

Selective Cleavage of Methoxy Protecting Groups in Carbohydrates

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The selective cleavage of methoxy protecting groups next to hydroxy groups is achieved using a radical hydrogen abstraction reaction as the key step. Under the reaction conditions, the hydroxy group generates an alkoxyl radical that reacts with the sterically accessible adjacent methoxy group, which is transformed into an acetal. In the second step, the acetals are hydrolyzed to give alcohols or diols. A one-pot hydrogen abstraction—hydrolysis procedure was also developed. Good yields were usually achieved, and the mild conditions of this methodology were compatible with different functional groups and sensitive substrates such as carbohydrates.

Introduction

The methoxy protecting group has been frequently used in carbohydrates and many other substrates¹ since it can be readily formed and is stable under a wide range of reaction conditions. On the other hand, its removal often poses problems and requires harsh conditions not compatible with other functional groups. Additionally, when a molecule presents several methoxy protecting groups, the selective removal of one of them is difficult. Both problems are particularly important with highly functionalized substrates which require mild deprotection conditions, such as carbohydrates.

To overcome these difficulties, we devised a methodology to selectively remove methoxy groups next to hydroxy functions (Scheme 1). By transforming the hydroxy group into an alkoxyl radical (as for $1 \rightarrow 1a$),² an intramolecular hydrogen abstraction (IHA) could take place, which would generate acetals such as 2. These acetals would then be hydrolyzed to afford diols 3 and/or alcohols 4.

SCHEME 1. Selective Removal of Methoxy Protecting Groups

The feasibility and scope of this reaction were studied with different furanose and pyranose carbohydrates **5–15** (Figure 1) derived from D-glucose, D-xylose, D-galactose, and L-rhamnose. The results obtained with primary and secondary hydroxy groups were compared, and the effects of the ring size and the stereochemistry of the functional groups were also studied, as described later in this article.

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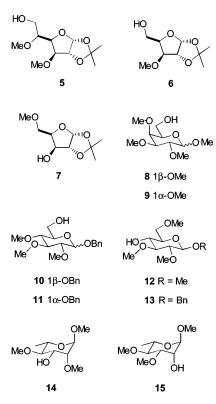


FIGURE 1. Substrates used to study the selective removal of methoxy groups.

SCHEME 2. Synthesis of D-Glucose Derivative 5

Results and Discussion

Synthesis of Precursors for the IHA Reaction. The precursor 5 was obtained from 1,2-O-isopropylidene- α -D-glucofuranose (16).³ Silylation of the primary hydroxy group yielded 17, which was transformed into the dimethoxy derivative 18. The latter was treated with TBAF, affording compound 5 (Scheme 2).⁴

The precursors **6** and **7** were prepared from known 5-O-(tert-butyldimethylsilyl)-1,2-O-isopropylidene- α -D-xylofuranose (**19**)⁵

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SCHEME 4. Synthesis of the D-Galactose Derivatives 8 and 9 $\,$

(Scheme 3). Thus, treatment of **19** with methyl iodide afforded compound **20** and the rearrangement product **21**. The removal of the silyl ether from **20** yielded the IHA precursor **6**.⁶ Similarly, when **21** was treated with TBAF, the alcohol **7**⁷ was obtained in excellent yield.

The methyl galactose derivatives **8** (β -anomer) and **9** (α -anomer) were obtained from D-galactose **22** (Scheme 4), which was treated with TBDPSCl to give the silyl ether **23**. The methylation of the free hydroxy groups afforded product **24**, which was treated with TBAF to yield substrate **8**.⁸ The β -anomer **8** was then transformed into the α -anomer **9**. Thus, acetylation followed by treatment of acetate **25** with trimethylsilyl trifluoromethanesulfonate⁹ gave the α -epimer **26**. Finally, removal of the acetate group afforded the precursor **9**.¹⁰

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SCHEME 5. Synthesis of D-Glucose Derivatives 12 and 13

The glucose derivatives **10** and **11** were obtained from D-glucose according to literature procedures. ¹¹

The synthesis of compound 12 was carried out from commercial D-maltose 27 (Scheme 5), which was permethylated¹² and then hydrolyzed to afford the desired product 12,¹³ together with the pentamethyl-D-glucose derivatives 28 and 29.^{9,14} In a similar way, the 1-O-benzyl maltose derivative 30¹⁵ was transformed into the glucose substrate 13 and products 28 and 29.

The rhamnose substrates **14** and **15** were synthesized from commercial L-rhamnose (Scheme 6), which was transformed as reported in the literature¹⁶ into its 2,3-benzylidene acetal **31**.¹⁷ Reductive cleavage of the benzylidene protecting group¹⁸ and methylation of the crude product mixture afforded the benzyl ethers **32**¹⁹ and **33**. Hydrogenolysis of **32** and **33** generated the rhamnose substrates **14**^{19,20a} and **15**,²⁰ respectively.

Study of the Selective Transformation of Methoxy Groups into Acetals. The transformation was first studied with substrate

SCHEME 6. Synthesis of L-Rhamnose Derivatives 14 and 15

5, which was treated with (diacetoxyiodo)benzene (DIB) and iodine and irradiated with visible light to generate the alkoxyl radical **5a** (Scheme 7). Once formed, the alkoxyl radicals can evolve in different ways, mainly by hydrogen abstraction and β -fragmentation.²¹ In the case of radical **5a**, both reactions took place, but the desired hydrogen abstraction was the major process.²² Thus, the alkoxyl radical abstracted a hydrogen from the methoxy group at C-5, giving a C-radical **5b** from which were formed the acetals **34** and **35**, as well as the formate **36**, in 40% global yield.²³ On the other hand, the β -fragmentation²⁴ afforded a C-radical **5c**, which originated a separable mixture of the diastereomeric acetoxy acetals **37** and **38** (**37/38**, 3.5:1) in 23% yield.

A plausible mechanism for the formation of the hydrogen abstraction products 34-36 is shown in Scheme 8. Thus, the

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SCHEME 7. Hydrogen Abstraction versus Fragmentation with Furanose Substrate 5

SCHEME 8. Mechanism for the Formation of Hydrogen Abstraction Products 34-36

C-radical **5b** reacted with iodine to give the iodoacetal **5d**. Extrusion of the iodo group with formation of an oxycarbenium ion **5e** and intramolecular nucleophilic addition of the hydroxy group would afford the acetal **34**. Then an intermolecular hydrogen abstraction would take place to give a second oxycarbenium ion **34a**, ²⁵ which could be trapped by different nucleophiles, such as the hydroxy group from **5** to give the dimeric product **35**. On the other hand, trapping of the oxycarbenium ion **34a** by water during the workup would generate an orthoformate **34b** from which the formate **36** would be formed.

Similarly, the acetates **37** and **38** resulting from the β -fragmentation were formed by oxidation of the C-radical intermediate **5c** to an oxycarbenium ion, which was trapped by acetate ions from the reagent.²¹

When the xylose precursor **6** (Scheme 9) was treated under similar conditions, the 1,6-hydrogen abstraction was the main process, affording the acetal **39**.

SCHEME 9. Formation of the Acetal 39

In the case of substrate 7 (Scheme 9), if the IHA from the 5-OMe group took place, the previously described acetal **39** would be obtained. However, the β -fragmentation could be an important side reaction or even the main process. In fact, secondary O-radicals give mainly scission when the resulting C-radical is stabilized by oxygen functions.²⁴

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SCHEME 10. IHA—Nucleophilic Addition with Pyranose Substrates^a

^a Intramolecular [a] and Intermolecular [b] Addition of Nucleophiles to the Intermediate Oxycarbenium Ions 8a or 9a

The alkoxyl radical derived from substrate **7** generated a complex mixture of products, from which the acetal **39** could not be isolated. Presumably, the IHA process competed with undesired C_2 – C_3 and C_3 – C_4 fragmentation reactions, which afforded epimerization products²⁶ or unstable scission products.

To explain the differences in the reactivity of substrates **6** and **7**, MM calculations were carried out.²⁷ In the case of substrate **6**, several of the low-energy conformations presented a C_5 – $O\cdots H$ – CH_2O – C_3 distance of 2.6–2.8 Å, which was suitable for H-abstraction.^{22,24j} Therefore, this process took place, generating the acetal **39**. However, in the case of substrate **7**, the 5-OMe group was oriented away from the furanose ring and from the 3-OH group (a C_3 – $O\cdots H$ – CH_2O – C_5 distance of 4.1–4.6 Å was obtained for the lowest-energy conformations). Since in this case the IHA was not favored, the fragmentation predominated.

The transformation of methoxy groups into acetals was then studied with pyranose substrates **8**–**15**. The substrate **8** (Scheme 10), on treatment with DIB and iodine, afforded the methylenedioxy acetal **40** as the major product, and the *O*-methyl acetate **41** as the minor one, in 81% overall yield. The other galactose anomer **9** also gave good yields (82%) of the 1,6-IHA products **42** and **43**.

Products **40** and **41** were formed from the same intermediate, the oxycarbenium ion **8a** $(1\beta\text{-OMe})^{28}$ which was trapped intraor intermolecularly by nucleophiles, such as hydroxy groups (route a) or acetate ions from the reagent (route b). In a similar

SCHEME 11. IHA-Nucleophilic Addition with Glucose Substrates 10-13

way, products 42 and 43 were generated from the oxycarbenium ion 9a (1 α -OMe).

The 1β -benzylglucose substrate 10 (Scheme 11), under the usual IHA conditions, afforded a cyclic acetal 44 as the sole isolated product, in 51% yield. The 1α -benzyl epimer 11 gave the cyclic acetal 45 in 66% yield.

While substrates **10** and **11** presented primary hydroxy groups, the glucose substrate **12** (Scheme 11) possessed a secondary hydroxy group. Depending on whether IHA is favored or not, the scission of the resulting secondary alkoxy radicals is a side reaction or the main process. MM calculations were carried out to determine whether 1,6-IHA was favored in our case. The calculations showed that the 6-OMe group was oriented away from the pyranose ring (a $C_4-O\cdots H-CH_2O-C_6$ distance of 4.2–4.7 Å was obtained for the lowest-energy conformations), and therefore no hydrogen abstraction from this position would take place. However, the distance between the oxygen at C-4 and the 3-OMe hydrogens was 2.5–2.9 Å, suitable for H-abstraction, and thus this process was expected to predominate.

To our satisfaction, the IHA from the 3-OMe group was the main reaction, and the O-methyl acetate **46** was obtained in 54% yield, although the expected methylenedioxy acetal **47** could not be isolated. Presuming that it was a volatile product, the protecting group transformation was repeated with the 1β -O-benzyl analogue **13**, yielding the O-methyl acetate **48** as the major product (52%) and the cyclic acetal **49** as the minor product (17%).

The rhamnose substrate **14** (Scheme 12) also presented a secondary hydroxy group. The MM calculations showed that several conformations of similar energy could coexist at room temperature (26 °C). For some conformations, IHA from the

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SCHEME 12. IHA-Nucleophilic Addition with Rhamnose Substrates 14 and 15

2-OMe group was favored, while for other conformations, the IHA from the 4-OMe group was preferred, and thus several functionalization products were possible (for instance, 2- or 4-O-methyl acetates, 2,4-di-O-methyl acetates, 3,4-dioxolanes, 2,3-dioxolanes, etc.). The fragmentation of the secondary alkoxyl radical could also take place. In fact, when the reaction was carried out, a complex mixture of products was obtained, and no pure products could be isolated therefrom.

However, when the IHA was carried out with the other rhamnose substrate 15 (Scheme 12), an excellent result was obtained. Previous calculations showed that the distance C_2 – $O\cdots$ H– CH_2O – C_3 (2.4–2.9 Å for some of the low-energy conformations) was suitable for hydrogen abstraction. As expected, the reaction only afforded products from 3-OMe functionalization; the major product was the O-methyl acetate 50 (80%), and the minor product was the methylenedioxy acetal 51 (10%) (90% overall yield).²⁹ As can be seen from the previous examples, the MM calculations help to predict the possible reaction outcome. In those cases where the IHA is favored and can take place only from one position, this process is an efficient way to selectively transform methoxy protecting groups into acetals.

Study of the Selective Hydrolysis of *O*-Methyl Acetates and Methylenedioxy Acetals. Once the hydrogen abstraction process has selectively transformed a methoxy group into an acetal, the cleavage of the latter would afford an alcohol or a diol function.

In the case of IHA product **34** (Scheme 13), the methylenedioxy acetal group was expected to be more resistant to hydrolysis than the 1,2-isopropylidene acetal. In effect, although different conditions were studied, the hydrolysis of **34** afforded either the 1,2-diol **52** (conditions in Scheme 13) or complex mixtures (e.g., with trifluoroacetic anhydride/AcOH). The best results were obtained with the system trifluoroacetic acid—water [(TFA)/H₂O, 1:1], which generated product **52** in 88% yield.

The 4,5-diol 53³⁰ was obtained by saponification of the formate 36, under very mild conditions and in excellent yield.

SCHEME 13. Conversion of the IHA Products 34 and 36 to Diols 52 and 53

SCHEME 14. Conversion of the IHA Products 40 and 41 to Diol 56

However, the methylenedioxy acetals can be selectively hydrolyzed in the presence of many functional groups, even other acetals. The hydrolysis of the methylenedioxy groups was studied under different conditions, and the best results were obtained with the system glacial acetic acid/trifluoroacetic anhydride (TFAA)³¹ (Experimental Section, method D). For instance, the IHA reaction from product 8 (Scheme 14) afforded the cyclic acetal 40, which on treatment with TFAA generated an intermediate 40a, which underwent an S_N2 reaction with AcOH. The resulting ring-opening product 40b probably generated an oxycarbenium intermediate by extrusion of trifluoroacetic acid. Finally, the addition of acetate afforded the O-methyl acetate derivative 54 in satisfactory yield. The acetal 54 was partially hydrolyzed in situ to the alcohol 55. In both compounds, the oxygen functions at C-4 and C-6 are differently protected, and hence further selective manipulation of the molecule is possible.

The diacetate **54** and the monoacetate **55** were transformed into the diol 56^{32} on treatment with 1 N NaOH in MeOH/H₂O (9:1) in 90 and 89% yield, respectively. The other IHA product **41** also underwent basic hydrolysis to give the diol **56** in very good yields.

⁽²⁹⁾ The IHA examples suggest that the formation of *O*-methyl acetates predominates over the generation of five-membered dioxolane rings. On the contrary, the formation of six-membered methylenedioxy acetals between the C-4 and C-6 positions is favored over the generation of *O*-methyl acetates

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SCHEME 15. Transformation of IHA Products 44 and 45 into Diols 58 and 61

SCHEME 16. One-Pot Transformation of Substrate 13 into Diol 62

The IHA products derived from glucose were treated under similar conditions to obtain the diols (Scheme 15). Thus, treatment of the 1β -benzyl-4,6-methylene glucose derivative 44 with acetic acid and trifluroacetic anhydride generated the acetate 57 in 53% yield. Interestingly, the 1-O-benzyl group was not affected by the cleavage process conditions. The basic hydrolysis of 57 gave the 4,6-diol 58 in 95% yield.

The 1α -benzyl-4,6-methylene glucose derivative **45** (Scheme 15), formed from substrate **11**, was cleaved under the usual conditions, affording the *O*-methyl acetate **59** and its hydrolysis product **60** in 87% global yield. Both products **59** and **60** underwent saponification to give the 4,6-diol **61** in excellent yields (91% from **59** and 93% from **60**).

As for the *O*-methyl acetate **48** (Scheme 16), derived from substrate **13**, its saponification afforded the diol **62** in good yields. At this point, the direct conversion of IHA substrates

into diols seemed an interesting challenge. The conversion of substrate 13 into diol 62 is described below.

One-Pot Conversion of IHA Substrates into Diols. The substrate 13 (Scheme 16) was treated under the usual IHA conditions. Once the reaction was completed, the solvent was removed under vacuum and 1 N NaOH in a 9:1 methanol/water solution was added. After 1 h, the reaction mixture was extracted and purified by column chromatography, affording the diol 62 (Table 1, entry 1). The yield obtained in the one-step procedure (50%) was comparable to the overall yield for the two-step procedure (46%).

The direct conversion of substrates **8**, **10**, and **11** into their corresponding diols was also studied (entries 2–4). Since these substrates gave methylenedioxy acetals as the major IHA products, the conditions for the one-pot reaction were modified. Thus, substrates **8**, **10**, and **11** were treated with DIB and iodine and irradiated with visible light. Once the starting material was totally transformed, the solvent was evaporated under vacuum and AcOH was added as a solvent. The solution was cooled to 0 °C, and TFAA was added. After being stirred at 26 °C during the time stated in Table 1, the solvent was again removed under vacuum and 1 N NaOH (in MeOH/H₂O, 9:1) was added. To our satisfaction, the yields were in general comparable to or even slightly greater than those obtained in the multiple-step procedure.

Summary

A mild and efficient methodology to selectively cleave methoxy protecting groups next to hydroxy functions was described. This method used a radical hydrogen abstraction reaction as the key step. The procedure was carried out with xylose, glucose, galactose, and rhamnose substrates. In the first step, the methoxy protecting group was transformed into a methylenedioxy acetal or an *O*-methyl acetate. Then the acetal groups were hydrolyzed in good to excellent yields.

A direct conversion of the carbohydrate substrates into diols was also developed. This one-pot procedure avoids the purification of the intermediate acetals, and the yields are comparable to those obtained in the two- or three-step methodology.

Experimental Section

Generation of Alkoxyl Radicals and Subsequent IHA. General Procedure. A solution of the substrate (0.2 mmol) in dry dichloromethane (4 mL) was treated with DIB (97 mg, 0.3 mmol) and iodine (51 mg, 0.2 mmol) under nitrogen. The reaction mixture was irradiated with two tungsten-filament lamps at 22–25 °C for 1 h, and then it was poured into aqueous 10% sodium thiosulfate and extracted with CH_2Cl_2 . The organic layer was dried (Na_2SO_4) and evaporated under vacuum, and the resulting residue was purified by column chromatography on silica gel.

IHA Reaction of 1,2-*O*-Isopropylidene-3,5-di-*O*-methyl-α-D-glucofuranose (5). Substrate 5 was treated under the standard IHA conditions, affording after column chromatography (hexanes/EtOAc 9:1, then 8:2) 1,2-*O*-isopropylidene-3-*O*-methyl-5,6-*O*-methylene-α-D-glucofuranose (34) (19%), 1,2-*O*-isopropylidene-3-*O*-methyl-5,6-*O*-methylene-oxy-(6'-*O*-1',2'-*O*-isopropylidene-3',5'-di-*O*-methyl-α-D-glucofuranose)-α-D-glucofuranose (35) (5%), 5-*O*-formyl-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-glucofuranose (36) (16%), (5*R*/S)-5-*O*-acetyl-1,2-isopropylidene-3,5-di-*O*-methyl-α-D-xylodialdo-1,4-furanose (37) (5%), and (5*R*/S)-5-*O*-acetyl-1,2-isopropylidene-3,5-di-*O*-methyl-α-D-xylodialdo-1,4-furanose (38) (18%) (overall yield 63%). Dioxolane 34: syrup; [α]_D -55 (*c* 0.12, CHCl₃); IR (CHCl₃) 1082, 924 cm⁻¹; ¹H NMR (500 MHz) δ _H 1.32

TABLE 1. One-Pot IHA Hydrolysis Reaction

entry	substrate	reaction conditions ^a	one-pot IHA-hydrolysis.	two- or three
			products and yield (%) ^b	-step process.
				Global yield (%) ^b
1	OMe HO OBn Me MeO OBn 13	DIB, I_2 , hv; CH_2CI_2 , then 1N NaOH, MeOH-H $_2$ O 9:1, 1h	OMe HO OBn MeO 62 (50%)	46%
2	MeO OH MeO O:Me OMe	DIB, I_2 , hv; CH_2CI_2 then AcOH, TFAA, 0 $^{\circ}C$ to 26 $^{\circ}C$, 2h, then 1N NaOH,	HO OH MeO OMe OMe	65%
3 4	8 OH MeO O OBn Me MeO 10 β-OBn 11 α-OBn	MeOH-H ₂ O 9:1, 1h DIB, I ₂ , hv; CH ₂ CI ₂ then AcOH, TFAA, 0 °C to 26 °C, 2h, then 1N NaOH, MeOH-H ₂ O 9:1, 1h	56 (77%) OH HO OBn Me MeO 59 β-OBn, 31% 61 α-OBn, 61%	59 β-OBn, 26% 61 α-OBn, 52%

^a Conditions: See general procedure (Experimental Section) for more details. ^b Yields are given for products purified by chromatography on silica gel.

(3H, s), 1.50 (3H, s), 3.46 (3H, s), 3.79 (1H, d, J = 3.2 Hz), 3.98 (2H, m), 4.16 (1H, dd, J = 3.2, 7.6 Hz), 4.26 (1H, ddd, J = 5.9, 6.8, 7.1 Hz), 4.58 (1H, d, J = 3.7 Hz), 4.86 (1H, s), 5.03 (1H, s), 5.87 (1H, d, J = 3.7 Hz); ¹³C NMR (125.7 MHz) $\delta_{\rm C}$ 26.2 (CH₃), 26.8 (CH₃), 58.0 (CH₃), 67.7 (CH₂), 72.0 (CH), 80.6 (CH), 81.8 (CH), 83.8 (CH), 95.1 (CH₂), 105.2 (CH), 111.8 (C); MS m/z (rel intensity) 245 (M⁺ – H, 2), 173 (M⁺ + H – 1,3-dioxolane, 100); HRMS calcd for $C_{11}H_{17}O_6$, 245.1025; found, 245.1032; calcd for $C_8H_{13}O_4$, 173.0814; found, 173.0809. Anal. Calcd for $C_{11}H_{18}O_6$: C, 53.65; H, 7.37. Found: C, 53.32; H, 7.67. Compound 35: noncrystalline solid; $[\alpha]_D$ –50 (c 0.14, CHCl₃); IR 1082 cm⁻¹; ¹H NMR (500 MHz) $\delta_{\rm H}$ 1.31 (3H, s), 1.32 (3H, s), 1.47 (3H, s), 1.48 (3H, s), 3.43 (3H, s), 3.46 (3H, s), 3.47 (3H, s), 3.65 (2H, m), 3.77 (1H, d, J = 3.1 Hz), 3.85 (1H, d, J = 3.0 Hz), 3.94 (1H, d, J = 9.4 Hz), 4.09 (2H, m), 4.13 (1H, dd, J = 6.6, 8.0 Hz), 4.27 (1H, dd, J =3.0, 9.0 Hz), 4.34 (1H, ddd, J = 6.5, 6.6, 8.9 Hz), 4.55 (1H, d, J= 3.8 Hz), 4.56 (1H, d, J = 3.7 Hz), 5.86 (2H, d, J = 4.5 Hz), 5.86 (1H, s); ¹H NMR (500 MHz, C_6D_6) δ_H 1.11 (3H, s), 1.12 (3H, s), 1.42 (3H, s), 1.46 (3H, s), 3.00 (3H, s), 3.10 (3H, s), 3.41 (3H, s), 3.77 (1H, dd, J = 6.1, 10.2 Hz), 3.79 (1H, d, J = 2.7 Hz), 3.87 (1H, ddd, J = 1.6, 7.2, 8.7 Hz), 3.89 (1H, d, J = 3.0 Hz), 3.99 (1H, dd, J = 7.1, 7.1 Hz), 4.11 (1H, dd, J = 1.6, 11.0 Hz), 4.19 (1H, dd, J = 6.3, 8.0 Hz), 4.28 (2H, m), 4.39 (1H, dd, J =3.1, 9.2 Hz), 4.54 (1H, ddd, J = 6.5, 6.5, 8.9 Hz), 4.59 (1H, dd, J= 3.0, 9.0 Hz), 5.79 (1H, d, J = 3.9 Hz), 5.82 (1H, d, J = 3.7 Hz), 5.90 (1H, s); 13 C NMR (125.7 MHz) $\delta_{\rm C}$ 26.1 (CH₃), 26.2 (CH₃), 26.5 (CH₃), 26.6 (CH₃), 57.4 (CH₃), 58.1 (CH₃), 58.5 (CH₃), 65.6 (CH₂), 67.2 (CH₂), 72.0 (CH), 76.4 (CH), 78.7 (CH), 81.2 (CH), 81.4 (CH), 82.0 (CH), 83.4 (CH), 83.5 (CH), 105.0 (CH), 105.1 (CH), 111.5 (C), 111.7 (C), 115.7 (CH); MS m/z (rel intensity) $477 (M^+ - Me, 2), 245 (1,2-O-isopropylidene-3-O-methyl-5,6-O-isopropylidene-3-O-isop$ methylene- α -D-glucofuranose — H, 100); HRMS calcd for $C_{21}H_{33}O_{12}$, 477.1972; found, 477.1975; calcd for C₁₁H₁₇O₆, 245.1025; found, 245.1043. Anal. Calcd for C₂₂H₃₆O₁₂: C, 53.65; H, 7.37. Found: C, 53.39; H, 7.67. Formate **36**: non-crystalline solid; $[\alpha]_D$ -44 (c 0.12, CHCl₃); IR 3605, 1728 cm⁻¹; ¹H NMR (500 MHz) $\delta_{\rm H}$ 1.33 (3H, s), 1.49 (3H, s), 3.48 (3H, s), 3.90 (1H, d, J = 3.2 Hz), 4.15 (1H, dd, J = 3.2, 7.8 Hz), 4.19 (1H, m), 4.27 (1H, dd, J = 5.9,11.5 Hz), 4.48 (1H, dd, J = 2.5, 11.6 Hz), 4.60 (1H, d, J = 3.8Hz), 4.75 (1H, br s), 5.91 (1H, d, J = 3.7 Hz), 8.13 (1H, s); 13 C NMR (125.7 MHz) $\delta_{\rm C}$ 26.1 (CH₃), 26.7 (CH₃), 57.7 (CH₃), 66.0 (CH₂), 67.6 (CH), 79.1 (CH), 81.2 (CH), 84.4 (CH), 105.1 (CH), 111.9 (C), 161.0 (CH); MS m/z (rel intensity) 262 (M⁺, <1), 87 $(HCO_2CH=CHOH - H, 100); HRMS calcd for C_{11}H_{18}O_7, 262.1053;$

found, 262.1077; calcd for C₃H₃O₃, 87.0082; found, 87.0074. Anal. Calcd for C₁₁H₁₈O₇: C, 50.38; H, 6.92. Found: C, 50.00; H, 7.29. Less polar acetate 37: syrup; $[\alpha]_D$ -26 (c 0.10, CHCl₃); IR 1740 cm⁻¹; ¹H NMR (500 MHz) $\delta_{\rm H}$ 1.33 (3H, s), 1.50 (3H, s), 2.15 (3H, s), 3.43 (3H, s), 3.50 (3H, s), 3.80 (1H, d, J = 3.4 Hz), 4.19(1H, dd, J = 3.3, 7.8 Hz), 4.56 (1H, d, J = 3.7 Hz), 5.90 (1H, d, J)J = 3.7 Hz), 5.96 (1H, d, J = 7.8 Hz); ¹³C NMR (125.7 MHz) $\delta_{\rm C}$ 21.3 (CH₃), 26.3 (CH₃), 26.8 (CH₃), 57.6 (CH₃), 57.9 (CH₃), 80.1 (CH), 81.6 (CH), 84.0 (CH), 96.2 (CH), 105.4 (CH), 111.9 (C), 171.0 (C); MS m/z (rel intensity) 261 (M⁺ – Me, 18), 101 (2,2dimethyl-1,3-dioxole + H, 100); HRMS calcd for C₁₁H₁₇O₇, 261.0974; found, 261.0956; calcd for C₅H₉O₂, 101.0603; found, 101.0598. Anal. Calcd for C₁₂H₂₀O₇: C, 52.17; H, 7.30. Found: C, 51.98; H, 7.55. More polar acetate **38**: syrup; $[\alpha]_D$ -28 (c 0.12, CHCl₃); IR (CHCl₃) 1744 cm⁻¹; ¹H NMR (500 MHz) $\delta_{\rm H}$ 1.32 (3H, s), 1.49 (3H, s), 2.11 (3H, s), 3.33 (3H, s), 3.53 (3H, s), 3.70 (1H, d, J = 3.5 Hz), 4.28 (1H, dd, J = 3.5, 7.6 Hz), 4.56 (1H, d, J =3.7 Hz), 5.88 (1H, d, J = 7.6 Hz), 5.94 (1H, d, J = 3.7 Hz); ¹³C NMR (125.7 MHz) $\delta_{\rm C}$ 20.7 (CH₃), 26.2 (CH₃), 26.7 (CH₃), 57.7 (CH₃), 57.8 (CH₃), 80.4 (CH), 81.2 (CH), 83.8 (CH), 95.9 (CH), 105.4 (CH), 112.0 (C), 169.7 (C); MS m/z (rel intensity) 275 (M⁺ - H, 4), 101 (2,2-dimethyl-1,3-dioxole + H, 100); HRMS calcd for $C_{12}H_{19}O_7$, 275.1131; found, 275.1148; calcd for $C_5H_9O_2$, 101.0603; found, 101.0613. Anal. Calcd for C₁₂H₂₀O₇: C, 52.17; H, 7.30. Found: C, 52.22; H, 7.53.

IHA Reaction of Substrate 6. Compound **6** was treated under the standard IHA conditions and after column chromatography (hexanes/EtOAc, 9:1) yielded 1,2-*O*-isopropylidene-3,5-*O*-methylene-α-D-xylofuranose (**39**) (45% yield) as a colorless oil: $[\alpha]_D$ –16 (*c* 0.10, CHCl₃); IR 1181, 1087 cm⁻¹; ¹H NMR (500 MHz) δ_H 1.33 (3H, s), 1.49 (3H, s), 3.89 (1H, dd, J = 1.9, 13.2 Hz), 4.01 (1H, s), 4.16 (1H, d, J = 1.8 Hz), 4.28 (1H, d, J = 13.2 Hz), 4.55 (1H, d, J = 3.7 Hz), 4.62 (1H, d, J = 6.5 Hz), 4.98 (1H, d, J = 6.5 Hz), 6.04 (1H, d, J = 3.7 Hz); ¹³C NMR (125.7 MHz) δ_C 26.1 (CH₃), 26.7 (CH₃), 66.0 (CH₂), 72.8 (CH), 77.8 (CH), 83.6 (CH), 91.6 (CH₂), 105.6 (CH), 111.8 (C); MS m/z (rel intensity) 187 (M⁺ – Me, 100); HRMS calcd for $C_8H_{11}O_5$, 187.0606; found, 187.0611. Anal. Calcd for $C_9H_{14}O_5$: C, 53.46; H, 6.98. Found: C, 53.35; H, 7.14.

IHA Reaction of Substrate 7. The general procedure afforded a complex mixture of products.

IHA Reaction of Substrate 8. Compound **8** was treated under the standard IHA conditions, affording after column chromatography (hexanes/EtOAc, 9:1) methyl 2,3-di-*O*-methyl-4,6-*O*-methyl-4

ylene- β -D-galactopyranoside (40) (32.8 mg, 70%) and methyl 2,3di-O-methyl-4-O-(methyl acetate)- β -D-galactopyranoside (41) (6 mg, 11%). Compound 40: crystalline solid; mp 118-120 °C (from EtOAc/*n*-pentane); $[\alpha]_D + 3$ (*c* 0.29, CHCl₃); IR 1173 cm⁻¹; ¹H NMR (500 MHz) $\delta_{\rm H}$ 3.20 (1H, dd, J = 3.7, 9.6 Hz), 3.34 (1H, d, J = 1.2 Hz), 3.42 (1H, dd, J = 7.8, 9.6 Hz), 3.51 (3H, s), 3.55 (3H, s), 3.59 (3H, s), 3.82 (1H, dd, J = 1.5, 12.3 Hz), 4.03 (1H, d, J = 1.5, 12.3 Hz)J = 3.6 Hz), 4.18 (1H, d, J = 12.2 Hz), 4.19 (1H, d, J = 7.7 Hz), 4.73 (1H, d, J = 6.3 Hz), 5.19 (1H, d, J = 6.3 Hz); ¹³C NMR $(100.6 \text{ MHz}) \delta_{C} 56.8 \text{ (CH}_{3}), 58.1 \text{ (CH}_{3}), 60.8 \text{ (CH}_{3}), 67.0 \text{ (CH)},$ 68.6 (CH₂), 72.5 (CH), 79.6 (CH), 81.3 (CH), 93.5 (CH₂), 104.3 (CH); MS m/z (rel intensity) 234 (M⁺, 1), 75 (MeOCH=CHOH + H, 100); HRMS calcd for $C_{10}H_{18}O_6$, 234.1103; found, 234.1118; calcd for C₃H₇O₂, 75.0446; found, 75.0447. Anal. Calcd for C₁₀H₁₈O₆: C, 51.27; H, 7.75. Found: C, 51.43; H, 7.74. Compound **41**: syrup; $[\alpha]_D + 10$ (c 0.30, CHCl₃); IR (film) 3518, 1735 cm⁻¹; ¹H NMR (500 MHz) $\delta_{\rm H}$ 2.10 (3H, s), 3.16 (1H, dd, J = 3.0, 9.7Hz), 3.30 (1H, dd, J = 7.7, 9.6 Hz), 3.46 (1H, dd, J = 6.3, 6.5 Hz), 3.53 (3H, s), 3.54 (3H, s), 3.58 (3H, s), 3.68 (1H, dd, J = 6.6, 11.4 Hz), 3.78 (1H, dd, J = 6.5, 11.4 Hz), 4.17 (1H, d, J = 4.1Hz), 4.18 (1H, d, J = 7.4 Hz), 5.35 (1H, d, J = 6.1 Hz), 5.38 (1H, d, J = 6.1 Hz); ¹³C NMR (100.6 MHz) $\delta_{\rm C}$ 19.6 (CH₃), 56.9 (CH₃), 59.0 (CH₃), 60.4 (CH₃), 60.8 (CH₂), 73.6 (2 × CH), 80.7 (CH), 83.4 (CH), 89.9 (CH₂), 104.7 (CH), 169.9 (C); MS m/z (rel intensity) $234 (M^{+} - MeCO_{2}H, 2), 75 (MeOCH=CHOH + H, 100); HRMS$ calcd for C₁₀H₁₈O₆, 234.1103; found, 234.1091; calcd for C₃H₇O₂, 75.0446; found, 75.0449. Anal. Calcd for C₁₂H₂₂O₈: C, 48.97; H, 7.53. Found: C, 49.14; H, 7.33.

IHA Reaction of Substrate 9. When the standard IHA reaction was carried out with compound 9, followed by column chromatography (hexanes/EtOAc, 9:1), two products were isolated: methyl 2,3-di-*O*-methyl-4,6-*O*-methylene-α-D-galactopyranoside (**42**) (68%) and methyl 2,3-di-O-methyl-4-O-(methyl acetate)-α-D-galactopyranoside (43) (14%) (overall yield 82%). Compound 42: noncrystalline solid; $[\alpha]_D + 108$ (c 0.13, CHCl₃); IR (film) 1173, 1110, 1091 cm⁻¹; 1 H NMR (500 MHz, $C_{6}D_{6}$) δ_{H} 3.05 (1H, br s), 3.13 (3H, s), 3.23 (1H, dd, J = 1.8, 12.1 Hz), 3.29 (3H, s), 3.30 (3H, s),3.54 (1H, d, J = 3.6 Hz), 3.59 (1H, dd, J = 3.5, 10.0 Hz), 3.89(1H, dd, J = 3.5, 10.0 Hz), 3.90 (1H, d, J = 12.2 Hz), 4.31 (1H, d, J = 12.2 Hz)d, J = 6.2 Hz), 4.79 (1H, d, J = 3.5 Hz), 5.07 (1H, d, J = 6.2 Hz); ¹³C NMR (100.6 MHz, C_6D_6) δ_C 55.2 (CH₃), 56.9 (CH₃), 58.8 (CH₃), 63.7 (CH), 68.9 (CH₂), 73.2 (CH), 77.8 (CH), 77.9 (CH), 93.3 (CH₂), 99.4 (CH); MS m/z (rel intensity) 234 (M⁺, 2), 75 (MeCH=CHOH + H, 100); HRMS calcd for $C_{10}H_{18}O_6$, 234.1103; found, 234.1084; calcd for C₃H₇O₂, 75.0446; found, 75.0438. Anal. Calcd for C₁₀H₁₈O₆: C, 51.27; H, 7.75. Found: C, 51.34; H, 7.81. Compound 43 could not be totally purified from its mixture with the major product 42. ¹H NMR (500 MHz, C_6D_6) δ_H 1.65 (3H, s), 3.13 (3H, s), 3.21 (3H, s), 3.26 (3H, s), 3.51 (1H, m), 3.71 (2H, m), 3.80 (2H, m), 4.03 (1H, d, J = 2.9 Hz), 4.73 (1H, d, J = 3.5Hz), 5.34 (1H, d, J = 6.1 Hz), 5.36 (1H, d, J = 6.1 Hz); ¹³C NMR (100.6 MHz, C_6D_6) δ_C 16.4 (CH₃), 55.0 (CH₃), 55.2 (CH₃), 58.2 (CH₃), 61.1 (CH), 70.3 (CH₂), 75.6 (CH), 78.8 (CH), 80.0 (CH), 88.9 (CH₂), 98.5 (CH), 167.4 (C).

IHA Reaction of Substrate 10. Compound **10** was treated under the usual IHA conditions. Standard workup followed by column chromatography (hexanes/EtOAc, 9:1) afforded benzyl 2,3-di-O-methyl-4,6-O-methylene- β -D-glucopyranoside (**44**) (51%) as a crystalline solid: mp 117–119 °C (from n-pentane); [α]_D –55 (c 0.18, CHCl₃); IR 3090, 3063 cm⁻¹; ¹H NMR (500 MHz) δ _H 3.12 (1H, dd, J = 7.8, 8.1 Hz), 3.23–3.30 (3H, m), 3.48 (1H, dd, J = 9.8, 10.2 Hz), 3.60 (3H, s), 3.61 (3H, s), 4.20 (1H, dd, J = 4.3, 10.6 Hz), 4.48 (1H, d, J = 7.6 Hz), 4.60 (1H, d, J = 6.3 Hz), 4.64 (1H, d, J = 11.8 Hz), 5.05 (1H, d, J = 6.3 Hz), 7.28–7.36 (5H, m); ¹³C NMR (125.7 MHz) δ _C 60.8 (CH₃), 60.9 (CH₃), 66.2 (CH), 68.5 (CH₂), 71.3 (CH₂), 80.7 (CH), 82.5 (CH), 84.2 (CH), 93.6 (CH₂), 102.9 (CH), 127.8 (2 × CH), 127.9 (CH), 128.4 (2 × CH), 137.1 (C); MS m/z (rel intensity) 219 (M⁺ – PhCH₂, <1), 91 (PhCH₂, 100); HRMS calcd for C₉H₁₅O₆,

219.0869; found, 219.0891; calcd for C_7H_7 , 91.0548; found, 91.0546. Anal. Calcd for $C_{16}H_{22}O_6$: C, 61.92; H, 7.15. Found: C, 62.17; H, 6.82.

IHA Reaction of Substrate 11. Compound 11 was treated under the standard IHA conditions and after column chromatography (hexanes/EtOAc, 9:1) afforded benzyl 2,3-di-O-methyl-4,6-Omethylene- α -D-glucopyranoside (45) (66%) as a crystalline solid: mp 121–123 °C (from *n*-pentane); $[\alpha]_D$ +151 (*c* 0.14, CHCl₃); IR (CHCl₃) 3090, 3067 cm⁻¹; ¹H NMR (500 MHz) $\delta_{\rm H}$ 3.22 (1H, dd, J = 9.4, 9.7 Hz), 3.25 (1H, dd, J = 3.8, 9.4 Hz), 3.39 (1H, dd, J= 10.5, 10.5 Hz), 3.41 (3H, s), 3.63 (3H, s), 3.65 (1H, dd, J = 9.3, 9.4 Hz), 3.73 (1H, ddd, J = 4.9, 10.0, 10.0 Hz), 4.01 (1H, dd, J =4.9, 10.2 Hz), 4.60 (1H, d, J = 6.3 Hz), 4.62 (1H, d, J = 12.2 Hz), $4.73 \text{ (1H, d, } J = 12.2 \text{ Hz)}, 4.98 \text{ (1H, d, } J = 3.8 \text{ Hz)}, 5.06 \text{ (1H,$ J = 6.3 Hz), 7.31 (1H, dd, J = 7.1, 7.1 Hz), 7.37 (2H, dd, J = 7.1, 7.6 Hz), 7.39 (2H, d, J = 7.0 Hz); ¹³C NMR (125.7 MHz) $\delta_{\rm C}$ 58.6 (CH₃), 61.0 (CH₃), 62.7 (CH), 68.7 (CH₂), 69.5 (CH₂), 79.5 (CH), 81.6 (CH), 81.7 (CH), 93.7 (CH₂), 95.8 (CH), 128.0 (CH), 128.3 $(2 \times CH)$, 128.4 $(2 \times CH)$, 136.9 (C); MS m/z (rel intensity) 219 $(M^+ - PhCH_2, 2)$, 91 (PhCH₂, 100); HRMS calcd for $C_9H_{15}O_6$, 219.0869; found, 219.0938; calcd for C₇H₇, 91.0548; found, 91.0545 Anal. Calcd for C₁₆H₂₂O₆: C, 61.92; H, 7.15. Found: C, 61.87; H, 7.11.

IHA Reaction of Substrate 12. The general procedure afforded methyl 2,6-di-*O*-methyl-3-*O*-(methyl acetate)- β -D-glucopyranoside (**46**) (54%) as a syrup: [α]_D -22 (c 0.13, CHCl₃); IR (film) 3518, 1742 cm⁻¹; ¹H NMR (500 MHz) δ _H 2.10 (3H, s), 3.01 (1H, dd, J = 8.2, 8.3 Hz), 3.41 (1H, m), 3.42 (3H, s), 3.53 (3H, s), 3.54 (3H, s), 3.55 (1H, m), 3.64 (1H, dd, J = 5.1, 10.3 Hz), 3.68 (1H, dd, J = 3.8, 10.4 Hz), 4.19 (1H, d, J = 7.8 Hz), 5.38 (1H, d, J = 6.0 Hz), 5.46 (1H, d, J = 6.0 Hz); ¹³C NMR (125.7 MHz) δ _C 21.1 (CH₃), 57.0 (CH₃), 59.6 (CH₃), 60.6 (CH₃), 70.5 (CH), 72.6 (CH₂), 73.8 (CH), 82.5 (CH), 84.3 (CH), 89.9 (CH₂), 104.4 (CH), 170.7 (C); MS m/z (rel intensity) 234 (M⁺ - MeCO₂H, <1), 74 (MeCH=CHOH, 100); HRMS calcd for C₁₀H₁₈O₆, 234.1103; found, 234.1053; calcd for C₃H₆O₂, 74.0368; found, 74.0360. Anal. Calcd for C₁₂H₂₂O₈: C, 48.97; H, 7.53. Found: C, 49.29; H, 7.84.

IHA Reaction of Substrate 13. Compound 13 was treated under the usual IHA conditions. Standard workup followed by column chromatography (hexanes/EtOAc, 9:1) afforded benzyl 2,6-di-Omethyl-3-O-(methyl acetate)- β -D-glucopyranoside (48) (52%) and benzyl 2,6-di-O-methyl-3,4-O-methylene- β -D-glucopyranoside (**49**) (17%). Compound **48**: syrup; $[\alpha]_D - 12$ (c 0.10, CHCl₃); IR (film) 3592, 1739 cm⁻¹; ¹H NMR (500 MHz) $\delta_{\rm H}$ 2.10 (3H, s), 3.11 (1H, dd, J = 8.0, 8.8 Hz), 3.40 (1H, m), 3.42 (3H, s), 3.50 (1H, dd, J =8.8, 9.2 Hz), 3.54 (1H, dd, J = 7.5, 9.0 Hz), 3.56 (3H, s), 3.65 (1H, dd, J = 5.1, 10.5 Hz), 3.70 (1H, dd, J = 3.7, 10.4 Hz), 4.40(1H, d, J = 7.8 Hz), 4.63 (1H, d, J = 11.9 Hz), 4.93 (1H, d, J = 11.9 Hz)11.9 Hz), 5.38 (1H, d, J = 6.1 Hz), 5.45 (1H, d, J = 6.0 Hz), 7.35–7.42 (5H, m); 13 C NMR (100.6 MHz) $\delta_{\rm C}$ 30.0 (CH₃), 60.0 (CH₃), 61.1 (CH₃), 70.8 (CH), 71.4 (CH₂), 73.8 (CH₂), 74.3 (CH), 83.0 (CH), 84.7 (CH), 90.3 (CH₂), 102.8 (CH), 128.1 (2 × CH), 128.2 (CH), 128.8 (2 × CH), 137.7 (C), 164.8 (C); MS m/z (rel intensity) 295 (M⁺ - [MeOCH=CHOH + H], <1), 91 (PhCH₂, 100); HRMS calcd for $C_{15}H_{19}O_6$, 295.1182; found, 219.1191; calcd for C₇H₇, 91.0548; found, 91.0546. Anal. Calcd for C₁₈H₂₆O₈: C, 58.37; H, 7.08. Found: C, 58.07; H, 7.43. Compound 49: syrup; $[\alpha]_D$ -33 (c 0.11, CHCl₃); IR (film) 3095, 3067 cm⁻¹; ¹H NMR $(500 \text{ MHz}) \delta_{\text{H}} 3.49 (1\text{H}, \text{m}), 3.43 (3\text{H}, \text{s}), 3.51 (1\text{H}, \text{m}), 3.53 (1\text{H}, \text{m})$ m), 3.61 (3H, s), 3.65 (1H, dd, J = 3.8, 8.4 Hz), 4.13 (1H, m), 4.35 (1H, dd, J = 4.5, 4.5 Hz), 4.67 (1H, d, J = 11.9 Hz), 4.81(1H, d, J = 7.6 Hz), 4.94 (1H, d, J = 11.9 Hz), 4.97 (1H, s), 5.23(1H, s), 7.27–7.38 (5H, m); 13 C NMR (125.7 MHz) $\delta_{\rm C}$ 59.4 (CH₃), 59.6 (CH₃), 70.7 (CH₂), 71.7 (CH), 71.9 (CH₂), 73.1 (CH), 75.8 (CH), 77.7 (CH), 95.7 (CH₂), 99.8 (CH), 127.6 (CH), 127.7 (2 × CH), 128.3 (2 × CH), 137.3 (C); MS m/z (rel intensity) 267 (M⁺ $[CH_2=CO + H]$, 3), 91 (PhCH₂, 100); HRMS calcd for $C_{14}H_{19}O_5$, 267.1232; found, 267.1227; calcd for C_7H_7 , 91.0548; found, 91.0541. Anal. Calcd for $C_{16}H_{22}O_6$: C, 61.92; H, 7.15. Found: C, 62.27; H, 7.46.

IHA Reaction of Substrate 14. The general procedure afforded a complex mixture of products.

IHA Reaction of Substrate 15. The usual reaction conditions afforded methyl 4-O-methyl-3-O-(methyl acetate)-α-L-rhamnopyranoside (50) (80%) and methyl 4-O-methyl-2,3-O-methylene-α-L-rhamnopyranoside (51) (10%). Compound 50: syrup; $[\alpha]_D$ -66 (c 0.17, CHCl₃); IR (film) 3580, 1740 cm⁻¹; ¹H NMR (500 MHz) $\delta_{\rm H}$ 1.31 (3H, d, J=6.3 Hz), 2.10 (3H, s), 3.12 (1H, dd, J=9.4, 9.4 Hz), 3.35 (3H, s), 3.50 (3H, s), 3.60 (1H, dddd, J = 6.2, 6.3,6.4, 9.6 Hz), 3.82 (1H, dd, J = 3.4, 9.3 Hz), 3.95 (1H, dd, J = 1.6, 3.3 Hz), 4.65 (1H, br s), 5.31 (1H, d, J = 6.3 Hz), 5.46 (1H, d, J = 6.3 Hz) = 6.2 Hz); 13 C NMR (100.6 MHz) $\delta_{\rm C}$ 17.7 (CH₃), 21.1 (CH₃), 54.8 (CH₃), 61.0 (CH₃), 67.3 (CH), 70.1 (CH), 80.6 (CH), 81.4 (CH), 88.7 (CH₂), 100.0 (CH), 170.4 (C); MS m/z (rel intensity) $204 (M^{+} - MeCO_{2}H, 1), 72 (MeOCH=CHMe, 100); HRMS calcd$ for $C_9H_{16}O_5$, 204.0998; found, 204.0963; calcd for C_4H_8O , 72.0575; found, 72.0534. Anal. Calcd for C₁₁H₂₀O₇: C, 49.99; H, 7.63. Found: C, 49.67; H, 7.98. Compound 51 could not be totally purified from its mixture with the major product **50**. ¹H NMR (500 MHz, CDCl₃) $\delta_{\rm H}$ 1.26 (3H, d, J = 6.3 Hz), 2.75 (1H, dd, J = 9.3, 9.3 Hz), 3.40 (3H, s), 3.51 (3H, s), 3.58 (2H, m), 3.72 (1H, dd, J = 9.3, 9.2 Hz), 4.67 (1H, d, J = 3.9 Hz), 5.40 (1H, d, J = 6.3 Hz),5.49 (1H, d, J = 6.3 Hz); ¹³C NMR (100.6 MHz, CDCl₃) $\delta_{\rm C}$ 17.6 (CH₃), 55.1 (CH₃), 60.9 (CH₃), 66.7 (CH), 72.1 (CH), 82.9 (CH), 84.7 (CH), 89.6 (CH₂), 99.0 (CH).

Hydrolysis of IHA Product 34. Method A. Compound 34 (50 mg, 0.2 mmol) was added to a 7:3 acetic acid/H₂O mixture (2 mL). The solution was heated to 65 °C and stirred for 24 h. After cooling to 26 °C, the reaction mixture was poured into cold aqueous NaHCO₃ and extracted with EtOAc. The organic layer was dried and concentrated, and the residue was purified by column chromatography on silica gel (hexanes/EtOAc, 1:1), yielding 3-Omethyl-5,6-O-methylene-D-glucofuranose (52) (20 mg, 48%). Method B. The dioxolane 34 (49 mg, 0.2 mmol) was added to a 1:1 trifluoroacetic acid/H2O mixture (0.5 mL) at 0 °C. The solution was allowed to reach 26 °C and was stirred for 6 h. Afterward, the reaction mixture was poured into cold aqueous NaHCO3 and extracted with EtOAc. The organic layer was dried (Na₂SO₄), filtered, and concentrated under vacuum. The residue was purified as in Method A, affording product 52 (36.2 mg, 88%) as a syrup $(\alpha/\beta \text{ anomers, 2:1})$. $[\alpha]_D$ -4 (c 0.20, CHCl₃); IR 3609, 3571 cm⁻¹ ¹H NMR (500 MHz, CDCl₃ + D₂O) major anomer (α): $\delta_{\rm H}$ 3.44 (3H, s), 3.81 (1H, dd, J = 1.9, 4.5 Hz), 3.89 (1H, dd, J = 5.9, 8.8)Hz), 3.93 (1H, dd, J = 2.3, 8.6 Hz), 4.13 (1H, dd, J = 1.9, 4.0 Hz), 4.20 (1H, m), 4.39 (1H, dd, J = 4.5, 5.9 Hz), 4.83 (1H, s), 5.01 (1H, s), 5.48 (1H, d, J = 4.1 Hz); minor anomer (β): δ_H 3.50 (3H, s), 3.78 (1H, d, J = 3.7 Hz), 4.01 (1H, dd, J = 1.4, 10.2 Hz), 4.02 (1H, d, J = 10.3 Hz), 4.24 (1H, dd, J = 6.2, 6.3 Hz), 4.26(1H, br s), 4.31 (1H, m), 4.86 (1H, s), 5.03 (1H, s), 5.13 (1H, s); ¹³C NMR (125.7 MHz) major anomer (α): $\delta_{\rm C}$ 58.0 (CH₃), 66.9 (CH₂), 73.1 (CH), 74.8 (CH), 79.0 (CH), 85.5 (CH), 94.9 (CH₂), 96.7 (CH); minor anomer (β): $\delta_{\rm C}$ 58.9 (CH₃), 67.9 (CH₂), 72.9 (CH), 76.9 (CH), 81.9 (CH), 84.3 (CH), 95.2 (CH₂), 103.5 (CH); MS m/z (rel intensity) 205 (M⁺ – H, 8), 73 (1,3-dioxolane – H, 100); HRMS calcd for C₈H₁₃O₆, 205.0712; found, 205.0699; calcd for C₃H₅O₂, 73.0290; found, 73.0289. Anal. Calcd for C₈H₁₄O₆: C, 46.60; H, 6.84. Found: C, 46.87; H, 6.71.

Hydrolysis of IHA Product 36. The formate 36 (26 mg, 0.1 mmol) was added to a 5% NaHCO₃ methanolic solution (0.5 mL), and the mixture was stirred at 26 °C for 1 h. Then it was poured into water and extracted with EtOAc. The organic layer was washed with aqueous 5% HCl and water, dried, and concentrated under vacuum. The residue was purified by silica gel chromatography (hexanes/EtOAc, 1:1) affording 1,2-*O*-isopropylidene-3-*O*-methyl-α-D-glucofuranose (53)³⁰ (23 mg, 98%).

Hydrolysis of IHA Products 40, 41, 44, 45, 48, 54, 55, 57, 59, and 60. General Procedures. Method A. To a solution of the

IHA product (0.1 mmol) in glacial acetic acid (25 μ L, 0.5 mmol) at 0 °C and under nitrogen was added dropwise trifluoroacetic anhydride (37.5 μ L, 0.5 mmol). The reaction mixture was stirred at 26 °C for 3 h and then slowly poured into cold saturated aqueous NaHCO₃ and extracted with CH₂Cl₂. The organic layers were washed with water, dried (Na₂SO₄), and concentrated under vacuum. The resulting residue was purified by chromatography on silica gel (hexanes/EtOAc).

Method B. The IHA product (0.1 mmol) was added to a 1 N NaOH solution in MeOH/ H_2O (9:1, 0.5 mL). The reaction mixture was stirred at 26 °C for 1 h, then poured into cold 5% aqueous HCl and extracted with EtOAc. Usual drying and evaporation, followed by column chromatography on silica gel (hexanes/EtOAc), afforded the hydrolysis products.

Methyl 6-O-Acetyl-2,3-di-O-methyl-4-O-(methyl acetate)-β-D-galactopyranoside (54) and Methyl 6-O-Acetyl-2,3-di-O-methyl- β -D-galactopyranoside (55). Compound 40 was treated under Method A conditions, affording products 54 (17 mg, 51%) and 55 (12 mg, 46%; global 97%). Compound 54: crystalline solid; mp 51–53 °C (from *n*-pentane); $[\alpha]_D$ –24 (*c* 0.31, CHCl₃); IR (film) 1740 cm⁻¹; ¹H NMR (500 MHz) $\delta_{\rm H}$ 2.08 (3H, s), 2.09 (3H, s), 3.13 (1H, dd, J = 3.0, 9.6 Hz), 3.30 (1H, dd, J = 7.6, 9.6 Hz), 3.52 (3H, s), 3.54 (3H, s), 3.56 (1H, dd, J = 6.3, 6.6 Hz), 3.57(3H, s), 4.11 (1H, d, J = 2.9 Hz), 4.15 (1H, d, J = 7.6 Hz), 4.17(1H, dd, J = 6.3, 11.2 Hz), 4.25 (1H, dd, J = 6.4, 11.2 Hz), 5.34 (1H, d, J = 6.4 Hz), 5.42 (1H, d, J = 6.4 Hz); ¹³C NMR (125.7) MHz) $\delta_{\rm C}$ 20.8 (CH₃), 21.0 (CH₃), 56.8 (CH₃), 59.0 (CH₃), 60.8 (CH₃), 62.7 (CH₂), 71.1 (CH), 73.2 (CH), 80.4 (CH), 83.2 (CH), 89.0 (CH₂), 104.5 (CH), 170.6 (C), 170.8 (C); MS m/z (rel intensity) 277 (M⁺ – OCOMe, 1), 88 (MeOCH=CHOMe, 100); HRMS calcd for $C_{12}H_{21}O_7$, 277.1287; found, 277.1236; calcd for $C_4H_8O_2$, 88.0524; found, 88.0497. Anal. Calcd for C₁₄H₂₄O₉: C, 50.00; H, 7.19. Found: C, 50.09; H, 7.22. Compound **55**: syrup; $[\alpha]_D - 11$ (c 0.24, CHCl₃); IR (film) 3570, 1740 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) $\delta_{\rm H}$ 2.09 (3H, s), 3.17 (1H, dd, J = 3.2, 9.3 Hz), 3.24 (1H, dd, J = 7.7, 9.2 Hz), 3.51 (3H, s), 3.54 (3H, s), 3.57 (3H, s), 3.59 (1H, dd, J = 5.8, 6.8 Hz), 3.99 (1H, d, J = 3.2 Hz), 4.16 (1H, d, d, J = 3.2 Hz)J = 7.5 Hz), 4.34 (2H, d, J = 6.2 Hz); ¹³C NMR (125.7 MHz, CDCl₃) $\delta_{\rm C}$ 20.9 (CH₃), 56.8 (CH₃), 57.9 (CH₃), 60.8 (CH₃), 63.0 (CH₂), 65.5 (CH), 71.7 (CH), 80.1 (CH), 82.5 (CH), 104.3 (CH), 170.8 (C); MS m/z (rel intensity) 247 (M⁺ - OH, <1), 88 (MeOCH=CHOMe, 100); HRMS calcd for $C_{11}H_{19}O_6$, 247.1182; found, 247.1196; calcd for C₄H₈O₂, 88.0524; found, 88.0533. Anal. Calcd for $C_{11}H_{20}O_7$: C, 49.99; H, 7.63. Found: C, 50.13; H, 7.52.

Methyl 2,3-Di-*O*-methyl-β-D-galactopyranoside (56). Compound 56 was obtained from three different substrates, which were treated as in Method B. Thus, compound 41 afforded product 56 in 89% yield. Alternatively, compounds 54 and 55 gave the diol 56 in 90 and 89% yield, respectively. The diol 56 was previously reported.³²

Benzyl 6-O-Acetyl-2,3-di-O-methyl- β -D-glucopyranoside (57). Compound 44 was treated as in Method A, affording product 57 (53%) as a non-crystalline solid: $[\alpha]_D$ -38 (c 0.31, CHCl₃); IR (film) 3597, 1737 cm⁻¹; ¹H NMR (500 Mz, C_6D_6) δ_H 1.64 (3H, s), 2.40 (1H, br s), 3.05 (1H, dd, J = 9.0, 9.0 Hz), 3.14 (1H, ddd, J =2.4, 4.8, 9.7 Hz), 3.18 (1H, dd, J = 7.9, 9.5 Hz), 3.42 (1H, dd, J= 9.3, 9.4 Hz), 3.48 (3H, s), 3.49 (3H, s), 4.35 (1H, d, J = 7.7Hz), 4.40 (1H, dd, J = 2.4, 12.0 Hz), 4.45 (1H, dd, J = 4.8, 12.0 Hz), 4.52 (1H, d, J = 12.0 Hz), 4.91 (1H, d, J = 12.0 Hz), 7.08– 7.23 (3H, m), 7.32 (2H, d, J = 7.3 Hz); ¹³C NMR (100.6 MHz) $\delta_{\rm C}$ 21.4 (CH₃), 61.1 (CH₃), 61.7 (CH₃), 63.7 (CH₂), 70.6 (CH), 71.8 (CH_2) , 74.2 (CH), 84.4 (CH), 86.3 (CH), 103.2 (CH), 128.54 (2×10^{-2}) CH), 128.57 (CH), 129.2 (2 \times CH), 138.0 (C), 172.2 (C); MS m/z(rel intensity) 233 (M^+ – PhCH₂O, <1), 91 (PhCH₂, 100); HRMS calcd for C₁₀H₁₇O₆, 233.1025; found, 233.0948; calcd for C₇H₇, 91.0548; found, 91.0488. Anal. Calcd for C₁₇H₂₄O₇: C, 59.99; H, 7.11. Found: C, 59.72; H, 7.23.

Benzyl 2,3-Di-O-methyl-β-D-glucopyranoside (58). Compound 57 was treated as in Method B, yielding compound 58 (95%) as a

non-crystalline solid: $[\alpha]_D$ -36 (c 0.21, CHCl₃); IR 3597, 3088, 3064, 1603 cm⁻¹; ¹H NMR (500 MHz) δ_H 3.09 (1H, dd, J = 9.0, 9.1 Hz), 3.13 (1H, dd, J = 8.6, 9.1 Hz), 3.33 (1H, ddd, J = 3.9, 5.0, 9.4 Hz), 3.50 (1H, dd, J = 9.0, 9.3 Hz), 3.60 (3H, s), 3.63 (3H, s), 3.77 (1H, dd, J = 5.2, 11.8 Hz), 3.90 (1H, dd, J = 3.5, 11.8 Hz), 4.46 (1H, d, J = 7.7 Hz), 4.68 (1H, d, J = 11.9 Hz), 4.89 (1H, d, J = 11.9 Hz), 7.98–7.37 (5H, m); ¹³C NMR (100.6 MHz) δ_C 60.3 (CH₃), 60.9 (CH₃), 62.7 (CH₂), 70.4 (CH), 71.5 (CH₂), 74.8 (CH), 83.8 (CH), 85.7 (CH), 102.9 (CH), 127.8 (2 × CH), 127.9 (CH), 128.5 (2 × CH), 137.3 (C); MS m/z (rel intensity) 267 (M⁺ — MeO, 1), 91 (PhCH₂, 100); HRMS calcd for $C_{14}H_{19}O_5$, 267.1232; found, 267.1231; calcd for C_7H_7 , 91.0548; found, 91.0465. Anal. Calcd for $C_{15}H_{22}O_6$: C, 60.39; H, 7.43. Found: C, 60.20; H, 7.68.

Benzyl 6-O-Acetyl-2,3-di-O-methyl-4-O-(methyl acetate)-α-D-glucopyranoside (59) and Benzyl 6-O-Acetyl-2,3-di-O-methylα-**D**-glucopyranoside (60). Compound 45 was treated as in Method A, giving products **59** (49%) and **60** (38%). Compound **59**: syrup; $[\alpha]_D$ +158 (c 0.29, CHCl₃); IR 3091, 3067, 1740 cm⁻¹; ¹H NMR (500 Mz) $\delta_{\rm H}$ 2.08 (3H, s), 2.10 (3H, s), 3.21 (1H, dd, J = 3.7, 9.2Hz), 3.41 (3H, s), 3.55 (1H, dd, J = 8.5, 8.8 Hz), 3.58 (1H, dd, J= 8.0, 8.5 Hz), 3.60 (3H, s), 3.78 (1H, ddd, J = 3.5, 3.7, 9.4 Hz), 4.15 (1H, dd, J = 3.8, 12.4 Hz), 4.17 (1H, dd, J = 4.0, 12.5 Hz), 4.59 (1H, d, J = 12.1 Hz), 4.70 (1H, d, J = 12.2 Hz), 4.98 (1H, d, J = 12.2 Hz)J = 3.7 Hz), 5.33 (1H, d, J = 6.3 Hz), 5.42 (1H, d, J = 6.3 Hz), 7.30 (1H, dd, J = 6.9, 7.0 Hz), 7.34 (2H, dd, J = 7.0, 7.6 Hz), 7.37 (2H, d, J = 7.0 Hz); ¹³C NMR (125.7 MHz) $\delta_{\rm C}$ 20.8 (CH₃), 20.9 (CH₃), 58.4 (CH₃), 61.2 (CH₃), 62.8 (CH₂), 68.1 (CH), 69.2 (CH₂), 77.5 (CH), 81.7 (CH), 82.5 (CH), 89.2 (CH₂), 94.9 (CH), 128.0 (CH), 128.3 (2 × CH), 128.4 (2 × CH), 136.8 (C), 170.5 (C), 170.8 (C); MS m/z (rel intensity) 353 (M⁺ – OCOMe, <1), 91 (PhCH₂, 100); HRMS calcd for C₁₈H₂₅O₇, 353.1600; found, 353.1588; calcd for C₇H₇, 91.0548; found, 91.0546. Anal. Calcd for C₂₀H₂₈O₉: C, 58.24; H, 6.84. Found: C, 58.19; H, 6.99. Compound **60**: syrup: $[\alpha]_D + 113$ (c 0.23, CHCl₃); IR 3595, 3090, 3066, 1736 cm $^{-1}$; 1 H NMR (500 Mz) $\delta_{\rm H}$ 2.11 (3H, s), 3.22 (1H, dd, J = 3.7, 9.5 Hz), 3.39 (3H, s), 3.41 (1H, dd, J = 9.3, 9.6 Hz), 3.52 (1H, dd, J = 9.2, 9.2 Hz), 3.65 (3H, s), 3.78 (1H, ddd, J =2.3, 4.5, 10.9 Hz), 4.14 (1H, dd, J = 2.2, 12.2 Hz), 4.41 (1H, dd, J = 2.2, 12.2 Hz)J = 4.5, 12.1 Hz), 4.62 (1H, d, J = 12.2 Hz), 4.73 (1H, d, J = 12.2 Hz) 12.2 Hz), 5.01 (1H, d, J = 3.7 Hz), 7.30 (1H, d, J = 7.1, 7.1 Hz), 7.35 (2H, dd, J = 7.0, 7.6 Hz), 7.40 (2H, d, J = 7.0 Hz); ¹³C NMR $(125.7 \text{ MHz}) \delta_{C} 20.8 \text{ (CH}_{3}), 58.1 \text{ (CH}_{3}), 61.3 \text{ (CH}_{3}), 63.2 \text{ (CH}_{2}),$ 69.5 (CH₂), 69.6 (CH), 70.0 (CH), 81.6 (CH), 82.3 (CH), 95.1 (CH), 128.0 (CH), 128.3 (2 × CH), 128.4 (2 × CH), 136.9 (C), 171.4 (C); MS m/z (rel intensity) 341 (M⁺ + H, <1), 91 (PhCH₂, 100); HRMS calcd for $C_{17}H_{25}O_7$, 341.1600; found, 341.1568; calcd for C_7H_7 , 91.0548; found, 91.0539. Anal. Calcd for $C_{17}H_{24}O_7$: C, 59.99; H, 7.11. Found: C, 59.75; H, 7.37.

Benzyl 2,3-Di-*O***-methyl-α-D-glucopyranoside** (**61**). Compound **61** was obtained from two different substrates, which were treated as in Method B. Thus, compounds **59** and **60** afforded product **61** in 91 and 94% yield, respectively. Compound **61**: non-crystalline solid; $[\alpha]_D + 139$ (c 0.27, CHCl₃); IR (film) 3593, 3090, 3067 cm⁻¹; ¹H NMR (500 MHz) δ_H 3.21 (1H, dd, J = 3.5, 9.3 Hz), 3.39 (3H, s), 3.51 (1H, dd, J = 9.3, 9.6 Hz), 3.53 (1H, dd, J = 9.2, 9.2 Hz), 3.64 (3H, s), 3.67 (1H, ddd, J = 3.7, 3.9, 9.4 Hz), 3.76 (1H, dd, J = 3.7, 11.9 Hz), 3.78 (1H, dd, J = 3.9, 11.9 Hz), 4.61 (1H, d, J = 12.2 Hz), 4.74 (1H, d, J = 12.2 Hz), 5.00 (1H, d, J = 3.7 Hz), 7.30 (1H, dd, J = 7.0, 7.2 Hz), 7.35 (2H, d, J = 7.1, 7.6 Hz), 7.39 (2H, d, J = 7.2 Hz); ¹³C NMR (125.7 MHz) δ_C 58.0 (CH₃), 61.2 (CH₃), 62.3 (CH₂), 69.3 (CH₂), 70.4 (CH), 71.0 (CH), 81.8 (CH),

82.6 (CH), 95.0 (CH), 128.0 (CH), 128.3 (2 \times CH), 128.4 (2 \times CH), 137.0 (C); MS m/z (rel intensity) 280 (M⁺ - H₂O, <1), 91 (PhCH₂, 100); HRMS calcd for C₁₅H₂₀O₅, 280.1311; found, 280.1297; calcd for C₇H₇, 91.0548; found, 91.0552. Anal. Calcd for C₁₅H₂₂O₆: C, 60.39; H, 7.43. Found: C, 60.33; H, 7.68.

Benzyl 2,6-Di-*O*-**methyl-***β*-**D-glucopyranoside** (**62**). Compound **48** was treated as in Method B, yielding product **62** (88%) as a syrup: $[\alpha]_D$ –34 (c 0.10, CHCl₃); IR (film) 3592, 3461 cm⁻¹; ¹H NMR (500 MHz) δ_H 2.93 (1H, br s), 3.06 (1H, dd, J = 7.8, 8.9 Hz), 3.40 (1H, m), 3.43 (3H, s), 3.49 (1H, m), 3.57 (1H, dd, J = 8.5, 10.0 Hz), 3.61 (3H, s), 3.69 (2H, d, J = 4.7 Hz), 4.43 (1H, d, J = 7.8 Hz), 4.63 (1H, d, J = 11.9 Hz), 4.93 (1H, d, J = 11.9 Hz), 7.34–7.44 (5H, m); ¹³C NMR (100.6 MHz) δ_C 59.6 (CH₃), 60.7 (CH₃), 71.0 (CH₂), 71.3 (CH), 72.7 (CH₂), 73.8 (CH), 76.2 (CH), 82.8 (CH), 102.3 (CH), 127.8 (3 × CH), 128.4 (2 × CH), 137.3 (C); MS m/z (rel intensity) 235 (M⁺ – [MeOH + MeO], <1), 91 (PhCH₂, 100); HRMS calcd for C₁₃H₁₅O₄, 235.0970; found, 235.0975; calcd for C₇H₇, 91.0548; found, 91.0550. Anal. Calcd for C₁₅H₂₂O₆: C, 60.39; H, 7.43. Found: C, 60.46; H, 7.49.

One-Pot Protecting Group Transformation Hydrolysis. Gen**eral Procedures. Method A.** A solution of the substrate (0.2 mmol) in dry dichloromethane (4 mL) was treated with DIB (97 mg, 0.3 mmol) and iodine (51 mg, 0.2 mmol) under nitrogen. The reaction mixture was irradiated with two tungsten-filament lamps for 1 h at 22-25 °C. Then the solvent was evaporated under vacuum, and glacial acetic acid (25 μ L, 0.5 mmol) and trifluoroacetic anhydride (38 μ L, 0.5 mmol) were added at 0 °C under nitrogen. The reaction mixture was allowed to reach 26 °C and stirred for 2 h. Afterward, the reagents were removed under vacuum, and the residue was treated with 4% NaOH (MeOH/H₂O, 9:1, 0.5 mL). After being stirred at 26 °C for 1 h, the reaction mixture was poured into water, neutralized with aqueous 5% HCl, and extracted with EtOAc. The organic layer was dried (Na₂SO₄) and evaporated under vacuum, and the resulting residue was purified by chromatography on silica gel (hexanes/EtOAc). Following Method A, compounds 8, 10, and 11 were transformed into diols **56** (77%), **59** (31%), and **61** (61%), respectively.

Method B. A solution of the substrate **13** (0.2 mmol) in dry dichloromethane (4 mL) was treated with DIB (97 mg, 0.3 mmol) and iodine (51 mg, 0.2 mmol) under nitrogen. The reaction mixture was irradiated with two tungsten-filament lamps for 1 h at 22-25 °C. Then the solvent was evaporated under vacuum, and the residue was treated with 1 N NaOH (MeOH/H₂O, 9:1, 0.5 mL). Workup and purification as in Method A afforded the diol **62** (50%).

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Supporting Information Available: General procedures and synthesis of IHA substrates 5–9 and 12–15. Spectroscopic data for compounds 13, 17 and 18, 20 and 21, 23–26, and 33, and the ¹H and ¹³C NMR spectra for the new IHA or hydrolysis products (compounds 34–46, 48–52, 54–55, 57–62). This material is available free of charge via the Internet at http://pubs.acs.org.

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