure of **24** was then fully verified by ^{1}H and ^{13}C NMR experiments. The β-cyclopropanated sugar **26** was prepared by Simmons-Smith cyclopropanation of benzylated glucal **2**.[20]

The NIS- and NBS-mediated openings of these and related cyclopropanes in the presence of simple alcohols have been reported,[17,21] but the direct preparation of the corresponding glycosyl acetates has not. The α-cyclopropanated derivatives were accordingly treated under the standard conditions described above (Sch. 5) to produce, respectively, the novel 2-*C*-iodomethyl glycosyl acetates **23a**,**b** and **25a**,**b** in excellent yields. The structures of these products were established with the help of NMR spectroscopy. The anomeric protons of **23a**,**b** resonated as doublets in the appropriate downfield region at δ_H 6.36 and 5.59 with the coupling constants of 3.6 Hz and 8.4 Hz, respectively, suggesting the former is the α-anomer and the latter the β-anomer. Further



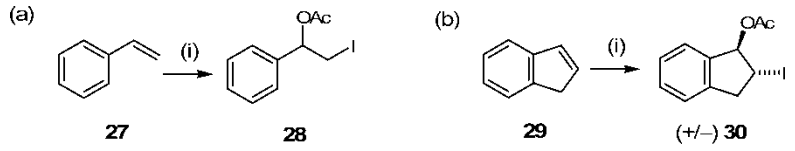
Scheme 5: (i) 50% aq NaOH, $CHCl_3$, $Bn(Et)_3NCl$, 35°C, 4 h, 73%; (ii) LAH in THF, 8 days, 75%; (iii) a. Ca, liq. NH_3, 10 min; (iv) Ac_2O, pyridine, rt, 15 h, 60% (over two steps); (v) NH_4I, H_2O_2, Ac_2O, AcOH/CH_3CN (1:1), 0°C → rt, <1 h, 100% (**23a** : **23b** = 3 : 2); (vi) NH_4I, H_2O_2, Ac_2O, AcOH/CH_3CN (1:1), 60°C, 15 h, 95% (**25a** : **25b** = 7:3); (vii) Zn, $CuCl_2$, CH_2I_2, AcCl in ether, 40°C, 2 h, 95%.

crucial ^1H NMR evidence for opening of the cyclopropyl ring concerned the signals for H-7_a and H-7_b. They appeared as doublets of doublets in the region between δ_H 2.60 and 3.80, which was considerably further downfield than the multiplet for the C-7 protons at δ_H 0.70 in the spectrum of the parent cyclopropanated compound **22**. The NMR spectrum of **25a**,**b** showed a similar pattern of signals. In addition, a DEPT spectrum of iodoacetates **23a**,**b** and **25a**,**b** confirmed that the iodinated C-7 was a methylene and not a methine carbon, indicating that ring opening had taken place as opposed to ring expansion.

These results therefore represent a simple entry to variously protected glycosyl donors, which incorporate a synthetically useful iodomethyl substituent at the 2-position. The β-cyclopropanated derivative **26** did not, however, react under these conditions, a result that is consistent with previous observations of its sluggish reactivity toward electrophilic opening due to steric hindrance.[17]

The broader generality of the iodoacetoxylation reaction was briefly explored by successfully converting styrene (**27**) and indene (**29**) to their corresponding iodoacetates **28** and **30** (Sch. 6). However, attempts to form 1,2-iodoacetates from the less reactive olefins such as those in cholesterol and cholest-5-ene were not successful, with no evidence for reaction under the standard iodoacetoxylation conditions used for the glycals.

Concerning the proposed mechanism and stereoselectivity of the reactions, we consider firstly the generation of the active reagents. While it is presumed that hypoiodous acid HOI is present, the observation of a brown/yellow color in the reaction solutions upon addition of H_2O_2 to the other reactants suggests the presence of molecular I_2, formed either by reaction of I^- with H_2O_2 under acidic conditions[22–25] or by reaction of I^- with peracetic acid, generated upon



Scheme 6: (i) NH_4I, H_2O_2, Ac_2O/AcOH, CH_3CN (solvent), 0°C → rt, <1 h.

addition of H_2O_2 to acetic anhydride in the presence of acetic acid.[26] The reaction then presumably proceeds by addition of I^+ to the olefin, or by rapid formation of a π-complex between the olefin and I_2 followed by a rate-determining abstraction of I^- by the peracetic acid.[26] The high degree of stereoselectivity in solvolysis of the resulting iodonium species and the fact that in the absence of acetic anhydride the iodoacetates predominate over iodohydrins suggest that acetic acid attacks the iodonium species directly, probably in a concerted process. The presence of an excess of acetic anhydride ensures that the concentration of water in the reaction mixture is minimized, allowing for successful addition of the acetate or acetic acid to the cyclic iodonium species.

The stereoselectivities observed are generally in agreement with reported studies on addition of electrophilic halogen species to the glycals. The stereochemistry of addition of electrophiles to glycals has been extensively investigated. The face selectivity is dependent inter alia on the nature and steric demand of the electrophile, the substitution patterns in the glycal as well as the electron-withdrawing or electron-donating character of substituents, stereoelectronic effects, and solvent and other reaction parameters. Our iodoacetylation results are in agreement with the widely observed phenomenon of β-face selectivity of iodonium species to glucal derivatives and concerted additions of electrophile and nucleophile. Figure 1 illustrates the conformational possibilities for the glycals: with the exception of the silylated derivative **7** (R = TBDPS), the $^4H_5$ half-chair conformation **I** is expected to predominate for the glucals, and while β-face addition of iodonium species is unexpected on steric grounds alone, it would be stereoelectronically favored in that a chair-like transition state would ensue. This, together with the fact that α-attack of the nucleophile is favored due to the stereoelectronic α-anomeric effect, accounts for the dominance of α-*manno* products. In the

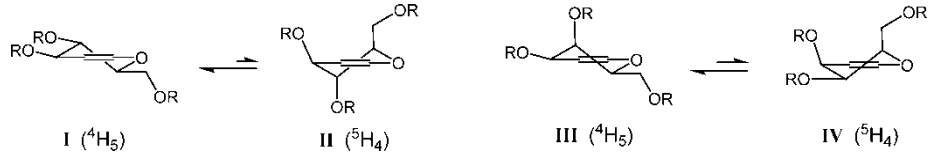


Figure 1: Conformational preferences of glycals.

case of **7** (R = TBDPS), the $^5H_4$ half-chair conformation is thought to predominate to alleviate steric interactions of the substituents, with consequent lowering of selectivity of the addition. In galactal derivatives the energy differences between conformation **III** and **IV** may not be as large, but the pseudo-axial substituent at C-4 in **III** will provide steric hindrance to the β-face addition. This is reflected in the resulting 3:1 ratio of *talo*- to *galacto*-isomers resulting from benzylated galactal **19** compared to the 91:9 ratio of *manno*- to *gluco*-isomers resulting from benzylated glucal **2**. Reactions involving bromine electrophiles are known to proceed via a different mechanism, with oxocarbenium ion intermediates favored over cyclic bromonium ion intermediates. In our case the observation of exclusive 1,2-*trans* addition products seems to suggest a concerted addition of electrophile and nucleophile, rather than the existence of a long-lived oxocarbenium intermediate. This would almost certainly have given rise to α-*gluco* products due to the anomeric effect, but these were not observed. It seems therefore that the highly polar reaction conditions favor the concerted pathway.

In summary, we have shown that the simple, cost-effective, and environmentally benign combination of NH_4I (or NH_4Br), 50% aq. H_2O_2, and Ac_2O/AcOH in CH_3CN at low temperatures achieves efficient and highly stereoselective haloacetoxylation of protected glycals and α-1,2-cyclopropanated sugars.

EXPERIMENTAL

Solvents were dried according to standard methods and freshly distilled. Commercial reagents were used without further purification. Reactions were monitored by thin layer chromatography (TLC) on aluminum-backed Merck silica gel 60 F_{254} plates using an ascending technique. The plates were visualized by spraying with ceric ammonium sulphate in 8 M sulphuric acid or a 1:1 solution of 5% *p*-anisaldehyde in ethanol and 10% sulphuric acid in ethanol baking at 150°C. Gravity column chromatography was done on Merck silica gel 60 (70–230 mesh). Melting points were determined using a Reichert-Jung Thermovar hot-stage microscope and are uncorrected. Optical rotations were determined on a Perkin-Elmer 141 polarimeter in chloroform solutions unless otherwise stated. The concentration *c* refers to g/100 mL. Infrared spectra were recorded using a Perkin-Elmer Spectrum One FT-IR spectrometer. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded, unless otherwise specified, as deuteriochloroform solutions using tetramethylsilane as an internal standard on a Varian Mercury 300 MHz or a Varian Unity 400 MHz spectrometer. Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded on the same instruments at 75 or 100 MHz using tetramethylsilane as an internal standard. Chemical shifts are reported in ppm. Elemental (C, H, N) analyses were carried out using a

Thermo Flash 1112 Series analyzer. Low-resolution FAB mass spectra were recorded on a VG70 SEQ micromass spectrometer.

General Iodoacetoxylation Procedure

To a solution of a glycal (0.37 mmol) or 1,2-cyclopropanated sugar in AcOH/CH_3CN (1:1, 2 mL) was added NH_4I (0.44 mmol) and Ac_2O (0.5 μL) and the resulting reaction mixture was allowed to cool to 0°C. Fifty percent aq H_2O_2 (0.44 mmol) was added and the solution was stirred at 0°C (or at 60°C if necessary) until TLC showed the reaction to be complete. A solution of sodium thiosulphate (0.1 M) was then added until the brownish color disappeared, and the solution was cooled in an ice-water bath before adding 10% aq NaOH until the solution became slightly basic. The resultant mixture was extracted with ethyl acetate, and the combined organic phases were washed successively with water, 10% sodium thiosulfate, and brine; dried over $MgSO_4$; and concentrated. The diastereoisomers were separated by column chromatography on silica gel using a mixture of ethyl acetate and petroleum ether as eluent.

The following compounds were prepared using the foregoing iodoacetoxylation procedure:

From tri-*O*-acetyl-D-glucal (**1**): 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-iodo-α-D-mannopyranose (**10a**)[7,22] (71%) and 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-iodo-β-D-glucopyranose (**10b**)[7,22] (14%).

From tri-*O*-benzyl-D-glucal (**2**): 1-*O*-acetyl-3,4,6-tri-*O*-benzyl-2-deoxy-2-iodo-α-D-mannopyranose (**11a**)[1] (91%) and 1-*O*-acetyl-3,4,6-tri-*O*-benzyl-2-deoxy-2-iodo-β-D-glucopyranose (**11b**),[1] colorless crystals, m.p. 90–95°C (lit.[1] reported as oil) (1%).

From 6-*O*-*tert*-butyldiphenylsilyl-3,4-di-*O*-acetyl-D-glucal (**5**): 1,3,4-tri-*O*-acetyl-2-deoxy-2-iodo-6-*O*-*tert*-butyldiphenylsilyl-α-D-mannopyranose (**12a**) (93%), colorless crystals, m.p. 153–155°C; $[\alpha]_D = +31.9$ (*c* 1.0, $CHCl_3$); δ_H ($CDCl_3$, 300 MHz): 7.77–7.34 (m, 10H, 2 × Ph), 6.45 (d, 1H, $J = 1.5$ Hz, H-1), 5.63 (t, 1H, $J = 9.6$ Hz, H-4), 4.60 (dd, 1H, $J = 4.2$ and 9.6 Hz, H-3), 4.52 (dd, 1H, $J = 1.5$ and 4.2 Hz, H-2), 3.98–3.92 (m, 1H, H-5), 3.72 (d, 2H, $J = 2.7$ Hz, H-6_a and H-6_b), 2.12, 2.09, 1.93 (3s, 9H, 3 × CH_3CO_2), 1.08 (s, 9H, Me_3C-Si); δ_C ($CDCl_3$, 100 MHz): 170.0, 169.0, 168.2 (3 × CH_3CO_2), 135.8, 135.7, 133.2, 133.1, 129.7, 129.6, 127.6 (2 × Ph), 95.0 (C-1), 74.0 (C-5), 69.2 (C-3), 67.1 (C-4), 62.0 (C-6), 27.3 (C-2), 26.7 (Me_3C-Si), 20.9, 20.8, 20.5 (3 × CH_3CO_2), 19.2 (Me_3C-Si). IR ($CHCl_3$): 1751 cm^{-1}. Anal. calcd for $C_{28}H_{35}IO_8Si$: C, 51.38; H, 5.39. Found: C, 51.42; H, 5.31. LRFAB MS calcd for $C_{28}H_{35}IO_8Si$ $[M\text{-}OOAc]^+$ 595.6, found 594.8; and 1,3,4-tri-*O*-acetyl-2-deoxy-2-iodo-6-O-*tert*-butyldiphenylsilyl-β-D-glucopyranose (**12b**), (7%), white crystals, m.p. 149–156°C; $[\alpha]_D = +44.0$ (*c* 1.0,

$CHCl_3$); δ_H ($CDCl_3$, 300 MHz): 7.67–7.33 (m, 10H, 2 × Ph), 5.87 (d, 1 H, $J = 9.3$ Hz, H-1), 5.30 (dd, 1H, $J = 9.3$ and 11.2 Hz, H-4), 5.12 (t, 1H, $J = 9.3$ Hz, H-3), 3.98 (dd, 1H, $J = 9.3$ and 11.0 Hz, H-2), 3.80–3.65 (m, 3H, H-5, H-6_a and H-6_b), 2.18, 2.09, 1.89 (3s, 9H, CH_3CO_2), 1.04 (s, 9H, Me_3C-Si); δ_C ($CDCl_3$, 100 MHz): 169.6, 169.3, 168.4 (3 × CH_3CO_2), 135.7, 135.6, 133.1, 129.7, 129.7, 127.7, 127.6, 127.5 (2 × Ph), 94.0 (C-1), 75.7, 75.4, 68.8, 62.2 (C-3, C-4, C-5 and C-6), 29.7 (C-2), 26.7 (Me_3C-Si), 20.7, 20.6, 20.5 (3 × CH_3CO_2), 19.2 (Me_3C-Si); IR ($CHCl_3$): 1759 cm^{-1}. Anal. calcd for $C_{28}H_{35}IO_8Si$: C, 51.38; H, 5.39. Found: C, 51.50; H, 5.55. LRFAB MS calcd for $C_{28}H_{35}IO_8Si$ $[M-7H]^+$ 647.6, found 647.2.

From 6-*O*-*tert*-butyldiphenylsilyl-3,4-di-*O*-benzyl-D-glucal (**6**): 1-*O*-Acetyl-3, 4-di-*O*-benzyl-2-deoxy-2-iodo-6-*O*-*tert*-butyldiphenylsilyl-α-D-mannopyranose (**13a**), (88%), colorless oil, $[\alpha]_D = +55.2$ (*c* 1.0, $CHCl_3$); δ_H ($CDCl_3$, 400 MHz): 7.77–7.18 (m, 20H, 4 × Ph), 6.45 (d, 1H, $J = 1.6$ Hz, H-1), 4.97 (d, 1H, $J = 10.4$ Hz, CH_2Ph), 4.74 (d, 1H, $J = 11.6$ Hz, CH_2Ph), 4.65 (d, 1H, $J = 10.4$ Hz, CH_2Ph), 4.57 (d, 1H, $J = 11.6$ Hz, CH_2Ph), 4.48 (dd, 1H, $J = 1.6$ and 4.4 Hz, H-2), 4.26 (t, 1H, $J = 9.4$ Hz, H-4), 3.40 (dd, 1H, $J = 3.2$ and 11.6 Hz, H-6_a), 3.88–3.82 (m, 2H, H-5 and H-6_b), 3.25 (m, 1H, H-3), 2.01 (s, 3H, CH_3CO_2), 1.11 (s, 9H, Me_3C-Si); δ_C ($CDCl_3$, 100 MHz): 168.5 (CH_3CO_2), 135.9, 135.7, 129.6, 129.6, 128.5, 128.4, 128.1, 128.0, 127.9, 127.7, 127.6, 127.5 (4 × Ph), 95.8 (C-1), 75.6, 75.5, 75.4, 75.1, 71.2 (C-3, C-4, C-5, and 2 × CH_2Ph), 62.2 (C-6), 31.2 (C-2), 26.9 (Me_3C-Si), 20.8 (CH_3CO_2), 19.3 (Me_3C-Si). IR ($CHCl_3$): 1750 cm^{-1}. Anal. calcd for $C_{38}H_{43}IO_6Si$: C, 60.80; H, 5.77. Found: C, 61.14; H, 5.94. LRFAB MS calcd for $C_{38}H_{43}IO_6Si$ $[M-2H]^+$ 748.7, found 747.9; and 1-*O*-acetyl-3,4-di-*O*-benzyl-2-deoxy-2-iodo-6-*O*-*tert*-butyldiphenylsilyl-β-D-glucopyranose (**13b**), (7%), colorless oil, $[\alpha]_D = +25.3$ (*c* 1.0, $CHCl_3$); δ_H ($CDCl_3$, 400 MHz): 7.70–7.21 (m, 20H, 4 × Ph), 5.84 (d, 1H, $J = 9.6$ Hz, H-1), 4.98 (d, 1H, $J = 10.4$ Hz, CH_2Ph), 4.91 (d, 1H, $J = 4.2$ Hz, CH_2Ph), 4.89 (d, 1H, $J = 4.2$ Hz, CH_2Ph), 4.77 (d, 1H, $J = 10.4$ Hz, CH_2Ph), 4.00 (dd, 1H, $J = 9.6$ and 10.4 Hz, H-2), 3.95 (m, 2H, H-6_a and H-6_b), 3.87 (t, 1H, $J = 9.0$ Hz, H-4), 3.78 (dd, 1H, $J = 9.0$ and 10.4 Hz, H-3), 3.53–3.49 (m, 1H, H-5), 2.19 (s, 3H, CH_3CO_2), 1.05 (s, 9H, Me_3C-Si); δ_C ($CDCl_3$, 100 MHz): 168.8 (CH_3CO_2), 135.9, 135.5, 129.6, 126.5, 128.5, 128.4, 128.2, 128.0, 127.9, 127.7, 127.6, 127.5 (4 × Ph), 94.4 (C-1), 85.4 (C-3), 78.9 (C-4), 76.6 (C-5), 75.8, 75.1 (2 × CH_2Ph), 62.0 (C-6), 30.5 (C-2), 26.8 (Me_3C-Si), 20.7 (CH_3CO_2), 19.3 (Me_3C-Si). IR ($CHCl_3$): 1760 cm^{-1}. Anal. calcd for $C_{38}H_{43}IO_6Si$: C, 60.80; H, 5.77. Found: C, 61.18; H, 5.75. LRFAB MS calcd for $C_{38}H_{43}IO_6Si$ $[M-H]^+$ 750.7, found 749.0.

From 3,4,6-tri-*O*-*tert*-butyldiphenylsilyl-D-glucal (**7**): 1-*O*-Acetyl-2-deoxy-2-iodo-3,4,6-tri-*O*-tert-butyldiphenylsilyl-α,β-D-glucopyranose (**14a**, **14b**)[11] (94%,

α:β = 17:83); pure crystalline **14b** was obtained after separation of the mixture on a column of silica gel; m.p. 153°C (not reported in literature).

From 3-*O*-acetyl-4,6-*O*-benzylidene-D-glucal (**9**): 1,3-di-*O*-acetyl-4,6-*O*-benzylidene-2-deoxy-2-iodo-α-D-manno and -β-D-glucopyranoses (**17a** and **17b**) (86%, *α-manno*:*β-gluco* = 56:44); δ_H ($CDCl_3$, 300 MHz): 7.49–7.34 (m, 5H, Ph), 6.40 (d, 0.56H, J = 1.0 Hz, H-1 of **17a**), 5.98 (d, 0.44H, J = 9.3 Hz, H-1 of **17b**), 5.61 (s, 0.56H, H-7 of **17a**), 5.53–5.47 (m, 0.88H, H-3 and H-7 of **17b**), 4.69 (dd, 0.56H, J = 1.3 and 4.4 Hz, H-2 of **17a**), 4.51 (dd, 0.56H, J = 4.6 and 9.7 Hz, H-3 of **17a**), 4.38–3.56 (m, 4.44H), 2.17, 2.16, 2.14 (3s, 6H, CH_3CO_2); δ_C ($CDCl_3$, 75 MHz): 169.9, 169.1, 168.3 (CH_3CO_2), 136.8, 136.6, 130.8, 129.2, 129.2, 128.8, 128.3, 128.2, 126.2, 126.1 (Ph), 102.1 (C-7 of **17a**), 101.6 (C-7 of **17b**), 95.7 (C-1 of **17a**), 94.4 (C-1 of **17b**), 79.4, 76.6, 73.7, 68.4, 68.2, 67.6, 67.5, 66.8, 30.4, 29.2, 21.1, 20.9, 20.8, 20.6. Anal. calcd for $C_{17}H_{19}IO_7$: C, 44.17; H, 4.14. Found: C, 44.77; H, 3.98. LRFAB MS calcd for $C_{17}H_{19}IO_7$ $[M-2H]^+$ 460.2, found 460.0.

From tri-*O*-benzyl-D-galactal (**19**): 1-*O*-acetyl-3,4,6-tri-*O*-benzyl-2-deoxy-2-iodo-α-D-talopyranose (**20a**) and 1-O-acetyl-3,4,6-tri-*O*-benzyl-2-deoxy-2-iodo-α,β-D-galactopyranoses (**20b**, **20c**),[3,27] (96%, *α-talo*:*β-galacto*:*α-galacto* = 15:1:4, colorless oil).

From 3,4,6-tri-*O*-benzyl-1,5-anhydro-2-deoxy-1,2-*C*-methylene-D-glycero-D-gulo-hexitol (**22**): 1-*O*-acetyl-3,4,6-tri-*O*-benzyl-2-deoxy-2-*C*-iodomethyl-α- and -β-D-glucopyranoses (**23a**, **23b**) (inseparable, colorless oil, 100%, α:β = 2:3); δ_H ($CDCl_3$, 400 MHz): 7.35–7.16 (m, 15H, 3 × Ph), 6.36 (d, 0.44H, J = 3.6 Hz, H-1 of **23a**), 5.59 (d, 0.56H, J = 8.4 Hz, H-1 of **23b**), 4.99 (d, 0.56H, J = 10.8 Hz), 4.95 (d, 0.44H, J = 11.2 Hz), 4.84–4.58 (m, 4H), 4.50 (dd, 1H, J = 4.4 and 12.0 Hz), 3.89–3.65 (m, 4.4H), 3.60 (ddd, 0.56H, J = 2.0, 3.2 and 9.6 Hz), 3.54 (dd, 0.56H, J = 3.0 and 10.2 Hz), 3.46 (dd, 0.44H, J = 3.6 and 10.0 Hz), 3.28 (dd, 0.56H, J = 3.0 and 10.2 Hz), 2.85 (dd, 0.44H, J = 10.2 and 11.0 Hz), 2.24 (tt, 0.44H, J = 3.4 and 10.8 Hz, H-2 of **23a**), 2.14 (s, 1.68H, CH_3CO_2 of **23b**), 2.10 (s, 1.32H, CH_3CO_2 of **23a**), 1.56–1.50 (m, 0.56H, H-2 of **23b**); δ_C ($CDCl_3$, 100 MHz): 168.8 (CH_3CO_2), 168.7 (CH_3CO_2), 138.1, 137.8, 128.4, 128.3, 128.2, 127.9, 127.8, 127.7, 127.6 (Ph), 94.9 (C-1 of **23b**), 93.6 (C-1 of **23a**), 81.3, 80.7, 78.8, 78.4, 75.5, 75.4, 74.8, 74.6, 73.6, 73.5, 73.3, 68.1, 46.6 (C-2 of **23a**), 45.0 (C-2 of **23b**), 20.8 (CH_3CO_2 of **23b**), 20.7 (CH_3CO_2 of **23a**), 4.1 (C-7 of **23a**), 0.6 (C-7 of **23b**). IR ($CHCl_3$): 1759 cm^{-1}. Anal. calcd for $C_{30}H_{33}IO_6$: C, 58.45; H, 5.40. Found: C, 57.99; H, 5.28. LRFAB MS calcd for $C_{30}H_{33}IO_6$ $[M-3H]^+$ 613.5, found 612.9.

From styrene (**27**): 1-acetoxy-2-iodo-1-phenylethane (**28**)[28] (67%).

From indene (**29**): *trans*-1-acetoxy-2-iodo-indane (**30**)[10] (90%).

3,4,6-Tri-*O*-acetyl-1,5-anhydro-2-deoxy-1,2-*C*-methylene-D-glycero-D-gulo-hexitol (**24**): a solution of **21** (300 mg, 0.60 mmol) in dry THF (1 mL) was added dropwise to a stirred solution of calcium metal (60 mg, 1.50 mmol) in predried liquid ammonia (~10 mL) at −78°C and the reaction mixture was stirred under reflux for 10 min. The blue color was discharged by careful addition of ammonium chloride and the ammonia was allowed to evaporate at rt. The solid residue was then dispersed in pyridine (10 mL) and treated with acetic anhydride (5 mL) and a catalytic amount of DMAP. After stirring overnight at rt, the reaction was quenched by addition of water and the aqueous phase was extracted several times with ethyl acetate. The combined organic phases were then washed with 1N aq HCl solution, followed by water, and then dried over $MgSO_4$. After filtration, the solvent was evaporated in vacuo and the residue purified by column chromatography on silica gel (ethyl acetate/petroleum ether, 1:9) to give the title compound **24** (103 mg, 60%) as a low viscous oil; $[\alpha]_D = +26.6$ (*c* 1.0, $CHCl_3$); δ_H ($CDCl_3$, 300 MHz): 4.95 (dd, 1H, $J = 3.0$ and 6.3 Hz, H-3), 4.83 (dd, 1H, $J = 4.5$ and 6.3 Hz, H-4), 4.51 (dd, 1H, $J = 7.5$ and 12.0 Hz, H-6_a), 4.14 (dd, 1H, $J = 4.1$ and 12.0 Hz, H-6_b), 3.88–3.83 (m, 1H, H-5), 3.62 (dt, 1H, $J = 3.0$ and 6.0 Hz, H-1), 2.09, 2.08, 2.04 (3s, 9H, 3 × CH_3CO_2), 1.02–0.93 (m, 1H, H-2), 0.86 (tdd, 2H, $J = 4.6$, 10.1, and 12.3 Hz, H-7_a and H-7_b); δ_C ($CDCl_3$, 75 MHz): 170.6, 169.8, 169.7 (3 × CH_3CO_2), 73.7 (C-5), 70.2 (C-3), 69.6 (C-4), 62.4 (C-6), 48.8 (C-1), 21.0, 20.8, 20.7 (3 × CH_3CO_2), 13.7 (C-2), 11.1 (C-7). Anal. calcd for $C_{13}H_{18}O_7$: C, 54.54; H, 6.34. Found: C, 54.68; H, 6.21.

From 3,4,6-Tri-*O*-acetyl-1,5-anhydro-2-deoxy-1,2-*C*-methylene-D-glycero-D-gulo-hexitol (**24**): 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-*C*-iodomethyl-α and -β-D-glucopyranoses (**25a** and **25b**) (colorless oil, 96%, $\alpha{:}\beta = 3{:}7$); δ_H ($CDCl_3$, 400 MHz): 6.39 (d, 0.3H, $J = 3.6$ Hz, H-1 of **25a**), 5.65 (d, 0.7H, $J = 8.8$ Hz, H-1 of **25b**), 5.28–5.16 (m, 1H, H-3), 5.12–4.99 (m, 1H, H-4), 4.35–4.24 (m, 1H, H-6_a), 4.11–3.96 (m, 1.3H, H-6_b and H-5 of **25a**), 3.87–3.78 (m, 0.7H, H-5 of **25b**), 3.22 (dd, 0.7H, $J = 3.3$ and 10.9 Hz, H-7_a of **25b**), 3.16–3.07 (m, 1H, H-7_b of **25b** and H-7_a of **25a**), 2.87 (t, 0.3H, $J = 10.6$ Hz, H-7_b of **25a**), 2.40 (tt, 0.3H, $J = 3.6$ and 10.8 Hz, H-2 of **25a**), 2.16, 2.15, 2.07, 2.06, 2.02, 2.01 (6s, 12H, CH_3CO_2), 1.85–1.75 (m, 0.7H, H-2 of **25b**); δ_C ($CDCl_3$, 100 MHz): 170.5, 170.4, 169.8, 169.6, 169.5, 168.4, 168.3, 94.7 (C-1 of **25b**), 92.8 (C-1 of **25a**), 72.8, 72.4, 72.0, 69.8, 69.0, 68.3 (C-3, C-4 and C-5), 61.7 (C-6), 45.4 (C-2 of **25a**), 43.4 (C-2 of **25b**), 20.8, 20.7, 20.6, 20.5 (CH_3CO_2), 0.43 (C-7 of **25b**), −2.0 (C-7 of **25a**). Anal. calcd for $C_{15}H_{21}IO_9$: C, 38.15; H, 4.48. Found: C, 38.55; H, 4.86.

1-*O*-Acetyl-3,4-di-*O*-benzyl-2-bromo-2-deoxy-6-*O*-*tert*-butyldiphenylsilyl-α,β-D-mannopyranose (**15a, 15b**): To a solution of glucal **6** (488 mg, 0.86 mmol) in AcOH/CH_3CN (1:1, 24 mL) was added NH_4Br (102 mg, 1.04 mmol), Ac_2O (0.9 mL), and 50% aq H_2O_2 (60 μL, 1.04 mmol). After stirring at rt for 4 h, the reaction mixture was diluted with 0.1 M sodium thiosulfate

solution, then cooled to 0°C and 10% aq NaOH added until the solution became slightly basic. The resultant mixture was extracted with ethyl acetate and the combined organic phases were washed successively with water and brine, dried over $MgSO_4$, and concentrated to dryness. The product mixture was separated by column chromatography on silica gel (ethyl acetate/petroleum ether, 1:9) to give **15a** and **15b** as colorless oils:

15a (106 mg, 17.5%), $[\alpha]_D = +21.8$ (*c* 1.0, $CHCl_3$); δ_H ($CDCl_3$, 400 MHz): 7.79–7.23 (m, 20H, 4 × Ph), 6.40 (d, 1H, $J = 1.6$ Hz, H-1), 5.00 (d, 1H, $J = 10.8$ Hz, CH_2Ph), 4.79 (d, 1H, $J = 12.0$ Hz, CH_2Ph), 4.68 (t, 2H, $J = 11.4$ Hz, CH_2Ph), 4.38 (dd, 1H, $J = 1.8$ and 3.8 Hz), 4.35 (t, 1H, $J = 9.4$ Hz), 4.05 (dd, 1H, $J = 3.2$ and 11.6 Hz), 3.96 (dd, 1H, $J = 3.8$ and 9.0 Hz), 3.90 (dd, 1H, $J = 1.6$ and 11.2 Hz, H-2), 3.85–3.75 (m, 1H, H-5), 2.04 (s, 3H, CH_3CO_2), 1.13 (s, 9H, Me_3C-Si); δ_C ($CDCl_3$, 100 MHz): 168.3 (CH_3CO_2), 138.2, 137.4, 135.8, 135.5, 133.6, 132.9, 129.5, 128.4, 128.3, 128.0, 127.9, 127.8, 127.6, 127.5 (4 × Ph), 94.2 (C-1), 76.7, 75.4, 75.3, 73.7, 71.3, 62.1 (C-3, C-4, C-5, C-6 and 2 × CH_2Ph), 49.8 (C-2), 26.7 (Me_3C-Si), 20.7 (CH_3CO_2), 19.2 (Me_3C-Si). Anal. calcd for $C_{38}H_{43}BrO_6Si$: C, 64.85; H, 6.16. Found: C, 64.88; H, 6.34. LRFAB MS calcd for $C_{38}H_{43}BrO_6Si$ $[M]^+$ 703.7, found 703.1.

15b (318 mg, 52.5%), $[\alpha]_D = +28.4$ (*c* 1.0, $CHCl_3$); δ_H ($CDCl_3$, 400 MHz): 7.71–7.22 (m, 20H, 4 × Ph), 5.78 (d, 1H, $J = 8.8$ Hz, H-1), 5.01 (d, 2H, $J = 10.4$ Hz, CH_2Ph), 4.93–4.88 (m, 2H, CH_2Ph), 3.96–3.86 (m, 4H), 3.80 (dd, 1H, $J = 8.8$ and 10.0 Hz, H-2), 3.53 (dt, 1H, $J = 2.4$ and 9.6 Hz, H-5), 2.21 (s, 3H, CH_3CO_2), 1.07 (s, 9H, Me_3C-Si); δ_C ($CDCl_3$, 75 MHz): 168.9 (CH_3CO_2), 137.8, 135.9, 135.6, 133.5, 132.9, 129.7, 129.6, 128.5, 127.7, 127.5 (4 × Ph), 93.6 (C-1), 85.1, 78.5, 76.5, 76.3, 75.2 (C-3, C-4, C-5 and 2 × CH_2Ph), 62.1 (C-6), 51.4 (C-2), 26.8 (Me_3C-Si), 20.8 (CH_3CO_2), 19.3 (Me_3C-Si). Anal. calcd for $C_{38}H_{43}BrO_6Si$: C, 64.85; H, 6.16. Found: C, 64.95; H, 6.03. LRFAB MS calcd for $C_{38}H_{43}BrO_6Si$ $[M]^+$ 703.7, found 703.0.

1,3,4,6-Tetra-*O*-acetyl-2-bromo-2-deoxy-α,β-D-mannopyranose (**16a, 16b**): Using the procedure described above for the synthesis of **15a** and **15b**, bromoacetoxylation of acetylated glucal **1** at 60°C afforded, as colorless oils, the separable bromoacetates **16a** (51%) and **16b** (31%).[7,22]

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